

My prog-MS ezine

For people with progressive MS and other interested people

Issue number 26, July/August 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 what the present situation is regarding CBD (cannbidiol) and MS in the UK . The second feature looks at the issue of getting older with progressive MS – something that is of particular interest to those of us secondary progressive MSers like me (aged 60!) . See page 10.

IN THIS ISSUE



Cannabidiol - changes in rules that threaten its availability pages 5-6

More evidence for role of inherited retrovirus in MS – page 2
Could blood plasma from young donors help prog MSers? p3

Inherited retrovirus HERV-W is key to nerve tissue damage in MS progression

In a new study published in PNAS, (Proceedings of the National Academy of Sciences) researchers from the University of Dusseldorf and other institutions have shed light on an axon damage mechanism believed to drive the disease process in MS and its progression.

In the paper Dr. David Kremer of Cleveland Clinic in the US explains that the envelope (ENV) protein of the pathogenic human endogenous (inherited) retrovirus type (pHERV-W) is a major contributor to nerve damage in prog-MS. In collaboration with research teams in the U.S. and Canada, the paper demonstrates that the ENV protein drives CNS (Central Nervous System) resident microglial cells to damage myelinated axons.

Alongside the scientific research into the damage mechanism, clinical development aiming at neutralizing the harmful ENV protein in MS patients has also progressed. Two clinical studies conducted under the supervision of Professor Dr. Hans-Peter Hartung of the Department of Neurology, Heinrich Heine University, Dusseldorf have already successfully tested the ENV-neutralizing antibody temelimab (a drug already being used in clinical trials). MRI scans of participants treated in the study showed reduced damage to the nerve tissue.

The Düsseldorf-based researchers and their colleagues can therefore explain why neurodegeneration is decreased in patients treated with temelimab. This antibody specifically binds to the ENV protein of the retrovirus and blocks its activity in the CNS. Professor Hartung says future clinical studies in progressive MS patients will now have to demonstrate whether temelimab treatment can also improve clinical symptoms resulting from neurodegeneration.

Temelimab (GNbAC1) targets a human endogenous retrovirus (HERV) believed to play a role in the development of MS. This treatment approach, or mechanism of action, differs radically from those of currently approved medications.

In terms of background information HERVs are genetic elements that are either hereditary, replicated from a host cell, or result from a germ. The viral envelope protein encoded by one HERV has been found in active MS lesions. The drug Temelimab (GNbAC1) is being developed by Swiss biopharma company Geneuro and has reached Phase 2b stage of clinical trials.

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

Young blood plasma improves muscle mass and energy in older MS patients, study says

The Neurology Center in Houston, Texas, USA, has released three-month results from an ongoing study showing improvements in MS patients receiving intravenous infusions of fresh frozen plasma obtained from young blood donors.

The study will be of particular relevance to patients with secondary progressive MS which tends to affect older people.

Earlier studies have shown that infusions of young mice's blood could reverse cognitive and neurological impairments in older mice. Further preliminary data has suggested that the intravenous administration of fresh frozen plasma obtained from young human blood donors (yFFP) could reverse the neurological effects of MS.

To test its potential as an MS therapy, researchers are conducting a randomized, placebo-controlled study called the Young Plasma Blood Study. It is assessing the average clinical and functional improvements in MS patients (eight patients) upon yFFP administration — NuPlasma yFFP — compared with a placebo-administered control group (six patients).

According to a press release, the team, which includes neurology and anti-ageing specialists, found that patients receiving yFFP showed improved functions in areas that often are affected in MS. Among these changes, they discovered that yFFP-treated patients experienced reduced urination frequency (39.1% reduction), joint pain (18.8%), and headaches (17.1%), compared with placebo controls.

Patients treated with yFFP also showed improved muscle strength (28.9% improvement), sex life satisfaction (26%), and energy (10.7%) compared with control patients.

The current results were observed three months after study start, passing the point of yFFP still circulating in the blood of the patients. The team attributes these improved outcomes directly to the infusion treatment.

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

Siponimod Improves Cognitive Processing Speed in SPMS Patients, Trial Results Show

Treatment with Mayzent (siponimod) provided sustained improvements and prevented deterioration of cognitive processing speed in patients with secondary progressive multiple sclerosis (SPMS), regardless of cognitive function prior to therapy, according to results of a Phase 3 clinical trial.

Among other benefits reported were an improvement in cognitive processing speed in patients with or without relapses (referring to active or non-active SPMS, respectively) within two years of treatment.

