Update on the Proposed HD Stem Cell Therapy Clinical Trials at UC Davis

CIRM Grant DR2A-05415

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

Jan Nolta, PhD
Director, Institute for Regenerative Cures, UC Davis

May 4, 2013
Huntington’s Disease

- Slowly progressive, hereditary, degenerative neuropsychiatric disease
- Inherited as autosomal dominant
- Estimated prevalence in US: 7-10/100,000
  - 30,000 people with HD in US
  - 150,000 at-risk in US
  - 2000 new cases annually in US
  - Estimated costs: $2.5 billion US
- World-wide occurrence in all populations
- Death after 15-20 years

Woody Guthrie, 1943
**Introduction to HD**

- **Normal**: CAGn < 26 CAG
- **Unstable**: 27 - 35 CAG
- **Reduced penetrance**: 36 - 38 CAG
- **Huntington disease**: > 38 CAG

**HTT gene → htt protein**

- **HTT gene**
- **htt protein**

**Medium Spiny Neuron**

**HD patient, age 45**

**Same patient, age 50**
Treatments for HD

- Supportive: HDSA support groups, counseling, benefits programs (GHPP)
- Advocacy: Patients, families, HDSA
- Symptomatic: palliative treatments for motor, psychiatric and cognitive symptoms
- Research: Huntington Study Group, Euro HD Network, US government and pharmaceutical funding

- No effective treatments exist to slow progression or prevent death from HD.
Strategies for Treating HD

- Neuroprotection: a therapy that would delay onset or slow progression
- Cure: a therapy that would prevent the mutant htt from killing brain cells
- Switch off production of mutant htt:
  - Small, interfering RNA (siRNA)
  - Anti-sense oligonucleotide therapy (ASO)
• 2004: California voters passed Proposition 71, the California Stem Cell Research and Cures Initiative.

• 2005: The California Institute for Regenerative Medicine established

• The Independent Citizens Oversight Committee ("ICOC") is the 29-member governing board for the Institute. The ICOC members are public officials, appointed on the basis of their experience earned in California’s leading public universities, non-profit academic and research institutions, patient advocacy groups and the biotechnology industry.

The mission of CIRM is to support and advance stem cell research and regenerative medicine under the highest ethical and medical standards for the discovery and development of cures, therapies, diagnostics and research technologies to relieve human suffering from chronic disease and injury. CIRM is the largest source of funding for embryonic and pluripotent stem cell research in the world.
Huntington’s Disease

Dr. Jan Nolta and Dr. Gerhard Bauer

2009: Dr. Nolta received $2.9 million CIRM grant to help develop stem cell therapy for HD.

CIRM Grant TR1-01257, 2009-12

Opened 2010
>100,00 sq feet research space
>200 scientists and physicians working together
2010 – CIRM Spotlight on HD

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**

- **Adult stem cells**
  - Hematopoietic (HSC): blood-forming
  - Mesenchymal (MSC): support cells
    - CIRM Grant TR1-01257 2009-12, Nolta PI

- **Pluripotent cells**
  - Embryonic (ESC)
  - Induced pluripotent (iPS)
    - Currently used to study HD
Mesenchymal Stem Cells (MSC)

Adult stem cells cannot form an entire tissue, unlike embryonic or induced pluripotent stem cells.

MSCs can be engineered to secrete copious amounts of factors for delivery to other cells and tissues in the body.
Mesenchymal Stem Cells (MSC)

Advantages:
- Long safety record in human trials
  - Harvested from bone marrow
- Home in on sick and dying cells
- Immunologically privileged
  - Shelter themselves from the host immune system
  - Can be transplanted without tissue matching
- Regulate inflammation
- Secrete factors → promote axonal connections
- Can be easily and safely engineered to transfer molecules and proteins to target cells
Mesenchymal Stem Cells (MSC)

We are using MSC as “paramedics” to attack the htt protein and to rescue sick and dying neurons in the brains of HD mice, and later patients.

