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20th International Conference on Biological Inorganic Chemistry

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Abstracts

Plenary Abstracts

Abstract Number: 431

Protein metalation in cells

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"For you to be here now, trillions of drifting atoms have come together in an intricate and curiously obliging manner to create you. Why atoms take the trouble is a bit of a puzzle" (adapted from the opening lines of reference [1]). Among the gathered atoms are essential metals that drive catalysis in almost a half of enzymes [2, 3]. However, proteins commonly bind one or more wrong metals many orders of magnitude more tightly than their required metal(s), further confounding the puzzle. This phenomenon will be exemplified by four proteins [4]. Aberrant binding can be nonconservative: Using a sub-set of the normal ligands, recruiting additional ligands and/or distorting the geometry of the binding site. This raises questions about how living cells avoid widespread mis-metalation. Metalation is sometimes assisted by delivery proteins which raises yet more questions about how the correct metals partition onto the delivery proteins.

The specificity of metalation of nascent proteins is influenced by metal availabilities at protein folding [5]. Living cells have elaborate mechanisms that control intracellular metal availabilities. These mechanisms are commonly regulated by metal-sensors which include DNA-binding metal-sensing transcriptional regulators. The sensors are somehow tuned to detect departures from the optimal intracellular availabilities of their cognate metals. By calculating the metal-sensitivities of metal-sensors a long-standing hypothesis has been found to be true: That (cytosolic) metal availabilities, expressed as free energies for complex formation, are maintained to the inverse of a Universal affinity series, the Irving-Williams series [6, 7]. By reference to these intracellular free energies of available metals, the metalation puzzle has been solved for the four exemplar proteins [4, 6, 8, 9]. Online metalation calculators have been produced [8, 10]. The calculators are now being tested and applied to understanding and optimizing cellular metalation, for example in industrial biotechnology.

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Abstract Number: 432

Addressing the Clinical Challenges of Platinum-based Anticancer Agents

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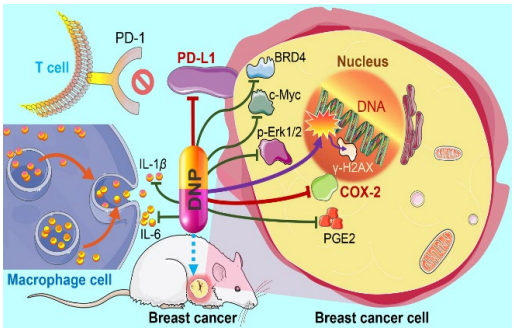
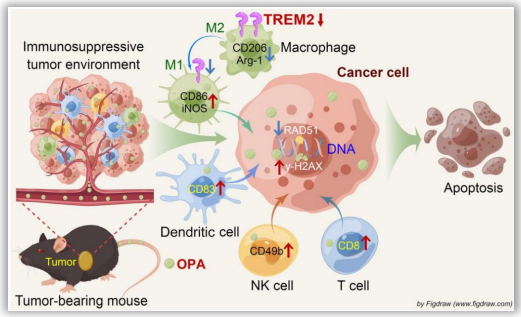
Platinum-based anticancer drugs play an important role in the treatment of various malignancies such as colorectal and testicular cancers. However, drug resistance and toxic side effects are challenging problems that hinder their wider clinical applications. Rational design of novel platinum complexes could provide useful tools for understanding the biomedical effects of platinum anticancer complexes in cellular energy conversion, metabolism and apoptosis, and enables the incorporation of multi-functionalities in the platinum core.

In this lecture, I will focus on the molecular design of platinum-based antitumor complexes with multi-modalities. These results demonstrated that in addition to DNA binding, bio-energetic pathways may also play crucial roles in the antitumor activity of mitochondrion-targeted platinum complexes. The combination of chemotherapy and immunotherapy in one molecule offers potential superiority for combating cancers. Radiation-induced activation of platinum(IV) prodrugs could become a powerful tool in combining the advantages of both chemotherapy and radiotherapy.



Mulfti-specific Pt(IV) prodrugs [3]



(IV) prodrugs remodel immunosuppressive licroenvironment[4]

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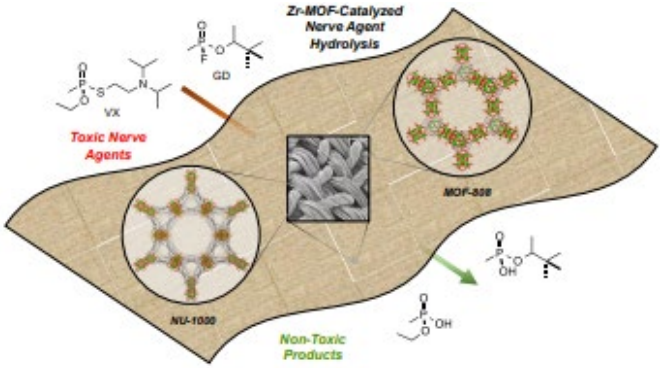
Abstract Number: 428

Smart and Programmable Crystalline Sponges for Protection From Bench to Market

Professor Omar Farha

Abstract: Metal-Organic Frameworks (MOFs) are a class of porous, crystalline materials composed of metal-based nodes and organic ligands that self-assemble into multidimensional lattices. I n contrast to conventional porous materials such as zeolites and activated carbon, an abundantly diverse set of molecular building blocks allows for the realization of MOFs with a broad range of properties. We have developed an extensive understanding of how the physical architecture and chemical properties of MOFs affect material performance in applications such as catalytic activity for chemical warfare agent detoxification. This talk will focus on MOFs for hydrolysis from solution-phase to solid-state reactivity. Moving MOFs from bench to market within industrial sectors will be discussed as well



Abstract Number: 370

Bioinorganic redox modulation, catalysis and signaling for biology, chemistry, medicine and more

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The talk will illustrate how investigations of redox reaction mechanisms (inner-sphere, proton or metal coupled electron transfer as efficient mechanism for chemical energy conversion) with involvement of metal complexes and some small inorganic entities, such as superoxide radical anion, oxygen, nitrogen species or hydrogen sulfide can lead to new approaches for: i) modulation of oxidative stress, biological redox signaling, its (patho)physiological consequences and development of potential pharmaceuticals, adjuvants and therapy enhancers (for approaching longevity, cancer radiation therapy, neurovascular regulation of blood pressure and heart function, enhancement of antiviral therapy and posttranslational redox modifications) and ii) (electro)catalytic or stoichiometric transformations of (small) molecules of environmental and energy relevance. Presented will also be applications of variety of physicochemical techniques (e.g., cryo-MS, cryostopped-flow, high-pressure stopped-flow, high-pressure NMR and high-pressure electrochemistry) for thermodynamic and kinetic studies, as well as number of Mn, Fe and Zn complexes that mimic functions of some enzymes or activate small molecules and their crosstalk.

Abstract Number: 402

Metal Coordination-driven Supramolecular Chemistry: Array, Space, Motion and Asymmetry

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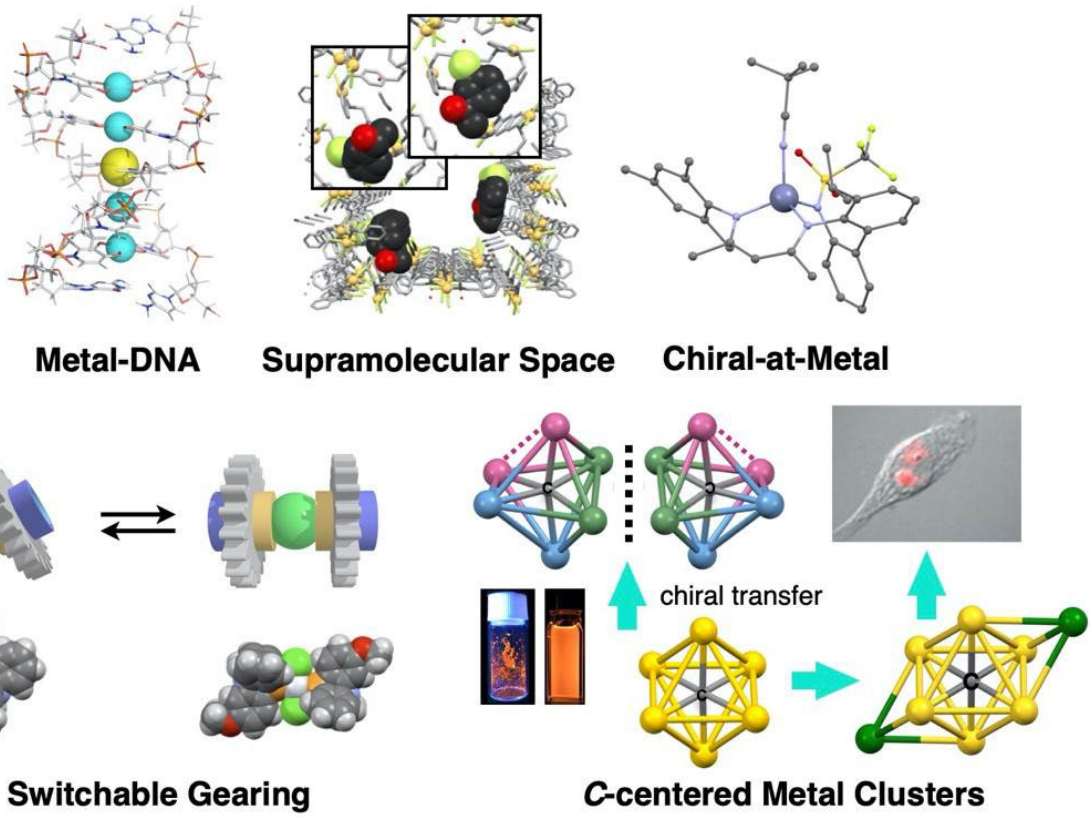
Supermolecules in which a designed fixed number of organic building blocks and metal ions self-assemble through directional, dynamic bond formation can provide elaborate molecular systems that can express functions specific to *array*, *space*, *motion* and *asymmetry*. The design of supramolecular metal complexes, taking into account the types of molecules and ions that make up the complex, the nature of the surfaces that allow interactions, and the chemical environment, is one of the most exciting aspects of supramolecular chemistry. On the other hand, unexpected structures and functions may be encountered as a result of more complex self-assembly than expected, which often opens up new frontiers in chemistry.

This lecture will discuss future directions and challenges in supramolecular chemistry[1] with recent examples on artificial metal-DNA,[1,2] supramolecular spaces,[3] molecular rotors,[4] asymmetric induction of metal-centered chirality[5] and *C*-centered Au^{I}-Ag^{I} clusters.[6]



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Abstract Number: 433

F-block dinitrogen chemistry; from rarity to catalysis in a few simple steps

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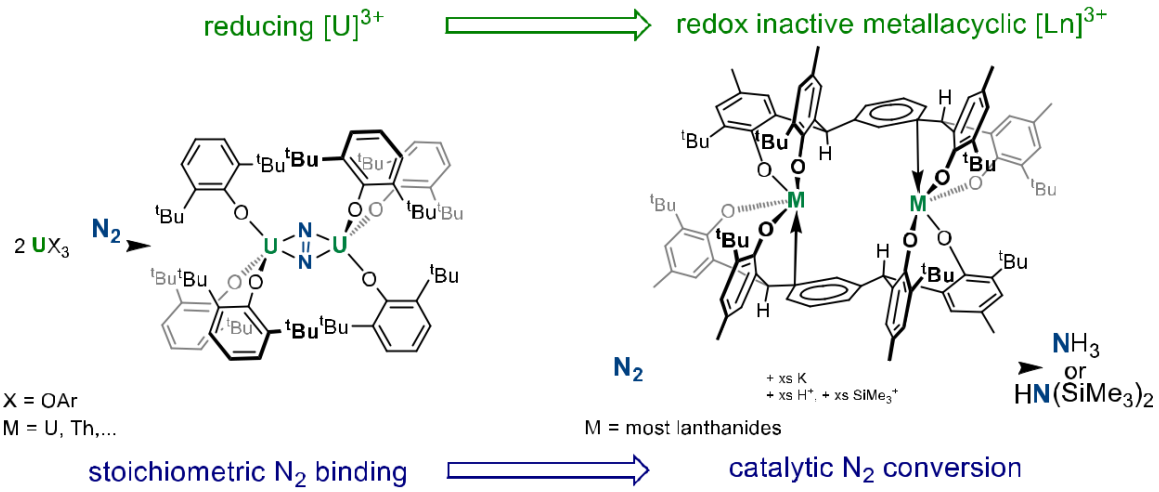
Chemists have spent more than a century trying to copy Nature to make catalysts that can convert atmospheric dinitrogen (N2) to ammonia (NH3), or directly to amines (NR3) under mild conditions. Hundreds of complexes based on metals from the d-block are now known to bind N2, and a few catalysts for N2 conversion to ammonia or tris(silyl)amine have been developed.

However, the picture for the metals at the bottom of the periodic table, the f-block, many of which have been deemed 'critical elements' for technology, is completely different. The binding of dinitrogen to any f-block metal cation was considered impossible until the turn of the millennium, but a small yet growing number of weakly-bound N2 complexes are now being reported. Studies of these weak binding interactions contributes to the fundamental understanding of bonding and electronic structure in these large, and energy-relevant elements.

We will show what we have learnt about N2 binding to f-block centers over the last decade, and our recent development of the first molecular f-block complexes that can catalyse the reduction and functionalisation of dinitrogen, first using actinide, and now earth abundant lanthanide cations. We will also discuss how structural control by the molecular framework can enable the first catalytic conversion of dinitrogen into a secondary silylamine by any metal.



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Abstract Number: 430

Exploring the functional versatility of the catalytic reaction of molybdoenzymes

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Molybdoenzymes are widespread in all domains of life and catalyze key steps in carbon, sulfur and nitrogen metabolism. In the DMSO reductase family of molybdenum enzymes present only in prokaryotes, the molybdenum coordination sphere generally is composed of two dithiolene groups from two molybdopterin (MPT) guanine dinucleotide (MGD) molecules, one amino acid ligand from the protein backbone and a Mo=O or =S group as sixth ligand. Overall Mo-containing enzymes were shown by Holm and coworkers in the 1980ies to catalyze classical oxygen-atom transfer (OAT) reactions[19]. In OATs the oxygen atom from water is transferred to the substrate which is oxidized, or in the opposite direction, from the substrate to yield water; these reactions are coupled to the reversible transfer of two electrons and two protons in the course of the transformation cycles[38]. The electrons are directly transferred to the Mo metal ion of the cofactor and the metals cycle between the Mo^{IV} and Mo^{VI} oxidation states with Mo^{V} as intermediate state. However, some enzymes have been proposed to present exceptions from this reaction to catalyse substrate reduction or oxidation without classical oxygen atom transfer. We critically want to discuss these exceptions and present a model for the reaction mechanism possibly catalysed by molybdoenzymes of the DMSO reductase family.

Keynote Abstracts

Abstract Number: 441

A Radical Solution for C(sp3)–C(sp3) Bond Formation during the Biosynthesis of Macrocyclic Membrane Lipids

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Archaea synthesize isoprenoid-based ether-linked membrane lipids, which enable them to withstand extreme environmental conditions, such as high temperatures, high salinity, and low or high pH values. In some archaea, such as Methanocaldococcus jannaschii, these lipids are further modified by forming carbon–carbon bonds between the termini of two lipid tails within one glycerophospholipid to generate the macrocyclic archaeol or forming two carbon–carbon bonds between the termini of two lipid tails from two glycerophospholipids to generate the macrocycle glycerol dibiphytanyl glycerol tetraether (GDGT). GDGT contains two 40-carbon lipid chains (biphytanyl chains) that span both leaflets of the membrane, providing enhanced stability to extreme conditions. How these specialized lipids are formed has puzzled scientists for decades. The reaction necessitates coupling two completely inert sp3 - hybridized carbon centers, which has not been observed in nature. Here we use X-ray crystallography, high-resolution mass spectrometry, chemical synthesis, and biochemical analyses to show that the gene product of mj0619 from M. jannaschii, which encodes a radical S-adenosylmethionine enzyme, is responsible for biphytanyl chain formation during synthesis of both the macrocyclic archaeol and GDGT membrane lipids.

Abstract Number: 326

Conversion of myoglobin to artificial metalloenzymes

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Myoglobin is a well-known dioxygen storage protein which has a heme cofactor within the protein matrix via multiple interactions. The heme cofactor of myoglobin, protoheme IX (heme *b*), is removable under an acidic condition from the heme pocket, and a metal complex can be incorporated into apomyoglobin under neutral pH conditions. From this point of view, our group has focused on converting myoglobin to a biocatalyst, an artificial metalloenzyme, by artificial metal cofactors.[1] Recently, we have generated new metalloenzymes in which the heme *b* cofactor bound to myoglobin was replaced by artificial metalloporphyrinoids composed of porphycene, corrole or corrin metal complexes. Particularly, metalloporphycene, a constitutional isomer of metalloporphyrin, is one of the attractive artificial cofactors for myoglobin (Figure 1). Myoglobin reconstituted with iron porphycene is found to accelerate peroxidase reaction such as thioanisole sulfoxidation. Furthermore, manganese porphycene in myoglobin can promote hydroxylation of inert alkanes upon the addition of H2O2. For example, ethylbenzene, toluene and cyclohexane are converted to the corresponding alcohols at 25 °C with the turnover numbers of 10–20 at pH 8.5. The intermediate, Mn(V)oxo species, was successfully detected by stopped-flow analysis and X-band EPR spectroscopy. Furthermore, we have also reported that myoglobin with iron porphycene catalyzes cyclopropanation of styrene upon addition of ethyl diazoacetate via iron carbenoid species as an intermediate. The initial rate of the cyclopropanation catalyzed by the reconstituted protein is significantly accelerated by 35-fold compared to native myoglobin. In addition, iron porphycene was recently found to catalyze the dehydration of aldoximes to yield the corresponding nitriles with high turnover numbers (over 4000) under mild conditions. In addition, to enhance the enzymatic activities and/or stereoselectivities of the above reactions, the heme pocket as a second coordination sphere has been modified by mutagenesis technique. In this presentation, we will introduce some examples of artificial metalloenzymes using the myoglobin matrix.

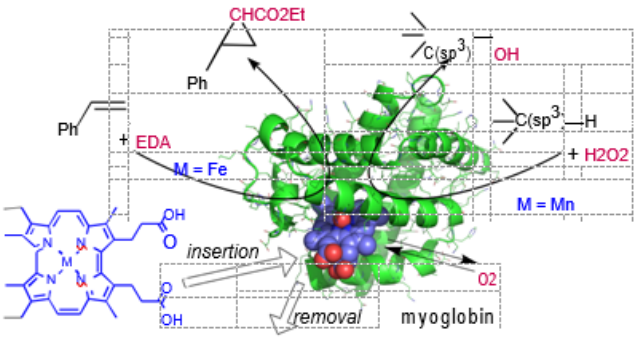

Figure 1. Overview of catalysis by myoglobin reconstituted with metalloporphycene.

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Abstract Number: 285

MRI-responsive agents for quantitative in vivo mapping of labile zinc in deep tissues

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Realizing the importance of Zn^{2+} to numerous biological processes, it is unsurprising that dozens of fluorescent Zn^{2+} sensors are now available and in routine use and that new ones with improved properties are continuously being developed. Indeed, many aspects of fluorescent Zn^{2+} imaging sensors have been perfected, ranking them as *state-of-the-art* imaging reporters for studying dynamic changes in cellular Zn^{2+} levels. Nevertheless, religion on light and fluorescent imaging sensors cannot be used to study deep tissues of live, intact subjects noninvasively and longitudinally. We proposed various types of MRI-responsive agents to obtain ^{19} F-MRI of labile Zn^{2+} without interfering with background signals, quantitative capabilities, and ^{19}F-frequency-specificity. Several design strategies will be discussed. ^{19}F-MRI probes for zinc recognition based on fast binding kinetics and molecular reactivity will be described, and their performances in vivo will be shown.[1] An alternative strategy for zinc recognition, one that uses molecular reactivity, will also be described. Such an approach shows several advantages, especially in the detectability of transient changes in ion levels and enhanced contrast-to-noise changes of the obtained MRI maps.

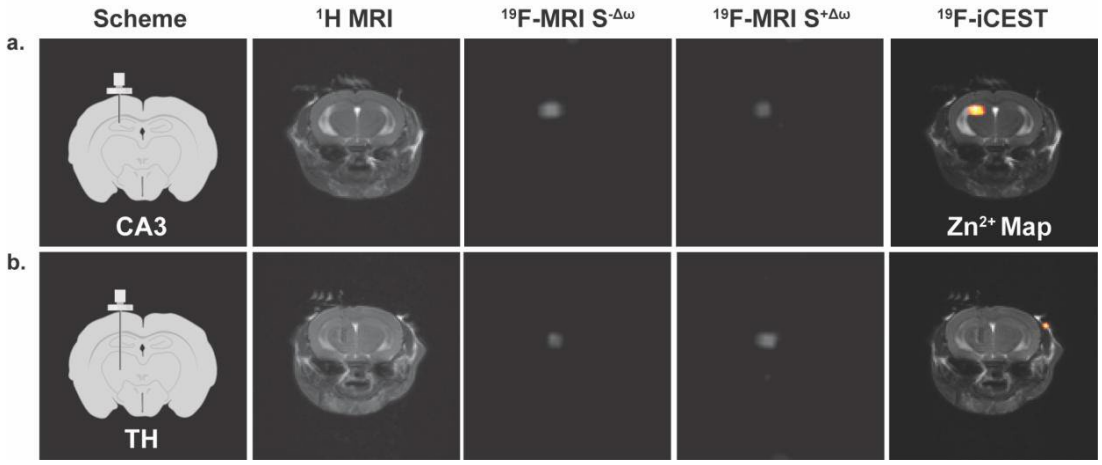

Figure 1. ***In vivo*** **^{19}F-iCEST maps of labile Zn^{2+} pools in the mouse brain**. Schematic illustration of the setup used to deliver **iCEST-probe** to two regions of the brain (a) CA3 in the hippocampus (zinc-rich ROI), or (b) the thalamus (TH, zinc-poor ROI). From left-to-right are the ^{1}H MRI, the^{19}F-MRI $S^{+\Delta\omega}$ (pre-saturation pulse applied at Δω = -3.2 ppm, i.e., "off-resonance"), the ^{19}F-MRI $S^{+\Delta\omega}$ (pre-saturation pulse applied at Δω = +3.2 ppm, i.e., "on-resonance"), the ^{19}F-iCEST contrast (Zn^{2+} map) overlaid on ^{1}H MRI obtained from subtracting ^{19}F-MRI $S^{+\Delta\omega}$ from ^{19}F-MRI $S^{-\Delta\omega}$. MRI scans were performed at 15.2 T.

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Abstract Number: 90

Controllable activation of platinum anticancer prodrugs in vivo

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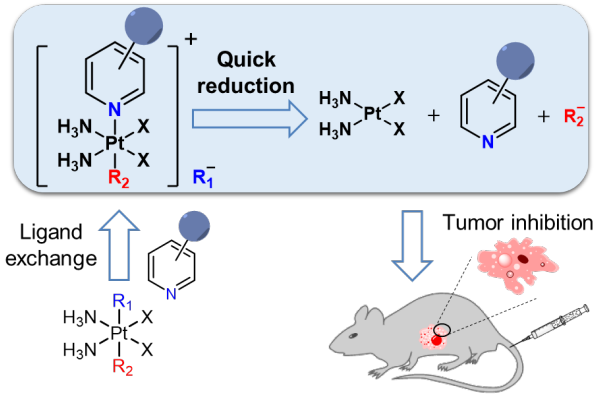
Despite the broad clinical applications of platinum-based anticancer drugs including cisplatin, their side effects and resistance issues have encouraged researchers to look for novel metal-based anticancer complexes. Non-traditional platinum compounds especially Pt(IV) complexes have been extensively studied and they hold great promise to be further developed as the next-generation platinum drugs.[1,2] Selective activation of prodrugs within a tumor is particularly attractive because of their low damage to normal tissue. In this presentation, I will introduce the design, photoactivation mechanism, and antitumor activity of visible light-activatable Pt(IV) prodrugs.[3-5] These small-molecule prodrugs have controllable activation properties: they are shown to be inert in the dark but under short-period irradiation with low intensity of visible light, and without the need for any external catalyst, the prodrugs are rapidly reduced. The prodrugs display superior antitumor activity both in vitro and in vivo in human carcinoma models. I will also introduce our recent progress in the delivery of platinum drugs and novel types of multifunctional platinum prodrugs.[6,7] The controllable activation property and superior antitumor activity of these prodrugs may suggest a novel strategy for the design of next-generation platinum prodrugs to reduce the adverse effects and conquer the drug resistance associated with traditional platinum chemotherapy.



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Abstract Number: 406

Stimuli-responsive, Heteroleptic Coordination Cages as Basis for Complex Systems

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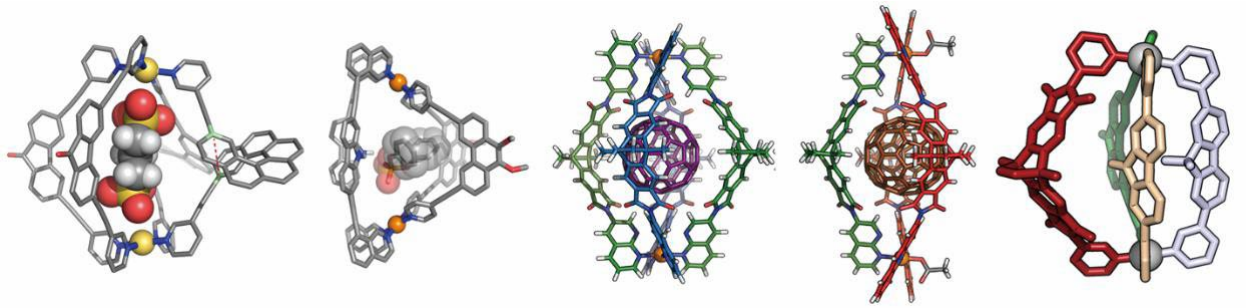
Advanced self-assembly strategies enable the targeted synthesis of supramolecular systems and materials with increasing structural and functional complexity. We react bis-monodentate ligands with transition metal cations to coordination compounds showing a broad range of topologies. To combine different functionalities in the same metallosupramolecular structure, we develop non-statistical assembly strategies such as "shape complementary assembly" (SCA) and "coordination sphere engineering" (CSE).[1] With a focus on multi-chromophore systems, we showed for example that the co-assembly of donor- and acceptor-functionalized ligands (or guests) leads to cages capable of light-induced charge separation, as revealed by transient absorption spectroscopy.[2] By combining chiral with emissive ligands, heteroleptic cages showing guest-modulated circularly polarized luminescence (CPL) are obtained.[3,4] We further introduce stimuli-responsive behaviour in photochromic cages allowing to control guest affinity[5] and established a light-fueled dissipative system.[6] Cages capable of fullerene encapsulation[7] give rise to confinement-controlled reactivity, such as long-term C60 radical anion stabilization.[8] Recently, we mastered the non-statistical and robust assembly of dinuclear Pd(II) cages containing four chemically different ligands [Pd2ABCD].[9] The collected results now set the stage for looking into 'complex systems' behaviour by following the stimuli-responsive population and evolution of co-existing species in mixtures. For example, we study multi-step cage interconversions, guest-binding/release cascades and propagation of chiral information.



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Abstract Number: 72

Towards *in Silico* Design of Valence Tautomeric Molecular Switches

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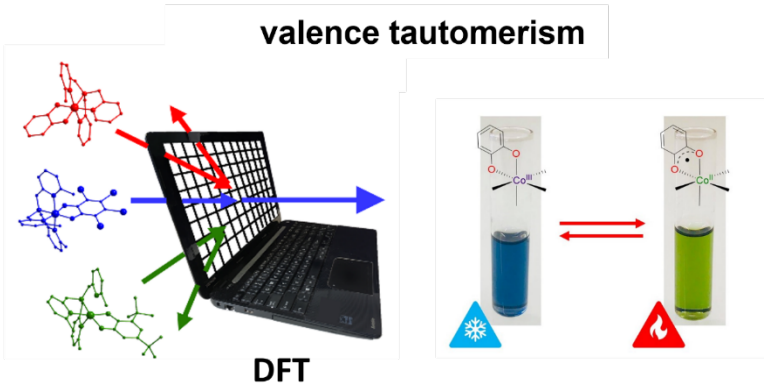
Molecular materials that can be switched between distinguishable forms by application of an external stimulus, such as heating and cooling, are of interest for future applications in displays, sensors and molecular spintronics. Promising examples include valence tautomeric (VT) complexes, which undergo a stimulated intramolecular electron transfer between a metal centre and a redox-active ligand. For cobalt-based systems, the most common type of VT complexes, the electron transfer is accompanied by a spin transition at the cobalt centre.

Our work in this field has spanned investigation of discrete mono- and dinuclear complexes up to coordination polymers, focusing on determining the molecular requirements for VT interconversions. Our recent efforts with computational collaborators have explored the use of density functional theory to predict both the likelihood of an interconversion for metal complexes, as well as the switching characteristics, including transition temperature.[1–3] We have also targeted the development of neutral switchable complexes for better incorporation into films,[4] as well as materials that exhibit pressure-induced interconversions. Our aim is to be able to computationally design new metal complexes with properties suitable for applications prior to synthesis and experimental validation.



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Abstract Number: 440

The structural biology of complex IV assembly

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The mitochondrial oxidative phosphorylation (OXPHOS) system generates the bulk of cellular ATP, fuelling the energy demands of most eukaryotes. Five multi-subunit protein complexes in the mitochondrial inner membrane, termed Complexes I to V, comprise the OXPHOS system. Complex IV is the last complex of the electron transport chain, transferring electrons from cytochrome *c* to molecular oxygen, and in the process, pumping four protons across the inner membrane. In humans, this complex is composed of 14 subunits with the three mtDNA encoded subunits (COX1-3) forming the catalytic core of the enzyme.
Assembly of complex IV requires the participation of a host of cysteine-rich proteins of the mitochondrial intermembrane space (IMS), which take part in a tightly choreographed series of intermolecular interactions for complex IV assembly. However, the identities of all proteins involved, their respective roles and the sequence of their participation in complex IV biogenesis are not known. Crucially, disruptions in this pathway lead to defects in complex IV assembly, inhibition of oxidative phosphorylation and, in humans, manifests in mitochondrial disease.
This presentation will describe our recent studies of complex IV assembly factors, which reveal the roles of these proteins in complex IV assembly and importantly, explain the molecular mechanisms of pathogeneses that occur as a result of identified patient mutations.

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Abstract Number: 354

Siderophore Chirality in Microbial Iron Acquisition

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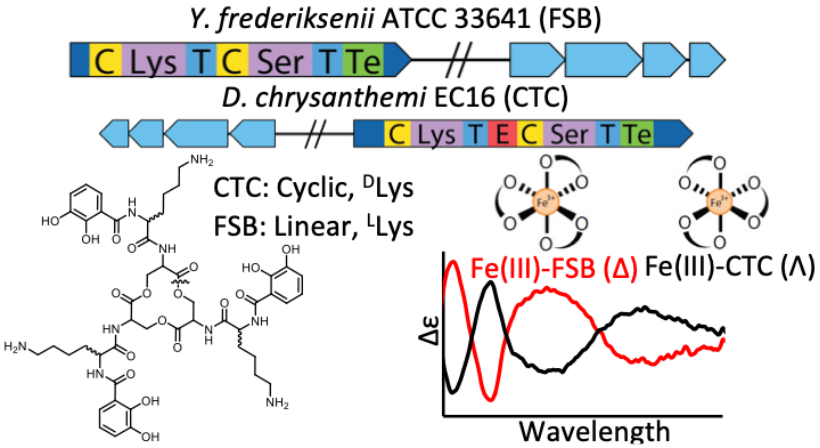
Bacteria require iron to grow and thus iron is an object of competition among microbes. To facilitate Fe(III) uptake, bacteria often produce siderophores. In turn, structural variation within siderophore ligands, microbial competition may be enhanced. Through genomic screening we identified sets of diastereomeric siderophores that coordinate Fe(III) with opposing chirality, including a combinatoric suite of triscatechol siderophores with D- and L- amino acids which are produced by marine and pathogenic microbes (Figure).[1] Variation in chirality of amino acid components of siderophores, and also in chirality on coordination of Fe(III) affects microbial growth in different ways. Our current investigations are focused on identifying the points of stereospecific discrimination in these biological iron uptake pathways.



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Abstract Number: 79

Development of ^{19}F Magnetic Resonance Imaging Probe for in vivo Sensing Biomarkers

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Magnetic resonance imaging (MRI) is a powerful tool for molecular imaging with high spatial resolution in deep tissues. In particular, ^{19}F MRI is a promising tool that enables visualization of ^{19}F-containing contrast agents without background signals from endogenous molecules. For imaging biomarkers *in vivo*, our group have developed OFF-ON activatable ^{19}F MRI probes by conjugating ^{19}F nuclei with a paramagnetic Gd^{3+} complex through an enzyme-cleavable linker.[1] The ^{19}F MRI signal of the probe is quenched by paramagnetic relaxation enhancement (PRE) effect. After cleavage of the linker, the signal is increased by dissociation of the Gd^{3+} complex from the ^{19}F nuclei. Based on this mechanism, enzyme activities were detected by ^{19}F MRI. We have also developed fluorine-accumulated silica nanoparticles for MRI contrast enhancement (FLAME) by encapsulating a large number of perfluorocarbons with a robust silica shell.[2] FLAME has high sensitivity in ^{19}F MRI, surface modifiability, biocompatibility, and sufficient in vivo stability. Recent works on activatable and nanoparticle-based ^{19}F MRI probes will be presented. We developed a series of activatable ^{19}F MRI probes in response to Cathepsin K[3] and other enzymes by changing the cleavable linker between ^{19}F nuclei and a paramagnetic Gd^{3+} complex. In addition, we addressed the limitation of nanoparticle-based probes that show liver accumulation for prolonged time. The biodistribution of nanoparticles depends on the size, the material, and the surface modification. We prepared new perfluorocarbon-encapsulated silica nanoparticles with the decreased size and polymer nanoparticles with the elasticity and deformability. The biodistribution of these nanoparticles in living mice was visualized with ^{19}F MRI to evaluate the effects of the size and the softness on the biodistribution.

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Abstract Number: 196

A Water-Soluble, Cell-Permeable, Fluorescent Sensor for Imaging Mn^{2+} Ions in Living Cells

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Developing selective, cell-permeable, fluorescent sensors for Mn^{2+} ions remains a coordination chemistry challenge. While several groups tried to develop small-molecule based fluorescent sensors (including work from our group, Figure 1 left, M1 sensor)[1] and recently a genetically-encodable[2] fluorescent biosensor for Mn^{2+} ions, a water-soluble, cell-permeable sensor for imaging Mn^{2+} ions in living cells is yet to be achieved. To address this, we designed a computational-workflow to predict the feasibility of photo-induced electron transfer (PeT) in fluorescent metal ion sensors. The idea was to first draw 'chalkboard' structures of a library of metal ion sensors that could potentially detect Mn^{2+} ions. We introduced functionalities to improve the water-solubility of cell-permeable Mn^{2+} binding scaffolds[1] (Figure 1). The designed molecules were evaluated based on the computational workflow and molecules which were computationally-predicted to show PeT were synthesized. Two modular synthetic schemes based on an SN2 reaction and Cu-assisted 'click' reaction were employed for dye attachment to the Mn^{2+} binding scaffolds. In line with our computational predictions, molecules synthesized by both synthetic schemes afforded sensors that showed PeT. A molecule developed via the 'click' strategy could selectively detect Mn^{2+} ions over other physiologically relevant metal ions. The sensor was water-soluble, non-toxic, entered living cells within 15 min of incubation, and was applied for imaging the uptake of Mn^{2+} ions in living cells. The computational-workflow that we developed for predicting PeT is general and can be used to develop any binding-based metal ion sensor. Ongoing directions include using the workflow to develop organelle targetable variants of our novel water-soluble Mn^{2+} sensor. I will present our journey in the Mn^{2+} sensing path in this talk.

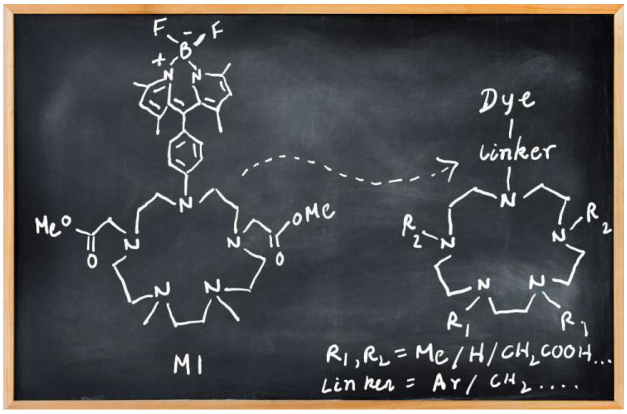

Figure 1. Designing water-soluble Mn^{2+} ion sensors.

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Abstract Number: 192

Rates and intermediates. Off-equilibrium control of Cu(II) distribution between proteins and low molecular agents

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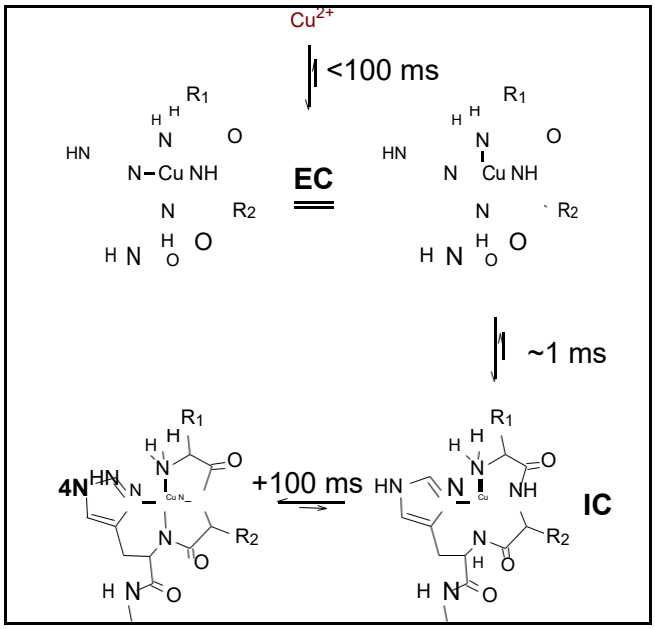
ATCUN motifs, present in several hundred human proteins/peptides, are implicated in copper transport, for the high Cu(II) affinity and for presence in serum albumin (HSA) and hCtr1, the cellular copper transporter. We discovered a general multistep mechanism of Cu^{2+} binding to these motifs, featuring an intermediate two-nitrogen (2N) macrochelate complex (IC), preceding the final 4N complex (Scheme). The IC are characterized with unexpectedly long lifetimes (t½ of 100 ms to several seconds, depending on the sequence). The 4N complex formation may be further delayed by formation of additional/alternative intermediates, enabled by the presence of additional Cu(II) binding residues/sites in the interacting molecules, and/or other Cu(II) chelators forming ternary complexes with the IC. Confronting their lifetimes with the timing of physiological processes related to copper delivery, we propose that such intermediates, rather than the 4N ATCUN complexes are functional copper carriers in blood.[1] Similar mechanisms coupled with specific physiological cycles may operate in other physiological contexts, such as copper signalling in neurotransmission. In this case the 100 ms t½ for IC of the ATCUN motif of the Aβ4-16 representative of beta-amyloid peptide subfamily 4-x corresponds with the pace of synaptic transmission and is consistent with the proposed brain copper scavenger function of these peptides. Other emerging factors modifying the rates of formation of 4N ATCUN complexes include the parallel interactions of host peptides/proteins with biological membranes and the interfering presence of other metal ions. Taken together, these findings support the kinetic, associative mechanisms of copper distribution in the organism and propose a number of layers of physiological feedback. These can provide a basis for designing biological experiments aimed at elucidating the nature and role of copper imbalance, observed in a number of civilization diseases, including Alzheimer's Disease.



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Abstract Number: 101

Thinking about iron: the molecular and cellular mechanisms of dietary iron absorption

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What is your image of "iron"? If you are a researcher in the field of biological inorganic chemistry, you may have an image of iron as being the active center of metal complexes or metalloenzymes for a wide variety of metal-specific chemical reactions, but you might have ignored where this iron comes from. It is vital to understand the uptake, trafficking and regulation of iron in living beings to answer many outstanding questions within the field.

Iron is an essential "nutrient" for supporting life. In humans, approximately 70 mg of iron/kg of body weight is present, which is derived from iron nutrients (*e.g.,* heme iron and iron ions) ingested from foods. Iron nutrients are absorbed from the mucosal epithelial cells of the duodenum (upper small intestine) and after intracellular sensing, transport and storage, are eventually distributed as serum iron to organs and muscles throughout the body[1]. Iron ions can undergo redox, and although Fe^{2+} is water-soluble and easily accessible, it reacts readily with O_2 to produce reactive oxygen species, which are cytotoxic. On the other hand, Fe^{3+} is not a source of reactive oxygen species, but is less water soluble. Therefore, the body cleverly uses a variety of proteins to avoid toxicity by Fe^{2+} and strictly regulates iron homeostasis. Failures in this coordinated system that sustain iron homeostasis can lead to iron overload or deficiency. To help introduce the protein framework that dictates human iron dynamics, my focus lies mainly on dietary iron absorption via membrane proteins[2] and chaperones[3]. I will talk about the structural studies of these proteins at atomic/molecular levels and the functional analysis at a cellular level, helping us understand the Fe^{2+}/Fe^{3+} relay via protein-protein interactions in the cells. Our work might provide a platform to create new outstanding metal complexes as nutritional supplements in the future.

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Abstract Number: 424

Molecular Engineering of Gold for Cancer Treatment

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With marvellous anticancer activity and efficacy, the gold (Au) compounds have attracted attention among non-platinum anticancer drugs. In contrast to the DNA targeting mechanism of Cisplatin, Au anticancer agents target thioredoxin reductase (TRxR) or other thiol-rich proteins and enzymes, leading to apoptosis.

Continuing our 30 years of research into developing novel gold complexes[1-2] for cancer treatment,[3-5], we have engineered a range of Au^{I}-Au^{I}, Au^{II}-Au^{II}, Au^{III}-Au^{III} and Au^{I}-Au^{III} compounds, including ionic Au^{I}-Au^{III} complexes, showing remarkable anticancer activity. Here, we report our 30 years of journey of gold research in a nutshell.

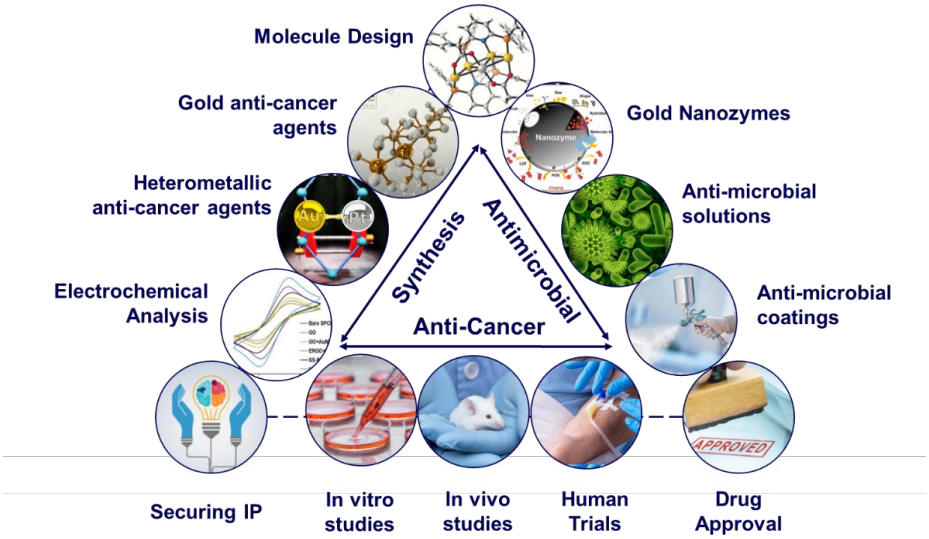

Figure 1. The molecular engineering of gold for cancer treatment.

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Abstract Number: 103

Photofunctional Transition Metal Complexes for Bioorthogonal Labeling, Bioimaging, and Photocytotoxic Applications

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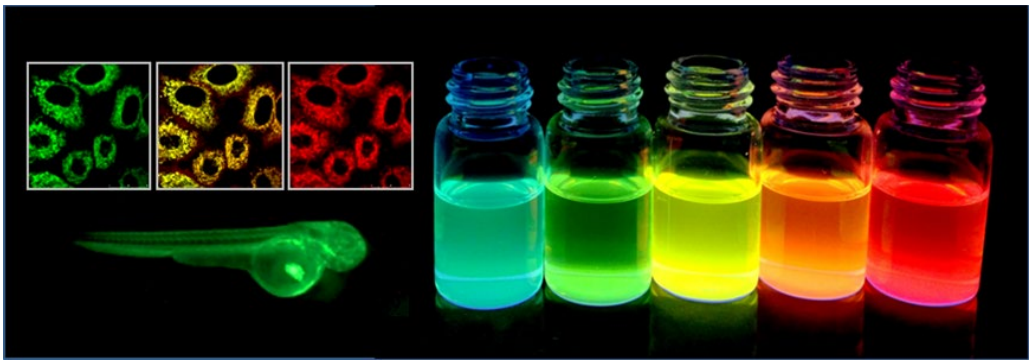
Photofunctional rhenium(I), ruthenium(II), and iridium(III) polypyridine complexes have been widely exploited for the development of new biological reagents due to their attractive photophysical and photochemical properties. The highly environment-sensitive emission and singlet oxygen-photosensitization behavior of these metal complexes are beneficial for both diagnostic and therapeutic applications. In this presentation, I will introduce our strategic designs of luminescent transition metal polypyridine complexes appended with functional moieties such as poly(ethylene glycol), cyclooctyne, tetrazine, nitrone, sydnone, perfluorobiphenyl, and polysilsesquioxane. I will illustrate the influence of these moieties on the photophysical properties, bioorthogonal labeling capability, cellular uptake, and photocytotoxicity of the metal complexes.



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Abstract Number: 64

Secondary metabolite chelators as a platform to broaden the chemical space of coordination chemistry

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Bacteria and fungi produce a range of secondary metabolites that have inherent or incidental metal binding capacity. Functional metal-binding metabolites are produced in the microbial world to manage metal ion homeostasis or as antibiotic agents to challenge inter-species competition. The structural complexity of these natural product chelators identifies opportunities to open new coordination chemistry beyond that defined by the set of known synthetic chelators.

Our group is developing methods, with a focus on the Fe(III)-binding hydroxamic acid siderophore desferrioxamine B (DFOB),[1] to improve access to these natural product chelators, and to extend these methods towards structural diversification. Using foundational knowledge of siderophore biosynthesis,[2,3] we have engineered suites of new DFOB analogues, some with useful properties.[4,5,6] We are dovetailing synthetic chemistry[7,8] with chemical biology[9] to use recombinant siderophore biosynthetic enzymes to generate a wide range of siderophore analogues and screening metal binding profiles. Inspired by the structural diversity of natural product chelators, our aim is to expand chelator chemical space to enable broader metal sequestration applications in the environment and biomedicine.

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Abstract Number: 74

Reactive Intermediates Relevant to Oxidative Degradation of Neurotransmitters in Alzheimer's Disease

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Alzheimer's disease (AD) is a neurodegenerative disorder that has generally been associated with the accumulation of amyloid beta (Aβ) peptides and formation of partially reduced oxygen species (PROS) catalyzed by redox active transition metals like Cu and cofactors like heme which can bind Aβ peptides in the brain.

Degradation of neurotransmitters is a hallmark feature of AD. The heme bound Aβ peptides can act as peroxidases and degrade neurotransmitters like serotonin through reactive intermediates like compound 0 and compound I, which have been trapped and characterized. Cu bound Aβ peptides are also found to catalyze the oxidation of serotonin in the presence of H_2O_2. While both, a Cu(II)-OOH species and a dimeric, EPR silent, Cu_2O_2 bis-μ-oxo species are formed under the reaction conditions, the Cu(II)-OOH species is the reactive intermediate responsible for serotonin oxidation. Second sphere amino acid residues play significant roles in the reactivities exhibited by these metal-Aβ complexes. These may provide valuable insights into the AD paradigm.

Recently we studied the interaction of heme with Aβ that remains membrane bound using membrane mimetic SDS (sodium dodecyl sulfate) micellar medium. Heme bound Aβ in this membrane mimetic environment exhibits peroxidase activity similar to its aqueous analogue. This can potentially be more detrimental as the active site remains close to membranes and can hence oxidise the neuronal cell membrane, which may in part provide an explanation for the Aβ mediated damage to neuronal cell membranes that is typical to AD.

Abstract Number: 267

Exploring the Unique Properties of Metallothioneins in Plants, Fungi, and Bacteria

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Metallothioneins (MTs) are a superfamily of ubiquitous proteins characterized by an unusually high cysteine content and rather small molecular mass. They are capable of coordinating various soft metal ions, but in vivo, their physiological function is primarily homeostasis of Zn(II) and Cu(I), depending on the sub- form and producing organism. MTs also play a significant role in detoxifying heavy metals such as Cd(II) and Hg(II) by forming thermodynamically stable complexes. The low amount of regular secondary structural elements in MTs, such as α-helices and β-sheets, allows for flexibility in the unfolded peptide chain of metal-free (apo-) MT resulting in effective wrapping of metal ions with little steric constraints. The cysteine residues are positioned towards the inner core, where they coordinate the metal ions to form metal-thiolate clusters. MTs acquire their most rigid fold only when fully metalated, stabilized by metal cluster formation. At this point, their three-dimensional structure can sometimes be investigated. However, functionally of larger relevance are often the metal-free or sub-metalated species, in particular for their physiological function as metal ion binders. In turn, these species are highly flexible, making it difficult to investigate their structural changes during metalation. Our research aims to investigate both metalation pathways1 and fully structured MT species2 by combining spectroscopic measure-ments with biochemical methods, determining proto-nation constants3 of potential ligands, mutating specific residues, and evaluating domains or truncated ver-sions of the MT of interest.4 We focus our study on MTs from three families, namely plants, fungi, and bacteria.

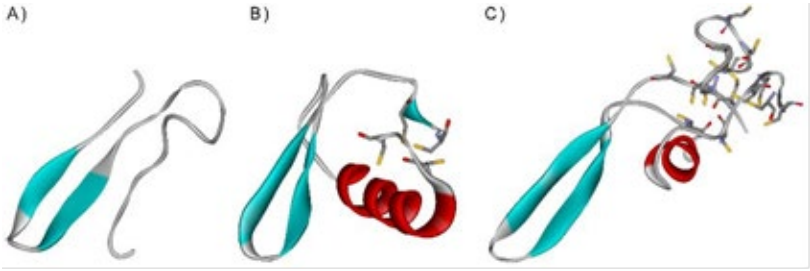

Figure 1. Proposed 3D structures of a plant MT, showing the changes upon metalation: A) apo-MT fragment, B) sterically restricted fragment with connected termini, C) full-length structure with metal cluster (metal ions omitted).4

Acknowledgement
Project funding by the Swiss National Science Foundation (SNSF), the Science Faculty of UZH, and the University of Zurich is gratefully acknowledged.

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Abstract Number: 138

Chemistry in Confined Space of Self-Assembled Molecular Vessels

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Properties and functions of chemical entities in confined molecular space are expected to be different from their conventional bulk behavior due to restricted motions in confined space. This restricted degree of freedom along with other non-covalent interaction/s may allow to stabilize unusual conformations of the chemical entities in confined nanospace of molecular cavity. My lecture will focus on the unusual behavior of some photochromic compounds as well as stabilization of transient isomers in confined molecular vessels. Our recent efforts on designing chiral molecular vessels including their chiral recognition will be discussed in my lecture. A recently developed strategy on constructing enantiopure cage (Figure 1) without using chiral donor/acceptor will be highlighted in the lecture. My lecture will also focus on the use of confined space for the separation of polyaromatic hydrocarbons by aqueous extraction.

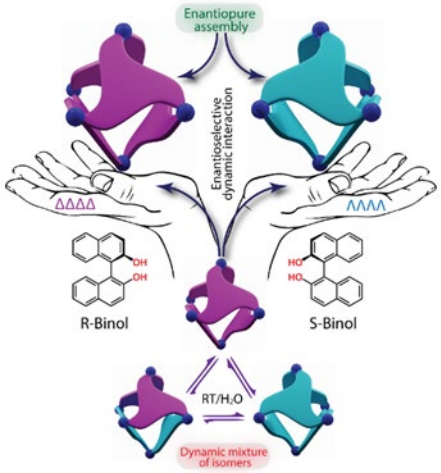

Figure 1 Guest induced enantiopure cage formation.

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Abstract Number: 300

Electrochemical control over hydrogenase crystals: dynamic mechanistic study in the solid state

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Metalloenzymes cycle through a complex series of redox states during catalysis of oxidation/reduction reactions on small molecules, H2, CO, CO2, O2 or N2. It is often difficult to target specific redox states of an enzyme in structural work, or to relate structures to spectroscopy. Focusing on the hydrogenases, active catalysts for hydrogen cycling, we show how electrochemistry can be used to manipulate protein crystals into specific redox states and facilitate structures of defined catalytic intermediates. We combine electrochemical control with IR microspectroscopy to map out the speciation of the hydrogenase active site over a wide range of potential and pH,1,2 and then use this insight to prepare crystals for structural study. The electrochemically manipulated crystals still diffract to high resolution, offering important opportunities for precisely-controlled structural studies. Furthermore, some of the chemical steps relevant to the hydrogenase mechanism are slowed in crystallo, making it possible to resolve transformations that are too fast to observe in solution.2 Overall, we show how electrochemical control over crystals of a complex metalloprotein opens up exciting new opportunities to unify structure-function-activity insight and bridges diverse research areas across biological chemistry, with applicability to other systems such as nitrogenase.3

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Abstract Number: 197

Cracking the code of in-cell protein stability: another brick in the resistance wall

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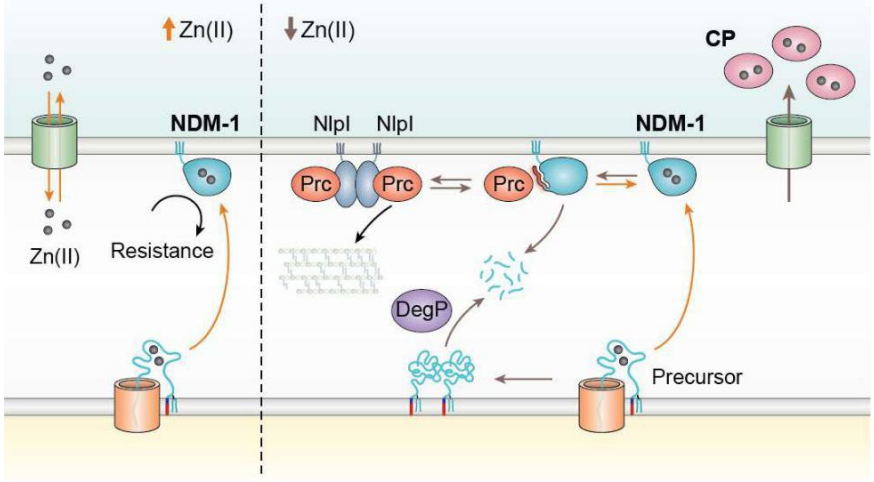
Protein stability is an essential property for biological function. In contrast to the vast knowledge on protein stability in vitro, little is known about the factors governing in-cell stability. Here we show that the metallo-β-lactamase (MBL) NDM-1 is a kinetically unstable protein upon metal restriction that has evolved by acquiring different biochemical traits that optimize its in-cell stability.[1] The non-metalated (apo) NDM-1 is degraded by the periplasmic protease Prc that recognizes its partially unstructured C-terminal domain. Zn(II) binding renders the protein refractory to degradation by quenching the flexibility of this region.[2] Membrane anchoring makes apo-NDM-1 less accessible to Prc and protects it from DegP, a cellular protease degrading misfolded, non-metalated NDM-1 precursors. NDM variants accumulate substitutions at the C-terminus that quench its flexibility, enhancing their kinetic stability and bypassing proteolysis. These observations link MBL-mediated resistance with the essential periplasmic metabolism, highlighting the importance of the cellular protein homeostasis**.**



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Abstract Number: 106

Supporting active anticancer compounds in inorganic matrices to modify its modes of action

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In the recent advanced development of metallodrugs, copper compounds have deserved a special interest among other stimuli-responsive metal complexes. Besides having redox activity that improves its cytotoxicity versus tumour cells, copper centres are often coordinated to biologically active ligands as imines, triazoles or dithiocarbamates that stabilize its oxidation states, frequently acting as antioxidants or inhibitors of selected proteins in a synergistic effect. A common strategy to modify and improve its cytotoxicity is inserting them into inorganic nanoporous materials that can contribute significantly to its biological activities.

The insertion of an antitumor oxindole-copper(II) complex, [Cu(isapn)], in synthetic beidellite (BDL) clay leads to BDL- [CuL] hybrid material very stable and able to derail tumor HeLa cells, with corresponding IC_{50} values in the 0.11–0.41 mg/mL range. Results demonstrated that BDL is a suitable carrier to promote modified-release of this metallodrug.[1]

Further, in a novel strategy of improving cytotoxicity against metastatic melanoma cells this complex, [Cu(isapn)], was immobilized on a modified Polyhedral Oligomeric Silsesquioxane (POSS) matrix, and dimerized as revealed by EPR spectroscopy.[2] An assured correlation between CW- and pulsed EPR spectroscopies provided a complete characterization of the actual active dinuclear species, its coordination environment, as well as the efficiency and selectivity of the bioconjugate materials.

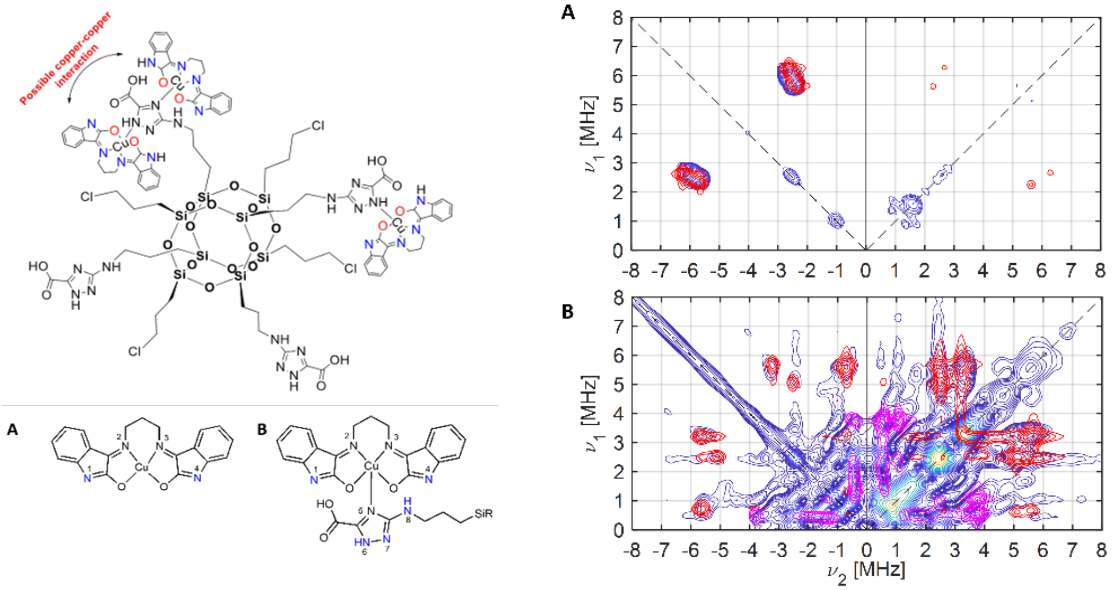

Figure 1 – Representation of [Cu(isapn)] complex immobilized in the modified-POSS matrix (complex **2**); B) Experimental (blue) and simulated (red: N1,4; magenta: $N_{triazole}$ (N6, N7)) X-band ^{14}N HYSCORE spectra of (A) free compound **1** and (B) compound **2**, schematically represented.

These results can help in establishing a new approach to obtain more efficient and selective cytotoxic agents against melanoma cells.

Acknowledgements: FAPESP – CEPID Redoxoma; University of Manchester; CNPq.

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Abstract Number: 34

Ruthenium and osmium coordination complexes as inhibitors of mitochondrial calcium uptake

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The excessive influx of calcium ions into the mitochondria triggers the phenomenon known as mitochondrial calcium overload. Once this event occurs, the mitochondrial permeability transition pore opens, the mitochondrial membrane potential becomes depolarized, and apoptosis-inducing factors are released, ultimately leading to cell death.[1] Given the detrimental effects of mitochondrial calcium overload, it is not surprising that it has been implicated in a number of pathological conditions including ischemia-reperfusion injury, heart disease, and neurodegenerative disorders.[2] As such, the development of chemical inhibitors of mitochondrial calcium uptake has arisen as a promising therapeutic strategy.[3]
In this presentation, we will discuss efforts to develop new mitochondrial calcium uptake inhibitors as both therapeutic candidates and chemical biology tools. Through these studies, we have identified dinuclear ruthenium and osmium complexes to be particularly effective inhibitors of mitochondrial calcium uptake.[4,5] The structure-activity relationships of this compound class will be discussed, and then our current understanding of their mechanisms of action will be summarized. Furthermore, a detailed analysis of the biological fate off these species in cells and biologically relevant solutions will be presented. This work highlights the promise of coordination complexes as mitochondrial calcium uptake inhibitors that can be leveraged for the treatment of disease.

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Abstract Number: 302

De Novo Designed protein with a pH-induced switch in coordination (His to Cys) of the heme cofactor: A HYSCORE EPR and resonance Raman study

Anabella Ivancich,[a] Guillaume Gerbaud [a], Barbara Schoepp-Cothenet,[a] Stéphane Grimaldi,[a] Winston Pitts,[b] Joseph Phillips,[c], Anna F. A. Peacock,[c] Vincent L. Pecoraro [b]

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Natural heme-containing enzymes are versatile catalyst for biologically-relevant chemical reactions, also of interest for industrial/pharmaceutical applications. Studies of the heme (i.e. FeIII protoporphyrin IX) catalytic sites using site-directed mutagenesis, structural biology and molecular spectroscopy provide essential information on these natural systems that delimit the catalytic processes. Yet, the complexity of the natural systems often masks the specific behavior of the metal cofactor. For this reason, smaller artificial proteins capable of binding heme at specified sites are being developed1,2. Our approach is to use coiled coils, i.e. α-helical scaffolds to provide ligation to the heme as cofactor to explore heme axial ligand selectivity, to define how to control the iron coordination geometry when a heme is afforded the opportunity to bind either histidine (imidazole) or cysteine (thiolate) ligands. UV-Vis, Electron Paramagnetic Resonance/HYSCORE and resonance Raman spectroscopies, as well as spectroelectrochemistry, were applied to characterize heme ligation and differences in heme coordination as a function of pH [3,4]. We have uncovered an unprecedented pH-dependent switch in the heme binding mode within a single synthetic protein. The resulting miniature protein, that folds as a dimer of antiparallel two-stranded coiled coils upon heme complexation, can catalyze O2 reduction (as cyt P450 monooxygenases) as well as substrate oxidation (as peroxidases). The further approach of introducing a Trp in order to mimic the concerted reactions of heme&Trp radical as redox cofactors enhancing the catalytic reactivity and mimicking the case of natural heme bi-functional KatGs will be discussed.

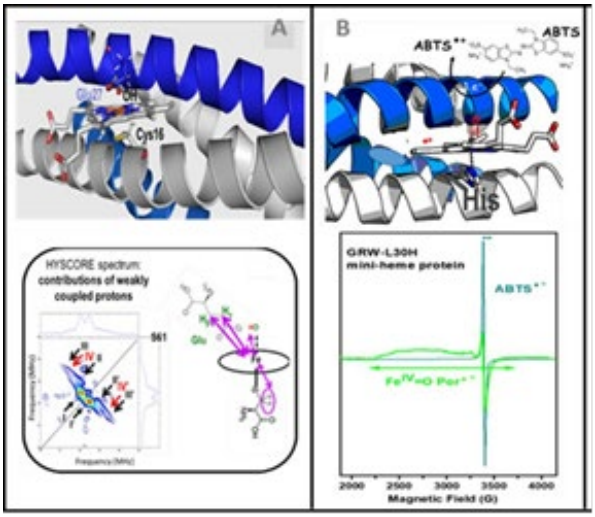

Figure 1: (Panel A) Our proposed Pymol structural model of the GRAND-L2WL16C scaffold in complex with heme (top), based on the crystal structure of a de novo designed antiparallel 4SCC with no metal cofactor (PDB code: 2b1f), representing the GRAND peptide self-assembling as elucidated by UV-Vis, EPR, Analytic Ultracentrifugation studies. The heme position relates to our HYSCORE EPR spectroscopy distances information (bottom). (Panel B) Proposed Pymol structural model of the GR-L2WL30H scaffold in complex with heme (top). The 9-GHz EPR spectrum of [FeIV=O Por□+] intermediate (light green trace) obtained upon reaction of the GR-L2WL30H ferric mini-heme protein at pH 7.0 with hydrogen peroxide as oxidant, and the 9 -GHz EPR spectrum of the ABTS□+ product (dark cyan trace), detected when the reaction with H2O2 was performed in the presence of ABTS as substrate, are both shown (bottom).

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Abstract Number: 439

Mn-based catalytic antioxidants known as superoxide dismutase mimics: evaluation in cells: bioactivity, quantification, speciation, location

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Superoxide dismutases are redox metalloproteins that protect the cell against oxidative stress. These enzymes are highly efficient in catalysing the dismutation of superoxide, with several physico-chemical parameters that have been carved by evolution. We get bio-inspiration from these tremendously efficient enzymes to design low-molecular-weight Mn-based complexes with a catalytic anti-oxidant activity,[1,2] and we study these SOD-mimics in cellular models of oxidative stress.
To be active in cells, these antioxidants must reach their target and cellular assays are key to characterize their bio-activity. HT29-MD2 are intestinal epithelial cells very sensitive to bacterial lipopolysaccharide that triggers a strong inflammatory response mediated by oxidative stress.[3] In this model, SOD-mimics have shown an anti-inflammatory activity.[4–6] The LPS-activation is associated with an over-expression of an series of proteins that is partly reversed by co-incubation with SOD-mimic able to complement for SOD. These results will be discussed, along with subcellular imaging using X-fluorescence (mapping of Mn),[4,5] evidence for a link between oxidative stress and inflammation and studies of speciation in cells.[7]

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Abstract Number: 78

Ruthenium(II) complexes as broad spectrum theranostics for antimicrobial resistant pathogens

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Due to the rapidly emerging global emergency caused by antimicrobial resistance, the revolutionary work by the Dwyer group[1] in the mid-twentieth century has provided inspiration for a renaissance in research into metal complex-based therapeutic leads.[2,3]
In this context, the Thomas group has been investigating derivatives of a mononuclear-ruthenium anticancer therapeutic[4,5] and dinuclear-analogues based on a non-toxic eukaryotic cell probe.[6]

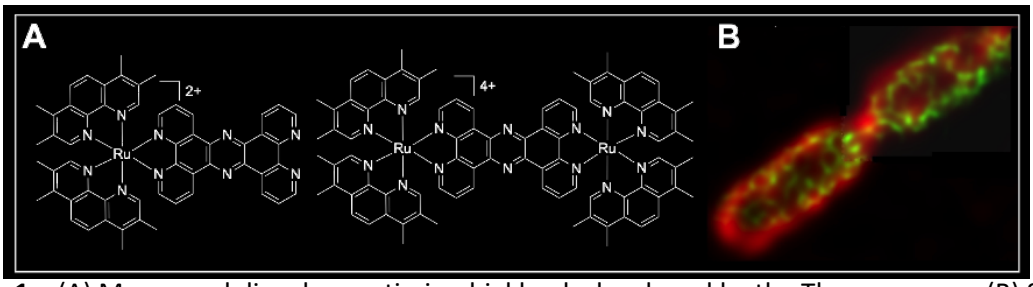

Fig 1 – (A) Mono- and dinuclear antimicrobial leads developed by the Thomas group. (B) Super-resolution STED image of pathogenic E coli bacteria treated and imaged with the dinuclear complex.

These studies have led to the identification of two lead complexes, Fig 1A, that display broad spectrum activity against both Gram-positive and Gram-negative pathogens.[7,8] We have used the intrinsic multi-modal imaging properties of these compounds, Fig 1B, to identify their mechanism of their uptake and mode of action.[9,10] These properties have also been exploited to monitor the successful treatment of AMR strains of ESKAPE pathogens in an infection model organism.[11]

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Abstract Number: 237

Sixty Years of Biological Inorganic Chemistry

Prof Anthony Wedd[1]

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The pleasures and lessons of collaborative research over 60 years will be reviewed, canvassing molecules whose molar masses spanned 100 to 300,000 Daltons. The emphasis will be on 'how much we knew then' compared to 'how much we know now'. Contributions of colleagues will be prioritised, as will their development of new research tools. Particular prominence will be given to the challenges of isotope-substituting a cow.

Abstract Number: 178

From Gold-Based Drug Design to Metalloglycomics

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In this lecture I will focus on two aspects of my research career in the field of medicinal inorganic chemistry. The first is a long-standing interest in the development of gold-based therapeutic agents. The application of gold in medicine is traceable for several thousand years and gold compounds have been used clinically to treat rheumatoid arthritis since the 1920s. I will discuss the transition that has occurred from serendipity to drug design, following recognition of the unique chemistry of gold (high affinity for cysteine and selenocysteine residues), combined with the emergence of a variety of thiol and selenol protein drug targets, whose dysfunction in cells can cause or contribute to a variety of human diseases (e.g. cancer, rheumatoid arthritis, viral and parasitic diseases).[1,2] The second is the exploration of a new research area, metalloglycomics, the interaction of metal compounds with carbohydrates, which has broad implications for the future development of new compounds for therapeutic and analytical applications.[3] One example is the recent demonstration that the strong binding of polynuclear platinum complexes to sulfated-oligosaccharides provides a new approach to glycan-based targeting, altering the profile of platinum agents from cytotoxic to anti-metastatic.[4,5]

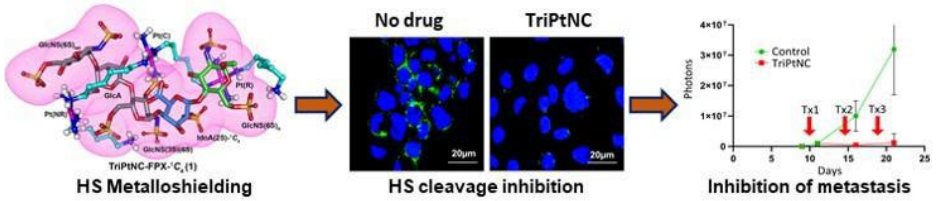

Fig. 1. Metalloshielding of a model heparan sulfate (HS) pentasaccharide by the highly cationic TriPlatinNC modifies the conformational preference of the critical iduronic acid residue. Structural modulation of HS can result in inhibition of cellular cleavage by hepara(i)nase with a consequence in tumour cells being prevention of metastases.[5]

I am indebted to many former members of my research group for their contributions, as well as my collaborators, in particular Mark McKeage, Aleksandra Filipovska, Nicholas Farrell and Mark von Itzstein.

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Abstract Number: 213

Serial crystallography approaches to investigate time-resolved reactions in heme enzymes

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Heme enzymes play crucial roles in catalyzing a myriad of oxidative reactions essential to aerobic life. Defining the three-dimensional structures of heme enzymes in resting, oxy-bound intermediate and substrate bound states is particularly challenging, not least because of the extreme susceptibility of the Fe(III) and Fe(IV) redox states to radiation induced chemistry caused by intense X-ray or electron beams. The availability of novel sources such as X-ray free electron lasers (XFELs) has enabled structures that are effectively free of the effects of radiation induced chemistry and allows time-resolved structures to be determined.[1]

In this talk I will discuss the application of serial crystallography at synchrotron and XFEL sources to investigate the time-resolved reactions of H2O2 and NO binding to a heme peroxidase belonging to the dye decolorizing peroxidase family.2,3,4 Serial crystallography measures a single diffraction pattern from many thousands of microcrystals (< 20 µm in size) at ambient temperature (where catalysis can proceed) because each microcrystal is only exposed to synchrotron X-rays for a few tens of milliseconds or at an XFEL, femtoseconds, thus minimizing the problems associated with radiation damage and also providing a temporal resolution matched to the life-time of intermediates. Reaction initiation is triggered by injection of picolitre-sized droplets of H2O2 onto the peroxidase microcrystal (Fig. 1), and for NO binding by photoexcitation of N,N'-bis-(carboxymethyl)-N,N'-dinitroso-p-phenylenediamine to release NO. We have also explored, under anaerobic conditions, the use of an O2 releasing photocage complex, (µ-peroxo)(µ-hydroxo)bis[bis(bipyridyl)cobalt(III)] to initiate heme O2 binding.

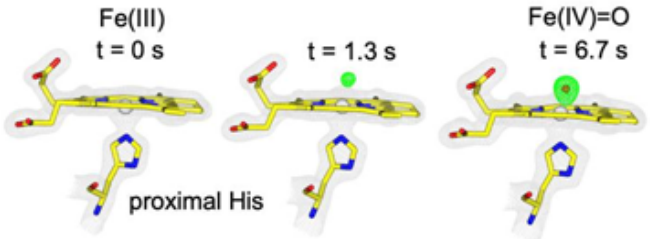

Fig. 1: Time-resolved formation of Compound I in a dye decolorizing peroxidase. Green mesh contoured at 3 s indicates electron density for the formation of an oxo group post-mixing. The 6.7 s structure (1.9 Å resolution) shows a modelled oxo group (red sphere).

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Abstract Number: 342

Enzyme Grafting with Metal-Organic Architectures for Divergent Photocatalytic Purposes

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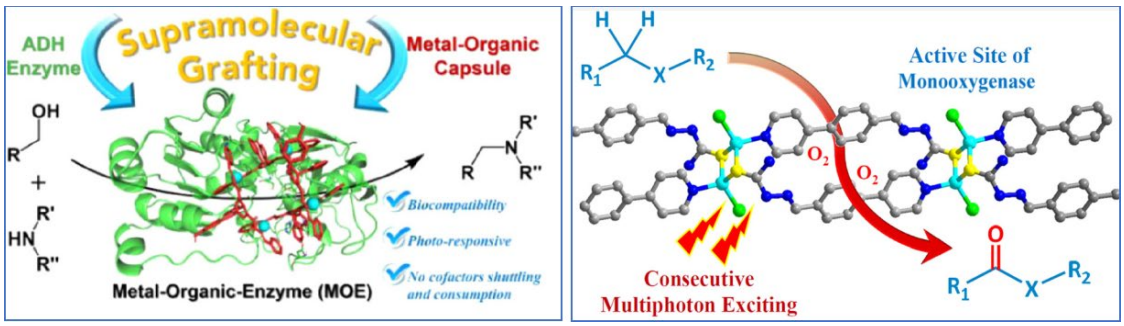
Supramolecular assemblies are essential for biological function normal operation of large molecular machines (such as enzyme-catalyzed transformation) couldn't be separated from supramolecular action. Metal-organic architectures, which form as the thermodynamically favored product from the spontaneous organization of metal ions and organic ligands, are simpler in supramolecular structure than natural enzymes, and could facilitate abiotic mechanistic manifolds, utilizing host–guest interactions to offer a confined microenvironment mimicking the pocket of enzymes. Construction of metal-organic architectures with a unique species of functional molecular containers has obtained increasing attention due to its outstanding electron transport and smaller structures that could grafting with enzymes. Because of the promising functionalities of architectures as artificial metalized host platforms, it is possible for these molecular hosts to imitate enzymes or grafting with enzymes to catalyze the reaction process in series, trigger biological cascade reactions, simulate enzymatic reactions. Photosensitive motifs are introduced into metal-organic architectures through metal nodes, ligands, guests, and the excited state of the complex within the metal-organic architectures-docking artificial enzyme is expected to directly transport proton/electrons between the biotic and abiotic counterparts to form artificial photoenzymes, which are used for the expansion of biological cascade specifications in different biological fields. The metal-organic architectures could effectively catalyze the production of highly active oxidants for their active center structure of enzyme, and by adjust the functional ligands in response to redox substances or the chiral configuration, photocatalytic metal ions node could realize the switching of in organisms. The introduction of photosensitive groups in the cavity will form a stable charge transfer pair, showing good photoconversion efficiency, providing a supramolecular platform for photo-dynamic therapy or photothermal therapy. High catalytic conversion capacity with structure tunable according to the organism environment, enabling the metal-organic architecture to be used as a new material for green and sustainable catalysis and biological applications.



Scheme 1 Enzyme grafting with metal-organic architectures for biomimicking applications

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Abstract Number: 221

Platinum Anticancer Agents: The Past, Present, and Future

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The platinum drugs, cisplatin, carboplatin, and oxaliplatin are a mainstay of cancer chemotherapy around the world and four related compounds are in use in a number of countries. Despite the severe acute and chronic side effects these drugs cause, attempts over many decades to develop new metal-based anticancer agents have not led to widespread approval of any additional drugs. In this talk, I will discuss possible reasons for this lack of success along with the prospects for the future with a particular focus on the need for selectivity in the delivery and action of cytotoxic agents.

I will also describe progress on the development of the platinum(IV) anticancer agents which currently represent the largest single area of focus. Here too, I will concentrate on the mechanisms for achieving selectivity in the action of these agents and work to date in this area.

Abstract Number: 311

Nickel Catalyzed Small Molecule Conversion Inspired by Enzymatic Reactions

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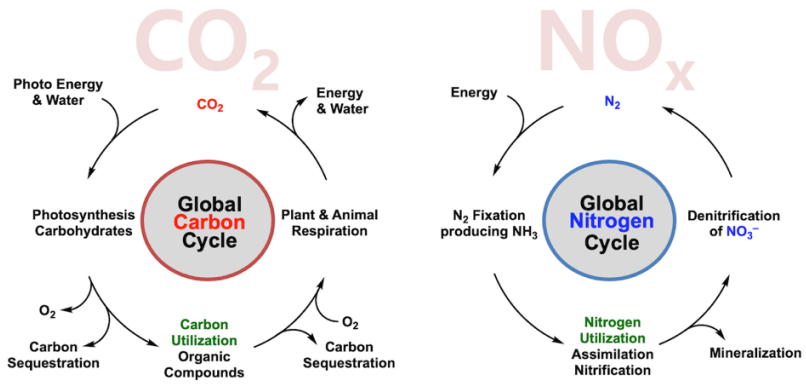
Global carbon and nitrogen cycles are significantly influenced by various human activity. Unbalancing those cycles may be further related to the current environmental issues. In this regard, the activation of small molecules such as CO_2 and NO_x mediated by transition metals is recently drawing much attention. This is a way not only to provide reasonable solutions for the environmental problems, but also to find synthetic methods for sustainable chemical industry. To achieve such goals, it is important to understand various enzymatic reactions. In this presentation, two topics based on low-valent nickel chemistry will be presented. The first topic is about a study focusing on selective CO_2 conversion to CO with synthetic nickel species inspired by Ni-containing enzymatic catalysis. Since the binding and reactivity toward CO_2 is controlled by the geometry of a L_3Ni scaffold, we have explored the chemistry of low-valent nickel supported by pincer systems (E = N or P). With a structurally rigidified ^{acri}PNP ligand, the Ni(0)-CO species reveals the selective addition of CO_2 to give a nickel(II)-carboxylate species with the expulsion of CO. The closed synthetic cycle for CO_2 reduction to CO was established with a (^{acri}PNP)Ni system.[1] The second topic related to denitrification is about a pincer nickel species employed to explore NO_x conversion, which involves an unprecedented nickel catalysis for NO_x conversion and utilization (NCU) technology. The catalysis starts with converting Ni–NO_x to a nickel nitrosyl species via deoxygenation with CO(g), which is followed by transfer of the *in-situ* generated nitroso group to organic substrates. Successful catalytic production of oximes from benzyl- and alkyl-halides using NO_x anions under mild conditions was established. As a key step, a nickel(I)$^{-\bullet}$NO species activates alkyl halides, involving the formation of a N–C bond, which was evaluated by experimental and theoretical methods.[2]



Scheme 1. Global carbon and nitrogen cycles requiring small molecule activation.

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Abstract Number : 153

Development and Immobilization of Redox-reversible Artificial Metalloenzymes

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Artificial metalloenzymes (ArMs) aim to combine the reaction scope of synthetic catalysts with the selectivity and biocompatibility of proteins. We have developed an iron-binding siderophore anchor to connect synthetic transfer hydrogenation catalysts to siderophore-binding proteins, thereby creating artificial transfer hydrogenases. In the presence of Fe(III), the siderophore-based anchor binds with high affinity, but on reduction to Fe(II), dissociation takes place and the ArM disassembles, thereby allowing the protein scaffold to be reclaimed and recycled. This reversible 'catch-and-release' approach, illustrated in Figure 1 (a), enables the replacement of catalysts that have lost activity, for example due to poisoning or decomposition, and the switch to different catalysts. The immobilization of protein scaffolds on solid supports and the use of redox-control and flow techniques to direct ArM assembly provides new opportunities for biocatalysis, in particular component recycling and incorporation into flow processes, Figure 1 (b).

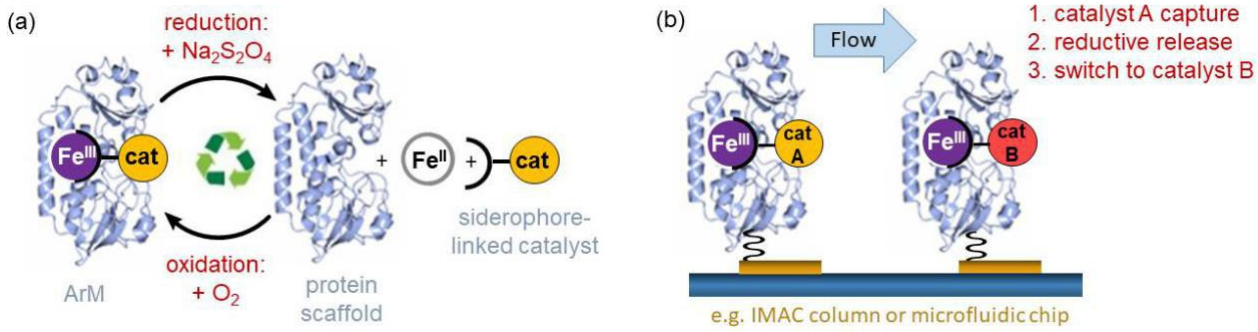

Fig. 1: Catalyst 'catch-and-release' concept: (a) redox-reversible ArM assembly in solution and (b) catalyst replacement in flow, enabled by an immobilized protein scaffold.

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Abstract Number: 418

Understanding Mercury Toxicity using Hg Lα1 HERFD-XAS – A New Tool for the Bioinorganic Chemist

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X-ray absorption spectroscopy (XAS) has played an important role in developing our understanding of bioinorganic systems. The XAS is divided into two regions; the extended X-ray absorption fine structure (EXAFS), which gives radial structure information and the near-edge spectrum which gives information state on electronic structure. EXAFS has contributed much to our knowledge metalloprotein active site structures, but the information available from the near-edge portion of the spectrum is limited by poor spectroscopic energy resolution primarily due to what is known as lifetime broadening. High energy resolution fluorescence detection (HERFD) XAS is a newly-available method that can overcome lifetime broadening through measurement of X-ray fluorescence with much better resolution that the natural linewidth of a fluorescence line,[1,2] yielding dramatically better-resolved near-edge spectra (e.g. Fig. 1). The method also affords enhanced sensitivity for low and ultra-low concentrations through effective elimination of background signals.[1,2]

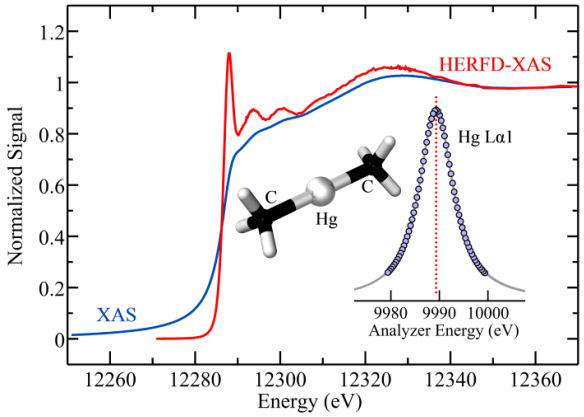

Fig. 1: Example of resolution enhancement using Hg Lα1 HERFD-XAS relative to conventional XAS for a dilute solution of dimethyl mercury. The insets show the structure and the Hg Lα1 emission spectrum.

The compounds of mercury can be more toxic than those of any other non-radioactive element, yet it is ubiquitous in the environment, with rising levels due to pollution and climate change. The potential of organometallic mercury compounds for devastating effects on the structures and functions of the central nervous system are of particular concern, yet its mechanisms of action remain obscure. Inorganic mercury also presents significant potential risks, and can cause genetic damage that is not reversible by DNA repair mechanisms. Despite its importance, our understanding of human and environmental health risks posed by mercury is incomplete. This presentation will show how Hg Lα1 HERFD-XAS can be used to probe the in-situ bio-inorganic chemistry of mercury[3,4] and its complicated relationship with the essential element selenium,[5] probed using Se Kα1 HERFD-XAS.[4]

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Abstract Number: 54

Selective Uptake and Binding of Lanthanides and Actinides Using Lanthanide-dependent Bacteria and their Biomolecules

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Lanthanides (Ln) are essential ingredients sprinkled in a multitude of applications in our daily life, especially important for sustainable and clean energy applications. However, owing to their chemical similarity, separation of Ln is tedious. In the past decade, the role of Ln for many bacteria has been firmly established, and bacterial strains that take up Ln and use them in the active sites of quinone-dependent alcohol dehydrogenases have been extensively studied.[1] Our studies with the strictly lanthanide-dependent extremophile *Methylacidiphilum fumariolicum* SolV demonstrate, that the trivalent actinides americium and curium can also support growth in the absence of the essential lanthanides. In fact, the bacteria seem make no distinction between lanthanide and actinide ions if they have the correct size and oxidation state. Time-resolved laser-induced fluorescence spectroscopy, liquid scintillation counting, and inductively coupled plasma mass spectrometry confirm the bacterial uptake of Am and Cm. The interchangeability of f-block elements is supported by very similar enzymatic activities of recombinant methanol dehydrogenase reconstituted with different metal ions. Our combined *in vivo* and *in vitro* results establish that actinides support growth of methylotrophic bacteria.[2]

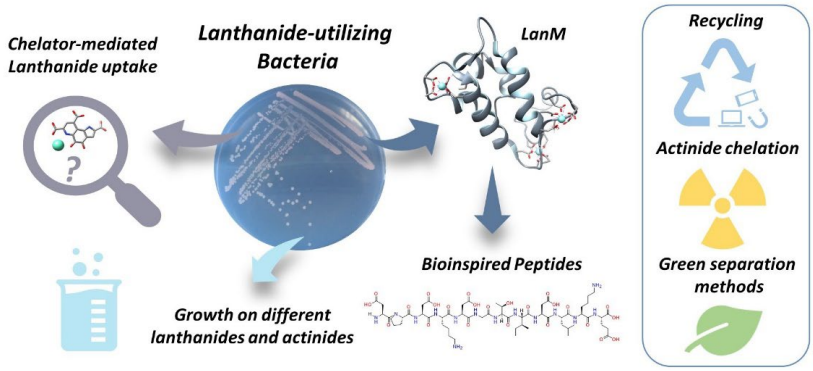

Figure 1 Bacteria that use Ln have evolved several biomolecules capable of binding Ln and actinides.

From Ln-using bacteria, proteins and small chelators with remarkable selectivity and affinity for lanthanides have been identified.[3-7] This lecture will give a glimpse into possible avenues for lanthanide and actinide separation methods using bacteria or their bioinspired small chelators. Specifically, we present the extremophilic and strictly Ln-dependent bacterial strain SolV as a platform for the recovery of

lanthanides from different sources. SolV can efficiently extract the early Ln such as La and Nd from artificial industrial waste sources, natural Ln-containing and post-mining waters.

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Abstract Number: 438

The Effect of Pressure on Metal Complexes and Porous Framework Materials

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Over the last 10 years or so, high-pressure techniques have been used to induce an eclectic range of phenomena on metal complexes and frameworks. Inducing spin-crossover,[1] Jahn-Tellller switching,[2] magnetic exchange[3] and has been used to explore the uptake of guest species in the pores of metal-organic frameworks (or MOFs).[4] In our own work, we do this by taking advantage of the fact that the driving force for most of these phenomena, is the reduction in volume of the system, while the small molecules that encompass the pressure transmitting fluids used frequently in high-pressure experiments, can penetrate the pores of MOFs on increasing pressure. This has revealed unexpected flexibility, explains unusual adsorption phenomena under milder pressures, and increases the reactivity of MOFs. Here, we will give an overview of the effect of high-pressure on metal complexes, micro and nanoporous materials, highlighting some recent work where pressure can be used as a tool to determine structure: property relationships, for example in the Cu-based framework bis[1-(4-pyridyl)butane-1,3-dione]copper(II) (CuPyr-I, Figure 1), which undergoes pressure induced phase transitions, negative linear compressibility, piezochromism and pressure controlled Jahn-teller switching.[2]

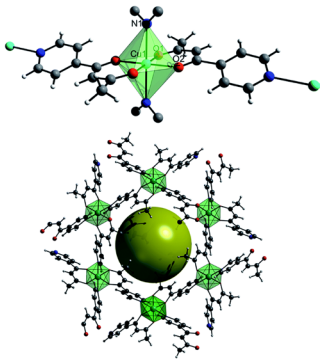

Figure 1. Ball and stick model showing the coordination environment around the Cu^{2+} ion in CuPyr-I, and 3D-pore structure as viewed along the *c*-axis direction.

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Abstract Number: 309

Metal Ion Effects on Hydride Transfer Chemistry of Dihydropyridinates

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Dihydropyridinate functional groups play a central role in biologically mediated hydride transfer chemical reactions. Example cofactors that contain the dihydropyridinate moiety are nicotinamide adenosine diphosphate (NAD+) which is ubiquitous, and the nickel pincer nucleotide (NPN) cofactor essential to hydride transfer function in lactate racemase (LarA). One significant challenge in modelling the reaction chemistry of these organohydrides lies in achieving a biologically relevant redox potential for the pyridine/dihydropyridinate redox couple. A second challenge lies in effecting reduction reactions (ie. electron transfer) without any additional chemical influence of the chemical reducing reagent such as dithionate. In this work I will present advances on both of these fronts. I will present pyridine ligand complexes of Al(III) and Ga(III) which have metalloaromatic electronic structures and support ligand-based proton transfer and electron transfer chemistry to model the chemistry of dihydropyridinate cofactors at biologically relevant redox potentials. The kinetic effects of the metal-ligand interactions enable reduction of pyridine hundreds of mV more anodic as compared to purely organic dihydropyridinates. To address the second concern of chemical side reactions electrochemical approaches to electron transfer and coupled electron proton transfer chemistries will be described.

Abstract Number: 244

Development of Molecular Catalysts for Photosynthetic Reactions

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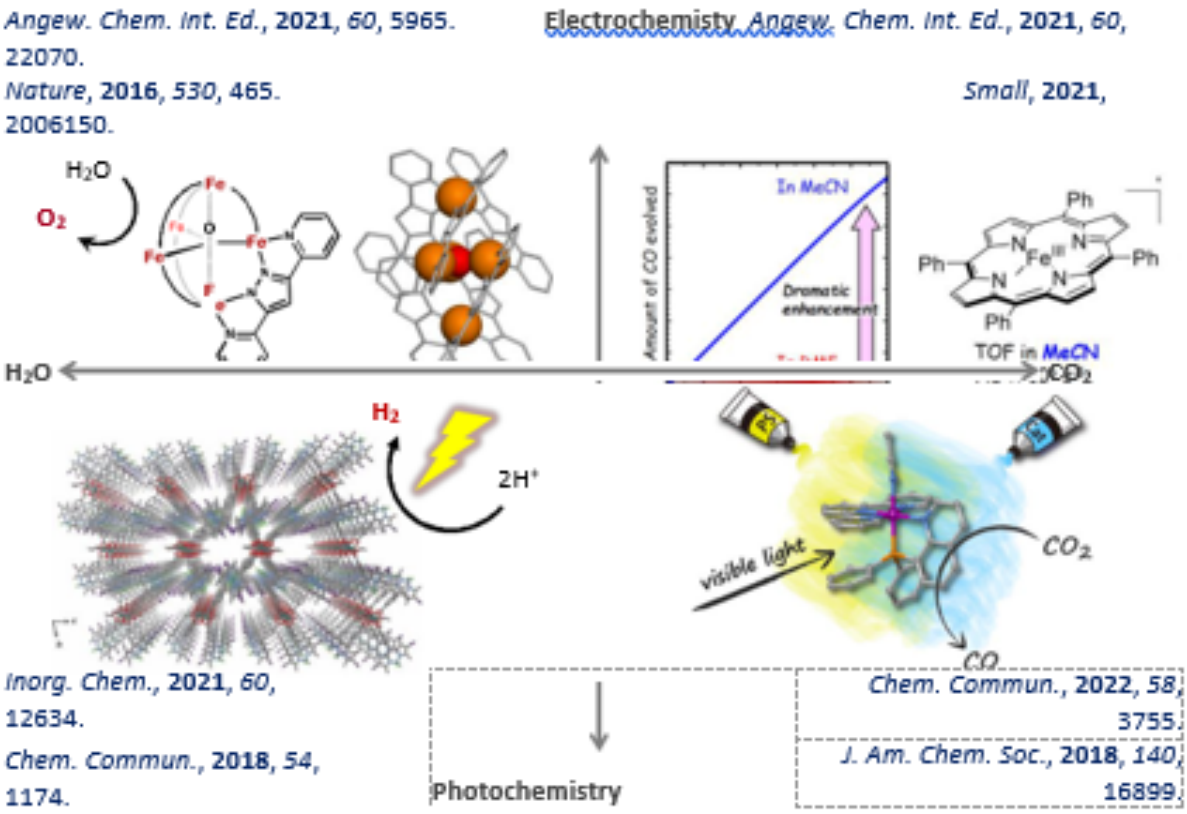
Photosynthesis is a biochemical reaction that converts carbon dioxide and water into carbohydrates and concomitantly stores the energy of sunlight into the products (carbohydrates) as chemical energy. In photosynthetic reactions, solar energy is converted to electrochemical energy via charge separation, and the resulting electrochemical potentials triggers multi-electron redox reactions of small molecules to achieve solar-to-chemical energy conversion. To artificially reproduce the photosynthetic reactions, our group has investigated the development of molecular catalysts for small-molecule conversions involving multi-electron transfer. Recent achievements in our group include (i) development of pentanuclear complexes as active centers for photo/electrochemical small-molecule conversions,[1] (ii) construction of highly efficient catalytic systems for photo/electrochemical small-molecule conversions,[2] and (iii) investigation of photo/electrochemical small-molecule insertions into low-reactive organic molecules.[3]

References



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Abstract Number: 375

Molecular Probes Illuminate Cellular Homeostasis of Divalent Cations

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Divalent metal cations are essential for a wide variety of physiological processes, and disrupted metal homeostasis has been related to some of the major ailments affecting modern society, including neurodegeneration, diabetes, immunodeficiency, and cancer. Cation-selective luminescent indicators offer the possibility of tracking metal accumulation patterns at the (sub)cellular level by optical microscopy techniques, enabling mechanistic studies of the connection between metal imbalance and disease. We have developed innovative fluorescent indicators and imaging strategies for the detection of divalent cations with enhanced selectivity, brightness, and sub-cellular targetability. This seminar will focus on our efforts on the development of new ratiometric indicators for the detection of cellular magnesium(II) levels with high selectivity against other divalent cations. We will discuss their application toward uncovering chronic changes in Mg2+ accumulation patterns in non-alcoholic fatty liver disease (NAFLD)1 and drug-induced liver injury (DILI)2 , and the possible roles of this cation on regulation of intracellular ion signals, endoplasmic reticulum stress, and metabolic activity in the pathophysiology of liver diseases. Pioneering work on the development and application of molecular indicators for multiplexed divalent cation detection by vibrational spectroscopies will be discussed as well.

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Abstract Number: 156

Engineering of Nitrogenase in Eukaryotes

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Nitrogen fertilization is often used to increase crop productivity, causing groundwater pollution and the emission of greenhouse gasses. One strategy to increase the biological nitrogen fixation process in cereals that have little associative relationship with nitrogen fixing organisms could be the transfer and incorporation of the prokaryotic nitrogenase genes into the plant's genome. Nitrogenase harbors three distinct metal prosthetic groups that are required for electron transport and N2 reduction. The simplest one is a [4Fe-4S] cluster located at the Fe protein (NifH) nitrogenase component. The MoFe protein (NifDK) component carries an [8Fe-7S] group called P-cluster and a [7Fe-9S-C-Mo-R-homocitrate] group called FeMo-co. Formation of active nitrogenase requires the participation of several accessory proteins. The nitrogenase clusters are additionally very sensitive to oxygen making nitrogenase engineering in plant cells extra challenging. To overcome the oxygenic and hostile environment in the eukaryotic cell, we are targeting the expressed nitrogenase proteins to the mitochondria where respiration could protect its metalloclusters by consuming oxygen. Central components for the biosynthesis of FeMo-co are the proteins NifB, NifEN and NifH. NifB is a radical S-adenosylmethionine (SAM) enzyme that catalyzes the synthesis of the [8Fe-9S-C] intermediate complex NifB-co by using [4Fe-4S] clusters donated by NifU, SAM, and a source of sulfide. NifEN functions as a scaffold protein that incorporates Mo and homocitrate into NifB-co in a reaction that also requires NifH, creating FeMo-co that is then donated to NifDK to activate it. We have identified NifB, NifH, and NifEN variants that present superior properties regarding solubility, stability, oxygen resistance and functionality in yeast and plant mitochondria. We have shown that these proteins accumulate metalloclusters in vivo and are functional in vitro when isolated from mitochondria of yeast, tobacco, and transgenic rice, representing the first major steps towards the engineering of functional nitrogenase in cereal crops.

Abstract Number: 318

Zinc Finger Proteins: Modulating Activity via H2S Signaling and Exogenous Metals

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Zinc finger proteins (ZFs) are a large class of proteins that use zinc as a structural cofactor. ZFs have critically important functions in modulating transcription and translation. 1 The accepted dogma for the role of ZF proteins is that they are structural sites; however, there is emerging evidence for reactivity of ZFs with endogenous signaling molecules including H2S, as well as with exogenous metals. 2,3 H2S is a gasotransmitter that is involved in a myriad of biological processes including neuromodulation and inflammation. The molecular targets of H2S include heme and non-heme iron proteins, reactive oxygen-, sulfur-and nitrogen species, and cysteine residues on proteins. The interaction of H2S with protein cysteine residues (P-SH) involves a post-translational modification (PTM) called persulfidation - the addition of sulfur to protein cysteine residues (P-SH à P-SSH). We have discovered that ZF proteins are targets of H2S in cells, using a persulfide specific chemoselective proteomics approach. The mechanism by which ZFs are persulfidated has been evaluated in several of the ZFs identified in the proteomics screen, and we have discovered a common mechanism that involves Zn serving as a conduit to bring H2S and O2 together for electron transfer. ZFs are also targets of exogenous metals – both beneficial and toxic. These include gold, which has anti-inflammatory properties and lead, which is known to be toxic. To understand how exogenous metals target ZFs, we have focused on tristetraprolin (TTP) a cytoplasmic ZF protein that regulates inflammation and is a proposed target for exogenous metals. Using a variety of biophysical and mass spectrometric approaches, we have discovered that Au and Pb can exchange with the Zn center of TTP, and affect RNA binding affinity and selectivity. 4,5 These findings as well as work to link metal exchange in cells will be presented.

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Abstract Number: 445

Development of new catalytic reactions using a combined experimental and computational approach

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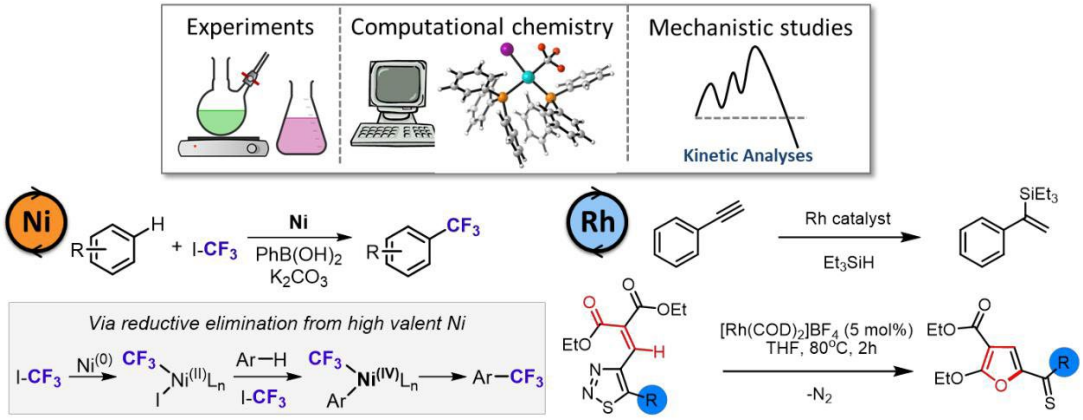
Complex organic compounds are ubiquitous in the pharmaceutical, agrochemical and materials chemistry industries, with these compounds often featuring a diverse range of functional groups. To meet the continuing demand for efficient, sustainable and selective strategies to access complex organic compounds, our toolbox of synthetic methods needs to continually expand.

To address these challenges, my research focuses on applied organometallic catalysis and photocatalysis, to allow new synthetic methods to be developed. In particular, I am interested in rationally designing catalysts to facilitate challenging and high-value chemical transformations, with detailed mechanistic studies used to guide catalyst design, to understand trends in chemical reactivity and to direct the choice of experimental parameters. We use a range of different mechanistic tools to provide unique insight into reaction mechanisms, including kinetic analyses, computational studies and a suite of X-Ray based techniques. This presentation will focus on our recent work where combined experimental and computational studies have been used to develop new reactivity, such as C-H trifluoromethylation,[1] nickel-catalysed cross coupling reactions,[2] denitrogenation reactions of thiadiazoles[3,4] and photocatalysed oxidation reactions.[5-7]



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Abstract Number: 317

From metallomics and metalloproteomics to drug development: metallo-agents for emerging infectious diseases

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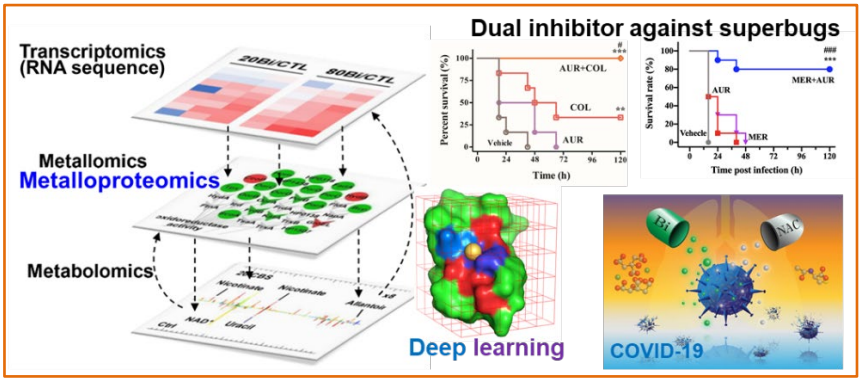
Metals are essential for lives and certain metal compounds have long been used in medicine and healthcare. Metal-/metallodrug-protein interactions play a crucial role for metals in life processes and the action of metallodrugs. It is important to identify metal-protein interactions at a proteome-wide scale which are difficult due to diversity of metal-protein interactions.[1,2] We have integrated metallomics with metabolomics, transcriptomics and deep learning to examine multiple cellular changes to the numerous intracellular process affected[3] and to quantify the metals for rapid metallome/proteome-wide profiling of metal-binding proteins. We even uncovered a correlation of metalloproteome with immunity regulators.

Based on our integrative metallomic/metalloproteomic approach, we have found that metallo-agents (e.g.Bi(III) and Au(I)) interfere with Zn(II) biochemistry in pathogens, and propose to use Bi(III) complexes to inhibit Zn(II) enzymes in superbugs (metallo-β-lactamases (MBLs)) and coronaviruses.[4] We show that colloidal bismuth subcitrate (CBS), and related Bi(III) complexes irreversibly inhibit different types of MBLs and have demonstrated a high potential of Bi(III) compounds as the first broad-spectrum MBL inhibitors to treat MBL producing bacterial infection in combined use with existing carbapenems.[5] We then showed that auranofin serves as a dual inhibitor to resensitize carbapenem- and colistin-resistant bacteria to antibiotics.[6] We further expand repurposing metallodrugs in combination with different families of antibiotics can synergistically eliminate multidrug-resistant *P. aeruginosa* by targeting iron homeostasis.

We recently have demonstrated that Bi(III) drugs effectively suppress SARS-CoV-2 replication and relieves virus-associated pneumonia in Syrian hamsters. The metallodrug may inhibit multiple viral Zn(II) enzymes including helicase and ExoN/MTase.[7] Our integrative metallomic approach can be readily extended to other essential metals and metallodrugs, opening a new horizon for metallo-biology and inorganic chemical biology as well as precision medicine.



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Abstract Number: 154

Metalloenzyme (electro)catalysis for hydrogen and ammonia production

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Following the industrial revolution, centralized processes now produce key global chemical commodities that are vital to support the growing human population. One example is the HaberBosch process, which produces ammonia from hydrogen and dinitrogen over iron-based catalyst beds. 1 Importantly, most of the hydrogen required by this process is produced by steam-reforming natural gas. While engineering has resulted in highly efficient centralized processes, decentralization is thought to provide the means to improve environmental sustainability. As such, there is interest in developing new catalytic systems to produce chemicals such as hydrogen and ammonia from renewable electricity. One such catalytic system, “enzymatic electrocatalysis”, seeks to employ metalloenzymes such as nitrogenases2 and hydrogenases3 as bioelectrocatalysts in new biotechnologies. 4 To achieve this, possible limitations such as (i) poor electron transfer to these enzymes and (ii) poor enzymatic stability must be surmounted. This talk will present our recent progress ultimately aimed at enzymatic electrocatalysis of nitrogenase for ATP-independent dinitrogen fixation. First, [FeFe]-hydrogenase electrodes yielding relatively large and stable electrocatalytic currents for hydrogen production are discussed, which also double as model enzyme electrodes for the design of nitrogenase electrodes.5 Our recent research into the partial inactivation of nitrogenases will also be discussed, with the view to determine whether the site-specific orientation of nitrogenase’s MoFe protein on planar electrode surfaces (important to minimize the distribution of heterogeneous electron transfer rate constants) can result in a biocatalytic film that is able to reduce dinitrogen to ammonia. References 1. Chen, J. G. et al. Beyond fossil fuel–driven nitrogen transformations. Science (80-.). 360, eaar6611 (2018). 2. Einsle, O. & Rees, D. C. Structural Enzymology of Nitrogenase Enzymes. Chem. Rev. 120, 4969– 5004 (2020). 3. Lubitz, W., Ogata, H., Rüdiger, O. & Reijerse, E. Hydrogenases. Chem. Rev. 114, 4081–4148 (2014). 4. Milton, R. D. & Minteer, S. D. Nitrogenase Bioelectrochemistry for Synthesis Applications. Acc. Chem. Res. 52, 3351–3360 (2019). 5. Liu, Y. et al. Facile Functionalization of Carbon Electrodes for Efficient Electroenzymatic Hydrogen Production. JACS Au 3, 124–130 (2023).

Abstract Number: 346

Biomimetically constructing a hypoxia-activated programmable phototheranostics at the molecular level

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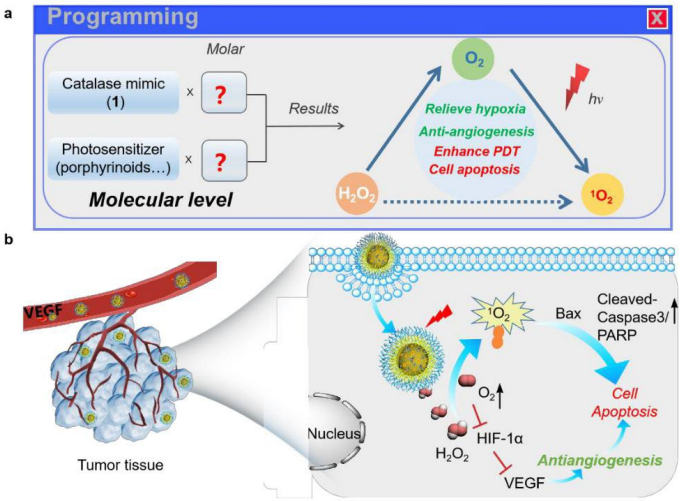
The hypoxic microenvironment is considered the preponderant initiator to trigger a cascade of progression and metastasis of tumors, also being the major obstacle for oxygen consumption therapeutics, including photodynamic therapy (PDT). In this work, we report a programmable strategy on the molecular level to modulate the reciprocal interplay between tumor hypoxia, angiogenesis, and PDT outcomes by reinforcing synergistic action between H2O2 scavenger and O2 generator and photosensitizer. The modular combination of a catalase biomimetic (tri-manganese cryptand, **1**) and a photosensitizer (Ce6) allowed the rational design of cascade reaction beginning with dismutation of H2O2 to O2 in hypoxic conditions to enhance photosensitization and finally photooxidation. Concurrently, this led to the decreased expression of vascular endothelial growth factor (VEGF) and effectively reduced unwanted growth of blood vessels observed in chick chorioallantois membrane (CAM). Notably, the proof-of-principle experiments using the tumor-bearing model proved successful in enhancing PDT efficacy, prolonging their life cycles, and improving immunity, which could be monitored by magnetic resonance imaging.



Scheme. Programmable phototheranostics. **(a)** Schematic illustration of Programmable phototheranostics
containing catalase mimic and photosensitizer. **(b)** The proposed synergistic mechanism of PDT combining with anti-angiogenesis for dealing with hypoxia of tumor environment.

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Abstract Number: 111

Illuminating the Bioinorganic Chemistry of the Extracellular Space

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Metals such as copper and iron are essential micronutrients in biology, as their redox activities facilitate basic cellular processes ranging from antioxidant defense to respiration along with emerging regulatory roles in cell signaling. However, this redox activity can be detrimental when their homeostasis is disrupted, leading to oxidative stress and damage associated with diseases. The context in which a metal resides within a biological environment significantly influences its activity and function. Recent years have seen a rise in tools for monitoring metal ions in biological conditions and have illuminated the complexities of metal speciation, but many of these tools are focused on probing metals in the intracellular space. The state-of-the-art methods for assessing metal status in extracellular fluids such as blood plasma focus either on absolute quantitation or evaluate a limited number of metal-containing species. While these methods have offered important insight into extreme cases of metal deficiency in overload, subtle imbalances are more challenging to diagnose and understand with the available methods. This talk will describe our efforts to expand and elucidate the metal speciation of the extracellular space, specifically in the blood plasma. Specifically, I will discuss our approaches to understanding the interactions of metals with peptide hormones in the context of the protein-rich blood plasma and the complementary development of chemical biology tools for investigating metals and metal-containing species in this milieu. We focus our studies on th extracellular metal dynamics to the diagnosis and prognosis of metabolic disorders like diabetes.

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Abstract Number: 301

The Development of Technetium Bis(thiosemicarbazonato) Imaging Agents

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Nuclear imaging has been shown to improve the diagnostic accuracy and to allow for earlier detection of prostate cancer.[1] This can be achieved by attaching a radionuclide to a molecule that targets a receptor overexpressed in prostate cancer cells, known as the prostate specific membrane antigen (PSMA). Technetium-99m (^{99m}Tc: *t*1/2 = 6.02 h, 90% γ 141 keV) radiopharmaceuticals are used in over 30 million scans worldwide, accounting for over 80% of the total nuclear imaging procedures. The use of ^{99m}Tc in molecular imaging is possible using chelators that are capable of binding ^{99m}Tc with sufficient stability *in vivo* to target the areas of disease. Tetradentate bis(thiosemicarbazone) (BTSC) ligands with a technetium-nitrido ($[TcN]^{2+}$) core group have recently been investigated for potential new ^{99m}Tc radiopharmaceuticals.[2] We developed a simple kit-based procedure to generate ^{99m}Tc-nitrido complexes with tetradentate BTSC. The compounds were shown to be inert to transmetalation by human serum. The *in vivo* biodistribution behaviour of the lipophilic ^{99m}Tc BTSC complexes was investigated using planar imaging and organ biodistribution studies on BALB/c mice and were found to have high brain uptake and excretion through the kidney and hepatobiliary pathways. A series of bifunctional bis(thiosemicarbazone) chelators were synthesised and attached to the PSMA binding motif (BTSC-PSMA). The chelators were radiolabelled with $[^{99m}Tc][TcN]^{2+}$ in a one-pot synthesis at 85°C for 10 min, with the radiolabeled products achieving high radiochemical purity (>99%). *In vitro* and *in vivo* evaluation of the $[^{99m}Tc][TcN(BTSC\text{-}PSMA)]$ complexes demonstrated their high selectivity for tumor cells expressing the PSMA receptor. The new radiochemistry and pre-clinical evaluation presented here demonstrates that bifunctional BTSC chelators are promising agents for SPECT imaging of PSMA with ^{99m}Tc.

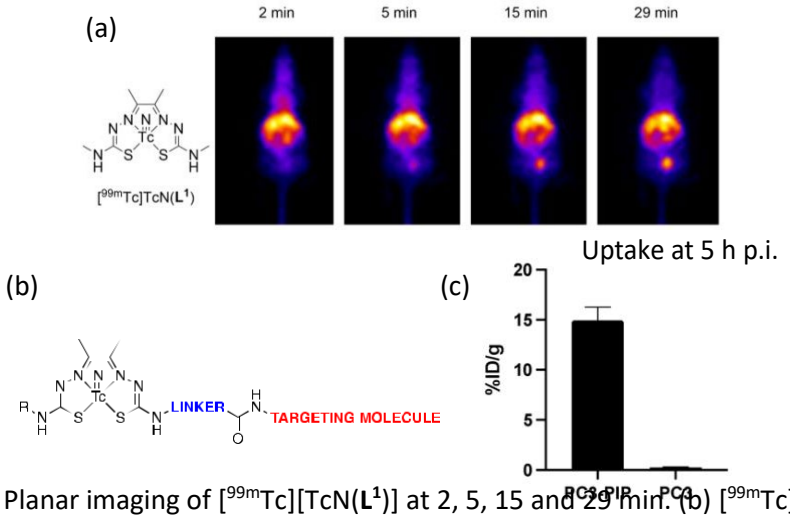

Figure 1 (a) Planar imaging of $[^{99m}Tc][TcN(\mathbf{L^1})]$ at 2, 5, 15 and 29 min. (b) $[^{99m}Tc][TcN(\mathbf{BTSC})$-PSMA] complex for imaging prostate cancer with SPECT. (c) Selective uptake in PSMA+ (PC3-PIP) vs. PSMA-(PC3) prostate cancer cells at 5 h post injection (p.i.).

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Abstract Number: 69

The Molybdenum Cofactor and Pyranopterin Mo Enzyme Catalysis

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Pyranopterin molybdenum enzymes possess a unique Mo-bound pyranopterin dithiolene (Mo-MPT = Moco) cofactor.[1] These critical enzymes are essential to human health and life processes, catalyzing important chemical transformations in the metabolic pathways of sulfur, nitrogen, and carbon compounds.[2] New work from our laboratories has contributed to a greater understanding of late stage Moco biosynthesis,[1] Moco sulfuration[3] and insertion into apo-enzymes, formal hydride[4] and oxygen atom transfer reactivity,[5] and the role of the pyranopterin (MPT) in catalysis.[6-9] Here, we will highlight our synthetic, structural, spectroscopic, computational, and molecular biology approaches to solving some of the most important problems in this exciting field.

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Abstract Number: 373

In designing catalysts for clean energy- is the nature of the active site always the right question to ask?

