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Intro: You're listening to audio from one of our Third Thursdays Webinars on Parkinson's research. In these webinars, expert panelists and people with Parkinson's discuss aspects of the disease and the Foundation's work to speed medical breakthroughs. Learn more about the Third Thursdays Webinars at michaeljfox.org/webinars. Thanks for listening.

Brian Fiske, PhD: Hello and thank you everyone for joining us today. I am Brian Fiske. I'm Senior Vice President of Research Programs here at The Michael J. Fox Foundation for Parkinson's Research. I'm excited to be moderating our discussion today on a really hot topic about stem cell therapies for Parkinson's disease. It seems like every other meeting or webinar we host, questions about stem cells come up. They're always at the top of the list. And so today our goal and hope really, is to give you an a status update and really answer as many questions as we can.

All right, so let us get started. So what we are going to cover today really is try to have you walk away with three key messages here. So we're going to talk a little bit about, again, what are stem cells, for those of you who might be a little new to this topic. We're going to importantly, because I think this is why many of you are here, talk about stem cell therapies for Parkinson's disease, and what they are and what they're not.

And then we're also going to talk about another use of stem cells that's really important for Parkinson's as well, their use as a research tool. And so we'll talk a little bit more about that. And then of course at the end we'll have time for your questions. So fortunately for me and for all of you, I'm joined today really by two excellent panelists. Each are experts in their fields and they'll be helping me and helping us really understand the state of stem cell science and treatments for Parkinson's disease. So we'll start first with Dr. Claire Henchcliffe, who is a professor of neurology at Weill Cornell Medical College in New York. And her work focuses on developing and testing stem cell therapies. And so we're excited to have you here. Thanks for joining us, Claire.

Claire Henchcliffe, MD, DPhil: Thanks Brian. Thanks for inviting me. I'm really excited to be involved in this.

Brian: Great, great. We also have Dr. Julia Kaye who is a scientific program leader at the Center for Systems and Therapeutics at Gladstone Institutes in California. And Dr. Kaye uses stem cells to model brain diseases in the lab with a particular interest in exploring genetic contributors to Parkinson's disease. So thanks for calling from the West coast, Julia.

Julia Kaye, PhD: Very happy to be here. Thank you.

Brian: Great. All right, so we are going to get started. So our first question really, in concept we want to walk through what actually is a stem cell? Because it's really important for us to understand this when we think about therapies and how we use stem cells to research. So I'm going to start with you Claire, and I wonder if you could walk us briefly through this slide. Again, what are stem cells, what do they normally do and why are they so exciting for us?

Claire: Okay. Well this slide is a great summary of what a stem cell is. Actually, we talk about these as if they're new things, but these have really been discussed since the early 20th century, and the first time anyone spoke about stem cells was way back in 1908. That was Alexander Maksimov who had the idea that you could have these cells that would create different types of cells. And he was talking about the different types of cells in the blood. But basically a stem cell is, it's a single cell and it can either go on and make more of itself, so it can replicate itself pretty well indefinitely, or it can follow a different pathway. So stem cells are what we call undifferentiated. They don't have the differentiated characteristics that we're used to seeing in cells like skin cells or blood cells.

And those are characteristics that make them different from the other cells. So they contribute to their own specific properties that we need. So what this undifferentiated stem cell can do is to turn into these different specific cells. And in the body, we've got stem cells. I mean, we all develop from the zygote, which is the ultimate stem cell that turns into the embryos. So we all develop from these cells, but we have these in our bodies as well. And what these cells can do is differentiate into many different cell types that you can see here are examples of nerve cells or blood cells or pancreas cells or skin cells. So as we have the wear and tear of everyday life and day to day living, we have to renew our tissues. And two examples would be in the gut or in the bone marrow, for example, where you've got to make more blood cells.

And these are what the stem cells will do in our daily life. And we do have them in the brain as well. So they're present throughout the body. And I think what makes this so exciting is that in a disorder like Parkinson's disease, we appreciate the possibility that we can derive specific differentiated cells from stem cells that might be able to replenish, repair, help regenerate some of the cells or some of the processes that have been lost in Parkinson's disease. So I think that's what makes stem cells so exciting when we're thinking about developing new treatments for Parkinson's.

Brian: Great. Thanks. Thanks for walking us through that. So yeah, so just maybe to carry on that theme, then when we think about different types of stem cells that are relevant to thinking about for Parkinson's, we often talk the different kinds of stem cells and the different sources of those. Now I wonder if, Claire, if you could continue the conversation. Talk about a couple of different approaches here and I've put them up here on the slide. What are these different types of stem cells and how do we isolate them?

Claire: Yeah, sure. So really, you can divide stem cells, although there are many, many, many different types, but you can divide them into two broad categories. And one is the embryonic stem cells and the others, which are very exciting, are the adult stem cells that we called somatic.

