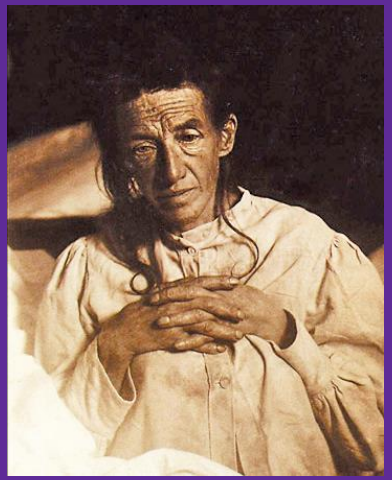
Alzheimer’s Disease

What do we know about risk, resilience, and treatments?



Alois Alzheimer's patient Auguste Deter

A bit about us

Mette Peters

- Bainbridge resident since 1998. Born in Norway, grad school in the USA. Started career with a focus on cancer genetics and have spent her professional life working in for- and non-profit companies. Mette is currently a Senior Advisor at the National Institute on Aging/NIH where she focuses on questions related to data science and data sharing as applied to aging and Alzheimer's and related dementias.

Adrian Hobden

- Bainbridge resident since 2011. Born and educated in England. He joined Glaxo in 1981 as a research scientist where he was asked to determine how the new techniques of gene cloning could be used in the search for novel drugs. In 1996 he relocated to Glaxo's facility in North Carolina to manage the Company's interactions with the biotech industry. He was recruited to Myriad Genetics to establish a pharmaceutical company. As head of that organization, Adrian oversaw two Phase 3 trials of an experimental medicine for Alzheimer's Disease.

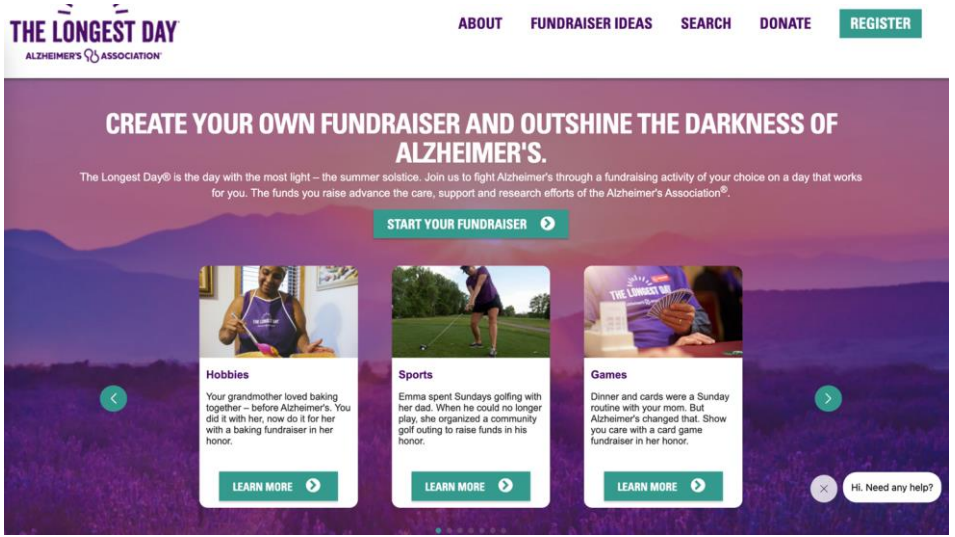
Disclaimers

- (mette) The opinions expressed here are the presenter's own and do not reflect the view of the National Institute on Aging, the National Institutes of Health, the Department of Health and Human Services, or the United States government.

- This presentation is not intended to provide medical advice.
- We will discuss genetic risk factors. Please confer with a genetic counselor before undergoing genetic testing.

Resources on Alzheimer’s and related dementias

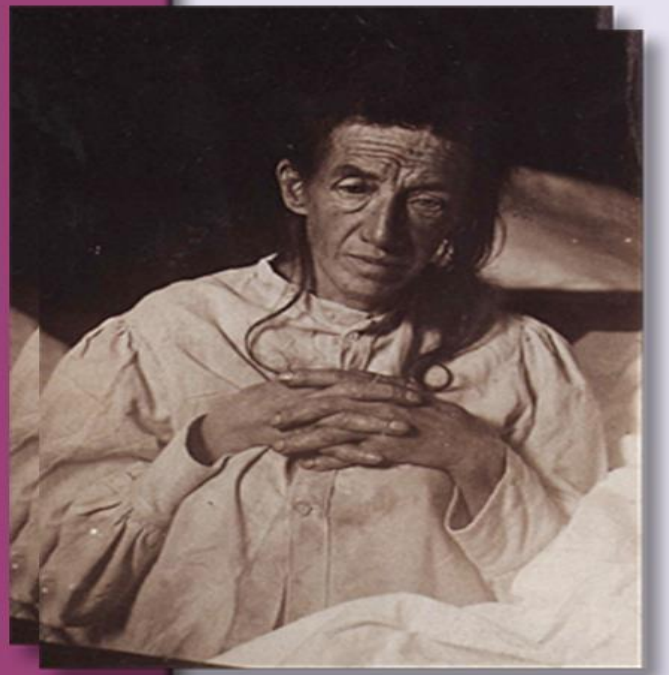
- The NIA Alzheimer’s and related Dementias Education and Referral Center
- Alzheimers.gov
- Alzheimer’s Association
  - Join the longest day



Who was Alois Alzheimer?

