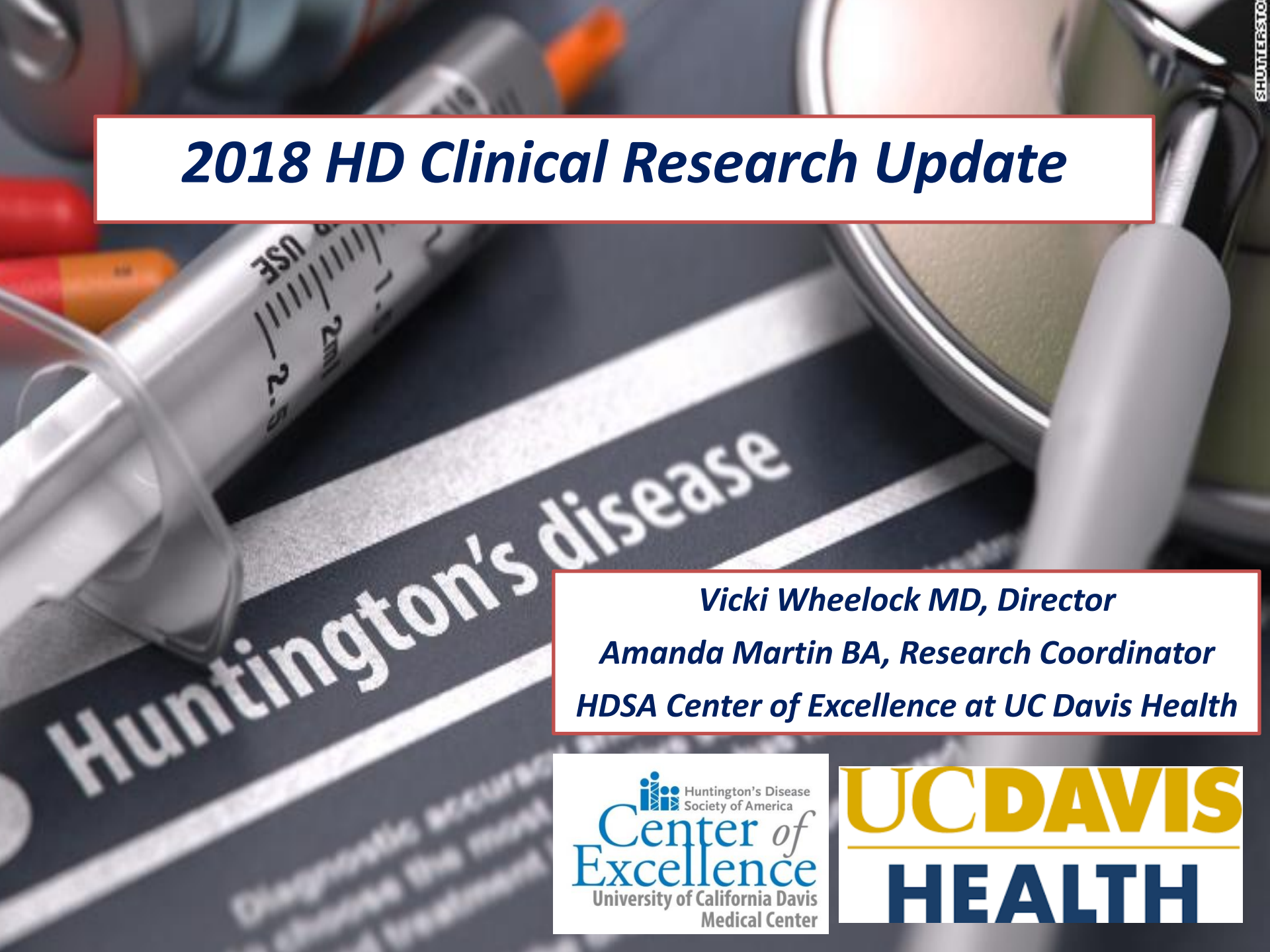


2018 HD Clinical Research Update

Vicki Wheelock MD, Director

Amanda Martin BA, Research Coordinator

HDSA Center of Excellence at UC Davis Health

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

UC DAVIS HEALTH

What's new in HD research??

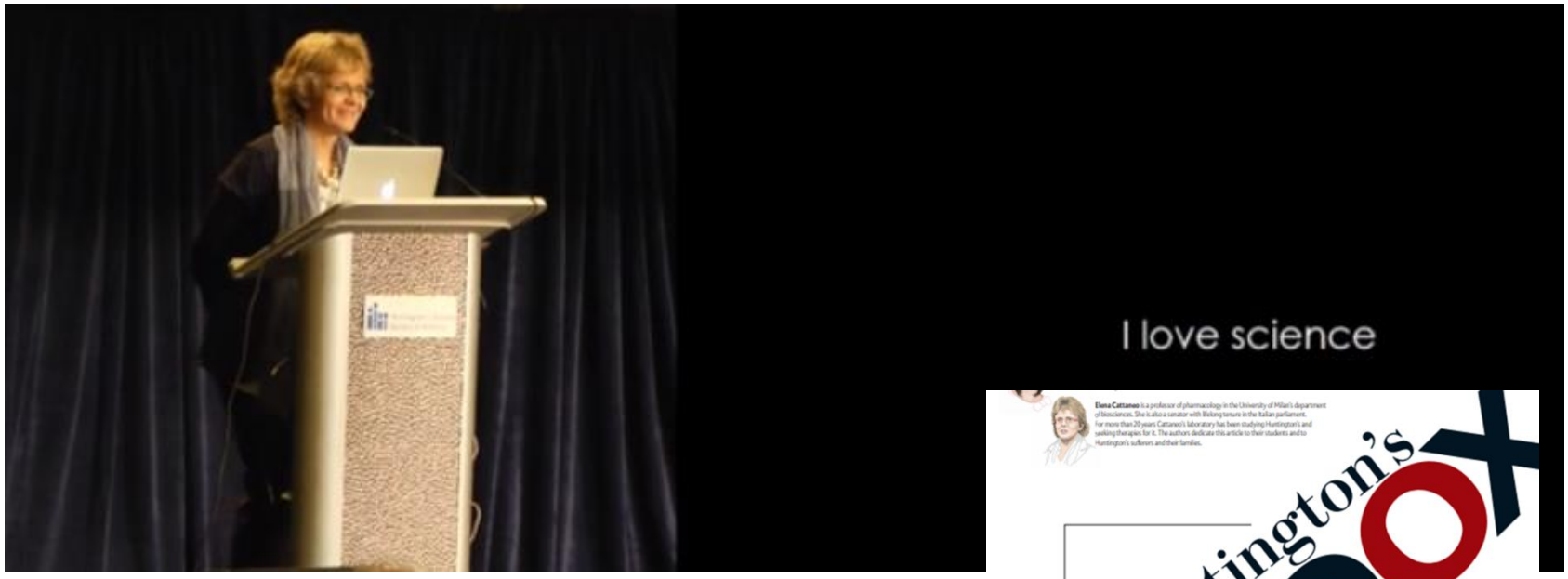
- Dr. Cattaneo's Keynote Address, HDSA 2017
- On-going studies:
  - Enroll-HD
  - STAIR trial: targeting irritability and aggression
  - SIGNAL trial: targeting neuro-inflammation
- New research:
  - Huntingtin-lowering therapies
    - Ionis-HTTrx
    - Wave Life Sciences
    - Others
  - Stem cells – 2018 ☺

