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.

Speaker 1: Welcome to a recap of our latest third Thursday webinar. Hear directly from expert panelists as they discuss Parkinson's research and answer your questions about living with the disease. Join us live next time by registering for an upcoming webinar at Michaeljfox.org.

Karen Jaffe, MD: Hi, I'm Dr. Karen Jaffe. I was diagnosed with Parkinson's Disease in 2007. I'm a retired OB-GYN, the co-founder of InMotion, which is a community wellness center for people with Parkinson's in Beechwood, Ohio. And I'm a member of the Michael J. Fox Foundation Patient Council.

Today we're going to be talking about stem cells and cell replacement therapies for Parkinson's disease. Today's webinar received support from Blue Rock Therapeutics, so we've got a lot to discuss here. So let me first introduce our panelists.

We have Dr. Alfonso Fasano, who is a neurologist and holds the chair in neuromodulation and multidisciplinary care at the University of Toronto and University Health Network. He's a clinician researcher and is investigating stem cell treatments. He has received research support from Blue Rock. Welcome, Alfonso.

Alfonso Fasano, MD, PhD, FAAN: Thank you.

Karen Jaffe, MD: Dr. Gaia Skibinski is the director of Translational Therapies at the Michael J. Fox Foundation. Thanks for being here. Gaia

Gaia Skibinksi, PhD: Great to join today.

Karen Jaffe, MD: Dr. Mark Cookson is the cell biologist and the senior investigator at the Laboratory of Neurogenetics at the National Institute on Aging. Thanks for joining us today, Mark.

Mark Cookson, PhD: Of course. Lovely to be here.

Karen Jaffe, MD: So we're going to talk about stem cells today. And Mark, I'd like to start with you so we can just get a level playing field on what our audience knows about stem cells. If you could tell us what is a stem cell and if we have some extra time, what is pluripotent stem cell and what is an induced pluripotent stem cell?

Mark Cookson, PhD: So stem cells are all throughout our body, and the defining factor that makes a stem cell rather than a differentiated cell is that they're capable of self-renewal and they then go make the cells that make up our tissues, our organs, our brains, and the like. We can isolate stem cells typically from very young animals or individuals.

Secondly, and you asked about iPSCs, so induced pluripotent stem cells, those are taken from mature cells typically in the skin of blood cells and then reprogrammed using genetic factors to retain that stem as that ability to differentiate into all the cell types of our body.

Karen Jaffe, MD: How long have we been able to do these kind of transitional work on cells?

Mark Cookson, PhD: Well, so the technology for the reprogramming for mature cells is about 27 years old. It was discovered in Kyoto University in Japan amongst other places. But knowledge that we have stem cells goes much further than that, probably 50 years or so. But again, in most tissues they're quite rare. And understanding them and isolating them is always very challenging.

Karen Jaffe, MD: Alfonso, where in how do stem cells typically work in the body?

Alfonso Fasano, MD, PhD, FAAN: So there are different types of stem cells in the body especially in tissues with high reproduction of cells, especially early in life, even the brain as tissue stem cells that are maturing, becoming neurons. But this soon after birth, little by little, this pool of cells diminish. And so stem cells in neurology are not typically retrieved from the body of adults.

But in other organs, for example, the blood there are circulating stem cells. These cells are not necessarily able to become every cells, we'll talk about it, but they're able to become any, for example, blood type of cell. And they are typically used nowadays in dermatological indications for blood diseases. Nowadays, we can actually retrieve stem cells and use it for clinical purposes.

Karen Jaffe, MD: Gaia, why are stem cells of interested Parkinson's researchers?

Gaia Skibinksi, PhD: There are several reasons why we're really interested and excited about stem cells. The first is that as Mark was saying, you can take these stem cells and make them into dopamine-producing cells. And so that's been one really exciting area of cell therapy for Parkinson's disease patients replacing cells that die in the brain with these stem cell-derived dopamine-producing neurons. So that's one area.

So in the clinic, we're trying to test back these stem cells. The other area is actually in the laboratory where we're looking to understand the mechanism of what's happening in the brains of Parkinson's disease patients. We can now take these stem cells and make them into brain cells in a dish and then look at what's happening in the cells in a dish.

And we can take cells from healthy individuals and cells from Parkinson's disease patients and effectively look for differences between those different cell-type cells, so cells from patients and then cells from healthy individuals. So a bit like playing spot the difference, which I'm sure many of you have done before. So you're really looking for these differences.

And then what's really exciting is that the source of stem cells are renewable, so we can make effectively as many cells as we want now, and they're human cells, so we can use them for drug testing in the laboratory so we can look for drugs that can actually take the patient neurons or brain cells and convert them back into the healthy cells.

