Biological Inorganic Chemistry
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Lecture 59
Metal ion based drugs and metallotherapeutics

Hello, students. So, a very good morning to everybody.

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So, today we have reached to module number 12 where we are talking you know that the metal ions in brain as well as in the medicine. So, in this lecture we will be talking about metal ion dependent some drugs and the corresponding metallotherapeutics what we should know.

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So, we all know that we can have also the metal ions as it is a primary constituent of our blood, we all know that it can also be used for your different diagnosis as well as treatment in case of the health and the diseases. So, we will be talking about the metal ions in the different treatments whether we can use metal ions in drugs or not. Then not only the metal ion complexes, but also some metal ion typical compounds can also be used as drug and we will just give a typical example on anti-cancer therapy. And since we are using some metal ion complex we will talk it as the corresponding chemotherapy. That means we will be using chemicals for its therapy.

Similarly, we can also see two other examples which is used for anti-arthritis and anti-HIV. So, these we should know about what are the anti-arthritis compounds, particularly if I ask you that, okay, you know the anti-arthritis compounds what is that, what is arthritis and what is that anti-arthritis compounds and what metal ion is there. Not only the knowledge of the metal ion is important, but also its surrounding that means how much you know about the corresponding compounds.

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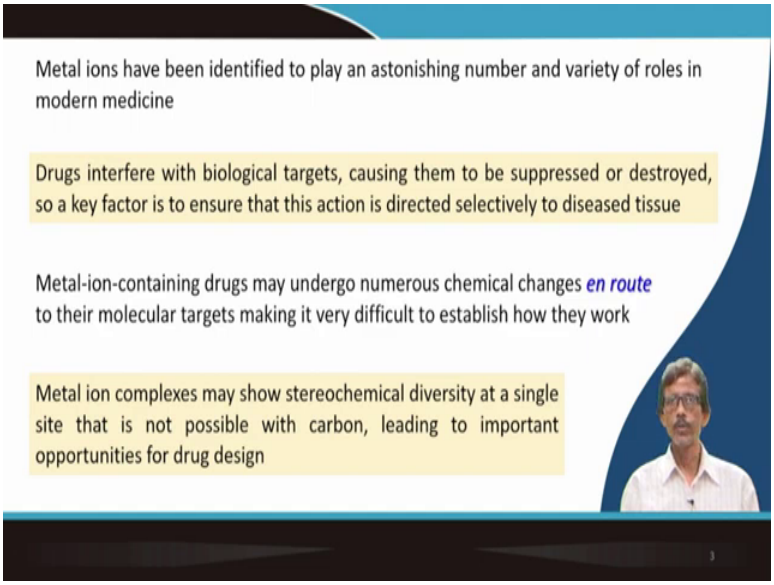

So, in many years what we have accumulated the knowledge is that it can identify to play an astonishing number and variety of roles in modern medicine. So, we can talk in terms of the corresponding metal ions in medicinal chemistry, we can call it as inorganic medicinal chemistry or metal ion-based medicinal chemistry. So, what do we know about the drugs basically the drugs can have some important biological targets. If you have tumor in your body, if you have some brain cancer in your body, obviously, the drugs should go and reach to that particular site such that it can go for the corresponding treatment.

So, basically when we use that biological target for the drugs, so what we can do, we can do only the suppression of some activity, suppression of the protein activity or the metalloenzyme activity or we can simply destroy it. So, that is the most important factor which can confirm that this action is directed selectively to the diseased tissue. So, and have some selectivity for that particular purpose also, if we have the diseased tissue, if we have the diseased tumor area or if we have some cancerous area, we should go for that particular transport of the drug molecule now, not the metal ion transport is important.

So, metal ion containing drugs may therefore undergo numerous chemical changes while it is traveling. What is that, what is the route basically? We are traveling from one point x to another point y so en route, while they are traveling, there is some changes basically there. So, it is basically a typical dynamic process where we can see the molecular targets making it very

difficult to establish how they work. So, if you have a simple metal ion complex we will see also that metal ion complex while it is traveling from one point to the other, there is no guarantee that all the groups which are attached to the metal ion is still bound to that. The way we have learned also that when we have the corresponding iron insertion within the ferritin molecule or when the transferrin is accepting that iron molecule as ferric ion its AcO species.

While traveling basically some of the water molecules can be lost, it can have tricoordinated, it can have tetracoordinate species. In that way if we consider that we can have a very useful metal ion complex, but while traveling from one point to the other that means the where it has been injected to your body or you have consumed orally that can go for different changes. So, not only that particular advantage we can also have some advantages because the metal ion can function as the carrier molecule.

Metal ion complex is the whole molecule, but the metal ions center thing is important because it can have the stereochemical diversity at a single site. So, if you have a metal ion and four donor groups are around it or if it is iron six donor groups are surrounding that particular iron center. Apart from that, what we know that we have mostly many say 95% or 98% of these drug molecules or the medicinal chemistry is dominated by the carbon center treatment. We do not have the metal ions, but the advantage for this particular case is that you can have the stereochemical advantages, where the carbon center we do not have that much stereochemical advantages and that is why we can have the important opportunities for drug design based on metal ions.