- German neuro- psychiatrist and neuropathologist
- Described several brain diseases causing dementia
- Importance of his discovery not appreciated in his lifetime

Alzheimer's Disease



- 1907 - Dr. Alzheimer described patient August Deter
- 51 years old at diagnosis in 1901
- Rapid cognitive decline
- Psychosis (false beliefs)
- Died within 5 years
- AD had a mutation in the PSEN1 gene
- Alters the function of gamma secretase, and is a known cause of young onset Alzheimer's disease.

Alzheimer's Statistics

- Alzheimer's disease is the sixth leading cause of death in the United States
- More than 5 million Americans are living with the disease.
- 1 in 3 seniors dies with Alzheimer's or another dementia.
- 75-80% of dementia is diagnosed as Alzheimer's
- In 2012, 15.4 million caregivers provided more than 17.5 billion hours of unpaid care valued at $216 billion.

What is Alzheimer's Disease?

- Pathological
  - Initially in hippocampus
  - Brain shrinkage due to loss of nerve cells
  - Neurofibrillary tangles inside nerve cells
  - Accumulation of plaques outside cells
- Clinical
  - Progressive loss of memory and cognition
  - Progressive loss of ability to perform daily functions
  - Progressive emergence of behavioral changes
- Biochemical and Genetic
  - Plaques of Amyloid Beta42
  - Tangles of phosphorylated tau protein
  - Early onset familial disease

Risk factors

- Age
- Sex
- Family history/Genetics
- Health, environmental and lifestyle factors
- Hearing loss

Protective factors

- Physical exercise
- Heart healthy diet
- Social connections
- Intellectual activity
- Sleep

Genetics

- Deterministic genes
  - These are genes with certain variants (or dose effect) that makes the likelihood of getting a disease very high
  - There are 3 established deterministic genes associated with Alzheimer's: *Amyloid Precursor Protein (APP)*, *Presenilin-1 (PSEN-1),* and *Presenilin-2* (*PSEN-2*)
    - And potentially - the *Triggering Receptor Expressed on Myeloid cells 2 (TREM2)* gene
- Risk genes
  - These are genes with certain variants that increase the risk for disease, but does not guarantee that you will get it
  - There is one established risk gene associated with Alzheimer's: *Apolipoprotein E* (*APOE*)
    - *APOE* has 3 variants: *APOE-e2*, *APOE-e3*, and *APOE-e4* where *e4* carries a risk and *e3* may be protective

Genetics - families with dominant inherited Alzheimer's

How one Colombian family could solve some of Alzheimer's mysteries

By Kenneth S. Kosik April 12, 2016 Reprints

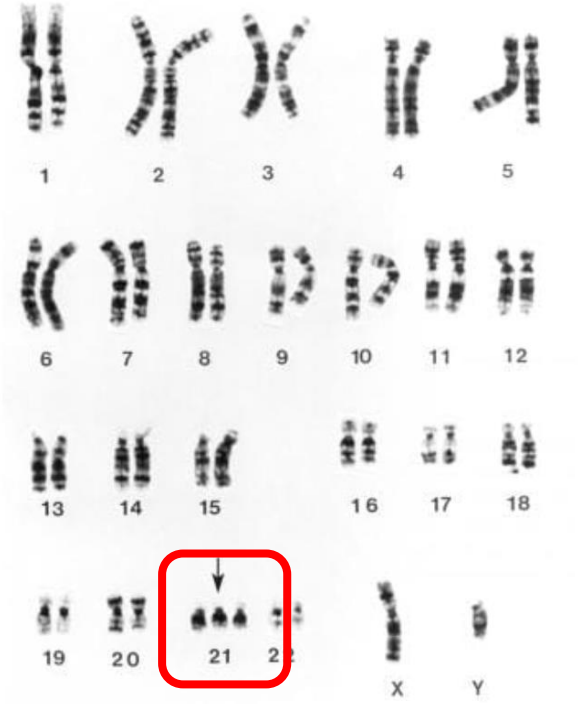
Francisco Lopera, Kenneth Kosik, and Lucia Madrigal on horseback outside Medellín, Colombia, a region where these neurologists have found the world's largest family with hereditary Alzheimer's disease.
TANGLED BANK STUDIOS, LLC

