INDIAN INSTITUTE OF TECHNOLOGY ROORKEE

NPTEL

NPTEL ONLINE CERTIFICATION COURSE

Biomedical Nanotechnology

Lec - 14
Nano Artificial Cells

Dr. P. Gopinath
Department of Biotechnology
Indian Institute of Technology Roorkee

Hello everyone I welcome all to the 14th lecture of this course, the 14th lecture is on nano artificial cells.

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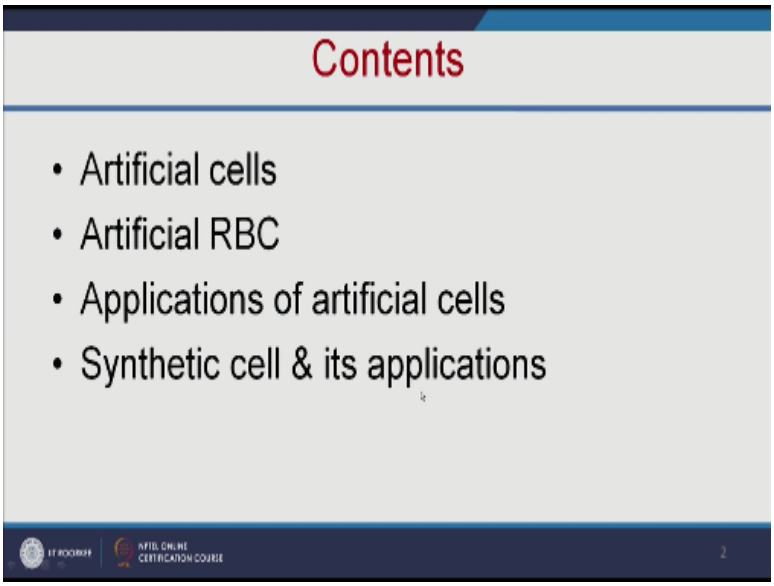

So in this lecture we are going to learn what is artificial cells, and how to make artificial RBC and also various applications of artificial cells. So in this lecture we also going to learn what is synthetic cell and its various applications.

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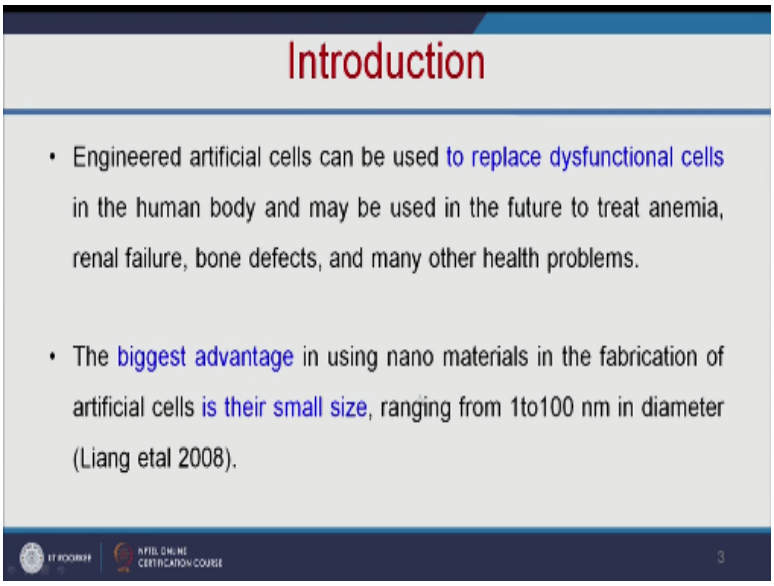

So in the previous lecture we have learnt how to replace the damaged tissue using tissue engineering approach. So in this lecture we are going to learn how to make artificial cell and how to replace the damaged cells using the artificial cell approach. So here this engineered artificial cells can be used to replace the dysfunctional cells and it may be used in the future to treat anemia, renal failure, and many other health problems okay.

So here the biggest advantage in using nanomaterials in the fabriciation of artificial cells is their small size.

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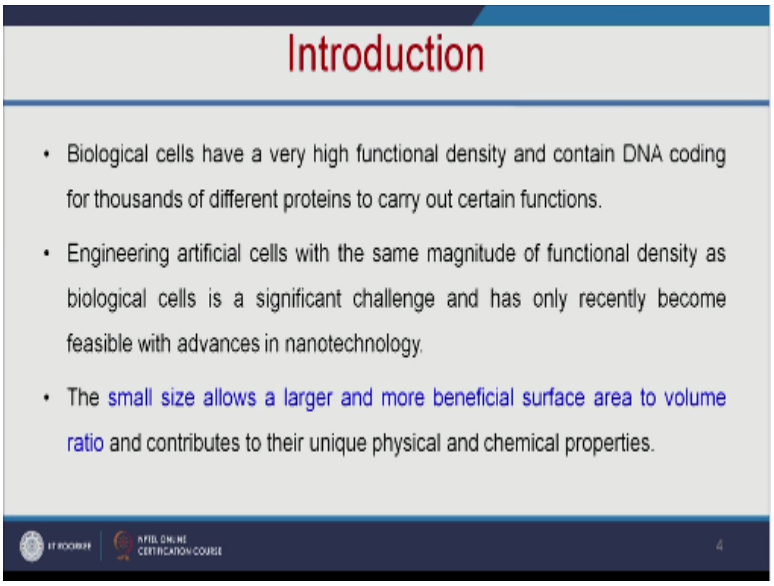

And as you know this biological cells have very high functional density and contained DNA coding for thousands of different proteins to carry out certain functions. So engineering artificial cells with similar function is the significant challenge okay. So with the help of nano technology we could be able to achieve those challenges. And here the small size allows a larger and more beneficial surface area to volume ratio.

So that is why when you use that nanomaterials for constraining artificial cells that could be more beneficial. So let us see the basic principles of early artificial cells.

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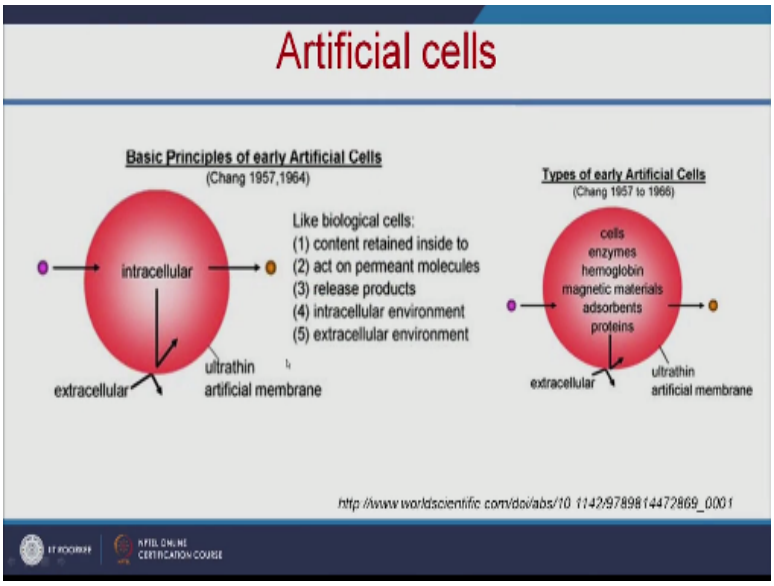

So these artificial cells are made up of ultra thin artificial membrane so it is having intracellular as well as extracellular environment. And here the content whatever you want encapsulate that will be inside the artificial membrane and this membrane is permient okay, so it will permit the sub state and it can also release the product okay. So these are the types of early artificial cells we can encapsulate cells, enzymes, hemoglobin okay and various other materials.

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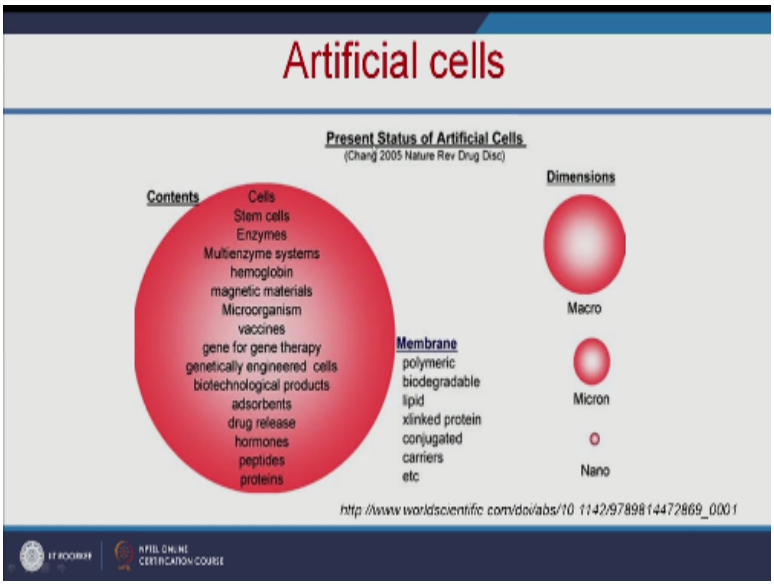

So let us see the present status of artificial cells. So you can see here we can encapsulate cells, stem cells, enzymes and everything inside the membrane, artificial membrane. So this membrane could be made up of polymeric or it could be made up of biodegradable membrane, lipid and protein based membranes okay. So these artificial cells are available in various dimensions, it can be macro or micro or nano, it depends on the cellular content which you want to encap it into artificial cells.

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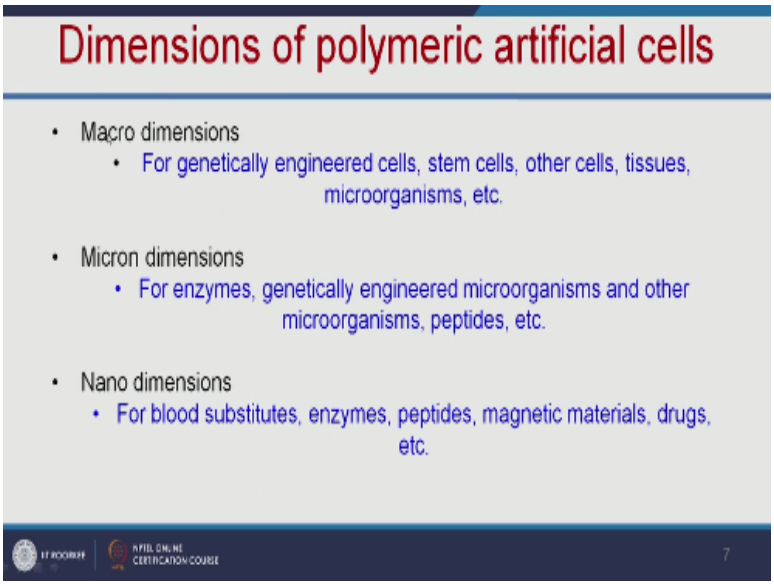

So let us see this in macro dimensions we can encapsulate genetically engineered cells, stem cells and even microorganisms. And in micron dimensions we can encapsulate enzymes or we can encapsulate some of the genetically engineered microorganisms and peptides and everything. And in the nano dimensions using the nano dimensions we can make blood substitutes or we can encapsulate enzymes and magnetic materials and drugs and other peptides okay.

So let us see these, how we can encapsulate these materials into this polymeric artificial cells and also what are the various applications of these artificial cells.

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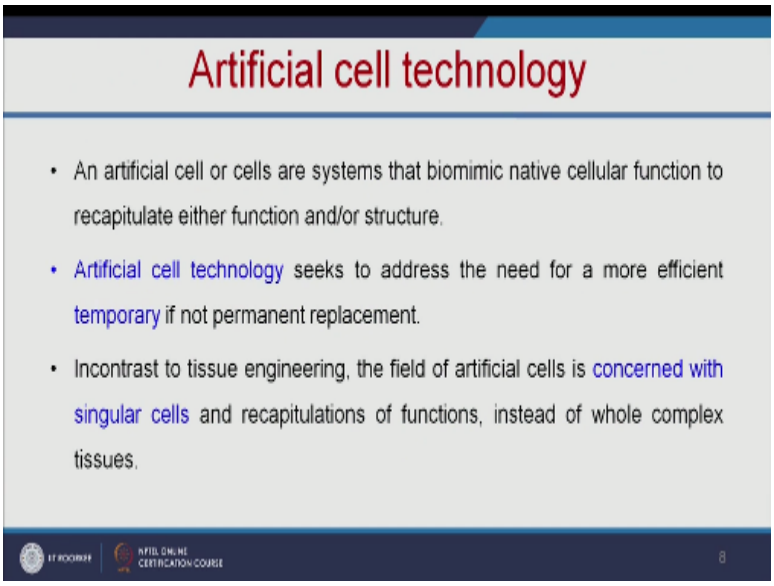

So here these artificial cell or systems that biomimic native cellular function to recapitulate either function or the structure. And this artificial cell technology seeks to address the need for more efficient temporary solution okay. So when compared to the tissue engineering, where you get the whole tissue will be replaced here we are going to focus mainly on the single type of cells okay. So in contrast to tissue engineering the field of artificial cells is concerned with singular cells okay, instead of the whole complex tissues.