In the trial 1,099 patients received Mayzent, (siponimod) while 546 were given a placebo. Results showed that the proportion of patients with sustained meaningful improvement in SDMT (the Symbol Digit Modalities Test) was greater for Mayzent than for placebo groups, in patients with or without cognitive impairment at the study's start. However, statistical significance was reached only in those without pre-study impairment, suggesting that patients treated earlier in their disease course and with less cognitive impairment benefited most from the treatment.

"The proportion of patients with sustained improvement in SDMT was most pronounced and significantly greater among Mayzent-versus placebo-treated patients in those patients with no cognitive impairment or patients with relapses," Benedict said.

The data further showed that treatment with Mayzent was associated with a significantly lower proportion of sustained deterioration in patients with or without cognitive impairment.

Overall, the results demonstrated that Mayzent treatment "had a significant benefit on processing speed (as measured by SDMT), a key cognitive domain affected by MS

For details of all news stories go to page 13



CBD and Me

The past few years have been difficult ones for MSers like me who use cannabidiol (CBD) . This is the non-psychoactive part of the cannabis plant which can help relieve MS symptoms like spasms and spasticity.

In 2015 the first cannabidiol (CBD) product, a CBD vaping device called Kanavape, became easily obtainable online for UK consumers. However, within a year there was a problem. The Medicines and Healthcare Products Regulatory Agency (MHRA) said CBD products, if advertised for medical purposes, needed to be licensed. As a result CBD oil is now marketed as a "food supplement" rather than a medical product and for the past few years CBD " food supplements" have been available at small specialist health shops as well as a few major high street retailers. However, selling CBD as a food supplement recently hit a whole new regulatory problem.

This came in the shape of the EU Novel Food Catalogue. The catalogue is an EU ruling, prepared over the past 20 years, and originally drawn up in the 1990s to regulate the development of genetically modified (GM) food, a "novel food" which had never been consumed by humans before. The EU Novel Food Catalogue imposes restrictions on selling certain "new or novel" foodstuffs and supplements. Over the past two decades the Novel Food Catalogue has been regularly updated and at the beginning of 2019 cannabidiol was deemed a new or novel food supplement in need of regulation.

In a series of tweets issued earlier this year the UK's Food Standards Agency, (FSA), made the following announcement: "There has been a recent change to the EU Novel Food Catalogue which affects some cannabidiol (CBD) products. Food businesses have not been able to show there was a significant history of consumption of these products in food and food supplements prior to May 1997 in the EU.

Under the Novel Food Regulations, foods or food ingredients which do not have a history of consumption need to be evaluated and authorised before they are permitted to be placed on the market.

continued on page 6



Continued from page 5 "We are considering the way forward in light of this clarification at EU level. We are meeting with relevant industry representative bodies, local authorities and other stakeholders to clarify how to achieve compliance in the marketplace in a proportionate manner."

At the time the Novel Food Catalogue was issued it was assumed cannabidiol would need to go through an approval process and it was thought that the FSA would ask local council trading standards officers to remove CBD products from sale until this approval process was complete, something which it was estimated could take 12-18 months.

Puzzlingly three months since the food catalogue was issued there seems little evidence of any approval process or the removal of any products from shops currently taking place. CBD products are still on sale at my local health food shop and at several UK online sites. When I looked in late June CBD oil and capsules were still being advertised on the websites of mainstream retailers such as Holland & Barrett. So what is going on? Is it just that the removal system has been very slow? Or is there something else?

Perhaps there is something else because it appears that several CBD suppliers are contesting the FSA's stand on CBD claiming the novel food catalogue is not legally binding and that any foodstuff like CBD which is part of the cannabis plant cannot be a "new or novel food" because cannabis and by implication CBD use by humans goes back thousands of years . Furthermore it has been claimed that any enforcement is likely to be unlawful because of this.

The website www.nutraingredients.com which provides news and analysis on supplements, health and nutrition suggests that things may go even further, carrying claims that one trade association for the UK's cannabis industry has announced its intentions to sue the FSA over its moves to classify cannabidiol (CBD)-containing products as a 'novel food'.

Whatever the outcome of these moves, it seems attempts to remove CBD from the marketplace are likely to be long and contested. In the meantime it seems like it is business as usual for CBD retailers like my local health food shop and CBD consumers like me. CBD is still being bought and sold so there's no need to panic, well not just yet. **For further details go to page 13**

Simvastatin's effect on SPMS is not related to lowered cholesterol, study suggests

Simvastatin, a widely prescribed cholesterol lowering drug, may slow brain atrophy and disease progression in secondary progressive MS (SPMS) for reasons unrelated to changes in blood cholesterol, a new analysis of a Phase 2 clinical trial says.

