POLSKY Center for Entrepreneurship and Innovation
THE UNIVERSITY OF CHICAGO

A Novel Approach for the Treatment of Spinocerebellar Ataxia Type 6

SUMMARY

Spinocerebellar ataxia type 6 (SCA6) is a rare dominantly inherited neurodegenerative disease that typically presents in adults in their 40s or 50s for which there is no disease-modifying treatment. As the disease progresses, patients develop loss of coordination, tremors, and uncontrolled muscle tensing. Current therapies are focused on management of these symptoms.

Dr. Christopher Gomez's team at the University of Chicago has identified a unique mechanism required for the translation of the protein that likely causes SCA6 pathology: an internal ribosomal entry site (IRES) in the messenger RNA (mRNA) arising from the CACNA1A gene. They have also recently discovered that microRNA 3191 could be used as a potential therapeutic approach via selective translational blocking of the IRES.

KEY RESULTS

Dr. Gomez has demonstrated that the protein product originating from the IRES leads to SCA6 symptoms in mice. His group has developed an expression assay that can differentiate expression of the full-length mRNA and translation originating from the IRES. A microRNA, 3191, selectively inhibits translation from the IRES. Furthermore, delivery of adeno-associated viral microRNA-3191 into SCA6-afflicted mice alleviated ataxia phenotypes..

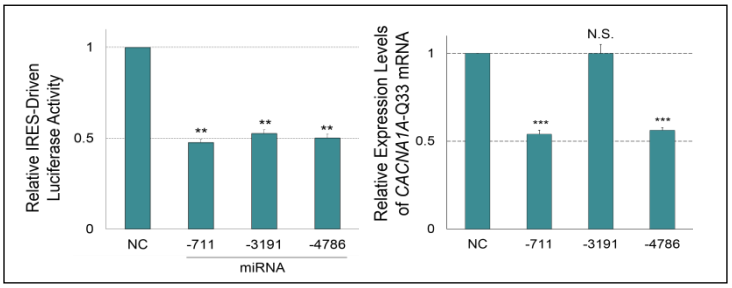
ADVANTAGES

- Fulfills an unmet need for treatment directed at SCA6 etiology.
- Utilizes a highly specific mechanism – side effects could be minimized.

APPLICATIONS

- Development of novel targeted therapies for SCA6.

microRNA-3191 selectively blocks translation of a pathological protein



Effect of miRNAs on IRES promoter activity and CACNA1A expression. Left: Luciferase activity of HEK293 cells cotransfected with microRNAs and dual luciferase reporter vector followed by the CACNA1A mRNA IRES. Right: qRT-PCR of above cells reveals that miR-3191 effects no change in CACNA1A mRNA expression, whereas other microRNAs significantly decrease CACNA1A transcript levels.

TECHNICAL DESCRIPTION

The relevant gene, CACNA1A, encodes a calcium channel subunit and contains an expanded polyQ repeat in diseased individuals. Efforts to identify a polyQ species of the calcium channel involved in disease progression have been inconclusive. Dr. Gomez's group has determined that the CACNA1A gene also encodes a second product, α1ACT, a transcription factor involved in neural outgrowth, for which the DNA origin was previously unknown. The polyQ species of α1ACT protein is likely the pathogenic entity in individuals afflicted with SCA6. Dr. Gomez and his colleagues have determined that production of α1ACT is the result of a translation phenomenon: the mRNA transcript resulting from the gene contains a cryptic cellular IRES. Recently, it was discovered that the microRNA-3191 specifically inhibits the CACNA1A IRES and a1ACT translation leaving the CACNA1A calcium channel product levels unaffected.

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REFERENCE
UCHI 2104, 2420

DEVELOPMENT STAGE
In vivo proof-of-concept in mouse models

THERAPEUTIC AREAS
Neurology, gene therapy

PUBLICATION
Yu Miyazaki et al. An miRNA-mediated therapy for SCA6 blocks IRES-driven translation of the CACNA1A second cistron. Science Translational Medicine. 2016 (347); 347ra94.

Du X, et al. Second cistron in CACNA1A gene encodes a transcription factor mediating cerebellar development and SCA6. Cell. 2013 154(1); 118-33.

INTELLECTUAL PROPERTY
PCT/US2014/045316
A second PCT application is pending.

INVENTOR(S)
Dr. Christopher Gomez, MD, PhD studies pathogenic mechanisms that cause ataxia, develop treatments and to identify disease and stage-specific biomarkers of ataxia. Dr. Gomez is an expert in neurogenetic disorders, gait and balance disorders, and in the diagnosis and treatment of patients with ataxias -- a family of rare neurodegenerative diseases.

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