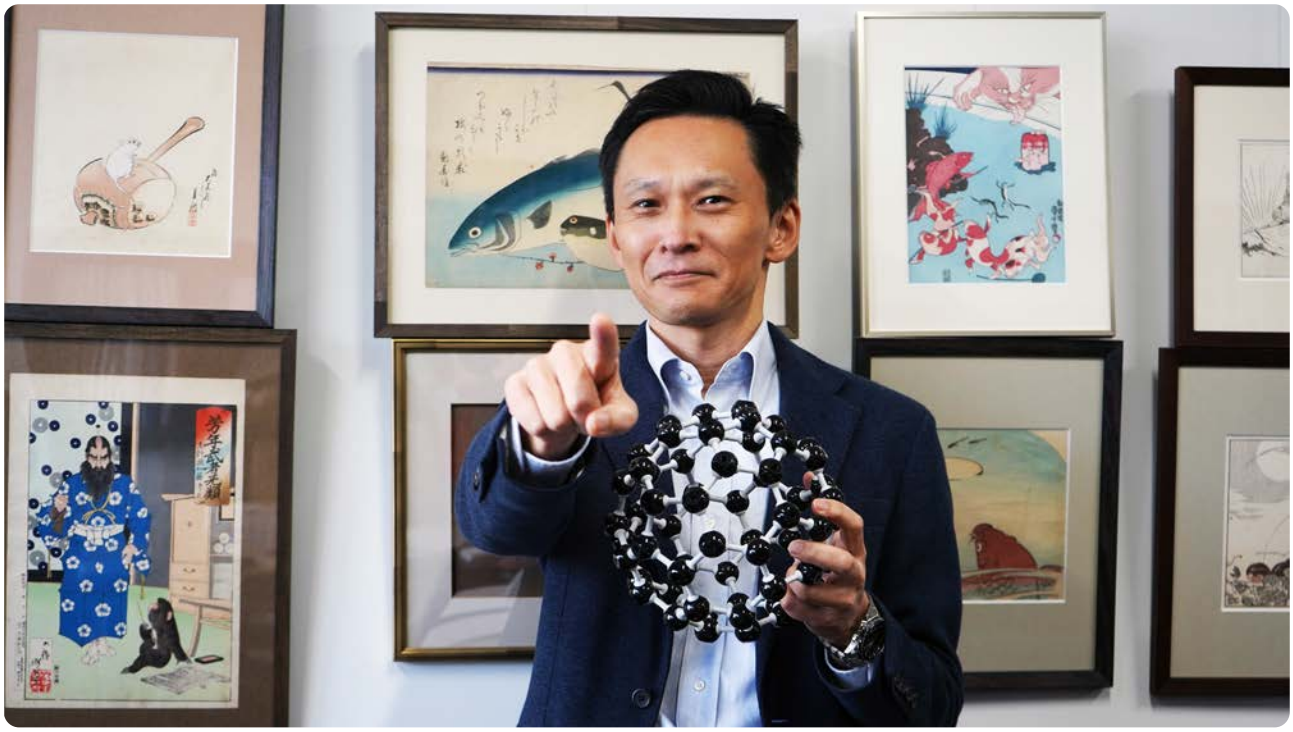
wpi World Premier International Research Center Initiative

2023

Institute of Transformative Bio-Molecules

Contents

Connect molecules, create value, and change the world



Director's message

Changing the world with molecules

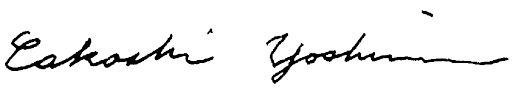
Looking back through history, we can see the revolutionary impact of life-saving drugs like penicillin and vital research tools such as green fluorescent protein. Our dream is to change the world through molecules, and by fusing state-of-the-art synthetic chemistry, biology and theoretical science, ITbM has developed a range of promising bio-functional molecules during its first ten years. Many of these molecules have been commercialized and utilized to discover the molecular mechanisms of important biological events.

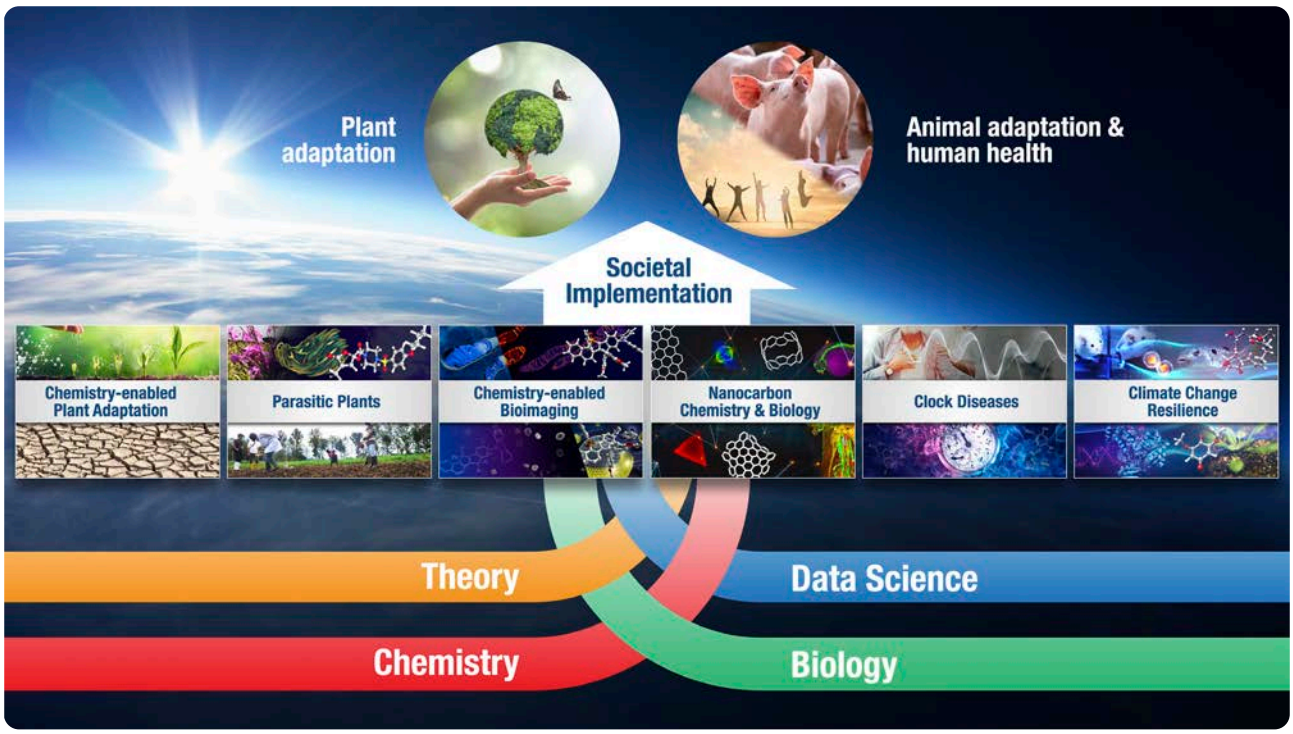
Our earth faces a number of critical issues that are vital to the sustainable future of humankind, such as achieving food security, combating climate change, protecting ecosystems and ensuring healthy lives. In ITbM's second chapter, 'ITbM 2.0', we will further accelerate and expand our research to solve these important social issues with the power of molecules. Novel molecular structures harbor new functions beyond our imagination. If we can utilize the power of such molecules to elucidate fundamental biological functions in plants and animals, we will be able to maximize their ability to grow, reproduce, and adapt to the environment, as well as understand and overcome various diseases.

Curiosity has always been the driving force behind research at ITbM. We will open up new frontiers with the power of molecules through curiosity-driven interdisciplinary research. We will nurture a new generation who can pioneer new science at the interface of multiple disciplines and attract top global researchers to face fresh challenges.

Takashi Yoshimura

Director, Institute of Transformative Bio-Molecules





ITbM at a glance

Interdisciplinary research between chemistry and biology

The Institute of Transformative Bio-Molecules (ITbM) at Nagoya University (NU) in Japan, is an international research institute that conducts interdisciplinary research between chemistry and biology. ITbM was selected in October 2012 as one of the centers of the World Premier International Research Center Initiative (WPI), a ten-year program funded by the Japanese Ministry of Education, Culture, Sports, Science and Technology (MEXT).

Officially launched in April 2013, ITbM's goal is to create a new interdisciplinary field of research through the collaboration of cutting-edge synthetic chemistry, animal/plant biology, and theoretical science, as well as to deliver bio-molecules that change the way we do science and we live, i.e., “transformative bio-molecules”.

Many transformative bio-molecules have been developed up to now, such as the discovery of penicillin, and the development of the highly effective anti-influenza drug, Tamiflu.

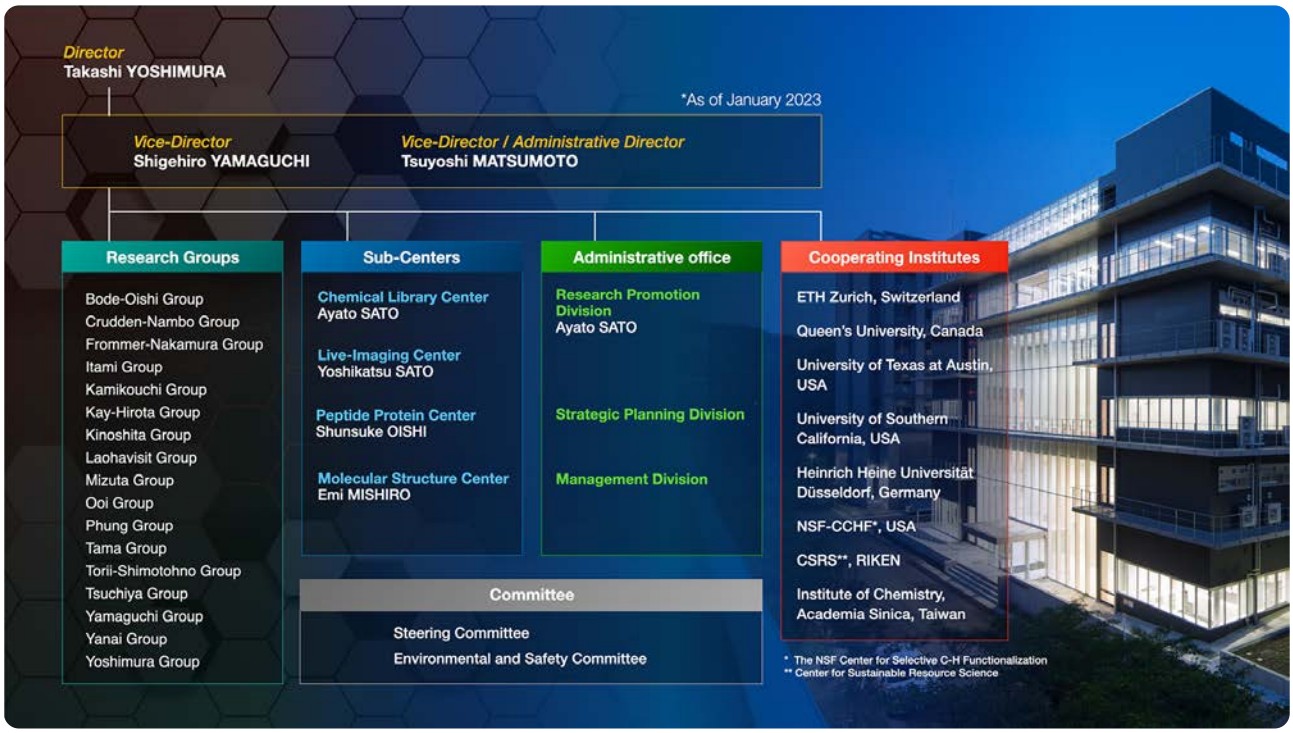
At ITbM, chemists, biologists and theoreticians are collaborating side by side to design, synthesize and evaluate new transformative bio-molecules, and to generate a new research area on the boundaries of chemistry and biology. By taking full advantage of our strengths, ITbM has been conducting ‘needs-inspired’ basic research and explored new research areas of “plant chemical biology”, “Striga”, “chemical chronobiology”, and “chemistry-enabled live imaging” at the beginning of ITbM, “ITbM 1.0”. Going forward with its mission/goal of developing transformative bio-molecules, ITbM set the strategy “ITbM 2.0”, and started the following challenges: “chemistry-enabled plant adaptation”, “parasitic plants”, “clock diseases”, “chemistry-enabled bioimaging”, “nanocarbon chemistry and biology”, and “climate change resilience”. These endeavors will address various social issues regarding the environment, food production, and medical technology.

ITbM has become a truly exciting and internationally visible institute where new interdisciplinary fields of research are emerging and new molecules are being born every day. Although some activities have been limited since FY2020 due to the COVID-19 pandemic, our dream of changing the world with molecules is clearly bearing fruit. ITbM’s challenge continues.

Members and organization

ITbM gathers world-leading researchers in the fields of synthetic chemistry, biology, and theoretical science, and they work together to conduct interdisciplinary research. In 2013, ITbM started with ten PIs (7 from NU, 3 from overseas), and added three more PIs (1 from NU, 2 from overseas) by 2016 to further advance its research. In 2022, under the initiative of the new Director, ITbM is working on research that contributes to human health, with a view of recent global climate changes and data science. With a view to promoting diversity, ITbM has appointed a new PI and three junior PIs who are necessary to tackle these research areas, and will take on the challenges for the next 5-10 years.

To enable world-class researchers to participate in ITbM as overseas PIs, ITbM has introduced the Co-PI system. Through this system, ITbM employs brilliant young researchers as Co-PIs who work full-time at ITbM while cooperating with the overseas PIs. This system enables the overseas PIs to carry out their-own research at ITbM with continuity, and has contributed to improving the global visibility of ITbM. Co-PIs were also allocated to PIs at Nagoya University (NU PIs) to enable them to focus on their research.



One of the keys is the Administrative Department of ITbM, especially the members of the Research Promotion Division (RPD) and the Strategic Planning Division (SPD). The RPD finds inventions and scientific discoveries from each research group at an early stage and achieves mainstream recognition from society through diverse activities such as public relations, science visualization, and so on. The SPD promotes technologize ITbM's research results through application of patents and academia-industry collaboration. The RPD also has the capability to provide local support to ITbM's foreign researchers and their families, enabling them to fully concentrate on their research. ITbM's four sub-centers (Chemical Library Center, Live Imaging Center, Peptide Protein Center, and Molecular Structure Center) also make significant contributions to ITbM's interdisciplinary research. ITbM's research activities are supported by many capable and dedicated staff in ITbM.

As international collaboration has been considerably enhanced by ITbM's internationalization and global visibility, ITbM has strategically expanded its collaboration network and strengthened international collaborative relationships with existing partners such as the Center for Selective C-H Functionalization (NSF, US), RIKEN Center for Sustainable Resource Science (CSRS, Japan), Institute of Chemistry (IoC) at Academia Sinica (Taiwan), and Kenya Agricultural & Livestock Research Organization (KALRO, Kenya). In 2020, the IoC Itami lab was launched and a faculty staff was allocated.

Research groups: Chemistry

Bode-Oishi Group

Jeffrey W. Bode

Position — **Principal Investigator; Professor, ETH Zürich**
Research interests — **Synthetic chemistry, protein synthesis, chemical biology**
Website — ***https://bode.ethz.ch/***

Shunsuke Oishi
(Co-Principal Investigator)

Research overview: The chemical synthesis of proteins can be accomplished by peptide ligation reactions. In our own research, we have developed a new amide-forming reaction of α-ketoacids and hydroxylamines (KAHA ligation) that allows the synthesis of proteins by combining peptide segments under aqueous conditions without coupling reagents or side chain protecting groups. Rendering the synthesis of proteins – including highly modified derivatives and covalent protein–protein conjugates – as routine and convenient as bacterial protein expression is the long term goal of our research program.

Crudden-Nambo Group

Cathleen M. Crudden

Position — **Principal Investigator; Professor, Queen's University**
Research interests — **Asymmetric synthesis, organometallic catalysis, nano materials**
Favorite molecule — **BINAP (chiral ligand)**
Website — ***http://www.cruddengroup.com/***

Masakazu Nambo
(Co-Principal Investigator)

Research overview: Research in the Crudden group focuses on catalysis and materials chemistry. We are interested in developing new reactions to prepare interesting organic molecules, in particular reactions that are enantioselective or enantiospecific. With our collaborators at ITbM, we aim to investigate the biological activity of these molecules for applications in the pharmaceutical and agricultural industries. We are also interested in the use of carbon–based molecules as ligands for metal surfaces and nanomaterials comprised of gold and other metals. With our collaborators at ITbM and other institutions across the world, we aim to investigate the applications of these materials in various fields, including catalysis and biological imaging.

