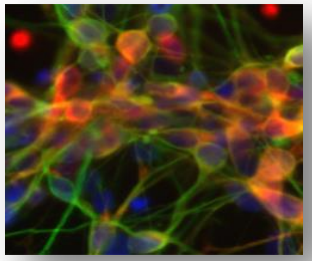
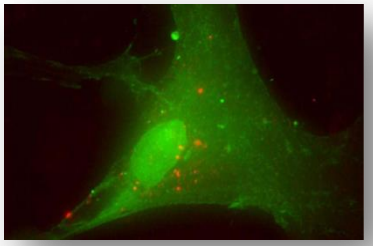




Potential new therapies for HD

2016 HDSA Northern California Annual Convention

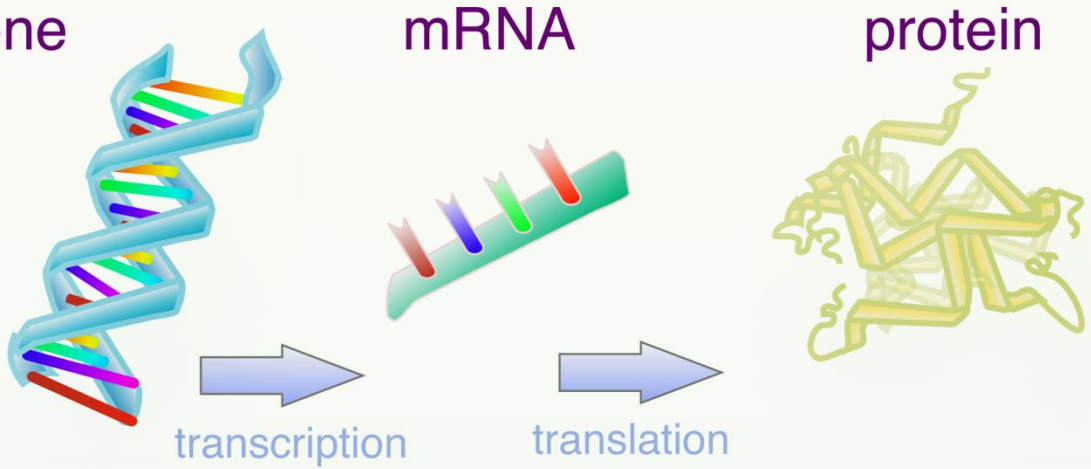
Vicki Wheelock MD
Director, HDSA Center of Excellence
at UC Davis

Saturday May 21, 2016
Sacramento CA

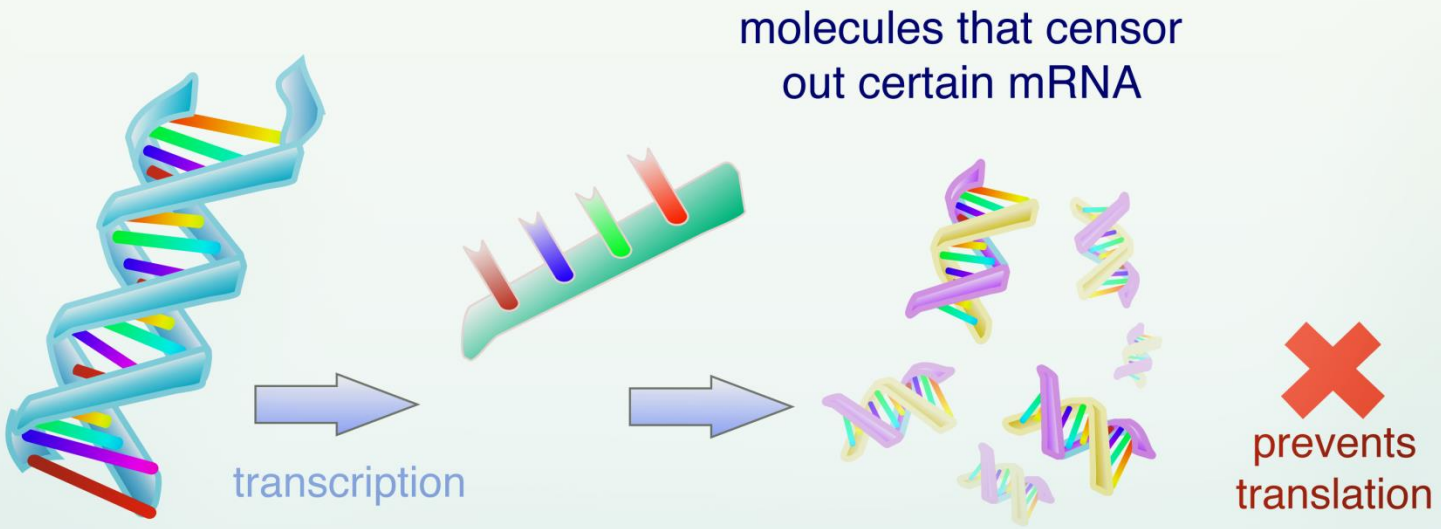
The quest for disease modifying treatments in HD

