

My prog-MS ezine

For people with progressive MS and other interested people

Issue number 27, September/October 2019

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 plus two features about issues that matter to prog-MSers. In the first feature (page 5) I look at squatting folding toilet stools . The second feature looks at the issue of magnets in progressive MS – something that is of particular interest to those of us secondary progressive MSers like me with leg spasms. See page 10.

IN THIS ISSUE



Taking the toil out of toileting – all thanks to 'squatting stools'

Thalidomide could be used to treat progressive MS - page 4
Asthma drug trial for SPMSers with Inactive Disease - page2

Asthma drug trial for SPMSers with Inactive Disease

A Phase 3 trial will confirm the safety and efficacy of oral ibudilast (MN-166) in treating people with secondary progressive MS (SPMS) without relapses, or those whose disease is not active, bio-pharma company MediciNova has announced.

If successful, data from this single Phase 3 study may be used to request marketing approval for ibudilast with the U.S. Food and Drug Administration (FDA), the company said in a press release.

Ibudilast has been approved in Japan and Korea to treat post-stroke complications and bronchial asthma for more than two decades. But it's believed it could work in secondary progressives with inactive disease

Ibudilast works to suppress three cytokines (small signalling proteins) that promote inflammation: IL-1ß, TNF-a, and IL-6. It may also increase the activity of the anti-inflammatory cytokine IL-10, and help block the signals of toll-like receptor 4 (TLR4) that is involved in inflammation.

The therapy's anti-neuroinflammatory and neuroprotective actions were shown in preclinical and clinical studies, warranting studies of it in progressive MS, amyotrophic lateral sclerosis (ALS) and other neurological diseases, as well as substance abuse and addiction.

"We are excited to announce our Phase 3 plan for MN-166 for progressive MS. Although two drugs have recently received FDA approval for relapsing secondary progressive MS [Novartis' Mayzent and EMD Serono's Mavenclad, both in March 2019], there remains a very large unmet medical need for secondary progressive MS patients without relapses, as the vast majority of secondary progressive MS patients do not have relapses and there is still no drug approved for long-term treatment of these patients," Yuichi Iwaki, MD, PhD, MediciNova's president and CEO, said in the release.

For details of sources for all news stories go to page 13

Rejuvenated brain stem cells may hold key to remyelination

New research, published in the journal Nature, demonstrates it is possible to restore older brain stem cells to a younger, healthier state – something that may help them to remyelinate.

A multi-disciplinary research team, based at the Wellcome-MRC Cambridge Stem Cell Institute (University of Cambridge), studied young and old rat brains and in particular the impact of age-related "brain stiffening" on the function of oligodendrocyte progenitor cells (OPCs).These are brain cells which make myelin and are damaged in MS. Their function also declines with age in healthy people.

To determine whether the loss of function in aged OPCs was reversible, researchers transplanted older OPCs from older rats into the soft, spongy brains of younger animals. They found the older brain cells were rejuvenated, and began to behave like the younger, more vigorous cells.

To study this further, the researchers developed new materials in the lab with varying degrees of stiffness, and used these to grow and study the rat brain stem cells in a controlled environment. The materials were engineered to have a similar softness to either young or old brains.

To fully understand how brain softness or stiffness influences cell behaviour, the researchers investigated Piezo1 - a protein found on the cell surface, which tells the cell whether the surrounding environment is soft or stiff.

Dr Kevin Chalut, who co-led the research, said: "We were fascinated to see that when we grew young, functioning rat brain stem cells on the stiff material, the cells became dysfunctional and lost their ability to regenerate, and began to function like aged cells. What was especially interesting, however, was that when the old brain cells were grown on the soft material, they began to function like young cells - in other words they were rejuvenated."

"When we removed Piezo1 from the surface of aged brain stem cells, we were able to trick the cells into perceiving a soft surrounding environment, even when they were growing on the stiff material," explained Professor Robin Franklin, who co-led the research with Dr Chalut. "What's more, we were able to delete Piezo1 in the OPCs within the aged rat brains, which lead to the cells becoming rejuvenated and once again able to assume their normal regenerative function."

