

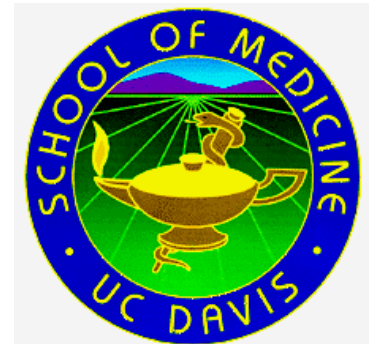
HD Research: Progress in Developing New Clinical and Disease-Modifying Therapies

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

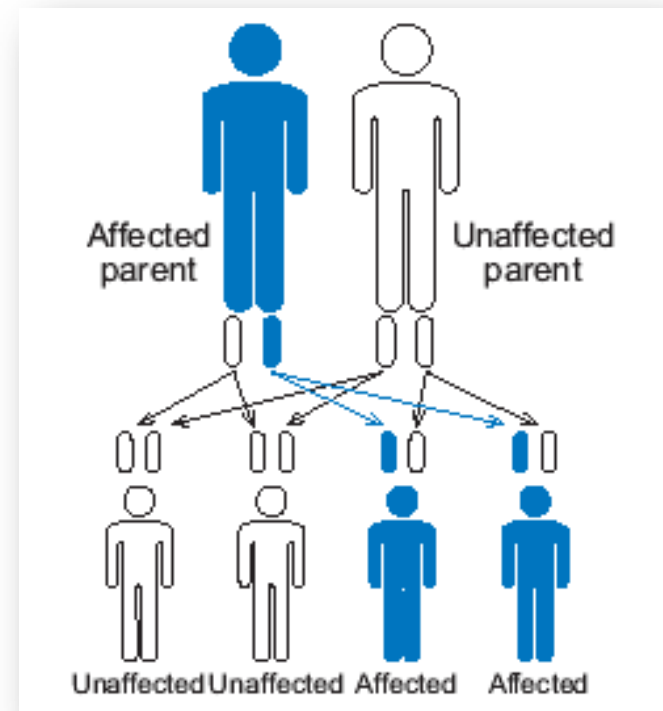
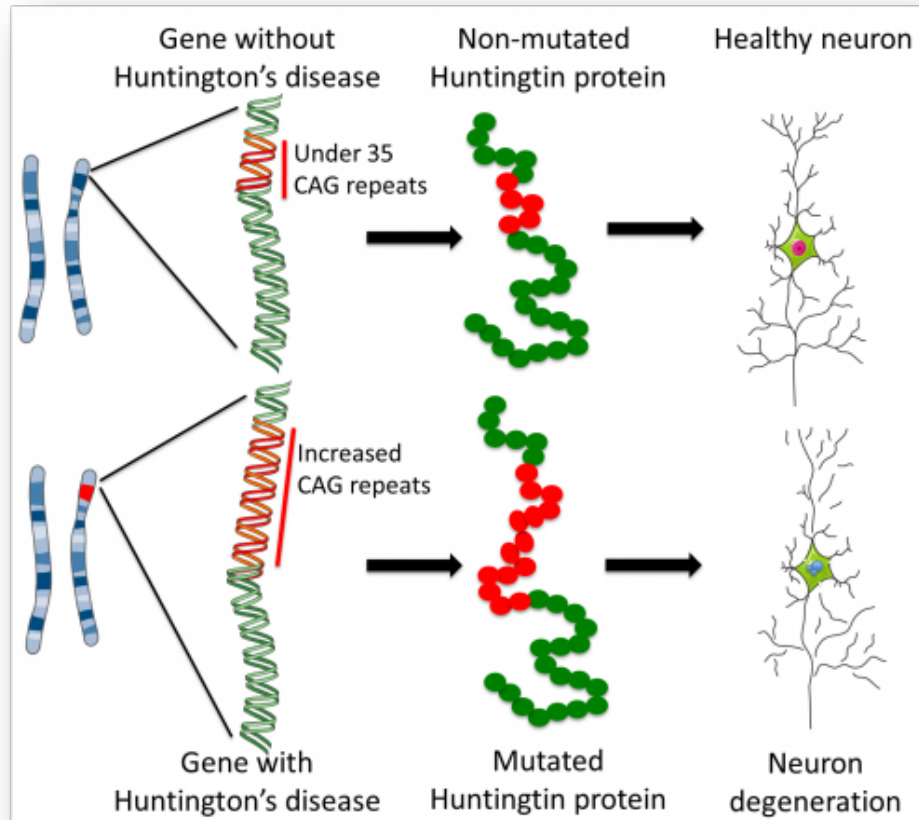
*** Estimated number of household members impacted by HD based on average family unit of 3.21 members

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

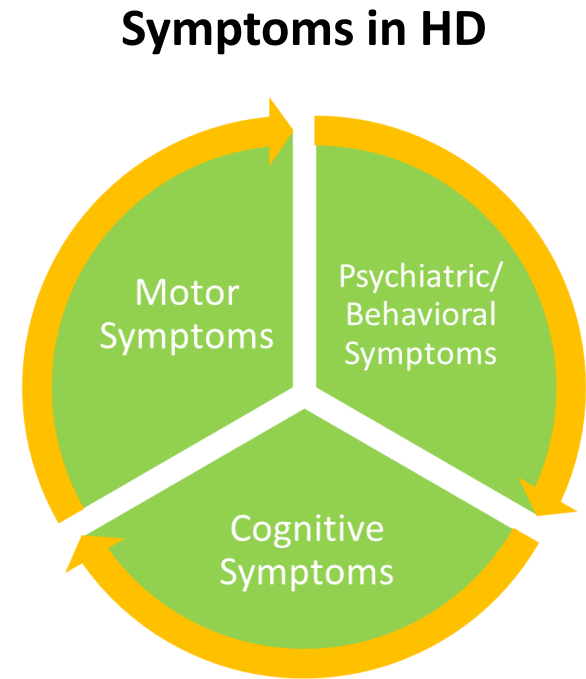
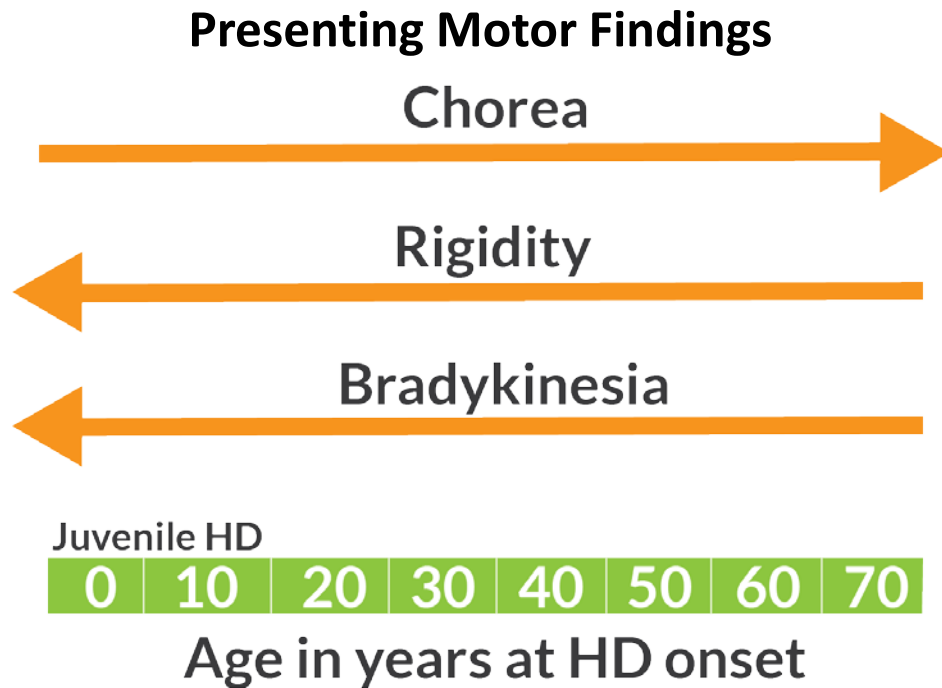
Who gets HD?

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™)

the
PHARMACEUTICAL JOURNAL
A Royal Pharmaceutical Society publication

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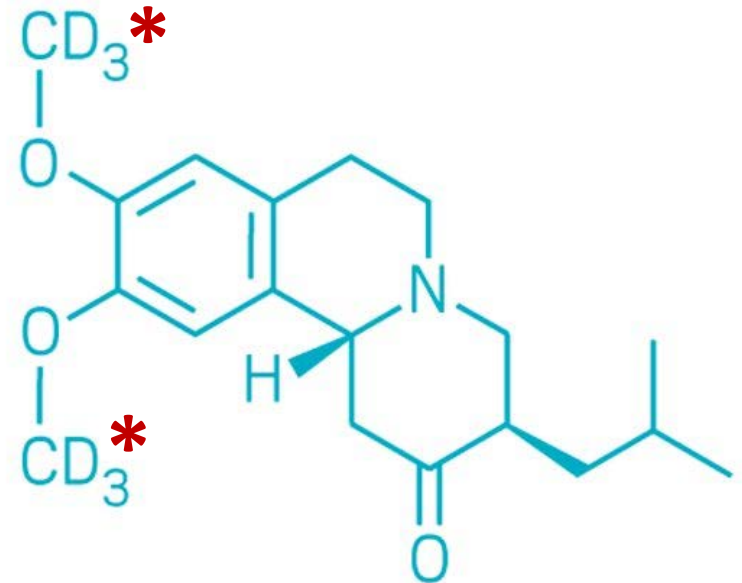
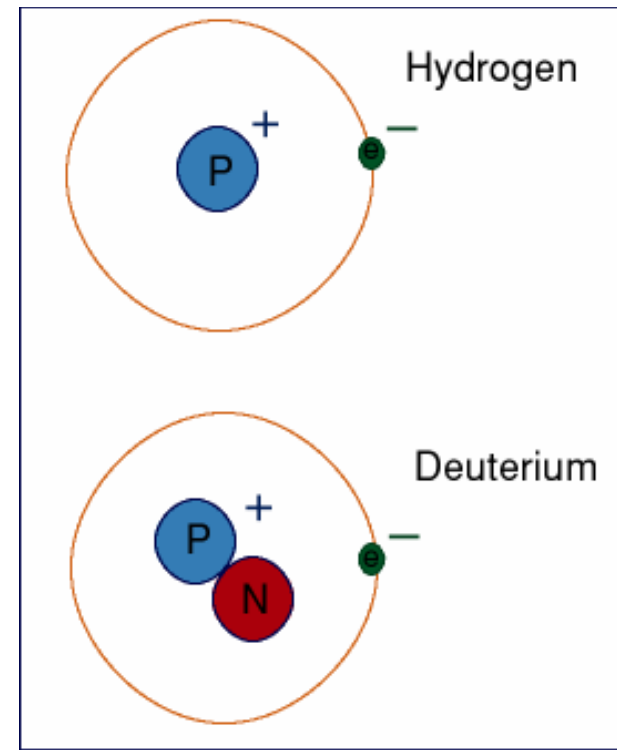
FDA approves Austedo for Huntington's chorea

 **Austedo™**
(deutetrabenazine)
tablets


TEVA PHARMACEUTICALS

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

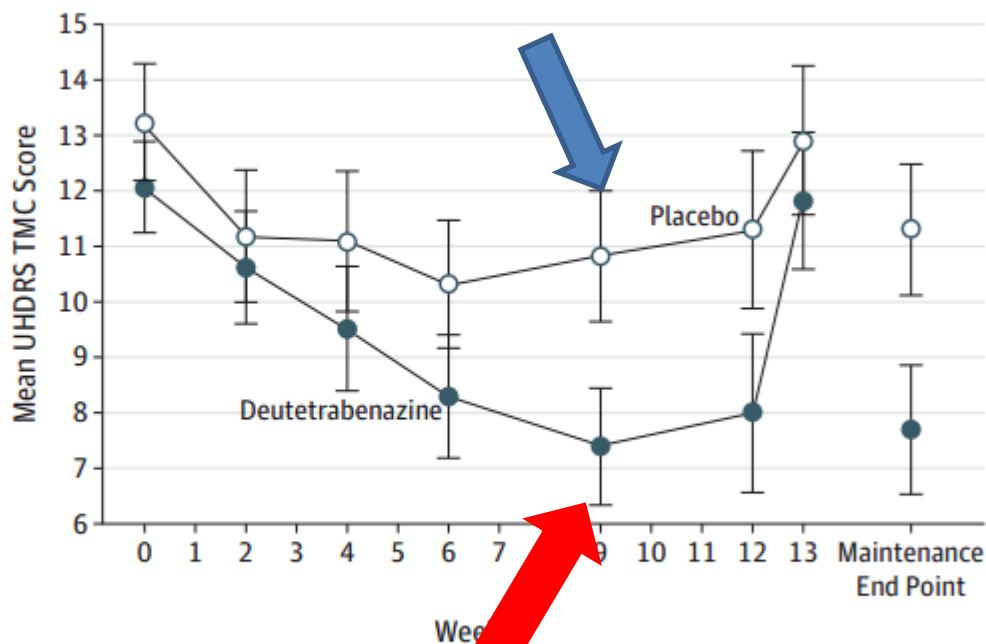
Effect of Deutetrabenazine on Chorea Among Patients With Huntington Disease

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



Week	Deutetrabenazine (n)	Placebo (n)
0	45	45
2	45	45
4	44	45
6	44	44
9	45	42
12	45	43
13	44	43
Maintenance End Point	45	45



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



The NEXT Generation of Neurologic Treatments
NIH-Network for Excellence in Neuroscience Clinical Trials

SRX246: **S**afety, **T**olerability, and **A**ctivity in **I**rritable Subjects with **HD (STAIR)**



MASSACHUSETTS
GENERAL HOSPITAL



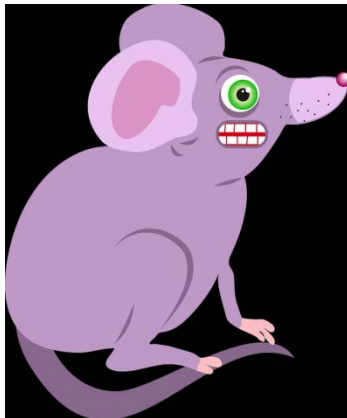
STAIR trial: Why treat Irritability in HD?

