Alzheimer’s Disease: Overall State of Research; Advances at the Linda Crnic Institute for Down Syndrome

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First Report of Down Syndrome

John Langdon Down, 1866

First Report of Alzheimer's Disease

Auguste Deter: “I have lost myself.”

Alois Alzheimer, 1907
The Problem:

Alzheimer’s Disease

- 5.7 million patients in U.S.
- $277 billion annual cost
- $1.1 trillion by 2050
- 10% of people over age 65
- 40-50% of people over age 85

Down Syndrome

- ~400,000 people in U.S.
- ~$19 billion annual cost
- 1/700 live births
- 100% develop AD brain pathology
The SOLUTION

A Team Pulling Together

Providing:
- Ideas
- Funding
- Translational Research
- Care
- Education

Affiliates:
- Global DS Foundation
- Crnic Institute for DS
- Sie Center for DS
- Adult DS Clinic
- RMADC

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RMADC Memory Disorders Clinic: CARE

• Academic Medical Center
  – 7 behavioral neurologists
  – 1 neuropsychologist
  – 1 fellow
  – 2 advanced practice providers
  – 3,000+ patients/year

• World-Class Memory Care
  – Accurate diagnosis
  – Latest treatments

• Opportunities to Participate in Research
  – Clinical trials
  – Longitudinal studies
Brain Amyloid in AD and DS

Autopsy

Brain Imaging RED=Amyloid

Normal

AD or DS
Correlating AD Pathology with Dementia

Adapted from Craig-Schapiro, Fagan, and Holtzman, Neurobiol Dis. 2009 August;35(2):128-140.
Current Alzheimer Drugs Only Enhance The Way Neurons Communicate With Each Other

SYNAPSE

- Namenda
- Aricept
- Razadyne
- Excelon

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Long-Term Solution: MORE RESEARCH

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Essential Tools: Transgenic Mice

Mouse Brain with Mutant Human AD Gene
ApoE is an Essential Amyloid Catalyst

Mouse Brain with Mutant Human AD Gene But *Lacking* the ApoE Gene
Measuring Short-Term Memory in AD Mice

Radial Arm Water Maze
Amyloid Cascade in AD and DS

Amyloid Precursor Protein

Merck  β-secretase  γ-secretase  Lilly

soluble Aβ

Aβ protofibrils

Aβ deposition in plaques

Aβ-secretase

γ-secretase

N- Aβ -C

Biogen and Esai: Aducanumab, BAN2401

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Searching for ApoE4-Blocking Alzheimer Drugs

ApoE4 → Aβ → Nerve cell death

NIH Drug Library
Searching for ApoE4-Blocking AD Drugs

**Graph:**
- **y-axis:** Aβ fibril formation (%)
- **x-axis:** Time (hours)
- Lines correspond to:
  - Gray: Aβ only
  - Black: Aβ + apoE4
  - Red: Aβ + apoE4 + Drug X
  - Green: Aβ + apoE4 + Drug Y
  - Blue: Aβ + apoE4 + Drug Z
Why are People with Rheumatoid Arthritis Protected Against Alzheimer’s Disease?
GM-CSF Reduces Aβ Deposition in AD Mouse Brain
GM-CSF Reverses Cognitive Impairment
GM-CSF Clinical Trials Summary

Current 3-Week Trial:
• 5 GM-CSF injections/week for 3 weeks; 45- and 90-day follow-ups

Results to Date:
• 30 subjects completed treatment phase plus both follow-ups
• No serious adverse events; no brain swelling or bleeding
• Improvement in MMSE at end of treatment

Future 6-Month Trial:
• 5 GM-CSF injections/week for 24 weeks (partially funded by Alz Assn)

Websites:
• ClinicalTrials.gov
• trialmatch.alz.org
GM-CSF Improves Cognition in Aged DS and Normal Mice

Dp16 mice + GM-CSF Control + GM-CSF

Time to reach platform (s)

Baseline, Post-treatment

P = 0.02

Baseline, Post-treatment

P = 0.001
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- Linda Crnic Institute for Down Syndrome
- Global Down Syndrome Foundation
- UC Denver SOM; Dept. Neurology; UC Health
- National Institute on Aging
- National Institute on Neurological Diseases and Stroke
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- Dana Foundation
- Alzheimer’s Association
- Bruce and Marcy Benson
- Other Philanthropists
- Hewitt Family Foundation
- MDC Richmond American Homes Fnd
- Dake Family Foundation
- State of Colorado
Colorado University Results
CURE

Anschutz Medical Campus

Hope!

Dementia on the rise
Alzheimer's Patients in the U.S.

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