Multiple sclerosis researchers find the effects of age on remyelination are reversible

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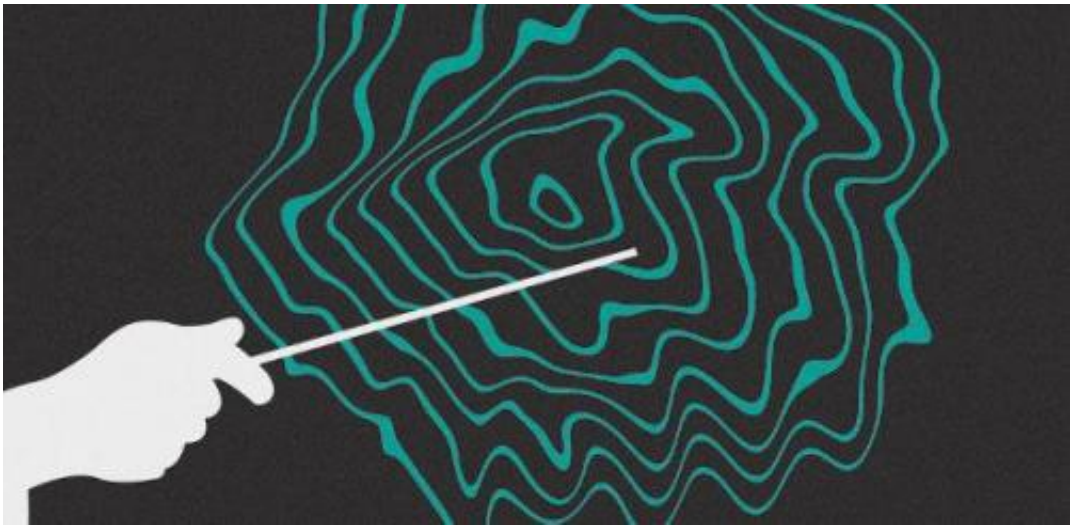

Conductor's baton. Credit: The District

(Medical Xpress)—Like conducting an errant orchestra to play together, researchers are guiding processes that go awry in multiple sclerosis to repair themselves.

The conductor walks to the stand and takes his place in front of the orchestra. He raises his baton and, with a dramatic flourish, one hundred individuals come to life. From nowhere, the stillness becomes a beautiful harmony as each member takes their part in a complex symphony.

Consider the workings and structure of the human brain – our most

complicated organ – in terms of this orchestra. When it works, it is capable of something more remarkable than the greatest musical compositions in human history, but when it is affected by a condition such as multiple sclerosis (MS), "the brain's tightly orchestrated biological functions become discordant – the conductor begins to fail at their job and several instruments go out of tune," said Professor Robin Franklin, Head of Translational Science at the Wellcome Trust-Medical Research Council (MRC) Cambridge Stem Cell Institute and Director of the MS Society Cambridge Centre for Myelin Repair.

His research team and those led by other Stem Cell Institute researchers Drs Thóra Káradóttir, Mark Kotter and Stefano Pluchino are each looking at a different aspect of this errant orchestra. They hope that their collective knowledge will one day help 're-tune' the brains of MS patients to self-repair.

In its simplest terms, MS is a disease in which the immune system turns on itself, destroying the oligodendrocytes that make a protective sheath called myelin, which encases nerve fibres. This halts the transmission of neural messages, and eventually leads to nerve fibre damage, resulting in a progressive loss of movement, speech and vision for the 100,000 people in the UK who have MS.

However, the complexities of treating the disease go beyond simply stopping the destruction of myelin, said Franklin: "The myelin damage causes a build-up of debris, which needs removing, and the environment surrounding the cells needs to be conducive to regenerating the sheath. When we think about repairing the damage, we need to be considering several different biological phenomena at the same time."

Left to right: Robin Franklin, Thóra Káradóttir, Mark Kotter and Stefano Pluchino

Although there are drugs available for modifying the early stages of MS – including alemtuzumab (Lemtrada), developed in Cambridge – there are no treatments that regenerate the damaged tissue. Moreover, although the disease evolves over decades, with periods of remission followed by relapses, there is no treatment once patients have reached the progressive stage (estimated to be about 50% of current patients).

Oligodendrocytes – the master manufacturers of myelin – are formed by a type of stem cell in the brain called oligodendrocyte progenitor cells (OPCs), and are responsible for re-wrapping, or remyelinating, the bare axons with myelin in response to injuries or diseases. But this regenerative ability decreases with age and MS. "As the disease progresses, the need for intervention that galvanises the natural healing process becomes ever more important," explained Franklin. "Working with colleagues at the Harvard Stem Cell Institute, we've shown that the effects of age on remyelination are reversible, which gives us some confidence that we can use the brain's own OPCs for myelin

regeneration."

However, to understand how to stimulate the brain's own repair mechanisms first requires an understanding of how the brain detects injury and initiates repair.

Thóra Káradóttir believes that one way the brain 'senses' problems are afoot is through the drop in how fast neural messages are passed across the brain. "The difference in speed between an intact neuron and a damaged one can be like comparing the speed of a cheetah to a tortoise," she said. "I'm eavesdropping on the information superhighway by attaching electrodes to neurons and OPCs."

Her findings show that damaged fibres release a molecule called glutamate. "It's their 'cry for help' to OPCs. If it doesn't happen, or if the OPCs don't 'hear', then repair is reduced." She is working with Numedicus, a company that specialises in developing secondary uses for existing drugs, to test drugs that she hopes will be able to amplify this signal and increase the repair process.

Meanwhile, Robin Franklin's team has shown that it's possible to kick-start OPCs, driving the formation of oligodendrocytes and sheath formation, using a drug that targets retinoid X receptor-gamma, a molecule found within OPCs. The results are positive and clinical trials will shortly commence in collaboration with Dr Alasdair Coles from the Department of Clinical Neurosciences and the MRC Centre for Regenerative Medicine at the University of Edinburgh.

What's interesting about the rejuvenation of remyelination is that the treatment primarily affected inflammation in demyelinating lesions, and specifically the recruitment of cells called macrophages. These are the body's 'big eaters' – their role is to search out and gobble up rubbish. "We have identified myelin debris as a potent inhibitor of stem cells.

Learning how it is being sensed by stem cells enabled us to overcome this inhibition by using drugs such as ibudilast. A clinical trial to test these effects is currently undergoing preparation," explained Mark Kotter.

Franklin and Kotter's work is representative of an interesting turn in MS research within the field. Increasingly, investigators are looking at how the environment around the damage can be improved to help natural remyelination. "It's a curious paradox," said Franklin. "MS is caused by the immune system but components of the immune system are also key to its recovery."

Stefano Pluchino's team, for instance, has shown that injecting brain stem cells into mice with MS works in a surprising way. Instead of making new oligodendrocytes (or other brain cells), the cells seem to work by re-setting the damaging immune response, creating better conditions for the brain's own stem cells to replace or restore what has been damaged. He is now developing more-efficient stem cells and new drugs, including nanomedicines, to foster the healing of the damaged brain.

Given the complex landscape of abnormal activities happening in the MS brain, will combination therapies be the way forward? "Certainly," said Franklin. "Over the next ten years we will see an increased understanding of the fundamental biology in MS, we will identify more targets which may yield effective drugs and we'll have more-refined strategies for running clinical trials. What makes Cambridge rare is the spectrum of skills here – from understanding the fundamental biology of myelin repair through to clinical trials."

Provided by University of Cambridge