Switching Off Huntington’s Disease in the Mouse

X. William Yang, M.D., Ph.D.

Center for Neurobehavioral Genetics, Semel Institute
Department of Psychiatry & Biobehavioral Sciences
David Geffen School of Medicine,
University of California at Los Angeles

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The Yang Lab @ UCLA
(http://yanglab.npih.ucla.edu/)

Supporting Our Research:
NIH (NINDS and NIDA),
Hereditary Disease Foundation (HDF)
CHDI Foundation, Inc.
McKnight Foundation
Human Brain: The Final Frontier

• Our Brain:
  -- 100 billion neurons;
  -- One trillion connections
  -- Perception, Action, Emotion, Memory, Language, Culture

• Brain Diseases: A large number of brain disorders with limited treatment options.

President Obama 2013 State of the Union Address: “A New Effort to Create the Human Brain Activity Map”
Degenerative Brain Disorders: A Challenge of Our Age

There are 36 million Alzheimer patients worldwide, 5.3 million of them are Americans or about 1 in 8 people older than 65. The number of patients will double every 20 years (66 million by 2030)!

Estimated of cost of care is $604b worldwide and $172b in the US in 2010

Extraordinary personal tragedy since the patients lost their ability to function as themselves or recognize their family members.

No effective treatment to prevent the onset or slow the brain deterioration in neurodegenerative disorders.
Age-dependent Degenerative Processes in the Brain: Early Treatment May Offer Better Therapeutic Outcome

Causes: Gene X Environment  Age-dependent Brain Damage Over Decades  Relentless Progression after Disease Onset

<table>
<thead>
<tr>
<th>Disease</th>
<th>Prevalence or Incidence</th>
</tr>
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<tbody>
<tr>
<td>1. Alzheimer’s Disease</td>
<td>5.3 million in US</td>
</tr>
<tr>
<td>2. Parkinson’s Disease</td>
<td>1 million in US</td>
</tr>
<tr>
<td>3. Frontotemporal Dementia</td>
<td>&lt;200,000 in US</td>
</tr>
<tr>
<td>4. ALS (Lou Gehrig Disease)</td>
<td>15,000 in US</td>
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<tr>
<td>5. Huntington’s Disease</td>
<td>30,000 in US; 75,000 in North America &amp; Europe</td>
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<tr>
<td>6. Chronic Traumatic Encephalopathy (CTE)</td>
<td>???</td>
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The Brain Pathology in Degenerative Brain Disorders

- Loss of Specific Types of Neuronal Cells
- Accumulation of Abnormal Clumps of Proteins
- Chronic Inflammation in the Brain
Many Genetic Causes of Degenerative Disorders Are Known

<table>
<thead>
<tr>
<th>Causal/Risk Genes</th>
<th>Genetics</th>
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<tbody>
<tr>
<td><strong>1. Alzheimer’s Disease</strong></td>
<td></td>
</tr>
<tr>
<td>App, Presenilin 1&amp;2; ApoE4 as Risk Genes</td>
<td>Sporadic &amp; Familial</td>
</tr>
<tr>
<td><strong>2. Parkinson’s Disease</strong></td>
<td></td>
</tr>
<tr>
<td>αSynuclein, Lrrk2, Parkin, DJ1, Pink1, VPS35</td>
<td>Sporadic &amp; Familial</td>
</tr>
<tr>
<td><strong>3. Frontotemporal Dementia</strong></td>
<td></td>
</tr>
<tr>
<td>Tau, VCP, Progranulin, C9ORF72</td>
<td>Sporadic &amp; Familial</td>
</tr>
<tr>
<td><strong>4. ALS (Lou Gehrig’s Disease)</strong></td>
<td></td>
</tr>
<tr>
<td>SOD1, TDP-43, FUS, Ataxin2, Profilin 1, etc</td>
<td>Sporadic &amp; Familial (10%)</td>
</tr>
<tr>
<td><strong>5. Huntington’s Disease</strong></td>
<td></td>
</tr>
<tr>
<td>Huntingtin (Htt)</td>
<td>Monogenetic (99%)</td>
</tr>
</tbody>
</table>
Huntington’s Disease (HD)

• Dominant genetic inheritance: Do not skip a generation; 50/50 chance for the children to inherit HD from an affected parent.

Image from http://geneticdisease2.wikispaces.com/Huntington's+Disease
Huntington’s Disease: Clinical Symptoms

• Average age of onset in the 40s (can be from 2-70 yrs).

