**Sensors and Actuators**
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**Lecture – 05**
**Sensors Part 5**

Hi, welcome to this module. So, this is a continuation of our previous few modules on sensors. So, we have seen several types of sensors till now including our heater and then you have interdigitated electrodes on the heater. Then you have seen that how the sensor can be used to measure the impedance change of these cells or of the tissues. Then you have seen how we can measure the change in the mechanical property, the elasticity of a material with the help of a piezoresistive microcantilever. And, then we also looked at how we can design a drug-screening tool to identify a drug for particular patients or in another way a patient-centric platform.

We have also seen that the sensors can be used to understand antibiotic susceptibility testing which antibiotic would be effective to that particular bacteria. Now, let us see microfluidic chip that can be used to understand angiogenesis and anti-angiogenesis properties. So now, what exactly angiogenesis means and what are the different combination of therapies that one can use to understand that how we can stop the angiogenesis ok. So, angiogenesis is a growing of blood vessels and in a way that when there is a cancer , then the nutrition; see cancer is what? It is a similar cell of our body just notorious one know.

So, if you if you know if you are more notorious you require more energy, if you are less notorious, calm sitting on the same place you require less energy. So, notorious cells requires more energy, if we stop energy to the notorious cells what will happen? Cells will die ; so, cancer are notorious cells and the best source of energy for our body is carbohydrates, carbohydrates. Where does carbohydrate come from? Wheat, rice all the kind of burgers, pizza potato, then sugar after carbohydrates sugar .

Carbohydrates also come from milk . So, if I cut the source of carbohydrates then the source of the energy that the cancer cells or the cells require has been stopped. So, what can be the other sources? How about I use all the vegetables instead or all the fruits instead of course, this vegetables has some amount of carbs, fruits has amount of carbs,

but lot of fibers . So, cutting the carbohydrate as a source of energy can be one way of not providing enough energy to the cells . Then the cells start consuming their fat cells so, fat cells would be dissolved and that is a way if you understand ketosis how it works.

But coming to cancer if I so, the point is it requires energy like any other cell . So, along with energy what else it requires? It requires blood flow and the energy to the cell will come through the blood . So, the blood should flow and the nutrients will diffuse through the blood to that cell, isn't it. So, for flowing the blood there should be a creation of vessels towards the cancerous tissue. This creation of vessels is called angiogenesis .

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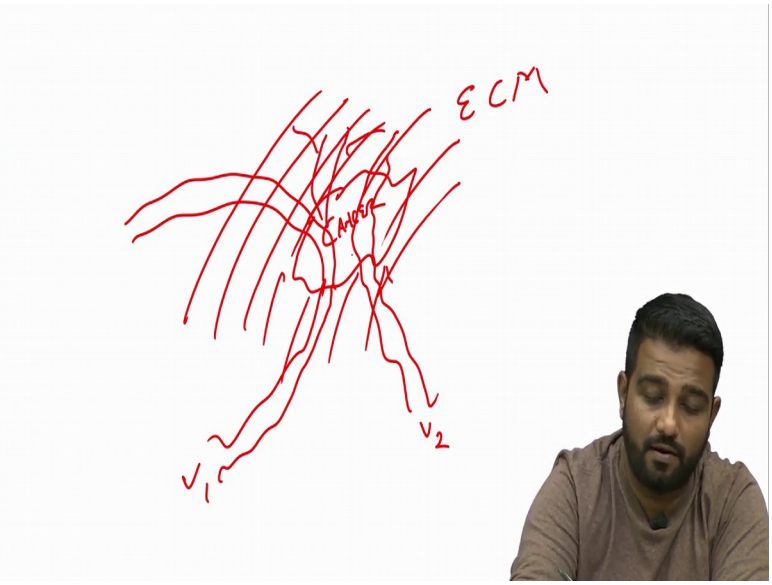


Now, let me show you on the screen how the cancer tissue looks like and how they discovered with the extra cellular matrix and how the vessels form , if you see the slide. So, assume that this is a cell, this is a tissue ok; tissue is composition of lot of cells. This tissue is covered with lot of what you call is covered with extra cellular matrix, this is a cancer tissue .

