

# **The Important Connection between Down Syndrome and Alzheimer's Disease - What you need to know**

Dean M. Hartley, Ph.D.  
Director of Scientific Initiatives  
Alzheimer's Association

# RAND Report - NEJM: Dementia Costliest Disease in the US

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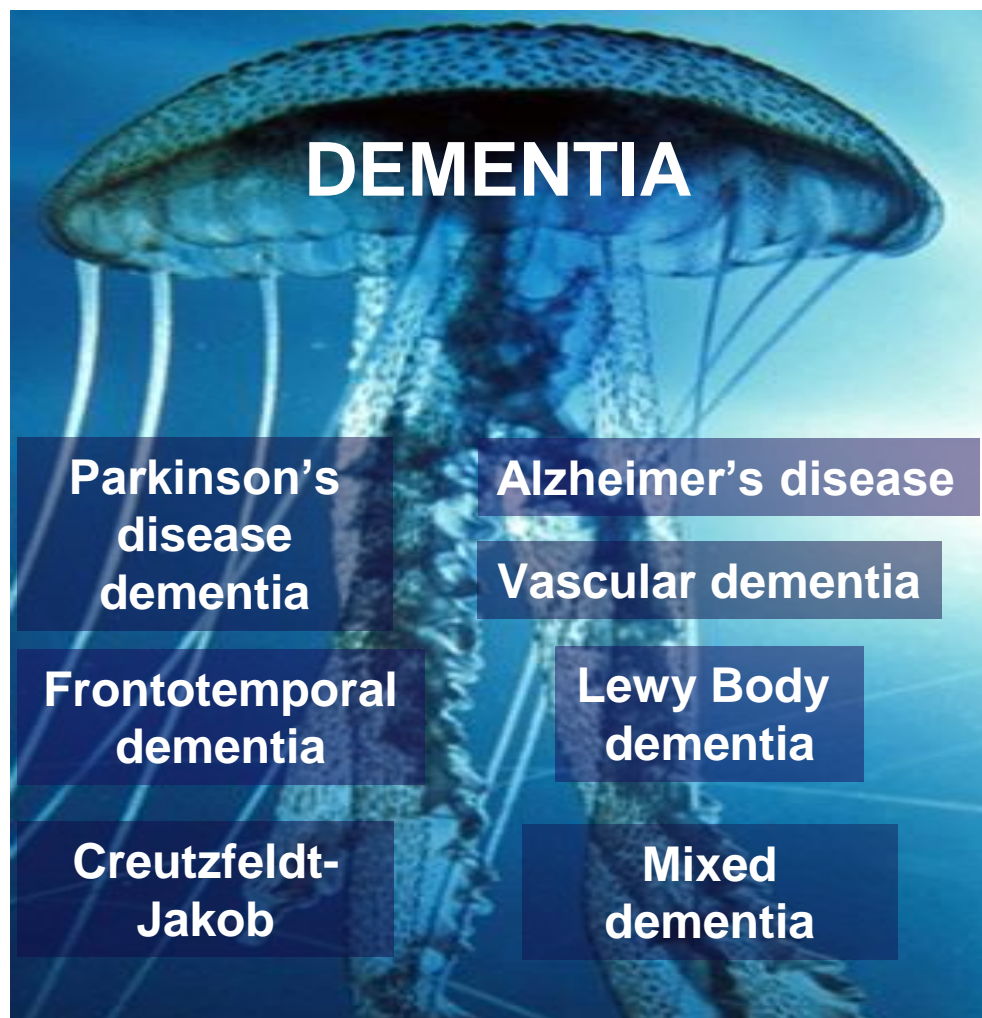
Technology

Markets &  
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## **Alzheimer's: The Costliest Killer**

**Dementia tops cancer, heart  
disease in cost**

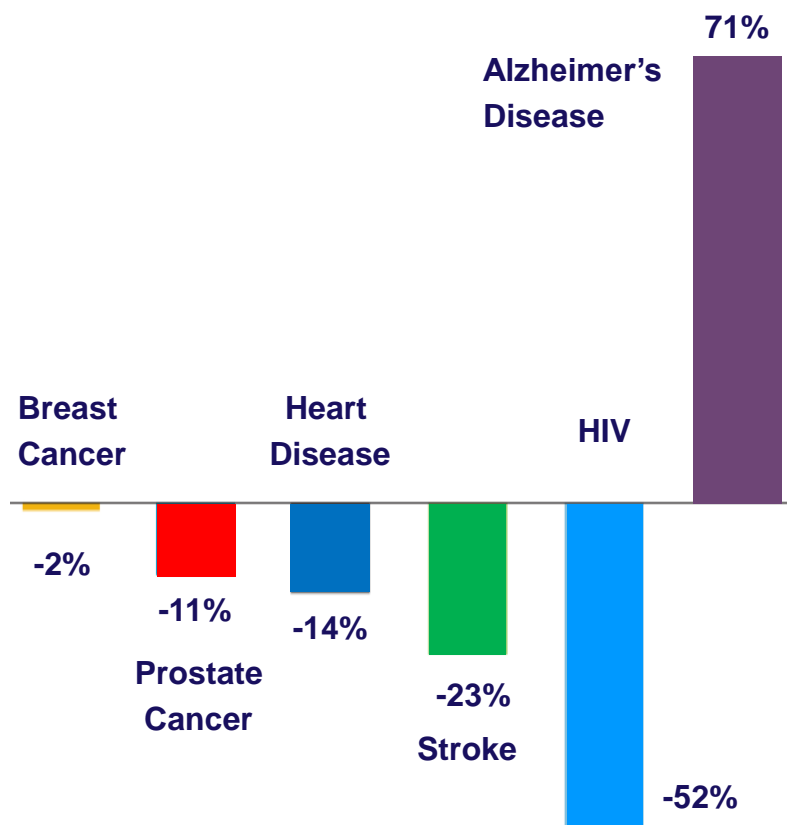
# Dementia is based on clinical symptoms



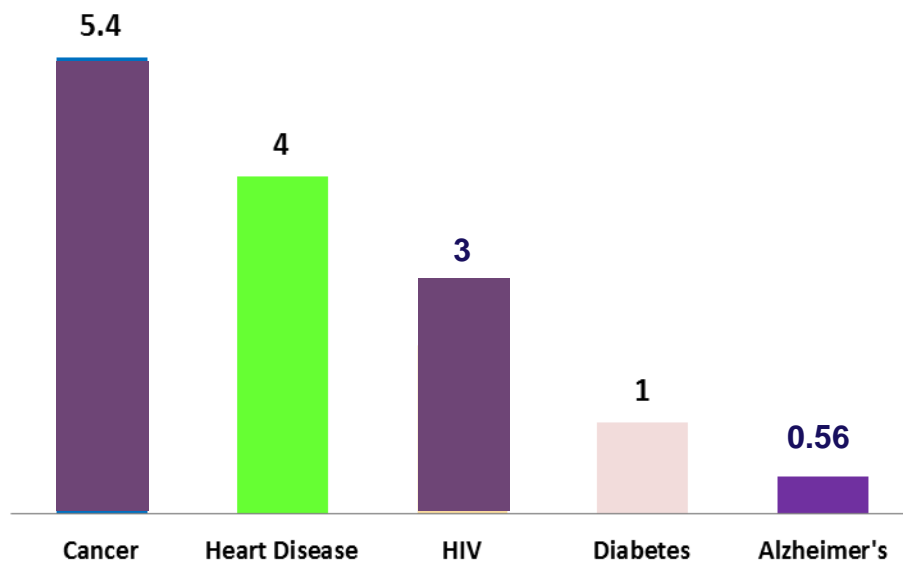
- Dementia manifest as problems with thinking and social abilities that interfere with daily functioning
- Alzheimer's is the most common form
- Many mixed cases
- Some dementia mimic Alzheimer's but are reversible

# Alzheimer's is Underfunded

## % Change in Deaths (2000-2013)



## Research Funding FY14 (in Billions)



# Our vision is a world without Alzheimer's disease

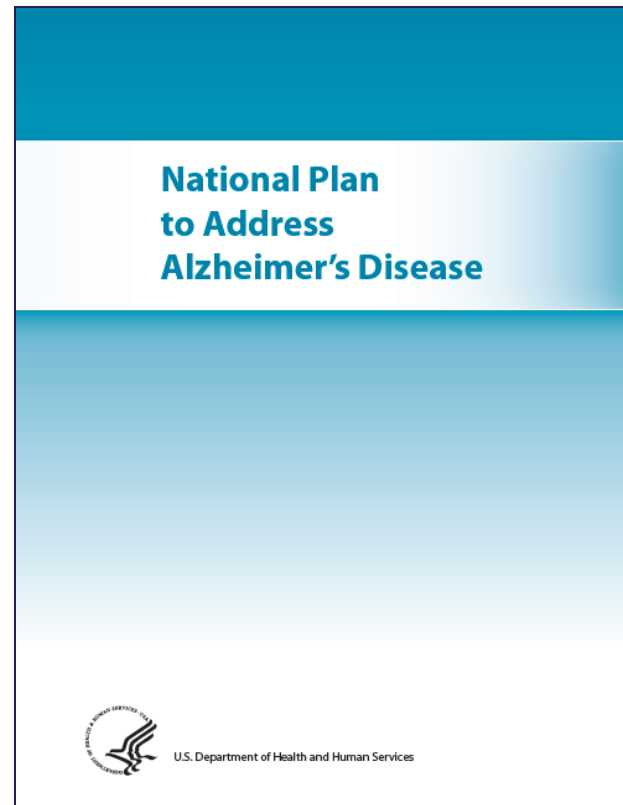


## Our goals:

- Provide care and support
- Increase Concern & Awareness
- Public Policy & Advocacy Efforts
- **Advance research**

# *The Alzheimer's Association championed 2 major legislations in the fight against Alzheimer's*

- 1. National Alzheimer's Project Act (NAPA)**
  - National Plan
- 2. Alzheimer's Accountability Act (AAA)**
  - Professional Judgment Budget





