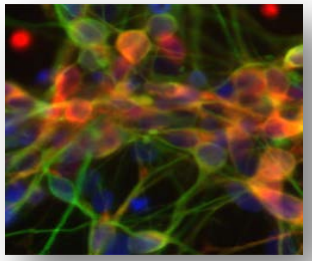
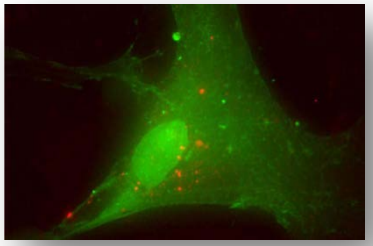




# *HD Research: Progress in Developing New Clinical and Disease-Modifying Therapies*

**Vicki Wheelock MD**

**Northern CA HDSA Annual Convention**
**May 20, 2017**
**UC Davis Medical Center/School of Medicine**
**Sacramento CA**

# *Huntington's Disease*


Woody Guthrie, 1943

Inherited degenerative neuropsychiatric disease

Estimated prevalence in US:

30,000 people with HD

150,000 at-risk

Onset: ages: 2 – 80,

commonly 30 – 40's

2000 new cases annually

Estimated costs in US: $2.5 billion

Symptoms: Involuntary movements, impairment of thinking abilities, mood and behavioral disorders

# Population affected by HD

| Location | Total Population | People with HD* | Juvenile HD | People At Risk** | Total affected and at-risk | Impacted family members*** |
|---|---|---|---|---|---|---|
| California | 39,250,017 | 3,925 | 390 | 26,494 | 30,419 | 97,644 |
| United States | 325,078,480 | 32,507 | 3250 | 219847 | 252, 354 | 810,056 |

US Census 2010

* Estimated, based on NIH quoted prevalence of 1/10,000

** Estimated based on 2000 estimate of 200,000 at risk = 6.75/10,000

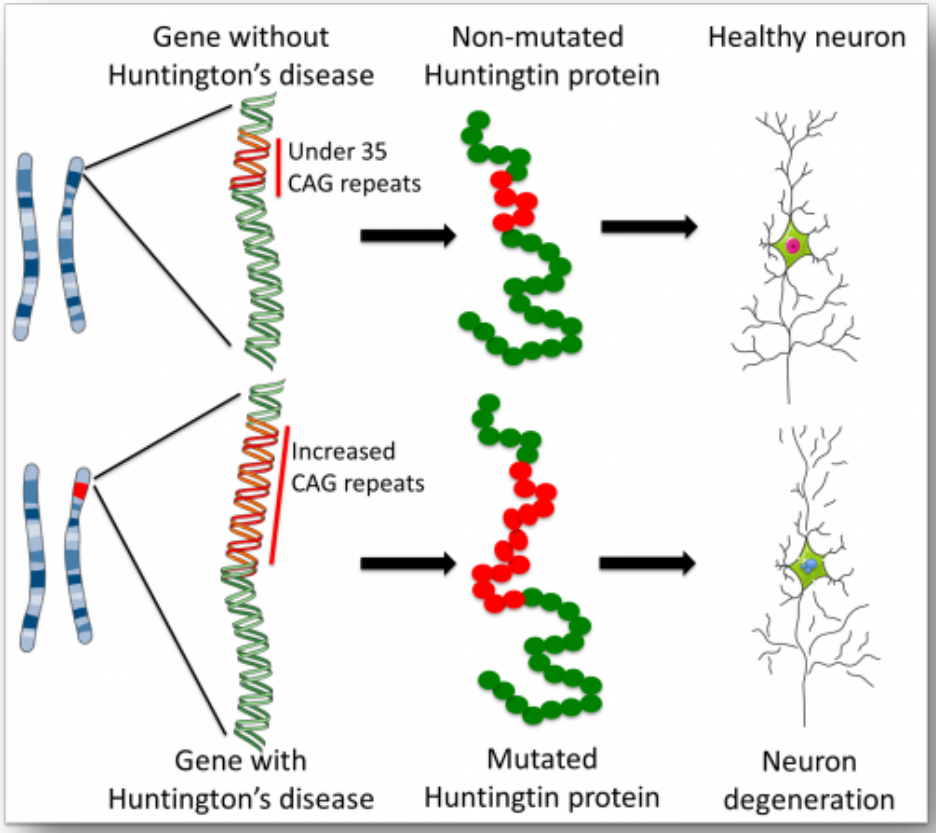
*** Estimated number of household members impacted by HD based on average family unit of 3.21 members

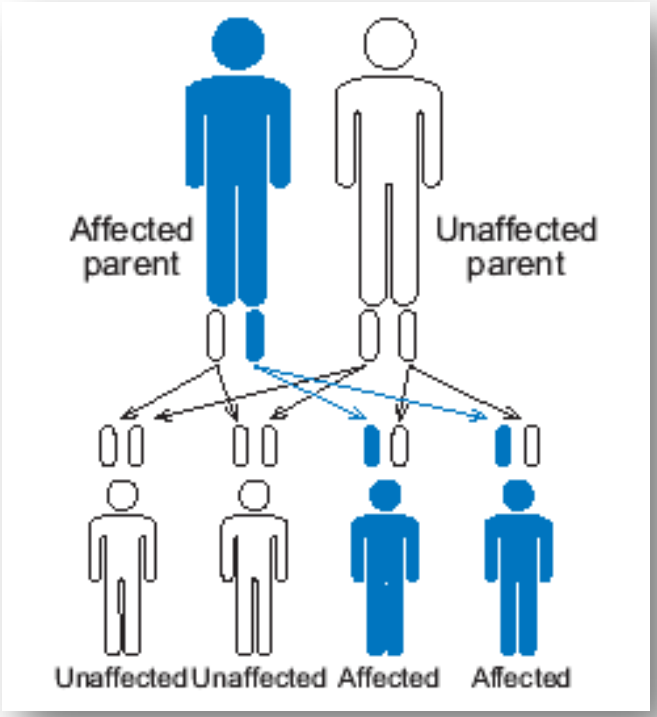
Source: Adapted from HDSA + US Census Population Clock 5/19/2017

# Who gets HD?

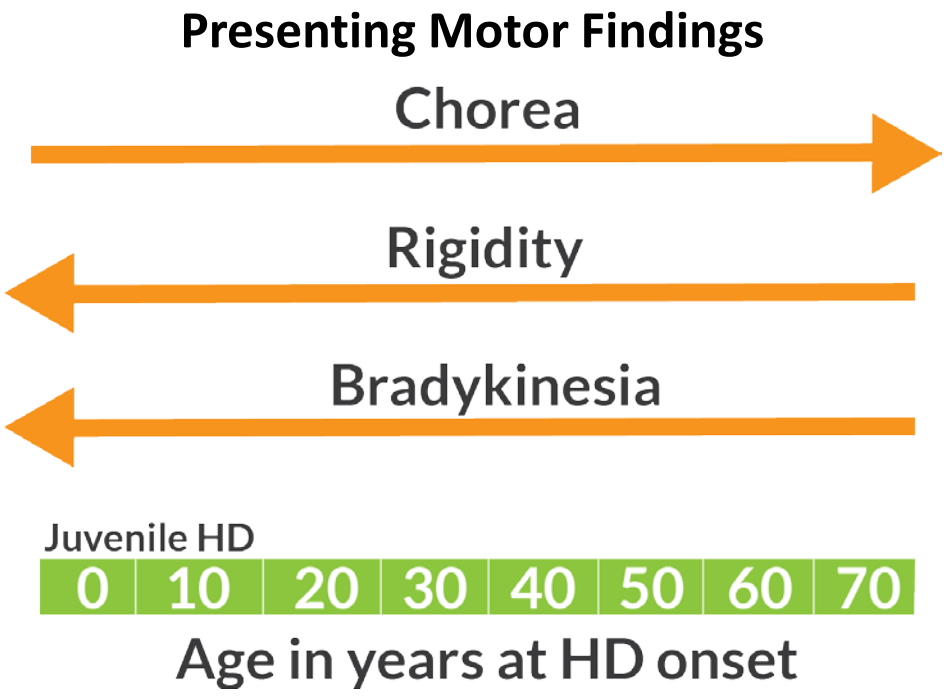
Each child with a parent with HD has a 50% chance of inheriting the disease.

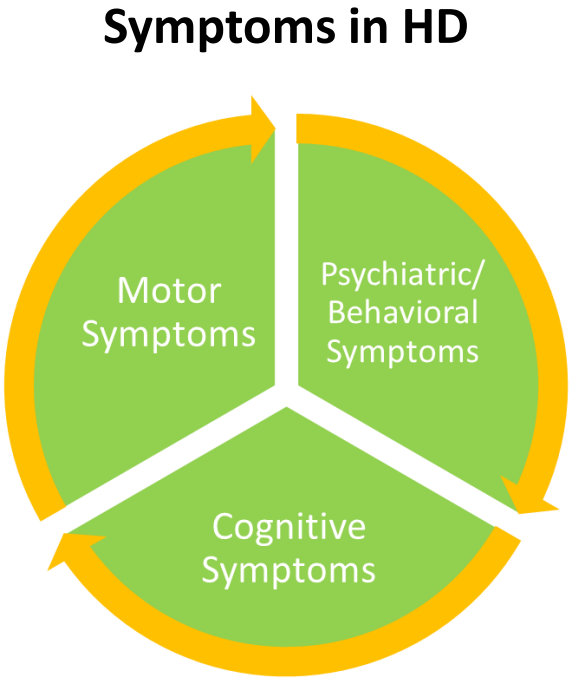
| CAG repeat length | |
|---|---|
| NORMAL | < 26 |
| Unstable | 27 – 35 |
| Reduced penetrance | 36 - 38 |
| Huntington's disease | >38 |



# Relationship Between HD Symptoms and Age




**Juvenile onset HD is defined HD onset before age 21**

- Only 5-10 % of cases of HD have juvenile onset
- Only 1-2% of cases have childhood onset, defined as onset before age 10 years

# Current HD treatments are symptomatic

- Anti-chorea therapies such as tetrabenazine, anti-psychotic drugs
- Psychiatric therapies such as counseling and medications
- No available drugs for cognitive difficulties
- Exercise, environment, physical, occupational and speech therapies are very helpful
- Palliative care and hospice in late-stage HD

# Progress in clinical care:
# New developments in managing HD symptoms

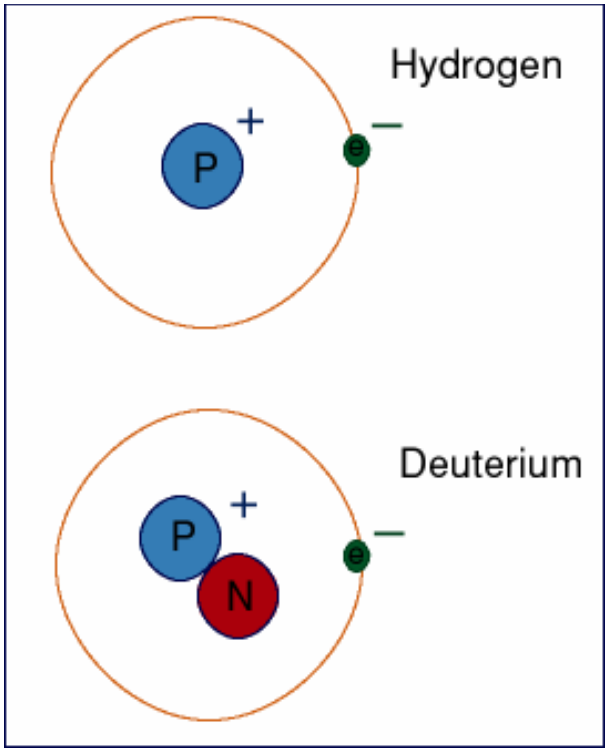
- Chorea: Deutetrabenazine approved 2017
- Anger and Irritability: NIH NeuroNext Study

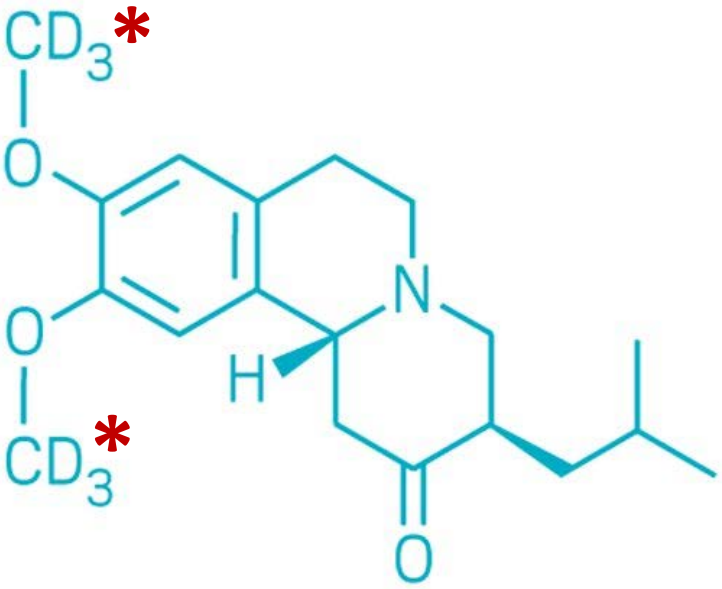



# Deutetrabenazine (Austedo™)

# Deutetrabenazine

- Deuterated form of tetrabenazine (FDA approved in the US in 2008 for the treatment of chorea in HD)
- Deutetrabenazine was designed by substituting naturally occurring deuterium molecule at 2 locations
- This results in slower metabolism and less variability in blood levels.



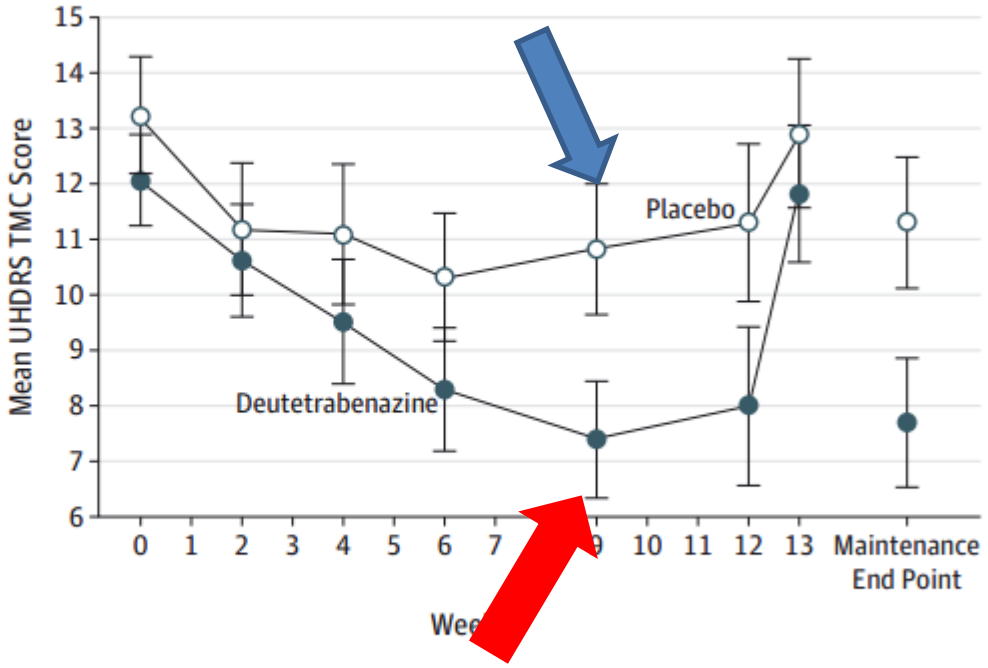
Original Investigation

# Effect of Deutetrabenazine on Chorea Among Patients With Huntington Disease
## A Randomized Clinical Trial

JAMA. 2016;316(1):40-50.