The analysis "Applying causal models to explore the mechanism of action of simvastatin in progressive multiple sclerosis," published in the journal PNAS (Proceedings of the National Academy of Sciences of the USA) looked at the results of a randomized and placebo-controlled Phase 2 trial (NCT00647348) that concluded in 2011, called MS STAT.

In the 2011 trial 140 adults with SPMS were assigned to either high doses of simvastatin (80 mg, once a day) or a placebo for two years. The trial results, published in 2014, found Simvastatin reduced brain atrophy (or shrinkage), a common consequence of nerve damage in MS, by 43% compared to placebo. Later analysis of MS STAT results also showed treated patients had improvements in cognitive function and a smaller, but significant slowing of disease progression, as measured by changes in EDSS scores, again compared to placebo.

But the University College London researchers who led that trial were not sure whether benefits shown were related to simvastatin's effects on blood cholesterol levels, or if other mechanisms of action were involved. The new analysis aimed to resolve this. Using mathematical models, researchers looked for possible reasons why treatment with simvastatin might lead to positive clinical outcomes in SPMS.

Analyses showed that the lessening in physical disability progression observed in treated patients were best explained by a combination of indirect treatment effects on reduced brain atrophy (31%) and a direct treatment effect on disability (69%). All these effects were independent of changes in blood cholesterol levels.

A new randomized and placebo-controlled Phase 3 clinical trial, called MS STAT2 is currently underway, and will specifically evaluate the effects of simvastatin at halting disease progression in 1,180 adults, ages 25 to 65 and with EDSS scores of 4.0 to 6.5, over three years. This primary goal, or endpoint, will be measured through changes in EDSS scores every six months compared to scores at the study's start.

For details of all news stories go to page 13

Vegetable-rich Diet, exercise and stress reduction, May Help Lower Fatigue in Prog- MS, Pilot Study Finds

One year of a vegetable-rich diet — combined with exercise, neuromuscular stimulation, and stress reduction techniques — is effective in easing fatigue in people with progressive multiple sclerosis (MS). Researchers say the results may be linked to changes in blood fat levels, in particular cholesterol.

This integrative intervention led to a rise in high-density lipoproteins (HDLs), or "good" cholesterol — and a drop in triglycerides and low-density lipoproteins (LDLs), known as "bad" cholesterol. The study, "Lipid profile is associated with decreased fatigue in individuals with progressive multiple sclerosis following a diet-based intervention: Results from a pilot study," were published in the journal PLOS ONE. Previous studies have suggested that high blood lipid content can have a negative impact on the outcomes of people with MS, contributing to increased inflammation and disability.

Cholesterol is essential for the proper working of cells, and for making important hormones and vitamins, as well as bile acids needed in digestion. It can be produced by the liver or obtained in foods, such as meat and dairy products. In the body, cholesterol is distributed through several components, namely LDL, HDL, and VLDL (very low-density lipoprotein).LDL is often called "bad" cholesterol because it can build up on artery walls, increasing the risk of heart disease. Conversely, HDL is known as "good" cholesterol because it carries lipoproteins from other parts of the body back to the liver to be removed. This keeps the cholesterol from building up in the arteries.

In the PLOS ONE study a team from the University of Iowa conducted a pilot trial (NCT01381354) to explore whether one year of a diet-based lifestyle intervention could significantly ease fatigue and improve walking, balance, and quality of life in people with primary or secondary progressive MS.

After completing one year of the diet-based programme, fatigue scores had significantly decreased among participants, from an initial mean score of 5.51, to 2.48 at 12 months, which is in line with previous studies' data. Importantly, fatigue reductions were accompanied by significant increases in HDL cholesterol, along with a reduction in LDLs, triglycerides, and BMI. In addition, changes in total cholesterol — which comprises HDL, LDL and VLDL — and in HDL alone, were associated with a reduction in fatigue over those 12 months.

For details of all news stories go to page 13

Cells that support blood vessel growth can also restore muscle mass

Researchers say they are able to help restore muscle mass lost as a result of immobility by injecting cells that support blood vessel growth into muscles depleted by inactivity.

The research, conducted in adult mice, involved injections of cells called pericytes which are known to promote blood vessel growth in tissues throughout the body. The injections occurred at the end of a two-week period during which the mice were prevented from contracting the muscles in one of their hind legs.