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POLITICS

## Hillary Clinton Calls for \$2 Billion in Alzheimer's Research, Cure by 2025

Democratic presidential front-runner seeks dramatic rise in government research spending



➤ **Hillary Clinton unveiled her plan:**

❖ **Spend \$2 billion a year**

❖ **Next 10 years**

# Global Leader in Alzheimer's Research

- Currently funding \$78 million  
350 active projects in 21 countries
- *Fund across critical research needs and gaps*
- *Global Impact*
  - Number 1 among worldwide profits
  - Ranked as 3rd highest impactful funder by publications\*\*



\*\* Based on Thompson Reuters Web of Science (2014)

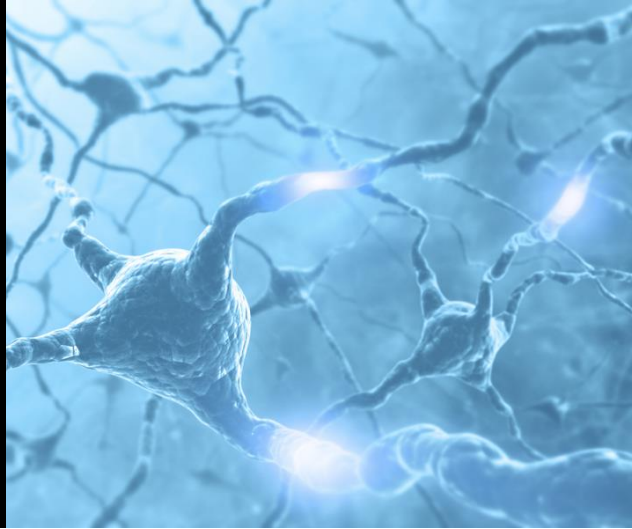


# Collaborative Research Initiatives Down Syndrome & Alzheimer's disease

**ALZHEIMER'S ASSOCIATION, LINDA CRNIC INSTITUTE FOR  
DOWN SYNDROME, AND GLOBAL DOWN SYNDROME  
FOUNDATION LAUNCH NEW RESEARCH GRANTS PROGRAMS**

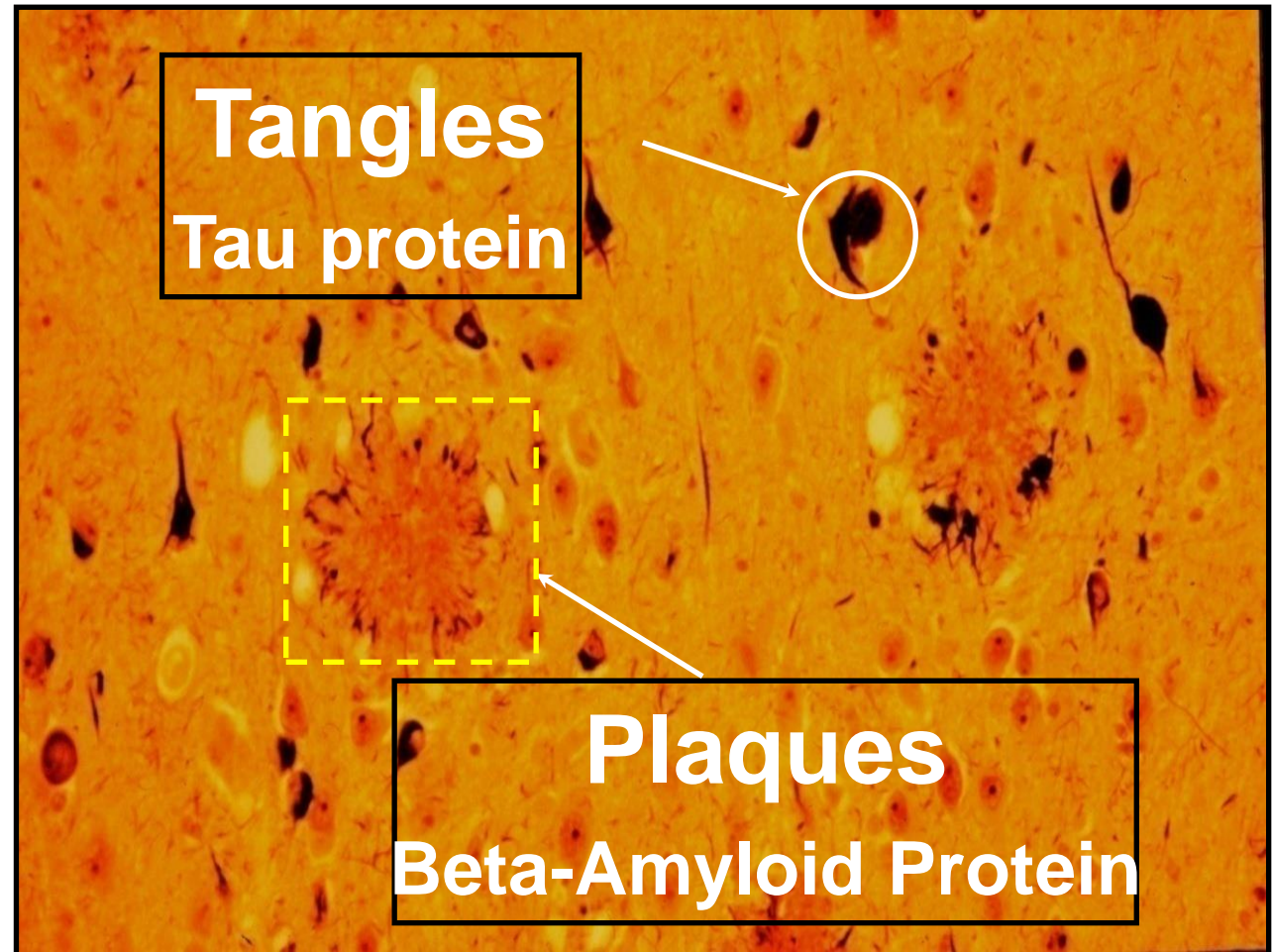
*\$2.2 million has been provided to fund research to  
understand the development of Alzheimer's in  
individuals with Down syndrome and the general  
population and possible treatments*



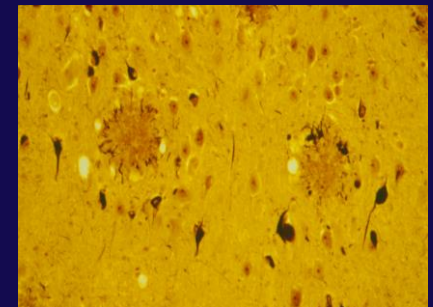
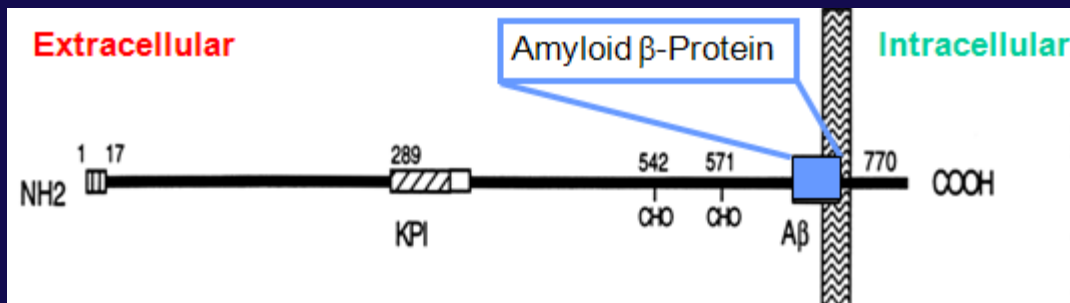
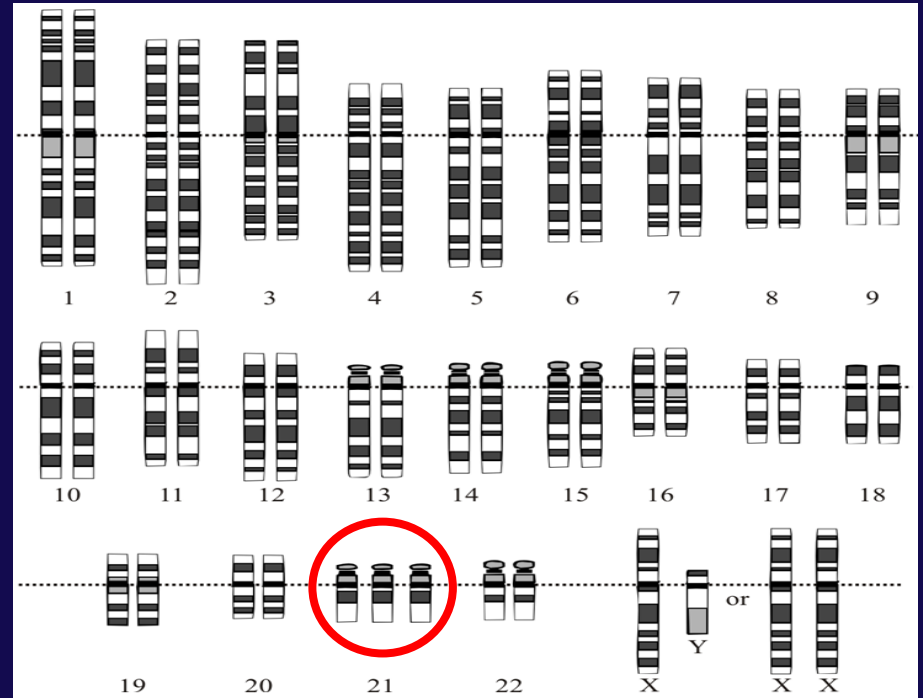