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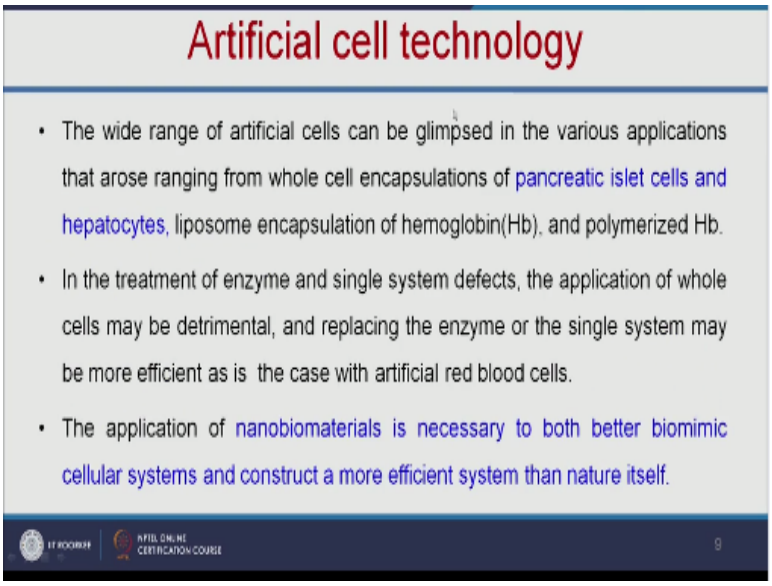

So for example, here the pancreatic islet cells can be encapsulate into polymeric capsules and it can act like your pancreatic cells to produce insulin in case of diabetic patients. And it can also encapsulate hepatocytes, so that can be useful for the patient with the liver failure okay. And in some cases like in the treatment of enzymes and the single system defects, so we do not need even the complete cell okay, we can encapsulate only the particular enzyme.

So the application of whole cells may be detrimental in case of single enzyme defects okay. So replacing the enzymes or the single system may be more efficient in those cases. And again the application of nano biomaterials is necessary to both better biomimic the cellular system and also to construct more efficient system than the nature itself. So using these artificial cell technology we can mimic the biological system and also we can make, better than the biological system okay. So let us see how we can make it.

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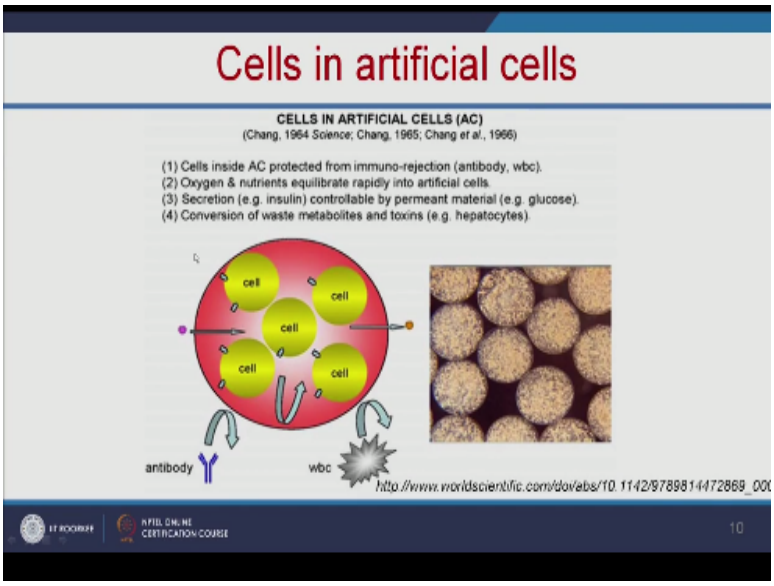

And this is the cells in the artificial cells. So here the cells are protected in the artificial membrane okay. So here the cells inside the artificial cells protected from the immune rejection. So when you inject the cells directly inside the body, so that will be rejected by your immune system, but when you protect these cells in your polymeric capsules so that will be protected from the immune rejection okay, immune rejection and here the oxygen and nutrients can easily pass over this okay. And again for example, if you are using this pancreatic cells so depends on the glucose level it can secrete the insulin.

And again if you are encapitulating the liver cells into this it will convert the waste metabolite and toxins okay.

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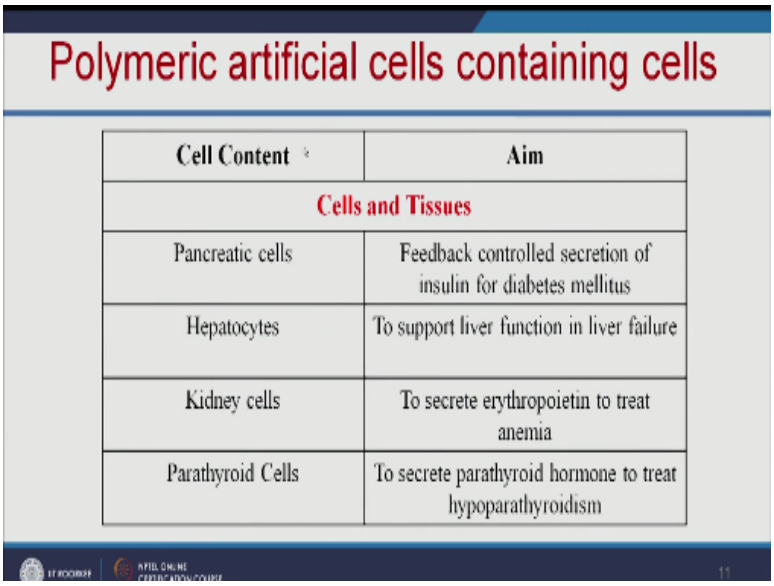

So these are some of the other examples, so if you are encapitulating pancreatic cells it will be secrete the insulin for diabetes patients and if you are encapitulating the hepatocytes it will support the liver function in the liver failure. And if you are encapitulating kidney cells it will secrete erythroprotein to treat anemia. And parathyroid cells to secrete parathyroid hormone to treat hypoparathyroidism.

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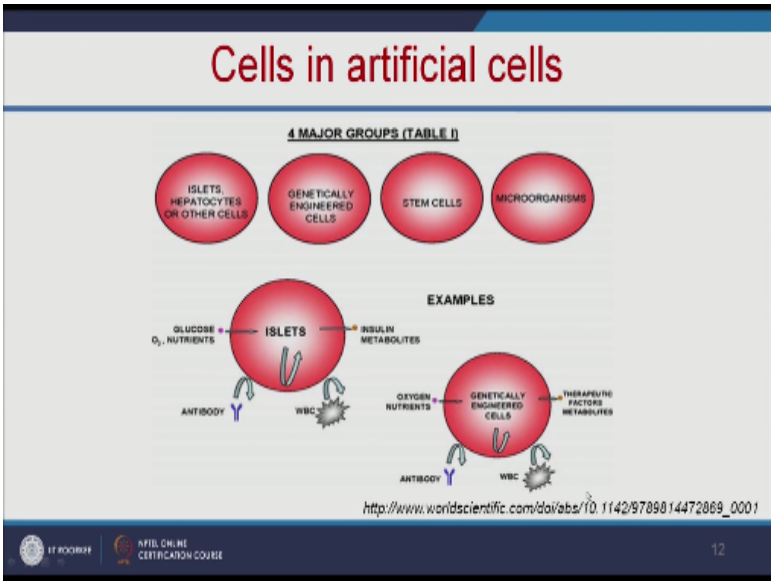

So we can also encapsulate genetically engineered cells, stem cells and even microorganisms okay. So in this example if I am encapitulating these islet cells, so it depends on the glucose level it will produce the insulin and if we are using this genetically engineered cells, so it can produce various therapeutic factors that could be useful for various therapeutic applications.

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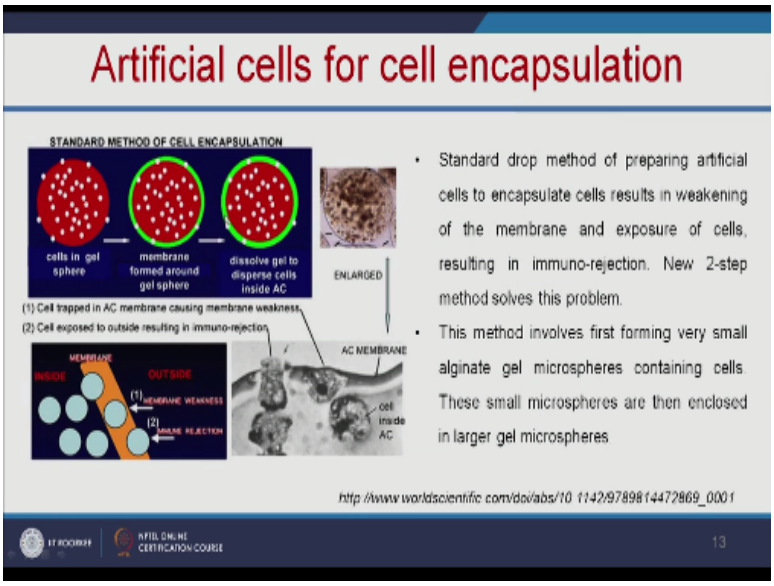

So let us see how to encapsulate these cells into the artificial cells, so here there are two methods the first one is standard method of cell encapitulation. So here the cells will be encapsulated in the gel sphere and followed by that the membrane are formed around the gel sphere okay, this green color is the membrane. And then dissolve the gel to dispose the cells inside the artificial cells okay.

So finally you dissolve the cells and dispose the cells into the artificial membrane. So here the major drawback is the cells strapped in the artificial cell membrane causing membrane weakness, you can see here some of this white color is your cells okay, so it is some of the cells are on the membrane. So due to which the cells expose to outside resulting in immune rejection, you can see here this white color is the cell and some of the cells are exposed to the outside environment okay. So which will leads to membrane weakness as well as immune rejection okay.

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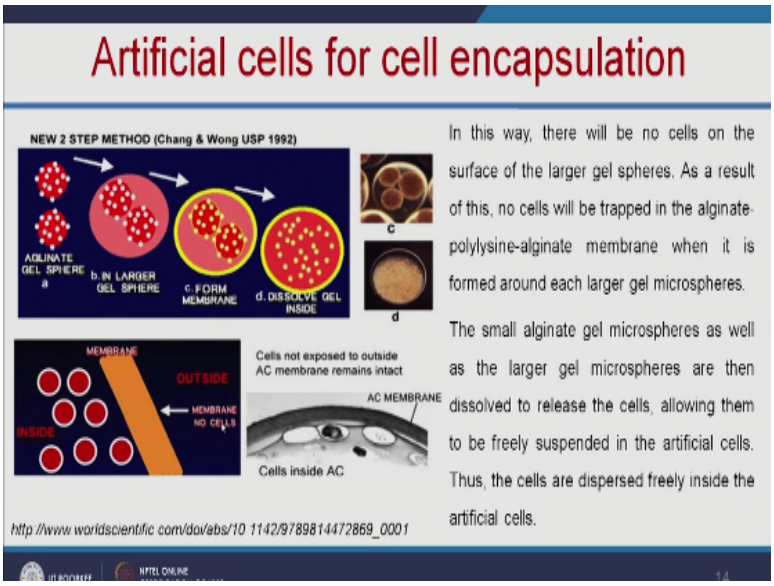

So to work on this there is another method called two step method, so in the two step method the first the cells are encapsulated into the alginate gel sphere then these smaller gel spheres are encapsulated into larger gel sphere okay. So then followed by that you form the membrane, this yellow color is the membrane, so then you dissolve this smaller spheres so all the cells are evenly dissolved into the artificial cells okay. And you can see here all the cells are safe inside the membrane and there is no cells exposed to the outside. So here the cells are no exposed to outside, so this artificial membrane remains in that.

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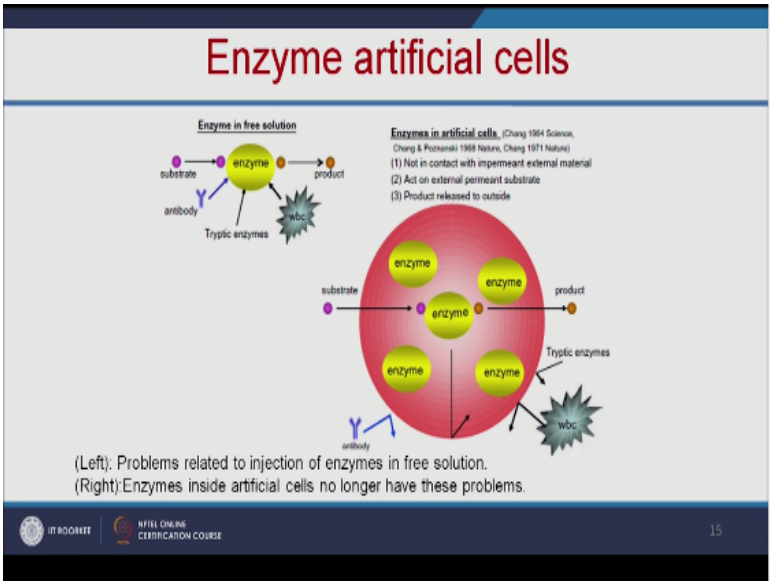

So let us see how to encapsulate the enzyme into this artificial cells, as I told you earlier in some of the cases we do not have to encapsulate the whole cell, so if you have some enzymes defects you can encapsulate only the particular enzyme and that could be also act like a therapeutic artificial cells. So when you inject the enzyme directly what happens is, antibody will be produce enzyme or your WBC will attack okay.

