HD Research: Progress in Developing New Clinical and Disease-Modifying Therapies

Vicki Wheelock MD
Northern CA HDSA Annual Convention
May 20, 2017
UC Davis Medical Center/School of Medicine
Sacramento CA
Huntington’s Disease

Inherited degenerative neuropsychiatric disease

Estimated prevalence in US:
- 30,000 people with HD
- 150,000 at-risk

Onset: ages: 2 – 80,
commonly 30 – 40’s

2000 new cases annually

Estimated costs in US: $2.5 billion

Symptoms: Involuntary movements, impairment of thinking abilities, mood and behavioral disorders

Woody Guthrie, 1943
# Population affected by HD

<table>
<thead>
<tr>
<th>Location</th>
<th>Total Population</th>
<th>People with HD*</th>
<th>Juvenile HD</th>
<th>People At Risk**</th>
<th>Total affected and at-risk</th>
<th>Impacted family members* **</th>
</tr>
</thead>
<tbody>
<tr>
<td>California</td>
<td>39,250,017</td>
<td>3,925</td>
<td>390</td>
<td>26,494</td>
<td>30,419</td>
<td>97,644</td>
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<tr>
<td>United States</td>
<td>325,078,480</td>
<td>32,507</td>
<td>3250</td>
<td>219847</td>
<td>252,354</td>
<td>810,056</td>
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US Census 2010
* Estimated, based on NIH quoted prevalence of 1/10,000

** Estimated based on 2000 estimate of 200,000 at risk = 6.75/10,000

*** Estimated number of household members impacted by HD based on average family unit of 3.21 members

Source: Adapted from HDSA + US Census Population Clock 5/19/2017
Who gets HD?

Each child with a parent with HD has a 50% chance of inheriting the disease.

<table>
<thead>
<tr>
<th>CAG repeat length</th>
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<tr>
<td>NORMAL</td>
<td>&lt; 26</td>
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<tr>
<td>Unstable</td>
<td>27 – 35</td>
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<tr>
<td>Reduced penetrance</td>
<td>36 - 38</td>
</tr>
<tr>
<td>Huntington's disease</td>
<td>&gt;38</td>
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</table>
Relationship Between HD Symptoms and Age

Presenting Motor Findings
- Chorea
- Rigidity
- Bradykinesia

Symptoms in HD
- Motor Symptoms
- Psychiatric/Behavioral Symptoms
- Cognitive Symptoms

Juvenile HD is defined HD onset before age 21
- Only 5-10% of cases of HD have juvenile onset
- Only 1-2% of cases have childhood onset, defined as onset before age 10 years
Current HD treatments are symptomatic

- Anti-chorea therapies such as tetrabenazine, anti-psychotic drugs
- Psychiatric therapies such as counseling and medications
- No available drugs for cognitive difficulties
- Exercise, environment, physical, occupational and speech therapies are very helpful
- Palliative care and hospice in late-stage HD
Progress in clinical care:
New developments in managing HD symptoms

• Chorea: Deutetrabenazine approved 2017
• Anger and Irritability: NIH NeuroNext Study
Deutetrabenazine (Austedo™)

FDA approves Austedo for Huntington’s chorea
Deutetrabenazine

- Deuterated form of tetrabenazine (FDA approved in the US in 2008 for the treatment of chorea in HD)
- Deutetrabenazine was designed by substituting naturally occurring deuterium molecule at 2 locations
- This results in slower metabolism and less variability in blood levels.
Deutetrabenazine significantly reduced chorea scores compared to placebo in a 13 week randomized placebo-controlled study.
Side effects

• Most common: somnolence, diarrhea, dry mouth and fatigue
• **Black Box Warning: risk of depression and suicide**
• Contraindications: patients with depression or liver disease
• Use with care in patients taking anti-depressant drugs such as paroxetine, fluoxetine, quinidine, bupropion which can raise the levels of deutetrabenazine, or other drugs which can affect heart conduction
• Patients already taking tetrabenazine can be switched over to deutetrabenazine
• Teva’s Shared Solutions program to support patients starting treatment

• Resources:
  – Nursing support
  – Education
  – Financial assistance program
Targeting behavioral symptoms in HD

Irritability and Aggression
SRX246: Safety, Tolerability, and Activity in Irritable Subjects with HD (STAIR)
STAIR trial: Why treat Irritability in HD?

