

My prog-MS ezine

For people with progressive MS and other interested people

Issue number 32, July/August 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 coronaviruses, and another on page 10 looks at walking and MS and a US engineering project to make "MS-friendly" shoes. See page 10.

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1st Prog- MS Patient Enrols in Phase 1b Study of Cell Therapy ATA188

US Biotech Atara Biotherapeutics has enrolled its first patient in a clinical trial testing ATA188, its off-the-shelf T-cell immunotherapy for people with progressive MS, following promising results in an earlier trial.

The Phase 1b trial (NCT03283826) follows promising safety and tolerability results from its open-label Phase 1a part, including a sustained lessening in disability among treated patients with primary progressive MS and secondary progressive MS. This study's placebo-controlled second part (phase 1b) will assess ATA188's safety, as well as its potential efficacy via measures of changes in patient disability, MRI imaging, physical and cognitive function.

ATA188 is a cell-based therapy designed to counter the harmful effects of Epstein-Barr virus (EBV, a common type of herpes virus). Multiple avenues of research increasingly point toward EBV infection as a likely cause of MS. EBV can cause another class of immune cell, called B-cells, to produce antibodies against the myelin sheath of nerve cells. In the EBV hypothesis of MS, the body's T-cells — which normally recognize and destroy foreign molecules like viruses — fail to clear infected B-cells. ATA188 provides patients with T-cells designed to selectively target EBV-infected B-cells. The ongoing double-blind and randomized Phase 1b study will assess the safety and efficacy of ATA188 versus a placebo in up to 97 people. Its aim is to look at the therapy's safety and tolerability, as measured by the number of side effects, and the change from baseline (study's start) in immunoglobulin G (IgG) index, a measure of immune system health.

Other changes looked at include changes from baseline in several standard disability measures, including the expanded disability status scale (EDSS) and timed 25 foot walk (T25FW; time taken to safely walk 25 feet), as well as measures of neurological health assessed by MRI. These will consist of changes from baseline in cervical spinal cord volume and whole brain volume, and the occurrence of new or enlarging brain lesions. Other measures include cognition and walking, patient-reported fatigue, and visual acuity. Participants will be given two cycles of ATA188, or a placebo, by intravenous (IV) infusion, and the trial's primary goals will be measured at 12 months. After this, all will receive active treatment with an additional 12 months of follow up. Patients who complete these two years of treatment will be eligible to enter into a three-year, open-label (no placebo group) extension study. The trial is recruiting adults with progressive MS at sites in the US and Australia. ***For details of sources for all news stories go to page 13***

Herbal compound Andrographolide Shows Promise for Non-active Progressive-MS

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 (PMS), 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.

Progressive MS can be divided into two main types: primary, in which the disease gradually worsens from onset, and secondary, in which progressive disease occurs following a period of relapse and remission. Patients can also be categorized as having active or non-active disease, depending on whether or not active inflammation sites are present in the central nervous system.

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. It can be bought online. The compound has emerged as a potential treatment candidate for MS patients, showing an ability to effectively modulate immune system activity. In animal models of multiple sclerosis (MS), andrographolide showed a number of clinical benefits, including a reduction in inflammation, mitigation of neurotoxicity from microglial cells, decrease in cognitive impairment, and increase in numbers of neurons.

Researchers at the Pontificia Universidad Católica de Chile and Universidad Austral de Chile launched a Phase 1/2 pilot trial (NCT02273635) to investigate the safety, tolerability, and efficacy of andrographolide in patients with non-active PMS.

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.

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UK draft guidance doesn't recommend siponimod for SPMS

UK drugs watchdog NICE has issued draft guidance for public consultation which does not recommend siponimod (also called Mayzent and made by Novartis) for treating secondary progressive MS .

Siponimod is licensed to treat this type of MS in adults with evidence of active disease, which means they have relapses or features of inflammatory activity that show up on an MRI scan.

