CHDI
Accelerating therapeutic development for Huntington's disease

Fondazione LIRH
LEGA ITALIANA RICERCA HUNTINGTON E MALATTIE CORRELATE - ONLUS

Accelerando le terapie per la malattia di Huntington

Una panoramica del portafoglio e del progresso di CHDI

Robert E. Pacifici, Ph.D.

Chief Scientific Officer

LIRH Foundation Annual HD Research Conference
Saturday December 2, 2017
h 09.30-16.00

Sala Loyola – Roma Eventi, Piazza della Pilotta 4 (Fontana di Trevi)

What I would like you to take away from my talk

- Introduction to Huntington's disease
  - What are the key features
  - What do we need to know to develop therapies
- A better understanding of CHDI
  - What is it?
  - How do we operate?
  - How do we fit into the landscape?
  - What are our biggest challenges?
- Huntingtin Lowering Efforts
  - Pre-clinical
  - Clinical
- How can HD Gene Expansion Carriers Help?
  - Genetics
  - Observational trials
  - Registries

Huntington's disease is a genetic disorder with an autosomal dominant inheritance pattern

THE

MEDICAL AND SURGICAL REPORTER.

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

ORIGINAL DEPARTMENT.

Communications.

ON CHOREA.

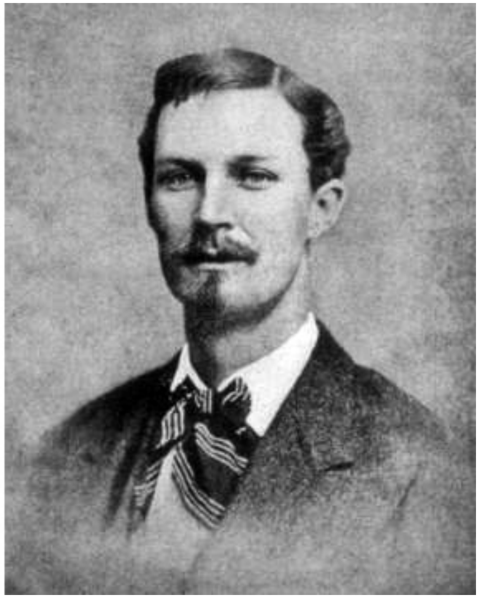
By GEORGE HUNTINGTON, M. D.,
Of Pomeroy, Ohio.

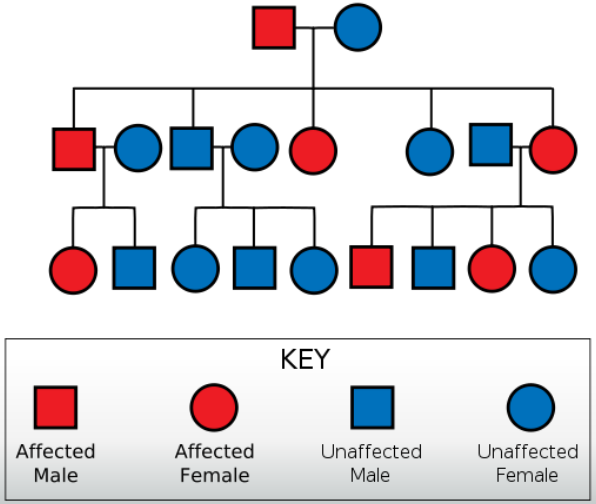
Essay read before the Meigs and Mason Academy of Medicine at Middleport, Ohio, February 15, 1872

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 char-

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





Huntington's disease affects multiple clinical domains

HD

Movement disorders

- *"Chorea"*
  - involuntary movements
- Dystonia
  - impairments in voluntary movements
- Most obvious *sign*
  - But least bothersome *symptom*

Cognitive disorders

- Slow progressive decline
- Loss of executive function
  - Decision making
  - Perseveration
  - Disinhibited outbursts
- Most troubling symptom for affect individuals

