Bioorganic Chemistry
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Lecture - 20
Metals in Medicine: Platinum based Anti-Cancer Drugs

Hi, everybody. Welcome back to this short course of Bioinorganic Chemistry. We have been discussing about the metals in medicine. Metal ions play very important roles in biological processes and the field of knowledge concerned with the application of inorganic chemistry to therapy or diagnosis of diseases is medicinal inorganic chemistry.

In my last lecture, I have tried to give you a brief overview of various practical applications of metal ions, in diagnosis and therapeutic applications. It is clear that inorganic chemistry will have a important role to play in medicines in the future. In my lecture today, I will discuss more details about the platinum based anti-cancer drugs and their mechanistic access.

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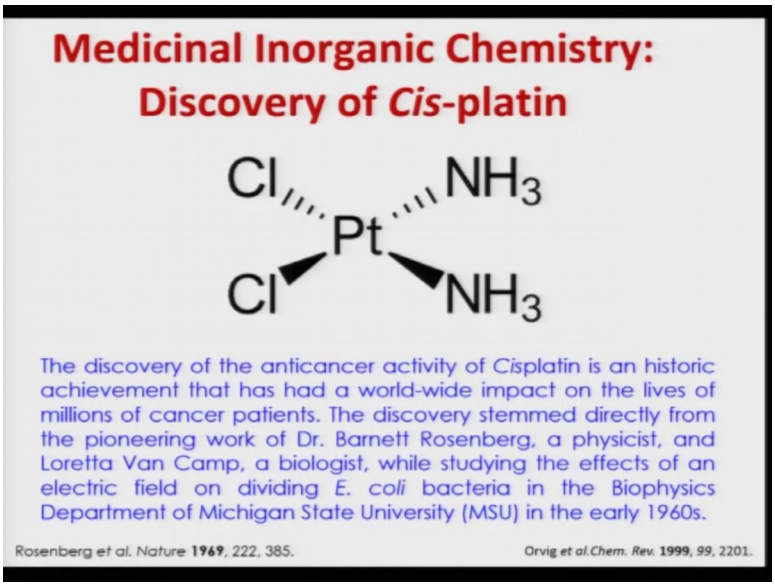

So, discovery of this *cis*-platin which an historic achievement that has had a worldwide impact on the lives of millions of cancer patients. The discovery stemmed directly from the pioneering work of Doctor Rosenberg, a physicist and Loretta Van Camp, biologist, while studying the effects of an electric field of dividing *E.coli.* bacteria in the Biophysics Department of Michigan State University in the early 1960s.

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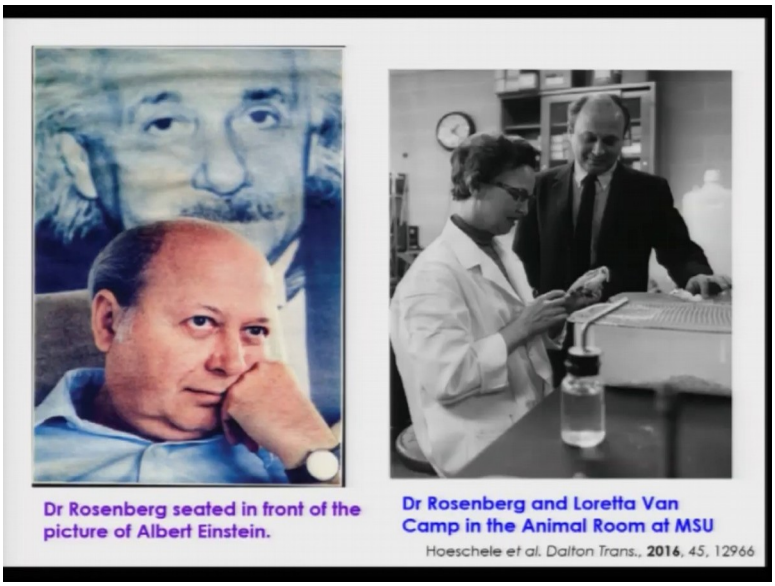

Doctor Rosenberg picture is shown over here is actually in this sitting in front of picture of Albert Einstein and here there is another picture is being shown that Doctor Rosenberg with Loretta Van Camp in the animal room at Michigan State University. This is what is Doctor Rosenberg.

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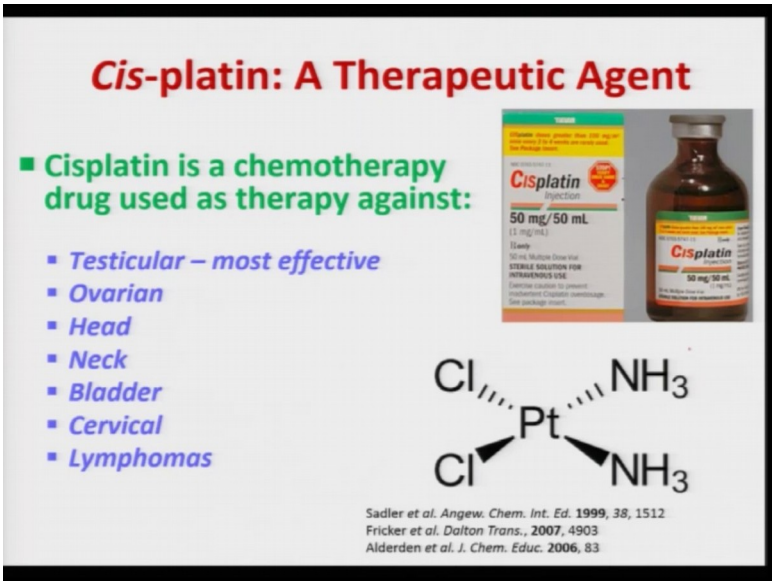

Now, *cis*-platin is indeed a therapeutic agent. *Cis*-platin is a chemotherapy drug used as therapy against testicular most effective, ovarian, head, neck, bladder, cervical, lymphomas and *cis*-platin structure is shown over here.

