Medicinal Chemistry
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Anti-Cancer Agents Part-2

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Welcome back, so in the previous lecture we spend quite a bit of time in looking at the various aspects of how cancers can develop and just to quickly recap there are various intricate mechanism by which growth and depth are actually regulated, so any of these processes can be in a state of imbalance which can result to the development of cancers, so we also looked at how you know there are two types of cancers one is the (())(00:45) cancers which are very local and those are fairly easy to cure or not that difficult to cure and the other one is the Malignant Cancer which actually do what is known as metastasis.

So we looked at various mechanisms by which metastasis can occur and how they evade the immune system or recognition systems that we have in our body and they can actually go to another part of the body to spread also these are the cancers that are more difficult to cure and can be fatal.

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Now we will look through some of the major strategies that are used to tackle cancer, a number of these strategies we have already discussed previously in the course, so I am not going to repeat the details, so the first major class of drugs that act on cancers are the ones that act on nucleic acids and so we have already looked at previously that there are agents known as intercalating agents which actually go and stack between DNA base pairs and these can sleep into the double helix and distort the structure.

So one of the examples that we have looked at of this Anthracycline best molecules including Doxorubicin, Daunorubicin and so on, so once this goes intercalates then the enzymes that are involved in the replication process and transcription process are actually inhibited.

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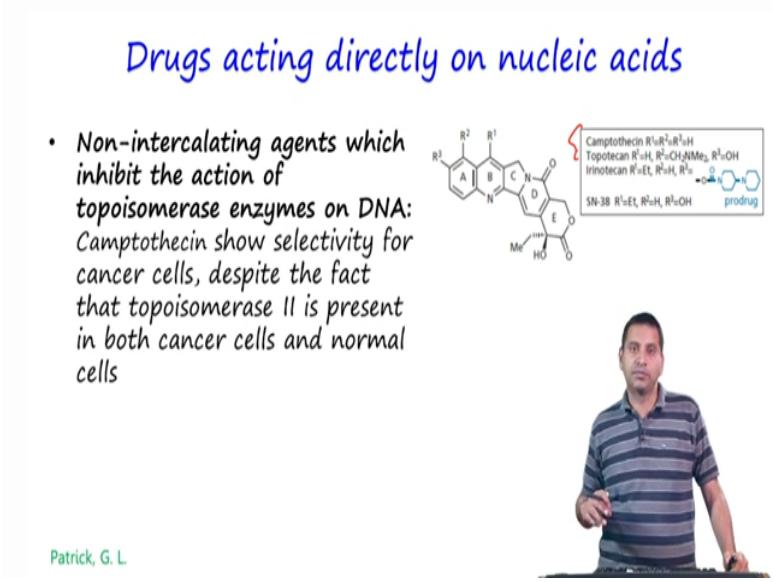

There are other agents which can act on directly on nucleic acids which are known as Non-intercalating agents, so the example that we have looked at was Camptothecin and so these are actually sort of poisons, so they act an on Topoisomerase 2 which is which an inhibited, ok. And this can of course happen in the case of both normal cells as well as cancer cells.

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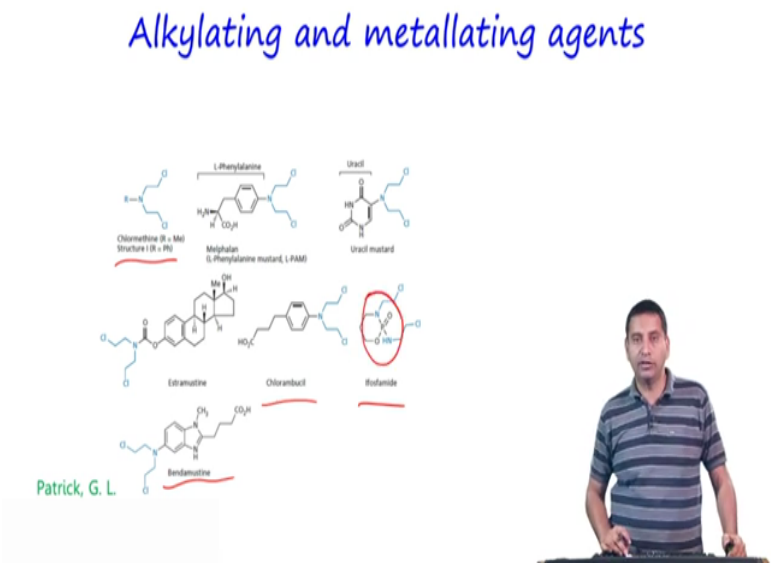

So we have also looked at a number of DNA Alkylating agents and we have looked in detail some of the mechanisms by which these act and so there are examples of these mustards which act an on DNA by cross linking it and so here are the various classes of these drugs that are used, ok. So you can also have Prodrug concept which we have looked at previously.

