MS AUSTRALIA

MS WIRE

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SUBMISSIONS: AN IMPORTANT ADVOCACY TOOL

WHAT ARE SUBMISSIONS FOR? WHO ASKS FOR THEM AND WHY?

MS Australia is the largest national not-for-profit organisation dedicated to funding MS discoveries and coordinating MS research in Australia. MS Australia's role is to also work on behalf of our state and territory MS Member Organisations to provide a voice for people living with MS across the country. As such, the focus of the issues raised and comments provided in our submissions are on key areas that will impact people affected by MS and other neurological conditions. Decisions made by the Australian Government and by various departments affect the entire MS community, particularly in the health, disability and aged care sectors, which can have an immediate impact on people living with MS, as can decisions in areas such as employment, housing, energy and transport.

Our submissions are one vital way to make sure the voice of the MS community is heard!

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MS AUSTRALIA ANNOUNCES FUNDING OF 'OUTSIDE THE BOX' IDEAS

MS Australia is delighted to announce the outcomes of the first incubator funding round of 2021 – awarded are seven new grants totalling nearly $150,000.

Incubator grants provide funding for the early stages of innovative new research, intending to generate preliminary data needed to support future grant applications from a range of funding sources.

CEO of MS Australia Rohan Greenland emphasises the significance of these grants, "Historically, for every dollar invested in this funding program, the scientists have managed to secure an additional 27 dollars in subsequent funding, accelerating their areas of research."

2021 INCUBATOR GRANTS

The effect of foetal cells in maternal blood on MS during pregnancy

Dr Michael Zhong from Monash University will investigate how pregnancy affects disability and biological ageing in women with MS. He has found that pregnancy delays time to symptom onset, slows biological ageing, and protects against disability accumulation. However, the mechanisms underlying these long-term effects of pregnancy on MS outcomes are not well-understood. One possible mechanism is foetal microchimaerism (FMC), the presence and effect of foetal cells in maternal blood or other tissues. Foetal cells enter maternal blood throughout pregnancy and can remain detectable for decades. FMC may foster immune tolerance that may be beneficial in MS, and this could help explain the disparity in MS outcomes between women who have and have not been pregnant, and between sexes.

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A WORD FROM OUR CEO

On November 25, the winners of the 2021 PRIME Awards will be announced in Sydney. These awards recognise and celebrate excellence in Australian healthcare communications and the pharmaceutical and life sciences industry. I'm pleased to say, MS Australia is a finalist in the 'NGO of the Year' category, along with fellow charities Ovarian Cancer Australia and the Macular Disease Foundation Australia. We want to thank Cube Public Relations for nominating MS Australia for this award and for their incredible ongoing pro bono support for our national fundraising campaign – The May 50K.

No matter the outcome, it's deeply encouraging to have been nominated for this award, let alone shortlisted. Earlier this year, we were also honoured to receive a Fundraising Institute of Australia 2021 Excellence in Fundraising award for The May 50K.

These nominations and awards have been made possible by you, the MS community. Your support, year after year, is what drives our research and advocacy programs. It's what makes our education and awareness activities possible. Accolades, of course, are great. But at the end of the day, our progress is measured not in trophies but better outcomes for people living with MS.

The ultimate award won't go to us but to the researchers we fund to drive us to our ultimate goal, a world free from MS, and to the supporters who provide the funding to make this happen.

Best wishes

Rohan Greenland

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SUBMISSIONS: AN IMPORTANT ADVOCACY TOOL

HOW DO WE GO ABOUT DRAFTING A SUBMISSION?

Depending on the topic, we usually begin by consulting with colleagues within MS Australia, with our colleagues in the state and territory MS Member Organisations, then more broadly with the MS community and via our other networks. We talk to individuals who we know are passionate about certain issues, we put calls out via our social media channels, and we consult with colleagues at other peak bodies – often we aim to align our messages with other advocacy bodies across the sectors.

We also scan the media, obtain case studies, comments and examples and sometimes hold focus groups. We review our key messages and look at previous submissions to see how the landscape has or hasn't changed over time. All of this work is then brought together into a single submission document.

