Pharmacological Treatment of Dementia

(What's happening with Alzheimer's Disease?)

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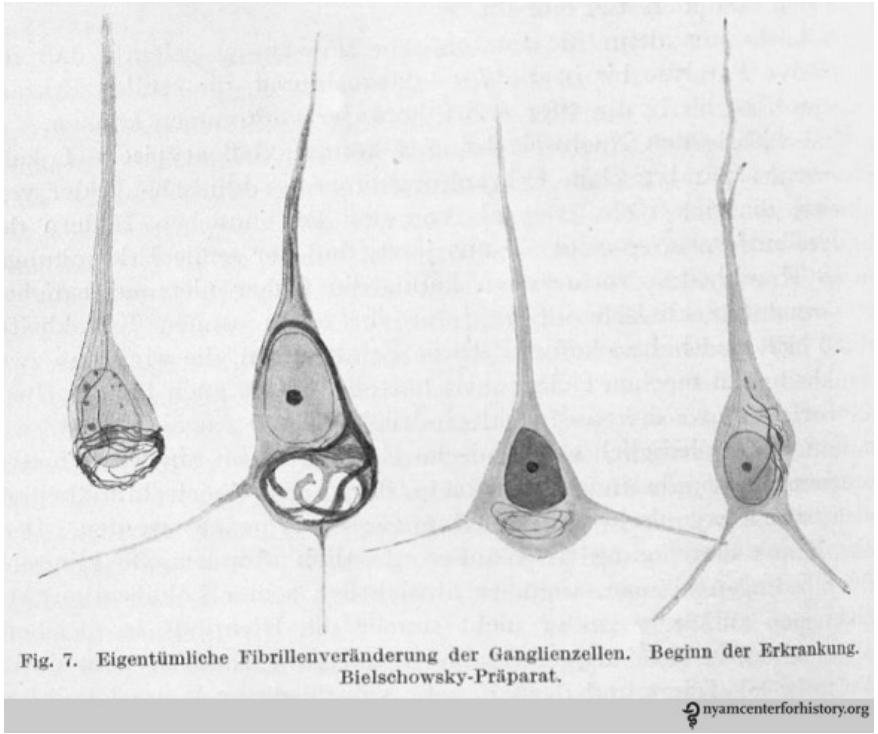
Alzheimer's disease (AD)

It was first described by German psychiatrist and neuropathologist Alois Alzheimer in 1906 and was named after him in 1910.



Drawings of brain cells from the “first” Alzheimer’s patient August D.

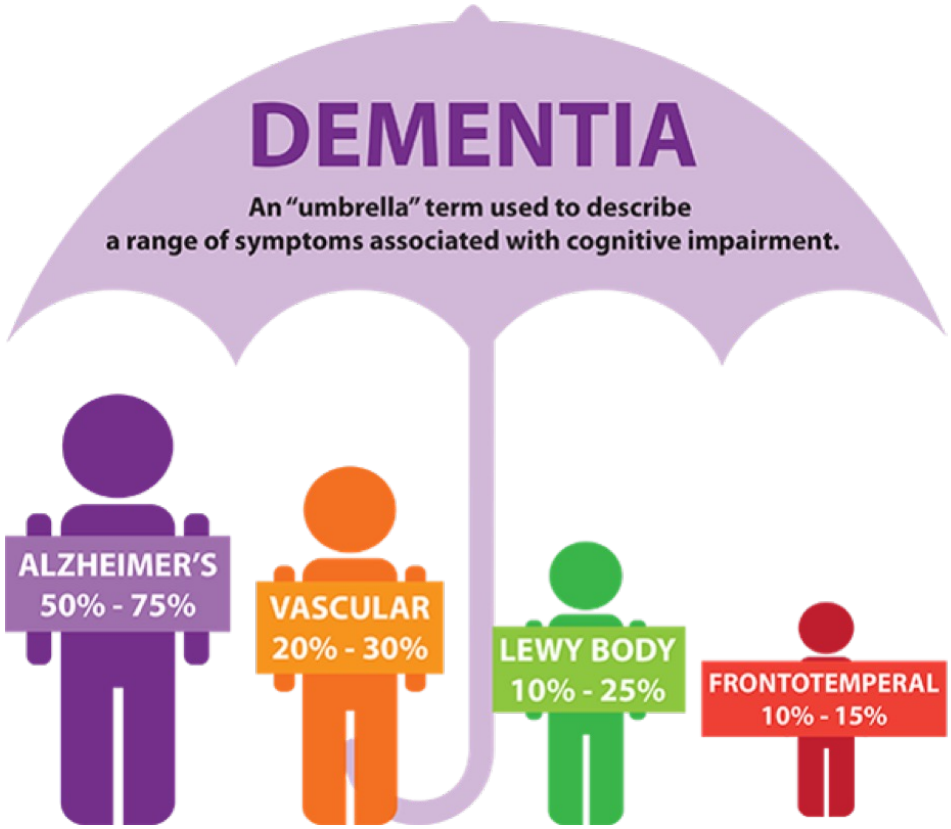
One of the first to suggest that psychiatric disorders had a physical basis.

These observations still drive present Alzheimer’s diagnosis and treatment.

Alzheimer's disease (AD)

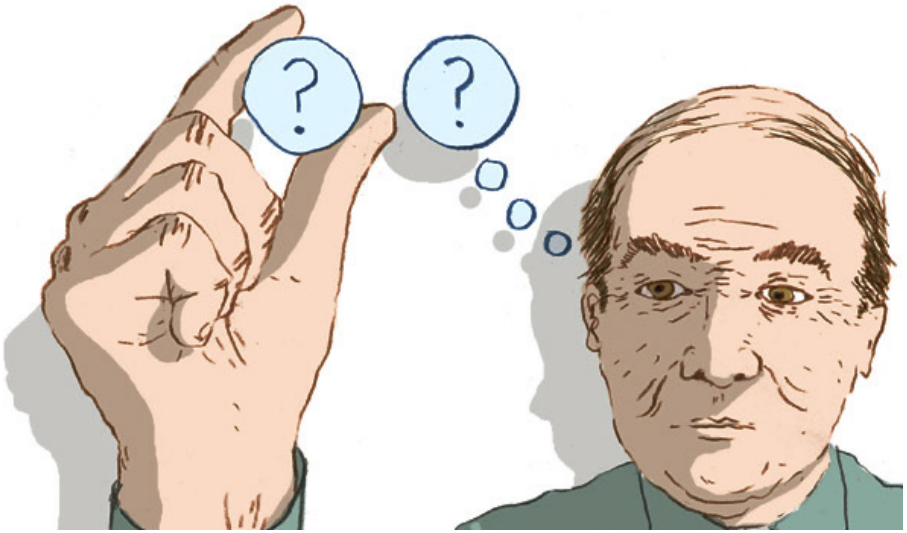
The most common form of Dementia.

~75% of all dementia cases are have some Alzheimer's pathology



Other forms of Dementia also exist that are distinct from or mixed with Alzheimer's.

Alzheimer's Dementia



<u>Initial Clinical Presentation</u>

Loss of working memory.

Loss of language.

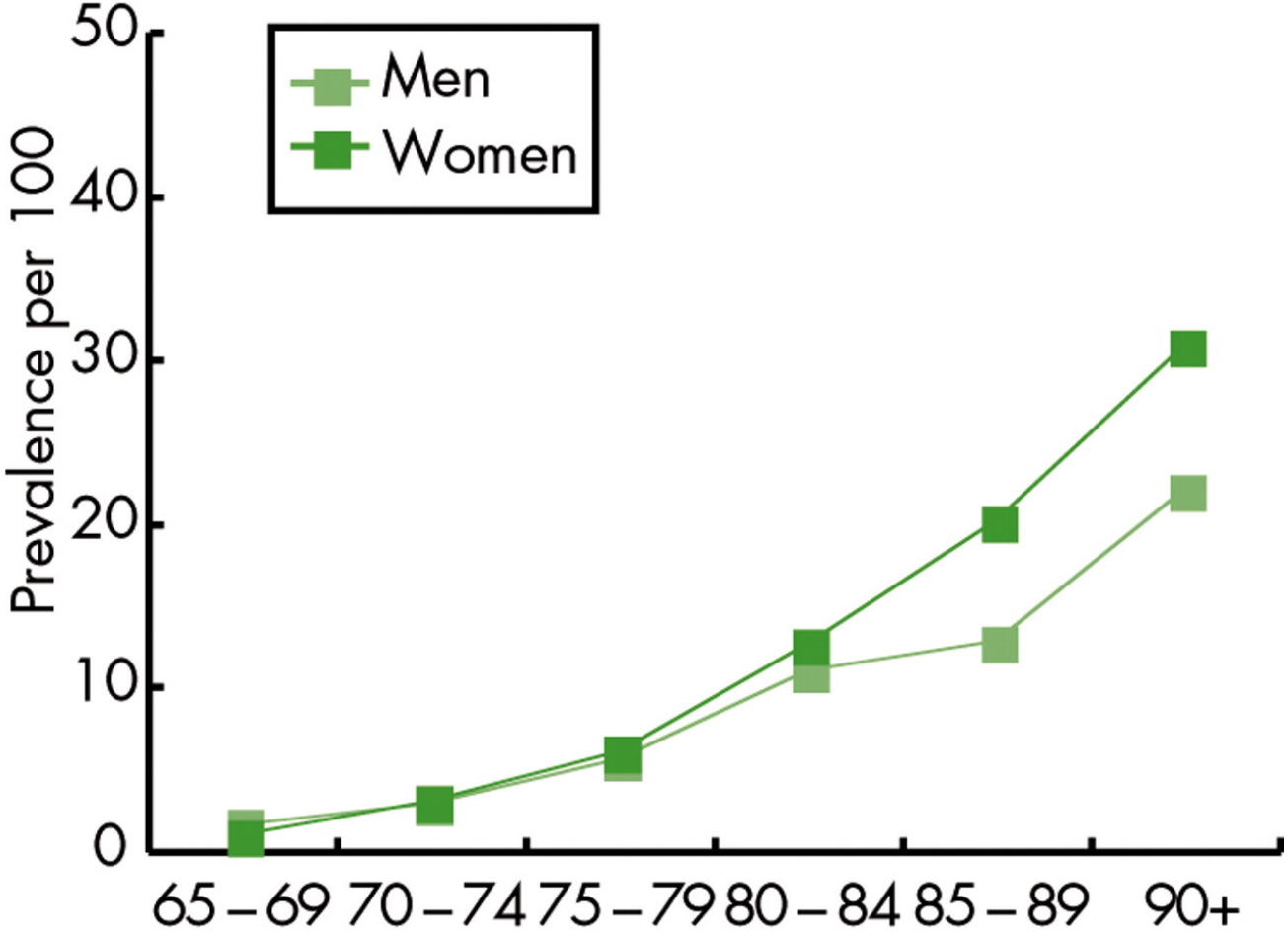
Alzheimer's disease is not:

Where did I put my car keys?

