Medicinal Chemistry
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Module 01
Lecture 02
Introduction to Medicinal Chemistry Part-2

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Drug discovery is about finding the right lead compounds...

How do we find a lead?

Okay, welcome back. So in the last lecture we looked at how to find a lead compound? Now the question that we asked in the last class was how do we find a lead?

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- The natural ligand or substrate!
- Another substance known to interact with the target of interest
- Random or targeted screening
- Fragment-based screening
- Computational approaches

After lead identification... what's next?

So we discussed many approaches the first approach being that in the case of an enzyme or a receptor we would look at the natural ligand or substrate for the enzyme, ligand for the receptor or substrate for the enzyme. Now the other way to do this is to look at known substances which are known to interact with the target of interest, okay. We looked at an example in last class.

The other approach is to do screening we described what screening was is which is basically using a collection of compounds and doing a test on it to look for activity and there are couple of ways in which we can do screening, one is the random or targeted screening and there are fragment-based screens that are available and lastly we looked at computational approaches which is basically virtual screening so where we do not really have a real compound but we know the active site of the protein or the ligand binding site of the receptor and we start screening for compounds which can go and bind, okay so this is virtual screening approach, okay. All these approaches lead to the identification of what is known as a lead compound, okay. So what do we do afterwards?

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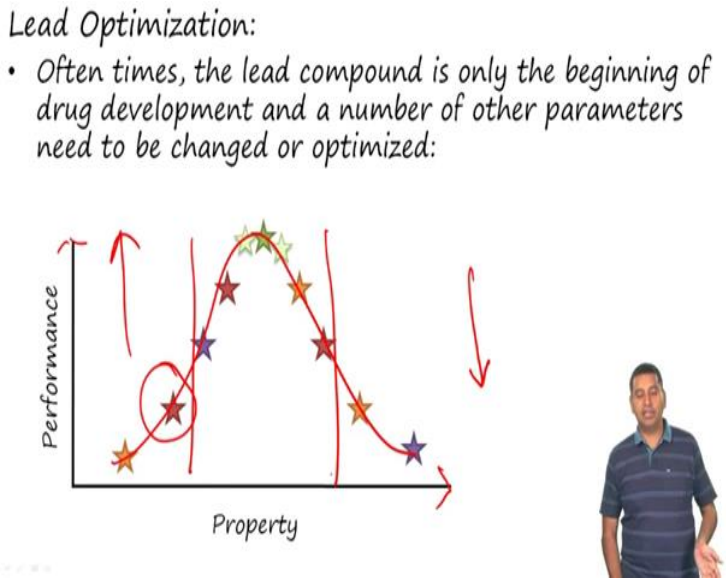

So then what we do is we do a process called as optimization, okay. So the lead compound that we attain by any of these approaches that we described would give us an interesting structure to begin with, okay this is only the beginning of the of drug development and we need to change the number of parameters or we have to do what is known as optimization. So for example in this plot if we look at performance versus property and here is the desired property that we want to look at, what typically happens is that you have you start with the lead compound over here and then you start making various modifications to the structure

and some lead to decrease in performance and some lead to increase in performance, okay and typically what happens is that you get a bell shape curve for performance versus property.

So therefore we are more or less restricted to a zone where we would like best performance with ideal number of with a particular when a particular property is optimized. So this optimization requires synthesis, it requires screening the compound once again and so on and so forth.

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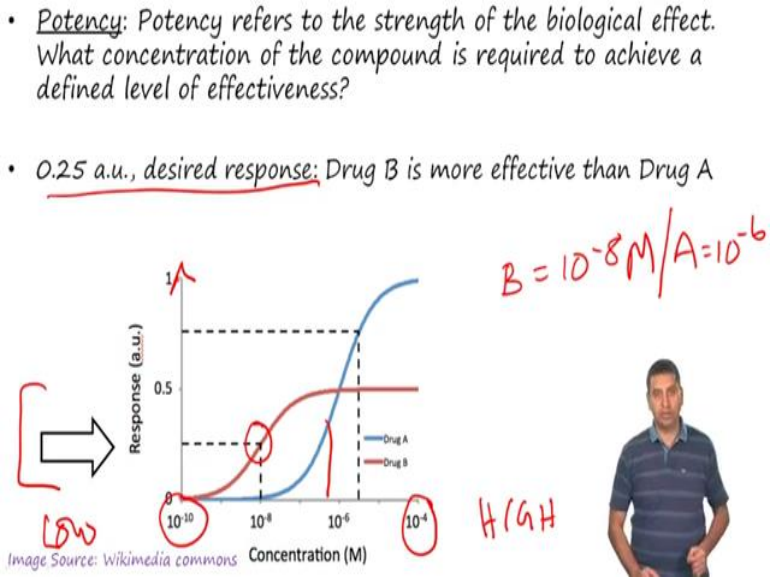

So the next aspect of optimizing a lead is potency, okay. Potency is nothing but the strength of the biological effect. So typically let us say looking at the inhibition of an enzyme what is the concentration at which the enzymes is effectively inhibited or if we are looking at a receptor what is the concentration at which the desired signal is being transmitted by the compound, if you are looking at inhibition at the signal what is the lowest concentration at which you would inhibit the signal and so on.