Interferon beta-1b is currently the only disease-modifying treatment available for people with active secondary progressive MS. However,NICE says few people take it because it can cause side effects such as flu-like symptoms. Most prog-MSers aren't aware it is even used in SPMS.

Clinical trial results show that siponimod reduces the number of relapses and slows disability progression compared with placebo. However, because there is no evidence directly comparing siponimod with interferon beta-1b, it is uncertain how effective siponimod is compared with that treatment.

The committee has requested further analyses to be included in the company's economic model. These include comparing siponimod with best supportive care and assuming that there is a reduction in its treatment effect over time.

Meindert Boysen, deputy chief executive and director of the Centre for Health Technology Evaluation at NICE, said: "We know there are currently few, if any treatments available for people with this form of MS, and that siponimod is a promising drug that has the potential to address this unmet clinical need. We are, therefore, committed to working with the company to help them address the issues identified by the committee that are highlighted in this draft guidance."

Siponimod costs £1,643.72 per pack of 28 tablets at its list price. The company has agreed a confidential commercial arrangement which would have made siponimod available at a discounted price.

Secondary progressive MS, which is estimated to affect around 9,000 people in England, is a stage of MS which comes after relapsing remitting MS. With SPMS a person's disability gets steadily worse and they're less likely to have relapses (when symptoms get worse but then get better).The draft guidance is now open to public consultation until 17 July 2020.

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The researcher looking into a link between Covid-19 and MS

One of the strange consequences of the current Covid-19 pandemic is that it has re-awakened interest in viruses as a cause of MS.

Covid-19 is a member of the coronavirus family of viruses and for a long time it has been thought that viruses may be the elusive environmental factor that, along with genes, cause auto-immunity that starts MS. For years researchers have looked at the Epstein-Barr virus (EBV) which causes infectious mononucleosis or glandular fever. But is it possible that coronaviruses, or a particular member of this family of viruses is involved, rather than EBV?

Research into coronaviruses and MS has been going on for at least 40 years and during this time much progress has been made in developing a theory about how a respiratory tract infection could lead to a neurological condition. A paper published in 2000 in the Journal of Virology titled "Neuroinvasion by Human Respiratory Coronaviruses" observed that upper respiratory tract infections of viral origin could be an important trigger of MS attacks. Moreover, it was said that coronavirus seasonal patterns fit the observed occurrence of MS relapses.

In another paper published in 2019 in the journal Viruses and titled "Human Coronaviruses and Other Respiratory Viruses: Underestimated Opportunistic Pathogens of the Central Nervous System?" it was observed that several respiratory viruses have neuro-invasive capabilities, being able to spread from the respiratory tract to the central nervous system (CNS). The 2019 paper said the following:

"Like other well-recognized neuro-invasive human viruses, respiratory viruses may damage the CNS as a result of misdirected host immune responses that could be associated with autoimmunity in susceptible individuals (virus-induced neuro-immunopathology) and/or viral replication, which directly causes damage to CNS cells (virus-induced neuropathology)."

One academic with a longstanding interest in the coronaviruses and their possible role in MS is Dr Pierre Talbot, Director of the Laboratoire de neuroimmunovirologie at Armand-Frappier Santé Biotechnologie research centre in Laval, Québec, Canada. Over several decades Dr Talbot has authored a number of academic papers including the above two which look at the coronavirus and its possible role in MS.

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Continued from page 5: In a third paper Dr Talbot detected the presence of coronaviruses in the brains of MS patients. Dr Talbot's research team in Canada have also determined that neuronal cells and cells of the glia in the brain (astrocytes, oligodendrocytes, and microglial cells) can be infected by human coronaviruses. In a paper published in the Annals of Neurology, he identified a striking human coronavirus-myelin cross-reactive T-cell response in MS patients but not in those without the condition. Studies in progress at Dr Talbot's research laboratory currently deal with the neurotropism of human coronaviruses (their ability to attack the nervous system) and the possibility that coronaviruses can trigger autoimmunity, which cause an auto-immune response in the body and neurodegeneration.

