

My prog-MS ezine

For people with progressive MS and other interested people

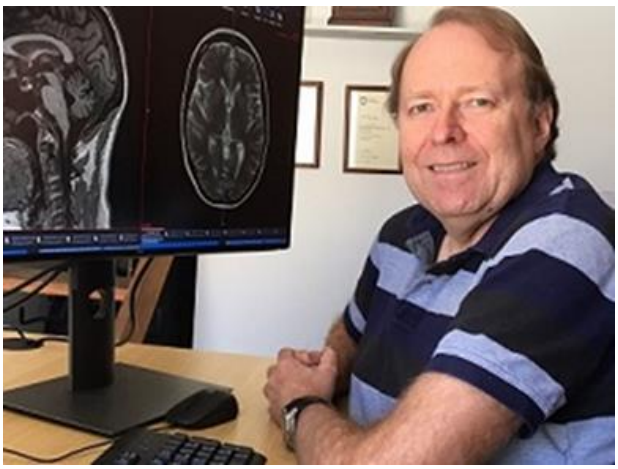
Issue number 41, January/February 2022

Hello and welcome to the later than usual 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 63.

In this issue are seven pages of prog-MS news stories. There are also two features. One on page 5 is about the vein theory of MS – something which we all thought was dead and buried with the demise of CCSVI. Not so, it appears.

There's also a feature on the International MS Alliance's view of where prog-MS research is going . See page 10 for details.

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News

Prog MS patients sought for London based re-purposed cancer drug study

Progressive MS patients who are not on a disease modifying therapy (DMT) are being sought for a London based clinical trial testing the efficacy of a drug called Ixazomib, presently used to treat multiple myeloma, a type of white blood cell cancer.

Multiple myeloma is a cancer caused by aberrant plasma cells. The purpose of this new study called Sizomus is to investigate whether ixazomib, a drug which targets these aberrant plasma cells, can reduce or clear oligoclonal bands (OCBs) from the cerebrospinal fluid from patients with MS. The trial will include prog-MS patients.

Oligoclonal bands" represent inflammation of the central nervous system (CNS) and are a hallmark of MS. They represent antibody proteins (or protein fragments) secreted by plasma cells, although why exactly these bands are present in MS, as well as which proteins these bands represent, and the exact role of plasma cells is not yet fully understood.

What is clear, however, is that antibodies in the MS oligoclonal bands (OCBs) are linked to plasma cells – which are known to be cells involved in the body's immune response. Recent evidence suggests that plasma cells are resident in the meninges (protective membranes of the brain and spinal cord) of people with MS.

The purpose of the Sizomus study is to investigate whether ixazomib can reduce or clear OCBs from the cerebrospinal fluid (CSF) of people with MS and potentially improve their condition.

Participants will be randomly assigned to receive either ixazomib capsules (active drug arm) or placebo capsules (placebo arm) for up to 24 months. Participants with progressive MS (who are not on disease modifying therapy) along with relapsing remitting MS (who are stable on disease modifying therapy) will also be invited to take part in the study.

For a clear description of the trial go to https://www.youtube.com/watch?v=vfftVAJfmuM where Professor Gavin Giovannoni, professor of neurology at Barts hospital in London gives a 4 minute explanation. Trial details, including eligibility criteria are at https://clinicaltrials.gov/ct2/show/NCT03783416

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News

AB Science to Start Masitinib Phase 3 Trial for Prog-MS

Bio-pharma company AB Science's request to launch a Phase 3 clinical trial to confirm the safety and effectiveness of an experimental drug called masitinib in adults with primary progressive MS and nonactive secondary progressive MS has got the go-ahead in France.

Masitinib is a tablet taken twice daily that works by blocking tyrosine kinase, an enzyme essential for the activity of innate immune cells — such as mast cells, microglia, and macrophages — which are thought to drive neuroinflammation and neurodegeneration in progressive MS. By suppressing innate immune cells, the therapy is expected to slow disease progression in progressive forms of MS.

