Webcast Transcript

Repairing the Nervous System in MS: Progress and Next Steps
January 11, 2011 – 2:00-3:00PM ET

Webcast Moderator:

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

Webcast Panelists:

- Dr. Peter Calabresi, Professor of Neurology and Director, Johns Hopkins MS Center, Baltimore, MD; Protecting the nervous system from MS damage, innovative ways to track repair

- Dr. Ian D. Duncan, Professor of Medical Sciences at the University of Wisconsin, Madison; Novel imaging technologies, transplanting cells to promote repair

- Dr. Charles ffrench-Constant, Chair of Medical Neurology, University of Edinburgh, UK; Transplanting repair cells and stimulating natural nervous system repair

- Dr. Gavin Giovannoni, Chair of Neurology at Barts and The London School of Medicine and Dentistry, UK; Screening molecules for their protective properties and conducting clinical trials

Dr. Timothy Coetzee: Good afternoon. Thank you for joining the National MS Society's webcast on Repairing the Nervous System in MS, Progress and Next Steps. I'm Dr. Timothy Coetzee, chief research officer of the National MS Society, live here in Times Square New York.

Though I may be new to this role, I'm not new to the MS movement. I've been focusing on the challenges of MS my entire career, and I'm pleased to begin my new role with the Society by bringing together some of the world's top experts on the subject for this conversation with thousands of you who are with us today.

We all share the urgency to advance research and international collaboration that will find the answers on how to restore function to people with MS. As we already know, MS is an extraordinarily complex disease that needs to be addressed collaboratively on multiple levels. This is one of the reasons that we are presently funding over 345 research projects around the globe in an effort to create a world free of MS.

This research is pursuing new leads to stop MS, to restore function in people living with MS, and end MS forever. They include studies looking at new treatments, studies looking at the potential relationship between CCSVI and MS, as well as risk factors and diet. In fact, by the end of the month we are going to provide our first six-month update on the work already underway from the current seven CCSVI projects being funded by the US and Canadian MS Societies.

Today, however, we are going to focus on the progress and next steps occurring in restoring function to people living with MS. And we've brought together four leading researchers who have played a pivotal role in this initiative. We have already received over 1,000 questions related to this topic, questions like can my brain be rewired, and are there any therapies that can repair damage? We're going to do our best to get as many of these questions answered as possible.

Now, five years ago the National MS Society tapped the world's experts to launch the largest collaboration of its kind to lay the groundwork for clinical trials to

repair and protect the nervous system in people with MS. Four teams from renowned institutions around the world were selected to join forces to share their results of their work. These teams involve over 70 researchers who span virtually every time zone. The teams just met this week for two days right here in New York City to discuss what they've accomplished and what our next steps should be.

I'm here now with four of the team leaders. Our first panelist is Dr. Peter Calabresi, who's a professor of neurology at the Johns Hopkins MS Center in Baltimore, Maryland. I'm also joined by Dr. Ian Duncan, who's professor of medical sciences at the University of Wisconsin in Madison. Our third panelist is Dr. Charles ffrench-Constant, who is chair of medical neurology at the University of Edinburgh, Scotland. And lastly we welcome Dr. Gavin Giovannoni, who's the chair of neurology at the Bart and The London School of Medicine and Dentistry in London. Gentlemen, welcome to New York.

Now, we are all keenly aware that the dream is stopping MS in its tracks and of restoring function that has been lost. This is topmost in the hearts and minds of people who have MS, as well as their loved ones. Understanding and then preventing progression in MS is really the centerpiece of our current research strategy, as well as restoring function that has been lost. Exciting progress is being made. Right now there are clinical trials testing therapies that could help people with progressive MS. And at least one possible therapy is in early clinical trials to see if it can repair myelin.

We know that MS involves immune attacks in the brain and the spinal cord. We've also heard for years that myelin is a target. But we also know that nerve wires, or axons, are also damaged. Now, Peter, your team has been studying ways to protect the nervous system from MS damage and trying to find innovative

ways to track how to repair the brain. I understand that one of your aims is to understand why axons are damaged in MS. What have you found and how will this help us protect against MS progression?

Dr. Peter Calabresi: Well, Tim, it appears that there are two major ways that axons can be damaged. Through novel imaging technologies, MRI or OCT, in laboratory models we're pretty clear that the axons can be damaged immediately by the infiltration of immune cells, the white blood cells that come from our blood. And that can cause immediate damage to the axons and transect them. But also now it's clear that there's a second type of damage that ensues after the demyelination, and this may play out over a longer period of time and perhaps is amenable to remyelinating therapies.

Dr. Timothy Coetzee: Terrific. So, Gavin, your team has also been focusing on protecting the nervous system by finding new molecules and conducting clinical trials. Can you explain for our audience what neuroprotection in MS means?

Dr. Gavin Giovannoni: Well, just to start off by reiterating what Peter said, that in multiple sclerosis in the actual acute inflamed lesion, that's the lesion that would cause a clinical attack or a relapse, you get actual damage from the inflammation to the nerves. And in some of them, the nerve fibers are left damaged, but they're still alive and they degenerate over time. So the idea with neuroprotection is to actually during the acute inflammatory phase give drugs to protect that axon from being cut, and then also to prevent the slow degeneration. And we've screened a whole lot of small molecules, drugs that you take once a day, to work both in the inflammatory environment and in the long term, to prevent regression.

Dr. Timothy Coetzee: Thank you. Peter, during our two-day meeting you described the efforts – your efforts to find potential therapies to protect nerves. Have you found anything of interest? And what needs to happen to bring those forward?

Dr. Peter Calabresi: Well, as Gavin said, we've been screening drugs, too. We've screened hundreds of drugs in the laboratory and found some that do appear to be protective, prevent neurons from dying. Some of these are drugs that actually are commercially available right now. They are indicated for another disease process, and so those can go immediately into clinical trials. And that's what we're planning on doing. Some of the other ones are less far along and need to be developed into drugs. We need to make sure that they are safe and not toxic before we give them to people.

Dr. Timothy Coetzee: Good. Thank you. So, let's shift gears now and talk about repairing the nervous system. Repair to most people means fixing areas that have been damaged and restoring function that's been lost. There are at least two possibilities for nervous system repair that are being explored. The first that we're going to talk about is an approach to simulating the body's own natural repair cells to be more active. Charles, your team has been working on transplanting repair cells and stimulating natural repair. What progress has been made towards simulating the body's natural repair abilities?

