CAG Triplet Repeat Diseases: Common Principles and Unique Mechanisms

June 4 - 9, 2017

Chair
Erich E. Wanker

Vice Chair
Christopher A. Ross

Mount Snow
89 Grand Summit Way
West Dover, VT, US

Conference Description

The CAG Triplet Repeat Disorders are a group of largely untreatable, heritable neurological disorders, which result from an expansion in a CAG trinucleotide repeat in mutant genes. They include Huntington's disease (HD), spinal and bulbar muscular atrophy (SBMA, Kennedy's disease), several spinocerebellar ataxias, and dentatorubropallidoluysian atrophy (DRPLA). Extended CAG repeats in the coding regions of genes result in abnormally long polyglutamine tracts in the mutant proteins. Marked similarities in the underlying genetics and the neurological symptoms suggest common pathogenic mechanisms. Exciting new efforts to unravel these mechanisms have recently been made in the area of proteostasis research, which is of high relevance to understanding proteopathies like CAG repeat diseases. To delineate the networks of cellular homeostasis in their entirety "-omics" approaches have moved into the focus and have unraveled surprising new connections between the molecules involved in disease. Seeding and spreading of misfolded protein species have recently been recognized as perhaps highly relevant to pathogenesis. Connected to these phenomena, innovative technologies to identify relevant targets, disease markers and effective therapeutics are in development. To increase the pace of molecular discovery and to accelerate translation into the clinic, a multidisciplinary effort is required.

The 2017 Gordon Research Conference on CAG Triplet Repeat Disorders and the associated Gordon Research Seminar (GRS) will gather young investigators and established senior scientists to deliver thought-provoking lectures on the cutting edge of science. In keeping with

the Gordon Research Conference tradition, there will be ample time for structured discussions led by peers and for informal discussion and social interaction. Strong emphasis is placed on training and mentoring, and time will be devoted to career issues. All participants are required to submit posters, based on which invitations for short talks will be issued. Priority will be given to women, minorities and persons with disabilities when selecting speakers.

Related Meeting

This GRC will be held in conjunction with the "CAG Triplet Repeat Disorders (GRS)" Gordon Research Seminar (GRS). Those interested in attending both meetings must submit an application for the GRS in addition to an application for the GRC. Refer to the associated GRS program page for more information.

Conference Program

Sunday	
2:00 pm - 9:00 pm	Arrival and Check-in
6:00 pm - 7:00 pm	Dinner
7:30 pm - 7:40 pm	Introductory Comments by GRC Site Staff / Welcome from the GRC Chair
7:40 pm - 9:30 pm	**Keynote Session: Disease Mechanisms and Phenotypes** Discussion Leader: **Leslie Thompson** (University of California, Irvine, USA)
7:40 pm - 8:20 pm	**Henry Paulson** (University of Michigan Health System, USA) "CAG Repeat Diseases: Genotype-Phenotype Correlations"
8:20 pm - 8:30 pm	Discussion
8:30 pm - 9:10 pm	**Judith Frydman** (Stanford University, USA) "Protein Quality Control and Protein Misfolding in Disease"
9:10 pm - 9:20 pm	Discussion
9:20 pm - 9:30 pm	General Discussion
Monday	

7:30 am - 8:30 am	Breakfast
9:00 am - 12:30 pm	**Common Pathogenic Mechanisms in Neurodegenerative Diseases** Discussion Leaders: **Diane Merry** (Thomas Jefferson University, USA) and **Harry Orr** (University of Minnesota, USA)
9:00 am - 9:25 am	**Jeffrey Rothstein** (Johns Hopkins University, USA) "Dysfunction of Nuclear Pore Complex in Huntington's Disease and ALS"
9:25 am - 9:35 am	Discussion
9:35 am - 10:00 am	**Robert Richards** (University of Adelaide, Australia) "Autoinflammatory Disease as a Common Mechanism for Late-Onset Neurodegeneration"
10:00 am - 10:10 am	Discussion
10:10 am - 10:40 am	Coffee Break
10:40 am - 10:55 am	Selected from Poster Abstracts: **Christopher Pearson** (The Hospital for Sick Children, Canada) "Parent-of-Origin Effect for Congenital Myotonic Dystrophy"
10:55 am - 11:05 am	Discussion
11:05 am - 11:20 am	Selected from Poster Abstracts: **Anna Pluciennik** (Thomas Jefferson University, USA) "Role of USP7 in the Pathogenicity of Spinal and Bulbar Muscular Atrophy"
11:20 am - 11:30 am	Discussion
11:30 am - 11:45 am	Selected from Poster Abstracts: **Joern Huelsmeier** (Trinity College Dublin, Ireland) "Endogenous Ataxin2 CAG Repeats and Intrinsically Disordered Domains Are Necessary for RNA-Granule Formation and Olfactory Long-Term Memory"
11:45 am - 11:55 am	Discussion