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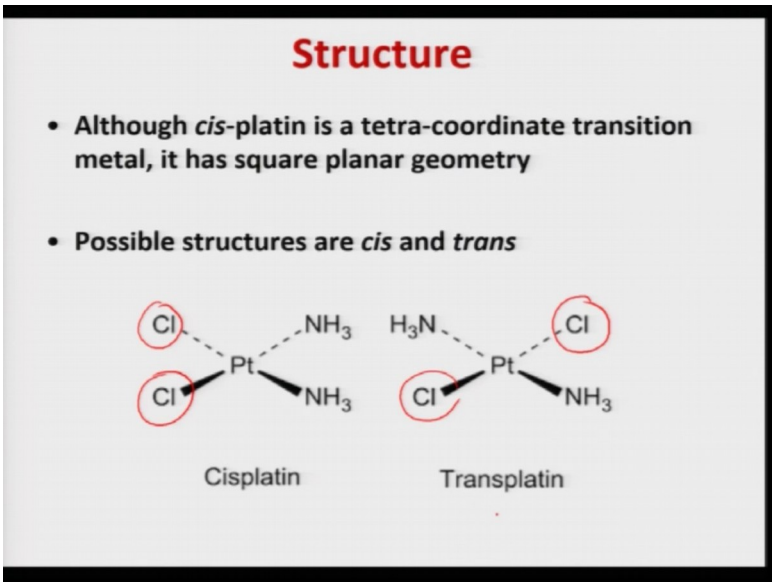

Now, although *cis*-platin is a tetra coordinated transition metal, it has square planar geometry Pt d^8 systems, so it stabilize square planar geometry. And there can be to possible structure *cis* and *trans*, you see that *cis*-platin where this two Cl is present in the *cis* position and *trans*-platin you see the two Cl is it in anti-position. So, this is *cis*-platin which is the most effective anti-cancer drug *trans*-platin; however, is completely inactive we will be talking about *trans*-platin also that why it is not active.

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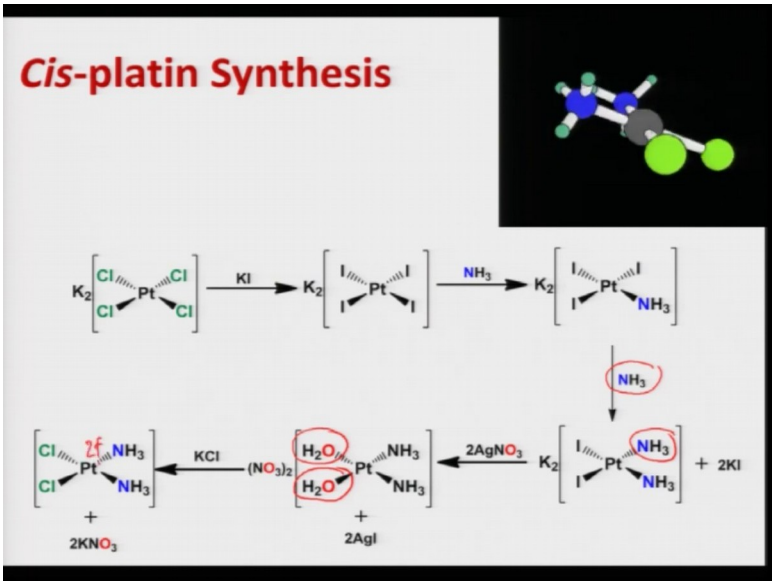

Now, synthesis of *cis*-platin is shown over here you can see that $K_2[PtCl_4]$ we start from that and once you add KI this Cl will be replaced by I^- and then you replace one I^- with one molecule of NH_3, then addition of another molecule of NH_3 will replace another I^- but they are in a *cis* position.

Now, addition of $AgNO_3$ precipitates AgI and this both I^- would be replaced by water molecule as shown over here and KCl will indeed replace water to dichloro and which are indeed the *cis*-platin which is in platinum is the Pt^{2+} state.

