Medicinal Chemistry
Professor Dr. Harinath Chakrapani
Department of Chemistry
Indian Institute of Science Education and Research, Pune
Tutorial 9
Nucleic Acids and Related Topics

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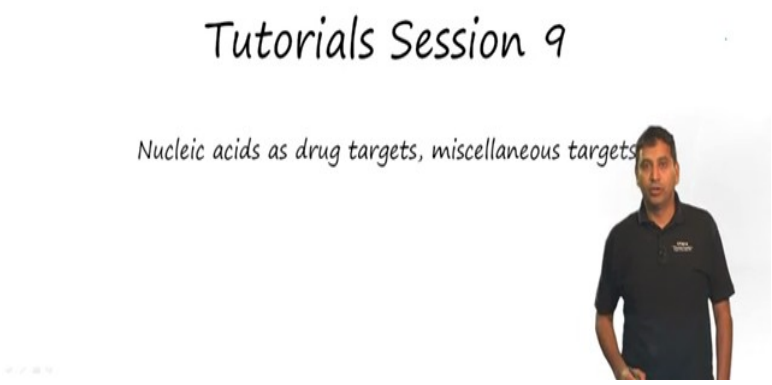

Welcome to the tutorial session. So in this session we will look at some problems associated with nucleic acids as drug targets and miscellaneous drug targets which we looked at in the previous two lectures.

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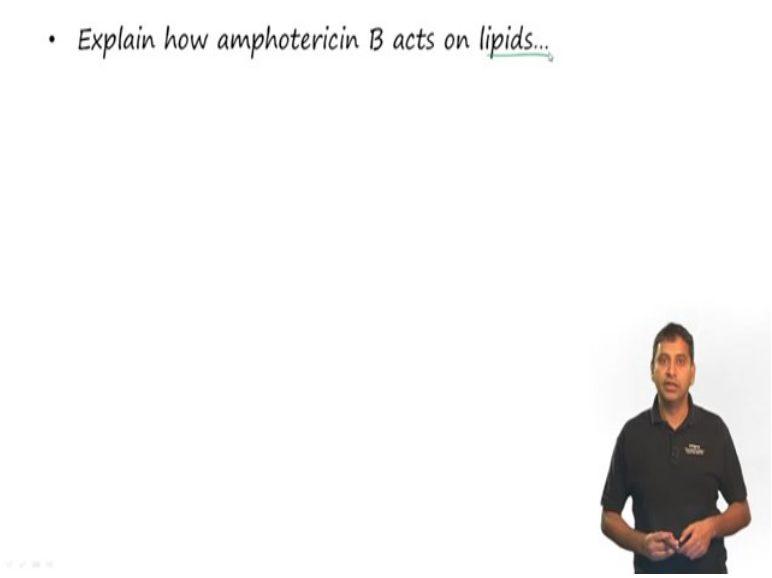

So let us start with the first question the question first question is explain how amphotericin B acts on lipids? So amphotericin B as you know is an antifungal compound and so now to answer this question let us go back to our what we discussed in the lecture previously.

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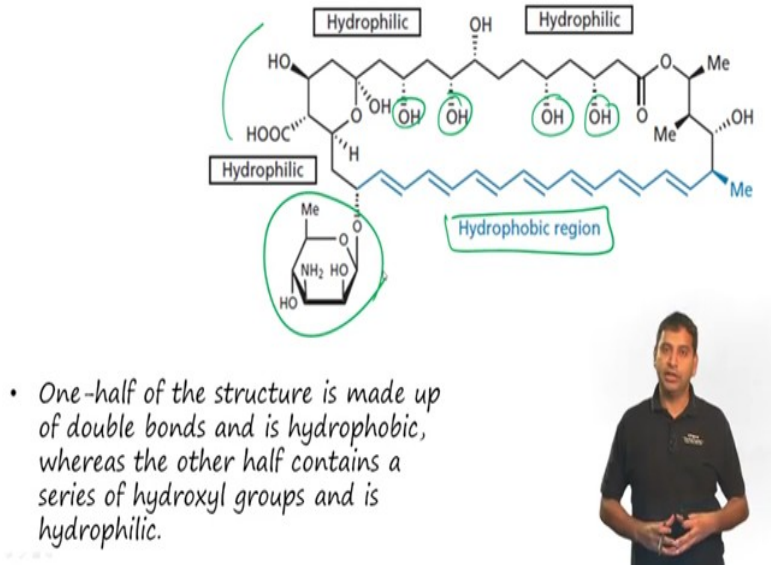

And so the structure of amphotericin B is very interesting, so it has got a very long hydrophobic domain over here which has got lots of double bonds in it and it also has quite a substantial hydrophilic domain in the presence because of this hydroxyl groups that are present over here and also it has got a some analogous something similar to a carbon sugar over here and an amino sugar over here and so all of this contribute to hydrophilicity, but has a distinct regions of hydrophobicity as well, okay. So together this gives this molecule a very interesting flavour.

