Medicinal Chemistry
Professor Harinath Chakrapani
Department of Chemistry
Indian Institute of Science and Engineering Research Pune
Prodrugs and drug alliances

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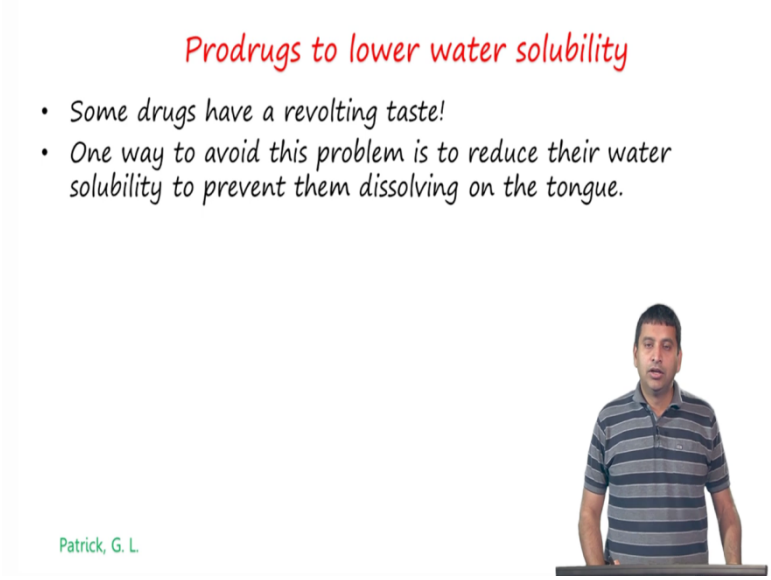

So the other way in which you can use prodrugs for is to lower the water solubility, so some drugs have pretty bad taste and so one way to avoid the bad taste is to be able to increase the hydrophobicity or reduce the water solubility. So what happens is that when you consume the target starts to dissolving the tongue so if you reduce that the solution then it is possible to make it less revolting okay.

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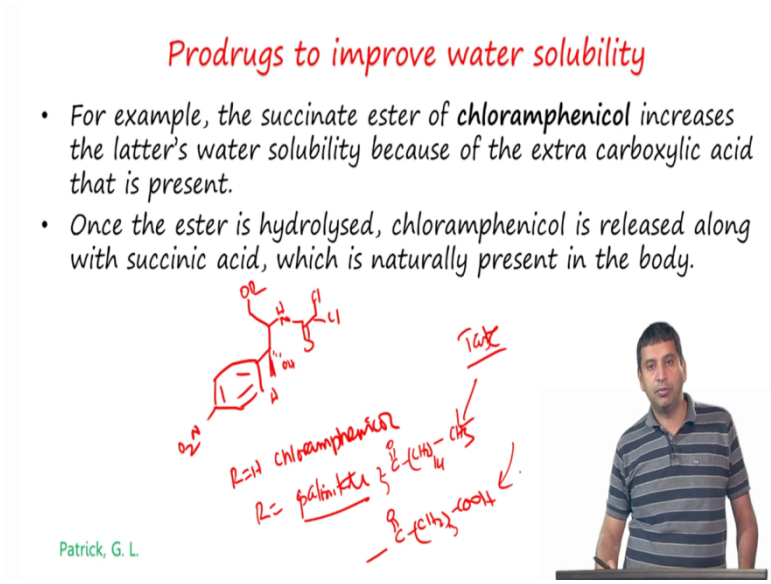

So the other contrasting concept is to actually improved water solubility so here what we will do is to add in hydrophilic groups so that you can improve the water solubility. So the reason why we would do this is that many drugs are actually given intravenously and so if they are very hydrophobic then you will have to give them at very small volumes and you know fairly high concentration. And it is also when you inject it intravenously sometimes it precipitates so in order to avoid all of this you want to increase the water celebrity okay. So the example that we are going to look at is chloramphenicol so let me just draw out the structure of chloramphenicol.

So R equals H is chloramphenicol and what we could do is, we could convert this R into a palmitate, so palmitate is basically a C double bond O with 14 carbons CH2 14 times and then CH3 so it is an extremely long hydrophobic chain and this is used to reduce the water solubility. And if you want to improve the water solubility then what you would do is you would do C double bond O CH2 3 times COOH and this actually improves the water solubility. So here this is actually given for taste so when you are giving this orally you would give this palmitate molecule and if you are going to give this intravenously you would give this carboxylic acid which is going to get hydrolysed and produce succinyl acid, which is naturally present in the body.

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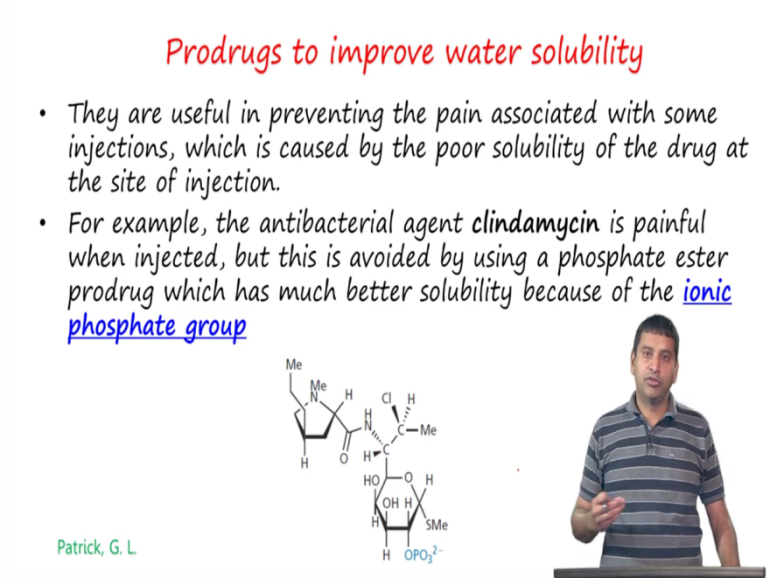

Also sometimes when you have you know molecules that have been given and the injection side can cause some pain okay because of poor solubility and we also mention that it can precipitate. And so for example this molecule called as clindamycin, this drug is very painful when it is injected, so in order to avoid this, what has been done is to convert this to a

phosphate ester. So because it has a phosphate ester it makes it quite ionic and water-soluble and so when it is injected it goes into the blood stream without any precipitation. And so because of the better solubility this is better tolerated when it is injected.

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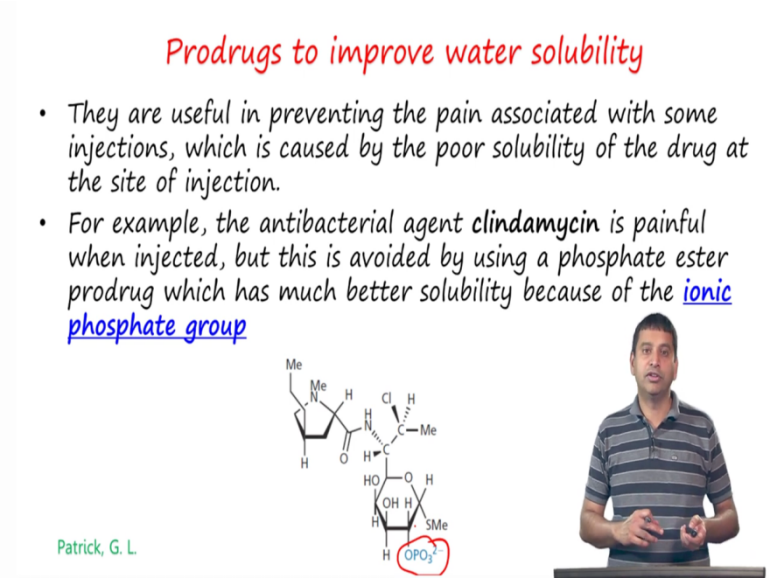

Prodrugs have also been used in targeting of drugs, so here as we have discussed so far the main objective of using prodrugs or one of the main objectives of using prodrugs is to minimise side effects. So one way to do is to actually make modifications which can help with the drug getting activated only with the area of interest ok, so although it produce toxic molecules side-effects these are since they are localized in particular organ the side-effects are not present in the not present themselves in other areas. So the example here is Methenamine whose structure is shown here, it is stable inactive compound when the pH is more than 5 ok.

And when the pH becomes more acidic than the compound degrades and produces formaldehyde so if you can see this molecule, it actually has CH2 attached here and this will degrade to produce formaldehyde and formaldehyde is actually quite irritating and it can be little bit toxic. So this molecule is used in urinary tract infections because urinary tract infections contain mildly acidic conditions and formaldehyde is very good at having it has antibacterial properties.

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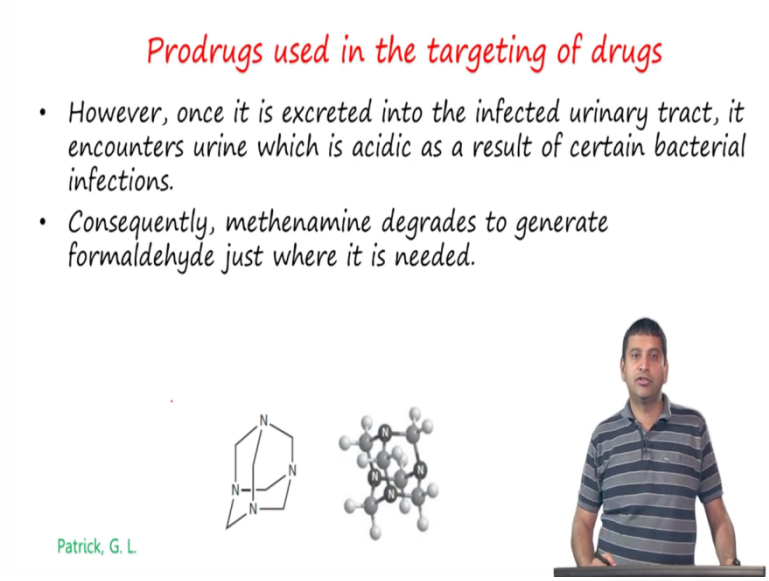

So the normal pH of blood being slightly alkaline can be used to our benefit so therefore this molecule actually does not undergo any change in the blood but once it reaches the infected urinary tract then it encounters urine which is acidic and as a result this molecule degrades to produce formaldehyde. And once the formaldehyde is produced since it has known antibacterial properties it can sort of reduce the infection. So methenamine is an example of an molecule which degrades only at the area of interest and this is a very useful way for targeting of drugs.

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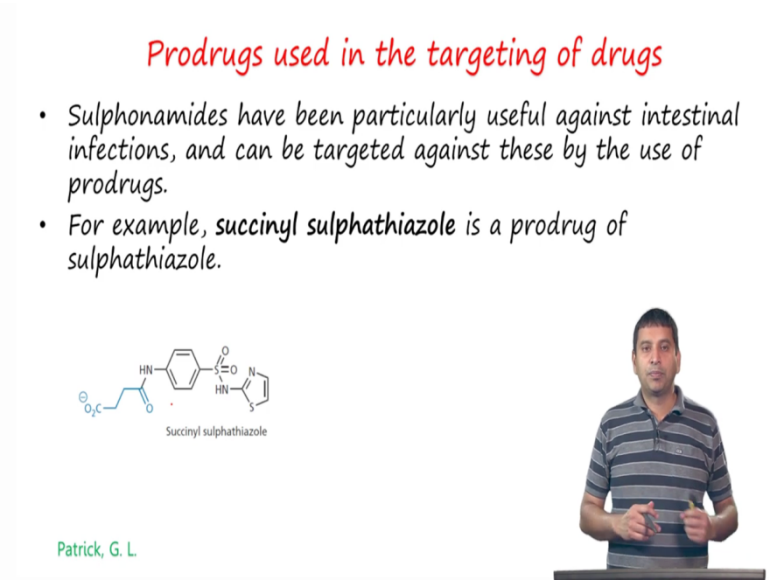

There are also examples of products of sulphonamide which have been used to target intestinal infections. So here intestinal infections which are associated with bacteria and this sulphonamide can be used as succinyl esters ok. So here is the structure of a molecule which is the active drug is shown here which is the which is a thiosol and you can convert it to a succinyl ester.

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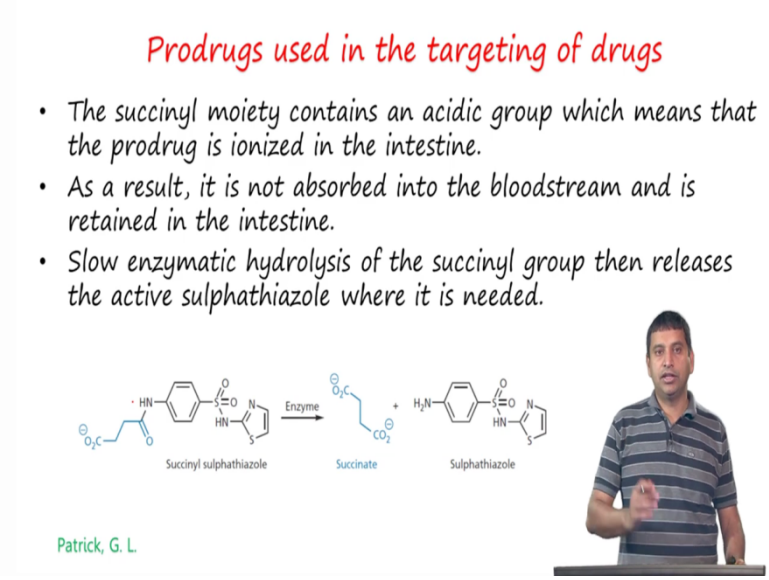

And once the succinyl ester is cleaved in the intestine than the sulphonamide is produced only in the intestine area okay, so because the succinyl moiety is an acidic group then the prodrug is actually ionised in the intestine and as a result, for example in the succinyl moiety would not be ionised in the stomach because of the pH. So once it gets into the intestine because it is ionise in the intestine it does not get into the bloodstream and then slow enzymatic hydrolysis of the succinyl group releases the active drug and succinyl which is tolerated very well inside the body.

