Another talk on offer is a physiochemical properties and what are they?

So what will be covered in this talk? First of all, we want to understand, is there any guidelines that drug discovery projects follow to monitor chemical progression? And when we talk about physiochemical properties, are there any important factors that we must consider?

One of these is actually permeability. And this is going to be a highlight of the following talk. But permeability isn't a physiochemical property. What is the physiochemical property?

One of them is lipophilicity. And we're going to understand, can this be controlled and how to can be incorporated into drug design? Is there a give-and-take with other physiochemical properties?

Highlighted or at least related to permeability is also pKa and solubility. And these two parameters will also be under study.

We mentioned previous that we wanted to be able to understand is there any guidelines? And some of these could be referred to as Lipinski's rules, which we will also be focusing on. However, to understand physiochemical properties, we must first start with what have we discovered.

First. Clinical success, what do we mean by clinical success? Clinical success is where a compound has made it through clinical trials, approved by the governing body and released onto the market for sale/distribution. Did you know that there is 95% attrition when it comes to clinical success! Which is awful.

There are so many projects entering the pipeline that just don't seem to make it into a clinical drug. Astrazeneca were aware of this failure. and wanted to understand more about their own projects. Is there something worth highlighting that can reduce this number?

In doing so, they looked at 142 of their own drug discovery projects within a five-year period from 2005 to 2010. Here is what they discovered.

they discovered that the number of successful projects dramatically reduced from pre-clinical to phase II. Looking more closely at the data, it was highlighted that Safety and Efficacy appeared to be the major causes. Why was this?

Explanation for efficacy can be understood with the drugs need to comply with safety procedures. In order to meet this, the dose of the drug can become altered and as a result the right dose to reach the desired efficacious effect may be harpoured.

What about safety? 75 % of safety closures were related to compound properties i.e. physiochemical properties. So why not tackle this early on to minimise attrition? How can this be tackled?

So where to begin when it comes to understanding compound properties? First of all, we need to know what type of drug will we be working with. What do I mean by type? Oral or IV. This talk is going to be mainly focusing on oral drugs.

You might already be aware. Here's the human body. I hope you're aware. How does an oral drug make into the body? It is first taken in via the mouth and then it transports itself down to the stomach. Following from the stomach, you get absorption through the intestines, which takes you into the hepatic portal vein and thus leading you to the liver. From the liver, if the drugs survives the liver, you then reach into the systemic circulation where you are then able to cause your efficacious affect.

What is happening to your drug here? There's absorption, distribution, metabolism, excretion, and toxicity. There is one compound physiochemical property that has a large impact on this and will be the highlight of this talk.

And that is permeability.

The type of permeability that we're going to speak about in the talk is actually passive diffusion. There are a number of different ways that drugs can pass through the membrane. This can be paracellular, it can be endocytosis, it can be active transport. But for the purposes of this talk, we're going to be talking about passive diffusion. And first we want to be able to look at the phospholipid bi-layer and get an understanding of it.

The phospholipid is comprised of a polar head group and a lipophilic tail. But lets look into its chemical structure. Here is Phosphatidyl choline. It's has a charged, polar choline head group. Being charged and existing in a bi-layer, we know this polar charged group must face into a polar environment to become stabilized.

The head group is often attached onto a phosphate and the phosphate is attached on to a glycerol backbone that is therefore subsequently attached on to its fatty acid chains.

Moving on from here, if you can have different head groups, and these are just a few of the more popular head groups. You can see here. One exists charged and polar, whilst the other contains many, many polar atoms.

What happens is, is that the polar head group is able to interact with its polar environment, often in this case, water molecules. But how does something actually cross the membrane?

So here you have your drug molecule and it is being solvated through hydrogen bonds with your aqueous environment. The drug must shed this polar solvent in order to cross the membrane. These interactions are then reformed in the other polar environment on the other side of the membrane.