- 5000 member group of related families scattered across villages in the Andes mountains
- All are descendants of 1 basque couple from the 1700s
- Very high rate of early Alzheimer's due to a variant of *PSEN-1*

https://www.statnews.com/2016/04/12/alzheimers-disease-colombia/

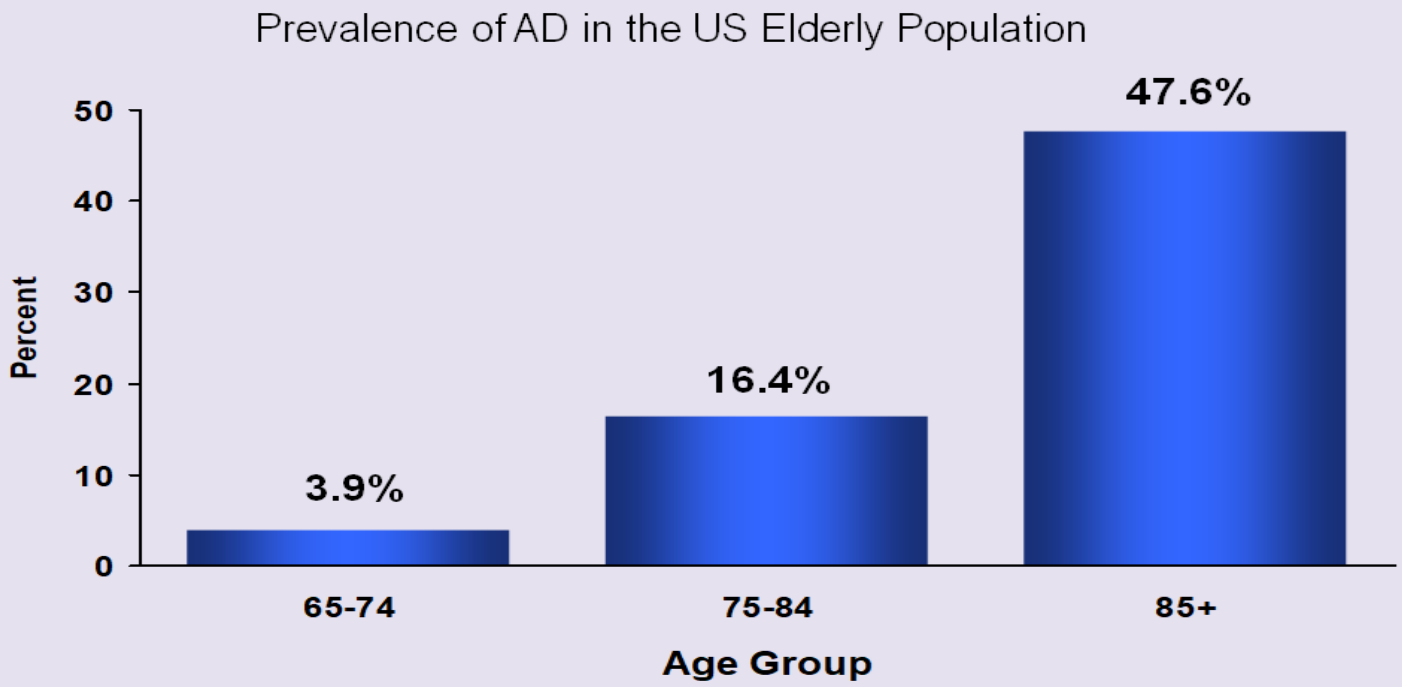
Genetics - Down syndrome and Alzheimer's

- Down syndrome is also called trisomy 21 because chromosome 21 has 3 instead of 2 copies
- As individuals with Down syndrome are able to live longer lives it has become clear that they are at high risk for Alzheimer's
  - ~30% of people with Down syndrome are diagnosed with Alzheimer's in their 50s
- The *Amyloid Precursor Protein* gene is located on chromosome 21
  - People with Down Syndrome make more of the APP



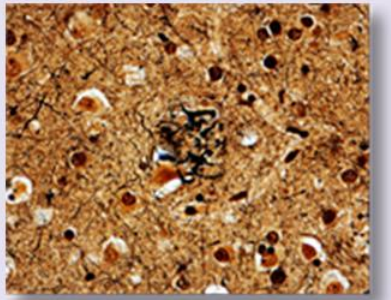
https://www.merckmanuals.com/professional/pediatrics/chromosome-and-gene-abnormalities/down-syndrome-trisomy-21

Will I Get Alzheimer's Disease?

