National Multiple Sclerosis Society

Webcast Transcript

Promising MS Research to Repair, Protect and Restore the Nervous System

December 5, 2013

WEBCAST MODERATOR: Kate Milliken

PANELISTS

Dr. Ben Barres, Professor and Chair of Neurobiology, Stanford University School of Medicine

Dr. Jonah Chan, Associate Professor of Neurology at UCSF who is the winner of the 1st international Barancik Prize for innovation and progress in MS

Dr. Timothy Coetzee, Chief Advocacy, Services and Research Officer of the National MS Society

Dr. Rhonda Voskuhl, Professor of Neurology and Director of the MS Program at UCLA

PRESENTATION

Kate Milliken: Hello and thank you for joining the National MS Society's live webcast, Promising MS Research to Repair, Protect and Restore the Nervous System. I'm Kate Milliken, your moderator, and I have been living with MS since 2006.

MS is complex and that necessitates a holistic approach to speed research and to create a comprehensive strategy for better knowledge, treatments, healthcare policies and new disease management therapies. The National MS Society is the driving force of MS Research to stop disease progression, restore function and end MS forever.

The Society supports and funds research activities in all stages of development, including early discovery research, translational research that brings promising ideas forward and clinical trials. This unique approach leaves no opportunity wasted in moving towards a world free of MS.

Today we will focus on progress and next steps in repairing, protecting and restoring function to people living with MS, and will answer the questions you have on this topic. Questions like, "Can my brain be rewired?" And, "How close are we to having therapies that might repair myelin damage in the nervous system?"

Throughout our live webcast, our panelists will address questions received, both in advance from participants and those received in real time during the live webcast itself. Check your webcast screen now on details for submitting questions during the panel discussions. We'll cover as many questions as we can. Let's get started.

I'm pleased to be joined by four panelists who recognize the importance of this research. Let me introduce them.

First, we have Dr. Ben Barres. Dr. Barres is the Professor and Chair of Neurobiology at Stanford University School of Medicine and a member of the National Academy of Sciences. Dr. Barres' leading research projects that try to better understand factors that control the growth and the repair of myelin, which may open new avenues for stimulating repair in MS to restore function. Glad to have you here, Ben.

Dr. Barres: Thank you

Kate Milliken: We have Dr. Jonah Chan. Dr. Chan is an Associate Professor, the Debby and Andy Radcliff Endowed Chair in Neurology and a neuroscientist at the University of California-San Francisco. He is the winner of the first annual Barancik Prize for innovation in MS Research for his work on brain repair in MS.

Jonah, thanks for being here.

Dr. Chan: Pleased to be here.

Kate Milliken: In addition, we have Dr. Timothy Coetzee. Dr. Coetzee is the Chief Advocacy Services and Research Officer of the National MS Society. And he oversees mission delivery efforts. Dr. Coetzee leads the Society's global investment in MS research. He is responsible for a diverse portfolio of research initiatives and recently spearheaded an effort to establish a global collaboration focused on research in progressive MS. Tim, nice to have you back.

Dr. Coetzee: Pleased to be with you, Kate.

Kate Milliken: Finally, we have Dr. Rhonda Voskuhl. Dr. Voskuhl is the Jack H. Skirball chair in MS research, the Director of the MS Program and Professor of Neurology at the David Geffen School of Medicine at the University of California in Los Angeles. Dr. Voskuhl is a leader in study in gender differences in MS. She is conducting clinical trials to see whether the sex hormone estriol can reduce disease activity in women with MS.

Rhonda, it's great to have you here.

Dr. Voskuhl: Thank you.

Kate Milliken: So here we go. Let's begin with you, Ben. You have a laboratory doing lots of different types of research projects dealing with repairing myelin. So give me the framework of what you're up to.

Dr. Barres: Sure. Well, as you know, Kate, myelin is the fatty insulation that sheaths axons. Myelin is made by oligodendrocytes. In thinking about the types of cells in the brain, it's important to remember there are three main classes of cells in the brain. There are neurons and then there's the so-called non-neuronal or glial cell types called the astrocytes, and oligodendrocytes.

The oligodendrocytes are making the myelin insulation around the axons, which is critical for the electrical signals for the neurons to propagate down the axon from one neuron to the next in the circuit and then there's the astrocytes. That's the other major class of cells in the brain and many people know less about the astrocytes. They're very mysterious cells. But just like the oligodendrocytes sheath axons to make myelin, the astrocytes sheath the synapses and they support the synaptic connections.

My lab has actually shown that the astrocytes play very active roles in controlling the synapses. Astrocytes actually secrete signals that stimulate the formation and the function, and even the elimination of synapses. My lab is focusing on understanding the functions of the astrocytes.

In particular, in relevance to today's discussion, the oligodendrocytes, we're trying to understand exactly how the oligodendrocytes lay down their myelin sheaths.

Kate Milliken: Jonah, with what you're doing, how does that tie in to what Ben is up to?

Dr. Chan: So my lab has been interested specifically in oligodendrocytes biology, understanding how these oligodendrocytes make the myelin, both during development and after demyelization, such as in MS.

So we're interested in understanding how these cells do what they do and understanding the environment that they're in and how this environment can influence their behavior.

Kate Milliken: OK. Rhonda, for you, one of your focuses is on neural protection. What does this mean?

Dr. Voskuhl: We've actually focused on clinical observations to drive our science and that would include examples such as pregnancy is good for MS, that men are less likely to get MS. We've focused on sex hormones primarily to ask whether treatments with those could potentially affect oligodendrocytes or astrocytes to cause repair.

So far we've completed a couple of clinical trials, have a couple ongoing, and another one planned.

Kate Milliken: So, Tim, with all of this research in the different kinds of domains, how does this fit in with the MS Society's research landscape?