Figure 2. Total Maximal Chorea Score by Week

**Deutetrabenazine significantly reduced chorea scores compared to placebo in a 13 week randomized placebo-controlled study**




First-HD
A Huntington Disease Research Trial

# Side effects

- Most common: somnolence, diarrhea, dry mouth and fatigue
- Black Box Warning: risk of depression and suicide
- Contraindications: patients with depression or liver disease
- Use with care in patients taking anti-depressant drugs such as paroxetine, fluoxetine, quinidine, bupropion which can raise the levels of deutetrabenazine, or other drugs which can affect heart conduction
- Patients already taking tetrabenazine can be switched over to deutetrabenazine


- Teva's Shared Solutions program to support patients starting treatment
- Resources:
  - Nursing support
  - Education
  - Financial assistance program

# Targeting behavioral symptoms in HD

**Irritability and Aggression**

NeuroNEXT

The NEXT Generation of Neurologic Treatments

NIH-Network for Excellence in Neuroscience Clinical Trials

# SRX246: Safety, Tolerability, and Activity in Irritable Subjects with HD (STAIR)

National Institute of Neurological Disorders and Stroke

Azevan Pharmaceuticals

Massachusetts General Hospital

The University of Iowa

# STAIR trial: Why treat Irritability in HD?

- No controlled treatment studies for irritability in HD. In fact, there are very few studies of how to treat emotional symptoms in Huntington's.
- Irritability causes family conflict; others avoid being around the patient; may cause danger to patient themselves or others in the household.
- Can lead to early placement in long term care because behavior can not be controlled at home.

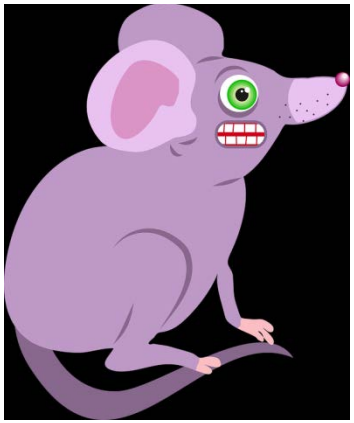
AZEVAN PHARMACEUTICALS

# How does SRX246 work?

- SRX246 blocks vasopressin$_{1A}$ receptors
- Vasopressin is increased in the brain during anger and aggression in both animals and humans.
- It may be helpful in treating irritability and aggression.

AZEVAN PHARMACEUTICALS

# Male Rat Intruder Model

***SRX246***

# NeuroNext STAIR Study

- **S**afety, **T**olerability, and **A**ctivity in **IR**ritable subjects with HD; Sponsor: NIH/Azevan Pharmaceuticals
- Therapeutic candidate: SRX246
- Mechanism: Vasopressin$_{1A}$ 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

# 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


If you are interested in possible participation in the STAIR study, please call Randev Sandhu at (916)734-4303 or Amanda Martin at (916)734-3514, or e-mail at:

rssandhu@ucdavis.edu

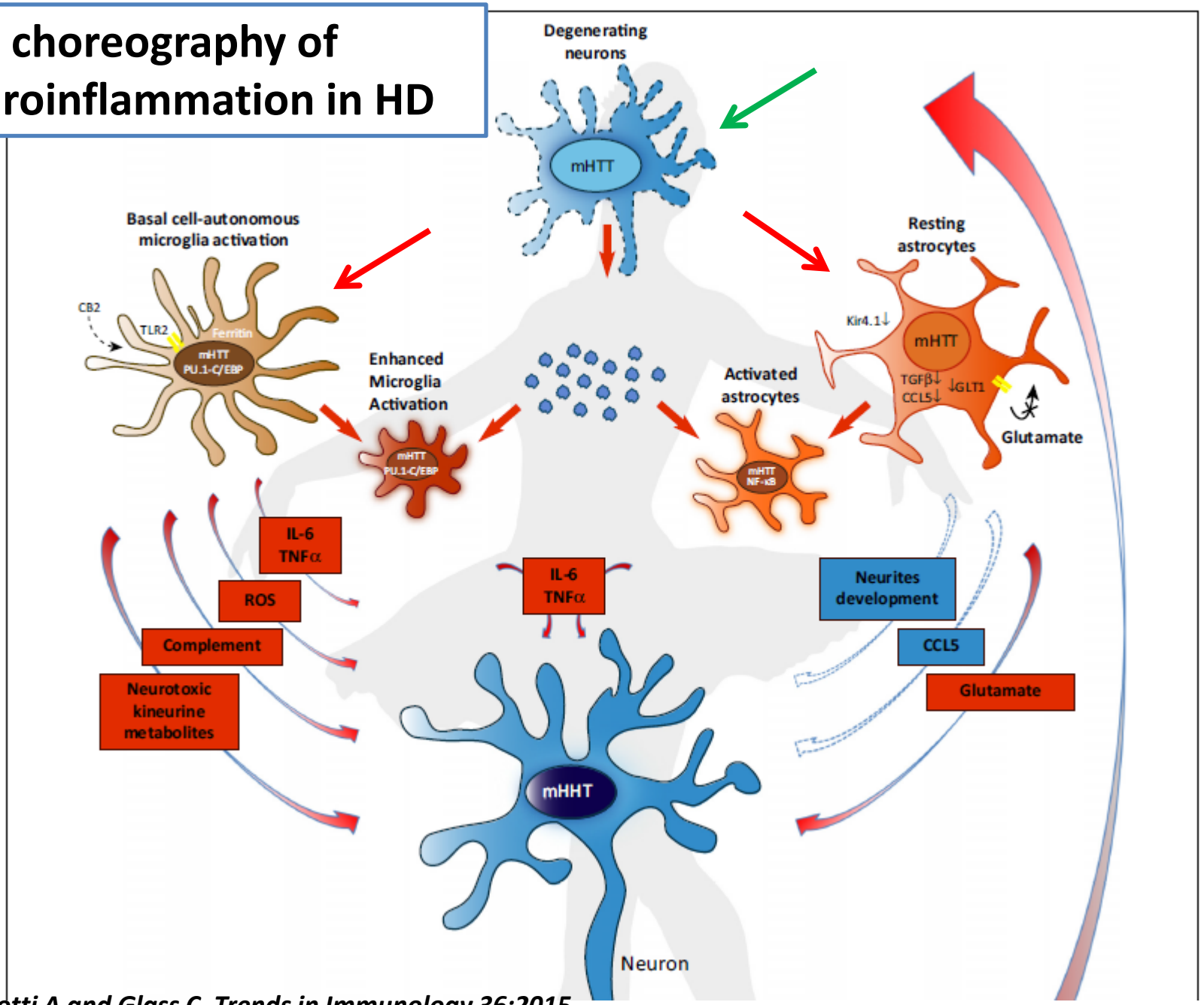
alema@ucdavis.edu

# Progress in disease modifying treatments in HD

Three new lines of research are currently under investigation:

- Immune modulating medications to reduce inflammation
- Stem cell research: Dr. Nolta and CIRM grant
- Gene silencing/editing:
  - Anti-sense oligonucleotide therapy to block production of the mutant HD protein
  - CRISPR/Cas9 and TALEs

# The choreography of neuroinflammation in HD




*Crotti A and Glass C. Trends in Immunology 36;2015*

# LEGATO-HD THE LAQUINIMOD HD STUDY 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

*Closest site: UCSF*

# 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

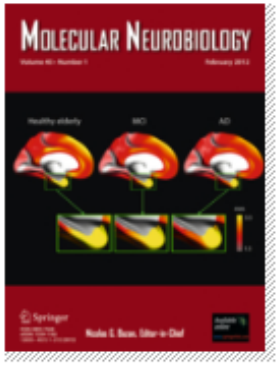
# SIGNAL Study


- 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.

# Stem Cell Research in HD: Partnership between families, researchers and CIRM


2010 – CIRM Spotlight on HD
California State Capitol

CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE


Molecular Neurobiology

Editor-in-Chief: Nicolas G. Bazan

ISSN: 0893-7648 (print version)
ISSN: 1559-1182 (electronic version)

Journal no. 12035

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**

# 2011: Grant application to develop MSC Engineered to produce BDNF as a treatment for HD

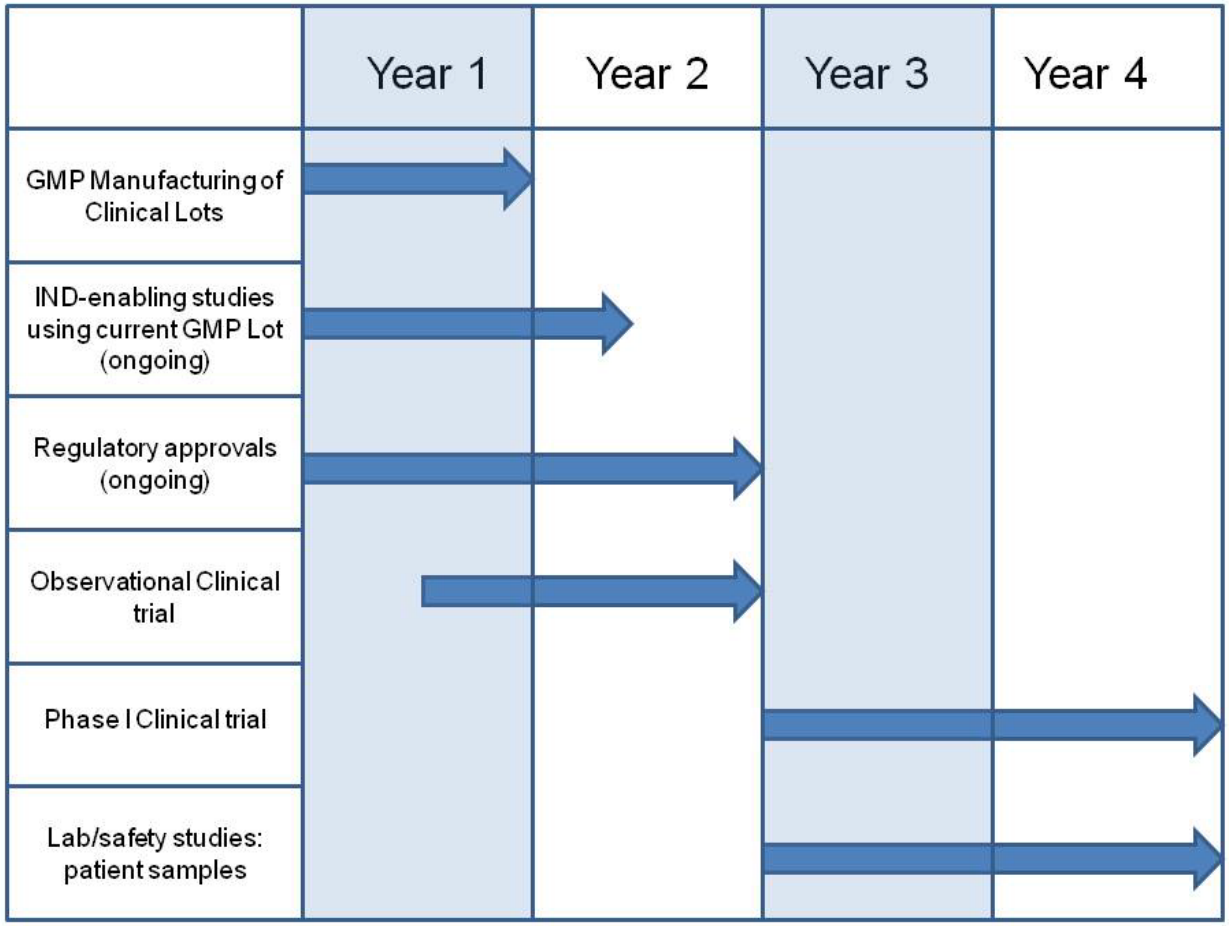
The grant is approved!
July 26, 2012
**CIRM Grant DR2A-05415**

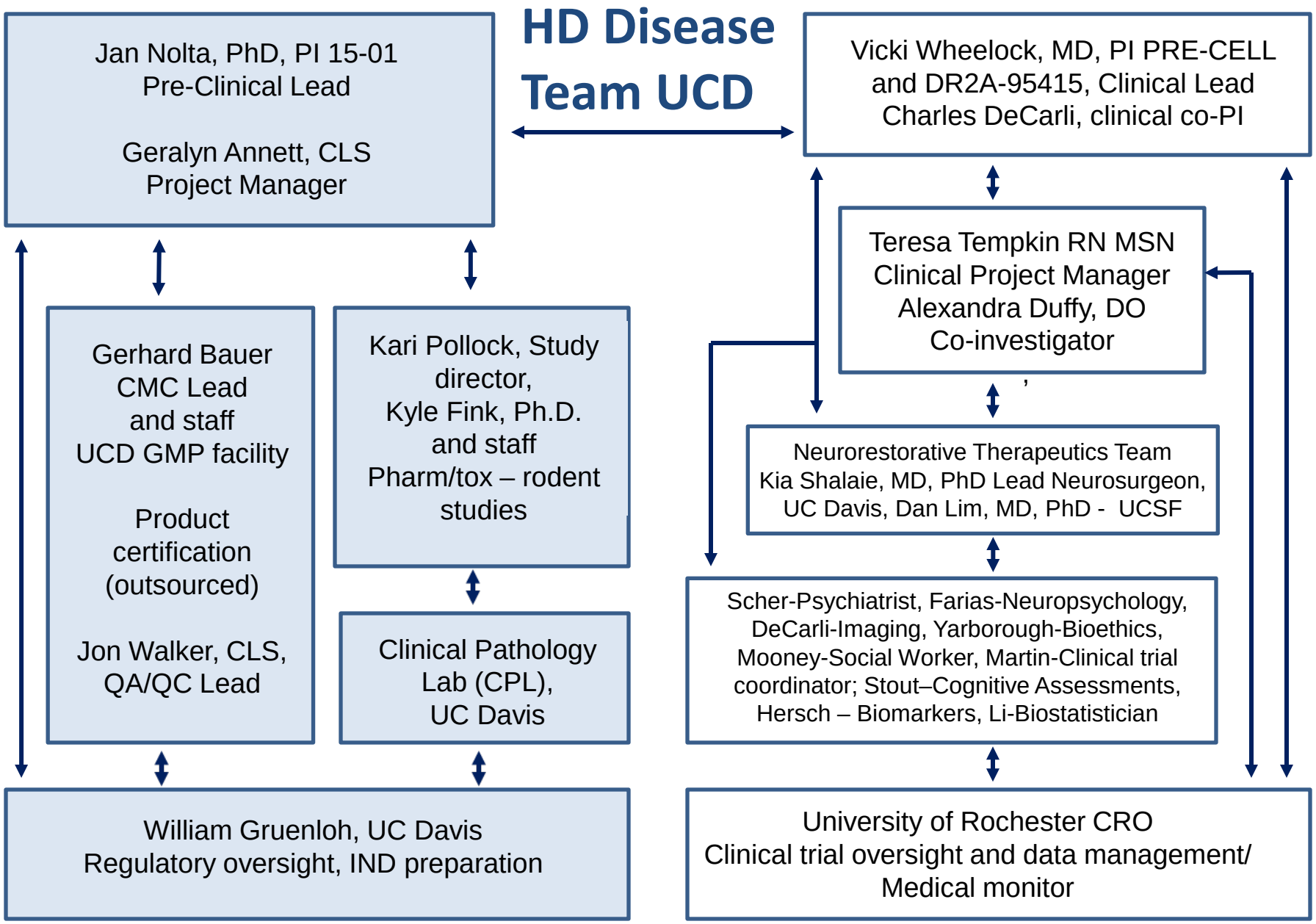
CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