So let me just say a couple of words about the embryonic stem cells. I mentioned a minute ago that the embryo, once you have a human egg fertilized by a sperm and it makes a cell called a zygote. So that turns into the embryo. It'll divide into two cells and four cells and eight cells and so on. So these are really the ultimate stem cells, if you think about it. We all develop from embryos, so everything, every tissue in our body, every cell in our tissues has to derive ultimately from these embryonic stem cells. And so these are cells in practice that can be isolated if we have eggs that are fertilized that outside of a woman's body. So in in vitro fertilization procedures, these can be donated for research with the appropriate consent and screening and so on. And these embryos can be used to derive embryonic stem cells. So, like I mentioned before, these cells have the capacity to become any cell type in the body. And basically when you get the embryo where you're going to derive the embryonic stem cells, you can divide that at four or five days.

You can think about it in two parts. And one part is what you call the outer cell mass, and that's going to go on and make the placenta. But the embryonic stem cells actually come from this tiny bundle of cells, which are undifferentiated, and that's called the inner cell mass. And that's going to be responsible for generating any particular cell that you could think of in the human body. So this is the embryonic stem cells.

And then what's really made advances in leaps and bounds over the past few years is the technology to use and investigate the adult stem cells. So I mentioned before that wear and tear in everyday life means that you've got to be able to regenerate some cells. So that's how, for example, if you have a cut in your skin, you would heal that wound. This is because your adult stem cells get activated.

So these cells, you find them among specialized cells in different body tissues and organs. So they're in the skin, they're in the blood, they're in the liver, really throughout the body. Now these are typically more restricted than the embryonic stem cells. So for example, the stem cells that are sitting in your skin, they're not going to be able to create brain cells sitting in your skin. So these really can differentiate only into cell types that are appropriate to their location. So a stem cell sitting in your skin is going to develop into different skin cells and cells that are found in the skin. So they really will turn into cell types of the tissue or organ where they're found.

Brian: Great. Thanks. So you alluded to this and I'll switch to the next slide here and maybe actually ask Julia to walk us through this. But this idea, this kind of exciting technology where, the first two cell type you mentioned obviously were things that we can isolate from the body, but we've also come up with ways to

create stem cells basically in the laboratory. And so Julia, could you walk us through this? What are these types of cells?

Julia: Sure. Yeah. So a little over 10 years ago, a couple of investigators, James Thomson and Shinya Yamanaka, they basically were really interested in finding sets of genes that can essentially turn differentiated cells, the cell that's very specialized, like a skin cell or a heart cell if they, that they're interested in finding a way to basically revert that cell back into a so-called embryonic stem cell-like state. And so what they did is they screened through lots of genes. So it turns out the genes, so the genes that comprise our makeup, and different genes are expressed in different cell types. And so the panel of genes that's expressed for example in the heart is really different than the panel of genes that are expressed in the brain. And so there's also a whole other set of genes that's expressed that basically tells those cells to not become specialized.

And so what they did is they found those genes and they now really developed this amazing technology, which I think is really revolutionized the way we can go about studying disease. Because what we can do is we can take fully differentiated cells and introduce these, we call them so-called reprogramming factors or they're genes, essentially. And what these genes do is they go into the cell and they say, okay, all of the specialized gene expression, it needs to be basically turned down, and then we're going to turn up the gene expression, for the genes that are important for pluripotency or important for cell division and basically all the characteristics that Claire described that make a so-called embryonic stem cell that can become any cell in the body.

Brian: That's great.

Julia: So then what we can do is we can introduce these factors and we wait some time and then we make this really amazing renewable source of cells. These are called induced pluripotent stem cells, and these can be grown and propagated pretty much indefinitely in the lab. But what's really exciting about this is that then we can take the cells and we can add certain factors which really push them or start to make them into specific cell types. And so we can make them into blood or brain cells. And so for Parkinson's disease, this is what's really exciting because we can make the specific cell type that's most affected in PD, and then we can study them in a lab.

Brian: Great. Great. And I know we'll talk a little bit more about that and some of the work that you do in that space later on in the webinar today. But yeah, really a powerful new technique, and I think one that's really revolutionized the... not just in Parkinson's but I think our understanding of a lot of different diseases.

All right. So moving on. So we talked a little bit about what stem cells are and some of the different types of stem cells, but how are we actually using these? And again, this will be what we'll spend the rest of the webinar really talking about. And you know, when we think about the different types of stem cells, scientists can use them really for a variety of things. We're going to talk a lot

about, here in a moment, about obviously the ways we could use them for treatments. And when we think about the uses of stem cells, we often think about stem cells really as either sources for making new or replacement cells and tissues, but also stem cells spit out a lot of different factors.