Dr. Coetzee: That's a great question. When the Society funds research -- we have a big portfolio and it starts with amazing scientists like the three we have with us today who are all in for solving MS.

We have a portfolio that has really three big buckets. We want to fund research to stop disease progression, to restore function and end the disease forever.

Nervous system repair and nervous system protection research fits into that second bucket of what are the strategies we need to rebuild the brain so that we can restore what's been lost and to really help people live their best lives.

Kate Milliken: Ben, what do we know about why nerves are damaged?

Dr. Barres: This is a very good question. As you know, Kate, MS often has two phases of the disease process. There's the early presenting stage where patients often experience demyelization and relapses and remissions. But then after MS patients have had the disease for perhaps 10 or 20 years, it sometimes enters what's known as a chronic progressive phase where there is a so-called neurodegenerative process that sets in.

Now, we're not talking about loss of myelin anymore, but we're talking about loss or so-called degeneration of the axons, as well as their synaptic connections. This is a more recently recognized process that's going on in MS brains that these synaptic connections and the synapses, by the way, are these points of contact between neurons where an axon communicates the electrical signal -- or relays the electrical signal -- from one neuron to the next neuron. If that synapse is lost or eliminated, then the electrical impulse cannot be relayed and the circuit stops functioning. It's very important to recognize in this neurodegenerative phase that synapses are being lost as well as axons.

So, as we think about new therapies, there are many targets for thinking about not only promoting myelin restoration but protecting the axons and getting axons to regenerate and repairing synapses.

Kate Milliken: Which explains exactly why you're doing so many things in your lab?

Jonah, are their clinical trials happening for myelin regeneration and repair?

Dr. Chan: Yes. I know two clinical trials that are ongoing right now. One is a Phase I trial for safety and the other is a Phase II trial for seeking efficacy. These are both antibody therapeutics for remyelination.

In fact, there is one other one that is our trial. We're doing a trial on a compound that we identified. It's an FDA approved drug already. It crosses the blood-brain barrier very efficiently. It has an excellent safety profile and so we decided to move forward with the clinical trial with this particular compound.

Kate Milliken: Tim, is there anything you want to add to that?

Dr. Coetzee: So I think what's amazing is you see the connection between some of the basic science of understanding how the brain works to really moving on to how we can make this relevant to people. And so what you see with what Jonah and Ben are talking about is how do we recreate and rebuild the brain. It's really touching back on Ben's work. You know this idea of connections and creating connections between nerve cells. That's really so important for us every day in terms of how we live and think. This loss of connection sometimes can -- in people with MS causes cognitive dysfunction. We hear from people a lot that it's a big, big challenge. And I wonder, Rhonda, as a clinician whether you see this in the clinic.

Dr. Voskuhl: Absolutely. I think this is definitely an unmet need in MS currently. The treatments are anti-inflammatory, but none of them really target the cognitive dysfunction aspect. Up to 65% of MS patients will have cognitive dysfunction.

It's very different than Alzheimer's. It looks nothing like that. But the patients know that they're not processing things as quickly and it does impact their work and their social situations.

And to that end, I think synapses are going to be an extremely important area. We've shown that estrogens and testosterone can actually re-establish some of these synapses that are lost in the MS model. And we're very hopeful in trials to have cognitive outcome measures which we currently are using. So, again, identify a drug that can re-establish synapses and also improve cognitive function.

Kate Milliken: And what's especially exciting about that is currently there are no therapies that are specifically handling cognitive issues. So tell me a little bit more about your work and how that's helping?

Dr. Voskuhl: You know, again, we start with clinical observations. It's been known for quite a while that women who lose estrogen through menopause or through hysterectomies and ovariectomies, they may have cognitive problems; but then when they replaced the estrogen, improvement is seen. It's been shown in the animal models, as well, that estrogen deficiency is bad for cognition. In men as well, testosterone replacement has been used to improve cognitive function.

So, again, focusing on the clinical aspect, we went to the animal system -- the mouse model of MS and we showed that we could improve cognitive function in these animals with MS -- the model of it. We improved their cognitive function. Now we have clinical trials that are ongoing and the primary outcome is cognitive testing. We're using these hormones that, again, have been shown to be extremely safe and they'll hopefully even be less expensive than the current therapies.

Kate Milliken: And we know that there are gender differences between men and women. How is that going to affect progress in the lab?

Dr. Voskuhl: I think that the treatments can be tailored for each gender. For example, you may end up at the same place in the end since testosterone is converted into estrogen in the brain and estrogen is known to be neuro-protective.

But when you go to treat people, you need to think about side effects. I think tailoring, again, estrogen for women -- because they will have good, beneficial effects from estrogen outside of their MS -- and also testosterone for men as a way to tailor the side effects so there are beneficial effects coming from these and you're still getting that therapeutic efficacy with neuro protection as it relates to synapses and remyelination.

Kate Milliken: Tim, obviously, we're hitting it from all sides here. What are some other things that are happening in this field that are exciting you?

Dr. Coetzee: Sure. This is amazing research; I think we see all these connections we made. I think another really fast-moving area in nerve repair, restoration and remyelination is stem cell research, really two kinds of stem cell strategies.

There's the kind where we try to use some sort of treatment or therapy to stimulate the stem cells we all carry around in our brains that are there to actually naturally repair the brain that don't always work properly in MS. We're really trying to figure out how we can take advantage of what we all have.

The other part is actually thinking about using things such as bone marrow stem cells and specialized kinds of stem cells to really reintroduce them into the brain to really rebuild and recreate what's happening in the nervous system.