- 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.

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.

Male Rat Intruder Model



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





The NEXT Generation of Neurologic Treatments
NIH-Network for Excellence in Neuroscience Clinical Trials

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

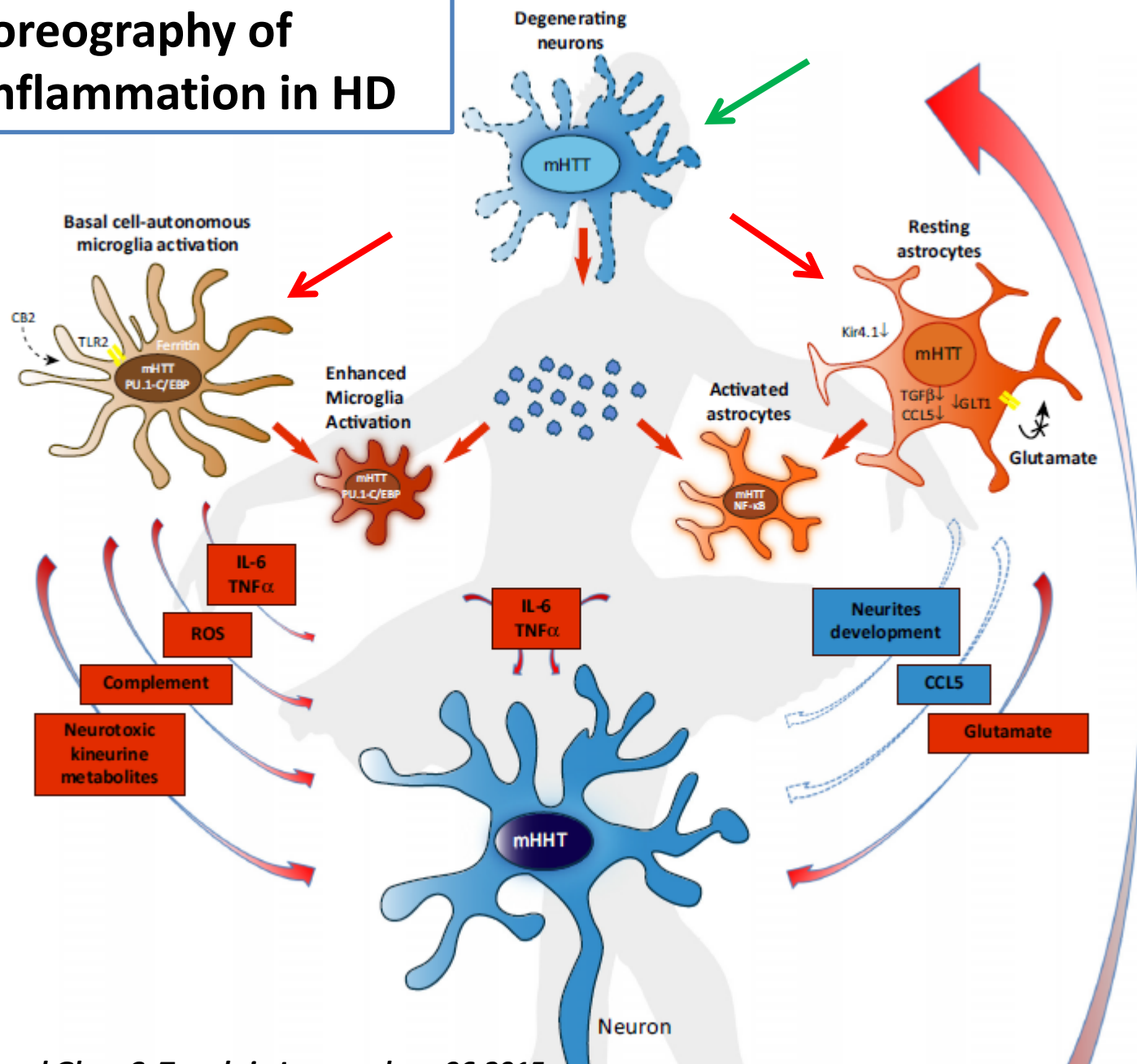
alema@ucdavis.edu

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. Nolte 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



LEGATO-HD Study

THE LAQUINIMOD HD 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



CIRM Spotlight on Huntington's Disease at the California Legislature, March 2010

Pictured clockwise from top left: Vicki Wheelock, Sherry (patient advocate), Claire Pomeroy, Judy Roberson and Jan Nolte

How patient advocates changed the course of science



A group of families impacted by Huntington's disease inspired a "Eureka!" moment for Jan Nolte, UC Davis' pioneering stem cell researcher

2010 – CIRM Spotlight on HD
California State Capitol



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. Nolte

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









Project Plan: MSC/BDNF for HD

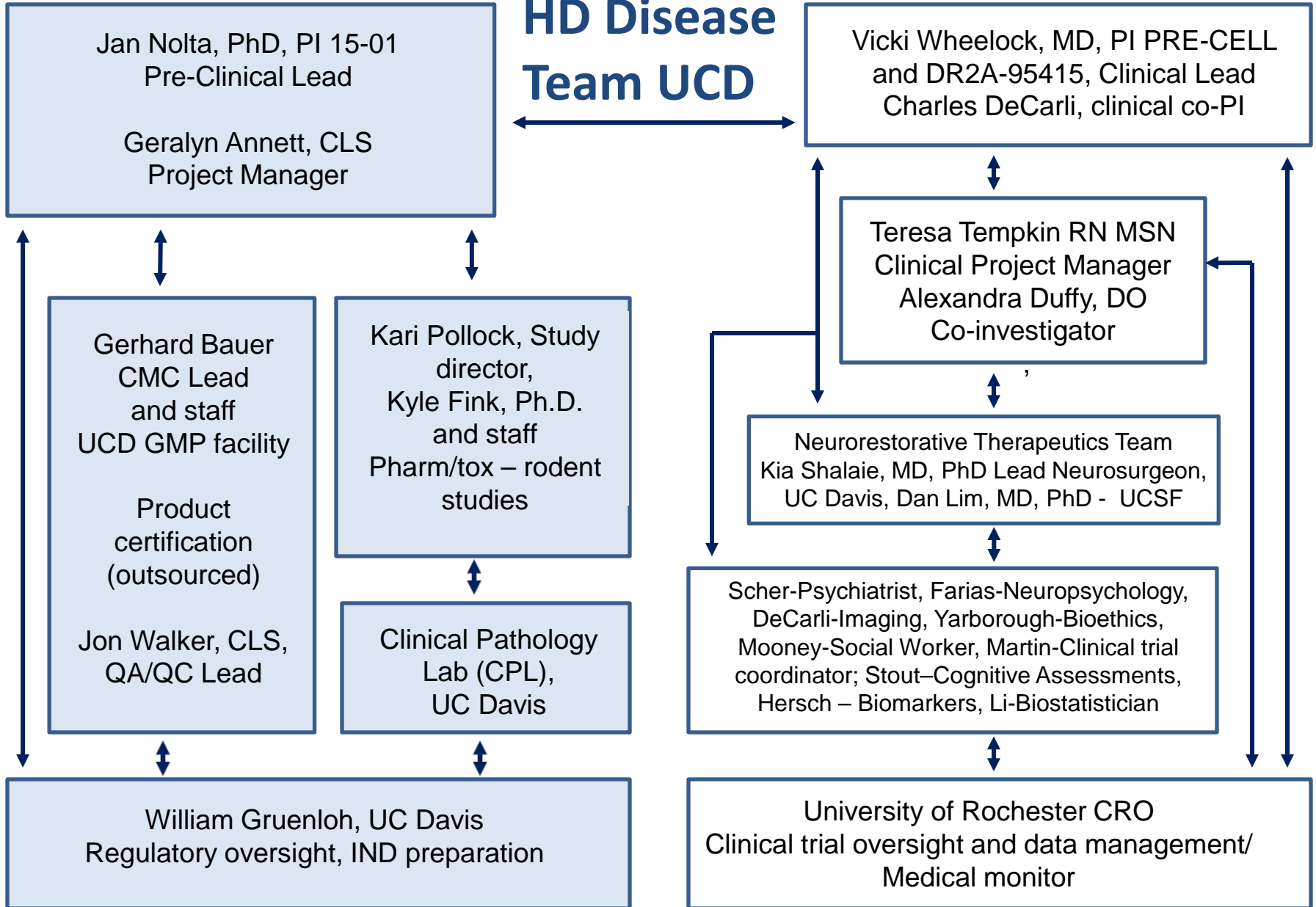
CIRM Grant DR2A-05415

PRE-CELL: Years 1&2

HD-CELL: Years 3&4

	Year 1	Year 2	Year 3	Year 4
GMP Manufacturing of Clinical Lots				
IND-enabling studies using current GMP Lot (ongoing)				
Regulatory approvals (ongoing)				
Observational Clinical trial				
Phase I Clinical trial				
Lab/safety studies: patient samples				

HD Disease Team UCD



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.

First-In-Human Stem Cell Trials in Huntington's Disease: A Bioethics Survey



Alexandra Duffy DO¹, Amanda Martin BA¹, Meaghan O'Keefe PhD², Marsha Michie PhD³, Mark Yarborough PhD⁴, Vicki Wheelock MD¹

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²Department of Biogeriatrics Studies, UC Davis, Davis, CA
³UCSF Institute for Health and Aging, San Francisco, CA
⁴Department of Bioethics, UC Davis School of Medicine, Sacramento, CA



Background

Experimental treatment approaches and first-in-human Phase 1 trials are ethically and logistically challenging to conduct. These studies create challenges for informed consent, more burdensome and complex, than standard clinical trials. These studies create challenges for informed consent, more burdensome and complex, than standard clinical trials. These studies create challenges for informed consent, more burdensome and complex, than standard clinical trials.

Methods

A cross-sectional survey of HD patients and family members regarding attitudes and beliefs about participation in a study that involved stem cells, gene therapy and neuroprotective agents was approved by the Institutional Review Board at UC Davis. The survey was offered on the HDUSA website from September-December 2014. The survey was offered on the HDUSA website from September-December 2014. The survey was offered on the HDUSA website from September-December 2014.

Demographic data were sorted and analyzed with descriptive statistics. Open-ended responses were analyzed by a multidisciplinary team of the individuals comprising a movement disorders neurology, a study coordinator with a degree in philosophy, and three bioethicists with backgrounds in philosophy, history, and risk reduction. After individually sort-coding open-ended questions, the team identified themes and reported on a standard template, with which team members were trained. All open-ended responses. The two coders and another team member coded all open-ended responses. The two coders and another team member coded all open-ended responses. The two coders and another team member coded all open-ended responses.

Results

208 met our inclusion criteria and were assessed on 21 either Group 1 or Group 2. 208 met our inclusion criteria and were assessed on 21 either Group 1 or Group 2. 208 met our inclusion criteria and were assessed on 21 either Group 1 or Group 2. 208 met our inclusion criteria and were assessed on 21 either Group 1 or Group 2.

104 were diagnosed with HD. 104 were diagnosed with HD. 104 were diagnosed with HD. 104 were diagnosed with HD. 104 were diagnosed with HD. 104 were diagnosed with HD. 104 were diagnosed with HD. 104 were diagnosed with HD.

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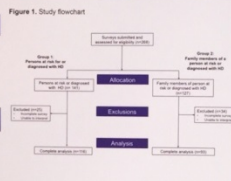


Figure 1: Study flowchart

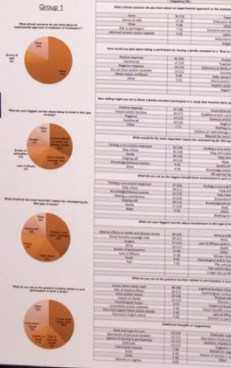


Table 1: Characteristics of respondents

Characteristic	Group 1 (n=114)	Group 2 (n=94)
Age (mean ± SD)	52.1 ± 12.3	51.8 ± 11.9
Gender		
Male	58 (51%)	45 (48%)
Female	56 (49%)	49 (52%)
Education		
High school or less	12 (11%)	10 (11%)
Some college	35 (31%)	30 (32%)
Bachelor's	48 (42%)	40 (43%)
Master's	15 (13%)	12 (13%)
PhD	12 (11%)	10 (11%)

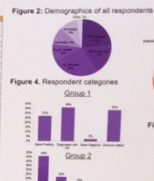


Figure 2: Demographics of all respondents

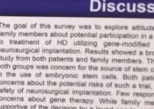


Figure 4: Respondent categories

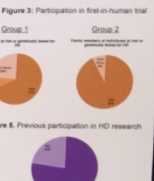


Figure 3: Participation in first-in-human trial

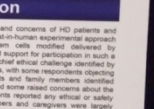


Figure 5: Previous participation in HD research

Discussion

The goal of the survey was to explore attitudes and concerns of HD patients and family members about potential participation in a first-in-human experimental approach to treatment of HD utilizing gene-modified stem cells modified delivered by neuroprotection. Results showed a great support for participation in such a study from both patients and family members. The chief ethical challenge identified by both patients and family members, with some respondents identifying concerns about the potential risks of such a trial, and some raised concerns about the safety of neuroprotective agents. Few respondents reported any ethical or safety concerns about gene therapy. Other family members and caregivers were largely more supportive of the decision by a loved one to participate in such a trial, they expressed medical side effects and possible death. The burden of study visits and logistics was important concern by family members. Both patients and family members reported taking an active stance against the disease, and helping others affected by HD. Additional thoughts from respondents included gratitude, support, remarks on urgency, and sharing of personal stories.

