

My prog-MS ezine

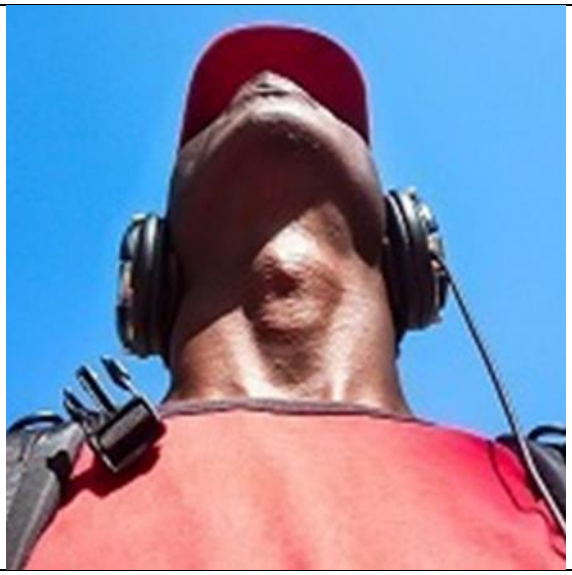
For people with progressive MS and other interested people

Issue number 36, March/April 2021

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 the tricky subject of how MS affects your swallowing. There's also a feature on new research and a new drug in development for the Epstein Barr virus – the virus most often inked to MS. See page 10 for details.

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News

New BioNTech MS vaccine project could treat prog-MS

The German biotech company behind the Pfizer Covid-19 jab is developing an "MS vaccine" which has been shown to lessen symptoms in mice infected with a "mouse model" of the illness, including mice with progressive forms. It is hoped human trials will soon take place.

The new "mouse MS" vaccine uses mRNA (messenger RNA) to stop the immune systems of mice infected with a mouse version of MS attacking mouse nerve cells. Studies show the vaccine stopped disease progression and also reversed some loss of motor function in the mice.

mRNA is genetic material which is also found in the human body. It is used by human cells to carry messages and give instructions. DNA's double-helix is split in half, becoming two strands of RNA which are sent out of the nucleus to relay the message.

One part of the cell then reads the RNA's genetic sequence — the message — and goes about doing as it is told, which often means making a specific protein. After providing the blueprint, the mRNA molecule is then destroyed by another part of the cell.

In a human MS vaccine it is believed a piece of mRNA would be inserted into a person's arm by injection, similar to the Covid jab, and then force the body's own cells to produce a protein that stops the body's immune system from attacking neurons in the brain and spinal cord, stopping demyelination.

Clinical trials in mice revealed the mRNA jab actually stopped disease progression and restored some motor skills which had already been lost suggesting remyelination might be happening. In humans the hope is that a vaccine could introduce genetic information which instructs the immune system of MS sufferers to not attack the proteins that lead to myelin sheath deterioration.

In mice the vaccine was given as an injection to a group that had autoimmune encephalomyelitis, an animal equivalent for human MS. 'The vaccine blocked all clinical signs of MS in mice, while those in the "control" group experienced the typical symptoms of the disease.

Some mice already had symptoms of MS before they received the vaccine, for example paralysis of the tail, and in these specimens the vaccine not only prevented further disease progression but also reversed paralysis, restoring motor functions. The full findings have been published in the prestigious peer-reviewed journal Science.

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

£1.85m grant to begin 'new era' of treatment for prog-MS

The MS Society has awarded a grant of £1.85m for a "Centre of Excellence" in Cambridge. The Society hopes the funding will help its scientists in Cambridge to find new treatments faster for people with progressive MS.

Scientists said the centre would be the start of a "new era" for MS treatment.

The charity has also awarded £1.85m to researchers at the University of Edinburgh.

The centres will work together closely with the aim of stopping MS and training the next generation of research scientists.

In order to stop MS, researchers need to find treatments which can replace lost myelin - the protective coating that surrounds nerves.

The MS Society Cambridge Centre for Myelin Repair will study remyelination in people of all ages with MS.

Dr Emma Gray, assistant director of research at the MS Society, said the work at the Cambridge centre was "inventive, innovative and incredibly exciting".

