The Past, Present and Future for Patients with Huntington’s Disease

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Principal Investigator Enroll-HD
Overview

• The Basics
• The Past
• The Present
• The Future
  - Where does HD research stand 2016?
  - Gene silencing for HD
• Challenges & Hopes
The Basics
George Huntington
THE MEDICAL AND SURGICAL REPORTER.

PHILADELPHIA, APRIL 13, 1872. [Vol. XXVI.—No. 15.

ORIGINAL DEPARTMENT.

Communications.

ON CHOREA.

BY GEORGE HUNTINGTON, M. D.,
Of Pomeroy, Ohio.

Essay read before the Meigs and Mason Academy of Medicine at Middleport, Ohio, February 15, 1872.

Chorea is essentially a disease of the nervous system. The name “chorea” is given to the disease on account of the dancing propensities of those who are affected by it, and it is a very appropriate designation. The disease,

The upper extremities may be the first affected, or both simultaneously. All the voluntary muscles are liable to be affected, those of the face rarely being exempted.

If the patient attempt to protrude the tongue it is accomplished with a great deal of difficulty and uncertainty. The hands are kept rolling—first the palms upward, and then the backs. The shoulders are shrugged, and the feet and legs kept in perpetual motion; the toes are turned in, and then everted; one foot is thrown across the other, and then suddenly...
George Huntington’s background
HD is devastating and progressive

Disease duration 15 – 30 years
Mean survival after manifestation 21 years
Huntington’s Disease is more than a movement disorder

Neuropsychiatric disorder:
- Personality changes
- Cognitive deficits
- Movement disorder

Trias of affected domains:
- Cognitive
- Behavioral
- Motor
HD is a systemic disease with pathology outside the brain as well.

(Van der Berg Lancet Neurology 2009)
HD affects individuals AND their families

• The impact of HD is devastating for individuals and their families … with a long trajectory… young people are aware that they may develop HD for years before there are symptoms
The natural history of HD

Disease signs

Healthy Neurons

Neuronal Dysfunction

Subjective Onset

Clinical Diagnosis

Neuronal Death
What is the root cause of HD?
23 years ago the root cause of HD was identified

A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington’s disease chromosomes

Marcy E. MacDonald, Christine M. Ambrose, Mabel P. Duyao, Richard H. Myers, Carol Lin, Lakshmi Srinidhi, Glenn Barnes, Sherryl A. Taylor, Marianne James, Nicolet Groot, Heather MacFarlane, Barbara Jenkins, Mary Anne Anderson, Nancy S. Wexler, James F. Gusella

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5 Center for Cancer Research Massachusetts Institute of Technology Cambridge, Massachusetts 02139, USA
Huntington’s Disease

- Autosomal dominant
- Monogenic
- Fully penetrant
- \((CAG)_n\) effect
- Differential cell vulnerability

- Ubiquitous expression
  - spatial & temporal
- Complex function
  - embryonic lethal
  - loss of function vs gain of function
- Cell autonomous vs. network/context mediated toxicity
Understanding the root cause of a disease is different from having an efficient treatment resulting in real life clinical benefits
One needs to understand how the disease ‘works’ in order to identify targets for therapeutical interventions
There is urgency – each HD expansion carrier feels time clocking away
Everybody has heard ‘The cure is *around the corner*’ often, but *around the corner* seems to be an awfully long distance
You have to have insights in why it takes time to establish therapies with real-life benefits in order to cope with waiting.
How frequent is HD?
Huntington’s Disease is a rare disorder

Prevalence: 4 - 12/100,000 inhabitants

**Systematic Review**

*Neuroepidemiology* 2016:46:144–153
DOI: 10.1159/000443738

**The Prevalence of Huntington’s Disease**

Michael D. Rawlins\textsuperscript{a}  Nancy S. Wexler\textsuperscript{b,c}  Alice R. Wexler\textsuperscript{b}  Sarah J. Tabrizi\textsuperscript{d}  Ian Douglas\textsuperscript{a}  Stephen J.W. Evans\textsuperscript{a}  Liam Smeeth\textsuperscript{a}
Highest prevalence of HD in populations of Western European origin
There is evidence for an increasing HD prevalence of between 15 and 20% per decade in studies from Australia, North America and Western Europe.
May be related with the distribution of ‘risk haplotypes’ on chromosome 4 in the general population

The ‘risk haplotypes’ are more common in the general population of regions that have an increased prevalence of HD
Why is there an increasing prevalence of HD?