And so some people have been using actually the concept of stem cells as ways to almost provide supportive factors for other cells in the body and other injured cells. So we're not going to spend a lot of time talking about that particular concept because I think that the field there is a little more difficult to talk about. But I did want to at least mention that there are some efforts and approaches looking at ways of using stem cells almost as vehicles for protective factors that could help other cells.

But again that at the end we'll talk a lot about, and Julia will walk us through this, about some of the ways we use again, stem cells for research purposes. For understanding Parkinson's and trying to find new treatments through our understanding.

All right, so moving on. We're going to start with therapies and I know that's really why a lot of people are on the call today. So we're going to spend a few minutes really talking through this and I'm going to ask Claire to help me here obviously and really just think about, what are some of the basic concepts here, Claire, about how we can think about using stem cells for therapies for Parkinson's? And probably touch a little bit on, what do we think they can help with, but also what do we think they probably are not going to be able to help with in the context of Parkinson's disease. So could you walk us through this?

Claire: Yeah, absolutely. Thanks Brian. And thanks for that great introduction. You brought up a lot of important points there. So I think like Brian was saying, that the major thrust so far of stem cell-based therapies in Parkinson's disease is really to look at replacing the dopamine cells that are lost. And there's a great history of trying to do this. We're not the first teams, the first scientists, the first researchers who are trying to take this approach. So if you think about it, back in the 1980s researchers were looking for sources of cells that might be appropriate for transplant into the brain where they could replenish the dopamine inputs that Parkinson's has taken away. And people had looked at cells from the adrenal gland, for example, or cells from what's called the carotid body. But I think the richest history has been looking at taking human embryonic cells and there's been some encouragement from that field.

But what we have the possibility to do now, as Julia was just explaining, you can take stem cells, either human embryonic stem cells, or you can take the iPS, the induced pluripotent cells, and start to develop cells. You can coax them along this pathway to become dopamine cells or junior versions, adolescent versions, if you like, of dopamine cells. And unlike any of the cell sources that we've had available in the past, when you develop these cells from stem cells, you've really got yourself a source that is very reliable. You can monitor the purity, you can make sure that these cells function well when you're doing the preclinical

testing. You can make sure that they're making dopamine. You can characterize them in any which way that you care to do so.

So one thing I want to say just before I go through the rest of the slide is that when we're talking about stem cell derived therapies, I just want to make sure that people understand, we're not talking about transplanting the stem cells themselves, because like you said before, these stem cells can make any type of cells, so you don't want to put stem cells in that could make hair or skin or liver or, or potentially tumors. That's the really scary one.

So actually what people are looking at is producing dopamine cells from these embryonic stem cells or the iPS cells and using those to implant into the brain. And the concept is pretty straightforward. You've lost dopamine implants into a part of the brain called the putamen, which is deep down on each side, within each hemisphere. And when you don't have sufficient dopamine inputs there that really can wreak havoc with movement and controlling coordination. And so the idea is very basic that implanting these replacements, if you like, dopamine cells or dopamine cell precursors, the juvenile forms, would be a substitute for the cell inputs that are lost. So as Brian said, that's the rationale is that most people are following. And so this is really what I'm going to talk about and more global approaches that we look at other parts of the brain I'm not going to talk so much about.

So if you think about it, if what you're doing is to replace dopamine inputs, it follows from there what, what would you expect this to help with? So for those of you who are familiar with taking Levodopa or taking dopamine agonists or any of the other Parkinson's medicines to help the symptoms of movement, these are the sorts of things that we're looking for these cells to help with. So we'd be looking at, for example, muscle stiffness and slowing and coordination. We'd be looking for the cells to help all of those things. And the tremor. So basically if you boil it down, it's probably not quite this simple, but if you think about it, anything that Levodopa could do, anything that the dopamine agonists are doing, then you could expect these cells to do.

Now that's great. And I think that would be a huge, a huge advance. And this would be conceptualized as a single time surgery. And if you could get over the movement problems with that, it would be amazing. But let me just come back to what Brian mentioned as well. It doesn't take care of everything. These cells as we see them right now are not going to be a magic bullet. The Parkinson's is still going to progress. And I think, as everyone knows, it's not just the dopamine cells that are affected in Parkinson's. So we've got serotonin cells, we've got cells producing acetylcholine. So you've got all of these other symptoms that may not be helped by this approach of replacing the dopamine cells. So for example, if you think about memory problems, thought processing problems, problems with executive function, multitasking, maybe things like that, we might not expect this sort of approach to work with. But still, I think that as researchers and as clinicians, we still think that if we could alleviate the burden on people with Parkinson's with the motor, then we

Claire: may be able to really help people's quality of life. There is a richness of this type of approach from using embryonic cells from humans before. It's true that the studies have shown inconclusive results overall, but I would say that some of the patients who've participated got some benefits. Some did not get benefit. We know that the cells survived because scans, for example, PET scans like fluorodopa PET scans could show that the cells survive.

