# Crossing the Line: The Challenges & Controversies in Finding a Cure for Alzheimers

Danielle Morgan

Literature Talk

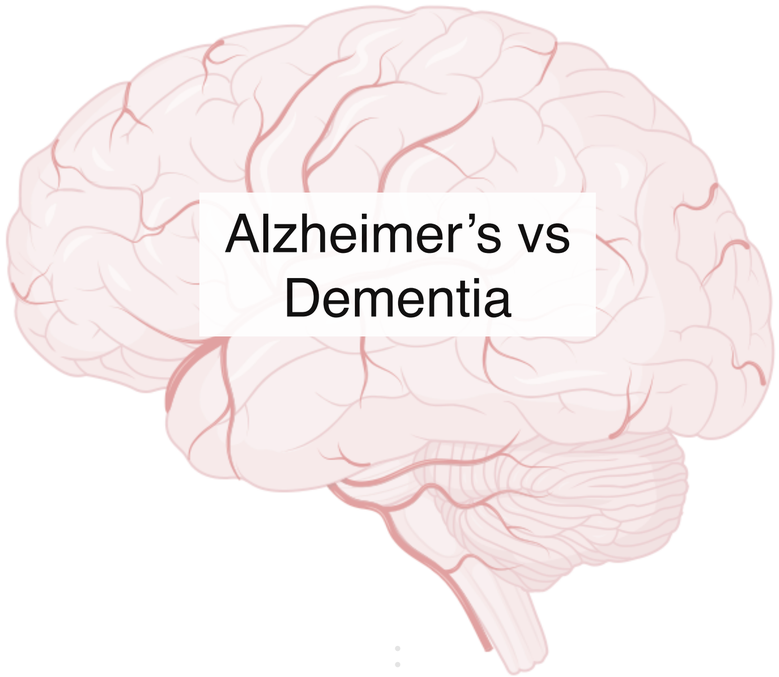
10th January, 2025

# Alzheimer’s vs Dementia

## Dementia….

cognitive **symptoms** associated with neurological diseases

e.g. memory loss, confusion etc..

