Hexanucleotide repeat translation in ALS and Frontotemporal Dementia

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Principal Investigators

TODD, PETER K

Institution

UNIVERSITY OF MICHIGAN

Contact information of lead PI
Country

USA

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Hexanucleotide repeat translation in ALS and Frontotemporal Dementia

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5

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Motor neurone diseases|Alzheimer's disease & other dementias

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Research Abstract

Amyotrophic Lateral Sclerosis (ALS) and Frontotemporal dementia (FTD) are common neurodegenerative disorders that are progressive, fatal, and without effective treatment. Recently, the most common known cause of ALS and FTD was identified as an intronic GGGGCC hexanucleotide repeat expansion in the gene C9orf72 (C9FTD/ALS). This repeat triggers synthesis of toxic proteins via a process known as Repeat Associated Non-AUG (RAN)

Translation. These RAN peptides kill neurons and are sufficient to cause neurodegeneration in model systems. We know very little about how RAN translation at C9 repeats (C9 RANT) actually occurs. The objective of this proposal is to determine the mechanisms underlying C9 RAN and to identify methods of blocking it as a first step towards novel therapeutic development. Our central hypothesis is that C9 RAN utilizes a non-canonical translational initiation pathway that can be selectively blocked. Moreover, we predict that preventing C9 RAN will stop neurodegeneration elicited by GGGGCC repeats. To test these hypotheses, we developed robust and quantitative in vitro and cell based assays of C9 RANT, as well as a collection of models derived from patient induced pluripotent stem cells, rodent neurons, and Drosophila. Using these tools, we will define the mRNA species that undergo C9 RANT, identify the critical RNA and protein based factors that allow for C9 RANT and test whether suppressing C9 RANT by modulating the surrounding sequence or protein factors can block toxicity in model systems. Together, these studies should provide us with a working map of how C9 RAN occurs and what steps can be taken to prevent it. This project has broad reaching implications both for our understanding of how RAN translation contributes to disease as well as providing a logical path towards therapeutic development in C9FTD/ALS and other neurodegenerative nucleotide repeat disorders.

Lay Summary
ALS and Frontotemporal Dementia are neurodegenerative disorders that lead to significant death and disability. Recently, a novel repeat mutation was identified as the most common cause of ALS and Frontotemporal Dementia. This repeat causes ALS at least in part by producing toxic proteins through an unusual process known as RAN translation. This proposal will use biochemical techniques, neurons and patient derived induced pluripotent stem cell models of to understand how RAN translation occurs and how it can be selectively blocked in ALS patients. These approaches will lay the groundwork for developing small molecule therapeutics for this currently untreatable disease.

Further information available at:

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Investments > €500k

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