So those are the three areas, cell therapy, which we're going to talk more about understanding the mechanism of the disease. So what's different about the patient cells versus the healthy and then trying to find new drugs to make the patient cells like the healthy cells.

Karen Jaffe, MD: So are the cells all related to dopamine production? Are there other functional cells that we're looking to find besides ones that were going to replace the dopamine depleted cells?

Mark Cookson, PhD: Well, certainly in a lot of talking about the modeling and treatment, which the second and third parts that Gaia mentioned in any neurodegenerative disease, there's likely interplay between neurons and non-neuronal cells, particularly the immune system. So there's this idea that inflammation in the brain is part of the disease process.

So when we're trying to build the more sophisticated models now, we really try and make all of those different cells you would find in the brain. And what we, in my lab, are doing in the moment is we make these, the little mini-brains are about the size of a pea, and you can see that they make neuromelanin-positive dopamine neurons within that. So that's one area where we're really looking not just the dopamine neurons, but also interactions with other cell types.

Alfonso Fasano, MD, PhD, FAAN: Maybe if I can add to that, in research so far though, in human studies the main source of cells have being dopaminergic cells. So the idea is to replace, at least for the time being dopaminergic cells in the brain of people with Parkinson's.

Karen Jaffe, MD: But Parkinson's is more complicated than just dopaminergic cells. So it'll be interesting to see how this progresses as time goes on. So scientists are trying to use brain cells to improve or rescue replace neurons or replace neurons in the brain loss due to Parkinson's. This is what we're talking about here is different approaches that we can take.

Mark, researchers are working on in these different approaches. How can the stem cell treat Parkinson's?

Mark Cookson, PhD: Well, so I think I'll defer a little bit to Alfonso, but in a simplest idea, if you have a group of cells that are damaged or missing and you mentioned dopamine neurons, you could replace those with authentic human cells that will develop into something that's functional and that does work.

You're right though there is a challenge there then that we now know Parkinson's disease is a multi-system disease, affected many different brain regions. So I

think we're still trying to think about how that might be approached at the moment.

But in principle, it's a way of replacing things in something that should be physiologically regulated rather than a drug which will come and go as you take it. But again, I'd like to invite Alfonso to speak a little bit more on that.

Alfonso Fasano, MD, PhD, FAAN: Yes. Thank you, Mark. I think the audience need to realize that it is simplistic to talk about cells that just replace the dopaminergic ones. There's no question that Parkinson's disease is not just about dopamine. But at the same time, the audience needs know that stem cells research has been going around and going on for decades.

So the first attempts were towards the late 80s, and as for sure, more in the future in the following years. So even though we've been trying to replace the papillary cells and the papillary cells alone, we haven't been really successful.

Things have changed recently, and we can talk about the reasons why things are different nowadays, but this is just to say that even with the simple task of replacing the papillary cells, so far, we haven't really seen breakthrough in research.

Karen Jaffe, MD: For those of us who've had Parkinson's long enough, we certainly know that there's a historical perspective to stem cell research. And I think that we could talk a little bit about what might've stalled stem cell research for a while, maybe 15 years ago, I think I recall, and how that changed the landscape of the research field back then.

Alfonso Fasano, MD, PhD, FAAN: So for sure, back in the days when the experience started, and it started mainly in North Europe, particularly in the City of Lund in Sweden, the biggest challenge was to retrieve embryos because neuronal stem cells able to become dopaminergic cells were retrieved from embryos.

And obviously this comes with a lot of ethical concerns and there been studies, these studies is showing some positive findings. But then we always have an issue with placebo because any study that is done, especially when it's an invasive study, especially when we're using such a fascinating idea that is replacing a part of the body with fresh cells, all of this increases the chance to have to deal with placebo effect.

So in the early 2000s, then two big studies were done. This is also because the political landscape in the states are changed, particularly from a legal perspective, so that finally studies could be done in a double-blind fashion, meaning that some people went for a fake surgical intervention that we call sham surgery, and other people living with the disease got the real treatment so that the two groups could be compared.

And these two trials were both negative, meaning that the group receiving cells on average weren't different from the people not receiving the real cells. So this

was obviously very disappointing and this has been a big problem. The community at this point were very excited and then they lose the excitement until in recent years we ended up using a different type of approach where the cells are created in the lab.

And this is because people like myself, a neurologist, is more in conversation with people like Mark. And this has introduced the concept of the floor plate protocols. This means that the cells are not retrieved from embryos anymore, but they're produced in the labs.

And this is where Mark, I'm sure can explain way better than me and also Garry can say, but I walk you through the challenges that as a medical community we faced and how things are becoming to be different nowadays.

Mark Cookson, PhD: So I think one of the things through all of this work that's been going on is really some aspects of development neurons. So how do they develop, what are the growth factors that are needed to make them and then to sustain them? And that's I think setting the basis for the next stages of trials.

