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Identification of and Therapeutic Targets in Neurofibromatosis Type 2
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>> Dr. Joseph Kissil is here to speak to us, ladies and gentlemen. He's going to discuss current research on basic mechanisms and therapy. He comes to us from Scripps Institute in Jupiter, Florida. I heard about your work at the DOD. Lobbying conference -- for NF2 in Washington in January of this last year. And we're very excited to have you speak to us so that we can learn what else is coming down the line. Thank you very much.

(Applause)

>> DR. KISSIL: First of all, really thank you for the invitation. To present. Some of the work we're doing.

And obviously normally I speak in scientific venues. And it's very technical and I'm going to try to keep this jargon down as much as I can.

So I'll just tell you that I trained as a molecular biologist and cancer biologist. And then started my post doctoral fellowship and was thinking that I needed to learn -- I was always interested in human disease and I was thinking I need to learn about generating models for human disease.

And some people ask me this, why NF2. I went into a very big lab with people working on lung cancer and. And there were about 40 people and one guy in the corner who was about to leave who was working on NF2. I said all right. That's what I'm going to do.

And it started out on this journey which I have been following up for 15 years now. Basically initially out of intellectual curiosity, but the more I learned about the disease, I realized how important it is and I'm just happy to be a part of the whole NF community.

So why did -- I had my own lab at the Wistar Institute for about eight years and then I decided to move to the Scripps Research Institute.

And the reason I decided was because Scripps has got a very interesting approach to doing science. Half of our faculty are chemists and half of our faculty are biologists. And onebasic idea is that the biologists come up with the disease-related question and the chemists have their tools and together we develop drugs or sensors or whatever. But we work to develop something practical. And then we try and, you know, bring that into therapy or into practice.

So that's what my talk is going to follow today.

I'll tell you about one project that we've been working on for a long time, and then I'll tell you about some of the future things that we're doing.

So again -- and I'll say this, Cristina Fernandez-Valle did a fantastic job introduction-wise. So she's saving me a lot of trouble. And in relation -- she described a process of unbiased drug

development. And I'm going to present the flipside of the coin which is guided, biased drug development.

So really in the process for us, it evolves through a few steps. The first is understanding the molecular events that underlie a disease, a Schwann cell that's behaving poorly and we want to understand why. What are the molecular events that underlie this?

We think that once we understand these, we'll be able to identify vulnerabilities in these mechanisms and somehow identify these vulnerabilities, validate them, prove that they are vulnerabilities, and eventually develop therapeutics to target these vulnerabilities.

And I think as Cristina stated eloquently, we're at a point where we probably don't understand the majority of what needs to be understood. But we understand enough today that we can start going after targets, and not only can we understand and validate targets, we're at a phase of development of therapeutics. I think things are going to accelerate, go a little faster and we're on the right track. So I think there is -- there is a reason to be optimistic.

Now, when we started working on this in 2003, we knew that Merlin, which is a protein coded by NF2, the NF2 gene, regulates one pathway. At the time the work I did while I was a post Doc, I found that Merlin regulates this protein called PAK. We'll get back to the PAKs. But since that point on, multiple different functions have been ascribed to Merlin, which include regulation of multiple different signalling pathways many and various groups are -- and we too are trying to attack and look for vulnerabilities along these pathways-- this is called the Hippo/Yap pathwayand this is the Rac signaling pathway. We're looking for vulnerabilities and lookingfor an approach that Cristina described. An unbiased approach. And I'll talk about that at the end.

Right now I'm going to focus on the PAKs.

Our interest in the PAKs goes back to 2002, 2003 when we identified it as a molecule that's regulated by Merlin. Merlin negatively regulates this protein called PAK, actually a group of proteins called PAKs. And in doing so it prevents its activity. But the PAKs do -- they're basically an enzyme. So they take a molecule called ATP, which is an energy source, and they take a piece of energy and they transfer it, they take a phosphate and they transfer it onto another protein. And that changes the function of that protein.

So think about it as a cascade of events. And one analogy I'd like to use is in a way, if you look at a car, the PAKs are the gas pedal, -- but it's always kind of in an on position.

And Merlin is the -- is the hand break. And the moment that hand brake it lost, that car takes off. And that's your Schwann cell.

