Medicinal Chemistry
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Module 01
Lecture 01
Introduction to Medicinal Chemistry Part-1

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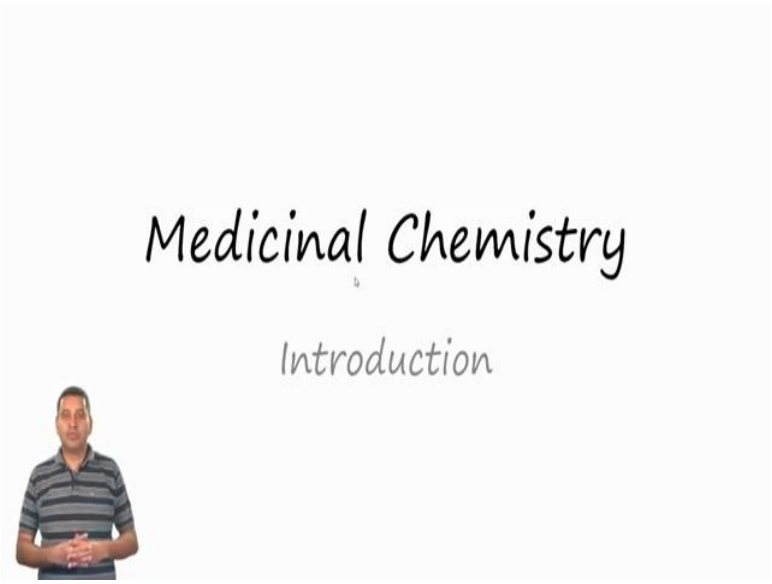

So welcome to the NPTEL course on medicinal chemistry, so today we will look at some of the ways in which drugs have been discovered.

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So what are medicines? Medicines are used to treat diseases and drugs are the active ingredients which are used in medicines and these are components of basically medicines which are used to which can be used to diagnose and diagnose means that you try to find out what exactly the disease of that the person is suffering from, it can also be used to cure which means that you completely get rid of the disease or it can be helped to reduce the effects of or mitigate the symptoms of course to be to treat or lastly it can also be used to prevent a particular disease.

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So with this broad definition of a drug that serves multiple purposes and so the field of medicinal chemistry includes isolation of compounds of nature as we will later on in this lecture a lot of drugs or medicines are acquired from nature and so you need to isolate these compounds from the natural sources. Once you have a small molecule or a drug you also need to look at the structure activity relationship which is basically nothing but trying to figure out which structure leads to the best activity, you also need to look at how the compound interacts with their targets which is what is meant by Elucidation of the interaction of the compounds with their receptors.

Once the drug is taken into the system we need to look at how it is observed, what is the bio distribution that is where it distributes across inside the body how it is transported from one part of the body to the other part of the body and what are the properties that are involved in this process, okay. Now lastly medicinal chemistry also involves how a drug is metabolised? So not just how it is being absorbed and distributed but how it is being transformed.

In our body there are multiple enzymes which can interact with the compound, it can oxidize it, it can reduce it, it can introduce a double bond, it can introduce other functional groups, it can make the compound more water soluble and so on so this is the field of metabolism of the drug. So medicinal chemistry encompasses all these aspects of study, so it is a highly interdisciplinary subject with lot of

input from organic chemistry, input from some biochemistry, enzymology, biology, pharmacology and other fields so this is the representation of a traditional medicine, so the question is how do we get from there to a drug store putted in a package which is what we consume.

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So the question that we ask is how does one discover a drug? So the traditional way in which we discover a drug is to rely on history, so many of us have exposure to traditional medicine these are practises which are passed on from one generation to the other and these are very important components of mitigating or even treating certain symptoms. The other way to look at how to discover a drug is completely by accident or by serendipity. So what this means is that you are looking for some other property of the molecule but you end up looking at (another) different property which results in a drug.

The last way to discover a drug is through rational design. So modern medicinal chemistry relies a lot on how to rationally design a drug. Of course once the drug has been discovered it goes through a very long road and it takes years and years for it to get from the point of discovery that is from the point you have an idea to actually put in a bottle and sold to people. So we look at this long road much later but very briefly it has to go through what are known as trials which are known as clinical trials before it goes it clinical trials it has to go in through animal models and then it has to go through a number of studies in healthy patients as well as in sick patients and they people look extensively at the safety and efficacy of the molecule and then only then it is approved for use by humans. In this course we will look at the entire process right from the idea to where it gets into how it gets into a bottle and is sold to humans, okay.

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So let us look at the first part of it which is drugs which are discovered without rational design, okay. So here the drugs were discovered basically relying on what is known as traditional medicine. So here is a person who has potion in his hand and he is administering it to a patient this is an old image this is an image from Iran and so the contents of the potion are what is going to create a desired effect and these are basically have been practised for thousands of years and they typically look for herbs, barks, roots, or fruits or berries which can be crushed and made into some sort of a potion which is then given to the patient, okay.

So this knowledge has been acquired from generation to generation by trial and error, okay. So the herbs that are used can vary from place to place, the same herb which is grown in a particular environment can have completely different effect in another environment and so there are number of issues with respect to the process by which these types of therapies work, however they have been used for thousands of years and so we can use them as a foundation for discovering new drugs.

So the earliest records that are available in writing are from ancient Chinese, Indian, South American and Mediterranean cultures and these consists of certain concoctions of certain herbs or certain potions extracts from plant sources mainly and these have been recorded to have therapeutic effects. So therefore relying on this traditional medicine helps us have a foundation for certain diseases.

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Let us look at an example so the example that we are looking at here is a bark which is derived from the plant called Cinchona which was known by native South Americans to cure chills and fevers, okay. So what they would do is they would extract the bark and use it for curing in fevers. So this was observed by the Spanish people who were there they took this bark and they took it back to Europe where Malaria was a huge problem and this bark was very effective in curing Malaria and this became the choice of drug or the choice of treatment for Malaria. Keep in mind at this time it was not known that Malaria was actually caused by a Mosquito bite and people were only curing or trying to address what was the symptom which is basically chills and high fever and this was one of the oldest examples of something that can be used to cure a disease.

