

My prog-MS ezine

For people with progressive MS and other interested people

Issue number 29, January/February 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 plus two features about issues that matter to prog-MSers. In the first feature (page 5) I look at standing frames and research showing that they help in prog-MS. The second feature looks at milk, MS and something in milk called colostrum which may have a role to play in treating MS. See page 10.

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Canadian research finds key molecule to stop progression

In a revolutionary breakthrough, researchers at the Université de Montréal (U de M) have solved the riddle of exactly how an MSer's own immune cells invade the central nervous system causing the cascade of events that lead to MS.

Normally, a certain type of immune cell - the B cell - is responsible for fighting infection and protecting against cancer. But in people with MS, B cells cross the blood-brain barrier and cause damage to brain tissue.

The U de M researchers discovered that people with MS have B cells that overproduce a molecule that makes it easy for those cells to cross the blood-brain barrier.

As well as answering this question the researchers then found a way to block the molecule, called ALCAM, in lab mice. The results of their study have been published in the journal Science Translational Medicine.

"By blocking this molecule in mice, we were able to reduce the flow of B cells into their brains and, as a result, slow the progression of the disease," said Dr. Alexandre Prat, a neuroscientist at the Centre de recherche du CHUM, and one of the authors of the study.

At present, there is no drug that Prat is aware of that specifically targets the ALCAM molecule. Still, he predicted it could take a pharmaceutical company five to six years to develop one, and then have it tested in a clinical trial.

"In the field of MS, we're getting very close to reaching a cure," he added. "Several of the medications that we use currently for the treatment of MS are extremely efficient and they do control the disease quite well. The problem we're facing is all the side effects that these medications have in terms of infection and cancer. If we can mitigate this aspect of the treatments we have, we'll be finally close to a cure."

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MS Specialist to Lead Trial of Temelimab in Progressive Disease Without Relapses

Swiss drugs firm GeNeuro is collaborating with clinical researchers at the Karolinska Institutet and the Academic Specialist Center (ASC) in Stockholm, Sweden, to open a new clinical trial of its new drug temelimab in people whose MS is progressing in the absence of relapses.

Fredrik Piehl, MD, PhD, a professor of neurology at Karolinska and head of research at the MS clinic at ASC, will lead this single-centre trial at the ASC's Center for Neurology, the largest MS centre in Sweden. The trial, to take place over the course of one year, will enrol MS patients who experience disability progression without relapses, according to a press release. It will evaluate temelimab's safety and tolerability at increasing doses, as well as its efficacy based on biomarkers associated with disease progression. Researchers aim to begin enrolling eligible patients in early 2020.

Temelimab is an antibody designed to neutralize a protein known as pHERV-W Env, which has been shown to activate microglia (immune cells that cause inflammation in the brain) and lead to aggressive attacks on myelin. pHERV-W Env has also been shown to impair the ability of the brain to remyelinate cells by preventing oligodendrocytes — cells that produce myelin — from maturing.

"It is evident that currently available disease modulatory therapies for MS exert very limited effects on the progressive aspect of MS, and that this phase starts early in the disease course. A role of pHERV-W Env in progressive disease worsening is supported by accumulating preclinical and clinical evidence," Piehl said in a press release.

This collaboration aims to build on positive results from GeNeuro's Phase 2b ANGEL-MS extension study (NCT03239860) in 219 relapsing-remitting MS patients, which were reported at ECTRIMS 2019. ANGEL-MS trial data showed that treatment with temelimab was associated with positive results at two years regarding key biomarkers of disease progression — namely lesser brain atrophy, preserved myelin, and slower disease progression. "Long-term data have confirmed the neuroprotective effect of temelimab in MS and demonstrated its potential to make significant improvements in the lives of patients," said Jesús Martin-Garcia, CEO of GeNeuro. "We are very proud to be working with Prof. Piehl, who is recognized for his leading research at the Karolinska Institutet and the ASC, to further advance the development of temelimab as a potential treatment against disability progression in MS."

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London research team seeks new treatments for inactive prog-MS

A research team at London's Barts Hospital (St Bartholomew's) is in the final stages of preparing an application to the UK MS Society for a grant to tackle "smouldering MS" or inactive SPMS and PPMS.