• Clinical “Triad” of Symptoms

1. Movement disorder:
   Chorea (“dance-like”),
   Dystonia (abnormal muscle twisting)
   Unsteady gait, etc.

2. Cognitive Impairment:
   Inability to concentrate
   Inability to carry out complex task
   Impaired judgment & impulse control
   Gradual loss of language skills

3. Psychiatric Symptoms:
   Anxiety, Depression, Irritability,
   Psychosis, OCD-like symptoms, etc.

• Relentless progression & death in 10-20 years after the onset.
HD Neuropathology: Loss of Neurons in the Cortex & Striatum

Medium Spiny Neurons (MSNs): 90% neurons in the striatum

Image from the Harvard Brain Tissue Resource Center
Motor control, Motor learning, Habit formation

Movement Disorders: Huntington’s Disease, Parkinson’s Disease, Tourette Syndrome

Skill & Reward Learning

Excessive Natural Reward; Drug Addiction

Higher Cognitive Function: Decision making; Language; Social interaction; Emotion

Schizophrenia; Autism; OCD;

HD Neurodegeneration Targets Critical Brain Regions Involved in Motor, Cognition, and Emotion

Cortex & Basal Ganglia (e.g. Striatum)
HD Genetic Mutation: CAG Repeat Expansion in Huntingtin (Htt) Gene

- Normal repeats: 10-20
- Huntington Disease repeats: 40-120
- The longer the repeat, the earlier the disease onset.
Advantages to Build Huntington Disease Mouse Model

Mouse Shares Greater than 90% of Genes with Human

Mouse Has Similar Brain Cell Types and Connections as Human

Mouse Exhibits Rich Behavioral Spectrums to Study Brain Dysfunction and Degeneration

We Have Great Tools to Genetically Alter the Mouse Genome
Inserting Large Pieces of Human Genomic DNA into Mouse: The BAC Transgenic Approach

An Average Mammalian Transcription Unit: 25kb

Gene X

Gene W

Gene Y

Large Piece of Human DNA on the BAC Has Most if Not All the “Bells and Whistles” to Drive Accurate Expression of the Human Genes in Transgenic Mice

Invented by Drs. X. William Yang & Nat Heintz at Rockefeller University (Yang et al, 1997)
How to Make a Mouse Carrying the Human HD Gene?

1. Engineer HD Mutation Into Human Genomic DNA Grown In Bacteria on a Dish
2. Purify the Intact HD BAC DNA from the Bacteria
3. Inject the HD BAC DNA into Mouse Eggs to Create a Living HD Transgenic Mouse
Meet “BACHD”

- Motor Impairment:
  - Poor coordination;
  - Reduced Locomotion;

- “Emotional” Symptoms:
  - Anxiety-like behaviors;
  - Depression-like behaviors

- Cognitive Deficits

- Brain Pathology:
  - Shrinkage of the Brain;
  - Clumps of Mutant Htt Protein

Expressing the Intact Human HD Gene in a Mouse

HD Mouse Models Allow Scientists to Study How Mutant Huntingtin Causes HD and to Identify New Therapeutic Targets.
This small region can be modified by two small chemical tags called phosphorylation:

• Such tags may alter HTT locations inside the cells;

• They may also help cells to locate and get rid of the toxic mutant HTT;

Joan Steffan, Leslie Thompson and Larry Marsh (UC Irvine)
Generating Tagged and Untagged HD Mice

Both Types of Mice Have the PolyQ Mutation of HD and Are Expected to Be Sick!
“SD Mouse” With Phospho-mimic Tags Has Normal Motor Coordination

Gu et al *Neuron* (2009)
“SD Mouse” With Phospho-mimic Tags Does Not Exhibit Excessive Anxiety

Gu et al Neuron (2009)
“SD Mice” With Phospho-mimic Tags Do Not Exhibit Htt Protein Clumps and They Are Free of Brain Weight Loss

Gu et al *Neuron* (2009)
The Molecular Switch Is Off

NT17 poly Q poly P

Mutant Htt Toxicities
The Molecular Switch Is Flipped On

Mutant Htt Toxicities Abolished in HD Mice
Resources for Science Teachers

1. Howard Hughes Medical Institute: Cool Science (http://www.hhmi.org/coolscience/);

1. Society for Neuroscience (http://www.sfn.org/public-outreach/education-programs) Brain Awareness Campaign (UCLA Has This Program)

3. Cold Spring Harbor Laboratory DNA Learning Center (http://www.dnalc.org/)

4. Huntington’s Disease Knowledge:
   • HOPES at Stanford (http://www.stanford.edu/group/hopes/cgi-bin/wordpress/)
   • Hereditary Disease Foundation (HDF, http://www.hdfoundation.org/home.php)
   • Huntington Disease Society of America (HDSA, http://www.hdsa.org/)
   • HDBuzz (http://en.hdbuzz.net/)

5. UCLA Brain Research and Outreach:
   • UCLA Brain Research Institute Science Outreach Program (http://www.bri.ucla.edu/bri_education/scienceoutreach.asp)
   • Center for Neurobehavioral Genetics at UCLA Semel Institute (http://www.semel.ucla.edu/neurogenetics)
   • The X. William Yang Research Group at UCLA (http://yanglab.npih.ucla.edu/)