So PAK is the accelerator. And the question was… is this a Vulnerability?

And the way you do those types of experiments is you take Schwann cells from a NF2 patient or from a mouse and which we genetically engineer to lose the NF2 gene. And if we take those cells and implant them into a mouse, they'll form a tumor.

And that's shown here. This is the control. So these are just schwannoma cells implanted in the side of a mouse. And what we do is we look for example at tumors after two weeks of being implanted in a mouse and we calculate their diameter. And this is what the

distribution of diameters would look like in a NF2 tumor.

And then we can use an artificial approach called RNAi. And I talked to some people about this. An RNA molecule that you can use to target different vulnerables in the cell.

And we use that to target the PAKs. Before we get all excited, RNAi is not currentlyamenable for use in patients. Because if it was, it would be fantastic. We would use it to target this vulnerability. But at this point it's more of an experimental tool.

What we were able to see is if we inhibit and interfere with the function of these PAKs, we can significantly prevent tumors from growing. Okay?

And -- this is just an example of the type of validation we need to do. So we figured out a picture, we figured out one molecule we want to go after, and now we target that molecule and make sure that it's giving us the desired effect.

Now, I apologize, I don't know if you can see here, but this was done in 2008. Just to give you a time frame, we originally discovered the involvement of these PAKs back in 2003, really. But it took us five years to reach a point where we had the technology to validate them.

Now, you know, this is 2003 to 2008, but this all happened ten years ago. I can tell you that today it would take us one year to do this.

When what only a decade ago took us five years, we can now do in one year.

So that's the good news.

Okay. So we validated these PAKs and now we have to start developing drugs. To target these PAKs.

Now, here's where it's going to get a little more technical. Because I want to walk you through the process it takes us to develop a drug.

So remember, Cristina took cells, either NF2 cells or normal cells, put them and screened 300,000 compounds and found some stuff, but she still doesn't know what's happening -- what -- she still doesn't know what chemicals are killing the cells, and she doesn't know how they function.

Another approach, which is just as valid, is to say I already know what I want to hit. I want to hit the PAK and now I'm going to go the other way. Find things that specifically target the PAK.

So we did this by many different approaches, but I'm going to tell you about the one which I think is the most successful.

And this is as story of a compound called FRAX597. It was developed by a small biotech in San Diego called Afraxis, interested in neuro degenerative diseases. At the time they weren't interested in NF2.

And we approached them and said, we know you have these inhibitors that you're developing, we think there's good reason to try these in NF2, because the target they're hitting, PAKs is relevant to NF2.

So they agreed to provide us some of their compounds.

And I guess the only one I'm permitted to talk about is 597.

And the first thing you do when you develop a compound like FRAX597 is you do biochemical studies. And you ask does it really hit a vulnerability. We think the vulnerability are PAK -- there are actually six different PAKs. 1, 2, and 3 are related. 4, 5 and 6 are related to another group.

And what see here is these graphs show you how the activity of the PAK is inhibited. As the concentration of the drug is increased. Basically as you increase more and more of the drug, you get more and more impairment of this protein function.

And that's shown here. And it works -- take my word for it -- it works pretty well for a PAK1, 2, and 3, it doesn't work at all for PAK 4. Which is a good thing because we're really interested in targeting PAK 1, 2, and 3.

But when you go to the FDA -- try to file an IND, which is an initial investigative drug trial, they want you to show what it does to other similar proteins in the cell.

And this is what actually is shown here. You know, it's a complicated graphical representation. But the point is that FRAX597 actually hit about 5 percent of all
similar proteins in our cells. That's a problem. Because when you go to the FDA, they say your drug is doing -- has so many side effects, you have to clean -- clean up your act or you're not proceeding.

So then to do that, we have to team up with structural biologists. And again there are many ways to do this. But what structural biologists do is they can take the protein -- in this case the PAK -- they can take the chemical, they can mix them together, and then create a crystal -- a solid crystal out of that combination.

And then -- and this can take several years to achieve this crystal structure. Then take it to an
x-ray source and you fire x-rays through this crystal and it gives you all these dots on a piece of film and a computer does all the calculations. And it comes up with a physical structure of the protein on the compound.

