

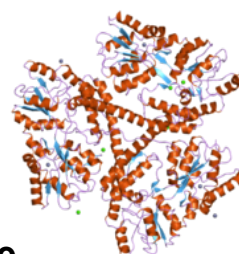


Huntington's Disease Research Update: A Time of Promise and Hope

Kathrin LaFaver, M.D.
Director of the Parkinson's and Movement Disorder Clinic
University of Louisville
Huntington's Disease Patient Education Day
10/03/2015

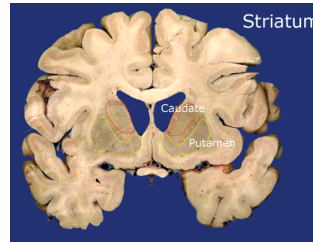
Outline

- **Overview of Huntington's Disease**
- **Research in Huntington's Disease**
- **Observational Studies**
- **New Wave of HD Clinical Trials Have Begun**



Huntington's Disease: The Basics

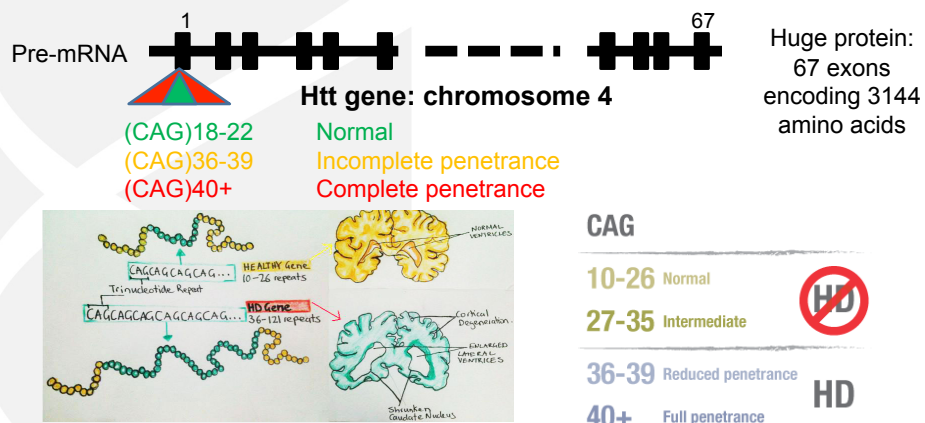
- Inherited Neurodegenerative disease
 - The striatum shrinks 50% by the time a patient exhibits their first motor symptom
- Prevalence
 - Typically "Late" onset, ~30-50
 - 1:10,000 affected, 1:200,000 at risk
- Symptoms
 - Behavioral/Emotional
 - Depression, Personality Changes, Mood Swings, Social Withdrawal
 - Cognitive Deficits
 - Short-term Memory Deficits
 - Forgetfulness, Difficulty Concentrating, Impaired Judgment
 - Motor
 - Chorea: Involuntary Movements
 - Rigidity in subset
 - Lack of Coordination
 - Difficulty Walking ("intoxicated" appearance)
 - Slurred Speech and Difficulty Swallowing
- Disease modifying therapy
 - None



 Huntington's Disease Society of America

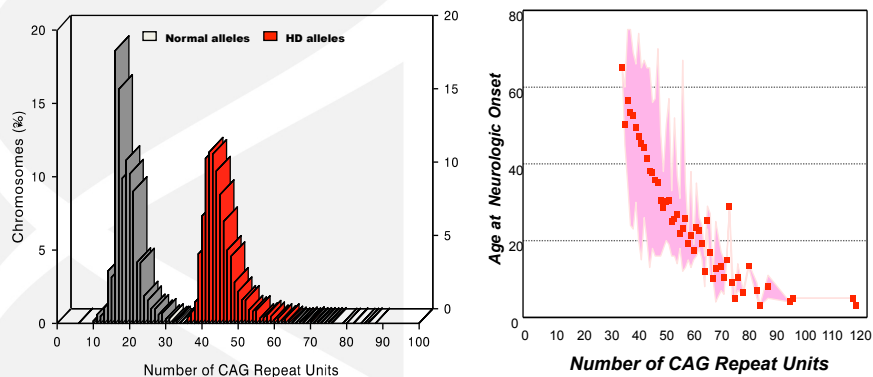
Mutant Huntingtin (Htt) is THE Target

- ALL of HD can be explained by a single mutation in a single gene (huntingtin)