WHAT MAKES A GOOD SUBMISSION?

We feel we have made a "good" submission if at the conclusion of the committee or agency inquiry, recommendations are made that align to the key messages and recommendations that we made in our submission, and that these recommendations are acted on and changes occur. A good example is the recent decision by the government to overturn the decision to introduce independent assessments to the National Disability Insurance Scheme. MS Australia added its voice along with many other peak disability bodies who also opposed this change. The government listened, and the decision to overturn independent assessments was made.

WORKING WITH ALLIANCES

MS Australia makes several submissions on many topics each year. You will also notice that sometimes MS Australia makes joint submissions with partners and other key stakeholders such as the Neurological Alliance Australia and the Assistive Technology for All Alliance. We do this when we agree with our partners and alliances that there are issues of mutual concern and where the voice of the MS community, joined with those of other communities, can be louder and more powerful.

SUBMISSIONS IN SUMMARY

MS Australia makes submissions to national inquiries on issues that affect our state and territory MS Member Organisations and people living with, and affected by MS. Submissions and our many other key advocacy tools allow us to seek opportunities to contribute to policy development and secure funding for vital MS research. We will continue to advocate on behalf of our four state and territory MS Member Organisations, to represent the over 25,600 people in Australia diagnosed with the disease, their carers and the broader MS community.

For more information on our submissions, please visit: msaustralia.org.au/advocacy/submissions/

IS A NATURALLY OCCURRING MOLECULE THE KEY TO REMYELINATION?

There is a group of drugs used to treat MS called sphingosine-1-phosphate (S1P) receptor modulators, which includes Gilenya (fingolimod), Mayzent (siponimod) and the newer addition, Zeposia (ozanimod). These three drugs mimic naturally occurring S1P in our bodies. They are immunosuppressive, therefore reducing inflammation in MS. There is evidence that some of these drugs can also protect against the loss of oligodendrocytes (specialised cells in the central nervous system that produce myelin) and promote remyelination in laboratory models of MS. What is unknown is whether S1P naturally occurring in our bodies is important in protecting against demyelination and is necessary for remyelination after a demyelinating event.

WHAT DID THE RESEARCHERS INVESTIGATE?

Published in *Glia,* MS Australia-supported researcher, Associate Professor Anthony Don and his team investigated the requirement for a protein called SphK2, which makes S1P in the brain, for the survival of oligodendrocytes, remyelination and protecting against demyelination using laboratory models of MS. To do this, the researchers "switched off" SphK2 in laboratory models of MS and compared this to laboratory models of MS where SphK2 was not switched off.

IS THIS PROTEIN (SPHK2) ESSENTIAL FOR REMYELINATION AFTER A DEMYELINATING EVENT?

The researchers found that demyelination was much more severe in laboratory models of MS deficient in this protein compared to models of MS that had this protein. When demyelination ceased in these models, remyelination occurred in the presence of SphK2 but not in the absence of it. Markers (signs) of myelin were also significantly lower in laboratory models of MS deficient in this protein, even after demyelination ceased. These findings suggest that the protein SphK2 is essential for remyelination.

DOES THIS PROTEIN (SPHK2) PROTECT AGAINST THE LOSS OF MATURE OLIGODENDROCYTES?

To address this, the researchers investigated whether the absence of this protein affected the number of mature oligodendrocytes in laboratory models with MS and without MS. In laboratory models without MS, deficiency of this protein did not affect the number of mature oligodendrocytes in the brain.

In laboratory models of MS, the researchers found greater loss of mature oligodendrocytes in the brain in the absence of this protein. Once demyelination stopped, oligodendrocytes recovered in the corpus callosum (region that connects each side of the brain) in both the presence and absence of SphK2. In contrast, oligodendrocytes did not recover in the cortex (the outer layer of the brain) once demyelination stopped and were significantly lower in the absence of this protein.

The researchers found that the number of precursor cells to mature oligodendrocytes, called oligodendrocyte progenitor cells (OPCs), increased in the brain in response to the loss of mature oligodendrocytes in laboratory models of MS. Interestingly, the absence of SphK2 didn't affect this.

