My prog-MS ezine

For people with progressive MS and those interested in it

Issue number 12, March/April 2017

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 five pages of news plus two features about issues that matter to prog-MSers.

The first feature on page 4 is about textured insoles for shoes that help me walk better. On page 8 I ask whether vitamin D is really helping me with my MS.

Finally I also have a website where you can sign up for future editions of the ezine. It is at:

http://www.mymsprogblog.com Thanks to fellow prog-MSer Pete Joyce for helping me with the site.

So, please send this ezine to all other MSers, MS nurses and neurologists in your address book, and we can share our knowledge about what it's actually like to live with progressive MS.

Best wishes, Ian Cook

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Toxic astrocytes may drive MS progression, claims US study

Astrocytes, a specific type of brain cell, may take on a "villainous character", destroying other nerve cells like myelin-making oligodendrocytes and driving MS progression. That's according to a study carried out at the Stanford University School of Medicine in the US.

Senior study author, Dr Ben Barres, (right) said: "We have learnt that astrocytes aren't always the good guys. An aberrant version of them turns up in suspicious abundance in all the wrong places in the brain-tissue samples from patients with Multiple Sclerosis (MS). The implications are profound."

Astrocytes are star-shaped connective tissue cells in the nervous system that link nerve cells to blood vessels. They do this by wrapping round brain capillaries and help form the blood-brain barrier. For every nerve cell in the human brain there are four astrocytes.

Up to now, the pharmaceutical industry has mostly targeted nerve cells, known as neurons. But now it is believed a broad range of brain disorders may be treatable by blocking astrocytes' metamorphosis into toxic cells, or by pharmaceutically countering the neuron-killing toxin these toxic astrocytes have been found to secrete.

Based on previous research in 2012 the Stanford team discovered the process involves brain immune cells, called microglia, becoming activated by Lipopolysaccharides (LPS) - molecules made from fats and sugars . In a series of experiments using laboratory mice, the scientists identified three pro-inflammatory factors whose production increased after lipopolysaccharides exposure.

Next, the researchers confirmed that these newly toxic astrocytes stop showing the nurturing qualities they'd had as resting astrocytes, which Barres' group has shown are essential to the formation and functioning of synapses, a structure which allows neurons (or nerve cells) to pass an electrical or chemical signal to another neurons. Further experiments showed that toxic astrocytes lose the capacity to prune synapses that are no longer needed or functional and whose continued existence undermines efficient brain function.

Finally, the researchers analysed samples of human brain tissue from patients with Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis (a form of motor neuron disease) and MS. In every case, they observed large numbers of rogue astrocytes clustering where the disease was most active.

An effort to identify the neurotoxin secreted by rogue astrocytes is underway. Barres said. "We're very excited by the discovery of neurotoxic reactive astrocytes because our findings imply that acute injuries of the retina, brain and spinal cord and neurodegenerative diseases may all be much more highly treatable than has been thought."

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Trial ends for highly promising new SPMS drug

A phase 2b clinical trial of a revolutionary new drug for secondary progressive MS will end on schedule by April 30 , and data is expected to be released in the Autumn.

The drug MIS416 is a micro-particle designed to target myeloid cells (a subset of innate immune cells not currently targeted by any other drug), and it is hoped the new drug will play a key role inside the brain of a patient with SPMS by decreasing inflammation, helping clear myelin debris and enhancing tissue repair processes.

Australia's Innate Immunotherapeutics, the firm behind the new drug, said that MIS416 is a biologically derived new immune modulator that can target both the regulatory and defensive functions of the innate immune system.

The current Phase 2b trial (NCT02228213) is an exploratory, double-blind, randomized, placebo-controlled study assessing the safety and effectiveness of MIS416 when administered once a week over 12 months.

The trial enrolled 93 SPMS patients between late 2014 and April 2016. The final 16 patients are set to complete the study with the final dose administered on April 19. The study has raised no safety concerns and its independent Data Safety Monitoring Board met on three occasions without any expression of concerns regarding the trial's outcomes, the company reported.

Following the final patient visit, Innate expects it to take up to four months to complete the entry, monitoring and analysis of data generated by the study. The final report should be released in August or September, though initial "top-line" data might be available before then.

