ALEX KOLEVZON: Some disclosures. This is always important stuff. I do get a variety of sources of support. And Mount Sinai and Dr. Buxbaum have a shared patent with IGF-1 in Phelin-McDermid Syndrome. And I'll be talking about IGF-1 as a potential treatment of Phelin-McDermid Syndrome. And of course, it's not an FDA approved treatment.

So this slide, I've showed a lot. And actually, Catalina got a hold of it recently and thought it was terrible. So she completely redid it and really enhanced the resolution. So I hope you appreciate the upgrade from the last time I presented this. So this has been sort of our model in terms of treatment development. And this is not a novel model, right? This is something that cancer treatment has been following for a long time.

But for us, again, this kind of window into these single genes provides opportunities to, a, you know, discover an actual gene that we consider to be pathogenic, as Catalina explained. And then we can sort of replicate that biological defect in a model system using rats, or mice, or fish, or even human neurons. And you can do things with these kinds of models that you obviously can't do in humans. And I'll talk about some of those details.

But then it helps you really understand what's going on in terms of the brain. Where, actually, are the defects occurring? What's the problem in terms of nerve cell communication? And eventually, you can start thinking on that basis, what types of treatments are going to be relevant? What can we use that could potentially reverse the behavioral changes in kids? And then, of course, the next thing you do is you actually do a clinical trial in humans.

So I'm going to describe this pathway as it relates to Phelin-McDermid syndrome in particular, and also give you a little bit of a look forward toward some new data and some of the new syndromes that we're really very interested in as of late. And so Catalina described some of the new kind of way of looking at the genetic architecture of autism.

But this slide is really meant to describe how challenging it is, because as you see, you can take a single gene cause of autism, like the SHANK3 gene, but it's only really representative of about 1% of autism cases. So of course, that's where the communities come in, because we need to collect more and more and more samples-- as Joe mentioned, 29,000 samples, for example-- 50,000 samples. And eventually, it's going to start to help us explain, hopefully, what is the majority of autism?

And these are all examples of sort of commonly known-- Fragile X syndrome being one of them, Rett syndrome being another-- where there's a single gene mutation or a section of the chromosome that's actually deleted, losing that gene, where there's a very high proportion of those patients that have autism or a behavioral phenotype that looks like autism. But among the universe of people with autism, each one of those single genes really only represents a small minority of cases.

And the really important thing-- this is also something that Joe alluded to, and of course Catalina described-- the more and more cases of autism that we're starting to identify, the more and more genes we're starting to learn are actually pathogenic, they seem to be converging on several common pathways. And this gets into kind of a complex landscape.

But let's talk specifically about the synaptic genes, which is something that Catalina mentioned, also. So this is a neuronal synapse. This is what's called a presynaptic neuron-- postsynaptic neuron. And this space is where different neurochemicals travel. And this neurochemical in particular, glutamate, is absolutely critical for things like learning and memory. It's the primary excitatory neurotransmitter in the brain.

And so what happens with these chemicals is they cross through this synapse, and they bind to these postsynaptic receptors, all of which are anchored by really critical proteins. And when you disrupt the function of these proteins, you get a developmental disorder, and often you get an autism kind of behavioral picture.

And so this particular gene-- we'll talk about this-- SHANK3, anchors these proteins and serves to sort of-- when it's missing or insufficient in some way, it basically destabilizes this whole kind of scaffold. And so the ability of nerve cells to communicate with one another is fundamentally impaired. This is the MECP2 gene, one that causes Rett syndrome. This is the FMRP. This is the protein that causes Fragile X syndrome. Catalina mentioned Tuberous Sclerosis, P10.

These are all single gene causes of autism. And you can see how they all kind of converge on these critical synaptic pathways. And the important thing, from my perspective, is that these are all potentially, like, druggable targets. If you start to see an insufficiency, like a decreased protein synthesis or increased protein synthesis around the kind of final product of these pathways, you can start to think about, how do I regulate that system?

And so in a very kind of simplified model, if you disrupt the function of one of these scaffolding proteins, it can actually lead to excess protein synthesis, or too much excitation, which is, obviously, potentially, toxic, or too little protein synthesis, or too little excitation. So that's still learning memory is impaired. And it kind of falls along two sides of this curve.

And the way that you think about treatment, obviously, is that you'd want to use things like growth factors here, or you're want to use things that actually block the synthesis, or block excitation in other forms of autism. So it becomes very important to understand what's the underlying biology before you start thinking about treatments.

And this starts to give you some sense of why, when you apply a single treatment to a very heterogeneous group of people with autism, you see totally diverse outcomes, right? Some kids get better, some kids get worse. Some kids are exquisitely sensitive to side effects, some kids aren't.

And I love this slide, also. I think [INAUDIBLE] actually gets credit for this slide initially, right? You took it from us. I didn't create the slide. It used to have circles. Pilar-- where's Pilar? Pilar's all the way in the back. So Pilar turned it into people, which I think is so appropriate. Catalina's talking about genes. They're little circles. Now we're talking about people.