# Project Plan: MSC/BDNF for HD

## CIRM Grant DR2A-05415

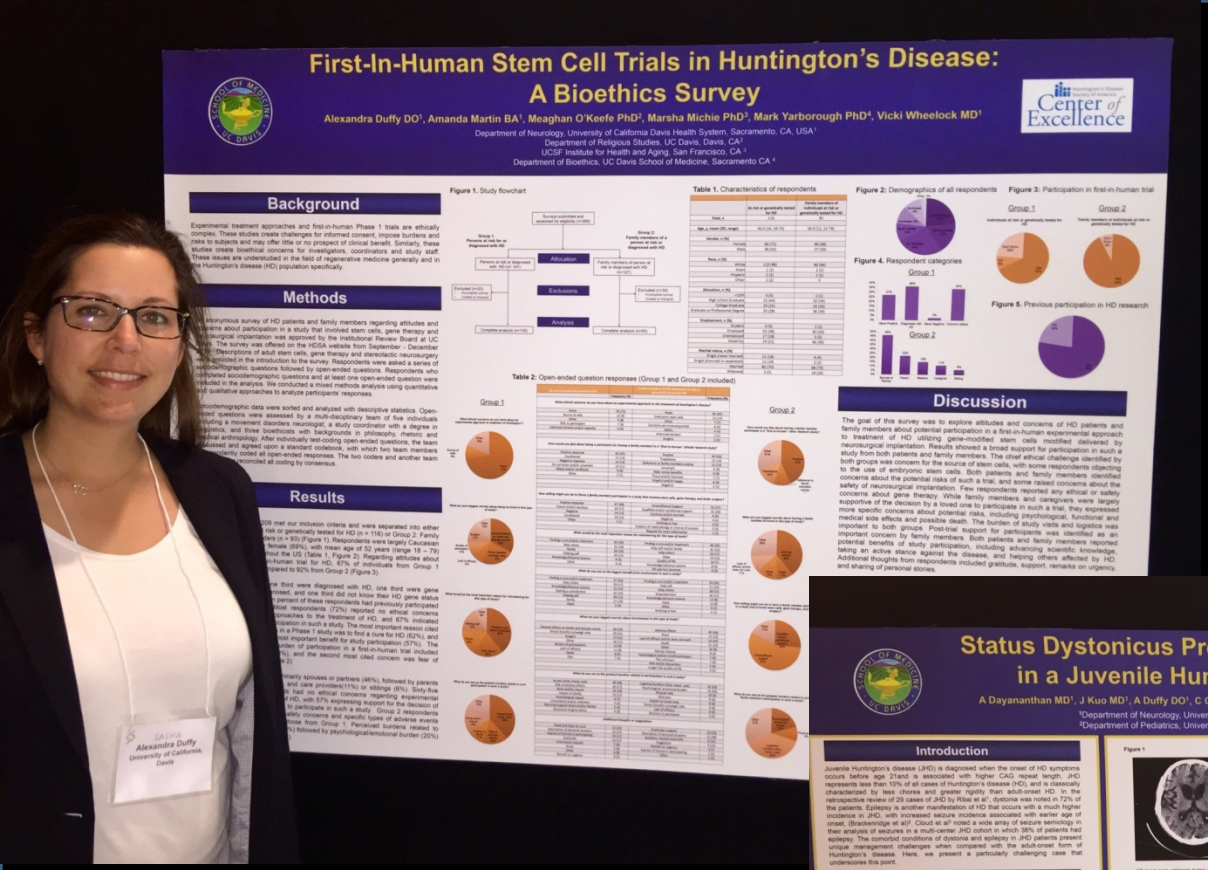
| **PRE-CELL:** Years 1&2 | **HD-CELL**: Years 3&4 |
|---|---|




HD Disease Team UCD
Jan Nolta, PhD, PI 15-01
Pre-Clinical Lead
Geralyn Annett, CLS
Project Manager
Vicki Wheelock, MD, PI PRE-CELL and DR2A-95415, Clinical Lead
Charles DeCarli, clinical co-PI
Teresa Tempkin RN MSN
Clinical Project Manager
Alexandra Duffy, DO
Co-investigator
Gerhard Bauer
CMC Lead
and staff
UCD GMP facility
Product certification (outsourced)
Jon Walker, CLS,
QA/QC Lead
Kari Pollock, Study director,
Kyle Fink, Ph.D.
and staff
Pharm/tox – rodent studies
Clinical Pathology Lab (CPL),
UC Davis
Neurorestorative Therapeutics Team
Kia Shalaie, MD, PhD Lead Neurosurgeon,
UC Davis, Dan Lim, MD, PhD - UCSF
Scher-Psychiatrist, Farias-Neuropsychology, DeCarli-Imaging, Yarborough-Bioethics, Mooney-Social Worker, Martin-Clinical trial coordinator; Stout–Cognitive Assessments, Hersch – Biomarkers, Li-Biostatistician
William Gruenloh, UC Davis
Regulatory oversight, IND preparation
University of Rochester CRO
Clinical trial oversight and data management/
Medical monitor

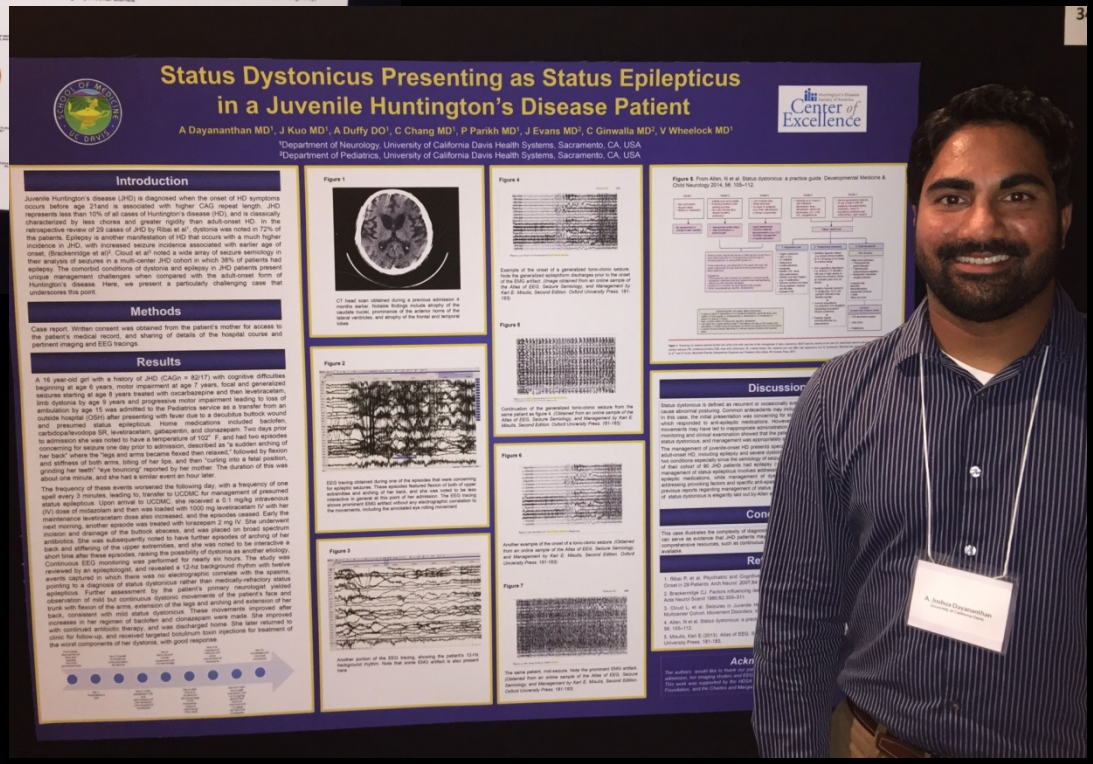
# PRE-CELL Study

- 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.
- Goal: to establish baseline characteristics and the rate of change in clinical, imaging and exploratory biomarker measures over 12 – 30 months.
- Study subjects: adults with early-stage HD, psychiatrically and medically stable, have no contraindications MRI or neurosurgical procedures, evaluated every 6 months.