• No controlled treatment studies for irritability in HD. In fact, there are very few studies of how to treat emotional symptoms in Huntington’s.

• Irritability causes family conflict; others avoid being around the patient; may cause danger to patient themselves or others in the household.

• Can lead to early placement in long term care because behavior can not be controlled at home.
How does SRX246 work?

- SRX246 blocks vasopressin$_{1A}$ receptors

- Vasopressin is increased in the brain during anger and aggression in both animals and humans.

- It may be helpful in treating irritability and aggression.
Male Rat Intruder Model

SRX246
NeuroNext STAIR Study

- **Safety**, **Tolerability**, and **Activity in IRritable subjects** with HD; Sponsor: NIH/Azevan Pharmaceuticals
- Therapeutic candidate: SRX246
- Mechanism: Vasopressin$_{1A}$ receptor blocker; also being tested in Intermittent Explosive Disorder and PTSD.
  - May have a milder side effect profile than other drugs currently used for this symptom.
- First study targeting irritability in HD
NeuroNext STAIR Study

• Study design: This is a 12 week, randomized, placebo-controlled, double-blind, dose escalation study of SRX246 in irritable subjects with early-moderate stage HD.
• Subjects: Must have current feelings of irritability, aggression or anger
• Treatment: SRX246 vs placebo
• Primary outcome measure: Tolerability
• Secondary outcome measures: Rating scales for irritability
If you are interested in possible participation in the **STAIR** study, please call Randev Sandhu at (916)734-4303 or Amanda Martin at (916)734-3514, or e-mail at:

[rssandhu@ucdavis.edu](mailto:rssandhu@ucdavis.edu)

[alema@ucdavis.edu](mailto:alema@ucdavis.edu)
Progress in disease modifying treatments in HD

Three new lines of research are currently under investigation:

– Immune modulating medications to reduce inflammation
– Stem cell research: Dr. Nolta and CIRM grant
– Gene silencing/editing:
  • Anti-sense oligonucleotide therapy to block production of the mutant HD protein
  • CRISPR/Cas9 and TALEs
The choreography of neuroinflammation in HD

Crotti A and Glass C. Trends in Immunology 36;2015
• Sponsored by Teva Pharmaceuticals with the Huntington Study Group and EHDN
• Therapeutic candidate: Laquinimod, an immunomodulator also being investigated for MS
• Multicenter, multinational, randomized, double blind, placebo controlled, parallel group study to evaluate the efficacy and safety of laquinimod (0.5 and 1.0 mg/day) as treatment in patients with HD
• Planned enrollment: 400
• Primary outcome measure: change in motor function measured by the Unified Huntington’s Disease Rating Scale

Closest site: UCSF
SIGNAL Trial

- Sponsor: Vaccinex and the Huntington Study Group
- Therapeutic candidate: VX 15/2503, a monoclonal antibody designed to target the semaphorin 4D (SEMA4D) protein
- Mechanism: reduction of neuroinflammation, possible increase neuronal progenitor survival, and increase oligodendrocyte migration and maturation
- First-time use of monoclonal antibody in HD
• Study design: Phase 2 multi-center, randomized, double-blind, placebo controlled study of VX15/2503.

• Subjects include 84 individuals who have undergone genetic testing for HD and have the HD gene expansion, with prodromal HD or very early stage HD.

• Treatment is via monthly intravenous infusions for 6 or up to 18 months.

• Primary outcome measure is safety and tolerability of VX15/2503.
Stem Cell Research in HD: Partnership between families, researchers and CIRM

How patient advocates changed the course of science

A group of families impacted by Huntington’s disease inspired a “Eureka!” moment for Jan Nolta, UC Davis’ pioneering stem cell researcher

2010 – CIRM Spotlight on HD
California State Capitol
Genetically Engineered Mesenchymal Stem Cells as a Proposed Therapeutic for Huntington’s Disease

Scott D. Olson • Kari Pollock • Amal Kambal • Whitney Cary • Gaela-Marie Mitchell • Jeremy Tempkin • Heather Stewart • Jeannine McGee • Gerhard Bauer • Hyun Sook Kim • Teresa Tempkin • Vicki Wheelock • Geralyn Annett • Gary Dunbar • Jan A. Nolta
2011: Grant application to develop MSC Engineered to produce BDNF as a treatment for HD

The grant is approved!
July 26, 2012
CIRM Grant DR2A-05415
## Project Plan: MSC/BDNF for HD