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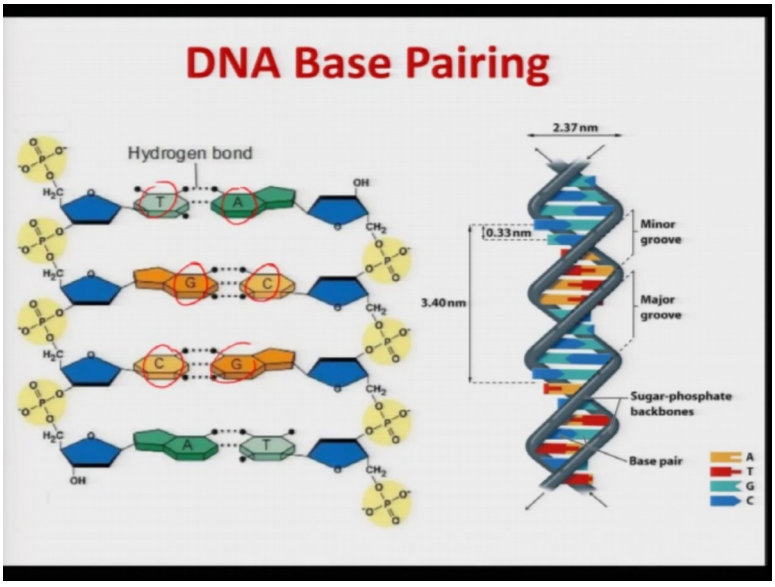

Now, you all know this DNA base pairing and you see that this is thymine, adenine, guanine, cytosine and guanine. So, this kind of base pairing is there and this is a double helix structure as shown over here, you see all details the distances also given in this particular slide for your informations.

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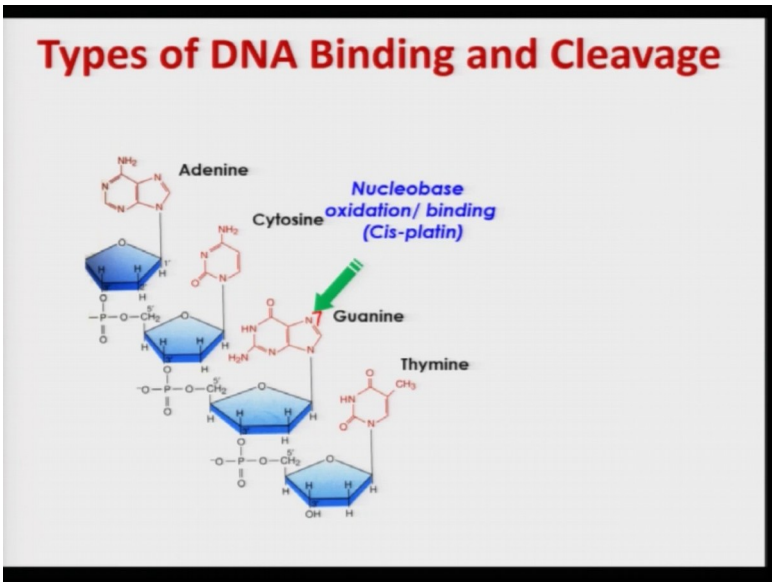

Now, *cis*-platin indeed able to bind this guanine nitrogen this is actually N7 position. This, it binds over here and we will see soon the details of these kind of binding, but it binds in the N7 position of the guanine, this is the most prefer positions in DNA.

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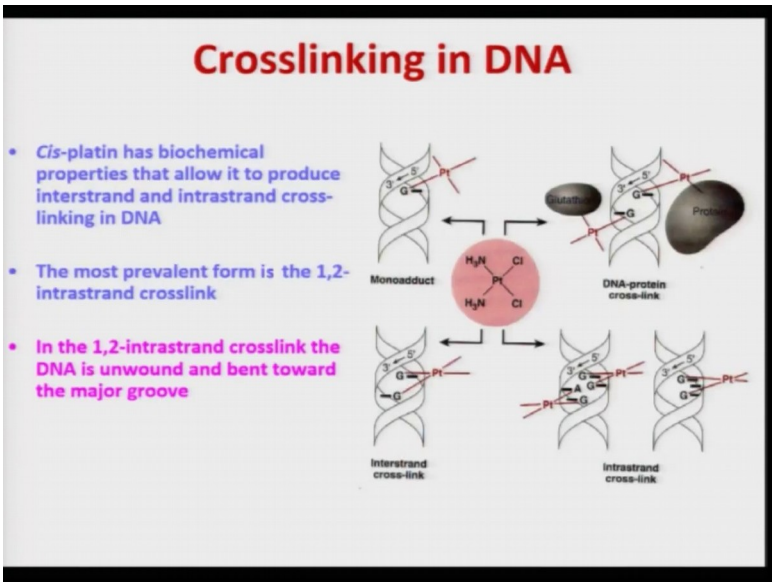

Cis-platin has biochemical properties that allow it to produce interstrand and intrastrand cross linking in DNA, both you see that intrastrand cross linking and interstrand cross linking also possible as you can see over here and there also can be possible this mono adduct formation and DNA protein crosslink also a possible confirmation. There is a

possibility and although this intrastrand crosslink product is the major product and we will talk about this in details.

Now, most prevalent form of the one to interstrand cross linking the DNA is indeed unwounded and bent towards the major groove.

