

Finding Solutions to the Alzheimer's Disease Epidemic in Indiana: Alzheimer's Research in Indiana

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Critical Role of Research in Fighting Alzheimer's Disease

◆ Introduction to Alzheimer's Disease (AD)

- ✓ What is AD?
- ✓ What are the Characteristics of AD?
- ✓ What Causes AD?
- ✓ What are the Treatments for AD?
- ✓ Difficulties in Studying AD

◆ Recent Significant Advances

- ✓ Brain Imaging
- ✓ Biomarkers/Diagnostics
- ✓ Genetics Has Revealed Novel Biological Pathways

◆ Alzheimer's Research in Indiana

- ✓ Eli Lilly and Company
- ✓ Indiana University/Stark Neurosciences Research Institute
- ✓ IUPUI/IUB/Purdue/Notre Dame

◆ Supporting Alzheimer's Initiatives in Indiana and Across the United States



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What is Alzheimer's Disease?

- ✓ Once considered a rare disorder, Alzheimer's disease is now seen as a major public health problem that is seriously affecting millions of older Americans and their families.



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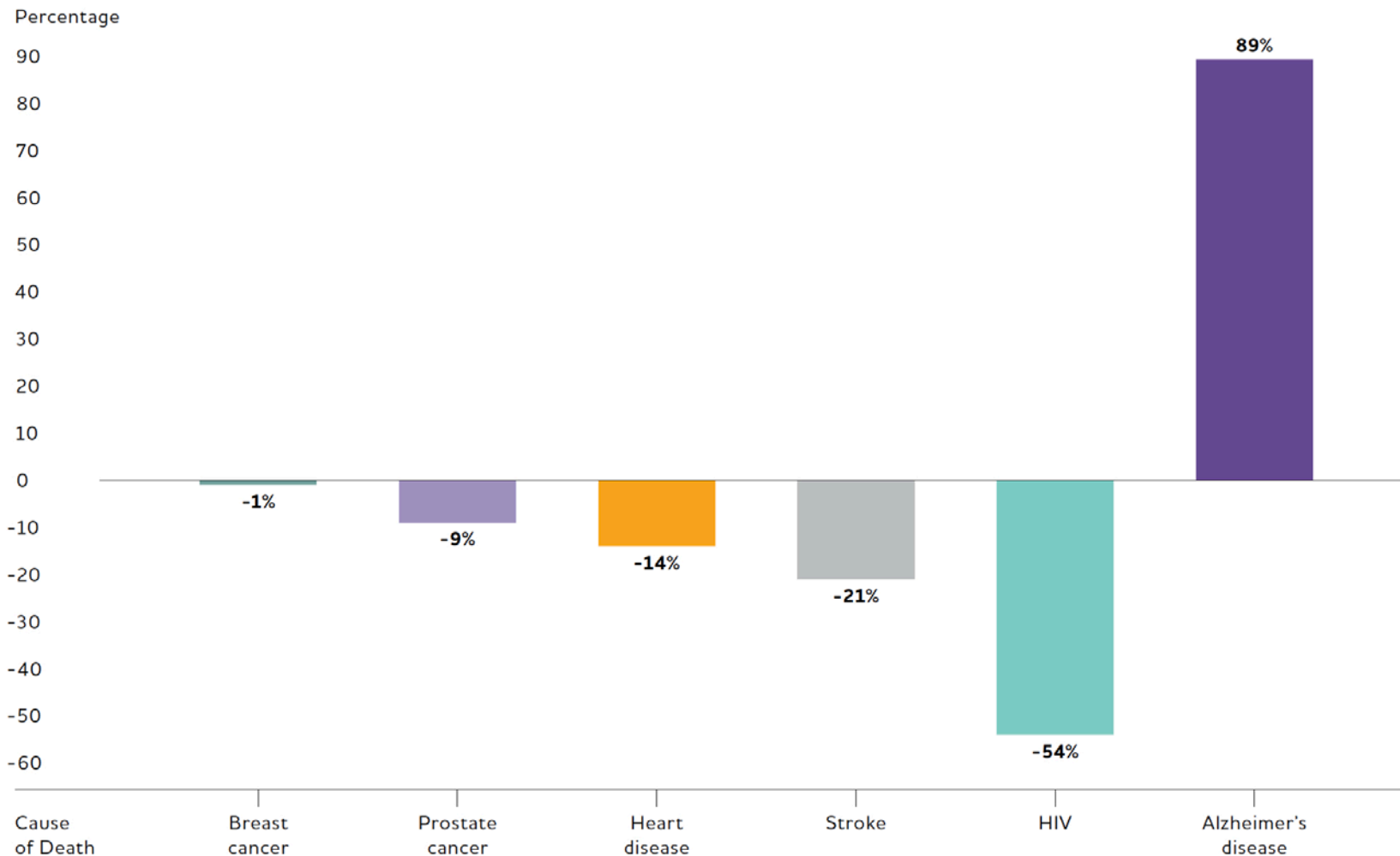
What is Alzheimer's Disease?

- ✓ Alzheimer's disease is an irreversible, progressive brain disease that slowly destroys memory and thinking skills.
- ✓ Although the risk of developing AD increases with age – in most people with AD, symptoms first appear after age 60 – AD is not a part of normal aging. It is caused by a fatal disease that affects the brain.



What is Alzheimer's Disease?

Percentage Changes in Selected Causes of Death (All Ages) Between 2000 and 2014



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Source: Alzheimer's Association

What is Alzheimer's Disease?

- ✓ AD is the most common cause of dementia among people age 65 and older.
- ✓ Scientists estimate that around 5.2 million people now have AD in America
- ✓ Every 70 seconds, someone in America develops AD
- ✓ For every 5-year age group beyond 65, the percentage of people with AD doubles.
- ✓ Estimated that 13.8 million Americans will have AD by 2050
- ✓ Estimated yearly cost for care of AD is \$236 billion!!