Medium spiny neurons – Damaged/Lost in HD – They control movement, cognition and emotion
Mesenchymal stem cells can restore synaptic connections between neurons by secreting factors (reviewed in *BMT*, 2007)
Brain Derived Neurotrophic Factor (BDNF) and HD

- Patients with HD have much lower levels of BDNF than usual: mutant htt protein blocks production of BDNF
- Low BDNF levels are a major contributing factor to the degeneration of affected brain cells.
- Our strategy, in collaboration with Gary Dunbar’s lab: deliver BDNF from specially engineered MSCs into the brain

HD research using mouse models: Human mHTT in mouse

Inspired by Dr. Christopher Breuer, Nationwide Children’s Hospital
Nesting Behavior

Wild Type

HD Mouse

Courtesy of Dr. H.S. Kim, Nolta lab 2011
An Example of At Least Partial Reversibility

Huntington’s disease mouse

- created with abnormal gene that can be turned off

<table>
<thead>
<tr>
<th>Control</th>
<th>18 wk</th>
<th>34 wk</th>
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<tbody>
<tr>
<td>Gene On</td>
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</table>

Brain pathology:
inclusions, loss of brain mass Characteristic full-body clasp

Gene Off

Reversal of brain pathology, recovery of normal behavior

Inhibiting Expression of polyQ-htt Allowed Amelioration of the Clasping Phenotype
Genetically engineered mesenchymal stem cells reduce behavioral deficits in the YAC 128 mouse model of Huntington’s disease

Nicholas D. Dey a,b,c, Matthew C. Bombard a,b, Bartholomew P. Roland a,b, Stacy Davidson a,b, Ming Lu a,b, Julien Rossignol a,b, Michael I. Sandstrom b, Reid L. Skeel b, Laurent Lescaudron d,e,f,g, Gary L. Dunbar a,b,c,*
Methods

- YAC 128 mouse model of HD (which expresses full-length human mHTT) used. Animals were treated at 4 months of age.

- Treatment arms:
  1. Mouse MSC (mMSC)
  2. mMSC engineered to overexpress BDNF (MSC/BDNF)
  3. mMSC engineered to overexpress nerve growth factor (MSC/NGF)
  4. Both types of mMSC in a 50/50 ratio (MSC/BDNF/NGF)
  5. Controls (injected with saline)

- Assessed monthly with behavioral testing

- Neuropathology: measured degree of neuronal loss after 13 months
MSC/BDNF reverse behavioral abnormalities in YAC 128 mouse model

A. YAC 128 mice receiving striatal transplants of MSCs that were genetically engineered to over-express brain-derived neurotrophic factor (YAC+BDNF) stayed on the rotarod at 15rpm as long as wild type (WT+DMEM) mice and significantly longer than vehicle-treated YAC mice (YAC+DMEM).

B. YAC+DMEM mutant HD mice clasped significantly more than WT+DMEM mice, and YAC 128 mice receiving striatal transplants of MSCs that were genetically engineered to over-express brain-derived neurotrophic factor (YAC + BDNF) were restored to wildtype levels. (Dey et al 2010)
Our collaborators in the Dunbar laboratory have shown that MSC/BDNF implanted into the striata in YAC 128 mice at 4 months of age significantly improved motor function over the 13 months of the study, as compared to sham-treated control HD mice.

MSC/BDNF, as compared to sham-treated control HD mice, also significantly reduced limb clasping, a hallmark behavioral defect in transgenic HD mice, over the same time period.

MSC/BDNF significantly restored neuron and medium spiny neuron levels closer to wildtype mice, as compared to sham-treated control HD mice.

These compelling data from our collaborators are a part of our data package for the FDA.
Human MSCs (green) Making BDNF in Mouse Striatum

Concurrent work in Nolta lab
Retention and safety of human MSC/BDNF in the brain
IND-enabling studies ongoing for the FDA
Biosafety Studies at the UC Davis California National Primate Research Center (CNPRC)

- Demonstrate safety in an animal with brain physiology similar to human
- Address questions that cannot be ethically answered in humans
- Study engrafted human cells in the primate host
- Accelerate development of therapies
Intracranial injection of human mesenchymal stem cells into non-human primate brain:

1. To date we have implanted 6 non-human primates with gene modified human MSCs.

2. After 5 months, human mesenchymal stem cells were still present in the brain tissue.

3. No tumors or other tissue abnormalities were detected.

SAFETY WAS DEMONSTRATED
-Initial paperwork was filed with the FDA
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
MSC Therapy for Neurodegeneration

Cells produced under:
GOOD MANUFACTURING PRACTICE (GMP), with QUALITY CONTROL (QC) and QUALITY ASSURANCE (QA)

Monitor patient for Potential improvement in UC Davis Movement Disorders Clinic

Stem cell infusion via catheter
UC Davis Good Manufacturing Practice (GMP) Facility

Cellular product manufacturing
Six stem cell clinical trials are currently ongoing at UCD
MSC batches are banked
# CIRM Press Release

**Funded Projects**

**Disease Team Therapy Development Awards**

<table>
<thead>
<tr>
<th>Number</th>
<th>PI</th>
<th>Title</th>
<th>Institution</th>
<th>Committed funds</th>
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<tbody>
<tr>
<td>DR2A-05415</td>
<td>Vicki Wheelock</td>
<td>MSC engineered to produce BDNF for the treatment of Huntington's disease</td>
<td>University of California, Davis</td>
<td>$18,950,061</td>
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<tr>
<td>DR2A-05309</td>
<td>Ahmed Ribas</td>
<td>Genetic Re-programming of Stem Cells to Fight Cancer</td>
<td>University of California, Los Angeles</td>
<td>$19,999,563</td>
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<tr>
<td>DR2A-05302</td>
<td>Nancy Lane</td>
<td>Treatment of osteoporosis with endogenous Mesenchymal stem cells</td>
<td>University of California, Davis</td>
<td>$19,999,667</td>
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<tr>
<td>DR2A-05423</td>
<td>John Lard</td>
<td>Phase I study of IM Injection of VEGF-Producing MSC for the Treatment of Critical Limb Ischemia</td>
<td>University of California, Davis</td>
<td>$14,184,595</td>
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<tr>
<td>DR2A-05736</td>
<td>Nobuko Uchida</td>
<td>Neural stem cell transplantation for chronic cervical spinal cord injury</td>
<td>StemCells, Inc.</td>
<td>$20,000,000</td>
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<tr>
<td>DR2A-05394</td>
<td>Robert Robbins</td>
<td>Human Embryonic Stem Cell-Derived Cardiomyocytes for Patients with End Stage Heart Failure</td>
<td>Stanford University</td>
<td>$10,000,800</td>
</tr>
<tr>
<td>DR2A-05320</td>
<td>Clive Sverdson</td>
<td>Progenitor Cells Secreting GDNF for the Treatment of ALS</td>
<td>Cedars-Sinai Medical Center</td>
<td>$17,842,617</td>
</tr>
<tr>
<td>DR2A-05365</td>
<td>Judith Shizuru</td>
<td>A monoclonal antibody that depletes blood stem cells and enables chemotherapy free transplants</td>
<td>Stanford University</td>
<td>$20,000,000</td>
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**Total**                                               |                                              |                                      | $150,976,602     |

http://www.cirm.ca.gov/PressRelease_2012-07-26
The grant is approved!

July 26, 2012
DR2A-05415 Objective

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.
HD and Stem Cells
## Project Plan: CIRM Grant DR2A-05415

<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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<tr>
<td>Pre-Cell Years 1 &amp; 2</td>
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<td>HD-Cell Years 3 &amp; 4</td>
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<td><strong>GMP Manufacturing of Clinical Lots</strong></td>
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<td><strong>IND-enabling studies using current GMP Lot (ongoing)</strong></td>
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<td><strong>Regulatory approvals (ongoing)</strong></td>
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<td><strong>Observational Clinical trial</strong></td>
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<td><strong>Phase I Clinical trial</strong></td>
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<td><strong>Lab/safety studies: patient samples</strong></td>
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**Timeline: Clinical Trials**

**Years 1-2 PRE-CELL:** Initiate enrollment of 26 - 40 patients with early-stage HD. We will collect clinical data (neurological exams, cognitive evaluation, volumetric brain MRI, and CSF studies) for a longitudinal baseline study every 6 months. We will determine 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.