Ten years ago I don't think we would have imagined we'd be at a place where there'd be actually stem cell trials happening. There are now trials being used to, first, look at the safety but next will probably be the effectiveness of these stem cell strategies in MS, which is another really important option as we think about restoring what's been lost.

Kate Milliken: People living with MS probably appreciate the fact that now the step cell option is going through these clinical trials. But I think there are people that are thinking that they're going to leave the country to try to make it go faster. Rhonda, what's your response to that?

Dr. Voskuhl: I actually don't think it's a good idea to leave the country to do stem cell therapies. The reason is because I think we have trials ongoing in the United States that are FDA regulated and the FDA is on our side. They are doing a very good job at not promising things that may not be achievable by testing very rigorously whether they are efficacious and weighing that efficacy with the risks and the safety issues that could go with them.

I think the safe way to do it is to look at the MS Society's website or clinicaltrials.gov and see the list of clinical trials that are ongoing that the FDA is overseeing and regulating and then you'll be safe. That's what I would do. I would stay in the United States and do a trial that's FDA regulated.

Dr. Coetzee: If I could add to that, I think if someone is going to travel, I'd say make sure you understand, talk to your doctor here. Try to understand where you're going because, obviously, it's important to talk to your healthcare provider and the people that are important in your life, to sort of understand what you're doing and really weigh all of that.

Rhonda made some really important points. But if people are going to travel, it's really to think about the implications of what you need to look at when you come home.

Kate Milliken: Ben, so one of the things you're doing in your lab is you are trying to look into regenerating nerve cells. What is the thing you're most excited about what's happening on that front?

Dr. Barres: Well, regeneration and repair in the brain involves not only regeneration of myelin but regeneration of axons and regeneration of synapses. They're all separate processes that are under differential control.

So one of the things I'm very excited about is that, as I mentioned before, there's been recent attention to the so-called gray matter degeneration in multiple sclerosis. This includes loss of synaptic connections, as I mentioned before. My lab has identified a pathway called the complement cascade. It's actually a well-described immune system pathway but people didn't really realize it was operating in the brain.

We found that this pathway is actually operating to destroy the excess synapses that are normally generated in the developing brain. Interestingly, the pathway turns off but in the setting of adult brain in neurodegenerative diseases, such as Alzheimer's disease and multiple sclerosis, the pathway turns on aberrantly seeking synapses once again and this leads to their destruction.

What happens is the complement cascade proteins gather on the synapses and then a nearby class of glial cells called microglia -- these are immune cells -- actually, literally eat the complement-coated synapse and remove it and destroy it.

I'm very excited about this because it represents an example of a drug target -- a defined drug target that we can develop a new therapy. I've actually started a start-up company that's made an inhibitor to complement cascade to completely block this process. So I'm very excited because if we can block the neurodegeneration process and the loss of the synapse, my hope is that we would have a therapy that would prevent the conversion from the relapsing-remitting phase of the disease into the chronic progressive phase of the disease. And more importantly, allow the brain to start to repair and rebuild the lost synapses. My hope is that will allow patients to rebuild some of their lost functions.

Kate Milliken: I think it's really important to put into context, too, that at one point some years ago the gray matter seemed passive. Right? So I feel like people need to know the kind of progressive steps and grab -- like you've grabbed onto something that's taking you further.

Jonah, for you, I know some of the stuff you're doing -- especially the recent prize work -- is translational research. Can you explain what that is?

Dr. Chan: Yes. Transitional research is when we take our basic understanding of the mechanisms involved in, let's say, biology and apply it to the disease itself, to patients.

This particular project in my lab actually started from a conversation, or more like a challenge from Stephen Hauser -- Dr. Stephen Hauser at UCSF. Basically, what he wanted to do was examine existing therapies that are already there, FDA approved drugs, ways in which we can kind of piggy back off those findings already. Then begin to look to see if they have potential for repairing or remyelinating the nervous system.

To do that, though, the greatest limitation or the major hurdle that we had to overcome was screening these compounds. There are numerous libraries of these therapies out there, but we're talking about hundreds of thousands of compounds, so to really begin to screen all of these compounds, we needed to develop a platform.

So that's what we've done, we've engineered a technology platform, a platform where we can actually screen for memory wrapping that's associated with myelination. So that's allowed us to begin to screen compounds.

Kate Milliken: Well, Dr. Hauser sounds awesome because on some level it's really nice to hear the whole idea of having gone through millions of dollars and all that time to see how you could kind of speed it up.

Dr. Chan: You know, I think it's really about the basic scientists and the clinicians working together if we're really going to do translational research.

Dr. Coetzee: You know, I think one of the things that, between Ben and Jonah, you're seeing that – imagine, we're having this conversation about how precise Ben is being. So we're not shooting in the dark here. He's like here's

the target. Here's where we're going. Jonah created this platform -- invented this platform that really lets us now think about these targets in a really incredibly precise way so that we're not just really taking pot shots, but being very targeted about what we do.

Kate Milliken: What are some other initiatives, Tim, that the MS Society is doing in this domain?

Dr. Coetzee: Sure, so we do a lot at the Society. We have a lot of different kinds of funding programs. We're investing in talent because you really need people in order to do the science. So we're investing in training the next generation of scientists, bringing them forward, and really increasing the number of young scientists that are committed to doing this kind of research.

We're creating international collaborations. We're working through the Progressive MS Alliance, which is an international effort of bringing MS Societies and actual researchers from around the world together saying we need to tackle progressive MS -- and neurodegeneration is probably an important part of progression. The idea is that we can't all work in our national silos. We all actually have to work together globally. And so we're spearheading an effort around that.

The other thing we're doing is really ramping up our investment. This year we're going to spend $50 million on research and a lot of that is going towards this area of nerve repair and regeneration. What we're seeing is a shift not just studying through the basic biology of how the brain works but taking it one step further. Like, we're hearing, "We got to figure out the biology." But to make it relevant to the person who lives with MS, it has to go somewhere.

