**Please Note:** The information here will continue to be updated for the presentation at the DSAIA Conference to capture the very latest significant developments in the research and NIH funding **

**DSAIA Conference – 2013**

Down Syndrome Cognition Research

Major Progress in Translating Discoveries into New Therapies – “Mind to Lab Bench to Bedside”

Michael M. Harpold, PhD

Chief Scientific Officer & Chair, Scientific Advisory Board

Down Syndrome Research and Treatment Foundation
# Down Syndrome Research Funding

## NIH FUNDING FY 2011

<table>
<thead>
<tr>
<th>CONDITION</th>
<th>US POPULATION (est.)</th>
<th>NIH FUNDING Millions $</th>
<th>NIH $ per CAPITA AMOUNT</th>
<th>Relative Funding</th>
<th>FY11 vs. FY10 % Increase / Decrease NIH Funding</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DOWN SYNDROME</strong></td>
<td>400,000</td>
<td>20</td>
<td>50</td>
<td>1.0X</td>
<td>-9.0%</td>
</tr>
<tr>
<td>Parkinson’s</td>
<td>1,500,000</td>
<td>151</td>
<td>101</td>
<td>2.0X</td>
<td>-2.0%</td>
</tr>
<tr>
<td>Crohn’s Disease</td>
<td>400,000</td>
<td>67</td>
<td>167</td>
<td>3.3X</td>
<td>1.0%</td>
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<tr>
<td>Autism</td>
<td>560,000</td>
<td>169</td>
<td>302</td>
<td>6.0X</td>
<td>5.6%</td>
</tr>
<tr>
<td>Multiple Sclerosis</td>
<td>400,000</td>
<td>122</td>
<td>305</td>
<td>6.1X</td>
<td>-8.3%</td>
</tr>
<tr>
<td>Duchenne MD</td>
<td>45,350</td>
<td>32</td>
<td>706</td>
<td>14.1X</td>
<td>-3.0%</td>
</tr>
<tr>
<td>ALS</td>
<td>30,000</td>
<td>44</td>
<td>1,467</td>
<td>29.3X</td>
<td>-6.4%</td>
</tr>
<tr>
<td>Fragile X</td>
<td>17,000</td>
<td>29</td>
<td>1,706</td>
<td>34.1X</td>
<td>16.0%</td>
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<tr>
<td>Huntington’s</td>
<td>30,000</td>
<td>56</td>
<td>1,867</td>
<td>37.3X</td>
<td>-13.9%</td>
</tr>
<tr>
<td>Cystic Fibrosis</td>
<td>30,000</td>
<td>79</td>
<td>2,633</td>
<td>52.7X</td>
<td>-8.1%</td>
</tr>
</tbody>
</table>

NIH funding for Down syndrome research continues to be disproportionately under-funded.
# Down Syndrome Research Funding

**Selected Private/Foundation Research Funding 2011**

<table>
<thead>
<tr>
<th>CONDITION</th>
<th>US POPULATION (est.)</th>
<th>SELECTED PRIVATE FOUNDATION FUNDING Millions $ (est.)</th>
<th>$ per CAPITA AMOUNT</th>
<th>Relative Funding</th>
</tr>
</thead>
<tbody>
<tr>
<td>DOWN SYNDROME</td>
<td>400,000</td>
<td>~3</td>
<td>~7.50</td>
<td>1.0X</td>
</tr>
<tr>
<td>Multiple Sclerosis</td>
<td>400,000</td>
<td>~40</td>
<td>~100</td>
<td>~13.3X</td>
</tr>
<tr>
<td>Fragile X</td>
<td>17,000</td>
<td>~1.5</td>
<td>~90</td>
<td>~12.0X</td>
</tr>
<tr>
<td>Cystic Fibrosis</td>
<td>30,000</td>
<td>~84</td>
<td>~2,800</td>
<td>~373.3X</td>
</tr>
</tbody>
</table>

Adapted from data posted by GuideStar [http://www.guidestar.org/]
Cognition, Learning Memory & Speech in Down Syndrome

Why Cognition Research in Down Syndrome?

- Neurological manifestations of Down syndrome are disabling.

- Early developmental & sustained cognitive disability & issues are most significant:
  - Extending across the lifespan
  - Development is globally slowed
  - Generally, mild to moderate cognitive impairment with marked involvement of memory, learning and speech
  - Significant related life issues: independence, speech/communication, sleep problems

- Majority of individuals with Down syndrome show the neuropathology of Alzheimer’s disease by the age of 40, and majority show further cognitive decline

- New biomedical research can significantly advance more detailed understanding of cognition in Down syndrome to not only yield safe and effective new therapies, but also new and more effective interventional strategies in education, employment and independence.
Rapid success and validation of the new Research Strategy achieved