These findings suggest that this protein, to an extent, protects against the loss of mature oligodendrocytes. They also show that this protein is not necessary for OPCs to restore oligodendrocytes but is instead necessary to produce new myelin by mature oligodendrocytes.

DOES THE ABSENCE OF THIS PROTEIN (SPHK2) DELAY REMYELINATION?

Since mature oligodendrocytes recovered once demyelination ceased, the researchers next checked whether remyelination is delayed in the absence of SphK2. Laboratory models of MS deficient in this protein were allowed to recover from demyelination for four weeks. Despite oligodendrocytes recovering after demyelination, remyelination only occurred in the presence of SphK2. These findings suggest that the absence of SphK2 does not delay remyelination and that this protein is essential for remyelination to occur.

STUDY OUTCOMES

These important findings show for the first time the essential role of the protein SphK2 (which makes S1P in the brain) in remyelination after a demyelinating event has occurred in addition to protecting against the loss of oligodendrocytes.

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MS AUSTRALIA ANNOUNCES FUNDING OF 'OUTSIDE THE BOX' IDEAS

Dr Michael Zhong | Rebecca Russell | Associate Professor Todd Hardy | Dr Maryam Zoghi

Developing an online nutrition education program for people with MS

Rebecca Russell from Curtin University will develop and run an online nutrition education program for people with MS. Evidence suggests that making healthier food choices is beneficial for people with MS and making dietary changes can give a sense of control over their disease. The free six-week program will be co-designed with people with MS and MS health professionals; and provide information on diet and MS. The findings will be used to improve the program and make it available in the long-term to people with MS across Australia in the form of a larger trial to test its effectiveness.

INCUBATOR GRANTS PROVIDE FUNDING FOR THE EARLY STAGES OF INNOVATIVE NEW RESEARCH, INTENDING TO GENERATE PRELIMINARY DATA NEEDED TO SUPPORT FUTURE GRANT APPLICATIONS FROM A RANGE OF FUNDING SOURCES.

Blood markers of myelin integrity in MS

Associate Professor Todd Hardy from the Brain and Mind Centre aims to measure myelin fats (lipids) in the blood of people with MS and people without MS. Myelin is the fatty coating around nerves that allows efficient conduction of nerve impulses. When demyelination occurs, it is thought that trace amounts of lipids from the myelin spill into the blood. Should the amount of myelin lipids in the blood be higher in people with MS than people without MS, it may be possible to use myelin lipids in blood samples to determine whether there is ongoing damage to the myelin in people with MS.

This may be sufficient to indicate a failure of treatment and the need to switch their MS therapy. These traces of myelin lipids might also be used as markers of protection and regeneration of tissues of the nervous system in trials of new experimental treatments in MS.

Non-invasive brain stimulation for pain reduction in patients with MS

Dr Maryam Zoghi from La Trobe University will assess the long-lasting effect of a non-invasive brain stimulation technique on pain reduction and improving the quality of life of people with MS. For many people with MS, pain can be a significant problem. It can have a severe impact on activities of daily living and can be difficult to manage with medications. This treatment will be delivered with a battery-operated device which is very safe with very little side effects. Should this stimulation technique effectively reduce pain for several weeks, it may provide a new option for pain relief and pain management for people with MS who experience pain.

Plant-derived amino acid as a novel environmental risk factor

Associate Professor Alessandro Castorina from the University of Technology Sydney will investigate whether a non-protein amino acid (npAA) called Aze is added into myelin mistakenly in people with MS. In addition to the 20 amino acids used for making proteins, there are hundreds of npAAs produced by plants to protect them from being attacked by insects or to block the growth of competing plants (e.g. beets that produce sugar). Due to its structural similarities with the amino acid, proline, the npAA Aze from our diets can be mistakenly substituted for proline when a human protein is made. This can cause structural changes to components of myelin. It is possible that such changes could induce the immune system to mistakenly attack the myelin.