- Demographic shift: people in the general population live longer and therefore HD expansion mutation carriers with short CAG repeat expansions live long enough to experience the signs and symptoms of HD.
The Past
‘This man has Huntington’s disease - I have not arranged to see him again. There is nothing more I can do.’
How is HD treated?
The Present
HD symptomatic domains and treatment options

Movement disorder
Behavioral syndrome
Cognitive Syndrome
Metabolic Disturbance
HD Phenotypic Expression Array

- none
- Mild, not a problem
- Mod-severe, Ongoing despite treatment
- Severe, terrible, Bad, active
HD Phenotypic Expression Array

- Paranoia/psychosis
- Dystonia
- Oral motor
- Chorea
- Apathy
- Judgment/disinhibition
- Depression/anxiety
- Hallucinations
- Seizures
- Aggressive/assaultive
- OCD
- Sleep

- none
- Mild, not a problem
- Mod-severe, Ongoing despite treatment
- Severe, terrible, Bad, active
Major symptoms to be dealt with in the clinic

- Psychiatric problems
- Cognitive problems
- Movement disorder
- Speech/swallowing disorders
- Balance and falls
- Weight loss
- Sleep disturbance
### Multidisciplinary care

- Neurologist
- Psychiatrist
- General physician
- Dentist
- Nurse (case manager)
- Research nurse
- Psychologist
- Neuropsychologist
- Physical therapist
- Occupational therapist
- Speech therapist
- Dietitian
- Social worker
- Genetic counselor
- Chaplain
- Lay group liaison
Can you as a HD patient get better with treatment?
An unequivocal ‘YES’
What we can do

• Low mood can be improved
• Irritability and aggression can get better
• Sleep problems can be fixed
• Lost weight can be regained
• Chorea can be suppressed (to some extent)
• The ability to move around can be improved
However, there are limits: all improvements do not last forever and new problems emerge.
Therefore we need HD research
Presentations on HD at the EAN 2016 in Copenhagen

**P 22085** Motor disorder in Huntington's disease may begin like tic disorder: atypical clinical presentation in a large Turkish pedigree
M. Gültekin, F.F. Erdoğan, F. Yetkin, R. Baydemir, M. Mirza
KAYSERI, TURKEY

**P 31283** Sleep disturbance in patients with Huntington’s Disease - polysomnography characteristics
E. Feketeova, M. Škorvánek, Z. Gdovinova
KOSICE, SLOVAKIA

EFNA PUBLIC AWARENESS DAY ON HD – Copenhagen, May 28, 2016

www.euro-hd.net
Presentations on HD at the EAN 2016 in Copenhagen

P 22156  Cerebrospinal fluid markers in premanifest and manifest Huntington’s disease: evidence of sequential development of neurodegeneration and inflammation

O 1133 15:15 Low cancer prevalence in polyglutamine expansion diseases

G. Coarelli¹, A. Diallo¹, F. Calvas¹, P. Charles¹, C. Tosi Marelli², C. Ewenczyk¹, C. Tranchant³, M. Tchikviladzé¹, M.-L. Monin¹, B. Carlander², M. Anheim³, F. Mochel¹, A. Brice¹, S. Tezenas Du Montcel¹, S. Humbert⁴, A. Dürr¹ ¹PARIS, ²MONTPELLIER, ³STRASBOURG, ⁴GRENOBLE, FRANCE
HD research needs speed
Therefore we need to work together
Working together worldwide to address a disease that affects people all over the world: Enroll-HD
Enroll-HD is intended to be an enabling platform for translational and clinical HD research

- Sites: 200+
- Countries: 27
- Languages: 16
- COHORT + Registry participants: ~13,000
- Expected max. visits/month: 600
- Est. new participants/month: 200
- Globally enabled IT, bio-repository and data monitoring systems

We are aiming for 25,000 to 30,000 participants within the next 5 years
Where does HD research stand 2016?
What makes the difference 2016:

- Compounds/potential drugs are SPECIFICALLY designed for HD, e.g.
  - Agents lowering the load of mutant htt gene products
    - Production/expression
    - Disposal/degradation
  - Agents modulating key pathophysiological mechanisms central to HD

There is a large scale TARGETED development of potential drugs for HD
CHDI

TEVA

Pfizer

Accelerating therapeutic development for Huntington's disease
Conceptually, there is a generic fix for all monogenetic dominant disorders: silence the mutant allele(s)
HD gene silencing

DNA → mRNA → The protein

Huntingtin

STOP Gene silencing

The HD gene

The message

ASO AAV-miRNA shRNA siRNA Sm Mol AAV-ZFP

EFNA PUBLIC AWARENESS DAY ON HD – Copenhagen, May 28, 2016

www.euro-hd.net
In HD models, gene silencing seems to work.
HTT Lowering Therapeutic Efforts, 2015
A first: the IONIS-HTT\textsubscript{Rx} trial
A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Multiple Ascending Doses of Intrathecally Administered IONIS-HTT$_{Rx}$ in Patients with Early Manifest Huntington’s Disease (PI: Sarah Tabrizi, London)
The compound

- IONIS-HTT$_{Rx}$ is an antisense oligonucleotide (ASO) targeting total human huntingtin (htt) – non-allele selective gene silencing
  - 5-10-5 Gen 2.0 MOE gapmer mixed backbone (PO/PS)
**History of antisense oligonucleotide medicinal chemistry - the most useful chemistries**

- **Most useful backbone to date**
  - Improves stability and PK
  - Adding charge does not improve cell uptake and makes PK worse

- **Isis Gen 2.5 Chemistry**
  - Improves potency with reduced toxicity risk

- **Most useful sugar modification to date**
  - Improves stability, affinity and potency; reduces non-specific toxicities

- **LNA**
  - Improves potency but increases hepatotoxic risk

- **Propynes**
  - Improve potency but are severely hepatotoxic

- **2′-O-methyl**
  - Improves stability and affinity a bit but inferior to MOE

- **5-methylcytosine**
  - Most useful heterocycle to date
  - Reduces immune stimulation and improves affinity
The compound

- IONIS-HTT<sub>Rx</sub> is an antisense oligonucleotide (ASO) targeting total human huntingtin (htt) – non-allele selective gene silencing
  - 5-10-5 Gen 2.0 MOE gapmer mixed backbone (PO/PS) that works through the RNase H mechanism

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Mixed PS/PO Nucleotide Backbone
Administration of the compound: intrathecal ASO delivery

- Lumbar puncture bolus injection

IHC against drug in monkey spinal cord following intrathecal delivery of ASO
Intrathecal ASO delivery: onset and duration of action

- Lumbar intrathecal “slow push” bolus administration of IONIS-HTT$_{\text{Rx}}$
  - Onset of action $\approx$ 4-6 weeks (maximal protein suppression)
  - Expected duration of action $\approx$ 4 months
The Primary Questions to be Answered

• Safety and tolerability of multiple intrathecal bolus administrations (primary objective)
  - maximum dose in the IONIS-HTT$_{Rx}$ study will be $\leq$ 3-fold lower than NOAEL as established in toxicology studies in sub-human primates
  - BUT concern about e.g. immunologically mediated inflammatory SAEs
    - Somewhat mitigated by apparently good tolerability of intrathecally administered ASO targeting SMN2 or SOD1 in > 100 patients, some treated for > 3 years
  - Concern about on-target SAEs
The design

**COHORT ENROLLMENT FLOWCHART**

- **Cohort A**
  - (N = 4)
  - screen
  - 10 mg
  - 10 mg
  - 10 mg
  - 10 mg
  - Post-treatment Period
  - Review*

- **Cohort B**
  - (N = 8)
  - screen
  - 30 mg
  - 30 mg
  - 30 mg
  - 30 mg
  - Post-treatment Period
  - Review*

- **Cohort C**
  - (N = 8)
  - screen
  - 50 mg
  - 50 mg
  - 50 mg
  - 50 mg
  - Post-treatment Period
  - Review*