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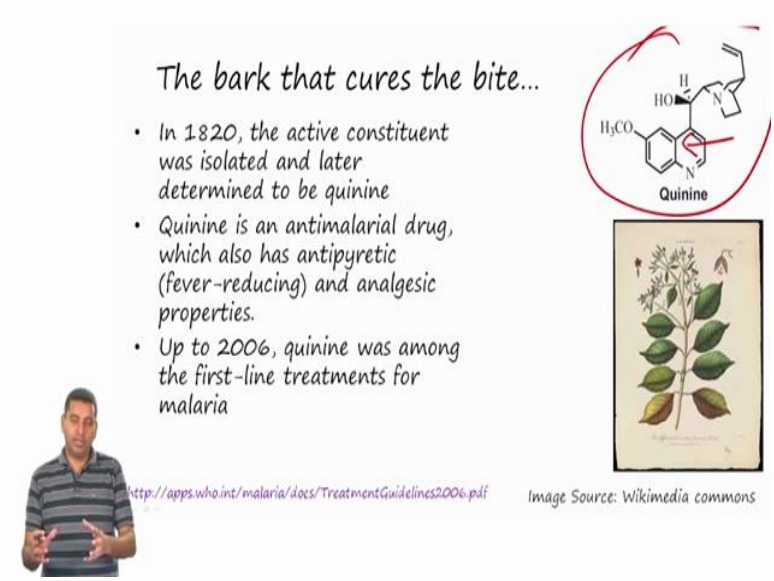

Much later in the 19th century the active constituents of this herb of this bark was found to be quinine, okay. So once the structure was determined then quinine was subsequently mass produced and it is been widely used as an anti-malarial drug. At this time it was also discovered that Malaria was actually caused by a Mosquito bite and it was caused by plasmodium falciparum and so on and so forth much into the 20th century a lot has been discovered but without knowing what the cause of the disease was people were still treating it and people were still it was still possible to cure it and quinine upto may be the last decade was among the first-line treatments for Malaria. So this is an example of how one could use traditional medicine to actually discover a drug.

Subsequently quinine structure can be the foundation for discovering new drugs, so you could think of making modifications to the structure of quinine that would help with improving the activity for example.

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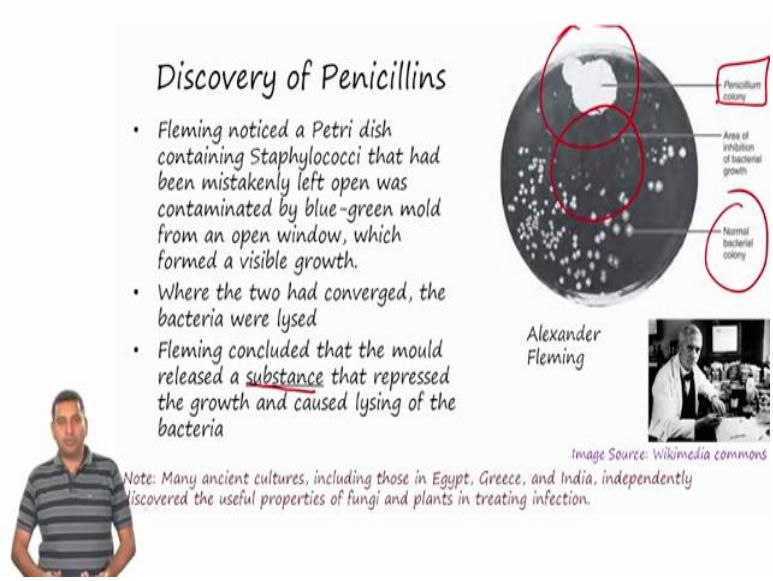

Now let us look at another example which is case number 2 which is of Serendipitous discovery. So Alexander Fleming who was a microbiologist was working with Staphylococcus Aureus and once during his many years in the lab, he left a Petri dish containing staphylococci and for several months and once he got back he found that there was some contamination in the Petri dish and so here is the normal bacterial colony which is Staphylococcus Aureus and he found that there was a colony of some mould which is basically fungus when that was growing in and this was subsequently identified to be Penicillium and in this area over here which is where there was a convergence between the Penicillium growth and the bacterial growth he observed that the bacteria were lysed, okay.

And so this led to the discovery that he hypothesize that the mould must secrete a substance which then repressed the growth of bacteria which cause lysing of the bacteria. So this is an important observation by Alexander Fleming and it was completely by accident, he was not looking for a cure

for Staphylococcal infections but he observed that the mould that was formed was able to lysed bacteria, of course if you go back in history there are many ancient cultures which independently discovered the useful properties of fungi and plants in treating such infections. However, this observation by Alexander Fleming made a tremendous impact because now if you could isolate the substance you could use it as a drug.

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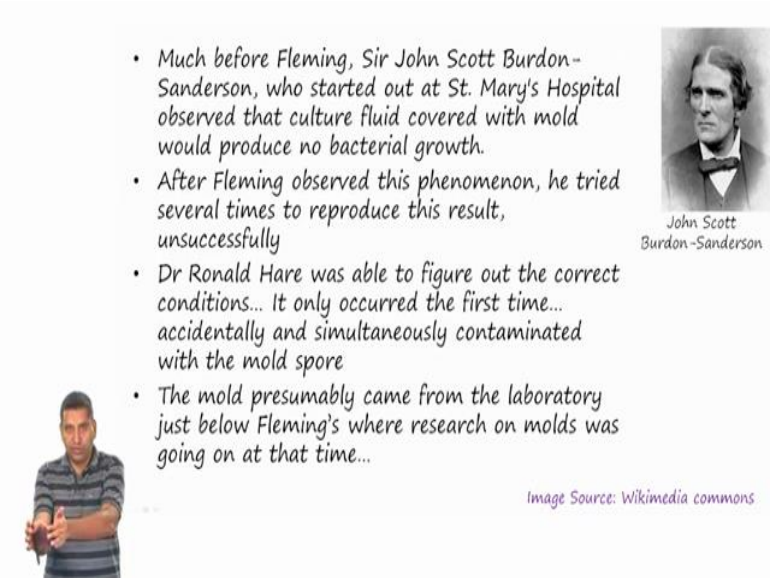

So in fact the observation that Penicillin or Penicillium this mould could inhibit bacteria was made by John Scott Burdon-Sanderson which was much before about 30, 40 years before, in the same hospital he observed that culture fluid which was covered with mold would produce no bacterial growth, okay but he did not pursue this observation further and the credit of finding discovering Penicillin was goes to Alexander Fleming.