And tryptic enzymes will digest to enzymes, but when you encapsulate this enzymes into artificial cells, so it is not in contact with the external material. So all the enzymes are protected in the artificial cell membrane okay, so when the substate enter inside the artificial cell and it will convert the substate in the product, and the product will be released okay.

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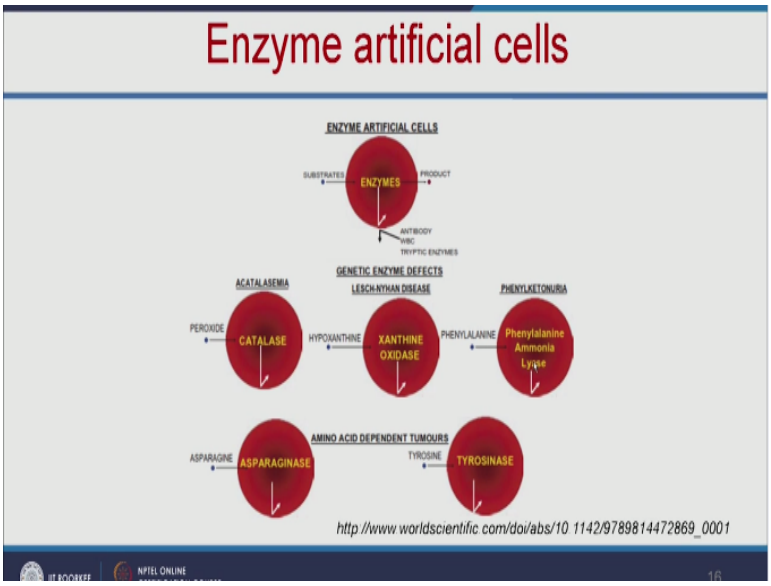

So let us see some of the examples okay, you can see here solid this is like acatalasemia it is due to lack of catalase enzyme and phenylketanoria it is due to lack of phenylalanine ammonia lysase okay. So when you encapsulate these enzymes into artificial cells that could be useful for treating the patients with lack of the particular enzyme. And another thing is we can also use it for cancer therapy.

For example, there are some of the tumors that are amino acid dependent tumors. For example, this enzyme like asparaginase it can remove the asparagines and also this tyrosinase enzyme that will remove the thyrocine which is recovered for melanoma growth.

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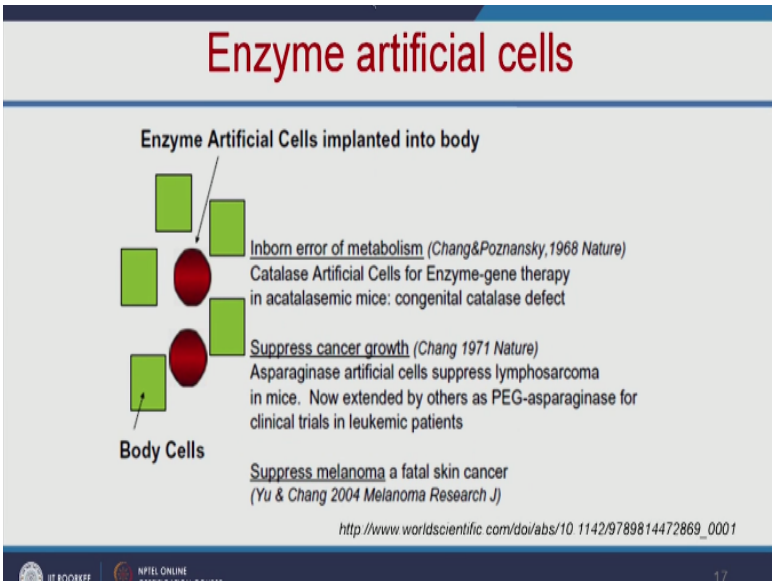

So let us see some of the examples of enzyme artificial cells. For example, here this catalyst artificial cells for enzyme gene therapy was used in mice model which is lacking the catalyst enzyme okay. And we can also use this asparaginase artificial cells which could suppress the lymposarcoma in mice model, and also it can also suppress the melanoma a fatal skin cancer. So we can encapsulate this enzyme at artificial cells and that could be useful for various therapeutic applications.

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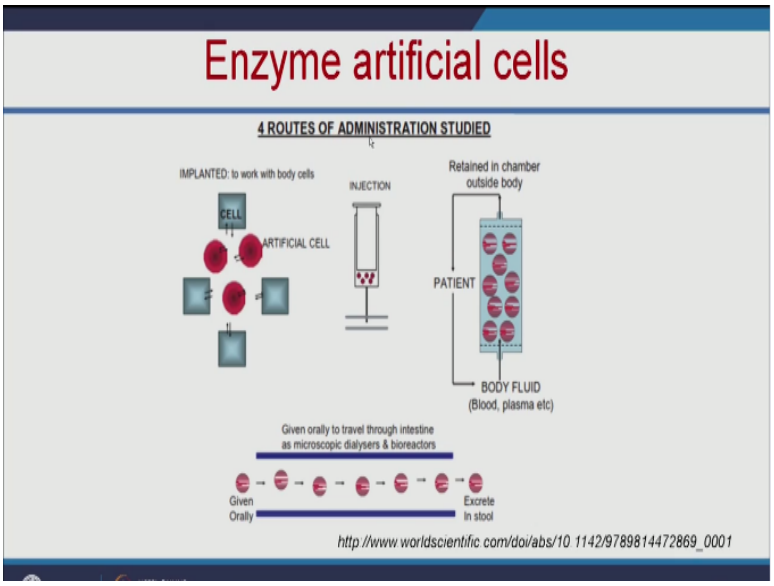

And there are four routes of administration for this enzyme artificial cells, so it could be implanted to work with the body cells or it could be injected okay, or it could be written in the chamber outside the body. So the patient's body fluid can pass through and filter and purify and it can go back to the patient. And another thing is could be taken orally and it will be known normally by the excretion process.

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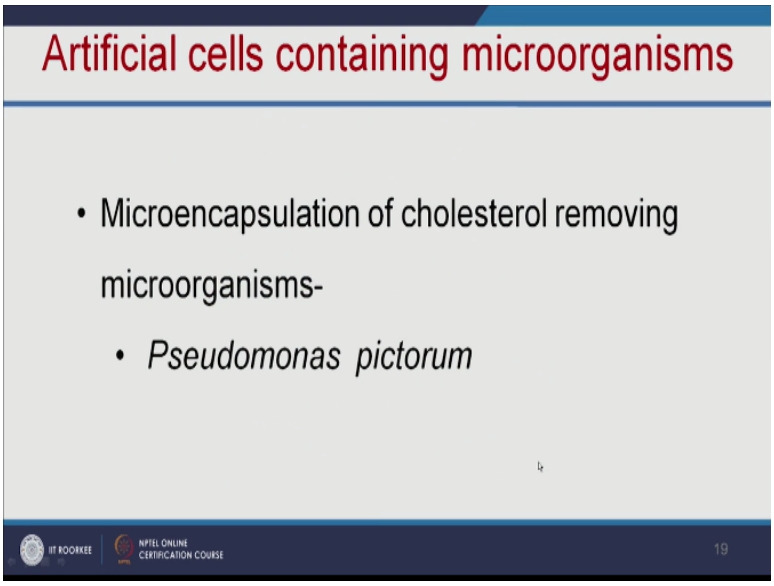

And not only the cells or enzymes we can also encapsulate the bacteria. So you can see here the microencapsulation system cholesterol removing bacteria pseudomonas pictorum, so we can use this kind of bacteria to remove the cholesterol from our body.

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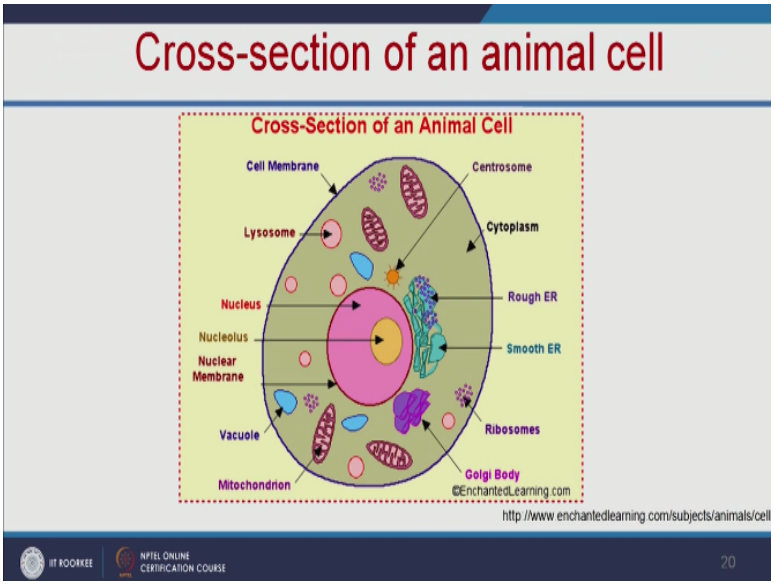

And these are typical cross section of an animal cell which you can see here bacteria and nucleus and various cellular organelles like mitochondria, liposome okay. So the question is can we make similar kind of artificial cells. So how to make such kind of artificial cells, you can see here this picture so each look like a small, small capsules. So the nucleus is looking like a small capsule and the mitochondria look like a small capsules.

So the idea is we can make a small, small capsules based on lipid carriers okay, and we can put those small capsules with a big size capsule. And we can make artificial biological cell okay.

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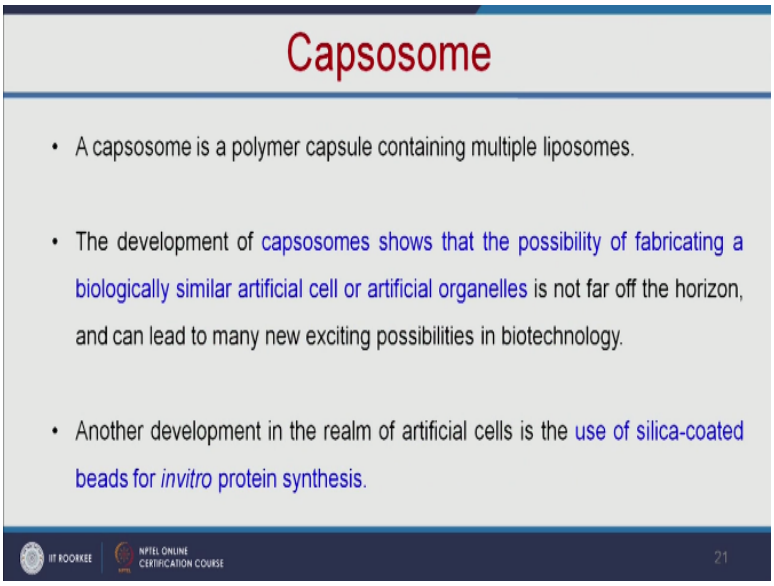

So that is called capsomes, so the capasome is a polymer capsule containg multiple liposomes okay. So the development of capasomes shows that the possibility of fabricating a biologically similar artificial cells are artificial organelles. So we can use the liposome based small capsules, so the each capsules can act like a mitochondria or nucleus or other cellular organelles, and all those capsules will be in a big size capsules okay.

So this complete set up is called as capasome, so which could mimic like your biological cell. So the another development the artificial cell is use a silicon coat of the beats for in theinvitro protien synthesis.

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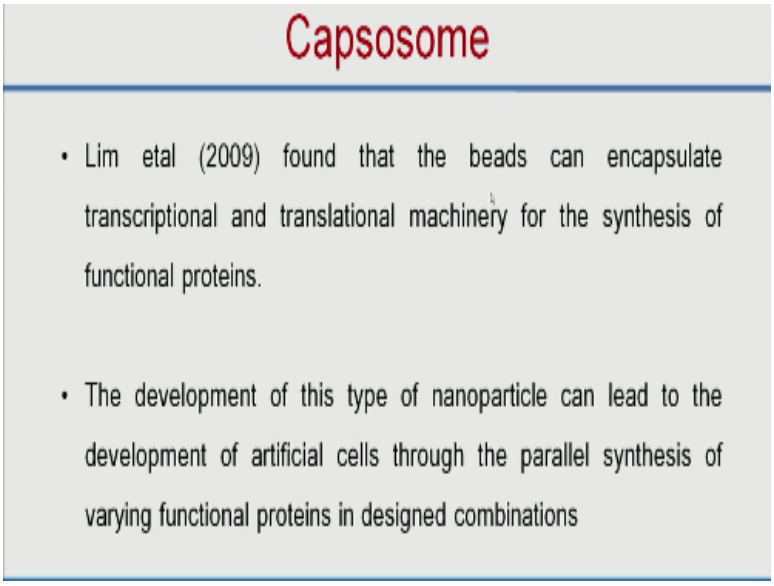

So the linited found that we can use the beats that can encapsed the transcript and the transmissional missonarie for the synthesis of the functional coatings. So we canuse the silica beats okay, that will have the all the ensumed transcrption and translation and it can also liked a trancrption and translation missionary.