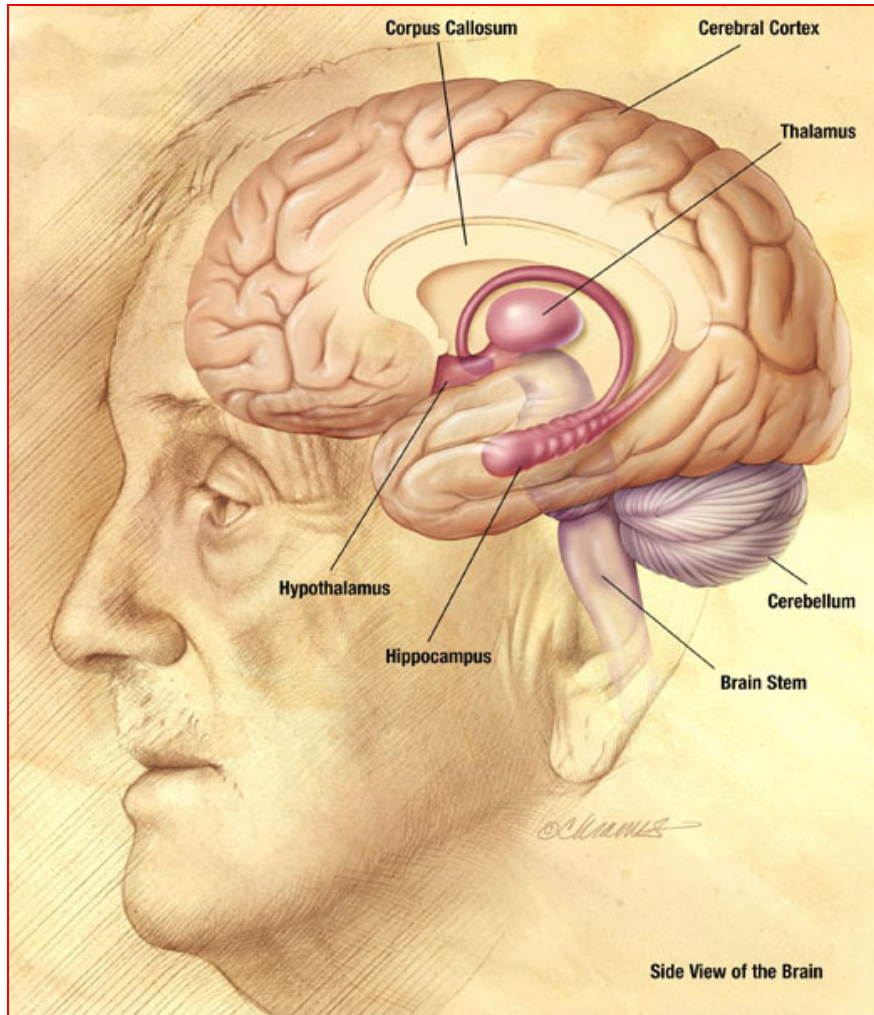
What is Alzheimer's Disease?

- ✓ In the state of Indiana, an estimated 110,000 people were diagnosed with AD in 2016 (14th highest)
- ✓ Estimates suggest that this will increase to 130,000 people by the year 2025 (18% increase)
- ✓ Total Medicaid costs in Indiana for AD in 2016 is an estimated \$935 million (14th highest)



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What is Alzheimer's Disease?



- ✓ To understand Alzheimer's disease, it's important to know a bit about the brain...

The Brain's Vital Statistics

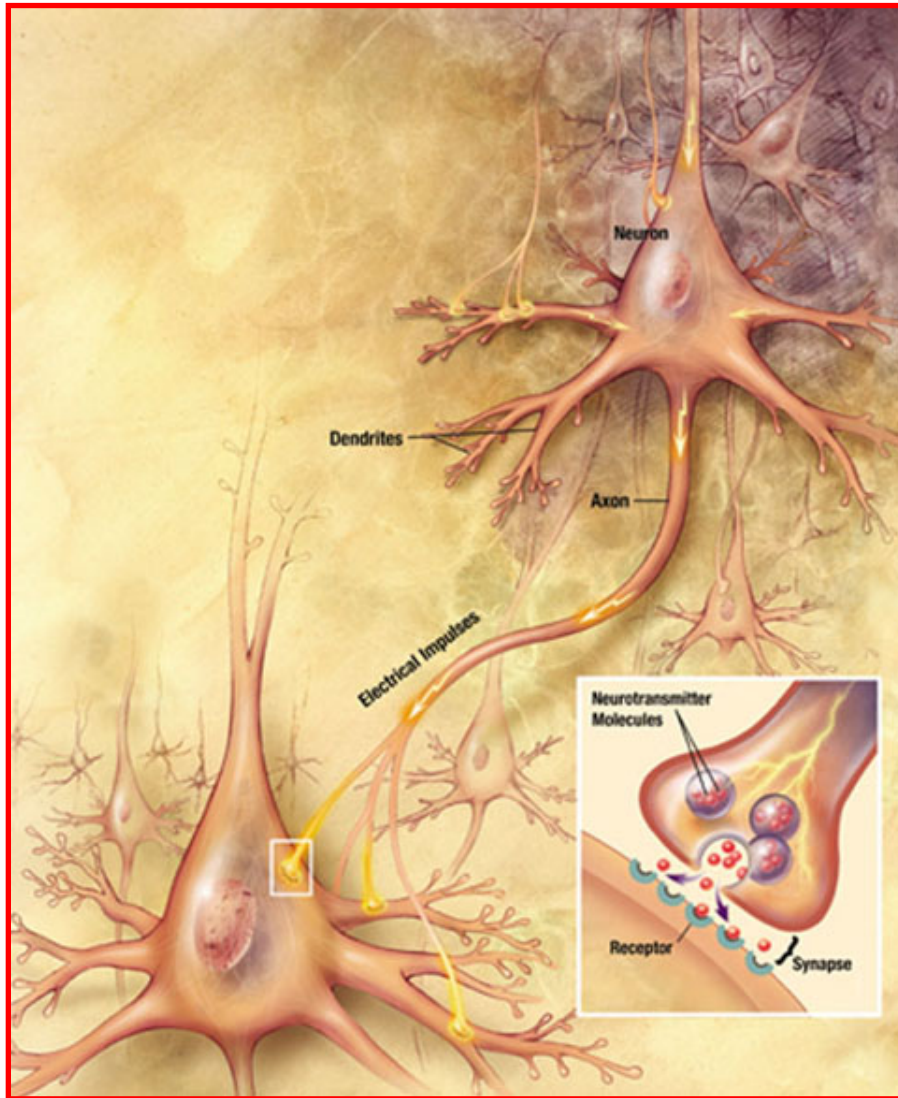
- ✓ Adult weight:
about 3 pounds
- ✓ Adult size:
a medium cauliflower
- ✓ Number of neurons:
100,000,000,000
(100 billion)
- ✓ Number of synapses
(the gap between
neurons):
100,000,000,000,000
(100 trillion)



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Source: National Institute of Aging

What is Alzheimer's Disease?