# What is Alzheimer's Disease?

# Alzheimer's Disease

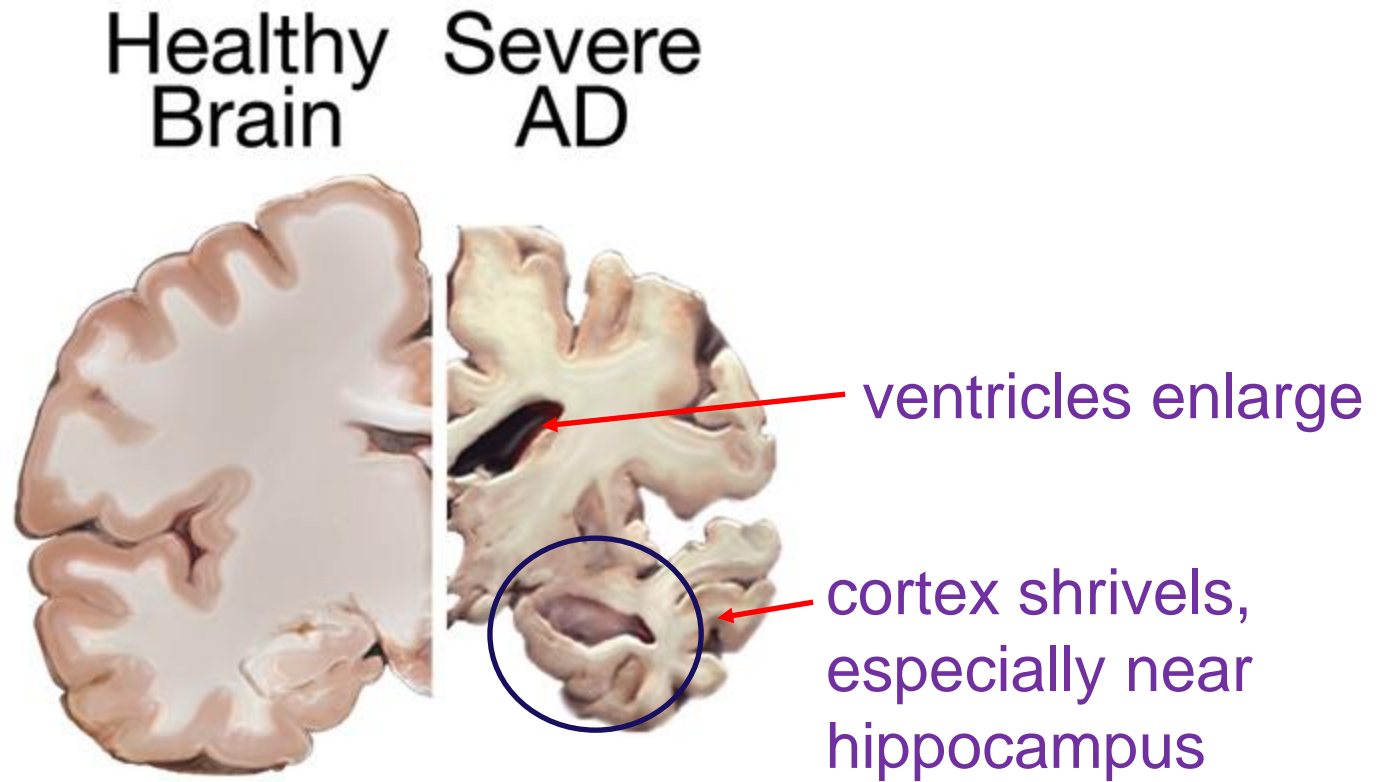


# Down's Patients Are at a Much Greater Risk to Develop AD

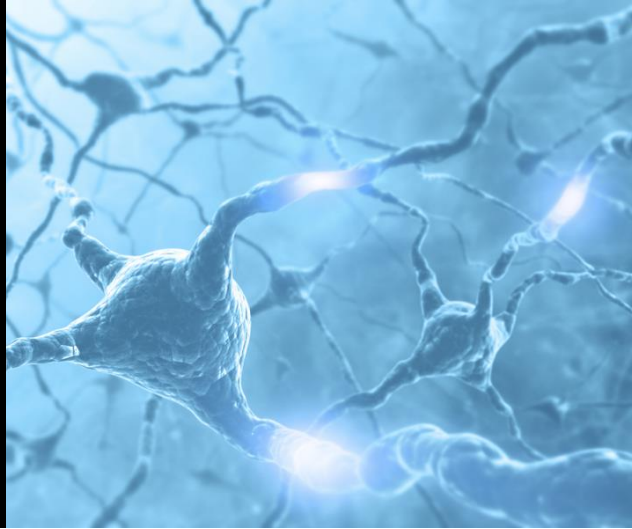




# What is happening in the brain?



AD brain = smaller overall



**What about treatments?**



# Pharmaceutical Alzheimer's Therapies and Diagnostics

## Therapeutic

### Cholinesterase Inhibitors

tacrine (Cognex; no longer marketed in US)  
donepezil (Aricept)  
rivastigmine (Exelon)  
galantamine (Razadyne)

### Glutamate Moderators

memantine (Namenda)

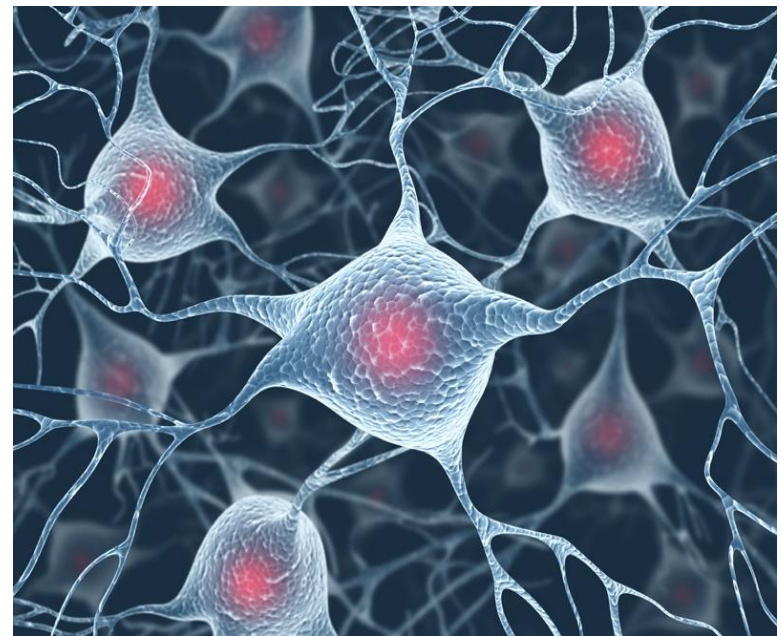
### Combination

donepezil/memantine (Namzaric;  
approved Dec. 2014)

## Diagnostic

### Amyloid PET Imaging

florbetaben (Neuraceq)  
florbetapir (Amyvid)  
flutemetamol (Vizamyl)



# Experimental Drug Trial Results: Potential Disease Modifying Treatments

- **Solanezumab (Lilly)**

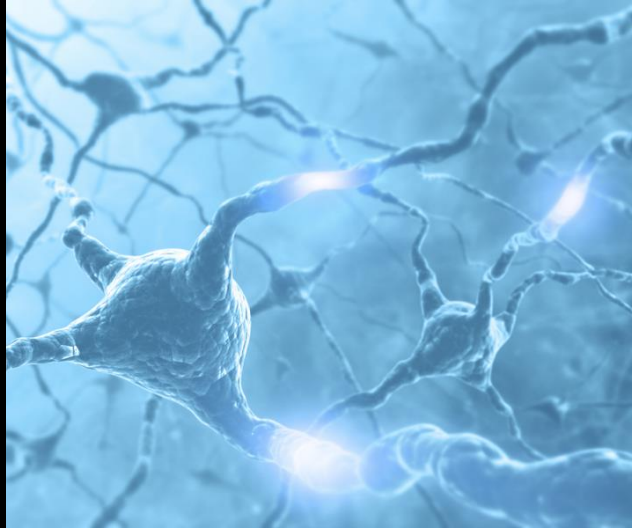
- New analysis of results from two prior phase 3 studies suggests it may slow cognitive decline
- On-going Phase 3 used Amyloid PET to enroll participants



- **Aducanumab (Biogen)**

- Small Phase 1b suggests may slow cognitive decline in people w/ mild Alzheimer's
- Launched two Phase 3 clinical trials using Amyloid PET to enroll participants