But again, this model is gone, right? The idea that autism is simply a collection of behavioral deficits is important to understand from a clinical assessment perspective. But from a treatment perspective, it really gets you tripped up, because here, now, we're talking about autism due to a specific gene-- so autism due to Fragile X syndrome, autism due to Rett syndrome, autism due to Tuberous Sclerosis, Phelin-McDermid syndrome.

And so that's how we want to start thinking about treatment, not from this kind of top down approach where we want to treat the anxiety, we want to treat the repetitive behaviors, and we just sort of lump all these kids into one big group, but actually more-- in a more refined way. So we want to treat these behavioral symptoms, but we want to treat it in a more homogeneous group as it relates to the underlying biology.

So this is our Phelin-McDermid syndrome story. We began-- actually, Joe began-- this is, what, 2008? 10 years ago or so-- with a little mouse, where he knocked out a copy of the SHANK3 gene. What happens when you have a child missing a copy of their SHANK3 gene is you get a very serious developmental disability syndrome.

So these kids have global developmental delays, intellectual disability. They've got absent or delayed speech. Almost all of them have low muscle tone. And many, many of them have these dysmorphic features that Catalina described. And just as an example, some of those dysmorphic features can include things like dolichocephaly, which is kind of an elongation of the head, or flaky toenails. And these are some of the key kids that we've seen over the years.

So we started a program-- and this is giving you a sense of some of what John alluded to-- to try to really characterize the behavioral features, or what we call the phenotype, right? We want to understand what really are the critical things about this syndrome-- what make it unique, what make it, you know, less specific. And what's the natural history of this syndrome in particular?

How do we expect it to develop over time? Because the trajectory of the disorder is really important for us in terms of trying to develop treatments. What are the ideal targets? What kinds of things just develop normally over time? What kinds of things are relatively stable? And what kind of symptoms are actually tractable from a treatment perspective? I'll talk a little about this today.

But we are also really interested in trying to do a better job, obviously, designing clinical trials. I think that in general, we can have the best medicine in the whole wide world, and we may have a lot of difficulty showing that it works in the context of the clinical trial. And that's because we're measuring behavioral features.

Behavioral features may not change in 12 weeks, right? Or six months, or whatever it might be. But if we had actually measures of the biological changes, something that we could really rely on, and something that was objective that didn't-- am I echoing? No. Just-- something that didn't rely on clinicians or, frankly, rely entirely on parents to tell us, oh, this child's really getting better, that would be very, very helpful for us.

And then finally, we want to develop treatments, right? And we started with IGF-1, which is sort of on the basis of some work that Joe had done with animal systems and [INAUDIBLE] at the time. And now we're kind of moving on to some other therapeutics, and I'll talk about that today, also.

So SHANK3-- you know, to me, you talk about genes, you talk about proteins, and it feels a little bit abstract. But actually, if you start to think specifically about the role of these proteins, I think it'll help you understand why, when these proteins are missing or deficient in some way, it really has a major impact.

So SHANK3 in particular-- we talked about this idea of a synaptic protein-- SHANK3 anchors particular receptors that act as transporters for glutamate. And then glutamate signaling, primary excitatory neurotransmitter in the brain. When it's disrupted in some way, you're just-- you're not learning. You're having trouble kind of holding on to information.

It also is really important for actually producing nerve cells and for contributing to nerve cell growth. And of course, this particular gene is potentially druggable. I hope I have a video that works-- or not. I can't even see-- oh, there it is. So you're actually going to see-- I think I've shown this before here.

You're going to see a fluoresced neuron that's in green. This is in a dish, where SHANK3 is sort of dropped into the dish that's kind of holding the neuron. You're going to actually watch-- or not-- how SHANK3 can produce neuronal growth. Or not. No media found. See, the Mac thing.

So if you could see the video, which is unfortunate-- but you've seen it before, because I know a lot of you are repeat customers here-- you'd see that the-- actually, in real time, I think the video occurred over about two hours-- you actually see the growth of the synapse, and it starts to make connection with new neurons, which is just kind of an amazing thing. And it highlights this idea that it's absolutely critical for neuronal growth.

So let's go back to our mice. I think, again, it's hard to understand why genes are so relevant to our kids and to treatments, specifically. It's even harder to understand why mice are relevant. But in this particular mouse, where, actually, one of the SHANK3 genes has been knocked out, it replicates the human condition.

So when you actually do things like look at the brain, or look at the memory center of the brain, which is the hippocampus, you can stimulate with, like, an electrode in one part of the hippocampus, in like a slice of it, and you can actually measure the strength of that signal downstream. This is a measure of what's called long-term potentiation, or nerve cell communication.

And what's happening right now as I'm speaking, you guys are getting information. You're creating, hopefully, new synapses. You're learning new stuff. You're pruning old synapses, because you're saying, oh, that's not relevant anymore. That's how we learn. That's how we form networks.

And so you can measure that in a mouse-- or, actually, in any brain tissue. This just happened to be a mouse. And what you see in SHANK3 is after the production of the initial kind of pulse of signal, there's a nice, healthy response downstream. But then that response very quickly sort of poops out. And that's not what you're supposed to see.