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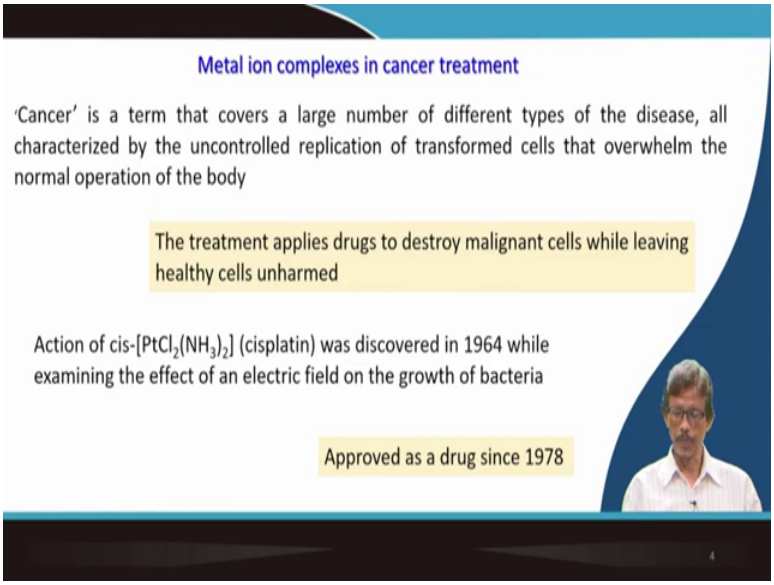

So, directly we will jump on a typical example such as your cancer treatment. So, we all know a very well known compound even doctors know and the common people know that we use cisplatin. So, what is that cisplatin that we can consider now? So, what is cancer basically, the typical definition that is the textbook definition of the cancer the terms what we can use basically it covers say different types of diseases.

So, is a large number of different types of disease, all characterized by some uncontrolled replication of transformed cells, so some cell is there and is the disease cell is there so it is getting transformed, that overwhelms the normal operation of the body. So, if there is any abnormality in that particular cell structure, there will be abnormalities in your body function, your metabolic function and your well being also so you will be a diseased person in that particular point.

So, what do you can apply for the treatment? The treatment basically consider the philosophy behind it is simply to destroy the malignancy, we call it as the malignant cell, the cancer cells we call it as a malignant cell, while leaving the healthy cells unharmed. So, we do not attack the healthy cells. We have to selectively attack the malignant cells. So, that is the challenge to the person who is trying to develop some molecule which can be metal ion dependent molecule and which can go for your treatment not only your diagnosis.

So, let us have some good idea about the corresponding molecule what do we know as the cisplatin. It is nothing but the molecular formula we should know since we are a coordination chemist. It is PtCl2NH3 whole twice. So, we all know that like water molecule, ammonia molecules are also very good ligands. But when you take the typical salt the platinum chloride is not that we are taking platinum chloride. Why platinum chloride, the PtCl2 platinum in the bivalent state, why the PtCl2 itself cannot function as a very good molecule for the cancer treatment, no, it is not. So, that is the application of the coordination chemistry.

You should be able to understand it nicely that you have to bring two ammonia molecules and you increase the coordination number. Your PtCl2 is still PtCl2. What we buy from the market as platinum chloride like your nickel chloride or palladium chloride they are all in the same group. You have nickel, you have palladium and you have the platinum. But we want to increase the corresponding coordination number, because the solid state structure of the palladium chloride is different. When you go for the mononuclear PtCl2NH3 whole 2 molecule we know that is the square planar four coordinate molecule.

Why we are bringing those ammonia molecules around platinum, because the platinum will ultimately do something which will destroy the malignancy of your cell in such a fashion that we get the advantage of that coordination as well as the removal of those groups, whether your ammonia will be removed or whether your chloride ions or the Cl minus groups will be removed from the platinum center that we will see. So, it is discovered around 1964. So, it is almost reaching 60 years old story. How it was discovered? It is the serendipity, the accidental discovery.

While the person who is working on it, trying to do something on the bacteria and he applied electric field through the use of the platinum electrode, so the platinum electrode if the particular medium is ammonia curl medium or ammonia buffered medium we all know then you can have plenty of these ammonia molecules around and if the platinum is leaching because the electrode has two functions the cathode and the anode, either it can donate electron or it can accept electron the simple strategy for your electrochemistry is that.

So, if you have the platinum as the electrode, the platinum metal as the electrode, platinum zero as the metal electrode, so during that particular process it can oxidize. So, one of the electrode

can be responsible for your oxidation. So, platinum will be least from there as the platinum 2 plus and if the surrounding medium you can have not only ammonia but also you can have the chloride ions. So, the buffered medium if had has two ligands available Cl minus and NH3 so you find that there will be a typical molecule it can form very quickly over there.

So, the electric field, the bacteria, its growth and the corresponding potential what is being applied give the corresponding serendipitous development or the serendipitous discovery of cisplatin. So, after 14 years basically because is the critical clinical trial and all these things it should be approved by many organizations for different countries and that can finally be approved as a drug and you can sell in the market. So, it is 1978, it was approved in that particular year.

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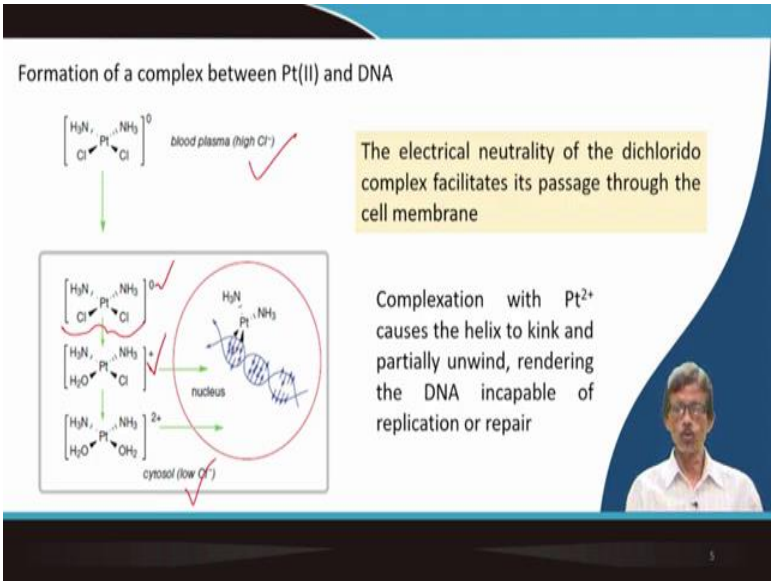

So, what is forming there and what is happening, so is not only the complexation reaction, so we the coordination chemists are always interested to know and try to explain in that way because the philosophy behind this understanding is that, okay, we are all the time trying to have the corresponding coordination compound or coordination complex. The way the platinum 2 center, the platinum, bivalent platinum is attracting the two ammonia molecules retaining these two original chloride ions around the platinum centers in your PtCl2 molecule what we see that like your ammonia functions over there it can also some affinity for the DNA molecule.