However, after Fleming observed this phenomenon, he tried several times to reproduce this result and it was not successful at all. So he spent several months trying to recreate the conditions under which Penicillin Penicillium was successful in inhibiting Staphylococcus but much later Dr Ronald Hare was able to figure out the right conditions, how it happened for the first time. It appears that it was simultaneous and accidental that the spore was contaminated or the bacterium was contaminated with the mold spore.

And the origin of this mold spore was actually a laboratory which was just below the lab of Fleming. So therefore this presents a case a unique case where the conditions were appropriate for the discovery of Penicillin and it just so happened that Alexander Fleming observed this, okay and subsequently the structure of Penicillin was discovered.

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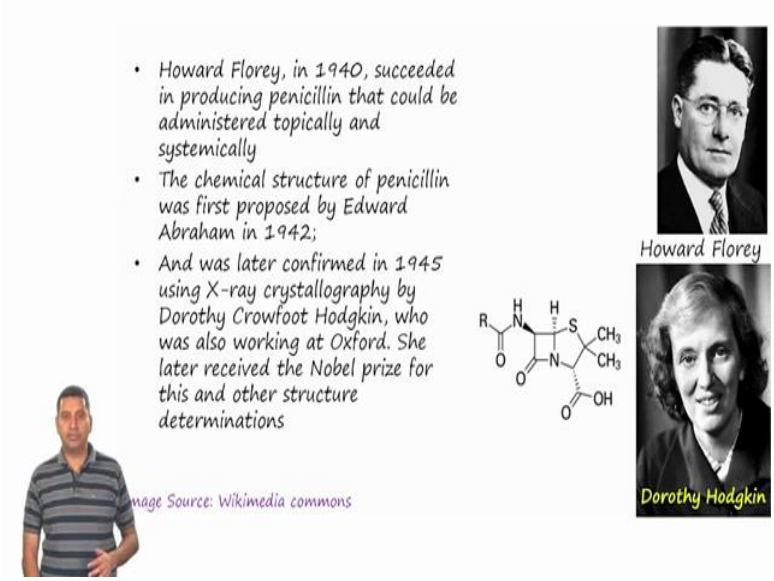

And in 1940 Florey was able to figure out a method where he could administer to he was able to mass produce this drug and then it was subsequently administered both topically as well as systemically. And in the meantime the chemical structure was found by Edward Abraham in 1942 and it was first confirmed by X-ray crystallography by Dorothy Hodgkin, who was working at Oxford. She later received the noble prize for this discovery as well as other structure determinations. Now this compound was used as a wonder drug at that time and it was well used in 1940's, 50's and subsequently and it was a very important discovery in the history of medicinal chemistry.

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Now let us look at another case where Serendipity which is the discovery of Librium, Leo Sternbach who was involved in a program to synthesize a number of new class of molecules in the 1950's they were very much interested Roche was very much interested in discovering new tranquilizer drugs.

Now they synthesize a series of compounds and none of them were found to be active and since they had no interesting properties they actually closed down this program but in 1957, when the lab was being cleaned up, they found a vial which they said okay now let us just try and find out whether this has any pharmacological activity and they sent it for testing and it was found that this compound which was stored in this vial had very promising activity in a number of tests as tranquilizer, okay.

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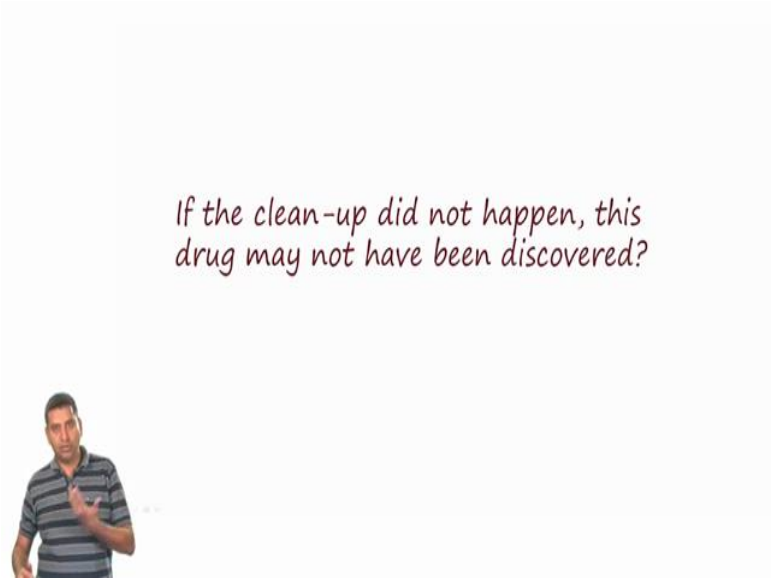

So the question is if the clean-up did not happen, this drug may not have been discovered? Just keep in mind that this subsequently became a multimillion Dollar drug and it was very widely prescribed so a lot of medicinal chemistry relied on chance. So if you see the example of Alexander Fleming or in the case of the discovery of Librium, it was completely by chance and these are only two examples of Serendipitous discovery, there are multiple number of other examples which can be discussed by in the interest of time we would not look at it in this class. So therefore it is unlikely for a scientific enterprise to rely completely on chance to discover new drugs.

