

My prog-MS ezine

For people with progressive MS and other interested people

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MSer Hello and welcome to the latest edition of my ezine about progressive Multiple Sclerosis and MS progression in general. My name is Ian Cook. I'm a secondary progressive MSer who lives in Birmingham, UK. I'm 62 years old.

In this issue are 7 pages of prog-MS news stories. There are also two features. One on page 5 is on Patrick Burke, a prog MS blogger with his own website. https://www.aid4disabled.com. Patrick talks about fatigue and progressive-MS. There's also a feature on 25 years of UK disability rights? What difference has it made to those of us with progressive MS? See page 10.

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Masitinib slows disability progress in PPMS, and some SPMS

A new experimental drug masitinib can safely and effectively delay disability progression in primary progressive and non-active secondary progressive MS, according to data from a phase 2b/3 clinical trial.

Masitinib, from AB Science, was found to significantly lower the risk of first and confirmed (three-month) disability progression, and reduce the risk of needing a wheelchair in a broad population of progressive MS patients, compared to those taking a placebo.

"These results are the start of a possible revolution in the treatment of multiple sclerosis, as it is the first time a treatment has shown efficacy in both progressive forms of this [disease]," Patrick Vermersch, MD, PhD, the trial's main coordinator, said in a press release.

Masitinib (formerly known as AB1010) is an oral, selective tyrosine kinase inhibitor that works by blocking the activity of mast cells, microglia, and macrophages — immune cells people are born with - that are believed to play important roles in progressive MS. By suppressing these cells, the therapy is expected to limit neurodegeneration in progressive forms of the disease.

Recently, a multicentre, Phase 2b/3 clinical trial evaluated masitinib's safety and effectiveness in 656 adults with primary or non-active secondary forms of progressive MS. Participants were randomly assigned to receive either one of two doses of masitinib or a placebo, twice a day, for 96 weeks (about two years).

The researchers also analysed the risk of disability progression (as first onset and three-month confirmed) and of reaching an EDSS score of 7.0 — reflecting a level of disability severe enough that the patient is restricted to a wheelchair. In both groups, the participants had a median age of 50, with advanced disease; about half of the patients were women. The results showed the patients treated with the low-dose therapy showing significantly slower disability progression than those in the placebo group, irrespective of their type of progressive MS. Those receiving masitinib's low dose were 39% more likely to have either reduced disability or fewer disability worsening events than those given a placebo. These masitinib-treated patients also showed a significantly lower risk of first disability progression — by 42% — and of confirmed (3-month) disability progression by 37% over a timeframe of 96 weeks — which, Vermersch noted, is clinically relevant.

The patients who received masitinib also had a 98% lower risk of reaching an EDSS score of 7.0 for the first time, and a 100% lower risk of reaching EDSS 7.0 for three months, compared with those in the placebo group. *For details of sources for all news stories go to page 13*

Starting Mayzent early benefits SPMS, new trial data shows

MSers with secondary progressive MS (SPMS) who begin treatment with Mayzent (siponimod) early and continue its use for years are less likely to experience disability progression than those starting the medication later in their disease course, five-year data from a study called EXPAND suggests.

Data from this same Phase 3 clinical trial further suggests that Mayzent can help preserve important tissues in the brain, delaying physical disability and slowing cognitive decline.

These findings were published in a supplementary issue of the journal Neurology following the cancellation of the 2020 American Academy of Neurology Annual Meeting due to the COVID-19 pandemic.

Mayzent (siponimod), developed by Novartis, is approved to treat active SPMS in both the United States and Europe. The oral therapy belongs to a class of medications called S1P receptor modulators. These work by 'trapping' immune cells in lymph nodes which can limit the inflammation that causes nervous system damage in MS.

The Phase 3 EXPAND clinical trial is continuing to evaluate the safety and efficacy of Mayzent in people with SPMS. In its second part, 1,224 people continuing with the study after three years entered an open-label extension phase, in which all were given the active treatment. New data cover this part of the trial.

In one abstract, "Long-term Efficacy and Safety of Siponimod in Patients with SPMS: EXPAND Extension Analysis Up to 5 Years," researchers compared disability progression patterns between individuals who switched from placebo to Mayzent in the extension with those getting this treatment since EXPAND's start. This comparison was to ascertain whether there were significant differences when treatment was started years earlier. The analysis data covered up to five years of follow-up.

