Inorganic Chemistry of Life Principles & Properties
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Lecture – 49
Inorganics in medicine – Introductory aspects & cis-platin

Welcome you to the next class on Inorganic Chemistry of Life Principles and Perspectives. During all these previous classes, we have looked at variety of introductory aspects, followed by huge number of enzymes, based on different metal ions, like transition metal ions transport in case of the alkali alkaline earth like ATPases etcetera. And enzymes based on the manganese, enzymes based on vanadium iron, of course, cobalt, nickel, copper, zinc, molybdenum, then we looked at the mercury reductase, selenium enzymes. So, we have more or less covered a huge variety of enzyme based biological inorganic chemistry, which is pertinent to the life.

A few more aspects are required to give a feel of inorganic chemistry into other aspects of life, and these are as follows. Inorganic compounds not only inorganic compounds, it is not only a part of the enzyme; as I said initially the inorganic ion center plus the protein. Then inorganic ionic ion center I talked to you as a primary coordination as a complex. So, it is like a inorganic complex suspended in a protein.

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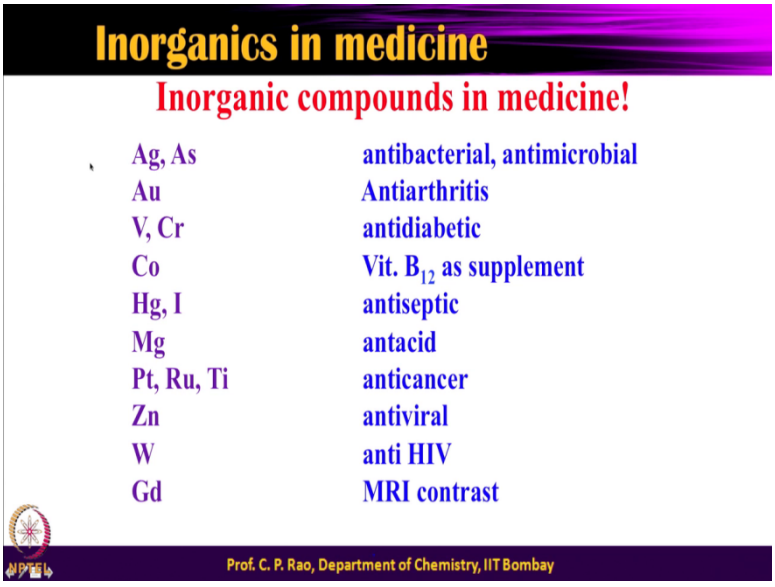

Now, we can take such inorganic compounds or simple inorganic compounds. These have found a great importance in medicine inorganic compounds see this particular slide. Based on silver based on arsenic, which is which we think it is a poison, based on gold, based on vanadium, based on chromium, cobalt, mercury, iodine magnesium, platinum, ruthenium, titanium etcetera, zinc, tungsten, gadolinium.

Variety of these things their compounds can be used in variety of aspects, like it could be antibacterial, antimicrobial, antidiabetic antiarthritis, antiacid, anticancer, antiviral, anti HIV variety of these things, also can be used was the contrast agents etcetera. So, therefore inorganic ions or widely spread as their compounds and complexes and salts in medicine.

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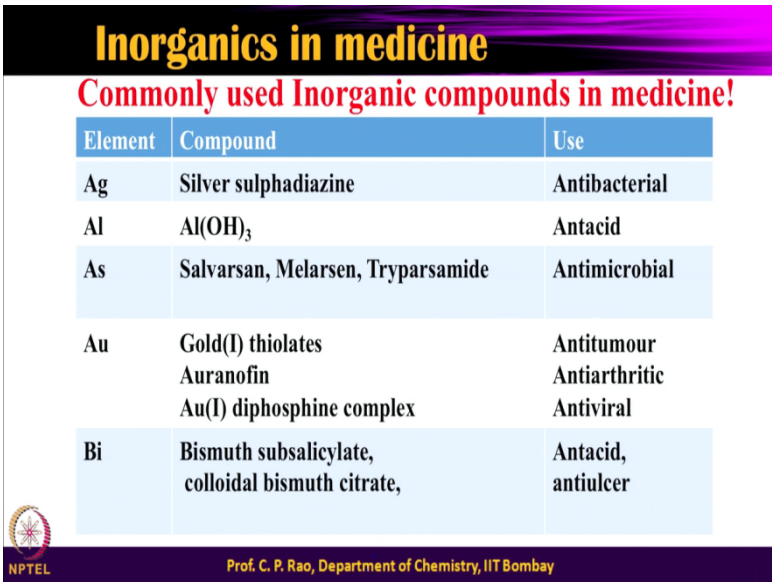

So, let us look at little bit more detail into this one. As we keep going through this particular slide we understand a lot of features ok. So, we were trying to look at a this particular table, where we have the inorganic compounds. Let us look at silver silver in the form of a silver sulphadiazine, it is antibacterial. And I am sure you would have seen some of the antibacterial drugs on the bottle you would see also the compounds that you have.