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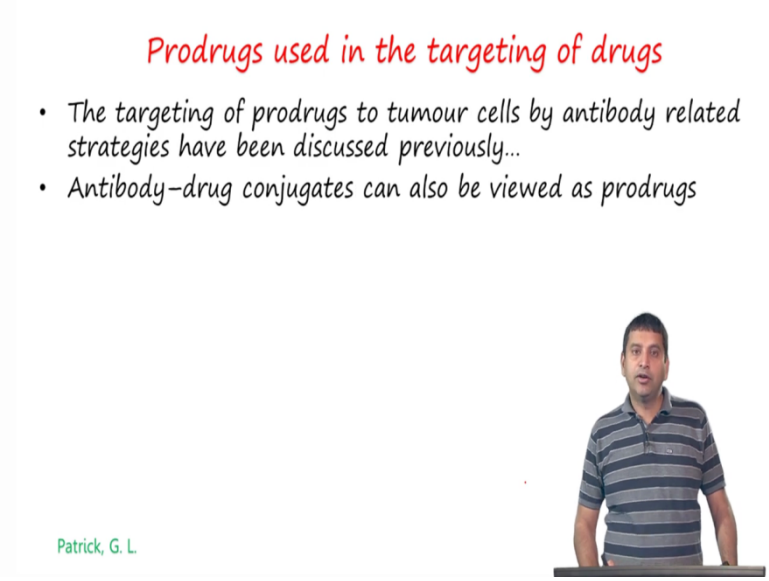

That targeting of drugs is also very useful in tumours you know for example, we have already looked at to know a lot of antibody drug conjugates. And these antibodies drug conjugates can also be viewed as prodrug in some form ok, so we have already discussed this previously so we will not spend much time but these antibodies are highly specific towards their antigen and the tumour cells present these antigen on the cell surface so the anti-body goes and binds to this antigen and along with it, it can take the drug with it ok.

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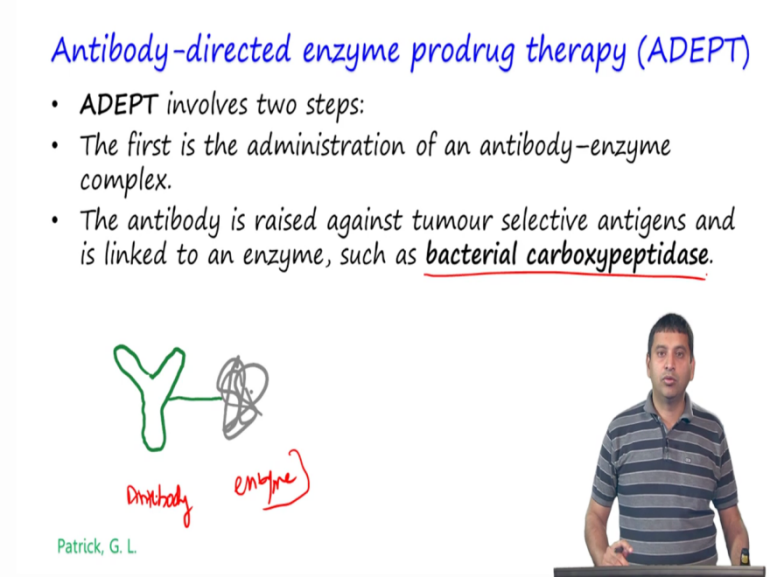

So using this concept there is also another whole field of prodrug therapy which is being developed which is called Antibody directed enzyme prodrug therapy. So there are 2

important steps in this antibody directed enzyme prodrug therapy or ADEPT. The 1st one is what we would need to do is we make an antibody enzyme complex, so here is the antibody and here is the enzyme ok. So once you make this antibody enzyme complex then it is administered to the patient, this antibody is raised such that it is going to go and bind selectively to tumour selective antigens okay. Now what we do is this enzyme is actually a special kind of enzyme which is present only in bacteria so for example, it is a bacterial carboxypeptidase.

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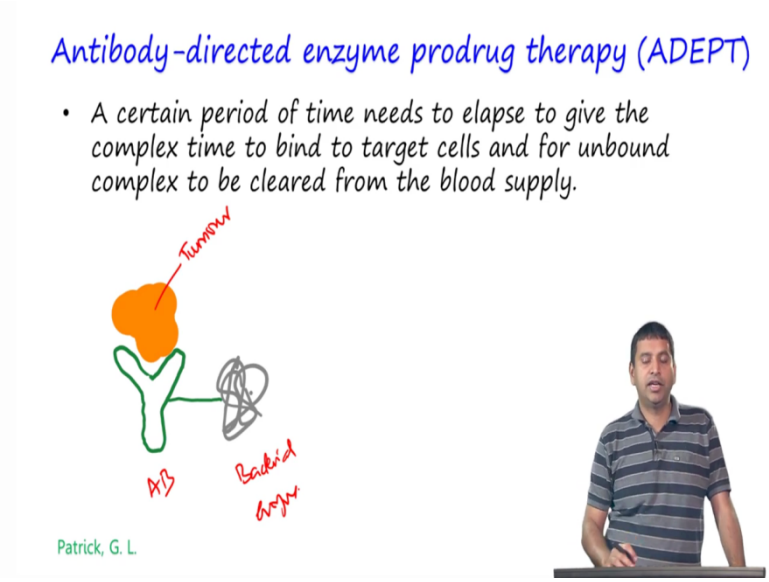

Now what happens is that after some time allow given then the antibody slowly accumulates in the tumour side, so here is the antibody, here is the bacterial enzyme ok. Now once you have this whole complex going and binding to the tumour then the rest of it which is not binding will be cleared from the blood supply. So you have a situation where this antibody goes and binds to the tumour side, appended to the antibody is an enzyme okay and this enzyme is not present in tumour cell, it is a bacterial enzyme ok.

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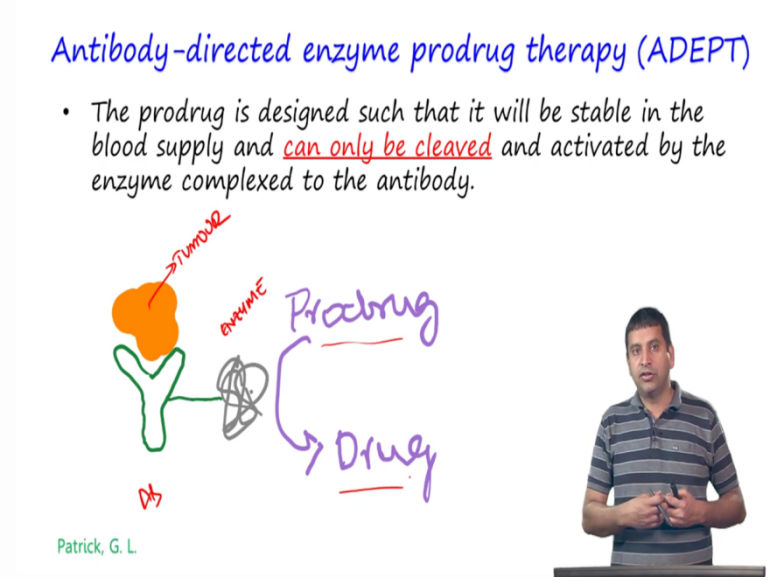

Now, if you can send a prodrug to the side of interest then what happens is that this is the tumour right, this is the antibody and this is the enzyme so since this enzyme is present and the enzyme as we have defined it is a catalyst so the prodrug can be activated in C2 to produce the actual drug right. And since the enzyme is actually a bacterial enzyme, this prodrug can be designed such that it is getting cleaved by a bacterial enzyme to enhance the success of this strategy.

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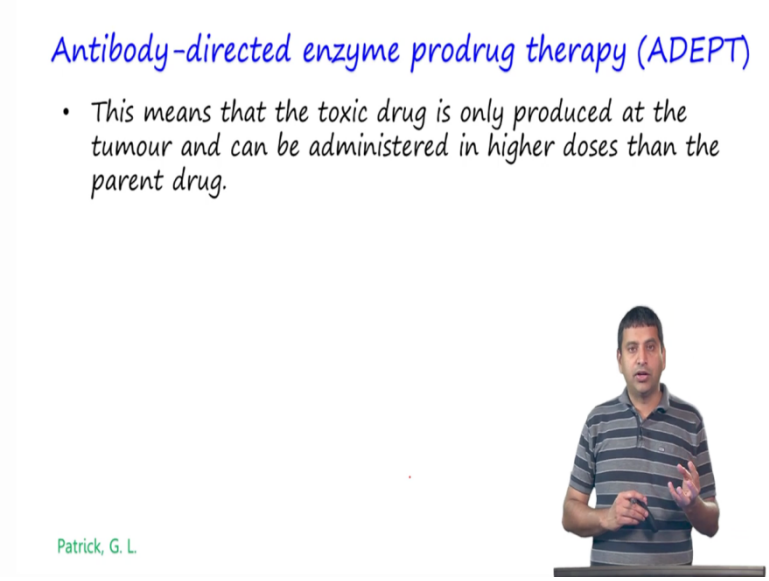

So therefore the cancer drug which is toxic is present to produce only in the proximity of the tumour and so therefore but we can do is we can actually administer the drug at a very high

dose and not worry too much about the toxicity. So the example that we can look at is this CJS 149 which is basically a molecule which is activated by bacterial carboxypeptidase. So the carboxypeptidase actually cleaves at this side and produces this amino acid and carbon dioxide ok. And here is the active drug and this case it is the DNA alkalytic agent. So what happens is that if you use this approach that we have shown so you have an antibody and you have the enzyme and so this and time is going to come and cleave and this happens only in the presence of a tumour.

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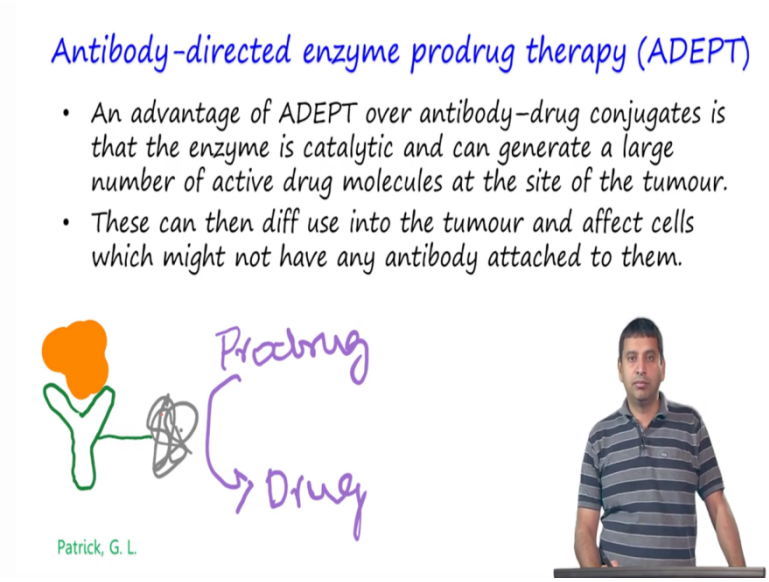

So that advantage of this methodology is that it can generate a large number of active drug molecules at the tumour side and these of course can diffuse and you know interact with the tumour and hopefully kill it right. And so therefore the amount of active drug that is present in the bloodstream goes down and the amount of active drug that is going to distribute across the body is also going to go down.

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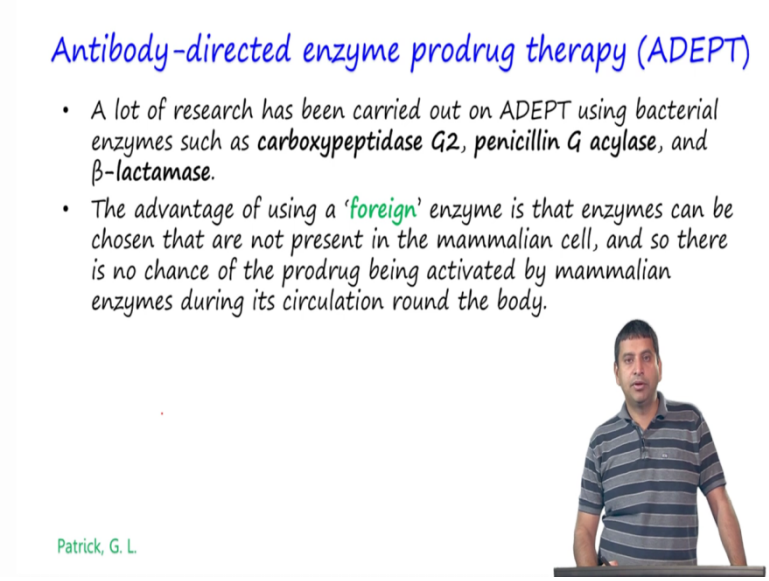

Of course, a lot of research has been carried out on ADEPT and the number of bacterial enzymes have been identified to carry out this process, so the example that we looked at is carboxypeptidase but you can also have penicillin G acylase and Beta lactamase. So as I mentioned earlier, the advantage of using an enzyme that is not present in human which is also called a foreign enzyme is that this can be the metabolism of the prodrug happens only where this enzyme is present okay. So since it is not present in mammalian cells or normal human cells, there is very little chance that the prodrug will get activated inside a normal cell okay so what we are doing in this process is we are highly localising the drug to the tumour ok.

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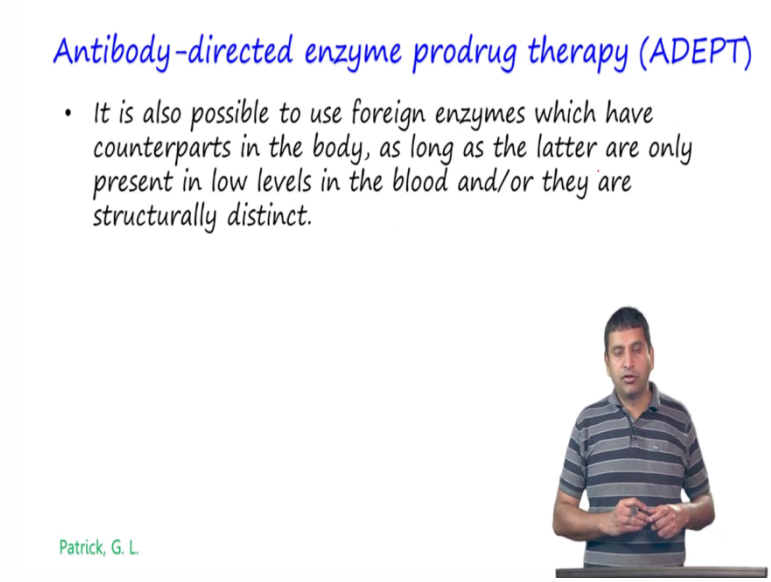

It is also possible to use foreign enzyme which have counterparts in the body as long as we are able to sort of figure out the enzyme which is present in extremely low levels in the blood or which are very structurally distinct.