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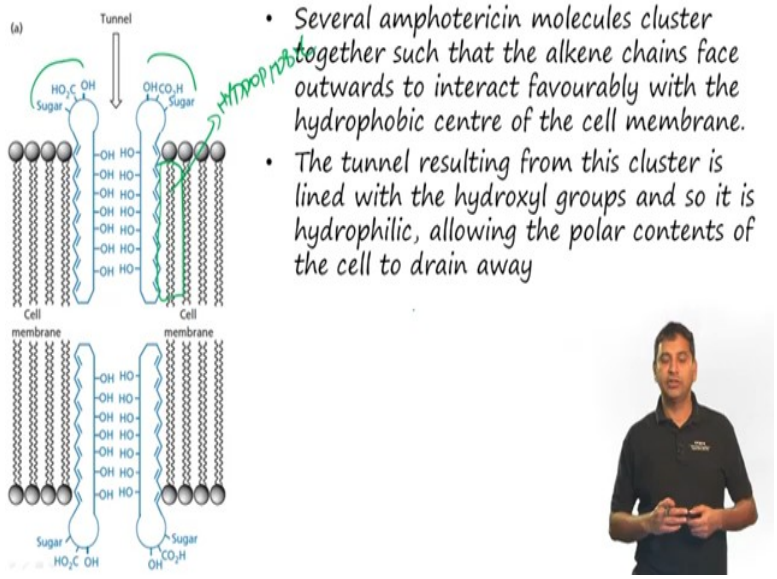

So what happens is that several amphotericin molecules they cluster together such that the alkene chains which are quite hydrophobic face towards the centre of the cell membrane, okay. So as we have discussed many times before the cell membrane domain here is going to be quite hydrophobic, right. So because it is quite hydrophobic you have this olefin region is going to come and sort of associate with it and in the process you can imagine that the hydrophilic region which is over here which is going to face the periphery as well as the hydrophilic region on the inside those hydroxyl groups that we looked at previously they can all align themselves in the through the membrane, okay.

And so if there are two such amphotericin molecules then they are going to form some sort of a situation where they are going to weakly interact with one another and this can form what is known as a tunnel and the tunnel resulting from this cluster is going to be lined with hydroxyl groups, okay. So because of this it is going to be quite hydrophilic and so what this does is it is going to draw out all the polar contents of the cell.

So as we have already discussed, many times the role of the lipid bilayer is to make sure that the contents of the cell remain intact, what it does because of the tunnel that is formed is to be able to drain away the polar contents this results in cell death.

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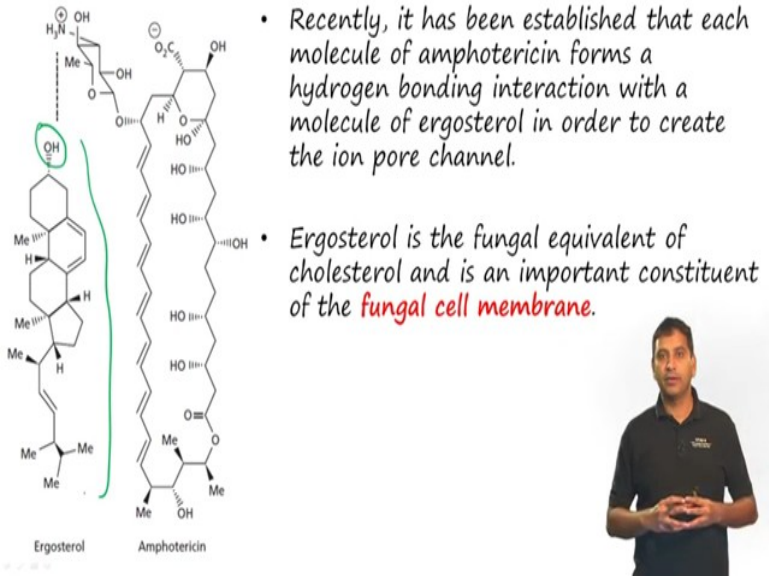

Very recently it has been established that each molecule of amphotericin B forms a hydrogen bonding interaction with the molecule of ergosterol and ergosterol which is shown here is lipid that is found in the fungal cell membrane, okay. So therefore this interaction has some value to it because it adds to some selectivity, right and the ergosterol is the cholesterol equivalent in fungi.