Now, what will happen is to provide the energy to the tissue there is formation of vessels, formation of vessels V 1 V 2 through which the nutrition will flow and then these vessels will be further divided into capillaries like that . So, through which the nutrition will flow say I will just remove the extra cellular matrix. So, not to confuse you with the other things , just let me quickly draw it again.

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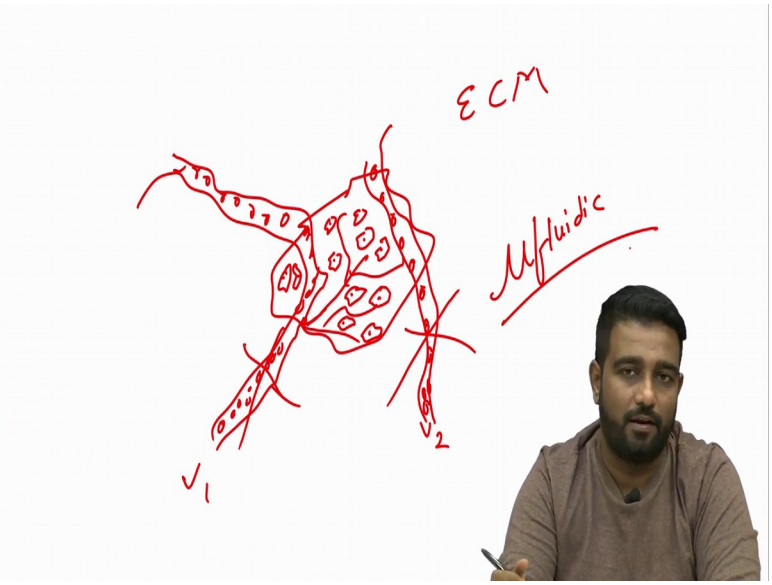


These are cell and then formation of vessels and then from vessel there are a lot of capillaries , same thing happens on whether a vessel 2 and then vessel 3 and so on. These vessels will carry the blood , this vessels is carrying the blood through this will diffuse in the capillaries and it will reach to the each cell within the cancerous tissue, each cell within the cancerous tissue.

The nutritions through these vessels will reach to the cell in the cancerous tissue and thus helping the cells to grow further, thus helping the tissues to grow further . What we want to know is can we use a drug or a combination of two drugs to stop formation of vessels. If I stop the formation of this vessel what will happen? If I stop the formation of this vessel what will happen, that the nutrition reaching to the tumor will reduce isn't it. How can I design a microfluidic platform, microfluidic to study such a effect hmm.

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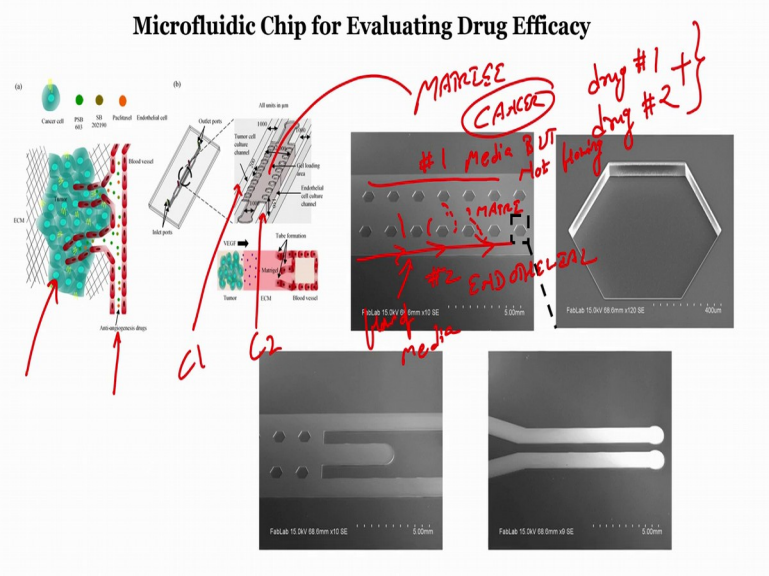


