Scientists develop new method to more efficiently generate brain stem cells

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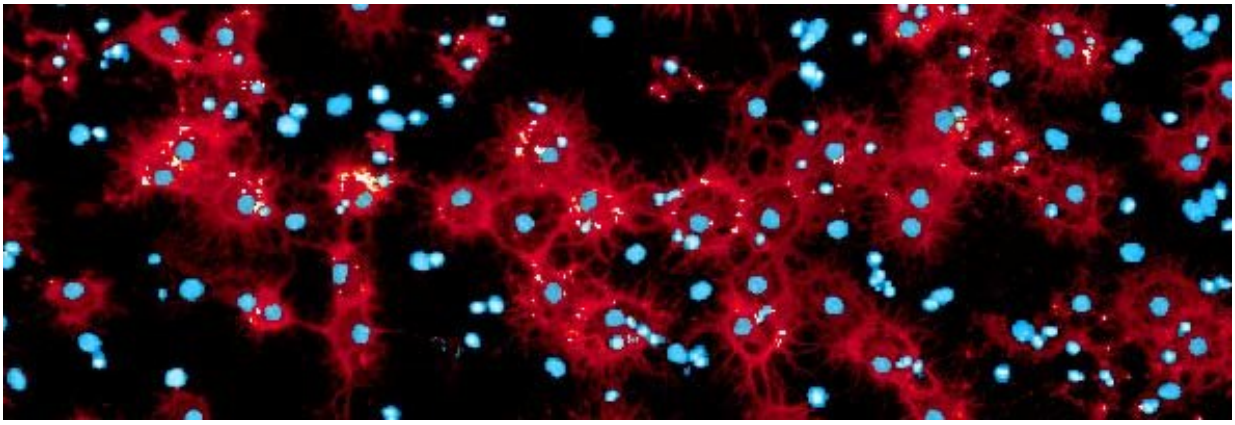

Mutant PMD oligodendrocytes rescued with drug-like compound Ro 25-698. Credit: Case Western Reserve University School of Medicine

In two newly published papers, a scientific team at Case Western Reserve University School of Medicine reports on the discovery and implementation of a new, more efficient method for generating an important brain stem cell in the laboratory. The findings pave the way for greater understanding of the underlying mechanisms of neurological disorders of myelin and ultimately, possible new treatment and prevention options. The studies were published in the September issues of *Nature Communications* and *Stem Cell Reports*.

"Making these specialized brain stem cells on a large scale at high purity

from pluripotent stem cells gives us a powerful tool to study previously inaccessible normal and diseased tissues in the central nervous system," said the senior author of the two papers, Paul Tesar, Ph.D., the Dr. Donald and Ruth Weber Goodman Professor of Innovative Therapeutics and associate professor of genetics and genome sciences at Case Western Reserve University School of Medicine. "We applied our technology to genetic models of myelin disease, which resulted in the discovery of a chemical compound that helps diseased myelin-producing cells to survive."

Myelin, a fatty substance produced by cells called oligodendrocytes, coats nerve fibers and enables electrical signaling in the brain and facilitates normal neurological function. Induced pluripotent stem cells are master cells that can potentially produce any cell the body needs. They are generated directly from existing adult cells. Embryonic stem cells are also pluripotent.

As reported in *Nature Communications*, first author Angela Lager, Ph.D., and colleagues developed a new methodology to generate large quantities of oligodendrocytes and their progenitor cells— known as oligodendrocyte progenitor cells or OPCs—from mouse embryonic stem cells and induced pluripotent stem cells. Many genes and cellular processes have been associated with oligodendrocyte dysfunction, but scientists have typically needed to make mutant mice to investigate these processes, often involving expensive, multi-year studies to examine a single aspect of this biology. To address this problem, the Case Western Reserve team developed a rapid and highly efficient method for generating OPCs and oligodendrocytes from pluripotent stem cells from any genetic background—providing new access to these relatively inaccessible brain cells in healthy and diseased states.

In *Stem Cell Reports*, first author Matthew Elitt, Ph.D., and colleagues leveraged this OPC generation technology to provide new insights and

therapeutic strategies for a fatal genetic disorder of myelin, Pelizaeus Merzbacher disease (PMD). The team found that there was an unexpectedly early critical phase in PMD-affected cells characterized by endoplasmic reticulum stress and cell death as OPCs exit their progenitor state. The endoplasmic reticulum is the part of the cell involved in the processing of protein. In PMD, which almost exclusively affects male children, oligodendrocytes are lost and myelin is not properly formed in the brain and spinal cord. Due to their diseased myelin, children with PMD exhibit often-debilitating problems of coordination, motor skills, verbal expression, and learning. Due to the disease's severity, patients typically die before adulthood.

To overcome this early cell death in PMD cells, the team screened thousands of drug-like compounds and found that one, known as Ro 25-6981, was especially successful in rescuing the survival of PMD oligodendrocytes in mouse and human cells in the laboratory and in PMD mice. "Our work is an important first step of a multi-phase process," said Tesar. "We have achieved survival of oligodendrocytes which normally die in the disease. The next step is to figure out how to coax these cells to efficiently myelinate and restore function to patients."

The Case Western Reserve team's findings have implications beyond PMD. Numerous neurological and psychiatric diseases are characterized by myelin loss or dysfunction, including multiple sclerosis, spinal cord injury, and schizophrenia. Measures to regenerate or restore myelin could offer patients hope in these and numerous other disorders affecting the brain and spinal cord.

More information: Angela M. Lager et al, Rapid functional genetics of the oligodendrocyte lineage using pluripotent stem cells, *Nature Communications* (2018). DOI: 10.1038/s41467-018-06102-7

Matthew S. Elitt et al. Chemical Screening Identifies Enhancers of

Mutant Oligodendrocyte Survival and Unmasks a Distinct Pathological Phase in Pelizaeus-Merzbacher Disease, *Stem Cell Reports* (2018). DOI: 10.1016/j.stemcr.2018.07.015