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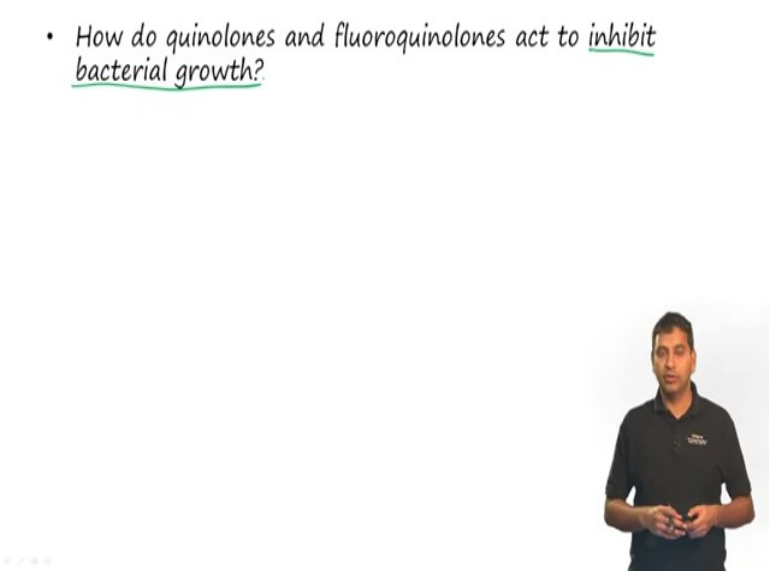

The next question is how do quinolones and fluoroquinolones act to inhibit bacterial growth? So bacterial growth inhibition by quinolones and fluoroquinolones is very important because they form some of the you know the front line antibiotics and so understanding how these inhibit bacterial growth is very important, okay.

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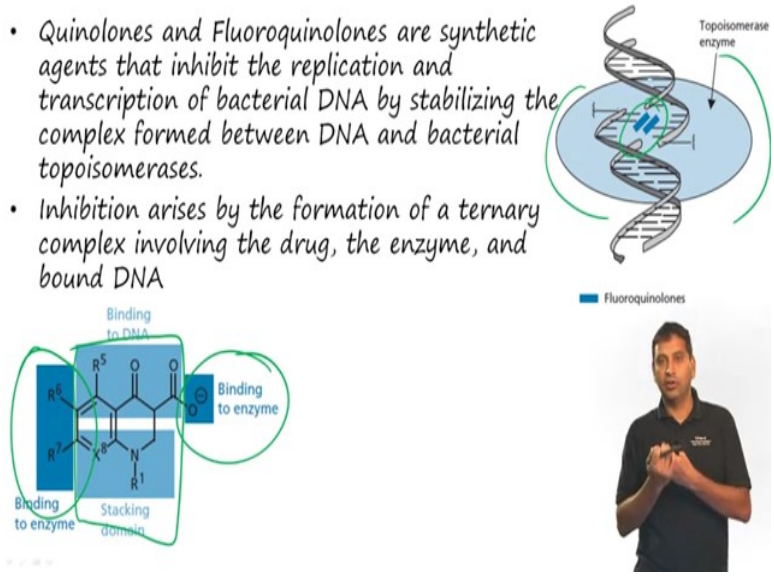

So let us first look at the structure of quinolones, so this is the structure that is shown of quinolones and they are actually synthetic agents and again we have looked through this in the lecture and there is an area over here which has a carboxylic acid, where it can bind to the topoisomerase enzyme we have already looked at topoisomerase enzyme previously the function of topoisomerase enzyme and here is the region which binds to DNA so what it can do is it can help with stacking interactions and here is the region which again binds to the enzyme, right.

So if you look at the topoisomerase DNA complex and you imagine that it is going to look like this then this is where the fluoroquinolones is going to bind and once it binds it is going to have a favourable interaction with binding to DNA as well as an interaction with the topoisomerase enzyme. So together what it does it is it actually inhibits the DNA enzyme complex and this results in inhibition of replication.

