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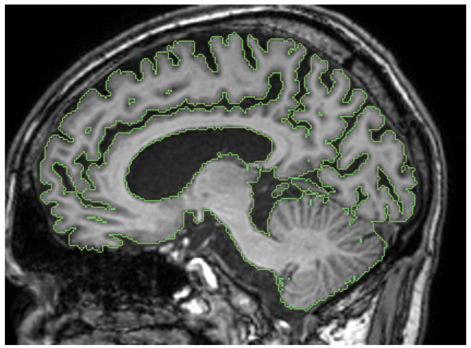
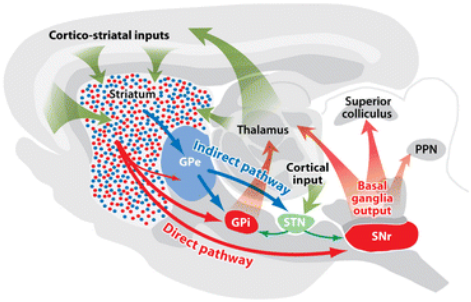
Accelerating therapeutic development for Huntington's disease

How CHDI Foundation approaches the treatment of Huntington's Disease





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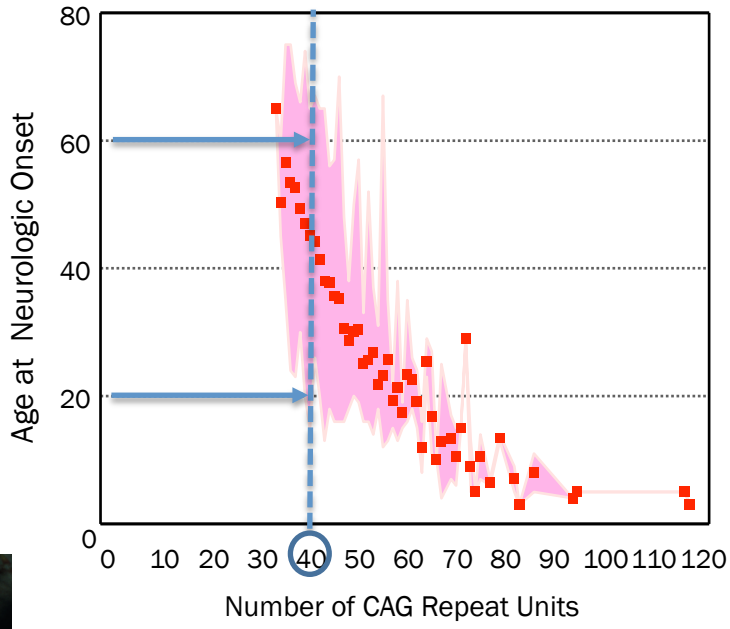
Huntington's Disease – not only a disease of the brain

Inherited neurodegenerative disorder

- Single mutation in HTT – exon 1 CAG expansion
- Autosomal dominant – 100% penetrant
- Prevalence: 1-2 per10,000
- Adult and juvenile forms – dependence on CAG length
- Progressive
- Lethal
- Age of onset modified by unknown genetic or environmental factors



Photos courtesy of Bernhard Landwehrmeyer

Classic neurological symptoms

- Motor – chorea, dyskinesias
- Cognitive –
- Psychiatric & behavioral

Other clinical features

- Weight loss
- Skeletal muscle atrophy
- Sleep disturbances
- Autonomic disturbances