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

Alexandra Duffy
 University of California, Davis

Status Dystonicus Presenting as Status Epilepticus in a Juvenile Huntington's Disease Patient

A Dayananthan MD¹, J Kuo MD¹, A Duffy DO¹, C Chang MD¹, P Parikh MD¹, J Evans MD², C Ginwalla MD², V Wheelock MD¹

¹Department of Neurology, University of California Davis Health Systems, Sacramento, CA, USA
²Department of Pediatrics, University of California Davis Health Systems, Sacramento, CA, USA



Introduction

Juvenile Huntington's disease (JHD) is diagnosed when the onset of HD symptoms occurs before age 21 and is associated with higher CAG repeat length. JHD presents with less chorea and greater rigidity than adult-onset HD. It is characterized by onset of HD by the age of 21 and is associated with a higher incidence of epilepsy. Epilepsy is another manifestation of HD that occurs with a much higher incidence in JHD, with increased seizure incidence associated with earlier age of onset. (Brockway et al. Child's Health and a wide array of secure semology in their analysis of seizures in a multicenter JHD cohort in which 38% of patients had epilepsy. The complex conditions of dystonia and epilepsy in JHD present present clinical management challenges when compared with the adult-onset form of Huntington's Disease. Here, we present a particularly challenging case that underscores the point.

Methods

Case report. Written consent was obtained from the patient's mother for access to the patient's medical record, and sharing of details of the hospital course and pertinent imaging and EEG findings.

Results

A 16-year-old girl with a history of JHD (CAG = 42/17) with cognitive difficulties beginning at age 8 years, motor impairment at age 7 years, focal and generalized tonic-clonic seizures starting at age 8 years treated with carbamazepine and phenytoin, and loss of consciousness by age 9 years and progressive motor impairment leading to loss of ambulation by age 12 years. She was admitted to the pediatric intensive care unit (PICU) after presenting with fever due to a skin lesion, headache, and presumed status epilepticus. Her vital signs were stable, and she had no focal neurologic deficits. Her physical examination was normal. She had a seizure prior to admission, described as a sudden activity of her arms and legs, and some became rigid. She was followed by her mother, who reported an episode of her arms, legs, and torso, and then "turning into a fetal position, grinding her teeth." An EEG recording revealed her mother. The duration of the seizure was about one minute, and she had a similar event an hour later.

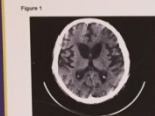


Figure 1: Axial MRI scan showing brain structure.

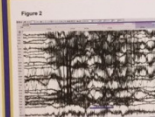


Figure 2: EEG tracing showing abnormal electrical activity.

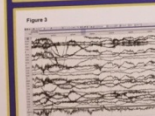


Figure 3: Another EEG tracing showing abnormal electrical activity.

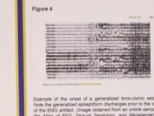


Figure 4: Another MRI scan showing brain structure.

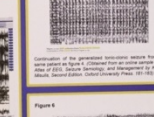


Figure 5: Another EEG tracing showing abnormal electrical activity.

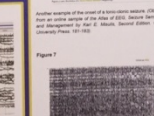


Figure 6: Another EEG tracing showing abnormal electrical activity.

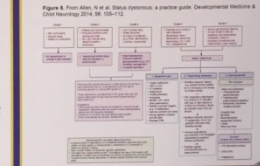


Figure 8: Flowchart of a generalized tonic-clonic seizure from the patient's medical record.

Discussion. The management of juvenile-onset HD presents unique challenges. The management of juvenile-onset HD presents unique challenges. The management of juvenile-onset HD presents unique challenges. The management of juvenile-onset HD presents unique challenges.

Conclusion

This case illustrates the complexity of managing a juvenile-onset HD patient who presents with status epilepticus. This case illustrates the complexity of managing a juvenile-onset HD patient who presents with status epilepticus. This case illustrates the complexity of managing a juvenile-onset HD patient who presents with status epilepticus.

Acknowledgments

The authors would like to thank the patient's mother for her cooperation and support. The authors would like to thank the patient's mother for her cooperation and support. The authors would like to thank the patient's mother for her cooperation and support.

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

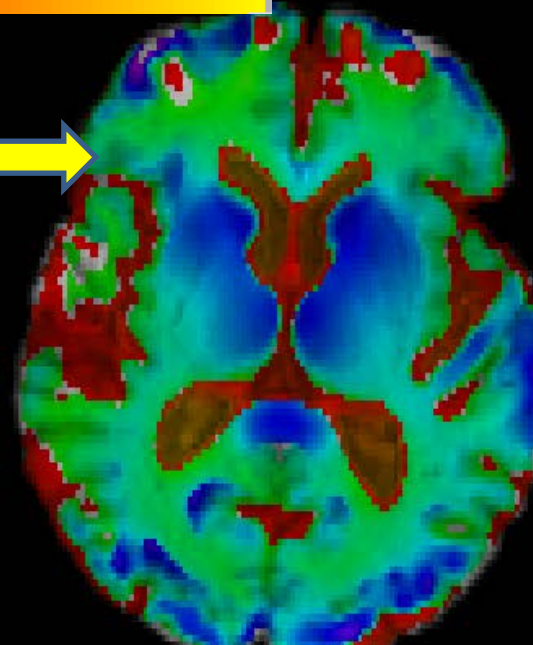
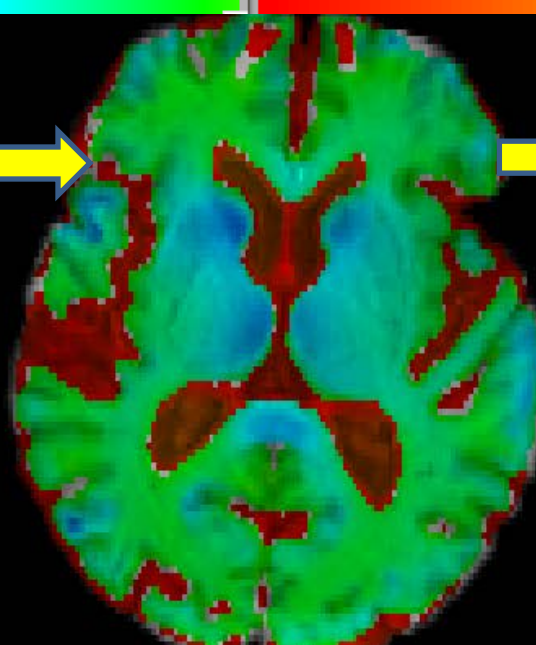
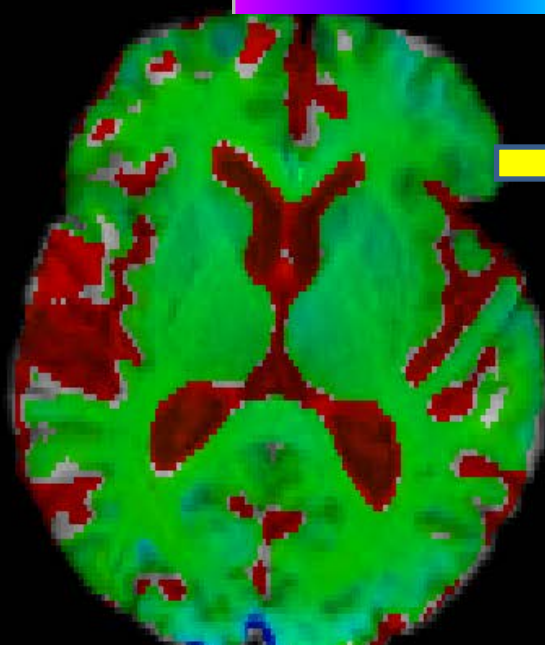
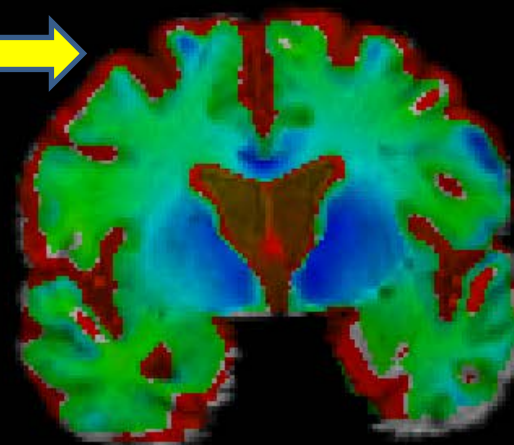
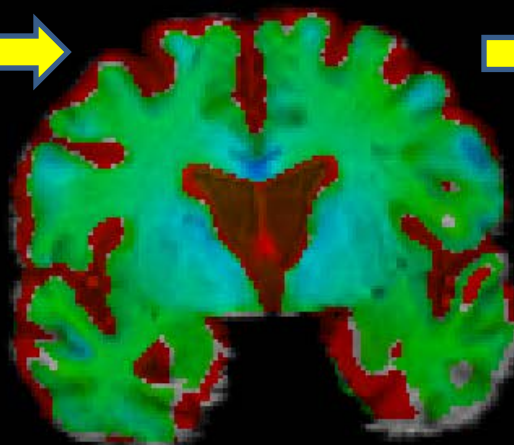
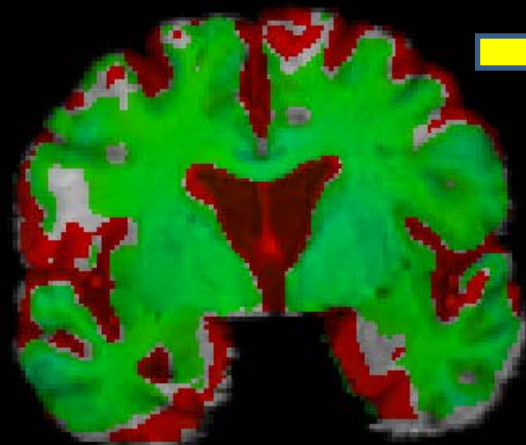
Ashok Dayananthan

Cross sectional Percentage Change Magnitude Images

6 months

12 months

18 months



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.



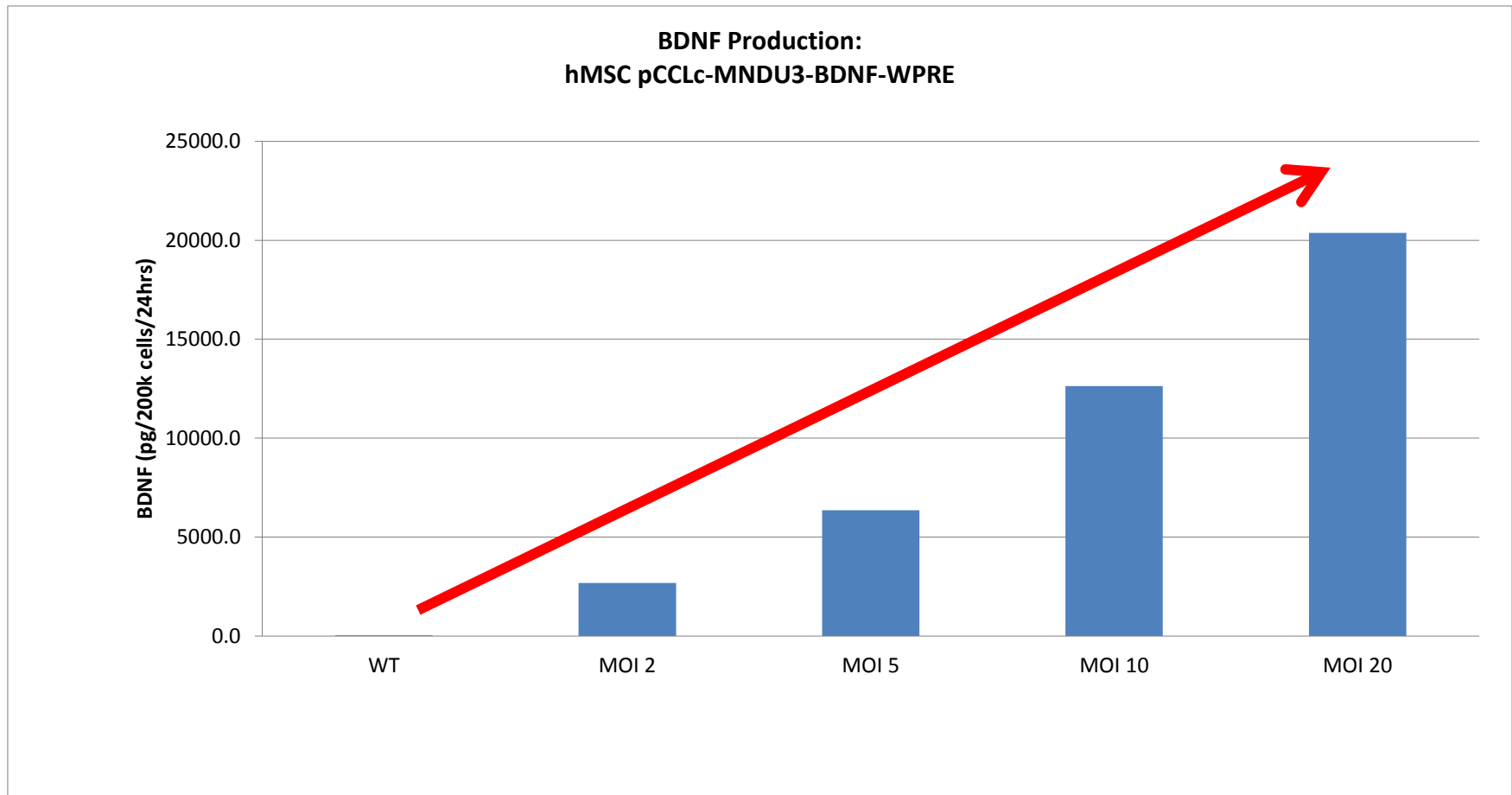
National Institutes of Health, Bethesda, MD; June 9, 2015