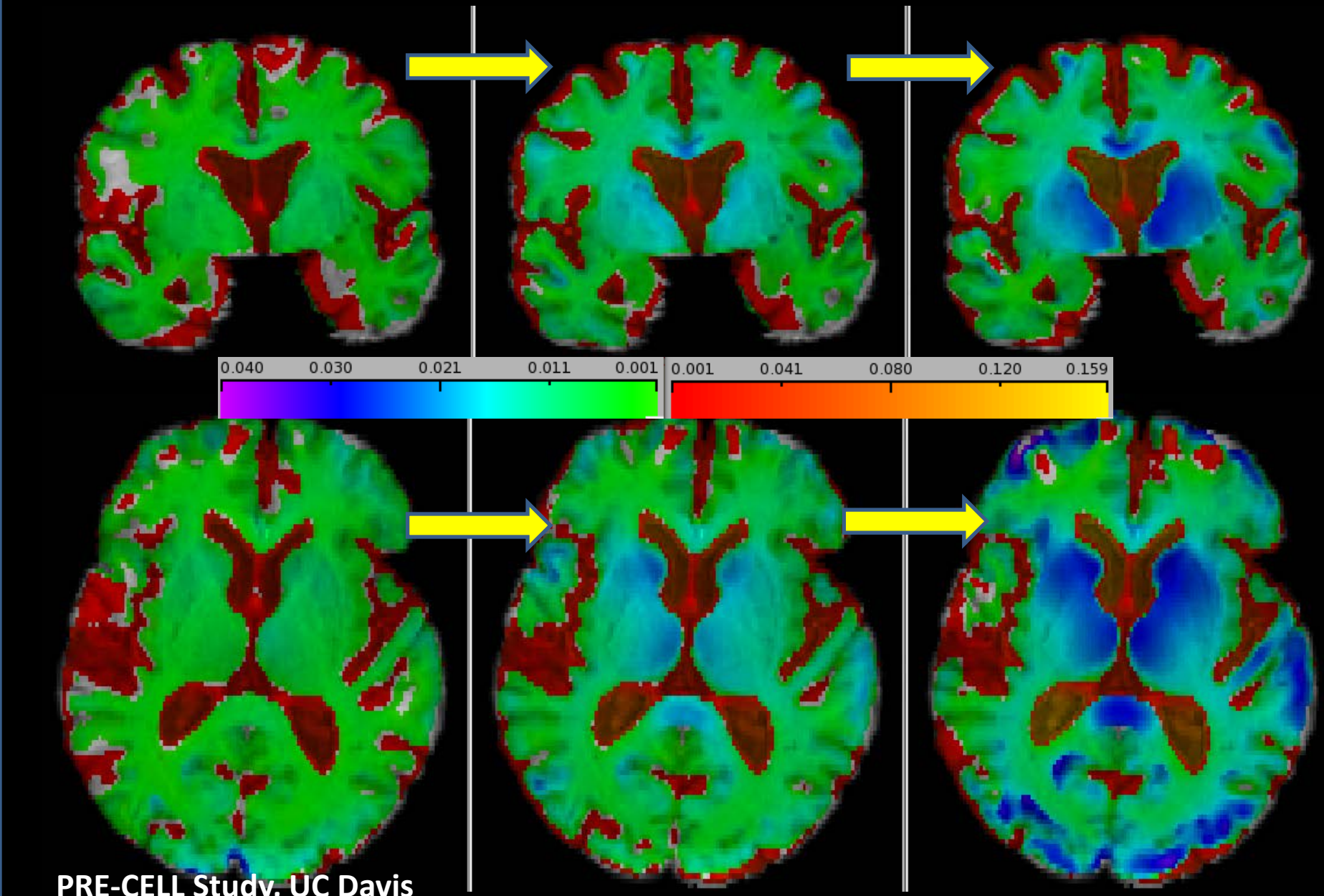



Dr. Sasha Duffy, Assistant Clinical Professor of Neurology, UC Davis

Dr. Ashok Joshua Dayananthan Assistant Clinical Professor of Neurology, UC Davis



# Cross sectional Percentage Change Magnitude Images




PRE-CELL Study, UC Davis

# PRE-CELL Biomarkers

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

BDNF
Mutant Huntingtin Protein

# We extend our sincerest gratitude to PRE-CELL subjects and care partners

# 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

Molecular Therapy

*Results of pre-clinical studies*

Official journal of the American Society of Gene & Cell Therapy

MT Open

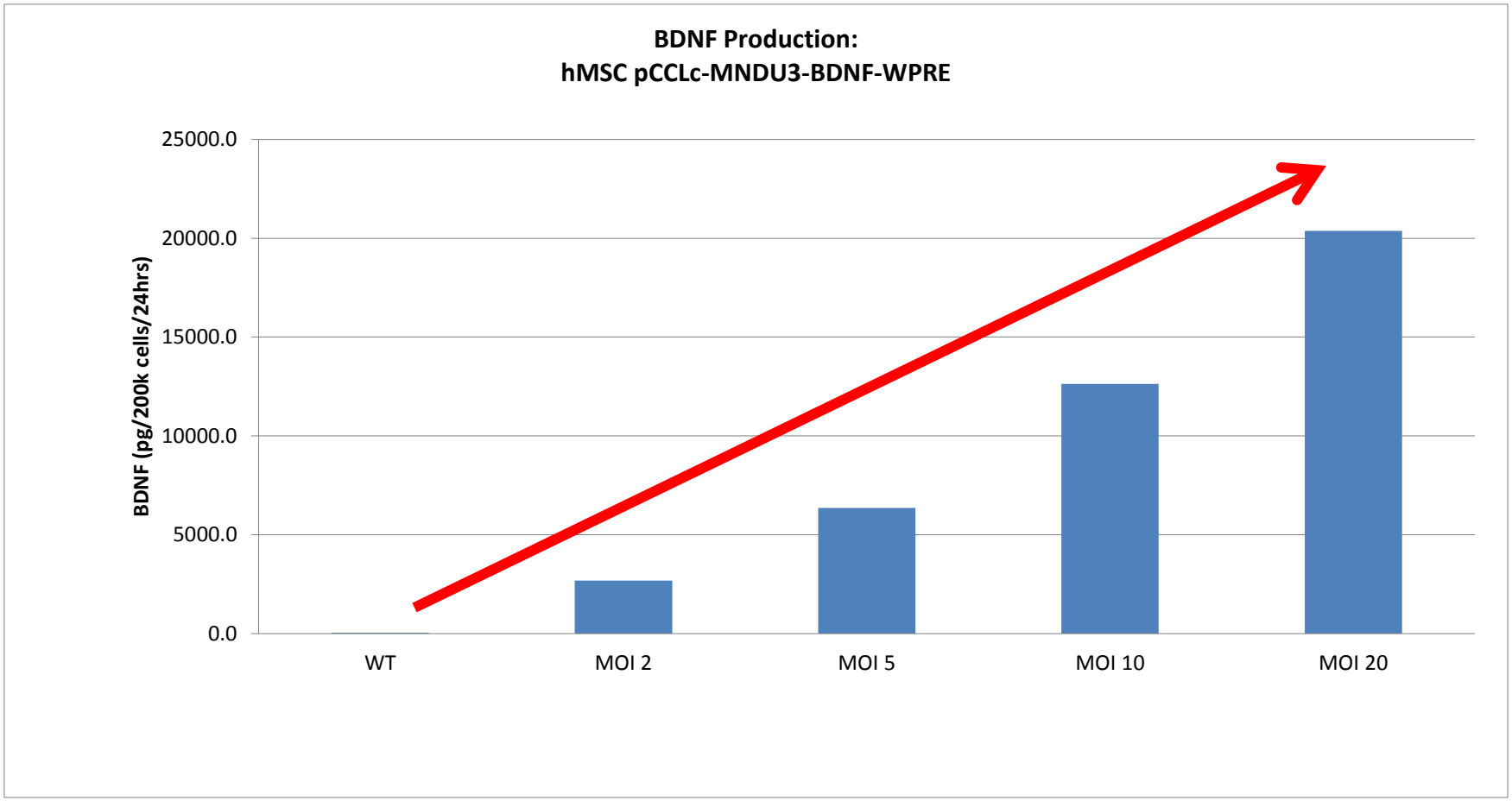
original article

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

Kari Pollock[1], Heather Dahlenburg[1], Haley Nelson[1], Kyle D Fink[1], Whitney Cary[1], Kyle Hendrix[1], Geralyn Annett[1], Audrey Torrest[1], Peter Deng[1], Joshua Gutierrez[1], Catherine Nacey[1], Karen Pepper[1], Stefanos Kalomoiris[1], Johnathon D Anderson[1], Jeannine McGee[1], William Gruenloh[1], Brian Fury[1], Gerhard Bauer[1], Alexandria Duffy[2], Theresa Tempkin[2], Vicki Wheelock[2] and Jan A Nolta[1]

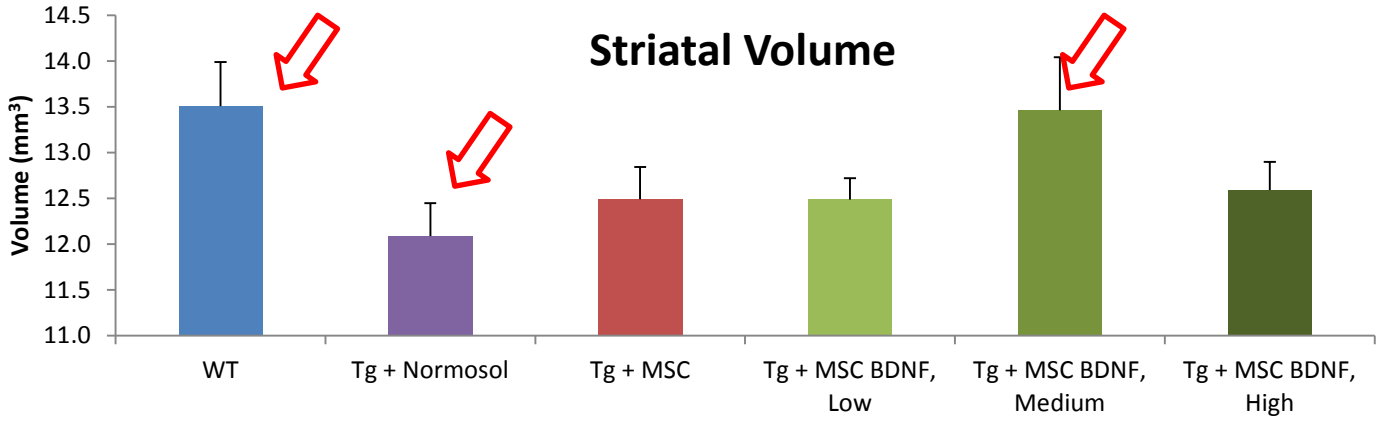
*[1]Stem Cell Program and Institute for Regenerative Cures, University of California Davis Health System, Sacramento, California, USA; [2]Department of Neurology, University of California Davis Health System, Sacramento, California, USA*

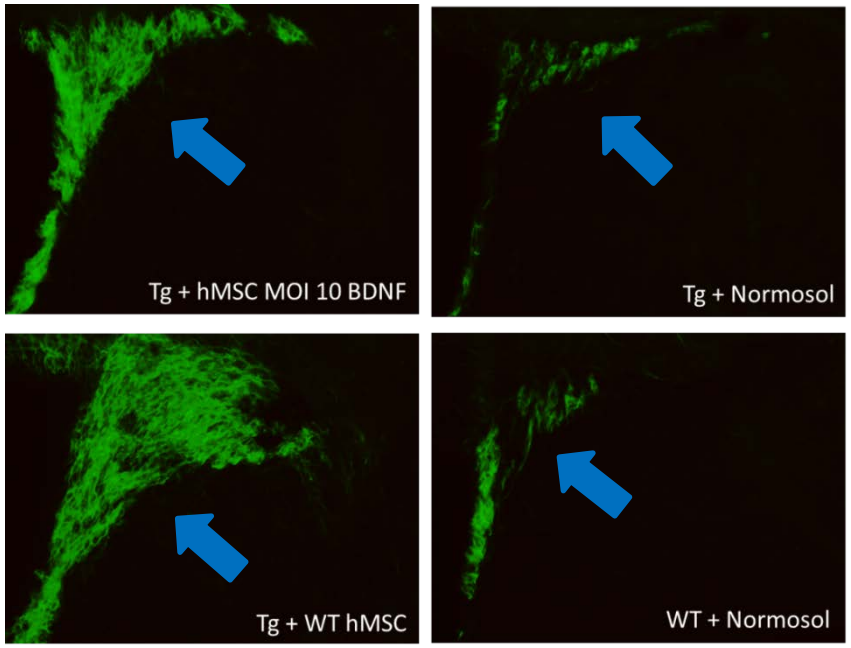
# BDNF production by the engineered MSCs



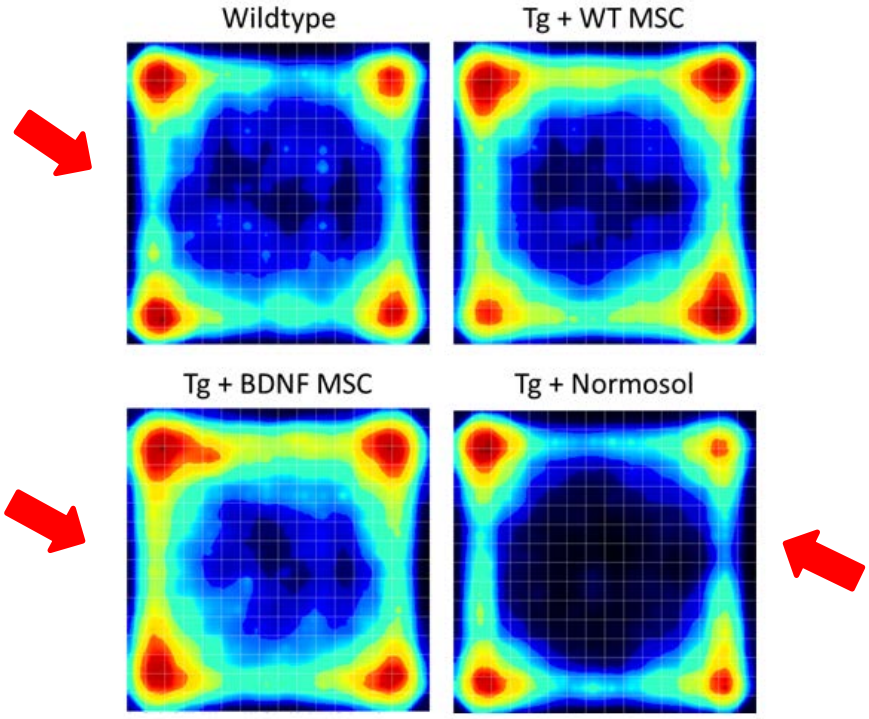

**BDNF Production:** Human MSCs were transduced with the lentiviral vector pCCLc-MNDU3-BDNF-WPRE at the indicated Multiplicity of infection (MOI). Increasing the MOI increases the amount of BDNF produced.

# HD Mouse Studies: treated with MSC/BDNF



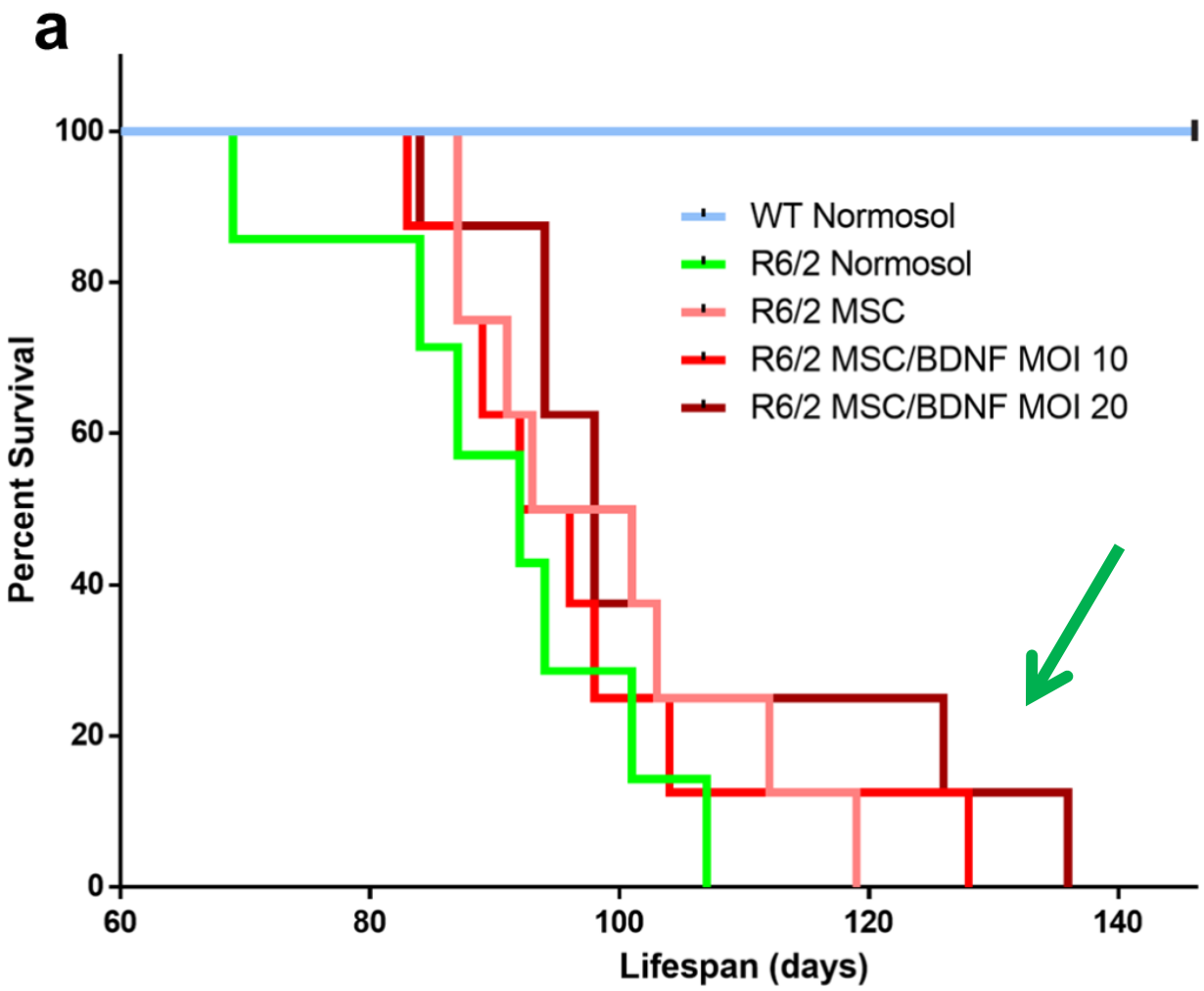



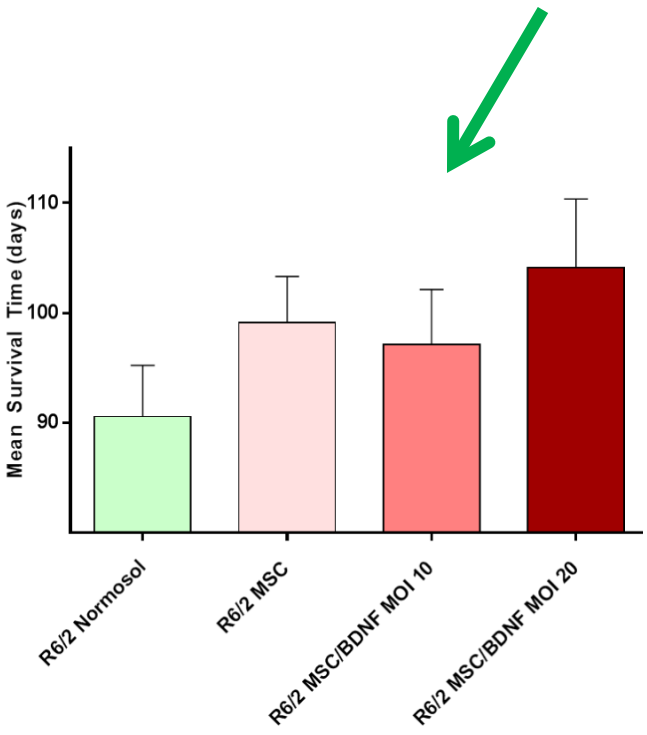

**Neurogenesis studies**




**Open Field Testing**

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




**10% increase for WT MSC, 7.7% increase for MSC BDNF MOI 10, 15.5% increase for MSC BDNF MOI 20.**

CIRM grant ended fall 2016; HD-CELL trial not started.

