Medicinal Chemistry
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Nucleic Acids as Drug Targets Part-2

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Welcome back. We have been looking at so far various targets for drugs inside the cell. So we looked at you know enzymes as possible targets and subsequently we have looked at receptors which are on the cell surface primarily as targets and in the last lecture we looked at the possibility of DNA and RNA as drug targets. So today we will continue with this topic and look at various ways in which drugs can interact with nucleic acids.

So we looked at for example, how intercalators work in the process of they go inside and they bind between the two base pairs and so that is one possible mechanism. So in continuation with that we also looked at various other ways in which DNA can be damaged through the generation of reactive oxygen species and so a drug can bind either to DNA or to DNA enzyme complex and so on and so forth. We also looked at how DNA alkylating agents work and how alkylation is a very important way in which DNA nucleic acids can be targeted.

So now today we will continue with this topic and also look at some other drug targets inside the cell other than enzymes, receptors and nucleic acids.

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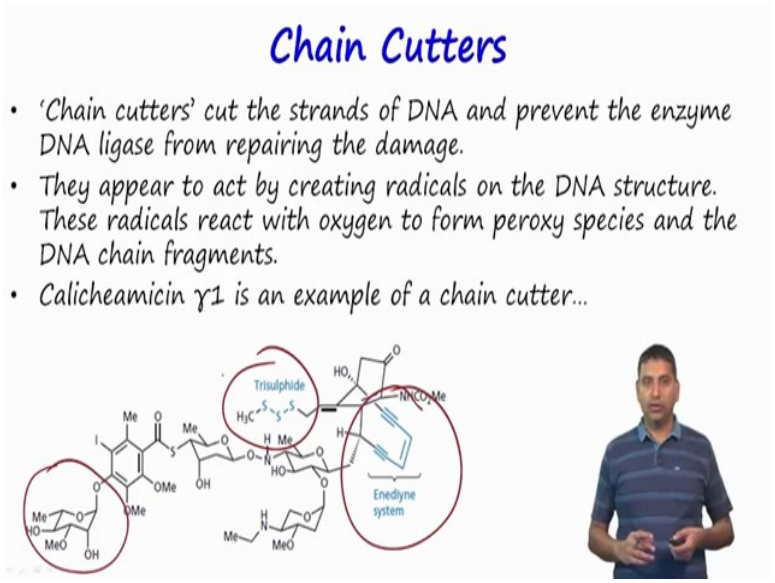

So the first concept that we will look at today is called chain cutters. So these are small molecules which can go and bind to DNA and they literally cut the chain of or cut the strand of DNA and this is done by preventing the enzyme DNA ligase from repairing the damage. So once DNA is damaged there are endogenous mechanisms or cellular mechanisms which are useful for repair and so if you inhibit this repair mechanism you will achieve the same target of damaging DNA.

So one of the ways in which they work is by creating radicals on the DNA structure and as we looked at earlier these radicals can react with oxygen to form peroxy species and so on and so forth and this can basically break down the DNA. So here is an example of a chain cutter, where you can see that it has got a very large structure and it has got a number of components in the structure it has got a sugar unit and it has got this very unique enediyne system and an important trisulphide pendent group, okay.

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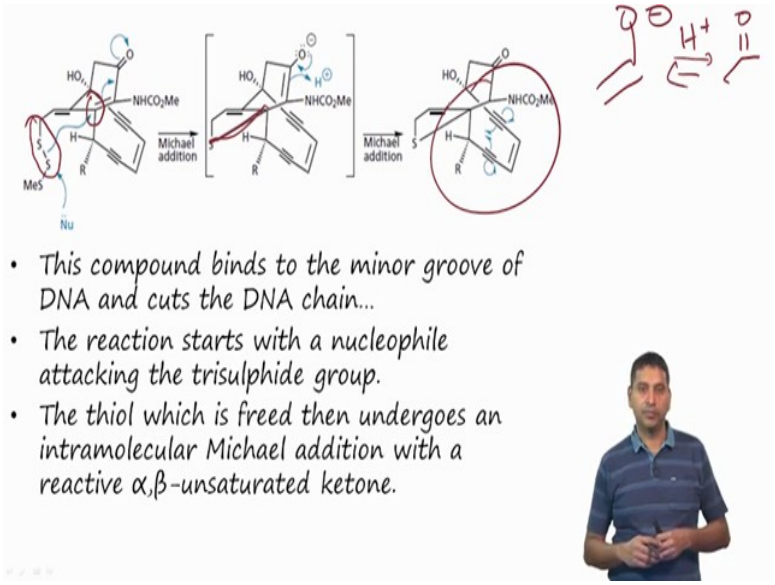

So we will now look at how this compound works and so the mechanism that is proposed is that since disulphides are known to be targets for nucleophiles, so they can react with the nucleophile and they free up this thiol sulphur over here which then can do can attack this carbon here which is actually a substrate for Michael reaction and so once it attacks this carbon it forms the covalent bond between sulphur and this carbon and it generates an enolate.