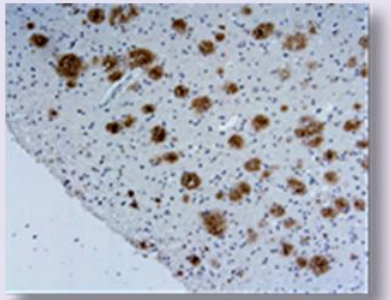


(Evans DA. *Milbank Q.* 1990;68:267-289)

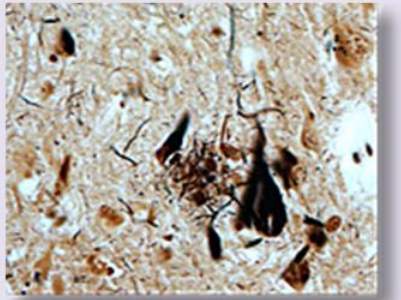
Pathology



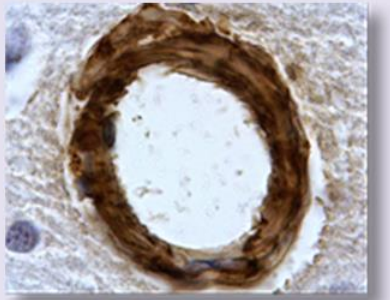
Neuritic plaque



Neuritic plaques in the cortex



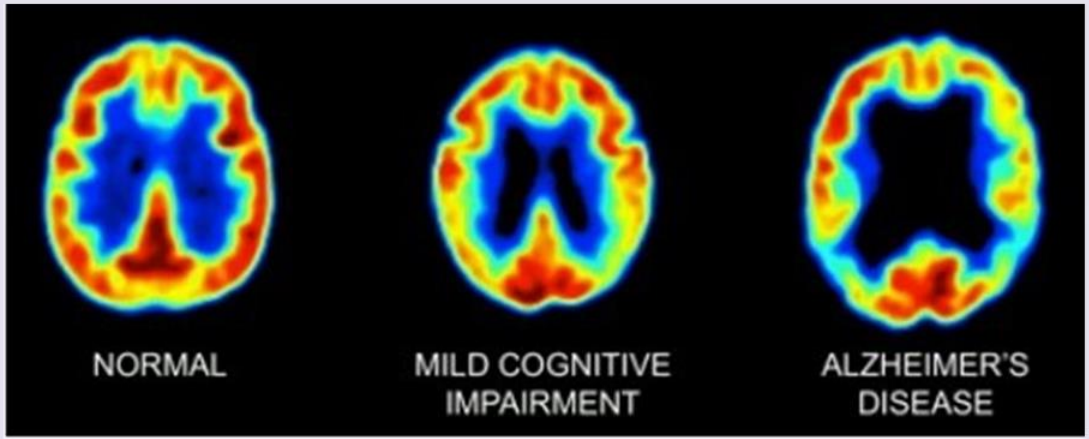
Neurofibrilllary tangles



Amyloid in the blood vessel wall

Brain Scans in AD

Decrease in brain mass and increase in vesicles



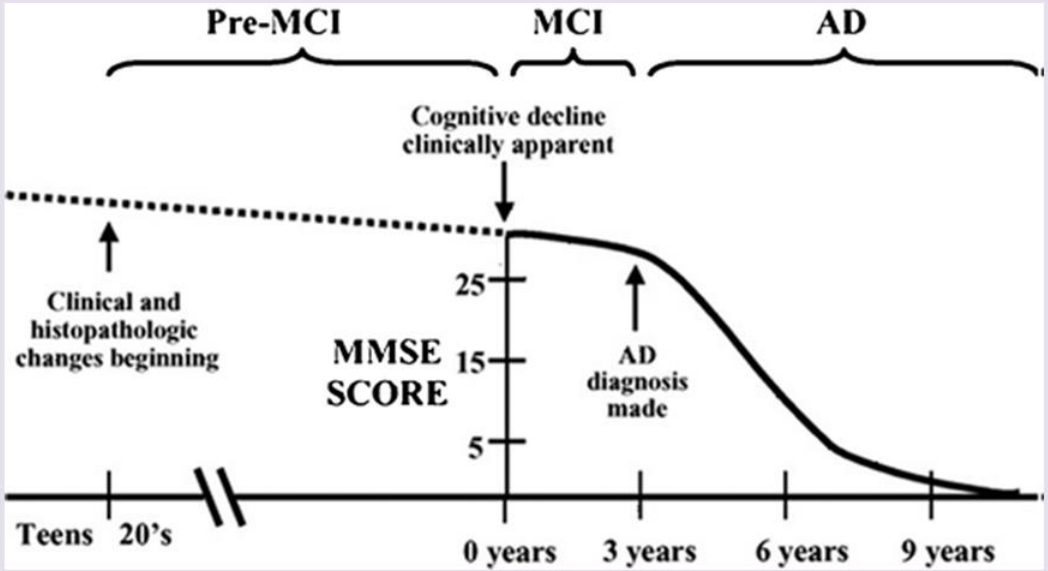
What is Alzheimer's Disease?

- Pathological
  - Brain shrinkage due to loss of nerve cells
  - Neurofibrillary tangles inside nerve cells
  - Accumulation of plaques outside cells
- Clinical
  - Alzheimer's disease is preceded by mild cognitive impairment (MCI)
  - Initial loss of memory and cognition
  - Progressive loss of ability to perform daily functions
  - Progressive emergence of behavioral changes
- Biochemical and Genetic
  - Plaques of Amyloid Beta42
  - Tangles of phosphorylated tau protein
  - Early onset familial disease

Mild Cognitive Impairment

- Complaint of memory or cognitive problems
- Impairment of memory or other cognitive functions out of proportion for age and education
- Generally intact activities of daily living
- Most (but not all) people with MCI eventually develop Alzheimer's disease

Cognitive Decline and AD



What is MMSE?

