Fabrication Techniques for Mems-based Sensors: Clinical Perspective

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Lecture – 02
Introduction to Microengineering Devices Contd

Hi, welcome this is the second module of our class 1 for course Fabrication Techniques for MEMS-based Sensors from clinical perspective. Now, what we have seen until now is, there are several sensors right that we can make for a solving some important problems in the area of medicine or in the area of biomedical engineering.

Same technology that we will be discussing in this particular course can also be used for fabricating devices, micro devices to be precise or devices based on MEMS based technology that is micro electromechanical systems based technologies that can also be used for other applications such as electronics, robotics, chemical engineering, mechanical engineering and so on. So, in our class 1, what we saw are few devices starting from the micro heater, right.

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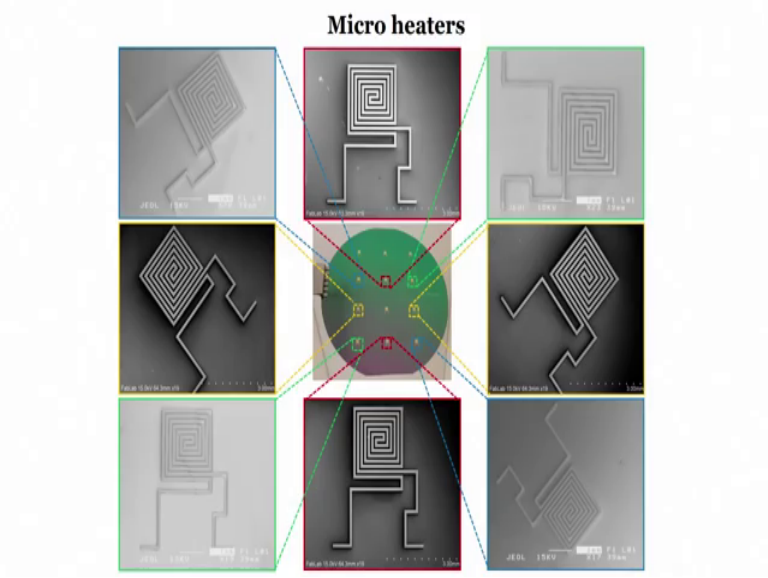

So today, what I want is, I will just show it to you how the heater pattern looks like. Now the pattern that I will be showing it to you would be different than what you have what you are looking at the screen. But the idea is that the micro heaters like I said can be patterned in a different way because it is nothing but a resistor right. So, resistor if you

want to have a resistance of a metal, if you want to increase the resistance of a metal, you can increase the length or decrease the area right. So, let me show you the micro heater which is right now with me, alright.

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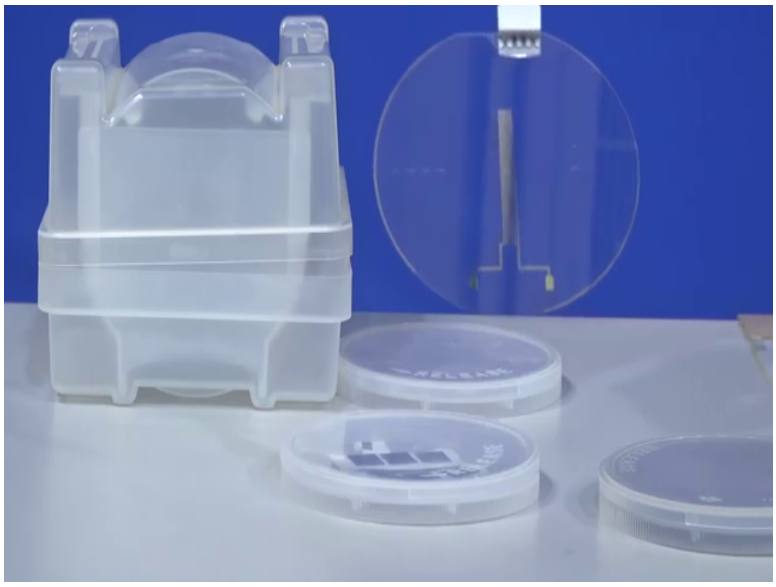

So, if you can see here right, this is your micro heater alright. This is a micro heater, you can see the pattern right pattern of the micro heater on the glass substrate right, see is a pattern of the micro heater on the glass substrate, alright. This is the back side of the heater, back side of the heater and what we are done, we have we have we have used chrome gold, we have used chrome gold as a metal. So, this is how the micro heater looks like. Now this is again you see that the length is high, the area is also high. So, the resistance would not be that low, but we for this heater was patterned with a particular application.

Now, another thing that you have may have observed is I am wearing gloves, right, so to avoid the finger prints, so to avoid the contamination on the device. Again this device is are for the demo and that is why even the recording studio is not a class clean room like last 1000 class, 10000 right. This is just to show you the devices outside the clean room right. But if you have a complete device, then the devices are of several types one that can only be used in a clean room environment, second that can only be that can be used anywhere else. So, we have to design the device, since it is a clinical approach clinical research, these devices should be able to go outside the laboratory and at the same time it

should not have contamination issues. That can be done when you package the complete device right because again the clinical environment, the hospital environment would be is considered to be cleaning, cleaner compared to compared to the dispensary. When I say cleaner, suppose the surgical room is there surgery room is there, it is around class 10000.

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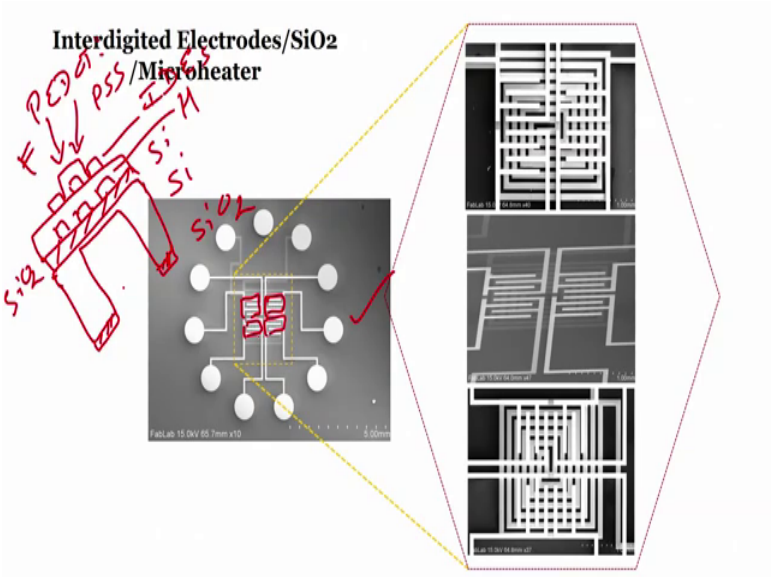

So, then what we have seen, we have seen an interdigited electrodes right. Then after interdigited, so in interdigited electrodes, what we have seen that there is a heater and on heater there is an insulator, on which there are I D E, patterns right. So, if you want to see interdigited electrodes, I will show it to you, I will show it to you here.

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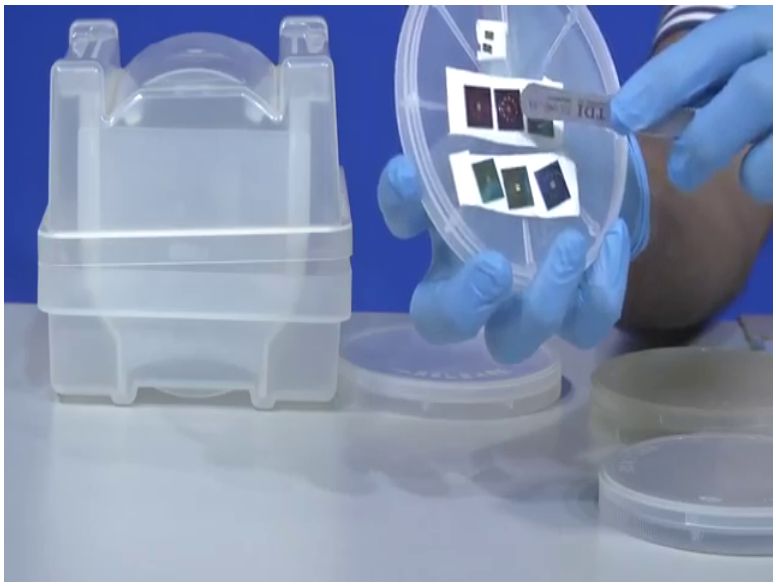

Now, if you see here, this one which I am pointing this one alright, this one this sensor this sensor here, this chip has a micro heater at the bottom and on that there is an insulator, on which there are interdigited electrodes made out of chrome and gold, this particular chip once again I am showing it to you, this chip ok, this chip. So, we will see we will see in detail about the fabrication of this chip with a better zooming angle when we are talking about these devices in detail. Right now, my idea is to show it to you how it looks like then we will go into detail how we can fabricate it, at the time we will even zoom it further to understand how it looks like from the from the actual design point of view.