Then the question is, can the stem cell therapies that have what we think is a superior type of cell to work with to the old cell types, could these really advance and give us better results than what's been seen before and overcome some of the variability. We do think that we've got better cell products to work with. The past studies have helped us to solve how to get the cells where we want them to be, and we think that we also understand a lot better about what to test for and what should improve and what are some of the strategies for following patients in the clinical trials.

I think this, there's a rich history here but we've got with new advances in stem cells, we have much superior types of cell products to work with than we've ever had before. I think that's the reason for the excitement.

Brian: Great. Why don't we move on actually. What does the current therapeutic pipeline actually look like for Parkinson's and stem cell-based therapies, and moving to this slide here. We try to put down some of the current trials that are at least publicly out there, and when we look at the clinical trial databases and the different approaches that are currently being tested in the clinic in Parkinson's disease. I was going to have you, Claire, maybe just walk us through the different approaches that are currently being used, and maybe just talk a little bit generally about what you think the pipeline looks like, maybe even some of the types of approaches you think are getting close to the clinic.

Claire: This is a really great slide. I think that rather than attempt to list every single clinical trial that's out there and every single clinical trial that's upcoming, there are four clinical trials here that really illustrate very nicely the diversity of the types of cells that are being investigated for this sort of approach. What these four clinical trials have in common is that everyone is trying to use the stem cells as a source of producing dopamine progenitors, dopamine cells that can then be transplanted into the brain, or the stem cells themselves are already on the pathway where they can produce these dopamine cells.

All of these trials are aiming to replenish, replace the dopamine inputs that have been lost. None of them are really looking outside of that. Just very briefly to walk you through the ISCO, ISCO, the International Stem Cell Corporation are running a trial with a sort of cell that is called parthenogenetic. We didn't talk about this before, but what they've done is developed cells from unfertilized eggs by manipulating them. These are a little bit different to some of the other stem cells that are out there.

Celavie Biosciences are taking a different approach, and they're using human neural progenitive cells, so these are progenitives that have been extracted. These are embryonic, human embryonic in origin. One of the studies that I think everyone's eyes are on right now is the TransEURO study. This is led by Roger Barker in Europe.

I mentioned already that there's a very rich history of looking at whether embryonic tissue as a source could help people with Parkinson's if transplanted. The whole idea is that the tiny little fragments of tissue, or these cells that are transplanted contain dopamine neuron progenitors, so they contain the precursors. What the TransEURO study is doing is basically learning from what's been done in the past. They've optimized their clinical trial design very nicely. They are repeating the studies but in an optimized clinical trial design using human embryonic tissue.

We're waiting on the results from that. They won't be out until 2021. Although there was just a paper published with a sort of update on the clinical trial design and what the rest of us are able to take away from that.

Then another study which I think is just incredibly exciting and incredibly innovative, and this is really bouncing off the technological platform that Julia was talking about a few minutes ago and using iPS cells. These are induced pluripotent cells. They've been derived from adult cells and, just like Julia explained, they've been manipulated to become pluripotent stem cells and then coaxed in the laboratory to become dopamine progenitors. I think everyone is watching this.

There was a press release in late last year. We know that one patient has had unilateral transplantation of these cells, and so far so good. Not hearing about any complications. We don't have the results that would help us understand whether this is working. The other thing that I wanted to mention is when we're looking at the timeline for this sort of trial and the ones that are coming up, I think in the short term people are very interested obviously to make sure that these are safe and that they're tolerable, that people are not getting too many side effects from these cell transplantations.

Some of them, bear in mind, a lot of these clinical trials are also giving immunosuppressive agents, so medications to prevent any kind of reaction against the cell. The first thing with these studies is really to make sure that they're safe, that they're tolerable. The next thing is when are we going to start to see whether there's actually some beneficial effects?

We know from previous studies with the embryonic stem cells that have been done that sometimes you don't see these effects straight away. Probably the cells need to mature and they need to make the right connections. Then the host cells are going to make connections on to them. We may not expect to see effects straight away. It could take a year or two years or three years or a little

longer. It requires some patience to see exactly what these cells can do, and, of course, it's going to be important to see the long-term follow-up.

Those are four great examples with four very different tissue or cell sources. Then I just wanted to mention that one example that's not in here because these are not ongoing yet is going back to you remember we talked about the human embryonic stem cells right at the beginning. Those are cells, they come out of that inner cell mass in the very early embryo called the blastocyst stage. There are multiple groups now who have managed to, again, coax those embryonic stem cells to become juvenile versions or progenitor versions of the dopamine cells that are lost in Parkinson's.

Our group is one of the groups who are taking this approach and there are other groups across the U.S. and across the world, including in Europe and including Roger Barker's group. He was the one I mentioned with TransEURO. I think we're going to be seeing several clinical trials starting up within the next couple of years. It's an incredibly exciting time. It's also good to see that people are using different types of stem cells, because although we obviously all think that we're taking the best approach no one group knows that their particular cells are going to be the best.

