Institution: University College London

Unit of Assessment: 4 - Psychology, Psychiatry and Neuroscience

Title of case study: vCJD prion infection: improving diagnosis and surveillance

1. Summary of the impact (indicative maximum 100 words)

The MRC Prion Unit was established at UCL in 1998 to address national public health issues posed by bovine spongiform encephalopathy (BSE) and variant Creutzfeldt-Jakob disease (vCJD). One of our key strategic priorities has been to create a validated blood test for vCJD in order to protect public health through the screening of donated blood and organs for transplantation. The blood test we have developed has been demonstrated to detect infection in over 70% of patients with vCJD with, to date, 100% specificity and is now in use at the National Prion Clinic for evaluation.

2. Underpinning research (indicative maximum 500 words)

Prion diseases remain a strategic priority area for both the MRC and the Department of Health, with early diagnosis a key aim. The confirmation of blood transfusion-associated vCJD has highlighted the need to advance blood-based diagnostics for prion infection to protect the UK blood supply. Further, the advances in therapeutics research in the Unit and Department of Neurodegenerative Disease necessitate parallel advances in early diagnosis and progression biomarkers to support imminent clinical trials.

Detection of disease-associated, abnormal forms of the prion protein such as PrP^{Sc} is the most specific criterion for the diagnosis of prion disease in humans and animals. However, the high specificity associated with PrP^{Sc} detection has always been counterbalanced by a limit on the sensitivity of detection. Research led by Professor John Collinge over the past few years has been successful in identifying new methods for the specific detection of abnormal forms of PrP without sacrificing sensitivity. These methods have been used in conjunction with our own monoclonal antibodies generated against unique, alternative folded conformers of PrP to develop sensitive ELISA and western blot methods capable of diagnosing prion infection from neural or tonsillar tissue biopsies.

Although the quantities of PrP^{Sc} deposited in neural tissues are sufficient during the symptomatic phase of illness for detection by conventional immunoassays, quantification of infectious titre using rodent models has indicated that the levels of infectivity in blood are extremely low and over a million-fold lower than in infected CNS material. Ongoing research studying the interaction of PrP with metals **[1, 2]** has led to the development of methods for the selective capture of PrP^{Sc} and prions on solid-state surfaces **[3]**. Combining our capture technologies with cells selected for susceptibility to prion infection has allowed us to describe quantitative cell culture assays for infectivity that approach the high levels of sensitivity required to detect the low levels of prions and abnormal PrP associated with blood **[4, 5]**. A similar approach has been adopted for the capture of abnormal PrP from whole human blood using an optimised solid-state capture matrix derived from investigation of an extensive range of potential binding surfaces coupled with direct immunodetection of the surface-bound material. The use of whole blood as an analyte ensures that all abnormal PrP is available for detection in the assay irrespective of which compartment it is associated with. Our previous work developing antibodies and methods for abnormal PrP detection avoids use of any proteolytic processing ensuring all abnormal PrP isoforms are available for detection.

The combination of our endeavours in monoclonal antibody production and selective capture of abnormal PrP have resulted in the first available blood test for vCJD **[6]**. The assay has been validated on a large set of samples from the USA, where exposure to BSE can be considered negligible, and has a determined specificity of 100% whilst retaining sensitivity for infection of 71%. The blood test is now in routine use within the National Prion Clinic as part of patient assessment

and differential diagnosis.

Researchers

Professor John Collinge, Professor Charles Weissman, Dr Graham S Jackson, Dr Julie A Edgeworth, Dr Simon Mead

3. References to the research (indicative maximum of six references)

[1] Jackson GS, Murray I, Hosszu LL, Gibbs N, Waltho JP, Clarke AR, Collinge J. Location and properties of metal-binding sites on the human prion protein. Proc Natl Acad Sci U S A. 2001 Jul 17;98(15):8531-5. http://dx.doi.org/10.1073/pnas.151038498