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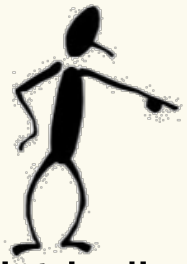
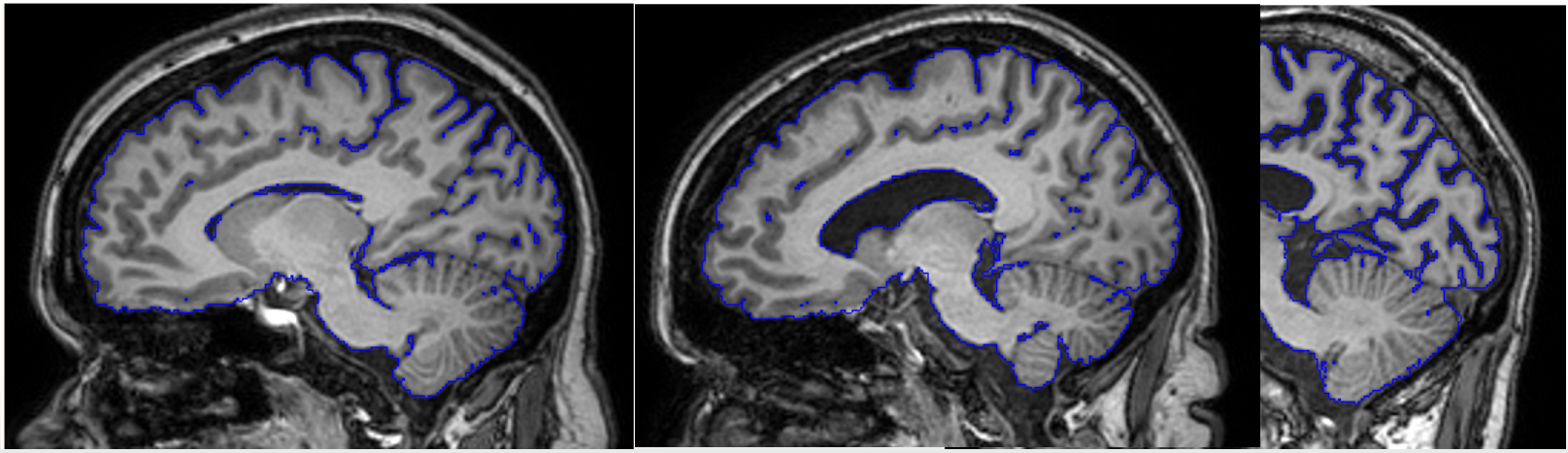


Psychiatric disorders

- Typically very early
  - Recognized as part of HD retrospectively
- Multiple symptoms
  - Depression, suicidal ideation
  - Irritability
  - Sleep and appetite changes
- Big contributor to familial dysfunction

So what do we understand about Huntington's biology?

- Late onset
  - ~40 years of age
  - 10-15 years to fatality
- Rare/orphan
  - Prevalence of 1in 30,000 in US
- Neurological disease
  - Affects the entire brain
  - Most dramatic dysfunction in the medium spiny neurons in the striatum
  - Basal ganglia dysfunction
  - Inverse



Control Pre Manifest HD

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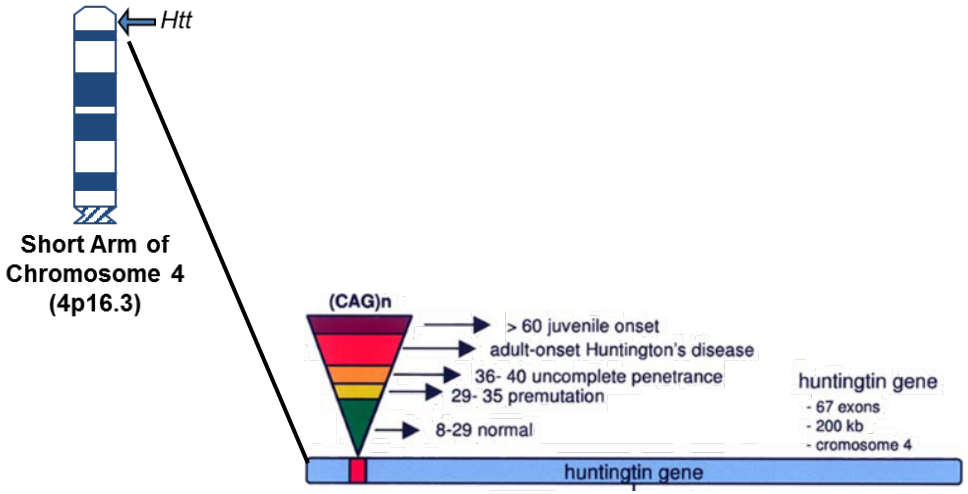


- Neurological disease
  - Affects the entire brain
  - Most dramatic dysfunction in the medium spiny neurons in the striatum
  - Basal ganglia dysfunction
- Mongenic
  - Second gene positionally cloned for a disease in 1993
  - Autosomal dominant inheritance with 100% penetrance
  - No idea what the protein does or how loss of function and /or gain of toxicity causes the disease

Qual è la nostra missione a CHDI?

