Drug Delivery Principles and Engineering
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Lecture – 43
Route Specific Delivery Intra articular and Intravenous Administration

Hello everyone, welcome to another lecture for Drug Delivery Engineering and Principles. I am Rachit, I am going to talk to you about Route Specific Delivery that we have been discussing in this course.

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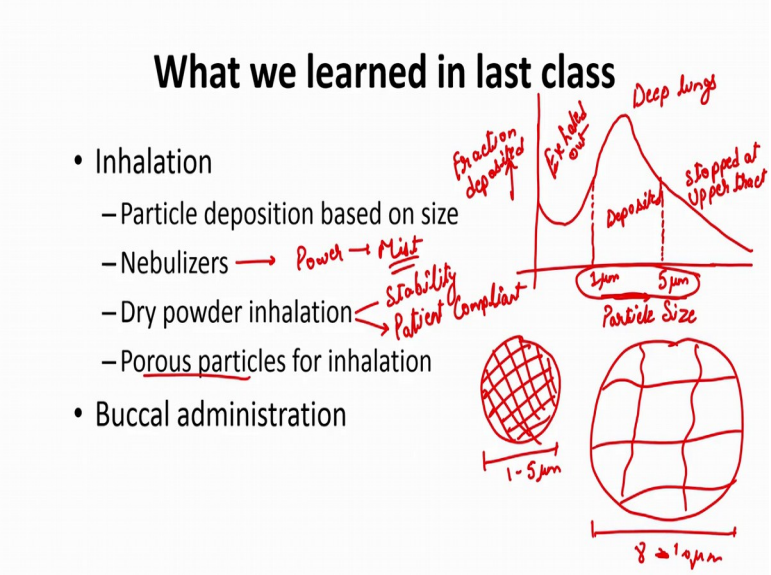

So, quick recap of what we learned in the last class; In the last class we learned about inhalation continuing our discussion on inhalation. So, one thing we talked about is; what is the right particle size for deposition in deep lungs. So, if I plot it on the x axis; let us say if I say particle size and on the y axis if I talk about fraction that is depositing.

And this defined for deep lungs which is our major concern, when we are talking about delivery. Then what do we get? We get, so we will get something of a curve like this; where, we have a see that anywhere between 1 to 5 microns. So, this is micron we get quite a high deposition and anything above that; we do not get much deposition deep lung anything, below that we also do not get much deposition in the deep lung.

So, this is the optimal range for let us say polymeric particles and I will come to that again in a moment. And we discussed why this is the case; it is the interplay of three different forces the gravitational sedimentation, the inertial impaction and the Brownian motion. And it just so happens that the velocity, that we deal with the lung this size range helps in better deposition. So, the deposited sizes in this range are exhaled out and sizes in this range are stopped at the upper tract.

So, that is what we discussed in particle deposition based on size; then we looked at nebulizers as one of the methods for lung delivery. And this involves using some power to generate mist and it works very well in the hospital setting. Again, you can generate this mist in the size range of 1 to 5 microns and it works very well in the hospital setting. But in the patient compliant department, this fails quite a bit just because the patients will have to go to the hospital every time, they want to do this. And then we discussed dry powder inhalation which causes first of all stability because these things are in dry powder.

And then not only that; this is very patient compliant and which is fairly obvious right? because the patients can actually inhale this themselves; it is not a very complicated procedure; its well accepted by the society as well; so and there is no stigma attached to it either; so, this is what we discussed. And then finally, we discussed how we can play around with these dry powder particles; if we are using particles in those cases where we can engineer the particles instead of having a solid matrix.

If let us say, if it was supposed to be a solid matrix then I would have required 1 to 5 microns from the actual diameter. But what you can do is, you can actually make a bigger particle, instead of a solid matrix. Well instead of a solid matrix you have a very porous matrix. So, very loosely bond and that then is starting to play around with the density of this particular particle. And because of that you can then increase the size range to let us say 8 to 10 micron and still have the same effect.

So, that is what we discussed; then we talked about Buccal administration and then this one we were saying that; this is very similar to the oral route where you still have to ingest the drug. But when you take it through the oral route, you do not have to actually let it go all the way down to the stomach; you can just put it under the tongue and keep it

there. So, what is going to happen is whatever the mucosa is present under the tongue and in mouth will causes the absorption of this route.