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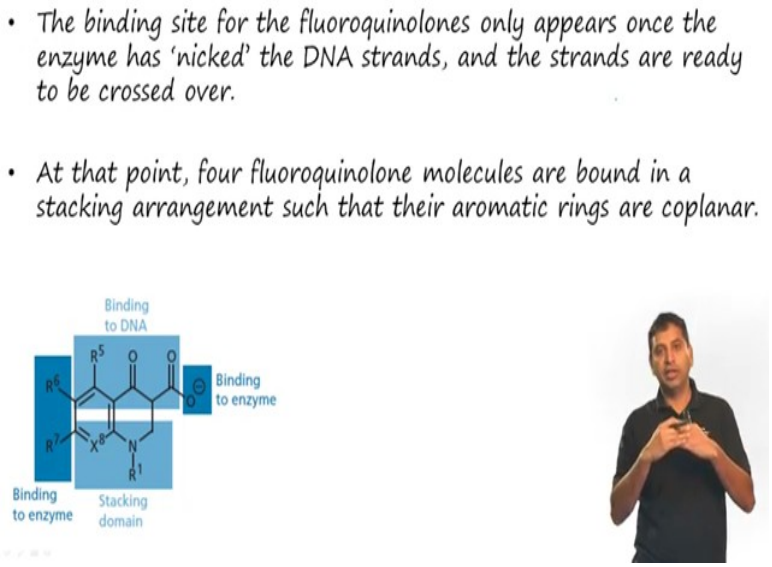

So the binding site for fluoroquinolones only appears once the enzyme has nicked the DNA strand and the strands are ready to be crossed over. So at that point, four fluoroquinolones molecules are bound in a stacking arrangement such that their aromatic rings are coplanar.

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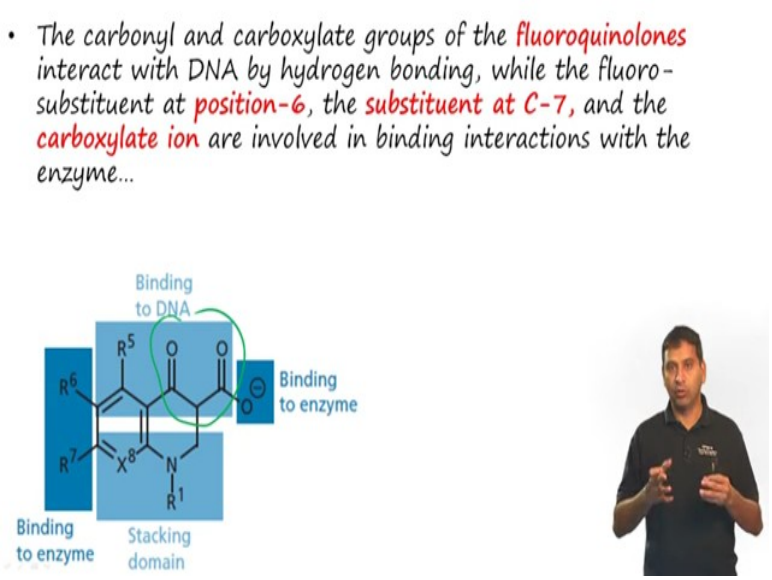

So as we looked at earlier the carbonyl and the carboxylate groups interact with DNA by hydrogen bonding and this while the fluorosubstituent at the position 6 and the substituent at position 7 and the carboxylate are involved in binding interactions with the enzyme.

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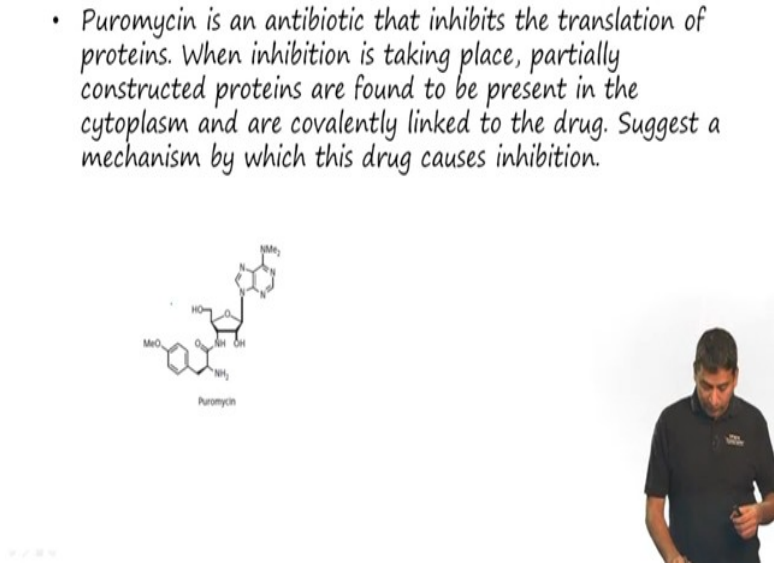

The next question is puromycin is an antibiotic that inhibits the translation of proteins. So when inhibition is taking place, partially constructed proteins are found to be present in the cytoplasm and the covalently linked molecule which are and they are covalently linked to the drug, okay. So suggest a mechanism by which this drug causes inhibition. So here is the structure of puromycin so let us look at this structure in little bit more detail.