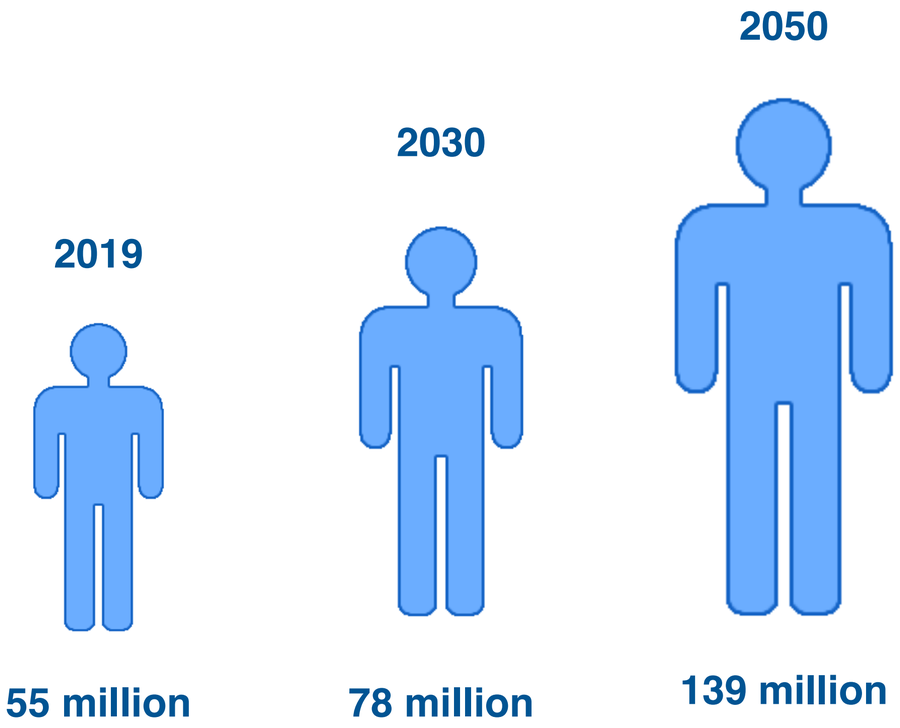



## Alzheimer’s….

specific neurological **disease** with dementia symptoms

60-80% of dementia cases are related to Alzheimer’s disease

# Global impact of Alzheimers



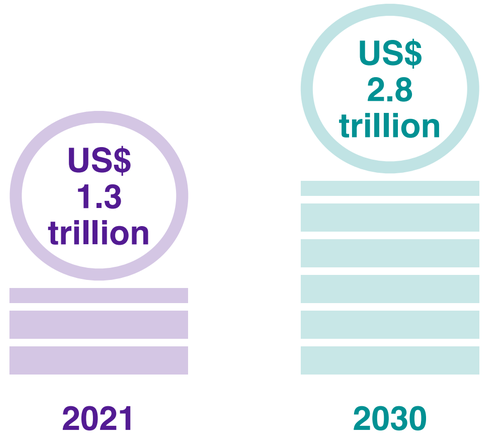

global no. of people with Alzheimer's

Medication

US - $1,000 per week

Dementia care homes

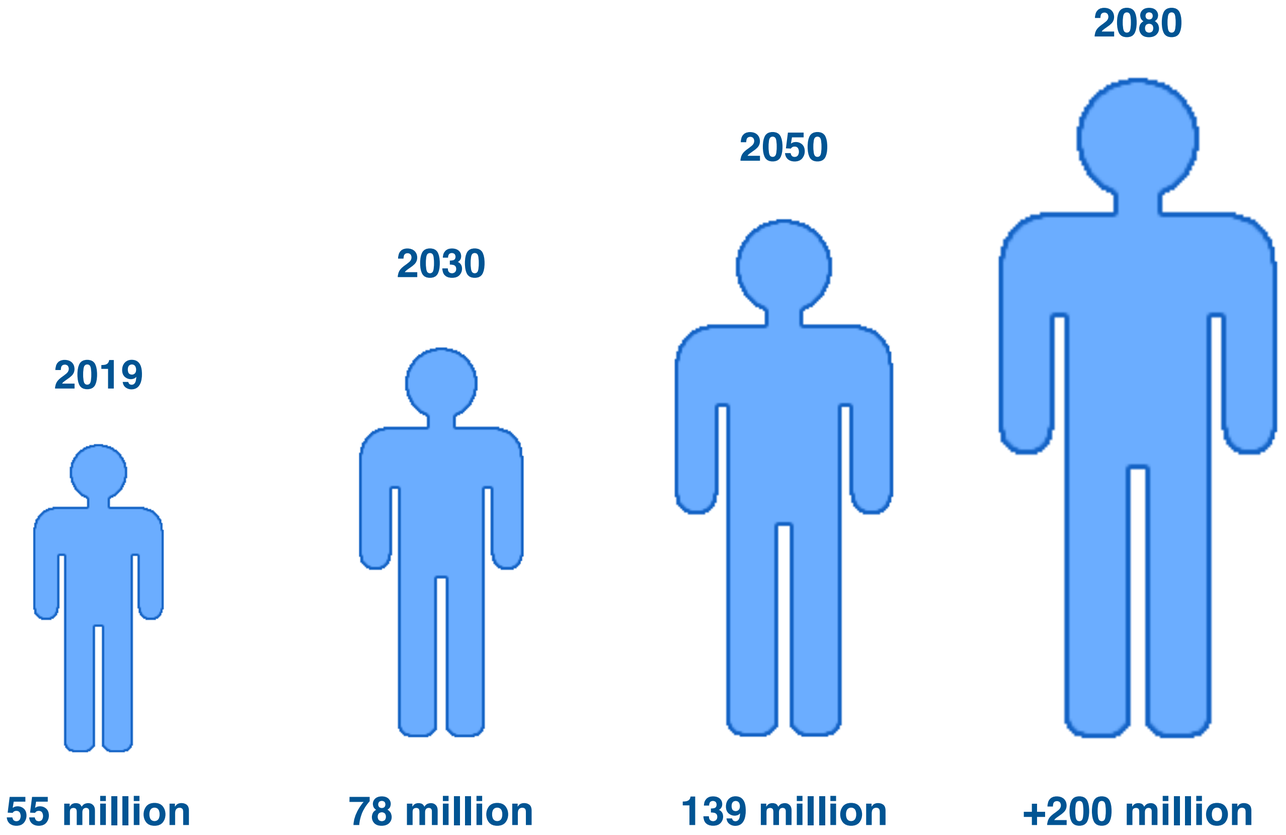