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

Kari Pollock¹, Heather Dahlenburg¹, Haley Nelson¹, Kyle D Fink¹, Whitney Cary¹, Kyle Hendrix¹, Geralyn Annett¹, Audrey Torrest¹, Peter Deng¹, Joshua Gutierrez¹, Catherine Nacey¹, Karen Pepper¹, Stefanos Kalomoiris¹, Johnathon D Anderson¹, Jeannine McGee¹, William Gruenloh¹, Brian Fury¹, Gerhard Bauer¹, Alexandria Duffy², Theresa Tempkin², Vicki Wheelock² and Jan A Nolta¹

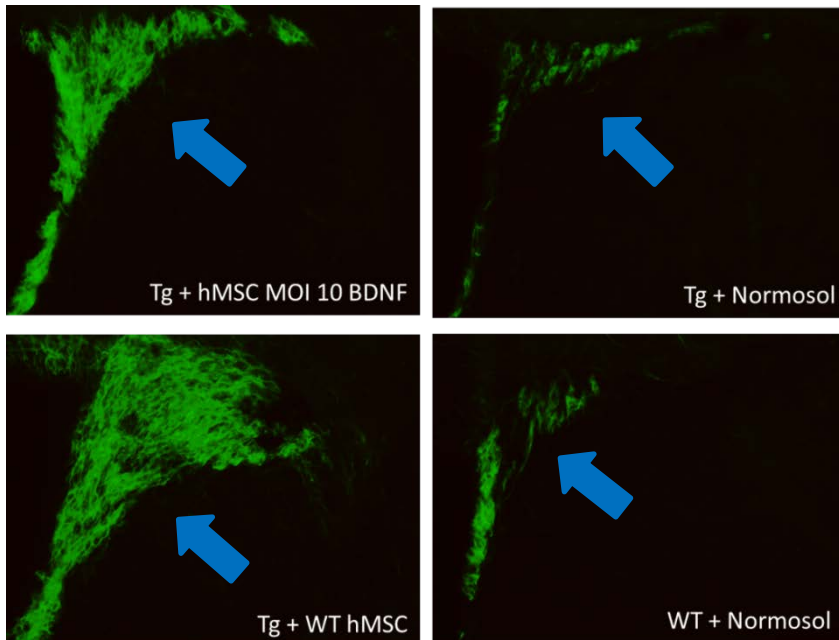
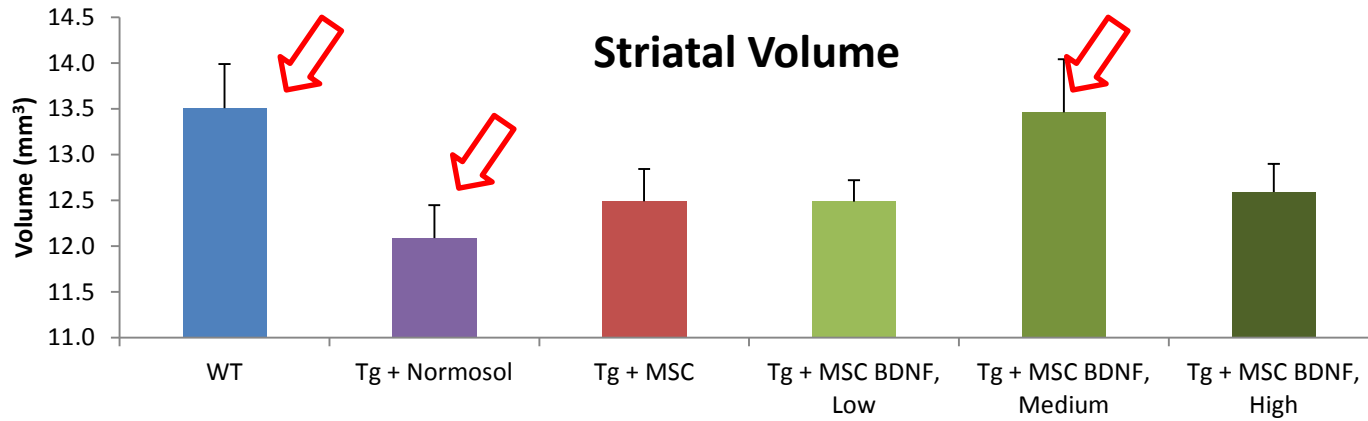
¹Stem Cell Program and Institute for Regenerative Cures, University of California Davis Health System, Sacramento, California, USA; ²Department of Neurology, University of California Davis Health System, Sacramento, California, USA

BDNF production by the engineered MSCs

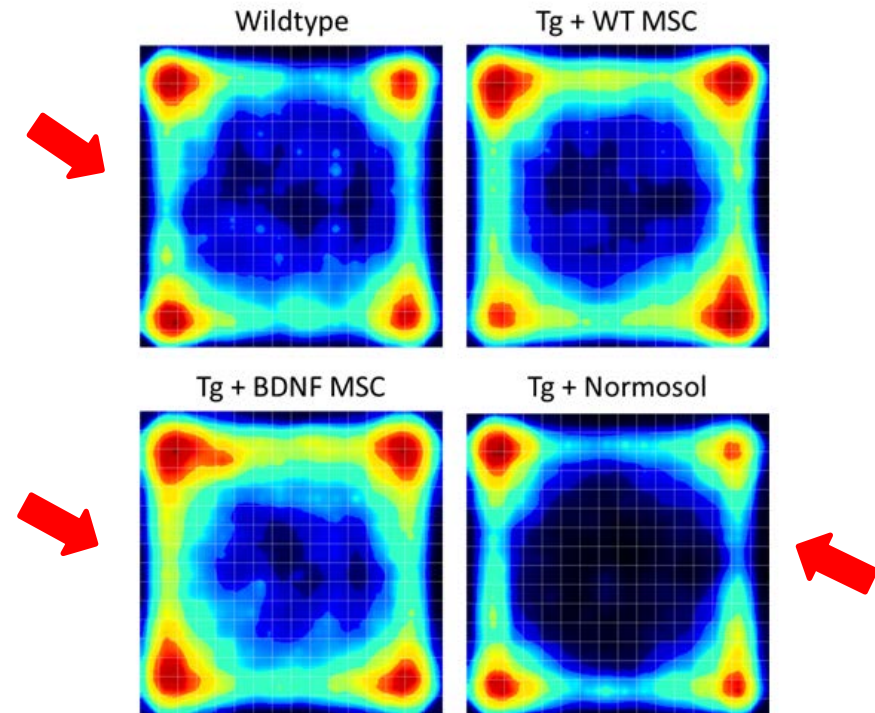


BDNF Production: Human MSCs were transduced with the lentiviral vector pCCLc-MNDU3-BDNF-WPRE at the indicated Multiplicity of infection (MOI). Increasing the MOI increases the amount of BDNF produced.

HD Mouse Studies: treated with MSC/BDNF

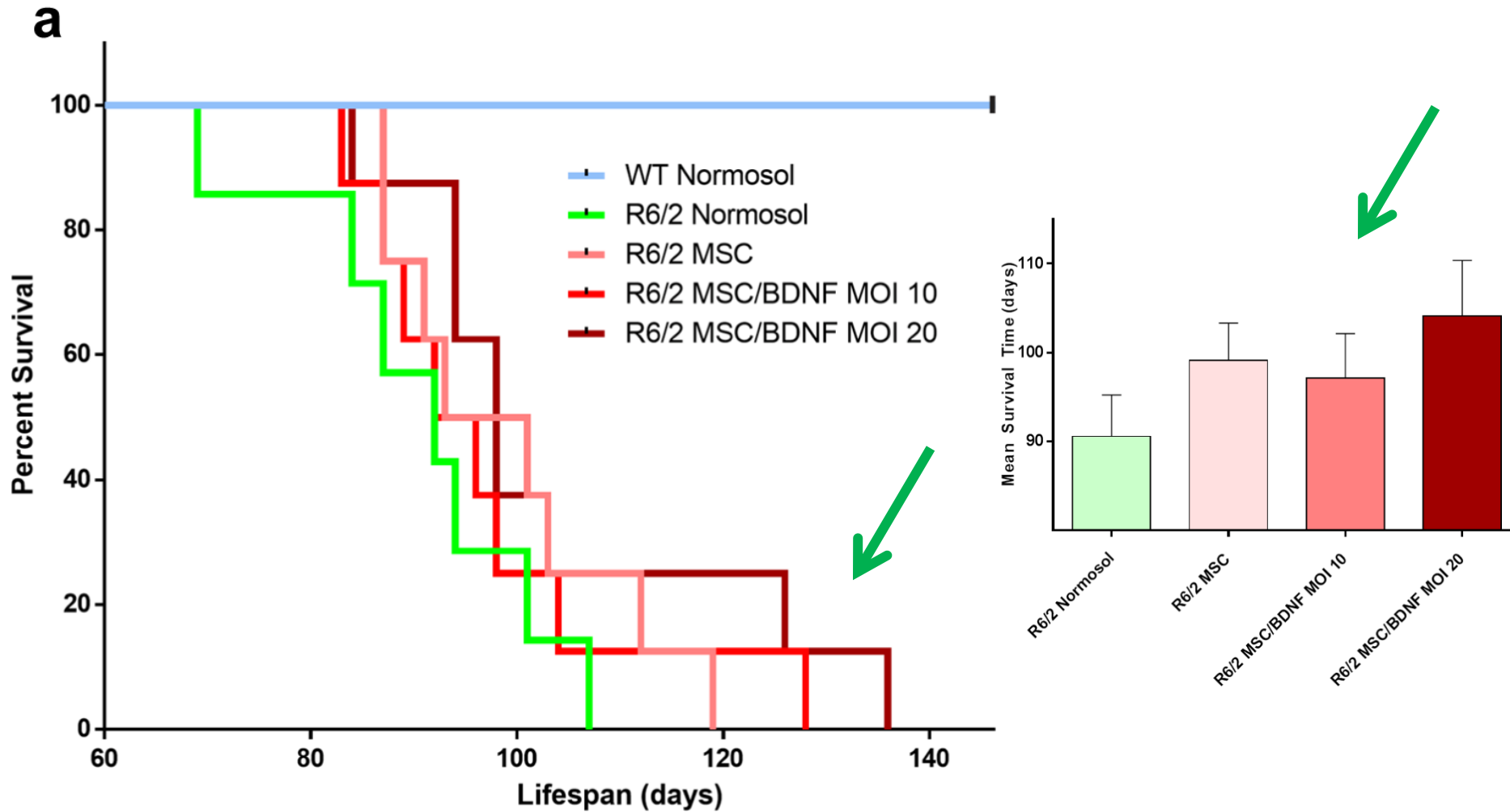


Neurogenesis studies



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.

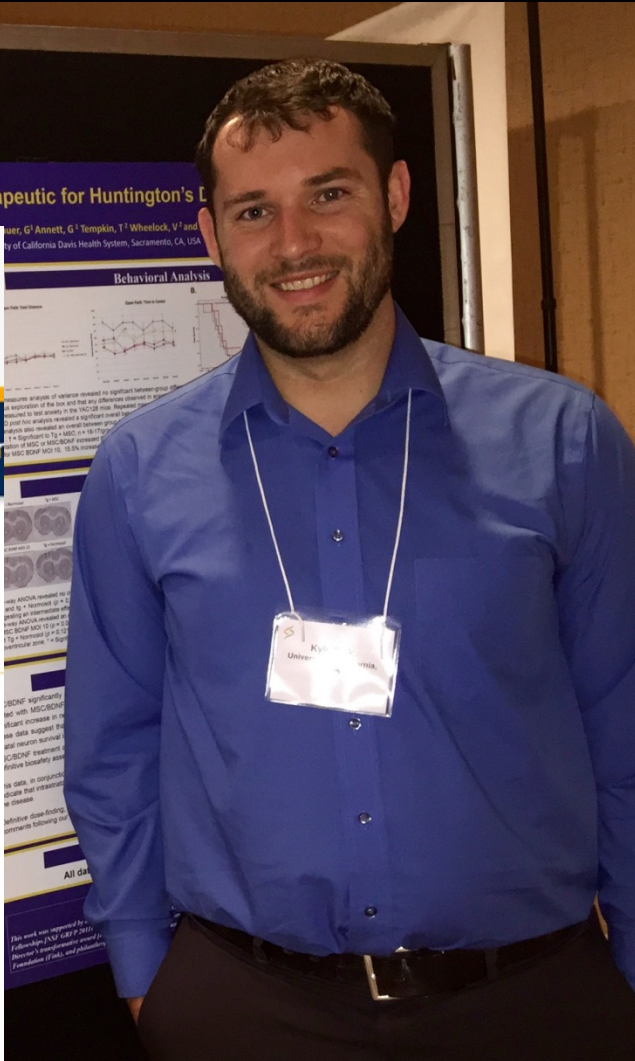
CIRM grant ended fall 2016; HD-CELL trial not started.

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!



The background image shows a man with a beard and short brown hair, wearing a blue button-down shirt and a white name tag that reads "Kyle Fink, Ph.D.". He is standing in front of a research poster. The poster has a purple header with the text "Genetically Engineered Mesenchymal Stem Cells as a Proposed Therapeutic for Huntington's L..." and lists authors: "L...aser, G' Annett, G' Templin, T' Wheelock, V' and ... of California Davis Health System, Sacramento, CA, USA". The poster also includes a section titled "Behavioral Analysis" with a line graph and various text blocks.