So, for that if you see this particular schematic you can see that this is a representative of a vessel, the red one, this is cancer, this is ECM matrix . Now what will happen that the blood will flow through this and it will diffuse into the tumor , that is what we have discussed. So, how this microfluidic platform will help us to understand which drug is called anti-angiogenesis drug, which anti-angiogenesis drugs or combination of it will stop the formation of vessels . To study that we will be using a microfluidic platform such that it has two channels, here is channel 1 here, there is channel 2; channel 1 channel 2 in between there is a Matrigel.

You see here also this is channel 1, this is channel 2 and in between this region there is a Matrigel ok. So, now what will happen that in channel 1 we will load cancer cells, in channel 2 we will load endothelial cells. What are endothelial cells? Endothelial cells are the cells which helps to form the vessels, to forms the vessels that will carry the blood, this cells . So now, I will and then I will flow the media on these endothelial cells and I will just load the cancer cells with media, I will not flow it . Because, the flow of the blood occurs in the vessels not the there is extra cellular matrix which provides the nutrition. This media will provide the nutrition, but it is in a stable condition we are not flowing it, it is stagnant .

So, what I said is that in the channel 1 there will be media, there will be media, but not flowing media. Channel 2 there is a flow of media, media is a solution to keep the cells

alive, media is solution which not the nutritions to keep the cells intact. In between what is there? This Matrigel is there. Now, I will see how there is a formation of channels because, the release of cytokines there is a formation of blood vessels from channel 2 towards channel 1 like this. When I flow it for 48 hours, I will see that there is a channel formation from channel 2 towards channel 1 ok.

I want to stop the formation of these vessels; I want to stop the formation of these vessels, for that what can I do? I will treat my cancer cells in channel 1 with drug 1 and again see how these vessels are forming from channel 2 to channel 1. Then I will treat the cells in the channel in the cancer cells which with drug 2. Again, I study the formation of the channels, then I treat the cancer cell with drug 1 plus drug 2. And, I will again check the formation of channels from channel number 2 to channel number 1 formation of vessels from channel number 2 to channel number 1.

What I will find is then a drug which is effective or combination of the drug which is effective will stop formation of channels or the channels would be broken like this. Because channels are broken or channels are not forming then the nutrition from the blood cannot reach to the cancer because, there is no channel carrying the nutrients got it. So, the idea is how to design this microfluidic system and this microfluidic system would be a platform to understand a combination of different drugs . So, we will study how to fabricate this in the class.

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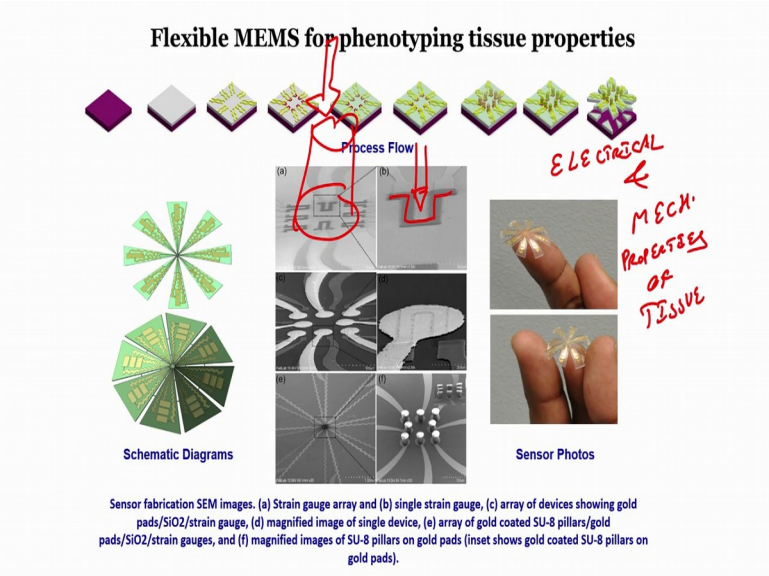