11:55 am - 12:10 pm	Selected from Poster Abstracts: **Edward Wild** (University College London, United Kingdom) "Neurofilament Light Protein in Blood as a Biomarker for Neurodegeneration in Huntington's Disease"
12:10 pm - 12:20 pm	Discussion
12:20 pm - 12:30 pm	General Discussion
12:30 pm - 1:30 pm	Lunch
1:30 pm - 4:00 pm	Free Time
4:00 pm - 6:00 pm	**Poster Session**
6:00 pm - 7:00 pm	Dinner
7:30 pm - 9:30 pm	**The Toxic Conformer: Does It Exist?** Discussion Leaders: **Laura Ranum** (University of Florida College of Medicine, USA) and **Christopher Ross** (Johns Hopkins University, USA)
7:30 pm - 7:55 pm	**Ronald Melki** (CNRS, France) "Propagation of **α**-Synuclein and HTT Aggregates"
7:55 pm - 8:00 pm	Discussion
8:00 pm - 8:20 pm	**Meewhi Kim** (University of Texas Southwestern Medical Center, USA) "Conformations of N-Terminal HTT Fragments: Structural Investigations"
8:20 pm - 8:25 pm	Discussion
8:25 pm - 8:50 pm	**Matthew Disney** (The Scripps Research Institute, USA) "RNA Structures as Mediators of Disease"
8:50 pm - 8:55 pm	Discussion
8:55 pm - 9:15 pm	**Louise Serpell** (University of Sussex, United Kingdom) "Amyloid Structures and Mechanisms of Toxicity"
9:15 pm - 9:20 pm	Discussion

9:20 pm - 9:30 pm	General Discussion
Tuesday	
7:30 am - 8:30 am	Breakfast
8:30 am - 9:00 am	Group Photo
9:00 am - 12:30 pm	**Impairment of DNA Repair and RNA Mechanisms in CAG Repeat Diseases** Discussion Leaders: **Kimberly Kegel-Gleason** (Massachusetts General Hospital, USA) and **Matthew Disney** (The Scripps Research Institute, USA)
9:00 am - 9:20 am	**Lesley Jones** (MRC Centre for Neuropsychiatric Genetics and Genomics, Cardiff University, United Kingdom) "DNA Repair in the Trinucleotide Repeat Disorders"
9:20 am - 9:30 am	Discussion
9:30 am - 9:50 am	**Hitoshi Okazawa** (Tokyo Medical and Dental University, Japan) "Impaired DNA Damage Repair in SCA1 and Other CAG Repeat Diseases"
9:50 am - 10:00 am	Discussion
10:00 am - 10:15 am	Selected from Poster Abstracts: **Jacob Loupe** (Massachusetts General Hospital, USA) "Functional Prioritization of Huntington's Disease Onset Modifiers in the Mouse"
10:15 am - 10:20 am	Discussion
10:20 am - 10:50 am	Coffee Break
10:50 am - 11:10 am	**Partha Sarkar** (University of Texas Medical Branch, USA) "DNA Damage-Response Pathways in SCA3 and Huntington's Disease"
11:10 am - 11:20 am	Discussion

11:20 am - 11:35 am	Selected from Poster Abstracts: **Vincent Dion** (University of Lausanne, Switzerland) "Contracting CAG/CTG Repeat Using the CRISPR-Cas9 Nickase"
11:35 am - 11:40 am	Discussion
11:40 am - 11:55 am	Selected from Poster Abstracts: **Shyam Ramachandran** (Children's Hospital of Philadelphia, USA) "Mutant Huntingtin Disrupts CELF1-MBNL1 Regulation in Patient Brain and Model Systems"
11:55 am - 12:00 pm	Discussion
12:00 pm - 12:15 pm	Selected from Poster Abstracts: **Carlo Rinaldi** (University of Oxford, United Kingdom) "More than One Protein: Role of Androgen Receptor Isoforms in SBMA Pathogenesis"
12:15 pm - 12:20 pm	Discussion
12:20 pm - 12:30 pm	General Discussion
12:30 pm - 1:30 pm	Lunch
1:30 pm - 4:00 pm	Free Time
4:00 pm - 6:00 pm	**Poster Session**
6:00 pm - 7:00 pm	Dinner
7:30 pm - 9:30 pm	**What Can We Learn from Large OMIC Data Sets for Disease Research?** Discussion Leaders: **Gillian Bates** (University College London, United Kingdom) and **James Rosinski** (CHDI Foundation, USA)
7:30 pm - 7:50 pm	**William Yang** (David Geffen School of Medicine at UCLA, USA) "Analysis of RNAseq and Proteomics Data in Models of HD"
7:50 pm - 7:55 pm	Discussion
7:55 pm - 8:15 pm	**Smita Saxena** (University of Bern, Switzerland) "The Synaptic Protein Homer-3 Influences SCA1 Pathophysiology"

