Interview Appendix

Interview Script for Professor Juliana Chan Interview

1. What do think about our project?

Free fatty acids are really an energy source through stressful time. You really don't want to use free fatty acids all the time. Because as I said, you know, it generates ketones. And also, sometimes, it generates lots of free radicals as well, what we call reactive oxidative species. So, the burning of oxygen, the burning of free fatty acids, gives rise to ketone bodies, and so gives rise to reactive oxidative species, which you know too much is not good to the body. So, what I have tried to say is actually, you know, I think if somebody is overweight and obese, I think helping them to actually use up some of these free fatty acids will be useful. But really on the long term basis, it is not be… you really want to just break the vicious cycle. Because if you reduce the free fatty acids, as I said, the free fatty acids they serve as a source of fuel competitors and it is a very potent source of insulin resistance. So, if you could reduce the free fatty acids, then reduce the insulin resistance so therefore the islets doesn't have to work so hard. Then maybe you break the vicious cycle and so as a result you know then the glucose can be taken up more effectively, the glucose level goes down, the free fatty acids go down the insulin now can come down. Then you try to restore the balance.

2. What are the potential problems that our project may encounter?

Because, you know, I think you want to have enough oxygen to burn whatever free fatty acids or glucose because if you burn this energy or burn these substrates in a not so rich oxygen environment, you can also have a lot of free radicals. So sometimes if people just keep on burning the fat, because you need burning it, you need oxygen right? So if you don't have enough oxygen then actually you generate a lot of free radicals that not good. So your idea is useful if these people do a lot of exercise as well. Because really you produce energy right? You want to actually burn the free fatty acids right? You need oxygen. You always need those tools: glucose, free fatty acids, and you need oxygen. That's what we call the respiratory fitness. That's why we ask people to do exercise. You do exercise so you breathe more, your heart will beat stronger. So you can deliver more oxygen to the body. So

you cannot solve one thing and don't solve the other thing. So ultimately you are going to have anaerobic respiration. You keep on burning the fatty acids, but you know very…Like we have talked about the Bunsen burners it's an incomplete combustion that is not really nice. Then there will be a lot of side products as well. So I think the concept is very interesting because you identify people who are obese and who have insulin resistance, right? And free fatty acids are a culprit. So if you can render them. You know, switch over to have free fatty acid metabolism. Then you reduce the free fatty acids, then you increase insulin activity, then you allow the use of glucose more effectively, which is a good energy source. And then also, the most important thing is to reduce the stress on the islets. But I think on the proviso that it is not really on a prolonged basis. Because ultimately you really just want to break that vicious cycle and you really just try to help people losing excess weight. Also, coupled with adequate oxygen, so that you don't enter to have partial burning of the free fatty acids and then generate a lot of side products. Ketones are also increased and the reactive oxidase species which can cause a lot of problems.

3. What are the current treatments to reduce insulin resistance?

I think one of the…Weight reductions is the best. If you reduce weight, (by exercising?) Yes, go back to basic. You know, changing life style is to eat less rice and do more exercise. But it's very hard. Human behave is very hard. There is always…And this is also survival trait. I think your body tends to hang on to your energy. So if these people are just reducing diet but not actually doing exercise, then very soon, they just have a lower metabolic rate. And then, you know, after they just restricting diet, and if they start eating the same amount, and then it will become too much for them. And that's reason why all these weight reducing methods are like yoyo. And that is they have not changed the fundamental problems. Now, secondly, I think there are…Currently, there are several, there have been many anti-obesity drugs to reduce insulin resistance. Reduce weight is the most important, right? So, basically, fundamentally, there are two ways. Since obesity is due to eating too much or doing too little. So eating too much, then the way to do is actually to suppress your appetite. There are a lot of… There are several drugs have been used to actually suppress your appetite. (Reduce part of the stomach?)That is surgery. That actually reduces the malabsorption state. So basically cut part of your stomach or they cut part of your gut as well. But this is more than just reduction in term of calories absorption. But, if you still remember, as I have said that…By the time you eat, there is a thought in the brain. You always want to eat, right? Secondly, when you eat, the gut actually senses the food is coming and already

