A HEALTHIER WORLD THROUGH BOLD INNOVATION






UCDAVIS HEALTH SYSTEM

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

CIRM Grant DR2A-05415

CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

Vicki Wheelock MD
Director, HDSA Center of Excellence at UC Davis
Jan Nolta, PhD
Director, Institute for Regenerative Cures, UC Davis

May 4, 2013

SCHOOL OF MEDICINE · UC DAVIS

Huntington's Disease

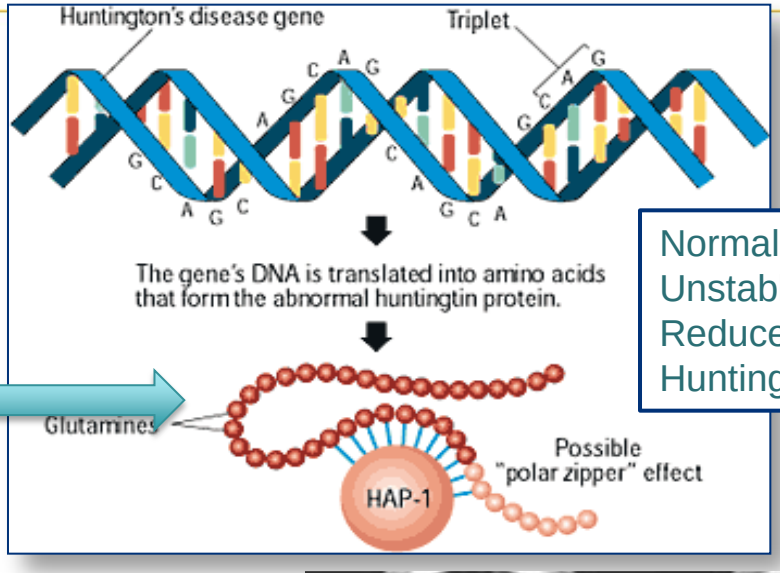
- Slowly progressive, hereditary, degenerative neuropsychiatric disease
- Inherited as autosomal dominant
- Estimated prevalence in US: 7-10/100,000
  - 30,000 people with HD in US
  - 150,000 at-risk in US
  - 2000 new cases annually in US
  - Estimated costs: $2.5 billion US
- World-wide occurrence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

Woody Guthrie, 1943

HTT gene → htt protein

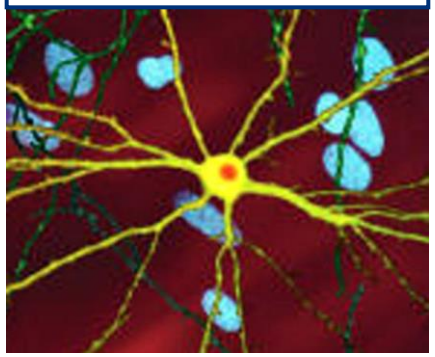
HTT gene

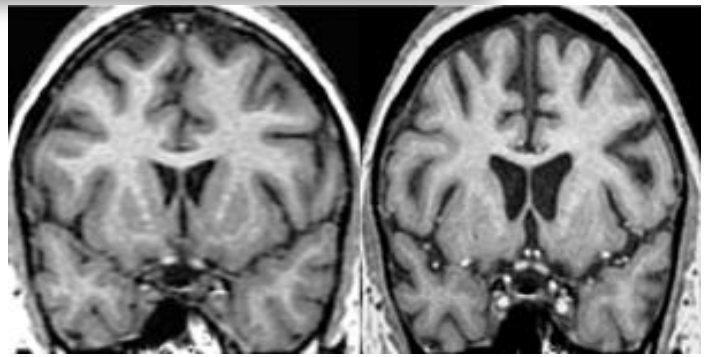
htt protein



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

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)

HD and Stem Cells

CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

- •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

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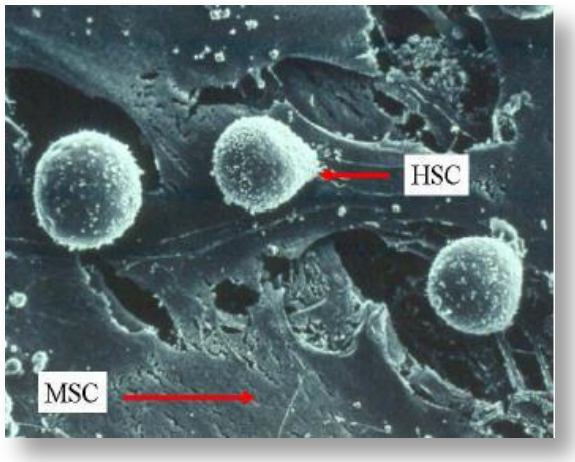
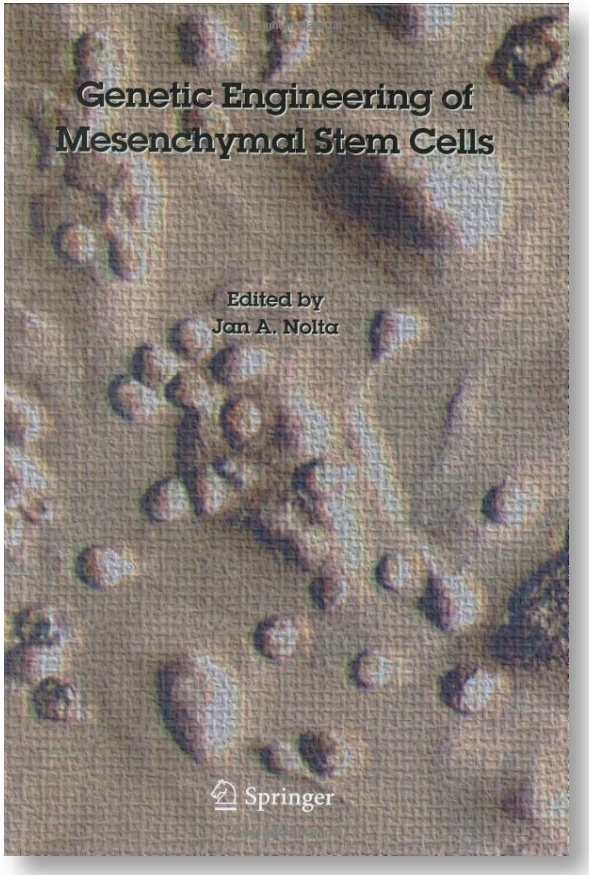
Types of Stem Cells