New insights: the Huntingtin gene and CAG repeats

Dr. Elena Cattaneo receives HDSA 2017 Research Award

Dr. Cattaneo's keynote address

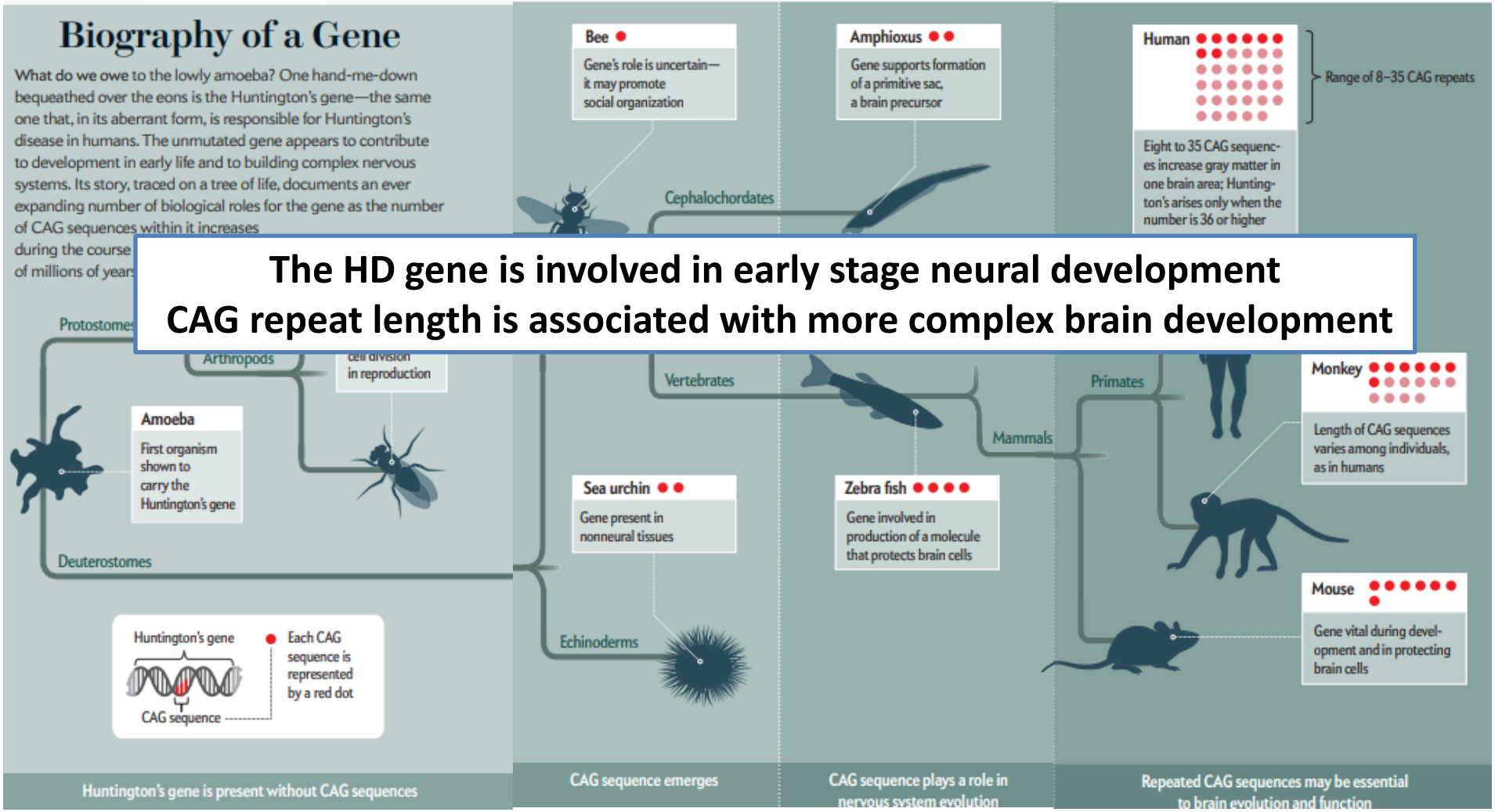
https://vimeo.com/223226694



Elena Cattaneo is a professor of pharmacology in the University of Milan's department of biosciences. She is also a senator with lifelong tenure in the Italian parliament. For more than 20 years Cattaneo's laboratory has been studying Huntington's and seeking therapies for it.

Relationship of the huntingtin gene and CAG repeat length to nervous system development

http://www.cattaneolab.it/wp-content/uploads/2016_08_Scientificamerican_CZ_EC.pdf



The HD gene is involved in early stage neural development
CAG repeat length is associated with more complex brain development

How do we study HD?

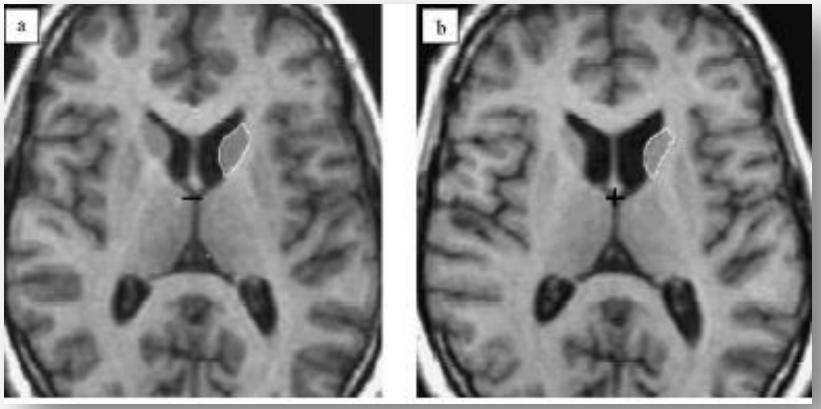
Fruit Flies

Mouse Models

Sheep

Pig

Enroll-HD



... and with observational studies and treatment trials in people with HD

Enroll-HD
Longitudinal Observational Trial

The Goal:

- To create opportunities for research participation for HD families on a **global scale**
- Through this effort, ENROLL- HD is creating a repository of unified clinical information and bio-samples critical for HD scientists world-wide.

Why Is This Important?

- This repository of data creates a wealth of information to better understand the disease and provide an important tool for future HD studies.
- Often studies require large numbers of individuals in order to be sufficiently powerful
- Enroll-HD investigators will be collaborating from across the globe to provide those large numbers of participants

Enroll-HD

Neuro NEXT

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

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

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

NeuroNEXT

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 Amanda Martin at (916)734-3514,

or e-mail at: alema@ucdavis.edu

June 2018: This study is now CLOSED.

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

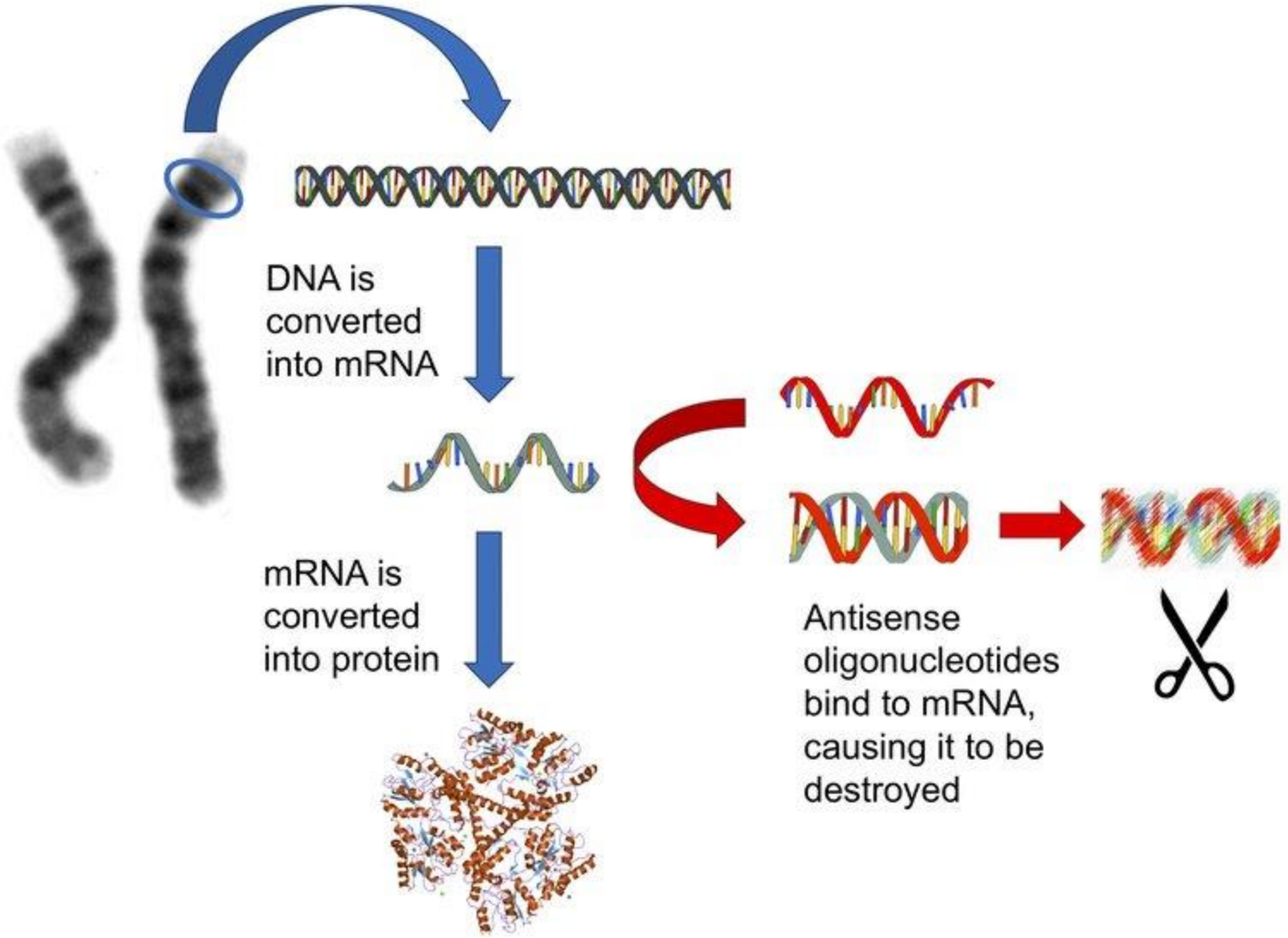
- Study design: Phase 2 multi-center, randomized, double-blind, placebo controlled study of VX15/2503.
- Subjects include 84 individuals who have undergone genetic testing for HD and have the HD gene expansion, with prodromal HD or very early stage HD.
- Treatment is via monthly intravenous infusions for 6 or up to 18 months.
- Primary outcome measure is safety and tolerability of VX15/2503.

