Down Syndrome Cognition Research
Carolyn Cronin
President/CEO
LuMind Research Down Syndrome Foundation

Why We Do What We Do

About LuMind Research Down Syndrome
• We are visionaries focused solely on cognition research in Ds
• Stimulate biomedical research
• Focused on development of treatments to improve cognition, memory, learning and speech
• Goal: safe and effective therapies
• Scientific advances point to possible medical therapies to treat intellectual disabilities and Alzheimer’s-related conditions
When We Talk to Parents…  
(and Grandparents)

- They love their children
- They appreciate the wonderful differences
- They want the most opportunities
- They worry about:
  - Social interactions at school and work
  - Care across a lifetime
  - Early onset Alzheimer's disease

Sound familiar?

When We Talk to People with Down Syndrome

- They want a career, not just a job
- They want to live independently
- They want a life partner
- They want meaningful relationships with friends and their families

They want what we all want!

We Are Shedding Light on the Science of Cognition Research

- Improve speech, learning, and memory
- 10-15% increase in cognition makes a HUGE difference in a person with Down syndrome
  - Inclusion vs. separate classroom
  - Job vs. career
  - Smoother social interactions
  - Living outside the home
- We envision safe and effective drug therapies to boost memory systems
- A focus on improving cognition can create more opportunities
Neurological Manifestations of Ds are Disabling

- Early developmental and sustained cognitive disabilities extend 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 Ds show the neuropathology of Alzheimer's disease by the age of 40, and majority develop further cognitive decline

Targeting Memory Systems: Hippocampus

- 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

Targeting 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
What Impact could Changing these “Memory Systems” Have in People with Ds?

- 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

Fighting the Myth: Down Syndrome is Too Complicated to Research

- There is no “language” or “everyday tasks” section of our brain that can be targeted
- These skills supported by memory systems
  - Being modifying in mouse models such as hippocampus and frontal cortex
- Changes in these systems can have a big impact in humans
- Only through regulated evidence-based clinical trials will we know if drugs work and how big the impact might be

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

The Elephant in the Room
Alzheimer’s Disease

“We are gratified that our son has experienced the benefits of full inclusion. Now, as my son is in his thirties, I am extremely worried about the increased likelihood of Alzheimer’s disease. Who will care for my son when we as caregivers are no longer around.”

Concerns about Alzheimer’s disease aren’t limited to the ageing Ds population – every parent of a newborn should be tracking this now!
Neuronal Degeneration  
Plaques Form & Lead to Neuronal Death  
Plaques Result from Aggregation of Aβ Peptide

- More than 5 million people in US, 35 million world-wide; doubling by 2030
- Formation of beta-amyloid plaques lead to damage and death of nerve cells years before detectable loss of cognitive function
- Early prediction of those who will develop AD is a major challenge for proving effectiveness of potential new drugs to prevent or halt AD

Alzheimer’s Disease and Down Syndrome

Development & Specific Pathological Characteristics

- Alzheimer’s Disease
- Down Syndrome

Addressing a Large Unmet Medical Need

- Historically, little funding was directed toward Down syndrome cognitive research
- Large unmet medical need for pharmacological therapies to address not only learning challenges, but also increased likelihood for Alzheimer’s disease
- Down syndrome cognitive research is underfunded

$2+ million per year needs to be TENS of millions per year to achieve success and incentivize needed support, including NIH and bio-pharmaceutical companies

NIH and Private Support for Ds Research Has Been Disproportionately Underfunded

<table>
<thead>
<tr>
<th>Condition</th>
<th>NIH FY 2014 $ funding/ Patient</th>
<th>Multiple higher than funding for Down syndrome</th>
<th>Private FY 2014 $ funding/ Patient</th>
<th>Multiple higher than funding for Down syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Down syndrome</td>
<td>$600</td>
<td>-</td>
<td>$600</td>
<td>-</td>
</tr>
<tr>
<td>Multiple Sclerosis</td>
<td>$600</td>
<td>$200</td>
<td>$200+</td>
<td>$10+</td>
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<tr>
<td>Duchenne Muscular Dystrophy</td>
<td>$575</td>
<td>$125</td>
<td>$575+</td>
<td>$10+</td>
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<tr>
<td>Alzheimer’s Disease</td>
<td>$1,400</td>
<td>$300</td>
<td>$1,400+</td>
<td>$10+</td>
</tr>
<tr>
<td>Fragile X</td>
<td>$1,113</td>
<td>$300</td>
<td>$1,113+</td>
<td>$10+</td>
</tr>
<tr>
<td>Cystic Fibrosis</td>
<td>$1,507</td>
<td>$400</td>
<td>$1,507+</td>
<td>$10+</td>
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Our Research Strategy