As Ocrelizumab and siponimod are only licensed for patients with active PPMS and active SPMS, there is nothing for those with inactive progressive MS ie prog-MS without relapses. This is in spite of the fact that these conditions affect thousands of progressive MS patients who are presently in the so-called untreated MS camp.

The team at Barts hope their grant would be able to identify and/or repurpose drugs to modify this stage of MS. They plan to do this by "deep phenotyping" and "biomarker studies" and try and discover new treatments directed at Central Nervous System B-cells and plasma cells, microglia inhibitors or activators, drugs that target astrocyte and oligodendrocyte biology, antiviral trials and in the future drugs targeting ageing mechanisms.

Siponimod could be on NHS by end of 2020

The European Medicines Agency (EMA) has recommended that a licence should be granted for siponimod (Mayzent) for the treatment of active secondary progressive MS (SPMS).

Active secondary progressive MS is defined as people experiencing relapses or showing signs of inflammation in MRI scans. The next step in the approval process is for the European Commission to grant the licence, taking into consideration the EMA's recommendation. Siponimod will then be appraised by NICE and SMC to decide whether it is a cost-effective treatment for the NHS.

NICE has already started the appraisal process for siponimod and a decision is expected in May . If NICE approves the use of siponimod, it could be available on the NHS by the end of 2020. Siponimod is taken as a tablet, once a day. In clinical trials for secondary progressive MS, siponimod reduced the risk of disability progression by 21% compared to placebo. Further analysis indicated a 33% reduction in the risk of progression for those with active SPMS (defined as those who had relapsed in the two years prior to starting the trial).

In clinical trials, low white blood cell count, increased liver enzyme levels, slower heart rate when starting treatment, macular oedema (swelling in the back of the eye affecting vision), high blood pressure, shingles, and convulsions occurred more frequently with siponimod than with placebo. **For details of all news stories go to page 13**



Standing up to progressive MS

I was recently really interested to read of research being carried out at Plymouth University, which was published in the Lancet, showing that people like John Kendrick (left) experienced "significant improvements" in movement and balance when they stood in a specialised standing frame for 30 minutes, three times weekly for 20 weeks. Participants had better movement and balance, reduced stiffness in their legs and improved bladder and bowel control.

The research involved 71 people with progressive MS who used a standing frame over 20 weeks, alongside their usual care. Participants were asked to stand in the frames for 30 minutes, three times weekly, over 20 weeks, with encouragement to continue standing for 36 weeks and beyond.

Results showed that, on average, people who used the standing frame scored more highly on an assessment of their movement and balance, as assessed by a physiotherapist. Better still, this improvement was measured as being "clinically important". The researchers also said that the use of standing frames, costing around £800, would be cost-effective in progressive MS, and they concluded that standing frames could be routinely implemented within MS care throughout the UK.

John Kendrick (67) who took part in the study lives in Sparkwell near Plymouth. He was diagnosed with relapsing remitting MS at 53. Secondary progressive MS followed four years later. With an EDSS of 6.5 he requires two walking aids – a pair of canes, crutches, etc. – to walk about 20m without resting.

John got on the standing frame trial as he had previously done trials with Plymouth University and says he kept volunteering for anything that was going. He believes enrolling on the walking frame trial was a smart move. "I think that the frame has helped keep me out of a wheelchair and without the frame I am sure that I would be much worse off and not be able to do as much as I am now able

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When I started the trial I would only stand on the frame and exercise for five or ten minutes. I gradually built up to the longer periods, when my muscles got stronger. I do believe that people in the same position as me would definitely benefit from the frame and the regular exercise it can bring into your life.”

John still uses the frame two or three times a week and says that after years of not being able to move a great distance, the best thing about his improved mobility is that he was able to walk his daughter Nicky down the aisle on her wedding day earlier this year. He said: "There is absolutely no doubt in my mind that had it not been for the standing frame, I would not have been able to walk my daughter into church to marry her husband. It was a challenge, using a crutch to help me and obviously holding on to her too, but I'm so proud I did it.”

Lead author of the study, Jenny Freeman, Professor of Physiotherapy and Rehabilitation at the University of Plymouth believes the trial has major implications for helping other people with secondary progressive MS, not just those who took part in the trial like John

She said: "Mobility is a major concern for people with MS—not just in terms of standing and walking, but also, for example, moving about in bed. Nearly 25 per cent of people with MS eventually become wheelchair dependent. However, until the trial very little research had taken place into how to preserve and improve mobility in people with more severe disability, or how effective the standing frame was for this patient group.