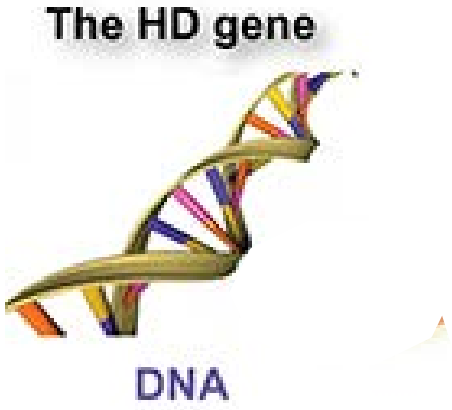
Additional pre-clinical studies are needed in HD mouse models and a large animal model before our team will be ready to apply for approval from the FDA to take MSC/BDNF treatment forward into patients.

***May 2017 Update: Dr. Nolta and Dr. Kyle Fink receive major 5 year NIH grant to continue to develop MSCs as a potential treatment for HD.***

# Thank you Dr. Kyle Fink!

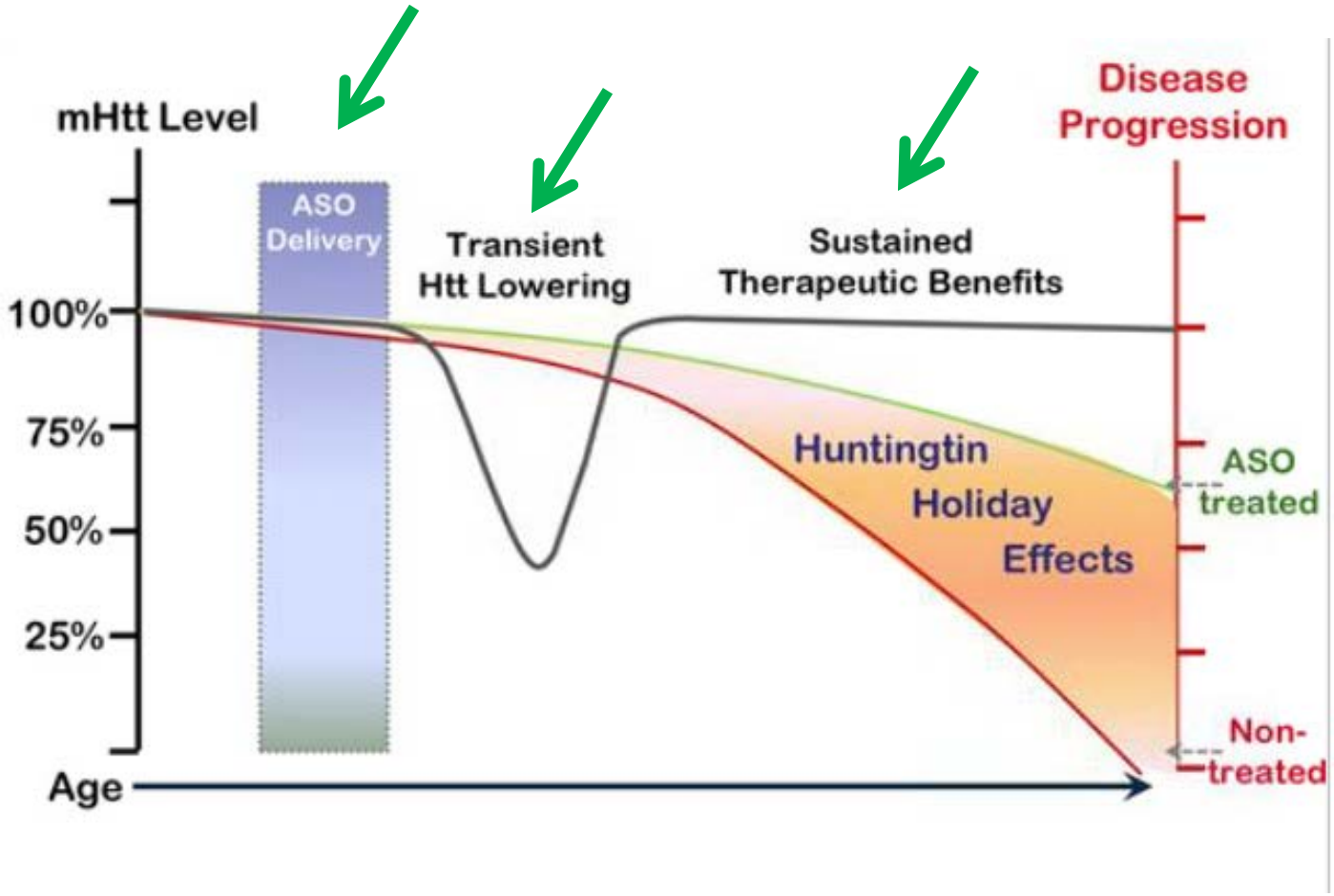
# Anti-sense oligonucleotides (ASOs)

- These are single-stranded DNA building block sequences that are designed to target specific messenger RNA that are complementary
- Once targeted, the RNA part of the DNA/RNA duplex is destroyed by an enzyme
- The ASO can then be recycled to act again and again.




https://en.hdbuzz.net/204

# “Huntingtin Holiday”




Lu XH and Yang XW. *Neuron* 2012;74(6): 964–966.

# Proof of concept in HD mouse models

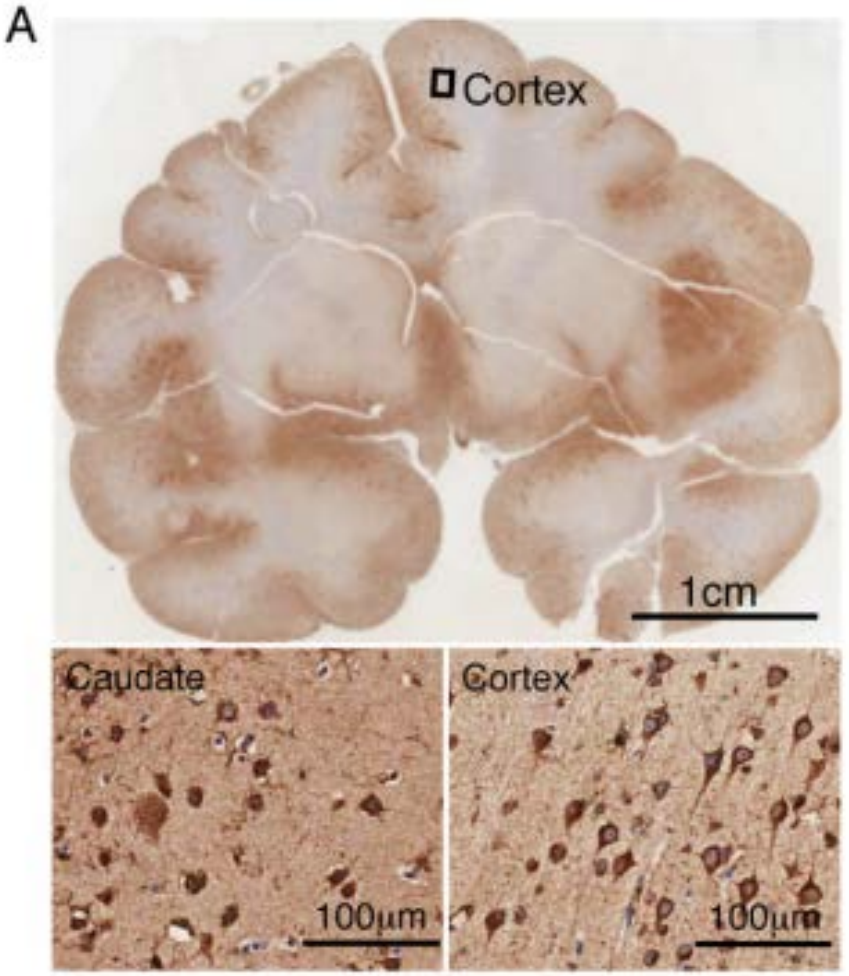
- R6/2 mouse (*similar to Juvenile HD*):
  - 4 week intraventricular infusion lowered mutant huntingtin protein levels by 60%, reduced brain shrinkage and prolonged survival.

- YAC128 mouse (*similar to adult HD*)
  - 2 week ASO infusion lowered mutant huntingtin protein levels by 80%, improved motor performance on rotarod, at 3 months but not at 6 months.

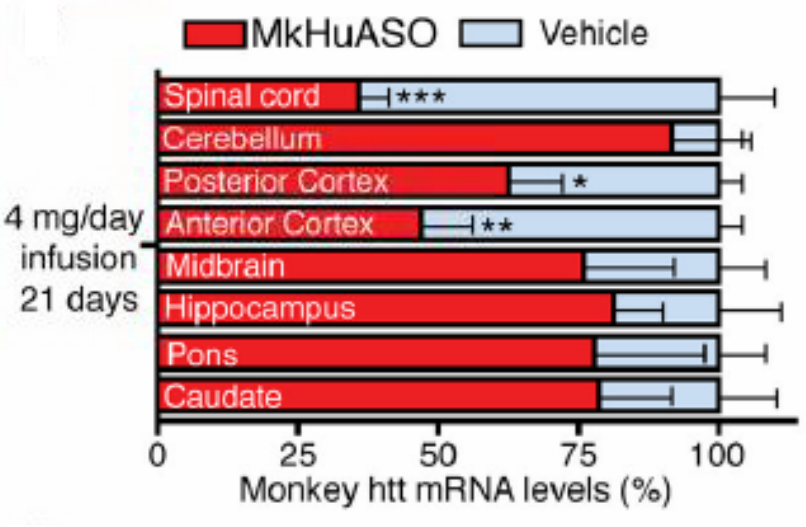
- BACHD mouse (*similar to adult HD*)
  - 2 week infusion at 6 months improved rotarod and open field exploration at 8 – 15 months, but did not rescue striatal atrophy or neuropathology changes.

Kordasiewicz H et al. *Neuron* 2012;74(6): 1031–1044

# ASO treatment in Rhesus monkey




- Rhesus monkey brain 180x larger than mouse, brain and 1/15$^{th}$ of human brain size.
- ASO given via spinal tap
- Mutant HTT was reduced in some brain areas (cortex) but not others (caudate)

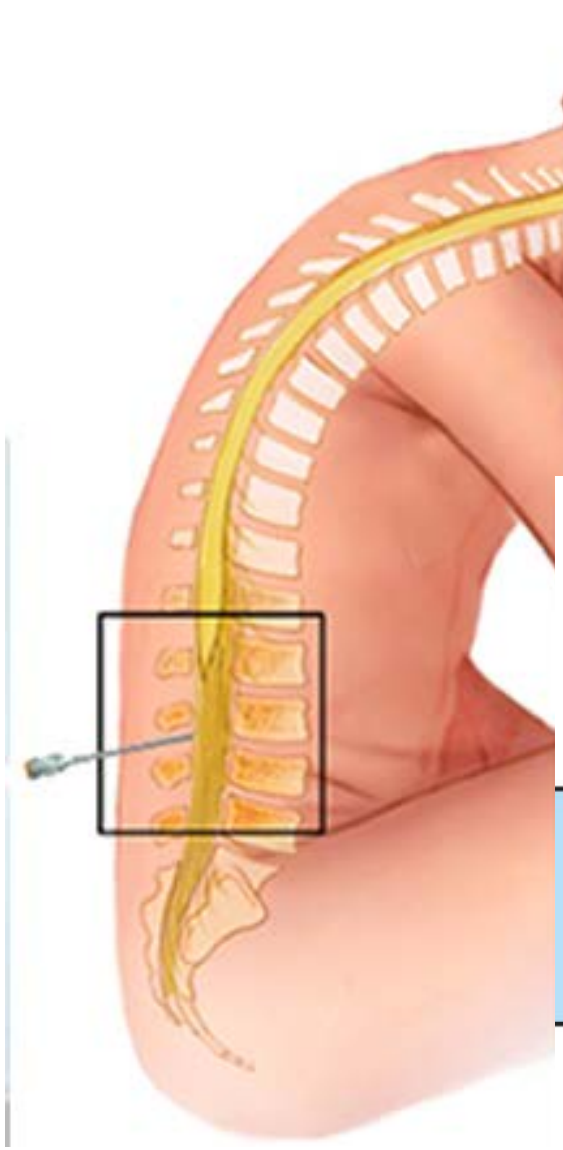


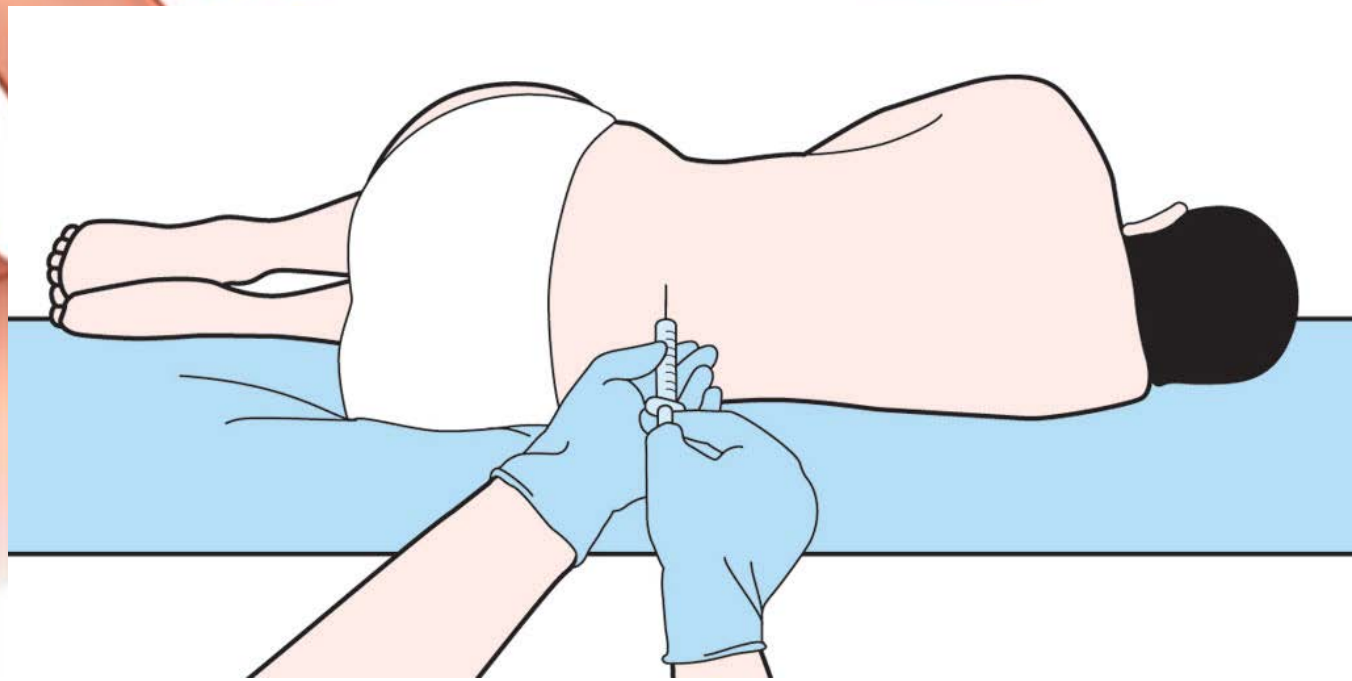

Kordasiewicz H et al. *Neuron* 2012;74(6): 1031–1044

# IONIS-HTT$_{Rx}$ trial

- Title: Safety, tolerability, pharmacokinetics, and pharmacodynamics of IONIS-HTT$_{Rx}$ in patients with early manifest Huntington's disease.
- Sponsor: IONIS Pharmaceuticals, in partnership with Roche Pharmaceuticals and CHDI
- Phase 1 randomized, placebo-controlled, double-blinded study to evaluate the safety and tolerability of ascending doses of IONIS-HTT$_{Rx}$ administered in 4 monthly intrathecal injections over a 13-week period.
- The study is being conducted in Canada and the UK.
- Planned enrollment is 36.