Can we generate something that's very authentic that really reflects an adult dopamine cell or other cell type, if you wish? How can we get them to survive in situ for a long period of time and those kind of questions. So I do want to express real excitement about this work, how important it is, and despite perhaps it not being a mainstay treatment, it is very something where we've made a lot of progress, especially in the last decade or so.

I want to come back a little bit to the idea of induced pluripotent stem cells. One of the ideas there is that you can understand the genetic makeup, and that means the genealogical makeup of those cells. And so at least in theory can limit the chances of things being projected. So again, there's been some real progress I think in the last decade or so to making these a little bit more robust and replaceable.

Karen Jaffe, MD: I'm wondering whether I'm remembering this correctly, but it seems to me that there were some looking at after they did the double-blinded study with the sham arm and they saw that there was no difference between the two arms.

Did it come out to be later reported that maybe that if they'd waited longer to look at the study, that they would've seen differences that they didn't see clearly enough or it wasn't therefore they'd stopped the child because there wasn't enough positive data? Am I remembering that correctly?

Alfonso Fasano, MD, PhD, FAAN: Maybe I can talk to this. So it is true that for any treatment that requires the implant to grow over time, in theory, you're expected to potentially see additional benefit over time. This has to be considering the context of a progressive disease like Parkinson's disease, and that alone complicates things, especially if you want to look at the results five years later.

But the one thing I would like to emphasize is that number one, in this studies, there were people where the improvement was significant, but the issues that it wasn't seen across the board, that's why I said on average there was no difference. And it's difficult to explain why in some people, cells were more effective than others.

But the more important thing to say is that even in terms of safety, some problems can arise over time. For example, I took care of a woman who was part of the studies, she's a Canadian woman who flew to New York to be enrolled in the study, the one we talked about. And this woman was under my care.

It was 10 years later when she started to develop a typical side effect of these implants or transplant of cells, which are a particular type of disabling [inaudible 00:14:54]. So it took many years for this person to develop this problem, which emphasizes that also the safety concerns that we might have in the long run.

Karen Jaffe, MD: Gaia, what's the difference between stem cell therapy and replacement therapy?

Gaia Skibinksi, PhD: Yeah, great question. So I think you can think of the terminology stem cell therapy as a very broad term that captures the idea of using stem cells. And you can either implant stem cells or you can, as Mark mentioned, you've actually got, we've got recipes now that we can add to the stem cells to make them into different types of cells.

So in Parkinson's disease, we're very interested in neurons, but we're also very interested in immune cells that are a part of the disease process as well. So stem cell therapy really captures this very broad category of using stem cells and making them into different types of cells and putting those back into the patients, whereas cell replacement therapy you can think of is a much narrow definition.

And when we think of Parkinson's disease patients and when people use the Tim cell replacement therapy, we're really thinking about replacing the loss of the dopaminergic neurons in the brains of patients. But I'm sure you are all familiar in the audience that maybe you've heard that these terms are interchanged between different conversations and different researchers or clinicians or even doctors may use them.

But really, you can think of stem cell therapy, broad terminology. And then cell replacement therapy is a type of stem cell therapy where you are replacing the dopaminergic neurons in the brain.

Karen Jaffe, MD: Alfonso, one audience member is asking us, they want to know what kind of symptoms that stem cells treat and what wouldn't they help.

Alfonso Fasano, MD, PhD, FAAN: Yeah, this is going back to comment you made before. The Parkinson's is not just dopamine, but at the moment these cells are meant to replace dopamine and therefore will be, in theory, helpful for the so-called motor fluctuations, the up and down on motor problems as the levodopa in the system goes down, tablets unfortunately don't last many hours.

So a cell that produces dopamine on ongoing basis is more physiological and it will in theory improve the off time, so medication so that over time, even when the medication weather, is this going to improve problems like mood problems, memory problems, balance problems? Ideally, it will not be effective because these problems we now know depend on non-dopaminergic cells.

So it would certainly help important problem of the disease like rigidity, slowness, tremor, to some extent, but not disabling problems like balance or memory problems.

Karen Jaffe, MD: Gaia, is there an understanding whether stem cells prevent disease progression?

Gaia Skibinksi, PhD: That's a great, great question. And Alfonso really mentioned this already, which is the therapies that are in clinical trials right now which have being tested on Parkinson's disease, patients are really focused on improving symptoms. So generally, they're in patients that have moderate to advanced Parkinson's disease.

So we're really trying to test whether B-cells can improve the symptoms and make a real impact on the day-to-day life of Parkinson's disease patients. The question of whether they can actually modify the disease progression we don't know yet is the answer to that. Maybe if we were to test these therapies in earlier patients, maybe there could be some degree of disease reducing progression of the disease.

