Huntington's Disease Society of America

Participating in clinical research

Martha A. Nance MD
Hennepin County Medical Center HD Center of Excellence
Struthers Parkinson's Center

Presenter Disclosures

Martha Nance

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

Research support from Medivation, Neurosearch, TEVA

The information provided by speakers in workshops, forums, sharing/networking sessions and any other educational presentation made as part of the 2011 HDSA convention program is for informational use only.

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.

Goals of research

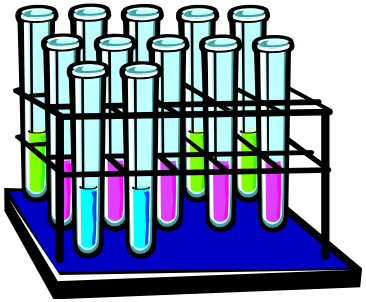
- To understand the clinical aspects of HD
- To understand the underlying biology (anatomy, biochemistry, genetics, pharmacology, neurophysiology, physiology…)
- To find better treatments

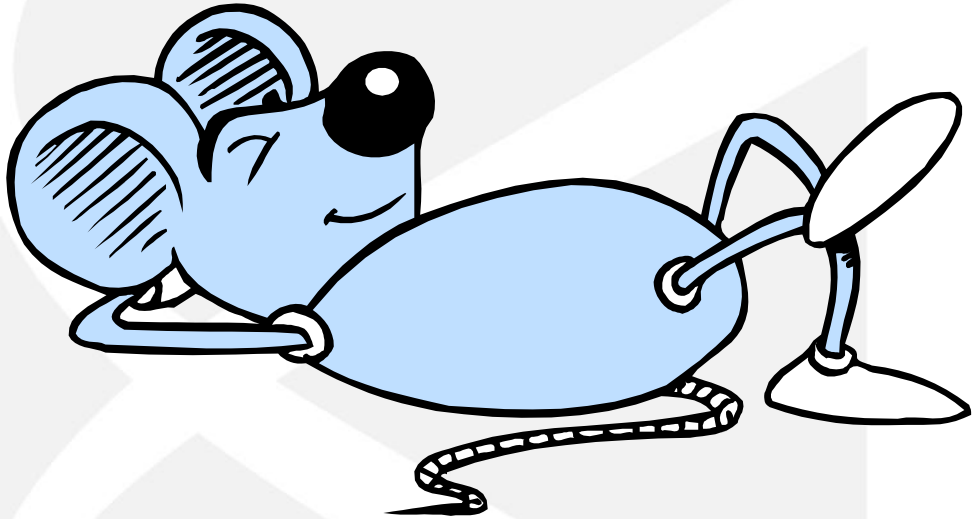
- To cure HD

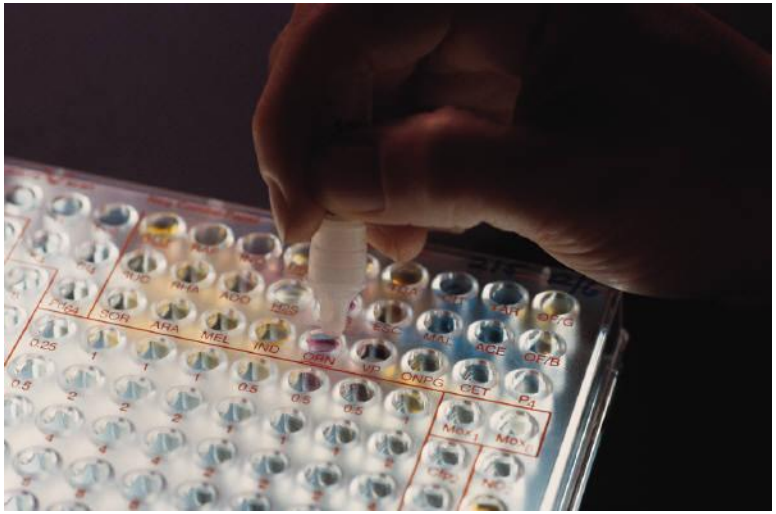
HD Research

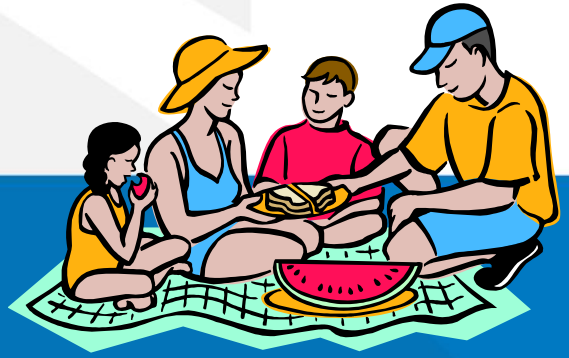
- Gene localized 1983
- Gene identified 1993
- Discovery of the HD gene permitted the creation of laboratory models for use in experimental research
- HD researchers learn from researchers in Parkinson's disease and Alzheimer's disease, and other "CAG repeat diseases". And vice versa

