

My prog-MS ezine

For people with progressive MS and other interested people

Issue number 33, September/October 2020

Hello and welcome to the latest edition of my ezine about progressive MS and MS progression in general. My name is Ian Cook. I'm a secondary progressive MSer who lives in Birmingham, UK.

In this issue are seven pages of important prog-MS news stories. There are also two features. One on page 5 is on MS and heat sensitivity, and another on page 10 looks at a supplement called androgrpholide that has posted some impressive results in a prog-MS trial. See page 10.

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News

Diabetes drug could prevent MS disability progression

A common diabetes drug could help enhance a natural mechanism that protects nerve fibres from damage and prevent disability progression in MS, according to a paper published in the journal Acta Neuropathalogia. The lead author of the paper Dr Don Mahad said therapies such as this one, that protect the nerve fibres, are the 'Holy Grail' of MS treatment.

In MS, the protective coating surrounding nerves known as myelin is damaged causing nerves to become less energy efficient which makes them vulnerable to further damage and causes disability over time.

Following a research programme spanning more than a decade, researchers at the University of Edinburgh have discovered a natural mechanism in the body that tackles this issue, which they are calling ARMD (axonal response of mitochondria to demyelination).

While researchers said this natural function alone does not provide enough energy to address demyelination in MS, its discovery raises the possibility of using a drug to enhance it, and the team said that after further research they were able to enhance ARMD and protect the vulnerable nerves using the diabetes drug pioglitazone.

Lead author Dr Don Mahad said therapies to protect the nerve fibres were the 'Holy Grail' of MS treatment. The senior clinical lecturer at the University of Edinburgh added: "Disability in MS is caused by a loss of nerve fibres following damage to the myelin that protects them. Although our understanding of MS has vastly improved over the last two decades, new therapies still do not protect nerve fibres.

"Such protection is the Holy Grail in MS treatment – not only for the relapsing form of MS, which has various options available, but for progressive forms too, where treatment continues to lag behind. Remarkably, we were able to enhance ARMD and protect these vulnerable nerves using the readily available diabetes drug pioglitazone. This is an incredibly important discovery – one we believe could finally bridge the gap in MS treatment."

Dr Emma Gray, assistant director of research for the MS Society, said: "This represents another important stride towards our goal of stopping MS – and we believe that MS treatment could in the near future look completely different. It will mean no-one needs to worry about their MS getting worse."

Do you have diabetes and take pioglitazone? If so, let me know if it has made your MS any better as I would be interested in writing about this.

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Cashew Molecule Promotes Remyelination And Halts Disease Progression in MS Mice

Anacardic acid, a compound found in cashew nuts, promoted myelin regeneration and prevented damage to neurons and disability in two mouse models of MS.

The protective effects were associated with the maturing of myelin-producing cells and production of IL-33, an immune-related molecule with a "neuro-reparative" role in the central nervous system (CNS, the brain and spinal cord). The findings suggest that treatment with anacardic acid may be a new potential therapeutic approach for MS.

"We see this as an exciting finding, suggesting a new avenue in the search for therapies to correct the ravages of MS and other demyelinating diseases," Subramaniam Sriram, MD, the study's senior author, said in a Vanderbilt University Medical Center (VUMC) press release. Sriram is VUMC's chief of neuroimmunology and the William C. Weaver III professor of neurology at the US university. The study, "Anacardic acid induces IL-33 and promotes remyelination in CNS," was published in the journal PNAS.

In the brain, damage of myelin (the protective sheath around nerve fibres that is lost in MS) attracts immature, stem-like cells called oligodendrocyte precursor cells (OPCs) to the lesion site. These OPCs then mature into oligodendrocytes, which are myelin-producing cells capable of restoring the myelin sheath. However, despite the presence of these progenitor cells in MS lesions, remyelination, or myelin repair, is incomplete or absent. Therefore, increasing efforts are focused on identifying potential therapeutic approaches to promote oligodendrocyte maturation and/or remyelination. IL-33 is an immune signalling molecule found at high levels in the CNS — particularly in oligodendrocytes — where it has immune-protective and neuro-reparative properties. It was shown to promote remyelination after CNS injury in mice and reduced disease severity in a mouse model of MS. These findings suggested that compounds known to increase IL-33 production potentially could be used to promote remyelination.