there are lots of hormones now. And then they will actually cross talk with the pancreas, cross talk with the liver, they cross talk with the fat. It seems that, you know, the surgery seems to destruct some of these signals. Somehow, you know, these people lose weight very quickly. But we still don't know why these people lose weight very quickly. These people actually get better even before they lose weight. So this is really interesting, this is really intricate kind of, the surgery style actually has that upper hand. You know the patients always said don't touch the stomach and of course I don't want to do that. But this is, for people are very obese, I think they (surgery) have a role. Somehow people really need to do some kinds of surgeries. But again don't forget that this is not just one thing. People ultimately still have to… need medication and education as well. As I said, there are a lot of drugs that have been developed. There is some work on these hormones in the brain. But unfortunately these hormones that tend to suppress the appetite also make some of these patients unhappy. So sometimes they have some side effects. Hormones are everywhere so sometimes they may be off-target. So, that's um… And some of these drugs also try to stimulate your body to burn… this excess energy. And sometimes they activate the stress hormones to burn. But as I have already said, you want to activate these stress hormones; sometimes you activate the blood pressure. So that may not be very good, right? So sometimes you do one thing, your body is very clever, right? You have to balance it. You can't just do one thing. Because innately, your body try to overcome something if you change the status. So the body will try and adjust a little bit. So that's the reason why some of this, now, there are also…So, then, of course there are drugs that purge add calories. One of the drugs is for example that basically gives you diarrhea. So they stop you from absorbing fat. So these people actually pass a lot of oily faces. They are quite effective but you know very inconvenient. There is um… and these are… There are now some drugs which are being developed which are injections. Some of these are actually injections, which are like gut hormones as I've already said. These are hormones secreted by the guts because the gut secretes some hormones that tell you have eaten enough. So they suppress your appetite. They are actually quite useful. But that kind of have to be injection as well. So the there are also some gut… so some hormones…So the other one is There is an interesting type of drugs which improve insulin resistance but paradoxically increase the body weight. And… There are a lot of take in, right? I am not if you are following. You have been following what I have been saying, right? I try to explain this but these are complex things, right? But if you remember, I have also said normally if you have too much energy, you can only store in two forms: either store in the liver or store in the muscles. Otherwise, they just store in the fat cells. But if you do not have enough fat cells, then it gets stored in some of the abnormal fat cells. And these are all in the liver

etc. So this is what we called aptotic fat. These aptotic fats, you know, they tend to generate more free fatty acids. So this is what a lot of Asians have. They are very small but they are very big here. Right, okay, they got big belly. But sometimes they are small and their beta cells are not very…They are pretty small and of course they don't need so many pancreas. They are born like that. They don't need to eat so much. You are small and then you know probably you are born in a very poor society. Then why do you need to be so big? So the whole body is designed. The pancreas are a little bit smaller. The kidneys area little bit smaller. So it is a design, a design problem. So even the fat cells are probably not so many. So now you actually are eating too much food so they have a lot call spill over fat. So this spill over fat generates a lot of free fatty acids. And these free fatty acid I should say cause insulin resistance. So there are types of drugs call Glitazones, TZD.And this is a PPARgamma agonist. Basically what happened is the transcription fats that turns on genes. Essentially, it actually causes your pre-fat cells into fat cells. So our body has a lot of stem cells. Some of them are also in a ready state. So this pre-activate, pre-fat cells, they can be converted into fat cells. They can store, they just like, here, sometimes I explain so much, my patients…For example, you know, I am quite tidy here, right? For example, if I have got no drawers, then everything will be there. So now basically I put in some drawers and then they put into right compartment. So you put them into compartments so everything will become quite clean. Okay, that's the reason why there are TZD's drugs. They actually paradoxically give you increased weight. The fat actually, the fat content increases. But they are actually mainly the subcutaneous fat. So the fatty acid, the fatty liver is gone, right? And then also sometimes even so fats in muscle or the fats in the pancreas is gone, right So actually the insulin resistance comes down, the free fatty acids come down, inflammation comes down. Right? Okay? And then the glucose gets better. But one of the problems of this kind of fat is that it increases so much weight. Because they haven't changed their eating habits. Right? And so as a result, they just become so fat. Sometimes they have other problems. For example, they retain water because too much fat is still not very good, right? So they still then, they may have high blood pressure. And then sometimes, they also have fractures and things like that. So these are really, so if you ask me about insulin resistance, these are the some of the drugs that have been working. So, you know, in short, by reducing body weight that works. And then it is lifestyle modification. Drugs that suppress your appetite. Drugs that actually stop you from reducing so much… absorbing so much energy. Drugs that help you burn the fat more. Or just now sometimes the drugs that actually help you to shift the fat compartment. They all have been shown to improve insulin resistance. Then, also, therefore would actually improve the beta cells function and reduce the risk of diabetes. And people with