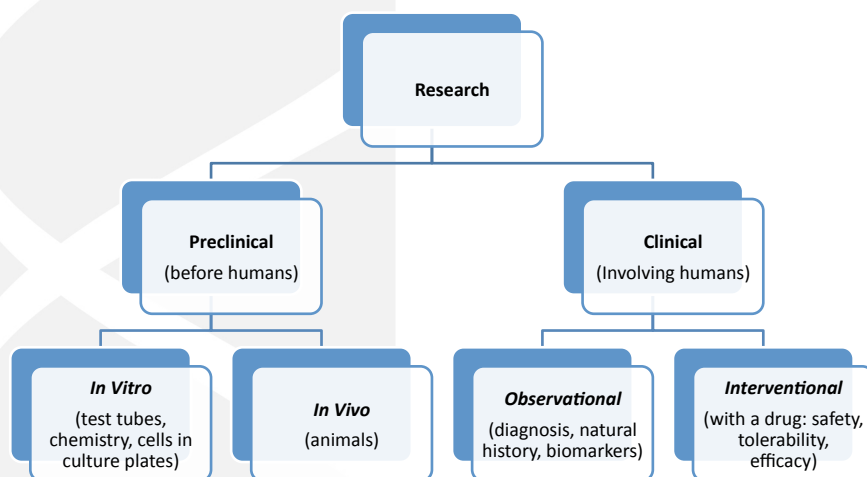
 Huntington's Disease Society of America

Increasing CAG Repeats are Inversely Correlated to Age of Onset



from J. Gusella, Harvard/MGH

Research Definitions



"Clinical Trials" = Experiments with People
(only one part of the research process)

Current State of Worldwide HD Research in 2015



- **CHDI Foundation**

- Non-profit biotechnology organization focused solely on finding therapies for HD.
- Both internal drug discovery programs and external funding
- ~\$100-120 million/year on R&D efforts

- **NINDS: National Institute for Neurological Diseases and Stroke**

- Division of NIH responsible for HD research funding
- ~\$57 million in FY2013

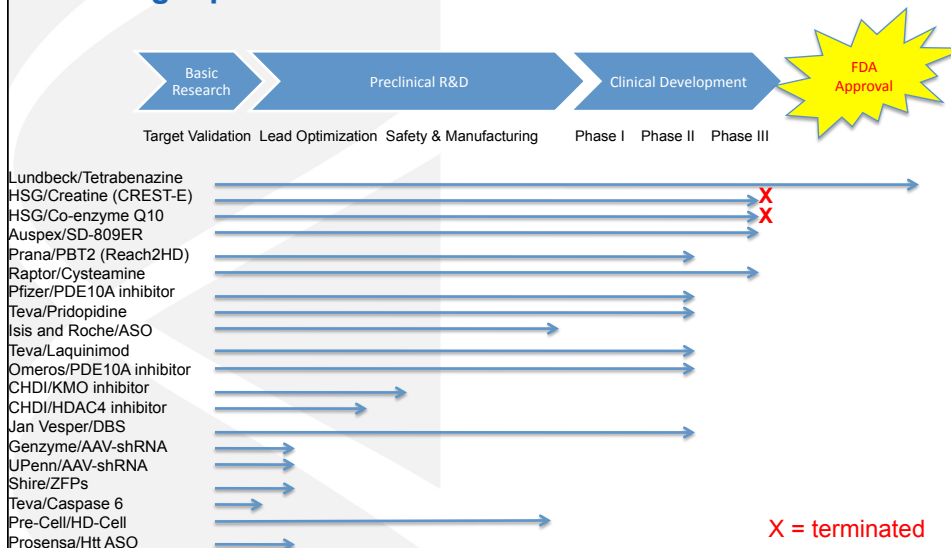
- **European HD Network (EHDN):** Funded by CHDI to support clinical trials in Europe

- **Huntington's Study Group (HSG):** approximately 104 clinical research sites located throughout the United States, Canada, Europe, Australia, New Zealand, and South America.

