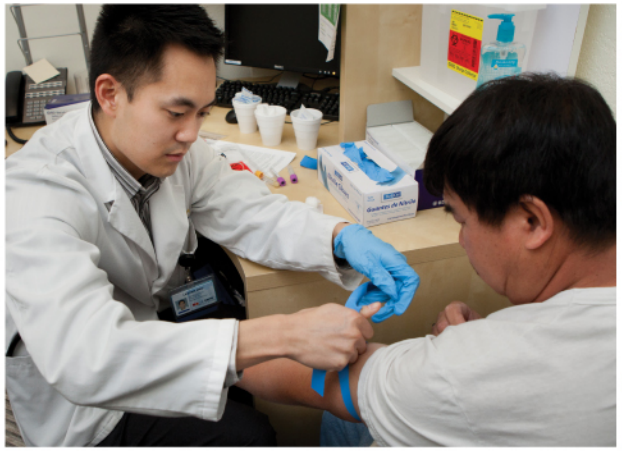
A HEALTHIER WORLD THROUGH BOLD INNOVATION






UCDAVIS HEALTH SYSTEM

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

Huntington's Disease Society of America Center of Excellence

UCDAVIS INSTITUTE FOR REGENERATIVE CURES

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)

California - November 2, 2004

- 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.

MSC/BDNF for HD

UC DAVIS HEALTH SYSTEM

UC DAVIS INSTITUTE FOR REGENERATIVE CURES

CIRM CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE
The State Stem Cell Agency

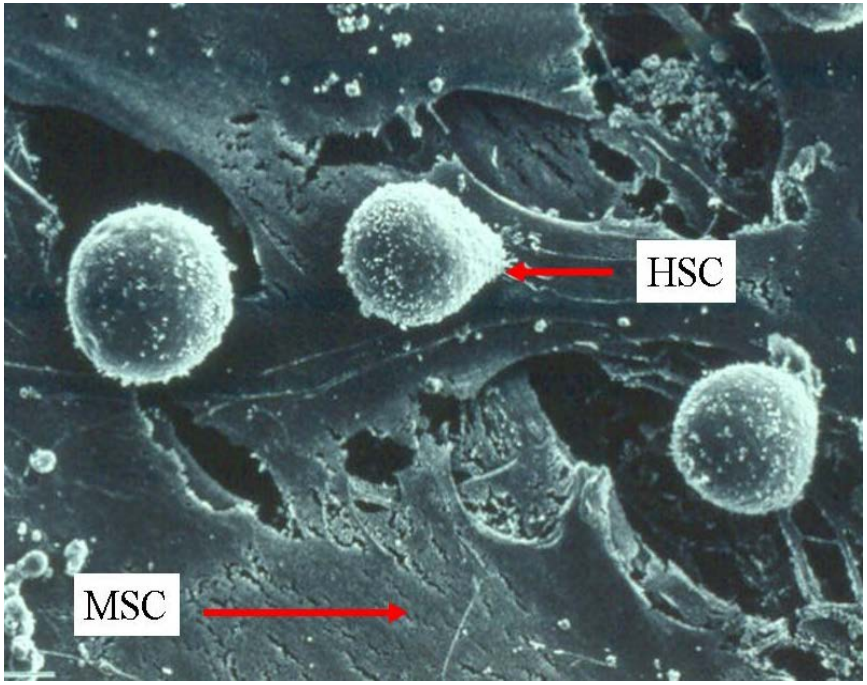
2010 – CIRM Spotlight on HD

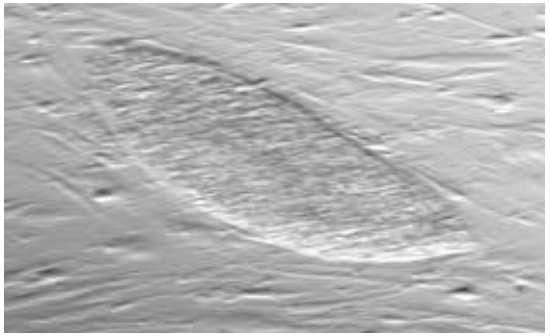
UCDAVIS INSTITUTE FOR REGENERATIVE CURES

CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

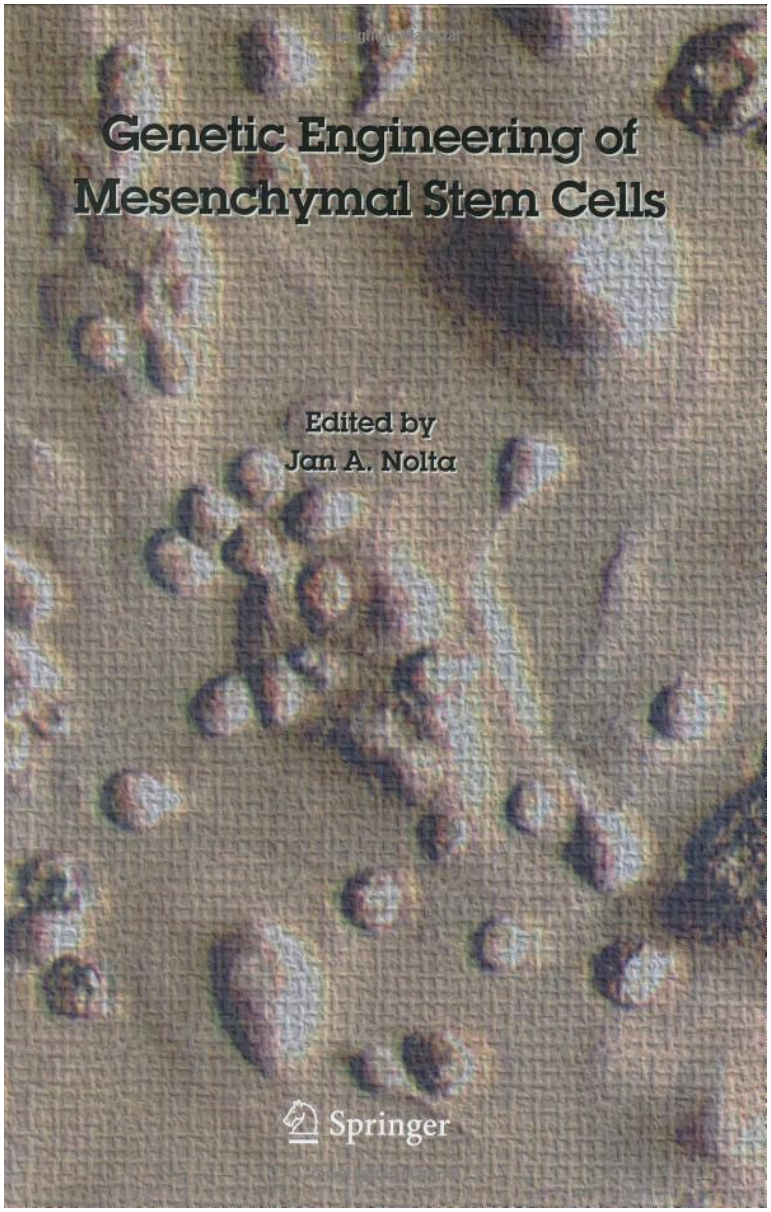
Types of Stem Cells

Adult Stem Cells	Pluripotent Cells
Blood forming (hematopoietic)	Embryonic
Mesenchymal (supporting cells)	Induced pluripotent stem cells





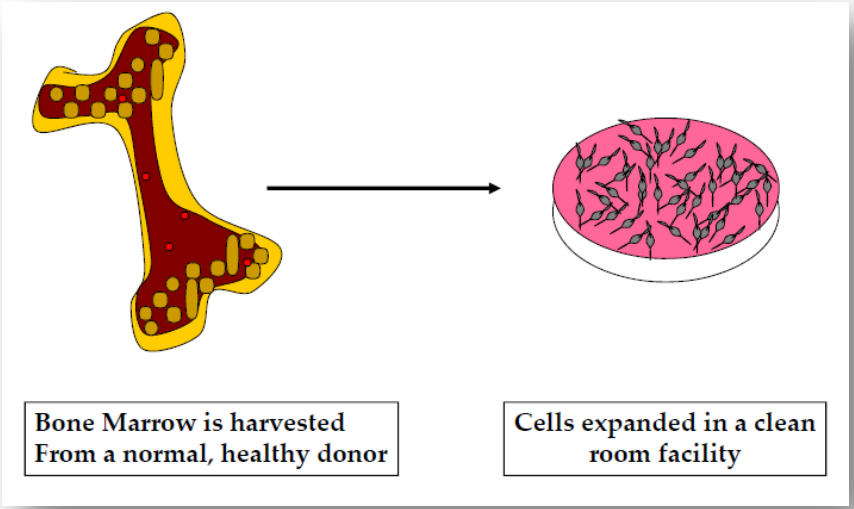
MSC/BDNF for HD

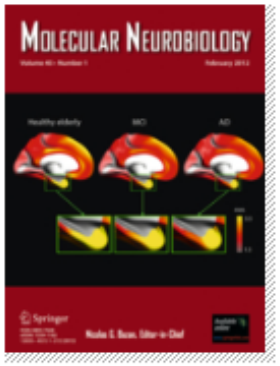


MSCs can be engineered
to secrete copious amounts
of factors for
delivery to other cells and
tissues in the body

Nolta Lab, 1987-present

Book published - 2006





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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. 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.