I think to have this multiplicity of approaches at this point seems very appropriate and good for the field.

Brian: Great. Thank you for walking us through that. Obviously one aspect of stem cell treatments, I think, is, and it's sort of the almost unique a little bit to this type of therapy is some of the challenges, I think, for the community to understand what are real treatments versus what are maybe treatments that are being offered directly to the patient community that may not be necessarily as regulated or definitely much more exploratory and unproven. I think this has become a growing issue in the last few years. Even the FDA has now had to step in more specifically.

There's an example here on this slide of a recent statement they had to actually put a permanent injunction on a group that was delivering these types of therapies. Claire, again, could you walk us through what are some of the concerns here? Maybe you could even talk a little bit about your own experience just with the patients that you see who maybe are looking into this type of approach. Why do we need to be worried and concerned about some of these approaches that are being offered?

Claire: Thanks Brian. This is a really tough area actually. I think what we've talked about so far are the really scientifically sound projects that are going on, that are just backed up by years and years and in some cases decades of pre-clinical work and very extremely careful and extremely slow work on trying to get the right cells and figuring out who are going to be the people who can benefit, and exactly what can these cells do. Like you brought up before, it's important to think about what they can't do.

We've got that on the one extreme, and then, if you like, on the other extreme we've got clinics who offer what they're calling stem cells treatments. These may be the adult stem cells that are sitting there in people's belly fat, or they're present in the blood. It's correct that there are stem cells within those tissues, but I think that some clinics are offering what they're marketing as treatments to patients really without having had any careful characterization of what those cells are doing.

When you see a clinic and everything that they're saying that's good is based on patient testimonials, and you really can't figure out what the details are, I think that's fairly clear on the other end that that may be a place where you don't want to get involved. Then I think there's a whole gray area in the middle. We said for this webinar we were going to focus on the human embryonic stem cells and the iPS cells, but, of course, there's this area of what they call mesenchymal stem cells, and these are adult stem cells. You can get them out of the blood, for example.

There are actually some very well-respected groups who have started to look at whether these can be used for Parkinson's or sometimes Parkinson's-plus for example. They're starting to understand a little bit how these cells might work. For cells like that, I would say that it really becomes an area where you want to get educated and find out what these people are doing. Because there's some very highly respected groups who are studying those cells, trying to figure out how they work. They're publishing their results.

For example, a group who published use of mesenchymal stem cells in multiple system atrophy earlier this year, and they went really into the details of what were some of the complications and what they thought might be some benefits. Then there are other groups where, again, they're using these types of cells that may have some science behind them but the way that they're being used is promoting hopes for probably what are unreasonable outcomes.

I would say in my experience I really encourage my patients if they're looking at therapeutics that are a little bit outside the box, it could be this, it could be any one of a number of other therapeutics, I really encourage them to come and talk to me about it. Sometimes it really means that I have to do a little bit of extra legwork and go look up references. Even sometimes talk to the people who are involved and try to see what they're doing.

This is a tough one. I would say for anyone who has Parkinson's who's thinking about this kind of thing, make sure you understand what's going on. Get as much information as you can. Get educated and discuss it with your doc.

Brian: Right. My understanding here too is they're real concerns. It could either be side effects, unexpected side effects of these types of approaches, but also there have actually been people who have been harmed and injured with, again, some of these unproven approaches.

Claire: That's exactly right. Actually, just yesterday I was looking at a paper that was published in the *New England Journal*. This was a mass that someone unfortunately developed in their spinal cord. This poor patient was a victim of this stem cell tourism. This can be serious stuff. These complications can include tumors, can involve damage and harm so these are not benign procedures.

Brian: I'm going to move us along, and we're going to switch gears here now and actually talk about a different way of using stem cells that I think is also critically important. Julia, I know this is the area that you work in. You told us before about some of the new technologies for making stem cells. Talk a little bit more in detail about that. How are you actually using these to understand Parkinson's disease?

Julia: The idea here is that we can take these cells from patients, and we make them into induced pluripotent stem cells. Then we can, as I said before, we can add specific factors that make them in to the specific cell type that's most effective in the disease. In the case of Parkinson's disease where people are really interested in making dopaminergic neurons, and so actually here, this is an image of cells that have been differentiated into cells that express some of the genes that we think are expressed by dopaminergic neurons in the brain.

The idea and what's really exciting is that we can essentially develop a platform. It's really a research-based platform where we can go in the laboratory and then ask questions about, for example, if there's different genes that may change the fate of these cells. These cells, again, they come directly from the patient. We can develop them into the specific cell type that's most effective in Parkinson's disease. Then we can either add small molecules, or we can change gene expression.