Kate Milliken: So I'd say, as someone living with MS, one of the things that's very exciting is the whole idea of regeneration and repairing myelin. You go in for an MRI. You see you have a lesion and you think -- it's the one way that you're diagnosed.

And I speak from my personal experience. I had a lesion that lessened or began to reverse. So, Rhonda, what does it mean when a lesion actually changes on an MRI?

Dr. Voskuhl: Well, first of all, one needs to realize that there are different types of lesions on an MRI. The MRI's are not as specific as some of the basic

cellular biology that we've heard about. Sometimes lesions will be merely water, which is reflecting swelling or edema around this inflammatory lesion.

Other lesions -- well, actually, they're called very dark holes where, basically, we think some of the tissue has been lost. Generally, it's thought some of those that are more reflective of subtle edema or inflammation that those can actually get better and they can go away, which is extremely promising.

On the other hand, some of those that are very dark and more destructive where the tissue's been lost, they may be less amenable to repair.

And so this brings home the point that I think all of these reparative strategies -- neuro protective strategies -- while we think of them as later in the disease, I actually believe they're going to have to be given very early in the disease because there will be a critical window for the patient and also for the lesion. Some of the lesions will be in their early stages and they're more likely to be reversible, as opposed to some of the lesions that are in the later stages and are more destructive.

Kate Milliken: So there is a difference?

Dr. Voskuhl: There is a difference in the lesions and some may very well be reversible but they're likely in the earlier stages of their evolution.

Kate Milliken: Jonah, what are some other impediments that deal with myelin repair?

Dr. Chan: That's very interesting that you bring that up. Examining lesions itself, right now is limited. So the major impediment right now is imaging myelin in a quantitative way and that can't be done.

Right now all the imaging techniques that exist are indirect measurements of myelin or water. And so to do a clinical trial -- a real trial for repair and remyelination -- we're going to need ways in which we can really image myelin.

Kate Milliken: So define what indirect means.

Dr. Chan: So like Rhonda was just saying, imaging the water around in a specific environment and the directionality of the water is a way where you can

see, let's say, approximately how much myelin is there. But it really doesn't tell you small changes and the amount of myelin that is present.

Kate Milliken: Right. You're not measuring it specifically.

Dr. Chan: No. So you can imagine how difficult it would be to do a trial in remyelination if you can't image the myelin that's being formed. But I do know there are terrific groups out there who are working on this and I think it is just a matter of time.

Dr. Voskuhl: And something to add -- I think there's been a lot of progress -- tremendous progress -- that has been made on what Ben was talking about -- the focus on gray matter. The imaging world has really taken this up and they've focused a lot on gray matter atrophy, tissue loss in the gray matter as a biomarker for this permanent disability or progression accumulation. And that's in contrast to these white matter lesions that come and go and they are really a reflection of relapses.

What Ben said is correct and that is that focusing on this gray matter degeneration may be where the money is for preventing this chronic progressive permanent disability accumulation.

Dr. Coetzee: I think one piece to add to that is the imaging technology is really moving incredibly fast. Where we are today compared to five years ago is amazing. I think that the other piece that the research community and doctors like Rhonda are doing is thinking about how we're going to measure how repair makes a difference in the life of a person with MS. Because, really, at the end of the day, the person with MS is going to be like, "It's great that you can see that my myelin is back there but I still feel pretty bad."

Kate Milliken: Right.

Dr. Coetzee: And so we're trying to bring the community together to see how do we measure that when people actually get better, that they feel better? That's really an important next hurdle in this because we need both pieces because it won't matter much if we can rebuild the brain and people don't feel better. We've got to be able to figure out how to measure that.

Kate Milliken: Ben, I'm going to pose this question to you. From your perspective -- when I come to tables like this with scientists, it seems like

progress is being made really fast or that there are things that are really happening. Why do you think that is?

Dr. Barres: Yes. This is an amazing time to be doing research. The new methodologies that are available to neuroscientists today compared with 20, or even just 10 years ago, are simply mind-boggling.

The average young scientist -- and let's face it, the young scientists are the ones that are doing the work in our labs -- they can actually come into a lab and within a few years they can start by addressing some important unsolved questions in neurobiology. How does myelination happen? How are astrocytes talking to oligodendrocytes? Things like that.

The average student can, within a few years of a Ph.D. thesis or post-doctoral fellowship, make a definite mechanistic or conceptual step forward. This is a sea change from even 10 years ago.

This is all because the methodologies that are available -- the rate of progress is incredible. New therapies in MS rest on a strong basic science foundation. We need to really understand how myelination happens, how myelination is controlled by neurons and by astrocytes, what the mechanism of wrapping is and so forth. As these molecular mechanisms unfold, new therapies will also unfold.

Kate Milliken: So at this point, can the brain rewire itself?

Dr. Barres: Well, actually, just in the last year there's been some really remarkable progress on this. You know, it's been known for a long time that the brain is remarkably plastic. But now with these new imaging technologies, for example, scientists are actually able to do this kind of experiment where, for example, they'll make an injury in a retinal tissue or a spinal cord tissue and then they can actually image the reformation of new neural circuits that not only are existent as new neural circuits but actually repair and restore function.

So we know that there's a tremendous ability of the brain to repair itself and what we need to do now is to figure out more how this works so we can tap into it and make that plasticity and that repair even stronger.

Kate Milliken: Rhonda on the subject of brains and cognition, is there any evidence for anything complementary, such as diet or supplements that you think would help with this making the brain better?

