AN UPDATE ON DOWN SYNDROME RESEARCH

A COLLABORATION BETWEEN DSRTF AND NDSS IN CELEBRATION OF DOWN SYNDROME AWARENESS MONTH

October 16th, 2012
The Status of Cognition Research in Down Syndrome: Agenda

- Patty White, DSRTF Co-Founder: *DSRTF’s mission, strategy and accomplishments*

- Dr. Roger Reeves, Ph.D. Johns Hopkins Univ. School of Medicine: *The Status of DS Cognition Research*

- Sara Weir: NDSS VP of Advocacy and Affiliate Relations: *NDSS advocacy initiatives and accomplishments*

- Q & A
Down Syndrome Research & Treatment Foundation’s Mission

• Stimulate and fund cognition research to improve learning, memory, and speech for individuals with Down syndrome

• Translation of research to deliver treatments to allow individuals to:
  • Participate more successfully in school
  • Lead more active and independent lives
  • Prevent or delay early cognitive decline
Why Cognition Research?

• Cognitive challenges present throughout life
• Generally, mild to moderate cognitive impairment
• Significant presence of neuropathology of Alzheimer’s disease by the age of 40
DSRTF Strategy

FOCUS
Pioneer in stimulating cognition research

RESOURCES
Leaders in funding and executing Ds-specific research strategy

COLLABORATION
Interdisciplinary coordination and communication

TRANSLATION
Accelerate the move from research to treatments
2003 Down syndrome Research

- No evidence of what causes impaired cognition in people with Down syndrome
- No targets on which to focus efforts
- Minimal government funding
- Few researchers focused on DS cognition
Research Advances

• Link between genes and cognitive ability
• Areas of the brain that work differently "mechanisms"
• Continued growth in number of candidate treatments
• Two clinical trials
Government Funding: NIH Per Capita Investment

Disproportionate Federal Funding

Number of Individuals affected in the U.S.

Adapted from NIH: http://www.nih.gov/new/43122017disproportionatefunding.html
Translational Research in Down Syndrome

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What do we know for sure about Down Syndrome?

Comparative mapping

Genes on human Chr 21 are found on Chr 16, 17 and 10 in mouse.
Ts65Dn (karyotype by Gail Stetten, Sarah South)

Muriel Davisson
Can a mouse have Down syndrome?

A.
- Short stature *
- Flat facies *
- Flat nasal bridge *
- Protruding tongue *
- Highly arched palate (*)
- Mental retardation, “DS type” *
- Small cerebellum *

* Denotes traits observed in Down syndrome.

Diagram of a mouse bone structure.
4. Mental retardation, “DS type”

Ts65Dn mice are significantly deficient in functions that require the hippocampus, like the Morris water maze test.

The Down syndrome (trisomic) brain: functional outcomes

- Hippocampal function is robustly affected in mouse DS models (Ts65Dn, Ts1Cje)
  

Child Development, January/February 2003, Volume 74, Number 1, Pages 75–93

The Neuropsychology of Down Syndrome: Evidence for Hippocampal Dysfunction

Bruce F. Pennington, Jennifer Moon, Jamie Edgin, Jennifer Stedron, and Lynn Nadel

Development and validation of the Arizona cognitive test battery for Down syndrome

J Neurodevel Disorders 2010

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

• Cerebellum
  – Tested core function(s): motor responsiveness, reaction times

• Prefrontal cortex
  – Tested core function(s): Holding of information in active or working memory to guide action selection; executive function

• Hippocampus
  – Tested core function(s): Storage of episodic information in long-term memory
Research Design

Sample
- Down Syndrome Group: $n = 74$, ages 7-38 years, IQ range = 40-75
- Mental Age (MA) Matched Control Group: $n = 50$, ages 3-6 years

Data Sources
- Neuropsychological testing, parent report of background factors, behavior and development
- Experimenter ratings of attention and cooperation

3 sites
- Arizona, Atlanta and Baltimore

(U. Wisconsin; Oregon Health Science Univ.; Children’s Nat’l. Medical Center; M.I.N.D. Institute, UC Davis; Children’s Hospital of Philadelphia)

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
Understanding the variability of cognition among individuals with Down syndrome