US - $2,500 per week



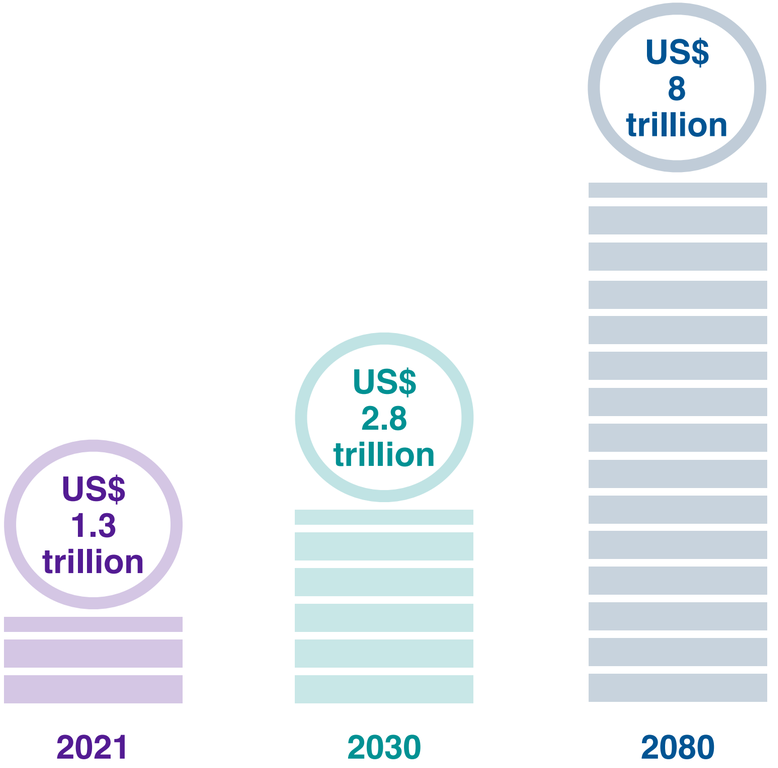

global cost of dementia

*WHO Global status report, 2021*

# Global impact of Alzheimers




global no. of people with Alzheimer's




global cost of dementia

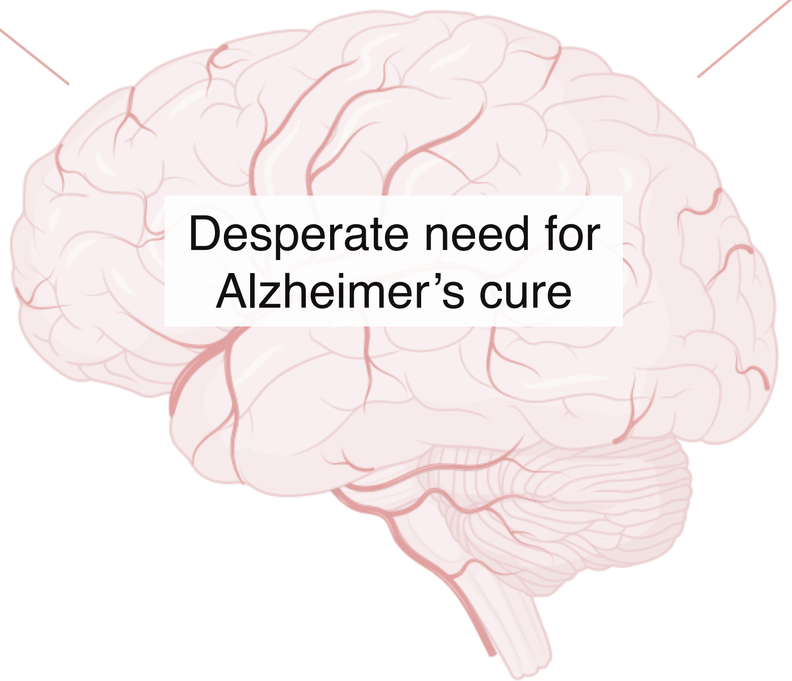
*WHO Global status report, 2021*

Only **8 FDA-approved** Alzheimer’s drugs

(mildly manage symptoms)