We can assay different methods really to see if we can change the fate of these cells, if we can make them healthier, for example, or if some of the pathologies that we observe in these cells can be restored by various treatments.

Brian: Great. I want to then now move on to, I think, what everybody's probably excited to be able to do is start hearing questions and answering them from our attendees. As we've been talking, we've been getting a lot of interesting questions come through the chat group. I want to try to start with a few that have popped up, and we'll touch on some of the themes that we've been talking about. Some of these come back to, again, the idea of the stem cells as treatments.

We had a lot of questions as we were going through that, that section, about, again, kind of back to this idea of who might be most appropriate for stem cell approaches. Are there any considerations? We had a few people ask if you've had DBS surgery does that mean you can't be a candidate for a stem cell approach in the future. Claire, I wonder if you could maybe talk a little bit more about some of that, again, and really in the context of who would be most appropriate for a stem cell type treatment.

Claire: Yeah. We've been talking a lot about that in our group and I know with other groups as well. Because as we're designing these first clinical trials, you have to think about, well, who stands to benefit? It really goes back to what we were talking about a bit before, what can these cells do? I said maybe a little simplistically, "Well, these cells can do what levodopa can do."

I think if you think about having the cells sitting in putamen and delivering dopamine in a fairly natural, fairly physiologic way, not completely but fairly, then it really means that, for example, people who respond to levodopa but the levodopa wears off. People with what we call the mode of fluctuations where the carbidopa/levodopa may cut out on them, they get wearing off, the Parkinson's symptoms come back. You would think that that would be a really great place where the cells could be helpful.

Because the cells are sitting there and they're just delivering the dopamine. It's not coming and going. It's really should be a good nice steady delivery. When we were thinking about it, we thought, "It's people who respond to levodopa, so we know they're responsive to dopamine itself coming from the levodopa." But where the oral delivery of levodopa just isn't holding them. We think to begin with that's a good place to start, in people who are a little bit further along with the Parkinson's, not early where they're doing very well with the medicines.

Who knows, we may be having this discussion in 10 years' time and we'll be saying, "Well, how early should we go in Parkinson's?" Because if you think theoretically about it, if this does turn out to be an efficacious, safe and tolerable treatment then why wouldn't you just start this early? Particularly where you've got younger people who we know that they're going to be more vulnerable to the complications of levodopa down the line with wearing off and with dyskinesia, why wouldn't we be thinking about them?

As things stand right now, I think that aside from the levodopa response, which we're all thinking is going to be a good predictor of who may benefit from the cells, but we have to think about people's age, for example. I mentioned before that the vast majority of the studies, to begin with, are going to be given immunosuppressive drugs. We know that older people, unfortunately, get more side effects from that. We have to think about having an age cutoff. The stage of Parkinson's, I mentioned, we think that people could benefit where they're in the stage of Parkinson's where they may be fluctuating, but if someone has had Parkinson's for many, many years and then is starting to have problems that we don't think the cells are going to be helpful for like, unfortunately, dementia for example. Or if someone's having terrible problems with their blood pressure and fainting all the time. Anything that's not coming from the dopamine part of Parkinson's, then maybe we have to think about that.

Unfortunately, people who have dementia from their Parkinson's probably shouldn't get this. Then we have to think about the level of general health. I think in these first studies, again, we're in a situation where we're primarily going to be looking for safety and tolerability. We're looking to follow people for

the long run and we're looking to give at least short-term immunosuppressants. People who are in good general health I think, are going to be more likely the participants in these early studies. And then a great question about deep brain stimulation, the studies, first in human studies and the early studies like TransEURO, in general, these are not going to be taking people who already have deep brain stimulation. I think, partly, there's a scientific reason for that. It's going to complicate the outcomes.

But also I think that once you've had one surgery, when we're thinking about something that's very novel, probably the best thing is to deliver the cells into people who have not already had a previous surgery. But down the line, you can imagine a lot of different scenarios and maybe people are going to be getting these in combination, or maybe testing is going to be done versus deep brain stimulation. I think right now I would say, if you've had DBS, it's very unlikely that you'll get into these studies, but I think down the line that's probably going to change.

Brian: Maybe a follow up question to that, and a few people have alluded to this as well, we talked about it earlier, this concept that, at least in the current vision of how stem cells could be used in Parkinson's, as replacement cells and things like that, but that the underlying disease process is going to continue, as the effects that are happening in the brains of people with Parkinson's. Can you talk a little bit more about that? I know there has been some evidences to suggest some of that disease process could even potentially spill over into replacement cells, and what some of your thinking around that and are there researchers in this space thinking about ways to address that in the future?