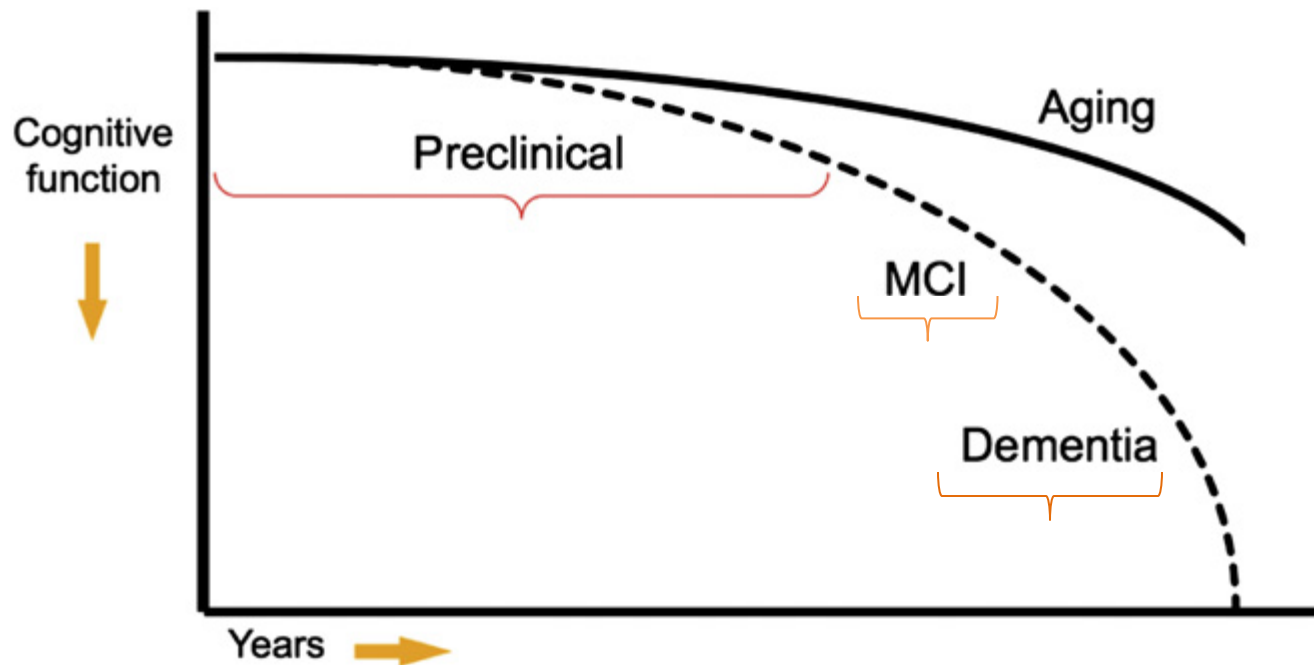


# **Early Detection & Diagnosis: Biomarkers and Modernizing Diagnosis of Alzheimer's**

# Modernizing the Diagnosis of Alzheimer's

Normal

Alzheimer's disease



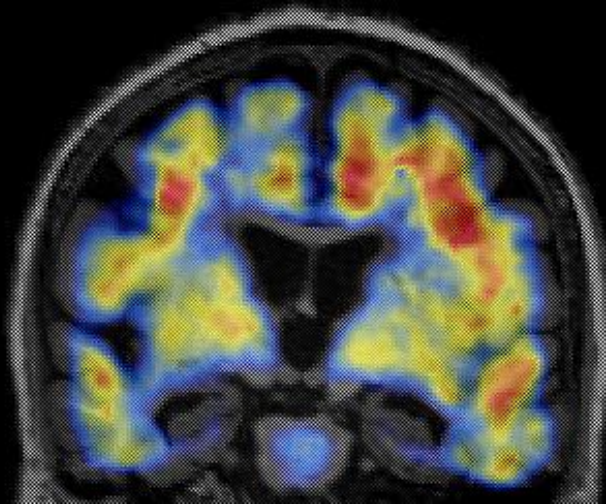
Adapted from Sperling et al. 2011



# Amyloid vs. Tau PET imaging

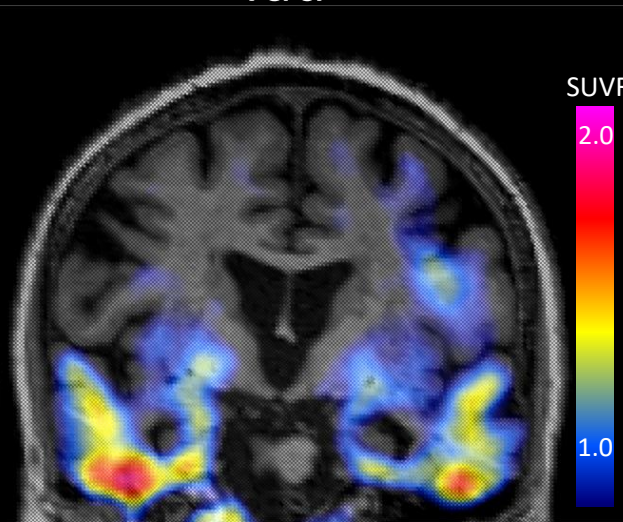
70 y/o MMSE =27

PiB



PiB

Tau



T807

SUVR

2.0

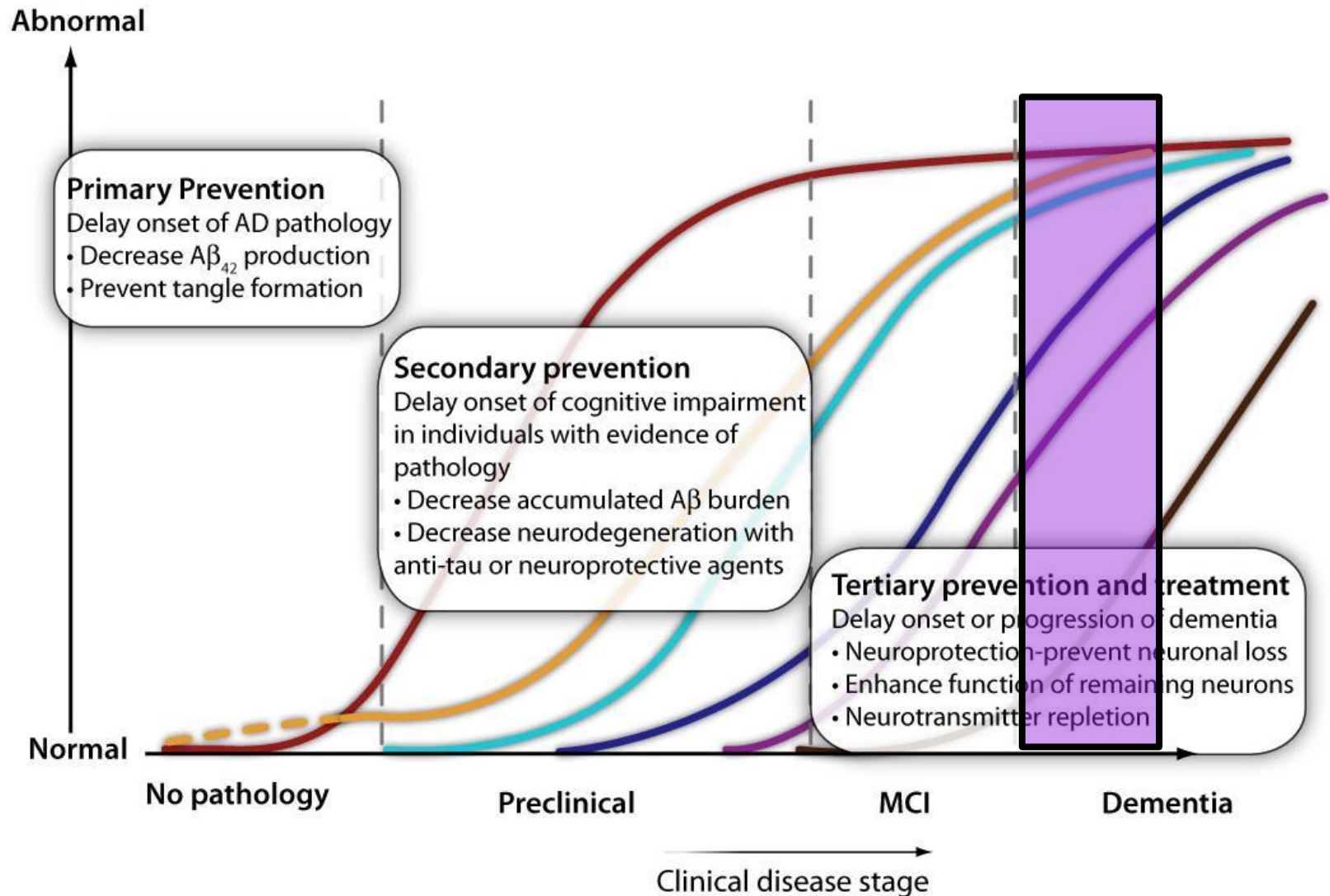
1.0

NFT stage III



Courtesy of Keith Johnson, MD  
First study AAIC 2013

# Possible Prevention of Alzheimer's?





# Possible Prevention of Alzheimer's

- **A4/LEARN** Anti Amyloid  
Asymptomatic Alzheimer's disease trial
- **API**: Alzheimer's Prevention  
Initiative Trials
- **TOMMORROW** Clinical Trial
- **DIAN – TU**: Dominantly Inherited  
Alzheimer's Network – Trials Unit



# alzheimer's association®

## trialmatch™

A first-of-its-kind, free, confidential, online and phone-based tool that provides comprehensive clinical trial information and an individualized trial matching service for people with Alzheimer's and related dementias.

**Colorado Chapter**  
**Linda Mitchell**  
**President & CEO**

**24-hour**  
**Helpline:**  
**1.800.272.3900**

**Offices:**

**Colorado Springs Office:**  
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**970-392-9202**

**Grand Junction Office:**  
**970-256-1274**

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**719-544-5720**

***Broncos Announce Flagship  
Partnership With Alzheimer's  
Association Colorado Chapter***



*Thank you*  
*You can make a difference!*

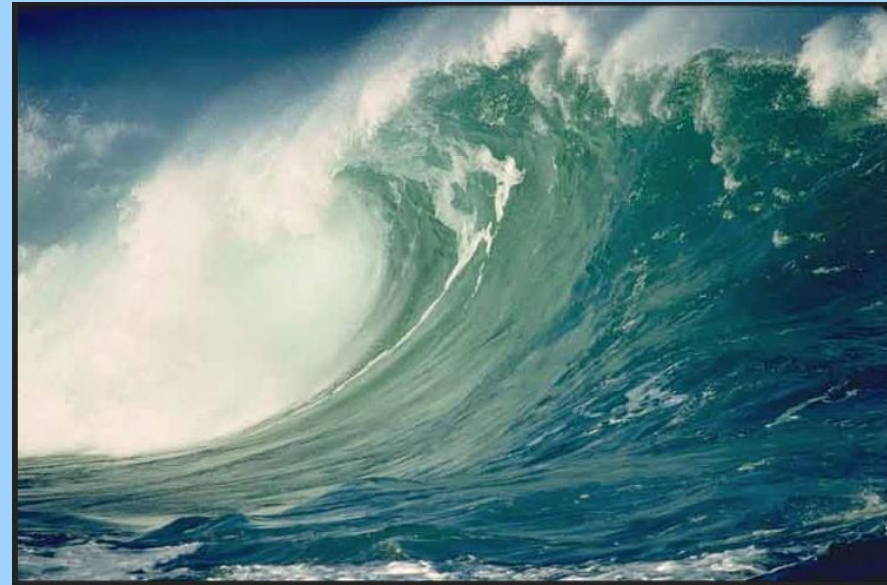
[www.alz.org](http://www.alz.org)