Alzheimer's disease is:

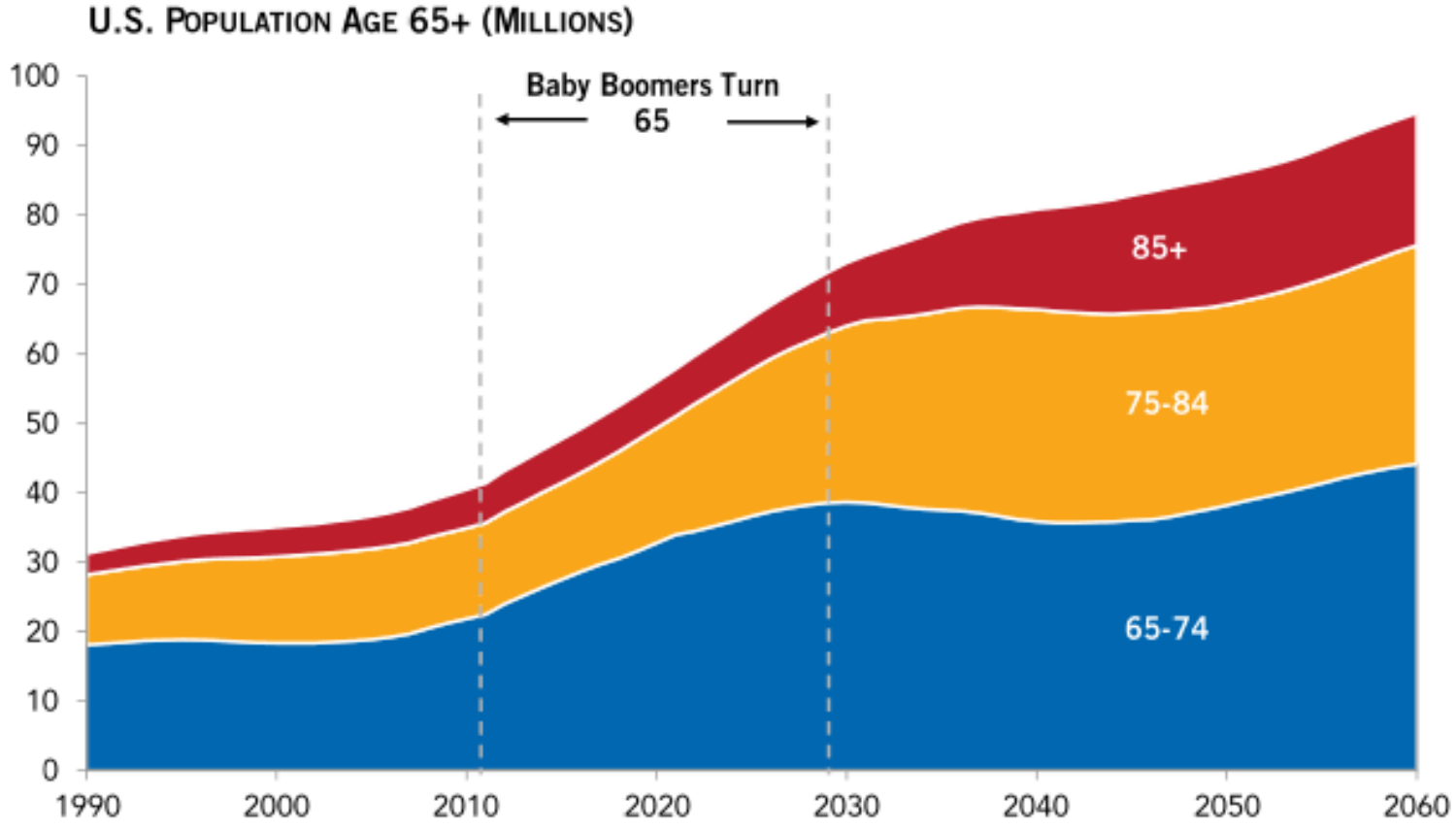
What are these metal objects on a ring?

Age is the primary factor that determines Alzheimer's Disease incidence.



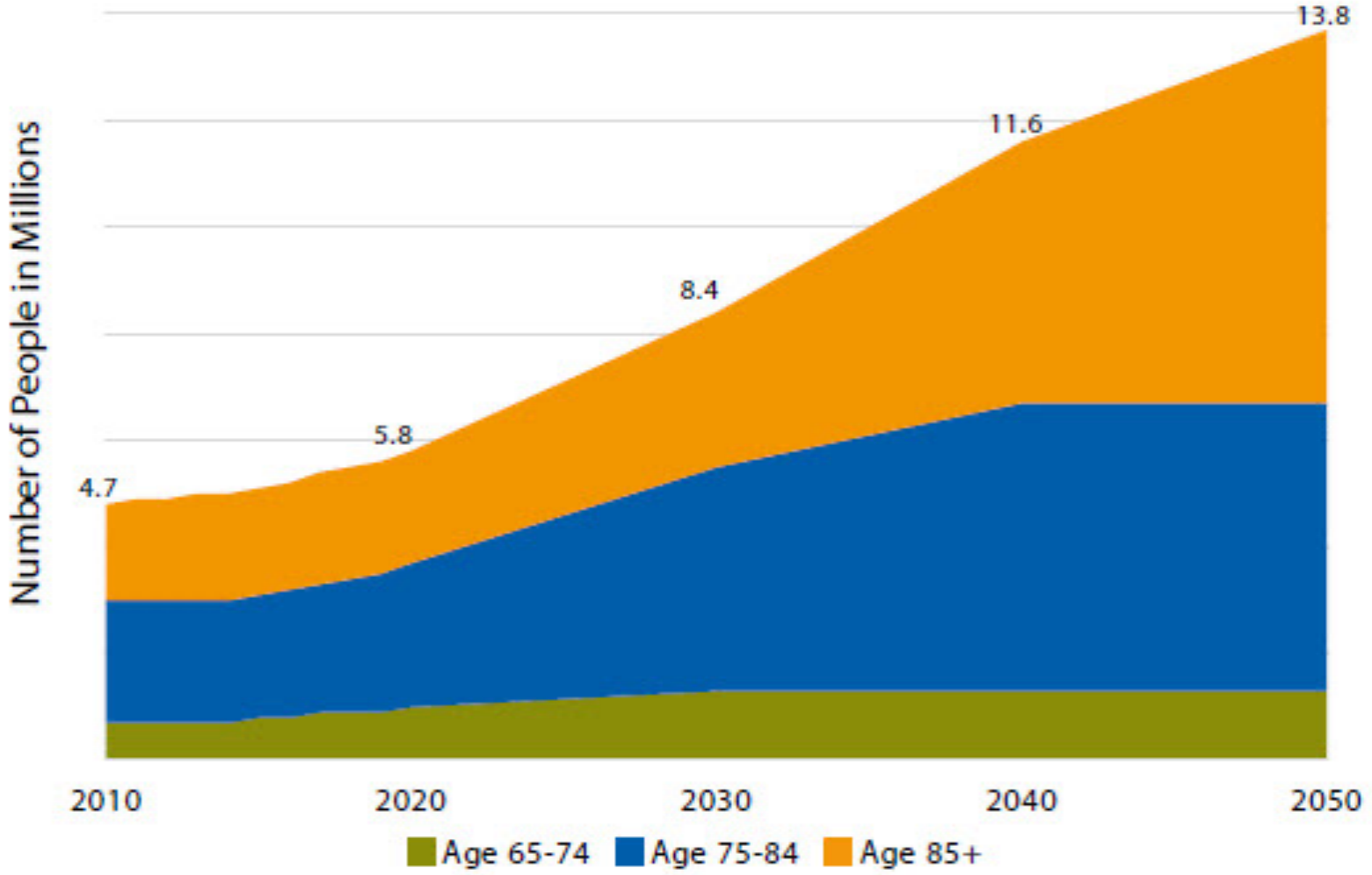
PETER G. PETERSON FOUNDATION

The elderly population is growing rapidly and living longer



SOURCE: U.S. Census Bureau, *National Intercensal Estimates; 2016 Population Estimates*, June 2017; and *2017 National Population Projections*, September 2018. Compiled by PGPF.

Projected Number of People Aged 65 or Older With Alzheimer's Disease, by Age Group, United States, 2010–2050



Source: Created from data in Hebert LE, Weuve J, Scherr PA, Evans DA. Alzheimer disease in the United States (2010–2050) estimated using the 2010 Census. *Neurology*. 2013;80(19):1778–1783.

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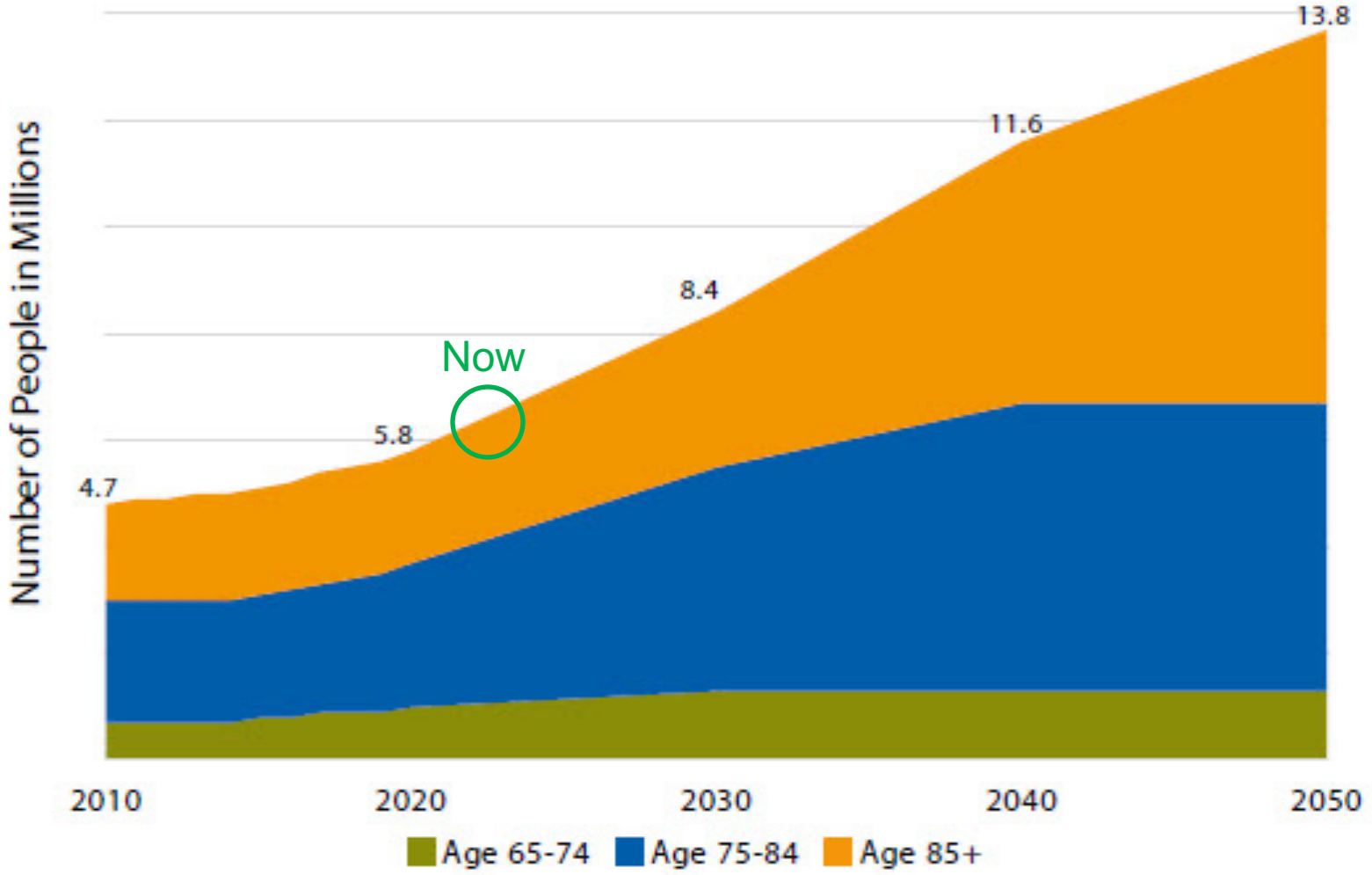

