Accelerating therapeutic development for Huntington's disease

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

Simon Noble PhD

Director, Scientific Communications

Health Research Alliance Members' Meeting

March 12, 2018

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

CHDI mission statement

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

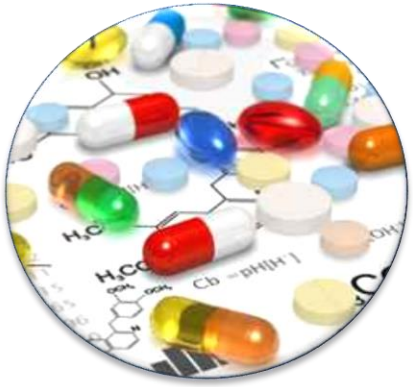
Directed strategy – purposeful managed activity

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

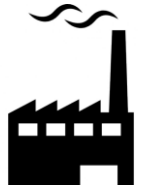
- Exclusively focused on HD
- Unambiguous continuity, focus, passion
- Develop meaningful therapies

Diverse external global partnership network

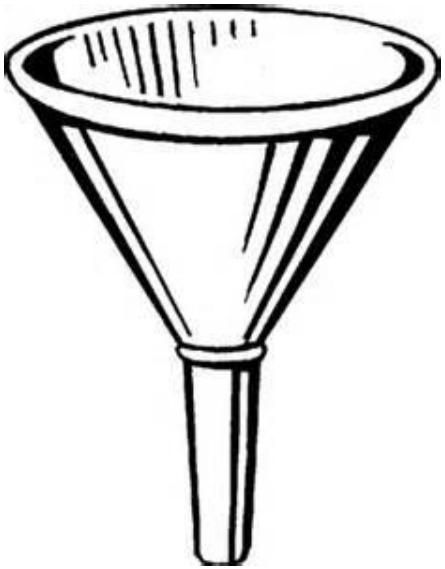

Academic

Internal / CRO


Biotech


Big Pharma

- 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

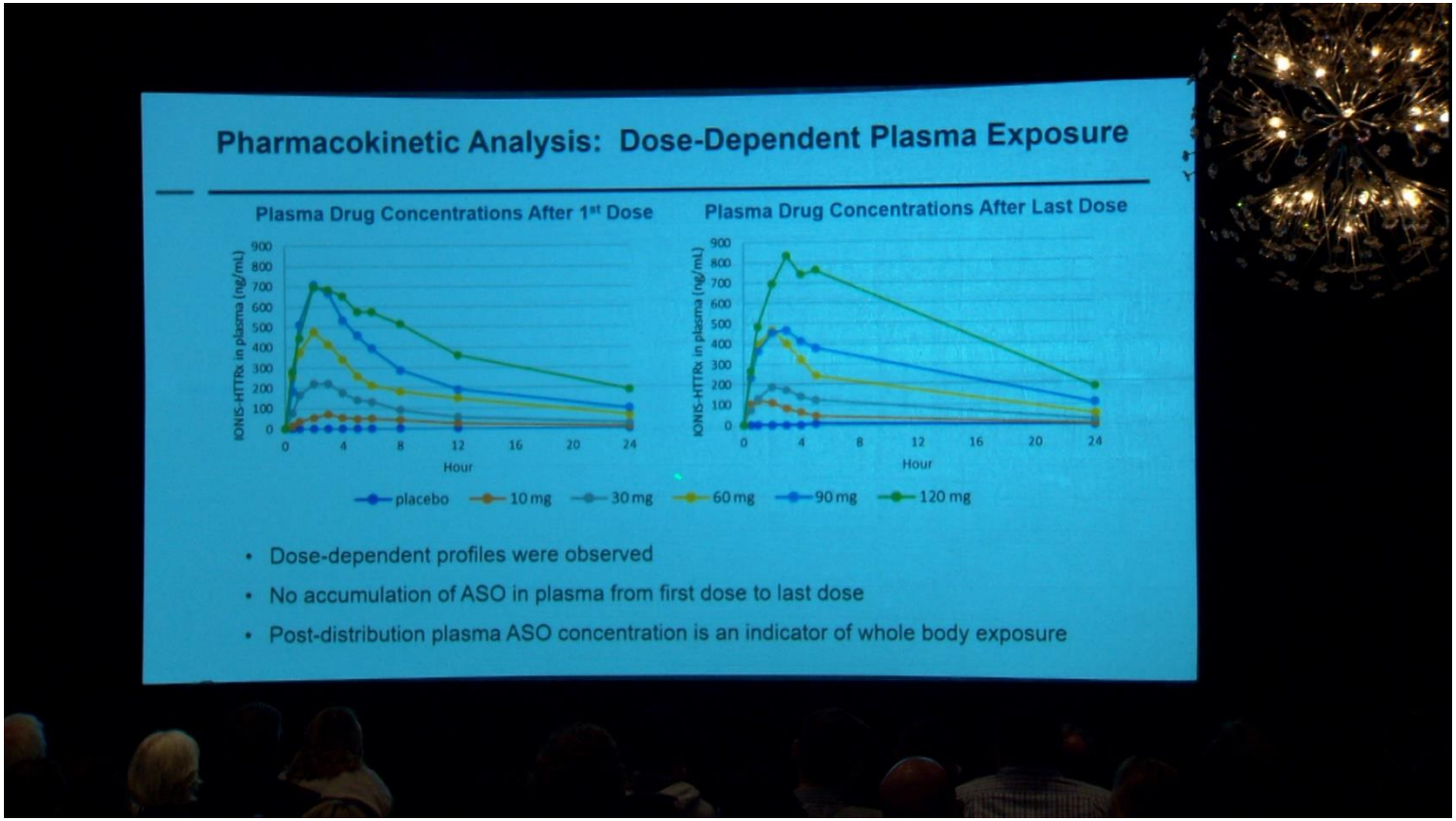
Joint gains from different interests

- 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?!