Although Dr Talbot has been working on coronaviruses and MS for decades he is aware that he has been swimming against a strong tide that sees other factors as causing MS. "People have always been sceptical about the role of viruses in MS, and most neurologists remain sceptical. Among those who aren't, Epstein-Barr virus is the only virus that attracts any interest," he says, adding that he hopes the current pandemic may change this.

Ultimately, if a link between coronaviruses and MS is established, then it is likely that there will be search for an anti-viral drug to be used as an MS therapy. Several anti-viral drugs have been used to treat influenza viruses which are closely related to covid-19. Could one of these treat MS? In the US there are four FDA (Food & Drug Administration) licensed influenza drugs- oseltamivir phosphate (available as a generic version or under the trade name Tamiflu), zanamivir (trade name Relenza), peramivir (trade name Rapivab), and baloxavir marboxil (trade name Xofluza).

Of these four drugs none has been in clinical trial for MS although intriguingly oseltamivir (Tamiflu) was given to a group of children and adolescents with acute disseminated encephalomyelitis (ADEM) . This is an immune-mediated disease that produces multiple inflammatory lesions in the brain and spinal cord and bears many similarities to MS. A study carried out in Turkey and published in the journal Paediatric Neurology in 2013 found that in 13 of 15 ADEM patients treated with Tamiflu all neurologic signs and symptoms resolved after treatment. Dr. Talbot is not sure that Tamiflu would work on MS and at present there are no coronavirus-specific anti-viral drugs so a new drug would need to be developed but he believes it is possible that when an anti-Covid-19 drug is developed it could be used for MS and it might even work . He says he certainly hopes it does.

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News

US Bio-Tech Aims to Treat MS through restoring myelin

US bio-tech company Autobahn Therapeutics has announced a project worth $76 million to support work on therapies for central nervous system (CNS) disorders, including the development of ABX-002, its lead candidate to treat diseases marked by the loss of myelin, such as MS.

“We stand well-positioned to advance our pipeline with funding from the highest quality investors and pharmaceutical leaders who share our mission of improving life health for people affected by these conditions,” Kevin Finney, chairman and CEO of Autobahn, said in a press release.

ABX-002 is a thyroid hormone receptor beta agonist that works by binding to thyroid hormone receptors in the brain and mimicking the action of the thyroid hormone, which stimulates the production of mature oligodendrocytes — cells that produce myelin, the protective sheath surrounding nerve axons that is lost in MS.

By increasing the number of oligodendrocytes available, ABX-002 aims to restore communication between nerve cells and to halt or possibly reverse MS progression.

Autobahn’s development of ABX-002 is based on the well-known role of the thyroid hormone for the production of myelin.

The company also leveraged its brain-targeting chemistry platform to minimize side effects of the therapy, which is taken orally in an inactive form. It is designed to only be activated in the brain by an enzyme known as fatty-acid amide hydrolase. “This approach maximizes brain activity and minimizes undesired peripheral effects,” Autobahn states on its website.

ABX-002 is being developed for use in combination with standard-of-care MS immunosuppressive therapies.

“Autobahn is harnessing the regenerative power of the human body to treat both rare and prevalent CNS disorders. We are coupling our deep knowledge of thyroid hormone biology and remyelination with our brain-targeting chemistry platform to restore the brain to a healthier state,” Finney said.

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Prog-MS Linked to Faster Retinal Thinning, Study Shows

People with progressive MS have faster and disease-modifying therapy (DMT)-resistant retinal atrophy (thinning), compared to those with relapsing-remitting MS (RRMS), a study shows.

Data also highlights that the thickness of deeper layers of the retina could be used as potential biomarkers of neurodegeneration in people with progressive MS and also shows the potential use of optical coherence tomography (OCT), a non-invasive eye test, to monitor such changes in clinical trials and clinical practice.

The study, "Progressive Multiple Sclerosis Is Associated with Faster and Specific Retinal Layer Atrophy," was published in the journal Annals of Neurology. A team of researchers at Johns Hopkins University School of Medicine, in Baltimore, Maryland, set out to assess retinal layer atrophy in progressive MS patients and whether it is different from that seen in RRMS patients.