**Years 3-4 HD-CELL:** 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 trial, and all subjects to be treated will receive bilateral intrastriatal implantation of MSC or MSC/BDNF. Four groups of 5-7 patients will receive specific doses of cells.
Planned Clinical Trials

**PRE-CELL**: a longitudinal observational study to enroll a cohort of early-stage HD patients who are potential candidates for the planned cellular therapy trial.
Planned Clinical Trials

**HD-Cell:** Phase 1 clinical trial of MSC/BDNF neurosurgically implanted into striatum using techniques similar to deep brain stimulator implantation.
The Pathway Forward

- FDA approval: Investigational New Drug (IND) license
  - Requires extensive testing of MSC/BDNF to assure stability, safety, effectiveness to meet all regulatory requirements before any patients can be treated

- Phase 1 trial: primarily assess safety. All patients will receive active treatment.

- All patients will have frequent clinical visits, brain scans, cognitive, psychiatric and neurological assessments.
# Project Consultants and Collaborators

<table>
<thead>
<tr>
<th>Name</th>
<th>Institution</th>
<th>Role</th>
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<tbody>
<tr>
<td>Gary Dunbar, PhD</td>
<td>Central Michigan University</td>
<td>Proof of concept in mouse studies</td>
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<tr>
<td>Anne-Catherine Bachoud-Levi, MD</td>
<td>INSERM, Paris</td>
<td>Human study design</td>
</tr>
<tr>
<td>Elizabeth Aylward, PhD</td>
<td>Seattle Children’s Hospital</td>
<td>Imaging studies</td>
</tr>
<tr>
<td>Steven Hersch, MD PhD</td>
<td>Massachusetts General Hospital</td>
<td>Biomarkers</td>
</tr>
<tr>
<td>Julie Stout, PhD</td>
<td>Monash University</td>
<td>Cognitive studies</td>
</tr>
<tr>
<td>Robert Deans</td>
<td>Athersys</td>
<td>MSC</td>
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<tr>
<td>Robert Mays</td>
<td>Athersys</td>
<td>MSC</td>
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<tr>
<td>Daniel Lim, MD PhD</td>
<td>UCSF</td>
<td>Neurosurgical consultant</td>
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# UC Davis Team

<table>
<thead>
<tr>
<th>Name</th>
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<tbody>
<tr>
<td>Charles DeCarli, MD</td>
<td>Director, Imaging Team</td>
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<tr>
<td>Sarah Farias, PhD</td>
<td>Director, Cognitive Team</td>
</tr>
<tr>
<td>Lorin Scher, MD</td>
<td>Director, Psychiatry Team</td>
</tr>
<tr>
<td>Kiarash Shalaie, MD, PhD</td>
<td>Neurosurgeon</td>
</tr>
<tr>
<td>Owen Carmichael, PhD</td>
<td>Imaging team</td>
</tr>
<tr>
<td>Mark Yarborough PhD</td>
<td>Bioethics</td>
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<tr>
<td>Gerhard Bauer, MD</td>
<td>GMP Director</td>
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<tr>
<td>Kari Pollock, MS</td>
<td>GLP Studies</td>
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<tr>
<td>Karen Pepper, PhD</td>
<td>Vector Core</td>
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<tr>
<td>William Gruenloh</td>
<td>Regulatory, IND</td>
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Progress to Date

- pre-Pre-IND call with the FDA scheduled for June 4, 2013
- IRB submission for PRE-CELL: April 12, 2013
- First enrollment projected: August 2013
pre-Pre-IND package for MSC/BDNF completed and submitted to the FDA

Information Package for:
Teleconference – Pre-Pre-IND Meeting
With University of California Davis
CBER Meeting ID: TBD
Date: TBD
UC Davis HD Team & Collaborators

THANK YOU!
HD patients, Families, and Patient Advocates!
Executive Team  
CIRM Grant DR2A-05415

- Vicki Wheelock, M.D., PI
- Jan Nolta, Ph.D., co-PI
- Geralyn Annett, CLS, Laboratory Project Manager
- Terry Tempkin, RN-C, ANP, Clinical Project Manager

We Can Do It!