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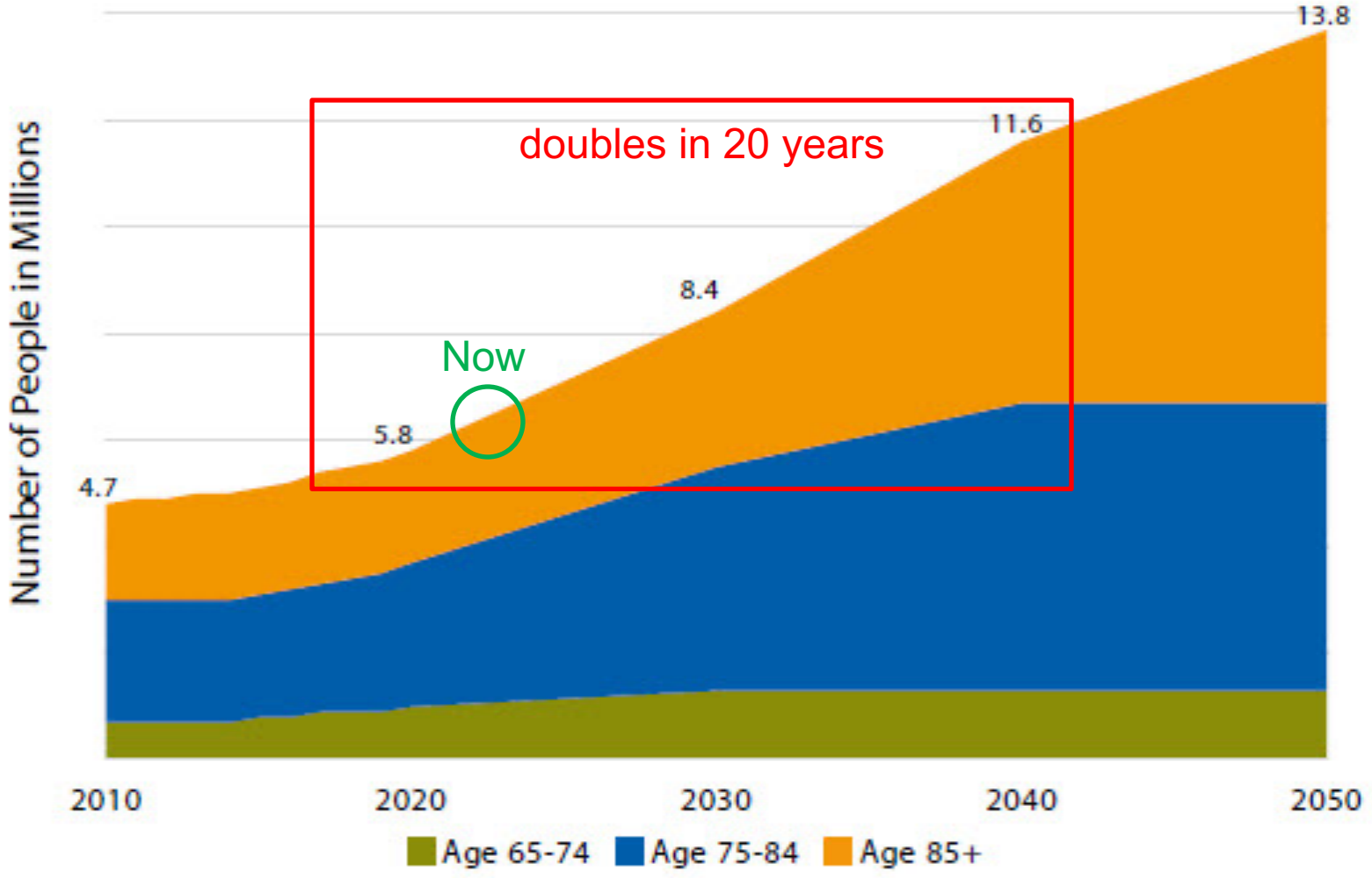

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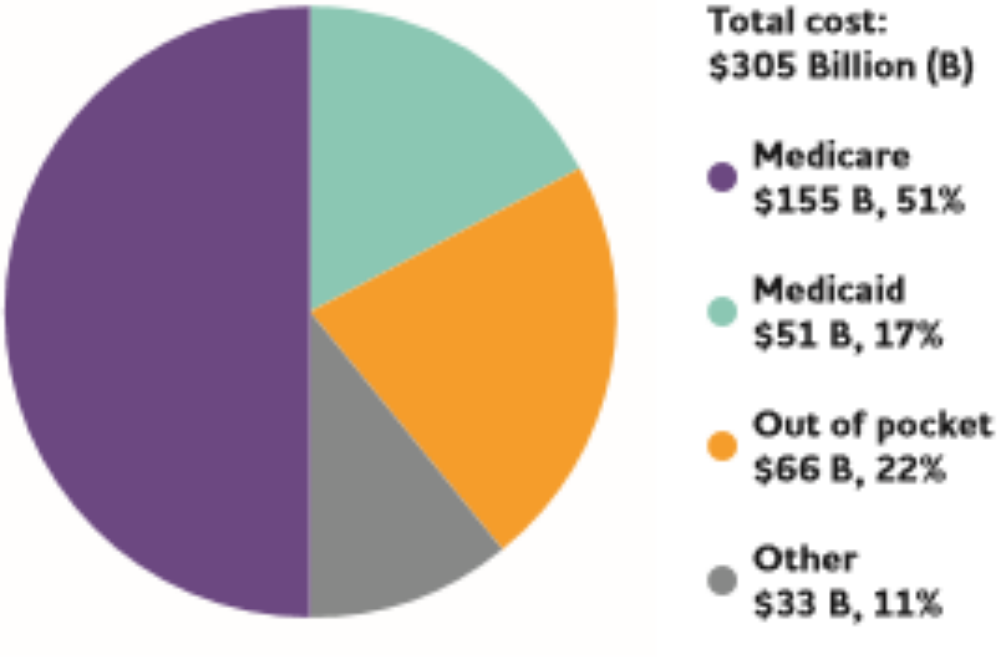
Distribution of Aggregate Costs of Care by Payment Source for Americans Age 65 and Older with Alzheimer's or Other Dementias, 2020*



*Data are in 2020 dollars.

Percentages do not total 100 due to rounding.

Created from data from the Lewin Model.[A16] "Other" payment sources include private insurance, health maintenance organizations, other managed care organizations and uncompensated care.

$55,000 annual cost per patient

2-20 years of care

5.8 million Americans are living with Alzheimer's

16 million friends and family help provide care for them

According to The Alzheimer's Association

docpanel

60 hours/week of care required

$45,000 estimated cost per patient

ECONOMIC IMPACT

15%* of 4.1 Trillion total health care costs in 2021**

37% projected by 2050

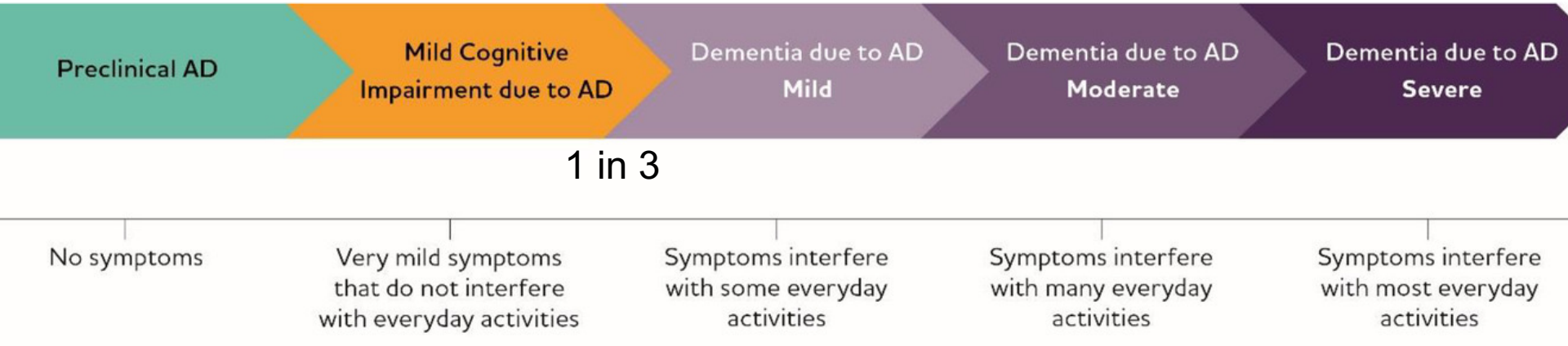
SOCIETAL IMPACT

5% of the U.S. population were AD caregivers* (20 hrs/wk)

13% projected by 2050

*Alzheimer's Association
**California Health Care Foundation

Stages of Alzheimer's Disease



AD Diagnosis in Living Patients

Educated guessing.

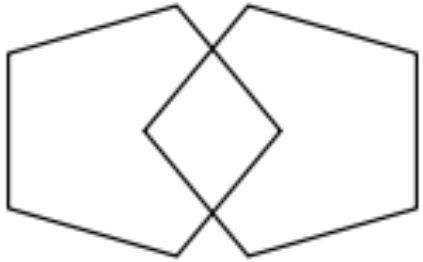
1. Short term memory problems that go beyond what is normal at that age.

Often ignored for a time. Nick's Dad story…..

2. When AD is suspected, initial diagnosis is based on tests that evaluate behavior and thinking abilities (about 80% accurate).

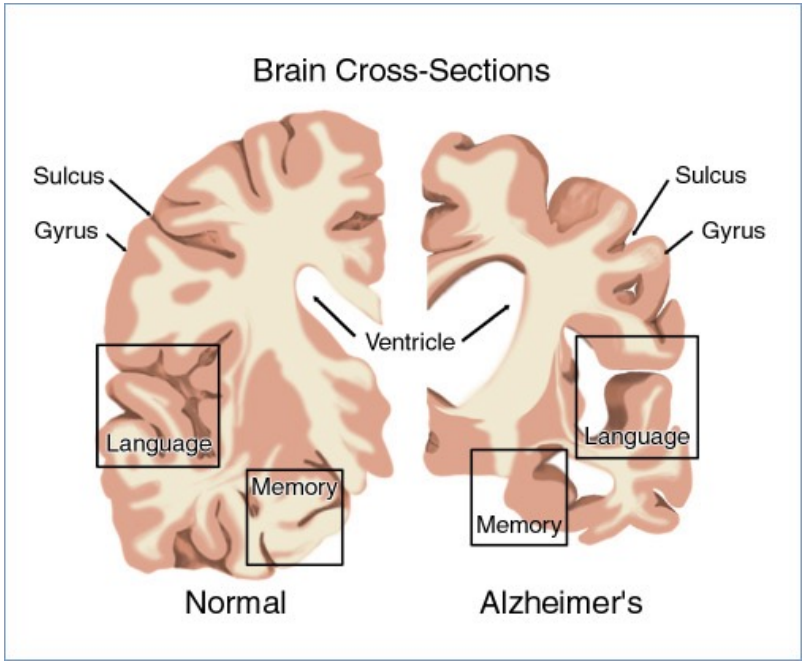
MMSE (Mini-mental state examination)

Copy shapes (like that on the right)
Remember details of a story
Reading a story
Subtract 2 big numbers



The only 100% reliable diagnosis = post-mortem examination of brain.

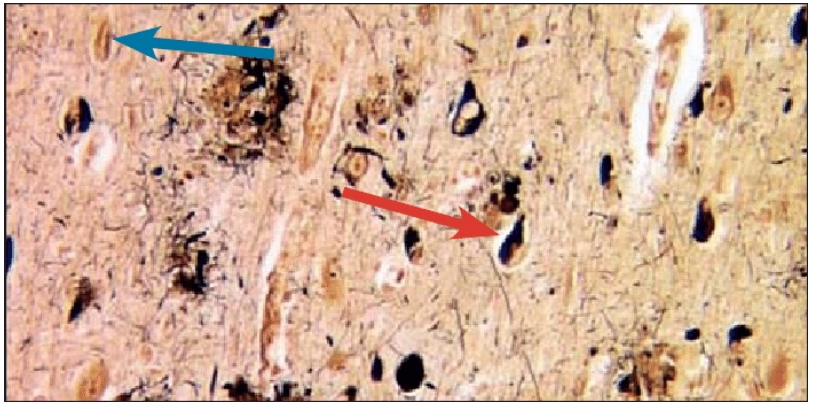
Memory neurons are disproportionately affected (hippocampus).



Hippocampus tissue shows

Plaques (β-amyloid protein)

Tangles inside neurons (tau)



Alzheimer's Disease is roughly placed into one of two groups.

Early onset: diagnosis before 65 (10%).

Late onset: diagnosis after 65 (90%).

Early onset

About 10% of AD cases are early onset (<65 years).

