DECEMBER 2018

MS RESEARCH AUSTRALIA

MS WIRE

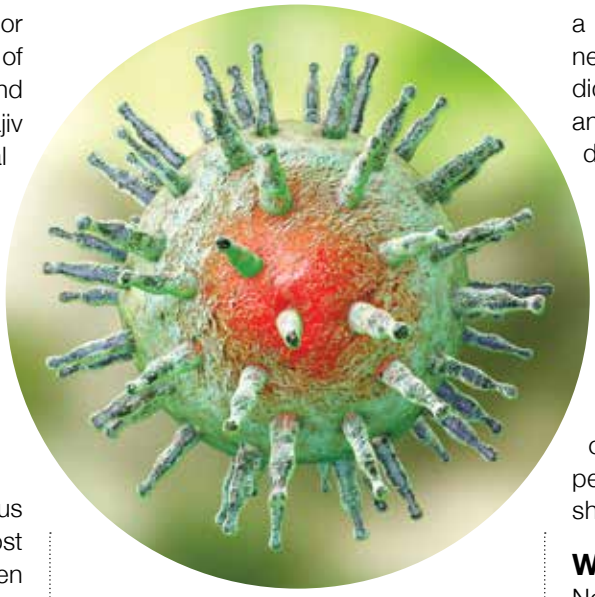
THE OFFICIAL NEWSLETTER OF MULTIPLE SCLEROSIS RESEARCH AUSTRALIA

Anti-EBV trial shows promise in Progressive MS

A treatment to target Epstein Barr Virus (EBV) called 'adoptive T cell immunotherapy' has been shown to be safe and may improve symptoms in some people with progressive MS in a world-first clinical trial.

The trial was carried out by Professor Michael Pender from The University of Queensland and Royal Brisbane and Women's Hospital, and Professor Rajiv Khanna from QIMR Berghofer Medical Research Institute.

MS Research Australia is proud to have contributed to the funding of this phase I trial in partnership with MS Queensland and other philanthropic organisations, as well as significantly supporting Professor Pender's research over the last decade.



What is EBV?

EBV is a common childhood virus with nonspecific symptoms and most people are unaware that they have been infected, but once infected you carry the virus for life. EBV infects a subset of white blood cells called B cells, these infected B cells are usually kept under control by T cells (immune cells), which kills the virus-infected B cells.

How did this trial come about?

Previously Professor Pender has shown that people with MS have a reduced number of T cells capable of killing EBV-infected B cells, compared to people without MS. This led to the idea that boosting a person's ability to kill EBV-infected cells might help treat MS.

Professor Pender then teamed up with Professor Khanna who had developed a technique where the T cells are removed from a patient, grown in the laboratory and primed to recognise and destroy EBV infected cells. The T cells are then returned to the patient where they act like heat-seeking missiles to kill the problem cells.

This type of treatment is called 'adoptive T cell immunotherapy' and this latest small phase I clinical trial was set up primarily to test the safety of the therapy in people with progressive MS.

What did the trial involve?

- 13 people with progressive MS were enrolled into the study.
- The scientists were able to collect the EBV-targeting T cells from 11 of 13 people and grow them in the laboratory.
- One participant dropped out due to an unrelated health condition.
- 10 participants remained in the trial (five with primary progressive MS and five with secondary progressive MS).
- The T cells that had been collected from the participants were primed against EBV and then infused back into their body. The participants were then monitored for 27 weeks.

Were there any improvements in MS symptoms?

Seven of the 10 participants showed a clinical improvement on the tests of neurological disability. Of the three that did not improve, two remained stable and one experienced worsening of disability.

Overall for the whole group, fatigue was significantly improved, this being a prominent feature in five of the seven patients who showed neurological improvements.

In general, the treatment did not appear to prevent the appearance of new or active lesions in the MRI scans of some of the participants, but these people were still among those who did show neurological improvement.

Were there any side-effects?

None of the 10 participants experienced any serious side effects. One participant experienced a minor alteration to their sense of taste, thought to be due to one of the chemicals used in the preparation of the cells.

What do the results tell us?