A team of researchers led by Sriram evaluated the effects of anacardic acid — a molecule found in the shell of cashew nuts and thought to potentially increase IL-33 levels — in rat OPCs grown in the lab and in two mouse models of MS. In the two MS models, anacardic acid treatment halted or delayed disease progression and myelin loss, improved remyelination, and reduced disease scores, compared with untreated mice. These clinical improvements were accompanied by an increase in the number of IL-33–positive oligodendrocytes in the areas of myelin loss. **For details of all stories go to page 13**

New drug shows potential to significantly regenerate myelin

NeuroScientific Biopharmaceuticals (NSB)'s new drug EmtinB can induce significantly greater myelin regeneration in a cell model of MS than Copaxone, the company has announced.

"These results represent a potential breakthrough in the treatment of MS as there are currently no approved therapeutic drugs available to patients that have demonstrated the ability to regenerate myelin in the central nervous system" Matthew Liddelow, NSB's CEO and managing director, said in a press release.

EmtinB is a lab-made molecule designed to mimic the neuroregenerative and neuroprotective effects of a protein called metallothionein-II (MT-II). EmtinB is believed to activate signalling pathways that promote nerve cell survival and regeneration, and also suppress neuroinflammation.

Previous data in a cellular model of MS showed that EmtinB significantly increased the number of oligodendrocytes — the cells that produce myelin. The study was conducted by an independent, French-based contract research organization called Neuron Experts, at NSB's request.

Then, NSB asked the same organization to assess EmtinB's ability to promote myelin regeneration in a cellular model of MS and compare it with that of Copaxone, a commonly-used disease-modifying drug for MS.

The new independent, preclinical study evaluated the regeneration of myelin around nerve fibres after treatment with one of five doses of EmtinB (15, 30, 60, 120 or 150 micrograms per milliliter, mcg/ml), or a dose of Copaxone (10 mcg/ml).

Data showed that almost every dose of EmtinB resulted in a significant increase in myelin sheet around nerve fibres, compared with untreated cells. At the higher doses (120 and 150 mcg/ml), EmtinB's boost in myelin regeneration was significantly superior — by more than 25–30% — to that achieved with Copaxone.

"Whilst we previously showed that EmtinB could positively influence the proliferation of myelin-forming oligodendrocytes in an MS model, these results go a step further to demonstrate that EmtinB significantly increases actual myelin formation", Liddelow said.

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Heat is on for new MS cooling drug

If you suffered from heat sensitivity this Summer you will know heat is a big Summer holiday spoiler, and as a symptom heat sensitivity doesn't get the coverage it deserves. Or it didn't until recently.

In recent years, researchers have tried to identify the exact mechanism through which heat sensitivity has an effect in MS. The first thing looked at was the fact that MSers overheat because we lose our ability to sweat as MS progresses. Normally adults can sweat up to 2–4 litres per hour or 10–14 litres per day and sweat cools the skin as it vaporises in a process known as "evaporative cooling". But in MS things don't work so well.

Research carried out in 2009 at Oulu University Hospital in Finland found MS patients sweated markedly less than people without the condition. After just 10 minutes of heating, sweating was significantly lower in the forehead, feet and legs of MS patients than in those who didn't have MS, meaning MSers were overheating as they were unable to benefit from evaporative cooling.