- 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

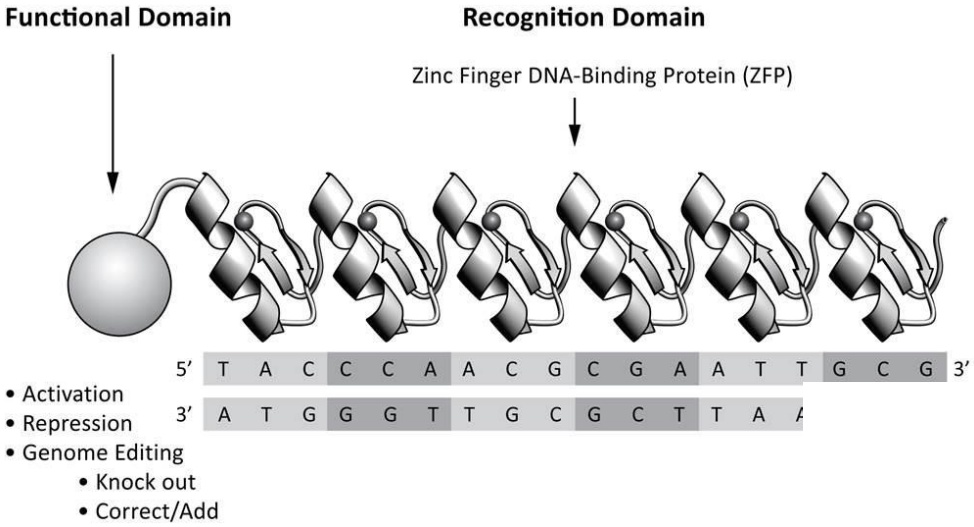
normal protein production

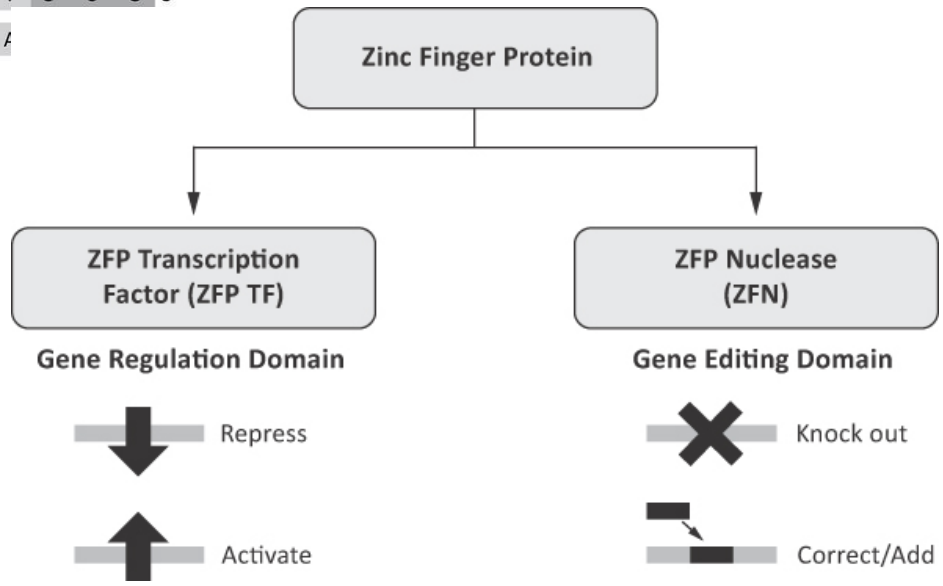


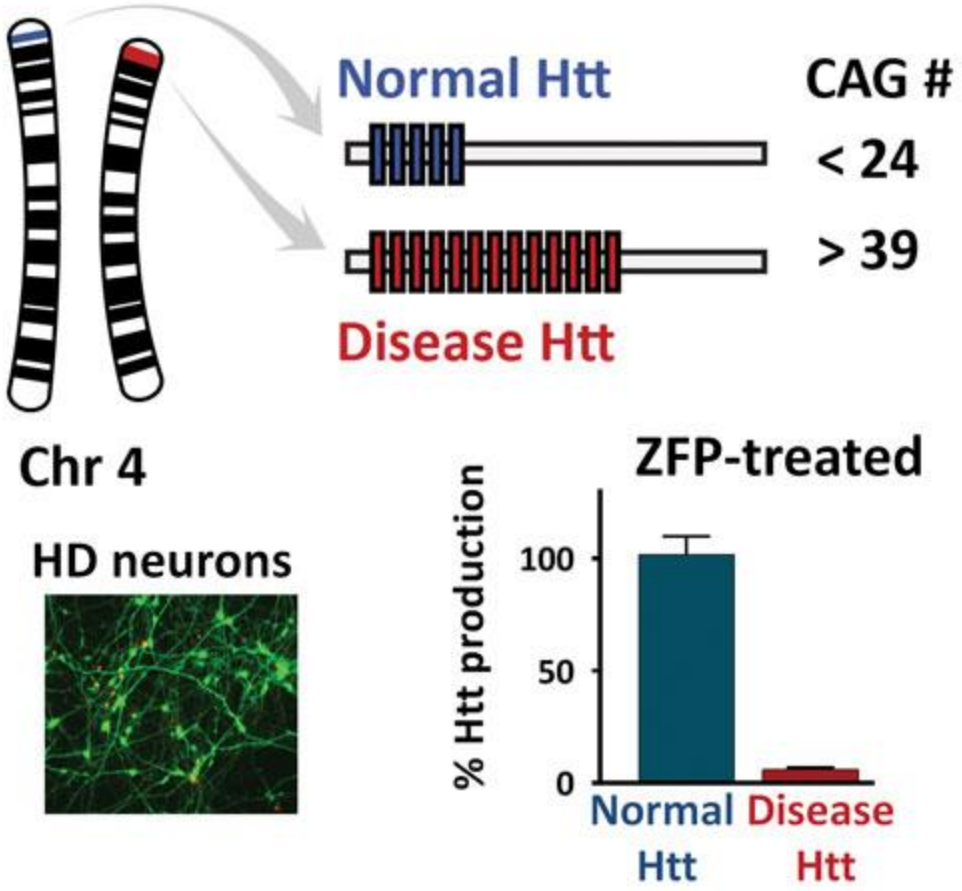
gene silencing



Zinc Finger Proteins: natural transcription factors







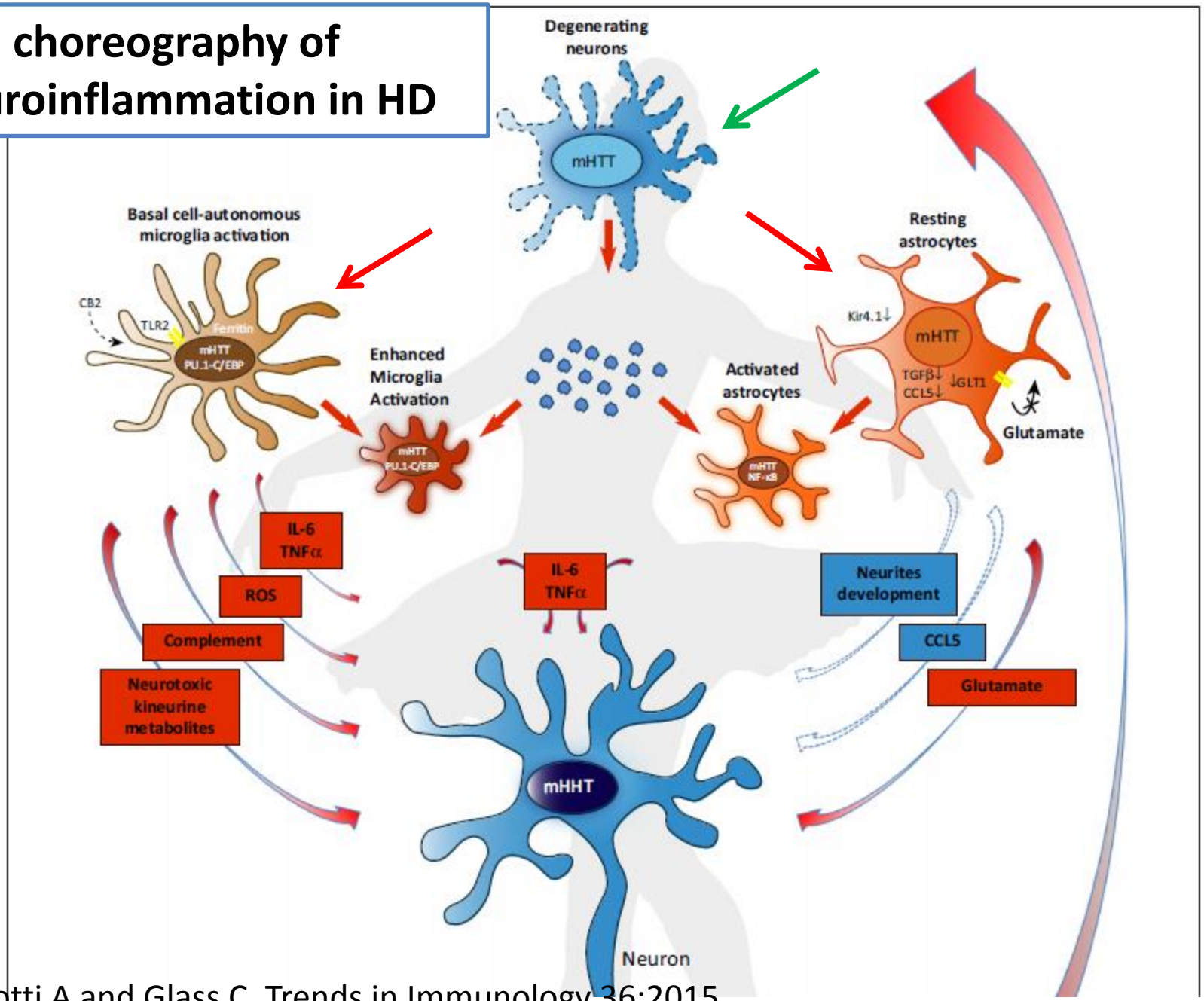
The schematic shows the normal versus the mutant Htt gene and the selective ZFP-mediated repression of expression of the mutant form of Htt in Huntington's disease derived neurons. [Sangamo BioSciences]

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

LEGATO-HD THE LAQUINIMOD HD STUDY Study

- 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$_{1A}$ 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

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

Pollock et al, Mol Ther. 2016 Jan 14. doi: 10.1038/mt.2016.12.12

Partnership between families, researchers and CIRM

2010 – CIRM Spotlight on HD
California State Capitol

CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

Springer

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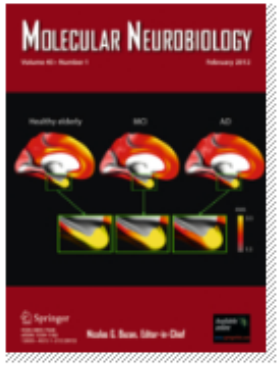
» Neuroscience Home > Biomedical Sciences > Neuroscience