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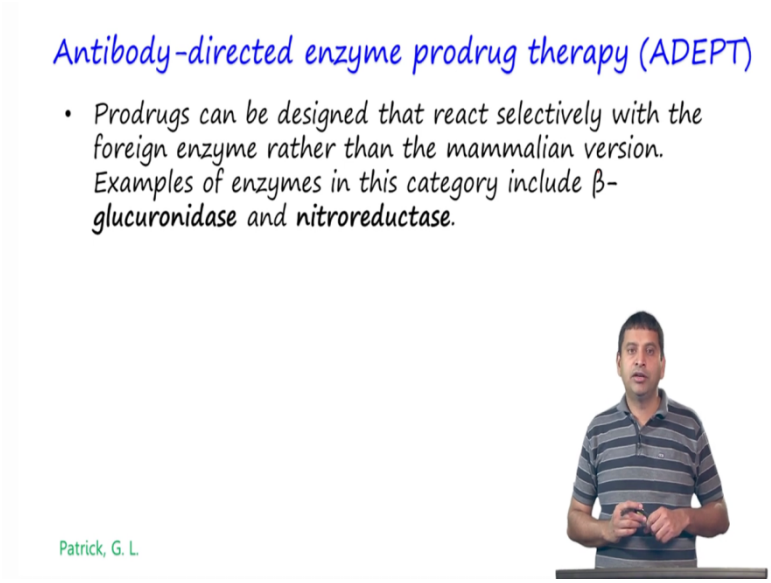

So for example, they can use enzymes such as beta glucuronidase which is present in our cells but it is present at very low concentrations or we can also use this enzyme called as nitroreductase which actually reduces the nitro group to hydroxylamine or an amine. So these enzymes although they are functional counterparts present in human but they are not very efficient or the reaction is actually reversible that means that nitro group can reduce to the amine but they get oxidised back but this bacterial enzyme will convert it completely to the amine.

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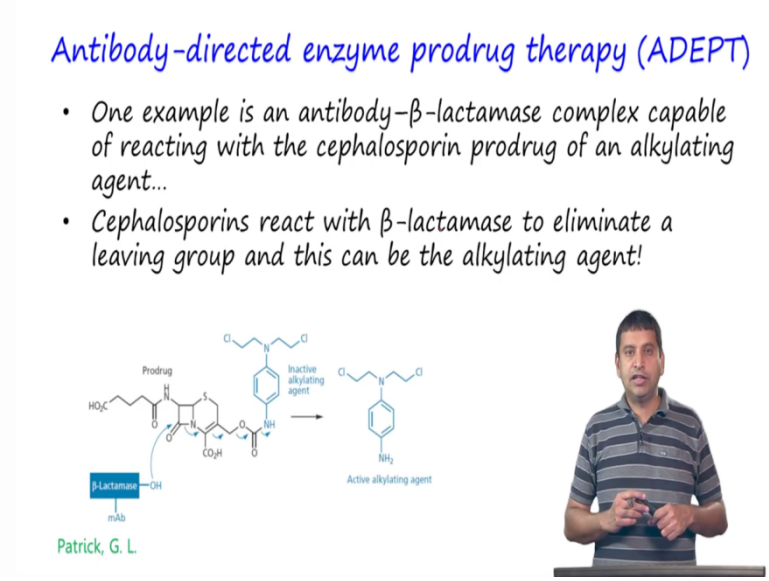

So the example that we are going to look at now is the Beta-lactanase complex so what we do is that we conjugate monoclonal antibody to beta-lactamase and this DNA alkylating agent which is shown here is actually conjugated in the following manner to produce this inactive molecule. So, on its own this molecule on the left is in active okay and now what you can imagine is that it will go because of the antibody it will get directed to the side of the tumour and on the side of the tumour it will get cleaved by this bacterial enzyme and produce the active alkalising agent ok. So this is a beautiful example for ADEPT that can be used to direct prodrug therapy ok.

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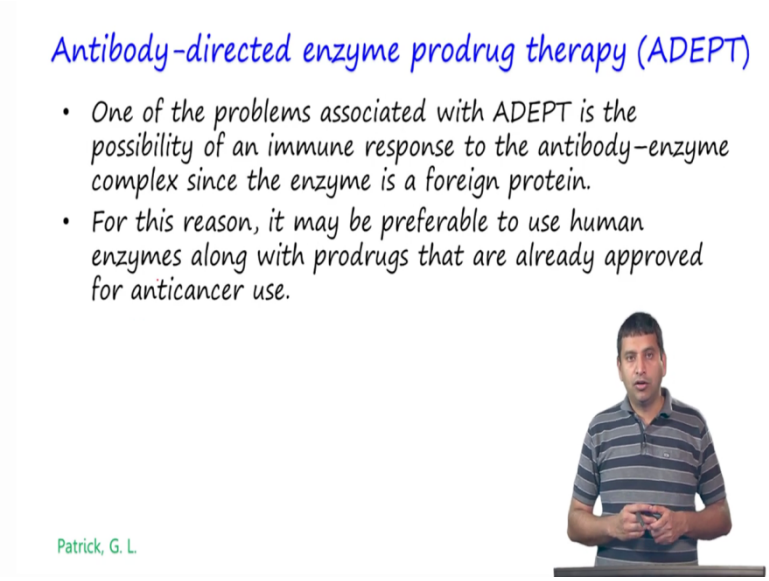

Of course, one of the problems associated with ADEPT is that you can have an immune response, so since you are injecting an antibody there is always a possibility of antibody with enzyme complex, this can be looked at as a foreign substance and of course the enzyme is a foreign protein. So because of this you can actually have an immune response which can clear up this complex completely, so it is for this reason that it is preferable to use human enzymes with prodrugs that are already approved for anti-cancer use.

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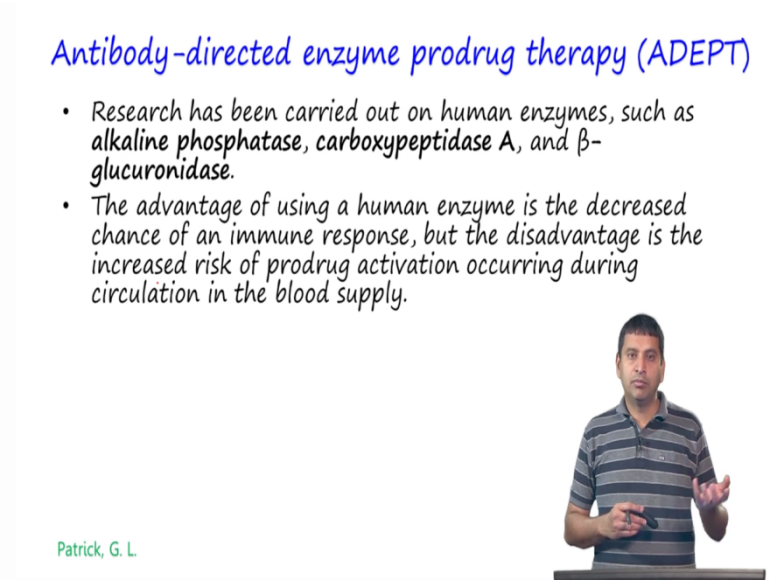

So some examples of human enzymes are alkaline phosphatases, you can have the human analogue of carboxypeptidase which is carboxypeptidase A, and as I mentioned earlier which is Beta-glucoronidase. Now Beta-glucoronidase is of course we need to express it as a higher concentration, so the advantage of using this human enzyme is that the immune response can go down, but of course the problem with this approach is that the product activation can also occur in various other areas because these enzymes are also present in these areas. Especially for example if they are present in the blood supply then they would be activated in the blood as well.

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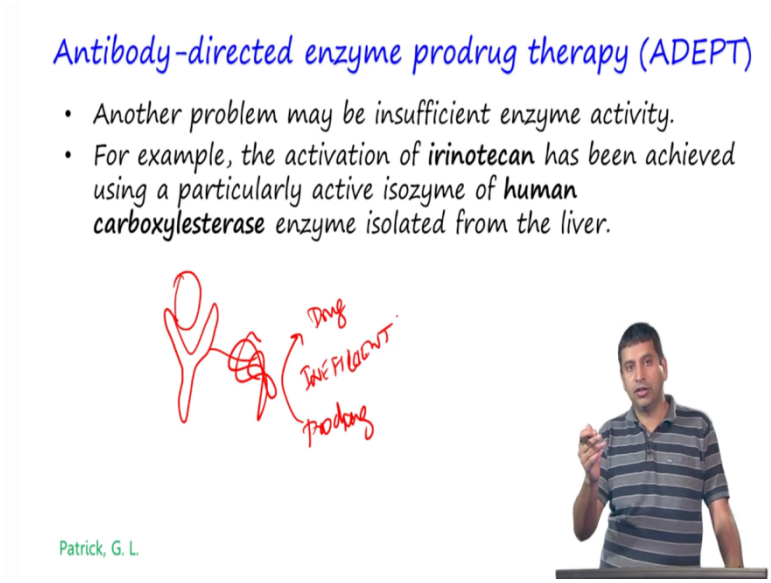

Another problem associated with ADEPT is insufficient enzyme activity so for example, if you conjugate this antibody with an enzyme right, so if the antibody is very good at targeting the tumour side the enzymes still has to be very active ok. So if the enzyme is not very active then the problem becomes the prodrug will not get efficiently converted to the drug right so this becomes a problem and therefore we would need to vary the enzyme isoform so that we can have the active isozyme of the enzyme so that we can improve the conversion ok. The example that we are looking at is this irinotecan which has a conjugate so that you have the human carboxylate enzyme which is isolated from liver ok.

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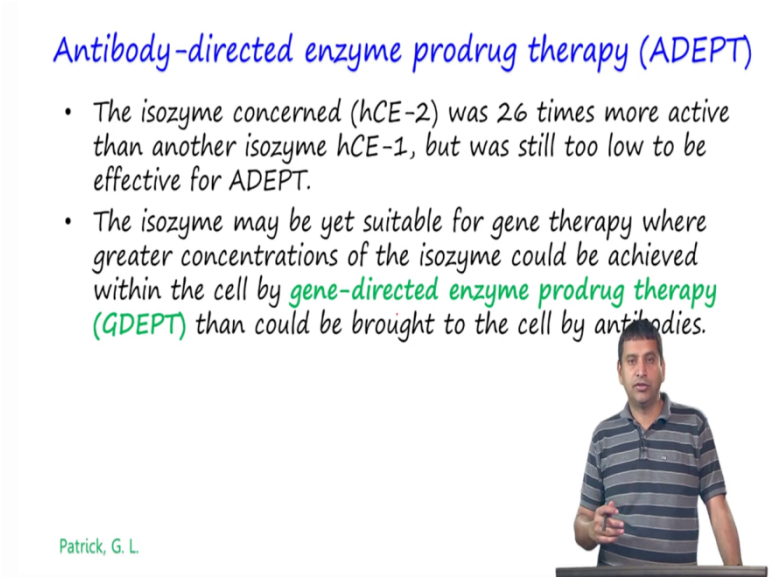

So here the isozyme that is concerned has 26 times for activity compared to the hCE-1, of course it is too considered low to be effective for ADEPT. So therefore, we would use an alternate strategy or a complimentary strategy known as GDEPT which is basically gene directed enzyme prodrug therapy, we shall look at this very shortly but what happens is that here you can increase the concentration of the isozyme is by transfecting the tumour cells with the gene which is responsible for the synthesises of the concern protein. We will look at it very shortly but this is a way in which you can increase the concentration of the enzyme or the isozyme in the area of interest.

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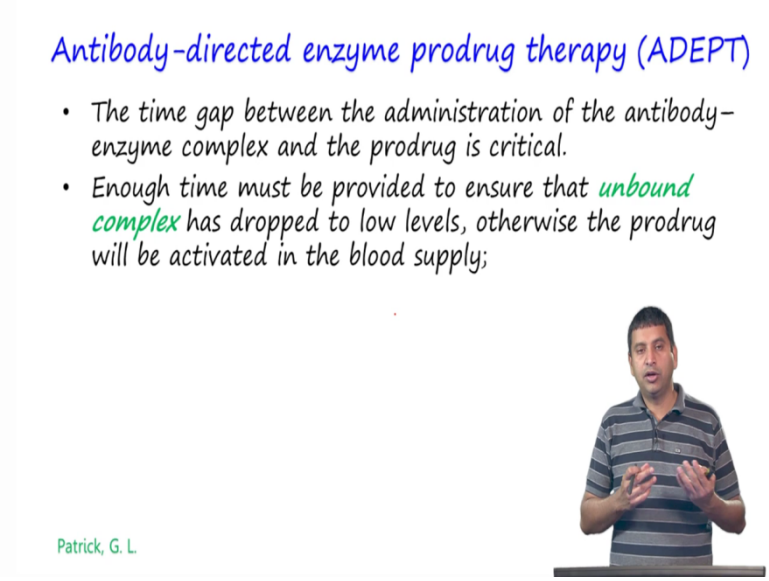

Another problem or another aspect of ADEPT is the time that is given between the administration of the antibody enzyme complex and the prodrug. So as we discussed, 1st we would administer the antibody enzyme complex and this has to go and Bind to the tumour okay. Now you also have to make sure that the unbound complex that is the one that is really circulating in actually removed, otherwise if it is not then as soon as you inject the drug or as soon as you consume the drug it is going to get activated and then that defeats the purpose of using this therapy.

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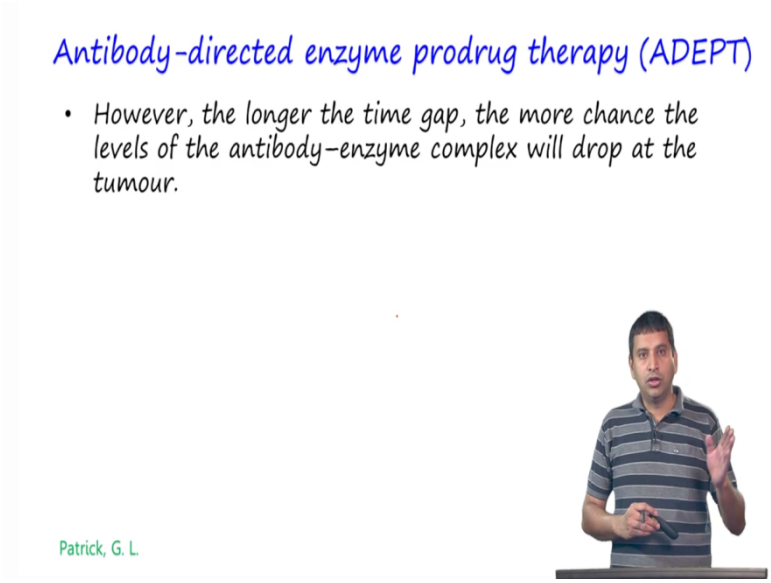

Now the longer the time that is given, the more chance that the levels of the antibody complex will drop at the tumour side also. So because the tumour side is also you know something that is perfectly capable of metabolising these complexes. So you need to optimise the time gap between the administration of the antibody enzyme complex and the drug.