Neurons

- ✓ The brain has billions of neurons, each with an axon and many dendrites.
- ✓ To stay healthy, neurons must communicate with each other, carry out metabolism, and repair themselves.
- ✓ AD disrupts all three of these essential jobs.



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Source: National Institute of Aging

What Are The Characteristics of Alzheimer's Disease?



Maurer, *Lancet*, **349**:1546-1549, 1997

November 3, 1906 in Tübingen



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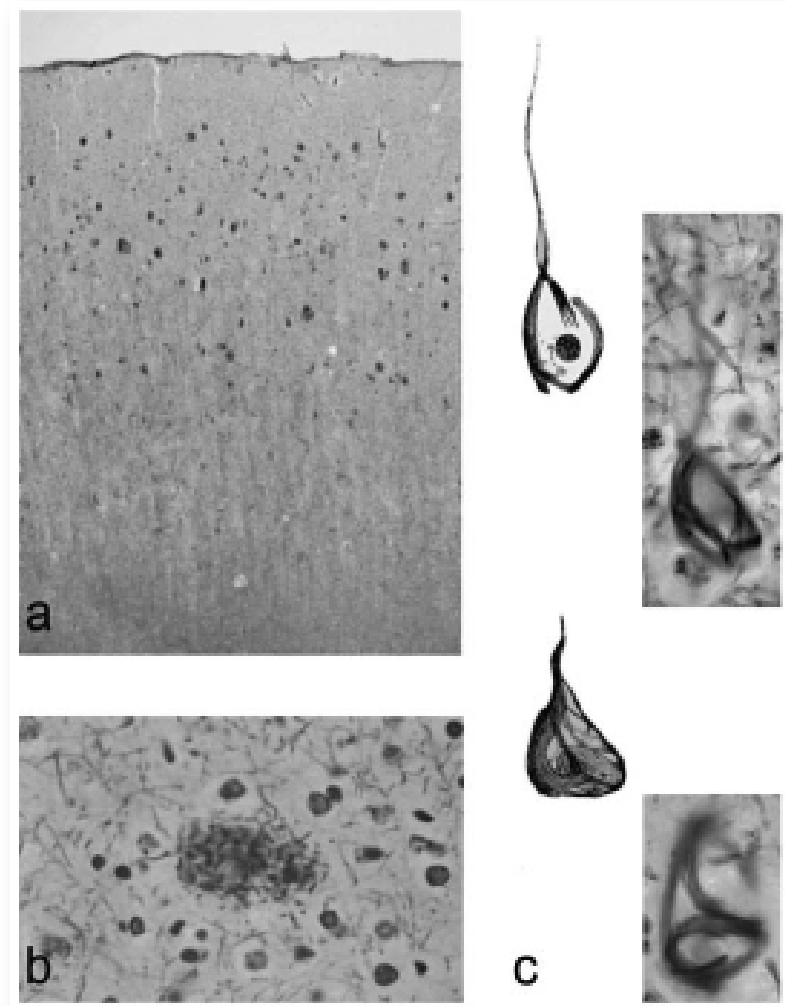
What Are The Characteristics of Alzheimer's Disease?

- ✓ “Throughout the whole cortex...one finds...deposition of a peculiar substance in the cortex”
(Beta-Amyloid Plaques)
- ✓ “there were very peculiar changes in the neurons...only a tangle of fibrils indicates where a neuron had been previously located”
(Tau Tangles)

Alzheimer, *Allg. Zeitschr. Psychiatr.* **64**:146-148, 1907.

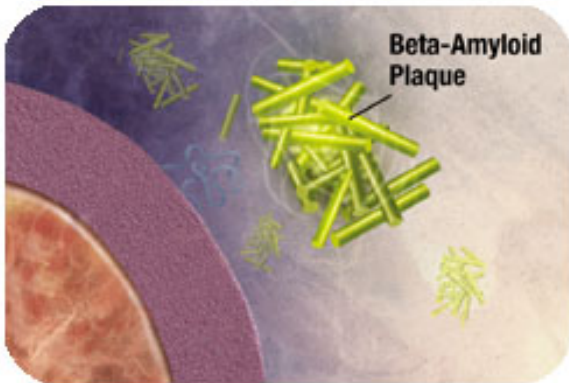
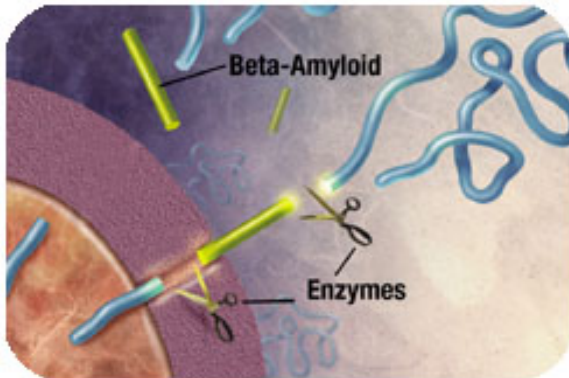
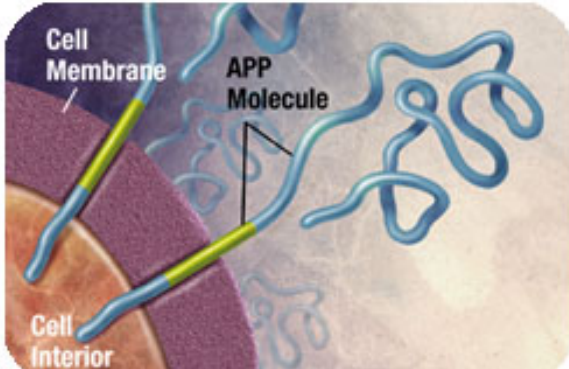


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Graeber and Mehraein, *Eur. Arch. Psychiatry Clin. Neurosci.* **249** (10):S10-S13, 1999.

What Are The Characteristics of Alzheimer's Disease?