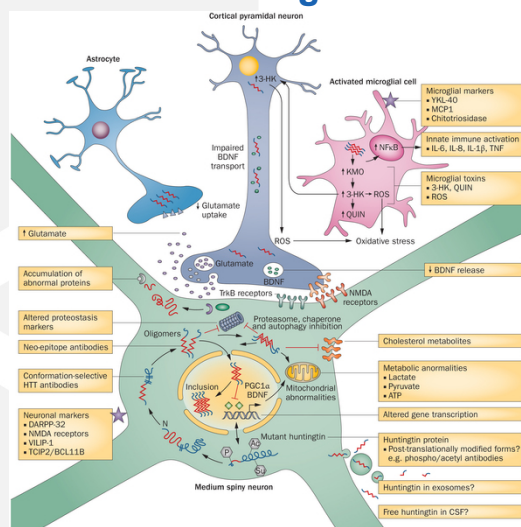
- **Additional HD Research Support:** Hereditary Disease Foundation (HDF), Huntington Society of Canada (HSC) and HDSA.



HD Drug Pipeline: 2015



What Doesn't Huntingtin Screw Up?



Huntington's Disease
Society of America

Many Approaches in Development to Correct HD

- Transcriptional: HDAC inhibition
- Protein clearance/folding: stimulate autophagy ("self-eating"), mTor inhibition
- Neuroinflammation/oxidative stress: laquinimod and KMO inhibition
- Synaptic function: PDEs
- Energy/mitochondrial function: creatine, olesoxime
- Neurotrophic support: trkB agonists, BDNF, HD-Cell
- Gene silencing: ASOs, shRNA, RNAi, ZFNs
- **New biology being uncovered everyday!!**

Huntington's Disease
Society of America

“HD is the Most Curable Incurable Disorder”

- **Diagnostic certainty**
 - Discovery of gene in 1993 led to accurate genetic diagnosis, allows identification of pre-symptomatic individuals
 - ALL of HD can be explained by a single mutation in a single gene (huntingtin)
- **Intense scientific activity**
 - Importance of attracting best scientific minds to the field has led to novel insights not only for HD but also for: neurodegenerative disorders, gene therapy, stem cells, informatics
- **Organized clinical networks**
 - “Trial ready” network of highly trained and committed clinicians collecting data in a uniform manner
- **Clinical Trials have already been successfully completed**
 - Includes one FDA-approved drug (Tetrabenazine)



Informing and Engaging the HD Community

- HDSA Research Webinar Series
- Monthly research seminars given by HD scientists
 - Given in easily understood language
 - Opportunities for questions
 - Archived for future reference @ www.hdsa.org



Recent webinars

George Yohrling, PhD
Neil Aronin, MD
Holly Kordasiewicz, PhD
David Howland, PhD
Beth Thomas PhD
William Yang, MD, PhD
Amber Southwell, PhD
Vicki Wheelock, MD & Jan Nolte, PhD
Michael Hayden, MD, PhD

The Year in Review for HD Research
Gene Silencing approaches for HD
ASOs
Progress in HD Animal Model Development
Histone Deacetylases (HDAC) as treatment for HD
Using mouse models to gain therapeutic insights for HD
Allele-specific silencing of Htt
Mesenchymal Stem cells for HD, Pre Cell Trial
Pride-HD

HDSA
UMass Medical School
Isis Pharma
CHDI
Scripps Research Instit
UCLA
UBC
UC-Davis
Teva



What Can I Do To Help?



- Be part of the research experience!
 - Sign up on HD Trial Finder for personalized HD trial information. HDTrialFinder.org
 - Join Enroll-HD
 - Download HD News App to stay on top of latest news and HD related events
 - Visit www.clinicaltrials.gov, www.hdsa.org or www.huntington-study-group.org for HD trial details
 - Become an HDSA Research Champion.
- Remember, NO drug to treat HD will ever be approved without clinical trials!

What is a Clinical Trial?

It is research that uses human volunteers to answer specific questions about a disease or to test a specific treatment.

Types of Trials –

An **observational trial** studies ways to diagnose or follow disease.

There is no drug or treatment being tested. Participants may have to take different kinds of tests to monitor for changes.