**CIRM Grant DR2A-05415**

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<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Year 4</th>
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<td><strong>PRE-CELL: Years 1&amp;2</strong></td>
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<td>GMP Manufacturing of Clinical Lots</td>
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<td>IND-enabling studies using current GMP Lot (ongoing)</td>
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<td>Regulatory approvals (ongoing)</td>
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<td>Observational Clinical trial</td>
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<td>Phase I Clinical trial</td>
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<td>Lab/safety studies: patient samples</td>
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<tr>
<td><strong>HD-CELL: Years 3&amp;4</strong></td>
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*Note: HD-CELL phase is on-going.*
Jan Nolta, PhD, PI 15-01
Pre-Clinical Lead

Geralyn Annett, CLS
Project Manager

Gerhard Bauer
CMC Lead and staff
UCD GMP facility
Product certification (outsourced)
Jon Walker, CLS, QA/QC Lead

Kari Pollock, Study director,
Kyle Fink, Ph.D. and staff
Pharm/tox – rodent studies

Clinical Pathology Lab (CPL),
UC Davis

William Gruenloh, UC Davis
Regulatory oversight, IND preparation

Vicki Wheelock, MD, PI PRE-CELL and DR2A-95415, Clinical Lead
Charles DeCarli, clinical co-PI

Teresa Tempkin RN MSN
Clinical Project Manager
Alexandra Duffy, DO
Co-investigator

Neurorestorative Therapeutics Team
Kia Shalaie, MD, PhD Lead Neurosurgeon,
UC Davis, Dan Lim, MD, PhD - UCSF

Scher-Psychiatrist, Farias-Neuropsychology,
DeCarli-Imaging, Yarborough-Bioethics,
Mooney-Social Worker, Martin-Clinical trial coordinator; Stout–Cognitive Assessments,
Hersch – Biomarkers, Li-Biostatistician

University of Rochester CRO
Clinical trial oversight and data management/
Medical monitor
PRE-CELL Study

• Lead-in observational study for subjects with early stage HD who may be candidates for a future planned trial of mesenchymal stem cells engineered to produce BDNF as a potential treatment for HD.
• Goal: to establish baseline characteristics and the rate of change in clinical, imaging and exploratory biomarker measures over 12 – 30 months.
• Study subjects: adults with early-stage HD, psychiatrically and medically stable, have no contraindications MRI or neurosurgical procedures, evaluated every 6 months.
Dr. Ashok Joshua Dayananthan
Assistant Clinical Professor of Neurology, UC Davis

Dr. Sasha Duffy, Assistant Clinical Professor of Neurology, UC Davis
Cross sectional Percentage Change Magnitude Images

6 months 12 months 18 months

PRE-CELL Study, UC Davis
PRE-CELL Biomarkers

Steven Hersch, MD PhD
Professor of Neurology
Harvard Medical School

BDNF
Mutant Huntingtin Protein
We extend our sincerest gratitude to PRE-CELL subjects and care partners.
We have generated new scientific knowledge in stem cell research to share with HD researchers worldwide.
Results of pre-clinical studies

Human Mesenchymal Stem Cells Genetically Engineered to Overexpress Brain-derived Neurotrophic Factor Improve Outcomes in Huntington’s Disease Mouse Models

Kari Pollock¹, Heather Dahlenburg¹, Haley Nelson¹, Kyle D Fink¹, Whitney Cary¹, Kyle Hendrix¹, Geralyn Annett¹, Audrey Torrest¹, Peter Deng¹, Joshua Gutierrez¹, Catherine Nacey¹, Karen Pepper¹, Stefanos Kalomoiris¹, Johnathon D Anderson¹, Jeannine McGee¹, William Gruenloh¹, Brian Fury¹, Gerhard Bauer¹, Alexandria Duffy², Theresa Tempkin², Vicki Wheelock² and Jan A Nolta¹

¹Stem Cell Program and Institute for Regenerative Cures, University of California Davis Health System, Sacramento, California, USA; ²Department of Neurology, University of California Davis Health System, Sacramento, California, USA
BDNF Production: Human MSCs were transduced with the lentiviral vector pCCLc-MNDU3-BDNF-WPRE at the indicated Multiplicity of infection (MOI). Increasing the MOI increases the amount of BDNF produced.
HD Mouse Studies: treated with MSC/BDNF

Striatal Volume

- WT
- Tg + Normosol
- Tg + MSC
- Tg + MSC BDNF, Low
- Tg + MSC BDNF, Medium
- Tg + MSC BDNF, High

Neurogenesis studies

Open Field Testing
Implantation with MSC/BDNF increased the lifespan of R6/2 (CAG 120) mice

10% increase for WT MSC, 7.7% increase for MSC BDNF MOI 10, 15.5% increase for MSC BDNF MOI 20.
CIRM grant ended fall 2016; HD-CELL trial not started.