So, what is the role of that, what the role of that devices was that now on this intergited electrodes you can, you can load let us say if I load piezoresistor piezoresistive material. And if I create a diaphragm on the backside, so what does it mean, I have this electrode right. So, you see here you see here, I have a oxidized silicon vapour. So, I will draw oxide sorry and then I have heater, then I have insulator, then I have interdigited electrodes, this is what this particular diagram is, alright.

Now, if I have piezoresistor, a piezoresistive material such as P dot PSS on this and if I apply a force or a pressure on this piezoresistor, I apply a force then it will not show change in resistance or it will show a very poor change in resistance or very small change in resistance. Why, because I am using silicon then I have silicon dioxide, then I

have silicon right again I have silicon dioxide, I have here heater right, I have here I interdigited electrodes right not because of this things because silicon is hard, silicon is hard material.

So, if I want to see the bending if there is a bending, then there is a strain in the piezoresistor right. For that, I have to create a diaphragm. So, what is the diaphragm means that we will etch silicon from backside in this particular fashion alright. So, this is your diaphragm that you have created this is the diaphragm that you have created. And now, if I apply a force, if I apply a force, the diaphragm will bend and this bending of the diaphragm would cause change in the resistance, will cause change in the resistance you got it.

So, if I want to deposit a material which is a piezoresistive material on these particular electrodes, then I had to have a diaphragm on the backside this can be one of the application. Another application is instead of piezoresistor instead of this p dot p s s right, what I will use.

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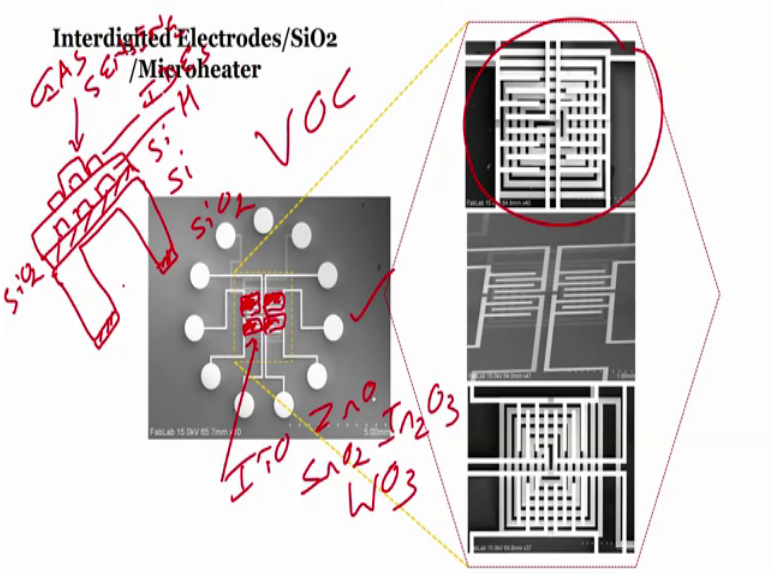

I will use a gas sensing material, gas sensing material. So, if this material is material used in sensing, material used in sensing gases right such as a semiconducting oxide materials, semiconducting oxide materials like indium, tin oxide zinc oxide, tin oxide right, indium oxide right, tungsten oxide.

Then, if in the presence of gas, in the presence of VOC volatile organic compound, there will be change in resistance because of the reducing because the VOCs are reducing gases, we will see detail how we can use it. I am just you that the application of this particular this particular device right now can be in many areas in many areas and two of which I have just shown it to you; one can be a force sensor, another can be a gas sensor right.

So, the device that you have seen right now which I have shown it to you right was a micro heater on which there is an insulator on which there are interdigited electrodes. Then what we have seen, then we have seen a device for Atrial Fibrillation.

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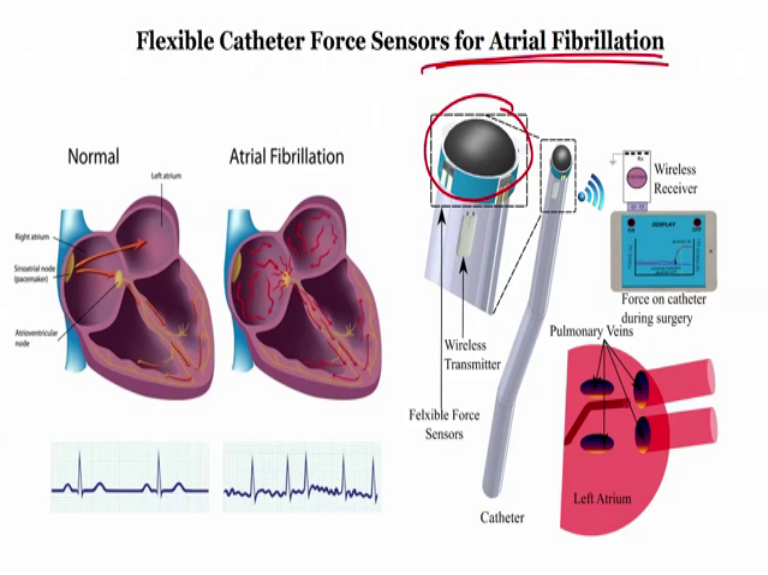

So, again we need a flexible force sensors right. So, I have to make a flexible force sensors and the tip of the catheter, at the tip of the catheter and I, I told you that we will discuss in detail Atrial Fibrillation. So, when we talk about tip of the catheter, then we need again a flexible force sensors right. So, what should be the sensing material? It can be just a strain gauge.

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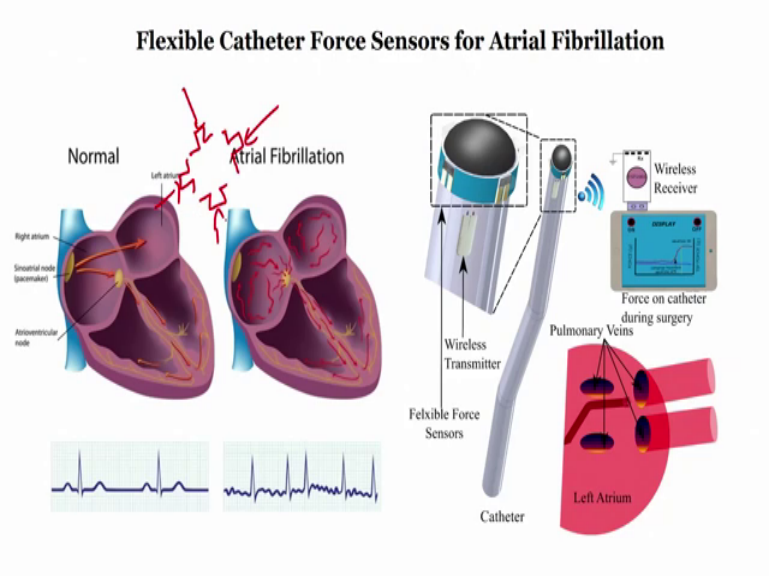

So, if I create a strain gauge or array of strain gauge like this right, then you can measure force correct. So, how can I create this array of strain gauge on flexible material. So, to see the pattern, so, see the pattern, I have I have here another wafer I have a another wafer which you will see, which you will see how the how the chip looks like. When the centre of this chip there are, there are mic there are four sensors you see here.

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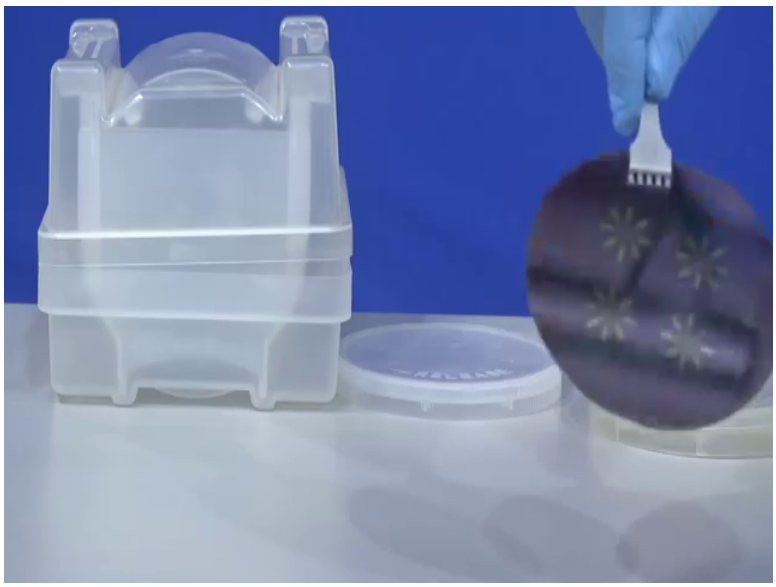

So, if I see if I show you this one right, then in the center in the center of this chip, there are four sensors center. And what is on centre of the chip, every these are four chips; one,

two, three and four and the centre of the chip, center of the chip there are four sensors, alright.

So, if I deposit if I create this kind of pattern, if I create this kind of pattern on flexible material, on flexible material, it will be a flexible force sensors, isn't it right? So, if you just look at me now and you see what I am holding right.