- **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

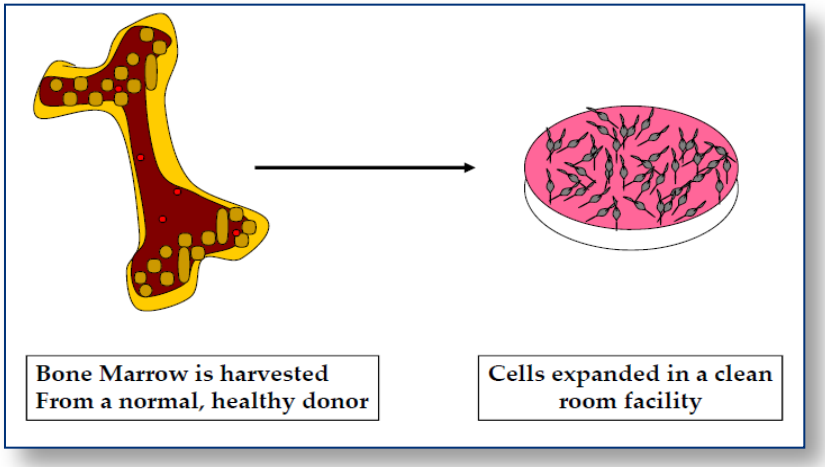


Mesenchymal Stem Cells (MSC)



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

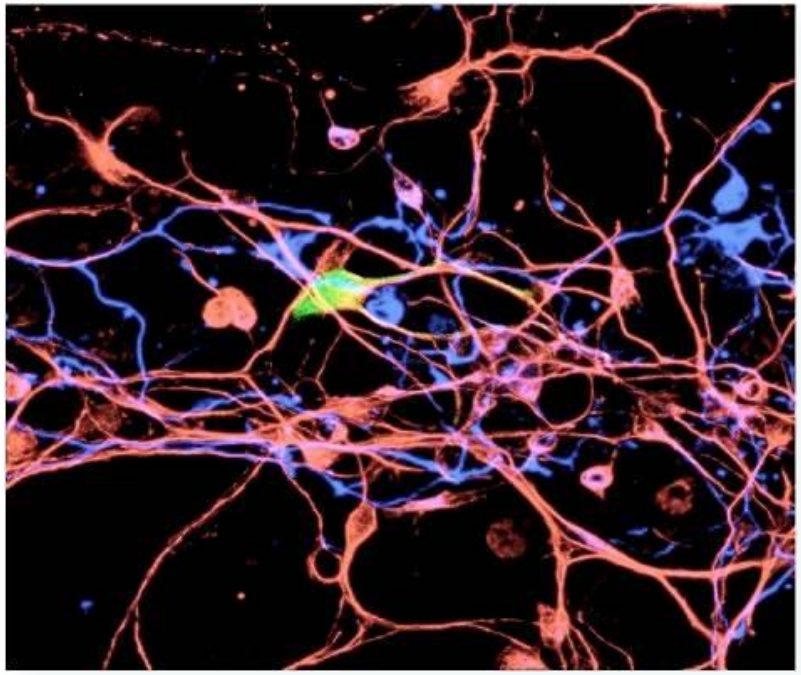


Mesenchymal Stem Cells (MSC)

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

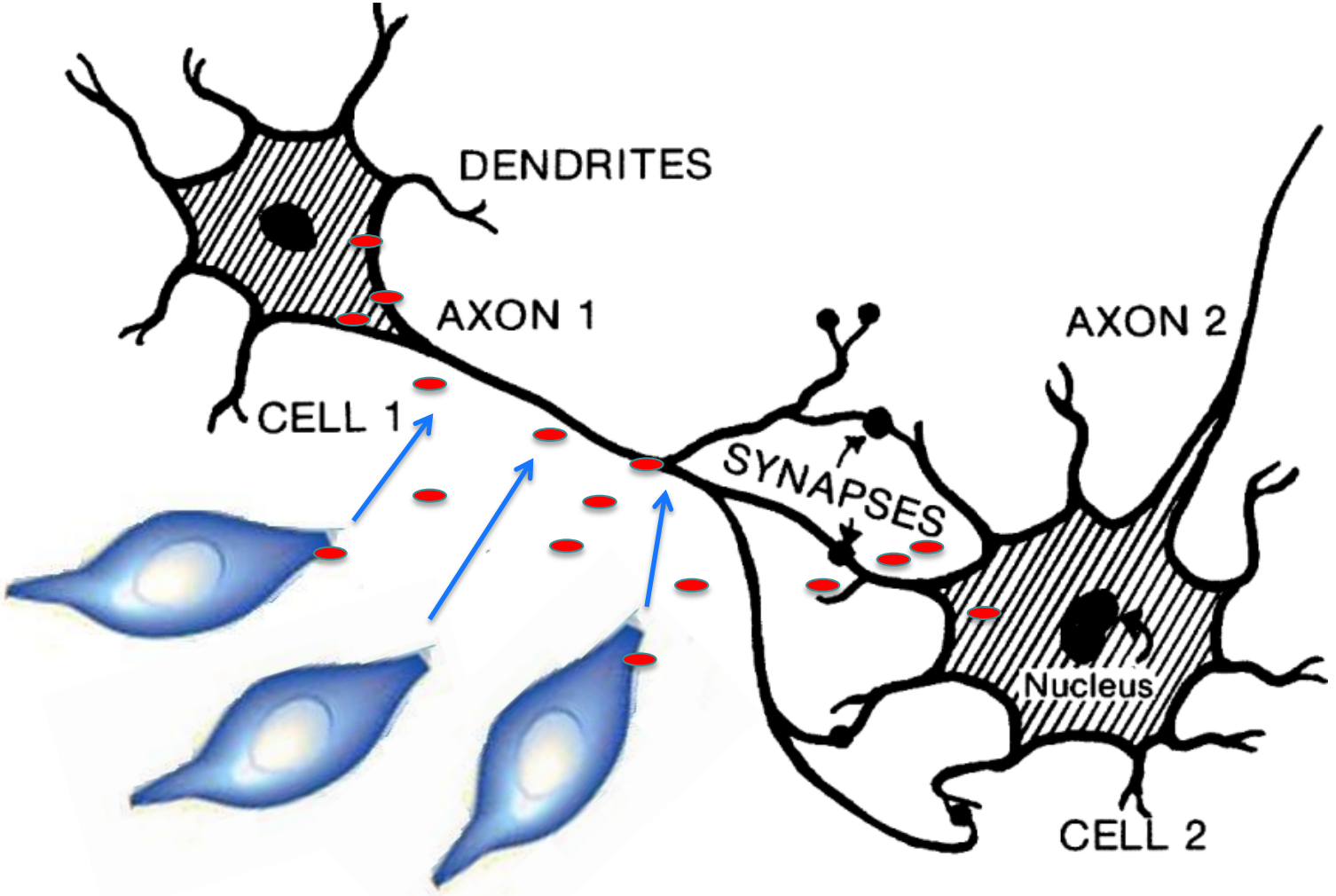
Mesenchymal Stem Cells (MSC)