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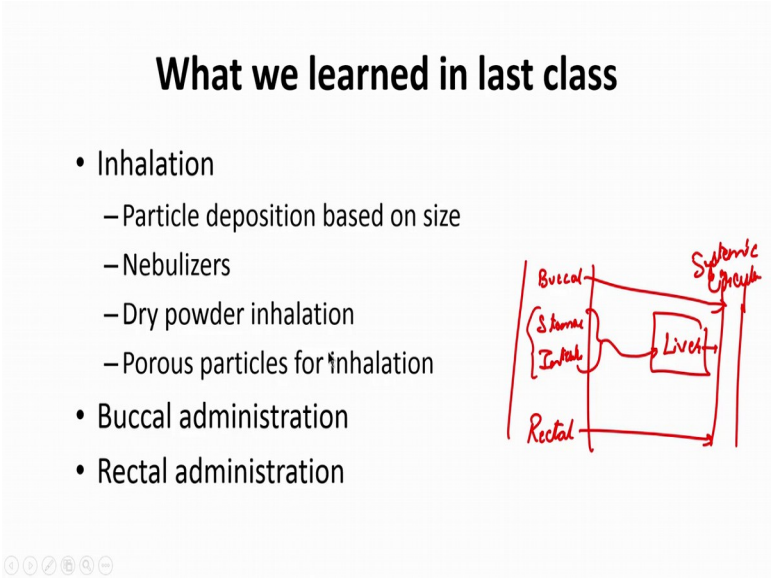

And what we also did is from the buccal cavity, so all this stomach and the intestine whatever is absorbed goes into the liver and then it goes to the systemic circulation. So, this is systemic circulation; however, from the buccal cavity it does not actually go to the liver, it directly goes into the systemic circulation through another vein.

So, that prevents this metabolism by the liver and that way you can have much higher drug in the systemic circulation compared to what you would have got if you, if you would have taken it down to the stomach. However, there are again challenges associated with this.

First of all, how do you get the drug to stay in that side for long because it is very uncomfortable for the patient to keep big tablet in their mouth. Then we also talked about rectum administration, so just like the buccal cavity, even in this case it also bypasses the liver and directly goes to the systemic circulation through another vein and this is another advantage; it is fairly rapid.

But then again there were some challenges treated with the biggest of them is again patient compliance; it is not very useful if the patients are not going to agree to this. So, that is a problem; however, with children and babies this could still be used because

parents can easily administer this without worrying about damaging the tissue, without worrying about finding a way in which even for a trained personal can be very difficult. So, that is some of the advantages why this is still around, compared to some other routes.

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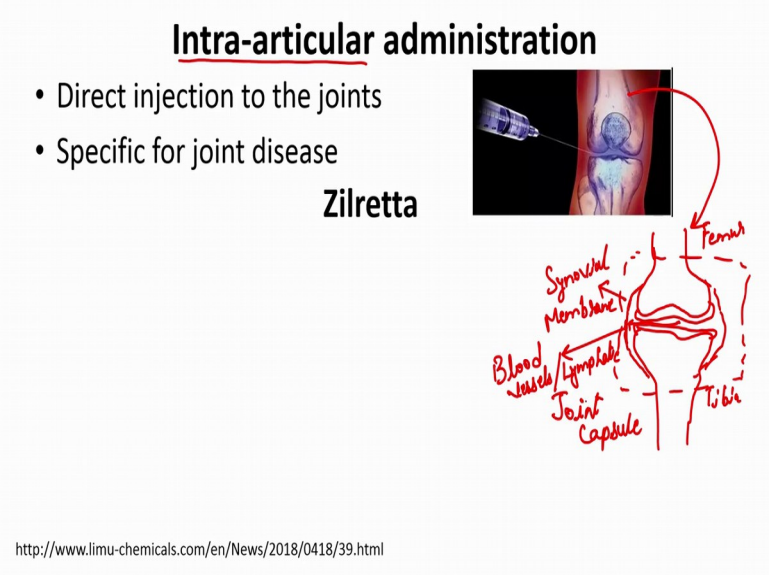

So, let us talk further about different routes; today we are going to talk about another mechanism which is intra articular administration and as the name suggests this is injection into the articulate joints.