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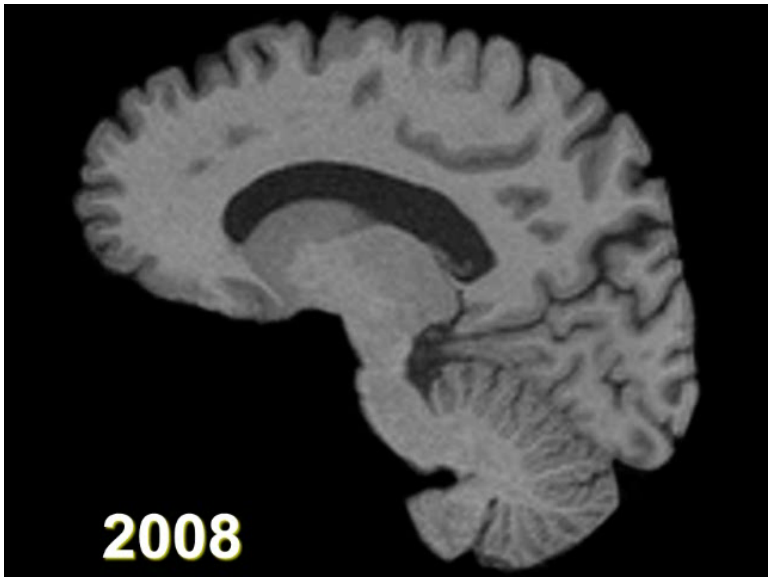
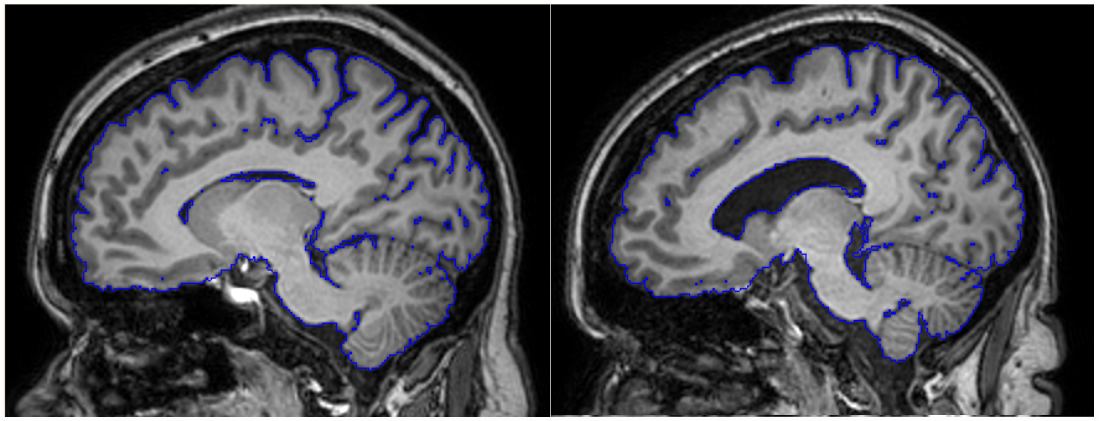
Huntington's Disease: dysfunction precedes clinical diagnosis





Courtesy of Sarah Tabrizi, IoN

Control

Pre-Diagnosis

HD

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CHDI Foundation – who are we?

Not-for-profit biomedical R&D organization
Solely dedicated to Huntington's disease

Resources not limiting

Research through partnerships

- >600 FTEs worldwide (CROs)
- >100 academic contracts
- Multiple pharma & biotech collaborations

- Understand the disease to treat it
- Drive drug discovery efforts – internal or collaborative
- Integrate knowledge
- Enable clinical trials and research

A Disease Foundation's "Wish List"

Enable the best academic investigators

- Provide structured funding – single contracts vs joint CHDI collaborations
- Unencumbered and QC'ed reagents

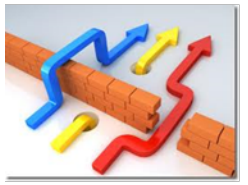
Leverage the billions of dollars Pharma has spent

- Access validating ligands for pharmacological POC studies
- Access significant drug development expertise

Access the most innovative Biotech approaches

- Novel modalities to lower HTT
- Delivery technologies – access to brain

Develop capabilities to drive internal campaigns



- Persevere where others have failed or abandoned
- Initiate ide novo efforts as needed
- Hands-on research experience critical

Enroll-HD

Identify and characterize every affected subject

- Available for observational and interventional trials
- Identify rare phenotypes (GWAS, clinical studies)
  - Large, isolated clusters exist (Venezuela, Colombia)