Results from a previous Phase 2b/3 trial, called AB07002 (NCT01433497), showed that two years of treatment with masitinib, at a daily dose of 4.5 milligrams per kilogram (mg/kg), was superior to a placebo at slowing disability progression in adults with PPMS and nonactive SPMS — meeting the trial's main goal.

These positive findings supported AB Science's plans to launch a Phase 3 trial to confirm the benefits of this treatment dose in a larger patient population.

The upcoming international Phase 3 trial, called AB20009 (2021-000639-30), will evaluate masitinib's safety and effectiveness against a placebo in up to 800 adults, 18–65 years, with PPMS and nonactive SPMS. The study is expected to recruit patients at 75 sites in Europe, the U.S., Canada, Israel, and South Africa.

Eligible patients must have an EDSS score between 3.0 and 6.0. They must also have no T1 gadolinium-enhancing brain lesions on MRI scans — a marker of MS lesions with active inflammation. Participants will be randomly assigned to receive either masitinib — starting at a daily dose of 3.0 mg/kg and increased to 4.5 mg/kg after four weeks — or a placebo for up to two years. The trial's main goal is to assess whether masitinib is superior to a placebo at delaying confirmed (three-month) disability progression, defined as a 1-point worsening when EDSS score at study start is 5.5 or lower, or a 0.5-point worsening if the score is higher than 5.5.**For details of all news stories go to page 13**

News

Cladribine trial up and running. Places may still be available

A clinical trial called Chariot MS is currently recruiting its last remaining patients with progressive MS at 20 UK sites testing a new MS drug taken as a tablet.

The drug, Cladribine, works by gradually reducing the numbers of certain types of white blood cell (T and B lymphocytes) thought to be involved in the abnormal immune response which attacks the myelin coating of nerve cells that causes MS damage. It is one of few disease modifying drugs that can be taken by progressive MSers with high EDSS scores.

The Chariot MS trial is described as " a multi-centre, randomised double-blind placebo-controlled phase IIb trial to test cladribine tablets (3.5mg/kg over 24 months) for safety, efficacy, and cost effectiveness, and to advance mechanistic understanding of its action in people with advanced MS (pwAMS).

A total of 200 patients are being sought, and it should be noted there is a "placebo arm" to the trial meaning there is a possibility participants will be assigned a dummy pill or two years. However, the trial is welcome in that it is aiming to recruit patients with high levels of disability - between 6.5 and 8.5 on the EDSS scale.

EDSS 6.5 means patients who require two walking aids – pair of canes, crutches, etc. – to walk about 20m without resting. EDSS 8.5 means patients essentially restricted to bed much of day but who have some effective use of arms and retain some "self-care functions"

The measures of whether cladribine is effective among advanced MS patients will be measured by patients' performance in the 9 hole peg test. This is a test used to measure finger dexterity. The patient takes pegs from a container, one by one, and places them into the holes on a special board, as quickly as possible. They then remove the pegs from the holes, one by one, and replace them back into the container.

The aim of the trial is to establish whether there is superiority of those taking cladribine tablets compared to those taking placebo pills in reducing deterioration of upper limb function as measured by the 9 hole peg test, The trial will also look at whether the proportion of patients who do not deteriorate at 24 months is greater in the cladribine group than those taking the placebo.

The trial sites are spread across the country from Edinburgh in the north to Plymouth in the South West. There is also a trial site in Belfast. Details of the trial can be found at https://clinicaltrials.gov/ct2/show/NCT04695080 Further details can be found at a site dedicated to the trial at https://www.chariotms.com/**For details of all stories go to page 13**



Top researcher asks if "vein theory" of MS deserves second chance?

At a time when the "vein theory" of MS is seen as being dead and discredited, a new paper has been published which is reviving interest in the subject.

The new paper is appropriately titled: "Does the venous pressure theory of multiple sclerosis pathophysiology deserve a second chance?" and has been published in the journal "Multiple Sclerosis and Related Disorders". It asks whether veins and their pressure are indeed part of the MS disease process.

The paper's lead author is Prof. Grant Bateman, Conjoint Associate Professor at the Department of Medical Imaging at John Hunter Hospital, Newcastle, Australia. In a summary of the paper Prof. Bateman and his fellow authors admit this is a controversial subject. However, they go on to say a more targeted approach to widening blocked or narrowed veins "may be beneficial."