SIGNAL Study

- Update: the first group of subjects have completed this trial.
- The sponsors have expanded the SIGNAL trial to 240 participants and it is still actively enrolling
- Study assessments will include monthly visits for infusions, motor, cognitive and behavior rating scales MRI brain scans and spinal taps

See the Huntington Study Group website for further details and list of sites.

Biggest news in HD research since 1993….



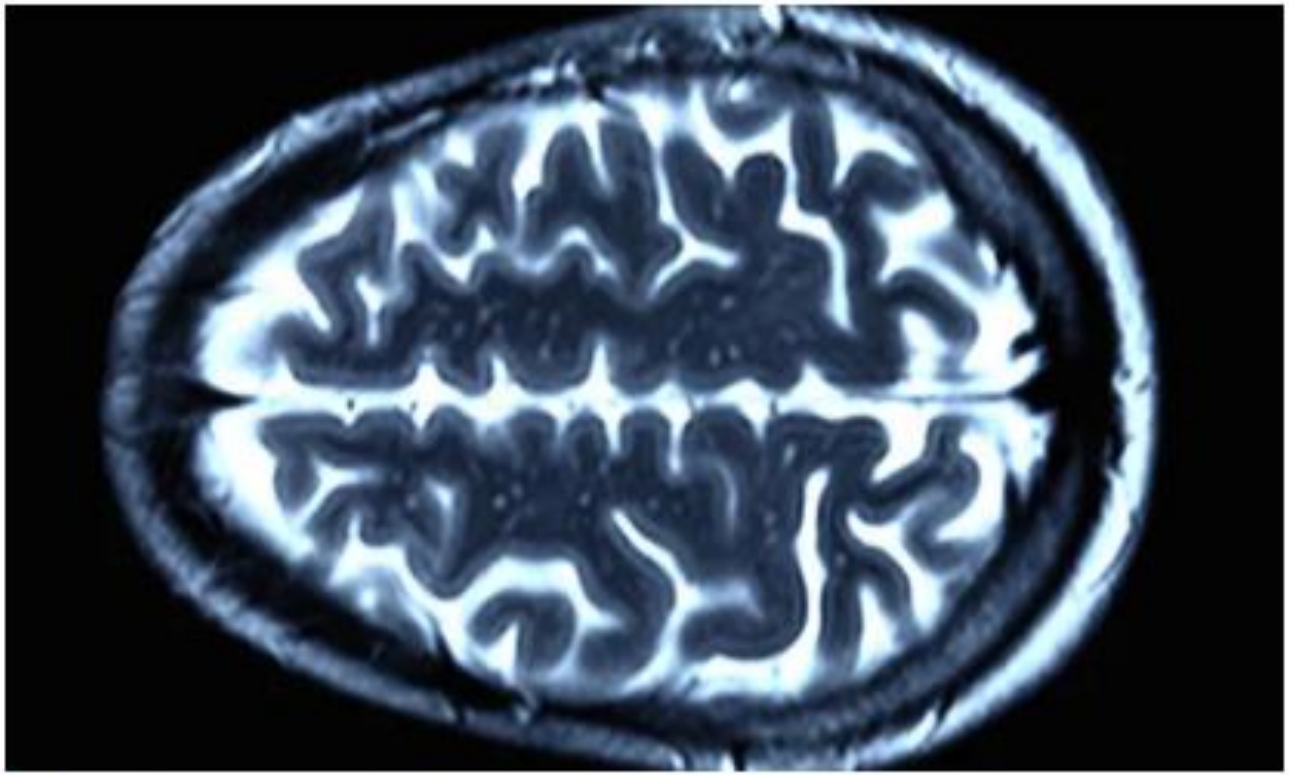
https://medicalxpress.com/news/2017-12-antisense-therapya-neurological-disease.html

12/11/2017

Excitement as trial shows Huntington's drug could slow progress of disease

The Guardian
US edition

Hailed as 'enormously significant', results in groundbreaking trial are first time a drug has been shown to suppress effects of Huntington's genetic mutation



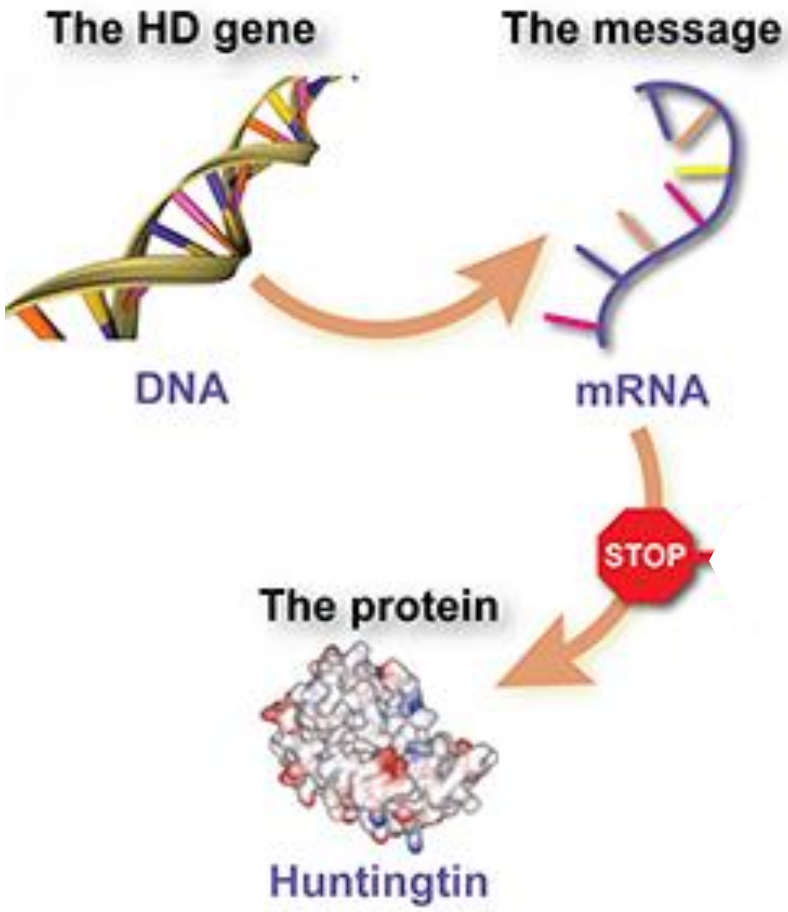
▲ An MRI scan of a healthy brain. In Huntington's patients, a genetic mutation causes irreversible damage to the brain. Photograph: Getty Images/Science Photo Library RF

A landmark trial for Huntington's disease has announced positive results,

https://www.theguardian.com/science/2017/dec/11/excitement-as-huntingtons-drug-shown-to-slow-progress-of-devastating-disease

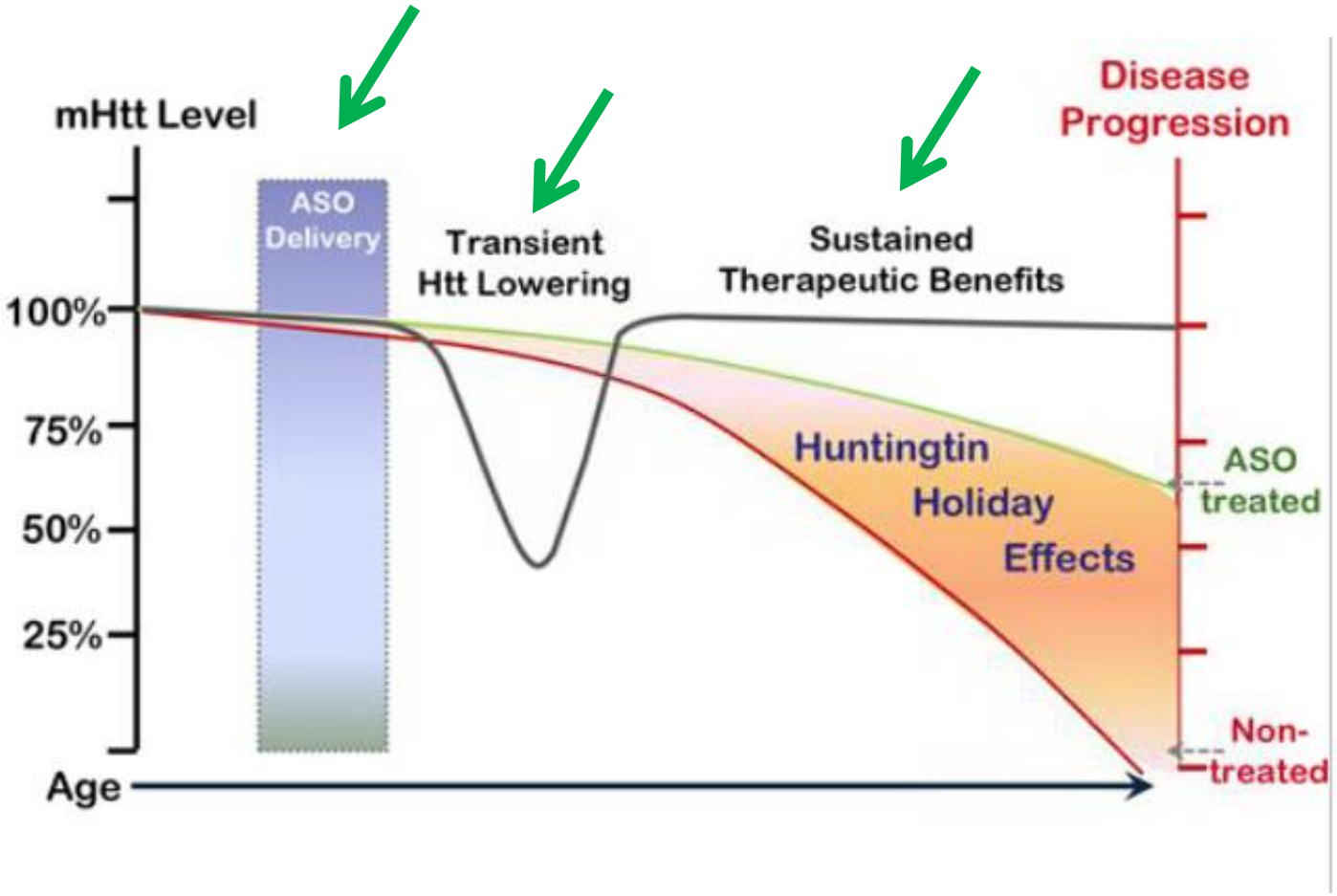
Anti-sense oligonucleotides (ASOs)

- 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.