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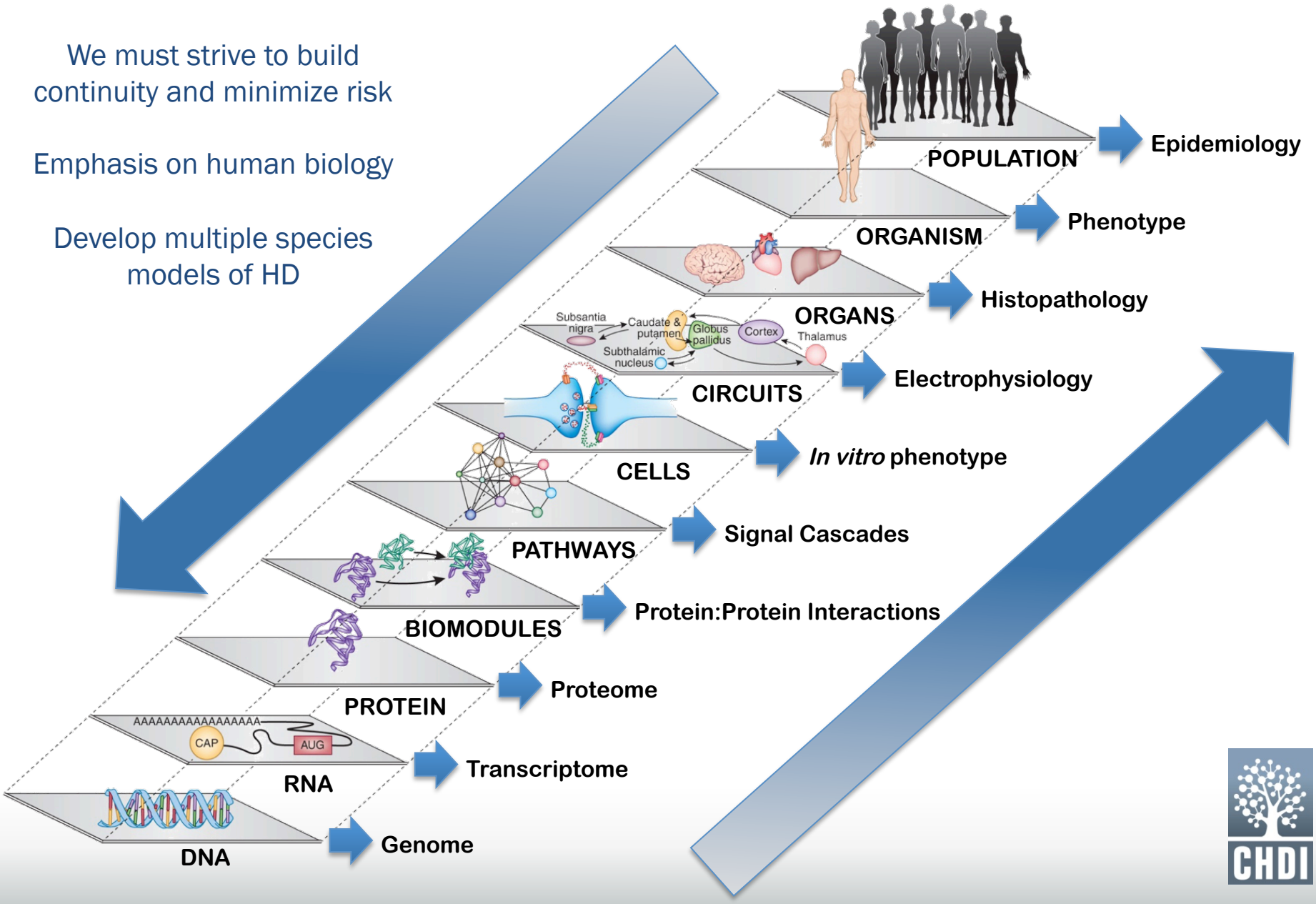
Challenges in Translational Research