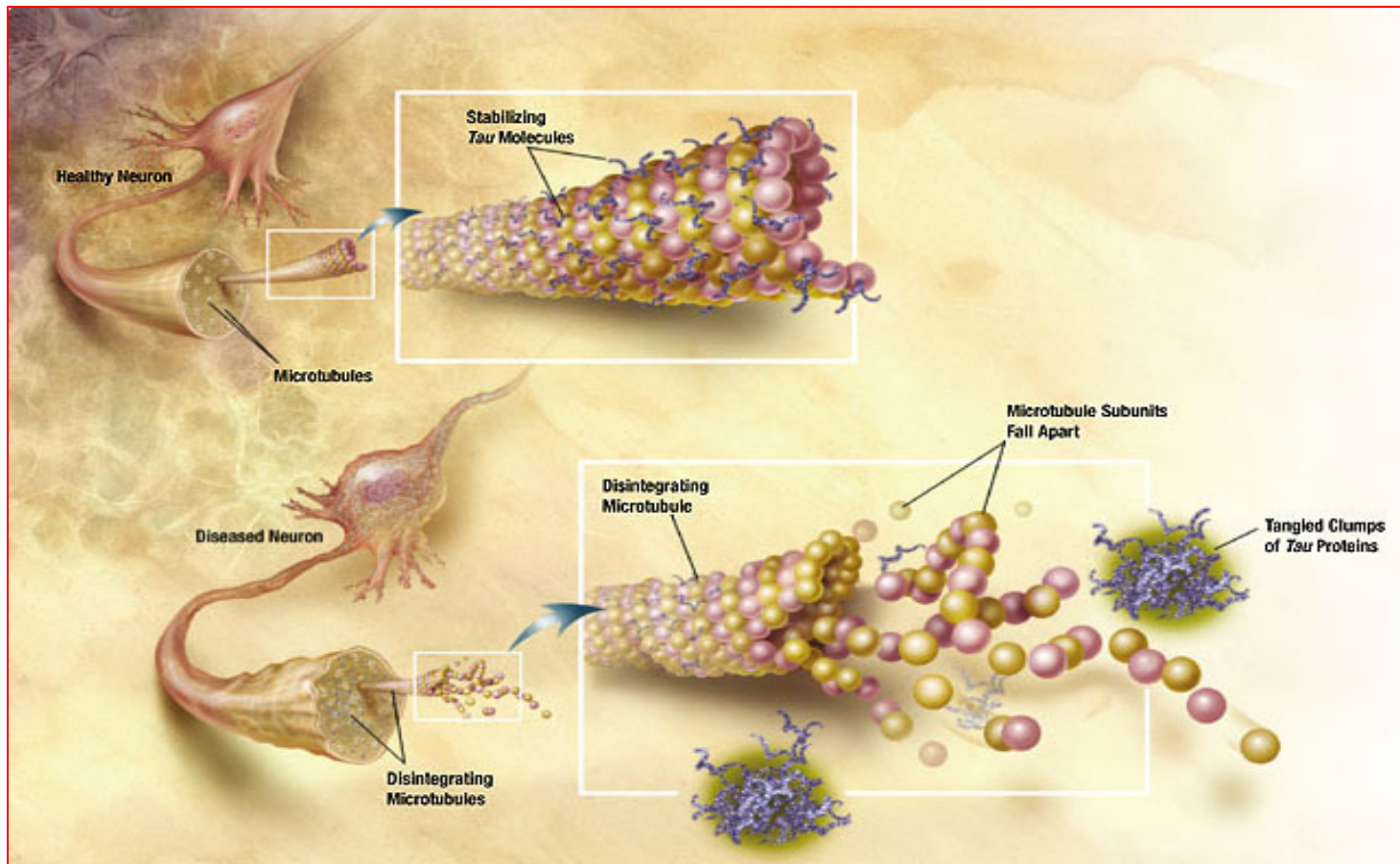
- ✓ APP sticks through the neuron membrane.
- ✓ Enzymes cut the APP into fragments of protein, including beta-amyloid.
- ✓ Beta-amyloid fragments come together in clumps to form plaques.



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Source: National Institute of Aging

What Are The Characteristics of Alzheimer's Disease?



- ✓ Neurons have an internal support structure partly made up of microtubules. A protein called *tau* helps stabilize microtubules. In AD, *tau* changes, causing microtubules to collapse, and *tau* proteins clump together to form tangles.



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Source: National Institute of Aging

What Causes Alzheimer's Disease?

- ✓ AD develops when multiple genetic, lifestyle, and environmental factors work together to cause the disease process to start.
- ✓ From studies of twins, it is estimated that upwards of 80% of AD may be caused by genetic factors. In recent years, scientists have discovered genetic links to AD.
- ✓ Major risk factors include age, family history, head trauma, etc.



Treatments for Alzheimer's Disease?

- ✓ Donepezil (Aricept, Approved 1996)
 - ✓ Rivastigmine (Exelon, Approved 2000)
 - ✓ Galantamine (Reminyl, Approved 2001)
 - ✓ Memantine (Namenda, Approved 2003)
 - ✓ Donepezil and Memantine (Approved 2014)
-
- ✓ These medications help slow the progression of AD (by slowing damage to neurons), but do not halt or reverse the disease. More recent studies examining “disease-modifying” therapies are currently being tested in clinical trials.



Treatments for Alzheimer's Disease?

- **Anti-Amyloid Therapies**
 - ✓ Antibodies
 - ✓ Secretase Inhibitors
 - ✓ Aggregation Inhibitors
- **Anti-Tau Therapies**
 - ✓ Antibodies
 - ✓ Kinase Inhibitors
 - ✓ Aggregation Inhibitors
- **Thus Far, These Therapies Have Failed in Human AD Clinical Trials**
- **Failure Rate of 99.6% (Cummings et al., 2014)**



