Molecular diagnostic strategies in prion disease

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Country

United Kingdom

Title of project or programme

Molecular diagnostic strategies in prion disease

Source of funding information

MRC

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01/04/2011

Total duration of award in years

5.0

The project/programme is most relevant to:

Prion disease

Keywords
Research Abstract
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) has been investigated as a means to replicate PrPSc to detectable levels from normal blood samples spiked with high dilutions of infected brain homogenate and from blood sampled from mice in the pre-clinical stages of experimental prion disease. We aim to dissect these reactions to define and understand the molecular events that constitute prion replication and identify what components of PMCA substrate (currently treated brain homogenate) are crucial for efficient prion replication. In parallel simplified amplification reactions in which recombinant PrP can be induced to fibrilise are being studied. Such reactions can be seeded and accelerated with preformed fibrils of recombinant PrP. These reactions can be also be catalysed by the addition of infected tissue homogenates or blood. We are investigated means to enhance the speed and sensitivity of such assays and aim to combine knowledge gained from understanding PMCA with recombinant PrP to enable purely synthetic, in vitro prion replication.||Separate projects are underway to increase the sensitivity of PrPSc detection in immunoassays by developing new methods for the capture and 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. We have made considerable progress and extended the sensitivity of immunodetection to levels greater than the sensitivity afforded by rodent bioassays, being able to detect infected vCJD brain homogenate at a dilution of 1010. Application of this methodology to both endogenous rodent and patient blood samples has confirmed that we are able to differentiate infected blood from control samples.

Lay Summary
Further information available at:

Types:
Investments > €500k

Member States:
United Kingdom

Diseases:
Prion disease

Years:
2016

Database Categories:

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