So, knee joint is one of the articular joints which is one of the major applications for this administration. So, you can take the injection and directly inject to the joints. So, it goes back again to what we had discussed, that it depends on the application. So, let us say if you are trying to treat osteoarthritis of a knee; then it does not make sense to inject everything into the whole system. Because what you will find is, if you inject 100 milligrams into the whole system; less than a microgram will actually go to the cartilage just because cartilage is not very well vascularized.

So, you would may want to directly inject into the joint; obviously, this is a very difficult injection; cannot be done by anybody, there is a big risk of these needle you can actually damage your cartilage. So, it should only be done by trained personnel then you would need an intervention by going to some hospital or something. But even then, it is much better because most of the drug will then localize into the joint and you can have much

higher joint retention of the drug compared to if you injected in IV or intra muscular, subcutaneous or some other side.

So, an example of this is Zilretta especially the bioengineering example. So, again you can inject quite a lot of things in the joint, but joint also suffers with a similar challenge that it has a good lymphatic system. So, if I actually expand on the joint capsule; let me just actually draw a joint.

So, let us say this is femur which is nothing but a bone and this is tibia which is this bone here. And then you have cartilage which is lining these two bones and then this is actually being encased by something we call synovial membrane and this whole system is called the joint capsule.

Now, that you have this joint capsule surrounded by the synovial membrane, this synovial membrane is actually very well vascularized. So, lots and lots of blood vessels are present and it is also having a good lymphatic system. So, now if you inject anything in this joint space, that drug is going to get absorbed into the lymphatics into these blood vessels and get cleared out from the joint. So, what do you find is even though you get high local delivery and still quite a high concentration for a little bit of time; most drugs typically within few hours 3 to 4 hours they start to decrease their concentrations significantly in the joint space and at that point you do not really have much controlled release.

So, whatever you are injecting is going to get released out fairly quick and the joint space will be empty of the drug within a day or so. If the drug is fairly small which most drugs are in this particular example, so going back to our concepts that we have learned in this course; we can engineer biomaterial to have a longer residence time.

What is typically seen that, if you increase the particle size, or the drug site, that will have a much longer residence time. Because now that the drug size is so big; it cannot really go into the blood vessels it cannot really go into the lymphatics very easily. So, that is what is being used here.

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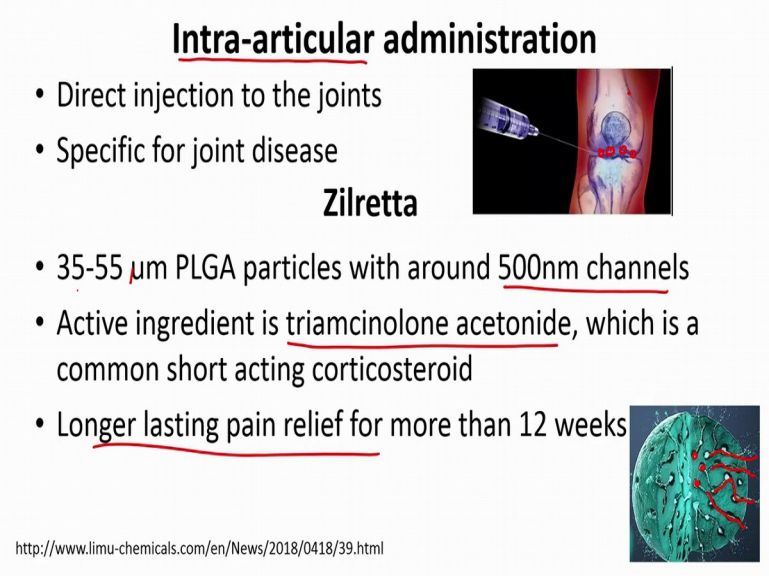

So, in this particular product which is zilretta; which is already again out in the clinics the whole concept is to use about 35 to 55 microns PLGA particles. And because these are so huge particles, that they cannot really escape out. Even the immune cells which are of the order of 10 to 20 microns cannot really clear these PLGA particles away. So, now, you have created deep on the system. So, this PLGA particle is going to sit in your joint space of course, it needs to be compatible. So, it does not damage your cartilage itself, but this is going to sit there and nothing can clear it out. And the only thing that is going to happen, it is going to start degrading and releasing whatever it is encapsulating over time.

