Neurodegeneration and Proteotoxicity Dissected in C. elegans and Mammals

https://www.neurodegenerationresearch.eu/survey/neurodegeneration-and-proteotoxicity-dissected-in-c-elegans-and-mammals/

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Country

USA

Title of project or programme

Neurodegeneration and Proteotoxicity Dissected in C. elegans and Mammals

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NIH (NINDS)

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€ 1,819,194.50

Start date of award

15/08/2011

Total duration of award in years

5

The project/programme is most relevant to:

Motor neurone diseases

Keywords

Amyotrophic Lateral Sclerosis, Caenorhabditis elegans, Suppressor Genes, Mammals, Nerve Degeneration

Research Abstract

Project Summary Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative

disease characterized by the degeneration of motor neurons. Protein misfolding and aggregation are a central feature of ALS and related neurodegenerative diseases. The complexity of neurodegeneration calls for large-scale unbiased screening studies. Over the past few years, we have made breakthrough observations that have significant implications for the understanding of cellular defense systems against proteotoxicity. Using a unique blend of biochemical, genetic, and cell biological approaches, we discovered a novel pathway to reprogram protein quality control, and with new genetic hits related to this pathway in hand. We now propose work to elucidate a previously unrecognized p53 network in protein quality control. The studies on this network could expand our understanding of proteotoxic-stress-responsive quality control systems in the cell, beyond the well-established heat shock response or unfolded protein response. Our unique potential to contribute to this field is both technical and conceptual: We have developed a unique tandem C. elegans/mammalian system to study neurodegeneration, and our recent success bodes well for future plans. For example, our expanding repertoire of diease models will allow us to conduct unbiased screening studies of proteotoxicity-associated neurodegeneration in vivo and extend the findings to mammalian models and patient cells. The findings will not only provide novel entry points for understanding the molecular causes of key ALS genes but also suggest new strategies for harnessing the cellular defense system to prevent and treat the relevant forms of ALS and other related neurodegenerative diseases. We predict that the advances gained through our research efforts will eventually lead to new therapeutic interventions to address these diseases in the world’s rapidly aging population.

Lay Summary
Project Narrative The work in this proposal is aimed at elucidating the basic pathogenic mechanisms and the regulatory pathways involved in amyotrophic lateral sclerosis and related neurodegenerative diseases. Although these diseases are becoming an increasingly relevant public health challenge in our aging society, the mechanisms underlying most of these neurodegenerative conditions remain poorly understood. The molecular and genetic studies outlined in this proposal could lead to novel therapeutic interventions for those neurodegenerative diseases, including ALS, for which effective treatments are still lacking.

Further information available at:

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Investments > €500k

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United States of America

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Motor neurone diseases

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