**NIH - US$3.98 billion** budget for 2026 funding

**Extremely expensive** for Pharma companies to bring drugs to market



Desperate need for Alzheimer’s cure

**Failure rate** of Alzheimer's drugs in clinical trials is ~ **99%**

(**1906 - now**)

**No cure** for Alzheimer’s - only treatments for symptoms

# Talk outline

**Part I**

- History of Alzheimer’s - Alois Alzheimer
- Alzheimer’s disease causing hypotheses

**Part II**

- Alzheimer’s drug treatment strategies
- Clinical case studies (controversial FDA approvals)

**Part III**

- Outlook & future directions - how are Pharma companies tackling Alzheimer’s

# History of Alzheimers - Alois Alzheimer

**Alois Alzheimer**

(1864 – 1915)

Bavaria

**1901**

Auguste died

**1906**

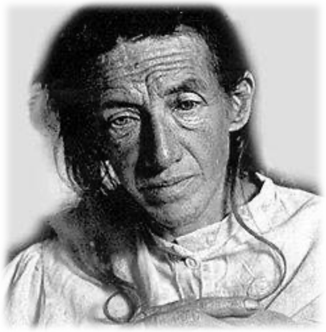
medical conference

**1907**

Aβ plaques & Tau tangles widely accepted

**mid-1900s**

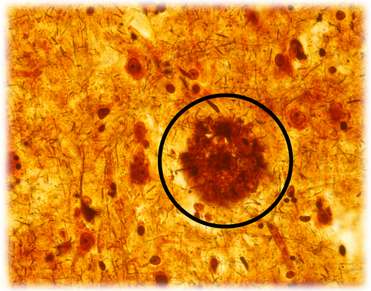
**present day**

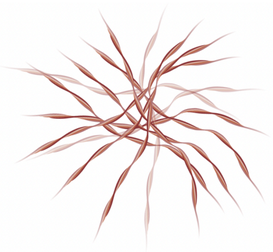


**Auguste Deter**

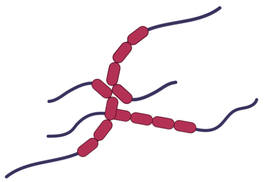
**observations:** memory loss, confusion, and behavioral changes

**postmortem:** “unusual plaques & tangles in the brain tissue”



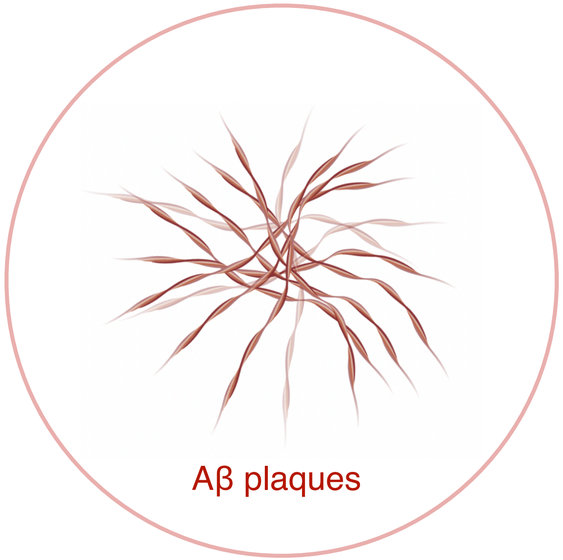


Aβ plaques



Tau tangles

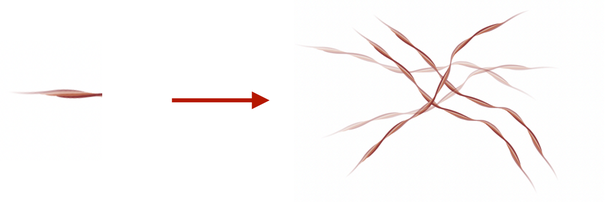
# Amyloid Beta (Aβ) & Tau tangles hypotheses