- Mini Mental State Exam
  - Maximum score 30
  - Contains a variety of questions, memory tests and tasks
    - Remember 4 objects
    - Key dates and people - What day is this? Who is the US president?
    - Spell WORLD backwards or start at 100 and subtract 7s
    - Praxis
  - 30 is normal, 28 MCI, 27-20 mild AD, 19-10 Moderate AD, <10 severe AD
  - BUT education can affect the score

Praxis

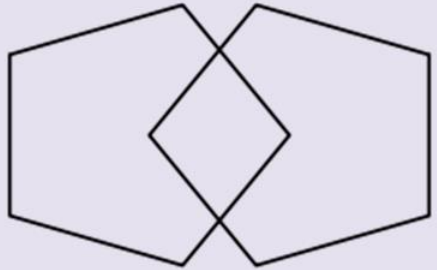
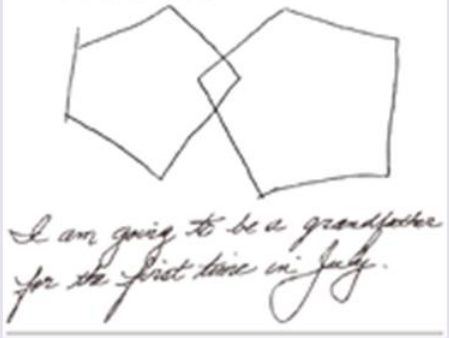
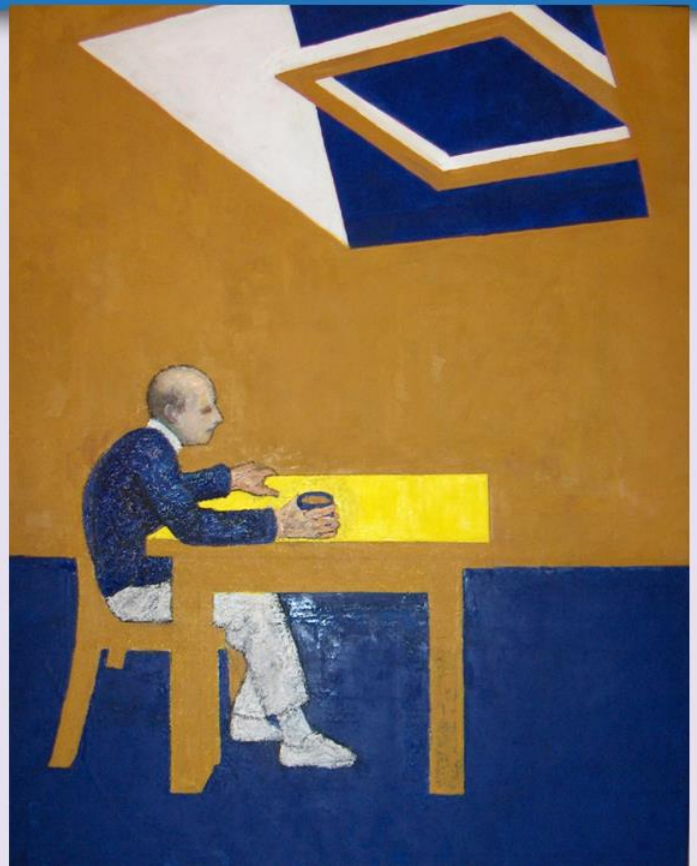


Figure 1. Mr A's Pentagon Drawing and Sentence From the Mini-Mental State Examination



1995
Blue Skies
William Utermohlen



1999 Erased Self-Portrait

William Utermohlen

What is Alzheimer's Disease?

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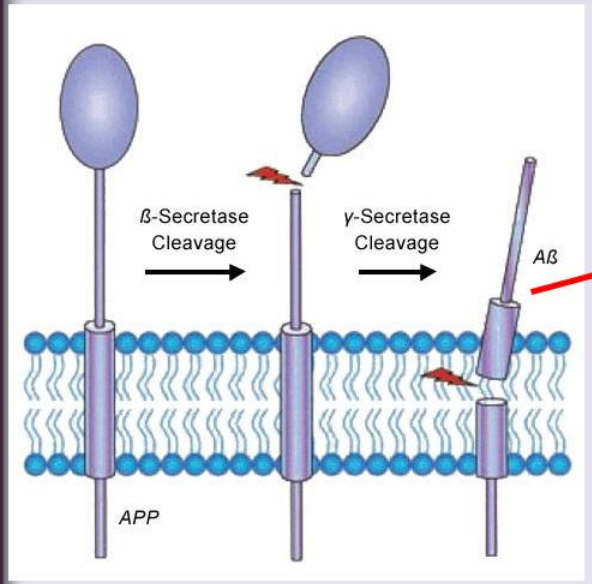
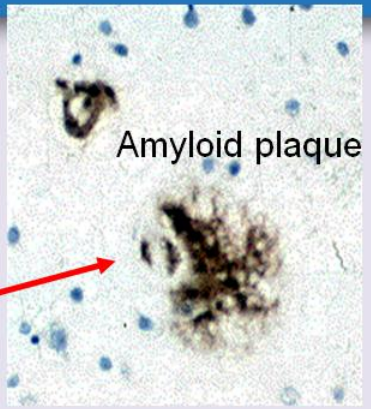
Amyloid Plaque

