CHDI Foundation funding strategy: A science management organization for Huntington’s disease therapeutics

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Health Research Alliance Members’ Meeting

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Working together to optimize the impact of investment in biomedical research and training to improve human health

Fostering open communication and collaboration

Addressing issues that are key to accelerating research discovery and its translation
CHDI mission statement

To collaboratively develop therapeutics that substantially improve the lives of individuals affected by Huntington’s disease

Directed strategy – purposeful managed activity

Expand the precompetitive space
What is CHDI exactly?

**Nonprofit Foundation**
- Biomedical research organization
- Motivated by time not money
- No competitors, only collaborators

**HD Drug Discovery & Development**
- Exclusively focused on HD
- Unambiguous continuity, focus, passion
- Develop meaningful therapies
Diverse external global partnership network

- 100+ CHDI internal employees
- Research - discovery through clinical development
- No internal “wet labs”
- >750 FTEs worldwide
- >100 academic collaborations
- Funded by generous private donors

- Collaborative enabler – models, reagents, assays, data, biosamples, tools, advice, etc.
Overall strategy

To de-risk therapeutic programs to the point where pharma will take them on
Funding strategy

NOT grants, NO RFPs, no study section-type periodic peer review
Independent CHDI scientists continuously seek out and review new approaches/technologies

Funding managed through legal agreement
• Detailed project description
  – sets expectations & timelines
• Quarterly Joint Steering Committee meetings (subset, HHMI-like)
  – new data appraised, next steps discussed and agreed
  – ensure therapeutic goals remain in focus
• Standard legal clauses
  – data sharing – period of exclusivity then we can publish (ICFs too)
  – confidentiality agreement – knowledge commons
Academic freedom

• Retain right to publish
  – CHDI staff sometimes qualify as authors – ICMJE rules

• Retain data exclusivity for agreed period
  – exceptions Enroll-HD & other clinical data – openly shared

• Intellectual property stance
  – ordinarily, CHDI requires no IP – BUT we do insist upon a license-in-perpetuity for anyone to use asset for HD research purposes
Advantages

Developed relationships with collaborators that respects their academic curiosity & freedom – they respect our mission to collaboratively develop therapeutics

Joint gains from different interests

• Share findings in real time
• Share data
• Advisory capacity
  – Independent Statistical Standing Committee
  – scientific rigor – experimental design & statistical analysis plans
• Coordination of activities
• Plug infrastructure gaps
  – assays, models, clinical observational studies, biomarkers, regulatory science
• Investigators don’t have to spend valuable time crafting convincing grant proposals!
Disadvantages

• Appears expensive – staff intensive
  – can be introduced more modestly
• Academics kicking & screaming!
  – no longer an issue
Does it work?! 

- Roche/Ionis antisense oligonucleotide Phase 1/2a trial
- Dose responsive lowering of huntingtin protein in CSF
- First CHDI funding to Ionis in 2005
Thank you!

Robi Blumenstein – President
Robert Pacifici – Chief Scientific Officer
Dave Rankin – Chief Legal Officer
Ruth Basu – Chief Administration Officer
Our donors
HTT lowering therapeutic strategies

**Transcription**

- HTT gene

**Translation**

- HTT mRNA
- HTT protein

Tools:

- ASO
- siRNA
- miRNA
- shRNA
- Sm Mol
- zLNA
Summary of HTT lowering intervention points and efforts

- CHDI/CROs
- Shire/Sangamo
- Biomarin
- CHDI/CROs
- Ionis/Roche
- Spark
- UBC
- uniQure
- UMass
- UTSW
- Voyager/Sanofi
- Wave

**Transcription**

**Translation**

**Clearance**

**Pharma companies**
Develop the Capabilities to Drive “Internal” Drug Discovery efforts

• Cannot rely on:
  – Repurposing existing compounds
  – Watching the “in box”

• If the biology is compelling
  – Initiate *de novo* efforts
  – Persevere where others have failed or abandoned

• Orchestrate across a network of fee-for-service contract research organizations
  – CHDI scientists design and oversee the research
  – CHDI owns the intellectual property
Huntington’s Disease

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ORIGINAL DEPARTMENT.

Communications.

ON CHOREA.

By George Huntington, M.D.,

Of Painesville, Ohio.

Chorea is essentially a disease of the nervous system. The term “chorea” is given to the disease on account of the dancing peculiarities of those who are afflicted by it, and it is a very appropriate designation. The disease, as it is commonly seen, is by no means a dangerous or serious affection, however disturbing it may be to the sufferer from it, or to his friends. Its most marked and characteristic feature is a sudden spasm affecting the voluntary muscles. There is no loss of The upper extremities may be the first affected, or both simultaneously. All the voluntary muscles are liable to be affected, those of the face rarely being exempted. The hands are kept moving—first the palm upward, and then the back. The elbows are shrugged, and the feet and legs kept in perpetual motion; the two are twisted in, and then exerted, one foot being thrown across the other, and then suddenly withdrawn, and, in short, every conceivable attitude and expression is assumed, and so varied and irregular are the motions that, through with, that a complete description of them would be impossible. Sometimes the muscles of the lower extremities are not.

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A Novel Gene Containing a Trinucleotide Repeat That Is Expanded and Unstable on Huntington’s Disease Chromosomes

Introduction

Huntington’s disease (HD) is an autosomal dominant neurological disorder characterized by motor disturbances, cognitive loss, and psychiatric manifestations. While the vast majority of HD patients carry pathogenic CAG expansions in the huntingtin (HTT) gene on chromosome 4q13, approximately 5% of individuals with HD have non-pathogenic expansions. This review will focus on the role of the non-pathogenic expansions and the mechanisms that lead to the development of HD.

Summary

The huntingtin (HTT) gene on chromosome 4q13 contains a trinucleotide repeat polyglutamine repeat that is expanded and unstable in Huntington’s disease. This repeat region is located within the first exon of HTT and is linked to the disease phenotype. In affected individuals, the CAG repeat is expanded beyond a normal range of 29 to 34 repeats, and this expansion is associated with the development of HD.

The Huntington’s Disease Collaborative Research Group

The Huntington’s Disease Collaborative Research Group (HDCRG) was established to study the genetics of HD and to identify potential therapeutic targets. The group has conducted numerous studies, including genome-wide association studies, to identify genetic factors associated with HD.

The HDCRG has also been involved in the development of novel therapies for HD, including clinical trials of various medications and gene therapies. In addition, the group has published several papers on the genetics and biology of HD, contributing to our understanding of the disease.

Identification of Genetic Factors That Modify Clinical Onset of Huntington’s Disease

Genetic modifiers of Huntington’s Disease (GmHD) Consortium

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http://dx.doi.org/10.1016/j.cell.2015.07.003
Using HD Animal Models for Proof of Principle HTT Lowering Biomarkers to Advance HTT Lowering Therapies

- **HD mice**
  - Many

- **HD rat**:
  - Q97 FL HTT

- **HD minipig**:
  - Q120 1-543 HTT

- **HD sheep**:
  - Q73 FL HTT

- **HD NHP**:
  - Q29 Exon 1 HTT
  - Q80 1-512 HTT
  - AAV Q82 1-171 HTT