- More than $9.0 million in new research funding since 2004
- Established critical biomedical expertise – Highly distinguished, accomplished & proactive Scientific Advisory Board, researchers & new collaborations
- Defined multiple mechanisms involved in cognitive impairment associated with Down syndrome
- Identified and pursuing at least eight new potential therapeutic drug targets
- Targeted grants to advance new therapeutic targets through drug R&D pipeline, including target validation, identification and evaluation of effective drug candidates
- Focused on accelerating toward innovative, safe and effective clinical trials together with the development of effective new therapies and new opportunities for all individuals with Down syndrome

** New clinical trials, including Biopharma engagement **

- Roche RG1662 Clinical Trial – Initiated September, 2011
- Balance Therapeutics BD-001 Clinical Trial – Initiated August, 2012

- Leveraged >$7 million in additional research funding from NIH, universities & other foundations
- Partnerships & collaborations in achieving breakthroughs
DSRTF SCIENTIFIC ADVISORY BOARD

David Cox, M.D., Ph.D. – *Biotherapeutics & Bioinnovation Center, Pfizer, Inc.*
- Senior Vice President and Chief Scientific Officer
- Genomics, Human Genetics, Quantitative Genotherapeutics, Systems Biology, BioPharma

Ronald Evans, Ph.D. – *The Salk Institute for Biological Studies*
- Professor and March of Dimes Chair & Investigator, Howard Hughes Medical Institute
- Molecular Endocrinology, Cell Physiology & Metabolism, Cell Signaling & Disease Mechanisms

Michael Harpold, Ph.D., Chair – *Down Syndrome Research & Treatment Foundation*
- Chief Scientific Officer
- Neuroscience, Molecular Cell Biology, Neurodegenerative Disorders, BioPharma, Drug Discovery

Leslie Leinwand, Ph.D. – *University of Colorado & Crnic Institute*
- Professor, Molecular, Cellular & Developmental Biology & Director, CSO Biofrontiers Institute, HHMI Professor
- Molecular Cell Biology & Physiology, Developmental Biology, Down Syndrome

Lynn Nadel, Ph.D. – *University of Arizona*
- Regent’s Professor, Psychology, Cognition & Neural Systems
- Neuroscience, Cognition, Down Syndrome, Neuroimaging, Alzheimer’s Disease

Roger Reeves, Ph.D. – *Johns Hopkins University School of Medicine*
- Professor, Physiology & McKusick-Nathans Institute for Genetic Medicine
- Genetics, Developmental Biology, Down Syndrome, Down Syndrome Mouse Models
The Research Strategy
A Revolutionary New Paradigm for Down Syndrome Research

Proactively Accelerating Discovery & Development of Effective New Therapies through an Evidence-based, Results-driven Strategy Focused on Establishing Critical Mass in:

- “Awareness” of Research Potential & Opportunities for both the Biomedical Research & Public Communities
- Development and Pursuit of Most Innovative, Cutting-edge Ideas Focused on Discovery & Translational Research
- Interdisciplinary Research Collaborations & Communications
- Research Expertise - Attracting and Facilitating Essential & New Research Talent
- Proactive Coordination, Prioritization & Targeting of Research to Optimize Synergy, Leverage & Progress
- Discovery and Pursuit of New Biological Mechanisms, Therapeutic Targets & Drugs
- Proactive Identification & Resolution of Roadblocks & Barriers Throughout the Drug Discovery & Development Pipeline
- Development and Implementation of Innovative, Safe & Effective Clinical Trials
- Engagement with Biopharma Industry
- Increasing and Efficiently Targeting & Leveraging Effective Research & Development Funding
The Research Strategy & Grants Program

Discovery, Development & Approval of New Therapies to Improve Cognition in Individuals with Down Syndrome

Key Strategic Drivers - Questions That Must Be Addressed

- Successful development and approval of effective new therapies, including essential enlistment of Biopharma companies and their expertise, requires answers to at least 3 key questions

- Are there evidence-based dysfunctional cognitive mechanisms together with associated validated specific drug targets & drug candidates to ameliorate that dysfunction?

- Are there specific assessment tools that can measure meaningful improvements (efficacy) resulting from treatment with new potential drugs – can success be demonstrated?

- Are there potential clinical trial capable sites and patient participants that can be sufficiently and efficiently recruited for successful new drug development and FDA approval?

As recently as 2004 there were no answers to any of these questions...
The Research Strategy & Grants Program

Coordinating, Integrating & Accelerating Progress Throughout Drug R&D Pipeline
‘Unprecedented’ Progress in Down Syndrome Biomedical Research

Defining dysfunctional cognitive mechanisms & drug targets – Question #1

- At least 8 new potential therapeutic drug targets have been discovered and shown to overcome specific impairments to improve cognition in mouse models for Down syndrome, a major step toward development of effective new therapies.