8:15 pm - 8:20 pm	Discussion
8:20 pm - 8:40 pm	**Harry Orr** (University of Minnesota, USA) "Spinocerebellar Ataxia Type 1: Molecular Basis of Neurodegeneration in the Cerebellum (Ataxia) and Brainstem (Lethality)"
8:40 pm - 8:45 pm	Discussion
8:45 pm - 9:00 pm	Selected from Poster Abstracts: **Christian Neri** (Pierre-and-Marie-Curie University, France) "Weighted Network Models of the Temporal Dynamics and Biological Outcome of Huntington's Disease"
9:00 pm - 9:05 pm	Discussion
9:05 pm - 9:20 pm	Selected from Poster Abstracts: **Andrea Reyes-Ortiz** (University of California, Irvine, USA) "Transcriptomic and Functional Analysis of HD iPSC-Derived Brain Microvascular Endothelial Cells Reveals Angiogenic and BBB Deficits"
9:20 pm - 9:25 pm	Discussion
9:25 pm - 9:30 pm	General Discussion
Wednesday	
7:30 am - 8:30 am	Breakfast
9:00 am - 12:30 pm	**Proteostasis and Protein Quality Control Mechanisms in Disease** Discussion Leaders: **Eric Reits** (University of Amsterdam, The Netherlands) and **Joan Steffan** (University of California, Irvine, USA)
9:00 am - 9:25 am	**Nico Dantuma** (Karolinska Institutet, Sweden) "Polyglutamine Proteins and the Ubiquitin/Proteasome System"
9:25 am - 9:35 am	Discussion

9:35 am - 10:00 am	**Janine Kirstein** (Leibniz Institute for Molecular Pharmacology, Germany) "Complete Suppression of HTT Fibrilization and Disaggregation of HTT Fibrils by a Trimeric Chaperone Complex"
10:00 am - 10:10 am	Discussion
10:10 am - 10:25 am	Selected from Poster Abstracts: **Mark Hipp** (Max Planck Institute of Biochemistry, Germany) "Architecture of PolyQ Inclusions"
10:25 am - 10:30 am	Discussion
10:30 am - 11:00 am	Coffee Break
11:00 am - 11:25 am	**Harm Kampinga** (University Medical Center Groningen, The Netherlands) "HSPs as Potential Therapy Targets in Neurodegeneration"
11:25 am - 11:30 am	Discussion
11:30 am - 11:55 am	**Ai Yamamoto** (Columbia University, USA) "Clearance of PolyQ Proteins in Mammalian Cells"
11:55 am - 12:00 pm	Discussion
12:00 pm - 12:15 pm	Selected from Poster Abstracts: **Rocio Gomez Pastor** (Duke University School of Medicine, USA) "Heat Shock Transcription Factor 1: A Neuroprotective Role in Huntington's Disease"
12:15 pm - 12:20 pm	Discussion
12:20 pm - 12:30 pm	General Discussion
12:30 pm - 1:30 pm	Lunch
1:30 pm - 4:00 pm	Free Time
4:00 pm - 6:00 pm	**Poster Session**
6:00 pm - 7:00 pm	Dinner

7:30 pm - 9:30 pm	**From Molecules to Humans: Selected Poster Presentations / Selected GRS Presentations** Discussion Leaders: **Åsa Petersén** (Lund University, Sweden) and **Sarah Tabrizi** (University College London, United Kingdom)
7:30 pm - 7:50 pm	**Beverly Davidson** (The Children's Hospital of Philadelphia, USA) "Development of Innovative Therapeutic Strategies for CAG Repeat Diseases"
7:50 pm - 8:00 pm	Discussion
8:00 pm - 8:15 pm	Selected from Poster Abstracts: **Nicolas Arbez** (Johns Hopkins School of Medicine, USA) "Modulation of Huntingtin Toxicity by Post-Translational Modifications"
8:15 pm - 8:20 pm	Discussion
8:20 pm - 8:35 pm	Selected from Poster Abstracts: **Anastasia Gromova** (University of California, San Diego, USA) "Elucidating Mechanisms of Skeletal Muscle-Driven Neurodegeneration in Spinal and Bulbar Muscular Atrophy"
8:35 pm - 8:40 pm	Discussion
8:40 pm - 8:55 pm	Selected from Poster Abstracts: **Anne Steinhof** (Max Delbrueck Center for Molecular Medicine in the Helmholtz Association, Germany) "Mutant HTT Seeding Activity: A Marker of Disease Progression in Models of Huntington's Disease"
8:55 pm - 9:00 pm	Discussion
9:00 pm - 9:15 pm	**Radhia Kacher** (CNRS / Pierre and Marie Curie University, France) "zQ175 Knock-In Mouse Model Helps to Decipher the Neuroprotective Role of CYP46A1, the Cholesterol Degradation Enzyme, in Huntington's Disease"
9:15 pm - 9:20 pm	Discussion
9:20 pm - 9:30 pm	General Discussion