I will go to the next platform. Now, this is a flexible MEMS sensor and this is to understand the electrical and mechanical, electrical and mechanical properties of tissue . How? You see what is there here? If I see there is this Ohm shape sensors are there 1 2 3 4 6 7 and 8; 8 sensors are there and if I zoom one of that it looks like Ohm. But in other way it also looks like a resistor, it looks like a resistor . So, what is it? It is a strain gauge, it is a strain gauge; that means, if I apply a pressure on this particular platform then there will be change in the strain and it is a piezoresistive strain gauge.

So, there will be change in the resistance in the strain gauge, resistance of the strain gauge would change. So, if I apply; if I put a tissue in the centre of this particular chip and if I apply force then there will be change in the resistance of the strain gauges depending on the elasticity of the tissue ok. Second thing on this strain gauge; on the array of the strain gauges we have an insulating material over which there are gold pads.

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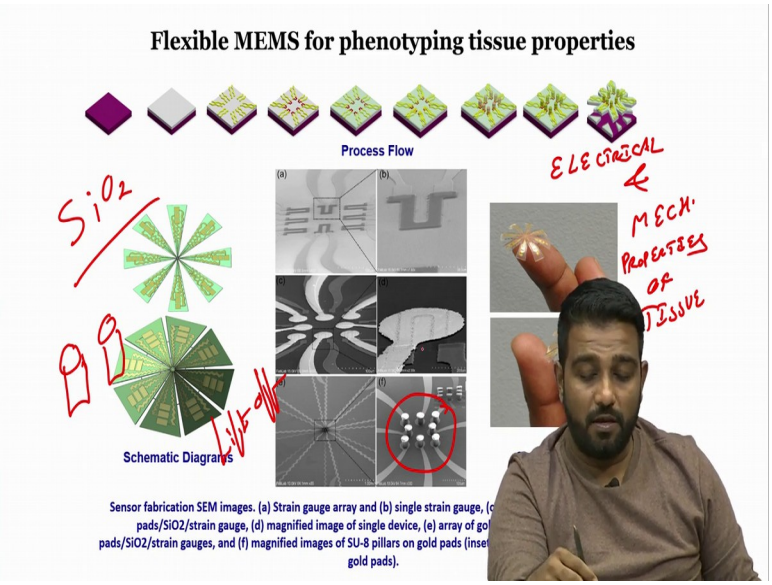


These are the gold pads 1 2 3 4 5 6 7 8 and I zoom one gold pad what do I find, I find that the gold pad looks like this. Why? Because, below gold pad there is an insulating material; wWhat is that insulating material? Insulating material is my silicon dioxide . So, silicon dioxide is used as an insulating material and we have a strain gauge on the bottom. So, it is like of strain gauge insulating material on that you have the gold pads, this guy .

Now, on this gold pad I will fabricate some pillars like this pillars and I will perform a process called lift off, lift off technique to coat these pillars with a metal. Now, when I place a tissue on these pillars what will happen that the if I place a tissue on these pillars like this.