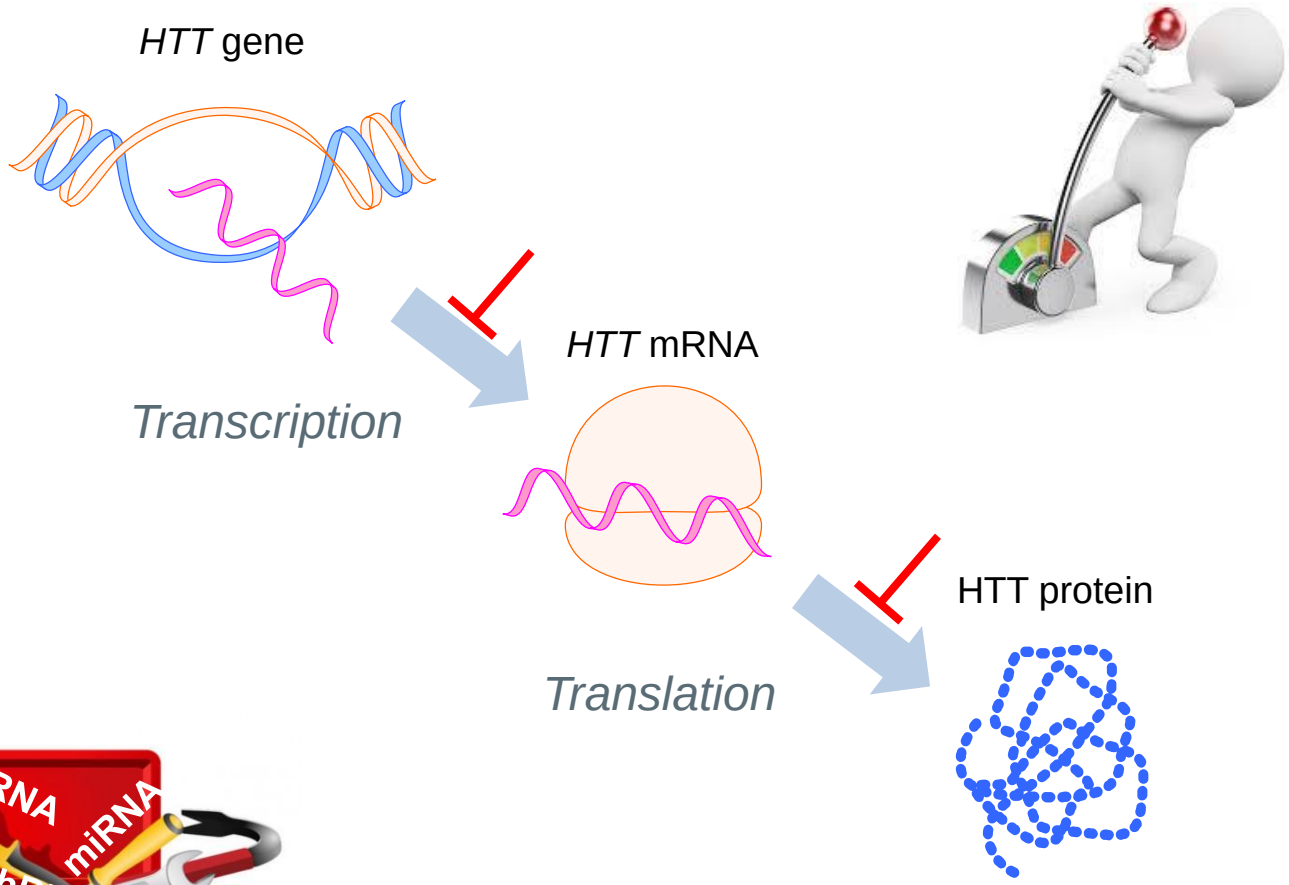


- Roche/Ionis antisense oligonucleotide Phase 1/2a trial
- Dose responsive lowering of huntingtin protein in CSF
- First CHDI funding to Ionis in 2005

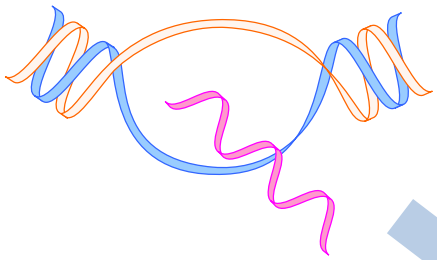
Thank you!

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

HTT lowering therapeutic strategies

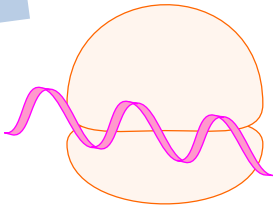


Summary of HTT lowering intervention points and efforts



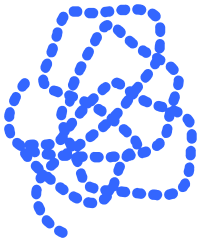