To accelerate the discovery and development of meaningful therapies for Huntington's disease

Accelerare la scoperta e lo sviluppo di terapie significative per la malattia di Huntington

What is 'CHDI'…Exactly?

Nonprofit Foundation

- Funded by generous private donors
- Motivated by time not money
- No competitors, only collaborators

HD Drug Discovery & Development

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

'Virtual' Organization

- Real staff of 90 in NY, NJ, LA
- Fully integrated across the pipeline
- Global network of over 700 FTE

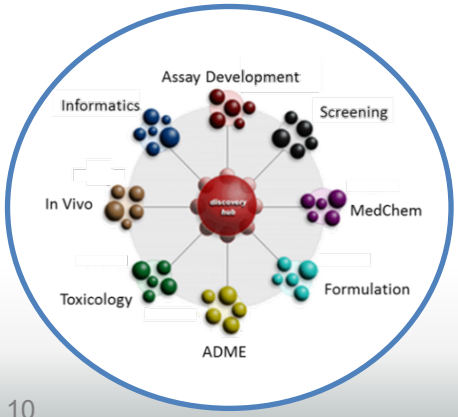
How Does CHDI fit into the HD landscape?

Collaborative Enablers

- Fund academic research contracts
- QC'd reagents, cell lines, animal models
- Data sharing
- Patient registries and outcome measures

Biotech & Pharma Partnerships

- Lower the barrier to entry with existing assets or technologies
- De-risk programs they own
- Provide HD domain knowledge