- Brain neuronal cell and circuit degeneration – Alzheimer’s disease connections: 4 Targets
  
  - APP & its products - Produced by over-expressed human chromosome 21 gene (UCSD/Stanford grants)
    
    • Lowering the levels of APP and its products reduces the degeneration of specific neural circuits involved in both learning and memory found in both Down syndrome and Alzheimer’s disease with aging.

  - Norepinephrine Neurotransmitter Restoration (UCSD/Stanford grants)
    
    • Drugs increasing norepinephrine (NE) levels in the brain overcome effects of degeneration of specific NE neural circuits and improve contextual learning and memory.
Increased APP

Decreased Synaptic Function
Neurodegeneration

Cognitive Loss & Dysfunction

Improved Synaptic Function
Halt Neurodegeneration

L-DOPS-mediated NE Increase

Decrease APP and/or Products

Improved & Maintained Cognitive Function

Brain neuronal cell and circuit degeneration – Alzheimer’s disease connections: 4 Targets

The Research Strategy & Grants Program

Defining dysfunctional cognitive mechanisms & drug targets – Question #1
The Research Strategy & Grants Program
‘Unprecedented’ Progress in Down Syndrome Biomedical Research

Defining dysfunctional cognitive mechanisms & drug targets – Question #1

Targeting Early Developmental & Sustained Cognitive Disability in Down Syndrome

- Impaired connections and communications in brain neuronal circuits: 3 Targets
  - **GABA_A Receptor** (Stanford/UCSD grants)
    - Drugs specifically reducing GABA_A receptor-mediated neurotransmission overcome excitatory-inhibitory imbalance in neural circuits and improve specific forms of learning and memory.
    - **Target of New Drugs in Roche & Balance Therapeutics Clinical Trials**
  - **GABA_B Receptor & GIRK2** (UCSD grants)
    - Drugs specifically reducing GABA_B receptor-mediated neurotransmission and/or GIRK2 overcome excitatory-inhibitory imbalance in neural circuits and improve specific forms of learning and memory.
The Research Strategy & Grants Program

Defining dysfunctional cognitive mechanisms & drug targets – Question #1

Impaired connections and communications in brain neuronal circuits: 3 Targets

**Greater Inhibition in Hippocampus**
- Excitatory-Inhibitory Imbalance

**Decreased Synaptic Plasticity**

**Suppression of Learning & Memory**

**GABA-A Receptor Inhibitors**

**GABA-B Receptor Inhibitors**

**GIRK 2 Blockers**

**Improved Synaptic Plasticity**

**Improved Learning & Memory**
The Research Strategy & Grants Program
‘Unprecedented’ Progress in Down Syndrome Biomedical Research

Defining dysfunctional cognitive mechanisms & drug targets – Question #1

Targeting Early Developmental & Sustained Cognitive Disability in Down Syndrome

- Neurogenesis – Impairment in formation of brain neuronal circuits: 1 Target
  - SHH Pathway (Johns Hopkins grants)
    - Drugs activating the brain SHH signaling pathway restore development of cerebellum and improve specific form of learning and memory.
The Research Strategy & Grants Program

*Defining dysfunctional cognitive mechanisms & drug targets – Question #1*

**Neurogenesis – Impairment in formation of brain neuronal circuits: 1 Target**

- **Impaired Neurogenesis in Cerebellum & Hippocampus**
  - **Impaired Development of Neuronal Circuits**
    - Motor, Learning & Memory Dysfunction
  - **Corrected Development of Neuronal Circuits**
    - Improved Motor, Learning & Memory Functions
  - **Shh Activators**
The Research Strategy & Grants Program
‘Unprecedented’ Progress in Down Syndrome Biomedical Research

**Measurement of cognitive improvement through new therapies & establishing clinical trials – Questions #2 & 3**

- Translational research initiatives address gaps and potential roadblocks in discovery and clinical R&D
  - Down Syndrome-specific Cognitive Test Battery – The Arizona Cognitive Test Battery (ACTB; University of Arizona grants)
    - Development of the ACTB – the first Down syndrome-specific cognitive test battery - to significantly enable efficacy determination in clinical trials.
  - DS Cognition Project - network of collaborating researchers with 10 US institutions (Johns Hopkins Research Center grants)
    - Creating scaffold for effective Down syndrome clinical trials network.
The Research Strategy & Grants Program
‘Unprecedented’ Progress in Down Syndrome Biomedical Research

*Measurement of cognitive improvement through new therapies & establishing clinical trials – Questions #2 & 3*

- Translational research initiatives address gaps and potential roadblocks in discovery and clinical R&D

- BioPharma Industry Engagement
  - Roche, the multi-national pharmaceutical company, initiated major new clinical trial in September, 2011
  - “A Study of RG1662 in Individuals With Down Syndrome”
  - New investigational drug, RG1662, targeting amelioration of inhibitory-excitatory imbalance in DS
  - Addresses overcoming cognitive and behavioral impairments in individuals with Down syndrome
  - Phase I (18-30 yrs of age) being conducted at 9 clinical trial sites across the US; 1 site in the UK
  - [http://www.roche-trials.com/trialDetailsGet.action?studyNumber=BP25543&diseaseCategoryId=266](http://www.roche-trials.com/trialDetailsGet.action?studyNumber=BP25543&diseaseCategoryId=266)
The Research Strategy & Grants Program
‘Unprecedented’ Progress in Down Syndrome Biomedical Research