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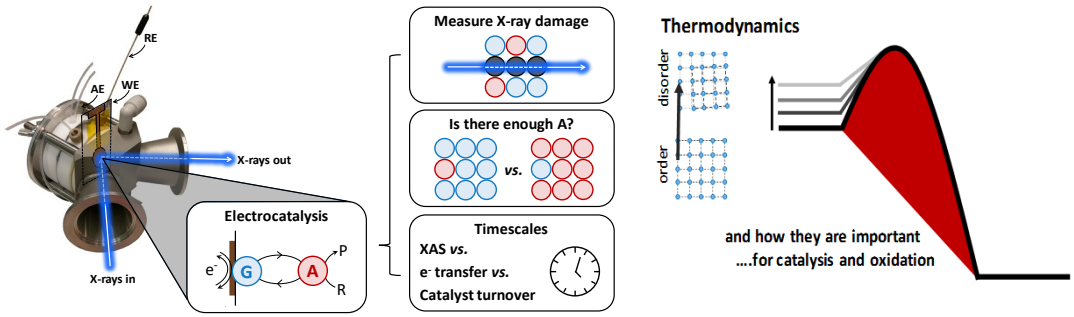
One of the greatest challenges of the 21st century will be securing cheap and renewable sources of energy. One of the most promising approaches to this challenge is to design catalysts from earth-abundant materials capable of implementing key chemical reactions, including splitting water into hydrogen and oxygen ($H_2O \rightarrow 2H^+ + O_2$); and both the oxidation ($H_2 \rightarrow 2H^+$) and reduction ($2H^+ \rightarrow H_2$) of hydrogen among many others. In studying catalysts, we often focus on the "nature of the active site" which for classical heterogeneous catalysts works well- but not all catalysts work by a surface sorption process alone. In some systems, it is increasingly realised that processes of precipitation and reformation may actually be key to catalysis. In this talk we explore the relationship between redox chemistry and catalytic chemistry using birnessite-like manganese oxides and iron sulfides as examples. We argue that structural disorder plays an overlooked role in some catalysts, as it alters thermodynamic stability affecting stability, electron transfer and product selectivity. The redox events between substrate and catalyst and the speed of these processes appear to play a key role in both engineering product selectivity and catalyst stability. Drawing on our *in situ* XAS work we examine how the events after catalysis may be key for understanding the active events of catalysis as well as mechanisms of decomposition.



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Abstract Number: 44

Ligand Design for Cooperative Bimetallic Complexes

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While metal-ligand cooperativity is a well-established approach in transition metal catalysis, metal-metal cooperativity remains an emerging strategy.[1-2] Work in this field has shown that catalysts that operate via cooperative bimetallic mechanisms can lead to differing reactivity and selectivity profiles compared to conventional monometallic catalysts. Ligand design has emerged as an important criterion to consider when designing systems capable of metal-metal cooperativity, and even metal-metal-ligand cooperativity.[3]

This presentation will outline our work towards bimetallic complexes capable of metal-metal or metal-metal-ligand cooperativity featuring 2,7-disubstituted-1,8-naphthyridine ligands. These rigid frameworks contain adjacent binding pockets capable of housing two metals in close proximity, but we have found that judicious selection of both the ligand architecture and the metal fragments is essential. Work detailing the synthesis and reactivity of bimetallic 1,8-naphthyridine complexes will be presented, encompassing systems with innocent ligands,[4] non-innocent ligands,[5] and redox-active ligands.[6]

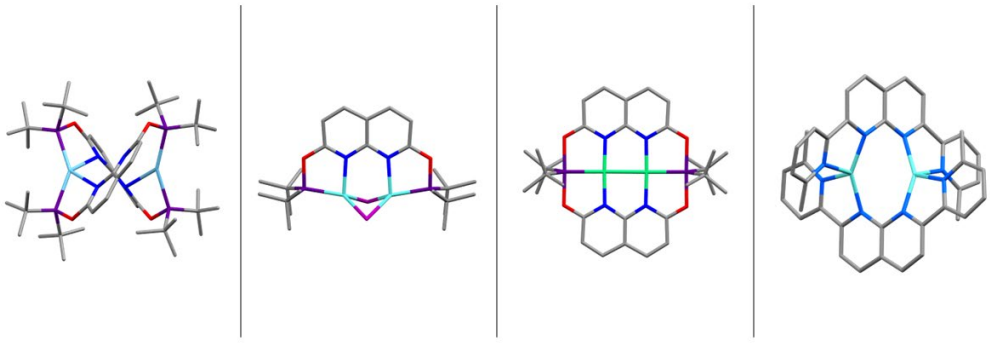

Figure 1. Bimetallic 2,7-disubstituted-1,8-nahthyridine complexes.

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Abstract Number: 162

Coordination Chemistry on the Brain: Applications to Neuroimaging in Alzheimer's Disease

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This presentation will report on the development of multifunctional compounds with high affinity for β-amyloid peptide aggregates and metal ions as potential positron emission tomography (PET) imaging agents for early diagnosis of Alzheimer's disease. We have successfully synthesized a series of benzothiazole, stilbene, and benzofuran-furfuryl bifunctional compounds with nanomolar affinity for β-amyloid aggregates.1-4 Radiolabeling with Cu-64 generates PET imaging agents that show appreciable *in vivo* brain uptake, leading to the successful PET imaging of β-amyloid aggregates in the brains of 5xFAD mice versus those of WT mice.5-9 In addition, the recent development of novel lipophilic metal chelators that can cross the blood-brain barrier (BBB) will be presented, as well as the generation of manganese complexes of these chelators for magnetic resonance imaging (MRI) applications in neurodegenerative diseases.

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Invited and Contributed Oral Abstracts

Abstract Number: 4

Organelle specific Ru(II)/Ir(III)/Re(I) based mono metallic and bimetallic complexes for cancer therapy

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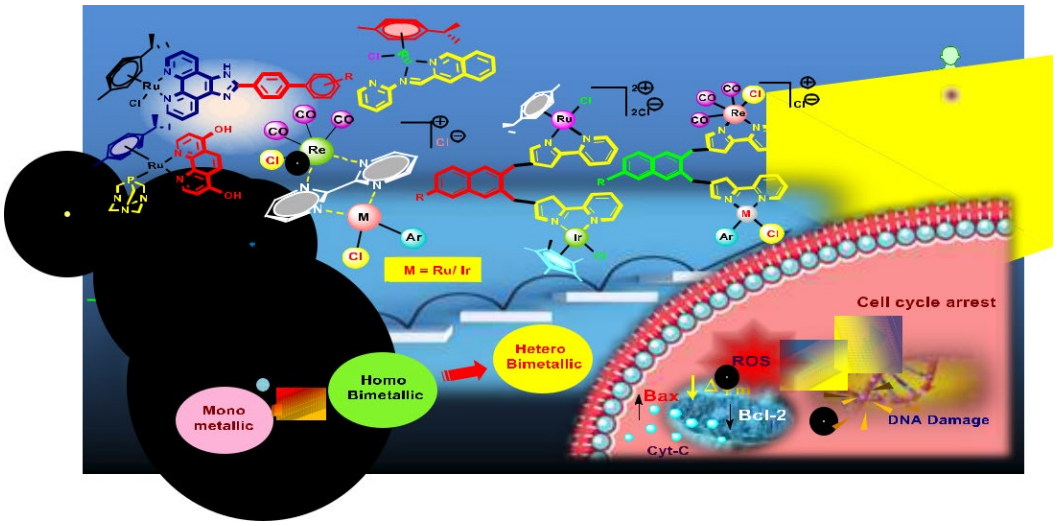
Chemotherapy is the most prevalent traditional cancer therapy but it lacks tumor specificity and thus it renders normal cells at risk. Therefore, considerable attention should be given on the design and synthesis of new metal complexes by following approaches including (i) selectivity in cancer cell by non-covalent modes of DNA interaction (ii) mitochondria specificity (iii) development of various photo-toxic agents as these produce reactive oxygen species (ROS) at the photo-exposed cancer cells leaving the unexposed healthy cells minimally affected. (iv) "Theranostic", which includes simultaneous diagnostic and therapeutic functions in a single system improving the outcome of a disease state. With respect to therapeutic regimes, improved treatment effect is achieved by effective localization at the tumor specific sites of the therapeutic agents whereas from diagnostic aspect imaging agents along with therapeutic agents combined with biomarkers (tumor specific markers) are carried from one system to another enabling them to differentiate the tumor cells from normal cells. In continuation of our present work on anticancer organoruthenium, organoiridium and organorhenium complexes, we have introduced the convenient and effective synthetic approaches for designing the monometallic and bimetallic Ru(II)/Ir(III)/Re(I) complexes which can address all three approaches. The operational simplicity, good yield, ease of isolation of the products and high chemoselectivity will be the main advantages of these methods (**Fig. 1**).[1, 2]



g. 1 Schematic diagram of metal complexes in cancer therapy

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Abstract Number: 7

Alkyl gallium quinolinolates, the next generation of anti-leishmanial agents

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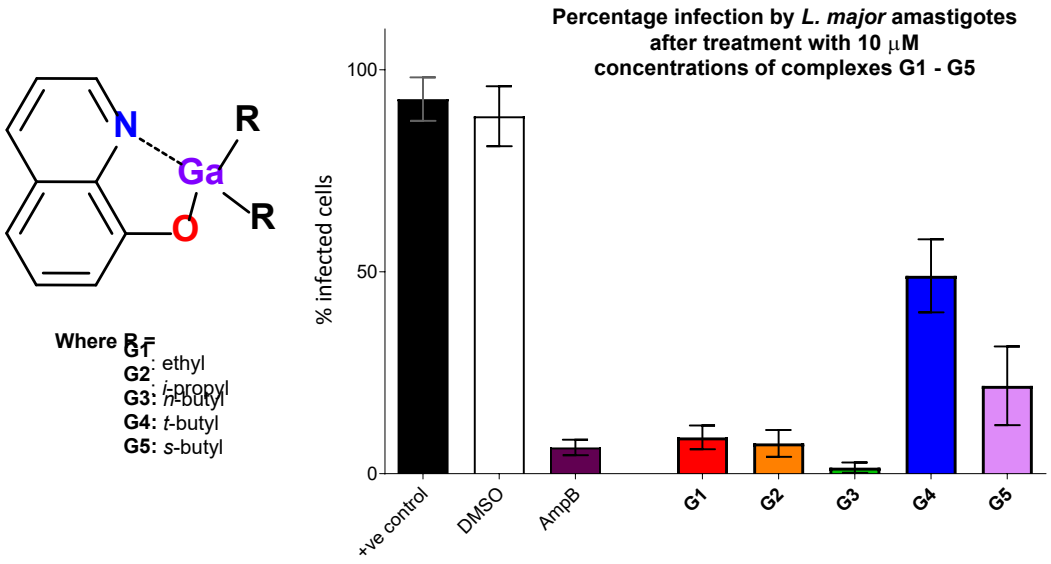
The prevalence of neglected tropical diseases is on the rise, with the parasitic ailment leishmaniasis being no exception. Its locality in 90+ tropical/sub-tropical low socioeconomic countries and increased cases of established drug resistance, makes the design and characterisation of new potentially low-cost drug candidates a high priority.[1, 2] Previous studies by Andrews *et al* found that the organometallic dimethyl gallium complexes of the medically active class of halide substituted 8-quinolinols had potent activity toward the parasites while maintaining a high degree of selective toxicity.[3] The hydrolytically stability of the Ga-C bond in chelated complexes is advantageous as is thought to prevent the scavenging and exchange of Ga (III) by Fe (III) containing proteins such as transferrin.[4] Parasites and bacteria often rely on exogenous source of iron and therefore scavenging form their hosts. Their inability to distinguish between Ga (III) and Fe (III) is thought to lead to preferential uptake of Ga (III) leading to metabolic distress and cellular apoptosis due to the inability of Ga (III) to undergo homeostatic biological redox.[5] As the previous dimethyl complexes exhibited a high degree of antimicrobial activity, modulation of the R group was next explored to investigate whether changes in alkyl chain length and complexity would lead to changes in antimicrobial activity and lipophilicity. Herein we present the synthesis, characterisation and biological application of a series of di-alkyl gallium 8-quinolinols against three strains of *Leishmania: L. major, L. amazonensis* and *L. donovani* (Figure 1).

Figure 1. Percentage infection of complexes G1 – G5 against L. major amastigotes in infected macrophages.



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Abstract Number: 10

"Socket-Plug" Complementarity: A DNA-DNA Recognition Paradigm Differentially Driven by Distinct Group I Metal Cations (Na^+, K^+, Rb^+)

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DNA is the key informational polymer in biology by virtue of its precisely defined self-assembling properties. Watson-Crick complementarity, which underlies DNA's self-assembly, is required not only in biology but has also proved powerful in the field of nanoscience, where it has been utilized to assemble complex 2D and 3D architectures and nanodevices built from the DNA double-helix. Aside from Watson-Crick base-pairing, however, DNA also participates in alternative base pairing schemes, giving rise to DNA triplexes and G-quadruplexes. We have recently described[1,2] "sticky-ended" DNA triplex-quadruplex composites that specifically recognize and bind to each other using a wholly different logic, "socket-plug" complementarity, a shape-sensing fitting of guanine "prongs" into guanine-lacking "cavities". A remarkable property of this kind of complementarity are the key roles played in it by specific Group I metal counter-cations. Thus, exclusive "self" socket-plug recognition occurs over "other" in Na^+ aqueous solutions while precisely the reverse (i.e. preference of "other" over "self") occurs in K^+ solutions. In sharp contrast to both Na^+ and K^+, Rb^+ drives "self" and "other" recognition equally[1]. We have used gel electrophoresis, Förster Resonance Energy Transfer, alkylation protection, and structural modeling to study this remarkable fundamental property of DNA, that we anticipate will find wide practical application[1].

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Abstract Number: 11

Divalent europium for imaging hypoxia in vivo with magnetic resonance imaging

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Divalent europium is isoelectronic with trivalent gadolinium, which is used in clinical settings as a contrast agent for magnetic resonance imaging. The divalent oxidation state of europium oxidizes to the trivalent state, completely changing the ability of the ion to enhance contrast. Because of the stark change in contrast enhancing ability in response to oxidation, the europium ion is an outstanding candidate for use in imaging of hypoxia. However, control of the switch in oxidation state is the key challenge to the use of europium for responsive imaging of hypoxia. I will share effort to use coordination chemistry to thermodynamically and kinetically control the switch in oxidation state. I will also share in-vivo examples of the use of the ion to delineate hypoxic and normoxic regions of tissue using magnetic resonance imaging.

Abstract Number: 12

Application of Novel Inorganic, Coordination and Supramolecular Chemistries to Respond to Chemical Warfare Agent Challenges.

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Military and National Security first responders encounter complex, time-constrained and challenging conditions when responding to scenarios involving chemical warfare agents (CWAs) and toxic industrial chemicals. As such, there is a requirement to innovate, develop and evaluate a broad suite of reliable, fast and efficient scientific and technological solutions to facilitate a customisable response to the management of chemical incidents in order to protect lives and return personnel and equipment to service faster.

The CBRN Defence Branch of DSTG has a specific interest in technologies that can be applied to the response of chemical incidents including:

Detection: development of sensing chemistries (e.g. colorimetric, fluorescent) and devices for the detection of vapours and deposited hazards (solid, liquid).

Decontamination: development of catalysts to accelerate the destruction of CWAs on scene.

Disclosure and Decontamination Assurance: techniques to visually disclose the location of contaminants on scene and visual indicators of decontamination success.

Forensics and Identification: strategies for sample preservation and presumptive identification.

Protection: new materials for PPE and assessment of PPE.

DSTG collaborates extensively with Academia to conduct innovative foundational and applied research to address these requirements and facilitate the transition of prototypes to Industry for the development into operationally useful technologies and products. In recent years, DSTG has applied numerous inorganic, coordination and supramolecular chemistry-based strategies to combat the challenges posed in chemical response including the development of:

1. Colorimetric, fluorescent and luminescent chemsensors,[1]
2. Novel, low toxicity simulants for R&D activities,[2]
3. Non-corrosive decontamination and decontamination assurance solutions,[3]
4. Multifunctional and target and trigger systems[4]
5. Disclosure sprays,[5]
6. Forensic sampling techniques.[6]

This presentation will provide an overview of some of these collaborative research programs and their application to CBRN Defence.

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Abstract Number: 13

Bispidine coordination chemistry for imaging and therapy

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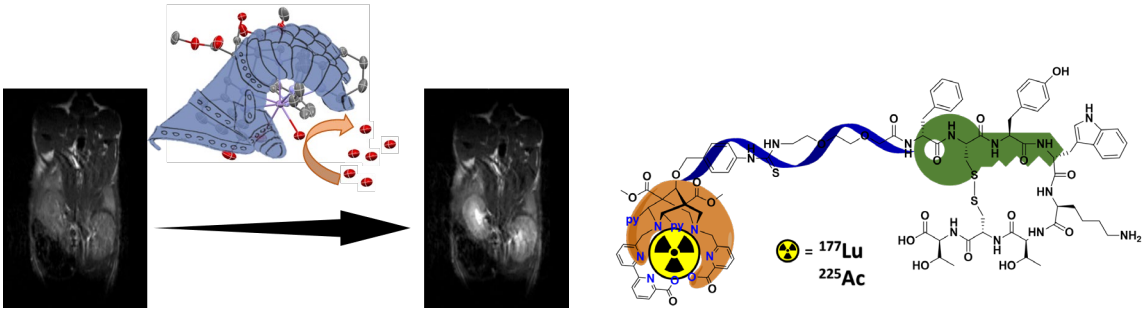
Multi-functional ligands for metal-ion-based imaging (SPECT, PET, MRI, OI) and radiotherapy generally need to be metal-ion selective, have fast complexation kinetics and produce inert complexes. The 3,7-diazabicyclo[3.3.1]-nonane (bispidine) scaffold has been used to develop very rigid up to decadentate, open-chained ligands with various donor sets. Discussed in this contribution are two recent examples: (i) Hepta- and octadentate ligands for Mn^{II} with unprecedented Mn^{II} complex stability (log*K* values of up to 24), Mn^{II}/Zn^{II} selectivity (difference of up to 10 log units), and high MRI efficiency.[1,2] (ii) Nonadentate ligands for imaging and therapy with $^{177}Lu^{III}$, $^{225}Ac^{III}$, $^{132}La^{III}$, $^{213}Bi^{III}$, and $^{203}Pb^{II}$, with fast complexation under mild conditions, high radiochemical yields and high radiochemical stability under physiological conditions.[3]



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Abstract Number: 14

Intermediate-spin iron(IV)-oxido species with record reactivity

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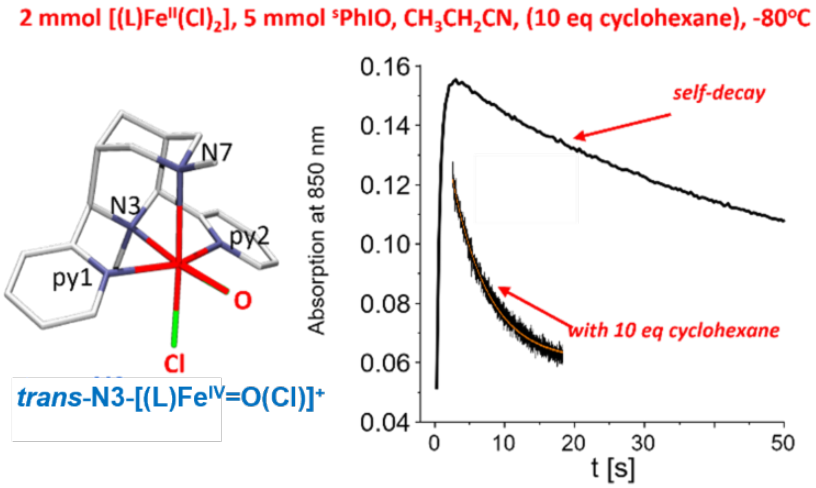
The nonheme iron(IV)-oxido complex *trans*-N3-[(L)Fe^{IV}=O(Cl)]$^+$, with a tetradentate bispidine as supporting ligand (see Figure), has an S = 1 electronic ground state (in contrast to enzymes with an S = 2 ground state), is the most reactive nonheme iron model system known so far, with a reactivity similar to nonheme iron enzymes (C-H abstraction of cyclohexane, -90°C (propionitrile), $t_{1/2}$ = 3.5 sec), and with 100% selectivity produces cyclohexyl chloride.[1-3] In absence of organic substrates, there are various self-decay pathways, one leading to an oxido-bridged diiron(III) species. The reactivity of this "resting state" as well as reasons for the unprecedented reactivity of *trans*-N3-[(L)Fe^{IV}=O(Cl)]$^+$ are discussed on the basis of temperature-dependent kinetics, a thorough spectroscopic analysis of the ferryl complex and the analysis of the electronic ground state involving ligand field and quantum-chemical methods.



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Abstract Number: 15

Targeted Delivery and Tracking of the Pt-based Chemotherapeutic, Oxaliplatin

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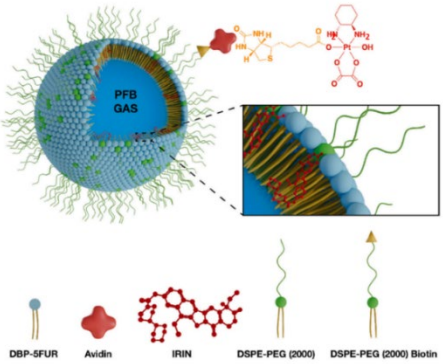
Oxaliplatin is one of three Pt-based drugs approved worldwide as an anticancer agent. Though platinum (Pt) drugs have played a very important and well documented role in treating cancer, the clinical efficacy of Pt drugs is limited by resistance and adverse side effects. Therefore novel methods are required to deliver cytotoxic Pt drugs more accurately to tumours to enhance efficacy, reduce off-target toxicity and improve the tolerability of the treatment.

Ultrasound targeted microbubble destruction (UTMD) is an emerging method of drug delivery and involves the rupture of micron sized bubbles (1-2 µm) using an ultrasound (US) stimulus. Strategies (i) to functionalise oxaliplatin for conjugation to microbubbles and (ii) to facilitate improved tumour-targeting of the FOLFIRINOX/ FOLFOXIRI drug combination using an ultrasound responsive microbubble formulation loaded with 5-fluorouridine, irinotecan and oxaliplatin (FIRINOX MB) were developed.[1] The efficacy of the FIRINOX MB formulation was investigated together with the non-toxic folinic acid in preclinical murine models of pancreatic and colorectal cancer. Our results suggest that UTMD enhances delivery of FIRINOX chemotherapy, making it significantly more effective at a substantially lower dose. In addition, the reduced systemic levels of 5-fluorouracil, irinotecan and oxaliplatin should also make the treatment more tolerable and reduce the adverse effects often associated with this treatment.[1]

Trackable drugs facilitate real-time imaging of important biological processes in cells and provide vital information concerning the biodistribution, cellular transport, subcellular localization, and mechanisms of action of drugs and mechanisms of resistance to drug treatment. An account of recent work undertaken to develop an oxaliplatin derivative with a click handle as a probe will be provided.[2]



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Abstract Number: 18

Leveraging Combinatorial Synthesis and Machine Learning towards Novel Metalloantibiotics

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Antimicrobial resistance (AMR) is now recognized as one of the most pressing healthcare challenges of the 21st century.[1] As conventional sources for antibiotics such as natural products and small organic molecules have run dry, alternative approaches have gained more attention. We have recently shown on a set of over 300,000 tested compounds, that metal complexes have significantly higher rates of antimicrobial activity compared to purely organic compounds (9.9% vs. 0.9%).[2] However at this stage the transition metal complex space still remains mostly uncharted for antimicrobial compounds. To meaningfully sample and explore this vast chemical space, conventional approaches, where compounds are made one by one, are not suitable.

In order to efficiently explore promising pockets of metalloantibiotics chemical space we have applied combinatorial synthesis strategies to metal complexes. This allowed us to synthesize >700 metal complexes (so far) and evaluate their antimicrobial properties in a time- and cost-effective manner. We identified several hit-compounds with high activity against drug-resistant bacteria and low toxicity. Promisingly, these compounds seem to possess modes of action distinct from known antimicrobials. Lastly, we have used the gathered data to train machine learning (ML) models capable of predicting metal complexes with antimicrobial activity from a virtual library of ~10^8 possible compounds.

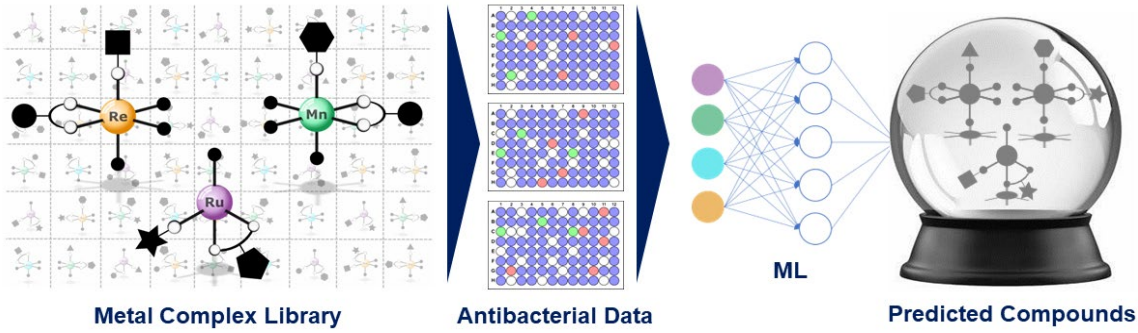

Figure 1. Schematic overview of the combinatorial synthesis approach applied to manganese, rhenium and ruthenium scaffolds, generating antibacterial data that can be utilized to train ML-algorithms to predict active metal complexes.

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Abstract Number: 21

Extended scope of metallohydrolases: Design and evolution of noncanonical β-stereoselective metalloglycosidases

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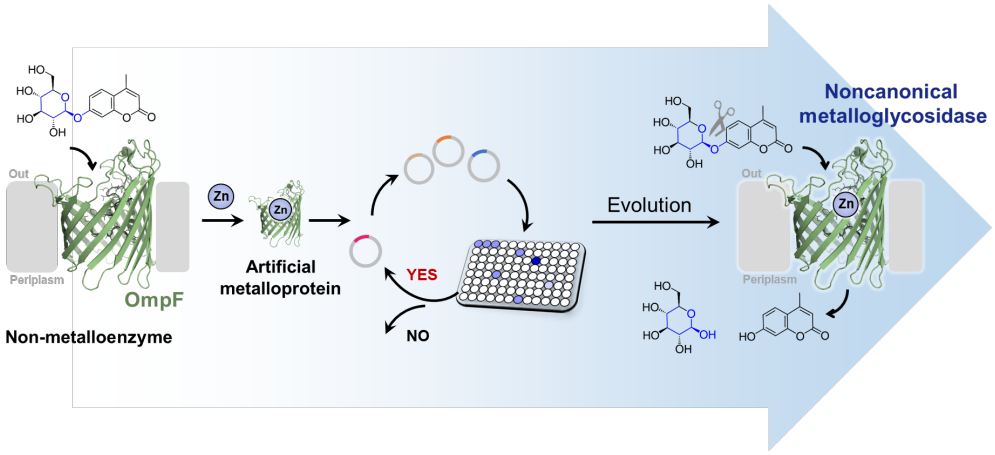
Metallohydrolases utilize various metal elements to activate a water molecule and facilitate its subsequent dissociation of diverse chemical bonds. Despite the diverse sequence, structure, and substrate cope of metallohydrolases, little was known about metal-dependent hydrolases, where metal ion plays a catalytic role in the reactions with glycosides. Herein, we synthesized artificial Zn-dependent metalloglycosidases by constructing a hydrolytically active Zn-coordination site in a non-metalloprotein, outer membrane protein OmpF.[1] Structure- and mechanism-based protein design and directed evolution have led to artificial metalloglycosidases with high catalytic proficiency and β-stereoselectivity. The newly installed Zn-binding site constitutes a catalytic motif along with at least one adjacent acidic residue, indicating that the scope of inorganic reactivities in proteinaceous environments has expanded, resetting the structural and functional diversity of metalloenzymes.



Design of noncanonical β-stereoselective metalloglycosidases

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Abstract Number: 24

Mechanistic and Structural Insights into Enzymatic Hydrolytic Dehalogenation

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Persistent anthropogenic environmental contaminants represent an increasing threat to both ecological systems and human health.[1-2] One of these, chlorinated aromatic hydrocarbons, include polychlorinated biphenyl, chlorobenzenes and atrazine, which are important industrial starting materials for the manufacture of dyes, drugs, and pesticides, to name a few. Aromatic carbon-chlorine bonds are typically very stable and hence, these compounds persist in soil and contaminant groundwater. While enzymatic dehalogenation offers a possible bioremediation solution for chlorinated aromatic compounds, a major impediment to understanding their bioremediation uses, is the lack of a detailed understanding of their catalytic mechanism. A relatively unknown biological dehalogenation process involves hydrolysis of a C-Cl bond.[3] Recently, we reported the X-ray crystal structure of the chlorothalonil dehalogenase from *Pseudomonas sp*. CTN-3 (Chd; PDB: 6UXU at 1.96 Å), a Zn(II)-dependent hydrolytic dehalogenase that selectively substitutes an aromatic chlorine-carbon bond in chlorothalonil (TPN; 2,4,5,6-tetrachloroisophtalonitrile), a fungicide that is a probable human carcinogen, to a non-toxic aromatic alcohol (4-hydroxytrichloro-isophthalonitrile; 4-OH-TPN) (Figure 1).[4] Chd exhibits an □□□□-sandwich fold that is commonly observed in the □-lactamase superfamily and is a "head-to-tail" homodimer, formed between two □-helices from each monomer. The active site Zn(II) ion resides in a slightly distorted trigonal bipyramid geometry with His117, His257, Asp116, Asn216, and water/hydroxide as ligands. The axial water/hydroxide ligand is hydrogen bound by the N$^{\varepsilon}$ nitrogen atom of His114 (~2.9 Å). Interestingly, H114 clearly occupies two orientations, the second of which is perpendicular to the hydrogen bound conformation. We have investigated the catalytic role of His114 by generating the His114Ala mutant and investigated both WT Chd and Chd H114A using EPR,[5] all-atomistic molecular dynamics (MD), and substrate docking studies to better understand the electronic environment and active site dynamics. In conjunction with prior studies, an updated model for the hydrolytic dehalogenation of TPN will be discussed.

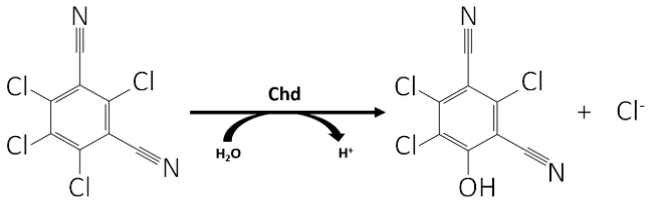

Figure 1. Hydrolysis of TPN to 4-OH-TPN and chloride by Chd.

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Abstract Number: 25

Characterizing and Engineering Nitrogenases of *Rhodobacter capsulatus*

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Nitrogenases are the only known family of enzymes that catalyze the reduction of molecular nitrogen (N_2) to ammonia (NH_3, Fig. 1A). The N_2 reduction drives the biological nitrogen fixation and the global nitrogen cycle. Besides the conversion of N_2, nitrogenases were recently shown to convert a whole range of other substrates, including carbon monoxide (CO)[1-3] and carbon dioxide (CO_2)[4-6], which are reduced to hydrocarbons (Fig. 1A).

Both nitrogenase reactions, the well-known formation of NH_3 (fertiliser) and the newly discovered hydrocarbon formation reaction are environmentally relevant and mimicked by large scale industrial processes: the Haber-Bosch and the Fischer-Tropsch process, respectively. Thus, characterizing and engineering nitrogenases will open new approaches for the use of nitrogenases in bioremediation (CO_2 fixation) and renewable hydrocarbon and energy production.

We have developed a directed evolution process and screening platform to engineer nitrogenases for the reduction of CO_2 in *R. capsulatus* (Fig. 1B). Several nitrogenase site saturation libraries were created targeting amino acids in proximity of the active site. We could identify nitrogenase mutants with an enhanced CO_2 reduction activity forming increased amounts of CO and methane. Currently, we are biochemically, spectroscopically and structurally characterizing the nitrogenase variants to elucidate and understand the underlying changes turning a nitrogenase into a CO_2 reductase.

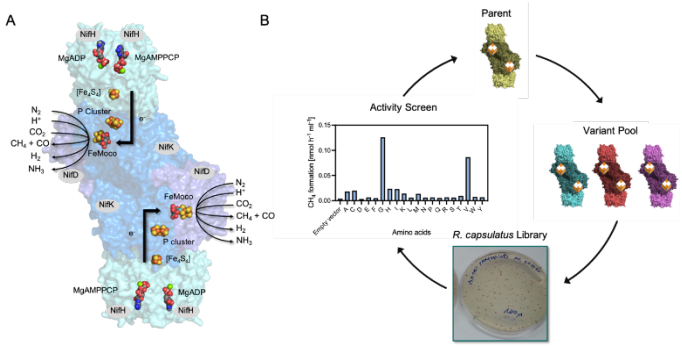

Figure 1. Nitrogenase structure, catalysis and screening platform. (A) The crystal structure of the Mo nitrogenase complex (transparent), [Fe_4S_4] cluster, P cluster, FeMoco and MgADP, MgAMPPCP are shown as space-filling models. B) Gas chromatography screening platform for the reduction of CO_2 and the formation of CH_4. Workflow: The plasmid encoding the parent Fe-only nitrogenase is diversified by PCR and conjugated into *R. capsulatus*. Individual colonies are transferred into. GC vials, grown anaerobically and CO_2 is added to the headspace. The vials are analysed for the formation of CH_4.

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Abstract Number: 26

A new catalytic active End-on Peroxido Dicopper Tyrosinase model Complex raising questions about the active species

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Moving chemical processes towards more sustainable procedures, one possible source of inspiration are diverse biological systems which have been optimized during extensive evolutionary developments.[1] Since the possibility to use molecular dioxygen for chemical oxidations would drastically enhance the sustainability replacing application of wasteful oxidants and toxic catalysts, understanding the steps of dioxygen activation and substrate conversion is crucial. While tyrosinase binds dioxygen between the two Cu centers of the active site as side-on peroxide(μ-η^2:η^2),[1] structurally simplified, artificial mimics of the enzyme's active site additionally show end-on μ-1,2-peroxido and bis-μ-oxido isomers.[1] Previous catalytic investigations of these tyrosinase model complexes result in a variety of side-on peroxido and bis-μ-oxido species exhibiting tyrosinase-like activity.[2] However, only few examples of catalytically active end-on μ-1,2-peroxido species have been reported so far.[3]

Herein, eight tetradentate ligands were synthetized for tyrosinase model systems. Three of them showed the ability to activate dioxygen forming an end-on μ-1,2-peroxido species at low temperatures which was confirmed via UV/Vis and Raman spectroscopy. Experimental results were compared to theoretical calculations obtaining more information about underlying mechanisms. Furthermore, one end-on μ-1,2-peroxido species showed tyrosinase-like catalytic activity which was confirmed UV/Vis spectroscopically and via product isolation. Therefore, the obtained results contribute to the discussion about the active species and prove again the large impact of small variations in the ligand design.

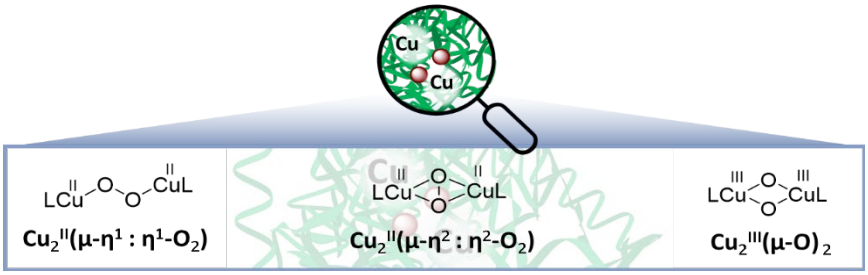

Figure 1. Overview of different Cu_2O_2 species.[1]

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Abstract Number: 27

Bioinspired Reactivity on the Length of Pyridyl Arm of Unsymmetrical ß-Diketiminato Copper Complexes

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Biological systems exhibit state-of-the-art control over reactivity through the choice of metal ions, ligand environments, and redox properties in many fundamental aspects of coordination chemistry. The diversity offered by biological coordination complexes/chemistry has inspired chemists amongst others to design and develop a multitude of small molecule bio-mimetics for various applications to manipulate biological processes. Our approach focuses on the ligand design and reactivity comparison of Cu(I)/Cu(II) complexes which could provide some viewpoints to understand the copper containing protein/enzyme behaviors. The β-diketiminato copper(II) **L1**CuCl–**L4**CuCl and their nitrite complexes **L1**Cu(O_2N) and **L2**Cu(O_2N) has been synthesized and characterized. The X-ray structure of the **L1**CuCl–**L4**CuCl complexes clearly indicates towards the mononuclear structure with a four-coordinated Cu(II) center bound by one chloride and three nitrogen atoms of unsymmetrical β-diketiminato ligands. The cyclic voltametric analysis of Cu(II) complexes shows that length of pyridyl arm control the Cu(II)/Cu(I) redox process. The EPR results confirm the geometry of the Cu(II) complexes are also controlled by the length of the chelating pyridyl arm. The oxygen atom transfer nitrite reduction of Cu(II) nitrite complexes leads the formation copper(I)-PPh_3 and O=PPh_3 which were confirmed by ^{1}H and ^{31}P NMR. The length of pyridyl arm of copper(II) nitrite complexes govern the NO-releasing ability. These findings illustrate the important bioinspired behavior and NO generation from nitrite via oxygen atom transfer of unsymmetrical β-diketiminato copper(II) complexes as compare to symmetrical β-diketiminato copper(II) complexes.

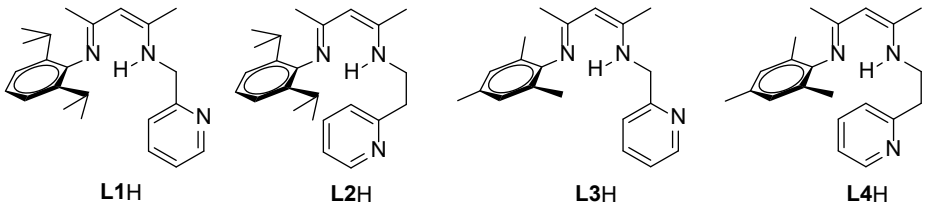

Chart 1. Representation of the *N*-aryl-*N'*-alkyl β-diketiminato ligand sets.

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Abstract Number: 28

Dinuclear homo- and hetero-metallic complexes as multifunctional bioprobes and theranostics

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Polypyridyl complexes of d^6-metal ions can interact reversibly with DNA with high binding affinities.[1,2] Although such complexes offer potential as *in cellulo* probes for luminescence microscopy, poor cellular uptake by live cells generally restricts the use of many such systems.
With the aim of constructing complex oligonuclear architectures, the Thomas group has used achiral mononuclear complexes as building blocks in the "modular" synthesis of non-threading dinuclear metallo-intercalators.[3] Using this approach metal ions, linkers, and intercalating ligand can all be individually selected – Fig 1a, allowing us to explore the properties of dinuclear Ru^{II} systems with two different intercalating ligands[4,5] or heterodinuclear metallo-intercalators[3,6,7], see for example Fig 1b

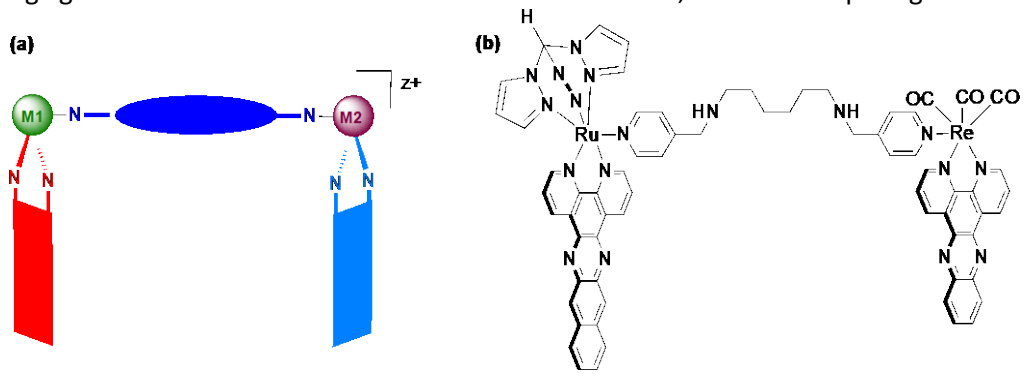

Fig 1 (a) Schematic showing generic "modules" that can be changed in synthesis of metallo-intercalating complexes (b) Example of a specific complex synthesized by this approach

In these studies, we have also found that even the bridging ligand used to tether the intercalating moieties together can influence the photophysical and biophysical properties of these complexes. This has led to the development of multifunctional systems with application as novel super-resolution probes, chemotherapeutics, and phototherapeutics.

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Abstract Number: 29

Structural organisation and mechanistic insight of cytochrome P450 17A1

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Cytochrome P450 17A1 (CYP17) is a haem-containing membrane-bound enzyme situated at a key branch of steroidogenic pathways. CYP17 is a dual function enzyme that catalyses 17α-hydroxylation of progestins to mineralo- or glucocorticoid precursors and an additional 17,20-lyase reaction of 17α-hydroxylase to synthesise androgen precursors. How CYP17 achieves this multi-functionality remains a mystery. Activity of CYP17 requires electrons delivered by cytochrome P450 oxido-reductase (CPR). The 17,20-lyase reaction requires and allosteric interaction with cytochrome b5 (cyt b5). We have shown that the protein-protein interaction of cyt b5 on CYP17 slows down the rate of electron transfer to CYP17. This kinetic coupling could enable the 17, 20-lyase reaction to proceed. Our Molecular Dynamics simulations supported formation of a CYP17 dimer that could bind both CPR and cyt b5, simultaneously. To examine the interaction of cyt b5 and CPR proteins with CYP17 we used Molecular Dynamics simulations. Within a membrane environment, CYP17 was simulated in the absence of substrate, or with a hydroxylase substrate (pregnenolone) or a lyase substrate (17α-hydroxy-pregnenolone). In addition, the effects of cyt b5 interacting with CYP17 was examined. Analysis of the trajectories provided insights into the allosteric coupling between the cyt b5 interface to the active site. Intriguingly, cyt b5 decreased the movement and flexibility within the active site of CYP17, however regions not necessarily obvious for haem-substrate rearrangement were also altered.
Using single molecule fluorescence microscopy, we have also gained insight into the structural organisation of CYP17 which has been tracked in real-time in the endoplasmic reticulum, providing kinetic data and sub-cellular localisation dynamics.
These new data build on previous biophysical data that supported CYP17 homodimerisation and give insight into the role of cyt b5 in the regulation of the 17,20 lyase reaction of CYP17.

Abstract Number: 32

The Reaction Mechanism of Formate Dehydrogenases

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Recent advances in our understanding of the mechanism of action of molybdenum-containing formate dehydrogenases and related enzymes will be presented, including rapid reaction kinetic studies and characterization of the active site molybdenum center by electron paramagnetic resonance spectroscopy.

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Abstract Number: 33

Bioinorganic Strategies to Study Multiple Facets in Alzheimer's Disease

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Abstract: Alzheimer's disease (AD), associated with degeneration of neurons and synapses in the brain, leads to motor impairment and eventual fatality. Neurodegeneration could be related to various interconnected features, including (i) plaque formation from amyloid-□ (A□) peptide fragments, (ii) metal ion dyshomeostasis and miscompartmentalization, as well as (iii) inflammation and increased oxidative stress due to overproduction of reactive oxygen species (ROS). The inter-relations between some of these pathological factors have been investigated. Metals are found entangled in the A□ plaque and likely contribute to A□ neurotoxicity and oxidative stress. ROS have been shown to increase the rate of A□ plaque formation. Our understanding of the correlation between these elements and AD neuropathogenesis has been very limited, however. There is currently no cure for AD; therapies are focused on symptomatic relief targeting the decrease in the levels of acetylcholine, only one of the multiple factors causing the disease.[1-3] To find a cure for AD, we require a better understanding of the relationship between various causative factors of this devastating disease. Towards this goal, we have been developing suitable chemical tools capable of targeting and regulating multiple underlying factors or identifying the pathogenic networks composed of their direct interactions and reactivities.[4-11]

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Abstract Number: 35

Designing Multifunctional Molecules to Control Protein Misfolding

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The interaction between metal ions, ligands, and biomolecules play a fundamental role in bioinorganic chemistry, from metalloenzymes to medicine. In addition to balancing charge, small molecules can tune stability and associated reactivity via diverse interaction pathways and redox activation. This talk will focus on the development of multifunctional molecules that target protein misfolding and aggregation in neurodegenerative disease and cancer. We are targeting the amyloid-beta (A) peptide in Alzheimer's disease by designing molecules to inhibit A aggregation and formation of toxic reactive oxygen species (ROS) associated with dysregulated metal ions.[1] We are also investigating the tumour suppressor protein p53. In over 50% of cancers, mutations render this protein inactive leading to loss or alteration of Zn-binding at the core site and aggregation.[2] We are developing multifunctional molecules that act as Zn metallochaperones, modulate mutant p53 aggregation, and rescue protein function.[3]

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Abstract Number: 38

Multiphoton Absorption at Metal Alkynyl-Based Materials

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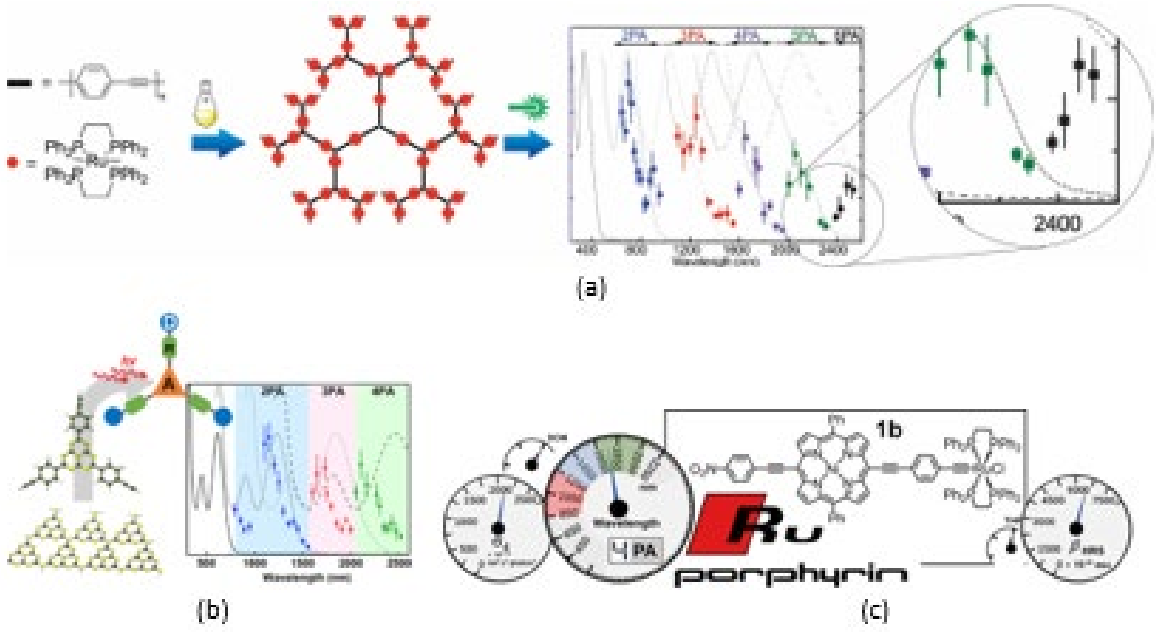
We have a long-standing interest in fundamental studies of the nonlinear optical (NLO) properties of molecular organometallic and coordination complexes, with a major focus on metal alkynyl complexes.[1] Although we have recently been pursuing studies of (i) second-harmonic generation-active inorganic crystals functioning in the IR and deep-UV regions (in conjunction with the Australia-China *Joint Research Centre for Functional Molecular Materials*) and (ii) two-photon absorption-active bio-compatible molecules (in conjunction with the CNRS International Associated Lab *REDOCHROM* and the CNRS International Research Project *MAITAI*),[2] we are continuing to explore the NLO properties of novel molecular architectures. This presentation will detail some of our recent studies of the multiphoton absorption behaviour of (a) metal alkynyl-based dendrimers, including rare examples of molecular five- and six-photon absorption, (b) heptazine-cored octupolar metal alkynyl complexes, including strongly red-shifted four-photon absorption, and (c) metal alkynyl-porphyrin hybrids, including record NLO coefficients and the first four-photon absorption seen with porphyrins.[3]



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[2] See, for example: (a) *Angew. Chem. Int. Ed.* **2021**, *60*, 3464. (b) *Angew. Chem. Int. Ed.* **2021**, *60*, 14806. (c) *Angew. Chem. Int. Ed.* **2021**, *60*, 27151. (d) *J. Am. Chem. Soc.* **2021**, *143*, 4138. (e) *J. Am. Chem. Soc.*

2021, *143*, 12455. (f) *Angew. Chem. Int. Ed.* **2021**, *60*, 22447. (g) *Angew. Chem. Int. Ed.* **2022**, *61*, e202208514. (h) *Angew. Chem. Int. Ed.* **2022**, *61*, e202115855. (i) *Angew. Chem. Int. Ed.* **2022**, *61*, e202203104. (j) *J. Am. Chem. Soc.* **2022**, *144*, 20394. (k) *J. Am. Chem. Soc.* **2023**, *145*, 3040.

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Abstract Number: 39

Spectroscopic characterization of hemerythrin-like proteins with unique reactivity toward nitric oxide and other NOx species

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Hemerythrin-like proteins (HLPs) are broadly distributed across taxonomic groups but very little is known of their functional roles and structural diversity in prokaryotes. Some HLP subgroups are known to function as O_2 sensors using a carboxylate-bridged nonheme diiron cluster with only one coordination site available at one iron center to bind O_2 in a reversible fashion. Other HLPs like YtfE from *E. coli*, contain a symmetric diiron cluster with four rather than five coordinating His sidechains and an open coordination site on each iron centers, as previously seen in NO-reducing flavodiiron proteins. Mycobacterial HLPs, which are important for infection and survival in macrophages, present yet another structurally distinct subgroup where a tyrosine sidechain coordinates one of the two iron(III) center. Recently, we showed how this asymmetric coordination sphere at the diferric center results in unusual spectroscopic signatures and unique reactivity toward nitric oxide (NO) (*Albert and Moënne-Loccoz 2022, J. Am. Chem. Soc. 144, 17611-17621*). In this oral presentation, I will review these published results and present new unpublished data on other Tyr-ligated HLPs. I will also show how the incorporation of fluorinated tyrosines impact the spectral features exhibited by these Tyr-ligated HLPs and how the redox properties and reactivity toward NO and other NOx species are modulated by the fluorotyrosine substitutions. While this fluorotyrosine-substitution approach has been used to investigate enzymatic Tyr electron transfer chains, I believe our work represents the first application of this approach to spectroscopic and kinetic studies of Tyr-coordinated nonheme iron proteins and show great promises for mechanistic investigations.

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Abstract Number: 40

Hijacking Beta-lactamase Activity: Beta-lactam Prodrugs Designed to Selectively Kill Drug-Resistant Bacteria

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The rise of bacterial resistance to conventional antibiotics is a serious threat to human health. Particularly concerning are multi-drug-resistant pathogens that are not sensitive to carbapenems or third generation cephalosporins, often causing severe infections or death. This resistance mechanism is primarily caused by bacteria acquiring and expressing beta-lactamase enzymes. Through evolutionary pressure and antibiotic misuse, mutations in BL have forged the extended-spectrum BLs (ESBLs), which present increased catalytic rates and promiscuous substrate recognition. Metallo-beta-lactamases (MBLs), such as NDM, VIM, and IMP, are a zinc-containing variety of ESBLs that have the broadest scope of enzymatic activity against antibiotics and are becoming more medically relevant. This mechanism of resistance will only be exacerbated and proliferated; therefore, new methods to combat pathogenic bacterial infections are needed. With the goal of targeting these pathogens, we have developed prodrugs that leverage the enzymatic reactivity attendant to resistance mechanisms in order to selectively kill drug-resistant bacteria, including those that produce MBLs. Our prodrug design presents improved MBL inhibition by proximal release of inhibitor moieties, 100x greater selective killing of drug resistant bacteria in monomicrobial environments, and selective killing of drug resistant bacteria in polymicrobial environments. This work presents the ongoing design development of prodrugs to overcome life-threatening bacterial infections due to MBL expression, while reducing toxicity against non-pathogenic bacteria and the infected host.

Abstract Number: 41

Electrophilic Aldehyde Oxidation & Selective Nitric Oxide Delivery for Vasodilation

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In this presentation, we will report on two topics: Electrophilic aldehyde oxidation & Selective nitric oxide delivery for vasodilation.

At first, we reports on the oxidation of aldehydes using a mononuclear manganese(III) iodosylbenzene complex, $[Mn(TBDAP)(OIPh)(OH)]^{2+}$ (**1**), including detailed kinetic and mechanistic investigations.[1] The electrophilicity of **1** in aldehyde oxidation was demonstrated through Hammett plot analysis and reaction rate studies. Kinetic isotope experiments and reactivity analysis revealed that the reaction occurs via rate-determining C-H bond activation at the formyl group. Density functional theory calculations showed that electrostatic interaction between **1** and the aldehyde occurs at a pre-equilibrium state, with the rate-determining step being hydride transfer from the aldehyde to the adduct. The study also presents catalytic reactions of aldehydes by **1**, demonstrating the broad substrate scope.

Retinal vascular occlusion is a prevalent cause of visual impairment. While various approaches, including vasodilators, have been investigated for the treatment, there is currently no effective method available. Herein, we presents a novel strategy for treating vascular occlusions by using a photo-responsive iron-nitrosyl complex, $[Fe(TBDAP)(NO)(H_2O)]^{2+}$ (**2**), which acts as a spatiotemporally controllable nitric oxide transporter.2 The complex **2** was synthesized and characterized using X-ray crystallography. Its ability to selectively dilate normal retinal blood vessels and reperfuse the occluded vessels was demonstrated in animal disease models.

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Abstract Number: 45

Design of Artificial Enzymes Using Transition Metals

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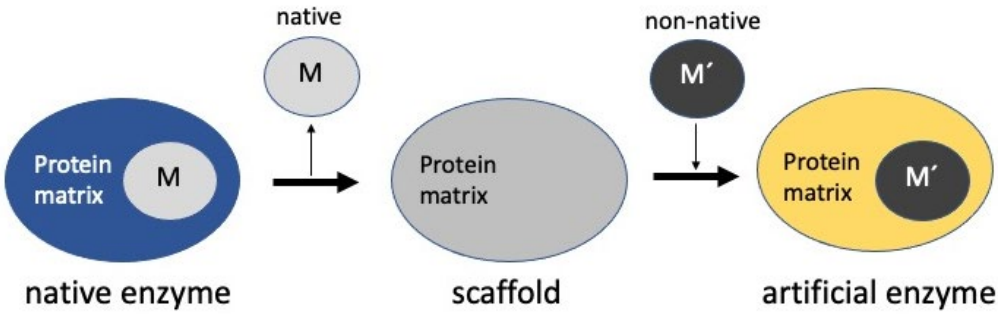
Enzymes are complex molecules where chemical transformations occur with amazing selectivity and at high rates. Metalloproteins and metal-containing enzymes are well known to be essential to life. The elucidation of structural and functional aspects of metal sites in enzymes has been a goal of model studies putting together Inorganic Chemistry and Synthetic Biochemistry related to the developing area of artificial / mimetic enzymes.
Synthetic peptides and small proteins involving rich sulfur coordination sites are extensively used, having the possibility of coordinating a wide variety of transition metal ions, with particular interest in aiming to model complex metalloproteins.

Acknowledgments: Work supported by PT national funds (FCT/MCTES) through projects PTDC/BTA-BTA/0935/2020, UIDB/50006/2020 and UIDP/50006/2020. Thanks are due to Biplab K Maiti, Pedro Bragança, Cintia Carreira, Maddalena Elia, Célia Silveira, Smilja Todorovic, Marta S. P. Carepo, Sofia R. Pauleta, Luísa B. Maia, Tyler B. J. Pinter, Vincent Pecoraro and Isabel Moura for various contributions.



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Abstract Number: 46

The unique copper cluster of nitrous oxide reductase and its role on N_2O (a green house gas) reduction to N_2

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Nitrous oxide (N_2O) is a powerful greenhouse gas that contributes to global warming. One way to mitigate its impact is through the use of nitrous oxide reductase (N_2OR), an enzyme that converts N_2O into nitrogen gas. N_2OR is found in certain bacteria and is composed of a copper cluster, which plays a critical role in its catalytic activity. In this study, we investigate the potential of utilizing N_2OR and copper clusters as a means of reducing N_2O emissions. We explore different methods for producing N_2OR and copper clusters, as well as their effectiveness in converting N_2O to nitrogen gas.

The microbial denitrification. pathway accounts for the dissimilatory transformation of nitrate and nitrite, in four reactions catalyzed by different metalloenzymes, that sequentially convert nitrate into dinitrogen (with nitrite, nitric oxide and N_2O as intermediates). In this talk we will address the structure/function relationship of the N_2Or that reduces N_2O, using a toolbox of spectroscopic, kinetic, electrochemical and structural techniques aiming to better understand the enzyme to enhance its N2O mitigation potential. Marinobacter hydrocarbonoclasticus N_2OR has two copper centers, CuA, the electron transfer center, and "CuZ", the catalytic center. "CuZ" is a unique center in biological systems, since it has a sulfide bridging a distorted tetrahedron of copper ions , and the copper ions are also coordinated by seven histidine side chains.

Acknowledgment : We thank Esther Pierce, E.Solomon, S.R.Pauleta, S.Dell'Acqua,Cíntia Carreira and José Moura for their contributions. The work was suported by the project from FCT(PTDC/QUI-BIQ/116481/2010, PTDC/BBB-BIQ/0129/2014 and PTDC/2022.01152).

Abstract Number: 47

Metal complexes for tumor diagnosis and therapy

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The precise and early detection and effective killing cancer cells are of great importance. Metal complexes have showed great potential for tumor imaging and therapy. In this talk, I will introduce our recent progresses on tumor imaging and PDT based on metal complexes. We developed an Ir(III) complex with synergistic response to both hypoxia and acidity of the tumor microenvironment[1], which could help improve the sensitivity of tumor imaging. Photosensitizers with O2-dependent ROS generation ability showed limit PDT effect due to tumor hypoxia, developing PSs with O2-independency is highly attractive. We developed Ru(II) and Ir(III) complexes based PSs, which showed type I PDT processes and low O_2-independence[2,3]. In addition, both complexes exhibited the ability to induce ferroptosis. The synergism of ferroptosis and apoptosis induced by our Ir(III) complex offered a powerful strategy for combating hypoxic and apoptosis-resistant tumor cells.

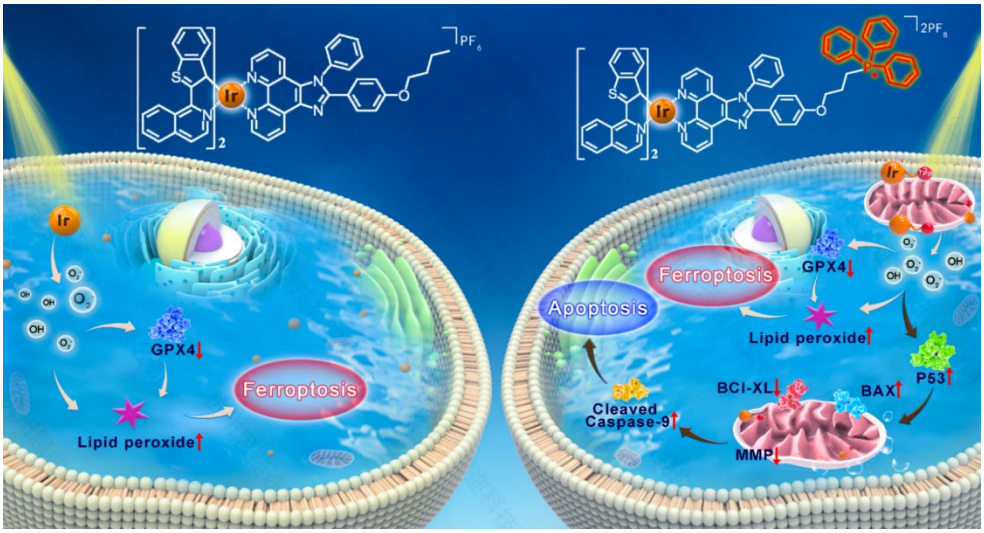

Fig. 1. Synergism of ferroptosis and apoptosis by an Ir(III) complex based photosensitizer

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Abstract Number: 50

Imaging Metals and Proteins in Synaptic Compartments

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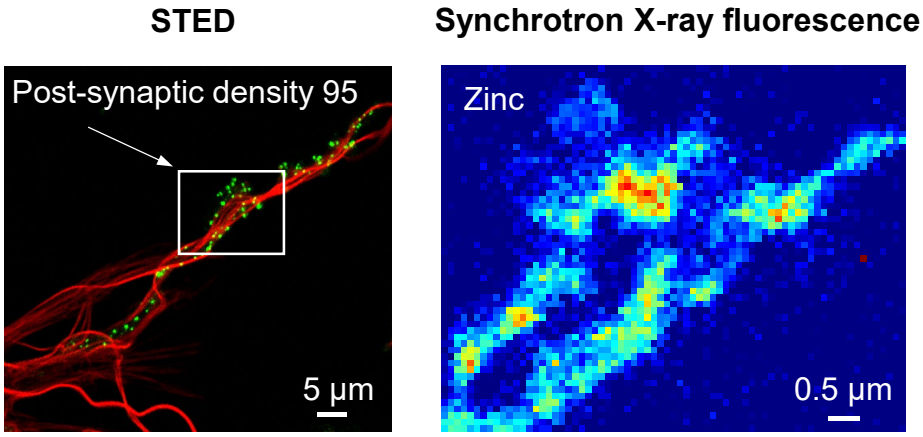
It is becoming increasingly clear that biological metals such as iron, copper or zinc are involved in synaptic functions, and in particular in the mechanisms of synaptogenesis and subsequent synaptic plasticity. Understanding the role of metals on synaptic functions is a difficult challenge due to the very low concentration of these elements in neurons and to the sub-micrometer size of synaptic compartments. To address this challenge we have developed a correlative nano-imaging approach combining metal and protein detection [1,2]. First, stimulated emission depletion (STED) microscopy, a super resolution optical microscopy technique, is applied to locate fluorescently labeled proteins. Then, synchrotron radiation induced X-ray fluorescence (SXRF) is performed on the same regions of interest, e.g. synaptic compartments. We will present the principle scheme that allows this correlative nano-imaging and its experimental validation. We applied this correlative nano-imaging to the study of the physiological distribution of metals in synaptic compartments of primary rat hippocampal neurons. We thus compared the nanometric distribution of metals with that of synaptic proteins, such as PSD95 or cytoskeleton proteins. We provide proof-of-principle for correlative imaging of metals and proteins at the synaptic scale and discuss the present limitations and future developments in this area.



Correlative nano-imaging of proteins and metals in synaptic compartments combining STED (stimulated emission depletion) super resolution microscopy and synchrotron X-ray fluorescence nano-imaging.

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Abstract Number: 51

Control of metal availability during host-microbe interactions

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Metals are essential micronutrients to microbes. Like all nutrients, too little of any metal will cause microbial starvation but too much will cause microbial poisoning.

During host-microbe interactions, the paradigm for the last half a century has been that hosts can control nutrient metal supply to promote microbial *clearance* (so-called "nutritional immunity"[1]). In response to *infection* by a potentially *pathogenic microbe*, *diseased* hosts secrete metal-binding molecules (effectors) that change metal speciation and, thus, availability at the site of infection. These effectors either limit nutrient metal availability and promote microbial metal starvation, or raise metal availability and promote microbial metal poisoning.

Although the overwhelming majority of host-microbe interactions do not result in disease, metal-dependent host responses to microbes in *healthy* hosts are not understood. Do host organisms also produce metal-binding host effectors that control nutrient supply to the host *microbiota* and promote microbial *colonisation*?

This talk will outline our recent work and ideas in this topic, focusing on the potential role of salivary histatins as candidate host effectors that control nutrient copper availability to microbes that reside in the human oral cavity.

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Abstract Number: 52

Responsive inorganic platforms for ^{19}F NMR and MRI

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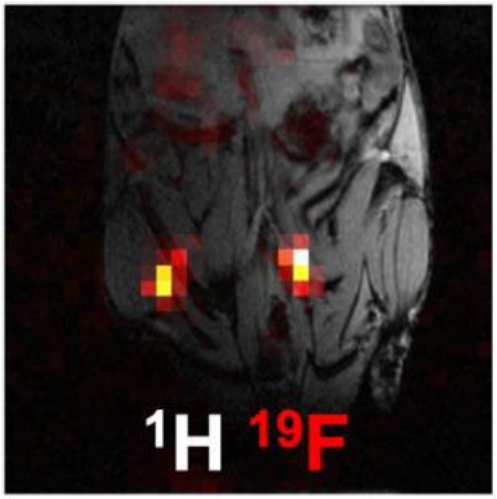
^{19}F Magnetic resonance imaging (MRI) is an *in vivo* imaging technique that shows great promise due to the favorable NMR properties of the fluorine nucleus (high sensitivity, large ppm range) and the lack of detectable fluorine signal in biological systems. Imaging agents can be designed that exhibit either a turn -on or chemical shift response that is selective for a specific biological molecule or event[1]. We are developing a series of inorganic platforms designed to report on biological species ranging from electrons (e.g. redox events) to proteins (e.g. thrombin. Emerging sensors from the lab utilizing iron will be the focus of this presentation.



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Abstract Number: 53

Fluorescent probes for monitoring the dynamic metalation state of metallo-beta-lactamases in cells

Emily L. Que,[a] Sky Price [a], Radhia Mehta[a], Dorothea Hudson[a], Walter Fast[b]

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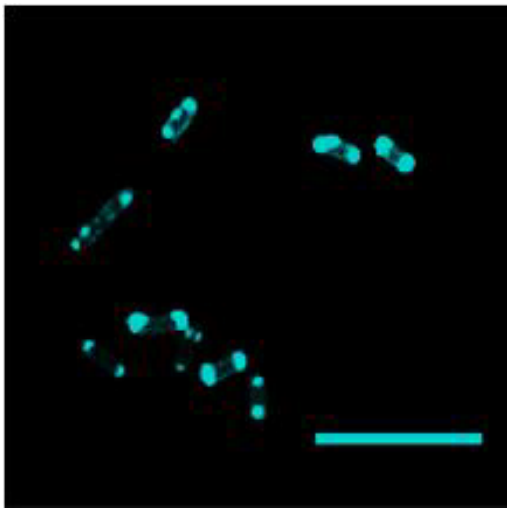
New Delhi Metallo-β-lactamase (NDM) grants resistance to a broad spectrum of β-lactam antibiotics including last-resort carbapenems and is emerging as a global antibiotic resistance threat. Limited zinc availability adversely impacts the ability of NDM-1 to provide resistance, but a number of clinical variants have emerged that are more resistant to zinc scarcity (*e.g.*, NDM-15). To provide novel tools to better study metal ion sequestration in host-pathogen interactions and the dynamic metalation state of NDM in these contexts, we are developing fluorescent probes that bind to the dizinc of active site of NDM.[1,2] The development of reversible turn-on fluorescent probes for the metalation state of NDM provides a means to monitor the impact of metal ion sequestration by host defense mechanisms and to detect inhibitor target engagement during the development of therapeutics to counter this resistance determinant. Recent developments in our lab along this research theme will be discussed.



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Abstract Number: 55

This $%#! Oxidizes Everything

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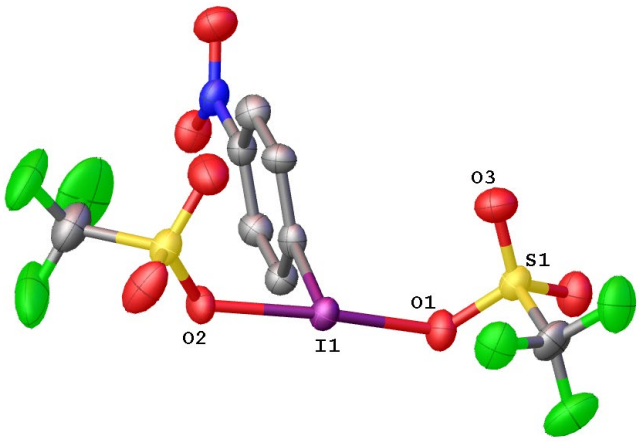
After over a decade of effort we have recently synthesized a genuine $ArI(OTf)_2$.[1] I(III) bearing two triflates was predicted to be the most oxidizing of $ArIL_2$ derivatives possible,[2] but until now no synthesis had been achieved. The key was the incorporation of a nitro group at the *para* position of the aryl ring, which shuts down decomposition via electrophilic aromatic substitution. In this presentation the synthesis of NO_2-C_6H_4-$I(OTf)_2$ and what we have initially discovered about its reactivity will be discussed, including direct C-H oxidations which have not previously been reported for hypervalent iodine and catalytic C-H chlorinations and brominations on substrates inert to Cl_2 and Br_2.



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Abstract Number: 56

Visible-light-responsive supramolecular assemblies

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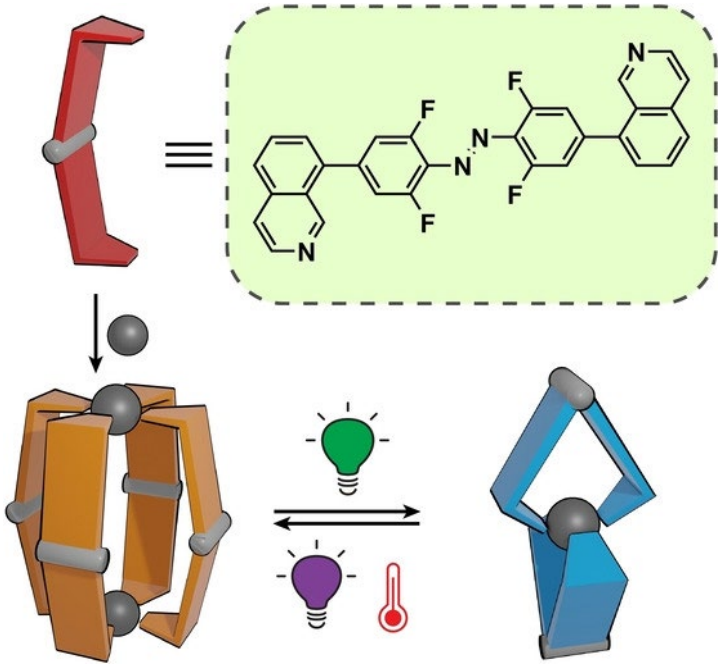
Some of our recent work developing visible-light-responsive molecules and assemblies will be presented. For example, using photoswitchable ligands and palladium(II) ions we self-assembled structures that can be manipulated using visible light to control their composition and recognition properties.[1,2]



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Abstract Number: 57

Catalytic and Mechanistic Studies of Copper(II) Complexes with Tetra-aza Macrocyclic Ligands for Atom Transfer Radical Addition

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Organic synthesis has a great reliance on transition metal catalysts to develop novel compounds with applications in the pharmaceutical and agrichemical industries. The development of new metal catalysed radical chemistry approaches via atom transfer radical polymerization (ATRP) and atom transfer radical addition (ATRA) has emerged as an excellent technique to solve long-standing organic synthetic challenges.[1]

To date, our group has studied a number of Cu(II) catalysts bearing polyamine chelating ligands that have high activity for ATRA.[2-4] As a further search for new catalysts we synthesized Cu(II) complexes supported by the pyridyl-containing tetradentate macrocyclic ligands **L1** and **L2** (Figure 1, left). The ligands and Cu complexes were fully characterised. Both complexes in their reduced Cu(I) form are very active in generating organic radicals in an electrocatalytic mechanism. This presentation will discuss how replacing one pyridyl moiety with a methylamino fragment affects the Cu complex structures and their catalytic properties. Furthermore, the intermediate steps involved in the catalytic cycles using cyclic voltammetry simulations and spectroelectrochemical data will be discussed. Analysis of these data will be used to tune the properties of the catalysts which in turn, could potentially impact the reactivity of these complexes in electrochemical organic synthesis in future studies.

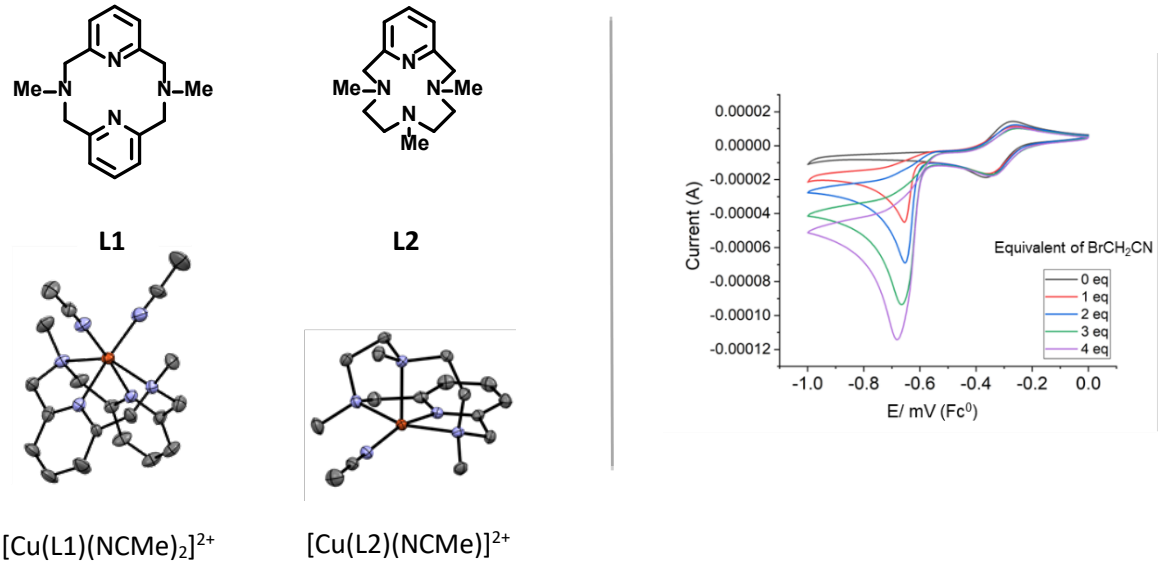

Figure 1: *The macrocyclic ligands **L1** and **L2** with the X-ray crystal structures of their corresponding Cu(II) complexes $[Cu(L1)(NCMe)_2]^{2+}$ and $[Cu(L2)(NCMe)]^{2+}$ (left), and cyclic voltammetry of the sequential*

addition of stoichiometric equivalents of $BrCH_2CN$ to 1mM $[Cu(L1)(NCMe)_2]^{2+}$ (MeCN, 0.1 Et_4NClO_4 at 100 mV s^{-1} scan rate) (right).

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Abstract Number: 60

Imaging the structural organization of chemical elements in growth cones of developing hippocampal neurons

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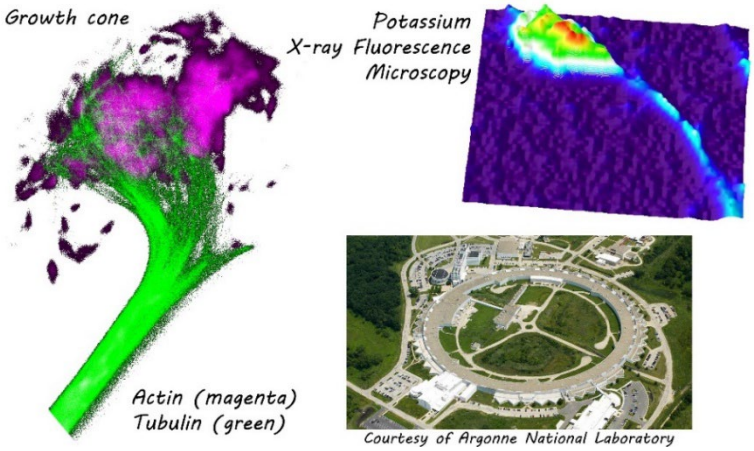
During neurodevelopment, neurons form growth cones, F-actin rich extensions located at the distal end of the neurites. Growth cones allow dendrites and axons to build synaptic connections through a process of neurite guidance whose mechanisms have not been fully elucidated. Calcium is an important element in this process by inducing F-actin reorganization. We hypothesized that other biologically active elements might be involved in the growth cone-mediated neurite guidance mechanisms. We performed super resolution and confocal microscopy of F-actin, followed by synchrotron X-ray fluorescence microscopy of phosphorous, sulfur, chlorine, potassium, calcium, iron and zinc on growth cones from primary rat hippocampal neurons[1]. We identified two main patterns of element organization. First, active growth cones presenting an asymmetric distribution of Ca co-localized with the cytoskeleton protein F-actin. In active growth cones, we found that the distributions of P, S, Cl, K, and Zn are correlated with Ca. This correlation is lost in the second pattern, quiescent growth cones, exhibiting a spread elemental distribution. These results suggest that Ca is not the only element required in the F-actin rich active regions of growth cones. In addition, highly concentrated Fe spots of submicrometer size were observed in calcium-rich areas of active growth cones. These results reveal the need for biological active elements in growth cones during neural development and may help explain why early life deficiencies of elements, such as Fe or Zn, induce learning and memory deficits in children.



Biological active metals are required in growth cones from developing neurons as revealed by synchrotron X-ray fluorescence nanoimaging.

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Abstract Number: 62

Expanding the palette of reactive-printed metal-organic frameworks

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We recently reported the first reactive extrusion printing (REP) method to simultaneously crystallise and deposit films of the iconic metal-organic framework HKUST-1 directly onto surfaces from copper acetate and trimesic acid.[1] This was achieved without any fabrication steps encountered with lithographic methods or the need for binders or surfactants or other additives. REP is distinct from existing printing methods involving preformed MOF particles in pastes, inks, gums or doughs. These methods are mainly concerned with shaping monolithic structures to obtain mechanical properties that may allow industrial implementation. REP has inherent benefits for MOF films of being an on-demand positioning and patterning technology, as shown schematically in Figure 1(a).

We have now expanded the palette of REP to another iconic MOF, ZIF-8. In this talk, I will present our results preparing micron-thick films of ZIFs directly onto modified glass substrates. During our study we encountered an interesting example of phase selectivity and I will describe how phase selection between ZIF-8 and ZIF-L can be achieved with control under REP conditions. The method produced high-quality nanoparticulate ZIF-8 (see Figure 1(b)) with good dispersity and porosity.

Our results suggest that REP may be useful for depositing many other discrete and polymeric materials in films.

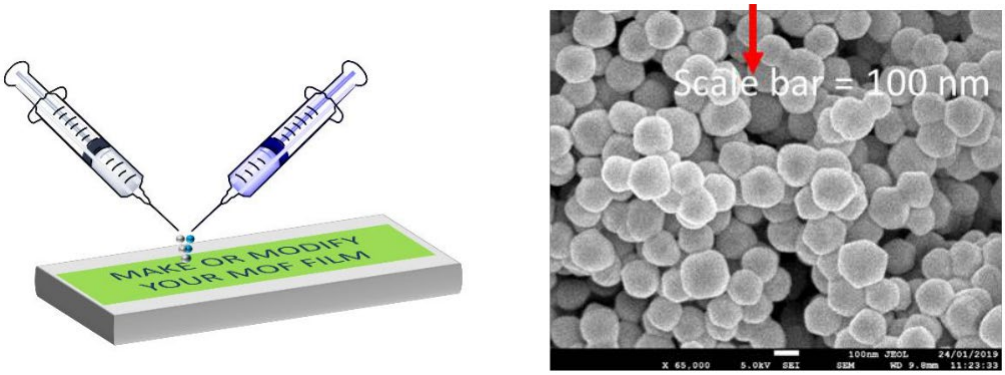

Figure 1(a) A schematic representation of the REP process; **(b)** A SEM micrograph of ZIF-8 particles produced via REP.

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Abstract Number: 63

A Chugaev-Type Dicarbene Ru(II) Photocage: Photophysics and Hydrazine Release

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Photorelease of ligands/small molecules from Ru(II) polypyridyl complexes has been gaining increasing attention, towards the goal of photoactivated chemotherapy.[1-2] In most complexes, photorelease occurs due to thermal population of dissociative ligand-field (^{3}LF) states from photogenerated non-dissociative metal-to-ligand charge-transfer (^{3}MLCT) states.[3]
In this presentation, I will discuss a Chugaev-type dicarbene Ru(II) photocage that releases hydrazine directly from the ^{3}MLCT state to form the corresponding bis(isocyanide) complex. The dicarbene complex can be regenerated by addition of hydrazine across the isocyanide ligands. The photophysics of this complex have been investigated using electrochemistry, optical spectroscopies and 2p4d resonant inelastic x-ray scattering at the Ru L_3 edge.

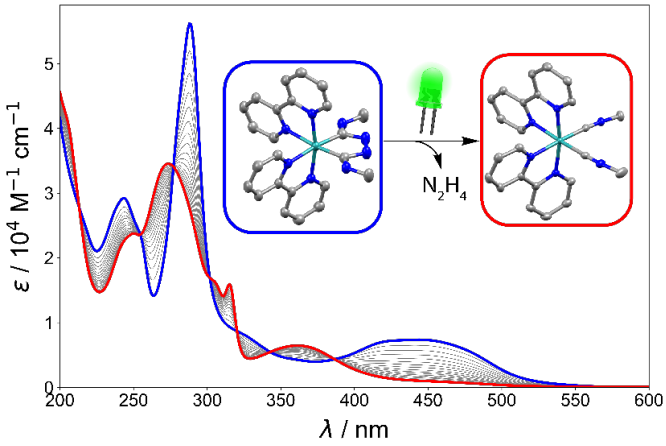

Figure 2. UV-vis spectral changes upon hydrazine photorelease from a Chugaev-type dicarbene Ru(II) photocage

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Abstract Number: 66

Bacterial Transcriptional Regulation by Monomeric Iron-Sulfur Proteins

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The WhiB-Like (Wbl) proteins are a family of unique iron-sulfur transcriptional regulators exclusively found in Actinobacteria, including *Mycobacterium tuberculosis* (*M. tuberculosis*). The seven members of WhiB-Like proteins (WhiB1-7) in *Mtb* play crucial roles in various biological processes, such as cell development, redox stress response and antibiotic resistance. Despite their significance to health and disease, the underlying mechanisms of action of Wbl proteins remained mysterious until most recently. *Mtb* Wbl proteins function as a monomer in the holo-form, distinct from all other dimeric Fe-S regulators characterized to date. They interact with region 4 of the primary sigma factor (σ^{A}_{4}) in the RNA polymerase, a common anchor of transcription activators. By applying structural and biochemical approaches, we have revealed the unusually tight interaction between WhiB1 and σ^{A}_{4} distinct from previously characterized σ^{A}_{4}-dependent transcription activators and thus provides critical evidence for a new bacterial mechanism of transcription regulated by WhiB1 (Wan, Nucleic Acids Res, 2020). Recently we have also determined the crystal structure of WhiB3 and WhiB7 in complex with both σ^{A}_{4} and DNA (Wan, Mol Cell, 2021; Wan, under the review). These structures show how Wbl proteins regulate gene expression by interacting with both σ^{A}_{4} and the subclass-specific DNA binding motif. By combining comparative structural analysis of the high-resolution σ^{A}_{4} -bound Wbl structures with the molecular and biochemical approaches, we have identified the structural basis of functional divergence between the three distinct subclasses of Wbl proteins in *Mtb*. The information gained in our research offers unique insights into the mechanistic understanding of redox-sensing, intrinsic antibiotic resistance in *Mtb*, and provides the structural basis for improving existing anti-tuberculosis therapies and discovering new antimycobacterial drugs.

Abstract Number: 67

Enzyme mediated assembly of hydroxamate macrocyclic chelators with a chemical handle.

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Immuno-positron emission tomography (immuno-PET) is a diagnostic technique used to image cancer. ^{89}Zr is a radiometal favoured for immuno-PET, although pre-clinical agents suggest a need to improve complex stability.[1] Macrocyclic chelators facilitating octadentate Zr(IV) coordination are attractive clinical agents, with an ideal agent also containing a chemical handle for conjugation to a targeting vector. Access to hydroxamate macrocyclic chelators such as $DFOT_1$ has been difficult due to multi-step syntheses.[2] Bacterial species such as *Erwinia amylovora* and *Salinispora tropica* enzymatically synthesize these hydroxamate macrocyclic chelators through the enzyme cluster DesABCD.[3] DesD the final enzyme in the DesABCD cluster, oligomerizes and macrocyclizes the monomeric substrates.[4] This molecular machine could be used to leverage macrocyclic chelator synthesis. This project aims to use DesD to incorporate non-native substrates bearing a chemical handle to generate hydroxamate macrocyclic chelators.

DesD is known to accept analogues of the native substrate *N*-hydroxy-*N*-succinylcadaverine (HSC) (Fig 1).[4] We are evaluating the potential of DesD to generate chelators with a chemical handle by using new HSC analogues. We are examining the chelator profile of DesD when incubated with *N*-hydroxy-*N*-3-hydroxy-3-methyl-glutaryl-cadaverine (HMG) or *N*-hydroxy-*N*-aspartylcadaverine (HDC) (Fig 1.).

This approach could deliver biocombinatorial libraries of macrocyclic chelators from a small substrate pool and demonstrates the potential for this system as a synthetic and discovery tool.

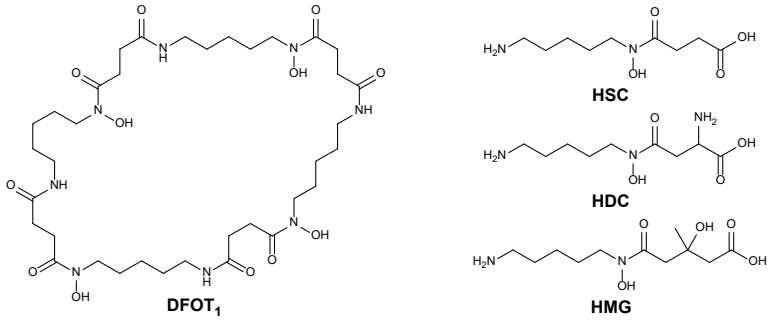

Figure 1: Chemical structures of hydroxamate macrocyclic chelator $DFOT_1$ and the native DesD substrate *N*-hydroxy-*N*-succinylcadaverine (HSC) and non-native substrates *N*-hydroxy-*N*-3-hydroxy-3-methyl-glutaryl-cadaverine (HMG), *N*-hydroxy-*N*-aspartylcadaverine (HDC).

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Abstract Number: 68

Photoactivated diazido platinum complexes for cancer therapy

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Diazido Pt(IV) complexes with the general formula $[Pt(N_3)_2(L_1)(L_2)(OR_1)(OR_2)]$ are a new generation of anticancer prodrugs designed for use in photoactivated chemotherapy. These complexes exhibit high dark stability and promising photocytotoxicity circumventing cisplatin resistance. Upon irradiation, they release anticancer active Pt(II) species, azidyl radicals and ROS, which interact with biomolecules and therefore affect cellular components and pathways. The potencies of these complexes are significantly affected by the derivatisation of the axial ligand OR. Conjugation with cancer-targeting vectors, anticancer-active fragments, and light antennae alter the cellular accumulation, reduction potential, ROS generation, activation wavelength, and photocytotoxicity. Diazido Pt(IV) complexes represent a series of promising anticancer prodrugs owing to their novel mechanism of action which differs from that of classical cisplatin and its analogues. Their diverse structures allow modification of drug-like properties.

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Abstract Number: 77

Probing Oxidant Effects on Superoxide Dismutase 1 (SOD1) Oligomeric States in Live Cells Using Single-Molecule Fluorescence Anisotropy

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The protein Cu/Zn superoxide dismutase (SOD1) is known to function as a dimer, but its concentration in cells (~50 □M) and the dimerization constant (K_d of 500 □M) results suggest that it exists in a monomer-dimer equilibrium. It is unclear how the oligomeric state of SOD1 changes when cells are initially exposed to high levels of extracellular oxidative stress. To address this problem, we introduced single-molecule fluorescence anisotropy (smFA) assay to explore SOD1 oligomeric states in live COS7 cells. smFA specifically probes the fluorescence polarization changes caused by molecular rotations where the fast-rotating molecules (either due to smaller hydrodynamic volume or less viscous environments) deteriorate the emission polarization and thus lowers anisotropy. After validating that smFA is effective in distinguishing monomeric and dimeric fluorescence proteins, we overexpressed SOD1 in live COS7 cells and investigated how its oligomeric state changes under basal, 2 h, and 24 h 100 □M H_2O_2 treatments. We found that treating cells with H_2O_2 promotes SOD1 dimerization and decrease cellular matrix viscosity in 2 h. Interestingly, prolonged H_2O_2 treatments show similar results as the basal conditions, indicating cells return to a new steady state similar to the basal state after 24 h, despite the presence of H_2O_2. Our results demonstrate that SOD1 changes its oligomeric state equilibrium in response to extracellular oxidative stresses. smFA will open new opportunities to explore the relationship between the SOD1 oligomer state and its H_2O_2-based signaling and transcription regulation roles.

Abstract Number: 81

Electrochemical CO_2 and Proton Reactivities of High-Valent W(IV)-Oxo Bis(dithiolene) and Low-Valent Co(II) Complexes

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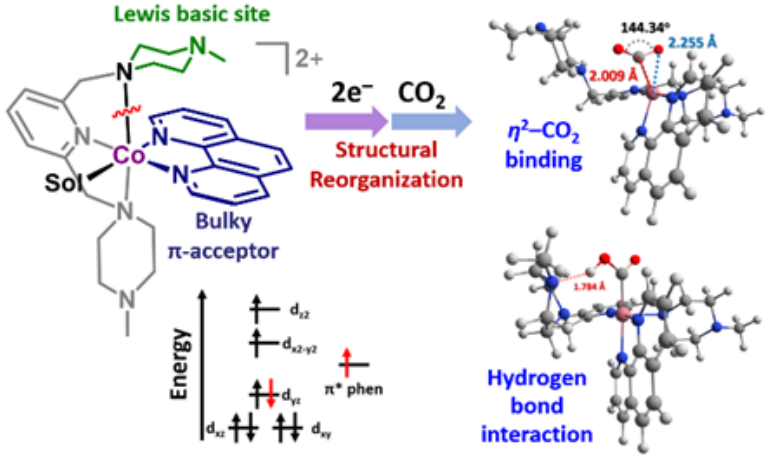
Main Similar to W-FDH active sites, the CO_2 and proton reactivities of W-oxo bis(dithiolene) complexes have obtained synthetic and biochemical research interests. The enzyme facilitates a reversible reaction between formate/CO_2 ($HCO_2^- \rightleftarrows CO_2 + H^+ + 2e^-$); thus, the study of synthetic analogs can provide an insightful understanding of the reactivity at the active site. The W-FDH active site has a high-valent W(IV) center coordinated by equatorial bis-dithiolene and axial chalcogenide (O or S) ligands. The dithiolene structure plays a role as an electron sink to accept/donate electrons from/to the metal ions while stabilizing the high valent reaction core, and the axial ligand determines the reactivity with substrates. This talk will discuss the current understanding of the (electro)chemical reactivity of bis(dithiolene) W-oxo complexes. In another part, we will compare the (electro)chemical reactivity of a low-valent Co(II) complex with CO_2 and proton. Electron input increases the nucleophilicity of a metal center and induces structural reorganization of coordination geometry, making a highly reactive metal site. An intrinsic property of a central metal and a ligand identity affect the CO_2 reaction pattern and proton reaction pathways. The comparative research results provide helpful information on the different (electro)chemical reactivities of the high-valent W and the low-valent Co complexes.



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Abstract Number: 82

Reactivity of molybdenum dependent enzymes and dithiolene bearing models thereof – substrate modulations, biomimetic and bioinspired methodologies

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The molybdenum (and tungsten) dependent enzymes, except for nitrogenase all bear one common structural motif: the molybdopterin ligand (see Figure).[1-2] The reactions they catalyse are oxygen atom transfer (OAT) and hydroxylations (OAT into a C–H bond) while water is the source or sink of the transferred oxygen atom. The back reactions are two proton coupled electron transfers to, e.g. NAD^+ or similar. Some enzymes are thought to be exceptional in this sense as they operate via distinct mechanisms. One example is the formate dehydrogenase (FDH) which catalyses the reversible oxidation of formate to CO_2 in a mechanism that was accepted to be a hydride transfer from formate to the active site. Recently we, in very close cooperation with the Leimkühler lab, have shown, that it is in fact also a common OAT that takes place.[3] This finding has enormous implications for the respective model chemistry.

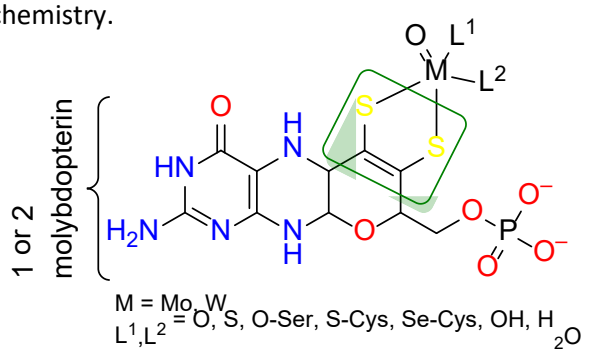

Figure 1: The generalized active site structures of molybdenum and tungsten dependent enzymes.

Dithiolene ligands, a class to which molybdopterin belongs (see boxed in atoms), are non-innocent ligands which may in some cases directly participate in, and in others tune the redox activity of their complexes. This leads to some unusual behaviour in reactions and electrochemistry, which is typically not easy to decipher. We have developed a method with which it is possible to carry out and record, essentially *in operando*, UV-vis and IR-spectroelectrochemistry and to decompose the respective cumulative spectra into pure component spectra.[4] With the support through DFT computations it is then possible to also characterize transient and non-isolable species. One particularly notable example, the complexes of which also exhibit ligand-ligand cooperativity, will be discussed.

Acknowledgements
Generous financial support by the DFG (SCHU 1480/4-2) and the ERC (project MocoModels, 281257) is gratefully acknowledged.

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Abstract Number: 83

The role of a G3E metallochaperone revealed from the metalation of vitamin B12 with cobalt

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The metalation of vitamin B12 with Co^{II} follows either of two pathways: In the 'anaerobic' (early Co^{II} insertion) pathway Co^{II} is incorporated into the B12-precursor sirohydrochlorin (SHC) by the chelatase CbiK while in the 'aerobic' (late Co^{II} insertion) pathway Co^{II} is incorporated into the B12-precursor hydrogenobyrinic acid a,c-diamide (HBAD) by the chelatase CobNST. Intriguingly, the late insertion pathway uses a Co^{II} metallochaperone (the G3E GTPase CobW) but the early insertion pathway does not. Here we find that Co^{II} transfer from the cytosol to SHC-CbiK follows a favourable thermodynamic gradient but that there is a highly unfavourable thermodynamic gradient for Co^{II} transfer from the cytosol to HBAD-CobNST, thus explaining the need for a metallochaperone. Co^{II} transfer from the cytosol to the CobW metallochaperone, in complex with it's cofactor $Mg^{II}GTP$ is highly thermodynamically favourable, enabling Co^{II} acquisition. Although Co^{II} release from $Mg^{II}GTP$-CobW to HBAD-CobNST is thermodynamically unfavourable, analogous Co^{II} release from the hydrolysed metallochaperone complex ($Mg^{II}GDP$-CobW) is favourable. Together, these data reveal two distinctly different thermodynamic pathways for B12 metalation and show how the CobW metallochaperone can overcome an unfavourable thermodynamic gradient for Co^{II} transfer from the cytosol to the CobNST chelatase by pairing GTP-binding with Co^{II}-binding, and then GTP hydrolysis with Co^{II}-donation.

This presentation celebrates the impact and influence of Professor Tony Wedd's research on robust quantification of metal-protein affinities and highlights how these important thermodynamic parameters can be powerfully employed to understand cellular metal handling.

Abstract Number: 84

Heteroleptic Palladium(II) Lantern-shaped Cages: An Ancillary Pairing Approach

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Since their inception,[1] lantern-shaped palladium(II) cages (Figure 1a) have been incredibly popular with metallo-supramolecular chemists, not least because their small cavities resemble those found in molecular machinery such as proteins. A general shortcoming in self-assembled metallo-architectures is their high symmetry, robbing them of the specificity and selectivity of natural analogues. Chemists have sought to address this in lantern-shaped cages, creating lower symmetry structures through sterics, hydrogen bonding, or geometric complementarity.

This has resulted in the reporting of heteroleptic cages, with more than one ligand present, such as the recent report of a tetraleptic cage from Clever and co-workers[2] (Figure 1b). An alternative approach has been to use low symmetry ligands to form low symmetry homoleptic cages, as with Lewis and co-workers[3] (Figure 1c). One could imagine a significant increase in complexity through the formation of heteroleptic cages with low-symmetry ligands (Figure 1d). We report an approach here which integrates different low symmetry ligands with positional and orientational control into lantern-shaped cages, through an ancillary pairings approach. Metal coordination sites come together controllably at the peripheries of the cages through complementarity driven through both denticity and hydrogen bonding (Figure 1e). This represents a substantial advance in the complexity of these structures.

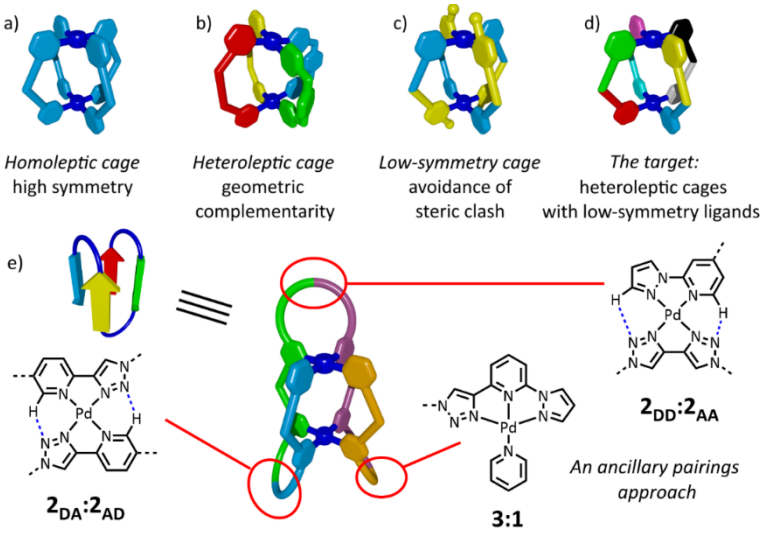

Figure 1 Methods to increase the complexity of lantern shaped cages

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Abstract Number: 85

Preparation of mono- and bis-aminoboranes via controlled hydroboration: synthetic, reactivity and mechanistic insights

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Hydroboration is one of the widely adopted synthetic methodologies for reduction of various unsaturated functional groups such as ketones, aldehydes, imines, etc., while HBpin (pin = pinacolate) and HBcat (cat = catecholate) are arguably the most used reagents in these transformations. However, after the reactions are complete, the boron reagents are normally sacrificed (e.g. via hydrolysis) to yield free alcohols, imines, etc. In our recent work (Figure 1) we have shown that controlled hydroboration of imines with a source of BH_3 (i.e. Me_2S-BH_3) could be used to form a series of mono-aminoboranes ($(R_2N)BH_2$) and bis-aminoboranes ($(R_2N)_2BH$).[1] The key synthetic step in the overall procedure appeared to be the isolation of imine-BH_3 adducts. During the synthetic and subsequent reactivity studies of these boron-containing compounds we have made several unique observations that were directly related to the mechanism of not only hydroboration but also reductive amination transformations.

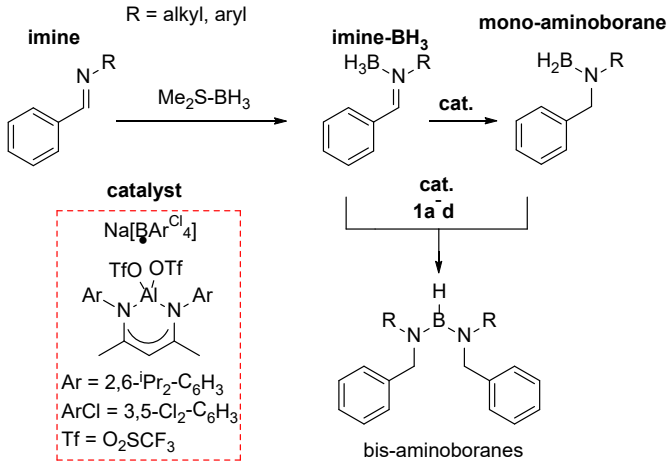

Figure 1. General synthetic methodology for the preparation of mono- and bis-aminoboranes via controlled hydroboration

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Abstract Number: 87

Al doping $SrTiO_3$ to enhance photocatalysis: the impact of doping density

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Strontium titanate ($SrTiO_3$), an ABO_3 perovskite metal oxide, is the current benchmark water-splitting photocatalyst with recent reports showing ~100% quantum efficiency (with 365 nm irradiation).[1-2] A major strategy to enhance photocatalytic performance of $SrTiO_3$ is aliovalent doping in which Al^{3+} is doped into the B site to replace Ti^{4+}. After doping with Al^{3+}, Ti^{4+} no longer self-reduces to Ti^{3+} and photocatalytic efficiency improves >100 fold.[3]

This presentation will investigate the effect of Al doping density on the photocatalytic breakdown of organic pollutants. $SrTiO_3$ was synthesised by the solid-state reaction of TiO_2 and $SrCO_3$. The obtained $SrTiO_3$ was then doped with controlled amounts of Al via a $SrCl_2$ flux-mediated reaction. The prepared photocatalysts were characterised with UV-Vis diffuse reflectance spectroscopy, XRD, SEM, Raman spectroscopy, and high-angle annular dark field (HAADF) STEM with energy-dispersive X-ray spectroscopy (EDS) and electron energy loss (EELS) mapping.

Photocatalytic performance was determined by the breakdown of an anionic organic test molecule (4-[(4-dimethylamino)phenylazo]benzenesulfonate) under irradiation with 365 nm light. It was found the degree of Al doping made a significant difference to photocatalytic degradation rate with the sample containing 1 mol% Al having the highest performance.

EDS mapping at the atomic scale was used to determine the location of Al doped into the SrTiO3 nanoparticle crystals. It was observed that at higher doping concentrations the Al forms an Al rich shell which is likely to restrict photocatalysis at the nanoparticle surface.

These findings are expected to be transferrable across all ABO_3 perovskite photocatalysts.

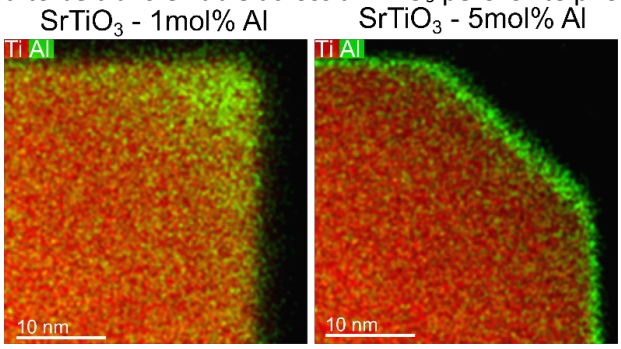

Figure 1. EDS elemental map of SrTiO3 doped with (left) 1 mol% and (right) 5 mol% Al.

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Abstract Number: 88

Bioorthogonal complex functionalization via iClick reaction: A versatile tool using luminophores and carrier groups

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The development of "click" reactions, including copper-catalyzed azide-alkyne cycloaddition (CuAAC),[1] has been crucial in enabling the synthesis of small molecules and bio(macro)molecule conjugates. In contrast, inorganic click reaction ("iClick) has evolved a catalyst-free cycloaddition reaction that takes place in the inner coordination sphere of a metal-azido complex with a dipolarophilic C≡X compound (where X = C, N), leading to the formation of metal triazolato complexes.[2]

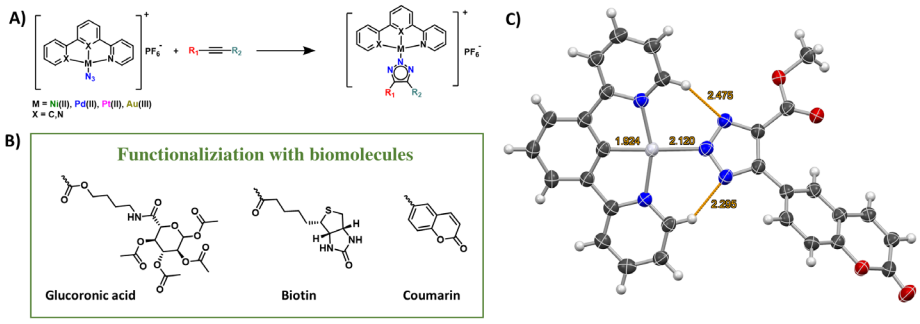

Figure 3: (A) iClick reaction monitored by ^{1}H NMR spectroscopy with different functionalized alkyne models (B) Biorelevant small molecules as carrier groups attached to metal complex via iClick reaction tuning their properties (C) Crystal structure of luminescent coumarin functionalized Pt(II) complex.

The following contribution offers a comprehensive model study examining the reactivity of square planar metal azido complexes (M = Ni(II), Pd(II), Pt(II), Au(III)) with functionalized terminal and internal alkynes R C≡C-R'. By analysing structural and electronic preferences of the reaction with kinetic data, we were able to highlight a general trend in reactivity. Additionally, we demonstrated the ability to modify these complexes through the attachment of alkynes to biorelevant small molecules such as coumarin, biotin, and sugars. Through this approach, we provide systematic insights into the behaviour of these metal complexes in the presence of modified alkynes and expand upon the potential for the functionalization of these complexes in Inorganic Chemical Biology.

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Abstract Number: 93

Developing self-assembled palladium(II)-based supramolecular architectures for orthogonal, stimuli-responsive guest recognition

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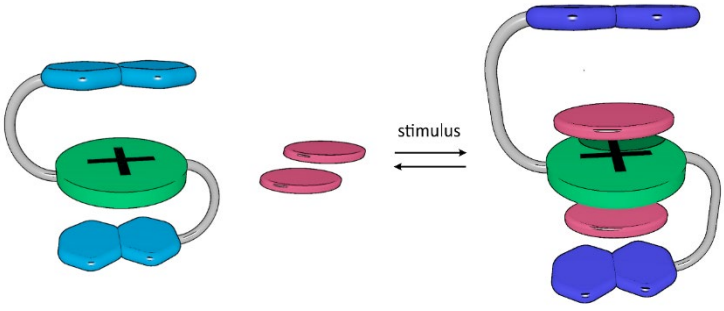
The capacity for self-assembled metallo-supramolecular architectures to interact with guests or substrates drives much of the interest in supramolecular systems. The ability to turn the binding event 'on' or 'off' is even more desirable as it would allow for greater control in self-assembly. Concentration and temperature have frequently been employed as a way to switch between self-assembled structures but have limited practical applications due to the sheer magnitude of systemic perturbation required for switching.[1,2,3]

Instead, we look to incorporate switchable functional groups into flexible systems to access biomimetic, stimuli-responsive molecular switches. To establish a practical method to do so, we have developed a flexible, self-assembled system capable of switchable molecular recognition of guests. Under standard conditions, π- π interactions exist between the aromatic tethers (Figure, blue) and the cationic panel (Figure, green) where the metal ion coordinates to each ligand. This results in self-recognition which occludes the cationic panel from the bulk solvent, and impairs the recognition of guests. By incorporating an additional coordination site into the aromatic tether, a second coordination event can occur as the metal-ligand stoichiometry is altered. The result is the production of a macrocycle in which the aromatic tethers and cationic panel have been separated such that self-recognition is disrupted. A similar approach can be used by instead incorporating a charge-alterable group into the aromatic tether. With the addition of acid, these groups acquire a positive charge which will result in repulsion and in turn separation between the aromatic tether and cationic panel. In either case the extent of self-recognition can be controlled to allow for stimuli-responsive molecular recognition of a range of guests. The two systems can even be combined and interact with guests controllably, reversibly and with a degree of orthogonal selectivity.



Cartoon representation of a generalized system capable of stimuli-responsive molecular recognition of guests

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Abstract Number: 94

Structural and functional analysis of heme-containing oxygen sensor protein HemAT in chemotaxis regulatory system

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Aerotaxis is a typical biological signal transduction system that consists of a signal transducer protein (MCP), CheA, CheY, and other Che proteins. Signal transducer proteins, sometimes called as MCPs (methyl-accepting chemotoxis proteins), bind a repellant or attractant in their sensor domain. Many chemical and physical stimuli act as a repellant or attractant, among which molecular oxygen is a typical gaseous signaling molecule. HemAT is a MCP responsible for aerotaxis control, which consists of two domains, the sensor domain and the signaling domain. Though the sensor domain of HemAT shows structural homology to myoglobin, it has a different heme environmental structure in the distal heme pocket from myoglobin. In the case of myoglobin, a distal His forms a hydrogen bond with the heme-bound oxygen to stabilize the heme-oxygen complex. However, there is no distal His in HemAT, in which a Thr is involved in the formation of a hydrogen bonding network upon oxygen binding to HemAT.

In this work, we have studied the molecular mechanisms of O_2 sensing and signal transduction of HemAT and HemAT/CheA/CheW complex based on the results of X-ray crystallography and cryo-electron microscopy (cyro-EM). We have determined the crystal structures of ferric-, ferrous (deoxy)-, and O_2-bound (oxy)-forms of the sensor domain of HemAT from *Bacillus smithii* (BsmHemAT) (Fig.1 and Fig.2). We will discuss the molecular mechanisms of O_2 sensing of HemAT by comparing these structures. We have also carried out cryo-EM single particle analysis to determine the structure of HemAT/CheA/CheW complex, which revealed that BsmHemAT, CheA, and CheW formed the complex in 2:1:1 ratio.

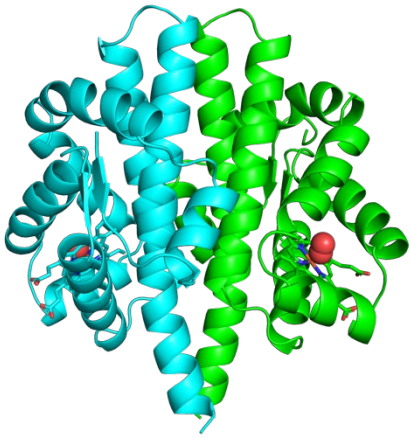

Fig 1. The overall structure of O_2-bound form of BsmHemAT (sensor domain)

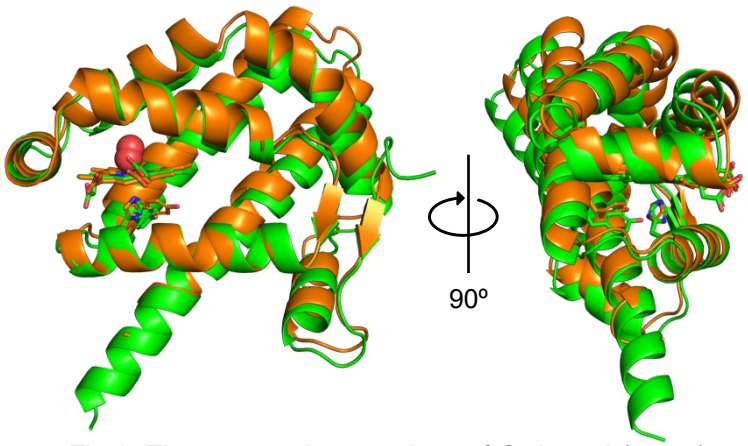

Fig 2. The structural comparison of O_2-bound (green) and reduced (orange) forms in BsmHemAT (sensor domain)

Abstract Number: 98

Unconventional Platinum(IV) Prodrugs

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Platinum(II) anticancer drugs are reported to be administered in ~ 50% of all chemotherapeutic treatments, despite the significant clinical disadvantages such as acquired resistance, cross-resistance and severe side effects that are to some extent moderated by a cocktail of additional medications. Overcoming these clinical disadvantages required us to create of complexes with inherently different modes of action.[1-3] In this search, we have designed, and developed number of platinum(IV) prodrugs that coordinate bioactive axial ligands onto the platinum(IV) scaffold. Examples, Pt^{IV}PHENSS, Pt^{IV}5MESS and Pt^{IV}56MESS have been characterized using high-performance liquid chromatography, NMR, UV and CD spectroscopy together with electrospray ionization mass spectrometry. The potency in human cancer cell lines has been determined to be almost always superior to cisplatin, oxaliplatin or carboplatin, and comparable with their Pt^{II} congeners, PHENSS, 5MESS and 56MESS they elicit their potency through mitochondrial and cytoskeletal damage.[1]

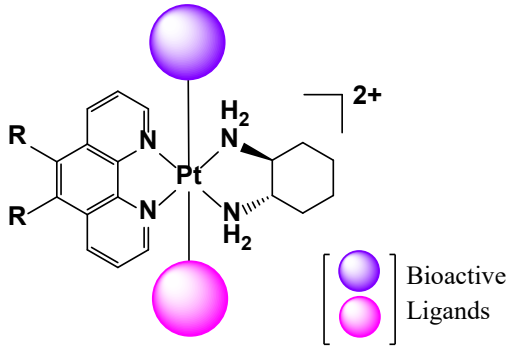

Figure 1 Pt^{IV} scaffold with two bioactive axial ligands

Table 1 Summary of the cytotoxicity of Pt^{IV} complexes

Pt^{IV} complex	**A2780** *Ovarian*	**ADDP*** *Ovarian*	**MCF-7** *Breast*	**HT29** *Colon*	**Du145** *Prostate*	**MIA** *Pancreas*
$[Pt^{IV}56MESS(OH)_2]Cl_2$	0.056 ± 0.0071	0.17 ± 0.12	0.48 ± 0.14	0.036 ±	0.015± 0.003	0.043 ± 0.0025

				0.007 1		
$[Pt^{IV}PHENSS(OH)_2]Cl_2$	0.80 ± 0.084	1.3 ± 0.35	16 ± 4.5	0.71 ± 0.30	0.31 ± 0.092	3.4 ± 2.2
$[Pt^{IV}PHENSS(4\text{-}PhB)(OH)Cl_2$	0.35 ± 0.038	0.30 ± 0.015	0.74 ± 0.15	0.16 ± 0.026	0.35 ± 0.084	0.18 ± 0.0033
cisplatin	1.0 ± 0.1	28 ± 1.7	6.5 ± 0.8	11.3 ± 1.9	1.2 ± 0.1	7.5 ± 1.3
carboplatin	9.2 ± 2.9	>50	>50	>50	14.7 ± 1.2	>50
oxaliplatin	0.16 ± 0.0	0.8 ± 0.1	0.5 ± 0.1	0.9 ± 0.2	2.9 ± 0.4	0.9 ± 0.2

*Platinum resistant clone of A2780 cells.

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Abstract Number: 105

The origin of substrate selectivity in Complex Iron-Sulfur Molydoenzyme (CISM) family: a case study with periplasmic nitrate reductase.

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The Complex Iron-Sulfur Molydoenzyme (CISM) subfamily is the most diverse family of molybdopterin enzymes, and the members of this family catalyze a myriad of reactions that are important in microbial life processes. While members of this family can transform multiple substrates, quantitative information about substrate selectivity is sparse, so the fundamental reasons for substrate selectivity remain unclear. Molybdenum coordination, specifically, the molybdenum coordinating residue, has long been proposed to impact the catalytic activity of the enzyme. This presentation discusses substrate preference and delineates the kinetic underpinning of the differences imposed by protein-based ligands to molybdenum using periplasmic nitrate reductase (Nap) as a vehicle. The catalytic subunit of Nap, i.e., NapA from *Campylobacter jejuni* has been heterologously overexpressed. Variants where the molybdenum coordinating cysteine residue has been replaced with a serine, aspartate or alanine have been produced and characterized. The kinetic properties of these variants are discussed and compared with those of the native enzyme, providing quantitative information to understand the role of the molybdenum coordinating residue in influencing substrate selectivity.

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Abstract Number: 107

Arsenic and Bismuth Binding of Human Metallothionein-3

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Group 5 metals bismuth and arsenic are known to bind to thiolate containing metalloproteins such as metallothioneins (MTs).[1,2] Bismuth is a component of metallodrugs used to treat diseases including gastric ulcers, whereas arsenic is a toxic metal with therapeutic benefits for specialized cases such as leukemia. MTs are physiologically essential cysteine-rich metalloproteins that can be induced by and bind Bi^{3+} and As^{3+}. MT isoform 3 (MT3), the protector of the brain metallome, however, has not been studied in the context of Bi^{3+} and As^{3+} binding.