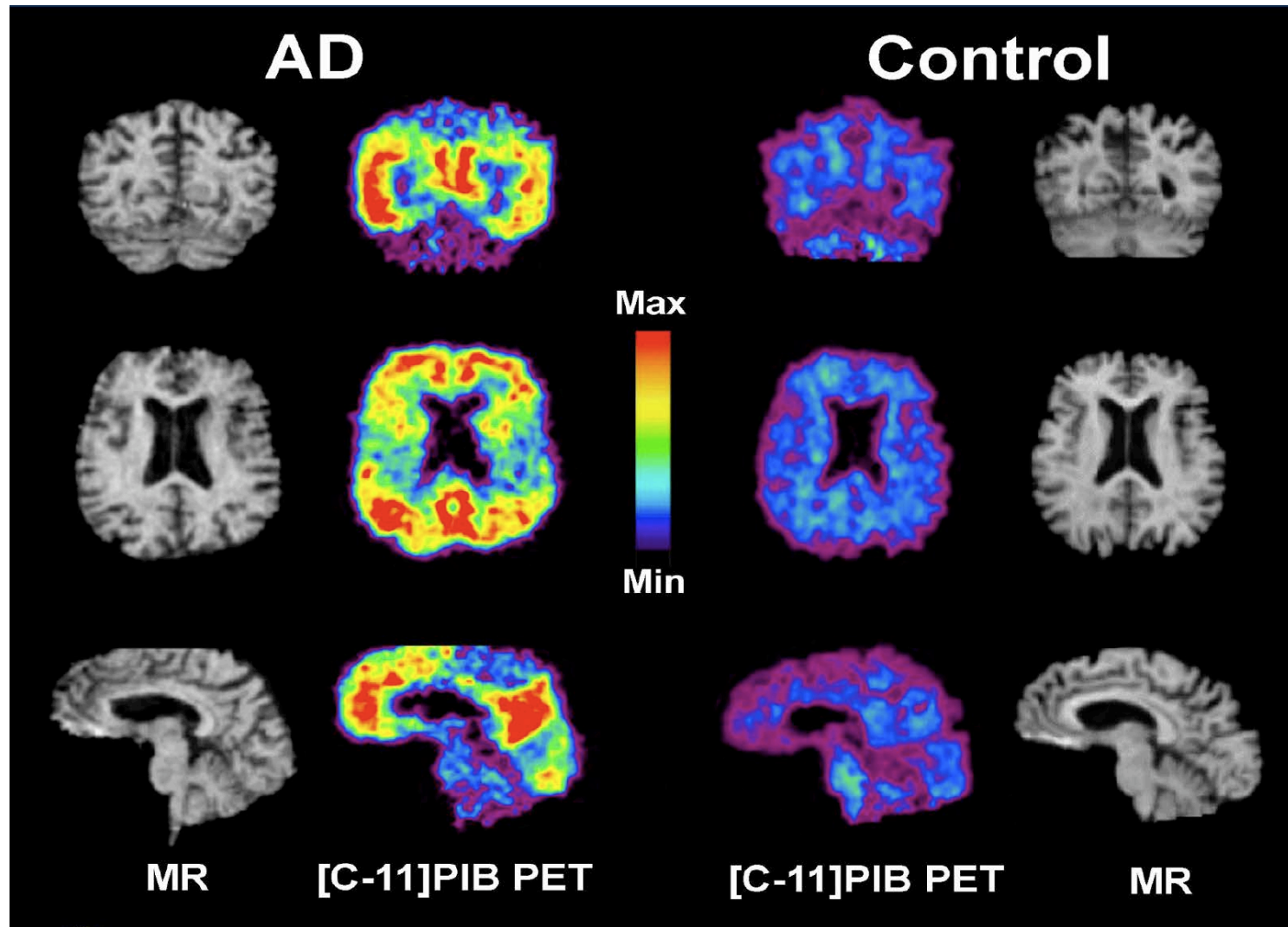
Difficulties in Studying Alzheimer's Disease

- ✓ Age-Related Disease
- ✓ Co-Morbidities
- ✓ No Accurate Diagnostic Markers
- ✓ Disease of the Brain Defined by Beta-Amyloid Plaques and Tangles
- ✓ Large Variation in Onset, Progression and Pathology
- ✓ Brain Changes Occur 20 Years Prior to Symptoms
- ✓ Lack of Accurate Animal Models



Recent Advances in Studying Alzheimer's Disease

- ✓ Brain Imaging (Amyloid and Tau)