Measurement of cognitive improvement through new therapies & establishing clinical trials – Questions #2 & 3

- Translational research initiatives address gaps and potential roadblocks in discovery and clinical R&D

- BioPharma Industry Engagement
  - Roche initiated 2nd major new clinical study in Spring, 2012
  - “A Non-Drug Study of The Suitability of Neurocognitive Tests and Functioning Scales for the Measurement of Cognitive and Functioning Changes in Individuals with Down Syndrome.”
  - Goal of this new study is to evaluate the suitability of neurocognitive tests and functioning scales for the measurement of cognitive and functioning changes in individuals with Down syndrome.
  - Currently seven clinical study sites internationally, including two in the US, two in the UK, two in France and one in Spain. The University of Arizona in Tucson, AZ and Duke University in Durham, NC represent the US clinical study sites. Dr. Jamie Edgin, Co-Principal Investigator of the Down Syndrome Research Group and grants-supported researcher, is the study lead at the University of Arizona
  - http://www.roche-trials.com/trialDetailsGet.action?studyNumber=BP25612&diseaseCategoryId=266
The Research Strategy & Grants Program

‘Unprecedented’ Progress in Down Syndrome Biomedical Research

*Measurement of cognitive improvement through new therapies & establishing clinical trials – Questions #2 & 3*

- Translational research initiatives address gaps and potential roadblocks in discovery and clinical R&D

- BioPharma Industry Engagement
  - Roche initiated 3rd major new clinical study in August, 2012
  - “A Molecular and Functional Brain Imaging Study in Individuals With Down Syndrome and Healthy Controls Following Single Dose RG1662.”
  - Goal of this new study is to evaluate the GABA\(_A\) \(\alpha_5\) receptor expression, occupancy and functional connectivity in the brains of individuals with Down syndrome and healthy controls, ages 18-30 yrs, following single dose RG1662.
  - Currently one clinical study site in the UK
  - [http://www.roche-trials.com/trialDetailsGet.action?studyNumber=BP25611&diseaseCategoryId=266](http://www.roche-trials.com/trialDetailsGet.action?studyNumber=BP25611&diseaseCategoryId=266)
The Research Strategy & Grants Program
‘Unprecedented’ Progress in Down Syndrome Biomedical Research

Measurement of cognitive improvement through new therapies & establishing clinical trials – Questions #2 & 3

➢ Translational research initiatives address gaps and potential roadblocks in discovery and clinical R&D

➢ BioPharma Industry Engagement

  • Balance Therapeutics, Inc. initiated significant new clinical trial in August, 2012
  • “Study of the Drug BTD-001 in Young Adults and Adolescents with Down Syndrome.”
  • Investigational drug, BD-001, targeting amelioration of inhibitory-excitatory imbalance in DS
  • Addresses overcoming cognitive and behavioral impairments in individuals with Down syndrome
  • Phase I (12-35 yrs of age) being conducted at clinical trial sites in Australia
The Research Strategy & Grants Program
‘Unprecedented’ Progress in Down Syndrome Biomedical Research

- **Pilot Research Grants** (University of Texas and VA Palo Alto Health Care System grants)
  - Attracting and supporting new investigators and new discovery research to assure dynamic and robust drug R&D pipeline and accelerate successful development of effective new therapies.

- Proactive advisory and strategic dialogue with NIH and Congress to enhance comprehensive new Down syndrome research, maximize synergy, and increase Federal funding.
  - NIH Down Syndrome Consortium with Down Syndrome Organizations
    - Down Syndrome Patient Registry
      - **Launch Goal: mid-2013**
    - NIH Down Syndrome Research Strategic Plan
Cognition, Learning Memory & Speech in Down Syndrome

Memory Systems: Hippocampus

One target - hippocampus and surrounding cortex

- Detects and stores novel information - allowing for quick adaptation
- Binds together pieces of information
- Talks to the rest of the brain to store and update knowledge
- Helps construct a “map” of the world in our brain. Memories are best recalled when this map is intact.
Cognition, Learning Memory & Speech in Down Syndrome

Memory Systems: Frontal Cortex

- Involved in “working memory” - keeping information online and working with it.
  - Alloway (2009) found working memory was a better predictor of school performance than IQ.
- Allows for flexibility; less “getting stuck” on a way of solving a problem
- Helps to plan actions - the CEO of the brain
- Regulates attention and keeps behavior in check
- Abstract thinking (e.g., concept of time)

Frontal cortex is the brain’s CEO
**Cognition, Learning Memory & Speech in Down Syndrome**

What impact could changing these “memory systems” have in Down Syndrome?