We must strive to build continuity and minimize risk

Emphasis on human biology

Develop multiple species models of HD



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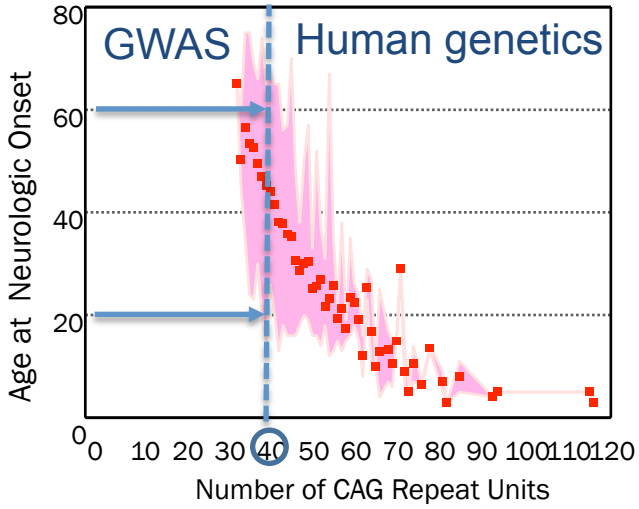
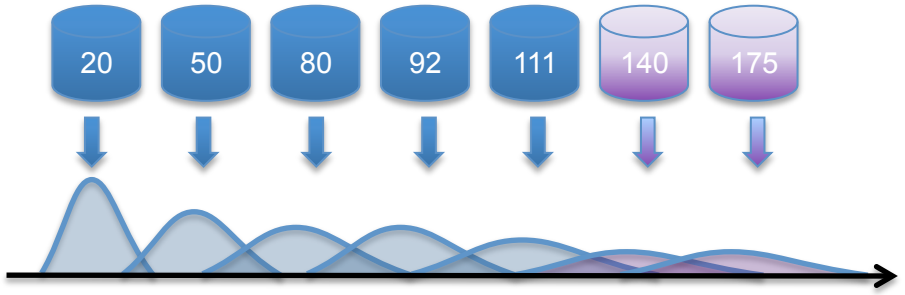
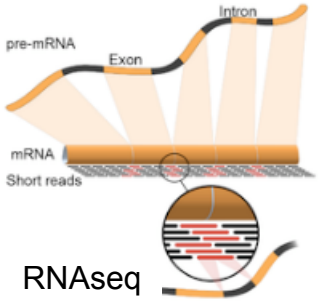
Discovery Research – emphasis on HD truths