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Humana Press

Mol Neurobiol (2012) 45:87–98
DOI 10.1007/s12035-011-8219-8

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

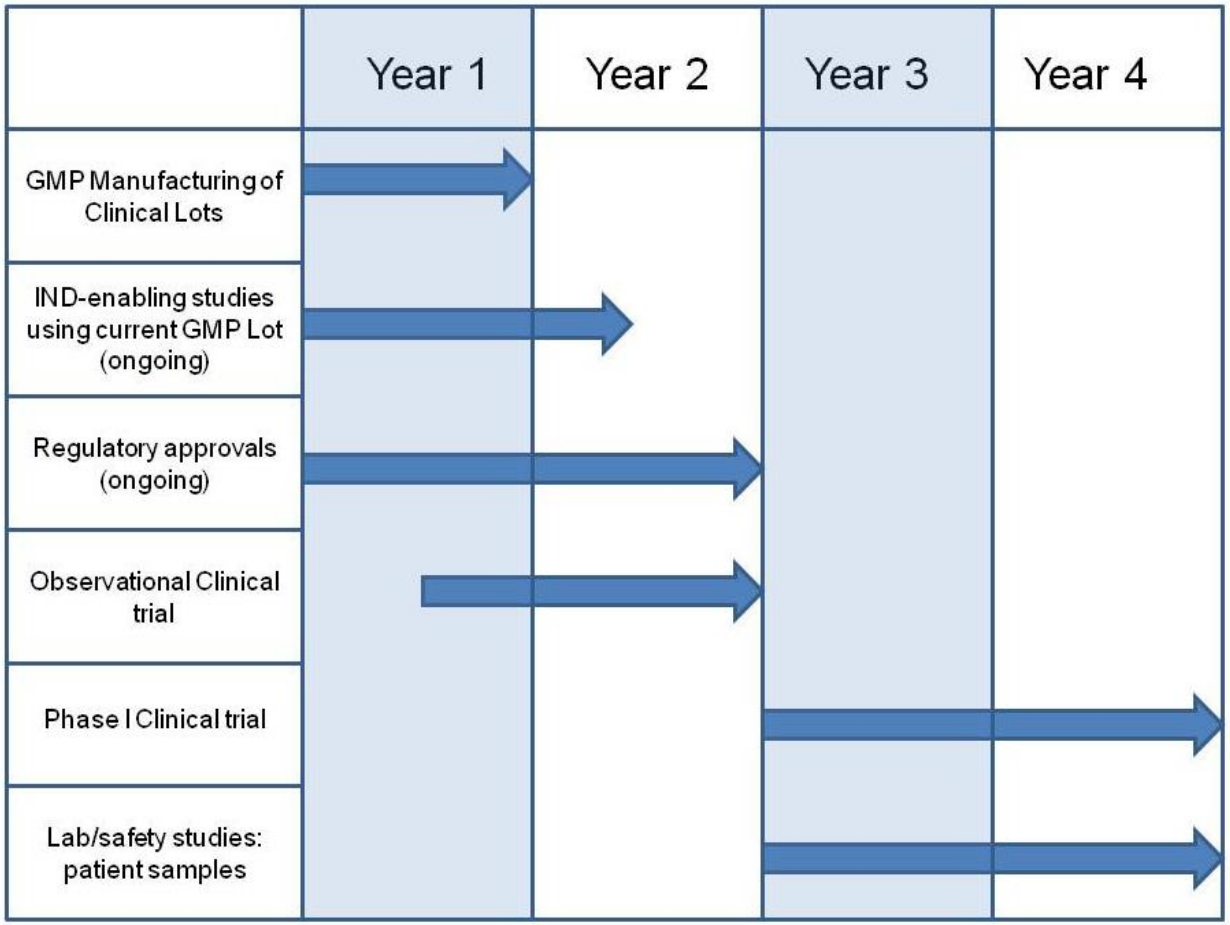
The grant is approved!
July 26, 2012
CIRM Grant DR2A-05415

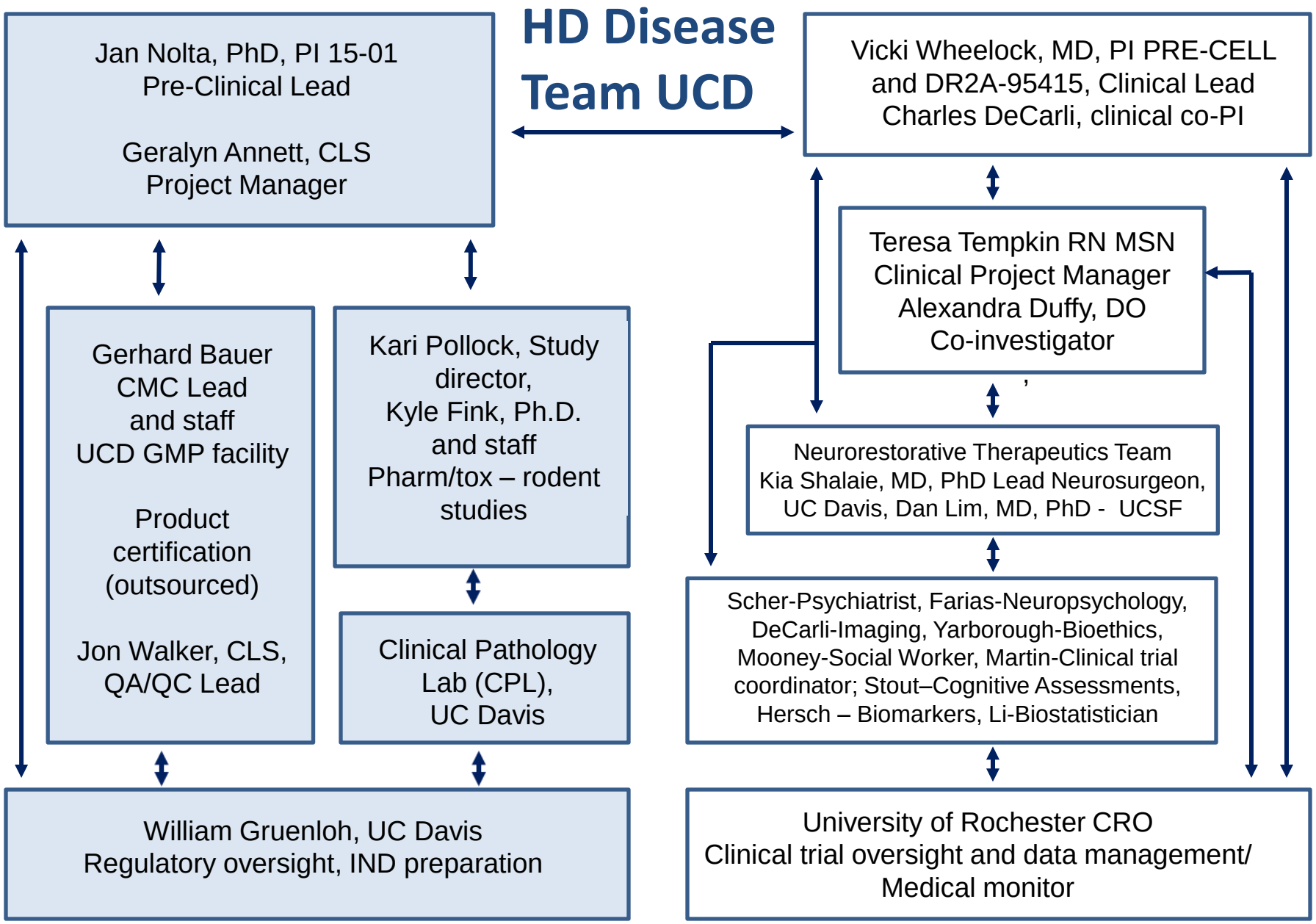
CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

Project Plan: MSC/BDNF for HD

CIRM Grant DR2A-05415

PRE-CELL: Years 1&2	**HD-CELL**: Years 3&4

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Project Manager
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Teresa Tempkin RN MSN
Clinical Project Manager
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Co-investigator
Gerhard Bauer
CMC Lead
and staff
UCD GMP facility
Product certification (outsourced)
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QA/QC Lead
Kari Pollock, Study director,
Kyle Fink, Ph.D.
and staff
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Clinical Pathology Lab (CPL),
UC Davis
Neurorestorative Therapeutics Team
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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
William Gruenloh, UC Davis
Regulatory oversight, IND preparation
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.
- 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

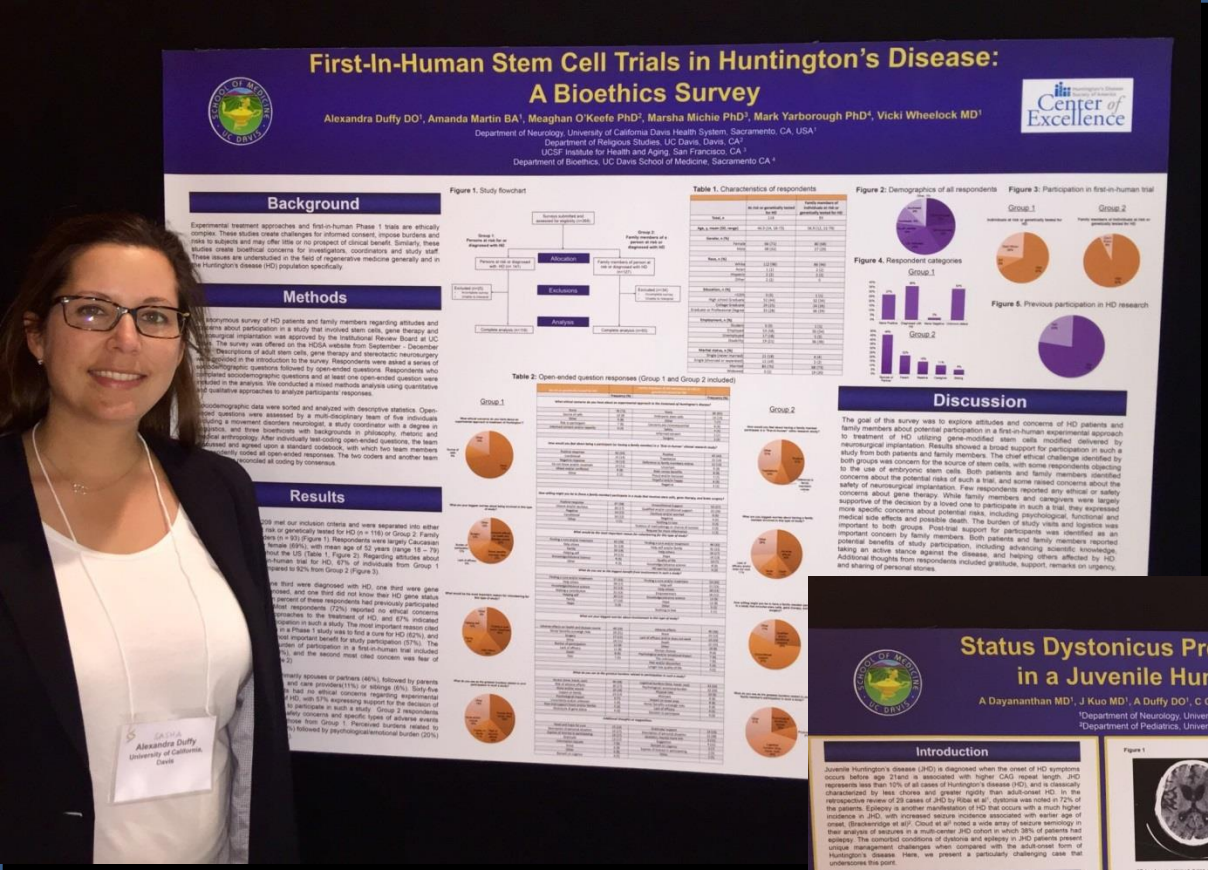
Lorin M. Scher, M.D.