You're supposed to see conduction of signal, holding onto the strength of that signal. And this is what happens if you have two copies of your SHANK3 gene. This is what happens if you're missing one copy. And just sort of hold onto this curve. This is, again, called a long-term potentiation curve.

So then what do you want to do? Think about our model, where you kind of go from mouse to pathophysiology, which we understand, to now thinking about treatment. So what we want to do when we think about treatment, well, what could sort of create additional growth? What could promote synaptic integrity?

And one of the things that we thought might do it-- or what Joe thought might do it-- was something called insulin-like growth factor. So insulin-like growth factor, or IGF-1 is a-- we know that it crosses into the brain. We know that it promotes neuronal growth, neuronal maturation. And also, it has a role on synaptic genesis, or creating more synapses.

So it's produced in response to growth hormone secretion from the brain. It's produced by the liver. And we know it has a clear effect on muscles, bones, and of course, brain, OK? And so one of the rea-- there's a lot of different potential ways that IGF-1 works. One way to think about it-- and again, remember our synaptic model-- is that it stimulates two pathways, both of which lead to increased protein synthesis. So basically, you know, contributing to this idea of neuronal growth.

One pathway is called a PI3K/AKT/mTOR pathway, and the other one's called the MEK/ERK pathway. And just remember those, because I think as you start to hear about new treatments developing in the future, I think many of these things are going to basically be trying to upregulate or downregulate these pathways.

One of the other ways in which IGF-1 may be working is by inhibiting programmed cell death. So it's basically preventing the death of cells. And the third way, or fourth, even, is by having an effect on Synapsin 1, which we think probably regulates the release of glutamatergic signaling, or other nerve cell signaling. And of course, on PSD-95, which if you go back to the synaptic model, is another scaffolding protein that's really critical for anchoring these receptors.

OK. So this is your IGF-1, and we're going to be talking about this a couple of times. So what happens when you give IGF-1 to this poor little mouse that's missing its copy of the SHANK3 gene? You actually see a reversal of the long-term potentiation deficits. So the deficits in learning, memory that's reflected by this electrophysiological test are essentially reverse.

And so now, all of a sudden, the hippocampal slices are behaving like they have two copies of their SHANK3 gene. So it's essentially a reversal. So that gets you very excited. You should be excited. And it got me excited. It got Joe excited. So it made us think we should be really studying this in kids, and that's exactly what we did.

But before we did that, in addition to wanting to look at brain slices and how things behave with electrophysiological tasks, it's also really important to understand, how does the mouse behave? And is the mouse's behavior, or any model's behavior-- is it similar to the way that kids behave, right?

And so our kids have low muscle tone. They have lots of gait problems. They have motor skill deficits. And those are things that you can actually replicate in mouse models. And so what's important to figure out is not does this mouse have autism, or do they have a phenotype that's exactly like the kids, but are there features that we can learn from?

Can the mouse folks learn from us in terms of what kinds of studies they want to do in the mice? And can we learn from the mice folks in terms of what kinds of things we want to test or measure in the kids? And so one of the things that we've come across that's pretty important is motor skills. And so you can take this poor little mouse-- let's see if the video is working here-- and you can put them on a rotarod. Oh, it looks like it is working. And you just-- oh, nope. Not working.

So it was working this morning, by the way. Max, yeah. So if you could see this, this is what's called a rotarod. And this mouse is basically just, like, walking on it. And over time, mice fall off. Mice with missing copies of their SHANK3 gene fall off much more quickly. You give that mouse IGF-1, and they can hold on much longer. And that's essentially what this graph shows.

So it makes us sort of hopeful not only are there potentially disease-modifying effects as it relates electrophysiology, but there's also behavioral effects as it relates to the motor skills. Taking it even a step further, amazing technology has been developed-- this is not work from Sinai-- but amazing technology has been developed where you can actually take blood from kids. You can reprogram that blood into stem cells and then generate neurons from it.

So it's really-- instead of using a mouse as kind of a proxy, you're actually using neurons derived from affected children. So it's potentially a much kind of closer model. But then you can do the same types of electrophysiological experiments in the neurons in a dish, of course. So it may be behaving differently in a dish than it would in the brain. But nevertheless, missing copy of the SHANK3 gene, and induced pluripotent stem cell into a neuron.

And then you test IGF-1 on that neuron, and you're actually seeing the same rescue of those electrophysiological deficits. So just more evidence that something exciting is potentially going on here. So again, we go to our clinical trial in kids. We published this in 2014. That's kind of small. And one of the things that we measured, of course, was this idea of social withdrawal.

The hope was IGF-1 is providing something of a disease-modifying effect. We think it's really targeting the underlying biology. And as such, it should have an impact on a core symptom, which is, of course, social withdrawal, because these kids have autism. And the other kind of core domain in autism, as Catalina pointed out, is restricted and repetitive behaviors. And we also saw an impact on restricted behaviors.