A **clinical or interventional trial** investigates the safety, tolerability or effectiveness of supplements, drugs, and other treatments like surgery and physical therapy.

Phases of Clinical Trials

Phase 1

- A *Phase 1* trial usually is a small group of participants that are testing the **safety** of the supplement, drug or treatment.

Phase 2

- A *Phase 2* trial tests the supplement, drug or treatment for **safety and best dosage** in a small group of participants who have the specific disease.

Phase 3

- Tests for **effectiveness** of the supplement, drug, or treatment in a larger group with the specific disease. Usually at least two Phase 3 trials need to be completed to convince the FDA that the drug is safe and effective

Phase 4

- A *Phase 4* trial is also called an “**after market**” study which means that companies collect data on safety and effectiveness after the drug has been approved by the FDA and is available to many more patients.

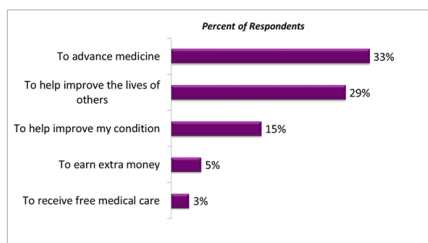
What's in it for me?

- Gain access to new treatments that are not yet available to the public
- Obtain expert HD medical care at a leading health care facility
- Playing an active role in your own health care
- Helping future generations of your family by contributing to medical research
- It can be an avenue to fight back against HD!

Why Participate in a Clinical Trial

- Being a participant gives you access to potential new research and treatments.
- While in a clinical trial, you receive more time with clinicians who are familiar with HD.
- You are helping others by contributing to medical research even if you may not benefit directly.
- You give HOPE to yourself and others
- Be an agent of change!

Top Reasons People Choose to Participate in Clinical Trials

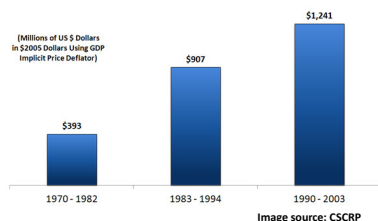


Source: CISCIP, 2013; N=5,701 people worldwide

Patient Participation is **IMPORTANT**

- The longer it takes to complete a trial, the longer it will take for the drug to be approved and placed on the market.
- The longer it takes to complete a trial, the more expensive it is for the sponsor
- The longer the trial, the more likely the sponsor (company) will deprioritize HD in their business strategy!
- Summary: Slow recruiting trials are bad for HD community!

Total Cost to Develop a single Approved Drug (Direct plus Capitalized Costs)



Trial Delays

30% of trials **NEVER** begin due to poor recruitment

50% of all trial delays are due to slow recruitment

86% of trials in the US fail to recruit on schedule

Source: CenterWatch

Questions to Consider Asking Before Enrolling

What is the purpose of the trial?

Does the trial involve a placebo? What are my chances of being assigned to the placebo group?

How will the treatment be given?

How long will the trial last and what will I be asked to do?

Is there any reimbursement for travel or other expenses?

Will I be able to see my own doctor?

Can I continue to take the drugs or supplements that I am currently taking?

If the intervention works for me, can I keep using it after the trial?

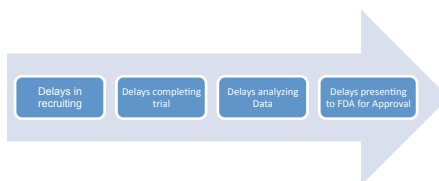
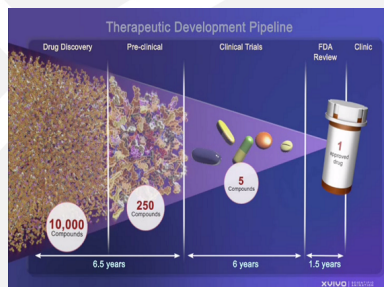
Can anyone find out that I am participating in a clinical trial? How will my information be kept confidential?

Will I receive follow-up care?



Why Does it Take So Long for a Therapy to Get to Market?