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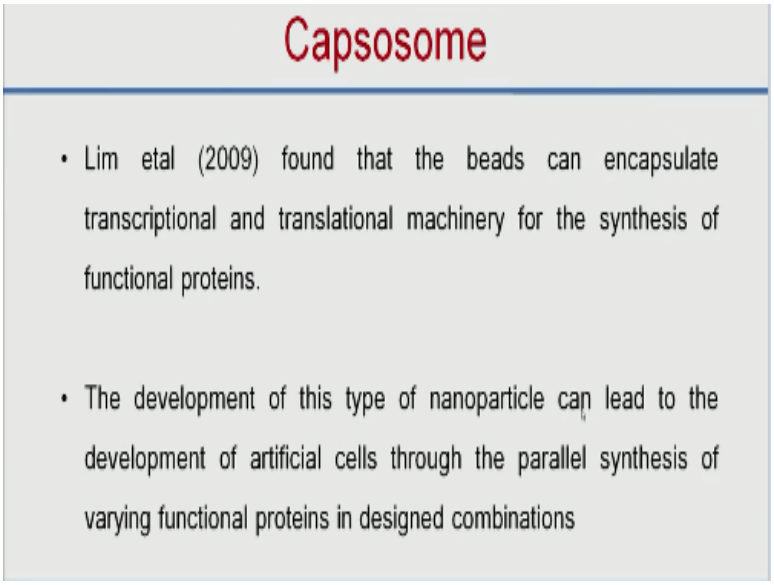

And the nano particle and the second lead to the efficient artifical cell and the development okay.

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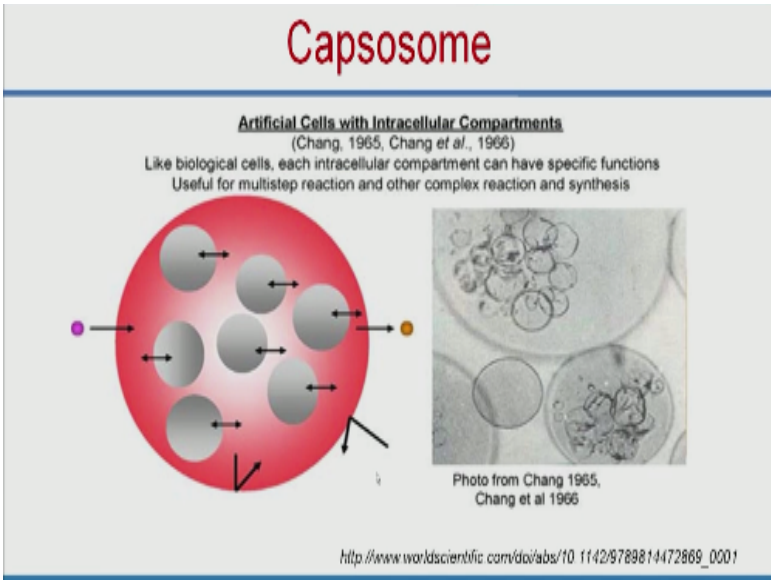

So let us see the capso zone so you can see here the like and the biological cell only so the each intra cellular compared to the at the deprtment have the specfic function okay, so it can function like a nuclearrs or it can function like a mictro condria and rthe liposome small capsolues are in the big size and the liquid based carrier and the capso zone and which mimic like a capso zone and in the biological cell.

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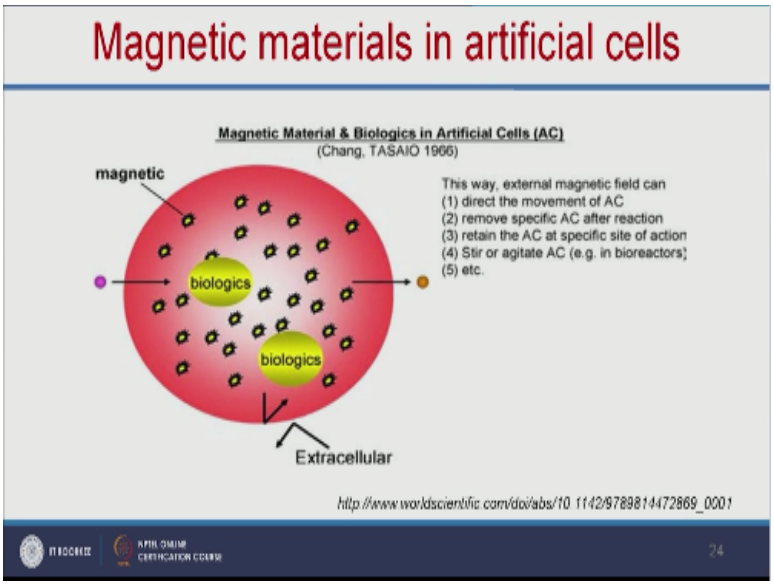

So the thing is the magnet material in the contribution cell in the capso zone we can also add the magnetic particles to the capso zone and the advantage is we can direct the moment of the direct cells we can move the artificial to the particular moment use the extend magnetic field and also we can remove the artificial cell after the reaction again we can retain the artifcal for the specfic cell so we can retasin in the particular locationusin the magnetic field in the location and in the bioreactors using the magnetis properties we are strivct te you can additative it.

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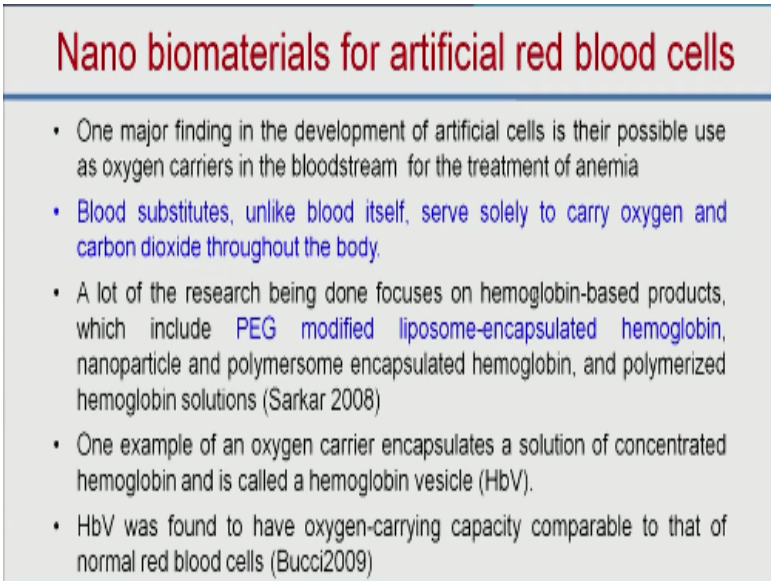

Do the blood through it will be in the nano biomaterials for the making the artifical RBC this is the red blood cells. So one of the major finding in the artificail cells is the possible use as the oxygen carrier and which could be find the treat the anemia and the other disease so here the blood circulation is substute the main function is the carry the oxgen and the remove the carbon di oxidefrom the body here the lot of the research has been done some of the examples we can use the polythelin liquid in the and also in the polymer zome.

So which will act like your artificial r b c and the red bloood substute and the other examples like we use a concretated hemoglobin and we can encrapt in the polymeric basicalll. So the hemagobin have to found the oxygen carrying capacity rbc so here the hameglobin moplecules extended from thr red blood cells are modified by the encrapt in the crossing substute and the linkage process and the stablete the hameglobin and also the a;llow the steleration of the products and the human in the virus and the other micro organism .

So as I told you this red blood substutes or the made up of polymer are it will allow the r b c substutes to sterlife which make sure that there is no viral infection of the blood sample okay.
And the membrane of the artificial cells allow the permium substates and then allow as I told you earlier so the molecule enter in to the we will artifical r bc and we allow the product go out throug the artificial cells.

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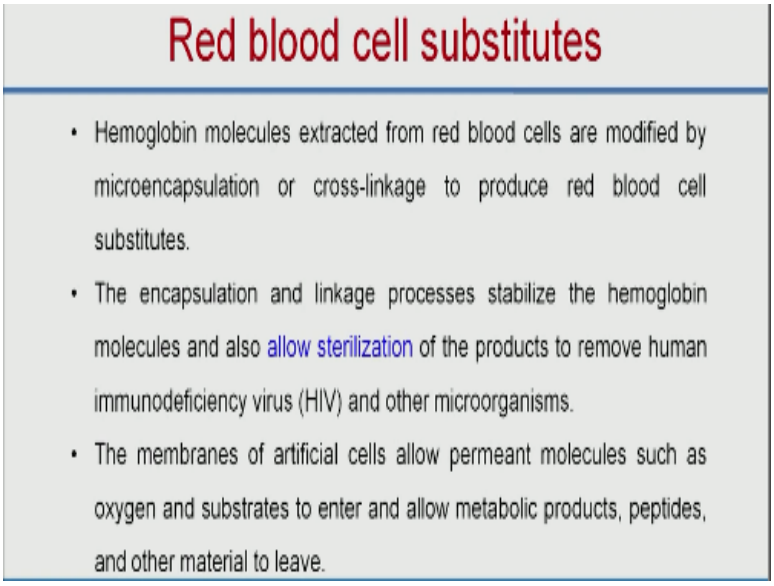

So the artifical are here in the artificial rbc this is product from the rejection so we are ni the cells are enter into the polymeric so the material so these are producted from the numeroligical rejectin and we need a RBC substutes in the most of the case are like the surgery in the emergency treatment the modified does not contain RBC memberane. So therefore blood group antigens, so ther vwill not need for the cross matching .

So as I told you earlier is the rbnc substutes are mainly made up of the polimers so you don't have in the blod group and the antiger on the surface so you will give this artificsial to any person like if the person is having the A group in the B group or O group there is no restriction and the artificial RBC to any person with any kind of the blood group That is the advantage of the RBC because it don't have the surface antigent okay.

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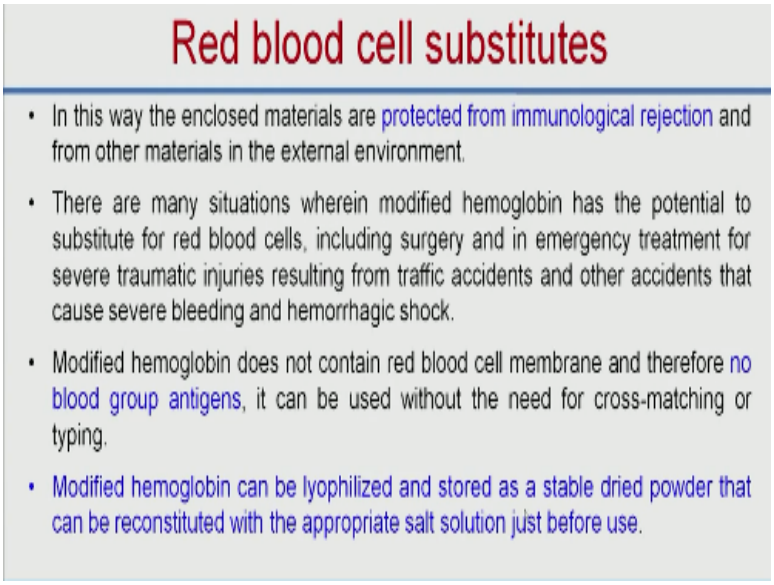

So the another advantage is this modified hameglobin can be lifolised and stored as a stable dried powder so that just means the RBC is stored in the 43 days in case that the several month it is for the yearts the in the sallinethis is the advantage of the RBC.

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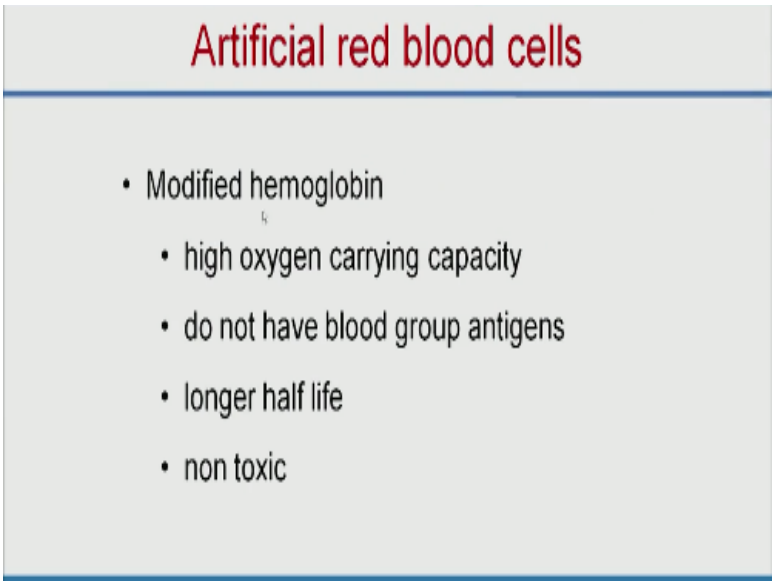

So let us see some as I told artificial RBC will having in the capacity normal rbc and there is any person to the any kind of the blood group and compare to the normal RBC it will have the longer life and also it is the non toxic and okay.