This was an interesting study, because we were sort of challenged by the cost of the drug. So the way that we designed it was had what's called a crossover design. So kids had 12 weeks of drug or placebo, and then they crossed over into the opposite treatment arm. And so everybody had drug, and everybody had placebo, but in random order. And we didn't know which order they were in, and the families didn't know, either.

But that creates some potential problems, because, of course, if you get drug first, you don't know, is the effect of that drug going to potentially carry over into the next trial? This was a very small, very preliminary study. There were only nine kids in it. So the most important thing is to try to replicate it, obviously. We need to do a bigger study. This was really sort of our very first pass. But we were pretty excited about it.

And so this is the first time I think I'm presenting new data in this audience. Is Michael here? Where's Michael? Oh, Michael. There you are. OK. So Michael rescued me, actually. Talking about rescue of deficits. You're supposed to laugh at that. I have a statistical deficit. Michael rescued it.

And so one of the things that we were trying to figure out is, what's the impact of IGF-1 in this smaller study? What happens when we combine the data sets? And then what happens when we look at the new data set alone? Really trying to dig through this data to figure out, what's our IGF-1 program going to look like, and how are we best positioned to kind of carry things forward?

So the first thing that Michael did was help us figure out, is there a carryover effect? So between the first phase and the second phase, were there impacts of where you started the drug, whether the first or the second? And then he discovered, thankfully, that there were not.

The other really important thing is, did we do a good job in collecting data, right? We collected some of the data in 2010, 2012, other data in 2013, 2015. So you can see how there could potentially be biases. But actually, the data collection was quite standard, thankfully. And there weren't any significant differences between those two data sets.

And the next question-- the most important one, really-- is, over time, was there an effect of treatment? So between baseline and week 12, did the behavioral rating scores go down? Or, go up, depending on the measure? And so these are, again, new data. So this is our first set of nine patients that we already published where you see a nice kind of healthy improvement in what's called the lethargy subscale of the aberrant behavior checklist.

This is also called the social withdrawal subscale. It definitely taps into social symptoms. It's a pretty standardized measure that's used in autism and developmental disabilities. And this is also the pilot data we saw. Small changes in the restricted behavior scale. The new data set flattened out.

So this was actually very disappointing for us. What you see here is relatively the same magnitude of difference in the response on the social withdrawal scale. But all of the sudden, the placebo response got way elevated. And that's something we see a lot in clinical trials in psychiatry in general.

But thankfully, the trend, when you looked at either only the first phase of the study-- so basically using a very kind of conventional parallel group design, eliminating the second phase of the study and pretending that everybody only had 12 weeks of treatment so it was just sort of a standard, parallel group-- half got placebo, half got drug, 12 weeks-- that's this phase here.

That, to me, is probably the ideal clinical trial design, or combined phase. You still see nice trends here. And then with regard to restricted and repetitive behaviors, again, the trends persist throughout and actually do reach significance when you combine both phases. So we sort of replicated, didn't quite replicate. It was disappointing, but still enough to make us feel like this is worthwhile pursuing as it relates to these two different symptom domains.

More interesting, though, is that new things started to emerge with the data. As you got more and more patients involved, we started to see more significant trends in terms of other things like hyperactivity. And again, these are things that we also see, obviously, in the kids. It's not just these random rating scales.

But we see hyperactivity as a problem in a subset of kids, for sure. The first pilot data set, when I looked at it just in terms of, like, visually and raw numbers-- this seemed pretty meaningful to me. This is a big drop. Obviously, there wasn't much change on placebo. This didn't reach statistical significance. In the new data set, it still didn't.

But when we combined and looked only at the first phase of the data, then it kind of-- it reached the threshold of statistical significance. And this is a clear trend throughout. So obviously, hyperactivity is something we want to be paying attention to with respect to IGF-1 going forward.

The other thing we've been really curious about is this idea of a sensory domain and how important sensory symptoms are in autism, in particular, but also in Phelin-McDermid syndrome. In Phelin-McDermid syndrome, it seems as if these kids have kind of a unique sensory profile. In sensory reactivity in general, you can have increased reactivity. You can have decreased reactivity. You can have a lot of sensory seeking behavior.

In Phelin-McDermid syndrome, it seems that these kids are underresponsive, in essence. They have a very high prevalence of high pain thresholds. It can become quite dangerous, actually. If they get injured, for example, they can develop infections, because they're not eliciting any signs of pain or distress. It affects them in a lot of different ways.

So we were curious about, you know, what's going on sensory-wise. For me, clinically, as we were kind of bringing these kids in through the studies, that was kind of the theme that emerged pretty consistently from parents, where they would say, you know, it seems as if the threshold is changing.

This is a drug-- I should've mentioned this earlier-- that's given through inter-- intra-- it's a subcutaneous injection, so you're using a needle. Needles are painful. Interestingly, at the beginning of the trial, parents were very concerned about the needles, understandably. Kids, not so much. I mean, these kids, again, are very intellectually disabled, so it wasn't as if they understood cognitively.