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

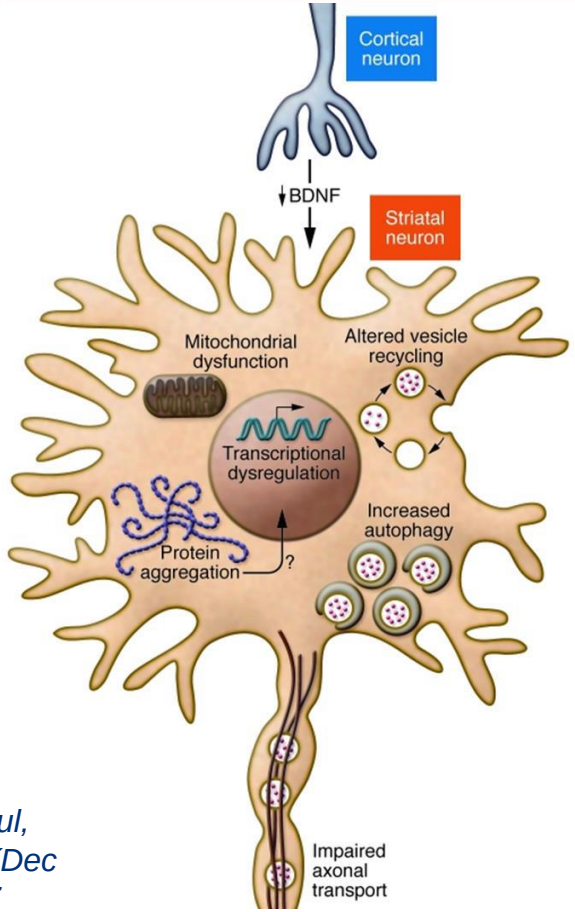
HD and Stem Cells



Mesenchymal stem cells can restore synaptic connections between neurons by secreting factors (reviewed in *BMT*, 2007)

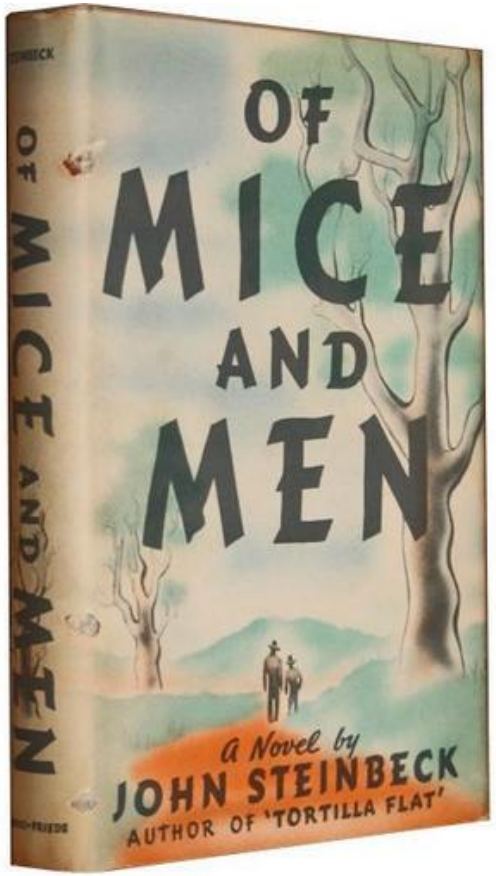
Brain Derived Neurotrophic Factor (BDNF) and HD

- 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



C. Zuccato, M. Valenza, E. Cattaneo, *Physiol Rev 90, 905 (Jul, 2010)* N. D. Dey *et al., Behavioural brain research 214, 193 (Dec 25, 2010)* Sah and Aronin, *J Clin Invest 2011;121(2):500-507*

HD research using mouse models:
Human mHTT in mouse



Inspired by Dr. Christopher Breuer, Nationwide Children's Hospital

Nesting Behavior

Wild Type

HD Mouse

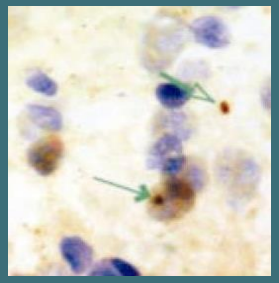
Courtesy of Dr. H.S. Kim, Nolta lab 2011

An Example of At Least Partial Reversibility

Huntington's disease mouse *Yamamoto et al. 2000*
– created with abnormal gene that can be turned off

Control **18 wk** **34 wk**

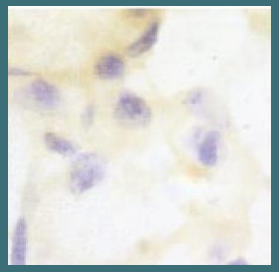
Gene On



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

Control **18 wk** **34 wk**

Gene Off



Reversal of brain pathology, recovery of normal behavior

Inhibiting Expression of polyQ-htt Allowed Amelioration of the Clasping Phenotype

HD and Stem Cells

ELSEVIER

Contents lists available at ScienceDirect

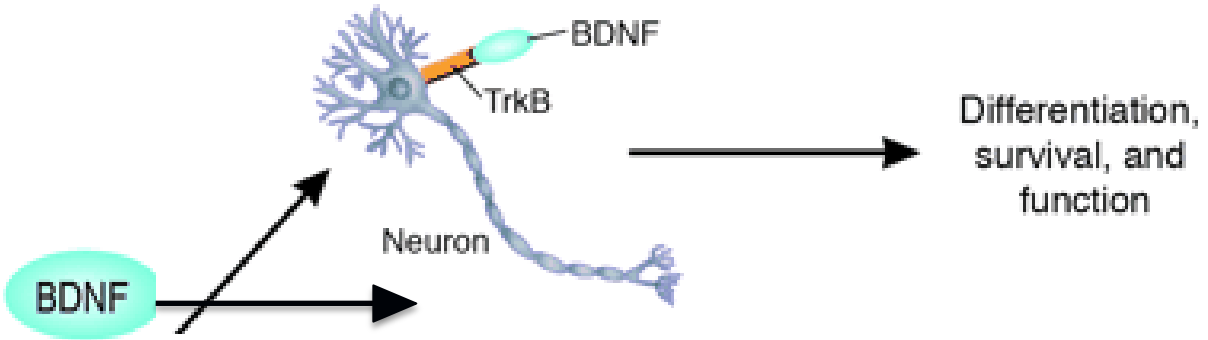
Behavioural Brain Research

journal homepage: www.elsevier.com/locate/bbr

Research report

Genetically engineered mesenchymal stem cells reduce behavioral deficits in the YAC 128 mouse model of Huntington's disease