- **Greater connections in their knowledge**
- **Better school progress**
- **Faster at processing and initiating activities**
- **Behavior Improvement** - e.g., “less stubborn”
- **Greater ability & willingness to try new strategies**

- **More Associations**
- **Better Attention and Task “Juggling”**
- **More Flexibility**
Cognition, Learning Memory & Speech in Down Syndrome
Evidence for links between memory and learning in Down Syndrome

- Binding of information on “hippocampal tasks” relates to adaptive behavior scores
- Memory for complex objects relates to language ability
- Auditory working memory is highly related to IQ

Cognition, Learning Memory & Speech in Down Syndrome

Bottom line:
If we don’t try, we won’t know what could be

- There is no “language” or “everyday tasks” section of our brain that can be targeted.

- These skills are supported by memory systems
  - the same systems we are modifying in mouse models such as hippocampus and the frontal cortex.

- Changes in these systems can have a big impact in the human.

Only through regulated evidence-based clinical trials will we know if these drugs work and how big the impact might be.
The Research Grants Program

- **Research Center Grants – Johns Hopkins University School of Medicine**
  (Dr. Reeves et al.)
  - “A Down Syndrome Virtual Center for Basic & Translational Studies - Cognition and Therapy in Down Syndrome”
  - Expands to more than 14 Principal Investigators at 9 institutions across US
  - More than $2.0 million total research funding since 2007

- **Research Center Grants – University of California, San Diego School of Medicine**
  (Dr. Mobley et al.)
  - “Defining the genes and mechanisms causing neurodegeneration in Down syndrome (DS) and discovering effective treatments”; and, “21Lab: A collaborative data sharing and data integration platform for the Down syndrome research community”
  - Expands to 5 Principal Investigators
  - More than $5.7 million total research funding to Dr. Mobley as Principal Investigator since 2004
The Research Grants Program
Current 2012-2013 Research Grants

- **Research Center Grants: Johns Hopkins Virtual Center Consortium**: with KKI, Emory, MIND Institute-UC Davis, University of Arizona, Pittsburgh, Oregon, University of Pennsylvania, CNMC Washington DC, & Waisman Institute/Wisconsin: Drs. Reeves & Sherman, Principal Investigators, Drs. Worley, Foster, V. DeLeon, Capone, I. DeLeon, Nadel, Edgin, Abbeduto, Feingold, Maslen, Lynch & Kuschner/Inge, & Seltzer, co-Principal Investigators

- "A Down Syndrome Virtual Center for Basic and Translational Studies-Cognition and Therapy in Down Syndrome"

- Continued DS Cognition Project (DSCP) development and site expansion will increase human data and infrastructure to define cognitive variability in DS; expand sites for clinical trials network; further develop components of importance for a DS phenotype-specific research registry, database and biobank; validate and incorporate DS language assessment test; and, further advance validation and acceptance of the ACTB as specific new biomedical standard and critical efficacy assessment component in clinical trials.

- Further determining the mechanism by which a single-dose treatment with a specific SHH growth factor-like drug, SAG, early in life of DS mouse model restores cerebellum structure/function and hippocampal-associated function involving learning and memory in DS may lead to significant new therapeutic strategies and insights.

- Investigation of hippocampal neural circuit/network dysfunction and abnormalities in synaptic function may lead to important insights to refine GABA\textsubscript{A} receptor-mediated therapeutic approaches and identify new potential therapeutic drug targets & biomarkers.

- Proposed research will further strengthen and provide results which increase leverage to attract subsequent Federal, or other additional, funding.
The Research Grants Program  
Current 2012-2013 Research Grants

- **Research Center Grants:** [UCSD]; Dr. Mobley, Principal Investigator, Drs. Belichenko, Kleschevnikov, Wu & Wagner, co-Principal Investigators

- “**Defining the genes and mechanisms causing neurodegeneration in Down syndrome (DS) and discovering effective treatments**”; and, “**21Lab: A collaborative data sharing and data integration platform for the Down syndrome research community**”

- Identification of additional over-expressed chromosome 21 genes (including Girk2, Dyrk1A, Tiam1, RCAN1, and/or Synj1) that may act together with APP to cause alterations in neurotrophic signaling and degeneration of neurons in mouse DS models may lead to the identification of new drug targets and therapeutic strategies to address the Alzheimer’s disease neuropathology in DS.

- Continuing investigation on mechanism(s) by which excess APP, and/or its products, may be involved in degeneration of specific neural circuits with age may lead to the identification of new drug targets, potential drugs, and therapeutic strategies to decrease APP and/or its products, and ameliorate age-related cognitive dysfunction and Alzheimer’s disease pathology associated with DS.

- Development and implementation of 21Lab as comprehensive, researcher-driven and universally available web-based DS research platform for sharing and exchange of DS research data, information, reagents, critical analysis and collaborations by the DS research community to enhance and accelerate research progress.