Aluminum, aluminum is in the aluminum hydroxide, and you know that aluminum hydroxide this is used absolutely, as the antiacid. Sometimes some of the cases even silica silicate based also people used, and the aluminum hydroxide. Arsenic arsenic compounds of various things, these are all commercial names they can be used in the antimicrobial too. Gold, gold thiolates gold as just we are looking at the heavy atoms, gold is also one of the heavy atom, and is a

soft ion. So, therefore, it can bind with the thiolates much better. So, gold one thiolates auranofin A U 1 diphosphine complexes. All of these can be used in anti tumour anti artiarthritic. So, basically antiarthritic and then, antiviral. So, gold compounds are also used a lot the kind of compounds you can see here. Bismuth, bismuth subsalicylate, bismuth colloidal, bismuth citrate all of these can be used also as a antiulcer as well as the antacid.

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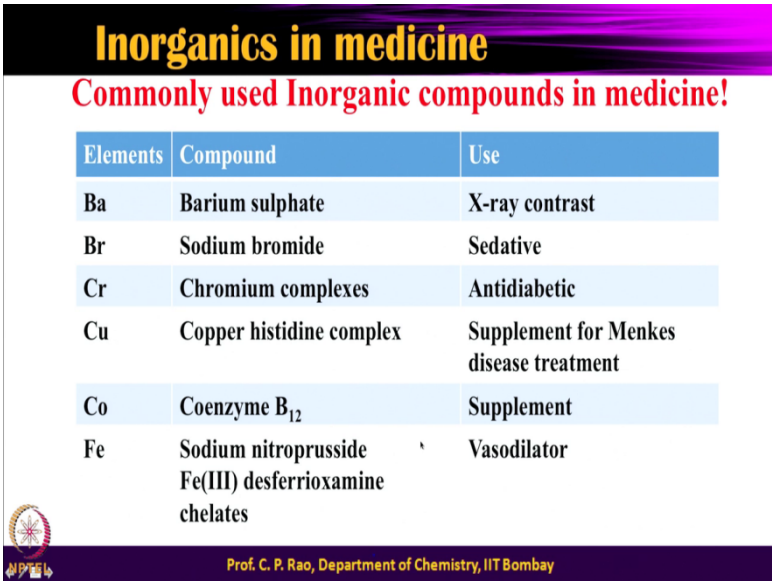

That is not the list completion we have lot more. Let us look at this particular slide also. Barium, you know the barium barium in the form of barium sulfate. Where do you know the barium sulfate, and people who are having some kind of a intestinal ulcer, in the hospitals the doctor will recommend you to get the X ray contrast picture for that they ask you to take the barium sulfate solution. After you drink barium sulfate solution, and then the X ray is taken. And from that you can get the where the ulcer is there in the intestines. This is also known as a barium meal test in the general context, because they give you to drink the barium sulfate solution, so therefore, it is called barium meal test ok.

Bromide in the form of sodium bromide is a sedative, the chromium complexes not proven very well, but they are in the antidiabetic site. Copper, copper of course, is a histidine complex the it is supplement from menkes disease, and the for various things of that kind too. Cobalt, cobalt is coenzyme B12, it is a supplement we take whenever we feel weak we always take that. Iron sodium nitroprusside, iron desferrioxamine chelates, all of these are as vasodilators.

So, the dilators is that vesicular dilators, because the blood thinness. If there are some kind of a the blood, has got some kind of a materials of non insoluble kind of things etcetera. Those kind of things can block the vasiculers. So, these things can be sort of cleared out by using such kind of things of course, people use even N O also for that as a dilator too.

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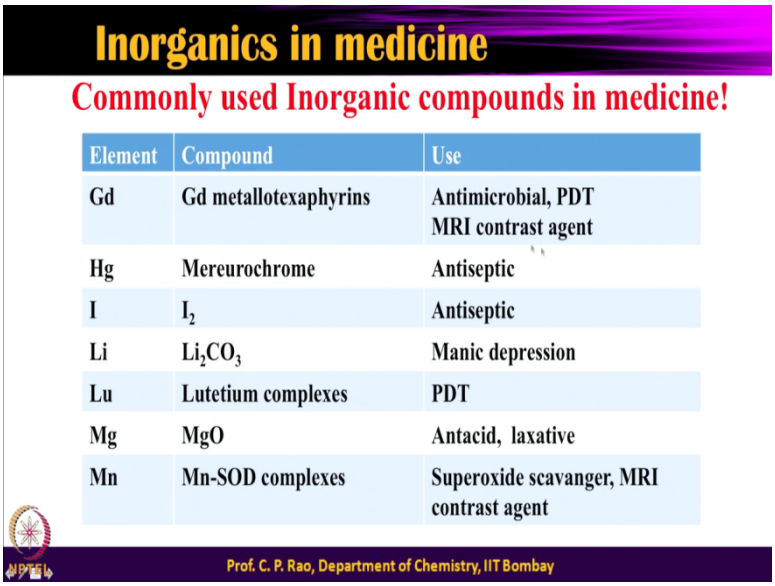

Gadolinium, gadolinium complexes are very good MRI contrast agents, and some of them may also be used in the PDT antimicrobial etcetera. So, mercury, mercurochrome antiseptic and as iodine we all know that iodine tincture, iodine we called as use that for as antiseptic. Lithium component from manic depression. Lutetium complexes a the photodynamic therapy PDT means, photodynamic therapy.