Itami Group

Kenichiro Itami

Position — **Principal Investigator; Professor**
Research interests — **Synthetic chemistry, catalytic chemistry, materials chemistry**
Favorite molecule — **Benzene**
Website — ***http://synth.chem.nagoya-u.ac.jp/***

Faculty members:

Hideto Ito
Akiko Yagi
Kazuma Amaike
Hayato Yamada
Atsushi Usami
Ayaka Ueda

Affiliated researchers:
Shinya Hagihara
Kei Murakami
Takehisa Maekawa

Research overview: The ultimate goal of the Itami group is to develop “transformative molecules”, innovative functional molecules that make a marked change in the form and nature of science and technology. With such a goal in mind, the work of the Itami group has centered on catalyst-enabling synthetic chemistry with broad directions. The emphasis is on the development of new catalysts for solving challenging synthetic problems, for realizing super-efficient chemical syntheses, for high demand molecule activations, and for producing as-yet unexplored molecules of significant interest in various fields.

Ooi Group

Takashi Ooi

Position Principal Investigator; Professor
Research interests Organic synthesis and catalysis
Website *http://www.chembio.nagoya-u.ac.jp/labhp/organic3/*

Faculty members:
Kohsuke Ohmatsu
Yoshitaka Aramaki
Tsubasa Nakashima

Research overview: We have been creating a bold stream of research on the molecular design of various organic ion pairs and their rational structural modifications for eliciting unique functions as molecular catalysts, providing a solid basis for the safe and sustainable supply of useful organic compounds. At ITbM, we develop innovative molecular catalysts that can revolutionize organic reactions and chemical syntheses in order to not only provide sustainable chemical processes, but also accelerate the discovery of transformative bio-molecules as a reliable means for solving problems of fundamental biological significance.

Yamaguchi Group

Shigehiro Yamaguchi

Position Vice-Director of ITbM; Principal Investigator; Professor
Research interests Physical organic chemistry, fluorescent molecules
Website *http://orgreact.chem.nagoya-u.ac.jp/*

Faculty members:
Masayasu Taki
Masahito Murai
Soichiro Ogi
Tatsuya Mori

Affiliated researcher:
Aiko Fukazawa

Research overview: We work on a variety of topics in the fields of main group chemistry and physical organic chemistry. In particular, the emphasis is placed on the construction of new π-conjugated scaffolds, which is crucial for pursuing the photo/electronic functions of organic molecules. At ITbM, we are pursuing the challenge of designing and synthesizing transformative fluorescent π-conjugated molecules for bioimaging applications. A number of fascinating fluorescent molecules have been developed so far, not only for optoelectronic applications like OLEDs (organic light-emitting diodes), but also for biological applications such as fluorescent probes.

Research groups: Biology

Frommer-Nakamura Group

Wolf B. Frommer

Masayoshi Nakamura
(Co-Principal Investigator)

Faculty members:

Satomi Kanno
Akira Yoshinari

Position — **Principal Investigator; Professor, Heinrich Heine Universität Düsseldorf, Max Planck Institute for Breeding Research, Köln**
Research interests — **Molecular biology, biochemistry, chemical genomics**
Favorite molecule — **isorhamnetin-3-O-β-D-glucopyranoside**
Website — ***https://www.itbm.nagoya-u.ac.jp/frommer-nakamura/***

Research overview: The research in the Frommer group at ITbM is carried out in the following four areas: (i) engineering of genetically encoded biosensors and sponges for *in vivo* biochemistry; (ii) characterization of the determinants of interactions between small molecules and transporters to help identifying novel drugs and agrochemicals; (iii) search for yet unidentified receptors for small molecules; and (iv) chemical genomics and imaging of processes related to cellular growth and dynamics.

Kamikouchi Group

Azusa Kamikouchi

Faculty member:

Matthew Paul Su

Position — **Principal Investigator; Professor, Graduate School of Science**
Research interests — **Neuroscience, Insect Physiology, Neuroethology, Acoustic communication**
Website — ***https://www.bio.nagoya-u.ac.jp/~NC_home/index3.htm***

Research overview: Kamikouchi conducts pioneering research using fruit flies as a model for studying hearing. Utilizing neuroanatomical, neuroimaging, and behavioral analyses, she has led ground-breaking investigations into the functional properties of the fruit-fly auditory system, uncovering a number of similarities to equivalent mammalian systems. At the ITbM, she will extend these findings to mosquito hearing research. Mosquitoes carry infectious diseases that kill hundreds of thousands of people each year. Hearing plays an essential role during the mating behavior of these mosquitoes, and thus provides a promising target for controlling their behaviors. At ITbM, she will be involved in developing molecules that can effectively disrupt hearing function by elucidating the fundamental molecular bases underlying mosquito hearing.

Kay-Hirota Group

Steve Kay

Tsuyoshi Hirota
(Co-Principal Investigator)

Faculty member:

Megumi Hatori

Position — **Collaborating Researcher; Professor, University of Southern California**
Research interests — **Chronobiology, chemical biology**
Website — ***https://www.itbm.nagoya-u.ac.jp/en/kay-hirota_group/***

Research overview: By using the resources of clock modifying compounds and genes in combination with state-of-the-art technologies at ITbM, the Kay-Hirota group aims to discover "transformative bio-molecules" that will revolutionize clock research and ultimately benefit human health. A unique combination of molecular, genetic, genomic, biochemical, and chemical biology approaches will allow us to reveal key regulatory processes of the circadian clock and define molecular links between the clock and rhythmic regulation of physiology and behavior. Proof-of-concept chemical probes will provide valuable tools to control clock function in a conditional manner and also act as starting points for developing therapeutics for circadian clock-related disorders.

Elucidating the function of molecules

Kinoshita Group

Toshinori Kinoshita

Position — **Principal Investigator; Professor**
Research interests — **Plant molecular biology**
Website — ***http://plantphys.bio.nagoya-u.ac.jp/en/***

Faculty members:

Yohei Takahashi
Yusuke Aihara
Koji Takahashi

Affiliated researcher:
Norihito Nakamichi

Research overview: Our research focuses on understanding the mechanism of how plants adapt and respond to ever-changing environmental signal. Stomata is the key in this process - since the pair of guard cells surrounding stomatal pores regulate CO_2 uptake for photosynthesis and water loss from leaves in response to environmental signals. We have been studying signaling pathways responsible for stomatal opening and closing, and have identified the key components that regulate this behavior. To elucidate the full signaling pathway of stomatal opening and closing, we are using genetic, biochemical and physiological approaches to uncover the full mechanism. Our discovery will allow generation of plants with high productivity and drought tolerance, simply through the regulation of stomatal openings.

Laohavisit Group

Anuphon Laohavisit

Position — **Principal Investigator; Designated Associate Professor**
Research interests — **Plant Signaling, Plant Physiology**
Website — ***https://www.itbm.nagoya-u.ac.jp/en/members/group/a-laohavisit.php***

Research overview: Plant signaling is central to plant physiology, from plant development to stress responses. Due to their sessile lifestyle, plants need to sense and respond appropriately to various stimuli in different environmental conditions. By using a multi-disciplinary approach, our group aims to 1) identify novel, endogenous and exogenous, signaling molecules 2) unravel their perception and their signaling mechanisms, and 3) determine their biological roles in plants. Such knowledge will enable us to exploit and manipulate beneficial signaling pathways through biology-based and chemistry-based rational designs in collaboration with other research groups. A better understanding of how plants sense and respond to different stimuli will facilitate the way to grow plants in today's fluctuating environment.

Mizuta Group

Yoko Mizuta

Position — **Principal Investigator; Designated Assistant Professor (YLC)**
Research interests — **Plant reproduction, Imaging, Pollen, Gene modification**
Favorite molecule — **Fluorescent proteins**
Website — ***https://www.itbm.nagoya-u.ac.jp/en/members/group/y-mizuta.php***

Faculty member:
Hidenori Takeuchi

Research overview: Even a small flower blooming on the side of the road has a magnificent drama of life hidden in it. We are trying to understand molecular mechanism of plant reproduction by using a microscopic imaging and genetic engineering technologies. Especially focusing on pollen, the genes and the mechanism of pollen tube attraction have been studied. We also developed methods for deep imaging inside a flower, genetic modification, and regulation of germ cells. By understanding how seeds are produced, my research aims to enrich our lives by increasing food production and plant breeding.

Torii-Shimotohno Group

Keiko Torii

Position	**Collaborating Researcher; Professor, The University of Texas at Austin; Investigator, Howard Hughes Medical Institute**
Research interests	**Plant development, cell-cell communication, peptides**
Favorite molecule	**LRR-RLK (plant kinase receptor), caffeine**
Website	***https://www.plant-stomata.org/***

Akie Shimotohno
(Co-Principal Investigator)

Affiliated researcher:
Naoyuki Uchida

Research overview: In the Torii-Shimotohno group, we strive to probe signaling dynamics and manipulate plant development via integrated approaches of synthetic cell biology, chemical biology, physiology and molecular genetics. Fully leveraged on ITbM's core strengths and ambitious mission to fuse catalysis chemistry and plant & animal biology, we aim to: (i) design small molecules to highjack inter- and intra-cellular signaling networks; and develop fluorescent probes to visualize signaling dynamics (synthetic cell biology); (ii) design and screen for small molecules to manipulate plant growth (chemical biology); and (iii) elucidate the functions of ligand-receptor pairs in plant development upon variable environmental stimuli (developmental genetics).

Tsuchiya Group

Yuichiro Tsuchiya

Position	**Principal Investigator; Designated Professor**
Research interests	**Chemical biology in plants**
Website	***https://www.itbm.nagoya-u.ac.jp/Tsuchiya_G_HP/main.html***

Faculty member:
Akira Morikawa

Research overview: The goal of our research is to save African farmers from a parasitic plant *Striga hermonthica* that has been causing a huge problem to crop production in Africa. The damage caused by the single species is devastating, as 10 billion USD worth of crops have been lost every year from the African continent and 300 million people's lives have been affected. We have been studying the mechanism on how *Striga* identifies the presence of host plants and am utilizing the information to develop small molecules to destroy the host-parasite communication. Using chemical genetics, I am trying to elucidate the signaling mechanism of strigolactones (SLs), which are released from the host root and stimulate Striga seed germination.

Yoshimura Group

Takashi Yoshimura

Position	**Director of ITbM; Principal Investigator; Professor**
Research interests	**Animal integrative physiology, chronobiology, systems biology**
Favorite molecule	**DHEA (anti-aging supplement)**
Website	***https://www.agr.nagoya-u.ac.jp/~aphysiol/en_index/***

Faculty members:
Taeko Ohkawa
Naohiro Kon
Tomoya Nakayama
Junfeng Chen

Research overview: Cyclic environmental changes such as day-night and seasonal cycles control all organisms on earth. To better adapt to these cyclic events, organisms have developed internal biological clocks during the evolutionary process. To understand animals' clever adaptation strategies to environmental changes, we apply interdisciplinary approaches to various animals that have highly sophisticated mechanisms. Our findings are currently fueling development of transformative bio-molecules that will improve animal production and human health.

Research groups: Theory

Calculating and analyzing molecules

Phung Group

Quan Manh Phung

Position — **Principal Investigator; Associate Professor**
Research interests — **metalloenzyme, biomimetic chemistry, computational quantum chemistry**
Favorite molecule — **Ferrocene**
Website — ***https://www.itbm.nagoya-u.ac.jp/en/members/group/q-phung.php***

Research overview: Our research focuses on understanding the electronic structure and reaction mechanism of metalloenzymes, which are capable of selectively catalyzing a large number of chemical reactions under physiological conditions, as well as countless biomimetic systems with high catalytic activities. To this end, we employ a wide variety of techniques, ranging from low-cost density functional theory to novel, highly accurate ab initio methods. Our goal is not only to find general patterns in transition metal chemistry but also to make predictions and guide new experiments for new chemical systems with high catalytic activity and selectivity.

Tama Group

Florence Tama

Position — **Principal Investigator; Professor**
Research interests — **computational biophysics**
Website — ***https://sites.google.com/view/computationalbiophysicslab/***

Research overview: Research in the Tama group focuses on the computational studies of structures and functions of large macromolecular assemblies. Dysfunctions of these bio-molecules may result in severe diseases, and in order to understand such diseases and develop treatments, the functional mechanisms of these bio-molecules need to be elucidated. To this goal, Tama's group 1) develops new computational techniques to determine 3D structures and dynamics of biological complexes; and 2) works in collaboration with experimental groups to elucidate functions of bio-molecules of interest.

Yanai Group

Takeshi Yanai

Position — **Principal Investigator; Professor**
Research interests — **Computational quantum chemistry**
Favorite molecule — **Nitrogen molecule and chromium dimer**
Website — ***https://www.itbm.nagoya-u.ac.jp/en/members/t-yanai/***

Faculty members:
Kazuhiro Fujimoto
Masaaki Saitow

Research overview: The heart of chemistry lies in the transformation of molecules. In the Yanai group, we investigate transformations of molecular systems through theoretical and quantum chemistry computational methods. The prime goal of our research is to elucidate the principles and mechanisms guiding chemical transformations, while recognizing the importance of the role of electrons in these systems.

Centers

Accelerating ITbM's interdisciplinary research

Live Imaging Center

Yoshikatsu Sato
Designated Associate Professor

The Live-imaging Center provides access of advanced optical microscopes to everyone–from ITbM members to researchers worldwide. We have many cutting-edge optical microscopes for high-sensitivity imaging, high-speed imaging, wide-field imaging, deep imaging, and fluorescence lifetime imaging. Up to now, researchers from 46 universities and research institutes have used our centers and published 99 original research papers. In addition to the supporting activities, we have developed transformative bioimaging molecules by collaborating with ITbM chemists, such as PREX 710, Mito PB Yellow, and Kakshine. In order to create further applications of these ITbM molecules, we are developing original research on the mechanisms of plant development and environmental response through Grant-in-Aid for Scientific Research (KAKENHI), Moonshot Target 3 (Cabinet Office), and CREST (JST) projects.

Chemical Library Center

Ayato Sato
Designated Associate Professor

Providing opportunities for researchers in different disciplines and creating novel bioactive molecules toward future transformative biomolecules.

The ITbM chemical libraries consisting of 85,000 compounds have been created by selecting natural products, pharmaceuticals, agrochemicals, and newly synthesized compounds. In addition, the center equips with an automated liquid handling workstation, clean bench, incubators, high performance liquid chromatography-mass spectrometer (LCMS), and devices necessary for synthetic chemistry, which are relevant to conduct chemical biology research. To date, the center has provided more than 2.5 million compounds to over 250 collaborators, and are used by researchers in academia and industry in Japan as well as around the world. The center has and will play as a hub where synthetic chemists bring the molecules and the biologists use them for their assays, to create transformative biomolecules.

Molecular Structure Center

Emi Mishiro
Designated Lecturer

The Molecular Structure Center is equipped with cutting-edge mass spectrometers and data analysis software for the structural determination of organic and biological molecules synthesized by members of ITbM. To facilitate analysis by ITbM members and other researchers, we will discuss the best analysis method for your purposes.(1) High performance liquid chromatography mass spectrometer equipped with a nanospray unit for proteomics analysis (nanoLC-MS/MS); (2) High performance liquid chromatography-mass spectrometer equipped with a Fourier transformation spectrometer for high accuracy synthesized molecules analysis (LC-MS); (3) High performance gas chromatography-mass spectrometer for metabolomics analysis (GC-MS); (4) Hydrogen/deuterium exchange mass spectrometer for protein interaction analysis (HDX-MS); (5) Proteome Discoverer software, etc.

Peptide Protein Center

Shunsuke Oishi
Designated Assistant Professor

The Peptide Protein Center provides tailor-made peptides and proteins to the research groups at ITbM. Using ligation chemistry developed by the Bode group, we can prepare not only simple linear peptides, but also cyclic peptides and synthetic proteins. Synthetic peptides and proteins can be tailored to suit different needs by incorporating chemical functionalization. We have successfully incorporated novel fluorescent molecules developed by the Yamaguchi group and unnatural amino acids synthesized by the Ooi group into synthetic peptides and proteins. We envision that these unique compounds will be transformative for research at ITbM.