Electrospray ionization mass spectrometry, UV-visible spectroscopy, and molecular modelling were used to probe the Bi^{3+} and As^{3+} binding pathways to apo-MT3 at pH 7.4 and under acidic conditions. We report the complete set of log Ks for Bi^{3+} binding to MT3 under both acidic conditions and physiological pH conditions. We identify the novel highly cooperative formation of Bi_2MT3 at physiological pH. This structure is identified using Extended X-ray Absorption Fine Structure spectroscopy as a cluster composed of a bridging cysteine where each Bi^{3+} ion is coordinated by three cysteinyl thiolates, with one of the thiolates bridging between the two Bi^{3+} ions. This cluster structure is disrupted by the addition of Zn^{2+}, acidification, and heat, and can be detected with a novel absorption band at 466 nm. This is the first reported presence of bridging cysteines and thus, cluster formation, for a xenobiotic metal in MT. For As^{3+}, the binding pathway to apo-MT3 is identified from both kinetic and equilibrium studies, with a full report on the rate constants and log Ks for As^{3+} binding to apo-MT3. In addition, partially and fully Zn-metalated MT3 was also subjected to As^{3+} binding for analysis of how this metal interacts with MT3 under physiologically relevant conditions.

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Abstract Number: 109

Aromaticity and antiaromaticity in porphyrinoids big and small

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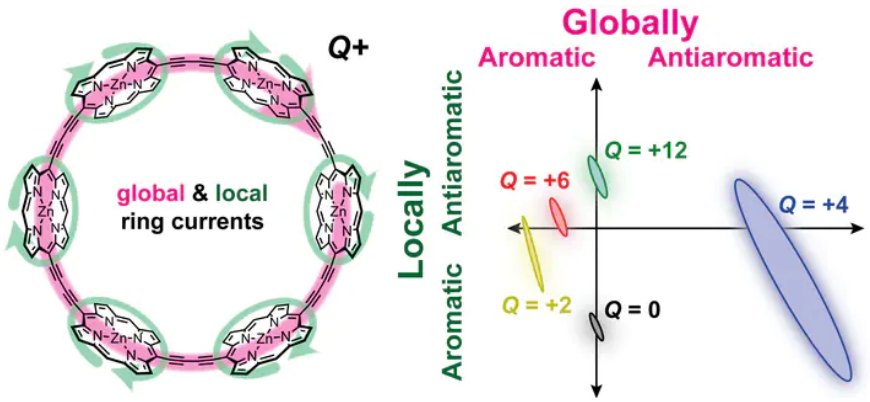
Aromaticity is a foundational concept in chemistry, yet its nature and definition remain hotly contested.[1] Porphyrinoids offer an opportunity to unravel some of the complexities of aromaticity and antiaromaticity, both by changing the structure and size of the porphyrinoid ligand itself, and by introducing the π-conjugated porphyrinoid ligand into larger structures.[2]
We have recently shown that NMR spectroscopy can be used to quantify the strengths of ring currents flowing through different π-conjugated circuits in complex multi-porphyrinoid complexes, revealing the surprising insight that these molecules – some of the biggest (anti)aromatic molecules yet prepared – can exhibit **both** aromatic and antiaromatic features the same time.[2] At the other extreme, we have studied truncated antiaromatic porphyrinoids, and will share insights into the interplaying effects of antiaromaticity and porphyrinoid size on metal-ligand interactions.



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Abstract Number: 110

Pd(II) and Pt(II) triazolato complexes for thioredoxin reductase inhibition (TrxR) – Spectroscopic studies with selenocysteine as a model system

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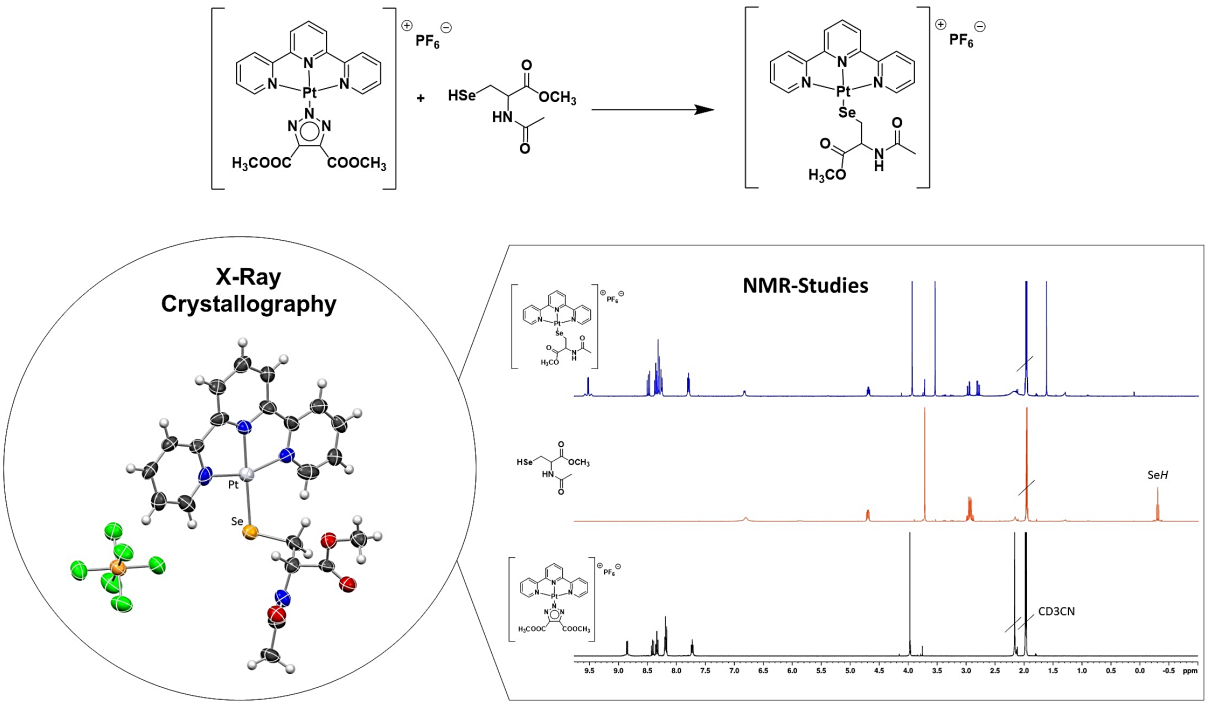
Thioredoxin reductase (TrxR) is one of the few selenium-containing enzymes in the human body. It is overexpressed in a number of cancers and a promising target for drug development. The TrxR active side contains a cysteine and a selenocysteine residue which might be targeted by soft metal centers of the late transition metals [1].



Therefore, [MX(terpy)]PF_6 complexes with M = Pd(II) or Pt(II), terpy = 2,2':6',2''-terpyridine and X = triazolate were synthesised by iClick reaction and their reactivity towards nucleophilic biomolecules was studied [2]. ^{1}H NMR studies of these complexes with *N*- and *C*-protected amino acids (*N*-acetyl-L-cysteine methyl ester, *N*-acetyl-L-selenocysteine methyl ester, *N*-acetyl-histidine methyl ester) and 9-ethylguanine as protein and DNA model compounds were performed to establish potential modes of action. For both metal complexes, a selectivity towards sulfur- and selenium-containing residues was observed, and these adducts were further studied by NMR, ESI MS, and single-crystal X-ray diffraction.

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Abstract Number: 112

Anion-responsive coordination cage hosts

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M_2L_4 coordination cages are a prevalent class of cationic hosts that offer well-defined cavities due to their symmetric arrangement of bis-monodentate ligands. These cage compounds possess an incredibly rich host-guest chemistry that can be exploited for a range of applications, including anion sequestration, drug delivery, and catalysis. Despite this, their highly symmetrical structures, and generally wide cavity apertures can limit their host-guest interactions and their efficacy for the above-mentioned applications. To address this, approaches to increase their structural complexity have recently received significant attention.[1] Some of these focus on introducing geometric constraints, steric hindrance, or asymmetry into one or more ligands as a means to access heteroleptic or low-symmetry structures. However, the preparation of these de-symmetrized coordination cages is often hampered by a significant and unavoidable increase in synthetic efforts.

We are interested in designing easy-to-access homoleptic Pd_2L_4 coordination cages that can adjust their structure and symmetry according to which anions they encapsulate. For example, we recently designed a fluxional Pd_2L_4 cage based on a bullvalene backbone – the archetypical shape-shifting molecule with no permanent carbon-carbon bonds.[2] This cage exists as a highly complex mixture of potentially thousands of interconverting M_2L_4 cage isomers. In the presence of suitable halide guests, this complex mixture significantly simplifies to an all-B M_2L_4 cage species, thus removing a huge fraction of complexity by shutting down other potential isomerization circuits. In another study, we discovered that maximizing the helical twist of Pd_2L_4 cages results in a tightly "wrapped" architecture that also adapts its cavity size when binding anionic guests of different size and shape (K_{exch} of 10^6 M^{-1} for ReO_4^- in MeCN).[3]

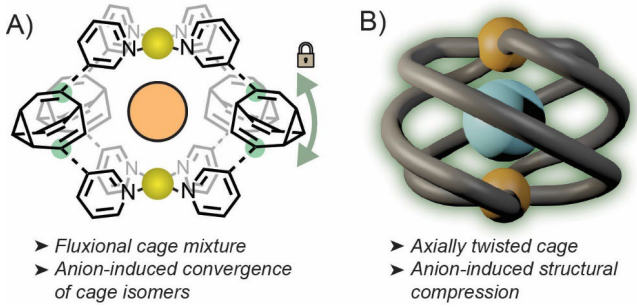

Figure 1: Examples of anion-responsive coordination cages.

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Abstract Number: 113

Modulating the Spin Crossover Behaviour in Dinuclear Fe(III) Complexes via Bridging Bis(dioxolene) ligands

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Molecular-based materials that interconvert between different distinguishable electronic states via application of a stimuli have potential applications in sensors, display devices and molecular electronics. A class of switchable molecules are those that display spin crossover (SCO), which switch between the high spin (HS) and low spin (LS) states typically with change in temperature.[1] Discrete dinuclear SCO complexes can access [LS-LS], [LS-HS], and [HS-HS] states, potentially giving rise to two-step SCO. This would allow for applications in ternary data and complex logic processing.

We have utilized a range of bis(dioxolene) ligands to construct the dinuclear Fe(III) SCO compounds: $[\{Fe^{III}(tpa)\}_2spiro](PF_6)_2$ (**1**), $[\{Fe^{III}(tpa)\}_2Br_4spiro](PF_6)_2$ (**2**) and $[\{Fe^{III}(tpa)\}_2thea](PF_6)_2$ (**3**) (tpa = tris(2-pyridylmethyl)amine, $spiroH_4$ = 3,3,3′,3′-tetramethyl-1,1′-spirobi(indan)-5,5′,6,6′-tetraol, $Br_4spiroH_4$ = 3,3,3′,3′-tetramethyl-1,1′-spirobi(indan)-4,4′,7,7′-tetrabromo-5,5′,6,6′-tetraol, $theaH_4$ = 2,3,6,7-tetrahydroxy-9,10-dimethyl-9,10-dihydro-9,10-ethanoanthracene).[2] Structural, spectroscopic, magnetic, electrochemical and computational analysis show all three undergo varying degrees of [LS-HS] ⇌ [HS-HS] SCO, with the SCO dependent the ligand field strength of the bis(dioxolene).

One-electron oxidation of the bis(dioxolene) ligand in **3** gives compound $[\{Fe^{III}(tpa)\}_2thea](PF_6)_3$ (**4**). The resulting mixed-valence bridging ligand ($thea^{\bullet 3-}$) and increase in ligand field strength converts the partial [LS-HS] ⇌ [HS-HS] SCO displayed by **3** to a two-step SCO transition following [LS-LS] ⇌ [LS-HS] ⇌ [HS-HS] for **4**. A further one-electron oxidation of **4** to $[\{Fe^{III}(tpa)\}_2thea](PF_6)_4$ (**5**) increases the ligand field, such that an incomplete [LS-LS] ⇌ [LS-HS] SCO is observed for **5**.

We have shown that the nature of spin crossover in Fe(III) dinuclear complexes can be tuned by both the class of bis(dioxolene) ligand and the oxidation state of the bis(dioxolene) ligand, opening multiple avenues to achieve multi-step SCO.

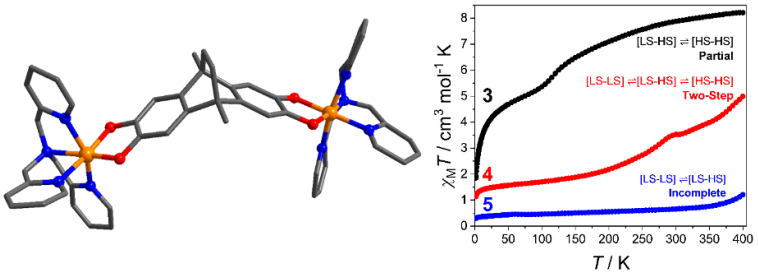

Figure 1: Crystal structure of compound **3** (left) and $\chi_M T$ vs T profile for **3**, **4**, **5** and their associated partial, two-step and incomplete SCO transitions (right).

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Abstract Number: 114

Reduction of Sulfur Dioxide to Sulfur Monoxide by Ferrous Porphyrin

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The reduction of SO_2 to fixed forms of sulfur can address the growing concerns regarding its detrimental effect on health and the environment as well as enable its valorization into valuable chemicals. The naturally occurring heme enzyme sulfite reductase (SiR) is known to reduce SO_2 to H_2S and is an integral part of the global sulfur cycle. However, its action has not yet been mimicked in artificial systems outside of the protein matrix even after several decades of structural elucidation of the enzyme. While the coordination of SO_2 to transition metals is documented, its reduction using molecular catalysts has remained elusive. Herein reduction of SO_2 by iron(II) tetraphenylporphyrin is demonstrated. A combination of spectroscopic data backed up by theoretical calculations indicate that $Fe^{II}TPP$ reduces SO_2 by $2e^-/2H^+$ to form an intermediate $[Fe^{III}–SO]^+$ species, also proposed for SiR, which releases SO. The SO obtained from the chemical reduction of SO_2 could be evidenced in the form of a cheletropic adduct of butadiene resulting in an organic sulfoxide. The reaction proceeds via formation of an initial intermediate which is characterized using EPR and resonance Raman spectroscopy. The presence of 2^{nd} sphere residues that assist in proton transfer mimics the lysine and arginine residues present in the distal site of Sir and accelerates the reaction.

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Abstract Number: 119

Water Harvesting and Purification Using the UiO-66 Metal-Organic Framework: Insights from Classical Molecular Dynamics Simulations

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Climate-change driven extreme weather conditions, population growth, and increasing levels of pollution are making clean water scarcity a compelling challenge of our age. In this scenario, developing cost-effective technologies for water harvesting and purification is a top scientific priority. In this contribution, I will discuss our recent work on the use of the UiO-66 metal-organic framework (MOF) for these applications. We use molecular dynamics (MD) simulations to unravel the molecular mechanism by which this MOF interacts with water and toxic arsenic oxyanions.

Our simulations provide molecular-level insights showing how the pore filling process evolves as more water is loaded into UiO-66 and show that the incorporation of hydrophilic functional groups into the MOF leads to an increase in water loading by facilitating the filling of the octahedral pores. Our MD results also shed light on the diffusion of the toxic arsenic oxyanions through the MOF pores and the role of diffusion vs. chemical interaction with the MOF in the ability of the MOF to remove these toxic oxyanions from water.

Abstract Number: 120

Towards new antibiotics: Compounds containing selenium or silver

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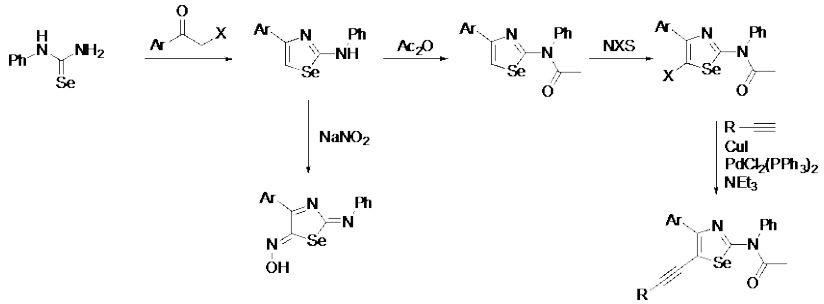
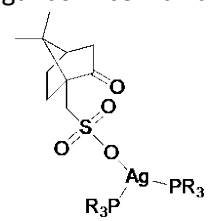
Resistance to current antibiotics is becoming a globally serious problem.[1,2] New structural motifs and substances with different modes of action are urgently needed. As an alternative to organic compounds, inorganic or organometallic species are being investigated as potential next-generation antibiotics.[3,4]
We have contributed to this problem by a systematic investigation of a library of selenium compounds, specifically 2-amino-selenazoles.[5] This class of heterocycles can be prepared by a condensation reaction of a selenourea derivative with an α-haloketone (Scheme 1). A large structural variety is thus accessible through a simple reaction. Furthermore, the heterocycles themselves can be functionalised at various positions allowing introduction of further functionality.



Scheme 1. Synthesis and functionalisation of 2-amino-1,3-selenazoles.

The selenium compounds under investigation were found not to be cytotoxic in the NCI-60 panel of cancer cells and were inactive against Gram-negative bacteria. However, some compounds were highly active (MIC values in the low nM range) in the fungi *C. albicans* and *C. neoformans var. grubii*.

Silver compounds have long been used as antibacterial agents, indeed silver sulfadiazine, used in treatment of burns, is included in the WHO list of essential medicines. Typically, most silver salts are however insoluble in water or other solvents and may precipitate in the presence of halide ions. In an effort to overcome these drawbacks, we developed a family of water-soluble and water-stable silver compounds containing camphorsulfonato ligands in combination with various phosphines (Scheme 2).[6]



Scheme 2. Camphorsulfonato silver complexes with phosphine co-ligands.

One of the silver complexes displayed very high and selective activity (MIC of 6 nM) against *Cryptococcus neoformans*.

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Abstract Number: 121

Cu(I) Binding Properties of Kidney Metallothionein 1A and Brain Metallothionein 3

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Copper is one of many essential metals in life. Many enzymes take advantage of the accessible 1+ and 2+ oxidation states and use this redox activity to carry out various electron transfer reactions, for example in cellular respiration. However, Cu(I) ions can become dangerous to the cell if uncontrolled. Cu-catalyzed Fenton reactions can create reactive oxygen species (ROS) that react with proteins and DNA. This can be avoided by tightly controlling the cellular locations and concentrations of Cu(I) through the use of metal chaperone and metal storage proteins.

The metallothionein (MT) protein family is an essential metal storage protein involved in Cu(I) and Zn(II) homeostasis. All human MTs contain 20 cysteines which are used to form metal-thiolate clusters. *In vivo*, Cu(I) likely binds to both apo and Zn-metallated forms of MT are expected. Relatively little is known about the exact mechanisms of metallothionein *in vivo* with regards to the metal stoichiometry. As a guide, the *in vitro* Cu(I) binding properties have been investigated for both apo MT1A and MT3 as well as Zn_7-MT1A and Zn_7-MT3 by electrospray ionization mass spectrometry (ESI-MS). Room temperature phosphorescence spectroscopy and lifetime measurements were used to probe the clustered environment of the Cu(I) ions. To solve the difficulty of measuring the mixed metal Cu,Zn-MTs caused by the overlapping Cu(I) and Zn(II) naturally abundant isotopes, isotopically pure ^{63}Cu(I) and ^{68}Zn(II) were used allowing for the detection of specific species with the same total number of metals but different Cu:Zn ratios.[1]

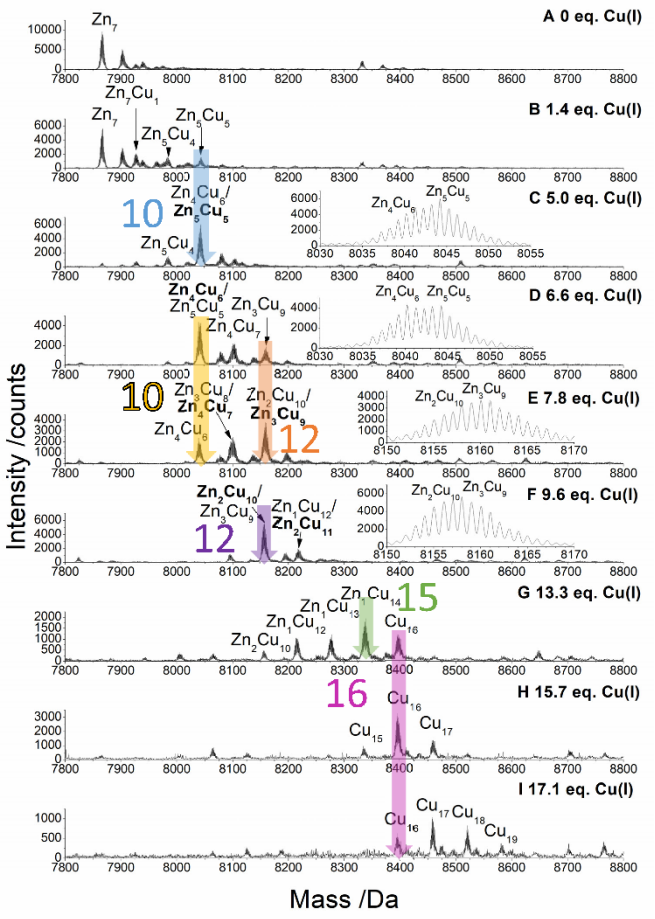

Figure 4 ESI-mass spectral data for the ^{63}Cu(I) titration of $^{68}Zn_7$-MT1A.

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Abstract Number: 122

Rational design of new multifunctional compounds including an organometallic Mn(I) centre: a comparative study with the Re(I) analogues

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Chagas disease (American Trypanosomiasis), produced by the protozoan parasite *Trypanosoma cruzi*, constitutes an overwhelming health issue in Latin America. The lack of an adequate chemotherapy makes it urgent to develop new efficient and not toxic drugs. Our group has contributed to demonstrate that the strategy of hybridization of a metal or organometallic centre and a bioactive organic ligand leads, in many cases, to antiparasitic compounds bearing improved biological properties in respect to the free ligands and affecting multiple parasite targets. In particular, we have recently developed five new multifunctional Re(I) tricarbonyls, *fac*-[$Re^{I}(CO)_3(NN)(CTZ)](PF_6)$, that include two different bioactive ligands with activity against *T. cruzi*: a bidentate 1,10-phenanthroline derivative NN and the monodentate azol Clotrimazole (CTZ). The compounds have been fully physicochemically and biologically characterized[1]. They were more active than the reference antitrypanosomal drug Nifurtimox, showing IC_{50} values in the low micromolar range. Stability in solution, lipophilicity, metallomics in *T. cruzi* (uptake and association to relevant biomolecules) and effect on molecular targets of the free ligands (DNA and CYP51 lanosterol 14-α-demethylase) were studied for the complexes. Based on these results, we recently expanded our research by exploring the potentiality against *T. cruzi* of Mn(I) tricarbonyl analogous compounds and performing a comparative study of both tricarbonyl families. The Mn(I) analogues were synthesized through a stepped procedure (Figure 1) and were fully characterized. Physicochemical (stability in solution, lipophilicity) and biological properties of both families of metal(I) tricarbonyls were compared and discussed to evaluate the potentiality of the new Mn(I) compounds as antitrypanosomal agents.

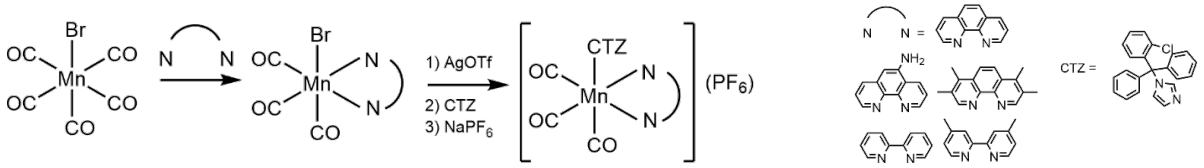

Figure 1: Synthesis scheme of $[Mn(CO)_3(NN)(CTZ)](PF_6)$ compounds

Acknowledgments: Agencia Nacional de Investigación e Innovación (ANII, Uruguay), grants FCE_1_2019_155971 and FCE_1_2021_1_166665. CDM acknowledges ANII, grant POS_FCE_2021_1_1010807.

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Abstract Number: 124

Structural Role of Cadmium and Zinc in Metallothionein Oxidation by Hydrogen Peroxide: The Resilience of Metal–Thiolate Clusters

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Oxidative stress occurs when there is an overabundance of reactive oxygen species (ROS) in a cell and is linked to aging and a variety of diseases such as Alzheimer's, Parkinson's, cardiovascular disease, cancer, and diabetes. The metal-binding protein metallothionein (MT) is thought to play a role in protection due to its high reduced cysteine content. Many studies have shown that MT will oxidize upon exposure to ROS, forming disulfide bonds and subsequently releasing bound metals. However, most studies have focused on displacement of the two-domain fully metalated structures Zn_7MT and Cd_7MT. Partially metalated structures have been largely neglected. In this study, we describe the oxidation and subsequent metal displacement pathway of fully and partially metalated MTs with hydrogen peroxide.[1] The rates of the reactions were monitored using electrospray ionization mass spectrometry (ESI-MS) techniques, which resolved and characterized the individual intermediate $M_x(SH)_yMT$ species (Fig. 1). It was found that the three metals from the M_3S_9 structure in the β-domain were the first to be released from the fully metalated MTs, with the M_4S_{11} cluster staying primarily intact. The Cd(II) in partially metalated Cd(II)-bound MTs rearranged to form a protective Cd_4MT structure upon exposure to the hydrogen peroxide, which did not occur with partially metalated Zn(II)-bound MTs. The results of this study highlight the importance of metal-thiolate structures and metal identity in MT's response to oxidation.

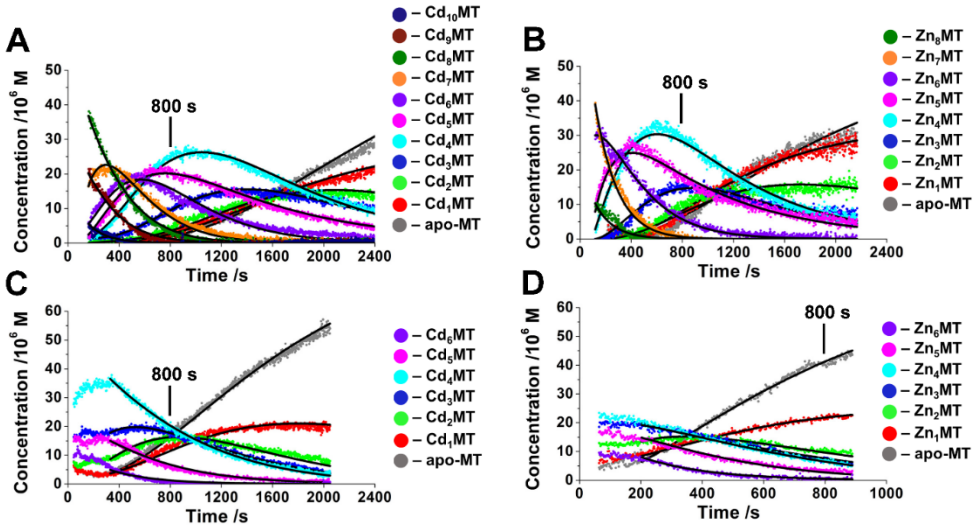

Figure 1. Fitted kinetic traces showing the metal loss over time due to a reaction of (A) 90 μM Cd_7MT, (B) 90 μM Zn_7MT, (C) 90 μM Cd_3MT, or (D) 90 μM Zn_3MT with 3 mM H_2O_2 (150 mol. eq.) at pH 7.4 monitored using ESI-MS. The kinetic traces show the concentration of the individual metallated species over time.[1]

References

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Abstract Number: 127

Multimodal and multivariate approaches to elucidating the inorganic chemistry of biological systems

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Understanding the biochemical composition of cells, organelles and body fluids is essential for uncovering both physiological and pathological processes. This requires the development of chemical tools to complement current imaging and bioanalytical techniques. We are working towards the development of a range of chemical techniques to enhance the understanding of biological systems, including multimodal imaging and sensor arrays for multivariate analysis.

Multimodal imaging is gaining traction in biomedical and clinical studies as it combines the relative advantages of two or more imaging techniques. We are interested in developing multimodal imaging agents to combine fluorescence imaging with additional modalities. For example, we have developed bimodal fluorescence-Raman probes, [1] bimodal fluorescence-X-ray fluorescence (XRF) probes and trimodal fluorescence-Raman-XRF probes. We have applied these probes to study the the chemical composition and distribution of lipid droplets in cells.

Copper is an essential trace metal that participates in various physiological pathways, but imbalanced brain copper content has long been associated with neurodegenerative diseases, such as Alzheimer's disease and Parkinson's disease. Selective copper sensors are useful in studying biological processes,[2] but their use *in vivo* is limited by poor tissue penetration of excitation and emission light. We have developed a dual fluorescence-photoacoustic imaging agent that is selective for Cu(II), and a dual fluorescence-PET imaging agent that accumulates in regions of high copper in the brain.

Cross-reactive sensor arrays coupled with multivariate statistical analysis are particularly useful for studying complex samples such as body fluids. We have developed a fluorescent sensor array for serum platinum levels, which can be used to gain information on the concentration of platinum drugs within clinical serum samples.[3]

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Abstract Number: 128

Synthesis and Characterisation of Fluorescent Novel Pt(II) and Pt(IV) Cyclometallated Complexes with Anticancer Activity.

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Cancer poses a significant threat to global health and new treatments are required to improve prognosis for patients. Previously, unconventional platinum complexes designed to incorporate polypyridyl ligands paired with diaminocyclohexane, have demonstrated anticancer activity in KRAS mutated cells previously thought to be undruggable and have cytotoxicity values up to 100 times better than cisplatin. In this work, these complexes were used as inspiration to design cyclometallated examples, whose fluorescence could be exploited to better understand the mechanism of action of these kinds of platinum drugs. The MTT assay results revealed that the Pt(II) cyclometallated complexes (CMCs) were less cytotoxic than the complexes that inspired them, the cytotoxicity profile is similar to cisplatin. Previously synthesised Pt(IV) complexes are significantly less cytotoxic than their Pt(II) precursors, where the Pt(II) IC50 value is typically 0.33% of the Pt(IV) value. In contrast, the IC50 values of Pt(II) CMCs are 60% of the Pt(IV) value. The CMCs also showed significantly higher selectivity indexes in breast cancer cell lines, MCF-7/ MCF10A. This prompted further investigation into their DNA binding properties, revealing they had good affinity to ctDNA. Their inherent fluorescence was utilised in the calculation of their DNA binding affinity and could be useful in future work. Furthermore, Pt(IV) CMCs were very stable in the presence of both glutathione and ascorbic acid in buffered solution, suggesting that the Pt(IV) complex will make it into the cell intact which may be beneficial in reducing *in vivo* toxicity.

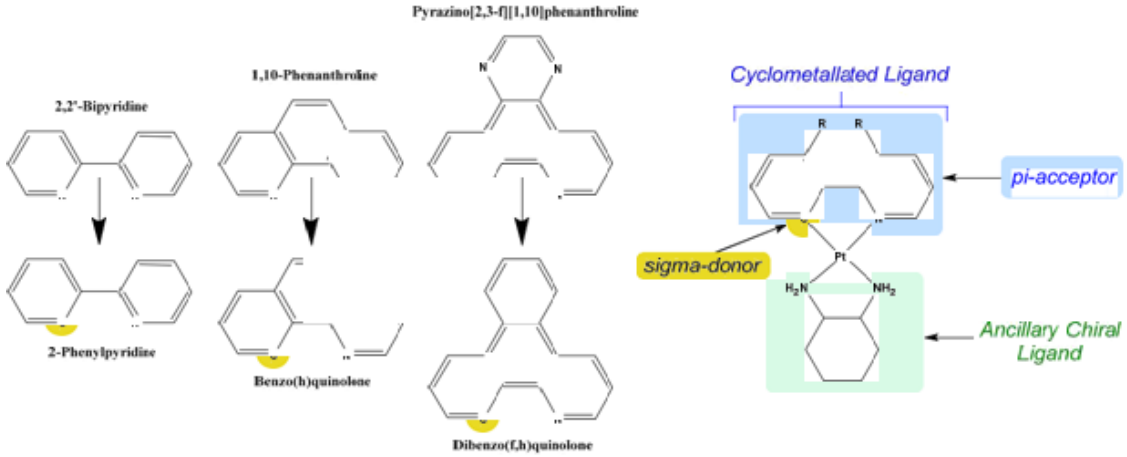

Figure 1: Polypyridal ligands (PL) previously incorporated in $[Pt(PL)(AL)]^{+2}$ complexes[1–3] and the comparable cyclometallated counterpart (CL) (left); and General structure of CMCs where * indicates stereocenter(right).

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Abstract Number: 132

Shining a Light on Chemical Sensors and Stimuli Responsive Materials

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The development of real-time, highly sensitive chemical sensors for the detection of very low analyte concentrations is of importance for monitoring harmful chemicals in the environment. Strategies to enhance the sensitivity and accuracy of sensors can be achieved through the incorporation of lanthanoid ions enabling the detection of low analyte concentrations, and through using a stimuli-switchable motif. By switching between different states of the chemical sensor, enhanced accuracy of detection in complex matrices can be detected.

Metal-Organic Frameworks (MOFs) are crystalline materials containing inorganic nodes bridged by linkers. The high tunability of MOFs enable the systematic modification of pore chemistry and size. Tailored pore environments can be designed, making these materials well-suited to act as chemical sensors and stimuli responsive materials.[1] Reports of lanthanoid MOFs containing a stimuli responsive motif are still relatively scarce in the literature despite the potential they have for enhanced chemical sensing and the development of switchable materials.

This presentation will detail our latest results in the design of chiral sensors and stimuli responsive materials. The chiral sensing properties of two BINOL-based Zn MOF systems will be highlighted[2], with varying degrees of fluorescence quenching. The mechanism of fluorescence quenching and guest position within the framework as elucidated through time resolved fluorescence and computational calculations will be discussed. The switchable and chemical sensing properties of an isostructural series of lanthanoid MOFs containing a redox-active viologen ligand (Figure 1) will also be presented. The reversible one electron reduction of the viologen from its dication to its radical cation state upon exposure to a light and pressure stimulus are elucidated from photoirradiation and high-pressure experiments on the MX1 beamline at the Australian Synchrotron.

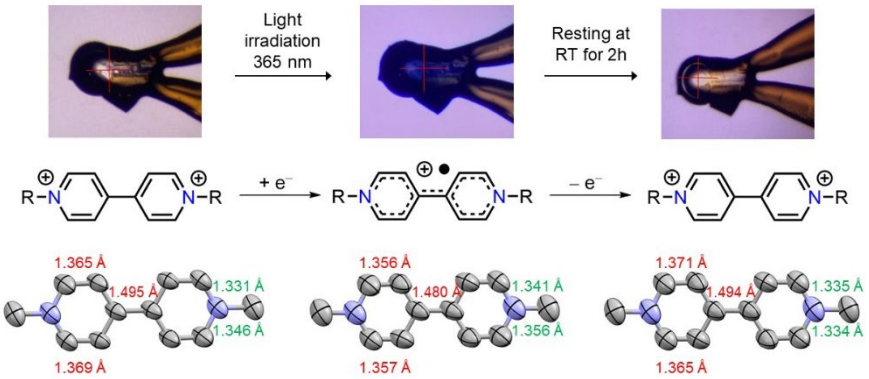

Figure 1. The reversible changes in colour and bond lengths upon irradiation of a single crystal of an Eu(III) viologen containing MOF at 365 nm. A vivid colour change from colorless to blue is observed.

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Abstract Number: 133

Allosteric Regulation of Catalysis in an $[M4L6]^{12-}$ Cage

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Biological systems, such as proteins and enzymes, are unrivalled in their ability to function as catalysts. This is due to the modification of bound substrates within their electrostatic active site and through allostery, the regulatory feedback mechanism of binding. These features are typical of biomolecules, yet remain difficult to incorporate into artificial systems. Here, we report a water-soluble anionic supramolecular cage which possesses two distinctly disparate binding sites: a single electrostatic internal cavity and four coordinative exterior binding pockets. The porous metal-organic architecture follows Michaelis-Menten kinetics and, utilising the inbuilt allosteric functionality, can regulate the rate of binding and catalysis of selective guests up to 650-fold in a controlled manner. Structural factors governing the allosteric functionality are also approximated

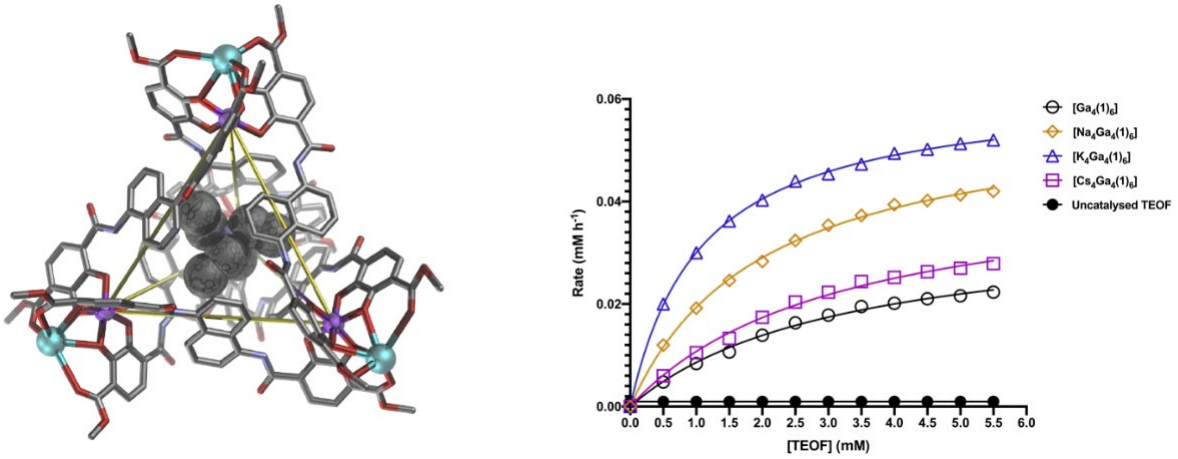

Figure 1: Left: Crystal structures of the [K4M4L6] cage with an encapsulated alkyl ammonium guest. The potassium ions can be readily swapped for other alkali earth metals. **Right:** Michaelis-Menten plots showing the differences in catalytic hydrolysis of the orthoformate substrate

Abstract Number: 135

Extremely Reactive Main Group Metal Complexes Stabilised a Bulky Diamido, Xanthene-Based Ligand

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In 2007, Emslie and co-workers reported the bulky, dianionic, semi-rigid, tridentate ligand [**NON**]$^{2-}$ (Figure 1), which was extensively studied in *f*-block metal chemistry.[1] Over the past 5 years, we have been investigating the use of this ligand in *s*- and *p*-block chemistry, during which we have found that the ligand has some remarkable stabilising properties, allowing isolation of various novel highly reactive main group metal complexes. Some highlights include: the isolation of a range of group 13 nucleophiles (including the first aluminyl anion);[2] a series of isolable group 14-centered radical anions (including the first isolable Sn(I) radical);[3] and a family of extremely reactive anionic group 2 hydrides (Figure 1).[4] Synthesis, characterisation and reactivity of these unusual **NON**-stabilised main group compounds will be discussed.

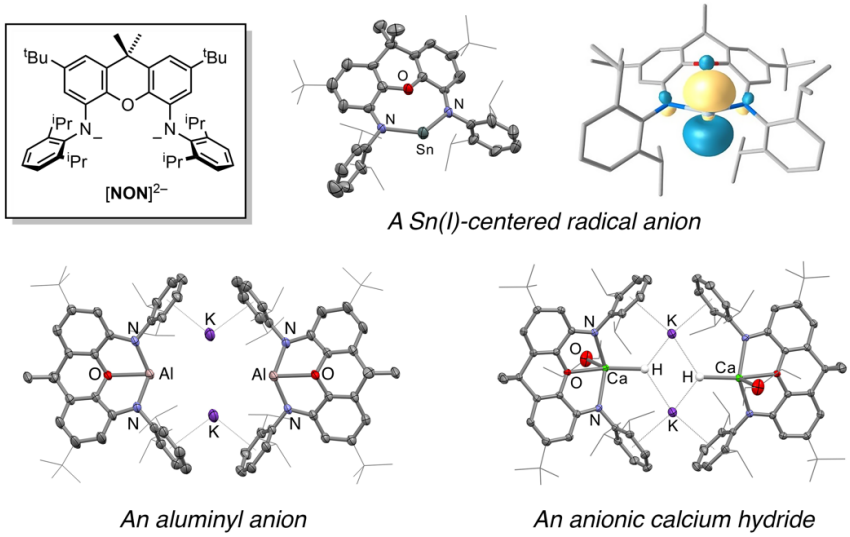

Figure 1. A selection of recently reported main group compounds featuring the [**NON**]$^{2-}$ ligand.

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Abstract Number: 136

Methods to modulate the fluorescence of naphthalimides

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Naphthalimides are attractive small-molecule fluorophores for use in designing chemosensors for biological and cellular applications owing to its high photostability, high quantum yields, and large Stokes' shifts.[1] They are highly tunable intermolecular charge transfer (ICT) probes, with applications in metal sensing, enzyme sensing, and sensors for toxic chemicals.[2] Recently, their synthetic versatility has been increasingly explored, by inputting recognition sites for the desired analyte, organelle-targeting groups, and moieties for fluorescence tuning, onto the naphthalimide scaffold.[3]

Photoinduced electron transfer (PET) is a phenomenon that often results in the quenching of fluorescence. PET quenching occurs when a nearby lone pair electron can relax into the highest occupied molecular orbital (HOMO) of a fluorophore, thus blocking the pathway for the excited electron in the lowest unoccupied molecular orbital (LUMO) from relaxing back to the HOMO, preventing fluorescence. In fluorescent sensors, PET quenching is often incorporated into a design, such that interaction with the desired analyte will inhibit PET quenching, leading to fluorescence. A series of pH-responsive naphthalimide-based sensors have been designed to understand how changes in structure will affect PET quenching (Figure 1).

Förster resonance energy transfer (FRET) occurs when energy is transferred between two fluorophores known as a "FRET pair". The FRET pair consists of a donor and an acceptor joined by a linker. When there is maximum FRET efficiency, the donor is excited and transfers all its energy to the acceptor, which fluoresces, while emission from the donor is not observed. Coumarin-naphthalimide FRET pairs with different linkers have been synthesised to understand how modifying the bridge between the two fluorophores will affect FRET efficiency, which can help illuminate ways of designing ratiometric probes.

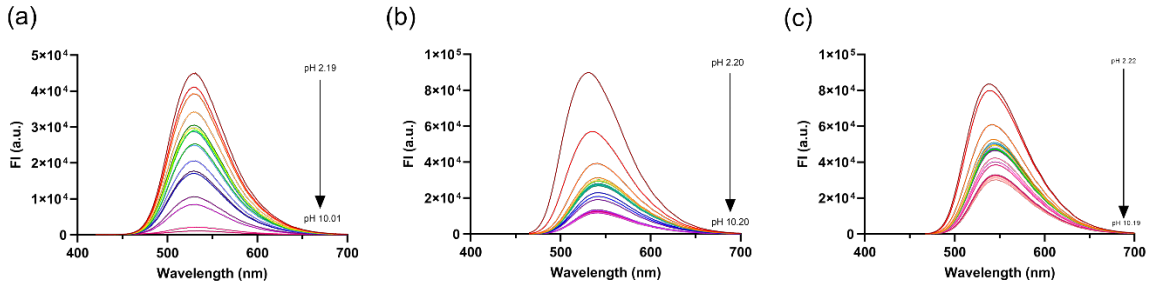

Figure 1: Changes in fluorescent pH response of naphthalimide-based sensors with modified structures.

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Abstract Number: 139

Fluorescence-based Metalloproteomics Approach for Metallobiology: Chromium(III) as a showcase

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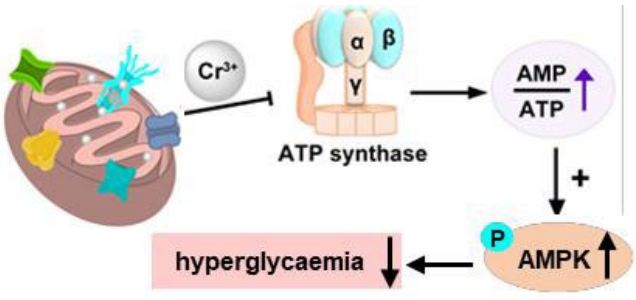
Metal ions play important roles in life processes and are also frequently incoporated into pharmaceuticals. Proteome-wide identification of proteins that bind to a metal or a metallodrug are critial for understanding the roles of metals in biology and medicine as metals or metallodrugs often functionally perturb the biological functions of proteins.[1] Metalloproteomic appraoch is particularly important for metallobiology research.[2] However, it remains to be challenging to track metalloproteomes particularly in live cells as the metal-protein interactions *in vivo* can be weak and even transient. This is the case for chromium(III), a metal ion used as supplements for the treatment of diabetes mellitus. However, the (bio)chemistry and pharmacology of Cr(III) are poorly understood largely owing to the failure to identify Cr(III) molecular targets

We have previously established a fluorescence-based metalloproteomic approach through unique metal chelation-based fluorescence probes, enabling various metalloproteomes to be identified in various prokaryotic and eukaryotic cells including bismuth, gallium, iron, copper/nickel as well as arsenic [2-7]. Here, we synthesized a novel chromium(III) probe (Cr^{3+}-NTA-AC) and visualized Cr(III) proteome in live cell, which is mainly localized in mitochondria. Subsequently we identified seven Cr(III)-binding proteins, which are enriched in ATP synthesis pathway. We further show that Cr(III) binds to ATP synthase at its subunit beta and suppresses ATP synthase activity, resulting in activation of AMPK as well as rescuing mitochondria from hyperglycaemia-induced fragmentation. Such a mode of action of Cr^{3+} in cells also holds true in type II diabetic mice. Through this study, we resolve the long-standing issue on how Cr^{3+} ameliorates hyperglycaemia stress at the molecular level. The methodology we developed provides a toolbox for understanding the role of metals in biology and medicine.



Proposed scheme showing that Cr^{3+} ameliorates hyperglycaemia stress via inhibiting ATP synthase, leading to activation of AMPK

Acknowledgements

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Abstract Number: 141

Shining light on the mechanism of nitroxyl release from photocaged Nhydroxysulfonamides

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There is currently considerable interest in the emerging biological signaling molecule nitroxyl (HNO). The biological and chemical reactivity of HNO is typically quite different from that of its much more well-known redox cousin nitric oxide.1 Furthermore HNO prodrugs show considerable promise in treating congestive heart failure.2 Its potential as a chemotherapeutic drug is also currently being explored.3 In addition to rapidly reacting with biomolecules, HNO rapidly dimerizes in aqueous solution. As a consequence of this, HNO donors – molecules that decompose to generate HNO – are required to explore its diverse reactivity. It has been known for decades that N-hydroxysulfonamides decompose in aqueous solution, to release HNO and sulfinate. However HNO generation from N-hydroxysulfonamides is typically slow and can require alkaline solution conditions. There is an urgent need for systems that generate HNO rapidly, upon demand. Excitation of molecules using light is a powerful technique to transform a stable molecule into an unstable species which subsequently decomposes to release the species of interest. In this presentation an overview of our recent results on the release of HNO from novel photocaged Nhydroxysulfonamides will be presented, with a focus on the wide range of experimental methods combined with computations that we use to elucidate the photodecomposition mechanisms of these complex systems. Interestingly, three pathways of decomposition are observed. The mechanism of photodecomposition is highly dependent on several factors, including the chromophore (photocaging group), the solvent, the protonation state of the parent molecule and the sulfonamide itself.

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Abstract Number: 143

Modulating spin crossover behaviour in nanoporous frameworks by secondary bonding interactions and guest disorder

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Crystal engineering enables the *a priori* design of metal–organic frameworks (MOFs) which, due to their modular construction, are excellent candidates for producing crystalline architectures that are predisposed towards exhibiting certain properties.

Spin crossover (SCO) is an electronic switching phenomenon associated with the thermally-induced shift between the paramagnetic high spin and diamagnetic low spin states of iron(II). The SCO response in MOFs can be tuned by incorporation of supramolecular interactions that lead to cooperative- or anti-cooperative communication pathways between the iron(II) nodes. Through this switching modality, the physicochemical differences between the iron(II) high spin and low spin states can be exploited to achieve sensing and data storage applications.[1]

Incorporating guest molecules within a host lattice offers another avenue to modulate SCO. We synthesised and characterised the 3D Hofmann-like MOF $[Fe^{II}(dpbtz)(Au^{I}(CN)_2)_2]\cdot 0.5$chrysene (**1**) (dpbtz = 4,7-di(4-pyridyl)-2,1,3-benzothiadiazole) by an array of structural and physical techniques. Encapsulation of the polycyclic aromatic hydrocarbon (PAH) chrysene within **1** results in a host–guest arrangement where the host lattice itself is periodic yet the arrangement of chrysene guest molecules is aperiodic. Framework **1** displays an unusual example of two-step SCO which we ascribe to a guest disorder effect in the chrysenes causing local site inequivalencies of the iron(II) nodes in the host lattice.[2] The principle of exploiting aperiodic moieties in an underlying periodic lattice is known to occur for example in DNA when comparing the structure of the double helix to the base-pair sequence itself. Such structures offer higher density information storage capacities due to the absence of a domain-size constraint that limits the amount of information that is accessible within each crystalline domain. Extending these ideas into the realm of materials chemistry is a challenging yet rewarding task for producing complex materials, one that we hope has been advanced by our work.

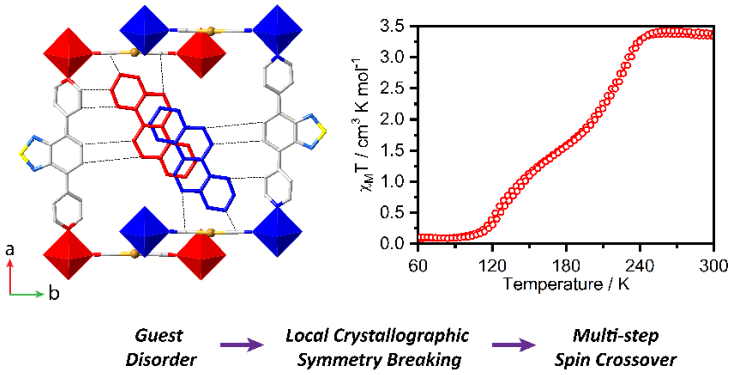

Figure 1. A chrysene-loaded MOF exhibits two-step SCO by guest-induced local symmetry breaking.

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Abstract Number: 144

Covalently-Tethered Heterobimetallic *N*-Heterocyclic Carbene Complexes for Metallaphotoredox Catalysis

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Metallaphotoredox catalysis marries the unparalleled capacity of transition metal catalysis to facilitate bond formation with the broad utility of photoinduced electron- and energy-transfer processes.[1] The vast majority of metallaphotoredox protocols employ a photosensitiser and transition metal catalyst as two discrete molecular entities. In this presentation, we report the synthesis and characterisation of a small library of new ruthenium- and iridium-based photoactive metalloligands (Figure 1). We have exploited the imidazo-phenanthroline core as a covalent tether to access heterobimetallic *N*-heterocyclic carbene nickel and palladium complexes with a view of augmenting catalyst performance in metallaphotoredox processes. Our progress in this area will be discussed.

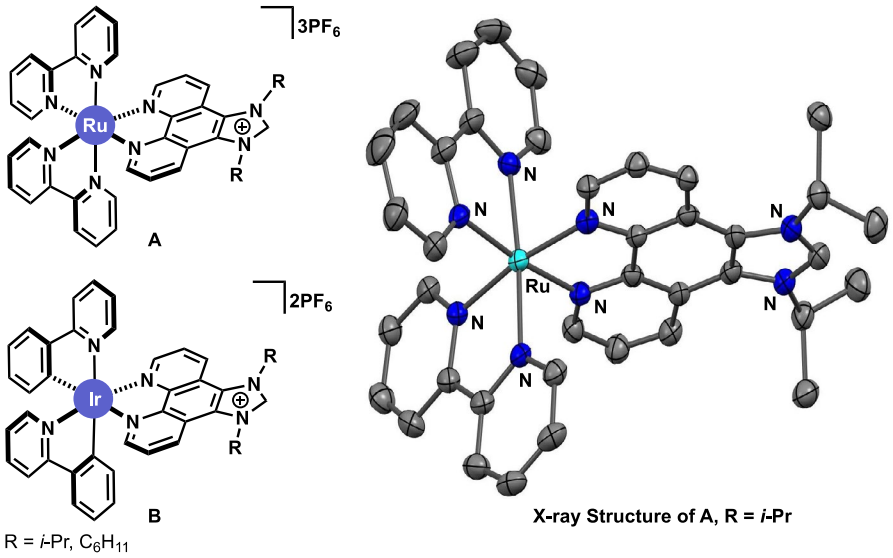

Figure 1. Photoactive ruthenium- and iridium-based metalloligands A and B.

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Abstract Number: 147

Tagging of proteins with chiral lanthanide complexes

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Protein structure and dynamics can be studied with chemical tags or spin labels. Lanthanide complexes are some of the tags used, exploiting the anisotropy of the magnetism about the lanthanide atom's axis to deduce directional and distance information.

Most lanthanides with unpaired electrons induce a shift in NMR resonances of nearby nuclei, arising from the contact shift (through-bond spin coupling, neglible due to the contracted 4*f* orbitals) and pseudocontact shift (through-space dipole-dipole coupling), as well as diamagnetic shift due to the rearrangement of electron density as a consequence of the presence of a metal.

Comparison of a paramagnetic lanthanide complex tag and a complex of its (relatively chemically interchangeable) diamagnetic analogue (La^{3+} $4f^0$, Lu^{3+} $4f^{14}$, or non-lanthanide Y^{3+} $4p^6$) allows for calculation of the pseudocontact shift contribution. The movement of ^{15}N HSQC resonances can be mapped.

A single stereoisomer of a chiral complex can bind to a chiral protein without peak multiplying in NMR. Short and rigid linkers minimise peak broadening from conformational flexibility and several have previously been developed to attach lanthanide tags to Cys residues. However, it is not currently clear what the most effective linkage is or how to best exploit the increased reactivity of Sec over Cys for selective tag conjugation. To establish this, a library of chiral complexes is being synthesised (examples in the figure are of SNAr or disulfide reactive tags) to evaluate reactivity for Cys and Sec residues by tuning, for example, substitution at the aromatic moiety.

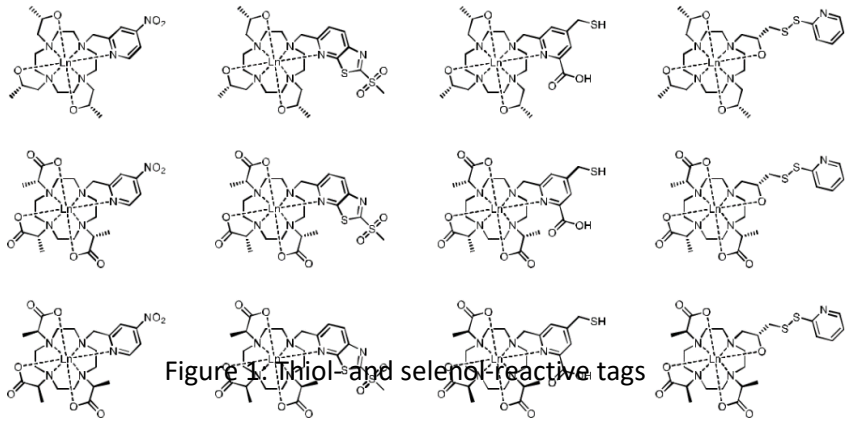

Figure 1: Thiol- and selenol-reactive tags

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Abstract Number: 148

Next Generation Platinum Antitumor Agents: Influence of Reactivity on Pharmacokinetics and Pharmacodynamics

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Even in the modern era of precision medicine and immunotherapy, chemotherapy with platinum (Pt) drugs, cisplatin, carboplatin and oxaliplatin, remain among the most commonly prescribed medication against a variety of cancers.[1] Despite spectacular clinical success, inherent and/or acquired chemoresistance increasingly reduce the effectiveness of Pt-based therapy. In addition to this, dose limiting toxic side effects such as nephrotoxicity, neurotoxicity and myelosuppression, limits the wider applicability. Our lab is actively involved in the search for novel Pt antitumor agents superior to clinically used drugs and understanding the structure-function relationship.[2-3] Since, kinetic lability or reactivity is the key determinant of anticancer efficacy, resistance and side effects, we embarked on an effort to rationally design next generation of Pt drugs by tuning the reactivity. Using a combination of *in vitro* and *in vivo* assay, we identified a few lead candidates with remarkable *in vivo* efficacy, low Pt-cross resistance and reduced systemic toxicity.[4] The design, in-depth *in vitro* mechanistic investigation, *in vivo* data and the impact of reactivity on pharmacokinetic and pharmacodynamic processes of these agents will be discussed in the presentation.

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Abstract Number: 155

Synthetic and structural studies of Ruthenium polypyridyl complexes as DNA major groove binders

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This project is focused on the synthesis, and structural studies via X-Ray crystallography of the first ruthenium polypyridyl complex which could bind in the major groove of DNA; as one component of a DNA-binding triplex forming oligonucleotide (TFO) assembly. All previous crystallographic work had shown intercalative binding from the DNA minor groove[1].

Ruthenium complexes have been selected as their chemistry is well-understood, because of their inertness to substitution and racemization. Furthermore, their octahedral geometry allows them the tuning of ligand affinities, substitution rates, and redox potential.

A ruthenium complex that contain an extended aromatic heterocyclic ligand, that is known to intercalate towards DNA major groove with Rhodium complexes, the 9,10- phenanthrenequinone diamine (phi) ligand, was synthesized. This intercalating ligand should provide a stable anchor in the major groove through intercalation[2].

The complex that was used to achieve our goal has been: $[Ru(phen)2phi]^{2+}$.

The successful combination in the crystallization experiment was that of the DNA decamer sequence d(CCGGTACCGG) with the lamba enantiomer: Λ-$[Ru(phen)2phi]^{2+}$.

Major groove

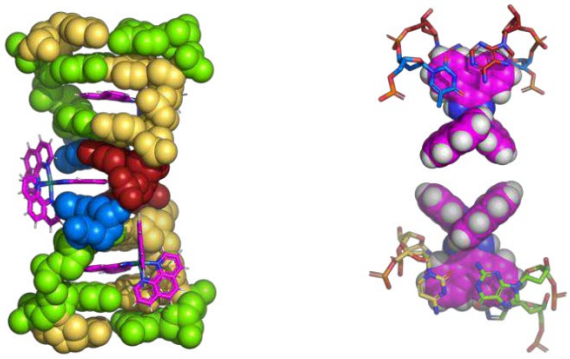

Figure 1. Crystal structure of Λ-$[Ru(phen)2phi]^{2+}$ bound to DNA duplex d(CCGTACCG) via the major groove

The electron density maps shows that the metal complex had intercalated in the major groove at the central TA/TA step, and in the minor groove at the adjacent GG/CC steps. The DNA helix is substantial unwound by this binding.

To our knowledge this is the first example of a ruthenium polypyridyl complex intercalated into DNA major groove. This knowledge can be exploited in the design of sequence specific binding assemblies, such as those containing TFO.

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Abstract Number: 158

The Zinc-Regulated Genes (Zrg): A New Family of ATP Binding Cassette Transporters for Zinc

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High-affinity zinc transporters of the ATP binding cassette (ABC) family are critical for pathogenic bacteria to compete with host systems for this limited, essential nutrient. Canonical zinc ABC transporter operons encode an intracellular ATPase, a 9-transmembrane helix membrane-spanning permease, and a periplasmic or lipoprotein solute binding protein (SBP) (Fig. 1A). Recently, a group of zinc-regulated genes (*zrg*) have been implicated in zinc import in *Vibrio cholerae* and *Pseudomonas aeruginosa*. The *zrgABCDE* operon is widespread across bacterial species and appears to encode an ABC transporter with ATPase (ZrgC), permease (ZrgB), and SBP (ZrgA) components, although the latter 2 share little to no sequence similarity to the canonical Zn ABC transporter proteins (Fig. 1B). Further, the *zrgD* and *zrgE* genes encode proteins of unknown function. Here we show that ZrgA is required for zinc import through the ZrgABCDE system in *V. cholerae*, confirming its function as an SBP. We also characterized zinc binding to *V. cholerae* ZrgA and solved its crystal structure. The results demonstrate high-affinity zinc binding to several sites in ZrgA, consistent with a function as a zinc SBP despite the fact that it shares no structural similarity to known zinc SBPs. Current work is focused on obtaining structural and functional data for ZrgE and the periplasmic domain of the permease ZrgB, which is absent from other ABC transporter permeases. Taken together, the data indicates that the Zrg system is a new type of ABC transporter for zinc with distinct structural and mechanistic properties.

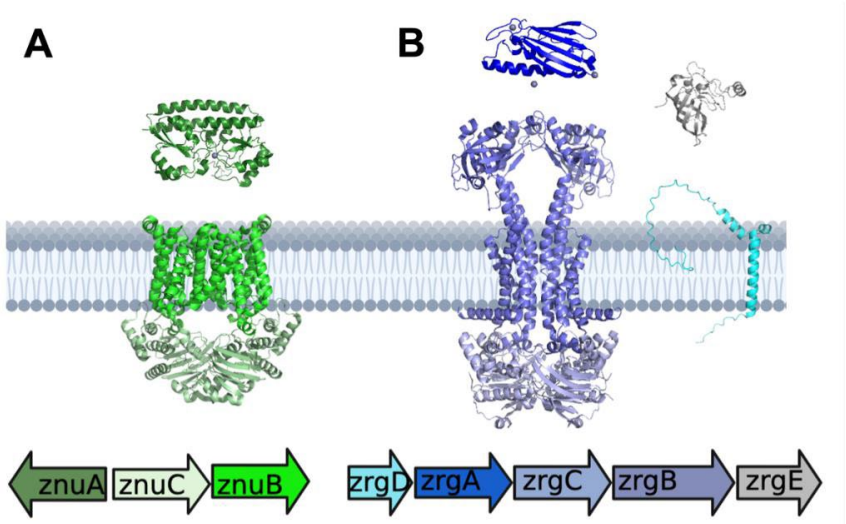

Figure 1. Operon organization and model structures for canonical ZnuABC (A) and ZrgABCDE (B) ABC transporters in *Vibrio cholerae*. Structures are taken from homologues[1-4] or AlphaFold predictions.

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Abstract Number: 159

SYNTHETIC HIGH-VALENT DIIRON COMPLEXES WITH Fe2(μ-O)2 DIAMOND CORES AS MODELS FOR INTERMEDIATE Q OF METHANE MONOOXYGENASE

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Intermediate Q is the reactive species in the reaction cycle of soluble methane monooxygenase, first identified by Lipscomb and Muenck to be responsible for the hydroxylation of methane. Early Mossbauer and EXAFS data on sMMOH-Q suggested the possibility of an FeIV2(μ-O)2 diamond core. Herein we present our recent efforts to synthetize such complexes. In one study, we have demonstrated the reaction of a diiron(II) precursor with O2 to form an [FeIII2(μ-O)(μ1,2-O2) intermediate (modeling sMMOH-P) that upon introduction of Sc3+ converts into a species with an FeIV2(μ-O)2 diamond core (modeling sMMOH-Q) (JACS 2020, 142, 4285; DOI: 10.1021/jacs.9b12081). Such a core can also be generated from a mononuclear FeIV=O precursor with the help of CeIV and HClO4 (ACIE 2020, 59, 22484; DOI:10.1002/anie.202010027). We have also obtained the first crystal structure of a complex with an FeIV2(μ-O)2 diamond core (Faraday Discuss. 2022, 234, 109-128; DOI: 10.1039/D1FD00066G), which can be compared with just published results of Kallol Ray and coworkers on the structure of a complex with an FeIII2(μ-O)2 diamond core (ACIE 2023, e202209437).

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Abstract Number: 160

The Organometallic Chemistry of Nickel Enzyme Mimics

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This presentation will focus on the chemistry related to two Ni-containing enzymes, acetyl-Coenzyme A synthase (ACS) and [NiFe] hydrogenase, which perform exquisite oxygen-sensitive organometallic chemistry in a biological environment. Recently, we have reported the development of catalytic and functional mimics of both [NiFe] hydrogenases and ACS.1-3 The novelty of our approach stems from the design of flexible multidentate ligands with mixed hard/soft donor atoms that allow the detection and characterization of both low- and high-valent organometallic Ni species, which are key reactive intermediates during catalysis.

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Abstract Number: 161

Minimising the Effect of Dispersion in Surface-Confined Voltammetry

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Our work is concerned with the mechanism of electron-transfer in metalloproteins, we have successfully distinguished a concerted two electron-transfer mechanism from a two sequential one electron-transfer process and deconvoluted the square scheme using voltammetry techniques.[1] However, dealing with the phenomena of dispersion is currently a limiting factor in the mechanistic study of metalloproteins by such techniques. Dispersion, in electrochemistry, refers to an underlying distribution of parameter values, typical on the reversible potential (E^0) or the charge-transfer rate constant (k^0). Dispersion may therefore be described as `the absence of a single value of the reversible potential, E^0, (thermodynamic dispersion) and/or heterogeneities in the charge-transfer rate constant, k^0, (kinetic dispersion) across the surface-confined species'[2]. In this paper we consider methods to overcome dispersion. We undertake a theoretical and analytical exploration on how to minimise the effects of dispersion, and propose an experimental design to ease parameterisation of experimental systems for which dispersion is present. By varying the amplitude of r-FTacV (ramped Fourier Transformed alternating current Voltammetry) we show the effect of dispersion can be minimised and we will show experimental results to confirm this.

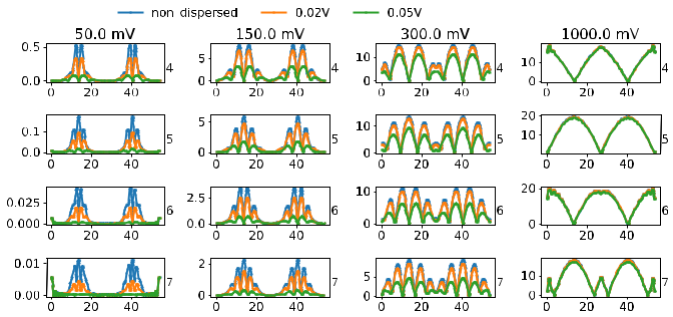

Figure 1 The effect of amplitude on dispersion. Harmonics 4-7 are shown for an applied amplitude of 50, 150, 300, and 1000mv with no dispersion, and Gaussian distributed dispersion with a standard deviation of 2 mV and 5 mV

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Abstract Number: 163

The Specificity and Selectivity of the Plectin–Plecstatin-1 interaction

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For further development of novel metal-based anticancer agents, elucidating the modes of action in preclinical studies is of utmost importance. Promising novel anticancer agents based on the piano-stool structural scaffold confer many favourable properties and are highly modulable through the choice of the metal centre and/or ligands. Such metal-based complexes are designed with specific functions in mind, e.g., to interact with biological targets selectively. N-Substituted 2-pyridinecarbothioamides (PCA) are ligands which attach to the organometallic piano-stool scaffold and led to the discovery of the promising chemotherapeutic plecstatin-1.[1] PCAs act as gastric mucosal protectants with high cytotoxicity and low acute toxicity *in vivo*. Oral administration to mice significantly reduced tumour growth in invasive melanoma xenografts. A proteomics-based target-response profiling approach revealed high selectivity (160-fold) for the scaffold protein and cytolinker plectin.[2-3]

Using our established bioanalytical toolkit to study the interaction[4-6] with the large protein plectin (4,684 amino acids). The multi-domain protein was divided into constructs with protein crystallographic hits achieved (Fig. 1). Individual constructs were incubated with plecstatin-1 and analysed by gel electrophoresis; the solid gel matrix was imaged using novel mass spectrometry methodology.[7] Furthermore, ESI-MS was employed to identify which constructs interacted with plecstatin-1. In *in vitro* anticancer activity studies, the nine cancer cell lines examined showed differing sensitivities to plecstatin-1. These studies represent essential steps toward the development of plecstatin-1 for the treatment of cancer.

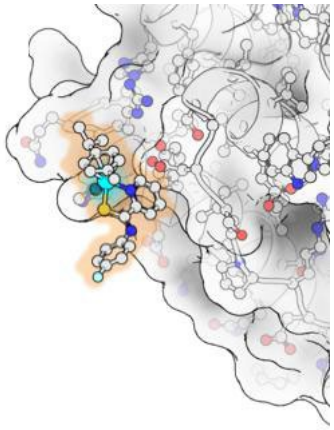

Figure 1: Plecstatin-1 interacting with plectin actin binding domain (ABD).

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Abstract Number: 166

Light-Driven Oxidation of CH4 to CH3OH and HCHO using O2 Catalyzed by a Homogenous $Ru^{IV}2(\mu\text{-}O)2$ Complex

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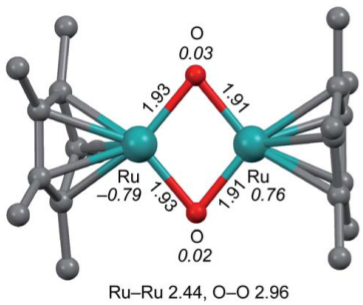
CH4 is one of the most promising resources of energy and materials because it has high affinity with renewable energy, and has become capable of being easily and abundantly obtained in biomethane form from biomass by means of recent technological developments.[1] In order to use CH4 in industrial processes instead of naphtha, innovative and useful transformation methods are now strongly demanded. However, its inertness in view of its physical and chemical properties makes CH4 one of the most unreactive molecules. To date, there have been three type of catalysts, *i.e.*, enzymatic, heterogeneous, and homogeneous, found for the direct oxidation of CH4 to CH3OH with O2 as an oxidant. Among these catalysts, we have focused on a homogeneous organometallic catalyst by mimicking the active site of methane monooxygenases (MMO). Therefore, we have synthesized a bis(μ-oxido) $Ru^{IV}2$ species as a model for MMO to achieve aerobic CH4 oxidation to CH3OH and HCHO with input of light energy.[2]

A water-soluble Ru^{II} complex, $[Ru^{II}(h^5\text{-}C5Me5)(H2O)^3]^+$ (**1**), was oxygenated by O2 in water to rapidly generate the bis(μ-oxido) $Ru^{IV}2$ species, $[Ru^{IV}2(h^5\text{-}C5Me5)2(\mu\text{-}O)2]^{2+}$ (**2**) (Fig. 1). Then, we investigated driven-induced CH4 oxidation using **2** in water. An aqueous solution of **2** under CH4/O2 (CH4 and O2 = 4 and 2 MPa, respectively) was irradiated by UV light (250–385 nm, 15 mW) for 5 h. Subsequently, we observed CH3OH and HCHO by GC-MS from the resulting aqueous solution. No HCOOH was observed by GC-MS. We determined the TONs of CH3OH and HCHO as 1.1 and 3.0, respectively; thus, the total TON was estimated to be 4.1. HCHO was formed by overoxidation of CH4 because we confirmed CH3OH oxidation to HCHO under the same condition. Besides, we conducted control experiments without **2**, UV light, CH4, or O2, all showing no product formation. When visible light (385–740 nm) was used instead of UV light, no reaction occurred. On the basis of experimental analyses and DFT calculations, we propose a reaction mechanism of photo-driven CH4 oxidation using O2 (Fig. 2).



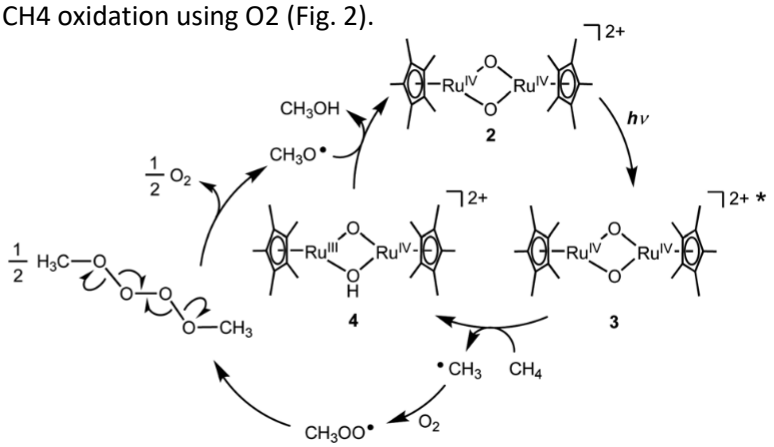


Figure 1. A DFT-optimized structure of RuIV2(μ-O)2 complex 2

Figure 2. A proposed mechanism for the photo-driven CH4 oxidation by Ru complexes using O2 in water

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Abstract Number: 167

Use of Decoy Molecules to Manipulate Cytochrome P450BM3 Biotransformations

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Cytochrome P450BM3 (P450BM3) is one of the most promising P450s as potential biocatalysts for applications in green synthetic chemistry, as they possess high activity for the hydroxylation of inert substrate C–H bonds. Because the substrate-binding is crucial for the generation of active species of P450BM3 (Compound I), substrates whose structures are primarily different from that of their native substrates (long-alkyl-chain fatty acids) cannot be hydroxylated by P450BM3. To enable oxidation of non-native substrates by P450BM3 without any mutagenesis, we have developed a series of "decoy molecules," inert dummy substrates, with structures resembling native substrates.[1] Decoy molecules fool P450BM3 into generating Compound I, enabling the catalytic oxidation of non-native substrates other than fatty acids (Fig. 1). The catalytic activity for non-native substrate hydroxylation was significantly enhanced by employing perfluorinated carboxylic acids modified with amino acids (PFC-Amino acids). We have demonstrated that various amino acids (N-acyl amino acids), as well as amino acid dimers having a completely different structure from fatty acids, can serve as decoy molecules (Fig. 2). Benzene was more efficiently hydroxylated in the presence of these decoy molecules. We also have confirmed that wild-type P450BM3 expressed in *E.coli* can be activated by adding amino acid derivatives as decoy molecules to the culture medium, and benzene was hydroxylated without supplementing with NADPH.[2,3] Activities of the whole-cell biocatalyst drastically varied depending on the structure of decoy molecules added to the cell suspension, suggesting that the difference in permeability between decoy molecules may affect the activation of intracellular P450BM3. The phenol yield reached 59 % when N-heptyl-L-prolyl-L-phenylalanine (C7-Pro-Phe) was employed as the decoy molecule. Recently, we have succeeded in further enhancing the catalytic activity for benzene and gaseous alkane hydroxylation by systematic screening of decoy molecules.[4] Furthermore, we have found that one of the

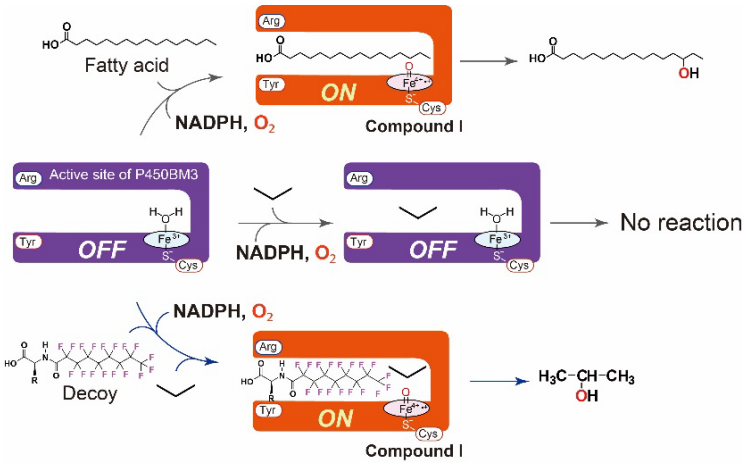

Figure 1. Schematic representation of fatty acid hydroxylation (upper) and propane hydroxylation in the presence of a decoy molecule (bottom) catalyzed by P450BM3. Reaction of propane in the absence of any decoy molecule (middle).

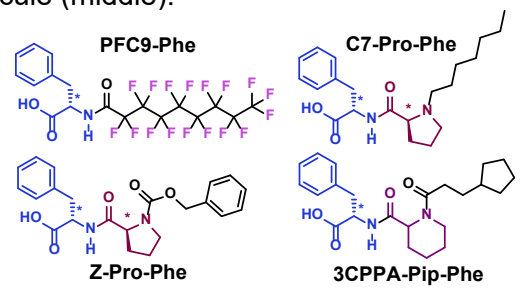

Figure 2. The structure of decoy molecules for nonnative substrate

decoy molecules can accelerate the crystallization of P450BM3 and reported crystal structures of the various flavours of P450BM3.[5, 6]

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Abstract Number: 168

Significant Enhancement of Catalytic CH4 Oxidation Activity of μ-Nitrido-Bridged Iron Phthalocyanine Dimer by Adsorption on Graphite

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Inspired by the fact that natural methane monooxygenases (MMO) utilize iron- or copper-oxo species as reactive intermediates for catalytic methane conversion into methanol under mild reaction condition, numerous metal-oxo-based molecular catalysts have been synthesized. However, efficient catalytic methane oxidation by metal-oxo-based molecular catalyst under mild reaction condition is still a difficult challenge because of the stability of methane. We have been working on the development of potent methane oxidation catalyst based on μ-nitrido-bridged iron porphyrinoid dimer,[1] which is known as a potent class of iron-oxo-based molecular catalyst for methane oxidation.[2]

We recently demonstrated that close stacking of a μ-nitrido-bridged iron phthalocyanine dimer with no peripheral substituents onto a graphite surface is effective for achieving high catalytic activity, almost comparable to that of pMMO in terms of C–H bond activation of methane, in an acidic aqueous solution containing excess H2O2 (**Figure**).[3] Electrochemical and DFT calculation studies suggested that stacking of the catalyst onto a graphite surface resulted in lowering the SOMO level of the reactive intermediate, thereby facilitating electron transfer from methane to the catalyst in the proton-coupled electron transfer (PCET) process. It was also suggested that cofacially stacked structure of the catalyst molecule is advantageous for preventing decreases in the oxo-basicity and generation rate of the terminal iron-oxo species.

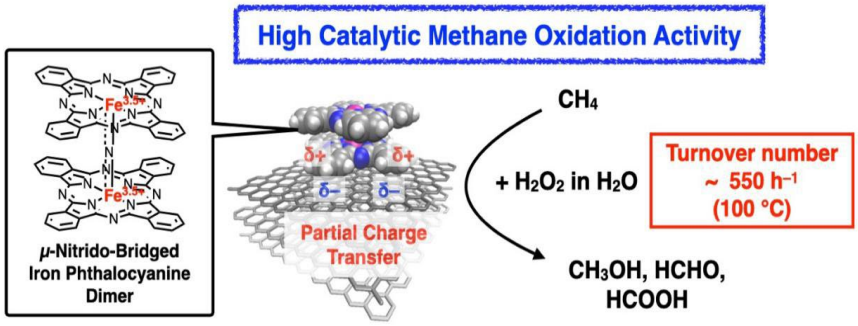

Figure. Efficient catalytic methane oxidation by graphite-supported μ-nitrido-bridged iron phthalocyanine dimer in the presence of H2O2 in H2O.

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Abstract Number: 174

The Intersection of Reactive Sulfur and Selenium Species: Characterization and Reactivity of Perselenide, Persulfide, Thioselenide, and Selenosulfide Anions

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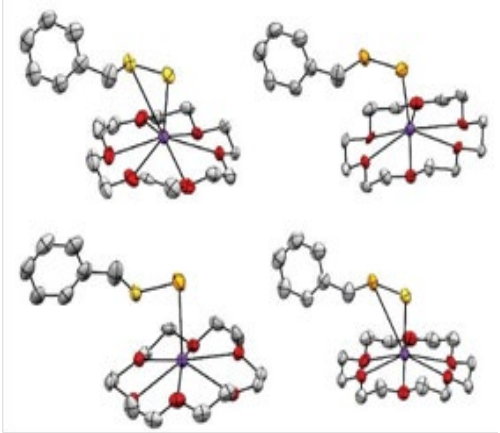
Nature uses S and Se broadly due to the versatile biological redox chemistry spanning from –2 to +6 of these elements. This redox availability enables the generation of a diverse array of complex and intertwined reactive sulfur and selenium species (RSS and RSeS), which are crucial in cellular signaling. Established RSS and RSeS typically contain S and Se in the –2 to 0 oxidation states, which allows these species to act as either pro- or anti-oxidants. More broadly, dichalcogenides highlight the intersection of RSS and RSeS, with persulfides (RSS–), thioselenides (RSSe–), and selenosulfides (RSeS–) being proposed intermediates in numerous biochemical processes, whereas perselenides (RSeSe–) have thus far been completely enigmatic. RSS– are the most established dichalcogenides, and glutathione persulfide anion (GSS–) and CysSS– are both readily generated under physiological conditions. By comparison, both glutathione thioselenide (GSSe–) and enzyme-ligated thioselenide (Enz-SSe–) have been proposed as highly reactive intermediates in rhodanese (RhdA) prior to reduction and HSe– or selenophosphate generation. Similarly, a Mo-bound SecSeS– is a proposed intermediate in the catalytic oxidation of formate by Mo formate dehydrogenase (FDH).

In this presentation, we will highlight the synthesis, isolation, spectroscopic and structural characterization, and initial reactivities of small molecule persulfide, perselenide, thioselenide, and selenosulfide anions. We will present fundamental reactivity data of these dichalcogenides with different reductants, electrophiles, nucleophiles, and other reactive small molecules to outline the different reactivities of these highly reactive molecules. We anticipate that these data will provide additional insights into the bioorganic and bioinorganic chemistry of these highly reactive dichalcogenides.



Abstract Number: 175

Silent partners: Unveiling the metallation pathways in human metallothioneins for Cu(I), As(III), and Bi(III)

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Zinc and copper are the key metal ions that the human protein metallothionein (MT) homeostatically controls in the cell. MTs are widely distributed in different organs in humans. Metallothioneins are unusual in that despite the presence of 20 reduced cysteinyl SH's there are no predefined metal ion binding sites and the metal -free or apo structure may be described as intrinsically disordered. The metallation properties of Zn(II) and Cd(II) are well known, with specific two-domain structures forming with exactly 7 metal ions added and analyzed as M3(SCYS)9 (beta domain) and M4(SCYS)11 (alpha domain)[1]. Electrospray ionization mass spectrometry (ESI-MS) revolutionized speciation analysis for the stepwise metallation pathways by identifying the change from single M(SCYS)4 formation with up to 5 metal ions to the clustered domains for 7 metal ions. Analysis of the ESI-MS data with partial metallation showed a reversible cooperative cluster formation at pH values less than 7. Relative binding affinities, KF, for each of the 7 steps can be determined using competitive chelation during stepwise metallation[2].

MTs form metal-thiolate structures that can be characterized by ESI-MS, absorption, CD and emission methods. Metallation reactions of Cu(I), As(III), and Bi(III), three very different elements, provide insight into the remarkable versatility of MTs to bind metal ions. Cu(I) forms a range of clusters with the 20 cysteinyl thiolates, but the exact sequence of the cluster formation between the two domains has only recently been determined using a combination of ESI-MS and excited state phosphorescence lifetimes to elucidate the pathways followed. The reactions of Cu(I), As(III) and Bi(III) with MTs are reported using detailed ESI- MS, phosphorescence spectra, EXAFS spectra, DFT results and stopped flow kinetic data. Unexpected, novel stoichiometries for structures that are cooperatively formed have been identified and will be described for Cu(I), As(III) and Bi(III).

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Abstract Number: 176

Homoleptic Nickel-Thiolate Complexes As Electrocatalytic Hydrogenase Models

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In the never-ending pursuit of powering the planet with alternative non-carbon-based fuel sources, hydrogen gas (H2) has emerged as one leading candidate. Biological systems involved in H2 processing are the hydrogenase (H2ase) enzymes, which utilize active sites with first-row transition metals such as iron and nickel to catalyze H2 evolution/H2 splitting. Among the most widely studied and, in some cases, O2 tolerant, of the H2ases are those that have a NiFe active site core, i.e., the NiFe-H2ases. Although both metals play a role in catalysis, only Ni participates in the redox processes critical for H2 interconversion. To better understand the chemistry that takes place at these active sites, synthetic chemists have employed mono- and dinuclear models that replicate some aspect of the structure and/or function of the native system. While advances in this arena have certainly been made, no synthetic models employ Ni complexes housed in a four-coordinate, thiolate-only, coordination sphere as found in the native enzyme. This talk will highlight our synthetic efforts in modeling the Ni-tetrathiolato site of NiFe-H2ase employing $[Ni(SR)4]^{2-}$(R = substituted arylthiolates). Under proper conditions such homoleptic models are modest electrocatalysts for the hydrogen evolution reaction (HER). Furthermore, installation of carboxamido-NH groups, as models of peptide NH---S H-bonds, ortho to the thiolato-S donors improves protic stability and overall catalytic performance. The synthesis and spectroscopic, electrocatalytic, theoretical properties of these thiolate-rich Ni-site H2ase models will be presented.

Abstract Number: 177

Principles of selective recognition of lanthanides in biology and their application to rare earth separations

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The separation of the rare earth elements (the lanthanides, La-Lu, as well as yttrium and scandium) is notoriously difficult, owing to the subtle differences in ionic radius and coordination number between these elements.[1,2] The discovery that certain lanthanides are specifically utilized by biological systems has opened new avenues for development of novel biochemistry-based strategies for highly selective recovery and separation of rare earth elements and actinides. [3] In this talk, I will describe our discovery of several dedicated lanthanide-binding proteins and the insights that the characterization of these systems have yielded into the coordination chemistry and supramolecular chemistry underlying biological recognition of lanthanides.[4,5] I will describe how picometer-scale differences in ionic radii can be propagated to large-scale protein conformational changes that impart non-linearities in affinity profiles.[6] Finally, I will illustrate how the principles illuminated by these natural systems can be leveraged to enhance the performance of biomolecule-based separation processes.[6-8]

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Abstract Number: 180

Simultaneous imaging of redox-active metal ions in two oxidation states to understand their roles in Alzheimer's disease and cancer

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Redox-active metal ions play important roles in biological processes and human diseases. A primary example is Fe^{2+} and Fe^{3+} whose redox chemistry are at the heart of ferroptosis that is a key process leading to neurodegenerative diseases such as Alzheimer's disease. Ferroptosis is also known to be an effective alternative therapeutic method to apoptosis for cancer. However, the mechanism of ferroptosis is still not understood because of lack of sensors that allow simultaneous imaging of both Fe^{2+} and Fe^{3+} in biological systems. Similarly, simultaneous monitoring of both Cu^{+} and Cu^{2+} is also important in understanding both diseases. Despite the importance, few sensors allow simultaneous imaging of redox-active metal ions in two oxidation states in vivo with high selectivity.

To address this issue, we report in vitro selection and development of DNAzyme sensors (Figure 1) with high specificity for either Fe^{2+}, Fe^{3+}, Cu^{+} or Cu^{2+}, which allows visualizing both Fe^{2+} and Fe^{3+} or both Cu^{+} and Cu^{2+} simultaneously in living cells and brain slices of AD mice models for the first time.[1] Interestingly, the sensors provided spatial distributions of Fe^{2+} and Fe^{3+}, as well as iron redox ratios, revealing a significant increase in the Fe^{3+}/Fe^{2+} ratio surrounding amyloid plaque regions but not in other brain regions. The results suggest that not only total iron, but also iron redox cycling play a key role in the progression of AD. These finding suggests a correlation between amyloid plaques and the accumulation of Fe^{3+} and/or the conversion from Fe^{2+} into Fe^{3+}, which providing potential direction for further functional study to understand metal redox in AD progression. Further applications of these DNAzyme sensors to in living cells and mice models of AD and cancers have provided deeper insight into the roles of redox cycling of labile iron and copper in these diseases. Latest results on this project will be presented.

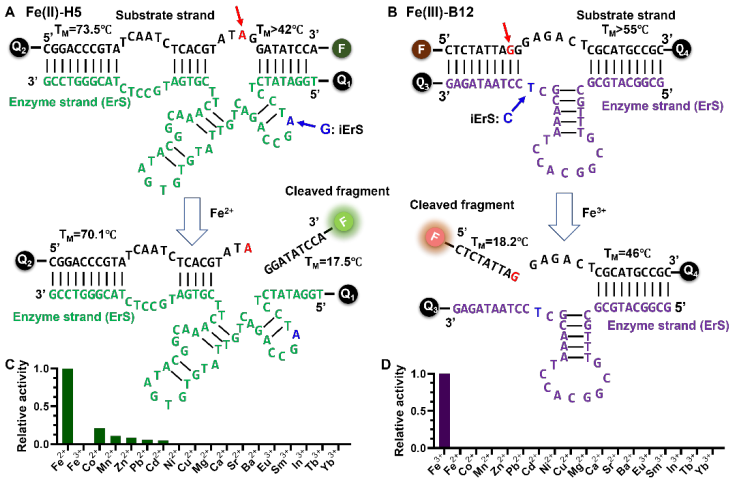

Figure 1. DNAzyme sensors that are selective for Fe^{2+} or Fe^{3+}.

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Abstract Number: 181

Electron transfer mechanism in sMMO through component interactions and allosteric effect

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Soluble methane monooxygenase (sMMO), a member of the bacterial multicomponent monooxgenases (BMM) superfamily, requires hydroxylase (MMOH), regulatory component (MMOB), and reductase (MMOR) for the hydroxylation of methane (CH_4). This harmful greenhouse gas, CH_4, has a higher heat capacity than that of carbon dioxide (CO_2) and its C-H activation is of major interest. The diiron active site in MMOH accepts electrons from nicotineamideadenine dinucleotide (NADH) to the diferric center (Fe^{3+}-Fe^{3+}) through MMOR, which has two domains including NADH-/FAD-binding and ferredoxin domain. Electron paramagnetic resonance (EPR) and structural analysis of MMOR from *Methylosinus sporium* 5 revealed its electronic environment. The annealing methods of EPR can extract electronic information about the MMOR-FAD binding domain. The reduced structure of FAD cofactor indicates the presence of a neutral flavin radical, and this was confirmed by density functional theory (DFT) calculations. In addition, the electronic and oxidation environments of $[2Fe\text{-}2S]^{+}$ were investigated with multi-frequency and multi-technique methods. The results indicated that Fe^{3+} is positioned near Cys50 with a distance of 2.7 Å. The structural information of MMOR has not been reported and was only obtained by nuclear magnetic resonance (NMR) studies. The X-ray crystallographic study of MMOR-FAD binding domain explained the atomic-level interactions. The hydrogen bonding network proposed an overall electron-transfer pathway and mutational studies proved that Tyr160 is a crucial residue for the structural and functional roles of sMMO catalytic activity.

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Abstract Number: 182

Regulating the Structure and Function of Heme Proteins by Diverse Post-Translational Modifications

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Metalloproteins/metalloenzymes have addressed much attention recently.[1,2] Of which heme proteins play diverse functions in biological systems, which are fine-tuned by various post-translational modifications (PTMs) (Fig. 1).[3, 4] Myoglobin (Mb) is an ideal model protein for heme protein design. In the last decade, we have found unique PTMs in the designed heme proteins, such as the Tyr-heme cross-links [5, 6] and the oxidation of Cys to a sulfinic acid (Cys-SO_2H).[7] Moreover, we have engineered some intramolecular disulfide bonds to regulate the structure and function of Mb, fulfilling the creation of functional heme enzymes.[8-10] We have solved some X-ray crystal structures of Mb mutants with the PTMs, which provide valuable insights into the structure and function relationship of heme proteins. The designed enzymes may also have potential applications.

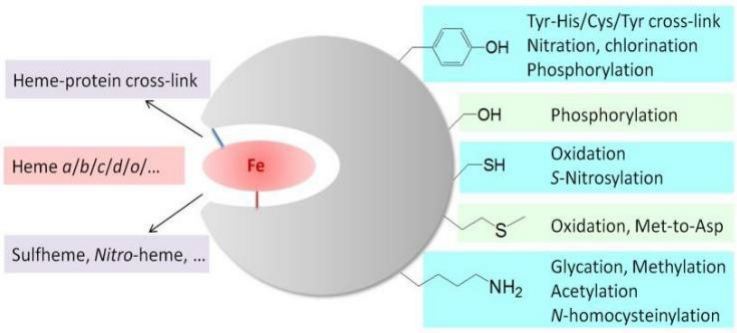

Fig. 1 Structure and function of heme proteins regulated by diverse PTMs.

Keywords: Heme protein, Structure and function, PTMs, Protein design, Enzyme

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Abstract Number: 183

Steric and Electronic Limitations of the Alkyne/Vinylidene Rearrangement

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16 Valence electron half-sandwich complexes of type $[M(dppe)Cp]^+$ (M = Fe, Ru) are known for their ability to coordinate and activate functional groups, including nitro (NO2)[1] and internal alkyne functionalities (Ar-C≡C-Ar', **2**).[2] Those reactive intermediates can be prepared *in situ* from their parent chloride complexes **1** upon halide abstraction (Figure 1). Their reaction with, for example, internal alkynes results in germinal vinylidene complexes of type $[M\{=C=C(Ar)(Ar')\}(dppe)Cp]^+$ (**3**) for which a migration of one of the substituents Ar/Ar' along the unsaturated bond is required.

The kinetics of this process and the impact of either electron donating or withdrawing groups are well investigated,[2] and additional donor functionalities, such as amines, allow for the synthesis of indole derivatives in a catalytic manner.[3] However, those examples are limited to substituents in which steric effects of additional groups are minimized. Furthermore, rearrangement processes at bisalkynes were not investigated until recently by our group.[4] Herein, the scope of the alkyne/vinylidene rearrangement is extended to sterically hindered alkynes, as well as bisalkynes of various substitution pattern, resulting in homo-bi- and hetero-tetra-metallic organometallic vinylidene complexes. Their properties, solid-state structures and redox properties (Ar/Ar' = ferrocenyl) will be discussed. For M = Fe, the competition between the vinylidene rearrangement and an iron-mediated nitro/nitroso reduction will be discussed for appropriate bifunctional substrates. Transition state analysis shows that coordination and rearrangement processes are equally important, a factor that has so far been overlooked.

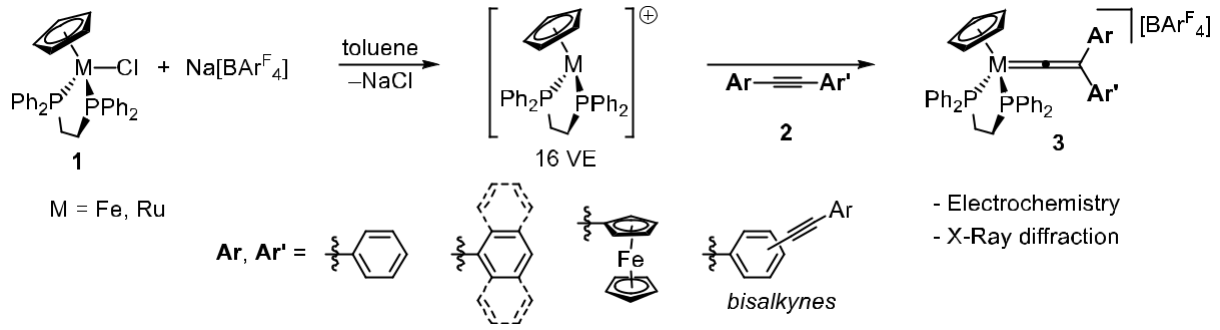

Figure 1. Formation of 16 Valence Electron complexes from half-sandwich chlorides **1** and their activation of internal alkynes **2** into bisarylvinylidene complexes **3**.

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Abstract Number: 184

Nitrite and Nitric Oxide Interconversion at Copper: Insights into the Bioactivities of Nitrosocyanin and Ceruloplasmin

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Though nitric oxide (NO) is a notorious toxin at high concentrations, it serves as a vital gasotransmitter in micromolar concentrations, and thus assists in various bioactivities including vasorelaxation, neuro-transmission, and anti-inflammation.[1] Biochemical processing of NO occurs through a set of tightly controlled complex transformations involving various transition metals (*e.g.* Fe, Cu, Mo). A number of recent studies underscore that nitrite ($NO2^-$) plays pivotal roles in modulating NO bioactivities.[2] For instance, ceruloplasmin mediated oxidative transformation of highly reactive NO to relatively more stable $NO2^-$ is crucial in maintaining the optimum flux of NO in blood plasma.[3] On the other hand, $NO2^-$ is a stable and circulating reservoir NO under hypoxia.[2] While the insights into the transformation of $NO2^-$ to NO at Type II Cu sites relevant to nitrite reductase (CuNiR) have been demonstrated previously,[4] a similar one-electron redox transformation at blue and red cupredoxin proteins remains poorly understood. For example, nitrosocyanin (NC), an unique red cupredoxin protein exhibiting structural and spectroscopic signatures of both Types I and II proteins, has been proposed to be involved in denitrification.[5] However, the reactivity profile of NC remains unknown to the best of our knowledge. We herein employ a set of structurally characterized copper(II/I) redox pairs to demonstrate the nitrite to NO transformation reactivity of NC in the presence of various biologically relevant reductants such as phenols (ArOH, a model for tyrosine) and 1-benzyl-1,4-dihydronicotinamide (BNAH, a model for NADPH).[6] Furthermore, NO-reactivity of copper(II) in the presence of water and triethylamine has been shown to provide nitrite and nitrate (NOx^-) through a plausible intermediacy of a $\{CuNO\}^{10}$ intermediate.[6] Thus, the present work not only sheds light on the NOx reactivity related to the plausible involvement of NC in denitrification, but also modelling the role of ceruloplasmin in maintaining NO/ $NO2^-$ homeostasis in blood plasma.

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Abstract Number: 185

Studying Pre-transmetalation Intermediates in the Suzuki–Miyaura Reaction: Synthesis of Palladium(II) Boronates

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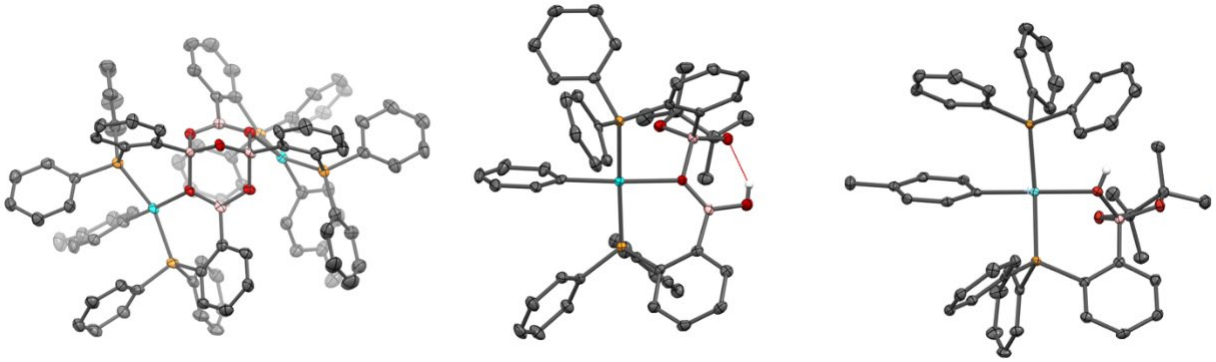
The mechanism of the Suzuki–Miyaura cross-coupling reaction has been the subject of much interest and fundamental on-cycle intermediates, such as palladium(II) boronate pre-transmetalation species, remain elusive.[1] Although these fleeting species have been extensively studied via low-temperature rapid-injection NMR spectroscopy in solution,[2] the structures of these molecules were not secured crystallographically until very recently.[3,4] Our efforts to synthesise and comprehensively characterise kinetically stable organopalladium(II) boronates and related species will be presented and discussed.[5]



X-ray crystal structures of isolated arylpalladium(II) boronates.

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Abstract Number: 187

Metallocomplexes as inducers of immunogenic cell death

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There is increasing evidence implicating the involvement of the immune pathways in the long-term and sustained effectiveness of anticancer therapeutics. One particular modality that has spurred recent interest is the induction of immunogenic cell death (ICD) in which compounds initiate a cytotoxic cascade in cancer cells that trigger a regulated immune response. The promise is that this adaptive immunological cascade leads to the development of acquired immunity against these cancer cells with prolonged anti-tumour protection. Most ICD inducers have been discovered either serendipitously or by library screening. Based on our previous work on non-alkylating cyclometallated Pt(II) complexes,1 we designed a class of Au(III)-dithiocarbamate complexes designed to exert endoplasmic reticulum (ER) stress.2 In this presentation, we will discuss the mechanism of action of these complexes, including its ability to trigger calreticulin translocation, an important damage-associated molecular pattern associated with ICD, and consequently, induction of ER stress-dependent phagocytosis in damaged cells.3

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Abstract Number: 191

Catalytic voltammetry of tungsten-containing aldehyde oxidoreductase from *Aromatoleum aromaticum* EbN1

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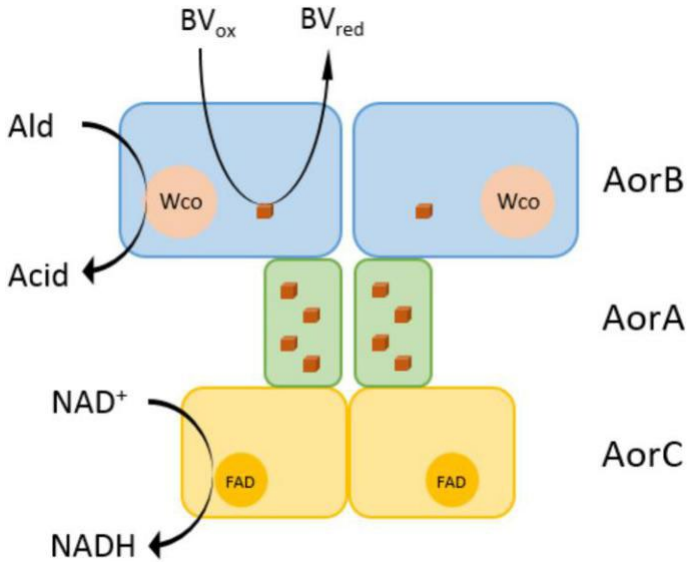
Tungsten (W)-containing aldehyde oxidoreductase (AOR) from *Aromatoleum aromaticum* EbN1 is a heterohexameric protein that contains seven redox-active cofactors in three different subunits, including a W-cofactor and a Fe-S cluster in the largest subunit (AorB), four Fe-S clusters in a small subunit (AorA) and one FAD cofactor in a separate subunit.[1] The W-cofactor (Wco) acts as a catalytic centre for AOR, and a wide variety of aldehydes are oxidized to the respective acid in the presence of physiological electron acceptor NAD^+.



We recently reported the mediated electrochemistry of AOR and demonstrated a remarkable catalytic response of AOR to a wide range of aliphatic and aromatic aldehydes.[2] A range of artificial redox dyes such as benzyl viologen (BV, –324 mV vs NHE), methylene blue (– 22 mV vs NHE), and 2,6-dichlorophenol-indophenol (+170 mV vs NHE) were used as electron transfer mediators to enable AOR electrocatalysis. The redox potential differences among the mediators deliver different electrochemical driving forces to AOR catalysis. Electrochemical simulation was performed to explore kinetic parameters associated with AOR catalysis. Furthermore, we have investigated the direct electrochemistry of AOR (without any mediators) allowing comparisons between these different approaches to be made with the same enzyme.

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Abstract Number: 193

Investigating Lanthanoid Sensitisation in Multinuclear Assemblies

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Efficient lanthanoid luminescence relies on sensitisation from the antenna effect, due to the symmetry and often spin-forbidden *f-f* electronic transitions. In general terms, the antenna effect is described as a chromophoric ligand absorbing energy to its singlet excited state, efficient intersystem crossing to a triplet excited state, followed by energy transfer to the lanthanoid *f** excited state. While the chromophoric moiety is usually an organic ligand, excitation of lanthanoid cations can also occur via charge transfer transitions of transition metal complexes or via lanthanoid-lanthanoid energy migration, which have received comparatively less attention. In this presentation, we will highlight our recent studies on lanthanoid sensitisation in multinuclear assemblies, formed by *d* and *f* elements or exclusively by *f* elements (figure 1).[1-4] Some unexpected results will showcase efficient sensitisation of the red emission of Eu(III) from Re(I), which, to the best of our knowledge, has never been reported before.

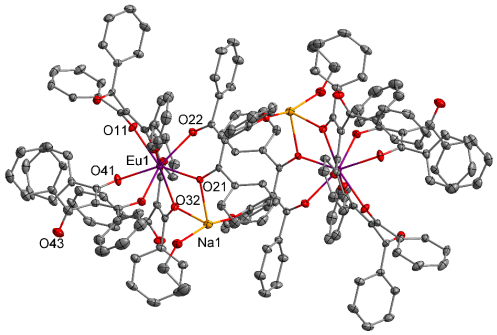

Figure 1. Example of multinuclear assembly displaying Eu-to-Nd energy transfer.

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Abstract Number: 194

Antibacterial silver and gold complexes of imidazole and 1,2,4-triazole derived N-heterocyclic carbenes

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Over the past two decades, there has been significant interest in the biological properties of gold and silver complexes of N-heterocyclic carbene ligands, with their potential use as treatments for cancer being widely investigated.[1] In addition, several studies have focused on using these complexes as antibacterial agents,[2-4] however to further develop structural activity relationships for these compounds, a greater variety of analogues is needed. To this end, a series of gold(I) and silver(I) complexes of 1,2,4-triazolylidene and imidazolylidene-based N-heterocyclic carbene ligands have been prepared, and their antibacterial activities evaluated.[5] The gold(I) complexes were found to be highly effective against Gram-positive bacteria, with the complexes of the 1,2,4-triazolylidene ligands being more active than the analogous imidazolylidene complexes. Selected silver(I) and gold(I) complexes were also active against multi-drug resistant bacteria (e.g. Figure 1). The potential for antibacterial resistance to develop against these metal-containing complexes was investigated and significantly, no resistance was observed upon continuous treatment, whilst resistance was developed against the widely used broad-spectrum antibiotic ciprofloxacin. The solution and gas phase stabilities of selected complexes were investigated to gain insights into the possible decomposition reactions for silver complexes in aqueous solution.

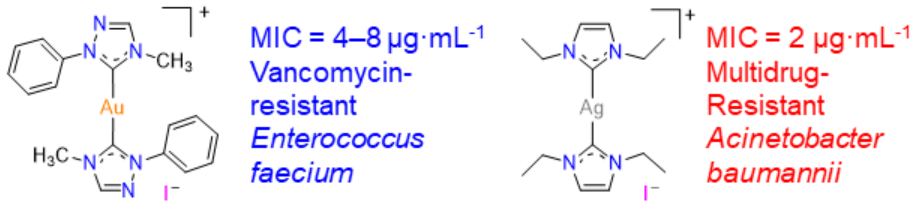

Figure 1. Minimum inhibitory concentration (MIC, μg·mL-1) values for gold and silver complexes against multidrug-resistant bacterial strains.

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Abstract Number: 201

Biosynthesis and Functions of the Nickel-Pincer Nucleotide Cofactor

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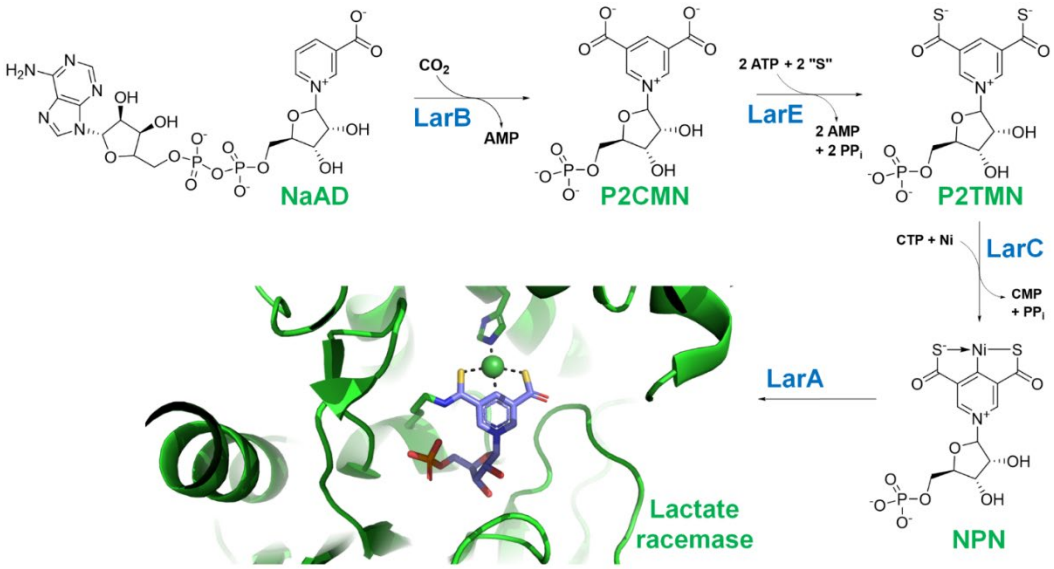
The nickel-pincer nucleotide (NPN) cofactor catalyzes the proton-coupled hydride-transfer reactions of selected racemases and epimerases. This novel organometallic molecule has a square-planar nickel atom that is tri-coordinated by a modified pyridinium mononucleotide forming C-Ni and two S-Ni bonds. Within the active site of enzyme, the nickel is additionally bound by a histidyl residue and in some cases the NPN cofactor is covalently tethered to a lysyl group. Biosynthesis of NPN is a three-step process. LarB uses nicotinic acid adenine dinucleotide (NaAD) as its substrate and catalyzes C5-carboxylation and phosphoanhydride hydrolysis to produce the dicarboxylated pyridine mononucleotide (P2CMN). LarE catalyzes an ATP-dependent sulfur insertion reaction that converts P2CMN into a species with two thiocarboxylic acids (P2TMN). LarC is a CTP-dependent nickel insertase or cyclometallase that transforms P2TMN into NPN. Recent developments in understanding the biosynthesis and utilization of the NPN cofactor will be described.



Biosynthesis of the NPN cofactor and incorporation into lactate racemase.[1]

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Abstract Number: 202

Widening the Scope of Molecular Modeling in Bioinorganic Chemistry

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Molecular modeling has become a significant asset in biomolecular chemistry, encompassing methods based on quantum mechanics (QM) and molecular mechanics (MM). Most applications in bioinorganic chemistry include the study of spectroscopic properties, enzymatic mechanisms, or dynamical events. However, some questions are still difficult to address. Among the most challenging ones are the bindings of metallic cofactors to proteins.

Here, I will present the advances made by our group in predicting the location and orientation of metallic cofactors in proteins, the assessment of the cofactor-protein intrinsic flexibility, and its impact on the catalytic mechanisms of metalloenzymes. I will first give an overview of our approaches, including multi-scale strategies, updated versions of protein-[metallo]ligand dockings, and predictors of metal binding sites in proteins (e.g., BioMetAll).[1,2] Then, successful applications of designing artificial metalloenzymes[3] and studying metal binding processes to therapeutic targets will be described.[4,5]

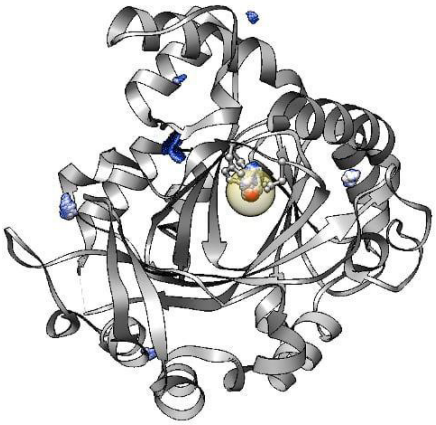

Figure 1. Example of the prediction of metal binding sites in a protein scaffold with BioMetall. Blue and red spheres represent low and high affinity sites. The golden transparent sphere corresponds to the one experimentally characterized.

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Abstract Number: 206

A multifaceted and analytical view on a metal ion-directed RNA-RNA interaction crucial for intron-splicing

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RNA tertiary interactions are crucial for larger RNAs to achieve their complex architecture, essential for proper function. While hydrogen bonding plays a vital role in mediating these interactions, metal ions facilitate or even enable them1. Here we focus on the recognition complex of a catalytic group II intron ribozyme, specifically on the intronic hairpin-loop structure that forms seven base pairs with its cognate sequence at the 3'-tail of the 5'-exon. We have solved the NMR structures of the intronic exon binding site 1 (EBS1) alone and bound to its intron binding site 1 (IBS1) strand2. A corresponding structure is formed upon binding to the respective DNA sequence dIBS1, as occurs during retro-homing into dsDNA3. Using circular dichroism (CD) spectroscopy, single molecule fluorescence resonance energy transfer (smFRET)4, and molecular dynamics simulations with enhanced sampling techniques, we obtained a detailed analytical view on the interplay between metal ions and the RNA-RNA binding event, including the local confirmation of individual nucleotides5. Prior CD spectra suggested that splice site formation crucially depends on Mg2+ and Cd2+ ions6. Our study showed that metal cations induce kinetic heterogeneity in IBS1-EBS1 binding7. Only upon fully saturated metal ion binding sites, homogeneous behavior of RNA-RNA binding is reached. The exchange rate of Mg2+ bound at certain sites is much slower than previously believed, with residence time half-lives of up to 40 seconds. Docking and undocking of the exonic RNA strand is directly dependent on metal ion coordination, as shown by the comparison of binding kinetics in the presence of different divalent metal ions. Docking rates for IBS1-EBS2 follow a classical IrvingWilliams series, while undocking follows the trend of metal ion-phosphate interactions, with a maximum at Mn2+. The RNA-RNA interaction is entirely abolished upon the exclusion of M2+ ions.

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Abstract Number: 208

Fluorescent approaches for nanoscale imaging of protein assemblies

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Amyloids are protein aggregates that form fibrils displaying a characteristic cross-β structure.[1] Amyloids are implicated in a wide range of neurodegenerative conditions, most notably Alzheimer's and Parkinson's diseases.[2] Prior to 2000, amyloids were believed to be nonfunctional pathogenic aggregates, but now >30 functional amyloids have been identified in organisms ranging from prokaryotes to humans.[1] We still lack fundamental understanding of the impact of amyloids on cells and how nature harnesses the signature features of amyloids (the cross-β structure) to serve multiple physiological roles. Therefore, tools and technologies that enable nano-scale visualisation of amyloids are highly sought after.

The nanoscale size and structural heterogeneity of prefibrillar and early aggregates, as well as mature amyloid fibrils, pose significant challenges for the quantification of amyloid morphologies. In this presentation, I will discuss our three strategies to decode amyloid assemblies at the nanoscale (i) Developing fluorescent sensors for imaging the nanoscale structure of amyloid assemblies (ii) Engineering molecular rotors to decode the nanoenvironment of amyloid aggregates and (iii) Devising a molecular nose to detect distinct isoforms and polymorphs of tau Recently, we develop a super-resolution amyloid sensor - AmyBlink-1[3] which exhibits a 5-fold increase in ratio of the green (thioflavin T) to red (Alexa Fluor 647) emission intensities upon interaction with amyloid fibrils. Using AmyBlink-1, we performed nanoscale imaging of four different types of amyloid fibrils, achieving a resolution of ≈30 nm. AmyBlink-1 enables nanoscale visualisation and subsequent quantification of morphological features, such as the length and skew of individual amyloid aggregates formed at different times along the amyloid assembly pathway. Quantitative analysis of the heterogeneity, on the nanoscale, during the formation and deposition of fibrils will open new doors to understanding the molecular mechanisms of amyloidrelated pathologies.

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Abstract Number: 211

Probing Biological Copper from the Femto- to Subzeptomolar Regime

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Cellular copper levels are tightly regulated through a complex interplay of proteins and biomolecules that form thermodynamically stable yet kinetically labile complexes with Cu(I), the prevalent oxidation state of copper inside the reducing environment of cells. Unraveling the molecular mechanisms that govern biological copper levels requires selective ligands capable of modulating the cellular Cu(I) availability or assessing the affinity of cuproproteins. To this end, we devised a family of high-affinity Cu(I) chelators and fluorescent probes based on phosphine-sulfide-stabilized phosphine (PSP) binding motifs featuring varying dissociation constants from the femto- to zeptomolar range.[1-3] Through conformational preorganization, subzeptomolar Cu(I) dissociation constants were realized, while other biologically relevant trace metals such as Zn(II), Fe(II), and Mn(II) did not bind, even at millimolar concentrations. Thus, the PSP ligand design strategy provides a robust foundation for building molecular tools to interrogate labile copper pools within complex biological environments. By immobilizing a PSP ligand on agarose, we devised a high-affinity sponge for selectively removing copper from growth media. Integrated within a donor-acceptor fluorophore platform, we created a Cu(I)-selective emission ratiometric probe, crisp-17, for visualizing dynamic changes in intracellular copper availability by two-photon excitation microscopy.[4] Combined with size exclusion chromatography - inductively coupled plasma mass spectrometry (SEC-ICP-MS), we employed a suite of PSP ligands to probe the labile copper pool of mammalian cell lysates and determined the exchange kinetics, buffer depth, and average set point. Altogether, these studies revealed that cells maintain a dynamic yet tightly controlled copper pool that is buffered at low attomolar levels through a polydisperse buffer with a broad molecular weight distribution.