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You can also hold the wafer in the way I am holding. It is similar to this right. Earlier wafer that we had was a micro heater right. So, there are two ways of holding it when you perform lithography, the best way of holding is always using tweezer.

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This is called tweezer, tweezer alright. So, we can hold with tweezer or you can even hold with the gloves like what I am holding right.

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Now, so you see there is a, so if I put it properly, then you can see the pattern properly right. So, in one side I have I have flexible force sensors, a pattern for flexible force sensors that I can use further. On another side, I have a heater is a heater this is a pattern for flexible force sensors right. So, heater we know, how we can use it. We now know that how we can use flexible force sensors right for the atrial fibrillation for measuring

the catheter contact force, right. So, so there are several ways of how people are comfortable by holding the wafer, again the best way is to hold with tweezers alright.

Now, depending on the dimension, depending on the primary flat and secondary flat, the wafer can be identified as p type or n type. You see there is a flat; one is primary flat here, secondary flat is at the bottom. So, it is at 90 degree. You see here there is another flat degree primary flat. If I see it is not circular, you see it is not circular wafer, the there is a primary flat here and then there is a another flat let me just show it to you which is here at the bottom. This is a 90 degree with respect to the primary flat, here is a flat here is a flat.

So, let us try to see if you can catch it. Yes, you see primary flat and secondary flat right. Secondary flat is always smaller with respect to primary flat. If we know where is a secondary flat with respect to primary flat, then we can understand whether the wafer is 1 0 0 or it is 1 1 1, whether it is n type or this p type alright. This is a advantage of primary flat and secondary flat we will again see primary flat and secondary flat.

So, we will see how the lithography is done, how can create this pattern a lot of other stuff in this particular course. That is a idea of this particular course to educate the students right in the area of micro engineering, particularly if when we can solve some very interesting problems right using this devices. So, then what we have seen? We have seen the flexible force sensors for atrial fibrillation followed by a cantilever, a piezoresistive, cantilever right.

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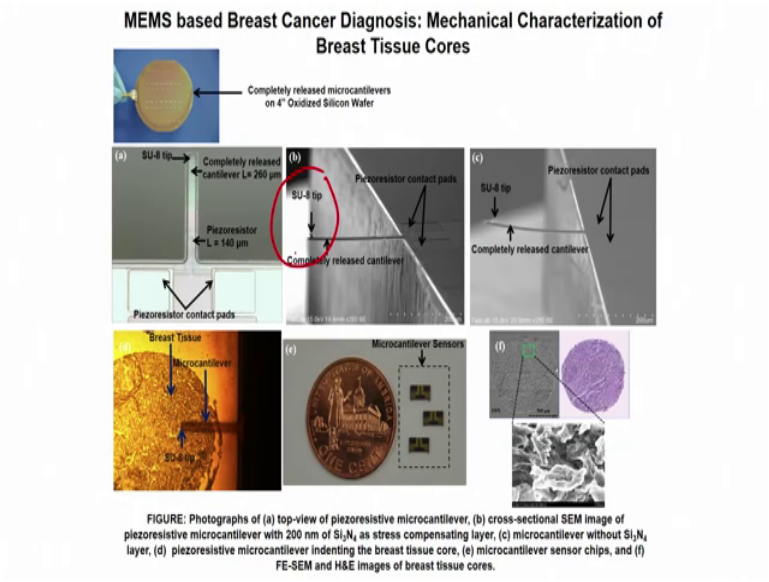

So, when we talk about piezoresistive cantilever right, I have told you that there is there is an s u 8 tip that is used for piezoresistive cantilever. And as a name suggests, there is a piezoresistor embedded within the cantilever piezoresistor embedded or integrated within the cantilever, right. How we can integrate a piezoresistor inside a silicon or a or on the cantilever we will see their factors.

Now, as we know if there is a piezoresistor, if I bend this cantilever, if I apply a force, then there will be change in the resistance, there will be change in resistance, right. So, how each cantilever looks like you said, you can see the chip here right.

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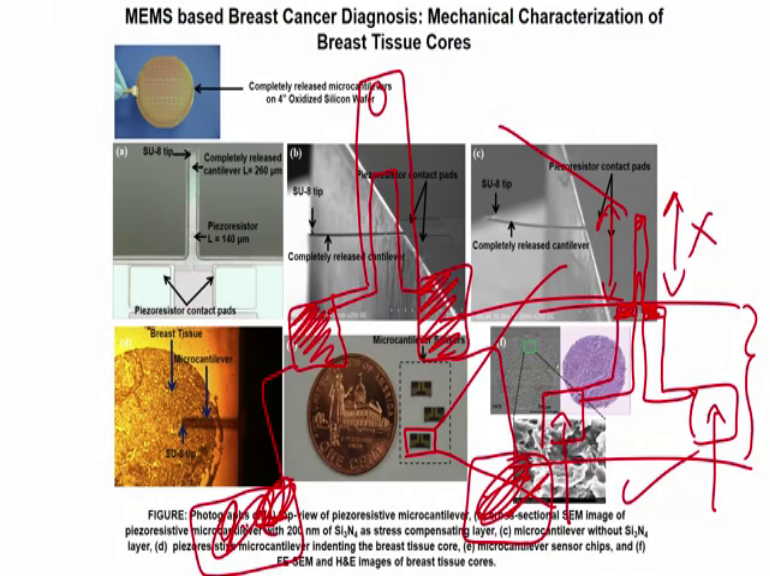

You can see the chip, but this chip at the end of this chip, so if I draw just a line like this, at the end of this chip if you if you if you just concentrate on this particular chip, the line that I have drawn is this cantilever. Now why I have drawn line because you cannot see, you cannot see with your naked eye, you have to go for a microscope to understand that there is a cantilever. So, how this chip looks like let us see here.

I have cantilevers for you if you can focus on the disk, yes. So, you see or let us do like this, let us focus I will put in my hand let us try to focus this yeah. So, the small things within here, right over here, this chips these are the chips these are the chips, but within this chip also, within this chip, at the end of the chip, there is a cantilever you guys see. So, it is so small. It is so tiny, super tiny right and we cannot see the cantilever coming out. We can only see the chip, we can only see the context that we can take the context out of the cantilever.

So, it is very difficult, it is very difficult to right, right now see the cantilever right. It is very difficult to see the cantilever with a naked eye even with the zooming factor of the microscope. We can see the pattern of the contact pads that is why if you see the screen, what we are looking at here is if you see the screen, the context the context that you can see which one this chip, you can see. And this chip if I zoom further, what is it is like this you see. So, you can only see this much, you can only see this much, you cannot see this hm.

So in fact, it is very difficult to see this as well right, but still you can see. So, what is this? These are contact pads, this one and this one, contact pads alright. Here is a is here is your cantilever that we cannot see and this is the contact to the cantilever, contact to the cantilever. So in fact, contact to not only cantilever, but there is a piezoresistor embedded in the cantilever. So, if I zoom it further, if I just say a cantilever right and that there are contexts for the cantilever right, this is a cantilever and there are contacts for cantilever, then then there is a piezoresistor, there is a piezoresistor and this is the contact to the piezoresistor. This one is contact to the piezoresistor.

And an further you go down and make a big contact, further you go down and make a big contact. These contacts are for the cantilever, this one, this one is for the cantilever the cantilever has a s u 8 tip. So, is super tiny as you can see, everything is super tiny right, it is in terms of micrometer. So, you assume that when it is micrometer, if it is like this if it is nanometer, you can definitely not see with your naked eye, correct.

So, and we have seen that this cantilever can be used for cantilever can be used for understanding the mechanical property of tissue. It can be also measure used for understanding mechanical property of cells, it can be used to measure the stiffness of the material right and we will see how we can fabricate and how we can apply this piezoresistive mechanical cantilever from clinical perspective, alright. So, next was interdigited electrodes that we have seen right.

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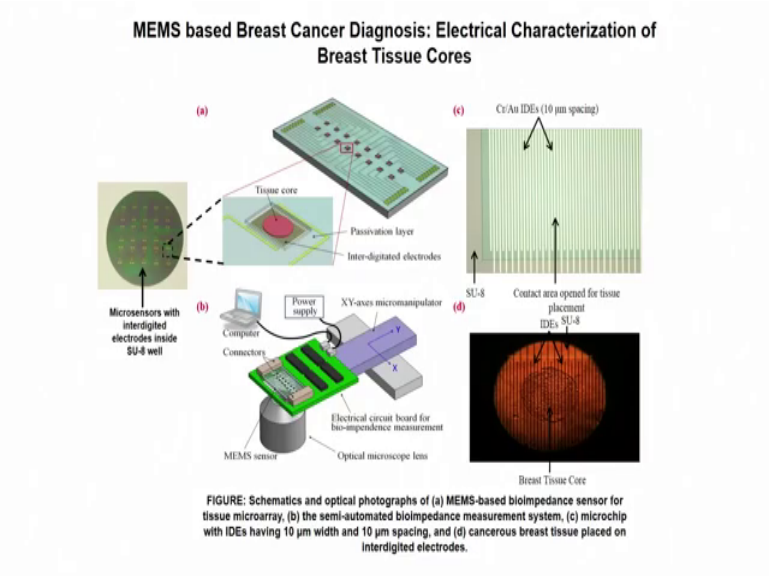

FIGURE: Schematics and optical photographs of (a) MEMS-based bioimpedance sensor for tissue microarray, (b) the semi-automated bioimpedance measurement system, (c) microchip with IDEs having 10 μm width and 10 μm spacing, and (d) cancerous breast tissue placed on interdigited electrodes.