Dr. Charles ffrench-Constant: Well, Tim, we know that the brain has stem cells within it that normally repair very effectively. And in early multiple sclerosis, we think that repair occurs most of the time. But as the disease progresses, this repair starts to fail. And we think that by promoting that repair we can approach the problem of progressive disease. So what we're trying to do is we're trying to

find ways whereby we can activate the stem cells in the brain to kick start this repair process again, replace the myelin, and protect the nerves.

Dr. Timothy Coetzee: Very good. so, another avenue that is being explored for nervous system repair is cell therapy or cell transplantation. When people think about -- when they hear the words cell therapy, they think immediately about stem cells. Most people think it's important to explore all types of stem cells for their potential to treat MS. Ian, your team has been exploring the potential of human embryonic stem cells for repair myelin. What have you learned? And is there still potential for treating MS with human embryonic stem cells?

Dr. Ian Duncan: Well, we certainly hope so. One of the great features about embryonic stem cells is that you can grow them in the lab and infinitely expand them in a very safe and reproducible way. What you have to do is to make them into myelin producing cells, however, in the culture dish before you transplant them. And we've learned a lot about how to do this, but there are technical challenges in this regard. So we're looking also at the same time, because embryonic stem cells, as you know, have ethical considerations in their use, at an alternative strategy. And that is to biopsy a patient, take a skin biopsy, for example, grow a skin cell, and then force it back in development to make it think it's like an embryonic stem cell. And then do the same thing, differentiate them towards myelin producing cells. So we're moving forward on both fronts. There are still technical challenges, but they both hold huge promise.

Dr. Timothy Coetzee: So, we have a question from our web audience for Charles. A lot of people talk about repairing myelin, but what about regenerating nerve cells? Are these separate things? And is anyone thinking about fixing nerves?

Dr. Charles ffrench-Constant: So this is a key question. We know that putting back the myelin will protect the nerves. And we also know that once we've done that, the brain has the ability to reroute pathways so that function could be restored in that way. We call that plasticity. But there will be loss of nerve fibers, and it's a big challenge to know how to replace those. But the good news is that this is a big challenge that other teams in other areas of neuroscience are also looking at. So people interested in neurodegenerative disease, or people interested in spinal cord injury are asking themselves the same questions. So the great thing is that teams from different fields will come together to address this critical problem.

Dr. Timothy Coetzee: So you could see a possibility where somebody working, say, in Parkinson's disease could help us understand MS as well as vice versa?

Dr. Charles ffrench-Constant: Absolutely. I think more and more we're realizing that these diseases share common mechanisms.

Dr. Timothy Coetzee: So great hope. Gavin, your team has been conducting a clinical trial with adult bone marrow stem cells, or mesenchymal cells, as we call them. What were the outcomes that you're hoping for and when do you think we could possibly have some results?

Dr. Gavin Giovannoni: So, there is this phase 1, preliminary safety clinical trial that's being done by Edinburgh, London and Cambridge. This is a research study funded by the Medical Research Counsel in the United Kingdom, and its primary outcome is safety. It's taking skin biopsies and driving stem cells from the skin, and then infusing them into patients. And the primary outcome is how safe is this, is there any complications attached to safety. And it's also testing the logistics,

the how you'd perform a clinical trial in people with multiple sclerosis using these stem cells. So the outcome sought really is safety and logistics, can we do it. The question about is it effective will likely need to be done in another trial with much larger numbers of patients, possibly with a different type of trial design.

Dr. Timothy Coetzee: Okay.

Dr. Gavin Giovannoni: But the important thing is it's the first step towards a cell-based therapy. We have to do this slowly.

Dr. Timothy Coetzee: Right. So you think that if it's shown to be safe, then the next step would be taking a bigger trial to see do these actually work in people with MS –

Dr. Gavin Giovannoni: On the other side of the coin are the other areas, other disease areas are doing very similar things. I think the overall message so far is that this strategy of infusing these mesenchymal stem cells seems to be a safe therapy.

Dr. Timothy Coetzee: Okay. So, Peter, is there any therapy available right now that can repair the nervous system?

Dr. Peter Calabresi: Unfortunately, Tim, there are no therapies right now that are approved to repair the nervous system. The good news is that the first therapy that might hopefully repair myelin, Anti-LINGO, is in phase 1 clinical trials and testing to see if it's safe and what's the appropriate dose. I think it's important to

point out, though, that some of the immunotherapies that we already have that are approved are so effective in quieting the attack on the immune system that we're seeing some patients get better. So there are natural repair mechanisms that can be allowed to work more efficiently with some of the therapies that we have right now.

Dr. Timothy Coetzee: And if I understand what you mentioned earlier, there are some FDA approved therapies that we could think about for protection. Do you think there might be a future where there might be other FDA approved therapies that we could bring back and try for repairing the nervous system in MS?

Dr. Peter Calabresi: Absolutely. I think one of the things that we've learned in the last five years, that there are pathways and targets that are already targeted by drugs available now that we could potentially try.

Dr. Timothy Coetzee: Okay, great. So, Charles, a couple of members of your team have been trying to transplant adult stem cells in mice. What are you learning from these studies?

Dr. Charles ffrench-Constant: So, these are studies being done where they're trying to see how much myelin you can make from transplanting cells into the brain. And the answer is a lot. In fact, my colleague, Steve Goldman in Rochester, has managed to completely myelinate the brain of a mouse with human cells. And this is a tremendously important finding because it tells us that it should be possible to generate new myelin by transplanting cells into the MS brain. And very exciting development, another colleague, David Rowitch in San Francisco, has started a trial transplanting cells into the brains of children who lack myelin. And this will be really important to see if this approach will work.

Dr. Timothy Coetzee: So for our audience, if I think -- I hear you right, what we may have a possibility is that Dr. Goldman has discovered that you can make myelin. That's an important first step with transplanted cells. And then Dr. Rowitch is actually trying to test that in people --

Dr. Charles ffrench-Constant: That's right.

Dr. Timothy Coetzee: -- and if it works in one type of disease where myelin is affected, you could see a future where it also comes to people with MS.