Dr. Voskuhl: You know, I already mentioned the hormone therapies, which I think are clearly a priority because loss of some of these hormones with aging can definitely have an effect on cognitive function.

There is evidence that exercise can be good for cognitive function and through very complex molecular mechanisms -- that I don't want to get into now but there are things like that that can be good.

With respect to diet, I would make sure that I have enough vitamin D in my diet or else vitamin supplements because there is evidence that vitamin D can be a good thing in MS. I would not, however, go so far as to say that one should limit their diet, take away certain foods that have not necessarily been proven in trials to be bad for MS.

I mean, as an example, 30 years ago they told women not to get pregnant; it would be bad for them. Now we know from the beautiful studies that have come from France that pregnancy is actually a very protective time for MS.

Again, I'm a little reluctant to take away things unless they've really been proven. So my view on diet is to have a well-balanced diet, make sure your vitamin D level is within the normal range but don't take away things unnecessarily from MS patients.

Kate Milliken: Is there vitamin D in chocolate cake? <laughter>

Dr. Voskuhl: Sounds great! <laughter>

Kate Milliken: I'm at the table, obviously, with three very active scientists. I'm sure the viewers who are watching this webcast want to know how can I get involved. Can I be part of any of these clinical trials? Thoughts?

Dr. Coetzee: So the easy way for people to find out if there's a trial happening in their area is to visit our website at the nationalmssociety.org. We list clinical trials in MS that are active. We can also go to clinicaltrials.gov, which lists all the clinical trials that are registered and recruiting.

The important thing is to look. Is there one in your area? Do you have the type of MS that they're recruiting for? Are you a candidate for it? Not everybody is the right candidate for a clinical trial but there are a lot of trials that are recruiting. Jonah is. I know Rhonda is recruiting.

The important thing is to really understand what you're getting into, but also to participate because so many of these therapies really only get developed because people with MS decide, "I want to participate in this to try to make a difference". It's a really important role that people with MS can play in making sure that we can develop the therapies we need.

Kate Milliken: I'm going to ask a dangerous question to Jonah. From your perspective or what you're seeing, can the effects of MS be reversed? I know scientists don't like questions like that.

Dr. Chan: Well, I think we all hope -- we all hope that we can restore function that's been lost. But we don't know that. We can't say for certain that we will restore all function.

I do know that there are clinical trials ongoing. So I think what we need to do is learn more about the repair and remyelination process in MS. We know very little about it. I think this is the first step. The first step is to do the clinical trial and then we're going to get so much more information that will come back to the bench and then go back to the bedside.

Kate Milliken: Anyone else?

Dr. Coetzee: Well, I'm going to go a little bit out on a limb. I do think that we are seeing, the research is telling us, that I think there is potential to restore what has been lost. There are still a lot of unknowns. But I think the fact that we're even asking the question -- can we restore what's been lost -- if you think about that, 20 years ago people weren't really asking if you could or you couldn't. We were much more skeptical. I think, today, the idea that you'd have stem cells, that you'd have immune therapies, that you could have a cocktail of therapies along with things like diet, exercise and rehab. You know, we're in a different place. We're really writing a different future for people who live with MS.

And so I think -- I am pretty optimistic. They're being conservative, but I'll go a little bit more out on a limb.

Dr. Voskuhl: I'm also somewhat optimistic. If you look at the history of MS and what happened. I mean, the immunologists really attacked this disease as an autoimmune disease. They jumped on it. They figured out the immune mechanisms. And then we do have a lot of very good anti-inflammatory treatments and they reduce relapses dramatically.

Now, we're seeing all the neuroscientists really jump on this issue and trying to find a neuro protective treatment. The clinicians are trying to find a different way to do trials where relapses are not their primary outcome, but a different clinical outcome is going to be the primary. The imaging people are looking at different things for neuro protection.

I think with all this focus now on neuro protection, we will come through, just like the immunologists did with the anti-inflammatories.

Dr. Barres: There's really one amazing example of this just in the last year. There have been incredible advances in our understanding of how to get axons to regenerate after they've been severed.

In animal models, for example, if you cut the optic nerve axons, they never regenerate. However, there's a new therapy that's been discovered -- a new way of treating these animals, which actually stimulates a very robust repair and regeneration of these axons. What's amazing is not only do they grow all the way back down to the optic nerve, but they keep growing into the brain, into their normal visual centers in the brain and they make their specific and appropriate, correct neural connections.

People are now studying whether this restores function. The expectation is that it probably will because this regeneration is so faithful to the way it would have happened during normal development.

I think that this is an incredible landmark advance in repairing our brains. I think it shows you the rate of progress that's happening now.

Dr. Coetzee: I think, just hearing Jonah's example of the clinical trail he's doing, is really a great example of how, really, things have just changed.

In, what, less than a year, you went from inventing a platform technology to doing a screen to now enrolling your first patients. Twenty years ago we would

have sort of fumbled around because we didn't understand the disease as well. We really didn't have the outcome measures but now you have one example of in less than 12 months we're out to doing trials. I think that's just going to keep revving up the cycle of getting more and more therapies built faster.

Kate Milliken: Jonah, I'll just throw this question at you. When you are doing your studies, how are you thinking about the people living with MS in terms of relapsing and remitting and progressive?

Dr. Chan: Yes. So when I think about people with MS and the whole process of repair and remyelination -- because this is what we study -- it's really about the axons. The axons and whether they're degenerating because we know that the underlying chronic disability in MS is the loss of these axons. It's this neurodegeneration that occurs.

So what we need to do is understand better how to keep these axons alive because remyelination therapies aren't going to work if the axons are not there.

More and more research has been showing that remyelination itself may be a means to prevent progression and neurodegeneration because they're intimately associated with each other it seems like.

Kate Milliken: Wow.

