Can the immune system help repair myelin?
2017 Rare Neuro-Immune Disorders Symposium
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Transcription from presentation available at https://youtu.be/bvBK9Ycg9YI

00:04 So first of all let me thank the organizers and in particular Chitra for inviting me to speak at this meeting. Am I actually started my research career looking at cows’ udders. And you did hear that correctly the part that makes milk and studying inflammation and cows’ udders. So how have I ended up here with this topic. So funny story six months in I was paralyzed with transverse myelitis. So interesting way to find your career I have to say. And clearly I did really well. I regained the ability to walk. I was very fortunate. And I can't fully tell you why that was. But that's kind of what my career is about trying to figure out how myelin does become repaired.

00:52 So these individuals that you can see here are a wonderful team of researchers that I'm very privileged to work with and Queens University Belfast and Northern Ireland. We decided to take our picture with Galileo because we realized we have a bit of gender imbalance in my group. We I think were eight to two of the moment so the boys have a bit of balance there. And I've also noticed our funders the Welcome Trust and Research Council similar to the National Science Foundation here in the US. These funders are the people who have allowed this sort of blue skies research to take place. So it's very exploratory. It's very early stage and I will emphasize that. So we're going to run through in in a brief 20 minutes or so is a little bit around drug development and why it takes so long.

01:44 I'll talk a bit more about myelin repair and the steps involved. You've heard about from previous speakers. And then I'll tell you a abbreviated version of some of our recent discoveries. I want to emphasize that it's all done in mice models so it's very early stage this is not human clinical trials or anything like that but it is how we can open up these new areas and these new concepts in biology that can help us.

02:09 Learn more about how the CNS can help to repair a myelin. And then at the very end I'll briefly talk a bit about clinical trials in remyelination.

02:21 So the drug development is a very long process and it's a very risky process and that is for both the companies that are trying to make the drugs and also for the people involved in the trials. So it's roughly speaking about 10000 compounds have to be screened to make one effective drug. That's a broad brush stroke statistic. And so we need to ensure that the drugs that have been chosen for testing have good solid basis wherever we possibly can. The risk for patients and
obviously going into clinical trial is a big decision. And there is not only the risk of whether there could be an adverse effect but there is also the fact that while the patient is in one trial they're obviously not able to be involved in other trials. And so it is a risky process. So this is a basic view of how we make drugs and where my group's researchers position is at this very early stage this discovery research or basic science.

03:23

So we want to understand more about basic biology and then make sure that what we learn in animal models translates to humans and look at clinical settings and from there we would develop drug discovery programs run clinical trials and make new treatments that would be available.

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And that's not what I'm going to talk about today so I hope you can stay with me and it's been a long two days. But it is very much basic science but it is new biology which we think is very exciting. So speaking of new biology I am about five years ago two groups one in Germany one in the U.S. and discovered a completely new role for myelin. So hands up if you know that you're myelin feeds your nerves.

04:07

You ever heard that before.

04:10

OK. So. So we know it's in the textbooks that myelin insulates nerves so that electrical signals can pass more efficiently. But what these groups discovered is that the oligodendrocytes which makes myelin also deliver substances like lactate.

04:26

In this case through the myelin layers into the nerve underneath into the axon that allows the axon make energy there and then very very quickly. So this is I am emphasizing the importance of having myelin and generating myelin when it is lost. So the outcomes of demyelination do vary. This is a cartoon showing neurons with their axonal projections here and you can see the paths of myelin that are produced by oligodendrocytes. When oligodendrocytes are damaged you lose myelin and you have two potential outcomes. And this is the outcome we want. We want remyelination where the myelin is repaired. It looks a little different when it's being repaired but it can restore function. What we want to avoid is this setting where we don't have remyelination and we can see within areas that there hasn't been remyelination.

05:23

They can have axons survive have neurons still intact. But you can also see other ones that degrade. So here this axon has lost its myelin and the axon itself is dying and the neuron is lost. And I think this is a very very important point in terms of being realistic about what remyelination therapies can deliver. So I'll be very clear about this remyelination therapies will put myelin back on these axons. Remyelination therapies will not help where an axon has been lost. That
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is an entirely different field of research where people are trying to regrow the nerves. So these two fields will eventually work together where if a permanent disability because the nerve has been lost we first need to regrow the nerve in order to have something dropped the myelin around.

06:13 So I think that's a very important point in terms of realistic outlooks on what remyelination therapies will do. So these I'm an immunologist I should say I study the immune system. I trained as an immunologist and these are currently my favorite cells and they're brain cells. And these are the oligodendrocytes progenitor cells and I'm going to call them OPCs for the rest of the talk. And they're basically late stage stem cells or early immature oligodendrocytes and what's great about these cells is that we have them for our entire lives. They make up between five and 10 percent of the CNS depending on where you look. And if you are over 80 you still have these cells there. And the reason that's important is that it means there are targets that we can get at and we just need to figure out how to get at them.