# Intra-thecal delivery: spinal tap



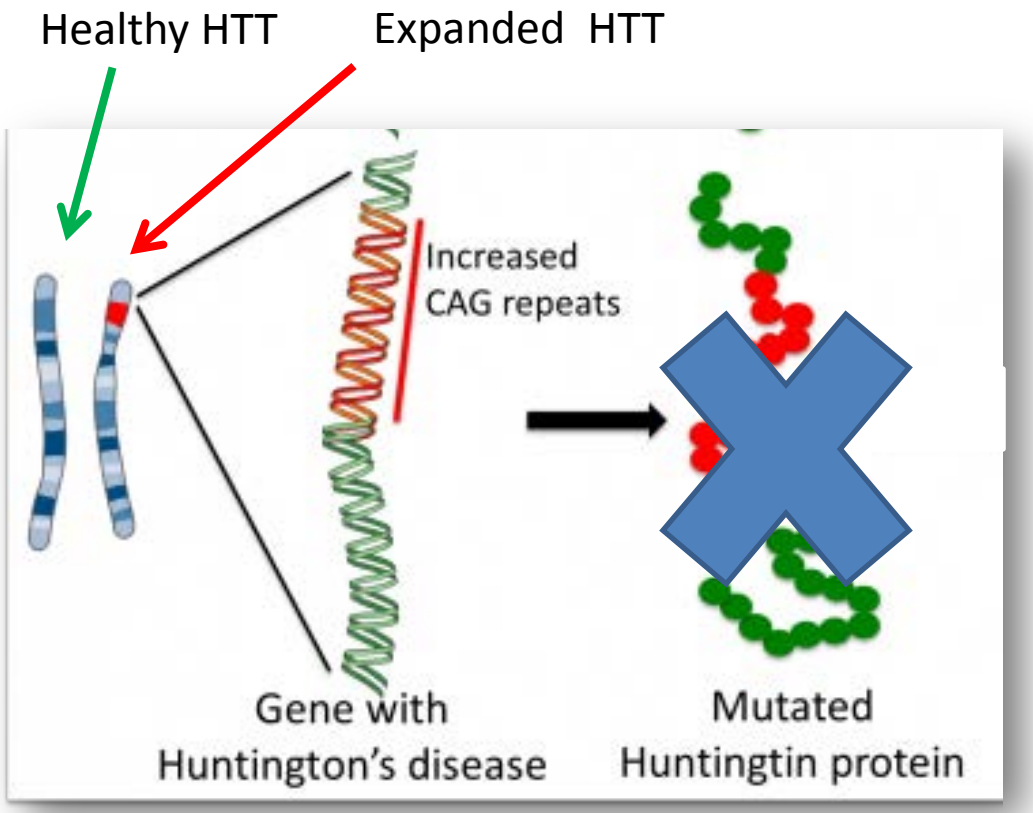


# Comments

- In a 2016 commentary about molecular genetic therapeutics in HD, Dr. Ira Shoulson raised questions about allele-specificity, 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 this historic trial.

# A new approach: Allele-specific ASO


In most HD patients, there are tiny genetic differences called SNPs in the huntingtin gene outside of the CAG repeat expansion region that can allow scientists to target ONLY the expanded huntingtin mRNA, leaving the health "wild-type" huntingtin mRNA unaffected.

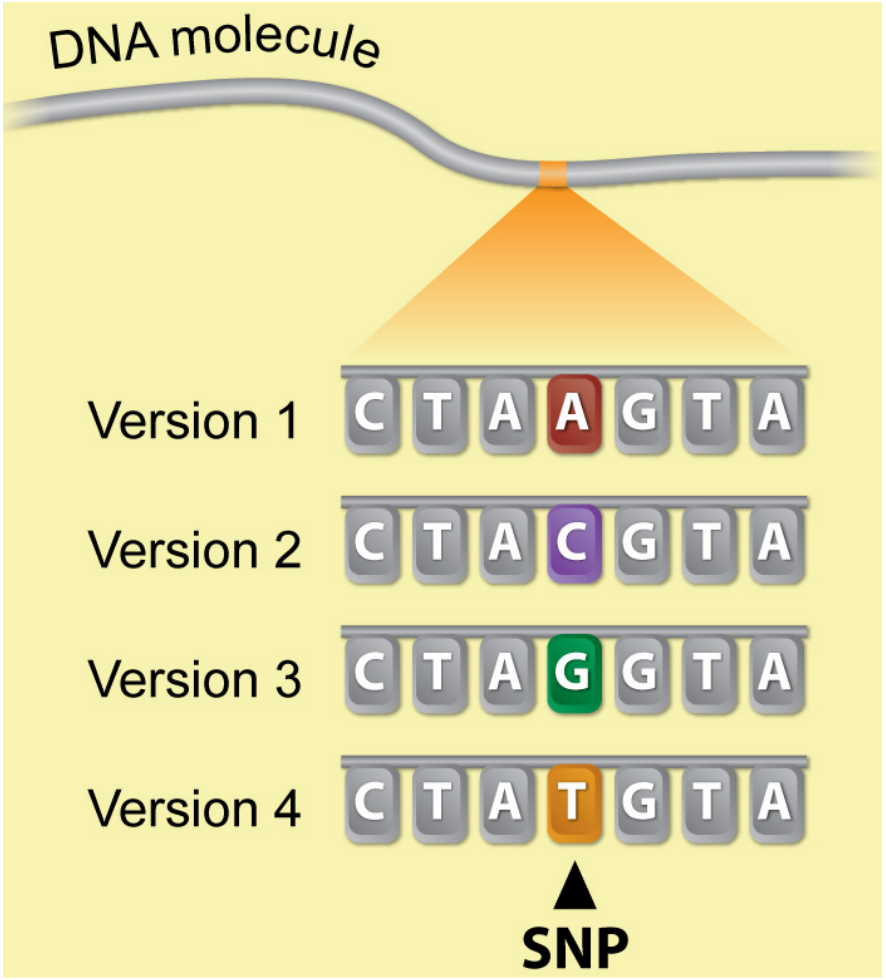



This approach may have less toxicity.

# Introduction to a new acronym: SNP

Single Nucleotide Polymorphism, pronounced "snip"

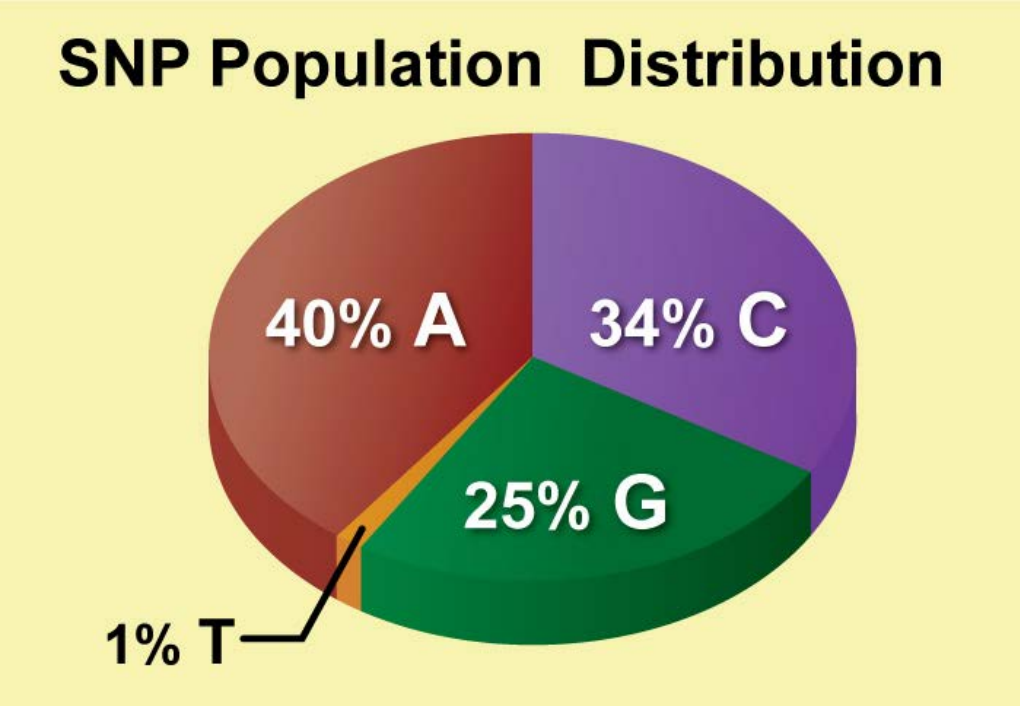
SNPs are single-nucleotide substitutions of one base for another. Each SNP location in the genome can have up to four versions: one for each nucleotide, A, C, G, and T.




http://learn.genetics.utah.edu/content/precision/snips

# Not all single-nucleotide changes are SNPs

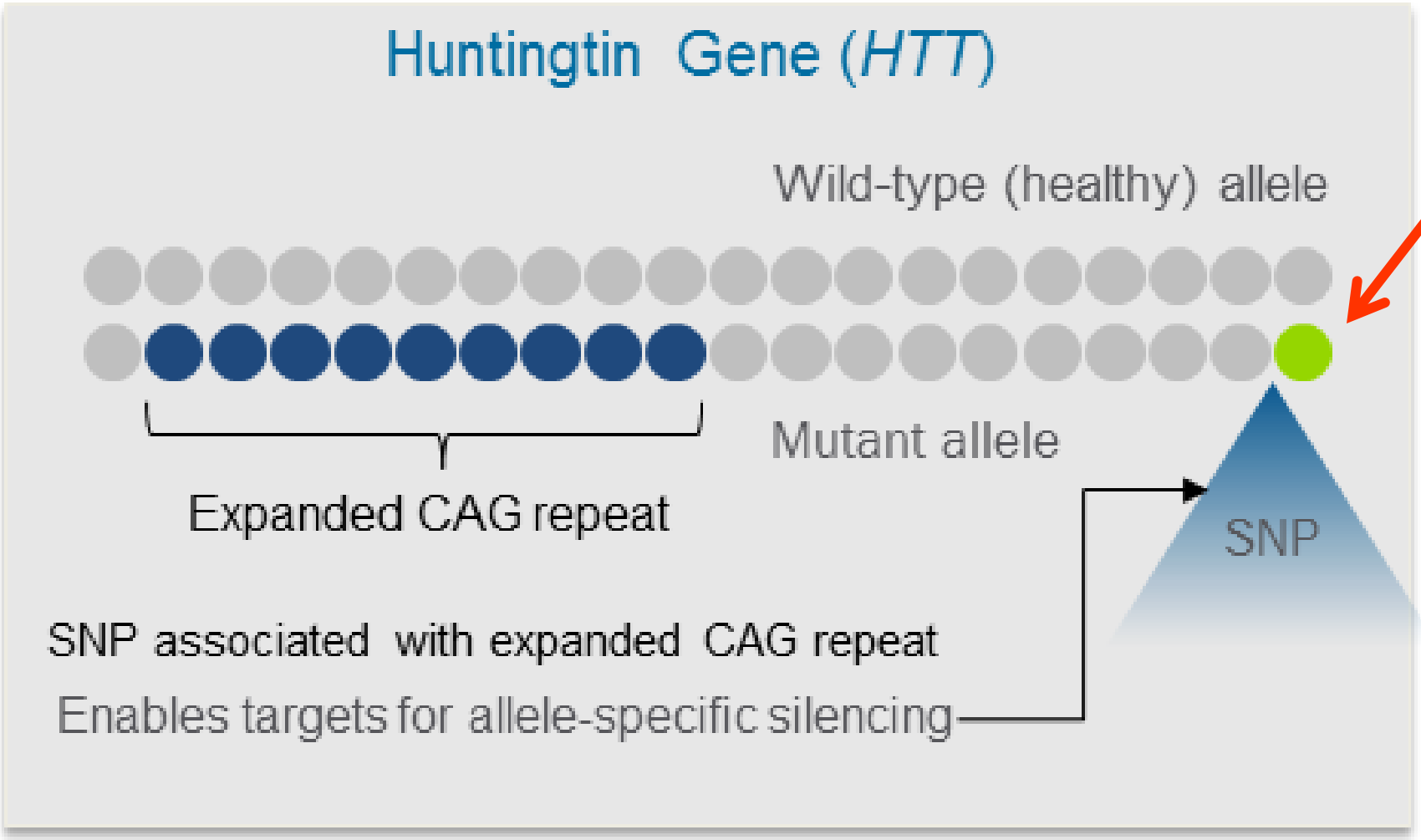
To be classified as a SNP, two or more versions of a sequence must each be present in at least one percent of the general population.




SNPs occur throughout the human genome: about one in every 300 nucleotide base pairs. This translates to about 10 million SNPs within the 3-billion-nucleotide human genome.