Dr. Chan: Yes.

Kate Milliken: Ben or Rhonda, anything to add? I know you guys have both kind of touched in on the difference of progressive and relapsing-remitting.

Dr. Voskuhl: Yes. They are clinically different but I don't know if it's -- they are linked to inflammation but then it's almost like the neurodegenerative process takes on a life of its own.

The surprising thing is that the gray matter, actually -- as we talked about -- as a marker for this progression, it actually occurs relatively early. It's just that people have a lot of compensation that they can use to overcome these differences.

I think that in some ways splitting these so severely between relapsing-remitting and secondary progressive may be an element of the old way of

looking at the inflammation, which is clearly dramatic in the initial relapsing-remitting group and not -- it basically wanes and goes away in the secondary progressive late group.

I'm not so sure this neurodegenerative process isn't going on all along as a substrate in the background and that these neuro protective treatments shouldn't necessarily -- and I actually do think they should be used in all groups -- relapsing-remitting, secondary progressive and primary progressive.

I think it's happening. Again, it's a different way of thinking things. It's a different way of thinking about trials, a different way of thinking about the sub-groups when you start talking about the neuro protective or neurodegenerative aspect.

Dr. Barres: I think an important point that I would extend that into is that once you realize that these are lifelong processes, that the brain is constantly adapting and overcoming some of the difficulties imposed on it by the disease process. One realizes that actually to develop a drug, you really don't have to do that much because this is a lifelong process. All you need to do is tip the balance a little bit in favor of the repair side and you might have an enormous benefit.

Dr. Coetzee: I think that's what's important. You think about this conversation, you know, five years ago we were -- a lot of the folks in relapsing-remitting MS, primary progressive and secondary progressive -- still don't have any treatment options. But we're talking about new therapies that targets all aspects of the disease, so whether it's secondary progressive, primary progressive, relapsing-remitting, really addressing the whole spectrum. There are trials now going on of therapies in progressive MS so that people who live with progressive forms of the disease will have -- can look forward to the same kind of future that people with relapsing-remitting MS have today.

Kate Milliken: Right. Or at the very least, get benefits that come from the research that's being done today, even if it's not whole.

Dr. Coetzee: Absolutely.

Kate Milliken: Tim, I have recently read an article that epsilon toxin actually destroying cells on myelin, preventing it from re-upping your myelin. What's the story?

Dr. Coetzee: What's the story? That's a great and interesting story. So epsilon toxin is something that's made by a bacteria called Clostridium perfringens.

Kate Milliken: Oh, boy.

Dr. Coetzee: Yes, I know. Sorry I had to nerd out on you for a second, Kate. <laughter> So it's a spore forming bacteria. The thing is, most of us aren't exposed to it but there was a researcher, Dr. Vartanian at Cornell discovered a person with MS had a flair-up and they kind of discovered that this person had this bacteria.

What they learned was that the Clostridium puts out a molecule, a toxin and it's a defense mechanism that the bacteria uses to protect itself but you put it in a human being, that's kind of a bad thing. It turns out that that goes to the brain and really causes some -- it latches onto the myelin, actually, for reasons that we don't quite know and really triggered some damage.

What they're doing now is -- of course this is one case, it's in a human being, a person that lives with MS but they studied it and they published it. Now they're looking at ways to figure out is this something that we see in other people and could that give us a clue as a potential trigger for the disease.

It's a connection how Mother Nature can really surprise you sometimes and also smart doctors looking and understanding, "Well, this is different. What I'm seeing with this person with MS, maybe there's some clues in here." And that's why you always have to really keep yourself curious about what's happening --

Kate Milliken: An environmental factor.

Dr. Coetzee: -- in the environment.

Kate Milliken: Right. Rhonda, specifically in your study, is it possible for a woman to take a birth control pill or a hormone replacement therapy and have a positive effect with the MS?

Dr. Voskuhl: I don't think MS is an easy disease. And I think by now, if birth control pills had had a major dramatic effect on ameliorating this disease we

would know it by now. Indeed, retrospective epidemiologic studies have shown that birth control pills don't.

The reason for that is because birth control pills are a very mixed bag that contain estrogen and different kinds of estrogen and progesterone. Some women take it three weeks and not in other weeks. Some take progesterone only, they don't take estrogen at all. These have generally all been lumped together -- oh, by the way, there's also high dose and low dose. We all know about that -- estrogen and birth control pills.

My view has been that I personally don't believe that oral contraceptives have a major influence and what we base our estrogen study on isn't that. We've based it on 'pregnancy?' Pregnancy has a novel estrogen called estriol that's made by the fetal placental unit. It's safer than the other estrogens that we know and love, or that we don't know and love that affect breast and uterus. Estriol is much safer and it is, again, the pregnancy estrogen. On top of that, we are giving a dose that is physiologically like pregnancy, which is a much higher dose than you would see occurring in the natural menstrual cycling level.

And so I think, again -- my view is to base things very much on Mother Nature. Mother Nature is very smart and during pregnancy there's a reason why you don't want to have a rejection of that foreign baby that you're carrying -- it's got half the father's proteins on it -- to be rejected. There's a reason why you might not want the baby to have myelin damage or neurological damage in the case of an injury. It makes sense that pregnancy might be a case where you have anti-inflammatory effects or you have neuro protective effects. It's all for the good of the baby but the point is that the mother with MS benefits.

I've tried to stick very closely to the pregnancy estrogen and the pregnancy dose and not take any liberties, to try to reflect what Mother Nature is doing naturally, to see if it works in a trial. And so far, the first trial was very promising. The second will end in January and a third one will end a year after that.

Kate Milliken: Let's stay specific. Something else that's come up -- anti-LINGO. Can you describe what it is and what's going on with the clinical trials?