Why it has affinity for coordination to the DNA molecule. That means from this particular point of time we should know that DNA can also function as a very good ligand. If suitable metal ion is present not only platinum, if our biogenic metal ion like copper, like iron, like cobalt, if it is available in our body and if DNA molecules are available for coordination, it can go and bind those metal ions. So, sometimes we try to find that also nicely because we cannot stop that particular coordination chemistry from the biological medium.

So, the electrical neutrality of the dichlorido complex, that means you have already two chlorido groups which were originally present in your PtCl2 molecule or the salt what we call like your sodium chloride as a salt, platinum chloride is also a salt to us a metal ion salt of different type it is platinum, which basically facilitates the passage through the cell membrane. So, cell membrane is lipid membrane. So, phospholipid membrane is there. It is also charged. And sometimes if the charge is not there, inside you do not have the charge, that means the hydrophobic cell inside and the hydrophilic part outside it can so happen that you can have the reverse.

So, the neutral molecule can pass very quickly towards that particular passage which is your cell membrane. It is not that all the time we require the corresponding receptor molecules for the particular passage. So, what is happening in our blood we know that we have high concentration of chloride ion, thanks to your consumption for sodium chloride, and many other food molecules where from you are getting the chloride ions. That is why you see when you are reaching at this particular point, you still talking about the chloride ion, what we have learned in our school days, the identification of the chloride ion in water, in your drinking water or in sodium chloride salt given to you as your unknown sample. We add silver nitrate, we get the silver chloride precipitation out of that.

But now you see that sample of chloride that what concentration you must have within the blood. We know that there is a difference in concentrations for the cell outside and the cell inside. But right now what we will be talking about that you can have the corresponding complex so it is the cisplatin complex. So, you have this particular one that means you have the corresponding one as your cis. So, you have, you see that particular one as your cis orientation of the two chloride groups. It is not the trans one. So, trans one is not your drug molecule. But think of it the

corresponding charge which is also important, is the neutral compound. So, it can allow to passage through the cell membrane.

Then what happens basically we can go for the corresponding hydrolysis reaction. The chloride groups, the chloride ions can also go from the platinum center because you have, if you are disturbing the corresponding high concentration of Cl minus, because within cytosol, within the cell you have the low chloride concentration. So, if you are disturbing the corresponding available chloride ions for this particular blood molecule what happens that the chloride Cl minus in lower concentration range it can function as a very good leaving group. We all, in terms of the organic chemistry or the inorganic chemistry or the coordination chemistry, we all know what is the leaving group and what is the entering group.

So, your water molecule is the entering group and one of the chloride is your leaving group. Leaving behind a charge monocationic complex which is in C2 we are producing within your body, within the blood cells and surrounding that particular cell where we are targeting that particular binding. And also you can have both the two chloride, because the rate of dissociation or the leaving group reparture from the platinum center is high for the first removal and for the second removal because you are accumulating the chart, you have 2 plus chart.

So, what is going inside you have the corresponding thing as your this particular helical structure. So, within the helical structure if you see that if you use the diAcO species, it will simply bind over there. So, binding that particular thing what we can consider as the complexation. So, basically what happens basically, why we require a particular type of clip, because we have the platinum, already you have two ammonia functions, but you have removed the water molecule so it will go and bind two such positions the available nitrogens on the DNA helix and those nitrogens can bind to the platinum center and you have some distortion.

So, helix to kink and partially unwind, because the winding is also important, for a very important reaction for the DNA which should be capable for your replication or repair reaction. We want to go for the replication from the DNA molecules more and more DNA molecules are formed and the repair where it is damaged. So, if we are able to stop it, so this is the mechanism therefore, that we want to stop these two things that means we want to stop the replication of the DNA molecule and we want to stop that repair of the DNA molecule from there.

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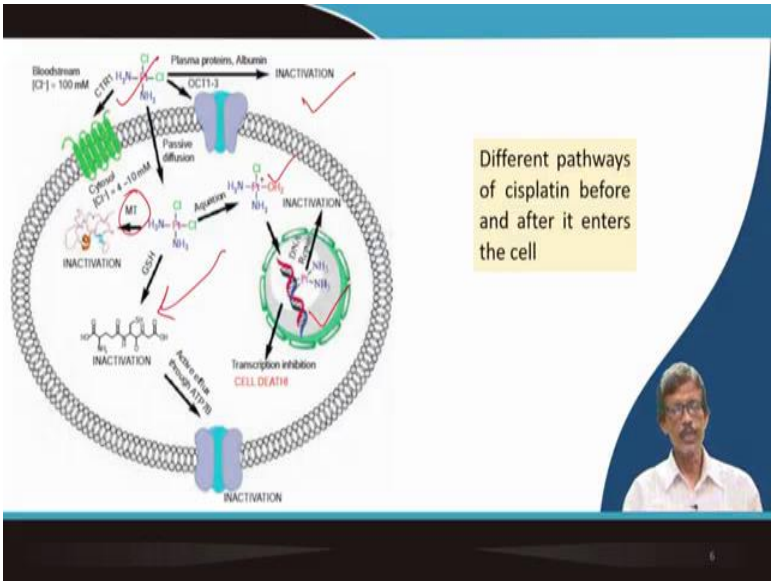