Sweating in simple terms is a two way process. Temperature receptors in the skin send messages through the nervous system to a part of the brain known as the hypothalalmus where heat sensitive nerve cells are located. These cells in return send messages to millions of sweat glands in the skin to release sweat causing "evaporative cooling". One of the key chemical elements involved in this process of efficient communication is sodium. As axons in the central nervous system heat-up, the amount of sodium moving into the nerve increases in a process known as "sodium loading" . However in MS this process goes into overdrive and excessive sodium makes it harder for messages to be sent efficiently up and down nerves to and from the sweat glands. This results in less sweating and, as a result, overheating. **Continued on page 6**



Dr Mark Baker (pictured) of Queen Mary, University of London is currently researching "sodium loading" in axons. Dr Baker is looking for a drug or drugs that could target MS heat sensitivity by reducing the amount of sodium travelling into nerve cells when the temperature increases, allowing messages to muscles to be sent more securely and therefore better communication with the sweat glands and more sweating, hence less over-heating.

One drug that is believed could have this effect is bumetanide. This drug is already used to reduce extra fluid in the body (oedema) caused by conditions such as heart failure, liver disease, and kidney disease so we know it's safe to use. It is thought bumetanide might be effective in tackling heat sensitivity because it reduces the amount of sodium entering cells. Dr Baker has been leading research into this area but says that bumetanide comes with major problems. It is poor at getting into the brain and nervous system and thus poor for accessing damaged axons. A side effect of bumetanide is increased urination – something that would be unwelcome by many of us MSers. Dr Baker says these facts are leading him to look for other drugs.

Although it is early days in Dr Baker's research, it is hoped that continuing work on heat sensitivity could lead to other drugs which would not have the side effects of bumetanide and may even have a neuroprotective role too. Until that day happens, MSers will remain reliant on the tried and trusted techniques for keeping cool such as fans, jackets or sprays. Meanwhile the heat, as they say, is on in the search for a new cooling drug.

Picture page 1 Ethan Robertson, Unsplash +p5 Thomas Passfield – Unsplash

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Tongue stimulator Review for MS Walking Problems

Helius Medical Technologies has filed an application with the U.S. Food and Drug Administration (FDA) asking for "de novo" classification and clearance of its portable neuromodulation stimulator (PoNS) device for the treatment of walking deficits in MS.

"Helius is excited to announce the submission of our request for de novo classification and clearance of the PoNS device for the treatment of gait deficit due to symptoms from multiple sclerosis, to be used as an adjunct to a supervised therapeutic exercise program in patients over 18 years of age," Philippe Deschamps, Helius' president, CEO, and chairman, said in a press release. "Our submission brings us a step closer to making our novel PoNS Treatment available for the 1 million U.S. patients estimated to be living with MS, a disease with a significant unmet medical need, particularly in addressing associated gait dysfunction," Deschamps stated.

The loss of neuronal communication in MS leads to symptoms such as fatigue, numbness, muscle weakness, muscle spasms, and problems with balance, all of which cause significant problems in walking. PoNS is a non-invasive medical device that is placed — but not implanted — on top of the tongue and delivers mild electrical signals to the brainstem. The brainstem is a region at the base of the brain that regulates vital functions (e.g., heart rate, respiration), as well as sensory perception and movement, and is connected to the tongue by two major cranial nerves.

By sending these electrical impulses, the PoNS device is believed to increase the brain's neuroplasticity, which essentially is the brain's ability to adapt or rewire itself in response to new experiences. According to Helius, "the process of neuroplasticity underlies all cerebral learning, training and rehabilitation." Patients are expected to use the device in combination with targeted functional therapy, including physical, occupational, and cognitive exercises. The rewiring of brain structures and reactivation of nerve cells promoted by the device is expected to improve the process of rehabilitation.

The PoNS device recently was cleared in Canada for use as a short-term treatment (14 weeks) for walking problems due to mild-to-moderate MS symptoms, as well as for chronic balance problems due to traumatic brain injury. For both indications, the use of the device must be combined with physical therapy. The recent filing to the FDA is asking for a de novo classification to the PoNS device, meaning that the regulatory agency agrees that no similar devices are legally marketed in the country and that the controls provided are enough to assure the safety and effectiveness of the device. In the event of a positive decision, the agency then provides a risk-based classification to the new device and authorizes its marketing. PoNS also is under review by Australia's Therapeutic Goods Administration

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News

First Prog-MS Patient Enrolled in Phase 2 Temelimab Study

Swiss Bio-pharma GeNeuro has said that the first progressive MS patient has enrolled in its Phase 2 trial assessing the safety and effectiveness of temelimab in people whose disease is progressing in the absence of relapses.