So therefore potency is a major of how strong the biological effect is? Now let us look at an example where we are comparing 2 drugs. Let us say that the desired efficacy is 0.25 which is represented in the Y axis here and on the X axis is the concentration and concentration this 10 to the power minus 4 is a high concentration and 10 to the power minus 10 is the low concentration in this axis.

So let us look at let us assume that the desired response is (10) is 0.25 and so therefore if I look at the concentration at which B is effective it is 10 power minus 8 molar, whereas if I

look at concentration of A which is required to achieve the same effect it is around 10 power minus 6. Therefore B in this example is far more effective than A if the desired response is 0.25 units.

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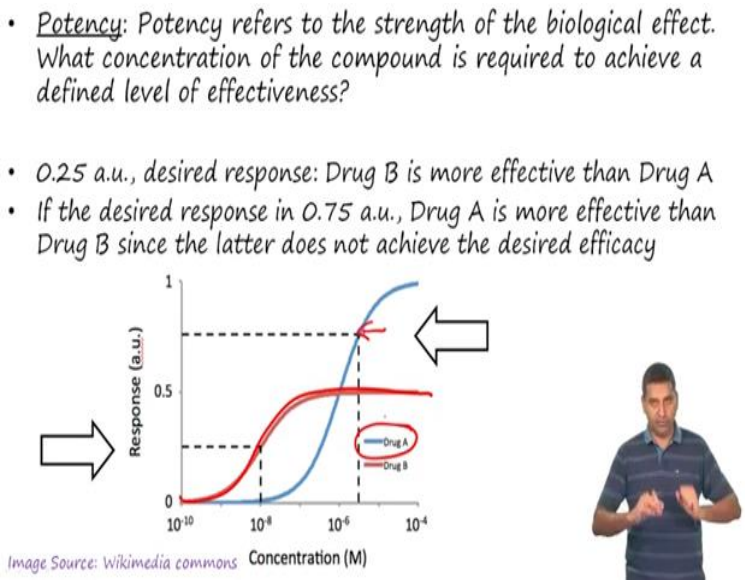

Now let us look at the same example but we look at a higher concentration where the desired response is required, higher units of 0.75 where you want to or I will repeat so let us say the desired efficacy is not 0.25 but it is actually 0.75, so that is marked by this arrow here. If you see this plot if I look at B, B does not reach 0.75 at all, okay. So therefore in this case drug A is actually better than drug B because the potency of drug A is higher than potency of drug B when the desired response is 0.75.

So to look at it in to understand potency one needs to understand what is the desired effect and what is the concentration at which the desired effect is being achieved?

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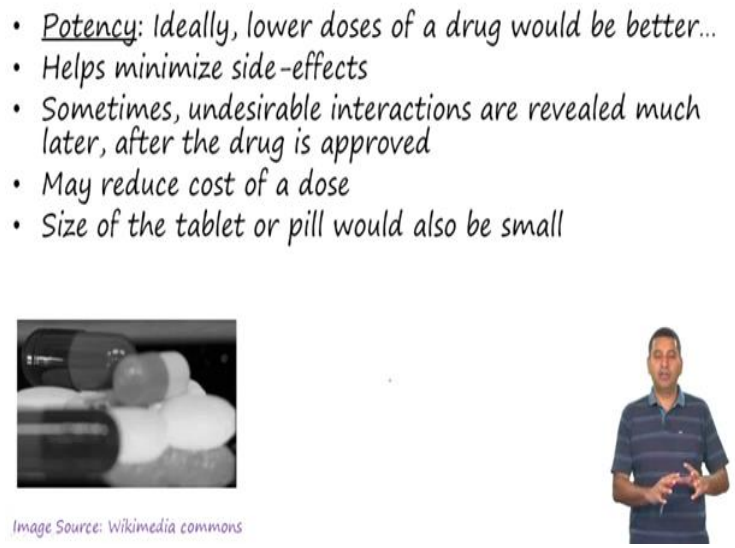

Now in an ideal world one would require an extremely low dose of a compound or the drug to be administered, this helps with reducing the size of the tablet or the pill, it also may reduce the cost of a dose because the lower the amount of compound that needs to be synthesized or prepared, the cost of it also goes down and more importantly there are undesirable interactions or side effects that we want to minimize.