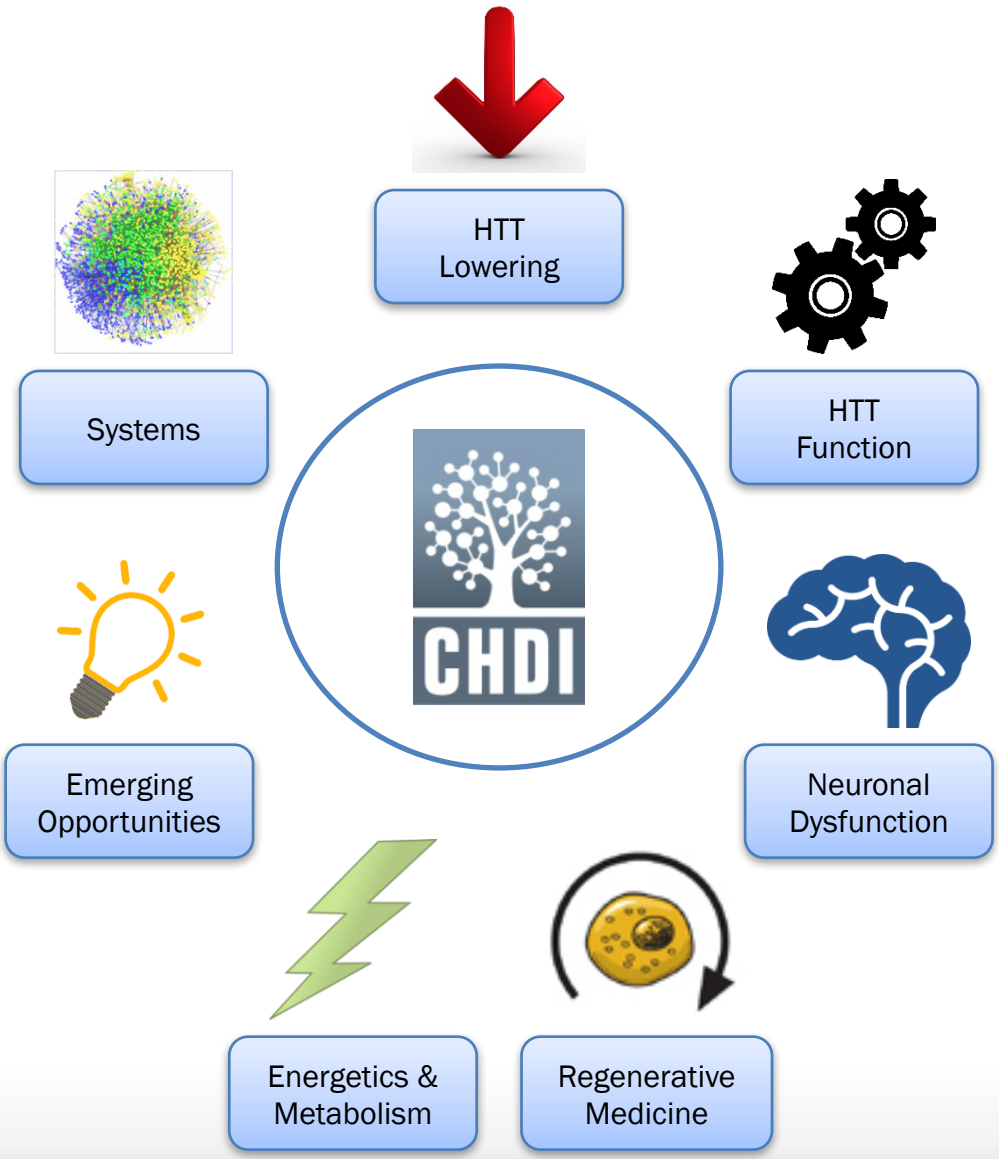


De novo Drivers of Programs

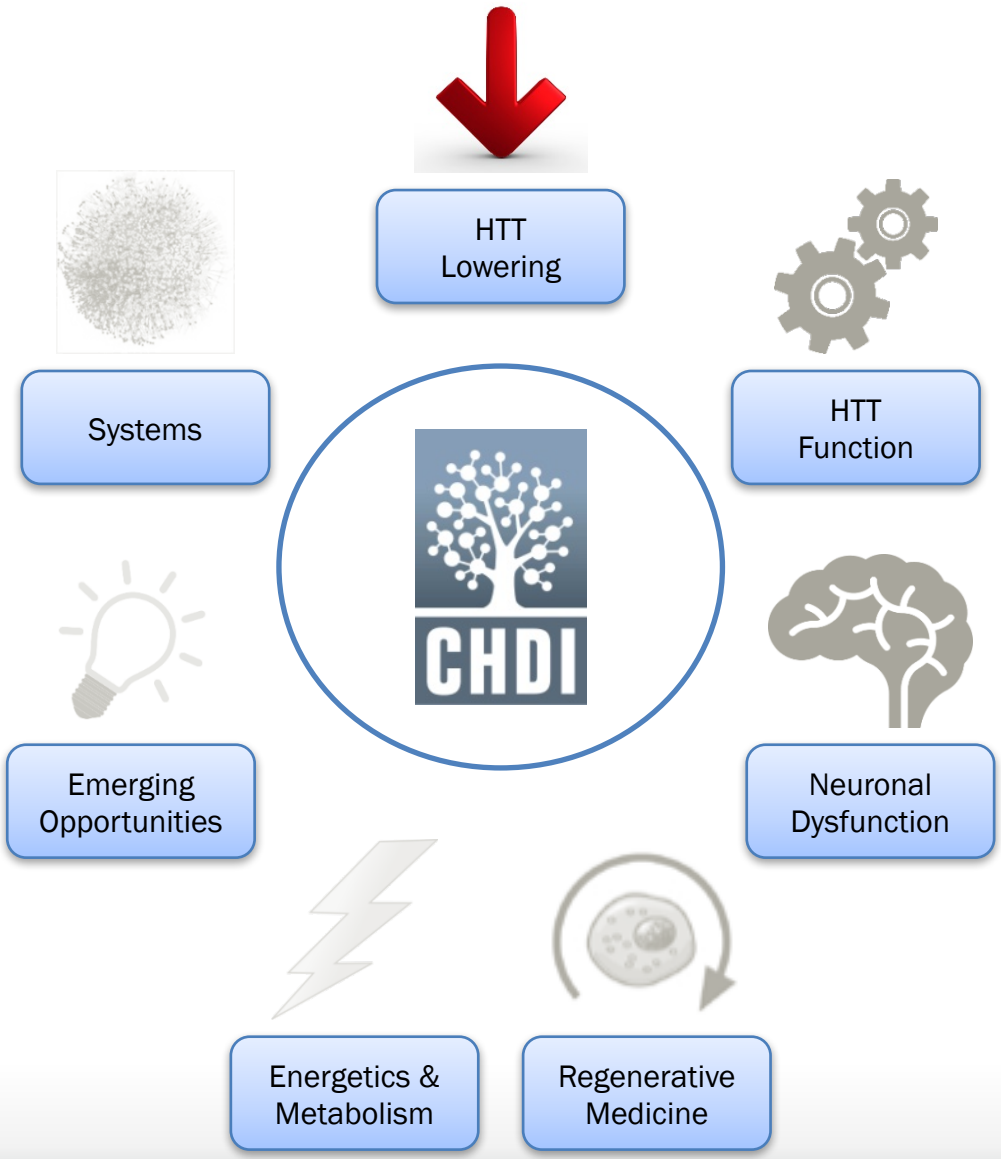
- Our ideas on next steps to push the science forward
- Prosecute and persevere where others have shied or failed
- Utilize network of CROs
- We own the IP to license out

