Cambridge Healthtech Institute’s 12th Annual

Transmissible Spongiform Encephalopathies

February 11-12, 2008
Sheraton Inner Harbor Hotel
Baltimore, MD

THE DEFINITIVE AMERICAN TSE MEETING

Featuring New Data

• Emerging Concerns: De novo Formation of Prions
• Pathogenesis
• Detection
• Cell Cultures: From the Bench to the Bed
• Treatment, Removal, or Inactivation

Hear From These Leading Organizations

Rocky Mountain Laboratories - NIH
Case Western Reserve University
Warwick University
Neurological Institute “Carlos Besta”
Amorfix Life Sciences
R-Biofarm AG
CJD Surveillance Unit - Edinburgh
University of Milan
University of California - San Francisco
University of Maryland and VA Medical Center
Istituto Superiore Di Sanita
....and many others

Lead Sponsoring Publications:

www.healthtech.com/2008/TSE
CHI’s Transmissible Spongiform Encephalopathies” is the longest running meeting of its kind in the world. This 12th Annual meeting will address the ongoing progress in the science of prion diseases, as well as the newest developments in the fields of pathophysiology, transmission, detection, removal/inactivation, treatment, and prevention. This conference will present the newest data on TSEs in the context of its application to the pharmaceutical, biological, environmental and device industries.

Scientific Advisors:
Larisa Cervenakova, M.D., Ph.D., Senior Scientist, Transmissible Diseases Department, Holland Laboratory, American Red Cross
Suzette A. Priola, Ph.D., Senior Investigator, Chief, TSE/Prion Molecular Biology Section, Laboratory of Persistent and Viral Diseases, Rocky Mountain Laboratories, NIH

Monday, February 11, 2008
7:00 am Registration and Morning Coffee

Emerging Concerns: De novo Formation of Prions

8:00 Welcome by Session Chairperson
Paul W. Brown, M.D.

8:15 Ultra-Sensitive Prion Assays Based on Seeded Conversions of Recombinant Prion Protein
Byron W. Caughey, Ph.D., Senior Investigator, Laboratory of Persistent Viral Diseases, Rocky Mountain Laboratories, NIH

PrPSc can seed the conformational conversion and polymerization of normal protease-sensitive prion protein (PrP-sen). Soto and colleagues have shown that this seeding activity allows ultrasensitive detection of prions using cyclical sonicated amplification (PMCA) reactions and brain homogenate as a source of PrP-sen. Building on the PMCA approach, we have developed faster, simpler prion detection methods using recombinant PrP-sen (rPrP-sen) which can discriminate normal hamster brain homogenates from scrapie brain homogenates containing <1 intracerebral lethal dose within 2-3 days. In periodically sonicated or shaken cell-free reactions, sub-femtomolar equivalents of PrPSc seeded the conversion of rPrP-sen into easily detected quantities of specific protease-resistant PrP fibrils. Diseased and normal hamsters were also distinguished using 2-μl of cerebral spinal fluid as seeds. The relative speed, simplicity, replicability and sensitivity of these reactions should facilitate both the development of practical prion assays and structural analyses of prion-seeded PrP polymers.

8:40 De Novo Formation of Purified Native Prions
Nathan R. Deleault, Ph.D., Department of Biochemistry, Dartmouth Medical School

To study the mechanism of prion formation biochemically, we conducted a series of serial Protein Misfolding Cyclic Amplification (sPMCA) reactions using purified native PrPC and synthetic polyanionic molecules as substrates. For the first time, we demonstrate that infectious, wild type prions can be: (1) propagated in vitro using purified substrates, and (2) generated de novo from non-infectious components. Furthermore, we have observed that polyanionic molecules are selectively incorporated into physical complexes with PrP during the formation of purified prions in vitro.

9:05 De novo Generation of Prion Infectivity in a Cell-Free System
Joaquin Castilla, Ph.D., Assistant Professor, Department of Infectology, Scripps Research Institute-Florida

