DSAIA Webinar October 16, 2013

The Research Landscape

Update on Down Syndrome Cognition Research & Ongoing Clinical Trials

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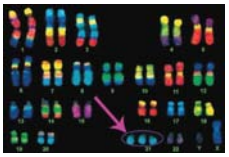
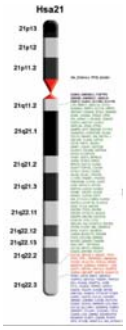
Down Syndrome Research and Treatment Foundation




Genetic Basis & Characteristics of Down Syndrome





- Down syndrome results from an extra (third) copy of chromosome 21
- Chromosome 21 contains 200-300 genes
- Different Down syndrome characteristics (phenotypes) result from excessive over-expression of a chr 21 gene, or groups of genes in one or more different tissues during development, maturation and aging.
- Small DNA sequence variations may correlate with observed variability (spectrum) in phenotypes between individuals
- All individuals with DS have developmental cognitive impairment & develop earlier neuropathology associated with Alzheimer's disease with majority developing dementia

Down Syndrome Research and Treatment Foundation
DSRTF

Founded in 2004
501(c)(3) Organization

Mission

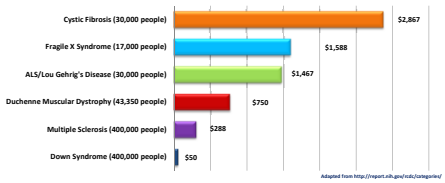
To stimulate biomedical research that will accelerate development of treatments to significantly improve cognition, including memory, learning and speech, for children and adults with Down syndrome.

Creating New Opportunities for All Individuals with Down Syndrome

- To lead more independent lives
- To participate more successfully in schools & employment
- To prevent additional early cognitive decline with aging & Alzheimer's disease

Down Syndrome Research Funding
NIH FUNDING FY 2012

2012 NIH Research Dollars Per Diagnosed Person

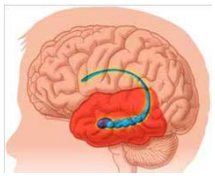


NIH & non-governmental funding for Down syndrome research continues to be disproportionately under-funded

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.

Cognition, Learning Memory & Speech in Down Syndrome
Memory Systems: Hippocampus



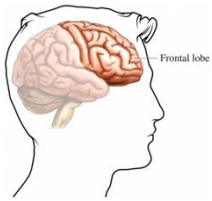
From Dr J Edgin

One target system- 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



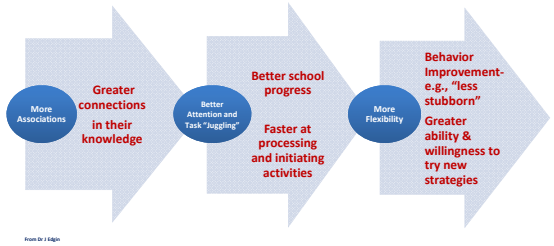
From Dr J Edgin

Frontal cortex is the brain's CEO

- 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)

Cognition, Learning Memory & Speech in Down Syndrome

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



From Dr J Edgin

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

Reviewed in Edgin et al. (2012). Merging human and mouse cognitive phenotypes in DS: Implications for Assessment. Progress in Brain Research.

Cognition, Learning Memory & Speech in Down Syndrome

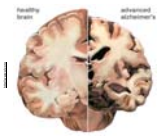
Bottom line:
If we don't try, we won't know what could be

- 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 being modifying in mouse models such as hippocampus and the frontal cortex.
- Changes in these systems can have a big impact in the human.

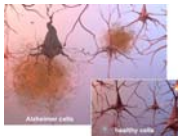
Only through regulated evidence-based clinical trials will we know if these drugs work and how big the impact might be.