So the lower the dose of the compound where the desired effect is achieved the better it is, okay and side effects are typically are sometimes unpredictable and sometimes the side effects are manifested even after the compound is approved for use. So potency is a very important parameter that we need to optimize when we are when we have a lead.

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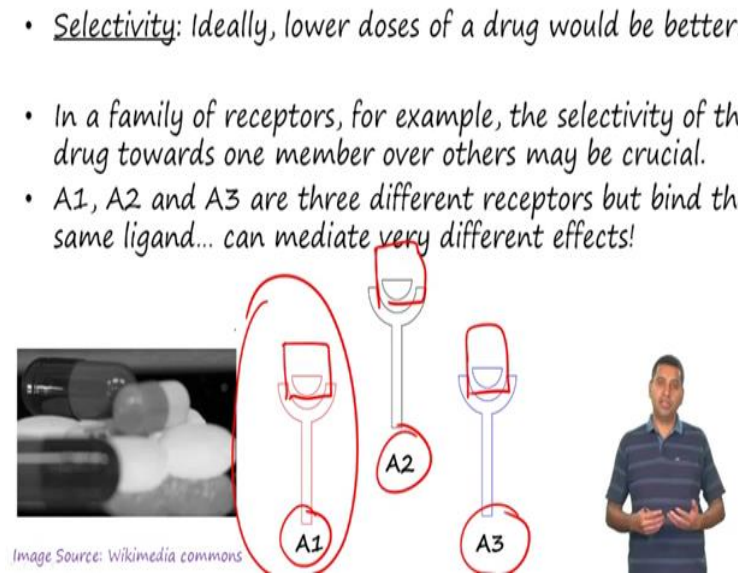

The next part of optimization requires is selectivity, okay. Again selectivity we would require lower doses of a drug because we would like to have less of target effects. Now let us look at this example, so we are looking at a lead compound which is going to bind to a receptor A and there are 3 families of this receptor A1, A2 and A3. Now this is the ligand that we have obtained, this is the lead compound that we have obtained, and if the lead compound binds equally well to all the 3 classes of the receptor then the possibility that A1 mediates a completely different effect compared to A2 is very real.

Therefore even among receptors of a similar family we need to optimize the lead compound so that it binds only to A1 in preference to A2 and A3. So this is the concept of selectivity, if you have an enzyme a family of enzymes can we develop an inhibitor that specifically inhibits one class in that family or one member of that family in comparison with the other members of the family and keep in mind that these families are classified based on the structure and based on the function of the receptor.

So this is an extremely challenging task and it is very difficult to optimize it at this stage but this is an important parameter that one needs to optimize even if we are able to achieve selectivity for 2 of the 7 members of a family that is highly desirable. So this is what this is the next major parameter that we would want to optimize.

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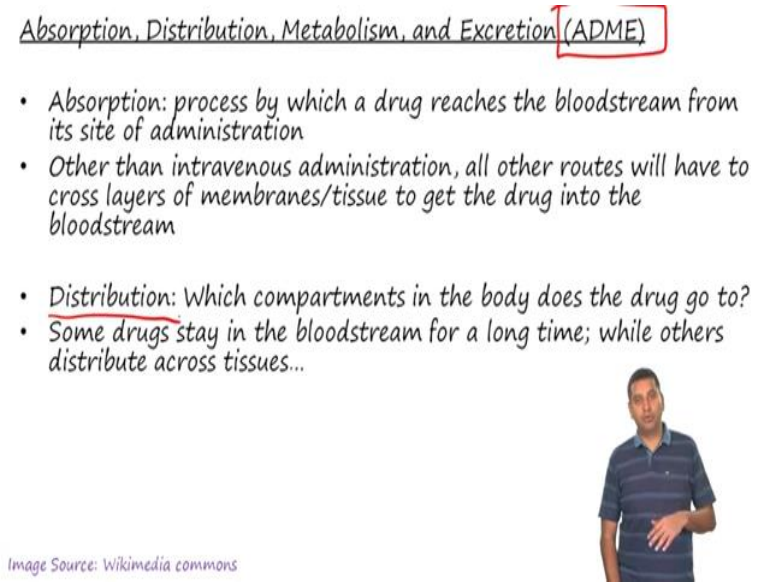

The next parameter is called ADME which is absorption, distribution, metabolism, and excretion. Now we will look at all of these terms individually. Absorption is the process by which the drug reaches the bloodstream from its site of administration. What this means is

that is I take a drug orally how long does it take for the active drug to reach the bloodstream? If one takes a drug through skin let us say I apply an ointment then how long does it take for it to cross the skin and get into the bloodstream is what we mean by absorption.