Transmissible spongiform encephalopathies (TSEs) are a group of neurodegenerative disorders affecting both humans and animals. There is no available treatment or therapy for these fatal diseases. The infectious agent associated with TSEs (termed prion) appears to be composed uniquely of a protein, which is a conformationally-modified version (PrPSc) of the cellular prion protein (PrPC). The disease is propagated by the conversion of host PrP into PrPSc induced by small quantities of PrPSc. Interestingly, prions occur in the form of different strains that show distinct biological and physicochemical properties. TSEs can have diverse origins, including genetic, sporadic (putatively spontaneous) and infectious. The occurrence of sporadic cases of prion diseases in humans and maybe in other species, i.e. atypical bovine spongiform encephalopathy (BSE) in European and USA cattle and atypical scrapie cases in sheep suggest that spontaneous prion diseases may happen infrequently but ubiquitously. However, there are no reported cases of spontaneously-occurring prion disease in experimental wild-type rodent models. We have used a novel technique, Protein Misfolding Cyclic Amplification (PMCA) to rapidly propagate prions in the test tube, using normal brain homogenate as substrate. Prions propagated in vitro are infectious in vivo and maintain their prion strain specificity. PMCA has been used to efficiently amplify a variety of prion strains from mouse, hamster, bank vole, deer, cattle, sheep and human. Therefore, to mimic spontaneous generation of infectivity in vitro becomes one of the most important challenges in the prion field. We show here, for the first time, the de novo generation of infectious prions from bank voles (Clethrionomys glareolus) starting with non-infectious brain homogenates. Several biochemically different prion strains were generated using two different wild-type vole genotypes. The de novo in vitro generated PrPSc was highly infectious after its inoculation in bank voles. We show an extensive characterization of this “spontaneous” phenomenon.

9:30 PMCA Amplification of Prion Amyloid without Amplification of Infectivity
Robert G. Rohwer, Ph.D., Director, Molecular Neurovirology Laboratory, Veterans Affairs Medical Center; and Associate Professor of Neurology, School of Medicine, University of Maryland at Baltimore

Employing the original protocol for PMCA developed by Soto and colleagues, we obtained a 16 to 32 fold amplification of PK resistant PrP as determined by two fold serial dilution to the starting concentration on Western blot. In comparison, there was no difference in titer, as measured by limiting dilution titration, between the frozen control, a sample that was incubated at 37°C without sonication and the sonicated sample that produced the amyloid amplification. The limiting dilution titration method is sufficiently sensitive to have detected even a 20% difference in titer between the samples. A two fold increase in titer would have caused the infection of nearly every animal at the limiting dilution and could not have been missed. If there is amplification of infectivity during PMCA, it must follow very different kinetics from the amyloid.

9:55 Silent Prions in Normal Brains
Wen-Quan Zou, M.D., Ph.D., Assistant Professor, Neuropathology, Case Western Reserve University

The co-existence of cellular prion protein (PrPC) and its pathological isoform (PrPSc) is a prerequisite for the pathogenesis of prion diseases. However, molecular mechanism of PrPSc formation in the spontaneous prion diseases including sporadic and familial forms remains poorly understood. Our recent studies indicate that in the uninfected brain there are small amounts of abnormal PrP species that may be involved in the pathogenesis of spontaneous prion diseases.
The origin of the causal agent is still unknown. This issue is of fundamental importance, since knowledge of the origin of the BSE agent is essential for prevention of future outbreak of the disease or variants thereof in cattle and other mammals. We carried out transmission studies with transgenic mice expressing bovine PrP and four lines of non-transgenic mice and found that an atypical form of spongiform encephalopathy of cattle, termed BASE or BSE-L, is caused by a prion strain distinct from that of classical BSE. Noteworthy, this newly characterized prion strain has the ability to convert into the classical BSE strain upon serial transmission to inbred mouse lines. According to these results, BASE—which is regarded as a sporadic form of prion disease in cattle—may be the origin of BSE, following conversion of the causal agent in an intermediate host.

The identification of forms of TSE diseases in cattle caused by prion strains different from BSE has raised new concerns on the possibility that these novel agents might induce disease in humans with a phenotype resembling sporadic CJD. The analysis of the distribution of the different molecular subtypes of sporadic CJD might give some answers.

Mortality from variant CJD continues to decline, but concerns for public health persist. These are based on uncertainty on the population prevalence of infection, the incubation period of vCJD and the potential for further cases of secondary transmission. Information from epidemiology, molecular biology and transmission studies may provide new insights into these issues.
Tuesday, February 12, 2008

8:30 am  Morning Coffee

**Cell Cultures:**
**From the Bench to the Bed**

9:00  Comments by Session Chairperson
Suzette Priola, Ph.D.

9:05  Exploring Pathogenesis in Cell Culture
Suzette A. Priola, Ph.D., Senior Investigator, Chief, TSE/Prion Molecular Biology Section, Laboratory of Persistent and Viral Diseases, Rocky Mountain Laboratories, NIH

The early events that occur during TSE infection are largely unknown. Using a tissue culture system that enables us to exclusively track abnormal prion protein (PrPSc) during acute exposure of cells to TSE infectivity, we have studied the initial interaction between PrPSc and the cell. Our data suggest that early events during TSE infection may be largely strain and cell-type independent. Understanding the acute stages of TSE infection may provide new targets and strategies for TSE prevention and/or therapeutics as well as advance our knowledge of basic TSE pathogenesis.