For details of sources for all news stories go to page 13

Thalidomide could be used to treat progressive MS

A paper published in the journal Multiple Sclerosis and Related Disorders raises the possibility that thalidomide could be used to treat progressive MS.

The paper "Plasma cell and B cell-targeted treatments for use in advanced multiple sclerosis" is written by top neurologists including Prof. Gavin Giovannoni of Barts Hospital in London .

Along with four other authors the paper says therapies that target B cells, including plasma cells, within the central nervous system are likely to play an important role in disease progression in progressive MS. Current B cell-targeting antibodies may not achieve this targeting of B cells because of their poor penetration into the central nervous system.

However, there are a number of inhibitors of B cell function and B cell depleting agents that have been developed for myeloma and B cell leukaemia and lymphoma, which could potentially be used off-label or as an experimental treatment for advanced (progressive) MS.

One of these drugs is thalidomide which is used to treat myeloma and is a potent inhibitor of TNF (tumour necrosis factor). Thalidomide however produces tetragenic effects (ie: it can disturb the development of the embryo or foetus).

However there are a number of drugs similar to thalidomide that have fewer side effects such as: lenalidomide, pomaldomide and apremilolast. Pomalidomide is used to treat multiple myeloma. It remains to be seen whether these drugs could target plasma cell responses in the CNS in MS.

For details of all news stories go to page 13



Taking the toil out of toileting

At my local hospital I see two other nurses as well as my MS nurse. One nurse, is known as the "pee nurse". The pee nurse, also called the "Urological Clinical Nurse Specialist", is in charge of prescribing catheters, pads etc. The other nurse I see is the "poo nurse". Lately I been seeing the poo nurse more than the pee nurse.

My bowel movements, which for decades were regular, with a bowel movement once a day usually after breakfast, have become less and less regular. Constipation and "faecal urgency" are now a real problem for me, and following one or two little "accidents" I have on occasions become wary of leaving home for fear of what is known as an "emergency evacuation" or "faecal incontinence".

It seems I am not alone in having these problems. According to a recent academic paper published in the journal "Health Technology Assessment" up to 80% of people with MS have various bowel problems known collectively as "neurogenic bowel dysfunction"(NBD) at some point. The academic paper discusses not just the problem of NBD but the depressing consequences of living with it. The paper says: "Constipation and fear of faecal incontinence can lead people to become housebound, spending hours trying to empty their bowels thus limiting their ability to work."

Not wishing to become another sad and depressing case study for researchers I decided to see if there was anything I could do about constipation and occasional faecal incontinence. But before looking at possible solutions I thought I would try to find out a little more about my problematic MS bowel and work out what exactly is going wrong when I attempt to poo**.** I discovered that spinal cord lesions in MS mean nerve pathways which control defecation don't transmit signals properly or at the right speed and in the right order. This means poo does not travel round the colon smoothly and tends to get stuck inside the rectum instead of being released smoothly and on demand

continued on page 6



Continued from page 5 "When I started to look at solutions for my growing problem I quickly came across an innovation called the "squatty potty".

This really is one of those devices that does exactly what is says on the tin. The "squatty potty" is basically a small plastic box you push under the toilet and which you place your feet on when you poo. The thinking behind the "squatty potty" is the simple observation that our ancestors squatted for centuries before the invention of the modern day toilet. In fact, the majority of the world's population still squats today.

The "Squatty Potty" sounded worth investigating. There was just one problem. It was rather expensive, retailing at £27. However I soon discovered cheaper alternatives were available online for less than half the price. So after a while I spent £8.98 on a "squatting folding toilet stool" which arrived just a few days later and I was all ready for my first squat.

From the moment I put the squatting folding toilet stool under the toilet, and placed my feet on it, adopting the squatting rather than the sitting posture, everything seemed more natural. At the risk of sounding rather indelicate I had my first really good sh** for months. The bowel movement was swift and easy.

My bowel felt totally empty afterwards and it was a good feeling. I have been using my squatting toilet stool for the past two months and it has probably been my best MS-related buy of 2019, hopefully it's good bye to poo problems for me.