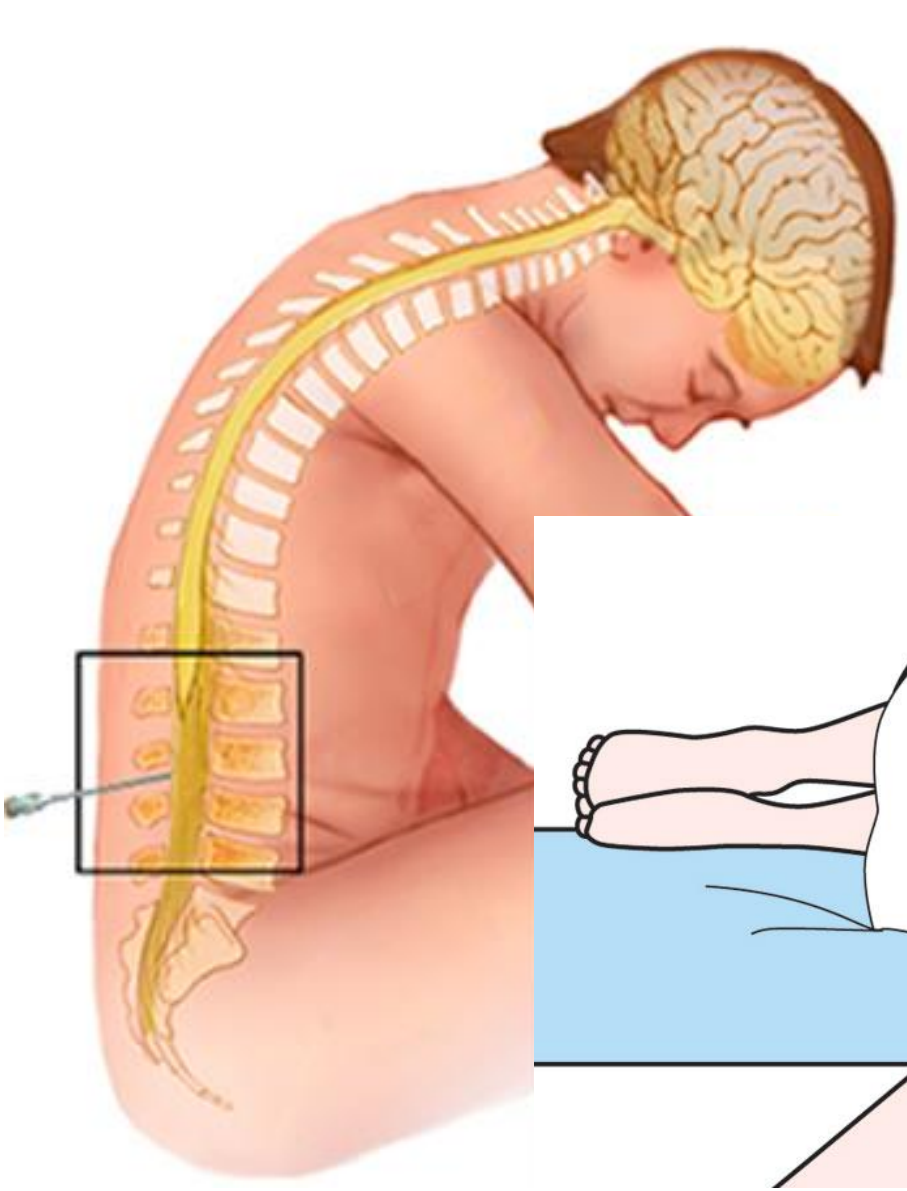
https://en.hdbuzz.net/204

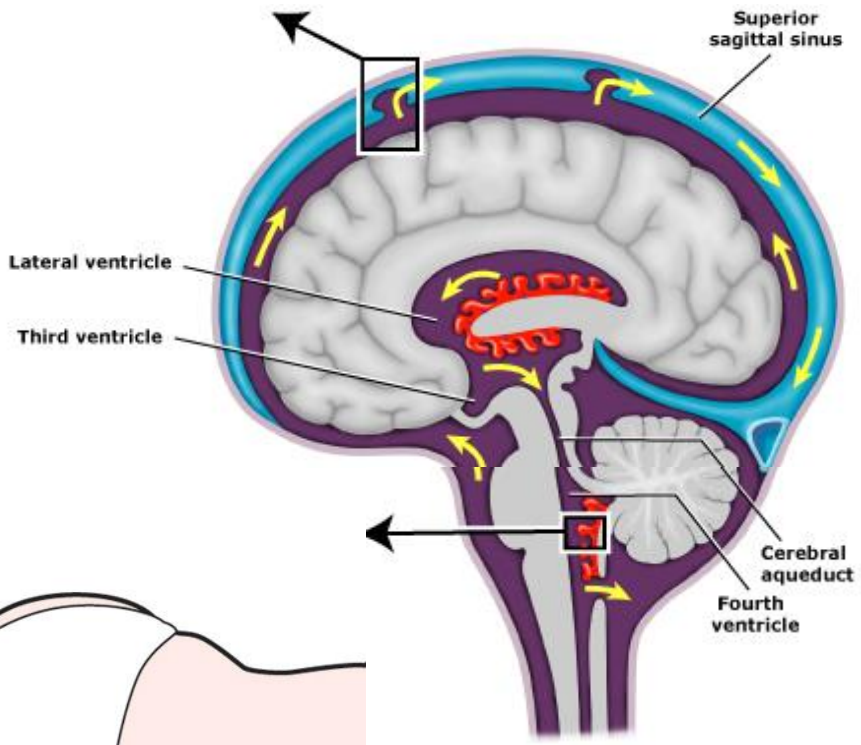
“Huntingtin Holiday”

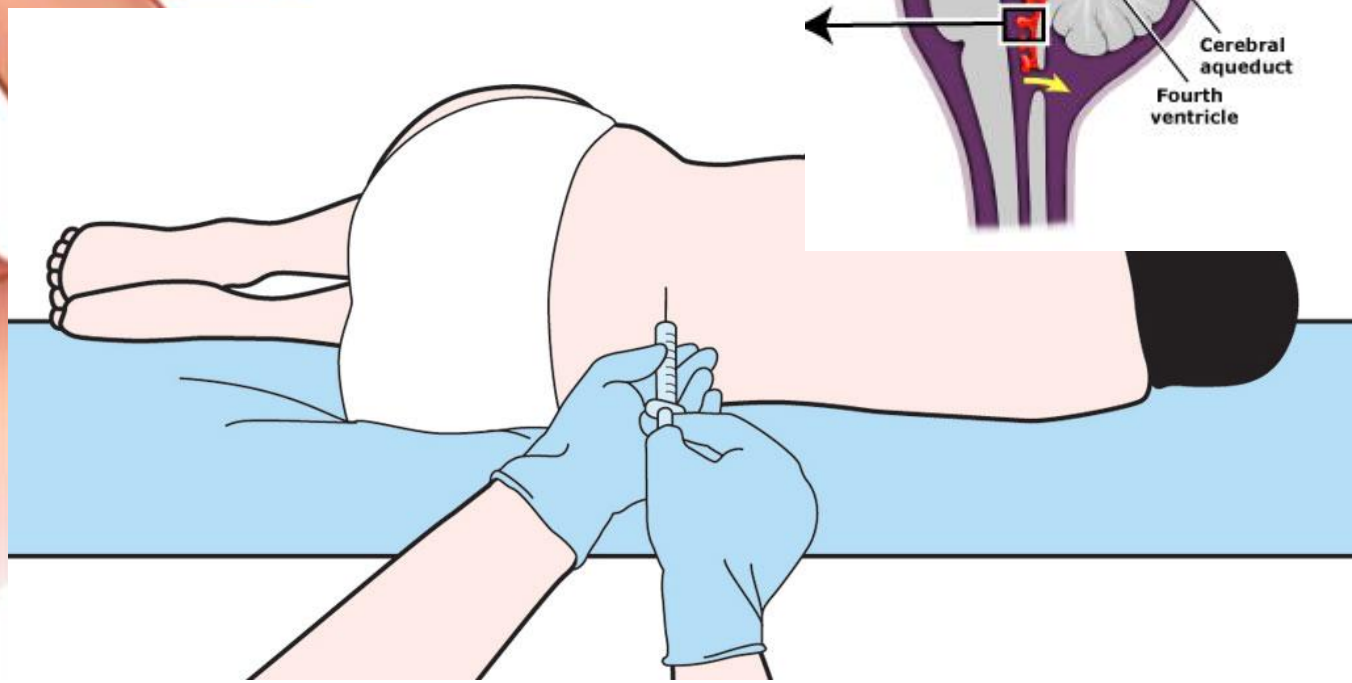


Lu XH and Yang XW. *Neuron* 2012;74(6): 964–966.