CHDI

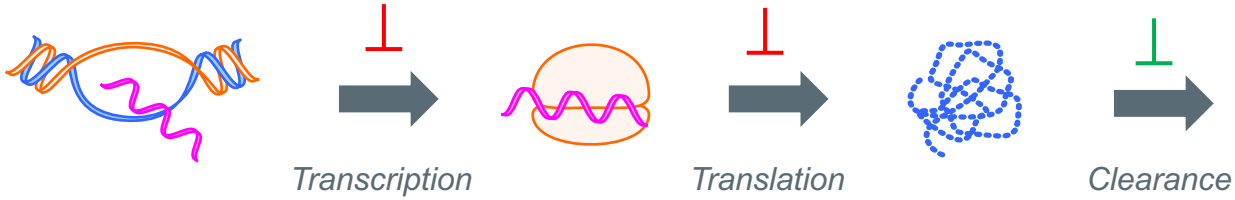
CHDI's Major Focus Areas



CHDI's Major Focus Areas



Landscape of HTT lowering efforts



Company	Modality	Target	Delivery	Stage
Biomarin	ASO	*mHTT* mRNA (CAG-directed)	?	Preclinical
Ionis / Roche	ASO	*HTT* mRNA (total)	IT	Phase 1
Wave	ASO	*mHTT* mRNA (SNP-directed)	IT	Phase 1
Spark / CHOP	AAV1-miRNA	*HTT* mRNA (total)	IPa	preIND?
UniQure	AAV5-miRNA	*HTT* mRNA (total, Exon 1-directed)	IPa	preIND
Voyager / Sanofi-Genzyme	AAV?-miRNA	*HTT* mRNA (total)	IPa	Preclinical
Medtronic / Alnylam	siRNA	*HTT* mRNA (total)	CED, IPa	Suspended
CHDI	Small molecule	*mHTT* or total *HTT* mRNA/protein (phenotypic)	TBD	Preclinical
PTC	Small molecule	*HTT* mRNA (total)	Oral	Preclinical
Sanofi-Genzyme / Evotec	Small molecule	*mHTT* or total *HTT* mRNA/protein (phenotypic)	TBD	Preclinical
Shire / Sangamo	AAV?-ZFP	*mHTT* mRNA (transcription, CAG-directed)	IPa	GLP tox
Neurimmune	HTT Ab	*mHTT* conformer	TBD	Preclinical

Academic	Modality	Target	Delivery	Stage
UBC	ASO	*mHTT* mRNA (SNP-directed)	?	?
UMass	AAV?-miRNA	*HTT* protein (total)	IPa	Academic POC
UMass	siRNA	*HTT* protein (total)	Ipa	Academic POC

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The first HTT lowering clinical trial is ongoing

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

Example: "Heart attack" AND "Los Angeles"
Search for studies: Se
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Find Studies | About Clinical Studies | Submit Studies | Resources | About This Site

Home > Find Studies > Search Results > Study Record Detail Text Size

Trial record **22 of 999** for: huntington disease
◂ Previous Study | Return to List | Next Study ▸

Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of IONIS-HTTRx in Patients With Early Manifest Huntington's Disease

This study is currently recruiting participants. (see Contacts and Locations)
Verified March 2016 by Ionis Pharmaceuticals, Inc.

Sponsor:
Ionis Pharmaceuticals, Inc.

Information provided by (Responsible Party):
Ionis Pharmaceuticals, Inc.

ClinicalTrials.gov Identifier:
NCT02519036

First received: August 1, 2015
Last updated: March 2, 2016
Last verified: March 2016
History of Changes

Full Text View | Tabular View | No Study Results Posted | Disclaimer | How to Read a Study Record

Purpose

This study will test the safety, tolerability, pharmacokinetics and pharmacodynamics of multiple ascending doses of IONIS-HTTRx administered intrathecally to adult patients with early manifest **Huntington's Disease**.