So, in this case encapsulated molecule is this acetonide and it is a short acting corticosteroid which is used to decrease the inflammation; as well as help with the pain. So, it gives you a very long-lasting pain relief for more than 12 weeks. So, single administration is enough for you to get relief for 3 months. So, it becomes very patient complaint in that regards and then what this particular particle is engineered by?

It is engineered with 500 nanometer channels. So, here is a graphic of a particle that the company is giving the zilretta that you have these depots inside these particles of the drug. And then the drug then slowly comes out through these 500 nanometer big channels that are present. So, as the particle degrades more and more channels open;

more and more depot of these drugs come out and that helps in the pain relief for this particular joint okay!

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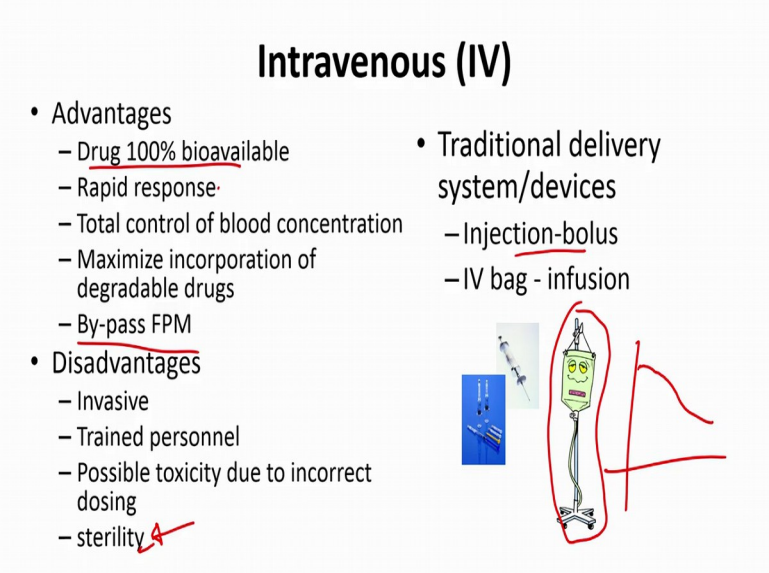

Next thing we are going to talk about is intravenous delivery and this is again by far one of the most used methods in the hospitals. There are several advantages to this the drug; it is immediately 100 percent bioavailable. So, the moment you inject, it is in the circulatory system, it is going to immediately distribute throughout the body. And it is going to be immediately bio-available and remember when you say bio availability it is basically when the drug is able to access wherever its target are.

So, once it is in the blood; it can go all over the place in the body and it will be bio available. It is very rapid response; again, goes back to the same point that is immediately available. So, it can act on its target much more quickly and very rapid response is seen. So, if a patient is actually suffering from let us say a condition in which if something is not done within few minutes; the patient may die, then IVs are out to go!

You cannot really wait to inject inter muscularly or subcutaneously and wait for 10-20 minutes for the drug to take effect. You want that drug to take effect immediately; maybe it is something that is causing the heart to stop and you want to give some biomolecules that may cause pumping of the heart to begin in normal scenario. So, in that ways the IV is the best route to go.

You have a total control on the concentration and this is important because again, even though you might be injecting somewhere intramuscularly or subcutaneously and you think all of that is going to go to the blood. But then there is a whole kinetic set as the things are building up in the blood; they are also getting excreted. So, you do not really actually know how much is the peak concentration, you may get in the blood at a time even though you might have done some experiments, but it will vary with the site to site you inject.

So, all of that variability is still there, but in the IV injection you know that whatever you injected is immediately in the blood; even before it gets start to gets eliminated. So, you have a fairly well control of what your pharmacokinetics is going to look like. Immediately you will have a certain blood concentration and only then it will start to drop out.

You then also maximize the incorporation of degradable drugs. So, what that means, is whatever drug you are injecting is, immediately getting incorporated into the blood system. Whether they are degradable or not going back to the point that if you injected intra muscularly or subcutaneously, they might start to degrade even at that site and again you do not know how much of the constant in the blood you are going to get.

And since not everything is going to pass through the liver, you bypass the first pass metabolism. And here are just some examples; so, what you are looking here is bolus doses of injections are typically given; I am sure you all of you must have seen these IV bags that are being infused to; infuse maybe some fluid into a patient or maybe some drug into a patient.

