PREQUEL Multicenter Phase II Therapeutic Trial in Pre-symptomatic ("pre-manifest") HD

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--Many slices adapted from Kevin Biglan
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HDSA encourages all attendees to consult with their primary care provider, neurologist or other healthcare provider about any advice, exercise, medication, treatment, nutritional supplement or regimen that may have been mentioned as part of any presentation.
Huntington’s Disease

- Selective neuronal degeneration in Basal Ganglia--Caudate and putamen, but also cerebral cortex and other regions
- CAG expansion mutation: longer CAG repeats have earlier onset and more widespread degeneration

\[ \text{CAG-CAG-CAG} \quad \text{(DNA)} \]

\[ \downarrow \]

\[ \text{CAG-CAG-CAG} \quad \text{(RNA)} \]

\[ \downarrow \]

\[ \text{Gln---Gln---Gln} \quad \text{(Protein)} \]

(Q) (Q) (Q)
CAG Repeat length and Age of Onset of HD

- CAG repeats of 35 or less do not cause HD
- Incomplete penetrance (delayed onset) for CAG 36 to 40
- Longer expansions result in earlier onset ages—thus can roughly predict onset age
- Determinants of the rate of progression are still unknown

Quantification of Caudate Volumes: Regions of Interest

--Aylward et al Neurology 2004
Caudate Atrophy in Pre-Symptomatic HD: Longitudinal Study in Hopkins Cohort

--Aylward et al, Neurology 2004
Predict-HD Multicenter
HD Presymptomatic Study

Motor Exam Score

Striatal Volume

Self-Timed Finger Tapping

Odor Identification

Word List Learning

Speeded Finger Tapping

--- Paulsen and REDICT-HD 2007
White Matter Alterations in HD Mutation-Positive Pre-Symptomatic Individuals

- DTI: Water diffusion for fiber tract directionality

- Fractional anisotropy measure of white matter integrity
- SPM map of significant differences—blue and green represent HD Pre-Sx less than control

--Reading, Mori et al 2005
fMRI Alterations in HD Mutation-Positive Pre-Symptomatic Individuals

- 7 Pre-Symptomatic HD
- 7 controls
- Stroop interference type task

- SPM subtractive analysis
  - Baseline from active (by group)
  - Pre-Sx from controls

Between-group differences of BOLD response with the “active” condition of the task

--Reading et al Ann Neurol 2004
HD Over the Lifetime

Neurobiological marker (arbitrary units)

Diagnostic (motor) threshold

Age

CAG < 30  CAG > 39 Untreated
Design of Therapeutic Trials for Pre-Symptomatic HD

Neurobiological marker (arbitrary units)

Age

20 25 30 35 40 45 50 55

Beginning of treatment

Diagnostic (motor) threshold

CAG < 30
CAG > 39 Untreated
CAG > 39 Treated: hypothetical
Study in **Pre**-manifest HD of Coenzyme Q10 (**Ubiquinone**) **Leading to preventive trials (PREQUEL)**

**DEFINITION:** “A literary, dramatic, or cinematic work whose narrative takes place before that of a preexisting work or a sequel”¹

**ORIGIN:** George Lucas²

First known use: Press materials for the Godfather II²

Popularized in American culture by the Star Wars trilogy prequel (episodes 1-3)²

¹http://dictionary.reference.com
²http://en.wikipedia.org/wiki/Prequel
Long Term Objective

• Development of future preventive therapeutic trials in pre-manifest expansion positive individuals (with Coenzyme Q10 and/or other compounds?)
Primary Aim

• To determine the highest dosage of Co-Enzyme Q10 (amongst 600 mg/day, 1200 mg/day, 2400 mg/day) that is well tolerated in a pre-manifest mutation positive cohort in the context of a randomized, double-blind, parallel group trial.
Secondary Aim

- To establish the biological activity of CoQ10 in this population by assessing changes in serum levels of CoQ10, 8OHdG/8OHrG
Additional Objectives

• To assess the feasibility of designing and implementing a therapeutic trial in a pre-manifest population
• To assess the relationship between serum levels of CoQ, measures of oxidative stress (8OHdG/8OHRG), DNA repair mechanisms (OGG1)
• To further validate functional measures of disease in a pre-manifest population
Significance

• First trial to evaluate potential therapy in participants 100% at-risk for HD
• Allow selection of dosage that is tolerable (and biologically active?)
• Provide insight into process and feasibility of trials in pre-symptomatic participants
Why Coenzyme Q10?

Ubiquinone, coenzyme Q\textsubscript{10}
HD Cell Biology

Jean Marx, Science 2005
Intersection of Transcription and Metabolism

---Ross and Thompson Nature Medicine 2006
Preclinical Efficacy in R6/2 HD Mouse Model

K.M. Smith et al. BBA. 2006;
CARE-HD: Suggestive Evidence in Manifest HD
Dose of 600 mg/day for 30 Months

HSG. Neurology. 2001;57:397-404
CoQ in PD (-Schults 2002)

- 80 PD patients, randomized, double blind, 16 months
- Placebo, 300, 600, 1200 mg/ day
- 300 or 600 mg/ day modestly beneficial
- 1200 mg/ day –more benefit
- --suggestive, not conclusive
Rationale for Safety and Tolerability

- Healthy subjects
- Long exposures
- Lower tolerability threshold in non-ill participants?
  - Suggestion of differential tolerability of CoQ in healthy vs. manifest HD (Pre2care)
8OHDG: A biomarker of DNA oxidative damage