The other thing that we haven't mentioned yet that much in detail, we've really been focused on cell therapies that replace the dopaminergic neurons. But in the laboratory right now, we're testing other cell therapies for Parkinson's disease patients that would help support the neurons in the brain. So they either secrete factors that help the neurons or brain cells survive or they actually support cells or the brain.

The brain isn't just made up of neurons, it's made up of other style that support the brain. And so there are very, very early the interesting results around stem cell therapies of support cells. And in that case, there could be a slowing of the progression of the disease, but it's very early and we're really focused right now on seeing if we can get stem cell the to improve symptoms.

Karen Jaffe, MD: What are some of the risks or side effects of stem cell therapies?

Alfonso Fasano, MD, PhD, FAAN: Yes, there are several, and that's why it is important to be receiving cells in centers that do this for research reasons. But to simplify the message, I think there are risks related to the insertion of the cells because these are inserted with a brain operation and therefore there's an infection like anytime there's an operation to the body, then there are risks related to the production of dopamine, for example, or other neurotransmitters.

And I mentioned earlier that the problem of dyskinesias. We haven't seen dyskinesias in the new cell trials, but in the past, once we have seen people developing severe dyskinesias requiring an additional intervention like deep

breast stimulation just to treat the side effects of the implants of cells. And in theory, there's also a potential that the cells will grow too much becoming a tumor.

So there is a potential that the cells expand and it become over time something that cannot be controlled and therefore that could be like a brain tumor. Thankfully, this is something that is possible but haven't been reported. So I will mainly focus on the first two risks that I mentioned, risk related to the procedure and risk related to the cells themselves doing what they're supposed to do, producing dopamine.

Karen Jaffe, MD: Now, Alfonso, you mentioned briefly, so we'll talk about it, I'll bring it back up, that there are clinics that offer unregulated stem cell treatments. It's not the same thing that we're talking about today. What do people living with Parkinson's know about these clinics?

Alfonso Fasano, MD, PhD, FAAN: Absolutely, this is a great point and this is the very same reason I was really happy to be invited to talk about this treatment on your platform because unfortunately, people are desperate and understand where they're coming from. They're looking for solutions that is not just a symptomatic treatment or a pill.

And so unfortunately, some centers are taking advantage of people's desperation and they will have beautiful websites with testimonials even where they offer stem cell treatments with their proprietary cells that nobody knows what they are for a price.

Now, I think the audience needs to realize that this is still experimental and is absolutely unethical to offer an experimental treatment for a price. So be careful when someone offers something to you, especially when they want money. My suggestion is always to discuss anything that you can think of as a solution with your own neurologist.

They are there to help you and guide you, and they can tell you if it's something with potentials or not. The scientific community has ways to understand if something is a scam or not. I will say that anytime a center offers stem cells for a price, that is something you should run away from. And this is not just because you're wasting your money and you are wasting your hopes, but also because it can lead to risks.

I mentioned before there are risks, and there have been some examples in other fields of medicine where unregulated stem cells treatment have led to tumor. This is for example, a history of a few decades ago with stem cells in the retina, in the eye for people with problems with their vision that led to a particular type of tumor never seen before. So it is extremely important that you discuss any of these options with your neurologist.

Karen Jaffe, MD: So what is the current status in the field of research with regards to stem cell? Where do we stand in terms of trials that are underway?

Gaia Skibinksi, PhD: Yeah, it's a really exciting time in terms of clinical trials for using stem cell, and this is the stem cell replacement therapy approach. So this is taking stem cells, making them into dopamine-producing cells and placing most cells into the brain. So we have several studies or trials that are ongoing right now.

And what's exciting about that is we actually have some initial results around those trials as well. So you may have heard of companies called Blue Rock Therapeutic or Aspen Neuroscience. There's another trial from Coyote University. There's several that are ongoing right now.

And the first stage of the clinical trial is really looking to see if the cells are safe. That's the most important first step that needs to happen when you carry out a clinical trial. And both from several of these studies, it's been demonstrated that when you put these stem cells that have be made into dopamine producing cells into the brains of PD patients, they look relatively safe.

There are no major adverse effects in all of the patients. And then also these early studies, we've also looked to see whether there's benefits to the symptoms, so improvements to the symptoms of Parkinson's disease patients. And the numbers are very small at the moment, but there are indications that the symptoms improve. And then also when you look into the brains of Parkinson's disease patients, you can scan the patients. You can also see that the brains are producing more dopamine, which is the neurotransmitter that's lost obviously in Parkinson's disease patients.

So these trials are ongoing there right now. And then the next step that's happening with many of these groups is to test the cells in a much larger group of patients. So that's going to be ongoing in the next few years. And then another exciting piece of information around the clinical trials is that the clinical trials are all slightly different.