So, these are very traditional forms of delivery that are extensively used in clinics. What are some of the disadvantages of the IV injection? So, first is of course, is extremely invasive we all have gone to injections; it is painful; we do not really want to get an IV injection unless we have to; so that is a major challenge. The second is not everybody can do this procedure; we cannot do it sitting at our home; we need some trained personnel to be able to find the right location of the blood vessel in which to inject it.

You do not really want to inject it in a side which is not correct, you do not want to damage a blood vessel either multiple times and trying to find a blood vessel. So, it has to be trained personnel who can do this and then there is possible toxicity to doing

incorrect dosing. So, let us say if you do inject it trying to inject it in the blood, but eventually having injected only some in the blood, some in the surrounding muscle you are doing some incorrect dosing and it may cause toxicity.

And not to mention that you have to be extremely precise with the dose, because it is going to build up the concentration in the in the blood immediately; so, if you do end up going to the toxic level, it will cause toxicity. And of course, one of the major challenges is the sterility which is also very important. So, if you are directly putting in the blood; you are giving if your injection is not sterile and it contains let us say some pathogen or some infectious agent; you then actually put it in the system of circulation which means that that pathogen has access to all parts of your body.

So, if let us say the pathogen only infects lung; it will be able to go to the lung as well because all blood goes to pretty much every organ that we have and that is a big problem. So, it is a very stringent procedure sterility and maintenance that should be followed before doing the IV injection. That is why you see patients before they get anything, they are swabbed by an ethanol wipe or something to sterilize the area as well. So, even if your drug is completely pure, but maybe your skin has some pathogen even that gets removed off. Okay!

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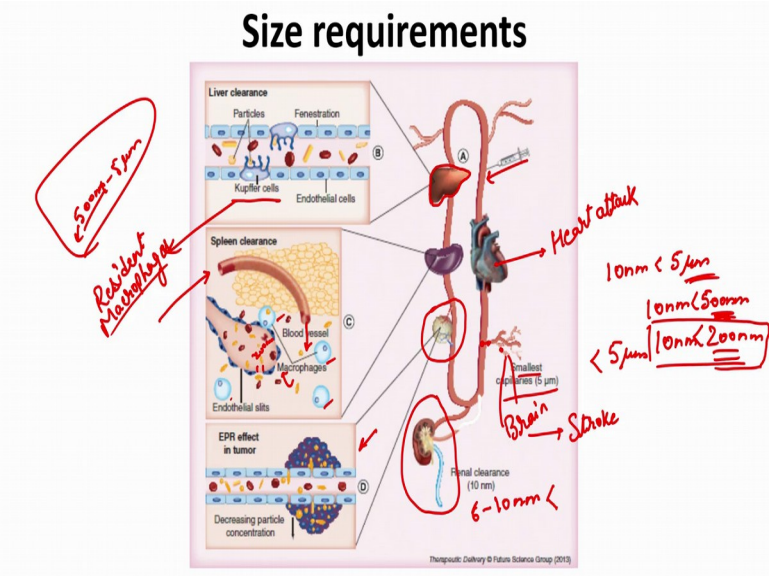

So, this was a basically many on the traditional form of delivery using IV injections; what about more on the bioengineering aspect of it? So, here is a diagram showing how

various aspects of the blood that needs to be considered when we are looking for the delivery through the blood.

You have seen this before; so, what it is? Let us say you are injecting some dose into the blood; you have a circulatory system. The first thing was going to happen is heart since its pumping continuously it is going to start pumping whatever you have injected in the blood to all parts of the body. And so, I have only shown few organs here, but it will pump it to every part of the body.

The smallest capillaries that we have are about 5 microns. So, which means that if you inject anything which is bigger than 5 microns; what is going to happen? Let us say if I inject this particle which is about 10 micron; it can flow through this big muscle no problem, it can then start to diffuse in and is pumped into the small vessels still it is ok, but as it goes down to a smaller and smaller vessels; it may just get lost there.

Because it is physically too big it; it has really no way to go because it cannot move forward unless it ruptures the blood vessel; it cannot go back because the flow is pushing it forward. So, it may clog this vessel, now if this vessel is going to your brain then basically, we talking about stroke. Because suddenly a part of the brain is not devoid of oxygen, the cells will start to die and as the cells die your brain will stop functioning a part of the brain will stop functioning and that will lead to stroke.