The findings published in the scientific journal *JCI Insight* show that:

- The treatment appears safe.
- It is possible to collect the EBV-targeting T cells from the majority of people with MS and grow them in the laboratory.
- While it was a small safety trial, these are potentially encouraging results for people living with primary and secondary progressive MS.

What's next?

Professor Khanna is now collaborating with biotechnology company Atara Biotherapeutics to conduct a larger, randomised controlled (double blind) trial of another 'off-the-shelf' version of this treatment.

A WORD FROM OUR CHIEF EXECUTIVE OFFICER

With over 12 months of preparation, numerous consultative workshops and very thorough planning, I am delighted with the Stop and Reverse MS Assembly which recently came to life over two action packed days in Sydney.

MS Research Australia is committed to taking a cross-sector approach to accelerating the research progress and reversing MS in the next ten years. Side by side at the Assembly were people living with or affected by MS, researchers, government, philanthropists, not for profit leaders, MS organisations, industry and corporate representatives.

The path that led to the Assembly was a long and winding one, but one of the constant elements was the consultative workshops held with a diverse and representative group of people living with MS, their carers, loved ones and other key individuals. Over 120 people across Australia living with MS were consulted for this Assembly which was underpinned by our survey on the research priorities of people with MS which included over 1,000 people from the MS community.

In a similar vein, over 80 of Australia's best MS researchers and specialists were invited to participate in pre-assembly discussions and workshops. All of the research areas and fields were covered, ranging from neurologists and immunologists to bio-statisticians, nurses and allied health specialists.

It was an intense two days but encouraging to see such dynamic and encouraging discussions with everyone coming together to answer one question "what would it take to stop and reverse MS within 10 years".

Over the coming months, MS Research Australia will work with the action groups and we will greatly look forward to keeping each and every one of you informed on what was agreed and what happens next.

Thank you for your continuing support. Together I know we can stop and reverse MS in the next 10 years.

Dr Matthew Miles, CEO

Sex hormones in MS

Multiple sclerosis (MS) is a disease that does not affect men and women equally, with three times more women than men diagnosed in Australia and the number of women with MS on the rise in most countries around the world.

In fact, women are more commonly affected by autoimmune diseases generally. Women tend to develop MS earlier and have more frequent relapses, while men progress faster and often have worse outcomes. This has led many to wonder whether differences in men and women are partly responsible and particularly about the role of sex hormones in MS.

What are sex hormones and what do they do?

Hormones are messenger molecules made by the body that are released into the bloodstream. Sex hormones control and regulate the reproductive system and also give men and women their different characteristics. While all sex hormones are made by both men and women, particular sex hormones are associated with each gender and are found at much higher levels in either women or men.

The main sex hormones in women are oestrogen and progesterone. These hormones are mostly produced by the ovaries and control reproductive development in girls. Progesterone also has important roles in pregnancy and breastfeeding. Testosterone is the sex hormone that is higher in men and is produced in the testes. Testosterone is important for sperm production and muscle mass. While these are the main roles of the sex hormones, they do also have effects in other tissues such as the brain, spinal cord and immune system.

> "Women tend to develop MS earlier and have more frequent relapses, while men tend to progress faster and often have worse outcomes."

Sex hormones and risk of developing MS

The risk of developing MS changes throughout life and most people are diagnosed in early adulthood. When MS occurs in children, boys and girls are affected equally, but after puberty the number of females diagnosed sharply rises. After menopause, the risk of developing MS in men and women is again similar. This is thought to be linked to the relative levels of sex hormones in women changing through the course of their lives. Low levels of testosterone in men is linked to a higher risk of developing MS; men with MS have lower testosterone than men without MS but the reasons for this are unclear.

Pregnancy and MS

Pregnancy affects the course of MS in women with the disease. During pregnancy, particularly in the second and third trimester, there is a protective effect with relapse rates dropping up to 70% compared to levels before pregnancy. However, there is also an increased risk of having a relapse after the baby is born, with women three times more likely to have

"There is no evidence to suggest that MS itself affects fertility, meaning people who have MS have the same chance of having children as those without MS."

a relapse in the 3-6 months immediately after giving birth. This is thought to be due to changes in the mother's immune system that occur during pregnancy that lead to increased immune tolerance (the immune system is 'calmer' and more tolerant of 'foreign' cells), to ensure that the mother's immune system does not attack the growing foetus.