- **Cohort D**
  - (N = 16)
  - screen
  - 70 mg
  - 70 mg
  - 70 mg
  - 70 mg
  - Post-treatment Period
  - Review*
The question NOT going to be answered is the question of clinical benefit. This is a phase I study.
Study Implementation

- Small study (targeted number of participants 36 - 48 HD stage I patients) of short duration (14 weeks of treatment, post-treatment observation up to week 29)

- Conducted in UK (PI Sarah Tabrizi), Canada and German HD centers with in-patient IC monitoring facilities
It happened: the first patients have been receiving the compound in September 2015; by now 10 patients have been treated
The Issues

• How widespread is the distribution of intrathecally administered IONIS-HTT_{Rx}?
Demonstration of ASO-IR in Spinal Cord and Brain in a Type 1 SMA Infant

- Autopsy material obtained from subject who received 3 doses of the ASO-compound (12 mg equivalent on study days 1, 15 and 85 autopsy performed study day 163)

- Immunohistochemical staining confirms presence of the ASO in all levels of spinal cord and in specific brain regions
The Issues

- How widespread is the distribution of intrathecally administered IONIS-HTT$_{Rx}$?
  - Basal ganglia/striatum?
  - lower cortical layers, harboring cortico-striatal projection neurons?

- Can we measure any changes in putative pharmacodynamic biomarkers?
  - mhtt levels in CSF?
  - reduction of cortical htt by 50%?
The Challenges

- Expectation setting
  - Patients are NOT missing the boat, if they do not participate in the IONIS-HTT$_{Rx}$ study
  - Establishing safe gene silencing therapies for HD resulting in clinical benefits will take time
A solid foundation is essential
The Future
Other approaches to gene silencing
Technologies to suppress gene expression

RNA silencing to reduce Htt protein levels by decreasing mRNA translation by:

- **Antisense oligonucleotides (ASO)**
  - Single stranded DNA molecule that is complementary to the target mRNA and forms a DNA/RNA hybrid complex that is degraded by RNase H

- **Small interfering RNAs (siRNA)**
  - A double stranded RNA molecule that is processed by Dicer, assembled into the RISC, and binds the target mRNA, resulting in mRNA cleavage and down-modulation

Intra-brain-parenchymal delivery using pumps

Description of Infusion Hardware

- **Intraparenchymal Catheter**: The IPa catheter was designed to be as minimally invasive as possible – improving tissue reaction response and minimizing backflow.
- **Cranial Anchor**: The cranial anchor was designed to have a minimal profile, and connect the IPa catheter to the pump catheter.
- **SynchroMed II Pump**: Implanted pump has 20 or 40 ml reservoir, is fully programmable and can accurately deliver drugs at rates from 0.04 to 14 µl/min.

![Diagram of infusion hardware](image)

**Figure 2(A)**: Chronic IPa delivery system components.

**Figure 2(B)**: The end of the IPa catheter. The diameter of the infusion tip is 300 µm, for reference a typical striatal neuron is 10 – 25 µm in diameter. The diameter of the IPa catheter is 1 mm.
Intra-putaminal convection enhanced delivery (CED) of Htt siRNA in a non-human primate

From Raghavan et al., Neurosurg Focus. 2006;20(3):E12

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rAAV as a Gene Delivery Vector for CNS Disorders

• Replication defective parvovirus
• Transduce non-dividing cells
• Nonpathogenic
• Vector production and purification methods have been established for clinical use
• A single intracranial administration AAV could provide long term suppression of Htt
AAV1-eGFP May Produced Widespread Transduction in the Striatum and Cortex
Cortico-striatal Connections Provide Avenues for AAV Transport

Suppressing exclusively the mutant htt gene copy
Zinc finger DNA binding domains can be engineered to recognize specific target sequences.
Engineered ZFPs for allele-specific repression of mutant Htt