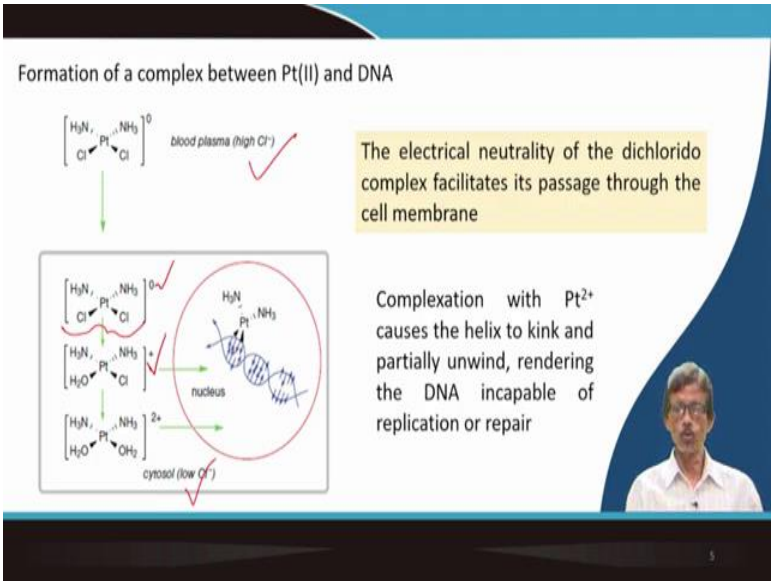

So, what are the different pathways basically? So, the different pathways what we can have before and after it is entering the cell. So, we have seen the cell and it is going. So, you have the corresponding neutral compound, you can have the corresponding positively charged one and the dipositive charge on the metal ions so which is very important. So, whether you are taking out the neutral ligand or whether you are taking the charged ligand from the metal ion center is also important, because the overall charge is the important because sometimes we will also find in our last class that how these charge can control to guide the metal ion to travel to your brain or to

your heart or to your liver or to your kidney. So, this charge is important. So, do not forget that thing. We will come back again in our next class.

So, what is happening there? So, is a big thing, that is not a very big one. You try to understand only what you can have the corresponding pathways. So, you start from there what we can have the corresponding cis compound. So, cis compound is there. We know now the concentration which is 100 millimolar up to right concentration is not 10 to power minus 3 molar concentration only. What we do. We can handle that concentration spectrophotometrically also while we do or we work in the chemistry laboratory.

But if you have the plasma membrane or the plasma protein from that side, so this particular plasma protein from the right hand side what we can find that you can have the corresponding plasma protein and these corresponding receptors molecules are available. So, if your plasma proteins are binding over there you can have the corresponding inactivation. But if it enters through that corresponding passive diffusion where it is reaching within the cytosol and that cytosol is basically something where we get that particular one as your corresponding concentration change.

So, it is reaching to a lower concentration of 4 to 10 millimolar and that particular point it can have either a dicationic species or a monocationic species. So, let us take that particular monocationic species is important. While it is further traveling inside the corresponding cell it can go for the corresponding double removal of the chlorido group and it can bind to that particular helical structure of the DNA that we have seen just now. So, if we can have the corresponding DNA repair, it is inactivated if you go for the corresponding transcription inhibition which we call as the cell death.

So, we try to kill, we try to destroy the cell in that particular fashion by stopping your repair work or by stopping your replication work, but there are different other avenues available where you can go for the destruction of these active species that means the cisplatin. You can have the corresponding aquation reaction because this particular AcO molecule on the platinum has high reactivity with this particular ligand also, is glutathione. So, you have the S minus group, you have the NH2 function and you have the COH minus function. So, not only the cisplatin itself,

but also you can inactivate the corresponding product which you get through the aquation reaction.

And also here also if you have the metallothionein here, so metallothionein can also take up this particular one and can inactivate also. So, always, we should be very much careful that there are many avenues which can deactivate the corresponding molecule, which after entering it is supposed to be the active one to destroy the cell particular DNA, but is not so if you have the higher concentration of GSH, if you have higher concentration of MT, it can basically go and deactivate that particular molecule and you will not get the corresponding active molecule for your activity.

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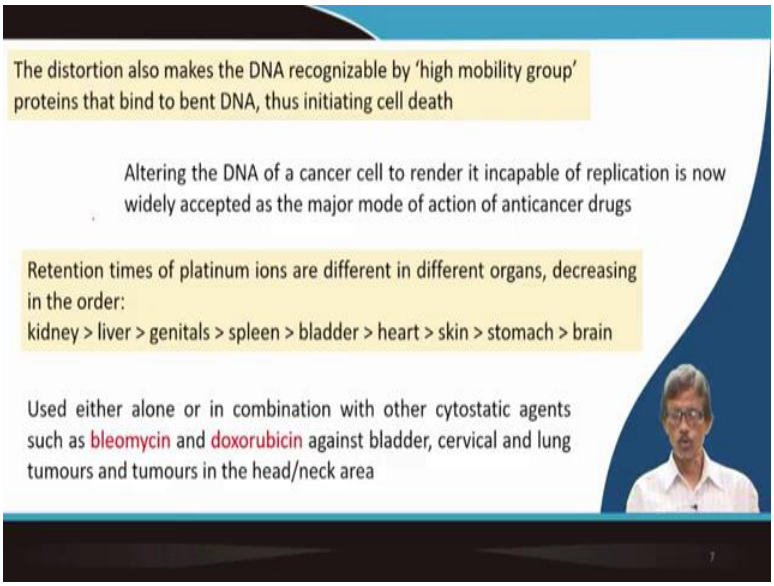

So, what we have learned now from this particular point that the distortion which makes the DNA recognizable by high mobility group, proteins are there which is known as high mobility proteins that bind to the bent DNA thus initiating the cell death. So, there are some protein molecules available which can basically recognize the distorted DNA and that distorted DNA will be bound to that particular protein and the activity of the DNA for its application taking the help of the RNA molecules will be stopped and it will close to go for your corresponding cell death.