Big population studies have suggested that, on average, having children does seem to reduce the risk of developing MS but pregnancies do not seem to affect the overall accumulation of disability in women with MS. Many MS medications are not suitable for use during pregnancy, so it is important for women with MS who are considering or planning pregnancies to discuss their treatment options with their medical team.

Breastfeeding

It has been difficult to determine the effect of breastfeeding on MS, with some research showing it may be beneficial and reduces relapses in women with MS while others have shown it has no effect. This is complicated by the fact that women who have more severe MS are less likely to breastfeed or breastfeed for shorter periods. Disease modifying therapies are also not recommended while breastfeeding, meaning many will make the choice to forgo breastfeeding in order to restart treatment. Women who breastfeed their babies also have a lower risk of developing MS and babies who are breastfed have a lower risk of paediatric MS and adult MS later in life.

Fertility and assisted reproductive technology (ART)

There is no evidence to suggest that MS itself affects fertility, meaning people who have MS have the same chance of having children as those without MS. As with the broader population, there will be some people who have MS who are also unable to have children naturally and some of these will use assisted ART. This usually includes the use of medications such as those that block or mimic the effects of gonadotrophin releasing hormone, to stimulate ovulation. For some women the resulting eggs are harvested and egg and sperm are joined together outside the body in a laboratory and returned to the uterus using a process called in vitro fertilisation (IVF).

In studies of women with MS who have undergone ART, there has been an increase in relapses observed following the use of ART, but this seems to be more likely in cases where a particular class of medications were used to stimulate ovulation (those that mimic gonadotrophin releasing hormone, known as agonists, rather than another class that block gonadotrophin releasing hormone, known as antagonists) or where the treatment failed. More research is needed to clarify whether this is linked to the medications used, the fact that the women are off their MS medications while undergoing treatment or the stressful nature of the situation.

Menopause and hormone replacement therapy (HRT)

Traditionally it has been thought that symptoms of MS worsen during menopause, although this is difficult to distinguish from the natural progression of disease with age. HRT is a treatment given to help alleviate the symptoms of menopause. HRT usually consists of oestrogen and progesterone, hormones that women stop producing at menopause. Newer studies have reported that women with MS who are treated with hormone replacement therapy saw an improvement of MS symptoms including fatigue and cognitive impairment and have a higher quality of life but further research is needed.

Oral contraceptives and MS

Oral contraceptives (medications given to prevent pregnancy) are also usually made up of oestrogen and/or progesterone. Research into whether oral contraception changes the risk of developing MS has failed to find a consensus, with some studies showing small decreases in risk, some showing increased risk and others finding no differences when compared to women who did not take oral contraceptives. Whether oral contraceptives affect symptoms of MS and progression of disability is similarly unclear, with both positive and negative reports on the effects of oral contraceptive use.

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Sex hormones in MS continued...

How do hormones affect MS?

Sex hormones produce their effects on the body through interactions with target cells in the body's tissues and it is now known that cells of the immune system also respond to sex hormones. Since MS is caused by immune cells attacking the brain and spinal cord, this means that sex hormones could be having a direct effect on the way MS develops and progresses in an individual.

Oestrogens are known to have mostly anti-inflammatory effects — that is they generally dampen down the immune system response. However, they can also promote inflammation and this may explain the higher rates of autoimmune diseases in women. The other female hormone, progesterone, is also generally anti-inflammatory, pushing the immune system towards a less active state.

Testosterone, the sex hormone associated with males, is thought to protect against autoimmunity by interacting with immune cells and supressing the immune system. This suppression is thought to be one mechanism that leads to the lower level of autoimmune conditions, including MS, in men. Testosterone can also enter the brain and may protect nerve cells from damage and act directly on the thymus (an immune organ located in the neck) to increase immune tolerance and reduce the chance of the immune system attacking the body.

What about hormones as a treatment for MS?

Given that sex hormones interact with immune cells and there is evidence that changes to MS disease activity and symptoms can happen in conjunction with changes to hormone levels, there has been great interest in whether sex hormones could be used as a treatment for MS.