Magnesium as magnesium oxide, magnesium hydroxide kind of things not necessarily oxider, these are antacid laxatives also they give certain times, when you complain that you have a problem from motion, then the doctor will recommend you to take the laxatives. Manganese supplements, manganese complexes these can be as a antioxidant. And manganese can also be used as a as a MRI.

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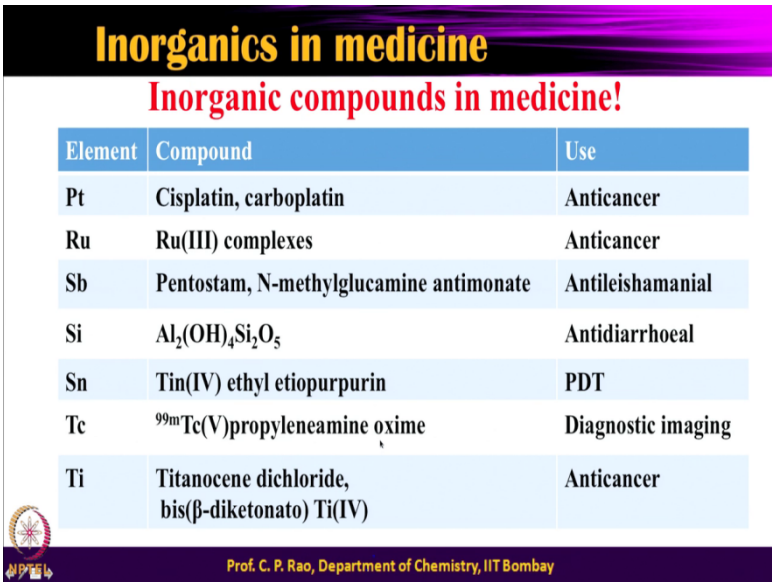

Still we have many more compounds for example, platinum. So, the platinum complex, which is a popular platinum complex, it is a cisplatin, everyone knows as an anticancer agent. Ruthenium complexes a lot of things, I will show you later these complexes too their anticancer.

Antimony ok, so N-methylglucamine antimonate, antileishamanial kind of activities. Aluminium silicon, aluminum silicates, antidiarrhoeal. And tin tin ethyl etiopurpurin is a photodynamic. Technetium, technetium again has a half life kind of things. So, therefore, that is also used for tracking, diagnosing, imaging ok. Titanium, titanium dichloride anticancer, these are proven and, but not used. Not all of them have been commercially used, some of them are well proven, but many of them are well used also.

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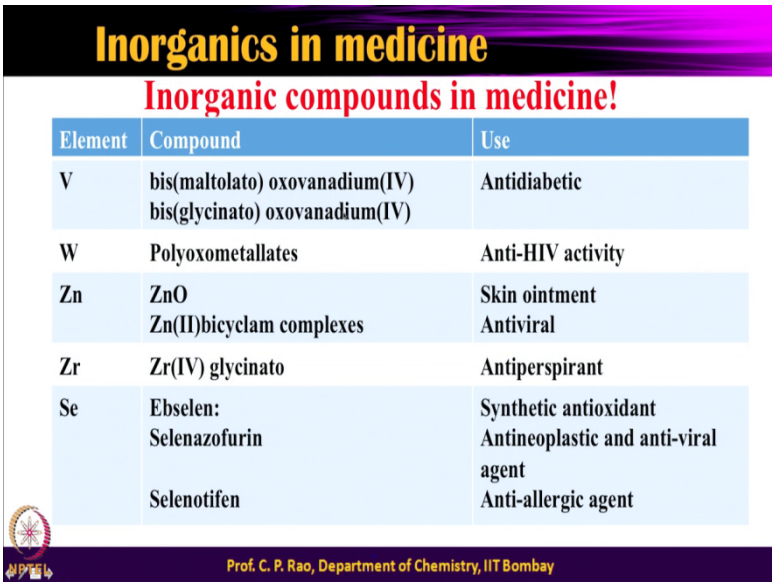

Vanadium, so you have some maltolato oxovanadium, glycinato oxovanadium these have shown antidiabetic activity, but not been continuously used. Then the polyoxometallates anti-HIV activity. Zinc oxide, zinc bicyclam complexes they are all, like skin ointment, antiviral etcetera. Jin zir zirconium the glycinato, antiperspirant. Selenium we have seen recently that the ebselen is the commercial kind of thing, selenazofurin, selenotifen, what are these is an antioxidant. So, therefore, antioxidant antidotes; so anti-viral anti-allergic thing that use [vocalized- noise].