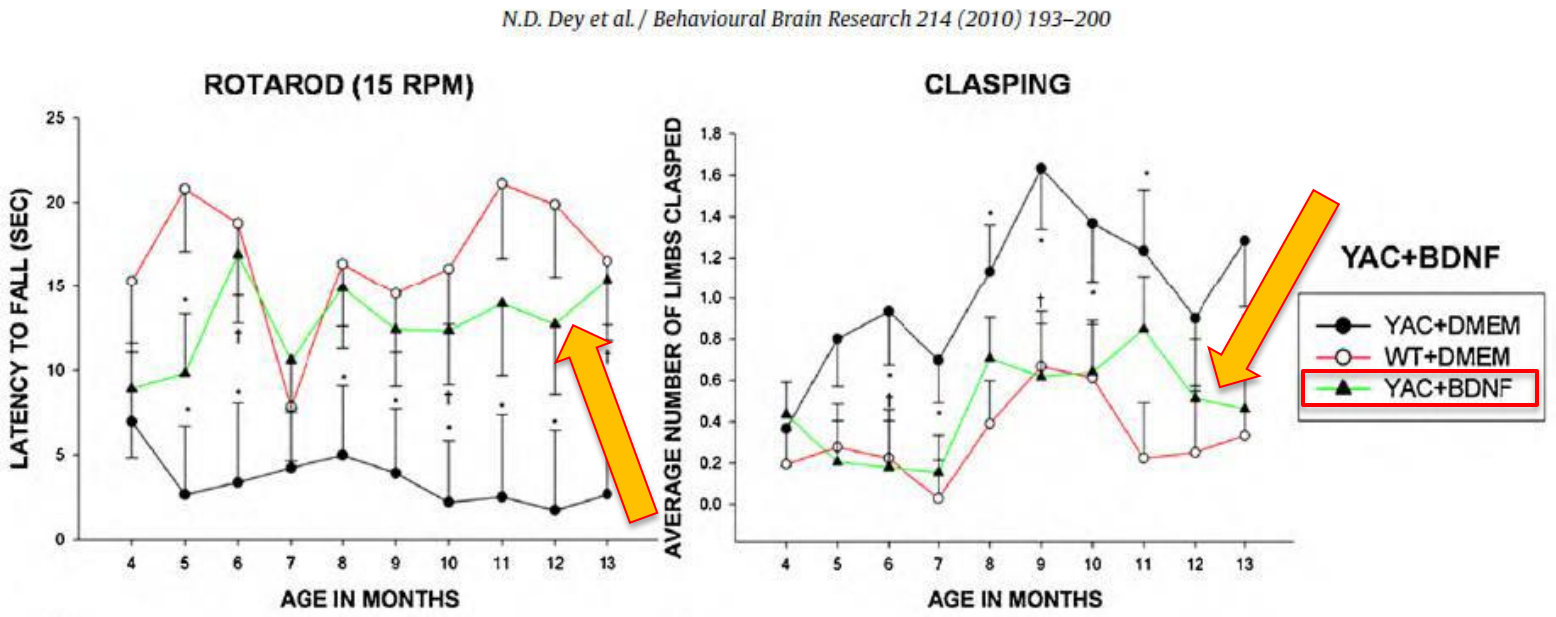
Nicholas D. Dey[a,b,c], Matthew C. Bombard[a,b], Bartholomew P. Roland[a,b], Stacy Davidson[a,b], Ming Lu[a,b], Julien Rossignol[a,b], Michael I. Sandstrom[b], Reid L. Skeel[b], Laurent Lescaudron[d,e,f,g], Gary L. Dunbar[a,b,c,*]



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



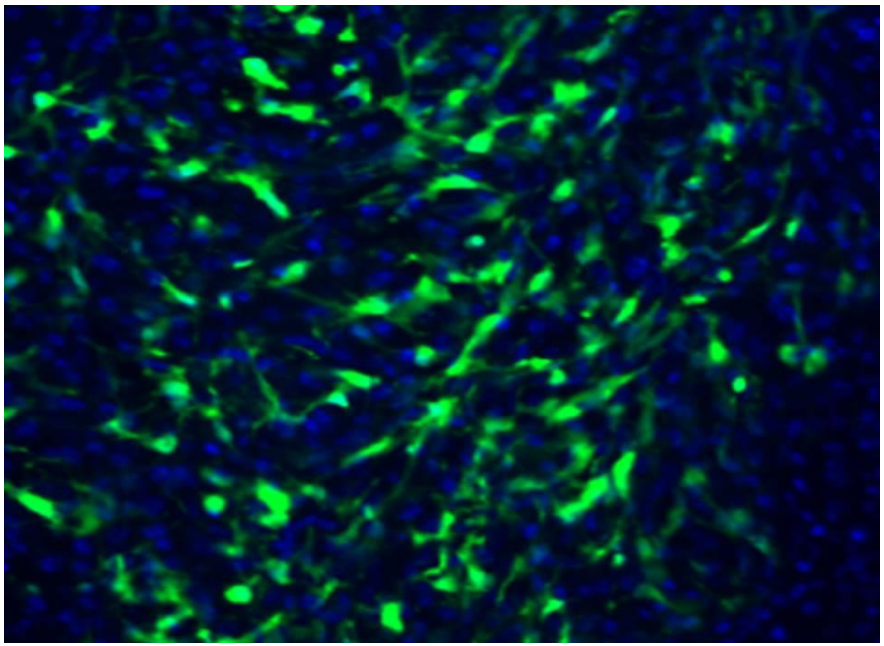
A. YAC 128 mice receiving striatal transplants of MSCs that were genetically engineered to over-express brain-derived neurotrophic factor (YAC+BDNF) stayed on the rotarod at 15rpm as long as wild type (WT+DMEM) mice and significantly longer than vehicle-treated YAC mice (YAC+DMEM).

