

**FOURTH GORDON RESEARCH CONFERENCE ON CAG TRIPLET REPEAT
DISORDERS-2007
SUMMARY OF THE CONFERENCE**

Diane Merry (Chair) and Jang-Ho Cha (Vice-chair)

The fourth Gordon Research Conference was held at Centre Paul Langevin, Aussois, France from May 13-18, 2007. In keeping with the spirit and philosophy of the Gordon Research Conferences, this provided a relatively isolated site, at which the conferees stayed together for the duration of the meeting and there was ample time for informal interactions to occur. Indeed, this site selection succeeded in the goal of having conferees remain for the entire week.

In order to encourage the presentation of unpublished data, Gordon Research Conferences operate an “off the record rule.” Any information presented at the Gordon Research Conference, whether in a formal talk, discussion or poster session is a private communication and is presented with the restriction that it is not for public use; printed reference to Gordon Research Conference oral presentations, posters and discussions are prohibited. Therefore, references in the following report to the information presented at the meeting will be kept to generalities and specific information will be mentioned only if it has already been published.

The program consisted of four and one-half days of scientific presentations organized into nine formal sessions and a keynote address given by Chris Ross on the evening session of the last day. In addition, more than 90 posters were presented in four poster sessions from Monday-Thursday afternoons from 4:00-6:00 p.m. The poster sessions continued in the evenings after the evening session concluded. These were presented enthusiastically by scientists at all stages of their careers and provided an excellent forum for sharing new data and establishing new collaborations. Early afternoons were dedicated to informal interactions and additional poster viewing.

The response from the conferees to all aspects of the conference was overwhelmingly enthusiastic. Evaluations showed an overall conference score of 1.3 out of 5.0 (84% conferees responded). Papers describing data presented at the conference are in the publication stage at this time; whether new grants emerge which include ideas emanating from the conference is unknown at this time. The conferees unanimously supported the development of another CAG Triplet Repeat Disorder GRC, and elected Drs. Jang-Ho Cha and Laura Ranum as the Chair and Vice-chair, respectively. This conference, pending approval from the GRC, is anticipated to take place in 2009.

Scientific Program

The scientific program is included on the following pages. The major focus of the 2007 conference was to examine mechanisms that were common to multiple CAG repeat disorders as well as to present new information on specific disorders. As with previous CAG Triplet Repeat Disorder Gordon Research Conferences, the sessions included clinical pictures of disorders, neuropathological alterations, mechanistic insights and new preclinical therapeutic advances. The conference began by addressing the clinical and pathological aspects of the polyglutamine diseases; however, while in previous meetings a talk was presented on neuropathology using histological approaches, in this meeting we instead had a talk from Dr. Diana Rosas focusing on pathological changes observed with the newest imaging technology.

The succeeding sessions focused on basic science aspects of disease, highlighted progress in understanding the molecular basis of diseases and dealt finally with translational research and experimental therapeutics. The Gordon Research Conference format allows a relatively small number of formal presentations, with the intention of dedicating large amounts of time to structured discussion. We set one session aside for late-breaking presentations in which several shorter talks were presented, as we felt it was important to give exceptional young investigators the opportunity to orally present their work to the entire conference. In addition, we interspersed three other short presentations, primarily by younger investigators, within the formal sessions. All session speakers were allowed 30-35 minutes for their presentation, followed by 10-15 minutes of questions and discussion. Each session was then followed by a structured discussion led by a discussion leader who was an expert in the field and whose job was to crystallize the issues for that particular session. Some of the discussions were organized around controversial questions in each area. The leaders of the discussion sessions probed the most controversial aspects of polyglutamine disease pathogenesis.

SCIENTIFIC PROGRAM

CLINICAL PRESENTATION AND NEUROIMAGING

Chair: Dr. Diane Merry (Thomas Jefferson University, USA)

Dr. Nicholas Wood (National Hospital for Neurology and Neurosurgery, UK)
Clinical Correlations Of The CAG Repeat Disorders

Dr. Diana Rosas (Massachusetts General Hospital, USA)
A Window In Time: What Neuroimaging Can Tell Us About Neurodegeneration In Triplet Repeat Diseases

Structured Discussion, Leader: Dr. Kenneth Fischbeck (NINDS, NIH, USA)

CELLULAR PATHWAYS FOR FOLDING AND CLEARANCE OF POLYGLUTAMINE PROTEINS

Session Chair: Dr. Lesley Jones (Wales School of Medicine, Cardiff)

Dr. Richard Morimoto (Northwestern University, USA)
Regulation of Protein Homeostasis by Lifespan and Stress Response Pathways

Dr. Ana Maria Cuervo (Albert Einstein College of Medicine, NY, USA)
Clearance of Misbehaving Proteins by Autophagy

Dr. Paul Taylor (University of Pennsylvania, USA)
HDAC6 rescues neurodegeneration and provides an essential link between autophagy and the UPS

Dr. Dimitri Krainc (Massachusetts General Hospital, Cambridge, MA), poster presenter
Acetylation of Mutant Huntingtin is Protective in Huntington's Disease

Structured Discussion, Leader: Dr. Ai Yamamoto (Columbia University, NY, USA)

POLYGLUTAMINE DISEASE PHENOCOPIES AND PATHOGENIC MECHANISMS

Chair: Dr. Gillian Bates (King's College, London)