[2] Hasnain SS, Murphy LM, Strange RW, Grossmann JG, Clarke AR, Jackson GS, Collinge J. XAFS study of the high-affinity copper-binding site of human PrP(91-231) and its low-resolution structure in solution. J Mol Biol. 2001 Aug 17;311(3):467-73. http://dx.doi.org/10.1006/jmbi.2001.4795

[3] Edgeworth JA, Jackson GS, Clarke AR, Weissmann C, Collinge J. Highly sensitive, quantitative cell-based assay for prions adsorbed to solid surfaces. Proc Natl Acad Sci U S A. 2009 Mar 3;106(9):3479-83. http://dx.doi.org/10.1073/pnas.0813342106.

[4] Tattum MH, Jones S, Pal S, Khalili-Shirazi A, Collinge J, Jackson GS. A highly sensitive immunoassay for the detection of prion-infected material in whole human blood without the use of proteinase K. Transfusion. 2010 Dec;50(12):2619-27. http://dx.doi.org/10.1111/j.1537-2995.2010.02731.x.

[5] Tattum MH, Jones S, Pal S, Collinge J, Jackson GS. Discrimination between prion-infected and normal blood samples by protein misfolding cyclic amplification. Transfusion. 2010 May;50(5):996-1002. http://dx.doi.org/10.1111/j.1537-2995.2010.02595.x

[6] Edgeworth JA, Farmer M, Sicilia A, Tavares P, Beck J, Campbell T, Lowe J, Mead S, Rudge P, Collinge J, Jackson GS. Detection of prion infection in variant Creutzfeldt-Jakob disease: a blood-based assay. Lancet. 2011 Feb 5;377(9764):487-93. http://dx.doi.org/10.1016/S0140-6736(10)62308-2.

4. Details of the impact (indicative maximum 750 words)

Our blood test is now in use at the National Prion Clinic (NPC) to allow diagnosis of vCJD. The immediate impact of this is that patients can be diagnosed quickly, other conditions can be excluded, and care plans can be put in place quickly. Impacts currently at an interim stage are the development of high throughput tests for screening blood in transfusion services both in the UK and overseas.

Using the existing World Health Organisation diagnostic criteria for vCJD, disease can only be classified as 'probable' in the presence of significant neurological deficit and confirmed as 'definite' by means of neuropathological examination. Despite their relentlessly progressive nature and devastating prognosis, securing a firm early diagnosis for these disorders remains crucial. This is firstly as the differential diagnosis of prion disease includes potentially reversible conditions, such as limbic encephalitis caused by voltage gated potassium channel antibodies, or primary central nervous system (CNS) vasculitis. Secondly, early diagnosis removes uncertainty, which in itself is distressing, and obviates the need for further investigation. Patient care plans can be established, patients and families counselled accordingly and appropriate infection control measures implemented **[a]**. Introduction of a sensitive and specific blood-based molecular diagnostic test for prion disease will facilitate early disease diagnosis and entry into therapeutic trials. In addition, such a test has obvious applications in reducing iatrogenic transmission of disease, screening of blood products for transfusion, food and medicinal products.

The National Prion Clinic (NPC) is the national referral centre for prion disease and is based at the National Hospital for Neurology and Neurosurgery **[b]**. The clinic is integrally linked with the MRC Prion Unit. Our blood test is in increasing diagnostic use in the NPC and samples are received for investigation from neurologists both nationally and internationally. Approximately 115 patients have been tested so far through the clinic **[c]**. In addition to its immediate clinical use the test is suitable for screening applications as an extended validation series of 5,000 control samples demonstrated that the test is 100% specific for prion disease.

A study by the Health Protection Agency (HPA) to determine the prevalence of prion infection in solid organs released preliminary results in August 2012 **[d]**. They found 16 definitively positive appendices out of 32,441 suitable samples examined, equating to a final prevalence estimate of 493 per million (95% CI: 282 to 801 per million). The central estimate of around 1 infection per 2,000 UK citizens is clearly alarming coupled with the known potential for transmission via blood transfusion, and demonstrates the long-term significance of our work. [text removed for publication].