The trial, taking place at the Karolinska Institutet's Academic Specialist Center (ASC), in Stockholm, had been postponed to reduce risk to MS patients during the global COVID-19 pandemic and to prioritize medical resources to treating those infected with this coronavirus.

Temelimab, previously known as GNbAC1, is a monoclonal antibody that blocks inflammation by neutralizing the pHERV-Env protein associated with MS (formerly known as MSRV-Env). This protein has been shown to activate microglia (immune cells that cause inflammation in the brain), leading to aggressive attacks on the protective myelin sheath of nerve cells.

This one-year, single centre Phase 2 study will assess temelimab's safety, tolerability, and efficacy in up to 40 people with primary progressive MS and non-active secondary progressive MS. It aims to build on the results of two previous studies of temelimab in people with relapsing-remitting MS which both reported positive results, including slower disease progression and lesser evidence of brain atrophy in treated patients.

"Temelimab has already been shown to have a neuroprotective effect in MS and it has the potential to address the key unmet medical need of disability progression," a company spokesman said. "We are looking forward to further exploring its therapeutic properties in this important study."

Treatment safety and tolerability will be assessed at increasing dose levels, and signs of efficacy evaluated through biomarker analysis. Results from this progressive MS study, led by Fredrik Piehl, MD, a professor of neurology at Karolinska and head of research at the MS clinic at ASC, are expected in the second half of 2021.

HERV (Human Endogeneous Retro-Virus) proteins are thought to be derived from viral DNA that has been embedded into the human genome. The activity of these proteins is normally suppressed, but GeNeuro speculates that they may be activated in MS, and potentially in other neurodegenerative and autoimmune diseases.

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Cannabis derivatives Trial to Open in Canada looking at CBD and THC to treat spasticity

The Multiple Sclerosis Society of Canada and its partner, the Canadian Institutes of Health Research (CIHR), have started a clinical trial that will investigate the potential of two cannabis derivatives — cannabidiol (CBD) and tetrahydrocannabinol (THC) — in treating spasticity (muscle stiffness) and other symptoms of multiple sclerosis (MS).

The money, worth about $1.1 million, will support the trial for the next five years, and is part of CIHR's Integrated Cannabis Research Strategy (ICRS). This initiative, involving several partner institutions, aims to generate strong scientific evidence to support policies and regulations governing the use of cannabis.

Since cannabis was legalized in Canada in 2018, there has been a growing need for clinical studies demonstrating its therapeutic efficacy. This trial, which will be led by Pierre Duquette, MD, with the Centre hospitalier de l'Université de Montréal (CHUM), intends to generate data necessary to create evidence-based guidelines regarding the use of cannabis products to treat MS symptoms.

The randomized, double-blind, placebo-controlled study will enrol a group of MS patients experiencing one or more typical symptoms of the disease. During the trial, some participants will be treated with cannabis derivatives (CBD and THC), and others given a placebo for four weeks. Those who respond during the month of treatment will be eligible to participate in a 12-week continuation phase.

The study's main goal is to assess the effectiveness of CBD and THC at alleviating spasticity. Secondary goals will look at how well they address other MS symptoms, including pain, fatigue, sleep problems, mood, and cognitive issues.

Study investigators will also evaluate the pharmacological properties of both compounds, and explore their effects on brain inflammation.

The study is titled "Is cannabis a useful adjunct in the treatment of symptoms of persons with multiple sclerosis? A formal trial of CBD and THC for the control of spasticity and other symptoms: assessing the clinical effects and the basic mechanisms."

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I try out a herbal supplement for my non-active Prog-MS

In the last issue I wrote about how andrographolide, a herbal compound with anti-inflammatory and neuroprotective properties, can slow brain atrophy and progression of disability in people with non-active progressive multiple sclerosis according to results from a Phase 1/2 clinical trial.

