Developing therapies to improve cognitive abilities of Individuals with Down syndrome
From research finding to approved drug: translational research and clinical development for Down syndrome
Down Syndrome Outline

• What is abnormal in the DS brain? How do these differences cause cognitive dysfunction?

• Abnormalities in modulatory neurotransmitter signaling contributes to cognitive impairment in DS (Ahmad Salehi)

• Excessive inhibitory tone also suppresses learning and memory function. One strategy to address cognitive dysfunction (Craig Garner)

• Clinical programs in Down syndrome
A new view on neurogenetic cognitive disorders – Brains can be fixed!

To understand what we are doing, it is necessary to have a different concept of the brain than is commonly held even by neurobiologists.

The brain is not like a puppet master just pulling the strings.

The brain is more like a symphony conductor, speeding up, slowing down, making some sections louder and others softer.

How do are brains work?
Brains are made up of billions and billions of nerve cells or **neurons**.

They send information to each other by electrical signals -- **nerve impulses** -- that travel along extensions of these cells.

At the end of these processes there are connections between the cells called **synapses**. But, there are gaps between the presynaptic and postsynaptic cells that the electrical signals cannot cross.

The information is carried across the gaps by chemicals called **neurotransmitters** released by the pre-synaptic cell and received by the post-synaptic cell.

These chemicals are **neurotransmitters** and they can either excite or inhibit their target cells.
The Translational Cycle

1. Human phenotype
   - characterization of disease
   - cognitive strengths and weaknesses

2. Human genotype
   - gene(s), mutations
   - inheritance, XCI
   - second-hit mutations

3. Animal genotype
   - transgenic mice and flies
   - inducible or tissue-specific
   - knockin of human gene(s)

4. Animal phenotype
   - behavioral tests of cognitive, motor, and social function
   - anatomy, neurophysiology

5. Therapeutic strategy
   - improve efficacy and safety in animal models
   - test various compounds

6. Drug development
   - modify lead compound for specificity, bioavailability, PK
   - dosing strategy

7. Clinical trials
   - safety, dosing, open-label and placebo-controlled trials
   - NDD-appropriate endpoints
Human phenotype

Zac Efron

Weird Al Yankovic

Arizona Cognitive Test Battery

Development and validation of the Arizona Cognitive Test Battery for Down syndrome

Jamie O. Edgin • Gina M. Mason • Melissa J. Allman • George T. Capone • Iser DeLeon • Cheryl Maslen • Roger H. Reeves • Stephanie L. Sherman • Lynn Nadel

J Neurodev Disord
DOI 10.1007/s41689-010-0054-3
Clinical Assessment

- Caused by the triplication of Chromosome 21 (~250 genes).
- Common Disorder: 1/600 Births: Incidence higher when mothers are over 35
- 350,000 afflicted in US; 500,000 Europe; > 3 Million world wide
- Cognitive impairment, mild-severe (IQ 20-80)
- Progressive cognitive decline
- Deficits in speech and language skills
- Deficits in short- and long-term memory
- Propensity for early onset Alzheimer Disease (~30 years of age)
Neuropsychological Assessment of Learning and Memory in Down Syndrome

(see Lynn Nadel, Genes, Brain and Behavior 2:156 2003)

– Learning is normal in very young subjects <6 month, but declines progressively in the first year.
– A second decline occurs in adulthood as the risk of early onset Alzheimer disease takes it toll.
– Impairment is not spread across all learning and memory systems
– Disproportionately affected are the hippocampus and prefrontal cortex.
– Impairment is most robust for explicit or declarative memory, though implicit or procedural memory is also affected.
– These directly affect speech, language and verbal short term memory and IQ.
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DS caused by the triplication of Chromosome 21 (~250 genes).
The Translational Cycle

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Animal models of genetic disorders
Meet the Ts65Dn Mouse: Our Workhorse, our Hero.

Karyotype analysis

(visual display of the chromosomes grouped by their size, number and shape)
Anatomy

Behavioral tests

Long-term memory

Motor behaviors

Social behaviors

As in humans, Ts mice exhibit learning and memory impairments
Physiology

Wang et al., Nat Neuro 2000
Neurons and synapses

Neurons use electrical and chemical signals to communicate: Synaptic transmission is impaired in mouse models of Down syndrome.
Synapses and synaptic plasticity in DS mice

- Brain anatomy is altered.
- Synaptic learning is impaired.
- Inhibitory synapses are too strong.
- Excessive inhibition appears to suppress synaptic plasticity in neural circuits critical for memory processing.
- Modulator synapses (cholinergic and noradrenergic) are also too weak.

Data suggest that altered synaptic transmission contributes to impaired learning and memory function in Down syndrome.
Abnormalities in modulatory neurotransmitter signaling contributes to cognitive impairment in Down syndrome

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### Mouse Models of Down Syndrome

<table>
<thead>
<tr>
<th></th>
<th>Down Syndrome</th>
<th>Tc1</th>
<th>Ts16</th>
<th>Ts65Dn</th>
<th>Ts1Cje</th>
<th>Ms1Cje/Ts65Dn</th>
<th>Ts1Rhr</th>
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</thead>
<tbody>
<tr>
<td>Number of Triplicated Genes</td>
<td>261-364</td>
<td>240-334</td>
<td>731*</td>
<td>104-132</td>
<td>81-85</td>
<td>22-46</td>
<td>33</td>
</tr>
<tr>
<td>Viability</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Cognitive Deficits</td>
<td>Moderate</td>
<td>Severe</td>
<td>ND</td>
<td>Severe</td>
<td>Moderate</td>
<td>Mild</td>
<td>ND</td>
</tr>
<tr>
<td>Change in Brain Structure/Function</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>
Overexpression of specific genes on HSA21

Abnormal Circuits

Cognitive Dysfunction
A Significant Loss of Dendritic Arborization in Dentate Gyrus Neurons in Ts65Dn Mice
Hippocampal Function is Modulated by Subcortical Regions with Extensive Projections
Locus Coeruleus Neurons in the Brainstem Project Extensively to the Hippocampus
Locus Coeruleus Neurons Send Extensive Projections to the Rest of the Brain
Locus Coeruleus Neurons Are the Sole Source of Norepinephrine for the Hippocampus
Methods to Study Cognitive Function in Ts65Dn Mice

- Novel Object Recognition
- Contextual Learning
Strategy Used to Increase NE Levels Only in the Brain
Failure in Contextual Learning in Ts65Dn Mice

Day 1
Total Freezing Time (s)
- Carbidopa
- Carbidopa + L-Dops
- 3M in 20.5 60 S
- Tone 8.5 40 S
- Shock

- Ts65Dn
- 2N

Day 2
Total Freezing Time (s)
- 3M in 20.5 60 S

Day 3
Total Freezing Time (s)
- 5 Min

Day 3

2N
CD
LD
0.876
0.150
0.182
0.196
0.0324
0.595

p value - Mann-Whitney U test

Uecker et al., 1991
Ts65Dn mice show traits of ADHD that are seen in some children with DS.

ADHD can be measured by their nest building behavior.

They can build good nests, but it takes more time.

Novelty makes the ADHD worse, motivation (cold) makes it better.

PTZ does not treat this trait, but other drugs do.
Increasing Norepinephrine Levels Significantly Improves Nesting in Ts65Dn Mice
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