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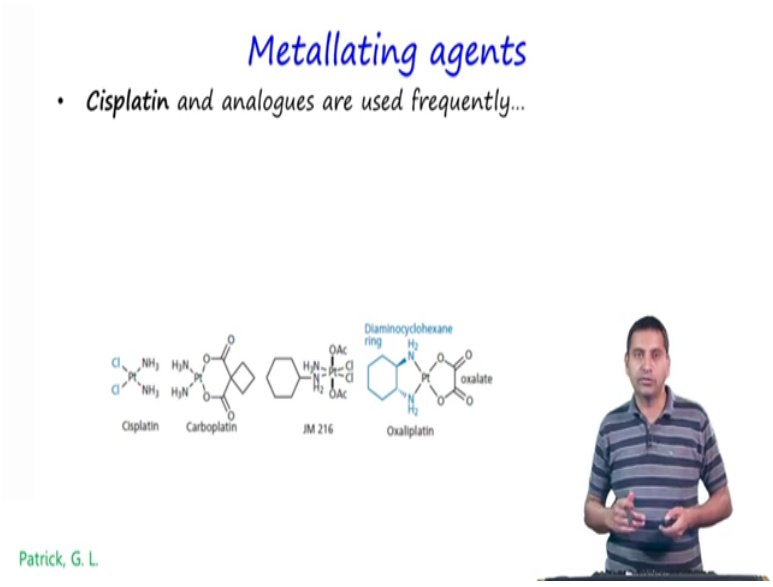

There also DNA Intercalating agents such as Cisplatin and the improved versions of Carboplatin and Oxaliplatin and these are very frequently used in the treatment of several cancers.

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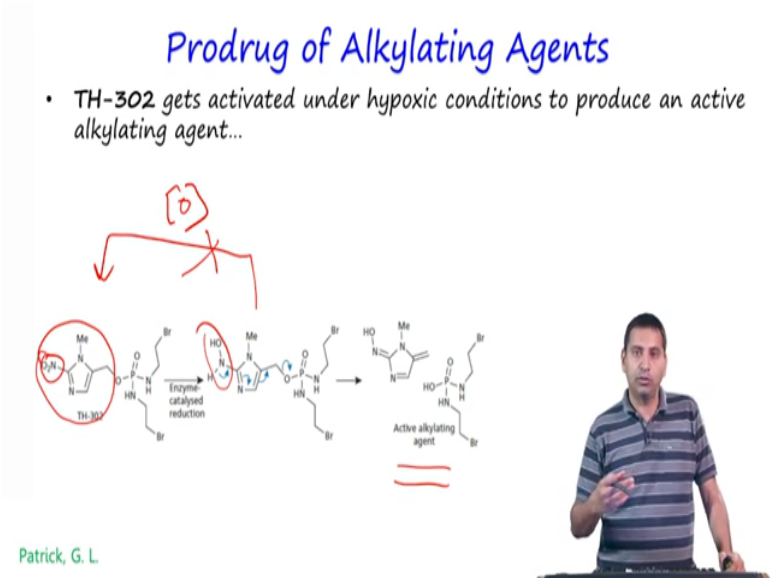

Now you can also have a Prodrug of Alkylating agents, so we have looked at previously one example but here we should look at another example which is TH-302 and as we discussed in the previous lectures there is a the centre of tumors or there are say region of tumors which have low oxygen tension and this is due to the you know random blood vessel generation or the unregulated blood vessel generation which leads to areas where there is less blood supply as a result there is a less oxygen tension and so what we could do is we could exploit the low oxygen tension to develop Prodrugs.

So here is an example of this molecule which is a Nitroimidazole structure here in the (pre) in the case of TH-302 and there are number of enzymes which act to reduce these nitro groups under hypoxic conditions this reduction of nitro group is actually promoted. Normally this kind of process would be reversible so in the presence of oxygen you would this would undergo oxidation and give you back the original molecule however under hypoxic conditions this process is slow or does not occur.

So once an electron withdrawing group as a nitro group is now converted to a fairly electron donating group this lone pair of molecules can then push you can push arrows to kick out the active Alkylating agent. So this is one strategy that is been used to selectively deliver an Alkylating agent to Hypoxic cells.