Oestrogens

In laboratory models of MS, treatment with different oestrogens delays the onset of symptoms and reduces disease activity. Treatment with synthetic oestrogens once symptoms have begun (which mirrors the treatment situation for people with MS) reduced the loss of myelin, protected nerve fibres from damage and increased myelin repair.

Some small clinical trials of oestrogen have also been done in women with MS with mixed results. One showed that lesions on brain scans were reduced compared to before the oestrogen treatment, while another that combined oestrogen therapy with MS medication glatiramer acetate showed lower relapse levels but no changes to lesions or brain volume on brain scans.

Progesterone

In laboratory models of MS, progesterone therapy reduced the severity of MS symptoms when given after symptoms had started (the treatment situation in people with MS). Progesterone and synthetic progesterone also protect the brain from damage in laboratory models of MS. However, a clinical trial of progesterone and oestrogen given together to women with MS immediately after giving birth (in an attempt to reduce the higher rates of relapse during this time) unfortunately did not lead to any improvements in relapse rates or lesions.

> "The mixed clinical trial results of sex hormones as a treatment for MS highlight the complex nature of this disease."

Testosterone

Giving testosterone as a treatment in laboratory models of MS reduced the activation of immune cells in the brain. Testosterone has been tested in a small clinical trial of men with MS and improved the rate of brain shrinkage seen on brain scans and also showed improvements in thinking and memory skills, however it did not affect MS lesions.

Looking to the future

The mixed clinical trial results of sex hormones as a treatment for MS highlight the complex nature of this disease. MS results from the combination of many factors such as genes, environmental factors such as smoking and vitamin D and the hormonal situation found in each individual. Large well controlled studies are needed to tease out the roles of each of these factors.

This type of research could lead to a role for sex hormones as part of a more personalised medicine approach, where treatments are tailored more closely to the individual circumstances of people with MS. If we can harness the power of sex hormones to protect the brain from damage or boost repair in humans this will provide a way forward for one of the great treatment needs in MS.

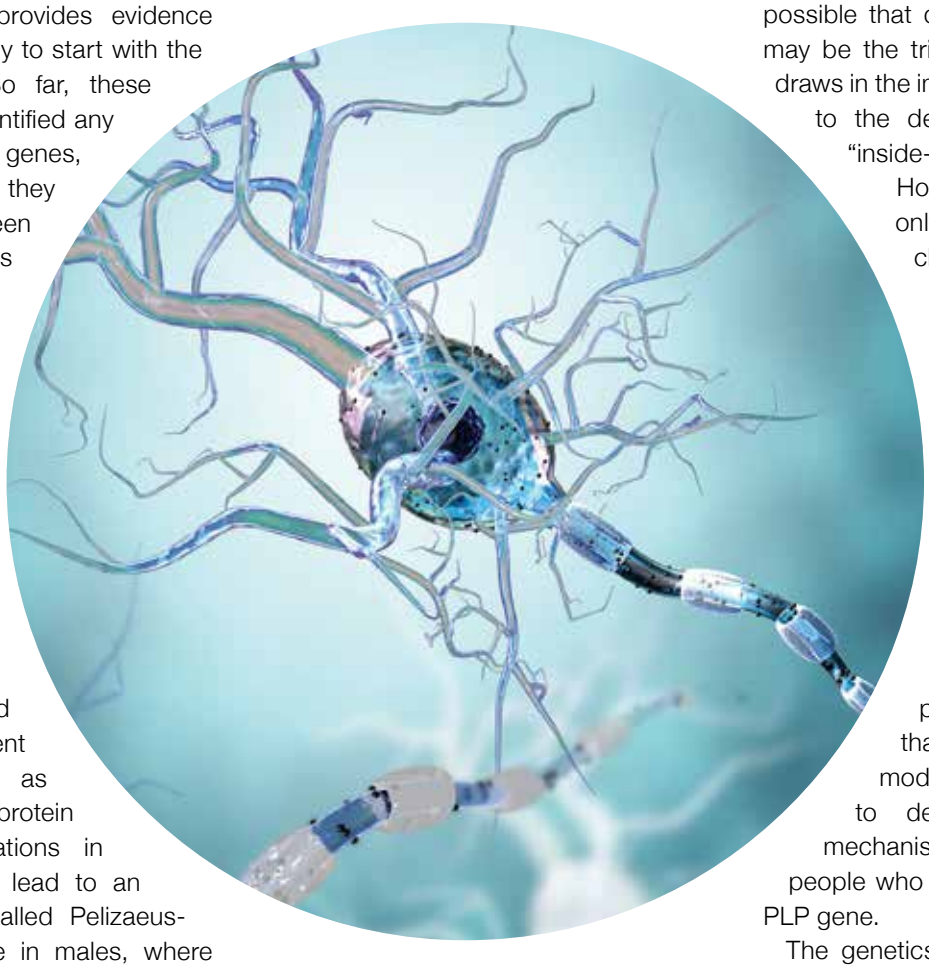
Inside-out or outside-in, how does MS begin?