Prof. Bateman has been researching brain diseases for about 20 years. His interest is in blood flow and CSF (cerebrospinal fluid) dynamics. He uses MRI imaging to measure flow and "pulsation volumes", which he explains as follows: "If you fully turn on a tap at the sink and then rapidly turn it off, a pressure wave will pass through the pipes as a loud bang called water hammer. If you did this 72 times per minute for years your pipes would fail and burst due to metal fatigue. The pulse you feel in your neck between the Adam's apple and the muscle is like a water hammer pulse. Normally the vessels remove the pulsation before the capillaries of the brain because the arteries are able to expand and contract and the CSF spaces and veins act as a type of shock absorber."

Much of Prof. Bateman's work has been in Hydrocephalus (water accumulation within the CSF spaces), idiopathic intracranial hypertension (elevated CSF pressure), dementia both vascular (white matter degeneration) and Alzheimer's which is a neuronal form of degeneration**. Continued on page 6**

Continued from page 5. He says he has shown that in vascular dementia and Alzheimer's disease, the body's shock absorption fails either because the pulsations are too large or the pulsation absorption and dampening afforded by the CSF and veins fail or there is a combination of all of these. Recently Prof. Bateman turned his attention to MS. He says he became interested in MS because it appeared to have some overlap into the diseases mentioned above. He points out that MS patients have increased CSF pulsations like hydrocephalus, and appear to have increased venous pressure like idiopathic intracranial hypertension (IIH) and increased vascular pulsation strength like dementia.

"My work in MS suggests a combination of increased pulsation volume in some, decreased pulsation absorption because the CSF spaces in the neck are too stiff in some and the veins are too stiff in many, or a combination of all of the above. In animal models, pulsation stress leads to the capillaries becoming leaky and the myelin to become degraded. Both of these would lead to the immune system being presented with an increase in myelin antigens (more immune cells exiting the capillaries and more degraded myelin to remove). In those predisposed to reacting to the antigens this could lead to MS inflammation"

By writing about venous pressure and a link to MS, Prof. Bateman is treading on dangerous ground. The better-known venous theory, called CCSVI and advanced by Paolo Zamboni in 2009, has been roundly rebutted by the "MS establishment". So, what makes Bateman think his "second chance" will be more successful than Zamboni's first effort to link veins and MS? He explains as follows:

"Firstly, Paolo Zamboni suggested that MS was caused by a pure increase in venous pressure originating from the neck and chest veins. I think this may be a small component at best. We have looked at the problem from a wider perspective than Zamboni. We have also compared MS patients with both age and sex matched controls (which Zamboni unfortunately did not do) and those with related diseases. We think our findings are thus harder to refute."

Does this mean Prof. Bateman thinks venous issues are the cause of MS or a cause? He answers as follows: "Given the above, if the veins are of increased pressure that would make them stiffer and destroy their dampening effect. So they are a cause, probably not the only cause, although it may be the major cause in many people. We have found the major venous problems are within the skull and at the skull base not in the neck like Zamboni said."

Finally, does Bateman's theory suggest any therapy that might treat the symptoms or even lead to a cure for MS? "If I am correct (a big if at the moment) then therapy could target the pulse volume in the neck by reducing blood pressure or heart rate (treat high blood pressure vigorously in MS). Increasing the compliance of the CSF spaces around the spinal cord which would involve surgery ie removing bony narrowing etc in those affected. Reducing the venous pressure to increase the dampening of the veins. Stenting venous narrowing in the venous sinuses intracranially may be beneficial. However, I am not advocating any of these at the moment because it is a bit too early, however, if the theory is correct then these are the available strategies." Those with open minds will watch Professor Bateman's work with interest and will hope that his "second chance" at solving the mystery of MS and veins is more successful than the controversial CCSVI link to MS made 12 years ago. **More information on page 13.**

Simvastatin trail ends recruitment. Results in three years

The 964th person with Secondary Progressive MS has now joined the MS-STAT2 trial. Professor Jeremy Chataway and his team have now met their recruitment goal and should have the results in 2025.