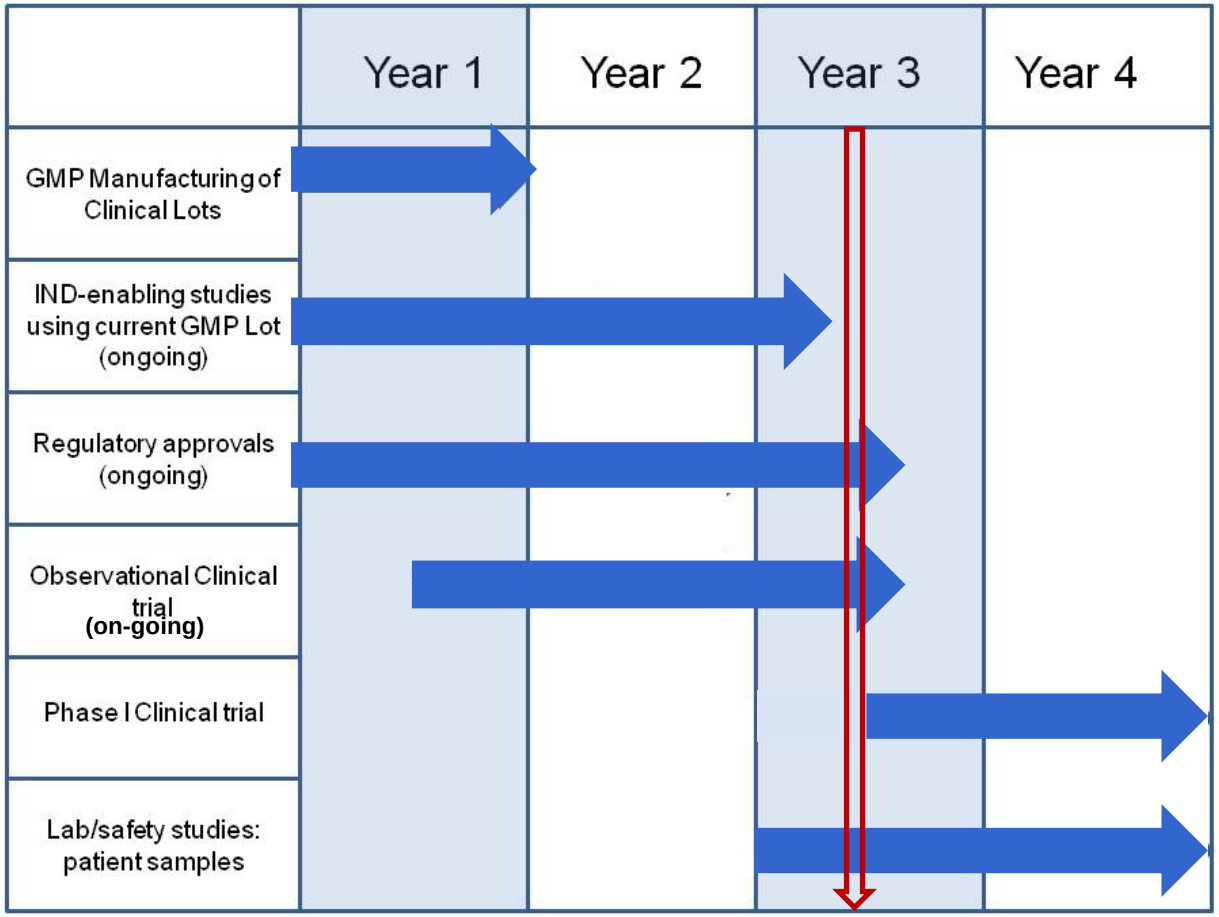
Project Plan: MSC/BDNF for HD

CIRM Grant DR2A-05415

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

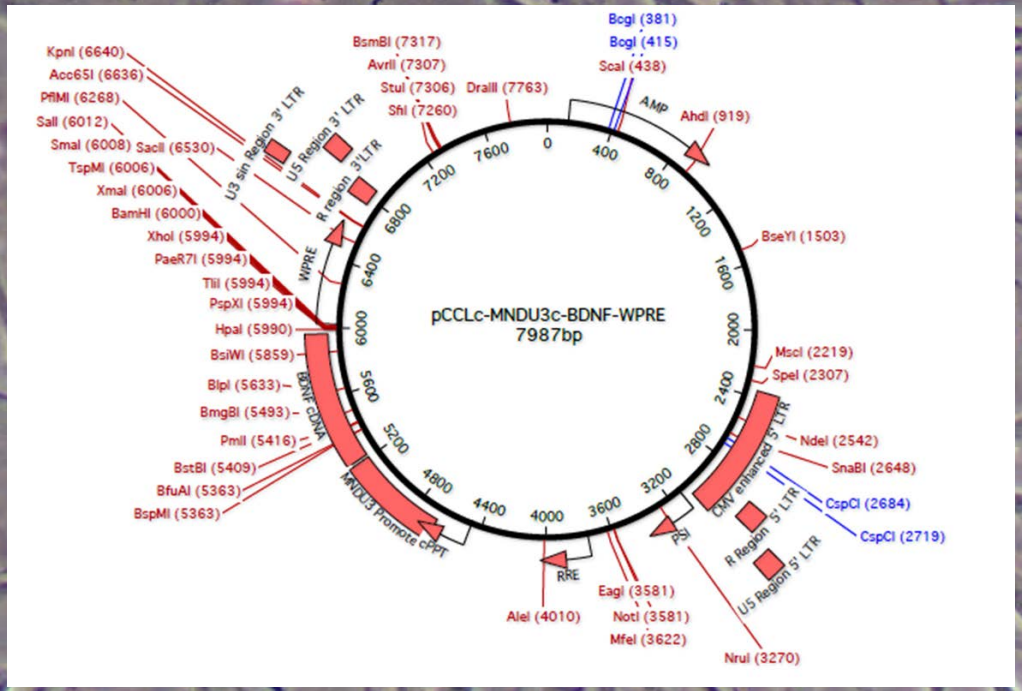
Pre-clinical

Clinical

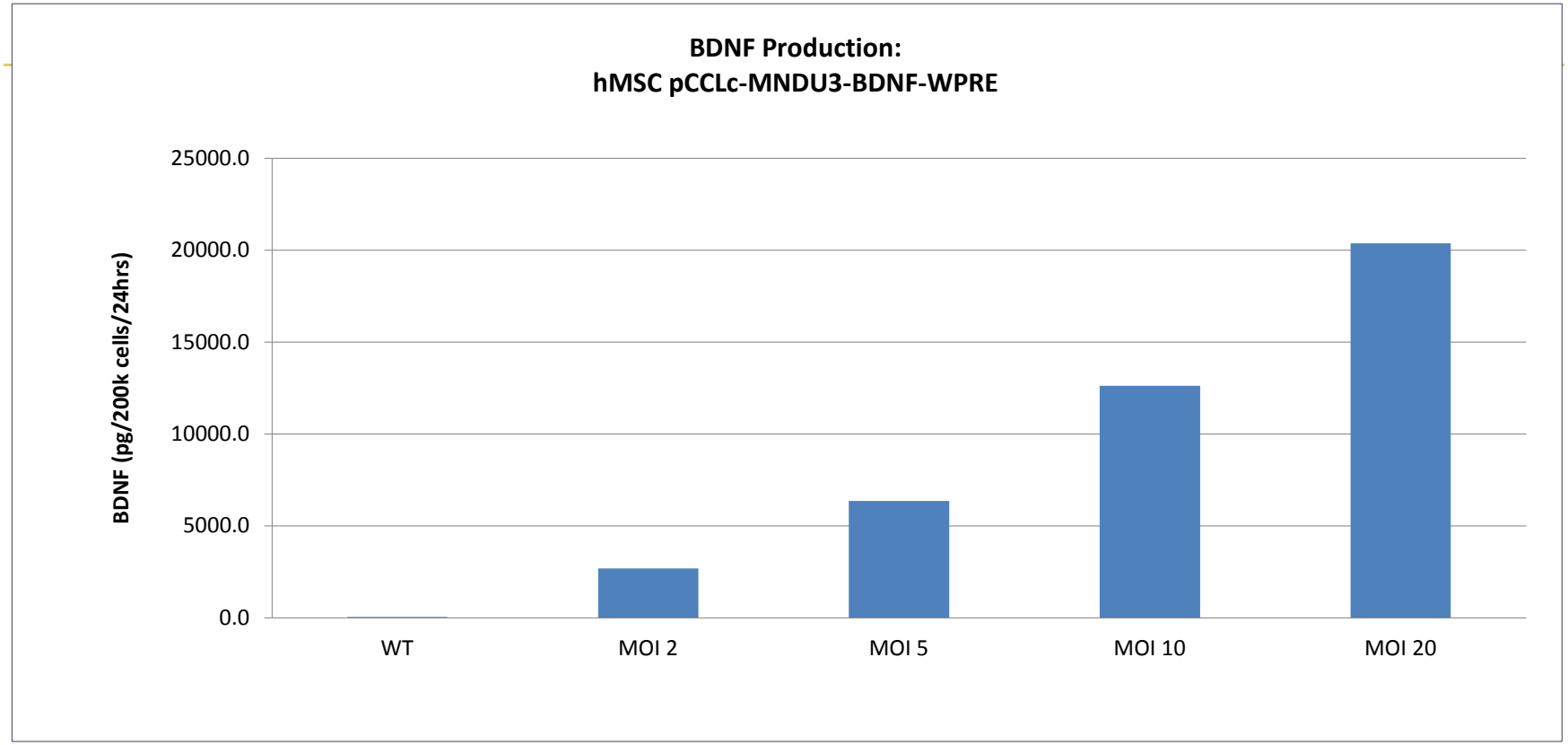


MSC/BDNF for HD

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

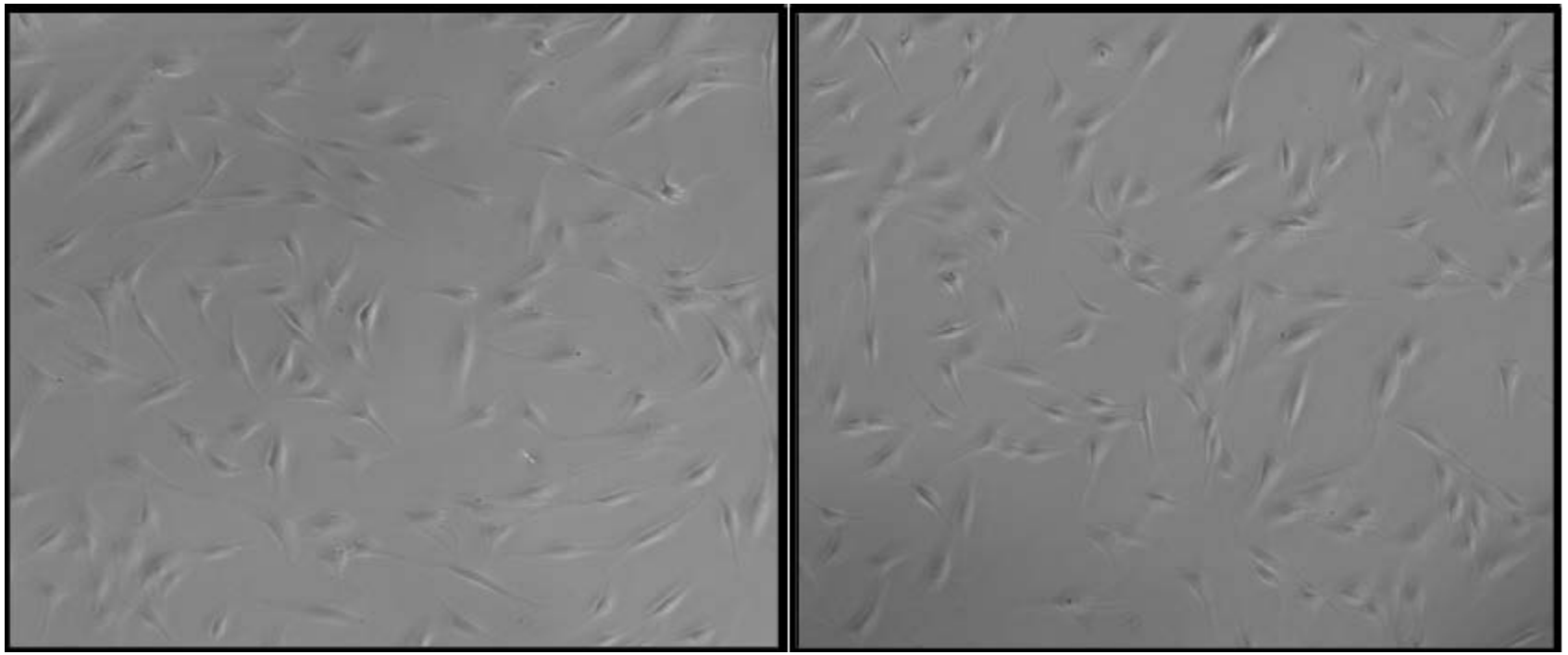


BDNF production by the engineered MSCs



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



Non-transduced

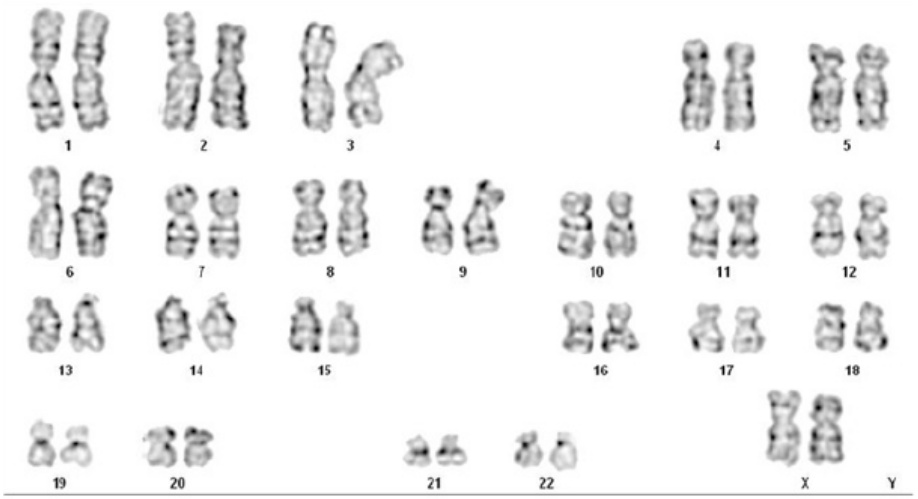
BDNF-transduced

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

NSC/BDNF Characterization: Stable Karyotype

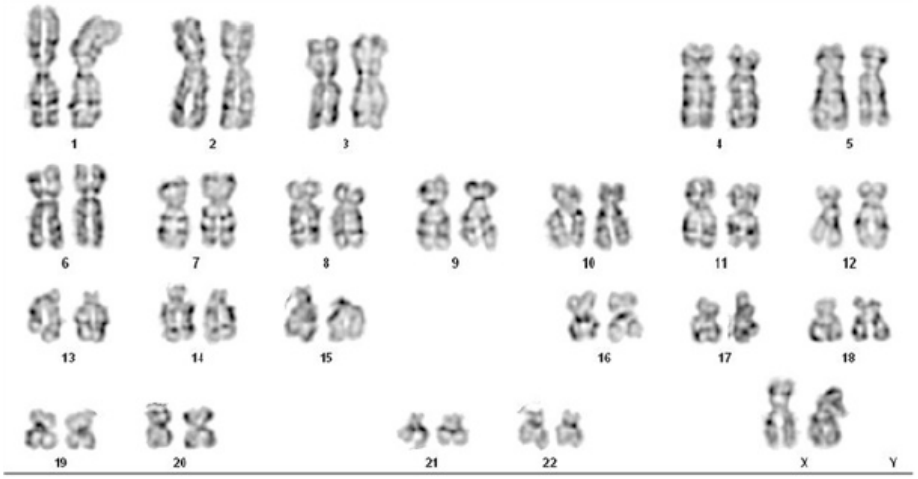
HD All Cells BMMSC p5

WT