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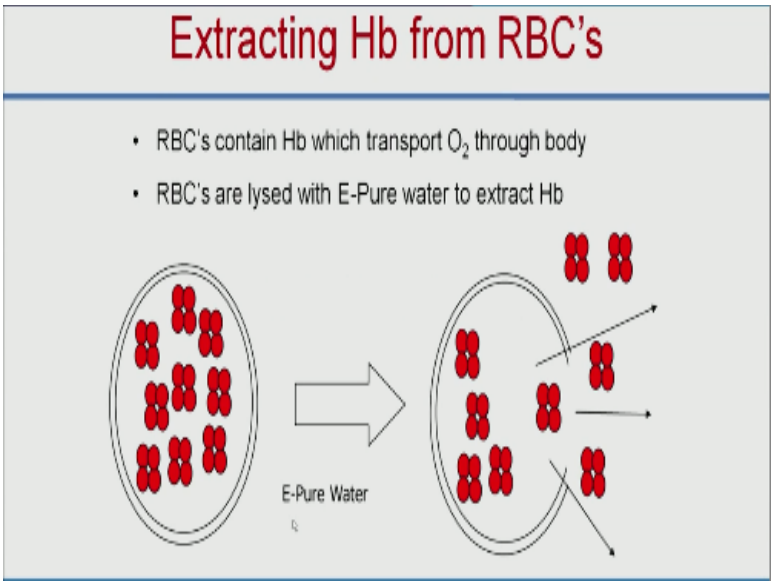

So there is a making procedure and the artificaial RBC and the extract the hameglobin ni the RBC and this RBC contains the ameghlobin which is going to the transfer the oxygen through out the body so these RBC can be realised ni the pure water. So just put the RBC put in th water and that will les and it will in the hameglobin in the inject the hameglobin directly and there is because.

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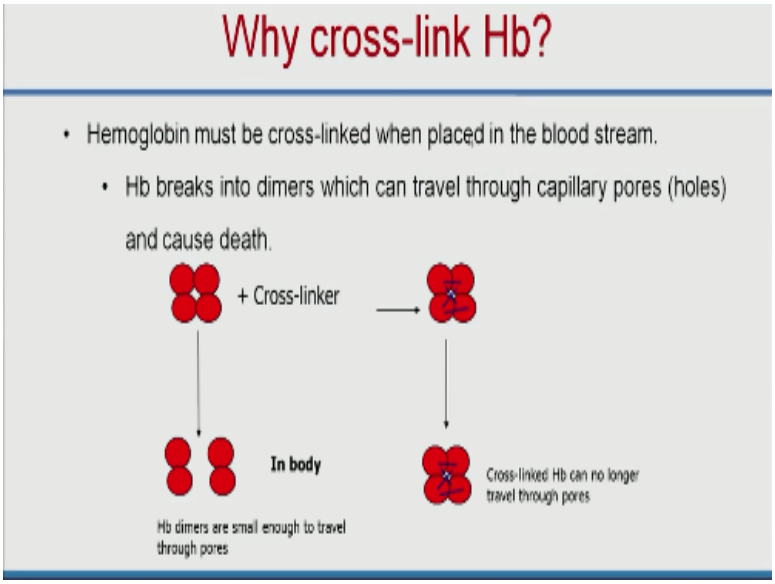

When placed in the hemoglobin and the brakes in to the diameters and which can travel through the capillary holes and they will hemoglobin should be cross links and this cross links will be hemoglobin travel through the pose. So we can en capitulate this and the polymer in the artificial RBC. So let us see the difference between the normal RBC and artificial RBC.

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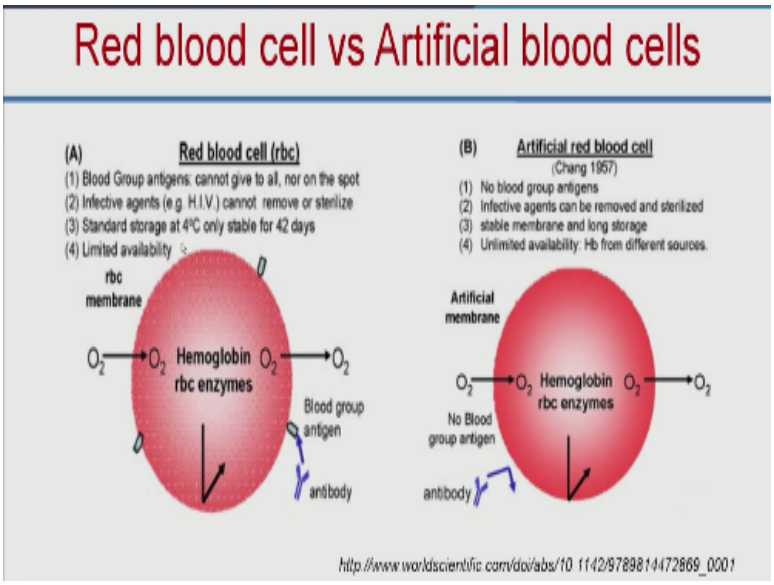

And the RBC will have the blood group and the antigens ,so we cannot give to all and we cannot give in the spot so we have to check the blood group and we have to check the computability and then only we will gives the blood donation okay. So also the another problem is there is a chance for the infecting like H I V okay which we cannot from the blood and the another thing is we can store the RBC at 4% for threw 42 days and the some of the blood groups are in the limited variability and there is also major issue but in the case of the artificial.

So there and there is no blood group antigens' will give to any group in the sterilized in the powder form we can use it will have in the artificial membranes in it and the artificial red blood cell.

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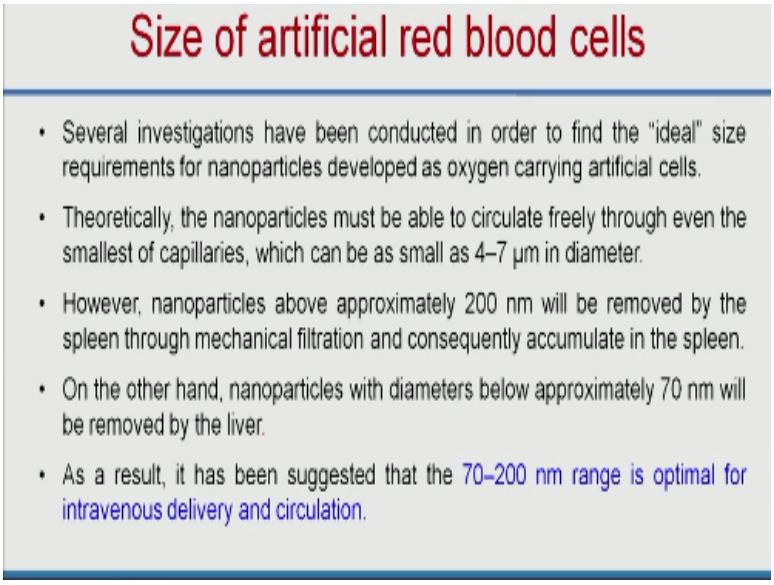

So when you make the artificial cells so the size is very important perimeter so the seven investigation has been do ne in the ideal size for the artificial RBC. So the theoretical on the normal RBC or in the between 4 to 7 micrometer okay, whenever we make the nanoparticle more than the 200 nano meter. So that will be removed by your sprain and the 17 nano meter and that will be removed by the lever the so we have to make the nano meter which has been 70 to 2000, so that it will be use full for the circulation.

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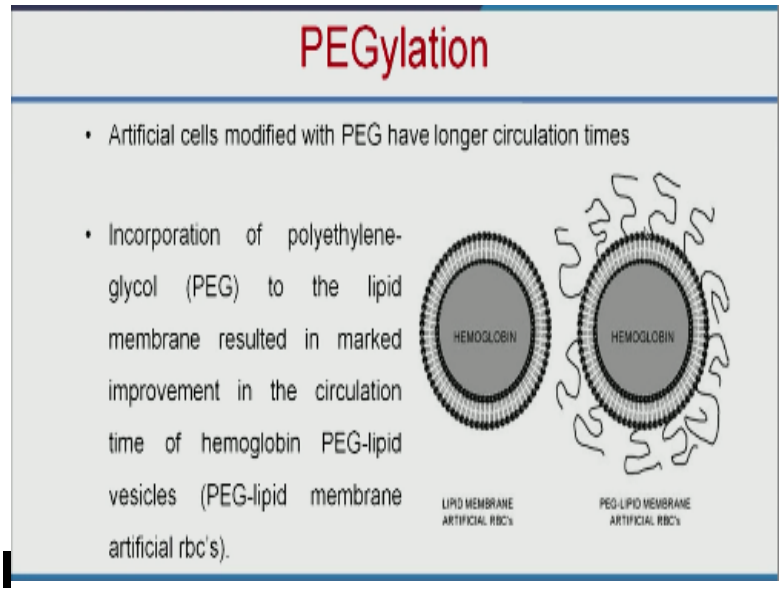

We can increase the circulation time by the adding the P G so that is called as the percolation and they will peculation. So we can add this poly thane glycol so that will improve the circulation and the it will improve the stability of the artificial cell.

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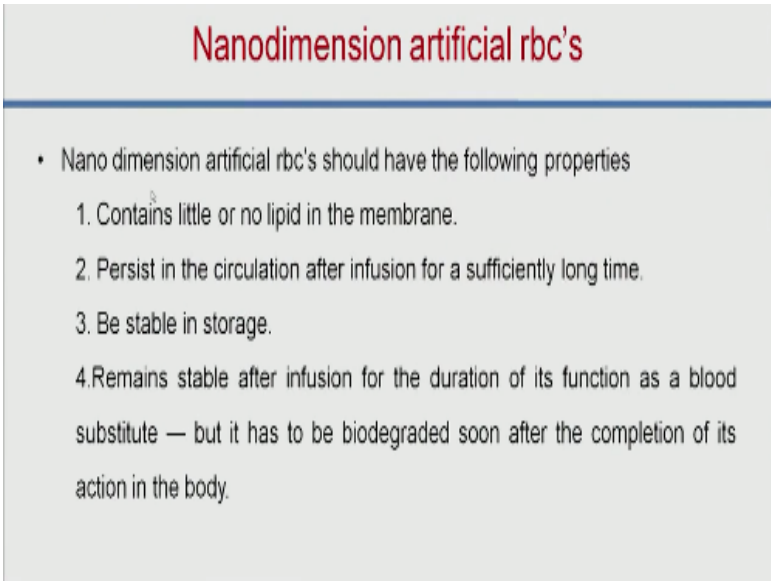

The nano dimension have thaw following properties and in the sufficient ant it stable in the duration as the blood sub state and the after the function over they will be biodegrade in the membrane material and it toxic.

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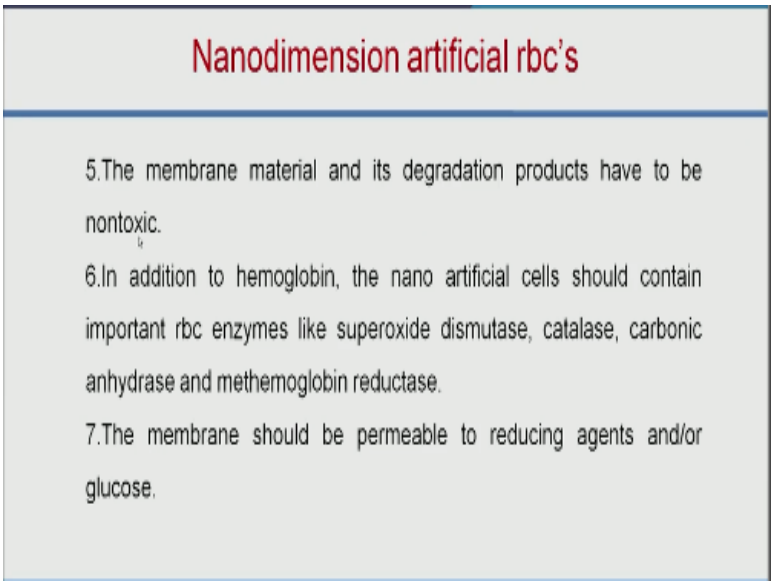

The toxic and the addition to the hemoglobin in the nano artificial cells could contain for the catalyst in the carbon anhydrides and the other enzymes okay. So the artificial RBC is the function of the is not only carrying the oxygen so it has to remove the carbonados oxide and it should also remove the radical it should have some other enzymes artificial RBC so that it can exactly mimic like your ordinal RBC and the membranes should be.

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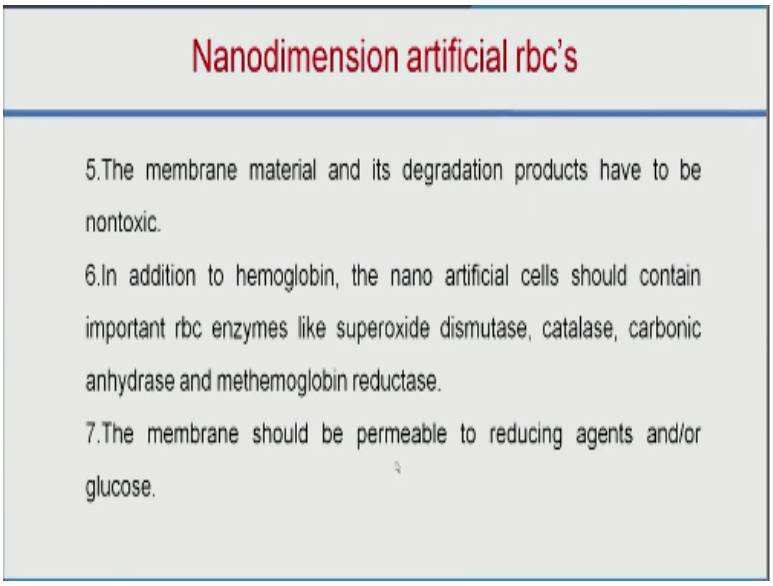

So the permeable to the reducing agents or the glucose okay, so the membranes also so be permeable. So that it can be in take the glucose and it can convert in to the product. So let us see the difference see here the normal size is between.

