HOT TOPICS in HD Research

Stem Cells and DNA Repair

2018 HDSA Annual Convention
June 7-9, 2018
Los Angeles, CA
HD: A Family Disease
HD: A Family Disease

ca 1920

1980

2007
What is the normal function of the huntingtin protein?

What is going wrong when the huntingtin protein is expanded?
From Gene to Protein

Normal Huntington Protein

Expanded Huntington Protein
Huntingtin moves to damaged DNA

High power laser stripe damages DNA

What is huntingtin’s role in DNA repair?

Is this important in HD?
DNA: Kind of a Big Deal

Francis Crick and James Watson solved the structure of DNA in 1953

DNA makes up our genes

Genes are the blueprints for proteins

Proteins do all of the work in the cell
    → Break down over time

BLUEPRINTS MUST BE PROTECTED!

    → Cancer
    → Neurodegenerative diseases
A Major Clue

42 CAG repeats

Cell
Volume 162, Issue 3, 30 July 2015, Pages 516-526

Article
Identification of Genetic Factors that Modify Clinical Onset of Huntington’s Disease
Genetic Modifiers of Huntington’s Disease (GeM-HD) Consortium

GENOME WIDE ASSOCIATION STUDY implicates
“DNA handling and repair mechanisms”
DNA repair genes are genetic modifiers for other neurodegenerative diseases caused by CAG expansion.
Factor 1: “Somatic” Expansion

Most cells

Brain cells

DNA repair gone wrong

CAG gene
Factor 1: “Somatic Expansion

DNA repair genes
acting as
 genetic modifiers
by affecting
somatic expansion
Factor 2: CAG Repeat Genes are DNA Repair Genes
Factor 2: CAG Repeat Genes are DNA Repair Genes

DNA repair genes acting as genetic modifiers by affecting the function of the expanded protein
HD and DNA Repair: Connections

➔ Links between DNA repair genes and other neurological disorders
  - Cockayne Syndrome
  - Xeroderma Pigmentosum
  - Trichothiodystrophy
  - Ataxia with Occulomotor Apraxia-1
  - Spinocerebellar Ataxia with Axonal Neuropathy
  - Ataxia Telangiectasia
  - A-T Like Disease
  - ATR-Seckel Syndrome
  - Nijmegen Breakage Syndrome

➔ Large human genetic studies in HD and SCAs
  - Identification of Genetic Factors that Modify Clinical Onset of Huntington's Disease, 2015
  - DNA repair pathways underlie a common genetic mechanism modulating onset in polyglutamine diseases, 2016
  - Identification of genetic variants associated with Huntington's disease progression: a genome-wide association study, 2017
HD and DNA Repair: Connections

→ Somatic expansion involves DNA repair

→ CAG repeat genes have roles in DNA repair
HD and DNA Repair: Connections

→ Damaged DNA in HD models and samples


→ Huntingtin moves to sites of damage and scaffolds DNA repair proteins

![DNA](image1.png)

![Huntingtin protein](image2.png)
How can we use this knowledge?

DNA Repair Pathways
How can we use this knowledge?

Finding huntingtin's DNA repair partners

How do they behave in HD?

Can we fix them?
Various types of stem cell exist

What is a stem cell?

A single cell that can

Embryonic

- Blastocyst
- Inner Cell Mass
- Trophoblast

Adult

- Bone marrow
- Stem cell
- White blood cell
- Red blood cell

Induced pluripotent

[References: http://slideplayer.com/slide/5665981/
https://www.singularityweblog.com/stem-cells-ips-cells/
http://www.justscience.in/articles/potential-benefits-risks-involved-stem-cell-research/2017/12/09]
Cell type can be controlled through cellular dedifferentiation
Reverse engineering skin cells

Skin cells → Reprogram Cells → iPS cells → Heart cells, Fat cells, Neurons, Pancreatic cells, Blood cells

Shinya Yamanaka, Kyoto University; UCSF

Jamie Thompson, University of Wisconsin
Uses of iPSCs

Patient → Patient cells → Patient-specific iPSCs

Modified from: Stadtfeld and Hochedlinger Genes Dev. 2010;24:2239-2263
Uses of iPSCs: Disease modeling

- Patient cells
- Differentiation in a dish
- Disease mechanisms
- Disease-relevant cells
- Developmental biology
- Target identification & validation
- Drug development
Mission of the HD iPSC Consortium:
1. Create a unique, patient-derived stem cell resource available for the HD research and industrial community

1. Combine international expertise to better understand HD and collaboratively tackle problems that would be difficult for a single lab to pursue

<table>
<thead>
<tr>
<th>CAG length of available iPSC lines</th>
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<tbody>
<tr>
<td>Control</td>
</tr>
<tr>
<td>--------</td>
</tr>
<tr>
<td>18</td>
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Disease modeling: Modeling HD-affected cell types


Disease modeling: the HD BBB *in vitro*

**blood vessel**

- Blood
- Endothelial Cell
- Brain

**Genes expressed & functional experiments**

Disease modeling: BBB is altered in HD

- Barrier properties decrease with Q length
Disease modeling: the Extracellular Matrix (ECM)

- ECM = cellular infrastructure
- Cells contribute to, and are influenced by, the ECM
- The ECM is constantly being remodeled to guide cell attachment, cellular movement, and cell survival
- In the brain, the ECM coordinates synaptic activity and provides neuroprotection
- Highly druggable
Overall goal: is the ECM therapeutic for HD?