MS-STAT2 is investigating whether cholesterol-lowering drug simvastatin slows disability progression in secondary progressive MS. It's a phase 3 trial. So it's the final, definitive stage of testing following positive smaller trials.

With recruitment finishing, researchers are a step closer to knowing whether simvastatin could be the first treatment for people with progressive MS that protects nerves from damage in MS.

Completing recruitment means the team have all the people they need taking part. So they won't be asking anyone new to join the trial. It's fantastic news and a really important milestone. Without enough people taking part in the trial, the team wouldn't be able to show whether simvastatin slows progression.

It also means MS-STAT2 is now the largest ever progressive MS trial that is not run by a commercial company. And this is in spite of COVID-19 forcing recruitment to pause for months.

Everyone stays part of the trial for at least three years. This is because progressive MS usually gets worse gradually. So there needs to be enough time to see whether the speed of worsening is different in the people taking simvastatin to the people taking the placebo.

Once all the participants have been in the trial for at least three years, the team will share the initial results.

For details of all news stories go to page 13

News

New drug to test myelin replacement in illnesses including MS

NervGen Pharma, a bio-tech company based in Canada, has received approval to begin testing multiple ascending doses (MAD) of NVG-291, an experimental drug which is hoped will promote the regeneration of lost myelin — the fatty substance that wraps around nerve fibres and is damaged in MS.

NVG-291 is an investigational small protein that aims to promote the regeneration of lost myelin — the fatty substance that wraps around nerve fibres and is damaged in MS. It does this by modulating the activity of the protein receptor tyrosine phosphatase (PTP) sigma.

PTP sigma receptors have been shown to halt the repair of nerve cells following an injury, either caused by a disease like MS or as a result of trauma, such as spinal cord injury.

After showing promise in animal models of MS, researchers initiated a Phase 1 clinical trial in Australia to investigate the safety and pharmacokinetics (movement into, through, and out of the body) of NVG-291 in healthy volunteers.

In part one, participants received a single dose of either a placebo or one of six doses of the therapy to determine NVG-291's best dose. The highest doses were higher than those tested and deemed to work best in animal models of nervous system injury.

Safety data from 37 participants showed that the therapy was well tolerated with only mild and transient side effects. No adverse effects were detected upon examination of vital signs, including heart function and lab tests.

In the next phase of research, the MAD part of the trial, participants will be randomly assigned to a placebo or one of three increasing NVG-291 doses, given over 14 consecutive days. The trial is expected to complete in the first half of 2022.

Later in the year, NervGen plans to initiate Phase 1b/2 trials of NVG-291 in MS patients and in people with spinal cord injury, as well as a Phase 1/2a trial for Alzheimer's disease.

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Wearable 'Neural Sleeve' Helps Foot Drop, And Aids Mobility in Study

People in a Neural Sleeve gait study were reported to show an "average improvement" of 143% in foot drop, a common symptom of multiple sclerosis (MS) and other conditions that hinder mobility, its developer, Cionic, reports.

The wearable "bionic" device — which analyses, predicts, and improves a person's movement — is designed to help people with conditions like MS move about with greater ease and independence.

Results from this San Francisco-area study and other tests are expected to support a planned application to the U.S. Food and Drug Administration for the right to market Neural Sleeve, Cionic reported. If approved, the sleeve may be the first algorithm-powered bionic clothing to help in restoring mobility to people with neurological conditions.

"This is a huge milestone for the company," Jeremiah Robison, Cionic's founder and CEO, said in a press release. "So much invention and hard work has gone into this first product, and we cannot wait to bring it to the many people living with a gait impairment."

The device, worn like a sleeve on a person's lower leg, uses advanced algorithms to "read" the signal sent from the brain to muscles, and is able to predict an individual's movement within a second before their foot lifts off the ground. The adaptive system, which employs sensors and electrical stimulation, send electrical signals that activate the body's muscles to produce a more natural movement, and provide real-time adjustments, Cionic reported.