And the way we are altering the DNA of a cancer cell to render it incapable for replication what we have seen and now widely accepted the contribution for its work, is how the anti-cancer drug

is working, it is going to the cell, it is basically in activating the corresponding repair work of the DNA and the replication work of the DNA. But, which is important, how long it will stay inside the cell, how long it can allow the deactivation pathways that means it will react with that of your glutathione molecule or the metallothionein molecule that means the retention time is also important. So, people have studied it nicely from your kidney to brain. So, next day we will be talking about, little bit about the brain for the charged molecules only, but those are for some other purpose.

So, the retention time for these platinum ions which are bound to the corresponding ammonia molecule, bound to the chloride group as well as is bound to the water molecule. So, in the active form, you see now, in one case you can have the three different molecules as your ligands, already present ammonia, already present chloride, but your new molecule, substitution of the chloride group by the water molecule so three different ligands are present to the platinum. So, that is why the activity of this platinum center is also important so the kidney which is greater than your liver to that of your brain. So, the retention time in the brain is the list and the maximum for your kidney.

But not only this particular one we can have some other thing that means how some other molecule can assist the function of your cisplatin molecule. Suppose we use something which can destroy that reaction, corresponding reaction pattern for your glutathione molecule or the metallothionein molecule or some other secondary reaction. So, the combination basically the hybrid drug molecules, nowadays we go for the treatment, not only the use of one particular ligand or the metal ion, ligand is your without metal and drug molecule and your metal ion bound ligand is your metal ion complex which can also be a drug molecule.

So, many other cytostatic agents we can use. Two of them are in colored in red one is bleomycin and doxorubicin, which can use this combination basically can helpful for treating bladder, cervical, lung, tumors in the head and neck area useful to the combination, whether you go for the cisplatin plus bleomycin or you go for the cisplatin plus doxorubicin.

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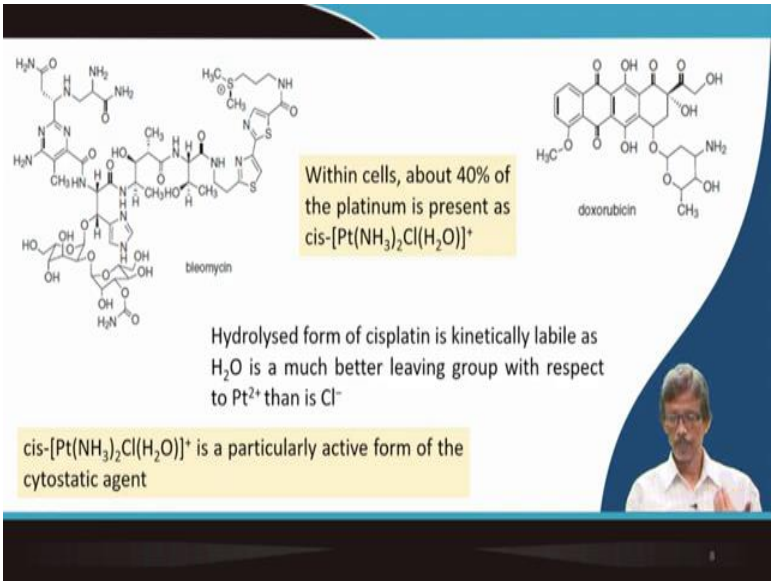

So, let us have some good idea about how big the molecule is for the bleomycin. If it is a organic chemistry class or if it is a bioorganic chemistry class or a biologic driven medicinal chemistry class people will only think about the bleomycin molecule you see such a huge molecule. But now it is basically a pro-drug for your cisplatin activity. It can use in combination with the very small and the simplest possible metal ion complex what we know like your AcO complex we always say the AcO complexes are the simplest possible metal ion complexes what do we know.

So, within the cells about 40% of the platinum is present as your monoaco species which is mono positive one also. So, 40% of these if it works basically so we forget about the remaining 60% for its work. So, 40% is fine for your curable dose. So, that is why the doctor thinks about the dose, how much dose should be administered to your body, depending upon your age, depending upon your body weight. So, what happens that hydrolyzed form, we are always interested to know about the hydrolyzed form that means the chloride group will be replaced by the water molecule and you have the corresponding kinetically labile form which is the cisplatin where water is bound is much better leaving group with respect to platinum to than your chloride go.

So, why it is bound to the aco molecule, because if you have the aco molecule that is the better leaving group so it can go and immediately interact with the DNA molecule and the nitrogen of the guanosine so N7 seven nitrogen of the guanosine base of the DNA molecule can be bound. That is why the result what we know from here is that you have the corresponding, particularly

active form, which has not been administered in your body that is difficult because it is the injectable form we go for the injection is not given orally. So, what is to be given orally that is also important.