State-of-the-art equipment and technologies are available in all centers. External access to the four centers can be arranged upon request.

ITbM administration

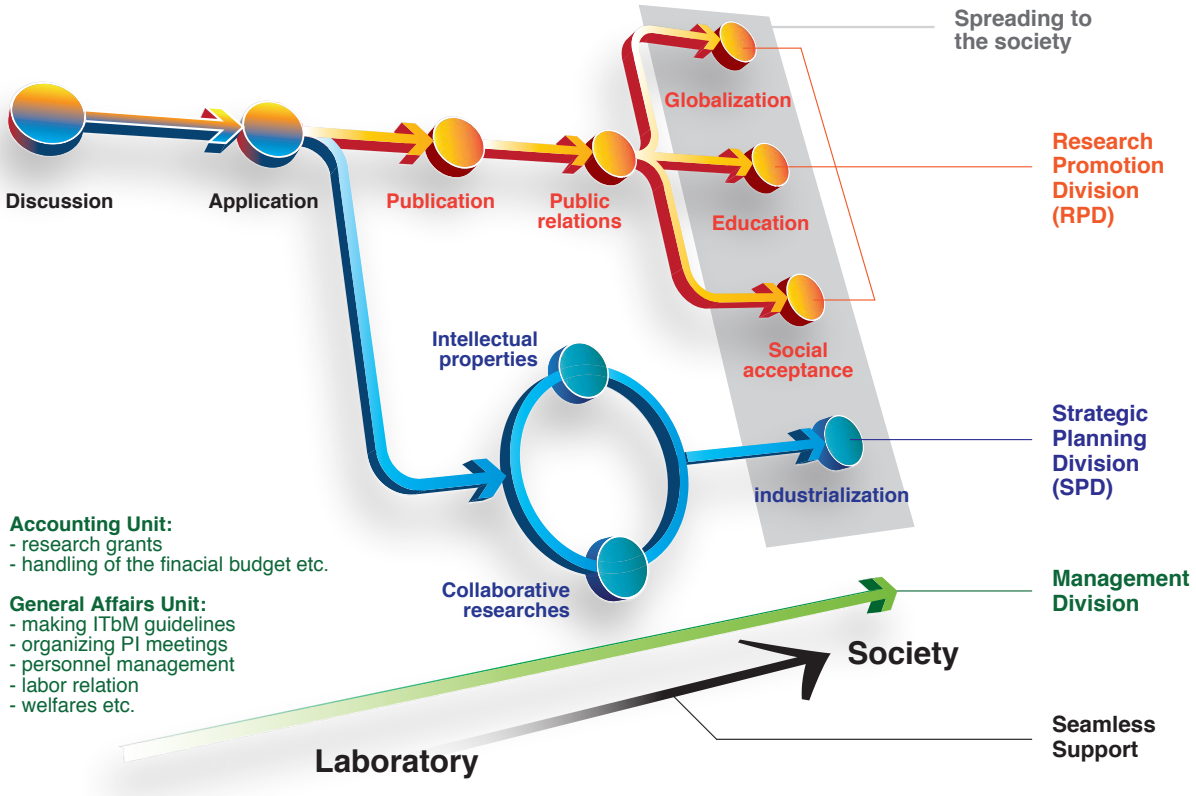
Promoting ITbM's interdisciplinary research

The ITbM Administrative Department plays a crucial role in supporting ITbM. Three divisions have been established: Management Division, Research Promotion Division (RPD) and Strategic Planning Division (SPD).

The Management Division consists of the General Affairs Unit and the Accounting Unit, both of which perform functions similar to those of a university administration. The General Affairs Unit is responsible for the development of ITbM's policies, the organization of PI meetings, personnel management and labor relations, as well as welfares. The Accounting Unit is in charge of matters related to research grants, as well as the handling of financial budgets that include personnel expenses, honoraria, travel expenses, and supplies.

The RPD is to create a bridge between researchers and university administration, and is involved in a wide range of activities (press release, science visualization, and so on) in ITbM. This includes support in the discovery of new seeds for collaborative research and obtaining research grants, support for overseas researchers' everyday life in Japan, and overall promotion of the institute through the organization of various events, such as symposia, seminars, workshops and meetings, along with internal/external communities. In order to promote the social implementation of the technologies developed at ITbM, the SPD was established as a spin-out from the RPD in May 2016. SPD plays a role in contributing to society by feeding research outcomes into society. SPD supports evaluation of inventions, patent applications, collaborative researches with domestic and overseas companies, license agreements, strategic construction of partnerships with companies aiming for industrialization/commercialization, running the ITbM/GTR Consortium and establishment of venture business, etc. Both RPD and SPD consisting of members who hold advanced degrees in science/engineering, support and promote ITbM research activities from basic to social stage consistently and seamlessly, cooperating with each other and using the expertise, resources and skills, to receive international recognition as a research center that conducts interdisciplinary research between chemistry and biology.

The ITbM Administrative Department provides both English and Japanese support to all ITbM members, both overseas and Japanese researchers. ITbM aims to create an international atmosphere, where researchers are comfortable and able to fully focus on their research.



Research environment

Promoting "mixing" of different fields

ITbM has set up Mix Labs to remove the physical barriers between research groups and to enhance interdisciplinary research across various fields and groups. Unlike traditional labs, where the labs are usually separated according to research groups, the Mix Labs incorporate large spaces, where researchers and students from different backgrounds share the same space and can have discussions on a daily basis. Each PI is in charge of their own research group. Nevertheless, the flexible interaction that exists between different research groups enables dynamic mixing of research that goes beyond the boundaries of conventional frameworks. Using “molecules” as the common keyword has advanced the understanding between different disciplines.

The Mix Labs have played an immense role in advancing collaborative interdisciplinary research at ITbM, as the faculty, postdoctoral researchers and students are able to communicate across different fields and put their research proposals immediately into action. A large number of interdisciplinary research themes have emerged from young researchers in the Mix Labs, and some of the research outcomes have already been released as patents and publications, as well as commercialization of reagents through technology transfer to industries.

The ITbM Research Award was established to promote interdisciplinary research proposed by young researchers working in the Mix Lab. The award provides start-up funding and is granted to outstanding collaborative research projects that are proposed by a team of researchers from different fields, which consist of at least one ITbM researcher (non-PIs). Many of the selected proposals have become representative projects at ITbM.

ITbM’s new research building that reflects the Mix Lab concept was completed in March 2015. The building’s whole area space is 7,934 m^2 and is a 6-storied building that consists of two sets of Mix Labs and Mix Offices. The labs and offices make up a 2-layer structure, where the Mix Offices are an open space over the windows that has a good view of the Mix Labs situated below.

The center is also equipped with a kids’ room to assist researchers with children, as well as refresh spaces, and a wooden deck in order to enable interactions between members. ITbM Tea break Meetings are held weekly to facilitate communication between members of the institute.

Towards globalization

International symposia and awards

ITbM is organizing a number of international symposia and awards each year. Through these international events, ITbM is establishing a strong network with leading researchers in the fields of synthetic chemistry, animal/plant biology and theoretical sciences. These activities are part of ITbM's globalization strategy, which aims to enhance globalization.

International Symposium on Transformative Bio-Molecules (ISTbM)

ITbM organizes its international symposium each year in Nagoya by inviting world-leading researchers who carry out research in ITbM's related fields. ISTbM contributes to the establishment of ITbM's international network and promotes international research collaborations.

Hirata Award

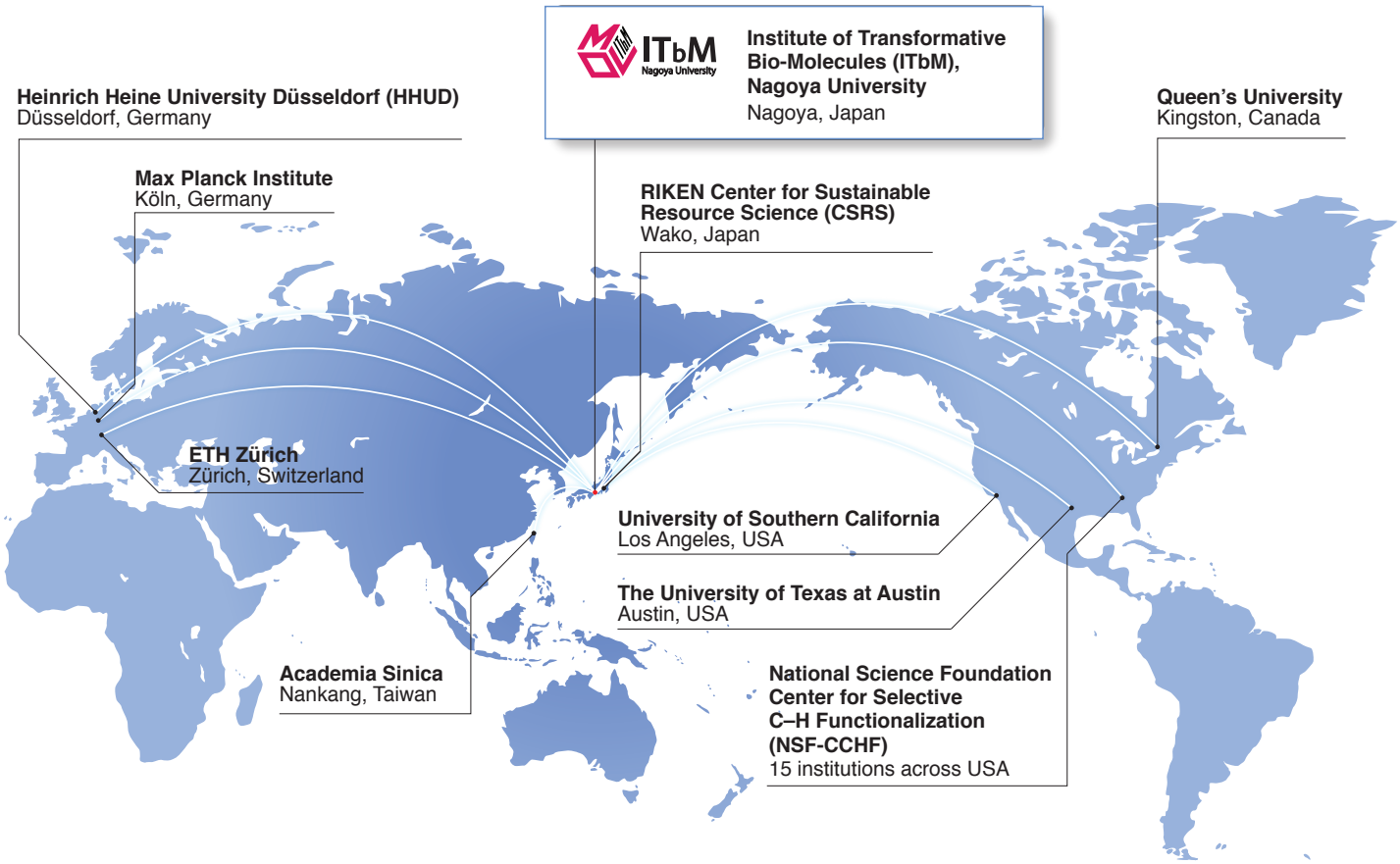
The Hirata Memorial Lecture started in 2005 at Nagoya University and is an international award granted each year to a rising star in the field of organic chemistry. This award was established in memory of the outstanding achievements of the late Dr. Yoshimasa Hirata, an Honorary Professor of Nagoya University. Dr. Hirata is known for the discovery of many natural products, including tetrodotoxin, a neurotoxin found in puffer fish, and greatly contributed to the advancement of natural product chemistry. Throughout the years, the Hirata Memorial Lecture has been given by many distinguished young chemists and has grown to become an internationally recognized honor in organic chemistry. From 2015, the Lecture has changed its name to the "Hirata Award" and is organized by ITbM.

Tsuneko & Reiji Okazaki Award

The Tsuneko & Reiji Okazaki Award was established in 2015 by ITbM in memory of the great achievements of Dr. Tsuneko Okazaki, Special Professor of Nagoya University and the late Dr. Reiji Okazaki, Honorary Professor of Nagoya University. Drs. Okazaki are known for their discovery of the Okazaki Fragments, which are short DNA fragments that are formed during DNA replication, and have contributed to advancing the field of molecular biology. Their efforts have also inspired subsequent generations of researchers. The Okazaki Award is an international award that is presented each year to a young leading scientist, who has made significant contributions in the field of life sciences through unique approaches and techniques.

Nagoya Medal of Organic Chemistry

The Nagoya Medal of Organic Chemistry is an international award that was established in 1995 by Dr. Ryoji Noyori, Special Professor of Nagoya University, and Dr. Hisashi Yamamoto, Honorary Professor of Nagoya University, under the support of the MSD Life Science Foundation (previously known as the Banyu Life Science Foundation International). Every year, the Nagoya Gold Medal is awarded to an organic chemist who has made significant original contributions to the field in its broadest sense, and the Silver Medal is presented to a promising scientist based in Japan, whose research has had a major impact on the field of synthetic organic chemistry. From 2023, Dr. Takashi Ooi, a principal investigator at ITbM, takes on the role of the Chair of the Nagoya Medal.

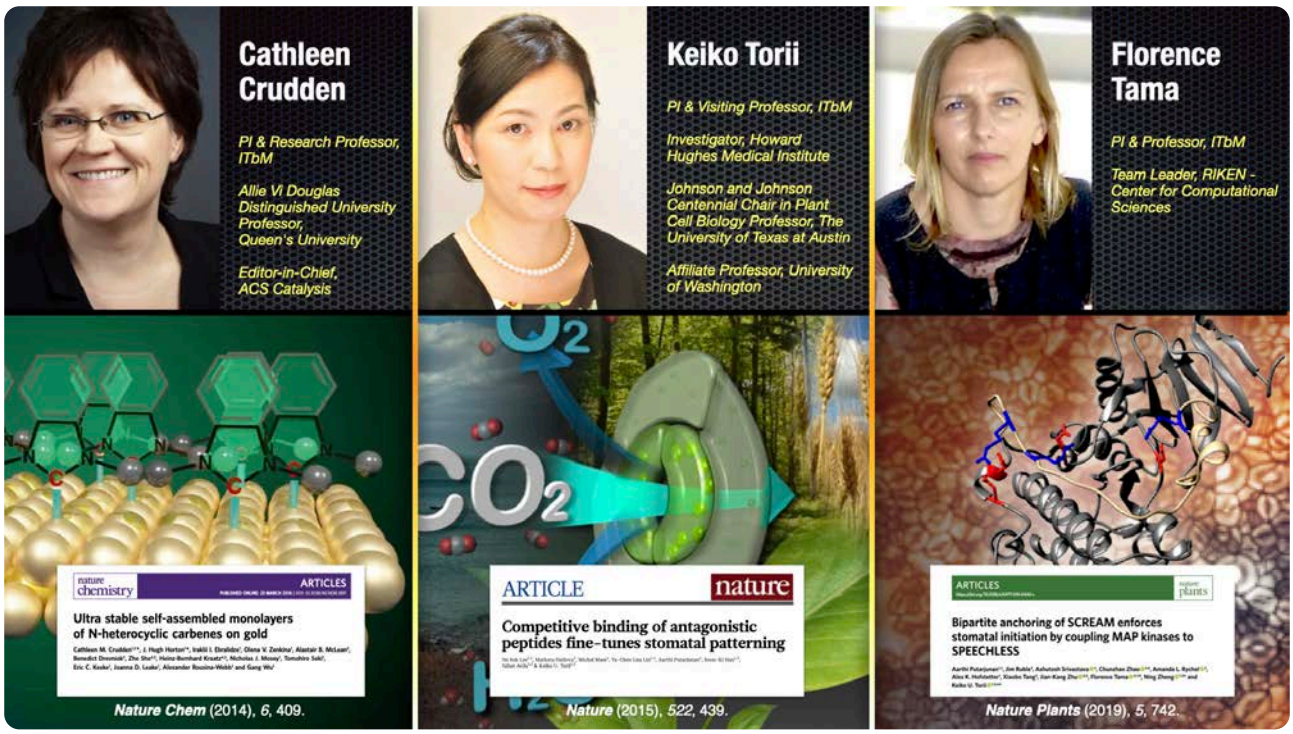


Partnerships and global networks

ITbM has collaborations with institutions worldwide. In addition to the universities/institutes where the overseas PIs hold posts (ETH Zürich, Queen's University, The University of Texas at Austin, University of Southern California, Heinrich Heine University Düsseldorf, and Max Planck Institute), ITbM is collaborating closely with the National Science Foundation Center for Selective C–H Functionalization (NSF-CCHF, Center Director: Dr. Huw Davies, Emory University), the RIKEN Center for Sustainable Resource Science (CSRS) and Institute of Chemistry, Academia Sinica. Joint workshops are held with these collaborating institutes. In addition, student and faculty exchanges are ongoing between ITbM and CCHF.