There has been ongoing debate in the scientific world about how MS begins – the so called "outside-in" or "inside-out" question — whether MS is a disease that starts in the immune cells circulating in the body which then enter the brain and attack, or whether damage within the brain, is the trigger that brings the immune system into the brain to cause further destruction.

Genetic studies are helping researchers to begin to answer this question. Recent massive international collaborations have uncovered over 230 individual genetic changes that affect the risk of developing the disease. Many of these genes play a role in the immune system, and this provides evidence that MS is most likely to start with the immune system. So far, these studies have not identified any changes in myelin genes, but importantly they have also not been able to rule out this possibility.

Researchers from the University of Queensland, funded by MS Research Australia and led by Associate Professor Judith Greer, have looked more closely at one gene that produces an essential and abundant component of myelin known as myelin proteolipid protein (PLP). Some mutations in the PLP gene can lead to an inherited disease called Pelizaeus-Merzbacher disease in males, where myelin production is highly disrupted, but mutations have also previously been identified in two people with MS.

The research team looked at another group of people with MS to see if they could find alterations in the PLP gene. The PLP gene is on the X chromosome, and, due to biological changes over a woman's lifetime, some genes on the X chromosome can switch on and off during the course of life. So to increase their chances of finding a genetic change that might be responsible for MS, the researchers concentrated their search only in women who developed MS at a later age.



Their findings were recently published in the Journal of Clinical Medicine. They screened 22 women who developed primary progressive MS after 40 years of age and compared them to 42 women who did not have MS. They identified a new mutation in the PLP gene in one person with MS.

When the research team introduced this new genetic change, and the two previously discovered, into cells grown in the laboratory, they found that all three mutations had the potential to damage the myelin producing cells of the brain. This shows that in a small proportion of people with MS, it is possible that damage within the brain may be the triggering event that then draws in the immune system and leads to the development of MS, the "inside-out" model of disease.

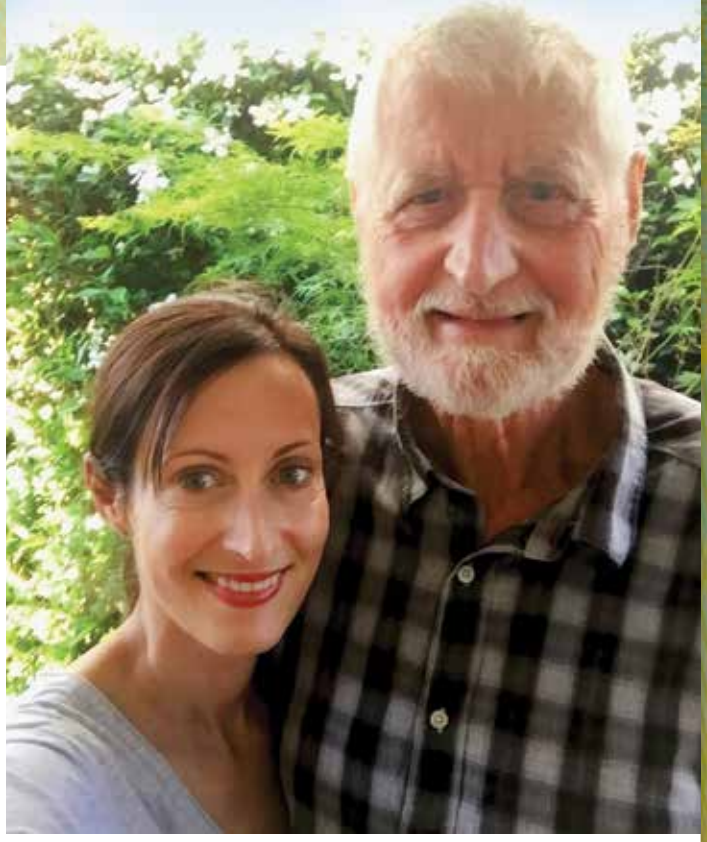
However, this is not the only way that PLP genetic changes could lead to MS. The research team also showed using computer predictions that the genetic change identified in this study would interact differently with a specific part of the immune system, potentially activating it in an autoimmune manner that could also potentially trigger MS – that is via the "outside-in" model. More work is needed to decipher exactly which mechanism might be at play in people who carry this version of the PLP gene.