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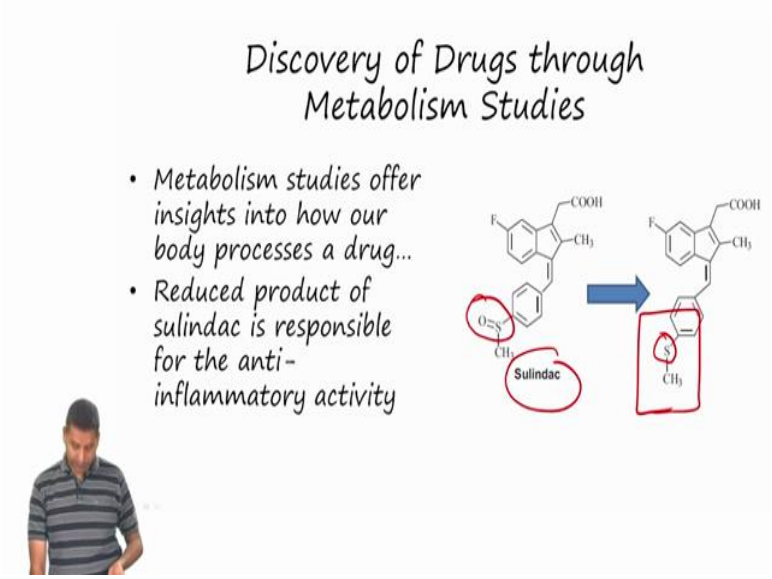

So there are other ways in which one could do this, one is to look at metabolism, if you remember we looked at how when a drug is consumed it goes through a number of transformations inside the body so the liver secretes a number of enzymes which carry out chemical reactions on the drug and so metabolism offers lot of insights into how whether a drug how a new drug can be or a new Scaffold can be discovered.

So here is an example of Sulindac which is basically a compound with an S double bond O, so what was observed that Sulindac itself is not responsible for the anti-inflammatory activity but it is a reduced form which is a Thioether which is responsible for the anti-inflammatory activity. So now therefore this Scaffold becomes a lead for us to look at new drugs, okay.

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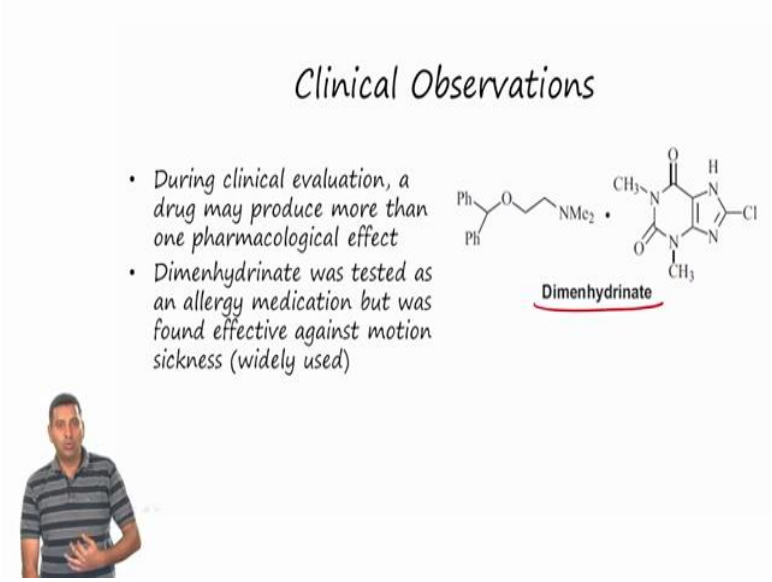

The other way to do this is to look at clinical observations, so when as we discussed earlier the particular compound goes through a number of tests before it is put in a bottle and sold to humans. So during these clinical studies, these drugs are put through a number of tests. So when this clinical evaluation happens it is possible that certain drugs have are being tested for a particular activity for example anti-inflammatory activity but they show completely different effects, so if one is receptive to these kinds of tests then one can also discover new drugs in this process.

So here is an example of a drug which is very widely used for motion sickness but was originally tested as an allergy medication and so therefore during the test it was observed that it was not effective as an allergy medication but instead helped people who had motion sickness.

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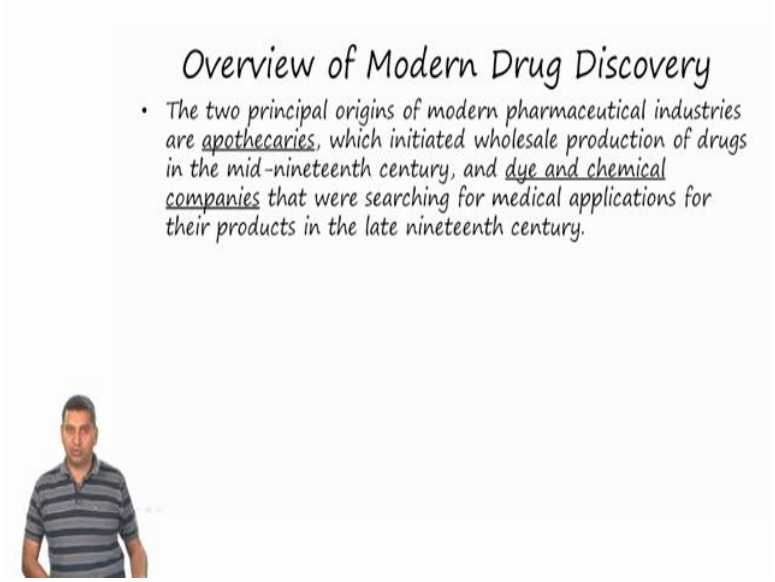

So all these are very interesting ways to look at how to discover new drugs but modern drug discovery does not rely exclusively on these processes but they would want to do what is known as a rational drug design, okay.

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The major origins of modern drug discovery are apothecaries, apothecaries is a term used for a medical professional who formulates and dispenses the materials that are required by physicians, surgeons of course and patients. The apothecaries grew in the 19th and 20th century in parallel the dye and chemical industry was also growing quite a bit.

So people had started having a the scientist were able to synthesize a number of compounds and they had mastered the art of synthesis to a good extent and therefore they were producing a large number of small molecules mainly for the dye and chemical industries but they were also searching for medical applications because there was an unmet need in society for discovering new drugs, the late 19th century was a very happening time where both these things happened and therefore it led to the modern pharmaceutical industry.