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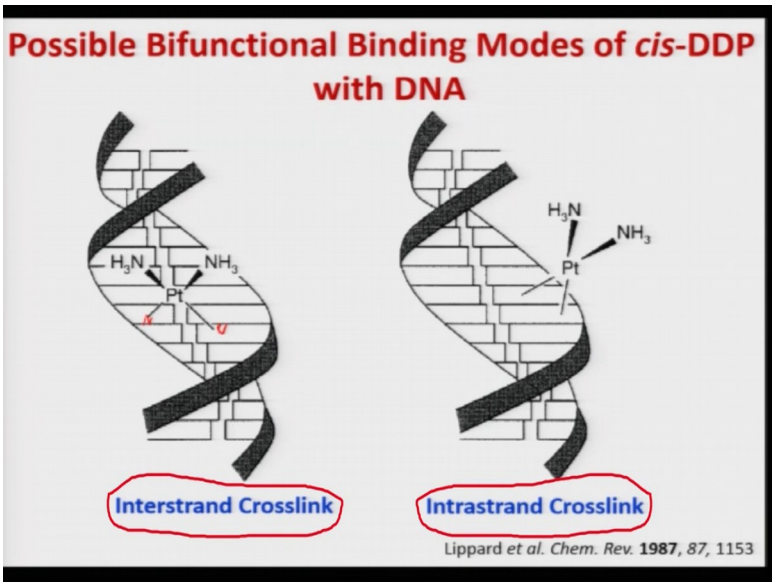

Now, this is what is interstrand and cross linking of the *cis*-platin with the DNA double helix, as you can see that platinum is coordinated with two nitrogen from two sides and this is the intrastrand cross linking of the *cis*-platin with the DNA. DNA protein crosslink is shown over here.

You can see that this is DNA is coordinated with platinum in a monodentate fashion, this nitrogen is coordinated and so DNA protein crosslink is shown here and bifunctional binding to guanine it is also shown here, but these are all very minor possibilities binding of *cis*-platin to DNA.

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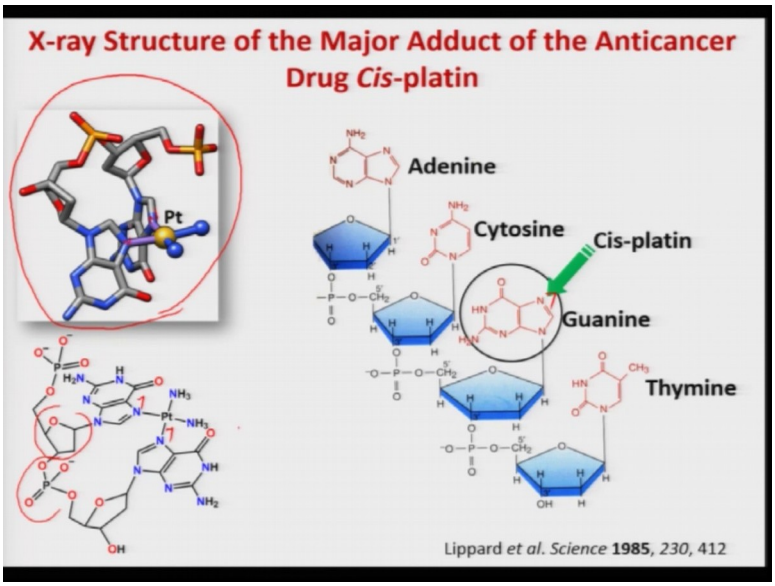

So, this X-ray structure of major adduct of anti-cancer drug *cis*-platin is shown here. This *cis*-platin as I have said earlier. The *cis*-platin preferentially bind this guanine nitrogen, this is the N7 position. And lipids group has made a ligand which is guanine deoxyribose phosphate dinucleotide, this is what is this ligand and where you see that two guanine is over here this is the ribose sugar which are linked with the phosphate. But this is a discrete molecules and small molecule and once platinum binds to N7 of guanine is also clearly visible over here.

Although, this is not the DNA, but this is a part of the DNA, they could able to make in a laboratory and they could show the world that how indeed *cis*-platin can bind to the DNA. So, this is the X-ray structure of the molecule is displayed where you can see that platinum is a of course, square planar and this two NH_3 is coordinated here and the guanine nitrogen is coordinated in the other two sides as shown in the X-ray structure.

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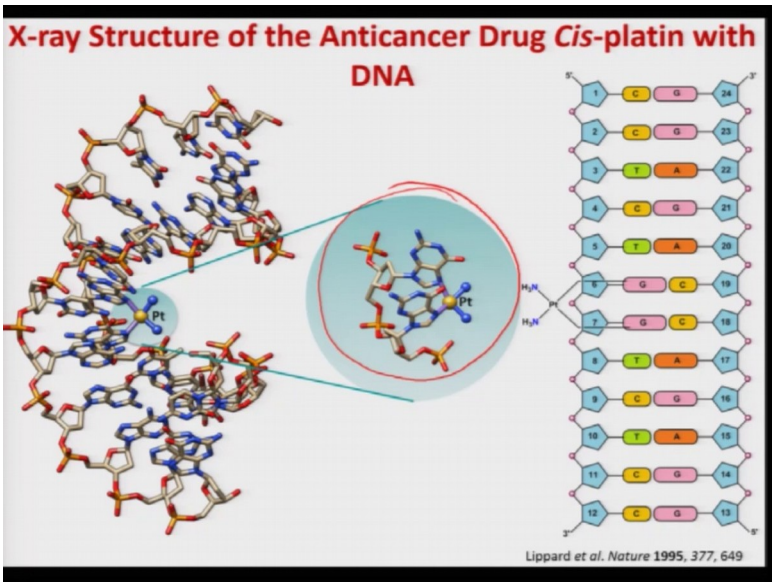

Now, indeed X-ray structure of *cis*-platin with DNA is also been published. You see that this platinum is how its binds this guanine nitrogen and 7 position and this is you know once I have zoomed that portion over here you can see very clearly how this platinum is actually coordinated to this guanine nitrogen N7 position very clearly and this has been also published long back by Lippard Group in 1995.