So the types of cells that are being used are slightly different. So in the Blue Rock Therapeutics trial, they're using allogenic cells. So you may have heard a bit of the word allogenic, which means that all of the patients in the clinical trial are used in the exact same cells. They're from one donor who's donated their cells to be used in this clinical trial.

And then in Aspen Neuroscience clinical trial, there's autologous cells, so they're actually from the individual patients in the trials, so they're the same cells as the patient. And so in the clinical trials, we're also experimenting with different types and sources of cells, and that's going to be important in terms of looking at how well these cells survive both in the short term and then also importantly in the long term for the patients.

Karen Jaffe, MD: What does it mean that somebody donate their cells? What does that mean for that person? What are they donating?

Gaia Skibinksi, PhD: Yeah, so in the case of when you have autologous cells, the patient, you are going to use the patient cells so that the actual patient will give their cells. In this

case, I don't know in the trial what they do, but oftentimes it's either blood cells, but they will donate or skin cells.

And remember what Mark said about this technology right at the beginning. The technology now enables you to take blood cells, make them into stem cells and make your own stem cells into brain cells and then put those brain cells or dopamine-producing cells back into the same patient. So it's actually an amazing technology that we're testing out. So that's what I mean by kind of donating the cells.

Also, in one trial, all the patients are donating the cells, but in other trials, everyone's getting the same cells from one patient. I could go into the details, but there's pros and cons of doing that, but at very high level, it's much more expensive to make the cells for each personalized patient, but there's benefits because they're the patient cells, so they're less likely to be rejected by the patient. So we can get into details a little bit later about the pros and cons of that.

Karen Jaffe, MD: But there is a chance that when they're coming from their own cells that they can reject them?

Gaia Skibinksi, PhD: But it's less likely. So if you get your own cells that are added back into you, that your body recognizes your own cells, so rejection is less likely. Whereas, if you've got cells from a donor but aren't your cells and they're put back into your body in those trials, actually people have been taking immune suppression medication to suppress the immune response to the donor's cells.

Karen Jaffe, MD: So can we wait to see if they have a reaction before we give those suppression drugs or do we assume that they're likely to have one so everybody gets them?

Gaia Skibinksi, PhD: Yeah, this is really interesting question because in the Blue Rock trial, this is where they got not their own cells. So cells from someone else was put into the brain, and so they were initially on immunosuppressants to suppress their own immune system and the cells were healthy, they started to produce dopamine. Maybe there was a mild benefit to the symptoms. We have to test that further.

But what was really interesting in that trial is they took the patients off the immunosuppressants and they wanted to see what would happen to the cells in the brain, and actually the cells continue to survive suggesting that maybe you don't need immunosuppressants for even cells that are not your own. And that's specific to the brain because the brain is a very special organ because we have this brain-blood-brain barrier around it that basically protects it from our peripheral immune system.

To some degree, there's some infiltration for the specialist out there, but generally so there's less of an immune response. So I think we just have to wait and see where when they move into a larger group of patients to see if we will need immunosuppressants or not for these technologies with autologous and allergenic cells.

Karen Jaffe, MD: The previous overview, Ann, I'm interested in this is a patient question coming from the audience. Can she say cord blood from future pregnancies to help her dad? Who wants to take that one?

Mark Cookson, PhD: Well, I will say you can make EFCs and induce blood protein stem cells from cord blood. We've done that, but of course, you're not strictly isogenic with a first degree relative, so you're 50% similarity as we know from the reason we scorn for blood groups in pregnancies is because you can't reject. So it could be done, but whether it really help is this much less said.

Karen Jaffe, MD: So the next question that came online was, can stem cell therapy prevent partitions in members who are at higher risk for contracting the condition but are not actually diagnosed yet with the condition?

Alfonso Fasano, MD, PhD, FAAN: Yeah, I think this is a common question, and the answer is no, because we don't know what these cells do at the moment. We have a lot of hope and there's a lot of research for sure, especially with an exponential growth in recent years.

But at the moment, the main goal is to really fix fluctuations and the motor complication of the disease. So it doesn't make any sense to talk about doing this in someone wasn't even displayed these problems. When we select people for trials or stem cells, we're looking at people that you will typically consider for deep brain stimulation or pump therapies.

I think the question at this point is how close we are to offer this to patients? What's the timeline, and if I might say. The good news is that now industry is interested in this topic. It's not just research groups in Japan or in North Europe, but it's also the investments of big industry.

And so things are moving faster than they used to move. For example, Blue Rock is now about to start a phase two, phase three trial, and this is very promising for people not familiar with phases. We have four phases before, so is commercialized. So if phase three is successful, that will go into phase four, which is really preliminary to making this available to the big public. So we never been so close to that.