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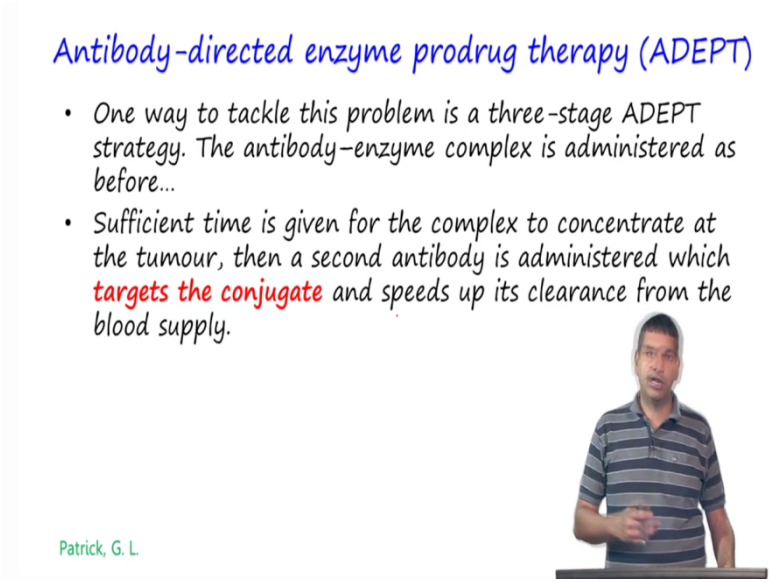

One way to address this is to use a 3 stage ADEPT okay, so here are the antibody and them complex is administered as we do normally. Then you give enough time so that the complex concentrates at the tumour, then we would add a 2nd antibody okay so this antibody actually is raised to target the conjugate that is the original conjugate that we have used, so this speeds

up the clearance from the blood. So once this 2nd antibody comes in then it is going to conjugate to this and that is cleared from the blood supply.

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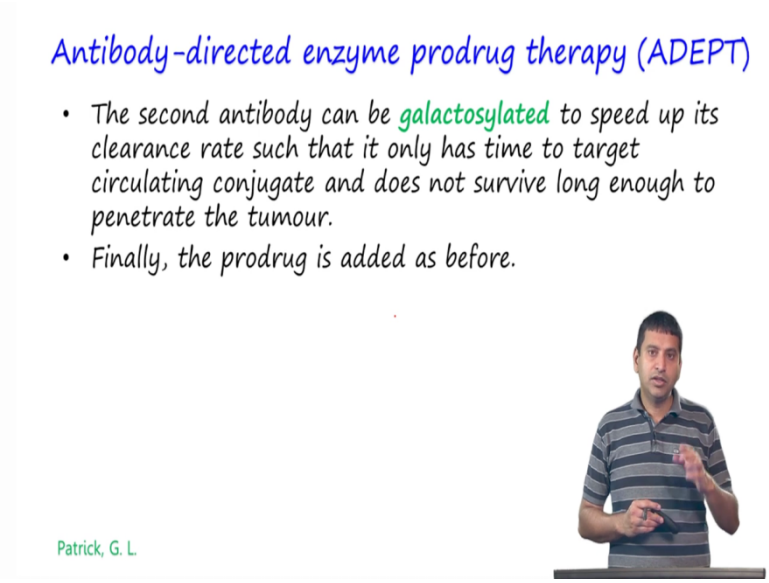

The 2nd antibody can be galactosylated, so now galactosylated is going to help to increase the clearance rate, but it has time to target the circulating conjugate but it does not survive long enough to penetrate the tumour then we add the prodrug. So here the tumour alone has a considerable amount of this antibody drug enzyme conjugate ok.

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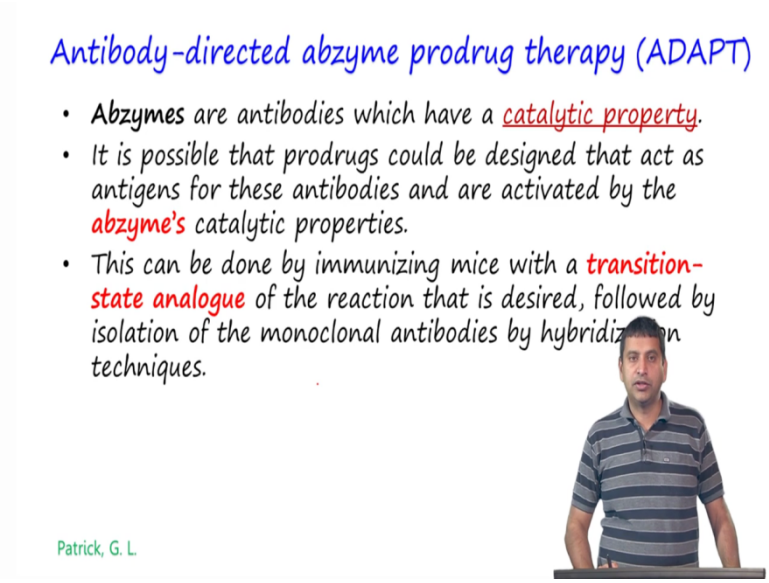

Another interesting strategy to prodrug therapy is antibody directed abzyme prodrug therapy which is call as ADAPT, so abzymes are antibodies which have catalytic properties so these

are relatively new in the literature maybe 20-25 years old, and there are number of antibodies which have catalytic properties. So the concept is to be able to exploit the catalytic property of this abzyme so that you can activate the prodrug in the proximity of the tumour. So what we do is that we can design a transition state analogue we have already looked at several examples of transition state analogues, so we would immunise the mice with a transition state analogue of the reaction, then once you isolate the monoclonal antibodies by hybridisation technique then you have your things setup for adapt.

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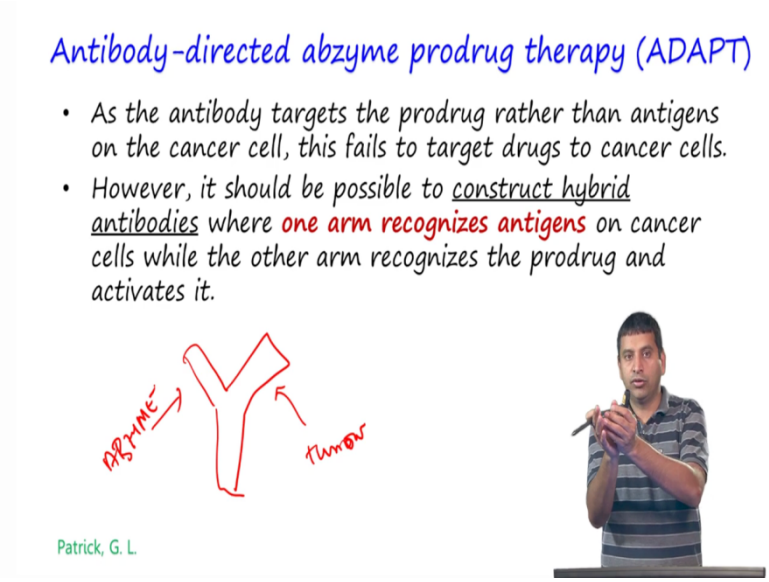

So since the antibody targets the prodrug rather than the antigens on the cancer cell, this is not going to target the cancer cell. However, if you construct a hybrid antibody okay so this hybrid antibody where you have one arm, so here this is going to be targeting the tumour and this is going to be the abzyme right. Therefore, if you convert one of these arms into an abzyme then what happens is that this is an antibody which has which goes and recognises the cancer cells and it also has the catalytic property which is going to activate the prodrug.

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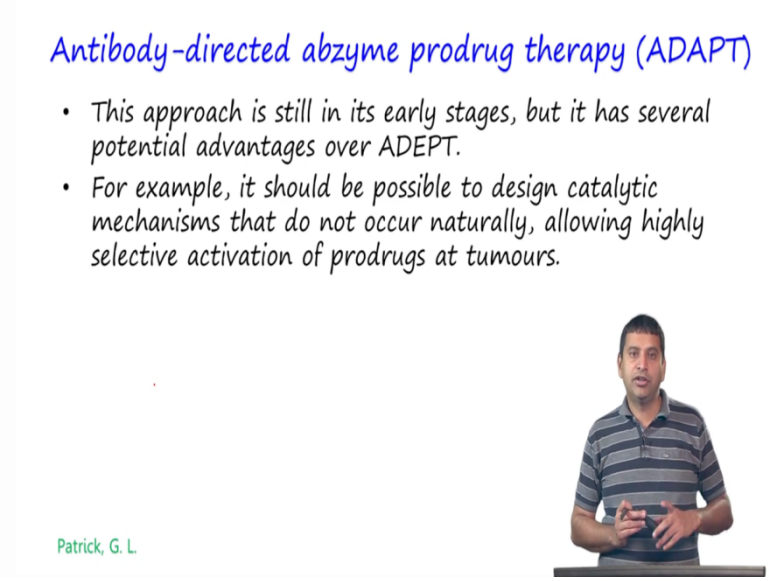

So of course this approach is still in its very early stages but it has several advantages over ADEPT. So for example, it should be possible to design a catalytic mechanism that do not occur naturally okay, so if you have a good understanding of how antibodies work then you can use this understanding to design new catalytic mechanism. It also allows for highly selective activation of prodrug at the tumour side.

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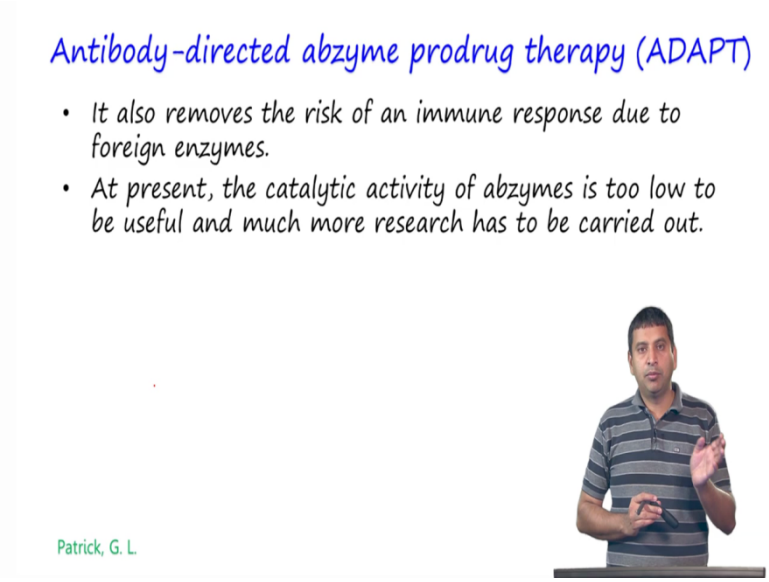

Now since the antibodies are raised using humanlike proteins or humanlike situations, it reduces the risk of immune response that is associate it with for example bacterial enzymes. So at present the catalytic activity of abzyme is too low for it to be useful, so there are

number of researchers who are working on improving the catalytic properties of abzymes so that you can use it for adapt.

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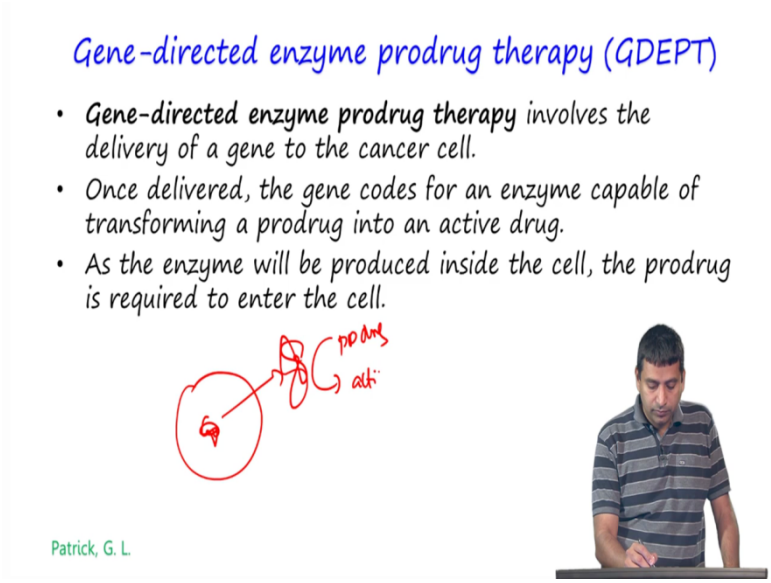

The next major concept of prodrug therapy is Gene directed enzyme prodrug therapy, we just looked at it briefly a few slides back but what this concept is basically what we try to do here is to deliver a gene to the cancer cell. So once the gene is delivered then the gene goes into the nucleus and expresses for a particular protein okay, so this protein is the one that is going to convert the prodrug to the active drug ok so this is the entire concept. Now since the enzyme will be produced inside the cell, the prodrug will have to get into the cell so all of this stuff has to happen within the cell.

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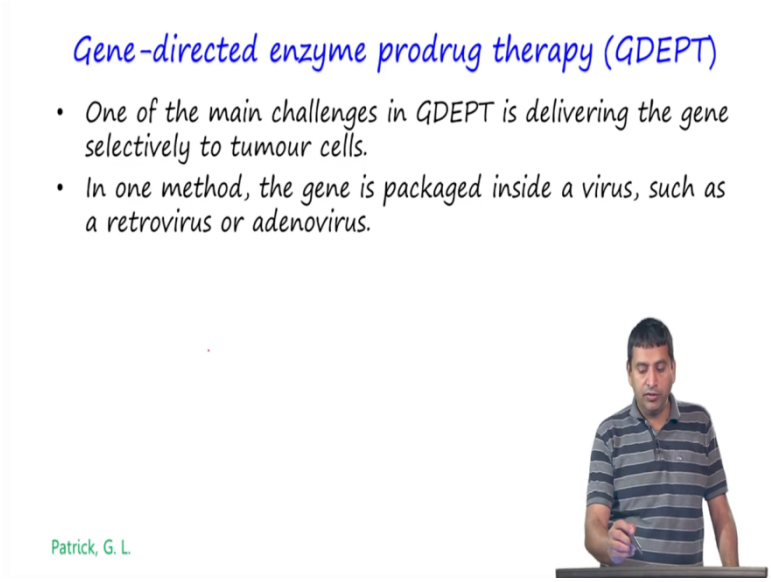

So one of the main challenge associated with GDEPT is how do you u get this gene into the nucleus okay. So one way to do is to package the gene inside a virus okay so as we all know viruses are excellent vehicles which can go and transfect and you know incorporate genes into normal cells into human ok. So what we would use is we would use a retrovirus or an adenovirus with the gene that of interest that is packaged inside.