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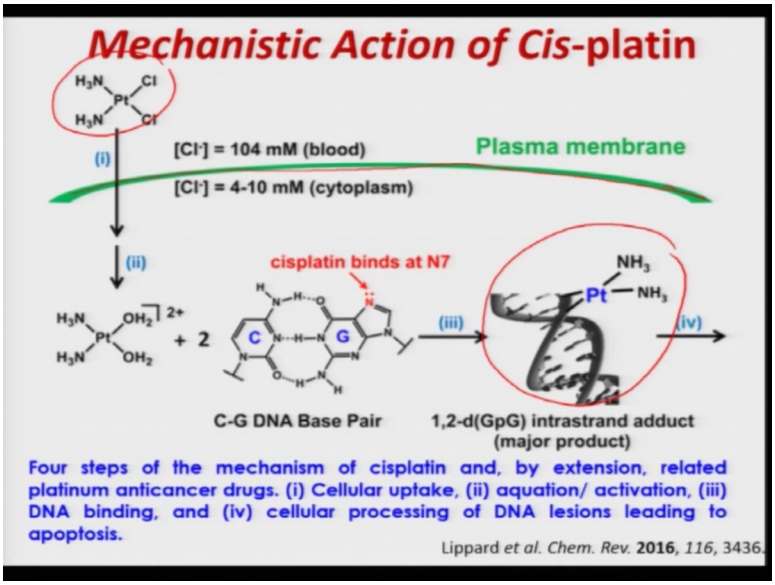

Now, let us talk about the mechanistic action of *cis*-platin that how indeed *cis*-platin works. And as you can see this is what is the *cis*-platin and then this is the plasma

membrane by diffusion and by other means also *cis*-platin enters within the cell, then they hydrolyze the chloride stepwise to form di aqua species. And why *cis*-platin do not hydrolyzed in the blood? Because it has been found that this chloride concentration is much more 104 mM solution of Cl^- there in a blood.

However, within this cell Cl^- concentration is only 4 to 10 mM in cytoplasm and that indeed helps *cis*-platin to hydrolyzed and as you can see that this is to water molecule is replacing this Cl^- and then they cytosine and guanine DNA base pair is shown over here and you can see that *cis*-platin binds very clearly the intrastrand attack which is actually the major product.

And this is shown over here and one *cis*-platin binds to the DNA then it goes to the cellular processing of the DNA legends leading to apoptosis. So, *cis*-platin comes inside the cell, it binds with the DNA and forms the intrastrand product and then cell becomes dead and this is what is happening with *cis*-platin.

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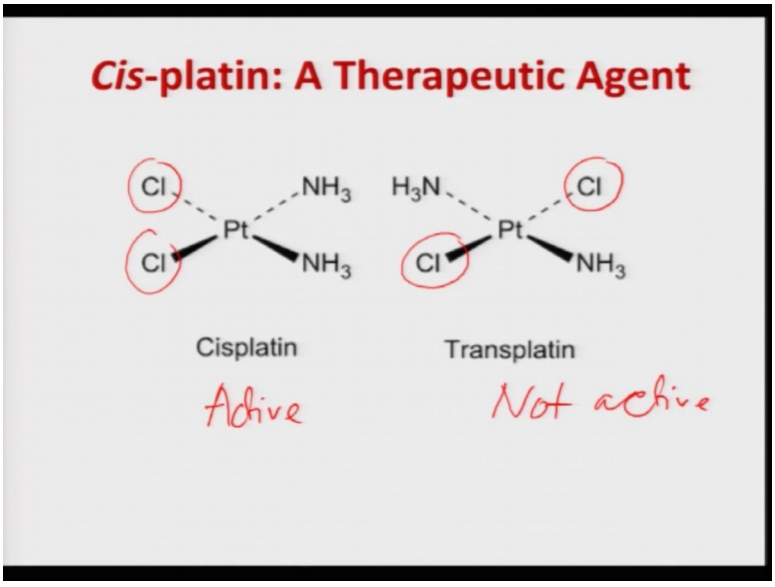

Now, *cis*-platin as I have said is a therapeutic agent. This is the structure of *cis*-platin where two Cl is in a *cis* position and transplant in this is where two Cl is in *trans* position. They are structurally very similar, however *cis*-platin is active anti-cancer agent whereas, *trans*-platin is not active.

The first difference in the anti-cancer activity of *cis*-platin and *trans*-platin may seem very surprising at first, giving there are structural similarity. However, this fact has been rationalized in terms of the greater reactivity of *trans*-platin compared to *cis*-platin. *Trans*-platin acquires approximately 4 times faster than *cis*-platin and following a 4 hour incubation with red blood cells transplatin reacts with 70 % of the glutathione whereas, *cis*-platin reacts with only 35%.