But when you gave them injections, they didn't really respond much. And either they learned to kind of anticipate the injection and realize that this was not a fun thing, or, actually, their pain threshold was going up. Because it seemed to be, over time, many, many parents were describing that the kids were much more reactive to the injection.

Even in my office, it's evident when kids are sort of bouncing around-- because some of them are quite hyperactive-- they'll bump into things. They'll hit their head. They'll fall over, because they've got a lot of low muscle tone and sort of balance issues. And they initially weren't responding. And then eventually, over time, you started to see kids respond. That was something the parents were picking up. So we were really curious about it.

And so both with regard to underresponsiveness, we saw differences with respect to IGF-1. They were sort of less underresponsive. This scale goes in the opposite direction. And then also in terms of modulation or body movement in space, which-- and those two things obviously go hand in hand. It's important to know that these are, again, kind of small subscales within a much larger measure.

Again, this is very kind of preliminary data. But we're thinking not, oh, this is what it's all about, and here we've really fixed a major domain. We're thinking, how do we design trials in the future both in terms of looking at biomarkers and developing better clinical measures, about, what's this medicine going to do? And how is going to have an impact on kids and their functional abilities?

OK. So that's sort of new IGF-1 data. We have a lot more work to do about that particular study. We're kind of in the midst of trying to get the company to give us the drug for free, and then we can do a much larger study that's going to be a lot more meaningful.

In the meantime, we've talked about these single gene causes of autism. We've now talked about Phelin-McDermid syndrome. But Catalina and I both mentioned, now, the idea that many, many of the different genetic causes of autism seem to converge on common pathways.

And you can do these kind of fancy protein interaction studies where you look at the proteins encoded by literally dozens of autism genes, and you see that there's many, many interactions between them. And there could be specific critical hubs, things like Fragile X and SHANK3, that play a critical role.

And so for me, when I look at this-- and I barely understand this, and nor should you-- for me, what it says is, if we can develop a treatment for a single gene cause of autism, like Phelin-McDermid syndrome or Fragile X syndrome, it may have relevance to many different kinds of autism. And we may be able to predict this idea of personalized medicine. May be able to predict, in advance, based on the underlying biology, who might be potentially responsive to certain treatments.

And sort of toward that goal-- this is a different group, although it includes Kristen Brennand, who's at Mount Sinai-- this is actually post-mortem brain tissue of kids with autism. Is it post-mortem brain issue? Maybe it's IPSEs derived from kids with autism. It was only eight kids. These are IPSEs, sorry.

But what they did with these things called multielectrode arrays-- so it's kind of fancy technology that's meant to be a proxy for how neuronal networks form, and neuronal circuitry, right? And so what you see is that compared to controls, these neurons in autism actually have many fewer spikes, which is, again, this measure of, like, neurogenesis, nerve growth, and synaptic integrity.

And what's important here is you're giving these kids-- not with Phelin-McDermid syndrome, but with idiopathic autism, right? All they had was brain overgrowth. That was the sole criteria for selecting them-- brain overgrowth plus autism. But you're giving them IGF-1, and you're basically rescuing this phenotype. So you're seeing nerve growth, and you're seeing a major change as compared to controls.

And so why is that important? Because it sort of supports this idea that IGF-1 can be used for subtypes of autism. I mean, it may not be the specific subset of macrocephaly, the enlarged head, which is what was used here. But this is sort of a way to start thinking about, how do we parse the much broader universe of people with autism?

And for that reason and others, we started to think about using IGF-1 in idiopathic ASD. And this has been an ongoing project now for-- it's probably on here somewhere-- yeah, for a long time. It's slow going, because again, these are subcutaneous injections, and this has been challenging.

And we're partnering up with Autism Science Foundation, and we have some of our advisory board members that have contributed to this effort. Where is ASF? Is Alison here? Ah. Alison missed-- she's been to 20 of these. She's missed her first one. Anyway, so ASF has been very supportive of this effort. OK. So that's IGF-1.

Oxytocin-- people have been very interested in oxytocin. We've been very involved in driving the oxytocin effort. I have until 11:30? 11:30? We've been very involved in driving the oxytocin effort up to the point where about six years ago, we became part of a national network with the task of recruiting 300 kids with idiopathic autism and seeing whether intranasal oxytocin would have a benefit, specifically on social symptoms, right?

Oxytocin is a core sort of social hormone. It promotes trust. It promotes bonding, in addition to the peripheral symptoms of, like, milk let down and promoting lactation. But hopefully next year-- well, maybe not next year. But hopefully at some conference in the future, they'll invite me to come present about the results of the oxytocin study.

Hopefully, they're positive results, because we've just now finished data collection, essentially. And we're expecting results in the next few months. But this is going to be very exciting. But because it's a prosocial hormone, because of all the interest in autism broadly, Hala, who's here-- where's Hala? Hi, Hala. See, I put your picture up there.

So Hala and Joe, and others in the lab, they created a-- not a mouse with a missing copy of the SHANK3 gene, but a rat-- one rat missing one copy, and one rat missing both copies. And they did the same kind of experiments that you saw with the SHANK3 mouse where they looked at the electrophysiological responses, this long-term potentiation curve.