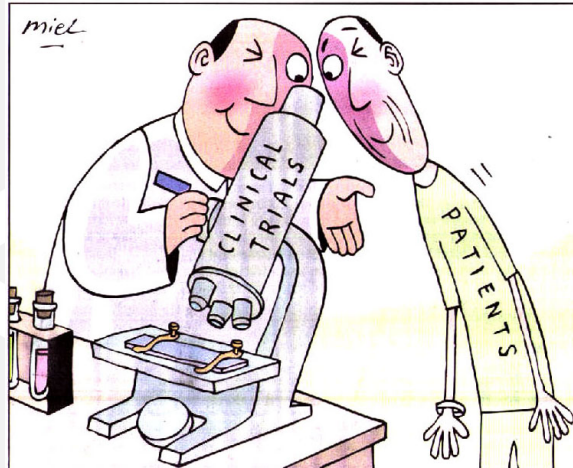
- Ensuring that a drug or treatment is safe, well tolerated by those using it, and effective, takes time.
- Getting enough people to volunteer for a clinical trial is a problem.



Delays lead to more delays



Current and Future HD Clinical Trials



HD Observational Trials

What is **Enroll-HD** ?



- Enroll-HD is a global longitudinal, observational study of Huntington's disease
- Research platform from where future HD clinical trials will be performed.
- Enroll-HD collects a common set of data for all participants across all sites around the world
 - Enroll-HD also collects blood samples for DNA and cell lines
 - All data and samples will be available to **share** with researchers to answer important questions about HD

What is involved in an **Enroll-HD** visit?



- Annual visits
- Questions about your health (thinking, behaviors, feelings, lifestyle)
- Neurologic exam
- Blood sample for genotyping and for bio-banking
- Family history (optional)
- Visit is about 1-2 hrs
- Travel support is available

Who can participate?

Enroll-HD  **is a family study!**

- Gene + (symptomatic, pre-symptomatic)
- Gene status not known (at-risk)
- Gene negative
- Spouses/Partners

Enroll-HD  **has three main goals**

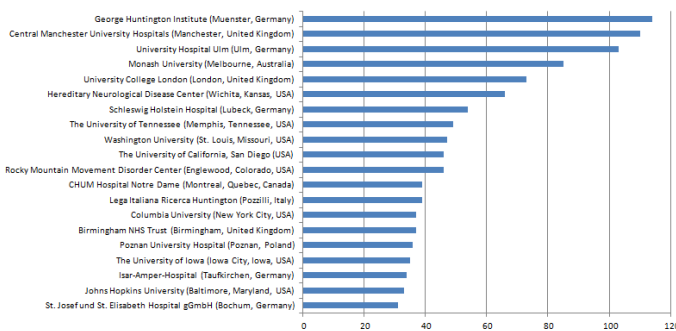
1. To improve our **understanding of HD** and find out what factors influence the progression
2. To **foster good clinical care** and improve the health of the participants
3. To enhance the design and **expedite the conduct of clinical trials**

Dramatic increase in the number of Enroll-HD participants since 2013

- April 2013: 433 in 29 sites
- February 2014: 1592 in 52 sites
- June 2014: 2351 in 75 sites
- October 2014: 3336 in 89 sites
- End of 2015: 200+ sites
- GOAL: 25,000-30,000 people worldwide