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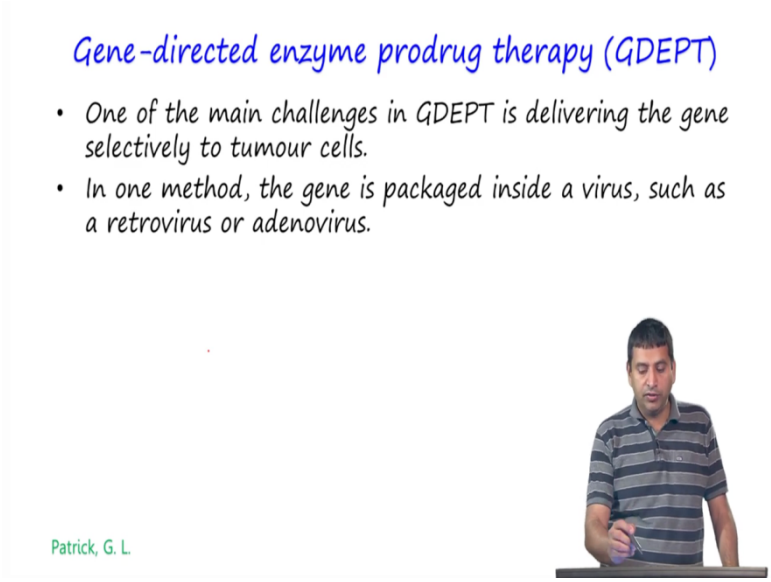

So once it gets in then the desired genes would be spliced into the viral DNA such that the virus inserts into the host cell DNA on infection. Now the virus is also genetically modified so that it is no longer able to it is not virulent that means it does not harm the normal cell okay, so then what it acts as is delivery vehicle right. So of course there are number of non-viral vectors that have also been used such as cationic lipids and peptides, but here the problem is always being the selectivity. So the selectivity of cancer versus normal cells is a huge problem so therefore the delivery vehicle has to be injected somewhere near the tumour side so that you can reduce the normal cells being affected.

So the new enzymes which are ultimately produced inside the cells should not be present in normal cells okay so because if they are present in normal cells then your prodrug therapy will not work very well because they will get activated normal cell as well so therefore the choice of these new enzymes is very important okay.

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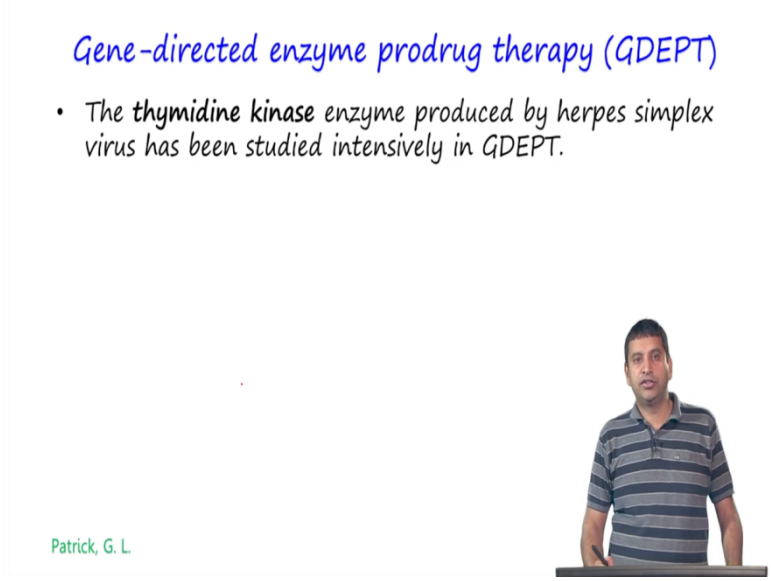

So one advantage of GDEPT over ADEPT is that since the foreign enzymes are generated inside the cancer cells, they are hidden from the immune response. So the example we are going to look at is this thymidine kinase which is produced in herpes simplex virus and has been studied quite extensively for GDEPT.

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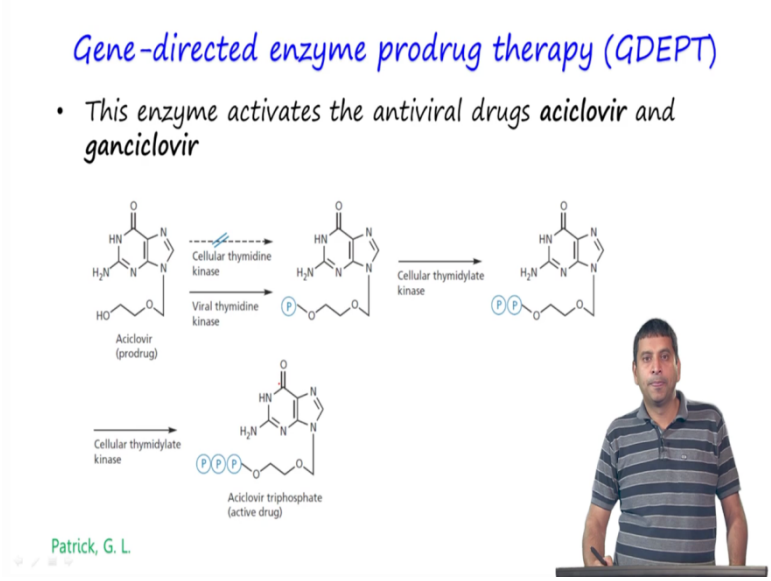

So the enzyme as shown here is actually going to, the viral counterpart of it is going to do a phosphorylation of the prodrug okay so here the cellular thymidine kinase keeps phosphorylating these groups. So as these drugs are very poor substrate for mammalian time

and I kinase, the activation will only be significant in tumour cells containing the viral form of the enzyme so number of clinical trials have been presently underway to test this approach

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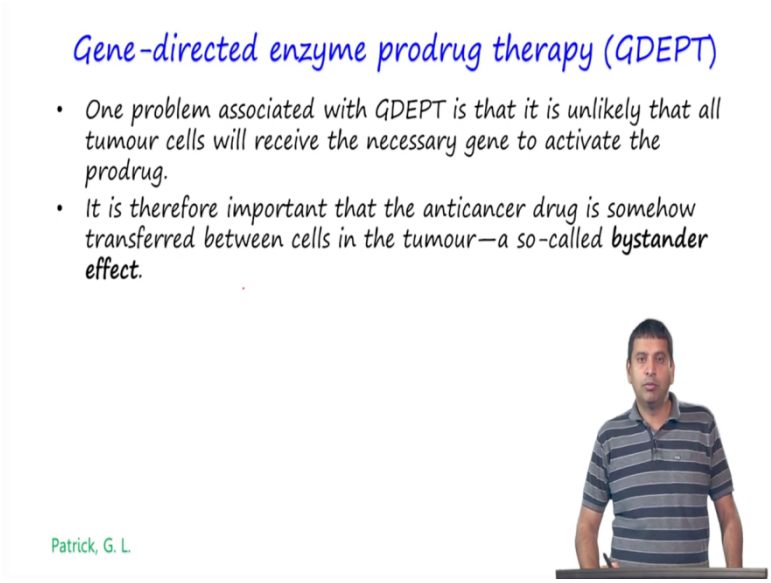

Of course, one problem associated with GDEPT is that it is unlikely that all the tumour cells will receive the necessary genes to activate the protein, so let us say you have you know a tumour cell such as this which has number of these cells right, so let us say you are able to deliver it only to a few of these cells, so only few of them are going to activate or they are going to produce the enzyme right. So therefore there is an important concept that comes here which is called and the bystander effect. So once the drug is active the prodrug is activated inside one of the tumour cell and produces the active drug then it is somehow transferred between the cells in a tumour and so the tumours which are which do not have the genes transfected are still going to get killed because of the drug that is present in the neighbouring cells, this is called as the bystander effect.

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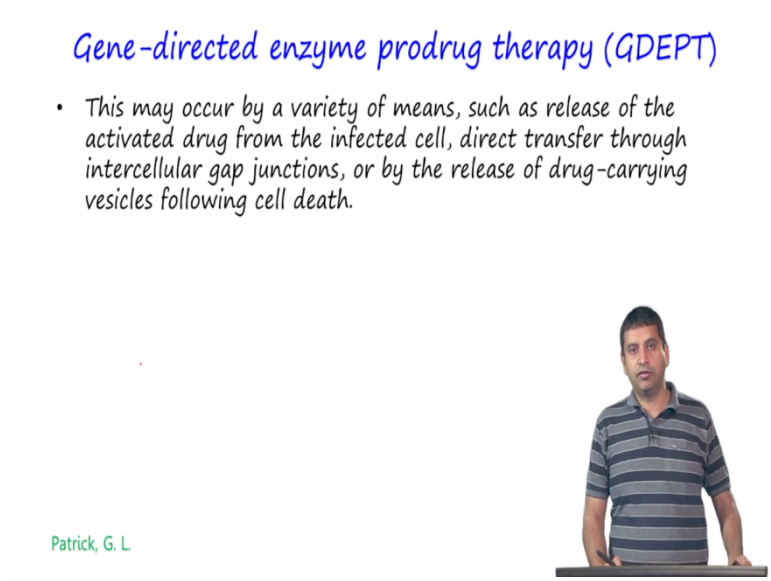

So this may occur by variety of means such as release of the activated drug from the infected cell, direct transfer through intercellular gap junction or by the release of drug carrying vesicles following cell death.

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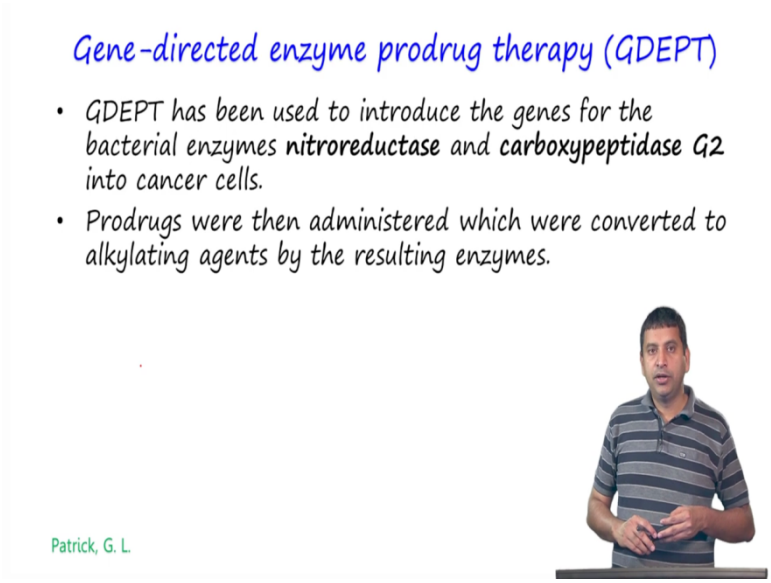

GDEPT has been used you know to introduce genes are bacterial enzymes such as nitroreductase and carboxypeptidase G2, so we have already looked at these 2 enzymes previously. So here the nitroreductase enzyme or carboxypeptidase is produced only in the cancer cell and since the basic level of reduction of these is not going to be very high in the

case of nitroreductase or cleavage of the peptide bond is not going to be very efficient in the case of carboxypeptidase G2, this will produce only the active drug in the tumour cell.

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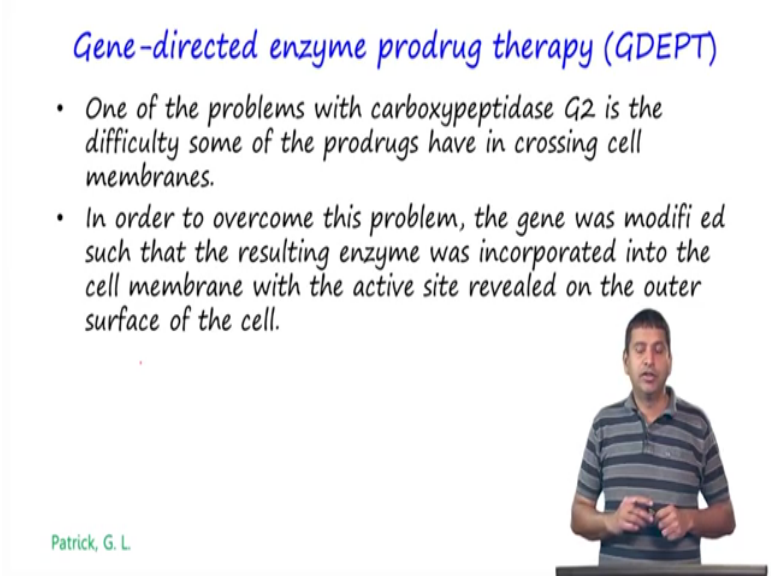

One of the problems with carboxypeptidase G2 is the difficulty of having these prodrugs cross the cell membrane. So in order to overcome this problem the gene was modified such that the resulting enzyme was incorporated into the cell membrane with the active side rather than being able to cross the membrane so therefore the gene modified such that the resulting enzyme could be incorporated in the cell membrane rather than the inside the cell.

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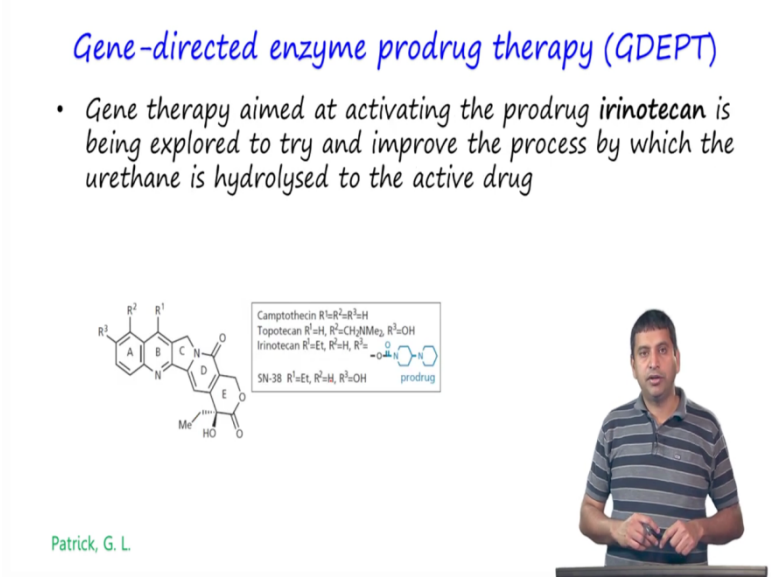

One of the examples of GDEPT is this Captothesin derivative, so here Captothesin is the where you have all of these R groups being hydrogen, and what we could do is we could make this irinotecan which is basically a prodrug and here R3 as shown here is actually modified as a carbonate. So this is actually a prodrug and once it gets cleaved by carboxypeptidase it would release the active drug so we need to encode we need to introduce the gene encoding more active carboxypeptidase into tumour cells. So for example, the rabbit liver carboxypeptidase is about 100 to 1000 times more efficient than the human form of the enzyme, so therefore we could deliver the gene encoding the rabbit liver carboxypeptidase so that it is more efficient than the human form in turning over this substrate.