- Amyloid plaque consists of an insoluble 42aa peptide call amyloid beta42 (Abeta42)
- This peptide is formed by the 'wrong' cut of a precursor protein – Amyloid precursor protein
- APP is 695aa protein
- The normal peptide is a soluble 40aa peptide
- Cleavage is by alpha and gamma secretases
- A small increase of Abeta42 production can lead to early onset AD
- Rare inherited gene mutations lead to overproduction of Abeta42 and early onset of AD

Cleavage of APP to Form Amyloid (Aβ)

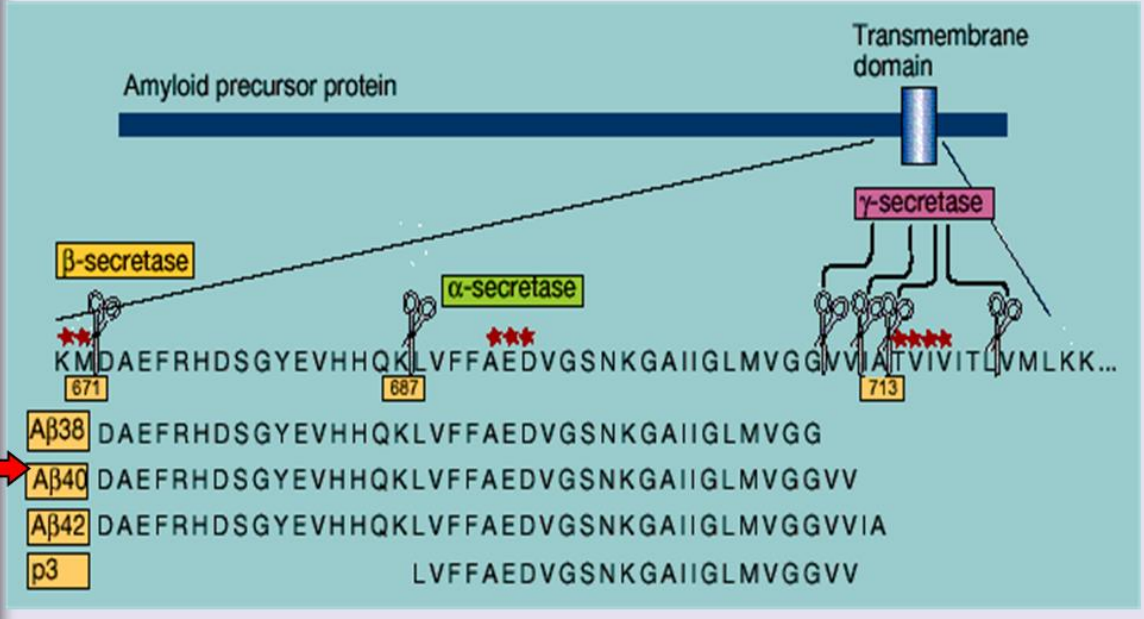




Alzheimer's Disease:
Accumulation of Aβ protein in the brain is a primary event in the pathogenesis of AD

Aβ42 is prone to aggregation, first to deposit in brain

Cleavage of APP: Aβ42 vs. Aβ40



*APP mutations causing early-onset familial Alzheimer's (FAD)

Current Treatments

Symptomatic

Cholinesterase inhibitors – preserves acetylcholine

- Donepezil (Aricept)
- Galantamine (Reminyl or Razadyne)
- Rivastigmine (Exelon)

NMDA antagonist – prevents damage by glutamate

- Memantine (Namenda)

Disease Modifying

Anti Amyloid biologics

- Lecanamab (Leqembi)

