Misfolded ALS-linked Profilin-1: a novel therapeutic target

https://neurodegenerationresearch.eu/survey/misfolded-als-linked-profilin-1-a-novel-therapeutic-target/

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USA

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Misfolded ALS-linked Profilin-1: a novel therapeutic target

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NIH (NINDS)

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3

The project/programme is most relevant to:

Motor neurone diseases

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profilin 1, Amyotrophic Lateral Sclerosis, new therapeutic target, Actins, Link

Research Abstract
DESCRIPTION (provided by applicant): Recently, we identified mutations within the profilin-1 (PFN1) gene that cause familial, or inherited, ALS (Wu, et al., Nature 2012). PFN1 encodes an actin-binding protein that modulates actin dynamics in the context of important neuronal

processes such as growth, motility and signaling. Our preliminary data demonstrate that ALS-linked mutations induce PFN1 to “”misfold”” (i.e., adapt an aberrant and potentially pathogenic conformation). Protein misfolding is a hallmark feature of ALS and other neurodegenerative disorders, and may contribute to disease pathogenesis through either loss-of-normal or gain-of toxic function mechanisms. We posit that a misfolded conformation of PFN1 functions upstream in the pathogenic cascade that culminates in ALS. Therefore, a focus of this proposal is to characterize the misfolded conformation of ALS-PFN1 variants and to then target these misfolded species with small molecules. Our preliminary data also suggests that altered actin dynamics is a downstream consequence of ALS-PFN1 misfolding. We aim to understand the mechanism of PFN1-mediated ALS, and to determine whether altered actin dynamics is relevant to this mechanism. The experiments proposed herein will allow us to achieve our ultimate goal, which is to move the ALS field forward towards effective therapies for this devastating disease.

Lay Summary
PUBLIC HEALTH RELEVANCE: Amyotrophic lateral sclerosis (ALS) is a devastating neurodegenerative disease with no cure. We recently identified mutations in the gene encoding profilin-1 (PFN1) that cause ALS. Our preliminary data demonstrate that these mutations induce PFN1 to misfold and misfunction in the context of actin assembly. The goals of this proposal are to define and correct the misfolded conformation of ALS-PFN1 and to understand the mechanism for how mutations in PFN1 cause ALS.

Further information available at:

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