. **For further details go to page 13**

Cannabidiol (CBD) Based Treatment Promotes Remyelination in Mice, Trial Planned in MS

A cannabidiol-based experimental therapy for MS called EHP-101 recovered myelin in damaged nerve fibres and lessened neuro-inflammation in a mouse model of MS, new research says.

The data on EHP-101 were shared at the 29th Annual Symposium of the International Cannabinoid Research Society (ICRS), held from June 30–July 3 in Maryland US, and suggests that EHP-101 may be a potential remyelination therapy. Results were presented in the poster "Effects of EHP-101 on inflammation and remyelination in murine models of multiple sclerosis."

EHP-101 is an oral formulation of VCE-004.8, a lab-made (or synthetic) molecule derived of cannabidiol (CBD), which constitutes a new chemical product patented by Emerald. Cannabidiol is a natural substance found in cannabis (marijuana) and hemp plants, and one considered non-reactive and non-psychotropic (ie: it doesn't give you a "high") .

According to Emerald, EHP-101's potential benefits exceed other cannabidiol products owing to its greater activity via the cannabinoid receptor called CB2. Prior research showed that this receptor helps prevent inflammation and demyelination in the central nervous system.

The study presented at ICRS 2019 evaluated EHP-101's activity in a mouse model of demyelination showing substantial myelin loss in the brain after six weeks, and an inability to naturally recover from demyelination. Emerald researchers reported that EHP-101 helped to speed myelin recovery, and at the same time eased neuroinflammation.

Emerald Health Therapeutics, the manufacturer of EHP-101, has announced plans to open Phase 2 clinical trials in patients by the end of this year.

For details of all news stories go to page 13

New Potential Remyelination Therapy for MS

Bio-pharma company NervGen wants to advance the development of its lead investigational therapy for spinal cord damage, NVG-291, as a potential remyelination treatment for MS, the company has announced.

Following preclinical data showing that NVG-291 promotes myelin repair and regeneration of damaged nerves in animal models of spinal cord injury and MS, the compound has attracted pharma's attention as a potential therapy for MS and other neurodegenerative conditions.

NVG-291 is based on NervGen's proprietary technology that inhibits the protein tyrosine phosphatase sigma (PTPσ), a neural receptor that inhibits nerve regeneration. It works in regions of scarring that result from nerve damage. Following such damage, the body responds with natural protective mechanisms, some of which prevent or inhibit regeneration of the nervous system — including the one mediated by PTPσ.

Blocking PTPσ with NVG-291 has been shown to promote regeneration of damaged nerves, improving nerve function in animal models for various medical conditions, according to NervGen. It plans to submit an Investigational New Drug (IND) application with the U.S. Food and Drug Administration (FDA) in late 2019. If that is approved the company expects to initiate a Phase 1 clinical trial in early 2020 to demonstrate the therapy's safety in humans.

In MS mouse models, ISP was seen to stimulate the production and migration into MS lesions of oligodendrocyte-precursor cells (OPCs), a type of cell involved in myelin repair and regeneration. It enhanced remyelination of damaged nerves, lessened neuroinflammation, and helped mice to recover part of their functional abilities.

At the molecular level, ISP was seen to increase specific protein-cutting enzymes (proteases) that digest and break down glial scar tissue, which would otherwise keep nerves from regenerating.**For details of all news stories go to page 13**

Researchers discover Schwann cells in peripheral nerves have the ability to generate myelin

Scientists have discovered that Schwann cells, a special type of nerve cell, are much more prolific in generating a protective myelin sheath covering nerve fibres than previously believed.

The revelation about Schwann cells raises the possibility of new avenues to treat nerve injuries and various forms of diseases where myelin is damaged or destroyed.

Two types of cells in the body produce myelin: oligodendrocytes in the brain and spinal cord, and Schwann cells in the rest of the body. Until now, scientists thought that only oligodendrocytes generated multiple myelin sheaths around axons, the slender projection of a nerve cell that carries electrical signals between cells. The new research, published in the journal Nature Communications, reveals that Schwann cells also are capable of spreading myelin across multiple axons.