And that's what you see here. This over here is the physical structure of the PAK protein. And this little itty-bitty thing here, that's your drug. Okay?

And this is the little bit of a magnification.

So now we physically know how these things look like, and we can say, okay, are there changes we can make to this little chemical that would clean up its act?

Can we make a change that would now focus in on the PAKs and stay away from all these other guys that it's hitting?

And I am not going to go into the details -- but a simple change -- see this change over here -- this is a small change, it's an addition of a small chemicalgroup. That was enough to shift the -- called a specificity of this drug. And now it became really more specific towards the PAK. And made it ready for prime time, I guess. Okay? So -- okay. So now this -- all this takes three years, you have a compound and now you're actually ready to try it.

And you have to characterize several different properties of these drugs. So one thing we look for is something called EC 50. Effective concentrationat 50%. If I take this drug, remember those -- this -- this stuff -- this stuff is all done really in a test tube.

Doesn't tell you anything about how the drug is going to behave in a cell or in the human body.

So the first step is test it in a cell. And what we do is we take cells, and in this case we take NF2-null Schwann cells and start adding the drug and we start looking basically for this line to

disappear. This line is an indication of the activity of the enzyme -- PAK. And you can see there's a point here where the intensity of the band starts to diminish. And at that point it's between 100 and 200micomolar.

When the band disappears to about 50 percent of what it is up here, that's the EC 50. Effective concentration 50. That's a very important parameter for us so we know what kind of dose to give our mice before we do the experiment.

We also check this in cells. We take the same type of cells and we just check can they survive when we give them this drug over time?

So you can see that the cells are doing quite well at 24 hours. These are nontreated cells, and these are cells treated with the compound. And what you can see is it has a good effect. It doesn't totally kill these cells, but it has a good effect. And this effect is enough to justify testing in animals.

Now, testing in animals is yet another hurdle. Because first of all, animals are expensive, second of all, I have to go through dozens of review panels that make sure that I'm treating the animals ethically. Which is important. But you know, at the end of the day, this is for human patients, And we have to start characterizing how the drug behaves in an
organism.

There are very important things to keep in mind. Number one, bio availability. In many caseschemo is
given by IV. Drug companies don't like that. They want you to be able to pop a pill. It's much easier. It involves a lot -- a lot less than injecting it. So they want you to make sure that your drug is orally bioavailable. So you actually have to get the animals to ingest the drug and you have to assess the levels of drug in their blood system. You basically now give the animals a dose of
drug and you start following the levels of the drug in their bloodstream over time.

And you have to figure out how long that level is sustained. Right?

Because if you give an animal a drug and one hour later it's out of the system, that means you're going to have to dose every hour -- which isn't practical; right?

So FRAX 597 behaved nicely. Dropped to 50 percent of its concentrationabout every 20 hours. That means probably one dose every 12hours will give you a pretty good level of FRAX in your system. And finally and most importantly, no toxicity. You want to treat animals with a high level -- this is 100 milligrams per kilogram for an extended period of time and make sure they don't develop any symptoms that would be worse than actually having the disease.

So this is quite exciting because FRAX 597 showed a very nice pattern. It was 70 percent of it was bio available orally. It had a PKof about 20 hours. Which is excellent. And no toxicity over two-week period. This was very exciting. This all looks very promising. And the next thing we do is now we need to test it in an animal model.

And as Cristina alluded to, there are different ways to do this. Traditionally you take cells, put them under the skin of the mouse and give the mouse a drug andsee what happens.

To be honest, we've cured cancer in almost every single mouse model

of cancer.

Almost every single mouse model when you use that technique, gets cured by anything you inject into it.

But it never works in humans.

And that's because in our bodies, the tumors are not under -- some are -- but the vast majority of tumors are not right under the skin. In NF2 They're in a myelinating nerve. There's a big emphasis on getting the tumor model right.

What we do to try and get this right is we take NF2-null Schwann cell, we
expose the sciatic nerve, a myelinated peripheral nerve and inject the cells into the nerve, hopefully coming close to what the disease looks like in human patient.