Transcription

CHDI/CROs
Shire/Sangamo



Translation

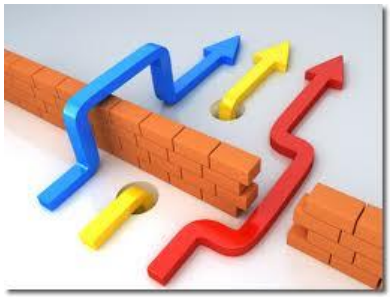
Biomarin
CHDI/CROs
Ionis/Roche
Spark
UBC
uniQure
UMass
UTSW
Voyager/Sanofi
Wave



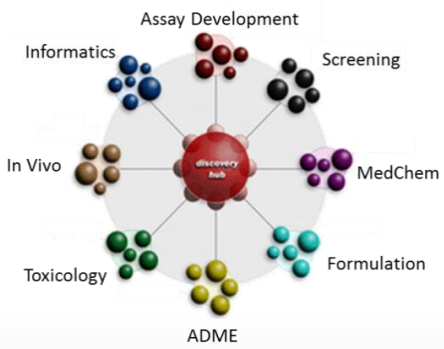
Clearance

CHDI/CROs
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



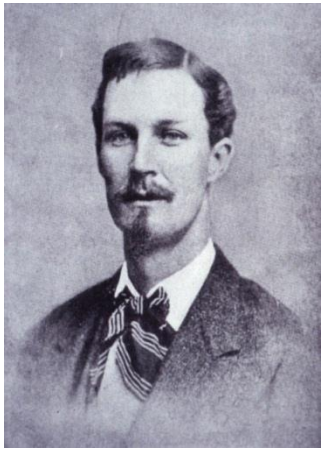
PsychoGenics
Redefining Drug Discovery Through Innovation

evotec

IRBM

BioFocus
A Galápagos Company

Huntington's Disease



MEDICAL AND SURGICAL REPORTER.