Accelerating Progress Throughout the Drug R&D Pipeline

<table>
<thead>
<tr>
<th>Phase</th>
<th>Time</th>
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</thead>
<tbody>
<tr>
<td>DISCOVERY</td>
<td>2-4 yrs</td>
</tr>
<tr>
<td>RESEARCH</td>
<td>1-2 yrs</td>
</tr>
<tr>
<td>TARGET VALIDATION &amp; DRUG DISCOVERY</td>
<td>1-3 yrs</td>
</tr>
<tr>
<td>PRECLINICAL DEVELOPMENT &amp; IND</td>
<td>2+ yrs</td>
</tr>
<tr>
<td>CLINICAL TRIALS - PHASES I-III</td>
<td>3-10 yrs</td>
</tr>
<tr>
<td>FDA REVIEW &amp; APPROVAL</td>
<td>2+ yrs</td>
</tr>
</tbody>
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A Revolutionary New Paradigm for Down Syndrome Research

- Increase “awareness” of research potential for biomedical research and public communities
- Pursue the most innovative and promising lines of research
- Foster interdisciplinary research collaborations
- Attract new research talent
- Pursue new biomedical mechanisms, therapeutic targets and drugs
- Resolve roadblocks throughout drug R&D pipeline
- Promote innovative, safe and effective clinical trials
- Engage with Biopharma Industry
- Leverage effective R&D funding

We Have Made Unprecedented Progress

- Remarkable progress has been made over a relatively short period of time
- Research aided by mapped human genome and Ds mouse model
- Researchers discerned multiple neurological pathways associated with cognitive impairment occurring with the developmental intellectual disability and Alzheimer’s disease in Ds which allows for the identification of potential drug targets
- Four human clinical trials are underway
Discoveries are Ignited at Leading Medical Research Institutions

LuMnd RDS supports and funds Down syndrome cognitive research conducted at preeminent research institutions:

- Johns Hopkins University School of Medicine
- Stanford University
- University of Arizona
- University of California, San Diego School of Medicine
- Emory University School of Medicine
- Palo Alto Veterans Institute for Research System

Accelerating Progress Throughout the R&D Pipeline

Current Research Grants

- 20 new grant applications assessed and reviewed by the 6-member Scientific Advisory Board
- Allocated $1,615,000 for new 2015-16 Research Grants
- Funded more than $13.4 million since 2004
- 7 Research 2015-16 Grant recipients
  - Johns Hopkins University School of Medicine
  - Emory University School of Medicine and Research Network Consortium
  - University of California, San Diego (UCSD) School of Medicine
  - University of Arizona
  - Stanford University
  - Palo Alto Veterans Institute for Research/VA Palo Alto Health Care System
  - AC Immune/UCSD School of Medicine
Johns Hopkins University School of Medicine

- Research Center Grant: A Down Syndrome Center for Fundamental Research-Cognition
  - Dr. R. Reeves, Principal Investigator, and Co-PI’s Drs. D. Foster and P. Worley
  - Grant Award: $227,500

Emory University School of Medicine and Research Network Consortium

- Research Center Grant: The Down Syndrome Cognition Project (DSCP)
  - Drs. S. Sherman (Emory) and R. Reeves (Johns Hopkins), Principal Investigators, and 9 Co-PI’s at 8 institutions KKI, U Arizona, UC, Davis/MIND Institute, U Pittsburgh, Oregon, CNMC Washington DC, U Penn/CHOP, Waisman Center/U WI
  - Grant Award: $275,000

UCSD School of Medicine

- Research Center Grant: Defining genes, mechanisms and treatments for neurodevelopmental and neurodegenerative causes of cognitive dysfunction in Down syndrome
  - Dr. W. C. Mobley, Principal Investigator, and Co-PI’s Drs. A. Kleschevnikov, C. Wu, S. Wagner, N. Singhal
  - Grant Award: $325,000
University of Arizona

- Innovation Research Grant: Brain Development, Sleep and Learning in Down Syndrome
- Dr. J. Edgin, Principal Investigator, and Co-PI’s Drs. L. Nadel, R. Gomez and C. Clark
- Grant Award: $250,000

Stanford University

- Innovation Research Grant: Mechanisms Underlying the Roles of Sleep and Circadian Rhythms in the Learning Disability of Down Syndrome
- Dr. H. C. Heller, Principal Investigator, and Co-PI’s Drs. C. Garner and M. Adorno
- Grant Award: $197,500

Palo Alto Veterans Research Institute/VA Palo Alto Health Care System

- Innovation Research Pilot Grant: Improving Adrenergic Signaling for the Treatment of Cognitive Dysfunction in Down Syndrome
- Dr. A. Salehi, Principal Investigator
- Grant Award: $140,000
Dysfunctional Cognitive Mechanisms and Drug Targets