Thursday	
7:30 am - 8:30 am	Breakfast
8:30 am - 9:00 am	**Business Meeting** *Nominations for the Next Vice Chair; Fill in Conference Evaluation Forms; Discuss Future Site and Scheduling Preferences; Election of the Next Vice Chair*
9:00 am - 12:30 pm	**Innovative Technologies, Model Systems and Quantitative Methods** Discussion Leaders: **Blair Leavitt** (University of British Columbia, Canada) and **Erich Wanker** (Max Delbrück Center for Molecular Medicine in the Helmholtz Association, Germany)
9:00 am - 9:25 am	**Andreas Weiss** (Evotec AG, Germany) "Quantitative CNS Disease Protein Assays for Screening and Biomarker Applications"
9:25 am - 9:35 am	Discussion
9:35 am - 10:00 am	**Elena Cattaneo** (University of Milan, Italy) "Organoid Models for CAG Repeat Diseases"
10:00 am - 10:10 am	Discussion
10:10 am - 10:25 am	Selected from Poster Abstracts: **Xiao-Jiang Li** (Emory University, USA) "CRIPSR/Cas9-Mediated Therapeutic Effect in HD Knock-In Mice"
10:25 am - 10:30 am	Discussion
10:30 am - 11:00 am	Coffee Break
11:00 am - 11:25 am	**Fanny Mochel** (Pierre and Marie Curie University, France) "Metabolic Imaging and Metabolomics in Polyglutamine Diseases"
11:25 am - 11:30 am	Discussion
11:30 am - 11:55 am	**Beatriz Alvarez-Castelao** (Max Planck Institute for Brain Research, Germany) "Identification of Newly Synthesized Proteomes in the Brain"

11:55 am - 12:00 pm	Discussion
12:00 pm - 12:15 pm	Selected from Poster Abstracts: **Danielle Simmons** (Stanford University, USA) "TSPO-PET Imaging Using ^{18}F-PBR06 Is a Potential Biomarker for Monitoring Therapeutic Efficacy in Huntington's Disease: Preclinical Evidence with the Small Molecule p75^{NTR} Ligand LM11A-31"
12:15 pm - 12:20 pm	Discussion
12:20 pm - 12:30 pm	General Discussion
12:30 pm - 1:30 pm	Lunch
1:30 pm - 4:00 pm	Free Time
4:00 pm - 6:00 pm	**Poster Session**
6:00 pm - 7:00 pm	Dinner
7:30 pm - 9:30 pm	**Innovative Therapeutic Strategies and Diagnostic Tools** Discussion Leaders: **Edward Wild** (University College London, United Kingdom) and **Henry Paulson** (University of Michigan Health System, USA)
7:30 pm - 7:50 pm	**Sarah Tabrizi** (University College London, United Kingdom) "Meeting the Therapeutic Challenge of HD"
7:50 pm - 7:55 pm	Discussion
7:55 pm - 8:15 pm	**Albert La Spada** (University of California, San Diego, USA) "Novel Therapeutic Strategies for PolyQ Diseases"
8:15 pm - 8:20 pm	Discussion
8:20 pm - 8:40 pm	**Gulin Oz** (University of Minnesota, USA) "Treatment Monitoring by Magnetic Resonance Spectroscopy in Neurodegenerative Diseases"
8:40 pm - 8:45 pm	Discussion

8:45 pm - 9:00 pm	Selected from Poster Abstracts: **Hayley McLoughlin** (University of Michigan, USA) "Toward Antisense Oligonucleotide Therapy for Spinocerebellar Ataxia Type 3"
9:00 pm - 9:05 pm	Discussion
9:05 pm - 9:20 pm	Selected from Poster Abstracts: **Matt Scaglione** (Medical College of Wisconsin, USA) "CHIPping Away at Polyglutamine"
9:20 pm - 9:25 pm	Discussion
9:25 pm - 9:30 pm	General Discussion
Friday	
7:30 am - 8:30 am	Breakfast
9:00 am	Departure

Contributors

Gordon Research Conferences	Carl Storm Underrepresented Minority Fellowship	Carl Storm International Diversity Fellowship
		IONIS PHARMACEUTICALS
CellPress	Kennedy's Disease Association	