Mesenchymal Stem Cells Engineered to Produce Brain-Derived Neurotrophic Factor as a Potential Treatment for Huntington’s Disease

Vicki Wheelock, MD
Director, HDSA Center of Excellence at UC Davis
HDSA National Convention
Dallas, TX - June 27, 2015
Overview

- Stem cells and genetic engineering
- Preclinical studies in transgenic HD mouse models in support of our proposed trial
- Manufacturing of MSC/BDNF in readiness for regulatory approval for a first-in-human Phase I trial
- PRE-CELL: lead-in observational study
- HD-CELL: Proposed Phase I open-label safety and tolerability trial
Abbreviations used in this talk

- MSC = mesenchymal stem cells
- BDNF = brain-derived neurotrophic factor
- MSC/BDN = MSCs engineered to express BDNF
- YAC128, R6/2 = mouse models of HD used for research
- FDA = US Food and Drug Administration
- IND = Investigational New Drug license
- DSMB = Data and Safety Monitoring Board
- PRE-CELL = A pre-cellular therapy observational study in early-stage HD
- HOPE = what we need!
August 9, 2001

Crawford, Texas
President Bush’s prime-time address to announce federal restrictions on embryonic stem cell research

Federal funding was restricted to 60 embryonic stem cell lines (only approx. 20 were suitable for research)
Proposition 71 was passed as a ballot initiative.

**Official Results**

Yes votes: 7,018,059 [51.9%]
No votes: 4,867,090 [40.9%]

Prop 71 authorized the sale of $3 billion of state bonds to create the California Institute for Regenerative Medicine (CIRM).

CIRM’s mission is to finance stem cell research through the construction of research facilities and the funding of research.

CIRM is the largest source of funding for embryonic and pluripotent stem cell research in the world.
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.
### Types of Stem Cells

<table>
<thead>
<tr>
<th>Adult Stem Cells</th>
<th>Pluripotent Cells</th>
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<tbody>
<tr>
<td>Blood forming (hematopoietic)</td>
<td>Embryonic</td>
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<tr>
<td>Mesenchymal (supporting cells)</td>
<td>Induced pluripotent stem cells</td>
</tr>
</tbody>
</table>

**Mesenchymal (supporting cells)**

![MSC and HSC](image)
MSCs can be engineered to secrete copious amounts of factors for delivery to other cells and tissues in the body.

Nolta Lab, 1987-present
Book published - 2006
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
**BDNF: a lead candidate for HD treatment**

- Survival and function of striatal neurons is dependent on brain-derived neurotrophic factor (BDNF).

- Mutant huntingtin protein blocks production of BDNF at the RNA level and reduces axonal transport from the cortical cells to the striatum. Levels of this trophic factor are significantly reduced in the brains of HD patients.

- Dey et al showed that MSCs engineered to over-express BDNF slowed the progression of HD in a transgenic mouse model.

- BDNF delivery triggers the recruitment of new neurons in HD transgenic mouse model.

C. Zuccato, M. Valenza, E. Cattaneo, *Physiol Rev* 2010;90:, 905
Dey ND et al. *Behav Brain Res* 2010;193-2000
Benraiss A. *Cell Stem Cell* 2013;787-799
MSCs: our candidate for delivery of BDNF

- MSCs secrete neurotrophic factors, reduce inflammation, reduce programmed cell death, enhance connections between neurons and reduce cell toxicity
- MSCs can be readily engineered using viral vectors to robustly deliver growth factors
- Vectors do not integrate into host cells
- MSCs do not require immunosuppression
  - Unlike embryonic or pluripotent stem cells, MSCs have a strong safety profile in clinical trials
  - 43 published, peer reviewed proof of concept studies have demonstrated efficacy for MSC, BDNF, or MSC/BDNF in HD mouse models (Reviewed in Deng et al, in press 2015)
MSC/BDNF for HD

July 26, 2012
MSC/BDNF grant is approved by CIRM!
Mesenchymal Stem Cells Engineered to produce BDNF as a treatment for HD  
CIRM Grant DR2A-05415

Objectives:

- To obtain FDA approval and to successfully complete a 2-year Phase I trial of cellular therapy in patients with early-stage Huntington’s disease (HD).