And in that what we have seen. And in that what we have seen, if you see the screen that we can place the tissue and we can measure the change in impedance. Again we will look at this in detail when we go into tell about each devices.

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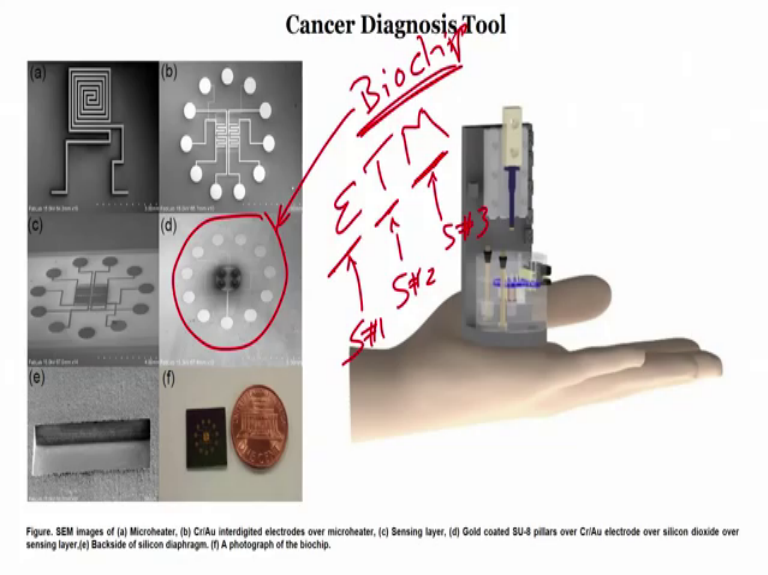

Figure. SEM images of (a) Microheater, (b) Cr/Au interdigited electrodes over microheater, (c) Sensing layer, (d) Gold coated SU-8 pillars over Cr/Au electrode over silicon dioxide over sensing layer,(e) Backside of silicon diaphragm. (f) A photograph of the biochip.

Then we have seen this chip right, this chip. And like I said, now we are interested in measuring the electrical thermal, mechanical, electrical, thermal and mechanical property of tissue. In this case, we should have a sensor that can measure the electrical property of tissue, that can measure the thermal property of tissue, that can measure mechanical property of tissue and to measure all these three properties, to measure all these three properties we should have a chip, we should have a chip that consists of or that is integrated with all three sensors right; sensor 1, sensor 2 and sensor 3. So, this we can call bio chip, bio chip, why bio chip because this chip is used for phenotyping or for understanding the change in the tissue properties.

And what changes? Electrical changes, mechanical changes and thermal changes of tissue properties, why it is important, how tissue property changes, why this whole idea of designing this tool comes into picture and really is it important to make this tool or because just we know micro engineering, we are kind of designing different sensors, lot of questions right and it should be there, it should be there. Before you design any device, before you start working on any device, the main thing is: what is the application of the devices, what is the gap in the current research that you are going to solve right.

By designing this device, am I going to solve a gap with really existing in the technology or is it really useful from diagnosis point of view and if yes, how, right. So, always understand the devices from the application point of view, first understand the application and understand the problem and then you and then you device your design or design your device accordingly, alright.

So, if I want to see this bio chip, how it looks like; I have a bio chip in my hand right and here we have to focus on, you have to you have to see this area, if I see the camera, yes you now you do not have to see the center this one, you have to see this one alright this one. All three of chips in bottom, you will see there is a there is a subtle difference because here you can see that there it looks different than this one right because now you have now you have a gold pad and on that you have s u 8 pillars, you have gold pad and you have s u 8 pillars. If I can show in this particular fashion yeah, if you can zoom it further please yeah.

So, you have here if you see this chip compared to you see there is earlier one we are looking at this chip right where it was having micro heater and interdigited electrodes. Now, we are looking at this particular chip; this three in the bottom, three in the bottom and here there is a clear change clear change in the design, you can see very clearly, you cannot clearly understand what are the patterns, but you can see that the chip looks different.

And we will see in detail by zooming each chip what are the patterns within the chip, but these are the bio chips integrated with three sensors the bottom one, bio chips integrated with three sensors; this three and this one ok, four. There is 4 indicated with three sensors; one micro heater, then piezoresistor and then electrodes alright. And we will see how we can use it; we will see how we can use it. So, if you come back to the slide, we come back to the slide, what we see here is that.

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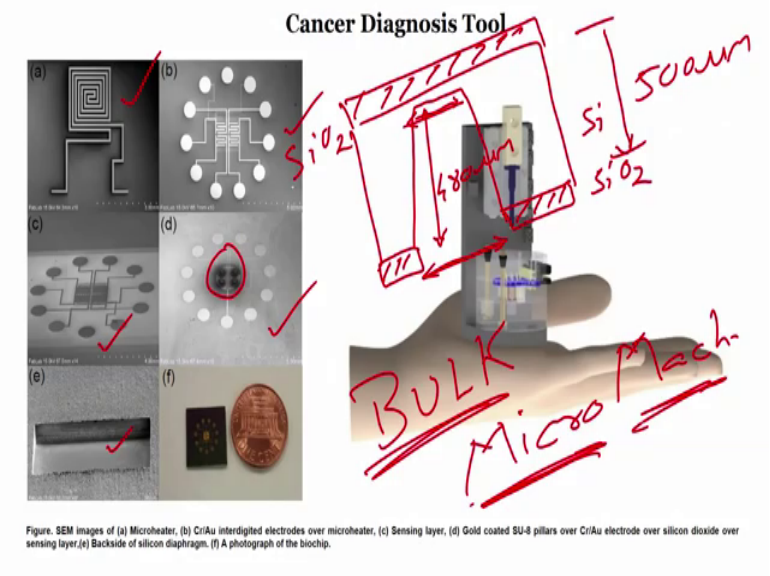

Figure. SEM images of (a) Microheater, (b) Cr/Au interdigited electrodes over microheater, (c) Sensing layer, (d) Gold coated SU-8 pillars over Cr/Au electrode over silicon dioxide over sensing layer,(e) Backside of silicon diaphragm. (f) A photograph of the biochip.

We have we have a heater, we have the interdigited electrode over which we have piezoresistor, over which we have electrodes electrode on which there are s u 8 pillars, you can see in the center right and on the back side there is a there is a etching of the silicon and this etching is done using bulk micromachining, bulk micromachining right. If you go to workshop right, then you machine the things right, you machine the things.

Here we are machining the things at micro scale, at a micro scale that is why micro machining. Why it is bulk because you are removing a bulk of silicon, you see if this is a silicon wafer right, if this is the silicon wafer and I am etching the silicon wafer from the backside, this is by silicon dioxide, this is silicon this is silicon dioxide and I will tell you why we why I am drawing such a pattern always silicon dioxide with silicon.

So, if I say that the silicon right is 500 micrometers and I am I am etching the silicon, I am etching the silicon about 480 micro meters, then the bulk of the material is etched, bulk of the material is etched right bulk. And then the diaphragm this one can be from 1 millimetre, can be from 500 micron, 200 micron, 100 micron right. This is the window, but this one what I am talking about this one the area 100 micron, 2 micron, 300 micron, 400 micron, 500 micron, it is in micrometers right, we are we are performing a micro machining technique micromachining technique right.

So, so etching of silicon from backside is done using bulk micromachining. See if there is a bulk micromachining, then there should be also surface micromachining, surface

micromachining right. So, what do you mean by surface micromachining, how it is different than bulk micromachining? We have to see that as well and we will see it, we will see it in some time alright, we will see it in some time. Now, we will see the bulk micromachining from what is difference between bulk and surface micro machining.

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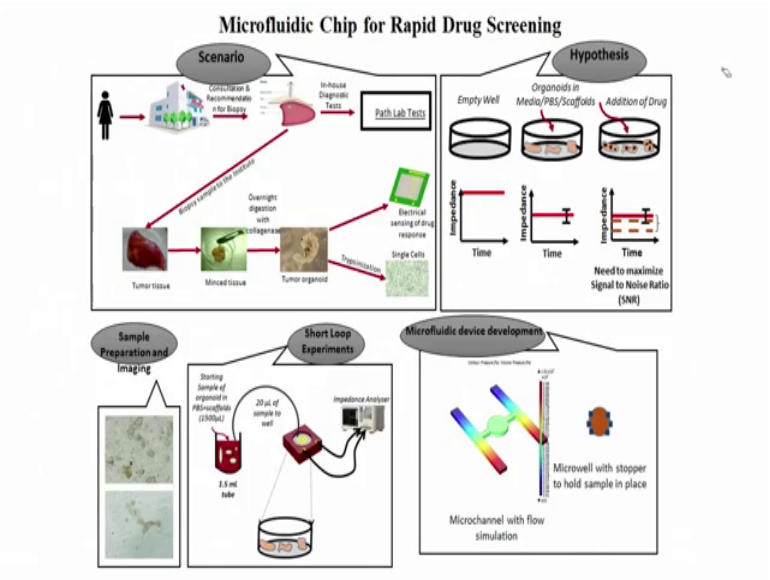

Then we have seen microfluidic chip for rapid drug screening and I have discussed with you why it is important right.