Additional pre-clinical studies are needed in HD mouse models and a large animal model before our team will be ready to apply for approval from the FDA to take MSC/BDNF treatment forward into patients.

May 2017 Update: Dr. Nolta and Dr. Kyle Fink receive major 5 year NIH grant to continue to develop MSCs as a potential treatment for HD.
Thank you Dr. Kyle Fink!
Anti-sense oligonucleotides (ASOs)

- These are single-stranded DNA building block sequences that are designed to target specific messenger RNA that are complementary.
- Once targeted, the RNA part of the DNA/RNA duplex is destroyed by an enzyme.
- The ASO can then be recycled to act again and again.

https://en.hdbuzz.net/204
“Huntingtin Holiday”

Proof of concept in HD mouse models

• R6/2 mouse (*similar to Juvenile HD*):
  – 4 week intraventricular infusion lowered mutant huntingtin protein levels by 60%, reduced brain shrinkage and prolonged survival.

• YAC128 mouse (*similar to adult HD*):
  – 2 week ASO infusion lowered mutant huntingtin protein levels by 80%, improved motor performance on rotarod, at 3 months but not at 6 months.

• BACHD mouse (*similar to adult HD*):
  – 2 week infusion at 6 months improved rotarod and open field exploration at 8 – 15 months, but did not rescue striatal atrophy or neuropathology changes.

ASO treatment in Rhesus monkey

- Rhesus monkey brain 180x larger than mouse, brain and 1/15\textsuperscript{th} of human brain size.
- ASO given via spinal tap
- Mutant HTT was reduced in some brain areas (cortex) but not others (caudate)

IONIS-HTT_{Rx} trial

• Title: Safety, tolerability, pharmacokinetics, and pharmacodynamics of IONIS-HTT_{Rx} in patients with early manifest Huntington’s disease.

• Sponsor: IONIS Pharmaceuticals, in partnership with Roche Pharmaceuticals and CHDI

• Phase 1 randomized, placebo-controlled, double-blinded study to evaluate the safety and tolerability of ascending doses of IONIS-HTT_{Rx} administered in 4 monthly intrathecal injections over a 13-week period.

• The study is being conducted in Canada and the UK.

• Planned enrollment is 36.
Intra-thecal delivery: spinal tap
**Comments**

- In a 2016 commentary about molecular genetic therapeutics in HD, Dr. Ira Shoulson raised questions about allele-specificity, effects of cumulative exposure, timeframe of the response, clinical safety and the issues of placebo effect.
- It’s safe to say that the entire HD world is watching this historic trial.
A new approach: Allele-specific ASO

In most HD patients, there are tiny genetic differences called SNPs in the huntingtin gene outside of the CAG repeat expansion region that can allow scientists to target ONLY the expanded huntingtin mRNA, leaving the health “wild-type” huntingtin mRNA unaffected.

This approach may have less toxicity.
Introduction to a new acronym: SNP

Single Nucleotide Polymorphism, pronounced “snip”

SNPs are single-nucleotide substitutions of one base for another. Each SNP location in the genome can have up to four versions: one for each nucleotide, A, C, G, and T.

http://learn.genetics.utah.edu/content/precision/snips/
Not all single-nucleotide changes are SNPs

To be classified as a SNP, two or more versions of a sequence must each be present in at least one percent of the general population.

SNPs occur throughout the human genome: about one in every 300 nucleotide base pairs. This translates to about 10 million SNPs within the 3-billion-nucleotide human genome.

http://learn.genetics.utah.edu/content/precision/snips
Taking advantage of SNPs: Allele-specific ASO

Huntingtin Gene (HTT)

Wild-type (healthy) allele

Mutant allele

Expanded CAG repeat

SNP associated with expanded CAG repeat

Enables targets for allele-specific silencing

Courtesy Dr. Michael Panzara, WAVE Life Sciences
HD SNP1 and SNP2 are found in about $\frac{2}{3}$ of HD patients.