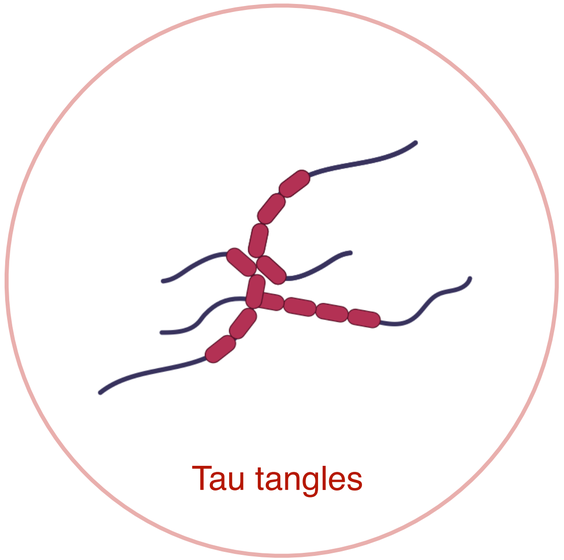
Aβ plaques

**Aβ**

(DAEFRHDSGYEVHHQKLVFFAEDVGSNKGAIIGLMVGGVV)

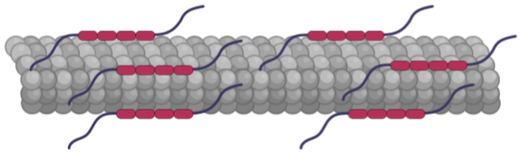


Aβ peptides aggregate



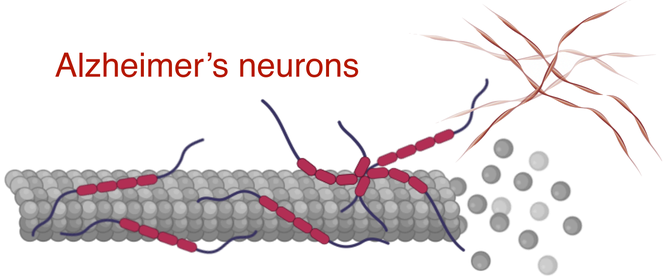
Tau tangles

healthy neurons



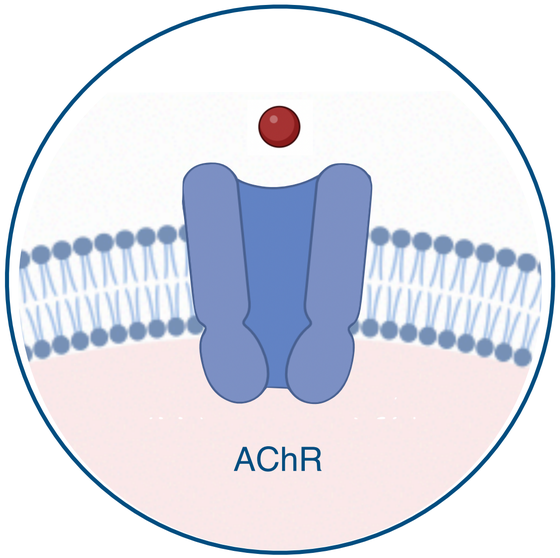
microtubules

Alzheimer’s neurons



blocks neuronal signals/functions

# Cholinergic hypothesis

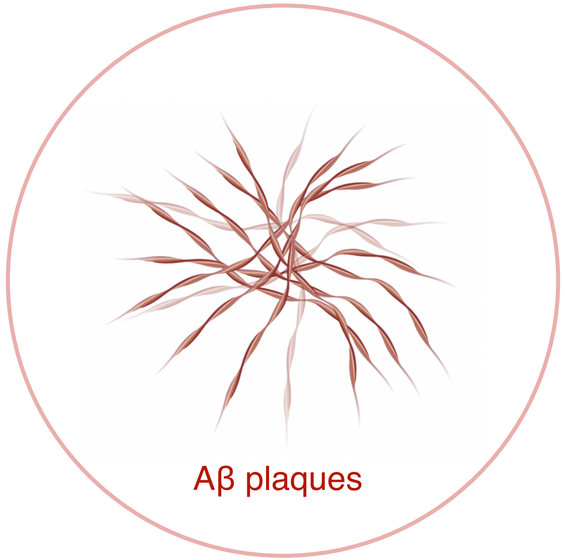