Currently 9 sites in the DSRTF network
The Down syndrome (trisomic) brain: functional outcomes

Altered Long-term Potentiation in the Young and Old Ts65Dn Mouse, a Model for Down Syndrome

R. J. SIAREY,1* J. STOLL,1,2 S. I. RAPOPORT1 and Z. GALDZICKI1*
Neuropharm 36: 1549, 1997

Hippocampal Long-Term Potentiation Suppressed by Increased Inhibition in the Ts65Dn Mouse, a Genetic Model of Down Syndrome

J Neurosci 2004

The functional nature of synaptic circuitry is altered in area CA3 of the hippocampus in a mouse model of Down's syndrome

Jesse E. Hanson, Martina Blank, Ricardo A. Valenzuela, Craig C. Garner and Daniel V. Madison

J. Physiol. 2007;579;53-67; originally published online Dec 7,
Pharmacotherapy for cognitive impairment in a mouse model of Down syndrome

Fabian Fernandez, Wade Morishita, Elizabeth Zuniga, James Nguyen, Martina Blank, Robert C Malenka & Craig C Garner

Ts65Dn mice, a model for Down syndrome, have excessive inhibition in the dentate gyrus, a condition that could compromise synaptic plasticity and mnemonic processing. We show that chronic systemic treatment of these mice with GABA$_A$ antagonists at non-epileptic doses causes a persistent post-drug recovery of cognition and long-term potentiation. These results suggest that over-inhibition contributes to intellectual disabilities associated with Down syndrome and that GABA$_A$ antagonists may be useful therapeutic agents for this disorder.
Experimental Protocol: Assessing the Cognitive Effects of Pentylenetetrazole in Ts65Dn Mice

Day 1 and 2: Home Cage Feeding

Day 3 and 4: Milk Intake in Feeding Tubes

Day 5 thru 21: Drug Administration in Feeding Tubes

Time

Test Day 14

Test Day 21
Pentylenetetrazole Treated Ts65Dn Mice Exhibit Improved Object Recognition Memory

Short term evaluation at the end of 2 wks. of treatment

Fernandez et al., Nat Neurosci., 2007
Pentylenetetrazole given to Young Adult Mice Causes a Lasting Improvement in Circuit Functionality (2-3 months)

Dentate LTP

wt

Ts65 + PTZ

Ts65Dn ctrl.

Fernandez et al., Nat Neurosci., 2007
Clinical Trial Protocol Registry

Trial information

A Study of RG1662 in Individuals With Down Syndrome

Status: Recruiting

Protocol number: BP25543

Sponsor: Hoffmann-La Roche

Company division: Pharmaceutical

Official Scientific Title: A multi-center, randomized, double-blind, placebo-controlled, multiple dose study to investigate safety and tolerability of RG1662 in individuals with Down Syndrome

Brief summary: This multi-center, randomized double-blind, placebo-controlled study will assess the safety and tolerability of RG1662 in individuals with Down Syndrome. Eligible subjects will be randomized in cohorts to receive either multiple oral doses of RG1662 or placebo. Anticipated time on study treatment is 38 days. Target sample size is 33.

Study phase: I

http://www.roche-trials.com/trialDetailsGet.action?studyNumber=BP25543/
Mouse clinical trial results:

1. Genetic models of trisomy 21 show features of DS
2. Hippocampal function is especially affected
3. Excessive inhibitory input to hippocampus results in reduced LTP and specific behavioral outcomes
4. Treatment with drugs that antagonize GABA-ergic transmission (antagonists, inverse agonists) normalize physiological and behavioral outcomes in mice
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Will drug therapy affect adaptive behaviour in people with DS? And if so, how will we know?
Transformative research support from DSRTF and NDSS

1. Next generation of drug therapy for cognition: PTZ, L-DOPS, SAG; high throughput drug screening in model systems

2. Sleep: Sleep patterns in mice, sleep studies in people, how does the disruption of sleep patterns contribute to cognitive effects in Down syndrome;

3. Behavioral neuroscience: New outcomes measures for clinical trials, measures for children, tests for language acquisition

4. Alzheimer Disease: Why is risk elevated in DS? How can we treat it? What does this tell us about treating the AD pandemic?