**Cumulative HD Patient Coverage**

- 1 SNP: ~55%
- 2 SNPs: ~71%
- 3 SNPs: ~77%
- 4 SNPs: ~80%

*Courtesy Dr. Michael Panzara, WAVE Life Sciences*
Huntington’s Disease
WVE-120101 Selectively Reduces mHTT mRNA and Protein

Messenger RNA levels

*These results were replicated in a patient-derived cell line

Courtesy Dr. Michael Panzara, WAVE Life Sciences
Huntington’s Disease
Distribution of WVE-120101 in Cynomolgus NHP Brain

- Stereochemistry enables improved protein binding and distribution
- ViewRNA depicting perinuclear distribution of WVE-120101 (red) in non-human primate (NHP) deep gray matter structures following intrathecal administration
- WVE-120101 detectable in deep gray matter structures following intrathecal administration

Animal # 42, Slice 8

In Situ Hybridization ViewRNA stained tissue

Red dots are WVE-120101. Arrow points to nuclear and perinuclear distribution of WVE-120101 in deep gray matter structures

Courtesy Dr. Michael Panzara, WAVE Life Sciences
**Huntington’s Disease**

Clinical Trial Design for WVE-120101 and WVE-120102

- First-in-patient dosing for both WVE-120101 (SNP-1) and WVE-120102 (SNP-2) trials expected mid-year 2017

- Two parallel global placebo-controlled trials targeting SNP-1 and SNP-2, respectively

- Primary Objective: Assess safety and tolerability of intrathecal doses in early manifest HD patients

- Additional Objectives: Exploratory pharmacokinetic, pharmacodynamic, clinical and MRI endpoints

- Patient SNP determination (SNP-1, SNP-2, other) at pre-screening visit

- Approximately 60 patients per trial

- Key inclusion criteria: Age ≥25 to ≤65, Stage I or Stage II Huntington’s disease

*Courtesy Dr. Michael Panzara, WAVE Life Sciences*
Genome editing with CRISPR, TALEs and others

JHD Gene Editing Team Led by Dr. Kyle Fink

Funding: Help4HD, NIH NINDS NRSA fellowship, Team KJ, Pharm T32 Grant, ClRM Bridges training program Philanthropic donors from the HD community, Dake Foundation
Allele-Specific Reduction of the Mutant Huntingtin Allele Using Transcription Activator-Like Effectors in Human Huntington’s Disease Fibroblasts

Kyle D. Fink,* Peter Deng,*† Josh Gutierrez,* Joseph S. Anderson,* Audrey Torrest,* Anvita Komarla,*† Stefanos Kalomoiris,* Whitney Cary,* Johnathon D. Anderson,* William Gruenloh,* Alexandra Duffy,‡ Teresa Tempkin,‡ Geralyn Annett,* Vicki Wheelock,‡ David J. Segal,† and Jan A. Nolta*
Potential applications to the HD patient population

Cortical and Striatal Co-localization

**LNP TALE Striatal Allele Expression**

- **Healthy** ($F_{(3,20)} = 1.175, p = 0.355$)
- **Mutant** ($F_{(3,20)} = 2.926, p = 0.071$)

**LNP TALE Cortical Allele Expression**

- **Healthy** ($F_{(3,20)} = 0.116, p = 0.949$)
- **Mutant** ($F_{(3,20)} = 4.194, p = 0.022$)

Dr. Kyle Fink
Summary: Progress in HD treatments and research

• New drug approved by FDA: deutetrabenazine
• First study of new drug for behavior in HD: SRX246
• New approaches to disease-modifying treatments:
  – 2 clinical trials targeting the immune system
  – Progress in stem cell research
  – Progress in gene editing research, with one active ASO trial, another planned, and yet more approaches through UC Davis led by Dr. Fink.
Thank you to Dr. Jan Nolta and the UC Davis Institute for Regenerative Cures for ground-breaking research collaboration to help patients and families with HD.
HDSA Center of Excellence at UC Davis
Thank You to HD Patients and Care Partners!

Our work in HD has been inspired and generously support by HD patients and family members.

We are grateful to the Joseph P. Roberson Foundation, the Charles and Margaret Pue Charitable Foundation, HDSA, Help4HD and many others who have contributed to our HD care and research programs at UC Davis.

We miss you, Terry 😊