So, we have seen a number of cases you see from here, this these are all given alphabetical order, silver, aluminum, arsenic, gold, bismuth, barium, bromine, chromium, copper, cobalt, ion, gadolinium, mercury, iodine, lithium, lutetium, magnesium, manganese, platinum, ruthenium, antimony, silicon, tin, technician, and titanium, vanadium or tungsten, zinc, zirconium, selenium every one of these. Now, you can you appreciate that, that a number of inorganic element based salts, complexes, compounds, they are involved in variety of as drugs in variety of diseases.

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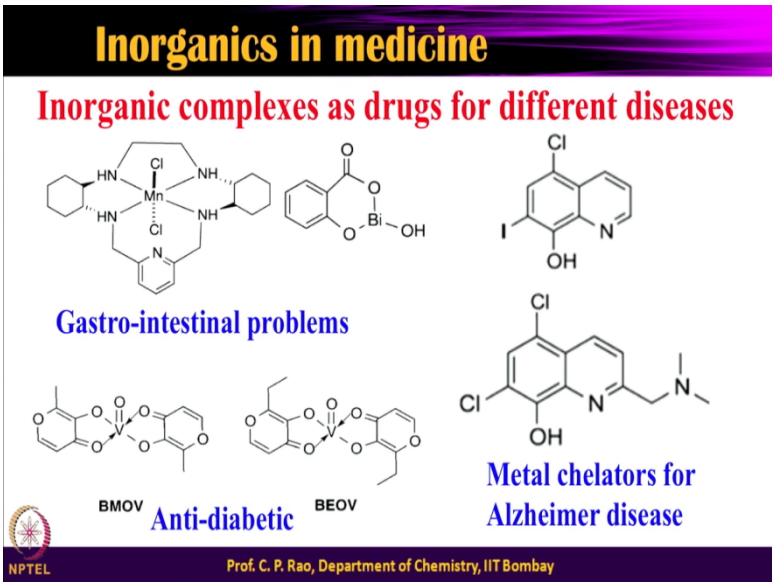

Now, let us look at some of the structures of these ones. Now, in this slide I have tried to show some compounds of inorganic complexes as drugs for different diseases. One of the thing here, you see is the gastro-intestinal problems. It is very common gat gastro-intestinal. So, this is one is the manganese, and this is what dichloride, so manganese 2, and this is a the kind of a cyclum type complex, covered, this is a kind ofa it is a cyclic ligand with the manganese.

Here you have gastro-intestinal, bismuth hydroxide, but bismuth hydroxide is coupled with this kind of a chelate. So, that you have only one hydroxy group. So, these are used in the gastro-intestinal problems. Vanadium you can see that this compound here, and the other compound a here, with some difference this is the methyl part; this is the ethyl part. Only the difference is that methyl ethyl derivative, these are used as anti-diabetic compounds.

See some things here. So, what do you see here, there is a nitrogen, there is a hydroxyl 1, 2, 3, 4. If you have a metal, it will become five membered. So, these can act like a chelate, and here again five member chelate. So, you have a metal chelaters for chelating some ions, ions like a zinc, ions like copper etcetera that is why they can act in alzheimer disease, because in the alzheimer disease the active ions or zinc and copper. So, these two these ions can be chelated and removed kind of things.

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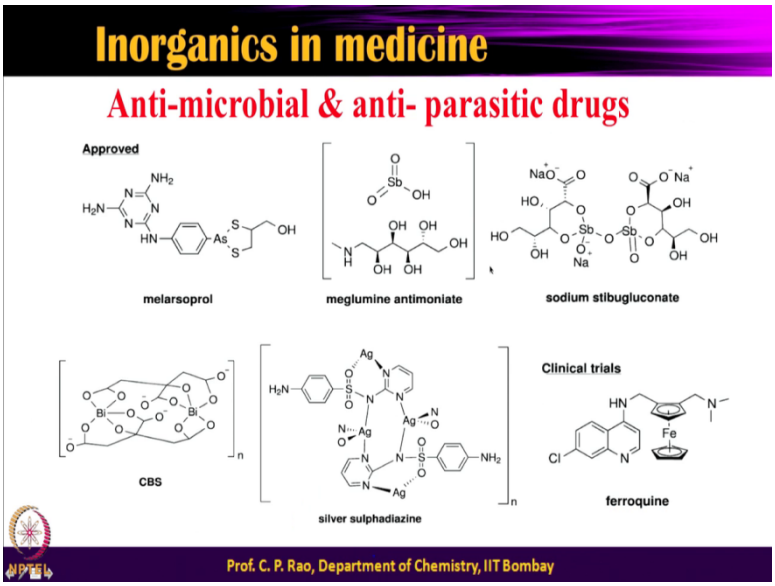

Let us look at some more ok, here we have some things like anti-microbial anti-parasitic drugs. So, this is the melar melarsoprol. So, where you have, what do you have arsenic, and it is a kind of a dithiol bridge binding chelation ok. And this is argono arsenic, argono arsenic kind of a compound with thiol. So, argono arsenic thiol based compound, this is what is called melaras melarsoprol ok.