“Just as the mice were becoming mobile again, we transplanted the pericytes and we found that there was full recovery of both muscle mass and the vasculature, too,” said University of Illinois kinesiology and community health professor Marni Boppart, who led the research.

The mice that received the injections had significantly better improvement than those that regained mobility without the injections. Boppart is a researcher in the Beckman Institute for Advanced Science and Technology at Illinois.

The team also observed that muscle immobility itself led to a significant decline in the abundance of pericytes in the affected muscle tissues. “This has never been documented before,” Boppart said.

The research is part of a long-term effort to understand the factors that contribute to the loss of muscle mass – in particular as a result of immobility.

“We know that if you are under a condition of disuse – for example, as a result of long-term bed rest, or the immobilization of a body part in a cast – you lose muscle mass,” Boppart said. “And even when you come out of that state of immobility and you start moving your muscles again, there’s this really long, slow process of recovery.”

Older adults might never fully rebuild the lost muscle mass after a period of immobility, she said.“They can’t recover, they become disabled, and there’s this downward spiral,” Boppart said. “They may become institutionalized and experience early mortality.”

Researchers have long searched for clinical interventions that can help restore lost muscle mass and impaired function as a result of inactivity, Boppart said.

“To my knowledge, no one has demonstrated that anything has been effective in improving the recovery process,” she said. “We’re excited by the new findings because we hope to one day use these cells or biomaterials derived from these cells to help restore lost muscle mass,” particularly in elderly or disabled adults who are most likely to see a decline in their overall health as a result of the decline in muscle viability.

For further information on news stories go to page 13



Getting on when you have progressive MS

It is usually assumed that secondary progressive MS and the changes that come with it are a direct result of the move from relapsing remitting to the progressive form of the illness, but is that assumption correct?

Not necessarily, because the changes which occur in secondary progressive MS are actually about not one but two things. The first is obviously the disease process itself, the second is ageing or getting older.

I am now 60 and I was diagnosed aged 35. Interestingly the human brain and spinal cord were not designed by evolution to last longer than roughly 35 years, the time by which nature expects us to have reproduced and raised our young. It is only relatively recently that as a species we have extended our lifespans and that has consequences. Once you go beyond approximately 35 years there is a gradual loss of nerve cells, axons and synapses.

This explains why, as we get older, we notice the effects of ageing such as reduced vision, loss of hearing, poor balance and age-related cognitive decline. Life has been rather cruelly called “an age-dependent neurodegenerative disease.” Harsh, but sadly true. When you combine this with another simple fact, that MS is also an age related neurodegenerative disease, then things get doubly bad for those of us getting older with prog-MS.

And to top it all there is also another factor to consider – our body’s repair mechanisms starts to fail earlier. In a paper “Cellular senescence in progenitor cells contributes to diminished remyelination potential in progressive multiple

Continued on page 11



Continued from page 10 sclerosis" neural progenitor cells (NPCs) from MSers with progressive MS were found to express cellular ageing markers when compared with age-matched controls, implying that cellular ageing or "senescence" is an active process in progressive MS and contributes to limited remyelination and recovery.

So, given this rather bleak news, can we prog-MSers do anything about what is premature or early ageing? Fortunately, yes, we can. We know from many well publicised studies there are many things that MSers can do to maximise brain and cognitive reserve like exercise, diet, sleep and avoiding smoking and excessive alcohol consumption.

Added to this there are new treatments on the horizon that reverse or slow down ageing in progressive MS. One of these is rapamycin, an immune-suppressant drug used to prevent organ rejection after transplantation. Expression of cellular senescence genes in neural progenitor cells (NPCs) in primary progressive MS (PPMS) was found to be reversible by treatment with rapamycin, which then enhanced PPMS NPC support for oligodendrocyte (OL) differentiation.

Another treatment is metformin, a diabetes drug that has recently been shown by scientists at Cambridge University to re-programme oligodendrocyte precursor cells in older animals to behave as if they were young cells and become more efficient at remyelinating axons.

So, while it is true that life may be considered an age-dependent neurodegenerative disease, life with progressive MS may in future be no worse than life without it. None of us are immortal but it would be nice if our lives with MS weren't so much shorter and worse than those without MS.

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

Early Safety Data from Phase 1 Study of Immunotherapy drug ATA188 in Prog-MS Patients shown at conference

Early, positive safety results from a Phase 1 trial testing a potential immunotherapy, ATA188, in people with progressive multiple sclerosis were revealed at the 5th Congress of the European Academy of Neurology (EAN) in late June.