However, what parameters influence the crossing of this membrane? So the first is size. Molecules of a high molecular weight cannot pass readily through these tightly-packed regions as small molecules can.

We next look at lipophilicity. Increasing the lipophilic nature of molecules means that they can become more *permeable* through the non-polar central core of the lipid bi-layer. but too lipophilic and the drug can be stuck in these membranes. If you also think about polarity. Too polar and the drug will not be able to permeate past the fatty acid portion of the bi-layer.

It should be noted that the highest energy barrier is where there are tightly packed, highly ordered region of the phospholipids side chains, which is near the glycerol backbone. That is the biggest energy barrier your drug must overcome on both sides of the membrane, once entering and once leaving.

The last parameter to mention is solubility. I do want to highlight that solubilty is actually more complex than what is going to be outlined here. A drug can dissolve into smaller drug molecules. And in doing so, these smaller drug molecules increase the surface area at the site of the membrane and can aid with the crossing over through the membrane. Just as described when we talked about size, is that large molecular weight compounds can't pass readily through the tightly packed region of the membrane.

But how else can solublity affect permeability. Just as we mentioned previously, a drug can solvate with its aqueous environment to reach the gut. Upon absorption, the drug must shed these polar interactions to ensure safe passage accross the membrane. To do so, however, costs energy!

However, that is not only why solubility has an impact on permeability. If a drug is poorly soluble it will not dissolve in the gut but instead will dissolve in fat globules and thus never reaching the systemic circulation.

Let's understand the lipophilicity. Molecular weight is kind of a given. Too big, not good. Small, good. So let's understand a little bit more about lipophilicity. Lipophilicity plays a massive role when it comes to understanding ADMET properties and involved in almost every single one of them. To be lipophilic means that you are lipid loving.

Anther word that you might have come across is "hydrophobic". Hydrophobic literally means water hating. And sometimes these two words can be used in the same context to mean the same thing. So to have high lipophilicity means that the drug or portion of the drug contains no or has minimal ionizable centers. To have low lipophilicity means that you are polar. You contain polar and/or ionizable centers.

What does it mean to be too high in lipophilicity? Low in lipophilicity? How can we actually measure if something is high and something is low? We have what is known as the partition coefficient, otherwise known as logP.

And the two solvents that are used for the study are often octanol and water.

Octanol, you can see, has a polar -OH and a long lipophilic hydrocarbon chain. It looks similar to what we have discussed in previous, which is the phospholipid.

However, not all drug molecules are neutral. Not all drug molecules have no or minimal ionizable centers. Quite to lots of drug molecules do contain ionizable centers. So how do we correct this logP measurement to account for this differences? It's what's known as the distribution coefficient, otherwise known as logD. And here your aqueous phase has been given a pH. Where a functional group could exist neutral or charged. The pH at which LogD is measured can be found in superscript next to where you find logD. It should be noted that usually the pH is measured at 7.4 but not always. So how does this affect us measuring lipophilicity?

We need to have an understanding of charge/ionaisability. How can we tell if the drug is charged, partially charged, neutral? We need to understand pKa. pKa is what determines your ionizability. An acid/base can exist in equilibrium with its conjugate acid/base, forever flipping between the two.

Take this acid, the acid can exist as neutral (HA) or charged as its anion (A-) accompanied with its cation (H+). The anion is the charged acid. At a neutral pH, here we have 7.4. We see here that there's a larger portion of the anion than there is of the neutral species. We know that only the neutral species can cross the cell membrane. You can see here by the size of the acid and the size of the arrow, that minimal amount of this is actually passing through the cell membrane. However, if you were to take an aqueous environment that is in favor of you forming this neutral species HA, you can see here that more of it is able to cross the cell membrane. To summarize this, you can now say that your drug appears more permeable at pH 4 than 7.4.