And here you have another compound, which is antimony based. So, this meglumine anti antimono by monolate antimon antimonlate. So, this is the antimonic part, and this is the a other organic part, which is bound together will form a drug, a complex, complex for the drug, so for the anti-microbial etcetera. Here is another case, where sodium stilbu this stibium stibuglucose. This part is a glucose, this part is a antimony, which is called stibuate and sodium, and this is also is there as a anti-microbial kind of thing.

Now, you have some more compounds here, bismuth based compounds, silver based compounds, and iron based compounds. This is basically what you see here, ferrocin. So, ferrocin based compounds with some additional quinoline moiety kind of a thing additional quinoline kind of moiety this is. So, these some of these are in clinical trials. So, these are used anti-microbial, anti-parasitic some of them too. So, do appreciate and understand, how varied the inorganic medicinal aspects are ok.

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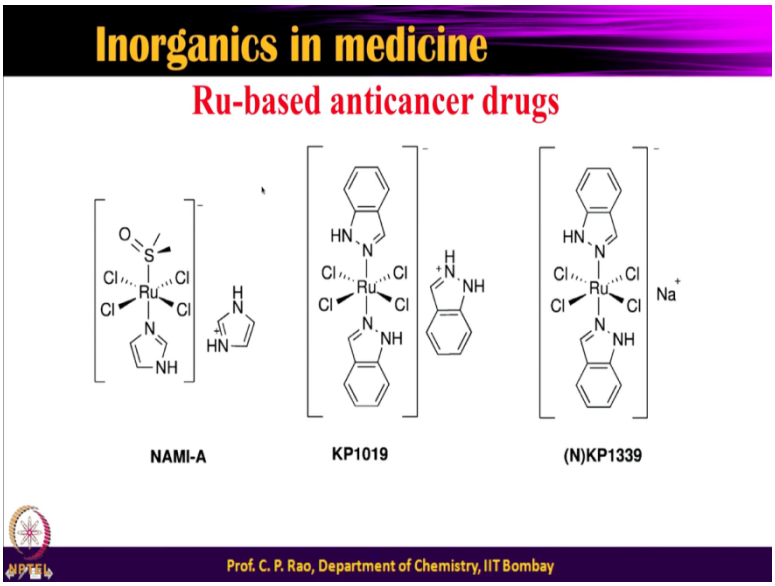

Then let us look at some anticancer activity, drugs there are a lot on the platinum, I will come to that in a while. Let us look at before going to platinum ruthenium based. Now, these are not much into the market, but they are shown at the laboratory level not at the at the at the commercial kind of a level, so these are all ruthenium based you see that. Ruthenium based, ahso kind of an anion, so you have a counter cation imidazolium ruthenium 3, 4 chlorides etcetera etcetera. Again instead of imidazolium, benzimidazolium kind of a thing, ben diazole kind of thing cation or you can have sodium. So, this two are same, but the counter cation is different, and this itself is different.

So, you have different kinds of anticancer base based agents, which are shown to have a good potential anticancer activity. Though they have not taken up to the level to bring it as a drug into the market, some of them may be going to the trials ok.

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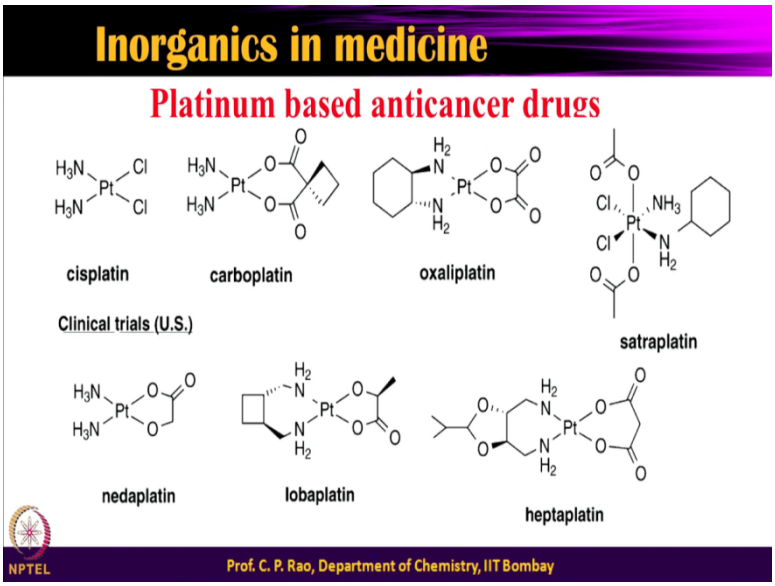

Come to the major class of the anticancer drugs we know very well, very well used in most of the countries still under use in some countries too, and the platinum based drugs. So, cisplatin and carboplatin and oxaliplatin and satraplatin and nedaplatin and lobaplatin and heptaplatin you see that all of them. So, they all have they either the di ammonia or diamine, see diamine kind of apart diamine part, diamine part, diamine part, and this is a different compound, and this is a platinum four based one ok.