Other than intravenous administration, where in intravenous administration you directly inject it into the bloodstream all other routes will have to cross multiple membranes or tissue to get into the bloodstream. So absorption is the process by which we measure the amount that gets into the bloodstream.

Distribution is nothing but after the drug is consumed where does it distribute in the body, does it preferentially go to the liver? Does it preferentially go to the kidneys? Some of the drugs end up in bone marrow and some of the drugs end up in muscular compartments and so on. So this is what we mean by distribution. So this is another important parameter that we want to study.

Some drugs will stay in the bloodstream for a very long time whereas others will preferentially distribute into the fatty layer. So this is important for us to optimize because once we get a compound into the clinic there is a large variation in the person in the patients and there is also large variation in the size of the person and other parameters about the individual so therefore (distribution) optimizing for distribution is very important.

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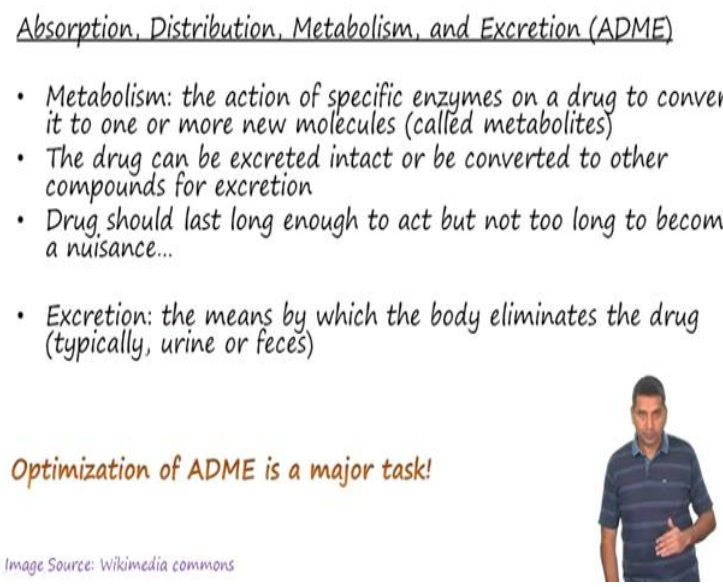

The next part is metabolism, metabolism is nothing but our body has number of enzymes which breakdown molecules and convert them into one or more new smaller typically smaller substances which are called as metabolites. So all the food that we consume is actually

broken down into smaller and simpler molecules which can be absorbed, so for example a complex carbohydrate can be broken down into glucose and so on so that we can get some energy and a complex protein is broken down into constituent amino acids.

Similarly when you take a drug, the drug is actually converted there are oxidation reactions, reduction reactions or other olefin formation reactions for example that occur which converted into other compounds. So we need to understand (what) how the drug is going to be metabolized so that we want to find out whether it is excreted intact or it is converted to something else? Now if the drug is excreted intact then we need to we will focus only on that compound and do that toxicity studies for that compound.

But let us say the drug is converted to something else we need to find out what that something else is so that we can do further studies on that because it is possible that the new compound that is being prepared is more toxic. So we need to study how the compound gets metabolized, okay. Now we would want to give to a administer a drug at lower frequency that means I would rather have a tablet once a day rather than 3 times a day, so we would want that drug to be present inside the body for a long time and last long enough for it to act.

However if the drug takes too longer time then it can become a nuisance. So we need to study these properties and how it gets metabolized for us to understand how this or we need to optimize for metabolism. The last part of ADME is excretion, excretion is the way in which the body eliminates these drugs which is typically through the urine or feces and there are so we would study how well the drug is eliminated by the body.

So when we have a lead compound and when we have promising results with the lead compound we would need to understand the absorption, distribution, metabolism and excretion and we would need to optimize for all of these so that we can get an effective drug, okay.

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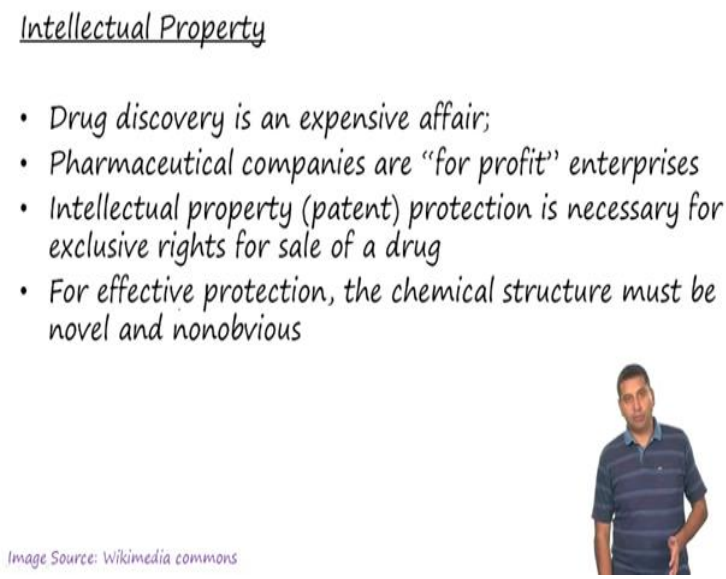