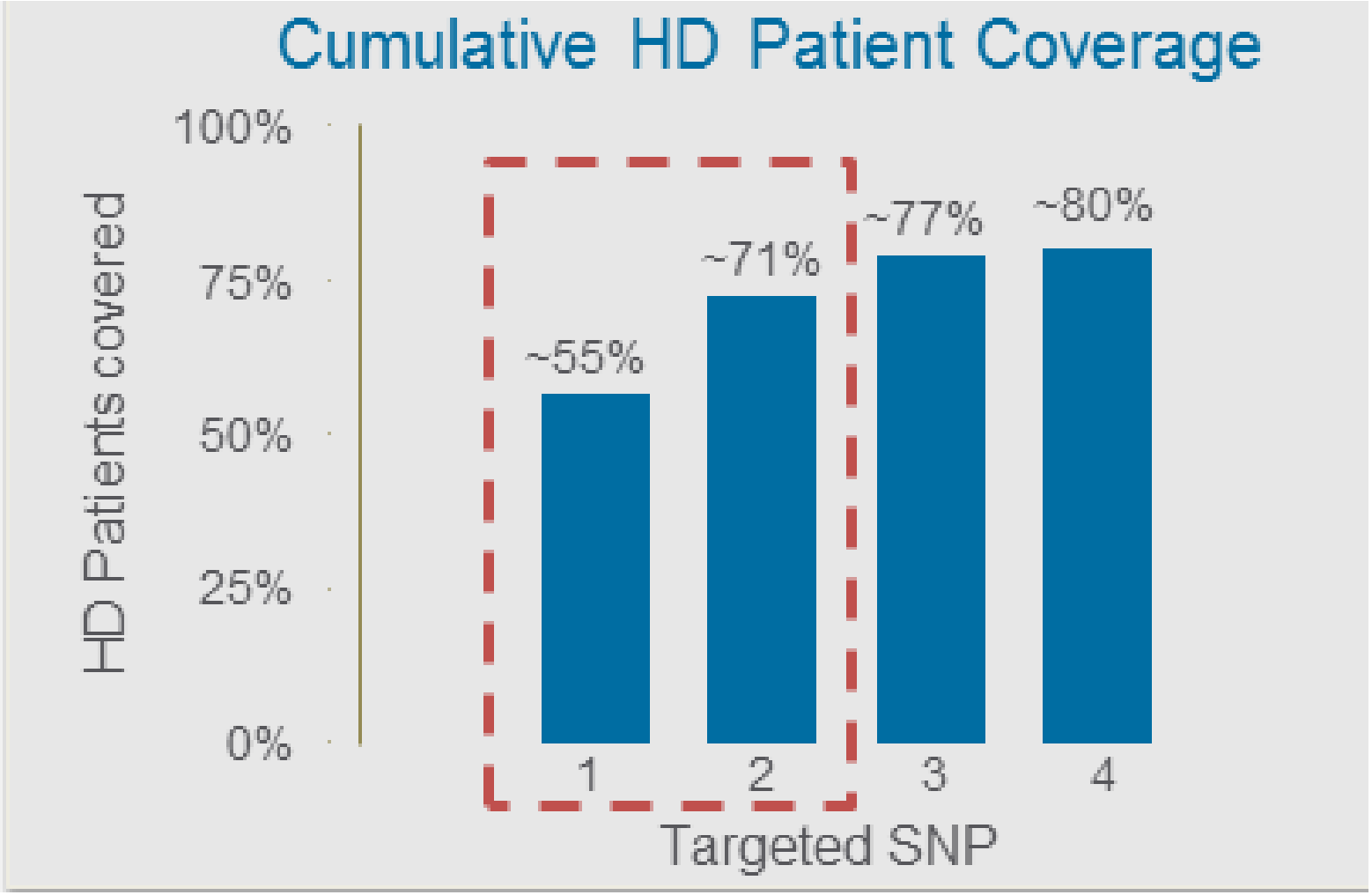
**http://learn.genetics.utah.edu/content/precision/snips**

# Taking advantage of SNPs: Allele-specific ASO




*Courtesy Dr. Michael Panzara, WAVE Life Sciences*

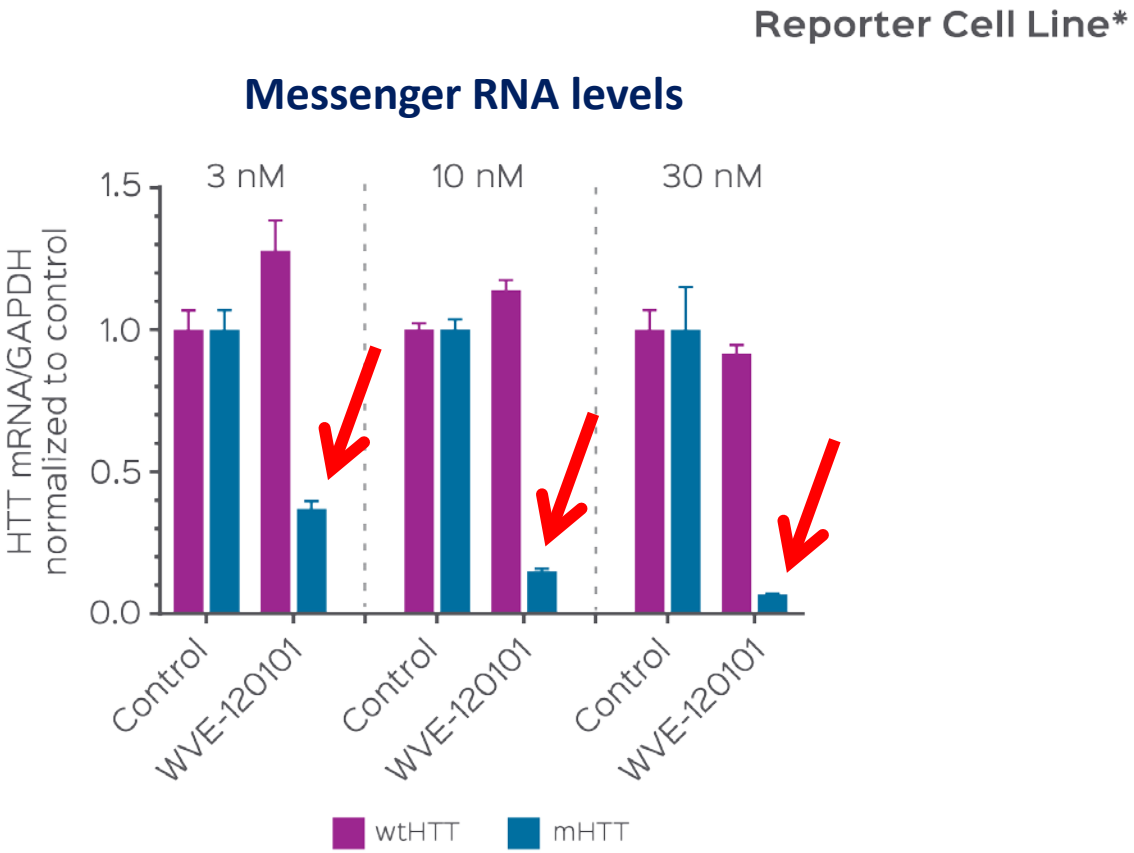
# HD SNP1 and SNP2 are found in about 2/3$^{rds}$ of HD patients




*Courtesy Dr. Michael Panzara, WAVE Life Sciences*

# Huntington's Disease

## WVE-120101 Selectively Reduces mHTT mRNA and Protein




*These results were replicated in a patient-derived cell line

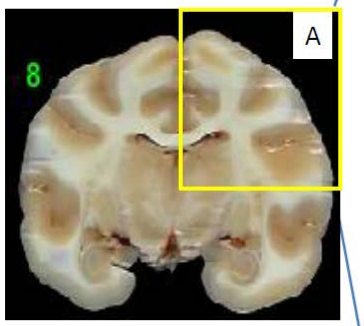
*Courtesy Dr. Michael Panzara, WAVE Life Sciences*

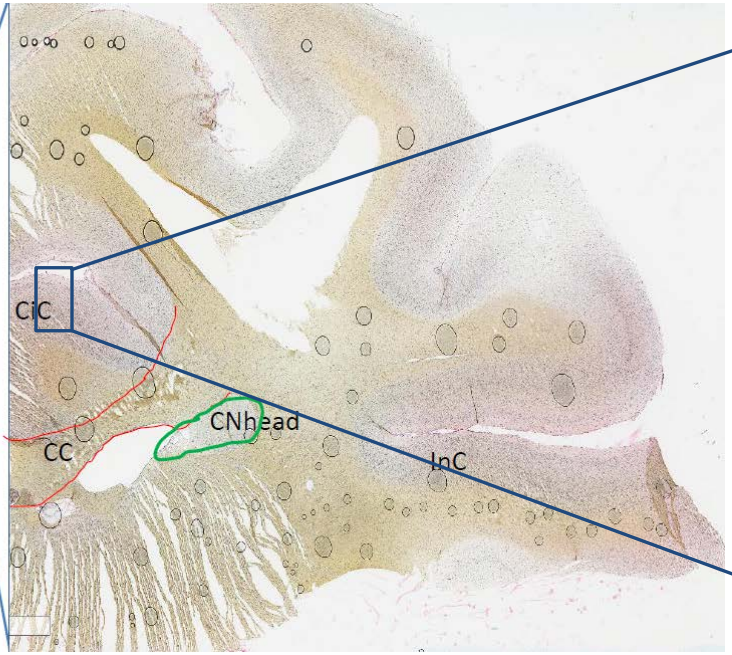
# Huntington's Disease

## Distribution of WVE-120101 in Cynomolgus NHP Brain

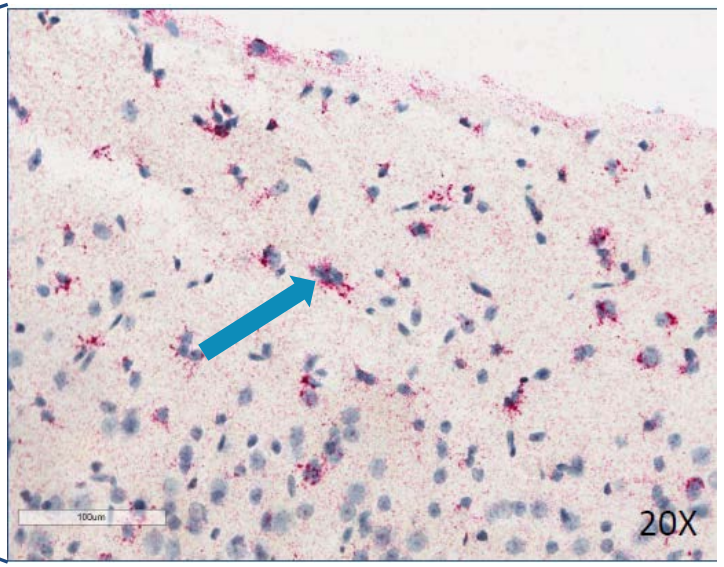
- Stereochemistry enables improved protein binding and distribution
- ViewRNA depicting perinuclear distribution of WVE-120101 (red) in non-human primate (NHP) deep gray matter structures following intrathecal administration
- WVE-120101 detectable in deep gray matter structures following intrathecal administration

Animal # 42, Slice 8




*In Situ* Hybridization ViewRNA stained tissue




Red dots are WVE-120101. Arrow points to nuclear and perinuclear distribution of WVE-120101 in deep gray matter structures

*Courtesy Dr. Michael Panzara, WAVE Life Sciences*

# Huntington's Disease

## Clinical Trial Design for WVE-120101 and WVE-120102

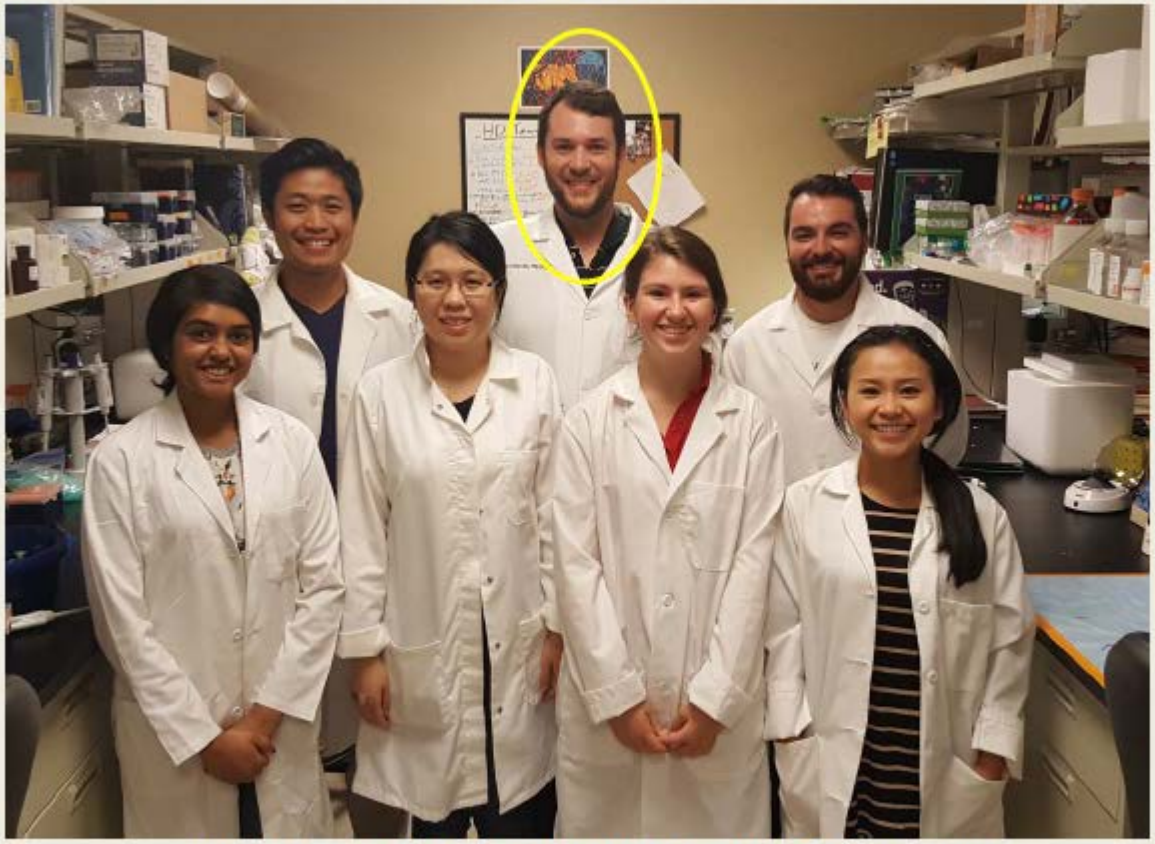
- First-in-patient dosing for both WVE-120101 (SNP-1) and WVE-120102 (SNP-2) trials expected mid-year 2017
- Two parallel global placebo-controlled trials targeting SNP-1 and SNP-2, respectively
- Primary Objective: Assess safety and tolerability of intrathecal doses in early manifest HD patients
- Additional Objectives: Exploratory pharmacokinetic, pharmacodynamic, clinical and MRI endpoints
- Patient SNP determination (SNP-1, SNP-2, other) at pre-screening visit
- Approximately 60 patients per trial
- Key inclusion criteria: Age ≥25 to ≤65, Stage I or Stage II Huntington's disease