Alzheimer's Disease

Specific Pathological Characteristics



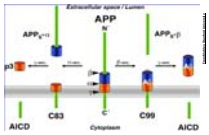
Neuronal Degeneration



Plaques Form Leading to Neuronal Death

Plaques Result from Aggregation of Aβ Peptide

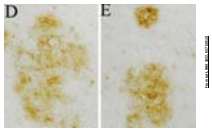
- The APP gene encodes a protein which is cleaved into multiple products, including the Aβ peptide
- Excess Aβ aggregates as "clumps" to form plaques which disrupt neuronal circuits & lead to neuronal death & cognitive impairment



Alzheimer's Disease & Down Syndrome

Specific Pathological Characteristics

Plaques containing Aβ in Brain Prefrontal Cortex

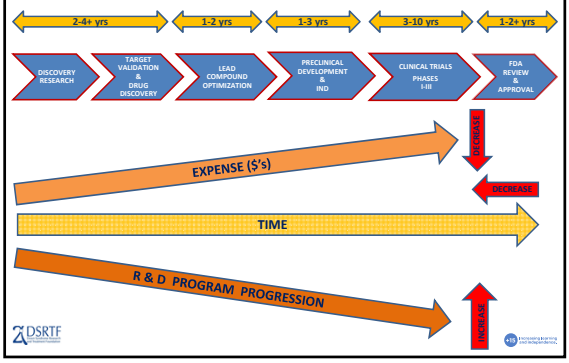


86 yr old w/o DS 31 yr old w/DS

- APP, a chromosome 21 gene, is over-expressed in DS
- APP protein & products over-expressed in DS
- Virtually all individuals with DS develop the characteristic neuropathology (amyloid plaque deposition) by their 4th decade & majority subsequently develop dementia

The DSRTF Research Strategy

Accelerating Progress Throughout the Drug R&D Pipeline



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

1. Are there evidence-based dysfunctional cognitive mechanisms together with associated validated specific drug targets & drug candidates to ameliorate that dysfunction?
2. Are there specific assessment tools that can measure meaningful improvements (efficacy) resulting from treatment with new potential drugs – can success be demonstrated?
3. 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?

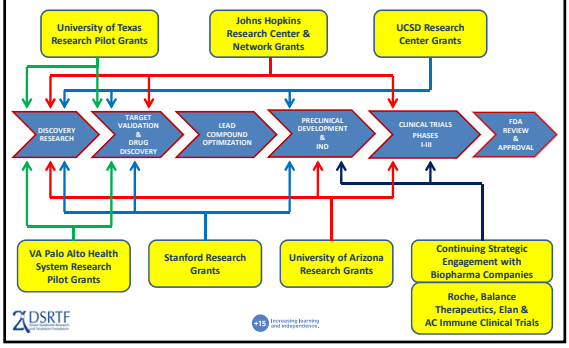
As recently as 2004 there were no answers to any of these questions…

The Research Strategy & Grants Program

Coordinating, Integrating & Accelerating Progress Throughout R&D Pipeline

Grants Program 2012-13

For additional research details on the new 2013-14 Research Grants: http://www.dsrtf.org/pages/our-research/2013-2014-grant-awards



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'Unprecedented' Progress in Down Syndrome Biomedical Research

Defining dysfunctional cognitive mechanisms & drug targets – Question #1

- *Targeting Early Developmental & Sustained Cognitive Disability in Down Syndrome*
- *Targeting Earlier Development of Alzheimer's Disease in Down Syndrome*

- Multiple mechanisms involved in cognitive impairment and/or decline associated with Down syndrome defined.
- At least 9 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.

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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
  - $GABA_A$**& $GABA_B$ Receptors & GIRK2 (Stanford/UCSD grants)
    - Drugs specifically reducing these targets'-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 **
- 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 hippocampal-mediated learning and memory.