This greater reactivity can be rationalized in terms of *trans* effect. The high reactivity of *trans*-platin results in rapid deactivation of the complex way in to site reactions on the way to its target that are likely to contribute to its lack of anti-cancer activity and that is the reason *trans*-platin is not indeed active. The major limitations to *cis*-platin therapy is its side effect. It has severe side effects.

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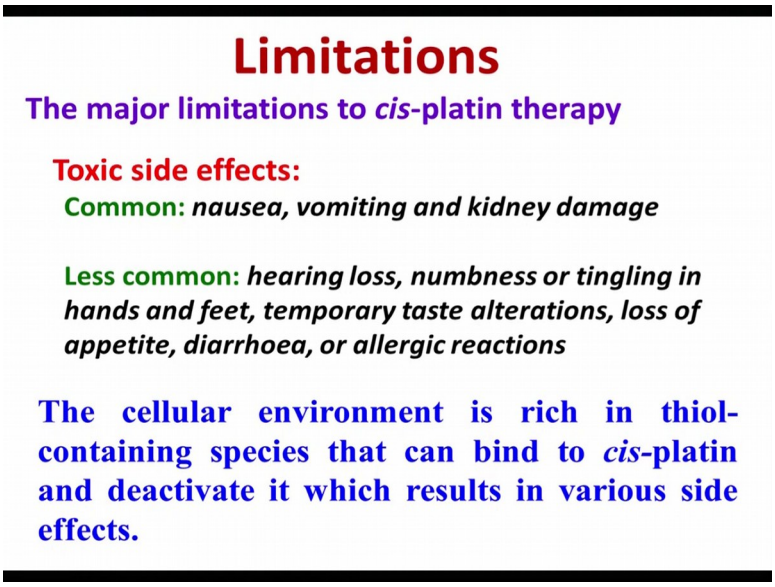

For example, the common side effects are nausea, vomiting and kidney damage and slightly less common side effects are hearing loss and numbness or tingling in hands and feet, temporary test alteration, loss of appetite, diarrhoea or allergic reactions sometimes people lose hear also.

Now, what is the reason of this toxicity? The cellular environment which indeed rich in thiol containing species that can bind to *cis*-platin and immediately deactivated. This deactivation is due to strong coordination of the soft sulphur donor coordinating to soft

platinum to in preference to harder ligands, such as amine nitrogen donors, a concept which all of you know as hard soft acid base SHAB principal.

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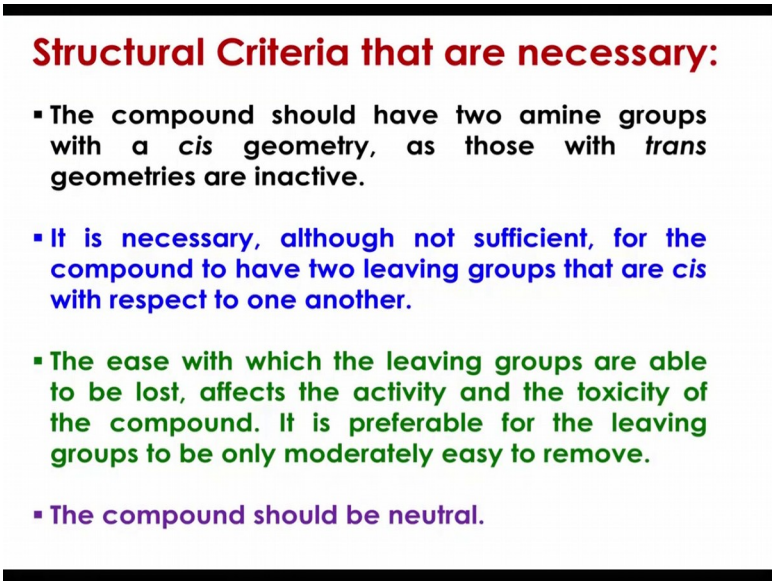

Now, in order to minimize those toxicity lots of people trying to make molecules and there are certain structural guidelines one should have before the design this platinum based drug. The compound should have two amine group with a cis geometry as those with trans geometry are completely inactive. It is necessary although not sufficient for the compound to have two leaving groups that are *cis* with respect to one another, I mean leaving groups are those groups on the molecule that are most easily lost.

The ease with which the leaving groups are able to be lost affect the activity and the toxicity of the compound. It is preferable for the leaving groups to be only moderately easy to remove, it only be removed inside the cell, if it be removed outside the cell then it creates lot of toxicity and also the compound should be neutral, ok. So, these are the criteria one should follow before it design some new anti-cancer drug.