And what they found, again, is that there were clear deficits at baseline when you're missing either one copy or two copies. And then when you were giving oxytocin now, those deficits were reversed. So it's the same kind of model where you start to think, oh, this is something that we should start thinking about for humans.

But before she did that-- she's already kind of further along, right? We learned a lot from the IGF-1 studies so that we started thinking, OK. What kind of behavioral experiments can you do that mimic the phenotype in the kids? And so one of those is a social recognition task.

So you take a little mouse-- oh, sorry. This is a rat. They look like mice, though. Anyway, rat or-- anyway, this is a rat. And you put the rat with a new rat. And they hang out for a little bit. They get to know each other. And then you introduce another rat. And the idea is that these rats should preferably kind of hang out with the unfamiliar rats, because everybody had gotten to know the other rats. So they should go sort of shift over.

What happens when you're missing a copy of their SHANK3 gene is you're kind of indiscriminate. It doesn't matter if it's a new rat. Doesn't matter if it's an old rat. You just-- you don't really care much. I mean, you're hanging out with them, but there's no significant difference between the two. That's not what you see if you have two copies of your SHANK3 gene.

And the important point here is if you add oxytocin to these rats that are either missing one or two copies of their SHANK3 gene, you basically rescue this effect. And now they start to behave like you'd expect them to. And there's a preferential hanging out with-- what you call it? Not hanging out, obviously. What's the-- preferential-- socializing, that's a good word-- preferential socializing with the unfamiliar rat.

So in addition to social stuff, the other idea was to try to figure out whether these rats had attentional problems. We see attentional problems as really critical in the kids the Phelin-McDermid syndrome. And so the ways that you want to try to measure-- and sort of have your animal studies inform your clinical studies, and have your clinical studies inform your animal studies-- that's what's called translational science, right?

And so Hala performed this thing called the five choice serial task-- five choice serial reaction task? That's what it is? Yeah. If any of you have had children who have been assessed for ADHD, and you have a continuous performance test where you're kind of pressing buttons on prompts, that's essentially what this is.

So there's a little rat in the chamber. There's these five holes. The holes light up. The rat touches the light with their nose, and they get a reward. And what happens is you kind of increase the speed of that, which is a measure of their attention. And you also don't have a light at all, which is a measure of their inhibitory control, right?

So obviously, the rats with missing copy, or two missing copies, of their SHANK3 gene had real deficits in their attention. And then you give those rats oxytocin, you rescue those deficits. So now we've identified two critical domains that are consistent with the human phenotype, and we've rescued both of them with oxytocin.

So of course, what do you do next? Do a clinical trial with humans. So we've designed this clinical trial, which is now ongoing. I think we have about eight patients, or maybe nine patients enrolled. And here, because oxytocin is cheap, thankfully, and quite safe, we're able to do a pretty standard parallel group design-- placebo for 12 weeks, oxytocin for 12 weeks.

And everybody gets, in an open label fashion-- so I know they're on treatment. They know they're on treatment. And then we can kind of see how this drug behaves over time, measure the safety over the long term, and try to see whether or not there's improvements in different domains, including socialization.

And then importantly, this idea of objective measurement, right? How do you measure attention? It's very hard in kids that have virtually none of it. And how do you measure social preference in my office when these kids are really so intellectually disabled? So one of the ways to do that is using eye tracking paradigms.

So Pilar, I know is here in the back. Ting's here. Where's Ting? Ah, Ting's here, also in the back. You guys are hiding in the back. So Ting and Pilar have been working on different eye tracking paradigms where you essentially measure preferential looking into social versus non-social objects and the time with which you shift your gaze, for example, and engage or disengage with various stimuli.

And all those things are potential proxies for measuring attention and for measuring social preference. But the important thing is that they're objective, right? They're quantifiable. And you just have a child that's sitting there, and you're just measuring their eye gaze. So it doesn't require a lot of subjectivity, which, for us, is very important. This has been pretty challenging to do, but we're hoping it's going to produce something that's meaningful in terms of a clinical outcome measure in the context of trials.

OK. So that's sort of Phelin-McDermid syndrome, clinical trials. And I thought I would tell you just a little bit about new directions that we're excited about. And again, using this pathway to develop personalized medicine and hoping that single gene causes are informative for autism more broadly, we started to focus on another gene called FOXP1 syndrome-- FOXP1 gene.

It's a gene that encodes for a transcription factor that basically is critical for neuronal growth, neuronal differentiation, and also really important for language production and language comprehension. We know that kids with FOXP1 mutations and deletions have autism traits. We know they have intellectual disability. We know they have psychiatric features.

And so we've now developed a program very similar to what we've worked on with Phelin-McDermid syndrome where we intend to comprehensive [INAUDIBLE] the phenotype so we can understand exactly what we should be going after in terms of improvement. We want to, obviously, track the natural history, develop biomarkers, and then, of course, prepare for clinical trials.