According to the company's website, the aim is for the lightweight garment to ultimately resemble a legging that can be worn under clothing but is sufficiently "fashionable" to be worn with a skirt, shorts, or similar clothing. Further studies in the San Francisco area in adults and children may be ongoing.

"What Cionic is doing is a garment-type design, so it's not so obtrusive when you're wearing it," a wearer said in the release. "My last visit I actually went out on the streets in North Beach in San Francisco, heavy population, all the flavours of San Francisco, and it was a feeling of inspiration for me that I haven't felt for two and a half years."

Robison added: "We're currently working with academic partners around the world and conducting trials for people whose mobility is limited by neurological injuries such as cerebral palsy, multiple sclerosis, and stroke, with a goal to scale this solution to help anyone living with a mobility difference."

For further information on news stories go to page 13



Major gaps remain in treating prog-MS, admit experts

Despite positive developments in the field, there are still "major gaps" in both the treatment and management of progressive MS.

That is the frank and rather disturbing admission of the International Progressive MS Alliance which has just proposed a global research strategy to find better ways to care for people with progressive forms of MS.

The Alliance detailed their proposal in the paper, "Charting a global research strategy for progressive MS—An international progressive MS Alliance proposal," published in the Multiple Sclerosis Journal.

"The publication of this paper is an important step toward a more coordinated, global approach to tackling challenges and realizing opportunities for improving quality of life for people living with progressive MS," Alan Thompson, MD, lead author of the paper and dean of the faculty of brain sciences at University College London, said in a press release.

The paper reviewed the current field of progressive MS treatment and research, noting common clinical challenges where improvements are needed.

For example, it highlighted the lack of clear criteria to determine when someone converts from RRMS to SPMS, and the lack of thoroughly validated biological markers of MS progression that can be easily measured in clinical trials. **Continued on page 11**

Continued from page 10 Although studies have suggested that some forms of exercise may ease symptoms like fatigue, the researchers said that finding ways to reliably evaluate the usefulness of rehabilitation and symptom management strategies "remains a major challenge." "People with progressive MS are looking for rapidly translatable approaches that treat their disease now, while the longer term disease-modifying treatments are developed," the group wrote.

The Alliance also noted that current MS therapies work by blocking inflammation, but "if we are to have a major impact on progression we need to develop agents that provide neuroprotection and/or encourage repair."

To address the gaps in progressive MS care, the researchers highlighted three areas that require "renewed focus and effort."

First, they stressed the importance of further studies to understand the biological mechanisms that underlie disease progression in MS, crucial to identifying viable therapeutic targets.

Second, they highlighted the need to accelerate progressive MS clinical trials. They outlined several potential ways to do this — for example, some trials are testing multiple therapies simultaneously, which is more efficient in terms of time and costs. The team noted that better markers of disease progression and more accurate methods of classification will be useful in designing more efficient clinical trials.

The third area of focus is better strategies for improving the well-being of people living with progressive MS. This can take many forms, from physical rehabilitation to social support and emotional help.

The researchers emphasized that solving these problems will require cooperation from all stakeholders, from academia to pharma to clinicians to regulatory authorities. "The ideal is to have global stakeholders engaged and working together to speed progress and dramatically increase the likelihood of success," Thompson said. The team also stressed the importance of including patients in the research process.

"Engaging people with progressive MS, as a key stakeholder, in research and measuring impact on outcome that matter most to them, will give research the direction to make all the relevant stakeholders co-accountable for social and wellbeing needs related to progressive MS," the researchers wrote. They added that this involvement "can take many forms, such as inclusion of people with MS in establishing research agendas, contributing to design of clinical trials, planning for and communicating research results, and informing funding decisions and/or other parts of the research continuum." **Page 10 Image by fernando zhiminaicela from Pixabay**. **For details of all news and features go to page 13**

News

New drug for PPMS and SPMS set to end phase III trials in 2024

Two new clinical trials are set to take place to test Tolebrutinib, a new drug treatment under investigation for secondary progressive and primary progressive multiple sclerosis (MS) taken as a tablet once daily.

