

Redesign Rat Model for ALS Research

<https://neurodegenerationresearch.eu/survey/redesign-rat-model-for-als-research/>

Principal Investigators

ZHOU, HONGXIA

Institution

THOMAS JEFFERSON UNIVERSITY

Contact information of lead PI

Country

USA

Title of project or programme

Redesign Rat Model for ALS Research

Source of funding information

NIH (NINDS)

Total sum awarded (Euro)

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Start date of award

15/08/2014

Total duration of award in years

1

The project/programme is most relevant to:

Motor neurone diseases

Keywords

Heterogeneous-Nuclear Ribonucleoproteins, Amyotrophic Lateral Sclerosis, Knock-in, Transgenes, Rattus

Research Abstract

DESCRIPTION (provided by applicant): Genetic mutation in certain genes causes familial forms of amyotrophic lateral sclerosis (ALS). Toward understanding the mechanisms of a disease mutation, a critical step is creating a desirable model for research. Whereas cellular models are important for testing some aspects of disease mechanisms, animal model is essential for

unraveling the mechanisms of complex neurodegeneration because findings from in vitro studies do not always translate to live animals. When a pathogenic mutation exhibits a dominant trait, animal models are often created by randomly inserting transgenes into host genome, incurring gene-insertional mutation and position effects. The levels and patterns of transgene expression largely depend on position effects and vary from line to line even when two lines carry the same copy of transgenes. The best control for genetic model is the transgenic strain that expresses wildtype form of a disease gene but develops no phenotypes observed in mutant transgenic strain. It is unlikely to obtain two lines that express wildtype and mutant proteins at similar levels and patterns. Authentic mechanisms are often obscured by the drawbacks of traditional transgenics. To avoid gene insertional mutation and unify position effect among individual lines, we will insert single copy of transgene at predetermined intergenic locus and will combine it with Tet-inducible system to amplify transgene expression such that plausible phenotypes can be induced within a rat's lifetime. Using these novel rats, we will examine the mechanisms of hnRNPA1 pathogenesis at a systematic level. We will validate the efficacy of this novel transgenic approach in disease induction by comparing phenotypic expression with those observed in the knockin rats that express disease gene at physiological levels and in its intrinsic patterns.

Lay Summary

PUBLIC HEALTH RELEVANCE: Using comprehensive approaches, this proposal is designed to redesign and establish a desirable animal model system for therapeutic and mechanistic study of amyotrophic lateral sclerosis.

Further information available at:

Types:

Investments > €500k

Member States:

United States of America

Diseases:

Motor neurone diseases

Years:

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Database Categories:

N/A

Database Tags:

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