Most are “sporadic” – there is no obvious genetic factor vs. late onset.

BUT - 0.1% of these early-onset cases are familial (strong genetic link).

Familial AD can be attributed to mutations in genes that code for the following two proteins:

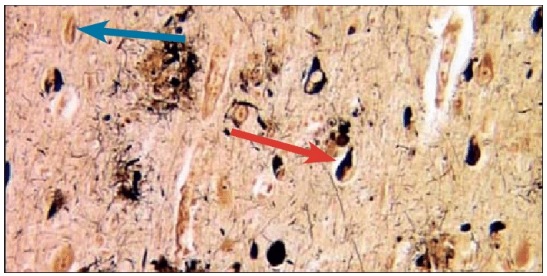
1. amyloid precursor protein (APP)

2. presenilins (two enzymes which chop APP into smaller pieces).

What is the relationship of theses genes (and their protein to Alzheimer’s Disease?

Presenlins chop APP to make a smaller fragment called beta-amyloid (Aβ).

Aβ is the main component of brain plaques.



Late-onset

APP and Presenillin chopping genes are normal (although amyloid plaques still form).

Biggest genetic risk factor is the inheritance of the ε4 allele of apolipoprotein E (APOE).

In general population, likelihood of ε4 allele presence on chromosome is 14%.

In AD patients, ε4 allele frequency per chromosome is 37%.

Each APOE ε4 allele = 3X the risk of the disease

Also, higher correlation in women and with maternal side of family.

Some suggestion that mitochondria inherited from maternal line is involved.

The cause and treatment strategy of Alzheimer's Disease (especially late-onset) is still debated.

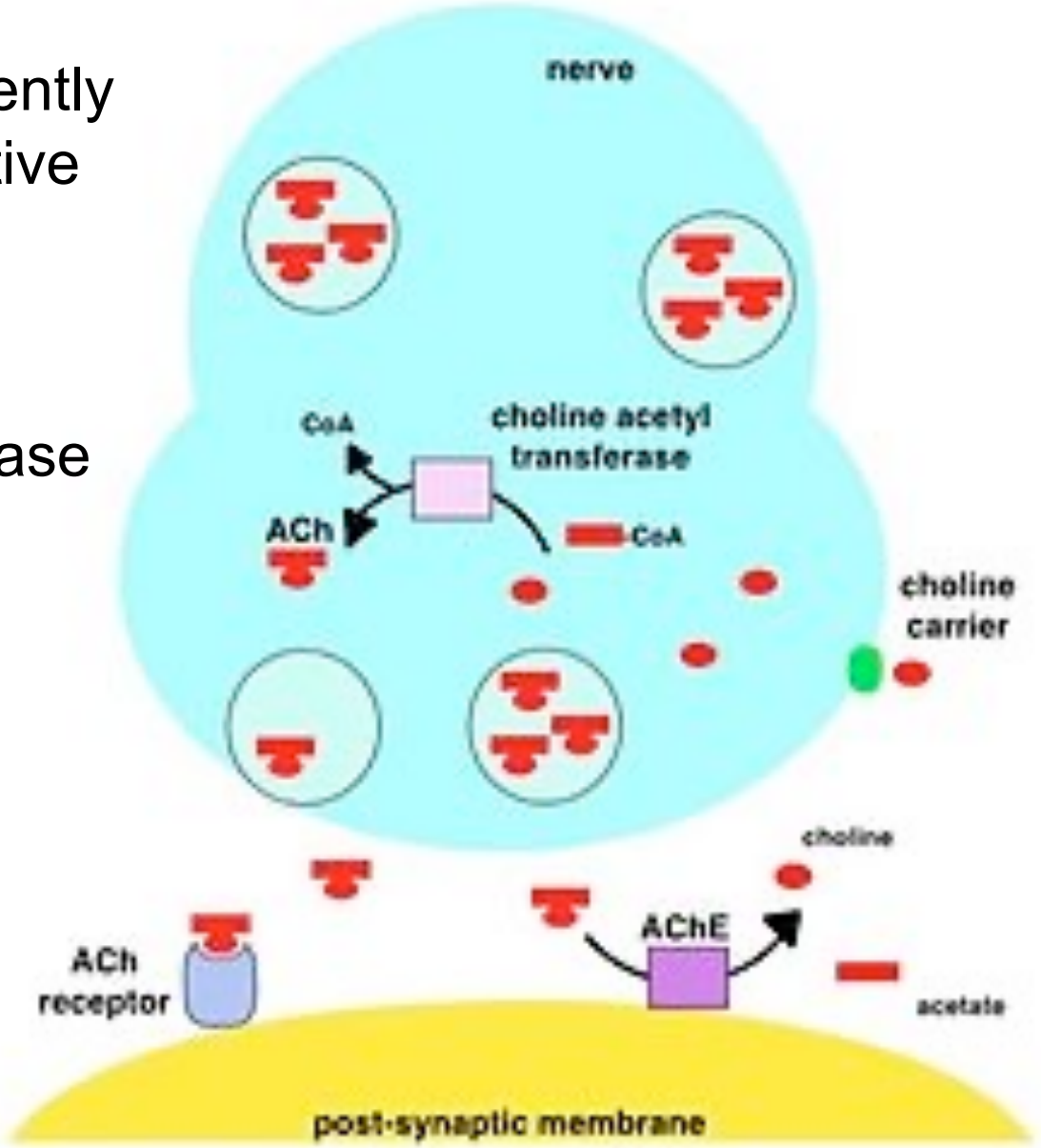
Minimal environmental/lifestyle factors.

Some correlation with heart disease factors.

Currently available Alzheimer's Drugs (approved prior to 2020)

4 medications are currently used to treat the cognitive problems of AD.

3 are acetylcholinesterase Inhibitors (AChE).



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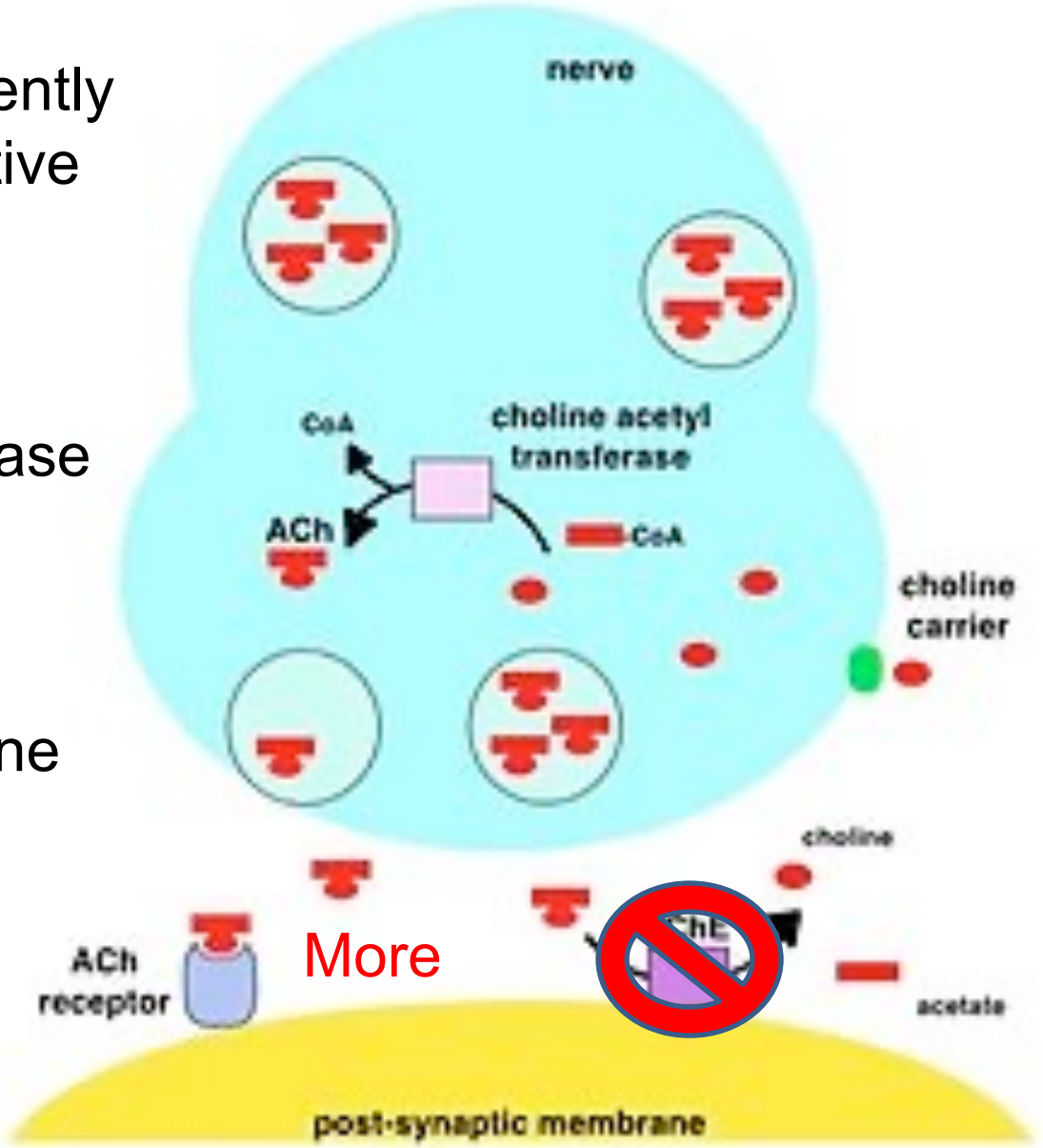
Make more Acetylcholine build up in synapse.

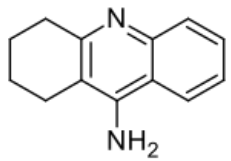


Tacrine/Cognex (1,2,3,4-tetrahydro-9-acridinamine) – NOT ACTIVE

-Originally investigated for treatment of drug overdose coma

-First Alzheimer's Therapeutic

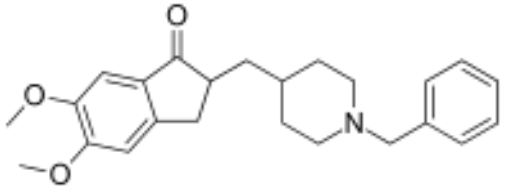
-FDA approval 1993-2013, discontinued over safety



Donepezil/Aricept

-Approved in 1996

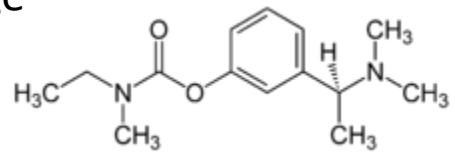
- Also activates sigma-1 receptors (in addition to ACE inhibition). Helps cells deal with stress.



Rivastigmine/Exelon

-Originally investigated for morphine-induced breathing stoppage

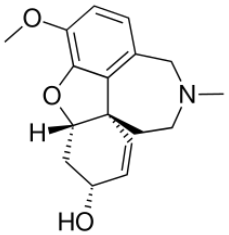
- 1997-present



Galantamine/Razadyne

-From snowdrop bulbs known to increase neural activity (The Odyssey).

-2001-present.