- Our cell/gene therapy development candidate is safety modified donor-derived human mesenchymal stem cells engineered to secrete brain-derived neurotrophic factor (MSC/BDNF), as a neuroprotective strategy to rescue brain cells that are degenerating in patients with Huntington’s disease.
Project Plan: MSC/BDNF for HD
CIRM Grant DR2A-05415

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

<table>
<thead>
<tr>
<th></th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Year 4</th>
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<tbody>
<tr>
<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 (on-going)</td>
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<tr>
<td>Phase I Clinical trial</td>
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<tr>
<td>Lab/safety studies: patient samples</td>
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</table>

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**Pre-clinical**

**Clinical**
MSCs divide to make more cells. We expand them to larger numbers following Standard Operating Procedures and add extra DNA to make BDNF.
**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.
MSC/BDNF Characterization

No differences in appearance were detected between gene-modified cells (MSC/BDNF) and unmodified MSCs.
MSC/BDNF for HD

NSC/BDNF Characterization: Stable Karyotype

HD All Cells BMMSC p5

WT
50/50
46,XX

WT Control 50/50 confirmed Normal 46,XX

MOI 10
50/50
46,XX

pCCLc-MNDU3-BDNF-WPRE MOI 10 50/50 confirmed Normal 46,XX
MSC/BDNF for HD

HD and JHD Mouse Model Studies
We used the YAC128 and R6/2 (120) strains of mice as models of HD and Juvenile HD.

- The YAC128 mouse has late onset, mild symptoms, and striatal atrophy.
- The R6/2 (120) mouse has early onset and seizures, and very early death (approx. 90 days).

Mice were immune suppressed to permit survival of human cells.

Mice were transplanted with 500,000 human MSC or MSC/BDNF in the brain.
In Vivo Retention of Human MSC

A combination of FK506 and rapamycin delivered via subcutaneous osmotic mini-pumps increased luciferase-MSC retention in the striata to levels similar to that observed in immune-deficient mice.
Pre-clinical Summary: YAC128 model

- Mice treated with MSC/BDNF had significantly greater exploratory behaviors in open field testing compared to controls, indicating a behavioral measure of reduced anxiety.

- Mice treated with MSC and MSC/BDNF had reduction in the degree of striatal atrophy compared to control mice.

- We have demonstrated both a behavioral and a structural improvement due to treatment in the YAC128 model.
MSC/BDNF for HD

R6/2 Neurogenesis: 2014-0825 Efficacy study

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

* = Significant to WT,
# = Significant to tg + Normosol
Pre-clinical Summary: R6/2 (CAG 120) model

- Mice treated with MSC or MSC/BDNF have a significant increase in neurogenesis-like activity in the subventricular zone compared to controls.

- These data suggest that MSC/BDNF could work through mechanisms of stimulating endogenous neurogenesis.

- Striatal implantation of MSC/BDNF increased the mean lifespan of the R6/2 (CAG 120) mice.

- Increasing neurogenesis and striatal neuron survival is a key goal of the planned future clinical trial, HD-CELL.
Pre-clinical Summary

- Taken together our results demonstrate that MSC/BDNF reduced anxiety, slowed down or prevented striatal atrophy, and increased the lifespan when using two different transgenic mouse models of HD.

- This recovery may be due to the stimulation and maturation of endogenous neurogenesis promoted by the MSC and enhanced by BDNF.
Clinical Trials

**PRE-CELL**: We have enrolled 30 patients with early-stage HD. We are collecting clinical data (neurological and psychiatric exams, functional abilities, cognitive evaluation, volumetric brain MRI, and exploratory serum and CSF biomarker studies) with assessments every 6 months. We are determining the rate of change in each parameter for every subject in order to enhance safety and permit exploratory measures of clinical efficacy and biomarkers in the planned Phase 1 trial.

**HD-CELL**: We propose to enroll eligible PRE-CELL subjects who have completed at least one year of longitudinal assessments into HD-CELL. This will be an open-label Phase I dose-escalation trial, and all subjects to be treated will receive bilateral intrastriatal implantation of MSC/BDNF. We plan to enroll 3 dosing groups with 5-7 subjects per cohort.
PRE-CELL Study

- Prospective, longitudinal observational study
- Primary objective: To establish the rate of change in clinical, imaging and biomarker measures in subjects
- Study approved by UC Davis IRB in July 2013, with first subject enrolled in September 2013
- Bioethics substudy of subjects and care partners added 2015

ClinicalTrials.gov Identifier: NCT01937923
PRE-CELL Inclusion Criteria

1. Men or women age 18 and older, English speaking, able to give informed consent and comply with study procedures.
2. HD diagnosis confirmed with genetic testing.
4. Clinically definite signs of HD.
5. Must have a caregiver or informant able to give feedback about the participant and willing to report observations about subject on standardized forms.
6. Subjects of child bearing potential must agree to adequate birth control measures.