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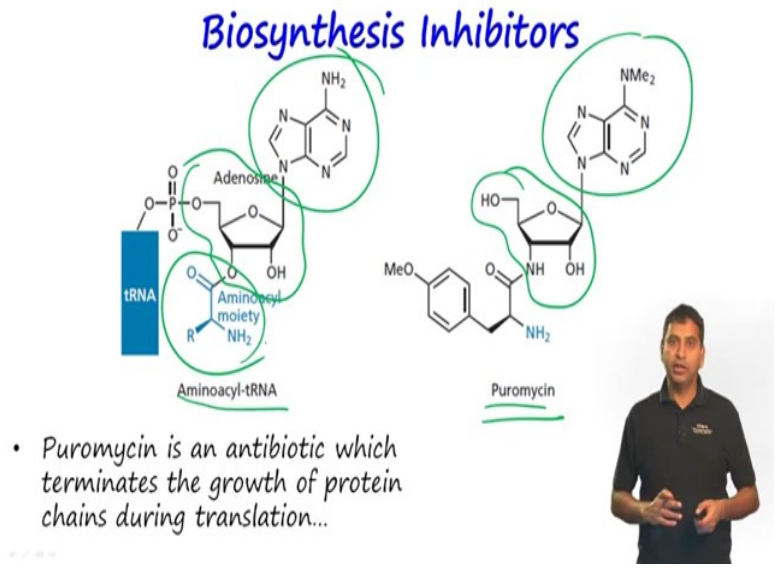

So puromycin structure is shown here and this is very much similar to adenosine and you know the core structure the nucleobase is identical, the sugar is somewhat similar, so if you see adenosine it is quite similar, but the major difference is in the amide versus ester linkage.

So here is the tRNA, aminoacyl tRNA which has got an adenosine moiety on it and it is charged with an amino acid.

So as we recall from the previous several weeks that this is a very key intermediate during protein biosynthesis and so this is the molecule that sort of goes and forms a amide linkage in the ribosome. So puromycin is an antibiotic which terminates the growth of proteins during translation. So let us look at the mechanism now.

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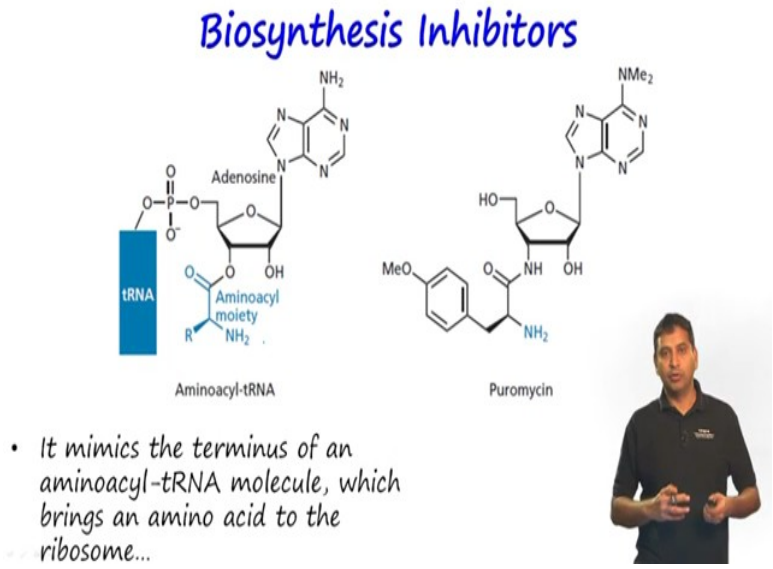

So what it does is it mimics the terminus of the aminoacyl-tRNA molecule, which brings an amino acid to the ribosome.

