Computational Systems Biology
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Lecture – 51
Guest Lecture: Modelling in Drug Development

Hello everybody, welcome to the next couple of hours of lecture, where we are going to be talking about modelling in the pharmaceutical industry in the context of drug development. My name is Rukmini Kumar, I started off with a Ph. D in physics and then I went on to competition biology in the last 15 years or so I have been working in this industry. So, who I represent I work and I co-founded this company called Vantage research where a small company in Chennai, where about 12 multi-disciplinary scientists.

What we do is; we developed mathematical models of physiological systems that is one of the big things that we do and we collaborate with big pharma working on important drug development projects across the world, so that is basically what we do. We worked in many different areas, diabetes, immuno oncology, nutrition, autoimmune diseases such as rheumatoid arthritis, psoriasis etc.

So, what I would like to convey to you in the next couple of hours in not only the technical aspects of why modelling is important in the Pharma industry but also the fact that it can really move and improved drug development in very interesting ways and I like to emphasise that point in the next couple of hours, okay, excellent. So, the key points I like you to leave with are the following.

How does drug discovery happen today, I think everybody in general, may have vague idea about the various pieces involved, I like you to leave with the more concrete notion of how that happens from end to end, I would like you to then think about how does modelling helps, so once we understand drug discovery, what problems there are, how does modelling help in that industry.

In particular, the kind of models that I work on are mechanistic physiological models, so this is the field called quantitative and systems pharmacology or QSP for short and I would like to kind of immerse you into that world, the methods, the techniques, the challenges what we face in this area. Then, to make it real, we will talk about an example of type 2 diabetes; I love to talk about diabetes in the context of modelling.

Because it is the disease which touches many, many lives and you know usually, I ask how many people in the audience know have family members that have diabetes and usually it is the (()) (02:40).

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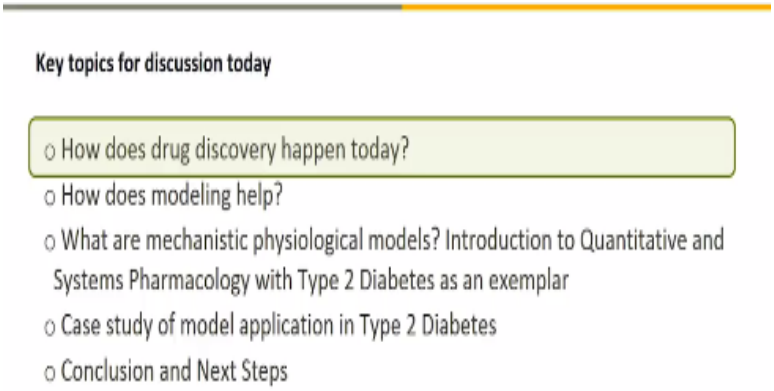

So, we can talk about diabetes and the kind of model that helps in diabetes and I like to conclude at the end by talking about the role of engineer's people with quantitative skill sets in pharma drug and development, okay excellent.

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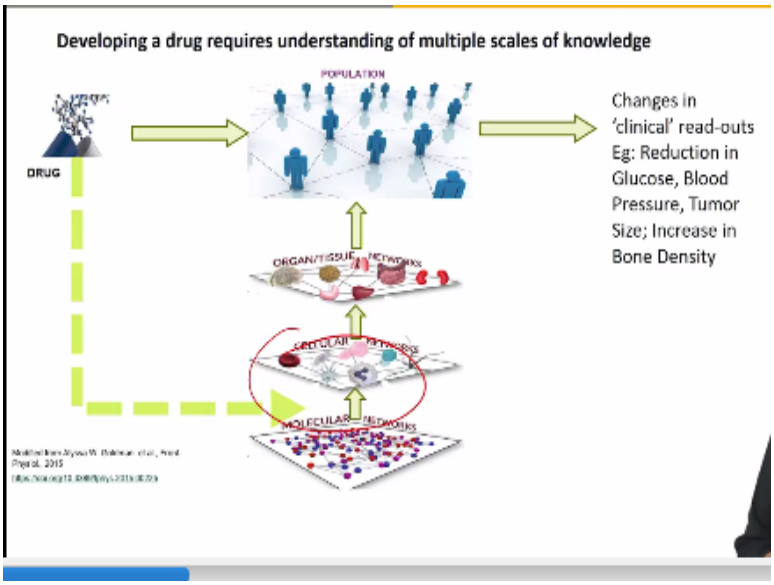

So, when you think about what is a drug and what is it do, really the image that should come in your head is some pharmacological agent usually, it is a small chemical sometimes, it is a protein that is given to a large number of individuals a population that is pre identify and then it causes a particular change that you want in that population. So, for instance if it is a drug for diabetes, you want to see a reduction in blood glucose.