Researchers made the discovery after conducting a genetic screen in zebrafish. They discovered some fish had more myelin than expected, and those fish carried a mutation in a gene called fbxw7. When they knocked out this same gene in genetically modified mice, they discovered an unexpected characteristic: individual Schwann cells began spreading myelin across many axons.

In discovering how Schwann cells generate myelin at the molecular level, the discovery may lead to new gene-therapy techniques to repair damaged myelin in peripheral nervous system disorders.

Targeting the fbxw7 gene - or downstream pathway molecules - could be a powerful way to promote myelin repair in the central nervous system researchers believe.

For further information on news stories go to page 13



The attraction of magnets in progressive MS

Some 20 years ago I started to suffer from leg spasms. The spasms would occur more or less any time of day or night. The fact they were so unpredictable was the main problem. They might happen repeatedly then they might disappear for a month.

Reluctant to start taking medications I tried various alternative solutions and was pleasantly surprised to discover one that one seemed to work. This was a wrap-around leg magnet which I bought online for about £5 and which decades later I still wear.

For centuries magnet therapy has been proposed as a treatment for a wide range of ailments but there remains no real understanding about how magnets might work. The main theory, as I understand things, is that magnets might improve blood flow in damaged parts of the body and aid in their recovery. This is just a theory and it should be pointed out mainstream medicine has traditionally been sceptical about magnetism.

However, there is some suggestion that things may be changing. A flurry of recent scientific research seems to suggest that magnets may have a role to play in treating MS after all. The most promising new scientific research looks at magnetism not delivered as static magnets like my leg wrap but as pulsed electromagnetic fields (PEMF).

Continued on page 13



Continued from page 10 This is where magnetism is administered by lying on a mat or using portable pads typically powered by AAA batteries. When very low levels of electricity are passed through the mat or the pad a magnetic field is created. It is believed PEMF stimulates ions and electrolytes in the body. PEMF has been looked at as a treatment of people with MS and 2016 paper published in the journal "Alternative Therapies in Health and Medicine" found that "exposure to pulsing, weak electromagnetic fields can alleviate symptoms of MS".

Another 2016 paper published in the journal Clinical Neurology and Neurosurgery found 35 MS Patients exposed to a magnetic field showed significant improvement in paraesthesia (pins and needles) compared to a group of patients given a placebo.

It remains to be seen whether this growing interest in PEMF results in any re-appraisal of static magnets such as the one I wear. However I am optimistic that magnets even leg magnets may one day play a role in treating MS. Whatever the outcome of current scientific enquiry I shall continue wearing my magnetic leg wrap simply because it works for me.

For further details of all news stories and features go to page 13

Lipids in prog MS cerebrospinal fluid rob neurons of energy

The cerebrospinal fluid (CSF) of people with progressive MS contains elevated levels of specific fatty molecules that disrupt the energy "powerhouses" of nerve cells, and appear to underlie the neurodegeneration seen on brain scans of these patients, a study reveals.

The research, which compared the CSF of patients with relapsing-remitting MS (RRMS) and progressive MS patients, identified mechanisms that may support new treatments aiming to effectively halt progressive forms of the disease. The study "A metabolic perspective on CSF-mediated neurodegeneration in multiple sclerosis" was published in the journal Brain.

Prior research suggests that the cellular structures that work as energy powerhouses — called mitochondria — are not functioning properly in the brains of people with progressive MS. However, the chain of events at the molecular level that underlies this process is still unknown. Researchers exposed rat neurons growing in the lab (cultured cells) to CSF samples collected from multiple MS patients, including 15 people with RRMS and 29 with progressive MS (15 with SPMS, and 14 with primary progressive MS or PPMS), to investigate potential mechanisms of neurodegeneration.

Visualizing neurons under a microscope revealed "dramatic differences" in the mitochondria of nerve cells exposed to the CSF of progressive MS patients. Such exposure disturbed the mitochondria's shape, making them fuse and elongate. Further analysis showed these changes rendered mitochondria less able to produce energy, resulting in nerve cell damage.