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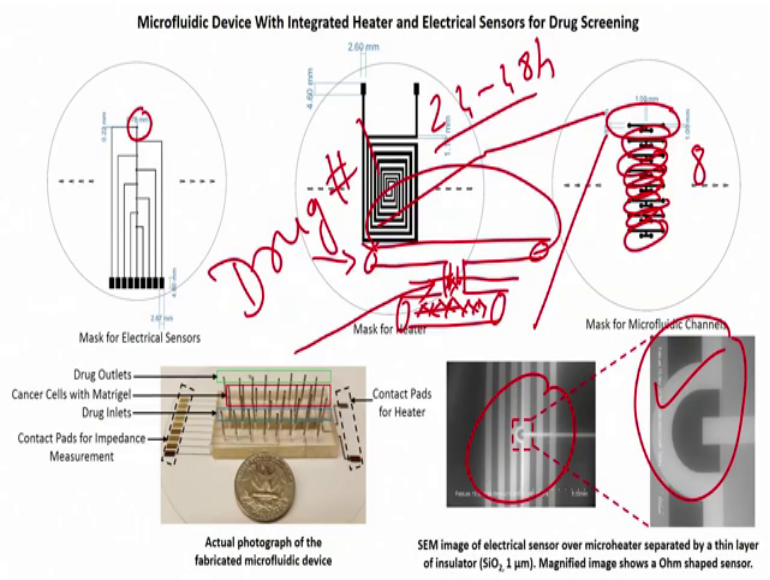

The importance of this particular device that you can see on the screen is that now you can test multiple drugs for the same patient. So, you can load, if you if I just zoom this particular one, zoom this one what is it is a channel like this connected with a smaller channel right, channel connected with a smaller channel and I can load cancer cells in this area. I can load cancer cells in this area, now below this below this there is the interdigited electrode here, you see here interdigited electrodes. If I zoom further, looks like this.

And below interdigited electrode there is a silicon dioxide and below silicon dioxide there is a heater. You can see this one, you got it there is a channel inside the channel in this area, in this particular area. There is an interdigited electrode which you can see from here, below interdigited electrode there is an insulator and below insulator there is a heater, guys. Now, I have loaded cancer cells in this particular channel and I am passing a drug, I am passing a drug 1, drug number 1 on this one alright and I am circulating continuously for some amount of time; let us say 24 to 48 hours, you can select anything, you have to optimize it ok.

Now, how many channels I have? I have eight of those. I have eight; 1, 2, 3, 4, 5, 6, 7 and 8; eight channels I have right. So, what will happen? I can test eight different drugs right because I have eight different channels. So, now, you can do a drug screening; that means, if when the drug is effective, the drug is effective the cells would die and the impedance would change we will see in detail how this things works.

But the idea is, now, what you can see, you can see that using this particular device you can test multiple drug for the same patient; that means that if you take the cells from the patient. And if you load in this channel and all the remaining seven channels, right, same patient and you can try different drugs to see whether drug is effective or not. Alternatively, you can load eight different patients in eight different channel and you can try the same drug and see whether drug is effective or not.

Both ways it is possible right either same patient, cells from same patient in all eight channels, you test eight different drugs or you take you take eight different patients cells from eight different patients and you try a same drug and see what is the what is the efficacy of the drug, how the drug is effective to kill the cancer cells or not right. It is a rapid drug screening device, a rapid drug screening device, right.

So, how does this rapid drug screening device looks like, you of course, you can see from the screen, but how exactly it looks like. So, I will just show it to you, I have brought one for you, just to see. So, I will put this back and take a tweezer right and then pull out this device right to show it to you. So, first let us see this device in my hand.

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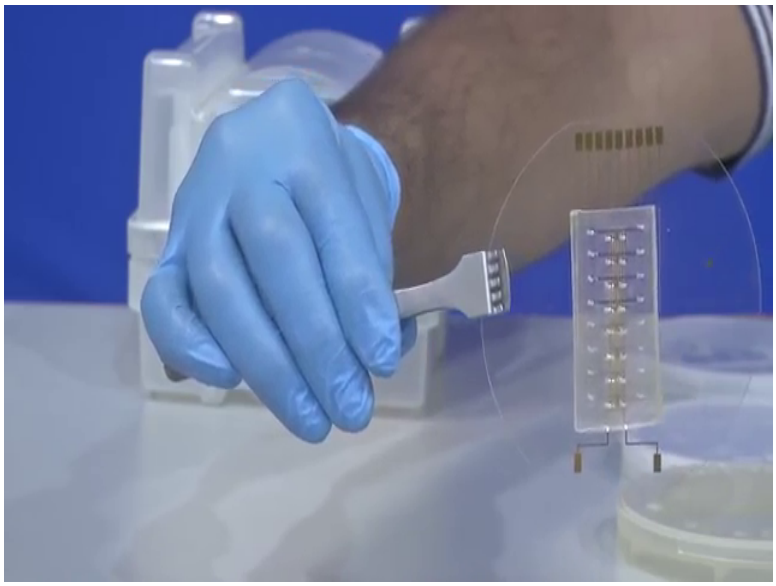

Right, what you can see is there are certain channels right, there are number of channels, number of channels is there and then below the channel there is a the in the center there are electrodes, below electrodes there is an insulator, below insulator there is a heater. So, if I show you from the back side, you can see the heater, you can see the heater right, you can see heater clearly and then you can see that there are lines going like this which are interdigited electrodes. So, heater is there, but I am showing from the back because you cannot see clearly from the front that is why I am showing from the back side; heater is there, on which there is an insulator, on which there is a interdigited electrode, on which there is there are channels and this are eight different channels. So, you can test eight different drugs right.

So, let me just show it to you let me just show it to you here right, you can see now there are channels and then there are contact pads. We can see contact pads right over here, right over here, there are channels and then there is below the channels, there are electrodes below that there is insulator you cannot see that and then there is a heater. So, in the back side back side let me hold it properly right. You can see now, there is a heater

right and this lines that are going, lines here right on the second side also, this are electrodes right and you can see also the holes for the channel right, this is backside. You can see heater first. When I say back side, from back side you can just see it there is no metal here. If I touch here, there is no metal there is no metal on the back side, there is no metal on the back side right guys. So, we will see in detail again by zooming it further when we are talking about the micro fluidic device for rapid drug screening.

But in principle, in principle this devices can be fabricated using the micro engineering technology right it can be fabricated using micro engineering technology and this can be used for rapid drug screening. So, that was that was about the micro engineering devices. But when you have when you have drug to flow, when you have some fluid to flow in such a channel which about 1 millimetre or 100 micron or 200 microns any anywhere between 100 to 1 millimetre right or 0.5 millimetre, then it comes as a micro channel. And a fluid flowing within the micro channel, we have to understand micro fluidics. That is why such a devices are also called microfluidic device or microfluidic chips, alright. These devices are also called microfluidic chips.

So, when you talk about microfluidic you have to also understand whether the fluid flowing from that will be a smooth flow or turbulence flow. You have seen right [noise, those the when the river flows right unevenly on this stone if there are if you have seen the river flowing very fast, you see a lot of turbulence is there. Then you have also seen river which is slow in nature right, smooth right smooth flow, turbulence flow, same way people who are travel in flights right you may have experience a air pocket.

Then suddenly, there is a turbulence right. So, we do not want turbulence right, we do not want turbulence. So, the flow should be smooth to understand this turbulence and smooth flow we should further understand something called Reynolds number, Reynolds number. So, we will discuss this when we will discuss about the microfluidic chip, alright. Now, if I go to the next slide, what I have see is.