If it is a drug for hypertension you want to see a reduction in blood pressure or tumour size if you are going after an oncology drug. On the other hand, there are some drugs that can increasing, you want to increase bone density, you want to increase muscle mass, those are possibilities as well, at the end of the day, you want some agent that changes something clinically meaningful in a person.

But that is a large kind of macroscope, I am sure all of you understand that at the end of the day, what a drug does, is going down multiple layers, so when you think of the human body, it is not just all the people who buy drugs in the pharmacy, there is a lot of magic going on a lot of a black box actually going on underneath those layers, there is a molecular network, cellular networks, organ tissue networks and then that; those can be extremely variable and that leads to the population.

And what we usually know is the drug manipulate something in one of these networks; in a cellular network or a molecular network and our job is to identify how that percolates up to the population, so that we have meaningful and safe results.

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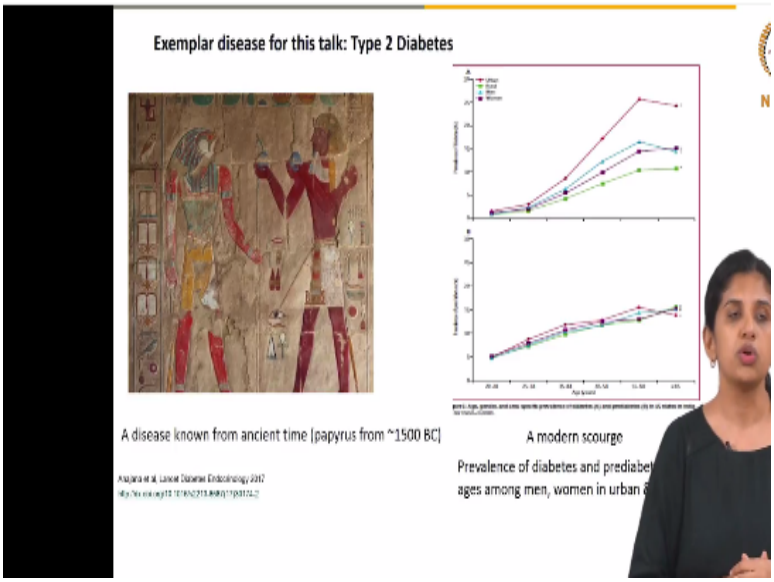

So, like as I said for this talk, I would like to talk about diabetes as an exemplar disease, again I love to ask how many of you know or have family members who suffer from diabetes, how many of these family members do you know that inject themselves with insulin once or twice a day? So, yeah, this is a disease much as we understand is a modern sketch, so the diabetes has been recorded from historic and prehistoric times.

There is you know, evidence from ancient Egypt from about 1500 BC about the description of diabetes as a disease where there is emaciation, lot of urination, weight loss, tiredness, dehydration and all the way to today on the right hand side, what you see there is epidemiological data collected from a group in Chennai actually which talks about the prevalence of diabetes in modern India, this is a rural urban.

And if you go into the paper, you will see that it is across high low socio-economic classes over age is what this graph shows at the age of between 20 and 24, what starts at 5%, it is also disease of age and you know, metabolic conditions, so it kind of increases all the way to 25, 30% as

people grow older. It is a major cause of public health concern and cast and human suffering, so that is what we want to talk about.