ATA188 developed by Atara Biotherapeutics is a drug designed to target Epstein-Barr virus-infected B-cells, which are believed to play an important role in the development of MS. A similar immunotherapy called ATA190, has previously been shown to result in clinical improvements in a small number of progressive MS patients.

The Epstein-Barr virus (EBV) infects, activates, and expands B lymphocytes, immune cells that produce antibodies. People with MS show what is believed to be a genetically determined deficiency in T-cells, which would normally kill EBV-infected B-cells.

This deficiency leads to higher EBV infection of B-cells. Scientists believe some of these EBV-activated and expanded B-cells are autoreactive, meaning they can produce pathogenic autoantibodies against myelin (the protective coat of nerve fibres that is destroyed in MS patients).

ATA188 consists of T-cells that are injected into MS patients to help kill EBV-infected B-cells. Initial safety results showed that ATA188 was well-tolerated by people in the first two groups of treated patients, with no dose-limiting toxicities or serious treatment-emergent adverse events.

“We are encouraged by the initial ATA188 safety results from the first two dose cohorts,” Dietmar Berger, MD, PhD, global head of research and development of Atara Biotherapeutics, said in a press release.

The early safety data was presented at EAN on June 30, in a poster titled “Preliminary phase 1 safety of ATA188, a pre-manufactured, unrelated donor (off-the-shelf, allogeneic) Epstein-Barr virus (EBV)-targeted T-cell immunotherapy for patients with progressive multiple sclerosis (MS).”

For further details of all news stories go to page 13

References contact details etc

Page 2 HERV story

David Kremer et al, pHERV-W envelope protein fuels microglial cell-dependent damage of myelinated axons in multiple sclerosis, Proceedings of the National Academy of Sciences (2019). DOI: 10.1073/pnas.1901283116

Page 3 Blood story

https://multiplesclerosisnewstoday.com/news-posts/2019/04/30/young-blood-plasma-multiple-sclerosis-study-three-month-results-show-sustained-improvements-in-critical-disease-conditions-such-as-frequency-of-urination-strength-sexual-satisfaction-joint-pain-headaches-and-energy/?utm_source=Multiple+Sclerosis&utm_campaign=b81169dea5-RSS_NON-US_EMAIL_CAMPAIGN&utm_medium=email&utm_term=0_b5fb7a3dae-b81169dea5-71290133

Page 4 Siponimod story

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

page 5-6 CBD feature

source: https://www.food.gov.uk/business-guidance/novel-foods

https://www.nutraingredients.com/Article/2019/04/01/CBD-trade-group-mounts-legal-action-to-challenge-possible-FSA-reclassification

page 7 simvastatin story

source: Source: https://www.eurekalert.org/pub_releases/2019-05/ucl-spt051019.php

page 8 diet story

https://multiplesclerosisnewstoday.com/news-posts/2019/06/19/lipid-profile-is-associated-with-decreased-fatigue-in-individuals-with-progressive-multiple-sclerosis-following-a-diet-based-intervention-results-from-a-pilot-

study/?utm_source=Multiple+Sclerosis&utm_campaign=9bd3afb603-RSS_NON-US_EMAIL_CAMPAIGN&utm_medium=email&utm_term=0_b5fb7a3dae-9bd3afb603-71290133

Page 9 exercise story

Devasahayam et al. Oxygen cost during mobility tasks and its relationship to fatigue in progressive Multiple Sclerosis. Arch Phys Med Rehabil. 2019 Apr 23. pii: S0003-9993(19)30257-6.

Plus https://multiple-sclerosis-research.org/2019/04/exercise-exercise-exercise/

Page 10-11 ageing feature

https://multiple-sclerosis-research.org/2019/05/what-has-getting-old-got-to-do-with-ms/

Nicaise et al. Cellular senescence in progenitor cells contributes to diminished remyelination potential in progressive multiple sclerosis. Proc Natl Acad Sci U S A. 2019 Apr 30;116(18):9030-9039.

Page 12 ATA188 story

https://multiplesclerosisnewstoday.com/news-posts/2019/05/15/initial-ata188-phase-1-safety-data-in-patients-with-progressive-multiple-sclerosis-detailed-at-ean-congress/?utm_source=Multiple+Sclerosis&utm_campaign=5f6b61c862-RSS_NON-US_EMAIL_CAMPAIGN&utm_medium=email&utm_term=0_b5fb7a3dae-5f6b61c862-71290133

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