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)

MSC/BDNF reverse behavioral abnormalities in YAC 128 mouse model

- 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



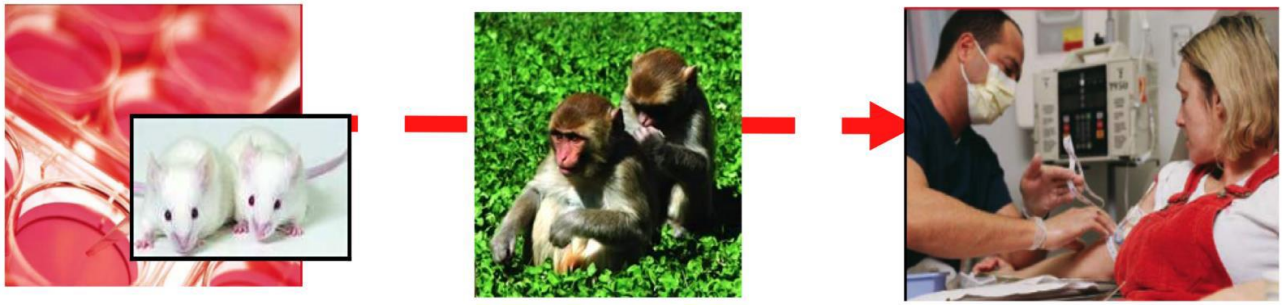
Concurrent work in Nolta lab

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

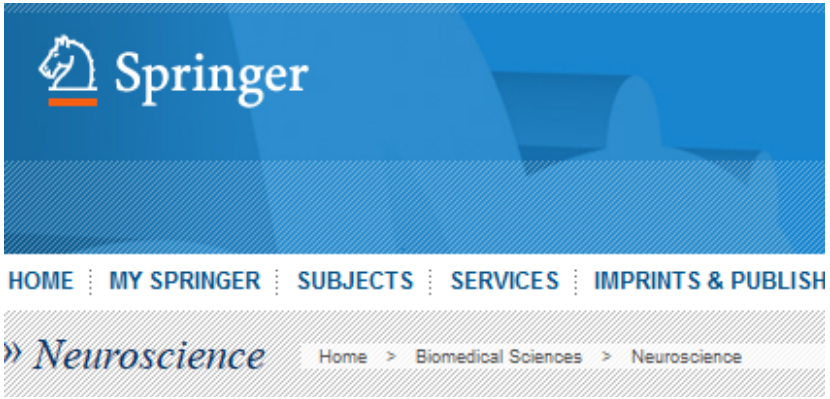


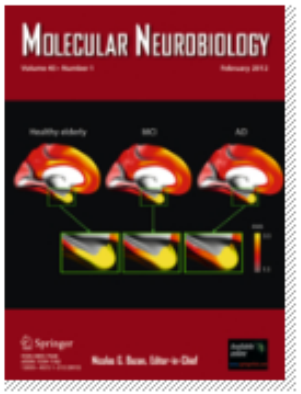
Intracranial injection of human mesenchymal stem cells into non-human primate brain:

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

HD and Stem Cells





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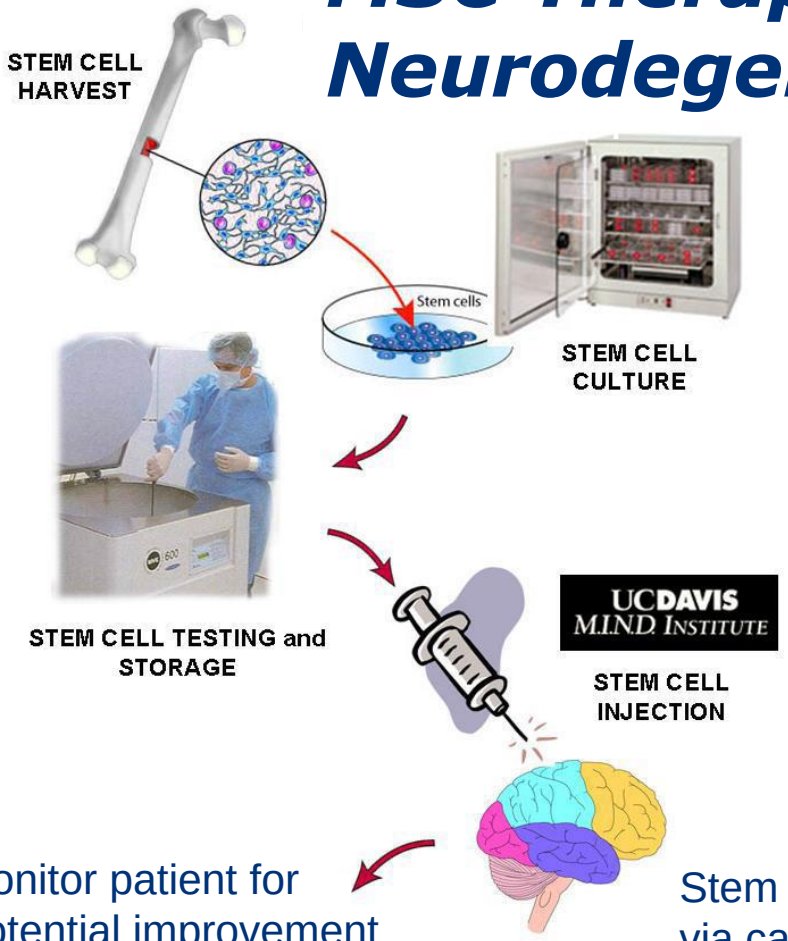
Humana Press