www.Enroll-HD.org

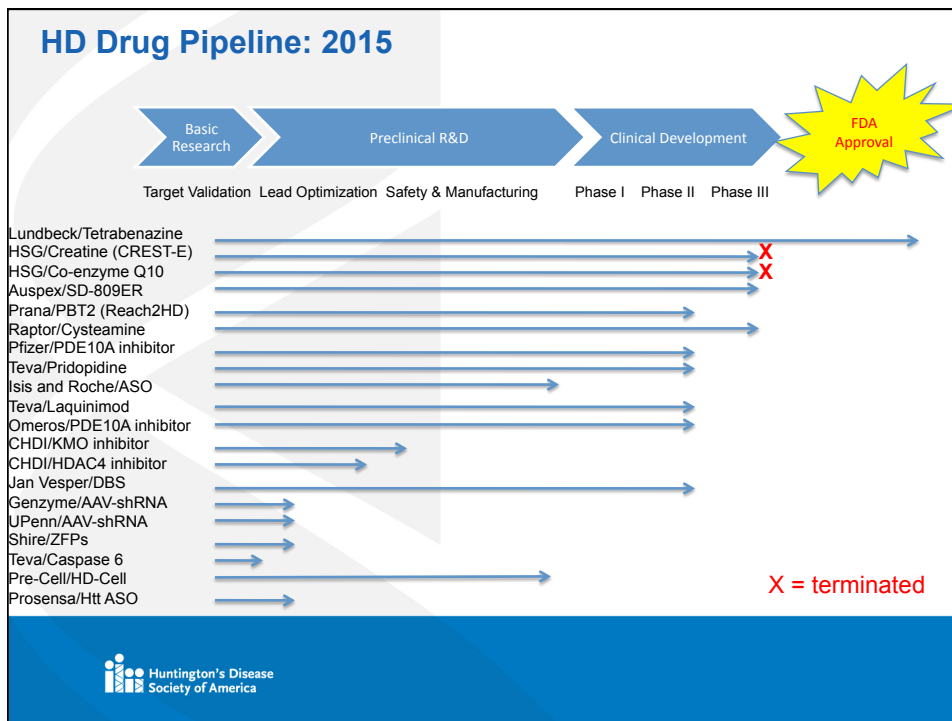
Top Enrolling Sites - Year to Date 2014



Huntington's Disease
Society of America

HD Interventional Trials

Huntington's Disease
Society of America



SIGNAL

Introduction to the SIGNAL Phase 2 Trial: A New Investigational Approach that May Delay Onset or Slow the Progression of Huntington's Disease

ACCINEX

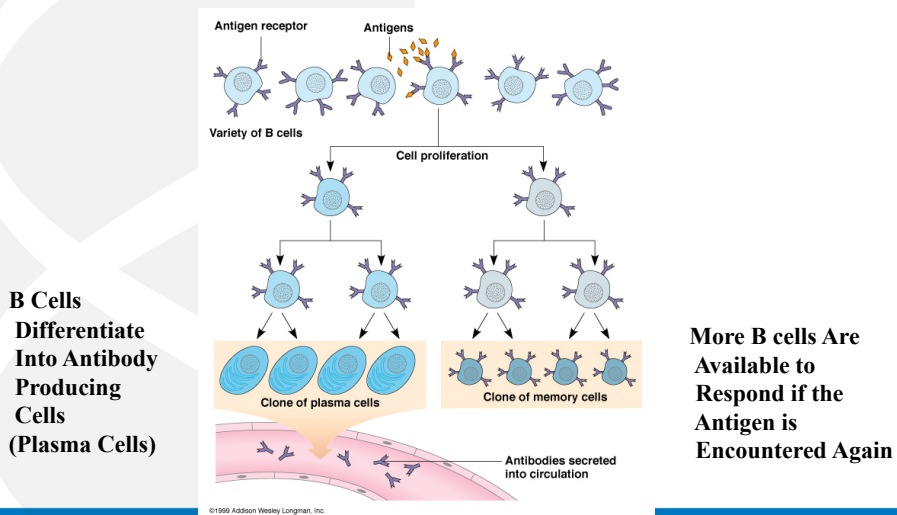
HUNTINGTON STUDY GROUP
seeking treatments that make a difference

Huntington's Disease Society of America

About Antibodies

- Cells of our immune system, B cells, are able to produce highly specific proteins, antibodies, that can bind to and neutralize foreign proteins expressed by bacteria or viruses
- Each B cell can produce a different antibody against these foreign proteins
- When a foreign protein binds to a receptor on a B cell, this stimulates the B cell to divide and grow into a group or clone of cells, all producing the same antibody – a monoclonal antibody
- These B cells secrete the antibody into our blood, where it protects us against bacteria, bacterial toxins and viruses

B Lymphocytes Produce Antibodies

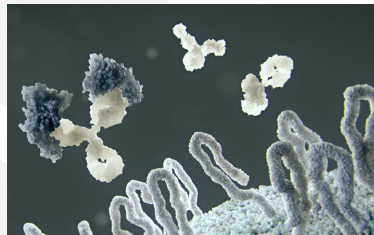


Clinical Uses of Monoclonal Antibodies

- Monoclonal antibodies are used clinically as targeted drugs to treat some diseases
- Antibodies are administered by injection or by infusion
- Some examples:
 - Rheumatoid Arthritis
 - Multiple Sclerosis
 - Cancer
 - Lupus

VX15 – An Investigational Monoclonal Antibody

- VX15 is a novel investigational monoclonal antibody that in preclinical models blocks the activities of Semaphorin 4D (SEMA4D), a protein that may promote inflammation in the brain
- VX15 is the first monoclonal antibody to be evaluated in a Huntington's Disease clinical study



What data do we have on VX15 ?