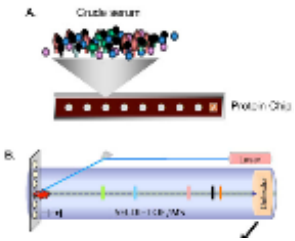


Allelic series in mice and hES

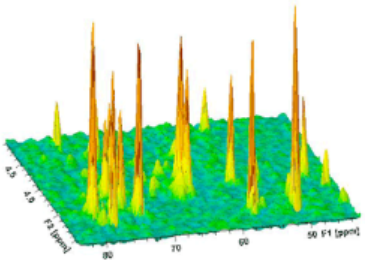
Systems Biology



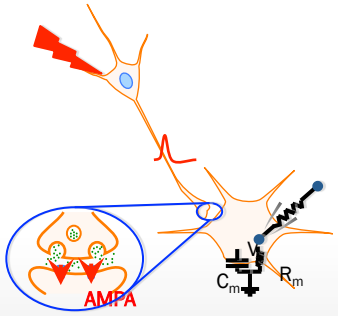
RNAseq



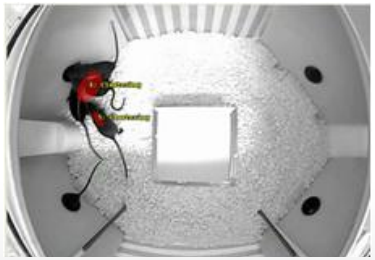
Proteomic Profiling



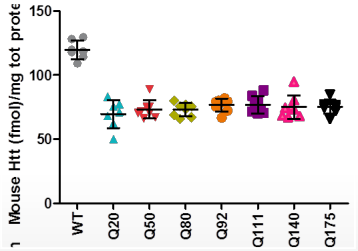
