

# ***Potential new therapies for HD***

*2016 HDSA Northern California Annual Convention*

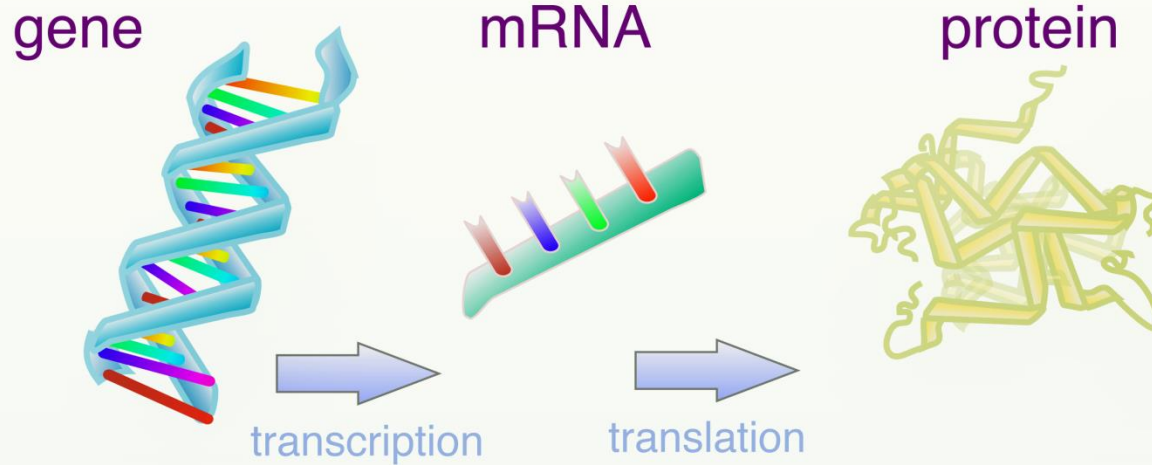
Vicki Wheelock MD  
Director, HDSA Center of Excellence  
at UC Davis  
Saturday May 21, 2016  
Sacramento CA



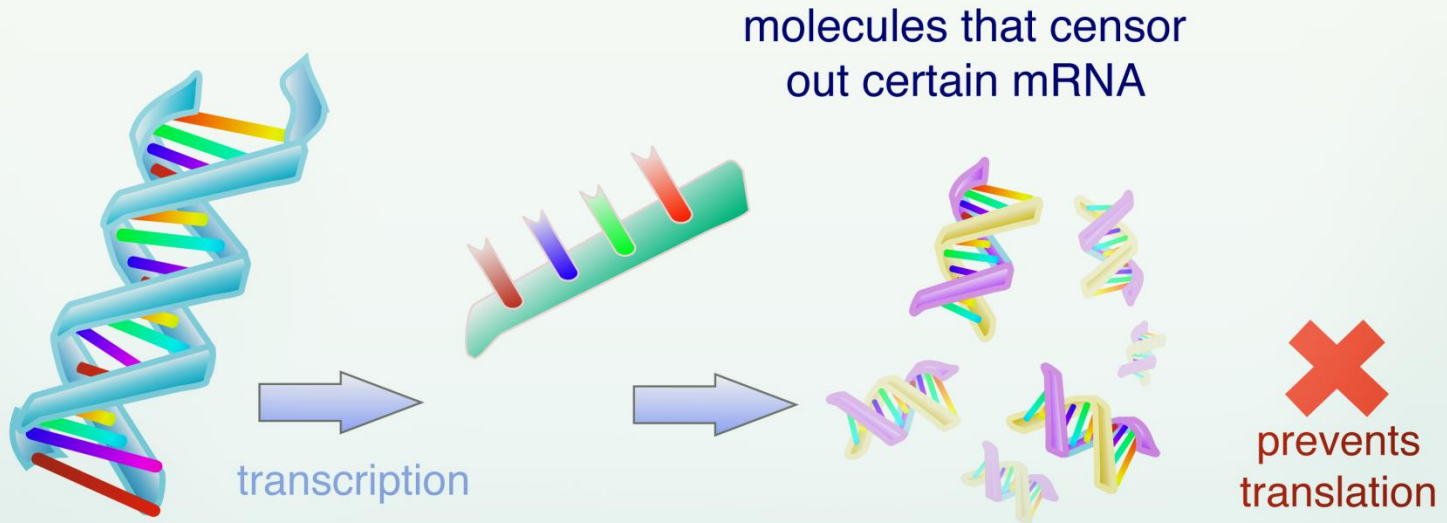
# The quest for disease modifying treatments in HD

- 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

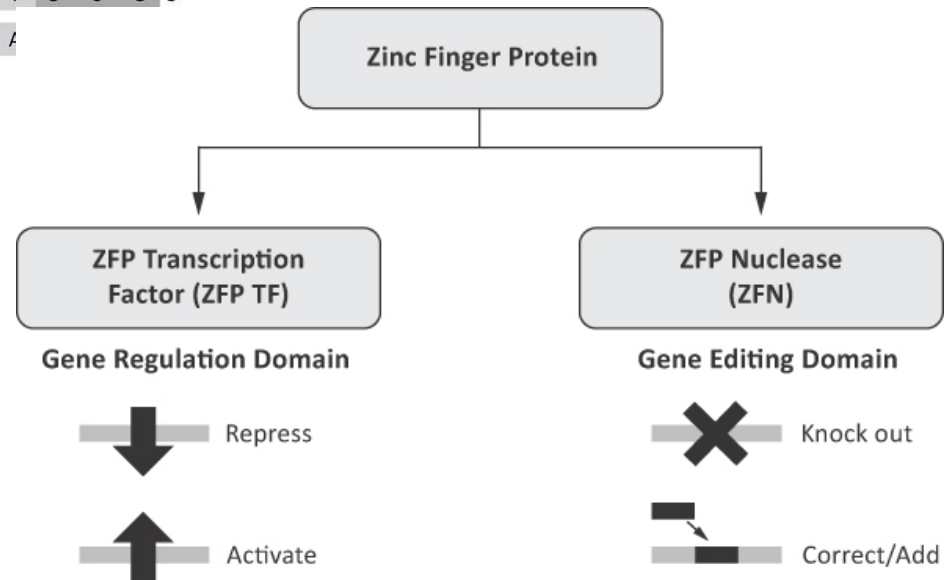
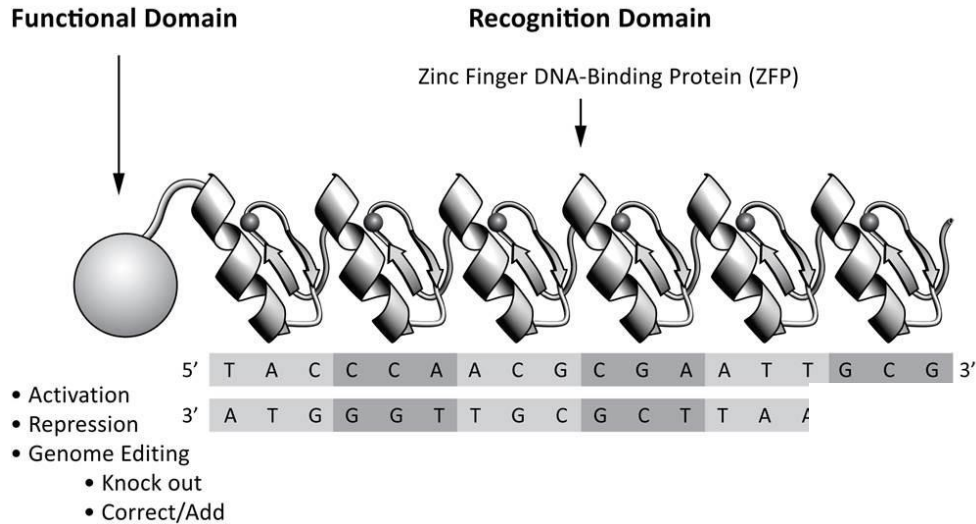
# normal protein production

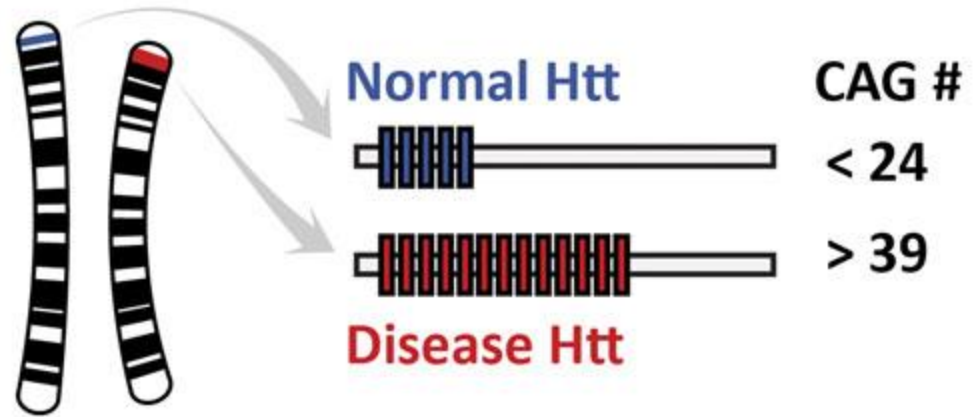


# gene silencing



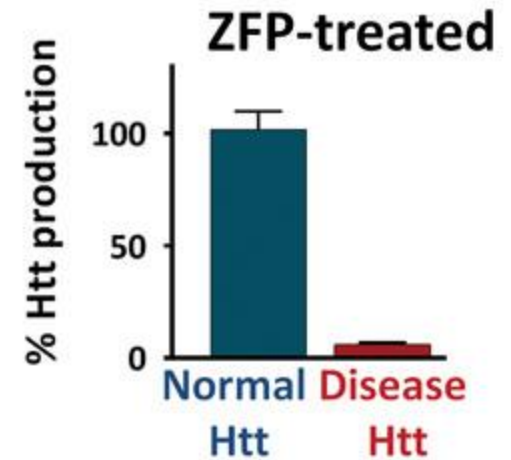
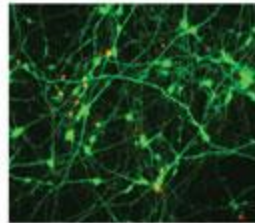
# Zinc Finger Proteins: natural transcription factors