- Targeting Early and Life-long Developmental Cognitive Disability in Ds
  - New Drug in Roche Clinical Trials
  - Balance Therapeutics Clinical Trials

- Targeting Earlier Development of Alzheimer’s Disease in Down Syndrome
  - Elan Clinical Trial
  - AC Immune Clinical Trial

- Multiple mechanisms involved in cognitive impairment and/or decline associated with Down syndrome defined
- At least 10 new potential therapeutic drug targets 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

Measuring Cognitive Improvement

- Down Syndrome-specific Cognitive Test Battery – The Arizona Cognitive Test Battery (ACTB)
  - Development of the ACTB – the first Ds-specific cognitive test battery (prefrontal cortex, hippocampus & cerebellum function) - to significantly enable efficacy determination in clinical trials
  - University of Arizona

- Ds Cognition Project (DSCP) – network/consortium of collaborating researchers with 9 US institutions
  - Creating scaffold for effective Down syndrome clinical trials network
  - Documenting cognitive variability in Ds
  - Emory University School of Medicine and research institutions consortium

Establishing Clinical Trials

- Engaging the BioPharma industry is critical to establishing clinical trials
- Biopharma firms need to see strong evidence-based research and potential for drug market
- Markets are gauged by an engaged community
  - DS-Connect® is an indicator of community support
### Success Indicator: Clinical Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Progress &amp; Current Status</th>
<th>Next Steps</th>
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</thead>
<tbody>
<tr>
<td>Roche RG1662</td>
<td>- LuMind RDS funded mechanism/target identification &amp; validation</td>
<td>- Last Phase 2 trial anticipated completion Q2 2016; Additional new Phase 3 trial approved Q3 2015, completed studies</td>
</tr>
<tr>
<td>Developmental Intellectual Disability in DS</td>
<td>- LuMind RDS engaged &amp; advised for clinical trial recruitment</td>
<td></td>
</tr>
<tr>
<td>Balance Therapeutics BTD-001</td>
<td>- LuMind RDS engaged in target identification &amp; validation</td>
<td>- Determination to advance to Phase 2 dependent on Phase 1b results analysis</td>
</tr>
<tr>
<td>Developmental Intellectual Disability in DS</td>
<td>- LuMind RDS support for clinical trial participant recruitment</td>
<td></td>
</tr>
<tr>
<td>Transition Therapeutics ELND-005 Alzheimer’s Disease &amp; Cognition in DS</td>
<td>- LuMind RDS support for clinical trial participant recruitment</td>
<td>- Ongoing plan: unreasonable advances follow on clinical trial</td>
</tr>
<tr>
<td>AC Immune ACI-24 Alzheimer’s Disease in Ds</td>
<td>- LuMind RDS approved to funding for Phase 1b trial</td>
<td>- Phase 1b trial to be completed Q1 2016</td>
</tr>
<tr>
<td></td>
<td>- LuMind RDS funded mechanism/target identification &amp; validation</td>
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### Research Has Impact Beyond Down Syndrome

- **Alzheimer’s Disease (AD) – Ds unique key**
  - New targets in learning, memory and neurodegeneration already identified through Ds research
  - DSBI expected to provide further support to why Ds could be a favored population to test drug candidates developed for AD with a higher probability of success
  - AD trials in a Ds population may lead to unexpected novel insights and new therapies

- **Solid tumor cancers**
  - Research has documented a lower incidence of a variety of solid tumors in Ds.
  - Evidence is emerging showing certain human chromosome 21 gene(s) when present in three copies suppress tumor formation.

- **Atherosclerosis**
  - Research has indicated there is a lower incidence of atherosclerosis in Ds

- **Other intellectual disabilities, including autism, obesity, aging**

A deeper understanding of Ds is uniquely contributing to tackling multiple other diseases

### Numerous Breakthroughs Published in Top Journals

- **Neuron**
  - Sales et al. (2009) Neuron 51, p93-102
  - Increased App Expression in a Mouse Model of Down’s Syndrome Disrupts NGF Transport and Causes Cholinergic Neuron Degeneration
  - Key biological mechanism identified

- **Science Translational Medicine**
  - Sales et al. (2010) Science Translational Medicine, 18, 1157:717
  - Restoration of Norepinephrine-Mediated Contextual Memory in a Mouse Model of Down Syndrome
  - New therapeutic approach and drug candidate identified!

- **Frontiers in Neuroendocrinology**
  - Formadita et al. (2007) Nature Neuroscience 10, p411-413
  - Pharmacotherapy for cognitive impairment in a mouse model of Down syndrome
  - New therapeutic approach and drug candidate identified!