The benefits seen with early Mayzent treatment were "sustained for up to 5 years, suggesting a continuous effect of siponimod, and underlining the advantages of early treatment initiation," the researchers wrote.

EXPAND's open-label extension will continue for a total of seven years; the trial is due to end in March 2024.

Importantly, previous data from EXPAND suggested that treatment with Mayzent can reduce the risk of people with SPMS becoming dependent on a wheelchair

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New drug shows potential to significantly regenerate myelin

NeuroScientific Biopharmaceuticals (NSB)'s new drug EmtinB can lead to significantly greater myelin regeneration in a cell model of MS than Copaxone, the company has announced.

"These results represent a potential breakthrough in the treatment of MS as there are currently no approved therapeutic drugs available to patients that have demonstrated the ability to regenerate myelin in the central nervous system" Matthew Liddelow, NSB's CEO and managing director, said in a press release.

EmtinB is a lab-made molecule designed to mimic the neuroregenerative and neuroprotective effects of a protein called metallothionein-II (MT-II). EmtinB is believed to activate signalling pathways that promote nerve cell survival and regeneration, and also suppress neuroinflammation.

Previous data in a cellular model of MS showed that EmtinB significantly increased the number of oligodendrocytes — the cells that produce myelin. The study was conducted by an independent, French-based contract research organization called Neuron Experts, at NSB's request.

Then, NSB asked the same organization to assess EmtinB's ability to promote myelin regeneration in a cellular model of MS and compare it with that of Copaxone, a commonly-used disease-modifying drug for MS.

The new independent, preclinical study evaluated the regeneration of myelin around nerve fibres after treatment with one of five doses of EmtinB (15, 30, 60, 120 or 150 micrograms per milliliter, mcg/ml), or a dose of Copaxone (10 mcg/ml).

Data showed that almost every dose of EmtinB resulted in a significant increase in myelin sheet around nerve fibres, compared with untreated cells. At the higher doses (120 and 150 mcg/ml), EmtinB's boost in myelin regeneration was significantly superior — by more than 25–30% — to that achieved with Copaxone.

"Whilst we previously showed that EmtinB could positively influence the proliferation of myelin-forming oligodendrocytes in an MS model, these results go a step further to demonstrate that EmtinB significantly increases actual myelin formation", Liddelow said.

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The long and tiring story of managing my MS fatigue

By Patrick Burke

Managing my MS fatigue is a long story. As recently as 1995 I played badminton singles in the local sports centre, after just half an hour I was physically exhausted and very sweaty.

I've now hung up my badminton racket, personally I blame multiple sclerosis.

I still suffer intense exhaustion but no sweating. Walking very slowly for an hour leaves me feeling wiped out. So, how do I manage my MS fatigue?

I describe my MS fatigue as follows: 'It's an overwhelming inability to continue but there is no obvious reason. ' Does that describe MS fatigue to you? It ticks my box and within my definition there is an implication of my frustration and helplessness.

Managing MS fatigue can be difficult but I sometimes think that's my own stupid fault. Recently I managed to walk continuously for an hour and at the end I had chronic fatigue. I walked less than a kilometre, raising money for the local MS Therapy Centre. My wife has forbidden me attempting a similar venture for a long time. **Continued on page 6**

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Did you say, “MS is different for everyone”. The same applies to my MS fatigue. Some things are becoming incrementally more difficult for me. Walking is a problem for almost everyone who has MS. There are so many subtle and not so subtle problems tied in with this disability. Over the last 25 years that ever-present elephant in the room, multiple sclerosis, has taken away all control and feeling from my left leg. It started as foot drop and slowly the control and movement of the leg has ebbed away. At least my right leg is in good nick.

But, something else has crept out of the woodwork over the last few years and I never saw it coming. My left hand is slowly going the same way. So far it’s only the dexterity of my fingers but where and when will it end? Writing is a struggle. So, what’s happening? Slowly but surely manual dexterity is slipping away, I can’t control my fingers. It’s little things like undoing knots in shoelaces, twirling spaghetti round a fork and writing shopping lists.