Obviously, we need to see what happens with this phase three, which is just one particular type of cells, one particular type of company. But there are other companies you heard and other group that are working on this. And at the moment, we're in phase one, phase two, but they're slowly progressing towards these additional phases. They are needed before we can have, for example, an FDA approval so that any person diagnosed with Parkinson's fulfilling certain criteria can undergo this treatment.

Karen Jaffe, MD: And are any of these clinical trials being fast tracked?

Alfonso Fasano, MD, PhD, FAAN: Well, fast track, I don't know what you mean by that for sure, because of the interest and the huge need to find something more effective for the treatment of

Parkinson's, there is a lot of investment, a lot of facilitation in a way from a regulatory bodies.

Fast-tracked is maybe a big word, but for sure, I've seen an evolution and a progression of things I've never seen before. And this is good news overall.

Karen Jaffe, MD: How many patients do you think have been treated that we're looking at right now and we're waiting for results on? And are there anybody who's being treated who's outside of the clinical trial?

Gaia Skibinksi, PhD: Not for cell replacement therapies. Everyone that's getting the cell replacement therapy is enrolled in a clinical trial and being very closely monitored. So as Alfonso mentioned before, it's very important to speak, obviously, to your doctor and at is only patients who are this treatment who are enrolled in these clinical trials and in other works, each of these clinical trials we're talking about tens of patients.

So that's when I mentioned earlier about the trials. They, as Alfonso mentioned, they've gone through phase one, which is the safety, and now they're moving into phase two and three, which is really testing on a much broader population of patients to see if these therapies can really improve symptoms.

Karen Jaffe, MD: Stem cells is a research tool. How, the question I'm seeing is how did genetics tie to the Parkinson's disease risk and how do cells react to the environmental triggers?

Mark Cookson, PhD: So I can take that one because this is really what we do in the lab every day. So we're very interested in genetic risk factors, and as many of you know, most Parkinson's has got a single genetic cause or multiple genetic risk factors that play into your overall risk in the context of aging.

So the reason the stem cells are really useful is of course they have the entire human genome. They're not like a cancer cell that has lots of genetic rearrangements and of the damages. They're really just the native exactly what we were finding in all of us.

And so what we can do there is use that to our advantage and take out individual genes of risk factors or variants we call them. And we can then, as guy was saying at the beginning of the seminar, do the spot difference? How does this cell containing this genetic risk factor react compared to this one that doesn't?

Now we do that using a technique called CRISPR-Cas-IX, which we can edit the genome. And that sounds kind of very science fiction, but it's actually become the last, I'd say, four or five years, very routine. And we do it all the time. Once we have those cells, then we can then look at how the cells differentially react to things that we think might be in an environment.

There's a lot of interest in pesticides, for example. So how does a cell with a genetic root factor and respond to a pesticide compared from one that doesn't?

And then obviously, in the end then guy might want to learn more about this later. How can we reverse those reactions? So we use them as a way, honestly, really to understand how genetics works in a way that other models don't allow us to do that, and we found them incredibly useful.

I would just a little shout-out to Fox and PPMI, many people who are part of the PPMI study donated their stem cells. We have those in the lab, and that gives us a real sense of what the variation is from people who live in Parkinson's disease. So if anyone gave those, we're very grateful.

Karen Jaffe, MD: The PPMI study has been ongoing now for 13, 15 years maybe. I only remember that because my husband graciously joined the PPI when it first opened up, and I thank him for that. Every day it's still open and enrolling patients for different person study. So it's an important way that people can help when they don't even have the disease.

So we have large groups of control patients in the study, and it's really a groundbreaking informational with the development of finding the biomarker for Parkinson's disease. So kudos to everybody who's joined in it. We hope that you'll continue to participate in this very, very important study.

I have a patient, a question from the audience, an identical twin who has Parkinson's disease and wants to know whether there's any... How they might assess the risks in their identical twin.

Mark Cookson, PhD: So I can take that. Again, for most people, genetics add some risk, but unless you have a very strong family history, that's not going to be deterministic. And in fact, there's many examples of twin studies where you get a discord, and so one person might have Parkinson's disease, the other one won't.

Obviously, it really depends on your family history. So if you have those concerns, probably the best thing to do is talk to neurologist and get in contact with a genetic counselor who could talk you through the family history. So again, we know that it can make a difference, but it's usually not a very black and white yes, no thing. So it's worth getting some expert advice on that.

Karen Jaffe, MD: We can question being right here from the audience.

Alfonso Fasano, MD, PhD, FAAN: Karen, there's one can probably answer. Are DBS and stem cells mutually exclusive? This is an easy one at the moment, the answer is yes, because in stem cells trials, we don't typically enroll people with DBS and apples. We typically expect we wait for a few years to see what's the effect. And DBS has such a profound effect on the disease that it might bias the results of the trial.