Now the last part or the next part is intellectual property. Drug discovery or lead discovery is very expensive affair, we would typically make thousands of molecules and we would have a number of tests that are carried out, we would also carry out animal experiments, we would also carry out other experiments which are quite expensive and these are expensive and pharmaceutical companies are "for profit" enterprises and now they are answerable to their shareholders in.

And therefore intellectual property protection is necessary for the pharmaceutical companies to be able to make a profit out of developing a new drug. So what happens is that once the drug is discovered the molecule or the set of molecules are protected under a patent and so this gives the company exclusive rights for sale of a drug for a set period of time, this allows the company to make money in that process so that they can go back and invest into a new set of new drug discovery effort.

However, for effective protection the chemical structure must be novel and it should not be an obvious extension of what has already been previously discovered. We will not deal too much with intellectual property in this course but suffice to say that is the very important part of drug discovery and if you make an obvious extension to a known drug it becomes very difficult to obtain protection under the intellectual property loss.

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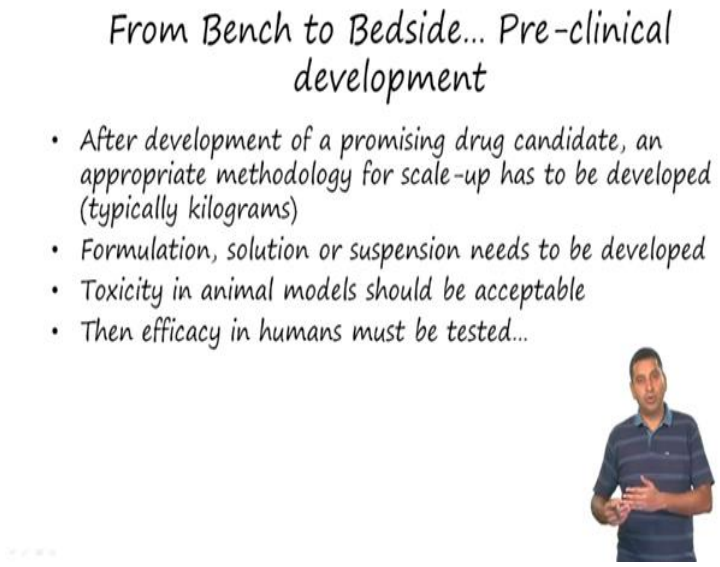

Now after you achieve a lead compound and if you are it looks very promising you go into animal studies and you find that animal studies are also quite effective, then we need to start thinking about how to translate from bench to bedside. So this is the process called as pre-clinical development, so here what we do is we take this molecule and we figure out how to synthesize the molecule in a large quantity.

So for many studies we would need upto kilograms of the drug and so if it takes 50 steps to make a drug then it becomes very difficult to scale it up to kilogram level but if the synthesis requires 6 to 7 steps perhaps then it is far easier to scale the compound up and once we have kilograms once we have kilograms of the compound then one needs to optimize for how to administer the drug? So we need to formulate the compound, maybe it would be in the form of a capsule or it could be in the form of a solution or in some cases a suspension and it depends on how the route of administration and so on and so forth, so those also have to be factored in when we are doing pre-clinical evaluation and by this stage the toxicity in animal model should be acceptable and therefore it can be one can take the compound forward to start looking at the efficacy in humans.

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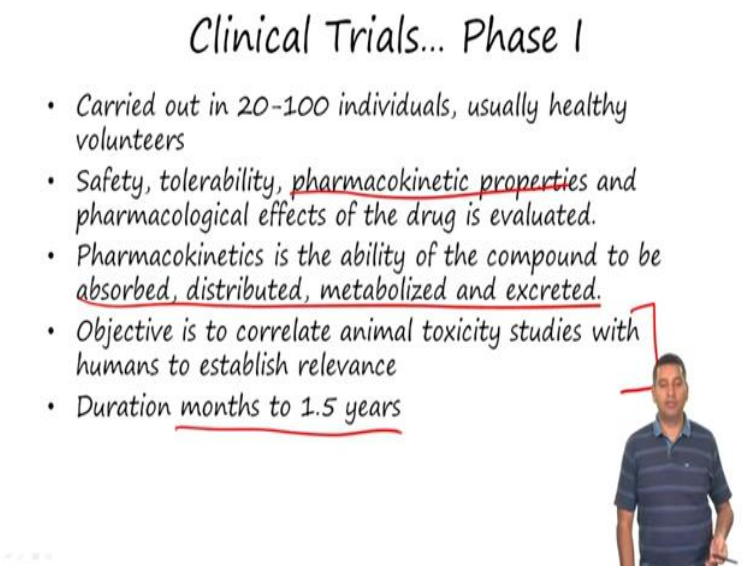