The centre previously discovered a way to increase myelin repair in rats and hopes to build on this to develop myelin repair drugs for humans.

Researchers will also explore new ways to test how effective the drugs are in clinical trials.

The Cambridge team hopes to be the first centre in the world to routinely assess myelin in people with MS.

Prof Alasdair Coles, who will co-lead work at the Cambridge centre with Dr Thora Karadottir, said: "We are excited to build on the Cambridge centre's strong foundations in developing new treatments for people with MS, and bring in what we believe will be a new era for MS treatment.

"Thanks to this generous donation, we can make discoveries that will benefit people living with MS worldwide - including the myelin repair therapies that are still so desperately needed."

For details of all stories go to page 13

Critical role of Oleic acid in fat tissue seen in MS progression

An abnormal immune system response that characterises MS, attacking and damaging the central nervous system, can be triggered by the lack of a specific fatty acid in fat tissue, according to a new study from Yale University in the US.

The study published in The Journal of Clinical Investigations suggests that dietary change might help treat some people with MS and slow down its progression

Fat tissue in patients diagnosed with MS lacks normal levels of oleic acid, a monounsaturated fatty acid found at high levels in avocados cooking oils, meats (beef, chicken, and pork), cheese, nuts, sunflower seeds, eggs, pasta, milk, and olives according to the study.

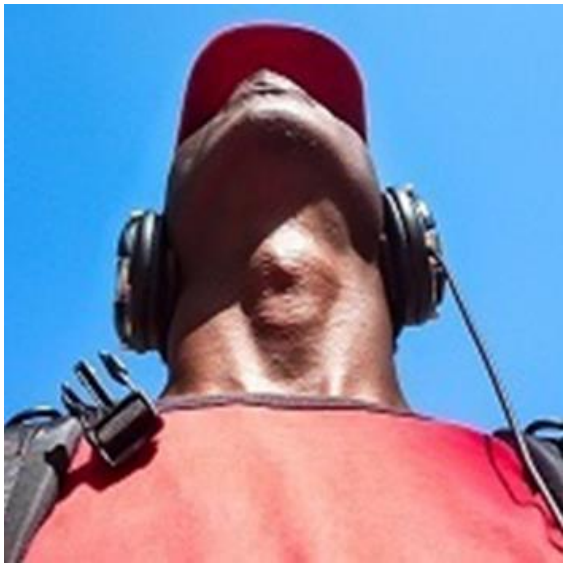
This lack of oleic acids leads to a loss of the metabolic sensors that activate T cells, that mediate the immune system's response to infectious disease, the Yale team found. Without the suppressing effects of these regulatory T cells, the immune system can attack healthy central nervous system cells and cause the vision loss, pain, lack of coordination and other debilitating symptoms of MS.

When researchers introduced oleic acids into the fatty tissue of MS patients in laboratory experiments, levels of regulatory T cells increased.

"We've known for a while that both genetics and the environment play a role in the development of MS,'' said senior author David Hafler, William S. and Lois Stiles Edgerly Professor of Neurology and professor of immunobiology and chair of the Department of Neurology. "This paper suggests that one of environmental factors involved is diet."

Hafler noted that obesity triggers unhealthy levels of inflammation and is a known risk factor for MS, an observation that led him to study the role of diet in MS. He stressed, however, that more study is necessary to determine whether eating a diet high in oleic acid can help some MS patients

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Some facts about MS that are hard for us to swallow

Living with MS can give you some fairly scary experiences, and no experience is scarier than choking.

My first choking episode came ten years after my diagnosis. One night I ate a chocolate soft creme mint. Nothing unusual about that, you might think. However, the moment I tried to swallow the mint I realised instantly something was wrong, very wrong. I was choking and despite my best efforts I couldn't stop choking, and the mint just wouldn't go down.

Everything I tried, like desperately gulping down water and getting my girlfriend to hit me on the back, Heimlich manoeuvre style, wouldn't dislodge the mint, and I was involuntarily gasping for breath. After several rather nerve-wracking minutes, when my life really did seem to flash before my eyes, I seemed to recover my composure and more importantly my breath. Thankfully my "near death" experience was over.