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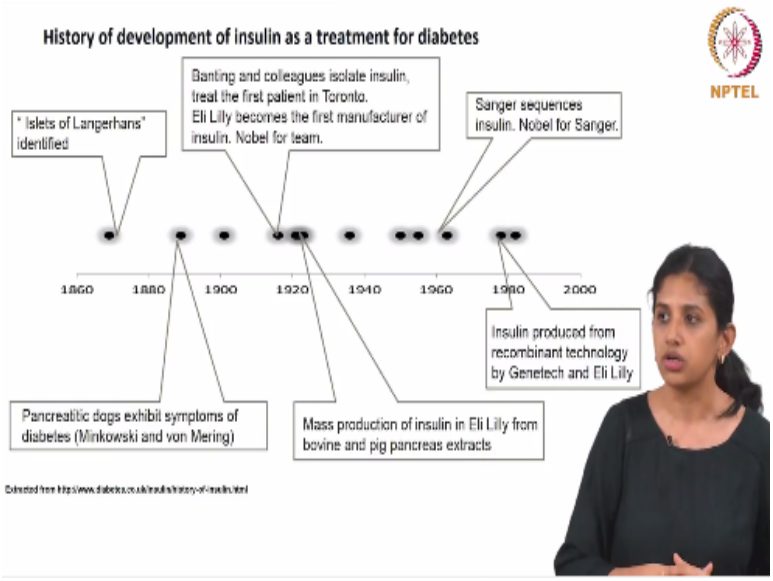

Now, it is a strange thing, you know we talk about diabetes, the ancient Egyptians knew about it today we know about it, our family members go into the pharmacy to buy drugs for diabetes but how do you go from one to the other, how do you go from seeing someone who is dehydrated and emaciated and figuring out what drug they need, so again we all have an understanding of how that process in between starts.

But I will talk about the development of insulin as a treatment for diabetes, how do we know we wanted to treat diabetics with insulin. So, the first thing which is of interest is anatomy itself, so early in 1860, people identified an organ called Islets of Langerhans, so these are sitting near the pancreas, so there was interesting that is something that you know is a curiosity but as we accumulated knowledge, there were animal experiments.

And in these experiment what they found was when you had dogs and you did pancreatitis to them, so you know, why the experiment came about is a harder question to ask and there is plenty of you know books written about the history of development of insulin but what they found this group Minkowski and Von Mering was if you take the pancreas out of dogs; out of healthy dogs, they have symptoms of diabetes.

So, they urinate excessively, they show extreme tiredness and at that point we also measuring blood glucose, so they see all of those symptoms in those dogs, so okay that is curious. The pancreas is somehow important and not having the pancreas causes symptoms of diabetes, then in kind of fascinating and pivotal work, group from the University of Toronto, banting, what they did was they not only isolated the secretion from the pancreas which was insulin.

They injected back the insulin to pancreatitic dogs, whose pancreas have been removed and they found that that injection alleviated the symptoms of diabetes, so here is a dog, you take out the pancreas, symptoms of diabetes, you inject back something that is secreted from the pancreas into the dog and the symptoms are alleviated, okay were onto something, so in what may have been the quickest turnaround between something that was discovered in a lab to something that was manufactured as a drug.

By late 1929, 1930 insulin was produced mass produced by Pharma company called Eli Lilly and marketed to people who have diabetes. So, before this, we think of diabetes as the lifestyle disease but before this diabetes could be a life sentence that means you know, you either lose your leg or if you have type 1 diabetes, you watch children die and there is not much you can do, so this change the way people think about diabetes.

But at that time, what is interesting is; will still in the dark ages when it comes to the genomic revolution, so people to make insulin what they had to do was look at other mammals like pigs and cows, take their pancreas, crush them up, extract the right amount of insulin and then put it in little vials to sell, so that was kind of you know still very path breaking but when we look back that is kind of work very difficult way to do these things.

Then, in the 60's Sanger, you know by this time, we know the structure of the DNA, we know DNA, RNA and we have got the fundamentals of molecular biology and insulin is sequenced. Once insulin is sequenced, then we know we can generate insulin using recombinant technology and then Genetech Eli Lilly by the time in 1980s, they were producing; mass producing

recombinant insulin, they still marketed as recombinant human insulin to distinguish it from the cow and the pig insulin that we had before.

And that was kind of again another path breaking development, so here you have end to end kind of the fascinating story and there is a lot of drama and you know, human element in the story going from one act to the other, I have presented a very simple story here but you can see all of the various elements that go into identifying what the problem is, finding what the solution to the problem is, generating that solution, mass producing it and then making sure it reaches the right people.