**1970s**

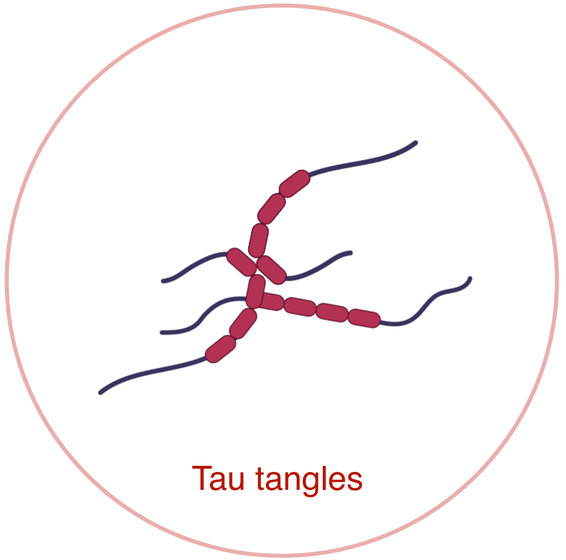
reduced synthesis of acetylcholine in AD patients

reduces neuronal signals/functions

# Amyloid Beta (Aβ) & Tau tangles hypotheses



Aβ plaques



Tau tangles

**Aβ**

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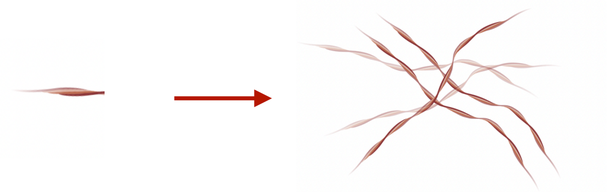

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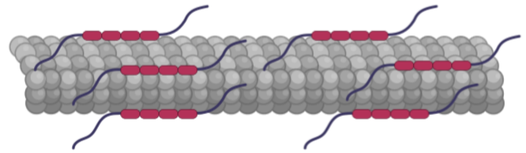
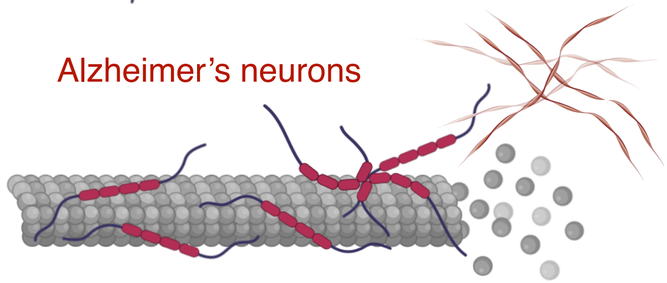