Claire: Yeah. I think that's really a fantastic question. This is all to answer. These are all questions that we have to look at. But I think what we can say from the previous studies where they've used human embryonic cells for transplantation, there is evidence that this so-called pathological hallmark of Parkinson's, which are the Lewy bodies, these little protein blobs that we see in the nerve cells in Parkinson's. You see those in the brain of people with Parkinson's, and they have also been seen in the cells that have been put in, in the grafts.

Scientists are still working out exactly how that spread occurs. I think we have a little way to go in terms of figuring out different vulnerabilities of the cells. I mean we're putting in cells that are actually quite young, and in Parkinson's, there's a definite effect of aging. Although there may be spread, there may not be significant spread. I would say in the autopsy studies where people have died of other causes, and scientists have been able to look at the engrafted cells in there, they can see that the pathology, the Parkinson's process has spread. But I would say it's to a more minor extent, and we don't know that that's actually had any clinical effect on the people where that's been documented.

I think down the line, it's going to be really interesting to see if we can, first of all, pin down how important that is. Second of all, it's going to be important to see, as we're starting to talk about people may be getting their own cells

transplanted. Julia might be able to speak a little bit more to that. But if they're getting their own cells transplanted, might they be more vulnerable? Are there some people where they should not have their own cells transplanted? Are there others where it would be perfectly fine? I think we have to pin that down.

Whether we could come up with some ways of being able to perhaps through a sort of combination therapy, be able to prevent spread and prevent this transmission of misfolded alpha-synuclein from the quote, host tissue, into the transplanted tissue. I think these are all questions that people are looking at right now. So we don't have answers yet, but it's a watch this space I think.

Brian: Right, right. Actually, so you raised some interesting points. I was going to maybe flip to Julia and talk about a couple of things too. Some of the themes, some of the questions that are popping through kind of in this broad context of again, who might be most appropriate. Again, thinking about use of stem cells from people with Parkinson's, to again, to understand disease, Julia, what are you seeing, maybe some more recently things we're learning about, again, Parkinson's through these types of approaches, and how that's maybe helping us understand, I think an important question in the field, which is the different types of Parkinson's disease that might be out there that might be related to different types of say genetic causes? I wonder if you could just maybe comment a little bit more on kind of generally what we're learning as we are looking at these different types of stem cells.

Julia: Yeah. I think early on, I think there was a lot of questions of, well, so there's different genetic backgrounds, or different mutations, or variants that cause Parkinson's disease. I think there was a lot of questions, "Well, if we take these cells, can we actually see any differences in their pathology, in the laboratory setting?" It turns out, in fact, we really do. There's different mutations in alpha-synuclein and LRRK2, on PINK1, PRKN, that those mutations and the ways that we think are altering the cells in certain functions, for example in mitochondria, or one big theme, not just in Parkinson's disease but in actually a lot of neurodegenerative disorders is this protein clearance or how the cell gets rid of unwanted or toxic proteins are misfolded proteins.

It turns out that a lot of the pathways if you will, the cellular pathways that we've sort of been hinted at, that have been affected in the disease, in fact, shows something called phenotypes. They show these basically problems that the cells in culture. That's quite promising because it suggests that if we can capture, if we can understand what the different pathologies are that are caused by different variants or mutations that we know are associated with Parkinson's disease, that will help us basically better understand the cellular pathways. Then also potentially, ways in which we can get in there and tweak those pathways or perhaps help the cells do better. For example, turnover the mitochondria better than, or similar to healthy cells.

Brian: Right. When we were preparing for the webinar, you and I, I think we had a brief conversation about an interesting idea that I've always been really fascinated

by, which is this concept of as you obviously learn more about the biology of stem cells, in many ways you're learning more about the biology of cell development. How a cell can go from essentially a single cell, an embryonic cell to make any cell type in the body, and leveraging that knowledge to identify mechanisms in say, the brain, where you might be able to go in and target that mechanism and actually have the brain repair itself. I know this is a fascinating idea, and there hasn't been a lot of therapeutic development in that space yet, at least to my knowledge. Could talk a little more about that concept? It feels a little sci-fi maybe, but this idea that you actually learn something from these cells to target in the brain.

Julia: That's a great question, and I think one that us as biologists, especially developmental biologists, in the lab, I think we're still really, I'd say, struggling with trying to understand. Human development is this very complex processes. There's cells talking to each other and there's changes in gene expression and it's this complex sort of communication or circuitry that really tells cells, "Okay, you're going to become a neuron and I'm going to become an astrocyte. This back and forth, I think, we don't really understand yet. We're still very early days, but by growing these cells in the lab and I think there's a lot of effort. There's been a tremendous amount of effort of trying to understand essentially what molecules or what genes that may better push these cells toward a specific cell type fate. In our case, we're really interested in dopaminergic neurons.

