CJD 2012
and the
Tenth Annual CJD Foundation
Family Conference

Summary of Scientific Proceedings

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Welcome

• CJD 2012 and Tenth Anniversary CJD Foundation Family Conference

• Learn about etiology of prion diseases from leading researchers in the field

• Input from family members and attendees worldwide

• Thanks to the ‘perfect team’:
  – Board of Directors
  – Organizers
  – Sponsors
  – Speakers
  – Participants
Conference Co-Chairs

Pierluigi Gambetti and Florence Kranitz
Keynote Address
First step in dealing with disease is to understand the problem: prion diseases involve misfolding of proteins in the brain.

Each brain cell contains billions of proteins (the chemical ‘machines’ of our body, regulating physiological function).

Proteins need to ‘fold themselves’ from a long chain to a precise structure to do perform their jobs.

Despite physiological quality control functions in the body, protein misfolding can lead to dysfunction and disease.

Misfolded proteins, or prions, can be infectious, with little immune response by the host.

Prions can ‘replicate’ through propagated misfolding.
• Rapid, sensitive tests for infection will facilitate early treatment

• Real-time quaking-induced-conversion (RT-QuIC) based on fluorescence detection of PrP amyloid: add potentially infectious PrP\textsuperscript{C} normal PrP protein, and measure fluorescence

• Extremely sensitive assay, with up to 1 billion fold amplification of infectious agent

• Test being adapted to test for vCJD, sCJD, gCJD, sheep scrapie, deer/elk CWD, and rodent adapted scrapie
• Can use CSF, nasal fluids, plasma as the basis for the test
• Human sCJD samples have shown 85%-89% sensitivity and 100% specificity
• Positive results currently may not occur until onset of early clinical signs
• Infectivity detected in nasal fluids from hamsters – can nasal fluids be used to test for CJD in humans?
• Blood may be used for testing, after concentration of infectivity: early results in hamsters suggest detection may be possible before onset of clinical signs
• Human plasma samples spiked with infectious material has shown positive results
New Discoveries
• Common mechanistic elements between Alzheimer’s disease (AD) and CJD
• Brain imaging can identify changes *two decades* before clinical symptoms occur
• Primary pathological feature of AD is the formation of sticky ‘amyloid plaques’, called Aβ
• AD associated with inability to clear amyloid from the brain (clearance mechanisms become progressively less efficient with age)
• ApoE protein is a key component of clearance
• *Key idea: Can we stimulate production of ApoE to prevent AD?*
• Existing FDA approved drug Bexarotene is known to stimulate ApoE production
• Experiments in mice have demonstrated that Bexarotene can restore cognitive function, by accelerating Aβ clearance, even in aged animals
• *Randomized clinical trial with AD patients treated with Bexarotene expected to begin in September, 2012*
• Bexarotene may be relevant to CJD and other neurodegenerative diseases, by suppressing glial inflammatory response and other neuroprotective actions
- New Prion Research Center recently established at Colorado State University
- Prions, which are devoid of informative nucleic acid, differ from all other infectious agents
- Prions propagate through in a ‘pseudo infectious process’ bases on formation of conformational copies of misfolded protein
- Research program focuses on species barriers and strains of infectious prions
- Prions may change their properties through species propagation
- Different strains can have different biological effects
• Prions may change their properties through species propagation

• Different strains can have different biological effects

• Use genetically modified (‘transgenic’) mice to understand the molecular mechanisms underlying prion disease

• Express gene for human prion protein in transgenic mice, rendering them susceptible to prion disease
Glenn Telling, Colorado State University

*Chronic Wasting Disease (3/4)*

- Fort Collins is ‘epicenter’ of chronic wasting disease, which has now spread to Canada and South Korea

- Transgenic mice expressing deer or elk prion protein became susceptible to prion disease: *mice inoculated with brain and muscle tissue from CWD infected deer developed prion disease*

- Different CWD strains demonstrate different incubation times (CWD1 and CWD2 have short and long incubation times)
Can CWD prions cause prion disease in humans?

Studies with ‘humanized’ transgenic mice have demonstrated transmission upon intra-cerebral inoculation with mixture of CWD1 and CWD2, although not all mice responded and pathology did not correspond to human disease.

