SEPTEMBER 2018

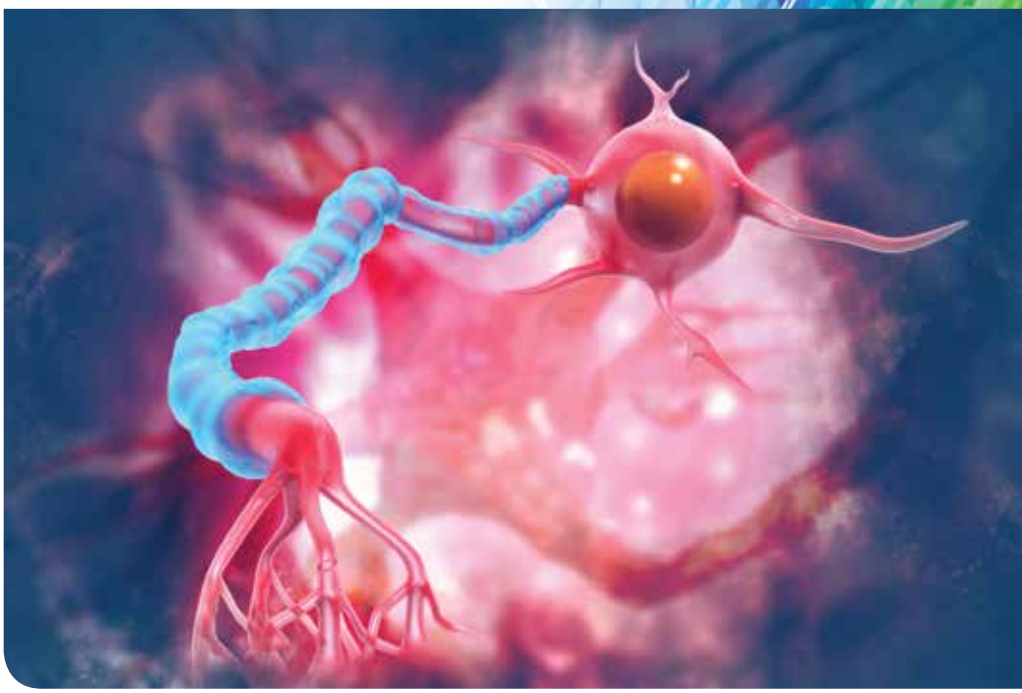
MS RESEARCH AUSTRALIA

MS WIRE

THE OFFICIAL NEWSLETTER OF MULTIPLE SCLEROSIS RESEARCH AUSTRALIA

Recoating frayed nerves

There has been an explosion of reports about potential myelin repair therapies, so what does it all mean? How close are we to being able to repair myelin damage in MS?



Myelin repair, also known as remyelination, has previously been thought of as a bit of a dream, but now it is getting closer to reality. However to appreciate the advancements made in this area and the potential benefits of remyelination, first we need to understand what is myelin and what happens to it in multiple sclerosis (MS).

- Myelin is a fatty substance that coats nerve fibres providing protection and insulation.
- In MS, the immune system mistakenly attacks and damages this layer.
- The brain has some ability to repair myelin damage, but sometimes it can fail or scarring can get in the way of repair.
- Hopefully through medical intervention we can trigger or enhance the natural repair processes.
- A number of drugs that might promote remyelination are in preclinical (laboratory) stages of testing, with a couple already in the early clinical trial phases.

Why is myelin important in our nervous system?

Myelin is a fatty substance produced by specialised cells that wrap themselves around the nerve fibres in the body. Within the fatty substance there are also specialised proteins which help the myelin keep its structure and function. This layer (also known as the myelin sheath) protects and insulates the underlying nerve fibres allowing the fast and efficient flow of signals along and between nerve cells. These nerve signals allow the communication between the brain and the body, so if they are not flowing efficiently this can affect our senses, the control of our muscles and our thought processes.

In MS, the immune system mistakes the myelin sheath as a foreign invader and attacks it, gnawing away at the protective layer. The resulting damage disrupts the nerve signals, slowing the signal or stopping it altogether. Not only does this damage impede the nerve communication but it can also leave the nerve cell exposed and vulnerable to death.