Symptomatic Therapies

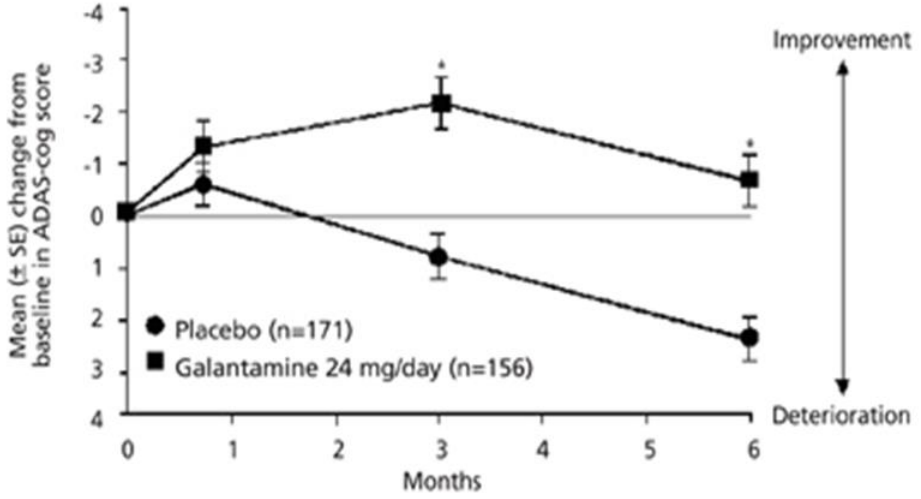


FIGURE 5. Mean Change From Baseline in ADAS-cog 11 Scores Over 6 Months (6-Month, Double-Blind International Trial)[11]

Adapted with permission from Wilcock GK, Lilienfeld S, Gaens E. Efficacy and safety of galantamine in patients with mild to moderate Alzheimer's disease: multicentre randomised controlled trial. Galantamine International-1 Study Group. BMJ. 2000;321:1445-1449.

ADAS-cog/11=11-item AD Assessment Scale cognitive subscale.

Dengiz AL, Kershaw P. *CNS Spectr.* Vol 9, No 5. 2004.

Disease Modifying

- Leqembi from Biogen/Eisai recently approved
- Monoclonal antibody that binds to Abeta
- Monthly infusions
- Clears plaque in the brain
- Slows decline by 25-33%
- Significant side effects
  - Amyloid Imaging Related Abnormalities (ARIA)
    - Headache, confusion, dizziness, seizures

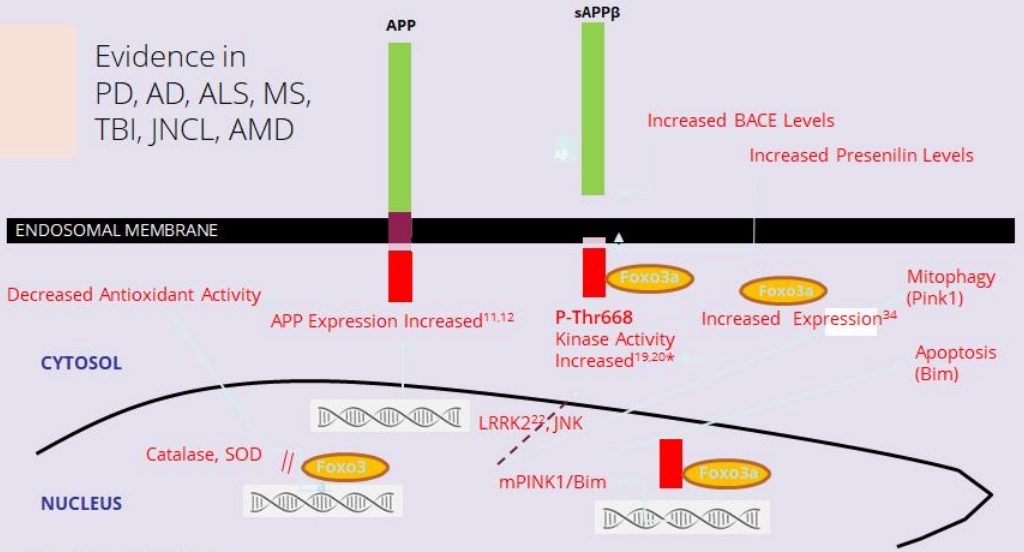
Future Treatments

Current Research is focused on inflammation in the brain

I. Model of Dysregulated Response to Oxidative Stress

CERESPIR™

Evidence in
PD, AD, ALS, MS,
TBI, JNCL, AMD



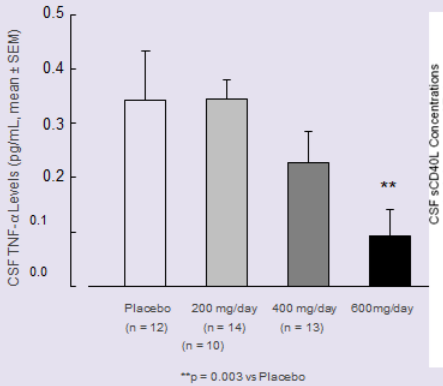
*Different kinases maybe involved in different diseases.