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

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

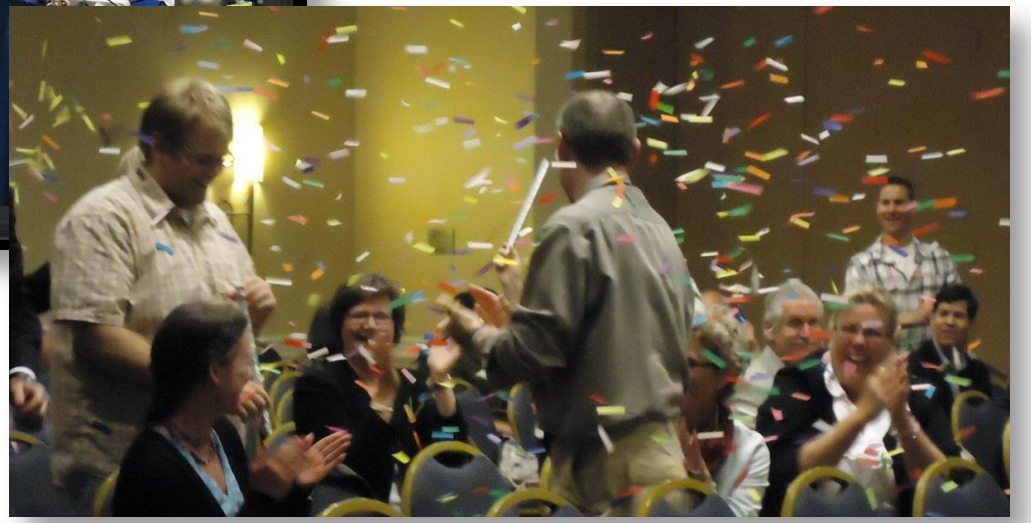
Disease Team Therapy Development Awards

CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

Number	PI	Title	Institution	Committed funds
DR2A-05415	Vicki Wheelock	MSC engineered to produce BDNF for the treatment of Huntington's disease	University of California, Davis	$18,950,061
DR2A-05309	Antoni Ribas	Genetic Re-programming of Stem Cells to Fight Cancer	University of California, Los Angeles	$19,999,563
DR2A-05302	Nancy Lane	Treatment of osteoporosis with endogenous Mesenchymal stem cells	University of California, Davis	$19,999,867
DR2A-05423	John Laird	Phase I study of IM Injection of VEGF-Producing MSC for the Treatment of Critical Limb Ischemia	University of California, Davis	$14,184,595
DR2A-05736	Nobuko Uchida	Neural stem cell transplantation for chronic cervical spinal cord injury	StemCells, Inc.	$20,000,000
DR2A-05394	Robert Robbins	Human Embryonic Stem Cell-Derived Cardiomyocytes for Patients with End Stage Heart Failure	Stanford University	$19,999,899
DR2A-05320	Clive Svendsen	Progenitor Cells Secreting GDNF for the Treatment of ALS	Cedars-Sinai Medical Center	$17,842,617
DR2A-05365	Judith Shizuru	A monoclonal antibody that depletes blood stem cells and enables chemotherapy free transplants	Stanford University	$20,000,000
Total				$150,976,602

http://www.cirm.ca.gov/PressRelease_2012-07-26

The grant is approved!



CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

July 26, 2012

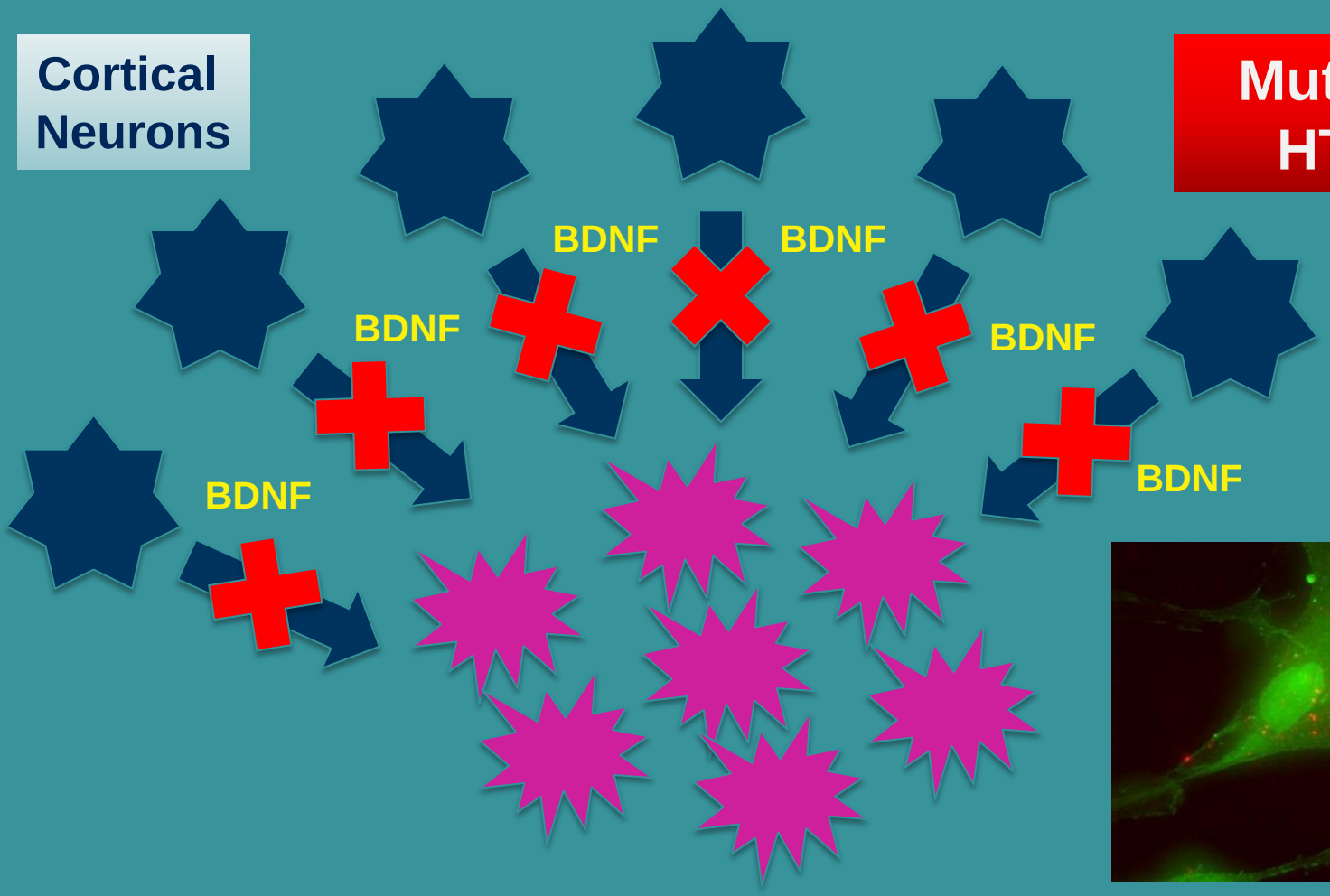
DR2A-05415 Objective

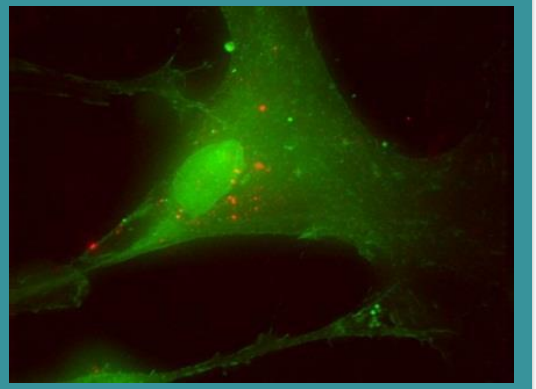
To obtain FDA approval and to successfully complete a 2-year Phase I trial of cellular therapy in patients with early-stage Huntington's disease (HD).