- Proposed studies will strengthen research results and leverage to secure further Federal, or other additional, funding.
The Research Grants Program

- **Innovation Research Grants – University of Arizona**
  - “The Neuropsychology of Down Syndrome”
  - Principal Investigators: Drs. L. Nadel, PhD and J. Edgin, PhD
  - More than $800,000 total research funding since 2008

- **Innovation Research Grants – Stanford University School of Medicine**
  - “Mechanisms Underlying the Roles of Sleep and Circadian Rhythms in the Learning Disability of Down Syndrome ”
  - Principal Investigators: Drs. H. C. Heller, PhD and Co-Principal Investigator: Dr. C. Garner, PhD
  - More than $4.1 million total research funding to Stanford since 2004
The Research Grants Program
Current 2012-2013 Research Grants

➢ Innovation Research Grant: University of Arizona; Drs. Nadel & Edgin, Principal Investigators

➢ “The Neuropsychology of Down Syndrome”

➢ Proposed research will extend and expand AZ Cognitive Test Battery (ACTB) development, including development and evaluation of specific language and communication assessment tests, for testing in a wider range of ages and ability; expand the ACTB application to toddlers and children <age 10, and adults for detection of changes associated with decline from dementia, to support clinical trials in these groups; and, further advance validation and acceptance of the ACTB as specific new biomedical standard in research and clinical trials and applications.

➢ Development of biomarker assessments, including EEG and analysis of eye-tracking patterns and evoked response potentials (ERP), of cognitive function and associated changes could provide critical additional functional and efficacy tests for DS cognitive research and clinical trials.

➢ Extending application of ACTB to sleep studies as well as analysis of genetic variations, in children with DS may provide new insights for evidence-based therapeutic strategies to address sleep disorders and also improve cognitive function.

➢ Proposed studies will strengthen position and leverage to secure Federal, or other additional, funding.
The Research Grants Program
Current 2012-2013 Research Grants

- **Innovation Research Grant: Stanford; Dr. Heller, Principal Investigator, Dr. Garner, co-Principal Investigator**

- **“Mechanisms Underlying the Roles of Sleep and Circadian Rhythms in the Learning Disability of Down Syndrome”**

- Studies further investigating the mechanisms of action of drugs, and/or diazepam-binding inhibitor (an endogenous gene product), that modify GABA$_A$ receptor function (excessive inhibition) in mouse DS models may provide additional insights on and modifications for potential therapeutic strategies to improve memory and sleep in DS.

- Studies further using EEG analysis and other physiological measurements together with pharmacological agents in mouse DS models may provide new insights on abnormal sleep mechanisms and specific correlations to cognition learning and memory dysfunctions in DS in addition to potential therapeutic strategies and/or biomarkers.

- Application of pharmacogenetic methods to investigate the circadian system & sleep in mouse DS models may uncover a role for neural components of the circadian system & sleep in learning, memory and sleep dysfunction, and whether modifications in circadian function & sleep can enhance learning and/or improve sleep function.
The Research Grants Program

- Innovation Research Pilot Grants – VA Palo Alto Health Care System
  - “Improving Beta-adrenergic Signaling for Treatment of Cognitive Dysfunction in Down Syndrome”
  - Principal Investigator: Dr. A. Salehi, MD, PhD
  - Awarded $230,000 in research funding since 2010

- Innovation Research Pilot Grants – University of Texas, Austin
  - “Molecular analysis of proneurogenic, neuroprotective drugs on prevention of APP-induced neurodegeneration in a model of Down syndrome”
  - Principal Investigator: Dr. J. Pierce-Shimomura, PhD
  - Awarded $160,000 in research funding since 2010
The Research Grants Program
Current 2012-2013 Research Grants

- Innovation Research Pilot Grant: VA Palo Alto Health Care System; Dr. Salehi, Principal Investigator

- “Improving Adrenergic Signaling for the Treatment of Cognitive Dysfunction in Down Syndrome”

- The proposed research will determine the potential for lower doses of L-DOPS in combination with Atomoxetine, an existing approved norepinephrine re-uptake inhibitor, and/or formoterol alone, an approved adrenergic β2 agonist, to restore contextual learning in the Ts65Dn mouse. Positive results could provide additional evidence and a rationale for accelerated clinical evaluation of L-DOPS, L-DOPS in combination with Atomoxetine, and/or formoterol in individuals with Down syndrome.

- Studies on the mechanisms of NE-mediated adrenergic β2 signaling impacting neurogenesis and neurodegeneration may lead to significant new therapeutic strategies and insights to improve cognition and addressing Alzheimer’s disease in individuals with Down syndrome.