** Das et al., Hedgehog Agonist Therapy Corrects Structural and Cognitive Deficits in a Down Syndrome Mouse Model (2013) Sci Transl Med 5: *201ra120*

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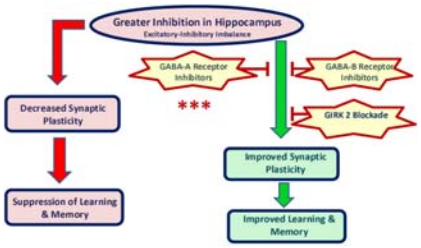
Defining dysfunctional cognitive mechanisms & drug targets – Question #1

Targeting Early Developmental & Sustained Cognitive Disability in Down Syndrome

Impaired connections and communications in brain neuronal circuits: 3 Targets



*** Target of New Drugs in Roche & Balance Therapeutics Clinical Trials

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Defining dysfunctional cognitive mechanisms & drug targets – Question #1

Targeting Early Developmental & Sustained Cognitive Disability in Down Syndrome

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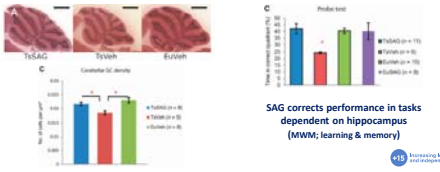

SAG corrects performance in tasks dependent on hippocampus (MWM; learning & memory)

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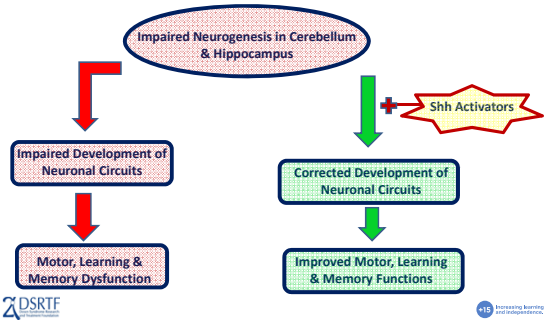
Defining dysfunctional cognitive mechanisms & drug targets – Question #1

Targeting Early Developmental & Sustained Cognitive Disability in Down Syndrome

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



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Defining dysfunctional cognitive mechanisms & drug targets – Question #1

Targeting Earlier Development of Alzheimer's Disease in Down Syndrome

- 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.
      - * Salehi *et al.* (2006) Neuron 51: 29-42
    - ** Aβ Target of AC Immune's New Drug & Planned Clinical Trial **
    - ** Aβ Anti-aggregation Target of Elan's New ELND005 Clinical Trial **
  - Norepinephrine Neurotransmitter Restoration (UCSD/Stanford/VA Palo Alto grants)
    - Drugs increasing norepinephrine (NE) levels in the brain overcome effects of degeneration of specific NE neural circuits and improve contextual learning and memory.
      - * Salehi *et al.* (2009) Sci Transl Med 1:7ra17; Dang *et al.* (2013) Biol Psychiatry, online July 3; (connection to AD: Heneka *et al.*(2010) PNAS 107: 6059-6063)

The Research Strategy & Grants Program

Defining dysfunctional cognitive mechanisms & drug targets – Question #1

Brain neuronal cell and circuit degeneration – *Alzheimer's disease connections*: 5 Targets

*** Targets of New Drugs in Elan & AC Immune Clinical Trials

The Research Strategy & Grants Program

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 (prefrontal cortex, hippocampus & cerebellum function) - to significantly enable efficacy determination in clinical trials.
      - * Edgin *et al* . (2010) J Neurodevelopmental Disorders 1: 149-164
  - DS Cognition Project - network of collaborating researchers with 9 US institutions (Johns Hopkins Research Center grants)
    - Creating scaffold for effective Down syndrome clinical trials network.