When I calmed down, I reflected on what exactly had gone wrong and, more importantly, what I could do to prevent a recurrence. There seemed no obvious explanation why the creme mint should have caused my choking (although interestingly marshmallows are on a list of foods that can cause choking according to safety group CE Safety) The short-term solution was blindingly obvious – don't eat creme mints again. To this day I haven't. Thin and elegant they may be, but for me they are a choking hazard and best avoided.

My second choking episode, a few years later, involved eating some small pickled onions. For some unknown reason vinegar seems to be a trigger for my choking. The pickled onion episode followed the same sequence of events as the earlier one. The moment I tried swallowing the pickled onion I found myself choking uncontrollably and gasping for air. After some rather nerve-wracking minutes when once more my life really did seem to flash before my eyes, I recovered my composure and more importantly my breath. My "near death" experience was over for a second time. After two such experiences I thought it was high time to take some action and start learning about choking and MS. Over the years I have learned a lot and continue learning. **Continued on page 6**

Continued from page 5. Choking, of course isn't just associated with MS. According to a 2019 report by the ONS (Office for National Statistics) 351 people die on average every year as a result of choking. It is believed the true toll may be higher, perhaps as high as 500. That's ten choking deaths a week.

The particular risk factors for choking are age (you produce less saliva as you get older) and medical conditions including several that are neurological and this includes MS. According to the MS Trust, studies have found that around a third of people with MS experience swallowing difficulties to some degree and more significant symptoms (like choking) are more likely if you have more advanced MS.

The reason is that chewing and swallowing involves the coordination of a number of muscles in the mouth and throat, including muscles which protect your windpipe when food and drink pass down your throat. Muscles can be weakened or the coordination of their movements disrupted by MS. If the muscles are weak, chewing can be effortful and tiring and food may lodge in your throat. You may need to swallow several times to clear one mouthful. If the muscle movements are slow or lack coordination, fluid or food particles might enter the windpipe, causing coughing. And if MS has weakened the coughing muscles, it may be more difficult to eject the particles causing choking. The food may enter your lungs putting you at risk of aspiration pneumonia.

A 2019 study published in the journal Multiple Sclerosis Related Disorders carried out by Turkish researchers found that dysphagia (difficulty swallowing) is a life-threating symptom in patients with MS not just because of choking but also because of aspiration pneumonia. The research also said that age was linked with dysphagia (ie: the older you are the more likely it is to occur), and those with progressive MS (like me with secondary progressive) are more likely to have a problem.

So, what can I do? Having consulted widely I have been told that if MS related swallowing problems mean it takes longer to eat, then try to have meals when you can, and take your time. Control the amount of food on your fork and the size of your mouthfuls of drink. Chew your food well and try to concentrate on swallowing. Taking sips from a drink with your meal can sometimes help if you are finding food tends to lodge in your throat. Also ask your GP about "artificial saliva" which can be prescribed as a spray or gel. Sometimes having smaller meals can be a useful strategy too. Alternatively having your largest meal when you are least tired can be of benefit. Adopting the best posture to swallow can help as well. This basically means sitting upright and not slumped over your plate.

Finally, be aware of types of food that are more likely to cause problems for you. If certain foods are more difficult, find ways to make them easier to swallow, such as altering the size of the mouthful you take, the cutlery you use or how you cook the foods. Alternatively, don't eat these foods. So pickled onions and creme mints are off the menu from now on for me.

Personally speaking I think all this is fairly easy advice to follow. And I do follow it for the simple reason that I don't want to be in hospital ending up with aspiration pneumonia or find myself in a situation that's far, far worse. **Picture: Andrew Itaga / unsplash**

GW Pharma Plans More Clinical Trials for Sativex

GW Pharmaceuticals is planning to continue recruiting patients into two pivotal Phase 3 clinical trials of Sativex (nabiximols), a mouth spray that contains cannabis extracts and is being investigated as a potential add-on therapy for people with MS and spasticity.

The company also is planning to launch additional clinical trials in the U.S. focused on exploring Sativex's therapeutic potential for the treatment of spasticity (muscle stiffness or spasms) associated with MS.