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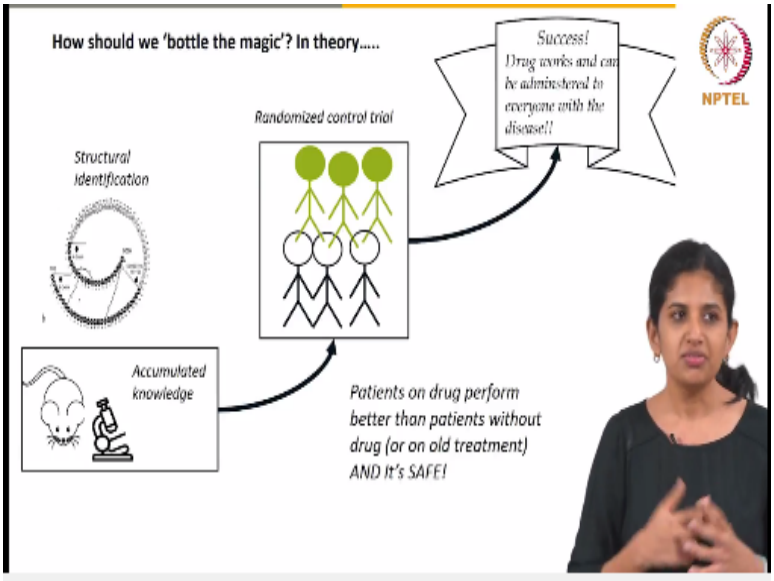

So, that is kind of that history which spanned about 100 years or so, now what we want to do is to bottle this magic, so we want to be able to you know go after difficult diseases, find what the problem is, find the right solution and find a way to get out of, you know to find the way to solve these things. So, if you kind of distilled, what happened in the; what I showed in the last thing, really you have you know what structure of chemical you what, you have all of these accumulated knowledge.

From there, you want to do what is called a randomised controlled trial and I will talk about that in a second but basically, what you want to do is you want to make sure that the drug works in humans that need it and once that is done, success if the drug works and it can be administered to

anybody that wants it. So, one of the key things that we should understand in modern drug development is the concept of a randomised clinical trial.

So, here what I have shown is you recruit say, 100 people, you want them to be case match, you want them to be very similar 100 people, then you divided them into 2 groups of 50 each, to one group you give your standard of care, whatever regularly people gave for diabetes, may be its metformin, maybe it is not much at that time, so you just leave them as it is, to the other group you give them your drug of choice.

Now, you have to be very careful with the randomised controlled trial usually, these are double blind as well, in the sense neither the patient nor the physician knows which is the control arm and the trial arm. So, if you are injecting the trial arm with insulin you have to find an injection with just serum or nothing in it to inject the control arm, so once this double blind trial by neither the patient nor the physician knows what the drug is who is getting treated.

Once that proceeds, then at the end of the trial in a predetermined time in 4 months and 6 months, you ask the question whether the treated people showed better symptoms or there was a disease improved compared to the untreated group, so this is a hard bar to across and there is lot of complications about placebo effect etc. so that is a whole other thing but the point that I want to make is drug development is challenging.

And often times, we heard about anecdotal things, you know herbal treatment this worked, an another therapy worked but the bark to cross for a treatment to work for everybody and to be signed off by authorities such as the FDA, the EMEA, Indian authorities and such is that you have to cross a randomised controlled trial. So, that is ideally the process that drug development takes, is it do you expect that it will be this smooth every time.

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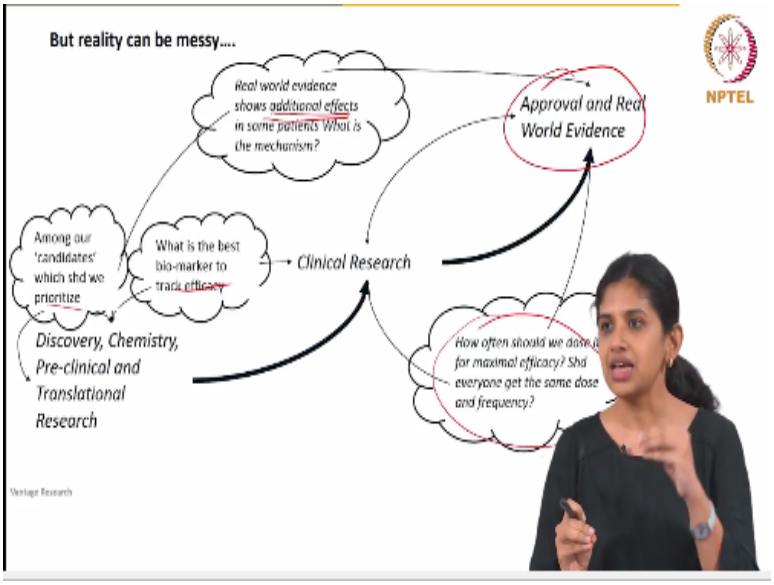