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So there are a number of proton pump inhibitors which are used as in the form of prodrugs which are activated by acidic conditions, we will look at this later during our case study.

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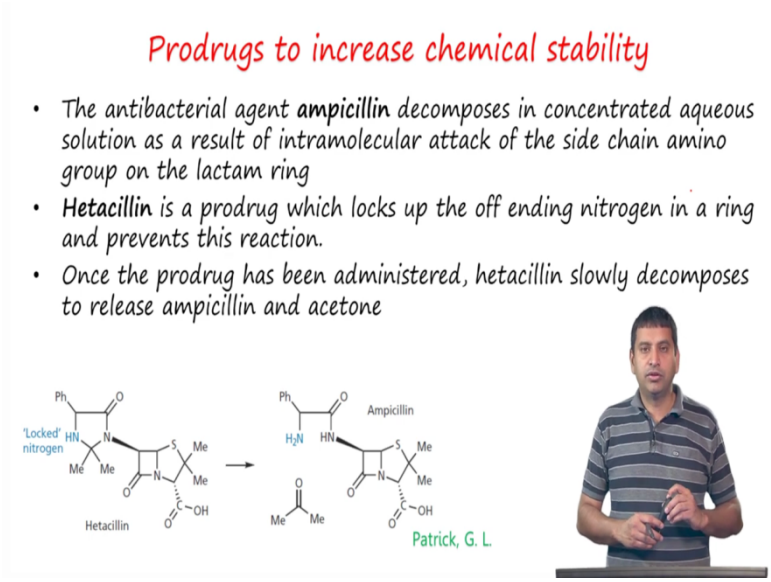

There are examples of prodrugs which will increase the chemical stability, so for example ampicillin which is shown below is actually decomposes and concentrated aqueous solution and because of the intramolecular attack of the side chains ok. So in order to avoid this what we do is, we convert this into a locked nitrogen form. So here is the prodrug form and the prodrug which sort of decomposes will give you acetone and active ampicillin. So once the prodrug has been administered it slowly decomposes to release ampicillin and acetone, so this is one of the ways in which you can increase the chemical stability of the drug.

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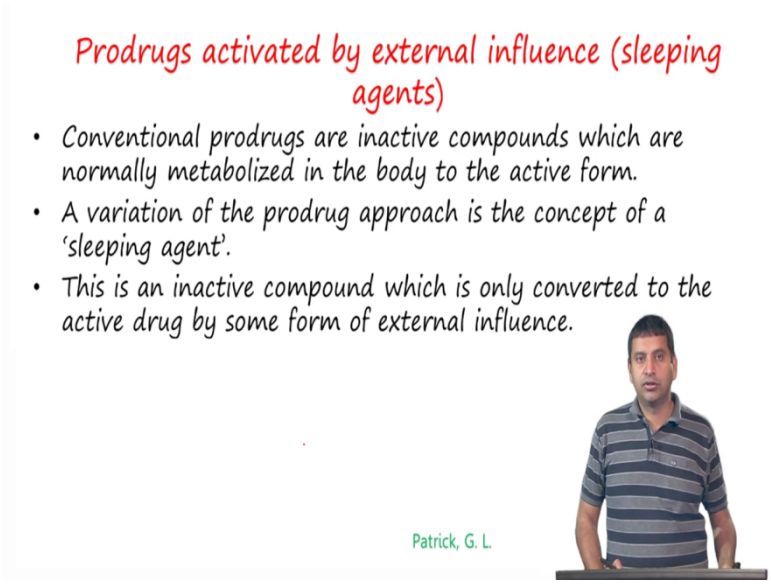

Now conventional prodrugs are inactive compounds and which are normally metabolised in the body to the active form. A variation of this prodrug approach is to use what is known as

the sleeping agent, so here the sleeping agent is an inactive compound which is converted to the active compound only by some external influence.

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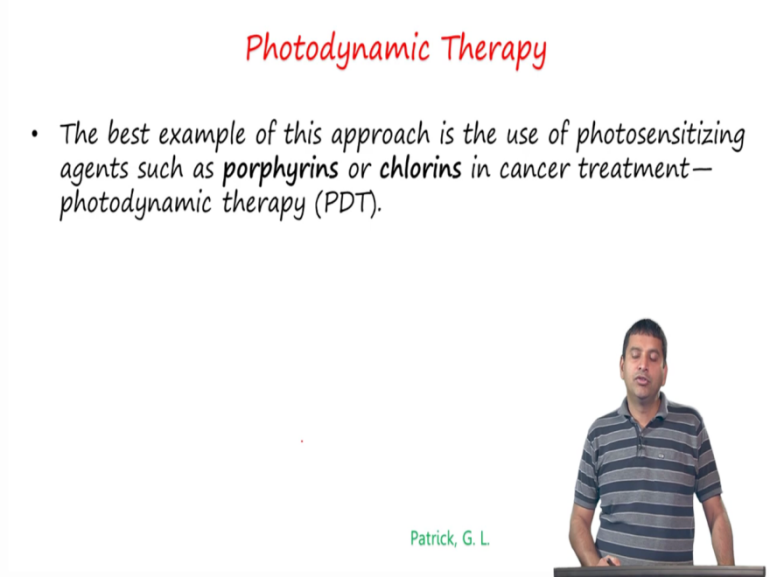

So the best example of this is the concept of photodynamic therapy, so here in photodynamic therapy there are molecules known as porphyrins are chlorins which are used. So what we do here is we use these molecules known as per porphyrins or chlorins, so here is an example of a porphyrin like molecule. So these actually so these molecules inside a normal cell are actually bound to metal ions.

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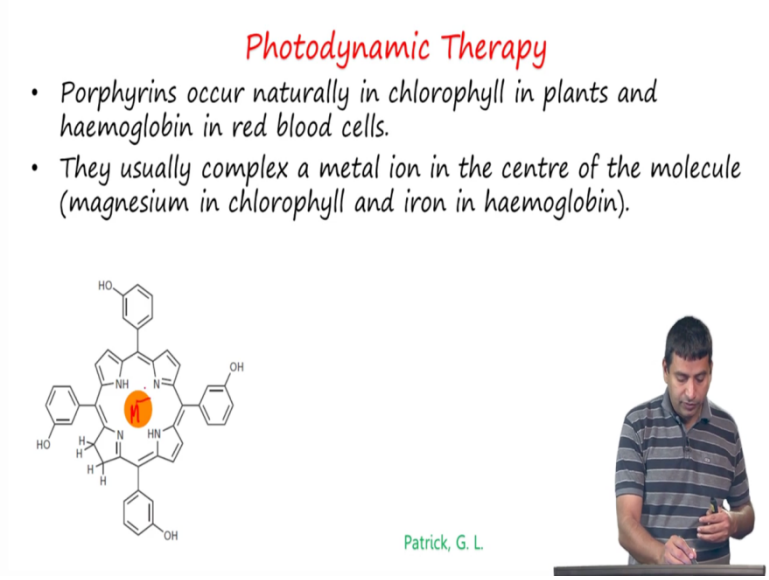

So here is metal ions that is typically present and once this metal ion is going to be chelated to this porphyrin these are extremely stable, so the examples are magnesium in chlorophenyl or Iron in haemoglobin, and since these are naturally present they are extremely stable.

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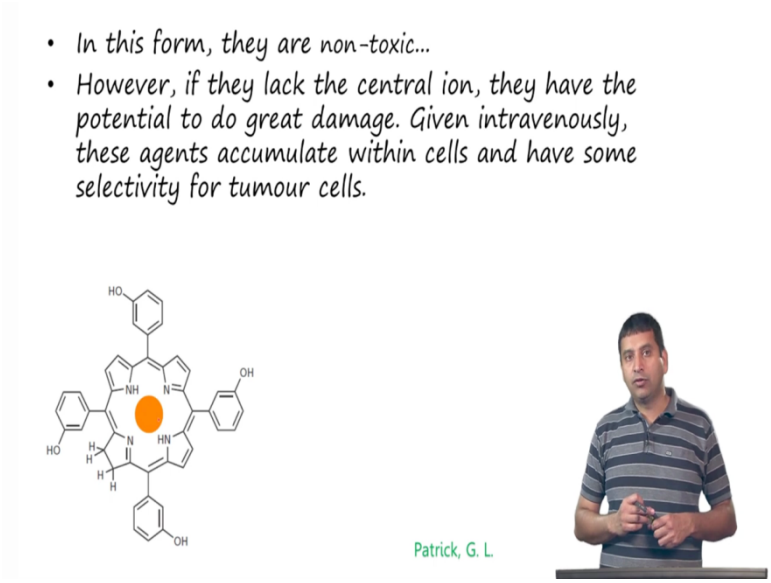

And in this form they are actually quite well tolerated and they are non-toxic. However, when they do not have the central ions then these agents become very toxic okay, so when the agents are given intravenously they are accumulate within cells and they have some selectivity towards tumour cells.

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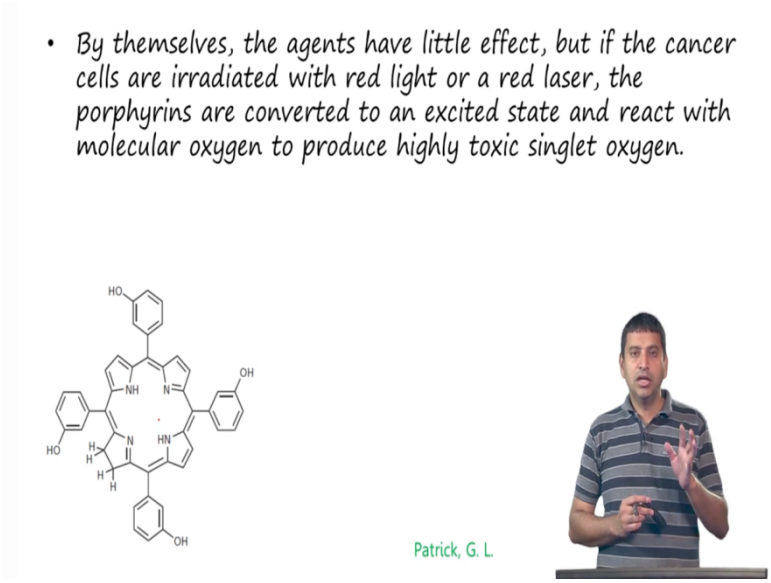

And of course these agents themselves have very little effect but if they are irradiated with a red light or a red laser then the porphyrins are converted to an excited state and this excited state reacts with molecular oxygen to produce highly toxic singlet oxygen. So oxygen produces singlet oxygen okay, so once you have the singlet oxygen then the singlet oxygen is

considered among the most reactive species and it is going to indiscriminately generate radicals which is going to kill the cell ok.

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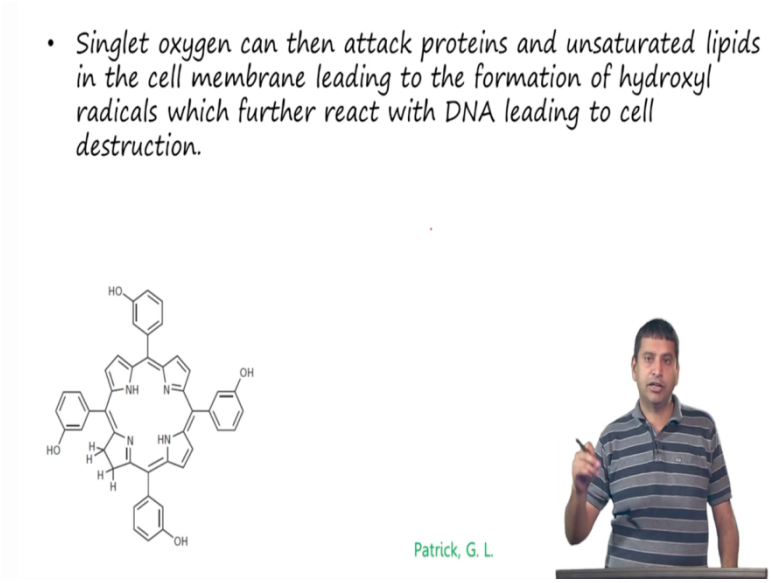

So the singlet oxygen basically reacts with unsaturated lipids or proteins, and also which can further reacts with DNA and all of this is going to be extremely toxic. And some of these effects are mediated by hydroxyl radicals, we have already looked at some of these examples previously when we were dealing with chain cutters as a way to target cancer ok.

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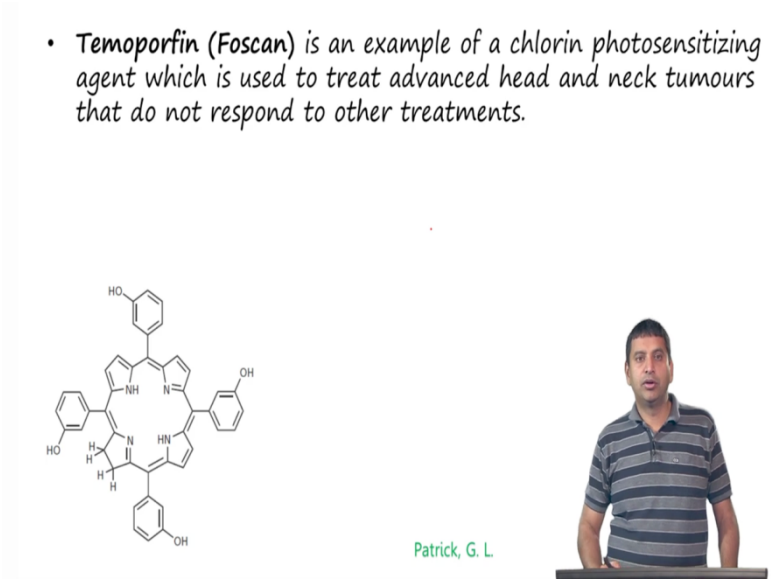

So the example here we are looking at is the Temoporfin and here this is a photosensitizing agent and it is used to treat advanced head and neck tumours and these are given in cases where you know these tumours do not respond to other forms of treatments.