WT Allele

Disease Allele

Transcription Start Site

Exon 1

CAG < 24

CAG > 39
Engineered ZFPs for allele-specific repression of mutant Htt

WT Allele

Disease Allele

Transcription Start Site

Exon 1

CAG < 24

CAG > 39
Genome-wide specificity of an allele-specific Htt repressor

>2-fold change
P<0.05
ZFP-driven repression of mutant Htt in R6/2 striatum

AAV injection at 5 weeks of age
Analysis at 12 weeks of age

NS

***

Normalized Expression

AAV2/6 qPCR
ZFP GFP Mouse Htt

R6/2 Transgene

www.euro-hd.net
ZFP expression rescues expression of medium spiny neuron markers in R6/2 mice

**Normalized Expression**

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Realistically it will take at least a decade before gene silencing therapeutics become a prescribe-able therapeutic option for HD expansion mutation carriers.
Beyond gene silencing
Identifying targets for therapeutical interventions: learn from the experiments of nature – genetic modifier studies
Identification of Genetic Factors that Modify Clinical Onset of Huntington’s Disease

Genetic Modifiers of Huntington’s Disease (GeM-HD) Consortium*
*Correspondence: gusella@helix.mgh.harvard.edu
http://dx.doi.org/10.1016/j.cell.2015.07.003

Cell 162, 516–526, July 30, 2015

The Genetic Modifiers of Huntington’s Disease (GeM-HD) Consortium was organized into the following groups: GeM Group 1: Jong-Min Lee, Vanessa C. Wheeler, Michael J. Chao, Jean Paul G. Vonsattel, Ricardo Mouro Pinto, Diane Lucente, Kawther Abu-Elneel, Eliana Marisa Ramos, Jayalakshmi Srinidhi Mysore, Tammy Gillis, Marcy E. MacDonald, and James F. Gusella; GeM Group 2: Denise Harold, Timothy C. Stone, Valentina Escott-Price, Jun Han, Alexey Vedernikov, Peter Holmans, and Lesley Jones; GeM Group 3: Seung Kwak and Mithra Mahmoudi; GeM Group 4: Michael Orth and G. Bernhard Landwehrmeyer; Registry Investigators: Jane S. Paulsen; PREDICT-HD Investigators: E. Ray Dorsey and Ira Shoulson; COHORT, PHAROS, and TREND-HD Investigators; Richard H. Myers; and HD-MAPS Investigators.
The concept of genetic modifiers is straightforward to understand.

Comparing two groups of beer lovers:
Duff beer is CAG expansion in the HTT gene.
Beer belly caused by drinking beer is HD.
TV time is a modifier of HD.

Jong-Min Lee, Ph.D.
Individual variation of onset age is in part (50%?) due to genetic variability in modifier genes
Modifiers may generate strong effects, collectively
GWA analysis to discover genetic modifiers of HD

Subjects: HD subjects (~4,000) with European ancestry and CAG 40-55 from MGH HD Center, HD-MAPS, PREDICT-HD, and EHDN

Phenotype: Residual age at onset of motor signs

Genotype: Minor allele count of a given SNP (after QC, ~ 8 million SNPS)

Statistical framework: Single SNP analysis using linear mixed effect model to correct relationship

Genome-wide significant signals (p-value < 0.00000005) at Chr15 and Chr8
Distribution of effect sizes of SNPs

Each circle represents a SNP
Red filled circles, LD-independent SNPs

-log10(p-value)

Effect size (years / minor allele)

Hasten or delay onset by 6 or 1.4 years, respectively

Genome-wide significance (p-value < 0.0000005)
Suggestive significance (p-value < 0.00001)
Summary

- Effects at the chr15 locus hasten or delay onset by 6 or 1.4 years, respectively.
- A single effect at the chr8 locus hastens onset by 1.6 years.
Can the genetic modifiers identified be used as new drug targets?
A continued effort: reducing the burden of HD by ameliorating disease signs and symptoms
Efficacy of interventions

Challenges & Hopes
Food for thought

• Asking people to see specialists and to take part in research activities implies some degree of disruption of a difficult to equilibrate life routine, in particular in more advanced stages

• On the other hand: without willingness to take part and to take some risks no progress is possible in real life
Getting on the bus
Getting BEHIND the bus (and push!)
Not everybody can help at all times

- That’s one of the reasons why we need a lot of volunteers and why Enroll-HD went global
We need to get the balance right: HOPE & HELP
For today (and tomorrow)
Thank you for your attention!

G. Bernhard Landwehrmeyer