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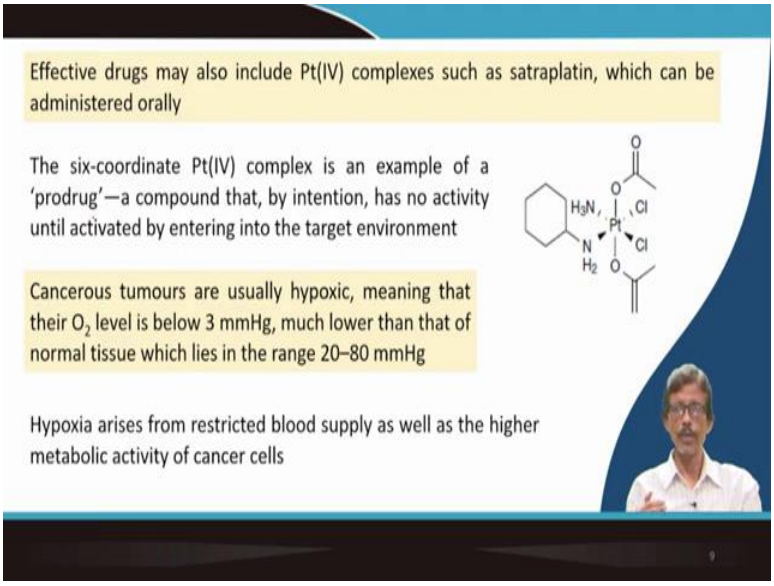

So, if you go for it change the oxidation state from platinum 2 to platinum 4 what do you get that you can have a six coordination now, your coordination number will be changing and that can function as a pro-drug because it will be changed after reaching your cell or after reaching your blood. So, it has no activity until it is activated by entering into the target environment. So, when you reach to the target, it has the activity that means, it will go the function similar to that of your cisplatin behavior. So, one ammonia group has been replaced by your cyclohexylamine only and two acetate functions and two other acid groups there and you had the two chlorido groups so very similar arrangement what we can have.

But how we take the advantage of its reduction? Platinum 4 can be reduced to platinum 2, because these cancer tumors are usually hypoxic, meaning it has lower oxygen level of three millimeters of mercury compared to that of your normal tissue level which is 20 to 80 millimeter of mercury. So, if you have less oxygen concentration that platinum 4 will not be stable enough there, it will immediately reduce within the cell when it is reaching there at low oxygen concentration level. So, hypoxia arises from restricted blood supply is one reason, blood is getting the oxygen as well as the higher metabolic activity. If you have the more metabolic

activity of the cancer cell, you produce carbon dioxide. So, carbon dioxide basically, giving you that environment which is oxygen less environment.

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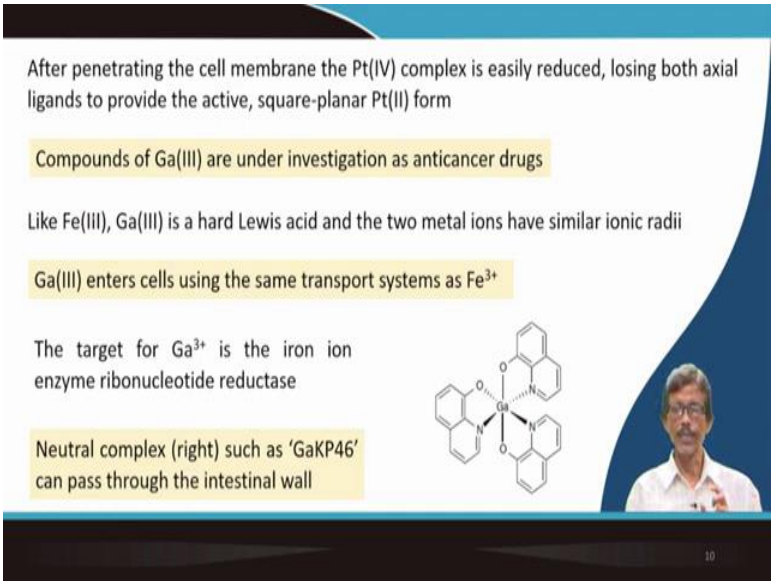

So, after penetrating the cell membrane the platinum is easily reduced and is losing the corresponding apical or axial ligands. Similarly, like platinum we can also use for gallium III which is very much similar to your ferric ion center because they have they are both hard Lewis acids and two metal ions having ionic, similar ionic radii.

So, when they are entering the cells same transport systems as Fe3 plus we can have and we get some compound which is commercially known as also GaKP46 can pass through the intestinal wall. So, it is orally active like your platinum 4 compound, orally we can go for this particular administration of this particular gallium based compound which is nothing but we all know the oxine ligand. So, it is 8-hydroxyquinoline attached to the gallium center. It is a neutral molecule again, but can give rise to the corresponding very useful activity in terms of its drug.

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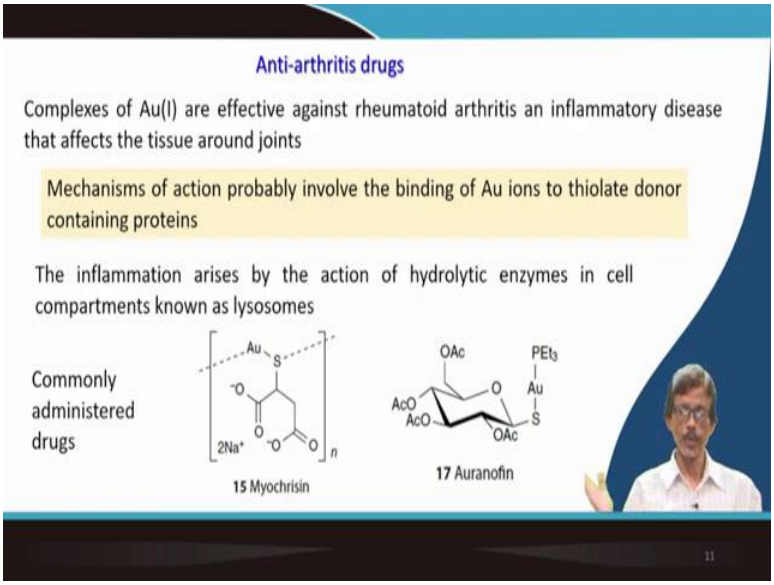

Then we quickly see the two other molecules which are anti-arthritis molecule or anti-arthritic drugs what we can have the gold compound. Now, you see all precious molecule, metal ions we are using the gold is one. Another way we are talking about the platinum, but they are not biogenic metal ions, but still we have to use it for your treatment. So, for rheumatoid arthritis we use it and the tissues we know the gout we know, we know the pain, the joint pains and all these things are due to that particular gout.