Chr 4

HD neurons



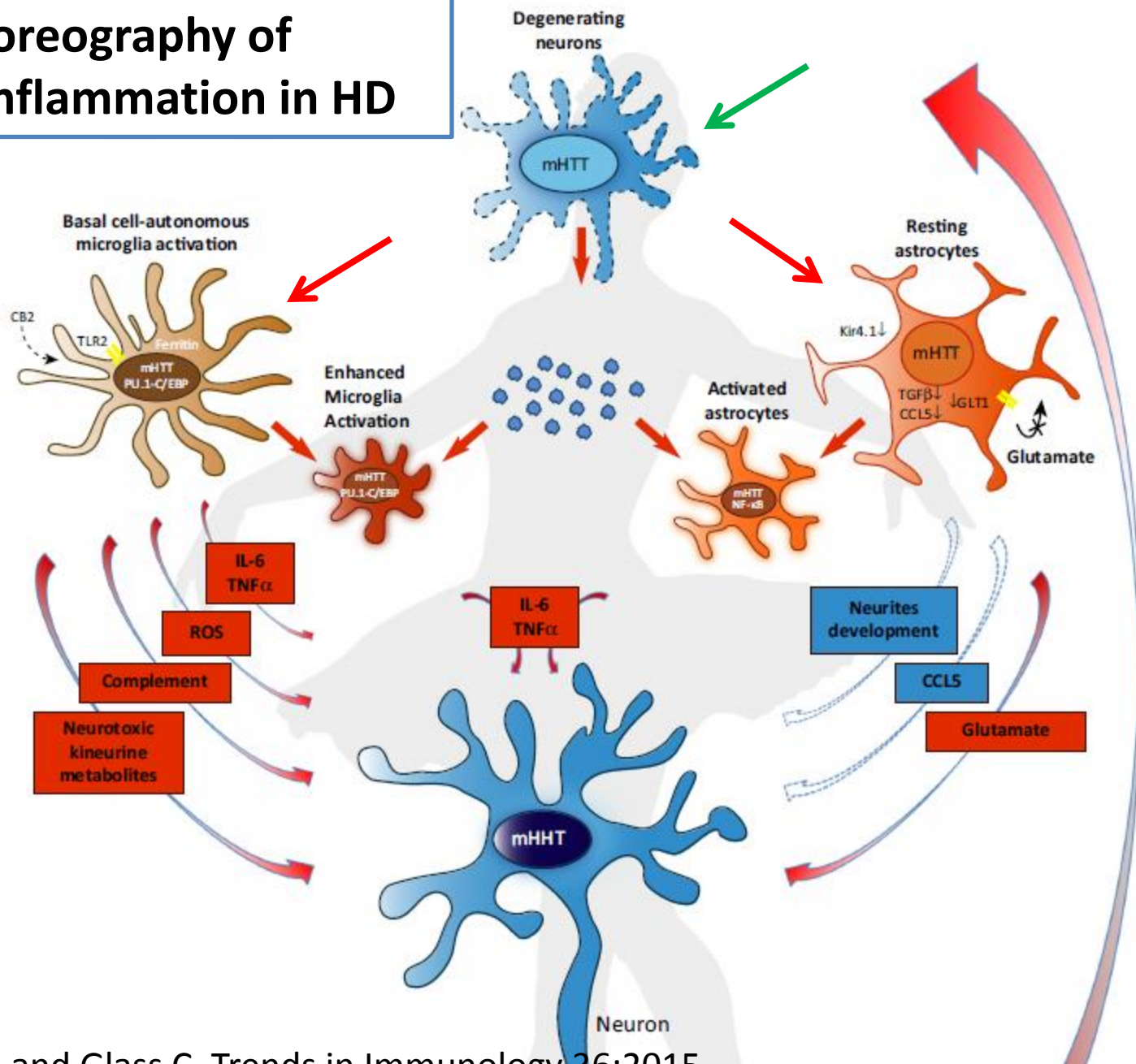
The schematic shows the normal versus the mutant Htt gene and the selective ZFP-mediated repression of expression of the mutant form of Htt in Huntington's disease derived neurons. [Sangamo BioSciences]

# 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



# LEGATO-HD Study

THE LAQUINIMOD HD 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<sub>1A</sub> 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



The NEXT Generation of Neurologic Treatments  
NIH-Network for Excellence in Neuroscience Clinical Trials

# 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



The NEXT Generation of Neurologic Treatments  
NIH-Network for Excellence in Neuroscience Clinical Trials

# 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.

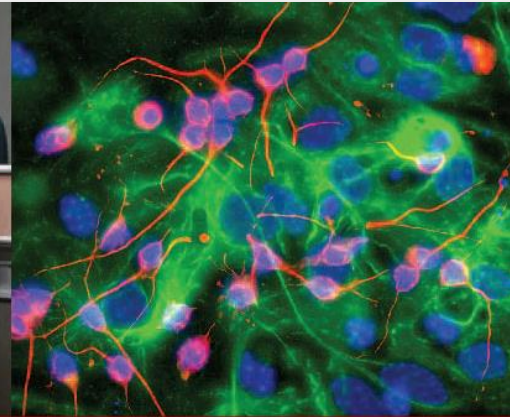
Olson SD et al. Molec Neurobiol45;2012:87-98

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

# Partnership between families, researchers and CIRM

CIRM Spotlight on  
Huntington's Disease at  
the California Legislature,  
March 2010

Pictured clockwise from  
top left: Vicki Wheelock,  
Sherry (patient advocate),  
Claire Pomeroy, Judy  
Roberson and Jan Nolte



## How patient advocates changed the course of science



A group of families impacted by Huntington's disease inspired a "Eureka!" moment for Jan Nolte, UC Davis' pioneering stem cell researcher

2010 – CIRM Spotlight on HD  
California State Capitol







Mol Neurobiol (2012) 45:87–98

DOI 10.1007/s12035-011-8219-8

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# 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. Nolte

