Wellcome Trust/MRC Strategic Award: Mechanisms of neurotoxicity of amyloid aggregates

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Title of project or programme

Wellcome Trust/MRC Strategic Award: Mechanisms of neurotoxicity of amyloid aggregates

Principal Investigators of project/programme grant

Title	Forname	Surname	Institution	Country
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Address of institution of lead PI

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Country

- United Kingdom

Source of funding information

Medical Research Council

Total sum awarded (Euro)

7151557.53

Start date of award

01-01-2010

Total duration of award in months

60

The project/programme is most relevant to

- Alzheimer’s disease and other dementias

Keywords

Research abstract in English

Some of the most important but unresolved questions about the pathobiology of Alzheimer's disease (AD) are: What are the neurotoxic species of Abeta? How do they injure neurons? How do they induce aggregation of intracellular proteins like tau, alpha-synuclein, and TDP-43? Why are the normal mechanisms for removal of these intracellular aggregation-prone proteins overwhelmed in AD? Answers to such questions will provide both insight into the early stages of disease pathogenesis, and starting points for the discovery of novel diagnostics and therapeutics.

We hypothesize that the neurotoxicity of Abeta arises from heterogeneous mixtures of soluble Abeta aggregates, which may have differing toxicities, but which activate complex, interlinked downstream pathways. To deconvolute this complexity we will apply an integrated suite of tools from physics, chemistry, engineering, systems biology and neurobiology to: 1) Investigate Abeta aggregation and its consequences in living cells and animals; 2) Identify its molecular targets; 3) Discover the downstream metabolic and signalling pathways activated by Abeta; 4) Identify the molecular mechanisms by which Abeta induces misprocessing of tau; and 5) Identify the regulators of autophagy (which is an important physiological mechanisms for removal of tau) and determine why autophagy is down-regulated in AD)

Lay Summary