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

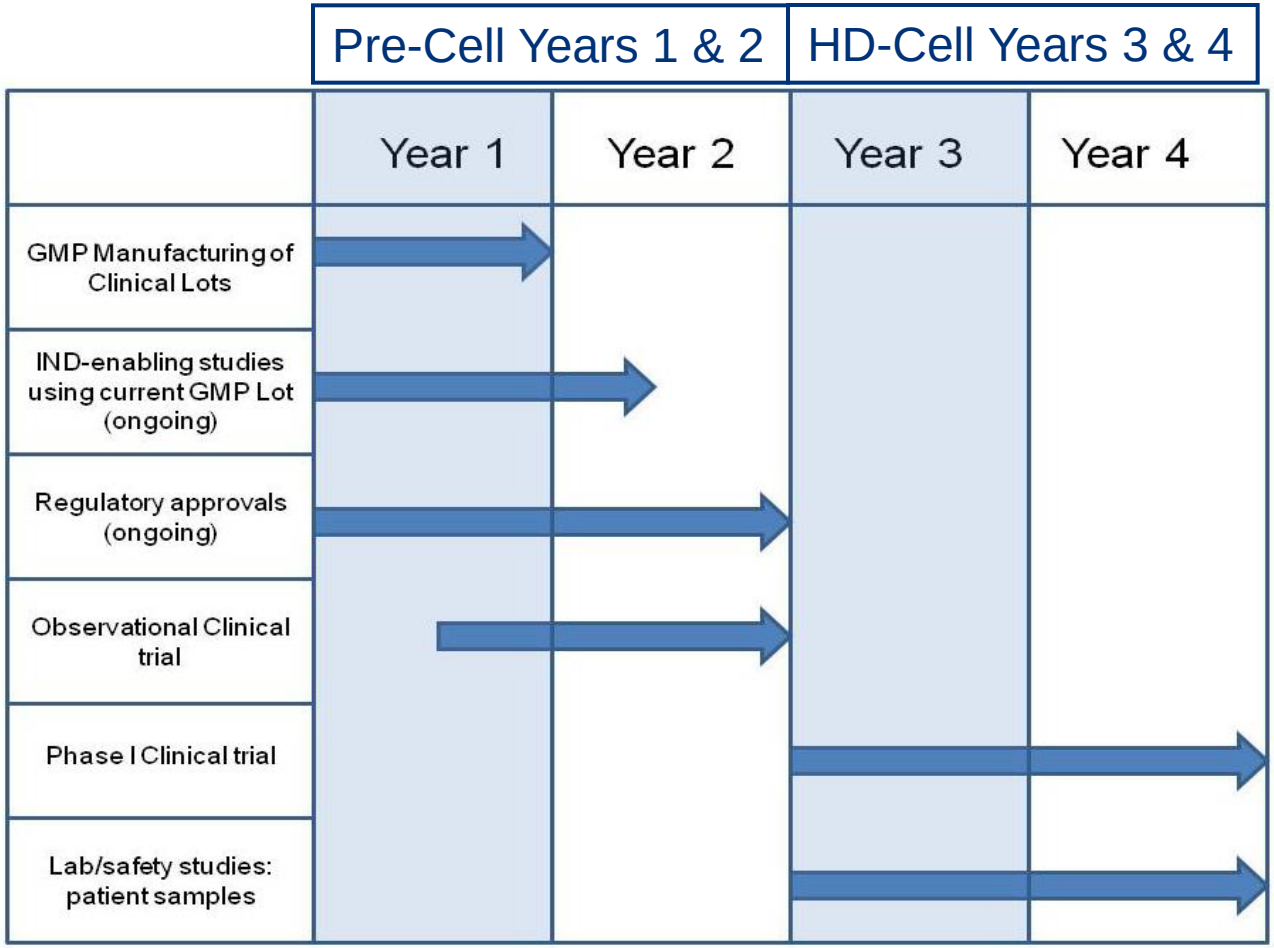
HD and Stem Cells





MSC/BDNF

Project Plan: CIRM Grant DR2A-05415



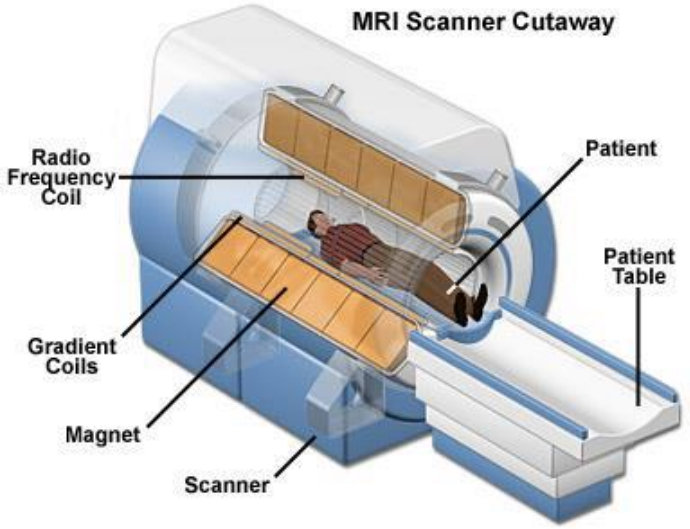
Timeline: Clinical Trials

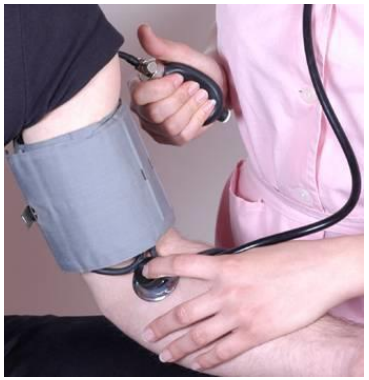
Years 1-2 PRE-CELL: Initiate enrollment of 26 - 40 patients with early-stage HD. We will collect clinical data (neurological exams, cognitive evaluation, volumetric brain MRI, and CSF studies) for a longitudinal baseline study every 6 months. We will determine the rate of change in each parameter for every subject in order to enhance safety and permit exploratory measures of clinical efficacy and biomarkers in the planned Phase 1 trial.

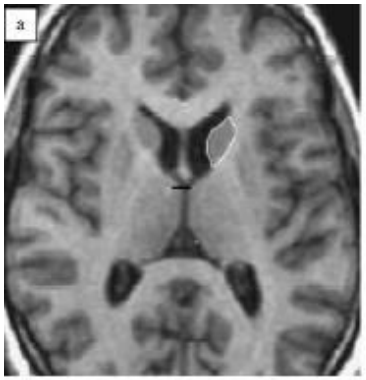
Years 3-4 HD-CELL: Enroll eligible PRE-CELL subjects who have completed at least one year of longitudinal assessments into HD-CELL. This will be an open-label Phase I trial, and all subjects to be treated will receive bilateral intrastriatal implantation of MSC or MSC/BDNF. Four groups of 5-7 patients will receive specific doses of cells.