diabetes, they also improve the diabetes control. The ultimate goal is cell replacement therapy and that is either transplantation. Because as I said, people ultimately do not have enough islets. So, a lot of people are working in the area and they are trying to…Because… how to get the islets? They are so few, right? So, you know, nobody donates islets. You know you have to donate pancreas. Getting people donate the pancreas is very difficult. So getting pancreas is very difficult. Firstly even people donate the heart, right, then…The pancreas because full of digestive juice. So, you know, they get digested. Everything get digested so you have to get this very quickly. And then you have to quickly extract all the islets. Out of hundreds cells to get that five cells. Then you have to gets that pellets of cells and usually you need two pancreas in order to get enough islets in order to be injected to be transplanted.

4. How do you think our project could be applied?

Sometimes people do cellular engineering, they will take the cells and then they just re-engineer the cell and put that cell back into it. Maybe you don't have because this cell, this genetics, this genes are everywhere. But how it expressed in different bodies we don't know. You can't just turn on the gene like that everywhere. Because you know, if you actually up regulate that gene in this cell type will be okay but if you up regulate that gene in that cell type, they may be a problem. And this is really all the biological challenges. So if you could actually work on cellular level, maybe it can. Now for example that you have stem cells. You know, and then change it into liver cells. And then you can actually have the right technique. And then switch on this parameter maybe just for short period of time. Smell the fat in the liver. I think that sounds just like a dose. I think that is doable. For example if you get some stem cells and you know you have this IPS cells (Induced pluripotent stem cells).You just use your skin cell, and then you can turn it into, under certain kind of environment, you will be able to differentiate it into liver cells.Or you can take the liver cells out. Which is still very invasive. Stick a needle into your liver and then take it out. And then maybe you can manipulate it then put that cell back into the liver. And that can be done. Because sometimes we put a needle into some of the big blood vessels. And then put it back into the cells. Put it back into the liver. Once they go into the circulation, they home in. That's very interesting. These cells once they are differentiated, once they… So initially they are really primitive. They can turn to anything. But if you actually, when they go through, they just like baby, right? It just like nurturing baby. Because you are mom, right? I am sure if you are born here, you Korean, you speak perfect Cantonese. It's your environment very

important. So the cells can be molded. So these cells can go to the liver for example. And then under certain environment, it can actually differentiate into certain types of cells. And then that certain types have to go to their home. So if you up to certain stage, it is the liver cells for example, then it goes into the liver. Then maybe, then you can actually help burn up these fatty acids.

5. Are there any regulations for gene therapy in Hong Kong?

Currently, we don't have particular rule in actually using genetic markers. I think of course it has to be done properly. I think the lab has to be credible. The most importantly, I think the person needs to explain the information. You don't use this kind of information and just put people worried. After action, it is even important than making that risk prediction. You predict risks and then you need to tell people what you can do.

6. How do new treatments get approved for commercial clinical use?

When you have this idea or if you have now discovered the way that actually deliver this gene. These are two genes and they are both in plants? (Yes)So actually plants and human, they sometimes crosstalk a lot of discoveries in the plants are quite applicable to human beings as well. So, it's worth pursuing. That's really interesting concept as I said. Then the next thing is to go through multiple tests (bioassay) on cell base. So, liver cells, fat cells, muscle cells, even islets cells. Just to make sure the over- expression of these two genes. Consequences and phenotypes in these cells. Then they go into animal models. Then usually now use rats, or mice, or mouse. Really, if you think it is hopeful, the industries now need several animal models. People even use monkeys or dogs. Then you have to work out the right dosage. For example, in this situation, you have to be aware how to fine tune. You don't want to over express too much, right? So just like tablets. Even if we deliver a drug, you know how much do you give, you give once a day or three times a day or something like that. So that is a big subject. Then later on, you have to see how do you deliver it. For some drugs, sometimes you take it orally or sometimes you inject it. For example, or sometimes, you know what the best formulation is. Then, after you have done all these, you will have to look for whether they cause cancer for example. If you give very super dose, it will induce cancer which people are worried about. They will actually cause mutagenesis that means they can actually induce abnormal baby growth for example. There is now very standard protocol that they

have to go through and that may take years. Usually, hundreds only one can get through because along the way they have already found that usually some of them may have side effects. Some of them actually cause cancers; some of them work in one species but doesn't work in other species. That really takes for about five or six years. Then they even have to take the right compounds, right formulation that have to been absorbed. Then they go into clinical studies. Then you have to test in normal people first, find the right dosage first. And then next they will have the phase 1.Then they have the type of patients they want to target. This situation may be obese subjects.

