Apolipoprotein E4 as a Therapeutic Target for Alzheimer’s Disease: Identification of Small-Molecule Structure Correctors That Prevent Apolipoprotein E4 Associated Neuropathology

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Country

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Title of project or programme

Apolipoprotein E4 as a Therapeutic Target for Alzheimer's Disease: Identification of Small-Molecule Structure Correctors That Prevent Apolipoprotein E4 Associated Neuropathology

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The Wellcome Trust

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06/12/2013

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3.0

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords
Research Abstract

Apolipoprotein (apo) E4 is the molecular target for our development of novel drugs to treat Alzheimer’s disease (AD). We have identified small-molecule apoE4 structure correctors (apoE4SCs) that block the pathogenicity of apoE4. A prototypical apoE4SC, PY-101, has effective apoE4 target engagement, moderate bioavailability and good central nervous system (CNS) penetration. Our key goal is to develop new chemical entities with improved potencies as apoE4SCs (at least 10 50-fold more potent than PY-101) while maintaining its good pharmaceutical properties. Numerate, using their predictive activity modeling technology for virtual screening and substructure and similarity searching, will identify novel chemotypes to develop as new active apoE4SCs. Using this approach, we will identify and prioritize two novel series of apoE4SCs for lead optimization. Representative compounds will display EC50 <100 nM for apoE4 engagement and favorable in vivo properties (F% !20, t1/2 !3 h, Cmax !3x EC50, brain levels > plasma levels), and significant target engagement in brain. Studies will establish the optimal procedures to test the efficacy of our early leads in animal models by administering PY- 101 to mice overexpressing human apoE4 that exhibit an age-associated cognitive decline and neuropathology reminiscent of AD. The new lead apoE4SC will be tested in these models for efficacy to provide support for further development in later-stage preclinical studies.

Lay Summary
Further information available at:

Types:
Investments > €500k

Member States:
United Kingdom

Diseases:
Alzheimer's disease & other dementias

Years:
2016

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