So, all others are platinum 2 based compounds, so this is 2 minus. So, therefore, 0 2 minus 02 minus is 0, so all of these (Refer Time: 16:24) nitrogen against being neutral. So, in fact, this is platinum has been very well used even carboplatin has also been used in many of the cases too, so therefore, you can see that a large. Of course, nowadays people have started using the platinum 4, so that they in C 2, it will be reduced to platinum 2, and then the further release are the things. And then also add some adjuvants to arrest these side reactions. So, in order to arrest the side reactions then people have started using adjuvants also binding to them ok.

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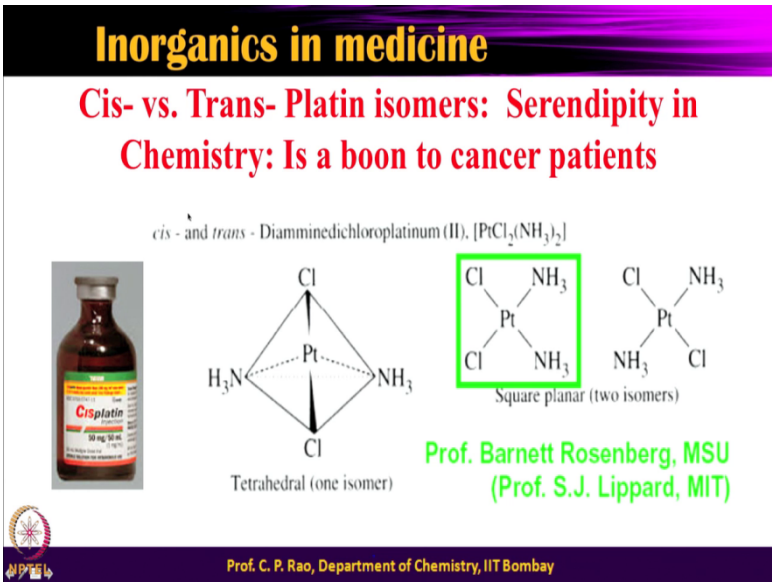

We know the cisplatin, this is the cisplatin and we know there is structural analog to this is called the transplatin, so these are the transcripts. So, it is a composition is exactly the same. So, one would expect that if the cisplatin works for cancer, transplatin should also work, but it is not true only cisplatin works, and transplatin does not work. So, so it is not that simple ok, and this is cisplatin itself is a boon to cancer patients. Invention of this as you know, initially it was a surrender pitous the exploration, when electrochemical work being conducted by barnett rosenberg, he could recognize there are certain kinds of a things are developed at the center at the platinum center, and then finally, found the compound being the platinum diaminedichloro thing.

And, so that is where, that is how, this has come and later on certain developments were made in lippards group at MIT as well ok. So, it is only the cisplatin, which works not there. So, this means the it is not only just the inorganic compound, it is geometry, it is coordination properties, it is redox properties all of these are important. In this case, it is a geometry, which is important. Splattering is shown over there ok.

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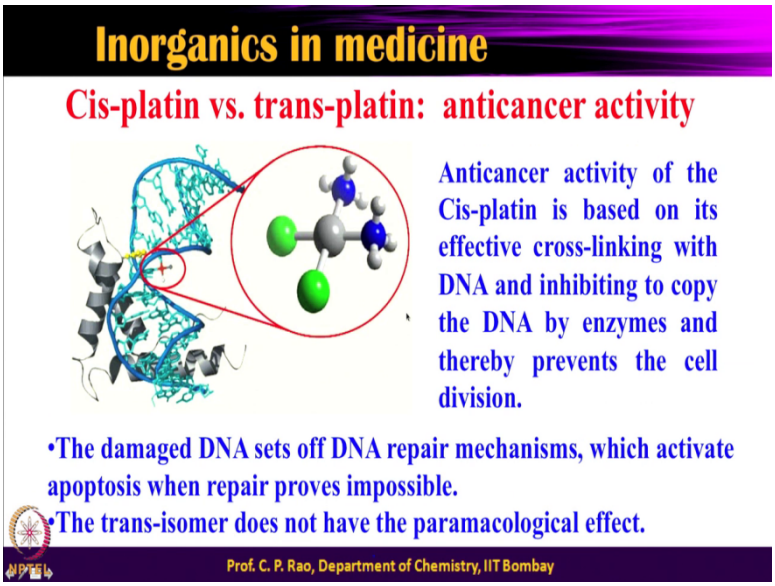