Dr. Charles ffrench-Constant: Yes. It would be a very important proof of principal that it could work in MS.

Dr. Timothy Coetzee: All right. Thank you. So, we have a couple of questions from our audience, asking how we can speed up clinical trials for repair strategies. Gavin, I know we talked about that quite a bit at length today. What are your thoughts about how we can make things faster to bring them to people with MS?

Dr. Gavin Giovannoni: I think there are two strategies. The one is trying to protect the nerve fibers in acute attacks. And we've discussed this trial of using optic neuritis inflammation that occurs in the optic nerve. I think those trials can be done very quickly and we've got very good outcome measures for that, for measuring the amount of nerve fibers in the retina. Instead of doing them in series, I would suggest we fund trials in parallel because each trial tests one or two drugs. We may be able to do three or four trials all at once because I think

that will work. When it comes to testing drugs in progressive multiple sclerosis, the current trial design is just too long. We've been talking about a trial in the United Kingdom that'll take five to seven years to compare four or five drugs. That's just far too long. So I think the best thing we can do is to develop a clinical trial design where we can do very short studies. And I propose using a marker in the spinal fluid of people with MS that is released from damaged nerves. When damaged, they release this particular protein. And if we can show that drugs can reduce the release of this protein, that'll give us an indication that they're working to protect the nerves. And I think by doing what I would call six months trials, we may be able to do a lot more in the time rather than wait five to seven years for the answer.

Dr. Timothy Coetzee: So you just referred to a marker from the spinal cord. So, is it something like recently I had a physical. I had to have my cholesterol level measured. Is what you're talking about a test like measuring cholesterol levels, essentially for taking the spinal cord and measuring whether somebody has something special?

Dr. Gavin Giovannoni: That analogy is a very useful analogy. You go in and have your spinal tap, have this particular protein measured. And if it's low, it means there's no degeneration going on. If it's high, it means it's going on. It's a nice analogy. And I think if we start thinking about these proteins like that, we'll get more lumbar punctures done, which is one of the hurdles of us doing these trials is their clinicians have gone off doing lumbar punctures. Now they prefer to do MRI scans. And I think we need to go back and actually start thinking about the biology, what actually happens when the nerve cell dies. And I really do think that this particular protein is a very, very sensitive way of measuring ongoing damage. I like that idea.

Dr. Timothy Coetzee: So, thank you. So, another way to think about measuring damage and seeing it is to try and look inside a brain of a person and see are we repairing the damage. So, at this -- it's what we call imaging technology. And so this week at our meetings we heard about imaging technologies that could visualize or look and actually see tissue damage and repair and protection.

Ian, tell us why we need to do imaging and tell us why we need to do this to see if the therapy is working. Why not just see if it makes people feel better?

Dr. Ian Duncan: Well, of course, what we're trying to do is improve function, or restore function. But there are intermediate steps that we need to watch along the way. For example, if we transplant cells, we'd like to know where they go and are they alive so we can label them with iron particles and by MRI follow their progress. We also want to be able to monitor tissue repair, i.e. to look at what remyelination looks like. Does it increase with time? And then we hope then, of course, that we'll match this with clinical improvement. And that'll be going on concurrently. But early on it's very important to know that what's happened to the cells, that they've caused no damage, there's no bleeding in the brain or spinal cord or wherever you put them. So imaging is going to be absolutely essential in future progress.

Dr. Timothy Coetzee: So, building on what Gavin said, what you could imagine is a future where a person is in a clinical trial for a potential therapy to rebuild the nervous system and they'd go to have the therapy, they would then go to an MRI and see what's happening -- the doctor would be able to say yes, it's working, or no, it's not working. And then also look at whether or not their function is better. Is that the future that you're looking for?

Dr. Ian Duncan: That's the plan. That's the hope. And many of us are working on this in labs throughout the world.

Dr. Timothy Coetzee: Good. So, we've gotten a question. This question came in from many of our audience members. It goes, I've had MS for many years. Is there any hope or promise for me? Peter, you see a lot of MS patients. So how would you answer that question with one of your patients?

Dr. Peter Calabresi: Tim, there's always hope. I always emphasize this point with all of my patients, that there's always something that can be done. And too often we see physicians out in the community say, well, it's too late, or there's nothing more we can do for your MS. But again, there are many symptomatic therapies that we can provide that improve quality of life. But in terms of repair, I think what we've learned in the last five years is that there's a lot of potential. So Dr. Robin Franklin from Charles' group has showed that he can rescue old animals with -- merging them with a younger animal. And so it may be that we can provide growth factors to stimulate repair even in older animals. And we're also finding, as Charles mentioned, that there are this pool of stem cells that live in the brain that we can tap into. So, I'm really excited about where we are and what the future holds.

Dr. Timothy Coetzee: Good. Gavin, would you like to add when you see a patient who has that question, how do you approach that?

Dr. Gavin Giovannoni: I agree. And there is always hope. And I'd at least reiterate that for the first time we're really starting to see the emergence of very, very effective drugs for treating inflammation. And the recovery mechanisms are profound. We've seen people who have got highly active disease going onto these

and improving. More than half of them improve substantially after going onto these therapies, which means that there is this repair mechanism. It is definitely there. With regards to people who unfortunately move on in the course of disease, the more progressive phase, that's what we're working on. We're working on drugs to slow down that process. And I can see emerging from -- one of the drugs we've all been looking at -- one of the 20 or 30 candidate drugs is bound to work, provided we do the clinical trial properly. And that's the real question, do we know how to do the clinical trial. And I think some insights that have emerged from the last five years make me feel confident that we've got the right trial design, or at least the beginnings of the right trial design in place.

Dr. Timothy Coetzee: So I'd like to open the floor up to more questions from our audience. This question comes from the audience and asks what's a reasonable timeline to start seeing benefits from the work, both the nerve repair work that we at the Society are funding as well as other nerve repair work that's happening in the field? Why don't I start with Ian, and then I can ask the other panel members.

Dr. Ian Duncan: It's the first and the most difficult question of all, and it's something that we're all asked all of the time. And of course we're notorious for getting it wrong. We hope that it's within, we would say, a reasonable period of time. I talk to people who feel confident that a clinical trial, some form of attempt at repair remyelination, will happen within five years, maybe at University of Wisconsin. We hope it will be. But I do think that within that period of time, given the sort of rate of progress on what we heard at this meeting, which is really exciting, we could hope for something like that. But it's a very difficult question to be exactly correct on.