The study included 178 RRMS patients, 126 people with SPMS, 60 PPMS patients, and 66 healthy individuals with similar age range (18–65 years) and sex ratio (roughly 70% female) to a typical group of MS patients.MS patients had no signs of optic neuritis within the six months prior to initial assessment. All participants underwent OCT — to measure changes in two external and two deeper retinal layers — every six to 12 months and were followed for an average of 3.7 years.

Data from the first OCT assessment showed that all studied retinal layers were significantly thinner in people with SPMS and PPMS, compared with RRMS patients and healthy individuals. There were no significant differences in retinal layer thickness between SPMS and PPMS patients, so a combination of both was often used in further analyses as a group of progressive MS patients. In addition, all four groups of participants showed significant atrophy in all studied retinal layers over time.

Compared with healthy individuals, MS patients showed significantly faster atrophy of the external retinal layers up to their 50–60s. From that point forward, these rates of retinal thinning in MS patients were similar to those expected with normal aging.

Overall, the team concluded that progressive MS "is associated with faster retinal atrophy independent of age," and that the atrophy of deeper retinal layers (inner and outer nuclear layers) "appear to predominate in the progressive phases of MS and seem to be unaffected by anti-inflammatory DMTs … and may accordingly represent novel biomarkers of neurodegeneration in PMS." **For details of all news stories go to page 13**

FDA Gives Breakthrough Device Designation to PoNS Device

The U.S. Food and Drug Administration (FDA) has granted breakthrough device designation to Helius Medical Technologies' portable neuromodulation stimulator (PoNS) for the treatment of walking impairments in MS patients.

The device, which is meant to be used in combination with therapeutic exercise programmes, works by sending mild electrical signals that travel through nerves that connect the tongue — where the device is placed — 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.

This mild electrical stimulation is thought to increase the brain's neuroplasticity — the brain's ability to adapt or rewire itself to preserve function following damage. The stimulation is expected to promote patients' physical rehabilitation.

"We are extremely pleased to receive this designation for our PoNS device," Philippe Deschamps, CEO of Helius, said in a press release.

"We look forward to working with FDA to process our application, with the ultimate goal of bringing our innovative technology to the aid of patients suffering with gait deficit due to MS-related symptoms, by providing them with a non-drug, non-implantable treatment that has the potential to significantly improve their ability to walk," Deschamps said. The device was approved recently by Health Canada to treat walking/gait deficits in patients with mild-to-moderate MS when used in combination with physical therapy for a short-term basis (14-week treatment).

In the U.S., European Union, and Australia, PoNS is still considered an investigational medical device and is not yet available commercially. In Australia, the device is under review for clearance by the Therapeutic Goods Administration (TGA).Similar to breakthrough therapy, the designation of breakthrough device is given to medical equipment that provides significant advantages over currently available options.

It is intended to accelerate the development, review, and approval of devices that have been designed to treat or diagnose irreversibly debilitating or life-threatening conditions, so that patients and healthcare professionals may have access to these devices sooner.

The designation also comes with a series of benefits to the device's manufacturer, including the ability to interact and receive early feedback from the FDA, and gain eligibility for priority review. **For further information on news stories go to page 13**



Taking MS in your stride

One of the things I have noticed when watching myself "walk" is that I seem to show greatly increased caution, and take far smaller steps overall.

Perhaps it's no surprise therefore that a study recently published by academics at Georgia State University in the US and published in the Journal of Biomechanics said more or less the same thing. The researchers said their findings could contribute to the development of better "walking rehabilitation" programmes.

Their study, "Influence of Multiple Sclerosis on Dynamic Gait Stability," says people with MS experience symptoms that include, among others, difficulty with walking and maintaining balance. These problems, they say, put MS patients at a higher risk of falling – something that came as no surprise to me, a habitual faller.