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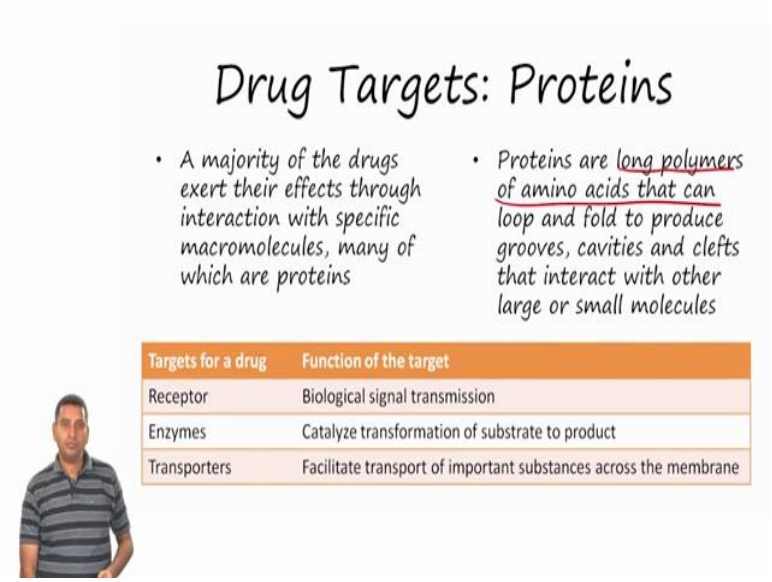

So now the way in which we think about designing new drugs is that we look at what are the components or what are the targets for a drug. So majority of the drugs that are in use today act on proteins, proteins are nothing but long polymers of amino acids that can loop and fold and go and produce these clefts and cavities wherein binding occurs and a lot of those function of the protein depends on the shape, it depends on the charge and depends on the cavity size and so this offer very unique properties to the protein and therefore they become important starting points for us to make compounds that can go and interact with a protein.

Proteins have majorly 3 functions one is they can act on a surface and they are receptor and what these receptors do is that they bind to a small ligand and they help in signal transmission. The second major function of proteins is to catalyse a reaction and to transform a particular substrate into a product. So this for example is an important place in which we can discover new drugs because these enzymes that are present in let us say a bacterium may be different from the enzymes that are available or used in humans, using these differences one can design a new drug.

The third major function of a protein that is used in drug discovery is a transporter, so transporters are nothing but proteins which help a substrate or a molecule get across the membrane, we will look later that the membrane consists of what is known as a lipid bilayer and not all molecules get across the membrane. Therefore transporters become very important targets for or potentially important targets where we can discover a new drug, okay.

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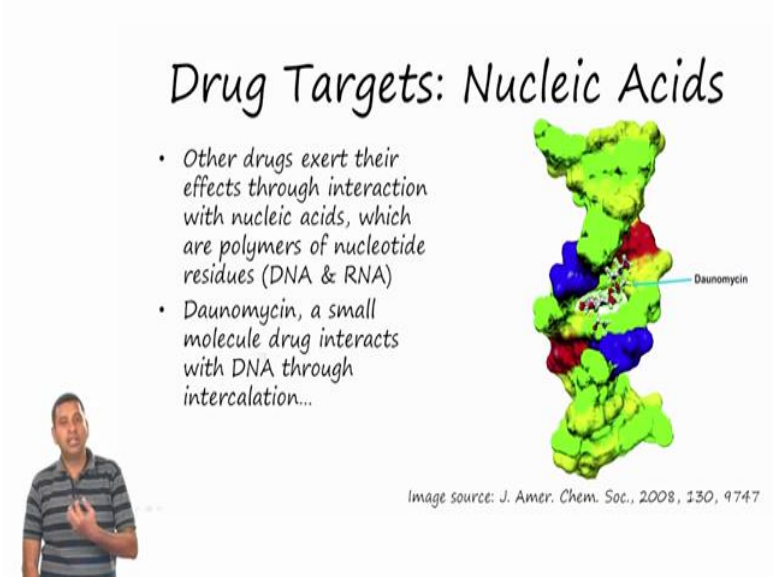

Now the other major target other than proteins are nucleic acids. Nucleic acids such as DNA and RNA are very important to store information and RNA can also catalyse reactions. So therefore if one could develop a molecule which can interact with DNA then it is possible that we may be able to discover a new drug. So here is an example of Daunomycin which through computational modelling

has been shown to intercalate in DNA. We will look in detail later as to what the process of intercalation is but suffice to say now that intercalation produces enough damage to the structure of DNA that it ultimately results in cell death. So therefore this drug has been used or intercalating agents have been used in the treatment of cancer.

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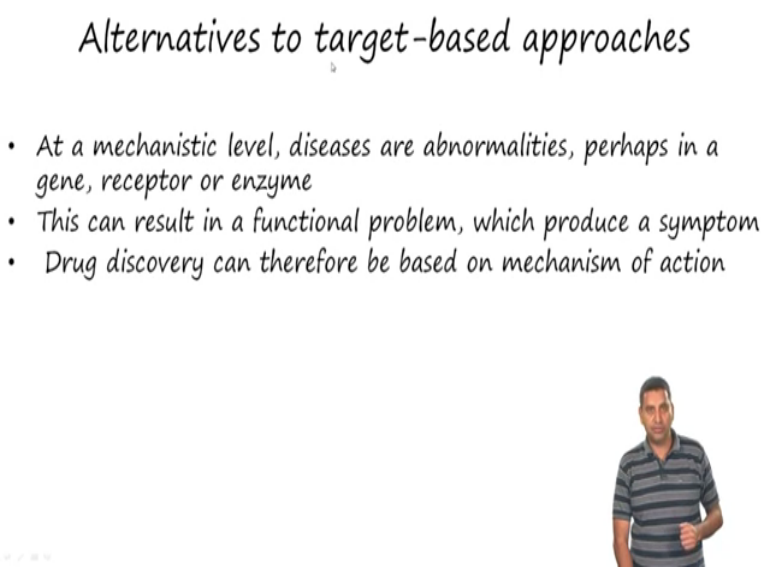

So in addition to the target based approaches where we look at a particular protein or DNA we can also look at non target-based approaches. So in typically a disease at a mechanistic level, diseases are nothing but abnormalities in the function of the cell or function of a tissue so which is typically linked to a particular to a gene, or a receptor or an enzyme. So what happens is that when there is an abnormality in the functioning of the tissue which results in a symptom. So therefore one could use this symptom or use this what is known as the phenotype to develop new drugs. So here in many cases the target is not completely known, so we only screen or look for compounds which can address the abnormality which is associated with a particular disease.