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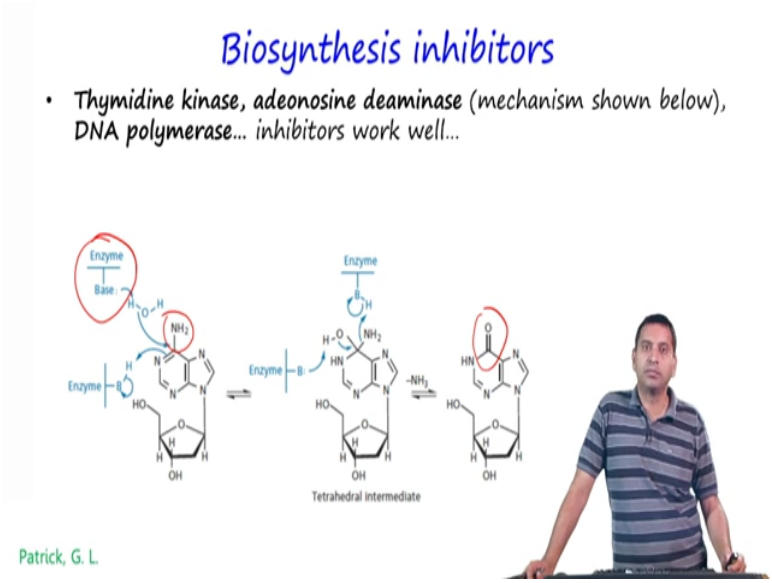

The other major mechanism by which we can target cancers is to inhibit Biosynthesis, so we have already looked that this cases previously so I will not spend much time but one could I think of inhibiting Thymidine kinase and here below is an example of Adenosine deaminase which is very important. So here the there is a the enzyme picks up H plus from a water molecule activating it which can then attack on this carbon here and subsequent rearrangement kicks out ammonia and gives you this amine over here, ok.

So based on this mechanism one can develop new inhibitors and there are also DNA polymerase inhibitors and these inhibitors works generally work quite well.

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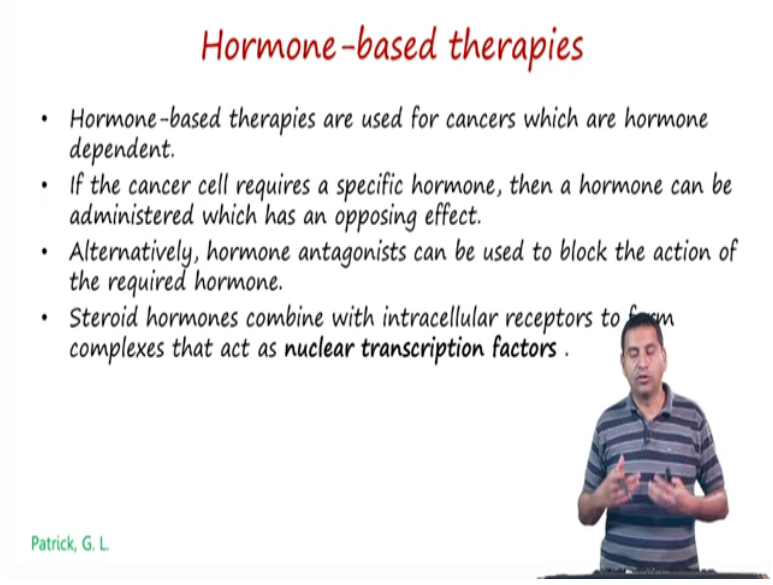

There are another major class of therapies that are used which are known as Hormone-based therapies, so here there are many cancers which dependent on hormones, ok so these hormones again they can help in stimulating growth and therefore if the cancer is dependent on the hormone one could use this mechanism to inhibited. So what we could do is then we could give a hormone which has an opposing effect that is it separates the growth of the tumor.

Alternatively the hormone antagonist can be used to block the action of the required hormone, so these Steroid hormones which then combine with the intracellular receptors to form complexes known as nuclear transcription factors. So by inhibiting this we would be able to reduce the growth of the tumor.

