Molecular diagnostic strategies in prion disease

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Title of project or programme

Molecular diagnostic strategies in prion disease

Principal Investigators of project/programme grant

Title	Forname	Surname	Institution	Country
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- United Kingdom

Source of funding information

Medical Research Council

Total sum awarded (Euro)

3733703.00

Start date of award

01-04-2005

Total duration of award in months

60

The project/programme is most relevant to

- Prion disease

Keywords

Research abstract in English

The emergence of vCJD, and the experimental confirmation that it is caused by the same prion strain as bovine spongiform encephalopathy (BSE) has dramatically highlighted the need for ante-mortem

diagnostic tests for prion disease and reliable methods for the destruction of prion infectivity. The extremely prolonged and variable incubation periods of these diseases, particularly when crossing a species barrier, and the demonstration of a discrete number of as yet uncharacterised genetic loci with a major effect on incubation periods, means that it will be some years before the parameters of any human epidemic can be predicted with confidence. In the meantime, we are faced with the possibility that significant numbers in the population may be incubating this disease and infect others via blood transfusion, blood products, tissue and organ transplantation and other iatrogenic routes. The recent demonstration of sub-clinical carrier states of prion infection in animal models is also relevant to public health, both with respect to prion zoonoses and iatrogenic transmission of human prions. The immediate solution to many of these problems is to provide a sensitive blood-based pre-symptomatic diagnostic test for prion infection. This programme aims to investigate basic aspects of prion biology that are directly relevant to methods for blood-based diagnostic testing, and to couple such basic research with translational research such as immunoassay optimisation and proteomics screening in order to provide a co-ordinated approach to ante-mortem diagnostics.

Key projects within the research programme are aimed at developing methods for the amplification of PrPSc and infectivity from patient blood samples. The nascent technology of PMCA (Protein Misfolding by Cyclic Amplification) is currently being investigated as a means to amplify PrPSc to detectable levels from normal blood samples spiked with high dilutions of infected brain homogenate. If successful this method will be used to amplify material from a longitudinal study in wild-type mice that has provided blood samples from various points throughout the incubation period of disease and ultimately in blood samples obtained from vCJD patients. In parallel, attempts are being made to ‘seed’ reactions in which recombinant PrP can be induced to fibrilise. Such reactions can be seeded and accelerated with preformed fibrils of recombinant PrP and if they can be also be catalysed by the addition of infected tissue homogenates or blood the incorporation of appropriately labelled recombinant PrP into fibrils could be sensitively detected by FRET.

Separate projects are underway to increase the sensitivity of PrPSc detection in immunoassays by developing new methods for the enrichment of disease-associated PrP prior to assay and by improving sandwich ELISA formats by screening a panel of over 80 monoclonal anti-PrP antibodies for optimum pairings.

Lay Summary