Now, how does it do? Cis-platin, cis-platin has got this the two chlorides here, and these two chlorides get ionized in the bloodstream in the cell, and converted by water ligands. And this is being a attacked at the guanine rich region, where the N 7 of the guanine will bind, N 7 of another granny will bind here, displacing the two water molecules prior to that chlorides. And why not (Refer Time: 19:08) trans? Trans cannot form intra strand, it can form inter strand, because there are two chlorides, and boosters, but the thing is that it is not the not the reason that it cannot bind like this, it can bind inter DNA cross trans. But the inter DNA cross trans can be repaired very easily by the repair enzymes. Whereas, the intra cross strand this one, which is formed by the cis-platin cannot be easily repairable.

It is the main reason is this one, the repair enzymes are not functional, in one case the repair enzymes are functional in the trans-platin case. Therefore, trans-platin is not effective cis-platin is effective. Not the trans-platin cannot make a complex with DNA, trans-platin can also make a complex with DNA, just like this cis-platin can make, but a different type of complex, and that that different type of complex can be easily repaired, whereas, the cis-platin cannot be repaired. And that is what I have explained over there, so you can look in to that ok. So, a what will what are we trying to look at, we are trying to look at how does this function.

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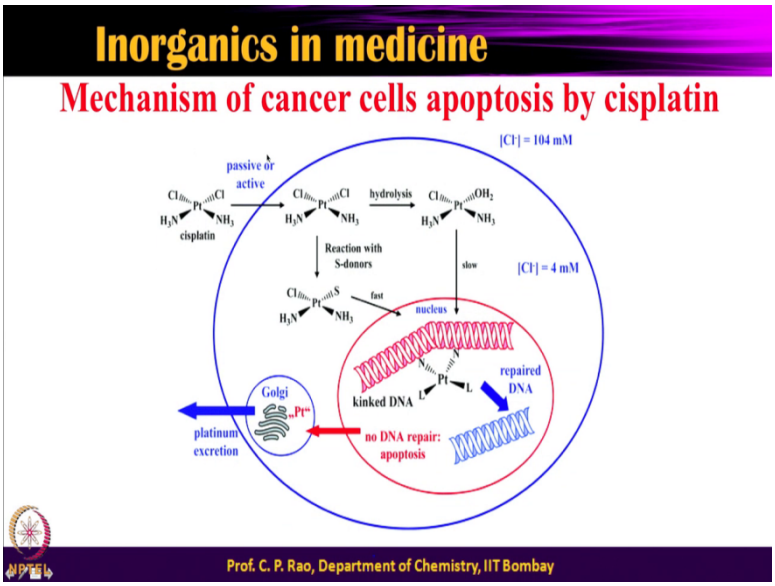

Let us look at some features of the mechanism of the cancer cell apoptosis. Apoptosis is cell, program, death, program death of the cells. And I will come into details in one of the lecturefully, I will take on the aspects of apoptosis, how what kind of inorganic complexes are involved in apoptosis of cancer cells. So, I will take in a future classes one or two classes on that covering on that too, at least one class covering that kind of a phenomena, and what kind of compounds in the future.

Now, for the time being let us look at the mechanism of action of thiscisplatin, already mentioned do cisplatin bind to the DNA in an intra stand fashion whereas, transplatin intra strand fashion. There are always repair enzymes, the repair enzymes can definitely repair the transplatin apoptosis, but nor the cisplatin apoptosis. Now, let us take this is platinum enters in, it will the dichloro part will get hydrolyzed to one chloro with one water both the waters etcetera. And this can further or you can have some other kind of a donors, one chloride, one donor this getting into the DNA, and forms a ahthe kind of a bond you see here, so bond here ok.

So, this is the kind of things that you have of the these ones, and these are coming from the from the guanine nitrogen to bind to this. So, if they are bond, a intra type and then this will be taken by gogly, and the platinum is extruded. So, repair enzymes can act, but repair enzymes cannot act on a cisplatin, but repair enzymes can act on a transplatin, as I said earlier, it is this kind of a thing, which is a basically making a difference.

Now, can you understand the cisplatin versus transplatin in composition is same just geometry. In one case the chloride searches or amine searches or in the other case the chloride or ammonia or trans. So, that is what we are looking at. So, trans will form in trans like inter strand products, and this will make inter strand products. And the enzyme can the repair the inter strand products, but not intra strand product. So, what does this tell basically, so just one example that I have explained you, and we will see their process may be some more examples in the in the future classes.

