

My prog-MS ezine

For people with progressive MS and other interested people

Issue 57, November/ December 2024

Hello and welcome to the 57th edition of my ezine about progressive Multiple Sclerosis and MS progression in general. My name is Ian Cook. I'm a secondary progressive MSer from Birmingham, UK. I'm 66. (EDSS 6)

In Issue 56, there are eight pages of prog-MS news stories about new trials and research and two features. One on page 5 looks at teeth and MS. We are all aware that MS can affect your eyes but research shows it can also affect your teeth, leading even to tooth loss. Go to page 5 to find out more.

There's another feature on page 10 looking at the subject of "baclofen zombies" If, like me you take this anti-spasm drug and do so at high doses you may find yourself increasingly nodding off in the afternoon and generally feeling sleepy. Has "zombification" begun because of your baclofen use? More on page 10.

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Rituximab can stabilise progression in late-stage MS

Treatment with rituximab, a CD20 inhibitor used off-label for progressive MS patients, can stabilize disability progression and reduce disease activity in people with secondary progressive MS. That's according to a review of several published studies.

Researchers found the benefits of Rituximab were reported over a mean follow-up of two years, and were particularly more prominent in patients with shorter disease duration and those with higher disability levels before starting the treatment. Based on their findings, the researchers suggested that longer-term treatment with rituximab might be helpful for patients in the later stages of MS.

"Considering the observed benefits, continuation of [rituximab] treatment in MS patients upon reaching the progressive phase could be a viable option, particularly for those with active disease," the team wrote. The study, "Rituximab in secondary progressive multiple sclerosis: a meta-analysis," was published in Annals of Clinical and Translational Neurology.

Rituximab (marketed as Rituxan and others) is an antibody-based therapy sometimes used off-label in people with RRMS. It targets the CD20 receptor at the surface of B-cells, leading to their death and easing inflammation. However, "data on its impact on SPMS disability progression are limited," the researchers wrote.

To know more about rituximab's effectiveness in SPMS, the team of researchers, from Thailand, examined data from 13 previously published studies that had assessed the outcomes of SPMS patients given at least one infusion of the medication, which is approved as a cancer treatment.

A total of 604 patients, mostly female (65.7%), were included in the analysis. They had a mean age of 44.6 and had been living with MS for an average of 14.2 years at the time they started rituximab. In most cases, treatment was given as an initial dose of 1,000 mg two weeks apart, followed by 500 to 1,000 mg doses administered every 6-9 months.

The results showed that, after about two years of treatment, there were no significant changes in the patients' mean disability levels, as assessed with the Expanded Disability Status Scale (EDSS). "This suggests a potential benefit of [rituximab] in stabilizing disability progression in SPMS," the researchers wrote.

Rituximab is given by Intravenous infusion every 6-12 months. Those taking the drug are also given blood tests for progressive multifocal leukoencephalopathy (PML) a rare but dangerous possible side effect. **For details of sources for all news stories go to page 14**

New drug Tolebrutinib works in ‘smouldering’ SPMS

French bio-pharma Sanofi’s new drug tolebrutinib significantly delays disability progression, by 31%, and may even lessen disability compared with a placebo in people with non-relapsing secondary progressive multiple sclerosis (SPMS). That’s according to new data from the HERCULES Phase 3 clinical trial.

Sanofi believes the new data indicates that tolebrutinib can target ‘smouldering inflammation’ a type of chronic and persistent inflammation that’s thought to contribute to MS progression even in the absence of the active inflammatory attacks that drive relapses. The company will use the new trial data for discussions with regulatory authorities worldwide, with plans to begin submitting applications for tolebrutinib’s approval with regulatory authorities in the second half of next year (2025).

Tolebrutinib, which is taken as a tablet, once daily, belongs to a class of therapies called BTK inhibitors, which block the activity of a protein called Bruton’s tyrosine kinase (BTK) that is important for the survival and activation of immune cell populations implicated in MS.

Sanofi’s Phase 3 clinical development program for tolebrutinib includes four clinical trials — dubbed GEMINI 1, GEMINI 2, HERCULES, and PERSEUS — involving distinct MS populations. Two of these trials are aimed at those with progressive MS, HERCULES for secondary progressive without relapses and PERSEUS for primary progressive MS.