No. 789.] PHILADELPHIA, APRIL 13, 1872. [Vol. XXVI.—No. 15.

Original Department.

Communications.

On Chorea.

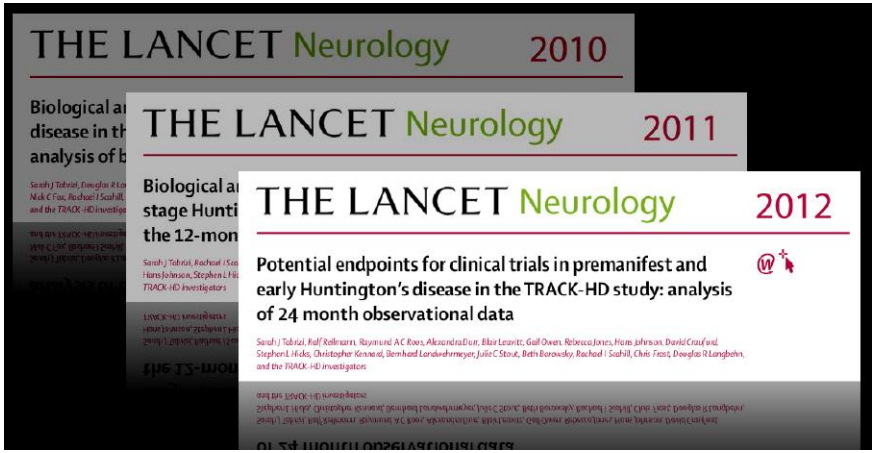
By George Huntington, M. D.,
Of Pomeroy, Ohio.

Essay read before the Meigs and Mason Academy of Medicine at Middleport, Ohio, February 15, 1872

Chorea is essentially a disease of the nervous system. The name "chorea" is given to the disease on account of the *dancing* propensities of those who are affected 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 distressing it may be to the one suffering from it, or to his friends. Its most marked and characteristic feature is a clonic 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.

If the patient attempt to protrude the tongue it is accomplished with a great deal of difficulty and uncertainty. The hands are kept rolling—first the palms upward, and then the backs. The shoulders are shrugged, and the feet and legs kept in perpetual motion; the toes are turned in, and then everted; one foot is 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 gone through with, that a complete description of them would be impossible. Sometimes the muscles of the lower extremities are not af-



Cell, Vol. 72, 971–983, March 26, 1993, Copyright © 1993 by Cell Press

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

The Huntington's Disease Collaborative Research Group*

Summary

The Huntington's disease (HD) gene has been mapped in 4p16.3 but has eluded identification. We have used haplotype analysis of linkage disequilibrium to spotlight a small segment of 4p16.3 as the likely location of the defect. A new gene, IT15, isolated using cloned trapped exons from the target area contains a polymorphic trinucleotide repeat that is expanded and unstable on *HD* chromosomes. A $(CAG)_n$ repeat longer than the normal range was observed on *HD* chromosomes from all 75 disease families examined, comprising a variety of ethnic backgrounds and 4p16.3 haplotypes. The $(CAG)_n$ repeat appears to be located within the coding sequence of a predicted ~348 kd protein that is widely expressed but unrelated to any known gene. Thus, the *HD* mutation involves an unstable DNA segment, similar to those described in fragile X syndrome, spino-bulbar muscular atrophy, and myotonic dystrophy, acting in the context of a novel 4p16.3 gene to produce a dominant phenotype.

Introduction

Huntington's disease (HD) is a progressive neurodegenerative disorder characterized by motor disturbance, cognitive loss, and psychiatric manifestations (Martin and Gusella, 1986). It is inherited in an autosomal dominant fashion and affects ~1 in 10,000 individuals in most populations of European origin (Harper et al., 1991). The hallmark of HD is a distinctive choreic movement disorder that typically has a subtle, insidious onset in the fourth to fifth decade of life and gradually worsens over a course of 10 to 20 years until death. Occasionally, HD is expressed in juveniles, typically manifesting with more severe symptoms including rigidity and a more rapid course. Juvenile onset of HD is associated with a preponderance of paternal transmission of the disease allele. The neuropathology of HD also displays a distinctive pattern, with selective loss of neurons that is most severe in the caudate and putamen. The biochemical basis for neuronal death in HD has not yet been explained, and there is consequently no treatment effective in delaying or preventing the onset and progression of this devastating disorder.