Current research focus on use of cell cultures, to circumvent the time and cost associated with the use of transgenic animals.
Emiliano Biasini, Boston University

*Novel Anti-Prion Compounds (1/2)*

- Distinguish between prion toxicity from infectivity
- Normal form of prion protein appears to be involved in prion pathology, in addition to the infectious form (interaction between normal and infectious form)
- Normal prion protein can be a ‘toxic receptor’ for other aggregates, such as amyloid Aβ
- Function of normal prion protein remains unknown
Dr. Biasini presented on the development of a novel anti-prion compound. The drug-based cell assay (DBCA) was developed for robotic high throughput screening of toxicity of prion proteins in vitro. The assay can be used to identify compounds that inhibit toxicity of toxic prion protein mutants, referred to as 'anti-prion' compounds. Out of 61 molecules tested, 24 showed potent preventive action. Some newly identified compounds may prove effective in blocking both infectivity and toxicity in vivo.
Use of Zebra Fish to Study PrP Function (1/2)

- Zebra fish used as a new model to understand how PrP can lead to neurodegeneration
- Neurodegeneration caused by misfolded prion protein requires the presence of normal prion protein
- Research question: What is the role of normal prion protein in biological function?
- Zebrafish have large numbers of transparent embryos, that develop externally
- In vitro studies have shown that normal prion protein (PrP) facilitates cell-to-cell communication and interaction
• Embryonic neurons need PrP-2 to develop normally

• PrP-2 controls the development and function of motor neurons

• Adding exogenous PrP can be neurotoxic

• Zebrafish can be used to identify specific neurotoxic PrP mutants, and understand molecular mechanisms of neurodegeneration
• Unusual patterns of CJD observed in Orava in Slovakia
• Research question: are these patterns due to exogenous (environmental, zoonotic) or endogenous (genetic) factors?
• Occurrence of genetic TSEs much higher in Slovakia (nearly 70% of all TSEs) than in Europe (approximately 10%) generally
• Clusters of E200K mutation seen in Slovakia and in some other countries
• Up to 2008, incidence of gCJD never exceeded 1.66 per million, doubled in 2009, and subsequently decreased
Eva Mitrová, Slovak Medical University

*Incidence of CJD with the E200K Mutation (2/3)*

- Genetic testing performed in 234 CJD patients and 426 relatives: E200K mutation present in 184 (67.9%) patients and 151 (35.5%) of relatives
- Earlier age at onset was observed in successive generations of E200K carriers
- Results inform the optimal age at which preventive doxycykline treatment should be started
- Although clinical results are available on only 5 patients to date, 2 patients appeared to demonstrate increased survival
Eva Mitrová, Slovak Medical University

*Incidence of CJD with the E200K Mutation (3/3)*

- Prevalence of E200K estimated to be 1.9 and 5.2/million in two gCJD focal areas, respectively, but only 0.5/million in extra-focal areas

- Recommend informing carriers of E200K about the limited clinical results of doxycycline (results may be inconclusive at this stage, but the drug is non-toxic)
Surveillance
Robert G. Will, University of Edinburgh

*European Surveillance Overview (1/3)*

- 10,435 CJD cases identified from 1993-2011, mostly sporadic
- Of the 226 vCJD cases, 173 occurred in the UK
- Of three US vCJD cases, 2 may have originated in the UK and 1 in Saudi Arabia
- Two new cases of vCJD occurred in France in 2012 (aged 20 and 24, possibly reflecting increased susceptibility at younger ages)
- vCJD peaked in 1999, and has been declining since
- Small numbers of cases may occur for some time to come
• sCJD incidence in the UK is about 1 per million population annually (very comparable to that in other countries worldwide)
• Slight increasing trend since 1990 may be attributable to better diagnosis
• Since a similar trend occurred in Australia, a country without BSE, the UK trend is not likely related to BSE
• RT-QuIC appears potentially useful in confirming diagnoses of CJD (validation study currently in progress in the European Union)
• Systematic review of case-control studies of sCJD cases has not revealed specific risk factors for this disease (confirming the hypothesis not caused by an acquired infection)
• Large case-control study of occupation has not indicated that doctors are at increased risk
• At present, there is no evidence that CJD is transmissible
• Although BSE epidemic in the UK resulted in 3,000 cases per week at its peak, only 6 cases occurred in 2011 – there is a risk that support for prion disease research may be reduced as a consequence
Pierluigi Gambetti, National Prion Disease Pathology Surveillance Center

_U.S. Prion Disease Surveillance and Autopsy (1/2)_

- Center set up to confirm clinically diagnosed cases through Western blot, immunohistochemistry, histology, and PrP gene sequencing

- Combination of all these factors leads to a final diagnosis

- Tissue from 4,520 cases have been examined by the at date; 2,674 have been confirmed as being prion disease (mostly sporadic, 389 familial, 6 iatrogenic, and 3 (imported) cases of vCJD
- CSF samples are also examined - currently introducing RT-QuIK to analyzing these samples
- CSF 14-3-3 and TAU tests will help to resolve ambiguous autopsy cases (autopsy rate is increased to 80% in CSF positive/ambiguous cases)
- Recent study did not demonstrate urine from sCJD cases was infectious in inoculated mice (this does not rule out infectivity, but indicates infectivity, if any, would be small)
- Although US Prion Disease Pathology Surveillance Center remains active despite reductions in funding, the future of the Center is uncertain
our program continues after the break