So, you can have iron and the ligand is very preferred ligand is always we know that the gold in plus 1 oxidation state has a very good affinity for sulfur as thioether or thiolate sulfur. Because we know that the different hydrolytic enzymes are there in cell compartments known as lysosomes and these lysosomes are going for the inflammation and that inflammation causes that particular pain. So, what are these commonly administered drugs is myochrisin.

Myochrisin gold is the inherent component and you have the sulfur and then you can have the corresponding other carboxylate acid groups and is the polymeric one through that sulfur chain. Then auranofin, auranofin is again the golden sulfur is the simple corresponding composition and if you add one particular triethylphosphine ligand which is basically stopping the molecule to be a polymer.

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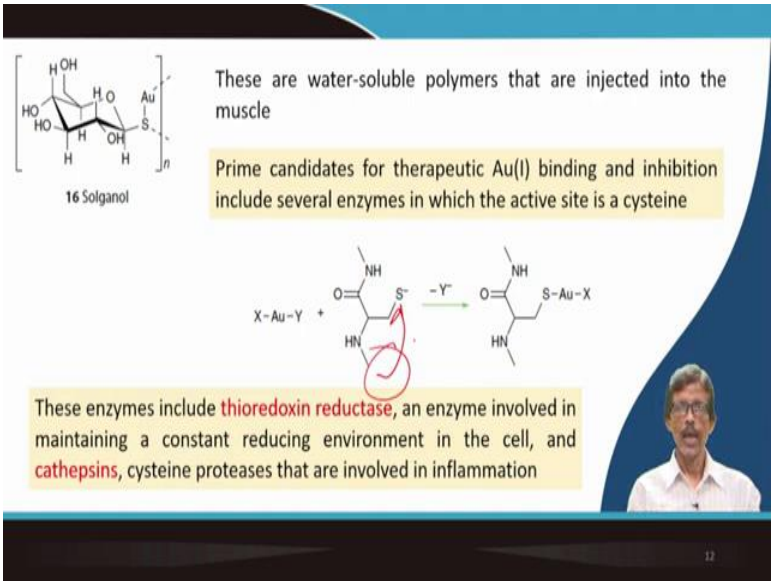

Then solganol, solganol is basically a sugar-based molecule, these are water soluble polymers that is why are injected into the muscle. So, we go for the injection. And the for the therapeutic gold 1 binding the inhibition includes several enzymes in which the active site is a cysteine site because it is providing the sulfur residue and that sulfur ratio can work in such a fashion that if you can have this particular sulfur, so this particular sulfur what you can have here is the see, this sulfur binding is important to that of your gold.

So, one particular important enzyme is your thioredoxin reductase involved in maintaining a constant reducing environment. So, the reductase is there that is why it is only you have the reaction environment and the cathepsins is a cysteine protease which is involved for your inflammation that can be hindered for its activity.

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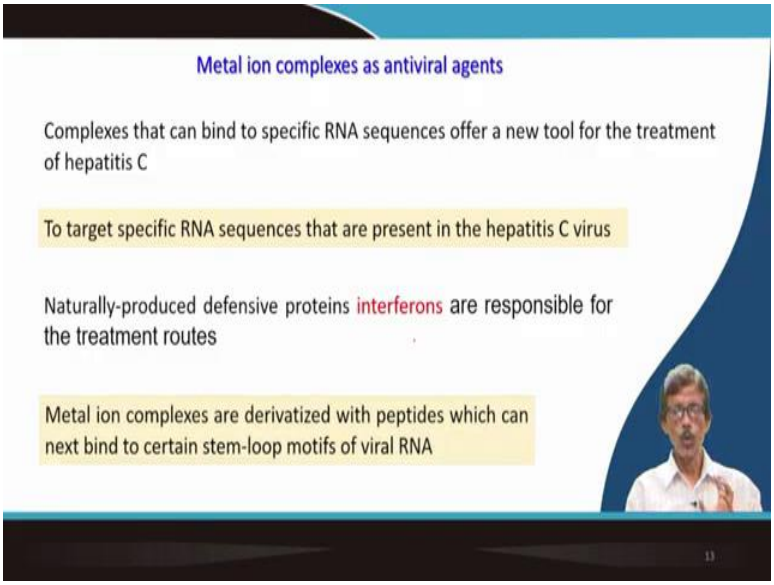

And lastly, we see the antiviral agent. What antiviral agent we can think of here is basically a very simple strategy for hepatitis C. This specific RNA sequence we must know and a new tool for the treatment of this particular disease. And is a target specific RNA sequence we can use for your hepatitis C virus and is naturally produce defensive protein for interferons which are responsible for this particular treatment route. So, metal ion complexes are derived with peptides which can next bind to certain stem-loop motifs of the viral RNA. So, viral RNA is important.