Eating is a social activity and when it comes to making spaghetti carbonara I can slice the bacon but I cannot separate the eggs. I can grate the Parmesan and mix ingredients together but my wife must put food onto plates and carry it to the table. I can confidently twirl the spaghetti round my fork half a dozen times. Then it becomes a task that requires more and more concentration and effort. By the end the intense focus required to manoeuvre the fork takes away all the pleasure in eating.

Sometimes I even have a glass of wine with my supper. Now I really must engage brain. I pick up the glass, transfer it to my lips, take a sip and return it to the table. More than once the glass has inexplicably slipped out of my hands and smashed on the kitchen floor or I have dribbled wine onto the plate. It’s so embarrassing.

Managing MS fatigue does not make me feel tired or want to yawn. It has stolen games of badminton from me that I enjoyed even though I invariably lost. Managing MS fatigue sounds easy but there’s always something unexpected round the corner. I must smile and keep on going. These are simple things I now need to understand.

To read more about Patrick and his MS visit his website at
https://www.aid4disabled.com

Diabetes drug Aids Remyelination in Ways Similar to Fasting

Metformin, a common diabetes treatment that works to mimic dietary fasting, promoted remyelination in the stem cells of elderly rats, suggesting it may be useful in treating progressive MS, a study shows.

"Metformin Restores CNS Remyelination Capacity by Rejuvenating Aged Stem Cells" was published in the journal Cell Stem Cell.

Researchers from Cambridge University led by Prof. Robin Franklin first showed that as rats age, their oligodendrocyte progenitor cells (OPCs) lose the ability to readily mature into functional oligodendrocytes, a process common to ageing. The researchers found that, if given the proper stimuli, about 60% of OPCs from young rats grow into mature oligodendrocytes, while in aged rats less than 20% mature to oligodendrocyte cells.

The researchers then compared OPCs from old (20–24 months) and young animals (2–3 months), and found that aged OPCs exhibit certain cellular changes that are associated with cellular ageing, particularly changes to their mitochondria (the cell's powerhouses where energy is produced).

The team wondered if targeting these cellular changes could improve the ability of oligodendrocyte progenitor cells to turn into oligodendrocytes and, by extension, promote remyelination.

Researchers used two approaches with the animals. The first was an alternate day fasting, where rats only ate every other day, which is known to limit cellular ageing; the second was giving them metformin, a "small-molecule fasting mimetic" used to lower blood-sugar levels in diabetics, which acts through a protein called AMPK. This protein plays an important role in helping mitochondria work to produce cellular energy as intended.

Results showed that both approaches could promote the formation of oligodendrocytes in elderly rats, leading to better myelin repair. It is hoped to move the research on into human trials soon.

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Simple Sugar Molecule May Repair Myelin in MS

A natural simple sugar called N-acetylglucosamine (GlcNAc) which is sold online as a dietary supplement prevents myelin degeneration and loss of motor function in a mouse model of MS.

Michael Demetriou, MD, PhD, the study's senior author and professor of neurology, microbiology, and molecular genetics at University of California–Irvine (UCI)'s School of Medicine, said: "We found that N-acetylglucosamine activates [myelin-producing cells] to promote primary myelination and myelin repair,"

"Our data raise the intriguing possibility that N-acetylglucosamine may be a simple therapy to promote myelin repair in multiple sclerosis patients," Demetriou added. Large well-controlled clinical trials are now needed to test this hypothesis.

GlcNAc is a simple sugar that works as a building block of complex sugar molecules and glycoproteins (proteins containing sugar molecules). GlcNAc branching is involved in several cellular processes, including signalling and maturation.

This sugar is found in several body fluids, including breast milk, and is sold as an over-the-counter dietary supplement to manage joint pain, inflammatory bowel disease, and to prevent heart disease and stroke. Clinical evidence supporting its benefits in MS are still to be confirmed, however.

In the present study, the team found that adding GlcNAc to mouse OPCs grown in the lab promoted their maturation into oligodendrocytes and myelin production. This process was dependent on GlcNAc branching and on the levels of PDGFR-alpha (involved in OPCs' differentiation) on the surface of OPCs.

