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# Mice stem cells guided into myelinating cells by the trillions

## Process paves way for research, possible treatments of MS and more

CLEVELAND – Scientists at Case Western Reserve University School of Medicine found a way to rapidly produce pure populations of cells that grow into the protective myelin coating on nerves in mice. Their process opens a door to research and potential treatments for multiple sclerosis, cerebral palsy and other demyelinating diseases afflicting millions of people worldwide.

The findings were published in the online issue of *Nature Methods,* Sunday, Sept. 25.

“The mouse cells that we utilized, which are pluripotent epiblast stem cells, can make any cell type in body,” Paul Tesar, an assistant professor of genetics at Case Western Reserve and senior author of the study, explained. “So our goal was to devise precise methods to specifically turn them into pure populations of myelinating cells, called oligodendrocyte progenitor cells, or OPCs.”

Their success holds promise for basic research and beyond.

“The ability of these methods to produce functional cells that restore myelin in diseased mice provides a solid framework for the ability to produce analogous human cells for use in the clinic," said Robert H. Miller, vice dean for research at the school of medicine and an author of the paper.

Tesar worked with CWRU School of Medicine researchers Fadi J. Najm, Shreya Nayak, and Peter C. Scacheri, from the department of genetics; Anita Zaremba, Andrew V. Caprariello and Miller, from the department of neurosciences; and with Eric. C. Freundt, now at the University of Tampa.

Myelin protects nerve axons and provides insulation needed for signals to pass along nerves intact. Loss of the coating results in damage to nerves and diminished signal-carrying capacity, which can be expressed outwardly in symptoms such as loss of coordination and cognitive function.

Scientists believe that manipulating a patient’s own OPCs or transplanting OPCs could be a way to restore myelin.

And, they have long known that pluripotent stem cells have the potential to differentiate into OPCs. But, efforts to push stem cells in that direction have resulted in a mix of cell types, unsuitable for studying the developmental process that produces myelin, or to be used in therapies.

Tesar and colleagues are now able to direct mouse stem cells into oligodendrocyte progenitor cells in just 10 days. The team's success relied upon guiding the cells through specific stages that match those that occur during normal embryonic development.

First, stem cells in a petri dish are treated with molecules to direct them to become the most primitive cells in the nervous system. These cells then organize into structures called neural rosettes reminiscent of the developing brain and spinal cord.

To produce OPCs, the neural rosettes are then treated with a defined set of signaling proteins previously known to be important for generation of OPCs in the developing spinal cord.

After this 10 day protocol, the researchers were able to maintain the OPCs in the lab for more than a month by growing them on a specific protein surface called laminin and adding growth factors associated with OPC development.

The OPCs were nearly homogenous and could be multiplied to obtain more than a trillion cells.

The OPCs were treated with thyroid hormone, which is key to regulating the transition of the OPCs to oligodendrocytes. The result was the OPCs stopped proliferating and turned into oligodendrocytes within 4 days.

Testing on nerves lacking myelin, both on the lab bench and in diseased mouse models, showed the OPCs derived from the process flourished into oligodendrocytes and restored normal myelin within days, demonstrating their potential use in therapeutic transplants.

Because they are able to produce considerable numbers of OPCs – a capability that up until now has been lacking - the researchers have created a platform for discovering modulators of oligodendrocyte differentiation and myelination. This may be useful for developing drugs to turn a patient's own cells into myelinating cells to counter disease.

The National Institutes of Health, CWRU School of Medicine, the New York Stem Cell Foundation, the Myelin Repair Foundation, the National Center for Regenerative Medicine, and the Case Comprehensive Cancer Center funded the research.

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Founded in 1843, Case Western Reserve University School of Medicine is the largest medical research institution in Ohio and is among the nation's top medical schools for research funding from the National Institutes of Health. The School of Medicine is recognized throughout the international medical community for outstanding achievements in teaching. The School's innovative and pioneering Western Reserve2 curriculum interweaves four themes--research and scholarship, clinical mastery, leadership, and civic professionalism--to prepare


students for the practice of evidence-based medicine in the rapidly changing health care environment of the 21st century. Nine Nobel Laureates have been affiliated with the school of medicine.

Annually, the School of Medicine trains more than 800 MD and MD/PhD students and ranks in the top 25 among U.S. research-oriented medical schools as designated by *U.S. News & World Report* "Guide to Graduate Education."

The School of Medicine's primary affiliate is University Hospitals Case Medical Center and is additionally affiliated with MetroHealth Medical Center, the Louis Stokes Cleveland Department of Veterans Affairs Medical Center, and the Cleveland Clinic, with which it established the Cleveland Clinic Lerner College of Medicine of Case Western Reserve University in 2002. http://casemed.case.edu.