Although the number of transfusion recipients positively identified as having received packed red cells contaminated with vCJD is small, much larger cohorts of at-risk individuals exist including around 6,000 recipients of contaminated plasma products, haemophiliacs and thalassaemics.

Other groups identified and also notified by the HPA as being at heightened risk of prion disease include the highly transfused, surgical contacts of prion disease patients and recipients of cadaver-derived human growth hormone. Whilst most notified individuals appear to understand and accommodate the health protection message, it is not surprising that the NHS National Prion Clinic is regularly referred and counsels distressed individuals in such risk groups who may also have had their healthcare disrupted by misunderstanding on the part of NHS professionals. The availability of a blood test will provide better risk assessment and resolve issues of personal risk in notified groups **[a]**.

Several commercial organisations have had historical interest in developing a blood test for prion disease but abandoned their research efforts after reaching the conclusion it was not possible. As a result there is renewed interest within industry to develop such tests, knowing that blood does contain sufficient abnormal PrP for detection. The test has been patented as a step towards commercialisation **[e]**.

vCJD has been the subject of intense public and policy debate; publication in the Lancet of our blood test method and preliminary results has resulted in considerable press coverage. Recent press reports (for example, *The Telegraph*, 28 April 2013) have highlighted the importance of a blood test in protecting public health in the UK with predictions of up to 1,000 people likely to die from vCJD as a result of receiving contaminated transfused blood. Coverage in the *Daily Mail*, 3 February 2011, attracted comments from members of the public welcoming the test and wishing for reassurance that they were not at risk **[f]**.

5. Sources to corroborate the impact (indicative maximum of 10 references)

[a] The potential of the test to benefit patients and notified groups can be corroborated by the Chairman of the Management Committee, CJD Support Network. Contact details provided.

[b] National Prion Clinic, blood test availability: http://www.prion.ucl.ac.uk/clinic-services/investigations-tests/#BloodTest

[c] Confirmation of the numbers of patients tested at the National Prion Unit, and the meeting of the Advisory Committee on Dangerous Pathogens (ACDP) Risk Assessment Sub Group on transmissible spongiform encephalopathies (TSE) and the UK Blood Services Prion Working Group can be provided by Consultant Neurologist and Clinical Lead at the National Prion Clinic. Contact details provided.

[d] Summary results of the second national survey of abnormal prion prevalence in archived appendix specimens, see HPA news archive:
http://www.hpa.org.uk/hpr/archives/2012/news3212.htm#bnrmlprn

[e] Patent details:
Application Number: PCT/GB2011/001341
Collinge J, Edgeworth JA, Jackson GS, Assay for Prions,
Priority date Sep 16 2010, publication date May 3 2012
http://www.google.com/patents/WO2012035296A3

[f] Examples of media coverage:

- The Telegraph, 28/4/2013
  http://www.telegraph.co.uk/health/healthnews/10024078/Mad-cow-infected-blood-to-kill-1000.html
- Channel 4 News, 13/01/2012
  http://www.channel4.com/news/blood-test-breakthrough-for-mad-cow-disease
- Sky News, 3/2/2011
  http://news.sky.com/story/835198/first-reliable-test-for-mad-cow-disease
- The Guardian, 3/02/2011
  http://www.guardian.co.uk/uk/2011/feb/03/human-bse-blood-test
- BBC News, 03/02/2011
  http://www.bbc.co.uk/news/health-12343896
- The Telegraph, 03/02/2011
  http://www.telegraph.co.uk/health/healthnews/8298592/vCJD-blood-test-developed.html
- The Express, 03/2/2011
  http://www.express.co.uk/news/uk/226872/New-blood-test-for-mad-cow-disease
- The Mirror, 03/02/2011
  http://www.mirror.co.uk/news/uk-news/first-reliable-blood-test-for-human-108183
- Daily Mail, 03/02/2011
  http://www.dailymail.co.uk/health/article-1353135/vCJD-blood-test-raises-hopes-screening-human-mad-cow-disease.html