U.S. Department of Health and Human Services/Food and Drug Administration:
Neurodegenerative Diseases

Using mouse models of neurodegeneration disease in the aging brain, we showed that loss of normal connections between neurons precedes nerve death; and we are studying the impact of accumulating abnormal protein deposits in neurodegenerative disease.

Lead Agency:

U.S. Department of Health and Human Services (HHS), Food and Drug Administration (FDA)

Agency Mission:

The FDA is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation. The FDA is also responsible for advancing the public health by helping to speed innovations that make medicines and foods more effective, safer, and more affordable; and helping the public get the accurate, science-based information they need to use medicines and foods to improve their health.

Principal Investigator:

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Partner Agencies:

Center for Biologics Evaluation and Research (CBER)
Office of Blood Research and Review (OBRR)
Division of Emerging and Transfusion-Transmitted Diseases (DTTD)
Laboratory of Bacterial, Parasitic and Unconventional Agents (LBPUA)
National Institutes of Health (NIH), USA
Biotechnology and Biological Sciences Research Council (BBSRC), UK

General Description:

Transmissible spongiform encephalopathies (TSEs or prion diseases) are neurodegenerative diseases that affect humans and animals. The most common human TSE is Creutzfeldt-Jakob disease (CJD), which the Centers for Disease Control and

Prevention estimates strikes about one in 9,000 persons. Patients with TSEs become progressively demented and develop movement disorders.

Although TSEs are different from the more common Alzheimer's disease (AD), doctors sometimes find it difficult to tell the two diseases apart. Patients with AD tend to survive much longer; and unlike CJD, AD is not associated with a transmissible agent that could infect others. Therefore, it is critical to develop better criteria to diagnose the two dementing diseases of adults correctly.

Investigators in LBPUA, DETTD, OBRR, CBER, FDA, developed a quantitative system that might assist in the laboratory diagnosis of TSE. Currently, under the auspices of the National Institute of Allergy and Infectious Diseases (NIAID) interagency agreement, we are leading a project entitled "Potential of Candidate Cell Substrates for Vaccine Production to Propagate the Agents of Transmissible Spongiform Encephalopathies." In both TSEs and AD, aggregates of abnormally folded proteins called "amyloids" (that in some instances form microscopically visible plaques) accumulate in the brain—prion protein (PrP) in CJD and Aβ protein in AD. It has long been thought that amyloid plaques are accumulations of toxic proteins that cause neurodegeneration. A collaborative research project between an FDA staff member with investigators from Indiana University, Washington University, and the University of Edinburgh (funded in part by NIAID-NIH-FDA Interagency Agreement [see above]), has developed lines of transgenic mice with various genetic mutations implicated in the pathogenesis of some TSEs. These mice have already yielded useful information for better understanding basic mechanisms of human neurodegenerative diseases. Recent results indicate that specific alterations in connections between nerve cells of the brain (synaptic damage) preceded cell death and might be a common feature in the pathogenesis of neurodegenerative diseases. Others have proposed that, because some degenerating nerve cells show evidence of the phenomenon termed programmed cell death ("cell suicide") or apoptosis, treatments to inhibit apoptosis might be clinically useful. However, we found that such treatments failed to rescue mice with neurological disease. Thus, it seems unlikely that anti-apoptotic therapies alone will have a beneficial effect in human neurodenerative diseases unless combined with other treatments aimed at preventing synaptic damage and neuronal dysfunction. In a related project, we found that substantial amounts of amyloid proteins accumulated in brains of transgenic mice that developed no overt illness, no tissue changes of "spongiform" degeneration—the pathologic hallmark of TSEs—and contained no transmissible infectious agent. We propose that amyloid plaques may form as part of a "*protective*" mechanism that sequesters small toxic proteins; if that is true, then therapies designed to disrupt amyloid plaques might paradoxically enhance disease rather than reversing it. We are now investigating abnormalities in the brain that take place early in the course of neurodegeneration, seeking both a better understanding of the process and more promising targets for possible therapy.

Excellence: What makes this project exceptional?

This research program is based on our previous work (published in peer-reviewed, high-impact scientific journals) that showed that transgenic mice we developed have faithfully

reproduced some of the same clinical and pathologic features found in patients with dementing diseases of aging. The ongoing research program takes advantage of a close collaboration between laboratories at FDA and academic institutions in the United States and the United Kingdom. The importance of our published studies was recently recognized by the editorial board of the Proceedings of the National Academy of Science, USA, which selected a publication for special editorial comment in the area of neuroscience.

Significance: How is this research relevant to older persons, populations and/or an aging society?

Converging lines of evidence suggest that progressive accumulation of misfolded proteins in the brain plays a central role in causing neurodegenerative diseases of aging, such as Alzheimer's disease, as well as some forms of transmissible spongiform encephalopathies. Our work is shedding light on the causes of those diseases and suggesting new ways to treat them.

Effectiveness: What is the impact and/or application of this research to older persons?

A number of important questions about neurodegenerative diseases affecting older people cannot be answered by studies in cell culture systems and require animal models. We developed several lines of transgenic mice as models for human neurodegenerative diseases in which abnormal forms of prion protein accumulate in the brain. Those models have been useful for better understanding basic processes causing neurodegeneration and offer an opportunity for testing effects of new therapies.

Innovativeness: Why is this research exciting and newsworthy?

Our work challenges the long-held assumption that amyloid plaques are toxic and trigger the neurodegeneration that ultimately damages the aging brain. Instead, our findings suggest those conclusions might not be true.

Future studies aim to better explain the basic mechanisms of amyloid formation and neuronal cell death and to seek new targets for therapeutic intervention in neurodegenerative diseases of the aging brain.