Dr. Russell Margolis (Johns Hopkins University, USA)
HDL2 Pathogenesis

Dr. Tetsuo Ashizawa (University of Texas Medical Branch, USA)
SCA10 Pathogenic Mechanism

Structured Discussion, Leader: Dr. Anne Young (Massachusetts General Hospital, Cambridge, USA)

POLYGLUTAMINE AND AMYLOID STRUCTURES AND IDENTIFICATION OF THE TOXIC SPECIES

Chair: Dr. Yvon Trottier (IGBMC, INSERM-CNRS-Universite Louis Pasteur, Strasbourg, France)

Dr. Paul Muchowski (Gladstone Institute of Neurological Disease, UCSF, USA)
Towards a Structural Basis of Polyglutamine Pathogenesis: From Polar Zippers to Oligomers

Annalisa Pastore (National Institute for Medical Research, London, UK)
From Ataxin-3 to Josephin: The Role of Protein Context on the Aggregation Properties of PolyQ

Dr. Dominic Walsh (University College, Dublin)
ABeta Oligomers: From Cells to Alzheimer Brain

Dr. Yoshitaka Nagai (Osaka University, Osaka, Japan), Poster presenter,
Toxic Conformers Of Soluble Polyglutamine Protein Formed In Vitro And In Vivo

Structured Discussion, Leader: Dr. Steve Finkbeiner (Gladstone Institute of Neurological Disease, UCSF, USA)

IMPACT OF NORMAL FUNCTION/METABOLISM OF POLYGLUTAMINE PROTEINS ON DISEASE

Session Chair: Dr. Angelo Poletti (Institute of Endocrinology, Milan)

Dr. Ullrich Wuellner (University of Bonn, Germany)
Phosphorylation of Ataxin-3: Clues to Localization

Dr. Michael Hayden (University of British Columbia, CA)
Protein Modification of Huntingtin: Clues to the Pathogenesis of HD

Structured Discussion, Leader: Dr. Lisa Ellerby (Buck Institute for Age Research, Novato, CA, USA)

CELLULAR SEQUELAE IN POLYGLUTAMINE DISEASE

Chair: Dr. Ruth Luthi-Carter (Swiss Federal Institute Of Technology (EPFL), Lausanne)

Dr. Leslie Thompson (University of California, Irvine)
Cellular Pathways To HD Pathogenesis; Protein Modification Of The Amino- Terminal Region

Dr. Didier Devys (CNRS/INSERM/ULP, Illkirch, France)
Dysfunction Of TFTC/STAGA Coactivator Complex In SCA7

Dr. Nico Dantuma (Karolinska Institute, Stockholm, Sweden)
The Ubiquitin/Proteasome System in Neurodegeneration

Jamie Johansen (Michigan State University, USA), poster presenter
Over-expression of wt Androgen Receptors in Skeletal Muscle Fibers Induces a Neuromuscular Disease Resembling Spinal Bulbar Muscular Atrophy (SBMA)

Structured Discussion: Leader, Dr. Anne Messer (Wadsworth Center, Albany, NY)

DYSFUNCTION OF NEURONAL CIRCUITRY

Session Chair: Dr. Marie-Francoise Chesselet (UCLA, USA)

Dr. Michael Levine (UCLA, USA)
From Genes to Circuits: Every Neuron Needs Good Contacts

Dr. Jenny Morton (University of Cambridge, UK)
Pharmacological imposition of sleep slows cognitive decline and reverses dysregulation of circadian gene expression in a transgenic mouse model of Huntington's disease

Structured Discussion: Leader, Dr. Asa Petersen (Wallenberg Neuroscience Center, Lund, Sweden)

EXPERIMENTAL THERAPEUTICS

Session Chair: Dr. Nancy Wexler (Columbia University, USA)

Dr. Flint Beal (Weill Medical College, NY)
Novel Therapeutic Approaches for Huntington's Disease

Dr. Ira Shoulson (University of Rochester, USA)
Experimental Therapeutics of Manifest and Pre-Manifest Huntington's Disease

DATA BLITZ: FOCUS ON NOVEL THERAPEUTIC STRATEGIES Chair: Dr. Beverly Davidson (University of Iowa, USA)

Dr. Miguel Diaz-Hernandez (Universidad Complutense Madrid)
Involvement Of The Purinergic System In Huntington's Disease: Development Of New Therapeutic Strategies

Dr. Anne Hart (Massachusetts General Hospital Cancer Center, USA)
Multiple Genetic Pathways Associated With Lifespan Extension Suppress Polyglutamine
Mediated Neurodegeneration In *C. Elegans*

Dr. Ben Hoffstrom (Columbia University, NY, USA)
Identification of a Novel Drug Target Using "Click-Chemistry"

Dr. Lisa Ellerby (Buck Institute for Age Research, Novato, CA, USA)
HD Target Validation: SiRNA Screens In HD Cell Culture Models

Structured Discussion and Panel Discussion: Leader, Dr. Blair Leavitt (University of British
Columbia, Vancouver).

Panelists: Dr. Bernhard Landwehrmeyer (Euro-HD)
Dr. James Wang (Cure HD Initiative)
Dr. Carl Johnson (Hereditary Disease Foundation)
Dr. Dennis Choi (Boston Univ. Medical School)

KEYNOTE ADDRESS

Chair: Dr. Jang-Ho Cha (Massachusetts General Hospital, USA)

Dr. Christopher Ross (Johns Hopkins University, USA)
Huntington's Disease: from Targets to Therapeutics