So here the food and drug administration in United States has come up with a set of guidelines about how to take the compound from a situation where you have very promising animal data to be used in a clinic or to be used in a commercial setting. So there are several phases of this let us look at the phase 1. So phase 1 of clinical trials typically involves individuals healthy individuals somewhere between 20 and 100 individuals and these are volunteers and what is done is that a single dose is typically given to these volunteers and we would people would study what happens where it goes like pharmacokinetic properties would be studied we will look at in more detail about what pharmacokinetic is in a later lecture.

We will also study whether it is safe and whether it is tolerated well all these are evaluated in phase 1, okay. Now pharmacokinetics is nothing but is the ability of the compound to be absorbed, distributed, metabolized and excreted. So we looked at these ADME parameters just sometime back we looked at this and so therefore one needs to study pharmacokinetics of the drug.

Here the objective of the study is actually to correlate whatever we have done in animal models it has to be correlated with humans and established whether the results of the animal model are actually relevant in humans. It has happened many times that a very good compound which has shown very promising study data in a canine model fails completely in humans because the metabolism is very different or the distribution is very different.

So this is a very important part of the pre-clinical development because we need to understand how well the 2 models a particular animal model and a human model correlate

with each other. The duration of this study is typically few months to a year and a half and keep in mind the objective of this is not to find out whether the drug is efficacious of not, the objective of phase 1 is to just see whether the compound is safe it is tolerated well and how it distributes across a few individuals?

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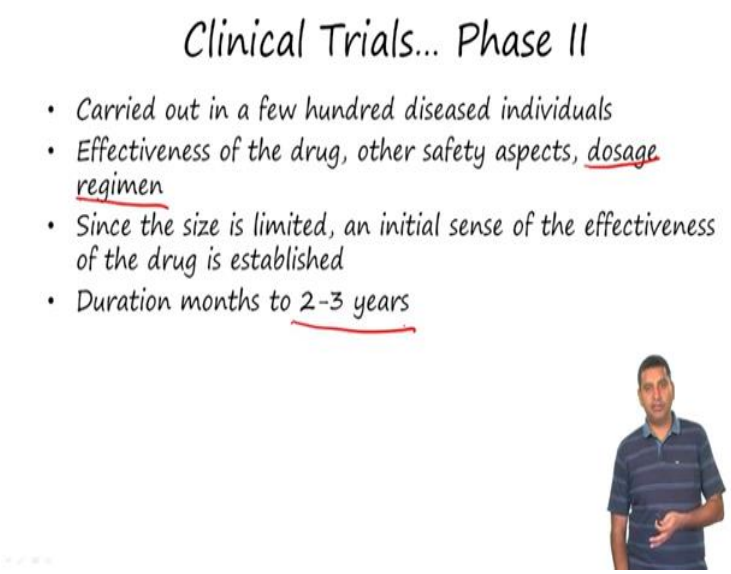

Once we get reasonable promising data in terms of phase 1 we move into phase 2, in phase 2 what is look for is we look for people who have a disease (who) these are typically patients and who are tested with tested with this compound. Here the effectiveness of the drug is what is important and it is studied. So what they do is they find out what is the dosage regimen? Whether we should give once a day, twice a day, or once in 2 days and so on and other safety aspects of drug are also studied in this case but the focus of this study is to find out whether the drug is efficacious or not?

But the size of this cohort is only a few 100 people and therefore it is not possible to study completely study the effectiveness of the drug but it is very useful to find out whether the drug is efficacious or not at this stage and this phase lasts for about 2 to 3 years.

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After the drug crosses this phase that means that there is some evidence for efficaciousness of the or effectiveness of the drug it is taken into phase 3. In phase 3 a few thousand individuals are recruited and once they are recruited a number of things are monitored including adverse effects, whether there are off target effects, whether there are any allergies and so on and thorough study is carried out and importantly it is also compared with other with similar drugs in the market, is your drug equal or better or worse than what is already existing in the market.

So here a lot of scientific controls are carried out and a number of statistical methods are applied, we will not have time to go into the details of this but at the end of it we would arrive at a conclusion whether the compound can be approved for human use or not and this lasts for somewhere between 2 to 6 years, after a lengthy and expensive trial the compound is introduced into the market, even after it is introduced in the market there is a lot of effort carried out to study individual reactions some people report what are known as adverse reactions to a particular drug. So those are also closely monitored and make sure that the compound is well tolerated in among many individuals.