Dr. Timothy Coetzee: This questioner has asked, and this is a very important question, there are stem cell therapies that are being offered in other countries and a lot of people ask, what should I do in this situation about seeking stem cell therapy in another country? I know, Charles, this is something that you're interested in. Ian, I know you are. So, Charles, perhaps you could share with us your thoughts on that?

Dr. Charles ffrench-Constant: Well, as you say, this is a very, very important question because a number of people are going to have these unlicensed and untried treatments. And I think it's very important to remember that we have no evidence that this is actually going to help because everything we've learned about stem cells is that in order to get them to work you have to prepare them in a particular way, you have to give them in a particular way, and this is an incredibly challenging task.

And then, in order to find out whether they're going to work, you have to give them in the context of a trial so that the patients can be properly assessed. And none of this is happening in these clinics.

Dr. Timothy Coetzee: Ian, I know stem cells are close to you and --

Dr. Ian Duncan: Right. Well, I mean, what I would add is that I think what patients and families should do is simply go online and Google the international stem cell research -- or research center, ISSCR. And they've got a wonderful set of guidelines that advise people and give them the kind of background information and the questions that they should ask about the clinics that they found online, usually these are countries outside of the US. And as soon as people start to ask those questions, a penny drops and they go, well, maybe that's not for me. Maybe what we found out so far here is that claims that a therapy that will treat Alzheimer's and will treat Parkinson's disease, will also treat multiple sclerosis

cannot be so. No single drug can do that. And I think this is a great resource and the best resource to go to find out more about this in the moment. As Charles said, there's not one of these clinics that has definitive hard evidence that they've improved people with multiple sclerosis.

Dr. Timothy Coetzee: Thank you. We've received a question from Laurie asking what does it mean when lesions disappear or shrink as seen in an MRI? Does that mean they've been repaired or are being repaired? Gavin, could you answer that question?

Dr. Gavin Giovannoni: Depends on the type of MRI. What you've got to realize is when you get a new focal or a new lesion that potentially is linked with a relapse and you do a particular type of MRI scan, it's this thing called a T2, you'll see a white lesion there. And if you give a contrast agent called gadolinium, it might light up and show you that it's actively inflamed. Now, the majority of those lesions will get smaller as the inflammation resolves. And the lesion may disappear, in about 25% of cases will disappear, which is a good sign because if lesions stay behind, and particularly if they leave a black hole on a scan called a T1 scan, that's an indication that there's destruction there. So a lesion that comes and goes is a good sign. It means it's less destructive than a lesion that comes and leaves a black hole behind.

So the answer, then, is it's a good sign. It means it's a less destructive lesion.

Dr. Timothy Coetzee: So we're seeing repair in those lesions, possibly.

Dr. Gavin Giovannoni: Yes. There are some lovely MRI studies looking at particular types of markers that can pick up nerve cells. And they've shown in

those types of lesions that those cells are much more likely to survive. So it is a good sign.

Dr. Timothy Coetzee: Peter, your group works on this as well. Do you want to take a crack at that question?

Dr. Peter Calabresi: I would agree with what Gavin said, is that much of what we're imaging on the conventional type of MRIs is inflammation. And we know that MS exacerbation is common, and they do quiet down and as they go into remission. The inflammation subsides and one sees the lesion shrink down. Or sometimes, if it's small to begin with, it will disappear on an MRI. But interestingly, as we track these lesions more, we are seeing some, even in the spinal cord, after a year or two appear to disappear. And we're hopeful that that may indicate that there are some of these natural repair processes going on.

Dr. Timothy Coetzee: Great. So, we now want to take another question from our audience. So, here's a provocative question. So I'll ask Charles this question. Can the brain rewire itself to create new pathways within the brain?

Dr. Charles ffrench-Constant: The evidence is that the brain has a very limited, but nonetheless definite capacity to do that. It varies from different places in the brain. In the developing brain, there's clearly an enormous ability to do that. But the brain seems to make molecules that actually sort of lock it down as it gets older. Why it does that we could debate for hours. It might be a way of making sure that you don't get the wrong connections. But there is quite nice data coming out of the work on spinal cord injury that if you block those lockdown molecules, you can actually increase the amount of rewiring that the brain will do. And this really goes back to the point I made earlier. Those sorts of findings are

very exciting for people with multiple sclerosis as well, even though they're being done by scientists working on spinal cord injury.

Dr. Timothy Coetzee: I've heard it described that it's almost as though the nervous system has a series of fences and that nerve cells have a hard time getting across those fences. Is when you talk about lockdown, are you talking about putting new molecules in that would break down those fences and make it easier for the nerve cells to rewire themselves? Is that it, to help our viewers get a picture of that in their mind?

Dr. Charles ffrench-Constant: Yes. I'd just like to extend your analogy, if I could. I mean there are fences around areas that are sort of no-go areas for cells. But what also happens is that when a nerve cell has established a set of contacts, it seems to lose the ability to move any more than that. And it's really these molecules that stop it moving that we're targeting.

Dr. Timothy Coetzee: So it's a complex environment. So it's –

Dr. Charles ffrench-Constant: It is.

Dr. Timothy Coetzee: -- possible that there might be a way that we can encourage the nervous system to rewire itself if we can find new molecules and therapies to overcome that.

Dr. Charles ffrench-Constant: Absolutely. And as I said, this is a very hot area in spinal cord injury at the moment. And there's some very exciting work going on.

Dr. Timothy Coetzee: Any of our other panelists want to add to that?

Dr. Peter Calabresi: I would just like to add that functional MRI has suggested this idea of compensation going on such that if one sees an area with an MS plaque, the adjacent areas of the brain sometimes will light up, indicating that they're metabolically active and trying to compensate.

Dr. Timothy Coetzee: Well, let me just step back and say when you talk about functional MRI, what does that mean? Does that actually mean that you're getting a picture of a living brain, in a sense, with functional MRI?

Dr. Peter Calabresi: There are MRI techniques that look at the blood oxygen level and measure what we commonly refer to as the metabolism going on in the brains, or the activation of cells in the brain. There are ways of looking at this by MRI and seeing if that part of the brain's being utilized at the time. So a patient is asked to do a task, and then you image them and you can see what lights up.