Nurturing young researchers is a key mission of ITbM and critical for our future development. ITbM financially supports Ph.D. students going abroad and has sent 39 Ph.D. students on overseas exchanges (as of March 2021). A notable number of postdoctoral researchers have carried out research at ITbM, and are currently in outstanding academic and industrial positions in Japan and overseas. The ITbM spirit is everywhere and ITbM has been recognized as a key hub in the global talent pool.

Academia Sinica
Nankang, Taiwan



ITbM's female scientists

ITbM has also been proactive in appointing and promoting female researchers. Including three female PIs, there are 22 female researchers at ITbM, representing 32% of the total number of researchers as of March, 2023.

Female scientists at ITbM have been recognized nationally and globally for their high-quality science, published in high-impact journals such as *Nature Chem* (2014), *Nature* (2015), *Nature Plants* (2019).

Many of ITbM's female scientists have been appointed to academic positions and students have won prestigious awards for their research, such as the L'Oreal-UNESCO Award for Women in Science. ITbM students have won this award two years in a row.

ITbM outreach

ITbM has strategically established a wide range of networks, not only with top scientists, but also with journalists, artists, high school teachers/students, and the general public. Based on this network, ITbM has actively organized various outreach activities, including scientific symposia/seminars, exhibitions, public lectures, science education, etc. ITbM's research activities were presented to more than 5,000 high school students in two years (FY2017 and 2018), and ITbM organized many outreach events for the general public (more than 50 outreach events every year). These events are not only effective in fostering future scientists (high school students), but also in encouraging the younger generation, such as elementary school students, including their parents, to develop curiosity about molecules.

GTR
Transformative Chem-Bio Research
Nagoya University

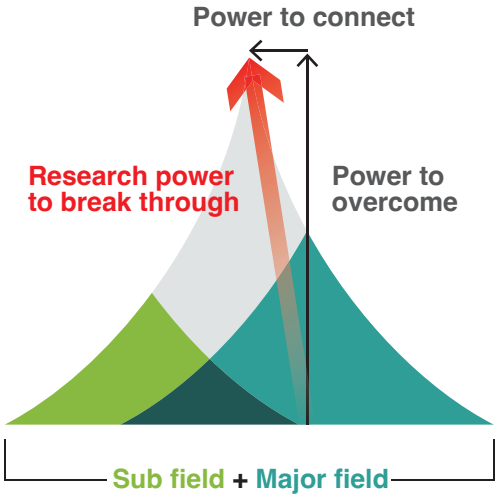
Graduate Program of Transformative Chem-Bio Research

The best way to acquire real research power is to accumulate experience with promoting and accomplishing exciting high-quality research on your own initiative

Our new graduate program, GTR (Graduate Program of Transformative Chem-Bio Research), aims to train scholars who will pioneer interdisciplinary frontiers in the areas of chemistry and life science. In order to achieve sustainable development of society, many challenges must be overcome, including environmental and energy problems, stable food production, the development of materials leading to industrial and technological innovations, and life science research that contributes to health. To address these issues faced by science and society, the roles of chemistry and life science research are becoming increasingly important. To break through these issues, both advances in research in each field and promotion of interdisciplinary research are necessary.

To bridge the gaps between traditional disciplines, we need outstanding "research power to break through," which consists of two elements: "the power to overcome" and "the power to connect." The former is based on experience, confidence, and solid practical knowledge and skills that can be fostered through promoting and accomplishing high-quality research on important topics. On the other hand, the latter leads to the creation of innovative ideas through free and vigorous discussions across research fields.

The GTR program provides a practical course for acquiring these important research capabilities through challenge to exciting interdisciplinary research in diverse research environments in which each student benefits from the guidance of two mentors.



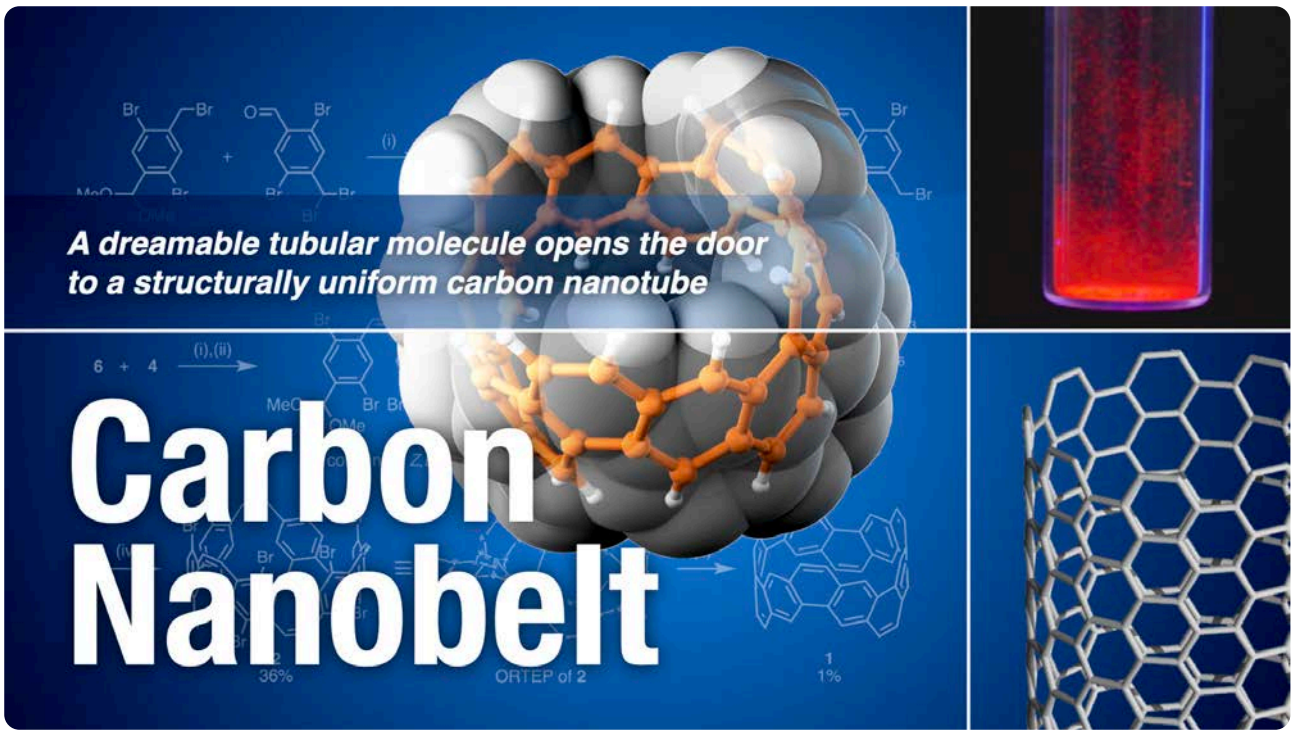
Nagoya University:
Institute of Transformative Bio-Molecules (ITbM); Graduate School of Science; Graduate School of Engineering; Graduate School of Bioagricultural Sciences; Graduate School of Pharmaceutical Sciences

Cooperative Institutions:
RIKEN, Institute for Molecular Science, National Institute for Basic Biology (Graduate University for Advances Studies); Kaneka Corp.; Konica Minolta Inc.; Japan Tobacco Inc., Plant Innovation Center; ITbM consortium (16 companies, 2019)

http://gtr.itbm.nagoya-u.ac.jp/en/index.html

Research

Transformative Bio-Molecules



Bottom-up synthesis of carbon nanobelts for the first time in the world

Carbon nanobelts are “short” carbon nanotubes with a uniform structure. Because of its breathtaking beautiful structure and potential as a future molecule, the synthesis of a carbon nanobelt, comprising a closed-loop of fully fused edge-sharing flat benzene rings, has been an elusive goal in organic chemistry for more than 60 years, before the discovery and synthesis of carbon nanotubes.

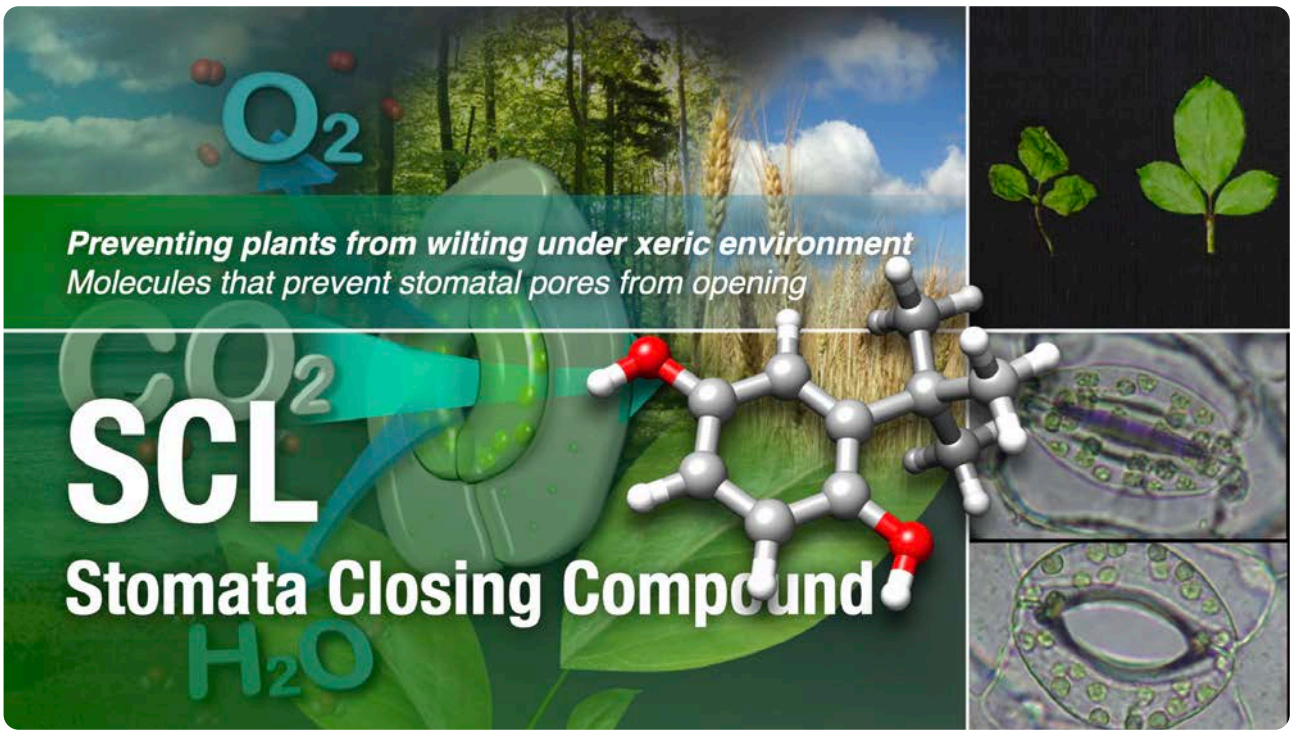
The research group succeeded in the bottom-up synthesis of carbon nanobelts for the first time in the world from para-xylene (one of the components of petroleum) as a starting material through a synthetic method they developed by themselves. Through various analyses of carbon nanobelt (x-ray crystallography, UV absorption, Raman spectroscopy, etc.), this molecule could potentially serve as a seed for the preparation of structurally well-defined carbon nanotubes. In addition, carbon nanobelt was commercialized in 2018, and researchers around the world are conducting applied research by using this molecule.

Molecules that will revolutionize the future nanocarbon science

Carbon nanobelts are a new form of carbon that no one has ever seen before. As the history of the soccer-ball-shaped fullerene (Nobel Prize in Chemistry, 1996) proves, a beautiful and new shaped molecule led to unpredictable functions, applications, and/or development at the time of discovery. Carbon nanobelt is expected to expand its areas of activity by leaving its home, ITbM. We believe “Functions follow Forms.”

Reference:

“Synthesis of a Carbon Nanobelt” by Guillaume Povie, Yasutomo Segawa, Taishi Nishihara, Yuhei Miyauchi, Kenichiro Itami, *Science* **2017**, *356*, 172. DOI: 10.1126/science.aam8158.



SCL; molecules that prevent stomata from opening

Stomata are pores in the epidermis of plants which open in response to sunlight, and the intake of carbon dioxide and the release of oxygen and water are regulated by stomata. For the pores to open, the plasma membrane proton pump (H^+-ATPase), which acts as an engine to open the pores, needs to be driven by light.

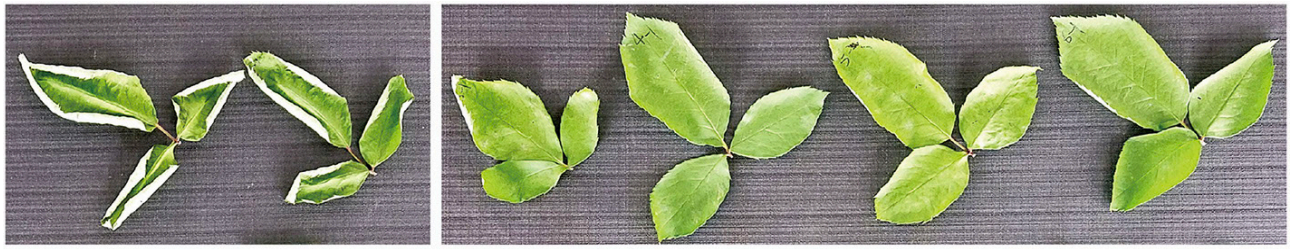
The ITbM research groups found compounds "SCL (Stomatal Closing Compounds)" that inhibit stomatal opening. These compounds exhibit stomatal closing acidity through the inhibition of H^+-ATPase and act in a different pathway from the phytohormone abscisic acid, which closes the stomata.

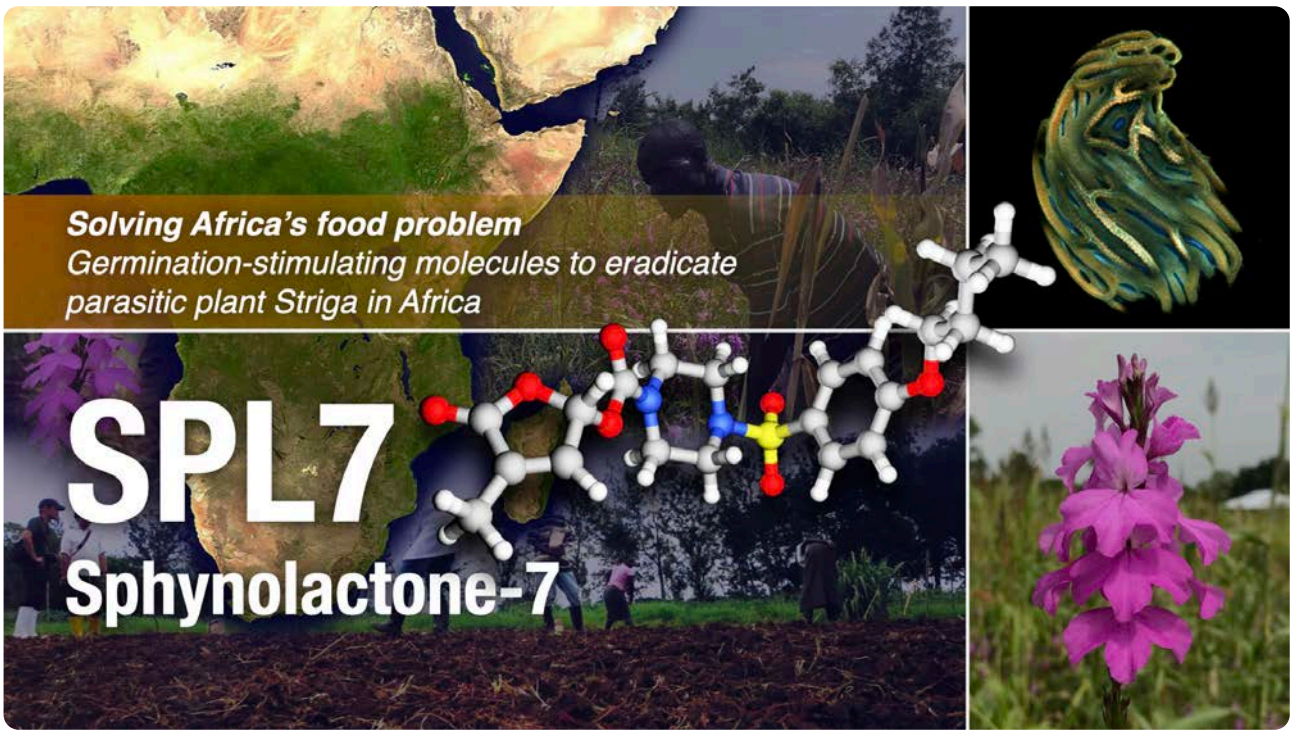
Closing pores to suppress wilting

By spraying these compounds on the leaves of roses and oats, they revealed that the wilting of the leaves under the dry condition was suppressed. This result is expected to be used as molecules that keep the freshness of cut flowers and flower arrangement, reduce transportation costs, and give drought tolerance against practical plants.