So we just completed data collection on nine patients in collaboration with University of Washington. And it seems as if these kids may have something of a relatively unique phenotype, at least in some domains. But they do have motor and language delays. Interestingly, their expressive language is better developed than their receptive, which is not often what you see in autism or developmental disabilities.

They've got visual-motor integration deficits, like eye-hand coordination, a very wide range of intellectual deficits, all the way from profound intellectual disabilities, so nonverbal to even average IQs, but relatively evenly developed verbal and nonverbal. Again, somewhat unique within the kind of world of autism.

They certainly have autism symptoms, but many of these symptoms seem to be focusing around their repetitive behavior domain. So they may not be specific for autism, and many of them are not-- they're not really presenting with kind of core social cognitive deficits that you'd expect to see in autism. And many of the ones that we're seeing, at least, aren't really meaningful criteria for autism.

So this is something that's interesting for us to understand. Again, this idea that autism, as we're calling it, is somewhat of a arbitrary diagnosis, and you really want to be capturing what the symptoms are. They do certainly have a lot of anxiety, attention deficit hyperactivity symptoms. Obsessive compulsive symptoms are pretty prominent in this group. And some of them have been pretty aggressive.

And then just sort of looking through medical records, for example, and having these kids get brain scans, it seems that they do have some structural abnormalities on their MRIs. And because FOXP1 probably plays a role in immune regulation, they also have increased risk of different kinds of infections.

So another single gene cause of autism that we just started to be introduced to in the last six months or a year, which we think is a very important one, is something called activity-dependent neuroprotective protein. So this is a gene on chromosome 20. And it produces a neuroprotective factor that, again, is really important for brain development, brain growth. It's another one of these transcription factors.

And a particular snippet of it is going to end up being important, as I described it a little bit, because we know this particular snippet acts for kind of promoting neurite outgrowth, nerve outgrowth, and promoting synaptogenesis. And these kids, too, have intellectual disability, autism spectrum disorder, psychiatric features, language delays, and so on.

So there've been other studies. We have not been involved in these. We're just now starting to develop a program. But you see this is a series of about 10 patients. They all had developmental delay, for the most part. Most of them had-- they all had intellectual disability. Autism was highly prevalent. ADHD, low muscle tone.

These are all things you're starting to see is kind of common across these syndromes, right? They do have some relatively unique dysmorphic features, like this notched eyelid, prominent foreheads, and so on. So the most kind of interesting thing about this syndrome, and one of the reasons this came to our attention, is because there's already a potentially druggable target here.

And this particular protein called NAP, or neuroprotective activity protein? Neuroprotective-- yeah, that's what it's called-- you can actually do these kind of model system experiments. And you see that this particular protein plays a role in kind of stabilizing what's called microtubules, which form, like, some of the structure of the skeleton of cells, and are really important for cellular transport, cellular communication.

And they also serve to stabilize and protect these things called tau proteins. And if you don't have that kind of protection in place, you end up getting, like, excess tau protein aggregation, or what's called tangles. And that's this kind of world of what's called tauopathies. And tauopathies, we know, contribute to neurodegenerative diseases, contribute to dementia.

So the presence of all these sort of tau proteins are probably not a good thing. And what happens when you give these models, anyway, this particular NAP factor, is that you actually promote growth, and you stabilize this connection between the microtubules and the tau protein.

And so we think about that as a really kind of interesting potential target for these kids with ADMP deficiency, for obvious reasons. And it's already been a drug that's been used in some kids with-- or adults, rather-- with schizophrenia, and some cases of cognitive impairment and dementia, or neurodegenerative disorders. And there does seem to be some promise there.

So you know, we're a little bit ahead of ourselves with this particular syndrome, because we haven't even learned about it in such depth. But we're already starting to think about, how do we prepare various [INAUDIBLE] for trials, because here there is an actual drug that was developed by a company in Israel, and they want us to kind of get started already with it. So hopefully I'll be talking more about this in years to come.

OK. So that's good. I have 10 minutes left. So that's our sort of clinical trial development story. But you know, what I left out of the story is, how do we actually get from the drug to designing a trial where we can see some significant change? Because these are very, very challenging things to do. You don't do trials for a year. You don't necessarily know what to start with. You don't know what to target. So that's why this idea of biomarkers are so important to kind of bridge the gap.

And so Paige-- where's Paige? Paige is here, and Jen is here, I'm sure. I put your pictures up. These guys hate when I put pictures up, but I did it anyway. So Paige and Jen have been working on different kinds of electrophysiological measures in the kids, many of which mimic the kinds of measures that we can use in the animals. So again, that kind of cross translation is very important.

But in particular, we're really interested in trying to identify subtypes of developmental disorders based on these excitatory-- glutamate-- and inhibitory-- GABA-- profiles. We think this is going to do a lot to inform personalized treatments, help us monitor treatment response, and determine who's optimally responding, and also to identify associations between the electrophysiological responses and clinical outcomes.

So for example, if the extent of your excitatory activity actually correlates with the extent of your sensory reactivity, that would be something that's very interesting for us to know. And it may say to us, so this is a group of kids who have a certain response on a given EEG measure-- because this is all done using EEG-- who we think might improve clinically based on their sensory profiles.