"The participants in this study endure a wide range of MS-related debilitating symptoms and we deeply appreciate the commitment and fortitude with which so many of them have adhered to the requirements of what is an intensive course of treatment and tests over a 52 week period," Innate CEO's, Simon Wilkinson, said in a press release

New PPMS drug Ocrevus (Ocrelizumab) is on the way

The U.S. Food and Drug Administration (FDA) is expected to approve Ocrevus, (generic name ocrelizumab,) for use as a therapy for primary progressive multiple sclerosis at a meeting on March 28.

Clinical trials have shown the drug to be a promising therapy for primary progressive MS for which there is no approved treatment .If all goes to plan the European equivalent the EMA will look at the drug which could take up to 12 months and then NICE will have to look at its cost effectiveness, which typically takes 6-12 months and then post-NICE there is a 3 month delay before NHS England allows neurologists to use it. This means that the dug may not be in clinic in the UK until 2019

More details of all news stories are on page 12

Can textured insoles <u>really</u> improve your walking?

Specially textured shoe insoles may help MS patients walk with more assurance and ease. The insoles, similar to ones pictured left, have been developed by an Australian-led research team which is seeking 176 patients to test them in a trial.

The three month trial is being led by a physiotherapy professor at the University of Queensland's School of Health and Rehabilitation Sciences in Australia. "Many people with MS experience problems with walking which can make day-to-day activities difficult and often leads to falls, so improving walking ability is of primary importance in maintaining health, independence, and quality of life," said Anna Hatton the study lead.

"Evidence suggests that wearing textured shoe insoles, which are designed to stimulate receptors on the soles of the feet, may be one possible option to help improve gait," she added. "We now need people with MS to help us investigate whether the novel insoles influence the way the leg and trunk muscles work while walking on both even and uneven surfaces."

The team will also investigate changes in the perception of sensations in the feet and awareness of the foot's position, as these play a key role in keeping the body balanced when walking.

"We know from previous studies that people with MS often have poor sensation on the soles of their feet," Hatton said. "Therefore, wearing a specially designed shoe insole, which enhances sensory information at the feet, could help people affected by MS to walk better."

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Researchers hope that this study will result in a relatively inexpensive and easy-to-use treatment approach that might give MS patients a more autonomous lifestyle.

Previous research (left) carried out in the UK in 2014 gave 46 MS patients three types of insoles in a random order: control (smooth), Texture 1 (Algeos) or Texture 2 (Crocs™pictured on p4)- which I wear.

Participants were allocated at random to wear one type of textured insoles for 2 weeks, after which they were retested. It was found that although the textured insoles had no significant immediate effects on balance or gait, both types of textured insoles showed significant effects on spatio-temporal parameters of gait, with mean stride length increases of 3.5cm (Texture 1 - Algeos) and 5.3cm (Texture 2 Crocs) when wearing the insoles.

The researchers concluded that after two weeks of wear, there were improvements in "spatio-temporal parameters of gait".(I have been wearing the Crocs insoles pictured on page 4 for the past two years and think they help me walk and balance better, ed.)

For Australian patients interested in taking part the new and longer study, it will take place at Queens University's Gait Lab. Interested MS patients can contact Hatton at a.hatton1@uq.edu.au, or by calling +61-7-3365-4590 or +61-7-3365-3299.Study participants must be older than 18, diagnosed with MS, be able to walk 100 meters (about 110 yards) independently or with only minor assistance from a mobility aid, and have no other neurological disorders or cognitive impairment.

Pictured above Dr John Dixon, a Reader in the School of Health & Social Care, together with PhD student Jenny Baron at Teesside University testing the insoles in 2014

For further research on insoles and MS go to page 12

Fingolimod could treat secondary progressive MS

A drug already used to treat relapsing remitting MS may hold promise as a treatment for secondary progressive MS according to a study carried out by researchers at Brigham and Women's Hospital (BWH) in the US.

Scientists from the hospital have discovered that the drug Fingolimod appears to reduce the pathogenic activities of astrocytes which it is believed may contribute to the neurological damage seen in SPMS. (see story on p2)

"One of the most important unmet clinical needs in MS is to design therapeutic approaches for the progressive phase of the disease," said senior study author Francisco Quintana, PhD, a researcher in the Ann Romney Center for Neurologic Diseases at BWH. "And a key unanswered question related to that is what are the biological processes that drive disease pathogenesis at this stage?"