# Alzheimer's and Down Syndrome

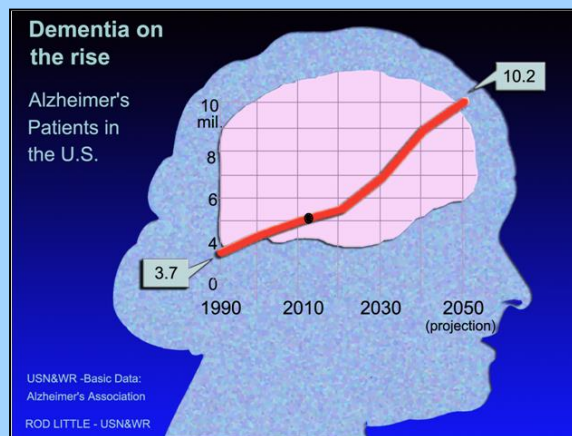
*Working together to solve a  
\$trillion problem*

**Huntington Potter, Ph.D.**

Professor and Director  
Alzheimer's Disease Programs  
Department of Neurology and Linda Crnic  
Institute for Down Syndrome  
CU Denver/AMC



# The Down Syndrome and Alzheimer's Disease Connection



## Alzheimer's Disease

- >5 million patients
- ~\$172 billion annual cost
- 10% of people over age 65
- 40-50% of people over age 85

## Down Syndrome

- ~400,000 patients
- ~\$19 billion annual cost
- 1/691 live births
- 100 % acquire features of AD



**Problem:** Need to Forge Links between  
AD and DS Efforts

**Solution:** COLLABORATION in  
Research, Education and Advocacy

# A Network of Affiliates

The Global Down Syndrome Foundation is part of a network of affiliate organizations that work closely together on a daily basis to deliver on our mission, vision, values, and goals:

## Global & Affiliates



❖ **Global:** was established as a 501(c)3 in 2009 and is “Dedicated to significantly improving the lives of people with Down syndrome through Research, Medical Care, Education, and Advocacy”

❖ **Affiliates are:**

- Established with a lead gift from Anna & John J. Sie Foundation
- Must work closely together to benefit people with Down syndrome
- Must be self-sustaining financially

# Collaboration between **Global Down Syndrome Foundation and Alzheimer's Association**

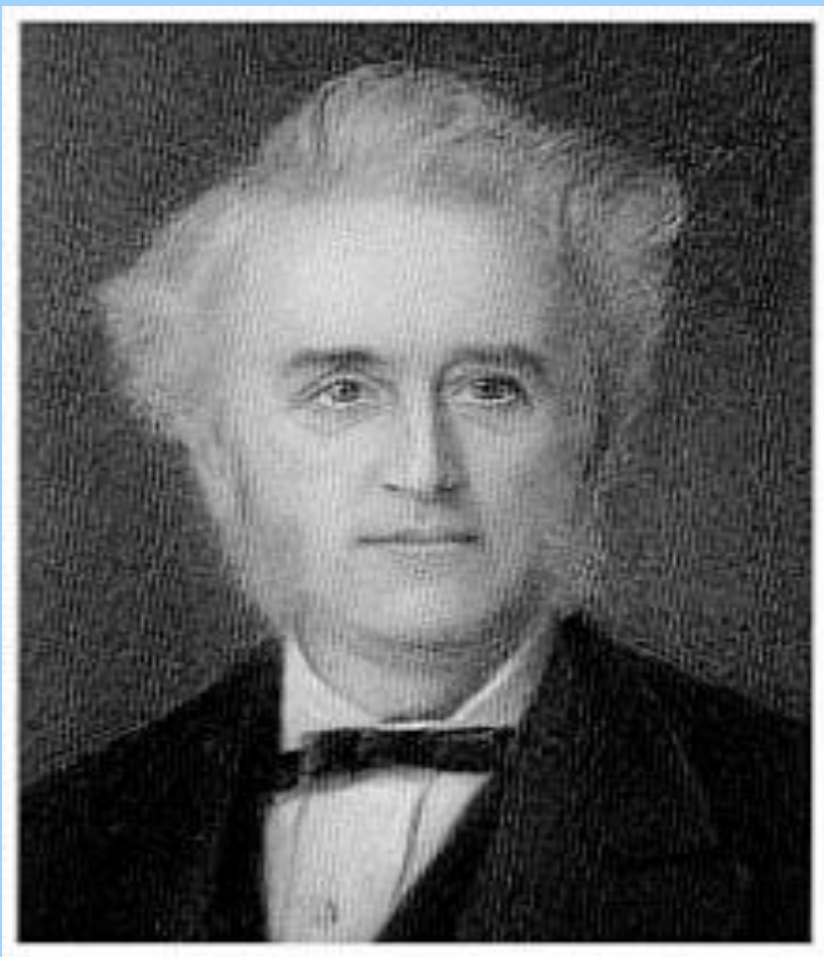
1. 2012 DS-AD Workshop in Chicago
2. Joint Grant Program for Research on AD in DS  
\$2.2 million 2013-2015
3. 2015 DS-AD Workshop in Chicago  
Cognition  
Imaging  
Biobanking  
Pathology  
IRB/Consent

Collaboration between  
**Global Down Syndrome Foundation and  
NIH**

1. 2010 Meeting/Workshop with **NICHD** on DS  
NIH establishes **DS-Connect**

2. First **NIH** 'Request for Applications' on AD and DS:  
'Biomarkers of Alzheimer's Disease in Down syndrome'  
\$5 million/year for 5 years  
Multiple applications from AD/DS experts world-wide
3. Advocacy and Education  
Multiple meetings with **legislators**  
\$500,000 per year from state of Colorado  
Media education  
***Washington Post*** May 22, 2015:  
"Why Studying Alzheimer's in People with  
Down Syndrome Could Help Everyone"