Please see http://clinicaltrials.gov/show/NCT01937923
Recruitment and Enrollment

### PRE-CELL Recruitment and Enrollment (June 2015)

<table>
<thead>
<tr>
<th>Screened</th>
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<th>Pending enrollment</th>
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<td>31</td>
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### Number of subjects completing scheduled visits

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<th>Baseline</th>
<th>V01 (6 mo)</th>
<th>V02 (12 mo)</th>
<th>V03 (18 mo)</th>
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<tr>
<td>41</td>
<td>31</td>
<td>25</td>
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</table>

**PRE-CELL enrollment will end June 2015**
MSC/BDNF for HD

PRE-CELL Interim Results

- Rate of change in clinical measures, including functional abilities, independence, motor exam, psychiatric symptoms and cognition
- Rate of change in MRI scan measures
- Rate of change in serum and CSF BDNF and mutant huntingtin protein levels
PRE-CELL Interim Results: estimated trajectories

**Total Functional Capacity Score**

**Independence Score**

**Total Motor Score**

**Total Problem Behavior Assessment Score**
Cognitive Assessments

Sarah Farias, PhD  
Associate Professor of Neurology, UC Davis

Julie Stout, PhD  
Professor, School of Psychological Sciences  
Monash University
Structural MRI Analysis

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

MSC/BDNF for HD
Volumetric MRI Brain Analysis

Volumetric analysis showing areas of reduced striatal volume in PRE-CELL subjects (areas in blue)

Volumetric imaging analysis showing change in brain volumes at 6 months

DeCarli IDeA Lab, UC Davis
MSC/BDNF for HD

PRE-CELL Biomarkers

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

BDNF
Mutant Huntingtin Protein
Ethical considerations regarding a first-in-human stem cell gene therapy trial for Huntington’s disease
**HD-CELL:** Proposed Phase 1 safety and tolerability trial of MSC/BDNF neurosurgically implanted into striatum using techniques similar to deep brain stimulator implantation

Treatment Cohorts

- Low dose MSC/BDNF: $5 \times 10^6$ cells per striatum
- Medium dose MSC/BDNF: $10 \times 10^6$ cells per striatum
- High dose MSC/BDNF: $20 \times 10^6$ cells per striatum
## HD-CELL Schedule of Activities

<table>
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<tr>
<th></th>
<th>Screening + Pre-op</th>
<th>Surgery within 30 d</th>
<th>V1 - 4 mo 1-2</th>
<th>V5 3 mo</th>
<th>V6 6 mo</th>
<th>V7 9 mo</th>
<th>V8 12 mo</th>
<th>15-24 mo</th>
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<td>Adverse events</td>
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<td>X</td>
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</table>
Interventional Magnetic Resonance Imaging-Guided Cell Transplantation into the Brain with Radially Branched Deployment

Matthew T Silvestrini, Dali Yin, Alastair J Martin, Valerie G Coppes, Preeti Mann, Paul S Larson, Philip A Starr, Xianmin Zeng, Nalin Gupta, S S Panter, Tejal A Desai, Daniel A Lim

1Department of Neurological Surgery, University of California, San Francisco, San Francisco, California, USA; 2Department of Radiology, University of California, San Francisco, San Francisco, California, USA; 3Department of Surgery, Veteran’s Affairs Medical Center, San Francisco, California, USA; 4Buck Institute for Research on Aging, Novato, California, USA; 5Department of Bioengineering, University of California, San Francisco, San Francisco, California, USA; 6Eli and Edythe Broad Center of Regeneration Medicine and Stem Cell Research at UCSF, San Francisco, California, USA. Present address: Department of Bioengineering, University of California, Davis, Davis, California, USA.

a iMRI-guided RBD

b Standard stereotactic targeting of a straight cannula
Regulatory Milestones Progress

- FDA Pre-preIND 2013
- CIRM Clinical Development Advisory Panel 2014
- NIH Recombinant DNA Advisory Committee June 2015
- FDA pre-IND July 2015
- FDA IND application Fall 2015
Thank you HD patients and families!

Source: Katie Jackson, Help4HD
UC Davis HD Team and Collaborators

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

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

THANK YOU! HD patient advocates, patients and families

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