The current study, published in PNAS (Proceedings of the National Academy of Science) and led by Francisco Quintana, PhD sheds new light on the role of sphingosine-1-phosphate, a type of lipid, and its receptors in SPMS. The researchers found that blockage of these signals with Fingolimod had important effects on astrocytes in both mice and humans, decreasing their pro-inflammatory and neurotoxic properties while also increasing the cells' anti-inflammatory capabilities.

The study results suggest Fingolimod may help lessen some symptoms of SPMS in humans. But it should be noted that a clinical trial of a highly related drug Siponimod , led by Novartis, is now underway and encouraging preliminary results have been recently released, Quintana added.

The Siponimod study involves more than 1,600 patients in 31 countries

Siponimod set to enter the SPMS market in 2018

A new disease modifying drug for secondary progressive MS could be in clinic as soon as 2018, according to a feature published in Pharmaceutical Online.

The feature, written by John Crowley, Ph.D a former postdoctoral fellow at Harvard Medical School says the Decision Resources Group (DRG) a leading healthcare research and consulting company forecasts a Siponimod launch for SPMS as early as 2018.

This prediction follows a favourable reception of the drug's latest efficacy data delivered at the European Committee for the Treatment and Research in Multiple Sclerosis (ECTRIMS) held in Setember 2016.

This data revealed a 21-percent reduction in the risk of three-month confirmed disability progression versus placebo in the Phase III EXPAND study of 1,651 patients with SPMS (relapsing and non-relapsing)

The drug's impact was most pronounced in younger patients, those who experienced a relapse in the two years prior to enrolment and patients with gadolinium enhancing lesions at the start of the trial. Siponimod outperformed a placebo on annualized relapse rate (56 percent reduction), change in T2 lesion volume (79 percent reduction), and percentage brain volume change (23 percent improvement). However, those who took the drug failed to show better results on the timed 25-foot walk than the placebo group.

Details of all news stories are on page 12.

US stem cell project aimed at progressive MS

A stem cell project at the University of Rochester in the US is aiming to develop a stem cell-derived oligodendrocyte progenitor-based therapy for progressive MS.

Progressive demyelination of axons and the neuron from which they come accounts for a substantial component of the disability of late-stage progressive MS, both primary and secondary. Furthermore, preclinical studies indicate that demyelinated axons may be remyelinated by the introduction of human oligodendrocyte progenitor cells.

The aim of this project is therefore to develop a strategy that can both remyelinate axons before they are lost and to also restore function to already demyelinated brain and spinal cord tissue.

The project will compare oligodendrocyte progenitor cells obtained from three different sources (human induced pluripotential cells, directly induced neural stem cells, and human embryonic stem cells) and look at their effects on transplantation into mouse models of chronic demyelination, identifying which is the most effective for treating progressive MS.

Unlike most cell therapeutics for MS, which are targeted at non-brain cells to suppress inflammation, this project aims to begin clinical trials of stem cell-derived brain cells transplanted directly into the brain to achieve remyelination and structural repair of the already injured, demyelinated brain.

Prog-MS patients' small improvement after stem cells

New research from Dr Paolo Muraro, of the Department of Medicine at Imperial College, London, recently reported further evidence that autologous hematopoietic stem cell transplantation (AHSCT) may be an effective treatment for progressive multiple sclerosis.

His research assessed data from 25 treatment centres across 13 countries, identifying 281 patients with multiple sclerosis (MS) who underwent AHSCT from 1995-2006. Of these patients, 78 per cent had progressive MS.

Of the 281 patients studied, 46 per cent saw no MS progression five years after receiving AHSCT treatment. Patients with relapsing remitting MS (RRMS) had the best outcomes, with 73 per cent experiencing no worsening of symptoms five years after AHSCT. Patients with progressive MS fared less well than relapsing remitting patients seeing their EDSS score improve by 0.14 a year after treatment, while patients with RRMS experienced a 0.76 improvement in their EDSS score.

Patients with a younger age, few immunotherapies prior to AHSCT, and a lower EDSS score at study start showed better outcomes with the treatment. However, eight patients died within 100 days of treatment and Dr Muraro and his team warned that further trials are needed to determine the efficacy and safety of AHSCT.

More information on all stories on page 12.

I've been taking these pills for years but are they <u>really</u> helping my MS?