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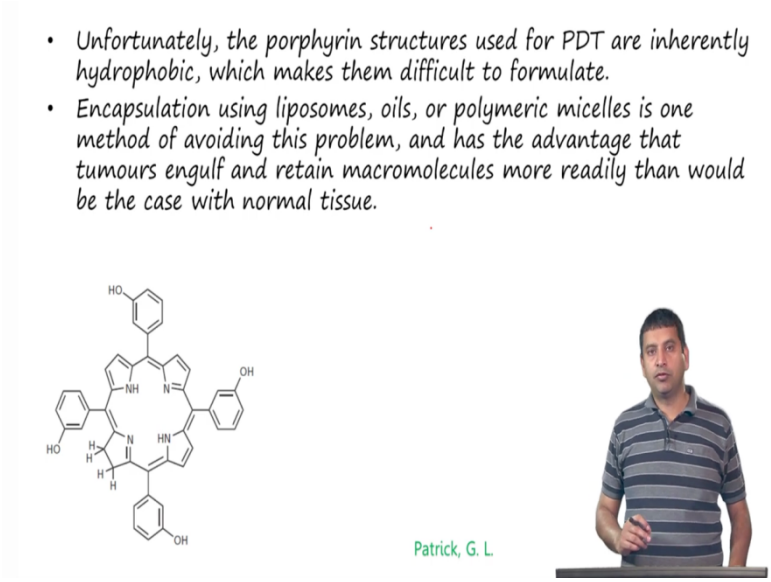

So unfortunately the problem with porphyrin structure is that they are inherently hydrophobic and they make them very difficult to formulate, so what is done is that they use liposomes or oil or polymeric micelles to make these molecules to be water-soluble I mean to be solubilised. Of course, this also has an advantage using this methodology because these tumours are known to have enhanced permeation and retention effect so they engulf and retain these macromolecules more readily than would be the case with normal tissue. And this is because the tumour vasculature is quite random and they are quite leaky as well so larger molecules are absorbed better and therefore when compared to normal cells these are much better at permeation as well and retention, this is called as the EPR effect which we will be looking at later.

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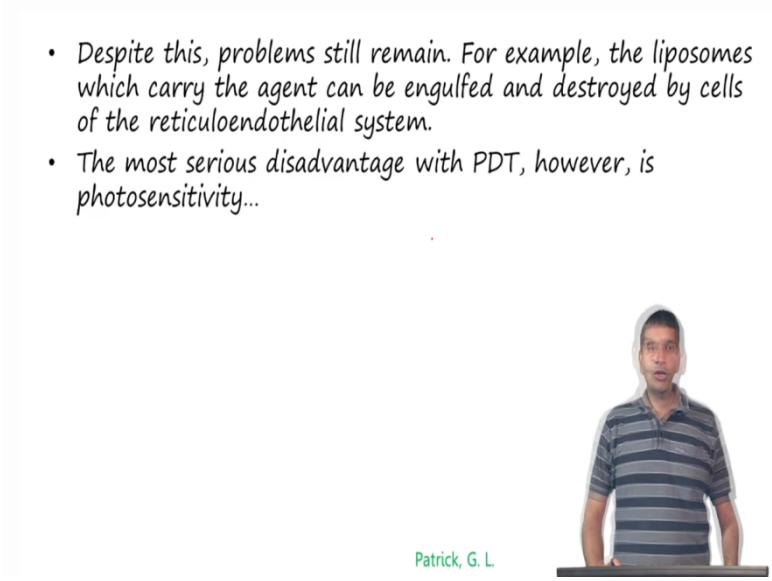

So despite this, there are some problems associated with this so for example, the liposome which carry these agents can be engulfed and destroyed by cells in the endothelial system. However, the most serious disadvantage with PDT is the photosensitivity.

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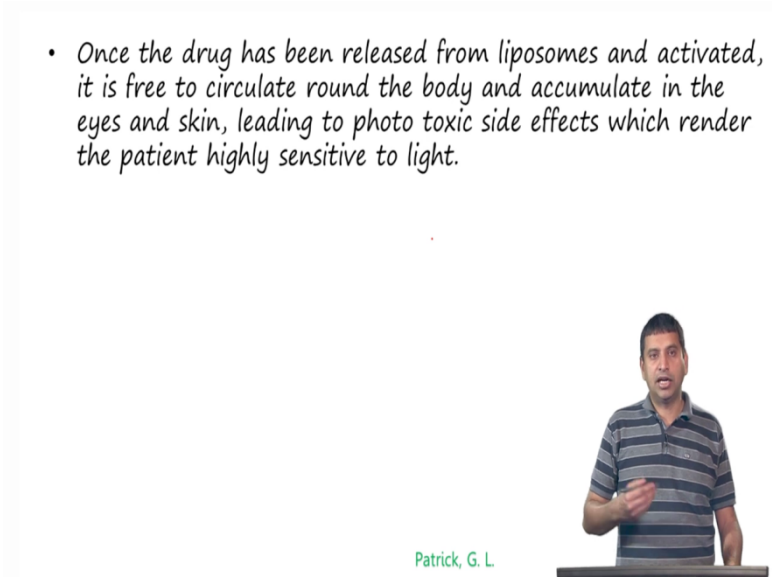

So once the drug has been released from liposome and activated, it is free to circulate around the body and it accumulates in the eyes and the skin. Now when the person goes out in the sun then there is going to be activation of these molecules to produce singlet oxygen and therefore the person the patient becomes highly sensitive to light. In fact, this is the property that helped with discovery of porphyrins in photodynamic therapy.

So there is a disease called as Porphyria in which there is a genetic problem wherein the person accumulates porphyrin in skin okay and this results in photosensitisation and disfigurement. So the victims of this disease are unable to tolerate sunlight and disfigurements can include erosion of the gums to reveal red Fang like teeth. So now you can think about all the vampire stories that you have heard before, where these people do not want to go out in the sun and they come out only in the night and they have you no red Fang like teeth ok.

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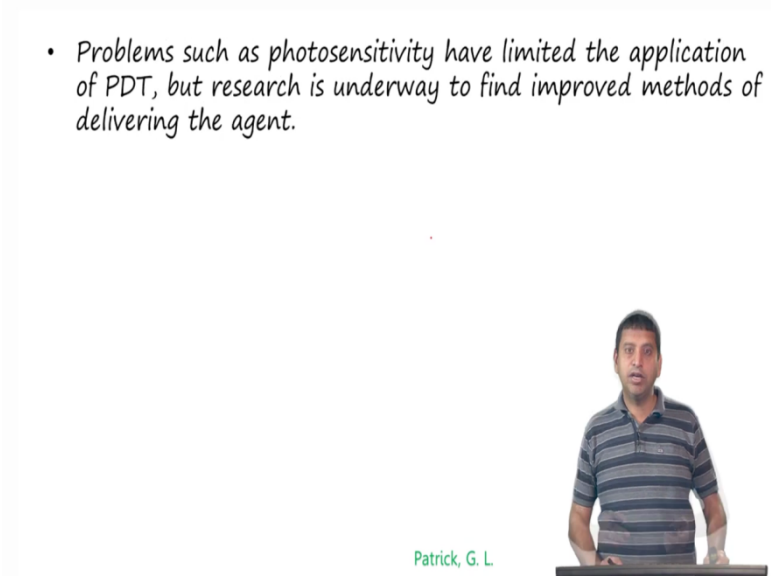

So the photosensitivity is a huge problem, so people are trying to figure out how to improve the method of delivering this agent. The other example of photosynthesizer is 5-Aminolevulinic whose structure is shown here, so here this molecule is used to treat skin blemishes which may actually turn cancerous. So it is a biosynthetic precursor of porphyrin and once you apply this, what happens is that it starts to synthesise this for porphyrin enzyme in the affected area and then you can do photodynamic therapy with this molecule.

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Okay so the next concept that we are going to look at is drug Alliance, so here there are some drugs affect the activity of the properties specially the pharmacokinetic properties of other drugs and so knowledge of this helps us actually put it to good use. So what happens is that a 2nd drug is administered along with the principal drug and this can be done in order to guard it or assist it. So for example, if there is enzymes that metabolises the principal drug and makes it inactive then you send the 2nd drug along with this 1st drug so that it prevents or inhibits the enzymes ok.

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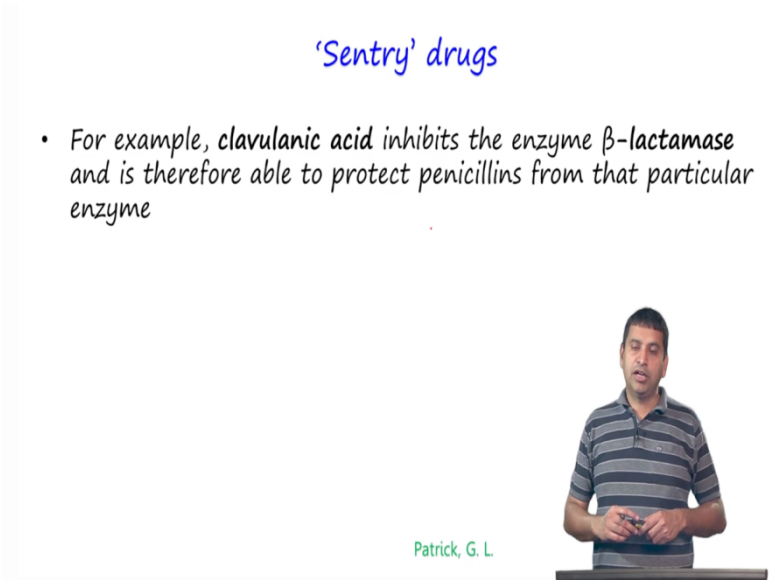

So the classic example here is Clavulanic acid which inhibits the enzyme beta-lactamase ok, and this is very useful when we give penicillins as a drug.

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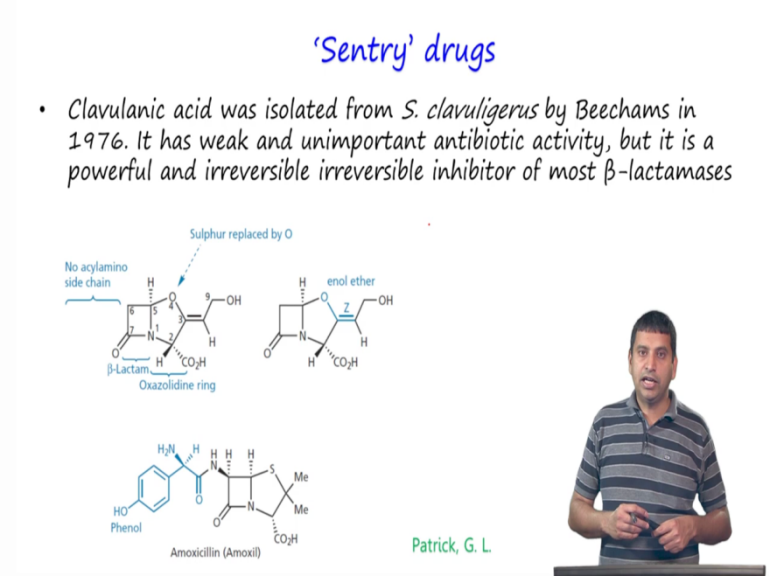

So clavulanic acid was isolated from this species by Beechams in 1976, it itself had very weak and perhaps not very important antibiotic activity but it is an extremely powerful and irreversible inhibitor of most Beta-lactamases. So here is the structure of the molecule and you have an Enol ether, the sulphur is replaced by oxygen and you do not have a side chain amino acid. And here is the structure of amoxicillin which is very susceptible to Beta-lactamases. So the strategy that we would employ is to give amoxicillin along with this clavulanic acid.

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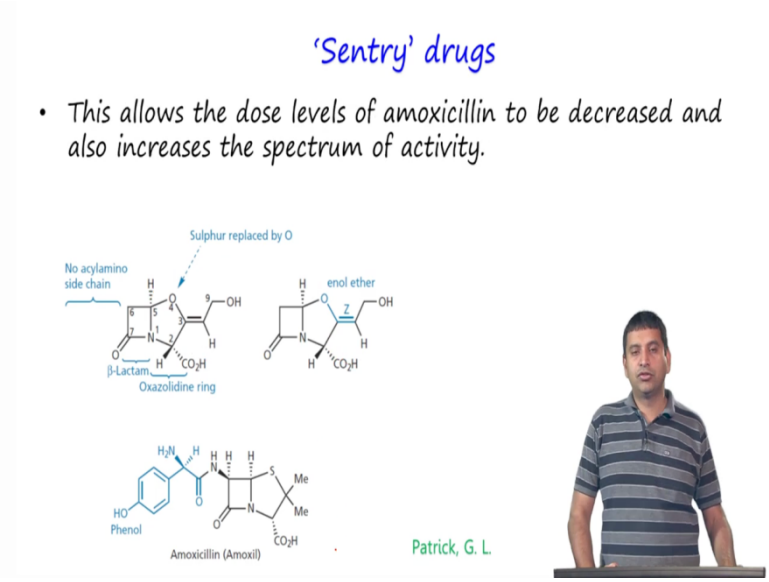

So what happens is that once Beta-lactamases are expressed then this Beta-lactamases actually cleave this clavulanic acid in preference to amoxicillin, and say for amoxicillin is protected so that it can display its anti-bacterial activity.

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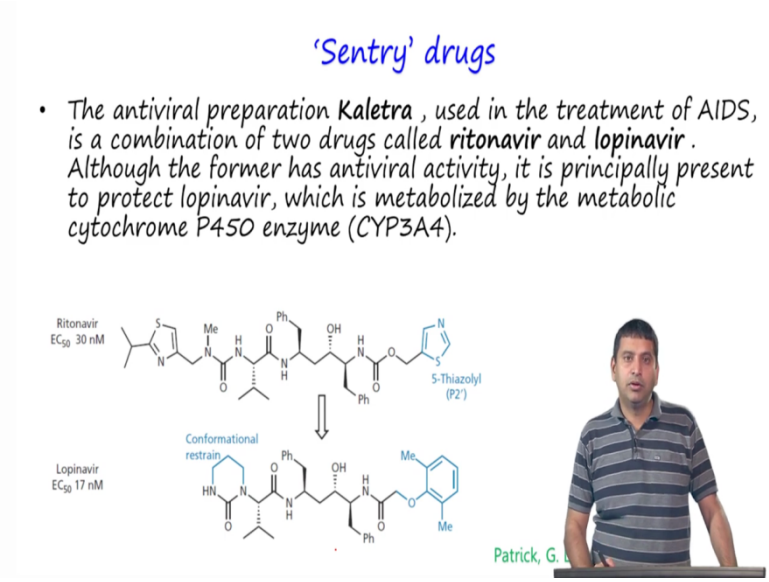

Another example is the anti-viral preparation Kaletra okay which is used in the treatment of AIDS. It is a combination of 2 drugs which is ritonavir and lopinavir, so these 2 drugs have very good anti-cancer activity but what happens is that one of these drugs that is lopinavir is actually metabolised by cytochrome P450, the isoform is CYP3A4 and in order to protect this we administer this other molecule along with it.