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Abstract Number: 212

Binding of exogenous cyanide reveal new active site states in [FeFe] hydrogenases

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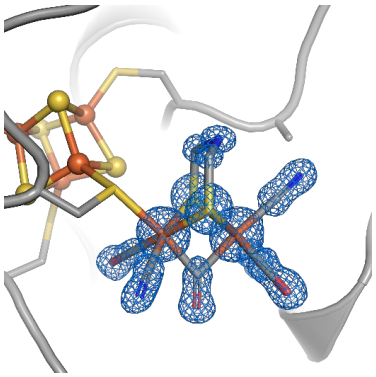
[FeFe] hydrogenases are highly efficient metalloenyzmes for hydrogen conversion. Their active site cofactor (the H-cluster) is composed of a canonical [4Fe-4S] cluster ($[4Fe\text{-}4S]_H$) linked to a unique organometallic di-iron subcluster ($[2Fe]_H$). In [2Fe]H the two Fe ions are coordinated by a bridging 2-azapropane-1,3-dithiolate (ADT) ligand, three CO and two CN^- ligands, leaving an open coordination site on one Fe where substrates (H_2 and H^+) as well as inhibitors (e.g. O_2, CO, H_2S) may bind. We investigated two new active site states that accumulate in [FeFe] hydrogenase variants where the cysteine (Cys) in the proton transfer pathway is mutated to alanine (Ala). Our experimental data, including atomic resolution crystal structures and supported by calculations, suggest that in these two states a third CN^- ligand is bound to the apical position of $[2Fe]_H$. These states can be generated both by "cannibalization" of CN^- from damaged $[2Fe]_H$ subclusters as well as by addition of exogenous CN^-. These results highlight how the interaction between the first amino acid in the proton transfer pathway and the active site tunes ligand binding to the open coordination site and affects the electronic structure of the H-cluster.



Crystal structure of the *Dd*HydAB C178A mutant bound to a CN^- ligand in the Hinact-like state.

Abstract Number: 217

Investigations into N-O-N Chelating Ligands in the Stabilisation of Boron(I) Anions

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The stabilisation of highly reactive low-oxidation state compounds is an area of considerable interst in current main group chemistry.[1] Boryl anions are a class of low-oxidation state boron compounds where the boron centre occuplies the formal +I oxidation state, contains a lone pair of electrons, and consequently react as nucleophilic source of boron. To date, seven boryl anions have been reported.[2-4] In each of these boryl anions, the coordination of the ligand around the boron(I) centre constrains the boryl within the a 5-membered heterocycle.[2-4] As a result, there has been little investigation into how a change in geometry about the boron(I) centre effects a boryl's reactivity.

To this end, the synthesis of a boryl anion with a wider coordination angle is being investigated, through the use of two tridentate ligands, **NON** and **^{F}NON** (Figure 1). Upon coordination to boron, both ligands form an eight-membered heterocycle allowing for a wider coordination angle, and therefore a potentially more reactive boryl anion. Boron(III) halide precursors have been synthesised with both ligands (Figure 1), and reduction studies to give the corresponding boryl anions are currently underway. Results will be discussed.

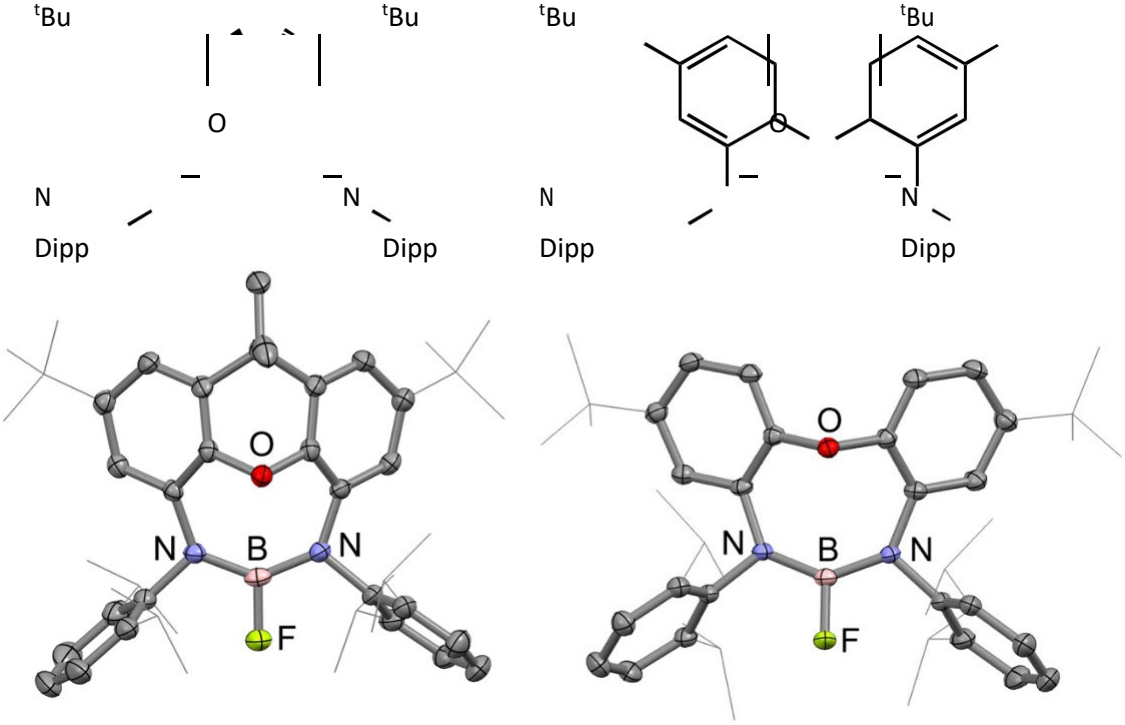

Figure 1. The **NON** ligand (top left) and **NON** boron(III) fluoride precursor (bottom left), and the **^{F}NON** ligand (top right) and **^{F}NON** boron(III) fluoride precursor (bottom right)

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Abstract Number: 218

Synthesis and Reactivity of Heavier Anionic Group 2 Hydrides

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Small molecules such as CO2, CO, N2O and SO2 are commonly regarded as the waste products of various industrial and biological processes. They are notorious for their role as greenhouse gases and are major contributors to climate change.[1, 2] In recent years, there has been a rise in interest to upcycle these waste products, such as using them in the synthesis of high value commodity chemicals. However, these molecules are thermodynamically stable and kinetically inert, therefore require activation prior to use. This often requires the use of a rare, expansive noble transition metal complex.

Calcium is widely considered to be non-toxic, environmentally benign, abundant and affordable. Hence the possibility for calcium to replace noble transition metals in the activation of small molecules have gained significant interest. One class of compounds that have demonstrated potential for this purpose are molecular calcium hydrides.

To date, vast majority of reports involving molecular calcium hydrides have focused on *neutral* and *cationic* systems.[3] However anionic calcium hydrides are potentially even more reactive than their neutral counterparts, due to a calculated increased polarisation of the Ca-H bond (by DFT).

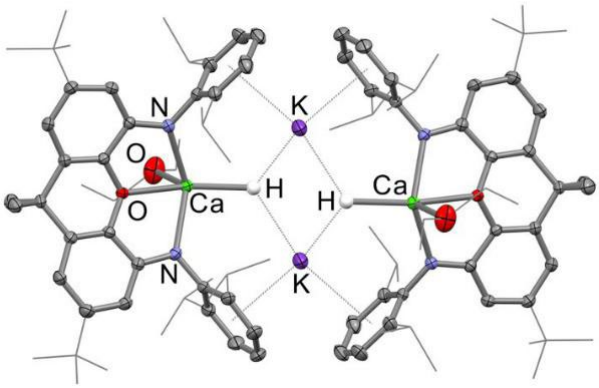

Figure 1. The *anionic* calcium hydride, K2[(**NON**)CaH(OEt2)]2 as determined by X-ray crystallography.

With this in mind, the *anionic* calcium hydride, K2[(**NON**)CaH(OEt2)]2, has recently been reported (Figure 1).[4] The complex is dimeric in the solid state, held together by potassium cations forming various interactions between the two anions. Investigation into its reactivity so far have shown that the anionic calcium hydride reacts rapidly with a wide range of small molecules, including CO, CO2 and alkenes. The results of these reactivity studies will be discussed, along with ongoing investigations targeting the heavier congeners, anionic strontium and barium hydrides.

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Abstract Number: 219

Crystalline Ge(I) and Sn(I) Centered Radical Anions: Synthesis and Electronic Structure

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A class of main group compounds that have remained relatively elusive are low oxidation state radicals, which arises as a result of their highly reactive nature.[1] This renders them prone to dimerisation, disproportionation or any number of alternate decomposition pathways.[2] As a result, the potential of low oxidation state main group radicals in small molecule activation is comparatively under-explored.[2,3] This work seeks to address the paucity in low valent main group radicals, and describes the synthesis of the first isostructural series of monomeric, anionic group 14 E(I) radicals (E = Ge, Sn, Pb) alongside a detailed characterisation of their electronic structure.[4] The series includes the first crystallographic characterisation of a Sn(I) radical (Figure 1, right) alongside the first reported example of a Pb(I) radical to date.[4] Further characterisation and reactivity will be discussed.

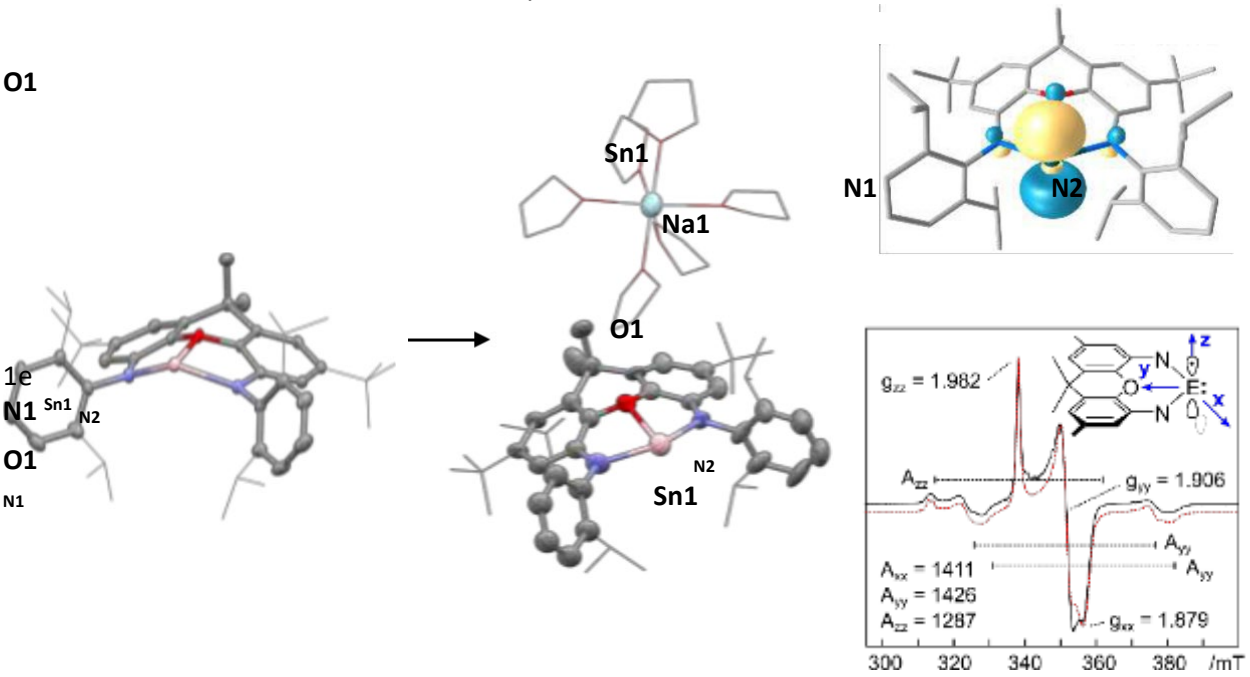

Figure 1: The one electron reduction of a Sn(II) precursor complex (left) to an anionic Sn(I) radical (centre) – the first Sn(I) radical to be crystallographically characterised. DFT studies (top right) constrain most of the spin density to the 5*p* orbital of the Sn(I) centre, confirmed experimentally *via* X-band EPR spectroscopy (bottom right).

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Abstract Number: 233

Nickel-catalyzed upcycling of nitrate and nitrite

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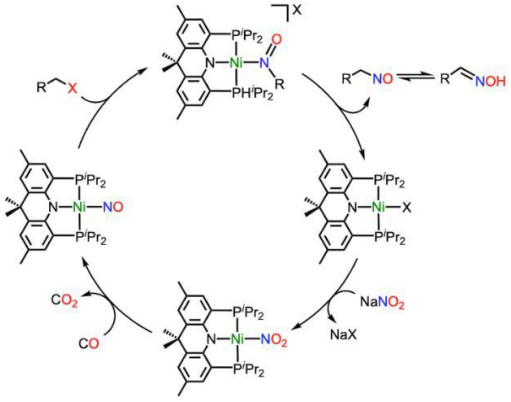
Nitrogen oxides (NOx) are serious environmental pollutants and their reduction is crucial to balance the global nitrogen cycle.[1] Analogous to the biological denitrification process, a pincer-type nickel scaffold was previously devised to deoxygenate NOx to dinitrogen (N2).[2] Here, similar to the conversion of CO2 to value-added organic products, using the NOx waste as a nitrogen source to make N-containing organic products is appealing. In this regard, a novel catalysis based on a Ni-pincer system supported by a rigidified ^{acri}PNP scaffold (^{acri}PNP^{-} = 4,5-bis(diisopropylphosphino)-2,7,9,9-tetramethyl-9*H*-acridin-10-ide) has been developed, effectively converting Ni–NOx to Ni–NO through deoxygenation with CO(g).[3] The catalyst efficiently transfers the nitroso group from the Ni–NO moiety to alkyl halides to generate nitroso alkanes that tautomerize to oximes with a turnover number of >200. While the resulting products of nitrite-deoxygenation are useful, the usage of nitrate anion remains challenging and the mechanism of nitrate deoxygenation needs to be evaluated. In order to understand the mechanism for the conversion of the nickel-nitrate complex, [(^{acri}PNP)Ni(NO3)] (**1**) to a nickel-nitro species [(^{acri}PNP)Ni(NO2)] (**2**), detailed kinetic and theoretical studies have been undertaken. As a result,
f nickel-carbonyl species, [(^{acri}PNP)Ni(CO)]$^{+}$ was identified as an important intermediate during the deoxygenation of nitrate. Finally, the usage of nitrate as a NO-resource for the catalytic NOx conversion and utilization (NCU) technology has been verified. This NCU technology is a step toward achieving a sustainable N-neutral chemical industry.



Scheme 1. Nickel mediated catalytic NOx-deoxygenation using CO(g) followed by nitroso group transfer to an organic substrate.

References

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Abstract Number: 234

Molybdoenzyme electrochemistry: redox properties and electrocatalysis

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The successful coupling of oxidoreductase enzymes with an electrochemical working electrode is the foundation of electrochemical biosensors. Here the intrinsic substrate selectivity of the enzyme may be exploited to generate a sensor that can function in the presence of a complex mixture of analytes.

We have been particularly interested in the mononuclear molybdenum (and tungsten) enzymes. There is a remarkable diversity of substrates within this family but the catalytic reaction in each case can be written the following general form that includes both the oxidases/dehydrogenases (left to right) and reductases (right to left)

$$Mo^{VI}{=}O + X \rightleftharpoons Mo^{IV} + XO$$

where '*X*' can be either an inorganic or organic species depending on the enzyme. The Mo^{VI} and Mo^{IV} oxidation states are the two forms involved in catalysis, although some interesting single-electron transfer reactions are also known. O-atom transfer between the substrate and the Mo active site is a common feature in this class of enzyme. A number of the enzymes we are investigating contain multiple redox cofactors which act as electron relays.

After turnover the electrons consumed or generated by substrate oxidation or reduction, respectively, must be exchanged between the enzyme and the electrode. In some cases heterogeneous electron exchange can occur directly with the enzyme. Alternatively, a mediator is required which shuttles between the electrode and the enzyme.

Here we shall present some of our recent work in this area, where we have applied electrochemical approaches to gain insight into electron and atom transfer reactions at the active site.

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Abstract Number: 235

Development of fluorescent analogues of vitamin B12 and the cobinamide precursor for antibacterial applications

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The development of antibiotic resistance is a major global health concern.[1] New technologies and/or drugs are urgently required to combat this issue. Development of antibiotic conjugates which are actively transported into bacterial pathogens is of interest, [2] but has only resulted in one clinically utilised cephalosporin-siderophore conjugate antibiotic, Cifederocol (Fetroja).[3] Our research proposes to hijack the native vitamin B12 uptake pathway, essential to almost all bacteria, for the delivery of established antibiotics into bacterial cells. Others have shown that B12 can carry a wide range of cargo into mammalian and bacteria cells.[4,5] Selectivity for bacterial versus human cells may be achieved by using naturally occurring vitamin B12 precursors. It has been shown by others that the B12 precursor, cobinamide (Cbi), is not taken up by human cells except for hepatocytes[6]. Most bacterial species have uptake mechanisms to scavenge the Cbi precursor.[7,8] In proof-of- concept studies, fluorescent conjugates of B12/Cbi have been synthesized. These conjugates have been used to assess the uptake of B12/Cbi into mammalian and bacterial cells. Initial studies employed stable linkers between the B12/Cbi moiety and the fluorophore; however, significant fluorescence quenching was observed. The inclusion of a cleavable linker (cystamine) between the B12/Cbi moiety and the fluorophore resulted in intracellular release of the fluorophore from the conjugate, restoring the fluorescent properties. Related conjugates incorporating fluorophores that fluoresce in the near infrared region with stable linkers were also synthesized to limit fluorescent quenching. Uptake of these conjugates by monitoring fluorescence showed successful intake of both the B12 and Cbi conjugates into bacteria. Importantly, these studies confirmed the desired selectivity as Cbi conjugates were not taken up by select mammalian cell lines. Currently studies are underway in which the fluorescent moiety will be substituted for an established antimicrobial drug and the antimicrobial properties of these compounds investigated.

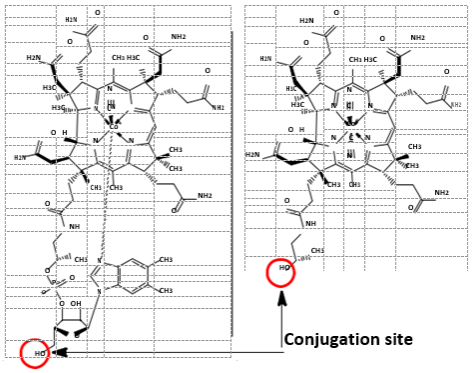

Figure 1: Structure of vitamin B12 (left) and dicyanocobinamide (Cbi, right), with the site of conjugation highlighted.

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Abstract Number: 238

Synthesis and in vivo Evaluation of DFO-8-WS, an Octadentate Ligand For 89Zr-ImmunoPET

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The choice ligand for 89Zr-ImmunoPET imaging, desferrioxamine B (DFOB), provides suboptimal hexadentate coordination to 89Zr, which may lead to metal-ligand complex instability.1 Octadentate DFOB analogues (i.e DFO*) have been reported, displaying marked increases in complex stability when compared to the hexadentate Zr-DFOB complex (logβcalc(Zr(DFOB))=41.20, logβcalc(Zr(DFO*))=51.56).1,2 Despite greater complex stability, some candidates have reduced aqueous solubility, which can complicate the use of these compounds clinically. DFO-8-WS was synthesised as a further optimisation of a previously reported octadentate DFOB analogue, DFOB-PPH-O2.3 DFOB-PPH-O2 possessed two ether oxygen atoms within the ligand backbone, which aimed to improve aqueous solubility. DFO-8-WS introduced a polyethylene glycol unit (PEG4) to the DFOB-PPH-O2 backbone, aimed at further improvements to aqueous solubility. A functionalised variant with potential for antibody conjugation, DFO-8-WS-Bn-SCN, was benchmarked against DFO-Bn-SCN to assess aqueous solubility, antibody conjugation, radiolabelling efficiency and in vivo/ex vivo biodistribution in a murine HT-29 xenograft model. Preliminary LC-MS analysis of the free ligands suggested that DFO-8-WS-Bn-SCN possessed greater aqueous solubility than DFO-Bn-SCN. DFO-8-WS-Bn-SCN was shown to conjugate to a monoclonal antibody with negligible impact to protein stability. Compared to DFO-Bn-SCN, DFO8-WS-Bn-SCN was found to radiolabel faster with greater efficiency (>95%, <5 mins) and similar stability in human serum over 7 days. In vivo 89Zr-ImmunoPET imaging showed DFO-8-WS-BnSCN gave reduced off-target signals in the liver and knee/shoulder joints with similar tumour uptake when compared to the DFO-Bn-SCN control. Ex vivo biodistribution was found to be similar for both compounds across all assessed tissues. Further work is needed to quantify the potential improvement to complex stability and aqueous solubility of DFO-8-WS-Bn-SCN when compared to DFO-Bn-SCN and other octadentate 89Zr ligands.

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Abstract Number: 239

Conformation exchange and interactions of XIAP with copper ion and Smac by combination of NMR and EPR

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The X-chromosome linked inhibitor of apoptosis, XIAP, is mainly known as the inhibitor of caspases by direct interaction with caspases with its baculoviral IAP repeat (BIR) domains. XIAP has three BIR domains and each BIR domain contains a zinc binding site, normally known as zinc finger motif. Recent studies showed that XIAP is involved in copper homeostasis in cells and the BIR domains bind copper ion. In this work, we have characterized the structural properties of BIR1, BIR2 and BIR3 with copper ion and the solution conformation of BIR3 by using paramagnetic NMR. Combination of NMR and double electron-electron resonance (DEER), the interaction of XIAP with Smac was elucidated.

Abstract Number: 246

Can we conjugate peptides to arsenic to improve its selective uptake into, and toxicity towards, specific cancers?

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Arsenic trioxide, marketed as Phenasen® and Trisenox®, successfully cures up to 90% of patients suffering from acute promyelocytic leukemia (APL).[1] The mechanisms of action of arsenic are multi-faceted and include the targeting of the cysteine-rich region of the PML -RARα fusion protein associated with the 15:17 chromosomal translocation that is characteristic of this disease. Clinical trials show that extension of this treatment to other blood cancers and solid tumours requires higher doses of arsenic, which ultimately increases the likelihood of serious side effects.

Consequently, we have patented a class of arsenic-peptide complexes with cancer cell targeting peptides, to develop a selective treatment.[2] The synthesis and characterisation of our primary complex, PhAsLHP (LHP = leukemia homing peptide containing a lymph mode homing motif and cell penetrating properties), are discussed. Evidence for the existence of interconverting isomers, detected using HPLC and 2- D NMR, is presented. X-ray absorption spectroscopy, showing the stability of the complex over 24 h, highlights its suitability for *in vitro* testing, while microprobe XRF mapping shows uptake of the complex into leukemia cells within 4 h. The results of graphite furnace atomic absorption spectrophotometry, showing selective uptake of the arsenic-peptide into leukemia cell lines (K562, HL-60, Kasumi-1 and KARPAS 45 cells) and its exclusion from peripheral blood cells and liver cancer cells (HepG2 cells), will be presented. Finally, proof of concept will be presented wherein *in vitro* toxicity studies show a 1000x reduction in the IC50 value of PhAs(LHP) in leukemia cells compared with non-leukemic cells.

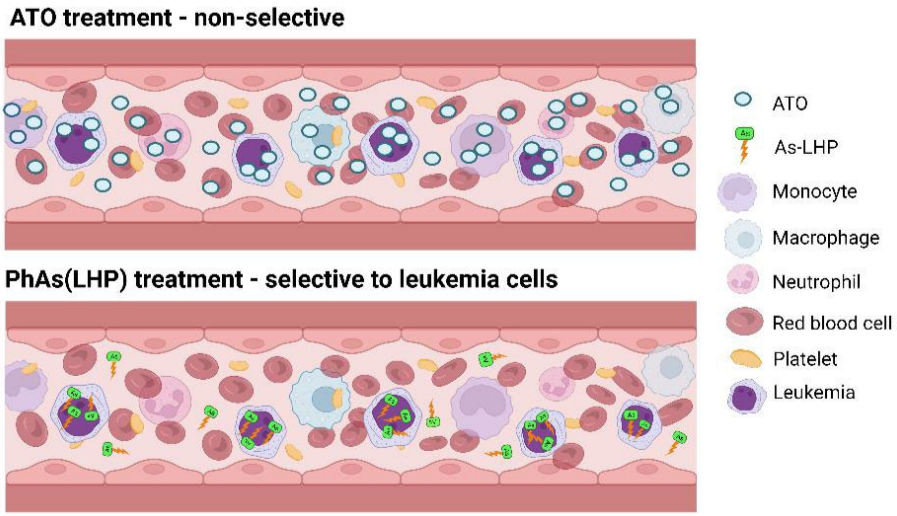

Figure 1. Selective targeting of leukemia cells following treatment with arsenic coordinated to a leukemia homing peptide. Figure created using BioRender.

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Abstract Number: 248

Novel fluorescent probe for sensing pH environment in biological context

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Small molecule fluorescent sensors are excellent tools to probe cellular environments with temporal and spatial resolution. We have developed a fluorescent lifetime sensor sensitive to intracellular pH environment, which is an important parameter that has significant roles in homeostasis, proteolysis, ATP production and apoptosis.1,2 Dysregulation of pH environment often inflict stress to cells, leading to diseased state. For example, cancer cells often exhibit abnormal pH values between acidic pH 4-5, which conditions them better against cancer therapy and metastasis.3 With fluorescent pH probes, the relationship between the acidification of pH environment and the corresponding disease pathology can be investigated. Herein, our fluorescent pH sensor can respond to pH environment through modulating its emissive intensity and fluorescence lifetime, which can be used in confocal microscopy imaging and fluorescence lifetime imaging microscopy (FLIM). We will report their photophysical properties towards pH and explore their biological compatibility and applications in monolayer cancer cell lines and 3-dimensional tumour spheroids. In addition, we aim to expand the sensing range by grafting previously reported and novel fluorescent sensors onto non-toxic and highly stable nanoparticles. We envisage that this will create a powerful tool that can sensitively differentiate pH values in the biological relevant range of pH 4-8.

Abstract Number: 250

Versatile π-Stacking and H-bonding Connectors in the formation of porous Metal-Organic Materials

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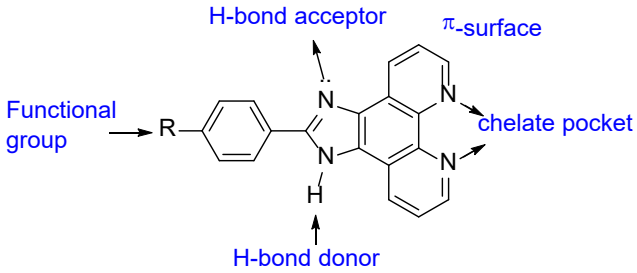
Ligands with increasing functionality and complexity are being used in metal organic framework (MOF) chemistry. Ligands based on imidazo[4,5-f]-1,10-phenanthrolines provide a great degree of synthetic versatility. They can be prepared in a step-wise "clip together" fashion allowing a variety of functional groups and different substitution patterns to be easily incorporated in to the connector design. They are excellent connectors for the formation of MOFs as they bind to a variety s-, d- and f-block metals. Inherently, they provide π-surfaces and have hydrogen bonding motifs which help to engineer the MOFs they produce.



We will present our recent results using differently substituted imidazo[4,5-f]-1,10-phenanthroline-based connector ligands to produce a range of MOFs with s-, d- and f-block metals. The strong π-interactions between ligands often lead to double-walled structures providing structural robustness. H-bonding interactions also assist with inter-ligand interactions contributing to the formation of porous channels. Gas adsorption and Far-Infrared studies will be reported as part of our investigation of solvent behaviour in these systems

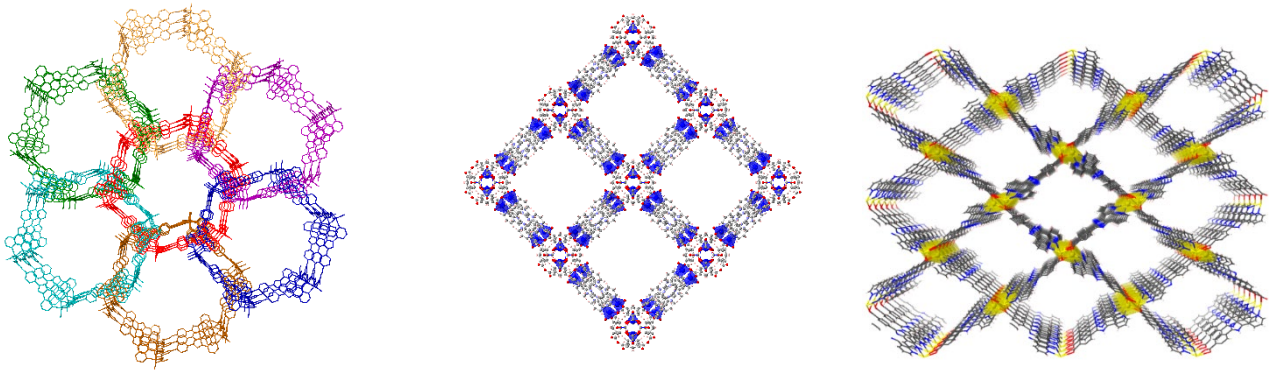


Figure 1: Phenanthroline-carboxylate ligands based networks: (left) Interpenetrated Zn(II) Metal-Organic Nanotubes (middle) Cu(II) porous MOF (right) Na-based MOF.

Abstract Number: 251

Fly ash-derived iron oxide nanocatalysts for bio-oil upgrading and green syn-gas synthesis

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Iron oxide is a cost-effective catalyst for a variety of catalytic reactions including ketonisation of acidic compounds in bio-oil, high-temperature water-gas shift reaction and chemical looping methane dry reforming. To date, most iron oxide catalysts for these applications were synthesised upon using of reagent-grade chemicals, and via a bottom-up approach in which varying dopants were introduced stepwise into iron oxide. Herein, we report a different approach, namely topdown synthesis of nano-sized iron oxide catalyst from a Fe-rich fly ash (FA), an abundant waste derived from coal-fired power plants. More specifically, FA sample was initially subjected to grounding and washing by sodium carbonate to remove unwanted sulphur and unburnt carbon within it. Subsequently, it was dissolved into HCl to selectively dissolve elements, in particular iron within it. Afterwards, the leachate was titrated with a base solution to increase its pH from 3 to 12. Resultant precipitates were then dried, annealed in nitrogen and finally reduced in H2 (10%) to convert into desired magnetite catalyst. Interestingly, the catalyst was confirmed to bear a Fe@Fe3O4 core-shell structure, accompanied by surface segregation of impurities including Al, Mg, Ca and Ti that were dissolved with Fe together in the acid leaching stage. Reduction-induced restructuring significantly enhances both surface acid and base properties, with extended (5 h) reduction favoring medium strength Lewis acid sites, promoting ketonisation through synergistic activation of two acetic acid molecules. High activity and on-stream stability of FA-derived reflects a combination of relatively high surface area, oxygen vacancies and mixed Lewis acid/Bronsted base characteristics. With the protection of magnetite-shell on sintering, FA-derived catalysts also exhibited improved activity, thermal stability and long-term durability for afore-mentioned three catalytic applications. Apart from Al3+ being a textual promoter enhancing the interfacial area of catalysts, the minor impurities also promoted the redox rate and basicity of catalysts.

Abstract Number: 252

Photochromic Molecular Assemblies of Polyoxometalates and Diarylethenes

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Polyoxometalates (POMs) are molecular metal oxides composed of predominantly early transition metals in high oxidation states, however, there are now numerous exceptions. The remarkable structural, compositional, and resulting electronic diversity of POMs is undeniable and is responsible for these compounds attracting general interest across the sciences. [1-2] Intrigued by the opportunity that the combination of DAEs and POMs in a molecular assembly would present to investigate this balance of photochemical processes, we designed and prepared hybrids bringing together these components. In this presentation, I will discuss our experimental findings in terms of the solid-state properties, structure and stability in addition to the photochemical behaviour of the resulting compounds following excitation.

By using the molecular metal oxide $\{PMo_9O_{31}\}$ as a building block, we have successfully taken advantage of well-defined surface reactivity that supports the ordering of ligands in the assembly *via* directional intramolecular contacts between the ortho hydrogen atoms of the pyridyl groups of the DAE and the adjacent terminal oxido ligands. In terms of molecular design, the principle objective was to mitigate coordination of the photochemically inactive (O_P) isomer, which was achieved due to steric implications imposed by $\{PMo_9O_{31}\}$, akin to our previous report using an alternative POM scaffold with only one point of coordination. [3-4]

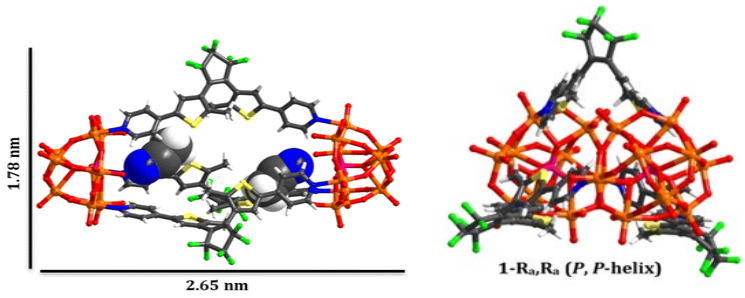

Figure 1. Graphical representation of the molecular capsule $[(PMo_9O_{31})_2(DAE)_3]^{6-}$

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Abstract Number: 253

Linking of Metal-organic Cages into Porous Multi-cage Frameworks

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Porous, crystalline materials such as metal-organic frameworks (MOFs), are ultra-porous solids with topologically diverse structures. Formed from metal ion and organic ligand building-blocks in one-pot, the potential combination of these components in MOF synthesis, and their respective forms, are limitless. In general, the wide selection of these precursor components enables the preparation of materials with tuneable properties for targeted applications including sensing, drug delivery, catalysis and as adsorbents.[1]

However, despite the field's maturity, limitations to the wider application of MOFs persist. This includes the lack of processibility following material application.[2] Coordination bonds construct the framework, dictating the need for harsh conditions to disassemble and subsequently regenerate the pristine framework post-application, making such an avenue undesirable.[3] Another consideration stems from synthetic difficulty to incorporate multiple metal ion and ligand types under conventional one-pot conditions.[4]

Recently, our group has demonstrated the use of Rh_4L_4 and Cu_4L_4 metal-organic cages (MOCs) as supramolecular building-blocks to realise multivariate MOFs through Rh-aniline coordinative linking, overcoming the aforementioned issues.[5] We are expanding this approach through the preparation of novel MOCs with variable geometries to imitate reticular chemistry principles in MOFs. By targeting MOC combinations with defined connectivities, predicted multivariate MOF architectures will be pursued.

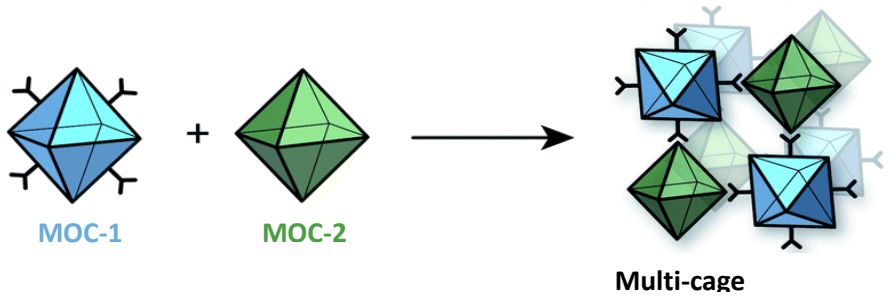

Figure 1. Strategy to synthesise multi-cage frameworks from different MOCs.5

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Abstract Number: 254

Extending photoredox catalyst activity through choice of electron donor

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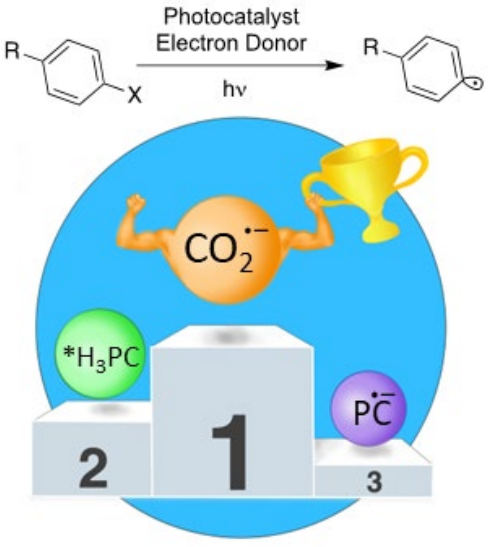
Visible light photoredox catalysis promises a more sustainable approach for producing valuable chemicals without relying on high temperature or pressures. Transition metal complexes (particularly d^6 ruthenium(II) and iridium(III)) still represent the catalytic performance benchmark, and readily act as potent single electron reductants and oxidants in their optically excited state.

Successful photoredox catalysis is energetically limited by catalyst redox properties (in both the ground and excited electronic state) as well as irradiation wavelength (visible light, ~400-700 nm, does not exceed 3.1 eV in energy). Multiphoton excitation strategies (i.e., the input of more than one photon per product output) are evolving to provide access to demanding reactions with lower photon energies, but advancing photocatalytic methodology beyond these inherent energy limits remains an ongoing challenge.

Sacrificial additives are commonly employed in photoredox catalysis as a convenient source of electrons, but what occurs after electron transfer is often overlooked. Tertiary alkylamines initially form a radical cation following electron transfer, which readily deprotonates to form strongly reducing, neutral α-amino radicals. Similarly, the oxalate radical anion ($C_2O_4^{\bullet-}$) rapidly decomposes to form $CO_2^{\bullet-}$ (E^0 ~ -2.2 V vs SCE). We show that not only are these reactive additive intermediates generated under photoredox conditions, but how they also impact the desired photochemistry both productively and unproductively. Photoredox systems using oxalate as an electron donor can engage substrates with greater energy demands, extending reactivity past the energy limits of single and multiphoton transition metal catalysts. Furthermore, oxalate offers better chemoselectivity than the commonly employed triethylamine when reducing substrates with moderate energy requirements.



Abstract Number: 255

Inelastic Neutron Scattering to Probe Lanthanide Exchange and Relaxation Dynamics

Marcus J. Giansiracusa,[a] Maja A. Dunstan,[a] Richard A. Mole,[b] Colette Boskovic[a]

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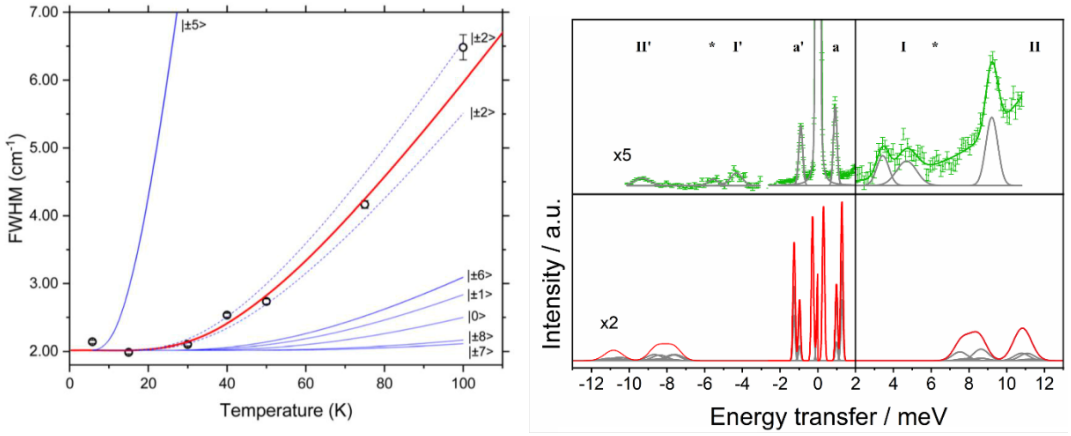
Inelastic neutron scattering (INS) spectroscopy represents a powerful technique to investigate low energy states of lanthanide (Ln) complexes.[1] The intrinsic spin of the neutron allows discrimination of magnetic excitations from similar energy excitations arising from phonons. As such, it can be applied to directly measure of the crystal field splitting as well as having sensitivity to weak exchange interactions characteristic of Ln complexes. Understanding these magnetic states is essential for designing Ln complexes for applications, with the literature radical containing Dy2I3 complex exhibiting remarkable magnetic properties.[2] Our recent work has demonstrated that INS can probe relaxation dynamics as a broadening effect to the spectroscopic features.[3] This has significant implications in the molecular-magnetism community where retention of magnetic moment is essential for applications including in data storage or spintronics devices and as quantum bits.[4] These investigations are supported by CASSCF-SO calculations to provide a quantum mechanical understanding for the origin of these properties.



Left) FWHM of INS excitations versus temperature, indicated a lifetime broadening **Right**) Experimental INS spectrum (**green**) showing direct measurement of Ln-radical exchange (peak **a**) along with CASSCF-SO simulation (**red**)

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Abstract Number: 256

Probing Formation of Phenylcopper (II) Complexes via Three Different C-X Bond Activation Pathways.

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Copper-catalysed cross-coupling reactions have a rich history dating back over a century ago to Ullmann's reports on homo- and heterocoupling reactions for the synthesis of biaryls, diaryl amines, and diaryl ethers.[1] Despite offering significant cost and environmental benefits when compared to conventional Pd analogues,[2] their mechanistic features remain poorly understood and may involve Cu(I), Cu(II) and Cu(III) intermediates. While copper(II) aryls have been invoked as intermediates copper catalyzed decarboxylative C-N coupling reactions,[3] rarely have such complexes been structurally characterised.[4]

Here multistage mass spectrometry experiments using an ion-trap mass spectrometer as well as DFT calculations are deployed to examine the possibilities of forming organometallic $Cu^{(II)}$ complexes $[(phen)nCuPh]^{+\bullet}$ (n = 1, 2) via three different C-X bond activation pathways: transmetalation, decarboxylation or desulfination (eq. 1). Two other pathways were found to operate in competion: (i) electron transfer (eq. 2) and (ii) ligand loss (eq. 3).

$[(phen)nCu(XPh)]^{+\bullet}\rightarrow$	$[(phen)nCuPh]^{+\bullet}$	+(X)	(1)(X = CO2, SO2 or BPh3)
$\rightarrow$	$[(phen)nCu]^{+}$	$+(XPh)^{\bullet}$	(2)
$\rightarrow$	$[(phen)n\text{-}1(XPh)]^{+\bullet}$	+(phen)	(3)

The reactivity of these organocopper cations $[(phen)nCuPh]^{+\bullet}$ (n = 1, 2) towards a range of neutral substrates will be described. Prelimary results with allyliodide and dimethyldisulfide reveal that $[(phen)CuPh]^{+\bullet}$ abstracts $I^{\bullet}$ and $CH3S^{\bullet}$.

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Abstract Number: 257

Utilising Zr-MOFs as Supports and Templates for Highly Selective Ternary CO2 Hydrogenation Catalysts

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Carbon dioxide (CO2) hydrogenation is a promising reaction for industrial carbon capture and utilisation (CCU), enabling the conversion of captured CO2 to a C1 building block for value added fuels and chemical feedstocks.[1] Supported copper/zinc oxide (Cu/ZnO) nanoparticles are active for CO2 hydrogenation into methanol and are already in use for industrial scale reactions however, low conversion and/or poor selectivity currently reduces their overall performance, making them less economically favourable.[1,2]

Due to their exceptionally high surface areas, highly connected porous structures, and chemically mutable structures, Metal-organic Frameworks (MOFs) represent a novel class of support materials for such catalysts.[1,3] Zirconium-based MOFs have been investigated as supports for Cu/ZnO nanoparticles as they are highly stable, and zirconium is a known promoter for Cu/ZnO methanol synthesis catalysts, able to significantly improve selectivity.[1] This contribution will present our recent efforts to examine the influence of the structure metrics and composition of different zirconium-based MOFs as supports for Cu/ZnO nanoparticles (Cu/ZnO@MOF catalysts). We report synthesis of the pre-catalysts, their activation, assess their performance for CO2 hydrogenation into methanol in batch, and the characterisation of the samples post-catalysis. In addition, we report the activity and form of MOF-derrived catalysts accessed by exposing Cu/ZnO@MOF templates to oxidative and reductive conditions.

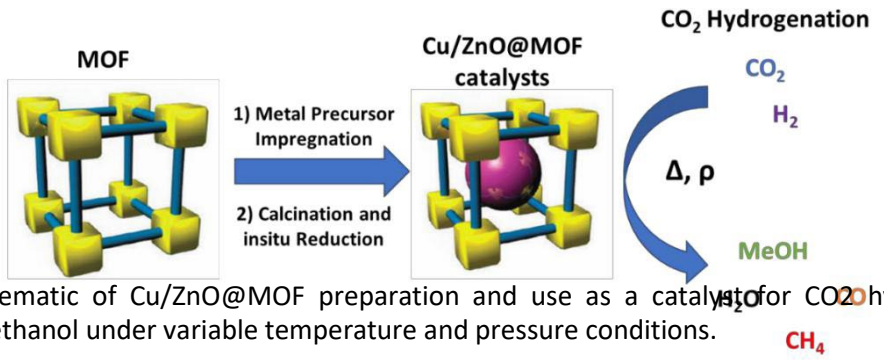

Figure 1: Schematic of Cu/ZnO@MOF preparation and use as a catalyst for CO2 hydrogenation to synthesise methanol under variable temperature and pressure conditions.

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Abstract Number: 259

Engineering plants that can fix nitrogen

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Engineering non-legume plants that can fix nitrogen and thereby reducing the need for synthetic nitrogen fertilizer has been a long-standing goal in biotechnology. This could be achieved by transferring the genes that code for nitrogenase - the enzyme that catalyses nitrogen fixation - into plants. Nitrogenase is a two-component enzyme consisting of the dinitrogenase reductase, the Fe protein, and dinitrogenase. There are three different classes of nitrogenase, the MoFe nitrogenase, the VFe nitrogenase and the Fe-only nitrogenase. These are named after the metal present in the cofactor, [XFe7S9C-homocitrate] (X = Mo, V or Fe). In addition to the cofactor, where N2 is reduced to NH3, dinitrogenase also contains the P-cluster, [Fe8S7], and the Fe protein contains a [Fe4S4]-cluster. These clusters are highly oxygen sensitive. To protect nitrogenase from oxygen when expressed in a plant cell, we are expressing nitrogenase in the plant mitochondrial matrix as the concentration of free oxygen in this organelle is thought to be low. In addition to the structural enzymes, nitrogenase requires accessory proteins involved in iron-sulphur cluster biosynthesis, which are at a minimum NifS, U, B, FdxN and V for the Fe-only nitrogenase and NifS, U, B, FdxN, V, EN, Q and M for the MoFe nitrogenase. Furthermore, specific electron transport proteins, such as NifF and NifJ, will likely have to be co-expressed to direct electron flow to nitrogenase. In our lab we are working on the assembly of the MoFe and the Fe nitrogenase in plant mitochondria. One challenge that needs to be overcome is the low solubility of some nitrogenase proteins when heterologously expressed. Furthermore, the iron-sulphur clusters need to be successfully assembled and this requires the interplay of several accessory proteins. Here we show our progress regarding the expression and activity of nitrogenase components expressed in plants.

Abstract Number: 260

Fluorescent Tools to study ferritin in *Caenorhabditis elegans*

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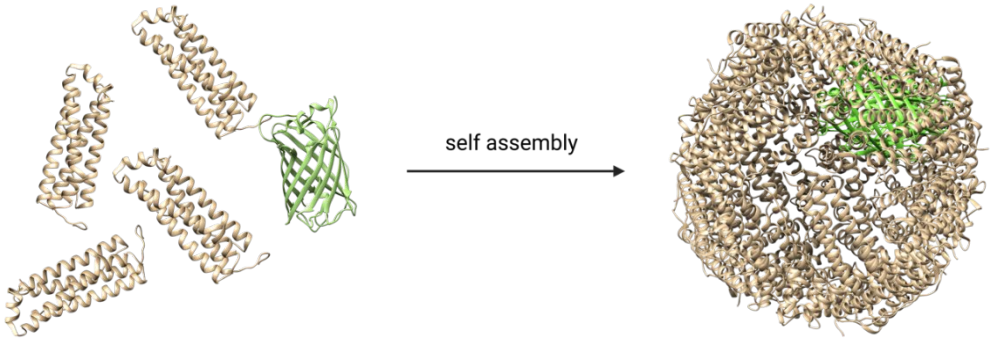
Ferritin is an iron storage protein that plays a central role in iron homeostasis by storing ~2500 iron atoms as an iron-oxide mineral core.[1] Although many studies[2] have explored iron uptake, there are still open questions as to how it functions in a multicellular organism, especially with respect to how iron is released. We recently overexpressed and purified the two ferritin homologues of the model organism Caenorhabditis elegans, FTN-1 and FTN-2, and described them structurally and shown they have ferroxidase activity, as suggested by their sequence alignment.

One advantage of C. elegans is it is small (~1 mm long) and transparent and thus amenable to microscopy. We have now explored fluorescent labelling of FTN-2, the major ferritin homologue expressed in C. elegans to investigate protein transport and iron release. A mixture of strategies has been applied ex vivo, including genetic engineering and chemical conjugation to attach GFP, fluorescein and iridium complexes. The advantages and disadvantages of these methods will be discussed, along with how these labels affect iron storage and fluorescence quenching.



Self-assembly of FTN-2-GFP

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Abstract Number: 261

Enhanced photocatalytic performance of ultrathin Ru-CdIn2S4 nanosheets for simultaneous H2 production and biomass conversion

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Semiconductor-assisted photocatalysis is one of the sustainable and ecofriendly technologies for hydrogen (H2) production, where H2 is a promising substitute for non-renewable fossil fuels.[1] CdIn2S4 (CIS), is an exciting photocatalytic material because of its high visible light harvesting capacity and tunable band gap (2.0-2.4 eV).[2] However, the main drawback of CIS photocatalysts is rapid electron-hole recombination. The incorporation of metal atoms/ions can enhance the photocatalytic performance of CIS.[3] Herein, we focused on the fabrication of ultrathin CIS nanosheets *via* a facile hydrothermal method with in-*situ* deposition of Ru atoms to enhance the optical properties and photocatalytic performance of CIS toward the photocatalytic H2 production in the presence of a biomass intermediate, Furfuryl alcohol (F-OH), as a hole scavenger, **Figure 1a**. The results showed the successful synthesis of CIS nanosheets (**Figure 1b**) with the typical cubic crystalline structure (**Figure 1c**). Besides, the results showed the positive effect of the dispersion of Ru on the CIS to shift the absorption edge of CIS and further enhance its absorbance in the visible region (**Figure 1d**). Additionally, about 6:43-fold enhancement was achieved in the x%Ru-CIS samples where the 1%Ru-CIS sample achieved a H2 production rate of 2781 µmol g^{-1} h^{-1} compared to the bare CIS nanosheets that achieved 65 µmol g^{-1} h^{-1} (**Figure 1e**). Hence, these outstanding results showed the synergetic effect of Ru atoms to enhance the optical absorbance and photocatalytic performance of CIS nanosheets *via* improving the optical absorbance, enhancing the charge separation, and consequently, augmenting the H2 production rates.

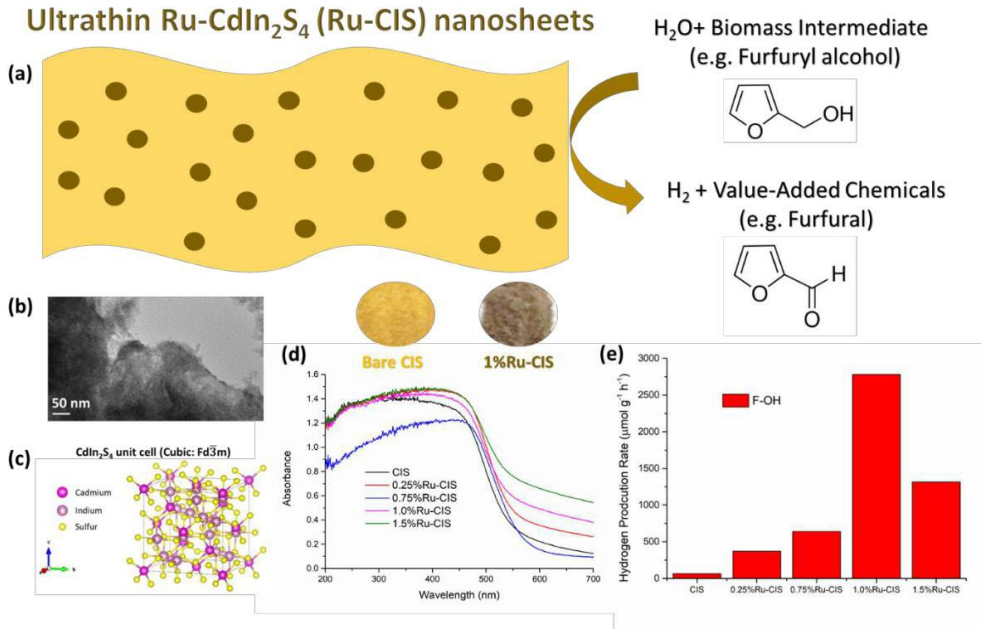

Figure 1. (a) Schematic representation of dispersion of Ru atoms on the ultrathin CIS nanosheets for simultaneous H2 production and biomass conversion, (b) TEM image of CIS nanosheets, (c) the unit cell of CIS, (d) the DRS spectra (insets: photographic images of bare CIS and 1%Ru-CIS), (e) the photoproduced H2 production rates of bare CIS and x%Ru-CIS nanosheets in the presence of F-OH.

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Abstract Number: 262

Bioavailability of selenium from selenotrisulfides in cultured cells

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Selenium is a nutritionally essential trace elements in most animal species. This element is taken up in inorganic or organic compounds from the food supply and finally incorporated into the selenoproteins as selenocysteine. Selenotrisulfide (-S-Se-S-, STS) is one of a metabolic intermediate of selenium and can react with free cysteine (Cys) thiols in proteins through the thiol-exchange reaction (R-S-Se-S-R' + R"-SH → R-S-Se-S-R" + R'-SH). We reported that thiol-exchange reactions of free Cys thiols in human hemoglobin and serum albumin are involved in the metabolism and transport of selenium in blood.[1] Thiol-exchange reaction was also presumed to occur in other organs and tissues since there are several STS reactive proteins in rats.[2] Rat liver fatty acid binding protein, Cystatin-12 precursor, myoglobin and peptidyl-prolyl *cis-trans* isomerase A have free Cys thiols and can bind selenium through STS bond. In this study, primary cultured neurons and human hepatoma (HepG2) cells were incubated with small molecular mass STS and protein bound STSs to investigate the absorption of selenium from STSs.[3]

Rat dorsal root ganglion (DRG) neurons were obtained from male Wistar rats and cultured in 10% fetal bovine serum supplemented Dulbecco's modified Eagle medium. HepG2 cells were cultured in the same medium as the DRG neurons. Penicillamine selenotrisulfide (PenSSeSPen, Fig. 1) was synthesized from selenious acid (SA) and L-penicillamine according to the previous report.[1]

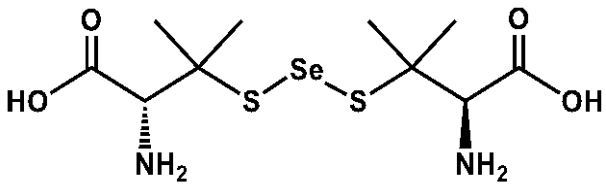

Fig. 1 Structure of L-penicillamine selenotrisulfide (PenSSeSPen).

Human serum albumin (HSA) was reduced with dithiothreitol. Reduced HSA and human hemoglobin (Hb) were mixed with PenSSeSPen and the mixture was dialyzed to remove unreacted PenSSeSPen. PenSSeSPen, STSs bound to HSA (HSA-SSeSPen) and hemoglobin (Hb-SSeSPen) were added to the medium to make selenium concentration 1 μM. Selenium concentration in cell lysate and cellular selenium-dependent glutathione peroxidase (GPx) activity of DRG neurons and HepG2 cells were measured after 6-24 h incubation with STSs.

During the incubation time of 6-24 h, cellular selenium concentration in DRG neurons increased along with the incubation time. The GPx activity of STS supplemented DRG neurons increased in a time dependent manner and selenium from PenSSeSPen and HSA-SSeSPen was utilized as effective as that from SA at incubation time of 72 h. In HepG2 cells, cellular selenium concentration and GPx activity significantly increased after the incubation with selenium for 24 h. During the incubation time of 6-72 h, similar increasing pattern of the cellular selenium concentration and GPx activity were observed in the HepG2 cells incubated with SA and PenSSeSPen. On the other hand, the cellular selenium concentration and GPx activity of the HepG2 cells incubated with protein bound STSs was lower than those incubated with small molecular mass selenium compounds. Although selenium absorption mechanisms were

thought to be different between the DRG neurons and HepG2 cells, selenium from STSs was absorbed and utilized for increasing the cellular GPx activity. STS compounds were proved to be effective as selenium source in primary cultured neurons and human hepatoma cells.

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Abstract Number: 269

From Organometallic Molecular Wires to Functional Devices: Redox Switching in a Molecular Circuit

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Molecular electronics is largely driven by the study and control of charge transport through molecules assembled between two or more macroscopic electrodes. While many studies focus on wire-like molecular conductance, methods to incorporate additional electrical features such as switching, rectification and memory effects feature in many modern studies.[1] To these ends, redox active systems that display distinct electrical features in different redox states are of interest.[2] Ferrocenes offer excellent electrochemical reversibility between the ferrocene/ferrocenium redox couple at low voltage and considerable synthetic versatility.[3] However, there are considerable challenges to embed ferrocenes into functional molecular components due to the ready rotation of the Cp rings around the Cp-Fe axis which often leads to binding of ferrocenes in a 'hairpin' conformation to a single electrode surface.

In this presentation, the syntheses, molecular structures, and redox properties of 1,1'-diethynyl ferrocene and ferrocenium functionalized with thio-methyl and 3,3-dimethyl-2,3-dihydrobenzo[*b*]thiophene (DMBT) surface binding groups will be described. Single molecule conductance profiles determined from STM break-junction measurements reveal conductance switching or transistor-like response arising from a simple electrochemical gating event which leads to a difference of 1 – 2 orders of magnitude between the two redox-related states.

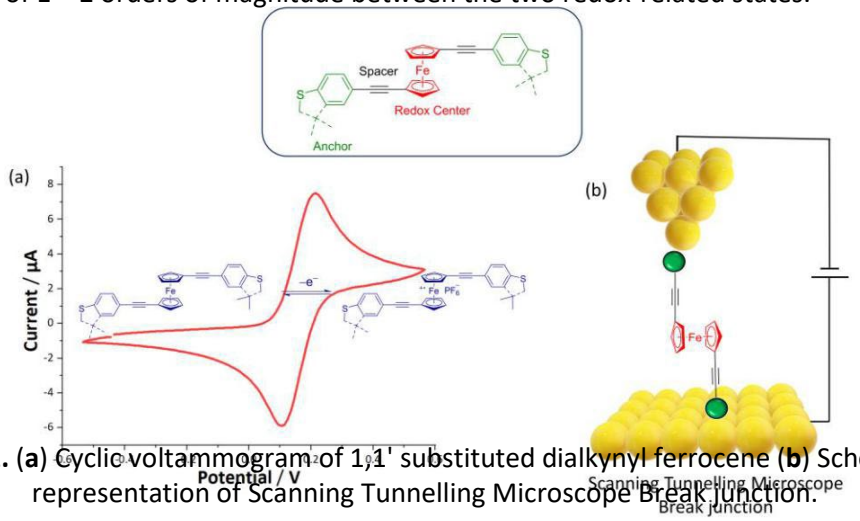

Figure1. (**a**) Cyclic voltammogram of 1,1' substituted dialkynyl ferrocene (**b**) Schematic representation of Scanning Tunnelling Microscope Break Junction.

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Abstract Number: 270

Functional diversification of molybdenum-containing S-oxide reductases drives novel physiological roles in bacterial fitness and pathogenicity

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Despite being among the first molybdenum enzymes that were studied in structural and spectroscopic detail, the exact physiological functions of Mo-containing S-oxide reductases (S-ORs) are often not well defined. S-ORs are found in several molybdo-enzyme families and a large variety of bacteria, including many pathogenic species[1]. In these bacterial pathogens, a diversification of the substrates converted by S-ORs can be expected, as canonical substrates such as dimethyl sulfoxide are generally absent from vertebrate bodies. Additionally, it can also be expected that expression patterns of these enzymes would have changed compared to related enzymes found in environmental bacteria to support the physiological needs of pathogenic bacteria.

Using the respiratory pathogen *Haemophilus influenzae* as a model organism, we have shown that the presence of the two Mo-containing S-oxide reductases, MtsZ and DmsA, is required for long-term survival during infections in mice and primary human epithelia[2], and both enzymes are induced by host responses to infection. Kinetic and structural analyses revealed that for MtsZ and related enzymes, small changes in a previously unrecognized part of the substrate-binding pocket are likely responsible for the known substrate specificity diversification within this group of enzymes[3]. Interestingly, the catalytic profiles of MtsZ and the structurally unrelated DmsABC S-oxide reductase were highly similar and included methionine sulfoxide but also biologically relevant N-oxides. Our data indicate that Mo-dependent S-oxide reductases support virulence in a variety of bacterial pathogens other than *H. influenzae*.

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Abstract Number: 271

Molecular Complex Perspective of Oxygen-Stable Inhibited State of [FeFe] Hydrogenase

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[FeFe] hydrogenases display catalytic H2-evolution and oxidation ability, which offers an opportunity for the implementation to applications of H2-production devices and fuel cells. One drawback of [FeFe] hydrogenases is its oxygen sensitivity toward degradation of the active site. It is found that the vacant site at the Fe^d center (the Fe distal to the attached [4Fe4S] subset), which is open to substrate binding, is susceptible to the coordination of molecular oxygen. It leads to the formation of a transient superoxide/peroxide species, resulting in the degradation of the H-cluster. Recent discoveries suggest that the presence of the Hinact state of the H-cluster mitigates the influence of O2 attack. In the O2-resistant Hinact state, the terminal apical site of the Fe^d is blocked by an exogenous sulfide (SH^-) or a cysteine residue (C367) of the peptide loop in the proximity of the Fe^d. We herein report the inhibitor-bound 2Fe2S model complexes with biological relevance to the Hinact state. The complexes are characterized to compose of the terminal Cl- (or SH-) ligation to the Fe center with the inverted geometry bearing the bridging CO group. The t-X (X = Cl, SH) coordination, revealing the terminal inhibitor-binding behavior, is labile and kinetically controlled. The t-SH ligation is weaker than the t-Cl analog, and is easily replaced by exogenous Cl^- salts for the formation of the more stable t-Cl species. The Fe2 core displays 2 fully oxidized Fe(II) centers, consistent with the results of the biochemical study. Both inhibitor-bound species are resistant to O2 coordination and decomposition. The catalytic activity investigation involving halides might have suggested the other candidate to the oxygen-tolerant, catalytic inactivated state.

Abstract Number: 272

LUMINESCENT IRIDIUM(III)-BORONIC ACID COMPLEXES FOR SENSING CARBOHYDRATES

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Carbohydrates are essential to human life as we know it; however, carbohydrate imbalances in the human body have been associated with a myriad of negative health effects including diabetes, autoimmune disease1 and cancer.2 Hence, accurate and selective detection of carbohydrates in biological systems is crucial for timely diagnosis of carbohydrate-related health issues. Luminescent molecules functionalised with boronic acid groups have shown great potential for sensing and imaging carbohydrates.3, 4 Here the synthesis of a family of cyclometalated iridium(III) complexes of the general form [Ir(X)2(L)]+, (where X = 2-phenylpyridine, 1- phenylpyrazole, 2-phenylbenzothiazole or 1-phenylindazole and L = 2-pyrazole-1-yl-pyridine substituted with a boronic acid group at two different positions) are reported. The capacity for these compounds to form cyclic boronic acid esters with the sugars glucose and fructose has been evaluated using photoluminescence titration studies. The iridium(III) complexes form adducts with both glucose and fructose, with increased levels of boronic acid cyclic esters being formed with the carbohydrates at higher pH values. The titration studies show that there is either an increase or a quenching of the luminescent emission intensity with increasing pH or sugar concentrations depending on the structure.

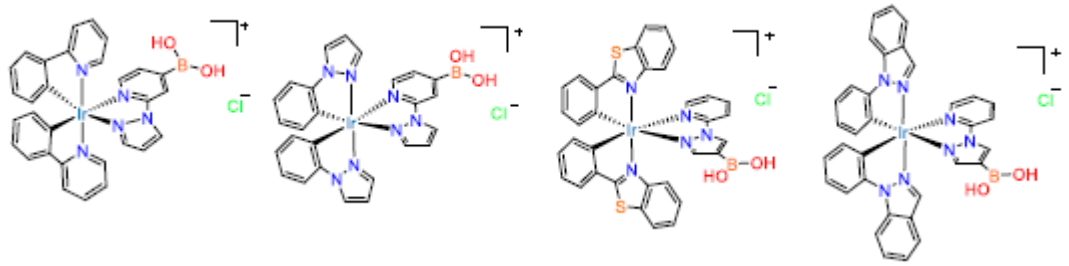

Figure 1: Family of cyclometalated iridium(III) complexes bearing a boronic acid functional group

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Abstract Number: 273

Novel azacryptand host molecules and their alkali and coinage metal complexes

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Cryptands are known for their unique ability to selectively encapsulate ions, neutral molecules and for the high thermodynamic and kinetic stability of their metal complexes.[1] These compounds are typically composed of donor atoms arranged in a cage-like structure and they are of interest for applications including catalysis, ion sensing, drug delivery, and molecular recognition.[1-2] In this project a series of azacryptand ligands derived from the macrocycle CYCLEN with pyridyl and phenylene linker units have been synthesised using a versatile one-pot reaction.[1] Depending on the choice of carbonate base used in the synthesis, proton, sodium, potassium and caesium complexes of these ligands were isolated, with a variety of structures formed as a result of the group 1 metal cation radius. Deprotonation of the cage molecules was achieved with the base DBU and the capacity of the free base cages to form coordination complexes with the group 11 metals Cu and Ag were investigated. Dinuclear complexes were isolated with the Cu complex being redox active. The ligands and complexes have been fully characterised using NMR, MS and X-ray crystallography.

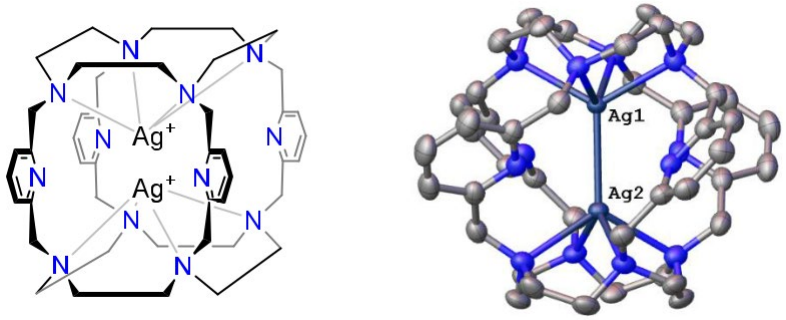

Figure 1. Structure of dinuclear Ag(I) N12-azacryptate complex and the corresponding X-ray crystal structure of this compound.

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Abstract Number: 275

Exploring the effect of bulky 3D-linkers on MOF host-guest interactions

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Aromatic ligands, with polycarboxylate or multitopic functionalities, govern the synthetic chemists' toolbox when forming metal-organic frameworks (MOFs) due to their rigid nature, commercial availability, and their variable coordination modes. Conversely, despite their extensive success in creating a rich foundation for MOF development, restriction to solely phenyl interactions within adsorbates represents a possible limitation and reduced variation in the pore chemical environment of the materials.[1] Our research explores how aliphatic 3D-linkers in MOFs can influence the pore environment and overall structural properties of MOFs. Our team explores linkers such as cubane-1,4-dicarboxylic acid (H2cdc), bicyclo[1.1.1]pentane-1,3-dicarboxylic acid (H2pdc) and p-carborane-1,12-dicarboxylic acid (H2pcarb). These linkers are structurally similar to benzene-1,4-dicarboxylic acid (H2bdc) and therefore can be used to create analogues of well-known bdc MOF systems, to be used for direct host-guest behavioural comparisons. Using this approach, single and multicomponent MOFs have been synthesised, where the significant differences between these systems lie in the host-guest interactions between the MOF and gaseous and hydrocarbon guests.

5 will give an overview of these host-guest interactions within 3DL-MOFs (3D-linker MOFs) and how they differ from their aromatic analogues. Through the incorporation of 3D-linkers into prominent MOF architectures, we demonstrate the striking effects a contoured, aliphatic pore environment has on gas and hydrocarbon adsorption, compared with its aromatic counterpart, and explore the potential separation capacities these frameworks may pose.[1,2] 3DL-MOFs show enhanced selectivity and separation behaviour over their aromatic counterparts due to the highly contoured surface of the pore and the extra functionalities which protrude from the linker body into the MOF cavity. Furthermore, structural studies using neutron and synchrotron powder diffraction highlight the differences relating to negative thermal expansion behaviours between these MOF systems. These can be attributed to a multitude of properties relating to the linker, including influencing the pore size and shape, chemical environment and structural rigidity.

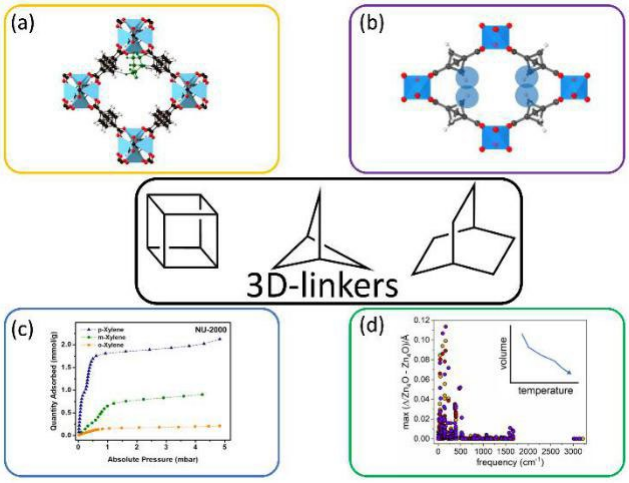

Figure 1. 3D-linkers have made impact in (a) selective host-guest chemistry, (b) enhancing MOF structural rigidity, (c) hydrocarbon separations, (d) structural sub-angstrom influences.

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Abstract Number: 276

Bioinspired Photocatalysis: Harnessing Multiphotons for Organic Transformations

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Photon absorption enables redox transformations of a variety of organic substrates under mild conditions. The photoinduced conversions require photoactive catalysts with wide photoelectrochemical windows. We have demonstrated that the radical ion redox catalysis is ideal for transforming substrates with redox-resistive bonds.[1] The catalytic cycle includes unimolecular sequential absorption of two photons which produces the excited-state radical anion of a catalysis having a very cathodic redox potential. This mechanism is reminiscent of the *Z*-scheme of the natural photosynthesis, but differs from the *Z*-scheme in that the two-photon absorption involves an identical radical ion intermediate. Mechanistic investigations were performed, which revealed that the success of two-photon-driven redox catalysis depended sensitively on the kinetic suppression of deactivation steps. As an alternative strategy to achieving two-photon-induced redox catalysis, we exploited the bimolecular triplet–triplet annihilation.[2] Pt(II) octaethylporphyrine absorbed 550 nm photon to produce the long-lived triplet excited state with a unitary quantum yield. Dexter-type triplet–triplet energy transfer to 9,10-diphenylanthracene occurred, and two triplet excited states of 9,10-diphenylanthracene subsequently recombined to generate the high-energy singlet excited state that produced blue fluorescence. This anti-Stokes shift fluorescence was harnessed to activate flavin adenine dinucleotide (FAD), a cofactor of photodecarboxylase from Chlorella variabilis (*Cv*FAP). This multi-component photoredox catalyst was capable of performing decarboxylation of fatty acids in vivo.

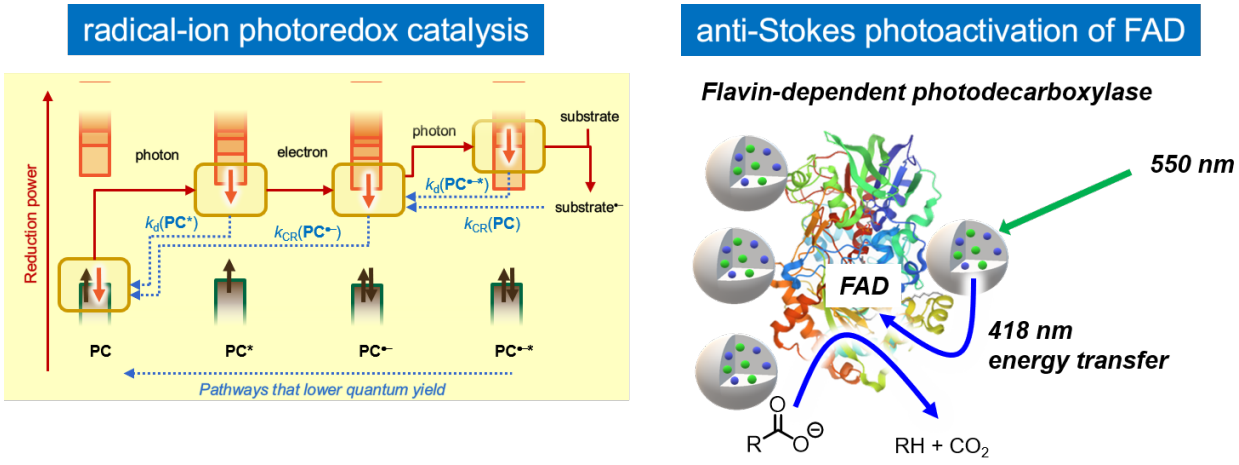

Figure 1. Bio-inspired (left) and bio-conjugated approaches to improving the photocatalysis.

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Abstract Number: 277

High-Temperature Pyro-hydrolysis of $CaCl_2$ Waste for HCl Regeneration: Experimental and DFT investigation on the Mechanism Underpinning the Role of Silica and CO_2

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With the increased use of renewable energy, smartphones, and electric vehicles, the production of critical energy metals via hydrometallurgical leaching of both natural minerals and e-waste is receiving increased attention. Consequently, a large quantity of by-product solid waste, such as calcium chloride ($CaCl_2$) is being produced. Additionally, this solid waste is produced from the traditional Solvay soda (Na_2CO_3) process [1,2]. For the high-temperature recovery of hydrochloric acid (HCl) out of chloride wastes, namely pyro-hydrolysis, to date, it has yet to be successful for $CaCl_2$, due to the fact that this reaction is thermodynamically unfavourable for $CaCl_2$ (ΔG = 128–791 KJ at 500–1000 °C) [3]. For the first time, we have discovered the promoting role of silica and CO_2 on the successful pyro-hydrolysis of $CaCl_2$. Extensive experimental investigation and density functional (DFT) calculation have been conducted to elucidate the underpinning reaction mechanism. It was determined that the pure $CaCl_2$ can only be pyro-hydrolysed into Ca(OH)Cl with around 12% HCl being produced even at 900 °C. However, its HCl release extent can be enhanced to 50% upon the addition of SiO_2 [4], and 80% upon the use of high-pressure CO_2 within the carrier gas at 900 °C [5]. The DFT calculation confirmed that both SiO_2 and CO_2 can reduce the energy requirement for water dissociation on the $CaCl_2$ surface, promoting water splitting and providing hydroxyl ions that are crucial for the conversion of $CaCl_2$ into Ca(OH)Cl [4,5]. The produced Ca(OH)Cl then quickly reacts with SiO_2 or CO_2 to finally convert into Cl-free $CaSiO_3$/$CaCO_3$. These results are of great significance for understanding high-temperature chlorine science and developing HCl regeneration technology that is ultimately beneficial to the development of critical mineral circular recycling as well as environmental protection.

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Abstract Number: 284

Mixed-valence probes of quantum interference effects

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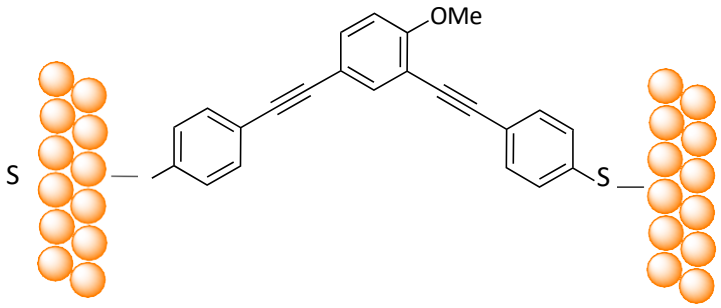
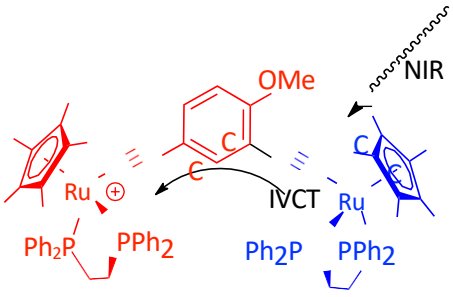
The influence of the topology, or site of connectivity, on the capacity of a molecular bridge to relay or transmit electronic effects has been clearly demonstrated in the context of both charge transfer processes within donor-bridge-acceptor (D-B-A) molecules,[1] including mixed-valence examples (M-B-M$^+$),[2] and the charge transport processes that underpin the electrical properties of molecular junctions.[3] The bridge structures that give rise to stronger coupling between donor and acceptor sites in discrete molecules are usually found to lead to higher molecular conductance when connected between two electrodes (i.e. within a molecular junction).[4] Beyond models of charge transport in terms of coherent tunnelling or thermally activated hopping mechanisms, quantum interference patterns also play a critical role in controlling electron transport within molecular junctions.[5] In this presentation, we show that the rules that predict the quantum interference effects on molecular conductance when 1,3-diethynyl benzenes are included within molecular junctions also correlate with the properties of the IVCT transitions, and hence underlying electronic coupling, in 1,3-diethynylbenzene-linked mixed- valence complexes. The correlation offers a new avenue for the design and exploration of mixed-valence complexes and intramolecular charge transfer processes using theories and structure-property relationships developed from consideration of quantum interference phenomena. Equally, the results point to the potential use of MV complexes as probes or predictive models for QI effects in molecular junctions, providing powerful, yet experimentally simple, tools to explore molecular structures for use in molecular electronics before the investment in more time-consuming and technically demanding single-molecule junction studies.[6]



substituent enhanced modulation of destructive quantum interference = enhanced molecular conductance



substituent enhanced electronic coupling = more intense IVCT transition

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Abstract Number: 289

Putting Nitrogenase in the Electric Chair

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Nitrogenase is a unique enzyme that catalyses the reduction of N2 to NH3 and H2 at room temperature and atmospheric pressure. Nitrogenase is a classic member of the two component metalloenzyme class, where the ATP-dependent reductase (encoded by NifH) donates electrons to the dinitrogenase (encoded by NifDK) to reduce the inert triple bond of N2.

The traditional method for assaying nitrogenase activity relies on performing an acetylene reduction assay (ARA) due to its ease to set up, trust within the nitrogenase field, and reliability. The ARA measures the conversion of acetylene to ethylene (an alternative substrate to N2) and is termed a 'back end' assay. This assay has proven useful for determining many mechanistic insights of nitrogenase and specifically useful for determining specific activities. However, the assay essentially only provides one data point per sample and cannot provide explicit mechanistic insight for electron transfer through the system.

The technique of cyclic voltammetry (CV) has been recently embraced by the nitrogenase community due to its 'front end' capabilities for measuring electron transfer. CV was found to be a powerful tool to observe nitrogenase catalysis after it was deduced that methyl viologen could be employed as a mediator to complete the electrochemical system (Figure 1).1,2 Cyclic voltammetry can provide more than a qualitative response to 'is it catalytic?'. The technique enables the determination of rate constants, calculation of the number of electrons being transferred, identification of the number of species in solution, determination of substrate specificity and information on the system based on the shape of the voltammogram (to name a few). Recent utilisation of the technique reported *kobs* values determined for the nitrogenase system using a variety of mediators.[2]

This talk will focus on what we've learnt from undertaking electrochemistry measurements on nitrogenase and what mechanistic information we've been able to obtain thus far.

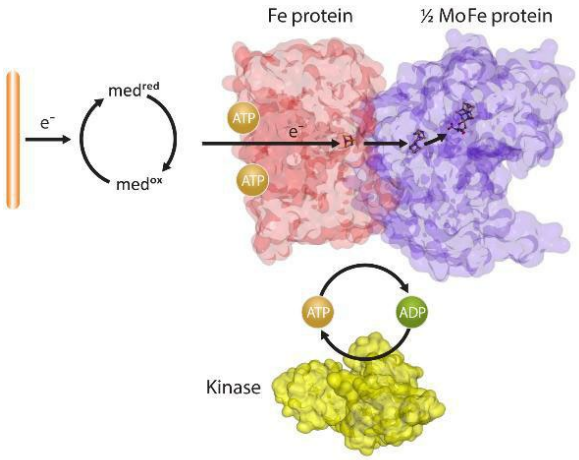

Figure 1. Electron transfer chain used to drive nitrogenase in a cyclic voltammetry experiment. An electron is transferred from an electrode to a mediator which aligns with the redox potential of the reductase, NifH. NifH then proceeds to transfer the electron to dinitrogenase (NifDK) to perform catalysis.

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Abstract Number: 290

Investigating the potential of dimethylgallium(III) compounds as novel antibacterial agents towards pathogenic bacteria

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There is an urgent requirement for the development of novel, non-traditional antibacterial agents to treat and prevent infections caused by multidrug-resistant (MDR) bacteria. One strategy is the use of metal-based compounds, which have been utilised since antiquity for their antimicrobial properties and offer unique mechanisms of action compared to traditional organic antibiotics.

Iron is an essential metal used by all organisms, and is a particularly important micronutrient with respect to bacterial virulence and pathogenesis.[1] The group 13 metal gallium, which occurs as the trivalent Ga(III) ion in aqueous conditions, has similar charge-to-size ratio and coordination preferences to Fe(III). Accordingly, molecules designed to sequester and transport Fe(III), such as transferrin and bacterial siderophores, also bind Ga(III) with high affinity; facilitating the uptake of Ga(III) into mammalian and bacterial cells. Unlike Fe(III) however, Ga(III) cannot undergo a reduction to Ga(II) under physiological conditions, and thus cannot replicate the redox activity of the Fe(II)/Fe(III); leading to inhibition of iron-dependent metabolic pathways. These Fe(III)-mimicking properties of Ga(III) have prompted the development of several Ga(III)-based anticancer and antibacterial agents, including Ga(III) *tris*(8-quinolinolate) and Ga(III) nitrate.[2]

We are interested in the synthesis and biological evaluation of novel classes of Ga(III)-based complexes as non-traditional antibacterial agents, particularly compounds containing Ga–CH3 bonds, which have the potential to exhibit activity unique from homoleptic Ga(III) chelates and simple Ga(III) salts. In this presentation, we report on the synthesis and evaluation of the antibacterial and mammalian cytotoxicity of a series of Ga(III)-flavonolate complexes with composition [Ga(CH3)2(flav)] (flav = substituted flavonolate, see Figure 1). Flavonols are important bioactive molecules of plant origin have a major role in human disease prevention. The prepared complexes show potent antibacterial activity towards Gram-negative pathogen *Klebsiella pneumoniae* in iron-poor media. The bioactivity of the Ga(III)-flavonolate complexes compared to a simple Ga–CH3 derivative, [Ga(CH3)2(OH)], is also discussed.

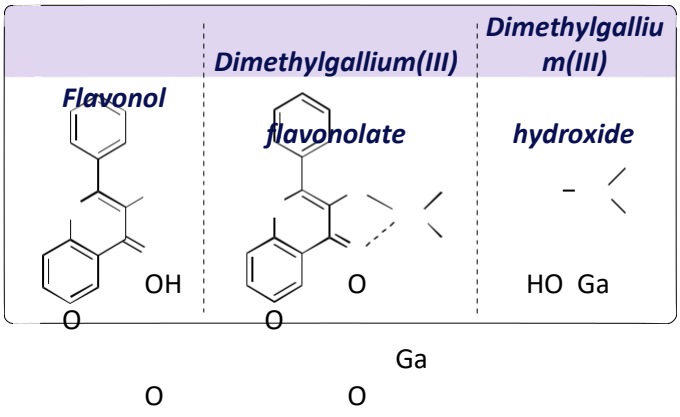

Figure 1: Basic structure(s) of the compounds investigated as novel antibacterial agents: flavonol (left), dimethylgallium(III) flavonolate (middle), and dimethylgallium(III) hydroxide (right).

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Abstract Number: 291

Tetrakis(isoquinoline) Pt(II) Anion Transporters as Anti-Cancer Agents

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Synthetic anionophores capable of transporting chloride across lipid membranes have been shown to induce apoptosis and interfere with autophagy in cancer cell lines as a result of chloride transport and proton/chloride co-transport.[1] While there have been considerable developments in the research of organic anionophores, research into metal complexes as discrete transmembrane chloride transporters is limited. In addition, there have been very few examples of metal complexes that do not rely on ligand exchange to achieve anion transport.[2]

Tetrakis(isoquinoline) platinum receptors have been shown to bind chloride strongly;[3] however, their chloride transport activity has not yet been tested. This presentation details the synthesis, characterisation, and transport activity of a series of platinum-based isoquinoline complexes (**Figure 1**). The complexes represent one of the few examples of metallic anionophores that do not rely on ligand exchange for anion transport. Instead, the complexes use traditional hydrogen-bonding interactions between urea groups and chloride. Mechanistic investigations into the mode of chloride transport were done using model POPC vesicles and indicate the complexes function as proton/chloride co-transporters. Furthermore, anticancer studies in MCF-7 cells (human breast cancer) indicated three complexes show stronger activity than cisplatin.

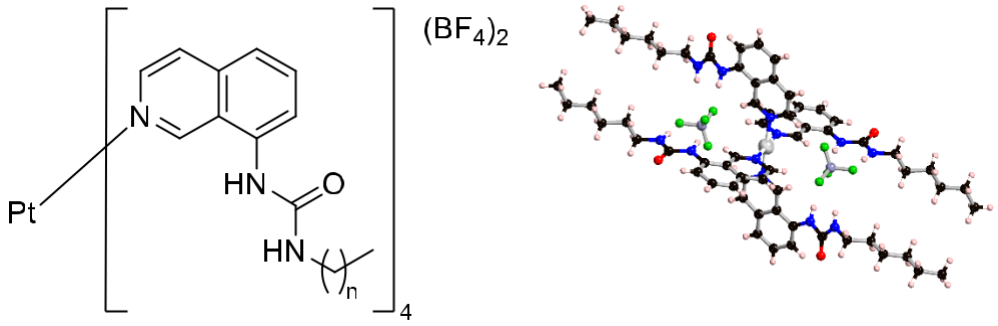

Figure 1. Left. General structure of the Pt(II) complexes investigated. **Right**. Crystal structure of one of the Pt(II) complexes.

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Abstract Number: 292

Artificial enatioselective photoenzymes with unnatural amino acid

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Designing artificial enzyme that could catalyze unnatural reaction is of great interest for expanding enzymatic reactions and could be highly useful for biosynthesis of unnatural products. Particularly, taking the advantages of enzyme's extraordinary enantioselectivity, developing unnatural enzymes for asymmetric is particularly attractive. Over the last half century, the remarkable advance in the field of asymmetric catalysis has drastically innovated the procedures of chemical synthesis of enantiomerically pure compounds. However, the vast majority of these transformations are centred on thermochemistry wherein the product chirality is generally established at the ground state. Stereochemical control of photochemical reactions remains a formidable challenge with the existing small molecule catalysts owing to the intrinsic high reactivity of the excited state. Enantioselective enzymatic catalysis might able to provide a alternative solution for the stereochemical control of photoreactions. However, the photoenzymes in nature are highly limited which are not suited for catalyzing the unnatural reactions. Therefore, we developed a method to create artificial photoenzymes with desired reactivity for unnatural reactions. The genetically encoded, chemically evolved triplet photoenzymes were developed which embedded with a benzophenone synthetic photosensitizer via genetic code expension. Structural optimization through four founds of rational mutagenesis afforded proficient variants. They promoted enantioselective intramolecular [2+2] photocycloaddition of indole derivatives with good substrate generality and excellent enantioselectivites (up to 99% enantiomeric excess). X-ray crystal structure of photoenzyme-substrate complex elucidated the important multiple noncovalent interactions that work synergistically to induce high enantioselectivity. This study shows that by merging the empowering mechanism of triplet energy transfer catalysis with the delicate supramolecular cavity of proteins, the triplet photoenzymes artificially expand the fundamental reactivity with respect to enzyme catalysis and unlock an integrated approach to valuable enantioselective photochemical synthesis that are not accessible with either the synthetic or the biological world alone.

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Abstract Number: 293

Controlling structure specific recognition and binding of nucleic acids with a novel class of rotaxanes

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Essential cellular processes such as replication and repair are dependent on the formation of non-canonical nucleic acid secondary structures, making these assemblies attractive targets for three-dimensional shape specific binding[1].

A novel class of supramolecular rotaxanes developed by the Hannon group use a nucleic acid junction-binding helicate in place of the usually linear, two-dimensional axle[2]. A di-metallo tri-ligand cationic helicate is thread through the portals or a cucurbit[10]uril macrocycle and alkylation with bulky stopper groups to mechanically lock the ring in place. The presence of the macrocycle prevents the non-covalent interactions between nucleic acids and the helicate, and gel electrophoresis studies have shown that DNA three-way junction binding capability is restored. This change in activity is further evidenced by cell proliferation assays, in which the capped and uncapped helicates show cytotoxic activity that is not observed in their rotaxanated form[2].

Bulky, photocleavable protecting groups are now investigated as capping groups for a redesigned rotaxane. Using mass spectrometry and UV-Visible spectroscopy, the removal of such capping groups in response to irradiation (365 nm) and the subsequent helicate release is monitored. This builds to an exciting approach towards the spaciotemporally controlled release of a supramolecular helicate and reactivation of structure specific junction binding activity in response to an external trigger.

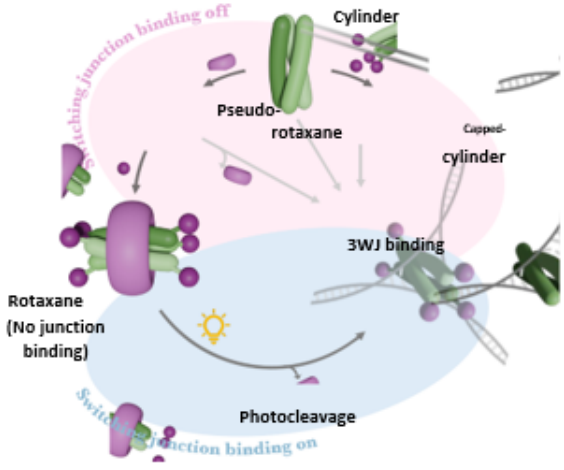

Figure 1: Graphical abstract showing the synthesis of the supramolecular species investigated, and how they can be used to control three-way junction binding.

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Abstract Number: 294

Bioinspired Reactivity of Oxygenation and Nitrite Reduction Mediated by Metal Centers Containing Thiolato(phosphine) Ligands

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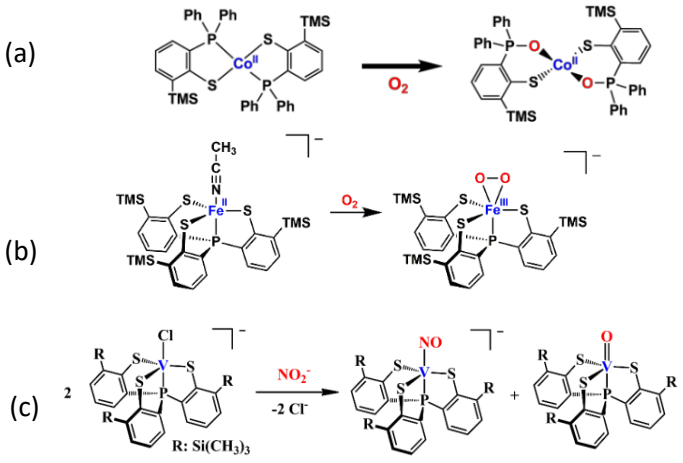
Our laboratory has investigated metal-mediated bio-inspired reactivity using thiolato(phosphine) ligands. In this article, we present three recent findings. Firstly, a Co(II) complex with a P2S2 coordination environment was found to activate dioxygen and produce a novel ligand-based oxygenation product, a distorted tetrahedral Co(II) complex bound to two (thiolato)phosphine oxide. This type of metal-mediated oxo transformation has not been observed in a well-defined square planar Co(II) complex before (Figure a).

Secondly, we created a ferric-superoxo complex by adding O2 to a Fe(II) precursor (Figure b). Despite different O-O bond lengths in three crystallographic forms, the complexes had similar solid-state and solution spectroscopic properties. The electronic structure of the complexes is best described as an intermediate-spin ferric center antiferromagnetically coupled to a superoxo radical, resulting in an overall triplet state. This suggests that relying solely on the structural parameter of the O-O bond to assess the electronic structure of metal-dioxygen intermediates may be questionable.

Lastly, we observed that a V(III) complex mediates nitrite reduction in the absence of external protons or oxophilic substrates (Figure c). The metal site plays two roles in nitrite binding and deoxygenation, and we monitored the reaction using spectroscopies and isotopic labeling experiments. {VNO}^{4} was characterized as the formation product



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Abstract Number: 295

Artificial copper metallolyases for stereoselective Michael addition reactions

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By exploiting the additives such as *C*2-symmetric chiral ligands and precious metals, stereoselective reactions have been established thanks to the enormous efforts of our predecessor. However, the resolution of compounds bearing multiple chiral centers is still challenging and a current topic of interest from the viewpoint of industrial and economic demands. To address such problems, artificial metalloenzymes have garnered much attention over past decades. They are the promising hybrid biocatalysts, where intrinsic chemical reactivity and selectivity of the introduced metal ion or metal complex can be enhanced by modifying the secondary coordination sphere of the chiral biomolecules. We repurposed the metal-binding cupin superfamily protein into easy-to-use macromolecular ligands toward the creation of the promising methods to construct artificial metalloenzymes. Interestingly, this protein can bind various transition metals including the heavy and precious metals.[1] To fulfill diastereo- and enantio-selective reactions, we have attempted to use the library-like mutant-series of a cupin type protein as a screening strategy.[2] We have created efficient biocatalysts by harnessing the copper-containing protein for diastereo- and enantio-selective Michael addition reaction of nitroalkanes to an α, β-unsaturated ketone. Furthermore, we converted the metal-binding site of a cupin superfamily protein into the 2-his-1-carboxylate facial triad, which is one of the common motifs in natural non-heme enzymes, to construct artificial metalloenzymes that can catalyze new-to-nature reactions.[3] H52A/H58E mutant that catalyzes the stereoselective Michael addition reaction was found to contain a pliable metal-binding site in the high-resolution crystal structure (Figure 1). Moreover, the H52A/H58E/F104W variant accommodated a water molecule between a carboxylic oxygen atom of Glu58 and nitrogen atom of Trp104 indole moiety, presumably leading to high stereoselectivity (Figure 1). Here, we present some topics about the 2-his-1-carboxylate facial triad and reaction mechanism.

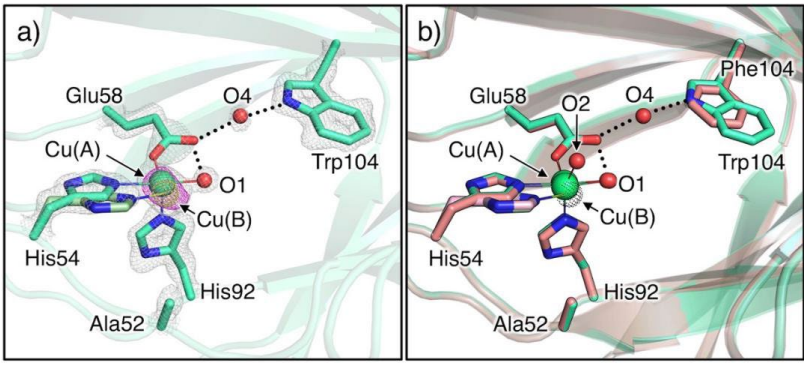

Figure 1 The crystal structure of highly seleoselective mutant (H52A/H58E/F104W). a) the activesite of H52A/H58E/F104W. b) superimposed structure H52A/H58E/F104W and H52A/H58E mutant

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Abstract Number: 297

Shifting paradigm: High relaxivity, Gadolinium & Manganese based Dual Modal Imaging/Theranostic Agents

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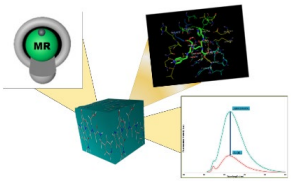
Individual imaging modalities such as Magnetic Resonance Imaging (MRI), Positron Emission Tomography (PET), and Optical Imaging (OI) have shortcomings such as lack of specificity, lack of spatial resolution, and quantifying difficulty respectively. A combination of multiple molecular imaging techniques has been suggested to overcome these difficulties. However, the problem could not be resolved by the simple addition of two types of imaging agents, unless they have identical pharmacodynamic properties. Therefore, the necessity for the introduction of dual-purpose contrast agents or multimodal imaging probes has been justified. Additionally, the toxicity of Gadolinium and Manganese in their own right invoked the need to have stable metal complexes as dual-modal imaging agents. On contrary, despite the great wealth of information they provide, their synthesis is far from trivial. Herein we report the modular approach adapted for the synthesis of ligand systems based upon polyamino-polycarboxylates containing versatile auxiliary groups *via* an easy-to-make, one-pot synthesis.

Initially, we synthesized centrally and terminally functionalized chromophore-bearing DTPA analogues *via* multistep synthesis and subsequently prepared gadolinium complexes. We reported highly reproducible, markedly higher relaxivity than other DTPA-based contrast agents for the centrally functionalized chromophore bearing DTPA analgoue for the first time. We also showed that the ligand-based fluorescence is not quenched upon complexation with Gd. However, complexes based on Gd, specifically, some extracellular gadolinium-based contrast agents could trigger the development of Nephrogenic Systemic Fibrosis (NSF), a fibrotic disorder generally observed in renal failure patients. This has led to regulatory actions by FDA and EMA. This has prompted the resurgence of research on non-gadolinium-based analogues.

Inspired by the success of preparing dual-modal imaging agents based on DTPA analogues, we embarked on the preparation based on EDTA bisamides, targeting transition metal complexes. More specifically, we synthesized and characterized Manganese and Copper complexes with 4-(aminomethyl)pyridine and 2-aminoanthraquinone as fluorescent auxiliary groups. In particular, the manganese complex of EDTA bisamide of 4-(aminomethyl)pyridine (MnL^1) exhibited relatively higher relaxivities (3.52 $mM^{-1}s^{-1}$ (at 30 MHz, 37 °C) than commercial contrast agent Teslascan® and comparable relaxivities with performance comparable to the commercially available gadolinium-based contrast agents, Magnevist® and Dotarem®. Furthermore, the versatility of the respective ligand **L^1** to act as *on-off type*, fluorescent-based chemosensors for Cu (II) along with its potential for live-cell imaging via time-gated fluorescence spectroscopy also well established. Moreover, structure-based virtual screening unveiled the potential anticancer activity of **L^1.** Apart from acting as MRI/OI agent, given the momentous changes taking place towards the application of Mn^{55} isotope in PET imaging, the application of MnL^1 and CuL^1 as PET/OI imaging agents is also hereby envisaged.



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Abstract Number: 298

Hydrogen Peroxide Reduction by Electrode-Immobilised Human Mitochrondrial Amidoxime Reducing Component (mARC)

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Human mitochondrial amidoxime reducing component (mARC) 1 and 2 reduce *N*-hydroxylated prodrugs via their molybdenum cofactor (Moco) while immobilized on glassy carbon electrodes.[1] In this work, mARC1 and mARC2 are shown to catalytically reduce hydrogen peroxide, a reactive oxygen species involved in the signaling of several processes including cell differentiation, inflammation, tissue repair and aging.[2-3] Voltammetry of the electrode-immobilized enzymes show reduction of H2O2 in the presence of artificial electron mediators benzyl viologen, anthraquinone sulfonate and safranin T. These electrochemical studies provide further clues towards identifying the enzymes' physiological substrate in humans.

A B

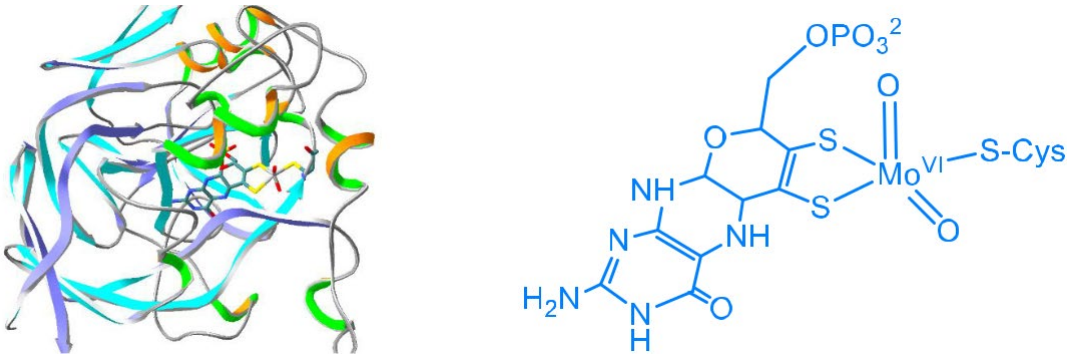

Figure 1. (A) Crystal structure of human mitochondrial amidoxime reducing component (mARC) 1, and (B) chemical structure of its molybdenum cofactor (Moco).

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Abstract Number: 299

Construction of supramolecular probe and its application in tumor

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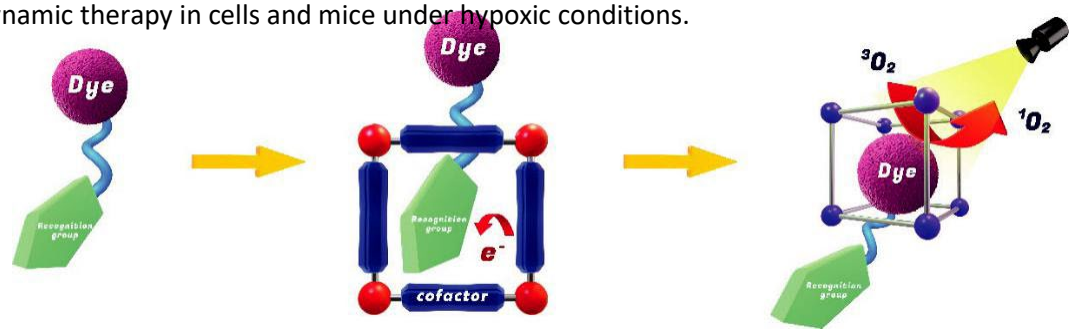
Early diagnosis and treatment of malignancies is essential to improve survival, prognosis and quality of life, as they pose a serious risk to human health. Receptor tyrosine kinases (RTKs) which located on cell membrane have been shown to have aberrantly high expression in tumor tissues, and RTKs have been evaluated as surrogate markers for tumor angiogenesis. The linear molecular structure of probes favor a high-density arrangement of the membrane surface, and fluorescence probes were constructed with the effective skeleton of targeted drug used as the identification group and fluorophores with high fluorescence quantum yield through long flexible groups. Probes are fluorescence quenched in body fluids, and probes could detect tyrosine kinase in cell and mice due to conformational conversion of probes. Hypoxia is closely related to various physiological activities of tumors, and the detection of hypoxia enzyme content in vivo was highly dependent on the content of cofactors. The stable cofactor-substrate supramolecular fluorescence probes were formed by host-guest interaction with the fluorescence substrates and a metal-organic macrocyclic hosts, and the hosts were self-assembled with active part of the cofactor as ligand skeleton and metal ions. The cofactor-substrate supramolecular fluorescence probes could eliminate the potential concentration dependence of the cofactor through the electron transfer process between the host and the guest, and realize the fluorescence tracing in cells and mice. Double-substrate catalytic process is optimized into a single-substrate process, and the reaction time is shortened. Oxygen activation is a key issue in photodynamic therapy (PDT), constructing supramolecular structures with hosts with efficient oxygen activation capabilities that combine with targeted molecules as guests is a worthwhile way to solve this problem. Supramolecular structures could target tumor cells, increase the efficiency of oxygen activation, and increase the efficiency of photodynamic therapy in cells and mice under hypoxic conditions.



Scheme 1 Schematic diagram of supramolecular probe

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Abstract Number: 304

NEW T*PP LIPOPHILIC CATIONS FOR ENHANCED MITOCHONDRIAL UPTAKE

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Triphenylphosphonium moieties are traditionally used to deliver a wide range of molecular cargo to mitochondria organelle.[1] However, benefits associated with the modification of this simple and widely used moiety used as a mitochondrial transporter remains largely unexplored. We have demonstrated the drastic change in properties displayed by a new series of TPP derivatives (*i.e.*, mono and dicationic) (**Figure 1**).[2-3] We have also confirmed the complementary nature of our approach to current linker modification strategies towards enhanced mitochondrial accumulation.[4]

Our approach can be successfully applied to enhance the accumulation of rhenium carbonyl complexes into cells.[6] In addition, we have also developed novel non-conventional main group mitochondrial delivery vectors with enhanced properties.[6]

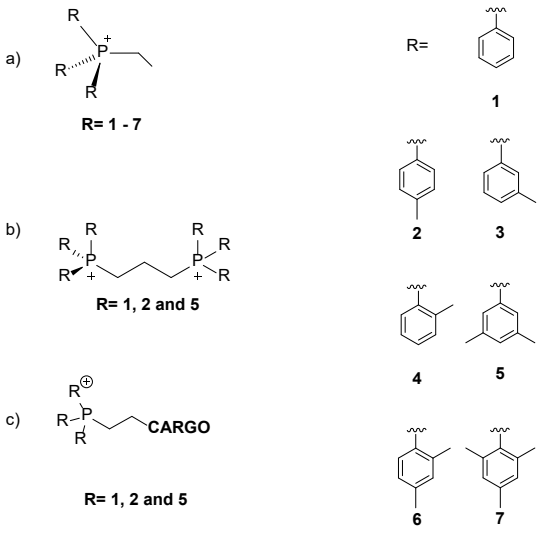

Figure 1. a) General structure of monocations (**1a**-**7a**) and dications (**1b**, **2b** and **5b**) studied. b) General structure of conjugates (**1b**, **2b** and **5b**).

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Abstract Number: 305

Main Group Mechanochemistry: Challenges and Opportunities

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Traditionally, solution-based processes have dominated laboratory set-ups and industrial manufacturing protocols. However, the past decade has seen the renaissance of solid-state synthetic routes, driven by the need for more sustainable chemical processes. Within this context, mechanochemistry (i.e., chemical transformations initiated or sustained by mechanical force) has rapidly evolved from being a laboratory curiosity to a widely applicable synthetic technique that not only enables greener chemical transformations but offers exciting opportunities for the synthesis and screening of molecules and materials.

The talk will focus on the recent developments in reactive mechanochemistry of main group compounds and materials.[1] The novel application of mechanochemistry to the synthesis of phosphorus-nitrogen frameworks[2] – from orthogonal synthesis[3] to "unattainable" molecules[4] – will be discussed, followed by their implementation in the rational design of high-order organic-inorganic hybrid multicomponent cocrystals.[5] This will be followed by a brief introduction of the challenges facing the broader adoption of mechanochemistry in industry,[6] with focus on the upscaled synthesis of metal complexes[7] and energy materials.[8]

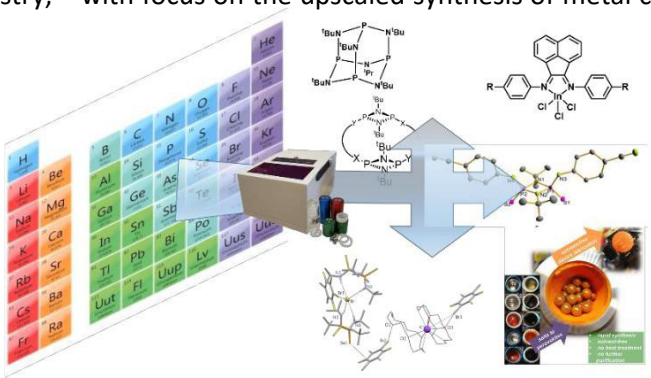

Figure 1.

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Abstract Number: 307

Alzheimer's-implicated APOE protects against ferroptotic cell death

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Background: The biochemical mechanisms underlying the increased risk for Alzheimer's disease contributed by the ε4 allele of APOE are debated. Furthermore, the mechanism of neurodegeneration in Alzheimer's disease has not yet been established. One potential neurodegeneration mechanism is ferroptosis, a recently identified cell death pathway involving iron, which is supported by clinical findings linking brain iron load with accelerated cognitive decline. Ferroptosis involves the activation of intracellular iron (especially the degradation of ferritin during autophagy) to cause lethal lipid peroxidation, which is inhibited by the master regulator, GPX4. Recently, we unexpectedly observed that people with the e4 allele have elevated biomarkers of brain iron. Here, we test whether APOE impacts on iron-mediated ferroptotic cell death.

Results: We found that APOE potently inhibits erastin-mediated ferroptosis – it is 10x more potent than the best-in-class compounds. APOE was however not protective against RSL3-dependet ferroptosis, which demonstrated that APOE acts upstream of GPX4. We showed that APOE inhibited the degradation of ferritin by autophagy and release of toxic iron by stimulating AKT-dependent inhibition of mTORC1. APOE was shown to reduce autophagy activation during amino acid starvation and ferroptosis induction (shown by GFP-LC3 microscopy and western blot), and pharmacological inhibitors of the PP2-PI3K-AKT pathway abolished APOE-dependent autophagy blockade and ferroptosis suppression. We show that allelic variation to the ApoER2 receptor is associated with slowed cognitive decline in two longitudinal clinical cohorts of Alzheimer's disease, and the same polymorphism conferred increased protection against ferroptosis in cell culture studies.

Conclusions: These findings provide a new perspective into the function of APOE and its role in Alzheimer's pathogenesis.

Abstract Number: 308

Amyloid peptides and the control of copper ion coordination to lipid membranes

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Zinc, iron and copper ions are particularly abundant in the synaptic cleft, because of the involvement of these ions in the synapse physiology1 . But copper and iron ions are toxic because of the catalysis of oxidative reactions when the ions are not tightly bound to well structured proteins. Part of this reactivity is indeed required by neuron membrane remodeling and synaptic plasticity. We provided a model where the binding of Cu2+ to amyloid-beta peptides in monomeric form was found as a possible mechanism to prevent interactions between free divalent cations and the membrane headgroups2 . On the other hand, amyloid beta oligomers were experimentally correlated to toxic forms3 . We present investigations of the coordination of free Cu2+ ions to models of lipid membranes, as a further step to understand this mechanism. The series of divalent cations Mg2+, Ca2+, Zn2+, Fe2+, and Cu2+ was studied by using empirical models of DMPC lipids and DMPS:DMPC 1:5 lipid mixtures, as phospholipids abundant in synaptic membranes. More accurate density-functional calculations performed on the most likely configurations obtained by empirical models described the unique efficient transfer of unpaired electrons from the Cu center towards the ester linkages of the lipid molecules. The ability of amyloid-beta oligomers to efficiently load copper ions away from the lipid bilayer has been also investigated. These results provided further support to the requirement of an accurate control of copper reactivity in the synaptic cleft and of the possible involvement of amyloid precursor protein in this control.

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Abstract Number: 312

The Versatility of 6-fold interpenetrated 1D to 3D Metal Organic Nanotubes

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Metal-Organic Nanotubes (MONTs) are a relatively new and rare subclass of inorganic material stemming from the rise in popularity of Metal-Organic Frameworks. In theory, a MONT can have the same functionality as a MOF however this is commonly let down by the lack of thermal stability that is present in most structures. With only a hand full of examples present in the literature, the majority do not work well as functional materials due this thermal instability.[1]

Using a mixed donor, T-shaped ligand, and a self-assembly approach, we have synthesised two isomorphous, multifunctional MONTs. These show a complex 1D to 3D, 6-fold interpenetration while being while retaining 2 nm pores that are present throughout the material via through a large amount of pi-bonding. This provides thermal stability to the material, as well as keeping the 1D channels, allowing for the host guest interactions within the structures. We present gas adsorption data showing the uptake of N_2, CO_2 and H_2 at values that compete with large cavity MOFs. In addition, results from high pressure crystallography preformed in a diamond anvil cell, showing the strength and flexibility of the material. Finally, VT-THz studies showing the breathing modes and strength of the material, backed up DFT calculations.

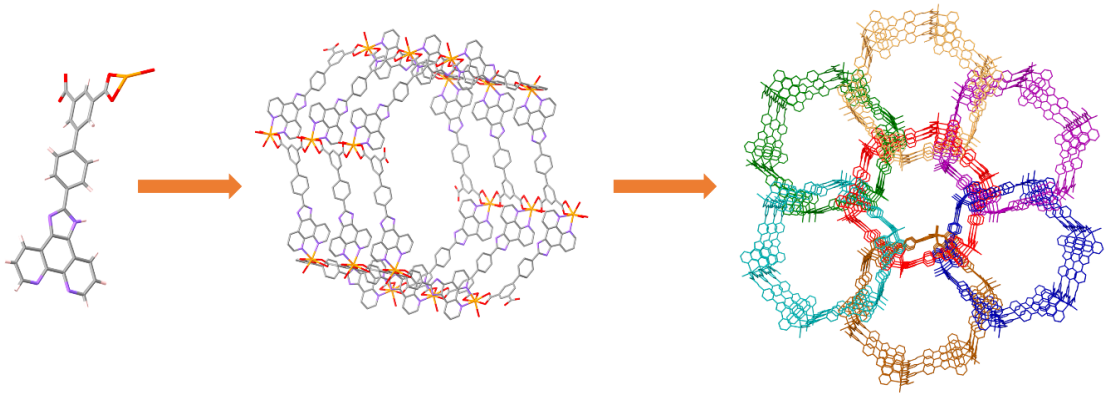

Figure 1: Scheme showing the details of a six-fold interpenetrated MONT.

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Abstract Number: 314

"Smuggling" a toxic metal to the active site of urease

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Urease is a nickel-containing enzyme that hydrolyses urea into ammonia, which helps the pathogen *Helicobacter pylori* to survive in acidic human stomach. Biosynthesis of active urease requires the delivery of nickel ions to a buried carbamylated lysine residue at the active site. This maturation process is assisted by four urease accessory proteins, UreD, UreE, UreF and UreG. Metal ions at the top of the Irvine-Williams series such as Ni^{2+} are toxic because they can displace weaker ions such as Mg^{2+} from the active site of essential enzymes (e.g. GTPase). To avoid toxicity, nickel ions are delivered from one protein to another via the formation of specific protein complexes so that the toxic metal ions do not diffuse into the cytoplasm. Our group has previously determined the crystal structures of UreFD [1], GDP-bound UreGFD complexes [2] and nickel-/GMPPNP bound UreG dimer [3]. We have recently determined the cryoEM structure of *H. pylori* UreFD/urease and *Klebsiella pneumoniae* UreD/urease at 2.3 and 2.7 Å resolutions, respectively. Combined with mutagenesis and biochemical studies, we show that the formation of UreFD/urease complex opens a 100-Å long tunnel, where the nickel ion is delivered through UreFD to the active site of urease.