The genetics of the X chromosome has not been studied as much in MS and research studies like this one highlight the value of looking more closely at individual genetic changes to determine how they might lead to disease or contribute to disease progression. If we can better understand the mechanisms of MS, we can develop better medications to target the disease more precisely and effectively.

Motivated to support research into MS

The festive season is a time to celebrate life with loved ones and give thought to how we plan to live our dreams with those we cherish most, over the coming year.

Dr Paul Yates is a passionate supporter of MS Research Australia and he has kindly agreed to share the inspiring story of his much loved daughter Dr Felicity Prylis, and their journey together in the fight against her MS. It is through the support of generous donors like Dr Yates that MS Research Australia can continue to fund research that will solve MS. Please send a gift to MS Research Australia today so that families like the Yates family can continue to live out their dreams together.



Dr Paul Yates and his daughter, Dr Felicity Prylis

From Dr Paul Yates...

"I was a general practitioner in the inner Brisbane suburb of Ashgrove for over 43 years. Particularly in the early years of practice, my experience of MS was usually of a debilitating relentlessly progressive disease, with a poor outcome. Meanwhile my daughter Felicity was enjoying great success following her dreams and my own career into medicine. Felicity outshone me academically, qualifying as a specialist physician in the shortest possible time. My wife and I could not have been more proud. Then in 2005 Felicity was diagnosed with MS. It seemed a devastating blow to all of us.

Fortunately it has not turned out that way. Modern treatments, developed by medical research, mean that Felicity has had no manifestations of disease since the initial diagnosis, and she has negligible symptoms and no disability. Her specialist career has been fulfilling and successful, she has enjoyed the support of her husband Alex, and they have presented us with two magnificent grandchildren. All of this has been made possible by research into the search for better treatments and a cure for MS.

We feel strongly motivated to support MS Research Australia, of course because of Felicity's condition, but also for the many other patients, many of them young women, in a similar position. Felicity's good outcomes have only strengthened our enthusiasm to support MS Research Australia. MS Research Australia funds research into the causes, effects and management of MS.

There has already been great success in the area of containing established disease, but what is yet to be done is to provide a strategy to prevent the disease altogether. The understanding of the role of Epstein Barr virus (EBV) in the causation of MS is a prominent success of MS Research Australia's sponsored research in Australia, and development of effective prevention of EBV infection in young people may represent a massive advance in prevention.

MS Research Australia needs ongoing funding and support, until the moment is reached when this cruel disease is beaten. As a medical practitioner and especially a father and a grand-father, I encourage you to support MS Research today."

With your generous gift, together we can fund research, change the lives of people with MS just like Felicity and ultimately find a cure.

Donate at **www.msra.org.au/donate, call 1300 356 467** or **complete the donation coupon on the back of the newsletter** and help those with MS and their families live out their dreams.

2018 The year Kiss Goodbye to MS took over the world!

We said 2018 was going to be the year our global movement really gained momentum – and it was!

Our Aussie founded Kiss Goodbye to MS campaign went global in 2016 and we have been growing each year, with 2018 being our biggest global year yet, both in terms of involvement and money raised.

Kiss Goodbye to MS was celebrated in 15 countries across the world, with Egypt and Lebanon being welcomed to the campaign this year. Together we are now funding more research into MS than ever before, and that's all thanks to you – our MS Squad! In only three years, you've raised more than $4.5 million for the worldwide research efforts into MS, so that one day we can Kiss Goodbye to MS once and for all!