Using mini-brains to see how brain cells are affected by altered NF-kB

Dr Jun Yan from the University of Queensland is interested in a molecular pathway called the NF-kB pathway. This pathway doesn't operate in the same way in all types of cells. Activating this pathway in immune cells causes inflammation, while activating this pathway in brain cells appears to protect nerve cells from damage. Dr Yan and her team have previously found that people with MS have a lower-than-normal level of a molecule, called IkB-a, that blocks the NF-kB pathway. This means that immune cells in people with MS are more activated and inflammatory. Currently, there is nothing known about how the lower-than-normal levels of this molecule seen in people with MS might affect the cells in the brain. Dr Yan will explore whether she can use stem cells to produce brain cells and brain organoids ("mini brains" in a dish) to look at the effects of low levels of this molecule in brain cells.

Artificial intelligence analysis of brain imaging

Dr Minh-Son To from Flinders University aims to develop artificial intelligence tools to analyse magnetic resonance imaging (MRI) scans to assist clinicians and radiologists with decision making. The main aspect of neuroimaging to be addressed is detecting lesion changes on images taken at various intervals over an extended period. This is because the appearance of new lesions or evidence of new activity can influence the choice of therapy. Once he has validated this on a retrospective dataset, he will develop a software interface for deploying this tool in a clinical environment. This will enable future prospective trials to take place.

The standard of applications was extremely impressive, reflecting the high calibre of science underway in Australia. It is vital that our fundraising efforts continue to ensure we maintain the momentum of quality MS research towards our common goal of a world without MS.

Associate Professor Alessandro Castorina

Dr Jun Yan

Dr Minh-Son To

For more information about these grants and other research projects currently funded by MS Australia please visit: www.msaustralia.org.au/projects/

NATURE'S FINGOLIMOD: HOW UV RADIATION SUPPRESSES AUTOIMMUNITY

WHAT IS ALREADY KNOWN ABOUT UV AND IMMUNE SUPPRESSION?

UV light is known to be a powerful suppressant of the immune system. This is perhaps best understood in the skin, where the local suppression of skin immunity by UV in sunlight increases the risk of skin cancer.

However, UV light not only suppresses immunity in the skin but also whole-body immunity, at sites distant from the area exposed to the UV radiation. This is likely to be important in autoimmunity because UV exposure is associated with protection from autoimmune diseases such as MS.

While suppression of whole-body immunity by UV light has been observed for many years, how this happens has been poorly understood until now. In this study, Professor Scott Byrne and his team at the University of Sydney asked whether UV exposure might be changing whole-body immunity by changing the way that immune cells circulate in the body. They focused on how T cells circulate, because T cells drive the misdirected immune response against the brain and the spinal cord in MS.

WHY IS IMMUNE CELL CIRCULATION IMPORTANT IN AUTOIMMUNE DISEASE?

Immune cells normally move around the body, conducting 'surveillance' of body tissues. The lymph nodes are an important site where foreign substances are collected and processed, and immune responses are activated.

Activated T cells can then leave the lymph node, enter the blood stream, and migrate to the area of infection (or to body tissues targeted in autoimmune diseases) to mount an immune attack on the perceived threat. So, movement of T cells in and out of the lymph nodes is critical for both immune system surveillance and activation of the immune response.

WHAT DID THE RESEARCHERS INVESTIGATE?

The researchers asked whether UV treatment changes whole body immunity by changing the way T cells move around the body. T cell movement is stimulated by certain molecules released in the body.

One of the molecules is called sphingosine-1-phosphate (S1P), and T cells have specific sensors for this molecule called S1P receptors. S1P is found in higher levels in the blood than in the lymph node, so it attracts T cells out of the lymph node and into the blood.

WHAT DID THE RESEARCHERS SHOW?

In their recent publication in the prestigious *Journal of Immunology,* the team first looked to see whether UV radiation changed the number of T cells in different sites in the body. They found that UV treatment of the skin increased the number of T cells in the lymph nodes close to the skin, and in parallel, reduced the number of T cells in the blood.