- Proposed research will further strengthen results and leverage to attract subsequent Federal, or other additional, funding for continuation of investigator’s research focused on Down syndrome.
The Research Grants Program
Current 2012-2013 Research Grants

- Innovation Research Pilot Grants – University of Texas, Austin; Dr. J. Pierce-Shimomura, PhD, Principal Investigator

  - “Molecular analysis of proneurogenic, neuroprotective drugs on prevention of APP-induced neurodegeneration in a model of Down syndrome”

  - Studies will advance the use of a major animal neurobiological model in DS research based on initiation of a new approach to more quickly and comprehensively evaluate roles of a significantly large number of chromosome 21 genes, singly and in combination, in neural and motor function/dysfunction; may lead to identification of potential new mechanisms, drug targets, and insights relevant to cognitive dysfunction in DS

  - Studies provide additional new insights concerning the role of excess APP in selective neurodegeneration in Down syndrome and Alzheimer’s disease and amelioration of those effects by specific drugs
The Research Strategy & Grants Program
Coordinating, Integrating & Accelerating Progress Throughout R&D Pipeline
Grants Program 2012-13

For additional research details on these research projects: http://www.dsrtf.org/pages/our-research/2012-2013-grant-awards
Down Syndrome Biomedical Research

Why is it important for the wider community?

- **Alzheimer’s Disease**
  - Because of the shared neuropathology and higher incidence of earlier age onset of Alzheimer’s disease (AD) in individuals with Down syndrome, the Down syndrome population may benefit from drugs developed in AD research.
  - Significantly for the same reasons, greater understanding of AD and new drugs to treat AD for the wider population can also result from Down syndrome biomedical research.

- **Solid Tumor Cancers**
  - Research has documented a lower incidence of a variety of solid tumors in Down syndrome – Why?
  - Initial evidence is emerging showing human chromosome 21 gene(s) which when present in three copies suppresses tumor formation
  - Down syndrome research may lead to widely applicable new therapies for solid tumor cancers.

- **Atherosclerosis**
  - Research has suggested a lower incidence of atherosclerosis in Down syndrome – Why?
  - Down syndrome research may lead to widely applicable new therapies for atherosclerosis.

*Individuals with Down syndrome are uniquely contributing to all of us!*
What Will Be Required to Sustain and Expand the Momentum to Further Accelerate the Development of Effective New Therapies?

*How Can You Be Involved and Make a Real Difference?*

- Continue to become well educated supporters and “consumers” of evidence-based Down syndrome biomedical research.
  - Partnership together for leveraging resources to accelerate realization of effective new therapies & new opportunities for all individuals with Down syndrome

- Critical need for participation in validated evidence-based clinical studies
  - **New Therapeutic Drug Clinical Trials**
  - **New Down Syndrome Patient Registry**

- **Down Syndrome Heart Project**
- **Down Syndrome Cognition Project**
Down Syndrome Biomedical Research

Creating New Opportunities for All Individuals with Down Syndrome Through Cognition Research

➢ “Seize-the-moment” – Unusually Significant Opportunity Now

➢ The ‘unprecedented’ results and progress achieved signify that effective new treatments and greater independence are within reach for people with Down syndrome.

➢ Understanding and Treating Down Syndrome Is:
  ➢ No longer too complex or difficult – New research and tools, increased understanding and progress
  ➢ Not too late - Cognitive function can be modified, even in adults

➢ Compelling case for significant and proportionate increase in funding & investment in more fundamental & translational Down syndrome research to build upon new momentum
  ➢ Significantly more promising & needed new research than current resources available

➢ Requires building upon & increasing cooperation, collaborations & partnerships
  ➢ Researchers, clinicians, their institutions, the Down syndrome community and organizations, Federal agencies including across the different NIH institutes, and Biopharma companies
The Research Strategy & Grants Program

Creating New Opportunities for All Individuals with Down Syndrome Through Cognition Research

Building major new momentum in Down syndrome research for new opportunities for children and adults with Down syndrome to further realize their dreams!

Join together with us in partnership and...

Be a part of the breakthroughs !!!

www.dsrtf.org

www.dsrtf.org/plus15
The Research Strategy & Grants Program
Creating New Opportunities for All Individuals with Down Syndrome Through Cognition Research

Down Syndrome Cognition Research
Major Progress in Translating Discoveries into New Therapies – “Mind to Lab Bench to Bedside”

Michael M. Harpold, PhD
Chief Scientific Officer & Chair, Scientific Advisory Board

Down Syndrome Research and Treatment Foundation

Supplementary Information
Cognition - Learning and Memory

*Where and how does it develop?*

From Mobley, Stanford University
• Distinct neuronal circuits control learning & memory

• These circuits may be disrupted in Down syndrome by specific impairments involving:
  • Neuronal cell and circuit degeneration
  • Faulty connections and communications – Neuronal Circuit Dysfunction
  • Neurogenesis – formation of neuronal circuits

• Each identified impairment demonstrated to be improved by pharmacological approaches
The Research Strategy & Grants Program
‘Unprecedented’ Progress in Down Syndrome Biomedical Research