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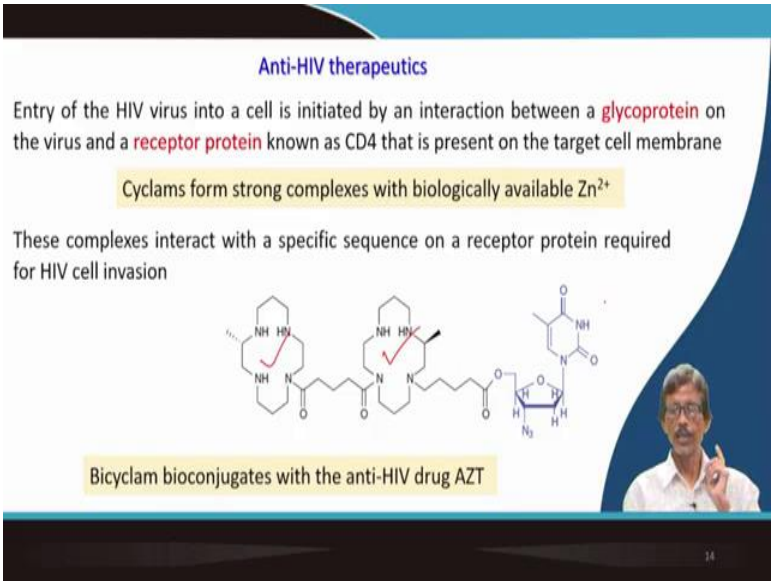

Then to then we can go for the HIV therapeutics also in a similar fashion. We can have the receptor protein which is known as CD4 protein. And that CD4 protein with that of your target cell membrane which can be used for your cyclam is a very good ligand which can bind zinc we all know is a macrocyclic ligand. So, these complexes then, if the complex formation is taking place, which interact with a specific sequence of receptor protein required for HIV cell invasion. So, that means, we are targeting the HIV cell and we can get some very beautiful arrangement which is known as the bioconjugate.

We have two bicyclam molecules, where the positions are fixed for your coordination of the zinc ion center. So, one coordination site is this particular pocket and this is another pocket for zinc binding what we have in our body, but the tail is your corresponding AZT drug. So, drug can be carried to that particular side to that particular availability of the zinc in your body as well as the corresponding cyclam ligand.

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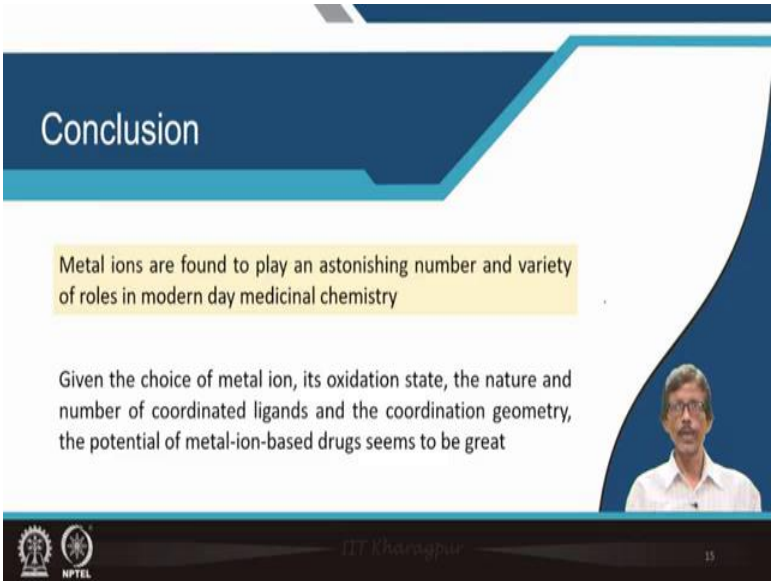

So, what we have seen is that the metal ions what we have found is known to play some very useful astonishing number and variety we told earlier also roles which can play in modern day medicinal inorganic chemistry, medicinal coordination chemistry as a whole. So, the role of metal ions we are talking. We are not going anywhere from the metal ion and given the choice of the metal ion its oxidation state, nature and the number of coordinated ligand and the geometry, the potential of the metal ion based drugs are seem to be very great.

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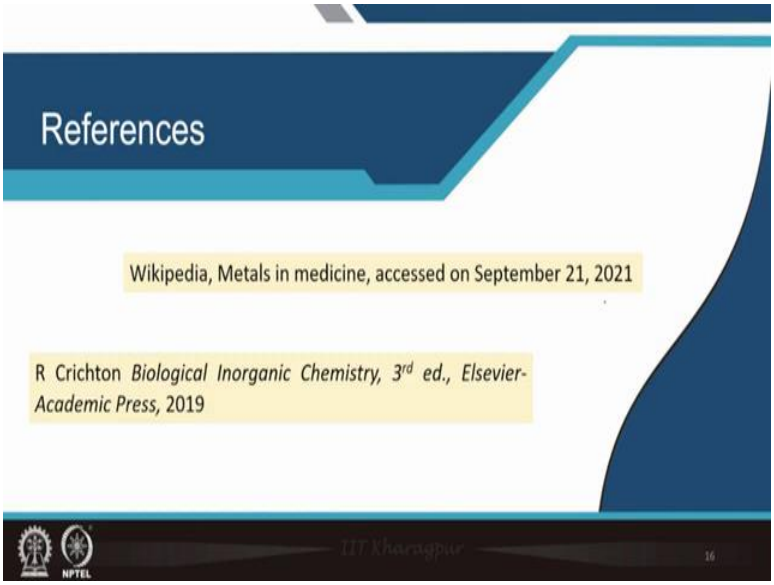

So, we will talk about the metals in medicine. The Wikipedia page is not defined or not edited in a fashion what we love to take call it as the metal ions in medicine if the metal ions are not in the zero oxidation state and also the book of Crichton. So, thank you all for your kind attention.