# Prion kinetics, toxicity and synthesis and its wider relevance

https://neurodegenerationresearch.eu/survey/prion-kinetics-toxicity-and-synthesis-and-its-wider-relevance/

**Title of project or programme**

Prion kinetics, toxicity and synthesis and its wider relevance

**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)**

2131676.93

**Start date of award**

01-04-2008

**Total duration of award in months**

24

**The project/programme is most relevant to**

- Alzheimer’s disease and other dementias
- Prion disease

**Keywords**

**Research abstract in English**

Prions are lethal pathogens of mammals which occur in multiple biological strains, and yet appear

devoid of nucleic acid and composed of aggregated conformational isomers of a host-encoded glycoprotein. Their unique biology, allied with the risks to public health posed by prion zoonoses such as BSE, has focused much attention on understanding the molecular basis of prion propagation and pathogenesis. However, it is clear that the underlying molecular mechanisms, involving aggregation of a misfolded host protein, are of much wider significance and, indeed, analogous protein-based inheritance mechanisms are recognised in yeast and fungi. The common neurodegenerative diseases also involve accumulation of misfolded host proteins and parallels, at multiple levels, in particular with Alzheimer's disease, are becoming increasingly apparent. Recent advances suggest that prions themselves are not directly neurotoxic, but rather their propagation involves production of toxic species which may be uncoupled from infectivity. We have proposed a general model to encompass these phenomena, centring on the kinetics of prion propagation, and will test this model using various experimental systems. Our development of an automated, high-throughput, culture-based prion bioassay (ASCA) will be applied to study in vivo kinetics of prion propagation in multiple models and relate this to neurotoxicity and clinical onset. We aim to specifically characterise the determinants of chronic carrier states of prion infection. ASCA will also be used in large-scale studies to attempt high-titre prion synthesis from purified components, an approach completely impractical by conventional rodent bioassay, and determine the role of co-factors. The hypothesis that prion neurotoxicity is mediated by oligomeric species will also be directly investigated. We also aim to develop cell lines to efficiently propagate hamster and human prions to allow extension of these studies beyond mouse-adapted scrape strains and to provide rapid assay of vCJD prions. Interactions between prion and Alzheimer pathogenesis will be explored at several levels, and we will investigate the possible wider role of PrPC in neurotoxicity. Molecular reagents we have developed to target PrPC will be used to investigate possible wider therapeutic strategies in neurodegeneration. Our prion models also provide a test bed for investigating generic approaches to protein misfolding diseases.

**Lay Summary**