SCHOOL OF MEDICINE
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Department of Neurology

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Faculty | Professors

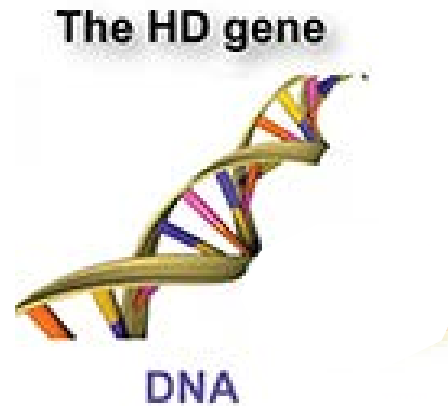


Kyle Fink, Ph.D.
Assistant Adjunct Professor
Neurology and Institute for Regenerative Cures

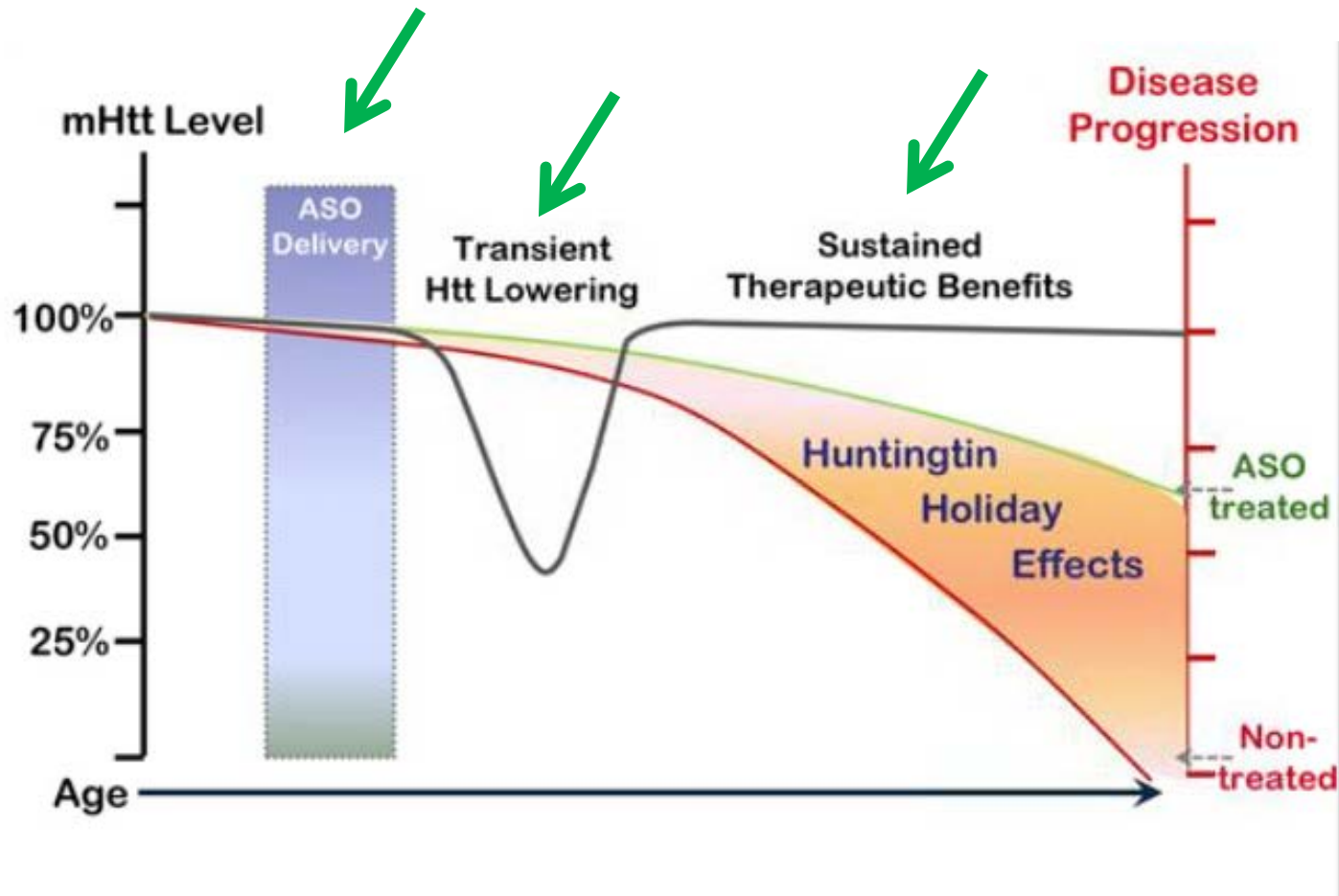
Stem Cell Program
2921 Stockton Blvd., Room 1300
Sacramento, CA 95817
(916) 703-9300

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.



“Huntingtin Holiday”



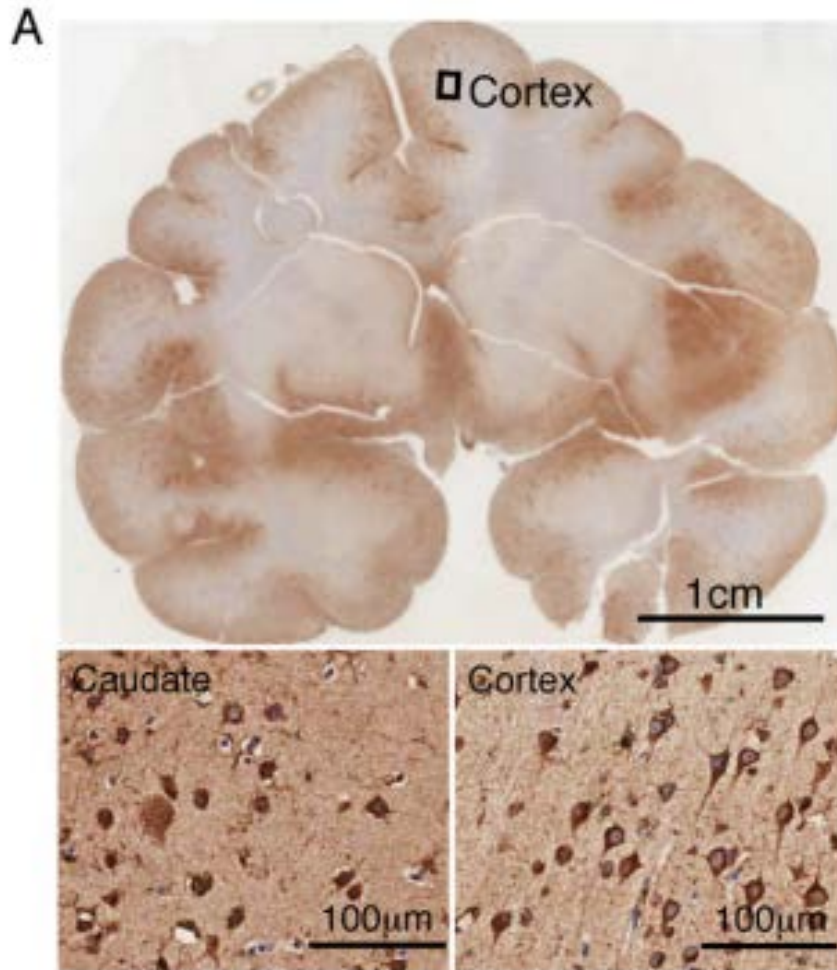
Lu XH and Yang XW. *Neuron* 2012;74(6): 964–966.

Proof of concept in HD mouse models

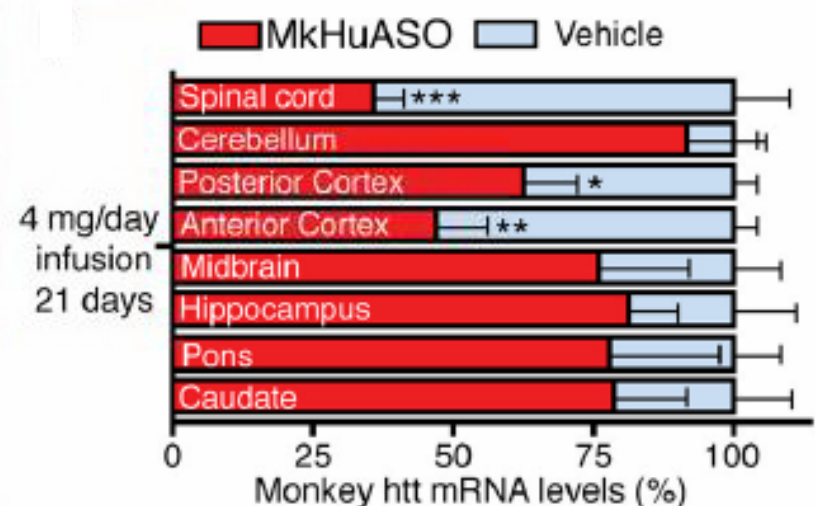
A white mouse is positioned at the top of the frame, looking towards the camera. Below it, a brown mouse is seen from the back, resting on a white, textured surface. The background is a plain, light-colored wall.

- 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.

ASO treatment in Rhesus monkey



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

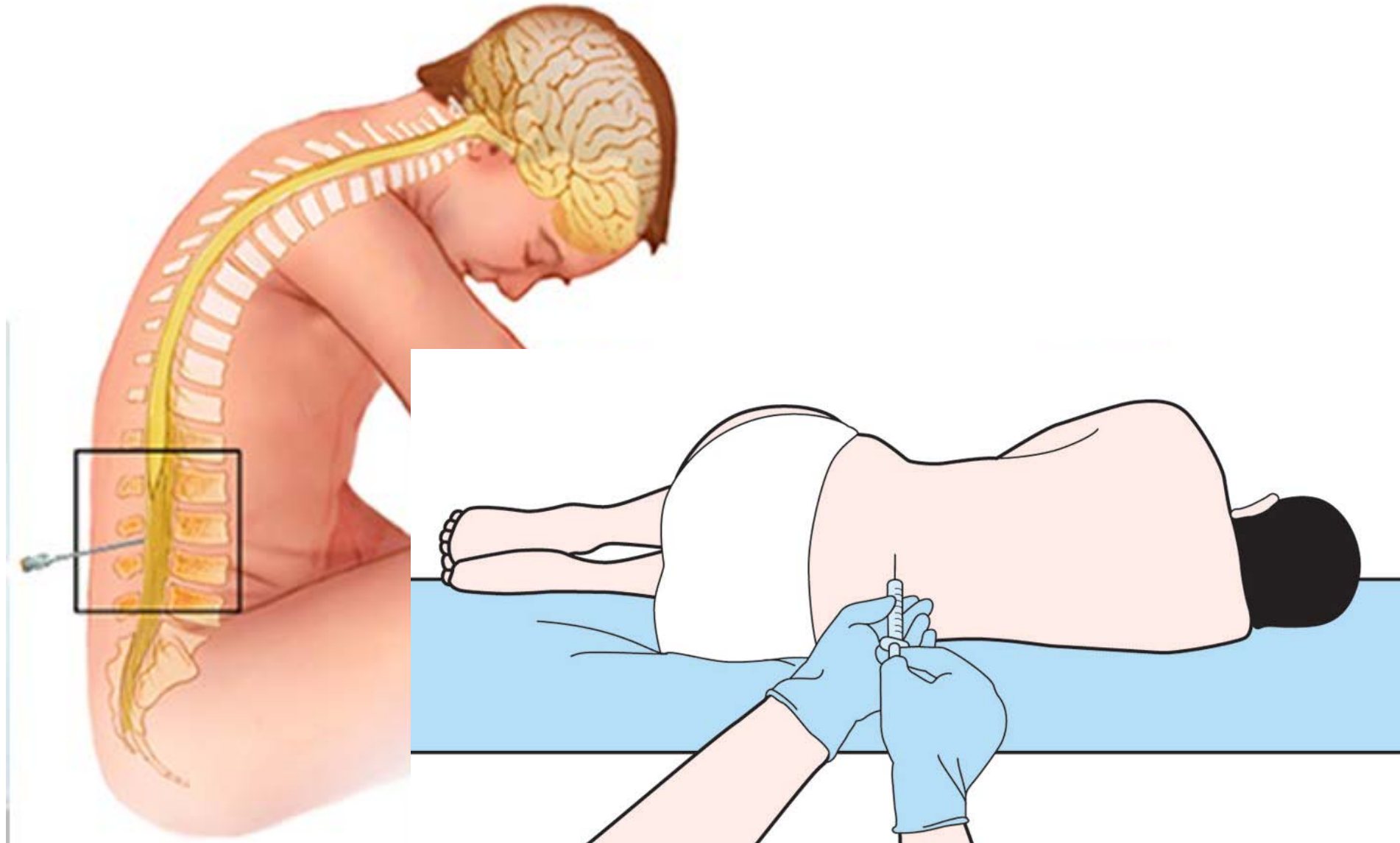


IONIS-HTT_{Rx} trial



- 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

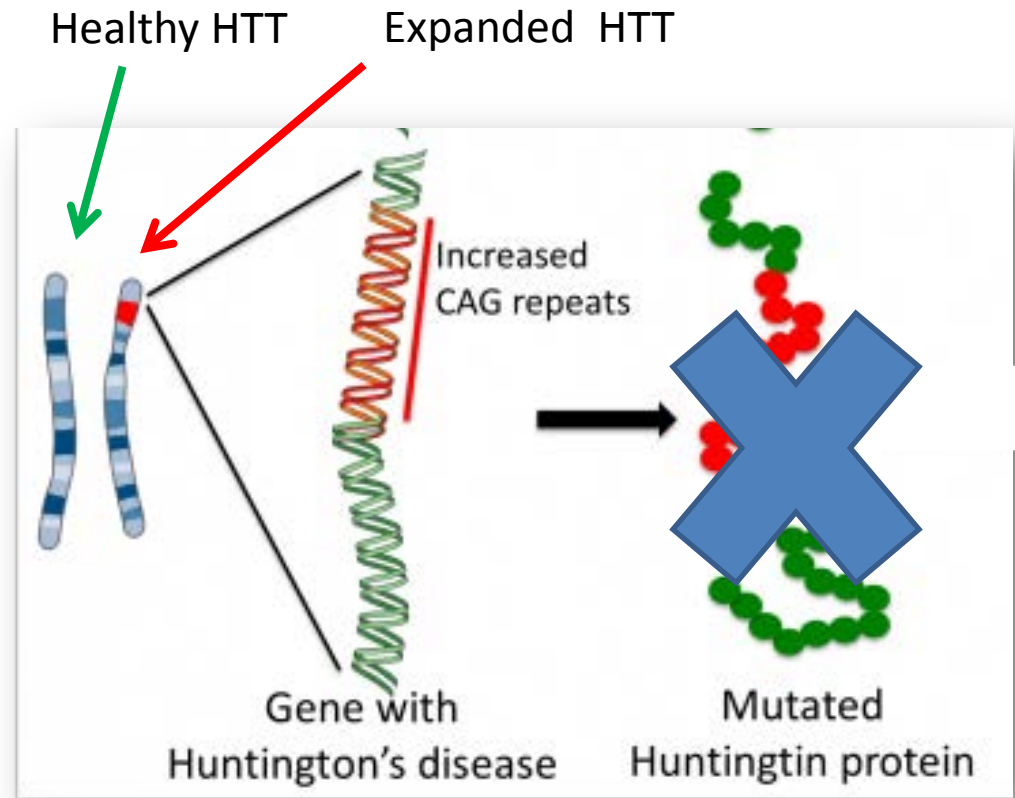


- In a 2016 commentary about molecular genetic therapeutics in HD, Dr. Ira Shoulson raised questions about allele-specificity, effects of cumulative exposure, timeframe of the response, clinical safety and the issues of placebo effect.
- It's safe to say that the entire HD world is watching this historic 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.