Memantine (sleep drug)

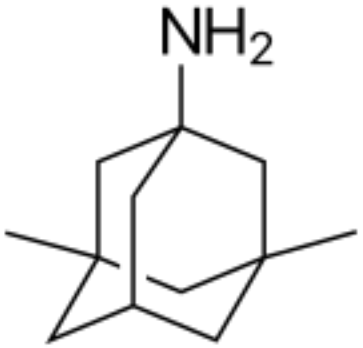
-<u>NOT</u> an acetylcholinesterase inhibitor

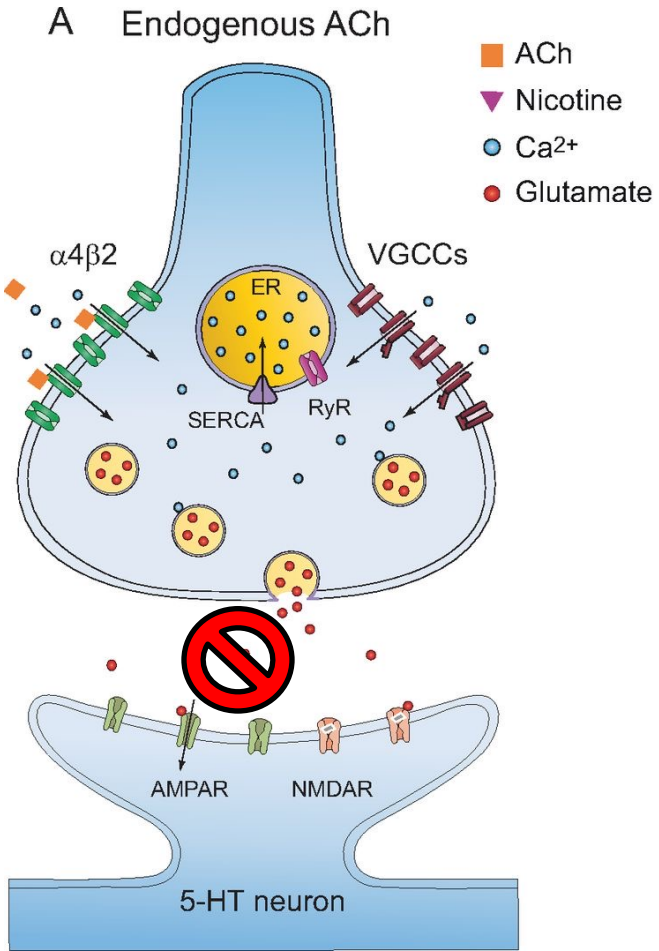
-NMDA receptor anatagonist (uncompetitive with Glu)

-Reduces “excitotoxicity” by excess Glutamate

-Many other receptor interactions
- -alpha7 nAChR receptor antagonist
- -5HT3 serotonin receptor antagonist
- -D2 Dopamine receptor agonist
- -σ1 opioid-like receptor agonist (σ1R inhibits ability of Glu to activate receptor)

-Minor benefit for moderate AD patients (not mild)





FOR ALL DRUGS APPROVED PRIOR TO 2020

The benefit from their use is small and only addresses symptoms.

No medication has been shown to delay or halt the progression of the disease.

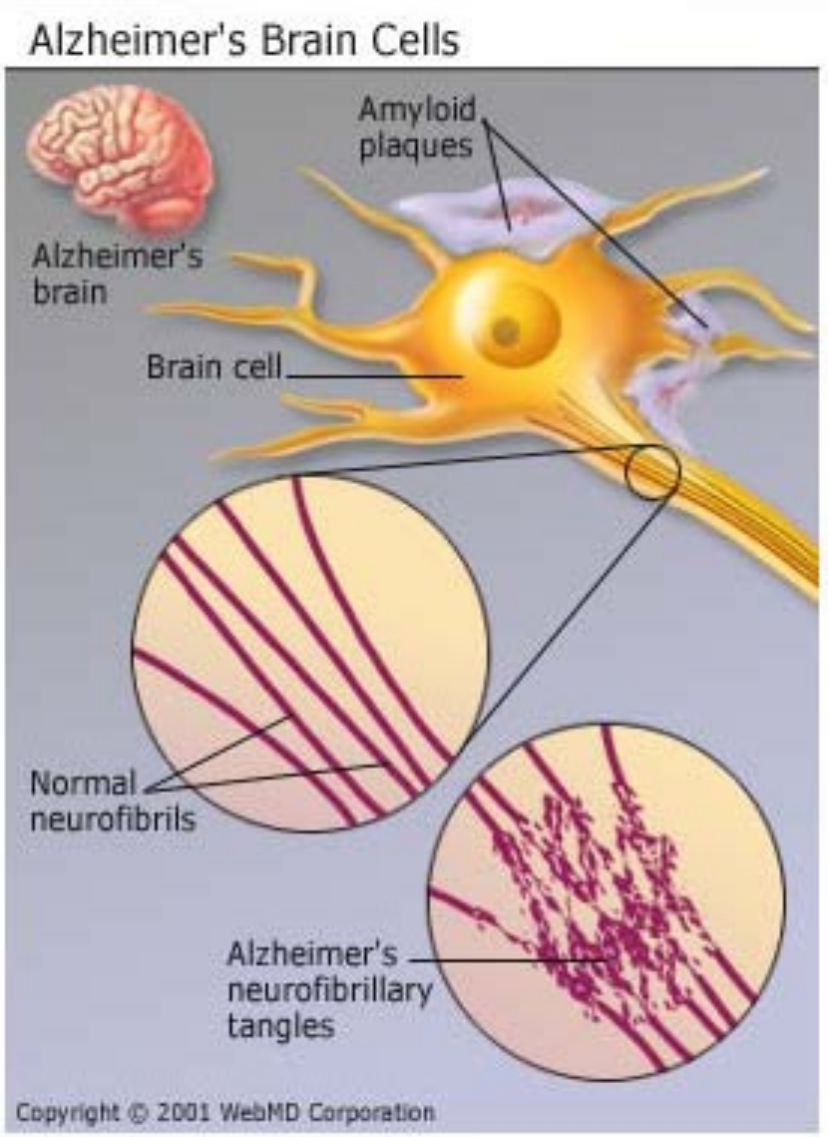
Neuropathology of Alzheimer's disease

FIRST:

AMYLOID PLAQUES
Outside brain cells
Made of Aβ protein fibrils

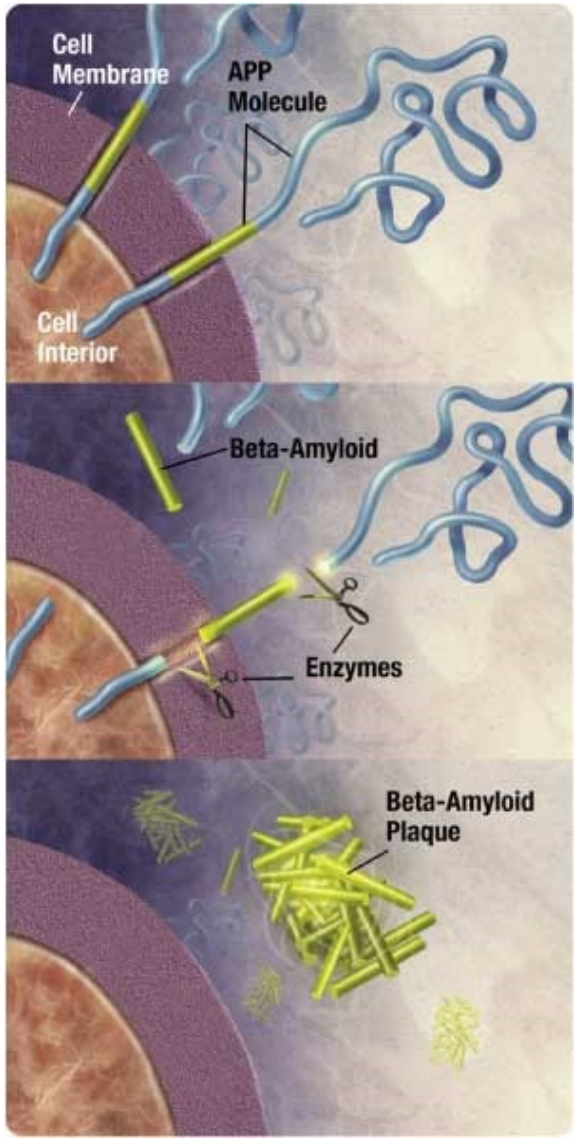
LATER:

NEUROFIBRILLARY TANGLES
Inside brain cells
Made of Tau protein

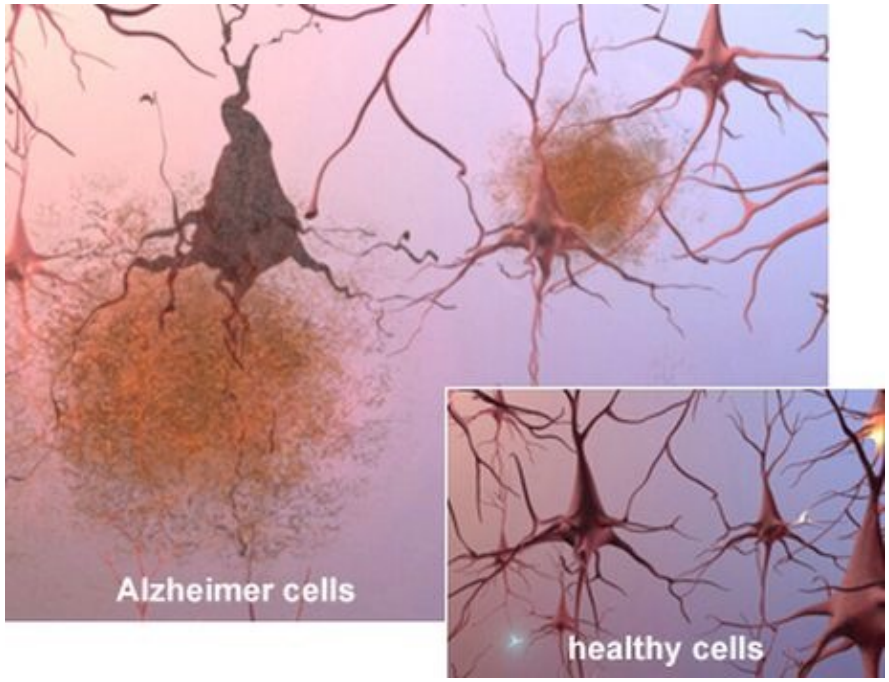


The Amyloid Hypothesis: Currently a Popular Drug Design Concept

1. Aβ forms insoluble plaques.



2. Plaques kill neurons.

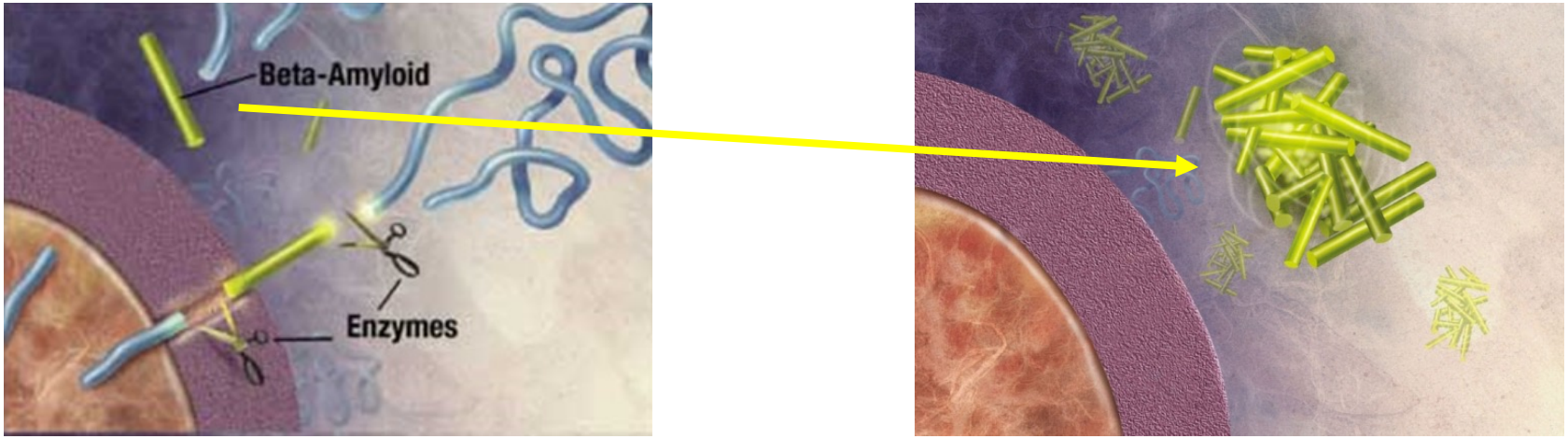


Rationale:

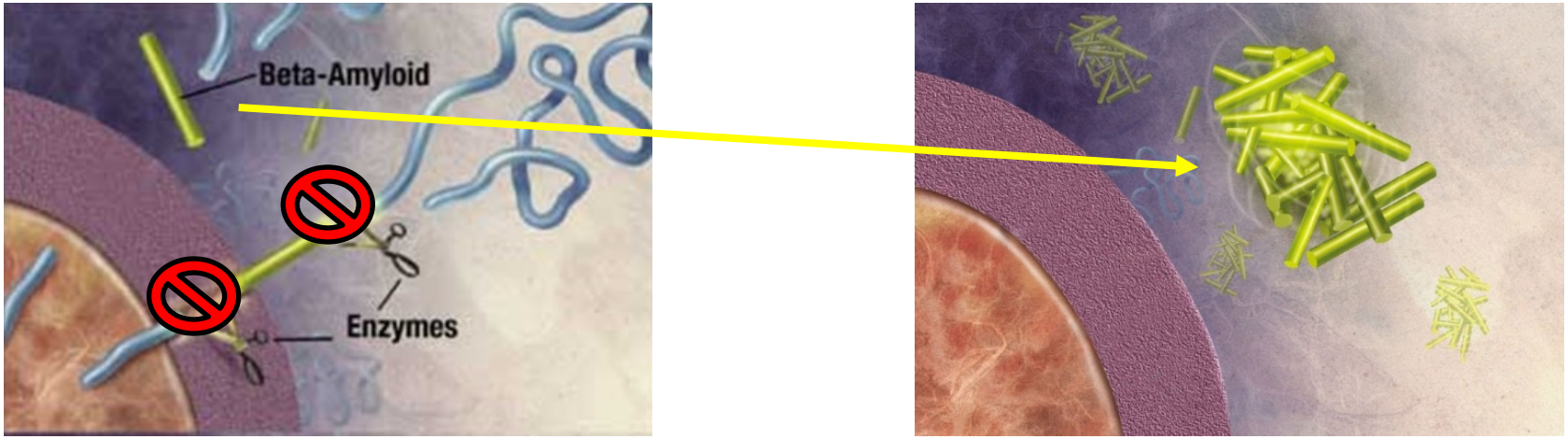
1. Diagnostic hallmark of AD.
2. All early onset AD patients (<40 years) have mutations in Aβ fragment or APP.

How might we stop this process?

Amyloid-Based Drugs

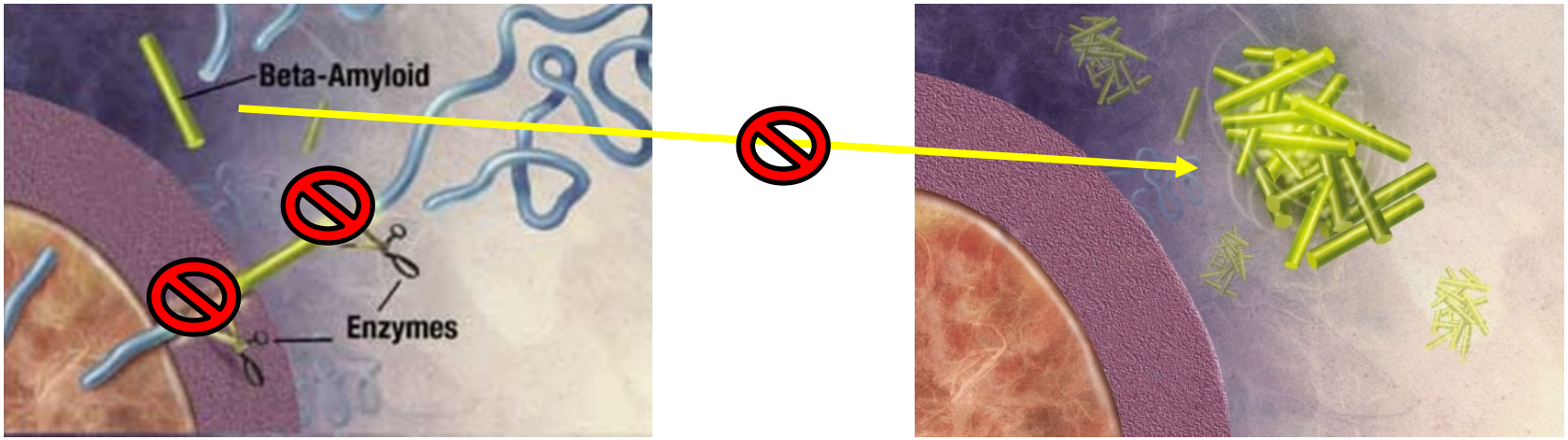


Amyloid-Based Drugs



1. Inhibit presenilins (cutting enzymes).

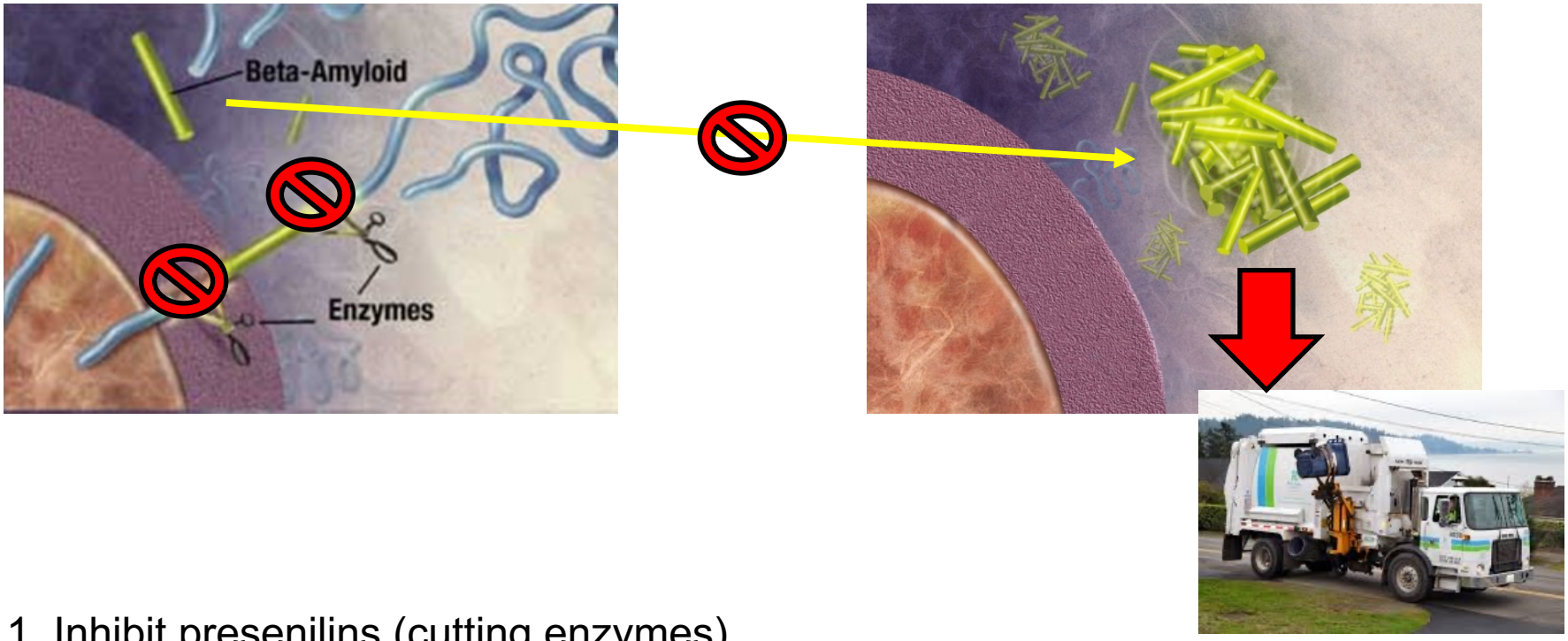
Amyloid-Based Drugs



1. Inhibit presenilins (cutting enzymes).

2. Block amyloid assembly.

Amyloid-Based Drugs



1. Inhibit presenilins (cutting enzymes).

2. Block amyloid assembly.

3. Remove existing amyloid.

Finding a drug.

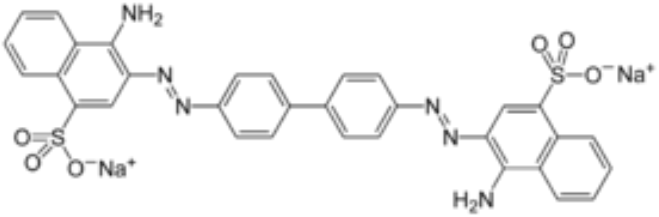
Step 1: Identify a “disease target”.

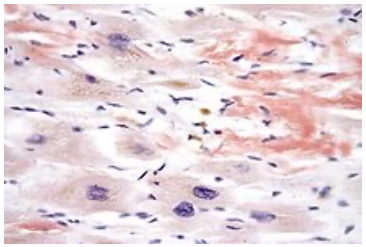
Step 2: Find a molecule that sticks to the target.

Other steps = get lucky.

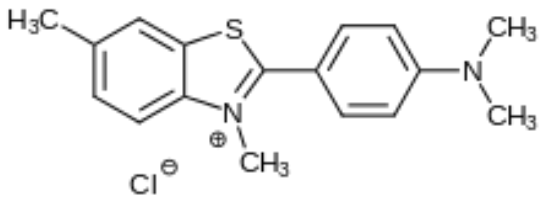
Known molecules that stick to amyloid

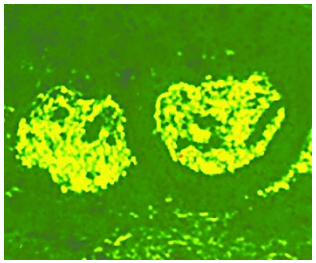
Congo Red





Thioflavin T

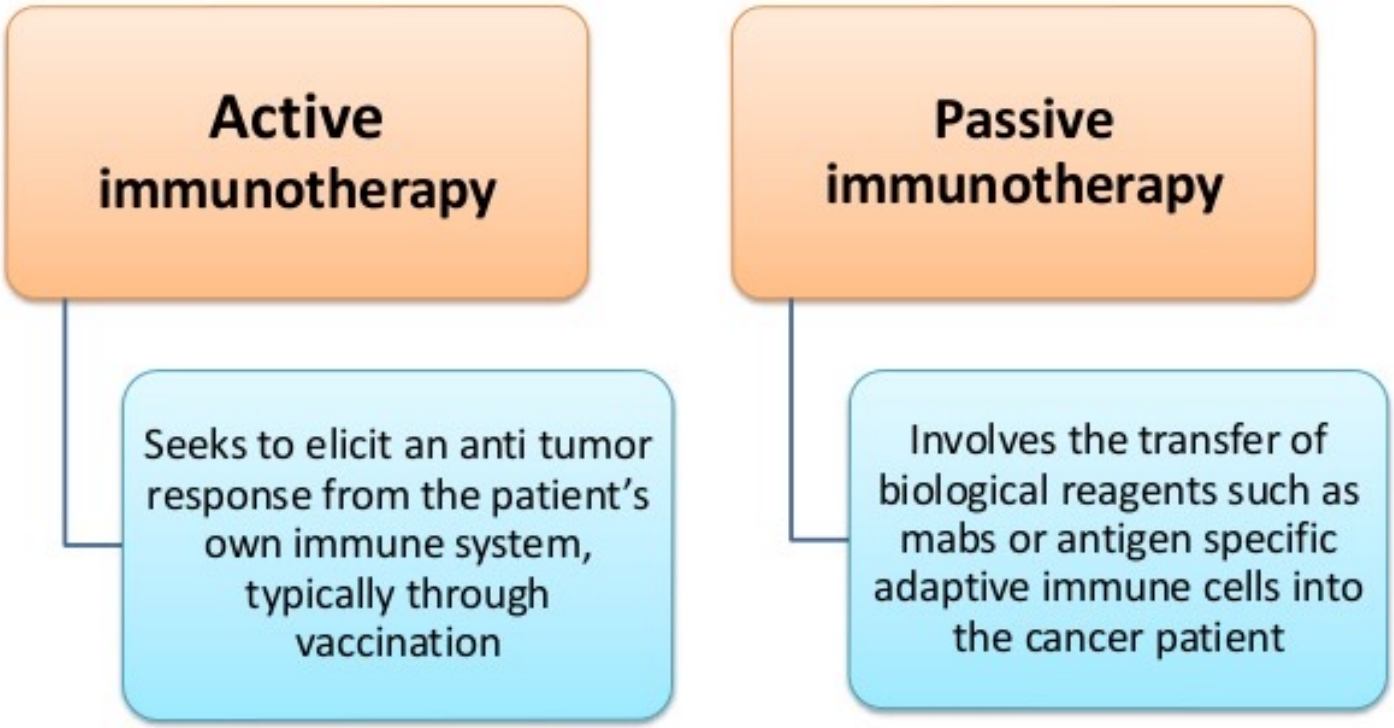




Why aren't these or similar compounds used as drugs?