Dr. Timothy Coetzee: Okay, so you could see where somebody's actually doing something and you're sitting in the booth watching it happen and their brain's actually working under MRI?

Dr. Peter Calabresi: Right.

Dr. Timothy Coetzee: That's a very high technology. Another question from our audience. So, the question is, are there findings that will help us address the cognitive issues in MS? So one of the issues with MS is people have a challenge with cognition or thinking process. Are there possibilities and findings that are going to help us with that? I'll turn to our physicians. So are there drugs out there that can help somebody with their cognition, or are there possibilities that that will happen?

Dr. Peter Calabresi: Well, I think the MS process is scattered throughout different parts of the brain and spinal cord. And the same process is probably occurring in the motor pathways, the sensory pathways and in the thought centers of the brain. So, the kinds of therapies that we're talking about today that help reduce the inflammation and repair the myelin are likely to also help with cognition, just as much as they are with strength and sensation.

Dr. Timothy Coetzee: Okay, so, preserving the brain as well as repairing it could really do more than just help with, as you say, with movement, could actually help us with our thinking.

Dr. Peter Calabresi: Absolutely.

Dr. Timothy Coetzee: Good. Gavin or Charles, anything to add to that?

Dr.Charles ffrench-Constant: Only to echo exactly that, that the fundamental wiring that underlies cognition is similar to that that underlies our motor function. And MS can affect both.

Dr. Timothy Coetzee: Okay.

Dr. Gavin Giovannoni: Also, another aspect of cognition is fatigue and tiredness. There is some evidence that it's linked to inflammation. So if there's -- you all know how you feel when you have influenza or flu. You just feel exhausted. You can't think, you can't concentrate. And that's happening in the brains of people with MS with active inflammation. So there is some tantalizing data that if you can suppress the inflammation, the fatigue improves and cognition improves. And some of the trials that have add-on cognitive scale, they're just add-on, they're not definitive, indicate that these anti-inflammatory strategies are effective in preserving cognition. So that brings back the whole message. We have to control the inflammation first of all, step one. And then step two is to then protect the damaged nerves from dying off. Step three, restore function.

Dr. Timothy Coetzee: That's great. So, there was an article published in the Times of London in December '06 by Sam Lister, the health editor, who describes what he calls a biochemical switch that's been shown to trigger repair in nerve damage in MS. I'm interested in the panel's study about these switches and what might future studies look like for switching the nervous system on and off to repair it in MS. Do we have that possibility of that kind of technology? As our panel thinks about it. Ian?

Dr. Ian Duncan: Well, it would have been good to have read the article. Unfortunately, we don't have it in front of us, so I think we're kind of guessing at what he was thinking about.

Dr. Timothy Coetzee: Sure. I have another question from the audience. Could you repeat that, please? Ah, okay. So the question is can you make too much myelin? Could a therapy lead to us having too much myelin in the brain? And we've talked about myelin being a good thing, but could it be too much of a good thing, and how do you control that? So, Charles, you're –

Dr. Gavin Giovannoni: You have to give it to the neurobiologist.

Dr. Charles ffrench-Constant: That's a problem I'd love to have to worry about, that ’s the first thing I would say. Because, of course, the problem that we're facing is that the repairing brain doesn't make enough myelin. However, there have been some studies done in development where too much myelin has been generated, and I think it's clear that you can get some subtle problems. But as I say, this is a problem that we would love to have to be thinking about.

Dr. Timothy Coetzee: So, Ian, you're --

Dr. Ian Duncan: Well, we have to prioritize, and that's the least of our problems, as Charles has just said right now. And I really don't envision that being a problem for a long time. If we have it as a problem, we've really become too efficient.

Dr. Gavin Giovannoni: I'm almost certain it was discussed and the question was raised at the meeting that there must be some kind of biological mechanism, maybe a sensing mechanism to make the oligodendrocytes switch off making myelin. So that may emerge as a bit of scientific knowledge in the next few years. And I'd be surprised if the things we're trying to do interfere with that mechanism.

Dr. Charles ffrench-Constant: Yes, and I think it's clear that the problem that we're facing is more with the switch that gets the oligodendrocyte to turn on myelin, rather than turn it off. And I think it's clear from a lot of the studies that have been done looking at the pathology of the brain that the oligodendrocytes will contact the nerve fibers, but they simply won't switch on the myelinating process.

Dr. Timothy Coetzee: Peter, what do you think on that?

Dr. Peter Calabresi: Well, I agree with what's been said. I think one of the appealing things about the drugs that we talk about for endogenous repair, tapping into Mother Nature's natural mechanisms, is that perhaps we can boost that. And through imaging technologies, when we find there's enough or the patients are starting to get better, that we can stop the therapy. So perhaps the remyelinating therapies would be something that one would give right after an attack or for a period of a month or two, and then we could always stop it.

Dr. Timothy Coetzee: So the idea, though, the concept of a switch and using therapies to switch parts of the myelin making pathway on and off is not -- it's not science fiction, it's actual reality that some of the research that you're doing will lead us towards.

Dr. Charles ffrench-Constant: Well, absolutely. The brain develops by a series of switches, if you -- the cells perform one part of their behavior, and then they switch to another part. And each of those switches you can define particular molecules that are involved in controlling it and what we're finding is that it's the

same molecule failing to function that often cause the diseases where repair has -- is not working properly.

Dr. Timothy Coetzee: Ian, do you want to jump in here and say anything else?

Dr. Ian Duncan: Oh, I think Charles has answered it very well. The idea of promoting the brain to repair itself in MS will sometimes just need a kick start. And there's proof already from work that they have done and perhaps some others that you can identify molecules that could be used. So it's really very, very exciting. And perhaps use these, I would add, along with and combined with the cell therapies. So these two approaches are not necessarily, as we've said many times at this meeting, mutually exclusive, a combination of the two.

Dr. Gavin Giovannoni: There is one caveat, though. The caveat in the brain of people with MS, the actual environment, like the soil really the cells live, is abnormal, maybe abnormal. And that may be where the block is. So if you put cells into that, that's not going to work. So we have to change the -- what we call the microenvironment. But it looks like the powerful anti-inflammatory therapies do that. So I'm almost certain that -- to me it's a no-brainer. We're going to have to develop these repair mechanisms on top of effective anti-inflammatories.