Dr. Coetzee: Sure. So anti-LINGO is a therapy being developed by Biogen Idec. It's an antibody therapy and the idea there is to try to sort of clear out some of the damage that is preventing myelin-making cells from wrapping around axons. There's been a lot of the basic science. It's cleared through some of the human trials and now it's moving into Phase II to really show -- I think maybe even approaching Phase III, eventually.

They're in Phase II studies trying to understand does the therapy actually have a beneficial effect, at least by imaging and some of the technology. The idea is if it shows that it works in the Phase II trial then, obviously, the next step is Phase III, which would bring us to the first, if it were successful, FDA approved therapy for myelin regeneration, which would be a big step forward in MS.

Kate Milliken: Ben, just so people understand -- why does the body lose its ability to make myelin?

Dr. Barres: Oh, that's such a great question, Kate. This is really the $64 million question because we know that oligodendrocyte precursor cells are right there in, for example, a demyelinating plaque and sometimes they're even touching the axon. So why aren't they remyelinating it?

I can just give you a flavor for some of the ideas for which there is some evidence but we haven't actually sorted out exactly which one of these is correct.

For one thing, when you have a demyelinating lesion, the glial cells undergo a response called gliosis. They start to make some molecules -- inhibitory molecules -- that some people believe -- and there's evidence that suggest -- that those inhibitory molecules signal to the oligodendrocytes precursors and say 'inhibit their ability to myelinate.'

So that's one possibility, that inhibitors become -- and another class of inhibitors, as it turns out, that the degenerating myelin itself is strongly inhibitory to remyelination. There's a big mystery in the brain so when the peripheral nervous system is injured, the myelin debris is very quickly cleared away. The debris is cleared away so it's not there to inhibit remyelination and for that matter, those inhibitors also inhibit axon growth.

But in the CNS -- in the brain and in the spinal cord, when you have an injury, oftentimes the myelin debris is not efficiently cleared or even completely cleared. It may stay there for a long time afterwards and inhibit the oligodendrocytes precursor cells from remyelinating.

Another idea -- and this is the last one I'll throw out because I don't want to talk all day about this -

Kate Milliken: But you'd like to, right -- <laughter>

Dr. Barres: You read my mind. <laughter> But the other very interesting idea -- and evidence is emerging for this -- is that, actually, electrical activity itself -- so the electrical impulses generated in axons actually send a signal to the oligodendrocytes precursor cells to tell them to start to divide and to myelinate. And so the problem is if you lose your myelin, at some point when you lose enough myelin, the axons no longer can conduct because that myelin insulation is critical for normal electrical conduction.

So what happens if you lose so much myelin the axon can no longer conduct well then that might inhibit the remyelination repair process if you need that activity to stimulate remyelination. These are some of the ideas that scientists are working really hard now to address because an answer will tell us, will guide new therapies.

Dr. Coetzee: I think an interesting aspect of what Ben's talking about is it's really sometimes helpful to think about the brain as having an environment and really, what you're trying to do is create a positive environment. The thing is MS kind of creates a negative environment. There are lots of poisons coming up, the immune cells are attacking the brain, the nerve cells start getting damaged. They create all this garbage that gets accumulated in the brain.

One of the things we need to do is really try to create a much more positive environment with some of the cells that are creating more beneficial molecules, there's always sort of a balance. We're really trying to overcome some of the negative things that are the result of MS.

Some of the work that Ben is talking about is what are the environmental factors that we need to sort of switch on and off to get the good things

happening and really start reducing some of the more negative things that are preventing the brain from repairing itself?

Dr. Barres: Another clue may come from the fact that if one looks at the normal development of our brains, when does myelination occur? It only occurs after axons reach their appropriate target and make synaptic connections with their target.

So one pathway -- actually, pathologists can actually date a human fetal brain by looking at which pathways have been myelinated because this is all orchestrated on a time course. So some pathways reach their target and they get myelinated. Other axons reach their targets later and then they get myelinated. The point is there's a target signal that's signaling back somehow to the oligodendrocytes to say 'myelinate now.'

The reason I mention this is because I mentioned there's increasing evidence for a gray matter component of MS where you're losing the synaptic connections. If you lose the synaptic connections or what's connecting an axon to the target -- and so losing that connection may be causing the remyelination problem because you may be disconnecting that target signal.

This is one of the reasons I'm so excited about the new drugs that we're trying to develop to block the synapse-loss process because my hope is that that would allow the lost synapses to be rebuilt to prevent further loss of synapses, and hopefully to stimulate that remyelination.

Kate Milliken: One thing that just came up that I think is worth clarifying -- maybe, Tim, we could start with you and everybody could talk about the whole idea of environmental factors. But there are two types of environmental factors, right? The environment -- the outside environment and what's happening within the body. So can you kind of break that down?

Dr. Coetzee: The breakdown of the environment factors a bit more? So I think within the brain we tend to think about what's going on inside the brain in terms of what it takes to repair, rebuild, and regenerate the nervous system.

Externally, there's also the environmental factors that are triggers for MS. Things like maybe you have low vitamin D. You take a certain genetic profile, add the low vitamin D, throw on a bacteria or a virus or two and that really starts to trigger on a cascade that we don't expect. Or some of this research

with the bacterial -- the epsilon toxin -- those are environment factors as well that really can affect whether or not a person develops MS.

When we think about environmental factors in MS, you need to think both about the triggers and about what the environmental factors in the body are that need to be managed in order to ensure that both the disease can be controlled and some of these barriers can be overcome.