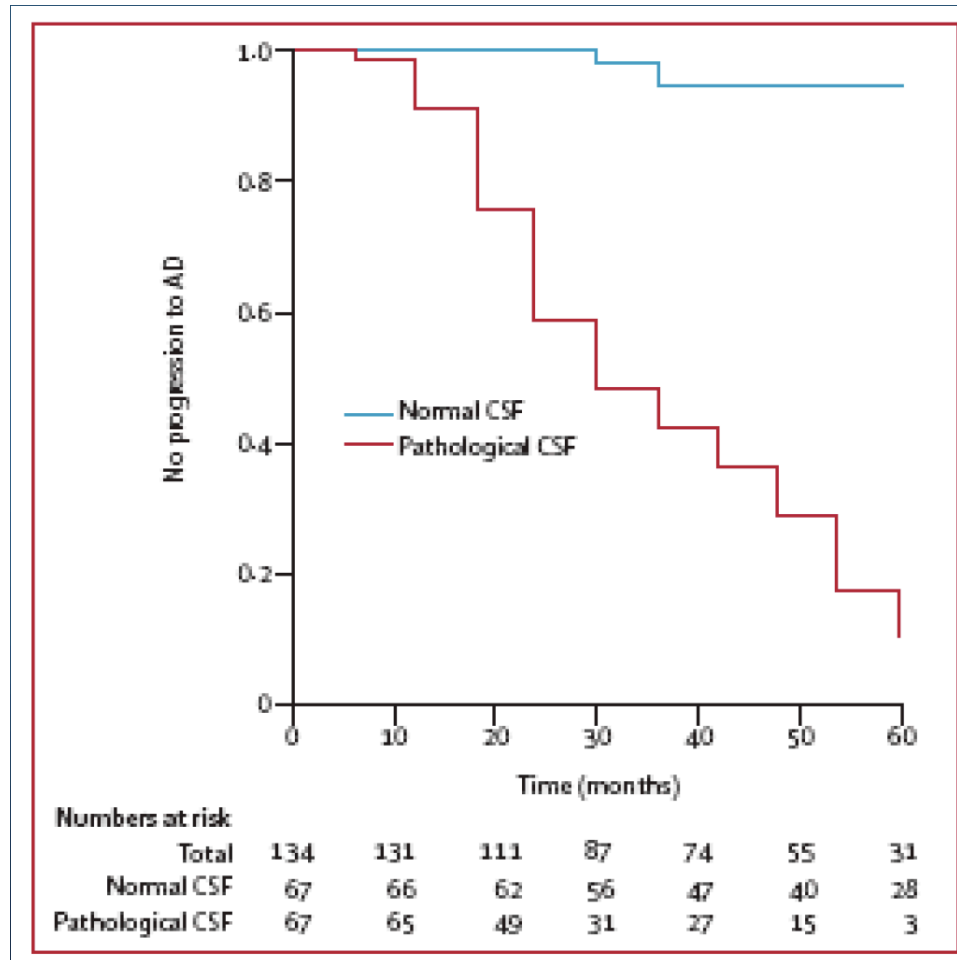


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DeKosky and Colleagues

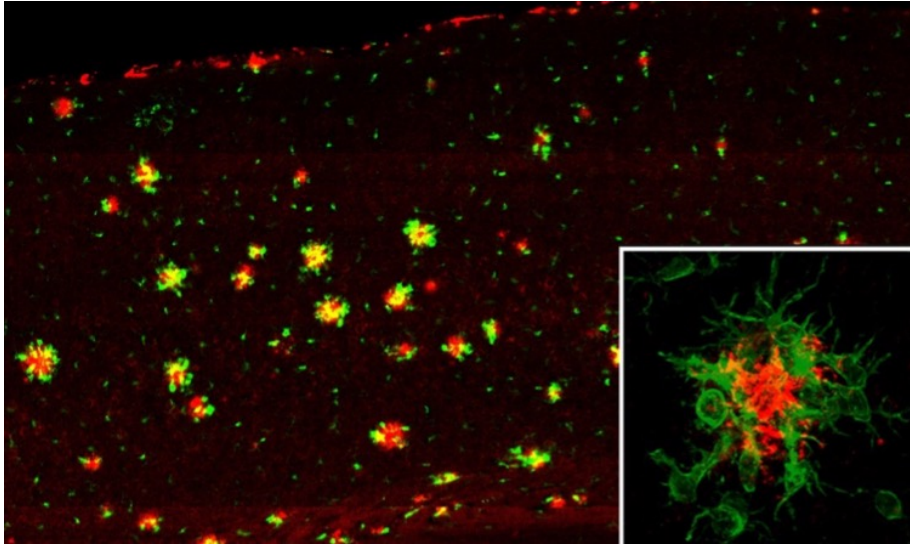
Recent Advances in Studying Alzheimer's Disease

- ✓ Combination of Biomarkers (Beta-Amyloid and Tau Levels in Cerebral Spinal Fluid)

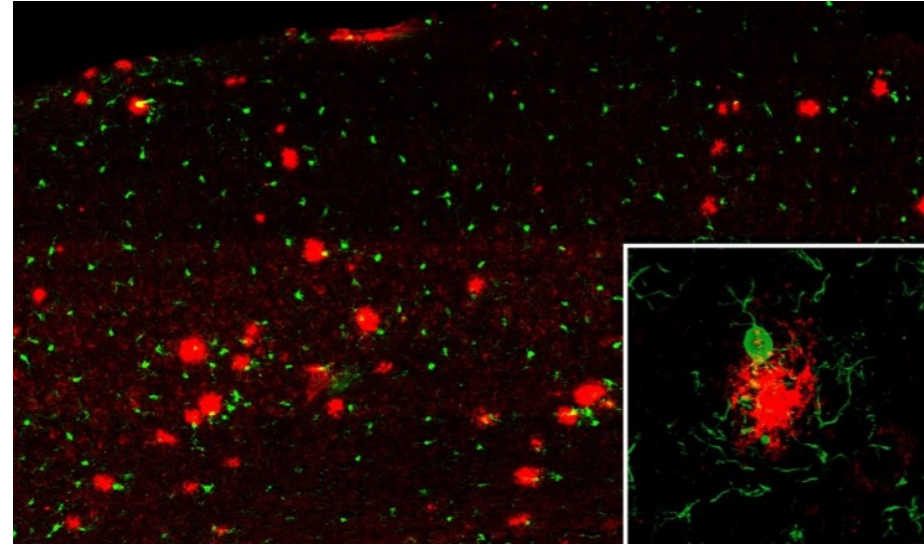


Recent Advances in Studying Alzheimer's Disease

✓ Immune Pathways in Alzheimer's Disease



Mouse Model of AD



Mouse Model of AD Lacking
Immune Receptor

Amyloid (Red)/Immune Cells (Green)



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Lamb and Colleagues

Alzheimer's Research in Indiana

◆ Eli Lilly and Company

- ✓ Major Research Programs in Alzheimer's Disease
- ✓ Multiple Different Therapeutic Targets Being Considered
- ✓ Pioneer in Brain Imaging (Amyloid and Tau Imaging)
- ✓ Multiple Drugs in Human AD Clinical Trials

◆ Indiana University/Stark Neurosciences Research Institute(SNRI)

- ✓ Indiana Alzheimer's Disease Center (Established by Dr. Dino Ghatti in 1991, Current Director, Dr. Andy Saykin)
- ✓ SNRI Established in 2000
- ✓ Paul and Carole Stark Endowment
- ✓ Neuroscience Institute for Interdisciplinary and Collaborative Translational Studies
- ✓ MODEL-AD Center Established in 2017
- ✓ LEAD Study Established in 2017