Of mice and men









Huntington's Disease Society of America

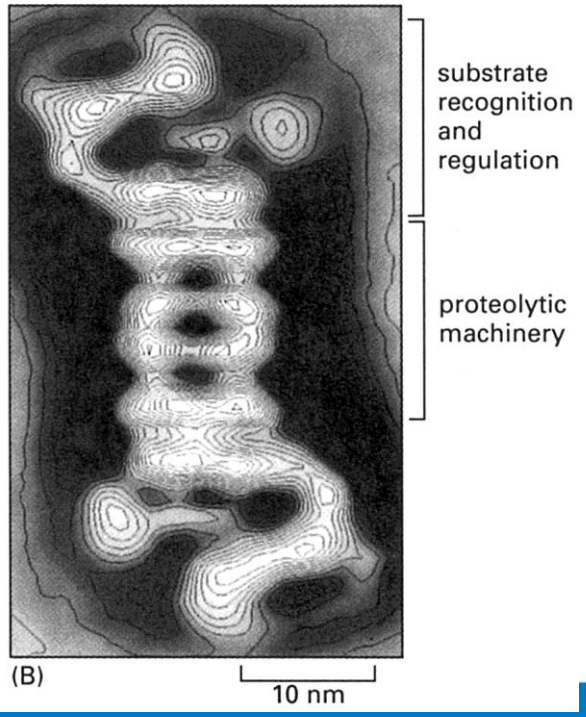
Experimental research tools

	Cells in culture	Roundworm	Fruitfly	Zebrafish	Mouse	Human
HD						
Other CAG repeat diseases						
Other neurodegenerative diseases (PD, AD)						

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

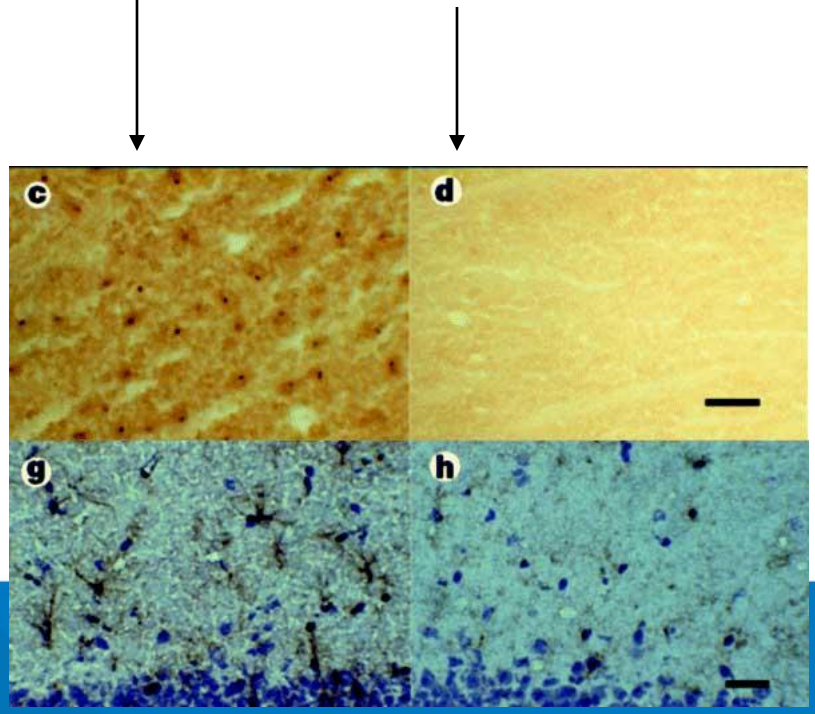
- Proteasome—the cell's garbage disposal