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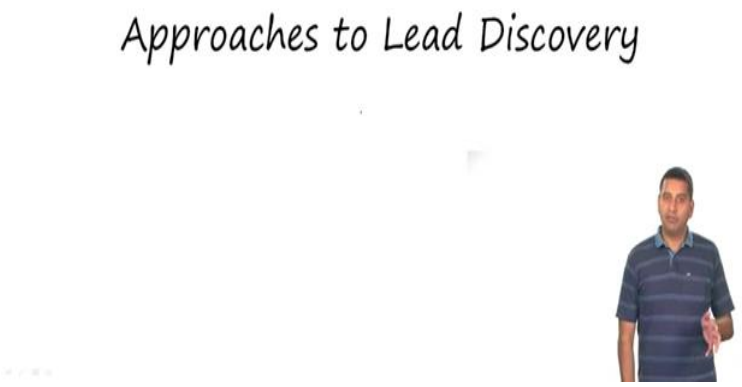

So at this juncture we would like to have reasonable approaches to discover a lead.

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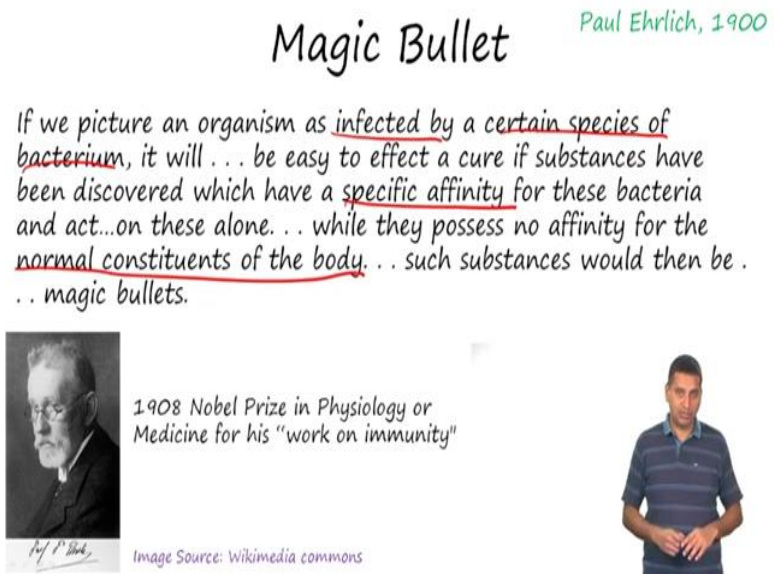

So the concept of magic bullet was introduced by Paul Ehrlich and what he said was if we picture an organism as infected by certain species of a bacterium, then it would be easy to cure it if we can discover a substance that would have specific affinity for these bacteria and only this bacteria and they should have not affinity for normal constituents of the body and such substances which he defined them as magic bullets, okay.

Paul Ehrlich received the noble price in 1908 for his work on immunity, he had discovered a number of dyes which were used to stain histological samples and so on but this was the

concept that he sort of came up with saying that you need to have high selectivity, high potency and if that compound is efficacious then we would be able to discover a new drug which is called a magic bullet.

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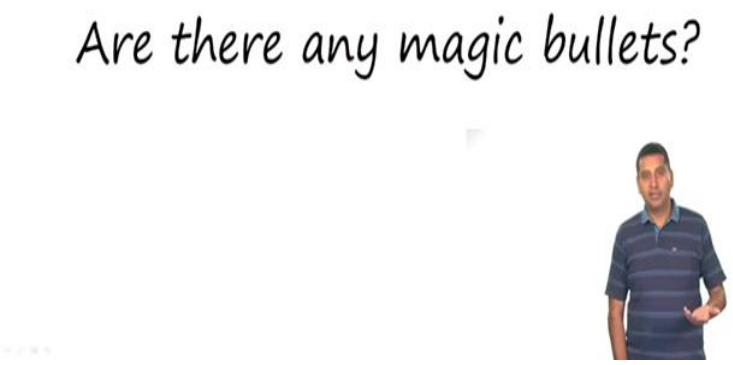

In reality there are no magic bullets one can approach towards this by using rational techniques.