Condition	Intervention	Phase
Huntington's Disease	Drug: IONIS HTTRx Drug: Placebo	Phase 1 Phase 2

Study Type: Interventional
Study Design: Allocation: Randomized
Endpoint Classification: Safety Study
Intervention Model: Parallel Assignment
Masking: Double Blind (Subject, Investigator)
Primary Purpose: Treatment

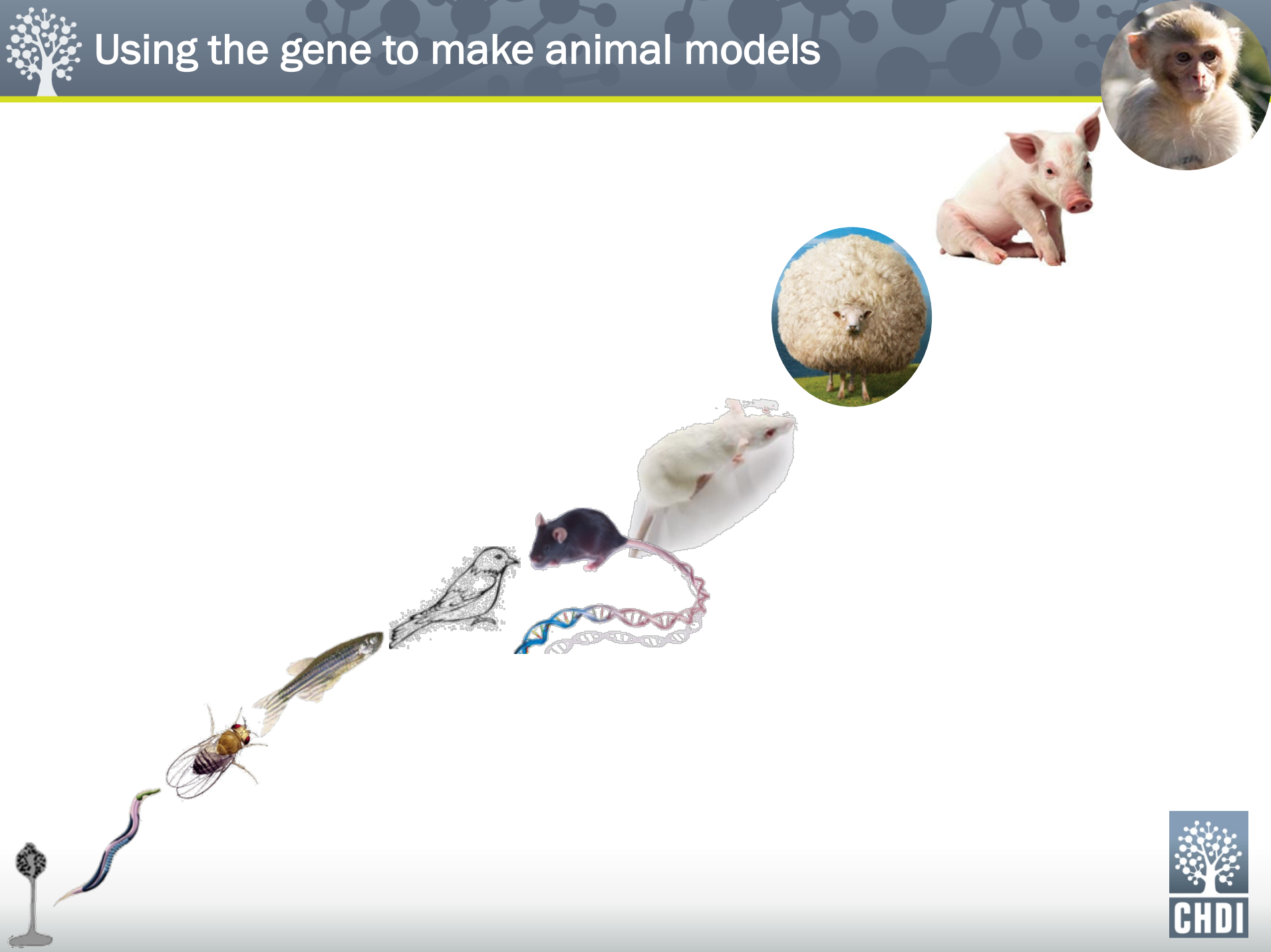
Official Title: A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Multiple Ascending Doses of Intrathecally Administered ISIS 443139 in Patients With Early Manifest **Huntington's Disease**

CHDI

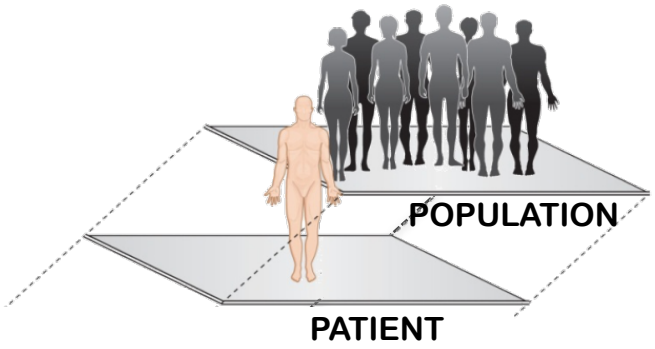
The many tethers to Huntington's disease