50/50
46,XX



WT Control 50/50 confirmed Normal 46,XX

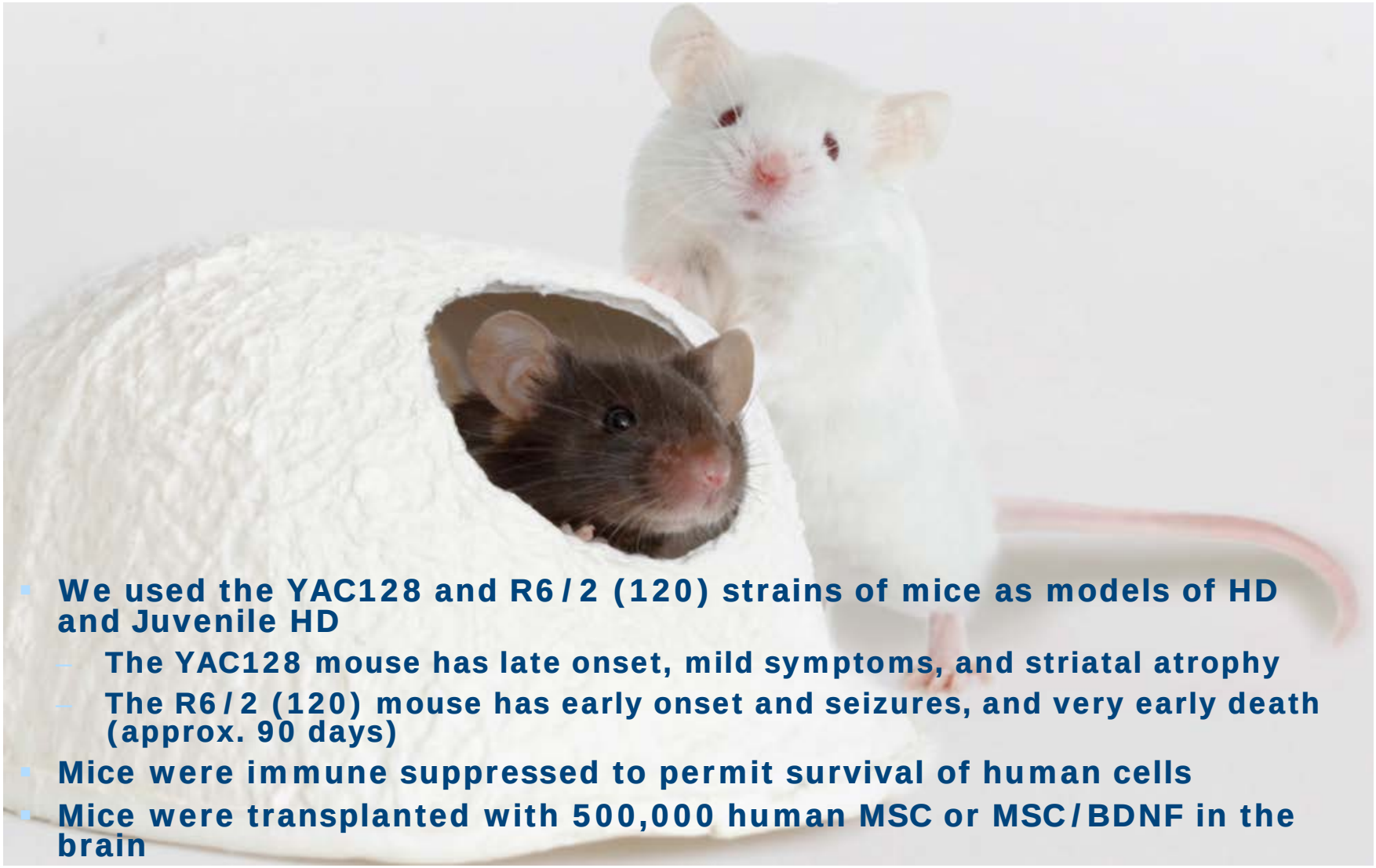
MOI10
50/50
46,XX



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

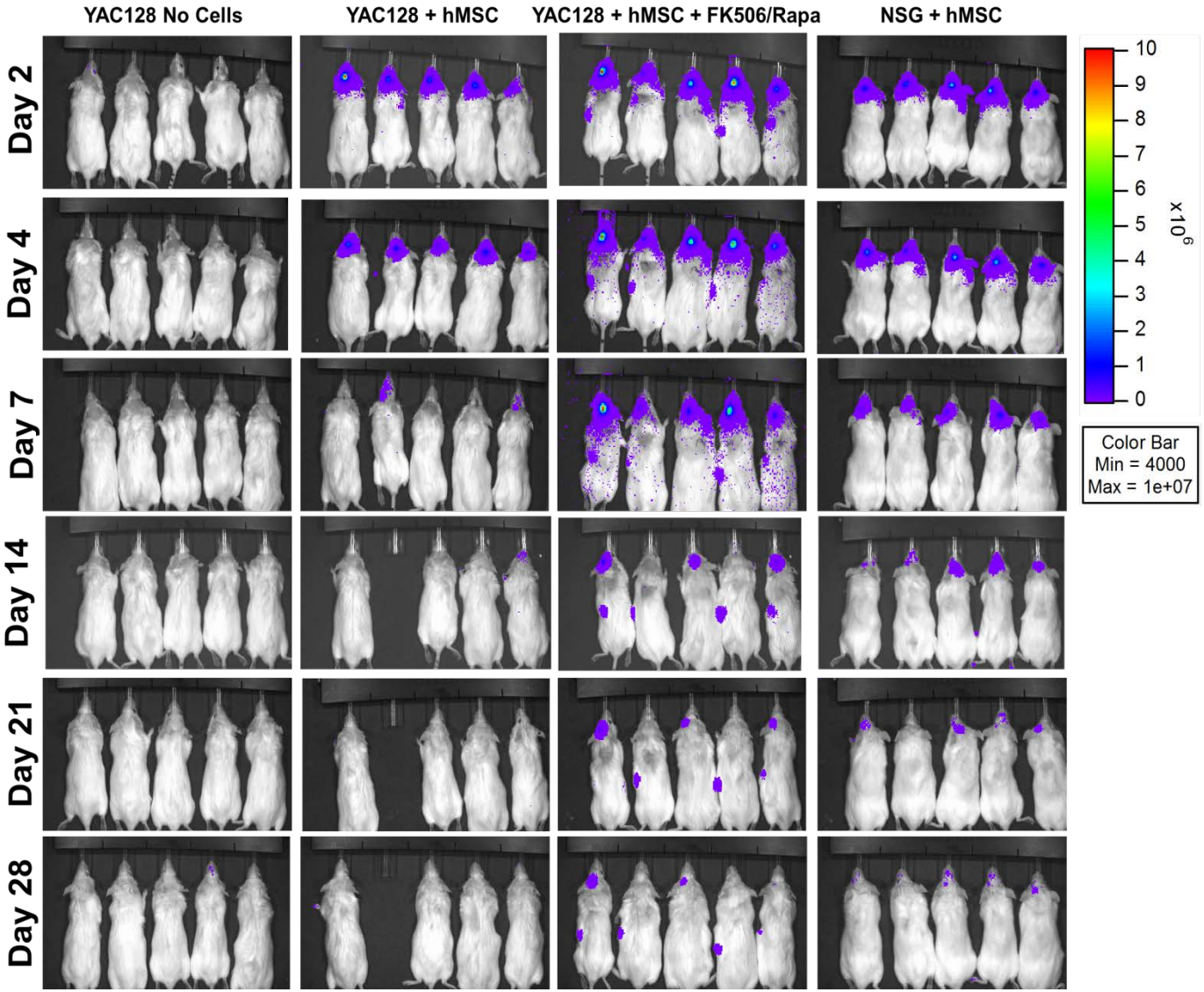
HD and JHD Mouse Model Studies

Mouse models of Huntington's disease



- 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

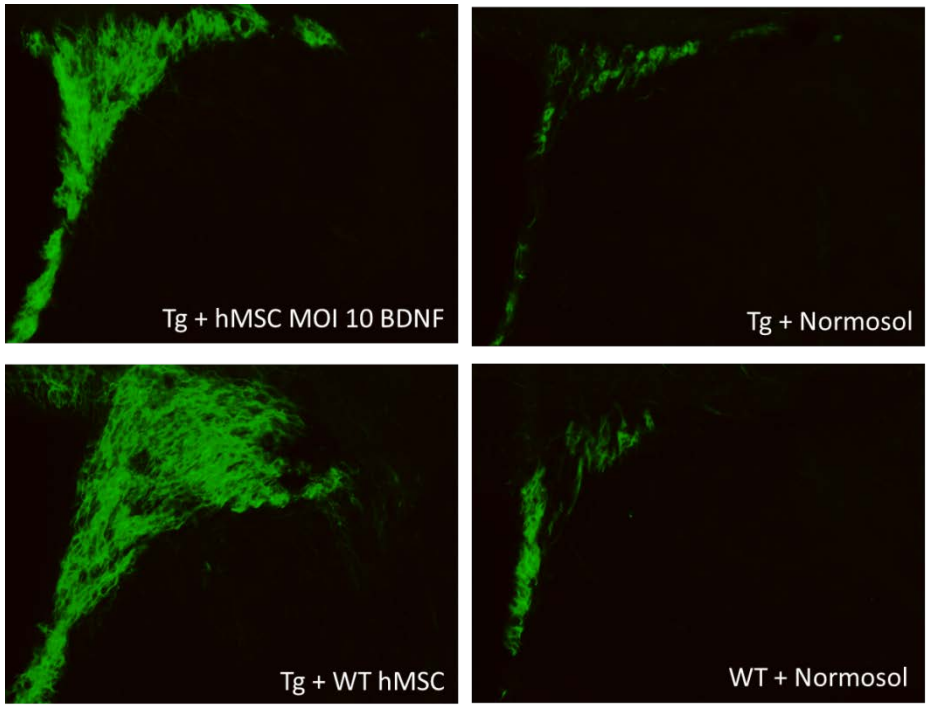


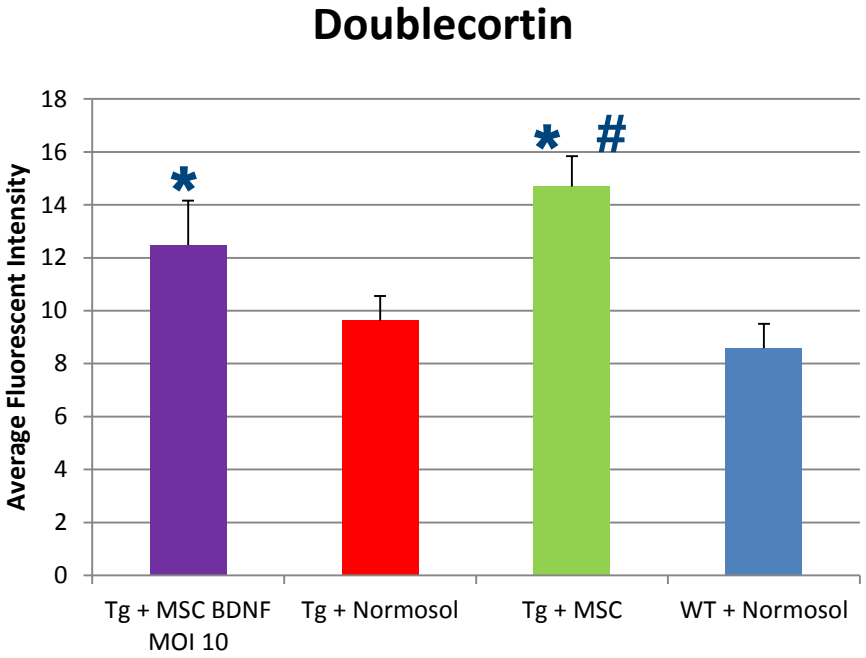
A combination of FK506 and rapamycin delivered via subcutaneous osmotic mini-pumps increased luciferase-MSC retention in the striata to levels similar to that observed in immune-deficient mice

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.

R6/2 Neurogenesis: 2014-0825 Efficacy study