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- Screening of potential drug candidates can be for normalizing the abnormal function:
  - Growth processes
  - Hormone secretion
  - Apoptosis (cell death)
- Or, on physiology of an organ or in animal models
- Historically, animal models were the first to be used; now, it is used in advanced pre-clinical evaluation

So what we do is we start you know in order to identify potential drug candidates we need to start screening for compounds and this screening is done with typically with small molecules which look to normalize the abnormal function. So what this means is that let us say there is a growth defect in a particular individual or a particular organ, what we could do is we could setup an assay or a test which in which the compounds that are screened the purpose of those compounds would be to restore the growth process, okay.

In another example you can look at hormone secretion where it leads to imbalance in the normal functioning of the body and if we are looking at either increasing the hormone secretion or decreasing the hormone secretion one could look for molecules which can normalize it. So in the case of where you want to decrease hormone secretion you need to inhibit it and in the case where you want to increase hormone secretion you may want to activate it.

And the other way in which one can look for normalizing an abnormal function is in the case of cancers. So cancers are nothing but uncontrolled proliferation of cells and you may want to screen for compounds which can induce cell death or apoptosis. So these are some of the ways in which we can screen for potential drug candidates. Now the alternative is to look at the physiology of an organ let us say there is an enlarged organ and you want to reduce that size of the enlarged organ then you may want to screen for drug candidates which can do that, which is typically done in an animal model.

So historically animal models were very widely used even before the cellular based assays were actually developed but now it is exactly the reverse, most assays or most modern discovery methods depend on cellular assays or even you go one step back and you look at assays with purified protein or purified DNA for example and from there you build up the model go into cells, go into tissues and so

on and so forth. So animal models are used pretty much towards the end of the pre-clinical evaluation unlike what used to happen previously.

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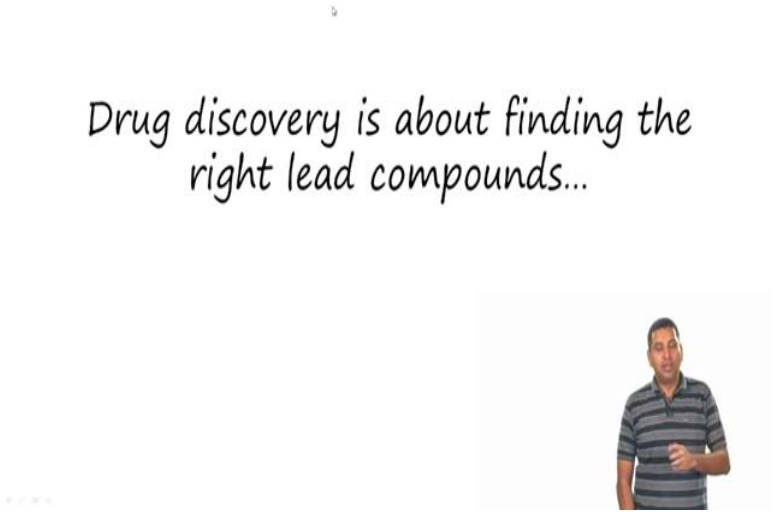

So drug discovery in a nutshell is about finding the right lead compounds.

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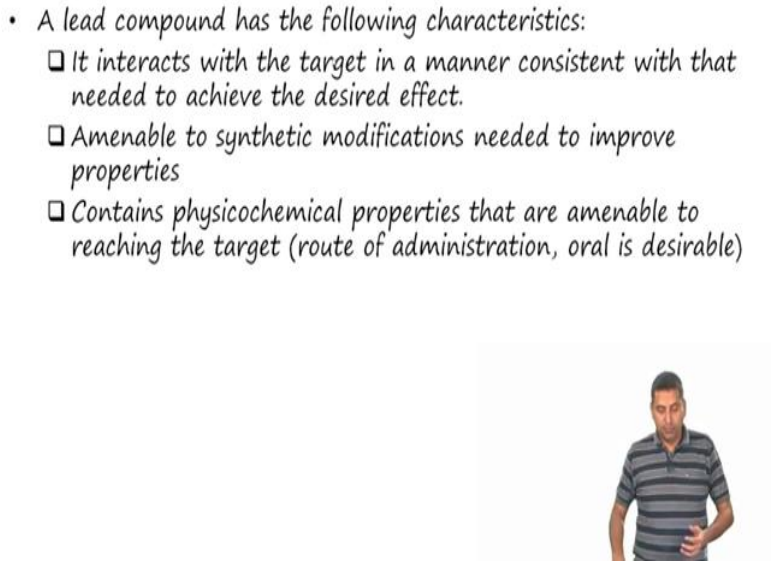

So the question is how does one find a lead compound and what are the characteristics that we need to look for. So in the case of a lead compound you look for a following characteristics which is it interacts with the target in a manner which achieves the desired effect, okay and this lead compound should also be amenable to synthetic modifications. So here you want to make the structure so fairly versatile so that you can make multiple modifications around the Scaffold.

We look at this in detail towards the later part of the course but you may want to design the compound such that you can help make modifications and why we need this modifications is because we need to improve the properties and the properties that we want to improve are many times linked to how well how easily it is observed, how long it stays inside the body, what is the ideal route of administration so most drugs that are very widely used many drugs which are which we want to develop are taken by mouth or oral and that is the most desirable kind of drug that we want to develop. Now there are certain properties which we will look in detail of drugs which are orally administered. So therefore the lead compound has to have all these characteristics for it to be taken forward.

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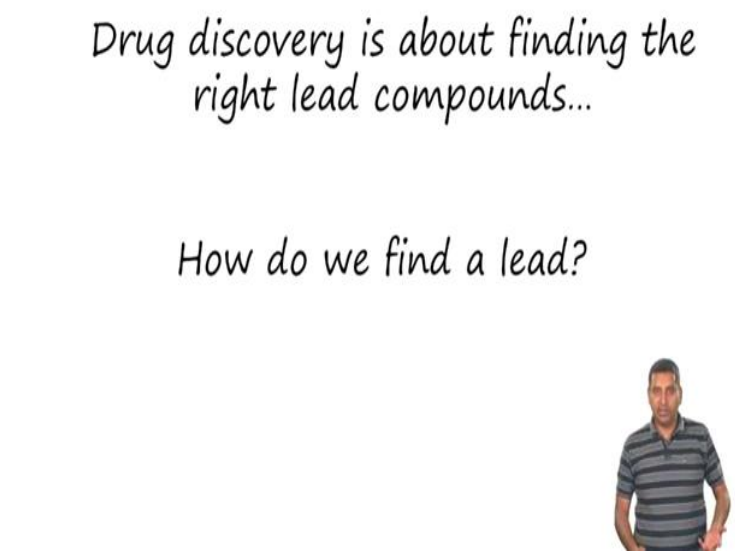

So as I mentioned earlier drug discovery is about finding the right lead compounds. So the question is how do we find a lead?