Metabolite Profiling



Physiology



Behavioral testing



HTT levels

Integrative Phenotyping

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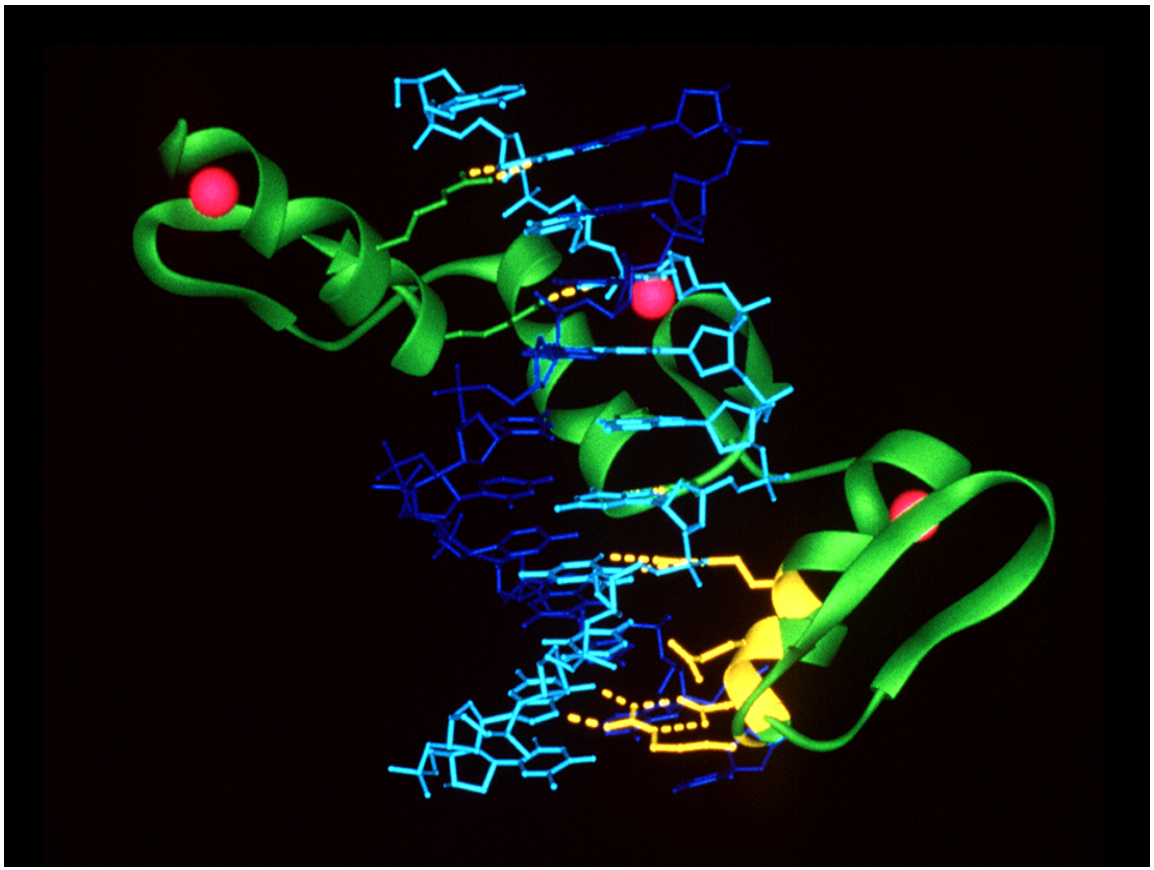
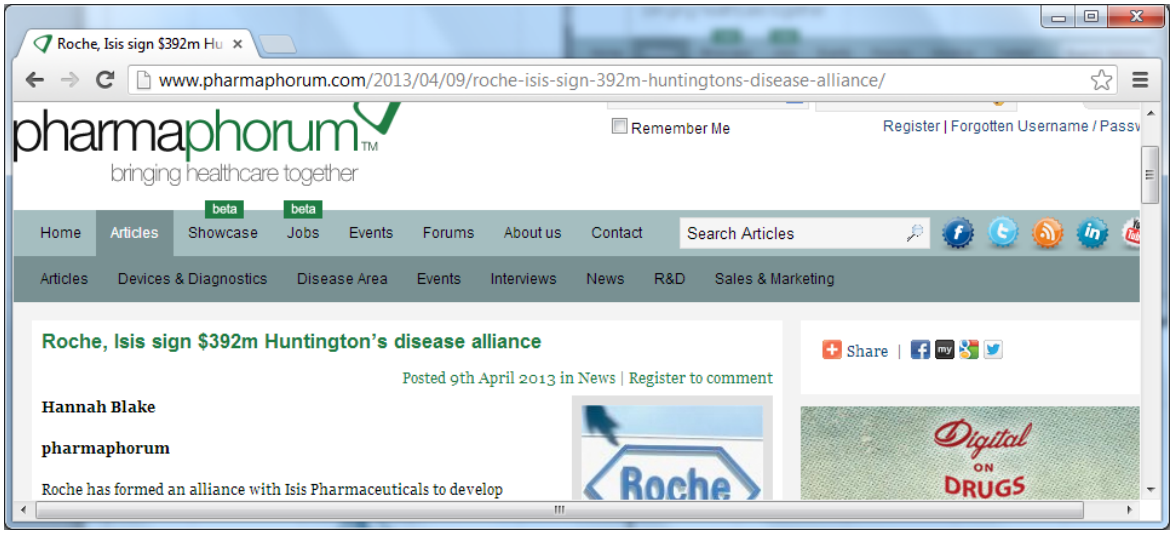
CHDI's focused areas for therapeutic development