Given the key role myelin plays in MS there is vast interest in repairing it. This goal is looking increasingly possible, and has potential to help reverse early damage associated with MS and restore function more quickly. However, it is also important to note that where there has been long-term damage or serious injury resulting in the permanent loss of the nerve fibres themselves, remyelination efforts are unlikely to be effective.

> “Given the key role myelin plays in MS there is vast interest in repairing it.”

(continued next page...)

A WORD FROM OUR CHIEF EXECUTIVE OFFICER

Most would agree that it's been a very strange couple of weeks in politics.

MS Research Australia recently launched its important Health Economic Impact of MS Report in Canberra in collaboration with the Menzies Institute for Medical Research who undertook the seminal research project for us.

Under the strong glare of the cameras and political journalists, the then Treasurer, the Hon Scott Morrison MP, stood to officially launch the report at Parliament House, a full 8 years since the last incarnation of the MS Research Australia economic report in to MS.

In less than 36 hours time, he would be sworn in as our next Prime Minister.

You can visit our website to read the full report and a shorter summary. The headlines are that the prevalence of MS in Australia is steadily increasing and the annual direct and indirect costs of MS is spiralling to now $1.75 billion per year.

Despite the stellar rate of progress and improvements in MS, it's still costing the Australian people an extra $80 million a year, every year. This highlights how we need to redouble our efforts and never accept some sort of ill-informed status quo.

Employment outcomes for many people with MS have improved markedly in 8 years. More people work with MS - we are greatly encouraged by this.

It would be tempting to get lost in the facts and figures. But MS Research Australia surrounds itself with people affected by MS to ensure that it is always brought back to the reason why we exist. After two rousing speeches from someone living with MS and a beautifully passionate point of view from a loved one whose sister has MS, it was on to the PM, whose brother-in-law has primary progressive MS, to have the final word. In a heartfelt and sometimes emotional speech, he continually brought it back to where it belongs by saying "I know exactly what the impact of MS is .... I can see it everyday when I look at my brother-in-law and his family".

Our PM is one of the 7.6 million Australians who know or love someone with MS. With a simple yet poignant comment he beautifully seemed to sum up what I think many people in the packed room were also thinking. A truly remarkable event.

Dr Matthew Miles, CEO

Recoating frayed nerves continued...

How does myelin grow?

To understand how myelin repair might work we need to understand how myelin gets on the nerve fibres (also known as axons) in the first place. In the central nervous system (CNS), which includes the brain and spinal cord, there are specialised cells called oligodendrocytes that wrap the nerves in this myelin. The wrapping of a nerve fibre in myelin begins when an oligodendrocyte sends out a thin projection, a bit like extending a foot from the body of the cell. When the foot comes into contact with an axon, it sticks to it and starts to encircle the axon, ultimately wrapping multiple layers of myelin around the axon.

This process mainly takes place during a baby's development and continues throughout childhood as the brain develops. However, it also continues to some degree throughout life, because the length and thickness of the myelin sheath have to change to accommodate the axon as it grows in length and diameter and as new connections are made between nerve cells in the brain – like an ongoing process of re-wiring. It is a carefully balanced process, controlled by signals sent from nerve cells and other support cells in the brain, some that encourage myelin production and some that tell it when to stop. This ability to remodel the myelin also gives the body some abilities to repair the myelin should it get damaged.

> "Huge research efforts have been exploring different parts of the remyelination pathway to try to encourage the natural repair process."

Can we use our knowledge of myelin growth to repair myelin after injury?

Why the immune system starts to attack and damage this myelin coating in MS remains unclear. Over the last two decades there has been huge progress in the development of MS treatments that aim to stop the immune system attacking the myelin. These treatments can't repair the damage that has already been created, although some natural repair does happen once the immune attack is under control. However, with the immune system in check, can we find ways to enhance or stimulate a much stronger and effective repair response to help reverse some of the symptoms of MS and restore function?