GW Pharmaceuticals anticipates it will announce preliminary data from at least one of these studies in the coming months. If positive, these findings may support the submission of an application requesting the therapy's approval for MS related spasticity. "Our goals in 2021 include … advancing multiple US pivotal trials for nabiximols in the treatment of MS spasticity, with first data expected this year," Justin Gover, CEO, said in a press release.

Sativex is an oral spray that contains cannabidiol (CBD) and tetrahydrocannabinol (THC), two of the most abundant cannabinoids found in the cannabis plant. The medication is approved in Europe and other regions as an add-on therapy to alleviate spasticity in MS patients with moderate-to-severe muscle tightness, who fail to respond to treatment with other anti-spastic agents. In the U.S. two pivotal Phase 3 trials (NCT04203498 and NCT04657666) are assessing the safety and effectiveness of Sativex, compared with a matched placebo, at easing spasticity symptoms in adults with MS.

The first trial intends to assess whether Sativex outperforms a placebo at lowering the frequency of muscle spasms in MS patients. Additional study goals include the therapy's safety and effects on several vital signs and clinical parameters. The trial is currently recruiting participants at two sites in Poland. Information on U.S. trial sites is yet to be announced. Top-line data from this trial is expected in 2022.

The second pivotal trial aims to enrol 52 MS patients who failed to experience adequate symptom relief after receiving other anti-spasticity medications. Like the previous study, patients participating in this trial will be treated with Sativex, or a placebo, both self-administered as an oral spray in the morning and evening, up to 12 times daily for 12 weeks. Yet, unlike the previous study, the main goal of this trial is to assess the effects of treatment on lower limb muscle tone. This study is scheduled to conclude by May.

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News

T Cells Linked to Myelin Implicated in monkey MS-Like Disease

Scientists have uncovered new clues implicating a type of herpes virus as the cause of a central nervous system disease in monkeys that's similar to MS in humans.

The findings, published in the Annals of Clinical and Translational Neurology, expand on previous work to understand the cause of the disease and potentially develop antiviral therapies. The work was carried out by scientists at Oregon Health & Science University led by Scott Wong Ph D.

The new study reveals the presence of two kinds of T cells, a type of white blood cell that's a critical part of the body's immune system. In this case, scientists determined the T cells were associated with an immune response involving the loss of myelin, the protective sheath that covers nerve fibres.

Myelin and nerve fibres become damaged in MS, which slows or blocks electrical signals required for us to see, move our muscles, feel sensations and think. "We found that some of the T cell epitopes targeting myelin in these animals are identical to those found in humans with MS," Wong said.

By linking these specific T cells to the loss of myelin, scientists say the new study opens the possibility of developing an antiviral therapy that could be especially useful for newly diagnosed cases of multiple sclerosis.

The work builds on a chance discovery in the colony of Japanese macaques at the primate centre. In 2011, scientists at OHSU published research identifying a group of monkeys at the primate centre with a naturally occurring disease known as Japanese macaque encephalomyelitis. Since then, scientists have been working to understand the cause and progression of the disease in the macaques with an eye toward applying possible therapies in people.

The latest study points toward developing strategies to combat the disease leveraging the body's immune response.

"If we can understand how it's doing it, we may be able to test vaccine strategies," Wong said. "I'm not sure we can prevent virus infection, but we may be able to prevent virus-associated disease."

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GeNeuro completes patient recruitment in temelimab

GeNeuro, a biopharma company focused on stopping factors driving the progression of neurodegenerative and autoimmune diseases such as MS, has completed patient recruitment in its Phase 2 trial of temelimab in progressive MS patients, being conducted in Stockholm, Sweden.

Temelimab is a monoclonal antibody (an antibody made by cloning a unique white blood cell.) The monoclonal antibody is designed to neutralize a pathogenic human endogenous retrovirus. Human endogenous retroviruses (HERVs) are sometimes called fossil viruses because they are pieces of ancient viral infections which were incorporated into our DNA millions of years ago.

One of these HERVs produces a protein (pHERV-W Env) which is found in active MS lesions and has been shown to activate microglia (immune cells which cause inflammation in the brain) and block the development of oligodendrocytes, cells which maintain the myelin coating of nerve cells. Temelimab blocks the action of this protein; it is proposed that this in turn will promote remyelination, thereby slowing down or stopping MS progression.