*Courtesy Dr. Michael Panzara, WAVE Life Sciences*


UCDAVIS
HEALTH

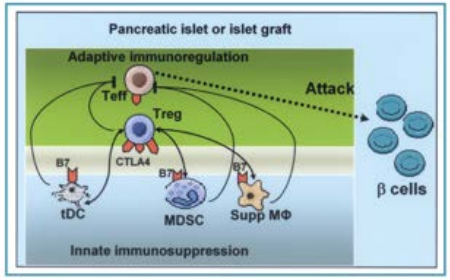
# Genome editing with CRISPR, TALEs and others

**JHD Gene Editing Team Led by Dr. Kyle Fink**



Funding: Help4HD, NIH NINDS NRSA fellowship,
Team KJ, Pharm T32 Grant, CIRM Bridges training program
Philanthropic donors from the HD community, Dake Foundation

CELL TRANSPLANTATION
The Regenerative Medicine Journal



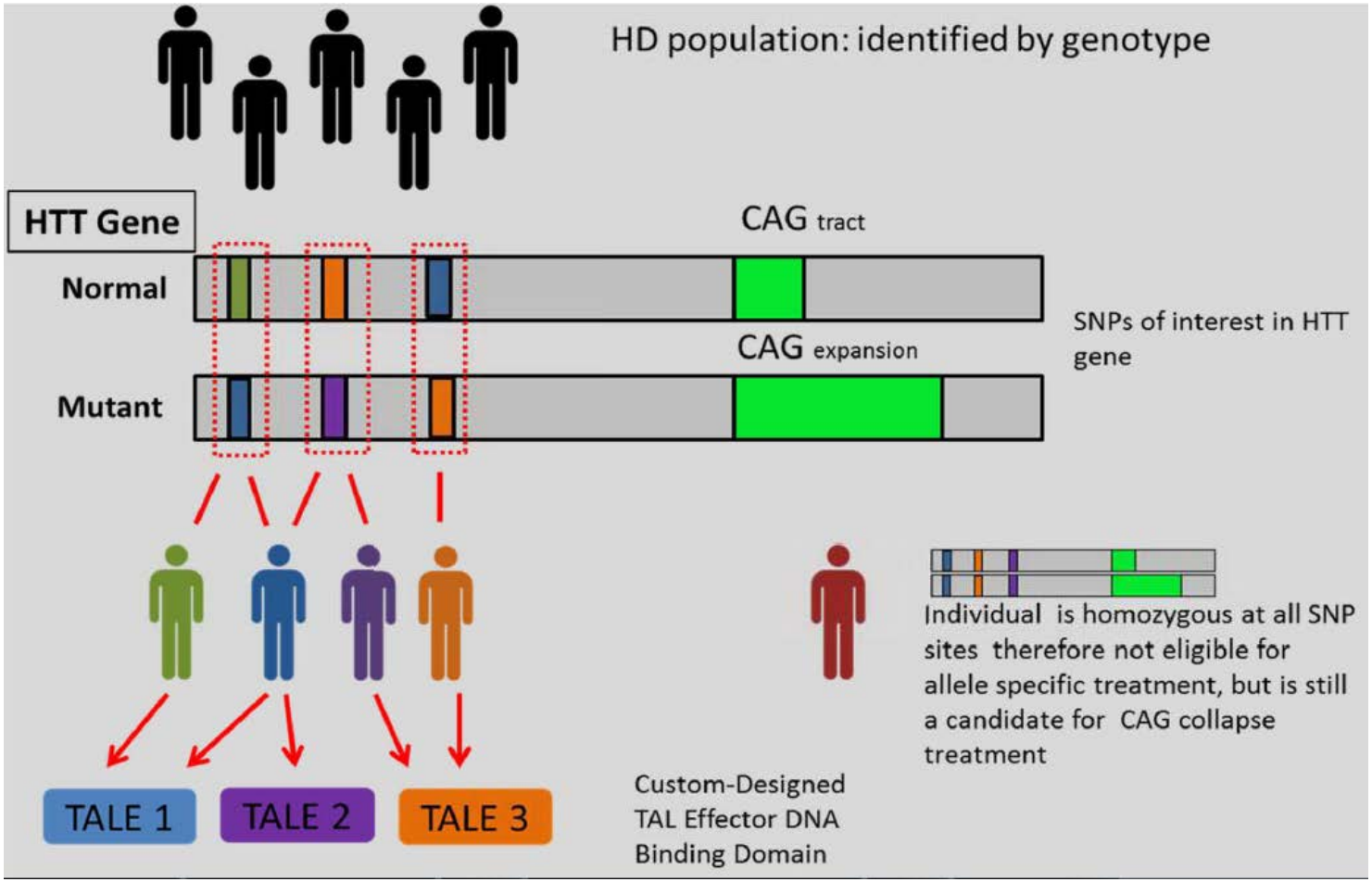

0963-6897/16 $90.00 + .00
DOI: http://dx.doi.org/10.3727/096368916X690863
E-ISSN 1555-3892
www.cognizantcommunication.com

# Allele-Specific Reduction of the Mutant Huntingtin Allele Using Transcription Activator-Like Effectors in Human Huntington's Disease Fibroblasts

Kyle D. Fink,* Peter Deng,*† Josh Gutierrez,* Joseph S. Anderson,* Audrey Torrest,* Anvita Komarla,*† Stefanos Kalomoiris,* Whitney Cary,* Johnathon D. Anderson,* William Gruenloh,* Alexandra Duffy,‡ Teresa Tempkin,‡ Geralyn Annett,* Vicki Wheelock,‡ David J. Segal,† and Jan A. Nolta*

*Stem Cell Program and Institute for Regenerative Cures, University of California Davis Health Systems, Sacramento, CA, USA
†Genome Center, MIND Institute, and Biochemistry and Molecular Medicine, University of California, Davis, CA, USA
‡Department of Neurology, University of California Davis Health Systems, Sacramento, CA, USA

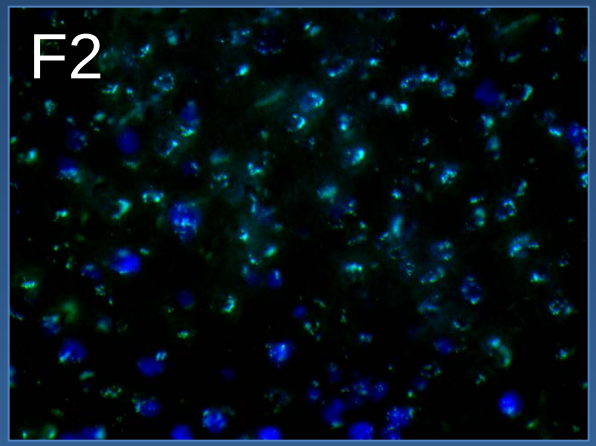
# Potential applications to the HD patient population

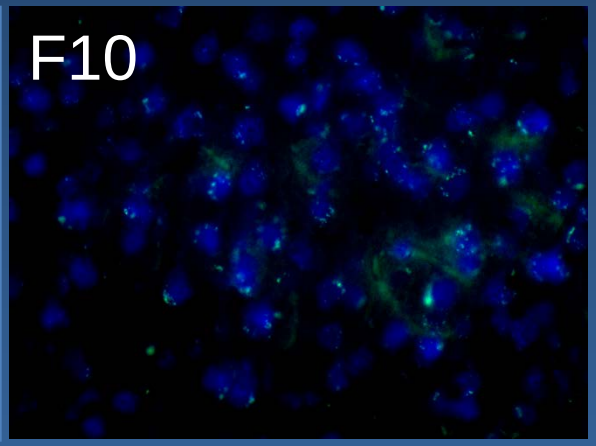


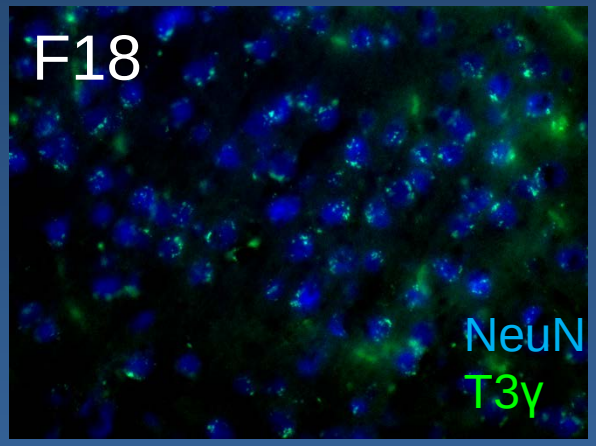

*Fink KD et al. Cell Transpl 2016 (25);677-686.*

Cortical and Striatal and Co-localization

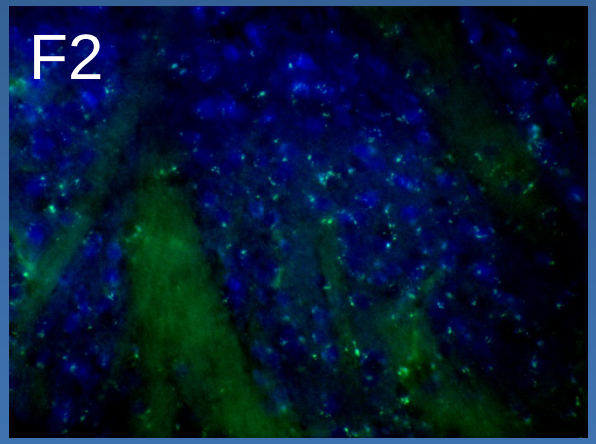
Cortical Co-Localization

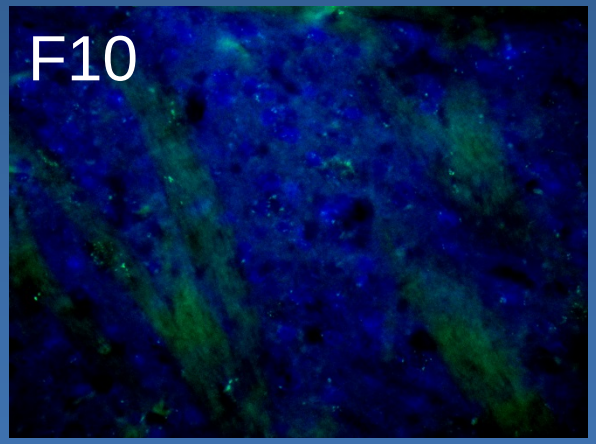


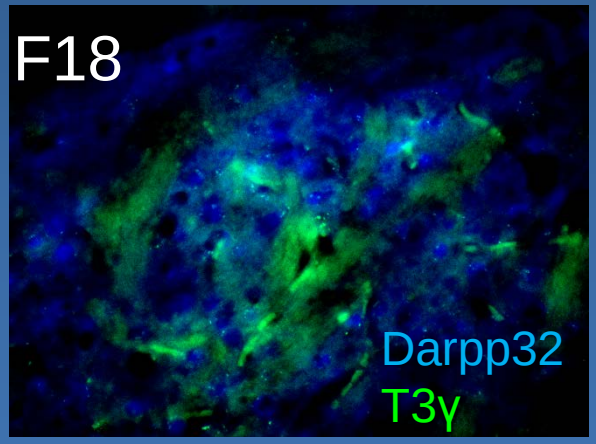



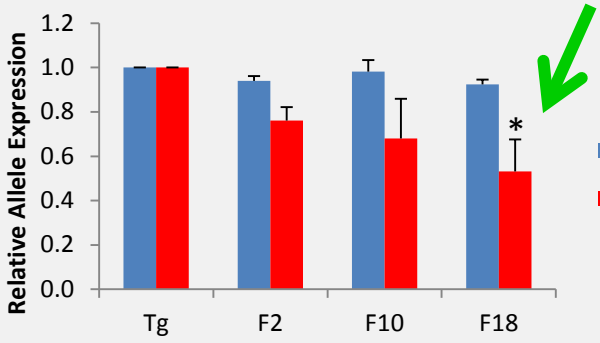

Striatal Co-Localization



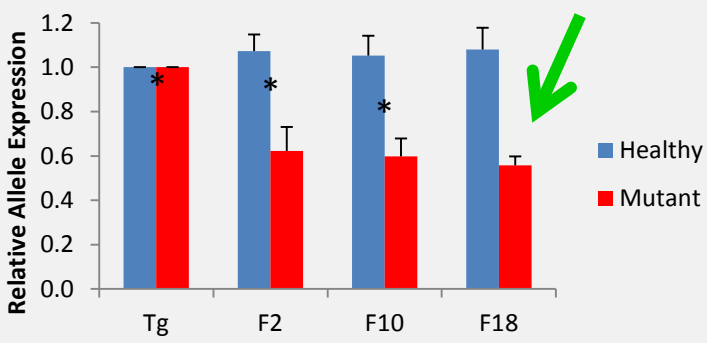




Dr. Kyle Fink




Healthy [$F_{(3,20)}$=1.175, $p$ = 0.355]
Mutant [$F_{(3,20)}$=2.926, $p$ = 0.071]




Healthy [$F_{(3,20)}$=0.116, $p$ = 0.949]
Mutant [$F_{(3,20)}$=4.194, $p$ = 0.022]

# Summary: Progress in HD treatments and research

- New drug approved by FDA: deutetrabenazine
- First study of new drug for behavior in HD: SRX246
- New approaches to disease-modifying treatments:
  - 2 clinical trials targeting the immune system
  - Progress in stem cell research
  - Progress in gene editing research, with one active ASO trial, another planned, and yet more approaches through UC Davis led by Dr. Fink.


HOPE

**Thank you to Dr. Jan Nolta and the UC Davis Institute for Regenerative Cures for ground-breaking research collaboration to help patients and families with HD.**

Huntington's Disease Society of America
Center of Excellence
University of California Davis Medical Center

UCDAVIS
INSTITUTE FOR REGENERATIVE CURES

CIRM
CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE
*The State Stem Cell Agency*

# HDSA Center of Excellence at UC Davis
# Thank You to HD Patients and Care Partners!

Our work in HD has been inspired and generously support by HD patients and family members.

We are grateful to the Joseph P. Roberson Foundation, the Charles and Margaret Pue Charitable Foundation, HDSA, Help4HD and many others who have contributed to our HD care and research programs at UC Davis.

***We miss you ,Terry☺***