CHDI

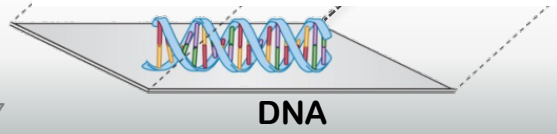
Using the gene to make animal models



Observational studies have been very useful



"There is nothing more valuable to a drug-hunter than a robust observation that is made in the population that they seek to treat"

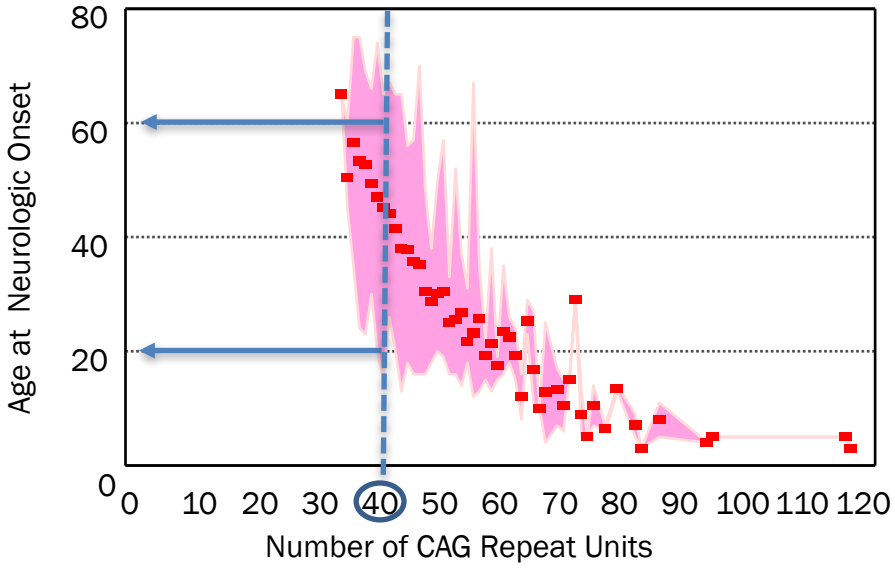


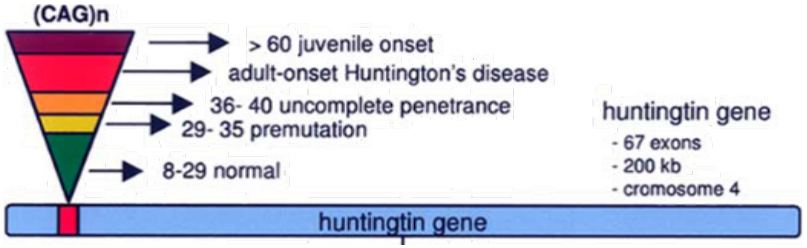
Can we identify & characterize everyone at risk for HD?

- Huntington's is a rare disease
  - Important to have the largest possible catch basin
- Sub populations may have unique features
  - Genetic modifiers
  - Environmental factors
  - Large isolated kindred's
- Enroll HD
  - A global prospective observational study
  - Worldwide registry of patients and physicians
  - Integrated global clinical research infrastructure
    - Informatics
    - Bio-banking
  - A platform to facilitate clinical studies in experimental medicine, observational studies and therapeutic trials

Huntington's patients continue to provide the keys

- Is it possible that the size of the triplet expansion affects the age at onset?





