The Four Repeat Tauopathy Neuroimaging Initiative

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Country

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Title of project or programme

The Four Repeat Tauopathy Neuroimaging Initiative

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 14,012,115.60

Start date of award

30/09/2010

Total duration of award in years

6

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

Acquired Cognitive Impairment... Aging... Alzheimer's Disease... Alzheimer's Disease Related Dementias (ADRD)... Alzheimer's Disease including Alzheimer's Disease Related Dementias (AD/ADRD)... Bioengineering... Brain Disorders... Clinical Research... Clinical Research - Extramural... Clinical Trials and Supportive Activities... Dementia... Diagnostic Radiology... Frontotemporal Dementia (FTD)... Neurodegenerative... Neurosciences... Orphan Drug... Pick's Disease... Rare Diseases... Translational Research

Research Abstract
? DESCRIPTION (provided by applicant): New treatments that target tau, a neuronal scaffolding protein that accumulates in neurodegenerative diseases, are entering human clinical trials. Increasingly, clinical trials of such tau directed therapies are focusing on pure 4 microtubule binding repeat (4R) tauopathies (4RT) including corticobasal degeneration (CBD) and progressive supranuclear palsy (PSP). We previously designed the 4RT Neuroimaging Initiative (4RTNI) to develop biomarkers of disease progression to support clinical trials of tau directed therapies in 4RT. During the first four and one half years of the project, we exceeded our planned enrollment, developed structural MRI biomarkers of disease progression, and determined that CSF neurofilament light chain (NfL) levels are correlated with disease progression. We validated our findings in a large international clinical trial in PSP that we designed and led. Based on these studies, we identified two major knowledge gaps that must be addressed prior to future trials: 1) a need for better pharmacodynamic biomarkers that can demonstrate the expected biological effects of treatments (including target engagement); and 2) patients need to be diagnosed at earlier stages of disease to give therapies the best chance of demonstrating efficacy. This competitive renewal will address these gaps by taking advantage of three recent scientific advances: the development of the new tau PET ligand 18F AV1451, new diagnostic criteria for an early form of 4RT called oligosymptomatic PSP (oPSP), predicted to allow diagnosis 2-3 years earlier than current criteria, and the recognition of retinal nerve cel damage in PSP. We will focus efforts on characterizing progression of insoluble tau deposition in 4RT, particularly in oPSP cases. We will recruit 55 CBD, 55 PSP and 60 oPSP participants and 60 age- matched controls, and study each for one or two (oPSP, controls) years using clinical rating scales, 18F AV1451 tau PET scans, 3T MRI scans, new non-invasive ophthalmologic neuronal injury assessments and CSF biomarkers. Individuals will undergo longitudinal clinical and MRI evaluations at baseline, 6, 12, and 24 months, with annual PET and CSF measurements, at five leading 4RT research centers (UCSF, UCSD, Harvard, U. Toronto, and U. Pennsylvania) with a strong track record of collaboration and supported by a new rare disease clinical research consortium called Advancing Research and Treatment for Frontotemporal Lobar Degeneration (ARTFL). We aim to: 1) Determine the natural history of brain insoluble tau deposition as measured by 18F AV1451 uptake on PET scans in 4RT as compared to controls. 2) Quantify longitudinal changes in retinal thickness and vertical saccade gain as measured by optical coherence tomography and infrared oculography. 3) Quantify longitudinal changes in CSF NfL levels compared to other fluid biomarkers. 4) Determine the clinical, MR imaging and neuronal injury marker correlates of 18F AV1451 uptake. Achieving these aims would enable us to intervene earlier in the course of 4RT disease and design more rigorous clinical trials of tau lowering drugs. All data will eventually be made available for use y other researchers.

Lay Summary
PUBLIC HEALTH RELEVANCE New drugs that target tau, a neuronal protein that is

dysfunctional and accumulates in Alzheimer’s disease (AD), corticobasal degeneration (CBD), and progressive supranuclear palsy (PSP), are entering human clinical trials; however, the best methods for assessing whether these drugs are effective have not yet been established. This project will study the four repeat (4R) tauopathies, CBD and PSP, because there are no effective treatments for these disorders and they are more likely to respond to tau-directed therapies than AD. The data generated from this project will allow researchers to design better clinical trials to test the efficacy of new tau-directed drugs in humans.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

Diseases:
Alzheimer's disease & other dementias

Years:
2016

Database Categories:
N/A

Database Tags:
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