The genetic defect causing HD was assigned to chromosome 4 in 1983 in one of the first successful linkage analyses using polymorphic DNA markers in humans (Gusella

***The Huntington's Disease Collaborative Research Group comprises:**

Group 1:
Marcy E. MacDonald,[1] Christine M. Ambrose,[1] Mabel P. Duyao,[1] Richard H. Myers,[2] Carol Lin,[1] Lakshmi Srinidhi,[1] Glenn Barnes,[1] Sherryl A. Taylor,[1] Marianne James,[1] Nicolet Groot,[1] Heather MacFarlane,[1] Barbara Jenkins,[1] Mary Anne Anderson,[1] Nancy S. Wexler,[3] and James F. Gusella[1†]
[1]Molecular Neurogenetics Unit
Massachusetts General Hospital
and Department of Genetics
Harvard Medical School
Boston, Massachusetts 02114
[2]Department of Neurology
Boston University Medical School
Boston, Massachusetts 02118
[3]Hereditary Disease Foundation
1427 7th Street, Suite 2
Santa Monica, California 90401

Group 2:
Gillian P. Bates, Sarah Baxendale, Holger Hummerich, Susan Kirby, Mike North, Sandra Youngman, Richard Mott, Gunther Zehetner, Zdenek Sedlacek, Annemarie Poustka, Anna-Maria Frischauf, and Hans Lehrach
Genome Analysis Laboratory
Imperial Cancer Research Fund
Lincoln's Inn Fields
London, WC2A 3PX, England

Group 3:
Alan J. Buckler,[1] Deanna Church,[1] Lynn Doucette-Stamm,[1] Michael C. O'Donovan,[1] Laura Riba-Ramirez,[1] Manish Shah,[1] Vincent P. Stanton,[1] Scott A. Strobel,[2] Karen M. Draths,[2] Jennifer L. Wales,[2] Peter Dervan,[2] and David E. Housman[1]
[1]Center for Cancer Research
Massachusetts Institute of Technology
Cambridge, Massachusetts 02139
[2]Division of Chemistry and Chemical Engineering
California Institute of Technology
Pasadena, California 91125

Group 4:
Michael Altherr, Rita Shiang, Leslie Thompson, Thomas Fielder, and John J. Wasmuth
Department of Biological Chemistry
University of California
Irvine, California 92717

Group 5:
Danilo Tagle, John Valdes, Lawrence Elmer, Marc Allard, Lucio Castille, Manju Swaroop, Kris Blanchard, and Francis S. Collins
Department of Internal Medicine and Human Genetics
and The Howard Hughes Medical Institute
University of Michigan
Ann Arbor, Michigan 48109

Group 6:
Russell Snell, Tracey Holloway, Kathleen Gillespie, Nicole Datson, Duncan Shaw, and Peter S. Harper
Institute of Medical Genetics
University of Wales College of Medicine
Cardiff, CF4 4XN, Wales

[†]*Correspondence should be addressed to James F. Gusella.*

Cell

Article

Identification of Genetic Factors that Modify Clinical Onset of Huntington's Disease

Genetic Modifiers of Huntington's Disease (GeM-HD) Consortium*
*Correspondence: gusella@helix.mgh.harvard.edu
http://dx.doi.org/10.1016/j.cell.2015.07.003

CHDI

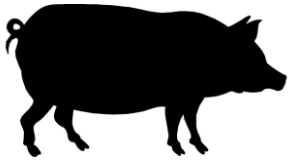
Using HD Animal Models for Proof of Principle HTT Lowering Biomarkers to Advance HTT Lowering Therapies

HD mice

- Many

HD rat:

- Q97 FL HTT

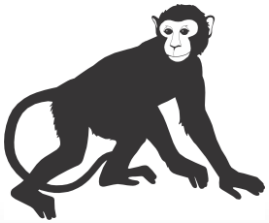


HD minipig:

- Q120 1-543 HTT

HD sheep:

- Q73 FL HTT



HD NHP:

- Q29 Exon 1 HTT
- Q80 1-512 HTT
- AAV Q82 1-171 HTT

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