- **VX15 has been tested in animal studies and two clinical trials (Safety studies) in patients with cancer and multiple sclerosis, a total of 80 patients**
- **VX15 showed reduced brain shrinkage and better spatial memory in a mice model for Huntington's disease**
- **VX15 infusions in patients were well tolerated, no significant adverse effects were observed.**



Contents lists available at ScienceDirect

Neurobiology of Disease

journal homepage: www.elsevier.com/locate/ynbdi



Anti-semaphorin 4D immunotherapy ameliorates neuropathology and some cognitive impairment in the YAC128 mouse model of Huntington disease



Amber L. Southwell^a, Sonia Franciosi^a, Erika B. Villanueva^a, Yuanyun Xie^a, Laurie A. Winter^b, Janaki Veeraraghavan^b, Alan Jonason^b, Boguslaw Felczak^a, Weining Zhang^a, Vlad Kovalik^a, Sabine Walti^a, George Hall^a, Mahmoud A. Pouladi^{c,d}, Ernest S. Smith^b, William J. Bowers^b, Maurice Zauderer^b, Michael R. Hayden^{a,*}

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^c Translational Laboratory in Genetic Medicine, Agency for Science, Technology and Research, 138648, Singapore

^d Department of Medicine, National University of Singapore, Singapore

Study Period - Approximate Duration of Subject Participation

- 6 months VX15/2503 or placebo (1:1) → 6 months VX15/2503
 - Screening visit → Baseline visit within 30 days of screening
- 12 monthly treatment visits
- 3 months of follow-up post final infusion
 - 1 month follow-up safety phone call
 - 3 month follow-up safety visit
- Total duration for each subject will be approximately 16 months

Eligibility - Inclusion Criteria

- Male or female ≥ 21 years of age at Screening
- Must fulfill one of the following criteria at Screening:
 - Late prodromal HD
 - Early manifest HD, must be independent in daily activities
 - Have undergone genetic testing with a known CAG repeat greater than or equal to 36
 - Must use reliable contraception throughout study (male and female)

Eligibility - Exclusion Criteria

- Marked cognitive impairment
- History of HIV, hepatitis B or C infection
- Substance abuse in past year
- Suicide attempt in past year
- Relevant heart, liver or kidney disease or cancer
- Pregnancy
- Unable to undergo MRI imaging

Study Questions?

- *Can a subject be on tetrabenazine?*
Yes, if dosage stable 1 month prior to Baseline
- *Can a subject take medication for anxiety prior to MRI?*
Anti-anxiety meds are not allowed on the day of the scan
- *Are there any meal restrictions?*
No
- *How long are subjects observed post infusion?*
30 minute vital signs and blood draws are completed

SIGNAL Clinical Trial Cities

Birmingham, AL	Baltimore, MD
La Jolla, CA	Ann Arbor, MI
San Francisco, CA	St. Louis, MO
Aurora, CO	Durham, NC
Washington, DC	Winston-Salem, NC
Atlanta, GA	New York, NY
Iowa City, IA	Rochester, NY
Chicago, IL	Cincinnati, OH
Kansas City, KS	Columbus, OH
Wichita, KS	Toledo, OH
Louisville, KY	Nashville, TN
Charlestown, MA	Burlington, VT

UofL Contact Information

Site Primary Investigator:

Kathrin LaFaver, M.D.

Study Coordinator: Annette Robinson, R.N.

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Additional Resources

- www.hdsa.org/research
- www.hdtialfinder.org
- www.clinicaltrials.gov
- www.hdbuzz.net
- www.Huntington-Study-Group.org
- www.enroll-hd.org



THANK YOU!