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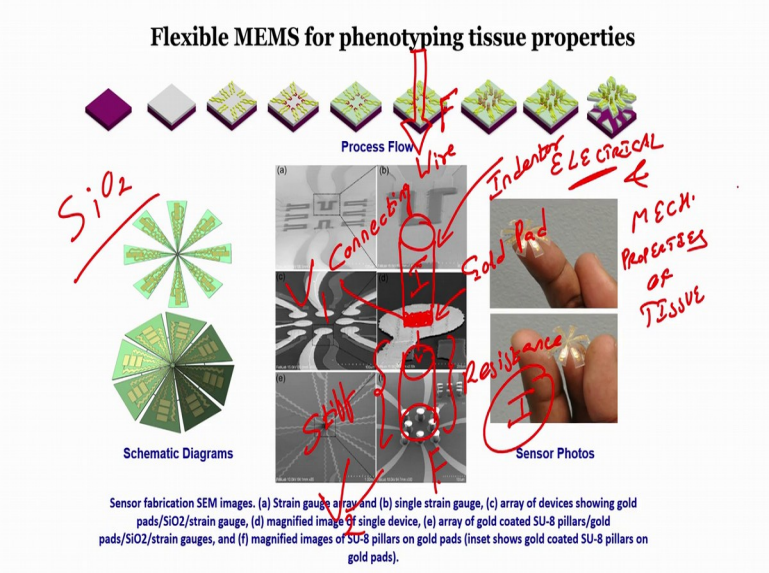


And, if I apply a force so, let us say I have equip; I have a tool which looks like this and it has the gold pad . This one is a gold pad and there is some connection to this gold pad . So, this is a connecting wire, connecting wire, this is the indenter . What will happen if I apply a force with this indenter onto the tissue the tissue that amount of force that I am applying here , the amount of force as a sensor will experience is based on the elasticity of the tissue or stiffness of the tissue . If I apply a force through this indenter  this one, you apply force to this indenter onto the tissue then the amount of force the sensor will experience will be based on the stiffness of the tissue.

Second point is if I apply a voltage you see there is a gold pad . So, apply a voltage let us say V 2, this is V 1 voltage between V 1 and V 2 are pad 1 and pad 2. Then depending on the resistance of this tissue; depending on the resistance of this tissue I will see different change in current, you got it. If I apply a voltage between the top pad and the bottom pad, at the top one is on the indenter, the bottom one is on the chip . And, if I apply a voltage between two pads I would be able to see the change in resistance of the tissue. Thus, you can measure the electrical property which is the resistance and

mechanical property which is the stiffness of the tissue with the help of this particular chip.

So, there is a mechanical sensor and then there is an electrical sensor, both are integrated on a single chip. And, this chip can be used to measure the change in this electro mechanical properties from onset to the disease progression.

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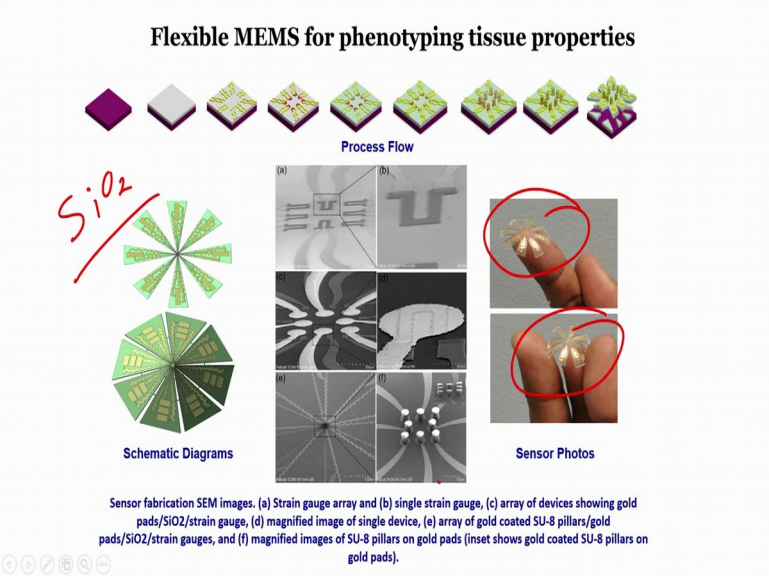


Since it is made up of flexible material that is why we can bend it and then I will show it to you after you fabricate, fabricate this sensor how to use it for your experiments ok.