The HERCULES trial enrolled 1,131 adults, aged 18-60, with non-relapsing SPMS, who were randomly assigned to receive daily tolebrutinib tablets (60 mg) or a placebo for up to four years.. Significantly fewer people on tolebrutinib experienced six-month CDW (confirmed disability worsening) relative to those in the placebo group (26.9% vs. 37.2%). This amounted to a 31% lower risk of disability progression with Tolebrutinib.

Tolebrutinib also was associated with a significant, 38% reduction in new or enlarging brain lesions, but there was no significant slowing of brain volume loss. A Sanofi spokesperson said that the “surprising discordance between the disability rates and the brain volume loss rates” was a puzzle or in their words “a little bit of a head scratching.”

Sanofi is still running the PERSEUS Phase 3 trial (NCT04458051), investigating tolebrutinib against a placebo in people with primary progressive MS. Top-line data from that trial is expected in the second half of 2025.

For details of all news stories go to page 14

Interim results show promise of new drug for PPMS and SPMS

A new drug treatment for progressive MS called “Vidofludiumus” has shown a 20% reduction in nerve damage suggesting that the drug, may be effective in stopping the neuro-degeneration which characterises progression in MS.

Vidofludimus. Also called “Vidofludimus calcium” is a new drug treatment under investigation for secondary progressive and primary progressive MS. It is taken as a tablet once daily. A Phase II trial for secondary progressive MS is currently taking place. Results are expected in April 2025 and interim results are very positive according to the Immunic, the bio-pharma carrying out the clinical trial.

Vidofludimus reduces the activity of T-cells and B-cells, which are types of white blood cell involved in the immune response that damages myelin coating of nerves in MS. Vidofludimus blocks an enzyme (dihydroorotate dehydrogenase, DHODH) which is essential for the growth of activated T-cells and B-cells - white blood cells involved in the aberrant immune response that damages the myelin coating of nerves in the brain and spinal cord. The drug is thought to reduce inflammation around the nerves. It has a similar mechanism of action to Aubagio (teriflunomide) but is expected to have a more targeted effect, reducing the risk of side effects.

The trial called CALLIPER – vidofludimus compared to placebo, in secondary and primary progressive MS is currently taking place. An interim analysis published a few months ago indicated that people in the study taking vidofludimus calcium had 22.4% reduction in serum neurofilament levels. Neurofilaments are used as an indicator of nerve damage, so the researchers interpret this as showing that vidofludimus calcium acts in a neuroprotective way.

on top of this Vidofludimus acts as DHODH inhibitor. Inhibition of dihydroorotate dehydrogenase (DHODH) is an established mechanism for the treatment of relapsing-remitting multiple sclerosis (RRMS) and it is believed that it can target the underlying neurodegenerative process, which is ongoing despite or independent of relapses.

“We did an interim analysis in the CALLIPER study, and we really, on a group level, read out a biomarker called NFL, neurofilament light chain. And we ourselves were very impressed about the reduction of NFL in the treated group compared with the placebo group. So, for example, in the so far untreatable population, we have seen a 20% reduction of NFL compared to placebo. That's a strong signal,” said an Immunic spokesperson.

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Advanced MS and teething problems

MS and teeth are subjects rarely discussed outside a long-lasting debate about amalgam fillings. But is there a bigger story we are missing here?

The reason I ask this question is that I have just had one back (molar) tooth extracted after it spectacularly collapsed while I was flossing one evening. I'd had some problems with the tooth for ages but at the extraction the dentist told me that lack of "nerve support" to my teeth caused by demyelination had probably weakened the big back tooth over the years.

He said this was something he had seen in the mouth of another MSer, probably also as a result of years of demyelination. The dentist went on to explain he had another older patient with MS who, like me, had developed two "problematic back molars" both of which he had extracted. Worryingly, it sounded like the dentist knew what he was talking about.

As if my dentist's observation wasn't sufficiently disquieting, a friend and fellow MSer who is about the same age as me (early 60s) has just had all his teeth taken out at the local dental hospital. So can demyelination have an impact on your teeth, and if so, what can you do about it?