Whether you've held a fundraising event, donated, attended an event, volunteered or put on your game face and supported us on social media, we would like to say a huge thank you! You are the reason we can keep funding the invaluable work of our MS researchers.

Looking back on what has been an incredible year, we've included some of our favourite moments for you, and can't wait for an even bigger and better 2019 with our Kiss Goodbye to MS family!

KISS GOODBYE TO MS

Highlights

1. Our MS researchers launched the campaign on Red Lab Coat Day with 9 creative videos by competing in the Battle of the Labs, and our colleagues from the Netherlands and Ireland also switched to red lab coats!

3. Kiss Goodbye to MS is the world's biggest international community of people raising funds for research into MS. We are on 5 continents, speak over 9 languages and are now in 15 countries.

5. The global MS Squad put on their game face and raised awareness for the invisible symptoms of MS and vital MS research all over the world.

2. The Ride for a Cure cousins Ed, Henry, Jack and Rob took on the Mongol Derby and raised an incredible $189,325 – a wild ride for MS research!

4. Our Ambassador Katrina Hemingway completed the Pennine Way by walking 430km through England with her sister Belinda and brother-in-law Neil. Despite sore feet and blisters, they made it to the end and raised $23,244 for Kiss Goodbye to MS.

6. City2Surf 2018 in Sydney was our biggest year yet, as our fabulous runners raised over $30,000 for MS research, they walked, danced and ran to the finish line.

Thank you for an incredible 2018!

We've got huge plans for 2019, be sure to visit us at **www.kissgoodbyetoms.org**

AFA Foundation commitment to MS Research

The Association of Financial Advisers (AFA) Foundation has been a long term supporter of MS Research Australia dating back to 2006. It is the generous support of organisations like the AFA Foundation that enable MS Research Australia to be the largest not-for-profit funder of MS research in Australia.

The AFA Foundation encourages its Financial Adviser members to get involved and give back to the community to change lives. They do that by working with a number of charity partners to make a meaningful difference to people in need.

This year, MS Research Australia was once again very fortunate to be chosen as one of the five charity partners of the AFA Foundation and invited to participate in the 2018 AFA National Conference held in the Gold Coast.

MS Research Australia along with the Black Dog Institute, Make a Wish Foundation, Legacy Brisbane and Rural Aid, were provided with a complimentary trade booth at the conference which presented a wonderful opportunity to meet the delegates and raise awareness of MS research.

Development and Events Coordinator Samantha Rosenfels said that a number of delegates welcomed the opportunity to hear about the impact their contributions are making and the exceptional progress of MS research broadly. She also said that many of the advisers valued the financial transparency provided with our audited financial statements and annual impact reports.

This year the AFA Foundation has raised more than $300,000 for its partner charities through various fundraising efforts, including raffles, a three day conference and a Kokoda Trail fundraiser, which was completed by members and friends of the AFA.

Over the years, MS Research Australia has established relationships with not just the Foundation but a large number of the members, who have a personal connection to MS. Development and Events Coordinator Samantha Rosenfels said "It's such a pleasure working with the AFA Foundation, we have a wonderful collaborative working relationship and we are so grateful for their long term support and commitment to funding MS research."

The AFA Foundation members, Dave Slovinec, Colette Thunig, Olivia Sarah-Le Lacheur and Melissa Favaloro along with MS Research Australia's representative Samantha Rosenfels.

HELP MS RESEARCH AUSTRALIA FIND A CURE FOR MS

Donate (Donations over $2 are tax deductible)

To support MS Research Australia's vital work I would like to:

- ☐ Make a one off donation of $
- ☐ Make a monthly donation of $
- ☐ Learn more about leaving a bequest in my Will
- ☐ I have already made a bequest to MS Research Australia in my Will

Contact details

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Payment method:

- ☐ Cheque (made payable to MS Research Australia)
- ☐ Direct Debit Request *(copy of service agreement can be provided on request)*

Financial institution:

BSB number:

Account number:

Account holder's name:

- ☐ Credit Card

Mastercard ☐ Visa ☐ Amex ☐

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