So this is a trial design. We do the surgery when the mice are 10 weeks of age and we start following the tumor. It usually take the tumor five weeks to develop and we start treating it,, image the mice and enroll them in the study. Give them a drug for two weeks and at the end we terminate the experiment and collect the tumors from these animals.

And this is what it looks like. On the left-hand side you'll see mice with the tumor that are treated with control compound. Basically just vehicle, no compound.

And you can see that these animals have a strong signal which corresponds to a relatively large tumor, a large schwannoma in their sciatic nerve. In comparison animals that were treated with the compound FRAX 597, show little tumor, in most cases at two weeks, we couldn't detect the signal, in a few cases we detected a very small signal.

So then we enlist of help of bio statisticians, and they create the model. And think about this is how quickly the tumor is accelerating. You can see without treatment the tumor grows pretty quickly. But with treatment, the tumor slows down. It's not by all means eliminated. But it slowed down.

Another thing we can look at is simply we took the tumors out, we can weigh them.

So this is what it looks like in animals that were treated just with the control. You can see these are pretty big tumors, this is a tumor to body weight ratio. And treated mice, significantly reduced that.

So that's where this specific compound stands as far as what I can tell you. I'll tll you in a moment what's going to happen with it.

But the conclusions from everything I told you were that the PAKs are needed to promote tumor growth when NF2 is lost. We can develop the specific inhibitors through structure and form design, which is what I showed you. We're able to crystallize and get a physical structure of the protein we want to target and the projectile we're trying to hit it with.

So the PAKs represented target of opportunity in NF2-associated tumors. FRAX 597 is a novel small molecule competitive inhibitor of the PAKs. Low toxicity, inhibited for the proliferation of Schwann cells and displayed antitumor activity in an animal model.

Therefore FRAX 597 presents a promising lead compound towards development of group PAK inhibitors as therapeutic agents.

Now, why am I saying lead compound?

Why is this not the drug?

There still are some issues with this compound. First of all, I showed you it really slowed things down, it didn't totally prevent tumorgrowth. So maybe we can improve this drug to be more potent.

The other thing is even though we cleaned it up a little bit as far as hitting only the target we want to hit, there's still some dirtiness left in there. It's still hitting things it's not supposed to do.

So the end of the story is both good and bad.

I'll start -- and I think for patients it's actually good.

From my point of view, I can't work on this anymore because the companyAfraxis that developed that drug sold the rights to a company -- a huge company called Roche. One of the biggest drugcompanies in the world. And they're very interested in this and we are no longer part of the picture.

But that's fine, because you know, we have the thing -- what's the end point of this?

The end point of this is getting a drug to the NF community. It doesn't matter who does it as long as it gets done.

And I have a feeling -- and with the resources Roche has things should move faster now towards delivering a drug that will target the PAKs.

As I mentioned, Roche, don't necessarily care about NF2-- this thing might be useful in lung cancer and breast cancer That's why they're interested. That's a big market. They're going to develop this and eventually once it makes it out, your clinician -- once it's FDA approved, your clinician might be able to prescribe it off label and try it in NF2. Okay.

So I think that's the good news.

I just want to caution -- on a cautionary note here is that, you know, not all these drugs eventually make it to market. So what I told you is about 597. Roche are going to improve it. And it could be that it's just notworking.

So I don't -- I don't have insight into that. Of course I'm no longer part of this process. But you know, it's good to know that a big company is interested in the PAKs as a target and will develop a suitable drug at one point.

Yes? -

So let me tell you about the different projects we have ongoing, where we are with them and what limitations we have. And maybe where the NF community can help.

So as I mentioned, we will continue to develop additional inhibitors against the PAKs. We've done it before. We did it with a compound called FL172. The problem with that compound was that it had a heavy metal ion in it. And when we tried it in mice, it wasn't good news for the mice. And at that point we stopped. Because there's no point -- right.

But we're going to try different approaches to develop more PAK inhibitors. The other thing I can tell you is that I showed you that FRAX alone didn't have a dramatic effect. But actually another way that people are now improving upon effective drugs is by using combinations. Right?

So this started when people were realizing that they were giving drugs and the tumor shrunk but then eventually grew back. And it grew

back because the -- these devious cancer cells developed resistance.
So then people said, well, let's combine a few different classes of drugs together in a smart way, figuring out what we know about the disease and see if that has an improved effect.