The more we understand what those molecules are or those genes are that can really push that cell to become a specialized cell, that opens up, I think a very large field of study, to help us potentially harness those same genes or ways of turning on those genes that we could do the same in the brain. If you've lost a lot of your dopaminergic neurons, well one idea would be, rather than for example, replacing them, which I think is a very exciting prospect, when one I think, that we'll see how in the next few years with the clinical trials. But the other idea would be to just be able to harness the brain itself to say, okay, if we can target these specific genes and turn them on, we can basically essentially have the brain replace the cell it needs. And so that's kind of the idea. Again, I think it's very far out there, but I think it's a very potentially exciting approach that could come to fruition, the more that we understand about really development of how these cells are generated and how they're made.

Brian: Right. Right. My, graduate work was in brain development, and so I think even back then, I was pretty fascinated by that concept, as well, and look forward to continued progress on that idea. Another reason I think of why I asked the question, we've had a lot of questions from the attendees, kind of in this broad theme again of stem cell replacement type therapies, and how they are currently delivered. Again, Claire, maybe just to reemphasize and walk us back through on the different approaches. And that the majority of them, again I think to my knowledge, all involve brain surgery and placement of cells into the brain. Maybe again, talk a little bit about the actual procedure itself. What's the surgery involved in these types?

Claire: Yeah, absolutely. In fact, I'm glad you mentioned that because I also think that we needed to get into a bit more of the specifics about that. All of the approaches that I've talked about, the examples of the trials that you saw on the previous slide, what we're planning to do, what other groups are planning to do with the replacements, I think I said rather glibly, "Oh, we want to get the cells into the putamen. It's deep down in the brain, obviously. It needs a surgery." The surgical delivery of the cells needs someone to be... Right now the way that it's done needs a general anesthesia.

It goes back to a little bit of this, what I was saying about you need to be in pretty good health for this sort of thing. So, it's a general anesthesia. It's making little burr holes in the skull, so that you can thread a cannula. If you think about the deep brain stimulation surgery, similar principle, right? But instead of threading in an electrode, in this way, you're threading in a needle, a cannula. Once you're where you need to be in the putamen, and different people are going to do this in very slightly different ways, then the cells get injected. The needle can be moved, the cells injected against, so you want to get quite good coverage of the area where you're trying to deliver your cells. You don't want to end up with just a few hotspots that might overly help one thing, and not help other features. It's going to be quite... a surgery that demands a lot of precision in the way that the cells are delivered.

I think we have really fantastic technologies now. For example, here, we have an MRI that's in the operating room, so you can actually follow at intervals, what's going on. The technology for the surgery is being developed all the time. I think I would just say that we've learned a lot. We're standing on the shoulders of giants with this surgery. The deep brain stimulation field, has obviously worked very hard to figure out the best ways of doing these surgeries. Now, we have people who have pioneered gene therapy and are also looking at different ways of doing the surgery. I think we're all watching these fields, see are there ways to improve? But yeah, it needs a surgery, and then after the surgery is completed, like I mentioned before, you're not done then because most groups are going to give probably some months or a year or maybe more, of immunosuppressive drugs.

Brian: Right, right. Now, I know that some of the treatments that are being offered directly to patients out there involve approaches that are more injecting cells into the bloodstream. I'm wondering if you could talk a little bit about that as well?

Claire: Everything that we've talked about for the dopamine cell replacement, will need the sort of surgery that I described, at least with the current technologies. When you read about cell deliveries, for example, these mesenchymal cells that are your own cells and they come from your blood or from the belly fat, and that can be injected into the veins. There are also instances where it's been injected into the spinal fluid, but I think a lot of the clinics are injecting into the veins. It's really a completely different principle. The cells are not really expected to get up to the brain and get to the right spots, and survive, and make dopamine on their

own. It's a very different principle. Like I mentioned before, there are some teams who are doing really fantastic work with this sort of approach.

I mentioned the paper in multiple system atrophy, and the idea is that these cells would work in a different way. They probably, if they have effects, it would have effects by secreting factors. There's this concept of something called the secretome, and it means if you're a cell, all of the different factors that you're releasing and some of those can be anti-inflammatory, or some may prevent cell death. These are some of the mechanisms that are being investigated. But thanks for bringing that up Brian, because I don't want people to think that getting an injection into the bloodstream is going to get the cells up to your brain and replace the dopamine cells that have been lost.

Brian Fiske: Well, so we are at the end of the hour. I'm always surprised how quickly these webinars go, and I know we could probably spend the next three or four hours answering everybody's questions. I did want to thank our panelists, Claire and Julia. I know you're both busy, have busy day jobs, working hard, trying to understand and find new ways to treat Parkinson's. We obviously appreciate you taking the time today to talk to us.

Claire: Thanks for your interest.

Julia: Yeah. Thank you.

Michael J. Fox: This is Michael J. Fox. Thanks for listening to this podcast. Learn more about The Michael J. Fox Foundation's work and how you can help speed a cure at michaeljfox.org.