Exploring the potential of multi-target treatment for Alzheimer's disease: towards an integrated and transdisciplinary approach

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Country

Netherlands

Title of project or programme

Exploring the potential of multi-target treatment for Alzheimer's disease: towards an integrated and transdisciplinary approach

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ZonMw

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01/11/2014

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4.0

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords
Research Abstract
This project explores the potential of multi-target treatment of AD to halt disease progression. We hypothesize that, to develop therapeutics that effectively halt AD, the multifactorial complex

character of this disease should be acknowledged.

We selected four previously established early disease markers including neuroinflammation, oxidative stress, plaque deposition and Abeta oligomer toxicity. A currently clinically trialed drug, Atrosab (Baliopharm), has been selected against neuroinflammation and efficacy of this drug will be established. We will make use of the Abeta scavenger compound library developed by Crossbeta Biosciences and optimize and select a (combination of) suitable compounds from this library based on reduction of Abeta oligomer load. As the Abeta proteolytic cleavage apparatus seems hampered in the AD brain, currently known Abeta degrading enzymes will be compared for suitability as therapeutic intervention. A cell-based assay has already been developed within the consortium to assay for degrading activity of Abeta in various aggregation states by such enzymes. Last, a selection of anti-oxidant compounds will be assayed for anti-oxidant activity. The combined effect of the selected compounds is first validated using an in vitro approach to obtain insight into the mechanism of action and to evaluate for drug-drug interactions upon administration in combination.

We will develop well-defined biodegradable nanoparticles, which will be designed and functionalized to encapsulate the selected drugs, enabling them to cross the blood-brain-barrier, and upon passage, will dissociate and release the active compounds at the appropriate location. Blood-brain-barrier passage of the nanoparticles will be evaluated using a revolutionary blood-brain-barrier on a chip approach. Successful candidates will be subjected to further toxicology profiling, first using a human neuroblastoma cell line followed by detailed analysis of toxicity using primary neuronal cultures. The efficacy of the developed multi-target delivery system will ultimately be tested for their impact on disease progression by means of in vivo cognition assays using an AD mouse model at various ages, to obtain approximate insight into the efficacy of our proposed therapeutic approach at various stages of disease progress. Collectively, this project proposes a potentially high-impact novel therapeutic multi-target strategy to tackle the complex character of AD in combination with the blood-brain-barrier permeability challenge.

Lay Summary
Further information available at:

Types:
Investments > €500k

Member States:
Netherlands

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Alzheimer's disease & other dementias

Years:
2016

Database Categories:
N/A

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