* = Significant to WT,

\# = Significant to tg + Normosol

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

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.

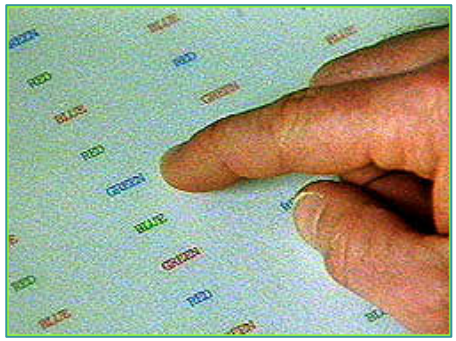
Clinical Trials

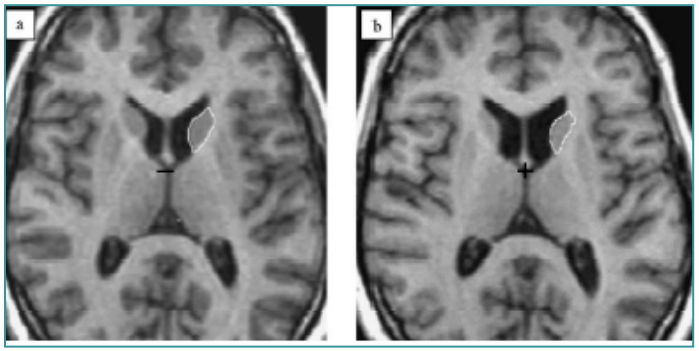
PRE-CELL: We have enrolled 30 patients with early-stage HD. We are collecting clinical data (neurological and psychiatric exams, functional abilities, cognitive evaluation, volumetric brain MRI, and exploratory serum and CSF biomarker studies) with assessments every 6 months. We are determining the rate 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.
3. Early stage HD with Total Functional Capacity (TFC) score of 9-13.
