CDMRP
Department of Defense

National Prion Research Program

Vision
To eliminate the occurrence of human transmissible spongiform encephalopathies.

Mission
To develop a diagnostic test to detect the presence of prion disease.

History

The Department of Defense National Prion Research Program (NPRP) was established in fiscal year 2002 (FY02) by Joint Appropriations Conference Committee Report No. 107-350, which provided $42.5 million for research on prion disease. The Senate Appropriations Committee Report No. 107-109 also specified that "the priority goal of the [program's] first phase is to rapidly develop a diagnostic test to detect the presence of prion disease." The Congressionally Directed Medical Research Programs (CDMRP) was established within the U.S. Army Medical Research and Materiel Command (USAMRMC) to manage programs such as the NPRP that were specified by Congress.

After receipt of the FY02 appropriation for research on prion disease, a stakeholders meeting was held in May 2002 in which military, scientific, regulatory, industry, and public health stakeholders provided input on the major issues in transmissible spongiform encephalopathies (TSE) research. A smaller programmatic advisory group, called the Integration Panel, was then assembled to recommend the program's vision and investment strategy.

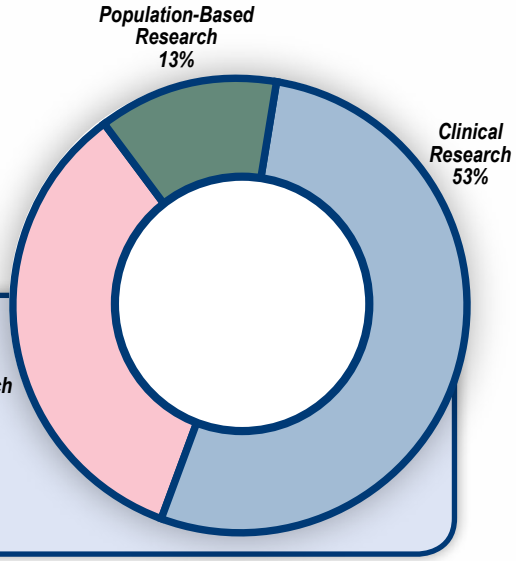
The NPRP supported 38 awards across two training award mechanisms and two research award mechanisms. Awards were made using a two-tier review process composed of peer and programmatic reviews to ensure scientific merit and attainment of program goals. Additional information about the CDMRP and the two-tier review system can be accessed at http://cdmrp.army.mil/.

Program Outcomes

The outcomes of the NPRP-funded research can in part be gauged by the number of resultant publications (169), abstracts/presentations (222), and patents (20) reported to date by the awardees. Projects funded by this program span prevention, transmission, and pathogenesis of TSE research, and the program's portfolio is illustrated in the figure at right. Details on each award funded are located on the CDMRP website under Search Awards at http://cdmrp.army.mil/.

NPRP-Supported Initiatives

Consistent with congressional intent, researchers funded by the NPRP sought to develop a diagnostic test for the detection of prion diseases. Prion diseases are a family of progressive neurodegenerative disorders that affect both humans and animals. Prion diseases in humans, while relatively rare, typically manifest as progressive



FY02 NPRP Portfolio by Research Area

Population-Based Research (13%)
- Research Resources (8%)
- Epidemiology (5%)

Clinical Research (53%)
- Detection and Diagnosis (45%)
- Clinical and Experimental Therapeutics (5%)
- Primary Prevention (3%)

Basic Research (34%)
- Cell Biology (13%)
- Genetics and Molecular Biology (8%)
- Immunology (8%)
- Pathobiology (5%)

dementia as well as impaired coordination resulting in death. Prion diseases have been well documented in hoofed animals also presenting with impaired coordination. Transmission of prion disease from cattle ("mad cow disease" or transmissible bovine spongiform encephalopathy) to humans (variant Creutzfeldt-Jakob disease, CJD) has been documented; however, a definitive diagnosis of prion diseases can only be made at autopsy. The ability to detect prion diseases in living animals and people is essential.

- NPRP-supported investigator Dr. Man Sun Sy sought to better understand the biology of prion proteins, the pathogenesis of prion disease, and the development of an assay to detect infectious prion. These efforts resulted in the publication of over 20 journal articles that were partially or entirely supported by the NPRP. Significant findings include the development of a sensitive in vitro assay, termed Am-A-FACTT, which detects prion aggregates in the blood of infected but asymptomatic mice and the detection and quantification of infectious prion proteins in infected human brains.

- NPRP-supported researcher Dr. Richard Rubenstein sought to develop an antemortem test for prion diseases regardless of the presence of symptoms. He developed and validated an ultrasensitive assay termed SOFIA (surround optical fiber immunoassay) to detect the abnormal isoform of the prion protein associated with prion diseases. This new technology combines an immunocapture assay in combination with a uniquely designed, highly sensitive fiber optical-based laser-induced fluorescence detection scheme. Results indicate that SOFIA represents a sensitive assay suitable as a platform for antemorten detection of prion diseases in biological fluids.

- NPRP-supported investigator, Dr. Stanley Prusiner, whose earlier work on the discovery of prions led to a Nobel Prize, sought to advance the understanding of the biology of prion disease progression as well as establish new diagnostic protocols. With support from the NPRP, Dr. Prusiner identified more than 50 unique, putative biomarkers for end-stage prion disease in the mouse brain. He also found that peripheral granulocytes, monocytes, T cells, platelets, and B cells of patients with sporadic, clinical prion disease (i.e., sporadic CJD) do not carry detectable levels of the disease-causing isoform of the prion protein called PrP^{Sc}. Further, he created a highly sensitive immunoassay for detecting PrP^{Sc} in human tissues. While the high sensitivity of the PrP^{Sc} immunoassay facilitated studies on the pathogenesis of prion disease in humans and animals, it was unable to distinguish blood samples from sporadic CJD patients and controls. Whether using biomarkers other than PrP^{Sc} will be a more successful approach to identifying living people with prion disease remains to be established.