Huge research efforts have been exploring different parts of the remyelination pathway to try to encourage the natural repair process. These approaches have included stimulating the production of new oligodendrocytes from progenitor cells (like baby myelin producing cells that are waiting quietly in the wings), or pushing myelin-producing oligodendrocytes to be more active in producing myelin and wrapping axons. Another crucial approach is to try to block the scarring that occurs when myelin is damaged and to block any signals coming from scarred areas which might be preventing the growth of new myelin. This research is being conducted both internationally and here in Australia, with many great Australian scientists making important contributions to this field. See below for some of the Australian myelin researchers contributing to the field, funded by MS Research Australia.

Testing myelin repair treatments

This research has led to several new experimental treatments being developed. Most are still being tested in the laboratory and in animal models of MS-like disease.

MS Research Australia has funded many projects looking at myelin repair. Some of these include:

Professor Trevor Kilpatrick
Working on a protein called Tyro3 which causes oligodendrocytes to produce more myelin.

Associate Professor Richard Hughes
Using synthetic compounds (potential drugs) to stimulate the pathway to promote remyelination.

Dr Carlie Cullen
Investigating whether increasing brain activity using transcranial magnetic stimulation leads to an increase in the number of oligodendrocytes and more myelination.

Dr Tobias Merson
Investigating whether increasing the electrical activity of nerve fibres can enhance myelination.

Professor Bruce Taylor and Dr Kaylene Young
Working towards clinical trials by first testing if non-invasive magnetic stimulation can promote myelin growth in preclinical models of MS-like disease.

Dr Steven Petratos
Repurposing of medications to promote nerve survival and myelin repair and determining which molecules are responsible for the nerve fibre damage in MS.

One of the important approaches to finding myelin repair therapies has been assessing if we can 're-purpose' existing medications that have already been tested in humans for safety, by conducting massive screening experiments of existing 'libraries' of drugs. To do this researchers have developed clever laboratory-based tests with oligodendrocytes grown in hundreds of tiny 'test-tubes' in the lab. Thousands of drug molecules can be rapidly screened this way to see if they promote myelin production by the cells. This approach has revealed a number of medicines that could potentially be repurposed, with some already being tested in clinical trials. This includes an anti-histamine, Clemastine, which has shown some early promise, and an antipsychotic medication, Quetiapine. Both of these trials are at the phase 2 stage and if successful will need to go through a third phase before entering the clinic.

Despite these successes it remains a challenging area with a number of unanswered questions, including what will be the best time to target myelin repair therapies in people with MS, how long the therapies might need to be given and, importantly, what is the best way to measure remyelination in a person so that we can see whether the drugs are working in clinical trials.

> "Despite the challenges, MS treatments are entering an exciting phase, with the possibility of remyelinating therapies just around the corner."

Another therapy that had shown promise, known as Anti-Lingo, had been tested in clinical trials but failed to show a significant effect on myelin repair. This may be in part due to the difficulty of measuring myelin repair, through brain scanning and nerve conduction tests, but the trial was an important milestone as it taught the company and researchers a great deal about how to best design myelin repair clinical trials.

Despite the challenges, MS treatments are entering an exciting phase, with the possibility of remyelinating therapies just around the corner. These therapies are tantalising given their promise to help repair damage caused by MS. It is possible, given the important role of myelin in protecting nerve cells and its ongoing remodelling throughout life, that myelin repair therapies may end up providing benefit across the whole spectrum of MS, from the earliest stages to more advanced MS. While we need to keep any advances in perspective it is a period of great hope, and an excellent example of the benefits that research is creating.

Dr Hamish Campbell,
Research Development Coordinator,
MS Research Australia @DrHCampbell

A repurposed asthma medication has shown promise

An international phase II clinical trial has shown that an experimental medication may halve the rate of brain tissue loss in progressive MS.

Loss of brain tissue has been associated with poor outcomes for people with MS, so this encouraging result suggests further trials of the drug should be conducted to see if it can slow disability accumulation.

The drug, known as ibudilast, is a medication that is already in use in Asia to treat asthma, but it has since been identified as a potential drug that can cross into the brain and influence the activity of the immune system there.

The drug was previously tested in people with relapsing MS, but in the initial trial, ibudilast failed to prevent relapses or the development of new lesions seen on MRI scans, but it did slow the progression of brain atrophy (shrinkage). On this basis, the drug has now been tested in progressive forms of MS to see if it could protect the central nervous system and prevent disease progression.