Then few hundreds, you know, very careful. So they take the medication and test a lot of things. Then they have to find multiple doses that are five or six doses and finally design one dose. Then they could go to faze 3. Thousands of patients. And then finally get all these information and give them to regulation agency.

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7. What do think about our project?

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8. What are the potential problems that our project may encounter?

Because, you know, I think you want to have enough oxygen to burn whatever free fatty acids or glucose because if you burn this energy or burn these substrates in a not so rich oxygen environment, you can also have a lot of free radicals. So sometimes if people just keep on burning the fat, because you need burning it, you need oxygen right? So if you don't have enough oxygen then actually you generate a lot of free radicals that not good. So your idea is useful if these people do a lot of exercise as well. Because really you produce energy right? You want to actually burn the free fatty acids right? You need oxygen. You always need those tools: glucose, free fatty acids, and you need oxygen. That's what we call the respiratory fitness. That's why we ask people to do exercise. You do exercise so you breathe more, your heart will beat stronger. So you can deliver more oxygen to the body. So you cannot solve one thing and don't solve the other thing. So ultimately you are going to have anaerobic respiration. You keep on burning the fatty acids, but you know very…Like we have talked about the Bunsen burners it's an incomplete

combustion that is not really nice. Then there will be a lot of side products as well. So I think the concept is very interesting because you identify people who are obese and who have insulin resistance, right? And free fatty acids are a culprit. So if you can render them. You know, switch over to have free fatty acid metabolism. Then you reduce the free fatty acids, then you increase insulin activity, then you allow the use of glucose more effectively, which is a good energy source. And then also, the most important thing is to reduce the stress on the islets. But I think on the proviso that it is not really on a prolonged basis. Because ultimately you really just want to break that vicious cycle and you really just try to help people losing excess weight. Also, coupled with adequate oxygen, so that you don't enter to have partial burning of the free fatty acids and then generate a lot of side products. Ketones are also increased and the reactive oxidase species which can cause a lot of problems.

9. What are the current treatments to reduce insulin resistance?

I think one of the…Weight reductions is the best. If you reduce weight, (by exercising?) Yes, go back to basic. You know, changing life style is to eat less rice and do more exercise. But it's very hard. Human behave is very hard. There is always…And this is also survival trait. I think your body tends to hang on to your energy. So if these people are just reducing diet but not actually doing exercise, then very soon, they just have a lower metabolic rate. And then, you know, after they just restricting diet, and if they start eating the same amount, and then it will become too much for them. And that's reason why all these weight reducing methods are like yoyo. And that is they have not changed the fundamental problems. Now, secondly, I think there are…Currently, there are several, there have been many anti-obesity drugs to reduce insulin resistance. Reduce weight is the most important, right? So, basically, fundamentally, there are two ways. Since obesity is due to eating too much or doing too little. So eating too much, then the way to do is actually to suppress your appetite. There are a lot of… There are several drugs have been used to actually suppress your appetite. (Reduce part of the stomach?)That is surgery. That actually reduces the malabsorption state. So basically cut part of your stomach or they cut part of your gut as well. But this is more than just reduction in term of calories absorption. But, if you still remember, as I have said that…By the time you eat, there is a thought in the brain. You always want to eat, right? Secondly, when you eat, the gut actually senses the food is coming and already there are lots of hormones now. And then they will actually cross talk with the pancreas, cross talk with the liver, they cross talk with the fat. It seems that, you know, the surgery seems to destruct some of these signals. Somehow, you know,