# 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

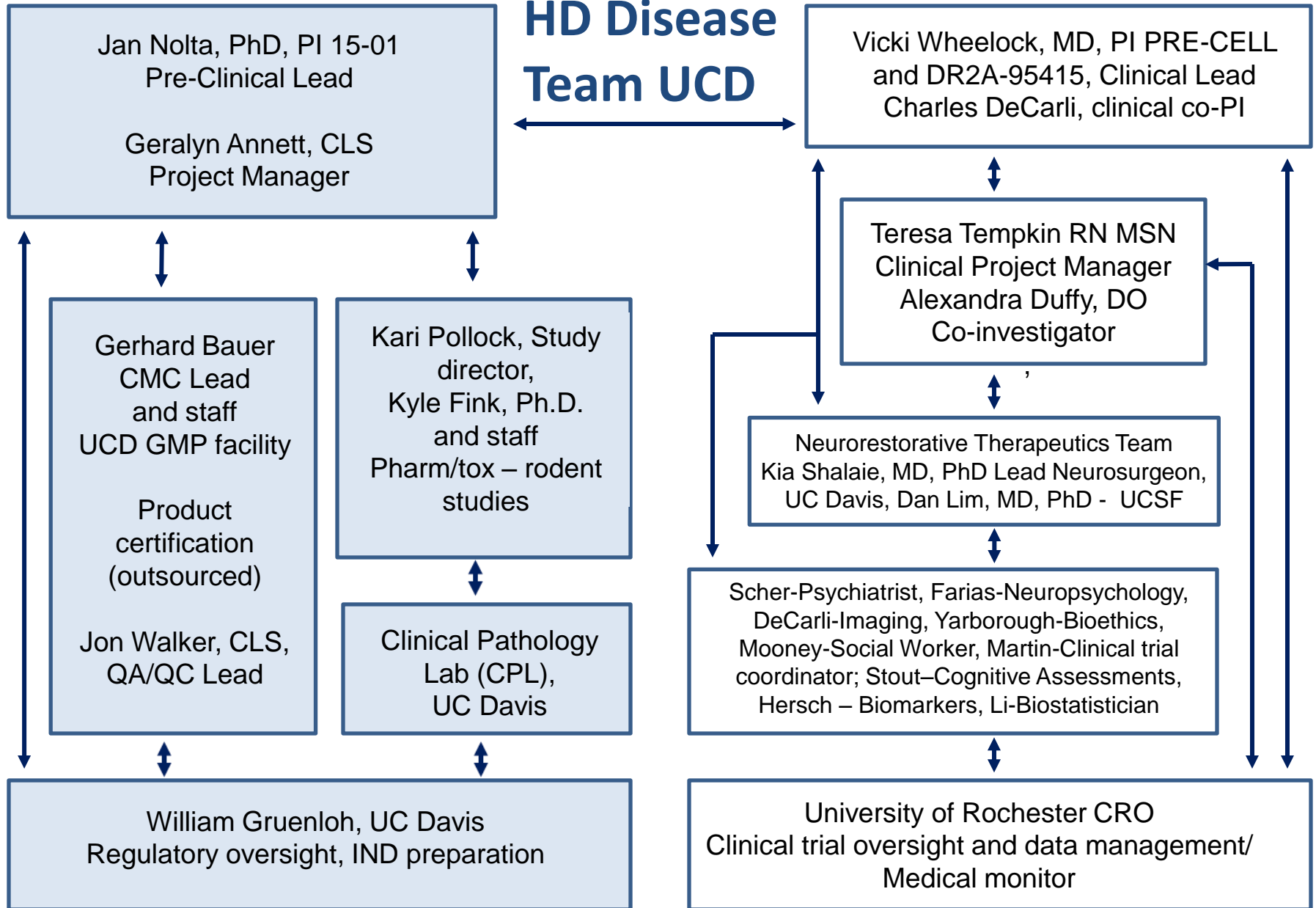
## CIRM Grant DR2A-05415

**PRE-CELL: Years 1&2**

**HD-CELL: Years 3&4**

|  | Year 1   | Year 2 | Year 3  | Year 4 |
|--|--|--------|---|--------|
| GMP Manufacturing of Clinical Lots                   |     |        |   |        |
| IND-enabling studies using current GMP Lot (ongoing) |     |        |   |        |
| Regulatory approvals (ongoing)                       |    |        |   |        |
| Observational Clinical trial                         |  |        |   |        |
| Phase I Clinical trial                               |  |        |  |        |
| Lab/safety studies: patient samples                  |  |        |  |        |

# HD Disease Team UCD



# 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!



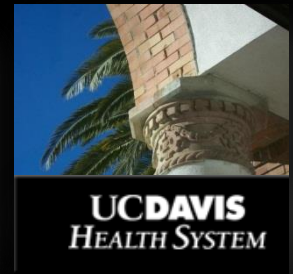
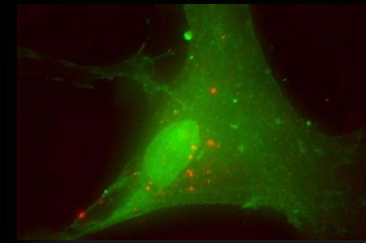
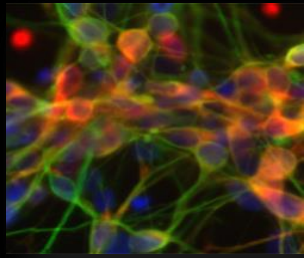
Amanda Martin, BA  
Study Coordinator



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

# First-In-Human Stem Cell Trials in Huntington's Disease: A Bioethics Survey



Alexandra Duffy DO<sup>1</sup>, Amanda Martin BA<sup>1</sup>, Meaghan O'Keefe PhD<sup>2</sup>, Marsha Michie PhD<sup>3</sup>, Mark Yarborough PhD<sup>4</sup>, Vicki Wheelock MD<sup>1</sup>

<sup>1</sup>Department of Neurology, University of California Davis Health System, Sacramento, CA, USA  
<sup>2</sup>Department of Biogeriatrics Studies, UC Davis, Davis, CA  
<sup>3</sup>UCSF Institute for Health and Aging, San Francisco, CA  
<sup>4</sup>Department of Bioethics, UC Davis School of Medicine, Sacramento CA



## Background

Experimental treatment approaches and first-in-human Phase 1 trials are ethically and logistically challenging to obtain consent, ensure safety and efficacy, and provide adequate monitoring. This study addresses these challenges by assessing the impact of a bioethics survey on the recruitment of HD patients and family members to a study that involved stem cell gene therapy and neurotrophic factor administration as approved by the Institutional Review Board at UC Davis. The survey was offered on the HDUSA website from September - December 2013. The survey assessed the impact of a bioethics survey on the recruitment of HD patients and family members to a study that involved stem cell gene therapy and neurotrophic factor administration as approved by the Institutional Review Board at UC Davis. The survey assessed the impact of a bioethics survey on the recruitment of HD patients and family members to a study that involved stem cell gene therapy and neurotrophic factor administration as approved by the Institutional Review Board at UC Davis.

## Methods

A cross-sectional survey of HD patients and family members regarding attitudes and concerns about participation in a study that involved stem cell gene therapy and neurotrophic factor administration as approved by the Institutional Review Board at UC Davis. The survey was offered on the HDUSA website from September - December 2013. The survey assessed the impact of a bioethics survey on the recruitment of HD patients and family members to a study that involved stem cell gene therapy and neurotrophic factor administration as approved by the Institutional Review Board at UC Davis. The survey assessed the impact of a bioethics survey on the recruitment of HD patients and family members to a study that involved stem cell gene therapy and neurotrophic factor administration as approved by the Institutional Review Board at UC Davis.

## Results

Our study included 108 patients and 108 family members. The survey assessed the impact of a bioethics survey on the recruitment of HD patients and family members to a study that involved stem cell gene therapy and neurotrophic factor administration as approved by the Institutional Review Board at UC Davis. The survey assessed the impact of a bioethics survey on the recruitment of HD patients and family members to a study that involved stem cell gene therapy and neurotrophic factor administration as approved by the Institutional Review Board at UC Davis.

Figure 1. Study flowchart

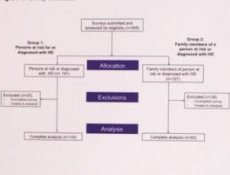


Table 1. Characteristics of respondents

| Characteristic           | Group 1 (n=118) | Group 2 (n=118) |
|--------------------------|-----------------|-----------------|
| Age (mean)               | 58.2            | 59.1            |
| Female (%)               | 78              | 75              |
| Education (years)        | 16.5            | 16.2            |
| Income (\$/yr)           | 45,000          | 46,000          |
| Employment (%)           | 65              | 68              |
| Insurance (%)            | 85              | 82              |
| Marital status (%)       | 65              | 68              |
| HD duration (years)      | 12.5            | 13.2            |
| Genotype (%)             | 95              | 92              |
| Family history (%)       | 80              | 78              |
| Previous HD research (%) | 15              | 18              |

Figure 2. Demographics of all respondents

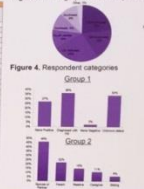


Figure 3. Participation in first-in-human trial

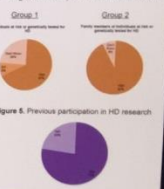


Figure 4. Respondent categories

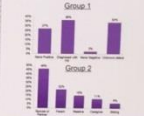


Figure 5. Previous participation in HD research



Table 2. Open-ended question responses (Group 1 and Group 2 included)



## Discussion

The goal of the survey was to explore attitudes and concerns of HD patients and family members about potential participation in a first-in-human experimental approach to treatment of HD utilizing gene-modified stem cells modified delivered by neurotrophic implantation. Results showed a broad support for participation in such a study from both patients and family members. The chief ethical challenge identified by both patients and family members was the safety of the stem cell gene therapy and neurotrophic factor administration. Safety concerns were the most common, followed by concerns about the potential risks of the stem cell gene therapy and neurotrophic factor administration. Safety concerns were the most common, followed by concerns about the potential risks of the stem cell gene therapy and neurotrophic factor administration.



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

Alexandra Duffy  
University of California  
Davis

# Status Dystonicus Presenting as Status Epilepticus in a Juvenile Huntington's Disease Patient

A Dayananthan MD<sup>1</sup>, J Kuo MD<sup>1</sup>, A Duffy DO<sup>1</sup>, C Chang MD<sup>1</sup>, P Parikh MD<sup>1</sup>, J Evans MD<sup>1</sup>, C Gimwalla MD<sup>1</sup>, V Wheelock MD<sup>1</sup>

<sup>1</sup>Department of Neurology, University of California Davis Health System, Sacramento, CA, USA  
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## Introduction

Juvenile Huntington's disease (JHD) is diagnosed when the onset of HD symptoms occurs before age 21 and is associated with higher CAG repeat length. JHD is characterized by less chorea and greater rigidity than adult-onset HD. In the retrospective review of 23 cases of JHD by Gill et al, patients were noted to have epilepsy. Epilepsy is another manifestation of HD that occurs with a much higher incidence in JHD, with increased seizure incidence associated with earlier age of onset. (Brockmeyer et al, 2004; Choi et al, 2004) A wide array of seizure semiology in their analysis of adults in juvenile HD cohort in which 80% of patients had epilepsy. The complex conditions of dystonia and epilepsy in JHD presents present unique management challenges when compared with the adult-onset form of Huntington's Disease. Here, we present a particularly challenging case that underscores this point.

## Methods

Case report. Written consent was obtained from the patient's mother for access to the patient's medical record, and sharing of details of the hospital course and pertinent imaging and EEG findings.

