Structural Biology of Amyloid Disease

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Country

USA

Title of project or programme

Structural Biology of Amyloid Disease

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 1,636,524.77

Start date of award

01/09/2007

Total duration of award in years

10

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... Rare Diseases... Transmissible Spongiform Encephalopathy (TSE)

Research Abstract

DESCRIPTION (provided by applicant): Progress in diagnosing and treating amyloid diseases has been hindered by lack of information on the structures, pathways of formation, and modes

of toxicity of amyloid fibers and oligomers. In contrast to the increasingly successful attack on cancer, infectious, and metabolic diseases, treating amyloid diseases has proceeded in a near vacuum of knowledge about the structure and action of the etiologic agents. Amyloid diseases include not only Alzheimer's, which afflicts more than 5 million Americans today, but also Parkinson's, prion diseases, diabetes type II, senile systemic amyloidosis, light chain amyloidosis, and many more. All of these conditions are associated with elongated, unbranched protein fibers, 10-20nm in diameter, but in each disease the associated fiber is formed from a different protein. In the systemic amyloid diseases, fibers seem to be the etiologic agents; in the neurodegenerative amyloid diseases, small oligomers of the fiber-forming proteins are the causative agents. The overall goal of this project is to understand at the molecular level how amyloid fibers and oligomers form and kill cells. This knowledge will speed the design and testing of diagnostics and therapeutics for amyloid diseases. In previous work we determined structures of fibers and oligomers working with crystals that are 30,000 to 100,000 times smaller than the protein crystals normally used for structure determination. This has necessitated pioneering new methods of microcrystallography. With these new methods in the past grant period, we determined structures of some 90 amyloid fiber-like structures of segments of amyloid proteins that reveal the atomic level architecture of disease related fibers. Recently this approach has turned up two new types of structures that seem to explain prion aggregation and amyloid small oligomers. We will extend studies of these new types of structures, including of their pathways of formation and their biological toxicity. And by studying the structure of an amyloid oligomer in complex with an antibody that recognizes toxic oligomers of different proteins, we will identify the common features of toxic amyloid oligomers. As a start to designing chemical and biochemical interventions for amyloid disease, we have determined atomic structures for small molecules bound to amyloid segments. We have also designed two inhibitors of amyloid fiber growth. In the new grant period we will seek to understand the mechanisms of amyloid formation and toxicity. Because of the complexity of the scientific study of amyloid disease, we have developed a wide network of collaborators-local, national, and international–with whom we share information and methods.

Lay Summary
Amyloid diseases, including Alzheimer's, Parkinson's, diabetes type II, and the related Lou Gehrig's and Huntington's diseases, afflict millions of Americans. Our goal is to enable ways to slow or reverse these diseases by determining the mechanism of formation and toxicity of their causative agents. Using frontier methods, we learn the molecular properties of these agents, and the way they interact with potential biological and chemical inhibitors.

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:
N/A