Intra-thecal delivery: spinal tap





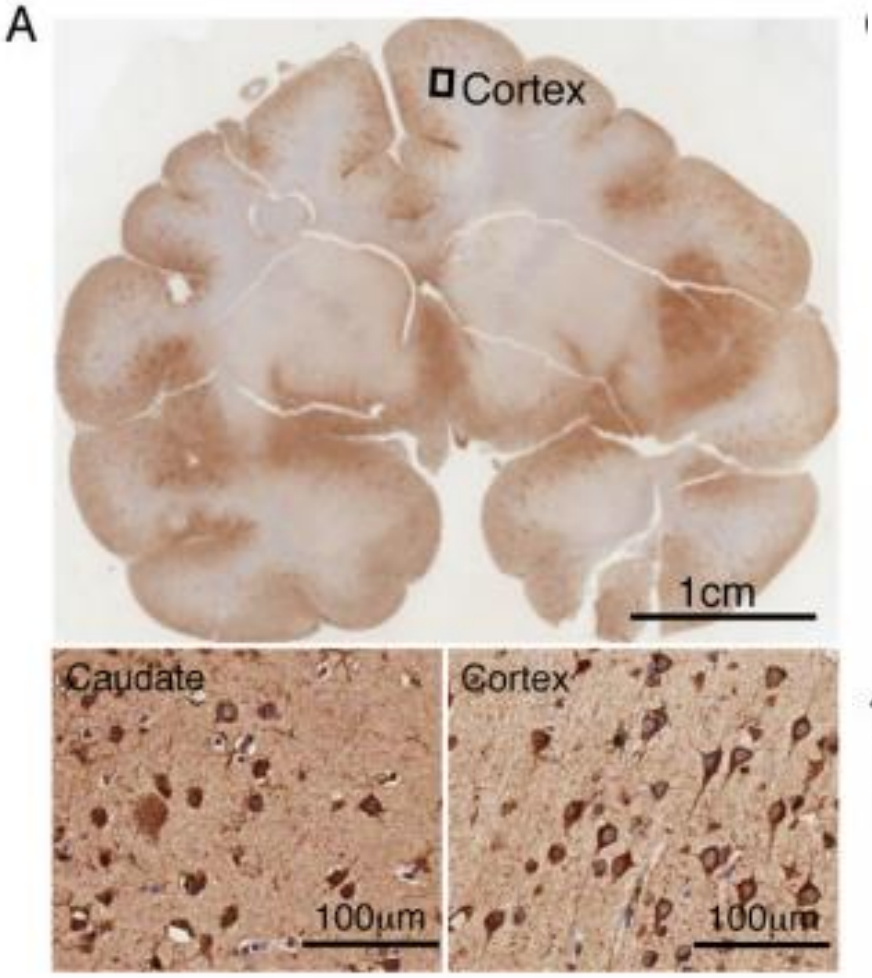


SPINRAZA™
(nusinersen) injection 12 mg/5 mL

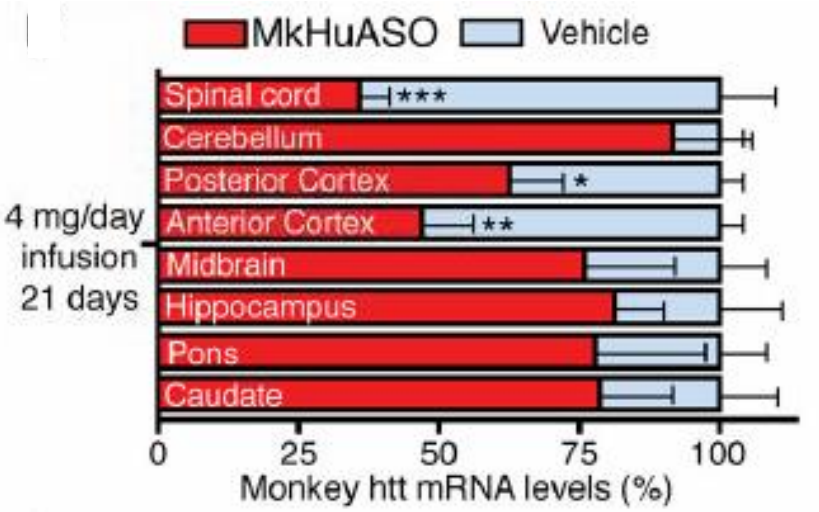
- Spinal muscular atrophy (SMA): motor neuron disease in infants and children
- Developed by Ionis and Biogen
- **The first ASO drug for neurological disease approved by FDA December 2016**
- Given via spinal tap every 2 weeks

for three doses, then once every 4 months

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)



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 1/2 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 was conducted in Canada and the UK.
- Planned enrollment was 36.

Dec 11, 2017:
Phase 1 /2 Study results

- **46 people with early stage HD were treated for 13 weeks** with four intrathecal injections of 10 mg, 30 mg, 60 mg, 90 mg or 120 mg of IONIS-HTT_{Rx} or placebo, administered monthly.
- **Significant, dose-dependent reductions in mHTT were observed in CSF** of treated participants with mHTT reductions of up to approximately 60%

http://ir.ionispharma.com/news-releases/news-release-details/ionis-htt-rx-rg6042-top-line-data-demonstrate-significant

Dec 11, 2017:
Phase 1 /2 Study results

- **No serious side effects** were reported in treated participants. Most were mild and considered to be unrelated to study drug. No participants discontinued from the study.
- **An open-label extension study** for patients who participated in the Phase 1/2 study is ongoing.

http://ir.ionispharma.com/news-releases/news-release-details/ionis-htt-rx-rg6042-top-line-data-demonstrate-significant

The next step….

- Will be to conduct a safety and efficacy study to investigate if decreasing mutant huntingtin protein with IONIS-HTT_{Rx} can benefit people with Huntington's disease.
- Future studies for the program will be conducted globally, including the U.S.
- Roche will announce details about studies, including eligibility criteria and planned start dates, as this information becomes available.

Genentech

A Member of the Roche Group

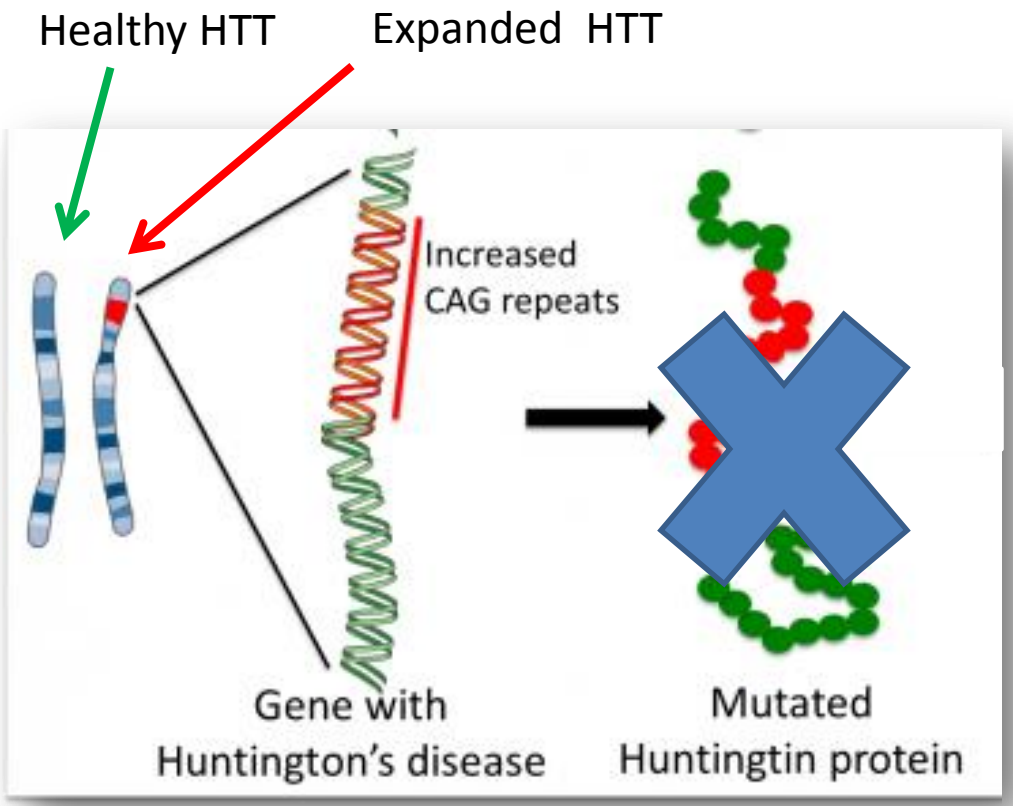
Questions about the next study

Dr. Leora Fox, HDSA

- What is the significance of the Ionis study findings?
- Does IONIS-HTT_{Rx} really work?
- What are the next steps?
- How long will this take?
- Can I sign up for the trial, or put my name on a list?
- What can I do right now?