## Results

A 10-year-old girl with a history of JHD (CAG = 42/17) with cognitive fluctuations began at age 5 years, motor impairment at age 7 years. Rigid and generalized seizures starting at age 8 years treated with carbamazepine and later to topiramate. Her seizures began at age 8 years and progressive motor impairment leading to loss of ambulation by age 11 years. She was admitted to the Pediatric Intensive Care Unit (PICU) after presenting with her first seizure. She was noted to have rigidity and generalized tonic-clonic seizures. Two days prior to admission she had a seizure with tonic arm extension and tonic arm abduction to admission she was found on the floor prior to admission, and presented with tonic arm extension and tonic arm abduction. She was found on the floor prior to admission, and presented with tonic arm extension and tonic arm abduction. She was found on the floor prior to admission, and presented with tonic arm extension and tonic arm abduction.

Figure 1



Figure 2



Figure 3



Figure 4



Figure 5



Figure 6

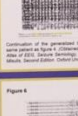


Figure 7

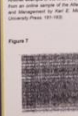


Figure 8

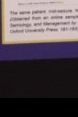


Figure 9



## Discussion

The management of juvenile HD patients with epilepsy and rigidity is challenging. The management of juvenile HD patients with epilepsy and rigidity is challenging. The management of juvenile HD patients with epilepsy and rigidity is challenging. The management of juvenile HD patients with epilepsy and rigidity is challenging. The management of juvenile HD patients with epilepsy and rigidity is challenging.

## Conclusion

The case illustrates the complexity of managing juvenile HD patients with epilepsy and rigidity. The case illustrates the complexity of managing juvenile HD patients with epilepsy and rigidity. The case illustrates the complexity of managing juvenile HD patients with epilepsy and rigidity. The case illustrates the complexity of managing juvenile HD patients with epilepsy and rigidity. The case illustrates the complexity of managing juvenile HD patients with epilepsy and rigidity.

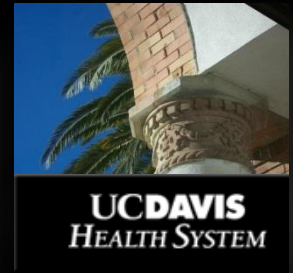
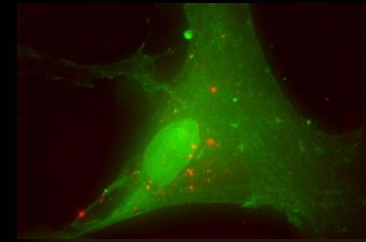
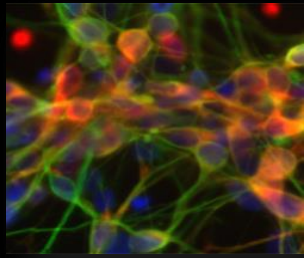
## References

1. Gill M, et al. Huntington's disease in children. *J Child Neurol* 2004; 19: 100-105.
2. Brockmeyer J, et al. Juvenile Huntington's disease: a retrospective review of 23 cases. *J Child Neurol* 2004; 19: 106-110.
3. Choi J, et al. Epilepsy in juvenile Huntington's disease. *J Child Neurol* 2004; 19: 111-115.
4. Brockmeyer J, et al. Juvenile Huntington's disease: a retrospective review of 23 cases. *J Child Neurol* 2004; 19: 106-110.
5. Choi J, et al. Epilepsy in juvenile Huntington's disease. *J Child Neurol* 2004; 19: 111-115.
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9. Choi J, et al. Epilepsy in juvenile Huntington's disease. *J Child Neurol* 2004; 19: 111-115.



Ashok Dayananthan  
University of California  
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# Cognitive Assessments



Sarah Farias, PhD

*Associate Professor of Neurology, UC Davis*



Julie Stout, PhD

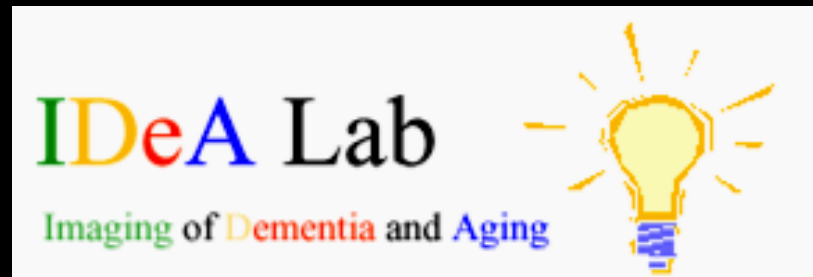
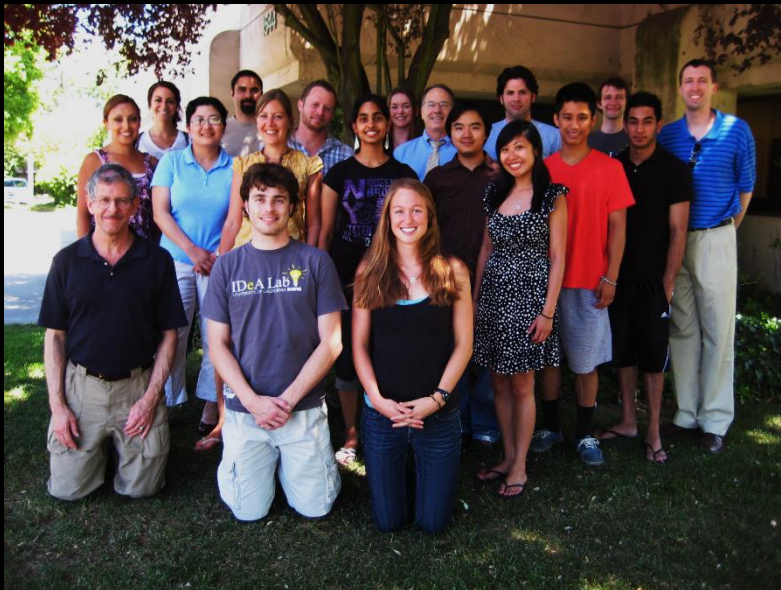
*Professor, School of Psychological Sciences*

*Monash University*

# Structural Imaging Analysis



Charles DeCarli, MD  
*Professor, Department of Neurology*  
*Director, IDeA Lab at UC Davis*  
*Co-Clinical PI*

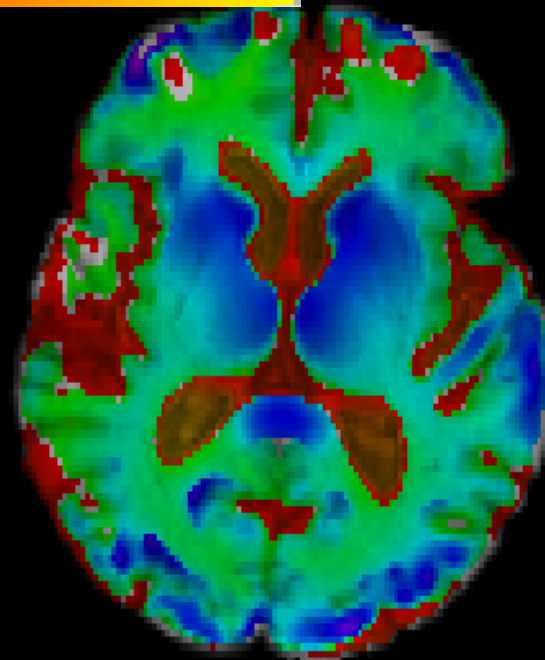
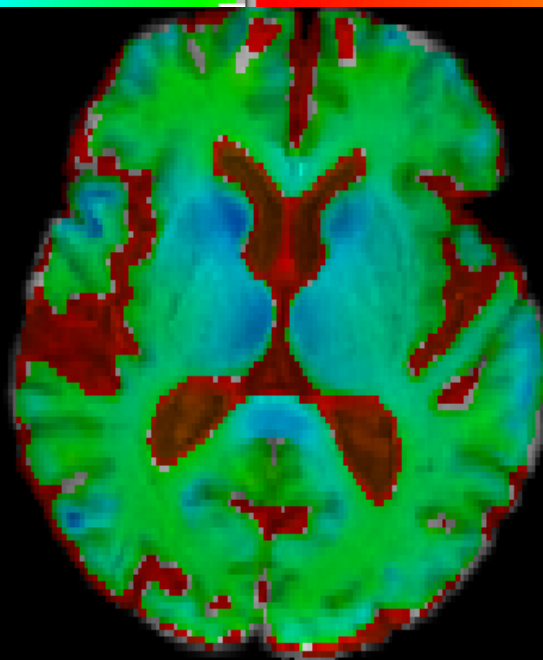
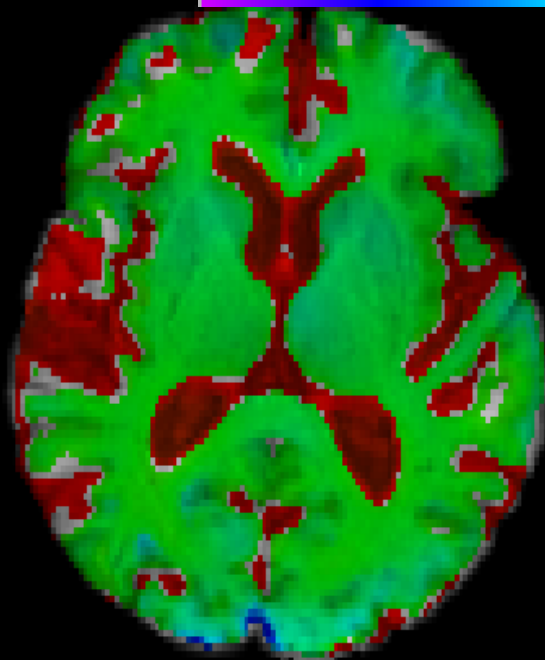
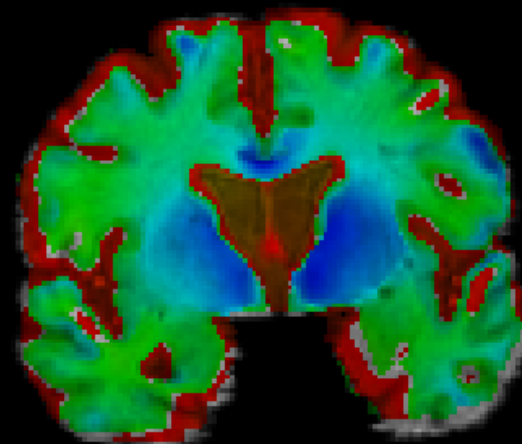
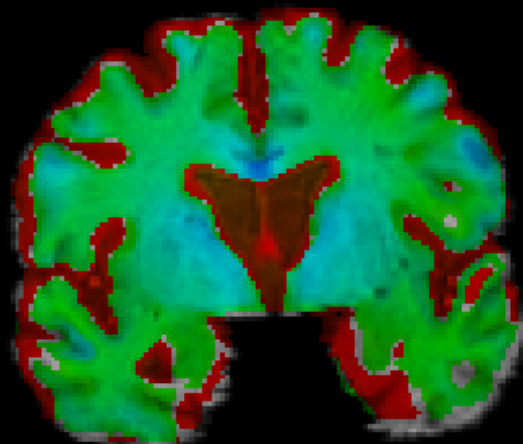
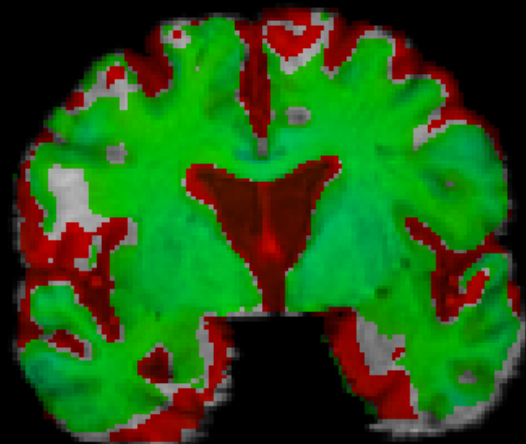