When my MS turned progressive in 2008 I started to clutch at straws. I hoped that I would find a miracle cure or at the very least something similar to stop the relentless progression of the illness.

But, deep down I remained a realist. I knew in my heart that for secondary progressive MSers there is very little realistic hope of a miracle cure . So while I clutched at straws I was selective or picky about which straws I would clutch at. They had to have a realistic chance of success.

Something I thought might be worth trying was vitamin D. It's cheap, easy to buy and take, and highly unlikely to damage you. I had started taking it when diagnosed in the early 1990s but when my MS became progressive in 2008 I started taking massive doses. First of all 5,000 IU then occasionally as much as 10,000 IU daily. As I result my levels rose dramatically from 30 nmol/L to more than 100 nmol/L so now I have plenty of vitamin D in my body.

Sadly, despite taking vitamin D in ever larger amounts, I still have MS and it's still progressing so I would be hard pressed to claim that vitamin D has achieved anything. All of which leads me to ask a couple of uncomfortable questions about vitamin D and MS

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The first is a sort of chicken and egg question. Most of us have heard there's a correlation between low levels of vitamin D and MS, but which came first? Did low levels of vitamin D cause MS or did MS cause low vitamin D levels?

If you read through the academic literature you will find papers which argue both points of view and the only light I can throw on the subject is that since taking my daily doses of 5,000 IU or even 10,000 IU, sitting out in the Summer sun and tanning shops I have failed to raise my levels to more than 140 nmol/L and now (at the end of Winter it is just 100 nmol/L so perhaps MS is depleting my vitamin D levels.

The second question I ask myself about vitamin D is one of time - Am I shutting the stable door after the horse has bolted? Am I taking vitamin D too late in my life? I am 58 years old and some academics have argued it is low levels of vitamin D in your mother's womb that means that you enter life deficient in this vitamin and start life with an immune system primed to get MS . Add childhood glandular fever and youthful smoking – both acknowledged risk factors- and yes I have have experienced both - and I get a plausible answer to the question: why do I have MS?

So, if I was primed to get MS at birth or early in life, taking vitamin D supplements at the age of 58 isn't going to do much to stop MS because it started before I was even born. But I continue to do so – more in hope than expectation I admit I am clutching at straws or a single straw to be precise but when you have secondary progressive MS clutching at straws is one of the few options left open to you. I am sure you understand. You probably clutch too.

For more information on vitamin D go to page 12

Tiny molecules in blood could show progression, study says

MicroRNAs in the blood could serve as biomarkers to monitor the progression of MS as well as help identify which mechanisms are at play in each patient, such as inflammation and tissue damage, according to new research.

MicroRNAs are tiny RNA (Ribonucleic acid (molecules that can control gene expression and regulate protein production. They have the ability to bind to an mRNA molecule (a copy of the coding information required to produce a protein) and block production of a given protein. MicroRNAs can bind to many different mRNA molecules, which makes them powerful regulators.

Although microRNAs are produced within the cells, where they function, some can be secreted into several body fluids. They are highly resistant to degradation, so circulating microRNAs could be ideal biomarkers to follow the progression of certain diseases.

These findings were reported in the study, "Association Between Serum MicroRNAs and Magnetic Resonance Imaging Measures Of Multiple Sclerosis Severity." It was published in the journal JAMA Neurology.

Study author Karen Regev, MD, of Harvard Medical School, and her colleagues previously demonstrated that MS patients had a specific set of microRNAs in their blood, and that those molecules could be biomarkers to diagnose the disease. Using magnetic resonance imaging (MRI), they've now found that those microRNAs correlate with brain and spinal damage. The team also found that specific microRNAs were associated with lesions or atrophy. Their presence could help doctors identify which mechanisms are at play in each patient's MS.

"These findings tell us the disease is heterogeneous," (diverse in character or content.) Rohit Bakshi, MD, MA, one of the study's senior authors, said in a news release. "There's a complex set of mechanisms at play, and it may vary from patient to patient. Another implication of this research is that it could eventually lead to us having a blood test to identify the subtype of MS in a patient, to help guide therapeutic decisions and prognosis," he added.

"MicroRNAs could serve as biomarkers of the underlying MS disease processes, once validated and standardized for clinical settings," said Roopali Gandhi, PhD, the study's other senior author. "In addition, these markers have the potential to provide novel treatment targets."