The short answer to the first question appears to be "yes" it can. Although MS is generally regarded as a disease of the central nervous system (CNS), several studies have reported that people with MS can also have demyelination in the peripheral nervous system (PNS) too. The PNS is that part of your nervous system lying outside your brain and spinal cord where nerves receive and send messages to outlying body parts, like your teeth..

A paper in the 2020 Journal of Neurology, Neuroimmunology and Neuroinflammation was titled: 'Is MS affecting the CNS only?' The paper concluded that 'PNS involvement in MS might be more frequent than is generally assumed.' Given that nerves in both parts of the nervous system are myelinated it would seem strange that an auto-immune disease that targets myelin would leave myelinated peripheral nerves alone. Anyway, back to dentistry.

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Continued from page 5 Another paper" Multiple Sclerosis—A Demyelinating Disorder and Its Dental Considerations" published in 2023 in the journal "Brain Sciences" said that periodontal diseases (teeth and gums) are more prevalent in MS patients. The article showed a picture of an MSer's mouth where two molar teeth had been extracted.

As well as dental problems caused by less peripheral nerve support to our teeth, we MSers may also suffer other related problems which can put us at significantly greater risk of tooth loss. One of these problems is a dry mouth caused by a poorer flow of saliva. MSers suffer from this problem for the same reasons that we often suffer from dry eyes. The same process that stops us producing enough tears also stops us producing enough saliva, and a moist mouth is hugely important when it comes to good dental health.

Saliva cleans the inside of your mouth, and any food debris left in your mouth is carried away by saliva. A good saliva flow stops food from collecting and "fermenting" in your mouth which causes tooth decay. As well as this, saliva delivers minerals to your teeth and protects against acids breaking down tooth enamel, so saliva is highly important for good dental health.

A 2020 study in the Journal of Dental Medical Problems entitled "Salivary profile and dental status of patients with multiple sclerosis" found significantly lower salivary flow rates in a group of 25 MS patients compared to 25 healthy controls. Interestingly, the same research found the number of cavities and missing molars was significantly higher in the MS patients than people without the condition.

Reading around the subject has made me realise there is far more than just the disease itself causing poor tooth health in us MSers. Medications used to treat MS can also contribute significantly to the onset and symptoms of gum disease and tooth decay. Many MS medications which aim to control MS symptoms have the side effect of dry mouth. Baclofen (anti-spasm), and clonazepam (anti-spasticity) are two medications I take daily and "dry mouth"is among their side effects, particularly baclofen, which means I am losing the protection that plenty of saliva gives my teeth.

So, what can be done about all this? Good dental care is incredibly important for us MSers. Good teeth cleaning habits -things like using an electric toothbrush rather than a manual one, using small interdental brushes and flossing can reduce debris and tooth decay. It is also important to schedule regular dental visits where you can get to see a dentist. Depending on how well you clean your teeth at home, dental appointments may be needed more frequently with the hygienist too. The take away message I suppose is to recognise MS can affect your teeth and therefore it's important to keep your teeth clean and your mouth well hydrated. As well as the dentist, remember that the best help is often self-help. **Pic p1 & 5 False Teeth Wikipedia public domain** **For further details of sources for feature see page 14.**

News

Simvastatin Fails to Reduce Progression in Phase 3 Trial of SPMS

A phase 3 trial of high dose simvastatin revealed the drug doesn't significantly slow disability progression in non-active secondary progressive MS. However, research continues into statins and MS (see next page)

The phase 3 trial called MS-STAT2 (treatment with simvastatin- a medication for high cholesterol,) showed the drug demonstrated no evidence of benefit in reducing disability progression in non-active progressive secondary progressive MS (SPMS). MS-STAT2 was a follow-up to a previously completed phase 2b trial, dubbed MS-STAT (NCT00647348), that first showed the potential of simvastatin in SPMS.

The failure of the Phase III trial following the success of earlier trials presents researchers with a puzzle as lead researcher Jeremy Chataway, professor of neurology at University College London, acknowledged. "How exactly simvastatin helps in MS isn't fully understood, but it appears to work through "a number of different mechanisms. Simvastatin may reduce the overactive inflammatory response that's damaging to nerve cells in the brain and spinal cord. At the same time, it's thought that simvastatin may protect nerve cells from damage and improve blood flow in the brain, which could slow the progression of MS symptoms.