07:08 So these are the cells that we are trying to trigger. So a lot of people ask me about stem cell therapies and I say well my own research is trying to trigger our own stem cells that are already in there because they're in the right place we don't need to figure out how to get them into the CNS. But we do need to learn an awful lot more about their biology and that is a challenge.

07:30 So this is a basic description of the development of these cells that go from these very simple looking cells early on and when there has been damage when myelin has been damaged. They get called into that area. They get recruited and they make copies of themselves so they always keep that pool of cells that I said you have throughout life. So they multiply and then they have to mature. And that's a very key step because that's when they switch on their myelin production. And you can see even these little clouds here. And when they're mature then they can grab on to these cables these axons and start remyelinating them and what we have learned from studying Multiple Sclerosis is that at least one of the bottlenecks in failed remyelination is this step where they go from this immature cell to being this myelin producing cell.

08:23 And the reason we know that if we look into lesions from patients that died with MS, we can see that in the lesions that don't repair. These OPCs these progenitors got to the site and they're actually proliferating. They're making copies of themselves but they're stuck in that stage. So

08:42 So in one particular study 80 percent of lesions that didn't repair had their OPCs so the cells got there they just got stuck. And so that's one of the bottlenecks that we're trying to address. So in broad brush strokes and my research is trying to understand the mysteries of how remyelination occurs because in my mind if
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we have that knowledge we can then use it to make drugs. Our CNS has actually an immense capacity to repair myelin and we have evidence of that but it doesn't always happen. And if we can figure out why we can make therapies to replicate that. So I mentioned I'm an immunologist and this is the slide that strikes the fear in my second year medical students when I put it up. But it does the same to me. OK. So immunologist love their acronyms, love their pathways putting everything together.

09:37 But actually what we need to do is go the other way we need to think very simplistically break things down and understand what individual components do before we put them all back together. So I have a very basic concept of an immune response. The three R's reaction, sorry, recognition, reaction and resolution. So in recognition what it means is your immune system can sense threats it can sense when there's danger from infection or from a tumor or from badly dying tissue. And what you want is an immune response to to deal with that. Usually it's cells. They come into the area that cause inflammation and that inflammation to clear the trash. And. In general terms the inflammation has go signals that switch it on. And it has stopped signals that switch it off.

10:32 OK so this balance and the immune system is actually extraordinarily exquisite and complex and it has a lot of regulation and it has a lot of regulation because it needs to be able to switch itself off again. It needs to be able to resolve the inflammation and repair the damage so we know quite a lot in immunology about how we sense danger how we respond and actually how we switch off inflammation. So we know a lot about that. We know very little about how the immune system helps to repair damage which sounds a little non-intuitive because that's often the key part right at the end of an immune response. And this is my last introductory slide to the immune cells. And my personal favorites are T-cells for I won't go into the reasons why. But even within T-cells you have lots of different types.

11:22 So some of them are killer T-cells and they go in and they'll kill an infected cell or a tumor cell. Some of them are helper cells and they help other immune cells do different things. But the ones that we started with the ones we wanted to study first of all are T-reg. They're called regulator free or regulatory. Since I'm back in the U.S. regulatory T-cells and their job is to stop inflammation. OK. The reason we thought to be good to start with those cells to see what they might do in tissue repair is because when you're stopping inflammation it's the time at which you want to start repair usually for stopping inflammation that threat is gone and now you need to initiate repair. So we developed the hypothesis that these T-reg would promote myelin repair.

12:10 Now we have. My group is very international but our mice are even more international and the mice that we started the study with came from New York
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via London in fact. So they flew from New York to London. There were expanded there and then they flew to Belfast in Northern Ireland via Frankfurt actually and that's due to animal rights activists. But I can tell you more of us and what we did is we use these mice to find out how myelin repairs when we don't have T-regs present these T-cells. So this is a living system experiment. This is a live mice and I'm going to just describe the damage. It's a very small area of damage within the spinal cords that we create with a toxin that melts myelin. So it's about a 20 minute surgery with a very tiny needle into the spinal cord.

13:07
And the reason we use this particular model is because it repairs really well. Rodents are remarkable are repairing their myelin and they're very very very good at it. So we created this myelin damage. And then we watched well it repaired in a normal group of mice or in a group of mice that we had deleted their T-regs from so we deleted their anti-inflammatory T-cells these special mice from New York. And what you're looking at here on the left is the control group and everything in blue is an axon that has had myelin restored. OK. It's very thin myelin that's a feature of repaired myelin. And what you're looking at a cross-section so you're looking across all these different axons and the purple ones are the ones that haven't been repaired. So when we looked at the mice that didn't have their T-regs anymore they didn't have their own inflammatory T-cells we saw very little repair.

14:01
We actually did this experiment with collaborators in Cambridge who blindly assessed them so they didn't know which mice were which. And we counted the number of remyelinated axons in the control group here on the left compared to the mice that didn't have these T-cells. So this was the first evidence that these T-cells are in some way important for the repair of myelin and we actually took it to quite a long time to convince people of this because the model that we use to create the damage wasn't known for its T-cell involvement. You know it wasn't the typical one and in fact the T-cell numbers in the lesion are quite small but they seem to be doing some very important work there.