The trial known as SPRINT-MS, led by Professor Robert Fox of the Mellen Center for Multiple Sclerosis at the Cleveland Clinic in Ohio, USA, was conducted across 28 US sites and published in the prestigious *New England Journal of Medicine.*

> "After 96 weeks on treatment, the amount of brain shrinkage in people receiving ibudilast was half that of those on placebo."

The trial enrolled 255 people with secondary and primary progressive MS. Participants received either 100mg ibudilast daily or a placebo (dummy pill) and were tracked using MRI brain scans. The primary scan measure was the change in total brain volume over the study period. Other scan measurements known as diffusion tensor imaging and magnetisation transfer ratio were performed to measure the integrity of brain tissue. The optic nerve is also commonly damaged in people with MS and so scans were also performed to measure the thickness of the retinal nerve fibre layer in the back of the eye. Disability progression was measured using the EDSS score.

After 96 weeks on treatment, the amount of brain shrinkage in people receiving ibudilast was half that of those on placebo. This equated to approximately 2.5ml less brain tissue lost across the trial period for those on ibudilast.

The other outcome measures of brain tissue integrity, retinal nerve fibre layer thickness and EDSS scores also showed some differences but the trial was not designed to statistically assess these differences with certainty.

As with any medication being tested in a new situation, adverse events were also tracked to identify potential side effects. The number of participants experiencing any type of adverse event was slightly higher in the ibudilast treated group compared to placebo but they were predominantly gastrointestinal (nausea, diarrhoea, abdominal pain and vomiting), headache and depression. No differences were seen with respect to infections.

While it is not possible to directly compare the results from different clinical trials, the researchers did note the significant effect of ibudilast on brain atrophy was at least comparable to other recent clinical trials of some other MS medications which slowed atrophy by 15% (siponimod), 17.5% (ocrelizumab) and 43% (simvastatin).

While this trial did not demonstrate a clear clinical impact of the treatment on disability, the slowing of brain tissue loss and the apparent safety of the treatment is very encouraging. Further trials are needed to confirm the effect on brain atrophy and determine if it can translate to a slowing of disability progression.

Dr Lisa Melton, Head of Research at MS Research Australia said, "These trial results are a very welcome development. Treatments to slow and halt progressive MS are the greatest unmet need currently facing the MS community and one being tackled by MS Research Australia and our collaborators in the International Progressive MS Alliance. We can learn a lot from this trial and it brings hope that we are heading in the right direction."

Tracking treatment response using epigenetics

A simple blood test identifies epigenetic changes in people with MS and tracks their responses to an MS medication.

Research undertaken over many years has led to a number of gene discoveries with over 200 genetic changes identified with respect to the risk of developing MS. To better understand the role of genes in MS, researchers are now setting their sights on a related field that focuses on gene regulation. The field of epigenetics refers to the study of a variety of factors that influence the way DNA code is read by cells, without changing the actual DNA sequence. Epigenetic factors turn genes on and off within different cell types and they can be influenced by environmental factors – providing a link at the molecular level between genes and the environment.

Professor Jeannette Lechner-Scott, Hunter Medical Research Institute

The team at the Hunter Medical Research Institute, led by Professor Jeannette Lechner-Scott, are interested in the way genes are regulated in MS. They have completed several studies looking at different epigenetic factors in MS.

The first study examined changes to epigenetic markers in red blood cells in MS, with the hope that they might be able to uncover some new biomarkers for use in diagnosing and monitoring MS. Awarded an MS Research Australia incubator grant in 2017, Professor Lechner-Scott and her team investigated microRNA levels in red blood cells in people with relapsing remitting MS and people without MS. MicroRNAs are short molecules of DNA-like material that are known to play a role in the activity of genes. The researchers found that microRNAs do differ in people with MS in comparison to people without MS. Published in the medical journal *BMC Medical Genomics* the study identified three microRNAs that were altered in MS. One of the microRNAs, in particular, was shown to be linked with the recent results of cognitive function tests (thinking and memory) in the people with MS. In addition, when the levels of the three microRNAs were combined they provided a "signature" that could distinguish people with relapsing remitting MS from people without MS.