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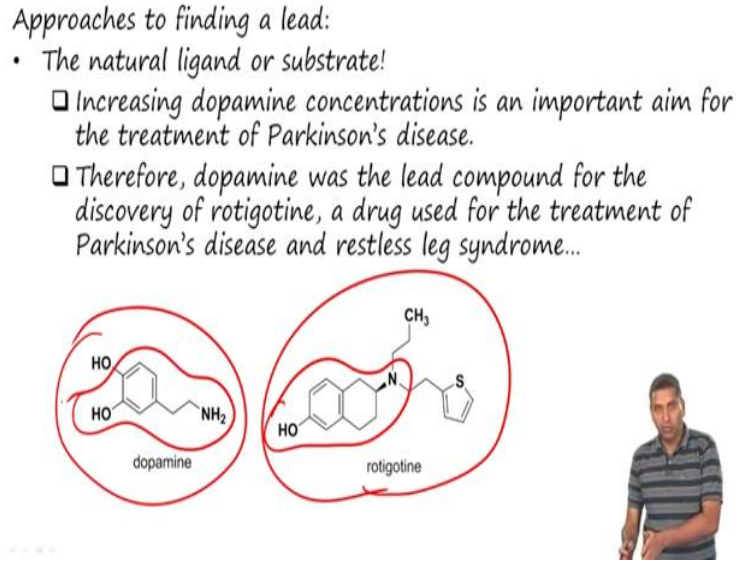

So one of the approaches to finding a lead is to use the natural ligand or substrate for the target, so for example to treat this disease known as Parkinson's disease it has been proposed that one could increase dopamine concentration, okay. So now in order to mimic the effect of dopamine we would need to use the structure of dopamine as the lead and here is the structure of dopamine and in order to develop a lead compound one uses the structure of dopamine and using this it has been found this compound rotigotine is a very interesting very important lead and if you notice here the structure of this compound is quite similar to the structure of the natural ligand which dopamine, right. Therefore using dopamine as the starting point one could develop a new lead compound or even a drug.

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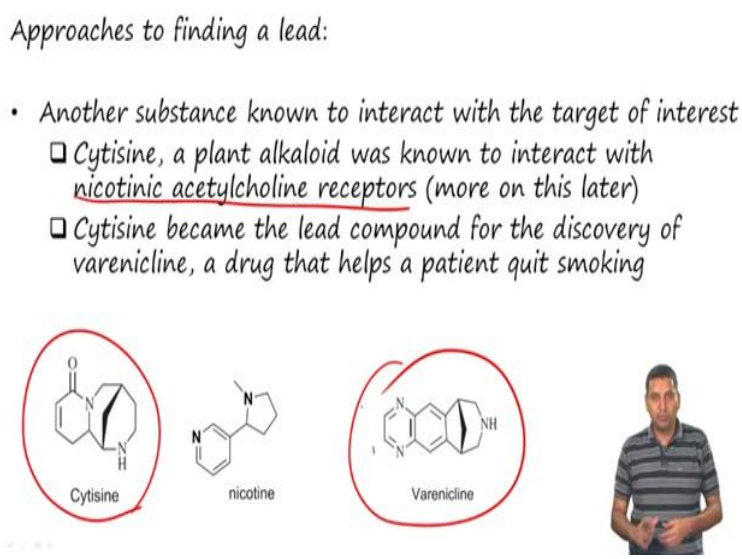

The other way to do this is to look at substances which are known to interact with the target of interest. So here is an example of Cytisine, which is a plant alkaloid, alkaloid is nothing but a set of molecules which are present which are natural products and this alkaloid is known to interact with (acetylcholine) nicotinic acetylcholine receptors, okay. So the kind of the drug that the company wanted to develop the kind of drug that was required to be developed was to help people quit smoking.

So based on this alkaloid which is known to interact with nicotinic receptors, this drug which is known as Varenicline was developed, okay and this drug helps patients to quit smoking. So therefore you could either use the natural ligand or substrate or use knowledge of structures which are known to interact with the targets of interest and these become the foundation for developing a new lead.

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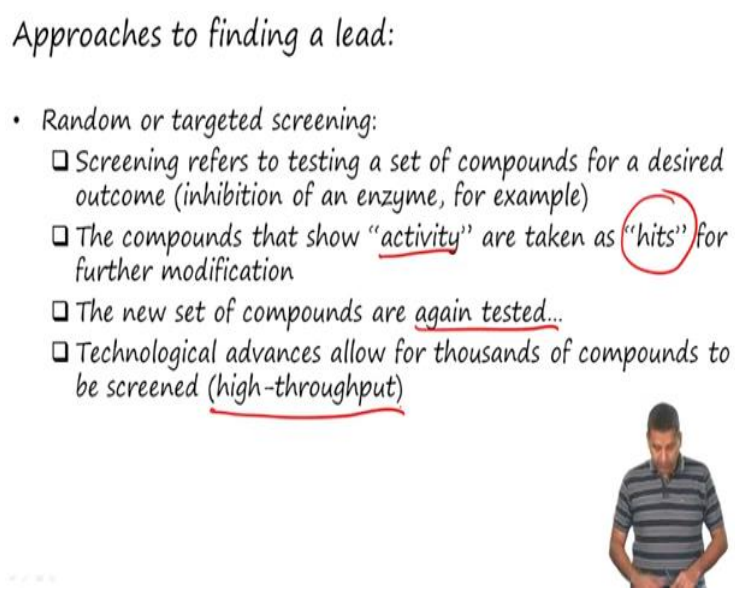

Now there are other alternate methods which one could use which is known as screening, okay. So screening is typically of 2 types which is random or targeted we will look into these details shortly. But screening refers to basically testing a large number of compounds or a set of large number of compounds for a desired outcome, okay. So the example that we could think of is let us say we have identified a particular enzyme in a bacterium as a target that we want to inhibit this enzyme.