Dr. Voskuhl: Yes. To further follow up on that, I think it's important for MS patients to realize that even though viruses and bacteria have been talked about quite a bit, it's understood that MS is not a contagious disease. And, actually, the impact of the environment on MS, susceptibility, for sure, is actually at the age of zero to 15. There are migration studies and there are global studies looking at areas on the globe where MS occurs more, basically, in North America or Canada there's a higher incidence of MS, around Mexico it's a lower incidence. And in some of these, even across genetic backgrounds, whereas some climates tend to have more MS. Some climates can have less MS.

This tends to be where you live when you were less than 15 years old and that may very well be how it shaped your immune system, how it shaped your nervous system during development. It's not necessarily something that you're encountering as an adult. It's not been proven that it's transmissible. So that's something patients shouldn't worry about.

Kate Milliken: Any of you guys want to add on this front? For me, obviously, you all got involved with MS because you were interested in the field and have been at it for a while. Has it gotten any less complicated?

Dr. Coetzee: Not all at once.

Dr. Chan: No. I think things are progressing rapidly.

Kate Milliken: In a good way.

Dr. Chan: In a good way. It's very exciting. We heard a little bit about the technology, the breakthroughs. We've talked a lot about the treatments available, about clinical trials. So it's really very exciting.

But science progresses in a certain way and so understanding the mechanisms, what these cells are doing. We were just talking about the environment. The brain itself is a very heterogeneous environment. And so we're talking about micro environments within the brain. The optic nerve is very different than another white matter, with the corpus callosum and then the cortex, the gray matter so it's very heterogeneous.

There is a complexity but with terrific people dedicating their time, committed to studying MS. I think we're making great progress.

Dr. Coetzee: I'd say yes, it's gotten more complicated. It's also gotten simpler in some respects. So certainly, we're hearing this conversation now. Twenty years ago when I started working in MS, we would not have imagined that we would be talking about remyelination, repair. We just had one therapy on the market. Now we have 10 therapies. We have symptomatic treatments. And so the place we are today there's just enormously more knowledge about MS.

Now, has it become more complicated? Sure. I mean, the idea of synaptic connections, gray matter that we didn't --

Kate Milliken: It looks like the more you know, the more things to think about.

Dr. Coetzee: Exactly. But when you think about it, think about where we started. We talked about synaptic connections and then linking that to what happens with cognitive challenges. So now what do we have? We have a target that says, okay, we're not casting about in the dark. We've a place we can go to safely rebuild connections. We can perhaps rebuild function in the brain. And we were not able to actually even think that that was possible even 10 years ago.

Kate Milliken: Awesome. Before we wrap up, I want to ask each of you -- and I'll start with you, Ben -- with your world, what are you most excited about on the horizon?

Dr. Barres: Well, it's hard to say, there's so many things. I'm very excited about the new insight that we're getting with all these powerful tools into understanding glial cells and understanding what they do. So I'm very excited about work that we're doing in our lab to actually elucidate the mechanisms by which oligodendrocytes are able to wrap their myelin sheaths.

I'm also excited about work we're doing in our lab where we're studying how astrocytes control synapse formation, synapse function and synapse elimination because I think that all of these advances are leading directly to new therapies for neurodegenerative diseases.

Kate Milliken: Jonah?

Dr. Chan: I think I'm most excited about the identification of real compounds that can be therapeutic for patients with MS for remyelination and repair. So I guess the hope is to improve the quality of life for MS patients. I think that's what I'm most excited about.

Kate Milliken: Okay. Rhonda?

Dr. Voskuhl: I'm excited about the neuroscience that has come to bear on this. I agree with Ben about this kind of tipping point about it's a downhill cycle where there's less synapses, there's less myelin, there's less conduction, therefore, there's less synapses, less myelin and less conduction.

If we can just take a multi-pronged approach to take the tipping point the other way where we have more synapses, we have more conduction, and we have more myelin. And it's all going to feed -- escalate up in a vicious -- in a pleasant cycle upwards instead of downwards. I think we're right at that point to know how we're ready to shift that balance at the neuroscientific level.

Kate Milliken: Tim.

Dr. Coetzee: Yes. I think when I look at the spectrum of what we're doing, in the first place I come back is talent. The number of people that are involved in MS research today is just amazing. There's thousands of scientists around the world that are all linking up together to study different aspects of the disease, whether it's on the early genetics, whether it's on understanding the environmental factors, whether it's stimulating myelin regeneration and repair.

So when I think about the future, I think the base -- the amount of information we're generating today about the disease is incredible. And now we have all those technologies. So the kind of technology that Jonah has invented; the kind of work that Rhonda has been doing taking therapies off the shelf, basically, and really repurposing them for MS.

When you think about that set of connections, it's just incredible.

Then when we look forward, you can think about now we're tackling progressive MS and not just relapsing MS, but the whole spectrum of research, including things like adding rehabilitation. You can imagine a future where you could have an individual living with MS who has a therapy to perhaps manage the immune system, protect the brain from damage and restore what's been lost and, oh by the way, let's talk about rehabilitative strategies and perhaps dietary strategies so you can live this incredible life.

It's really rewriting the future for people with MS. I think that's what we can be incredibly hopeful for. That's why we need incredible talents like we have at the table today to really lead that for us.

Kate Milliken: Wow. Well, it's been a total honor hearing about, especially, someone living with MS. So thank you.

I want to thank our panelists, Doctors Barres, Chan, Coetzee and Voskuhl for being here today and sharing their expertise with us. I also want to thank you, our viewers, for joining us.

If your question was not answered, please speak directly to your healthcare provider. Or visit the Society website at nationalmssociety.org. You can also contact the Society's Information Resource Center and speak with one of our MS Navigators at 1-800-344-4867.

Please note that today's webcast will be archived and available for viewing at nationalmssociety.org. Thank you all. Goodbye from San Francisco.