# Cross sectional Percentage Change Magnitude Images

6 months

12 months

18 months



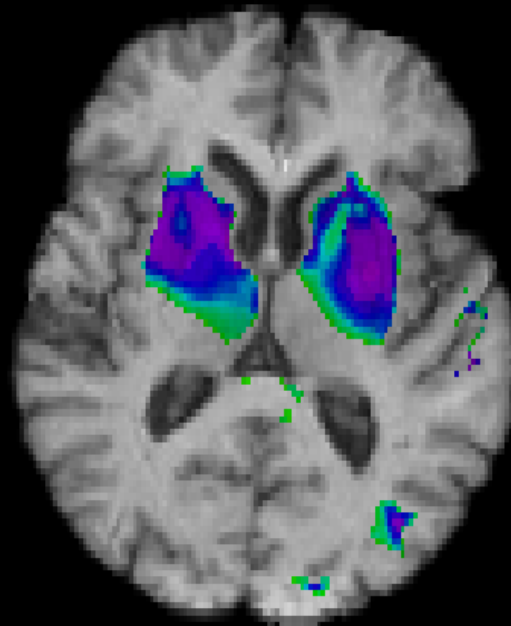
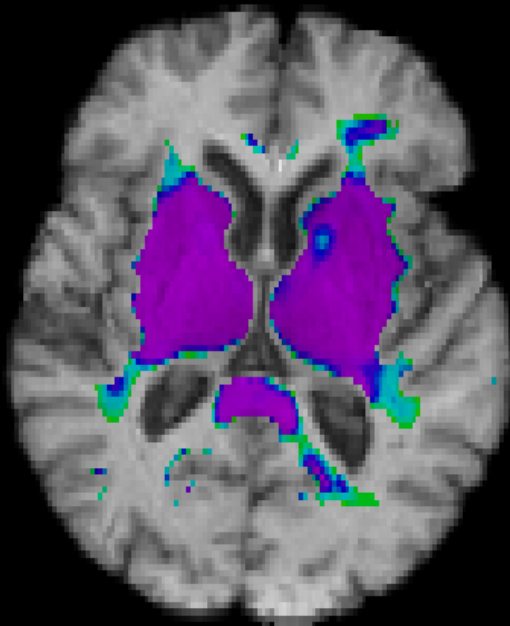
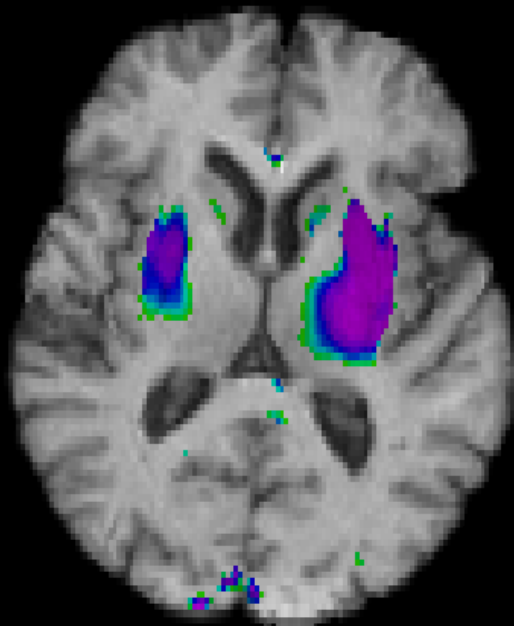
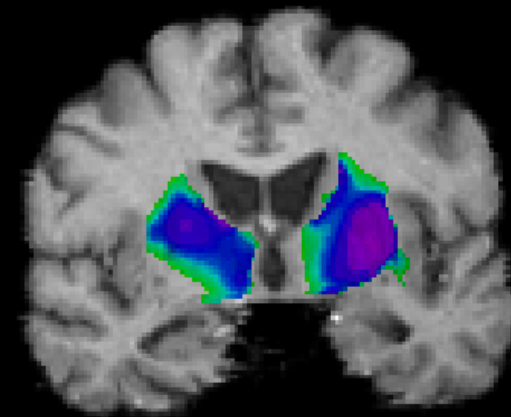
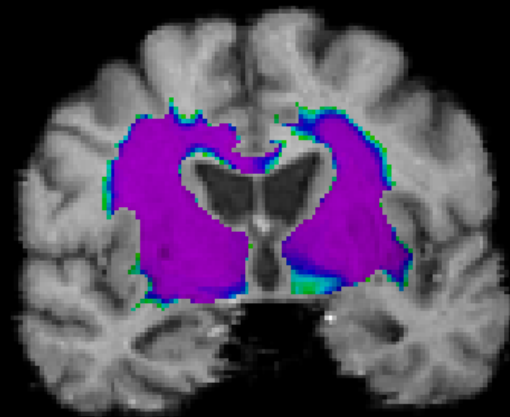
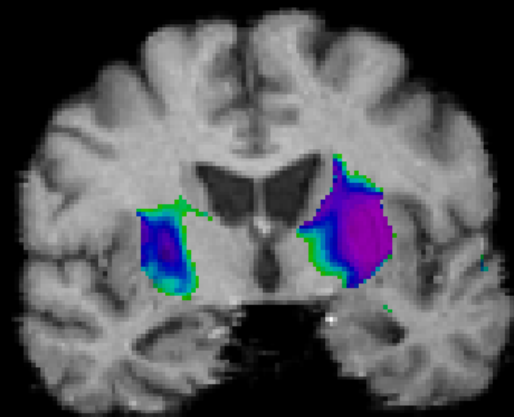