The second study was interested in whether DNA methylation, another type of epigenetic marker, is associated with the risk of developing MS and whether they are associated with disease progression, that is, the conversion from relapsing remitting MS to secondary progressive MS. DNA methylation occurs when molecular tags known as "methyl groups" are added to the DNA at specific locations and these tags are able to change the activity of the underlying genes.

Funded through an MS Research Australia project grant with funding support from the MS Angels and MS WA, the study published in the journal *Multiple Sclerosis Journal – Experimental, Translational and Clinical.* The study focussed on the role of DNA methylation specifically in people with relapsing remitting MS who were being treated with the MS medication dimethyl fumarate. Since methylation changes in different cell types, they looked at a specific type of immune cell from the blood known as a CD4 T cell and compared the methylation levels before and after treatment with dimethyl fumarate. This is the first time that methylation levels have been investigated over time with respect to this treatment.

They found 945 areas overall that showed differences in methylation, and of these, almost all showed higher levels of methylation after the treatment. Four of the genes were singled out as particularly important since they were affected by multiple methylation changes in regions associated with the regulation of gene activity. This may provide evidence for exactly how dimethyl fumarate is working in MS.

Epigenetic markers in the blood, either microRNAs or DNA methylation, are of immense interest since they may provide a way to track changes in an individual's disease or response to treatment through a simple blood test. Biomarkers may also be useful as an outcome or tracking measure in clinical trials. These types of biomarkers are urgently needed to help shorten the length of clinical trials and speed up results from clinical studies. Changes to gene regulation will also give us clues about the mechanisms underlying MS and provide new targets for developing therapies.

Today's legacy is tomorrow's hope

Leaving a Gift in your Will is a wonderful way to ensure that Australia's cutting-edge research continues into the future, allowing those affected by multiple sclerosis to find answers, better treatments and hope.

Over the years, some of our ground-breaking research has only been made possible thanks to the generosity of the people who remember MS Research Australia in their Will.

And it's a myth that you have to be wealthy. Even a small legacy, provided after taking care of friends and family, can allow a charity to perform transformative work.

According to new research from Include a Charity, some 25% of Australians say they would like to leave a gift in their Will to a charity that is important to them. But in stark contrast, only 7.4% of people actually get around to making the bequest official via their Will.

Meg Alwyn is one such advocate who has already made the arrangements to leave a gift in her Will.

Her own diagnosis with MS was forty years ago, when far less was known about the disease and certainly, both bedside manner and treatments were scant.

"My life changed overnight when I was told I had MS," explains Meg. "It was a different time then, and many people just didn't know much about how to treat or manage people with MS or inspire them that life could indeed go on.

"I experienced a turning point where I just felt we needed to do everything possible to invest in research so as others didn't go through what I did."

At MS Research Australia, we encourage people to think about your own legacy today, thus ensuring a greater outcome for those in the future.

"I was connected so personally to MS," said Meg. "And I feel that I live quite well with MS and I value every day. But at its core, it had affected my life and that of my family and friends so dramatically.

"There was just never a question in my mind that I didn't want anyone else to experience that feeling. For me, outdoor travel is now on a scooter – this from a lady who hitched round the world in her twenties. I am playing as best I can with the cards I have been dealt but maybe life would have been so much better without my constant companion MS. You could call my bequest a legacy, but really it was just me doing my little bit."

Meg Alwyn is leaving a gift in her Will

HOW TO LEAVE A GIFT IN YOUR WILL

STEP 1. Speak to your family and loved ones

This is a personal decision for you to make, but we recommend letting your family know that you are planning to leave a gift to MS Research Australia, so they are aware of your decision.

STEP 2. Decide what kind of gift to leave

There are three main ways to leave a Gift in your Will.

Residual: You can make a gift of the remainder, or a percentage of the remainder, of your estate once your loved ones and expenses have been taken care of.

Specific: You can make a specific bequest by simply stating the dollar amount in your Will that you wish to leave for MS Research Australia.

Asset: You may wish to make a gift of a specific asset, for example real estate, shares or bonds, or an item of particular value.

