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PRESS RELEASE
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NEW TREATMENTS ON THE HORIZON FOR MULTIPLE SCLEROSIS

Finding a way to help repair the damage caused to nerve cells by multiple sclerosis (MS) is a big ambition for MS scientists. Researchers in California, USA and Cambridge, UK have come a step closer to identifying new treatments.

MS is an autoimmune condition, meaning that the body's immune system attacks healthy parts of the body. In MS, the immune system destroys the myelin sheath that surrounds and protects the nerves, interrupting the transmission of nerve impulses. Around 350,000 people in Europe have MS.

Most people with MS have the 'relapsing remitting' form of MS, periods when the immune system attacks the myelin sheath causing neurological symptoms followed by periods of remission. As the disease progresses, disease remission starts to fail. Cells known as oligodendrocyte precursor cells (OPCs) are responsible for repair and remission. During the progressive phase of disease, OPCs are blocked and fail to repair the myelin.

Dr Jonah Chan from the University of California, San Francisco, **Professor Luke Lairson** from Scripps Research Institute, and **Professor Robin Franklin** from the University of Cambridge have been on a quest to find potential drugs that might unblock the OPCs.

One drug that is showing promise for the treatment of MS is clemastine fumarate. A clinical trial conducted by **Dr Chan** demonstrated a for the first time a modest but significant degree of remyelination.

Fifty patients whose average age was 40 and who have had MS for up to 15 years took part in the trial. In this first randomised controlled crossover trial to document the efficacy of a remyelinating drug, the patients were given clemastine or a placebo for 90 days and then were switched for a further 60 days.

"It was a really pleasant surprise," said Dr Chan today (10 July) at the FENS Forum of Neuroscience in Berlin. "The magnitude of the remyelination was not huge, which we anticipated because we were examining patients with chronic MS, but there was a noticeable and significant improvement. There were no serious side-effects, although some patients did become fatigued."

The results were measured using electrodes placed over the brain's visual areas at the back of the head to test how long it took for a flickering light signal to travel via nerve fibres from the eye to the visual areas of the brain which is directly correlated with the myelination of the nerves.

Dr Chan pointed out that the patients were under-dosed due to the nature of clemastine, meaning that the concentration of the drug used in the trial only targeted a small

percentage of the cell receptor. To be fully effective the medication would need to be increased dramatically but patients would not be able tolerate higher doses without major concerns of side-effects and safety.

The next stage of the research is to apply the results of the clemastine trial and use the same tests that were performed in patients now in mice. "Going from the laboratory bench to bedside and back again will help us plan, predict and execute our next phase two trials," he said.

Recently, **Professor Lairson** and his team identified a naturally-occurring molecule named taurine that is important for the body and brain. Taurine is found in high levels in cells during the production of oligodendrocytes. When added to cells in test tubes in the laboratory, taurine dramatically enhanced the maturation of OPCs to functional cells.

"We are excited by these early laboratory experiments. We have shown they can work in rodents and with further investigation, we hope this work could lead to clinical trials with taurine as part of a combination therapy for the treatment of MS," he said today (10 July).

Professor Lairson envisages that drugs for MS developed from taurine and benztropine could be used in combination with other existing therapies, such as fingolimod or B cell targeting antibodies. He hopes the amount of benztropine administered to a patient could be significantly lowered if given in combination with an immunosuppressant and taurine.

"We are still at a very early stage of research into these new compounds, and in no way do we advocate that taurine found in commercial food and drink products could have any effect on MS. Nor should benztropine, currently available for people with Parkinson's disease, be taken 'off-label' by people with MS," he cautioned

One of the challenges for scientists studying remyelination is the natural ageing process. "As we get older we become less good at regenerating new myelin," said **Professor Robin Franklin** from the University of Cambridge, UK today (10 July). "MS progresses over many decades, and therefore, the need for therapies to enhance remyelination increases."