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.

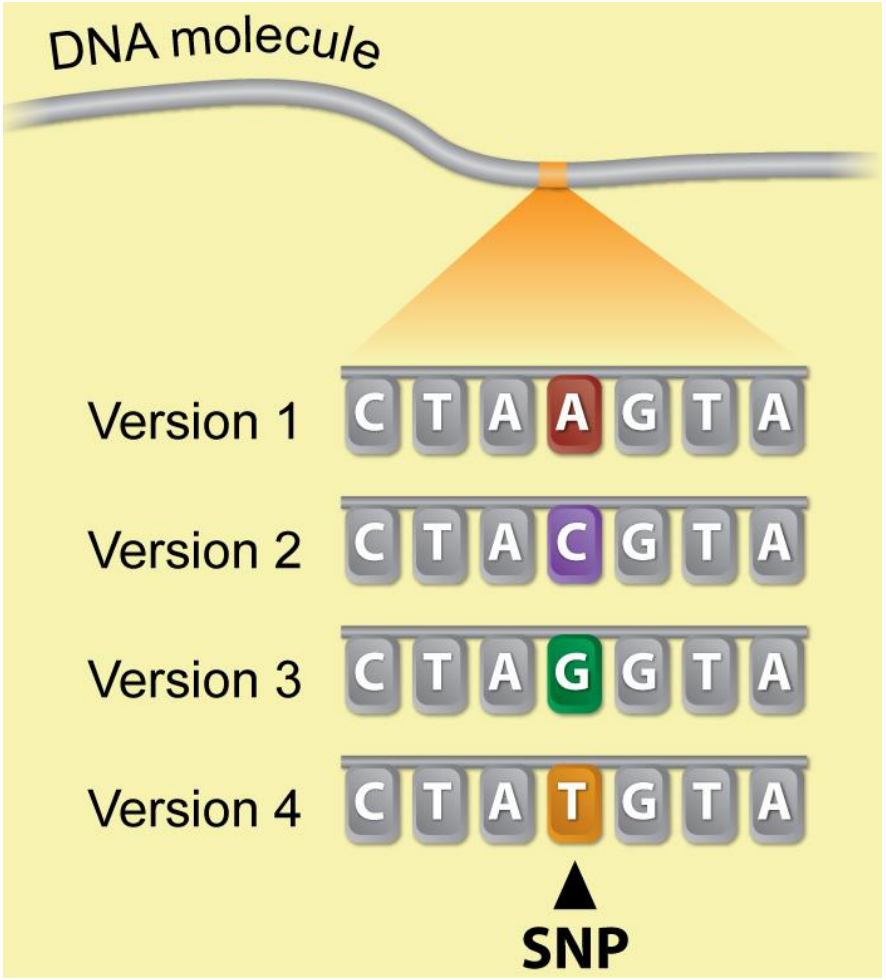


This approach may have less toxicity.

Introduction to a new acronym: SNP

Single Nucleotide Polymorphism, pronounced "snip"

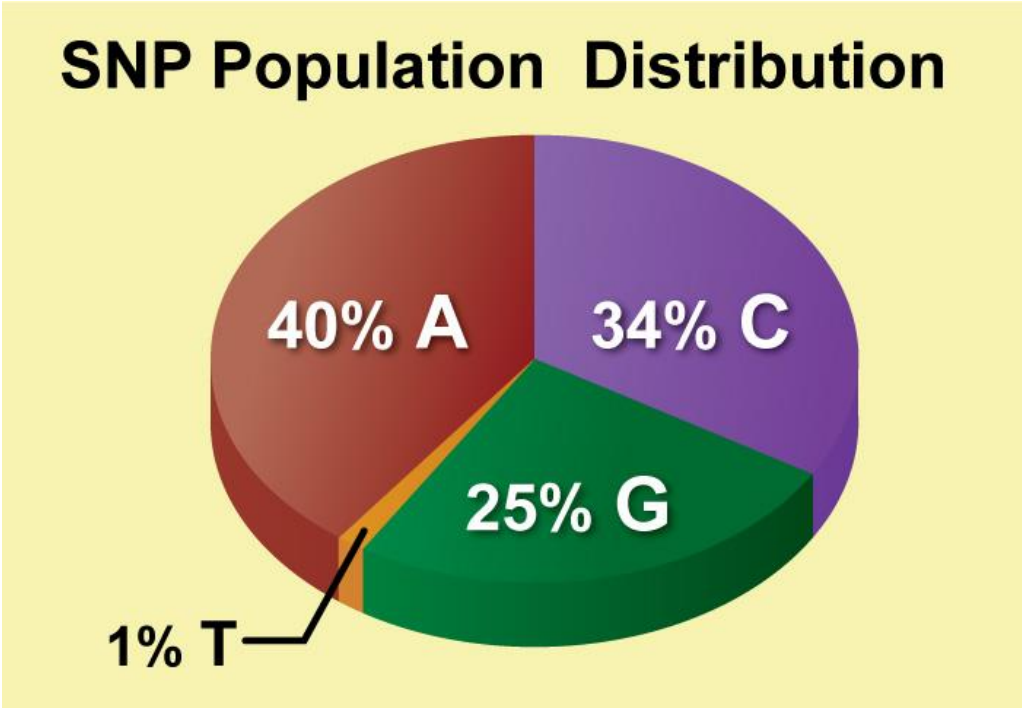
SNPs are single-nucleotide substitutions of one base for another. Each SNP location in the genome can have up to four versions: one for each nucleotide, A, C, G, and T.



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

Not all single-nucleotide changes are SNPs

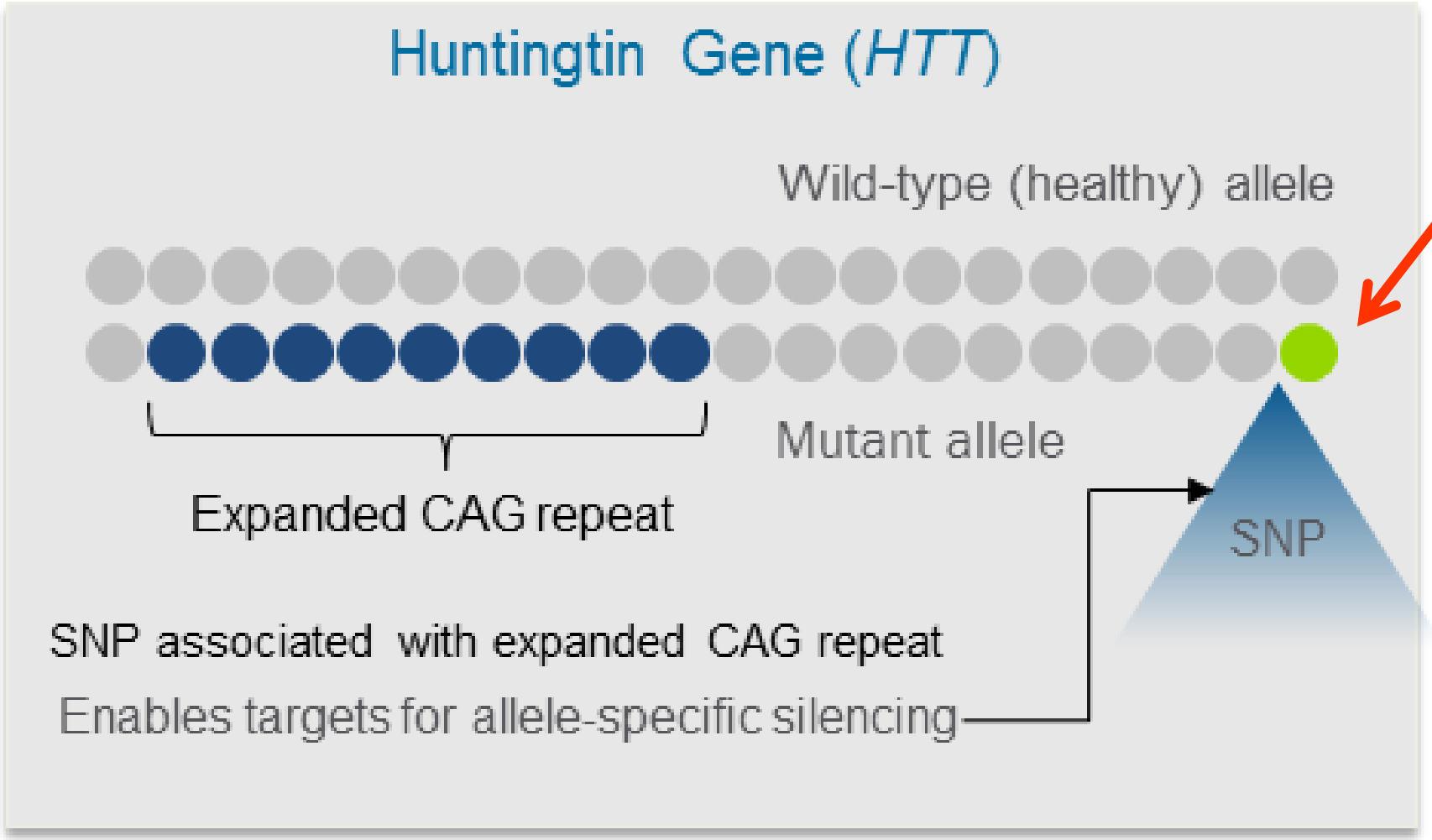
To be classified as a SNP, two or more versions of a sequence must each be present in at least one percent of the general population.