Dr. Charles ffrench-Constant: Yes, I think we're all agreed, aren't we, that the MS clinic of the future, patients will be taking drugs to damp down the inflammation, and drugs to promote repair at the same time.

Dr. Timothy Coetzee: Well, that's an interesting question. Did you want to say –

Dr. Ian Duncan: Well, I was going to say, however, one response there is that there's a lot of experimental data actually that shows that transplanted cells actually do surprisingly well in a milieu of inflammation. Perhaps the right part of inflammation. There are good and bad parts to inflammation, some of which you actually need to promote repair. And a lot of that is what we're working on right now. Too much of it, though, I would agree with you, Gavin, is a bad thing.

Dr. Gavin Giovannoni: Yes. But all the models we use where there isn't a problem with the microenvironment is the brain doesn't seem to have a problem repairing itself in terms of myelination if you put toxin in there to kill the oligodendrocyte, as lesions remyelinate very quickly, very efficiently and very well. That's very different to what we think happens in MS.

Dr. Charles ffrench-Constant: Provided it's not too old. We know that the old brain actually doesn't repair itself terribly well. And that may be very important in MS as well.

Dr. Timothy Coetzee: Well, let's talk about different causes and potential prospective methods. So, in terms of determining strategies for repairing the nervous system, is there a difference between relapsing/remitting and more progressive forms of MS? And is there something different about a relapsing/remitting brain versus a progressive brain as we think about treating and repairing the nervous system? And if so, how? So, Peter, why don't I start with you?

Dr. Peter Calabresi: I'm not so sure that clinical nomenclature that we use is all that helpful, to be honest with you. We tend to sort of lump people into

relapsing/remitting and progressive, but one finds that sometimes a patient who's been called progressive will have an attack and that there's quite a bit of inflammation going on. And in those situations they actually do respond to some of the approved immunotherapies. And so I think it's not quite so cut and dried. But in a general sense, as Charles said, as time goes on with MS, the battle becomes a little bit more challenging. But the good news is that although the old brain right now doesn't seem to repair well, we understand that the capacity is there, that there are cells that are dormant or asleep in the brain that we just maybe need to wake up a little bit and get them to repair things.

Dr. Timothy Coetzee: It's interesting you've referred to the old brain, new brain. Is this idea of the brain having its own ability to repair itself an old idea, a new idea? And how is the work we're doing shifting that? And I know you've referred to that quite a bit, Charles.

Dr. Charles ffrench-Constant: Well, certainly the -- I mean it's been known for over a century that the brain can repair itself. The German neuropathologist who studied MS over a century ago recognized remyelination. They recognized these plaques in the brain that looked slightly faint. And they called them shadow plaques. And that's been a very important concept in driving the research forward. So, no, it's like a lot of things in multiple sclerosis. Like axon loss and nerve fiber loss in multiple sclerosis, it's been known about for a long time. What hasn't been understood until very, very recently is how it's going, how it's happening.

Dr. Timothy Coetzee: So, Gavin, the idea of natural repair, how has that shaped your thinking as you lead these teams?

Dr. Gavin Giovannoni: Well, one of our strategies was always just to improve natural repair, change the microenvironment, provide the right soil, the right fertilizer to promote natural repair using growth factors. So I think five years ago these ideas were the same, can we hijack the natural repair mechanisms rather than trying to put in artificial repair mechanisms. But I think both strategies may be necessary. And you mentioned that you may find certain lesions don't have enough of these stem cells to enable natural repair. We may have to transplant into those lesions stem cells exogenously from outside to do the repair.

Dr. Ian Duncan: Or there may be inhibitory signals in the areas that you're trying to repair. And what you have to do is – when you find there are no cells there, you put cells in there, but you also inject a substance which gets over, prevents or gets around this inhibition. So that's the sort of combined therapy. So you can think of a number of different scenarios or something that will promote the division of the cells or the migration of the cells, for example.

Dr. Timothy Coetzee: So earlier we talked about the fact that there's one drug that's right now in an early clinical trial to figure out safety for nervous system repair. So that's one in the clinic. Let's talk -- I know it's always hard to predict time horizons - still let's perhaps talk a bit, about what would be the time horizons for the next therapy or the next generation of therapies? And what are the things that we need to do in order to shorten up that time horizon? So let me start with Peter, and then I want to get the group's thoughts on this.

Dr. Peter Calabresi: Well, of course, I can't predict the future. But as you said, they're already is a remyelinating therapy in phase 1 human clinical trials. So that's exciting. And I think we're going to see many follow-on strategies to that happen over the next five years. Hopefully anti-LINGO will hit and be the first one. But if it's not, there will be several others that are tried and maybe one of the

follow-ons will work. It's challenging, though. I always say that I don't think we're going to cure all MS overnight. It's going to be a little bit like cancer, where some of these therapies may be effective in some people at certain stages of the disease, and that will be fantastic and incredible. But then we'll have to jump the next hurdle and figure out how to get it to work in some people who are refractory, where there's a certain type of lesion that may just not be open to remyelination.

Dr. Timothy Coetzee: Charles or Gavin, you want to jump in on the time horizons?

Dr. Gavin Giovannoni: I think it's very important that we manage expectations. The reason being is that we promise five-year time horizons, we won't deliver on them. And the reason I say that is we've got licensed therapies for multiple sclerosis. And we look at the history of development of these therapies, just take interferon-beta, for example. One of the people in my group was instrumental in cloning the interferon-beta 1A gene, and that happened in 1980, and the drug only reached market in 1993 and 1995. So we're talking about a delay from discovery to coming to being approved of about 15 years. So we talk about LINGO, LINGO is in phase 1 and I will be surprised even if it goes through and it's an effective therapy if it'll be available for general use anything under 10 years. And that's not the problem with the science or the trials. It's just the way the regulatory hurdles are time consuming. We can't -- it's very difficult to fast track that.

Dr. Timothy Coetzee: So --

Dr. Gavin Giovannoni: Anybody involved in trials knows how long it takes to do trials.

Dr. Timothy Coetzee: So you're saying that part of the issue is that when you're doing a trial to make sure that a drug works, the organizations like the FDA have specific requirements that you have – that companies will have to meet and there's no -- there's no way to speed that up specifically.