1. Toxic
2. Require high concentrations to inhibit amyloid formation

Recent Approaches: Immunotherapy

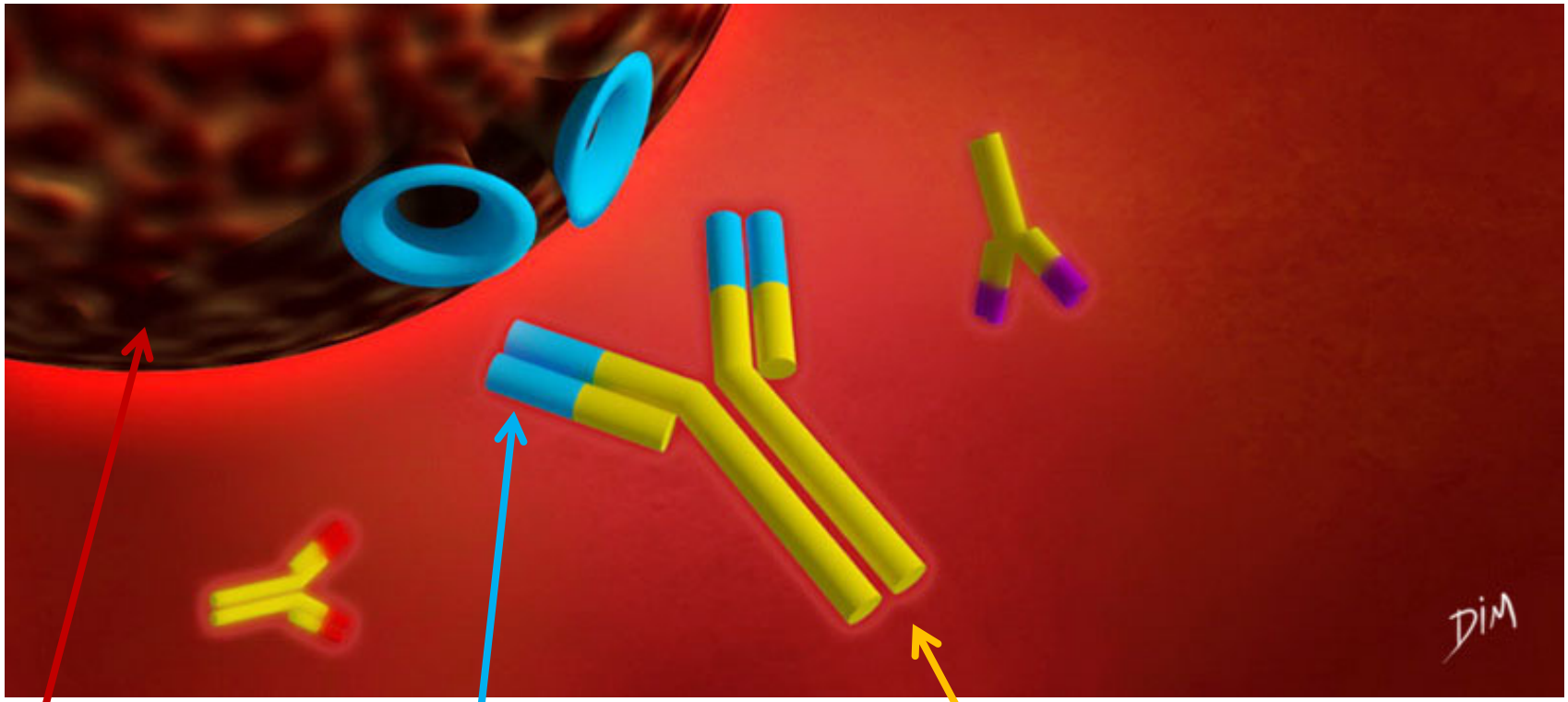


Antigen = something in your blood that is perceived by your immune system as "non-self". This is fixed shortly after you are born.

Virus, microbe, cancer cell, amyloid (possibly)

Antigen exposure can be unintentional (i.e. staph infection) or intentional (i.e. immunization, antibody production).

We will focus on active and passive immunotherapy approaches that generate antibodies against AD targets.



Antigen

Targeting part (binds)

Signaling part (recruits immune system)

Antibody Therapy

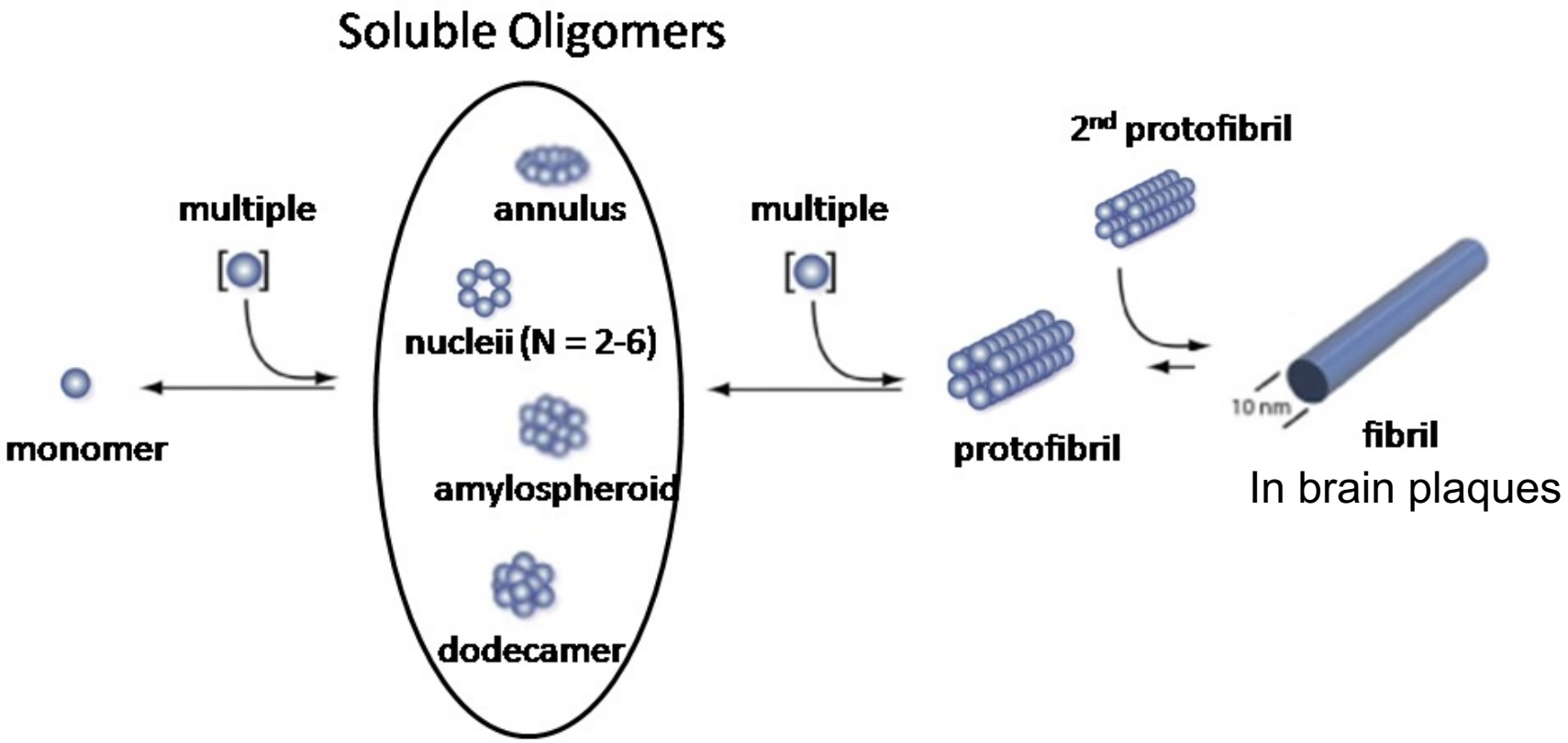
Therapeutic antibody

Target cell/molecule (antigen)

Binding

Target elimination

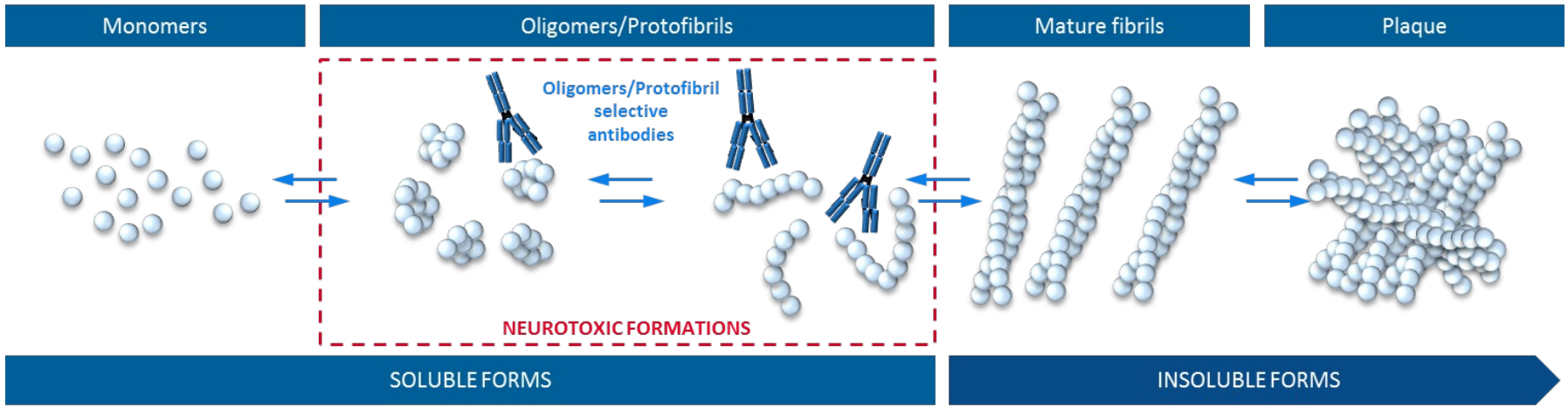
Added Complications to the Amyloid Hypothesis



In brain plaques

Also toxic and might cause trouble.