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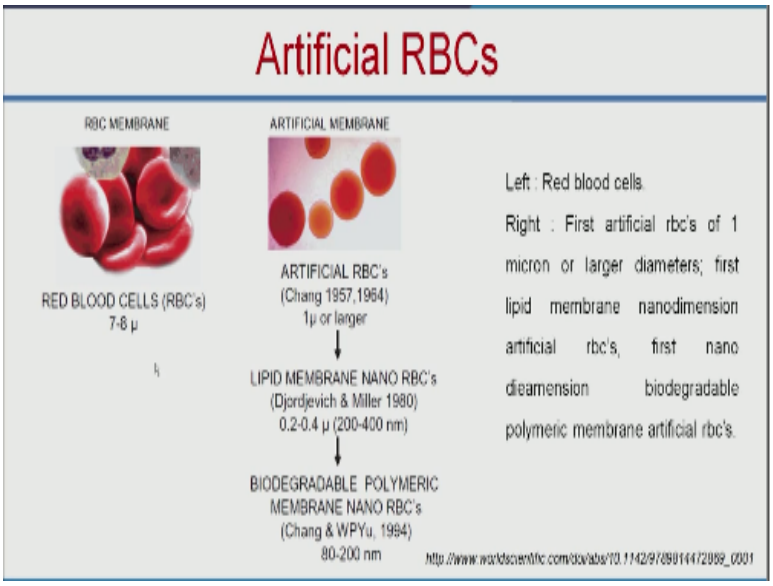

And the micrometer and the artificial are in the first artificial RBC in the size of one micrometer or the larger and the later the size is reduced to the 0.2 to 0.4 micron and that is okay the 200 400 nano meter it is the pid waste and the nano RBC and now what ever having is bio degradable poly numeric membrane and in the RBC here is the size between 80 to 200. So that it could escape from the liver as well as splint.

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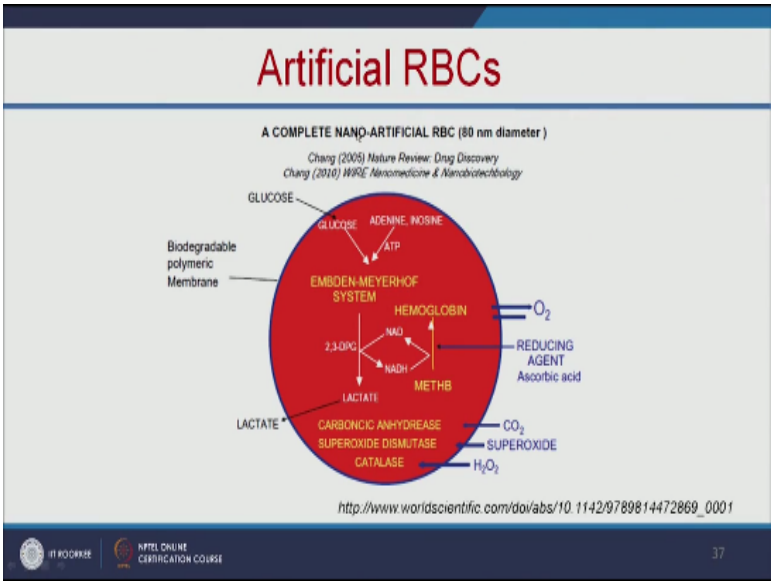

So this is the completer nano artificial RBC you can see here it is having hemoglobin for carrying oxygen and also it is having enzymes like carbonic anhydride for moving the carbon dioxide and it is also having enzymes like super oxide dismutase and catalase to remove the free radicals in your blood.

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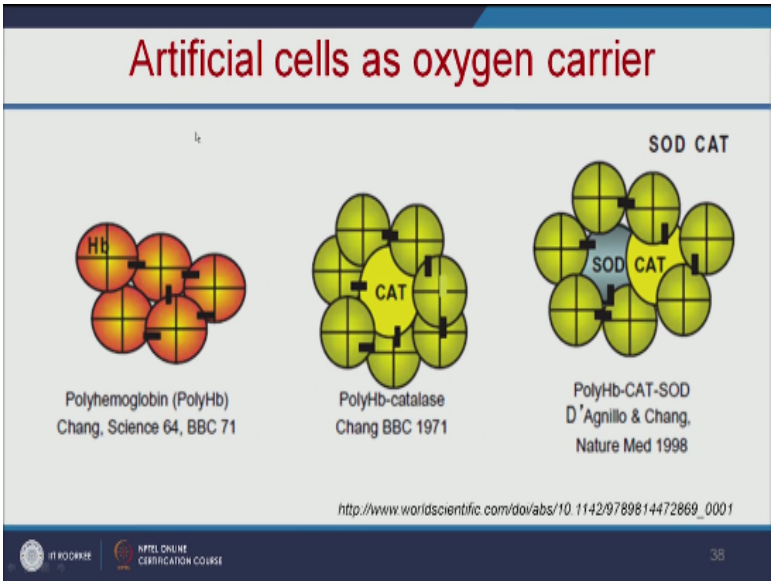

So let us see some of the applications of artificial cells so artificial cells as oxygen carrier so we can have a polyhemoglobin so that will have more amount of oxygen carrying capacity. And we can also add SOD that is supper oxide dismutase and careless enzymes so that will remove the free radicals.

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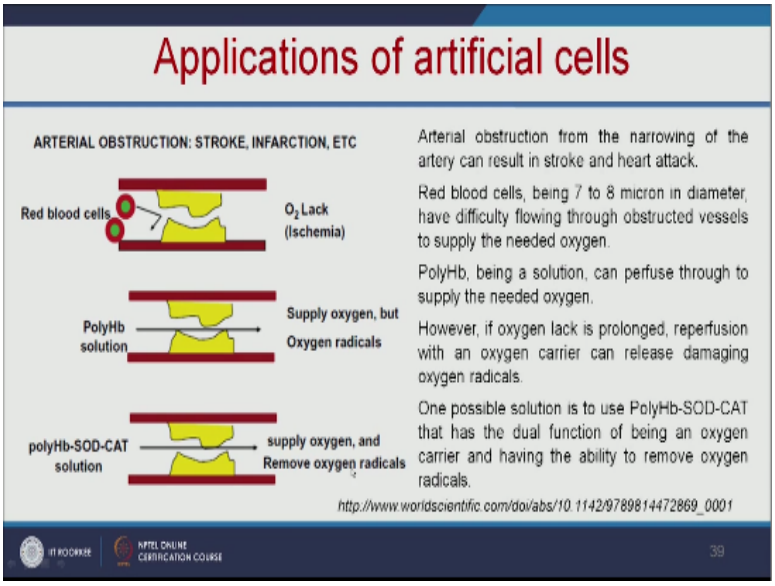

So here we can use this artificial cells for Ischemia okay. So here when there is a arterial obstruction and that will narrow the artery so that will result in stroke and heart attack okay, so the normal RBC which is in the size of 7 to 8 m in diameter it cannot pass through this small passage okay and due to make of oxygen there is the high chance for getting this stroke as well as heart attack so when you use this poly hemoglobin solution it is in the size of nano so it can easily pass through this and it can supply the oxygen.

But the problem is so if there is a oxygen lake is prolong so due to reperfusion with an oxygen carrier it can release damage in oxygen radicals, so it may produce some oxygen radicals okay. So in this case we can use that poly hemoglobin with SOD and Catalase enzyme solution, so it can be supply the oxygen and also it will remove the oxygen radicals it is having dual function okay.

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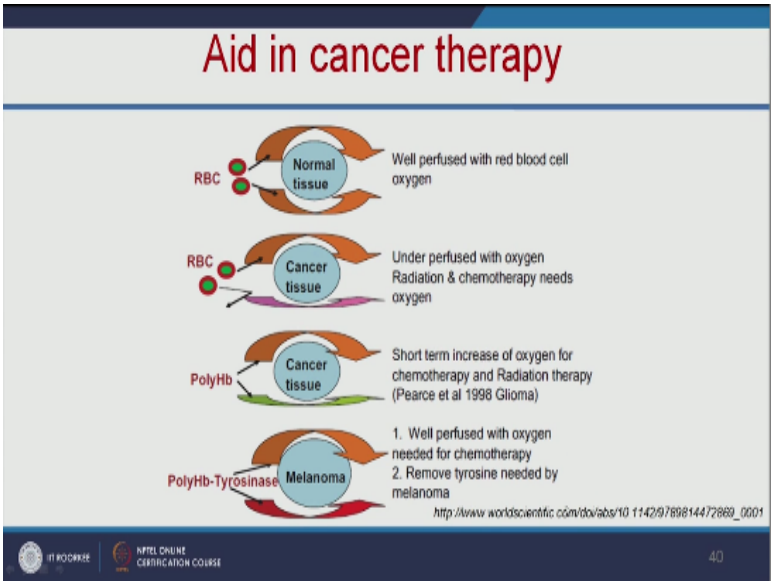

So let see how we can sue this artificial RBC for cancer therapy so in the normal tissue so it is well perfused with RBC and oxygen but in case of cancer tissue it is under perfused with oxygen but for successful radiation chemotherapy you need oxygen so the normal RBC cannot enter ion to the cancerous tissue okay. So we can use the poly hemoglobin so due to small size it can easily enter the cancerous tissue, and it can increase the oxygen which could be useful for successful chemotherapy and radiation therapy.

And another thing is along with the poly hemoglobin we can also add a enzyme tyrosine's okay, so it will remove the tyrosine which is needed for the melanoma growth, so the first function is it will give the oxygen which is needed for chemotherapy and radiation therapy and it will also remove the tyrosine which is needed for melanoma growth. So in this way it is suppress in the cancer growth. So next thing is we can also use it for Hemoperfusion.

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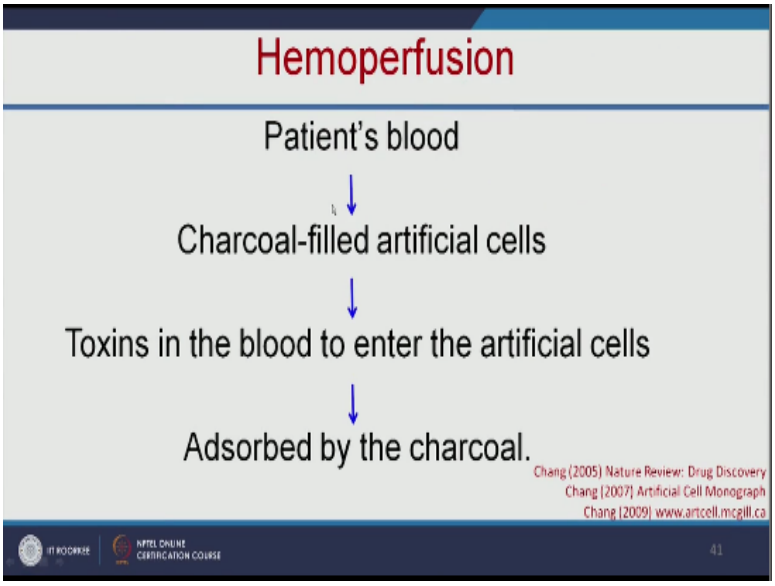

So if there is a toxin in the patient blood that could be removed by charcoal filled artificial cells so the charcoal can be fill in the artificial cells so that toxins in the blood will enter the artificial cells and all the toxins will be absorbed by the charcoal inside the artificial cells.

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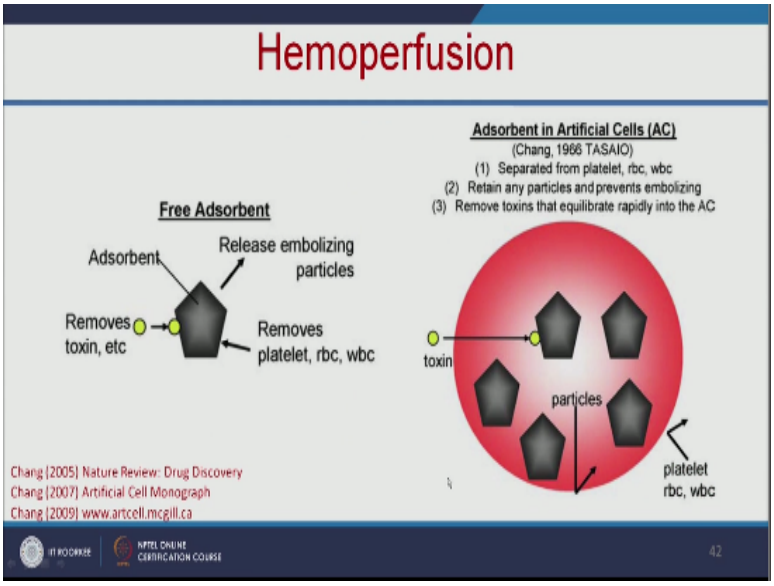

So we can see here when you inject the free adsorbent what happens is it will remove the toxin but the problem is our platelet in RBC will go and attack it okay, so when you en caplet in though artificial cells it is separated from the platelet RBC and WBC and all the particles are inside the artificial cells so the toxins can enter inside and it can purify the blood.