This is due in part to the declining ability of cells called macrophages to remove the myelin debris which in turn slows down the formation of new myelin. Understanding how age affects remyelination is therefore critical to devising new therapies.

In experiments in mice, Professor Franklin has shown how the action of genes involved in myelin regeneration decrease with age. He has been able to devise ways to reverse the damaging effects, increasing the clearance of debris by the macrophages and thereby releasing the factors responsible for remyelination.

In further experiments the function of ageing macrophages was reversed by using drugs that target the RXR family of nuclear receptors, which are also involved in stimulating adult brain stem cells to become new replacement oligodendrocytes. This work is the basis of ongoing clinical trial using the RXR agonist bexarotene as a regenerative medicine in patients with multiple sclerosis.

Professor Anna Williams at the University of Edinburgh has found a way to localise the demyelination in slices of cultured rodent brain tissue while the surrounding white matter remains healthy. This technique more closely resembles the disease process of MS as it is the healthy tissue that heals the damaged area.

She applies a tiny patch containing a toxin to a precise location on the cultured brain slice causing demyelination. She can watch the axons under a microscope being repaired as they would do naturally, monitoring in real time the arrival of the new cells to restore the myelin, which takes around two weeks in rodents. However, although remyelination can

occur in people with MS, it is inefficient and usually leads to further damage and irreversible disability.

"Our new technique is a way of localising a chemical, like a detergent, that dissolves myelin in a specific area of the brain tissue and watch the repair take place," she said today (10 July). "The way we do this is artificial but we believe it provides a good representation of repair that we want to achieve in MS. It also is easier to see and manipulate in a dish and reduces the number of animals in our research as we can minimise the amount of brain tissue necessary in these experiments," she continued.

If Professor Williams' team can understand where the repair cells come from and how quickly, it will help direct the search for drugs to enhance this natural but inefficient process of repair to the myelin sheath in the human form of the disease.

END

Symposium: S43 - Promoting Myelin repair in multiple sclerosis
Abstracts: J. Chan - Remyelination therapies for MS: From the bench to the bedside and back again
L. Lairson - Identification and preclinical evaluation of remyelination enhancing agents
R. Franklin Remyelination therapies: from targets to trials
A. Williams - Testing candidate pro-remyelination molecules in relevant in vitro systems

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NOTES TO EDITORS

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Professor Robin Franklin, Department of Clinical Neuroscience, University of Cambridge, UK https://www.neuroscience.cam.ac.uk/directory/profile.php?rjf1000
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The 11th FENS Forum of Neuroscience, the largest basic neuroscience meeting in Europe, organised by FENS and hosted by the German Neuroscience Society will attract more than 7,000 international delegates. The Federation of European Neuroscience Societies (FENS) was founded in 1998. With 43 neuroscience member societies across 33 European countries, FENS as an organisation represents 24,000 European neuroscientists with a mission to advance European neuroscience education and research. https://forum2018.fens.org/

Further Reading
(Chan) Clemastine fumarate as a remyelinating therapy for multiple sclerosis (ReBUILD): a randomised, controlled, double-blind, crossover trial. A Green, J Gelfand, B Cree, C Bevan, W J Boscardin, F Mei, J Inman, S Arnow, M Devereux, A Abounasr, H Nobuta, A

Zhu, M Friessen, R Gerona, H Christian von Büdingen, R Henry, S Hauser, J Chan *The Lancet* Volume 390, No. 10111, p2481–2489, 2 December 2017
http://dx.doi.org/10.1016/S0140-6736(17)32346-2

(Franklin)
Retinoid X receptor activation reverses age-related deficiencies in myelin debris phagocytosis and remyelination M Natrajan, A de la Fuente, A Crawford, E Linehan, V Nunez, K Johnson, T Wu, D Fitzgerald, M Ricote, B Bielekova and R Franklin *Brain*, Volume 138, Issue 12, 1 December 2015, Pages 3581–3597,
https://doi.org/10.1093/brain/awv289