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)				
Screened	**Enrolled**	**Excluded**	**Pending enrollment**	**Scheduled for screening**
41	**31**	**9**	**1**	**0**
Number of subjects completing scheduled visits				
Screened	**Baseline**	**V01** (6 mo)	**V02** (12 mo)	**V03** (18 mo)
41	**31**	**25**	**17**	**5**

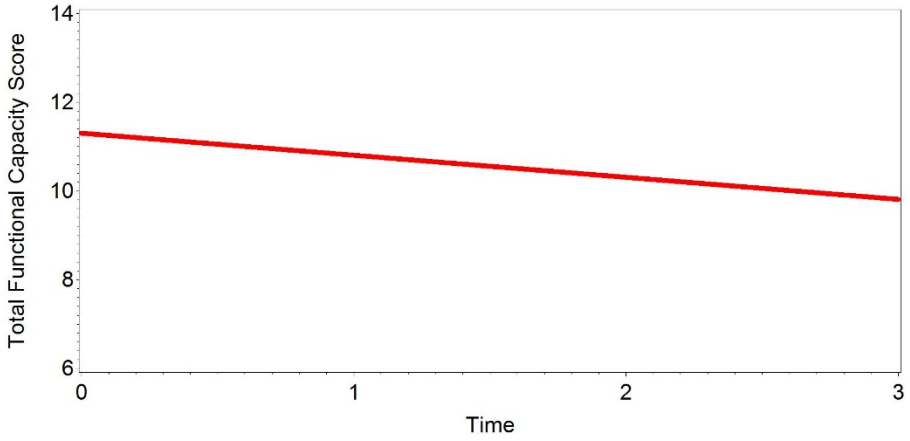
PRE-CELL enrollment will end June 2015

PRE-CELL Interim Results

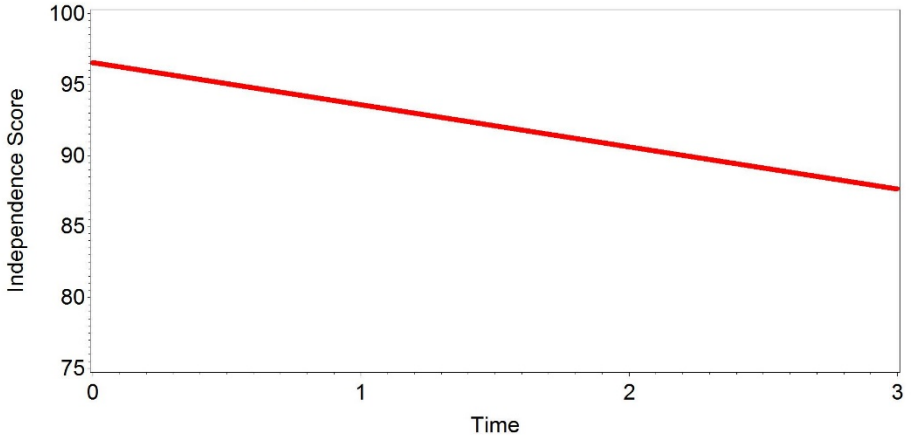
- Rate of change in clinical measures, including functional abilities, independence, motor exam, psychiatric symptoms and cognition
- Rate of change in MRI scan measures
- Rate of change in serum and CSF BDNF and mutant huntingtin protein levels