So now what we would do is we would purify this enzyme, we look at how to setup these assays in detail later but you would purify this enzyme and setup an assay or a test for inhibitors of the function of this enzyme or the activity of this enzyme. So therefore now we would assemble a set of compounds and then look for compounds which can inhibit this activity. Now these compounds out of these set of compounds there may be a few compounds which show some "activity" and these are known as "hits", okay. So these compounds whose structure we already know because we have assembled the portfolio of compounds or these compounds are taken for further structural modifications.

Once we do these structural modifications we have a new set of compounds and we again setup the screen and then this process is repeated again to identify the best compound which is then taken forward for further testing. So this is one of the ways in which we can do it, now in the past 20 or 30 years there have been a large number of technological advances which allow for thousands of compounds to be screened in parallel, okay. So these approaches are known as high throughput screening approaches and again we will look at this in detail in shortly but therefore the limiting factor in this some of these assays is to develop the assay or to develop the right kind of target, okay because there is a large library of compounds that are already available which can be tested or screened.

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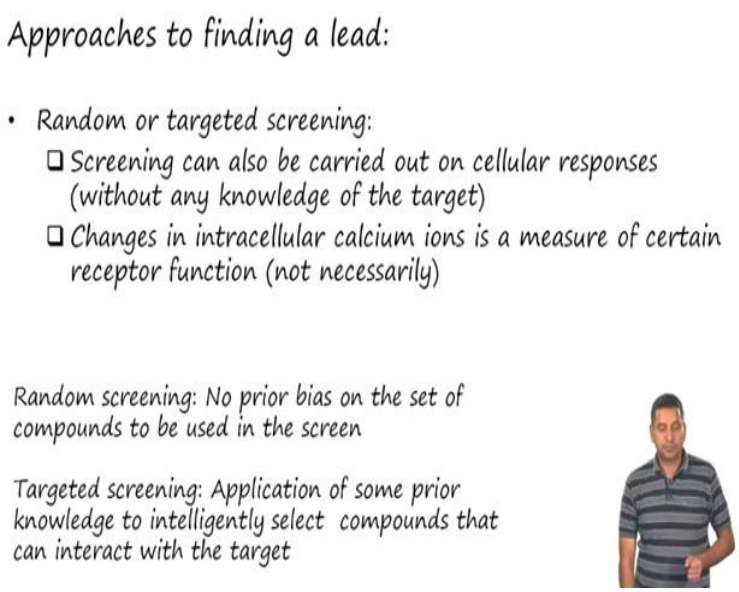

So screening can also be carried out on responses to cells, so here we don't have any prior knowledge of what the target is. So what we do is we look for a certain type of response so it can be inhibition, it can be growth, it can be many other things, right. So once we start setting up screens for looking at a phenotype or a cellular response then we do the same process, we look for "hits" and then we go ahead with further structural modifications.

An example that one could look at is intracellular calcium levels which is a measure of how well certain receptors function, it is not necessarily related to only receptor function but it can be a good measure of certain of looking at cellular responses. So one could look for molecules which can increase intracellular calcium levels or decrease intracellular calcium levels as the need may be this is another way to look for a lead.

Now the difference between random screening and targeted screening is very simple. In random screening in the set of compounds that are assembled we look we don't have any bias, okay. What that means is that we will look at a diverse Scaffolds or diverse set of structures so that we can maximize the chemical space that we are working with. In targeted screening on the other hand we apply some prior knowledge that we have. So for example we may know the crystal structure of the protein and we may know we may look for a particular binding site but we may not know exactly what how best the structure would bind but we may want to apply some prior knowledge and intelligently select compounds that can interact with the target. So this is the difference between random screening and targeted screening, okay.

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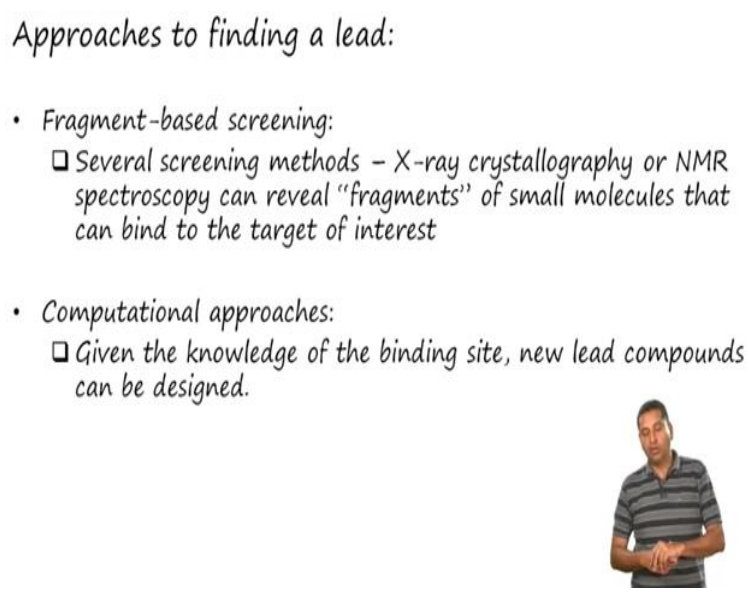

Now an alternate approach is somewhat related to the targeted screening that I mentioned is called as a Fragment-based screening. So in Fragment-based screening what typically happens is that there is prior knowledge of the structure of the protein or receptor and what we do is we look for domains of the protein which are functionally important. Now this is obtained by X-ray crystallography or NMR spectroscopy and once we identify these functional domains in the protein revels to a certain "fragments" of small molecules which can interact or bind with these targets of interest.

So once we have this information that becomes the foundation for us to screen for more molecules. So we would take a particular fragment from this build up structures add methyl, ethyl, phenyl groups and so on and then try to achieve the right kind of or most efficient binding compound, okay. Of course the very popular method is to use Computational approaches. So here again we should have knowledge of the binding site, once we have that knowledge you can design new lead compounds through what is known as virtual screening.

So there are certain interactions which are important in the binding site, and those interactions are exploited to design compounds (to hit them) to hit the target. So again we will go into this in detail during the latter part of the course but (this is) these are the major ways in which one could find a lead compound.