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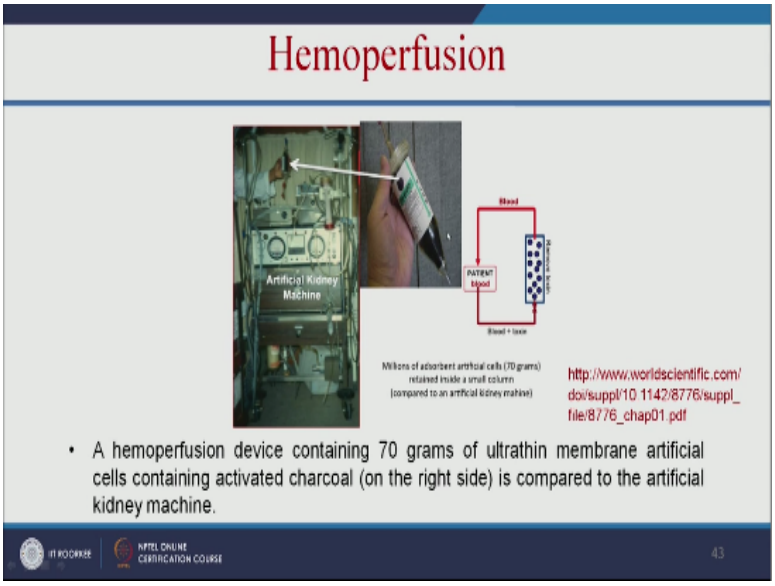

So we can see here this one is millions of adsorbent material of artificial cells and the patient blood will pass through the artificial cells and the purified blood will be come to the patient and when compare to the artificial kidney machine we can see the smallest size so this hemoperfusion device containing 70g of ultrathin membrane artificial cells which containing activated charcoal and which could be the size could be compare with the artificial kidney machine okay.

And it can perform the removal of toxin from the blood so which can perform equivalent to this artificial kidney machine and it can remove all the toxin from your blood.

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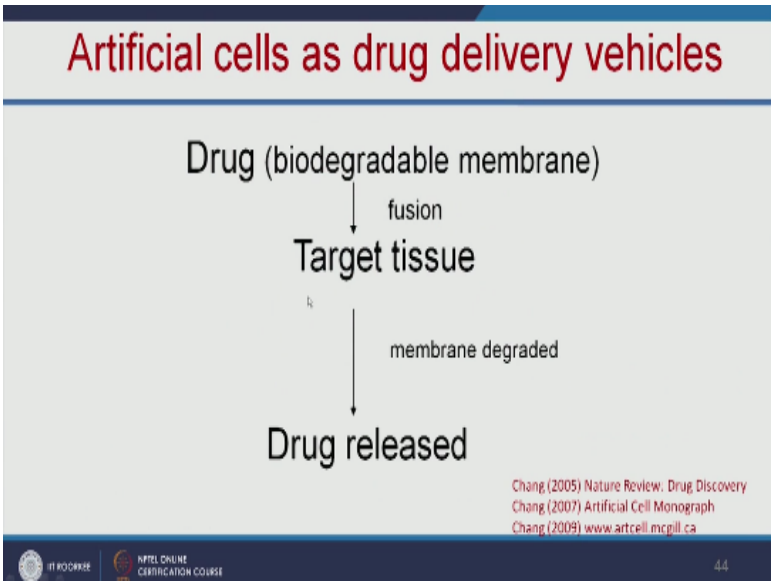

And we can also use this artificial cells as a drug delivery vehicles so this artificial cells are made up of biodegradable membrane so we can add some kind of drugs or therapeutic molecules and this can be release at the particular location we can target this artificial cells to deliver the drug in to the particular location for various therapeutic applications.

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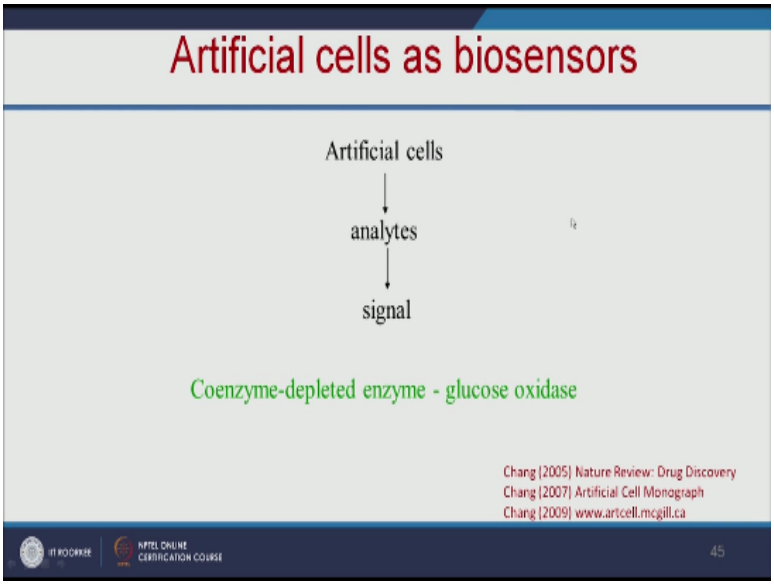

And this artificial cells can also act like a biosensors so which will have some analyze okay so for example if there is a glucose level is more in the blood so it can interact with the glucose and it can produce some kind of flows and signal okay. So this artificial cell can also act like biosensors.

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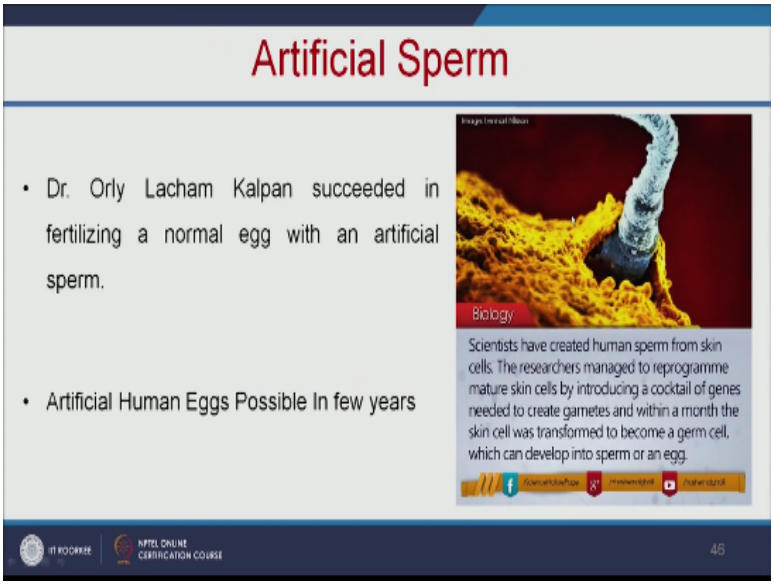

And reason break through is this group they have made a artificial sperm okay so now it is a major problem is infertility okay so this research group they have made a artificial sperm and they have trying to make also artificial human eggs which could be possible in few years. So how they created so they have created the human sperm from skin cells and they reprogrammed this skin cells by introducing some genes and within a month the skin cell become a germ cell. So which can be developing in to sperm R and egg?

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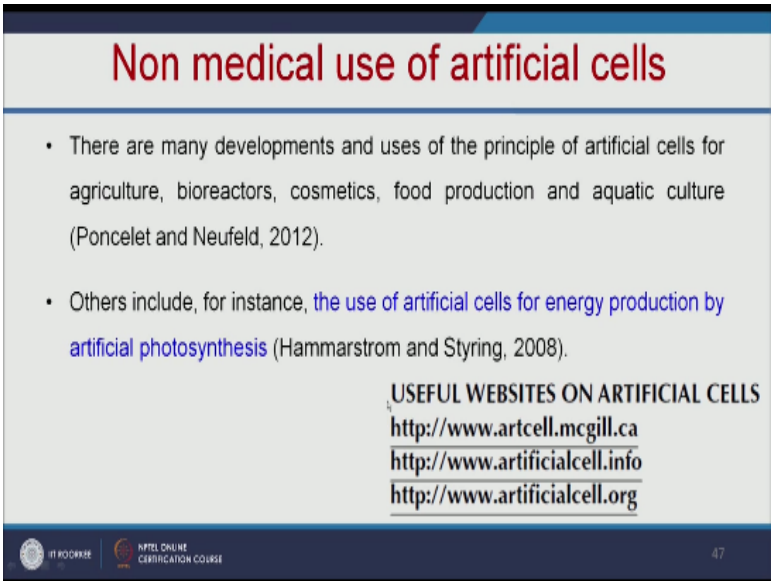

So this artificial not only for medical applications it can be also useful for non medical use for example it could be useful for cosmetics as well as food product and other application and also this artificial cells can also be useful for energy production by artificial photosynthesis and these are some of the useful websites if you want to get more information about the artificial cells, so before I conclude I want to discuss the another area that is synthetic or minimal bacteria cells.

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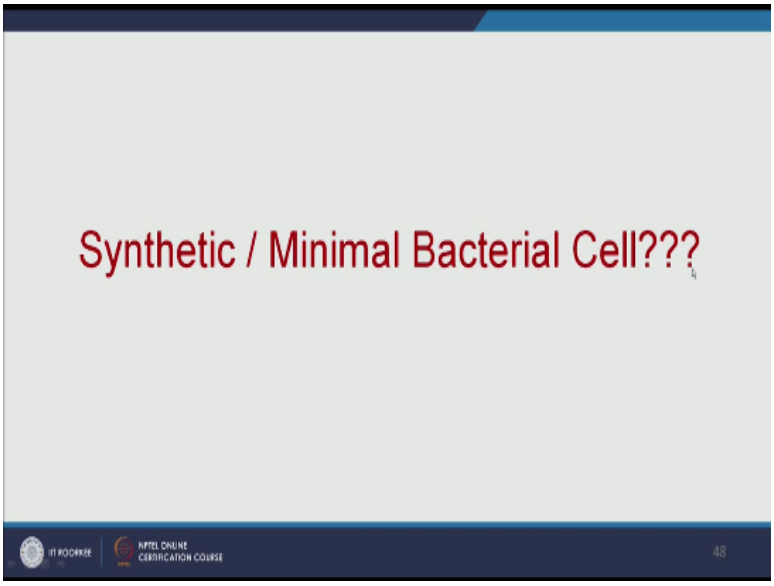

So this is different from the artificial cell so let us see what is synthetic or minimal bacterial cell.

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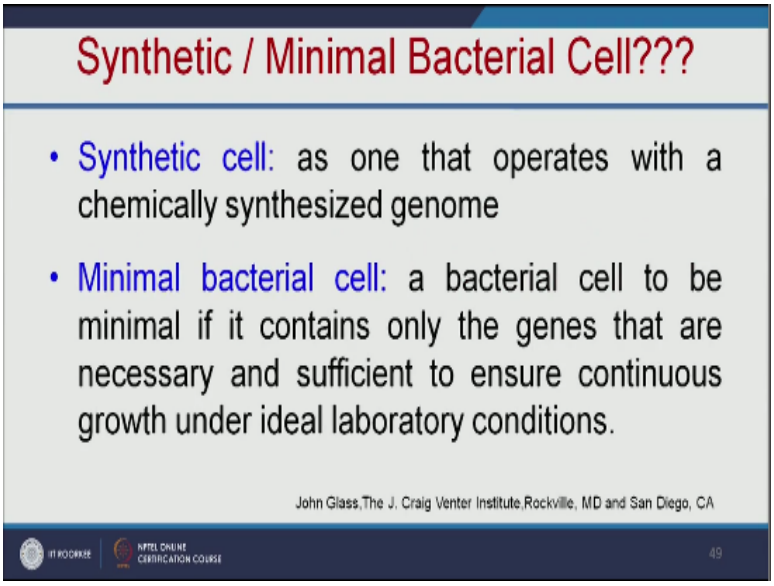

So here the synthetic cell is a cell that operates with a chemically synthesized genome, and the minimal bacteria cell is a cell so it contains only the genes that are necessary and sufficient to ensure continuous growth under ideal laboratory conditions.