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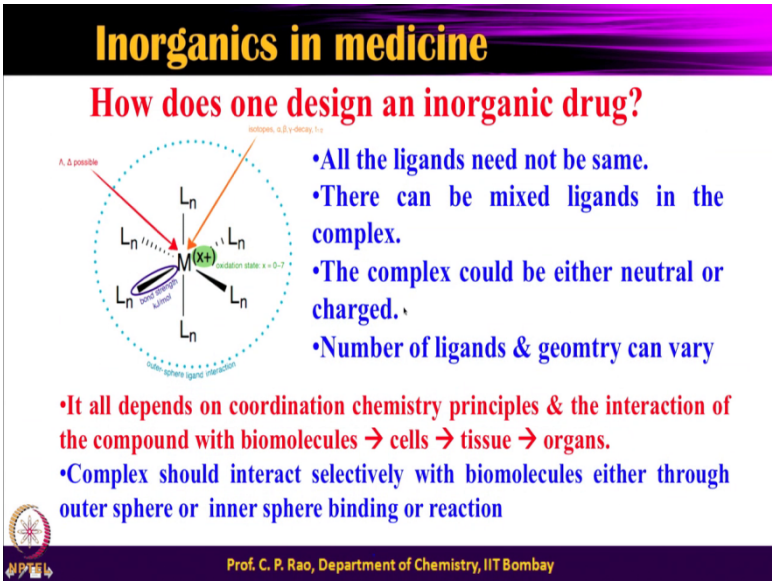

And let us look at overall, how does one design and inorganic drug. So, to design in an organic drug, you choose a metal ion you choose an oxidation state, you choose a coordinating ligands, you chese choose a coordinating coordination geometry many of these things. So, it is does not mean that all the ligands have to be same since I have put as L n L n, please do not take that all these are the same ligands, it can be same ligands, it can be different ligands, or it can be two, three different ligands etcetera, all of these are possible. It need not be acta octahedral, it can be tetrahedral, it can be stapler, it can be linear, it can be trigonal bipyramidal, any kind of geometry and number of ligands accordingly, so there is no fixed like that.

So, that means, you have a plethora of possibilities of an of in organic complex can be made. So, when you make such complexes, you also have parallely there isomerism playing your own, could be structural isomerism, geometrical isomerism, the optical isomerism. Various

kinds of isomerism is also there, so some of these isomers may not be active, some of the isomers may be active, just like we have seen the example of cisplatin is active, transfer active is not active.

So, that means, you one once you plan a design you make a lot of complexes. These complexes can be checked with the further activity, some of them bind, some of them may not bind, some of them will bind and react, some of them may not bind may bind, but not react, all of these things are possible. So, it is all depends on the basically, and the coordination chemistry principles. Coordination chemistry principles are what? Coordination, coordinating ligands, they are number the type, nature, chelation, non chelation.

So, the cy macro cyclic effect, chelate effect, all these kinds of things. Then geometries the 2, 3, 4, 5, 6and mostly 5 4, 5 and 6 are very common for transition metal, occasionally could be 7 and sometimes you can have 2 and 3 also. So, all of these, so many things that you have.

So, there is a huge level of inorganic chemistry design as possible, and so many different metal ions are there, so many different oxidation states are there. So, it is as wide as the organic drugs, where the people do deratization on the on the aromatic rings. The deratization using nitrogen ligands, phosphorous ligands, sulfur ligands, oxygen ligands etcetera. Similarly, you can complex with a various kinds of ligands. And ligands can also be active maybe you can use the non-active ligands, active ligands all of these as possible.

Thus you can have a plethora of inorganic complexes, we cannot call all of them as drugs. Only those, which show activity and some enzymes, on some cells, on some tissues, and some organs etcetera. So, those things we can call it as a drugs, and all of the things are simple the inorganic compounds, inorganic complexes. So, then this complex or compound a drug, what you say, should interact selectively with some biomolecules not every, that means, with some enzymes, but not be the every enzyme if we take, because if it binds to every enzyme, unwanted things happen, this is what we refer in the medical thing as a side effects.

So, there are large number of drugs, which are very good, very effective on the disease, but they are bad, because they show lot of side effects. That is why, always there is the design, new design, new improvement or the inorganic complexes, inorganic drugs keeps on, going on. In order to reduce the side effect, in order to increase the potency a potential, in order to increase the selectivity. So, that it will not attack all the molecules, all the kinds of cells in the

body, but they will attack selectively only certain molecules, and certain ions, certain molecules and certain cells etcetera.

So, the complex should interact selectively with biomolecules either through outer sphere or through inner sphere binding mechanism of all this. So, what have we looked at, so far we have looked at a very large number of a inorganic ions are important not only as the metalloenzymes, but as drugs. Their salts, their complexes, we have seen almost A to Z, they are involved in some activities, like antidiabetic, anticancer, antiarthritis, so antibacterial, antifungal or what not anti HIV all kinds of activities, so all these kinds of activities are shown by this.

So, therefore, there is a huge future for developing inorganic drugs based on their metal ion complexes, complexes can be neutral, complexes can be ionic, ligand need not be same, ligand can be same, ligand can be different, and geometries can be varying etcetera etcetera. So, therefore, a huge amount of inorganic chemistry things and as I said I will discuss the apoptosis program cell death in the future class.

Thank you very much.