CERESPIR™

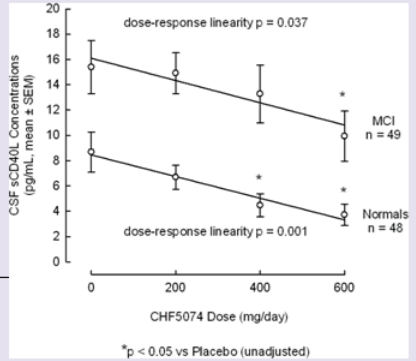
ITANAPRACED

Clinical proof of concept achieved, delivering significant decrease in proinflammatory cytokines relevant to AD

CSF TNF-α at Week 12



CSF sCD40L at Week 12

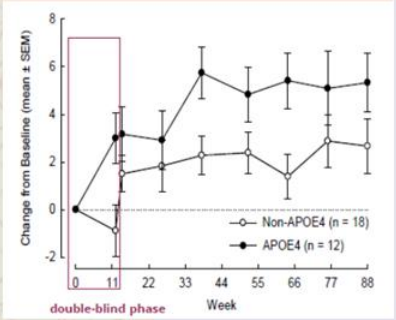


TNF-α AND sCD40L Dose-dependent Decrease

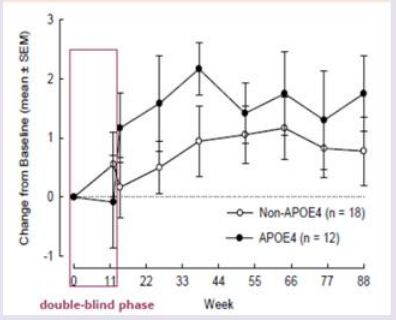
Cognitive Data

LONGITUDINAL COGNITIVE PERFORMANCE

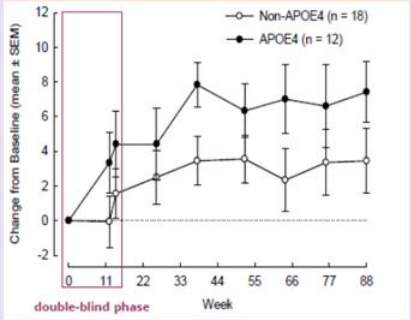
Immediate Word Recall



Delayed Word Recall



Total Hopkins Verbal Learning Score



Results show changes from baseline assessments.

Note: Preliminary data that is subject to change.

Resilience

Resistance to autosomal dominant Alzheimer's disease in an *APOE3* Christchurch homozygote: a case report

Joseph F. Arboleda-Velasquez, Francisco Lopera, Michael O'Hare, Santiago Delgado-Tirado, Claudia Marino, Natalia Chmielewska, Kahira L. Saez-Torres, Dhanesh Amarnani, Aaron P. Schultz, Reisa A. Sperling, David Leyton-Cifuentes, Kewei Chen, Ana Baena, David Aguillon, Silvia Rios-Romenets, Margarita Giraldo, Edmarie Guzmán-Vélez, Daniel J. Norton, Enmanuelle Pardilla-Delgado, Arabiye Artola, Justin S. Sanchez, Juliana Acosta-Uribe, Matthew Lalli, Kenneth S. Kosik, ... Yakeel T. Quiroz

+ Show authors

Nature Medicine **25**, 1680–1683 (2019) | Cite this article

Resilience to autosomal dominant Alzheimer's disease in a Reelin-COLBOS heterozygous man

Francisco Lopera, Claudia Marino, Anita S. Chandrahas, Michael O'Hare, Nelson David Villalba-Moreno, David Aguillon, Ana Baena, Justin S. Sanchez, Clara Vila-Castelar, Liliana Ramirez Gomez, Natalia Chmielewska, Gabriel M. Oliveira, Jessica Lisa Littau, Kristin Hartmann, Kyungeun Park, Susanne Krasemann, Markus Glatzel, Dorothee Schoemaker, Lucia Gonzalez-Buendia, Santiago Delgado-Tirado, Said Arevalo-Alquichire, Kahira L. Saez-Torres, Dhanesh Amarnani, Leo A. Kim, ... Yakeel T. Quiroz

+ Show authors

Nature Medicine **29**, 1243–1252 (2023) | Cite this article

- Recent studies have identified 2 individuals in the Colombian families that have the *PSEN-1* variant but did not start developing symptoms until lates 60s and 70s (ie, as much as 30yrs later than average)
- Both had very high amyloid plaque but limited Tau tangles
- The first individual had a rare *APOE-e3* variant (called Christchurch)
- The second individual had a variant in another gene (*Reelin*) that may be the protective effect

Cognitive superagers - the longevity genes project

- A study of 500 healthy Ashkenazi Jews between 95 and 112 + their children - led by Dr Nir Barzilai
- What is it that allows them to be cognitively and physically healthy? Dr Barzilai:
  - “They tend to remain disease-free until a few weeks or even just a few days before they die,”
  - “Their long health spans can’t be attributed to their environment—quite a few centenarians we’ve studied, for example, have been lifelong smokers,” he noted. “Instead, evidence strongly suggests that centenarians possess rare genetic differences that slow their aging and make them resistant to diseases.”

Nir J. Barzilai, MD

https://www.einsteinmed.edu/centers/aging/longevity-genes-project/