Scientists develop RNA-targeting strategy to repair genetic cause of ALS and dementia

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Jessica Bush, a graduate student at UF Scripps Biomedical Research, confers with her mentor, chemistry department chair Matthew Disney. Disney's group has developed a compound that addresses a cause of ALS and dementia in a new way. Disney is the senior author and Bush is the first author on the discovery, which is described in the journal PNAS on Nov. 21, 2022. Credit: UF Scripps Biomedical Research

Scientists at University of Florida (UF) Scripps Biomedical Research have developed a potential medicine for a leading cause of ALS and dementia that works by eliminating disease-causing segments of RNA. The compound restored the health of neurons in the lab and rescued mice with the disease.

The potential medication is described this week in the scientific journal *Proceedings of the National Academy of Sciences*. It is designed to be taken as a pill or an injection, said the lead inventor, professor Matthew Disney, Ph.D., chair of the UF Scripps chemistry department. Importantly, experiments showed that the compound is small enough to cross the blood-brain barrier, a hurdle other approaches have failed to clear, he said.

Amyotrophic lateral sclerosis, or ALS, progressively destroys neurons that control muscles, leading to worsening muscle loss and eventually death. The mutation, a leading cause of inherited ALS, is referred to as "C9 open reading frame 72," or C9orf72. This mutation also leads to one form of frontotemporal dementia, a brain disease that causes the brain's frontal and temporal lobes to shrink, resulting in changes in personality, behavior and speech, ultimately resulting in death.

The C9orf72 mutation features an expanded repeat of six "letters" of genetic code, GGGGCC, on chromosome 9, which may be duplicated between 65 and tens of thousands of times. When this mutated stretch of RNA is present, it results in the production of toxic proteins that sicken and eventually kill affected neurons. The compound developed by Disney's lab targets the RNA carrying those genetic instructions, thus preventing the toxic proteins from being assembled in the cells.

"The compound works by binding to and using natural cellular processes to eliminate that disease-causing RNA by alerting the cell's degradation machinery to dispose of it as waste," Disney said.

This approach could conceivably work for other untreatable neurological diseases in which toxic RNA play a role, he added.

The paper's first author is Jessica Bush, a graduate student within the Skaggs Graduate School of Chemical and Biological Sciences at UF Scripps, who works in Disney's lab. Other co-authors include Leonard Petrucelli, Ph.D., of the Mayo Clinic in Jacksonville, and Raphael Benhamou, a former Disney lab postdoctoral researcher now on the faculty of the Hebrew University of Jerusalem.

"This was identified from a large screen of compounds from the Calibr library at Scripps Research, which is comprised of 11,000 drug-like molecules," Bush said.

From that initial screen, they identified 69 compounds that inhibited translation of the toxic C9 mutation. They then further refined the compounds by eliminating those that could not cross the blood-brain barrier based on size, weight, structure and other factors. This resulted in 16 candidate compounds, one of which was selected for further refinement based on its potency and structural simplicity.

"A battery of tests in neurons derived from ALS patients and in vivo models showed that compound 1 bound selectively and avidly to the toxic RNA, forcing it to be degraded by the body's own natural processes," Bush said.

Patients being treated for ALS at the Johns Hopkins University School of Medicine's Laboratory for Neurodegenerative Research donated skin samples for research purposes. These skin cells were genetically reverted into stem cells, after which Disney's team treated the cells over several months to develop into neurons.

"Four different patients' cells were used for the assessment, all of which

showed dose-dependent reduction in known ALS markers while having no off-target effects," Bush said.

They also tested the compound in mice bred to have the C9orf72 mutation and show behaviors and blood markers typical of ALS. The mice were treated daily for two weeks, after which the mice displayed significantly reduced markers for disease and improved health.

The next steps will be to further study the compound's effects on cellular health and rodent models of C9 ALS, Disney said. The evidence so far shows that this approach represents a notable advance in the field of RNA drug discovery, he said.

"We show for the first time that you can make brain-penetrant molecules that eliminate toxic gene products," Disney said. "The fact that we have highlighted this in ALS shows that this can be a general approach for other neurological diseases, including Huntington's, forms of muscular dystrophy and others."

More information: Jessica A. Bush et al, A blood–brain penetrant RNA-targeted small molecule triggers elimination of r(G 4 C 2) exp in c9ALS/FTD via the nuclear RNA exosome, *Proceedings of the National Academy of Sciences* (2022). DOI: 10.1073/pnas.2210532119

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