Reference:

"Identification and Characterization of Compounds that Affect Stomatal Movements" by Shigeo Toh, Shinpei Inoue, Yosuke Toda, Takahiro Yuki, Kyota Suzuki, Shin Hamamoto, Kohei Fukatsu, Saya Aoki, Mami Uchida, Eri Asai, Nobuyuki Uozumi, Ayato Sato and Toshinori Kinoshita, *Plant Cell Physiol.* **2018**, *59*, 1568. DOI: 10.1093/pcp/pcy061.





Innovative molecule, "Sphynolactone-7 (SPL7)" toward solving food problems in Africa

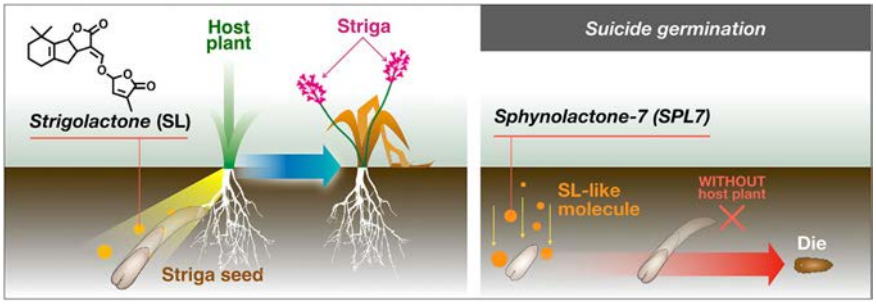
Striga is a plant which parasites on crops, causing the host plants (grain) to die out. The parasitic plant "*Striga*," also known as "Witchweed," has had a significant impact on crop production and its spread has become a major threat in Africa. The ITbM research group focused on the germinating characteristics of *Striga* and succeeded in developing an innovative molecule "SPL7" for eradicating it. SPL7 is a molecule that strongly induces germination of *Striga* so that, by using SPL7, *Striga* is forcibly sprouted and died out before planting the seeds of the host plant. By this method, we will reduce the opportunity of invasion of host plants such as grains and eventually eradicate it.

Verification of SPL7 toward practical use in Kenya

SPL7 has little effect on the biological environment such as bacteria in crops and soil, and can promote the germination of *Striga* at extremely low concentration ($1/10^{13\text{-}15}$mol/L). This activity is comparable to that of the naturally occurring germination stimulator (strigolactone) produced by the host plant, resulting in the artificial strigolactone molecule with the highest activity so far. Based on this result, we will conduct field tests of SPL7 against *Striga* that has caused heavy damage to the crop production in Kenya and will verify them toward practical use.

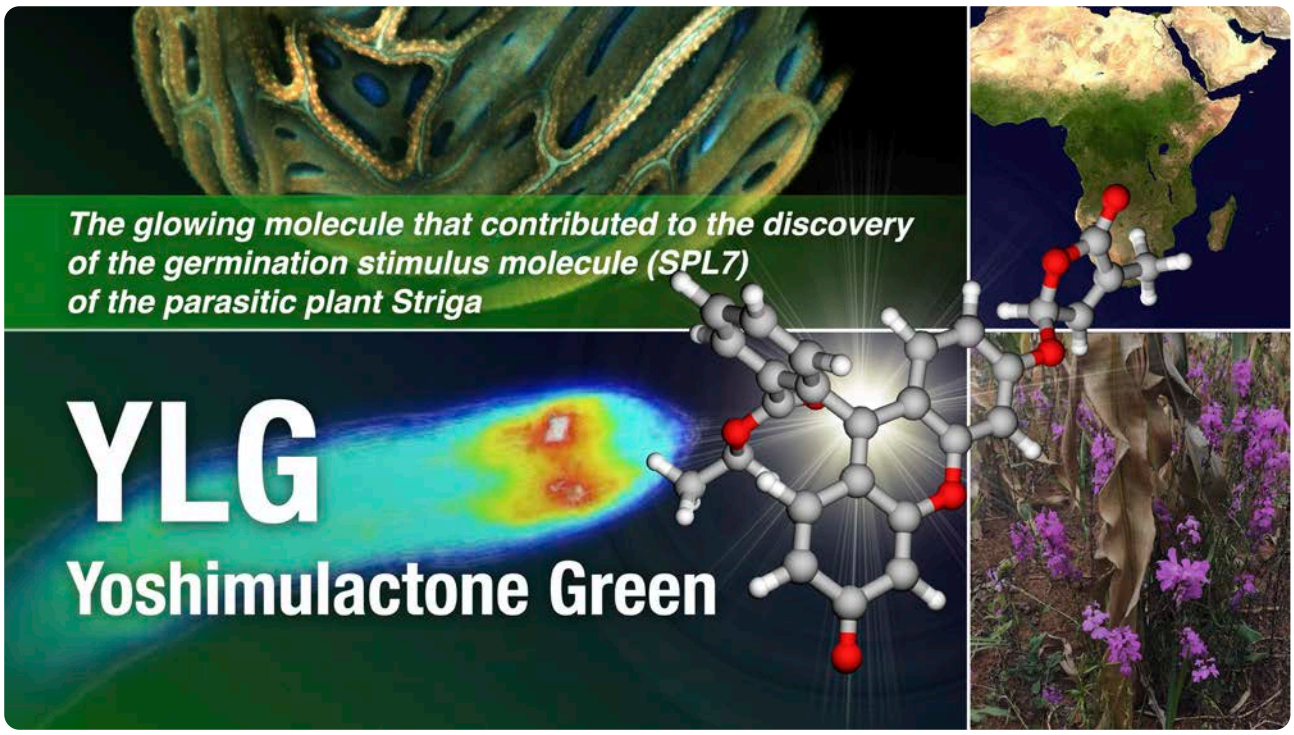
Reference:

"A femto-molar range suicide germination stimulant for the parasitic plant *Striga hermonthica*" by Daisuke Uraguchi, Keiko Kuwata, Yuh Hijikata, Rie Yamaguchi, Hanae Imaizumi, Sathiyanarayanan AM, Christin Rakers, Narumi Mori, Kohki Akiyama, Stephan Irle, Peter McCourt, Toshinori Kinoshita, Takashi Ooi, Yuichiro Tsuchiya, *Science* **2018**, *362*, 6420. DOI: 10.1126/science.aau5445.



SL-like molecules work as inducers of suicidal germination to purge the soil of viable Striga seeds before planting the crop seed.

Kinoshita Group, Ooi Group, Irle Group, Molecular Structure Center



The successful discovery of a method for observing the germination process of *Striga*

The parasitic plant *Striga* has dealt a heavy blow to the production of cereals in Africa. In order to eradicate it, it is necessary to clearly understand the process by which it infects its host plant. Although it was already understood that *Striga* responded to a molecule released from the roots of the host plant, the mechanism by which it did so was unclear. In order to understand this germination mechanism, the ITbM research group developed a molecule known as Yoshimulactone that would produce a green fluorescence when exposed to a particular protein present in *Striga*. Through the use of this molecule, they were not only able to see in detail the process of *Striga* germination, but also find the protein (the receptor) that induced the germination.

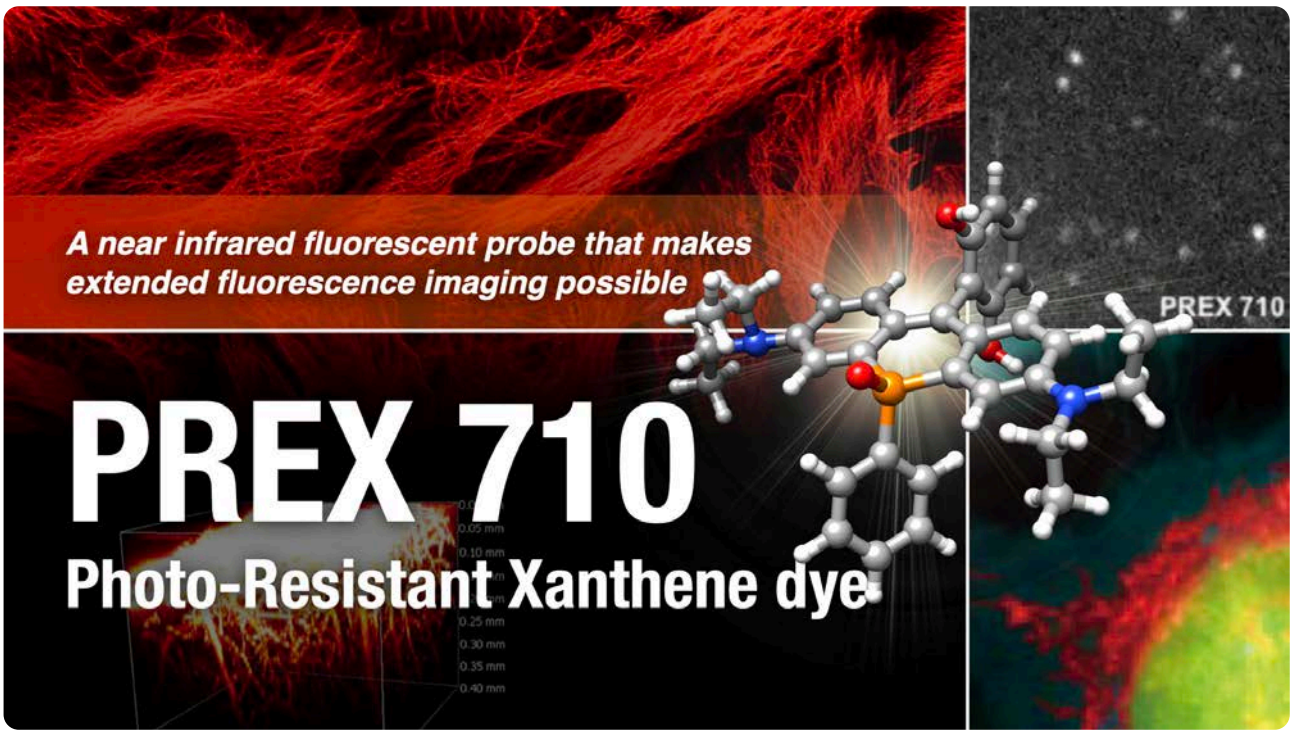
The story behind Yoshimulactone

In a now-legendary meeting, Mr. Masahiko Yoshimura, at the time a graduate student, was eating ramen with researchers when he was struck by an idea: a molecule that would fluoresce at the exact point that it bonded with the *Striga* seed's receptor. This idea focused on two properties: firstly, that the shape of existing fluorescent molecules resembled the shape of germination-stimulating molecules produced by host plants, and secondly that the breaking down of the germination-stimulating molecules would occur in a particular place significant to the understanding of the germination process. As a result of the development of Yoshimulactone, as well as finding out when and where the receptor is activated at the point of germination, through using synthetic germination-stimulating molecules and Yoshimulactone competitively it has become possible to identify germination-stimulating molecules, representing an immediate step forward in this field of research.

Reference:

"Probing strigolactone receptors in *Striga hermonthica* with fluorescence" by Yuichiro Tsuchiya, Masahiko Yoshimura, Yoshikatsu Sato, Keiko Kuwata, Shigeo Toh, Duncan Holbrook-Smith, Hua Zhang, Peter McCourt, Kenichiro Itami, Toshinori Kinoshita and Shinya Hagihara, *Science* **2015**, *349*, 6520. DOI: 10.1126/science.aab3831.

Itami Group, Kinoshita Group, Live Imaging Center, Molecular Structure Center



The super fluorescent dye that life scientists have been waiting for.

A variety of molecules have their own individual roles in sustaining life. Fluorescence imaging is a powerful tool for understanding the dynamics of biological processes, including their functions, movements, and structural changes. However, with existing imaging technology which only makes use of visible light and ultraviolet spectra, damage to cells due to exposure to light and noise in images caused by autofluorescence (fluorescence produced by existing matter within the organism's structure) have been consistent problems. In addition, since visible light can only reach a very limited depth, it is not suitable for the observation of blood vessels or internal organs. This problem can be overcome by making use of the near-infrared spectrum instead. However, with the limited chemical and photostability of currently available near-infrared dyes, it has not yet been possible to make these observations for anything other than a very short period of time.

The ITbM research group has successfully developed a near-infrared dye, PREX 710, with exceptionally high chemical and photostability as a new tool for life science research. When PREX 710 is used as a marker, it is possible to observe a living specimen in a non-invasive fashion for longer periods of time without noise, a technology that researchers in both the life science and medical fields have been eagerly waiting for.

A wide range of practical applications, from tracing a single molecule to deep tissue imaging

The single molecule imaging method is a technique that involves marking the biomolecule that is to be observed, for example a protein, with a fluorescent dye and following it at the molecular level. The strong laser beam required for this causes existing fluorescent dyes to lose their color in a matter of seconds, but PREX 710 produces a detectable signal for over two minutes. In addition, since near-infrared light can easily penetrate living tissue, it is possible to observe deep biological tissue, such as capillary blood vessels in the brains of mice, in 3D. It is not an overstatement to say that PREX 710, with its wide range of applications from single molecule to deep tissue imaging, is a transformational molecule in its field.

Reference:

"A Highly Photostable Near-Infrared Labeling Agent Based on a Phospha-rhodamine for Long-Term and Deep Imaging" by Marek Grzybowski, Masayasu Taki, Kieko Senda, Yoshikatsu Sato, Tetsuro Ariyoshi, Yasushi Okada, Ryosuke Kawakami, Takeshi Imamura, and Shigehiro Yamaguchi, *Angew. Chem. Int. Ed.* **2018**, *57*, 32. DOI: 10.1002/anie.201804731.

Yamaguchi Group, Live Imaging Center

A fluorescent molecule allowing the observation of the mitochondrial inner membrane in living cells

Mitochondria have an inner and outer membrane, with the inner membrane being made up of folds known as 'cristae', a structure which increases the efficiency of energy production necessary for the cell. The structural changes of these cristae are heavily involved in cell functions and responses, but it has not been possible to observe the cristae inside a living cell using existing techniques.

The ITbM research group has successfully developed a highly colorfast fluorescent probe (MitoPB Yellow) that specifically dyes the mitochondrion's inner membrane, and with the use of a super high resolution STED microscope able to pick out minute structures, were successfully able to capture the fine details of the cristae within a living cell. Following the discovery of this molecule, it is hoped that it will find practical use in the diagnosis and treatment of diseases related to mitochondrial damage.

A mechanism for dying only the inner membrane, and high colorfastness

MitoPB Yellow exhibits high fluorescence in hydrophobic environments such as lipid structures. Based on the molecule's particular properties, when it gathers in the mitochondria, it is able to bond with proteins present in the inner membrane, and produces a strong observable fluorescence. Because the pigment is able to pass through the cellular membrane, it is able to highly selectively dye the mitochondria simply by being added to the cell. Moreover, because it is extremely colorfast, it is possible to repeatedly capture the same area with a strong laser such as that of a STED microscope without the color fading. Thus, with the use of super resolution imaging, it is possible to observe the changes in the structure of the cristae as a result of mitochondrial fusion and swelling.