PRE-CELL Interim Results: estimated trajectories

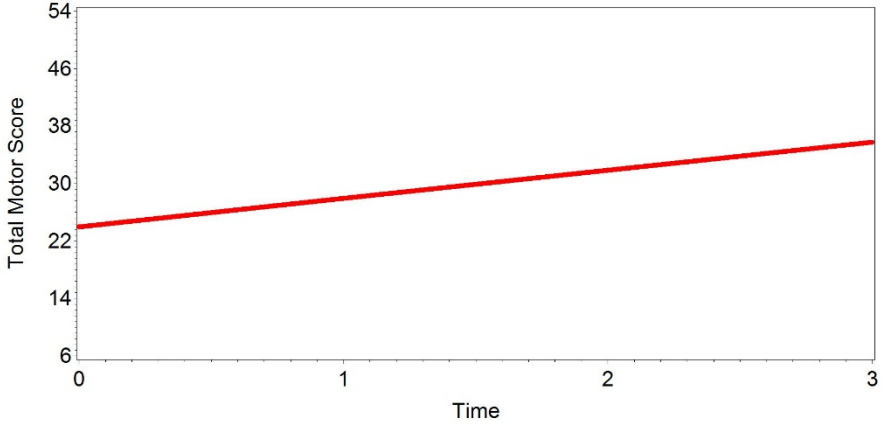
Total Functional Capacity Score



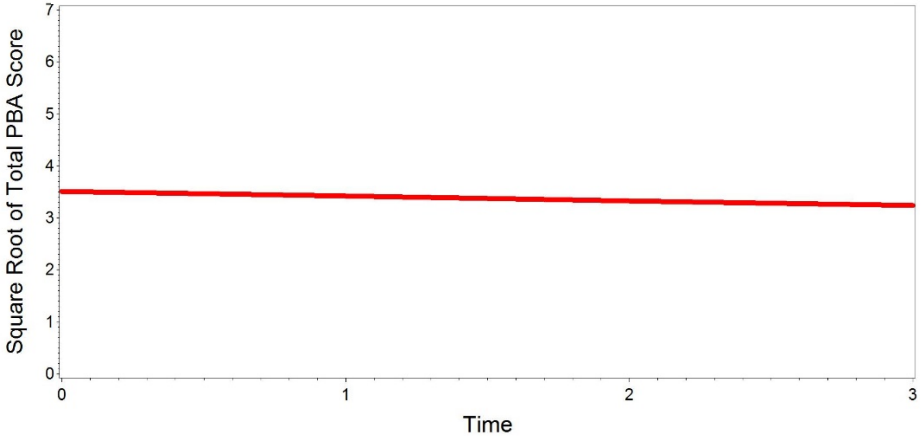
Independence Score



Total Motor Score



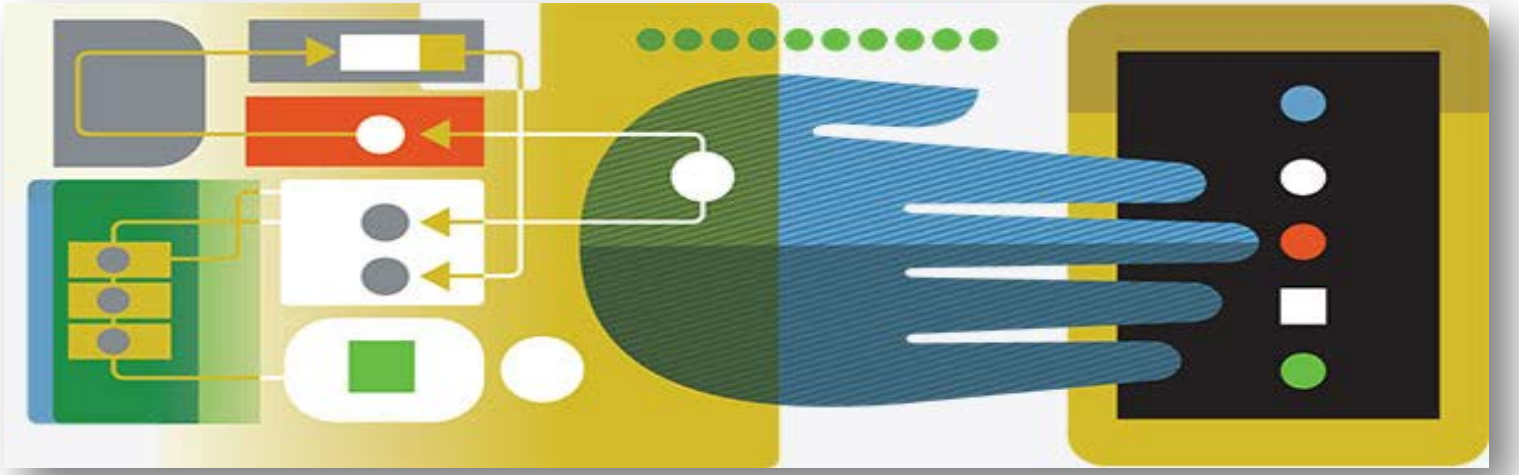
Total Problem Behavior Assessment Score



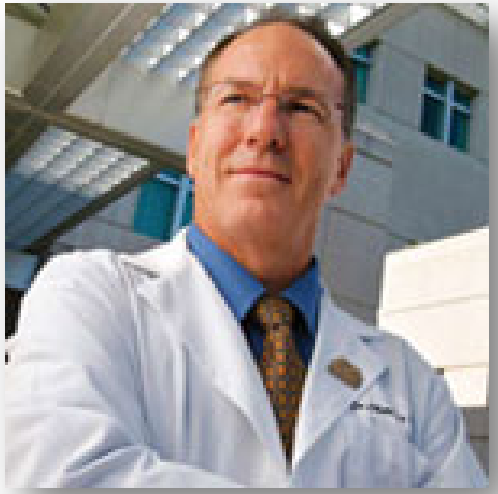
Cognitive Assessments

Sarah Farias, PhD
Associate Professor of Neurology, UC Davis

Julie Stout, PhD
Professor, School of Psychological Sciences
Monash University



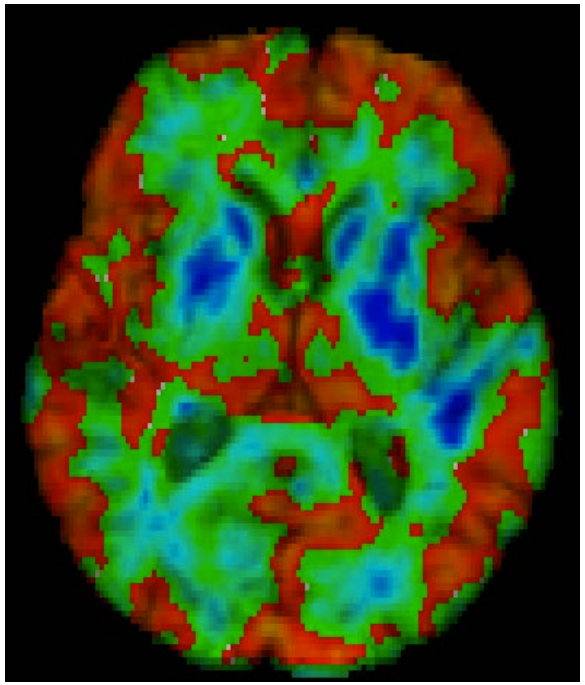
Structural MRI Analysis



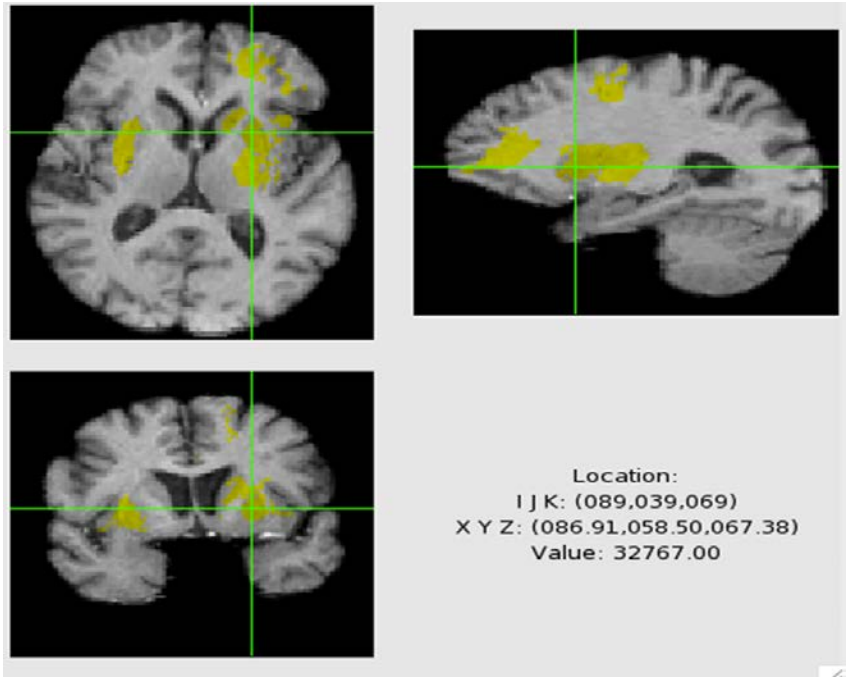
Charles DeCarli, MD
Professor, Department of Neurology
Director, IdEA Lab at UC Davis
Co-Clinical PI

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

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

Kyle Fink, PhD
Alexandra Duffy, DO
Vicki Wheelock, MD
Mark Yarborough, PhD
University of California, Davis

HD-CELL: Proposed Phase 1 safety and tolerability trial of MSC/BDNF neurosurgically implanted into striatum using techniques similar to deep brain stimulator implantation

WOC Lopez et al. Stereotactic planning software for human neurotransplantation. *Restor Neurol and Neurosci* 2014;31:579-595. 2014.