So how did we know that the change in the pH would lead to more neutral form available to cross the membrane?

pKa. pKa is the pH at which you have 50% of the neutral form and 50% of the ionized form of your drug. The take home message from these diagrams shows that by increasing the pH with an acid, you lead to more of the charged species. Whilst the opposite is true for the base. A lower pH favors the charged species. In order to cross the cell membrane, mainpulation of the pKa of your molecule is common practice.

So we now know that polarity is needed for solvation and gut absorption but lipophilicty is need to cross the lipid bi-layer. Too much of either could lead to permeability issues. Whats the right balance?

Here we have epinephrine. It has many polar centers as well as even a basic centre indicated here. Epinephrine was attempted to be used for the treatment of glaucoma. But they realized that epinephrine had poor corneal permeability. We know, to aid with permeability we need to make our compound more lipophilic, mask ionisable centres, increase solubility.

The group decided to mask epinephrine's 2x polar phenol groups with 2x t-butyl esters. The compound, dipivefrin, boosted its lipophilicity and aided in corneal permeability. This technique is common practice in prodrug design.

That was just one property. What about the balance of properties?

Here is a HIV protease inhibitor and the only bit that we're going to look at is the R group. Here.

As polarity is added onto this position, the lipophilicity is seen to decrease. The greatest decrease is noted through the addition of the basic 3-pyridyl group. High polarity we know is not good for permeability. With this enhancement of polarity/ionisability, there is a noted increase in solubility. In order to get enough of the pyridyl derivative absorbed, there had to be a balance of solubility and lipophilicity. Thus leading to Indinavir being marketed for the treatment of HIV.

Staying with solubility, lets look into this a bit further. Solubility is needed for intestinal absorption and oral bioavailability. That makes sense with what has been talked about so far. Not soluble enough and the drug is absorbed by fat globules. Intestinal absorption is poor leading to not enough of the drug making it into the systemic circulation.

What else do we know about solubility? Solubility can be different in different environments. Why is this? Well, this comes down to ionasation, pKa of the drug. Where, if anywhere, is the drug ionised?

Solubility can be different in a biological assay media that contains 1% of DMSO. This could be favorable or detrimental. If carrying out experiments prior to testing your drug in a biological system, it is important to know how was it tested. What medium?

How do we influence solubility? So we saw in the previous diagram that through the addition hydrogen bond donors and hydrogen bond acceptors. Interacting with its aqueous environment, we can enhance its solubility.

Here's a a simple case here. We have this molecule here that contains low solubility. By adding on this methylene hydroxyl, we can actually make it more soluble. However, that's a good case. and let say that does make a drug in the end. However, when is doing something bad? When it's doing something good? So here we have a compound that is very very soluble, possibly because of these di acid here. However, this compound suffers from low permeability. And why is this? Well, these acids could be charged. We know the ionized species can't cross the membrane, thus leading to its low permeability. However, by giving a little sacrifice of solubility. By adding on these methyl esters on both, we actually are able to greatly increase its permeability because now this molecule can pass through the membrane as it's no longer or it's minimally charged.

So what are the different properties that are influential for solubility? Well, we talked about lipophilicity already. We have size. We have pKa.

you also have what is known as a crystal packing. If you can distrutpt this you can enhance solubility.

So what do we know?

Drugs have to be of a particular size to cross a lipid bi-layer. But what size? We didn't discuss, is there any value that we should be looking out for? We don't know.

Drugs have to be unionized or neutral state, but how do we know what state they will be in? How do we know if they can form this ionized state or unionized state?

We also need to exhibit reasonable solubility. But we've talked about how to achieve this, but we don't know what's too much or too little.

And how can drugs be designed with this awareness? This is where Lipinski came into play. Lipinski took a study of oral bioavailable drugs. And in this study he undertook just over 2 thousand compounds. And what he did was, he used phase II selection process as a filter. why phase II? Insoluble and poorly permeable compounds would have been eliminated thus all compounds entering into phase II should have correct permeability and or absorption to be able to enter this phase.