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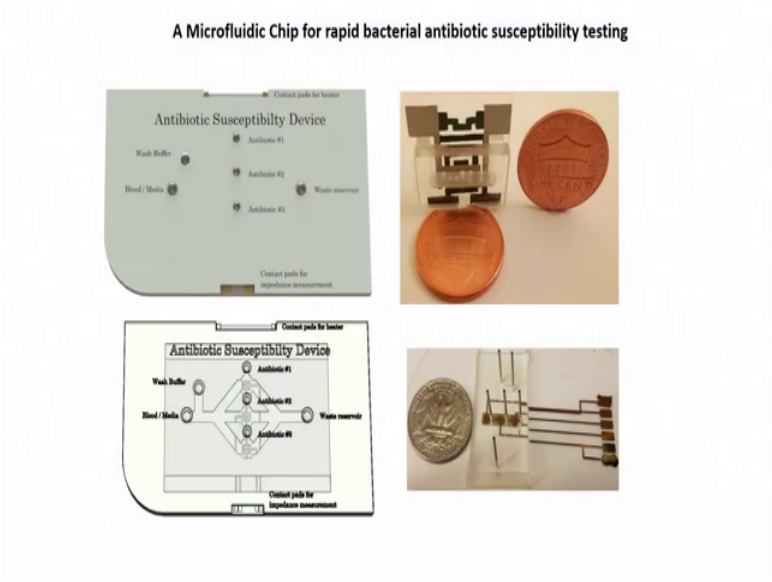

I see a device that can be used to understand the antibiotic susceptibility testing, for what? For bacteria and like we discussed in the last module that the material antibiotics susceptibilities extremely important problem since lot of neonates gets affected with several bacterial infections; And the report right now comes in 24 to 48 hours right which is which is too long for a neonate to wait for and because of this lot of neonate dies, lot of babies dies, that is one thing.

Second thing is even for us right, even for the grownups generally we have to take multiple antibiotics, tropical antibiotics and we do not want to do that right. We want to we want to create a technology that can aid the doctor to give a particular antibiotic within a shorter period of time rather than waiting for the reports to come back from path lab are in 24 to 48 hours or even sometimes 72 hours right. So, for that can we design a micro fluidic chip that can perform this kind of rapid testing or can we have a just a microchip that can do rapid testing.

So, we will see that particular work as well and for you guys, I have also brought you this micro fluidic chip, again we will discuss this microfluidic chip in detail when we are talking about the talking about this particular topic in detail, but right now let us see how it looks like right. So, in my hand, there is a microfluidic chip that can be used that can be used to understand the antibiotic resistance antibiotic resistance right. This is this is how chip looks like.

Now, again you see this is all about the design right and here we have used P D M S, this material is called P D M S silicon alright. We will see how we can create this kind of channels.

But suppose I want to now commercialize this one right and I want to put it in each and every path lab, so that I can rapidly diagnose which bacteria is there and then rapidly diagnose whether bacteria is the resistant to particular antibiotic or not. What should I do, because the wafer that I am holding right now right itself is costly, it is a glass thin glass right, I can use a glass slide instead of that one way.

Now, there are gold patterns and then there is a P D M S, again you will see that when you want to create a P D M S channels in P D M S is a it is our pain. It is not so easy right and then it is costly suppose we have a excellent skills right, we should if we have a excellent skill in micro fabrication, but if the if the fabrication is costly we cannot use this, we cannot use this right we cannot use this technology. In that case, we have to opt for some different technology.

So, instead of creating a channel in P D M S, can I create a channel in plastic, can do plastic moulding, can I stick a plastic on this on the electrodes and heater, can I make entire device on the plastic, entire device right. It will solve a lot of problem if I have entire device on the plastic because it will be cheaper right, it is robust, this it is this is fragile this fragile. If I just leave it, it will break into pieces right.

So, the point is that we not only have to design a device first, of course, for research we can design a device we can test the device whether the concept works or not. What we are thinking whether it works or not? It is good for that particular area once you have designed the device it works well, you have to now go further and reduce the price. Now this is not necessary for every medical technology, for every medical devices, no right.

But for some yes, when you reach masses where people cannot afford, where people cannot afford the high end technologies for understanding; whether they have a particular bacterial infection or not or something else. This is I am just giving an example, then if you have a alternative technology which is similar which gives a similar performance which has similar performance to this costly technologies right and that everyone can afford. If I make everything in plastic right and if I have the total cost of the device

around 5, 5 dollars, they are about 250 rupees 300 rupees then each patient has to just pay 2, 3 rupee, 2 to 3 rupee, maybe 5 rupees maybe 10 rupees, maybe 250 right.

We are not like 100, not like 300, not like 500, not like 100 no we have to try to make technologies, we have to try to design technologies that can reach each and everyone in our society. No one should die because they cannot afford affordable technologies, alright. That is the idea, that is the interest that should be the interest. Either I can create sophisticated device with you know and sell it for like a few lakhs or I try to understand the concept, use my research, try to bring the cost down and still maintain the performance then this device can be used for a common man like you and me and people who cannot afford at all right.

Can we put this device or such devices in government hospitals and can it be used for free government has a lot of subsidies, right. So, you see that that if you if you really understand the concept, you can make technologies which are low cost and we can be used for betterment of human life alright. Anyway, we will discuss this in detail, how it can be used, this is really hot topic and very important topic right now for the in the area of research antibiotic resistance; Again, when you want to understand any topic if I talk about drug screening or if I talk about antibiotic resistance or if I talk about atrial fibrillation or if I talk about cancer diagnosis tool right.

Every time if I use a word try to see more, try to look at videos, try to try to look at the technologies available, try to read research papers right. More you read, more you understand. How the technologies are or how the technologies work and how we can create different technologies compared to the existing technology, right and how it will be better than what we are creating, right. So, after saying that let us see the next one, next one what we saw if you see on the screen.

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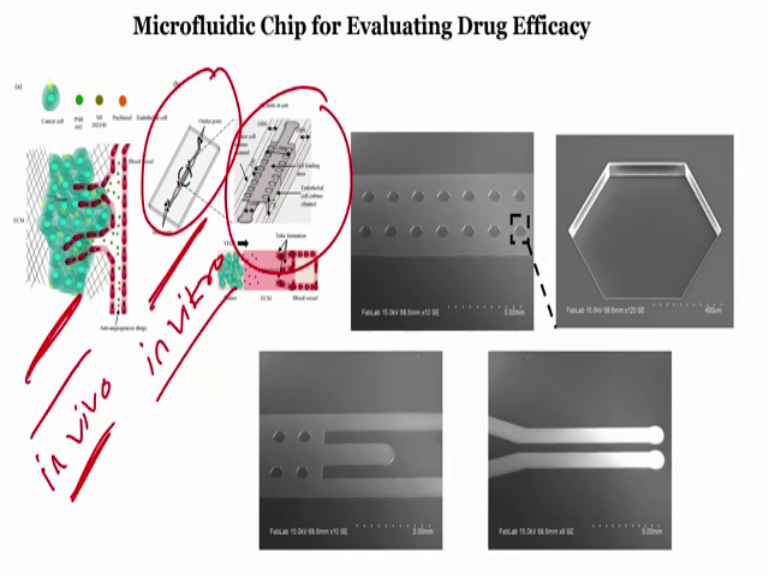

That is the microfluidic chip for evaluating drug efficacy right and here we discuss about that this device, we can mimic the in vivo situation on in vitro platform, right. We can mimic the in vivo situations on in vitro platforms right, this is a in vitro microfluidic chip. So, if I want to mimic this one, I can create a device right which will have a similar kind of a design which is within the body, within the body. This is very simple microfluidic chip. Now, people are also working on organ on chips organ on chips. So, to have this kind of pattern if I want to have this kind of pattern, these are all S E M images like I said for I am sorry about this is like this.

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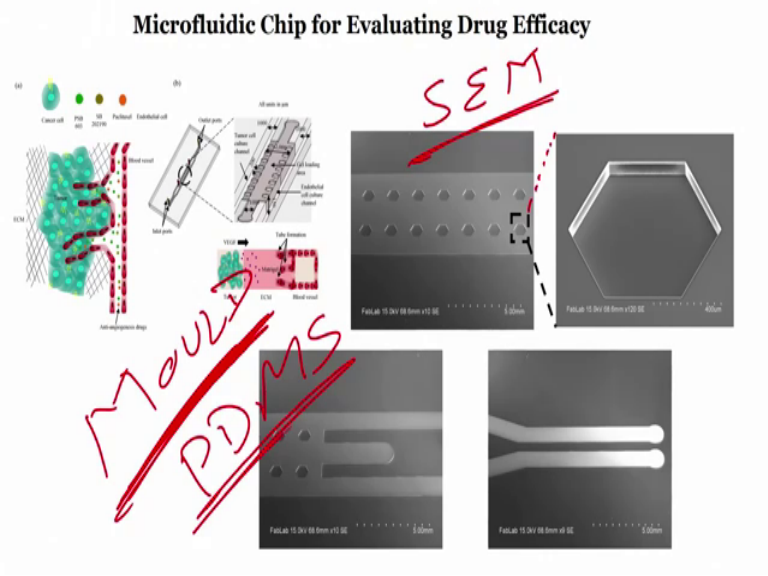

So, if I want to have if I want to create the microfluidic chip right, I have to have a mould and this mould is of silicon and this what you can see this these are all S E M images, scanning electron microscopy, scanning electron microscopy. This are all S E M images right and this images are of the mould. And using this mould, we will create the P D M S channel, the channels in PDMS, all right. So, how this device looks like? How this device looks like? Let us see if you see what I have I will just show you the pattern, I will show you the pattern see.

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What I am showing it you is this one. So, this is the channel that we are looking on the S E M and then in between the channel, if you see the central region here, we can load the we can load the metrigel. On one side, we can load the cancer cells, on another side of the channel here, this device there are two channels, you can see right. So, one channel we can load the cancer cell another channel, we can load the epithelial cells or huec cells huec cells is a right way way, h u e c huec cells.