Next, they looked to see whether there were changes in the S1P system that could explain this response to UV. First, they found that T cells in these lymph nodes had lost this receptor molecule on the cell surface. From prior work it is known that sometimes S1P receptor levels are reduced by the cell when there is excess S1P present in the environment. So, the researchers measured the levels of S1P and found UV exposure increased S1P levels in the lymph nodes.

Finally, they asked why S1P levels were increasing in the lymph nodes. By monitoring chemical changes in the lymph node, they were able to show that UV exposure increased the activity of a protein called SphK1 that produces S1P. To confirm this was the case, the researchers blocked the SphK1 protein in the skin prior to UV exposure. This prevented S1P production and, in turn, prevented the trapping of T cells in the lymph nodes once exposed to UV light.

WHAT DID THE RESEARCHERS CONCLUDE?

Overall, the research showed that UV exposure increases the level of S1P in the lymph nodes with the knock-on effect of reducing the S1P receptor on T cells. This leaves T cells unable to sense that there is more S1P in the blood, which would normally help draw them out of the lymph node and into the blood. This is the same way that the class of MS therapies called S1P receptor modulators works, whereby the UV mimics the mode of action of these effective MS therapies (Gilenya (fingolimod), Mayzent (siponimod) and Zeposia (ozanimod)).

These drugs trap T cells in the lymph node, so they are unable to migrate via the blood to the brain and spinal cord, where they cause damage to the myelin sheath in MS. This work demonstrates the powerful effect of UV light on the immune system, and has demonstrated for the first time, the mechanism by which UV light has far-reaching effects on whole-body immune function.

SARAH'S TRIBUTE TO MS RESEARCH

Every moment, every sensation and every symptom that leads to a person's MS diagnosis can be crucial. For Sarah, there's one moment that stands out.

First, let's rewind back to early September 2015. Sarah was on a trip around America and experienced tingles in her feet. The tingles progressively spread up Sarah's legs and arms, and eventually to most of her body – "it felt like my body was constantly reverberating."

Approximately a week later, Sarah experienced what is commonly known as an 'MS hug': a feeling of pressure around the chest or abdomen. Coupled with intense lethargy, Sarah visited a GP who concluded it was likely a pinched nerve or magnesium deficiency.

Once home, Sarah's mother insisted she see another doctor to investigate these symptoms further, who subsequently referred Sarah to a neurologist.

The appointment with the neurologist initially provided no answers, as an MRI was deemed unnecessary at that point.

However, as Sarah was about to leave, she bent down to pick up her bag and felt an electric shock down her spine: a pivotal moment.

"It was a symptom I now realised I had before the other symptoms, but I barely noticed it. That moment changed everything."

Sarah told the neurologist what had happened and said, "when I put my chin to my chest, I get this electric shock down my spine". Sarah's neurologist immediately reversed his earlier decision, now deeming an MRI necessary. Less than a month later, Sarah was officially diagnosed with MS.

Sarah, now 32, is taking on the Kiss Goodbye to MS K'gari (previously known as Fraser Island) Trek in May 2022. She is doing this as a "tribute to all the people who fundraised before me and funded the research that led me to be on the medication that I'm on that has saved my life."

When reflecting on her journey up to that point, Sarah knew very little about MS prior to her diagnosis, aside from her friend's dad living with MS.

> "I HAD TO RELINQUISH CONTROL TO MY DOCTORS AND FOCUS ON THE THINGS THAT I COULD CONTROL LIKE DIET, EXERCISE, SLEEP AND STRESS, BUT MOST IMPORTANTLY, MY ATTITUDE."

"The not knowing makes it more terrifying," Sarah says. "To learn it often hits women my age, in the prime of their lives, seems more devastating. Why didn't I know this?"

At the beginning, Sarah felt quite alone and said "I cried pretty much every day for about six months. It's a weird grief that no one really understood."

She had three lesions on her brain and experienced limited symptoms, saying that her "battle was more mental than physical", with one of the biggest things being unable to find stories about people like her: a rapid diagnosis and not heavily impacted by their symptoms.

Sarah found however that the best way to cope for both herself and her family, was to read as little as possible about other people's experiences and take on her own MS journey.