9:30  Talk Title to Be Announced
Larisa Cervenakova, M.D., Ph.D., Senior Scientist, Transmissible Diseases Department, Holland Laboratory, American Red Cross

9:55  Clearance and Prevention of Prion Infection in Cell Culture by Anti-PrP Antibodies
Thomas M. Wisniewski, M.D., Professor, Neurology, Pathology and Psychiatry, New York University School of Medicine

10:20  Discussion with All Session Speakers

10:35  Coffee Break, Poster and Exhibit Viewing

**Treatment, Removal, or Inactivation**

Chairperson: Robert G. Rohwer, Ph.D., Director, Molecular Neurovirology Laboratory, Veterans Affairs Medical Center; and Associate Professor of Neurology, School of Medicine, University of Maryland at Baltimore

11:05  Anti-TSE Immunization in a Hamster Model
Giorgio Poli, Professor, DVM, Veterinary Pathology, University of Milan

Vaccination has been shown to be effective in mouse models for neurodegenerative conditions characterized by protein misfolding, such as Alzheimer’s disease (AD) and Transmissible Spongiform Encephalopathies (TSEs) and many different immunogens and strategies of intervention have been proposed. Here we show that the immunization of hamster with a synthetic oligopeptides Prp 119-146, corresponding to the central part of hamster prion protein, prolonged the survival time (>23 days) in animals challenged with the 263K strain of scrapie agent. The immunized hamster mounted a specific, but weak, antibody response, and developed also a specific cell-mediated response (as shown by proliferation assay on splenocytes). Moreover, the results obtained with RT-Real Time PCR showed an over-expression of mRNA for GFAP and pro-inflammatory cytokines (TNF-a, IL-18#946;) in brain of infected controls compared to immunized animals and healthy controls, as well as an decrease in IL-10 expression. Increased survival after challenge was also associated with reduction of cerebral lesions, glial fibrillary acid protein (GFAP) and PrP deposition (both in brain and spleen). Our results indicate that a humoral and cell mediated immune response can slow down PrPres deposition and decrease neuroinflammation; nevertheless, it is conceivable that the vaccination can activate in peripheral organs specific different and interacting mechanisms, as observed in other scrapie mouse models.

11:30  Application of PRDT Affinity Binding Technology to a Reduction of Risk of TSE Transmission in the Blood and Biopharmaceutical Industry
Luisa Gregori, Ph.D., Assistant Director MNV Laboratory and Assistant Professor University of Maryland, BREF, University of Maryland and VA Medical Center

Transmissible spongiform encephalopathy (TSE) diseases are neurodegenerative illnesses that can be transmitted by blood transfusion. Precautionary measures against the spread of TSE through the blood supply have been implemented, but alone those measures are not sufficient. Pathogen Removal and Diagnostic Technologies, Inc. (PRDT) developed a new strategy based on the use of ligands derived from a combinatorial chemistry approach that specifically adsorb the TSE agent. After screening several million compounds, PRDT identified a ligand that when coupled in resin format reduced the TSE causative agent from blood to the limit of detection of a bioassay. This resin was incorporated into a prion reduction filter, the P-CAP™ filter, manufactured by MacoPharma. The product has already demonstrated utility in reducing infectivity > 3log10 (brain derived infectivity in red blood cell concentrate - RBC) and > 1.2log10 (endogenous whole blood derived infectivity).

11:55  Differential Resistance of Prions Strains to Inactivation
Kurt Giles, Ph.D., Assistant Adjunct Professor, Institute for Neurodegenerative Diseases, University of California San Francisco

Understanding prion inactivation is essential for avoiding iatrogenic transmission of CJD via surgical instruments, and ensuring the safety of the food supply. Using a range of transgenic mouse models sensitive to naturally occurring and rodent-adapted prion strains, we have determined the difference in resistance to inactivation for a range of prion strains. By applying a set of rigorous statistical approaches we have produced the most comprehensive study of prion inactivation.

12:20  Closing Comments by Scientific Advisors

12:30  Close of Conference
Sponsor and Exhibitor Information

Showcase your company’s expertise, brand your solutions and develop revenue-generating opportunities with qualified decision-makers by Exhibiting or Sponsoring. Sponsorship packages are designed to achieve your business development and networking goals and objectives. Sponsorship benefits include pre-conference, at-conference and post-conference marketing efforts. The earlier you secure your sponsorship, the more opportunity for exposure. Numerous promotional and sponsorship programs exist and are flexible to allow any size company to participate.