But in the future, let's say when stem cells of a certain type are approved for human use, then I don't see why a person cannot have at the same time, well, maybe one first and then the other if needed, stem cells first and then DBS the other way around. But we will be there only when the stem cells treatments are approved by, let's say the FDA.

Karen Jaffe, MD: I know that there's several studies because of cancer risks, the oncogenic potential of cancer in this, as somebody who's had a previous cancer, let's say basal cell cancer, be excluded from a study like this,

Gaia Skibinksi PhD: You would have to check all the clinical trials have exclusion criteria. So we would have to check the exclusion criteria

Karen Jaffe, MD: As a client, is a patient who people come to me a lot and asking me why they get excluded because of that, but I suppose that there is a cancer risk in Parkinson's disease, melanoma. So I'm not sure whether that's where that comes from. But I thought I'd ask you. I can see whether could clarify that or not, but I suppose just checking with the individual study is me to start with that.

Gaia Skibinksi, PhD: There's one question about the surgical procedure for giving the stem cells. I can give the first round and then feel free others, I'll pass it on to Mark. It is what's called, to some degree, invasive surgery. So you're effectively adding the cells. You have to actually inject the cells into the patient's brain.

And just in terms of whenever those injections are happening, there happening in a part of the brain predominantly called the putamen as part of the striatum, and the idea there is to add the cells back to the area of the brain striatum that's really controlling your movement. But Alfonso or Mark, if you want to add anything extra to that.

Alfonso Fasano, MD, PhD, FAAN: I just want to emphasize what you just said. Absolutely agree. And this goes back to those clinics offering stem cells because sometimes they say that it just requires an IV injection or an intramuscular injection. Unfortunately, the cells are not able in humans to go where we want them to go. So it's really unfortunately a situation where we need to physically place the cells there.

So if you hear about centers saying, don't worry, we'll inject the stem cells in your blood. It's simply simply not possible that those cells will migrate exactly where we want them to go. In the future, we may have a possibility to use focus ultrasound that opens the brain barrier in the area where we want the cells to migrate.

And if we combine focus ultrasound with a certain type of cells, maybe one day we'll be able to do that, not at the moment. So again, it's important to emphasize that this is a surgical procedure.

Karen Jaffe, MD: Is the goal to stop progression or reverse it or just mediate it?

Gaia Skibinksi, PhD: It's a tough one, but I think the goal certainly of the Fox Foundation is to stop the progression of Parkinson's disease. We're really keen to get out of business is the take your message for the Fox Foundation, but we have to do it in stages. We have to do it in steps. And so really the stem cell therapy, the first step is to see if we can improve symptoms, and that's what we're testing right now.

And then with time, but we can then expand our stem cell therapy approaches to then try new techniques to see if we can slow the progression of the disease. This is really stopping the cells that are already in your brain from dying, and that's very in the discovery work, but there's lots of work actually in the laboratory going on right now to test out those hypotheses. Alfonso and Mark, I'm not sure what your response would be.

Mark Cookson, PhD: Well, I think there's a question in the Q&A here, which is successful to dub me stem cell replacement. Would that mean less than no medication? What does success look like? And I think for many people, they find early in their disease if they work with a great clinician, Alfonso. Some of those things are somewhat manageable.

And so I think success here would be probably keeping someone early stages where the levodopa or other medications are relatively effective and not having that progression aspect. So I think that's where we would like to get to. I think we're away off that, but that's where we would like and that would really, I think, be a substantive success.

Gaia Skibinksi, PhD: Yeah. I think there's a question in the chat around how and if AI is leveraging stem cell, how has it been leveraged in stem cell research. I can go first. We're definitely seeing the use of imaging-based models that allow us to detect those differences that Mark and I were talking about in the laboratory, taking patient cells and healthy cells and trying to use images to match those cells or look for differences.

So that's definitely been one big area that's taken over in the last five years. And I'll just add one extra thing, which is I also mentioned that these cells have been used to screen drugs, hundreds of thousands of drugs. And so again, these images have been used to look to see if you can find the match of the disease or the patient's cell being brought back to the healthy stage using these deep learning models. But maybe Mark you've got other areas as well?

Mark Cookson, PhD: No, I would say we've been using, it's not really artificial intelligence, but machine learning models in the analysis part of our lab for many years. They have some advantages. They're generally faster. They're sensitive to things, smaller effects and models. We've used them for quite a while, and that's across cell biology, genetics, really all the things that we do here. So it's very well established now, and I think there's some really positive outcomes from.

Karen Jaffe, MD: Is there an age, somebody who can have stem cell replacement?

Alfonso Fasano, MD, PhD, FAAN: I can take this one. Maybe there is not a formal age limit. Then every study, as we heard before, as inclusion and exclusion criteria. Unfortunately, science has strict rules because it's not an easy task anyways. So sometimes there's an age limit that is mainly coming from the safety of the procedure. Obviously, doing a brain operation in someone who is 85 is riskier than doing it in someone who is 65.