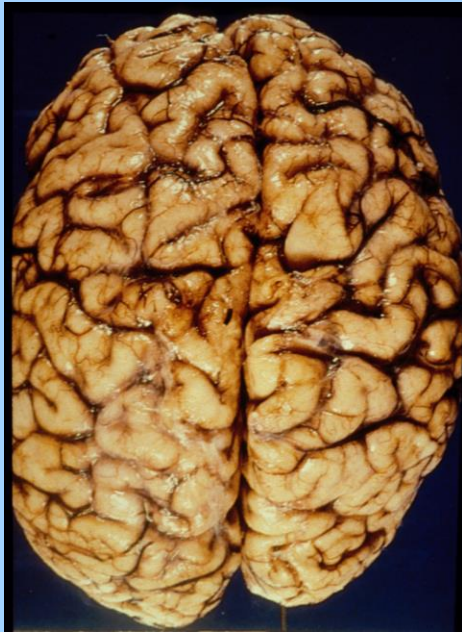
John Langdon Down, 1866



Alois Alzheimer, 1907

# BRAIN PATHOLOGY IN ALZHEIMER'S DISEASE

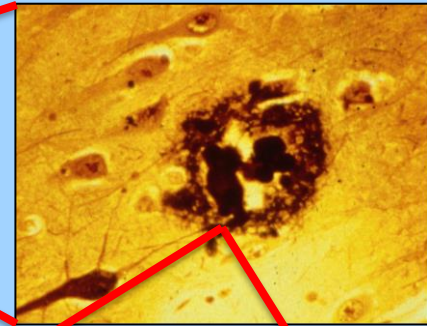
Normal Brain



Alzheimer's Brain



Plaques and tangles

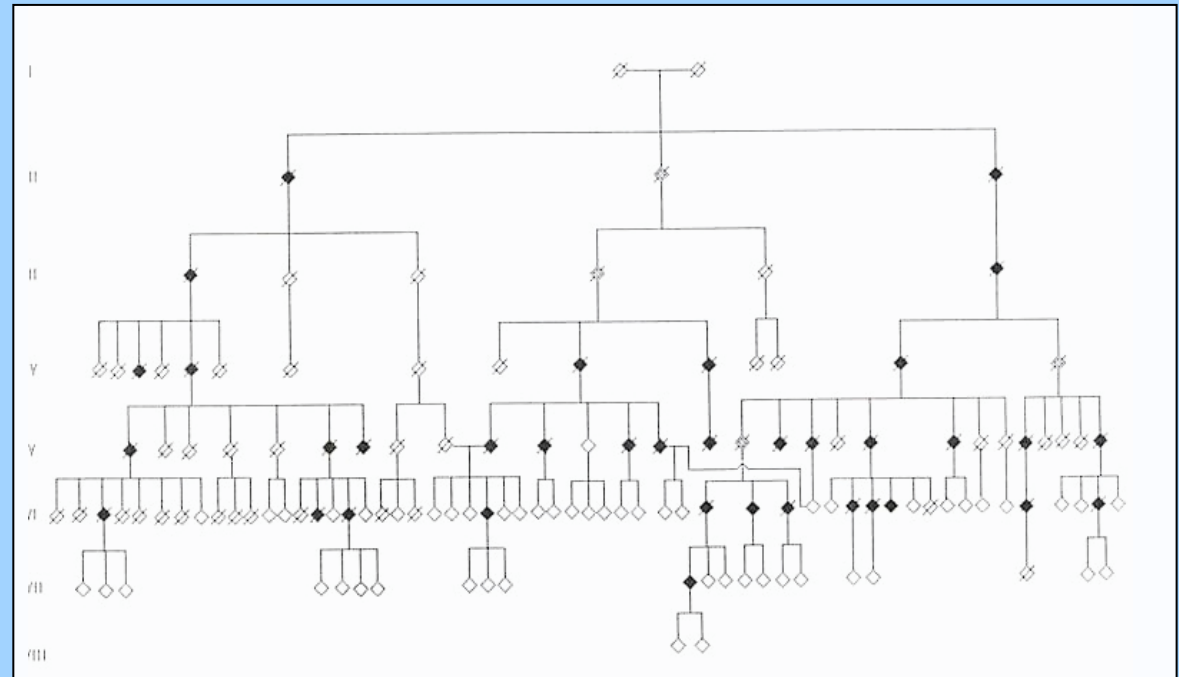
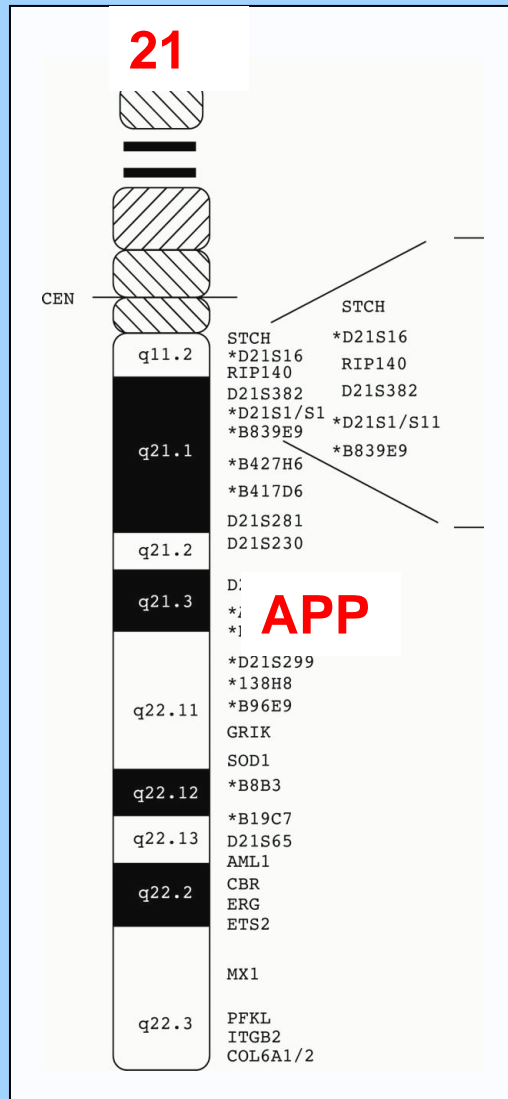


George Glenner and Caine Wong 1984

DAEFRHDSGYEVHHQKLVFFAEDVGSNKGAIIGLMVGGVVIA

**A $\beta$  Peptide**

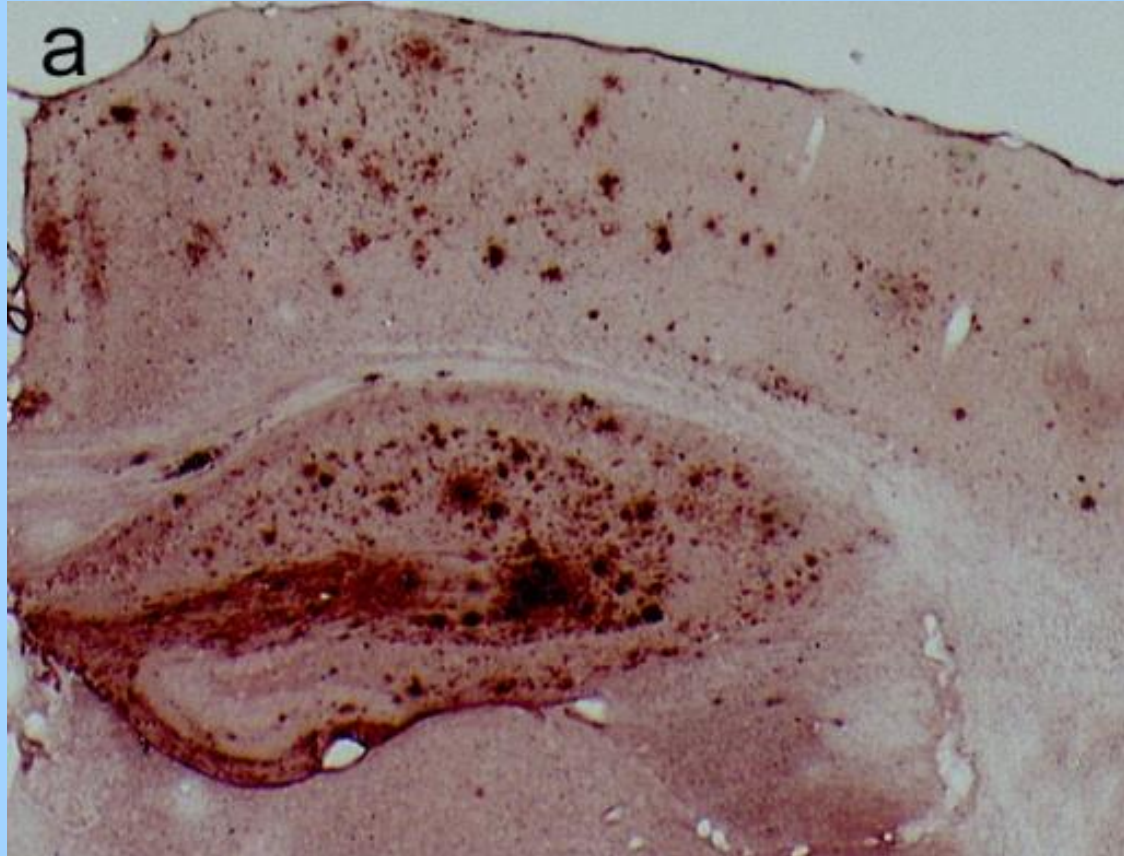
# The Amyloid Precursor Protein Gene Is Encoded on Chromosome 21



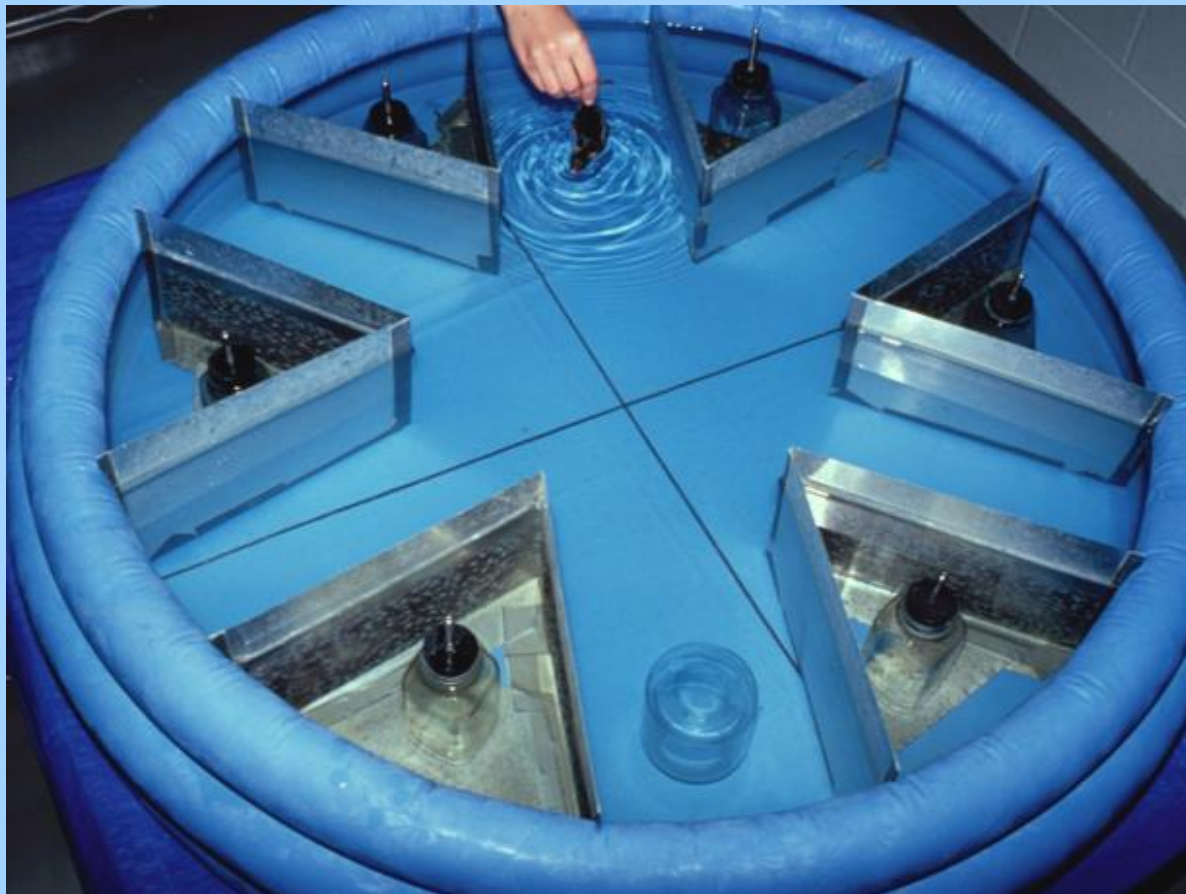
## The 'Swedish' Alzheimer's Disease Family Inherits a Mutant APP Gene