"This is one of the first physiotherapy interventions proven to be effective in this group of people and as it was tested within an NHS context it's something that could be rolled out almost straight away." John Kendrick agrees. “I do believe that the cost of the frame makes it a worthwhile affordable addition to our fight with MS; and yes I would definitely have bought one had I not been on the trial.”

John’s words made me determined to get a standing frame, hopefully through MS services locally or perhaps I could find a hefty £800 and buy one myself. A standing frame may be expensive but it could be argued that the price of immobility, is far higher than that of an £800 mobility aid.

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$495K award to Study Biomarkers in Phase 2 Trial of cell therapy 'NurOwn' in Progressive MS

Drugs company BrainStorm Cell Therapeutics has received a $495,330 grant from the US National Multiple Sclerosis (MS) Society to support biomarker studies in its ongoing clinical trial testing the cell therapy 'NurOwn' in patients with progressive MS.

NurOwn is a treatment based on the patients' own bone marrow-derived mesenchymal stem cells (MSC) that have been engineered to secrete growth factors. These factors are believed to protect nerves from damage, promote the repair of myelin (the protective coat of neurons that is destroyed in MS), and ultimately slow or stabilize disease progression.

BrainStorm received the grant through the society's Fast Forward program, which was created to help support commercial organizations working to develop new therapies and diagnostic tools for MS.

"This research funding will help advance our investigational therapy NurOwn as a potential unmet need for patients with progressive MS. MS continues to devastate the lives of patients and their families, and we thank the National MS Society for helping us advance our innovative research program," Chaim Lebovits, president and CEO of BrainStorm, said in a press release.

The Phase 2 clinical study (NCT03799718) is currently enrolling up to 20 adults with either secondary progressive or primary progressive MS at three U.S. sites: the Keck School of Medicine of USC, the Stanford School of Medicine, and the Cleveland Clinic.

This trial is multi-dose and open-label, meaning all enrolled will be treated. Participants will undergo a bone-marrow aspiration to obtain their stem cells, then be given three NurOwn transplants into the spinal fluid (intrathecal transplant) over 16 weeks. Each will be followed for at least another 12 weeks to assess the treatment's safety and efficacy.

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MetP Pharma Awarded US Patent for Potential Remyelination Therapy

A patent application by pharmaceutical company MetP Pharma for a new method to treat demyelinating and neuroinflammatory diseases, including MS has been approved by the United States Patent and Trademark Office (USPTO).

The patent, titled "Treatment of Demyelinating Diseases" (U.S. Appl. No. 16/506,830), is valid until 2039, and covers the use of a steroid hormone, such as testosterone, in combination with a "Hedgehog pathway modulator".

Steroid hormones are a class of hormones defined by a particular molecular structure, and they play a variety of important roles throughout the body. Testosterone, in particular, is best known for its role in male sex development, but it also plays roles in the regular functioning of the brain, and has been proposed as a therapeutic target for demyelinating diseases (those characterized by the loss of myelin, the protective coat of neurons).

The hedgehog pathway (named for the way flies with mutations in these genes look) is a molecular pathway through which cells transmit information to each other. It is best known for its importance in the development of numerous organ systems, including the brain, and also has been implicated in playing a role in protecting neurons from demyelination.

Research suggesting that treatment with testosterone, together with a compound that modulates (changes the activity of) the hedgehog pathway, can drive remyelination and promote neural repair is the basis of the new patent.

The patent broadly covers the use of this therapeutic approach in demyelinating and inflammatory diseases of the nervous system, including MS, amyotrophic lateral sclerosis (ALS), Devic's disease, Alzheimer's disease, Guillain-Barré syndrome, and chronic inflammatory demyelinating polyneuropathy.

The patent covers any route of administration, favouring nasal spray. It also allows the administration of the two components together, one at a time, or some variation thereof.

According to MetP Pharma, this new therapeutic approach offers a new regenerative strategy with the potential of repairing already damaged myelin, whereas current therapeutic strategies lack an efficient regenerative potential. MetP Pharma noted it is pursuing other patent applications in all major markets worldwide.

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Astrocytes in Brain are Possible Trigger of Progressive MS

A class of brain cell known as astrocytes may be central to inflammation and damage to the nervous system seen in progressive MS, a study in mice has found. The study could open new ways of treating MS, especially in its progressive forms, the US National MS Society said in a news report.