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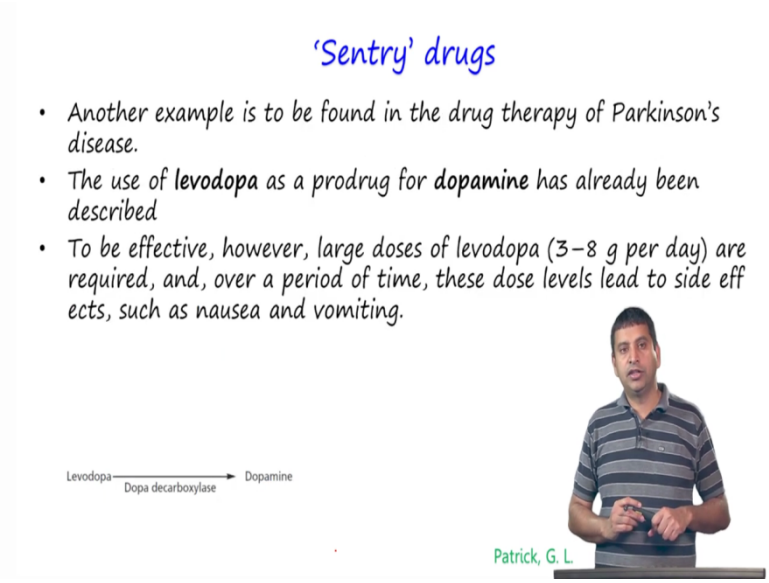

Another example which is in the treatment of Parkinson's disease, we just looked at it in the Levodopa example so which is basically a prodrug of dopamine. However, in order for levodopa to be effective you need a very high dosage that is about 3 to 8 grams per day and over a period of time these dose levels lead to severe side-effects such as nausea and vomiting. So just to remind you, this levodopa is converted by decarboxylase to produce dopamine.

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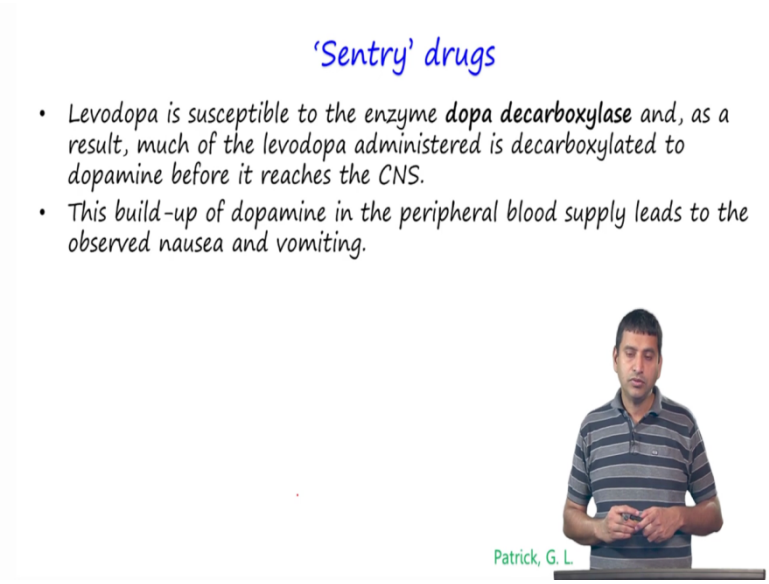

Now, Levodopa is susceptible to do the enzyme dopa decarboxylase, and as a result much of levodopa which is administered is decarboxylated to dopamine even before it reaches the central nervous system. So this build-up of dopamine the peripheral blood supply leads to the observed problems.

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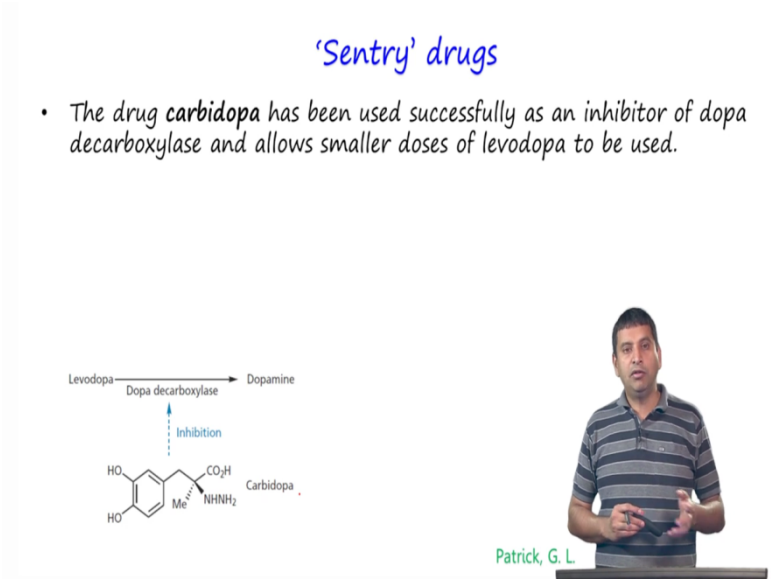

So one way is to actually inhibit this dopa decarboxylase in areas which are other than the brain, so what is done is that this molecule carbidopa is an inhibitor of this dopa decarboxylase, and so this molecule when it is given along with the parent drug allows for smaller dose of levodopa to be used.

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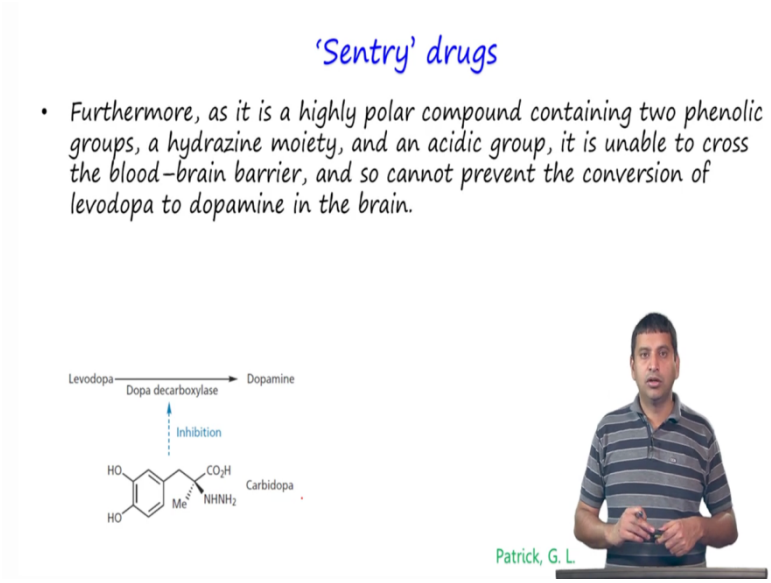

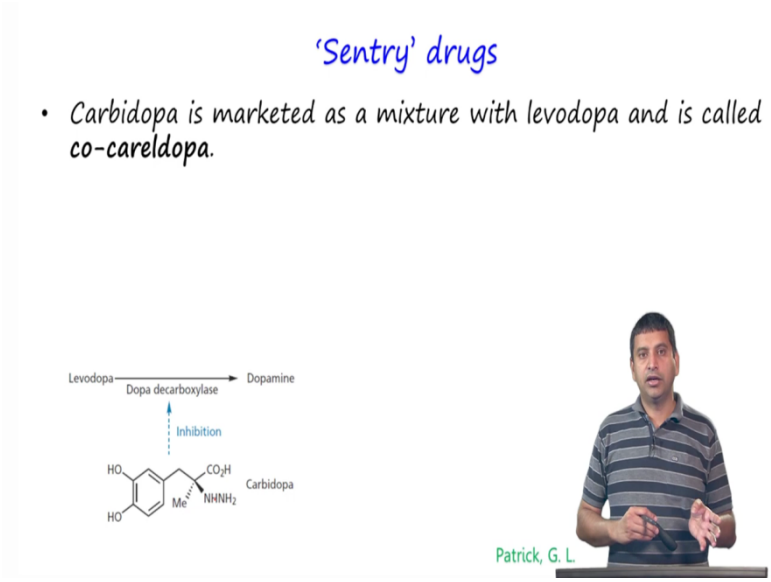

Furthermore, because it is a highly polar compound which contains two phenolic groups as shown here and hydrazine this molecule is unable to cross the blood brain barrier so all the inhibition of this dopa decarboxylase to produce dopamine happens outside of the brain. So carbidopa is marketed as a mixture of Levodopa and it is also called as co-careldopa.

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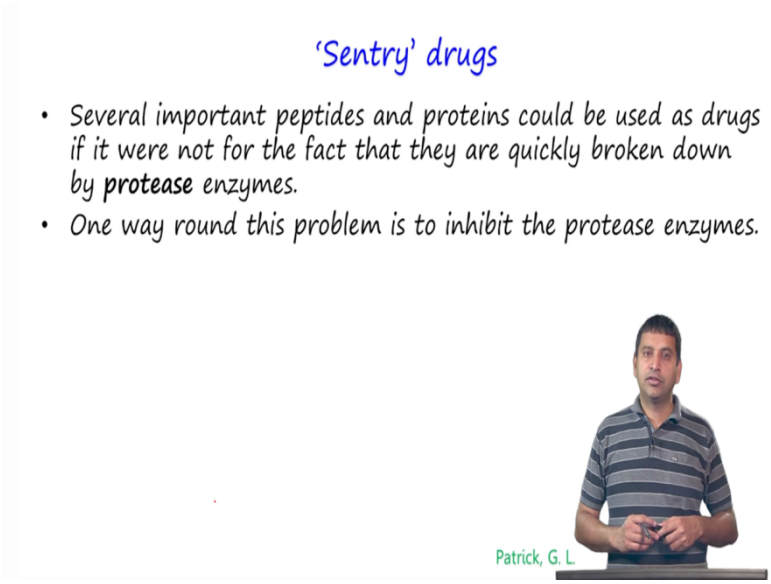

There are several important peptides and proteins which can be used as drugs okay and the one-way to do is it to actually prevent the activity of proteases, so because all the peptides and proteins are actually going to be cleaved by proteases, so what we could do is to administer these drugs along with proteases and time.

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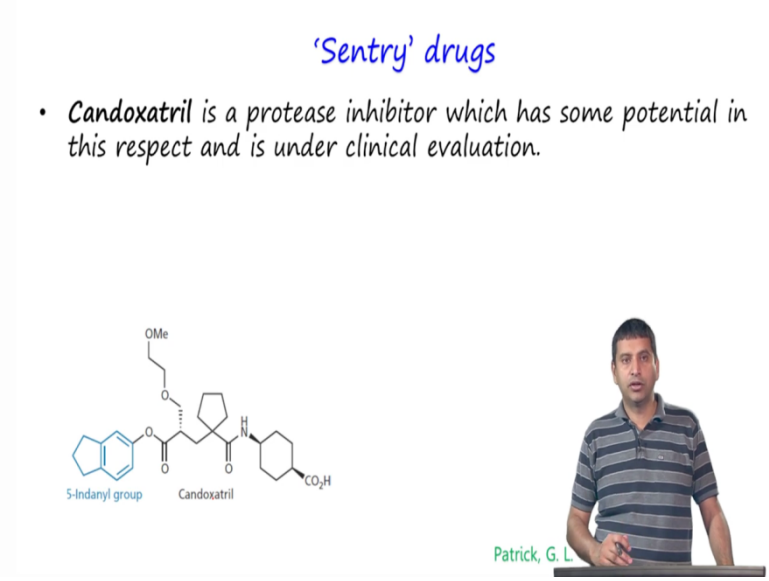

So example here is to use this molecule called as Candoxatril which is actually a protease inhibitor, and it is under presently under clinical evaluation.

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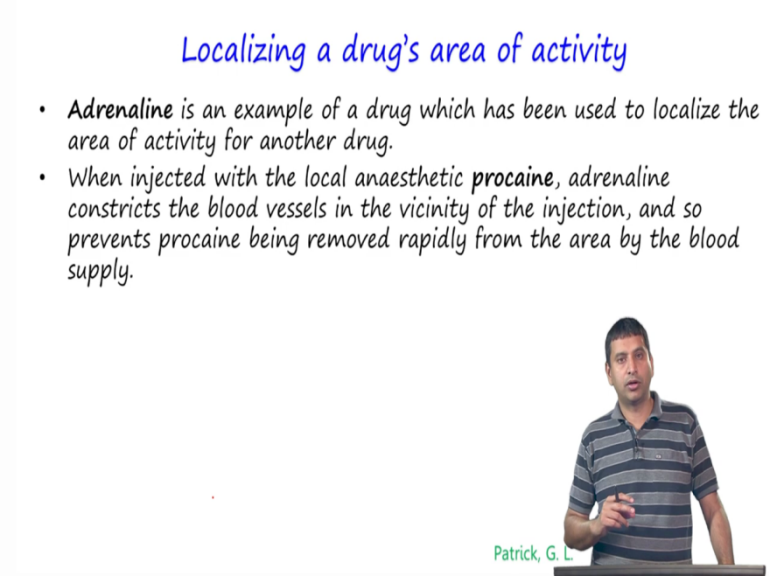

Another example of a prodrug concept is a localised drug area of activity. So adrenaline is an example of a drug which is being used to localise the area of activity of another drug, so we are talking or interaction between 2 drugs. So when injected with local anaesthetic procaine, adrenaline constricts the blood vessels in the vicinity of the injection so what happens is that procaine is not distributed across using the blood supply. So you would inject adrenaline along with procaine so that you can increase the presence of the anaesthetic locally.

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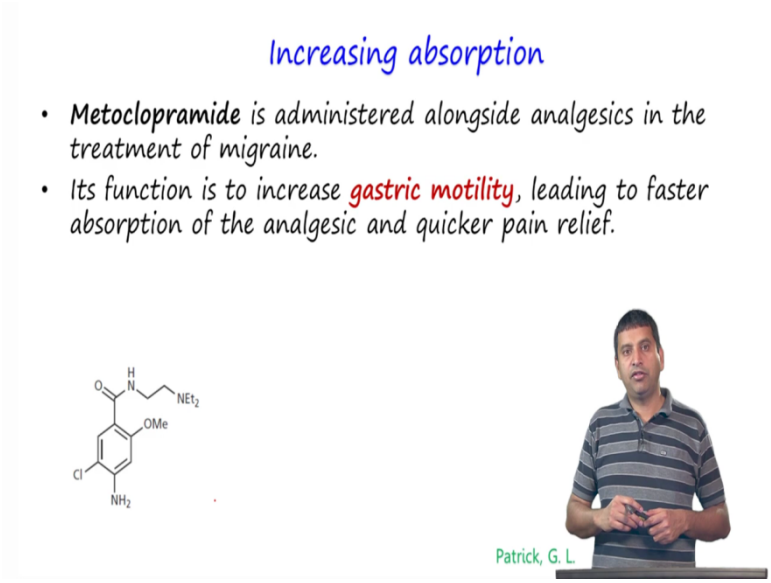

Another strategy that is used is to help with increased absorption, so this drug metoclopramide is that administered along with analgesics in the treatment of migraine. So what this drug does is that it increases gastric motility leading to faster absorption of than algebraic and quicker pain relief.