# Mice With Mutant APP Gene Accumulate Amyloid Deposits



# RADIAL ARM WATER MAZE START





# RADIAL ARM WATER MAZE FINISH LINE



# A RECIPROCAL AD—DS CONNECTION

*Am. J. Hum. Genet.* 48:1192–1200, 1991

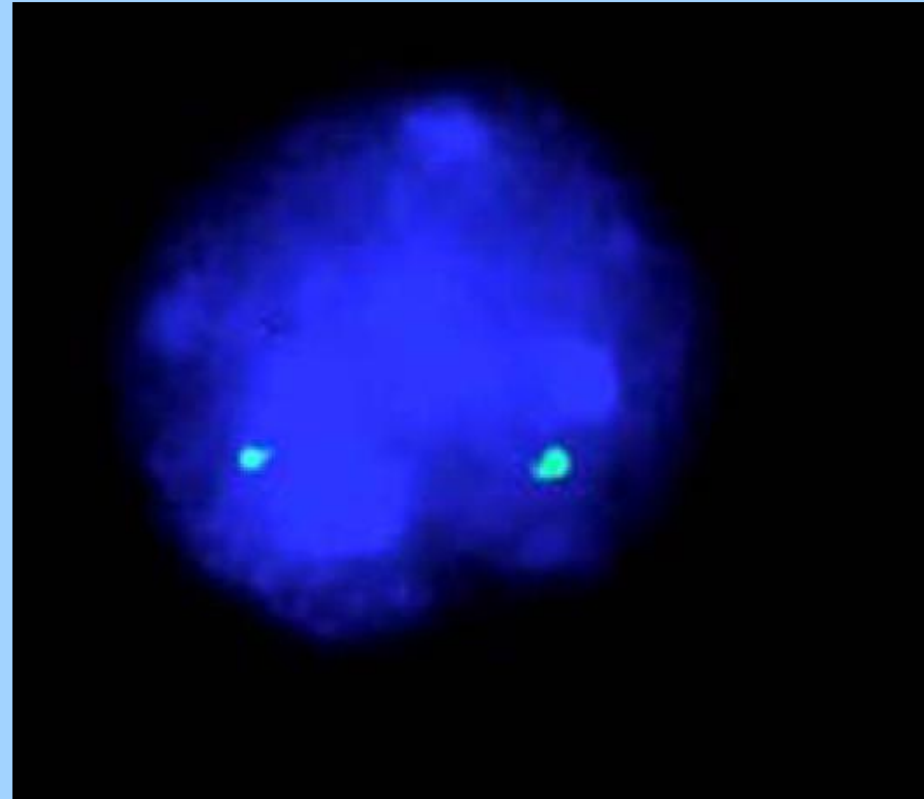
## **Review and Hypothesis: Alzheimer Disease and Down Syndrome—Chromosome 21 Nondisjunction May Underlie Both Disorders**

Huntington Potter

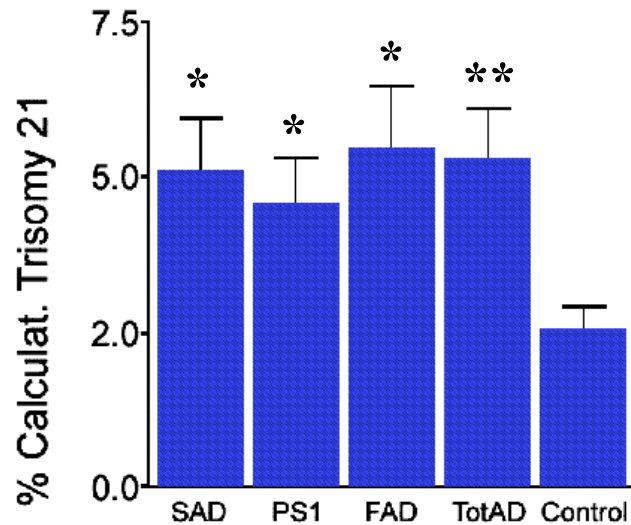
Department of Neurobiology, Harvard Medical School, Boston



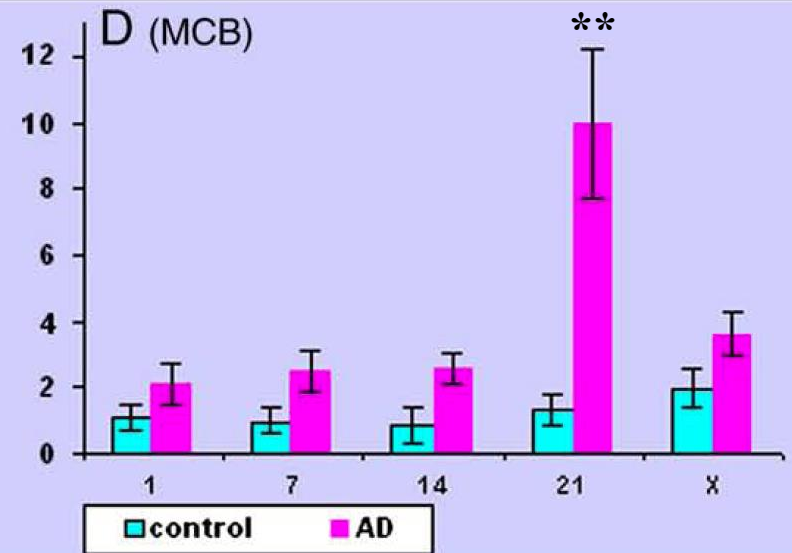
# COUNTING CHROMOSOMES



# Trisomy 21 In Alzheimer's Disease



Skin Cells



Nerve Cells

## **CONCLUSION**

**Alzheimer's Disease and  
Down Syndrome  
Are**

**TWO SIDES OF THE SAME COIN**

**And should be studied together**





# IS ENVIRONMENT IMPORTANT?



LINDA CRNIC  
INSTITUTE  
FOR DOWN SYNDROME™



GLOBAL  
DOWN SYNDROME  
FOUNDATION®

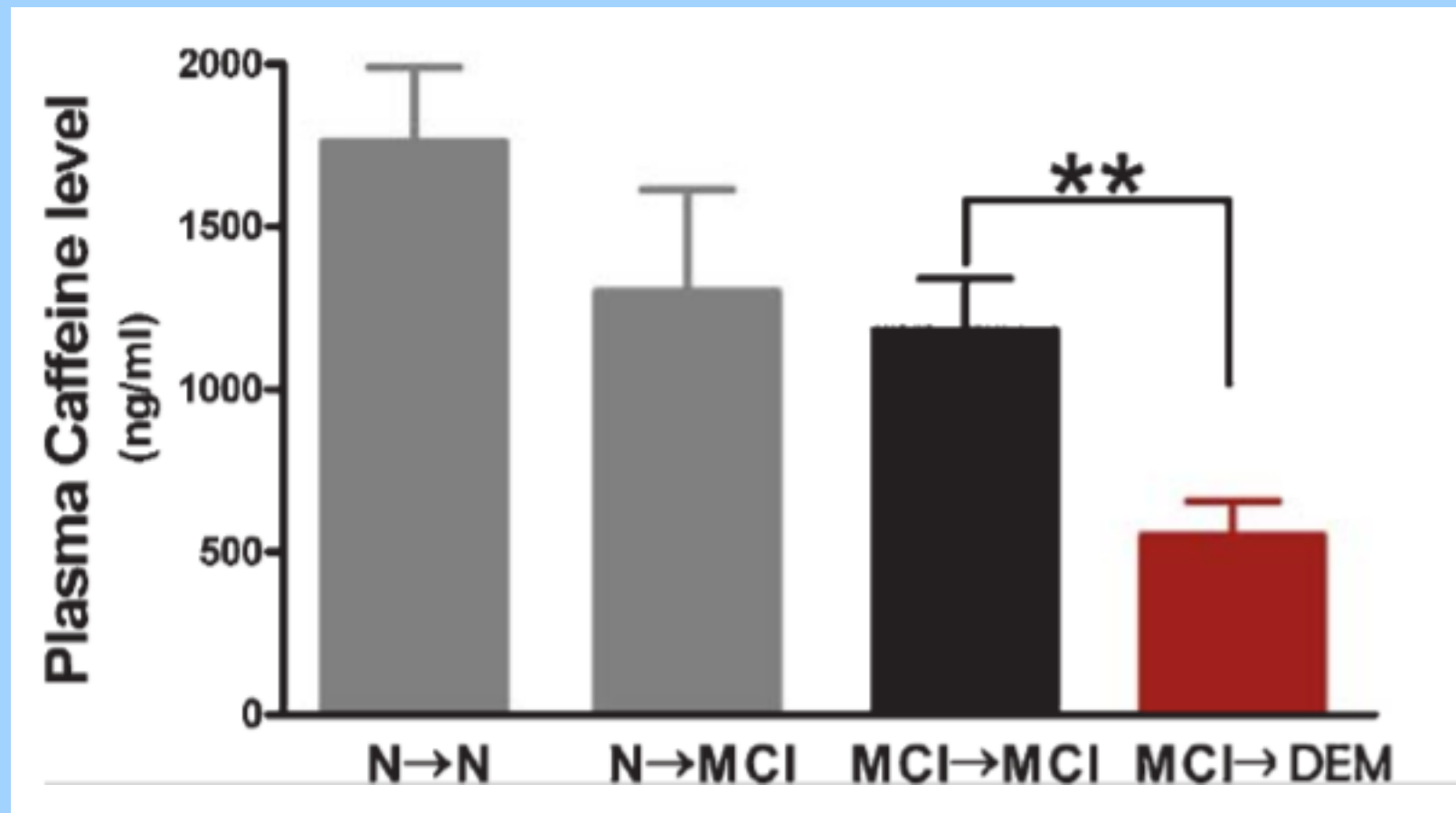


Rocky Mountain Alzheimer's Disease Center  
SCHOOL OF MEDICINE | UNIVERSITY OF COLORADO ANSCHUTZ MEDICAL CAMPUS