Health Sciences Associate Professor

Department of Psychiatry and Behavioral Sciences

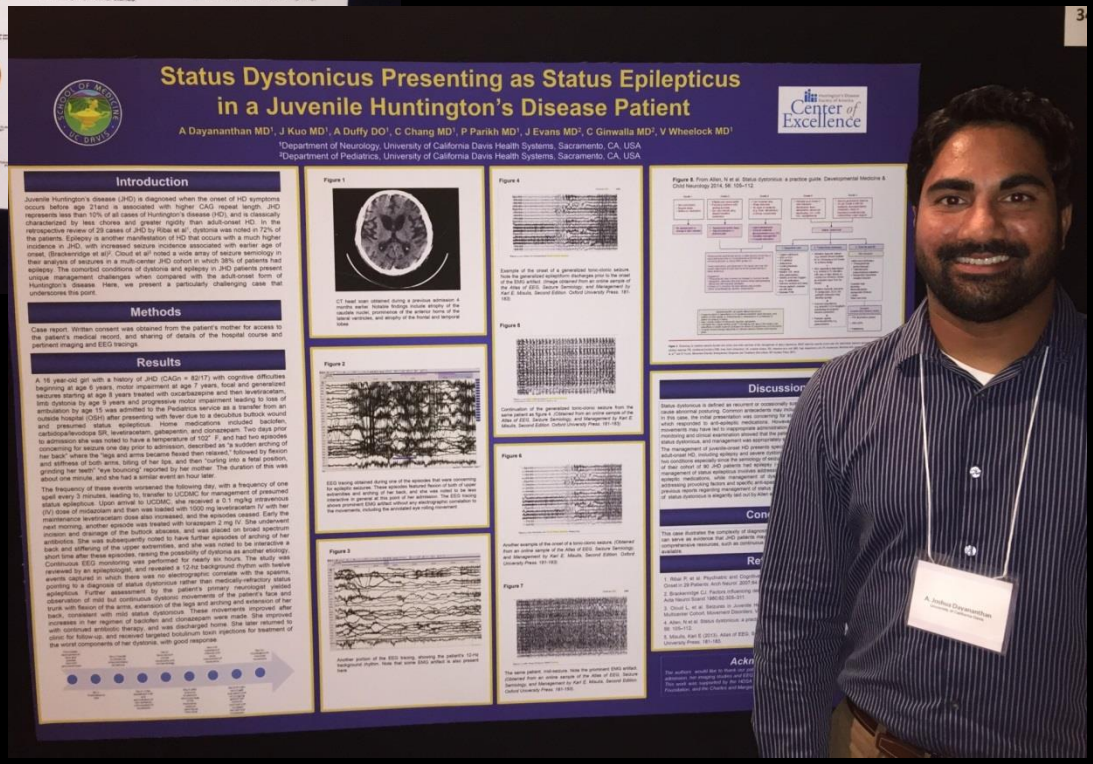
Lisa Mooney, LCSW

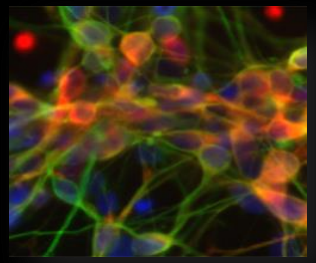
HDSA COE at UC Davis Social Worker

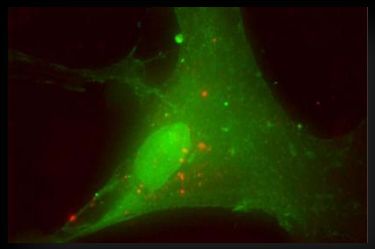


Dr. Sasha Duffy, Assistant Professor of Neurology Movement Disorders Neurologist

Dr. Ashok Joshua Dayananthan Movement Disorders Fellow








Cognitive Assessments

Sarah Farias, PhD

Associate Professor of Neurology, UC Davis

Julie Stout, PhD

Professor, School of Psychological Sciences

Monash University

Structural Imaging Analysis

Charles DeCarli, MD