The study, "Efficacy of andrographolide in not active progressive multiple sclerosis: a prospective exploratory double-blind, parallel-group, randomized, placebo-controlled trial," was published in the journal BMC Neurology. I have secondary progressive MS and it is non-active meaning I no longer have relapses. My neurologist has confirmed this. So in that sense I am similar to the patients who took andrographolide in the study and had positive results.

Andrographolide is a molecule isolated from the plant species Andrographis paniculata, commonly known as green chiretta, an East Indian herb often used in Chinese medicine. The compound has emerged as a potential treatment for MS patients, showing an ability to effectively modulate immune system activity. In animal models of multiple sclerosis, andrographolide showed a number of clinical benefits, including a reduction in inflammation, moderation of neurotoxicity from microglial cells, a reduction in cognitive impairment, and an increase in numbers of neurons.

Researchers at the Pontificia Universidad Católica de Chile and Universidad Austral de Chile thus launched a Phase 1/2 pilot trial to investigate the safety,

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Continued from page 10 tolerability, and efficacy of andrographolide in patients with non-active progressive MS. Sponsored by InnoBioscience, the study enrolled 44 adults with a near equal mix of primary and secondary progressive MS, who had no evidence of relapses or new lesion formation in the year before entering the trial. The proportion of patients experiencing three-month disability progression was lower on andrographolide (30%) than on placebo (41%). It was also much lower than the 80% seen in the year prior to enrolment among patients who went on to receive andrographolide.

Based on these findings and the fact that it is possible to buy an extract containing Andrographis paniculata online, it seemed like the proverbial no-brainer not to give it a go and see if I could obtain the same benefits as the patients on the InnoBioscience trial. Sadly I could not find a supplement containing the same levels of Andrographis paniculata online, but I did find Andrographis extract made by Now Foods which I noticed did contain Andrographis paniculata but sadly only in small amounts (10% of a 400 mg tablet.) Taking up to three tablets a day which was recommended meant I would be getting 80mg daily. In the ImnoBioscience trial patients took tablets containing 140 mg andrographolides twice a day meaning that I was only getting a third of the daily amount of the patients in the trial.

Perhaps it should come as no surprise to say that I noticed no improvement in any of my symptoms, but as I was only been taking the supplement at lower amounts for a month this is pretty much what you would expect. In spite of this I am determined to see if there is anything else I can do.

I am reluctant to start taking the supplements in higher doses than is recommended but emailed the trial organisers asking them if they are planning to do any more trials on this herbal substance which seems to have some effect on non-relapsing secondary progressive MS, my MS, and the type of MS for which there seems to be no licensed treatment. The organisers got back to me the next day saying they too would like to see a larger trial taking place but that it was ultimately a decision that would need to be taken by the trial sponsor, to whom I have also written. I just hope someone continues to pursue this promising avenue of research ***Details of the Chilean study on page 13***

News

Approval sought for arbaclofen - long term muscle relaxant

An amended new drug application (NDA) has been filed with the U.S. Food and Drug Administration (FDA) requesting the approval of arbaclofen extended release tablets for treating spasticity in people with MS.

Arbaclofen ER (brand name Ontinua), is an extended release formulation of arbaclofen, a compound similar to the muscle relaxant baclofen that is approved to alleviate spasticity (muscle stiffness) in people with MS.

The therapy is based on Osmotica's Osmodex drug delivery technology, which allows the production of tablets containing one or more ingredients for immediate, controlled, delayed, or extended release.

This extended release formulation of arbaclofen releases the medication's active ingredient gradually over longer periods of time, potentially allowing for less-frequent dosing and likely reducing the risk of side effects.

"We are excited to have resubmitted our NDA for arbaclofen ER, our novel treatment, using the Osmodex technology, for MS spasticity," Brian Markison, CEO of Osmotica Pharmaceuticals, said in a press release.

"The safety and efficacy results from several studies, together with the entire data package from our clinical development program, supports the clinical significance of arbaclofen ER as a potential treatment for MS spasticity. We look forward to working with the FDA during the course of its review," Markison added.

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