

Innovating Technologies: meeting the **Prion** Challenge



D-Gen

the Prion specialists

profile

D-Gen is a research-based bio-medical company which innovates in the field of prion-related disease by identifying, developing and exploiting proprietary diagnostic and therapeutic targets and technologies. D-Gen is committed to utilising the latest research in developing products and services that meet the global animal and public health challenge posed by prion disease.

D-Gen was formed in May 2000 as a University spin-out company to commercialise relevant research emanating from the work of Professor John Collinge's team at the Medical Research Council (MRC) Prion Unit (now based at the Institute of Neurology, University College London). The MRC Prion Unit was set up to create an international centre of excellence. It plays a key role in linking basic science to clinical research and has contributed to some of the most significant advances in the field of prion disease. These include:

- producing the first experimental evidence of a link between BSE and CJD
- replicating the conversion of normal prion protein into the abnormal disease associated type in the laboratory using a genetically engineered form of the prion protein
- developing a novel test to detect abnormal prion protein in human tonsils and to diagnose vCJD *in vivo*
- developing methods for prion decontamination of surgical instruments
- showing that monoclonal antibodies could form the basis of future medicine to treat CJD.

D-Gen's shareholders include Imperial College London, The Medical Research Council (MRC), The Wellcome Trust Ltd, University of Bristol and a number of inventor scientists.

Prion disease

Prion diseases or Transmissible Spongiform Encephalopathies (TSEs) are fatal neurodegenerative disorders characterised by the deposition of an abnormal amyloid protein PrP^{Sc}, in the brains of infected animals and humans. No therapy currently exists though the MRC Prion Unit is currently conducting therapeutic trials. TSEs are transmitted by inoculation with or dietary exposure to infected tissues and cause various diseases as shown:

HOST	PRION DISEASE
Human	Creutzfeldt-Jakob Disease (CJD), variant CJD (vCJD), Gertsman-Sträussler-Scheinker Syndrome (GSS), Fatal Familial Insomnia (FFI)
Cattle	Bovine Spongiform Encephalopathy (BSE)
Sheep	Scrapie
Mule, Elk, Deer	Chronic Wasting Disease (CWD)
Nyala, Oryx, Kudu	Exotic Ungulate Encephalopathy
Mink	Transmissible Mink Encephalopathy (TME)
Cats	Feline Spongiform Encephalopathy (FSE)

technology portfolio

A dynamic integrated research programme focused on basic research, diagnostics (human and veterinary), therapeutics and public health and safety has resulted in an extensive proprietary technology portfolio including amongst others:



- **Novel protein β -PrP:**

conditions for preparing a monomeric, soluble and stable recombinant human prion protein, rich in β -sheet structure and designated β -PrP have been established. β -PrP has many properties in common with the disease-associated form of the prion protein PrP^{Sc}. It has potential applications in research, diagnostics, prophylaxis and therapeutics.

- **Stable PrP core peptides:**

a core region of PrP^C has been identified that resists denaturation. The ability to make peptides of this region and antibodies that recognise them has potential uses in the diagnosis, prevention and treatment of prion disease.

- **Typing and discrimination of human prion diseases:**

a diagnostic test that allows rapid molecular diagnosis and differentiation of sporadic and iatrogenic CJD from variant CJD in humans has been developed. This allows for relevant classification of human prion disease and its aetiology. The test is important for both diagnostic and public health planning purposes.

- **vCJD susceptibility test:**

genetic biomarker tests are being developed to indicate potential susceptibility to vCJD in humans. Such approaches will be used for diagnosis and for population risk assessment studies.

- **Prion decontamination of surgical instruments:**

Prions are extremely resistant to heat and chemicals rendering most existing sterilisation technologies ineffective in their deactivation. Conditions normally used for inactivating prions – typically powerful oxidising agents or strong alkalis – are highly corrosive to the instruments and washing equipment used in hospital sterilisation units. Prions have been shown to bind avidly to surgical stainless steel and act as a source of infectivity. The prolonged incubation periods for human prion disease mean that individuals may be symptomatic but infectious for more than a decade leading to increased risks of iatrogenic transmission – a formidable public health challenge. A practical enzyme-based decontamination technology has been developed and extensively tested both *in vitro* and *in vivo*. Results show that the introduction of this technology as a pre-treatment in the sterilisation process would reduce the risk of iatrogenic transmission by at least five orders of magnitude over and above the reduction in infectivity afforded by autoclaving.