It was found progressive patients had higher CSF levels of a specific ceramide (C24), a family of waxy lipid molecules abundant in the membrane of cells, the screening revealed. Supporting ceramide-driven neurotoxicity, rat neurons exposed to C24 showed mitochondria impairments and neuronal damage akin to those neurons put in contact with CSF from progressive MS patients. The scientists further discovered Ceramides impaired the ability of neurons to make energy by directly damaging the mitochondria. They also forced neurons to more rapidly uptake glucose in an attempt to provide energy for the cell. Consistent with this, adding glucose to the cultured rat neurons rescued the neurotoxic effect of the CSF.

"Thus, ceramide levels in the CSF of patients with progressive multiple sclerosis not only impaired mitochondrial respiration, but also decreased the bioavailability of glucose by increasing its uptake," the researchers wrote. "Together these data suggest a condition of 'virtual hypoglycosis' [low glucose levels] induced by the CSF of progressive patients in cultured neurons, and suggest a window of intervention for the rescue of the metabolic impairment of neuronal bioenergetics underlying neurodegeneration," they concluded.

For further details of all news stories go to page 13

References contact details etc

Page 2 Ibudilast story

https://multiplesclerosisnewstoday.com/news-posts/2019/07/12/medicinova-announces-phase-3-clinical-trial-plan-for-mn-166-ibudilast-in-progressive-ms/?utm_source=Multiple+Sclerosis&utm_campaign=325714ad27-RSS_NON-US_EMAIL_CAMPAIGN&utm_medium=email&utm_term=0_b5fb7a3dae-325714ad27-71290133

Page 3 Rejuvenated brain stem cells may hold key to remyelination

https://www.medicalnewstoday.com/articles/326066.php

Page 4 Thalidomide story

https://multiplesclerosisnewstoday.com/2019/04/05/aan2019-mayzent-improves-cognitive-processing-speed-in-spms-patients-phase-3-trial-shows/

page 5-6 Toiletting feature

For squatting folding toilet stools check out ebay. One example is https://www.ebay.co.uk/itm/Bathroom-Toilet-Foldable-Squatty-Step-Stool-Potty-Squat-Aid-For-Constipation/123647285522?hash=item1cc9f3d912:g:TlUAAOSwLdJcZqhw

page 7 cannabidiol story

source: https://multiplesclerosisnewstoday.com/news-posts/2019/07/02/emerald-health-pharmaceuticals-demonstrates-repair-of-nerve-damage-related-to-multiple-sclerosis/?utm_source=Multiple+Sclerosis&utm_campaign=656771d141-RSS_NON-US_EMAIL_CAMPAIGN&utm_medium=email&utm_term=0_b5fb7a3dae-656771d141-71290133

page 8 potential remyelination story

https://multiplesclerosisnewstoday.com/news-posts/2019/06/26/nervgen-pharma-launches-multiple-sclerosis-program-targeting-nerve-remyelination/

Page 9 Schwann cells story

Source; Nature Magazine https://www.nature.com/articles/s41467-019-10881-y

Page 10-11 magnets feature

Leg care wrap medium at https://www.amazon.co.uk/Magnopulse-BP05B-LegCare-Wrap-Medium/dp/B00C2DLQOC.

Page 12 Lipids story

https://multiplesclerosisnewstoday.com/news-posts/2019/07/15/differences-in-ms-patients-cerebrospinal-fluid-may-be-key-to-drugs-that-halt-progression/?utm_source=Multiple+Sclerosis&utm_campaign=d7f0242611-RSS_NON-US_EMAIL_CAMPAIGN&utm_medium=email&utm_term=0_b5fb7a3dae-d7f0242611-71290133

To Contact me email iancookjournalist@yahoo.co.uk or via twitter@iancookMSer

DISCLAIMER:

This ezine is strictly a news and information ezine/website about MS . It does not provide medical advice, diagnosis or treatment. This content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Always seek the advice of your doctor or other qualified health provider with any questions you may have regarding MS or any a medical condition. Don't disregard professional medical advice or delay in seeking it because of something you have read in this ezine.

To Contact me email iancookjournalist@yahoo.co.uk or via twitter@iancookMSer