So the good news is that at some point, even if FRAX is approved and it doesn't have -- the way I see it now, it will probably be a drug that can slow down tumor growth. But possibly combining it with other drugs that are already FDA approved would even give you a bigger effect.
So that's something we're actively pursuing. And the children's tumor foundation has been very helpful in promoting this.
I want to tell you a little about the identification of new targets. So I talked about the PAKs. But we're always interested -- we don't want to put our eggs in one basket. You want to identify good targets. And one -- there's several approaches you can take. I'm going to describe two. And the first approach is basically what's known about the genetics of NF2.
We know NF2 is the onegene that's mutated systematically. But we don't really know much about the other genetic events of NF2.
So what we decided to do is an approach called whole exome sequencing, because of a genome project, technology to genome sequencing has dropped dramatically. About $1,000 a genome. We can actually take patient samples and just sequence the whole genome and see if there are other mutations other than NF2. And that might give us a clue on what other targets to look at.
So -- and the best way to do this is to get patients to donate tumor material and their normal blood.
>> How do you do that?
>> DR. KISSIL: I'll get to that. That's really important. Because if I could get -- well, I have it now, but the idea is to get a tumor sample and a blood sample from the same person, get the DNA out of it, and then run it through these machines which do the whole exome sequencing. I had money for this project that was laying around for two years because I couldn't find the number of samples that I needed. And I needed 12 patients. That was all I needed. And I couldn't get in a material.
>> Wow.
>> DR. KISSIL: And the reason is, number one, I don't know how many of you are asked by your physician to donate this type of material.
I don't know. But -- but when I would talk to patient, they would say we were never asked. We would happily donate -- I have patients come over and say can I give you a sample?
I can't take it. It has to go through the clinician, there has to be something called an IRB process. But they were never asked.
So what I think you as patients can do is say to -- next time you're going in for -- for some kind of treatment where assume more will be biopsied, is to say, you know, could this material be preserved and is there a tissue bank here at the hospital and if not, is there any way to get it to a tissue bank?
And a tissue bank exists at Johns Hopkins, a tissue bank exists at Mass General Hospital. And if you want, you could e-mail me and I could put you in touch with such -- a tissue bank, CTF, the children's

tumor foundation is trying to organize this as a resource. I imagine there are more than 12 patients that would be willing to share their material, right?

So you know, people are just not asked, I guess, to donate this material.

So that's where you could be helpful.

The other thing is, once you donate it, to make a note, please share this with the scientists who are asking for it, because sometimes it doesn't get shared.

>> I guess would be like Schwann cells; right?

Seems like all your research is based on schwannomas and not meningiomas. You know, with what you did with this five bank set. You know, everything is focused on Schwann cells.

>> DR. KISSIL: So it already has been done with meningioma cells in another group. Garrett Evans in the U.K. has done this type of study with meningioma. So we're looking at a different aspect of it. He's looking at meningioma. We're looking at schwannoma. And of course what I'll tell you is that all these components that we're looking at, we're also testing them in meningioma cells. So we're not only limited to NF2. Everything we've done with FRAX, I just don't have time to show you all that data, all the combinations we're trying, we're trying in meningioma cells as well.

So we also thought of doing mesothelioma. That's a different type of cancer. We tried everything on both schwannoma and meningioma.

>> Now, since you mentioned the genome project, quite interesting because I just returned from NIH and I was waiting to -- get into to see my doctor. I picked up Medline plus and NIH publication and I was reading this article on the genome project. And it's talking about gene therapy. And it says they are doing some -- what seems to me very exciting research at NIH, researchers are testing several approaches to gene therapy including replacing a mutated gene that causes diseases with a healthy copy of the gene inactivating or knocking out a mutated gene that is functioning improperly. And finally, introducing a new gene into the body to help fight a disease.

Is that anything that you are aware of that's happening with NF2?

Because that made me think, wow, we have a genetic disease. And Merlin is not functioning properly.