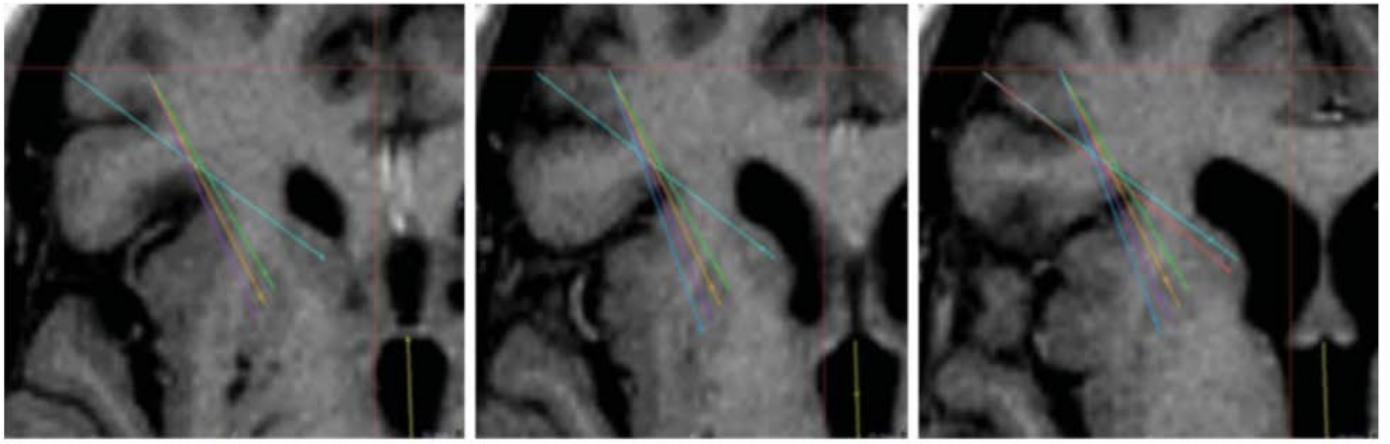
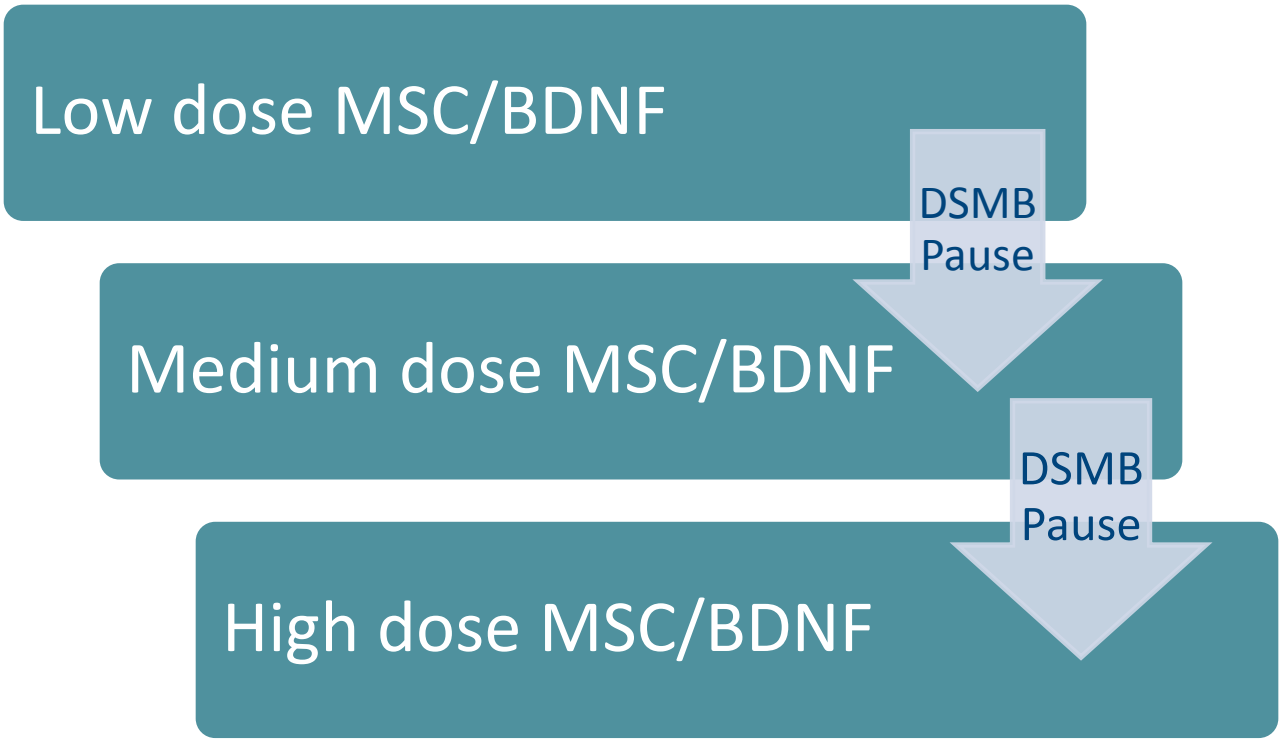


Fig. 1. MRI T1w, showing typical views obtained from the STP3 –planning workstation. Three coronal projections with tracts going to the caudate nucleus and to the putamen on the left side.

Treatment Cohorts

- Low dose MSC/BDNF: 5 x 10^6 cells per striatum
- Medium dose MSC/BDNF: 10 x 10^6 cells per striatum
- High dose MSC/BDNF: 20 x 10^6 cells per striatum



HD-CELL Schedule of Activities

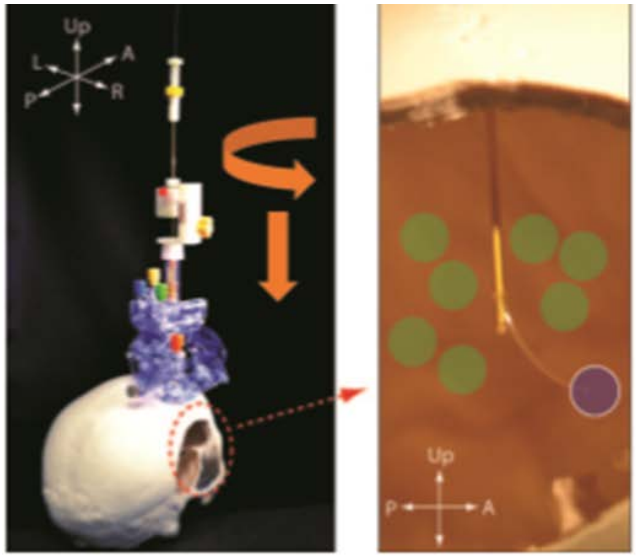
	Screening + Pre-op	Surgery within 30 d	V1 - 4 mo 1-2	V5 3 mo	V6 6 mo	V7 9 mo	V8 12 mo	☎ 15-24 mo
Informed consent	X							
Inclusion / exclusion	X	X	X	X	X	X	X	X
General exam	X		X	X	X	X	X	X
Neuro exam	X	X	X	X	X	X	X	X
UHDRS	X		X	X	X	X	X	X
Safety labs	X	X	X	X	X	X	X	X
Cognitive battery	X		X	X	X	X	X	X
Mood / behavior	X		X	X	X	X	X	X
Functional / QOL / CGI			X	X	X	X	X	X
MRI brain scan	X	X	X	X	X	X	X	X
Biomarkers	X		X	X	X	X	X	X
Lumbar puncture			X	X	X		X	X
Adverse events	X	X	X	X	X	X	X	X

Interventional Magnetic Resonance Imaging-Guided Cell Transplantation into the Brain with Radially Branched Deployment