Tolebrutinib interferes with the function of immune cells called macrophages which have been linked to MS progression and of B cells, a type of white blood cell which is involved in the immune response that damages the myelin coating of nerves.

The drug inhibits an enzyme called Bruton's tyrosine kinase (BTK), reducing the activation of B cells and inhibiting macrophages which have been linked to MS progression. By inhibiting BTK, it is thought tolebrutinib will reduce the damage caused to nerve cells by MS.

In animal studies, tolebrutinib appeared to prevent the loss of myelin by preventing microglia from engulfing and destroying the myelin sheath produced by oligodendrocytes in the animals' brain, while ensuring the survival of myelin-producing cells.

In a phase II study, participants with relapsing remitting MS took one of 4 doses of tolebrutinib for 12 weeks either before or after taking placebo for 4 weeks. Compared to the placebo period, treatment with the highest dose of tolebrutinib resulted in an 85% relative reduction in new T1 lesions, and an 89% relative reduction in T2 lesions. T1 lesions are areas of active, ongoing inflammation; T2 lesions are areas where inflammation has caused damage, regardless of whether there is ongoing inflammation at the time of the scan.

Further trials are set to take place which will involve patients with both primary progressive and secondary progressive MS. Of particular interest is a trial called HERCULES – tolebrutinib compared to placebo, in secondary progressive MS This phase III study is recruiting 1290 participants with non-relapsing (non-active) secondary progressive MS. One half will take tolebrutinib and the other half will take placebo for up to four years. The main aim of the study is to assess the effect of tolebrutinib on disability progression, measured as worsening of disability which persists for six months. Other measures include walking speed, manual dexterity, cognitive function, MS activity on MRI scans, and quality of life. Estimated completion date is October 2024. Another trial PERSEUS – sees tolebrutinib compared to placebo, in primary progressive MS This phase III study is recruiting 990 participants with primary progressive MS. One half will take tolebrutinib and the other half will take placebo for up to four years. The main aim of the study is to assess the effect of tolebrutinib on disability progression, measured as worsening of disability which persists for six months. The main side effects reported in earlier phase II clinical trial were headaches, chest infections and the common cold. **For further details of all features go to page 13**

References contact details etc

Page 2 Sizomus study

For a clear description of the trial go to https://www.youtube.com/watch?v=vfftVAJfmuM where Professor Gavin Giovannoni, professor of neurology at Barts hospital in London gives a 4 minute explanation. Trial details, including eligibility criteria are at https://clinicaltrials.gov/ct2/show/NCT03783416

Page 3 Masitinib trial

https://multiplesclerosisnewstoday.com/news-posts/2022/01/05/ab-science-okd-start-masitinib-phase-3-trial-progressive-ms/?utm_source=MS&utm_campaign=d9ef91eb46-RSS_EMAIL_CAMPAIGN&utm_medium=email&utm_term=0_b5fb7a3dae-d9ef91eb46-71290133

Page 4 Cladribine trial

The trial sites are spread across the country from Edinburgh in the north to Plymouth in the South West. There is also a trial site in Belfast. Details of the trial can be found at https://clinicaltrials.gov/ct2/show/NCT04695080

Further details can be found at a site dedicated to the trial at https://www.chariotms.com/

Page 5-6 Veins and MS

“A comparison between the pathophysiology of multiple sclerosis and normal pressure hydrocephalus: is pulse wave encephalopathy a component of MS?.” Fluids Barriers of the CNS, 2016 Sep 22;13(1):18. doi: 10.1186/s12987-016-0041-2.

Page 7 Simvastatin story

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Page 8 NervGen trial

https://multiplesclerosisnewstoday.com/news-posts/2022/1/3/ascending-dosing-will-start-trial-nvg-291-healthy-volunteers/?utm_source=MS&utm_campaign=d9ef91eb46-RSS_EMAIL_CAMPAIGN&utm_medium=email&utm_term=0_b5fb7a3dae-d9ef91eb46-71290133

Page 9 Neural sleeve story

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pages 10-11 Progressive MS Alliance feature

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Page 12 Tolebrutinib story

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