>> DR. KISSIL: Yes. So we talked about this actually -- someone brought this up yesterday. And the concept of -- this is a bit of a sidebar. But the concept of gene therapy has been around for quite a while. The problem -- and originally this was tried with some leukemia patients. And unfortunately during the trials -- and this was when I was at the University of Pennsylvania -- patients died.

Patients died. And therefore there's a moratorium on those experiments. That doesn't mean they're not going to move forward at some point in the future. But right now it's -- they are just not allowed.

>> Okay.

>> DR. KISSIL: Okay?

But I can -- what I can tell you is that it took me two years to get 12 patient samples. And we eventually went -- were able to get all this done. And we now have normal peripheral blood from patients and

DNA from tumors. And we have the DNA sequences.

Now, the main challenge that's now left is for the computer programmers and bio informaticists to assemble all this data. The first was obtaining, the next is the computer scientists trying to figure out what's going on in there. Hopefully next time I'll be able to tell you, you know, we've identified something new.

Finally, I'll just touch on -- I saw Dr. Cristina Fernandez-Valle's slide. I said I'm going to show some of those slides too.

I said we are really interested in also unbiased approaches.

So similar to what Dr. Fernandez has shown, we take a cell which is mutated for NF2, and want to see whether we can find drugs that hit that cell indiscriminately.

Or not indiscriminately but without even knowing what it's hitting. And then we figure if we find something, we'll work our way backwards and identify what that something is.

So the way we do that is we have -- this is for us -- Cristina goes to Sanford Burnham. The Scripps I told you is based -- half our faculty are chemistry, half are biologists. We have our own -- we have our own screening lab. And don't tell Cristina I said this, ours is better.

(Laughter)

>> DR. KISSIL: But we have actually close to a million compounds in this library. And it's proprietary. Meaning that it's developed by chemists at Scripps. Some of these guys are Nobel prize winners in chemistry.

And what we're going to do is we use the plates that are 1536 wells, and
using this we can screen a million compounds in about eight days. So once the robots are working, they work for eight days straight. On what they're going to do is take these million different compounds and put them on the schwannoma cells and ask are these things killing the cells?

Now, once we find those, we'll take those compounds, we'll do some tests to make -- to confirm. We'll test them on meningioma cells to make sure they hit meningioma cells as well, we're hoping for a hit rate of half a percent. If we get 5,000 compounds out of this million, that would be pretty nice.

And then you have to bring it down to a handful which are manageable.

So here's the other area where you can help. Anyone have an idea how much it costs to screen one of these million compound things?

It's about 100,000$

So -- and I know you're doing this anyway, but you need to talk to your Congressmen and representatives. That's what's holding us back. I have a grant that's submitted to NIH that's supposed to be reviewed in two weeks and it's not going to get reviewed in two weeks because of the government shutdown.

So that's where the NF community -- and I know you're doing this, but you know, whenever you get a chance to talk to a politician, these are the kind of things we need help with. I can write the grants and apply for them. But if there's no one on the other side even receiving them, that's a problem.

So you know, hopefully if the government reopens sometime soon, this will be assessed. We'll be given a score. And we'll be able to move

forward with it.

So I want to get back to where we are.

We've made significant insights into the molecular mechanisms underlying the disease. We don't understand everything. Maybe we understand 5 percent. But that 5 percent is enough to identify new targets and to validate them.

And development of therapeutics existing targets is in early stages. There are already some drugs that have gone to trial. Avastin, there's aRAD-001 trial I think being initiated by House Ear Institute.

Hopefully in the near future there will be an FRAX trial.

But you know, I think we -- we've gotten to the point where we can actually have drugs where ten years ago we weren't even close. We didn't even know what to look at.

So I -- I think you should be optimistic.

I think, you know, it's not a long time -- it's not a long period before we have more drugs coming in to trial.

Now -- this is the view during sunrise. And it didn't come out.

But this is the group of dedicated individuals who are doing this work. We -- 80 hours a week, weekends. These are current members of my lab and former members of my lab.

A lot of the work I described here was done by Chunling Yi, a post doc in my lab; and now has her own lab at Georgetown, so there's another group that's dedicated to NF2 study.

Recent work regarding FRAX was done by Chun and Sylvia. And of course we have to work with collaborators, and it's fun to work with collaborators. And these individuals from all over the word, Mass General Hospital, Penn, Sweden, Philadelphia. Were instrumental in providing resources and expertise.