Professor, Department of Neurology

Director, IDeA Lab at UC Davis

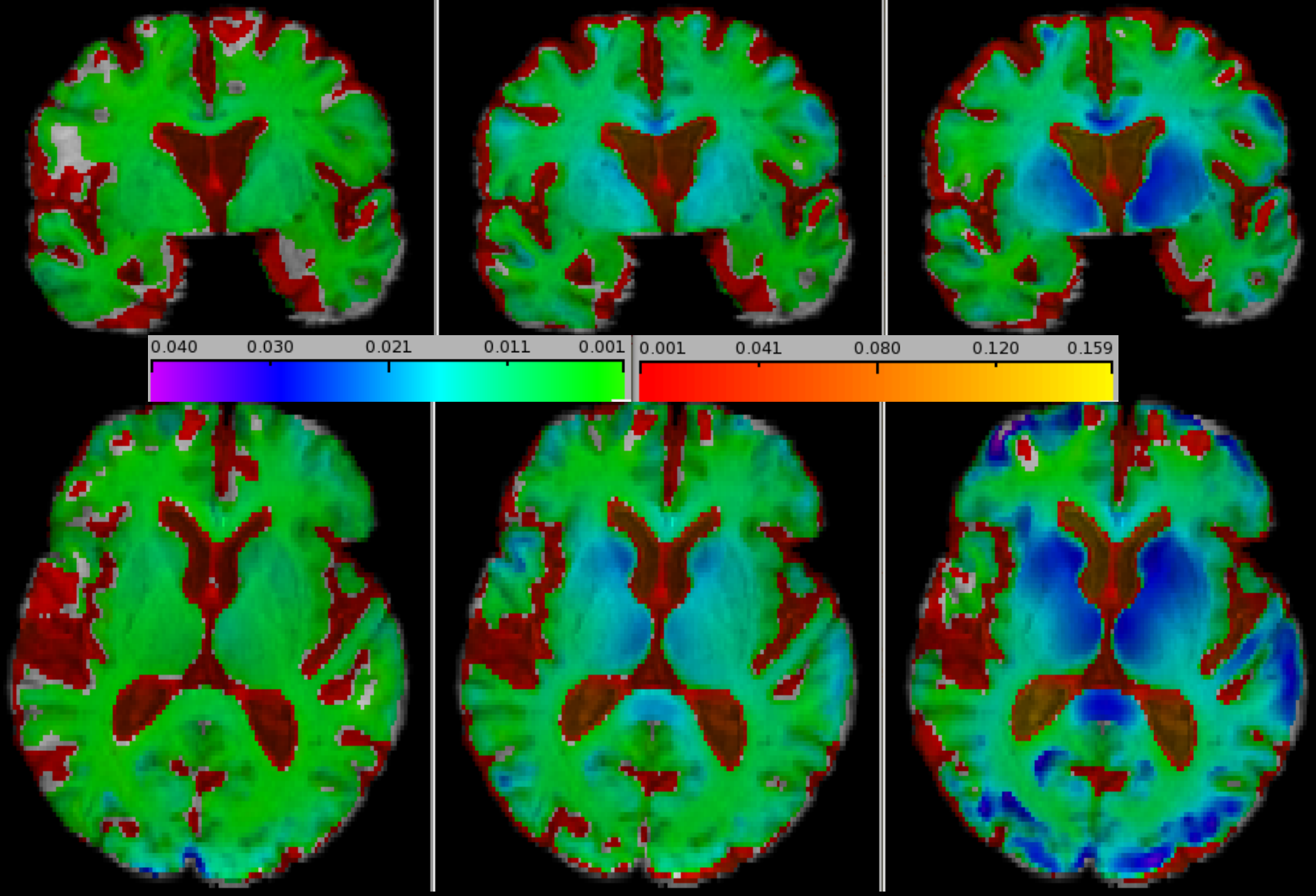
Co-Clinical PI

IDeA Lab

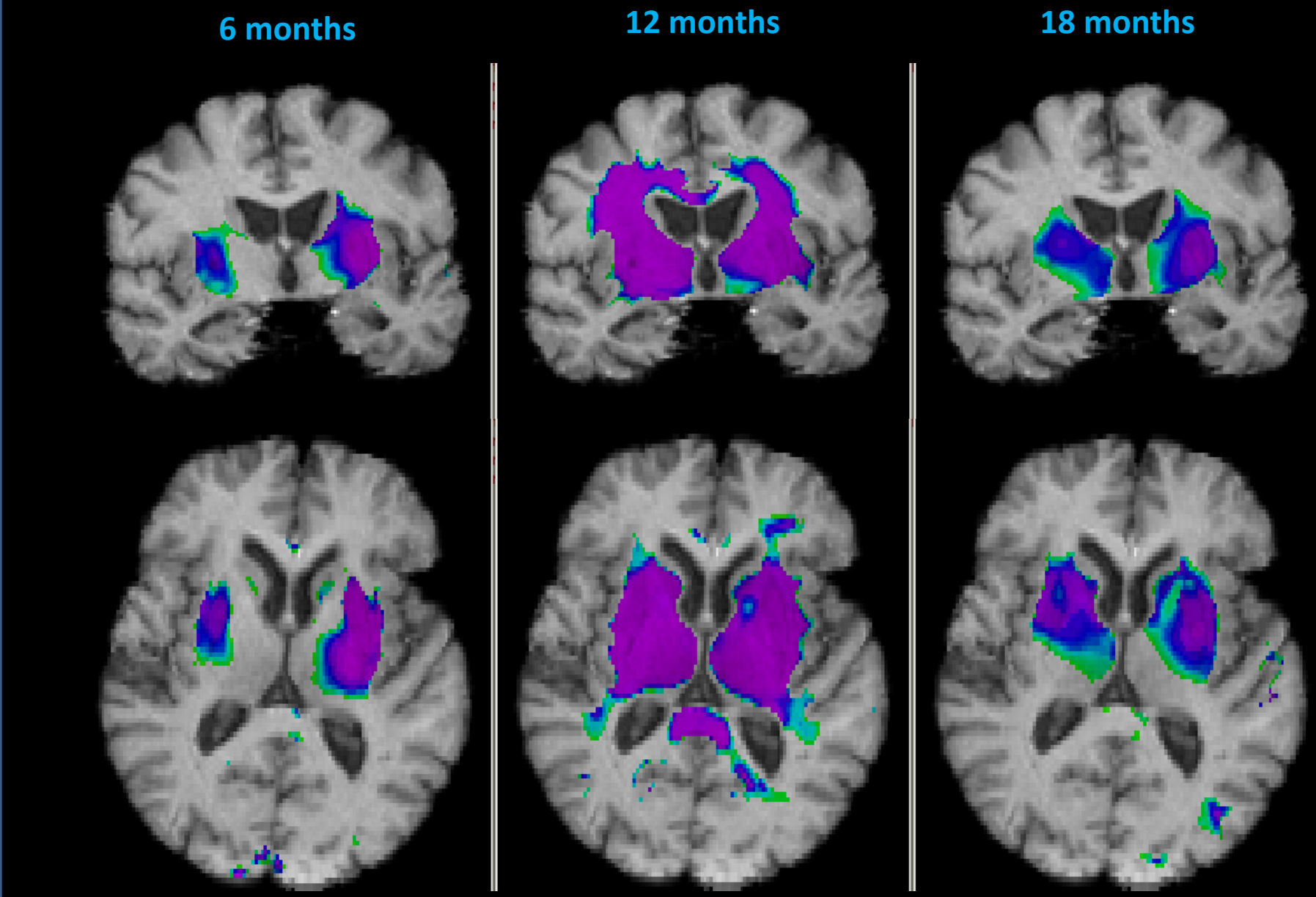
Imaging of Dementia and Aging

Cross sectional Percentage Change Magnitude Images

6 months 12 months 18 months



Unbiased Estimate of Voxel Based Significant Differences

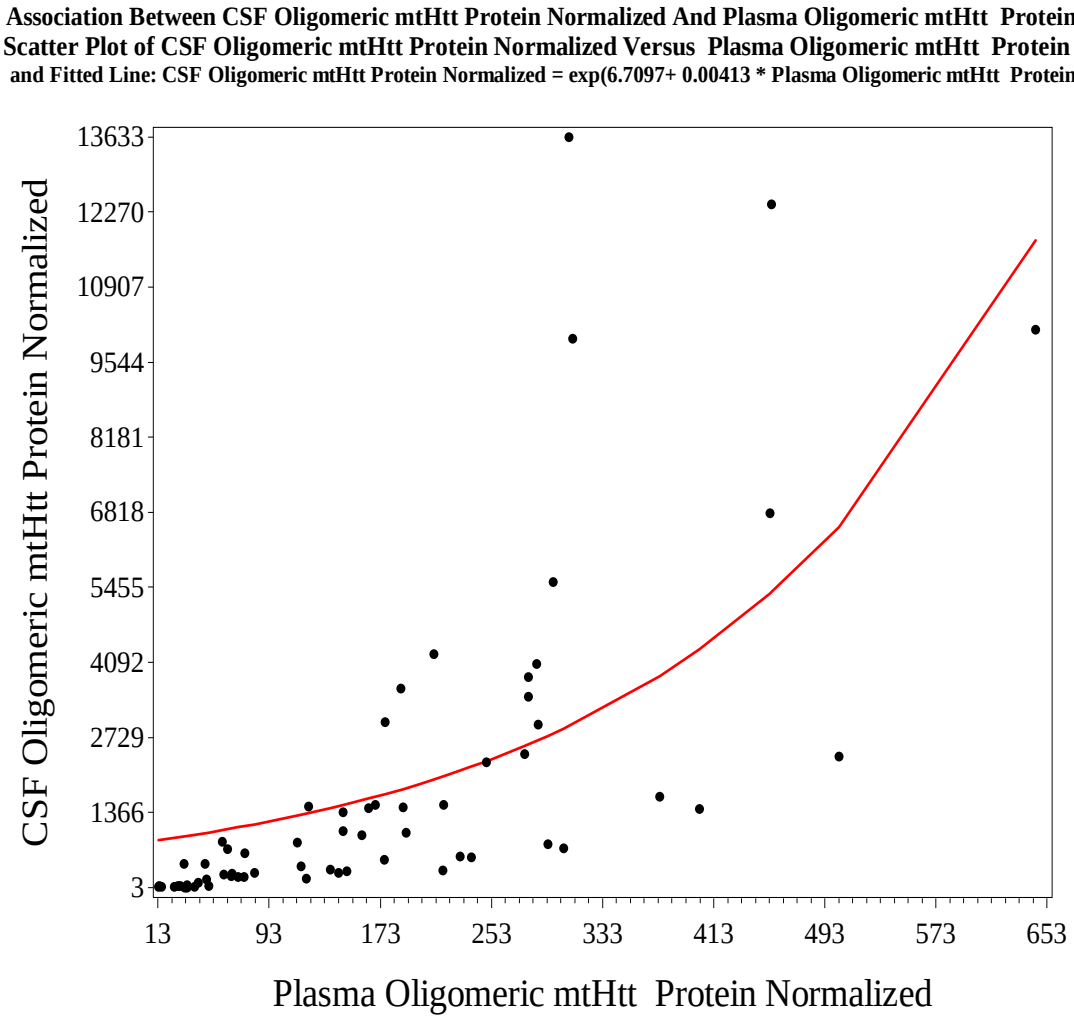


PRE-CELL Biomarkers

Steven Hersch, MD PhD
Professor of Neurology
Harvard Medical School

BDNF
Mutant Huntingtin Protein

Cerebrospinal fluid and Serum mutant Huntingtin Protein (mtHTT) levels



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.