The present study, called ProTEct-MS, has enrolled 42 patients being treated with temelimab at three different doses and compared to a group taking a placebo or dummy drug. The patients included in the study had confirmed disability progression without relapses, following previous treatment with the antiCD20 drug rituximab, a highly potent drug against acute disease activity (relapses and brain lesion formation) and commonly prescribed in Sweden for secondary progressive MS.

The double-blind placebo-controlled study has been designed to assess safety, tolerability and efficacy measures based on the latest biomarkers associated with disease progression. Temelimab has already been shown to have a neuroprotective effect in MS and GeNeuro's temelimab Phase 2 trial in MS patients at the Karolinska Institutet's Academic Specialist Centre follows the successful results achieved in its 96-week extension Phase 2b clinical trial, ANGELMS, which confirmed the neuroprotective effect of temelimab in MS and demonstrated its potential to suppress the progression of the disease.

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Australian researcher leads research into EBV and MS

One of the many theories about the cause of MS is that a virus is involved. The main suspect viruses are members of the same family of virus – the herpes family. The herpes virus that has attracted most interest is the Epstein-Barr virus (EBV).

Interestingly, a recent German study found EBV infection was present in 100% of MS patients. This 100% correlation is a fairly striking fact and it is disappointing that there has until recently been little headway in proving the seemingly obvious theory that EBV is actually the cause of MS. All this may be about to change, and this is due largely to the work of Michael Pender, (pictured above) a consultant neurologist at the Royal Brisbane and Women's Hospital and Professor of Medicine at The University of Queensland.

Professor Pender believes that a large body of evidence shows that infection with Epstein-Barr virus (EBV) which causes glandular fever, also known as infectious mononucleosis, has a role to play in the development of MS several years after the original EBV infection. One of the reasons is that after infection the virus lives on in B cells, the white blood cells that make antibodies. Once a person is infected with EBV, they carry the virus in these B cells for the rest of their life.

Professor Pender believes that in MS, infection with EBV leads to the creation of "autoreactive" B cells, which accumulate in the brain. Once there, these autoreactive cells produce anti-brain antibodies which ultimately lead to the destruction of myelin in the brain and other parts of the central nervous system.

By living on after the initial infection, EBV is behaving in a similar way to other members of the herpes family of viruses. This is something you may know from personal experience. After infection with herpes simplex virus (cold sores or Human Herpes Virus 1 (HHV 1) the herpes virus hides inside nerve cells, hibernating there for life, and periodically waking up from its sleep to reignite infection, causing the cold sores to recur. If you have ever had chickenpox (HHV3) you will also know this can later recur as shingles, the virus also going into dormancy hiding again in nerve cells until returning years later in nerves that lead to the skin. **Continued on page 13**

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Professor Pender's theory about EBV (HHV4) has made several predictions which have subsequently been verified, including the presence of EBV-infected B cells in the brain in MS. Perhaps most importantly, over the past few years, working with other researchers, Professor Pender has gone on to use an immunotherapy which involves growing immune cells from the blood of MS patients with fragments of EBV proteins to retrain killer CD8 T cells (another type of white blood cell) to be potent killers of EBV-infected B cells. The retrained killer CD8 T cells are then administered to the patient by intravenous infusion. This treatment, known as "autologous EBV-specific T cell therapy", does not require the use of any drugs.

A Phase 1 clinical trial tested the safety and tolerability of this therapy in patients with primary and secondary progressive MS. The results of the study were recently published in the journal JCI Insight. Of the 13 recruited participants, 10 received the full course of T cell therapy. The majority showed improvement, with six experiencing both symptomatic and objective neurological improvement, together with a reduction in fatigue, improved quality of life. All six patients receiving T cells with strong EBV reactivity showed clinical improvement, whereas only one of the four patients receiving T cells with weak EBV reactivity showed improvement. There were no serious side effects associated with the treatment.