- Modulate mutant *Huntingtin* expression
  - DNA-directed therapies (Sangamo)
  - RNA-directed therapies (ISIS, Genzyme, etc)
  - Small molecules (protein degradation, unknown MOA)

Molecular therapies for HD are entering the clinic



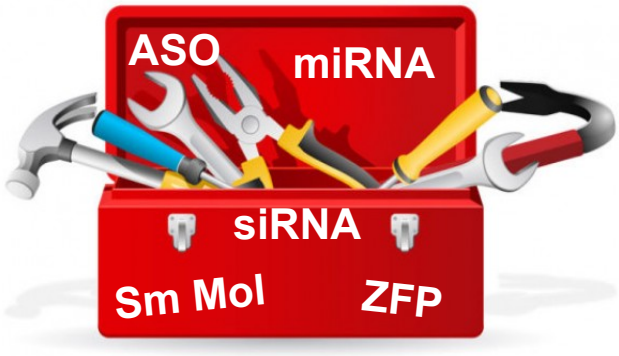
ISIS PHARMACEUTICALS

SANGAMO

How is CHDI helping now?

Support clinical development efforts – preclinical testing and enabling the trials

Genzyme
ISIS-Roche
Medtronic
Sangamo-Shire
Spark
Uniqure
UMass
Voyager

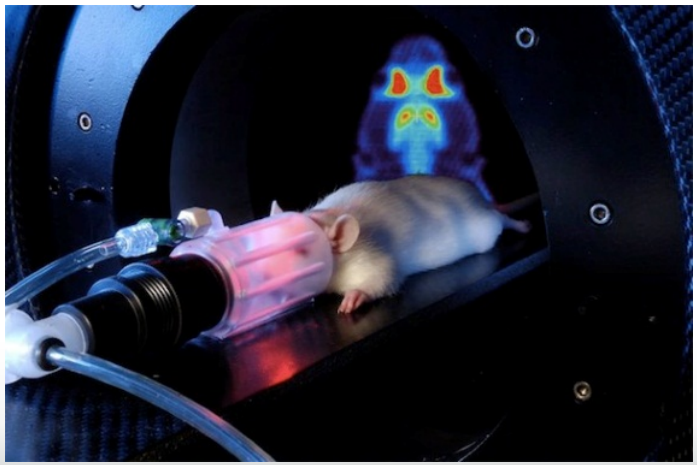


Implement a robust biomarker strategy

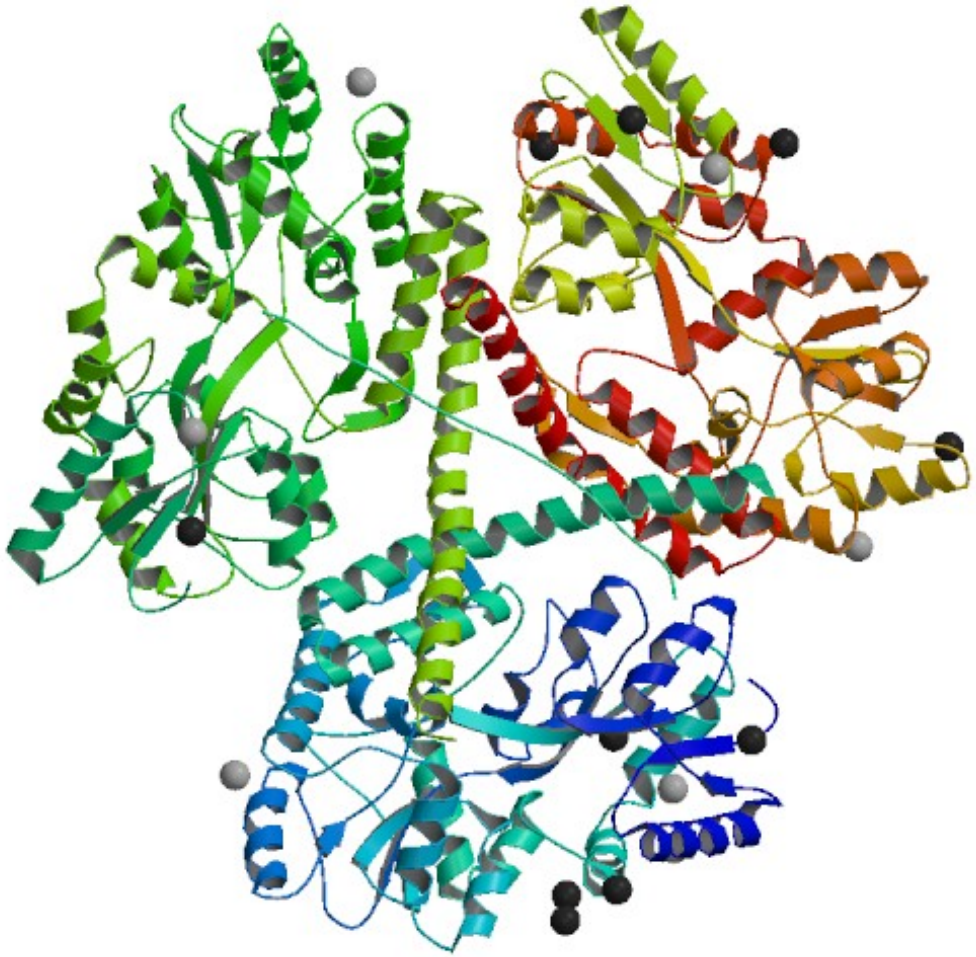
Molecular Markers
HTT levels in CSF
HTT-PET ligand development
Proteomics
Static & Dynamic (labeled)