And so Paige, in particular, has been working with things called visual evoked potentials. So these are all derived from the visual cortex where she shows them certain stimuli. And she measures a particular wave form that's elicited through the EEG. And this wave form is pretty standard across, hopefully, all of us.

And there's sort of-- this comes out kind of small, but there's sort of two major components to the wave. There's the difference between this first and second peak, which is called N75, which is a reflection of excitatory input. And then there's this second peak, which is called P100, which is a reflection of the kind of-- the inhibitory response, right?

So again, excitatory is glutamate. Inhibitory is GABA. And it shows you what a standard wave form should be, and it shows you how our systems should be in balance. And that's how we all kind of function, right? If there's an imbalance in the system, we're going to have learning, memory deficits. If there's an imbalance in the system, we might be prone to seizures.

And there's all kinds of problems that can occur. In Phelin-McDermid syndrome in particular, this first peak is almost absent, right? And if you think back to our synaptic model, the role of the SHANK3 protein, which is what's deficient in Phelin-McDermid syndrome-- the role of the SHANK3 protein is to stabilize these glutamatergic postsynaptic receptors.

So the absence of SHANK3 is basically showing that you don't produce the typical excitatory response. That's a big problem, right? But it's especially interesting when you look across kids who are typically developing, kids with idiopathic autism, and kids with Phelin-McDermid syndrome, you see a kind of a beautiful stepwise decrease in the extent of their excitatory input.

You can even parse kids with Phelin-McDermid syndrome according to whether they have very large deletions-- so many genes affected-- very small deletions, or point mutations, where only SHANK3 is affected. And you see, again, this kind of stepwise change. So this starts to make us think this could be kind of an interesting biomarker in Phelin-McDermid syndrome.

And so what do you do? You start to measure pre and post treatment, the change in these frequencies, right? And so using the visual evoked potential, you can measure different bands of the frequency response. And essentially, across every band-- and this is the frequency bands-- between baseline of the drug trial and week 12, you see bumps. You see changes, right? Increases.

This is a tiny, little study. Most of these are not significant. But it starts to show, wow, that these bands that are otherwise stable over time-- we know they're stable-- seem to be increasing in response to drug. And one band in particular, what's called a low gamma band, this has had a lot of interest in the community.

This might be a reflection of awareness, or conscious awareness, or even attention, perhaps. We saw a significant change in the low gamma frequency pre and post treatment with IGF-1 in the context of our Phelin-McDermid syndrome trial. And so Paige is now rolling this out across all of our trials, right? We want to see all these kids at every single time point and see what's happening with the VP wave form.

And then in another trial with idiopathic autism where kids are getting oxytocin-- this is a very small subset of kids. We knew they were all on oxytocin. Yeah, I think I-- I have enough time. We know they were all on oxytocin. So this is kids that are typically developing, kids with idiopathic autism, and the idiopathic autism plus oxytocin. And what's interesting to see here is the kids that have idiopathic autism-- this is the excitatory peak. Sorry, I should orient you. And this is the inhibitory peak.

Kids with idiopathic autism basically look like kids that are typically developing, if not even more robust of a response. They looked like kids with idiopathic autism when they're under influence of oxytocin treatment. Does that make sense? So without oxytocin, there's deficits, as you'd predict. With oxytocin, you rescue those deficits.

It's kind of exciting. It makes us think, wow, this could be an interesting biomarker. If you look at the entire universe of people with Phelin-McDermid syndrome, for example, and the universe of people with idiopathic autism, it seems as if there's a small subset, about 30%, of people with idiopathic autism that have VP profiles, or wave forms, that are similar to those with Phelin-McDermid syndrome.

And so what that means to us is that we're starting to be able to think about ways to select kids among the universe of-- see all this heterogeneity in idiopathic autism? Much less so here. How do you select from this universe of kids who might respond to certain treatments? And it may be that the VP is a marker to do that. It just gives you some sense of the clinical utility of biomarkers, right?

So finally, in sum, for us, the most important thing now is to really collect a lot of clinical information about these kids. We really need to develop specific measures to the syndrome and the phenotype, because you can't just think about autism as one group. It's really important to us to develop and validate biomarkers, because I think that's going to be the key to clinical trial success.

As I said, we could have the best medicine in the world. Unless we have the right measure and the right way to measure it, it's not going to make a difference. I think, you know, moving forward, we focus a lot on things like irritability, anxiety, aggression. Those are obviously very important domains.

We're also really interested in more functional outcomes-- motor skills, language, cognition, even. This, obviously, would be the kind of Holy Grail. You can't do that in 12 weeks, but nonetheless. I think it's going to be important, going forward, to use much younger kids in our trials.

Often, trials don't start until five. The brain is obviously much more plastic at earlier ages, and I think we have to start to consider having longer durations of treatment. It may be that the standard clinical trial phase with medicines that are not going to have whopping sedative effects, for example-- 12 weeks may not be enough to produce really meaningful changes in terms of behavior. That's it.

[APPLAUSE]