Genome Medicine

Review

Huntington's disease: the case for genetic modifiers

James F Gusella and Marcy E MacDonald

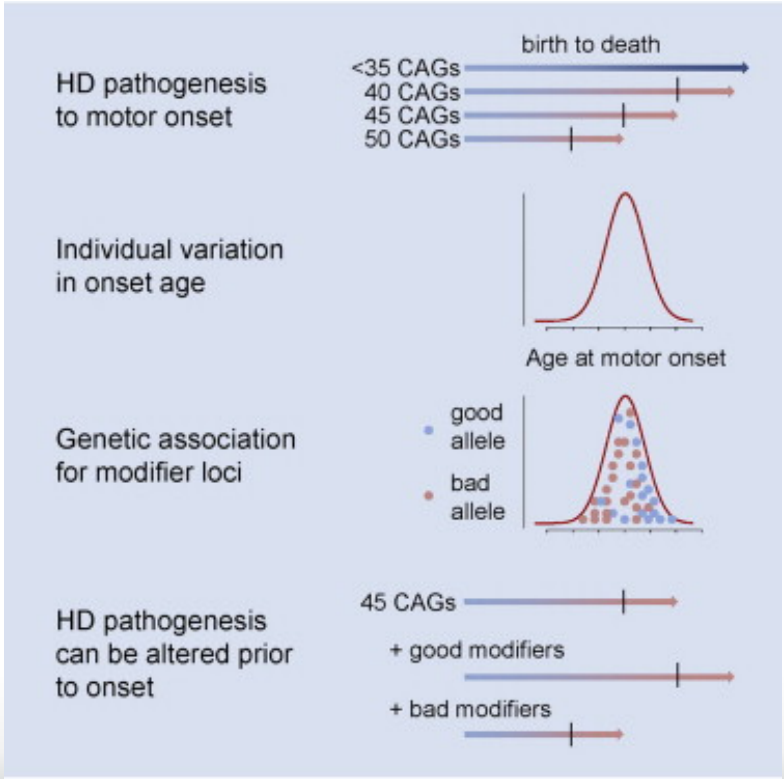
Address: Molecular Neurogenetics Unit, Center for Human Genetic Research, Massachusetts General Hospital, Boston, MA, 02114, USA.

Correspondence: James F Gusella. E-mail: gusella@helix.mgh.harvard.edu

CHDI

Huntington's patients continue to provide the keys

- A massive ~5000 subject GWAS was conducted
- Several loci reached genome wide significance
- Found both 'accelerators' and 'retarders'
- Well validated candidates genes
  will soon be elucidated

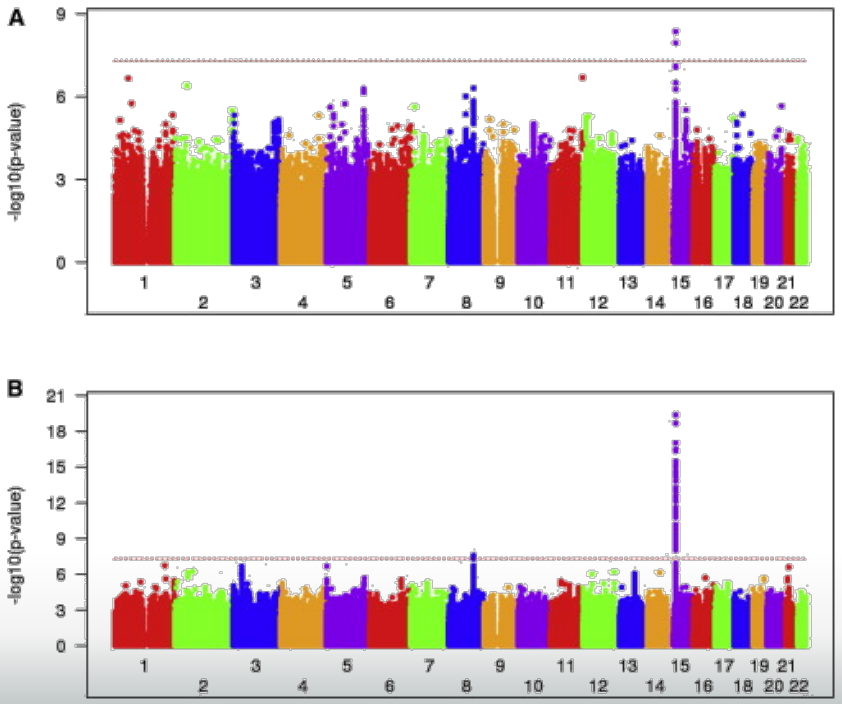


Cell

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



It's All About YOU

Huntington's Disease Society of America HDTrialfinder

HD Human Biology Project

WE WANT YOU!

CHDI

What I would like you to take away from my talk

- CHDI Foundation
  - Well-funded drug discovery organization
  - Very passionate and committed only to HD
- How can HD Gene Expansion Carriers Help?
  - Patients and their families have already made huge helpful contributions to our research efforts
  - Need to keep participating in any and all trials that you are eligible for
  - We are so grateful for your time, effort, and consent
- Huntingtin Lowering Efforts
  - Many credible efforts moving forward in parallel
  - Each has it's own unique profile
  - First agent is already in the clinic and blazing the trail
- Other approaches
  - Not a "one trick pony"
  - Constantly exploring other ways to modify the disease

Adriana Pacifici

28/07/1923 - 25/11/2017


Grazie!