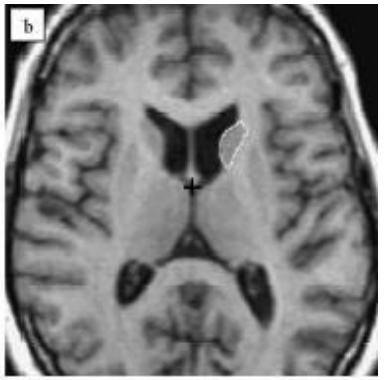
Planned Clinical Trials

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



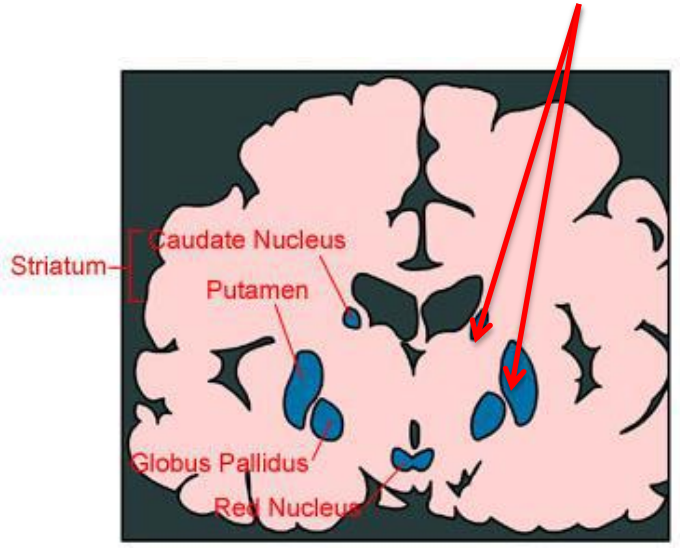






Planned Clinical Trials

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

Name	Institution	Role
Gary Dunbar, PhD	Central Michigan University	Proof of concept in mouse studies
Anne-Catherine Bachoud-Levi, MD	INSERM, Paris	Human study design
Elizabeth Aylward, PhD	Seattle Children's Hospital	Imaging studies
Steven Hersch, MD PhD	Massachusetts General Hospital	Biomarkers
Julie Stout, PhD	Monash University	Cognitive studies
Robert Deans	Athersys	MSC
Robert Mays	Athersys	MSC
Daniel Lim, MD PhD	UCSF	Neurosurgical consultant

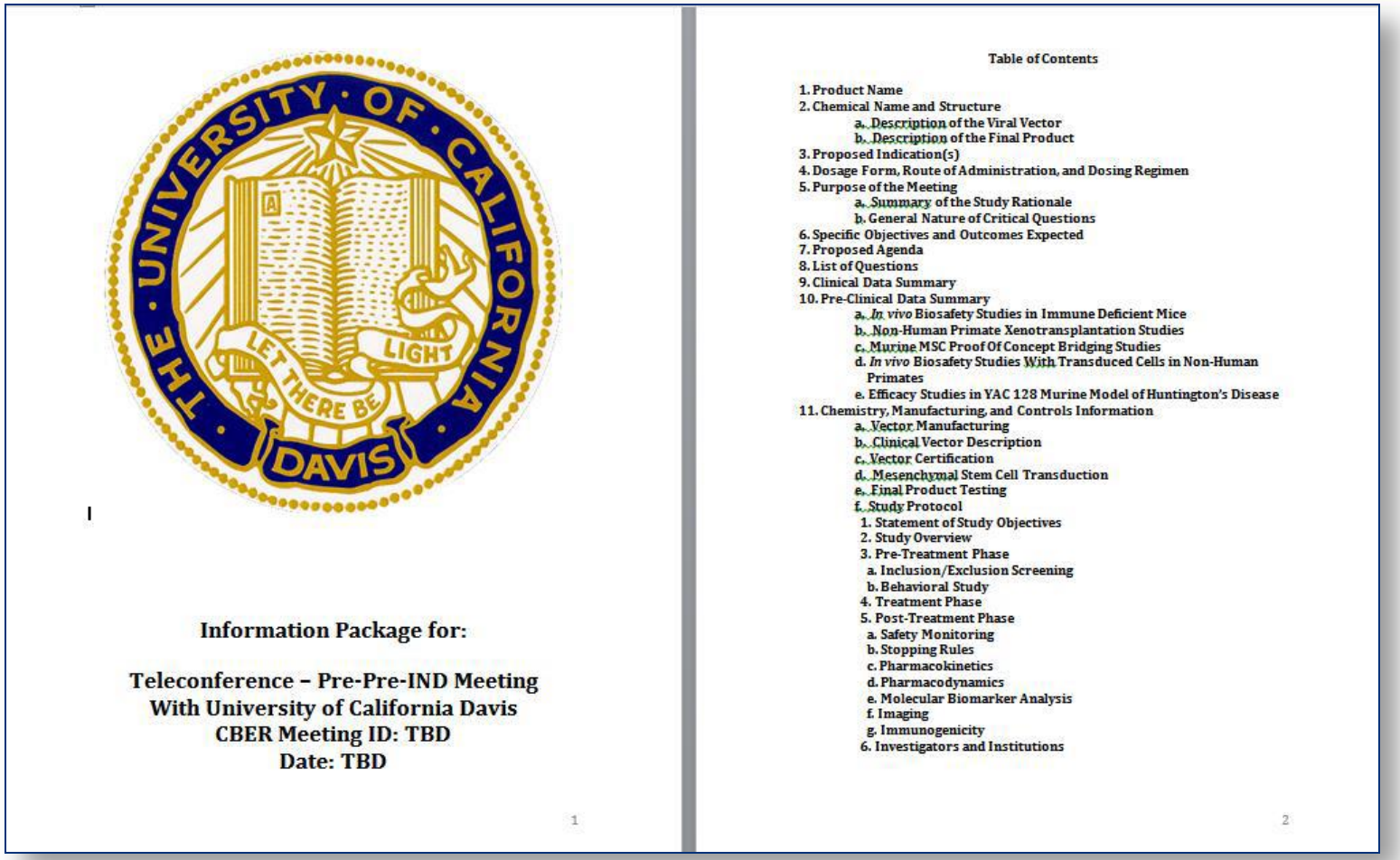
UC Davis Team

Name	Role
Charles DeCarli, MD	Director, Imaging Team
Sarah Farias, PhD	Director, Cognitive Team
Lorin Scher, MD	Director, Psychiatry Team
Kiarash Shalaie, MD, PhD	Neurosurgeon
Owen Carmichael, PhD	Imaging team
Mark Yarborough PhD	Bioethics
Gerhard Bauer, MD	GMP Director
Kari Pollock, MS	GLP Studies
Karen Pepper, PhD	Vector Core
William Gruenloh	Regulatory, IND

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

1

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UC Davis HD Team & Collaborators

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