Reference:

"A photostable fluorescent marker for the super-resolution live imaging of the dynamic structure of the mitochondrial cristae" by Chenguang Wang, Masayasu Taki, Yoshikatsu Sato, Yasushi Tamura, Hideyuki Yaginuma, Yasushi Okada, Shigehiro Yamaguchi, *PNAS* **2019**, 201905924. DOI: 10.1073/pnas.1905924116.

Yamaguchi Group, Live Imaging Center

From the screening of existing drugs, the discovery of a molecule that can change the circadian rhythm of mice

We all have a biological clock inside our bodies that marks out a rhythm of approximately one day. This is known as the circadian clock, and physiological functions such as sleep, body temperature, blood pressure and metabolism all align with this rhythm. Thus, if the circadian clock becomes chronically out of alignment, the risk of illness is increased. The elucidation of this process was so keenly desired in medicine that the discovery of the molecular mechanism of the circadian rhythm was awarded the Nobel Prize in Physiology or Medicine in 2017.

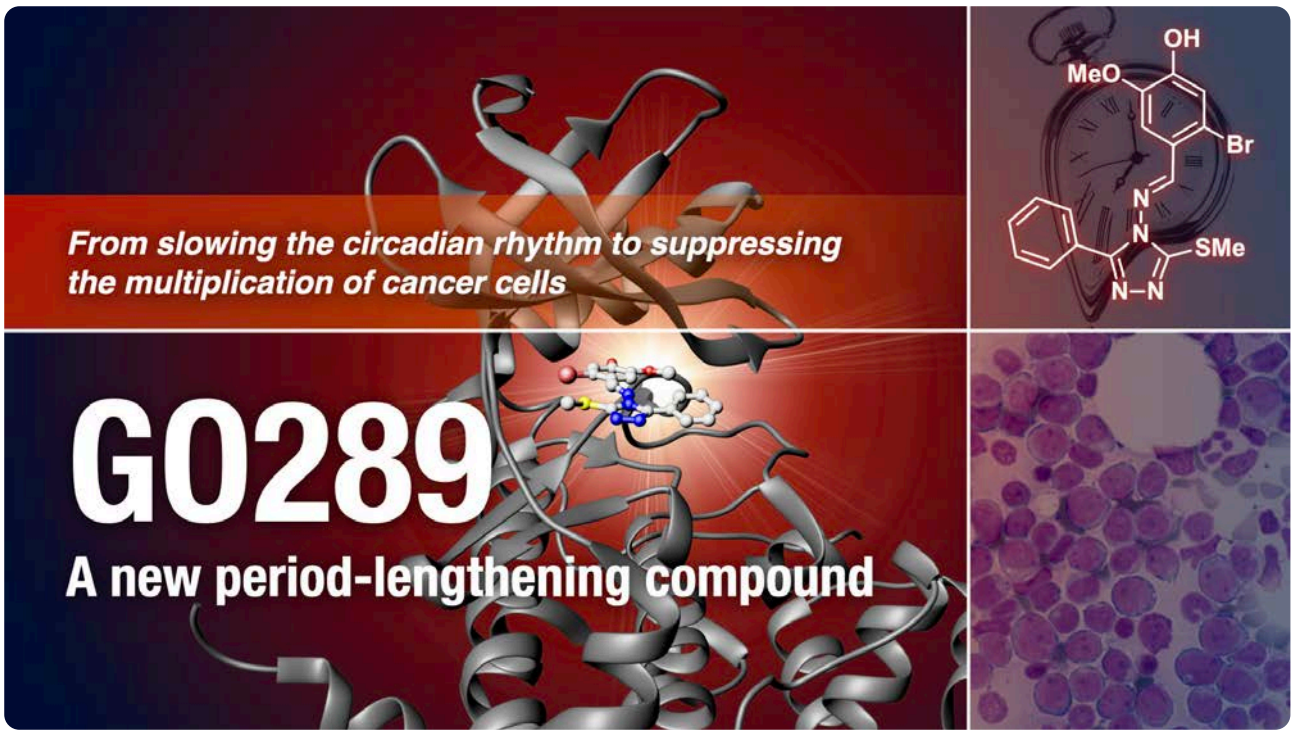
The ITbM research group, using drug repositioning, tested over 1000 drugs to find molecules that could speed up and slow down the circadian clock in human cells. Among the molecules found to increase its speed is the important human hormone, also known as a rejuvenating drug, dehydroepiandrosterone (DHEA). When DHEA was mixed with the food of mice, it was found to reduce symptoms of desynchronosis (jet lag).

What is drug repositioning?

Although a large amount of money is currently spent on drug development, there is by no means a high success rate. Drug repositioning is a method of finding out whether existing drugs, which are known to be safe and effective, can be used as new methods to treat other diseases. By continuing to evolve this process, it is hoped that an existing drug can be used in the future to treat circadian rhythm disorders.

Reference:

"Identification of circadian clock modulators from existing drugs" by T. Katherine Tamai, Yusuke Nakane, Wataru Ota, Akane Kobayashi, Masateru Ishiguro, Naoya Kadofusa, Keisuke Ikegami, Kazuhiro Yagita, Yasufumi Shigeyoshi, Masaki Sudo, Taeko Nishiwaki-Ohkawa, Ayato Sato, and Takashi Yoshimura, *EMBO Molecular Medicine* **2018**, *10*, 5, e8724. DOI: 10.15252/emmm.201708724.



The discovery of a new molecule that prolongs the circadian rhythm of mammals

The circadian clock controls a large number of physiological responses through the course of a single day, starting with sleeping and waking. When this function is disturbed, it is known to have a variety of effects, including diseases such as sleep disorders and cancers.

The ITbM research team, using human cultured cells, discovered a new molecule, GO289, that lengthens the circadian rhythm. They found that it strongly and accurately inhibited a kinase called casein kinase 2 (CK2) in cells, and succeeded in observing its action at a molecular level using X-ray crystallography.

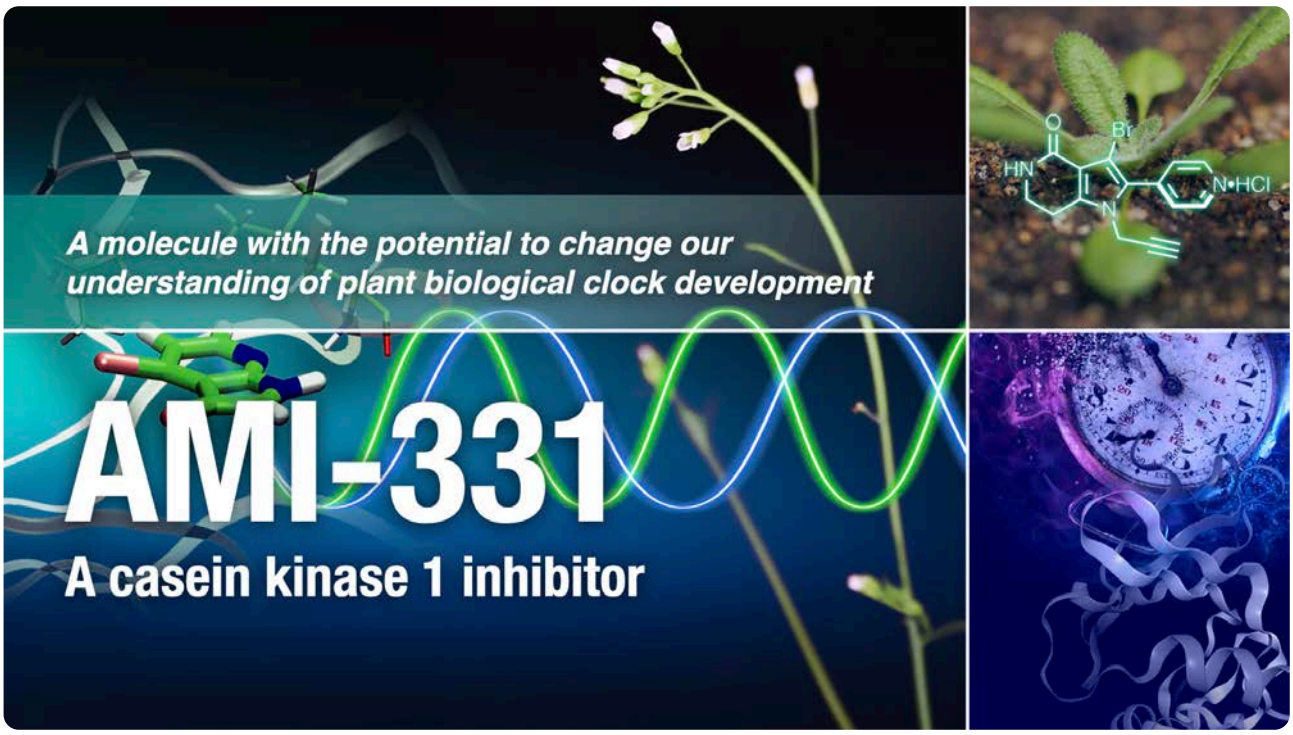
Suppressing the multiplication of cultured acute myeloid leukemia cells

CK2 participates not only in the control of the circadian clock, but also in the cell cycle and cell death. They found that when GO289 was administered to cultured cells of acute myeloid leukemia, a blood cancer, it heavily suppressed their multiplication by inhibiting CK2. Thus, GO289 is expected to find use in medical fields where the control of diseases influenced by the circadian rhythm is desired, such as the suppression of cancer cells.

Reference:

"Cell-based screen identifies a new potent and highly selective CK2 inhibitor for modulation of circadian rhythms and cancer cell growth" by Tsuyoshi Oshima, Yoshimi Niwa, Keiko Kuwata, Ashutosh Srivastava, Tomoko Hyoda, Yoshiki Tsuchiya, Megumi Kumagai, Masato Tsuyuguchi, Teruya Tamaru, Akiko Sugiyama, Natsuko Ono, Norjin Zolboot, Yoshiki Aikawa, Shunsuke Oishi, Atsushi Nonami, Fumio Arai, Shinya Hagihara, Junichiro Yamaguchi, Florence Tama, Yuya Kunisaki, Kazuhiro Yagita, Masaaki Ikeda, Takayoshi Kinoshita, Steve A. Kay, Kenichiro Itami, and Tsuyoshi Hirota, *Science Advances* **2019**, *5*, 1, eaau9060. DOI: 10.1126/sciadv.aau9060.

Kay-Hirota Group, Itami Group, Tama Group



From searching for the target of a circadian rhythm lengthening molecule, to the discovery of the workings of the plant biological clock

In order to react to the day and night cycle and changing of the seasons caused by the earth's rotation and revolution, all living things on Earth have acquired a genetically encoded body clock, known as a circadian clock. While this evolutionary mechanism is well understood in animals, plant chromosomes multiply to two or three times their original number, and as this results in the existence of many duplicate genes (multiple identical genes in one specimen), this has been difficult to explain.

The ITbM research group succeeded in discovering a low molecular weight compound which changed the rhythm of the plant circadian clock in thale cress, a plant with a high level of gene multiplicity. They found that the target protein, the casein kinase 1 (CK1) family, was linked to the clock. Furthermore, they were able to identify the directly CK1 controlled clock-related protein, PRR. Based on this discovery, and combining the fields of biology and synthetic chemistry, they succeeded in developing a new molecule 100 times more effective than CK1, known as AMI-331.

A discovery that changes the way we think about biological clock evolution

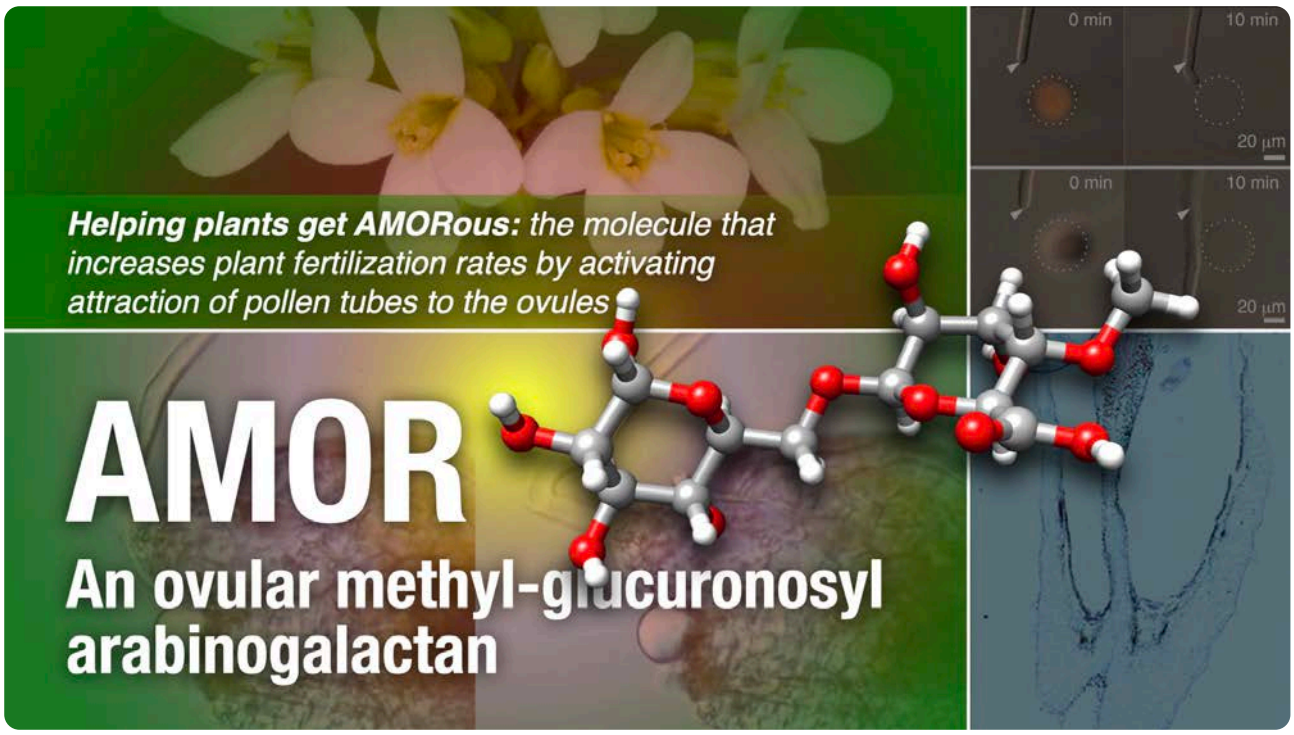
In previously presented theories, it was thought that different kinds of organisms – bacteria, molds, animals, and plants – had each developed individual biological clocks with proteins of different evolutionary origins. However, in this research, it was found that CK1 is present in plants, as well as animals and molds. In other words, this discovery suggests that there is a common protein connected to the biological clock, and should encourage a re-evaluation of current evolutionary theories related to time molecules.

Reference:

"Structure–function study of a novel inhibitor of the casein kinase 1 family in Arabidopsis thaliana" by Ami N. Saito, Hiromi Matsuo, Keiko Kuwata, Azusa Ono, Toshinori Kinoshita, Junichiro Yamaguchi, and Norihito Nakamichi , *Plant Direct* **2019**, *3*, 9, e00172. DOI: 10.1002/pld3.172.

"Casein kinase 1 family regulates PRR5 and TOC1 in the Arabidopsis circadian clock" by Takahiro N. Uehara, Yoshiyuki Mizutani, Keiko Kuwata, Tsuyoshi Hirota, Ayato Sato, Junya Mizoi, Saori Takao, Hiromi Matsuo, Takamasa Suzuki, Shogo Ito, Ami N. Saito, Taeko Nishiwaki-Ohkawa, Kazuko Yamaguchi-Shinozaki, Takashi Yoshimura, Steve A. Kay, Kenichiro Itami, Toshinori Kinoshita, Junichiro Yamaguchi, and Norihito Nakamichi, *PNAS* **2019**, *116*, 23, 11528-11536. DOI: 10.1073/pnas.1903357116.

Kinoshita Group, Kay-Hirota Group, Itami Group, Yoshimura Group, Molecular Structure Center



Activation of pollen tubes for gamete delivery to the ovule

In flowering plants, pollen collects at the tip of the pistil, extending what are known as 'pollen tubes' down through the pistil towards the ovules, which contain the egg cells. In order to avoid getting lost on their long journey down the pistil, the pollen tubes must receive signals which guide them towards the ovules.

In mammals, the system known as 'capacitation', in which the male gamete is activated by an agent originating in the female system, has long been understood. In plants, the molecular mechanism by which pollen tubes, which transport the immobile plant sperm cells, are activated, has remained a mystery.