National Institutes of Health, Bethesda, MD; June 9, 2015

Molecular Therapy

Results of pre-clinical studies

Official journal of the American Society of Gene & Cell Therapy

MT Open

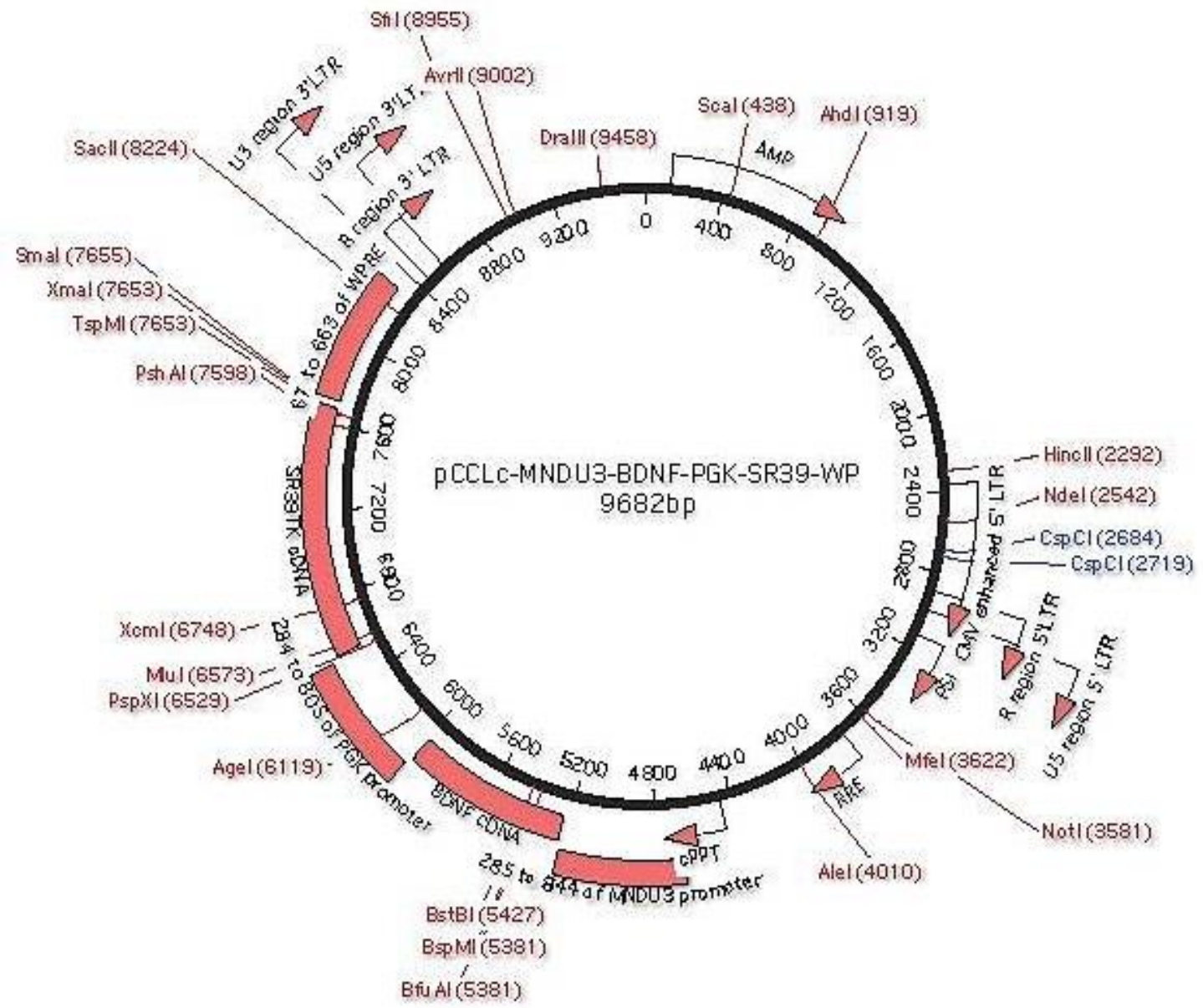
original article

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

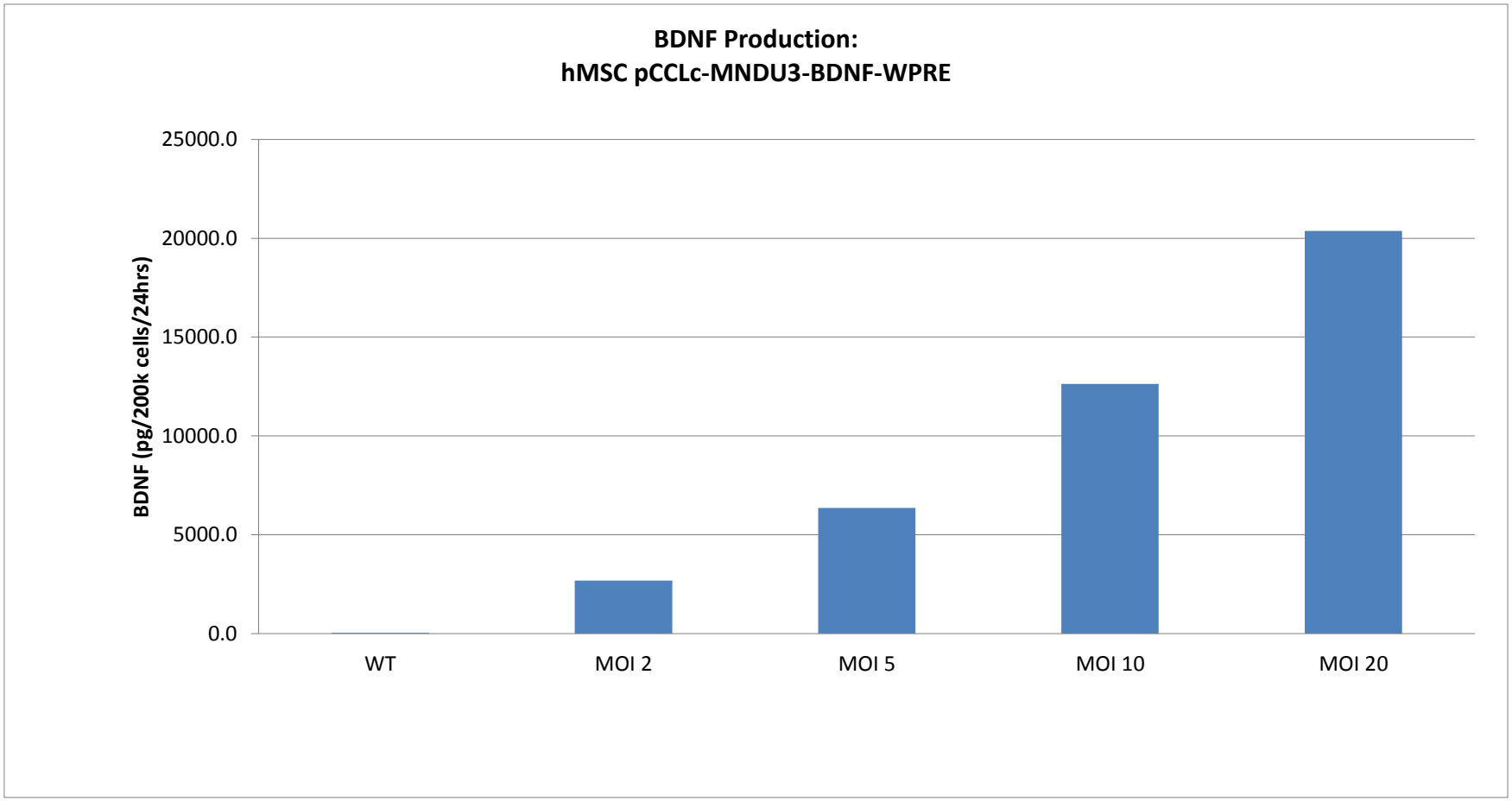
Kari Pollock[1], Heather Dahlenburg[1], Haley Nelson[1], Kyle D Fink[1], Whitney Cary[1], Kyle Hendrix[1], Geralyn Annett[1], Audrey Torrest[1], Peter Deng[1], Joshua Gutierrez[1], Catherine Nacey[1], Karen Pepper[1], Stefanos Kalomoiris[1], Johnathon D Anderson[1], Jeannine McGee[1], William Gruenloh[1], Brian Fury[1], Gerhard Bauer[1], Alexandria Duffy[2], Theresa Tempkin[2], Vicki Wheelock[2] and Jan A Nolta[1]

[1]Stem Cell Program and Institute for Regenerative Cures, University of California Davis Health System, Sacramento, California, USA; [2]Department of Neurology, University of California Davis Health System, Sacramento, California, USA

pCCLc-MNDU3-BDNF-PGK-WPRE lentiviral vector

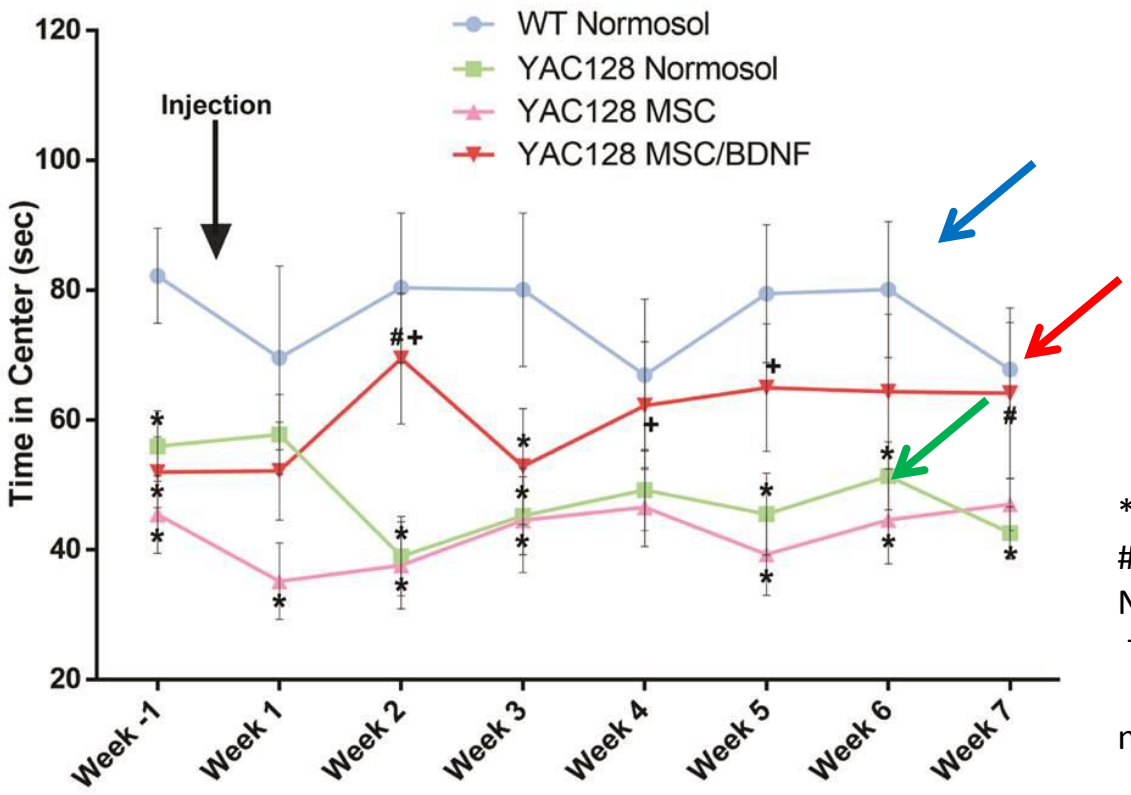


BDNF production by the engineered MSCs



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.