The same thing can happen in the heart also; similarly, if one of these vessels is feeding the heart cells; then and that suddenly stops then you are talking about a heart attack. So, it is a very serious problems; if you inject something which are bigger than 5 microns. So, definitely we will not be able to inject things which are bigger than 5 microns.

Then the other organ you already talked about quite extensively is liver; now liver as I had already mentioned is a metabolizing organ for most things and lot of the blood does pass through the liver it is a fairly large organ. And so, it will metabolize quite a bit of your drug when you inject it into the circulation. And not only that the liver cells are actually very good in sampling anything for it. So, the blood vessels in liver are actually lined with this Kupffer cells which are the resident macrophages in liver tissue.

So, these resident macrophages keep on sampling whatever is flowing. So, if there is just a blood cells or our bodies own cell these do not really do anything, but when they find

any foreign particle or pathogen that is flowing through this; they will engulf it and try to kill it. So, that is one place where you lose quite a lot of your particles and again since I said its macrophages and we discussed in the inhalation part of the things that macrophages do have fairly high up take between 1 to 5 microns.

And in fact, even we can say that from 500 nanometer; they will start to clear things. So, now we said, we cannot have bigger than 5 microns; the other thing we are saying is even at 500 nanometers; we will get some clearance. So, ideally, we want long circulation, we would want to go below this size; now let us talk about another organ.

So, here is kidney and this is in the very early part of this course; we discussed that kidney can clear anything below 6 to 10 nanometers. So; that means, if size is less than 6 nanometer or 10 nanometers; it will have a very fast clearance from the body because this kidney will continue to filter it out.

So, that is again something that we do not want because if you want the long circulation; we want to make sure that not everything that you have put in, goes out through the kidney. So, you want to make sure your particles are greater than 10 microns. So, now we have already said here we are saying less than 5 microns; here we are saying greater than 10 nanometers; so that is one limit.

Now we are saying that the liver will also take out 500 to 5 microns; even though with not very good efficiency, but it will still take them out. So, ideally, we really want long circulation we are talking about 10 nanometers to 500 nanometers. And now another major organ the spleen and so what does spleen do? so this is a bit of a repetition, but the blood that comes into this plane actually gets filters out in this spleen.

So, most of the blood empties itself in the spleen and then goes back into your blood vessels. Now these blood vessels are comprising of all these endothelial cells and all kinds of smooth muscle cells. So, they create a pore size here which is about 200 nanometer in a healthy; in the healthier person; so, if now you have anything which is greater than 200 nanometer it will be very difficult for it to go through this. So, what will happen is that will start accumulating in the spleen and in the spleen is rich in lots and lots of immune cells and they will come and start gobbling these cells these particle cell.

And we discussed previously that if you can play around with elasticity; so that it can actually become soft enough, so it can squeeze through. But in generally speaking, these 500 nanometers are now becoming 200 nanometers. Because again if you have particles between 200 to 500 nanometer range; they will tend to be cleared out by the spleen.

So, these are some of the major limitations that have been put by our bodies internal healthy organs that we need to take care of when we are looking into IV delivery; using some bio material based particles. Of course, you cannot put any macro device; so that is completely off the question; since that has to be less than 5 microns. And then further if you want long circulation; it has to be within this range of 10 nanometer to 200 nanometers.

And then finally, we have in this particular example I have also given tumor here and it is been described here and we will go into a lot more detail of this in this next slide.

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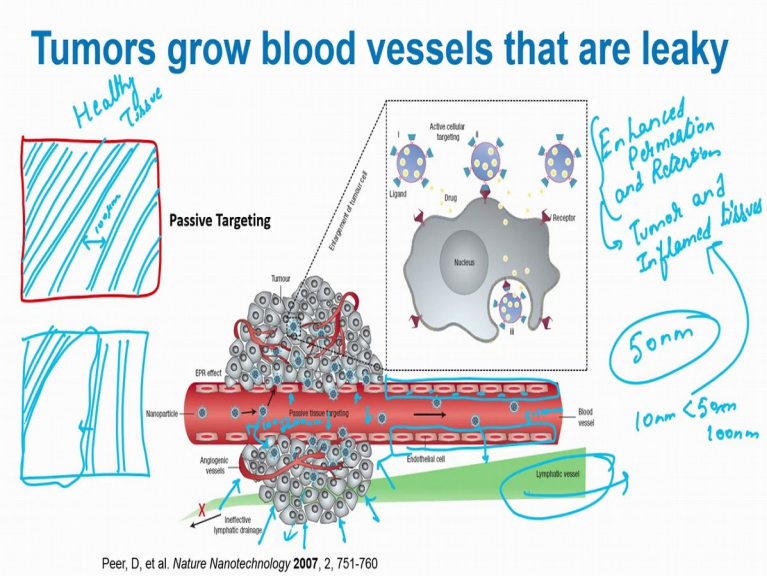