"For example, simvastatin may reduce the overactive inflammatory response that's damaging to nerve cells in the brain and spinal cord. At the same time, it's thought that simvastatin may protect nerve cells from damage and improve blood flow in the brain, which could slow the progression of MS symptoms," he added.

The primary outcome, confirmed disability progression up to 48 months, did not significantly differ between simvastatin and placebo-treated patients. Chataway and his colleagues also reported certain secondary outcomes, including a multi-component measure of confirmed disability progression up to 36 months, as well as relapse rate up to 36 months.

The study included only patients with a confirmed diagnosis of MS who had entered the secondary progressive stage. These individuals, aged between 25-65 years old, had steady progression rather than relapse as the major cause of increasing disability in the 2 years prior to study onset.

MS-STAT2 was a follow-up to a previously completed phase 2b trial, dubbed MS-STAT (NCT00647348), that first showed the potential of simvastatin in SPMS. **For further details of all news and features go to page 14**

New Study Uncovers Cholesterol's Role in MS progression

Researchers at the University of Colorado Anschutz Medical Campus, in collaboration with colleagues at the University of Cambridge, have found that when the body makes more cholesterol, it can be harmful to brain cells in people with progressive MS.

This research, which opens up a whole new line of inquiry into statins and MS, shows that higher cholesterol production may contribute to the worsening of the disease by damaging the nervous system. That's according to a study published in the journal 'Cell Stem Cell'. The team behind the research took skin cells from patients and transformed them into brain-like cells, which helped them discover a new problem in how these cells use energy that makes the MS worse. The finding could lead to new treatment options for the disease.

In progressive MS neuronal degeneration, rather than just the loss of myelin, is central to the irreversible worsening of symptoms over time. In advanced stages, the interplay between ageing and MS becomes more pronounced, indicating that age-related changes may intensify neuronal loss.

The reported findings shed light on a condition called cellular senescence, (ageing) which has been seen in certain brain cells. This state can make it harder for the brain to heal and can worsen damage in progressive MS. The researchers found that in brain-like cells from MS patients, there's a problem with how the cells handle energy, leading to too much cholesterol. This extra cholesterol creates harmful substances that damage nerve cells. They discovered that simvastatin, a common drug that lowers cholesterol, can help improve this harmful process and create a healthier environment for the cells.

"Cholesterol metabolism has been extensively investigated in cardiovascular disease, and more recently, in cancer," said D'Alessandro, co-senior author on the study. "Common drugs that target cholesterol metabolism have been proven to be safe and effective in humans. Our findings suggest that these drugs could be repurposed in the treatment of MS." The researchers say this work confirms the close relationship between cellular ageing and problems with how cells use energy (dysmetabolism). The results show how cells manage fats, including cholesterol, is important for the way they communicate with each other to function properly.

The team believes this discovery paves the way for new treatments focused on how the body processes cholesterol. By targeting cholesterol metabolism, they hope to reduce nerve damage and slow down the progression of multiple sclerosis (MS).

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New study links ancient viral genes in human DNA to MS

Abnormal activity of ancient viral genes may play a role in MS, its progression and other neurological disorders like motor neurone disease, a new study has found.

It has been known for some time that a large portion of the human genome is not human at all. Substantial stretches of human DNA contain genes from viruses that got incorporated into human DNA during ancient infections. A budding field of research is now exploring how these viruses, called human endogenous retroviruses, or HERVs, may play a role in human diseases like MS.

“These HERV sequences are not just static fossils derived from ancient viral infections — they must be actively influencing brain function in ways we are only beginning to understand,” says Rodrigo Duarte, PhD, co-lead author of the study “Ancient viral DNA in the human genome linked to neurodegenerative diseases,” which was published in the journal “Brain, Behavior, and Immunity.

In the study, scientists in the U.S. and U.K. set out to examine the role of HERVs in neurological diseases using a technique called retrotranscriptome-wide association studies. This type of analysis involves cross-referencing data on HERV activity with data on known genetic risk factors for disease. If HERV activity is altered in the presence of genetic risk factors, it stands to reason that modifying HERV activity may be one of the mechanisms through which these risk factors play a role in disease.

“Using large genetic datasets and a new analysis pipeline, this study is well equipped at pinpointing which specific HERVs are important in increasing susceptibility for neurodegenerative diseases,” said Timothy Powell, PhD, co-lead author and senior lecturer at King’s College, London.