YAC128 Behavioral Efficacy Study – Open Field Assay



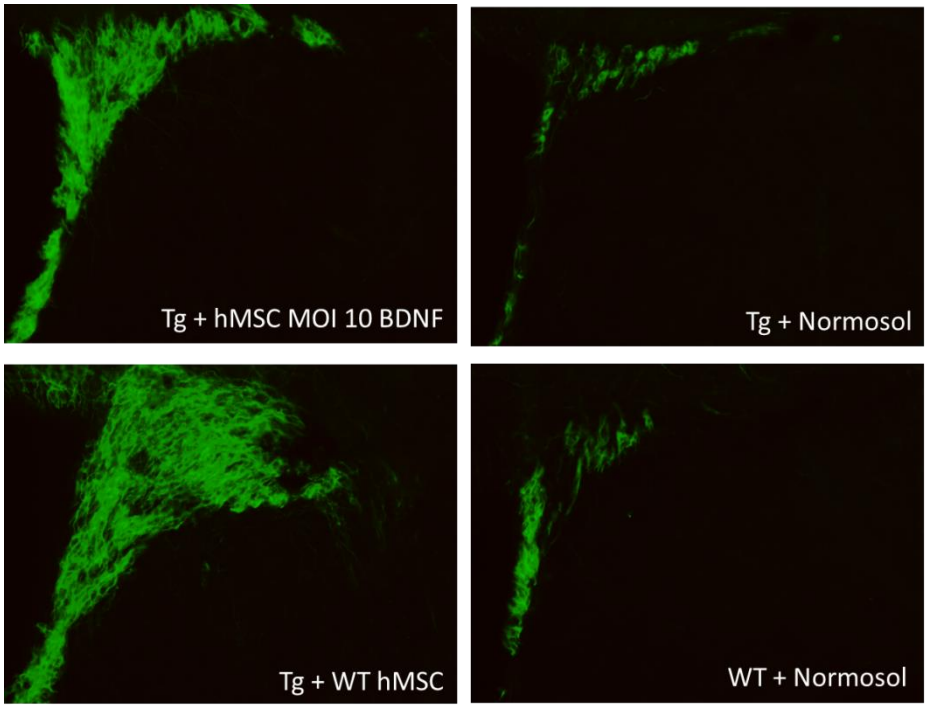
* = Significant to WT
# = Significant to Tg + Normosol
† = Significant to Tg + MSC

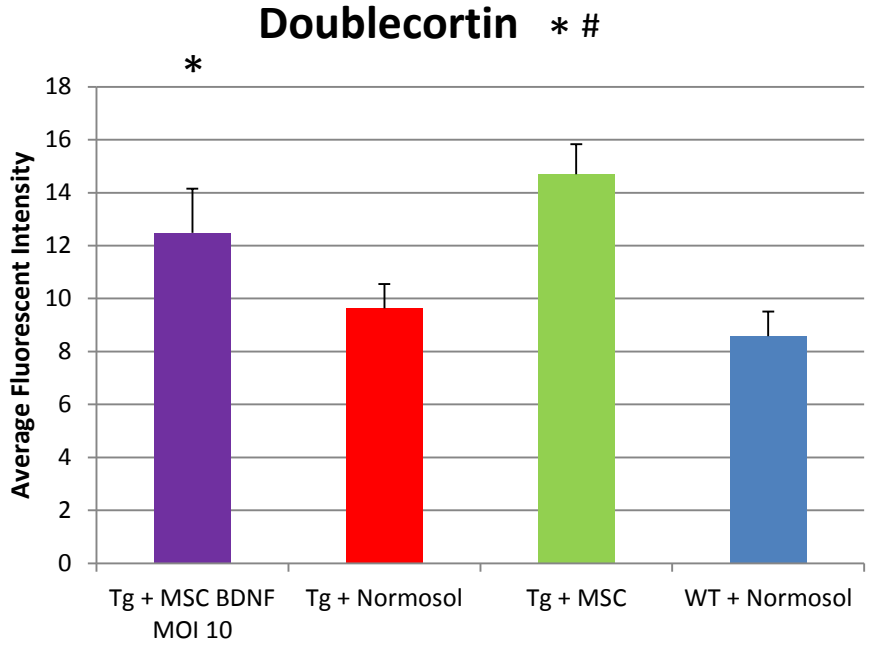
n = 16-17/group.

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).

R6/2 Neurogenesis: 2014-0825 Efficacy study





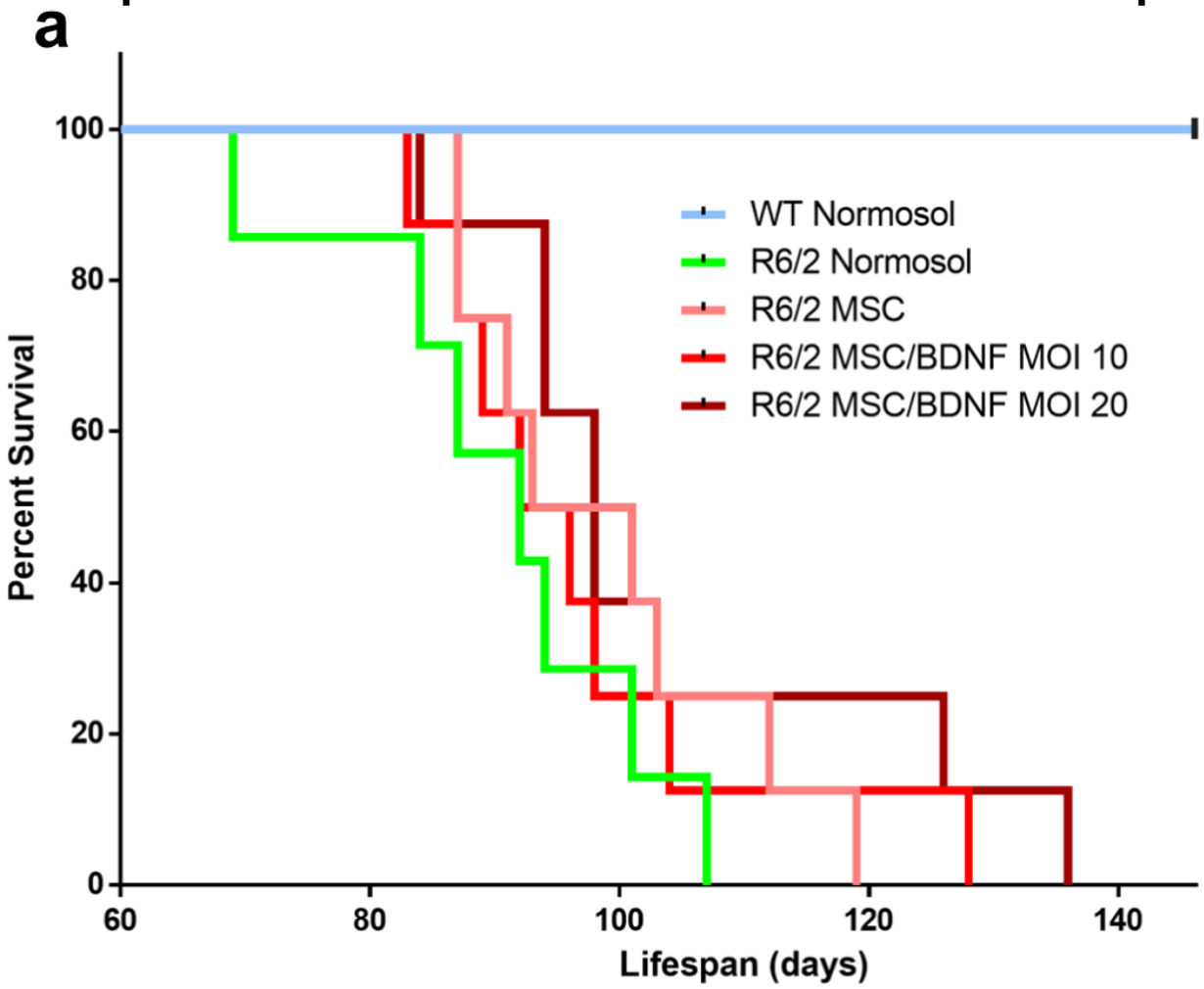
* = Significant to WT, # = Significant to tg + Normosol.