And in center, we can load matrigel and then we can test different combination of drugs. So, how this works we will see when we are discussing this device into detail, this is the pattern of the device, pattern how the mould would look like now. This is just to show it to you how the pattern looks like, this is not a mould again. To create a mould, we have to create this kind of pattern on silicon and then to etch the silicon, to etch the silicon. When you etch the silicon, so opposite of whatever is there in the silicon will come in the

channel, opposite of whatever is there in silicon will come in the channel. If it is too confusing, let us see what does I what do I mean by opposite of that.

So, if you see the screen

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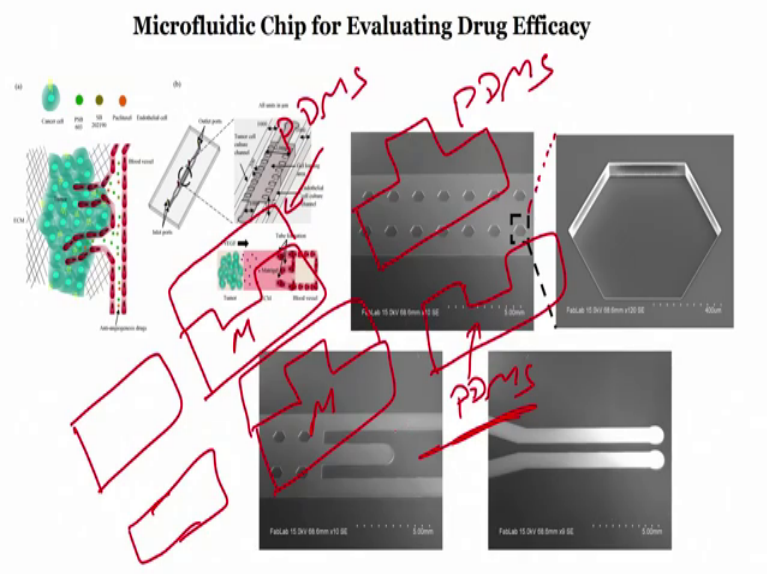

If I have silicon like this right and I create something like this right and if I have a P D M S, if I acquire P D M S, this layer is P D M S, if I acquire p d m s, my P D M S will look like when I peel it off when I peel P D M S off my p d m s will look like this. Do you want this; we do not want this, right. We want channels in P D M S. So, if I take a silicon and if I etch the silicon in this particular fashion right, then if I pour p d m s, then my P D M S will look like right. That is that we have created a channel in P D M S right, this is my p d m s, we have created a channel in P D M S. So, what I mean by opposite is, whatever the mould is this is mould right this is mould.

Whatever the pattern on the mould is opposite will come here, you see there is a hill here is a valley here is a valley here, there is a hill here right. So, you can see here what we have is a valley. So, opposite of that would be hills. If there is a hill which you can see here right clearly, then opposite of that would be in the P D M S. That is what I mean by opposite, we will see in detail how we can fabricate this device as well when we talk about the combinational therapy; The devices that can be used for understanding the combination of drugs.

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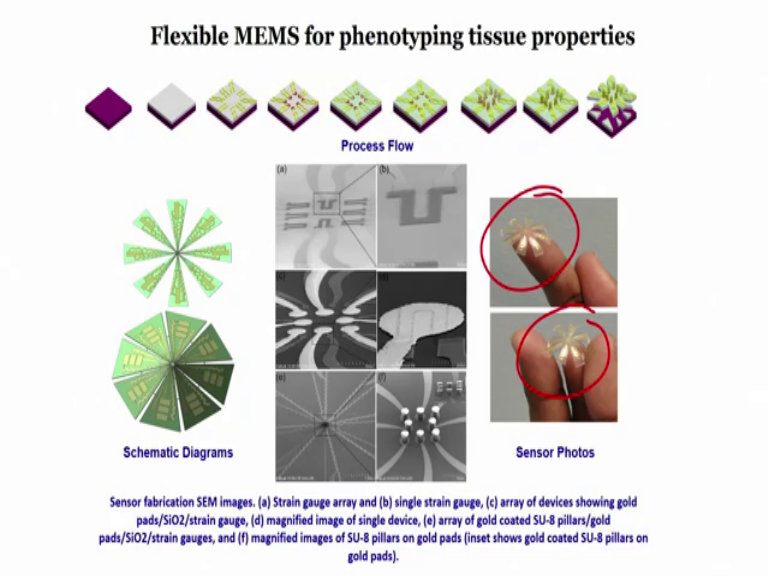

Then, we also talked about the flexible MEMS for phenotyping tissue properties, right and this is similar to that we have seen earlier also. If you see this one, this one right or this one right, it has two sensors; one is electrical sensor and another one is a piezoresistive sensor and this device looks like this which we have seen earlier just to show you quickly once again I am showing it to you, this is similar device which I am holding in hand right.

This is a device that you see on the screen as well. This is the device that I am holding right now. This has a piezoresistor and it has a electrode and everything is in the center, everything in the center rest is just a chip rest is just a bio chip, alright. So, that is what we are looking at on the screen right and it is it is a on the flexible material, that is why we say it is a flexible MEMS and can be used to understand the tissue property. That is why we say that the flexible MEMS for phenotyping tissue properties right.

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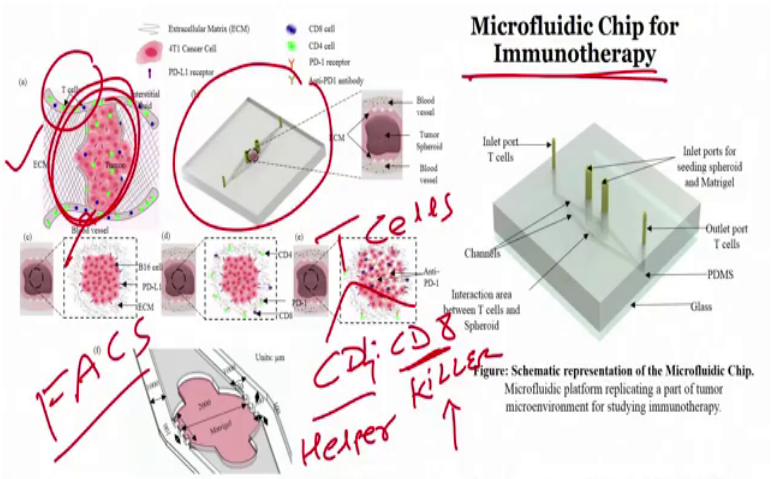

Figure: Schematic representation of the Experimental Design. (**a**) Tumor microenvironment and interaction of tumor with T cells, (**b**) Microfluidic platform replicating a part of tumor microenvironment for studying immunotherapy, (**c**) 4T1 (mouse breast cancer) cells spheroids embedded in the extracellular 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.

Now, let us talk about one more technology called immunotherapy called Immunotherapy. So, immunotherapy is therapy that will activate your immune system as the name says immunotherapy right. It will it will work with your immune systems and again immunotherapy a have several divisions, we will just talk about one particular division in which we need to understand whether the immunotherapy drug will be effective or not, right.

So, you understand very simple thing here and then we will discuss in detail later on. Right now, when the when there is a tumour which you can see this particular figure right and there are cells that flows in the blood vessels right, then within the cell there are something called t cells. We will discuss about t cells later on. And depending on the tumour if the immune system is working well, if the immune system responds well to the tumour, then there is a change in C D 4 and C D 8 concentration sorry, C D 4 is to C D 8 concentration.

Now you understand this thing C D 8 are called killer cells, killer this C D 4, C D 8 are in t cells we will see what is t cell how C D 4, C D 8 becomes right now just understand C D 8 is killer C D 4 is helper cells. So, what I said if the immune system responds well to tumour the killer cell should be higher in number right, killer cell should be higher in number.

So, the blood is taken from the patient and C D 4, C D 8 ratio is measured using something called flow cytometer, flow cytometer flow cytometry you understood this much. Now, if I want to create the similar kind of environment which is my in vivo environment, on to in vitro platform I can design a microfluidic chip, I can design microphone a chip which will mimic this in vivo situation. What I will do, now what I will do.

I will create the channels and load the tumour in the center of the channel, in the center like you see here right, you can see the magnified view of the channel with dimensions in figure number F, in figure F right.