Dr. Gavin Giovannoni: I mean the FDA does try. There is a thing called the orphan disease route where there's a mess of unmet need and they allow certain regulatory hurdles to be bypassed so you get fast – I mean in one big clinical trial. But that may not be the playing field for LINGO, for anti-LINGO, for example. So it's very, very -- I know depressing and lowers people's expectations when they look at the time horizons. But it's very difficult to overcome those time horizons.

Dr. Timothy Coetzee: Tell me, as leaders of large collaborative teams, does collaboration and creating these collaborative teams speed that process up in any way?

Dr. Peter Calabresi: Well, it certainly speeds up the discovery process. So what we found in our center is that by having multiple teams think about different aspects of the problem, we can specialize, much in the way a factory does, so that not any one scientist can actually think about all the problems that are necessary to move a target, validate it and then get it into clinical trials. So we need a physician to take care of the patients, experts in clinical trials, experts in the imaging technologies. And this kind of infrastructure that we've established and then the other groups have established I think really is helping to move things forward more quickly.

Dr. Timothy Coetzee: And I know, Charles, your team has, I think, at least six countries represented. How do you manage a large team across so many countries, so many people? How has that helped in speeding up the process of discovering those targets that I know your group has identified for nerve repair?

Dr. Charles ffrench-Constant: Yes, we're very pleased. We've discovered three targets in the last five years. And just to go back to the question that was asked before about speeding the whole thing up, obviously what we will do first is we'll see whether there are any drugs that are already out there that would hit those targets. Because if there were, that might be one way of speeding process up a little, although everything that Gavin said I completely agree with. Clinical trials take time if they're done properly and there's no way around that. The team has been a pleasure and a privilege to manage. And the two things we've done that have made a huge difference, firstly we've obviously used the internet extensively for regular communications and keeping everybody in contact. But the other things we've done are we've recruited post docs and graduate students who have spent time in all of the different labs. They've moved around. So we've had post docs and graduate students moving between San Francisco and Cambridge, between Cambridge and Edinburgh, between Edinburgh and Paris. And this is tremendous for two reasons. Firstly, it increases the amount of collaboration. But secondly, it trains the next generation of the scientists that we need in multiple sclerosis. So I think these large multinational teams are very important.

Dr. Timothy Coetzee: It's very exciting. So, a question for all of you. What are the biggest obstacles today to progress and how can we remove them? And I'll start with Ian.

Dr. Ian Duncan: Well, from our work and our perspective, it's this generation of sufficient numbers of cells that we would use for human therapies. And then I

think secondly, definitive proof from our imaging technologies that we can do, as I said previously, that we can follow them and we can follow the results of their biological function following transplantation. And we're really pretty close. Sometimes it's frustrating the progress. I share, by the way, how people in the MS community get very tired by lack of progress. I do, too. I'm not the most patient of people. But these would be the two things that, as I say, I really do believe within three or four years my colleagues are going to have made the breakthroughs necessary and we'll be then on the cusp of using them in a clinical trial.

Dr. Timothy Coetzee: So, Gavin, what do you think are the biggest obstacles to progress?

Dr. Gavin Giovannoni: Well, one of the outcomes of our program has been to do a clinical trial. And it was great to hear the news two days ago that the National MS Society of the US and of the UK are going to fund a clinical trial of a neuroprotective agent in optic neuritis. So in my personal opinion, all we need to do is get these trials going as soon as possible. We need to start doing trials. We've got the ideas, we've got the compounds, we have to do the trials. And we'll learn from the trials. We may not get it right the first time around, but we should design the trials so that we learn from them. And this is where the collaboration is important, is that we should be all talking to each other about trial design and how we finesse them and make them better to speed up the recovery.

Dr. Timothy Coetzee: Peter, as a clinician?

Dr. Peter Calabresi: As Gavin said and I'd like to reiterate that we need to be doing more than one at a time. So one of the challenges is that the old scientific

way was generate a hypothesis, test it in the laboratory, move it forward, and see if it works in the clinic. And then it can be ten years later and you might find that it doesn't work. And so I don't want to have all my eggs in one basket. There are many things that we've discussed today and we need to be trying different strategies. We need to be trying different drugs. We need to take advantage of what business models do where they use high throughput systems. So in the laboratory we're using high throughput screens, robots to test things. They can work faster, test more compounds. In the clinic we need to have a collaborative infrastructure where we all get together and test these multiple agents in clinical trials.

Dr. Timothy Coetzee: Charles, your thought?

Dr. Charles ffrench-Constant: Our biggest obstacle five years ago was that we didn't have any potential strategies for enhancing repair. Now we've got a number. Our biggest obstacle now is the next step, if you like. It's actually developing ways of manipulating those that would be suitable for use in patients. And once we've done that, then the obstacle will become the clinical trials. The point I'm making is that there isn't one huge obstacle and you get through that and it's clear from there.

There's a series of steps that we have to go through. And the progress has been fantastic over the last five years.

Dr. Timothy Coetzee: Ian, you want to make a point?

Dr. Ian Duncan: Could I just add that the realistic situation right now, at least for us and I think for many others, is that this work needs funding and funding is

critically short right now in medical research. And that certainly is a barrier to some progress, depending on the lab you're in.

Dr. Timothy Coetzee: Okay.

Dr. Gavin Giovannoni: The other thing I would like to say about funding is that up until now there's been a little bit of skepticism from the pharmaceutical industry about whether or not we can get neuroprotection and neurorestorative therapies working. And I think we need to engage them a lot more because a lot of those companies have compounds that have been developed or in development that we could potentially partner with them. And they -- the reason why I say that, they have the resources and the in-house capabilities of really getting trials off the ground quickly. Much quicker than investigators can, because we don't have big teams like the pharmaceutical companies do.

Dr. Timothy Coetzee: Okay. So I'd like to ask each of you -- each of you about your ideas of what you think a key progress is from your work. So for the last five years of funding your groups, if you were to look at what's the thing that you were most proud of from your work, through these collaborative efforts, what would it be? Short answer. So, Gavin, let's start with you.

Dr. Gavin Giovannoni: Animal model. We've got a very, very good animal model for testing compounds. And out of that has come at least 10 compounds that we want to put into clinical trials. Without the animal model, we wouldn't have had the compounds. And so that's really our innovation is the animal model.