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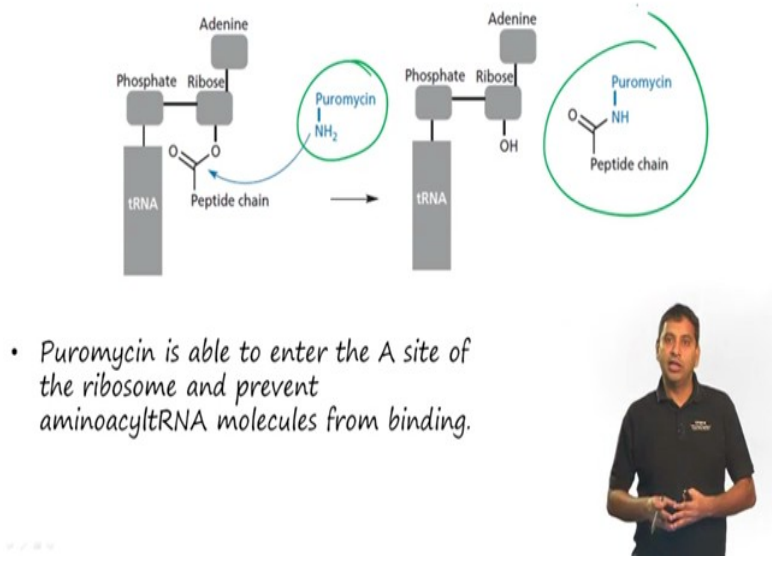

In doing so what happens is that the puromycin which is shown here actually attacks the growing peptide chain and because it does not have any way in which the chain can be elongated further the peptide chain is truncated or terminated, so which is why you find that in the cells that have been inhibited you find that there are long peptide chains which are covalently modified with puromycin.

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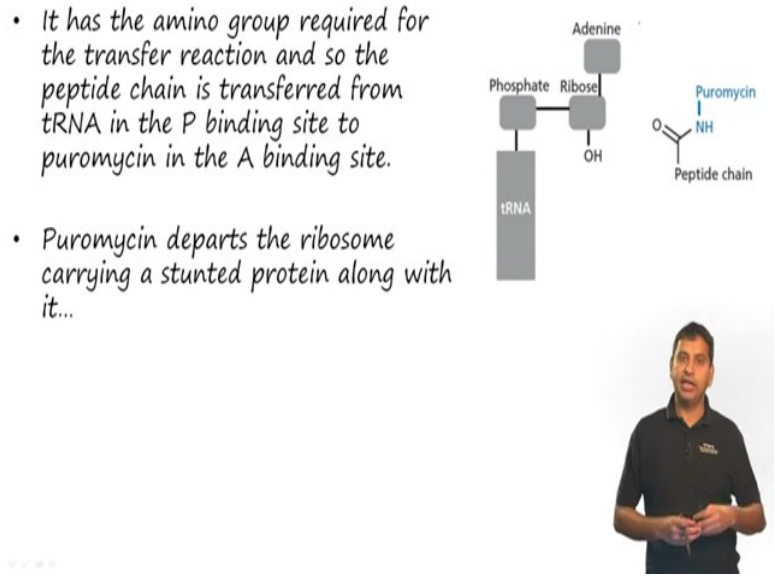

So it has the amino groups required for the transfer reactions, so the peptide chain is transferred from the tRNA in the P binding site to the puromycin in the A binding site, but what happens is that it departs the ribosome carrying a stunted protein along with it.

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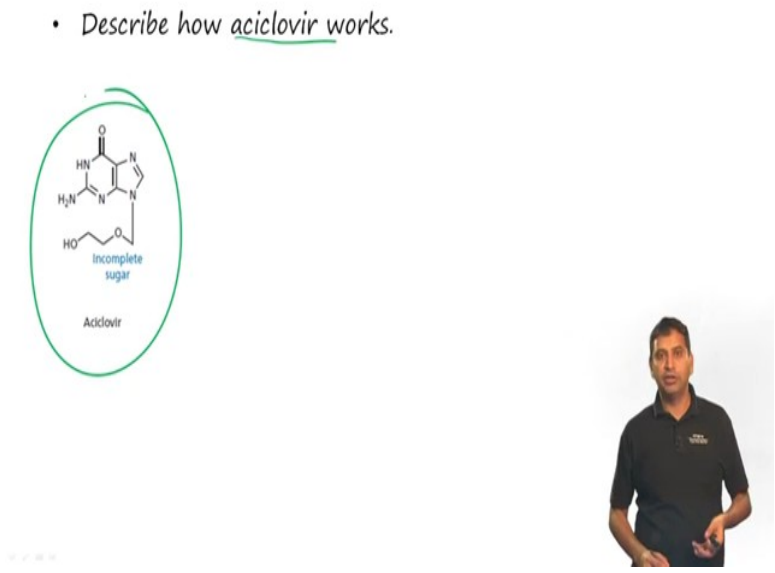

The next question is describe how aciclovir works? So aciclovir has the following structure as shown here and you can start to draw analogies over here because this looks remarkably like you know like nucleobase except that it has an incomplete sugar.