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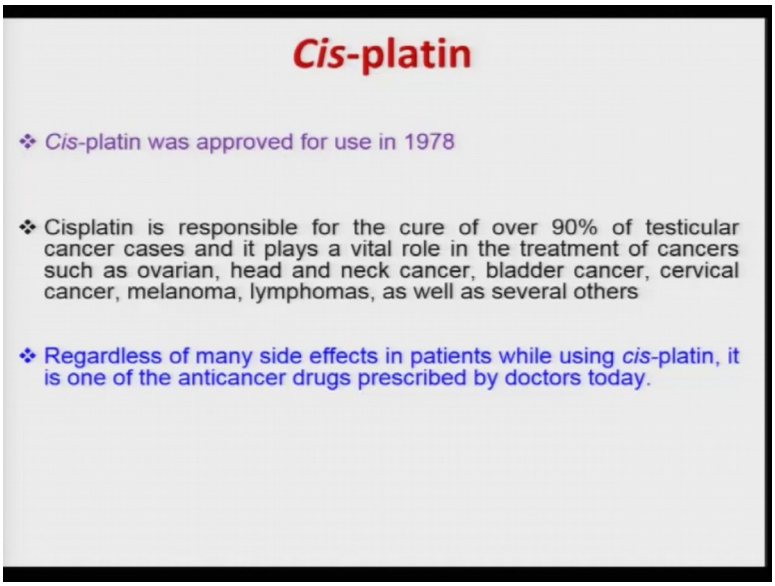

Let us look back *cis*-platin once again. *Cis*-platin was indeed approved for use in 1978 and *cis*-platin is responsible for the cure of over 90% of testicular cancer cases, and it plays a vital role in the treatment of cancers such as ovarian, head and neck, cancer, bladder cancer, cervical cancer, melanoma as well as several others, regardless of many side effects in patient while using *cis*-platin. It is one of the most prescribed anti-cancer drug till today by the doctor.

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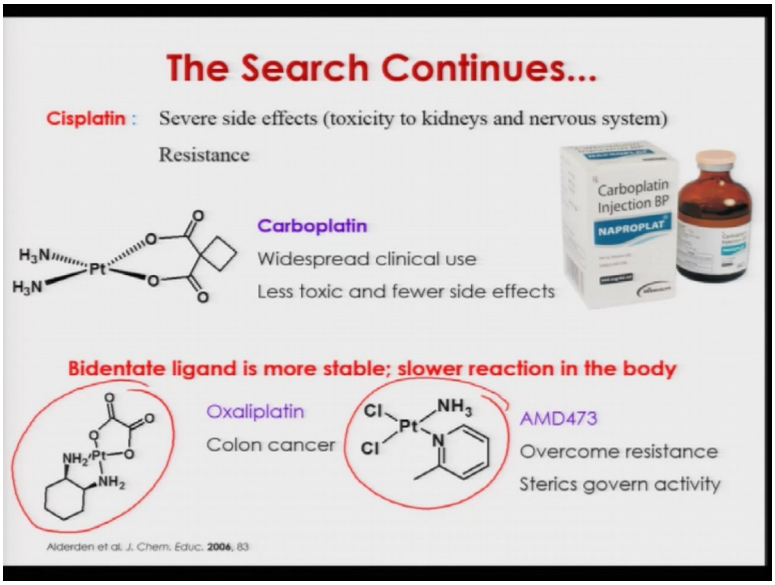

The problem with *cis*-platin is it has severe side effect toxicity to kidney and nervous system and also its resistance. Carboplatin also being designed which are now used also in clinically and which are less toxic and much lesser side effects. So, carboplatin is now very popular, it can also replace *cis*-platin because it is less toxic.

Now, bidentate ligands is more stable, slower reaction in the body and some of this anti-cancer drug is also shown over here. You see that oxaliplatin which is used for treatment of colon cancer and then the another platinum complex which actually overcome the resistance also.

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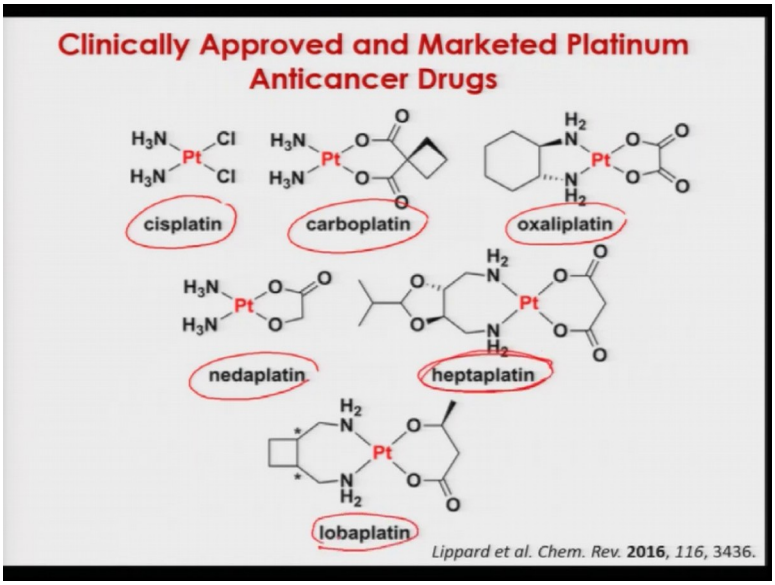

So, clinically approved and marketed platinum anti-cancer drugs are displayed over here. As one can see there are several such platinum to complex like cis-platin, carboplatin, oxaliplatin, nedaplatin, heptaplatin and lobaplatin is shown here.

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And this is what is the list where you can see that what is the research name of this molecule and what is indeed the trade name and when it has been approved and where it is being utilized. As one can see that *cis*-platin, carboplatin, oxaliplatin are utilized globally whereas, nedaplatin is in use in Japan, which has been approval granted in 1995, then heptaplatin which are now used in Korea and approved in 1999 and lobaplatin which are approved in 2010 has been in use in China now.