Dr. Timothy Coetzee: Ian, so for you, --

Dr. Ian Duncan: Well, I think probably the most exciting thing that's happened most recently in this sense, and like Gavin, we've discovered a new animal model which we can now use to explore the natural healing process, or endogenous remyelination. It's hugely exciting and it's given us possibilities to image repair, to look at molecules that are involved in promoting the endogenous remyelination in a very, very reproducible way. And that, I think, is probably the most exciting stuff we've done. And the fact is we know, and we think everyone agrees here, that at least in this system it unequivocally shows that remyelination restores function. And that hadn't formerly been absolutely proved in the global sense before.

Dr. Timothy Coetzee: Much to be proud of. Charles, your thoughts?

Dr. Charles ffrench-Constant: I would highlight, too, firstly our discovery of three potential targets for enhancing repair. And second, the demonstration that by transplantation you can form myelin throughout the nervous system of the recipient.

Dr. Timothy Coetzee: I'm realizing that we haven't defined what a target is. Is a target a pathway that you develop a drug for?

Dr. Charles ffrench-Constant: Yes. It's cells work by activating molecules linked up in pathways. And one tries to identify key parts of that pathway that act as triggers, and those are the targets.

Dr. Timothy Coetzee: Great. So, Peter, last, what are you most proud of from your group's work?

Dr. Peter Calabresi: Don't know that I could pick just one thing because we have almost 60 people at Johns Hopkins in our center who are thinking about MS. And I would do a disservice if I just picked one thing. But in a general sense, I'm very pleased with the group's ability to understand how the myelin talks to the axon, the communication there. Why do axons that have been lost -- stripped of their myelin degenerate? And we're starting to understand this pathway, which, as Charles refers to, and have developed actually peptide therapies that seem to protect the axon that are very translatable. And from a clinical standpoint, I think the optical coherence tomography, the OCT, has provided us a window into the brain. We can actually look through the pupil and see the nerves in patients and track what's happening to them. And I think that's going to be extremely helpful as we move forward.

Dr. Timothy Coetzee: So, just that I understand the technology, it's possible that as a patient I could come in and I sit down at a machine and you look inside my eye and it gives you a sense of what's happening with MS?

Dr. Peter Calabresi: Exactly. Ophthalmologists and neurologists have been using ophthalmoscopes for 100 years to look at part of the brain, the head of the optic nerve. And now we have a machine that gives us a microscopic picture, and it turns out that what's happening in that part of the brain is somewhat reflective of what's happening in other parts of the brain. And so I think it's going to be very useful.

Dr. Timothy Coetzee: That's really exciting. It's exciting to hear your story. So, it's time for us to wrap things up. One more question. What can be done to help us spur more collaboration by the world's top scientists to speed research, the research that we need to bring new treatments to people with MS to help us stop

progression and restore function. So, I know, Ian, you have some ideas about what we can do.

Dr. Ian Duncan: Well, I mean I think probably we share the same ideas. It's like meetings that we've just been attending whereby you hear colleagues present interesting information and you realize that you're quite close, that it would just take some kind of joint experiment between the two of you sharing the expertise, something that you don't have that other people will have. You can't force people to collaborate. They have to see the opportunity themselves. And when we talk, when we present, this is when ideas crop up.

Dr. Timothy Coetzee: Great. Charles?

Dr. Charles ffrench-Constant: Yes. And as I said earlier, I think one of the key things here is training the next generation of scientists, but training them in a collaborative environment so they naturally work with colleagues from all over the world. I think that would make a huge difference.

Dr. Timothy Coetzee: Teamwork. So, Gavin, you're –

Dr. Gavin Giovannoni: I think you started something especially in the sense that we've had three repair meetings. And a lot comes out of these meetings in terms of ideas, hypotheses, exchanges of research. And I think you should commit yourself to doing this in the future. Every two years you should have a repair meeting to update the world about what's been happening. And open it up. It shouldn't be a closed meeting. We should get industry, other groups in. And I

think a meeting focused on this will, just by itself, be a catalyst for further innovation.

Dr. Timothy Coetzee: So people being together and being in a big network really matters.

Dr. Gavin Giovannoni: Well, that's why societies are successful, because they network. –There's a whole new science about this called network theory. And that's probably why certain societies are more successful than others because they have a better ability to network. I mean just a social group actually. So I think you hit the nail on the head.

Dr. Timothy Coetzee: So, Peter?

Dr. Peter Calabresi: I certainly agree with what everyone else has said. I think a critical unmet need is to have a clinical trials infrastructure where we can collaborate and not have each academic center do one small clinical trial, or even in one country. I learned this morning that UK MS Society has a clinical trials program where they're working with all the centers in the UK to bring them together. And I'd like to see that happen on an international level where we could all agree on a trial design to systematically test drugs in multiple centers across the world.

Dr. Gavin Giovannoni: I think we should learn from the oncology networks that exist already, not only in the US, but in Europe. And they're linked, talk to each other. And every patient has got a particular cancer and has had standard therapy goes into a trial –

Dr. Timothy Coetzee: Yes.

Dr. Gavin Giovannoni: -- like a rolling set of trials.

Dr. Charles ffrench-Constant: And they've been doing this for decades.

Dr. Gavin Giovannoni: Decades, yes.

Dr. Timothy Coetzee: So learning from other diseases, other networks. Thank you, gentlemen. Thank you, everyone.

Well, that's all the time we have for questions today. We are going to continue to move our work forward and share it worldwide in order to continue to speed research to repair the nervous system in MS. I would like to thank our four panelists and thank all of you for participating and submitting your questions. We do hope you found this both informative and timely.

Today's webcast is going to be archived and will be available for viewing at our website, **www.nationalmssociety.org/webcasts**.

If your question wasn't covered today or if you have additional questions about MS and the topics addressed by our speakers, we encourage you to visit our website, the National MS Society's website, **www.nationalmssociety.org**, or

contact one of our MS Navigators at our Information Resource Center. You can call them at 1-800-344-4867.

For additional details on repairing the nervous system, we encourage you to watch the Society's MS Learn Online programs, which can be found in our multimedia library at **www.nationalmssociety.org/MSLearnOnline**.

Thank you and good afternoon.