◆ IUPUI/IUB/Purdue/Notre Dame



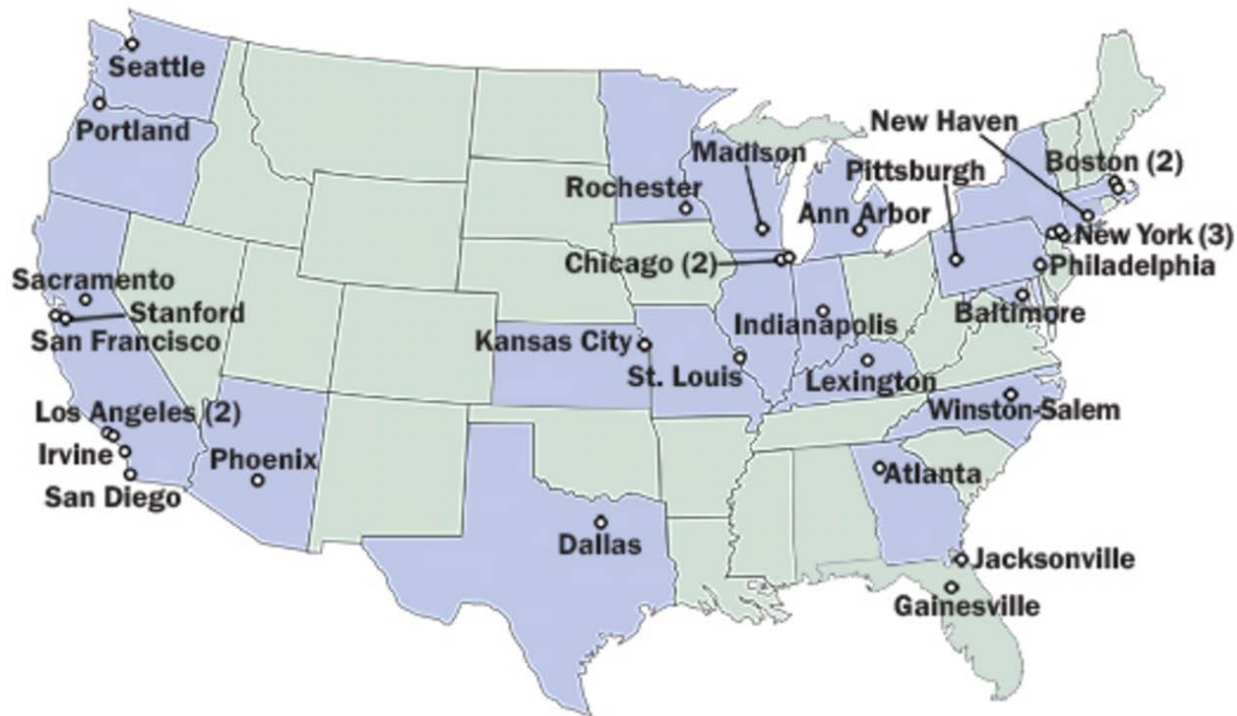
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INDIANA UNIVERSITY

INDIANA ALZHEIMER DISEASE CENTER

School of Medicine



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<https://www.nia.nih.gov/alzheimers/alzheimers-disease-research-centers>



INDIANA UNIVERSITY

INDIANA ALZHEIMER DISEASE CENTER

School of Medicine

- Aim 1: Support, enhance, and expand innovative research on Alzheimer's disease and related dementias targeting causes, diagnosis, treatment, and prevention.
- Aim 2: Provide critical research resources and infrastructure to support existing studies and enable new innovative research, including a well-characterized longitudinally followed cohort of research participants.
- Aim 3: Strongly support local, regional, and national/international dementia research collaborations to further the goals of the National Plan for Alzheimer's disease, as well as the National Institute of Health Neuroscience Blueprint and related federal priorities.
- Aim 4: Provide educational and training opportunities related to Alzheimer's disease and other dementias for learners of all levels and needs including academic programs for professionals and programs for patients, caregivers and family members, and the community at large.



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INDIANA UNIVERSITY

INDIANA ALZHEIMER DISEASE CENTER

School of Medicine

Notable Projects/Centers

- Site and genetics core (PI, Saykin) for the international Alzheimer's Disease Neuroimaging Initiative (ADNI)
- Location of the National Cell Repository for Alzheimer's Disease (NCRAD; PI, Foroud)
- Multiple, funded National Institutes of Health projects
- Over 30 ongoing Alzheimer's Clinical Trials (PIs, Farlow and Brosch)

New Projects/Centers

- Primary Site for the new Model Organism and Development and Evaluation for Late-onset Alzheimer's Disease (MODEL-AD; PI, Lamb) Consortium
- Primary Site for the Longitudinal Early-Onset Alzheimer's Disease Study (LEADS; PI, Apostolova)



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New Ventures: The Model Organism Development and Evaluation for Late-Onset Alzheimer's Disease (MODEL-AD) Consortium

- ✓ 5 Year, \$25 Million Project
- ✓ Consortium Between Indiana University, The Jackson Laboratory, University of California, Irvine, and Sage Bionetworks (PI, Lamb)
- ✓ Generate Novel Late-Onset Alzheimer's Disease Models Using State-of-the-Art Genome Editing Technologies
- ✓ Deep Phenotype (Pathology, Gene Expression, Imaging, etc.)
- ✓ Develop a Drug Testing Pipeline and Test Therapies in Models Generated
- ✓ Make all Data and Animals Publically Available
- ✓ Help Speed Development of Alzheimer's Therapies



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Contact: modelad.iupui.edu

New Ventures: The Longitudinal Early-Onset Alzheimer's Disease Study (LEADS)

- ✓ 5 Year, ~\$45 Million Project
- ✓ Consortium Between 13 US Academic Institutions (PI, Apostolova)
- ✓ Identify Novel Genetic Factors Responsible for Early-Onset Alzheimer's Disease
- ✓ Recruitment Goals: 400 AD Subjects and 100 Controls (Ages 40-65)
- ✓ Study Clinical and Cognitive Outcomes, Imaging and Fluid Biomarker Changes in Relation to Genetic Factors
- ✓ Uncover Novel Genetic Risk Factors and Therapeutic Pathways
- ✓ Interactions Between LEADS and MODEL-AD



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Stark Neurosciences Research Institute

Mission Statement:

“The Purpose of the Stark Neurosciences Research Institute is to bring together School neurosciences faculty into a dynamic, organizational arrangement to advance knowledge of the nature of neurosciences diseases, and associated conditions, and to disseminate that knowledge to the prevention, treatment and cure of affected individuals.”

-Stark Gift Agreement



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Stark Neurosciences Research Institute

- ✓ Finished in 2014, 138,00 Square Feet
- ✓ Houses Basic Science, Translational and Clinical Researchers Across Departments Organized Thematically
- ✓ Interconnected with Clinical Neurosciences in Goodman Hall
- ✓ Vertical Vivarium with Procedure Rooms



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Stark Neurosciences Research Institute

Areas of Research Focus

◆ **Neurodegeneration**

- ✓ Alzheimer's Disease, Parkinson's Disease, Frontotemporal Dementia, Amyotrophic Lateral Sclerosis...
- ✓ Indiana Alzheimer's Disease Center (Dr. Andy Saykin)
- ✓ MODEL-AD Center (Dr. Bruce Lamb)
- ✓ LEAD Study (Dr. Liana Apostolova)
- ✓ Neurodegeneration Research Group (Dr. Ruben Vidal)

◆ **Traumatic Brain Injury/Spinal Cord Injury**

- ✓ Mechanisms of Degeneration/Regeneration
- ✓ Spinal Cord and Brain Injury Research Group (Dr. Xiao-Ming Xu)

◆ **Addiction/Alcohol**

- ✓ Animal Models, Imaging and Genetics
- ✓ Indiana Alcohol Research Center (Dr. David Kareken)