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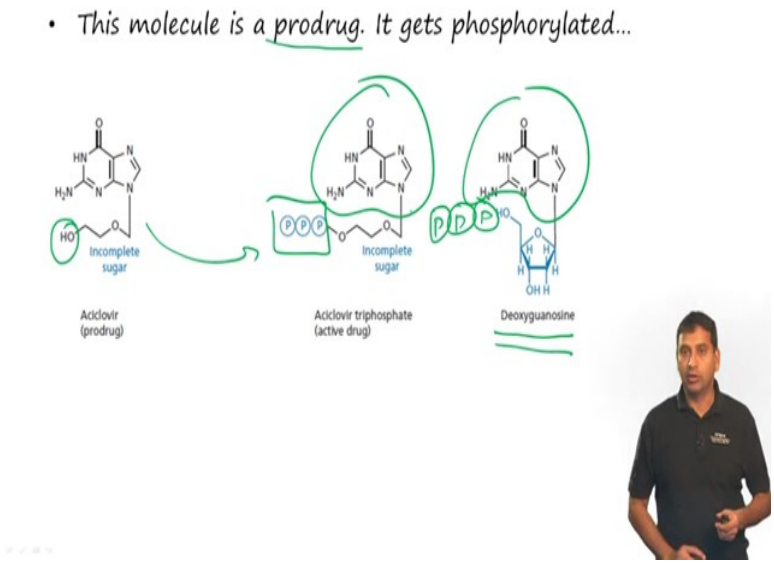

So let us now see what happens with this molecule and so here is deoxygaunosine which is the where you have the guanine base over here and what this does is actually this molecule is what is known as a prodrug. We have looked at very briefly what a prodrug is. A prodrug is a molecule that by itself is inactive, but once it gets into the cell it starts to it either gets undergo some metabolism which (makes it) converts it into an active drug.

So here what happens is that this OH group once it this molecule once it gets into the cell its get phosphorylated and it forms the triphosphate over here, but now this molecule is very similar to the corresponding phosphate analogue of deoxygaunosine but what this molecule is actually a chain terminator.

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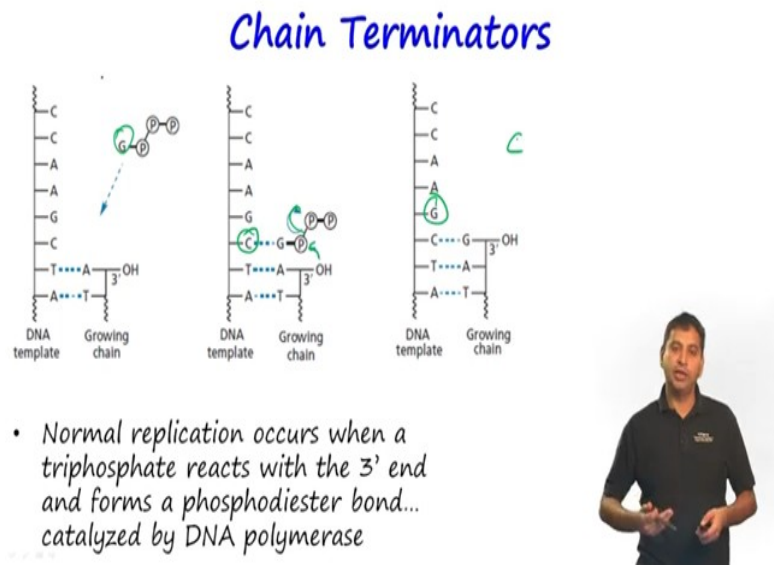

So now let us look at how the normal replication process occurs and then we can figure out what is going on with this molecule. So during a normal replication process the guanosine base comes in and once it recognizes the complementary base pair which is cytosine over here it interacts itself with hydrogen bonding and then the hydroxyl group over here comes in and kicks out this bisphosphate or diphosphate and then the chain grows.

So now the next molecule with the C as the complementary base pair will come and sit and similarly this is going to elongate, okay so this is catalysed by the enzyme DNA polymerase.