Different antibodies drugs target different amyloid species



Bapineuzumab (1st passive)

IVIG (Octagam, Gammagard)

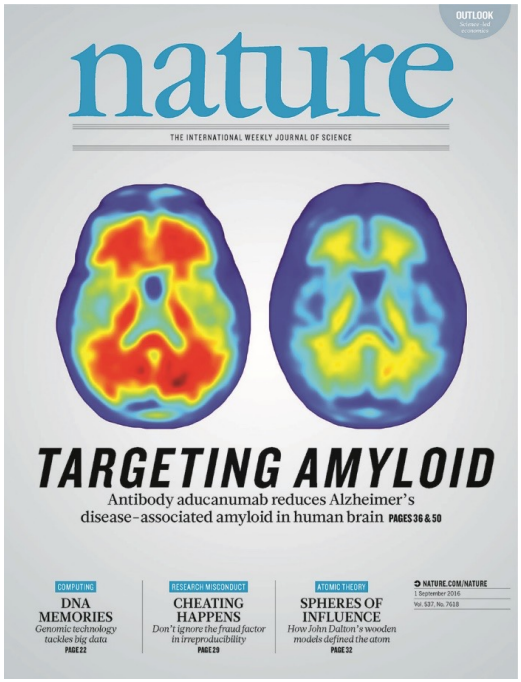
Solanezumab (human m266), Crenezumab

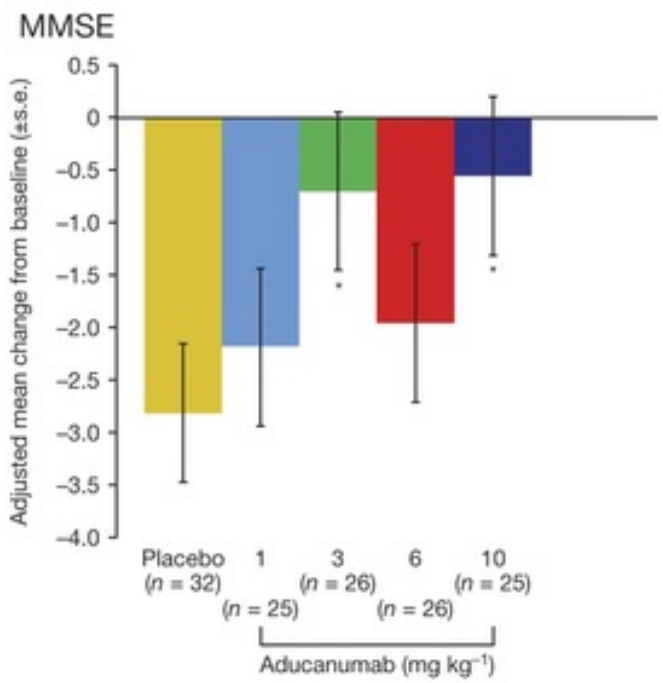
Gantenerumab, Aduhelm

Lecanemab

None has met clinical endpoints in most recently completed Phase 2 or 3 trial.

Controversial drug Aduhelm (Aducanumab)





Sevigny et. Al. (2016), Nature, **537**, 50-56.

In Phase I, Aduhelm reduced beta-amyloid and slowed Alzheimer's at higher doses (2014).

Then 2 Big "Phase 3" (4000 subject) studies were begun.

First Trial reported in and showed no significant effect.

BIOGEN AND EISAI TO DISCONTINUE PHASE 3 ENGAGE AND EMERGE TRIALS OF ADUCANUMAB IN ALZHEIMER'S DISEASE

March 21, 2019 at 7:00 AM EDT

Analysis of the second trial showed a 22% reduction in cognitive decline.

24 Oct 2019

On October 22, Biogen stunned the Alzheimer's field by announcing that aducanumab—presumed dead last March after failing a futility analysis—appears to have worked in one of its two Phase 3 trials, after all. Based on the results of a new analysis, and interactions with the Food and Drug Administration, Biogen will file for regulatory approval in early 2020.

Aduhelm's checkered history in Alzheimer's disease

CLINICAL TRIALS ARENA

But wait! The story continues….

New York Times 9/27/22

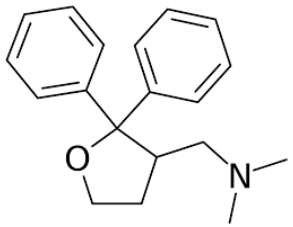
Alzheimer's Drug Slows Cognitive Decline in Key Study

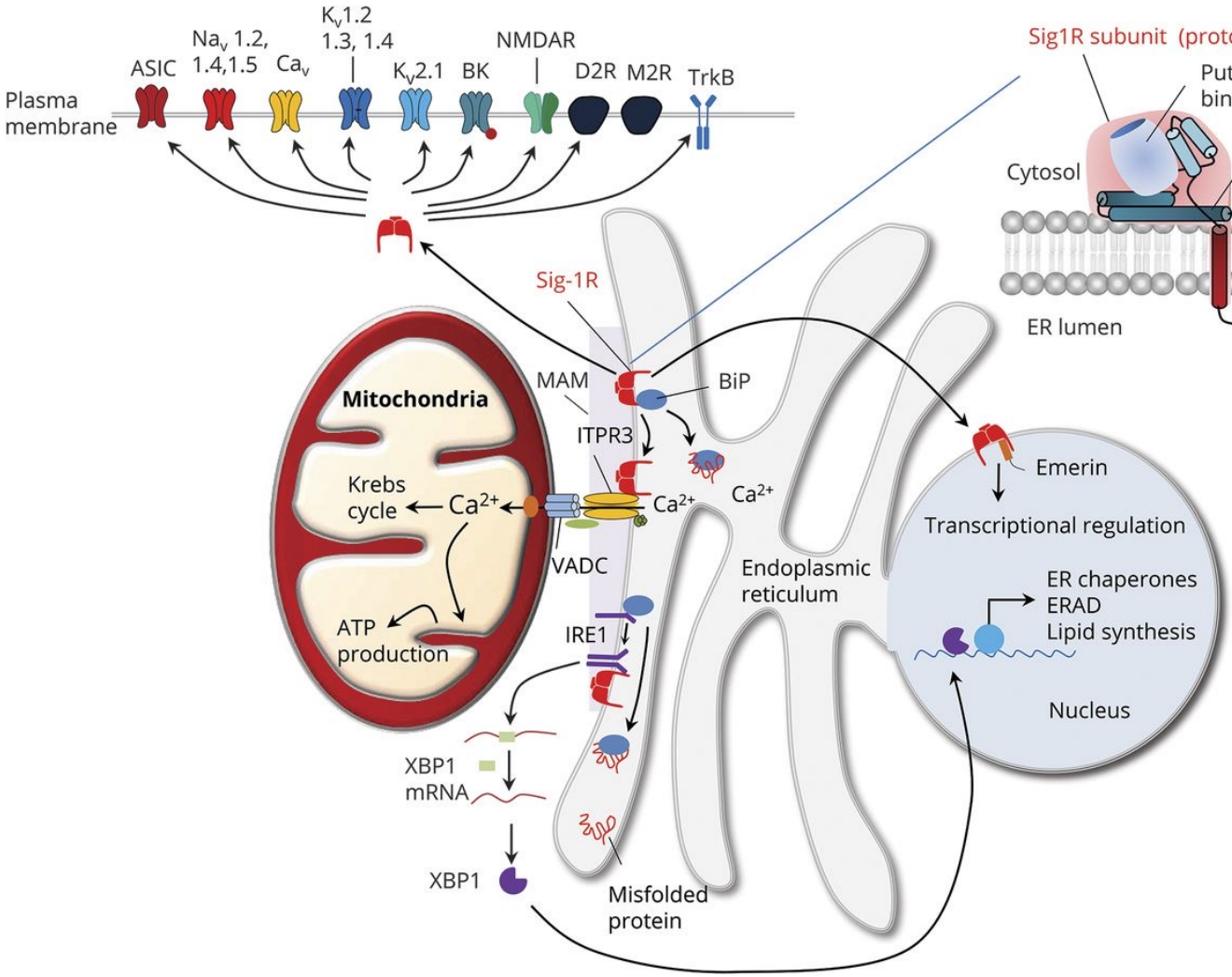
Biogen and Eisai reported the finding from a large late-stage clinical trial of lecanemab, a drug they are developing.

27% reduction in clinical trial completed in Fall 2022.

FDA approval in January 2023

Other Alzheimer's drugs in Phase III: ANAVEX2-73





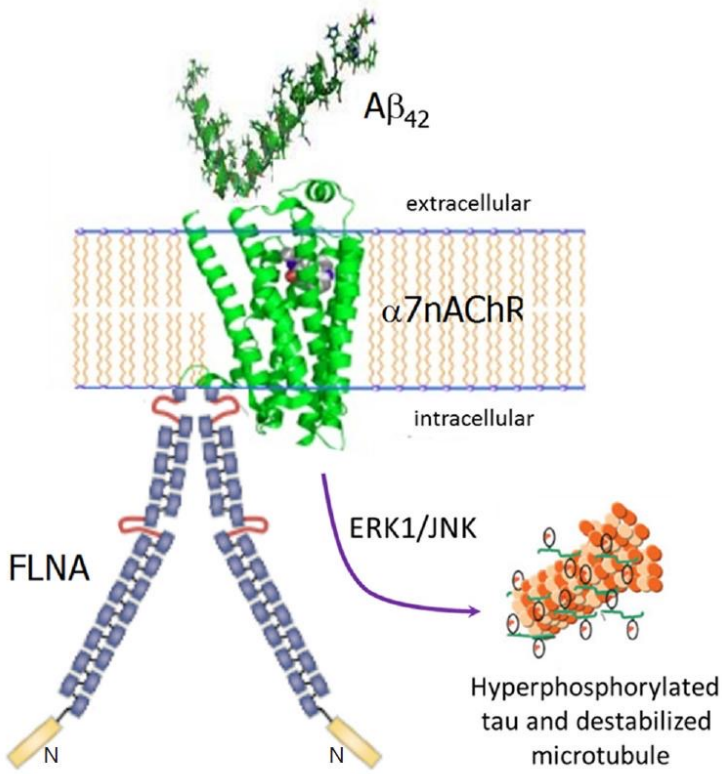
Binds Sigma 1 Receptor (similar to Aricept)

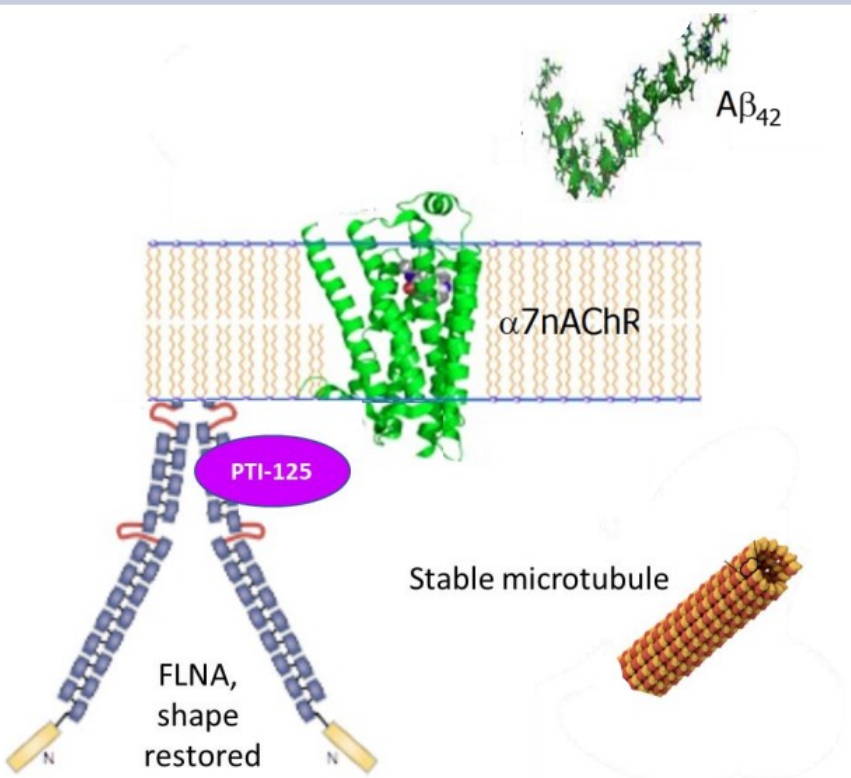
Helps distressed cells survive.

Leads to reduced amyloid production.

PTI-125/Simufilam (Cassava Biosciences)

Blocks toxic effect of beta-amyloid





Phase II - Reduced decline in mild AD, not in moderate AD.

No placebo group (a relatively small open label study)

Like it or not, Alzheimer's drugs targeting amyloid species will likely be in the pipeline for some time.

The story of Sydney Farber and cancer.