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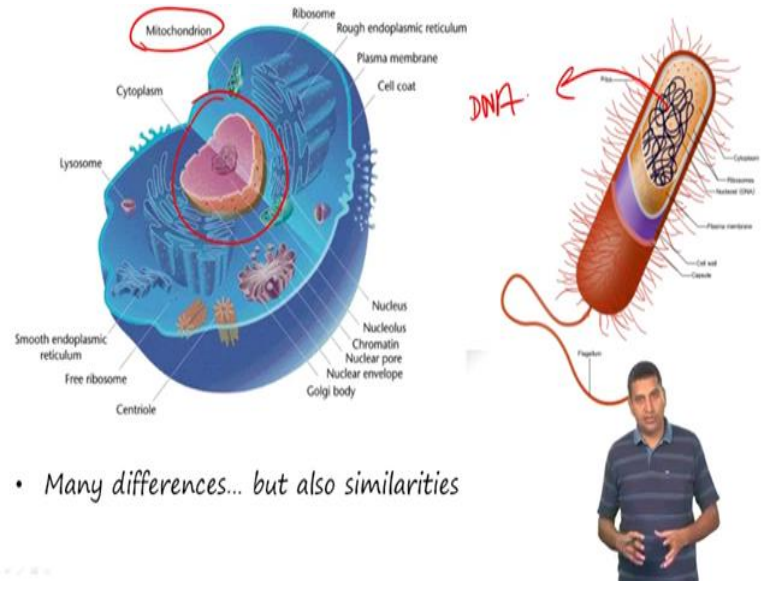

So for example let us look at a the similarities and differences between bacteria and human cells, on the left is a typical mammalian cell so here you have a mitochondrion, you have a nucleus and then you have golgi body, ribosomes and so on and this is a typical structure of a

human or a mammalian cell and on the right here is an example of a bacterium you also have here you also have you don't have a nucleus but you have DNA and you have a membrane that encompasses the bacterium and so on.

So there one could sit down and list all the differences between eukaryotic and prokaryotic cells but there are many differences but they are also similar in some respects they also use DNA as the genetic code or genetic machinery and they also use translation and transcription and so on and so one has to understand the differences between these two the way in which these two cells function for one to develop a new approach or an approach to target specifically bacteria over humans.

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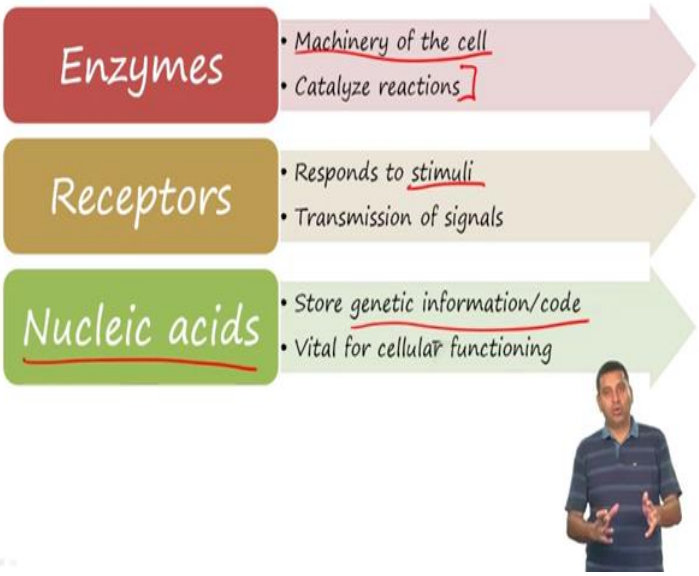

So if you look at the cellular machinery the cellular machinery starts with DNA which has the genetic code, the code is then transferred to RNA and RNA is then transfers the information to make proteins. So proteins are considered as the workhorses inside a cell and proteins can be classified typically into 2 types one is they are enzymes which are used to turnover a number of substrates inside the cell. Metabolism for example and they also catalyse reactions not all proteins are enzymes and not all enzymes are proteins there are RNA based enzymes for example but for the purposes of this discussion we shall assume that a large number of enzymes are proteins.

Now receptors on the other hand they are very useful for transmitting signals, these are typically located on the cell surface and once the ligand comes and binds to the receptor there is a signal that is transmitted inside the cell which makes the cell do something. So this is

very useful in responding to stimuli and it has to be rapid otherwise the organism may it may be fatal for the organism. So these are 2 important proteins which can be targeted or which one can find out differences between bacterial enzymes and human enzymes and once can figure out if we can target these.

On the other hand if you are looking at cancers, cancers are again they have many human like qualities or human cell like qualities which are very difficult to target because the differences are fewer in number. However, one characteristic of cancers is that they rapidly divide and so here one attractive approach is to target nucleic acids because in a rapidly dividing cell you need to synthesize DNA, you need to synthesize RNA very quickly and you need to divide much faster than other cells that are growing.

So here as I mentioned earlier DNA is a source of it has a storage for the genetic information or genetic code. So therefore these are the 3 broad ways in which one can develop approaches towards magic bullets.