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Abstract Number: 315

Making neutral molecular receptors for anion binding in water

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Naturally occurring transmembrane proteins such as the sulfate binding proteins, phosphate binding proteins and ClC channels/transporters achieve high-to-modest affinity anion binding in water through multiple hydrogen bonding interactions from polar amino acid residues to the encapsulated anion within a hydrophobic protein microenvironment. In many of those biological systems, the bound anion is stabilised solely by dipole interactions (hydrogen bonds) without forming ion pairs with counterions in proximity. Creating synthetic systems to mimic the function of anion binding proteins is a key academic challenge in supramolecular chemistry. In water, most biologically relevant anions such as chloride, sulfate, phosphates and carboxylates are strongly hydrated. This imposes a large enthalpic penalty for a synthetic receptor to (partially) remove the anion hydration shell and bind an anion. A further energetic cost is incurred due to the high dielectric constant of water diminishing non-covalent interactions provided by a synthetic receptor. Unlike nature, the majority of synthetic anion receptors functioning in water are multiply charged metal complexes or polyammonium organic molecules, where strong Coulombic attractions with a bound anion underpin the success of these systems. Very few charge-neutral anion receptors functioning in water are available and these compounds require lengthy syntheses.[1] I will present our recent examples where anion binding in water was achieved by simple neutral receptors synthesised in 1-3 steps.[2-3]

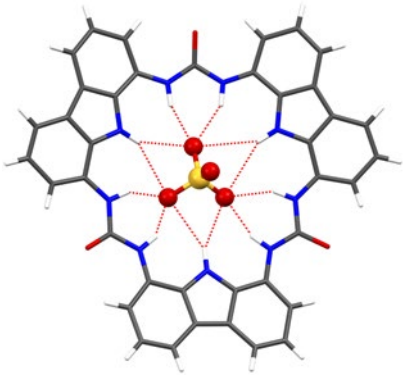

Figure 1 Crystal structure of a macrocycle binding a sulfate anion

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Abstract Number: 316

Metal complexes for sonodynamic therapy

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Sonodynamic therapy (SDT) is a new non-invasive treatment strategy. It uses ultrasound (US) to trigger the sensitizer to produce reactive oxygen species (ROS) to kill cancer cells. Compared with light, US shows deeper tissue permeability, which has great advantages in the treatment of deep tumours.[1,2] However, so far, the mechanism of ROS generation by SDT is not clear, one of the most representative and reasonable mechanisms is called "sonoluminescence". This mechanism indicates that light will be generated during the irradiation of the solution with US. This light can further stimulate the acoustic sensitizer to generate electron-hole (e - h^+) pairs, and finally achieve the effect of ROS generation in water environment. The sonosensitization efficiencies and ROS quantum yields are essential prerequisites for SDT. Therefore, designing and developing excellent sonosensitizers is a crucial topic in the development of SDT.

Recently, a large number of metal complexes with a variety of structural groups have been synthesized so far and have shown very promising biological activity in vivo and in vitro in terms of their anti-tumor properties, especially in the field of chemotherapy and photodynamic therapy (PDT). Nevertheless, there are few reports of metal complexes as sonosensitizers in the field of SDT. As a result, the exploration of metal complexes with US sensitization effect is of significance for the application of metal complexes in SDT.

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Abstract Number: 319

Spectroscopic and Functional Characterization of CPSF30: A CCCH Type Zinc Finger Protein with a Redox Active 2Fe-2S Cluster

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Metals play key roles in biology with iron and zinc serving as key nutrients to maintain optimal health and allow proteins and enzymes to function.[1,2] Understanding how proteins utilize certain metals and understanding their interactions with other species provide both fundamental biochemical insight and contribute to our understanding of roles in disease. Of importance, zinc finger (ZF) proteins are proteins with cysteine/histidine rich domains that bind zinc and fold. Once folded, ZFs play roles in gene regulation at the translational and transcriptional levels.[3,4] An increasing number of ZF proteins have been found to be involved in RNA regulation; however, in many cases, the mechanism(s) of metal mediated RNA recognition for these ZFs is not well understood.

One important RNA-binding ZF protein is CPSF30. Cleavage and polyadenylation specificity factor 30 (CPSF30) is a 'CCCH' type ZF protein involved in pre-mRNA processing that is a potential therapeutic target for lung, colon, and breast cancers.[5-8] Targeting CPSF30 could be a potential therapeutic strategy to control cancer cell development, however its mechanism of action is not well described. Originally annotated as a 'zinc finger,' CPSF30 was found to have a 2Fe-2S cluster cofactor that is important for its function.[9,10] Using a whole protein and a peptide maquette approach coupled with a variety of spectroscopic methods, I have determined the site of the Fe-S cluster and a potential role in function. Utilizing metal catalyzed oxidation coupled to mass spectrometry, I discovered that the second CCCH domain houses the Fe-S cluster. The cluster can be reduced with dithionite to the Fe(II)-Fe(III) species, as monitored by UV visible, EPR and Mossbauer spectroscopies. Reduction of the iron center does not affect RNA binding, suggesting a structural role for the cluster. In cells, the CPSF30 protein is upregulated during hypoxia, suggesting a connection between between oxidative stress and protein function.

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Abstract Number: 322

An Evolving Tale of Chromium Bioinorganic Chemistry: Carcinogen, Dubious Dietary Supplement and Pathogen Virulence Factor

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In the 1980's when my group first began to study Cr chemistry, Cr(VI) was already established as a human carcinogen, while Cr(III) was considered to be a likely essential trace element and was an important dietary supplement. For more than 30 years my research group has developed probes and techniques to study the coordination chemistry, redox chemistry and bioinorganic chemistry of Cr(III), Cr(IV), Cr(V) and Cr(VI) both extracellularly and intracellularly. The greater the depth of Cr bioinorganic we probed, the more we realized that many of the assumptions that were the foundation of the literature in this area 40 years ago did not stand up to scrutiny.

In the area of Cr(VI) carcinogenicity, the discovery that Cr(V) and Cr(IV) complexes generated from Cr(VI) with a variety of biologically important ligands, were stable enough to be isolated or generated in a pure form in solution was made. The structural characterization of many of these complexes by multiple-scattering analysis of X-ray absorption spectroscopic data and EPR spectroscopy (for Cr(V)), and the demonstration that they were very damaging to DNA, led to our hypothesis that intracellular Cr(V) and Cr(IV) were the intracellular carcinogenic species. This hypothesis met with strong resistance at the time, but now is widely accepted.[1]

During studies on the effects of Cr(VI) on cells, long-lived Cr(V) EPR signals typical of the species we characterized above proved that such species were present in cells treated with Cr(VI).[2] However, the signals were much longer lived than was expected from studies of the isolated complexes. This led to the hypothesis that there was intracellularly redox recycling between Cr(III) and Cr(VI). Subsequently, we established that Cr(III) could be oxidized to Cr(VI) in an extracellular environment by physiologically relevant concentrations of biological oxidants present under conditions of oxidative stress, including diabetes.[3] Finally, we discovered that Cr(VI) and Cr(V) were present in adipocytes treated with Cr(III) supplements.[4] This and other evidence will be discussed on why Cr(III) is not an essential trace element and the consumption of Cr(III) supplements are not only ineffective, but present a potential cancer risk.[1,5] These studies led on to the most recent research to be discussed on the reasons why pathogens hyperaccumulate chromium and other metals to resist immune system response. Recent research in this area and the potential consequences of these discoveries in reducing the ability to fight infections and other potential health effects, such as cancer, will be outlined.

I would like to acknowledge the many important contributions of all of my students and co-workers who have been on the journey with me in unravelling new and surprising aspects of Cr bioinorganic chemistry and, in particular, Dr Aviva Levina who has been my colleague in this research area for more than 30 years.

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Abstract Number: 323

Lightweight Metal Organic Frameworks with Mixed Donor Ligands

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Metal organic frameworks (MOFs) have become well known for their gas adsorption properties due to their ordered porous structures. One approach to further increase the amount of gas adsorbed with MOFs is to decrease the density of the framework. The vast majority of metals used in MOF synthesis are heavy transition metals. The s-block metals are significantly lighter allowing for the creation of lower density frameworks. These metals come other advantages including a high natural abundance and low toxicity when compared to their transition metal counterparts. The use of s-block metals in MOFs, while only making up a minor fraction of published MOF structures have been growing in popularity. The most notable lightweight MOF is Mg-MOF-74 due having the highest known CO_2 uptake of 23.6 wt. %.[1] Mg-MOF-74 as with the majority of other lightweight MOFs primarily use carboxylate as their donor group to bridge together the metal nodes.[2]

This work details the use of the mixed-donor phenanthroline-carboxylate ligand HNCP and the linearly extended ligand HNCPP with the lightweight metals, lithium, sodium, magnesium, and calcium. The crystal structures collected with single crystal X-ray diffraction shows that the resulting MOFs are ordered, porous, and low-density. Subsequent gas adsorption analysis has shown promising selectivity for the uptake of carbon dioxide.

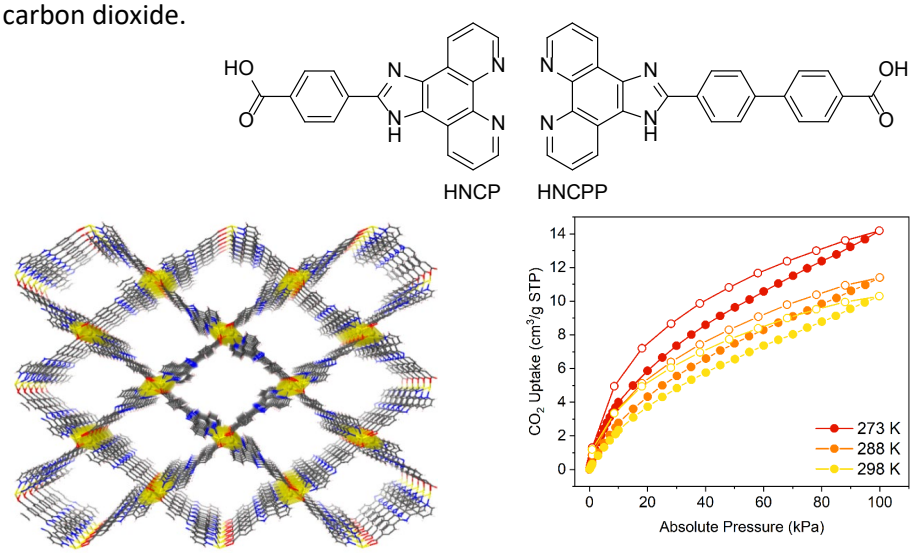

Figure 1: Phenanthroline-carboxylate ligands (top), Na-HNCP MOF (left), Na-HNCP MOF CO_2 adsorption (filled circles) and desorption (hollow circles) isotherms (right).

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Abstract Number: 327

The "UV-vis-silent" coordination chemistry of cobalamin with oxidizing agents: contrasts between iron-porphyrin and cobalt-corrin complexes

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In heme-containing proteins, redox-active agents such as peroxides or oxyanions of halogens/sulfur/nitrogen offer a rich chemistry involving high-valent iron, free radical reactions and small molecule activation.[1] By contrast, until recently our knowledge of the reactivity of cobalamin with oxidizing agents has been confined to processes where, especially with strong oxidizing agents, the corrin ring is covalently modified by oxygenation or halogenation, or where Co(I) or Co(II) are oxidized to Co(III) in an outer-sphere manner (at times in pseudocatalytic cycles where reducing agents are also present) – but no complexes of Co(III) with oxidizing agents, and no ensuing high-valent Co centers.[2] We have, however, recently reported that H2O2 does in fact form a stable and reversible complex with cobalamin, assigned as Co(III)-hydroperoxo based on UV-vis and NMR spectra complemented by density functional (DFT) calculations.[3] We describe here UV-vis (including stopped-flow), NMR, DFT, resonance Raman and mass spectrometry results showing that m-chloroperoxobenzoic acid (MCPBA) at low concentrations yields a relatively stable complex with Co(III) cobalamin. Using the same experimental toolkit – centered mostly on ^{1}H-NMR spectroscopy and DFT calculations – we then describe a stable adduct of Co(III) cobalamin with chlorite, and rationalize the stability of this complex in contrast to the known instability of the putative heme-chlorite complex in the enzyme chlorite dismutase. With stopped-flow UV-Vis complemented by DFT, we then report on transient complexes formed by aqua and by cyano Co(III) cobalamin with hypochlorite.

A common theme of the complexes described here is the fact that the typical exploratory method for colored bioinorganic centers – UV-vis spectroscopy – appears largely blind in cases where clear differences are observed in NMR spectra (see, e.g., Figure 1). Under these conditions, the "UV-Vis silent" area of coordination chemistry in corrin complexes may be expected to still offer surprises.

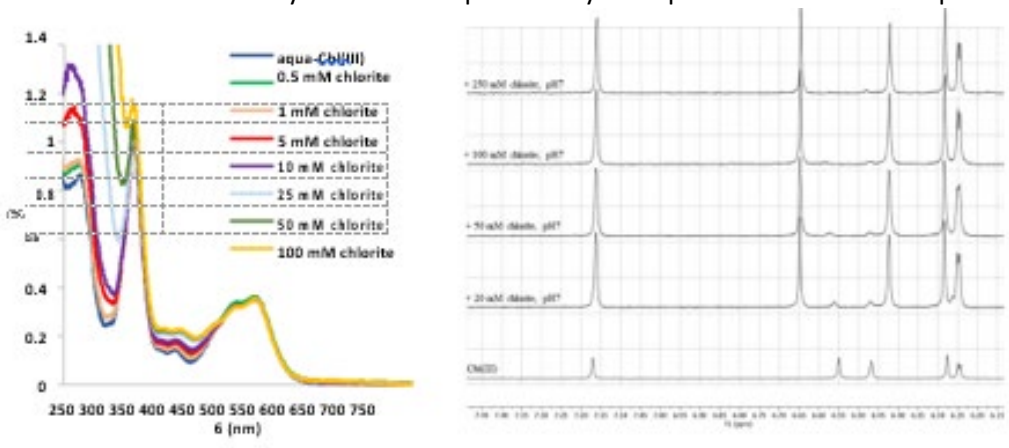

Figure 1. UV-vis and ^{1}H-NMR spectra of Co(III) cobalamin with chlorite.

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Abstract Number: 328

Tau-selective super-resolution fluorescent probes for deciphering Alzheimer's pathology

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Dementia affects 55 million people across the world and is the second leading cause of death in Australia[1,2]. Alzheimer's disease (AD) is the most common form of dementia. Amyloids play a critical role in the development of AD but there is still a lack of clear understanding of pathology of this disease. A robust correlation has been established between the load of tau amyloid aggregates resulting from tau proteins and the progression of AD[3] which makes it a biomarker of importance for studying the complexities of AD. However, tau amyloids have not yet been explored as thoroughly as Aβ, the other biomarker of AD[4]. Understanding the role and stages of tau assemblies in AD pathology requires studying them at the molecular scale. While super-resolution imaging can afford imaging at the nanoscale, to our knowledge there are no super-resolution fluorescent probes selective for tau.

We here synthesize a library of super-resolution fluorescent probes selective for tau amyloids. These probes comprise a tau-binding moiety which is linked to a photoswitching fluorophore *via* linkers of variable length. From the binding affinity data, we demonstrate the several-fold selectivity of these probes for tau amyloids over Aβ. We also explore the impact of linker lengths on the binding affinity and fluorescence properties of these probes. Ultimately, we use a super-resolution imaging technique - dSTORM, to elucidate the morphology of tau assemblies, thus shedding more light on tau pathology and helping decode the unsolved puzzle of Alzheimer's disease.

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Abstract Number: 329

Naphthalimides: A Novel Scaffold for Sensing the Micro-Environment of Amyloids

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Amyloids are macromolecular aggregates that form when proteins assemble in a manner that generates a cross-β structure. [1] Toxic amyloids are famously implicated in a wide range of diseases, most notably Alzheimer's and Parkinson's diseases, however less well known are functional amyloids that play important roles in normal biological functions. [2-5] Despite two decades of research on functional amyloids, it remains unclear how cells can produce both toxic and functional amyloids under physiological conditions. To better improve our understanding of amyloids, it is important to understand the microenvironments (e.g., polarity, viscosity) presented on their surface, and how these affect solubility and stability of amyloid assemblies and govern their interactions with lipid membranes and other hydrophobic surfaces in the cell.

The challenges associated with studying amyloid are many. Structurally, amyloids and their pre-fibrillar oligomers can be heterogeneous in structure and size. [6] In addition, traditional techniques such as fluorescence microscopy, electron microscopy, PET and SPECT [7] do not give information about micro-environments. Fluorescence lifetimes are incredibly sensitive to the environment (e.g., polarity, viscosity) surrounding the fluorophore. [8] Fluorescence lifetime microscopy (FLIM) can be used in conjunction with environment-sensitive probes in order to gain information about minute differences in micro-environments in amyloid assemblies that cannot be visualised with other techniques

In this presentation, I will discuss the design and testing of a library of naphthalimide-based fluorescent sensors that show both polarity and viscosity dependent fluorescence emission properties. I will also discuss their use in FLIM of amyloids, allowing us to distinguish different forms, as well as allowing mapping of micro-environments present within amyloid. We also extend this methodology to 3DFLIM, enabling 3-dimensional analysis of amyloid micro-environments.

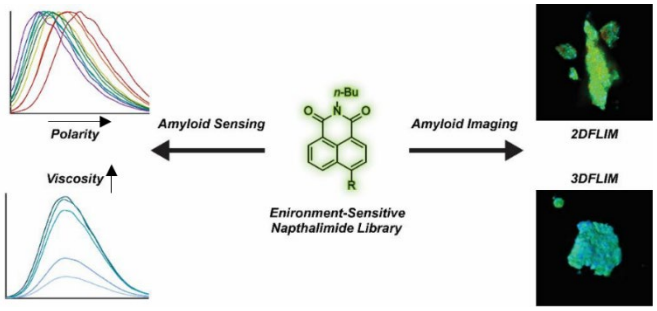

Figure 1: A library of naphthalimide-based probes allows polarity and viscosity sensing or amyloids, as well as fluorescence lifetime microscopy.

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Abstract Number: 330

Cytotoxicity of *fac*-[Re(CO)3(*N,N'*)L]$^{-/0/+}$ Complexes with *S*-donor Ligands (L)

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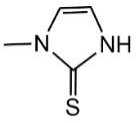
Diimine Re(I) tricarbonyl complexes, *fac*-[Re(CO)3(*N,N'*)L]$^{0/+}$, attract great interest due to their chemotherapeutic and photophysical activities. After Wilson's group discovered anticancer properties of the *fac*-[Re(CO)3(*N,N'*)(H2O)]$^{+}$ complexes,[1] where (*N,N'*) = 2,2 '-bipyridine (bpy), 1,10-phenanthroline (phen) and 2,9-dimethyl-1,10-phenanthroline, our group has studied how interactions with *S*-donor ligands affect the cytotoxicity of such complexes.

Reacting *fac*-[Re(CO)3(bpy)(H2O)](CF3SO 3) (**1**) with the amino acid cysteine (H2Cys) to get the neutral [Re(CO)3(bpy)(HCys)] (**2**) complex reduced the cytotoxic activity toward the MDA-MB-231 breast cancer cell line. Elemental distribution maps from X-ray fluorescence microscopy (XFM) revealed that cysteine coordination reduces cellular accumulation of the Re complexes.[2]

Considering the effectiveness of sodium thiosulfate (STS; Na2S2O3) in reducing toxic side effects of cisplatin (such as hearing loss), we investigated the effect of STS on Re(I) aqua complexes. Crystalline Na{ *fac*-[Re(CO)3(bpy)(S2O3)]} (**3**) obtained when reacting **1** with STS, showed considerably lower toxicity toward the MDA-MB-231 cell line. According to XFM images thiosulfate coordination hinders transport of the Re complex.[3]

We prepared a series of *fac*-[Re(CO)3(*N,N'*)(MMI)]$^{+}$ complexes (*N,N'* = bpy, phen, dmphen) using the antithyroid drug methimazole (MMI). Our hypothesis was that free MMI ligands from hydrolysis of the Re-MMI complexes would lower the level of thyroid hormones *in-vivo,* and together with the cytotoxic Re-aqua species reduce tumor growth. However, our studies showed that the Re- MMI complexes were stable in aqueous media, with similar cytotoxic activity as the corresponding Re-aqua complexes.[4]



MMI

To conclude, our studies show that *S*-donor ligands form stable Re(I) complexes, and their overall charge has significant effect on their cellular uptake, and level of cytotoxicity.

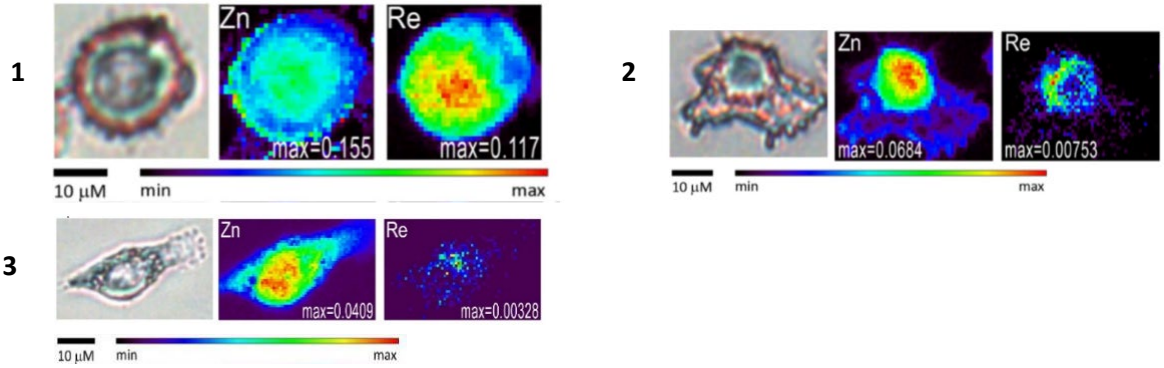


Figure 1. Optical micrographs (*left*) and XRF elemental distribution map (Zn and Re) of MDA-MB-231 cells treated with **1, 2** and **3** for 6 h. The maximum elemental area densities (quantified from standards and expressed in µg cm^{-2}) are given in the bottom of each map. The scale bar represents 10 µm.

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Abstract Number: 331

Determinants of copper reactivity at the histidine brace

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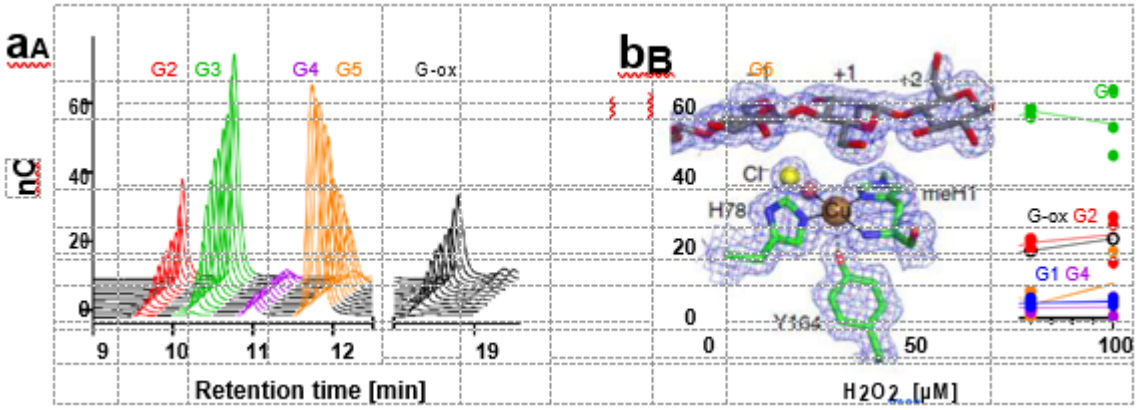
The histidine brace is a copper-binding motif that is associated with both oxidative enzymes and proteinaceous copper chelators. This site is defined by a bidentate N-terminal histidine and a second internal histidine side chain. Lytic polysaccharide monooxygenases (LPMOs) are His-brace enzymes capable of cleaving glycosidic bonds in recalcitrant biopolymers such as cellulose[1]. LPMOs are currently used in the production of lignocellulotic ethanol and have an important role in degradation of biopolymers in Nature. To understand better the determinants of reactivity, we have been studying the biochemical and structural properties of a well-described cellulose-specific LPMO from *Thermoascus aurantiacus* in comparison with that of CopC from *Pseudomonas fluorescens* (PfCopC) and with the LPMO-like protein Bim1 from *Cryptococcus neoformans*[2]. PfCopC was then used as a model to study the histidine brace through expression and characterization of a series of amino acid variants[3]. Although some variants were expected to, none of them were redox active. Surprisingly, it was found that another cellulose active LPMO from *Lentinus similis* was also not redox active when bound to the substrate. In contrast, the enzyme-ligand complex reacts very fast with hydrogen peroxide to cleave glucosidic bonds[4]. New data from amino acid variants of this LPMO will be presented.



Cleavage of glucosidic bonds at the histidine brace. A) HPAEC chromatogram of oligosaccharide products from cleavage of β-1,4-glucopentaose (G5) by *Lentinus similis* LPMO with H2O2 as co-substrate[4]. B) Crystal structure of the active site of this LPMO with oligosaccharide substrate[5].

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Abstract Number: 332

Discovery of β-cyclocitral-derived mono-carbonyl curcumin analogs as anti-hepatocellular carcinoma agents via suppression of MAPK signaling pathway

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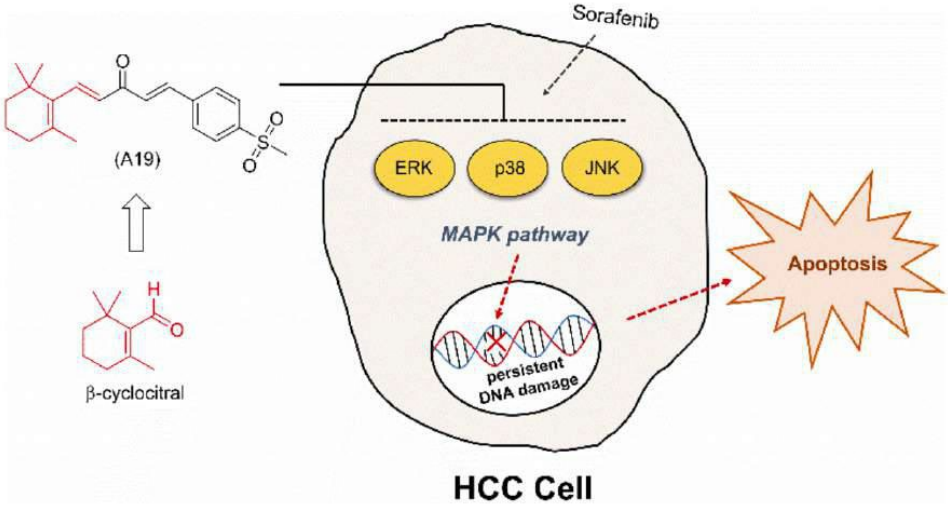
Hepatocellular carcinoma (HCC) is one of the most common malignant tumors with a high recurrence and mortality rate. In this study, a series of β-cyclocitral-derived mono-carbonyl curcumin analogs were synthesized and their anticancer properties were evaluated. Among the series, A19 exhibited the strongest cytotoxic activity by inhibiting cell viability and colony formation, inducing cell cycle G2/M phase arrest and cell apoptosis of HCC HepG2 and Huh-7 cells, while having almost no cytotoxicity on normal liver MIHA cells. Mechanistically, our results demonstrated that A19 triggered intense DNA damage via suppression of the ERK/JNK/p38 MAPK signaling pathway. Additionally, a combination of A19 with sorafenib significantly induced synergistic cyto- toxicity in HCC cells. Overall, our results indicate the potential of A19 as a novel chemotherapeutic drug administered either separately or in combined therapy for HCC treatment.

Graphical abstract



Abstract Number: 333

Metal, and metalloprotein, dysfunction are shared pathways associated with nerve cell death in Parkinson disease and motor neuron disease

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Metal dyshomeostasis results in, or is strongly associated with, a range of neurodegenerative diseases. The accumulation of iron in the brain in the common neurodegenerative disorder Parkinson disease has been well described but a further feature of the Parkinson brain is a marked deficiency of copper, and copper-regulating proteins, restricted to degenerating regions[1]. Copper-dependent proteins are important for normal brain function and are altered in the vulnerable regions of the Parkinson brain. We described structurally-disordered, deposited forms of the cuproprotein superoxide dismutase 1 (SOD1) in degenerating regions of the Parkinson disease brain[2]. Further we showed that deposited SOD1 in Parkinson disease appears to be abnormally metalated. Interestingly, while misfolded, mutant SOD1 protein is linked to motor neuron death in some forms of familial amyotrophic lateral sclerosis (ALS, a motor neuron disease), in Parkinson disease aberrant SOD1 is wildtype protein. We subsequently showed that structurally-disordered, mismetallated wildtype SOD1 is also present in the degenerating ventral spinal cord in sporadic ALS[3]. We hypothese that, in a copper-deficient environment, post-translational maturation of mutant and wildtype SOD1 is altered, resulting in structurally-disordered, aggregating protein with a toxic gain-of-function[4]. A novel mouse strain expressing human wildtype SOD1 protein in a copper-deficient brain resulted in age-associated deposition of misfolded SOD1, dopamine cell death and movement dysfunction. Our data suggest aberrant SOD1 can form from mutant or wildtype protein via shared pathways and may be characteristic of vulnerable tissues in several neurological disorders. These pathways may represent promising targets for development of disease modifying treatments, either by restoring normal maturation of SOD1 or improved removal of aberrant toxic forms of the protein.

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Abstract Number: 335

XANES mapping of Mn speciation in leaf tissue infected with a fungal pathogen: investigating the role of nutritional immunity

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Wheat and barley contribute to approximately 18% of human calorie intake globally.[1] Plant fungal diseases (such as yellow spot, powdery mildew, and net blotch) are major biotic threats affecting wheat and barley production and result in yield losses of up to 50%.[2, 3, 4]

Nutritional immunity is a defence mechanism used by organisms involving active restriction or accumulation to toxic levels of various metals. Plant cells maintain balanced levels of metals (e.g. Mn, Zn, Cu) and their biological functions are closely related to chemical speciation (ligand type and arrangement around the metal ion). To determine the role of nutritional immunity in wheat infected with yellow spot, synchrotron X-ray fluorescence microscopy (XFM) was used to reveal significant accumulation of Mn in the symptomatic lesions on wheat leaves, however this was not observed in infected barley leaves.[5] To further investigate the role of Mn in symptom development and subsequent reduction of green leaf area, we have used X-ray absorption near-edge structure (XANES) spectroscopic mapping to characterise the distribution and speciation of Mn in both wheat and barley infected with fungal diseases (yellow spot and spot form net blotch, respectively).

Well-established in animal immunity,[6] knowledge of nutritional immunity in plants is lacking, and could provide an alternative pathway to improve crop resistance and tolerance to disease via selective breeding.

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Abstract Number: 336

Mass Spectrometry Imaging of Copper-Delivering Agents and Disease-Relevant Metals in Mouse Brain

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Transition metals such as copper (Cu) are essential for the health and function of neurons; regional dyshomeostasis of Cu is a major hallmark of central nervous system (CNS) conditions including amyotrophic lateral sclerosis (ALS)[1] and Parkinson's Disease (PD)[2]. Thus, established or emerging therapies for these disorders aim to restore CNS Cu levels from pathological levels (high or low).[3] Treatment with Cu-delivering agents (e.g., Cu(II)-ATSM) for ALS and PD patients addresses the localised Cu-deficiency observed in the Cu-proteome within the CNS.[1] Yet, there is no direct evidence for the Cu-delivery agent or related metabolites to localise in central nervous tissues, or if and how these enter the cell. There is only indirect evidence of their effect through detected changes of transition metal concentrations within CNS sections, e.g., through laser ablation inductively coupled plasma mass spectrometry (LA-ICP-MS).

This project aims to (1) determine the phase I and II metabolites of Cu(II)-ATSM via a liver microsome assay followed by MS-led discovery metabolomics and (2) employ a targeted metabolomics approach using high-resolution mass spectrometry (HR-MS) and HR-MS imaging to determine the spatial distribution of neuroprotective metal-delivering agents and their metabolic derivatives in individual mouse brain sections derived from a treatment pilot study. In the microsome assay (0-60 min incubation), six compounds have been identified as phase I and II metabolites. These metabolites are currently being mapped in dissected tissues, with MS imaging to occur next. Downstream, the disease-relevant transition metals will be mapped in the same tissues by LA-ICP-MS to validate the mechanistic effects of the identified compounds in the tissues. The scoped work will provide complementary data and direct insights into molecular mechanisms underpinning effects of a Cu-delivery agent in the CNS.[4]

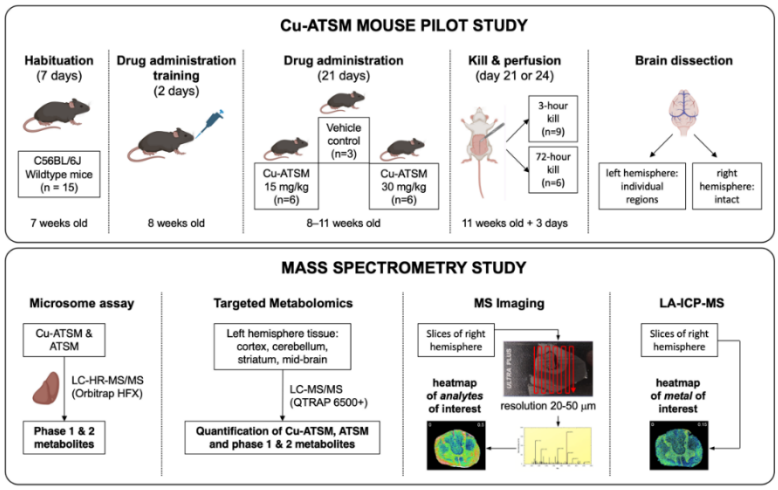

Figure 1. Schematic representation of the workflow.

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Abstract Number: 338

Deciphering a Membrane-Bound Hydrocarbon-Producing Metalloenzyme

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The increasing concerns about global warming due to the use of fossil fuels have triggered enormous interest in developing renewable and eco-friendly Biofuels.1 Since hydrocarbons such as alka(e)nes are the major components of fossil fuels, their biosynthesis in a sustainable fashion has gained tremendous attention in the past few decades.1 In this regard, a hydrocarbonproducing metalloenzyme (HPM) has gathered significant interest in the production of 1-alkenes. However, despite its importance, this enzyme remained enigmatic due to its membrane-bound nature. HPM, so far, could not be purified and has eluded biochemical and mechanistic investigation. Recently, we made efforts to decipher this enzyme's long-standing mystery. We purified the HPM for the first time to homogeneity.2 We thoroughly characterized the enzyme biochemically and investigated the mechanistic plot of this enzyme. We established the metal identity of the enzyme and identified the key residues essential for the activity of HPM.2 Further, we established that HPM is an oxygen and redox-dependent enzyme and have identified the optimal redox partner proteins to support the in vitro activity of HPM.2,3 We also determined the substrate specificity and Michaelis-Menten kinetics parameters of the enzyme. Moreover, we obtained the first mechanistic insights of HPM.2 Further, we made efforts to engineer the HPMsystem for the efficient production of 1-alkenes. Our results provide a robust framework for further characterization of HPM and also aid in evaluating the properties of HPM and engineering it for efficient biosynthesis of 1-alkenes that have a multitude of applications in various industries.

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1 Iqbal T, Chakraborty S, Murugan S and Das D.* Chem. Asian J., 2022, 17, e2022001 [Featured as the Front Cover of the journal]
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Abstract Number: 341

Pore environment tuning for the isolation of unusually distorted organometallic complexes in new Zr-MOFs

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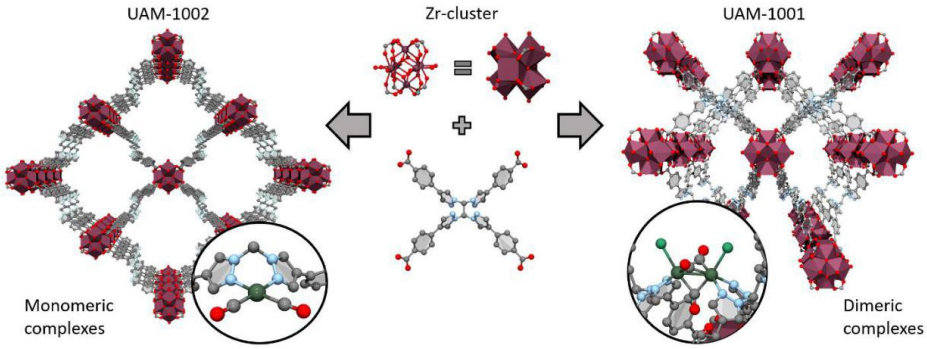
Metal-organic frameworks (MOFs) are highly porous solid-state materials that can be modified by incorporating metal salts into the structure by post-synthetic metalation (PSMet).[1] This allows for the tuning of the optical, magnetic, or catalytic properties of MOFs.[2] PSMet can be achieved at the MOF node or an organic linker site, depending on whether the linker contains a free coordinating moiety. While commonly used organic linkers containing 2,2'-bipyridine[3] or porphyrin[4] moieties have been studied as components of chemically and thermally stable Zr-MOFs, their limited flexibility and high symmetry have restricted the range of organometallic complexes that can be studied using single crystal X-ray diffraction (SCXRD). Previously, with a manganese-based MOF (MnMOF-1) which possesses free bis pyrazolyl moieties, we showed a wide range of metal salts could be introduced and could be characterised by SCXRD.5 However, its application is limited due to relatively poor water and chemical stability.

Herein, we present the synthesis of two new, more robust Zirconium-based MOFs (UAM-1001, UAM-1002), using a linker which contains a similar bis-pyrazolyl moiety. Due to significant differences in network topologies, a different distribution of the free bis-pyrazolyl moieties allows the insertion of monomeric complexes in UAM-1002 and dimeric complexes in UAM-1001. In the case of UAM-1001, SCXRD reveals the MOF drives the isolation of unusually distorted dimeric complexes with very short metal-metal distances. This confirms the bis-pyrazolyl moiety allows the study by SCXRD of a wide variety of metal complexes in MOFs and highlights the importance of the network topology for the formation of new species.



Schematic representation of UAM-1002 (left) and UAM-1001(right) with enlargements of the bis-pyrazolyl units metalated with [Rh(CO)2Cl]2 to form a monomeric and dimeric complex, respectively.

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Abstract Number: 343

Why is copper toxic, and how can we direct it for benefit?

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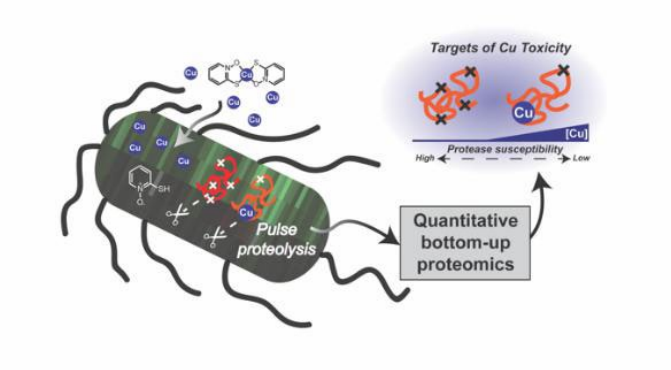
Normal and pathogenic cells require a menu of metal nutrients for optimal growth, but also strategies to mitigate toxicity associated with misregulated or excessive levels of metals, including copper. Cells adjust copper homeostasis mechanisms depending on cell type, local growth conditions, and in response to stress. These situations present opportunities to manipulate cellular copper as a therapeutic strategy against several diseases, including cancer and infection. But what are the targets and mechanisms of copper toxicity? Here I will present new approaches to interrogate cellular proteomes for protein targets of copper overload. By combining conventional protein expression level analysis with measurements of protein folding stability changes across a cellular proteome, our data reveal proteins involved in multiple biological processes that are directly disrupted by changes in copper status induced by pharmacological manipulation.[1, 2] More broadly in the context of infectious diseases, we are using these and other approaches to explore how cellular responses at the metallomic and proteomic level affect and are affected by microbial susceptibility and adaptation to antimicrobial treatment.



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Abstract Number: 344

Biochemical and spectroscopic studies of chalcogen resistant bacteria

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Tellurium is a formerly undesirable by-product of mining that is now sought after for electronic and solar applications. However, it is extremely toxic and its biological interactions are unknown. Here we describe the spectroscopic and biochemical aspects of a Te-resistant bacterial operon.

Abstract Number: 345

Crystal field splitting, magnetoelastic coupling and quantum tunneling: Inelastic Neutron Scattering as a tool in molecular magnetism

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Single molecule and single ion magnets are molecules that display a magnetic bistability. Varying the structure and coordination environment of the magnetic ions in these materials using synthetic chemistry can tune the ground state and allow both the energy barrier for reorientation to be changed, and quantum tunneling through the barrier to be introduced. As such these molecules have been touted as potential candidates for molecular scale data storage, qubits and as components in spintronic applications. Inelastic neutron scattering is one of the most accurate techniques for studying these molecules,1 as it allows individual transitions between states to be measured rather than a thermal average of all states. Historically this has made it the most precise way to determine the crystal field splitting in the absence of an applied magnetic field. Recently we have also demonstrated that magnetoelastic coupling is also encoded into the INS data.2 This has allowed us to explore vibrational relaxation mechanisms in candidate single ion magnets. However, there are multiple different relaxation mechanisms, in this contribution I will demonstrate, through recent results, that we can not only determine the magnitude of the crystal field splitting,3 but also that INS is also sensitive to the lifetime of quantum tunnelling and demonstrate that unique information can be extracted in this way.

Abstract Number: 347

Bulky Dihydroacridine-Based Ligand and Uses in Low-Valent Group 14 Chemistry

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Judicious ligand design is core to the stabilisation of highly reactive main group species.[1] Sterically demanding, monoanionic, nitrogen-based ligands (amido ligands) form a commonly used and widely successful class.[1] The extent of their steric protection is dependent on the angle between flanking groups, leading to a natural progression of steric protection shown in Figure 1.[2] This leads us to the synthesis of aryl substituted dihydroacridinide architectures.[3]

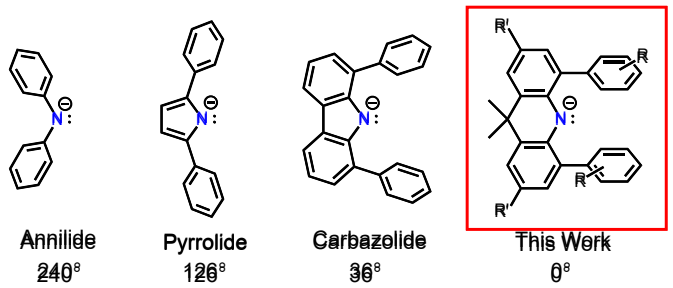
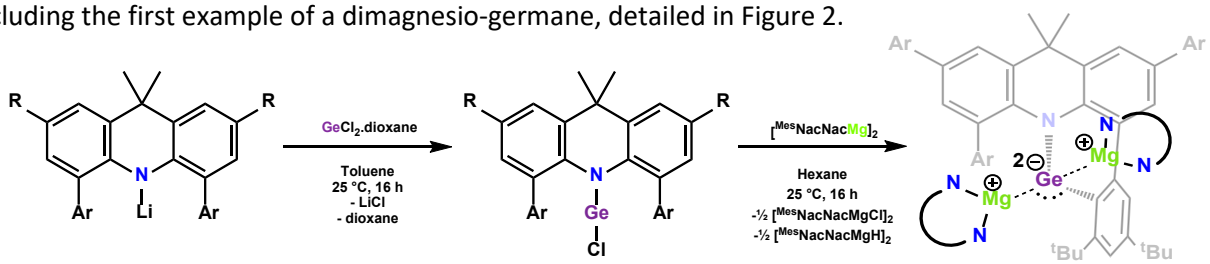


Figure 1. Amido ligands presented in order of increasing steric protection and decreasing angle between the flanking arenes, culminating in the family of ligands developed in this work.

Group 14 chemistry has shown great promise to display not only fundamentally interesting novel electronic structures, but increasingly reactivity such as Driess' heavy carbone analogues.[4] This in turn leads the way in less toxic, environmentally sound, main-group metal alternatives. This work reports the synthesis, reduction, characterization, and reactivity of low-valent germanium and tin complexes, including the first example of a dimagnesio-germane, detailed in Figure 2.



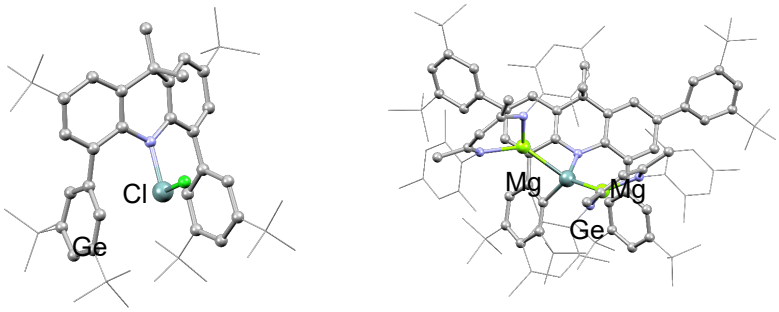


Figure 2. Top: reaction scheme showing the synthesis of a germylene and the subsequent reduction to dimagnesiogermane. Bottom: solid state structures of the germylene (left) and dimagnesiogermane (right). ^{Mes}Nacnac = $[HC\{C(Me)NMes\}_2]^-$; Mes = 2,4,6-trimethylphenyl.

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Abstract Number: 349

The structure of the complex between the arsenite oxidase from *Pseudorhizobium banfieldiae* sp. str. NT-26 and its native electron acceptor cytochrome c_{552}.

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Arsenic, a toxic metalloid is naturally found in the environment but can exist as a harmful pollutant generated from industrial waste waters and gold mines. This poses a great threat to human health by contaminating the ground water system[1]. Arsenic can exist in both organic and inorganic forms and in four oxidation states, arsines and methyl arsines (As^{3-}), elemental arsenic (As^{0}), arsenite (AsO_3^{3-}) and arsenate (AsO_4^{3-}). Although arsenic is toxic and hazardous to human health, some prokaryotes have developed unique mechanisms that utilize inorganic forms of arsenic, such as arsenite (AsO_3^{3-}) and arsenate (AsO_4^{3-}) for respiration[2].

The organism *Psuedorhizobium* sp. str. NT-26 respires with arsenite and employs the arsenite oxidase (AioAB) for its crucial respiratory activity, which catalyzes the oxidation of arsenite to arsenate. The AioAB enzyme consists of two subunits: AioA (contains a molybdenum center and 3Fe-4S cluster) and AioB (contains a Rieske [2Fe-2S] cluster). Arsenite is oxidized to arsenate at the Mo site, concomitantly reducing Mo(VI) to Mo(IV). The electrons are then passed to the 3Fe-4S cluster, the Rieske cluster in AioB and to an electron acceptor, which is cytochrome c_{552} (cytc_{552})[2,3]. The crystal structure of the AioAB/cytc_{552} electron transfer complex reveals two A_2B_2/(cytc_{552})$_2$ assemblies per asymmetric unit. Three of the four cytc_{552} molecules in the asymmetric unit dock with AioAB in a cleft at the interface between the AioA and AioB subunits, with an edge-to-edge distance of 7.5 Å between the heme of cytc_{552} and the [2Fe-2S] Rieske cluster in the AioB subunit. The interface between the AioAB and cytc_{552} proteins features electrostatic and non-polar interactions and is stabilized by two salt-bridges. This presentation will discuss the transient and catalytically efficient nature of the AioAB/cytc_{552} complex that underpins the ability of this organism to respire using the arsenite present in contaminated environments.

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Abstract Number: 353

The development of a high-throughput workflow for the design and screening of metalloproteins for critical materials isolation

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The global effort toward sustainable energy has put increasing pressure on the sourcing of critical elements. Platinum group elements (PGEs) are essential to sustainability efforts due to their catalytic roles in energy production and emission reduction. Many strategies are required to resolve these challenges, though one vision for PGEs is to bolster the up-stream supply from non-conventional sources. In this light, metalloproteins offer a promising strategy for critical materials isolation given their inherent propensity for metal specificity and their potential for tailoring to stability in harsh environments. We have implemented a design, build, test, learn cycle to address the protein-mediated isolation of PGEs. Our strategy is focused on a prototypical metalloprotein that has been previously shown to bind PGEs. We expand this work into a diverse panel of related protein sequences and have developed a high-throughput analytical workflow for screening of potential PGE binding proteins to serve as input into a machine learning (ML) and artificial intelligence (AI) architecture that informs the design of improved sequences for PGE isolation.

Abstract Number: 355

Iron-sulfur cluster trafficking and iron regulation in fungal pathogens

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Maintaining adequate, non-toxic levels of the essential nutrient iron is crucial for the survival of organisms ranging from microbes to humans. In humans, dysregulation of iron metabolism can lead to anemia, iron overload disorders, and neurodegenerative diseases. Iron regulation is also critical for yeast that infect humans since iron is a vital resource during infections. The human host and invading pathogens battle for this limiting nutrient, employing competing strategies for binding and sequestering available iron pools. To exploit the dependency of fungal pathogens on iron, our research group is teasing out the mechanistic details of iron sensing and regulation in yeast model systems.[1] Our studies are focused on characterizing the roles of monothiol glutaredoxins Grx3/Grx4 that bind iron-sulfur (Fe-S) clusters with BolA partner proteins. These binding partners together regulate the function of different yeast transcription factors that control iron uptake, storage, and utilization genes. Using a combination of protein biochemistry, spectroscopy, mutagenesis, and yeast genetics and cell biology, we have demonstrated how Grx3/4 and Bol2 proteins signal and control iron bioavailability in yeast via Fe-S cluster trafficking and transfer.[2] We have identified residues in Grx3/4, Bol2, and their transcription factor targets that play key roles in donor-target recognition and influence Fe-S cluster binding and transfer rates. Taken together, these studies provide a detailed picture of the dynamic interactions between these Fe-S binding partners that govern iron regulation in yeast, and demonstrate that Grxs and BolA proteins have evolutionarily conserved roles in iron regulation. Thus, our studies will provide critical information that may add in the development of therapeutic strategies to neutralize or destroy fungal pathogens.

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Abstract Number: 357

Bio-Inorganic Hybrid Catalytic Approach Inspired By Metalloprotein

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Metal ion is an important research object in bio-inorganic chemistry. In living organisms, metals can form coordination with proteins and act as the active center of metal enzymes, playing important physiological functions such as electron transfer and Redox. Biomimetic simulation of metal enzyme catalysis under biocompatible conditions is one of the important research topics in chemical biology. We developed a bioinorganic hybrid system for photocatalytic hydrogen production under aerobic conditions by combining light-harvesting semiconductors, hydrogenase catalysis, and self-aggregation of whole bacterial cells. We induced hydrogen production via self-photosynthesis in engineered Escherichia coli cells, which were originally designed for bioremediation, with in situ biosynthesis of biocompatible cadmium sulfide nanoparticles using a metalloprotein surface-displayed system. This biohybrid catalytic approach may serve as a general strategy for solar-to-chemical production.[1]
Recently, a special biomimetic silver binding peptide AgBP2 was introduced to develop a facile synthesis of biocompatible Ag_2S quantum dots (QDs). The AgBP2 capped Ag_2S QDs exhibited excellent fluorescent emission in the second near-infrared (NIR-II) window, with physical stability and photostability in the aqueous phase. Under 808 nm NIR laser irradiation, AgBP2-Ag_2S QDs can serve not only as a photothermal agent to realize NIR photothermal conversion but also as a photocatalyst to generate reactive oxygen species (ROS). The obtained AgBP2-Ag_2S QDs achieved a highly effective disinfection efficacy of 99.06% against *Escherichia coli* within 25 min of NIR irradiation, which was ascribed to the synergistic effects of photogenerated ROS during photocatalysis and hyperthermia. Our work demonstrated a promising strategy for efficient bacterial disinfection.[2]

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Abstract Number: 362

Sulfite reductase employs siroheme rather than heme due to higher efficiency in transferring electrons incoming from the [4Fe4S] cubane cofactor

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Sulfite reductase (SiR) contains in the active site a unique assembly of siroheme and a [4Fe4S] cluster, linked by a cysteine residue. Siroheme is a doubly reduced variant of heme that is not used for a catalytic function in any other enzyme. We have used[1] non-equilibrium Green's function methods coupled with density functional theory computations to explain why SiR employs siroheme rather than heme. The results show that direct, through vacuum, charge-transfer routes are inhibited when heme is replaced by siroheme. This ensures more efficient channelling of the electrons to the catalytic iron during the six-electron reduction of sulfite to sulfide, limiting potential side reactions that could occur if the incoming electrons were delocalized onto the macrocyclic ring.

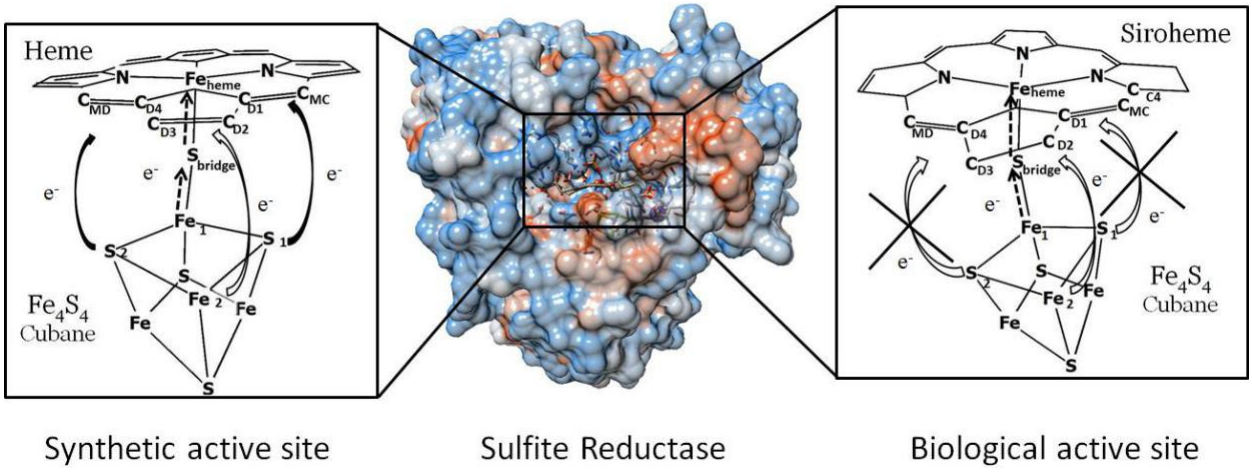

Figure 1. As opposed to heme, siroheme inhibits the charge transfer from the cubane via direct routes.

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Abstract Number: 364

Theranostics with Metallic Radionuclides that Target Metalloenzymes and Immune Checkpoints

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The use of the same molecule for both diagnosis and therapy is called 'theranostics'. One approach to theranostics is to use one radionuclide for diagnostic imaging and another radionuclide to deliver therapeutic radiation. Selectivity for cancer tissue is possible by incorporating metallic radionuclides into chelates that are attached to molecules that selectively bind to enzymes or receptors that are over-expressed in tumours.

Copper-64 is a b^+-emitting radionuclide that can be used for diagnostic positron imaging tomography (PET) imaging whilst b-emitting copper-67 can be used for targeted radiotherapy. Our work into designing copper complexes that target prostate specific membrane antigen (PSMA), a zinc enzyme that is overexpressed in prostate cancer, will be presented. The synthesis of bivalent sarcophagine ligands that bind to PSMA and form very stable complexes with copper-64 and copper-67, their pre-clinical evaluation in animal models and first-in-human studies will be presented.

Targeted a-particle therapy with actinium-225 (t1/2 = 9.9 days) is an alternative to therapy with b-emitting radionuclides as a-particles have a higher linear energy transfer. Antibodies take several days to clear from the blood and accumulate in target tissue but offer exquisite selectivity. Our work in labelling antibodies that target Carbonic Anhydrase IX (CAIX), a zinc enzyme that is overexpressed in renal cancer, with actinium-225 will also be presented.

Certain cancer cells evade the immune system by developing the ability to interfere with 'immune checkpoints'. Tumours that upregulate a protein called Programmed Death Ligand 1 (PD-L1) develop the ability for immune escape. Treatment with antibodies that re-engage the patient's own immune system is known as immune checkpoint therapy. Our research into labelling antibodies that bind to PD-L1 with zirconium-89, a b^+-emitting radionuclide well suited for PET imaging with antibodies, will be presented.

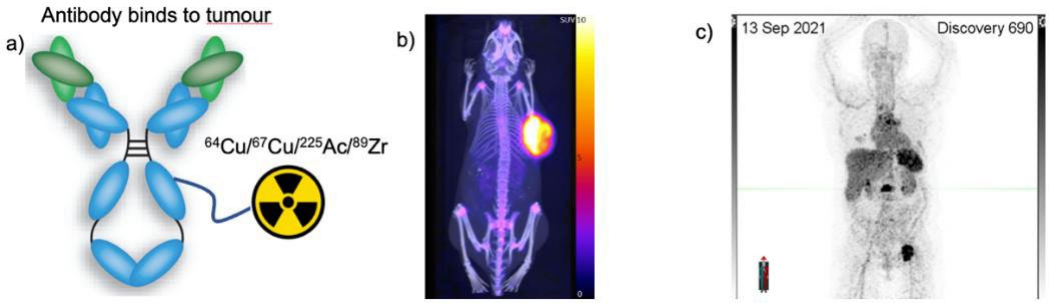

Figure 1. a) Radiolabelled antibodies can be used for imaging and therapy. b) PET imaging with a ^{89}Zr-PD-LI antibody in PDL1 positive mouse model. c) ^{89}Zr-PD-L1 antibody in lung cancer patient.

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Abstract Number: 367

New Researches on the Metal-based Antitumor Drugs of Active Ingredients of Traditional Chinese Medicine

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Alkaloids are active ingredients of traditional Chinese medicine and have a wide range of biological activities. We propose the idea of using the coordination and immunoregulation effects between the active ingredients of traditional Chinese medicine and the active centers of metals to design metal drugs, which provides a new model for the development of metal anticancer drugs. On the basis of previous studies, we have made new explorations on Mcl-1, tublin, Par-4 and glucose metabolism in cancer. A series of antitumor metal complexes of alkaloids □-carboline, oxoaporphine, quinoline, isoquinoline and their derivatives were synthesized. A series of metal complexes of active ingredients of traditional Chinese medicine with high antitumor activity and good safety in vivo were obtained, which provided the possibility to overcome the resistance of metal-based antitumor drugs.

This work was supported by the National Natural Science Foundation of China(2207702) and Natural Science Foundation of Guangxi Province of China (ZY22096015 and AD17129007).

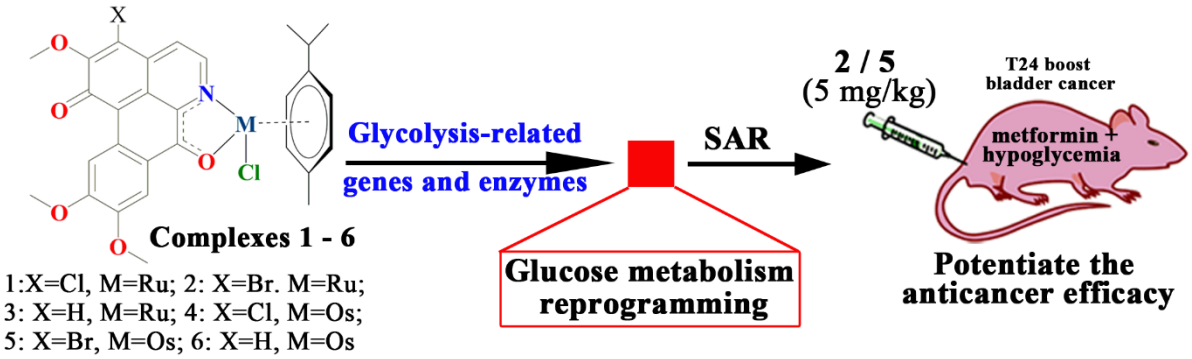

Fig. 1 Design rationale and verification scheme for the glucose metabolism reprogramming by oxoaporphine arene Os/Ru complexes.

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Abstract Number: 368

The Applications of Fluorescent Iron-based Nitric Oxide Release Molecules

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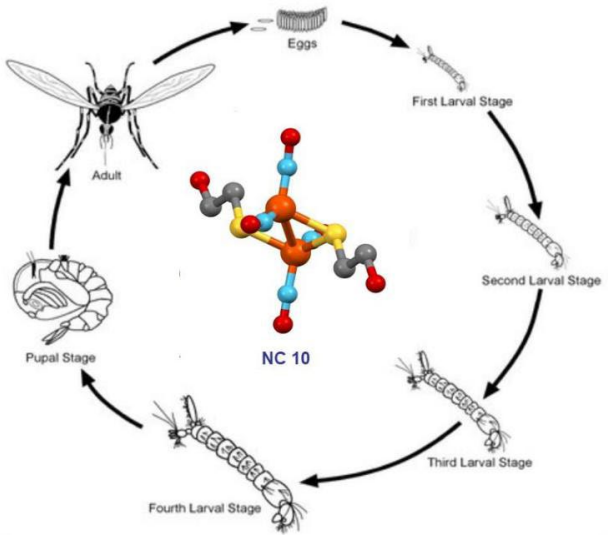
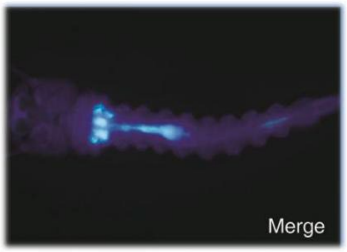
The iron-based nitric oxide (NO) release molecules, [(NO)2Fe(μ-SCH2CH2OH)2Fe(NO)2 (**NC10**)[1] and the fluorescent derivative, [(NO)2Fe(μ-SC6H4NHCHC16H9)2Fe(NO)2] (**PPIT-NC10**) are synthesized and characterized. It demonstrates the consequences of administration of **NC10** on mosquito larvae. **NC10** treatment is toxic to larvae, in a dose-dependent manner. Unexpectedly, in a small sublethal doses range (0.78 and 0.39 μM), **NC10** promotes the growth of larvae. As a result, larvae treated with **NC10** enter pupation earlier than those untreated. Transcriptome analyses of larvae treated with NC10 (0, 0.78 and 12.5 μM) show that the abundant transcripts of pupal cuticle proteins and odorant-binding proteins upregulated by **NC10**, and the abundant transcripts of the larval cuticle proteins, keratin and skin secretory protein xP2 downregulated. Several genes involved in carbohydrate metabolism, chitin metabolism and response to oxidative stress are also decreased. These results indicate that NO plays an intriguing role in the development of larvae, and these results may provide new thoughts in mosquito control for fighting mosquito-borne diseases.[2]





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Abstract Number: 369

Multi-modal Imaging to Visualize *In Situ* Interactions between Metallodrugs and Biological Targets in Single Cells

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Many drugs, in particular anticancer drugs exert their pharmacological functions by passing through cell membrane to target biological molecules, such as proteins and nucleic acids inside cells. For example, anticancer drug cisplatin attacks genomic DNA, inducing cell apoptosis and death. Therefore, *in situ* investigation of recognitions and interactions between drug molecules and intracellular targets is invaluable for drug discovery and chemical biology research of drugs. With virtues of label-free, high sensitivity and high spatial resolution, secondary ion mass spectrometry (SIMS) imaging has emerged to be a powerful tool to visualize small molecular drugs at single cell level.[1-3] However, direct *in situ* imaging of biological targets, such as proteins and DNA in single cells using SIMS is still a great challenge due to weak, or even absent signals of the corresponding molecular ions and/or informative fragment ions, largely limiting application of SIMS imaging for investigation of interactions between drugs and biological targets. To this end, we genetically incorporated fluorine-containing unnatural amino acids as a chemical tag into HMGB1 via genetic code expansion technique, enabling the co-localization of cisplatin-modified DNA and HMGB1 in single cells by ToF-SIMS imaging.[4] Recently, we developed a correlative optical and SIMS imaging (termed COSIMSi) strategy by optically labeling HMGB1 and DNA to visualize *in situ* the formation of cisplatin-DNA-HMGB1 ternary complex in single cells.[5] Furthermore, we combined gene editing and the CRISPR/dCas9-sgRNA site-directed labelling techniques to optically label specific gene loci, e.g. PTPRN2, allowing us to visualize *in situ* the recognitions and interactions between transcription factors and the specific gene locus in cells. We also developed a CRISPR/dCas9-sgRNA directed fluorescence resonance energy transfer (FRET) platform to visualize the interactions between the specific genes and transcription factor Smad3 in the cells treated with cisplatin. This genetically engineered FRET strategy could be extended to *in situ* investigate interactions of metal-based anticancer drugs with proteins and genomic DNA in single cells.

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Abstract Number: 374

Protein-induced crystal deformation in a hydrogen-bonded organic framework

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Enzyme immobilization within porous supports has been demonstrated to enhance biomolecule stability, allowing their activity to persist under harsh conditions that would otherwise cause protein denaturation.[1] Hydrogen-bonded organic frameworks (HOFs) are an attractive candidate for enzyme encapsulation, as they are metal-free and often have sizable pore apertures, allowing substrate and product diffusion through the composites. Moreover, they possess good stability to buffers in a biologically relevant pH range. Previous studies have shown HOFs can afford good protection to a range of encapsulated enzymes,[2-4] however; the mechanism of encapsulation is not yet well understood.

In this work, we studied the encapsulation of a range of enzymes in a HOF comprised of a tetraamidinium cation and diazobenzene-based dicarboxylate anion. Crystallisation of this HOF has previously been controlled by exploiting the photoswitching ability of the azo-compound,[5] and we proposed that slowing crystal growth could lead to improved protein loading and encapsulation. When HOF growth was slowed sufficiently (either by dilution or photoswitching of the ligand) deformation of the crystals was observed in the presence of some proteins. We propose that the extent of crystal deformation may be governed by differences in the type and strength of interactions between proteins and the surface of growing HOF crystals.

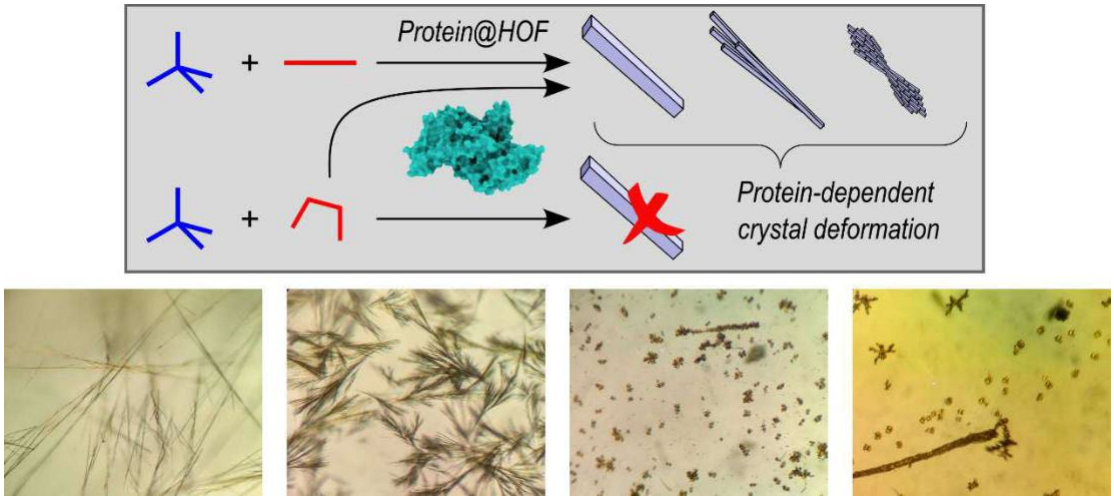

Figure 1: Schematic representation of HOF crystallisation, showing the variety of crystal morphologies accessible through the inclusion of different proteins when crystal growth is sufficiently slowed.

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Abstract Number: 377

Novel Pyridine-2-carbothioamide-Containing Transition Metal Complexes as Potential New Anticancer Agents

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While much progress has been made since the discovery of cisplatin, the area of organometallic metal-arene anticancer agents is still relatively unexplored. Ruthenium, and other platinum group metals, have become the main focus in this field as minor ligand modifications can entirely change their biological target and mode of action.[1] Preclinical trials have shown promise for some ruthenium-based complexes with a small number, including NAMI-A and KP1339, progressing into clinical trials.[2]

Pyridine-2-carbothioamides (PCAs) are bioactive compounds that have displayed potent cytotoxicity against several cancer cell lines. The ruthenium-based PCA, Plecstatin-1, displayed strong antiproliferative effects and the ability to target the scaffold protein plectin.[1] Previous work has explored the effect of substituting the para position on the phenyl ring with electron donating or withdrawing groups. N-(4-Aminophenyl)pyridine-2-carbothioamide was found to be moderate to poorly active, while its [Ru(η^6 – cymene)Cl] complex was not considered active.[3]

This work focused on substituting the amino group of N-(4-aminophenyl)pyridine-2-carbothioamide with lipo- and hydrophilic groups such as Figure 1 to investigate the effects on the activity of the new compounds. The triphenylphosphonium moiety is a delocalised lipophilic cation, whereas guanidine and biguanidine are more hydrophilic, a propyl group was chosen as a control, to investigate the impact of the triphenylphosphonium substituent on the activity of the compound. The effect on activity of changing from a pyridine-2-carbothioamide to a picolinamide-based ligand was also investigated, i.e. changing from a N/S binding motif to a N/O coordination motif. The resulting organo-Ru, Os, Rh and Ir complexes were investigated and their cytotoxicity compared to the ligands.

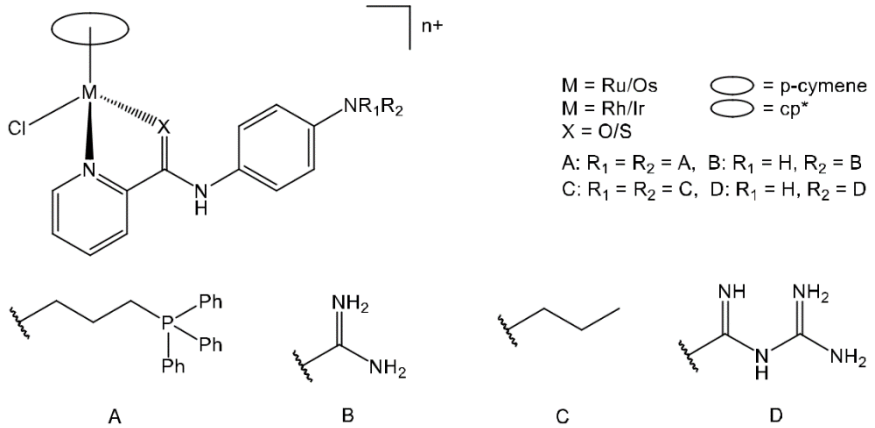

Figure 1: Core Structure of PCA-Containing Metal Complexes with Different Substituents

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Abstract Number: 378

Targeted Alpha Therapy with Actinium-225 Labelled Antibodies

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The emerging potential of radionuclide therapy with alpha (⍰⁺) emitting actinium-225 has stimulated significant interest in developing chemistry to enable the selective delivery of actinium to tumours. Ac-225 ($t_{1/2}$ 9.9 days) decays to the long-lived isotope Bi-209 ($t_{1/2}$ 1.9 x 10^{19} y) *via* the release of a total of four α-particles and two beta (β^-) particles. The high particle energy and linear energy transfer of α-emission delivers high doses of radioactivity, capable of causing double-stranded breaks in DNA across relatively short distances (40-90 µm). Therefore, there is significant interest in developing bifunctional chelators that form stable complexes with Ac^{3+}, which are easily conjugated to antibodies for targeted alpha therapy of cancer. Carbonic anhydrase IX (CAIX) is a metalloenzyme which is overexpressed on the surface of clear cell Renal Cell Carcinoma.[1] The monoclonal antibody Girentuximab selectively binds CAIX with high affinity (Figure 1a) and has the potential to selectively deliver therapeutic radiation to tumours.

A crown ether macrocyclic ligand functionalised with two picolinic acid arms, H_2macropa forms stable complexes with actinium (III), the largest trivalent cation in the periodic table.[2,3] In this work a new bifunctional variant with a pendant diethyl squarate ester, H_2macropa-tzPEG$_3$Sq, that allows the conjugation of the macrocycle to antibodies will be presented (Figure 1a). The conjugation of H_2macropa-tzPEG$_3$Sq to Girentuximab (and other cancer targeting antibodies) and radiolabelling with Ac-225 will be discussed. An evaluation of the therapeutic efficacy of [^{225}Ac]Ac-macropa-tzPEG$_3$-Girentixumab in a mouse model of renal cancer will also be presented (Figure 1b).

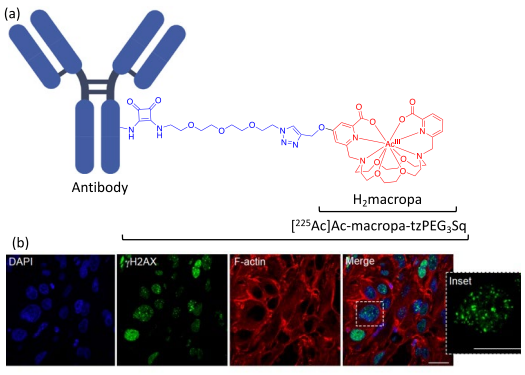

Figure 1. (a) Chemical structure of [^{225}Ac]Ac-macropa-tzPEG$_3$Sq conjugated to a monoclonal antibody, (b) confocal microscopy of SK RC-52 tumours harvested post-treatment and immunostained with antibodies against ɣH$_2$AX, showing double-strand DNA breaks.

We acknowledge the Australian Research Council, Australian Cancer Research Foundation, National Health and Medical Research Council, the Victorian Cancer Council and Telix Pharmaceuticals for supporting this research.

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Abstract Number: 381

Four-Electron Reduction of Benzene to the Tetra-Anion $[C6H6]^{4-}$ by a Simple Samarium(II) Alkyl

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Benzene is the archetypal cyclic hydrocarbon, since its initial isolation by Michael Faraday in 1825, its properties and functionalisation has been the focus of several scientific fields. Derived from two main feedstocks, crude oil and biomass, today benzene and its derivatives are central to the synthesis of materials, biomolecules and manufactured chemicals. Benzenes ubiquity is in part due to its exceptional chemical stability, derived from its aromaticity, the ability to host six delocalised electrons. This stability of benzenes aromatic ring results in a low reduction potential (–3.42 V)[1] which has led approaches to its functionalisation to focus on C–H activation, leaving the aromatic ring intact.[2] Consequently, reports on its reduction are limited, with all reductions to date resulting in isolation of either the benzene mono- or di-anion concomitant with a loss of aromaticity.[3] In comparison the hypothetical benzene tetra-anion, $[C6H6]^{4-}$, has been calculated to be stable and is predicted to exhibit aromaticity.[4] Herein, we demonstrate that a simple samarium(II) alkyl can undergo homolytic cleavage of the Sm–C bond to form a highly reactive transient Sm(I) complex capable of performing the 4-electron reduction of benzene to the tetra-anion, $[C6H6]^{4-}$ (Figure 1).

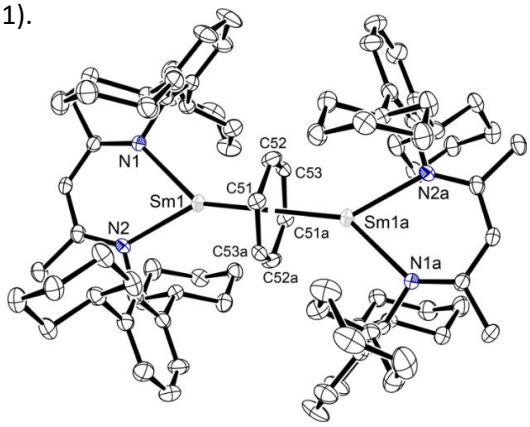

Figure 1: ORTEP representations (30% probability ellipsoids) of the inverted sandwich complex $[(BDI^{Dicyp})Sm(\mu\text{-}C6H6)Sm(BDI^{Dicyp})]$ (Dicyp = 2,6-dicyclohexylphenyl).

This reactivity has been extended to other substituted arenes which contain the respective arene tetra-anions. This process has been investigated both experimentally and computationally, and is proposed to involve an unprecedented 2-electron transfer process at a samarium centre.

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Abstract Number: 382

Flipping the redox switch: synthesis and reactivity of gas phase metallosupramolecular complexes

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Interlocked architectures and metallosupramolcular capsules or cages have proven to be attractive synthetic targets given their potential application in areas such as molecular sensing, enantioselective catalysis, drug delivery and in the development of stimuli responsive materials.[1] As structural complexity increases, new techniques are required for the synthesis and characterisation of more challenging topologically diverse species. Compared to the well-developed use of crystallography or NMR spectroscopy to this end, mass spectrometry is typically used only to determine the molecular weight and stoichiometry of supramolecular architectures.[2] Electrospray ionisation (ESI) preserves the integrity of the complex,[3] which can be spatially or temporally purified by tandem mass spectrometry (MS/MS).
By using an ion-trap mass spectrometer, gas-phase electrochemical reduction can also be deployed as a dual-function tool to synthesise and probe the reactivity of complexes beyond their conventional oxidation state(s). Such an approach is advantageous over solution-based methods due to the absence of competing reagents or solvents that would otherwise hinder the study of the intrinsic properties of the substrate. Through systematic investigation of a range of rotaxane, catenane and metallosupramolecular assemblies we have gained an understanding of the effect that precursor ion charge state, ligand structure, and guest encapsulation have on the reaction products and rates in the gas phase. [4]

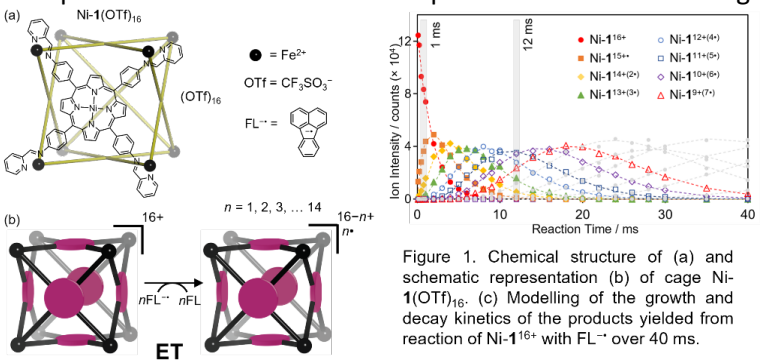

Figure 1. Chemical structure of (a) and schematic representation (b) of cage Ni-**1**$(OTf)_{16}$. (c) Modelling of the growth and decay kinetics of the products yielded from reaction of Ni-$\mathbf{1}^{16+}$ with $FL^{\bullet-}$ over 40 ms.

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Abstract Number: 383

Synthesis and Reactivity of Lanthanide(II) Hydrides

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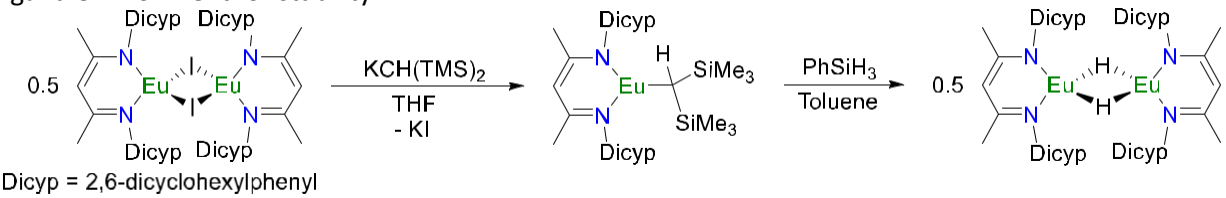
The development of trivalent lanthanide hydrido species has experienced impressive growth, so much so, that this chemistry has now been extended to most f–elements. Their reactivities have become well established in the literature, being found to favour small molecule activation as well as demonstrating high catalytic activity towards a range of chemical transformations.[1,2] In contrast, the synthesis and reactivity of lanthanide(II) hydrides is largely underdeveloped and was attributed to the assumption that the larger ionic radii and the strong reducibility of the metal ions posed a challenge in the synthesis and stabilisation of well defined, discrete lanthanide(II) hydrides. It has been demonstrated that this assumption is now continuously being defied, with the literature disclosing a total of six well-characterised ytterbium(II) hydrido complexes, in which the hydrides are exclusively bound to the metal centre.[3,4]
In contrast, there have been no reports on the synthesis of europium(II) hydrides, despite europium being more stable in the 2+ oxidation state in comparison to ytterbium. This means the lack of reported hydrido species for this element is likely ascribed to the larger ionic radius and the challenge of finding a suitable ligand environment for stability.



Scheme 1. Proposed synthesis of a heteroleptic europium(II) hydride.

We therefore aim to synthesise the first example of a molecular europium(II) hydride (Scheme 1). As their reactivity remains completely unexplored, it presents a unique opportunity to explore their catalytic abilities for the first time in relation to industrially relevant chemical transformations such as hydroamination, hydroboration, hydrosilylation, hydrogenation and polymerisation reactions.

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Abstract Number: 384

DNA cleavage and biological evaluation of dinuclear copper(II) complexes with phenol-based ligands with different thioether substituents

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Keywords: DNAse, antibacterial complexes, biomimetics

In the biological environment, metalloproteins, such as copper oxidases, are responsible for the electron transfer in biologically reactions, causing the oxidation of important organic substrates.[1] We report the synthesis, crystal structures, spectroscopic and magnetic properties of three new dinuclear copper(II) compounds (Chart 1) derived from phenol-based ligand containing different thioeter portions (aromatic and aliphatic), evaluating the influence of these modifications in solution as in solid state properties.

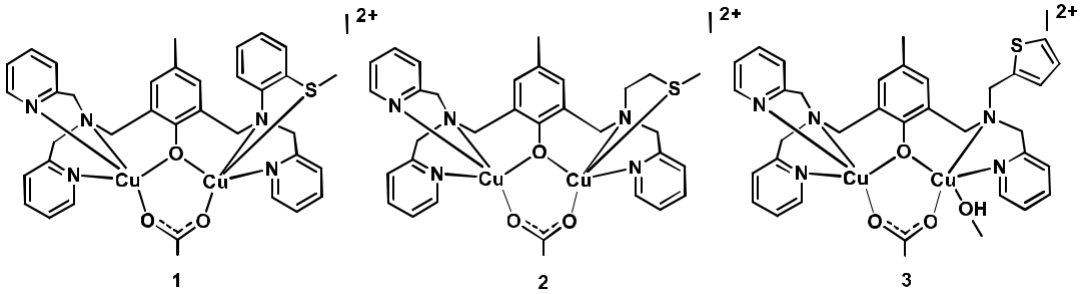

Chart 1 - Complexes synthesized in this study: **1**, **2** and **3**.

The present work also provides valuable insights towards the mechanistic aspects of catechol oxidase activity. In order to show the versatility of these copper complexes, we also investigated the peroxidative activity against different alkanes and alcohols.[2] In addition, we explored the in vitro biological activity showing good microbial and cytotoxic activity of these new copper complexes, proving to be biocompatible in normal cells and cytotoxic against human squamous carcinoma cells proving to be more potent than cisplatin. With studies of cleavage and interaction with DNA, it was verified that the complexes cleave this macromolecule through an oxidative process.

Acknowledgments: CNPq, CAPES, INCT-Catálise, FAPESC, CAPES-PrInt

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Abstract Number: 385

Examining the Reactivity and Speciation of Selenoneine *in vitro* via Synchrotron Radiation

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Selenium is micronutrient essential for human health. Twenty-five human proteins contain a selenocysteine at their active site, with most of these enzymes involved in cellular redox reactions.[1] The publishing of optimal dose guidelines for selenium is made difficult by the speciation problem; bioactivity is dependent upon the form of selenium ingested.[2]
In 2010 the major species of selenium in bluefin tuna was identified as selenoneine, a selenium-isologue of ergothioneine.[3] Eventually it was determined that selenoneine was the primary form of selenium found in a host of marine life, and was capable of bioaccumulating in humans.[4] The urea structure of selenoneine is unique amongst all dietary selenocompounds.

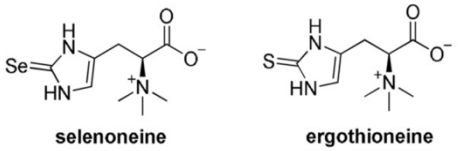

Figure 1. Structures of selenoneine and ergothioneine

In 2019, a total synthesis for selenoneine was published and a sample provided by collaborators from the University of Basel, Switzerland.[5] Using synchrotron radiation (X-ray Fluorescence Microscopy and X-ray Absorption Spectroscopy) uptake, distribution, and speciation information from A549 cells and human whole blood treated with selenoneine were obtained. Coupled with other techniques, such as oxidative stress assays and cell-uptake fractionation, new insight into the activity profile and metabolic pathway of this unique selenocompound have been discovered.

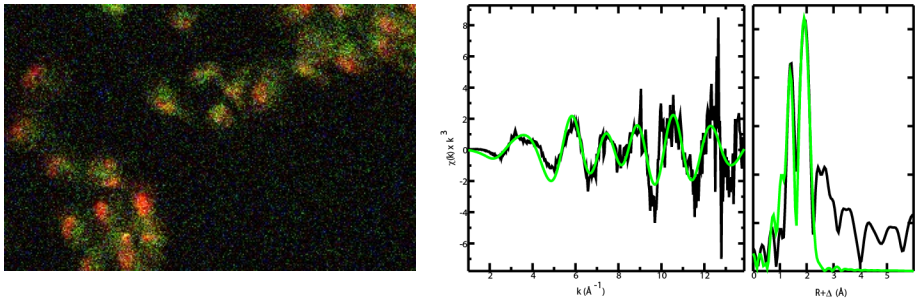

Figure 2. (Left) XFM image of A549 cells treated with 200 μM selenoneine for 4h displaying Se (green) and Zn (red) as an indicator of the nucleus; and (Right) EXAFS data and fit of an A549 cell pellet treated with 200 μM selenoneine for 4h indicating a large portion of the Se is now sulfur bound.

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Abstract Number: 386

Selenoprotein F and Glucose Metabolism

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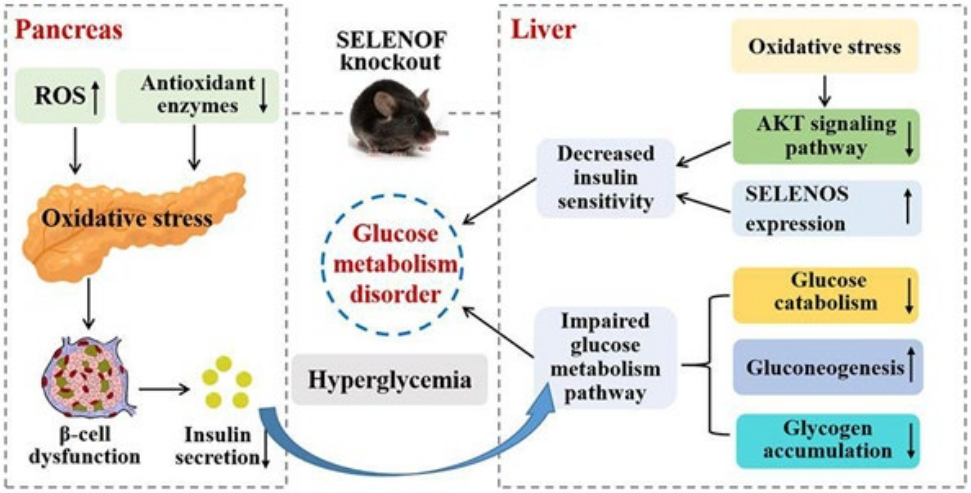
Much beneficial influence of selenium on health is attributed to its presence within selenoproteins as selenocysteine (Sec)[1]. Selenoprotein F (SELENOF) is an endoplasmic reticulum-resident protein that contains a Sec residue and its function has not yet been thoroughly addressed. To study the function of SELENOF, we used CRISPR/Cas9 to generate SELENOF knockout mice. The proteomic analysis of hepatic proteins by iTRAQ revealed that SELENOF deficiency in mice led to the differential expression of hepatic proteins associated with glucose metabolism. Furthermore, the phenotype analysis revealed that SELENOF knockout caused glucose metabolism disorders in young male mice even with a normal diet, characterized by hyperglycemia, serum insulin reduction, impaired glucose tolerance, decreased insulin sensitivity, decreased glucose catabolism, increased gluconeogenesis and impaired insulin signaling pathway. The mechanism involved might be that SELENOF knockout caused oxidative stress in the liver and pancreas. SELENOF might play a role in the regulation of redox homeostasis, which might be attributed to its thiol-disulfide oxidoreductase activity, but the exact role has remained unclear due to the lack of a reliable production method. We obtained multi-milligrams of human SELENOF through a three-segment two-ligation semisynthesis strategy. The thiol-disulfide oxidoreductase activity of SELENOF was further supported by its ability to catalyze the reduction and isomerization of disulfide bonds. Moreover, we found that the presence of Sec in the redox motif was the key for this activity. Our results suggested that SELENOF may be a potential therapeutic target for diseases caused by glucose metabolism disorder.



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Abstract Number: 387

Inorganic Arsenic-based Nanomedicine for Enhanced Cancer Therapy

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Considering that arsenic trioxide (As_2O_3) has now been approved by the U.S. Food and Drug Administration (FDA) as a frontline remedy for acute promyelocytic leukemia (APL), arsenic-based agents encouraged further exploitations in various solid tumor models. As a 2D Mono-elemental nanomaterials, arsenene has been subjected to extensive pharmacological and clinical analysis, and holds great promise for biomedical applications. Mechanism analysis in NB4 cells revealed that arsenene affected nuclear DNA replication, nucleotide excision repair, and pyrimidine metabolism pathways by downregulating the DNA polymerases POLE, POLD1, POLD2, and POLD3, holding great potential in leukemia treatment.[1] While in solid tumor treatment, arsenene was discovered to generate unexpected immune regulatory capability. Analysis of cell phenotypes in tumor microenvironment revealed that arsenene remodeled the tumor microenvironment by recruiting a high proportion of anticancer immune cells to eliminate the tumor. This unexpected discovery indicated for the first time that 2D inorganic nanomaterials could effectively activate direct anticancer immune responses, suggesting arsenene as a promising candidate nanomedicine for future cancer immunotherapy.[2]

In addition, arsenic(II) sulfide is also a stable inorganic arsenic compound with a different valence from arsenic trioxide, and has been widely applied to treat various diseases with low toxic side effects for a long time. In our work, PEGylated arsenic(II) sulfide nanocrystals displayed excellent anticancer and immune activation activity in breast cancer model, highlighting biocompatible arsenic(II) sulfide nanocrystals that induce ferroptotic cell death and activate antitumor immune responses, providing insights into the path towards the immunotherapy assisted chemotherapy for breast cancer.[3]

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Abstract Number: 388

Manipulation & Structural Characterisation of Coordination Driven SelfAssembled Systems Using Electrospray Ionization Ion Mobility Mass Spectrometry

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Coordination driven self-assembly is a neat method to generate a large variety of structures in a one-pot manner and low energic cost. Using bis-β-diketonates and cationic metal linkers, a satisfying array of structural diversity is accessible in resultant assemblies, networks and polymeric coordination structures. In this presentation, I will discuss our findings toward understanding solution phase structures analytically inaccessible by other methods using advanced electrospray ionisation ion – mobility mass spectrometry.1 This technique allows for analysis of structure, conformation and stability, along with dynamics of structural changes on a millisecond timescale. Such analysis is highly complementary with popular techniques such as NMR and X-ray crystallography In particular, I will highlight our research directed at understanding inducing changes to the structures of assemblies, in our efforts to understand mechanism and tune reactivity. We have been successfully able to change structural outcomes using: (i) timescales of mixing using specially designed ion sources, (ii) chemical templating, and collisional cross sections of resultant assemblies, and (iii) gas phase manipulation using traveling wave ion mobility and collisional activation. Along with an introduction to the technique, these examples will be discussed in context of what is already known and not known from other analytical techniques.

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Abstract Number: 389

Fully automated radiosynthesis of [^{89}Zr]ZrCl4 & [^{89}Zr]Zr-DFOSq PET tracers for centralized manufacturing of radiopharmaceuticals

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Fully-automated ^{89}Zr-radiolabelling processes have streamlined the production of ^{89}Zr-labelled PET agents, but these processes typically rely on the use of [^{89}Zr][Zr(ox)4]$^{4-}$ as starting material.[1,2] [^{89}Zr][Zr(ox)4]$^{4-}$ is commonly available in oxalic acid solution which is potentially harmful to human kidneys so [^{89}Zr][ZrCl4] has been proposed as an alternative precursor to [^{89}Zr][Zr(ox)4]$^{4-}$ for radiolabeling of mAbs.[3] This work present a fully-automated process for [^{89}Zr]ZrCl4 recovery from [^{89}Zr][Zr(ox)4]$^{4-}$ followed by radiolabeling of three clinically relevant agents containing the squaramide ester derivative of deferoxamine (DFOSq):[4] [^{89}Zr]Zr-DFOSq-bisPSMA (a bivalent inhibitor of prostate specific membrane antigen)[5], [^{89}Zr]Zr-DFOSq-octreotate (a somatostatin subtype-2 receptor-targeting peptide)[6] and [^{89}Zr]Zr-DFOSq-girentuximab (a CA-IX targeting mAb)

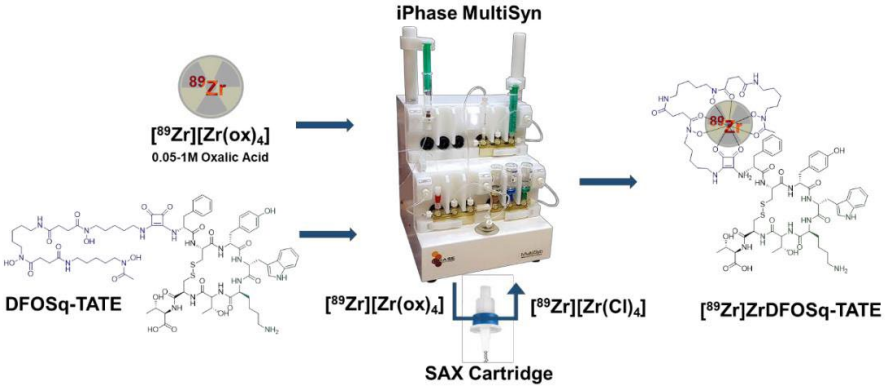

Figure 1 Schematic diagram of the automated ^{89}Zr-chloride production & radiolabeling of DFOSq Agents

An automated process for the ^{89}Zr-radiolabelling of DFOSq agents from [^{89}Zr][ZrCl4] was optimized on an iPhase MultiSyn synthesis module. The automated recovery of [^{89}Zr][ZrCl4] involved trapping of [^{89}Zr][Zr(ox)4]$^{4-}$ on a strong anion exchange cartridge then elution as [^{89}Zr]ZrCl4 (>95% recovery) with 0.1 N HCl in 1 N NaCl which is then reacted with DFOSq agents followed by sterile reformulation of resultant ^{89}Zr-labelled products and quality control via iTLC and radio-SEC/HPLC. The RCY of automated processes were 80-90% in greater than 97% RCP without the need of C18 (SPE) or PD-10 (SEC) purification. These automated processes are amenable to scale-up for centralized multiple-dose preparation and validation to current good manufacturing practice (cGMP) standards.

We acknowledge The Innovative Manufacturing CRC (IMCRC) for funding this research; PSD and AN from UoM are listed as an inventor and has licensed IP in this to Telix Pharmaceuticals; Part of this research was funded by a research Agreement between the UoM, Peter MacCallum Cancer Center, Cyclotek Pty Ltd, iPhase Technologies & Telix Pharmaceuticals.

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Abstract Number: 390

XANES spectroscopic mapping of metal speciation in brain tissue – does metal ion deficiency contribute to dementia?

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Memory loss occurs during natural ageing, neurodegenerative disease, or following brain injury, and has limited treatment options. The lack of effective therapies can be attributed in part to an incomplete understanding of how ageing, disease, or injury perturbs brain chemistry. Metal ions are known to be essential for healthy brain function, and at the bulk tissue level, altered levels of metal ions are associated with disease pathology. Specifically, elevated levels of ions of Fe, Cu, and Zn are frequently associated with brain pathology.[1,2]

Characterizing different chemical forms of metal ions that are altered in brain tissue during natural ageing and brain disease has long been an analytical challenge. X-ray absorption near edge structure (XANES) spectroscopy has well recognized capability to visualize metal ion speciation *in situ*, within cells and tissues. To this extent, our research team have been developing analytical protocols to visualize Fe, Cu, and Zn speciation within brain tissue sections (Figure 1).[3-6]

Through application of a multi-modal approach, incorporating X- ray fluorescence microscopy (XFM), XANES spectroscopy, and immuno-fluorescence, we have been able to associate metal ion accumulation with increased markers of brain inflammation in non- neuronal cells (glial cells in brain white matter).[7-9] Unexpectedly, we did not observe increased metal ion content within neurons, specifically the pyramidal neurons of the hippocampus, which is the brain structure responsible for learning and memory. In some animal models we have in fact observed metal ion deficiency within specific hippocampal cells, leading to a new line of research enquiry: does inflammation-mediated metal ion accumulation in glial cells result in downstream neuronal metal ion deficiency, and if so, what is its effect on brain function?

This presentation will discuss the specific brain regions and cells in which we have observed metal ions accumulation or deficiency in animal models of ageing and disease. Further, through development and subsequent application of XANES spectroscopic imaging protocols we have now begun characterization of specific chemical forms of Fe, Cu, and Zn that are increasing or decreasing during ageing and disease.

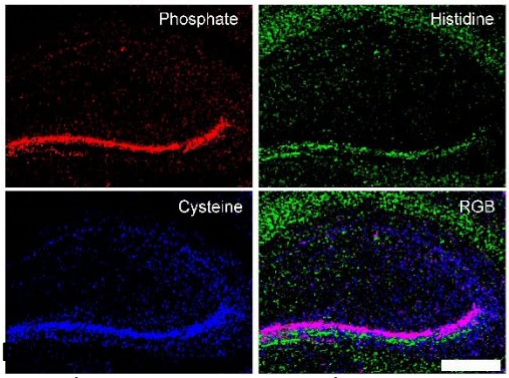

Figure 1. Zn K-edge XANES spectroscopic mapping of Zn speciation in murine brain tissue (hippocampus), revealing differences in distribution of Zn2+ coordinated to different biological ligands. Scale = 500 µm.

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i Hackett MJ, et. al. *ACS Chem. Neurosci.* **2019**, *10*, 2533-40.

Abstract Number: 391

Engineering C-C Bond Cleavage into a P450 monooxygenase Enzyme

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CYP17A1 is a heme-containing P450 metalloenzyme that catalyses an unusual C-C bond cleavage reaction involving α-hydroxy ketones that is essential for human steroid metabolism (Figure 1a). A series of experiments narrowed the key reactive intermediate of the C-C bond breaking step to either the nucleophilic ferric-peroxoanion intermediate or proton abstracting Compound I.[1, 2]

Seeking to study C-C bond cleavage reactions in mechanistic detail using a microbial P450, an α-hydroxy ketone probe (JCM 1, Figure 1b) was synthesised for a well-characterised benzoic acid metabolising P450, CYP199A4.[3] After observing low activity with WT CYP199A4, mutagenesis was carried out to generate mutant F182L with the aim to improve the activity of the desired reaction with this enzyme. Subsequent assays with the F182L mutant demonstrated enzyme-dependent C-C bond cleavage towards JCM 1 (Figure 1b).

Further experiments showed this C-C cleavage reaction was subject to an inverse kinetic solvent isotope effect in D2O solvent analogous to that observed in the lyase activity of the human P450 CYP17A1.[3] The D2O solvent hinders protonation that will inhibit Compound I formation (Figure 1a). This is suggestive that the C-C bond breaking step involves a reactive intermediate earlier than Compound I in the catalytic cycle. Co-crystallization of F182L-CYP199A4 with this α-hydroxy ketone showed that the substrate is bound in the active site with a preference for the (S)-enantiomer (Figure 1b) in a position which could mimic the topology of the lyase reaction in CYP17A1. This work demonstrates that rational mutagenesis was able to position the requisite substrate for C-C bond cleavage activity and provides a foundation for further biophysical and structural characterisation of the mechanism of this unique bioinorganic reaction.

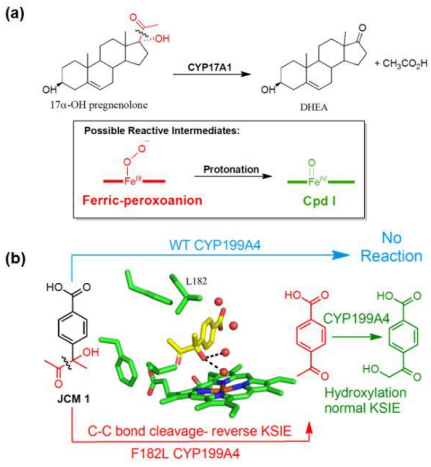

Figure 1: (a) C-C bond cleavage reaction of CYP17A1 with its physiological substrate. Possible reaction intermediates depicted inset. (b) Reaction of CYP199A4 mutants with JCM 1. Crystal structure of F182L-CYP199A4 in complex with JCM 1 is shown also.

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Abstract Number: 392

Revealing iron-induced alterations to lipids in live AML12 cells with Synchrotron time-lapse infrared microscopy

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Hepatocytes are essential for maintaining homeostasis of iron and lipid metabolism in mammals. Dysregulation of either iron or lipids has been linked with serious health consequences, including non-alcoholic fatty liver disease (NAFLD)(1) . Described as the hepatic manifestation of metabolic syndrome, NAFLD is characterised by dysregulated lipid metabolism leading to a lipid storage phenotype. Mild to moderate increases in hepatic iron have been observed in approximately 30% of individuals with NAFLD; however, the mechanism for this increase remains the topic of discussion. We sought to determine the consequences of iron overload on cellular lipid metabolism using live cell, time-lapse Fourier Transform Infrared Microscopy (FTIR) utilising a synchrotron radiation source to track biochemical changes for 8 hours following 16 h of iron loading. Iron loaded AML12 cells were observed to have perturbed lipid metabolism congruent with steatosis development (2). Iron loaded cells had approximately three times higher relative ester concentration compared to controls, indicating accumulation of triglycerides. The methylene/methyl ratio qualitatively suggested the acyl chain length of fatty acids in iron loaded cells increased over the 8-hour period of tracking compared to a reduction observed in the control cells. Furthermore, the olefinic band (cis C=CH-) shifted towards a higher wavenumber in iron loaded cells, indicative of increased lipid unsaturation per molecule. Follow up investigations utilising high spatial resolution Attenuated Total Reflection Infrared Microscopy (ATR-IRM) to map liver tissue confirmed that lipid poly-unsaturation increased in ironloaded steatotic liver sections. These findings provide direct evidence of a role for iron in stimulating hepatic lipid accumulation and remodelling existing lipids in NAFLD.

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Abstract Number: 393

Lighting up sugars: O-BODIPY sugar conjugates

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F-BODIPY dyes (4,4- difluoro- 4-bora-3a,4a-diaza-s-indacene) are well- known fluorescent molecules comprising a dipyrrin framework with a BF2 core and exhibiting sharp fluorescence emissions with high quantum yields. *F*- BODIPYs are used as probes for a wide variety of biomolecules, typically linked to the target analyte via a tether appended to the dipyrrin backbone. Although BODIPYs are widely used as fluorescent labels and chemosensors, chemical modifications, including the link to the tether, have been almost exclusively confined to the dipyrrin carbon framework, leaving the BF2 core intact. Various reports in the literature have described strategies for the synthesis of boron- functionalised BODIPYs by substitution of the *F*-BODIPY fluoride atoms, including methods for producing BODIPYs bearing 4,4-alkoxide or 4,4-aryloxide substituents (*O*-BODIPY). Many important biomolecules bear oxygen-containing functional groups, which suggested to us the possibility of directly linking an *O*-BODIPY fluorophore to a target biomolecule through the *O*-BODIPY oxygen atoms (Figure 1). We have explored the direct connection of *O*-BODIPY to carbohydrates through B-O-C links and have produced examples of 1:1 and 2:1 BODIPY mono- and di-saccharide complexes including glucose, fructose, xylose, ribose, maltose and sucrose. [1,2] The conjugates are characterised through a range of spectroscopic techniques, X-ray crystallography and absorption and emission spectroscopy and potential applications explored.

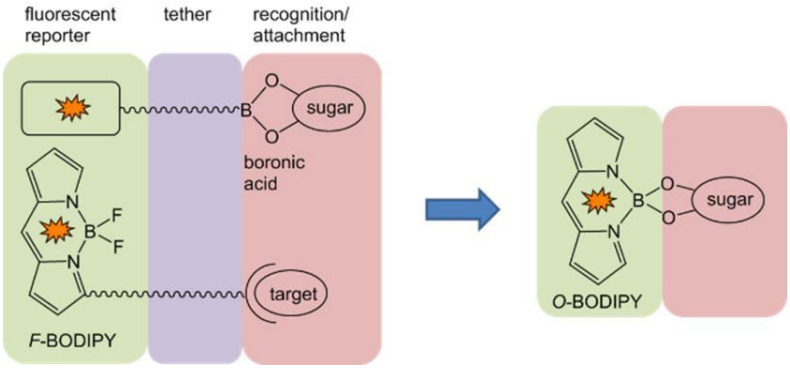

Figure 1. Conceptual design for direct attachment of O-BODIPY to sugars, realised in this work.

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Abstract Number: 394

Multicopper oxidase catalyzed abiological oxidative cross-coupling reactions

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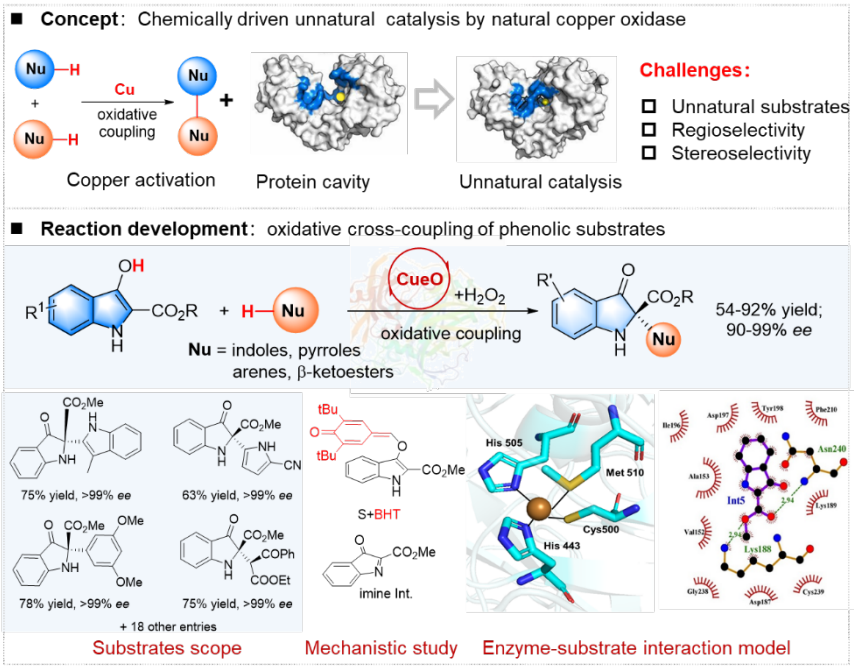
Owning to natural evolution, enzymes are generally applicable only for natural substrates and biological reactions. Merging the chemical activation of inorganic metal ion with the protein cavity renders provides a strategy to access unnatural selective catalysis, which can expand promiscuity of natural metalloenzyme to accommodate unnatural substrates toward value-added synthetic molecules. In this talk, we present our discovery of multicopper oxidase-catalyzed unnatural oxidative cross-coupling reactions of phenolic substrates with remarkable regioselectivities and stereoselectivities.[1,2] In particular, the biocatalytic coupling of 3-hydroxyindole esters with various nucleophilic partners delivers functionalized 2,2-disubstituted indolin-3-ones with excellent optical purity (90–99% ee), which exhibited anticancer activity against MCF-7 cell lines, as shown by preliminary biological evaluation. Mechanistic studies and molecular docking results suggest the formation of a phenoxyl radical and enantiocontrol facilitated by a suited enzyme chiral pocket. Our studies expand the catalytic repertoire of natural multicopper oxidases and also enlarge the synthetic toolbox for sustainable asymmetric oxidative coupling.

Unnatural oxidative cross-coupling catalyzed by multicopper oxidase



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Abstract Number: 396

Immune checkpoint imaging using desferrioxamine squaramide durvalumab

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The Nobel-prize winning discovery that we can 'release the brakes' of our own immune system and use it to fight tumour cells has heralded a breakthrough in cancer treatment. In a fully functioning immune system, the body's own healthy cells are discerned from those that have become cancerous by a mechanism known as immune checkpoint. The presence of specific cell surface proteins, such as PDL1, on healthy cells act as an 'off switch' for the body's immune system. Some cancer cells are able to hijack this system and overexpress PD-L1 in order to evade the body's own cancer defence systems.

Durvalumab, a therapeutic antibody that blocks the PD-L1 immune checkpoint signaling pathway, has been revolutionary in treating cancer. Patients are currently selected for this therapy by assessing PD-L1 status through a single, potentially non-representative tumour biopsy. To address this shortcoming we have developed a Positron Emission Tomography imaging agent, using our previously reported desferrioxamine squaramide (DFOSq) chelator.[1,2] We have prepared a conjugate of DFOSq with durvalumab (Figure 1) radiolabeled with zirconium-89, and will present the development and progression of this agent though preclinical studies as well as initial results from the IMMUNOPET[3] clinical trial.

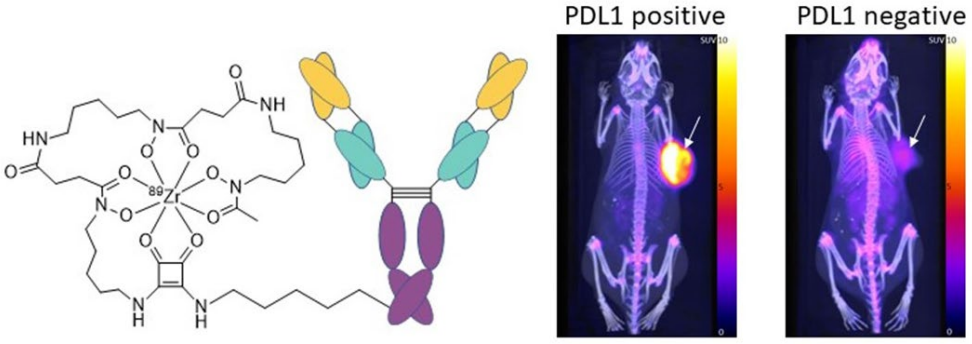

Figure 1. (Left) Proposed structure of [^{89}Zr]ZrDFOSq-Durvalumab and (right) PET/CT image of an NSG mouse with either PD-L1 positive HCC-827 or PD-L1 negative A549 xenograft.

We acknowledge the Australian Research Council, Australian Cancer Research Foundation, National Health and Medical Research Council, and the Victorian Cancer Council for supporting this research.

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Abstract Number: 397

Elucidating Structure-Activity Relationships in TTF-based MOFs

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Metal-Organic Frameworks (MOFs), with their highly crystalline repeating 3D structure, provide an ideal platform for the elucidation of structure-activity relationships (SAR) in the solid state. This work builds on the unique, multifunctional behaviour recently discovered in a TTF-based MOF that underwent a reversible single-crystal-to-single-crystal (SC-SC) double [2+2] photocyclisation (**Figure 1**).[1] Herein, a family of photoactive TTF-based MOFs, generated by the systematic variation of the framework constituents, are used to probe the effect of structure on the intervalence charge transfer (IVCT) and [2+2] photocyclisation inherent to these materials. This study, which takes a combined spectroscopic, electrochemical and crystallographic approach to elucidate structural perturbations,represents one of the first in-depth kinetic analyses in MOFs. Understanding the SAR associated with these processes is paramount if MOFs are to be developed into multi-stimuli responsive "smart" materials.

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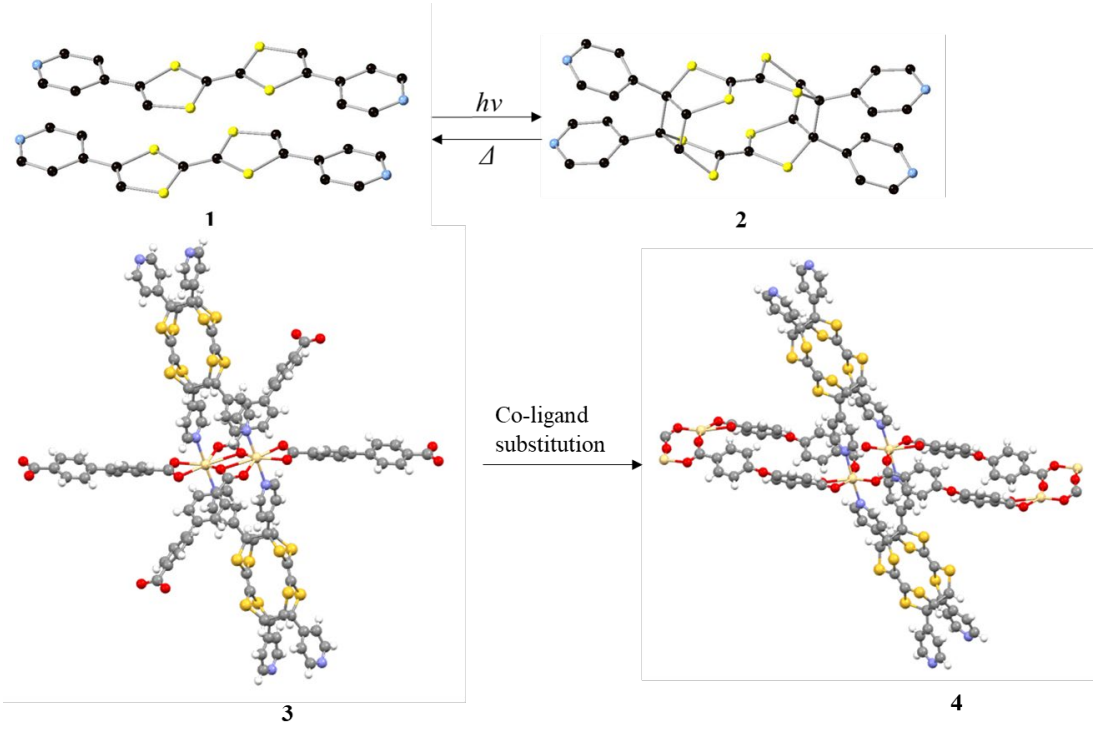

Figure 5: The double [2+2] photocyclisation observed in the parent framework (top) and the effect of ligand substitution on the framework topology (bottom)

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Abstract Number: 399

An Orthogonal Conductance Pathway in Spiropyrans for Well -Defined Electrosteric Switching in Single-Molecule Junctions

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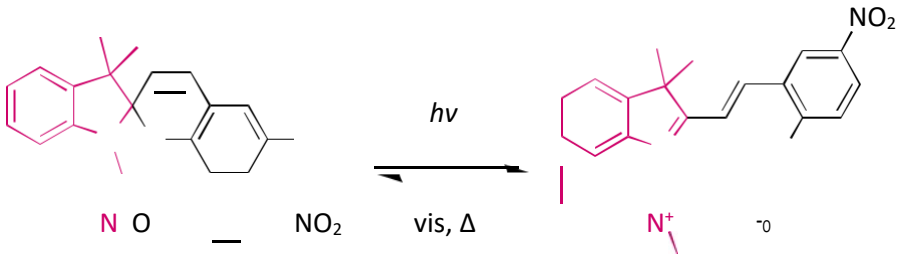
d Centre for Microscopy, Characterisation and Analysis, University of Western Australia, WA, Australia.

While a multitude of studies have appeared touting the use of molecules as electronic components, the design of a molecular switch is crucial for the next steps in molecular electronics. Some suitable candidates for single-molecule switches are currently being investigated. In this work, we describe single-molecule devices incorporating spiropyrans, made using break-junction techniques. Linear spiropyrans with alkynyl functional groups have showed multiple very low conductance peaks and removing the alkynyl spacer resulted in a loss of conductance. Herein, we have explored an orthogonal T-shaped approach to single-molecule junctions incorporating spiropyran moieties. This approach has provided single-molecule conductance features with good correlation to molecular length. Additional switching states were accessible using UV light and acid resulting in an increase in conductance. Theoretical data demonstrates that the isomerisation to the merocyanine acts as a photochemical and chemical gate by allowing the molecule to become more planar in the single-molecule junction and hence increase the conductance. This design step paves the way for future studies using spiropyrans in single-molecule devices.



SP **MC**

Scheme 1: Photochromic action of spiropyrans. Indoline moiety in pink, chromene in black.

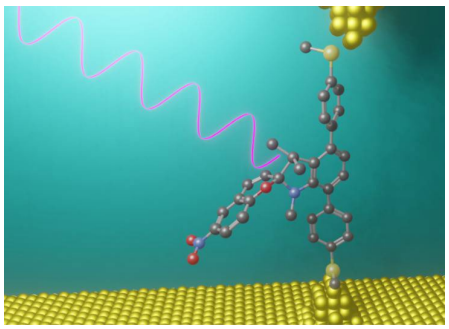


Figure 1: Graphical depiction of spiropyran in a single-molecule junction

Abstract Number: 401

The role of copper in the anticancer activity of the naphthoquionone plumbagin

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The phytochemical plumbagin (5-hydroxy-2-methyl-1,4-naphthoquinone) shows a broad spectrum of pharmacological activities ranging from antimicrobial, antifungal, and antiinflammatory activity to in vitro cytotoxicity against a plethora of anticancer cell lines. 1–4 The anticancer activity of plumbagin is linked to several molecular mechanisms related to apoptosis and autophagy.3,4 While the quinoidic structure enables redox cycling of plumbagin itself, the hydroxyl group in proximity to the quinone oxygen also offers a possibility to chelate metal ions. Thus, copper has been suggested to play a major role in the anticancer toxicity of Plumbagin. A bis-complex [CuL2] of Plumbagin, has been crystallized and showed superior activity as compared to the ligand in several cancer cell lines.5,6 Herein, we aim to investigate the role of copper in the anticancer toxicity of plumbagin. We find that the bis-complex suffers significant dissociation at physiological pH and that the mono complex turns out to be the predominant complex species even at higher ligand excess. Surprisingly, pre-mixed complexes with half- and equimolar metal-to-ligand ratios display reduced anticancer activity against the uterine sarcoma cell line MES-SA as compared to the free ligand. Applying complementary methods, we investigate the redox activity of the ligand and its copper complexes, as well as their reactivity towards GSH and H2O2 in the context of intracellular levels of reactive oxygen species (ROS) and anticancer toxicity. Our results show that upon reduction of the copper(II) complexes, plumbagin is released and undergoes reversible redox reactions.