In a mouse model of MS, oral treatment with GlcNAc also drove oligodendrocytes maturation and myelin production, preventing myelin and nerve fiber damage, as well motor function loss.

The team next assessed whether GlcNAc blood levels were associated with brain lesions in 180 people with MS.

Data showed that patients with low GlcNAc levels had significantly greater myelin and nerve fiber damage, suggesting that "N-acetyglucosamine deficiency may contribute to disease severity," said Alexander Brandt, MD, who led the clinical parts of the study.

Future clinical studies are needed to confirm the therapeutic potential of oral GlcNAc in MS.

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Could sunflower seeds hold back progression?

Researchers from Sweden have found a possible explanation for the progressive course of MS and how it can be reversed.

Researchers at Karolinska Institutet have shown that recovery from MS-like symptoms in mice depends on the ability of the CNS's own immune cells – microglia – to break down the remains of damaged cells, such as myelin.

In a study the processes was interrupted when the researchers removed a so-called autophagy gene, Atg7. Autophagy is a process where cells normally break down and recycle their own proteins and other structural components.

Without Atg7 the ability of the microglia to clean away tissue residues created by the inflammation was reduced. These residues accumulated over time, which is a possible explanation for the progression of the disease.

The study also showed how microglia from aged mice resembled the cells from young mice that lacked Atg7 in terms of deficiencies in this process, which had a negative effect on the course of the disease. This is a significant result since increasing age is an important risk factor in the progressive phase of MS. The researchers also show how this process can be reversed.

"The plant and fungi-derived sugar Trehalose restores the functional breakdown of myelin residues, stops the progression and leads to recovery from MS-like disease." says doctoral student Rasmus Berglund. "By enhancing this process we hope one day to be able to treat and prevent age-related aspects of neuroinflammatory conditions."

In plants, trehalose is seen in sunflower seeds, moonwort, Selaginella plants and sea algae. Within the fungi, it is prevalent in some mushrooms, such as shiitake (Lentinula edodes), oyster, king oyster, and golden needle.

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DDA – 25 years on. Time to celebrate?

November marks an important anniversary for all disabled people in the UK. It is the 25th anniversary of the UK's 1995 Disability Discrimination Act (DDA). The Act was intended to give disabled people the same right to equality that women and racial minorities had enjoyed for decades.

In 1995 racial and gender equality had already been part of UK law for decades. And in other countries there were laws making it illegal to discriminate against disabled people. But in Britain prior to 1995 it was totally legal to discriminate and exclude people on the basis of disability, and policy makers often refused to recognise the discrimination disabled people faced.

Back in 1995 I was working for an ITV networked disability programme called "Link" which was broadcast on Sunday mornings. I had been diagnosed with MS two years earlier, aged 35, and knew that the proposed legislation would almost certainly give me new rights because I would probably be classed as a disabled person as my MS progressed. The new law would make it far more difficult for employers to overlook me in the jobs market so I was a supporter of new disability equality and anti-discrimination laws.

As the producer of the ITV programme I visited the House of Commons to interview William Hague, the then minister for disabled people in a Tory government led by John Major and asked Hague about the new legislation which was working its way through parliament.

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Continued from page 10 Paradoxically on the day I arrived to interview him there was a demonstration outside parliament by disabled people opposing this very piece of legislation that was supposed to give the protestors new rights.

I asked Mr Hague whether he thought the disabled protestors had a point when they protested about his DDA not going far enough. He was quick to respond. He told me that the first thing he had done when appointed as minister for disabled people was to visit the USA where a piece of legislation called the ADA (Americans with Disabilities Act) had been passed. This Act, he pointed out, was far reaching but had brought about unintended consequences. One consequence was that the new law had led to businesses being legally obliged to make far reaching changes to their premises to accommodate disabled customers and this had led to some businesses becoming uneconomic and having to close down, something that was in nobody's interest, including disabled people's.

Mr Hague told me that he wanted legislation that would change the world of disabled people but only in a way that would not lead to the businesses that served them ceasing to operate. It seemed a fair point even though, judging by the noisy protest outside, it was not a view held by the protestors. So, 25 years on, who was right? Has the DDA changed the lives of disabled people or are we still, 25 years on, essentially second class citizens?