Imaging Markers
PET Imaging
MR Spectroscopy

Other Markers
Quantitative EEG

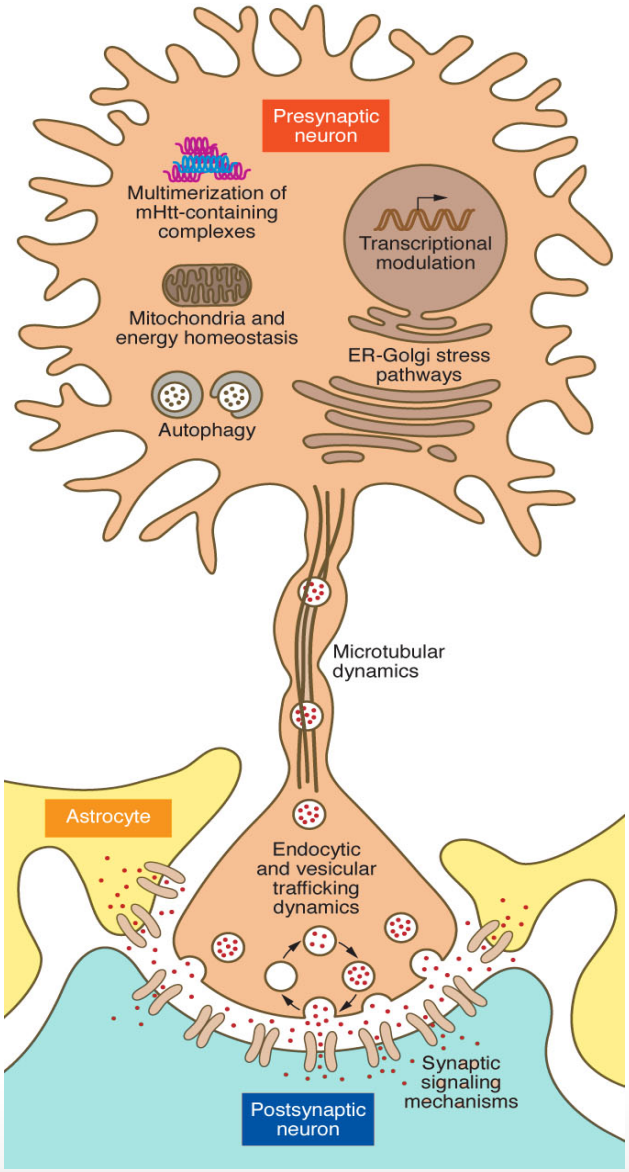


CHDI's focused areas for therapeutic development



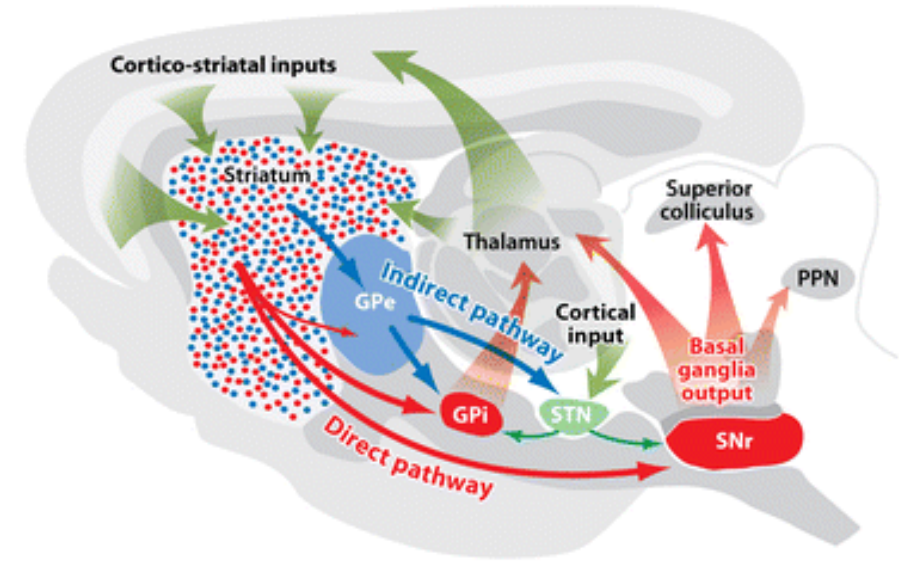
- Modulate HTT *structure-function* to decrease toxicity

CHDI's focused areas for therapeutic development



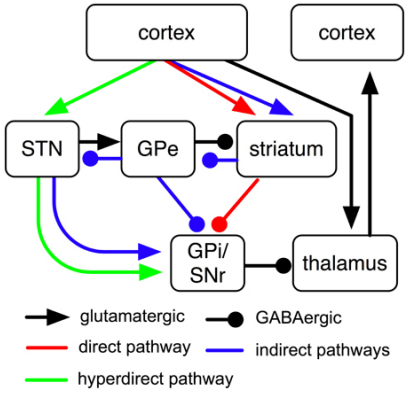
Munoz-Sanjuan and Bates, 2011

- Modulate key mechanisms central to HD
  - Synaptic physiology of the basal ganglia
  - Energetics (mitochondria-centric)
  - DNA repair
  - Lipid metabolism/signaling

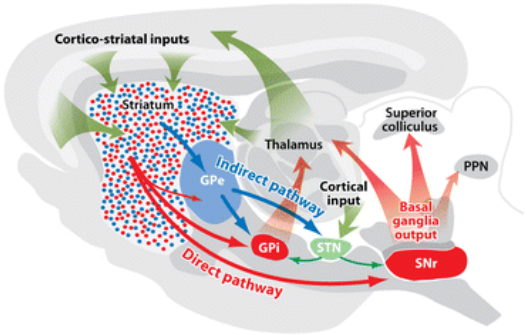


Courtesy of Dr. Surmeier

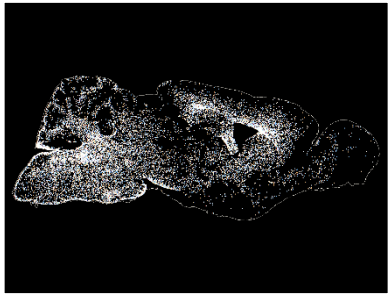
Targeting basal ganglia dysfunction for the treatment of HD



- Characterize neuronal dysfunction in HD models
  - Identify key synaptic deficits – most are acutely reversible
  - Basal ganglia circuitry recordings (*ex vivo* and *in vivo*)
  - Build a tool-box of HD models for optogenetic investigation
  - Use circuitry alterations to answer key questions for HTT lowering therapeutics



- Test pharmacological approaches to restore alterations
  - Explore cognitive and limbic systems with clinical assets (w/ Pharma)
    - Uncovered role for cGMP in disease (Pfizer PDE10 program; Phase II)



- Explore role of astrocyte biology in disease progression
  - Role of Kir4.1, Complement, and GLT-1
  - Transplantation of glial progenitor cells in HD models (Goldman)

- Support experimental medicine studies
  - Non-invasive imaging studies (PET, qEEG, MEG)
  - Deep brain stimulation (DBS) trials

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Acknowledgements