Researchers pioneer noninvasive measurement of gene expression at target locations in the brain

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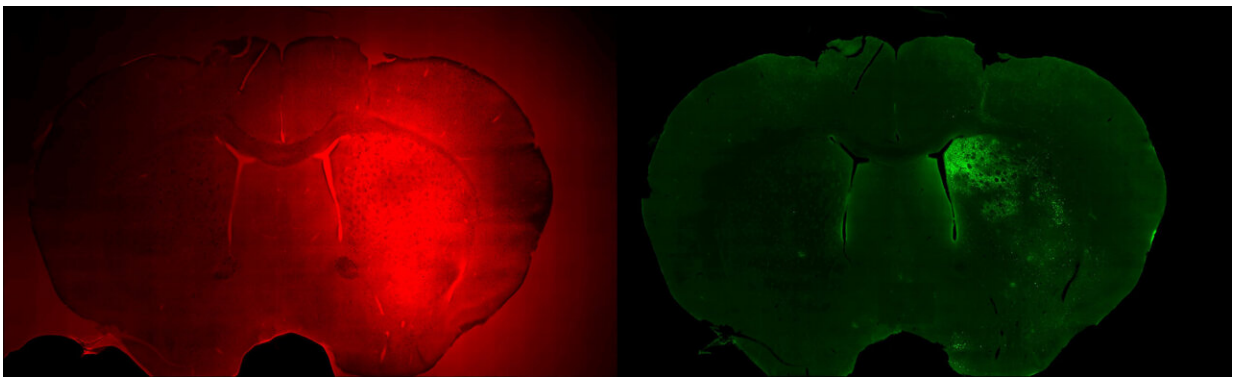

Striatum region (left) in rodent brain with opened blood-brain barrier. Green fluorescent protein expressed in striatum region in rodent brain (right) in response to induced neuronal activity. Credit: Laboratory for Noninvasive Imaging/Rice University

The ability to alter or prevent the expression of faulty genes in the brain could be leveraged as a powerful therapeutic against neurodegenerative disease. However, the molecular underpinnings of the living brain are still largely inaccessible, hampering progress on such promising therapeutics.

Available options for probing the brain are not quite up to the task. The

most effective way to record molecular information from multiple genes is biopsy — an invasive, high-risk procedure.

A study published today in *Science Advances* describes new technology developed by the Rice University lab of bioengineer Jerzy Szablowski that could be a game changer for brain-based gene therapy. Called "Recovery of Markers through InSonation," or REMIS, the new noninvasive tool can measure expression of gene therapy or endogenous genes in specific brain regions.

"Our limited ability to measure gene expression has significant consequences for the future of gene therapy," Szablowski said. "For example, in most cases it is not possible to noninvasively confirm whether gene therapy has successfully reached the brain, how long it stays there and which brain regions are being affected by it. Our study shows it is possible to measure gene expression and gene therapy delivery in specific brain regions with a relatively simple ultrasound procedure."

REMIS builds on prior work by Szablowski and collaborators that focused on engineered molecules known as released markers of activity (RMAs). With the RMA platform, the researchers introduced a synthetic gene expression reporter to the brain, which in turn produced a protein that could cross from the brain into the bloodstream, where it could be easily retrieved and measured with a blood test with exquisite sensitivity: RMA expression in as few as 12 neurons could be reliably detected in blood.

The downside to this initial version of the technology was that the markers crossed the brain-blood barrier indiscriminately and thus could not be traced back to specific brain regions. REMIS fixed the issue by using ultrasound to ferry engineered protein markers into the bloodstream only from targeted locations in the brain.

"Here we made markers that cannot cross these blood vessels until they are stimulated with ultrasound," Szablowski said.

Another advantage for REMIS is that it can also measure naturally occurring gene expression. One example is c-Fos, a gene that is used as a marker of neuronal activity. This highlights the potential of REMIS not only for gene therapy but also as a diagnostic and research tool.

"We are particularly excited about this technology, especially since our work has already led to a funded clinical trial with our colleagues at Baylor College of Medicine and MD Anderson Cancer Center," Szablowski said.

The trial will involve using focused ultrasound to release proteins present in the brain of patients with Parkinson's disease into the bloodstream, which could provide new insights into the molecular mechanisms involved in the disease. However, Szablowski said a more immediate application for REMIS is monitoring the success of gene delivery in the brain.

"Gene therapy is one of the most exciting frontiers in medicine, but we need to have tools to know whether the gene therapeutic reaches the part of the brain it's supposed to and works in the ways intended," Szablowski said. "REMIS provides a nonsurgical option to do so, potentially utilizing the gene therapeutic itself as a marker. This is a big advantage since methods such as PET scans entail the clinical development of new probes for every new therapeutic."

More information: Joon Pyung Seo et al, Acoustically targeted measurement of transgene expression in the brain, *Science Advances* (2024). DOI: 10.1126/sciadv.adj7686

Provided by Rice University