Then age is obviously just a number. It depends on the health of the individual. But in general, there are age limits mainly related to the safety. One question that people ask me often, and I'm sure the audience is also wondering about is how to sign up for studies, how to volunteer to receive stem cells or to be part of this cell replacement trials. And as I said before, the starting point is always your neurologist.

Obviously, you need to be followed by a movement disorder disorders expert. So Parkinson's experts are many out there. So that will be the first step. This will help you anyways. And then being a specialist, your neurologist can tell you if there is a study you can be referred to, you can participate. There are other ways, for example, the J. Fox Foundation as a tool of a trial finder where you can actually search for trials.

But I will always emphasize the need for you to discuss this with your own neurologist. Because your neurologist only wants the best for you. There will not be any reason for them to say, no, don't do that if they don't believe it will be good and appropriate for you. And through that, this is how the process start. And you can be referred to the center who does or enroll for the trial.

Karen Jaffe, MD: Guys, we have a question here that somebody wants to, they've not had success with their DBS placement, they'd like to turn it off and join a study. Is that something that's possible?

Alfonso Fasano, No, sorry. I was going to say, because the person has already a DBS electrode implanted, so usually these people are contraindicated. So this is a contraindication, it's an exclusion criteria for a stem cell treatment. But obviously, if the cell treatment becomes approved because it is successful and safe, then it can be done even in someone with an unsuccessful DBS procedure.

Gaia Skibinksi,: If people are interested on the clinical trials, there's a free website, clinicaltrials.gov and you can go and search for the trial, and there'll be... If you scroll down the page, you can also see the exclusion criteria, so the criteria to restrict you or prevent you from joining the trial.

Karen Jaffe, MD: And I assume that Gaia, we can access this through fact trial finder?

Gaia Skibinksi, : I assume so, yeah.

Alfonso Fasano,: Meanwhile, I can take another quick question. They're asking about trials outside the US. Yes, there is. As I said, already historically, this type of research started in North Europe and in Lund in Sweden, and also there's a lot of interest in Oxford in the UK, and they're starting a trial called StampED, which is using basically this floor plate cells, the new generation of cells not taken from embryos.

They've done that before, and now they're moving on the same type of approach used by big companies like Blue Rock or Aspen or even the team in Kyoto in Japan. There's also a research effort in Australia, so for sure, there's a lot going

on worldwide. But I will say that US is obviously very interested in this type of approaches, and many, many opportunities are for American patients.

Karen Jaffe, MD: Is there a difference between patients who have a genetic predisposition to Parkinson's disease, how they respond to these treatments versus somebody who doesn't have a genetic cause?

Mark Cookson, PhD: I don't think there's any data on that. To my knowledge, most of the trials have been aimed at people without a strong family history. There certainly aren't the numbers to be able to make a definitive statement.

Alfonso Fasano, MD, PhD, FAAN: But this is certainly a concern for autologous transplants because if you take your own cells and you inject them in your brain, obviously, this won't require any medication for suppression, which is great.

But in theory, if the Parkinson's cause is genetic and it's primarily genetic, we should not forget the role of environment, then in theory, these cells can trigger the same processes that led to degeneration in the first place. However, as we heard from Mark, nowadays, we have technologies that are already using animal studies to edit the DNA.

So in the future, maybe even when you have a genetic form of Parkinson's, you can take those cells from the skin, let's say, edit the DNA, make them cells like totipotent cells and then implant them in the brain. For a clinician, it's just science fiction. But Mark, you probably see this every day in your animal models.

Mark Cookson, PhD: We do edit those cells.

Gaia Skibinksi, PhD: I know we're coming up on time. We've only got two minutes left. I just want to jump in and just say, wrap up and say what I'm excited about. We've got the clinical trials that are ongoing right now, so we will all watchfully wait for the outcome of those trials, and hopefully, they'll show benefits to the PD patients, so improving the symptoms.

And then behind that, there's many other additional stem cells therapy approaches that are coming into clinical trials. And then right behind that, we've got people like Mark doing all of the research around understanding the mechanism of the disease and screening for new drugs that could then move into the clinic. So it's a really exciting time for all of us as we watch a progress from the stem cells field with Parkinson's disease.

Karen Jaffe, MD: And a really exciting time for those of us with Parkinson's disease. So I'd like to thank you all for joining us. Gaia, Mark, Alfonso, it's been a real pleasure. I've learned a lot myself, and I hope that our audience has as well.

Good luck, and hopefully we'll hear from you that you've been seeing positive results on your end as well. We appreciate all the work that you do, and we look forward to hearing from you.

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