5. FUNDING: Foundation support is critical, but NIH provides the bedrock and with a shrinking NIH budget, this has become increasingly political. NDSS has put much significant into working with law makers to influence policies and funding.

http://www.dsrtf.org/page.aspx?pid=357#9
Current challenges:
Genetic associations/ Co-morbidities

Define phenotypes.
Genome wide genetic analysis.
Co-morbidities.
Basic research that relies substantially on mouse models has changed the game for people with Down syndrome.

It appears that there is an important role for models of DS and AD in understanding both conditions.
Reeves lab
Donna Klinedinst
Huiqing Li
Annan Yang
Ishita Das
Sarah Edie
Duane Currier
Sarah Edie
Renita Polk
Tara Howard
Ben Devenney

Cognition
Lynn Nadel
Jamie Edgin
Stephanie Sherman

SAG
Paul Worley
Meifang Xiang
Joo-Min Park
Hoon Shin (NIH)

Craniofacial
Joan T. Richtsmeier

Clinical trial, Hopkins/KKI
Julie Hoover-Fong
George Capone
Willie DeLeon
Josh Ewan
Carrie Blout
Lisa Toole

Families, families, families
The legislative and policy priorities span the life experience of individuals with Down syndrome from birth through adulthood and range in issue from healthcare to asset development.

These priorities have been shaped by self-advocates, families, affiliate leaders and others under the direction of the NDSS Board of Directors and the National Governmental Affairs Committee (NGAC).
What does the NDSS Policy Center do?

- Works with Congress and federal agencies to develop and improve laws, regulations and other policies
- Trains and educates parents, self-advocates and others to advocate on the local, state and national levels
- Organizes and participates in coalitions of national disability organizations
- Leads national DS advocacy program
What is NDSS working now?

• **Congressional Momentum Around** [Down Syndrome Research Funding & Priorities](#)
  – Annual appropriations for NIH to advance the research priorities for Down syndrome
  – Current annual funding for Down syndrome at NIH is $22 million
  – 2012-2013 budget outlook /Sequestration

• **Advocating for the passage of the** [Trisomy 21 Research Act Package](#)
  – A package of legislation aimed at strengthening the research infrastructure for Down syndrome and improving the translational research opportunities for Down syndrome
    • Trisomy 21 Research Resource Act of 2011
    • Trisomy 21 Research Centers of Excellence Act of 2011

• **Collaborate with Leadership at National Institutes of Health (NIH) and Eunice Kennedy Shriver National Institute for Child Health & Human Development (NICHD)**
  – Participate in the [NIH Down Syndrome Consortium](#)
  – National Down Syndrome Research Plan – Request for Information Opportunity
  – New National Down Syndrome Patient Registry

• **New** [National Plan to Address Alzheimer’s Disease at HHS](#)
  – The US Department of Health & Human Services (HHS) published the Plan, which underscores the relationship between Down syndrome and Alzheimer’s disease
  – NDSS is work with HHS to engage a new taskforce on addressing the unique care challenges faced by people with younger-onset Alzheimer's disease, and improve access to long-term services and supports for younger people, including those with Down syndrome
How Can You Get Involved in Advocacy?

• **Join NDSS Online**
  – Follow NDSS on Facebook, Twitter, Pinterest
  – Subscribe to our NDSS e-newsletter
  – Subscribe to our NDSS Advocacy Alerts
  You can do all this by visiting [www.ndss.org](http://www.ndss.org)

• **Become a NDSS DS-Ambassador Program**
  – Join the over 100+ DS-Ambassadors from across the country
  – NDSS DS-Ambassadors are volunteers committed to taking part in the democratic process and serve as liaisons between NDSS and their Congressional Delegations

• **Attend the annual NDSS Buddy Walk® on Washington**
  – 2013 Buddy Walk on Washington will be March 13-14th
  – Buddy Walk on Washington is our annual two-day advocacy conference that brings the Down syndrome community together to advocate for legislative priorities that impact the lives of people with Down syndrome and their families
  – You can register for the Buddy Walk on Washington at [www.ndss.org](http://www.ndss.org)
THANK YOU