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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 - *Targeting Early Developmental & Sustained Cognitive Disability in DS*
    - **Roche**, the multi-national pharmaceutical company, initiated major new clinical trial in September, 2011 - cognitive and behavioral impairments in individuals with DS
      - "A Study of RG1662 in Individuals With Down Syndrome" – Phase 1 trial
      - New investigational drug, RG1662, targeting amelioration of inhibitory-excitatory imbalance in DS
      - Screening assessment trial (ages 12-30) in 2013 for Phase 2 trial
        - http://www.clinicaltrials.gov/ct2/show/NCT01920633?term=%22down+syndrome%22&rank=22
    - **Balance Therapeutics, Inc.** initiated significant new clinical trial in August, 2012 - cognitive and behavioral impairments in individuals with DS
      - "Study of the Drug BTD-001 in Young Adults and Adolescents with Down Syndrome."
      - Investigational drug, BTD-001, targeting amelioration of inhibitory-excitatory imbalance in DS
      - Phase I (12-35 yrs of age) being conducted at clinical trial sites in Australia
        - http://compose21.com/study.htm

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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 - *Targeting Earlier Development of Alzheimer's Disease in DS*
    - **Elan** initiated new clinical trial in adults with DS in September, 2013
      - "A 4-Week Safety Study of Oral ELND005 in Young Adults With Down Syndrome Without Dementia"
      - ELND005 (scyllo-inositol) targets β-amyloid anti-aggregation & reduction of myo-inositol related to cognitive impairment
      - Phase 2a clinical trial (18-45 yrs of age)
        - http://www.clinicaltrials.gov/ct2/show/NCT01791725?term=%22down+syndrome%22&rank=52
    - **AC Immune SA** received FDA approval in January, 2013 for IND for new clinical trial in adults with DS
      - Investigational drug, ACI-24, targeting amelioration of Alzheimer's disease (AD) neuropathology in DS
      - Addressing reduction in AD "plaques" & overcoming associated memory impairments in individuals with DS

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- 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 DS Organizations -http://downsyndrome.nih.gov/Pages/default.aspx
    - DS-Connect- The Down Syndrome Patient Registry - https://dsconnect.nih.gov/
      - Launched September 6, 2013
    - NIH Down Syndrome Research Strategic Plan
  - National Alzheimer's Plan (NAPA)
    - Increased inclusion of Down syndrome in plan & implementation
  - NIH Workshop – "Advancing Treatments for Alzheimer's Disease in Individuals with Down Syndrome, April, 2013
- Down Syndrome Biomarker Initiative (DSBI) – planning; private-public partnership - Ness, Rafii *et al.* (2012) Nat Rev Drug Discov 11: 655-656
  - Amyloid PET, FDG PET, vMRI, EBCC, retinal amyloid, serum biomarkers, APOE4, cognitive & functional tests

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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!

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+15 Increasing learning and independence.

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 ***
  - *** DS-Connect - New Down Syndrome Patient Registry ***
  - *Down Syndrome Heart Project*
  - *Down Syndrome Cognition Project*

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+15 Increasing learning and independence.

The Research Strategy & Grants Program

Creating New Opportunities for <u>All</u> Individuals with Down Syndrome Through Cognition Research

- Rapid success and validation of the new Research Strategy achieved
  - More than $9.6 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 <u>9 new potential therapeutic drug targets</u>
  - Targeted grants to advance new therapeutic targets through drug R&D pipeline, including target validation, identification and evaluation of effective drug candidates

DSRTF

+15 Increasing learning and independence.

The Research Strategy & Grants Program

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

- Rapid success and validation of the new Research Strategy achieved
  - 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 - Biopharma engagement **
      - Roche RG1662 Clinical Trials – Initiated September, 2011
      - Balance Therapeutics BD-001 Clinical Trial – Initiated August, 2012
      - AC Immune ACI-24 in Down syndrome IND Approved by FDA – January, 2013
      - Elan ELND005 Clinical Trial – Initiated September, 2013
  - Leveraged >$10 million in additional research funding from NIH, universities & other foundations
  - Partnerships & collaborations in achieving breakthroughs

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

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Down Syndrome Research and Treatment Foundation

DSAIA Webinar October 16, 2013

The Research Landscape

Update on Down Syndrome Cognition Research & Ongoing Clinical Trials

Thank You !

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The Research Strategy & Grants Program - Acknowledgements

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