Participating in clinical research

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Presenter Disclosures

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The following personal financial relationships with commercial interests relevant to this presentation existed during the past 12 months:

Research support from Medivation, Neurosearch, TEVA
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Goals of research

• To understand the clinical aspects of HD
• To understand the underlying biology (anatomy, biochemistry, genetics, pharmacology, neurophysiology, physiology…)
• To find better treatments

• To cure HD
HD Research

- Gene localized 1983
- Gene identified 1993
- Discovery of the HD gene permitted the creation of laboratory models for use in experimental research
- HD researchers learn from researchers in Parkinson’s disease and Alzheimer’s disease, and other “CAG repeat diseases”. And vice versa
Of mice and men
Experimental research tools

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<thead>
<tr>
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<th>Cells in culture</th>
<th>Roundworm</th>
<th>Fruitfly</th>
<th>Zebrafish</th>
<th>Mouse</th>
<th>Human</th>
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<tbody>
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<td>HD</td>
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<td>Other CAG repeat diseases</td>
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<td>Other neurodegenerative diseases (PD, AD)</td>
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Trouble taking out the trash

- Both normal and abnormal protein are produced
- Abnormal protein is not recycled or removed properly
- The abnormal protein sits in a heap inside the cell

- Proteasome—the cell’s garbage disposal
Abnormal processing of huntingtin

- Huntingtin is cut into (sticky) pieces by caspases
- Abnormal huntingtin is a more favorable target for caspases
- Blocking caspases might help HD

- Huntingtin inclusions
  - No inclusions when caspase blocked
Converging concepts

- HD—abnormal processing of huntingtin protein—intraneural inclusions
- PD—abnormal processing of synuclein protein—intracellular inclusions
- AD—abnormal processing of amyloid protein—plaques and tangles
- PD-like diseases—abnormal processing of tau protein—intracellular inclusions
Potential avenues for therapy

- Block caspase enzyme (involved in the initial processing of the HD protein)
  - minocycline
- Increase or help “chaperone” proteins (involved in removing and recycling proteins)
- “vaccines” to react to and remove the abnormal protein
- Prevent other normal proteins from collecting in the inclusions
  - phenylbutyrate

- Reduce secondary changes in the cell that lead to further damage (eg, injury to the mitochondria)
  - Creatine, Coenzyme Q10, antioxidans
- Prevent production of the abnormal HD protein in the first place
  - Antisense technology/ RNA interference
- Replace damaged cells with new ones
  - Stem cell, transplantation therapy
RNA interference

DNA (xerox) RNA (read) protein
DNA (xerox) RNA no protein

“block” the abnormal HD gene
Do not block the normal HD gene
Prevent production of the abnormal protein

HD has been prevented
HD clinical research milestones

- HD described
- HD gene localized
- HD gene identified
- HSG formed
- PREDICT-HD
- TETRA-HD
- CARE-HD
- PHAROS
- TRENDS-HD
- HART, HORIZON, CREST-E, 2CARE
- ENROLL-HD

1872
1983
1993
1994
1997
1999
2001
2002
2005
2006
2008-2010
2011
Why HD research is important to researchers

• Everyone with HD has the same root cause (CAG repeat expansion)
• We can determine ahead of time who will develop the disease
• Disease-modifying treatment effects can be studied in presymptomatic individuals
• Treatments that work for one neurodegenerative disease might also help another disease
Why HD research is important to patients and families
Why do we need clinical research at all?
Why should I participate? How can I participate?

• Partnership with the research team
• For the kids
• Being part of the solution
• If the drug works, you got it first!
• If the drug works, it was because of you!

• Stay connected
• HSG, HDSA, CHDI
• [www.clinicaltrials.gov](http://www.clinicaltrials.gov)
• Talk to your HD doc
• Visit a COE
Before participating in a research study, you should...

• Know EXACTLY what is required of you (how many visits, how long, how much flexibility)
• Know whether the study includes treatment, or just observation
• Know what the treatment is and what it is supposed to do, and what is known about possible adverse effects
• Know whether it is a “placebo-controlled” trial or not
• Know whether it is a “blinded” or “double-blinded” trial
• Know whether you will be paid, reimbursed, compensated in any way for your participation
• Know EXACTLY whom to call AT ANY TIME OF DAY if there is a problem
Do not…

• Try a research study for a few weeks just to see if you like it
• Deliberately take a study drug incorrectly
• Have someone else complete study procedures for you
Recently completed HSG trials

- RID-HD (riluzole: OK but not overwhelming; 2001)
- TETRA-HD (tetrabenazine: reduces chorea about 20%; led to FDA approval of this drug; 2004)
- TREND-HD (ethyl-EPA (“fish oil”): terminated early due to lack of effect; 2008)
- DOMINO (minocycline: not harmful but not worth pursuing; 2009)
- HORIZON (dimebon: not effective in treating cognition; 2011)
- HART (ACR-16 (pridopidine): full results pending, European study shows slightly favorable results; 2011)
- PHAROS (observational trial of at-risk individuals: full results pending)
- COHORT (observational trial of everyone: just ending, no results available)
Currently enrolling HSG trials

- 2CARE: coenzyme Q10
- CREST-E: creatine
- PREQUEL: coenzyme Q10 in presymptomatic, gene+ subjects
- PREDICT-HD: observational study of gene positive, not yet diagnosed subjects (and some gene negative individuals)
- ENROLL-HD: intent is to combine the best features of COHORT and REGISTRY (European study), emphasizing world-wide participation, modular design
What about stem cells? What about gene therapy?

- Dr. Nance’s views…
  - HD is not the first/best disease in which to try stem cell therapy
  - HD IS clearly the first/best neurodegenerative disease in which to try gene therapy, particularly RNA interference
  - Stay tuned…
What if…

• I just don’t want to “be a guinea pig”
  – Several large-scale studies are “observational” (do not involve any specific treatment)
  – How about helping someone else participate in research (drive them to their appointment; buy them lunch; babysit their children; etc.)
• I live far away from a “research center”
  – ENROLL-HD is working on this problem
  – Technology may help in the future
• My life is in turmoil
  – Your health trumps anyone’s research. Get help.
Together, we CAN solve the puzzle of HD