Results revealed two statistically significant associations between HERV activity and neurological disease. Activity of one HERV, (HERV W), showed a significant association with MS. Another HERV, (HERV K) was s associated with motor neurone disease

A phase II clinical trial (Lighthouse 2) testing out a potent HIV anti-retroviral drug in patients with Motor Neurone Disease (ALS) has just posted positive results and has led to a new Phase III trial testing out the drug in 390 patients with ALS over two years. The trial is due to post results in 2026. It may pave the way for a renewed interest in further exploring the link between MS and HERV-W, which was the subject of a small study in 2019. **For further information go to page 14**



Am I turning into a 'baclofen zombie'?

Like many prog-MSers I have been taking the anti-spasm drug baclofen for several years at increasingly higher doses. My baclofen use has grown over the past decade -- - from 10mg to 30mg daily.

So I was naturally concerned when I read a recent medical report in which the term "Baclofen zombie" was used.

I know that Baclofen has a sedating effect when used at high doses and am also aware that I am now taking three times the dose I was taking to begin with. So, after reading the medical report I asked myself: Am I in danger of becoming a "baclofen zombie"? Or worse still, have I already become one"? And, if so, why has nobody told me?

Zombies, as you no doubt know, are mythical creatures, partly alive but also partly dead. They appear in countless horror films including 'Night of the Living Dead' "Plague of the Zombies" and "Zombie Apocalypse". Although I was once a fan of zombie films, I never expected to worry about turning into one or find the term 'zombie' applied to people like me in medical literature. But there it was staring me in the face in the shape of Professor Gavin Giovannoni's MS-Selfie Substack case report and feature titled: "Are you a baclofen zombie?" Oh dear. Medically speaking, a "Baclofen zombie" is someone who becomes increasingly sedated or "zombie- like" during the day because of their heavy use of the drug, over the previous 24 hours or so.

I wouldn't say I have yet become a daytime baclofen zombie as a result of my night-time use but I do feel increasingly "sedated" or "zombiefied" during the day, sometimes nodding off in the afternoon probably because of my growing baclofen use at night.

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Continued from p10 The medical explanation for this is that Baclofen stimulates a receptor called the GABA-B receptor. GABA is a major "inhibitory neurotransmitter" in the central nervous system (CNS). In lay terms 'Inhibitory' means Baclofen inhibits or stops the spasms and spasticity that characterise MS. Like all drugs it has some side effects and taking it for a long time and at high doses is problematic.

The problem with Baclofen is that it needs to be present in your blood at relatively high levels to achieve an anti-spasm effect, which is at a similar level to that which causes sedation. As I take it at midnight night time sedation isn't really a problem because we all need to be sedated to sleep. If anything, it helps.

However, as you sleep the baclofen levels in your bloodstream start to wear off. This is called the drug's half-life or the time it takes for blood levels of that drug to fall by half. Baclofen has a short half-life of between 2-6 hours.

I take a 2mg dose at 11 pm, an hour before going to bed. which means that while it will help me fall asleep its effects will have worn off by around 5 or 6 am. At this point my spasticity problems are returning. And it's 's not just the drug wearing off there is another problem.

The human body has a diurnal (day-night) variation in spasticity which is naturally worse in the early morning hours (4-6 am). As my baclofen wears off, my body's natural 4am – 6 am increase in spasticity and spasms starts to kick in, and I mean "kick in" literally.

My spasms become more prominent and uncomfortable around 6 am which is when I tend to be awoken with spasms and painfully stiff legs. In view of this I feel I have no alternative but to take an additional dose of baclofen. On occasions I also stretch using a theraband for one minute on each leg. I then get back into bed and get another 2-3 hours sleep before I get up, having given up on restful sleep altogether.

The final dose of baclofen has probably left my body by lunchtime so it's hardly surprising that "Zombification" kicks in during the afternoon. I am not only tired after my disturbed night's sleep but it is also after eating lunch, meaning that the infamous 'after-dinner dip' or 'Postprandial somnolence' is also slowing me down. Given that I still have some baclofen in my system I now have the perfect recipe for 'zombification'. Well that's how I see it, but then again if I am a 'baclofen zombie' how would I really know what's going on, after all, as one of the"zombies" I am only half alive?

