Potential new therapies for HD

2016 HDSA Northern California Annual Convention

Vicki Wheelock MD
Director, HDSA Center of Excellence
at UC Davis
Saturday May 21, 2016
Sacramento CA
The quest for disease modifying treatments in HD

• Three new lines of research are currently under investigation:
  – Gene silencing/editing:
    • Anti-sense oligonucleotide therapy to block production of the mutant HD protein
    • Zinc Finger protein research
  
  • Monoclonal antibody therapy to reduce inflammation

• Stem cell research
normal protein production

gene

mRNA

protein

transcription

translation

gene silencing

transcription

molecules that censor out certain mRNA

prevents translation
Zinc Finger Proteins: natural transcription factors

Zinc Finger DNA-Binding Protein (ZFP)

- Activation
- Repression
- Genome Editing
  - Knock out
  - Correct/Add

Gene Regulation Domain
- Repress
- Activate

ZFP Transcription Factor (ZFP TF)

ZFP Nuclease (ZFN)

Gene Editing Domain
- Knock out
- Correct/Add
The schematic shows the normal versus the mutant Htt gene and the selective ZFP-mediated repression of expression of the mutant form of Htt in Huntington’s disease derived neurons. [Sangamo BioSciences]
Comments about gene silencing

• Challenges: Delivery of these molecules into the brain.
  – Pump into spinal fluid as for IONIS ASO trial?
  – Direct implantation via brain surgery?
  – Package into stem cells?
  – Hitch a ride on a virus?

• In a 2016 commentary about molecular genetic therapeutics in HD, Dr. Ira Shoulson raised questions about targeting only the mutant HD gene or mRNA, 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 the historic IONIS trial and waiting for the future planned Sangamo ZFP trial.
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
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
SIGNAL Study

• 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.
NN105 NeuroNext STAIR Study

- Sponsor: NIH/Azevan Pharmaceuticals
- Therapeutic candidate: SRX246,
- Mechanism: Vasopressin$_{1\text{A}}$ 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
NN105 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
Stem Cell Research in HD

• Fetal-derived cells
• Embryonic or induced pluripotent stem cells:
  – **Challenges**: Stem cells must
    – Be acceptable to the patients’ immune system
    – Differentiate into the correct cell type
    – Make functional connections with the host cells
• Human mesenchymal stem cells engineered to produce BDNF improve outcomes in HD mouse models.

Olson SD et al. Molec Neurobiol45;2012:87-98
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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**PRE-CELL:** Years 1&2  
**HD-CELL:** Years 3&4
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.
• The goal is to establish baseline characteristics and the rate of change in clinical, imaging and exploratory biomarker measures over 12 – 30 months.
• Study subjects are adults with early-stage HD who are psychiatrically and medically stable, have no contraindications MRI or neurosurgical procedures, evaluated every 6 months.
Terry Tempkin, RN, ANP
PRE-CELL Project Manager
Thank you to our PRE-CELL team!

Amanda Martin, BA
Study Coordinator

David Swadell, BA
Administrative Support
Data Management Guru

...and the CCRC Nursing Team ➔
Psychiatric Evaluation and Measures/Safety

Lorin M. Scher, M.D.
Health Sciences Associate Professor
Department of Psychiatry and Behavioral Sciences

Lisa Mooney, LCSW
HDSA COE at UC Davis Social Worker
Cognitive Assessments

Sarah Farias, PhD
Associate Professor of Neurology, UC Davis

Julie Stout, PhD
Professor, School of Psychological Sciences
Monash University
Unbiased Estimate of Voxel Based Significant Differences

6 months

12 months

18 months
PRE-CELL Biomarkers

Steven Hersch, MD PhD
Professor of Neurology
Harvard Medical School

BDNF
Mutant Huntingtin Protein
Cerebrospinal fluid and Serum mutant Huntingtin Protein (mtHTT) levels

Association Between CSF Oligomeric mtHtt Protein Normalized And Plasma Oligomeric mtHtt Protein Normalized Scatter Plot of CSF Oligomeric mtHtt Protein Normalized Versus Plasma Oligomeric mtHtt Protein Normalized and Fitted Line: CSF Oligomeric mtHtt Protein Normalized = \exp(6.7097 + 0.00413 \times \text{Plasma Oligomeric mtHtt Protein Normalized})
PRE-CELL Progress

• We have enrolled an extraordinary group of HD patients and care partners who have given selflessly to help advance HD knowledge
• We have successfully measured the rate of change in HD measures for each study subject and for the PRE-CELL cohort overall
• We have generated new knowledge about HD clinical, imaging and biomarker measures to share with HD researchers worldwide.
We have generated new scientific knowledge in stem cell research to share with HD researchers worldwide.
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
pCCLc-MNDU3-BDNF-PGK-WPRE lentiviral vector
**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.
Time spent in the center quadrant of the open field, a measure of anxiety, was significantly reduced in the vehicle treated HD mice (green) when compared to wild type (Blue).

This deficit was rescued in HD mice that received transplantation of MSC/BDNF (red).
Transplantation of MSC with and without BDNF significantly increases neurogenesis activity in the subventricular zone of the brain.

Time = 2.5 weeks

* = Significant to WT, # = Significant to tg + Normosol.
R6/2 Efficacy Study: 2014-1208

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.
Good science takes time. Additional studies will be needed in HD mouse models and a large animal model before we will be ready to apply for approval from the FDA to take MSC/BDNF treatment forward into patients.
**HD-CELL:** Future planned Phase 1 safety and tolerability trial of MSC/BDNF neurosurgically implanted into striatum using techniques similar to deep brain stimulator implantation.

*Fig. 1.* MRI T1w, showing typical views obtained from the STP3 – planning workstation. Three coronal projections with tracts going to the caudate nucleus and to the putamen on the left side.
UC Davis HD Team and Collaborators

Vicki Wheelock
Jan Nolta
Terry Tempkin
Geralyn Annett
Kari Pollock
Whitney Cary
Heather Stewart
Gerhard Bauer
Kyle Fink
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Karen Pepper
Jeannine McGee
Catherine Nacey
Kyle Hendrix
Claus Sondergaard
Sarah Farias
Kiaresh Shahlaie
Jeremy Tempkin
Haley Nelson
Mark Yarborough
Charles DeCarli
Sasha Duffy
Josh Dayananthan

THANK YOU! HD patient advocates, patients and families

UCSF: Phil Starr and Dan Lim
Michigan: Gary Dunbar
Boston: Steve Hersch
France: Anne Catherine Bachoud-Levi
Australia: Julie Stout
Washington: Elizabeth Aylward
Korea: Hyun-Suk Kim

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