STEP 3. Get the help of a professional solicitor

Leaving a Gift in your Will is not a complicated thing to do. Nevertheless, we do recommend that you consult a solicitor or legal advisor before writing or updating your Will. They will help you through the process and ensure that all your paperwork is in order.

By engaging a professional, such as a solicitor or public trustee with extensive experience in writing a Will, you can be confident that your Will covers all important aspects and considerations.

Written by Jillian Kingsford Smith
@JillianKS, Journalist, Author,
MS Research Australia Writer in Residence
and Kiss Goodbye to MS Ambassador

Meet Kiss Goodbye to MS Ambassador Jemma Barsby

She's one of the hottest talents in Australian cricket, a passionate barista and our newest Kiss Goodbye to MS Ambassador. Diagnosed at only 19 years old at the peak of her teenage years, Jemma's diagnosis could have been a real career game changer, but Jemma didn't let MS stop her from pursuing her dreams.

Jemma grew up in a very sporty family, where backyard cricket quickly deepened her love and passion for the sport and Jemma's dream of pursuing it on an elite basis. Thanks to her supportive coach and Jemma's ability to bowl with either hand, her training began to pay off when she was only 15, as she made her elite cricketing debut for Queensland Fire. Jemma is now one of the hottest talents in Australian cricket and made the Australian 'A' women's side in 2012.

Three years later as a young professional with a promising career ahead, Jemma was faced with her MS diagnosis. Although having dealt with some incredibly difficult times since her diagnosis, Jemma is now 22 years old and more determined than ever to not let MS get in the way of her love for cricket and representing her country. "It's made me not take life for granted," she said. "To be able to do what I love and to still be able to play cricket is amazing."

Some tiny adjustments now help Jemma on the field with her goal of becoming the best cricketer she can be. "Playing cricket isn't the most ideal sport for someone like me, as one of the triggers for MS symptoms is heat. I am fortunate to have a very supportive network at Qld Cricket as well as a wonderful supplier, Artic Heat, who've made ice vests in my team colours, which are designed to help manage my symptoms by keeping me cool on the field."

You would think a young professional like Jemma has enough on her plate, but no! Jemma's biggest dream ever since she was a kid, was to own a successful coffee shop. She now works as a barista at a Brisbane cafe and makes a mean cup of coffee. "I feel lucky to have not one but two jobs that I enjoy, and to be laying the foundation for a fulfilling life after cricket. The people around me are the real secret behind my success, and I'm grateful for them every single day."

We couldn't be more excited to introduce you to Jemma, who's been spreading the Kiss Goodbye to MS message since earlier this year by sharing her personal story. Jemma has been a role model for all young people living with MS, empowering them to pursue their sports, passions and goals in life despite their MS diagnosis – and that's what we are all about!

Jemma is a true gem who loves educating her community about MS and who's put her trust in research. Yep, the perfect addition to our Kiss Goodbye to MS family. Welcome to the MS Squad Jemma, we are so happy and proud to have you on board!

New Board member appointed

MS Research Australia is pleased to announce the appointment of one Australia's leading MS neurologists and researchers, Professor Helmut Butzkueven to the Board.

Professor Butzkueven has a long working history with MS Research Australia, initially awarded a Fellowship in 2006 to investigate protecting nerve cells from MS injury.

Most recently he has been an active member on a number of working groups and collaborative platforms as well as volunteering as MS Research Australia's Scientific Conference Convenor.

Professor Butzkueven has a great international perspective from his work with the MSBase clinical database, the MS Brain Health initiative and many other international collaborations. His clinical interests are largely around the use of registry data, MRI data, cognitive testing, genomics, immunology and patient self-monitoring data to evaluate treatment strategies that optimise benefit and safety of MS therapies.

Chairman Paul Murnane said "Helmut's specialty in the management of MS and real world MS research outcomes complements the Boards mix of skills and experience. He has a broad range of medical research and healthcare skills and is a welcome addition to the team."

> "Helmut's specialty in the management of MS and real world MS research outcomes complements the Boards mix of skills and experience."

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PO Box 625 North Sydney NSW 2059 Australia • 1300 356 467 • enquiries@msra.org.au • www.msra.org.au