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Abstract Number: 404

Chiral Coordination Cages From *C*4-Symmetric Cavitand Ligands

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Following Dalcanale's demonstration[1] of an early example of modern coordination cages, cavity-based metal assembly has become a focal point for inorganic and supramolecular chemists. Subsequently, cavity-based metal assembly split into two distinct categories: (i) cavity-based coordination cages and (ii) cavity-based metal complexes.[2] With the boom in host-guest chemistry, cavity-based coordination cages have transformed from co-facial cages into more complex multi-component assemblies. Meanwhile, cavity-based metal complexes have also become predominant as biomimetics.

In this work, we combined both aspects of cavity-based coordination cages and cavity-based metal complexes to synthesize a novel chiral mono-ligand cage architecture with just four coordination bonds (Figure). Tetradentate ligands based on an intrinsically-chiral resorcin[4]arene derivative[3] as a cavitand platform have been prepared with a range of linkers. Following introduction of a single metal, a coordination cage was formed by connecting the donor groups with a square-planer metal centre. The cages have been characterised and studied for guest binding using a range of analytical techniques.

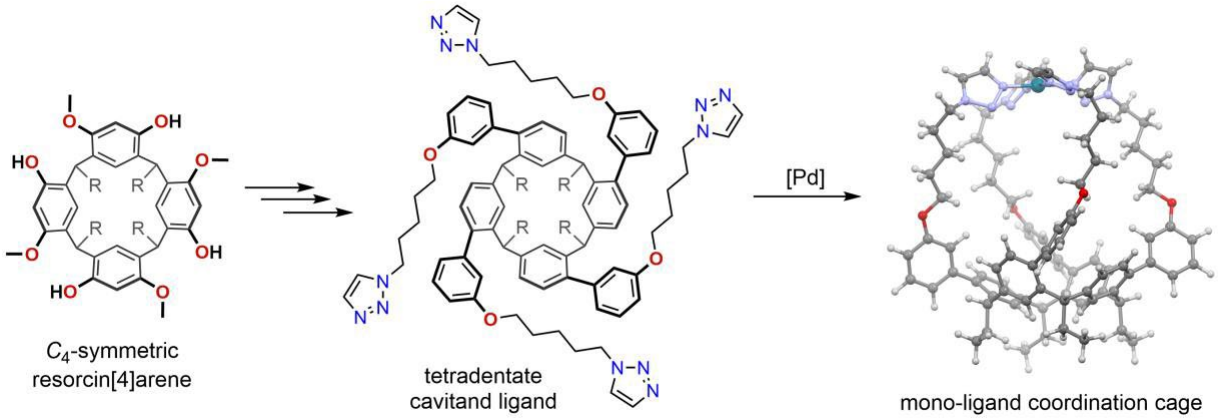

Figure. A *C*4-symmetric resorcin[4]arene is functionalised in a ten-step synthesis to a chiral tetra(triazole) ligand which assembles to a metallocage on addition of Pd(II).

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Abstract Number: 405

BRIGHT Beamlines: New Opportunities for Bioinorganic Chemistry at the Australian Synchrotron

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To date, the Australian Synchrotron has operated one X-ray fluorescence scanning microprobe (XFM) beamline and one X-ray absorption spectroscopy (XAS) beamline. While these instruments support a wide array of disciplines, both have and will continue to support investigations into bioinorganic chemistry, the latter with a focus on studying the local coordination environment of metal-bearing biomolecules or biomedically active compounds. At the same time, the former can reveal highly detailed information on local variations in speciation, composition and morphology. These instruments are now (or soon will be) augmented by a new suite of beamlines and science capabilities of interest to bioinorganic chemists.
We have built eight additional beamlines under the Australian Synchrotron's BRIGHT upgrade program, reflecting community demand. This activity has tripled the number of X-ray microscopy beamlines and doubled the number of X-ray spectroscopy endstations. These new beamlines include a dedicated hard X-ray scanning nanoprobe (NANO) and a pair of medium-energy X-ray absorption spectroscopy beamlines (MEX1 & 2), each with unique capabilities, including a medium-energy scanning microprobe (μMEX).
Traditionally, characterizing specific metal-ligand species requires isolation of the complex, necessitating disruption of biological systems, despite the loss of biochemical context and the attendant risk of mismetallation. Despite the confounding potential of typical preparation methodologies, the tools available to study biological coordination chemistry *in situ* remain limited. The recent explosion of high-energy-resolution fluorescence detection techniques in XAS and the synergy between synchrotron-based XFM and XAS represents powerful, evolving analytical approaches for studying bioinorganic chemistry *in situ* at the micro and nanoscale.

The NANO beamline will access *d*-block elements at sub-100 nm length scales and will be well-suited to generate high-detail maps of elemental content from its first day of operations: capabilities for performing nanoscale XAS will follow within five years. The instrument's field of view will be 3 × 3 mm^2, generating elements with over 1 billion pixels. The beamline targets some demanding challenges, including elemental tomography of an entire cell with ~8 hours of measurement time. Additional complementary imaging modalities will include ptychography for super-resolution-like imaging of specimen ultrastructure, differential phase contrast, and diffraction and small-angle X-ray scattering mapping.
Spanning 1.7 to 13.6 keV, the two MEX beamlines cover a capability gap between existing beamlines and offer unique capabilities for XAS in the life sciences. Access to the K-edges of the elements from silicon through selenium provides opportunities to study the local structure, speciation, and chemistry of many biological compounds, structures, and processes. Over the coming year, additional capabilities, including high energy resolution fluorescence detection (HERFD) and μMEX, will come online for User operations. Specifically, the μMEX endstation will harness X-rays between 2.1 to 13.6 keV allowing micro XAS-based chemical speciation studies and elemental mapping.

These new tools provide great depth to the facility and represent a substantial new resource for our community of bioinorganic chemistry researchers. Using illustrative examples and highlighting the

application of relevant techniques, this presentation will introduce two of Australian Synchrotron's new instruments, their capabilities, status, and future capability rollout.

Abstract Number: 408

Structural characterization of proteins using a non-natural amino acid, a new Gd^{3+} label, and Double Electron-Electron Resonance (DEER) Spectroscopy

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One way of obtaining structural information on biomolecules in near physiological conditions is to attach a pair of paramagnetic spin labels and then measure the magnetic dipolar coupling and thus distance between the two paramagnetic centres. This electron paramagnetic resonance (EPR) technique, referred to generally as dipolar EPR, has grown significantly over the last 20 years due to the development of suitable spin labels, and the development of suitable pulse EPR spectrometers and experiments (pulse sequences). The most common sequence to measure the distance between the spin labels is double electron electron resonance (DEER). For proteins, the only labelling scheme that is generally applicable relies on attachment of MTSSL (nitroxide radical) to a cysteine residue. The following steps are required to study protein structure by dipolar EPR: surface exposed wild type cysteines are replaced and two cysteines are introduced at chosen positions via mutagenesis, the pair of MTSSL molecules are attached, the sample is frozen to ca. 50K, the distance distribution between the labels is measured, and these sparse constraints are used to model structure and function.

In this presentation, I will give an overview of dipolar EPR for protein structure using selected examples[1-2] to highlight the success and limitations of the current methodology. The critical limitation is the reliance of the spin labelling chemistry on cysteine residues. I will discuss our recent progress on the development of a labelling scheme based on incorporation of a non-canonical amino acid (ncAA)[3] and its labelling with a new Gd^{3+} spin label that we are synthesising and attaching to the ncAA via a nitrile-aminothiol click reaction.

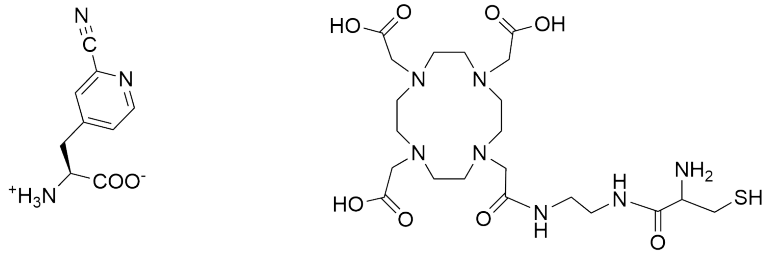

Figure The ncAA and the spin probe showing the ligand for Gd^{3+} (*S* = 7/2 electron spin)

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Abstract Number: 409

Examination of MIL-53 structures with PD and Isotherms to understand their flexibility with temperature and pressure

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Metal-Organic Frameworks (MOFs) have gained increased attention as leading porous materials for target applications, due to their synthetically manipulatable pore environment.[1] The ability to control pore environments through use of metal and ligand type has led to increased specificity for applications, such as separation of chemical mixtures.[2] Understanding the behavior of a material with temperature, pressure or the addition of guests is key for their function in an industry setting. MIL-53 [M(OH)(bdc)], a MOF constructed from metal hydroxide chains and benzene-1,4-dicarboxylate (bdc), is renowned for its 'breathing behavior' in response to temperature change. While this material has excellent separation capabilities, the uncontrolled flexible nature of this MOF can diminish its industrial adoption.

Our work has focused on the synthesis of a series of MIL-53 analogues to understand how flexibility varies with metal and ligand type. Using aluminium(III), gallium(III) and vanadium(III) MIL-53 MOFs were formed with either bdc or cubane-1,4-dicarboxylate (cdc) linkers. The flexibility of the MOFs in response to variable temperatures and CO2 guest environments was investigated using powder diffraction (PD) at the Australian Synchrotron Powder Diffraction Beamline. The use of variable temperature and pressure measurements has helped to elucidate the elastic properties of the different MIL-53 structures. For example, [V(OH)(bdc)] exhibits flexibility during both variable temperature PD (Figure 1) and variable CO2 pressure PD. This flexibility can be mapped during experiments, showing changes in the cell size indicating pore size changes. Interestingly, this is drastically reduced in [V(OH)(cdc)] due to the bulkiness of the linker.

This data has led to an understanding of how metal type and not just geometry impacts a materials flexibility. Additionally, it has provided further insight into the importance of considering use of aromatic or aliphatic ligands when designing MOFs for a particular application.

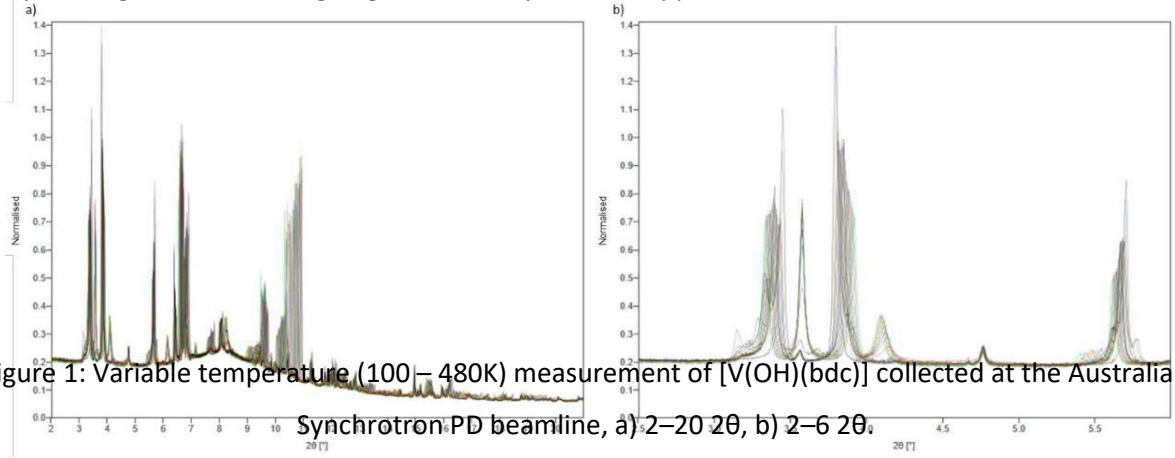

Figure 1: Variable temperature (100 – 480K) measurement of [V(OH)(bdc)] collected at the Australian Synchrotron PD beamline, a) 2–20 2θ, b) 2–6 2θ.

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Abstract Number: 413

Resisting zinc starvation: A QueD2 "low-zinc" enzyme paralog in *Acinetobacter baumannii* queuosine-tRNA biosynthesis

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In response to bacterial infection, the vertebrate host employs the metal sequestering protein calprotectin (CP) to withhold essential transition metals, notably Zn(II) to inhibit bacterial growth[1]. Previous studies of the impact of CP-imposed transition metal starvation in *A. baumannii* identified two enzymes in the *de novo* biosynthesis pathway of the tRNA modification queuosine (Q-tRNA) that become cellularly abundant, one of which is QueD2, a 6-carboxy-5,6,7,8-tetrahydropterin (CPH4) synthase that catalyzes the initial, committed step of the pathway[2]. Here, we show that CP strongly disrupts Q incorporation into tRNA[3]. As such, we compare the *Ab*QueD2 "low-zinc" paralog with a housekeeping, obligatory Zn(II)-dependent enzyme QueD. Although QueD2 possesses QueD-like 6-CPH4 synthase activity as expected, our structure of Zn(II)-bound *Ab*QueD2 reveals a distinct catalytic site structure, a distinct assembly state and a second nearby Zn(II) site 2 relative to QueD. An invariant Cys18 in a highly dynamic metal site 2 protects QueD2 from dissociation of the catalytic Zn(II) while maintaining flux through the Q-tRNA biosynthesis pathway in cells. We propose a "metal retention" model in which metal site 2 introduces coordinative plasticity into the catalytic site, significantly expanding the metal selectivity while slowing metal release. These studies reveal a complex, multi-pronged evolutionary adaptation to cellular Zn(II) restriction in a key zinc metalloenzyme in an important human pathogen, and has implications for our understanding of other "low-zinc" paralogs that have arisen during the course of evolution. Supported by grants from the US National Institutes of Health (R35 GM118157; R01 AI101171).

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Abstract Number: 415

The catalytic activity and structure of the lipid metabolising CYP124 cytochrome P450 enzyme from Mycobacterium marinum

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The CYP124 family of cytochrome P450 enzymes, as exemplified by CYP124A1 from Mycobacterium tuberculosis, is involved in the metabolism of methyl branched lipids and cholesterol derivatives1 . The equivalent enzyme from Mycobacterium marinum was investigated to compare the degree of functional conservation between members of this CYP family from closely related bacteria. We compared substrate binding of each CYP124 enzyme from using UV-vis spectroscopy. The catalytic oxidation of methyl branched lipids, terpenes and cholesterol derivatives by both enzymes was also investigated2 . The CYP124 enzyme from M. tuberculosis had a marked preference for cholesterol derivatives compared to the equivalent enzyme from M. marinum. The selectivity for oxidation at the ω-carbon of a branched chain was observed for both enzymes. The biggest difference was observed with cholesteryl sulfate which had induced distinct UV-vis spectra in each CYP124 enzyme. The CYP124A1 enzyme from M. marinum, in combination with several ligands, was structurally characterised by X-ray crystallography to 1.42 to 1.81 Å resolution. The 7-ketocholesterol-bound X-ray crystal structure of the CYP124 enzyme revealed that the substrate binding mode of this cholesterol derivative was different to those observed in the structure with farnesol and farnesyl acetate. The structures provide an explanation for the high selectivity of the enzyme for terminal methyl C-H bond oxidation. The work here demonstrates that, in contrast to other related enzymes, such as those of the CYP142 family, there were significant biochemical differences between the CYP124 enzymes from closely related bacteria.

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Abstract Number: 420

Visualization of Trace Elements

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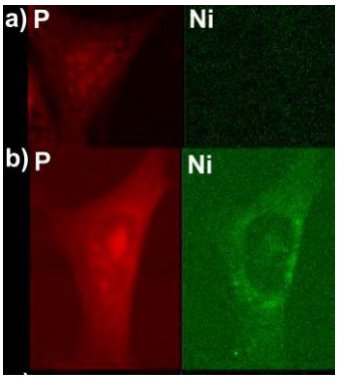
Our current understanding of disease pathogenesis for disorders that are associated with changes in trace elemental content, distribution, or chemical state is limited by the availability of tools to analyze their distributions. For inborn errors of copper homeostasis such as Wilson and Menkes disease questions of how the subcellular copper distribution might contribute to disease progression is still unclear although the underlying genetic alterations in copper transport have been identified almost 30 years ago.

A diverse array of methods to visualize and analyze trace elemental distributions in cells and tissues exist. One such method, X-ray fluorescence microscopy (XFM), has emerged as a powerful tool to quantitatively image total metal distributions in biological specimen and our lab has played an integral role in developing methods and protocols to apply XFM to biological questions. Current resolution for XFM approaches that of electron microscopy and the sensitivity is in the attomolar range. One of the major drawbacks of XFM is its inability of distinguishing cellular or subcellular structures unless they differ in elemental content. We are developing probes that will allow users to identify proteins or subcellular organelles associated with trace metal distributions in one XFM scan.



XFM P and Ni maps for MEFs. a) control, b) MEFs + Ni-SOA-PC-DT.

Together with our collaborators we have designed functionalized nanoparticles containing a nickel or a cobalt core for *in cellulo* and *in vitro* labeling of organelles and proteins. Our initial nickel prototypes to label mitochondria in mouse embryonic fibroblasts demonstrate good cellular uptake with minimal cellular toxicity. CoO nanoparticles clicked to a strained bicyclononane-PEG-maleimide which is bound to a COX2 antibody was synthesized and tested for its labeling properties in MEFs in vitro.

Abstract Number: 421

Fluorescent tools for imaging amyloids at the nanoscale

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Amyloids are self-assembled proteins with organized β-sheet macromolecular architecture. The misfolding of proteins into amyloid structures is characteristic of different neurodegenerative diseases such as Alzheimer's disease (AD). Different strains of disease-causing proteins lead to different pathologies, critically depending on their conformations and microenvironments.[1] Despite pathological and functional amyloids sharing the hallmark β-sheet structure, the mechanisms and interactions that result in these contrasting physiological behavior remains unclear.[2] This can be achieved using imaging tools that allow for the visualization of the structures and conformations of amyloids at nanoscale.
Biophysical methods such as solid state NMR and cryo-electron microscopy, allow us to study the amyloids with molecular-level detail, but are labor-intensive and involve stringent sample preparation with the sacrifice of spatial biological information.[2] In contrast, fluorophores have been successfully used as fingerprints to differentiate distinct microenvironments with spatiotemporal properties. Among various fluorophores, excited-stated intramolecular proton transfer (ESIPT)-based fluorophores with large Stokes shift (~200 nm), environmental sensitivity to local surroundings is particularly attractive for amyloid microenvironments sensing. In addition, the ESIPT-based fluorophores allow for ratiometric sensing, providing direct information about the concentration of analytes with internal calibration.[3]
Here, I will discuss the design and testing of a series of chalcone- and flavone-based fluorescent sensors that operate *via* ESIPT mechanism for the detection of amyloid fibrils. The synthesized fluorescent probes demonstrate turn-on or ratiometric fluorescent response towards amyloids fibrils. By modulating the electron-donating groups on the sensor scaffold and ESIPT properties we investigated the structure-activity relationships (photophysical and sensing properties) of the amyloid probes. We employed the developed probes in confocal and dSTORM, a super-resolution imaging technique, which allows us to examine the morphology of amyloid assemblies in greater detail. By shedding more light on the structural characteristics of these assemblies, we hope to advance our understanding of AD and its underlying mechanisms.

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Abstract Number: 422

Coordination of Ru(II)-arene fragments to dipyridophenazine ligands leads to the modulation of their in vitro and in vivo anticancer activity

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Despite extensive research on the anticancer properties of Ru complexes with dipyridophenazine (dppz) ligands, their in vivo efficacy is rarely investigated. Aiming to understand whether the coordination of certain half-sandwich Ru(II)-arene fragments might improve the therapeutic potential of dppz ligands, we prepared a series of Ru(II)-arene complexes with the general formula [(η6-arene)Ru(dppz-R)Cl]PF6, where arene fragment was benzene, toluene or p-cymene and R was -NO2, -Me or -COOMe. All compounds were fully characterized by 1H and 13C NMR spectroscopy and high-resolution ESI mass-spectrometry and their purity was verified by elemental analysis. The electrochemical activity was investigated using cyclic voltammetry. The anticancer activity of dppz ligands and respective Ru complexes was assessed against several cancer cell lines and their selectivity towards cancer cells was assessed using healthy MRC5 lung fibroblasts. The substitution of benzene with p-cymene fragment resulted in more than 17- fold increase of anticancer activity and selectivity of Ru complexes and significantly enhanced the DNA degradation in HCT116 cells. All Ru complexes were electrochemically active in the biologically accessible redox window and were shown to markedly induce production of ROS in mitochondria. The lead Ru-dppz complex significantly reduced tumor burden in mice with colorectal cancers without inducing liver and kidney toxicity.

Abstract Number: 423

A Frustrated Lewis Pair Solution to a Frustrating Problem: Mono-Selective Functionalization of C–F Bonds in Di- and Trifluoromethyl Groups

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Polyfluoromethyl groups generally suffer from 'over-reaction', where multiple C-F bonds are uncontrollably functionalized.[1] To solve this problem, we have developed Frustrated Lewis Pair (FLP) mediated C-F bond activation that allows selective monodefluorination via base capture of intermediate fluorocarbocations.[2] FLP mediated C-F bond activation can be applied to aromatic, heteroaromatic and non-aromatic difluoro and trifluoromethyl groups to generate selectively fluoride substituted phosphonium and pyridinium salts. These salts can be further functionalized via Wittig coupling, nucleophilic substitution, photoredox alkylation, nucleophilic transfer and hydrogenation reactions (*inter alia*) to install a range of functional groups into the activated C-F position.

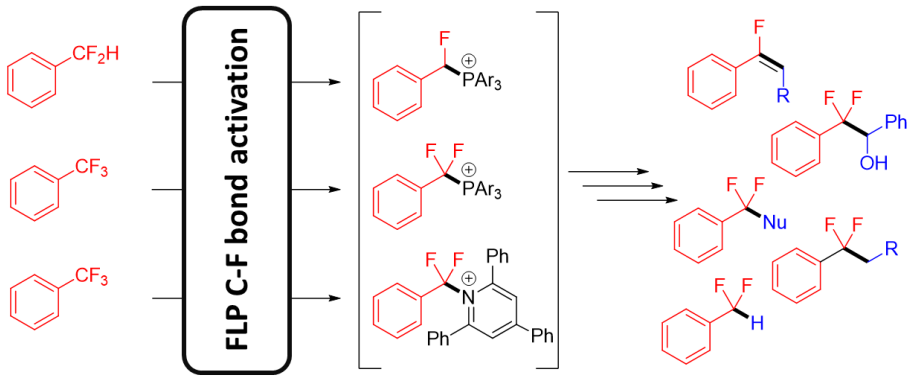

Figure 1. Selective activation and functionalization of difluoromethyl and trifluoromethyl groups mediated by frustrated Lewis pairs (FLPs).

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Abstract Number: 425

Cytotoxic Gold(III) Compounds Containing Cyclometalated Phosphine Sulfide Ligands

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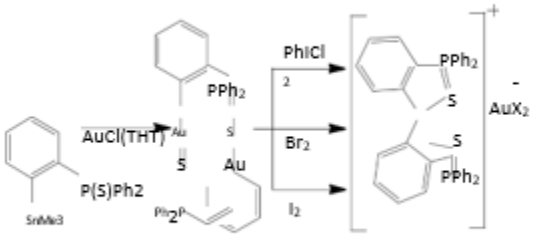
Despite the success of cisplatin as an anticancer agent, its severe side effects and natural or acquired resistance of tumours towards Pt limit its application.[1] The need to overcome these limitations promoted the research for new anticancer agents with other metals such as gold. Gold(III), being isoelectronic with and able to form isostructural complexes to platinum(II), soon attracted interest.

Continuing our research into developing novel gold complexes[2] for cancer treatment,[3] we were interested in preparing cycloaurated compounds containing phosphine sulphide ligands. The monocyclic gold(III) compounds [AuCl2{k^2-2-C6H4P(S)R2}] (R = Ph, NEt2) have been reported from which the thiosalicylate derivative, [Au(1,2-SC6H4CO2){k^2-2-C6H4P(S)NEt2}], was synthesized.[4] Here, we report a range of complexes containing two cycloaurated triphenylphosphine sulphide ligands.

The reaction of 2-Me3SnC6H4P(S)Ph2 with [AuCl(tht)] in dichloromethane gave the dinuclear digold(I) complex [Au2{μ-2- C6H4P(S)Ph2}2] (**1**) (**Figure 1**). The oxidative addition of **1** with Cl2 (as PhICl2), Br2, or I 2 afforded the ionic gold(I)–gold(III) complexes [Au{k^2-2-C6H4P(S)Ph2} 2] [AuX2] [X=Cl (**2**), Br (**3**), I (**4**)] with 80–90% of yields. The anticancer properties and mechanism of action of these gold(III) complexes containing C-S cycloaurated ligands were investigated for a wide range of cancer cells, as shown in **Table 1**.



(Here, THT = tetrahydrothiophene)

1

Figure 1. Synthesis of digold(I) complex [Au2{μ-2-C6H4P(S)Ph2}2] (**1**) and its oxidative addition.

Table 1. In vitro cytotoxicity (IC50) of the gold complexes and cisplatin towards various cell lines.

Compound	MDAMB-231 (Breast)	HeLa (Cervical)	HT1080 (bone)	HCT-116 (colon)	D24 (melanoma)	PC-3 (prostate)	Hek-293 non-cancerous
2	2.64±0.15	2.71±0.32	1.36±0.09	3.38±0.89	2.48±0.46	1.56±0.68	3.23±0.25
3	1.24±0.07	2.31±0.13	0.93±0.05	3.19±0.18	2.44±0.26	0.59±0.12	3.55±0.16

4	1.08±0.13	0.44±0.07	0.79±0.23	1.27±0.23	0.97±0.08	0.54±0.19	2.87±0.87
Cisplatin	17.56±0.87	3.04±0.23	0.54±0.16	13.5±1.68	23.5±1.68	4.60±1.23	4.81±0.25

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Abstract Number: 426

Insights into the mechanism of action of anticancer gold complexes

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Microbiome is a key regulator of cancer development, progression and modulation of various cancer therapies and can be used as a therapeutic target to treat different cancers.[1] Classically used chemotherapeutic agents are primarily associated with the induction of intestinal dysbiosis, which can lead to cancer progression. However, recent studies have demonstrated that manipulation of microbial communities within cancer microenvironment can lead to desirable effects that increase the efficacy of different cancer therapies. This manipulation can be achieved either through activation of favourable microbiome or inhibition of the unfavourable microbiome.

Gold complexes stand as one of the most promising metal-based anticancer compounds with diverse mechanisms of action, involving direct mitochondrial damage, proteasome inhibition or modulation of specific kinases and interaction with the host's immune system.[2] In this lecture, we will talk about whether the interaction of gold complexes with the microbiome could lead to tumor regression and antimetastatic activity.

Figure 1. Faeces from drug-treated mice were collected for analysis of intestinal microbiota.

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Abstract Number: 427

Heterometallic low-symmetry metallosupramolecular cages: Self-assembly, switching and molecular recognition

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Self-assembled metallosupramolecular architectures (MSAs) or metal-organic cages (MOCs), depending on whom you ask, are the smaller, more soluble cousins of Metal Organic Frameworks (MOFs). Like their MOF cousins MSAs/MOCs can be exploited for the molecular recognition of a wide range of guests including reactive molecules, intermediates, pollutants and drugs.[1] For the most part MSAs/MOCs have tended to be high-symmetry and homometallic species. More recently there has been a drive to generate lower-symmetry and heterometallic MSAs/MOCs as part of efforts to further enhance the properties of these systems.[2] Herein, I will described some of the strategies we have developed for the synthesis of lower-symmetry heterometallic MSAs/MOCs featuring palladium(II) and platinum(II) ions (Figure 1).[3] Additionally, the molecular recognition and switching properties of the heterometallic Pd(II)/Pt(II) MSAs/MOCs will be discussed.

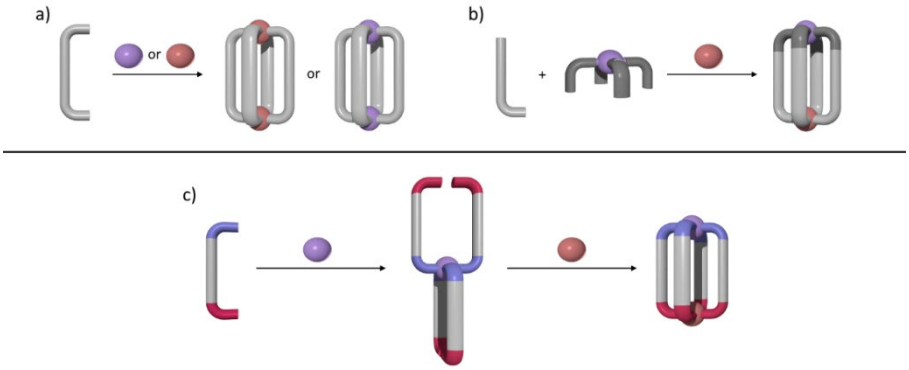

Figure 1: Cartoon representations of a) homometallic M_2L_4 cages systems (where M = Pd(II) or Pt(II)); b and c) related heterometallic $PdPtL_4$ systems.

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Abstract Number: 429

The Reduction Potentials of P450 Compounds I and II: Insight into the Thermodynamics of C-H Bond Activation

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We present a mixed experimental/theoretical determination of the bond strengths and redox potentials that define the ground state thermodynamics for C-H bond activation in cytochrome P450 catalysis. Using redox titrations with $[Ir(IV)Cl_6]^{2-}$ we have determined the compound II/ferric (or $Fe(IV)OH/Fe(III)OH_2$) couple and its associated $D(O-H)_{Ferric}$ bond strength in CYP158. Knowledge of this potential as well as the compound II/ferric (or Fe(IV)O/Fe(III)OH) reduction potential in horseradish peroxidase and the two-electron compound I/ferric (or $Fe(IV)O(Por^{\bullet})/Fe(III)OH_2(Por)$) reduction potential in aromatic peroxidase has allowed us to gauge the accuracy of theoretically determined bond strengths. Using the restricted open shell (ROS) method as proposed by Wright and coworkers, we have obtained O-H bond strengths and associated redox potentials for charge-neutral H-atom-reductions of these iron(IV)-hydroxo and -oxo porphyrin species that are within 1 kcal/mol of experimentally determined values, suggesting that the ROS method may provide accurate values for the P450-II O-H bond strength and P450-I reduction potential. The efforts detailed here indicate the ground state thermodynamics of C-H bond activation in P450 are best described as follows: $E^{0'}_{Comp\text{-}I} = 1.22$ V (at pH 7, vs. NHE) with $D(O-H)_{Comp\text{-}II} = 91$ kcal/mol, and $E^{0'}_{Comp\text{-}II} = 0.99$ V (at pH 7, vs. NHE) with $D(O-H)_{Ferric} = 85$ kcal/mol.

Abstract Number: 434

Biomimetic Metal-Oxygen Intermediates in Dioxygen Activation and Formation Chemistry

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Dioxygen is essential in life processes, and enzymes activate dioxygen to carry out a variety of biological reactions. One primary goal in biomimetic research is to elucidate structures of reactive intermediates and mechanistic details of dioxygen activation and oxygenation reactions occurring at the active sites of enzymes, by utilizing synthetic metal-oxygen complexes. A growing class of metal-oxygen complexes, such as metal–superoxo, –peroxo, –hydroperoxo, and –oxo species, have been isolated, characterized spectroscopically, and investigated in various oxygenation reactions. During the past decade, we have been studying the chemical and physical properties of various reactive intermediates in oxygenation reactions, such as high-valent iron(IV)- and manganes(V)-oxo complexes of heme and non-heme ligands in oxo-transfer and C-H activation reactions, non-heme metal-peroxo complexes in nucleophilic reactions, and non-heme metal-superoxo complexes in electrophilic reactions. The effects of supporting and axial ligands on structural and spectroscopic properties and reactivities of metal-oxygen adducts have been extensively investigated as well. In this presentation, I will present our recent results on the synthesis and structural and spectroscopic characterization of mononuclear nonheme metal-dioxygen intermediates as well as their reactivities in electrophilic and nucleophilic oxidation reactions.

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Abstract Number: 436

Activation of molecular dioxygen by copper-containing lytic polysaccharide monooxygenases

Flora Meilleur

Molecular and Structural Biochemistry, North Carolina State University
Neutron Scattering Division, Oak Ridge National Laboratory

Lytic polysaccharide monooxygenases (LPMOs) have been intensely studied since their first characterization in 2010 as a unique class of copper enzymes capable of oxidizing carbohydrates. LPMOs are mononuclear copper enzymes that require the input of electrons and of O_2 or H_2O_2 to achieve hydroxylation of one carbon in the glycosidic bond. Their enzymatic mechanism is still to be understood at the atomic level. We combine high resolution X-ray and neutron protein crystallography and computational simulations to address outstanding questions on the role of second shell residues in the activation of O_2 and to determine the chemical nature of the intermediates responsible for hydrogen atom abstraction from the substrate. The ability to pinpoint hydrogen atoms to determine protonation states at and around the active site through the catalytic pathway is key to deciphering the chemistry catalyzed by LPMOs. Our experimental approach deliver precise, all atom structures that reveal i) the positions and interactions of all hydrogen atoms in the enzyme, ii) atomistic details of the active site without perturbing the metal oxidation state, and iii) the chemical nature of the activated dioxygen species coordinated to the active site copper. We will present our recent X-ray and neutron crystallographic studies that provide insights into the LPMO mechanism.

Abstract Number: 442

Dissecting the role of antimicrobial copper at the host-pneumococcal interface

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Streptococcus pneumoniae (the pneumococcus) is a bacterial pathogen of global significance, exerting substantial disease burden through both healthcare costs and escalating morbidity and mortality. Treatment of S. pneumoniae requires antibiotic intervention to prevent systemic dissemination but this is complicated by increasing antibiotic resistance. As a possible avenue for new therapeutic development, previous studies have identified that high concentrations of copper are mobilised to sites of infection. However, the putative role of copper as an antimicrobial at the host-pathogen interface remained poorly understood. Here, we sought to investigate the changes in the chemical biology of the mammalian host in response to S. pneumoniae infection. Using a murine infection model, we induced invasive pneumococcal disease (pneumonia, bacteraemia and meningitis) and determined tissue copper abundance. Our data show that copper levels increase significantly in the blood and brain, with lung copper also moderately increasing. To interrogate how the spatial complexity of tissues impacted copper distribution, we conducted LA-ICP-MS on naïve and infected lungs. This analysis revealed accumulation of copper in highly spatially discrete ‘hot-spots’, containing copper concentrations ~100-fold higher than naïve levels. To investigate if this increased copper abundance could exert a direct antimicrobial effect on S. pneumoniae, mutant derivatives that lacked the primary copper resistance mechanisms were constructed (copper efflux; ΔcopA, copper buffering; ΔgshT, or both; ΔcopAΔgshT). A subsequent pneumonia infection model revealed that the ΔcopAΔgshT strain was significantly perturbed for in vivo virulence compared to wild-type. However, this perturbation was not observed when lung infection was bypassed in a bacteraemia infection model, illustrating the antimicrobial potential of the copper hot-spots in the lungs. Collectively, these data suggest that enhancing copper toxicity within the lung through subversion of resistance mechanisms may provide a novel therapeutic strategy to combat S. pneumoniae infection.

Abstract Number: 443

Inorganic click (iClick) reactions: A facile route to luminescent biomarkers and "light-up" probes

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In contrast to the copper-catalyzed azide-alkyne cycloaddition (CuAAC) and its strain-promoted variant (SPAAC), which was honored by the 2022 Nobel Prize in chemistry to Bertozzi, Meldal, and Sharpless, the reaction of metal-azido complexes with alkynes directly in the inner coordination sphere of a metal center without use of a catalyst and leading to stable triazolato products has received significantly less attention. However, since this *iClick (= inorganic click) reaction* was first popularized by Veige and coworkers about ten years ago,[1] we and others have systematically explored the scope and application of this approach to bioconjugation and functional molecules.[2-6] Steric and electronic factors which govern the kinetics of the iClick reaction have been identified and now allow for a systematic selection of the metal-azido and alkyne building blocks for different applications, from anticancer drug candidates to "smart" probes. An interesting aspect of the iClick reaction useful for biological labelling are the significant differences in luminescence of the azido complex precursor *vs*. triazolato "iClick" product.[7]

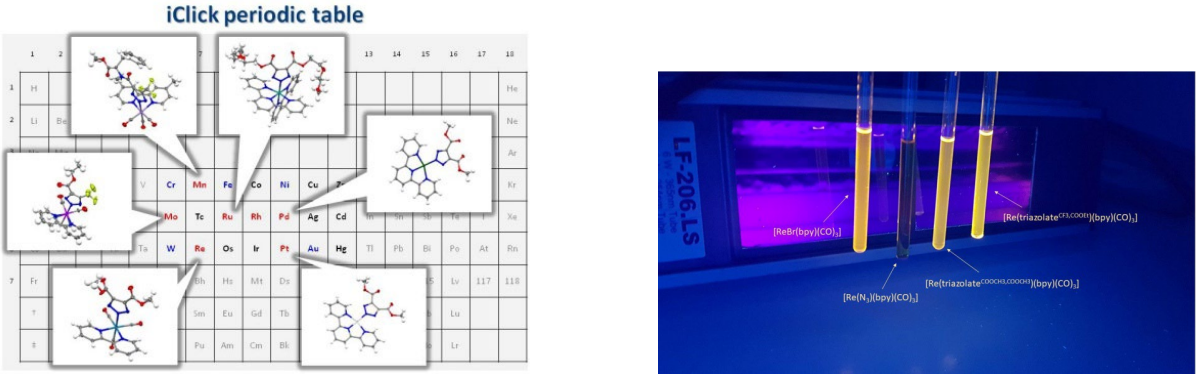

Figure 6: (Left) Overview of metal complexes for which the iClick reaction has already been established in our lab together with representative crystal structures and (right) differences in the luminescence of a metal-bromide complex, its azido congener, and two different triazolato complexes resulting from iClick reaction with electron-poor alkynes.

In the current presentation, examples of combinatorial iClick reactions carried out in a re-purposed HPLC autosampler will be presented, which allow facile labelling of a wide variety of metal complexes together with recent examples of *"light-up" probes*, in which the starting material is non-emissive while the resulting triazolato complex shows intensive luminescence. Furthermore, first results will be shown on how to impact chiroptical properties based on chiral alkyne "iClick" partners.

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Abstract Number: 444

Dysregulating bacterial zinc homeostasis to break antibiotic resistance

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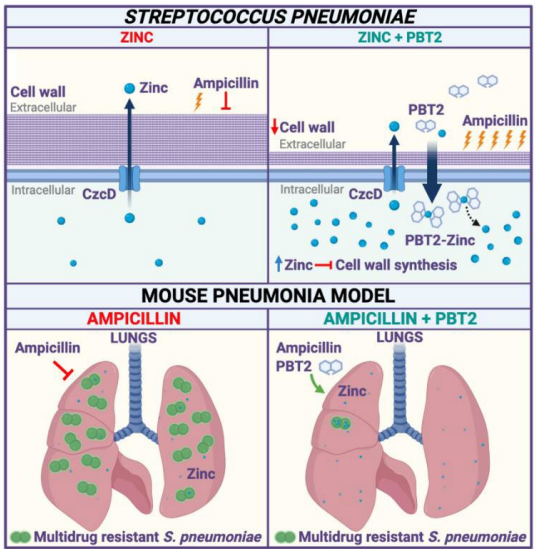
Streptococcus pneumoniae is the primary cause of community-acquired bacterial pneumonia despite widespread vaccination programs. This has been attributed to a rise in drug-resistant strains, with ~40% of all clinical disease isolates penicillin-resistant, and the capacity to escape vaccine prophylaxis due to capsule-switching. During infection, the innate immune response uses multiple insults against invading pathogens to control infection, including chemical stress as mediated by niche-specific modulation of zinc abundance. Here, we characterised how *S. pneumoniae* resists increased zinc stress and identified a single efflux pathway encoded by *czcD*. Disruption of *czcD* rendered *S. pneumoniae* hypersusceptible to zinc, with metabolomic profiling revealing impacts in central carbon metabolism, lipid biogenesis and peptidoglycan biosynthesis. Structural and biochemical characterisation of a pivotal metal-dependent peptidoglycan biosynthetic enzyme GlmU showed that zinc bound to the protein and impaired its essential acetyltransferase activity. Consistent with an impact in peptidoglycan biosynthesis, zinc stress rendered the D*czcD* strain highly susceptible to b-lactam antibiotics. However, zinc did not alter antibiotic sensitivity in the wild-type strain due to the protection provided by CzcD. To defeat zinc homeostasis, we used a metal-permeating ionophore. We investigated PBT2, a safe-for-human use ionophore, and showed that it could render drug resistant *S. pneumoniae* strains sensitive to b-lactams and other antibiotics. Using an invasive ampicillin-resistant *S. pneumoniae* strain, we successfully demonstrated the efficacy of PBT2+ampicillin for the treatment of *in vivo* murine lung infection. Collectively, these findings further elucidate the molecular basis of zinc toxicity in *S. pneumoniae* and show how this provides a pathway for development of a novel treatment modality that breaks antibiotic resistance in multidrug-resistant strains [1].



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Abstract Number: 446

Organometallic Chemistry and Strategies for the Development of Anticancer Agents

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The approaches taken to develop novel metal-based anticancer agents have considerably changed over the last 50 years since the discovery of the platinum drugs. The focus has shifted from cisplatin-type, me-too compounds, which would target DNA in a similar fashion to the parent complex, to compounds that interact with proteins overexpressed in tumors, show novel modes of DNA interactions or accumulate with higher selectivity in tumors, to name a few. The structural diversity investigated has steadily increased and compounds based on organometallic scaffolds are widely investigated. Organometallic chemistry has played an important role in drug discovery for a long time and organometallic catalysts are widely used in the synthesis of biologically active molecules, but their potential as drugs themselves cannot be negated. Over the years, bioorganometallic chemistry has developed into a thriving field of research and in particular the development of anticancer agents with bioactive co-ligands coordinated to the metal center (e.g. histone deacetylase inhibitors as shown in Figure 1) has received a lot of attention.[1,2] I will highlight in this lecture my group's journey of exploring new concepts in anticancer metallodrug design and metallomics strategies to interrogate their modes of action. In our research we aim to develop anticancer agents that interact selectively with biomolecular targets or accumulate selectively in tumor tissue. The coordination of bioactive ligands to metal centers may result in multimodal anticancer agents with ideally synergistic activity between the ligand and the metal center (Figure 1). Such approaches have led to compounds with significant anticancer activity and uncommon modes of action.[1,2] I will focus on novel ligand structures, such as *N*-heterocyclic carbenes (NHCs) and other mono- and bidentate scaffolds, and the exploration of the biological properties of their organometallic complexes.[3,4] Unexpected reactions and surprising behavior in the presence of biomolecules, studied by a combination of biophysical methods, have led to new compound types and to a deeper understanding of their modes of action.[5]

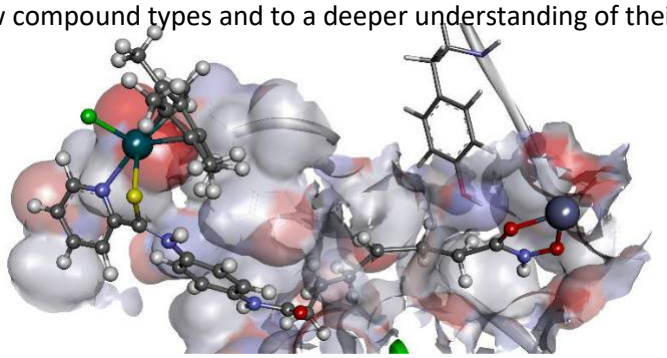

Figure 1. Histone deacetylase-targeted organorhodium pyridinecarbothioamide complex.

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Abstract Number: 447

Understanding CO2 fixation through structure

Dr Bonnie Murphy

Understanding the mechanism of redox proteins depends on an atomic-level understanding not only of the protein structure, but of structural changes associated with reduction and oxidation processes. Because structural studies by single-particle cryo-EM have only recently achieved the resolutions that allow for atomic-level insight into mechanism, the tools for preparation of samples under defined redox conditions are lacking. As our group has worked toward understanding the structure and function of redox proteins, we have brought together a set of tools for better assessing redox-dependent structural changes. Applying these tools to proteins involved CO2 fixation have provided novel insights into this process in anaerobic environments.

Contributed Poster Abstracts

Abstract Number: 1

Design and development of Cu(II)-Schiff base complexes containing thiadiazoline moiety to study DNA/HSA interactions and anticancer activity

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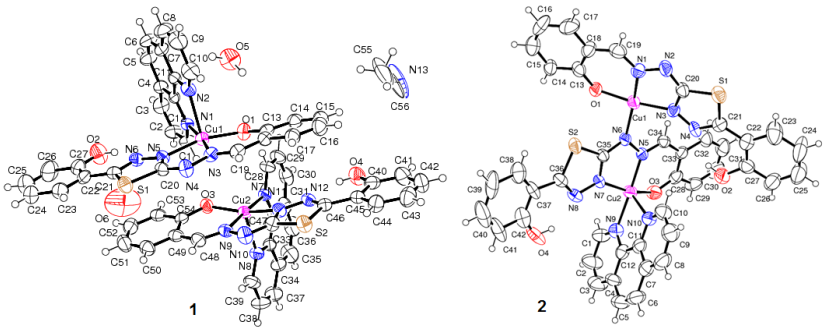
A mononuclear Cu(II) complex (**1**) and an asymmetric dinuclear Cu(II) complex (**2**) were prepared with the ligand formed *in situ* from cyclisation of the Schiff base 1,5-bis(salicylidene)thiocarbohydrazide. **1** was mononuclear in both solid and solution whereas **2** was dinuclear in solution but found to be tetranuclear in solid as revealed from X-ray crystallography. The complexes effectively interact with CT-DNA by intercalative mode, showing high DNA binding propensity (K_b ~10^5 M^{-1}). Both **1** and **2** showed significant oxidative cleavage of pUC19 DNA, additionally complex **2** was capable of catalyzing hydrolytic cleavage of *pUC19* DNA in dark and in absence of any external reagent. Interaction with human serum albumin (HSA) using fluorescence spectroscopy revealed that the complexes have strong ability to quench intrinsic fluorescence of HSA through a static quenching mechanism (bimolecular quenching constant k_q ~10^{13} $M^{-1}s^{-1}$). Förster resonance energy transfer (FRET) process may also be accounted for such high k_q value. The binding average distance r between donor (HSA) and acceptor (**1**-**2**) was estimated based on FRET theory. 3D fluorescence and UV-vis spectral studies showed that HSA structure was altered at secondary and tertiary levels upon binding with the complexes. Molecular docking studies indicated that the complexes primarily bind to HSA in subdomain IIA. *In vitro* cytotoxicity results (IC_{50} = 0.80 and 0.43 ⍰M for **1** and 2.2 and 1.2 µM for **2** with HeLa and MCF7 cells, respectively) suggested remarkable anticancer activity of **1** and **2**. Furthermore, the complexes showed significantly more potency than cisplatin for 24 h incubation under identical experimental condition, suggesting that **1**-**2** can be explored further as potential anticancer drugs. AO/PI and Hoechst staining studies suggested apoptotic mode of cell death. ROS generation was detected using H_2DCFDA assay which possibly is responsible for the oxidative DNA cleavage and apoptotic cell death.



Structures of **1** and **2**

Abstract Number: 3

Exploring and Expanding Metal-Binding Pharmacophores for Developing Metalloenzyme Inhibitor

Hyeonglim Seo,[a] Kathleen E. Prosser,[a] Moritz K. Jackl,[a] Alysia J. Kohlbrand,[a] Seth M. Cohen*[a]

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The use of metal-binding pharmacophores (MBPs) for fragment-based drug discovery (FBDD) has proven effective for targeting metalloenzymes. However, among clinically used metalloenzyme inhibitors, a limited number of MBPs have been employed to bind the active site metal ions and these common MBPs suffer from pharmacokinetic liabilities, which can undermine the development of such compounds into clinically effective therapeutics. In this presentation, several efforts are made to understand and develop a fragment library that broadens the scope of MBPs available for lead development.

First, a novel bioinorganic model system [M(TPA)(MBI)] (M = Ni^{2+} and Co^{2+}, TPA = tris(2-pyridylmethyl)amine) was used to study the binding of metal-binding Isosteres (MBIs). MBIs combine coordination chemistry with the concept of isosteres, where functional groups with undesirable physicochemical properties are replaced with less liable groups retaining biological activity. Picolinic acid, several picolinic acid MBIs, and 2,2'-bipyridine were studied in the aforementioned model system to compare their structural and electronic properties. The results demonstrate that bioinorganic model complexes are versatile tools to understand metal-ligand interaction and develop fragments for metalloenzyme inhibitor design.

Second, isosteric replacement of 8-hydroxyquinoline (8-HQ) was investigated. The quinoline pharmacophore and its bioisosteres are important building blocks to modulate drug-target interactions in the design of new bioactive molecules. In this respect, 8-HQ and its MBIs were investigated to explore unchartered territory in biochemical space and may improve potency and selectivity in FBDD. Their coordination chemistry, physicochemical properties, and related metalloenzyme inhibition activity were studied to establish drug-like profiles.

Lastly, thioamide-based MBPs have been studied as potent warheads to mask the typical reactivity of thiol MBPs. The reactivity, bioactivity, and structural studies show that thioamide-derived ligands can be used as stable, sulfur-based MBPs for Zn^{2+}-dependent metalloenzymes including human carbonic anhydrase II and matrix metalloproteinase-2.

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Abstract Number: 5

Active site structures of the of the *E. coli* hydroxylaminopurine resistance molybdoenzyme YcbX.

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MOSC domain proteins were first identified in a computational study and named due to their homology to the C-terminus of molybdenum cofactor sulfurases; it was proposed that they are involved in the assembly of metal-sulfur centres. However, many members of the MOSC superfamily, including the human mARC proteins and the bacterial protein YcbX, have been shown to act as oxidoreductases that reduce *N*-hydroxylated substrates. Thus, MOSC proteins constitute a novel family of enzymes that use the molybdenum cofactor, despite not sharing any sequence similarity with previously studied molybdoenzymes. It must be emphasised that the substrate spectrum of MOSC proteins is very different compared to that of other molybdenum enzymes.

The human mARC proteins have enjoyed considerable attention recently, as genome-wide association studies and murine knockout models demonstrate an involvement in lipid metabolism and liver disease. Nonetheless, it is unknown which mARC-catalysed reaction is responsible for this effect. To determine the physiological function of MOSC proteins and their role in human disease, insights into their active site structure and catalytic mechanism are needed.

We have examined the active sites of the *E. coli* enzyme YcbX, a close homologue of human mARC, by X-ray absorption spectroscopy. We present the active site structures of the for both enzymes in the fully oxidised Mo(VI) and the fully reduced Mo(IV) states.

The first coordination sphere of the molybdenum ion was determined from the EXAFS region of the spectra. Based on our EXAFS structures, we propose a reaction mechanism for MOSC proteins that involves a protonated oxygen ligand (*i.e.* *hydroxyl*) bound to Mo in the reduced enzyme form (Figure 1). This mechanism agrees with the substrate specificity of the enzymes including their preference for substrates that possess a hydroxyl group.

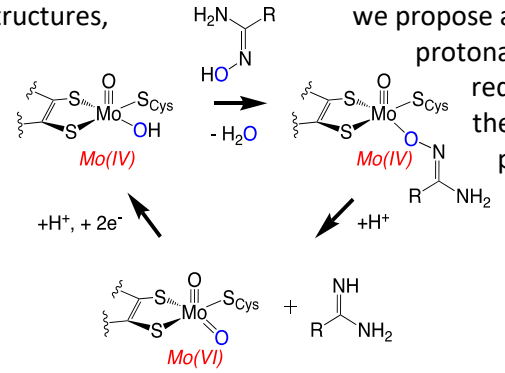

Figure 1. Proposed mechanism of substrate reduction by MOSC family enzymes, including YcbX. Note that the Mo(VI) → Mo(IV) reduction step is expected to proceed

Abstract Number: 8

Substituent-free corrole: synthetically different pathways and chemical dynamics of its cobalt complexes

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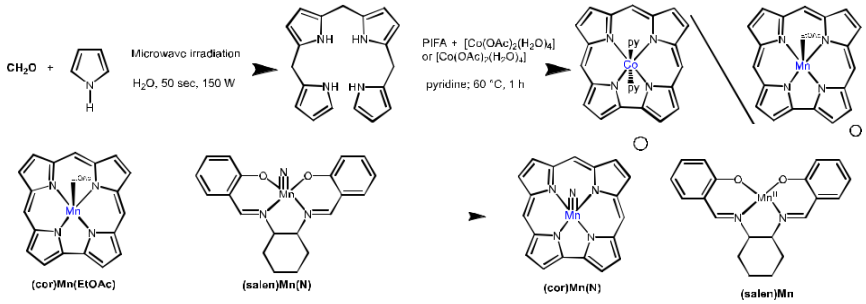
The science and technology of corroles, macrocycles that share structural similarity with the cobalt chelating prosthetic group of Vitamin B12 and numerous features with the iron chelating porphyrin present in heme proteins/enzymes, constantly crosses new horizons ever since stable derivatives became easily accessible. Particularly important is the increasing utilization of corroles and the corresponding metal complexes for the benefit of mankind, in terms of new drug candidates for treating various diseases and as catalysts for sustainable energy relevant processes. One still unmet challenge is to gain access to the plain macrocycle, as to allow for a full elucidation of the most fundamental properties of corroles.[1] We have obtained the substituent-free corrole by conceptually different pathways. Now we are presenting the corresponding cobalt complexes further coordinated by axial amines that differ significantly in their electron donating properties for studying their chemical dynamics.



Scheme 1. One-pot synthesis of (cor)Co and (cor)Mn via one-pot oxidative cyclization of TPM and metalation by cobalt(II) or manganese(II) acetate; and the preparation of the diamagnetic (cor)Mn(N) by nitrogen atom transfer from (salen)Mn(N) to the paramagnetic (cor)Mn.

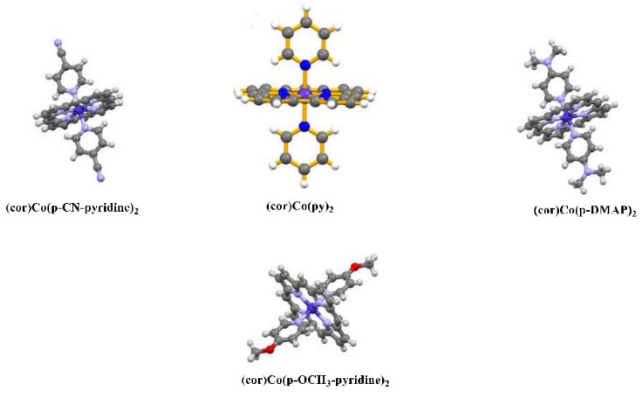


Figure 1. X-ray structures of parent-corrole cobalt complexes with different substituted pyridines as axial ligands.

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Abstract Number: 17

Axial Ligand Effects on H-Atom Abstraction by Oxoiron(IV) Complexes Featuring Triplet-Only Reactivity

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In nature, enzymes can activate dioxygen forming high-valent oxoiron(IV) species that are key intermediates for the hydroxylation of strong, non-activated C–H bonds.[1] Both, spin state and *trans*-axial ligands have been shown to significantly affect the reactivity of the oxoiron(IV) species. However, unambiguous disentangling of various influences by the study of models was largely hampered because of the accessibility of classical "two-state-reactivity" (TSR) due to a small energy gap ($\Delta E_{T,Q}$) between the triplet (S = 1) ground and the quintet (S = 2) excited state for N-ligated tetragonal oxoiron(IV) complexes (Figure 1).[2]

In previous work of our group, an oxoiron(IV) complex **1** ligated by a macrocyclic tetracarbene ligand was synthesized and fully characterized,[3] and was found to exhibit surprisingly high activity in H-atom abstraction (HAA) via a nonclassical "triplet-state-only" pathway due to large $\Delta E_{T,Q}$ (~18 kcal mol^{-1}) originating from the destabilization of the dx^2–y^2-orbital by the strong equatorial carbene ligands (Figure 1).[4,5] The single-state-reactivity of complex **1** provides an ideal platform for investigating intrinsic ligand effects on reactivity, where the interference from any spin-state crossover is eliminated. Here, we report a systematic study of the properties and HAA reactivity of a series of oxoiron(IV) complexes derived from parent complex **1**, bearing different axial ligands (Figure 1). These studies deepen our understanding on how high-valent oxoiron(IV) species activate C–H bonds, and how reactivity can be tuned by ligand variations.

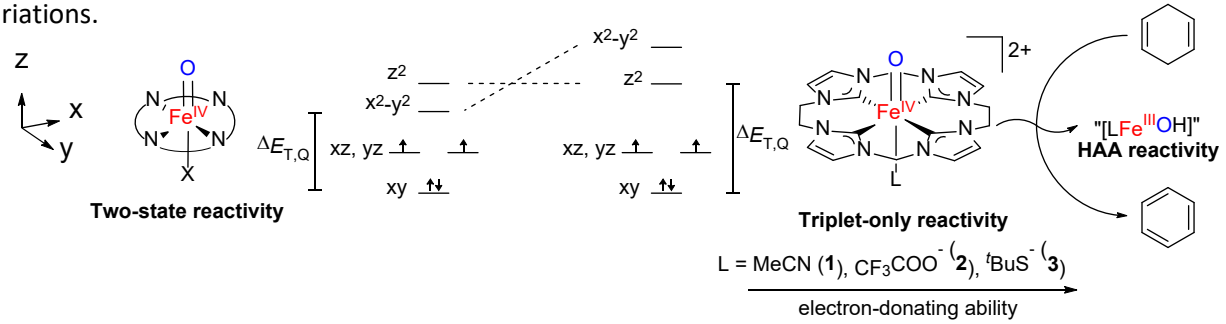

Figure 1: Orbital splittings of different oxoiron(IV) complexes and HAA reactivity.

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Abstract Number: 20

Bioinspired metal complexes with *N*-substituted bis(pyridylmethyl)amine ligands: Synthesis and biological activity

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Metal complexes containing bioinspired ligands are growing in a variety of medicinal applications such as biocide and antitumoral agents.[1] Among them, iron(III) and zinc(II) compounds have been developed as potential candidates as antineoplastic and antimicrobe agents.[2] Parallel to this, a good example of bioinspired ligand that can interact with DNA is the bis(2-picolyl)amine (bpma) which consists in a quite versatile tridentate ligand that can be easily functionalized with pendant groups during its synthesis.[3] Based on that, a series of $[MLCl_x]$ and $[ML_2](ClO_4)_x$ complexes (where M = Fe or Zn and L = L^{C5} or L^{C10OH}) was prepared (Fig 1, left).

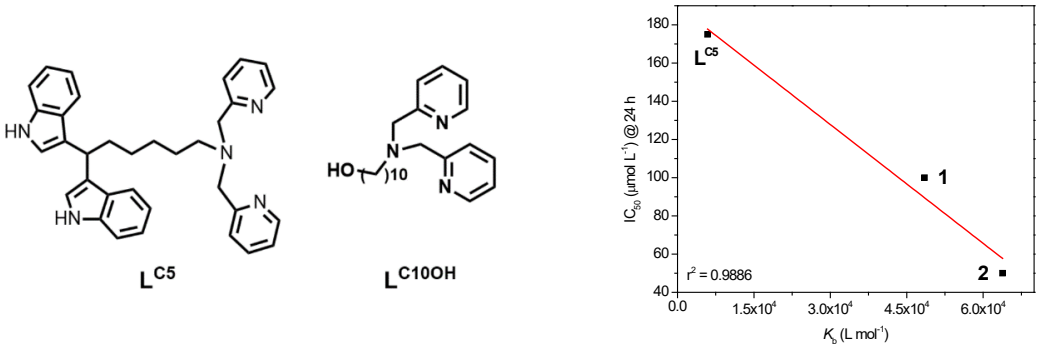

Fig 1. Bioinspired ligands herein studied (left). Linear relationship between the cytotoxicity studies at 24h (IC_{50} values) and DNA binding assays (K_b) for zinc complexes and L^{C5}.

All compounds were fully characterized by a suite of physicochemical methods. The interaction between these compounds and DNA was monitored where binding constants (K_b) were obtained (~10^3 to 10^4 L mol^{-1}). These data were corroborated by *in silico* analysis. All complexes confirmed their biocide activity against selected microorganisms: *S. aureus, E. coli, A. fumigatus* and *S. cerevisiae*. Particularly towards *A. fumigatus*, $[FeL^{C10OH}Cl_3]$ and $[Fe(L^{C10OH})_2](ClO_4)_3$ have shown better biocide activity (IC_{50}) than the positive control fluconazole (1.3 and 4.9-fold, respectively). The cytotoxic activity was also tested against the erythroleukemia K562 cell line, where zinc-containing complexes and L^{C5} presented a linear relationship between the K_b and IC_{50} values at 24 h (Fig 1, right). This is a good indicative that these compounds can enter cellular environment and bond to DNA molecule. Finally, for all biological studies, it was probed that the presence of bis(indolyl)methane (L^{C5}) or *n*-alkyl chain (L^{C10OH}) moieties, as well as the metal ions could increase the magnitude of the biological activity upon the selected targets.

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Abstract Number: 23

Ferritin role in ferroptosis: implication for neurodegenerative diseases

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Ferritin is well known for its role as an iron storage protein that function to regulate intracellular iron according to cellular requirements. Iron release from ferritin in the process termed ferritinophagy is also required for the execution of ferroptosis and we recently reported that apolipoprotein E, which is a major genetic risk factor for Alzheimer's disease protects from ferroptosis in neuronal cells via inhibition of ferritinophagy. In this study, we investigated possible implications of extracellular ferritin in the process of ferroptosis. We expressed and purified two recombinant human ferritins, heavy chain and light chain and found that both ferritins are potent inhibitors of ferroptosis with a potency superior to the gold standard anti-ferroptotic compounds. Increasing iron saturation of extracellular ferritin in vitro did not cause a decrease in antiferroptotic activity suggesting that iron binding is not the underlying mechanism of protection. Using a series of protein analyses and cellular localization assays, we further revealed that ferritin antiferroptotic activity is likely mediated via a receptor binding mechanism. In contrast to soluble ferritin, iron-rich ferritin combined with liposomes containing arachidonic acid was very toxic and primed the cells specifically to ferroptotic cell death. While liposomal ferritin formulation may have implication for cancer treatment, identification of the receptor and the underlying mechanisms implicated in the antiferroptotic activity of soluble ferritin will advance our understanding of processes such as cognitive decline in the aging process as increase in extracellular ferritin was associated with accelerated cognitive decline in aging, but the underlying mechanism remain unknown.

Abstract Number: 30

A Glimpse on Development of Mitochondria Specific Ru(II)/Ir(III)/Re(I)-based Luminescent Complexes as Dexterous Cancer Therapeutic Agents

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Cancer is the most incurable pernicious disease till date after the cardiovascular disease throughout the world with immeasurable rate of mortality. However, effective cancer therapy is still castles in the sky to the researchers being unable to develop appropriate anticancer drugs. In quest of an appropriate strategy to annihilate cancer, we have aspired to design a set of mixed metallic complexes having the cancer cell imaging and damaging capability with higher degree of cytoselectivity. These mixed metallic complexes are appreciably fluorescent with high quantum yield displaying the capability of diagnosing the cancer cells and have shown remarkable cytotoxicity against a series of cancer cell lines (HeLa, Caco-2, MDA-MB468, MCF-7, HT-29) accompanied with excellent binding efficacy with biomolecules (HSA, DNA) being resistant to glutathione(GSH) rendering the normal healthy cells unaffected. In line with this, complexes are highly capable of targeting the organelles (nucleus, mitochondria) and can destroy the cancer cells causing mitochondrial dysfunction through reduction of mitochondrial membrane potential (MMP) as well as triggering the emergence of ROS in association with damaging of DNA (**Figure 1**).[1, 2,3] Optimistically, it can be presaged that all these characteristics of these complexes will be beneficial for exploring the brilliant cancer therapeutic agents in imminent future.

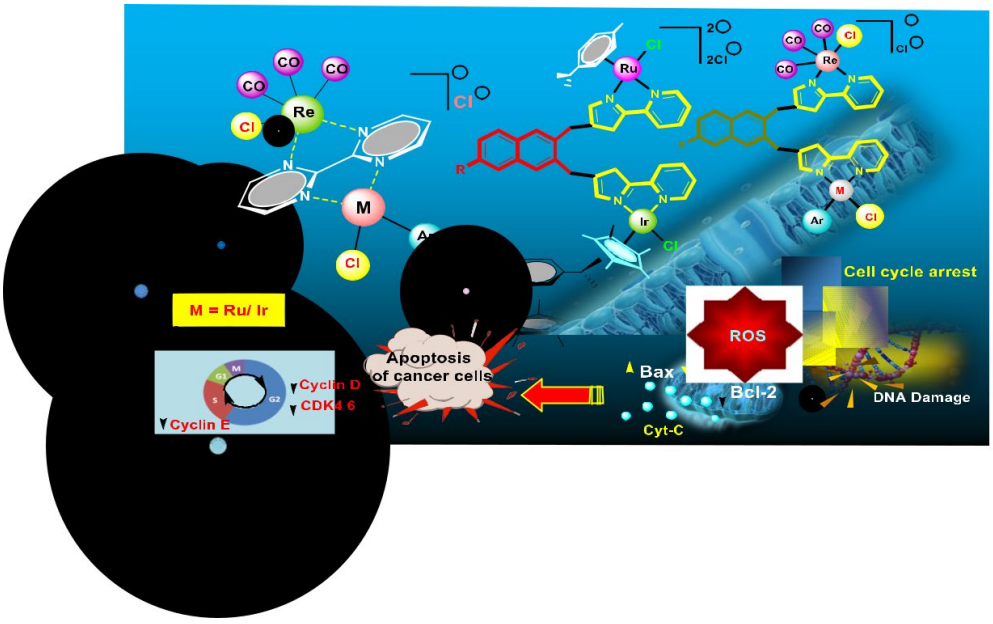

Figure 1. A Mechanistic Approach of the Complexes for Destruction of Cancer Cells

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Abstract Number: 36

Myths of the long-term used fungicide Maneb: Structural characterization and toxicological effects in *C. elegans*

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The class of ethylene bisdithiocarbamate (EBDC) fungicides have a highly effective multi-site mode of action and are therefore commonly used in mixtures with other fungicides as part of a resistance management strategy. Maneb, the manganese (Mn) containing derivate was patented 1950 and is still used in large quantities. Already in 1989 Ferraz *et. al* identified a correlation between extensive use of Maneb and the development of neurological symptoms in fieldworkers[1]. Surprisingly, despite its long history of use, the molecular structure of Maneb is still unknown. Mn plays an important role as an essential trace element in human health through involvement as a cofactor in several enzymes. However, exceeding the homeostatic range Mn can be accumulated in the brain and is associated with Parkinson's disease-like symptoms, termed as "manganism"[2].

In order to learn more about Maneb, a practical and reproduceable synthesis was developed and the resulting material was characterized using different analysis methods such as elemental analysis, single crystal- as well as powder X-ray diffraction and X-ray absorption spectroscopy. Toxicological studies including acute toxicity, bioavailability, neurotoxicity and oxidative stress were carried out using the nematode *Caenorhabditis elegans* (*C. elegans*) as an *in vivo* model organism. Maneb was compared with Mn(II) chloride and also with the EBDC sodium salt (Nabam) and the major EBDC metabolite ethylene thiourea (ETU). Bioavailability of manganese was measured *via* inductively coupled plasma with optical emission spectroscopy (ICP-OES). At subtoxic concentrations the uptake of Maneb was observed to be lower than that of $MnCl_2$, but Maneb was found to be about 10 times more toxic than $MnCl_2$ in the lethality assay. Therefore, further toxicological endpoints including oxidative stress markers and neurotransmitter levels were investigated.

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Abstract Number: 42

Synergy Effect of Aluminum Complexes During the Ring-Opening Polymerization Of -Caprolactone: Inductive Effects Between Dinuclear Metal Catalysts

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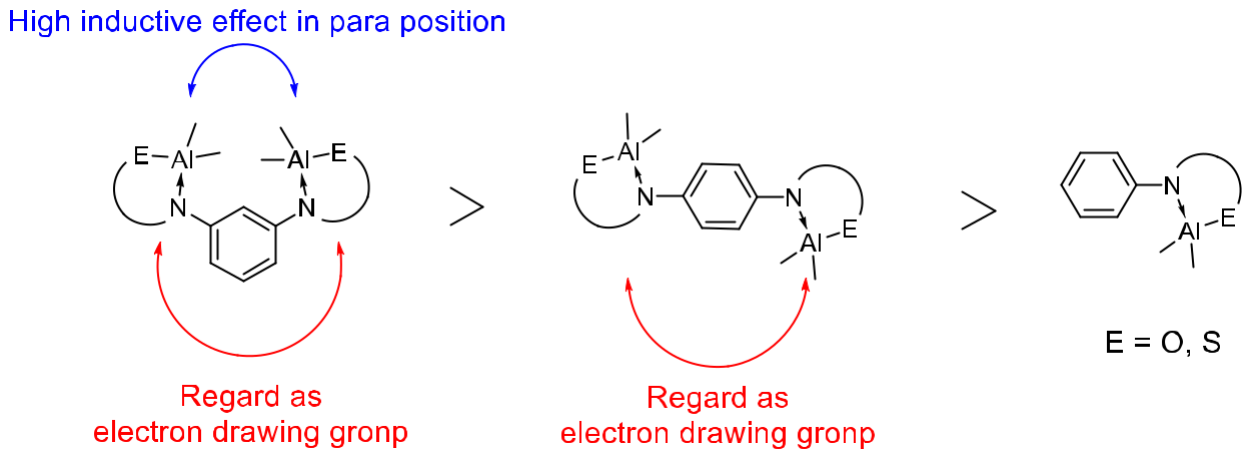
In this study, a series of mononuclear complexes and dinuclear aluminum complexes bridged by 1,3- and 1,4-substituted phenyl ligands were synthesized, and their activities for the ring-opening polymerization (ROP) of ε-caprolactone (CL) were investigated. All the dinuclear aluminum complexes exhibited higher catalytic activity than did the corresponding mononuclear Al complexes (2–6-fold for the kobs values), and most of the dinuclear Al complexes bearing 1,3-substituted phenyl ligands exhibited higher activity than did the corresponding dinuclear Al complexes bearing 1,4-substituted phenyl ligands (1.5–3-fold for the kobs values). The only exceptions were the Al complexes bearing benzothiazole ligands, for which the dinuclear Al complex with 1,4-bis(benzothiazol-2-yl)benzene exhibited higher catalytic activity than did the corresponding 1,3- bis(benzothiazol-2-yl)benzene complex. This higher activity of the dinuclear Al complexes was attributed to one of the Al atoms in the dinuclear Al system being regarded as an electron-withdrawing group. This group influenced the other Al atom through associated aromatic ligands to enhance the catalytic activity for the ROP of CL



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Abstract Number: 43

Characterization of cytochrome P450 CYP107J1 from *Bacillus subtilis*

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Cytochrome P450 monooxygenases (P450s) are a superfamily of heme-containing proteins that introduce one oxygen atom derived from molecular oxygen into an organic molecule. A heme iron center in P450 activates O_2 using electrons transferred from NAD(P)H by reductase components. These enzymes catalyze the direct oxidation of a variety of compounds in a regio- and stereoselective manner under ambient conditions. Thus, P450s are promising catalysts for use in the oxyfunctionalization of chemicals. Analysis of the *Bacillus subtilis* genome sequence revealed eight CYP genes. Of these, although seven CYPs have been well studied, the catalytic function of CYP107J1 remain almost unknown. There is only one report concerning CYP107J1; CYP107J1 was found to catalyze monooxygenation of testosterone enanthate using the FT-ICR/MS-based assay.[1] In this study, we examined the catalytic function of CYP107J1 in more detail. The CYP107J1 gene was coexpressed with putidaredoxin gene and putidaredoxin reductase gene from *Pseudomonas putida* to provide the redox partners of CYP107J1 in *Escherichia coli*. We explored the catalytic potential of CYP107J1 by whole-cell assays using the recombinant *E. coli* cells. When the recombinant *E. coli* cells were incubated with 4-propylbenzoate, a product was detected by HPLC analysis. This product was identified by mass spectrometry and NMR spectroscopy as 4-(2-hydroxypropyl)benzoate. In addition, although CYP107J1 exhibited no catalytic activity for 4-methylbenzoate and 4-ethylbenzoate, this enzyme efficiently oxidized 4-butylbenzoate and 4-pentylbenzoate. Furthermore, CYP107J1 exhibited no catalytic activity for 4-propylphenol, suggesting that the carboxyl group is essential to the recognition of the aromatic compounds by CYP107J1.

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Abstract Number: 48

Iridium Remote-NHC Complexes in Transfer Hydrogenation of NAD^+

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Catalytic metallodrugs are increasingly being suggested as a new approach to anticancer treatment. A growing number of papers have shown that metal complexes can catalytically convert biological substrates within a cellular environment leading to a host of disruptions eventuate in cell death (apoptosis).[1] The interconversion between $NAD(P)^+$ and NAD(P)H has been the most actively investigated reaction in this context. Formation of the former leads to the more traditional approach of apoptosis, through oxidative stress. However, Sadler *et al.* have demonstrated that formation of the latter causes reductive stress within the cellular environment leading to an increase in cytotoxicity.[2,3] This is achieved by catalysing the transfer hydrogenation reaction of NAD^+ to 1,4-NADH by the metallodrug that utilizes biologically active hydride sources such as sodium formate.

Preliminary testing of a range of remote-NHC iridium(III) complexes for catalytic activity in transfer hydrogenation was performed in *iso*-propanol on the substrate benzaldehyde under a range of conditions (different temp, solvents, formate concentration). The most active iridium(III) complex was selected for further study involving NAD^+ reduction, and has shown very good catalytic activity in the transfer hydrogenation of NAD^+ to 1,4-NADH under pseudo-biological conditions (PBS pH 7.4, 37°C) at 1 mol % catalyst loading have been obtained. Full details of these and related studies will be presented.

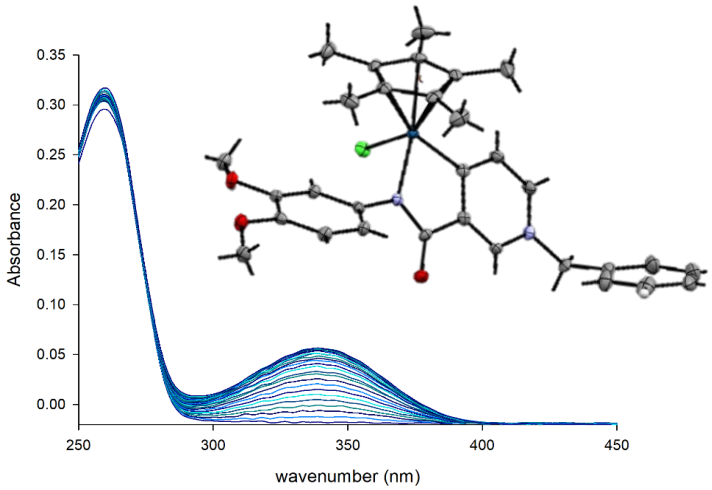

Figure 1. Monitoring the formation of 1,4-NADH (340 nm) over time (12 h) using UV-Vis spectroscopy

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Abstract Number: 49

TiO_2-Catalyzed Synthesis of Cyclohexylamine NONOATE

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Nitroxyl (HNO) has recently emerged as an important pharmacological agent.[1] Full elucidation of the chemistry of HNO is important for the continued development of HNO pharmacology. Fast dimerization of HNO[2] prevents storage and necessitates the need for HNO donor compounds. Primary amine NONOates are HNO donors that can be used to study and understand the chemical properties and physiological effects of HNO.[3] However, NONOate synthesis involves very high pressure and low temperature conditions, and requires specialized glassware and equipment.[4] In this study, a primary amine NONOate based on cyclohexylamine was synthesized at ambient conditions by catalyzing the synthesis reaction with TiO_2.

The TiO_2-catalyzed method yielded the desired product which was characterized via UV-Vis spectroscopy. The product exhibited λ_{max} = 250 nm, followed first-order decomposition and released both HNO and NO at physiological pH, which are characteristic of cyclohexylamine NONOate. The method yielded 5.98 mg cyclohexylamine NONOate which is equivalent to a percent yield of 0.0550%. The yield of the method was low but reasonable considering the yield of the conventional method (1-20 %) which requires –78 °C and 50 psi NO. Furthermore, the yield of this method is sufficient for chemical and biological assays.

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Abstract Number: 58

Unveiling the Mystery: Tracing the Metalation Pathway of Wheat E_c-1 Metallothionein's β_E-Domain

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Metallothioneins (MTs) are small cysteine-rich proteins which preferentially bind divalent metal ions such as Zn^{II}, Cu^{I}, and Cd^{II} and are attributed towards potential functions including metal ion homeostasis and detoxification[1]. The E_c-1 metallothionein from *Triticum aestivum* (common bread wheat) was the first plant metallothionein, for which our group was able to determine the solution structure.[2] As this structure only reflects the fully metalated state of the protein, we were further elucidating its metalation pathway, and the results obtained are presented here. The β_E-domain of wheat E_c-1 features two Zn^{II} binding sites (Fig. 1). The mononuclear site is composed of two cysteine and two highly conserved histidine residues, which form a motif analogous to certain Zn-fingers. The second site consists of a trinuclear Zn_3Cys_9 cluster resembling the well-known β-cluster type of MTs, found for example in vertebrate MTs. In this study, the metalation pathway of the β_E-domain is investigated by a combination of NMR, mass spectrometry and specific cysteine modification techniques[3]. As a result, we are able to pinpoint with high probability the consecutive binding sites for each of the four Zn^{II} ions and in addition obtained interesting and surprising insights into the folding pathway of the peptide backbone.

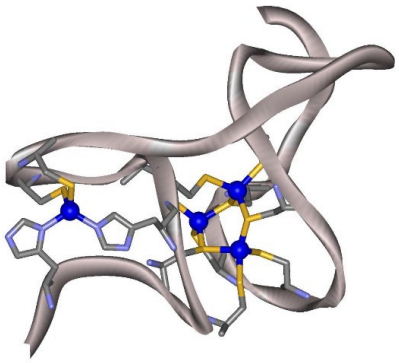

Figure 1. NMR solution structure of the wheat $Zn_4\beta_E$-E_c-1 domain (PDB code 2KAK).[2]

Acknowledgements
Financial support from the Swiss National Science Foundation, the Faculty of Science@UZH, as well as the CMSZH Graduate School is gratefully acknowledged.

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Abstract Number: 59

From Head to Tail: A Chemical Route for the Cyclisation of Metallothioneins

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Metallothioneins (MTs) are small, cysteine-rich proteins with low molecular weight that are capable of coordinating d^{10} transition metal ions, resulting in metal-thiolate clusters[1]. Due to their high affinity towards metal ions, MTs play a significant role in metal ion homeostasis, detoxification, and antioxidant defence against oxidative stress conditions. In a metal-free environment, MTs do not posses any secondary structures. However, when they coordinate metal ions, they adopt secondary structures that might trigger their function.

Head-to-tail cyclized proteins are characterized by covalent bonding between the N- and C-terminals, which is critical for the stability and usually also the function of the respective protein. In this study, we focused on two plant metallothioneins. The well-studied ɣ-E_c-1 domain from common wheat was used as a model protein to assess the feasibility of the synthetic route. This method was subsequently applied to mus-MT3[2] from banana. For both proteins, the effect of cyclization on the metal binding ability compared to the respective linear analog are studied.

The selected cyclization method in this study uses native proteins that were recombinantly produced in *E. coli*, and only then further modifications using a chemical reaction procedure were performed[3]. In this way, the size of the target protein is in theory not restricted. We were able to successfully execute all the reaction steps and demonstrate that this method is (i) a viable approach for the cyclization of ɣ-Ec-1 and (ii) can be extended to other metallothioneins. Currently, we are focusing on the purification of the cyclized product and the cyclization of mus-MT3.

Acknowledgements

Financial support from the Swiss National Science Foundation, the Faculty of Science@UZH, as well as the CMSZH Graduate School is gratefully acknowledged.

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Abstract Number: 65

Designing selective nano-cage adsorbents for the capture of persistent pollutants

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Per and polyfluoroalkyl substances (PFAS) are toxic persistent pollutants that are widespread due to their commercial production, stability and amphiphilicity.[1] Increasing evidence correlates PFAS as a global health burden.[1] Released through multiple exposure routes PFAS bioaccumulate and biomagnify over the lifetime of humans and biota.[1] Drinking water is one of the most significant PFAS exposure pathways where contaminated water includes a mixture of PFAS chain lengths.[1] Therefore it is critical to ascertain effective methods to capture and destroy PFAS. While commercial PFAS removal technologies are already in use they aren't selective for short-chained PFAS (five or less carbons).[2] This relates to a gap in knowledge and thus detailed studies on the aggregation and binding of PFAS within adsorbents are required. Metal-organic cages (MOCs) are self-assembled polyhedral architectures made from organic ligands and metal ion nodes. Their well-defined binding pockets and size/chemical selectivity have been exploited by applications such as catalysis, separations, and drug delivery agents.[3,4] MOCs may also have the potential to address environmental contamination by toxic PFAS, however, the encapsulation of PFAS using MOCs remains somewhat unexplored within the literature. We have discovered that Pd6L4 MOCs are able to encapsulate a wide range of PFAS, but with a preference for short-chain analogues. This project focuses on (1) further exploring the host-guest chemistry of MOCs and PFAS, and (2) utilising surface-functionalised MOCs to synthesise adsorbent materials. We envisage that the fundamental knowledge on PFAS binding and aggregation within MOCs will be applicable for the design of next-generation, supramolecular adsorbents.

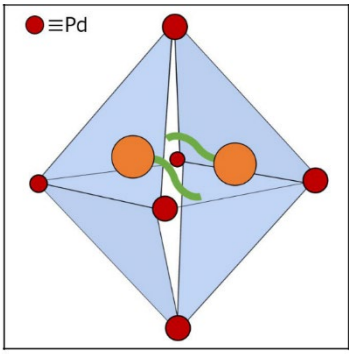

Figure 1. Pd6L4 metal-organic cage binding PFAS. The cage has size selectivity imparted by a well-defined binding pocket.

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Abstract Number: 71

Au-F Abstraction

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Historically gold difluorides are rare and exhibit unexplored avenues for chemistry. Recently our group presented a straightforward method for achieving Au^{III} difluorides that are uncharacteristically stable compared to previously reported complexes.[1] From this work we have found these Au^{III} difluorides to be susceptible to metathesis with TMS bound reagents, something not observed with either bromo or chloro analogues.[2] Recently we observed that abstraction of either one or both fluorides by TMSOTf leaves a potentially 'naked', reactive, and manipulatable Au centre that remains stable in solution long enough for subsequent *in-situ* reactivity.

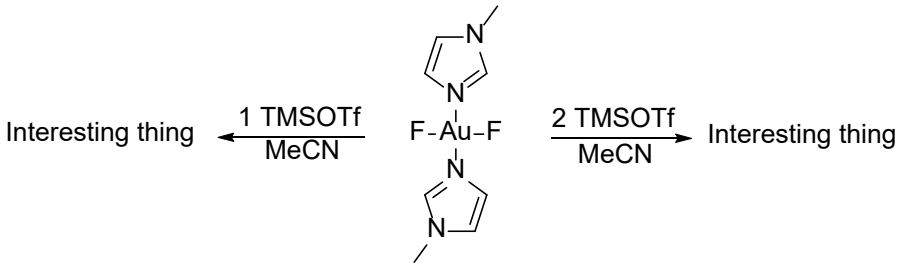

Figure 7: General Scheme on the formation of Au species

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Abstract Number: 75

Synthesis of bio-inspired nickel complexes bearing unsymmetrical β-diketiminato ligand

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Transition metal complexes with terminal oxo or oxyl ligand have been proposed as key intermediates in many biological and abiological catalytic oxidation reactions.[1] Synthesis and isolation of nickel complexes with terminal oxo or oxyl ligand is beneficial for chemist to understanding the catalytic behavior of nickel-containing metalloenzymes.[2] In this report, we chose an unsymmetrical β-diketiminato ligand with methyl pyridyl arm that can coordinate to nickel center. Treatment **L1**$Ni^{II}Cl$ with potassium graphite (KC_8) forms a unique paramagnetic nickel(I) species (**L1**Ni^{I}). Examination the paramagnetic nickel(I) species with bio-inspired gases (O_2, NO, CO) would give the corresponding nickel adducts with square-planar tetracoordinate nickel center. Interestingly, the nickel(I) nitric oxide adduct **L1**Ni(NO), as a {NiNO}^{10} species based on Enemark-Feltham notation, and nickel(I) carbonyl complex (**L1**$Ni^{I}CO$) were obtained and characterized by Infrared, NMR, and EPR spectroscopy.

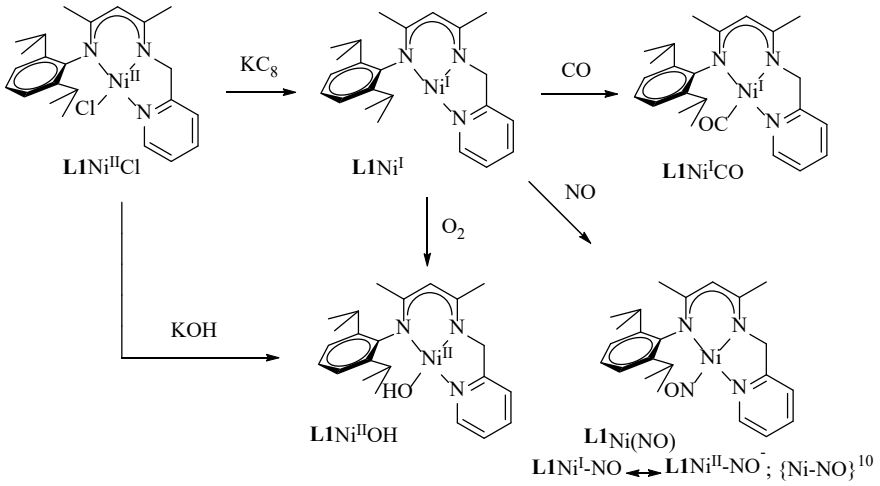

Chart 1. Synthesis of the N-aryl-N'-methylpridyl β-Diketiminato ligand nickel complexes.

References

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Abstract Number: 76

The Synthesis, Characterisation, and Anti-Leishmanial Activity of Tri-aryl Antimony(V) Hydroxamates

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Leishmania is a single-celled parasite responsible for the disease Leishmaniasis. Leishmaniasis is present in over 90 tropical and subtropical countries and results in one million infections per year worldwide.[1] Traditional pentavalent antimonials used to treat Leishmaniasis include meglumine antimoniate (MA) and sodium stibogluconate (SSG), which cannot be administered orally due to their high polarities and high hydrophilicities.[2] Instead, these antimonials must be administered daily via painful intramuscular or intravenous injections for a period of roughly 30 days, which has led to significant patient non-compliance.[2,3] Incorrect usage of these antimonials has led to drug pressure, resulting in drug tolerance and drug resistance.[4] Additionally, these traditional drugs cause a variety of undesirable side effects such as cardiotoxicity, nephrotoxicity, and pancreatitis.[2] Therefore, novel drug candidates are needed for the treatment of Leishmaniasis that are more selective, less susceptible to antimicrobial resistance, and can ideally be administered orally. A previous study by Andrews *et al*. successfully synthesised a series of tris-aryl antimony(V) a-hydroxy cyclometallate complexes, which identified trends in relation to changes in the aryl moiety.[5] In order to assess whether these trends continue with a similar doubly deprotonated class of organic molecules, we synthesised and characterised a series of novel triphenyl and tris-mesityl antimony(V) hydroxamates and assessed their potential antileishmanial activity (Figure 1).

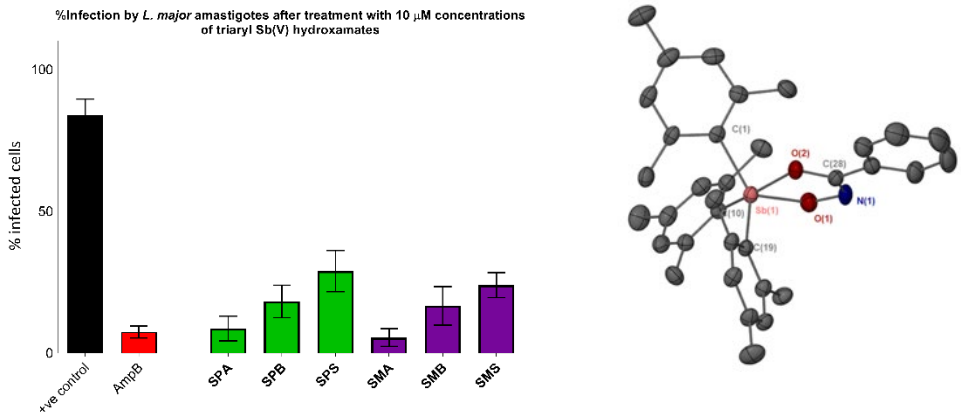

Figure 1. % of infected macrophages with *L. major* amastigotes after treatment with Sb(V) hydroxamates (left). Chosen x-ray crystal structure of a tri-aryl Sb(V) hydroxamate (right).

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Abstract Number: 86

A mutagenesis study of the active site of PnpC1C2, a hydroquinone ring-cleaving dioxygenase

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The hydroquinone dioxygenases (HQDOs) are members of a large family of non-heme Fe(II)-containing enzymes that catalyze the oxidative cleavage of an aromatic ring, of which the catechol extradiol dioxygenases are by far the best known and best studied. PnpC1C2 is an HQDO from the soil bacterium *Pseudomonas putida* DLL-E1 that is involved in the catabolism of 4-nitrophenol. Its native substrate is unsubstituted hydroquinone, but it is active towards a range of monosubstituted hydroquinones. To further explore the structure and function of this enzyme, with the eventual goal of engineering it with activity towards a wider range of hydroquinone substrates that could have relevance towards bioremediation of chlorinated aromatic compounds, two active site glutamate residues and nine hydrophobic residues were targeted for mutagenesis. The two glutamate residues were flagged as potentially crucial for the enzyme mechanism, and these were examined by site-directed mutagenesis and enzyme kinetics, looking at both the hydroquinone and O_2-concentration dependence. These results provide insights into the function of these glutamates. A series of nine mostly bulky hydrophobic residues that form the substrate binding pocket were varied by saturation mutagenesis, and the resulting mutants were screened for retention of activity towards the native substrate. These results provide insights into the plasticity of the substrate binding site, as well as providing a series of functional mutants that can serve as the basis for future studies of how the substrate specificity has been modified.

Abstract Number: 89

Modifications of amyloid-□ peptides by a mononuclear cobalt complex

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The deposition of amyloid-□ (A□) aggregates is a major hallmark of Alzheimer's disease (AD), the most common form of dementia. The pathological role of A□ peptides in AD, however, has not been fully elucidated due to their intrinsically disordered structures and their aggregation-prone nature[1,2]. To advance our understanding of a relationship between A□ aggregation and toxicity associated with AD, chemical reagents, particularly, transition metal complexes, that can modify A□ peptides and alter their aggregation profiles, have been developed[2-5]. The limited examples of transition metal complexes that are able to induce modifications of A□ peptides are known thus far[3-5]. In addition, various modifications cannot be achieved by these metal complexes. In this presentation, we illustrate a mononuclear Co(II) complex capable of carrying out notable modifications onto A□ peptides, including decarboxylation and deamination, fragmentation, and both, in the presence of O_2. These modifications onto A□ peptides by the Co(II) complex can redirect their aggregation pathways to yield relatively less toxic aggregates, compared to A□ aggregates produced without the complex. This work demonstrates that transition metal complexes can be rationally designed to effectively modify amyloidogenic peptides with the consequent impact on their aggregation and toxicity profile.

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Abstract Number: 91

Luminescent metal–organic frameworks constructed from dipyridyl benzochalcogenadiazole ligands

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Luminescent metal–organic frameworks (MOFs) have been investigated for their potential applications within non-linear optics, bio-imaging, photovoltaics, and molecular sensing.[1,2] Introducing tailored organic luminophores into MOF structures remains an appealing prospect in modulating their photophysical response. However, this can produce undesirable effects of solid-state fluorescence quenching which reduces the emissive yields and limits their potential applications.[3]
Benzochalcogenadiazoles are fused heterocyclic ring systems that have experienced renewed interest as functional components in organic light-emitting diodes and electroluminescent devices due to their large fluorescence quantum yields and tuneable electronic band and resonance structures. Herein, an isostructural series of three new multi-component MOFs containing different 2,1,3-benzochalcogenadiazole ligands was synthesised and characterised by an array of different crystallographic and physical techniques including X-ray diffraction and luminescent sensing experiments. These MOFs adopt the form [Cd(1,4-bdc)(L_X)] (1,4-bdc = benzene-1,4-dicarboxylate; L_X = **L_1-O** (oxadiazole), **L_2-S** (thiadiazole), or **L_3-Se** (selenadiazole)). This study investigates the effect of chalcogen swapping of the L_X ligand on the emissive properties of this MOF series and investigates their potential applications as host–guest sensors of small molecule solvents, nitroaromatic compounds, and heavy metal ions.

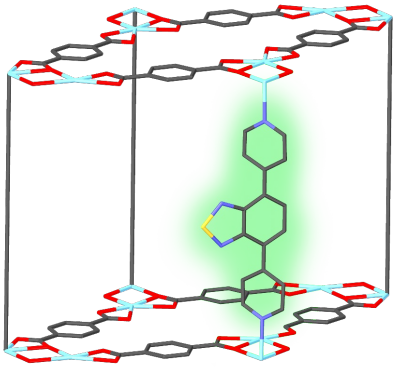

Fig 1. General structure of the new MOF series based on the fluorescent 4,7-di(4-pyridyl)-2,1,3-benzochalcogenadiazole ligands (**L_1-O** = oxadiazole, **L_2-S** = thiadiazole, and **L_3-Se** = selenadiazole). Atom colours: C (grey), N (blue), O (red), S (yellow), and Cd (light blue); long grey lines represent pillaring L_X ligands.

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Abstract Number: 92

Mechanistic Studies on the Catalytic Oxidation of Aldehydes by a Mononuclear Nonheme Manganese(III) Iodosylbenzene Complex

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Transition metal–iodosylarene complexes have been proposed to be key intermediates in the catalytic cycles of metal catalysts with iodosylarene. We reported the first X-ray crystal structure and spectroscopic characterization of a mononuclear nonheme manganese(III)–iodosylbenzene complex bearing a tetradentate macrocyclic ligand, $[Mn^{III}(TBDAP)(OIPh)(OH)]^{2+}$ (**1**; TBDAP = *N*,*N*-di-*tert*-butyl-2,11-diaza[3.3](2,6)-pyridinophane).[1] Herein, we present the oxidation of aldehydes into carboxylic acids by **1**.[2] The reactivity of **1** with aldehydes is analyzed by kinetic studies resulting in the electrophilicity of **1** with a kinetic isotope effect (KIE) value of 2.0. Density functional theory (DFT) calculations revealed that the rate-determining step is net hydride transfer composed of H atom abstraction and fast one-electron transfer from the C–H bond of a formyl group to **1**. To the best of our knowledge, this is the first mechanism study for the reaction of the metal iodosylarene species with aldehydes. Further, we observed catalytic oxidations of a broad scope of aldehydes by **1** in the presence of excess PhIO under mild conditions. The present results provide an unusual pathway for the oxidation of aldehydes into corresponding carboxylic acids with the potential as a new chemical catalyst.

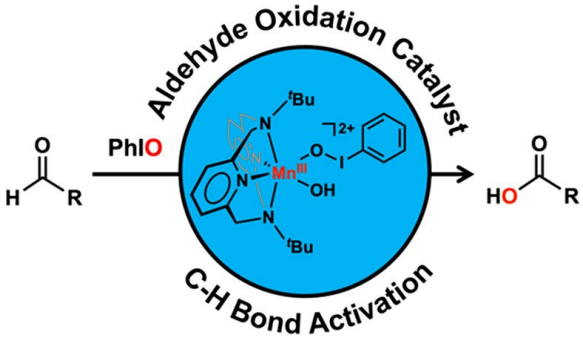

Figure 1. Graphical abstract for the oxidation of aldehyde by **1**

References

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Abstract Number: 95

Iron sensing by sensor kinase, VgrS, responsible for intracellular iron homeostasis

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Iron is an essential trace element for all organisms, which is used as active sites in iron proteins for electron transfer, chemical reactions, and gene regulation, etc. While it is essential, excess intracellular iron can generate reactive oxygen species, leading to oxidative stress and cellular damage. Therefore, iron homeostasis is essential for cells. Transcriptional regulators and/or iron uptake/export systems are responsible for regulating iron concentrations in cells[1, 2]. Several two-component systems are reported, which regulates intracellular iron concentration in response to iron repletion/deficiency. In *Xanthomonas campestris*, the two-component system, VgrS/VgrR, plays an important role for the regulation of iron homeostasis. The periplasmic sensor domain of histidine kinase VgrS senses extracellular iron ions (Fig. 1). However, detailed mechanism for regulating iron homeostasis by the two-component system has not yet been elucidated. Here, we examined the structure-function relationships of *X. campestris* VgrS in detail.

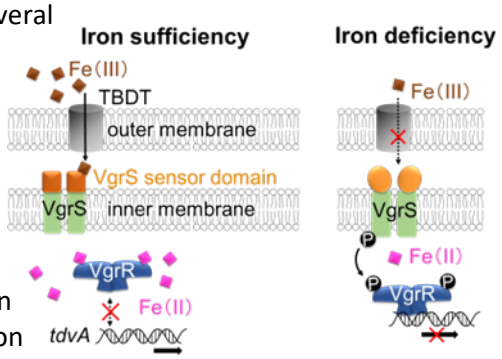

Fig. 1 Model Mechanism of VgrS/VgrR

To determine the stoichiometry of metal ion binding to VgrS sensor domain, ICP analyses was carried out, which revealed that VgrS sensor domain bound 2.5 equivalents Fe(III) or 1 equivalent Mn(II) or Co(II), respectively (Fig. 2). The ExxE motif in VgrS seems to be a metal binding site at which Fe(III) binds. To elucidate iron sensing mechanism of VgrS based on the structure, we prepared three constructs of the sensor domain of VgrS composed of Met1-Thr100, Met1-Met87, and Met27-Met87, respectively, to determine their crystal structures. The single crystal was obtained for the truncated sensor domain composed of Met27-Met87 while two other samples were not crystalized. In this poster, we will discuss iron sensing mechanism of VgrS based on the structure.

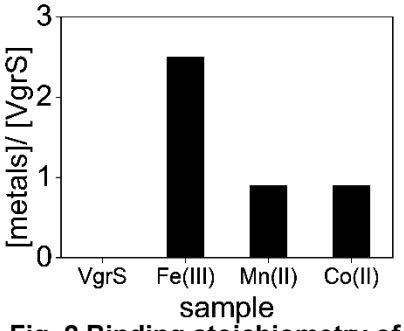

Fig. 2 Binding stoichiometry of metal to VgrS sensor domain

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Abstract Number: 96

Construction of Artificial Protein Assembly Using Heme Substitution Based on the TPP-based Supramolecules

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Heme substitution is one of the most powerful methods to alter the function of hemoproteins, which allows to construct artificial biocatalysts, biosensors, and supramolecular assemblies. Unfortunately, the available synthetic complexes for heme substitution are generally limited to those like heme because heme-binding sites of general hemoproteins strictly recognize the structure of heme. In contrast, heme acquisition system protein A (HasA) having its unique heme-binding site highly exposed to the solvent (Figure. a) can capture various synthetic complexes other than heme such as iron(III)-salophen and iron(III)-phthalocyanine.[1] Recently, we have found that HasA can capture iron(III)-tetraphenylporphyrin (Fe-TPP), which is the first example of a stable complex between a hemoprotein and a TPP derivative (Figure. b).[2] Focusing on the crystal structure of Fe-TPP HasA complex (Figure. b), Fe-TPP is coordinated by His32 and Tyr75 of HasA in the same manner as heme, and some phenyl groups of Fe-TPP are exposed to the solvent.

In this study, we have attempted to introduce an additional metal coordination site to HasA through TPP derivatives (Por-Ligand) inspired by TPP-based supramolecules, leading to formation of HasA assemblies based on metal coordination (Figure. c).[3] Since TPP derivatives have been applied to building blocks of supramolecular architectures in the field of coordination chemistry, we expected that the reported TPP derivatives can be utilized to develop artificial HasA assemblies. We incorporated Por-ligand into HasA in the similar method to metalloTPPs[2] and confirmed successful incorporation based on UV/Vis spectroscopy and ESI-TOF-MS. Moreover, the results of size-exclusion chromatography indicate that addition of some metal ions induced dimerization of HasA containing Por-Ligand. In order to identify the resulting dimer, structure analyses are undergoing.

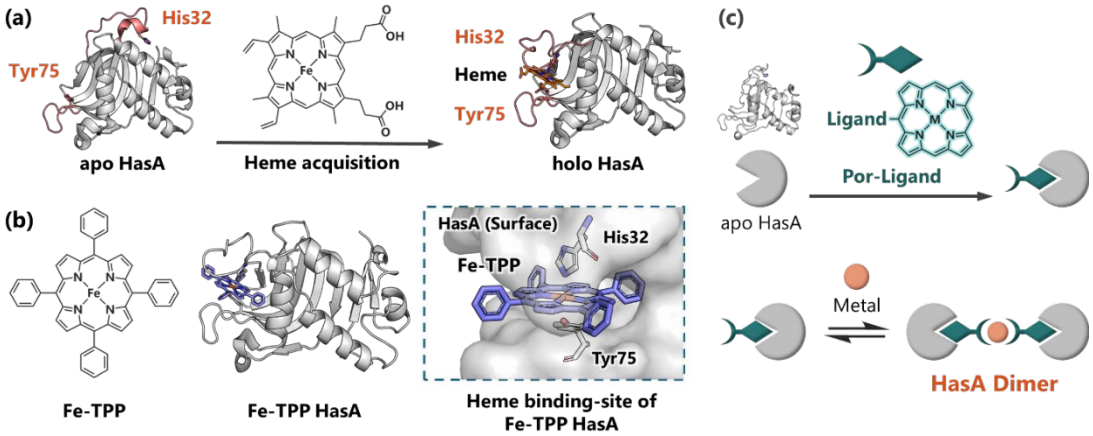

Figure. (a) The crystal structures of the heme-free form (apo form) and the heme-bound form (holo form) of heme acquisition system protein A (HasA), (b) The structure of Fe-TPP and Fe-TPP HasA, (c) The schematic view of dimerization of HasA using metalloTPP derivatives bearing a metal coordination site.

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Abstract Number: 99

Mechanistic Study of Bis(dithiolene) W-oxo Complex: Identifying Proton Transfer and Potential-Directed Pathways

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Dithiolene species have been found in molybdenum- and tungsten-containing oxotransferase and hydroxylase enzymes, as well as in formate dehydrogenase (FDH) and formylmethanofuran dehydrogenase (FMDH), used for converting of carbon dioxide to acetate or methane in organisms.[1] These enzymes facilitate multiple proton/electron transfers and proceed catalytic reactions with high efficiencies. Inspired by these enzymes, several groups have reported the coordination of dithiolene ligands to transition metals such as Co, Ni, and Fe.[2-5] Due to their easy one-electron transfer and unique electronic structure, low-valent metal complexes with bis(dithiolene) ligands exhibit unusual ligand-based interactions and numerous mechanistic and kinetic studies were reported.[6] Recently, electrochemical exploration using high-valent W complex with dithiolene ligands has been undertaken, which proposed a catalytic reaction mechanism involving intramolecular hydrogen evolution between W-OH and W-hydride in $W^{IV}OH(H)$ intermediate using DFT calculation.[7]

Herein, we investigated the electrochemical behaviors of Bis(ditholene) W-oxo complex with several proton sources and examined the W-oxo intermediates. As a result, we could observe a unique anodic shift after the electrochemical reaction and determine a new reaction pathway of proton reduction. In this poster, we will discuss the current understanding of the Bis(ditholene) W-oxo complex and propose a new catalytic pathway for proton reduction using DFT calculation.

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Abstract Number: 104

What We Can Learn from Nature's Toolbox: Lanmodulin-inspired Lanthanide-binding Peptides

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Our modern lifestyle strongly depends on lanthanides (Lns) as this group of metals are essential for many technological devices. Even though these elements are not rare, their mining and separation is extremely environmentally harmful, energy consuming and ponderous. The steadily increasing demand for Lns underlines the need for alternative green solutions for more environmentally friendly mining and separation methods as well as for Ln-recycling from end-of-life products.[1] One source of inspiration to develop such methods is nature as it is now well established that Lns are biorelevant. Of particular interest are Ln-binding proteins such as lanpepsy[2] and different lanmodulins.[3,4]

We used the protein lanmodulin which was isolated from *M. extorquens* AM1[4] as inspiration for short peptides with the goal to understand the remarkable features of lanmodulin as well as finding peptides suitable for the development of e.g. Ln-recycling methods by understanding nature's binding-sequence step-by-step.[5] The Ln-binding of the peptides was investigated for a selection of Lns *via* time-resolved laser-induced fluorescence spectroscopy (TRLFS) combined with parallel factor analysis as well as with isothermal titration calorimetry. To monitor structural changes circular dichroism spectroscopy (CD) was used in combination with molecular dynamics (MD) simulations and nuclear magnetic resonance (NMR) spectroscopy to gain a structural understanding of the formed complexes. Furthermore, the peptides were also tested for their potential for actinide-binding with Cm(III). We show that lanmodulin-inspired peptides have a low µM affinity for Lns and are an excellent starting point for developing bio-inspired chelators for environmentally friendly Ln-recycling, separation and mining methods.

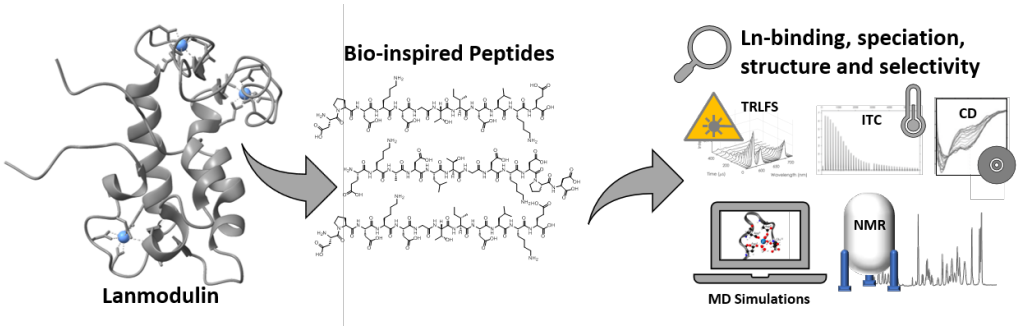

Figure 1 Graphical representation of the workflow and used analytical methods.

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Abstract Number: 115

Tantalum Based Metal Oxides for the Photocatalytic Degradation of PFAS

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There is an imminent need to develop degradation pathways for Per- or Polyfluoroalkyl Substances (PFAS) to relieve current global contamination. PFAS are toxic, ubiquitous and consist of the C-F bond which is recalcitrant to current degradation processes. This study considers tantalum-based perovskite metal oxides for the photocatalytic degradation of PFAS molecules. $ATaO_3$ (A = Li, Na, K) photocatalysts are among the most efficient photocatalysts reported to date.[1] However, their wide band gap (>3.5 eV) requires UV light which renders their use cost-prohibitive in most applications.[1] Since there is no alternative for PFAS remediation, photocatalytic degradation with UV light is a viable option.[2] Furthermore, the wide band gap gives the photocatalyst a large redox potential to drive the reduction/oxidation of the C-F bond.

$ATaO_3$ (A = Li, Na, K) were first synthesised via a solid-state high temperature synthesis with varying La mol% doping, following previous studies.[1] The band gap of the photocatalysts were determined from UV-Vis DRS, the crystal structure was determined by powder XRD, and the morphology and particle size were analyzed by SEM. Degradation reactions with PFAS were conducted in a continuous flow reactor system under UV-LED irradiation. PFAS conversion was monitored by Liquid Chromatography-High Resolution Mass Spectrometry (LC-HRMS) and fluoride was quantified using an ion selective electrode. Our results highlight the effect of La doping mol% and the A site element on photocatalytic PFAS conversion efficiency, and selectivity toward producing fluoride.

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Abstract Number: 117

Molecular structure, spectroscopic analysis, Frontier molecular orbital analysis, Molecular Docking and *in vitro* DNA binding studies of osmium(ii)-cymene complexes with aryl phosphine assemblies

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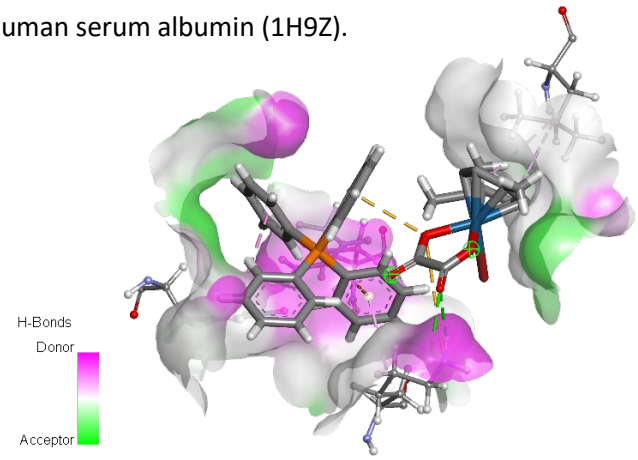
Non-covalent interactions play an important role in biological systems. The outer coordination sphere components can be manipulated through ligand modification to direct the reactivity of the complex. In this study, the molecular structures of the novel complexes $PPh_4[Os(\eta^6\text{-cymene})Br(\kappa^2\text{-}O,O'\text{-}C_2O_4)]$ (**1**) and $[Os(\eta^6\text{-cymene})(\kappa^2\text{-}O,O'\text{-}C_2O_4)PPh_3]$ (**2**) have been determined using X-ray crystallography and secondary coordination sphere interactions were investigated by Hirshfeld Surface Analysis (HAS).[1] The osmium complexes were docked against human serum transferrin, human serum albumin and DNA duplex. Molecular docking results showed significant differences in the binding energies of the two complexes with DNA. *In vitro* spectroscopic DNA binding data suggest that both complexes interact with DNA *via* intercalation due to strong π-π* stacking interaction between the DNA base pairs and aromatic chromophores of the complex.[2] Results in these study were found to be in agreement with *in silico* docking studies carried out to investigate the interactions of the complexes with human serum albumin (1H9Z). The optimized molecular geometries, energies of frontier molecular orbitals and chemical properties of these complexes were calculated using Density Functional Theory (DFT) methods.

Figure 8: Interaction of human serum albumin (1H9Z).



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Abstract Number: 118

Photo-triggered Nitric Oxide Transporter for Selective and Controllable Treatment of Retinal Vascular Occlusion

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Retinal vascular occlusion is a leading cause of visual impairment, but there is currently no effective treatment method available.[1] Despite various attempts to treat retinal vascular occlusion, such as vasodilators, ocular massage, and anterior chamber paracentesis, a suitable treatment strategy has yet to be developed.[1] Nitric oxide is a gaseous signaling molecule that serves as a vasodilator in various physiological processes in biological systems.[2] However, nitric oxide has a high diffusion rate and radical character, which limits its direct handling. Hence, it is important to study nitric oxide transporters with high stability and selectivity.[3] Here, we present a novel approach to pierce obstructed blood vessels using iron–nitrosyl complex, $[Fe(TBDAP)(NO)(H_2O)]^{2+}$ (TBDAP = *N,N*'-di-*tert*-butyl-2,11-diaza[3.3](2,6)pyridinophane), as a spatiotemporally controllable nitric oxide transporter. The iron–nitrosyl complex was synthesized and precisely characterized by various physicochemical methods, including X-ray crystallography. In animal models, the photo-responsive iron–nitrosyl complex was found to effectively dilate normal retinal blood vessels, and nitric oxide was delivered immediately using light to lead to reperfusion of occluded retinal blood vessels in animal disease models. These findings provide a promising and unprecedentedly selective and controllable treatment option for acute vascular occlusive diseases, including cardiovascular and cerebrovascular diseases.

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Abstract Number: 129

New metal based photocatalysts for the generation of biocompatible polymer hydrogels

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The field of tissue engineering aims to regenerate, repair and replace dysfunctional or deceased tissue/organ, providing a promising solution to the current issues faced with organ transplantation. To date, several biomaterials have emerged as potential tissue engineering scaffolds, but none have successfully facilitated the formation of functional tissues that can be used to replace a deceased organ. Hydrogels, a class of polymers that are reported to allow good permeability and diffusion of nutrients and oxygen through the network to the encapsulated cells have arisen as potential candidates as cell encapsulation matrices. In order to fabricate cell-laden hydrogels with good spatio-temporal resolution and tailorable mechanics, the photoinitiators that are pivotal in driving photopolymerization reactions are needed. Lim and co-workers have recently shown that visible light and $[Ru(bpy)_3]^{2+}$ as a photocatalyst can be exploited to photopolymerization functional biocompatible polymer hydrogels.[1] However, the photocatalysts activated by 600-800nm light sources are more desired considering the tissue optical window.
In the current project, a family of metal-based and boron-based photoredox catalysts are synthesized, tested and used to develop robust biocompatible polymer hydrogel gels for tissue engineering.

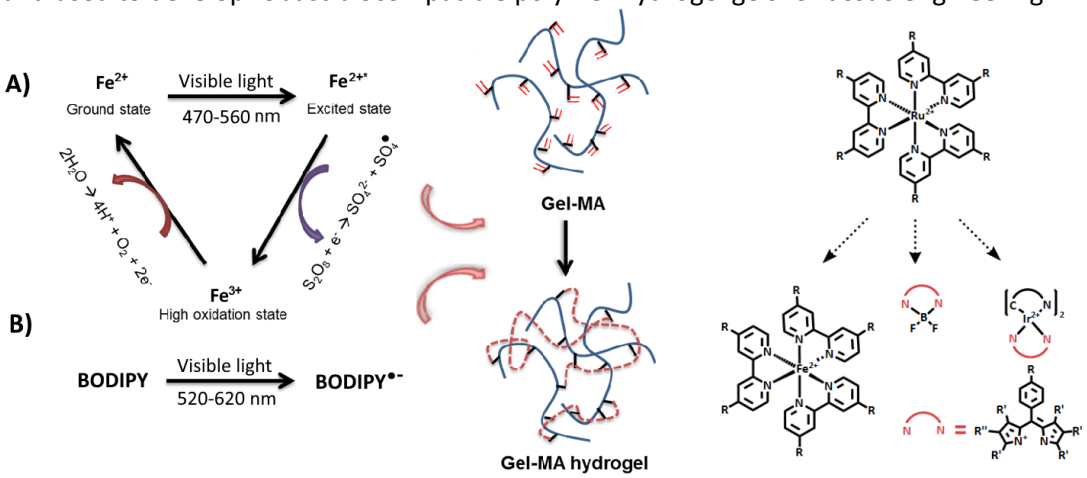

Figure 1. Schematic of the Gel-MA crosslinking process and candidates to replace Ru^{2+} based photoredox catalysts.[1-3]

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Abstract Number: 130

Complementarity of self-assembled metallo-supramolecular structures

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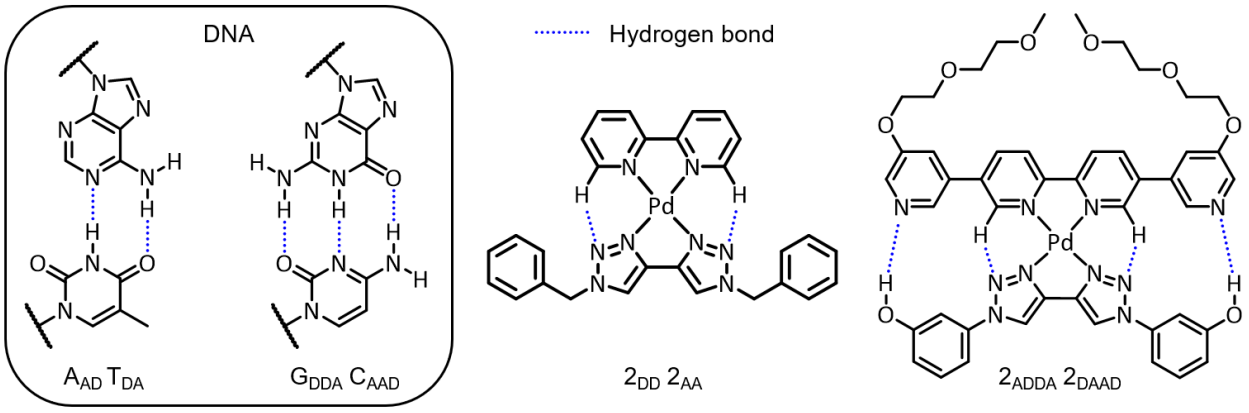
The fidelity of nature's biological molecules is overwhelmingly decided by the complementarity of its systems. One such example is DNA, where the base pairs are strictly encoded for according to favourable hydrogen bonding (Figure, left). Metallo-supramolecular structures offer a viable system for synthesising biomimetic architectures. These structures are formed via a reversible self-assembly process, typically generating a complex that is cyclic or highly symmetric.[1-4]

In contrast, our work seeks to dramatically increase the complexity and reduce the symmetry of these systems by expanding on the complementarity of the ligands. This has already been achieved with bidentate ligands forming an asymmetric heteroleptic complex (Figure, middle). Examples using denticity as a means of complementarity have also been reported.[5] We seek to expand on this set of orthogonal complementary pairs by creating new homoleptic and heteroleptic systems with additional ancillary hydrogen bonding sites (Figure, right). This methodology will produce a large set of orthogonal complementary pairings, which can then be drawn upon to produce systems of even greater complexity and lower symmetry. Stimuli responsive functional groups can also be incorporated into these systems, allowing better control and drawing further comparison to nature.