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



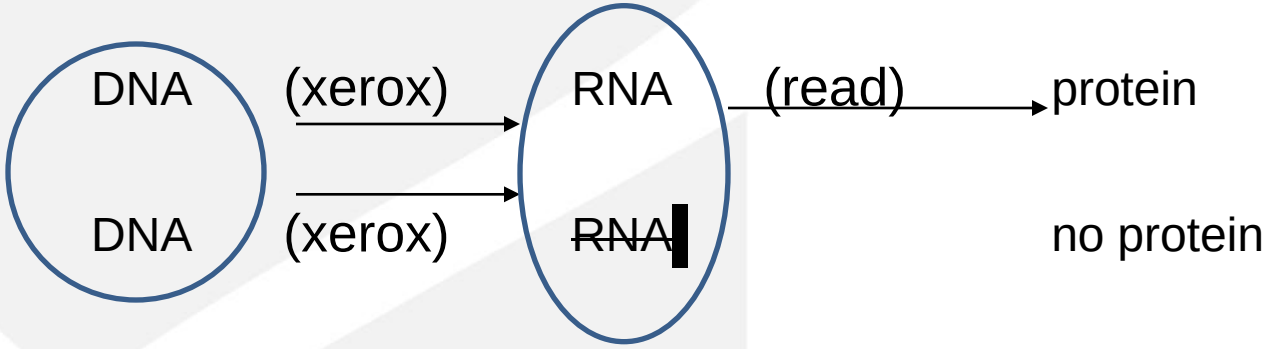
Converging concepts

- HD—abnormal processing of huntingtin protein—intranuclear 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, antioxidants
- 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

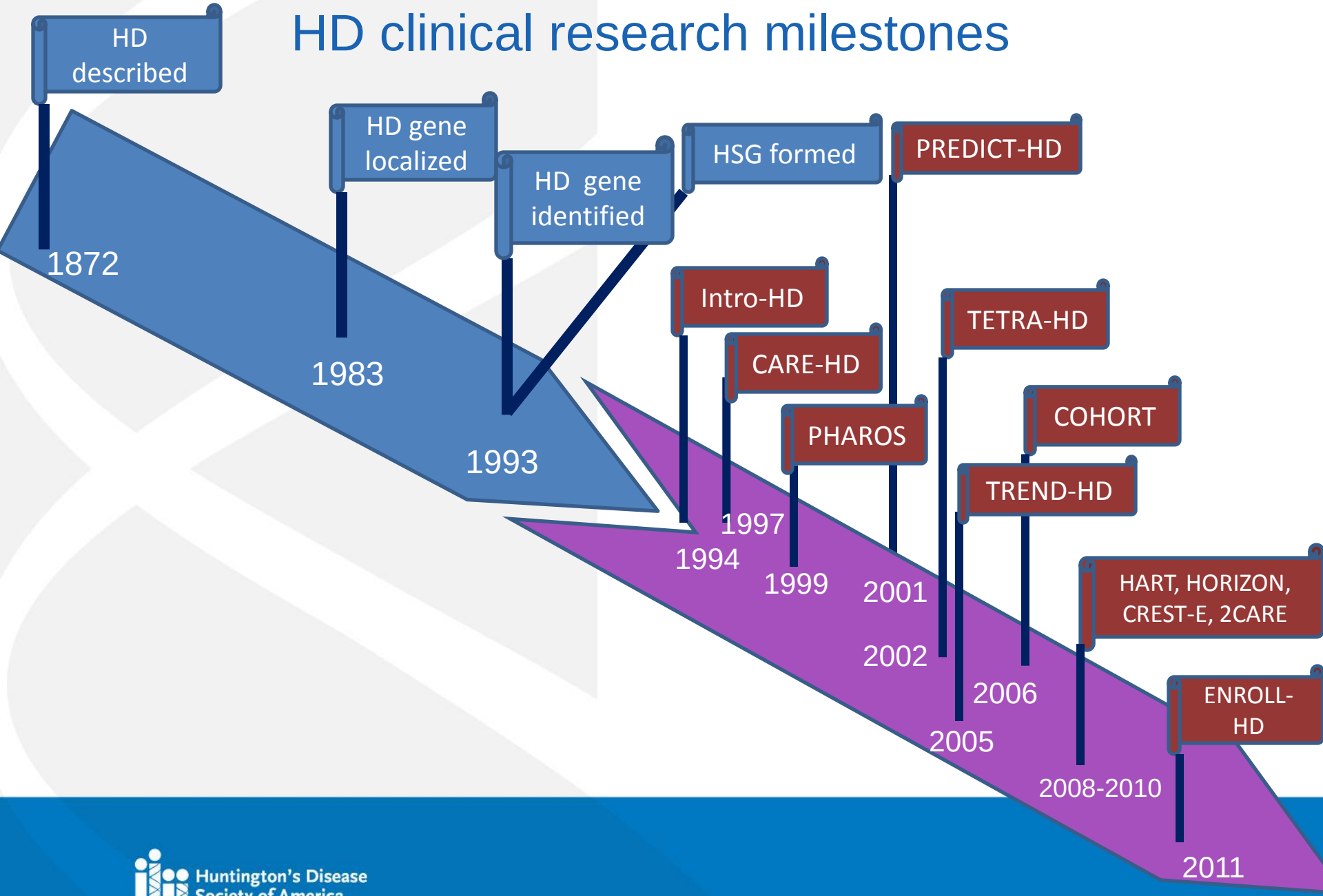
RNA interference



"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



Huntington's Disease Society of America

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
- 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