◆ **Pain**

- ✓ Chronic Pain
- ✓ Chemotherapy Induced Neuropathy



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Enhancing Neuroscience Research

Recruitments

- **Hongxia Ren (started 7/1/16)**
 - ✓ Links Between Diabetes and Alzheimer's Disease
- **Gary Landreth (started 1/1/17)**
 - ✓ Immunity and Alzheimer's Disease
- **Cristian Lasagna-Reeves (starts 3/15/17)**
 - ✓ Regulation of Tau Aggregation in Alzheimer's Disease
- **Patrick Sheets (started 1/2/17)**
 - ✓ Regulation of Chronic Pain



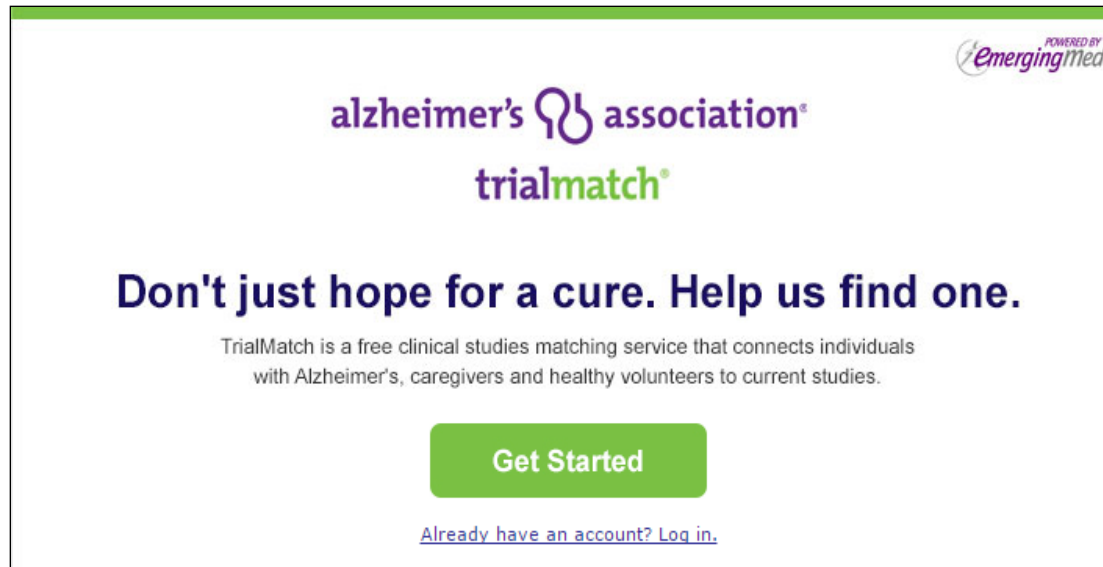
How to Support Alzheimer's Disease Initiatives in Indiana?

- ✓ Enhanced and Innovative Support for Caregivers
- ✓ Development of Dementia-Friendly Communities
- ✓ Reduce Disease Risk Through Public Health Initiatives
- ✓ Innovative Solutions to Anticipate and Alleviate Financial Burden
- ✓ Enhance and Promote Innovative Alzheimer's Research in Indiana
- ✓ Promote Collaborative Research Across State, University and Private Institutions
- ✓ Promote Enrollment/Participation in Research and Clinical Trials (trialmatch)
- ✓ Critical Role of the Alzheimer's Association



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What is TrialMatch?



TrialMatch is a **clinical studies matching service** designed to provide a **customized list** of potential study matches to each user.

What kinds of Studies are in TrialMatch?

Treatment Studies

Diagnostic Studies

Prevention Studies

Quality of Life Studies

Online Studies

250+ Clinical Studies

500+ Study Locations

To make research accessible and easy to understand, our science writers create lay-friendly summaries for each study listed in TrialMatch.

Who Can Sign Up with TrialMatch?

**TrialMatch
has
something
for nearly
everyone**

- People with Alzheimer's or another dementia.
- People with no current concerns about their memory (*referred to as Healthy Volunteers*).
- People who are caregivers for someone with Alzheimer's or another dementia.
- Anyone age 18 or older.

How to Support Alzheimer's Disease Initiatives in the United States?

On January 4, 2011, President Barack Obama signed into law the National Alzheimer's Project Act (NAPA) (Public Law 111-375), requiring the Secretary of the U.S. Department of Health and Human Services (HHS) to establish the National Alzheimer's Project to:

- ✓ Create and maintain an integrated national plan to overcome Alzheimer's disease.
- ✓ Coordinate Alzheimer's disease research and services across all federal agencies.
- ✓ Accelerate the development of treatments that would prevent, halt, or reverse the course of Alzheimer's disease.
- ✓ Improve early diagnosis and coordination of care and treatment of Alzheimer's disease.
- ✓ Decrease disparities in Alzheimer's for ethnic and racial minority populations that are at higher risk for Alzheimer's disease.
- ✓ Coordinate with international bodies to fight Alzheimer's globally.



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National Plan to Address Alzheimer's Disease

The National Plan (first released in 2012, updated annually) establishes five ambitious goals to both prevent future cases of Alzheimer's disease and to better meet the needs of the millions of American families currently facing this disease.

- ✓ Prevent and Effectively Treat Alzheimer's Disease by 2025.
- ✓ Optimize Care Quality and Efficiency.
- ✓ Expand Supports for People with Alzheimer's Disease and Their Families.
- ✓ Enhance Public Awareness and Engagement.
- ✓ Track Progress and Drive Improvement.



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Increased Funding for Alzheimer's Research

- ✓ Alzheimer's Accountability Act Passed by Congress in 2014, Which Directs NIH to Spell Out How Much Money is Required to Meet Goals Laid Out in NAPA
- ✓ Federal Funding of Alzheimer's Research Has Increased From ~\$448 Million in 2011 to ~\$1.4 Billion in 2017
- ✓ House Appropriations Committee Approved \$400 Million Additional in 2018
- ✓ Senate Appropriations Committee Approved \$414 Million Additional in 2018
- ✓ Urge Your Congressman/Senator to Bring Total Federal Alzheimer's Research Funding to \$1.8 Billion in 2018
- ✓ By Comparison: Total Spending for Cancer is \$6 Billion, HIV/AIDS is \$3 Billion



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Indiana Will Play A “Central” Role in Alzheimer’s Research, Treatment and Care!!!



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Thank You!
Contact: btlamb@iu.edu