Examples of existing (left, middle) and proposed (right) orthogonal complementary pairs

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Abstract Number: 131

Lanthanide molecular sensors for the detection and correlation of G-series organophosphorus chemical warfare agents and simulants

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The detection of organophosphorus chemical warfare agents (OP CWAs) is of critical importance for national security and defence purposes. Due to the dangers and restrictions associated with utilising organophosphorus nerve agents in a research environment, chemical simulants are often substituted in their place to mimic select properties. While simulant usage within research is generally accepted,[1] there is a lack of simulant to agent correlation within the field. Therefore, continued use of simulants is based off of previous literature entries as opposed to rigorous and or informed selection.

The work here aims to approach this question through a novel lanthanide molecular sensor system. The design of the novel lanthanide sensor utilises a macrocycle for lanthanide chelation and thermodynamic stability,[2] with a reactive group bound to the antenna that is capable of binding the OP CWAs. A key part of this design is that the OP CWA and or simulant will act as the bridging group to initiate the luminescence turn-on effect of the sensor; working in tandem with both the antenna as well as through coordination with the lanthanide center. This poster will describe the up-to-date work on the project thus far, involving the synthesis of the novel lanthanide sensor and the intended synthesis of the ligand analogue. Analysis of the sensor will include fluorimetry, x-ray crystallography, 13C & 1H-NMR spectroscopy, as well as 31P-NMR spectroscopic binding/interaction studies with G-series OP CWA simulants diethylchlorophosphate (DCP) and diisopropylfluorophosphate (DiFP). Simulant findings will be utilised as a reference model for intended correlation studies with OP CWAs.

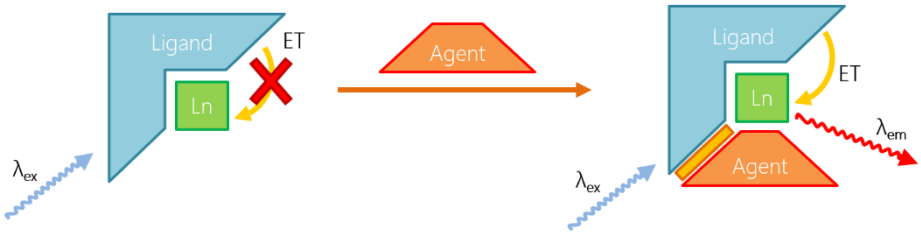

Figure 1. An example of the novel lanthanide sensor system, utilising a turn-on effect in the presence of an organophosphorus chemical warfare agent.

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Abstract Number: 134

Gallium(III) fluoroquinolonate complexes against multidrug-resistant bacteria

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The last decade has seen an emergence of multidrug-resistant (MDR) bacteria in community and hospital environments, enhanced by the broad misuse of antibiotics, resulting in a global public health issue.[1] Considering the impact of antimicrobial resistance there is an urgent need for the development of novel antimicrobial agents.

Bacteria can develop resistance easily to organic antimicrobial compounds compared to metal-based antimicrobials. This is due to bacterial metal import systems not being able to discriminate well between metal ions that are necessary for bacterial survival and ions that will harm them. Bacteria often require an exogenous iron source for their cellular activity. Ga(III) shares chemical similarities with iron(III) in charge, ionic radius and preferred coordination number therefore, it has become a potent inhibitor of important iron pathways. Unlike iron, Ga(III) is unable to be effectively reduced from 3^+ to 2^+ which is required for cellular iron pathways. Thus Ga(III) can be uptaken by bacterial cell instead of Fe(III) which leads to metabolic distress and cellular death.[2] Several gallium(III) compounds are known to be effective antimicrobial agents with observed activity against multidrug resistant bacteria.[3]

We are interested to synthesise and evaluate the activity of novel Ga(III) fluoroquinolonates complexes towards MDR bacteria. The goal is to repurpose the quinolones, many of which are no longer effective toward MDR, by combining with a metal (gallium III) centre to reinvigorate their antibacterial activity. In this presentation, we report the synthesis, characterisation and evaluation of biological application of a series of heteroleptic Ga(III) complexes (Figure 1).

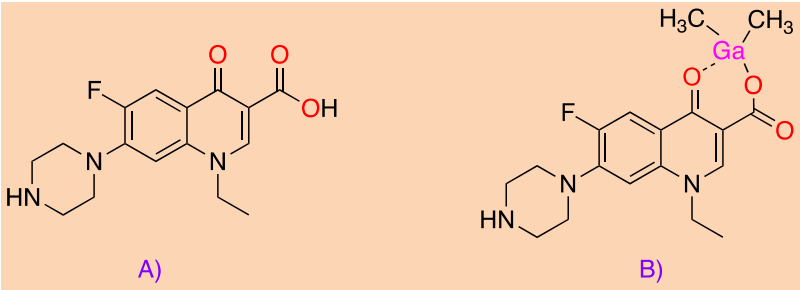

Figure 1: A) structure of Norfloxacin, B) structure of dimethyl gallium(III) norfloxacinate complex.

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Abstract Number: 137

LIBS-NIR combined technique for accurate diagnosis of gallbladder cancer utilizing both elemental and molecular information on human bile juice

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Laser-induced breakdown spectroscopy (LIBS) is an elemental analysis technique that utilizes optical emission with minimal sample preparation, while near-infrared (NIR) spectroscopy is an optical-absorption-based technique that provides information on molecular structures. In this study, we aimed to improve the diagnosis of gallbladder cancer (GBC) by combining LIBS and NIR techniques. We applied this LIBS-NIR combination to analyze bile juice samples from 50 patients (17 with gallbladder polyp, 26 with gallstone, and 7 with GBC) and 6 normal individuals, revealing the variations in elemental content and metabolite composition associated with pancreaticobiliary diseases.

The intensity ratios of emission lines observed in LIBS spectra or those of NIR absorption bands alone could not discriminate GBC cases from other gallbladder conditions. Therefore, we combined data from LIBS and NIR to enhance the accuracy of GBC identification. Combining the intensity ratio of the emission line of Na and that of K observed in LIBS spectra with the second NIR principal component scores significantly increased the discrimination accuracy for GBC cases from the others.

The use of complementary information from both spectroscopic techniques allowed us to better discriminate GBC from normal/gallstone/GB polyp cases, thus providing a more accurate diagnosis of this disease.

Abstract Number: 140

Aromatic C-H Bond Oxidation and Electron Transfer Reactivity of High-Valent Manganese(IV)-Hydroxo Species

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The development of a catalyst for C-H bond activation of hydrocarbons under mild conditions is a major challenge in environmental and biological chemistry.[1] Herein, a manganese(IV)-hydroxo complex, $[Mn^{IV}(CHDAP\text{-}O)(OH)]^{2+}$ (**2**), was reported, where it was synthesized and characterized by various physicochemical measurements, such as ultraviolet–visible (UV–vis), electrospray ionization-mass spectrometry (ESI-MS), electron paramagnetic resonance (EPR), and helium-tagging infrared photodissociation (IRPD) methods.[2] Redox titration of **2** gives a one-electron reduction potential of 0.93 V vs SCE. **2** was generated from a transient green species identified to a manganese(IV)-bis(hydroxo) complex, $[Mn^{IV}(CHDAP)(OH)_2]^{2+}$ (**2'**), which performs intramolecular aliphatic C–H bond activation. The kinetic isotope effect (KIE) value of 4.8 in the intramolecular oxidation was obtained, which indicates that the C–H bond activation occurs via rate-determining hydrogen atom abstraction. Moreover, under ambient conditions, **2** can perform the oxidation of C-H bonds of aromatic compounds, anthracene and its derivatives. The KIE value of 1.0 was observed in the oxidation of anthracene. The rate constant (k_{et}) of electron transfer (ET) from *N*,*N*'-dimethylaniline derivatives to **2** is fitted by Marcus theory of electron transfer to afford the reorganization energy of ET (λ = 1.59 eV). The driving force dependence of log k_{et} for oxidation of anthracene derivatives by **2** is evaluated by Marcus theory of electron transfer.[3] Aromatic C-H bond hydroxylation occurs via the rate-determining electron-transfer pathway based on detailed kinetic studies, such as the KIE value and Marcus theory of outer-sphere electron transfer.

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Abstract Number: 142

Developing luminescent lanthanide fibre optic sensors for reactive species – a key to early cancer detection

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Reactive oxygen species (ROS) is a group of highly reactive chemicals that regulate the antioxidant defence system in biological systems.[1, 2] Oxidative stress conditions, resulting from an imbalance in the ROS levels are associated with cancer, neurodegenerative diseases, and other pathologies.[1] Measuring ROS provides critical information on metabolism that can be used as an indicator for cancer. While much progress has been made to develop systems which can report on ROS with high sensitivity and specificity, there is a still an unmet need for technology which can achieve multiplex, real-time, *in vivo* measurements. Lanthanide complexes offer an ideal basis for developing fibre optic sensors as they are less prone to photobleaching (compared to organic fluorophores), emit across a range of wavelengths that can be exploited for multiplex sensing and can be matched with antennas to produce specific signals when reacted with different ROS species.[34] The fibre optic system can be used to provide the excitation and give a readout in real-time. Also, fibre optic cables are small enough to fit in a hypodermic needle, thus can be used for *in vivo* measurements without tissue destruction.

In this presentation we will report the synthesis, isolation, and characterisation of a range of responsive probes based on a napthalimide antenna. Promising data has already shown that the presence of HS- anion can be detected through the reaction of N_3 to NH_2 using a fibre optic setup (**Fig 1**).

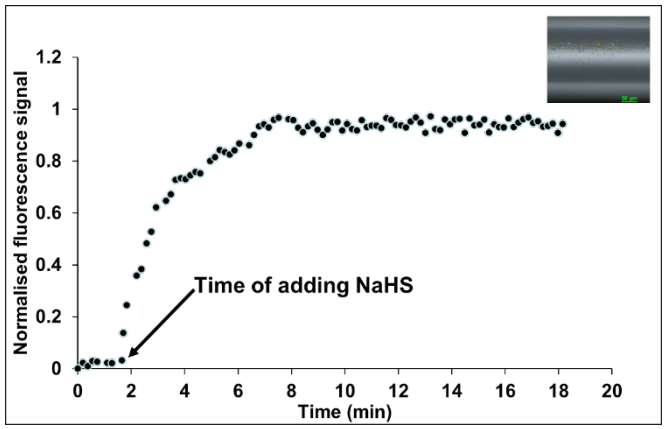

Fig 1. A fibre optic cable coated with a hydrogen sulphide sensor shows a significant increase in fluorescent signal. This was useful for proof of concept awaiting lanthanide complex synthesis.

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Abstract Number: 145

Effects of structures of bis N-heterocyclic carbene ligands in M3S2 complexes on their reactions with silver(I) ion

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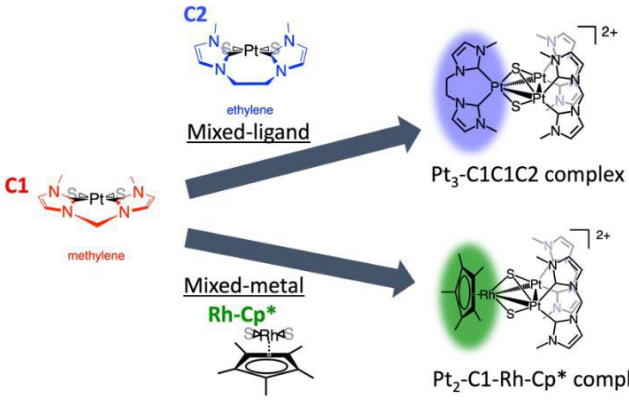
Sulfur-containing metal complexes have attracted much attention because they are related to metalloenzymes having a transition metal-sulfide core as activate sites for catalysis.

N-Heterocyclic carbenes (NHCs), which are well-known as strong σ-donors, form stable metal-carbon bonds leading to high stability of their complexes. Furthermore, bidentate NHC ligands (bisNHCs), in which an alkylene chain connects two NHC units, provide a rigid framework for their complexes through the chelate effect. For such bisNHC ligands, modification of the arrangements of two NHC moieties toward coordination planes of metal centers is possible by changing the lengths of the alkylene bridges. Dihedral angles between each NHC plane in a bisNHC ligand and the coordination plane of the metal center are varied with the alkylene bridges. The steric hindrance around the metal center can be controlled by using the chelating bisNHC ligands with a variety of alkylene bridges.

We previously reported the reactions of Pt3S2 complexes with Ag(I) ion. In the reaction of a Pt3S2 complex bearing the methylene-bridged bisNHC ligands with Ag(I) ion, the Ag ion bridges Pt–Pt bond to form a heptanuclear cluster.[1] On the other hand, in the cases of the reaction of a Pt3 S2 complex bearing the ethylene-bridged bisNHC ligands, the Ag(I) ion bridges sulfide ligands to form a different type of a heptanuclear complex.[2] These results suggested that the reaction sites of the complexes are controllable by the steric hindrance around the metal-sulfide core. In this study, we examin mixed-ligand or mixed-metal M3S2 complexes, which consist of diplatinum complex units with the methylene-bridged bisNHC and a Pt-bisNHC moiety with the ethylene bridge or a Rh-Cp* unit, respectively, and the reactions of the complexes with Ag(I) ions to evaluate the effect of dihedral angle of bisNHC ligands on reactions of metal-sulfide core in the M3S2 complexes.



Mixed-ligand and mixed-metal M3S2 complexes

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Abstract Number: 146

C-S bond formation using palladium thiolato complexes bearing sugar-incorporated N-heterocyclic carbene ligands

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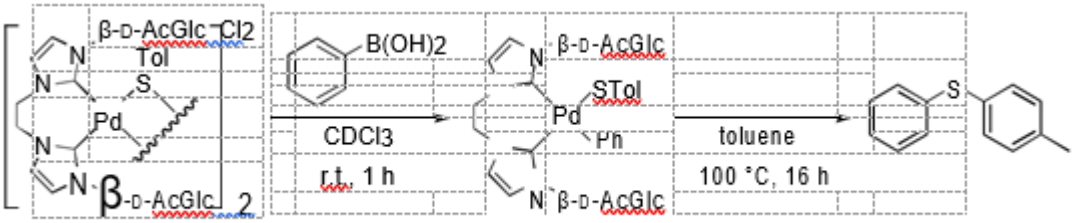
C-S coupling reactions are useful to construct frameworks of sulfur-containing organic molecules. However, due to the high affinity of sulfur and late transition metals, transition metal complex catalysts, such as palladium complexes, are hardly efficient catalysts. In a catalytic cycle of the C-S coupling reactions, bis-thiolato complexes suggested to be resting states.

We previously reported palladium complexes bearing sugar-incorporated N-heterocyclic carbene (NHC) ligands and their catalytic activities on the C-C coupling reactions.[1-3] The glucopyranosyl moieties are bulky substituents and incorporation of the moieties into NHC ligands of transition metal complexes could promote reductive elimination in the catalytic cycle of the C-S coupling reactions.

In the point of these views, we investigated palladium thiolato complexes with chelating bis-NHC ligands bearing acetyl-protected glucopyranosyl (AcGlc) groups as N-substituents. We synthesized palladium complexes with the bis-NHC ligands, in which two AcGlc-NHC moieties are connected by ethylene or *o*-xylylene groups affording different arrangements of the AcGlc groups around the palladium centers, to evaluate the steric effects.

Bis-*p*-tolylthiolato complexes were synthesized by the reactions of corresponding chloro complexes with slightly excess *p*-toluenethiol. The bis-thiolato complexes react with equimolar amount of the corresponding chloro complexes to afford bis-thiolato bridging dinuclear complexes. A phenyl thiolato complex with the ethylene-bridged bis-NHC ligand was obtained by the reaction of the bis-thiolato bridging dinuclear complex with phenyl boronic acid and the C-S coupling product generated by its thermolysis, while the same reaction did not proceed using the dinuclear complex with the *p*-xylylene bridged bis-NHC ligands. The difference on the reactivity probably due to the position of the AcGlc substituents, which more closely locate to the coordination sites in the complex bearing the ethylene-bridged ligand. Investigation of the detail of the steric effects and catalytic C-S coupling reactions using the complex as a catalyst are in progress.



Formation of palladium phenyl thiolato complex and its thermolysis product

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Abstract Number: 150

Whole-Cell Biocatalysts Expressing P450s Triggered by Fatty Acid Analogs for Pollutant Degradation without Genetic Modification

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Soil contamination is one of the environmental problems caused by toxic compounds including benzene derivatives, polycyclic aromatic hydrocarbons (PAHs) and dioxins. Bioaugmentation, one of the bioremediation methods, is the addition of cultured microorganisms to decompose contaminants. This cost-effective and sustainable technology can allow rapid degradation of persistent organic pollutants (**Fig. 1**). However, the number of bacterial species which had been practically used for this purpose is limited so far. This is because it is necessary to avoid negative impacts resulted from the used bioremediation methods on the surrounding ecosystems and human body.

P450BM3 isolated from *Priestia megaterium* (*Bacillus megaterium*) catalyzes direct functionalization of unactivated C-H bonds of long-chain fatty acids with high monooxygenase activity. Our group developed a unique reaction system called “the substrate-misrecognition system” using “decoy molecules”. The decoy molecules are inert dummy substrates with shorter chains and allow non-native hydroxylation reactions such as benzene hydroxylation by providing suitable space for small organic molecules.[1] Moreover, whole-cell biotransformation of benzene to phenol was achieved using a type strain of *P. megaterium* and recombinant *E. coli* cells expressing P450BM3 by simply adding the decoy molecule to cell suspension (**Fig. 2**).[2] This suggested that even species which are conventionally excluded from consideration can be utilized as potential bioreactors using decoy molecules. Also, this implied microorganisms with no pollutant-degrading ability can become novel bioremediation tools without genetic modification.

In the present study, we tested 11 bacterial species harboring homologs of P450BM3 whether they can hydroxylate benzene and the other several aromatic compounds in the presence of the decoy molecules.[3]

References

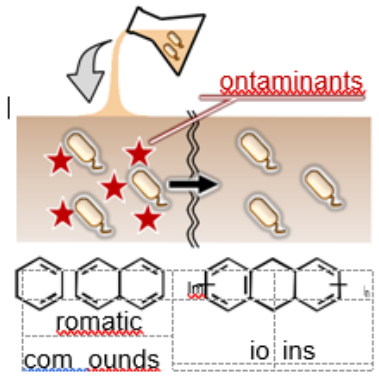

Fig. 1 Bioaugmentation.

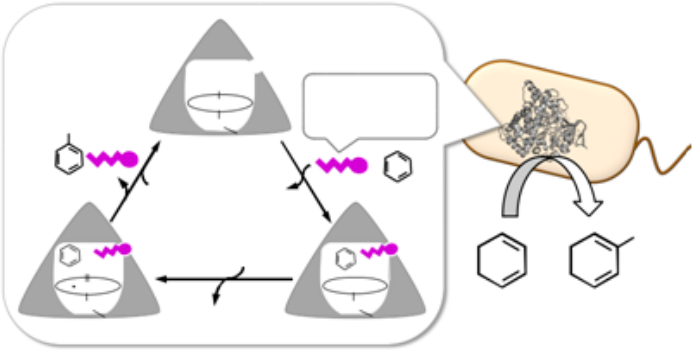

Fig. 2 Whole-cell biotransformation of benzene to phenol based on the substrate-misrecognition system.

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Abstract Number: 151

Impact of Lanthanides on the Activity of Lanthanide-Dependent Methanol Dehydrogenase in *Methylacidiphilum fumariolicum* SolV

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In recent years, lanthanides (Lns) have been firmly established to be biological relevant and widespread in divers eco systems.[1] In 2014, Pol *et al*. have discovered the strictly lanthanide-dependent acidophilic methanotroph *Methylacidiphilum fumariolicum* SolV in a volcanic mudpot.[2] SolV requires Lns in the active center of the pyrroloquinoline quinone (PQQ)-dependent methanol dehydrogenase (MDH) which is an essential enzyme for the growth of SolV. Methanol is oxidized while the PQQ cofactor is reduced which is regenerated through electron transfer to a cytochrome. Growth of SolV highly depends on the supplied Lns and diminishes across the series.[2,3] Similar trends were obtained using an artificial dye assay to assess the activity of MDH *in vitro*. Daumann and co-workers revealed that the enzyme activity increases if Nd^{3+} and Pr^{3+} were added to a partially occupied Eu-MDH and that the activity declines subsequently.[4,5] Another *in vitro* method to assess MDH activity is using the physiological cytochrome *cGJ* of MDH.[6,7] Preliminary experiments show a comparable trend although kinetic parameters KM and vmax are different indicating a disparate electron transfer mechanism. Indeed, the physiological processes are more complex involving "docking" of *cGJ* to MDH and docking of *cGJ* to a second cytochrome. Herein, we compare and present the differences in MDH activity determined by an artificial electron acceptor and its native electron acceptor. Additionally, we discuss the impact of Lns on the growth of SolV and the discrepancy to its *in vitro* activity.

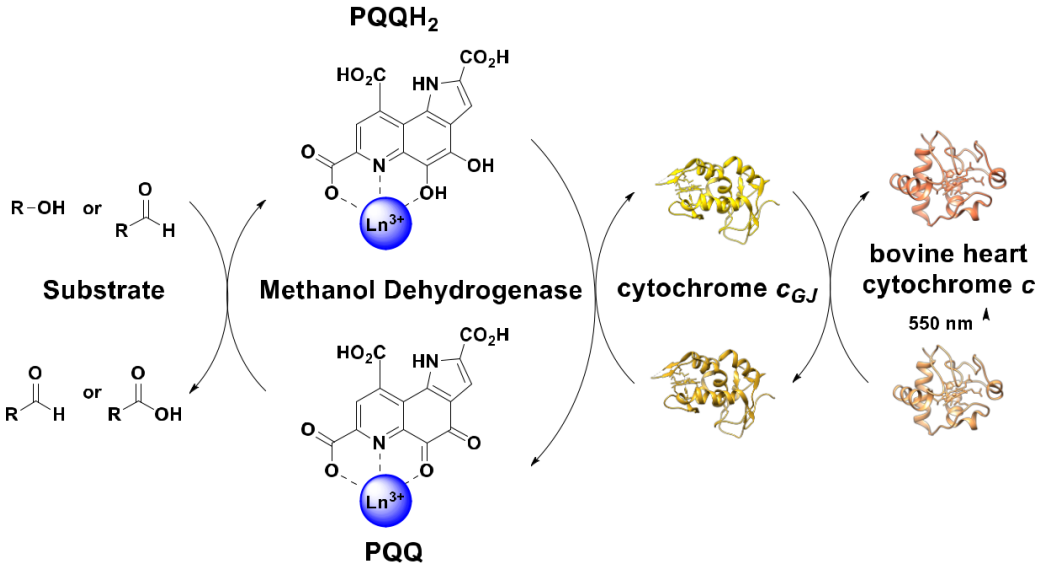

Figure 1 Overview of the MDH activity assay with its physiological cytochrome *cGJ*.[7]

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Abstract Number: 152

Hydroxylation of Gaseous Alkanes Catalyzed by Cytochrome P450BM3-overexpressing *E. coli* with Decoy Molecules

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Hydroxylation of gaseous alkanes is a method to promote use of natural gas as starting material of chemical products. To convert gaseous alkanes directly into alcohols under mild conditions, our research group has focused on cytochrome P450BM3 (P450BM3), a heme enzyme from *P. megaterium*. P450BM3 catalyzes hydroxylation of long-chain fatty acids at sub-terminal positions at an extremely high rate, thus it has been intensively studied for application in catalyzing the oxidation of non-native substrates. We have demonstrated that some amino acid derivatives named decoy molecules can facilitate the hydroxylation of non-native substrates such as benzene and propane by wild-type P450BM3 (Fig. 1).[1] Decoy molecules work to activate the enzyme and create a suitable reaction space for these small substrates. However, the reaction requires a stoichiometric amount of expensive cofactor, NADPH, as electron donors. To overcome this problem, we have established whole-cell biocatalytic hydroxylation of benzene by using P450BM3-overexpressing *E. coli* (Fig. 2).[2] Due to the metabolism and biosynthesis pathways in *E. coli*, the external addition of NADPH and enzyme purification became unnecessary, which leads to saving cost and effort.

In this research, we adapted the whole-cell catalysis to hydroxylation of gaseous alkanes. We succeeded in biotransformation of propane to propanol and developed a screening method for decoy molecules.[3]

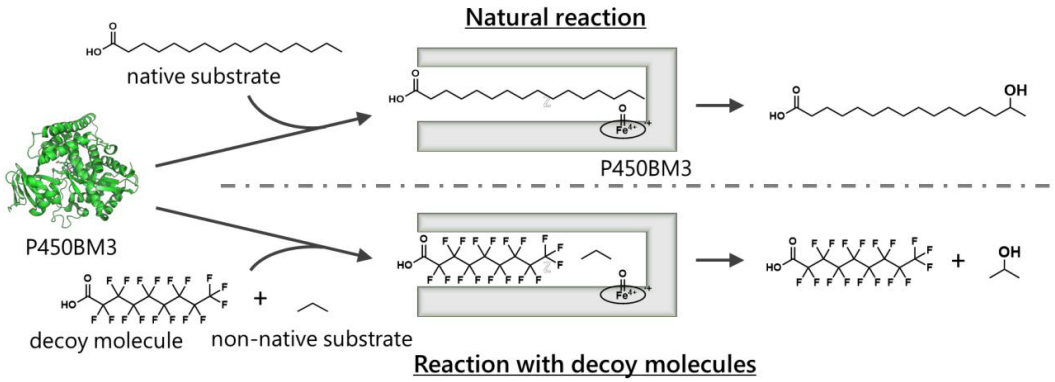

Figure 1 Hydroxylation of native substrate and non-native substrate catalyzed by P450BM3.

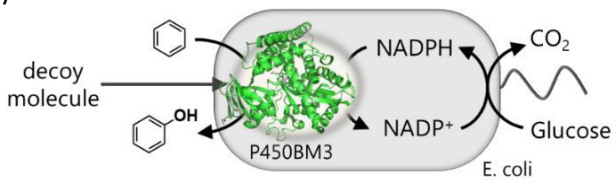

Figure 2 Whole-cell biocatalytic hydroxylation of benzene.

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Abstract Number: 157

Photoactivated Mo(VI)- and W(VI)-Schiff base complexes for biomimetic oxygen atom transfer reactions

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Molybdenum-based complexes containing oxo-ligands are established functional models of oxotransferase enzymes. To mimic the biological single-electron transfer mechanisms, recently reported Mo-[1] and W-catalysts[2] use UV-visible light for photoexcitation, yielding highly active oxygen atom transfer (OAT) agents. During previous investigations in our group,[3-4] it was observed that functional modifications to the tridentate salicylidene-aminophenol (SAP) ligands can promote photoactivation of *cis*-MoO2 and *cis*-WO2 based complexes towards phosphine oxidation (Figure 1a). Catalysts **1**-**12** were synthesised and fully characterised, and their photocatalytic activity for PPh3 oxidation was tested and monitored by ^{1}H NMR. The two most active catalysts, **2** and **5**, showed respective 78% and 97% PPh3 conversion after 3 h irradiation. The catalytic cycle of complex **2** was further investigated using TR-FTIR spectroscopic measurements on the second timescale. Distinctive shifts of the Mo=O bands in the 900-1000 cm^{-1} fingerprint region upon irradiation (Figure 1b) allowed the detection of a postulated monomeric oxo-Mo(IV) intermediate. Variable temperature ^{1}H NMR experiments provided further evidence for monomeric oxo-Mo(IV) species. Computational calculations revealed that upon photoexcitation the C=N bond order is diminished due to the HOMO-LUMO transition. Correspondingly, the N-Mo bond strengthens, whilst the Mo-oxo bonds weaken. Current work is focused on examining the excited states of the catalysts and further catalytic steps using computational simulations, and expanding the catalyst reaction scope towards more complex substrates and products with pharmaceutical or industrial interest.

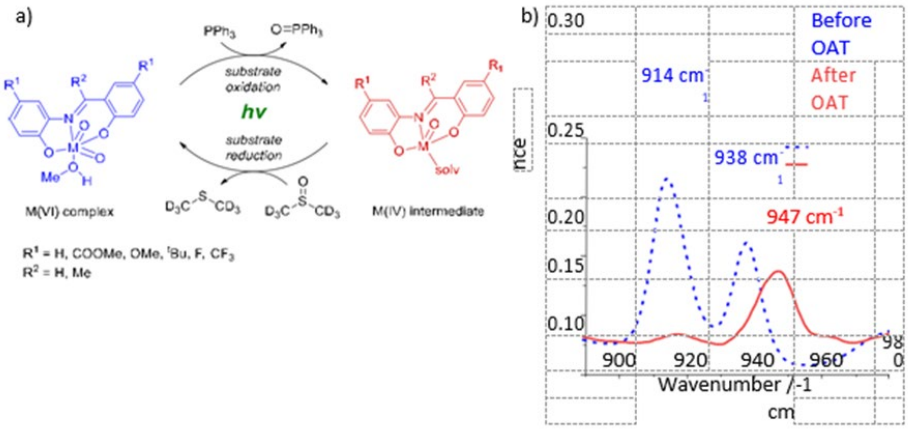

Figure 1. a) General photocatalytic OAT transfer cycle involving MO2-SAP type (M = Mo, W) complexes. 3 FTIR spectrum showing the *cis*-dioxo Mo-catalyst **2** (R^1 = COOMe, R^2 = H) initial state before OAT (blue dashed line) and mono-oxo Mo-catalyst intermediate state after OAT (red solid line).

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Abstract Number: 170

Fine-tuning substrate specificity of a molybdenum-containing sulfoxide reductase – three residues that rule them all

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Bacterial Dor-type S- and N-oxide reductases typically consist of a Mo-containing catalytic subunit that interacts with a membrane-bound cytochrome. MtsZ from *Haemophilus influenzae* (HiMtsZ) and TorZ from *Escherichia coli* (EcTorZ) are closely related enzymes from this group. Despite their nearly 60% sequence identity, research has revealed that HiMtsZ and EcTorZ primarily use methionine sulfoxide (MetSO)[1] and trimethyl amine N-oxide (TMAO)[2], respectively, as a primary substrate.
A previous study suggested that three residues in the substrate binding pocket (HiMtsZ: F157, R166 and H182) may be responsible for the distinct substrate specificity in different Dor-type enzymes[3]. Here, site-directed mutagenesis was used to modify these residues in the HiMtsZ active site to alter its substrate preference profile. We created both a *Rhodobacter capsulatus* DorA DMSO reductase-like enzyme (mutations: F157K, R166T, H182S) and an *E. coli* BisC biotin sulfoxide (BSO) reductase-like enzyme (F157R, R166S). The $MtsZ_{DorA}$ enzyme had a K_M-value of 0.037 mM for DMSO, which is 4-fold lower than that of the $MtsZ_{WT}$ (0.140 mM). Similarly, the K_M_S-BSO of $MtsZ_{BisC}$, 0.273 mM, was reduced 6-times compared to that of the wild-type enzyme. This confirms the hypothesis that only three residues are key to determining substrate specificity in this group of enzymes.
Interestingly, in EcTorZ, these three residues form a pattern that is intermediate to EcBisC and RcDorA, but does not closely resemble a TMAO reductases such as the *E. coli* TorA. In keeping with this, purified EcTorZ showed decent activity with a K_M_DMSO of 0.140 mM, and also a K_M_L-MetSO of 0.290 mM, and we are currently investigating additional substrates for this enzyme and physiological roles.
Overall, this study demonstrates that modifying only two to three residues, in an 813-amino-acid protein, can alter substrate specificity, emphasising that a high sequence similarity does not necessarily equal identical function.

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Abstract Number: 172

An Activity-Based Fluorescent Sensor for Detecting Cu Ions in Living Cells and Multicellular Organisms

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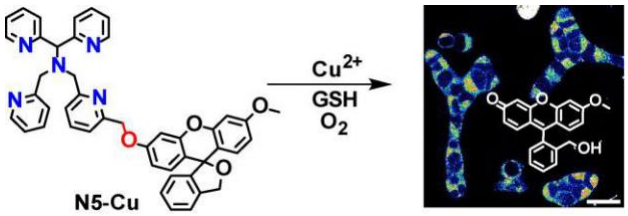
Activity-based fluorescent metal ion sensors comprise of a fluorophore conjugated to a metal binding scaffold.[1] Upon metal binding to the scaffold, a reaction catalyzed by the resultant metal ion complex leads to a bond-cleavage, thereby releasing the fluorophore.[1] This results in an increase in fluorescence intensity that allows metal ion detection. This strategy has significant advantages over other metal ion sensing strategies in which the fluorophore remains linked to the scaffold throughout the sensing event.[1] Since the fluorophore is released, quenching due to the metal ion can be avoided. Further, it might be possible to detect metal ions like Mn^{2+} and Fe^{2+} that are inherently weak binders,[2] as activity-based sensing does not solely rely on the metal-binding event. Finally, the synthesis of activity-based sensors is inherently modular since the dye and scaffold units can be separately synthesized and conjugated. Thus far most activity-based sensors were based on bi-, tri-, and tetra-N donor ligands with a prevalence of ligands with pyridine-N donors.[1] These sensors mostly detected transition metal ions that are stronger binders based on the Irving-Williams series.[1] To explore the effect of increasing the number of N-donor atoms to five, to possibly access sensors for metal ions that are weak binders, we developed a novel activity-based sensor with 5-N donor atoms. The sensor was selective for Cu ions and could detect Cu ions both in living cells and in a zebrafish larval model. The results indicated the need for fine-tuning scaffold design to access sensors for metal ions lower in the Irving-Williams series.[2] The sensor design, sensing mechanism, and biological studies will be presented.



Scheme depicting Cu ion sensing via the novel 5-N donor activity-based sensor

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Abstract Number: 173

Peptides for Targeted Delivery of Pt(IV) Pro-Drugs in the Treatment of Rare Cancers

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Despite the advancements in medicine, many cancers remain untreatable leaving patients with little to no options to help manage or treat their illness. This is the case with Diffuse Intrinsic Pontine Gliomas (DIPG), an incurable and highly aggressive pediatric brain tumor with a prognosis of only 1-2 years.[1] Treatment of DIPG with radiation provides no long-term benefits to patients and surgery is not possible due to the location of the tumor; additionally, the use of current clinically approved chemotherapies is ineffective due to complications in bypassing the Blood Brain Barrier (BBB).[1] The chemotherapies used in treating cancers usually involve Platinum (Pt) – a metal at the crux of various Food and Drug Administration (FDA) approved chemotherapeutics including Pt(II) complexes cis-platin, oxaliplatin and carboplatin. However, Pt(II) complexes have an array of complications including poor solubility and low specificity for cancer cells, and often demonstrate high off-target effects which result in detrimental side effects in patients.[2] Our aim is to overcome these limitations of Pt(II) complexes by synthesizing Pt(IV) 'pro-drugs', with a particular interest in pro-drugs specific for DIPG. By oxidizing a Pt(II) complex into Pt(IV) (Figure 1), an improved solubility, cellular uptake profile and even specificity towards tumor cells can be achieved.[2] Furthermore, the axial positions of Pt(IV) complexes allows for further functionalization with other components; these may include other cytotoxic agents that can increase the potency of pro-drugs towards cancer cells and/or peptides for targeted delivery towards the tumor site. The aim of our research is to synthesize multi-modal pro-drugs involving

2 a Pt(IV) complex, (ii) one or more cytotoxic agents (*e.g.* Histone Deacetylase (HDAC) Inhibitors) and (iii) peptides for specific delivery to cancer cells in DIPG, and explore methods to bypass the BBB. These pro-drugs may reduce off-target effects and improve the prognosis for DIPG patients.

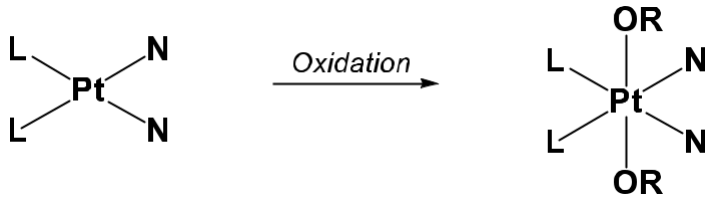

Figure 1: Oxidation of a Pt(II) complex (left) to a Pt(IV) complex (right); L = Ligand, N= nitrogen containing ligand, R= any substituent (*e.g.* peptides).

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Abstract Number: 179

Probing the Mechanism of Action of Clinically Relevant Anticancer Drugs using Novel Click-Functionalisable Pt(II) Complexes

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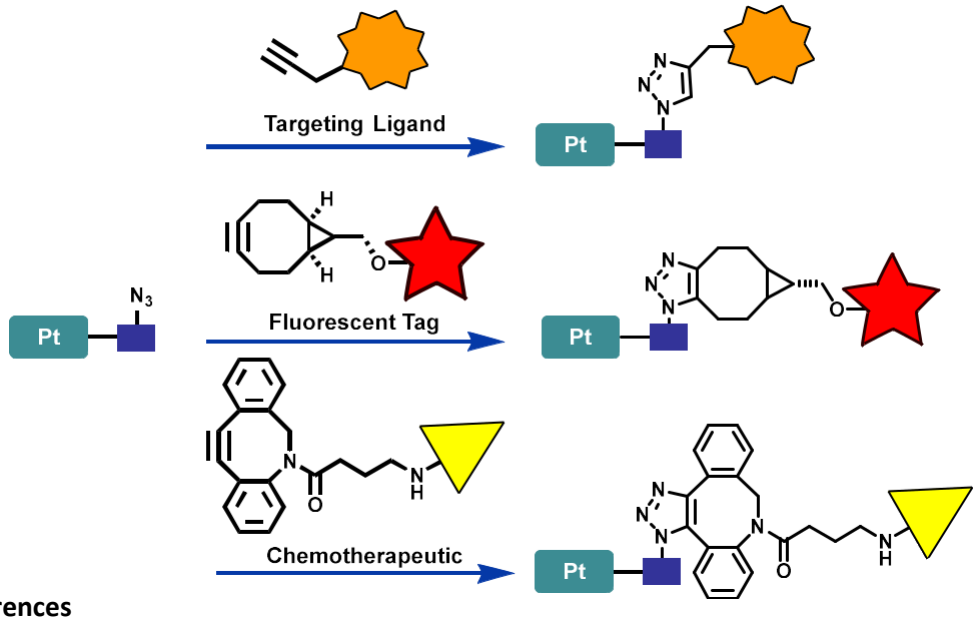
Platinum (Pt)-based drugs such as cisplatin, carboplatin and oxaliplatin play a very important and well-documented role in treating cancer, and are employed in nearly 50% of all anti-cancer regimens today. The primary mechanism of Pt-based drugs has long been associated with their ability to cross-link nuclear DNA; the Pt-DNA adducts interrupt transcription, generate DNA perturbation damage responses and ultimately induce apoptosis. Despite this, reports in recent years have highlighted that different mechanisms may be at play.[1] Moreover, the clinical effectiveness of Pt anti-cancer agents is commonly hampered by toxic side-effects and both intrinsic and acquired resistance mechanisms.[2]

There has therefore been a continued drive to develop novel classes of more effective and better-tolerated Pt(II) and Pt(IV) drug candidates. A better understanding of the precise cellular activity of Pt complexes is needed to achieve this goal.[3] The development of innovative azide-alkyne click based techniques to functionalise Pt(II) and Pt(IV)-based complexes is anticipated to greatly aid this enterprise. Click chemistry is widely used throughout synthetic chemistry and chemical biology, showing tremendous versatility whilst being atom-efficient and in some cases bioorthogonal.[4]

The synthesis of novel Pt(II) click-functionalisable complexes will be presented alongside their use as probes to study the mechanisms of action associated with clinically relevant Pt drugs.



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Abstract Number: 186

Design and directed evolution of noncanonical β-stereoselective metalloglycosidases

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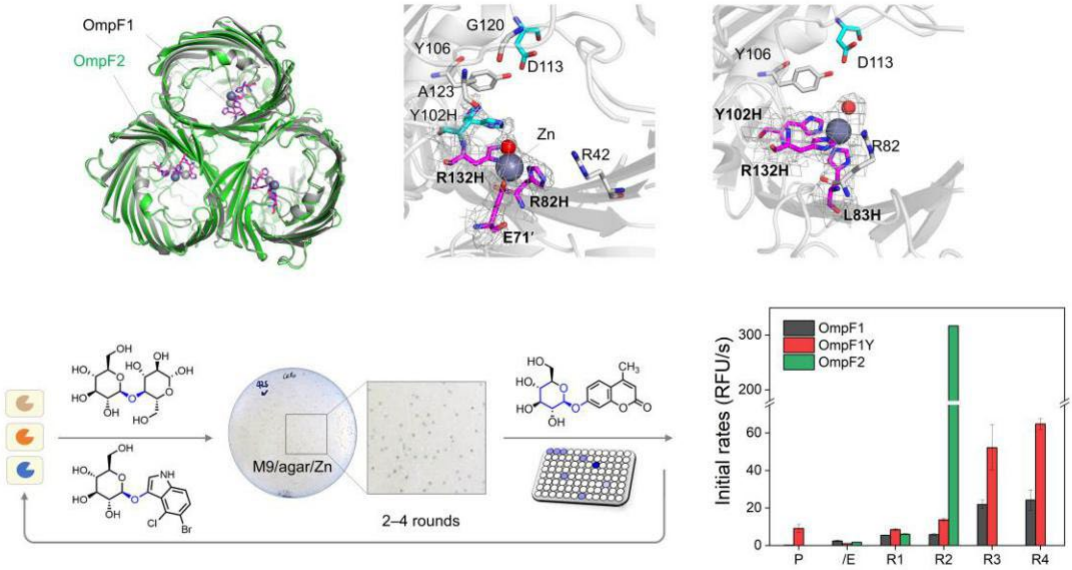
Metallohydrolases are ubiquitous in nearly all subclasses of hydrolases, such as esterase, peptidase, and β-lactamase, utilizing metal elements to activate a water molecule and facilitate its subsequent association into diverse chemical bonds in substrates. However, glycosidases, which react with glycosidic bond in sugars, is an exception. Despite their sequence diversity, very few glycosidases utilize a metal ion for activating a water molecule. Instead, canonical glycosidases primarily use a pair of acidic residues that function as catalytic motifs. Herein, we design three metalloglycosidases by installing a coordinatively unsaturated and hydrolytically active Zn-binding site within a β-barrel-shaped outer membrane protein F (OmpF). Structure- and mechanism-based redesign and directed evolution have led to the emergence of Zn-dependent glycosidases with high catalytic proficiency and high substrate selectivity for β-stereoisomers. Biochemical characterizations suggest that the Zn-binding site constitutes a key catalytic motif with at least one adjacent acidic residue. This work demonstrates that unprecedented metalloenzymes can be tailor-made, expanding the scope of inorganic reactivities in proteinaceous environments, resetting the structural and functional diversity of metalloenzymes, and providing the potential molecular basis of unidentified metallohydrolases and novel whole-cell biocatalysts[1].



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Abstract Number: 188

Targeting Pathogenic Formate-Dependent Bacteria with a Bioinspired Metallo–Nitroreductase Complex

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Nitroreductases (NTRs) constitute an important class of oxidoreductase enzymes that have evolved to metabolize nitro-containing compounds.[1] Their unique characteristics have spurred an array of potential uses in medicinal chemistry, chemical biology, and bioengineering towards harnessing nitro caging groups and constructing NTR variants for niche applications.[2] Inspired by how they carry out enzymatic reduction via a cascade of hydride transfer reactions,[3] we sought to develop a synthetic small-molecule NTR system based on transfer hydrogenation mediated by transition metal complexes harnessing native cofactors. We report the first water-stable Ru-arene complex capable of selectively and fully reducing nitroaromatics into anilines in a biocompatible buffered aqueous environment using formate as the hydride source. We further demonstrated its application to activate nitro-caged sulfanilamide prodrug and provoke oxidative stress *in situ* to potentiate therapeutic effects in formate-dependent bacteria, specifically pathogenic methicillin-resistant *Staphylococcus aureus* (Figure 1). This proof of concept paves the way for a new targeted antibacterial chemotherapeutic approach leveraging on redox-active metal complexes for prodrug activation via bioinspired nitroreduction.

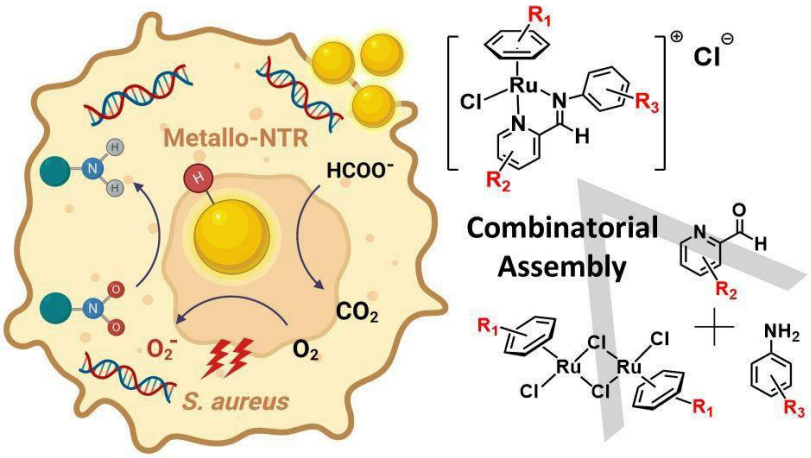

Figure 1. Synergistic nitroreduction and ROS induction mediated by the RAS complex as the Metallo-NTR.

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Abstract Number: 189

Understanding and rational alternation of tetrapyrrole substrate selectivity of nickelochelatase CfbA

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CfbA functions as a nickelochelatase catalyzing a Ni^{2+}-insertion reaction into sirohydrochlorin (SHC), a hydrophilic tetrapyrrole.[1, 2] In the SHC-binding to CfbA, many polar interactions contribute to binding of SHC in an appropriate position of the active site for the Ni^{2+}-insertion.[3] Meanwhile, substrate specificity of CfbA has been explored using some of SHC analogues such as uroporphyrin III (UPIII), uroporphyrin I (UPI), coproporphyrin III (CPIII), coproporphyrin I (CPI) and protoporphyrin IX (PPIX).[4] The exploration demonstrated that UPIII and UPI can be used as substrates but the others not; however, the structure-based substrate recognition mechanism of CfbA for the SHC-analogues was unclear.

To further understand the substrate specificity of CfbA, we performed X-ray crystal structure analysis of CfbA with SHC analogues. UPIII and UPI were visible in the active site, whereas the others not, which is relevant to the fact that UPIII and UPI could be used as substrates. The interactions between UPIII, UPI and SHC to the active sites were distinct each other. UPIII was bound at the equivalent position to SHC. However, UPIII had less polar interaction to CfbA than SHC, which appeared to be related to lower activity for UPIII than SHC. Unlike SHC and UPIII, UPI was positioned at the entrance of active site with polar interactions. This structural feature could also explain low activity for UPI.

Based on these SHC, UPIII and UPI-bound CfbA structures, site-directed mutagenesis was performed to rationally change the polarity of the active site of CfbA. As a result, a change in polarity of the active site via mutagenesis results in alteration of the substrate selectivity. Notably, activity for CPI (**Figure**), which was not a substrate for wild-type CfbA, could be used as a substrate for certain CfbA variant. Therefore, CfbA is a potent biocatalyst for synthesis of a variety of nickel-tetrapyrrole molecules.

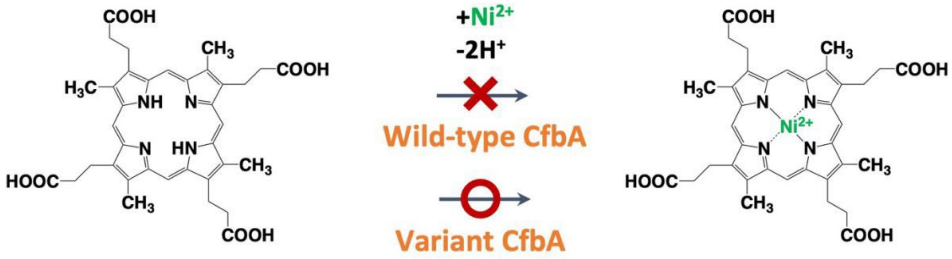

Figure. Nickel-chelatase reaction of CPI catalyzed by a CfbA variant.

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Abstract Number: 190

Trapping per- and poly-fluoroalkyl pollutants within coordination cage adsorbents

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Environmental contamination by a group of chemicals known as per- and poly-fluoroalkyl substances (PFAS) has become a widespread economic and health burden in Australia and around the world. Current adsorbents utilised for PFAS removal, such as activated carbon and ion-exchange resins, preferentially take up only long-chain PFAS ($C \geq 8$), and capture of other PFAS (e.g., short-chain variants, $C \leq 7$) remains unaddressed. This project aims to fill this gap by developing novel adsorbents that are selective to a broad spectrum of PFAS.

Metal-organic cages (MOCs), with their high degrees of customisability and well defined cavities, are ideal candidates for the capture of target molecules. A water-soluble Pd6L4 cage composed of tri-pyridyl ligands has shown promise to capture a range of fluorinated molecules (**Figure 1**).[1] This type of host offers a combination of hydrophobic and electrostatic interactions which promotes aggregation of these types of fluorinated guests within its cavity. We have found that MOCs of this type also have a strong affinity to capture PFAS, including short and long-chain variants. In order to access different cavity sizes and finetune the selectivity of MOCs for particular types of PFAS, tri-pyridyl ligands of various lengths may be utilised.

While MOCs have displayed capacity to capture PFAS on a laboratory scale, their incorporation into materials on a meaningful scale remains elusive. Hence the inclusion of reactive functional groups such as carboxylate groups on the surface of the MOCs opens up the possibility to bind them into porous adsorbents that are suitable for large-scale use.

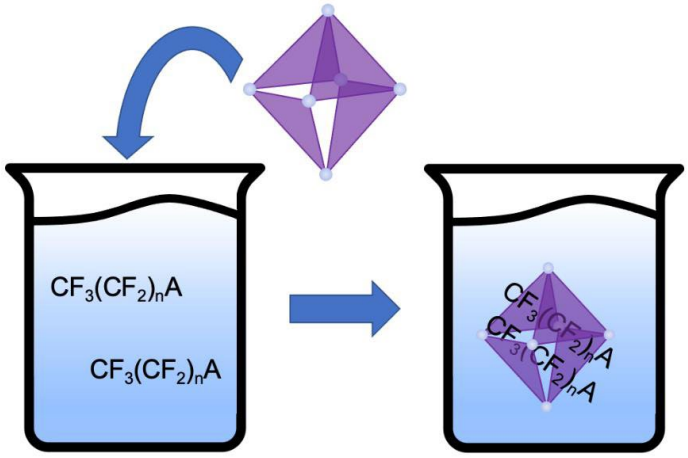

Figure 1: PFAS contaminated water treated with a water soluble Pd6L4 MOC, leading to adsorption of the PFAS within the cavity of the cage. A = polar end-group.

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Abstract Number: 195

A simple approach for monitoring the reduction of Platinum (IV) anticancer prodrugs

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While platinum-based chemotherapeutics such as cisplatin, oxaliplatin and carboplatin are widely used in the clinic for the treatment of cancers, the clinical utility of these agents is limited by their severe side effects. Platinum(IV) therapeutics are believed to be kinetically inert until reduced intracellularly to their cytotoxic platinum(II) analogue (Figure 1).[1] With this understanding on their mechanism of action, platinum(IV) anticancer agents are often referred to as prodrugs. To date, several platinum(IV) prodrugs have demonstrated promising therapeutic properties, but none have yet to be clinically approved.[2] The biggest obstacle in developing efficient platinum (IV) prodrugs remains the limited understanding of their reduction pathways.[2] The current gold-standard for evaluating Pt(IV) reduction is through the use of HPLC analysis. In this work (Figure 2), we were motivated to develop a modular colorimetric approach that can be used to rapidly observe and study reduction of Platinum (IV) prodrugs in solution in a high throughput manner. We present the synthesis, solution studies (UV spectroscopy) and reductant screening.

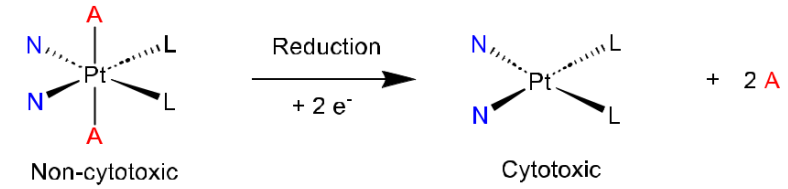

Figure.1 Overview of Platinum (IV) prodrugs

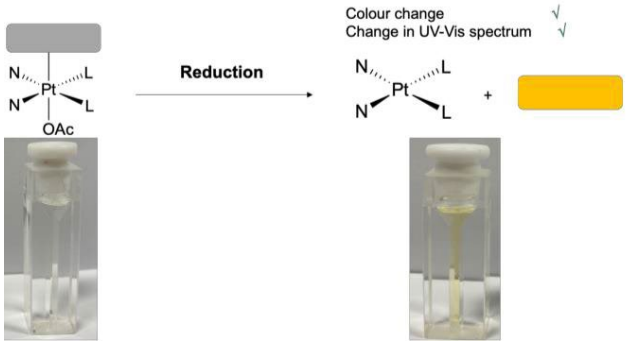

Figure.2 Overview of the modular colorimetric approach

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Abstract Number: 199

Stable Mononuclear {FeNO}$^{6/7}$ Complexes and a Bimetallic Fe^{II}/{Fe(NO)2}^{9} Moiety: Structure and Spectroscopic Characterization

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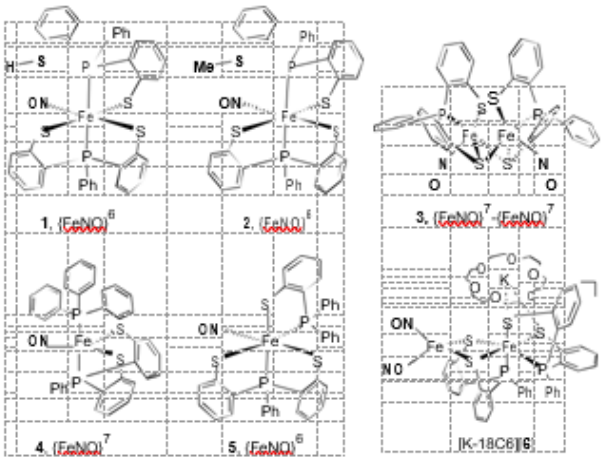
A series of Fe-NO complexes, [Fe(NO)(PS2)(PS2H)] (**1**, PS2H2 = bis(2-dimercaptophenyl)-phenylphosphine) with a pendant thiol, [Fe(NO)(PS2)(PS2CH3)] (**2**) bearing a pendant thioether, [Fe(NO)(PS2)]2 (**3**) comprising two {FeNO}^{7} units, monomeric {FeNO}^{7} [Fe(NO)(PS2)(PPh3)] (**4**) and [Fe(NO)(PS2)(PS)] (**5**) are spectroscopically and structurally characterized. One-electron reduction of **3** results in the isolation of thiolate-bridged bimetallic DNIC, [(PS2)Fe(μ-PS2)Fe(NO)2]$^{-}$ ([**6**]$^{-}$), confirmed by several spectroscopies including single-crystal X-ray diffraction studies. The bimetallic DNIC [**6**]$^{-}$ is a rare example obtained from the one-electron reduction of a dinuclear Fe-NO {FeNO}^{7} model complex. Based on IR data and magnetic properties, the electronic structure of [**6**]$^{-}$ can be described as a Fe^{II}/{Fe(NO)2}^{9} state. Isolation of the {Fe(NO)2}^{9} moiety coordinated by the Fe ancillary complex lends a strong support to the NO scrambling behavior in effectiveness of the flavodiiron nitric oxide reductases (FNORs) activity. In comparisons of the vNO in the IR spectra, absorption energy in UV/vis spectra and structural parameters from single X-ray diffraction studies, complexes **1**, **2**, and **4** share similarity in electronic structure. Complex **1** with a pendant thiol leads to NO and HNO production upon exposure to visible light. Photolysis of **2** bearing a pendant thioether only affords NO. Discriminative detection of HNO or NO from **1** or **2** is achieved by the presence of a NO trapping agent, [Mn^{III}(^{TMS}PS3)(DABCO)]. In contrast, **4** shows robustness toward visible-light stimulus. Photolysis and having pendant thiol/thioether group play key roles in the NO production from these iron-nitrosyl-thiolato complexes, that is, the Fe-NO bond is weakened by exposure to light and the noncovalent SH of **1** or SCH3 of **2** can serve as an incoming ligand to interact with Fe atom, resulting in a transient intramolecular [RS···Fe···NO] (R = H and CH3) interaction which could facilitate HNO or NO dissociation, respectively.



Structures of the Fe-NO complexes described in this work

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Abstract Number: 200

Development of Folic acid and Fe(III) ternary complex functionalized gold nanoparticles for next generation targeted photochemotherapeutic applications.

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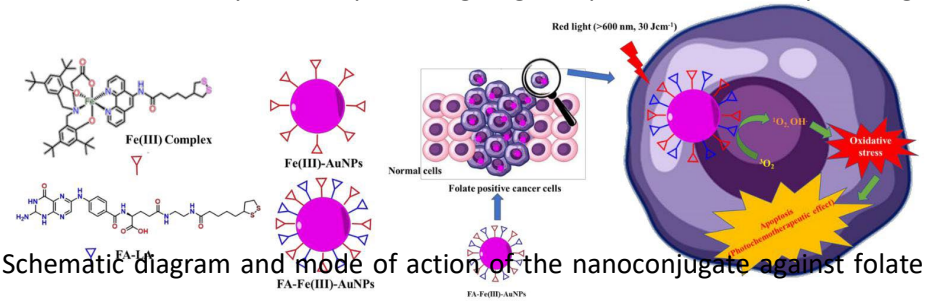
Cancer is a leading cause of mortality worldwide, and while chemotherapy is commonly used, its non-specific targeting and systemic side effects have limited its application. To address these issues, we have developed a novel photochemotherapeutic agent that selectively targets cancer cells and exhibit red light activated chemotherapeutic activity.

Fe(III)-O(phenolate or carboxylate) complexes are typically activated by high-energy light, which is beyond the PDT window[1]. However, when photoactivated, they generate hydroxyl radicals as ROS, that can induce apoptosis in cancer cells. By functionalizing with AuNPs, we observed a red shift of the SPR band to 660 nm, suitable for red light-induced photochemotherapy. Moreover, AuNP functionalization enhanced the singlet oxygen quantum yield to 0.59 with the generation of hydroxyl radicals under red light conditions. The nanoconjugate exhibited remarkable cytotoxicity in A549 cells with IC50 of 56.10 ug/mL. The nanohybrid exhibited some selectivity towards cancer cells than normal cells for the EPR effect of the cancer cells. But it lacks in terms of cancer cell selectivity[2].

Many tumors exhibit overexpression of folate receptors[3] which we exploited in our design of folic acid and Fe(III) co-functionalized gold nanoparticles (FA-Fe(III)-AuNPs) for targeted photochemotherapy. Our cellular uptake studies revealed that these nanoparticles are more efficiently taken up by folate-positive cancer cell lines such as HeLa or MDA-MB-231, as compared to folate-negative cancer cells. The uptake of the nanohybrid is minimal in normal cells.

Our designed nanohybrid selectively targets folate-positive cancer cells and induces red light-induced cytotoxicity with IC50 values of 27.83 µg/mL in HeLa and 39.91 µg/mL in MDA-MB-231 cell lines, compared to dark cytotoxicity of > 200 µg/mL. The red-light-induced cytotoxicity is attributed to the generation of light-activated ROS, which leads to induction of apoptosis in cancer cells upon light exposure. These properties establish our nanohybrid as a promising targeted photochemotherapeutic agent.



Scheme 1: Schematic diagram and mode of action of the nanoconjugate against folate positive cancer cells

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Abstract Number: 203

Increasing the Reactivity of Anionic Low-Valent Aluminium Compounds

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In recent years, low-valent main-group complexes saw a renaissance in organometallic chemistry that came along with renewed interest owing to the relatively non-toxic, earth-abundant, and cheap nature of these elements. A major driving force of this trend lies in the interesting reactivity that these compounds offer. Group 13 compounds, especially those based on aluminium, have traditionally been used as Lewis acids with a wide array of industrial and academic applications, however low-valent group 13 complexes that act as nucleophiles have lagged behind in their development. Recently, Hicks *et al.* reported an anionic Al^{+I} compound [K{Al(^{Dipp}**NON**)}]2 stabilised by the bulky xanthene based ligand [^{Dipp}**NON**]$^{2-}$ (shown in Figure 1).[1] The compound was found to react as the first nucleophilic source of aluminium, and its monomeric form is even able to activate a C-C bond of benzene.[2]

With our eyes set at the activation of even more stable bonds, a more reactive aluminyl would be desirable. To achieve this, we hypothesized that replacing the ligand's Dipp group(s) with *tert*-butyl group(s) would increase the electron-donating ability of the ligand and therefore result in a more reactive aluminyl anion. Accordingly, H2(^{tBu}**NON**) and H2(^{tBuDipp}**NON**) were synthesized via Pd-catalyzed Buchwald-Hartwig cross-coupling. The aluminium(III) iodide precursor complexes (^{tBu}**NON**)Al-I and (^{tBuDipp}**NON**)Al-I can be obtained by reaction between the potassium salt of the corresponding ligand with AlI3. First attempts at reducing the aluminium iodide precursors using strong reducing agents show promising results.

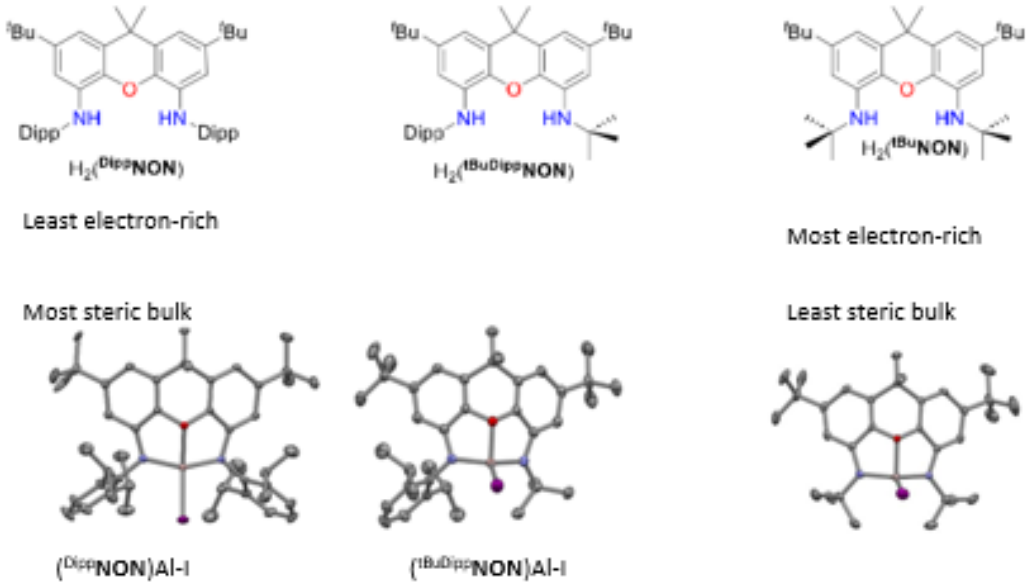

Figure 1. Series of Al(III) precursors and the corresponding pro-ligands under investigation in this study.

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Abstract Number: 204

Synthesis of Multi-Modal Metallodrugs as Anti-Cancer Agents

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The application of metallic complexes as potential anti-cancer agents was already reported in the sixteenth century, and to date, platinum complexes are amongst the most prominent anti-cancer agents with 50% of chemotherapy patients being administered a platinum-based drug.[1,2] The serendipitous discovery of cisplatin (*cis*-diamminedichloridoplatinum(II)) in the 1960s revolutionised the treatment of cancer and significantly promoted research in the field of metal-organic compounds for medical applications.[3,4] The challenges of both intrinsic and acquired resistance along with the severe dose-limiting side-effects of the chemotherapeutics demand further research into alternative approaches to platinum anti-cancer agents. New advances include the synthesis of prodrugs: kinetically more inert six-coordinate octahedral platinum(IV) complexes which are reduced *in vitro* to yield the active, cytotoxic square planar platinum(II) species.[5,6]

The aim of the research project lies in the synthesis and isolation of stable platinum(IV) complexes as candidates for anti-cancer prodrugs. Selective activation with irradiation of varying energy will render insight into the mechanisms as well as providing a handle for stimuli responsive anti-cancer agents. Here we present the synthesis of platinum-gold complexes based on [2+3]-cycloaddition reactions between azido platinum(II/IV) complexes and gold(I) alkynes. The complexes are characterised via single crystal X-ray diffraction analysis, mass spectrometry, UV-Vis and NMR spectroscopy.

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Abstract Number: 205

Fluorescence-based diagnostics for understanding Platinum-based therapy

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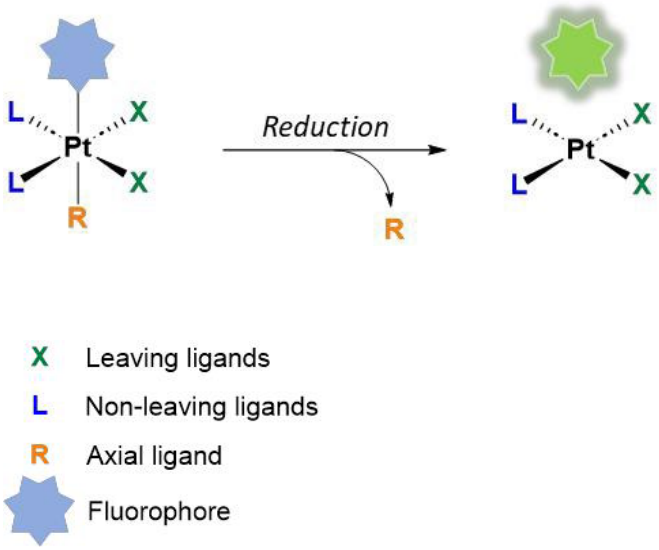
Platinum-based antineoplastic agents, cisplatin, carboplatin and oxaliplatin, are commonly applied in chemotherapy in the treatment of a wide range of malignancies. The clinical application of these platinum(II) drugs is however limited due to high systemic toxicities, intrinsic or acquired tumour resistance and severe side-effects induced by the lack of selectivity of the chemotherapeutic agents.1,2 To circumvent these problems, platinum(IV) complexes have been designed as prodrugs that can be activated by reduction to their platinum(II) counterparts. Several Pt(IV) prodrugs have already displayed promising pre-clinical results (overcome resistance, high tumour selectivity, low off-target toxicity…) but have failed to demonstrate therapeutic efficacy.3-5

In this work, we've focused on developing theranostic strategies which provide insights into Pt(IV) reduction within biological settings through switching on the luminescence from a released fluorophore. We believe that the information provided could help explain the poor therapeutic outcome observed in the clinical trials and facilitate the design of efficient platinum(IV)-based therapy.



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Abstract Number: 209

Modulating the behaviour of multifunctional lanthanoid complexes using ligand effects

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The study of the optical and magnetic properties of lanthanoid(III) compounds can open the field to exploit them as highly specialized engineering materials to be used in fields as wide as information storage or gas sensing. In this work, we present a series of heteroleptic compounds of formula [Ln(TPA)X3] (TPA = tris(2-pyridylmethyl)amine, X = $NO3^-$, Cl^-) and the investigation of their electronic properties by means of magnetic and spectroscopic studies. The measurement of the magnetic and luminescent properties give an insight into how modifying the ligands can change the electronic structure of the complex , thus completely changing its properties. The use of TPA provides a stable coordination environment where the electronic properties of the compound can be enhanced by modifying the other ligands, and the energy of its triplet state is suitable for effectively sensitizing the emission of the lanthanoid(III) ions. Furthermore, the results of dynamic spectroscopic studies on this type of compounds are presented, which give information about the type of orbitals involved in the sensitization process, aiding in the understanding of the electronic structure of lanthanoid complexes.

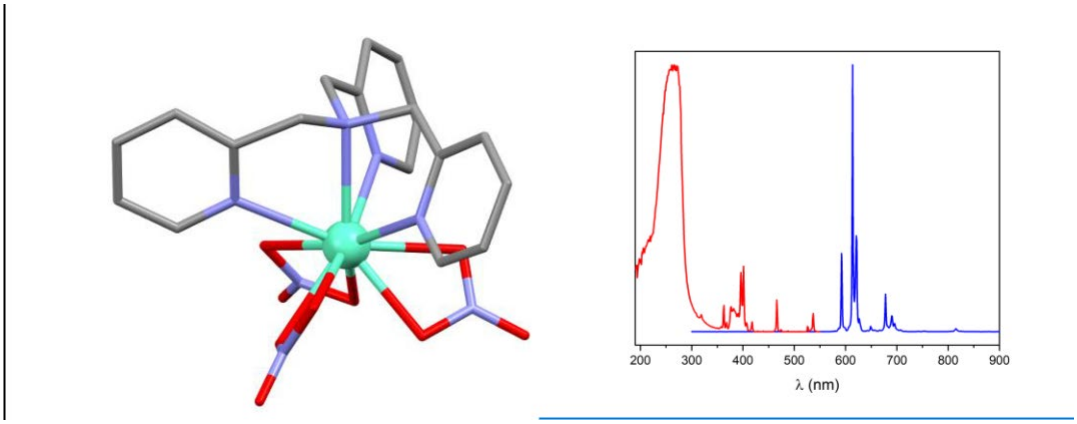

Figure 1. Structure of [Eu(TPA)(NO3)3] and its luminescence spectrum in the solid state.

Abstract Number: 214

Design and development of selective arsenic anti-cancer complexes specific to neurological cancer cells

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Arsenic trioxide successfully cures 90% of acute promyelocytic leukemia patients.[1] However, treatment of other cancers requires increased arsenic concentrations, potentially leading to serious side effects, and dose-reduction or cessation.[2] A potential method to improve treatment efficacy is the conjugation of a drug to a tumour-homing peptide.[3] Dillon and Carrall have previously patented an arsenic-tumour-homing peptide that exhibits 1000 times greater toxicity in leukemia cells over healthy blood cells.[4] The aim of this work was to develop PhAs(RGD), a third generation arsenic-tumour-homing peptide designed to target neurological cancer cells (brain/nervous system origin). Following the optimisation of reaction conditions, PhAs(RGD) was purified using preparative high performance liquid chromatography (HPLC) and characterised using electrospray ionisation mass spectrometry (ESI-MS), and one-dimensional (1D) and two-dimensional (2D) nuclear magnetic resonance (NMR) spectroscopy. PhAs(RGD) showed promising stability when assessed in DMSO (98%, 24 h) and selected cell media types (86%, 24 h, IMDM). Reduced stability was observed when examined in human plasma (53%, 24 h). Due to the reduced stability in plasma, 4-h MTT assays were performed in leukemia, liver and brain cancer cell lines using a monolayer cell model, and the results compared to those from human blood cells. The results of the MTT assays will be discussed with respect to the stability and potential uptake mechanisms of the complex. Overall, this preliminary work demonstrated the successful synthesis and characterisation of an arsenic-tumour-homing peptide designed to target neurological cancer cells.

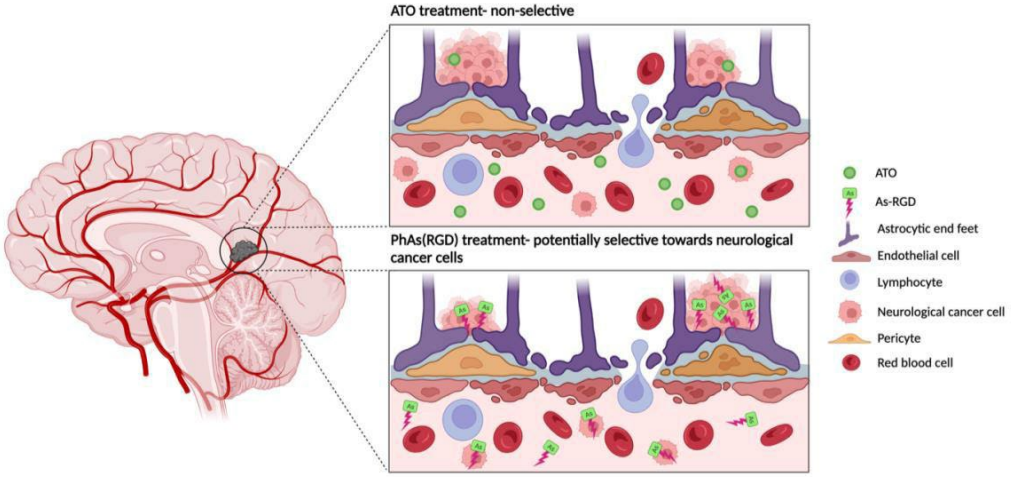

Figure 1: Hypothesised selectivity of PhAs(RGD) for neurological cancer cells in comparison to ATO (the frontline treatment for acute promyelocytic leukemia). Figure created using BioRender.

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Abstract Number: 214

Examining the potential role of macropinocytosis in the uptake of arsenic-peptides into cancer cells *in vitro*

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Arsenic trioxide has been found to dramatically improve the long-term survival of patients with acute promyelocytic leukemia (APL), resulting in clinical remission rates of ~90%[1]. This has sparked interest in the potential use of arsenic therapeutics to treat cancers such as pancreatic ductal adenocarcinoma. Previous work by Dillon and collaborators[2] have found that PhAs(LHP), where Ph = phenyl ring and LHP = leukemia homing peptide, shows selective toxicity towards K562 and HL-60 leukemia cells, as well as oncogenic *KRAS* MIA-PaCa-2 and PANC-1 pancreatic ductal adenocarcinoma cells. Cancers exhibiting *KRAS* mutations have been shown to utilise macropinocytosis to scavenge nutrients from the extracellular environment[3]. Consequently, the multi-faceted work described here aims to investigate whether the uptake of PhAs(LHP) into cancer cells is primarily facilitated by macropinocytosis. Firstly, the effectiveness with which cell-targeting peptides penetrate the cell membrane was explored by studying changes in the thickness and ion permeability of POPC/cholesterol and POPC/POPG/cholesterol tethered bilayer lipid membranes using electrochemical impedance spectroscopy. These studies indicated that the addition of several cell-targeting peptides, including LHP, resulted in a reversible, and minimal, negative change in bilayer conductance. Secondly, confocal microscopy was used to compare the level of FITC-dextran (macropinocytosis marker) and 5-carboxyfluorescein labelled peptide uptake into leukemia, pancreatic, and colorectal cancer cell lines. The results of these studies will be discussed with respect to the mechanism of uptake of PhAs(LHP) in the poster.

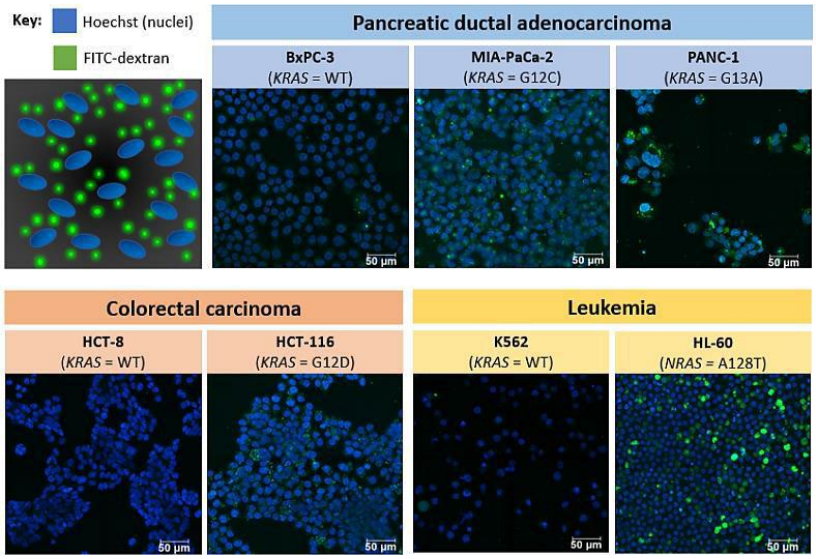

Figure 1: Uptake of the macropinocytosis marker, FITC-dextran (green), into pancreatic ductal adenocarcinoma, colorectal carcinoma, and leukemia cells co-stained with Hoechst33342 (blue).

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Abstract Number: 215

Fundamental Studies of Bismuth Flavonoid Complexes with Membrane Mimics

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Epidemiological studies have shown a positive correlation between a flavonoid rich diet and a lower risk of several cancers including colon, prostate, lung and breast cancer.[1] Metal-flavonoid complexes have shown selective uptake towards cancer cells with the *in vitro* cytotoxicity being greater than that of the flavonoid ligands.[2-3] It is hypothesized that bismuth flavonoids (BiFlavs) may exhibit potentially beneficial therapeutic and preventive properties. The first objective was to study how BiFlavs interact with membrane mimics in comparison to the corresponding flavonol ligand, using electrochemical impedance spectroscopy, quartz crystal microbalance and neutron reflectometry (Figure 1), providing insight into their potential *in vivo* bioavailability. Electrochemical impedance spectroscopy showed that all five compounds (Figure 2) interacted with 1-palmitoyl-2-oleoyl-sn-glycero- 3-phosphocholine (POPC) and POPC/cholesterol membrane mimics. Neutron reflectometry experiments were performed to gain a clearer understanding of these interactions and their localization within the membrane mimic. The interactions of the BiFlavs with the membrane mimic were non-reversible, compared to the flavonol ligands which interacted reversibly. BiPh(Flav)2 and BiPh(BrFlav)2 displayed increased interactions in the tail regions of the bilayer, whilst Bi(BrFlav)3 interacted with the headgroup region.

The results have been compared with viability and Bi uptake studies comparing the membrane interactions to the effects in a number of cancer cells. There was a correlation between the membrane interactions and the *in vitro* activity, whereby BiPh(Flav)2 shared the strongest membrane interactions and the greatest effect on cell viability. These results will be discussed with reference to future investigations of possible uptake mechanisms and cancer cell interactions to reveal the potential of BiFlavs as chemopreventive agents.

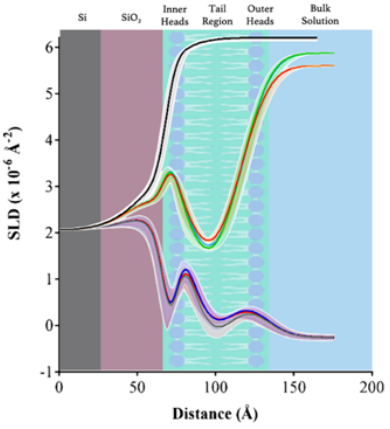

Figure 1. Scattering length density profile employing different contrasts (D2O or H2O), which allow the structural details of the membrane to be determined, including the inner and outer headgroups and the tail region.

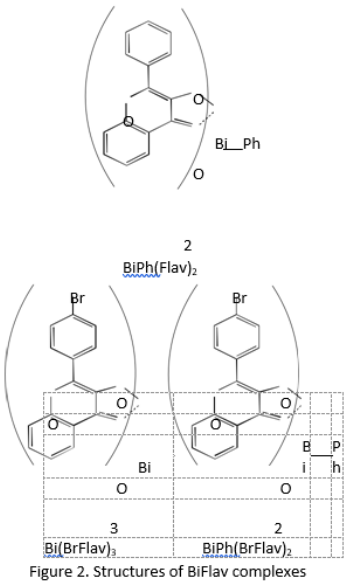

Figure 2. Structures of BiFlav complexes relevant to this study.

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Abstract Number: 216

Characterization of Novel Sulfite-Oxidizing Enzyme in *Ruegeria pomeroyi* DSS-3

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Sulfite is produced through desulfonation of sufur-containing compounds by organotrophic bacteria. Since sulfite can react with and damage biomolecules such as DNA and proteins, these bacteria can suffer from sulfite poisoning during the degradation of organosulfonates. To detoxify accumulating sulfite, bacteria use sulfite oxidizing enzymes (SOEs) that catalyze the oxidation of sulfite into sulfates.
A previous study identified a small,11.5 kDa protein encoded by the SPO3124 gene as possibly involved in sulfite oxidation in the marine bacterium *Ruegeria pomeroyi*. Here we report the purification and characterization of SPO3124 that has no sequence similarity to previously characterized sulfite-oxidizing enzymes.

SPO3124 is encoded in a gene locus that also contains a bacterial sigma factor gene, and *SPO3124* expression was induced following exposure of growing *R.pomeroyi* culture to sulfite.

To be able to study the enzymatic properties of SPO3124, it was expressed in *E. coli* with either an N- or C-terminal His-tag, or following export to the periplasm and purified through immobilized metal affinity chromatography. While N-terminal his-tagged SPO3124 produced good yields, significant enzymatic activity was only observed in the C-terminal his-tagged SPO3124 expressed in the *E. coli* periplasm. Using a potassium ferricyanide-based standard SOE assay, the purified SPO3124 had an average SDH activity of about 5 U/mg, which was less than activities of the typical, molybdenum-containing SOEs.
As previously characterized SOEs are molybdenum enzymes, however, the size and sequence of SPO3124 suggest that no molybdenum cofactor domain is present, but other metals may be relevant for catalysis. ICP-OES data showed that as prepared SPO3124 only contained trace amount of metals, so metal-loading experiments were conducted to determine SPO3124 bind metal ions that may improve SDH activity. The experimental results showed that the sulfite oxidation activity of SPO3124 could be improved by binding different metals.

Abstract Number: 222

Mechanochemical Approach for the Synthesis of Unconventional Platinum Anticancer Complexes

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Adjuvant chemotherapy is the modern standard regimen for the treatment of various cancer types. In chemotherapy, ~50% of all co-administered drugs are platinum(II)-based, a common example being cisplatin.[1] Although these drugs are successful in the treatment of several cancers, their use is accompanied by clinical drawbacks due to their lack of specificity for cancer cells. Reported side effects include nephrotoxicity, cardiotoxicity, neurotoxicity, and acquired and intrinsic resistance to platinum(II) treatment.[2] To surmount the drawbacks associated with platinum(II) drugs, platinum(IV) prodrugs have been the focus of current research. Platinum(IV) prodrugs exhibit superior anticancer potential due to their six-coordinate octahedral geometry. Their geometry enables greater flexibility in their design, which improves the overall stability, solubility, lipophilicity, specificity, as well as cytotoxicity.[3] However, the synthesis of unique platinum(IV) prodrugs is limited by the available methodologies. Mechanochemistry is an unexplored synthetic technique for platinum(IV) chemistry whereby mechanical forces are used to induce a chemical reaction. This "greener" technique can reduce or eliminate the use of solvents, increase the reaction rate and resulting yield, reduce reaction times and even facilitate the synthesis of complexes that are inaccessible in-solution.[4] Additionally, using an environmentally friendly approach will take into consideration the responsible consumption and production of materials as it is predicted to increase product output while reducing the amounts of waste generated. Thereby, the objective of this project is to explore the potential of merging the advantages of mechanochemistry with the production of efficacious platinum(IV) complexes. As such, sustainable methods will be developed to produce superior anticancer complexes with improved efficiency, which is of relevance to commercialisation.

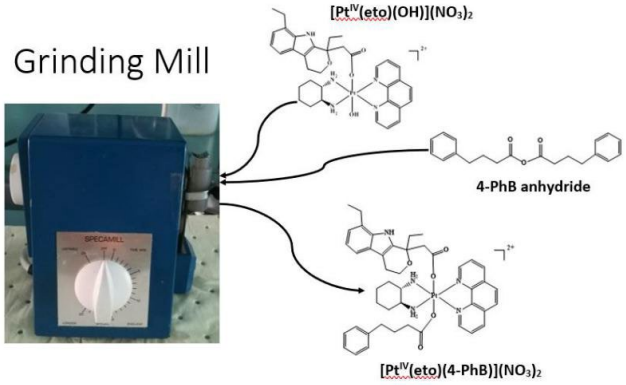

Fig. 1: Schematic diagram of a dry reaction synthesis of **[Pt^{IV}(eto)(4-PhB)](NO3)2** in a grinding mill including the chemical structures of **[Pt^{IV}(eto)(OH)](NO3)2**, **[Pt^{IV}(eto)(4-PhB)](NO3)2** and 4-PhB anhydride.

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Abstract Number: 224

Bismuth functionalised vinylphosphonate polymers as antimicrobial coatings

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The phenomenon of antimicrobial resistance (AMR) poses a significant current and future threat to human health. It has been estimated that over 80 % of microbial infections in medical and healthcare environments are biofilm mediated and the global cost of dealing with persistent and multi-drug resistant infections is in the range of US$368bn.[1]

Within the overall approach to managing and combatting AMR the development of bactericidal and bacteriostatic materials and coatings is therefore critical. One key strategy is the development of antibacterial polymers (cationic or anionic) loaded with a metal or a metal compound which can exert an antibacterial effect.

Bismuth complexes have antibacterial properties while displaying relatively low levels of toxicity to human cells. [2] Bismuth has been used with a number of different ligands as antimicrobial and its antibacterial activity is known to be ligand dependant.[3] Bi phosphonates have received very little attention and to our knowledge the antibacterial properties of bismuth phosphonates have not yet been explored. we have successfully synthesised, characterised homoleptic and heteroleptic bismuth vinylphosphonate complexes, and report the formation of bismuth loaded poly(vinylphosphonic acid) and its application as antimicrobial coatings.

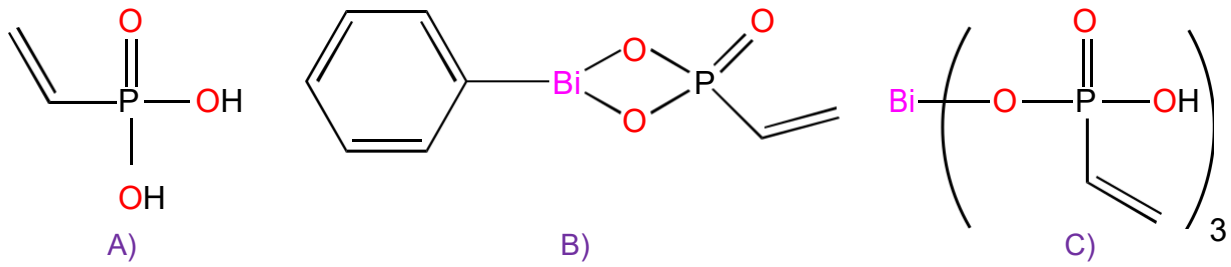

Figure 1: A) structure of vinyl phosphonic acid, B) & C) structures of Bi(III) phosphonate complexes.

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Abstract Number: 225

Synthesis and stability studies of gallium(III) hydroxyanthraquinone complexes

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With the rise in concern over antimicrobial resistance (AMR) leading to preventable infections and deaths worldwide, the need for new treatments has become apparent.[1] The use of metals to combat AMR has become an area of interest due to the unique chemistry and potential synergistic relationships between metals and bioactive organic compounds.[2]

Previous studies by Andrews *et al* found organometallic gallium complexes of halido-quinolinol to be effective anti-leishmanials.[3] Therefore, we aimed to expand on the library of organometallic gallium compounds to address a range of microbes, including resistant bacteria. Anthraquinones were selected as a ligand class due to reported Gram-negative and Gram-positive antibacterial activity.[4] Hydroxyanthraquinones offer a potential chelation site with a hydroxyl and β-ketone.

Unfortunately, it was found that the novel dimethyl gallium hydroxyanthraquinone complexes synthesised in this project were unsuitable for biological applications due to their instability in water. Interesting observations, however, were made on their solution and solid-state chemistries. Solid state data of the air stable compounds including FT-IR and XRD were collected and analysed. In contrast, their hydrolytic instabilities were traced with time dependent ^{1}HNMR studies. Herein, this poster presents the synthesis and characterisation of these novel compounds, and the stability studies that were performed.

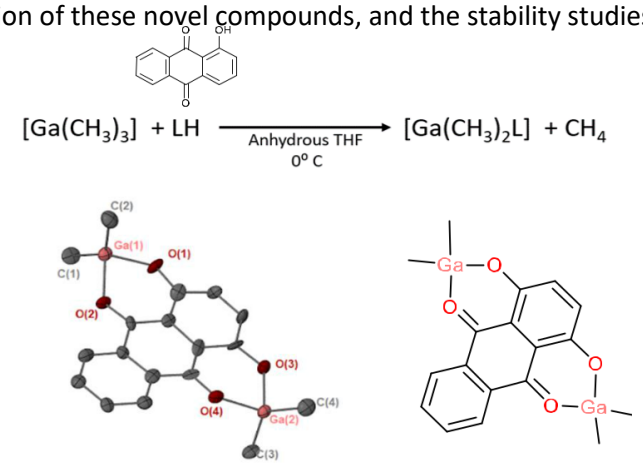

Figure 1. General synthetic scheme for dimethyl gallium complexes (top). X-ray structure of bis-(dimethyl gallium) quinizarin (left) and ChemDraw of bis-(dimethyl gallium) quinizarin (right).

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Abstract Number: 226

Complex formation between [NiFe] hydrogenase maturation factors responsible for Fe(CN)2CO biosynthesis

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[NiFe] hydrogenase is a metalloenzyme that catalyzes the oxidation of hydrogen and the reduction of protons reversibly. As its name implies, the metal cluster of [NiFe] hydrogenase is composed of nickel and iron. In the active center of [NiFe] hydrogenase, nickel is ligated by the three cysteine side chains of the protein, while iron is coordinated with two cyanide ions and one carbon monoxide in addition to the cysteine side chains. This intricate metal complex is not spontaneously formed, but is biosynthesized step-by-step in coordination with multiple proteins. The cyanide ions and carbon monoxide are also biosynthesized to form Fe(CN)2CO complex, which is then incorporated into hydrogenase. We are performing the structural biological analysis of the maturation factors responsible for Fe(CN)2CO biosynthesis in the thermophilic aerobic bacterium *Aquifex aeolicus*. We have reported the crystallographic analysis of HypX, which is an enzyme responsible for carbon monoxide biosynthesis during [NiFe] hydrogenase maturation[1]. Additionally, we showed that the HypC-HypD complex, which acts as a scaffold protein for Fe(CN)2CO biosynthesis, forms a complex with HypX.

Recently, we determined the crystal structures of A. aeolicus HypC, HypD, and HypE, which are involved in cyanide ion transport (Figure 1). The crystal structures of these maturation factors show high structural similarity to previously reported structures of corresponding proteins from archaea and bacteria. Although the transient complex formation between HypC-HypD complex and HypE has been proposed during cyanide ion transport, the HypC-D-E complex formation has not been observed in our system. In this presentation, we will present the latest structural findings on the HypC-HypD-HypX tertiary complex and discuss the relationship between HypC, HypD, HypX, and HypE based on structural knowledge.

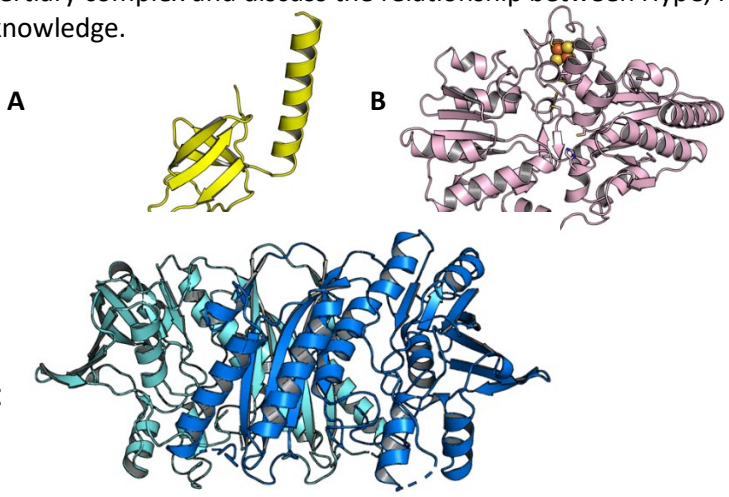

Figure 1. Overall structure of HypC (A), HypD (B), and HypE (C) from *Aquifex aeolicus*

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Abstract Number: 227

Whole-cell Hydroxylation of Benzene by Cytochrome P450BM3 Mutants Developed by Directed Evolution with Diffusible Decoy Molecule

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Cytochrome P450BM3 (P450BM3) is a heme enzyme that catalyzes the hydroxylation of long-chain fatty acids at their sub-terminal positions.[1] P450BM3 shows the highest mono-oxygenase activity toward its natural substrates among all the P450 enzymes (Figure 1a, left). On the other hand, P450BM3 has high substrate specificity, which causes quite low hydroxylation activities toward non-native substrates. Our research group has developed the "substrate mis-recognition system" in which synthetic dummy substrates, or "decoy molecules", enable efficient hydroxylation of non-native substrates such as benzene by P450BM3.[2] P450BM3 misrecognizes and binds decoy molecules which are shorter than the natural substrates, creating the space above heme. Subsequently, non-native substrates are accommodated above heme and hydroxylated by the active species compound I of P450BM3 (Figure 1a, right). Recently, we reported that one of the best decoy molecules promotes the whole-cell biotransformation of benzene to phenol by intracellular P450BM3 with a yield of 38%.[3] However, most of the developed decoy molecules are ineffective at the whole-cell reaction due to their low permeability through cell membrane, limiting the availability of decoy molecules for whole-cell reaction.

In this research, we employed diffusible natural products from some species of gram-negative bacteria as decoy molecules and performed the directed evolution of P450BM3 mutants accepting the natural products as efficient decoy molecules (Figure 1b).[4] While the employed natural product hardly induces the hydroxylation of benzene by wild-type P450BM3, it induces the efficient whole-cell hydroxylation of benzene with a product yield of over 40% by the evolved mutant, indicating that the natural product is suitable for the whole-cell reaction.

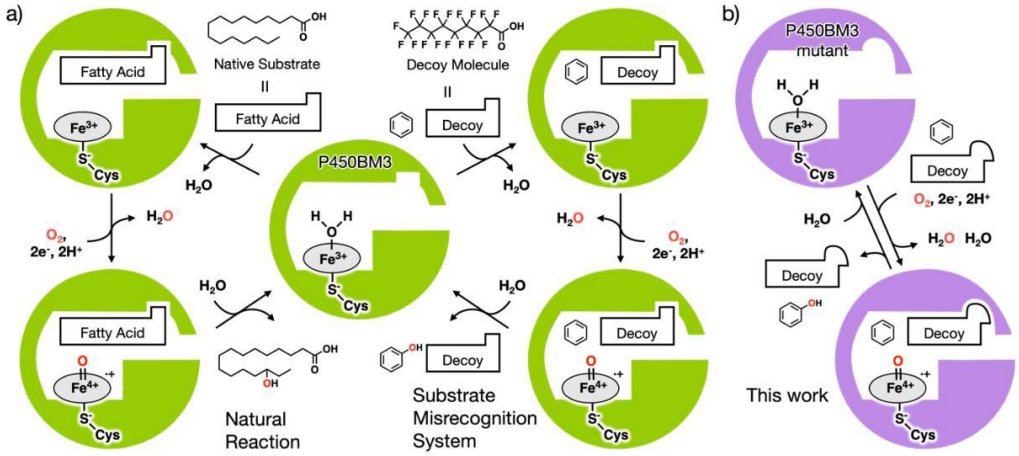

Figure 1 a) Hydroxylation reaction of long-chain fatty acids by P450BM3 (left) and substrate mis-recognition system for hydroxylation of benzene with a decoy molecule (right). b) Concept of this work.

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Abstract Number: 228

Bi(III) and Ga(III) complexes of indeno[1,2]quinoline derivatives as antimicrobial agents

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Antimicrobial resistance (AMR) – the decreased susceptibility of pathogenic microorganisms to available antimicrobial treatments – has become a life threating issue throughout the world.[1] It has been predicted that if no action is taken then there will be approximately 10 million deaths from AMR infections globally each year by 2050.[2] The urgent need for new antimicrobial agents has led to the synthesis and assessment of metal-derived compounds as therapeutics to combat resistant pathogens.

Ga(III) is considered as competitor of Fe(III) because of their chemical similarity, and interferes with iron homeostasis in biological systems and can inhibit the growth of bacteria.[3] Indeed, gallium(III) nitrate is in clinical trials for the treatment of *Pseudomonas aeruginosa* infections in patients with chronic cystic fibrosis. Bismuth(III) salts, such as colloidal bismuth subcitrate have been used for decades for the treatment of infections associated with *Helicobacter pylori*. A bismuth(III) complex of quinoline thiosemicarbazone derivative has been reported to effectively restore the carbapenem drug sensitivity in *Klebsiella pneumoniae.*[4]

The quinoline scaffold (Figure 1, left) occurs widely in natural products and pharmaceutical compounds, including antimicrobial agents.[5] Tetracyclic derivatives of quinolines such as indenoquinolines are also pharmacologically-interesting compounds that exhibit a wide variety of biological properties.[6] Despite this, there is a lack of literature reporting the therapeutic potential of 11-oxo-11H-indeno[1,2-b]quinoline-10-carboxylic acids (Figure 1, middle). This work investigates the use of the indenoquinoline carboxylic acid for the preparation of novel bismuth(III) and gallium(III) indenoquinoline-carboxylate complexes, with aims to evaluate their potential as novel antimicrobial agents towards several pathogenic gram-positive and gram-negative bacteria.

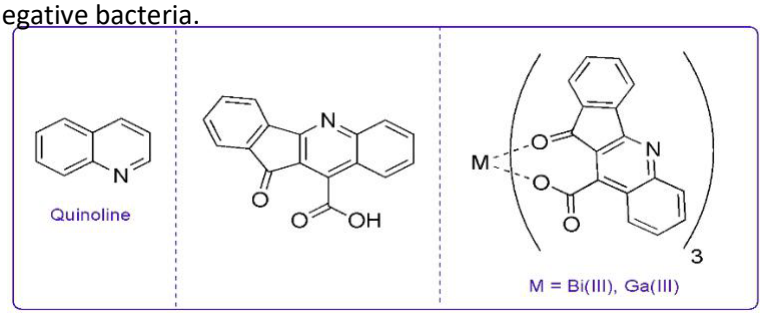

Figure 1: (Left): Structure of quinolone; (middle): basic structure of the indenoquinoline-carboxylic acid derivative; (right): targeted homoleptic Bi(III) and Ga(III) carboxylate complexes.

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Abstract Number: 229

Aspirin and bismuth-aspirin *in vivo*:
Effects in a chemically induced colorectal cancer mouse model

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Numerous rodent models have indicated the potential for aspirin to be used for the chemoprevention of colorectal cancer (CRC). A major limitation of using aspirin for CRC chemoprevention is the severe gastrointestinal side effects associated with its long-term use.[1] Bismuth is a non-toxic heavy metal with gastrointestinal sparing properties.[2] It is hypothesised that the coordination of aspirin to bismuth may allow the use of aspirin as a chemopreventive for CRC while combating the associated gastrointestinal side effects. The present study assessed the *in vivo* effects of aspirin and Bi(aspirin)3 in the azoxymethane/dextran sulfate sodium (AOM/DSS) mouse model of inflammation-driven CRC.

A short pilot study was conducted to assess the potential of using voluntary ingestion as a less stressful administration method to oral gavage (Figure 1). The study successfully showed that the mice voluntarily consumed a dose of aspirin/Bi(aspirin)3 mixed in Nutella®, reducing the animal stress levels over the short- and long-term studies. AOM/DSS was used to induce CRC in male FVB/nJAusb mice. Administration of aspirin resulted in a decrease in the tumour volume; however, this reduction was not significant. Unfortunately, administration of Bi(aspirin)3 resulted in a significant increase in colitis severity and tumour number, a non-significant increase in tumour volume and a poorer survival rate compared with the AOM/DSS positive control and aspirin-treated cohorts. Additionally, bismuth was found to accumulate in tissue from several organs. Overall, these studies have demonstrated that administration of Bi(aspirin)3 exacerbated the symptoms of colitis and colorectal carcinogenesis, possibly resulting from changes in physical properties or a lower than desired dose reaching the colon.

Figure 1: Administration of aspirin/Bi(aspirin)3 using voluntary ingestion of Nutella®.

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Abstract Number: 231

Electronic Effect on Phenoxide Migration at a Nickel(II) Center Supported by a Tridentate Bis(phosphinophenyl)phosphido Ligand

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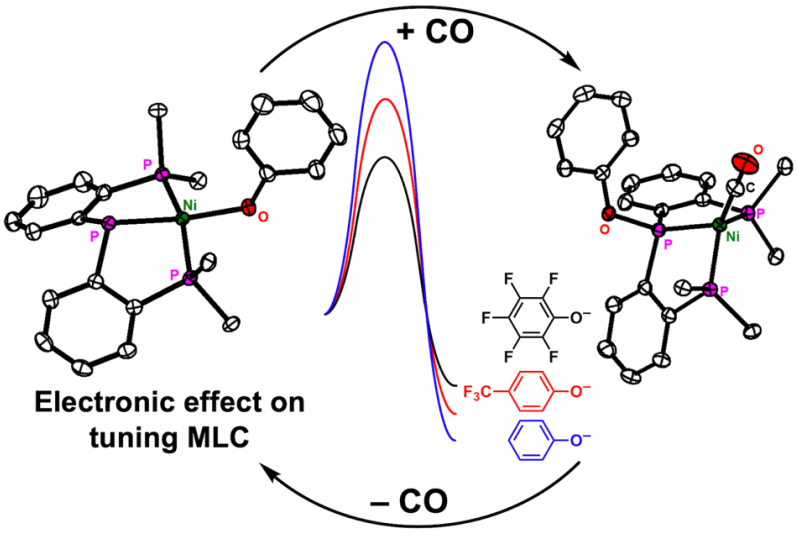
Phosphide containing a tridentate ligand reveals interesting metal ligand cooperative (MLC) transformation. This MLC reaction is well established with a (PPP)Ni scaffold (PPP^{-} = $^{-}P[2\text{-}P^{i}Pr_2\text{–}C_6H_4]_2$), which reacts with CO(g) to give a pseudo-tetrahedral nickel(0) monocarbonyl complex possessing a phosphinite moiety. A square planar nickel(II) alkoxide complex reacts with CO(g) revealing the group transfer to generate a P–O bond via the 2-electron reduction of a nickel(II) species. In order to understand the formation of a P–O bond, (PPP)Ni complexes with different *para*-substituted phenolate derivatives possessing different electronic properties were synthesized and the kinetic studies of their carbonylation were conducted. UV-vis kinetic studies and Hammett plotting show that the electron-deficient phenolate accelerates CO binding to Ni. The Eyring plot supports a transition state with a negative entropy at the rate-determining step. Two different pathways are possible for the phenolate liberation upon CO coordination; a nucleophilic attack of the phenolate on the phosphinite site or a radical-type coupling. During phenolate dissociation from a nickel(II) center, the resulting P–Ni moiety within the intermediate species can possess a P^{-}–Ni(II), P•–Ni(I), or P^{+}–Ni(0) character. Based on computational studies, a closed shell pathway is energetically favored, whereas the open shell pathway involving the homolysis of a Ni–O bond undergoes a high energy state, when phenoxyl radical is liberated. To support former mechanism, phenolate scramble experiment and radical trapping experiment also were conducted. As a result, the nucleophilic pathway was suggested for the carbonylation of nickel phenolate species.



Abstract Number: 232

A Bioluminescence Probe for Real-Time Monitoring the Reduction of Platinum(IV) Prodrugs in Vivo

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Platinum(IV) prodrugs are thought to be the most promising candidates as novel anticancer agents. The reduction of Pt(IV) prodrugs in cells is the most important and essential step to activate these complexes. However, the investigation for the reduction profile of Pt(IV) prodrugs is mostly limited to test tube assays[1] or cell lysate-based studies.[2,3] Herein, we reported a Pt(IV)-caged aminoluciferin, **33c**, a bioluminescent reporter for visualization of Pt(IV) complex in live cells and animals. **33c** uses a reduction-dependent cleavage reaction to release aminoluciferin. Concomitant to this reduction, the originally inactive aminoluciferin center of the complex now can be recognized and oxidized by luciferase to emit light, thus allowing a real-time in situ monitoring of the reduction process and distribution of Pt(IV) complexes in luciferase-expressing cells or tissues within an animal. The efficiency to release luciferin scaffolds among three different bioluminescent probes **33c**, **34b**, and **35c** in live cells and mice was tested, and the role of glutathione peroxidase 4 (GPX4) and cysteine in the reduction of Pt(IV) complex was also investigated.

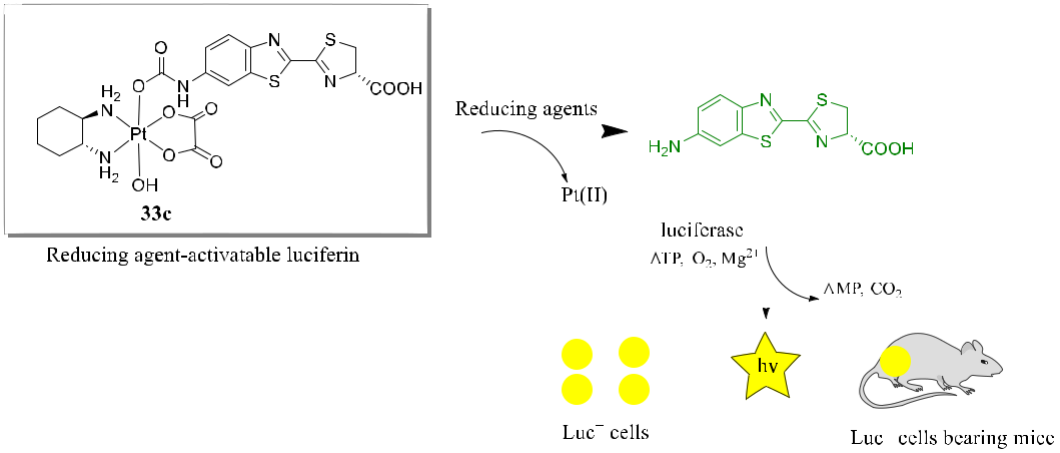

Fig 1. Design of **33c** through reducing agent-mediated reductive release of the aminoluciferin substrate.

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Abstract Number: 236

Developing light-responsive switchable metallo-interlocked architectures

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Metallo-supramolecular systems are potentially useful due to their ability to reversibly bind guests or substrates. When switching between different conformations, or structures, supramolecular architectures may also form molecular machines, binding guests to achieve certain tasks. Typically this conformational or structural switching has been driven by concentration or temperature, with changes in these conditions prompting switching between architectures. Unfortunately, such control mechanisms may also interfere with applications and lower feasibility.

Instead, we look to use light-sensitive functional groups in the backbone of supramolecular architectures to access light-driven molecular switches.[1] Light has the advantages of being non-destructive towards molecules, as well as more environmentally friendly for catalytic applications.

We have previously shown that ethylene glycol linkers can be built into the backbone of supramolecular architectures to control conformation of interlocked species as a function of linker length.[2] By incorporating a light-sensitive diazo functional group into the backbone, that can switch between trans and cis isomers, we can control linker length (Figure 1). We hope to synthesise supramolecular architectures that can act as light-responsive switches for guest or substrate binding, allowing greater control over the binding activity of these architectures and improving their applicability for functions such as catalysis.

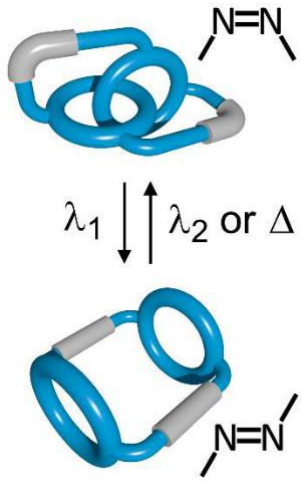

Figure 1. Cartoon representation of generalised metallo-interlocked system capable of light-responsive switching

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Abstract Number: 240

Photothermal conversion triggered by near-infrared light in a dithiolene-based metal-organic framework

432

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Photothermal metal-organic frameworks (MOFs) are a particularly interesting group of materials capable of absorbing light and converting it into heat.[1, 2] We present a novel efficient photothermal MOF containing Ni-dithiolene ligands, denoted Zn1, which has intensive absorbance in the near infrared (NIR) region and is capable of heating rapidly by irradiation with NIR light at a relatively low power density. By further incorporating Zn1 into a self-healable polymer, the mechanical damage of the composite can be recovered using irradiation with NIR light. The reversible dynamic covalent bonds in the polymer enable the recovery to be thermodynamically driven and responsive to heat.[3] Our results provide an opportunity to maneuver the point of repair and avoid shape changes in practical applications with the use of clean energy with lower power consumption, which can also be further developed for long-distance repair.[4]

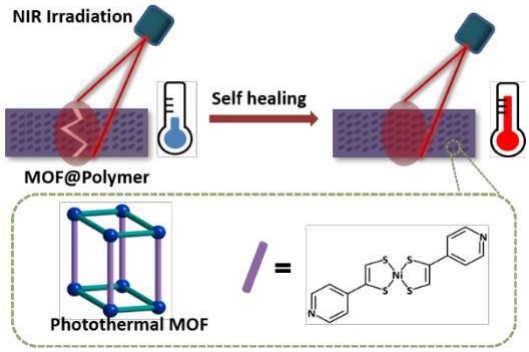

Figure 1. The self-healing process of Zn1@polymer composite under NIR irradiation.

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Abstract Number: 241

Charge-Driven Switching in Metallo Interlocked Architectures

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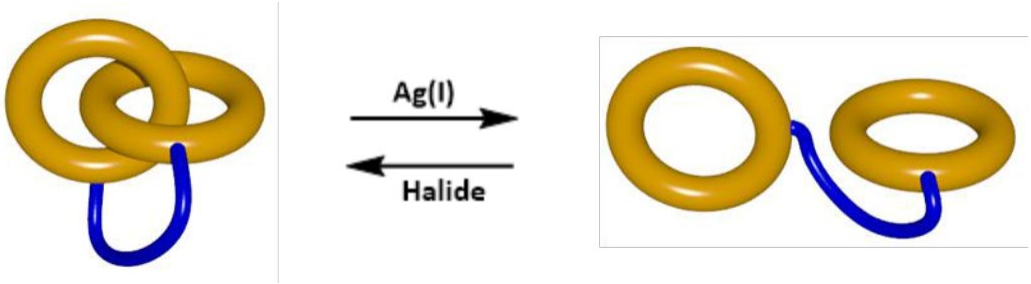
Quantitative self-assembly of interlocked architectures can be achieved through incorporation of reversible metal-ligand bonds allowing substituents to access non-interlocked and interlocked states based on thermodynamic equilibrium. Manipulation of this equilibrium has previously been used in the development of various molecular switches using concentration[1] or temperature[2] based switching.

A key issue in switch design has been overcoming the entropic cost of changing from multiple unbound substituents to a single interlocked complex, leaving the system highly susceptible to dilution effects[2]. To overcome this, we have used a linker between substituents so that the same number of substituents can exist on either side of the equilibrium.

As an alternative to these entropic methods which requires changes not accessible in biological conditions, the potential exists for modifying interlocking through enthalpic charge-driven switching. By incorporating Pd^{2+} binding sites to catenanes, subsequent halide-coordination and Ag^{+} abstraction can vary local charge between 2+ and neutral states[3]. This modifies the favourability with which net positive macrocycles may catenated. We investigate the switchability and diversity of application of this method and its potential as a model for further interlocking equilibrium modification through other enthalpic means.



Cartoon representation of linked macrocycles in an interlocking equilibrium

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Abstract Number: 243

Copper(I) in fused (bis)bipyridine ligand systems–chemical and electrochemical efforts towards bimetallic mixed-valence species

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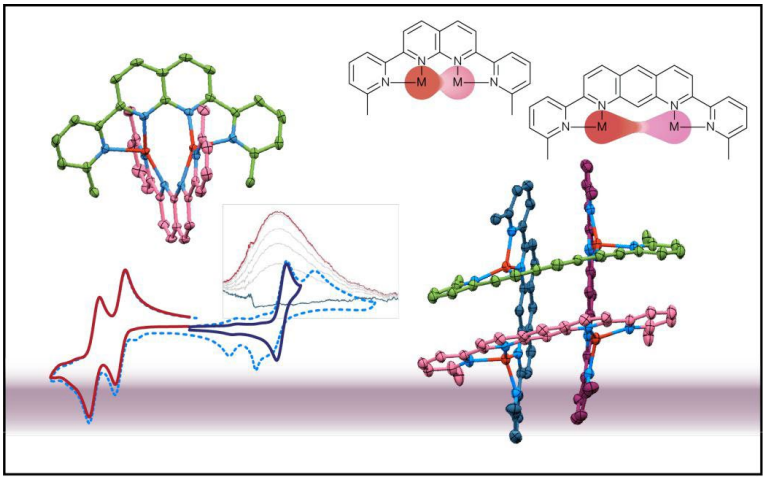
Investigations into the redox activity and coordination chemistry of bimetallic complexes have helped unveil new metal-metal cooperative reactivities.[1,2] In this work, copper complexes of ligand systems incorporating two fused bipyridine subunits are explored, in an extension of traditional 2,2'-bipyridine coordination chemistry: 2,7-bis(6-R-2-pyridyl)-1,8-naphthyridine, ^{R}**L1** (R = H, Me), and 2,7-bis(6-R-2-pyridyl)-1,8-diazaanthracene, ^{R}**L2** (R = H, Me). Copper(I) and copper(I)/(II) complexes of 2,7-disubstituted 1,8-naphthyridines have been reported for purposes including mechanistic investigations of copper-catalysed azide-alkyne cycloadditions;[3] copper chemistry of 1,8-diazaanthracene derived ligand systems has not been explored prior to this work.

The helical dicopper complex [Cu2(^{Me}**L1**)2](PF6)2 was found to crystallize from solutions containing highly fluxional mixtures of [Cu(NCMe)4]PF6 and ^{Me}**L1**. Electrochemical studies of this complex showed reversible access to the complex in four different redox states, which have been characterised computationally.[4] Current work is directed towards the spectroelectrochemical characterization of the different redox states, and synthetic preparation of oxidised forms of this complex via chemical and electrochemical methods.

Coordination of [Cu(NCMe)4]PF6 to either ^{H}**L2** or ^{Me}**L2** resulted in the formation of discrete 2×2 grid complexes [Cu4(^{H}**L2**)4](PF6)4 and [Cu4(^{Me}**L2**)4](PF6)4. Electrochemical and optical properties of these copper(I) grid complexes are under investigation with comparison to other copper(I) bipyridine complexes.



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Abstract Number: 245

More than Fe mimics: Establishing organometallic Bi, Ga and In complexes as effective antimicrobials

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The *World Health Organisation (WHO)* and the *United Nations (UN)* have identified Antimicrobial Resistance (AMR) as being critical health and economic challenges which require urgent scientific, administrative, and governmental action.[1] Since the introduction of antibiotics 80 years ago, the quantum of effective drugs for managing infections has diminished dramatically, coinciding with a dramatic decline in industry-based research and development into new antibiotics.[2]

As a sustainable and enduring strategy our work centres on the development of metal-based rather than natural or organic antimicrobial agents and is predicated on the difficulty microbes face in evolving mechanisms which allow resistance to metal-based compounds to emerge, particularly if the mode-of-action is intimately tied to the role of the metal itself.