So an enolate as we know is nothing but this which can sort of tautomerize to form the ketone and this is achieved by adding H plus. So once it tautomerizes, it forms this fairly interesting molecule which then does what is known as a Bergman cyclization reaction, okay.

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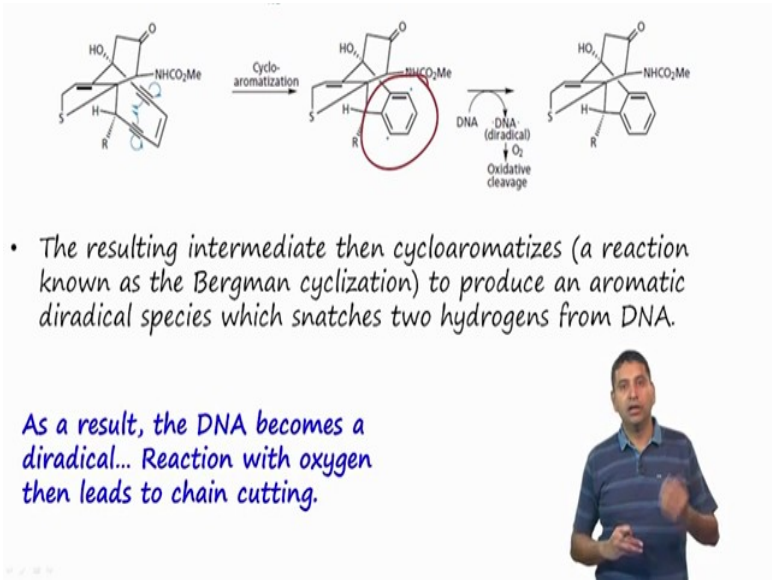

So Bergman cyclization reaction is nothing but what happens is that it undergoes rearrangement as shown here and it forms a diradical on a benzene ring, okay and so this diradical intermediate is quite reactive and then it can so do transfer a radical or react with DNA to produce a DNA diradical and that subsequently can react with oxygen to produce oxidative damage.

So at this point the reaction becomes quite nonspecific because you are generating a highly reactive species. So the objective of this or the way in which this compound works is that it produces a highly reactive radical species which can then cause oxidative damage. So this is a very interesting mechanism because Bergman cyclization is not very common reaction which happens in biology, but here is an example of that.

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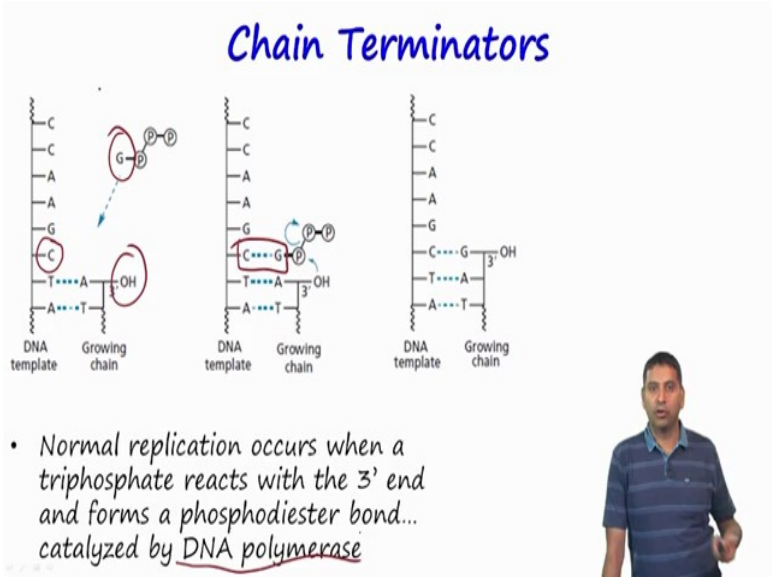

The next methodology by which one can target nucleic acids is to inhibit the growing chain of DNA. So here is what we have looked at previously which is a normal replication process. So in the normal replication process so you have nucleobase cytosine here for example and that is binds to the complementary nucleobase which is guanine and once it reacts with guanosine it produces a very strong hydrogen bonded intermediate and now since the growing chain is the 3 prime end of the growing chain is positioned in a manner such that the attack can happen, kick out di phosphate and chain elongates and this is we have already looked at is catalysed by the enzyme DNA polymerase. So if you want to inhibit this process we can think about a number of ways to do it.