- **Rapid cell-culture based prion infectivity assay:**

currently the gold standard for measuring prion infectivity is animal bioassay based on intracerebral inoculation of mice that is slow (~140 days) and costly. A quantitative *in vitro* assay for prion infectivity, the scrapie cell (SC) assay has been developed. This assay is about as sensitive as the mouse bioassay, 10 times

faster (14 days), orders of magnitude less expensive and suitable for robotisation and high throughput. To date the SC assay can be used to determine infectivity titres of mouse brain homogenates (RML). The SC assay will be particularly useful for prion clearance or reduction studies on manufacturing processes using bovine derived tissues or human blood products.

- **Prion inhibition:**

the effective suppression of peripheral prion replication using antibody therapy has been achieved. Two novel D-Gen monoclonal antibodies ICSM18 and ICSM35 have been demonstrated to prevent the development of prion disease in an *in vivo* mouse model system. This demonstrates the potential of using antibodies as immunotherapeutics to prevent and treat prion disease.

- **Innovative monoclonal antibodies:**

a long standing limitation of anti-PrP monoclonal antibodies has been their inability to recognise the disease associated isoform of PrP, PrP^{Sc}. Although several commercial antibodies are capable of reacting with denatured PrP^C and PrP^{Sc} on western blots, antibodies capable of detecting native PrP^{Sc} for use in FACS analysis, immunoprecipitation or *in vivo* studies have not been available. Utilising a novel recombinant immunogen several unique antibody specificities were identified and are now available. These monoclonal antibodies can react with both PrP^C and/or PrP^{Sc} in the native or denatured forms. The availability of these antibodies will be useful for basic research, diagnostics and possibly therapy.

The **NEW** rapid and sensitive PrionScreen BSE test from Roche Diagnostics uses the D-Gen ICSM18 and ICSM35 monoclonal antibodies. PrionScreen has been developed for routine BSE diagnostics and is expected to be available soon. The microplate format test has been designed for both manual and automated use to satisfy different laboratory throughput and workflow requirements.

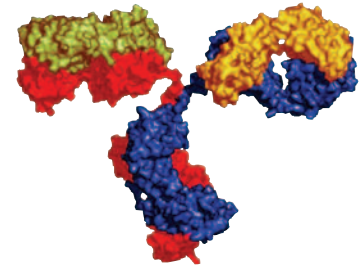


D-Gen seeks to exploit its inventions and technologies by bringing them to market through complementary collaborations and partnerships in a global context.

products

Anti-PrP monoclonal antibodies *(for research use only)*

D-Gen provides high-quality antibodies against prion proteins, which are ideally suited for immunohistochemistry, FACS analysis, ELISA, Western blotting and immunoprecipitation. Antibodies produced by D-Gen are raised against recombinant human prion proteins. The high purity of the recombinant PrP antigen as well as the culture methods used to produce the products results in antibodies of high specificity which do not cross-react with other proteins.



PrP monoclonal antibody products available from D-Gen

Description: Purified Mouse Immunoglobulin monoclonal anti-prion protein (PrP) Pack Sizes:100µg and 1mg

Name	Species Specificity	Human Specificity Native/Denatured PrP	Notes
ICSM3	Human, Cattle, Sheep, Mouse and Hamster	PrP ^C : Native and denatured PrP ^{Sc} : Denatured	Epitope not defined. Differentially distinguish between PrP glycoforms without denaturation
ICSM4	Human, Cattle, Sheep, Mouse and Hamster	PrP ^C : Native and denatured PrP ^{Sc} : Denatured	Epitope not defined. Differentially distinguish between PrP glycoforms without denaturation
ICSM10	Human, Cattle, Sheep, Mouse and Hamster	PrP ^C : Native and denatured PrP ^{Sc} : Denatured	Epitope not defined Differentially distinguish between PrP glycoforms without denaturation
ICSM15	Human	PrP ^C : Native and denatured PrP ^{Sc} : Denatured	Epitope not defined
ICSM18	Human, Cattle, Sheep, Mouse and Hamster	PrP ^C : Native and denatured PrP ^{Sc} : Denatured	Epitope within sequence 143-153 human PrP Particularly useful for mouse PrP
ICSM35	Human, Cattle, Sheep, Mouse and Hamster	PrP ^C : Native and denatured PrP ^{Sc} : Native and denatured	Epitope within sequence 93-102 human PrP

services

Provision of a range of services from prion reduction studies, in process validation and contract sample testing using technologies like the SC assay, Western blots and transgenic mice bioassays is being planned. Developments as they occur will be posted on our website. For full details on our products and services please refer to our website

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The logo for D-Gen, featuring the text "D-Gen" in a bold, white, sans-serif font inside a dark blue rounded rectangle.

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A company incorporated in England No: 3670478