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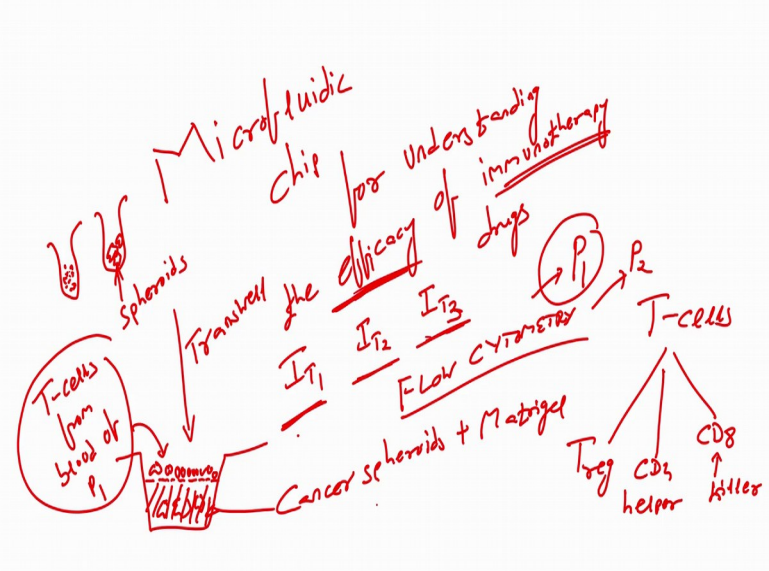

Let me move to the next part of the sensor and this is on the immunotherapy, a microfluidic chip sorry microfluidic chip for understanding the efficacy immunotherapy drugs; microfluidic chip for understanding the efficacy of the immunotherapy drugs . So, the idea here is that if there are three drugs I 2 I T 1 I T 2 and I T 3. These are immunotherapy drug 1, immunotherapy drug 2, immunotherapy drug 3 for a given there are patient 1 patient 2, ok there are two patients. We have to give which drug out of 3 to patient 1 and to patient 2? How we will design? How we will know that patient 1 out of 3 which drug would be more effective, which drug has more efficacy ? Same thing go for patient 2.

So, you have to design a patient centric platform that can help the doctor to identify which drug to subscribe or which drug patient 1 should be given or which drug patient 2 should be given out of given or available drugs in the market. We will discuss about immunotherapy later on. So, one way of doing it is using the transwell well. So, in the transwell I will I will take the cells from the patient, I will take the cells from the patient and then I will grow the spheroid. So, I will take the cells, I will put in a U bottom plate and after while I will see that the U bottom plate will have these plumped spheroids, it is called spheroids .

So, these spheroids I will load here in the, this is your transwell , then I will take the T cells and extract T cells from blood of the patient that is a patient 1. And, I will load T cells here, then these filters are such that, that T cells cannot go through this filter and this cancer cells or spheroids are covered with Matrigel. Now, what we have here? We have cancer spheroids plus Matrigel, here we have T cells . Now, because of the release of cytokines so, in T cells consists of when you say T cells is a white blood cells in a way.

And, the basic can be T regulatory cells CD 4 cells, CD 8 cells, CD 4 cells are also called helper cells, CD 8 cells are also called killer cells . So, when there is when we keep the T cells over the cancer spheroids which are covered with Matrigel then after 48 hours, if we take out the T cells and perform flow cytometry analysis; flow cytometry analysis. What we will find is that the CD 4 CD 8 ratio is different, CD 4 CD 8 ratio is different.