# Unbiased Estimate of Voxel Based Significant Differences

6 months

12 months

18 months



# PRE-CELL Biomarkers



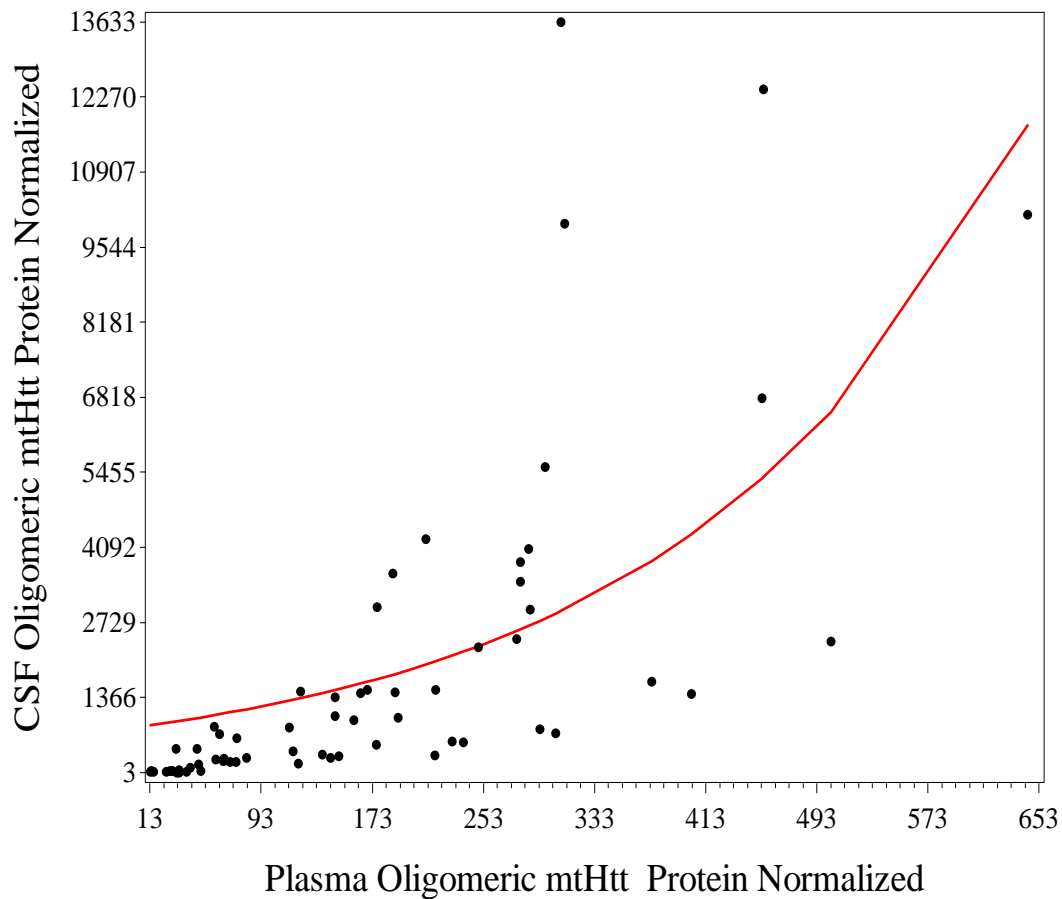
Steven Hersch, MD PhD  
*Professor of Neurology  
Harvard Medical School*

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 =  $\exp(6.7097 + 0.00413 * \text{Plasma Oligomeric mtHtt Protein Normalized})$



# 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.



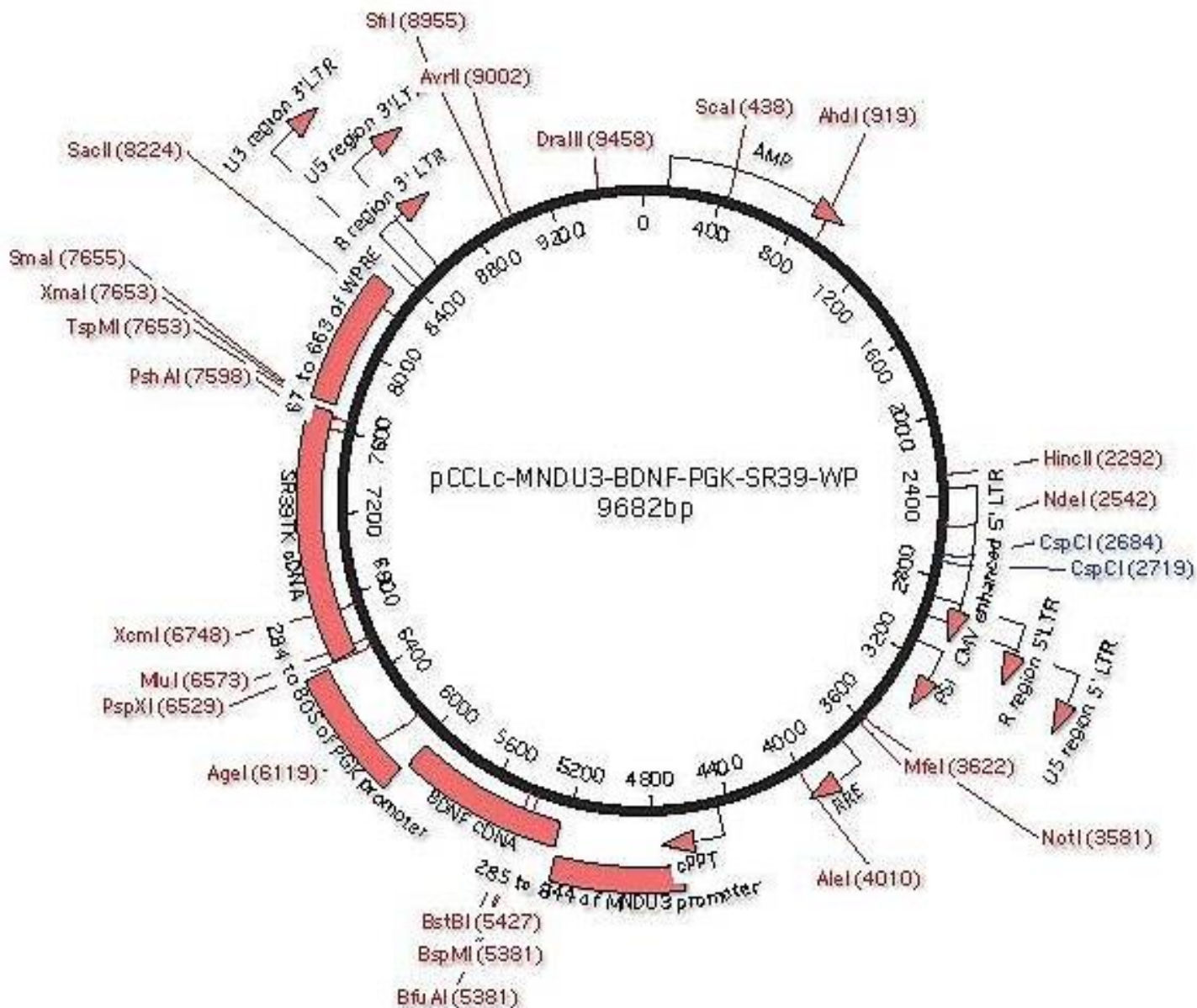
National Institutes of Health, Bethesda, MD; June 9, 2015

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

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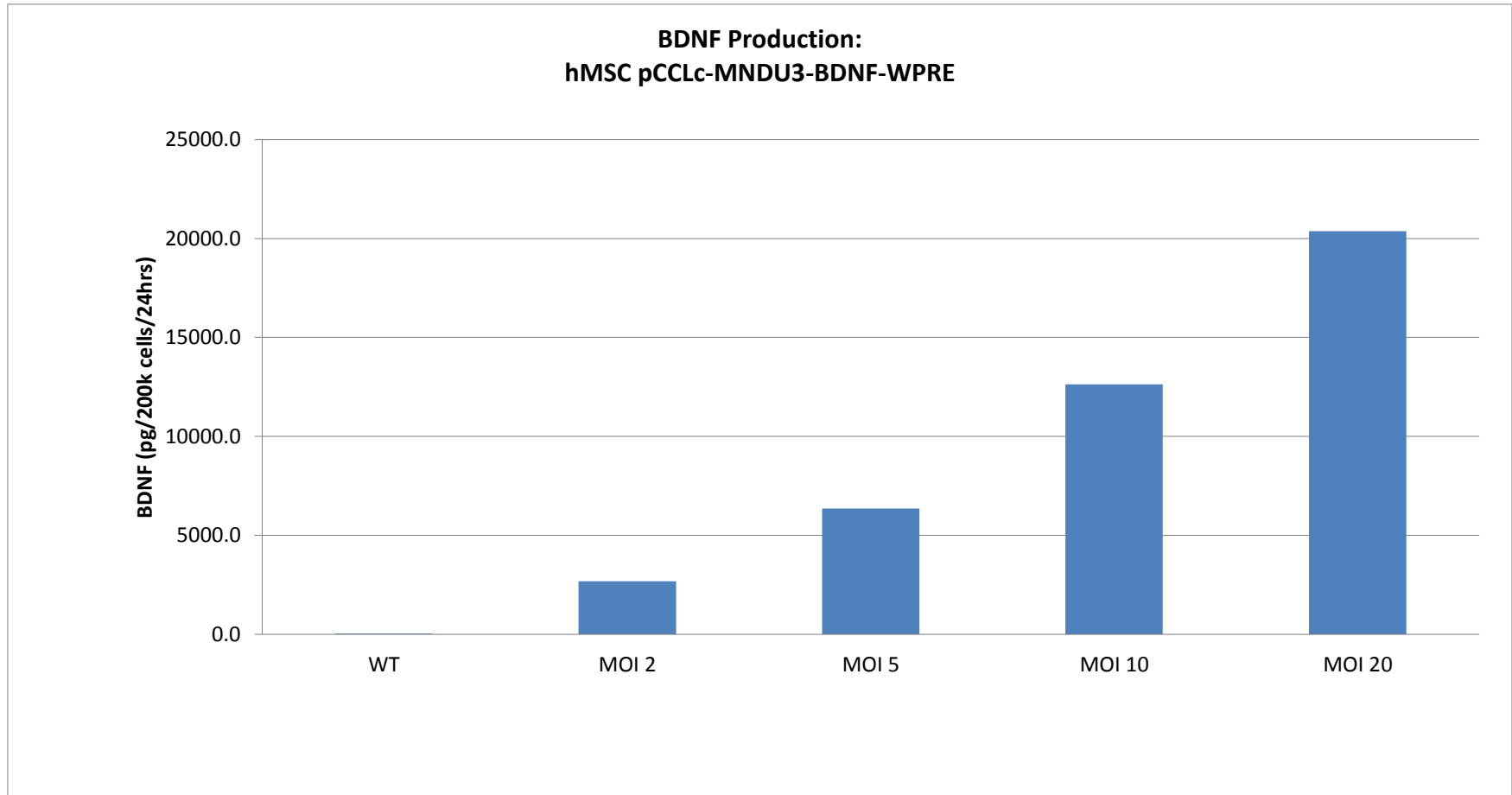
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# pCCLc-MNDU3-BDNF-PGK-WPRE lentiviral vector