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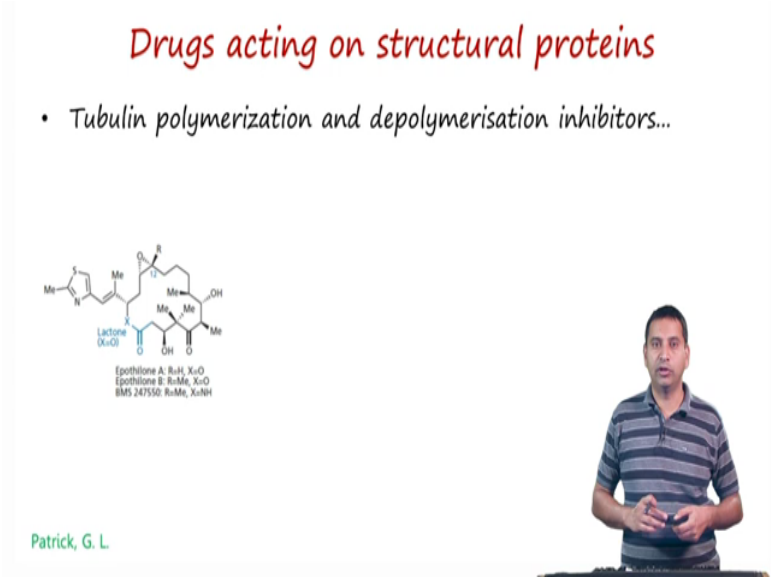

There are large class of drugs which act on structural proteins, so again this is something that we have discussed previously there are ways in which you can actually inhibit Tubulin polymerization or you can also inhibit depolymerisation, ok. So here is a structure of Epothilone that is depolymerisation inhibitor.

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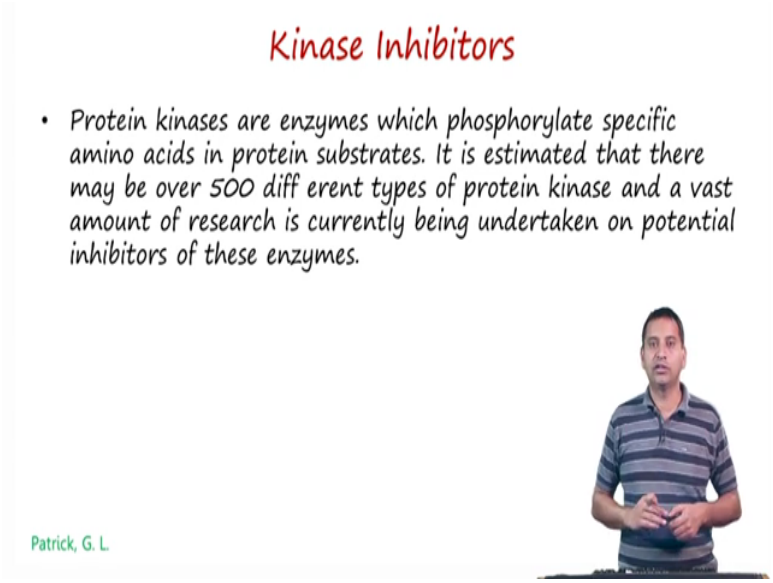

You could also have Kinase inhibitors as we discussed in detail number of the signaling processes are actually mediated by Kinases and these phosphorylate very specific amino acids in protein substrates, there are estimates which say that there are more than 500 different types of protein Kinases and a large amount of work is actually being done to study as well as inhibit these enzymes.

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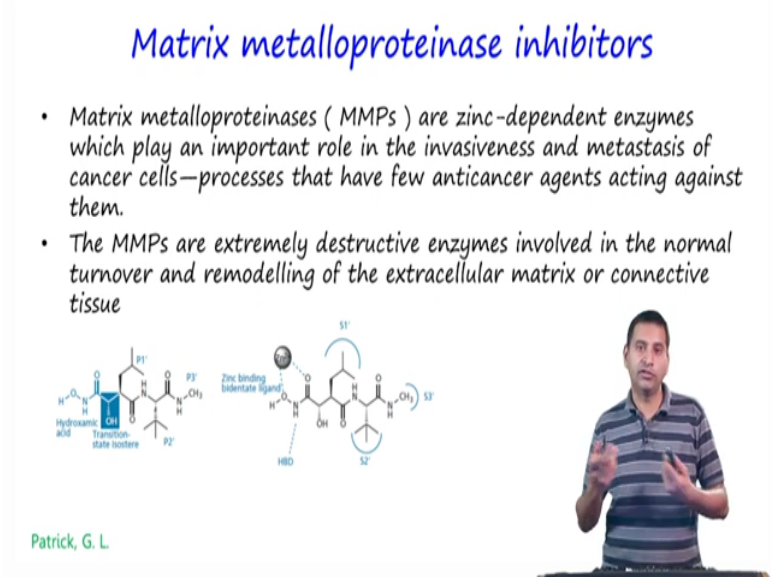

We discussed in some detail about these enzymes are known as Matrix metalloproteinase, so these are the ones that are go into help with metastasis and angiogenesis because they are going to help dissolve the matrix around the cancers and these are cysteine proteases and they

also contain you know they contain a they zinc dependent enzymes and there are few anti cancers agents that are available that act against them.