The work I described today was supported a little bit by children's tumor foundation. A lot by the American Cancer Society. They were the main sponsor of that work on FRAX. And a little bit by the government, NINDS.

So again, thank you for the invitation. And I'm happy to take any questions.

(Applause)

>> I'm going to ask you like some basic biology, because I'm interested in what scientists get from the mouse models. So if the mouse is injected -- a -- the model -- the NF minus mouse model, and it develops a schwannoma, do we know enough that the ws a mouse's -- you know, created schwannoma, will it present and manifest and grow -- is near enough information though that mimics human schwannoma growth?

>> DR. KISSIL: I think that's an excellent question. And the answer is we still don't know. You know, when Marco Govinani, created the mouse model, what he did was knocked out or impaired the NF2 gene specifically in schwann cells. And that mouse took a coupleyears to developthe disease. And it wasn't really all that close to the human disease.

Now, that's -- on the one hand, that might reflect the slow relatively slow progression of the human disease. But it's not amenable to testing drugs,especially when you're waiting for -- the cost of this is unbelievable.

So unfortunately that's not the best model.

There are other groups trying to generate models that would progress

faster.Our approach is to jump start the process. We take cells that already have lost NF2 and inject them back in. And that creates a model that we think represents -- still close to the human disease, and we can test drugs on.

Now, the only way to know if it will predict outcome is to actually have a drug that will be given to patients.

>> Yeah.

>> You could take a mouse and take out the NF2 gene, and one of these compounds that you put in has a lot of side effects or stops working, is this kind of analogous to like a liver transplant or something where you can put in something to stop the rejection?

>> DR. KISSIL: So, you know -- so I guess if I understand the question correctly, you have a scenario where you can take out the NF2 gene in a mouse and that gives you the disease. And then -- there are two options, one is you can try a drug and it works or not. But the other option is can you do something to repair whatever happened because you hit that NF2 gene.

And there is a possibility for that. There's a lot of work now being done on stem cells. And there is a hope that we would be able to isolate stem cells even from an adult. But maybe from an embryo and have those differentiate and turn into Schwann cells. Actually that can be done. But the question is can you now put these back into an individual with impaired Schwann cells, and will it repair the damage?

And that's just not known at this point.

I'm sure someone's going to try it. But at this stage it's just not known.

>> No one else -- about pain management and what do those do with learning disabilities and who do not get diagnosed at an early age and still have problem with comprehensions and basic things and motor skills.

What would they do to have holding a job because of motor skills and other nerve damage and the comprehensive problems. And recently learning of the illness and what it was. What should they do at this point? In the medications that they do give you for pain kind of makes it worse than what I'm taking the medications for.

>> DR. KISSIL: I think, you know, what -- what basically you're experiencing is symptom management. They're trying to control the pain, but it's not real addressing the core problem of the disease.

And I would argue that the main problem is the Schwann cells just growing out of control, impacting all these other structures that are causing the symptoms that -- that you're having.

And that by attacking the Schwann cells, hopefully will be able to address some of these issues.

But you know, it's -- it's the same -- it's the same story across the board. We just have to wait until these drugs are allowed to be -- come to FDA approval.

And then, you know -- you know, I'll give you an example. In NF1 -- NF1 is a little more advanced because the -- the molecular basis of the disease was discovered early on. Earlier than NF2.

So they're a little bit ahead. And there have been several trials with different drugs, including drugs that were proposed to impair some learning disabilities -- improve upon some learning disabilities that children with NF1 have. And those trials are still ongoing much and

that's probably going to eventually happen for NF2.
But I couldn't tell you when.
(Chuckling)
>> DR. KISSIL: You know, I'm sorry.
Well, thank you.
>> Thank you. Now I know...
(Applause)
>> I think we have kind of blown through our break. But that's okay.
Especially for those of you who are new to visiting us here at the symposium, if you guys are interested, we usually stay for the next half hour or so and just kind of talk amongst ourselves. About where we are as -- if you guys have questions. If those of us who have been around a little bit longer can answer them. If the speaker sticks around --
>> DR. KISSIL: I'm here.