Pic p10 Zombies as portrayed in the movie Night of the Living Dead, Wikipedia public domain **For details of all features go to page 14.**

Cell study shows sulfuretin may halt MS and its progression

US researchers have discovered a plant-derived small molecule that can promote the growth of cells that produce myelin, the protective coating around nerve fibres damaged in MS.

The naturally occurring molecule, sulfuretin, blocks the activity of an enzyme that is overactive in areas of myelin damage. This enzyme also contributes to the growth and spread of cancer cells, meaning the discovery has implications beyond MS.

“We think this is a drug that could have impact in a lot of different areas,” Larry Sherman, PhD, professor in the Oregon National Primate Research Centre at Oregon Health & Science University (OHSU), said in a university news release.

Details of the discovery were described in the study, “Distinct chemical structures inhibit the CEMIP hyaluronidase and promote oligodendrocyte progenitor cell maturation,” which was published in the Journal of Biological Chemistry.

In MS inflammation damages myelin, the nerve fibres, and the cells that generate myelin, called oligodendrocytes, triggering the onset of MS symptoms. Elevated production of an enzyme known as cell migration inducing and hyaluronan-binding protein, or CEMIP, which naturally degrades hyaluronic acid, has been implicated in the development of MS. Hyaluronic acid is a long, chain-like molecule that is important for many natural functions, including tissue lubrication, cell migration, and wound repair.

Studies show that CEMIP expression is elevated in demyelinating MS lesions, resulting in the excess production of certain hyaluronic acid fragments that can directly block the maturation of oligodendrocytes. However, small molecules that suppress the activities of some hyaluronidases, including CEMIP, have boosted functional recovery in MS rodents.

Using therapeutic small-molecule inhibitors to target CEMIP hyaluronidase activity may be “an efficacious method to promote repair following [brain and spinal cord] insults, reduce cancer cell metastasis to the brain, and reverse other pathological conditions linked to elevated [hyaluronic acid degradation],” the researchers wrote.

“Now we have an inhibitor that could actually stop” such activity, said Sherman, who is also a professor of cell, developmental and cancer biology at the OHSU School of Medicine.

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News

$1 million grant awarded to explore myelin repair mechanisms in MS

The National Multiple Sclerosis Society (USA) has awarded a grant of 1 million dollars to work on identifying mechanisms that control a special kind of brain plasticity, known as myelin plasticity. The goal is to find ways to stimulate myelin plasticity to regenerate nerve fibres affected in MS.

Dr. Isabel Pérez-Otaño, who leads the Plasticity and Remodelling of Neural Circuits laboratory at the Institute for Neurosciences (IN), a joint centre of the Spanish National Research Council (CSIC) and the Miguel Hernández University (UMH) of Elche is involved in the research. The grant is part of the NMSS 'Pathways to Cure' program that funds innovative therapeutic approaches to treat multiple sclerosis (MS).

Studies suggest that MS has an autoimmune origin. While advances have been made in halting the immune system's attack on oligodendrocytes; the cells that produce myelin; current treatments lose efficacy as the disease progresses. At present, no therapies exist that can restore lost or damaged myelin. "Our brains have an inherent repair mechanism called remyelination, which is activated after damage to form new myelin sheaths. But this repair capacity fails with age and disease progression, leading to irreversible disability.

Oligodendrocyte progenitor cells (OPCs) are abundant in the brain and spinal cord of MS patients, and offer an unmatched opportunity for generating new oligodendrocytes and promoting myelin repair. The challenge is to find ways to enhance their responses and improve their ability to form myelin.

The team has discovered a brain receptor that could help activate these stem cells and unlock the plasticity of myelin. The research will focus on developing gene therapy or pharmacological approaches and test their ability to bring back efficient myelination in mouse models. Additionally, the team is exploring the potential of combining gene therapy with pharmacological treatments and rehabilitation strategies to further enhance myelin repair after injury.

A breakthrough from this research could not only transform the treatment landscape for MS but may also have wide-ranging implications for other neurodegenerative diseases, such as Alzheimer´s or Huntington´s disease, where myelin failure has been implicated**.**

For details of all news stories see page 14

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