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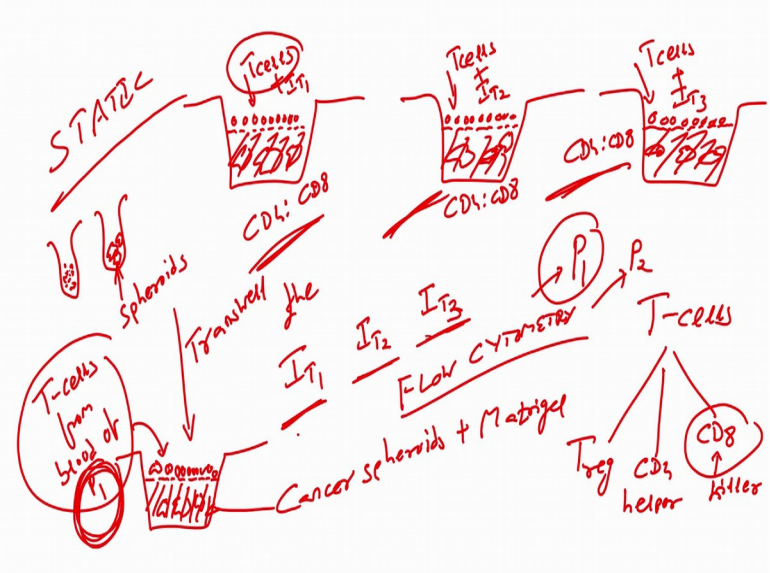


Now, similarly I take 3 different transwells; 3 different transwells and there is this transwell looks like this and I load the spheroids with Matrigel. If there are three we should keep it uniform and then there are cells here which are your T cells, T cells T cells. These T cells are treated with immunotherapy drug 1. These T cells are treated with immunotherapy drug 2, these T cells are treated with immunotherapy drug 3 ok. Now, after 48 hours when I take out T cells from here and I measure CD 4 CD 8 concentration or and then plot it in a ratio, same thing I will do for here and same thing I will do it for here.

What will happen that the drug which is more effective there will be more number of killer cells. The drug which is more effective will have more number of CD 8 cells. So, from this platform we can select which immunotherapy drug will work for our patient 1 . So, this can be used as a patient centric platform. What is the difficulty in this? The difficulty that you can see here is that each of these is a static platform, all three of these is a static platform. What we require? We require dynamic platform. Why we require dynamic platform? Because our body is dynamic.

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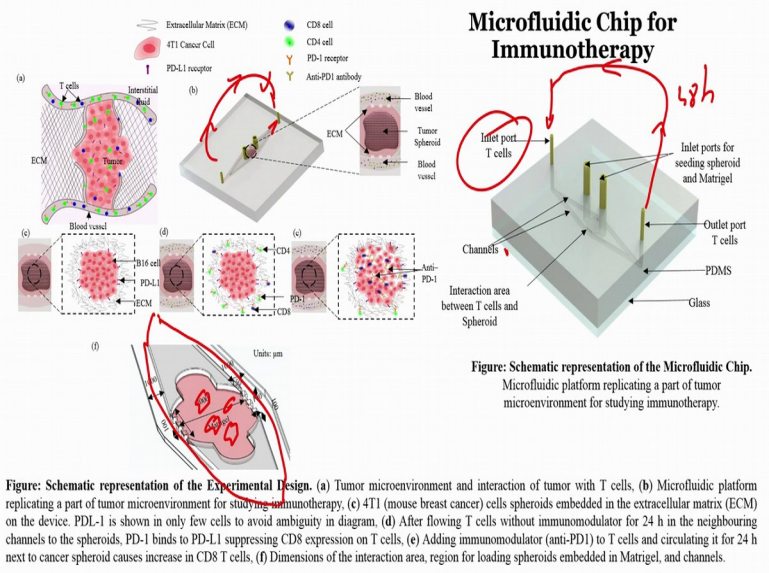


**Figure: Schematic representation of the Microfluidic Chip.** Microfluidic platform replicating a part of tumor microenvironment for studying immunotherapy.