- **Journal of Neurodevelopmental Disorders**
  - Development and validation of the Arizona Cognitive Test Battery for Down syndrome
  - Clinical assessment tool developed!
Numerous Breakthroughs Published in Top Journals

The Journal of Neuroscience


UpG5 contributes to somatic stem-cell defects in Down’s syndrome

*New drug candidate identified!*

*Nature* Translational Medicine


Hedgehog Agonist Therapy Corrects Structural and Cognitive Deficits in a Down Syndrome Mouse Model

*New therapeutic approach identified!*

*The Journal of Neuroscience*


Deficits in Cognition and synaptic plasticity in a mouse model of Down syndrome ameliorated by GABAβ receptor antagonist

*New drug candidate identified!*

Where We Are Going by 2020

• Fund multi-year grants at major research initiatives
• Grow DS-Connect registry to 12,000 participants across all age ranges
• Establish and fund new catalytic research initiatives 2+ new drug candidates ready for or in clinical trials in a Ds population
• Attract 10+ new principal researchers into the Ds field
• Leverage private funding (LuMind RDS) to encourage increased NIH funding to Ds Research from $18M to $30M annually

Milestones

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
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<tr>
<td>2003</td>
<td>Decoding of human genome opens door to cognitive research</td>
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<tr>
<td>2004</td>
<td>Mouse model for DS developed by researchers in London; Down Syndrome Research and Treatment Foundation (DSRTF) is founded</td>
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<tr>
<td>2005</td>
<td>DSRTF awards first grant to Dr. William Mobley of Stanford University</td>
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<tr>
<td>2006</td>
<td>First drug target, the APP gene, identified by Dr. William Mobley and team, linking cognitive impairment in DS to the cognitive decline experienced in Alzheimer’s disease</td>
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<tr>
<td>2006</td>
<td>DSRTF establishes its Scientific Advisory Board, the only scientific board in the U.S. dedicated exclusively to cognition research for DS</td>
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<td>2007-2010</td>
<td>DSRTF expands grant awards to include Johns Hopkins University, UC San Diego, University of Arizona, University of Texas, and the VA Hospital of Palo Alto</td>
</tr>
<tr>
<td>2011</td>
<td>Roche Pharmaceuticals begins clinical trial of the first potential therapy designed to improve cognition and adaptive behavior in individuals with Down syndrome</td>
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<tr>
<td>2014</td>
<td>DSRTF renamed LuMind Foundation</td>
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<tr>
<td>2015</td>
<td>Merged with Research Down Syndrome to create LuMind Research Down Syndrome Foundation, the largest source of private funding for DS cognition research</td>
</tr>
<tr>
<td>2016</td>
<td>Awarded more than $13.4 million in research grants; 9 potential drug targets; 4 clinical trials</td>
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We’re Propelling to the Next Level – Won’t You Join Us?

• Ambitious vision making a significant difference
• Strong collaborations in academia and biopharma
• Engagement with Ds community
• Outstanding track record - transformative research & accomplishments
• Deep network with scientists in Ds and cognition
• Internationally focused – transformative and best research, anywhere
• Strong ties with NIH (LuMind RDS engagement has led to >$39M from NIH for new Ds-related research projects)
• High quality team and world-class Scientific Advisory Board

Make a HUGE Difference in Down Syndrome Biomedical Research

• Down syndrome is no longer intractable, even in adults
• Momentum in Ds with many promising new research avenues with significant broader applications
• Significantly more promising research avenues than funds available
• “Unprecedented” track record with results and progress achieved with limited funding
• Good timing and strong case for significant increase in funding to Ds research

How You Can Make a Real Difference

• Continue to become well educated supporters and “consumers” of evidence-based Ds biomedical research
  • Partnership together for leveraging resources to accelerate realization of effective new therapies & new opportunities for all individuals with Ds
• Critical need for participation in validated evidence-based clinical studies
  • New Therapeutic Drug Clinical Trials
  • DS-Connect® - Down Syndrome Patient Registry
  • Down Syndrome Heart Project
  • Down Syndrome Cognition Project (DSCP)

Today’s generation of individuals with Ds are the new Pioneers!
“Seize-the-moment” - Unusually Significant Opportunity Now

• The ‘unprecedented’ results and progress achieved signify that effective new treatments and greater independence are within reach

• Understanding and Treating Ds is:
  • No longer too complex or difficult - New research & tools, increased understanding & 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 Ds research to build upon new momentum
  • Significantly more promising & needed new research than available current resources

• Requires building upon & increasing cooperation, collaborations & partnerships
  • Researchers, clinicians, their institutions, the Ds community and organizations, Federal agencies including across the different NIH institutes, and Biopharma companies

“Down syndrome advocates have facilitated health care advances and inclusion. Now it is our time to build upon these successes by supporting research to address learning challenges and prevent the early cognitive decline associated with Alzheimer’s disease.”

Thank You!