For more details of all news stories go to page 12

Protective molecules may boost myelin repair

An Italian based cell reprogramming project is seeking to identify molecules that may have a protective role in nerve cells or neurons and the capacity to promote myelin repair.

Yhe programme is called BRAVEinMS and involves an international research team led by Gianvito Martino of San Raffaele Hospital Milan (Italy) It is one of three projects that has received funding from the Progressive MS Alliance.

The research team are focusing their efforts in three phases: First they are identifying potential drugs or compounds using sophisticated "bioinformatics" tools which virtually reproduce the pathogenic mechanisms of progressive MS.

Secondly, they are screening these compounds for their ability to protect nerve cells or promote myelin repair in lab tests using both animal and human neurons and myelin forming cells. Finally, using animal models of progressive MS, they will investigate the therapeutic potential of the 'candidate' compounds

The research team believes that the project will pinpoint a limited number of previously unidentified molecules with a high chance of therapeutic power in progressive MS patients.

They expect that within four years from the start of the project which started last year they will identity one or two human grade compounds that can be used in Phase I/II clinical trials. As a result, the team aims to implement a clinical trial in the near future, by the end of 2020.

Clinical trial to look at extended release baclofen

A new clinical trial evaluating the effectiveness of extended-release baclofen capsules in relieving spasticity related to multiple sclerosis (MS) is taking place in six U.S. states, sponsored by Sun Pharma, the drug's developer.

Baclofen, an approved MS treatment available in different forms, acts as a muscle relaxer and an antispastic agent. As an extended-release treatment, Baclofen GRS distributes the drug's active ingredients over time in a patient's body, possibly allowing for less frequent dosing than is now common.

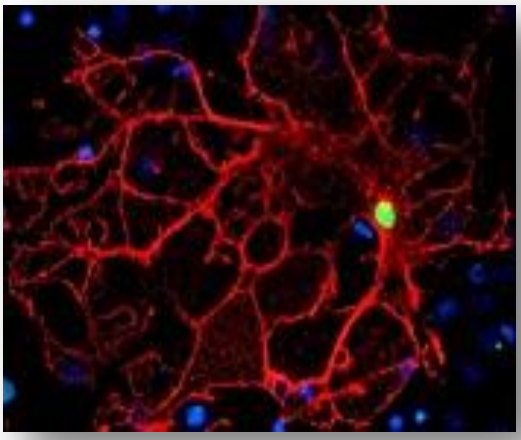
To take part, patients must be 18 or older and diagnosed with any form of MS, have a known history of spasticity, and already may be using baclofen in its current approved formulations.

More information about this trial, and how to participate, check out the trial's website at www.basisstudy.com.

For information on all news stories go to page 12

IN THE NEXT EDITION

UK researchers discover how to turn stem cells into cells which make myelin



References contact details etc

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Toxic astrocytes story

Source: Stanford University press release http://med.stanford.edu/news/all-news/2017/01/toxic-brain-cells-may-drive-many-neurodegenerative-disorders.html

Page 3 MIS 416 story

Source: Source: http://www.progressivemsalliance.org/wp-content/uploads/2015/09/Collaborative-Planning-Grant_Project-summaries_FINAL.pdf

Page3 Ocrevus (Ocrelizumab) story

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Pages 4-6 Textured insoles

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3.https://www.tees.ac.uk/sections/news/pressreleases_story.cfm?story_id=4432

page 7 Stem cells

story 1

http://www.progressivemsalliance.org/wp-content/uploads/2015/09/Collaborative-Planning-Grant_Project-summaries_FINAL.pdf

Story 2

Source: MS-UK (01/03/17) http://www.ms-uk.org/MSnews

P8 -9 vitamin D

I get my vitamin D levels tested at http://www.cityassays.org.uk/vitamins.html It costs me a little more than £20 per test.

page 10 micro RNAs

https://www.ncbi.nlm.nih.gov/pubmed/28114622

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Story 1 BraveinMS

Source: http://www.progressivemsalliance.org/research/research-projects-funded-by-the-alliance/collaborative-network-awards/#sthash.lD81N1Q9.dpuf

Story 2 Baclofen

More information about this trial, and how to participate, can be found on the trial's website at www.basisstudy.com.

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