To find out exactly why people like me have less "dynamic gait stability", the researchers sought to determine the specific walking problems in MS patients. They recruited 20 patients with MS, as well as a control group of 25 healthy volunteers matched by age and sex to the MS group. Each participant in the study was asked to walk 7.5 metres (24.6 feet) three times, with eight cameras placed around the designated area to capture their "walking mechanics".

The primary measurement of the study was something called "dynamic gait stability", which refers to a person's ability to maintain balance while walking. This gait measurement was recorded for the take-off and landing of each step, on each MSer's stronger and weaker side. Overall, the results showed that the dynamic gait stability was significantly lower for all measurements in patients with MS compared to those who didn't have the condition .

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"Our study confirmed that people with MS demonstrate impairments in maintaining dynamic gait stability in comparison with their healthy counterparts," Meng-Wei Lin, the study's first author, said. The researchers found that the landing angle of the foot was altered in people with MS in order to maintain balance – a finding that is consistent with my own observation that my walking is more like "shuffling". "Our results also revealed that people with MS develop strategies to accommodate impairments in dynamic balance," Lin added.

Meng-Wei Lin's team believes that the detailed analysis of walking patterns in people with MS will assist with the development of better rehabilitation programmes and ultimately reduce their risk of falling. "This study leads us to understand that step length and foot landing angle are two significant factors for maintaining body dynamic balance in people with MS, so they could be two targets for gait rehabilitation," Lin said.

While it is good to see MS researchers looking at walking, personally speaking I would like to see a greater focus on how we can make use of the limited "gait stability" and balance that we MSers experience every time we put one foot in front of another. I for one already focus on my "take off" and "landing" for each step, but I believed the solution may also lie in better shoe design.

Interestingly I read last year of some engineers in the US who had attempted to tackle the problem of poor walking of people like me by designing a shoe called "Cadence" The shoe, is in its stages of final design making it as lightweight, safe, and sleek as an ordinary running shoe.

The team is currently testing their final prototype with a volunteer who has foot drop to refine and improve the shoe as best as they can. Once complete, they will be working with local companies to put together a patent for this device. This team is excited about the future of this project and hope to make their shoe accessible to many people. I, for one, look forward to Cadence which will help people with MS like me who can still walk, well a little. Have a look at the Cadence You Tube video – details on page 18 and see what you think . It seems to help with step length and foot landing angle - definitely a step in the right direction.

Picture credit: Thanks to NeONBRAND for sharing their work on Unsplash. Details of walking study on page 13

More evidence of damaging role of astrocytes in MS

An inflammatory environment can turn astrocytes, key supportive cells for neurons, into their killers, fostering the progression of MS, a new study shows.

The work, led by researchers at the New York Stem Cell Foundation (NYSCF), created astrocytes derived from human induced pluripotent stem cells (hIPSCs). The group then placed these cells in an inflammatory environment, and observed what happened.

The study "CD49f Is a Novel Marker of Functional and Reactive Human iPSC-Derived Astrocytes " was published in the journal Neuron.

Astrocytes compose more than half of the cells of the central nervous system (brain and spinal cord), and work as support cells. They help to maintain brain homeostasis (stable equilibrium), provide neurons with metabolic support, enhance the connectivity of neural circuits, and control the brain's blood flow. Yet, these cells are also thought to be key players in the onset and progression of MS.

Researchers found astrocytes in an inflammatory environment were seen to decrease the electric activity of neurons and to increase their apoptosis — a programmed process of cell death that's a form of "suicide."

"These findings demonstrate the specific neurotoxicity of A1 hiPSC-derived astrocytes," the researchers wrote.

They also confirm previous work in mice, where researchers observed that inflammation turns astrocytes neurotoxic. This work was led by Shane Liddelow, PhD, an assistant professor at the NYU Grossman School of Medicine and an author of the current study.

"We observed in mice that astrocytes in inflammatory environments take on a reactive state, actually attacking neurons rather than supporting them," Liddelow said.

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

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