Using *Torenia fournieri* as a model plant, ITbM researchers succeeded for the first time in identifying the pollen tube activator. The activator is made of a plant-specific sugar chain, arabinogalactan, with the two-sugar unit (disaccharide) at its terminus being the active component. They named it Activation Molecule for Response-Capability (AMOR).

Steps towards a new development in plant sugar chain research

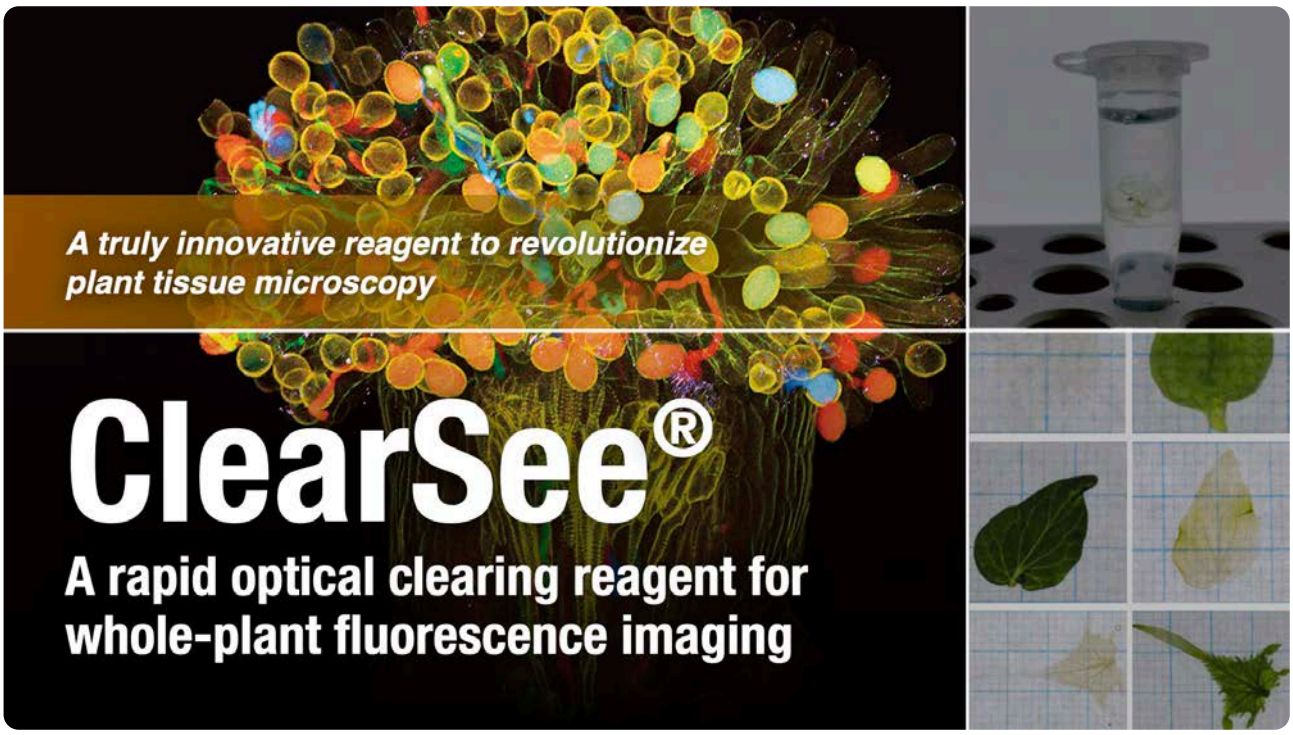
The researchers then synthesized the disaccharide they had found at the terminus, and added it to a culture medium containing pollen and an ovule. The pollen tubes in this culture changed their direction of growth towards the ovule. When the disaccharide was not added to the culture medium, the pollen tubes simply grew straight, their ends moving past the ovule. This clearly indicates that AMOR is essential to pollen tube guidance, living up to its name and acting as a matchmaker for the male and female plant gametes.

The discovery of AMOR is expected to contribute not only to the study of plant fertility rates, but also new research into the role of sugar chains in signaling in plants.

Reference:

"The AMOR arabinogalactan sugar chain induces pollen-tube competency to respond to ovular guidance" by Akane G. Mizukami, Rie Inatsugi, Jiao Jiao, Toshihisa Kotake, Keiko Kuwata, Kento Ootani, Satohiro Okuda, Subramanian Sankaranarayanan, Yoshikatsu Sato, Daisuke Maruyama, Hiroaki Iwai, Estelle Garénaux, Chihiro Sato, Ken Kitajima, Yoichi Tsumuraya, Hitoshi Mori, Junichiro Yamaguchi, Kenichiro Itami, Narie Sasaki and Tetsuya Higashiyama, *Current Biology* **2016**, *26*, 8, 1091-1097. DOI: 10.1016/j.cub.2016.02.040.

Higashiyama Group, Itami Group, Live Imaging Center, Molecular Structure Center



Overcoming the obstacles to fluorescence microscopy in plants

The discovery of fluorescent proteins has allowed for rapid progress in the analysis of the functions and structures of organic tissues through observation of the behavior of proteins. An important part of this process is making the structure to be observed transparent so that the target protein can be seen.

However, plant cells are a more difficult target for fluorescence microscopy than animal cells, as they contain autofluorescent substances such as chlorophyll, and observation is further complicated by the refractive index of other components such as the cell wall and surrounding air.

Through chemical screening, researchers at ITbM have discovered a highly effective surfactant that removes autofluorescence in plants while causing very little tissue damage, and a second compound that not only renders the observed tissue transparent but also preserves the fluorescent proteins. When a plant specimen was immersed in a solution of these two compounds, its tissue was rendered transparent in just a few days.

A truly innovative and easy to use reagent

Previously, it was necessary to thinly slice plant tissues in order to observe their internal structures at high resolution. The individual images would then have to be reconstructed into a 3D image in a lengthy and complex process.

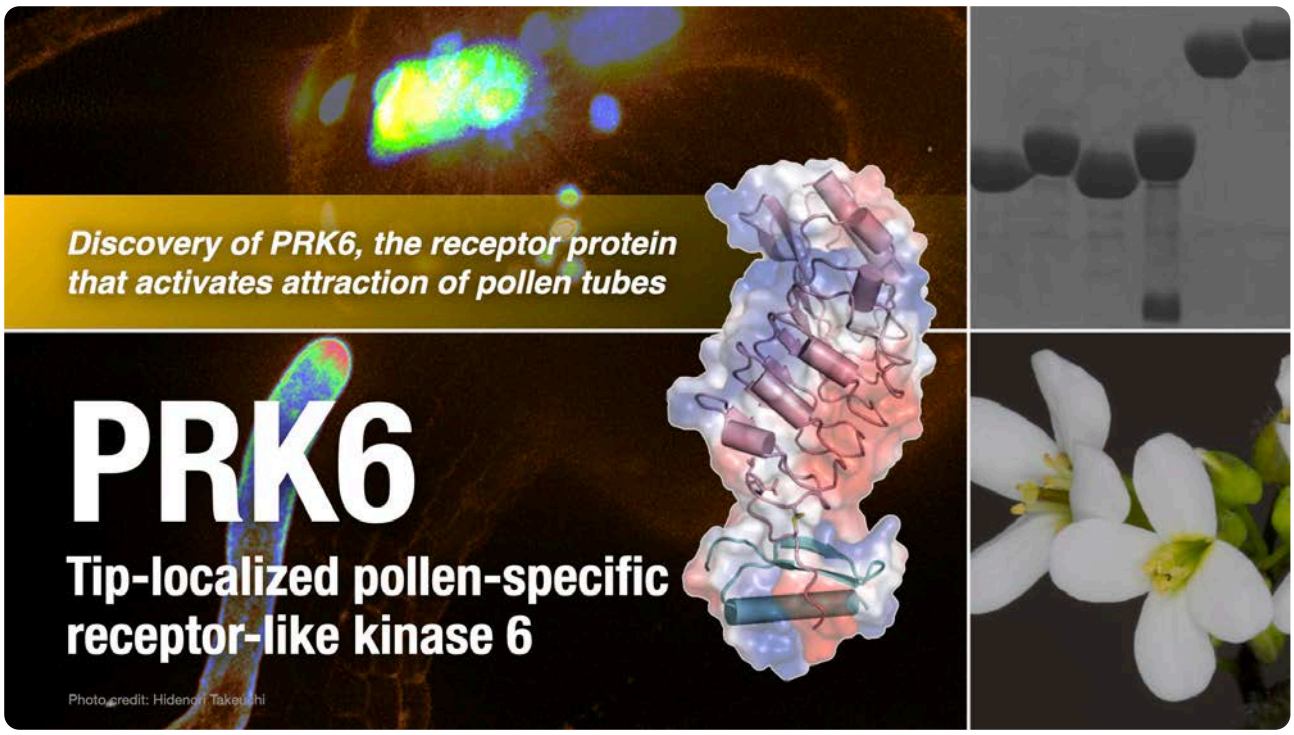
ClearSee® changes this in one fell swoop. Now, anybody can quickly and easily render plant tissue transparent and observe its internal structure without the need for special microscopy techniques. Since its discovery, the researchers have further developed it to be applicable to a wider range of plants and tissues, naming this improved version ClearSeeAlpha™. ClearSeeAlpha™ is expected to become a valuable tool for the acceleration of plant science research.

Reference:

"ClearSee: a rapid optical clearing reagent for whole-plant fluorescence imaging" by Daisuke Kurihara, Yoko Mizuta, Yoshikatsu Sato, Tetsuya Higashiyama, *Development* **2015**, 142 (23): 4168–4179. DOI: 10.1242/dev.127613.

"ClearSeeAlpha: Advanced Optical Clearing for Whole-Plant Imaging" by Daisuke Kurihara, Yoko Mizuta, Shiori Nagahara, Tetsuya Higashiyama, *Plant and Cell Physiology* **2021**, 62 (8): 1302–1310. DOI: 10.1093/pcp/pcab033.

Higashiyama Group, Live Imaging Center



Search for a receptor

In plant reproduction, the pollen tubes extend straight down the pistil from its tip until they near the ovule, before changing the direction of their growth towards the ovule until they make contact with and fertilize it. The ovule (female) part of the plant releases LURE, a pollen tube attractant, to guide the pollen tube towards it. However, without a receptor on the pollen (male) side, the pollen tube will not react, and will simply grow past the ovule without fertilizing it.

Using *Arabidopsis thaliana*, ITbM's researchers found the receptor, PRK6, which senses LURE. They discovered that the receptor contains several similar amino acid sequences, which work together to correctly interpret the attractor signal and control the growth and orientation of the pollen tube.

Two molecules, one big step for plant reproduction research

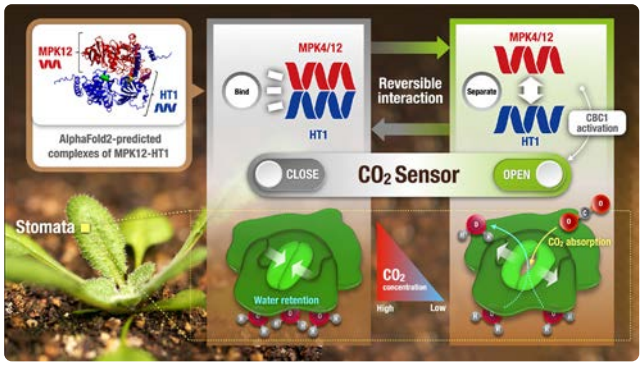
The researchers used X-ray crystallography to show how LURE and PRK6 form a 'lock and key'-like bond. The two molecules' structures vary between plants, meaning that only the right key molecule can fit the right lock molecule and thus ensuring that the correct type of pollen fertilizes the ovule. Through understanding the structure of the binding region, it is expected that progress can be made in creating viable plant hybrids whose breeding has been challenging. The discovery of LURE and PRK6 represents a significant step forward on the road to understanding the processes behind plant reproduction.

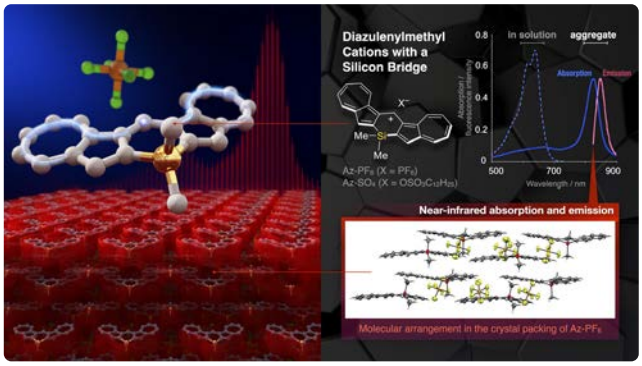
Reference:

"Tip-localized receptors control pollen tube growth and LURE sensing in Arabidopsis"by Hidenori Takeuchi and Tetsuya Higashiyama, *Nature* **2016**, 531, 245. DOI: 10.1038/nature17413.

"Structural basis for receptor recognition of pollen tube attraction peptides" by Xiaoxiao Zhang, Weijia Liu, Takuya T. Nagae, Hidenori Takeuchi, Heqiao Zhang, Zhifu Han, Tetsuya Higashiyama & Jijie Chai, *Nature Communications* **2017**, 8, 1331. DOI: 10.1038/s41467-017-01323-8.

Research Highlights



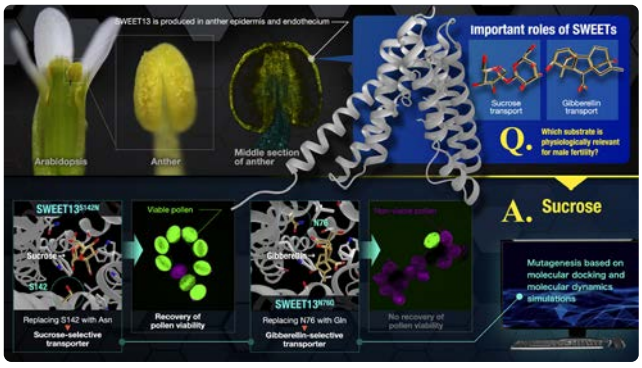


Kinoshita Group

Stomatal CO_2/bicarbonate Sensor Consists of Two Interacting Protein Kinases, Raf-like HT1 and non-kinase-activity requiring MPK12/MPK4. (*Science Advances* **2022**)

Yamaguchi Group

Diazulenylmethyl Cations with a Silicon Bridge: A π-Extended Cationic Motif to Form J-Aggregates with Near-Infrared Absorption and Emission. (*JACS* **2022**)

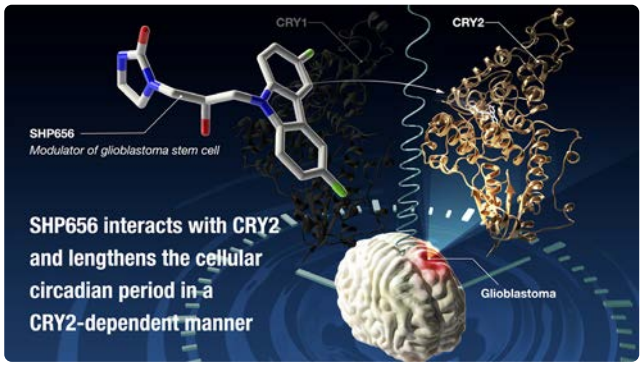


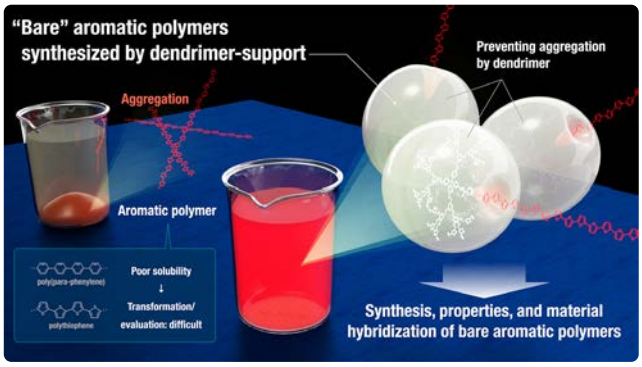
Yoshimura Group & CLC

A pheromone that explains why puffer fish spawn on beaches under moonlight. (*Current Biology* **2022**)

Frommer-Nakamura & Tama Group

SWEET13 transport of sucrose, but not gibberellin, restores male fertility in *Arabidopsis sweet13;14*. (*PNAS* **2022**)