Defining dysfunctional cognitive mechanisms & drug targets – Question #1

- Brain neuronal cell and circuit degeneration – Alzheimer’s disease connections
  - APP & its products - Produced by over-expressed human chromosome 21 gene (UCSD/Stanford grants)
    - Lowering the levels of APP and its products reduces the degeneration of specific neural circuits involved in both learning and memory found in both Down syndrome and Alzheimer’s disease with aging.
Alzheimer’s Disease
Specific Pathological Characteristics

• The APP gene encodes a protein which is cleaved into multiple products, and under certain conditions produces the Aβ peptide

• Excess Aβ aggregates as “clumps” to form plaques which disrupt neuronal circuits & lead to neuronal death & cognitive impairment

From Mobley, Stanford University
http://www.alz.org
Alzheimer’s Disease & Down Syndrome
Specific Pathological Characteristics

Neuronal/Brain Degeneration,

Plaques Form Leading to Neuronal Death

Plaques Result from Aggregation of Aβ Peptide

Plaques containing Aβ in Brain Prefrontal Cortex

86 yr old w/o DS  
31 yr old w/DS
The Research Strategy & Grants Program
‘Unprecedented’ Progress in Down Syndrome Biomedical Research

Defining dysfunctional cognitive mechanisms & drug targets – Question #1

Targeting Early Developmental & Sustained Cognitive Disability in Down Syndrome

- Impaired connections and communications in brain neuronal circuits: 3 Targets

  - **GABA_A Receptor** (Stanford/UCSD grants)
    - Drugs specifically reducing GABA_A receptor-mediated neurotransmission overcome excitatory-inhibitory imbalance in neural circuits and improve specific forms of learning and memory.
    - **Target of New Drugs in Roche & Balance Therapeutics Clinical Trials**

  - **GABA_B Receptor & GIRK2** (UCSD grants)
    - Drugs specifically reducing GABA_B receptor-mediated neurotransmission and/or GIRK2 overcome excitatory-inhibitory imbalance in neural circuits and improve specific forms of learning and memory.
The Research Strategy & Grants Program
Excitatory-Inhibitory Balance & Cognitive Impairment in Down Syndrome

**Synapses Are Abnormal**

**Normal** → **Down Syndrome**

Inhibition is too strong, exceeds excitation

**Proposed Mechanism for Decreased Synaptic Plasticity in Ts65Dn**

- Greater Inhibition in the Hippocampus
- Decreased Synaptic Plasticity
- Suppression of Learning

GABA Release → GABA-B Receptor → GIRK 2 Activation → Suppression of Learning

GABA-A Receptor
Initial research discovered increased size of Ts65Dn inhibitory (GABA) synapses & neurotransmission in hippocampus

- Decreased synaptic plasticity, suppression of “LTP”
- Drug blockade of $\text{GABA}_A$-mediated synapses restored “LTP”

Overcoming increased inhibitory circuit activity ameliorates certain learning & memory impairments

**Normal** → **Down Syndrome**

Excitatory inputs are not as active as inhibitory inputs:

1) **Inhibition too strong**:
2) Excitation too weak - NO
3) Both - NO

2N  Ts65Dn  DS
The Research Strategy & Grants Program
‘Unprecedented’ Progress in Down Syndrome Biomedical Research

Defining dysfunctional cognitive mechanisms & drug targets – Question #1

Targeting Early Developmental & Sustained Cognitive Disability in Down Syndrome

- Neurogenesis – Impairment in formation of brain neuronal circuits: 1 Target

- **SHH Pathway** (Johns Hopkins grants)

  - Drugs activating the brain SHH signaling pathway restore development of cerebellum and improve specific form of learning and memory.

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**Cerebellar volume is reduced in DS and in Ts65Dn mice**

From Keenli et al., Neurology, 1999, 48: 1039-1045

Ts65Dn cerebellum is overtly normal at P0, but significantly smaller by P6
The Research Strategy & Grants Program
‘Unprecedented’ Progress in Down Syndrome Biomedical Research

Measurement of cognitive improvement through new therapies & establishing clinical trials – Questions #2 & 3

- Development & validation of new & specific DS Cognitive Test Battery
  - Specifically designed & validated to assess cognitive function in prefrontal cortex, hippocampus & cerebellum - all brain areas demonstrated to be involved in cognitive dysfunction in DS
  - Selected to be non-verbal-based so as to separate neuropsychological skills from language demands; cross-cultural applicability
  - Test battery properties allow for correlation with animal model & genetic studies and clinical outcomes

- Sleep-Cognition Correlations in Down Syndrome
  - Quantitative assessment of sleep problems, including sleep apnea, hypoxemia & fragmentation, together with Cognitive Test Battery for correlations with cognitive dysfunction in DS
  - Potential to lead to new research directions, therapeutic targets & strategies