these people lose weight very quickly. But we still don't know why these people lose weight very quickly. These people actually get better even before they lose weight. So this is really interesting, this is really intricate kind of, the surgery style actually has that upper hand. You know the patients always said don't touch the stomach and of course I don't want to do that. But this is, for people are very obese, I think they (surgery) have a role. Somehow people really need to do some kinds of surgeries. But again don't forget that this is not just one thing. People ultimately still have to… need medication and education as well. As I said, there are a lot of drugs that have been developed. There is some work on these hormones in the brain. But unfortunately these hormones that tend to suppress the appetite also make some of these patients unhappy. So sometimes they have some side effects. Hormones are everywhere so sometimes they may be off-target. So, that's um… And some of these drugs also try to stimulate your body to burn… this excess energy. And sometimes they activate the stress hormones to burn. But as I have already said, you want to activate these stress hormones; sometimes you activate the blood pressure. So that may not be very good, right? So sometimes you do one thing, your body is very clever, right? You have to balance it. You can't just do one thing. Because innately, your body try to overcome something if you change the status. So the body will try and adjust a little bit. So that's the reason why some of this, now, there are also…So, then, of course there are drugs that purge add calories. One of the drugs is for example that basically gives you diarrhea. So they stop you from absorbing fat. So these people actually pass a lot of oily faces. They are quite effective but you know very inconvenient. There is um… and these are… There are now some drugs which are being developed which are injections. Some of these are actually injections, which are like gut hormones as I've already said. These are hormones secreted by the guts because the gut secretes some hormones that tell you have eaten enough. So they suppress your appetite. They are actually quite useful. But that kind of have to be injection as well. So the there are also some gut… so some hormones…So the other one is There is an interesting type of drugs which improve insulin resistance but paradoxically increase the body weight. And… There are a lot of take in, right? I am not if you are following. You have been following what I have been saying, right? I try to explain this but these are complex things, right? But if you remember, I have also said normally if you have too much energy, you can only store in two forms: either store in the liver or store in the muscles. Otherwise, they just store in the fat cells. But if you do not have enough fat cells, then it gets stored in some of the abnormal fat cells. And these are all in the liver etc. So this is what we called aptotic fat. These aptotic fats, you know, they tend to generate more free fatty acids. So this is what a lot of Asians have. They are very small but they are very big here. Right, okay, they got big belly. But sometimes they

are small and their beta cells are not very…They are pretty small and of course they don't need so many pancreas. They are born like that. They don't need to eat so much. You are small and then you know probably you are born in a very poor society. Then why do you need to be so big? So the whole body is designed. The pancreas are a little bit smaller. The kidneys area little bit smaller. So it is a design, a design problem. So even the fat cells are probably not so many. So now you actually are eating too much food so they have a lot call spill over fat. So this spill over fat generates a lot of free fatty acids. And these free fatty acid I should say cause insulin resistance. So there are types of drugs call Glitazones, TZD.And this is a PPARgamma agonist. Basically what happened is the transcription fats that turns on genes. Essentially, it actually causes your pre-fat cells into fat cells. So our body has a lot of stem cells. Some of them are also in a ready state. So this pre-activate, pre-fat cells, they can be converted into fat cells. They can store, they just like, here, sometimes I explain so much, my patients…For example, you know, I am quite tidy here, right? For example, if I have got no drawers, then everything will be there. So now basically I put in some drawers and then they put into right compartment. So you put them into compartments so everything will become quite clean. Okay, that's the reason why there are TZD's drugs. They actually paradoxically give you increased weight. The fat actually, the fat content increases. But they are actually mainly the subcutaneous fat. So the fatty acid, the fatty liver is gone, right? And then also sometimes even so fats in muscle or the fats in the pancreas is gone, right So actually the insulin resistance comes down, the free fatty acids come down, inflammation comes down. Right? Okay? And then the glucose gets better. But one of the problems of this kind of fat is that it increases so much weight. Because they haven't changed their eating habits. Right? And so as a result, they just become so fat. Sometimes they have other problems. For example, they retain water because too much fat is still not very good, right? So they still then, they may have high blood pressure. And then sometimes, they also have fractures and things like that. So these are really, so if you ask me about insulin resistance, these are the some of the drugs that have been working. So, you know, in short, by reducing body weight that works. And then it is lifestyle modification. Drugs that suppress your appetite. Drugs that actually stop you from reducing so much… absorbing so much energy. Drugs that help you burn the fat more. Or just now sometimes the drugs that actually help you to shift the fat compartment. They all have been shown to improve insulin resistance. Then, also, therefore would actually improve the beta cells function and reduce the risk of diabetes. And people with diabetes, they also improve the diabetes control. The ultimate goal is cell replacement therapy and that is either transplantation. Because as I said, people ultimately do not have enough islets. So, a lot of people are working in the area and

they are trying to…Because… how to get the islets? They are so few, right? So, you know, nobody donates islets. You know you have to donate pancreas. Getting people donate the pancreas is very difficult. So getting pancreas is very difficult. Firstly even people donate the heart, right, then…The pancreas because full of digestive juice. So, you know, they get digested. Everything get digested so you have to get this very quickly. And then you have to quickly extract all the islets. Out of hundreds cells to get that five cells. Then you have to gets that pellets of cells and usually you need two pancreas in order to get enough islets in order to be injected to be transplanted.