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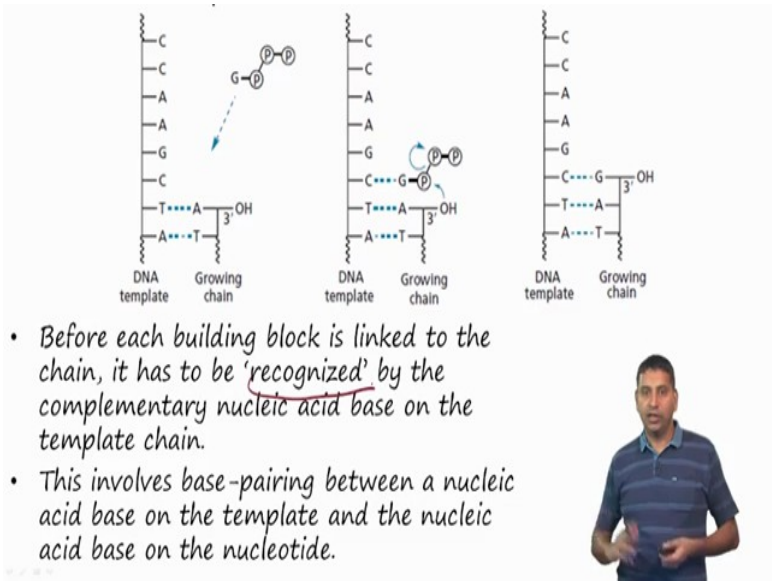

So one way to do it is that you can try and terminate the process before the link is made, so let us look at how that is done. So just to recap here before each building block is linked to the chain it has to be recognized by the complementary nucleic acid base and this base pairing forms the template for the growth of the chain. So this concept is very important in designing inhibitors.

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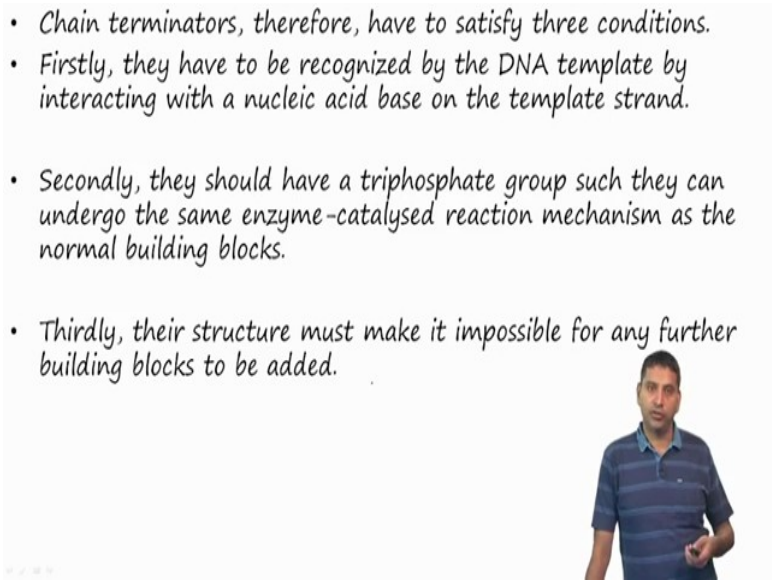

So what we do is that if we need to terminate this chain and for that we can come up with a set of three basically three conditions which need to be satisfied. Firstly, the inhibitor that we are or the chain terminator that we are designing should have should be recognized with the DNA template interacting with the nucleic acid base, so that means that when the chain

terminator comes in, it should be recognized by the complementary nucleobase and it should come and sit in the right area.

Secondly, they should have a triphosphate group otherwise what happens is that your reaction does not occur and therefore the termination may not happen and then thirdly, the structure should be such that it should not be possible for any further building blocks to be added, so all these three criteria have to be met with in order to design new chain terminators.

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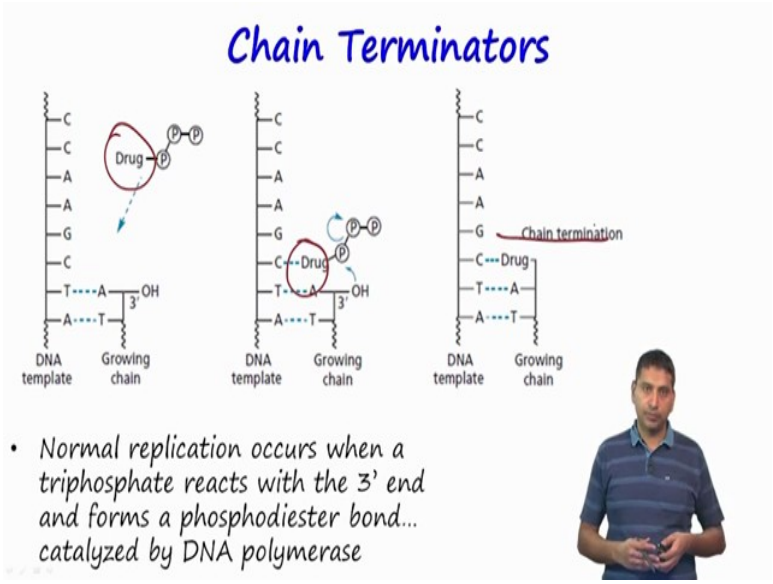