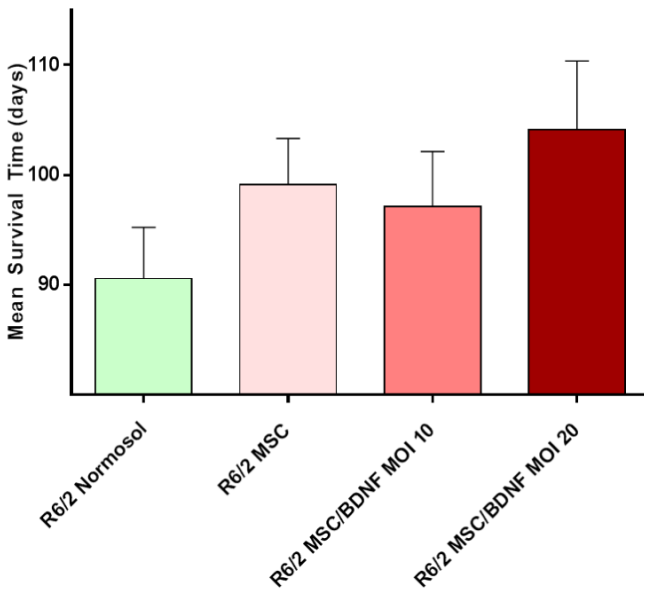
Time = 2.5 weeks

Transplantation of MSC with and without BDNF significantly increases neurogenesis activity in the subventricular zone of the brain.

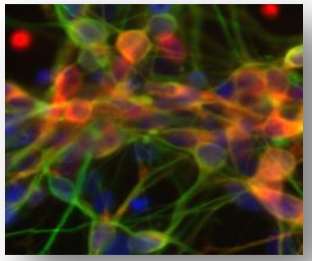
R6/2 Efficacy Study: 2014-1208

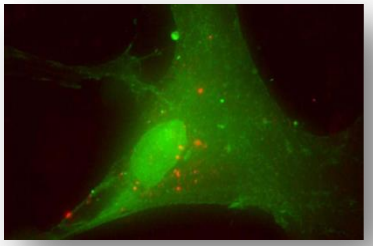
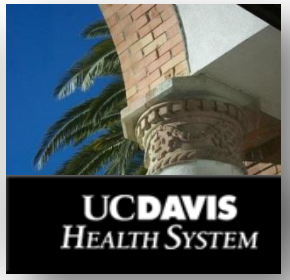
Implantation with MSC/BDNF increased the lifespan of R6/2 (CAG 120) mice





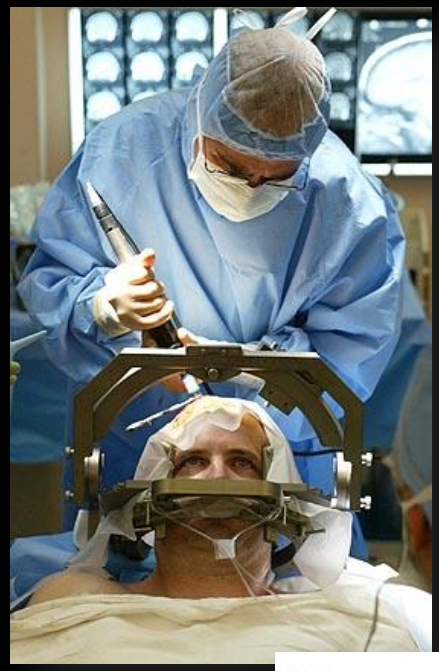
10% increase for WT MSC, 7.7% increase for MSC BDNF MOI 10, 15.5% increase for MSC BDNF MOI 20.



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.

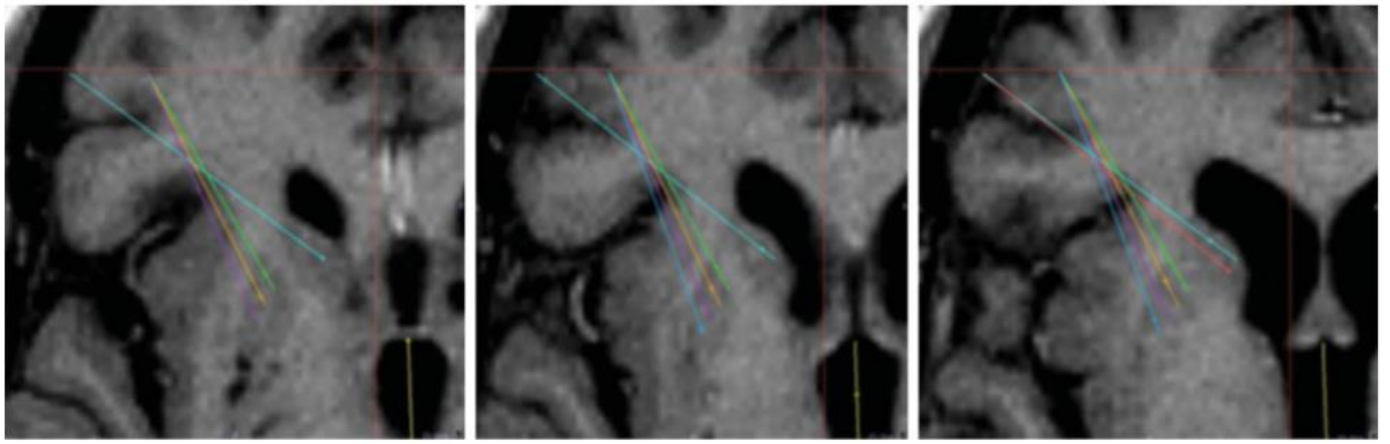


Fig. 1. MRI T1w, showing typical views obtained from the STP3 –planning workstation. Three coronal projections with tracts going to the caudate nucleus and to the putamen on the left side.

UC Davis HD Team and Collaborators

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Heather Stewart
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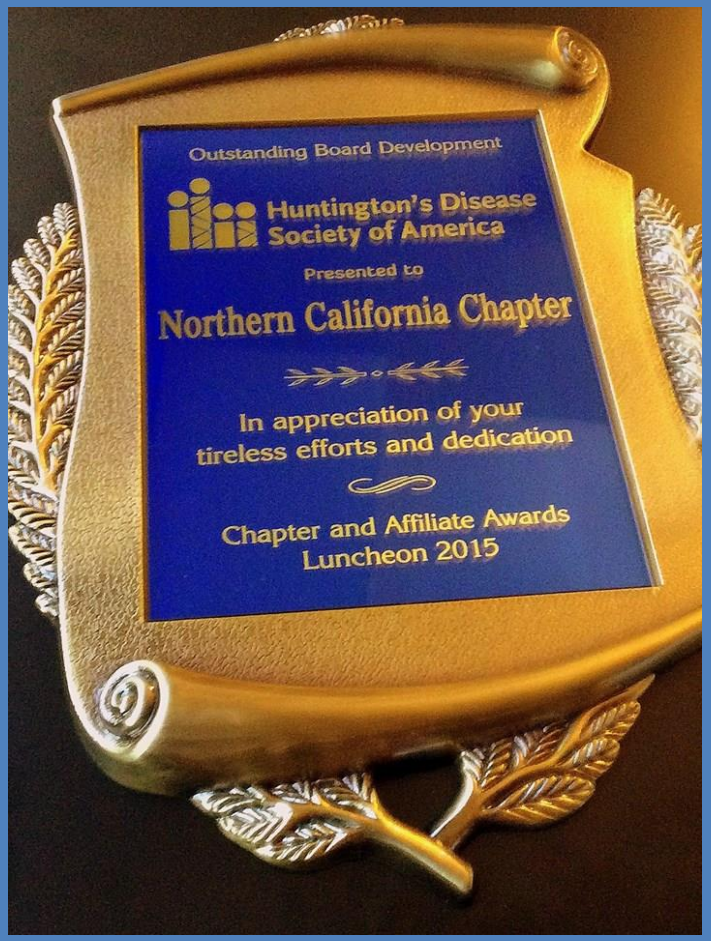
Michigan:	Gary Dunbar
Boston:	Steve Hersch
France:	Anne Catherine Bachoud-Levi
Australia:	Julie Stout
Washington:	Elizabeth Aylward
Korea:	Hyun-Suk Kim

THANK YOU! HD patient advocates, patients and families

Funded by the California Institute for Regenerative Medicine

Thank you
HDSA Northern CA Chapter!



Thank you Les Pue and Terry Tempkin!