So, let us look at more on the tumor environment and we have also discussed a bit of this, but what tumor is? It is an organ/tissue which was never supposed to grow there. So, this is extra mass of cells that have come in which body had never programmed.

So, if you look at healthy cells or healthy tissues; let us say if this is a healthy tissue then pretty much every part of this tissue is being fed by a constant supply of very regularly arranged blood vessels. So, these blood vessels have been growing as we were growing

and the tissues were growing and they ensured that pretty much every part of this tissue is well vascularized.

So, even the widest differences between the two blood vessels is never more than few hundreds of microns; so maximum 100 microns maybe. Now this is for the healthy tissue; however, when you compare this to a tumor tissue, the tumor was something that body had never programmed for it. So, the blood vessels had never really tried to grow in into the tumor tissue, but what is happening the tumor tissue is inducing blood vessel growth.

So, it can get nutrients while it is growing. So, when you look at let us say if I make a diagram of a tumor tissue; you may have certain regions which have high density of blood vessels and then you may have regions which have really no blood vessels. So, I mean all of that area is now relying on these blood vessels to feed them.

Now, this is a big area for things to diffuse into. So, what does tumor do? It causes the blood vessel to dilate and these blood vessels have formed also very rapidly; so, they are fairly immature. And so, what I am basically getting at is this diagram, where if you see blood vessels in healthy tissue; you see the lined very well and fairly mature with some very basic amount of gap between these cells.

However, when you look at the tumor blood vessels, these are fairly immature and the fairly leaky. So, you can find that there are actually gaps here which are 100 to 200 nanometers big; maybe these gaps are about only 5 to 10 nanometers. But these gaps are huge and because of that; if you now design a particle which is let us say 50 nanometers in size.

So, while that particle is flowing here; it is just physically too big to be able to go into your healthy tissue. Whereas, in the tumor tissue these particles can very easily diffuse out and go into the tumor; go into within the tumor cells. So, because of that we say that these tumor vessels have enhanced permeation.

So, this is called enhanced permeation and then the other thing which is shown here is lymphatic vessels. So, similar to that the lymphatic vessels are not very formed. So, the major job of the lymphatic vessels is to take extra fluid out from the system. So, since the

lymphatic vessels are not very good, you are getting fluid accumulated in the tumor region as well.

So; obviously these blood vessels are putting pressure on the tissue; on this direction, the lymphatic since it is not there. So, there is a lot of water which is putting the pressure on the tissue in this direction. So, because of that whatever particles that come in are not able to then diffuse out from this tumor. So, this pressure on this direction the pressure on from this direction. So, these particles are nowhere to live, but to get retained in the tumor this is called enhanced permission and retention.

And this is not only for tumor if there is a inflammation in certain place then that causes a lot of immune cells to go and very similar to the tumor there are lots of cells in the surrounding. So, they also have their vessels dilated and they also are slightly leaky. So, this works with both the enhancement permeation and retention which will be seen in tumor and inflamed tissues.

So, to be ideally speaking; anything below 100 nanometers will be able to utilize this effect and to a very nice effect; to a very nice extent. Whereas, anything above 100 nanometers may be difficult it may diffuse into certain areas, but not through all areas of the tumor vessels. So, ideally you want to have your particles anywhere between 10 nanometers to 50 nanometers, if you are trying to target these tumors and inflamed issues.

Even 200 nanometer is, but beyond that it is; it is not going to work very well at least with this concept. So, that is what people then do when they make these particles for tumor replication. And you will find them quite a bit in the literature and we will go over some of the examples; they will use anywhere between 10 to 100 nanometers. So, we will stop here and we will continue further in the next class.

Thank you.