- Stable in serum and may be useful biomarker of oxidative damage
- Increased in caudate, parietal cortex in HD post-mortem brains
- Increased in R6/2 mouse model
- Increased in ALS and Friedreich’s Ataxia

Trial Population

- 90 Pre-manifest participants (Diagnostic confidence ≤ 3)
- Previously tested expansion (HD mutation) positive through standard pre-manifest testing programs
- No concomitant medication restrictions
- No unstable medical/psychiatric illness
Design

- 1:1:1 Randomized to 600 mg/day, 1200 mg/day, or 2400 mg/day
- Double-blind parallel group trial
- Titrated over 4 weeks to assigned dosage
- Followed for 20 weeks after randomization
- Primary outcome is tolerability
Outcomes

• Primary Outcome
  – Tolerability: ability to complete study on randomized treatment assignment

• Secondary Outcomes
  – Additional tolerability: ability to complete study on active drug, AEs, # of dosage reductions
  – Safety: serum chemistries, UA, CBC, EKG
  – Serum CoQ levels
  – Serum 8OHdG/8OHrG levels and OGG1 levels
  – HD clinical and functional scales
Power Analysis

- Sample Size of 30 per group
- Observed tolerability compared to a tolerability that would be unacceptably low (<75%)
- 90% power to correctly detect dosage as tolerable
- 20% probability of incorrectly identifying dosage as tolerable if dosage is actually intolerable
## Sites

<table>
<thead>
<tr>
<th>Site #</th>
<th>Site Name</th>
<th>Investigator</th>
<th>Coordinator</th>
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<tr>
<td>1</td>
<td>University of Rochester</td>
<td>Peter Como, PhD</td>
<td>Amy M. Chesire, LCSW-R, MSG</td>
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<tr>
<td>7</td>
<td>Baylor College of Medicine</td>
<td>Joseph Jankovic, MD</td>
<td>Christine Hunter, RN</td>
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<td>24</td>
<td>University of Iowa</td>
<td>Leigh J. Beglinger, PhD</td>
<td>William H. Adams, BA</td>
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<td>27</td>
<td>Washington University</td>
<td>Joel S. Perlmutter, MD</td>
<td>Stacey K. Barton, MSW, LCSW</td>
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<td>28</td>
<td>Johns Hopkins University</td>
<td>Russell Margolis, MD</td>
<td>Claire Welsh</td>
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<td>Emory</td>
<td>Claudia Testa, MD, PhD</td>
<td>Joan M. Harrison, MN</td>
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<td>45</td>
<td>Indiana University</td>
<td>Joanne M. Wojcieszek, MD</td>
<td>Jo Belden, LPN, CCRC</td>
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<td>52</td>
<td>Colorado Neurological Institute</td>
<td>Rajeev Kumar, MD</td>
<td>Dawn Miracle, BS, MS</td>
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<td>University of California Davis Medical Center</td>
<td>Vicki L. Wheelock, MD</td>
<td>Margaret Sanders, BS</td>
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<tr>
<td>71</td>
<td>Hennepin County Medical Center</td>
<td>Martha Nance, MD</td>
<td>Dawn Radtke, RN, CCRC</td>
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<tr>
<td>73</td>
<td>UC San Francisco</td>
<td>Michael Geschwind, MD, PhD</td>
<td>Mira Guzijan, MA</td>
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</table>
Study Sites

- University of Rochester
- Baylor College of Medicine
- University of Iowa
- Washington University
- Johns Hopkins University
- Indiana University
- Colorado Neurological Institute
- University of California—Davis
- Hennepin County Medical Center
- University of California—San Francisco
## HD Drugs in the “Pipeline”

<table>
<thead>
<tr>
<th>DRUG</th>
<th>ACTIONS</th>
<th>STATUS IN HUNTINGTON’S</th>
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<tbody>
<tr>
<td>Coenzyme Q10</td>
<td>Antioxidant; protects mitochondria</td>
<td>Late clinical trials</td>
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<tr>
<td>Creatine</td>
<td>Stabilizes mitochondria</td>
<td>Early clinical trials</td>
</tr>
<tr>
<td>Cystamine</td>
<td>Decreases Htt aggregation?</td>
<td>Early clinical trials</td>
</tr>
<tr>
<td>Geldanamycin</td>
<td>Decreases Htt aggregation</td>
<td>Preclinical</td>
</tr>
<tr>
<td>HDAC inhibitors (butyrates, SAHA)</td>
<td>Counters Htt’s transcription effects</td>
<td>Early clinical trials</td>
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<tr>
<td>Memantine</td>
<td>Neurotransmission</td>
<td>Early clinical trials</td>
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<tr>
<td>Minocycline</td>
<td>Decreases cell death, Htt aggregation</td>
<td>Early clinical trials</td>
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<tr>
<td>Paroxetine</td>
<td>Protects neurons by increasing BDNF</td>
<td>Preclinical</td>
</tr>
<tr>
<td>Rapamycin</td>
<td>Decreases Htt aggregation by stimulating autophagy</td>
<td>Preclinical</td>
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---Jean Marx Science 2005---
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HD Cell Biology

Jean Marx, Science 2005
Predict-HD Multicenter HD Presymptomatic Study

--Paulsen and Predict-HD in preparation
Caudate Atrophy Predates Disease Onset