Bi(III), Ga(III) and **In(III)** are known to mimic common Fe(II/III) binding, transport and uptake processes in biological systems but lack the important redox chemistry {eg Ga(III)/Ga(II) -0.68 V versus Fe(III)/Fe(II) +0.77 V}. This exemplifies the 'Trojan horse' approach in using the target microbes natural iron acquisition and utilization processes to introduce an exogenous metal which, because of fundamental chemical differences, can impact negatively on critical processes in the cell, such as enzyme function and oxidative stress.[3-6]

Over several years we have demonstrated that heteroleptic organobismuth complexes [BiPh2(L)] can often show superior antimicrobial activity over their homoleptic analogues [BiL3].[7] We are now investigating related organogallium and indium complexes [MMe2(L)] (M = Ga, In) derived from known bioactive and/or biologically derived ligands systems, eg flavonoids, hydroxamates, quinolones.

The M-C bonds in Bi, Ga and In complexes can be stable to hydrolysis and largely inert providing for different mechanisms of transport and cell uptake than normally taken by Fe mimics, eg transferrin, serum albumen.

We will present our recent findings into the biological activity and selectivity of these new metal-based antimicrobials towards drug-resistant Gram positive and Gram negative bacteria, and provide some insight into different possibly new mechanisms-of-action.

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Abstract Number: 247

Tracing novel ruthenium-based anticancer drugs in biological samples

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Anticancer agents are often evaluated in simulated biological environments and cancer cells to better understand their modes of action[1]. Studying the speciation of metallodrugs in biological samples is crucial to achieve a more systematic way to select new potential anticancer compounds for further development. Capillary electrophoresis is an attractive technique for conducting metallodrug studies[2], as it is compatible with physiological buffer conditions, offers short analysis times and a good tolerance of protein-containing samples while ICP-MS, with its low detection limits, is an ideal technique for determination of cellular accumulation of metallodrugs[3]. A capillary electrophoresis method applicable for investigating the interactions of ruthenium-based anticancer agents with biomolecules was developed and applied to investigate the binding of novel ruthenium-based anticancer complexes to different biomolecules such as the abundant serum proteins albumin and transferrin, as well as to study their behavior in cell culture medium and human serum[4]. The results indicated that each complex behaved differently, emphasizing how important the choice of ligands is in the design of novel compounds. The selection of ligands allows the control of interactions with serum proteins, which will have a major impact on the mode of action. Furthermore, the efficiency of three different cell lysis methods was compared using ICP-MS, with the aim of finding the most suitable method for metallodrug studies in terms of providing a high lysis efficiency without compromising the sample integrity. Additionally, distribution and accumulation of ruthenium-based anticancer complexes was studied in zebrafish embryos using ICP-MS to quantify uptake and laser ablation ICP-MS for visualization of where the complexes accumulate.

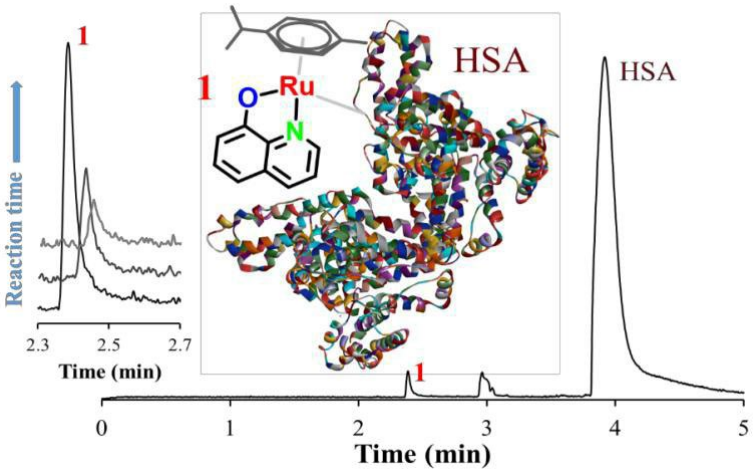

Figure 1. Tracking the binding of [Ru(cym)(8-HQ)Cl] to human serum albumin over time using capillary electrophoresis.

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Abstract Number: 249

Exploring Valence Tautomerism in Cobalt Complexes of Bidentate Mixed Donor (N,O) Redox-Active Ligands

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Development of switchable molecular materials that can be interconverted between two or more states by the application of an external stimuli are of potential interest in molecular electronics, display devices and sensors. Valence tautomerism (VT) is such a phenomenon in which molecules can be switched between tautomers that have varying geometrical, optical, and magnetic properties.[1]

Complexes comprised of cobalt and dioxolenes as the redox-active ligands are the most widely explored VT systems, with only a few reported complexes incorporating N-donor ligands.[2] Valence tautomerism is also known for cobalt complexes of mixed donor tridentate (NNO) and (ONO) ligands.[3,4] This study is focused on bidentate, mixed(NO) donor ligands with a tetradentate ancillary ligand Me_nTPA (TPA = tris(2-pyridylmethyl)amine, n = 0-3 corresponds to the successive methylation of the 6 position of the pyridine rings). We present families of complexes of the formula $[Co(Me_nTPA)(L_1)]^+$ and $[Co(Me_nTPA)(L_2)]^+$, where L_1 = 2-amino-3,5-ditert-butyl-phenol and L_2 = 2-anilino-4,6-di-*tert*-butylphenol. Structural, electrochemical, magnetic and variable-temperature UV-Vis spectroscopic studies indicate that complexes $[Co(Me_2TPA)(L_1)]BPh_4$ and $[Co(Me_2TPA)(L_2)]BPh_4$ undergo VT behaviour with temperature.

Density Functional Theory (DFT) studies are conducted using the pre-established method M06-L-D4-ZORA/def2-TZVPP(CPCM) that was used to explore VT in cobalt dioxolene systems.[5] The calculations reveal that the energetics of $[Co(Me_2TPA)(L_1)]^+$ and $[Co(Me_2TPA)(L_2)]^+$ falls within the VT range of the cobalt-dioxolene systems.

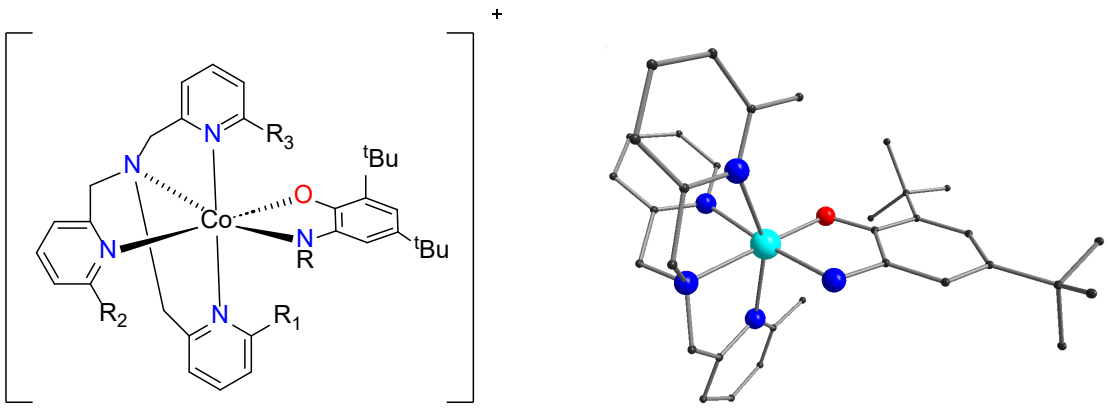

Figure 1. Complexes investigated in this study (R= H or phenyl) (Left) and crystal structure of $[Co(Me_2TPA)(L_1)]BPh_4$ (Right

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Abstract Number: 263

Evaluating Design Criteria for PeT-based 'Turn-on' Fluorescent Metal Ion Sensors

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Spatio-temporal fluctuations in distributions of bio-metals are functionally related to key cellular processes and disruptions are linked to severe pathophysiological conditions. For obtaining insights into metal ion dynamics in living cells, photo-induced electron-transfer (PeT)-based 'turnon' fluorescent sensors are proven successful chemical-tools. A method to predict whether PeT will occur in a designed fluorescent metal ion sensor a priori, can afford a path to pre-design effective 'turn-on' sensors. Hence, we have designed a density functional theory (DFT) and timedependent DFT (TD-DFT)-based workflow for screening molecules based on the ability to exhibit an efficient PeT quenched metal-unbound state. To experimentally test the workflow, we decided to develop PeT-based 'turn-on' fluorescent sensors for detecting Mn2+ ions within living systems. Mn2+ ions are necessary both in labile and protein-bound forms for all life forms ranging from bacteria, to plants and animals.1 Designing Mn2+ selective binding ligands is, however, challenging owing to low binding affinities of Mn2+ ions toward most N-, O-, and S-donor atom containing ligands.1 By scrutinizing the biological binders of Mn2+ ions, we opted for a planar pentacoordinate arrangement of N- atoms as an Mn2+ ion binding scaffold.2 A library of sensors was designed by linking the binding scaffolds with dye units in silico and two molecules for which PeT was feasible based on computations, were synthesized. PeT was observed for both molecules. One of the sensors was selective toward Mn2+ ions, water-soluble and cell-permeable, and was used to image Mn2+ ions in living cells. I will detail our computational work-flow, and applications of the novel Mn2+ ion sensor for Mn2+ ion detection in vitro and in living cells.

Abstract Number: 265

A Reversible, Water-soluble, 'Clicked' Fluorescent Sensor Detects Manganese Ions

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Manganese (Mn) ions are essential for all forms of life in both protein bound and labile forms.1 Recent studies have indicated the role of this metal ion in host-immunity against pathogens2 and its mis-regulation in cancers.3 A direct consequence of Mn2+ ion dysregulation is a neurological disorder with symptoms similar to Parkinson's disease.4 A chemical sensor that can permeate living cells and report on Mn2+ ion localization in a fluorescence confocal microscopy platform can provide key mechanistic information on both physiological and pathophysiological roles of Mn2+ ions. Hence, we have developed a reversible, water-soluble, cell-permeable fluorescent probe for Mn2+ ion detection. The molecule was designed based on a computational work-flow for pre-designing photo-induced electron transfer (PeT) based sensors, developed recently in our group.5 The designed molecule was synthesized in 13 steps via a 'Click' reaction-based scheme for attaching a dye unit to a water-soluble Mn2+ ion binding scaffold. With this molecule we could address the challenge of selectively detecting Mn2+ ions which are difficult to track due to low binding affinities of Mn2+ ions based on the Irving-Williams series. 1 The sensor selectively detected Mn2+ ions over other physiologically relevant metal ions in water. I will present the details of the synthesis and characterization of our novel watersoluble, small-molecule-based, 'turn-on' fluorescent Mn2+ sensor.

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Abstract Number: 266

Synthesis and Characterization of New Nickel Complexes Supported by Bismuth Pincer Ligand

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Metal-ligand cooperativity (MLC) has been employed as a synthetic methodology to tune the chemical properties of 1-row transition metals. As a part of MLC-like approach, hetero- and homo-bimetallic complexes contribute also to expand the utility of such base metals. Here, a series of nickel complexes supported by a bismuth containing pincer ligand are synthesized and characterized. To investigate the chemical property of a Ni–Bi moiety, a **BiP$_3$** ligand (**BiP$_3$** = Bi(*o*-P^{i}Pr$_2$-C$_6$H$_4$)$_3$) was prepared. Interestingly, by addition of Ni(0) to the ligand, a trigonal bipyramidal complex, (BiP$_2$)Ni(PPh) (**1**) possessing a Ni–C–C–P four-membered ring was synthesized, which involves the Bi–C bond cleavage of a **BiP$_3$** ligand. Reaction of **1** with MeI occurs to give a 5-coordinate nickel(II) complex (MeBiP$_2$)Ni(PPh)I (**2**). Upon heating or exposure to UV irradiation, compound **2** was transformed to a nickel(II) halide complex, (BiP$_2$)Ni(I) (**3**). Interestingly, **3** is significantly distorted away from a square planar structure revealing a sawhorse geometry compared to the previously reported nickel(II) halide pincer complexes, (NP$_2$)Ni(Cl) and (PP$_2$)Ni(I).[1–3] Such difference indicates that a bismuth donor can be employed as a structurally influencing cooperative site for a nickel(II) ion. Since CO-induced reductive elimination in a Ni(II) complex via metal-ligand cooperation of a PP$_2$ ligand was previously reported, CO was introduced to **1** to see if the **BiP$_3$** ligand could be regenerated from **1**.[3,4] Migratory insertion of CO into a Ni–C bond gives (BiP$_2$)Ni(COPPh) (**4**), which further leads to an analogous methylated product (MeBiP$_2$)Ni(COPPh)(I) (**5**) from the reaction with MeI. The bismuth–nickel moiety is expected to have a new-type of reactivity toward various chemical transformations owing to its bimetallic cooperativity and unusual bonding properties.

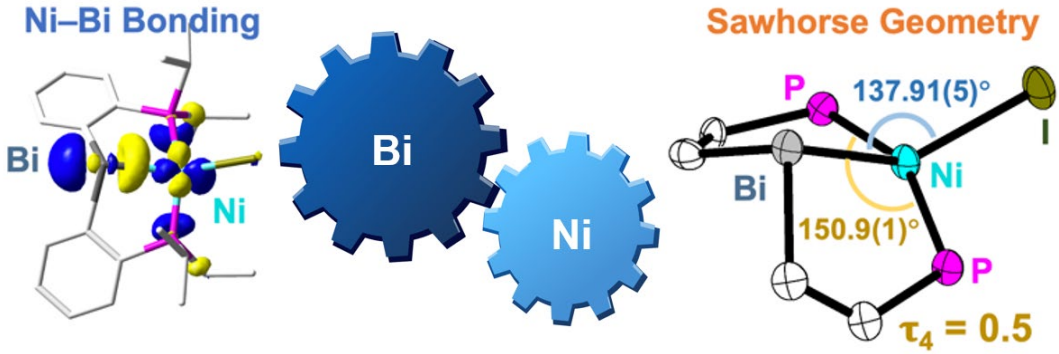

Figure 1. The metal-ligand cooperativity of a highly-distorted bismuth-nickel(II) complex.

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Abstract Number: 268

Oxaliplatin-induced peripheral neuropathy and redox modulation: evaluation of SOD mimics and dual action Pt(IV) prodrugs

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Oxaliplatin-induced neuropathy (OIPN) is the main dose-limiting side effect of oxaliplatin, a platinum-based anticancer agent mainly used for colorectal cancer (Figure 1). Its origins are intricate and unclear. However, it is accepted that a burst in oxidative stress, as well as mitochondrial damage and neuroinflammation are commonly present in patients suffering from this condition. Some strategies for trying to reduce and/or prevent this side-effect include combination treatments with antioxidants, anti-inflammatory agents, or ion-channel targets[1].

Superoxide dismutases are one of the front-line antioxidant enzymes in our body, protecting our cells against oxidative stress. They catalyze the dismutation reaction of superoxide anions into hydrogen peroxide and dioxygen. Small bioinspired metal complexes mimicking these natural enzymes are largely studied for therapeutic applications[2]. In our group, Mn1 (Figure 2), a Mn(II) complex mimicking the active site of MnSOD, and its derivatives are studied in the context of IBD (inflammatory bowel disease) for its antioxidant and anti-inflammatory properties[3]. Interestingly, Mn1 also showed, while combined with oxaliplatin, encouraging neuroprotective *in vivo* results on balb/C mice[4].

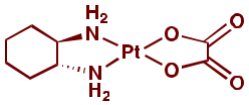

Figure 1. Oxaliplatin

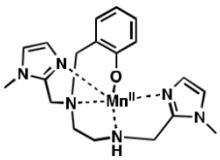

Figure 2. Mn1

From these results, a molecule bearing oxaliplatin and an antioxidant moiety would facilitate the administration, as well as, potentially, reduce the low selectivity problems of Pt(II) drugs. This option can be envisioned by employing Pt(IV) complexes, intrinsically more inert than their Pt(II) analogs that would be reduced at the tumor microenvironment. We present here the development of stable Pt(IV) conjugates and their *in vitro* and *in vivo* evaluation[5].

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Abstract Number: 279

A fluorescent sensor array for monitoring platinum chemotherapeutic agents

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Limited access to inexpensive and sensitive systems for heavy metal toxins and therapeutics is a prevailing issue in remote areas of Australia. Fluorescent sensors, in particular fluorescent sensor arrays, offer a solution to these challenges as they can sensitively detect and monitor analytes in complex mixtures on-site. In fluorescent array studies, instead of using single, highly selective sensor, specificity is achieved by having a set of cross-reactive sensors, which are tested in an array, and then subjected to statistical analysis.[1] Fluorescent arrays have already demonstrated beneficial progress towards distinguishing heavy metals and different cancer cell lines.

Even after 50 years in the clinic, platinum complexes remain frontline anticancer therapies, particularly in combination therapies. However, clinical dosages are poorly calculated and controlled, leading to devastating side effects. This can be attributed in part to the lack of accessible methods for detecting and quantifying these complexes in biological fluids. We have developed a fluorescent sensor array comprising six sensors that demonstrates progress toward the detection of platinum levels in chemotherapy patients.[2] Using linear discriminant analysis, the array was able to discriminate platinum from other metals with 100% accuracy, as well as to differentiate platinum complexes with different coordination environments. The array could also distinguish different concentrations of both cisplatin and oxaliplatin in human plasma. We have carried out preliminary studies of clinical samples from a cohort of 27 cancer patients at different stages of platinum chemotherapy, and were able to distinguish different concentration regimes. We anticipate that this array system will be useful in measuring active platinum drug in blood in clinical trials of new platinum-containing formulations, informing suitable dosage regimes going forward.

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Abstract Number: 280

Substrate Binding in Thiol Dioxygenases

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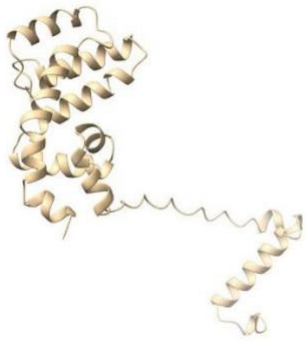
Thiol dioxygenases[1] are a group of non-heme ferrous iron dependent enzymes that catalyse the oxidation of a thiol to its corresponding sulfinate by addition of dioxygen. In mammals, thiol dioxygenases oxidise cysteine and cysteamine as part of thiol regulation through the oxidative catabolism pathway. In bacteria, specific enzymes oxidise cysteine, 3-mercaptopropionic acid and mercaptosuccininc acid, although in the case of the latter two it is still unclear for what purpose. Apart from cysteamine, which does not posess a carboxylate, all these enzymes control specificity by holding the substrate in place through a salt-bridge between arginine(s) in the active site and the carboxylate groups present on the substrates.[2]

More recently[3], a second sub-group of enzymes have been identified that oxidise the N-terminal cysteine of transcription factors that are present under hypoxic conditions. Conversion of the cysteine to a sulfinate by dioxygen ensures that the factor is degraded by the N-degron pathway[4]. This allows dioxygen concentration to act as a signal deactivating anaerobic gene. In plants, the enzymes called plant cysteine oxidases (PCO) use the presence of dioxygen to inhibit ethylene response transcription factors and thus drive energy production during germination. This is important in plant species, such as rice, that need to survive flooding. In mammals, it has been shown that cysteamine dioxygenase (ADO)[4] occupies a similar position to PCO by targeting regulated GTPases (RGS) when oxygen is present. We have been studying the protein-protein interactions of ADO and PCOs with hRGS5 and HRE1 respectively to try to understand what drives substrate binding and how this differs from the small molecule dioxygenases.



Regulated of GTPases (hRGS5) modelled protein. The structure was obtained by Modeller _Log1

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Abstract Number: 281

The Effects of Functionalised 3D Linkers in MOFs on Increased Supramolecular Host-Guest Interactions

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Metal–organic frameworks (MOFs) are porous materials constructed from metal clusters connected by organic linkers that have the ability to separate individual components from a mixture through selective adsorption. These characteristics give MOFs huge potential as a low-cost and energy-efficient alternative to traditional separation methods, with possible future applications in critical areas such as gas and water separation of environmental pollutants and CO2 remediation.[1,2] Many MOFs use linkers with an aromatic core as the chemistry required for linker modification is well-known and relatively straightforward. However, this synthetic aspect has resulted in poor diversity of the chemical and structural environment of the MOF pore, limiting the type and number of interactions with guest molecules. Recently, non-planar, bulky, '3D-linkers' have been employed in MOF synthesis to form 3D-linker MOFs (3DL-MOFs). 3D-linkers, such as cubane-1,4-dicarboxylate and bicyclo[1.1.1]pentane-1,3-dicarboxylate, have exhibited excellent selective adsorption and separation properties in comparison to their aromatic analogues with 2D phenyl rings.[3] By combining 3D linkers with the established ideas of functionalisation (pendant groups in the pores) and mixed-linker systems, the pore environment has been further changed. Single crystal X-ray diffraction (SCXRD) and gas adsorption was used to study the structural and behavioural properties of the MOFs created. The findings showed enhanced supramolecular host-guest interactions which improved gas and vapour selective adsorption, and boosted mixture separation. This research will lead to an increased understanding of the effects of linker type on the pore size and reactivity of MOFs, leading to advancements in industry and crucial new information and ideas in an emerging area of MOF chemistry.

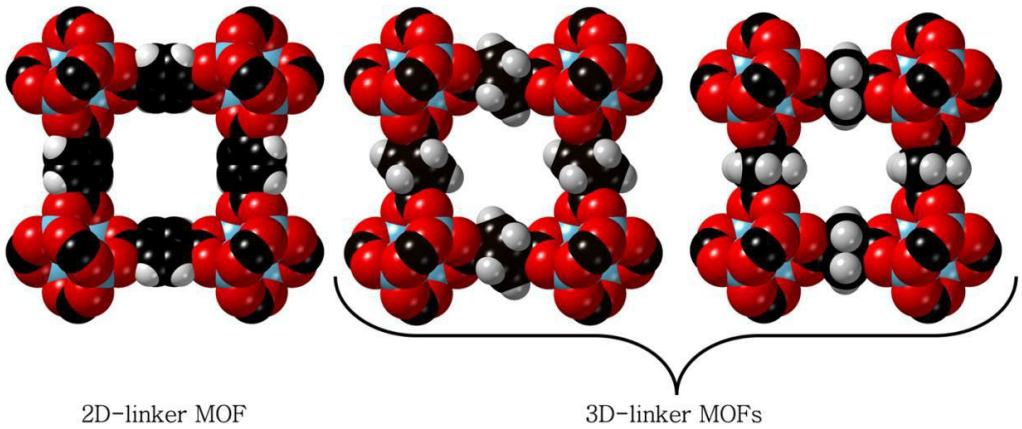

Figure 1: Space-filling models of 2D and 3D-linker MOFs highlighting the different pore shapes and sites of host-guest interaction.

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Abstract Number: 282

Molecular mechanism of iron trafficking into ferritin via iron chaperone

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Iron is a vital for life because it is used for important physiological functions such as oxygen transport and storage, energy production, and so on. In humans, the divalent metal transporter DMT1, which is localized in mucosal epithelial cells, is used to take up Fe^{2+} from foods into cells. The Fe^{2+} is cytotoxic due to its capacity to generate reactive oxygen species and causes cellular damage. Therefore, Fe^{2+} is tightly regulated for safe usage in cells, but the molecular mechanism is not fully understood.

In this study, we focused on an iron chaperone, PCBP, which has been implicated as an intracellular iron transport protein. PCBP has been reported to bind and securely transport Fe^{2+} taken up into the cell by DMT1[1], but the Fe^{2+} binding state and transport mechanism are not clear. PCBP has also been proposed to play a role in supplying iron ions to the iron storage protein ferritin[2], but the molecular mechanism of iron trafficking from PCBP to ferritin remains elusive. To unveil these mechanisms, we prepared recombinant human PCBP and investigated its properties. Iron binding assays using apo-PCBP revealed that one molecule of apo-PCBP can bind one Fe^{2+}, while Fe^{3+} does not bind, clearly showing PCBP can only bind Fe^{2+}. The complexation of Fe^{2+}-bound PCBP and ferritin H- or L-chain were investigated by size-exclusion chromatography (SEC), small-angle X-ray scattering and mass photometry [Figure 1]. These results indicated that Fe^{2+}-bound PCBP preferentially binds the ferritin H-chain compared to the L-chain. Since the ferritin H-chain acts as a ferroxidase, converting Fe^{2+} to Fe^{3+} for the safe storage of iron in ferritin, PCBP thus mediates safe and effective iron trafficking to ferritin in the cytoplasm.

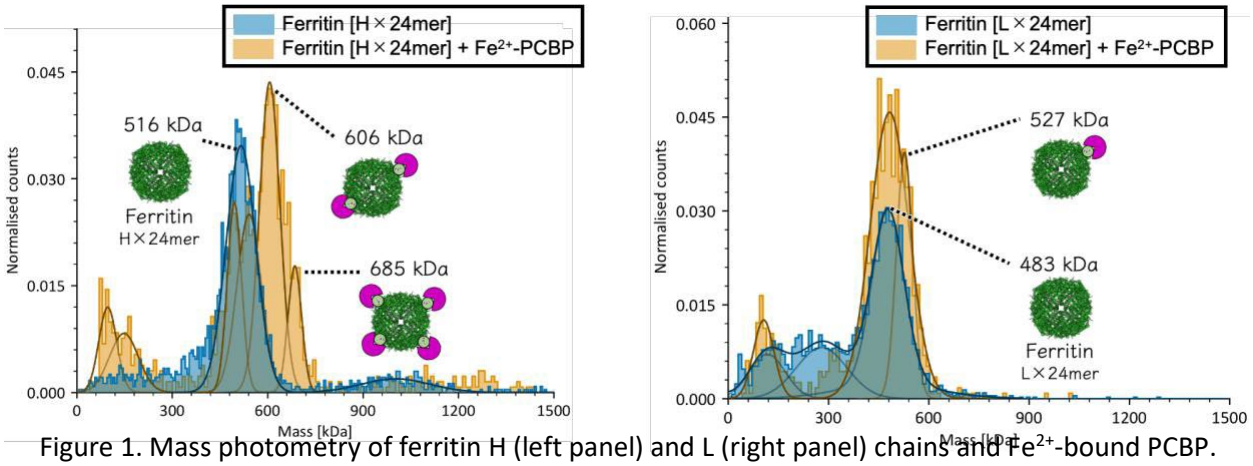

Figure 1. Mass photometry of ferritin H (left panel) and L (right panel) chains and Fe^{2+}-bound PCBP.

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Abstract Number: 286

Negative Thermal Expansion in 3D -linker Metal-Organic Frameworks

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Most materials naturally expand in response to an increase in temperature. However, some materials exhibit negative thermal expansion (NTE) whereby the material experiences volume contraction upon heating. When these properties are combined, composites with controlled thermal expansion coefficients can be produced for a range of applications including electronics and dental fillings.[1] In particular, metal-organic frameworks (MOFs) have been the perfect channel for exploring the transverse phonon vibration mechanism of NTE, due to their porosity and ability to vary linker components that contract into vacant interstitial sites.[2] There are several ways to influence NTE in MOFs such as varying the MOF topology, metal clusters and organic linkers. While the influence of organic linkers on NTE have been studied in-depth in MOFs, the influence of aliphatic linkers with a 3D-core has not been explored.

In this work, the NTE behaviour is investigated in a multicomponent MOF series derived from the Massey University Framework-77 (MUF-77) and the analogues CUB-30 and PDC-30. CUB-30 and PDC-30 embody the 3D-linkers cubane-1,4-dicarboxylate and bicyclo[1.1.1]pentane-1,3-dicarboxylate, respectively. Our investigation compares the effect of these 3D-linkers on lattice changes within the overall framework using a holistic approach to combine several techniques. For instance, variable temperature single crystal X-ray diffraction provides insight into the relative atomic positions of atoms in the framework, infra-red absorption with DFT simulations to highlight the collective motions of the lattice and phonon calculations to explore the ease at which individual dynamics are transferred through the framework. It is expected that the more flexible the MOF, the greater the degree of contraction and current preliminary results demonstrate this relationship (Figure 1).

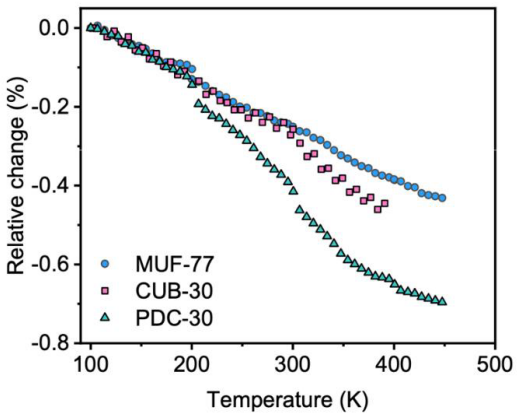

Figure 1. VT-PD data illustrating the relative change of lattice parameter a as a function of temperature.

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Abstract Number: 287

DETOXIFICATION STUDIES OF DL- PENCILLAMINE AND ITS COMPLEXES

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Applications of co-ordination chemistry in the medical science is appreciable in chelation therapy where metal poisoning has been successfully treated with the help of chelating agents.Co-ordination compounds play an important role in the biological system and the current Chelating agents form soluble stable non-toxic complexes which can readily be excreted. DL-Pencillamine is one of such potential chelating agents used for detoxification. It is a drug used for patients suffering from Wilson's disease and it promotes the urinary excretion of copper metal from the biological system. The present work includes formation of binary and mixed ligand complexes of DL-Pencillamine with various N-N, N-O- O--O- donors and toxic metals.

ACKNOWLEDGEMENTS

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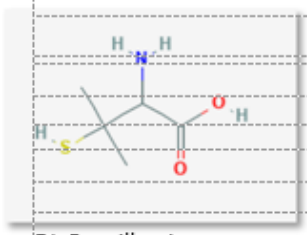
FIGURE



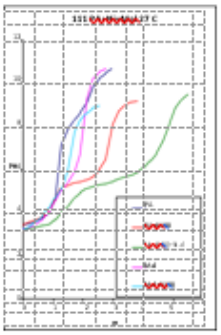
DL-Pencillamine

TABLE

Dissociation constants of ligands (Land A)

$t=37.0^0C$

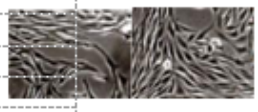
Ligand L or A	pK_a	pK_{2a}	pK_{3a}
DL-Pencillamine	10.426	18.057	20.87
Glycine	2.28	9.32	-



Formation constants for Binary Ni(II), Cd(II) and Pb(II) complexes with Ligand (L) = 0.15 M (KNO_3)

Ligand	27^0 c logK	37^0 c logK	47^0 c logK
DL- Pencillamine + Cd	10. 88	11.66	12.84
DL- Pencillamine + Ni	11. 40	13.40	15.40
DL- Pencillamine + Pb	12. 37	13.00	14.28

Toxicity experiments



Metal pencillamine metal

Pencillamine o-o donor

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Abstract Number: 288

The development of As-pancreatic cancer homing peptide complexes

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Arsenic trioxide (ATO, marketed as Trisenox® and Phenasen®) is a successful frontline treatment for acute promyelocytic leukemia.[1] However, its wider use in other malignancies has been restricted by its indiscriminate toxicity, sometimes resulting in life-threatening side-effects.[2] Dillon and Carrall have developed As-peptide complexes incorporating a leukemia homing peptide.[3] The most stable complex displayed up to 1000 times greater toxicity toward leukemia cells than to healthy blood cells.[3] The aim of this work was to investigate whether similar concepts could be utilised to create an As complex to target pancreatic cancers.

Confocal microscopy was used to examine and quantify the uptake of six peptide candidates (previously established as targeting pancreatic cancer) into three pancreatic cancer cell lines. The two peptide candidates displaying the greatest uptake were then incorporated into As-peptide complexes which were purified by HPLC. *In vitro,* cytotoxicity testing using the MTT cell viability assay on the three pancreatic cancer cell lines resulted in IC50 values up to sixty times lower than the values obtained following treatment with ATO.

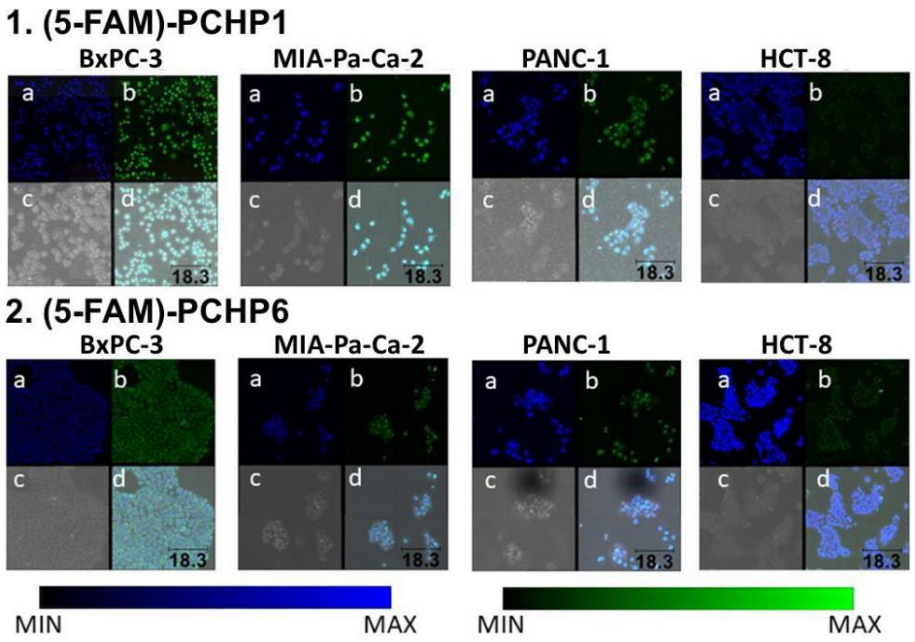

Figure 1: Confocal images (63x resolution) of indicated cell lines treated with 1) (5-FAM)-PCHP1 and 2) (5-FAM)-PCHP6). The images are: (a) Hoechst stained (405 nm), (b) (5-FAM)-peptide treated (455 nm), bright field, and (d) combined image. BxPC-3, MIA-Pa-Ca-2, and PANC 1 are human pancreatic cancer cell lines, while HCT-8, a human ileocecal adenocarcinoma cell line is a negative control.

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Abstract Number: 306

Design of Artificial Enzymes Using Transition Metals

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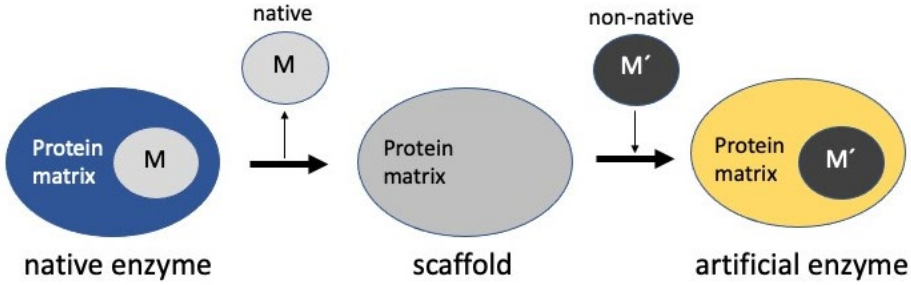
Enzymes are complex molecules where chemical transformations occur with amazing selectivity and at high rates. Metalloproteins and metal-containing enzymes are well known to be essential to life. The elucidation of structural and functional aspects of metal sites in enzymes has been a goal of model studies putting together Inorganic Chemistry and Synthetic Biochemistry related to the developing area of artificial / mimetic enzymes.
Synthetic peptides and small proteins involving rich sulfur coordination sites are extensively used, having the possibility of coordinating a wide variety of transition metal ions, with particular interest in aiming to model complex metalloproteins.

Acknowledgments: Work supported by PT national funds (FCT/MCTES) through projects PTDC/BTA-BTA/0935/2020, UIDB/50006/2020 and UIDP/50006/2020. Thanks are due to Biplab K Maiti, Pedro Bragança, Cintia Carreira, Maddalena Elia, Célia Silveira, Smilja Todorovic, Marta S. P. Carepo, Sofia R. Pauleta, Luísa B. Maia, Tyler B. J. Pinter, Vincent Pecoraro and Isabel Moura for various contributions.



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Abstract Number: 313

Synthesis, characterisation and reactivity of bimetallic complexes encompassing a pyrazole-derived ligand

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Bimetallic complexes have attracted a lot of interest in the field of organometallic catalysis due to their ability to cooperatively reduce small molecules and stabilize unique oxidation states.[1] This metal-metal cooperativity can be made possible by using either ligands that promote the second metal to act as an ancillary ligand to the first metal, such that all chemistry is localized on the first metal, or through the use of dinucleating ligands that allow both metals to cooperatively reduce substrates.[2,3] In this study, the later approach is employed where an unsymmetrical dinucleating pincer ligand, 3-(2-di-tert-butylphophine)pyridyl-5-(2-methyl)pyridine ($PNNNN^H$) is used, see Figure 1. The advantage with this approach is that the presence of two binding pockets allow for the formation of both homo- and heterobimetallic complexes.[4] The motivation behind the use of this ligand is that it will facilitate metal-metal cooperativity by bringing metals close enough to undergo stepwise catalytic reactivity with small molecules. Figure 2 shows a copper dimer complex that was formed from a reaction of [Cu(CH3CN)4]PF6 with one equivalent of the ligand.

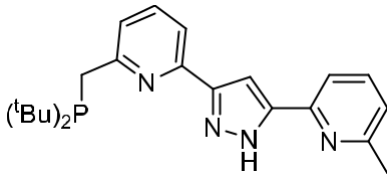

Figure1: 3-(2-di-tert-butylphophine)pyridyl-5-(2-methyl)pyridine ($PNNNN^H$) ligand.

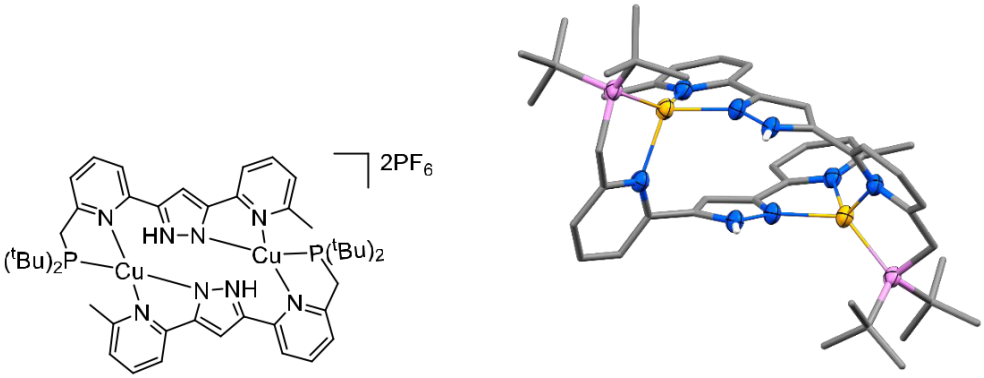

Figure 2: Copper dimer complex, [Cu2($PNNNN^H$)2]2PF6.

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Abstract Number: 321

Development of Radiomercury Theranostics

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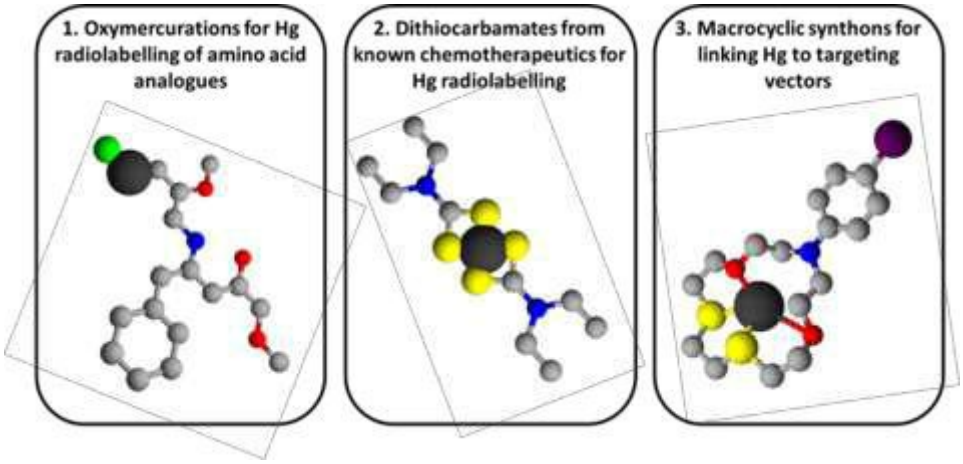
Targeted radionuclide therapies are currently used for the treatment of various forms of cancer.[1] These therapies often consist of (1) a radionuclide that emits therapeutic radiation, (2) a linker, and (3) a targeting vector.[1] A "perfect pair" theranostic approach utilizes different types of radiation emitted by the same radioisotope (or a chemically identical, but different radioisotope) for imaging, treatment planning and therapy.[1] This is a useful technique due to the ability to precisely determine the extent of disease (tumour burden via imaging) and then precisely deliver optimized amounts of therapeutic radiation to the individual patient.[1]

Although radioisotopes of mercury such as ^{203}Hg and ^{197}Hg were once used for brain lesion imaging,[2] these lost popularity upon the discovery of the neurotoxicity of mercury, and the emergence of the portable use of ^{99m}Tc[2,3]. Current advances within the production of the radioisotope $^{197m/g}$Hg have reignited interest in mercury therapeutics, due to appropriate radiation emissions for imaging and therapy, a longer half-life suitable for multiple classes of biological vectors, and the possibility of entry into the brain.[3] As the $^{197m/g}$Hg radioisotope not only emits short path length Auger electrons as therapeutic radiation, but also appropriate energy gamma radiation for Single Photon Emission Computed Tomography (SPECT), this isotope shows great potential for use as a theranostic.[2,3]

This research will show the current progress in three approaches to the development of radiomercury theranostics. These include (a) investigation and optimization of oxymercuration reactions for the radiolabeling of amino acids (L-phenylalanine analogues), (b) the development of chemotherapeutic chelates for mercury by the addition of dithiocarbamates to known chemotherapeutic drugs and (c) the synthesis of macrocyclic synthons for attachment to known radiopharmaceutical targeting vectors for the chelation of mercury radioisotopes.



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Abstract Number: 324

An imine-based linking strategy for unconventional Pt(IV) complexes

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For unconventional platinum(IV) complexes such as [Pt(1,10-phenanthroline)(1*S*,2*S*-diaminocyclohexane)(OH)2]$^{2+}$ (Pt^{IV}Phenss), axial carboxylate ligands are typically employed to enhance activity, uptake or selectivity.[1-3] To introduce molecules which do not contain a carboxylic acid moiety, such as amines, a linker must be used; however, there are presently few reported examples.[4] From our preliminary investigation, we found Pt^{IV}Phenss and its analogues were prone to reduction in alkaline conditions, limiting the use of strong bases and various primary amines. To address this, we developed a robust imine alternative which leveraged a hydrazone or oxime approach (**Fig. 1**).

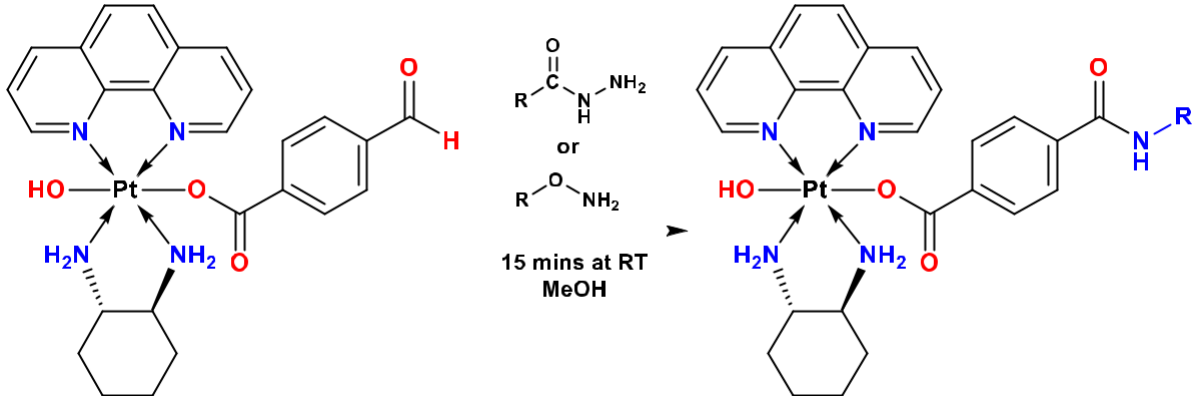

Fig 1. General synthesis of Pt^{IV}Phenss imine derivatives.

To allow for imine couplings, we utilised the ligand 4-formylbenzoate, to provide an accessible aldehyde site. Using this scaffold, we evaluated several commercially available hydrazide and hydroxylamine reagents. We report that most of these reagents afforded the desired imine products in high yields, with minimal or no reduction of the complex. Given the success of this method, there is scope to expand this to allow for the linkage of larger biomolecules.

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Abstract Number: 334

Synthesis of Copper Complexes of Tetradentate Bipyridine - thiosemicarbazone Ligands

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Copper complexes of thiosemicarbazone ligands have been studied intensively due to their potential applications as metal-based drugs and imaging agents.[1] In this work, a new series of hybrid bipyridine thiosemicarbazone ligands have been prepared. The new ligands form stable complexes with copper(II) and zinc(II).

A highly water soluble copper(II) bipyridine-thiosemicarbazone complex (Cubpytsb) was synthesized and characterized by X-Ray crystallography (Fig. 1a), cyclic voltammetry (E0 = -0.87 V vs. ferrocene) as well as UV-Vis spectroscopy (λmax = 412 nm, ε = 4800 L mol^{-1} cm^{-1}). The stability of these complexes has been investigated against common amino acids residues and human albumin serum using both HPLC and spectroscopic techniques. The zinc(II) analogue complexes have also been synthesized and characterized in a similar manner and by NMR spectroscopy and fluorescence spectroscopy (λmax = 480 nm).

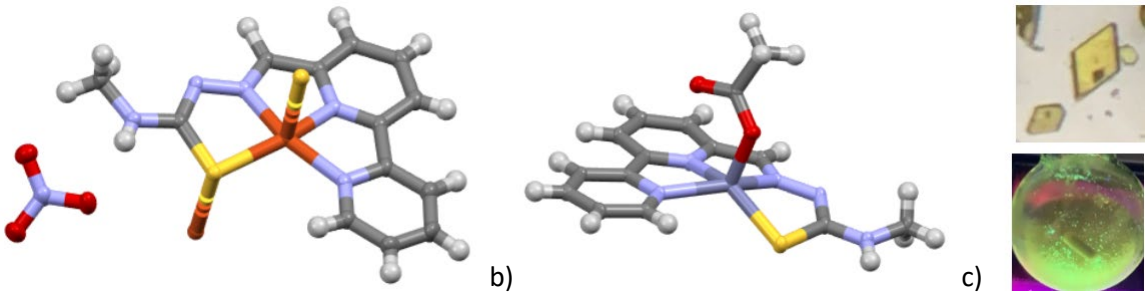

Figure 1. X-Ray crystallography structure of a) [Cu(bpytsb)]NO3 and b)[Zn(bpytsb)]CH3CO2H, c) photo of [Zn(bpytsb)]CH3CO2H crystals.

We acknowledge the Australian Research Council, Australian Cancer Research Foundation, National Health and Medical Research Council, and the Victorian Cancer Council for supporting this research.

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Abstract Number: 325

Lanthanide-dependent PQQ-containing quinoprotein as a catalyst for glucaric acid production

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Glucaric acid is one of a high-value chemical compound from biomass. It is expected to be used as a key material for polymers and is also attracting attention as a pharmaceutical and chelating agent. The compound can be produced synthetically from glucose via electrochemical, chemical, biochemical, and chemo-catalytic oxidation. However, the efficiencies of these existing methods are low for the industrial production of glucaric acid. Enzymatic processes could lead to a higher yield, selectivity, and environmentally friendly production from biomass in simple systems. Glucaric acid can be synthesized in two-step reactions by C-1 oxidation of glucose and C-6 oxidation of gluconic acid, or by C-6 oxidation of glucose and C-1 oxidation of glucuronic acid. Glucose dehydrogenases are well-known enzymes that oxidize the aldehyde group at C-1 of glucose. Although an enzyme that can oxidize the C-6 hydroxyl group of glucose or gluconic acid had been unknown, pyrroloquinoline quinone (PQQ)-dependent alcohol dehydrogenase from *Pseudogluconobacter saccharoketogenes* (PsADH) involved in glucaric acid production was identified in 2022[1]. In this study, we report a lanthanide-dependent PQQ-containing quinoprotein from *Youhaiella tibetensis* which has homologous sequences of PsADH. Ca^{2+} is coordinated with PQQ and amino acid residues in the active site of most quinoproteins, which is essential for activity. However, several recent studies have shown lanthanide ions instead of Ca^{2+}, such as Ln^{3+}-dependent methanol dehydrogenase (Ln^{3+}-MDH). The recombinant protein obtained by E. coli showed oxidative activity upon the addition of PQQ and Ln^{3+}. No activity was shown by adding PQQ alone or PQQ and Ca^{2+}. The enzyme oxidized gluconic acid, suggesting that it can convert to glucaric acid by C-6 oxidation. In addition to glucose and gluconic acid, it showed oxidative activity towards other sugars, sugar alcohols, and alcohols. The enzyme is Ln^{3+}-dependent dehydrogenase with a broad range of substrates.

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Abstract Number: 339

Novel Mn^{2+} complexes with macrocyclic ligands containing various pendant arms – a comprehensive study in the context of MRI

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Magnetic resonance imaging (MRI) is one of the most common modalities in diagnostic medicine. Its low sensitivity can be improved by the use of contrast agents (CA), which are all Gd(III) complexes in the clinical practice.[1,2] As more biocompatible alternatives, Mn(II) complexes are extensively studied due to their favorable properties, such as five unpaired *d*-electrons, long electronic relaxation times and fast water exchange.[3,4] However, combining high thermodynamic stability and kinetic inertness with inner sphere water molecule(s) represents a challenge for ligand design. Macrocyclic ligands provide typically higher thermodynamic stability for the Mn^{2+} complexes than non-cyclic chelators. A pyridine moiety in the structure rigidifies the ligand and leads to better kinetic inertness. In the past, several 15-membered pyridine-based macrocycles were investigated. They provided seven-coordinate Mn(II) complexes with two inner-sphere water molecules, but with insufficient thermodynamic stability.[5]

We have modified the parent 15-membered pyridine-based macrocycle (15-pyN3O2; Figure 1) with one acetic acid pendant arm (**L1**; Figure 1) to increase stability, solubility and kinetic inertness of the Mn(II) chelate.[6] A comprehensive X-ray, potentiometric, dissociation kinetic and relaxometric study revealed (i) a coordination number of seven for Mn**L1** with one inner sphere water, (ii) higher thermodynamic stability and kinetic inertness in comparison to the parent Mn(15-pyN3O2), and (iii) slow water exchange. 15-pyN3O2 was further modified with other, bulkier pendant arms such as pyridine (**L2**; Figure 1) and benzimidazole (**L3**; Figure 1). The effect of these substituents on Mn(II) complex stability, inertness as well as on the parameters governing relaxivity was investigated by potentiometry, dissociation kinetic measurements, ^{17}O NMR and ^{1}H NMRD profiles and these results will be also presented.

References

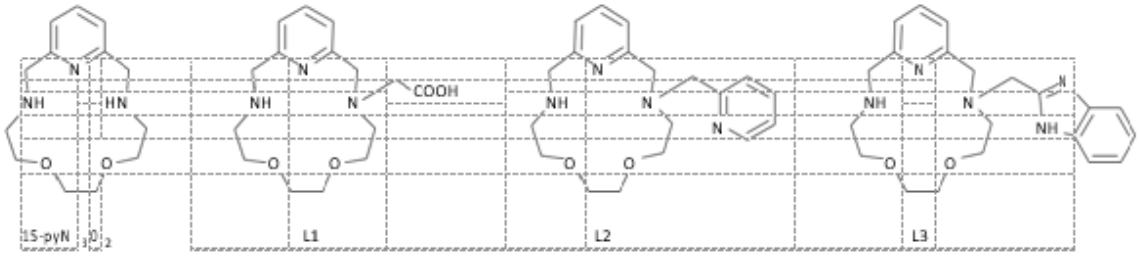

Figure 1. Structural formulas of discussed ligands **L1-L3** and parent macrocycle 15pyN$_3$O$_2$.

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Acknowledgement
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Abstract Number: 340

Modular Access to 2-Fluoroalkene Monoboronates via Pd Catalyst

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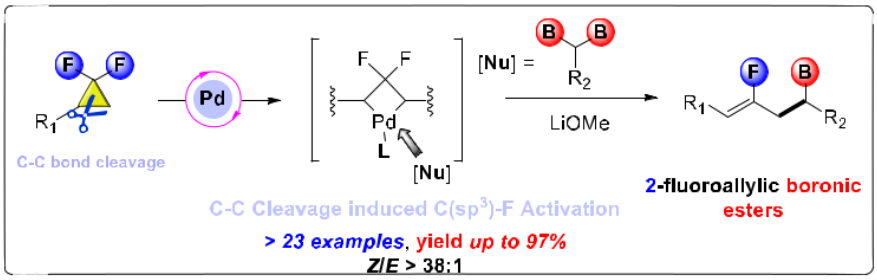
Fluorinated allylic scaffolds are important family of fluorinated compounds, have been studied for possible applications in medicines, agrochemicals, polymers, and materials science. These scaffolds can also be utilized as substrates for the synthesis of more complicated fluorinated compounds. Given their versatility, there is great interest in developing efficient methods for the preparation of various fluorinated alkene derivatives, especially monofluoroalkene boronic acid esters.[1] On the other hand, palladium-catalyzed cross-coupling reactions are widely used in organic synthesis, and the reactivity and properties of *gem*-difluorinated cyclopropanes have made them useful building blocks for the synthesis of numerous valuable and complex organic molecules. Despite the great successes, a general method for obtaining monofuoroalkenes under mild conditions is urgently needed to expand the scope and utility of monofuoroalkenes.[2] The aim of this study is to describe the first regioselective coupling of *gem*-difluorinated cyclopropanes with *gem*-diborylmethane promoted by a Pd catalyst as described in **Scheme 1**. This strategy provides a novel and competent route for the synthesis of 2-fluoroallyl monoboronate scaffolds with high *Z*-selectivity, which are themselves considered essential scaffolds in many biologically active molecules as well as in derived organic compounds. For example, δ-tocopherol, the canagliflozin intermediate, and bioactive estrone derivatives from *gem*-difluorinated cyclopropanes were used in this process and provided the corresponding molecules in good yields and perfect regioselctivities. In addition, *gem*-diborylethane is involved, providing an estrogenic carbon center of a fluorinated alkene in moderate yields and with perfect regioselectivity. Further transformations, such as oxidation to the form alcohol and Suzuki coupling, are included to produce the corresponding monofluorinated arylboronic esters. Trifluoroborylation is also occurred, resulting trifluoroborate salts in high yield.



Scheme 1. Palladium-Catalyzed C-C Cross-Coupling of *gem*-difluorinated

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Abstract Number: 348

Pyrazole Functionalised Group 13-Based Metal-Organic Frameworks for Post-Synthetic Modification

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The use of porous materials as adsorbents or components of membranes for gas separation may provide a means to reduce the environmental and energy footprint of the existing separation methods.[1,2] This is a challenge of global significance from both an environmental and economic perspective.

One class of porous materials, metal-organic frameworks (MOFs), are highly tunable crystalline materials formed through the coordination-driven self-assembly between organic ligands and metal nodes.[3] Through careful ligand design, a vast number of reactive groups or functionalities can be incorporated into MOF structures to provide characteristics that can be tailored to specific applications. Post-synthetic metalation is an additional, valuable strategy to introduce further functionality into MOFs via the insertion of a metal ion or metal cluster into the pores or a vacant coordination site.[4] These vacant coordination sites can be deliberately incorporated into the organic ligand precursor.

With the development of new adsorbents in mind, herein we present the synthesis of a family of group 13-based MOFs that possess vacant pyrazole coordination sites suitable for post-synthetic metalation. This family of MOFs features hexagonal pores with remarkably large diameters of approximately 19.6 Å, making them intriguing systems for probing potential applications in gas separation and even catalysis.

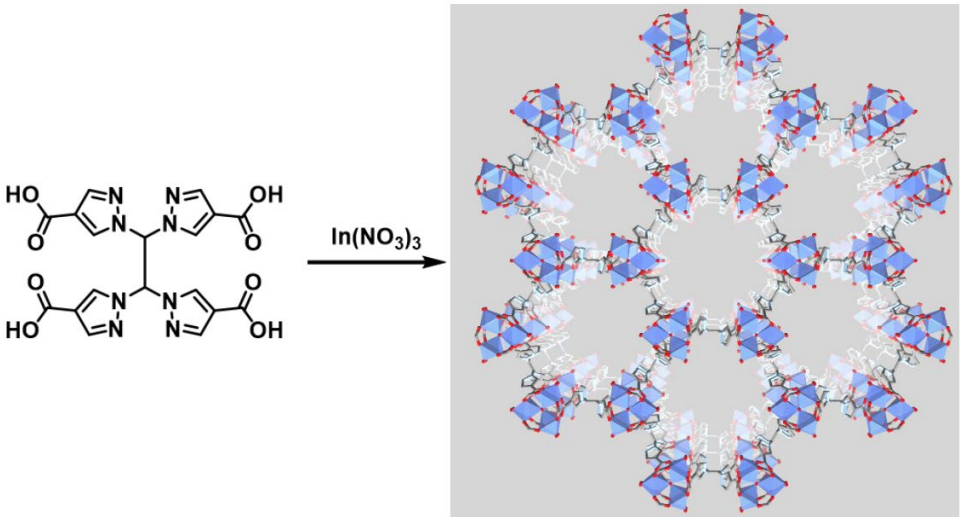

Figure 1. Reaction of tetrapyrazolecarboxylate ligand with In(NO3)3 and the crystal structure of the resulting indium-based MOF.

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Abstract Number: 356

Lowering the LUMO Energy of Aluminyl Anions

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The aluminyl anion is a rapidly emerging frontier of main group chemistry, with the first example synthesised in 2018.[1] Aluminium compounds typically act as electrophiles and are utilised heavily as Lewis acids. However, aluminyl anions feature the aluminium centre in the formal +I oxidation state, with a lone pair of electrons which inverts the reactivity allowing them to act as aluminium-centred nucleophiles. Aluminyl anions have shown some fascinating reactivity, including nucleophilic substitution, cycloaddition and oxidative addition including C-H activation. In this work, we are interested in synthesising an even more reactive aluminyl anion!

Aluminyl anions follow similar stabilisation to carbenes, where nitrogen atoms neighbouring the aluminium act to withdraw σ-electron density from aluminium to lower the HOMO, whilst simultaneously donating π-electron density from the N lone pair into the empty Al pz-orbital to raise the LUMO.[2] Reducing the overlap between these π orbitals decreases the strength of this interaction and destabilises the LUMO, as seen in the orbital energies going from the planar 6-membered aluminyl (Figure 1, left)[3] to the bent NON-aluminyl (Figure 1, centre).[1]

This project aims to extend this trend by synthesising a new aluminyl anion, stabilised by a related ligand (^{S}NON), but where the dimethylmethylene linker of NON is replaced with a 1,2-subsitited arene group. This is proposed to further decrease the π-donation into the Al empty p-orbital, producing a more reactive aluminyl anion. Synthesis of this novel aluminyl anion is currently underway and results will be discussed.

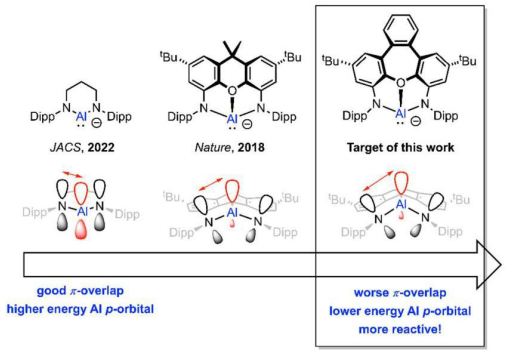

Figure 1. Two recently reported aluminyl anions along with the target of this work, showing decreasing π-donation into the Al empty p-orbital.

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Abstract Number: 361

Magnetic Manipulation of the Reactivity of Singlet Oxygen: From Test Tubes to Living Cells

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Although magnetism undoubtedly influences life on Earth, the science behind biological magnetic sensing is largely a mystery,[1,2] and it has proved challenging, especially in the life sciences, to harness the interactions of magnetic fields (MFs) with matter to achieve specific ends.[3] Using the well-established radical pair (RP) mechanism,[4] we demonstrate a bottom-up strategy for the exploitation of MF effects in living cells by translating knowledge from studies of RP reactions performed in vitro. We found an unprecedented MF-dependence of the reactivity of singlet oxygen ($^1O2$) towards electron-rich substrates (**S**), in which [$\mathbf{S}^{\bullet+}$ $O2^{\bullet-}$] RPs are formed by one-electron transfer from **S** to ^1O 2. Within the framework of the RP mechanism, MFs can modulate the electron-spin states of [$\mathbf{S}^{\bullet+}$ $O2^{\bullet-}$] through the Zeeman and hyperfine interactions of the two radicals, forming a basis for MFs to influence molecular redox events in biological systems (**Fig. 1**). The close similarity of the observed MF effects on the biologically relevant process of lipid peroxidation in solution, in membrane mimics, and in living cells shows that MFs can reliably be used to manipulate $^1O2$-induced cytotoxicity and cell apoptosis-related protein expression. These findings led to a "proof-of-concept" study on MF-assisted photodynamic therapy in vivo, highlighting the potential of MFs as a non-invasive tool for controlling cellular events.

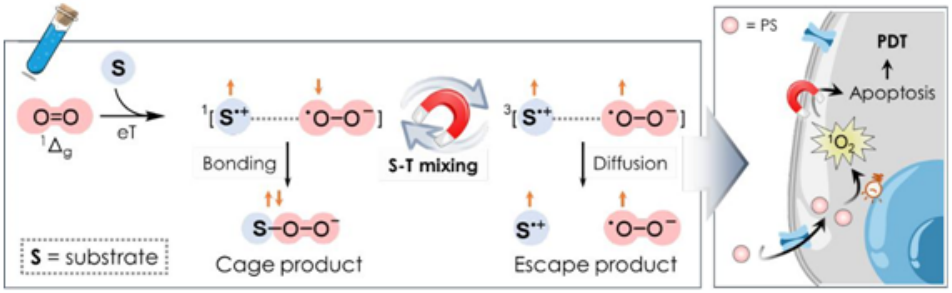

Fig1. Illustration of the RP mechanism for magnetical regulation of reactions of $^1O2$ with various substrates, guiding the magneto-medical applications such as MF-assisted photodynamic therapy (PDT).

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Abstract Number: 376

Biomimetically constructing a hypoxia-activated programmable phototheranostics at the molecular level

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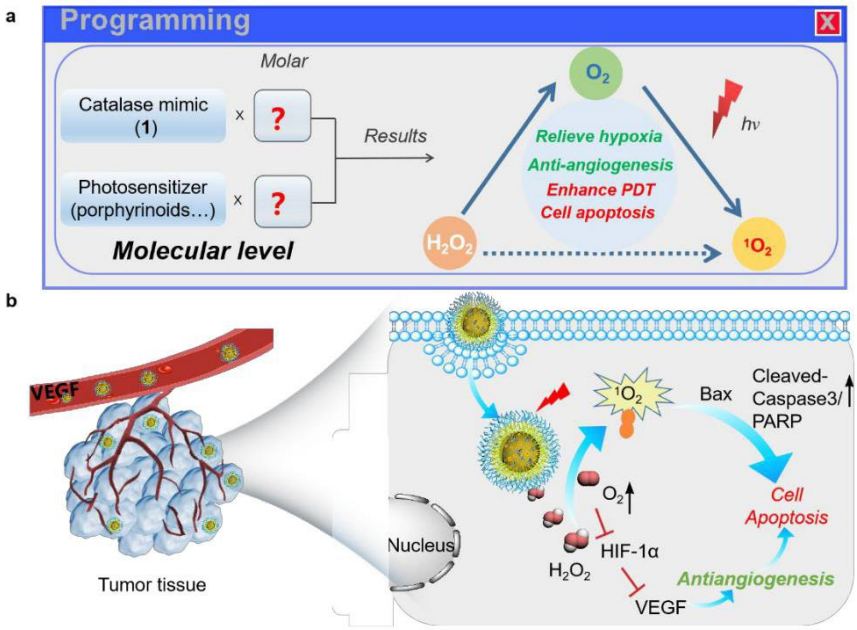
The hypoxic microenvironment is considered the preponderant initiator to trigger a cascade of progression and metastasis of tumors, also being the major obstacle for oxygen consumption therapeutics, including photodynamic therapy (PDT). In this work, we report a programmable strategy on the molecular level to modulate the reciprocal interplay between tumor hypoxia, angiogenesis, and PDT outcomes by reinforcing synergistic action between H2O2 scavenger and O2 generator and photosensitizer. The modular combination of a catalase biomimetic (tri-manganese cryptand, **1**) and a photosensitizer (Ce6) allowed the rational design of cascade reaction beginning with dismutation of H2O2 to O2 in hypoxic conditions to enhance photosensitization and finally photooxidation. Concurrently, this led to the decreased expression of vascular endothelial growth factor (VEGF) and effectively reduced unwanted growth of blood vessels observed in chick chorioallantois membrane (CAM). Notably, the proof-of-principle experiments using the tumor-bearing model proved successful in enhancing PDT efficacy, prolonging their life cycles, and improving immunity, which could be monitored by magnetic resonance imaging.



Scheme. Programmable phototheranostics. **(a)** Schematic illustration of Programmable phototheranostics containing catalase mimic and photosensitizer. **(b)** The proposed synergistic mechanism of PDT combining with anti-angiogenesis for dealing with hypoxia of tumor environment.

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Abstract Number: 379

Photoactivated H2O2-Enhanced Immunotherapy: A Case Study for Nickel(II) Phototheranostics

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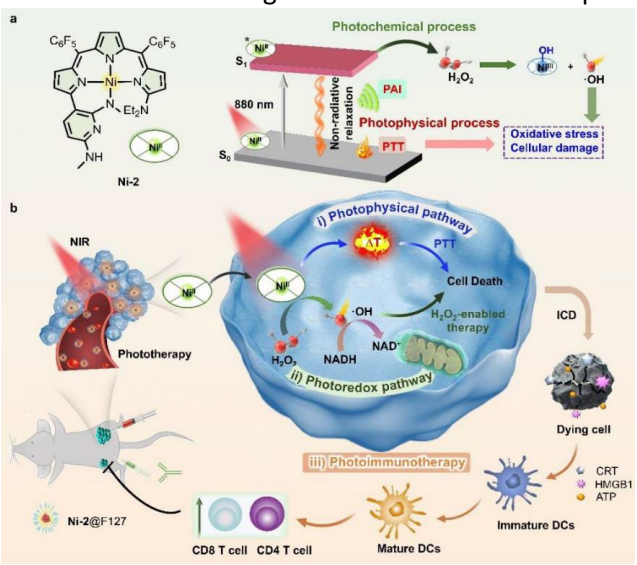
Phototheranostics have emerged and flourished as a promising pattern for cancer theranostics. However, current antitumor therapies still faced severe challenges to accurate diagnosis and completely elimination of tumor, such as insufficient supply of molecular oxygen, high rates of recurrence and metastasis, due to the specific tumor microenvironment (TME) and immunosuppressive state of cancer cells1. Herein, to exploring the possibility 3d transition metal complexes2, a dual-functional oxygen-independent phototheranostics agent Ni(II) linear tripyrrins (**Ni-2**) was rationally constructed for synergistic near-infrared (NIR) photoactivated thermal and hydroxyl radical (•OH) enhanced photoimmunotherapy. Under 880 nm laser irradiation, **Ni-2** exhibited high photostability, excellent photoacoustic/photothermal effect (photothermal conversion efficacy of 58.0%) *via* photophysical pathway, and novel photoredox property *via* photochemical pathway which can catalyze H2O2 to product the •OH and then impacts the ROS level by attenuating antioxidants (i.e., NADH) to regulate TME. This multifunctional photoagent **Ni-2** could not only inhibit tumor growth but also activate immune responses effectively *via* combination of photothermal and H2O2-enabled therapy. By further combining with anti-programmed death-ligand 1 (aPD-L1), distant tumor growth and cancer metastasis were successfully suppressed. Collectively, **Ni-2** showed huge potential to be a facile and efficient tool for photoimmunotherapy. More importantly, this study not only reported an “all- in-one” Ni-based phototheranostic agent but also shed light on the exploration of versatile 3d transition metal organic molecules for future practical applications.



Schematic illustration of **Ni-2** for synergistic NIR photoimmunotherapy. (**a**) Illustration of the photophysical and photochemical processes of phototherapy based on the **Ni-2**. (**b**) Mechanisms of photoactivatable **Ni-2**-mediated heat/H2O2-enabled photoimmunotherapy for cancer.

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Abstract Number: 380

An anticancer Gallium complex initiates ferroptosis through redox homeostasis regulation: trigger the trigger, break the brake

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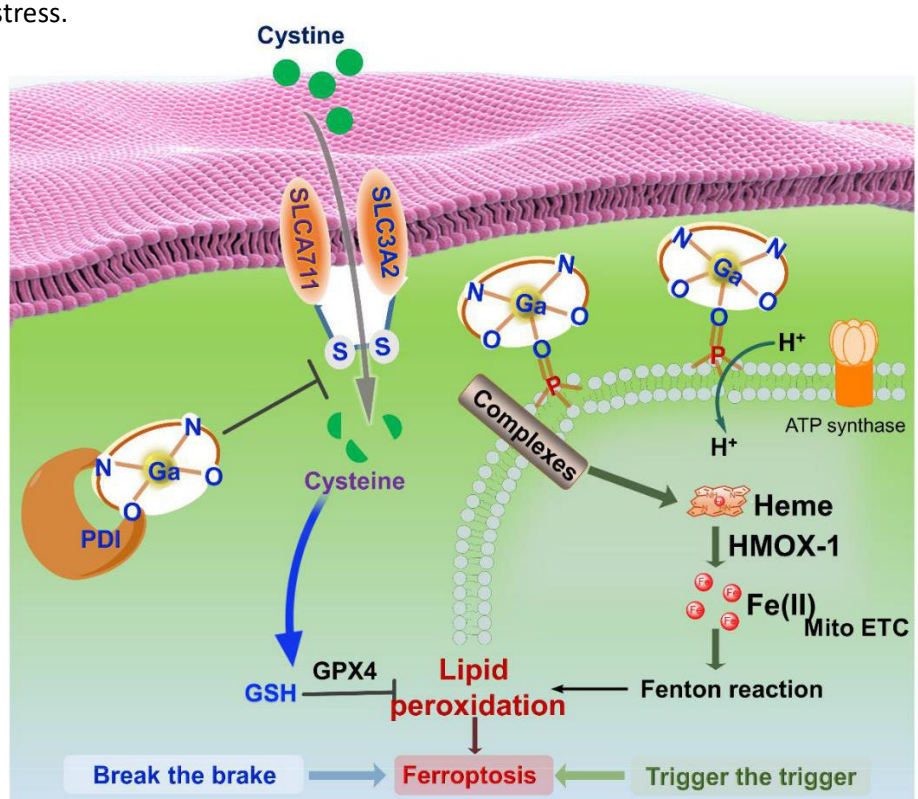
Ferroptosis is a non-apoptotic regulatory cell death caused by accumulation of lipid peroxides generated by Fenton reaction, and is also considered as new strategy for cancer treatment[1]. We developed an anticancer Ga(III) complex, **Ga-1**, with a planar tetradentate salen ligand (salen=2,3-bis[(4-dialkylamino-2-hydroxybenzylidene)amino]but-2-enedinitrile)][2], which induces ferroptosis through "trigger the trigger, break the brake" strategy. On the one hand, **Ga-1** anchors to mitochondrial membrane and leads to release of iron-containing coenzyme in electron transfer chain (ETC), so that triggers iron-overload and lipoperoxidation. On the other hand, considering protein disulfide isomerase (PDI) was previously identified as the potential target of **Ga-1**, we found inhibition of PDI enforces ferroptosis due to preventing the repairing of the glutathione (GSH) system as an antioxidant. As detailed below, our results serve to reveal a synergistic mechanism for **Ga-1** to induce ferroptosis, where the **Ga-1** disrupts the mitochondrial membrane and increases lipid peroxidation; meanwhile, it destructs GSH system upon **Ga-1** binding PDI and causes ER stress.



Proposed mechanism of ferroptosis induced by **Ga-1**: "trigger the trigger, break the brake". **Ga-1** induces ETC dysfunction on mitochondrial membrane, thus promoting the iron release and triggering lipid peroxidation. **Ga-1** breaks the antioxidant system, GSH system, through PDI inhibition.

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Abstract Number: 395

Phosphorescent Iridium Complexes for Specialised Biological Applications

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Phosphorescent d^6 metal complexes can be used as an alternative to organic fluorophores, quantum dots and fluorescent proteins. Their photostability, large Stokes shifts and long excited state lifetimes make them excellent candidates as fluorophores for specialised biological imaging applications such as fluorescent guided surgery or live cell imaging.[1]

Bidentate 1,2,3-triazole ligands can be easily synthesised by copper catalysed azide-alkyne cycloaddition reactions, which allows for straightforward incorporation of various functional groups into the ligands. These triazole ligands can be incorporated into polypyridyl complexes of iridium to provide a handle for bioconjugation.

A family of iridium complexes, incorporating substituted triazole ligands, was synthesised and their electronic properties were characterised using electronic spectroscopy. Their electronic properties were tuned by variation of the cyclometallating ligands.

Water-soluble iridium complexes were prepared by incorporation of polyethylene glycol functionalised triazole ligands. Reactive functional groups such as maleimides were also installed on the water-soluble complexes, which allowed for conjugation to proteins such as bovine serum albumin and girentuximab, an antibody that selectively binds to carbonic anhydrase IX.

Carbonic anhydrase IX is a zinc metalloenzyme overexpressed in some cancers such as renal cell carcinoma. The binding affinity of the iridium-girentuximab conjugates to carbonic anhydrase IX was measured and compared to the binding affinity of unconjugated girentuximab using an enzyme-linked immunosorbent assay.

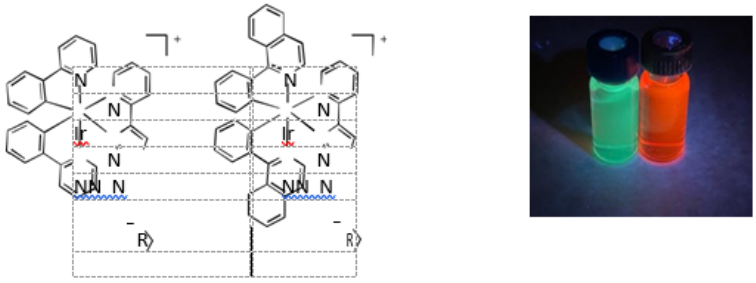

Figure 1: phosphorescent iridium complexes incorporating a 1,2,3-bidentate triazole ligand (left), two of the prepared complexes under UV irradiation (right).

Acknowledgements

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Manufacturing Cooperative Research Centre, and Telix Pharmaceuticals for supporting this research.

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Abstract Number: 398

Single Crystal Analysis of Photoactive Metal Complexes Isolated in a Zirconium MOF

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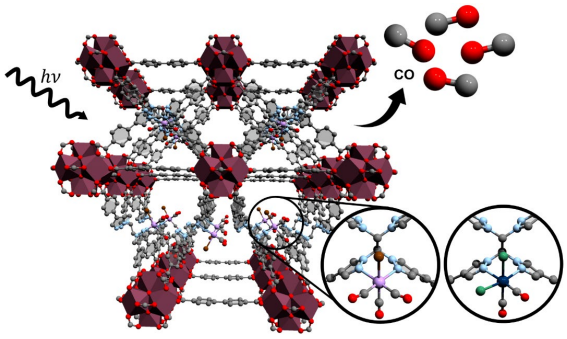
[b] *Australian Synchrotron, ANSTO, VIC, Australia.*

Clean energy is crucial for a sustainable future, and photocatalysis offers a promising approach for converting solar energy into useful fuels and chemicals. In the recent years, photoactive catalysts have been developed for a wide range of chemical transformations, including CO_2 reduction, or hydrogen evolution.[1] However, developing efficient photocatalysts that are both stable and selective remains a major challenge.[2] The high tunability of Metal-organic Frameworks (MOFs), their crystallinity, and the ability to imbue them with free ligating groups, has allowed the support of photoactive organometallic complexes and the formation of photocatalysts.[3, 4] However, the high symmetry of these MOFs typically precludes detailed study of these species and their reaction mechanisms. Our group has recently reported a new Zr-MOF (UAM-1001) containing free bis-pyrazolyl groups. The lower symmetry of the coordinating site in UAM-1001 has allowed the atomic scale elucidation of metal complexes and could be used to provide insights into the mechanism and development of known and future photocatalysts.

Here, we report the isolation of two photoactive organometallic complexes ($[Mn(CO)_3Br]$, $[Ru(CO)_2Cl_2]$) that have been isolated in UAM-1001. Single-crystal X-ray diffraction allows the atomic scale elucidation of both metal coordination environments in the MOF. Both adopt an octahedral geometry with the Mn(I) complex bound to the bis-pyrazolyl unit, three CO molecules and a bromide, and the Ru(II) centre bound to two CO molecules and two chlorides that are in a cis configuration. We are undertaking photocrystallography experiments to study the potential reactive complexes formed by photolysis.

A representation of UAM-1001 with enlargements of the bis-pyrazolyl units metalated with the photoactive metal species $[Mn(CO)_3Br]$ (left) and $[Ru(CO)_2Cl_2]$ (right), which are expected to undergo dissociation of CO upon phoysis.



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Abstract Number: 400

Naphthalimide Scaffolds for Optical-XRF Multimodal Probes

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Two promising techniques that provide the appropriate resolution and sensitivity to measure important analytes in cells are optical fluorescence and synchrotron-based X-ray fluorescence (XRF) imaging.[1,2] Alone, both techniques are limited however, utilizing both techniques in tandem would provide complementary information. Small molecular probes are useful tools for optical fluorescence imaging but are not easily detectable by X-ray fluorescence imaging due to the lack of a heavy element.[1] An ideal probe would be one that emits both optical and X-ray fluorescence signals.

The naphthalimide scaffold (Figure 1) has interesting physical properties for use in optical fluorescence imaging due to its high fluorescence and tunable Stokes shift.[1] Moreover, the synthetic ease of attaching multiple functionalities such as targeting groups and heavy element tags is beneficial for future modifications.

Bromine is an ideal candidate for XRF tagging due to its low biological concentration and is generally non-toxic when bound to an organic molecule.[2] Bromine has been used in a multitude of X-ray studies as an XRF tag.[2] Preliminary results of a bromine appended naphthalimide showed good biostability. Lanthanides have potential to be an XRF tag as they are absent in biological systems. Introducing gadolinium in conjunction with bromine allows for ratiometric XRF analysis, where elemental correlations can be compared to quantify the amount of probe in the system.

Herein we present the first prototype of a multimodal probe, featuring bromine and gadolinium as non-native XRF tags, capable of being quantified by both optical fluorescence and synchrotron-based X-ray fluorescence imaging.

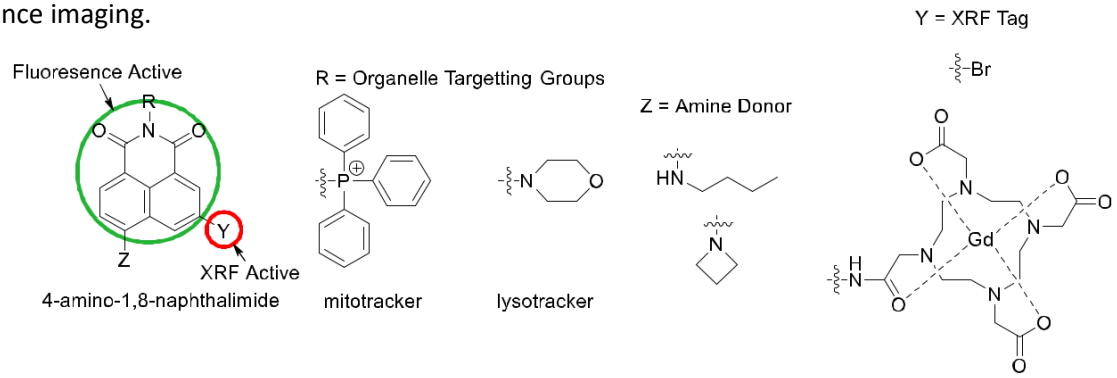

Figure 1. Proposed multi-modal probes, 4-amino-1,8-naphthalimides scaffold.

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Abstract Number: 403

Structure and Function of Bacterial Hemerythrin Domain Containing Oxygen and Redox Sensors

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Hemerythrin is an oxygen-binding protein originally found in certain marine invertebrates. Oxygen reversibly binds at its non-heme diiron center, which consists of two oxo-bridged iron atoms bound to a characteristic conserved set of five His residues, one Glu residue, and one Asp residue. It was recently discovered that several bacteria utilize hemerythrin as an oxygen- and redoxsensing domain in responding to changes in cellular oxygen concentration or redox status, and immediately adapt to these environmental changes in order to maintain important physiological processes, including chemotaxis and c-di-GMP synthesis and degradation. We characterized structure and function relationships of these hemerythrin domain containing sensor histidine kinase and phosphodiesterase1 , revealing characteristic features of this family of proteins2 .

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Abstract Number: 407

Unravelling the paramagnetic states and their redox potentials in formate dehydrogenase FdsABG using multi-frequency continuous wave and pulse EPR

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The molybdenum-containing enzyme dehydrogenase FdsABG catalyses formate oxidation to carbon dioxide, a key reaction in one carbon compound metabolism. FdsABG from *Cupriavidus necator* is a soluble NAD$^+$-dependent formate dehydrogenase and a member of the NADH dehydrogenase superfamily. The enzyme contains a series of Fe-S clusters that facilitates the transport of electrons between the active site Mo centre where formate is oxidised, and a FMN where NAD$^+$ is reduced. In total there are seven Fe-S clusters; 5 in subunit FdsA, 1 in FdsB, and 1 in FdsG. Previous low temperature continuous wave (CW) X-band EPR data have characterised the active site in the Mo^V state and 4-5 of the Fe-S clusters in their paramagnetic states but not their redox potentials. In this work we present EPR data aimed at determining the redox potentials of all the EPR visible paramagnetic Fe-S clusters as well as the Mo centre using a set of samples posed at known potentials. To assist in unravelling the extremely complicated set of overlapping EPR signals we employed both X-band (9-10 GHz) and Q-band (33-34 GHz) spectroscopy and present the first pulse EPR data on the enzyme to help clarify assignment of the observed EPR spectra to clusters in the enzyme. Lastly, the active site structure is studied by pulse EPR to determine the position and orientation of the hydride proton in the Mo^V state which is an intermediate species in the catalytic cycle.

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Abstract Number: 410

Mixed-donor phenanthroline-heterocyclic carboxylate MOFs

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Metal-organic frameworks (MOFs) have become one of the most attractive classes of material under investigation for their applications due to their special properties. However, precisely tuning the shape and pores size in MOFs remains a challenge. Using mixed-donor ligands is one of the most comment methods to control the use of multiple metals and achieve the targeted topologies in a framework.

Previously, our group used the phenanthroline-carboxylate ligand system to form a mixed-metal photoactive Ru-Co MOF (1H-imidazo [4,5-f][1,10]-phenanthroline ligand) with large pore apertures and resulted in high CO_2 sorption capacities and selectivity over N_2 (Figure 1) .[1] A few years later, our group used a longer phenanthroline-carboxylate ligand (2-(4-carboxy-1,1'-biphenyl)imidazo(4,5-f)(1,10)phenanthroline ligand) to form manganese (II) or zinc (II) MOFs (Figure 1b) which also photoactive and with favorable CO_2 selectivity.[2] Further investigations using the same ligand were performed using a mixed Eu-Ru system, which resulted in a photosensitizing MOF shows properties for selective CO_2 reduction.[3] With just a fine tune of the ligands length and metals choices, huge impacts in the framework CO_2 capacity and applications can result. Besides the choice of metals and lengths of the ligand, changing the angle in the system is also an interesting variable to investigate. Thus, the aim of this project is to employ a new strategy to modulate the angle of the phenanthroline-carboxylate ligand system using heterocyclic linkers which can offer a carboxylic acid coordination site in an adjusted position. The new phenanthroline-carboxylate ligands are formed with furan, thiophene, or pyrrole. The resulting ligands form MOFs with single or mixed metal species (i.e Ru^{II}, Co^{II}, Mn^{II}, Zn^{II}, etc.) and here we share their properties and structure using single crystal X-ray diffraction, powder X-ray diffraction, and gas sorption analysis.

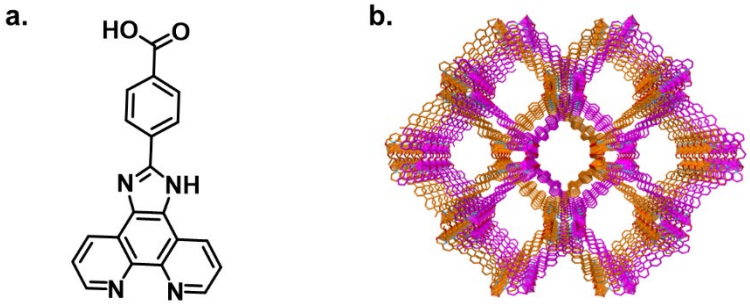

Figure 1. a) Phenanthroline-carboxylate ligand; b) Zn (II) Mixed-donor phenanthroline-carboxylate OF.[2]

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Abstract Number: 411

Cellular fates of bioactive ruthenium complexes using synchrotron-based X-ray metallomic techniques

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X-ray absorption spectroscopy (XAS) and X-ray fluorescence microscopy (XFM) are two synchrotron-based techniques frequently deployed to investigate the metallome – the endogenous and exogenous species that constitute the entire metal pool of a biological system. These X-ray methods confer advantages over other analytical techniques available to the inorganic chemist in that they are non-destructive and require minimal chemical or physical manipulation of the sample before analysis, conserving both chemical and spatial information of the element(s) under investigation.[1]

Ruthenium-265 (Ru265) is a μ-nitrido bridged binuclear ruthenium complex that is a potent and selective inhibitor of the mitochondrial calcium uniporter (MCU), an ion channel protein across the inner mitochondrial membrane responsible for regulating cytosolic Ca^{2+} concentration. Ru265 is a structural analogue of the μ-oxo bridged species Ru360, which was first discovered to have MCU inhibiting properties as an impurity in crude formulations of the trinuclear species ruthenium red. While Ru360 selectively inhibits the MCU with minimal off-target effects, cells must first be treated with a permeabilising agent to facilitate the cellular uptake of Ru360.[2] In contrast, the remarkably similar Ru265 is taken up readily by non-permeabilised cells.

XAS and XFM have been used to investigate the differing cellular fates of Ru265 and Ru360. We have used XFM on the 2-ID-D beamline at the Advanced Photon Source to observe the subcellular localisation of ruthenium in HeLa cells treated with either Ru265 or Ru360, previously reported in Angewandte Chemie.[1] Further to this, we have recently collected EXAFS data on diruthenium complexes in human blood models at the Australian Synchrotron in an attempt to elucidate the differing structure-activity relationships in these two remarkably similar compounds.

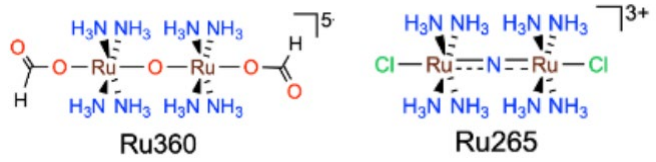

Figure 1. Structures of the mitochondrial calcium uniporter (MCU) inhibitors Ru360 and Ru265.

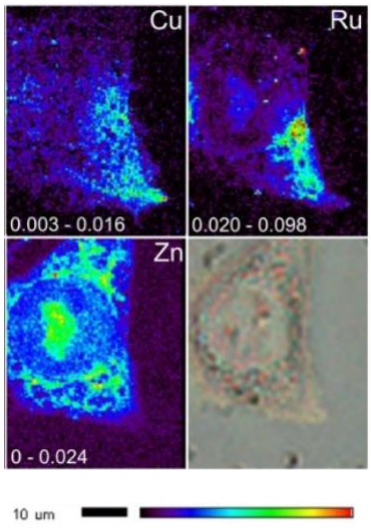

Figure 2. X-ray fluorescenc emicroscopy (XFM) elemental maps of Ru, Cu and Zn of a HeLa cell treated with 50 µM **Ru265** for 3 h. Elemental maps were recorded with an incident beam energy of 22.7 keV at the 2-ID-D beamline at the Advanced Photon Source, Argonne, USA. Bottom-right shows an optical micrograph of the cell.

Elemental concentration is given in units of areal density (µg/cm^2).

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Abstract Number: 414

Protein-inspired ligand functionalities incorporated into DNA G-Quadruplexes

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DNA can fold into a variety of structures besides the widely known double helix structure motif.[1] An exemplary non-standard DNA structure is the G-Quadruplex (G4), which is formed by Guanine rich sequences.[1] In this four stranded secondary structure, four Guanine nucleobases construct a planar G tetrad with eight Hoogsten hydrogen bonds and normally a sodium or potassium ion in the middle.[1] These tetrads can stack *via* π- π stacking onto each other.[1,2] Sequences which are able to form G4's are observed in the promoter region of oncogene and human telomeric DNA.[1-4] This in addition to the involvement of G4's in diseases makes this special secondary structure motif an interesting target.[1-4] Furthermore, modified nucleobases can be incorporated into G4 sequences *via* solid phase synthesis leading to different functions like acting as MetalloDNAymes for catalytic C-C bond formations[5] or metal induced topology changes.[6] In this context, the incorporation of amino acid-like ligands into the backbone of G4 forming sequences to act like DNAzymes is shown. The aim is to mimic the coordination environment of the enzyme hydrogenase, which have cysteine residues and an iron-sulfur cluster in its catalytic center.[7] For this matter, ligands with a threoninol backbone and thiol functions were synthesized and incorporated into G4-DNA. The idea is, that these cysteine functionalities can maybe form iron sulfur clusters.

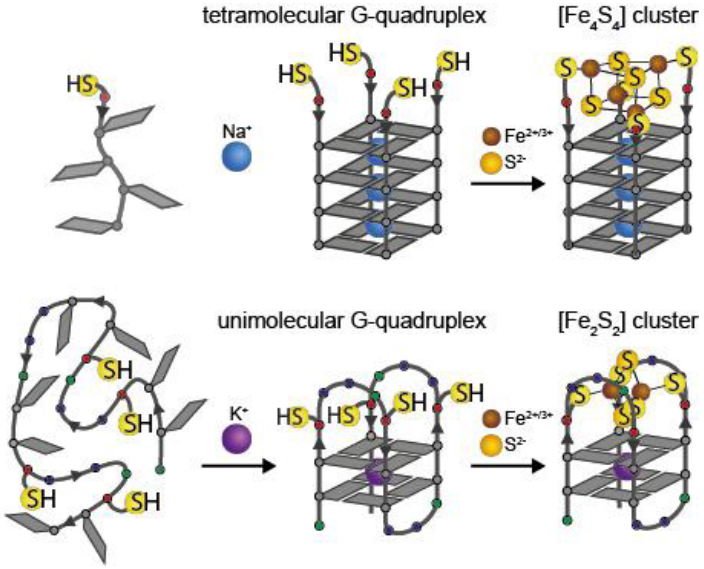

Figure 1: Idea of the formation of G-Quadruplexes and possible formation of iron sulfur clusters.[8]

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Abstract Number: 416

A non-perturbing spin probe to identify catalytic electron transfer pathways via redoxactive amino acids: KatG, tryptophans and the isoniazid prodrug paradigm.

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In metalloproteins, transition metals are responsible for the redox reactions inherent to their catalytic function, that can be enhanced by concerted metal-radical chemistry1 . The catalytic cycle of the bifunctional heme-containing peroxidases (so-called KatGs) includes a concerted heme&Trp□ reaction for the oxidation of substrates2,3. Site directed-mutagenesis and isotope labeling, combined with multifrequency EPR spectroscopy and X-Ray crystallography allowed us to identify Trp330, Trp139, and Trp153 as the radical sites for the heme iron-oxo/Trp□ intermediates in the catalytic cycle of B. pseudomallei KatG (BpKatG). Given the distance between the heme and Trp153, we anticipated that Trp95 and Trp94 should play the role of electron relays, crucially enabling the catalytically-relevant long-range intramolecular electron transfer (iET). Single and double BpKatG mutants on Trp94 and Trp95 allowed us to confirm experimentally their role as electron relays, based on our detailed studies of the catalytic intermediates using multifrequency EPR spectroscopy3 . In this work, we implemented the use of a nitroxide spin label as a convenient reporter to provide direct evidence of such iET process. We designed the a BpKatG triple variant in order to insert a surface exposed Cys residue serving to covalently attach the nitroxide adjacent to Trp94 and Trp95 (the Asp93 to Cys mutation), while removing both natural cysteines (Cys27 to Ser and Cys556 to Ser mutations). Proxyl□ is a stable nitroxyl free radical (N-O□) with a characteristic 9-GHz EPR spectrum, clearly distinct from those of the protein-based (Trp and Tyr) radicals. We have implemented the, so far unexplored, use of a nitroxide spin label that takes advantage of its redox properties, in particular the one-electron oxidation to the oxoamonium cation (Proxyl+), in order to provide a direct measurement and convenient tool for the identification of iET pathways in metalloproteins4 . The oxidation of Proxyl□ resulting from being placed in the catalytic e- transfer pathway of BpKatG can be readily monitored by 9-GHz EPR spectroscopy. Our approach of using Proxyl□ as reporter is then applicable to asses electron transfer pathways related to catalysis in proteins in general.

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Abstract Number: 417

Functionalised aza-macrocycles with potential applications in nuclear medicine

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Theranostics allows for personalized cancer treatment for patients using matched radionucleotides for imaging and treatment. The development of these techniques relies on the ability to attach radionucleotides to their carrier molecules with sufficient stability *in vivo* to minimize metal dissociation. Terbium has been of great interest in this field due to it's four theranostically relevant radioisotopes, making it capable of SPECT and PET imaging as well as alpha and beta/auger electron therapy. Macrocycles are often employed for metal chelation due to their increased kinetic and thermodynamic stability when compared to non-cyclic chelators. Higher denticity ligands also generally create higher stability complexes. Terbium (III) is capable of being 8-coordinate in a slightly disordered dodocahedral geometry which will act as a framework for chelator design.

We aim to synthesise a diammac derivative capable of binding with high affinity to radioactive terbium isotopes or other metals utilized in nuclear medicine. Diammac will be synthesized by employing template synthesis to make dinemac and then reduction.[1,2] The exocyclic amines will then be utilized for further functionalization to the ligand through condensation reactions, reductive alkylation and/or alkylation.[3] This will enable us to form higher dentate ligands, include point(s) for conjugation of targeting properties and tune physiological properties.

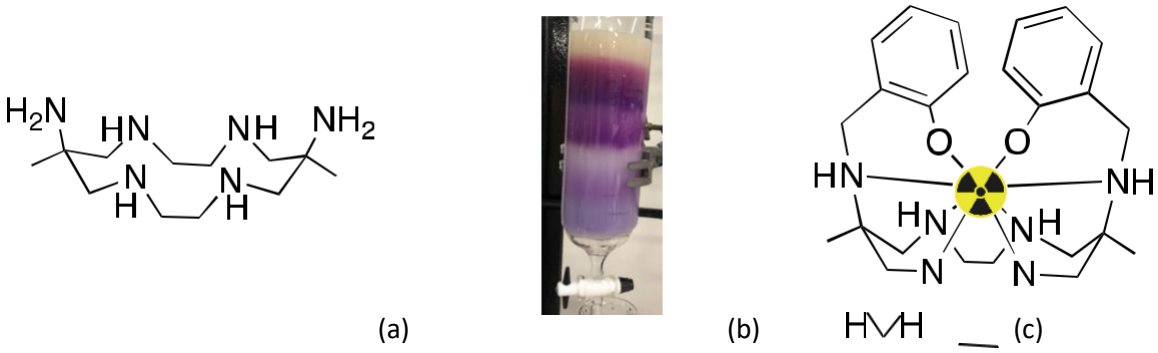

Figure 1: (a) diammac ligand (b) Sephadex column of diammac (c) Prospective ligand

We acknowledge the Australian Research Council, Australian Cancer Research Foundation, National Health and Medical Research Council, the Victorian Cancer Council and Telix Pharmaceuticals for supporting this research.

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Abstract Number: 419

Developing multi-targeting metallodrugs for cancer treatment

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Cancer is a "global killer". Just in 2020, it caused nearly 10 million deaths worldwide[1], and by 2040, almost 30 million new cases and 16 million deaths are estimated worldwide,[2] showing an urgent need for a cure. Today nearly 50 % of cancer patients who receive chemotherapy are treated with platinum (Pt) anticancer drugs such as cisplatin.[3] Despite the success, their severe side effects and natural or acquired resistance of tumours towards Pt limit their application.[4] Thus, new anticancer agents with a combination mode of action to complement the DNA-targeting mechanism of cisplatin are required to overcome these limitations.

This project aims to develop bimetallic anticancer drugs by integrating gold with platinum or Pd in a single molecule incorporating their complementary modes of action. Pt targets DNA, whereas gold inhibits an enzyme called thioredoxin reductase (TrxR) linked to drug resistance and targets mitochondria.[5]

For the synthesis of d^8- d^{10} heterobimetallic compounds (**3**), the ortho-metallated complexes of the type [M(C6R4L2) 2L'2], **2** (M = Pt, Pd, Ni; R = H, F, Cl; L= PPh2, PMe2; L' = PPh3, PMe3) are used as a host precursor. These can be obtained by the ring-opening reaction of the bis (*ortho*-metallated) complex *trans*-[M(κ²-2-C6F4PPh2)2][7], **1** in the presence of excess trimethylphosphine as a mixture of *syn*- and *anti*-isomers of [M(C6R4L2) 2L'2] (**Figure 1**).

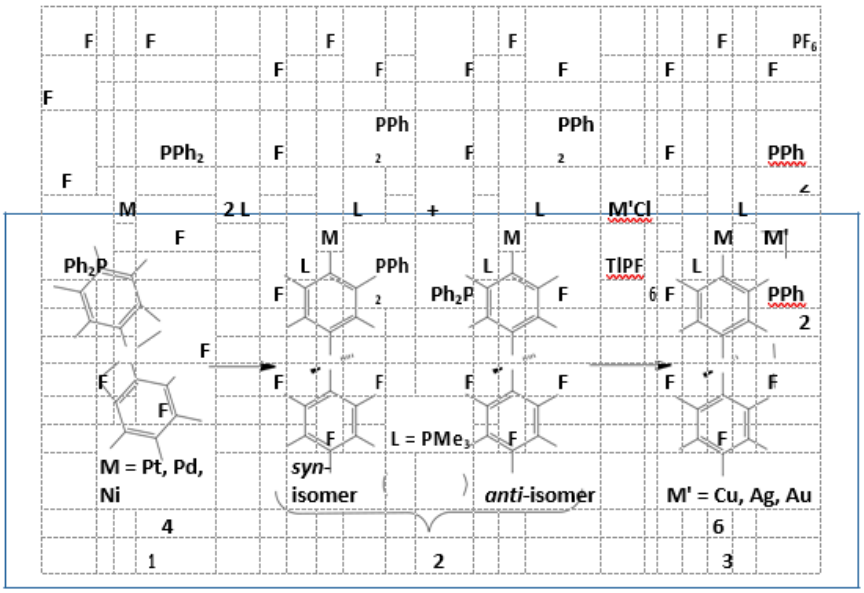

Figure 1. Synthesis of the d^8-d^{10} heterobimetallic complexes with [M(C6R4L2)2L'2] type precursor

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Abstract Number: 435

Amino acids derived carbon dots functionalized gold, silver and their bimetallic nanoparticles and their *in vitro* cytotoxicity

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Carbon dots, an emerging nanostructured form of carbon have been demonstrated as novel class of imaging agents, drug carriers, cancer therapy and many other biomedical applications by a virtue of their interesting optical properties, biocompatibility, and their porous nature. However, majority of the carbon dots have the disadvantage of nonselective interactions with both tumour cells and normal cells. Carbon dots that can mimic the large amino acids are recently shown for selective imaging and drug delivery to tumours. Hence, we used a synthetic strategy of making carbon dots from the amino acids that were bound to the metal nanoparticles, as the formed carbon dots surface can structurally mimic large amino acids and proteins. Carbon dots formation and their orientation on the surface are dependent on the composition of the underlying metal nanoparticles. In this present work, tyrosine amino acid functionalized gold, silver and the bimetallic nanoparticles were synthesized. These three nanoparticles were subjected to microwave mediated carbonization to form carbon dots functionalized gold, silver and bimetallic nanoparticles.

Further, these functional materials were characterized using UV-Vis spectroscopy, FTIR, zeta potential measurement and TEM. The in vitro cytotoxicity of these functional materials with different metal composition, concentration and the surface functionalization were evaluated by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. For this purpose, human cervical cancer cell line (HeLa) was treated with different concentrations of these nanomaterials. The impact of HeLa cells exposure to carbon dots on cell viability was assessed. Our results clearly indicate the role of functionalization, metal composition and doses have different cytotoxic effect on HeLa cells. These studies suggested that carbon dots functionalized gold, silver and their alloy nanoparticles can be explored for cancer imaging and therapy by selectively targeting the cancer cells.

Abstract Number: 448

Hierarchically Porous MOF Superstructure Catalysts Synthesised Using Sacrificial Metal-based Templates

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Metal-organic frameworks (MOFs) are high surface area, porous materials with chemically mutable structures, making them promising supports for heterogenous catalysts.[1] However, MOFs are synthesised as microcrystalline powders, which are not suitable for many industrial applications due to difficulty in handling and poor packing efficiency.[2] Many MOFs are also microporous in nature which can limit mass transfer, slowing the diffusion of reagents to the catalytically active sites within the framework.[3]

These challenges can be overcome through the structuralisation of MOFs into hierarchically porous superstructures.[4] Using a mesoporous metal template as the inorganic component, and introducing an organic linker under carefully controlled reaction conditions, can convert the 414
inorganic scaffold into a MOF through coordination replication.[5] The resultant MOF superstructure retains the mesoporous structure of the sacrificial templating metal source, while gaining new micropores inherent to the MOF to create a hierarchically porous solid. Additional metal species can then be introduced to this MOF support, through techniques such as incipient wetness impregnation or post-synthetic metalation, to synthesise catalytically active materials.

This work will establish the procedures to produce catalytically active MOF superstructures with hierarchical porosity from metal-based, porous monolithic sacrificial templates. The methods developed in this work have the potential to combine several combinations of metal and organic linker precursors, allowing for the synthesis of a broad range of MOF catalyst supports.

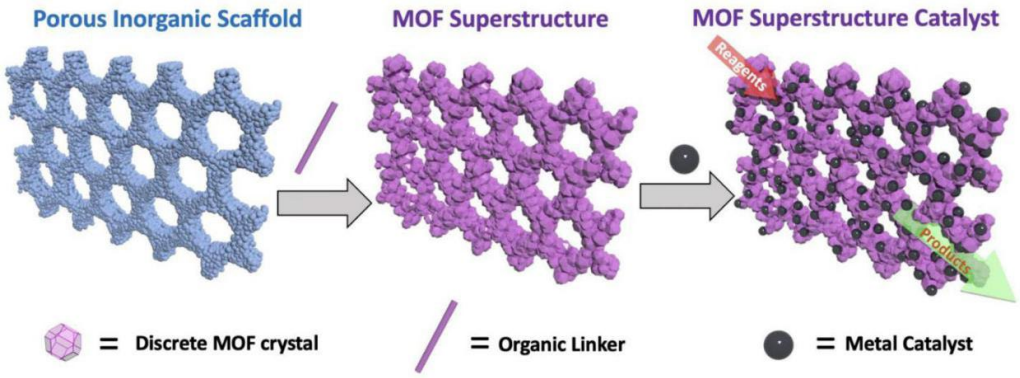

Figure 1. Schematic depicting the conversion of a metal-based template into a hierarchically porous MOF superstructure catalyst. The authors thank Prof. Paolo Falcaro for supplying the figure images.

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Abstract Number: 449

Electrochemical synthesis of Au-NHC complexes from Au metal and their direct use in catalysis

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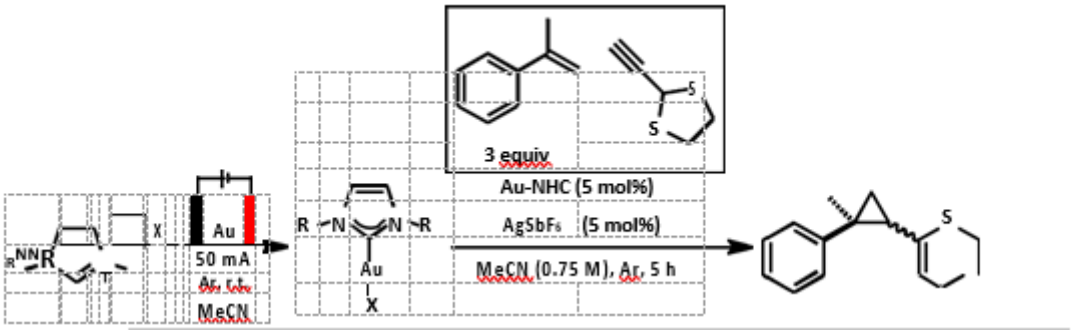
Gold-*N*-heterocyclic carbene (Au-NHC) complexes have been synthesized using an electrochemical methodology. The use of electrochemistry obviates the need for strong or weak base or Cu/Ag-based carbene transfer complexes. The Au-NHC complexes can be produced starting from just the imidazolium salt, Au metal electrodes, and electricity. There is no requirement for exogeneous redox agents or supporting electrolyte as the imidazolium salt itself is the electrolyte. The only by -product of the reaction is H2 gas which is released to the atmosphere meaning that at the completion of the reaction the only species in solution is the Au-NHC complex.

The Au-NHC complexes produced electrochemically can be used directly in catalysis without any work-up or purification. A telescoped Au-NHC- catalyzed vinylcyclopropanation reaction has been developed in which the Au-NHC complex is produced electrochemically and then transferred directly to the catalytic reaction mixture (Scheme 1).[1] Benchmarking experiments show that the telescoped procedure is equally as effective as using a pre-prepared Au-NHC complex despite the absence of work-up or purification.



Scheme 1. Telescoped synthesis of Au-NHC complexes and direct addition to a vinylcyclopropanation reaction.

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Abstract Number: 450

Metal-coding assisted serological multi-omics profiling deciphers the role of metals in COVID-19 immunity

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Metals are crucially involved in infectious diseases as immunity mediators, uncovering how host metals mediate the immune response against invading pathogens is critical for better understanding the pathogenesis mechanism of infectious disease (1). Clinical data shows that imbalance of host metal ions is closely associated with the severity and mortality of COVID-19. However, it remains elusive how metal ions, which are essential elements for all forms of life and closely associated with multiple diseases if dysregulated, are involved in COVID-19 pathophysiology and immunopathology. In this study, we built up a metal-coding assisted systematic multi-omic platform (2), i.e. serological metallome, immunoproteome integrated with single-cell proteome, aiming to characterize the multifaceted features of COVID-19 and explore the potential roles and influence of metal(loid)s on COVID-19 disease.

We found distinct metallome features in COVID-19 patients compared with non-infected control subjects, which may serve as a biomarker for disease diagnosis. Moreover, for the first time, we constructed a correlation network between the host metallome and immunoproteomes, providing a holistic view of the links between the host metallome and immunity of COVID-19. Importantly, we unbiasedly uncovered a strong association of selenium with interleukin-10 (IL-10). Supplementation of selenium to immune cells resulted in enhanced IL-10 expression in B cells and reduced induction of proinflammatory cytokines in B and CD4+ T cells. The selenium-enhanced IL-10 production in B cells was confirmed to be attributable to the activation of ERK and Akt pathways. We further validated our cellular data in SARS-CoV-2-infected K18-hACE2 mice, and found that selenium supplementation alleviated SARS-CoV-2-induced lung damage characterized by decreased alveolar inflammatory infiltrates through restoration of virus-repressed selenoproteins to alleviate oxidative stress. The integrative multi-omic approach provides a general platform for metalloimmunology study, which could be readily extended to other diseases to understand how the host defends against invading pathogens through the regulation of metallome.

Acknowledgement: This work was supported by the Research Grants Council [R7070-18, 2122- 7S04, CRF (C7034-E)], ITS (ITS/278/20) of Hong Kong SAR, and the University of Hong Kong (URC and Norman & Cecilia Yip Foundation).

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Abstract Number: 451

Coumarin amphiphiles as membrane-active antibacterial agents

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By 2050 antimicrobial resistance is predicted to become the direct cause of 10 million deaths annually.[1] Antibacterial agents that permeabilise or destabilise bacterial membranes exhibit potent broad-spectrum activity and rarely suffer from bacteria forming resistance against them.[2] Natural membrane-active antibacterial agents, such as antimicrobial peptides (AMPs), achieve membrane targeting by adopting an amphiphilic conformation, with potent agents containing cationic heads to facilitate phospholipid association, and hydrophobic lipid-like tails, to facilitate membrane disruption.[3-5] The functionalisation of low molecular weight scaffolds with amphiphilic features provides new classes of antibacterial agents which are more readily synthesised and exhibit improved metabolic stability compared to larger macromolecular structures.[6]

This project describes the synthesis and antibacterial evaluation of a series of cationic coumarin amphiphiles which display antibacterial activity against Gram-positive (*S. aureus*) and Gram-negative (*E. coli* & *A. baumannii*) bacteria. The most active of this series exhibits a minimum inhibitory concentration (MIC) of 2 µg/mL against methicillin-resistant *S. aureus* (MRSA). Moreover, these compounds have demonstrated growth inhibition of MRSA biofilms.

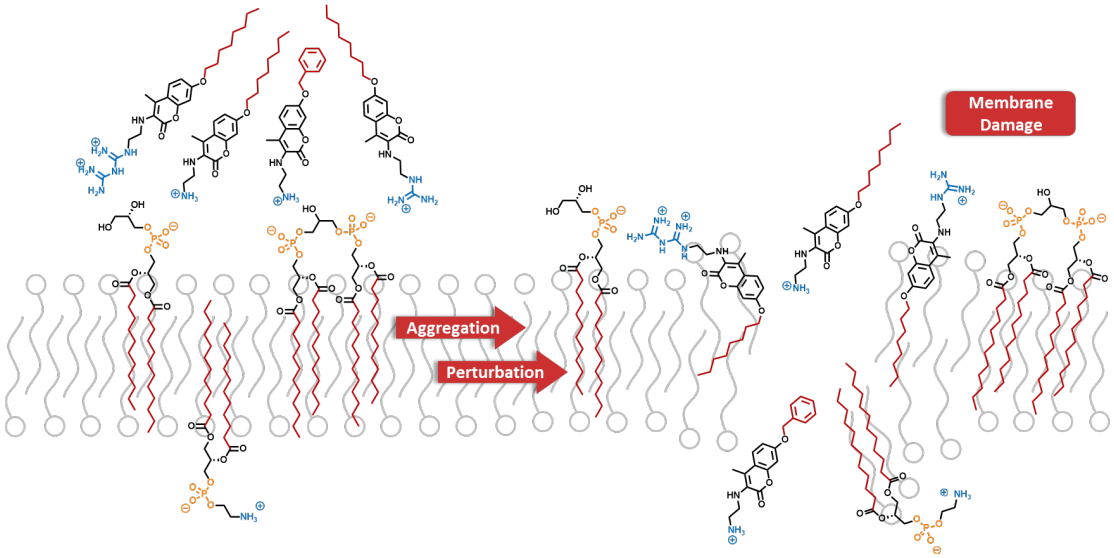

Figure 9: Proposed mode of action of coumarin amphiphiles.

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Abstract Number: 452

Design, in silico assessment, and synthesis of quinoxaline platinum complexes as ATPase competitive topoisomerase inhibitors

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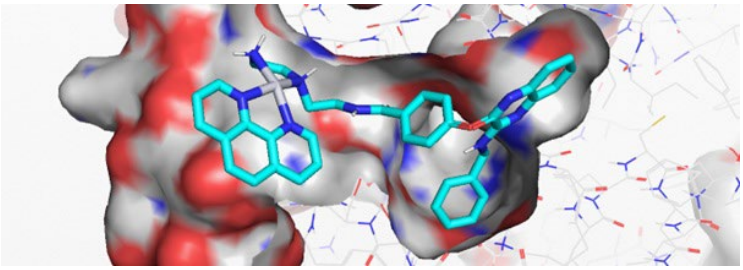
Cancer is the second leading cause of death worldwide and was responsible for the deaths of 9.96 million people in 2020. While the development of new cancer treatments has resulted in a 15 % decrease in cancer's mortality rate since 1990, there is still a need for more effective cancer treatments. One of the limiting factors of cancer treatments is the presence of dose limiting side effects due to off-site toxicity. As an example, the drug candidate XK469 showed promising antitumour effectiveness in preclinical testing but was withdrawn due to causing myelosuppression in phase I trials. As such, there remains a need to optimise the therapeutic ability of anticancer therapies.

The incorporation of metal-ion complexes into existing drug structures provides new opportunities for therapeutic optimisation. [1] The metal ion and coordinated ligands are able to modify drug properties including efficacy and target specificity, as evidenced by the etoposide derived compound etoplatin-N2α. [2] Therefore, this strategy has the potential to produce viable analogues of drugs that had initially shown potential in testing but were rejected due to undesirable side effects.

Accordingly, we have designed and synthesised a range of platinum-quinoxaline complexes derived from the lead compound XK469. Platinum-quinoxaline complexes were designed and their interaction with the target ATPase domain of the TOP2A enzyme was modelled with Autodock software. The complexes with the best calculated interaction were synthesized and characterised by NMR and mass spectroscopy. Finally, the complexes' anticancer efficacy was assessed *in-vitro* against the A549 tumour cell line (human non-small cell lung cancer), with two of the complexes showing activity comparable to the clinically used compound cisplatin.



An XK469 derived quinoxaline ligand conjugated to a platinum ion and 1,10-phenanthroline ligand, locating within the ATPase domain of the TOP2A enzyme.

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Abstract Number: 453

Perovskite Photocatalysts for Environmental Remediation

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Per- and polyfluoroalkyl substances (PFAS) are a ubiquitous class of stable, synthetic organic compounds that pose a significant threat to the health of humans and the environment. The fluorinated alkyl chain within PFAS molecules makes them impervious to environmental degradation and metabolic breakdown, exacerbating toxicity. There is a need to develop effective means of degradation.

Complex metal oxides with a perovskite (ABO_3) structure, such as $SrTiO_3$, are being investigated for photocatalytic water-splitting due to their unique photophysical properties. Aliovalent doping of Al^{3+} into the B site within these structures replaces the Ti^{4+}, thus preventing the self-reduction to Ti^{3+} mid-gap states and reducing recombination rates. This method has been shown to enhance photocatalytic efficiency by >100-fold relative to un-doped samples[1]. Aliovalent doping as a form of defect engineering may prove pertinent to improving photocatalysis activity across a range of applications.

This presentation will investigate the viability of transferring this technique to organic pollutant degradation, particularly PFAS. The effect of Al doping density on rates of photocatalysis using methyl orange as a model pollutant will be discussed, and results reported for a solid-state reaction of $SrCO_3$ and TiO_2 to yield $SrTiO_3$, which then underwent a $SrCl_2$ flux-mediated reaction with AlO_3 to dope controlled amounts of Al into the perovskite structure. Conformation of these structures was obtained through X-ray diffraction (XRD), UV-Vis diffuse reflectance spectroscopy (DRS), scanning electron microscopy (SEM), and energy-dispersive X-ray spectroscopy (EDS). Photocatalytic remediation of the model pollutant methyl orange showed a strong dependence on Al concentration.

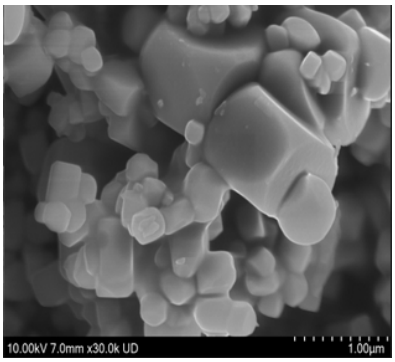

Figure 1. SEM imaging of $SrTiO_3$ doped with 5 mol% Al.

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