You know nothing is that is smooth in real life, so going from this part of discovery, chemistry pre-clinical is anything that happens in animal models not humans, so animals are you know in vitro systems anything that happens is preclinical, from there to clinical, which happens in humans and then to what is in the real world that is the thread but nothing is that simple, all kinds of questions come up.

So, as you can imagine very early in in the chemistry, you are not exactly sure how your; you know protein or the molecule your designing should be, so oftentimes companies have you know one early molecule, one late molecule with different properties, the other thing is what is the right thing to measure, in diabetes somewhat easy you measure glucose but in other diseases like arthritis, do you have elders, anybody have family members with arthritis, fewer but it is a disease of inflammation.

And often patients have a lot of pain in their joints, so then it is much harder to find what is the point of clinical efficacy, so what is the best biomarker to use that can be something that you know people struggle with when going from stage 1 to stage 2, very critical questions which models often answer is how much should I dose who should get a bigger or smaller dose, should that scale with the body weight of a person should that scale with severity of disease.

Somebody who is very diabetic versus somebody who is mildly diabetic, should they get different amounts of drug, all of those questions are important. Then often, when the drug; these clinical trials are usually conducted in 100's, may be 1000's of patients, then once you go into the real world and the drug is approved to be sold in the real world, then it could be potentially administered to millions of people.

Then you may start seeing signals that you did not see just because you have a much larger sample, then you have to worry both about the safety and efficacy, so those are again 2 important concepts in drug development; safety and efficacy. We have been talking about efficacy, which is if you are diabetic, I want to reduce your plasma glucose but we also have to make sure that we do not make you sicker; we do not make you faint.

Because you glucose is gone to low, so safety and efficacy are 2 sides of the same coin, so should we worry; you know what happens when you give the drug to millions of patients, are you expecting to see safety signals that you did not see in thousands of patients, so these are all just a snippet of some of the real world concerns that scientist in drug development face.

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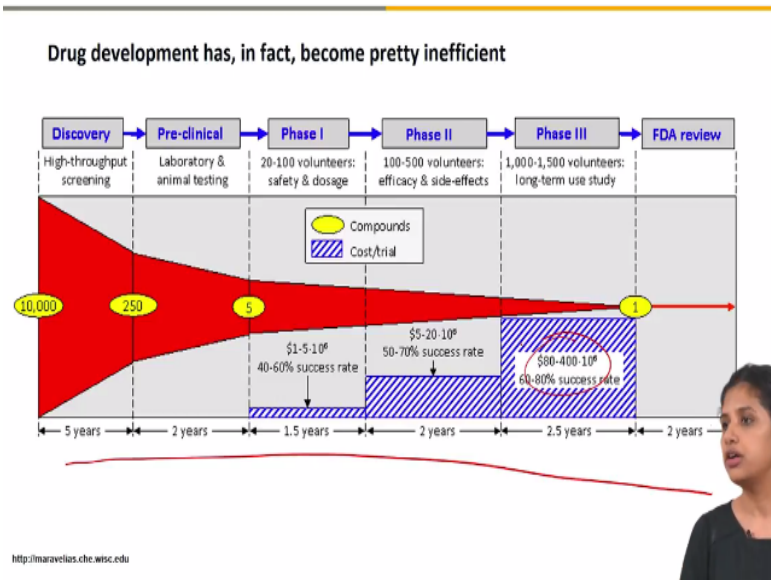

The crux of the matter is drug development is in fact very inefficient, so you may ask the question, you go to the pharmacy, you see so many medicines up there, what is it take, like how long does it take to go from idea to something being at the pharmacy, how much money does it

take, you know how much should a Pharma company or government etc. invest to get this drug out.