In the study the drug "miglustat" , an approved oral treatment for a rare metabolic disorder called Gaucher disease, was seen to ease symptoms in mice with progressive MS. The study findings are described in the academic paper "Metabolic Control of Astrocyte Pathogenic Activity via cPLA2-MAVS," published in the journal Cell.

Astrocytes are star-shaped cells present in the central nervous system (CNS; the brain and spinal cord), and are much more abundant than nerve cells (neurons). They are essential to maintaining CNS health, protecting the CNS from injuries. But they can also be involved in reactions that do harm, such as inflammation and neurodegeneration. Scientific evidence supports astrocytes being important contributors in MS development, particularly secondary progressive MS (SPMS).

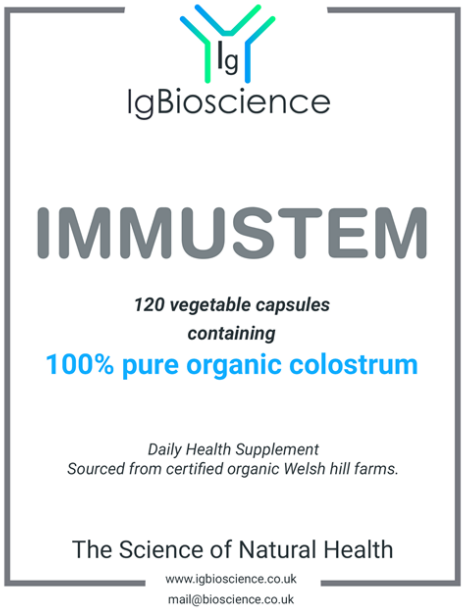
In this study, researchers further explored the role played by astrocytes and their related metabolic pathways in MS. Using a mouse model of MS, the team found that during the progressive phase of the disease, astrocytes in the brain switched on metabolic pathways that drove the production of lactosylceramide (LacCer). In turn, LacCer production activated a specific protein found in the mitochondria (the energy powerhouses of cells) known as mitochondrial antiviral signalling protein (MAVS). This sparked a switch that activated several pro-inflammatory genes, triggering inflammation in the brain and spinal cord.

Researchers then tested what happened if LacCer production was blocked by treating mice with oral miglustat. When given the mice before the onset of progressive MS, miglustat suppressed MAVS activation, and the pro-inflammatory signalling of astrocytes. Of note, it clearly eased MS-related symptoms in the mice, prevented CNS inflammation, myelin loss, and nerve cell death — all key causes of MS.

Based on the mice experiments with miglustat, the team also suggested miglustat could be "a candidate drug for repurposing to treat secondary progressive MS."

MAVS activation also happens in response to viruses, the researchers added, noting their findings could offer fresh insights into the ways in which certain viruses, which are considered possible triggers of MS, may contribute to the disease.

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Milk, MS and the alternatives

Milk, particularly cow's milk, has often had a bad press in the MS world, particularly because several MSers believe it plays a central role in the illness.

The reason for this belief is that MS is more common in countries where lots of milk is consumed and there have been various explanations for why this is. The basic theory is that proteins from dairy permeate the lining of our guts, throwing the door to the bloodstream wide open for all sorts of things—including bacteria—that then wreak havoc on the brain and other parts of the body.

A variant of this theory is that certain proteins in cows' milk are very similar to myelin basic protein and a process of molecular mimicry causes cells in the immune system to mistakenly attack myelin basic protein when milk is consumed, starting off the process of autoimmunity that causes MS. For years a case has been made for milk as a factor in causing MS, however the pendulum now seems to be swinging the other way .

Liz Rostand is director of IgBioscience Ltd, a small company producing 100% pure organic colostrum capsules (See above pic) Known colloquially as first milk, colostrum is the milk produced by mammals including humans immediately after giving birth. It contains antibodies to protect the newborn against disease and its protein concentration is substantially higher than that in later milk. Colostrum is known to contain immune cells and many other cells which form some of the components of the immune system. Colostrum also contains a number of growth factors.

