UNIVERSITY of ROCHESTER MEDICAL CENTER

RESEARCH

New Grant Will Unlock Workings of Brain's Waste Removal System

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A decade ago, researchers in the lab of Maiken Nedergaard, M.D., D.M.Sc., answered a basic question of biology that up to that point had eluded scientists: how is waste removed from the brain? The discovery of what is now known as the glymphatic system and subsequent research have transformed the way we study a range of neurological disorders and critical brain functions. A new $15 million grant from the National Institutes of Health (NIH) will bring together several teams of researchers to accelerate our understanding of the complex mechanics that control this system, with an eye toward the development of new therapies for diseases like Alzheimer's.

The new research program will be led by Nedergaard, co-director of the Center for Translational Neuromedicine, and involve scientists and engineers from the University of Rochester, Penn State University, Boston University, and the University of Copenhagen. The research is being funded through The BRAIN Initiative, a massive research program supported by NIH and several other federal research agencies that aims to fill gaps in our current knowledge of the brain's organization and function.

The glymphatic system – a network of plumbing that runs parallel to blood vessels and pumps cerebral spinal fluid (CSF) through brain tissue to wash away waste – was all but invisible to the scientific world until 2012 when it was first described in a study published in *Science Translational Medicine*. A paper in the journal *Science* a year later showed that this system operates primarily while we sleep and removes toxic proteins associated with Alzheimer's disease. These findings fundamentally changed scientists' understanding of the biological purpose of sleep and opened the door to potential new ways to treat neurological disorders.

Subsequent research from Nedergaard's lab and others have shown that circadian rhythms, certain patterns of neurological activity, and the flow of blood in the brain all play a role in controlling the system. Studies have also shown that the system deteriorates while we age and can be impaired in sleep disorders. The glymphatic system has a great potential in enhancing drug delivery to the central nervous system, which is one of the biggest challenges in treating neurological diseases. Nedergaard recently co-authored a perspective piece in the journal Nature Reviews Drug Discovery detailing how the glymphatic system could be harnessed therapeutically. While best described in mice, subsequent imaging studies have confirmed its existence in the human brain.

The new research program seeks to develop a detailed, mechanistic understanding of the movement of CSF across sleep and wakefulness, and the neural processes that control it. It will also seek to deepen our understanding of how the system specifically functions in the human brain. The effort will consist of several complimentary research projects:

- A team led by Douglas Kelley, Ph.D., with the University of Rochester Department of Mechanical Engineering, will build detailed fluid dynamics computer simulations that show how changes in blood vessels and neural activity drives the flow of CSF into and out of the brain. Kelley will also lead a data science core with co-PI's Mujdat Cetin, Ph.D., Director of the Goergen Institute for Data Science, and Jiebo Luo, Ph.D., professor of Computer Science. The core will provide

innovative methods for storing, organizing, processing, analyzing, and internally sharing the enormous, multi-modal data sets that will be generated.

- The Nedergaard lab will examine how certain patterns of neuronal signaling and activity, support cells called astrocytes, and the smooth muscle cells that control blood flow in the brain all combine to turn the glymphatic system on and off.
- A project led by Patrick Drew, Ph.D., with Penn State University School of Engineering will more closely study how brain rhythms control arterial dilation and contraction during different stages of sleep.
- Laura Lewis, Ph.D., with the Boston University Center for Neuroscience Systems, will integrate multiple MRI technologies to observe the flow of CSF in the human brain and combine this information with measures of brain activity.
- A team of researchers at the University of Copenhagen lead by Hajome Hirasi, Ph.D., will develop new tools that enable the team to observe the movement of CSF in the brain non-invasively and at a finer level of detail.

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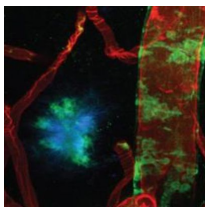

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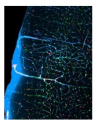

Scientists Discover Previously Unknown Cleansing System in Brain