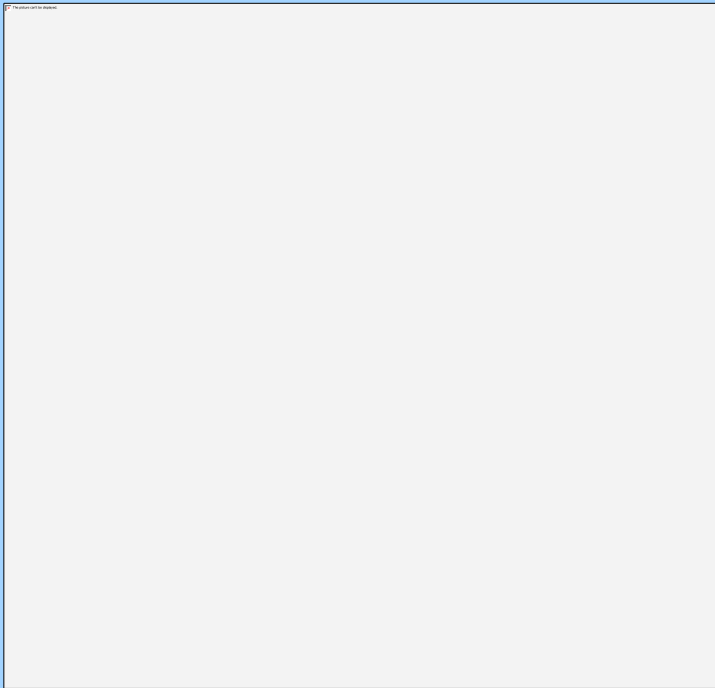
# Caffeine Consumption of AD Patients Is Half That of Normal Subjects



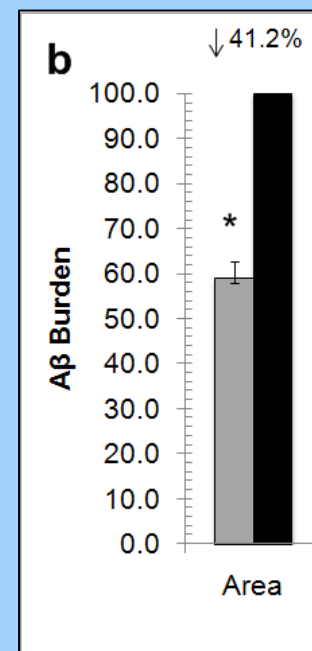
# High Blood Caffeine Levels are Associated With Memory Retention



# Why are people with Rheumatoid Arthritis protected against Alzheimer's disease?



# GM-CSF Reduces A $\beta$ Deposition In Vivo





# How Rheumatoid Arthritis/GM-CSF May Suppress Alzheimer's Disease

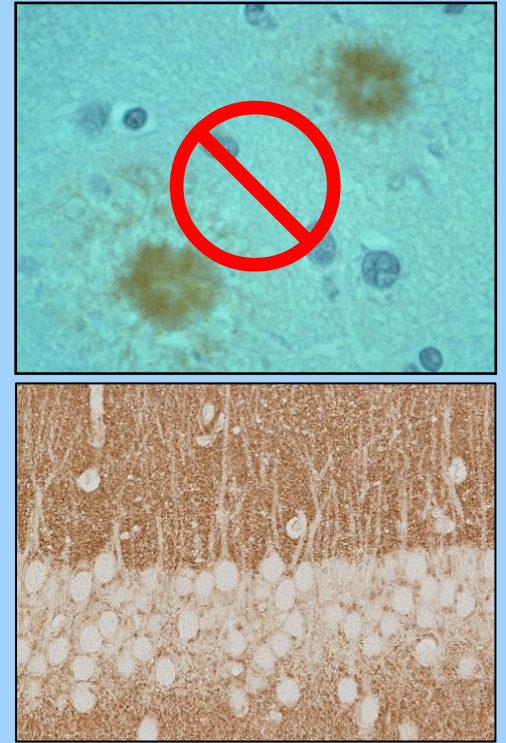
- Reduced Amyloid
- Increased Synapses
- Protected Neurons
- Improved Blood Flow



Macrophages  
Neutrophils  
Dendritic Cells  
GM-CSF

GM-CSF (Leukine®)

**NEXT STEP:  
TRANSLATION INTO HUMANS**



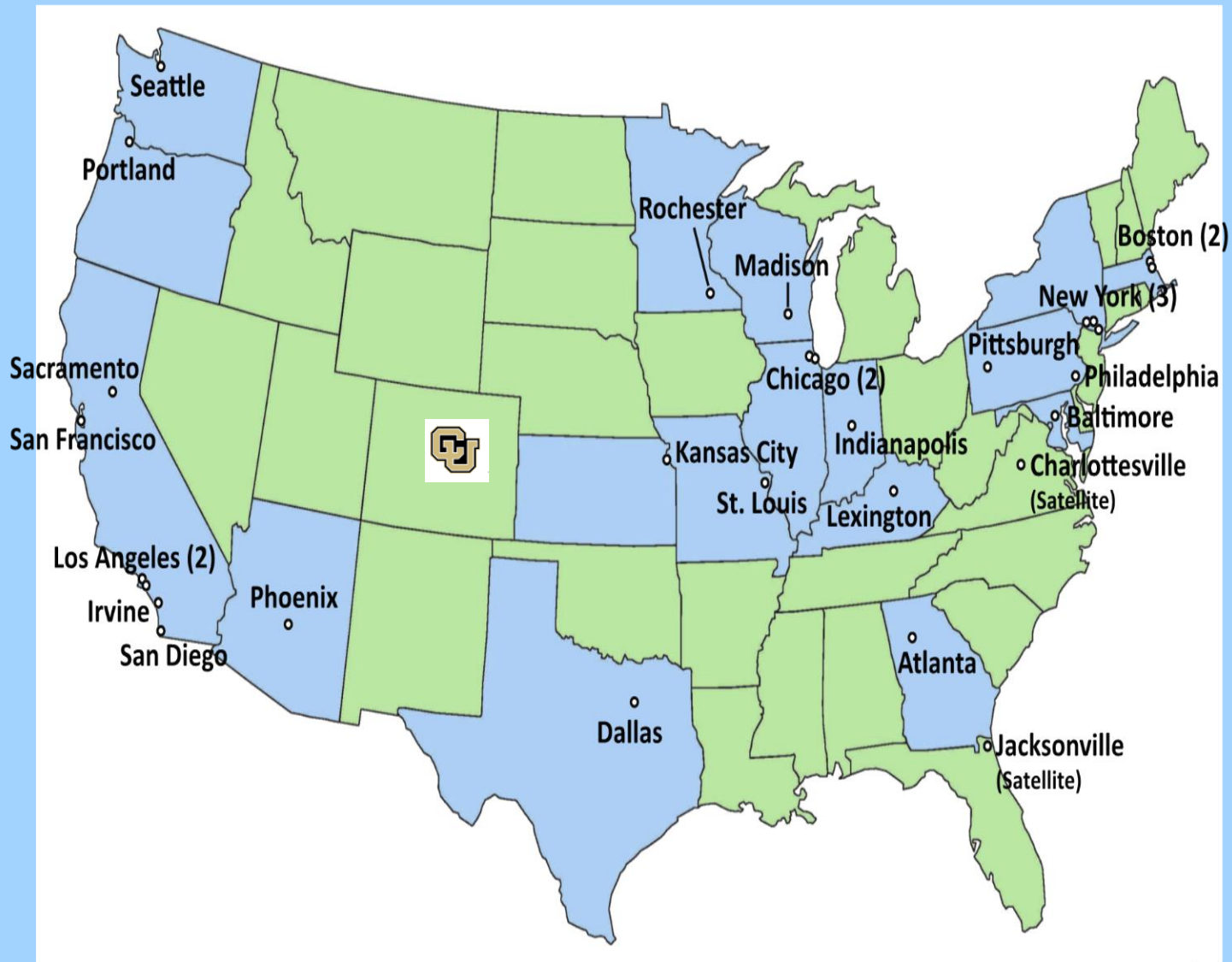
## First Steps:

1. Create an Academic Home for Down Syndrome Research



1. Create Rocky Mountain Alzheimer's Disease Center with a focus on Down Syndrome

# ROCKY MOUNTAIN ALZHEIMER'S DISEASE CENTER





UNIVERSITY OF COLORADO HOSPITAL  
Anschutz Medical Campus

## MEMORY AND DEMENTIA CLINIC

To make an appointment:

- Have your referring physician FAX your medical records, insurance information and demographic information to (720) 848-2106.
- Please allow 2 business days for processing of your paperwork. Then CALL (720) 848-2080 to schedule your appointment.
- Be sure to bring any MRI/CT scans, lab results, and pertinent medical records to your appointment.

We accept all PPO/HMO/POS plans. Please call your insurance carrier to verify benefits and coverage at University of Colorado Hospital. Medicaid and CACP are accepted in available resident's clinic only for a one-time consultation; wait list may apply.



UNIVERSITY OF COLORADO HOSPITAL  
Anschutz Outpatient Pavilion  
1635 Aurora Court | Aurora, CO 80045 | 720-848-2080



Jonathan H. Woodcock, MD  
Assistant Professor of Neurology  
Director, Memory and Dementia Clinic



Christopher M. Filley, MD  
Professor of Neurology



Huntington Potter, PhD  
Professor of Neurology  
Director, Alzheimer's Disease Programs

## Getting started:

### 1) Opened a Memory Disorders Clinic



**Getting started:**

## **2) Pilot Clinical Trial of Leukine (human GM-CSF) in Alzheimer's Disease**

# APPRECIATION

**Scientists:** Antoneta Granic, PhD  
Tim Boyd, PhD  
Julbert Caneus  
Michelle Norden  
Jaya Padmanabhan, PhD  
Jiashin Wu, PhD  
Sergiy Borysov, PhD  
Csilla Ari, PhD

**Funding:** Linda Crnic Institute for Down Syndrome  
Global Down Syndrome Foundation  
Sie Center for Down Syndrome @ Children's Hospital Colorado  
UC Denver COM; Dept. Neurology  
National Institute on Aging  
National Institute on Neurological Diseases and Stroke  
Dana Foundation  
Colorado Translational Research Imaging Center  
Bruce and Marcy Benson