And how did they decipher this? By using the USAN or INN names that are given to oral drugs when they enter this phase, is how they selected them. And what did they discover? They discovered a number of things, but they discovered four properties that kept on creeping up. These where molecular weight, these were lipophilicity, hydrogen bond donor and acceptor. Now do you see a pattern here? The size is influential to permeability. The lipophilicity is influential to permeability And its ability to solvate or interact with this aqueous environment, aka solubility, is also a factor of permeability. By undertaking the study Lipinski found that drugs that fall within this criteria appear to make it into phase II He then named his finding as the "rule of 5". However, much conflict later on has deemed it, yes, it's still known as the "rule of 5", but it's actually a guideline more than a rule because this can be broken for some drugs but should be treated with caution. Breaking these rules are likely to affect the developability of that compound later in in the drug discovery process.

Using this rule, how have we progressed our chemical matter through the drug discovery process. Well, we start to say, okay, as we start to move through the drug discovery pipeline, we see that we start to increase its molecular weight and increase its lipophilicity. As compounds get larger, we add carbon and hydrogens to the molecule, thus increasing our lipophilicity. It would not be possible to make the compound larger with many additions of only polar atoms.

From the diagram here, you can see that as chemical matter moves from lead to drug, this optimal drug space is below that of lipinski. Through further studies, pre-clincal toxicity has been associated with LogP > 3. Why is this? Highly lipophilic molecules are able to concentrate themselves within plasma membranes. And we know

that plasma membranes contain many signaling systems. And in doing so, the lipophilic molecules being sequestered here, thus potentially able to enhance toxicity. We've been given a guideline. We've been given Lipinski's rule of 5. That's fine. But are there other ways to try and help us to determine what sorts of physiochemical properties we need. Or how do we actually measure we are doing something meaningful and right? And this can actually be undertaken with some metrics such as Ligand efficiency, property forecast index. However, for the purposes of this talk, details into this have not been undertaken but will be provided in subsequent WCAIR talks.

So to finish upon this point, what do we know? We started to undertake the journey of physiochemical properties in drug design.

What are they? So one of the major factors we started to follow was permeability and absorption and why? We were interested in oral bioavailable drugs. That's why.

What properties mainly affect these? We found it was size. We found it was lipophilicity, and we also found out it was solubility. What did we start to study? We focused on passive diffusion. We started to understand these different physiochemical properties and how they affect this passive diffusion. We spent a lot longer on lipophilicity because it has a greater influence on its ADME properties than most other physiochemical properties. We discovered that too lipophilic a compound can result sequestering in the membranes and thus making the compound not able to come out on to the other side of its membrane. We found as well that too polar that the compound just won't be able to permeate.However, polarity is needed for solubility. So there must be a balance of these two properties.

We discovered that if you are to reduce this hydrogen bond donor and acceptor, that you're able to aid with permeability. But again, that leads into solubility. These two factors are required to get your drug to be soluble. Large molecules find it hard to cross by passive diffusion. And the reason being is because they just can't seem to pass through the tightly packed region of the lipid bi-layer, as a small molecule would.

Lipinski gave guidelines known as the rule of 5 to aid you with assessing your drugs physiochemical properties; molecular weight, lipophilicity, hydrogen bond donor, hydrogen bond acceptor. Lipinski gave guidelines, the rule of five. However, why are these guidelines? Subsequent studies later on, has shown that they're not disproven, but there are other additional factors that we have to take into consideration, such as toxicity. We discover that too lipophilic a molecule, a molecule with a clogP of perhaps greater than 3, could actually maybe enhance some pre-clinical toxicity later on.

It's important to know that physiochemical properties are important for drug design and hoping to try and minimize attrition later on in the discovery process. Safety is a massive factor when it comes to creating a new drug for human intervention. This talk was brought to you by the Wellcome Center of Anti-Infectives Research the University of Dundee, Scotland, UK.