Looking at the figures you do wonder how much has really changed. Government figures show a substantially higher proportion of disabled people still living in poverty, and still more likely to face unemployment than the non-disabled. Figures from the charity Scope reveal that three years ago 32% of disabled people and 22% of non-disabled people still felt there was a lot of prejudice against disabled people

Of course the acid test of the legislation is how it has affected you personally. For me it's a mixed picture. Over the past 25 years I have often struggled to find work and accessible housing, but have found in my daily life a greater understanding of disability in shops, restaurants and cafes. This is welcome although it could be argued that some of the changes have been limited and rather superficial. In conclusion I would say that the 1995 Act was good in so far as it went. I was pleased when the Act was revised by the 2005 Disability Discrimination Act. This made the situation for us MSers more transparent because the 1995 Act hadn't made it crystal clear at what point we were covered – at diagnosis, or at the arrival of first major disabling symptoms.

Buried away on page 37 of the 2005 Act is the following: "A person who has cancer, HIV infection or multiple sclerosis is deemed to have a disability and be a disabled person." So from 2005 we MSers have all been clearly and unequivocally deemed disabled and covered by anti-discrimination laws from the point of our diagnosis. Perhaps that is progress of sorts.

For further details of the UK's disability laws go to page 13

Roche Launches Phase 3 trial To Test Fenebrutinib in PPMS

Pharmaceutical company Roche has launched a Phase 3 clinical trial to evaluate fenebrutinib, its investigational oral BTK inhibitor, in people with primary progressive MS (PPMS).

Fenebrutinib developed by Roche's subsidiary Genentech, is a small molecule that can cross the blood-brain barrier. This barrier tightly regulates what substances from the bloodstream can access the brain, and crossing it is often a challenge for brain-targeting therapies.

The therapy works by blocking the activity of Bruton's tyrosine kinase (BTK), an enzyme important for the activation of B-cells and microglia — immune cells that drive the inflammation that damages the nervous system in MS. By blocking BTK, fenebrutinib is expected to prevent the activation of these cells, potentially slowing disease progression.

Fenebrutinib binds to BTK in a way that might increase its effectiveness. Safety data from more than 1,200 people with several inflammatory diseases treated with fenebrutinib suggest that its high selectivity may limit off-target effects — those on molecules other than BTK — and subsequently, the occurrence of side effects.

"The high selectivity and potency of [fenebrutinib] has the potential to be associated with fewer off-target adverse events and an improved MS therapeutic index compared with less selective BTK inhibitors," the researchers said.

A trial called FENtrepid, is planned and will enroll up to 946 people with PPMS. The participants in the PPMS trial will be randomly assigned to receive either fenebrutinib or Ocrevus (ocrelizumab), a therapy also developed by Genentech and approved for PPMS treatment.

The main goal of the trial will be to assess changes in patients' disability progression using the 12-week composite confirmed disability progression (cCDP12). The cCDP12 measures disability progression based on at least one of three disability measures: the expanded disability status scale (EDSS), the 9-hole peg test, and the timed 25-foot walk.

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Page 3 Mayzent (siponimod) story

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Page 4 Myelin drug story

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Page 5-6 Patrick Burke and MS fatigue

Patricks website is at https://www.aid4disabled.com

Page 7 Metformin story

https://multiplesclerosisnewstoday.com/news-posts/2019/10/11/diabetes-drug-metformin-promotes-myelin-repair-in-rats/

Page 8 Simple sugar molecule story

https://multiplesclerosisnewstoday.com/news-posts/2020/10/09/simple-sugar-molecule-may-be-potential-myelin-repairing-therapy-multiple-sclerosis-mouse-study/

Page 9 Sunflower seed story

https://neurosciencenews.com/microglia-ms-17178/

page 10-11 Disability laws UK feature

The best source of information on the contemporary situation about disability laws in the UK is at https://www.gov.uk/rights-disabled-person

Page 12 Fenebrutinib story

https://multiplesclerosisnewstoday.com/news-posts/2020/09/09/roche-expands-its-multiple-sclerosis-portfolio-with-investigational-btk-inhibitor-fenebrutinib-and-initiates-novel-clinical-trials-for-ocrevus-ocrelizumab/

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