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.

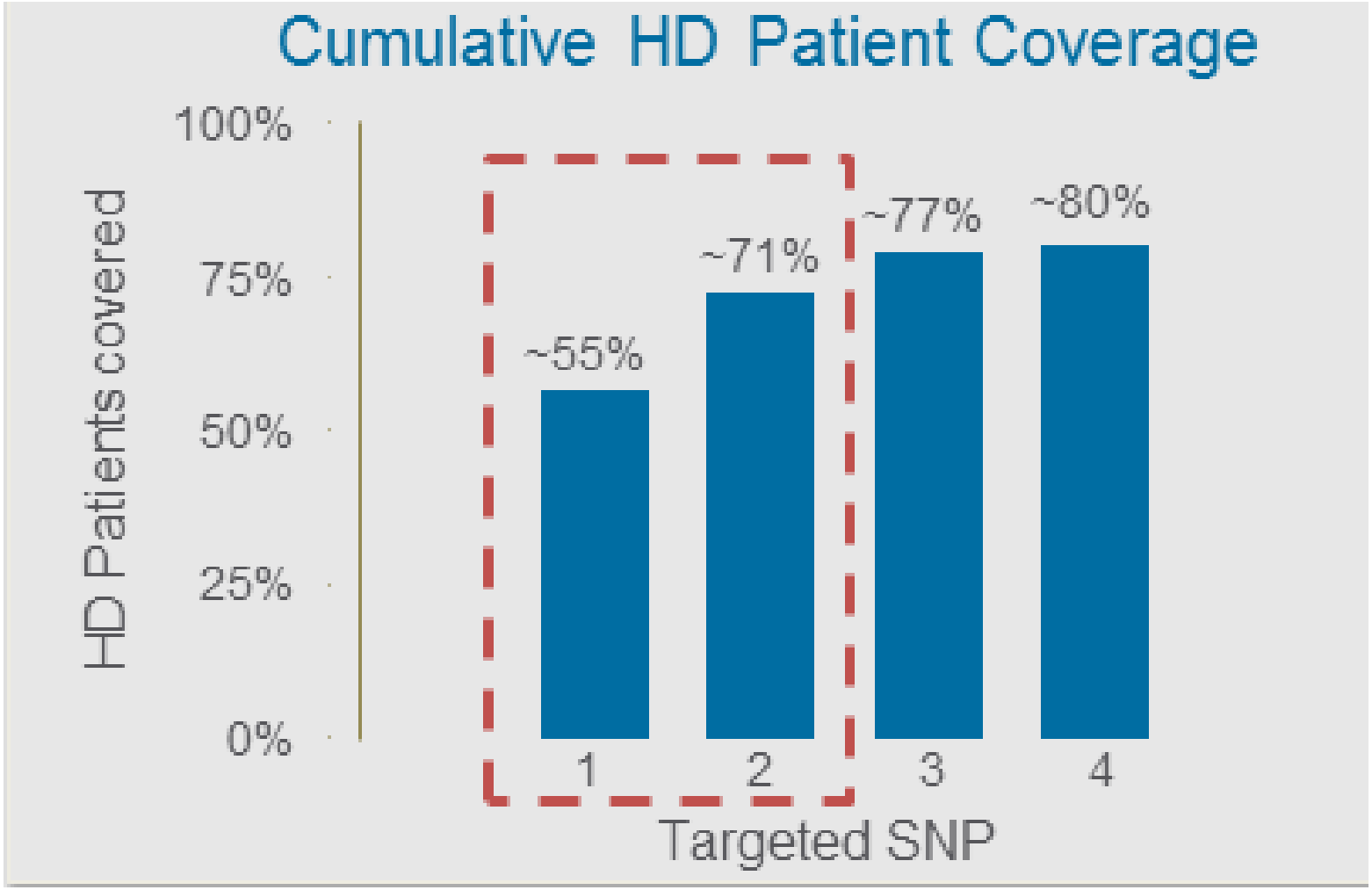
http://learn.genetics.utah.edu/content/precision/snips

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

WAVE ASOs for SNP1 and SNP2

In reporter cell and in patient cell lines:

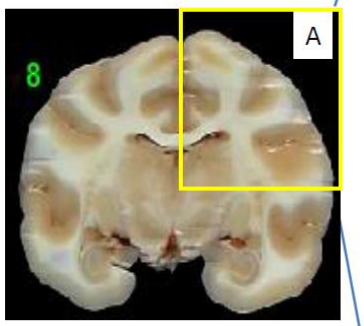
- Both significantly reduce the messenger RNA levels with minimal effect on wild type mRNA levels.
- Both significantly reduce the mutant huntingtin protein levels with minimal effect on wild type huntingtin

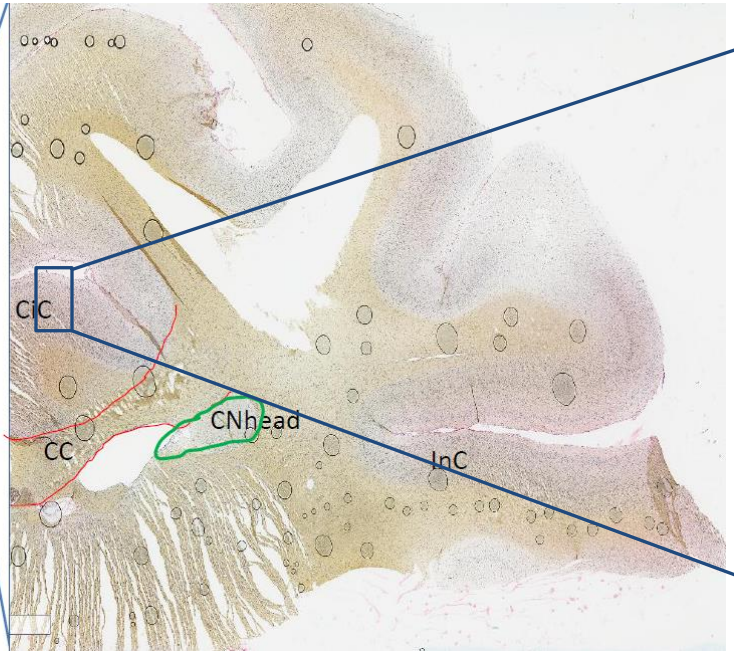
Courtesy Dr. Michael Panzara, WAVE Life Sciences

WAVE ASO for SNP1

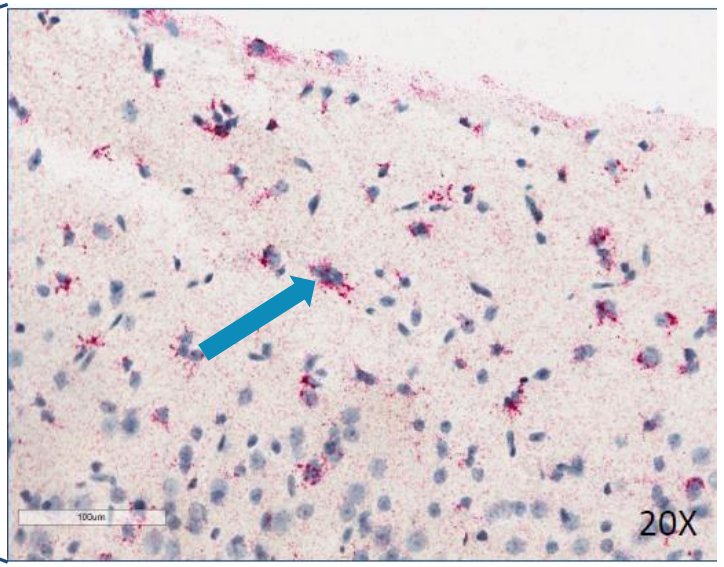
- In non-human primate studies
  - The ASO is easily detected in the cortex and the deep structures of the brain after delivery via spinal tap (“intrathecal route”)

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

PRECISION HD Trials
WAVE ASO 1 and ASO 2

- First-in-human Phase 1 trials initiated in 2017 in Canada and Europe, with start-up in US in 2018
- Primary objective: Assess safety and tolerability of intrathecal doses in early manifest HD patients
- 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