So these MMPs are extremely destructive enzymes and they are involved in the normal turn over and remodeling of the extracellular matrix and connective tissue. So one could inhibited this is one way to develop to prevent the cancer from growing.

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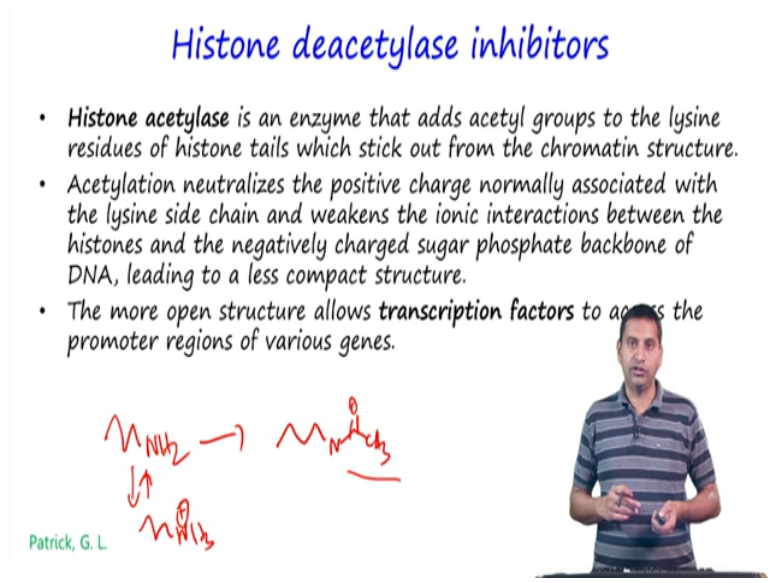

There is another class of enzymes which are known as Histone deacetylases, so Histone acetylase is an enzyme that adds in acetyl group to lysine residues, so you have a lysine residue to which it can from an acetyl it can add as an acetyl group, ok. So these histone tails actually stick out from the chromatin structure, so acetylation neutralizes the positive charge that would be normally associated with the lysine side chain.

So these would be an in equilibrium with the plus however by acetylating it what we have done is we have made the molecule neutral. So therefore this leads to a change in the DNA structure in terms of the in the packing and it weakens the ionic interaction between the histones and the negatively charged sugar phosphate backbone and this leads to what is known as a less compact structure, so the more open structure allows for transcription factors to access the promoter region of the various genes.

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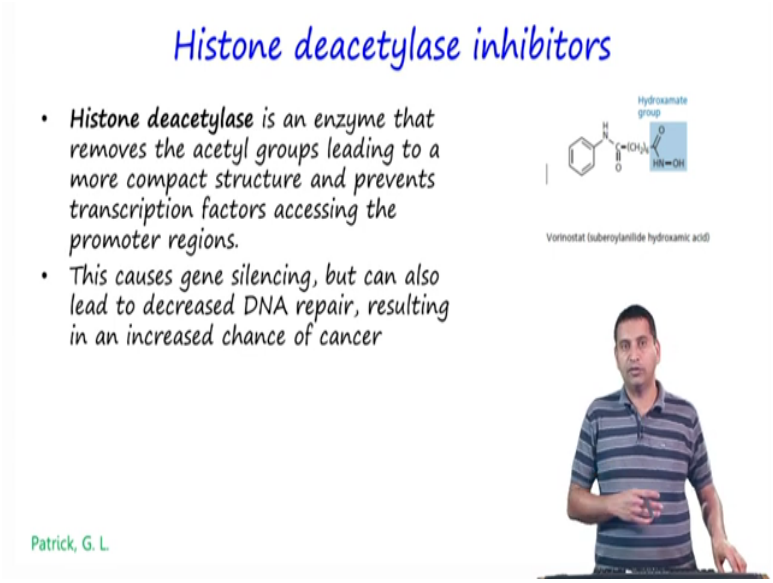

So histone deacetylase so the other hand is an enzyme that removes the acetyl group, so this leads to more compacting of the structure and prevents the transcription factors from accessing the promoter regions. So this process causes gene silencing and also can lead to decrease DNA repair resulting in a increase chance of cancer. So histone deacetylase inhibitors are something that can be used to effectively target cancers.