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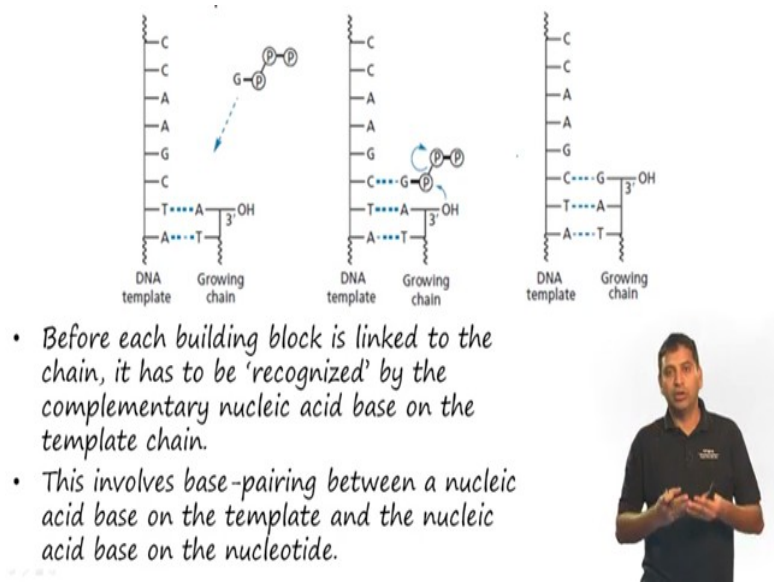

So before each building block is linked to the chain, it has to be recognized by the complementary nucleic acid. So this involves the first base paring between a nucleic acid base on the template and the nucleic acid base on the nucleotide.

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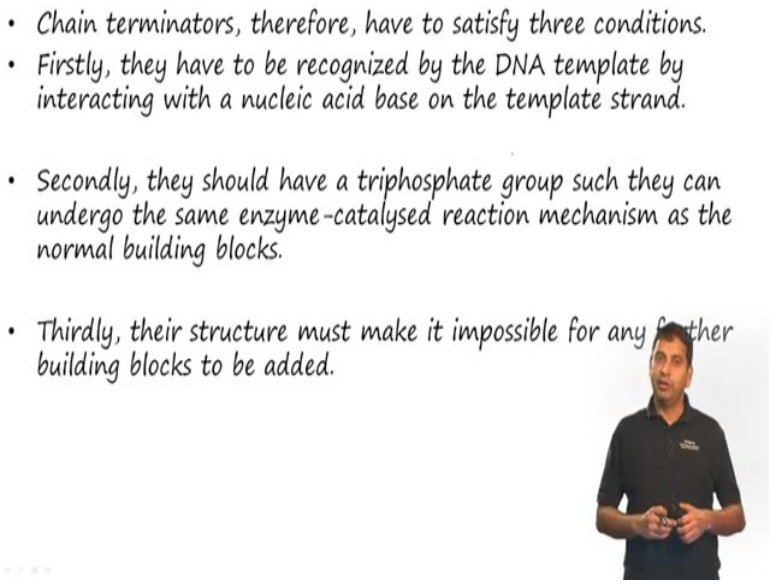

So chain terminators have to satisfy three conditions. Firstly, they have to be recognized by the DNA template interacting with the nucleic acid base on the template strand. Secondly, they should have a triphosphate group such that they can undergo the same enzymatic reaction as a normal building block. Thirdly, their structure must make it impossible for any further building blocks to be added.

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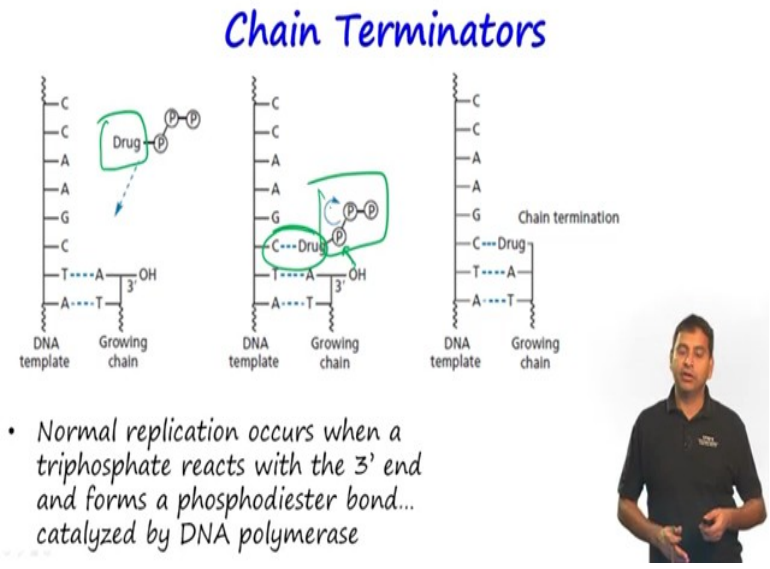

So with that let us look at how chain terminators work, so this is our chain terminator what it does is that it has the same base complementary base so it comes and sits here and does the base paring and since it also has a triphosphate this hydroxyl group is going to attack, kick out the bisphosphate and what it does not have is a hydroxyl group which is going to react further, right. So therefore the normal replication does not proceed.