So the way we do this is that when normal replication occurs if we can figure out a way in which a drug comes and binds exactly to the same region that we are interested in and it carries out the reaction of 3 prime hydroxyl attacking the phosphate and kicking out this but after this point onwards there is no further growth so this is how we would inhibit the normal replication process.

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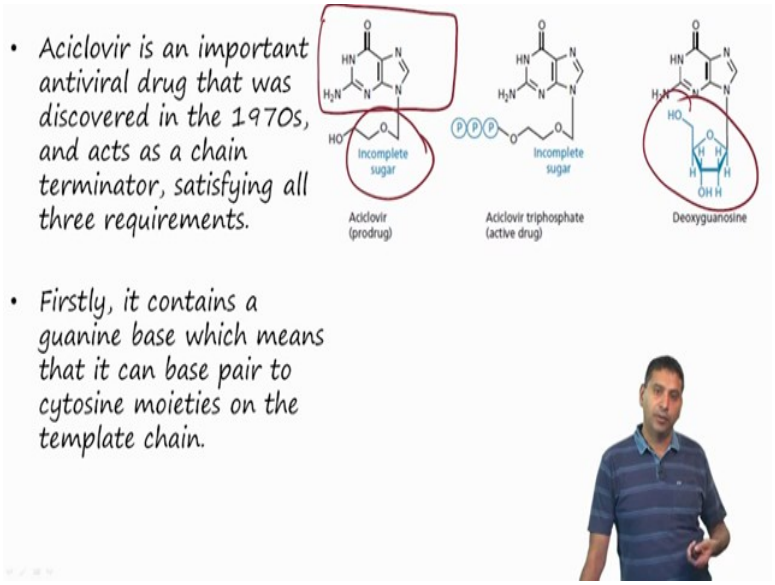

So an example of this is the antiviral drug whose structure is shown here, so this actually is a prodrug. We have already looked at what prodrugs are, prodrugs are compounds which get transformed inside the body or inside the cell to form the active drug, okay. So this prodrug as you can see here has an incomplete sugar, okay so once there is an incomplete sugar the first reaction happens because the recognition element for the hydrogen bonding comes from here, but the second after it recognizes it does not elongate or the chain does not you do not add another base because there is no (sugar) there is no hydroxyl group for it to react further.

So keep in mind we are looking at mimic of deoxyguanosine which is shown here. So therefore the guanine base to which it has to base pair is present and the cytosine is the complementary base pair there and once it recognizes it, it then sits on the correct place for the subsequent reaction to occur.

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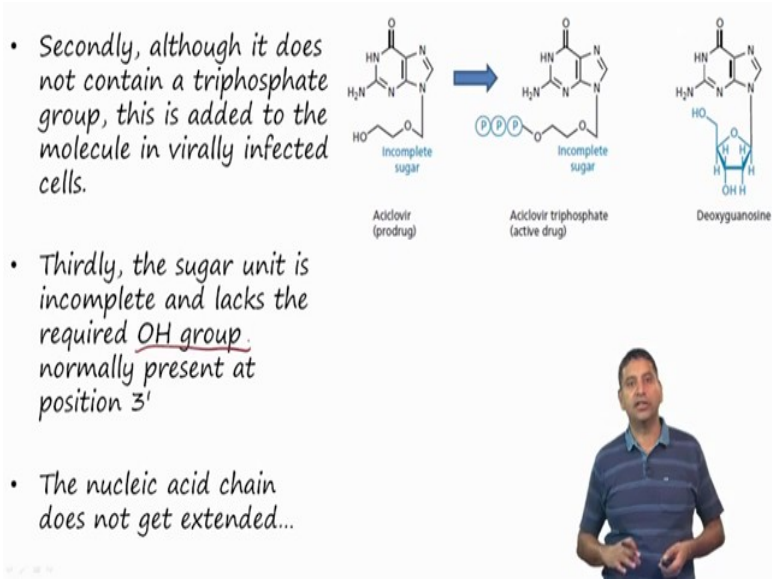

Secondly, although it does not contain a triphosphate it is added inside the infected cell so phosphorylation can occur inside the cell and the sugar unit is incomplete and so it lacks the required hydroxyl group for the next reaction to occur. So if this strategy works then the nucleic acid chain does not get extended.