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Continued from page 10 At IgBioscience Liz and her team produce ethically sourced colostrum from a small cooperative of organic hill farms in Wales. Ig Bioscience's first product "Immustem" has been helping people with autoimmune disorders including MS and has a growing client base of sufferers reporting significant improvements in their health. Liz Rostand has MS herself, and says colostrum has made a major difference to her symptoms and was the reason she helped start up the company.

Liz's experience of MS began in 1989 when she was 26." I was seen by a specialist at London's Moorfields Eye Hospital for Optic Neuritis in November 1989. Three years later I had a terrible attack and was bedridden and off work for six weeks. The medical establishment called my MS relapsing/remitting."

Liz started taking colostrum in 2016. At the time she says she was constantly tired. " I was at the stage where my legs had become so weak, and my balance was so affected, that everyday things were becoming very difficult; I was seriously contemplating using a walking stick.

"I heard about pure colostrum from an Australian journalist friend. He'd been caring for his wife for 10 years - a ballet dancer who'd declined fairly rapidly and finally had to use a wheelchair. They had heard about pure colostrum (very, very hard to find) and tried it. The Australian journalist's wife Shauna now no longer uses a wheelchair and leads a 'normal' life with her family and friends. She became a good friend and inspiration for me."

After taking colostrum for just two days Liz says she started to feel a lot better. Within nine months she was able to walk seven miles throughout the day on a holiday in Barcelona, with no ill effects.

"Before colostrum I had never gone away with friends because I was so worried about my MS ruining their time away. So socially it has been completely life changing and I feel more able to join in with everything - swimming, dog walking and just sharing more. I hadn't realised how alone and lonely MS was making me feel. I am now so much stronger - I am not cured and it's important to stress this is not a cure - but it can work wonders alleviating the symptoms of autoimmune disorders. My overall health has improved dramatically - I can exercise regularly, I can go for walks with friends (which I could never do before)."

Liz says the medical establishment now calls her MS "Benign MS". She explains: "I haven't seen anyone for MS for about three years now. They can't categorise me and I confuse them as they can't explain the alleviation in my symptoms. So I feel their time is best spent helping others whose need is greater than mine for the time being."

It was for this reason that Liz set up IgBioscience which sells colostrum to people with MS and other auto-immune conditions. "We've had so much success with it, helping other autoimmune sufferers. I - and now many others - are living testimony to this."

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Speed of Eye-to-Brain Signals May Measure Myelin Changes

Measuring the speed of signals sent to the brain by nerves in the eye could help assess if remyelination is taking place, a study in cats suggests. Such measurements could be used to evaluate MS treatments aiming to repair myelin in clinical trials — and be of particular interest to people with progressive MS, researchers said.

The study, "Evoked potentials as a biomarker of remyelination," was published in the journal PNAS. In it researchers at the University of Wisconsin-Madison demonstrated that remyelination could be assessed using a non-invasive test called visual evoked potential (VEP). VEP is a measurement of the electrical signal recorded through the visual pathway in response to a light stimulus. It involves giving a person a flash of light to the eye, which triggers an electrical signal that travels from the eye's retina through the optic nerve until it reaches the brain. Using electrodes on the person's scalp, it is possible to measure the specific brain activity resulting from the flash of light stimulus. The time lag between the light flash and the brain activity is called latency.

"When that latency increases, it's taking longer for the signal from the lights to get from the retina down the optic nerve to the brain," Ian Duncan, PhD, co-author of the study, said in a news story. "As MS progresses and demyelination of axons in the optic nerve worsens, the latency grows."

"If we could prove that a decrease in latency in the VEP truly reflected remyelination of nerve axons, then you'd have it," Duncan added. "You've got a way to tell if there's improvement in a patient, an outcome measure that can show whether the drug you are testing is successfully promoting myelin repair."

In the study, researchers used a cat model of MS to test their hypothesis. When cats are fed irradiated food, they undergo substantial myelin loss, including in their optic nerves. But when returned to a normal diet, cats recover the lost myelin (remyelination). The researchers took VEP measurements throughout this process, and compared these measurements to nerve samples. They found that, indeed, VEP latency correlated closely with the loss of myelin and its recovery.

"If you've got a drug to promote myelin repair in MS patients, we now have a proven outcome measure," Duncan said. "VEP can accurately quantify the drug's remyelinating effect in the optic nerve — likely reflecting remyelination throughout the central nervous system — and can help begin to sort the wheat from the chaff in potential remyelinating therapies for people with progressive MS," he added.

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

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