Unaffected ECM environment

HD ECM environment

Investigate expression and function of the ECM in HD cell models

- What exactly are these changes?
- How are these changes affecting the cells?
Drugs against ECM currently used to treat cancer

- Vectibix (panitumumab)
- FDA approved Sept. 27, 2006
- Approved by European agencies in 2007
- Approved by Canadian agencies in 2008
- Used to treat certain advanced, metastatic colorectal cancers
- Phase III trials for use in esophageal cancer, urothelial carcinoma, metastatic head and neck cancer, and liver metastasis in colorectal cancer
- Immune therapy
- Blocks ability of cell to communicate with the ECM
Uses of iPSCs: Cell therapies

Differentiation in a dish

Patient cells

CRISPR
Cell therapies: Fetal cell transplants into HD patients show variable results

<table>
<thead>
<tr>
<th>Los Angeles</th>
<th>Creteil</th>
<th>Tampa</th>
<th>NEST-UK</th>
<th>London</th>
<th>Florence</th>
<th>MIG-HD German Extension</th>
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<tbody>
<tr>
<td>Grafted patients (N)</td>
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<td>6</td>
<td>3</td>
<td>5</td>
<td>2</td>
<td>16</td>
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<tr>
<td>Available Clinical data (N)</td>
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<td>5</td>
<td>4</td>
<td>2</td>
<td>2</td>
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<tr>
<td>Autopsied cases (N)</td>
<td>7</td>
<td>7</td>
<td>5</td>
<td>2</td>
<td>10</td>
<td>10</td>
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<tr>
<td>Mean funct. capacity</td>
<td>FAS 17 ± 2.9</td>
<td>TFC 11.1</td>
<td>TFC 6.6</td>
<td>TFC 4 &amp; 8</td>
<td>Median 3.5 years (2.9-5.1)</td>
<td>FAS 9 ± 7.3</td>
</tr>
<tr>
<td>Pre/postop. follow-up</td>
<td>1-10 years</td>
<td>1-10 years</td>
<td>1-8 years</td>
<td>6 years ± 2.8</td>
<td>6 months</td>
<td>6-36 months</td>
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<tr>
<td>Nongrafted cohort (N)</td>
<td>22 External</td>
<td>Tissue SDH</td>
<td>12 randomized</td>
<td>6 external</td>
<td>1 Cyst</td>
<td>1 Cyst</td>
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<tr>
<td>Related adverse events</td>
<td>1 SDH, 1 Bone Infection, 1 Overgrowth, 2 Cytis</td>
<td>THIN SDH, Graft necrosis, Noncompliance, immunosuppression</td>
<td>3 SDH, Brain infection, Wound infection, Urea/creatinine</td>
<td>Anemia, 1 Urea/creatinine, 1 Meningoencephalitis</td>
<td>1 SDH</td>
<td>1 SDH, Overgrowth, abnor transplants, 1 Tight abscess</td>
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<tr>
<td>HLA antibodies</td>
<td>3(1)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1(1)</td>
<td>1(1)</td>
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<td>Durable benefit (%)</td>
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<td>52</td>
<td>0</td>
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Stem cell research advancing rapidly, with the goal to use for transplantation

Mission: to accelerate stem cell treatments to patients with unmet medical needs

Cell therapies: CA Institute for Regenerative Medicine

Total clinical trials: 43

New clinical trials in 2017 addressing devastating diseases for which there currently are no known cures: 16

Total patients enrolled in CIRM-funded clinical trials: 703

These trials have the potential to change the landscape of medicine and the future of those who suffer from these debilitating conditions.
Cell therapies: Curing immune diseases

SEVERE COMBINED IMMUNODEFICIENCY (SCID)

Donald Kohn, UCLA

David Vetter

Vacarro family

https://www.newbornscreening.info/Parents/otherdisorders/SCID.html
Cell therapies: HD NSC transplants successful in mouse models

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

Joseph Ochaba
HD community building on successful efforts
Exciting time in HD research
Stay Informed

Huntington disease research news.
In plain language. Written by scientists.
For the global HD community.
Go to www.HDBuzz.net to see what the Buzz is all about!

www.labscribbles.com

www.raytruantlab.wordpress.com