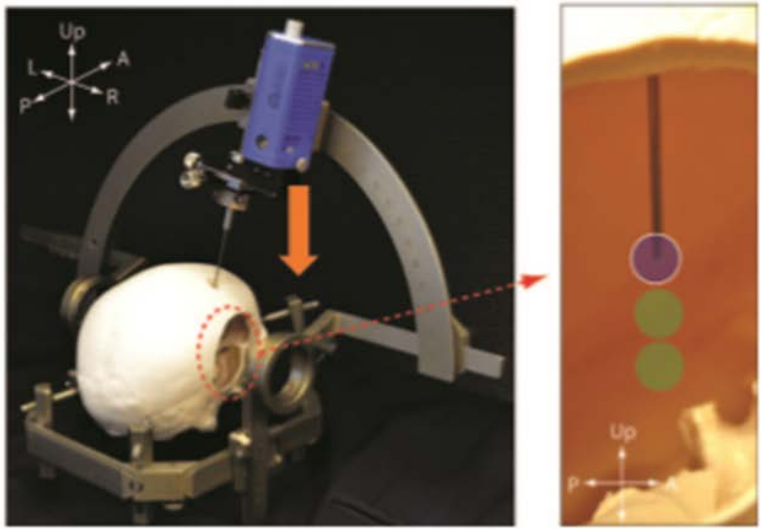
Matthew T Silvestrini[1,7], Dali Yin[1], Alastair J Martin[2], Valerie G Coppes[1,3], Preeti Mann[1,3], Paul S Larson[1,3], Philip A Starr[1], Xianmin Zeng[4], Nalin Gupta[1], S S Panter[1,3], Tejal A Desai[5], Daniel A Lim[1,3,6]

[1]Department of Neurological Surgery, University of California, San Francisco, San Francisco, California, USA; [2]Department of Radiology, University of California, San Francisco, San Francisco, California, USA; [3]Department of Surgery, Veteran's Affairs Medical Center, San Francisco, California, USA; [4]Buck Institute for Research on Aging, Novato, California, USA; [5]Department of Bioengineering, University of California, San Francisco, San Francisco, California, USA; [6]Eli and Edythe Broad Center of Regeneration Medicine and Stem Cell Research at UCSF, San Francisco, California, USA. [7]Present address: Department of Bioengineering, University of California, Davis, Davis, California, USA.

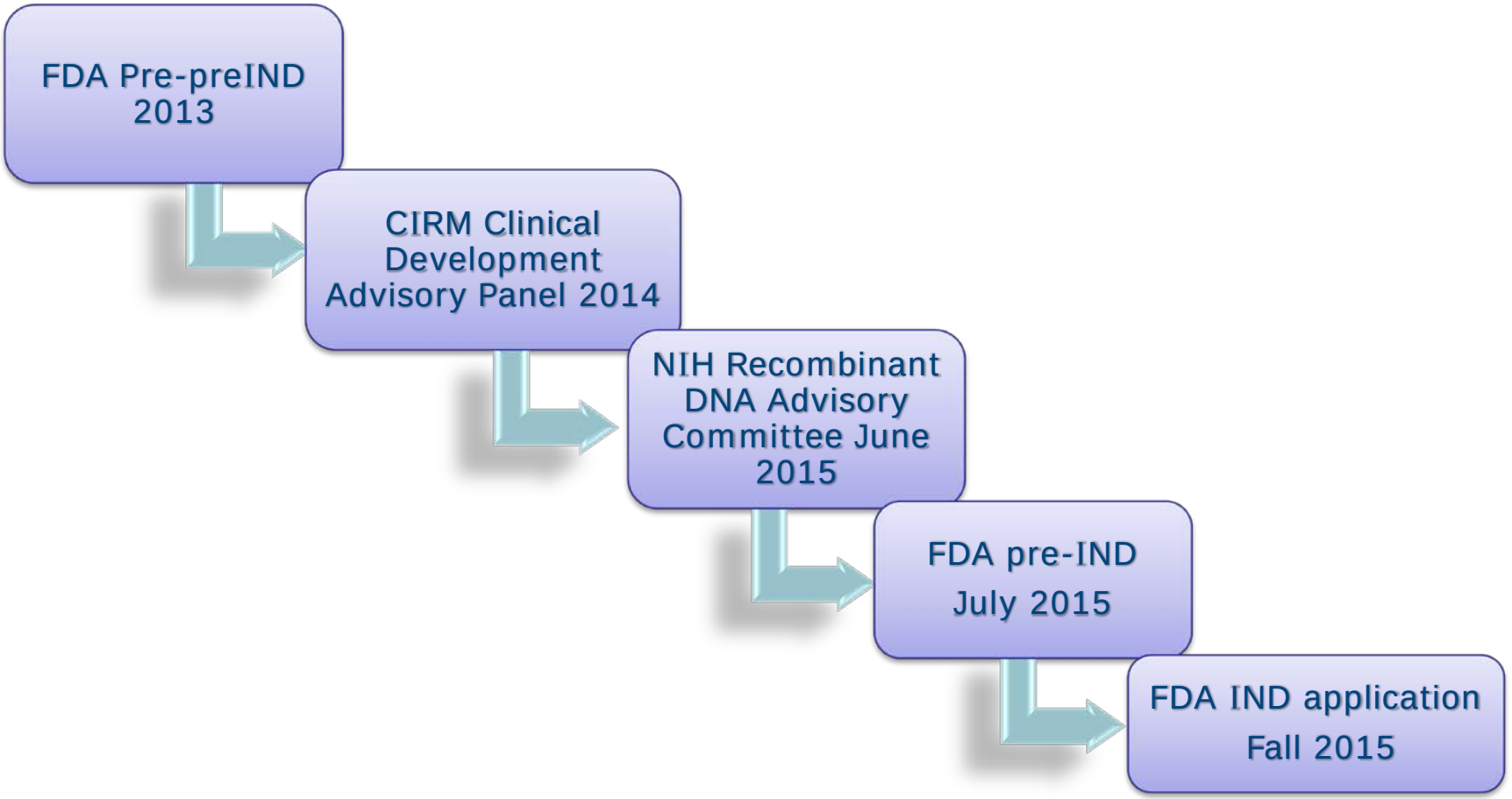
a iMRI-guided RBD



b Standard stereotactic targeting of a straight cannula

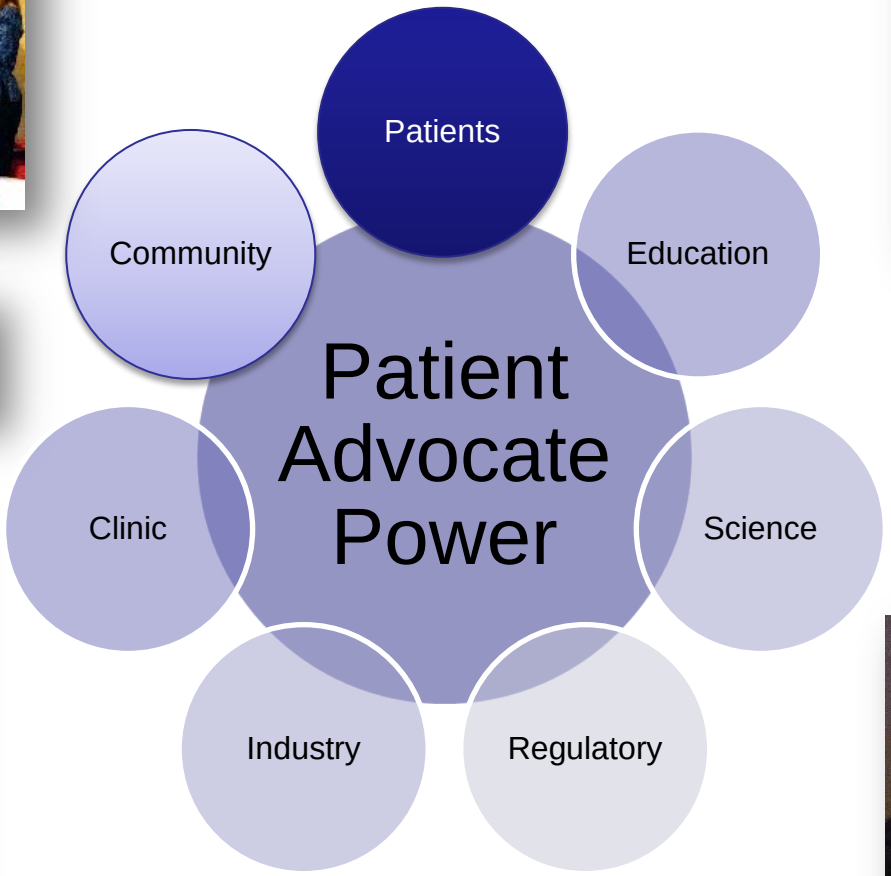


Regulatory Milestones Progress



MSC/BDNF for HD

Thank you HD patients and families!



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Source: Katie Jackson, Help4HD

MSC/BDNF for HD