Therapeutic Strategies for Cognitive Dysfunction in People with Down Syndrome

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Down Syndrome: A Malady of Angels

Adoration of the Christ Child, 1515 AD, Source: Met Museum of Arts
Characteristics of Down Syndrome

Physical Features:
- Dysmorphic facial features
- Growth retardation
Characteristics of Down Syndrome

Central Nervous System:
- Intellectual disability (I.Q. 35-70)
- Cognitive dysfunction
- Attention deficit & hyperactivity (ADHD)
Characteristics of Down Syndrome

Cardiovascular System:
Cardiac malformations
- Septal defects
- Tetralogy of Fallot
- Patent ductus arteriosus

Leading cause of mortality in Down syndrome
Characteristics of Down Syndrome

Musculoskeletal System:
- Dysplasia of the pelvis
- Hypotonia
Characteristics of Down Syndrome

Gastrointestinal System:
- Intestinal atresia
- Abnormalities of anus
- Hirschprung’s disease
  (absence of nerve cells in bowel-wall)
Alzheimer’s Disease Pathology in Adults with Down Syndrome

- Neurofibrillary tangles
- Plaques
Process of Drug Development

- Define the problems
- Discover genes and mechanisms
- Deliver treatment
- Discover treatments
Mouse Models of Down Syndrome

- **HSA21**
  - 21p
  - 21q

- **MMU16**

<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>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Duplicated 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>Range in Brain Structure/Function</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>
Target Abnormal Circuits

Overexpression of specific genes on HSA21

Abnormal Circuits

Cognitive Dysfunction
Dentate Gyrus Undergoes Significant Atrophy in Ts65Dn Mice
Quantification of Dendritic Tree in DGCs

Dentate Gyrus
A Significant Loss of Dendritic Arborization in DGCs in Ts65Dn Mice
Hippocampal Function is Modulated by Subcortical Regions with Extensive Projections
Locus Coeruleus Neurons Send Extensive Projections to the Rest of the Brain Particularly the Hippocampus
Locus Coeruleus Neurons Undergo Significant Degeneration in Ts65Dn Mice
Strategies to Increase Norepinephrine (NA) Levels in Ts65Dn Mice

1) Increasing brain NE levels.

2) ® adrenergic agonists.
Method of Increasing Norepinephrine Levels in the Brain
Failure in Contextual Learning in Ts65Dn Mice

Day 1
- Total Freezing Time (s)
  - Carbidopa
  - Carbidopa + L-Dops
  - Ts65Dn
  - 2N

Day 2
- Total Freezing Time (s)

Day 3
- Total Freezing Time (s)

Uecker et al., 1991
L-DOPS is able to restore cognitive function in the Ts65Dn mouse model of Down syndrome, but it is yet to be approved by the FDA.
Targeting $\beta_1$ or $\beta_2$ Adrenergic Receptors?

1) Cardiovascular complications are the most common cause of death in DS.
2) $\beta_2$ gene expression is more than beta1 in DGCs
3) Effects of NE on LTP is mediated by $\text{©} 2$.
4) $\beta_2$ mediates the effects of NE on ADE.
5) $\beta_2$ polymorphism has been linked to dementia of AD.
6) $\beta_2$ mediates the positive effects of NE on neurogenesis.
β2 Adrenergic Receptors in Dentate Granule Cells
Formoterol (FORM) is a long-acting specific β2-adrenergic receptor agonist used for the treatment of asthma.
No Adverse Effects of Formoterol on Respiratory System

The Effects of Formoterol Treatment on Respiratory System

Breath Rate (per minute)

- Nadolol
- Nadolol + Formoterol

Oxygen Saturation (%)

- Ts65Dn
- 2N
Formoterol Reduces Open Field Activity in Ts65Dn Mice

- **Velocity**
  - Nadolol
  - Nadolol + Formoterol
  - Significance: p=0.00003
  - Significance: p=0.00141

- **Total Distance Travelled**
  - Nadolol
  - Nadolol + Formoterol
  - Significance: p=0.00003
  - Significance: p=0.00109
Formoterol Improves Spatial Learning in Ts65Dn Mice
Short Term Use of formoterol Leads to a Significant Increase in the Synaptic Density in the Dentate Gyrus in Ts65Dn Mice
Increased Density of C-Fos-positive Neurons in the Dentate Gyrus of Ts65Dn mice
DoublecortinLabels Newly-born Cells Destined to Become Neurons
Formoterol Significantly Increases the Dendritic Complexity of New-born Neurons
Formoterol Significantly Increases the Dendritic Complexity of New-born Neurons

- \( p = 0.018 \)
- \( p = 0.0041 \)
- \( p = 0.0007 \)

![Graph showing comparison between Nadolol and Nadolol + Formoterol](image-url)
Acknowledgments:

Van Dang, DVM, Ph.D
Kara Martin, MS
Sarah Moghadam, Pharm. D.
Brian Medina, BS
Priyanka Naik, BS
Devan Patel, MD
Bill Lin, BS
Devsmita Das, MD, MPH
Martha Millan Sanchez, MD
Sri Patchala, MD
Vincent Wong, BS
Wes Ashford, M.D, Ph.D

UCSD
Bill Mobley
Pavel Belichenko