HD research pipeline update from the Huntington Study Group 2017 meeting

Company	Product/mechanism	Delivery
Ionis	HTT_{Rx} anti-sense oligonucleotide (ASO)	Intrathecal (spinal tap)
Wave	Allele-specific ASOs	Intrathecal (spinal tap)
UniQure	AAV5 vector carrying an artificial micro-RNA specifically tailored to silence the huntingtin gene.	Direct brain implantation
Voyager	AAV capsid and transgene to harness endogenous RNA interference pathway to knockdown mHTT	Direct brain implantation
Nuredis	small molecules to interrupt mHTT RNA transcription	Potential oral or subQ

Voyager® THERAPEUTICS

uniQure

NUREDIS

Latest stem cell research:

Leslie Thompson, UC Irvine, Jan 2018

Stem Cell Reports
Article

ISSCR

OPEN ACCESS

Human Neural Stem Cell Transplantation Rescues Functional Deficits in R6/2 and Q140 Huntington's Disease Mice

Jack C. Reidling,[1,11] Aroa Relaño-Ginés,[2,11] Sandra M. Holley,[3,11] Joseph Ochaba,[4] Cindy Moore,[5] Brian Fury,[6] Alice Lau,[7] Andrew H. Tran,[1] Sylvia Yeung,[1] Delaram Salamati,[1] Chunni Zhu,[2] Asa Hatami,[2] Carlos Cepeda,[3] Joshua A. Barry,[3] Talia Kamdjou,[3] Alvin King,[4] Dane Coleal-Bergum,[6] Nicholas R. Franich,[2] Frank M. LaFerla,[1,4] Joan S. Steffan,[1,7] Mathew Blurton-Jones,[1,4,8] Charles K. Meshul,[5,9] Gerhard Bauer,[6] Michael S. Levine,[3,10] Marie-Francoise Chesselet,[2] and Leslie M. Thompson[1,4,7,8,*]

STEM CELL REPORTS

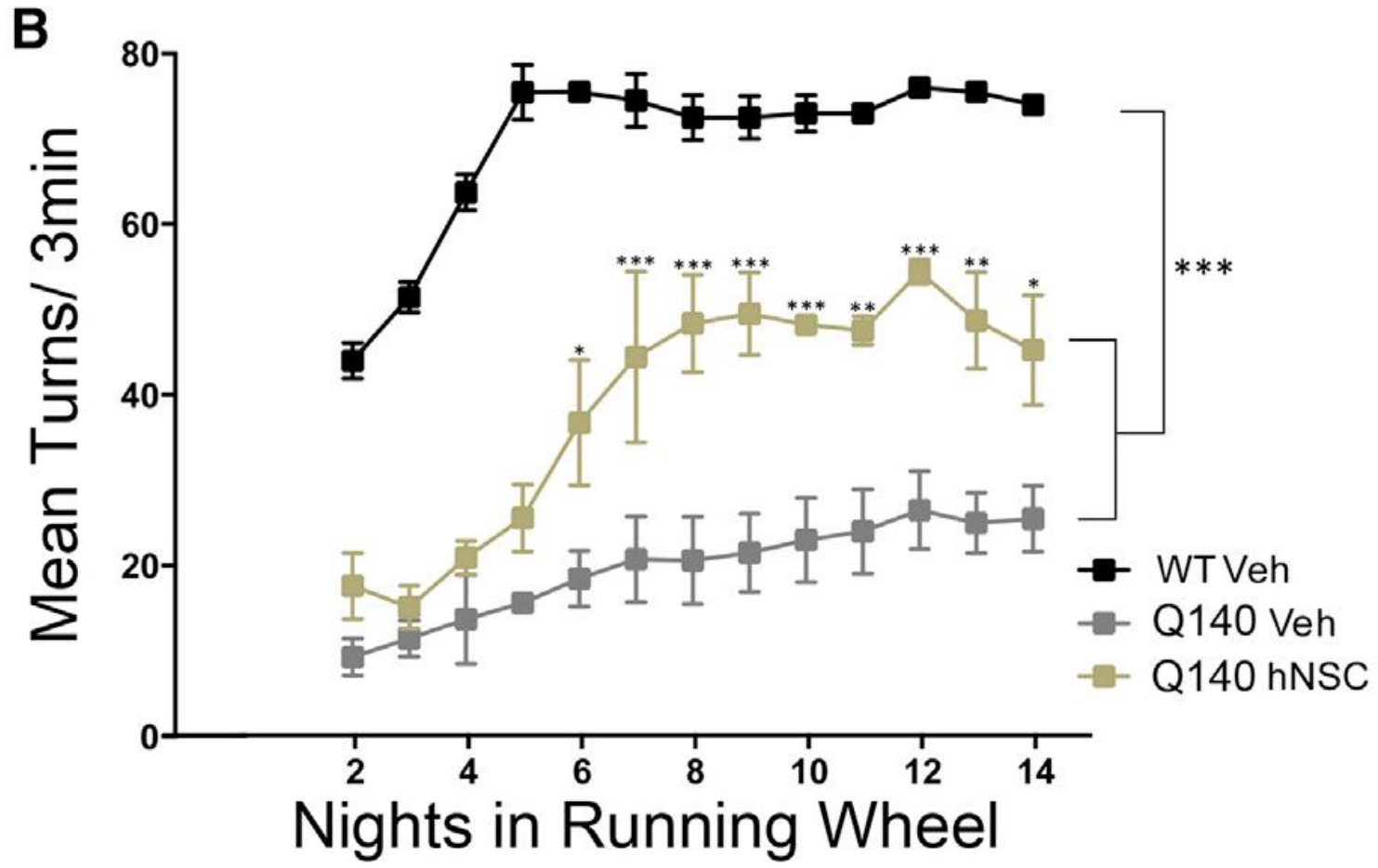
Results

Human embryonic stem cell-derived neurons

- R6/2 mouse, implanted age 5 weeks, sacrificed at 9 weeks:
  - Improved motor behavior
  - Implanted cells showed potential synaptic connections with the stem cells
  - Good cell survival
  - Decreased mutant huntingtin aggregation
- Q140 Knock-in mice, implanted at 2 months, sacrificed at 8 months
  - Improved pole test performance
  - Improved behavior (novel object recognition)
  - Good cell survival
  - Increased BDNF levels
  - Decreased microglial activation
  - Decreased mutant huntingtin aggregation

Results

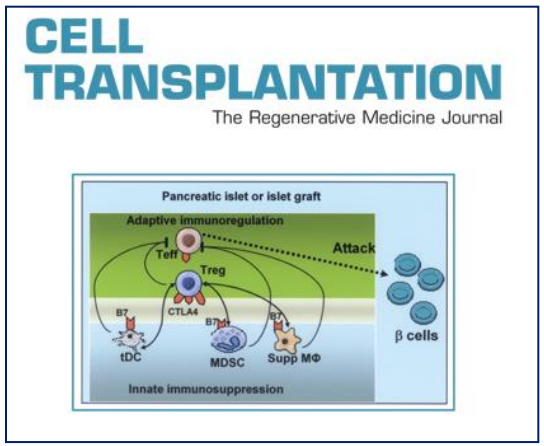
Q140 Knock-in Mouse following implantation

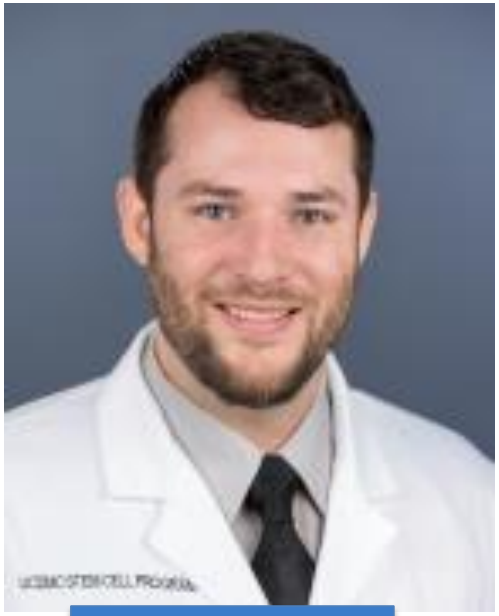


Next steps in HD stem cell research

- Dr. Nolta has 2 major NIH grants to continue research
- Dr. Thompson and other researchers starting a consortium to aid in design of development, testing, delivery of stem cell therapies

Gene Editing for HD





Kyle Fink, PhD

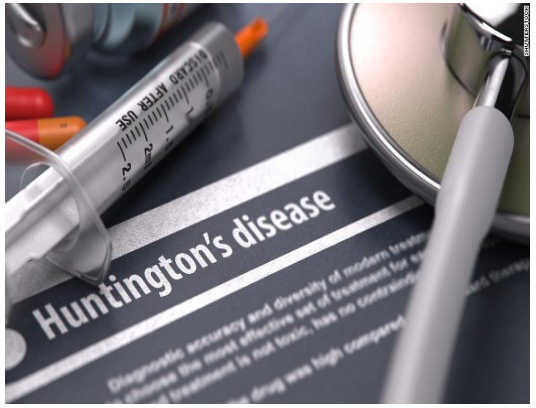
Peter Deng

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

Enroll-HD



Are you interested in HD research?

If you are interested in volunteering
for research participation,
please call Amanda Martin at (916)734-3514,
or e-mail her at: alema@ucdavis.edu

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.

https://www.ucdmc.ucdavis.edu/huntingtons/