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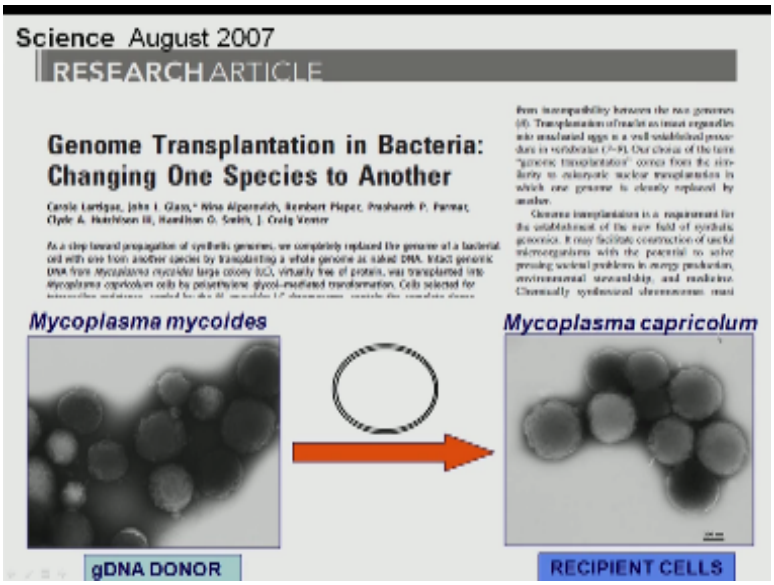

So this article is publish in science in 2007 okay so they have done the genome transplantation in bacteria so it will lead to changing from one species to another species so this kind of research was done by Craig Venter group okay so if the change in it from Mycoplasma mycoidesto mycoplasma capricolum.

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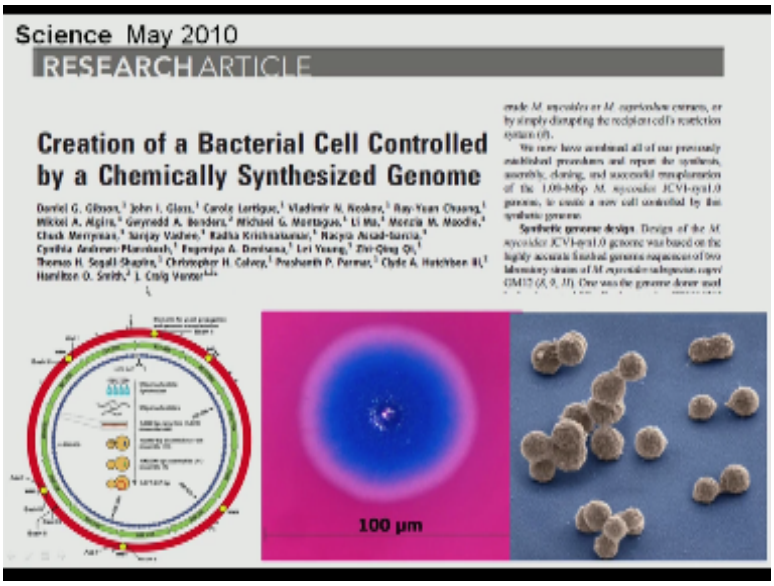

So there is a another research published from the same group Craig Venter group okay so this as in science 2010, so they created a bacteria cell which could be control by a chemically synthesis genome. So let us see the details.

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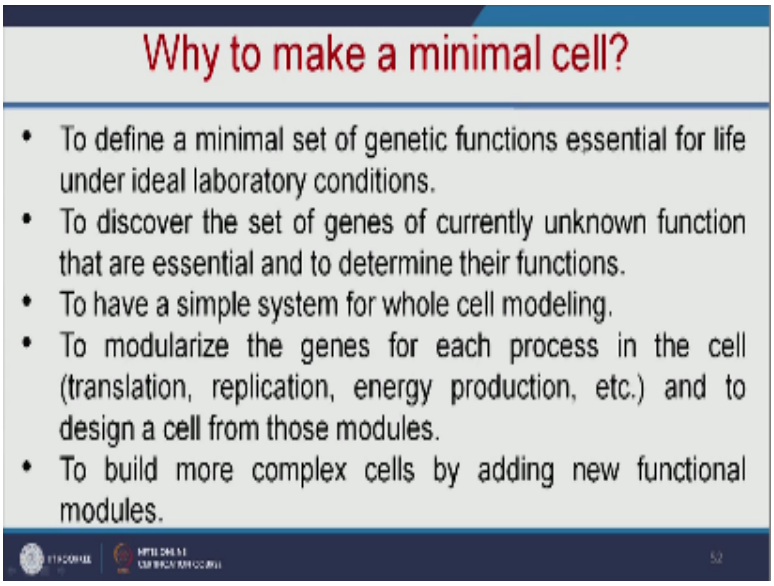

So why to make a minimal cell so to define a minimal set of genetic function essential for life under ideal laboratory condition and to discover the set of genes of currently unknown function that are essential and to determine their function and to have a simple system for whole cell modeling and to modularize the genes for each process in the cell okay. And to design a cell from those modules and to build more complex cells by adding new functional modules.

So the what are the idea is so we can make a minimal set of genetic functions okay which is essential for the survivor of the cell and we can also use there is a model system to understand if you have x gene what will be function if you have y gene what will be the function so it will act like a simple model system to understand the function of each and every gene.

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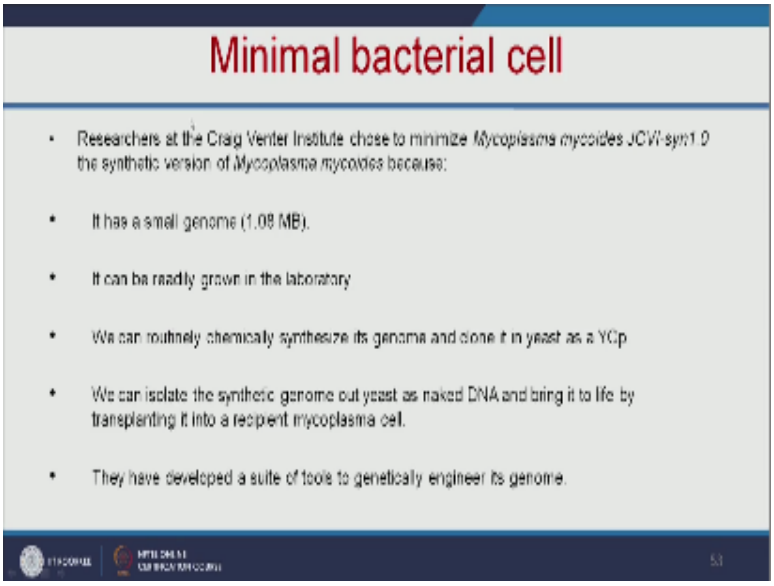

So for making the minimal bacterial cell researches at Craig Venter institute they have selected mycoplasma mycoides because it has a small genome which is only one MB okay and it can easily grown in the laboratory and we can easily synthesis genome and we can also isolate the synthetic genome from the yeast okay and they have several tools to genetically engineers genome. So that is why they have selected this mitcoplasma mycoids for making the minimal bacterial cell.

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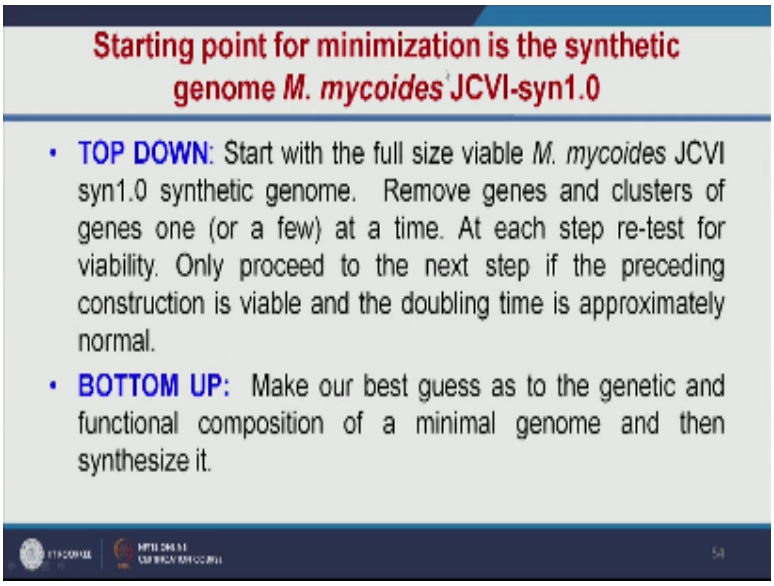

So how to make this minimal bacterial cells there are two approaches one is top down approach and other one is bottom up approach okay soothe top down approach is start with the full size viable bacteria then remove the genes and clusters of genes one at a time and that each step retest for viability and only proceed to next step if the presenting construction is viable and the doubling time is approximately normal.

So we can take the bacteria okay and remove a particular part of gen and just check it whether the bacteria is viable and the doubling time is normal so then only you can proceed to next step. So that is called as top down approach from the whole genome you are cutting down small, small pieces of genome or your are removing the small, small pieces of genome and you are making the minimal genome okay.

And next approach is bottom up approach okay so make our best guess to the genetic and functional composition minimal genome and then synthesis it, so the bottom up approach is a random approach so you can make a guess what are the genes required for the cell to be arrive okay so we can take those genes and we can synthesis those genes and put it in to the bacteria and we can check it whether the bacteria is arrive and how it is performing okay.

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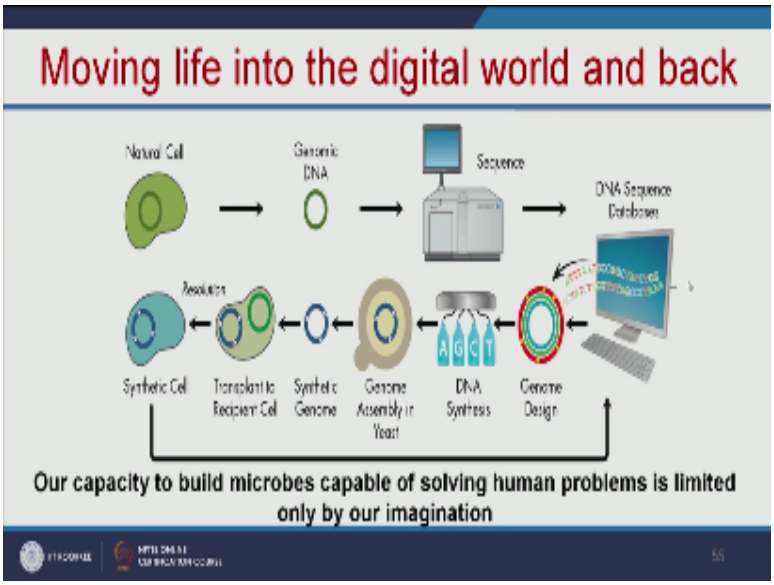

So how they made the minimal cells or synthetic cells so they taken the natural cell and they take the genomic DNA and the sequent the genomic DNA and after the squinting they made the own genome design and the synthesis genome and the all the genomes are assemble in the yeast and they transfer to the recipient cell then the recipient cell genome was degraded then you will get the complete synthetic cell with the minimal genome. So let us see the possible future uses of this synthetic or engineer species.

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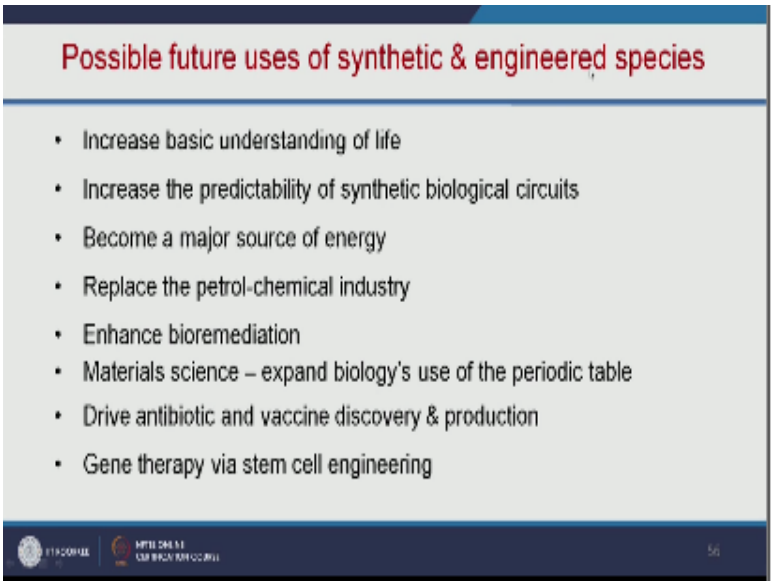

So it will increase a basic understanding of life okay and also it will increasing the predictability of synthetic biological circuits and it will replace the petrol chemical industry it will make the bio fuels okay and it will enhance the bioremediation and it will also play major role in material science and it will drive the anti biotic and vaccine discovery and production and we can also use it for gene therapy via stem cell engineering okay.

So as a summary of this lecture, so in this lecture we have learnt what is artificial cell okay and how to make enzyme with artificial cells as well as a artificial RBC and what are the various applications of this artificial cells how it can be useful for cancer therapy and how it can be useful for enzyme therapy and we have also learnt what is synthetic cell and what is minimal bacterial cell and also its various applications. So I will end my lecture here I thank you all for listening this lecture I will see you in another interesting lecture.

For Further Details Contact
Coordinator, Educational Technology Cell
Indian Institute of Technology Roorkee
Roorkee – 247667
E Mail: etcell.iitrke@gmail.com. etcell@iitr.ernet.in
Website: www.iitr.ac.in/centers/ETC, www.nptel.ac.in

Production Team
Sarath K. V
Jithin. K
Pankaj Saini
Arun. S

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