The numbers are actually staggering of late, I think the estimate is it takes about 10+ years to go from end to end of the process, so we were talking about one end being chemistry, the other end being DFT review, it can take a decade, it can take a billion dollars because the science is hard to do and in clinical trials can be expensive to do, so you want to run your trials in as efficient manner as possible and you want to make these entire process as efficient and smart as possible.

Not only because you will be saving money and time; time is important because then you reach drugs sooner to people that need them and the other thing is when you have more efficient extermination, you are saving animals and humans from potential harm, so that is the challenge that you know modern drug development is. Any questions, any kind of pre-existing notions that you have that you would like to talk about.

So, at the end of the day, a lot of you are interested in biology I think it is fascinating because biology in some ways a new frontier for a lot of knowledge to be discovered but this is the applied side of biology, at the end of the day you want biology to impact health, you want biology to make better drugs for people, you want biology to help live; people live for a longer healthier.

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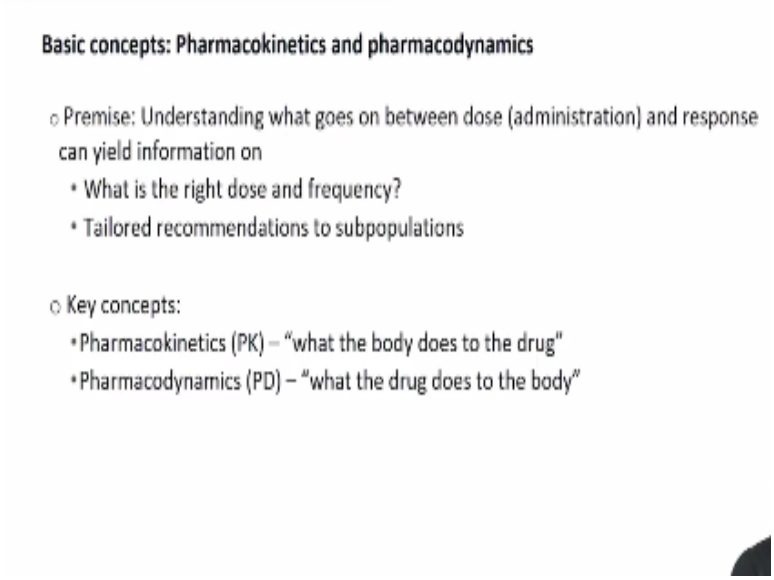

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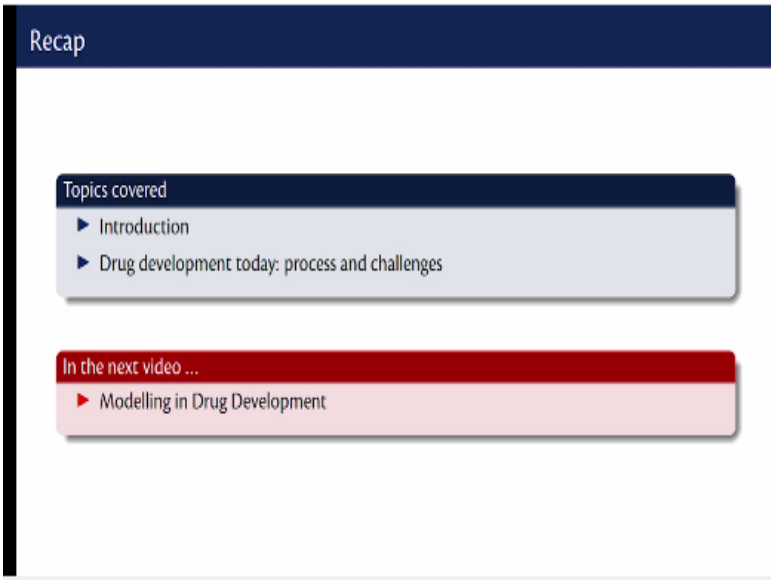

So, this is where kind of the rubber meets the road, when we are trying to get academic kind of knowledge applied to the real world. So, let us change as a little bit and talk about how does modelling help you know, why should we do modelling, what to people who do modelling do in drug development today.