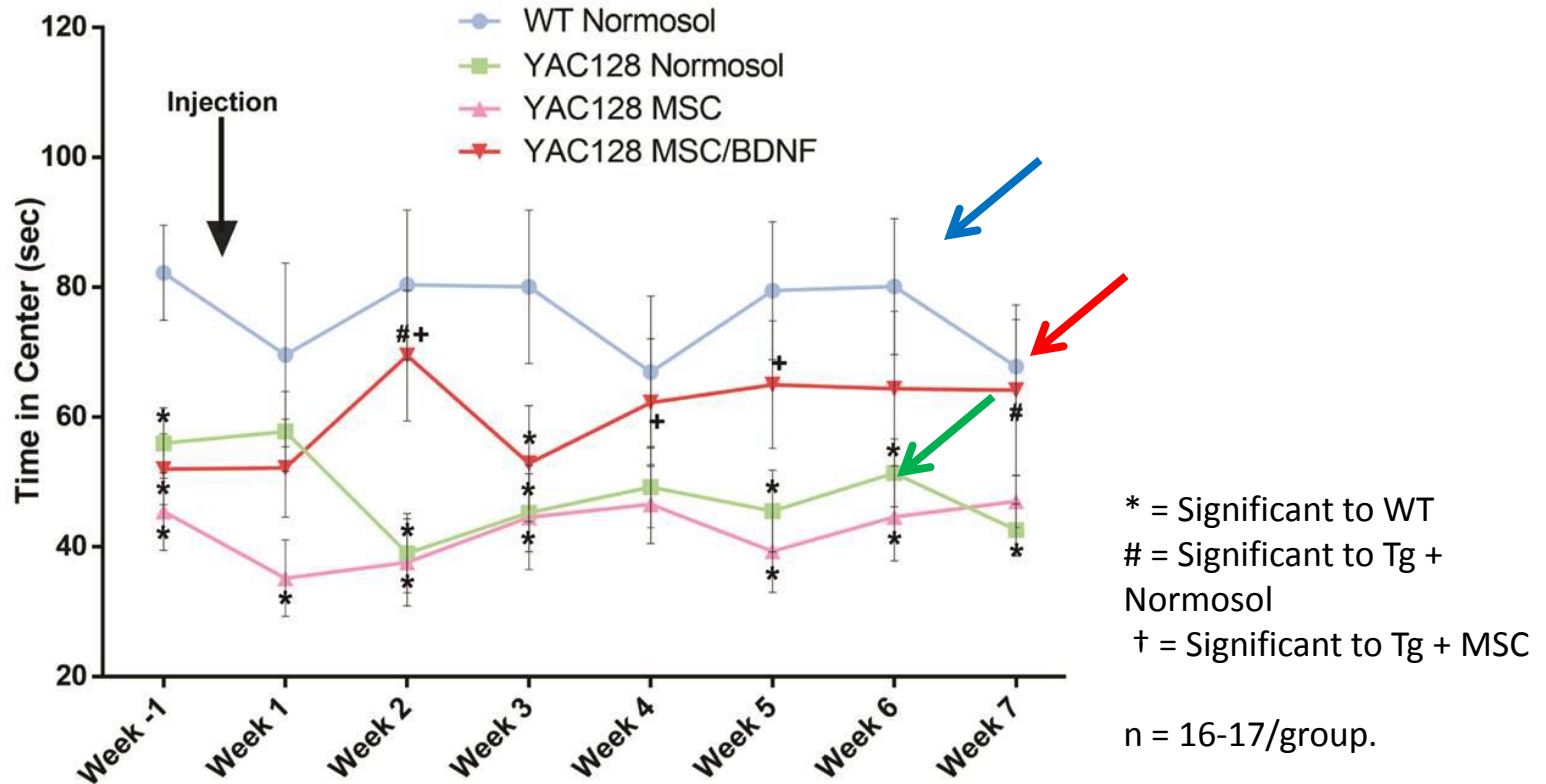


# BDNF production by the engineered MSCs



**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.

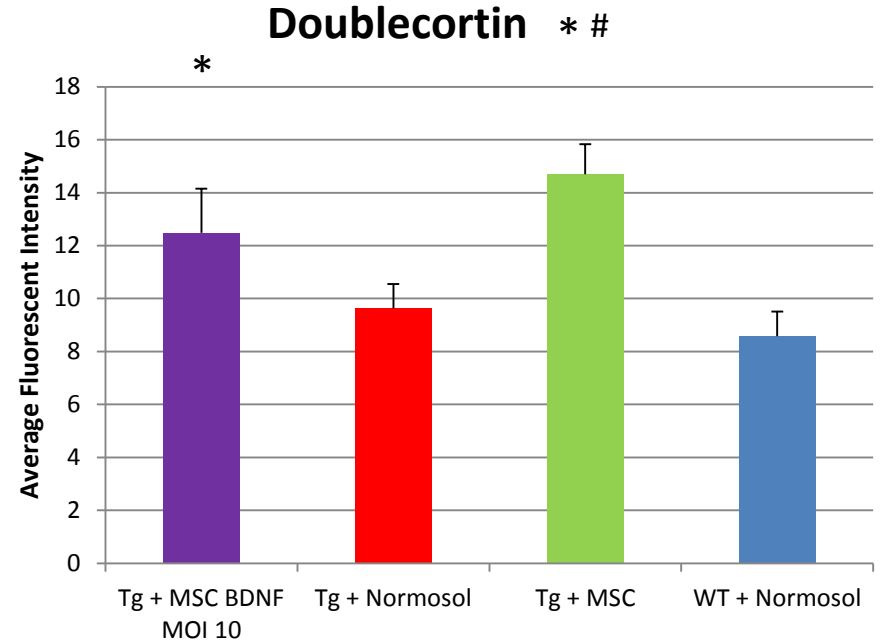
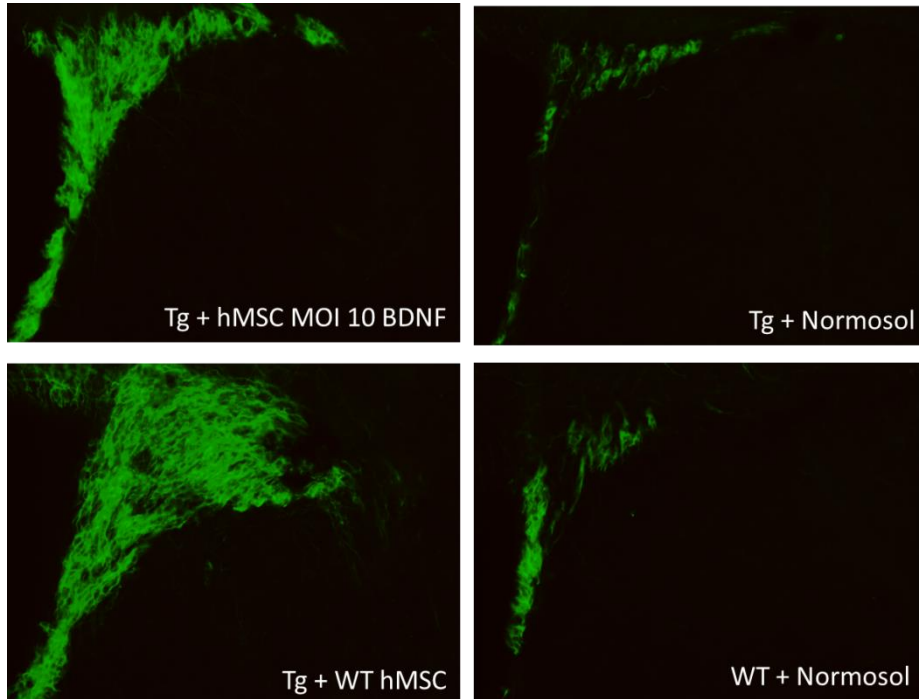
# YAC128 Behavioral Efficacy Study – Open Field Assay



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.