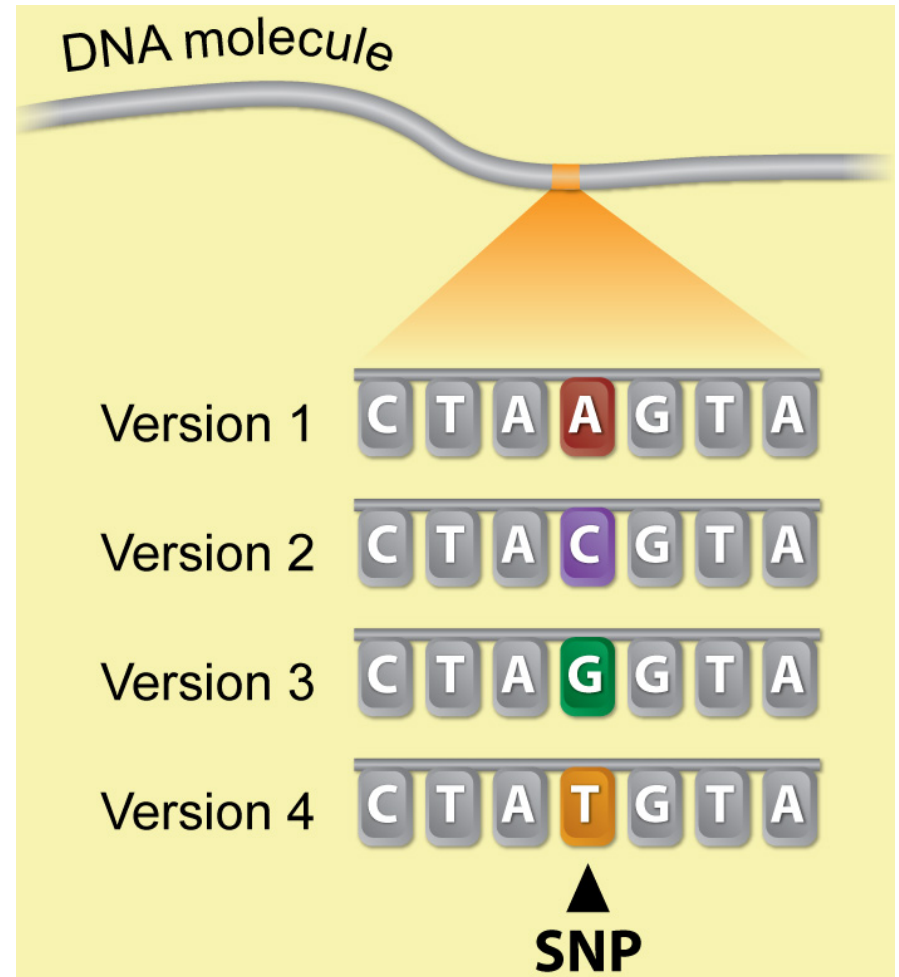


This approach may have less toxicity.

Introduction to a new acronym: SNP

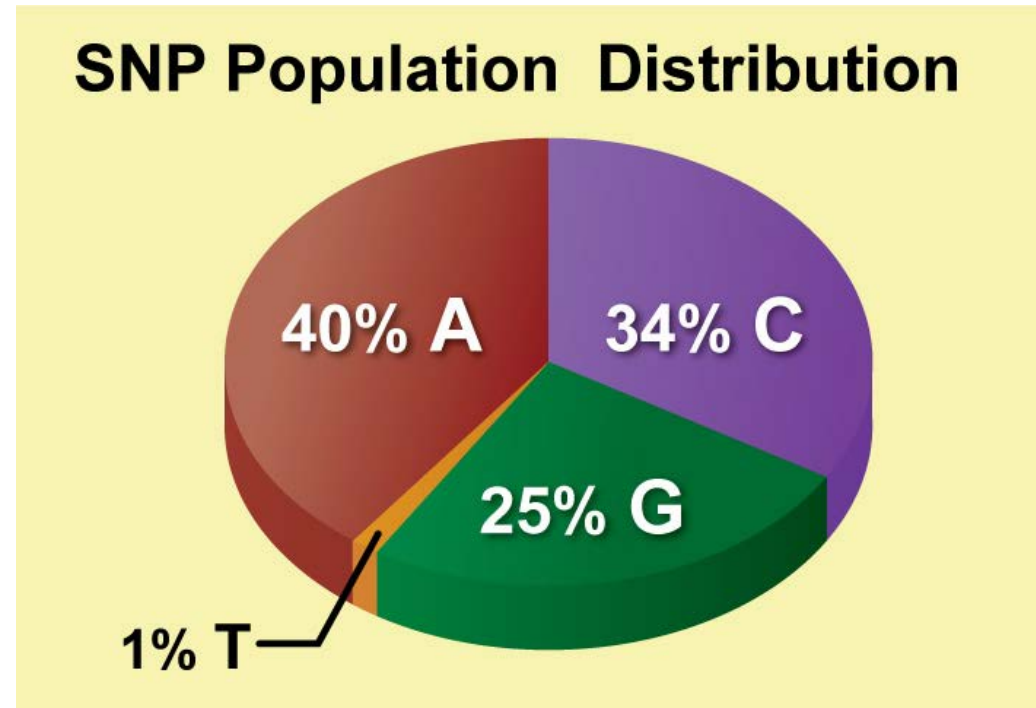
Single Nucleotide
Polymorphism, pronounced
“snip”

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.



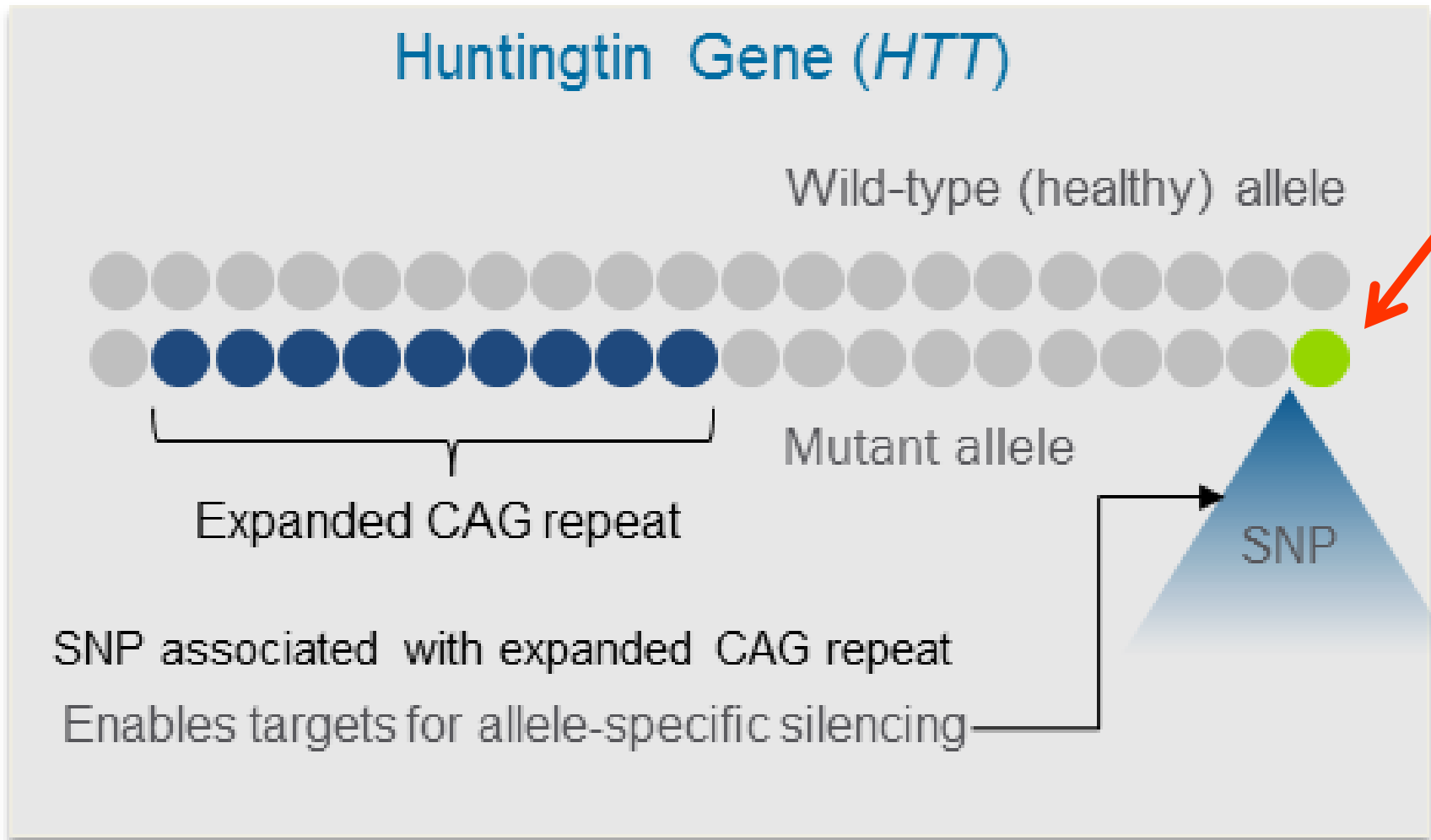
Not all single-nucleotide changes are SNPs

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.

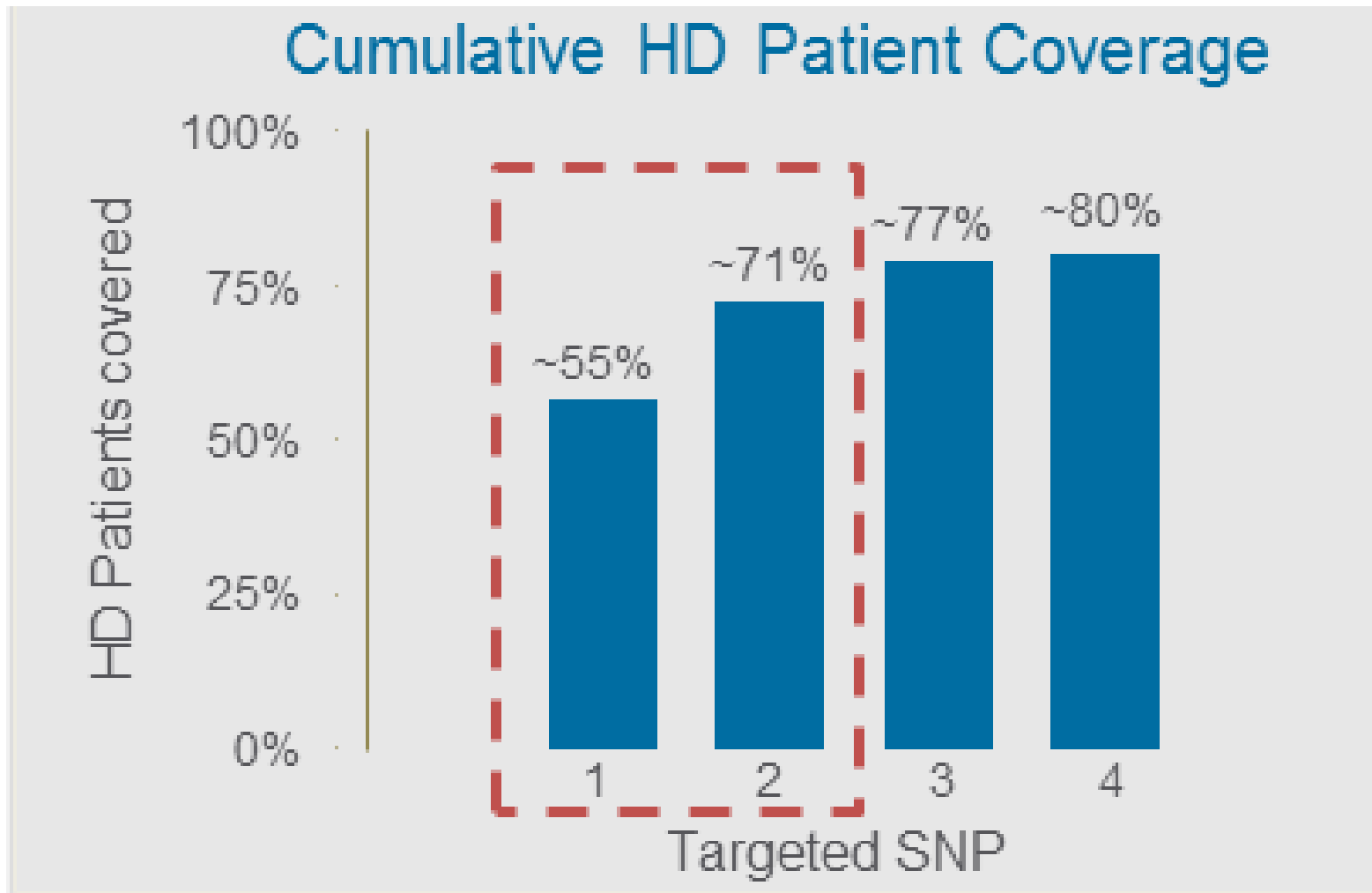


SNPs occur throughout the human genome: about one in every 300 nucleotide base pairs. This translates to about 10 million SNPs within the 3-billion-nucleotide human genome.