14:44
OK. So we've moved on and we wanted to understand how these T-cells work were working. And I should say that previous slide summarizes three years of work of a post-doctoral fellow. This slide summarizes a person's Ph.D. So this is Thomas O'Hagan who took on this model of brain slice culture and again it's from mice. This picture here shows brain slices in a dish. These are slices of tissue from the mice very young mice and we stay up here on the right. So you can see them. This disk would be about the size of a little bigger than a quarter since your currency conversion. There in my head. And so a bit bigger than a quarter. So you can see these are small slices but you can see them with the naked eye. And what we did with these slices we put them into the dish to allow them to develop their myelin and then we damaged their myelin.
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15:39 But when we damaged their myelin and we treated them with these factors that came from the immune cells that we were interested in these T-cols. So we wanted to know whether the factors the products coming out of these T-cols could actually help remyelinate a piece of brain if this video works what you should see in green our nerves without myelin, red are the oligodendrocytes in the myelin and yellow is where you have myelin back on a nerve. So this is our control slice and you're taking it. I guess a video down through the slices. Journey through the actual tissue in 3-D. And that's how we can see all these different pathways. And when we look at the slice that has had T-col products added to it what you should be able to see is a lot more yellow.

16:29 So the yellow is where the red and the green overlap it's where the red myelin is overlapping on the green axon. And so when these slices that got the products from T-cols we saw a lot more myelination or remyelination in fact a lot more repair. So this was very very encouraging.

16:49 So it was a question No sir.

16:52 And so when we started talking about this work everybody was asking us what is in your soup that you're making what is it that these T-cols are producing that help repair myelin and I'm sorry this is just the quantification just to show the level of damage that we created and then controlled repair and enhanced with T-col.

17:12 But I think the videos are even more convincing.

17:17 So we used another model of just cells in a dish to screen what factors might be having this effect. So what we did was we set up cultures of oligodendrocytes progenitors and we just allowed them to mature naturally and when they mature they turn red the red color here is is a myelin protein.

17:37 And when we added the immune cell proteins just to this dish. So there's no nerves here. It is literally just the OPCs and we could really boost how quickly they're able to mature. And to cut a very long story short took us about a year to figure out what protein was was doing it and it's not the entire story but we stumbled across a protein I'd never heard of. Nobody knew that T-cols could make it. In fact it's called CCN3 and it has four different parts to it. So it's a big bulky protein and it is at least partly responsible for this the fact that we were seeing. So the one thing I'll say is people have e-mailed us and asked us Where can they buy it and how much should they take. And the answer is please absolutely do not try and take CCN3 for for a couple of reasons.

18:23 One you can only by research grade CCN3 and it does not work. In our experiments. We have to make our own. And two it was first discovered in a
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tumor. OK. So it's associated with cancer. So please do not think that what I'm saying here is CCN3 is good therapeutic.

18:40 We're going to chop up the protein and find out which bit is actually having the effect and hopefully make a drug from that. So hopefully we are getting over one of these bottlenecks. So to summarize we have discovered that these T-regs can produce factors including CCN3 that help these OPC's mature into myelin producing oligodendrocytes that aids remyelination and we've looked at it in cells and tissue in dishes and in living animals.

19:09 I should add that we also studied the same process in the brain and we published this earlier this year and what I would emphasize is the teams that helped us this is such a collaborative effort. We weren't neuroscientist and so we had to set up all of those models as completely new models in my lab and we had a team from Cambridge, from Robin Franklin's lab who were fantastically supportive and a team from San Francisco Jonah Chan's lab who also helped us get this up and going.

19:36 On that I guess brings me to the last slide which is about remyelination clinical trials because what I've talked about is very early stage research.

19:45 But there are trials ongoing in predominantly multiple sclerosis looking at different agents that can promote remyelination. So this is just a list. I'll actually zone in on Clemastine which has already been mentioned. I'm probably biased because it's our collaborators who have run that trial. But in my mind it is the first agent that has been shown to promote and we believe remyelination that we can't actually measure it in a patient cohort 50 individuals. And what I liked about the trial was that they took clinically stable MS patients that had a residual deficit in vision from before. So these were not patients undergoing a lot of relapses because we have a lot of drugs already that can control those relapses. They took patients that were stable but had a deficit and they had a minor effect or was statistically significant.

20:40 This is not revolutionary but they had a minor improvement in the speed of the optic nerve. In the patients that were treated with Clemastine. And what it says to me as an experimental biologist is that it is possible to improve a previous stable disability even if it's in a very very small way. And so I won't go through the others in the interest of time but I think it very nicely brings us on to our next Talk about the how realistic these therapies may be in the future. And again I won't go through the acknowledgements in detail but I will give a shout out to our mice who've been very understanding with everything we've done to them in the last few months or years like us. Thank you very much.