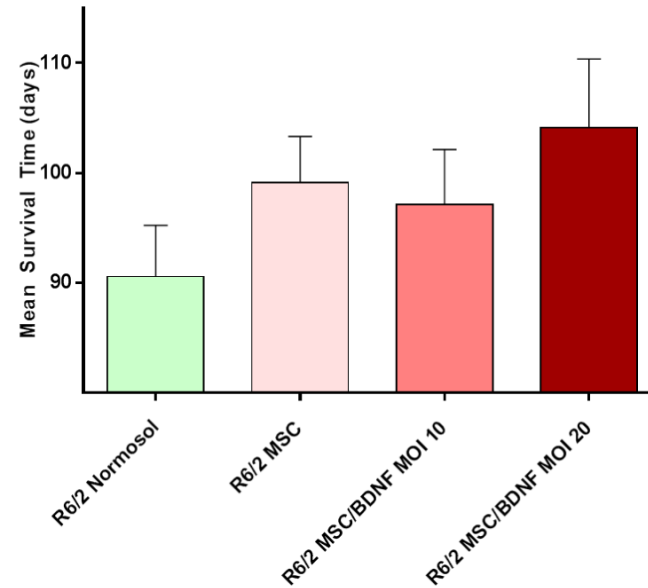
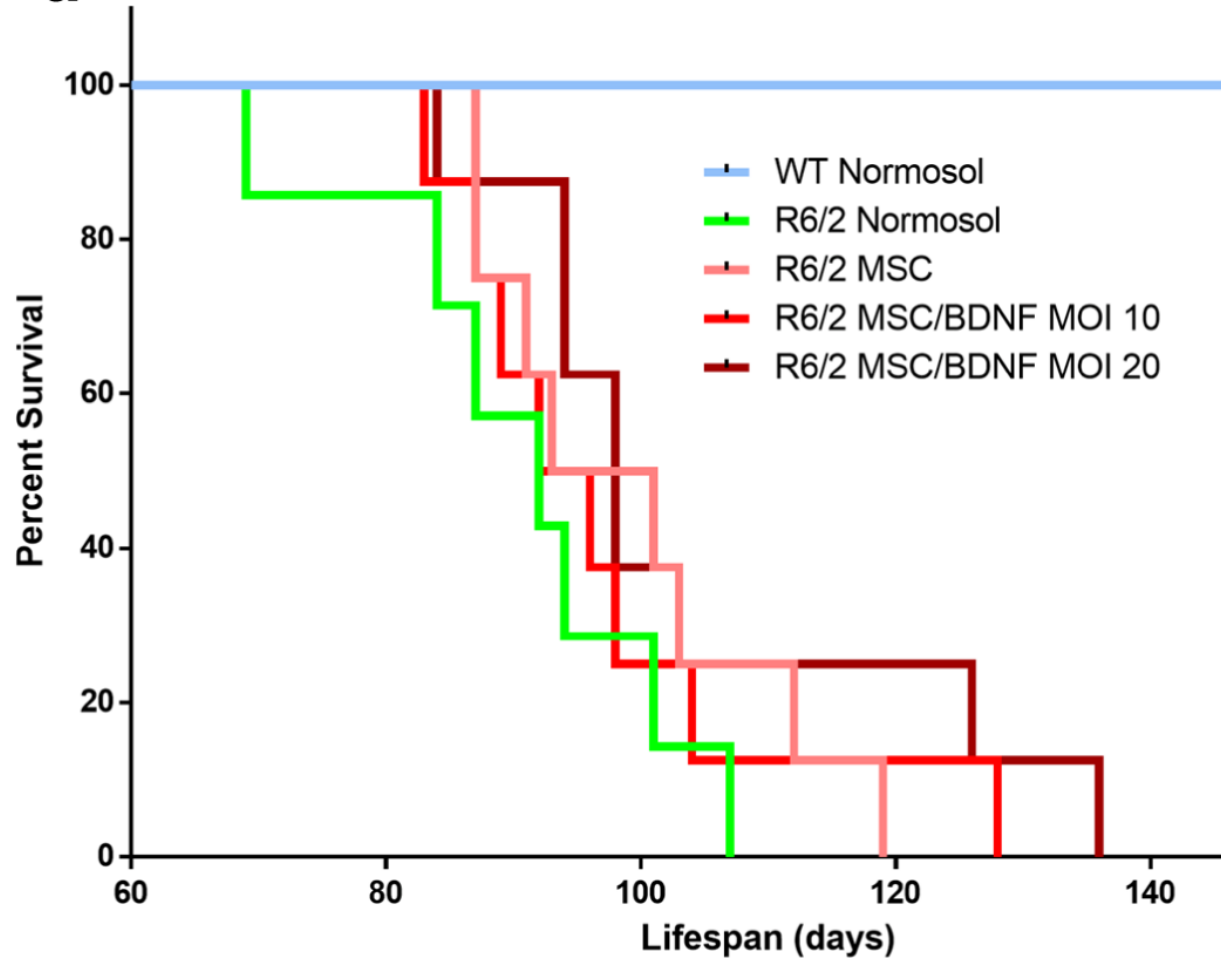
Time = 2.5 weeks

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

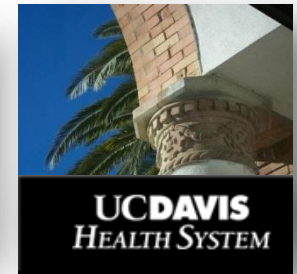
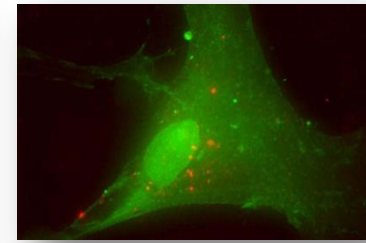
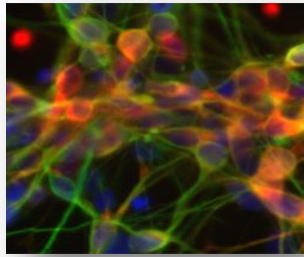
# R6/2 Efficacy Study: 2014-1208

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

**a**



**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.

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*W.O.C. Lopez et al. / Stereotactic planning software for human neurotransplantation*

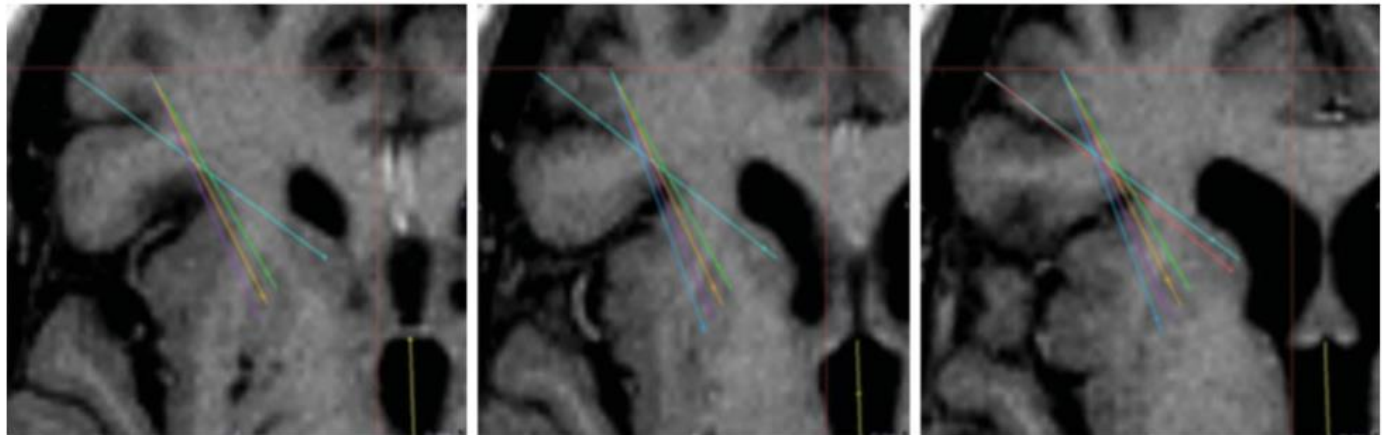


Fig. 1. MRI T1w, showing typical views obtained from the STP3 –planning workstation. Three coronal projections with tracts going to the caudate nucleus and to the putamen on the left side.

# UC Davis HD Team and Collaborators

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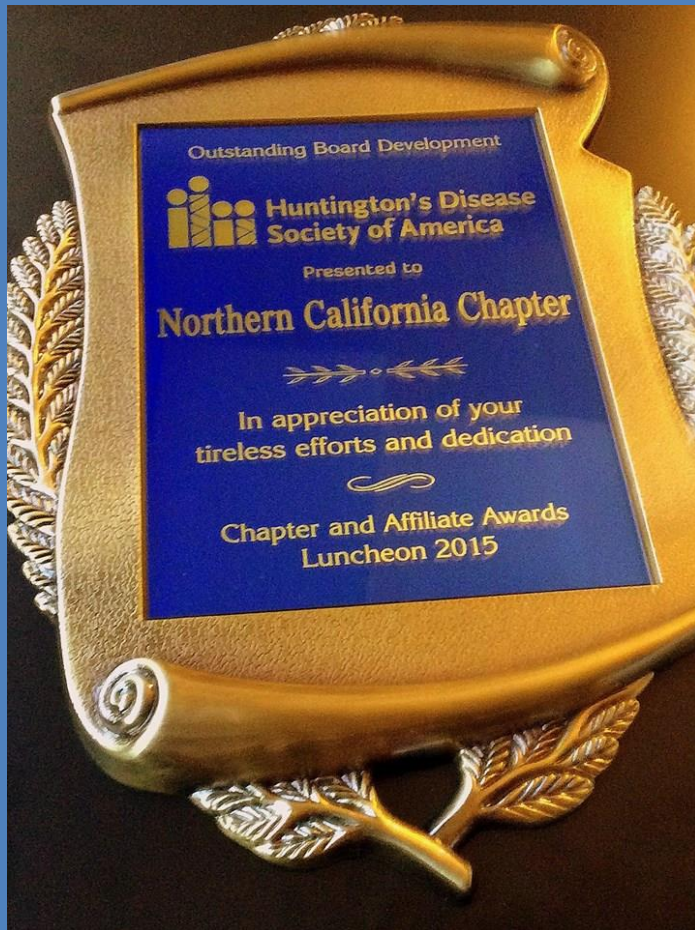
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Josh Dayananthan **THANK YOU! HD patient advocates, patients and families**

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# Thank you HDSA Northern CA Chapter!



*Thank you Les Pue and Terry Tempkin!*

