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New Therapeutic Target Identified for ALS and Frontotemporal Degeneration

A team of scientists led by researchers from the University of California, San Diego School of Medicine and Ludwig Institute for Cancer Research have identified a novel therapeutic approach for the most frequent genetic cause of ALS, a disorder of the regions of the brain and spinal cord that control voluntary muscle movement, and frontotemporal degeneration, the second most frequent dementia.

Published ahead of print in last week's online edition of the journal *PNAS*, the study establishes using segments of genetic material called antisense oligonucleotides – ASOs – to block the buildup and selectively degrade the toxic RNA that contributes to the most common form of ALS, without affecting the normal RNA produced from the same gene.

The new approach may also have the potential to treat frontotemporal degeneration or frontotemporal dementia (FTD), a brain disorder characterized by changes in behavior and personality, language and motor skills that also causes degeneration of regions of the brain.

In 2011, scientists found that a specific gene known as C9orf72 is the most common genetic cause of ALS. It is a very specific type of mutation which, instead of changing the protein, involves a large expansion, or repeated sequence of a set of nucleotides – the basic component of RNA.

A normal C9orf72 gene contains fewer than 30 of the nucleotide repeat unit, GGGGCC. The mutant gene may contain hundreds of repeats of this unit, which generate a repeat containing RNA that the researchers show aggregate into foci.

"Remarkably, we found two distinct sets of RNA foci, one containing RNAs transcribed in the sense direction and the other containing anti-sense RNAs," said first author Clotilde Lagier-Tourenne, MD, PhD, UC San Diego Department of Neurosciences and Ludwig Institute for Cancer Research.

The researchers also discovered a signature of changes in expression of other genes that accompanies expression of the repeat-containing RNAs. Since they found that reducing the level of expression of the C9orf72 gene in a normal adult nervous system did not produce this signature of changes, the evidence demonstrated a toxicity of the repeat-containing RNAs that could be relieved by reducing the levels of those toxic RNAs.

“This led to our use of the ASOs to target the sense strand. We reduced the accumulation of expanded RNA foci and corrected the sense strand of the gene. Importantly, we showed that we could remove the toxic RNA without affecting the normal RNA that encodes the C9orf72 protein. This selective silencing of a toxic RNA is the holy grail of gene silencing approaches, and we showed we had accomplished it,” Lagier-Tourenne added.

Targeting the sense strand RNAs with a specific ASO did not, however, affect the antisense strand foci nor did it correct the signature of gene expression changes. “Doing that will require separate targeting of the antisense strand – or both - and has now become a critical question,“ Lagier-Tourenne said.

“This approach is exciting as it links two neurodegenerative diseases, ALS and FTD, to the field of expansion, which has gained broadened interest from investigators,” said co-principal investigator John Ravits, MD, UC San Diego Department of Neurosciences. “At the same time, our study also demonstrates the – to now – unrecognized role of anti-sense RNA and its potential as a therapeutic target.”

Contributors to the study included lead authors Ravits and Don W. Cleveland, PhD, chair of Cellular and Molecular Medicine, professor of Medicine and Neuroscience, and Ludwig Institute for Cancer Research investigator; co-first author Michael Baughn, UC San Diego, along with researchers from Isis Pharmaceuticals of Carlsbad, CA and Cedars-Sinai Medical Center, Los Angeles, and Washington University School of Medicine, St. Louis.

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