The problem is all this platinum based anti-cancer drug has severe side effect and in order to reduce that people have been trying hard to make different molecules and try to think that how one can reduce the toxicity of this platinum based anti-cancer drug.

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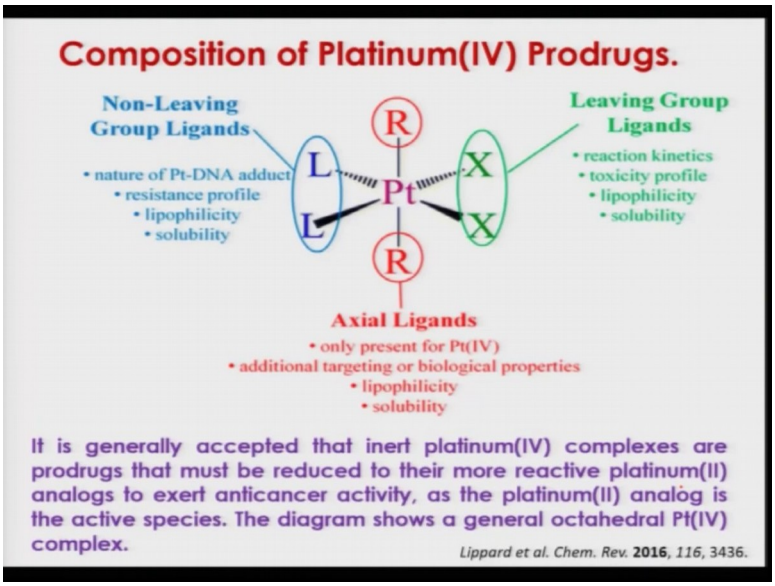

One such attempt was like if one can make Pt(IV) prodrug. Two non-leaving groups are here platinum is in octahedral structure and these two X is the leaving and there are two R group which one can play with that. Now, this anti-cancer potential of Pt(IV) agent has been recognized from the time of the original discovery of the biological properties of *cis*-platin, but their clinical value has only more recently been realized.

The physicochemical properties of Pt(IV) agents differ significantly from those of their Pt(II) counterparts. It is generally accepted that inert Pt(IV) complexes are prodrugs that must be reduced to their more reactive Pt(II) analogs to exact anti-cancer activity, as the Pt(II) analog is the active species.

This is the diagram where you can see that there is a scope to vary different groups and you can improve your anti-cancer drug and you can play in such a way that you can make your drug more friendly, less toxic, that would be of great help for the community. Unlike square planar Pt(II) complexes Pt(IV) complexes are nearly always 6 coordinate and adopt octahedral geometries.

The standard kinetically much more inert coordination sphere of Pt(IV) is more resistant to ligand substitution reaction then 4 coordinate ligand to centre. Thus minimizing unwanted side reactions with biomolecules prior to DNA binding, moreover the two extra ligand afforded it by low spin d^6 Pt(IV) centre provide a means to impact and fine tune desire biological properties such as lipophilicity redox stability, cancer cell targeting

and improved cellular uptake. If one can possibly use Pt(IV) prodrug and by that way one can reduce the toxicity.

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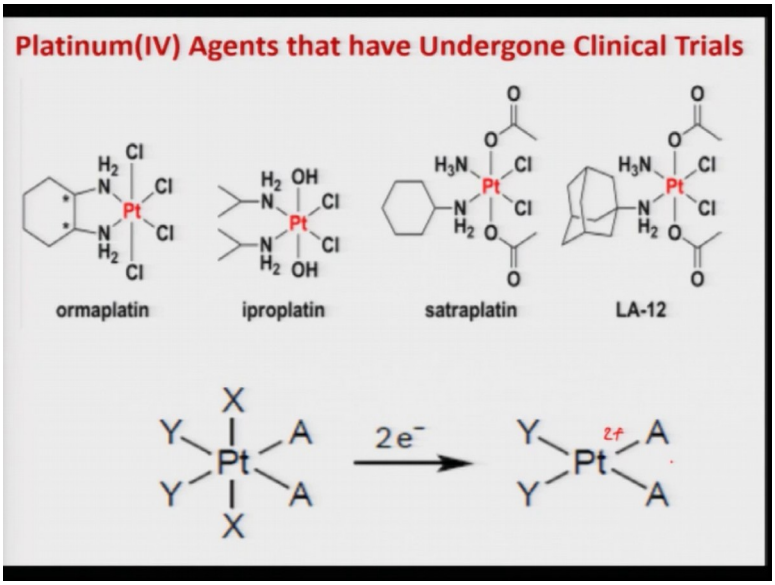

And indeed, there are several such Pt(IV) agents that are undergoing clinical trials at present and you can see some of these structures are shown here. However, as I have just said the Pt(IV) agents are actually prodrug the real drug would be Pt(II) plus and square planar. So, what is happening inside the cell; this undergo a reduction to produce this square planar platinum to complete which is actually the active anti-cancer agent in our body.

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So, while we are going now lots of new drug and new possibilities for metals in medicines. There is much research to be done to find anti-cancer drug with less toxicity, less side effect and then it would be; it would be actually very very useful for its applications. In summary, I have discussed today more details about platinum based anti-cancer drugs and their mechanistic action.

Hope you will enjoy the chemistry I have shown in last several weeks and thank you very much.