Taking advantage of SNPs: Allele-specific ASO



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



Courtesy Dr. Michael Panzara, WAVE Life Sciences

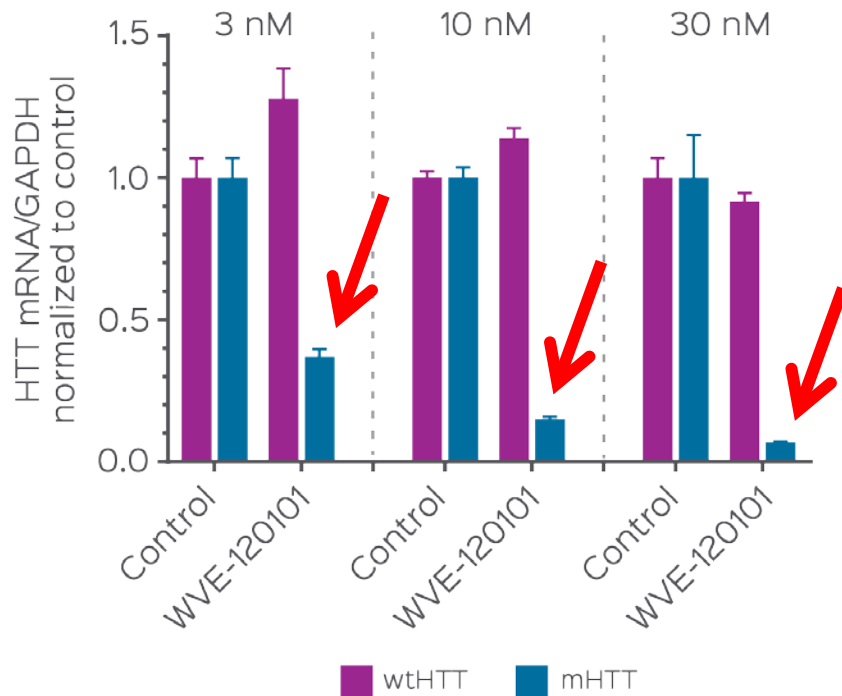
Huntington's Disease

WVE-120101 Selectively Reduces mHTT mRNA and Protein



Reporter Cell Line*

Messenger RNA levels



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

Courtesy Dr. Michael Panzara, WAVE Life Sciences

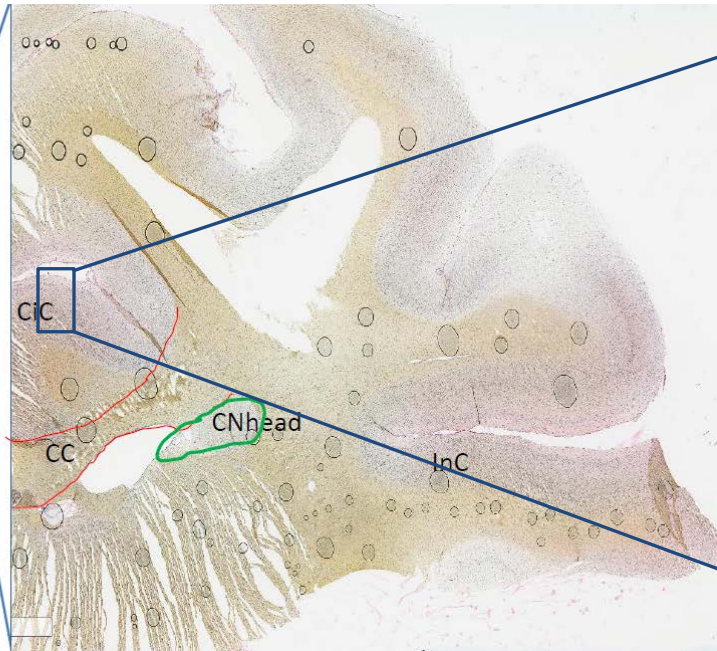
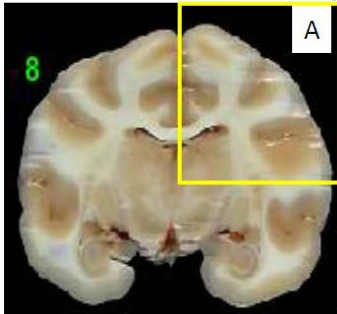
Huntington's Disease

Distribution of WVE-120101 in Cynomolgus NHP Brain

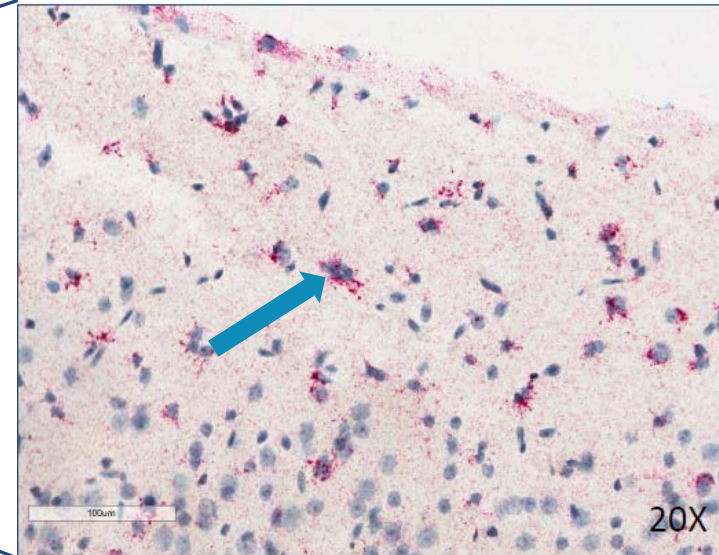


- Stereochemistry enables improved protein binding and distribution
- ViewRNA depicting perinuclear distribution of WVE-120101 (red) in non-human primate (NHP) deep gray matter structures following intrathecal administration
- WVE-120101 detectable in deep gray matter structures following intrathecal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

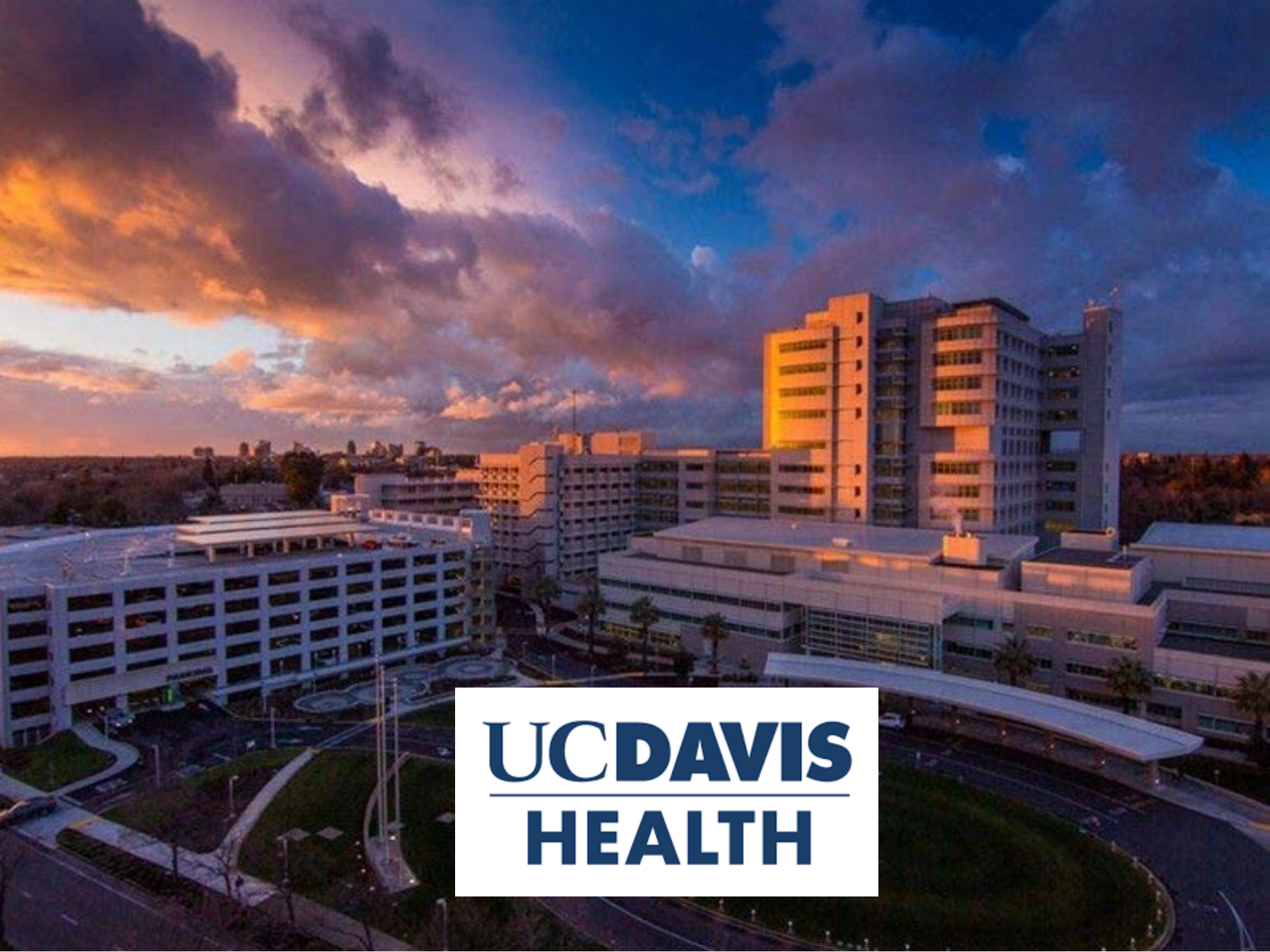
Courtesy Dr. Michael Panzara, WAVE Life Sciences

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

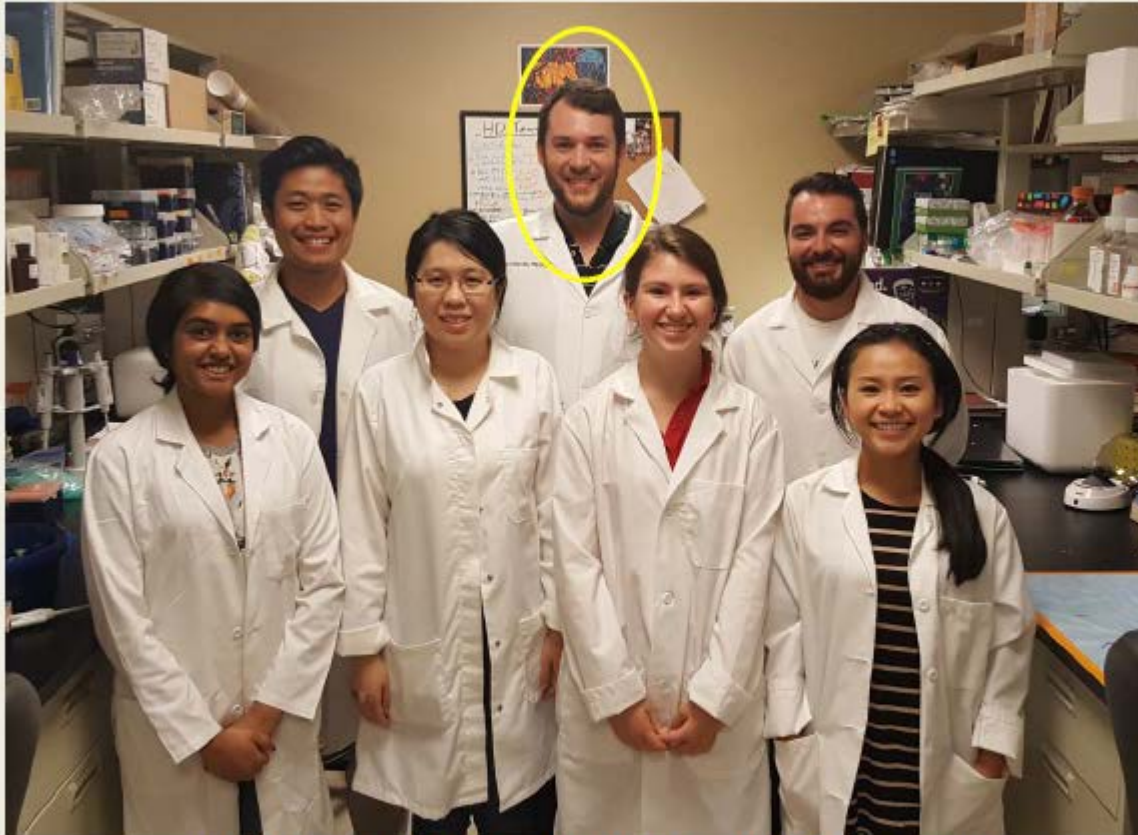


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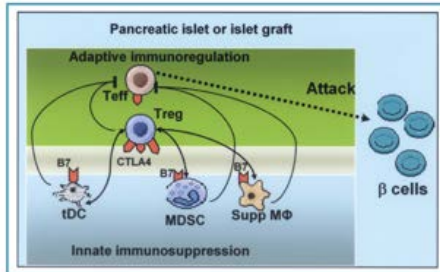
HEALTH