10. How do you think our project could be applied?

Sometimes people do cellular engineering, they will take the cells and then they just re-engineer the cell and put that cell back into it. Maybe you don't have because this cell, this genetics, this genes are everywhere. But how it expressed in different bodies we don't know. You can't just turn on the gene like that everywhere. Because you know, if you actually up regulate that gene in this cell type will be okay but if you up regulate that gene in that cell type, they may be a problem. And this is really all the biological challenges. So if you could actually work on cellular level, maybe it can. Now for example that you have stem cells. You know, and then change it into liver cells. And then you can actually have the right technique. And then switch on this parameter maybe just for short period of time. Smell the fat in the liver. I think that sounds just like a dose. I think that is doable. For example if you get some stem cells and you know you have this IPS cells (Induced pluripotent stem cells).You just use your skin cell, and then you can turn it into, under certain kind of environment, you will be able to differentiate it into liver cells.Or you can take the liver cells out. Which is still very invasive. Stick a needle into your liver and then take it out. And then maybe you can manipulate it then put that cell back into the liver. And that can be done. Because sometimes we put a needle into some of the big blood vessels. And then put it back into the cells. Put it back into the liver. Once they go into the circulation, they home in. That's very interesting. These cells once they are differentiated, once they… So initially they are really primitive. They can turn to anything. But if you actually, when they go through, they just like baby, right? It just like nurturing baby. Because you are mom, right? I am sure if you are born here, you Korean, you speak perfect Cantonese. It's your environment very important. So the cells can be molded. So these cells can go to the liver for example. And then under certain environment, it can actually differentiate into certain types of cells. And then that certain types have to go to their home. So if you up to certain

stage, it is the liver cells for example, then it goes into the liver. Then maybe, then you can actually help burn up these fatty acids.

11. Are there any regulations for gene therapy in Hong Kong?

Currently, we don't have particular rule in actually using genetic markers. I think of course it has to be done properly. I think the lab has to be credible. The most importantly, I think the person needs to explain the information. You don't use this kind of information and just put people worried. After action, it is even important than making that risk prediction. You predict risks and then you need to tell people what you can do.

12. How do new treatments get approved for commercial clinical use?

When you have this idea or if you have now discovered the way that actually deliver this gene. These are two genes and they are both in plants? (Yes)So actually plants and human, they sometimes crosstalk a lot of discoveries in the plants are quite applicable to human beings as well. So, it's worth pursuing. That's really interesting concept as I said. Then the next thing is to go through multiple tests (bioassay) on cell base. So, liver cells, fat cells, muscle cells, even islets cells. Just to make sure the over- expression of these two genes. Consequences and phenotypes in these cells. Then they go into animal models. Then usually now use rats, or mice, or mouse. Really, if you think it is hopeful, the industries now need several animal models. People even use monkeys or dogs. Then you have to work out the right dosage. For example, in this situation, you have to be aware how to fine tune. You don't want to over express too much, right? So just like tablets. Even if we deliver a drug, you know how much do you give, you give once a day or three times a day or something like that. So that is a big subject. Then later on, you have to see how do you deliver it. For some drugs, sometimes you take it orally or sometimes you inject it. For example, or sometimes, you know what the best formulation is. Then, after you have done all these, you will have to look for whether they cause cancer for example. If you give very super dose, it will induce cancer which people are worried about. They will actually cause mutagenesis that means they can actually induce abnormal baby growth for example. There is now very standard protocol that they have to go through and that may take years. Usually, hundreds only one can get through because along the way they have already found that usually some of them may have side effects. Some of them actually cause cancers; some of them work in

one species but doesn't work in other species. That really takes for about five or six years. Then they even have to take the right compounds, right formulation that have to been absorbed. Then they go into clinical studies. Then you have to test in normal people first, find the right dosage first. And then next they will have the phase 1.Then they have the type of patients they want to target. This situation may be obese subjects.

Then few hundreds, you know, very careful. So they take the medication and test a lot of things. Then they have to find multiple doses that are five or six doses and finally design one dose. Then they could go to faze 3. Thousands of patients. And then finally get all these information and give them to regulation agency.