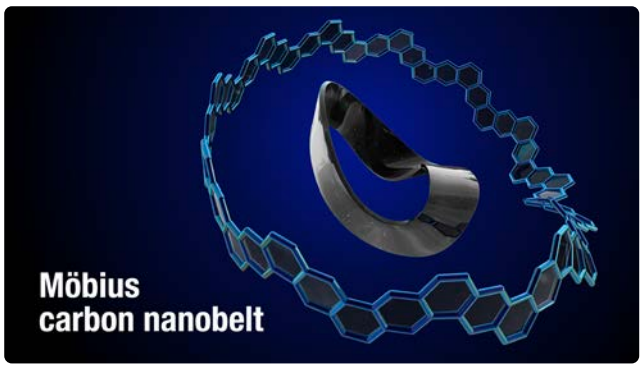


Kay-Hirota & Tama Group

CRY2 isoform selectivity of a circadian clock modulator with anti-glioblastoma efficacy. (*PNAS* **2022**)

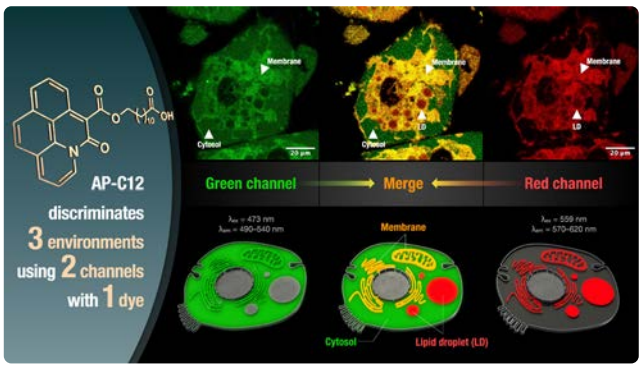
Itami Group

Synthesis, properties, and material hybridization of bare aromatic polymers enabled by dendrimer support. (*Nature Communications* **2022**)



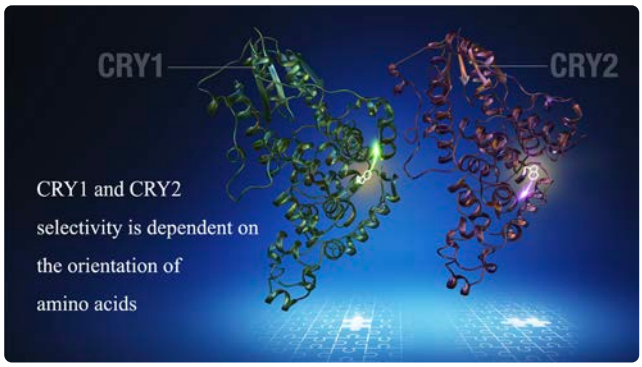
Itami Group

A Möbius band constructed solely by carbon atoms. (*Nature Synthesis* **2022**)



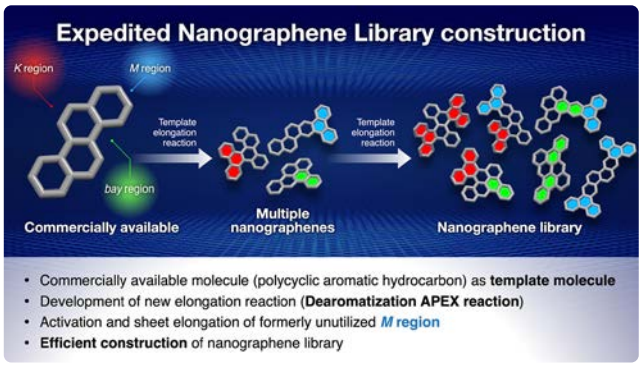
Yamaguchi Group & LIC

A negative-solvatochromic fluorescent probe for visualizing intracellular distributions of fatty acid metabolites. (*Nature Communications* **2022**)



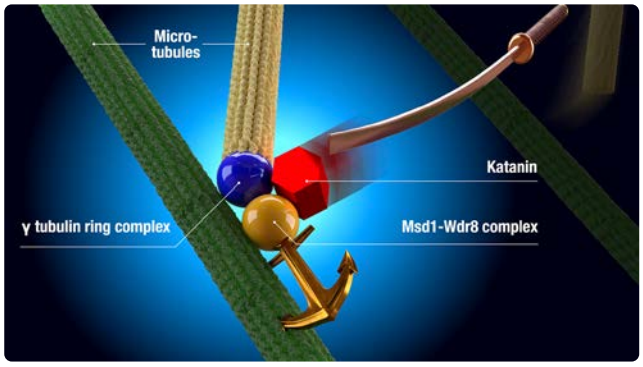
Kay-Hirota & Tama Group

Structural differences in the FAD-binding pockets and lid loops of mammalian CRY1 and CRY2 for isoform-selective regulation. (*PNAS* **2021**)



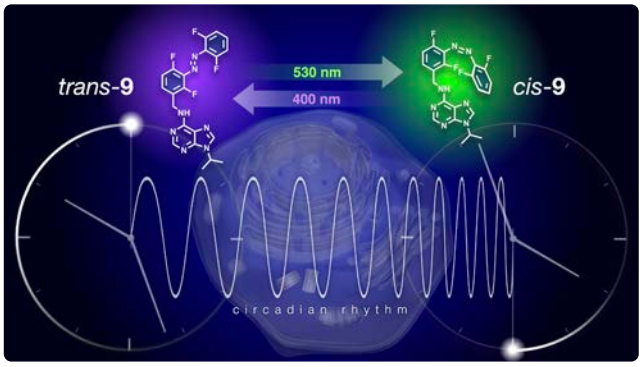
Itami Group

A template for fast synthesis of nanographenes. (*Nature Communications* **2021**)



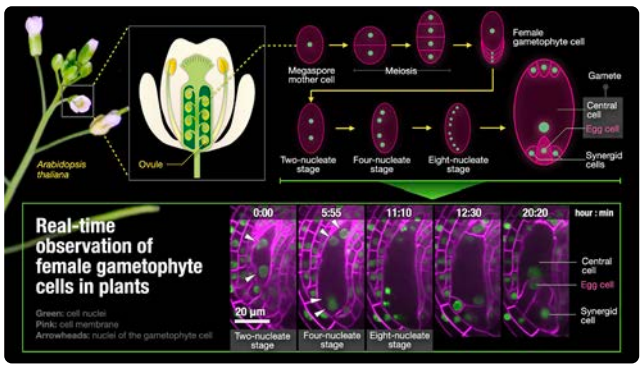
Frommer-Nakamura Group

The anchor and the sword: unlocking the secrets of microtubule formation in plants. (*Nature Communications* **2021**)



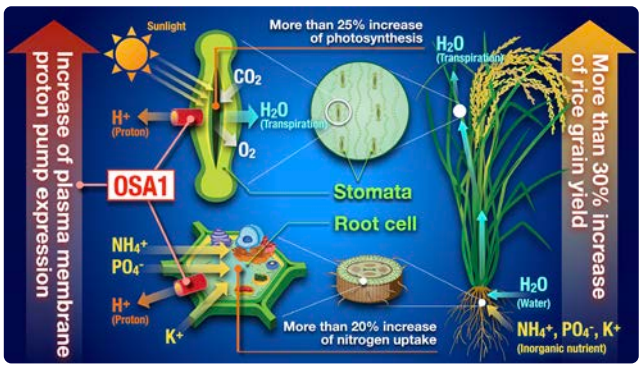
Itami, Tama & Kay-Hirota Group

Resetting the biological clock by flipping a switch. (*Nature Communications* **2021**)



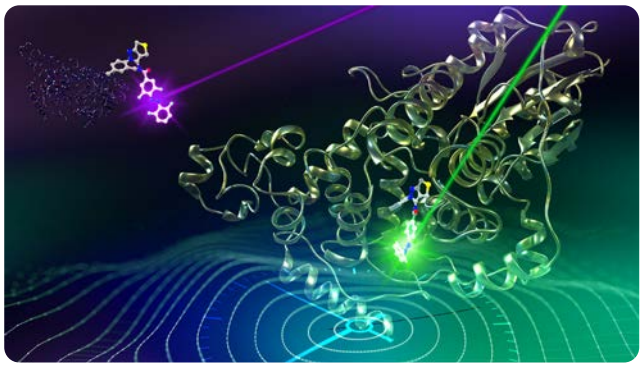
Higashiyama Group

Dynamics of the cell fate specifications during female gametophyte development in *Arabidopsis*. (*PLoS Biology* **2021**)



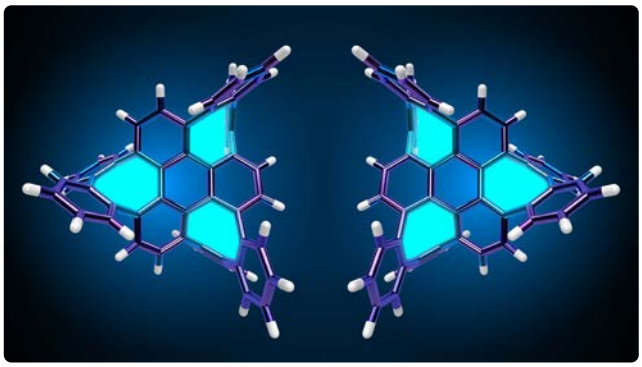
Kinoshita Group

A novel system for increasing rice crop yield. (*Nature Communications* **2021**)



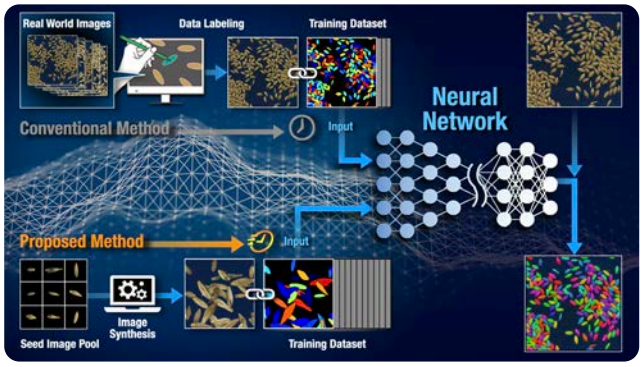
Itami, Tama, Kay-Hirota Group & CLC

Photopharmacological Manipulation of Mammalian CRY1 for Regulation of the Circadian Clock. (*JACS* **2021**)



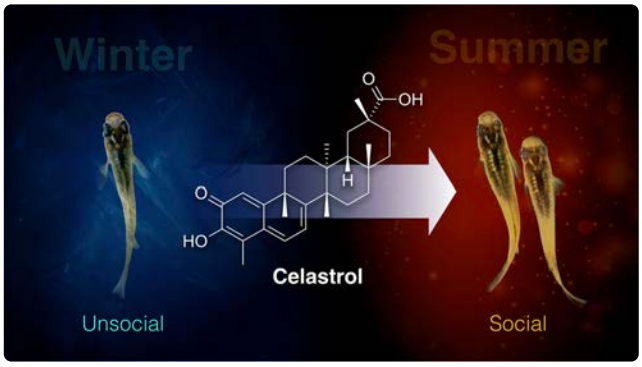
Itami Group

A new synthesis method for three-dimensional nanocarbons: Connecting carbon by catalysis to create octagonal structures. (*Nature Catalysis* **2020**)



Kinoshita Group

Training AI with synthetic data for measuring crop seed shape Development of an efficient method to accelerate the development of machine learning models for plant phenotyping. (*Communications Biology* **2020**)



Yoshimura Group & CLC

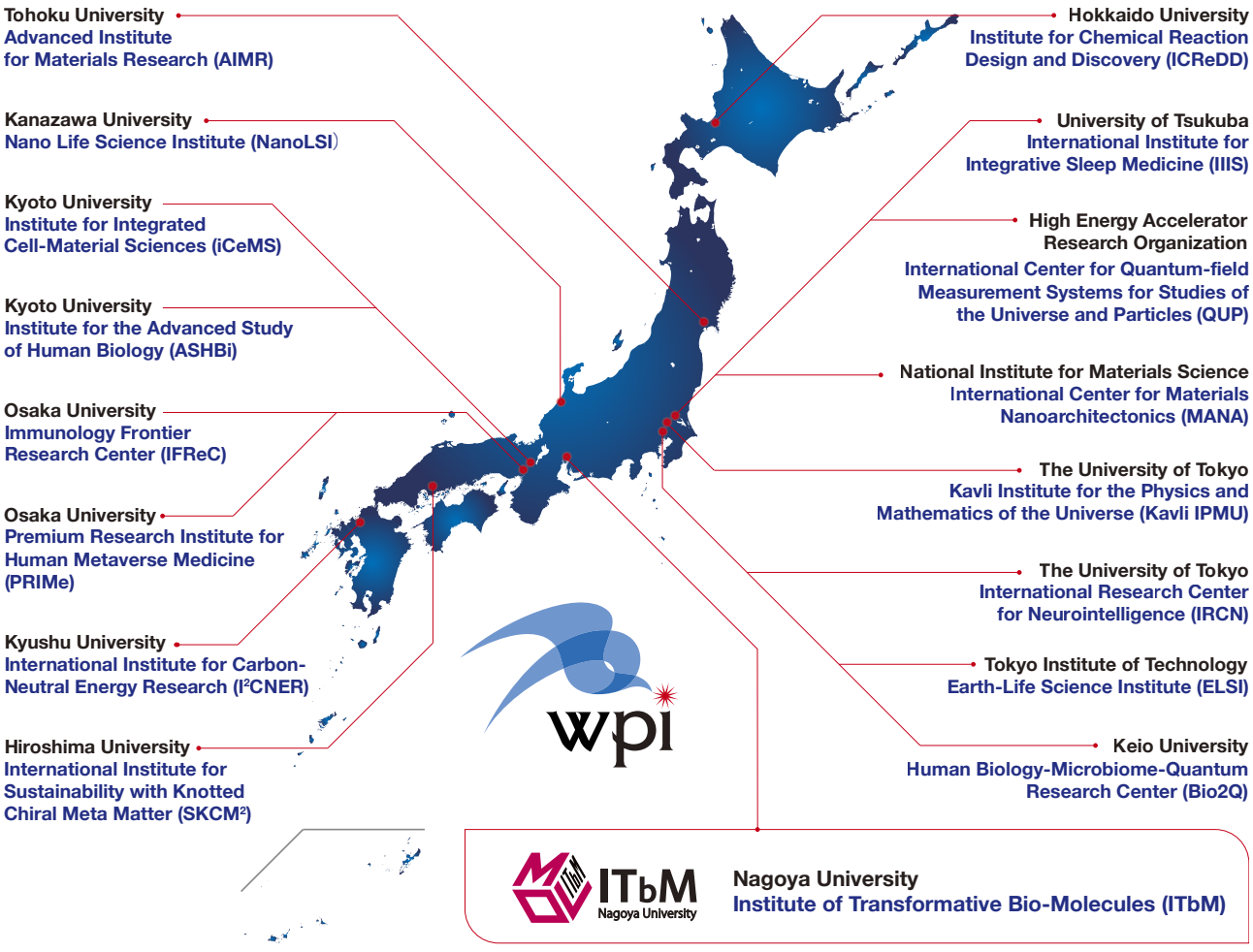
Discovery of a drug to rescue winter depression-like behavior. (*PNAS* **2020**)

WPI centers and support

About WPI

The World Premier International Research Center Initiative (WPI) was launched in 2007 by the Japanese government's Ministry of Education, Culture, Sports, Science and Technology (MEXT). It is a ten-year funding program that aims to build globally visible research centers in Japan,each with a very high standard of research and an outstanding research environment that will attract top researchers from around the world to come to work at these centers.

A total of 17 WPI centers have been selected across Japan up to now. Each center is being developed under the strong leadership of the center director to realize the four basic goals of the WPI program: (1) Science: advancing leading-edge research; (2) Fusion: creating interdisciplinary research fields; (3) Globalization: establishing international research environments; and (4) Reform: improving research organization.



Supporting ITbM

ITbM will continue to conduct basic research to contribute to solving the major challenges facing global society. In order to attract talented personnel, secure intellectual property, and continue to generate advanced results in research and technology transfer, action is still needed after the ten-year support from the WPI program ends in March 2022. Donations to ITbM will help ensure that ITbM can continue to respond to societal challenges in the future.

NAGOYA UNIVERSITY
Foundation page

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