**Figure: Schematic representation of the Experimental Design.** (**a**) Tumor microenvironment and interaction of tumor with T cells, (**b**) Microfluidic platform replicating a part of tumor microenvironment for studying immunotherapy, (**c**) 4T1 (mouse breast cancer) cells spheroids embedded in the extracellular matrix (ECM) on the device. PDL-1 is shown in only few cells to avoid ambiguity in diagram, (**d**) After flowing T cells without immunomodulator for 24 h in the neighbouring channels to the spheroids, PD-1 binds to PD-L1 suppressing CD8 expression on T cells, (**e**) Adding immunomodulator (anti-PD1) to T cells and circulating it for 24 h next to cancer spheroid causes increase in CD8 T cells, (**f**) Dimensions of the interaction area, region for loading spheroids embedded in Matrigel, and channels.

And, that is why you require a microfluidic chip for understanding the immunotherapy drugs, efficacy of the immunotherapy drugs . And, in a way that we can run in the dynamic platform which is your micro fluidic chip . So, we will see how you can design this microfluidic chip as a part of the course and I will stop here discussion about this two different sensors. Because, I feel that you know you have a smaller modules, it will be easier for you to understand a lot of new terms that came to say that certainly you have learned in this particular module like angiogenesis , vessel formation, endothelial cells, cancer cells, Matrigel, extra cellular matrix like efficacy of a drug, screening of the drug, flow cytometry, microfluidic chip.

So, many things that you have learned in this last few minutes; so, first digest those stuff, understand, Google it that what exactly each meaning means; efficacy what does it mean , flow cytometry how does it work. So, a lot of things that I say you have to catch up the words and go and see in detail each experiment. Because, I cannot cover everything in this particular course because that itself is a part of a different course . So, I will stop here and the only idea that I wanted to show is that you can design a microfluidic platform to study how to use this immunotherapy drug.

So, I will let me just show it to you this platform and then we will stop the lecture. If you can see the screen this microfluidic platform that we can see over here , there are two channels channel 1 and channel 2; channel 1 and channel 2. We can flow so, these both

the channels are merging at a point like here  both channels are merging. So, what we can do is we can first take the spheroids and load spheroids in the central region . Now, there are some spacers here and then we will flow the T cells and this and this. And, then with the help of the peristaltic pump we can do this flow for 48 hours , there is a inlet and there is a outlet.

So, if you connect the inlet with outlet after flow it will come back and again it will flow. So, when you allow it for 48 hours, after 48 hours you can check the CD 4 CD 8 concentration . And, then you treat the drug T cells with T cells with drug 1 and again flow it for 48 hours; understand the change in the CD 4 CD 8 drug 2, again 48 hours. See the change in CD 4 CD 8 drug 3, again 48 hours see the change in CD 4 CD 8 and the one with the CD 8 is higher you use that drug as a patient centric platform. This is just an idea of using a microfluidic chip as a dynamic system or a dynamic platform compared to the existing transwell . And, then we will talk about what is PD 1, what is PD L1 ; when we actually see how we can fabricate this particular chip in our process .

So, it is a immuno check points I will discuss in detail what is PD 1, PD L1, how the cancer cell looks like that is a part of study. But, since we are understanding the immunotherapy drug and the test T immunotherapy drug, we need to understand how the what are different terminologies that are used in this particular research area . So, here I will stop my class. In the next class we will see a very interesting problem called electronic or not actually a problem a technology that people are working which is a electronic nose to identify a very important problem which is a non-invasive way of detecting a disease.

Can we design a system that can help us to identify the disease just from understanding the breath signature. Whatever I am exhaling from that my exhale breath, can I identify a particular disease . We will see how the sensors for that particular application can be fabricated we will see in this class. But, how what why it is a important to do that analysis we will see in the next module . Till then you take care, any questions free to ask in the in the forum. And, I will see you in the next module, till that you take care. Bye.