Structure and Inhibition of Amyloid in Alzheimers Disease

https://www.neurodegenerationresearch.eu/survey/structure-and-inhibition-of-amyloid-in-alzheimers-disease/

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Country

USA

Title of project or programme

Structure and Inhibition of Amyloid in Alzheimers Disease

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NIH (NIA)

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1

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

Acquired Cognitive Impairment... Aging... Alzheimer's Disease... Alzheimer's Disease including Alzheimer's Disease Related Dementias (AD/ADRD)... Brain Disorders... Dementia... Neurodegenerative... Neurosciences

Research Abstract
Our hypothesis is that the lack of drugs to halt Alzheimer’s disease stems in large part from

ignorance of the structures of the most pertinent drug targets: the aggregated forms of the proteins tau and beta-amyloid. Here we propose to extend our studies of the structures of amyloid fibrils and oligomers to enable structure-based design of inhibiting compounds. For each of our proposed projects, structure determination will be followed by structure-based design of one or more inhibitors. Then each inhibitor will be assayed for effectiveness in inhibiting aggregate formation in vitro and inhibiting toxicity in cell models. The most effective inhibitors will then be assessed in animal models of our collaborators. Among our projects are the following: (1) Structure determination of oligomers of tau that can seed spreading of tau from cell to cell, and subsequent design of an inhibitor of oligomerization; (2) Inhibitor design of tau aggregation based on our newly determined structure of the amyloid-forming segment of tau with sequence VQIINK; (3) Evolution by ribosome display of inhibiting single-domain antibodies against tau aggregates, with the possibility that these may penetrate the blood-brain- barrier; (4) Optimization of existing crystals of the 20 residue segment of beta-amyloid with sequence GKLVFFGENVGSNKGAIIGL, which seems to form an oligomer. Improved crystals will be followed by structure determination and inhibitor design; (5) Crystallization of beta-amyloid or its segments in a lipid environment to gain possible insight into its toxic function; (6) Structure determination of a segment of beta-amyloid bound to its putative cell-surface receptor, followed by inhibitor design; (7) Exploration of the action of our newly discovered segment of the protein transthyretin which breaks up oligomers of beta-amyloid and inhibits toxicity. Each of these projects, if successful, opens a path to a possible therapeutic agent against Alzheimer’s disease. These paths have not been previously available because the pertinent structures have been unknown. We find the principal barrier to determination of amyloid structures is the miniscule size of the crystals. We propose to surmount this barrier by further exploitation of advanced methods of electron diffraction.

Lay Summary

To fill the void of therapeutics for Alzheimer’s disease, we are pursuing structure-based design of inhibitors of formation of amyloid oligomers and fibrils. We first identify promising amyloid-forming targets; then grow crystals of them and determine their structures by x-ray and electron diffraction. From the structures, we design inhibitors and test their ability to halt aggregation and toxicity.

Further information available at:

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Investments > €500k

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United States of America

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Alzheimer's disease & other dementias

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