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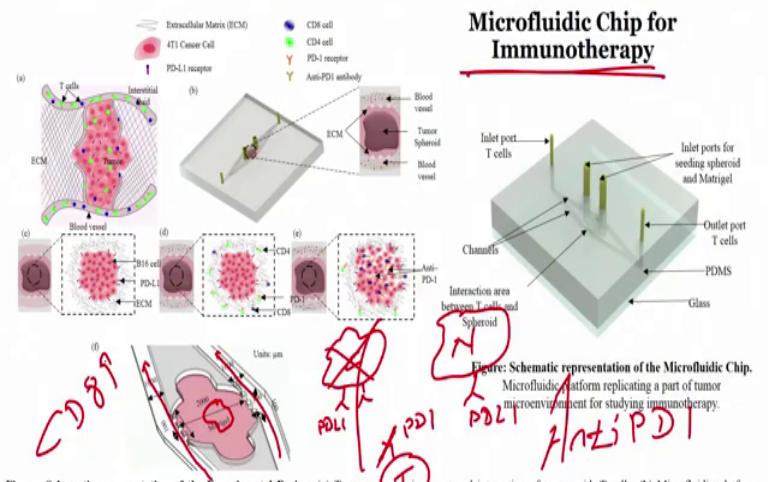

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So, here I will load the tumour and from here, I will pass the T cells pass the T cells, right. Now, immunotherapy is not so easy to understand, but just to help you out if, there is a cancer cell and there is something called immuno checkpoint immuno checkpoint, alright. So, one is called P D L 1 alright and on T cell correspondingly, there should be P D 1 P D 1 what is around a cancer cell P D l 1 cancer cell, this is T cell, what is on T cell? P D 1. This P D 1 will interact with P D 1 1 and it will think that the cancer is normal that because normal cells, normal cells also has P D l 1.

So, cancer the T, T cells cannot distinguish between normal and cancer t cell cannot distinguish between normal and cancer. In this case, if I block this P D 1, if I block P D 1, then P T cells will just kill cancer cells because it cannot it cannot find, it cannot have a

bonding between P D L 1 and P D 1. It cannot have interaction between P D L 1 and P D 1.

So, what will happen the T cells will start killing the cancer cells and more T cells will generate or we can also work on engineering T cells. That is a different topic. Right now, we are not interested in that. We are just interested in that, if I use a drug that can block P D 1 and that is why the drug name is called anti P D 1 anti P D 1. So, if I block the immuno checkpoint one of the checkpoints right on T cell and then if T cells cannot have interaction with P D L 1, the T cells will kill cancer cell. So, in this case if my C D 8 will start increasing, killer cells will start increasing. Number of C D 8 increasing; that means, my drug is effective my drug is effective right. So, I can use this anti P D 1 and similar kind of drugs similar kind of drugs right.

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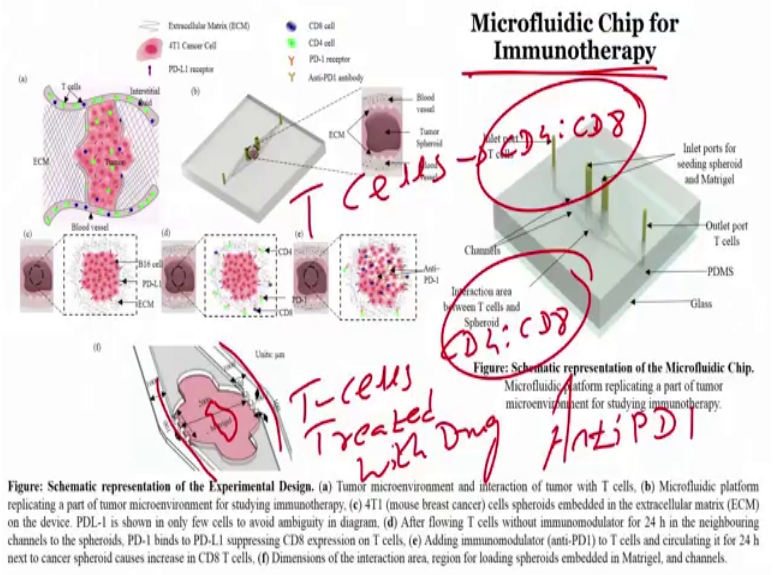

Figure: Schematic representation of the Microfluidic Chip. Microfluidic platform replicating a part of tumor microenvironment for studying immunotherapy.

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 test it by flowing this across this channel loaded with matrigel and tumour. And every time I flow after 48 hours, I measure the C D 4, C D 8 ratio; that means, I first flow just T cells, just T cells and measure C D 4, C D 8, then I float T cells treated with drug. Let me write down here.

T cells treated with drug T cells treated with drug and then I again flow in this channel. After 48 hours, I again measure C D 4, C D 8 ratio correct. Then, I try with T cells treated with another drug 3, drugs 4, drugs 5, drugs every time I measure C D 4 C D 8 ratio I keep on measuring C D 4, C D 8 ratio. Whichever drug is more effective, I will

get a better response for C D 4, C D 8 ratio, right; that means, that you can now based on the because see if there are three different drugs, you do not know which drug will be more effective for a particular patient. So, if you know with the help of patient cells, if you pass the if you extract the T cells from blood and you could treat the T cells with drug, you will know whether the patient will respond to particular and immunotherapy drug or not right because you see.

If there are three drugs, let us say there are three, F D a approved drugs. And right now, we just give one of the drug to the patient which whether the patient will respond to the drug or not, we probably do not know. So, if we can design a patient centric device, if you can design a patient centric device such that you can load the tumour or you can load the cells of the patient in the channel, you extract the blood and from that you extract T cells and you flow T cells without any drug next to this cells cancer cells or tumour within the microfluidic chip and you measure C D 4, C D 8 ratio.

Then you treat this t cells with a particular drug, let us say first drug and you flow it and you measure C D 4, C D 8 ratio. Then you treat the T cells with second drug and you again flow it in the channel and you measure C D 4, C D 8 ratio. Then you, take T cells the treated with third drug right, flow in the channel, again measure C D 4 C D 8 ratio in. If the drug is effective, if the blockage is well like anti PD 1 right, there are other immuno checkpoints as well, I am just taking an example of one immuno checkpoint.

Then what will happen what will happen, that the based on the C D 4, C D 8 ratio, we can know that yes look at this result this, the patient will respond probably better to this particular drug rather than the another two drugs in. If you can do that, then you can use this device as a patient centric platform in case of you know understanding the or evaluating the efficacy of the drug immunotherapy drug.

And this is very important because immunotherapy right now is given at that at the at the next stage like chemotherapy, radiation therapy immunotherapy, right. It is very interesting for people who really want to understand how cancer works and what kind of a you know therapies are there learn what is chemotherapy, what is the side effect of chemotherapy, what is radiation therapy, what are the side effects of radiation therapy, what is immunotherapy that we discussed, what are the side effects of immunotherapy. Now, the point is when you when you do research on immunotherapy, you will see that

68 percent of patients response well, 32 percent does not respond well. So, why 32 percent are not responding well when already this are f F D A approved drugs.

So, can we design a device that can be used in a fashion that we just discussed. So, again, to claim something we should have very strong data, right. This is another area which people are working on right and I am just talking about a subdivision of immunotherapy. Immunotherapy is vast area, any therapy is always fast right we have to understand a small portion and try to solve that portion, try to understand further. So, as a engineer I can only I, I know what are the what are the problems, but the point is I, I do not know lot of medical terms and that is why a very important thing is whenever you guys design, whenever you guys develop any device, always have a clinician as your partner right.

Because, doctors are the right person to talk to, if you want to work in the area of clinical research; as an engineer or scientist, you can help them to solve the problem, what is a problem and is it really a problem? After we do our study, we talk to the clinician we get the response from them we understand the problem and then you develop your device, then you design your device, then you perform your experiment, then you show the data and then the device will be actually useful. So, that is how you generally work in the area of biomedical or clinical research.

So, point was, can you design this device and the answer is yes. And we will see how we can how we can design such a devices and, again this is microfluidics. So, we call it as a microfluidic chip, alright ok. So, there are two more devices after this and we will we will discuss this in our third module, two or three devices left to show it to you in terms of micro engineering devices and that will finish our lecture 1. After that, we will start understanding technologies to fabricate my micro sensors and micro engineering devices or micro sensors or MEMS based sensors, right. And we will see how we can fabricate those devices. So, we have to understand a process flow, we have to understand recipe right. It is very simple. Let us see a micro technology also relies on process flow, it also relies on recipe, like our life right.

For example; if you want to make a sambar, if you may to make a sambar right, sambar with idli, sambar with dosa right, sambar with rice, sambar taste delicious right. So, the process flow to make the sambar is known, I also know, you also probably know right, but the recipe that we use, the way I will make my sambar will be different than yours.

And probably, the way that our grandmother used to make a sambar will be more delicious compared to what we will make right because they know correct recipe, correct recipe. Process flow is same, recipe is correct same way. When you want to fabricate the device, first is you should understand process flow. What is my first process, I should take a silicon wafer, what is the next process, I should clean my silicon wafer what is the next process right the process flow we know, I should etch, this metal how much time, what should be the thickness.

What should be the bonding time how can I mix my P D M S with my hardener. These are all recipes, recipes. If we do not know correct recipe, your device will not be, will not be working right. So, it is very important that you correlate the things in your life with research, it is easier to understand, process flow and it is actually called recipe guys. In micro engineering, this are called recipes and the process flow same thing like our life, same thing like cooking right.

So, just understand and merge both the real life applications with the academics and your research, your study will become easier. So, with that, just go through the all the things that we discussed today and we will discuss remaining devices in the next module.

Until then you take care, bye.