"I had to relinquish control to my doctors and focus on the things that I could control like diet, exercise, sleep and stress, but most importantly, my attitude."

Six years on, Sarah is incredibly open and comfortable with her story, and is happier and healthier than she's ever been! "I have a real sense of appreciation of all the things my body can do and the things I want it to do while it can."

One of those things is trekking 50km across K'gari for life-changing MS research! Sarah's love for bushwalking and hiking, mixed with her strong passion for MS research was the perfect catalyst for taking on the challenge.

"Research led to my treatment, and it will mean I get to live a relatively normal healthy life that, if I was diagnosed 10 years earlier, I never would have had that option. Research saved my life. It's that simple."

So far, Sarah has raised a phenomenal $4,349 to power world-class MS research, and gives thanks to her incredibly supportive family and friends, who always show up for all her fundraising activities!

We can't express enough our thanks to Sarah and her generous network, for playing a huge part in our mission to Kiss Goodbye to MS once and for all.

If you want to join Sarah across K'gari and explore the diversity of this world heritage listed island, now is your chance! Due to COVID-19, the challenge has been rescheduled to 10-14 May 2022. **Find out more here: www.events.inspiredadventures.com.au/events/kissgoodbyetoms-kgarilandtrek-2022/**

For more information on how you can raise funds for life-changing MS research, please head to: www.kissgoodbyetoms.org or contact the Kiss Goodbye to MS team on 1300 785 717.

MEET THE RESEARCHER

ASSOCIATE PROFESSOR ANTHONY DON

THE CENTENARY INSTITUTE AND THE UNIVERSITY OF SYDNEY, NSW

WHAT INSPIRED YOU TO GET INVOLVED IN MS RESEARCH?

The sense that my research would be able to help people with MS through the discovery of ways to promote myelin repair. I am reasonably new to the MS research field and was brought here through our unexpected discovery that the naturally occurring molecule S1P appears to be essential for the synthesis of myelin.

TELL US ABOUT YOUR CURRENT RESEARCH PROJECT...

A substance called myelin, which surrounds our nerves, is essential to the proper functioning of the nervous system. In MS our immune system destroys myelin, causing loss of nervous system function. Current therapies for MS suppress the immune system to stop it from causing damage to myelin and nerve cells. Whilst this is often effective in stopping the disease from getting worse, to restore normal health, we must stimulate myelin repair. This research project investigates firstly whether a naturally occurring molecule called S1P is required for the protection and repair of myelin; and secondly whether drugs that mimic the actions of S1P in our nervous system can stimulate myelin repair.

WHY IS YOUR RESEARCH IMPORTANT AND HOW WILL IT INFLUENCE THE UNDERSTANDING AND TREATMENT OF MS?

The aim of our research is to develop drugs that stimulate remyelination and can be used to help restore normal function in people living with MS. We aim firstly to determine if the molecule S1P, which is naturally present in our bodies, is essential for the protection and repair of myelin. Our current research indicates that this is the case, meaning that we need to mimic the natural actions of S1P to stimulate the formation of new myelin in people with MS. Next, we will determine if drugs that mimic the natural actions of S1P stimulate remyelination in a laboratory model. This group of drugs already exist and are used to treat MS. If we can demonstrate conclusively that these drugs protect myelin and stimulate myelin repair, this will influence clinical decision making regarding the relative benefits versus disadvantages of particular drugs. More importantly, I will be able to use this knowledge in designing drugs that are intended specifically to stimulate myelin repair in MS.

WHAT DO YOU ENJOY MOST ABOUT WORKING IN THE LAB AND WHAT ARE SOME OF THE CHALLENGES YOU FACE?

The best thing about working in a lab and running a research group is the excitement of scientific discovery and trying to solve the mysteries of life at the molecular level. The job is challenging but almost always interesting when the focus is on the science. You must keep your eyes open and be prepared for the unexpected – in my experience that is when you find something new and important. The biggest challenge is the constant need to justify your job and obtain funding to carry out the research and get paid. These are far bigger barriers to discovery and the useful application of research than anything biology can throw at us.