Most recently, and following on from Professor Pender's work, a US bio-technology company Atara Biotherapeutics has developed an experimental therapy called ATA 188 to treat both progressive and relapsing-remitting MS in this way. ATA188 is an EBV-specific T cell product derived from healthy people. This therapy is known as allogeneic EBV-specific T cell therapy and differs from autologous EBV-specific T cell therapy in that T cells are derived from healthy subjects (allogenic) rather the MS patients themselves (autologous).

A Phase 1 clinical trial is currently recruiting patients with relapsing-remitting MS and progressive MS to test the safety and tolerability of ATA188 as well as find the best dose for a Phase 2 clinical trial. The trial aims to recruit patients who will receive intravenous infusions of ATA188 at treatment centres in the USA and Australia. The study completion date is 2026.

Five years may seem a long way away for news about a revolutionary new treatment for MS. However, in an illness that was first identified more than 140 years ago, most MSers would agree that nothing happens quickly and sadly we will just have to wait and see. Hopefully, the wait will be worth it.

For details of all news and features go to page 13

Early-life trauma link to progression, mouse study suggests

Childhood trauma can affect disease progression of MS as well as treatment in adulthood, a study in mice suggests. The study shows that mice that experienced early-life trauma were more likely to develop an autoimmune condition and less likely to respond to common treatment with interferon beta.

The study, "Early-life-trauma triggers interferon-β resistance and neurodegeneration in a multiple sclerosis model via downregulated β1-adrenergic signalling," was published in the journal Nature Communications.

Although it is accepted MS is a progressive, multifactorial disease the underlying mechanism through which it alters MS progression remains unknown. To address this question, researchers at the University of Illinois Urbana-Champaign investigated how childhood trauma affected disease severity and susceptibility in mice with experimental autoimmune encephalitis (EAE, a mouse model of MS).

Researchers induced emotional and physical distress in mice when they were young by separating them from their mother and father and by giving them a saline injection, and compared them to mice without childhood stress.

Researchers found that EAE triggers the immune system through a receptor that binds to norepinephrine (a stress hormone). In mice, childhood stress caused a longer release of this hormone and activation of its receptor, which subsequently leads to a reduction in the levels of this receptor in immune cells, lowering the response capability of the immune system against stress or inflammation.

Mice subjected to early stress also were resistant to treatment with interferon beta. In turn, this common MS treatment was able to reduce disease progression in mice without childhood stress. Treatment with a compound that boosts norepinephrine response was found to prevent paralysis and to slow damage to the spinal cord, making mice able to respond to treatment with interferon beta.

"This receptor activator may be a therapeutic drug for MS patients with a history of childhood trauma," said Makoto Inoue, PhD, the study's senior author.

According to the team, the results "add to emerging evidence that [norepinephrine receptor] agents may be clinically useful as an immunomodulatory therapy for patients with MS who experienced early-life trauma. "**For further details of all news stories go to page 13**

References contact details etc

Page 2 MS vaccine story

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Page 3 Cambridge MS study story

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Page 4 Oleic acid story

https://news.yale.edu/2021/01/19/fatty-acid-may-help-combat-multiple-sclerosis

Page 5 Swallowing

For further details on swallowing and dysphagia check out https://mstrust.org.uk/a-z/swallowing

Page 7 Sativex story

https://multiplesclerosisnewstoday.com/news-posts/2021/01/13/gw-pharma-recruitment-pivotal-trials-sativex-ms/

Page 8 Monkey MS-like disease story

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Page 9 GeNeuro story

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page 10 EBV and MS feature

For details on Michael Pender's research go to
https://researchers.uq.edu.au/researcher/321

Atara Therapeutic's EBV work can be found at

https://www.atarabio.com/pipeline/ata188/

Page 12 Trauma story

https://multiplesclerosisnewstoday.com/news-posts/2021/02/12/early-life-trauma-affects-ms-development-treatment-mouse-study/

For further details check out the MS Trust's website at https://mstrust.org.uk/a-z/masitinib-ab1010 also look at the website https://www.ab-science.com/ab-science-presents-phase-2b-3-study-results-in-progressive-multiple-sclerosis-at-the-worlds-largest-multiple-sclerosis-research-conference/

Page 13 Stress and MS story

https://multiplesclerosisnewstoday.com/news-posts/2021/02/12/early-life-trauma-affects-ms-development-treatment-mouse-study/

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