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, Duke Foundation



0963-6897/16 \$90.00 + .00

DOI: <http://dx.doi.org/10.3727/096368916X690863>

E-ISSN 1555-3892

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

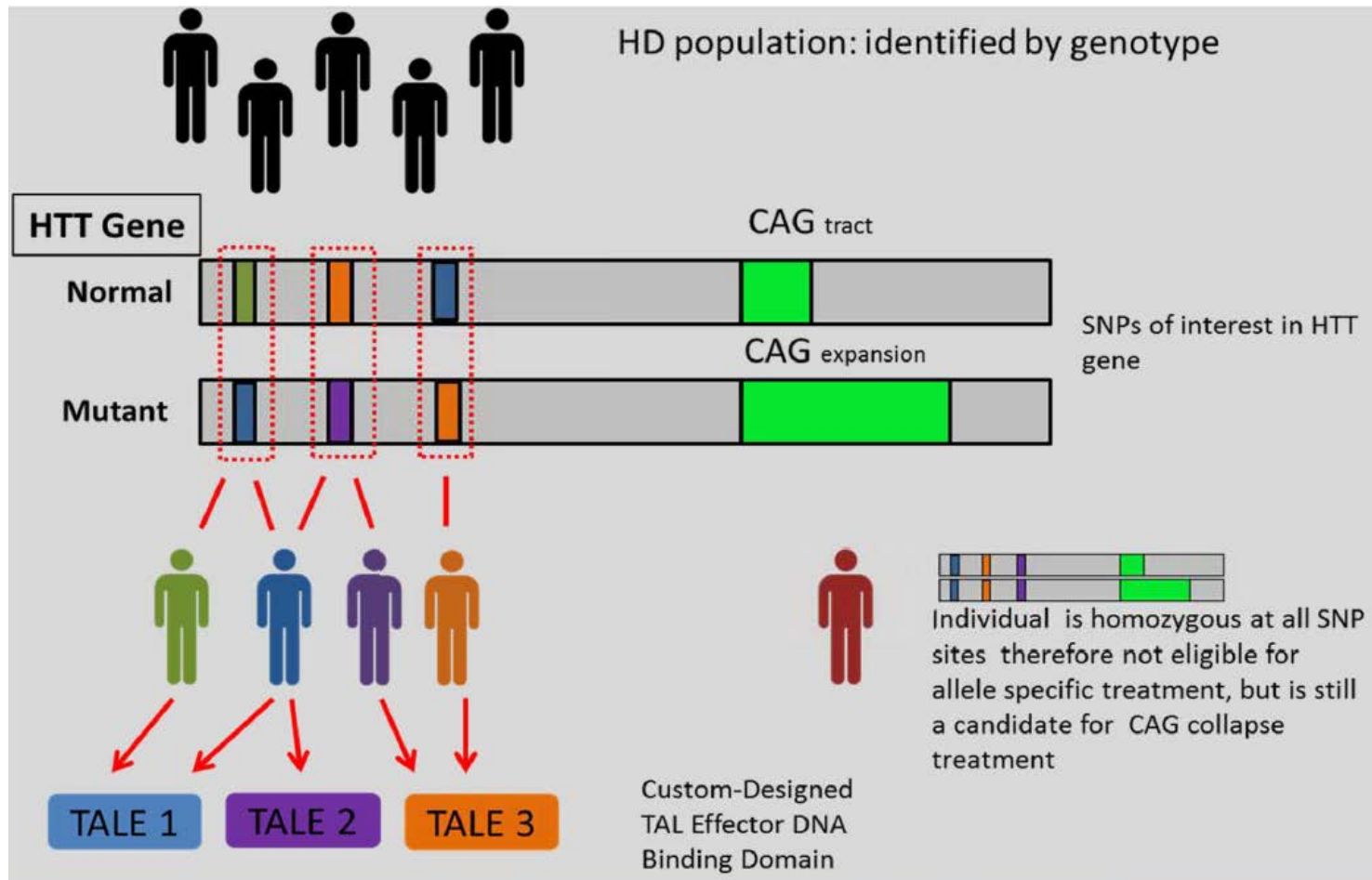
Kyle D. Fink,* Peter Deng,*† Josh Gutierrez,* Joseph S. Anderson,* Audrey Torrest,*
Anvita Komarla,*† Stefanos Kalomiris,* Whitney Cary,* Johnathon D. Anderson,*
William Gruenloh,* Alexandra Duffy,‡ Teresa Tempkin,‡ Geralyn Annett,*
Vicki Wheelock,‡ David J. Segal,† and Jan A. Nolte*

*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

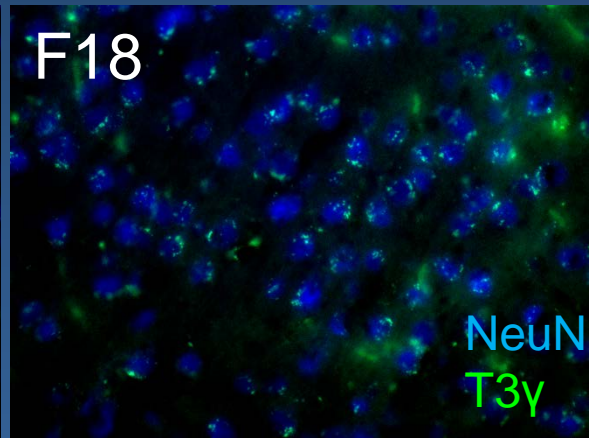
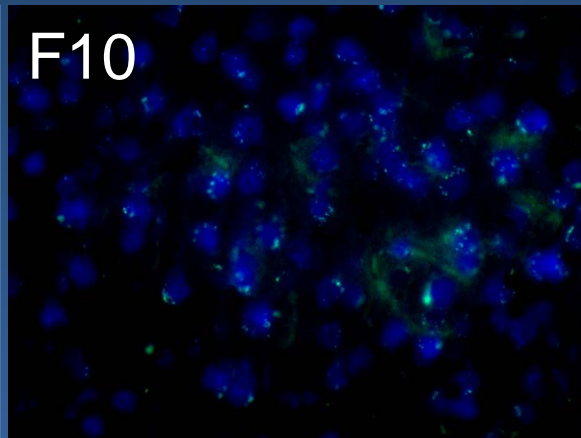
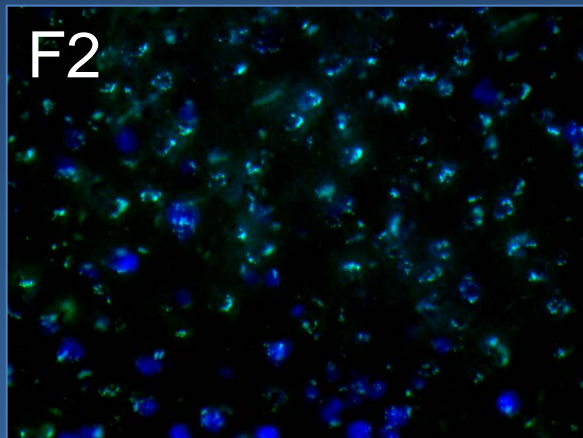
‡Department of Neurology, University of California Davis Health Systems, Sacramento, CA, USA

Potential applications to the HD patient population

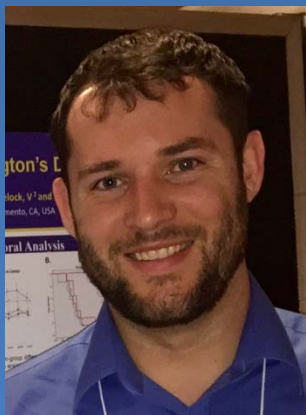
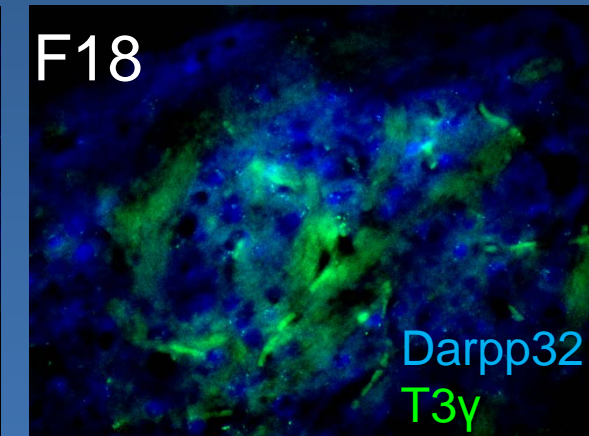
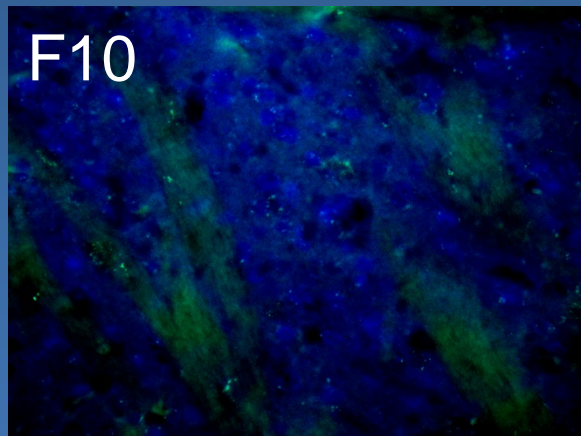
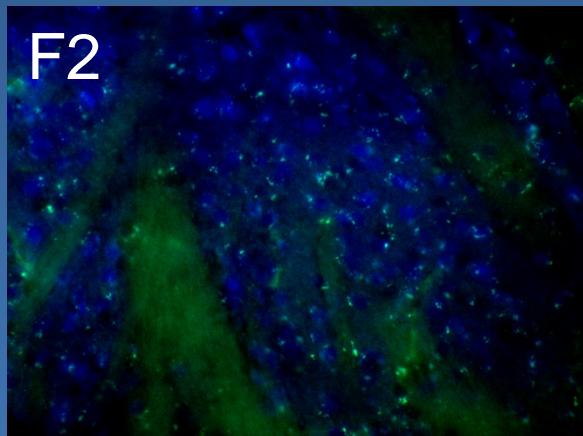


Cortical and Striatal and Co-localization

Cortical Co-Localization

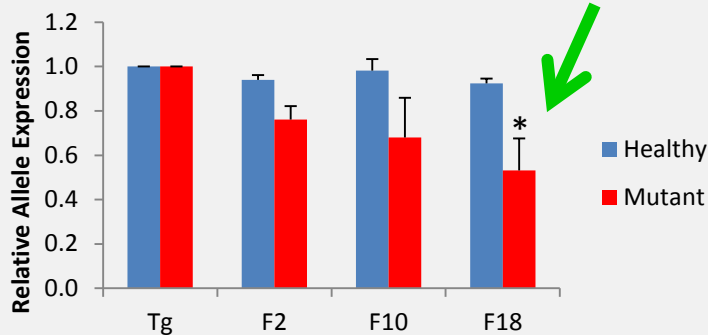


Striatal Co-Localization



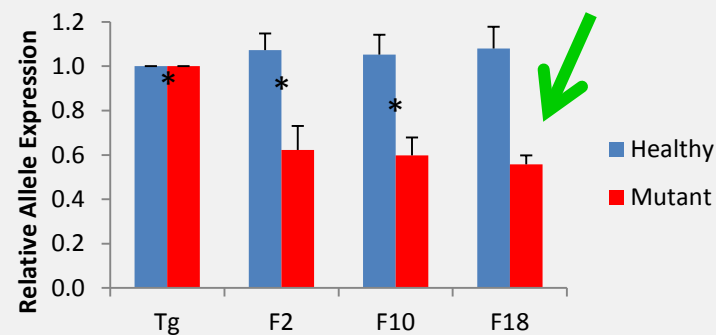
Dr. Kyle Fink

LNP TALE Striatal Allele Expression



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

LNP TALE Cortical Allele Expression



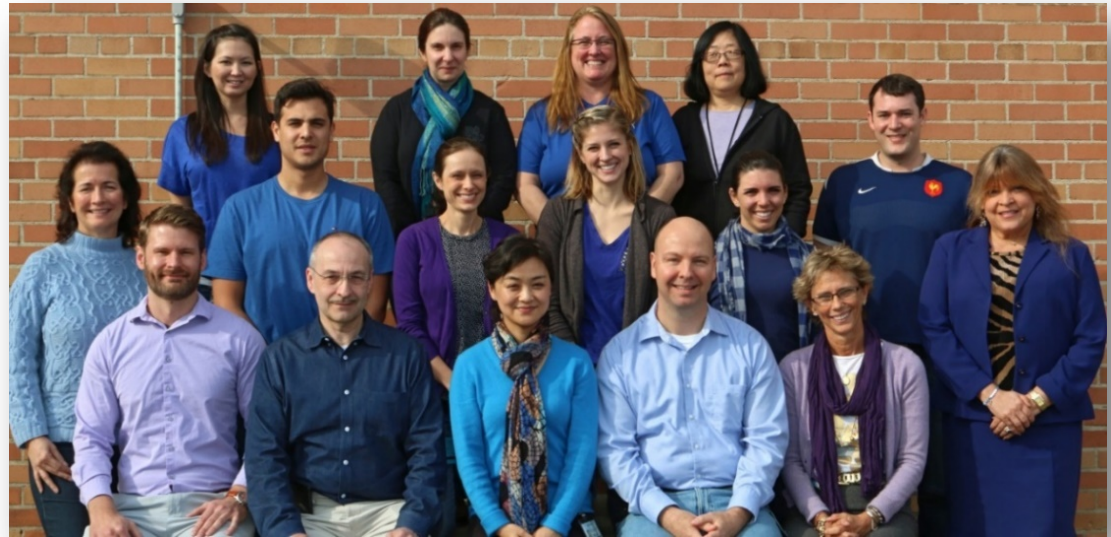
Healthy [$F_{(3,20)}=0.116, p=0.949$]
 Mutant [$F_{(3,20)}=4.194, p=0.022$]

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.



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.



HDSA Center of Excellence at UC Davis

Thank You to HD Patients and Care Partners!

Our work in HD has been inspired and generously supported 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 ☺