Sponsored speaking opportunities may include:
Technology Spotlight, embedded within the conference program
Breakfast or Luncheon Workshops, allow for podium time
Embedded Presentations

Other sponsorship opportunities include sponsoring an Invite-Only VIP dinner to access this audience at the highest level, and ensure optimum face-to-face networking.

For more information, to reserve booth space, or discuss sponsorships contact:
Katelin Martin, 781-972-5458 - kmartin@healthtech.com

Call for Posters

Reasons You Should Present Your Research Poster at Transmissible Spongiform Encephalopathies:

- Your poster will be exposed to our international delegation
- Receive $50 off your registration
- Your poster abstract will be published in our conference CD
- Your research will be seen by leaders from top pharmaceutical, biotech, academic and government institutes

Sponsoring Publications:

Web Partners:

Hotel Information

Sheraton Inner Harbor Hotel
300 S. Charles Street
Baltimore, MD 21201
Tel: 410-962-8300
Fax: 410-962-8211
Room Rate: $169 s/d
Reservation Cutoff: January 11, 2008

Car Rental Information

Special discount rentals have been established with AVIS for this conference. Please call AVIS directly at 800-331-1600 and you must reference your Avis Worldwide Discount (AWD) Number J868190.

Photo Credit: Dr. Al Jenny, 2003 (Content Providers(s): U.S. Dept. of Agriculture - Animal and Plant Health Inspection Service, APHIS)
Transmissible Spongiform Encephalopathies

February 11-12, 2008
Sheraton Inner Harbor Hotel
Baltimore, MD

YES! Register me for Transmissible Spongiform Encephalopathies

REGISTRATION INFORMATION

☐ Mr. ☐ Ms. ☐ Mrs. ☐ Dr. ☐ Prof.
Name
Job Title
Company
Address
City/State/Postal Code
Country
Telephone
Email*

Would you like to receive event updates via fax? ☐ Yes ☐ No Fax

*Email is not a mandatory field. However, by excluding your email you will not receive notification about online access to pre-conference presenter materials, conference updates and networking opportunities.

PAYMENT INFORMATION

☐ AMEX (15 digits) ☐ Visa (13-16 digits) ☐ MasterCard (16 digits) ☐ Diners Club (14 digits)

Card #
Exp. Date

Cardholder
Signature

Cardholder’s Address (if different from above)
City/State/Postal Code
Country

Please refer to the Keycode below:

TWO-DAY CONFERENCE

Advanced Registration until January 11, 2008 ☐ $1195 ☐ $620
Registration after January 11, 2008 or On-Site ☐ $1395 ☐ $695

Poster Discount ☐ $50 Off ☐ $50 Off

Present a Poster and Save $50!

Cambridge Healthtech Institute encourages attendees to gain further exposure by presenting their work in the poster sessions.

To secure a poster board and inclusion in the conference CD, your abstract must be submitted, accepted and registration paid in full by January 23, 2008. Register online to use the Poster Abstract Submission form or, if you register by phone, fax, or mail, you will receive Poster Abstract Submission guidelines via email.

I am interested in presenting a poster at ☐ Transmissible Spongiform Encephalopathies and will submit a completed one-page abstract by January 23, 2008 (Please Note: Registration must be paid in full to present poster.) Title

CHI insight Pharma Reports

A series of reports that evaluate the salient trends in pharmaceutical technology, business, and therapy markets. Keep abreast of the latest advances in pharmaceutical R&D, their potential applications and business impacts, and their current and future position in the marketplace. For a list of reports, visit Insightpharma.com, or contact Rose LaRaia, rlraia@healthtech.com, 781-972-5444.

Additional Registration Details

Each registration includes all conference sessions, posters and exhibits, food functions, and a copy of the conference CD.

Group Discounts

Special rates are available for multiple attendees from the same organization. Contact David Cunningham at 781-972-5472 to discuss your options and take advantage of the savings.

Handicapped Equal Access

In accordance with the ADA, Cambridge Healthtech Institute is pleased to arrange special accommodations for attendees with special needs. All requests for such assistance must be submitted in writing to CHI at least 30 days prior to the start of the meeting.

Substitution/Cancellation Policy

In the event that you need to cancel a registration, you may: Transfer your registration to a colleague within your organization Credit your registration to another Cambridge Healthtech Institute program Request a refund minus a $100 processing fee per conference Request a refund minus the cost ($250) of ordering the conference CD.

NOTE: Cancellations will only be accepted up to two weeks prior to the conference.

Program and speakers are subject to change. Video and audio recording of any kind is prohibited onsite at all CHI events.

Cambridge Healthtech Institute
250 First Avenue, Suite 300, Needham, Massachusetts 02494
T: 781-972-5400 or toll-free in the U.S. 888-999-6288
F: 781-972-5425 • www.healthtech.com