microtubules

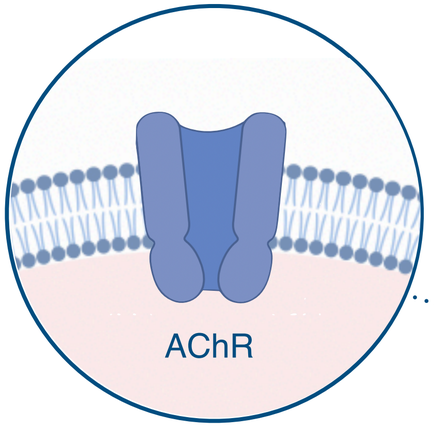
Alzheimer’s neurons

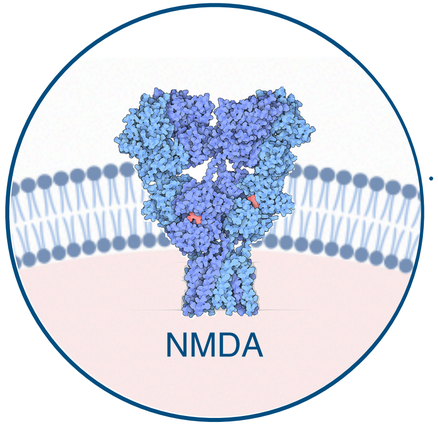


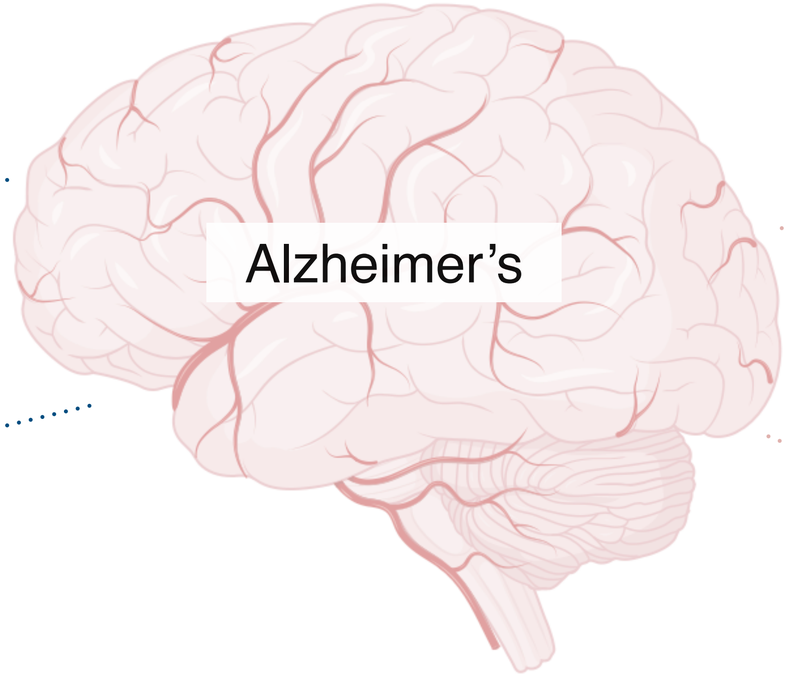
blocks neuronal signals/functions

# Alzheimers treatments & cures

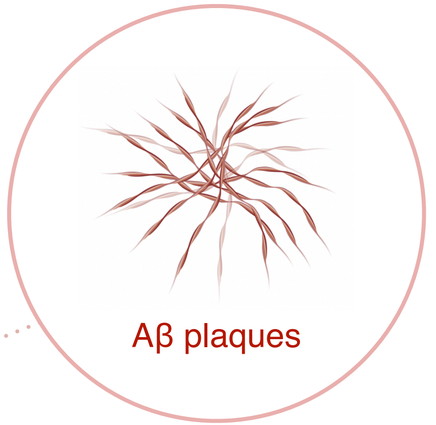
## Cognitive symptom management

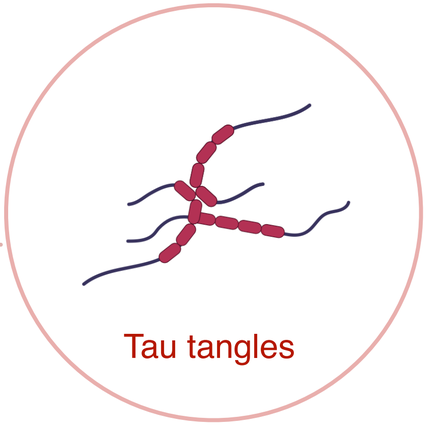


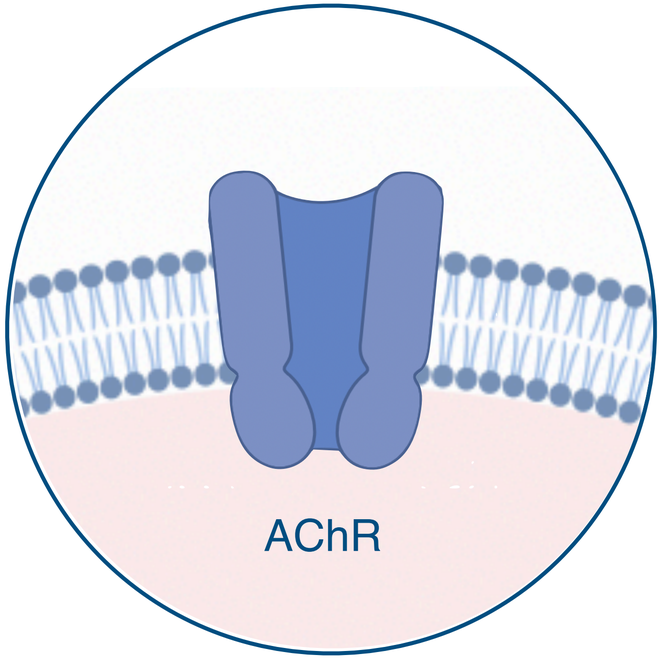




## Disease-modifying treatments (DMTs)



# Alzheimers treatments & cures



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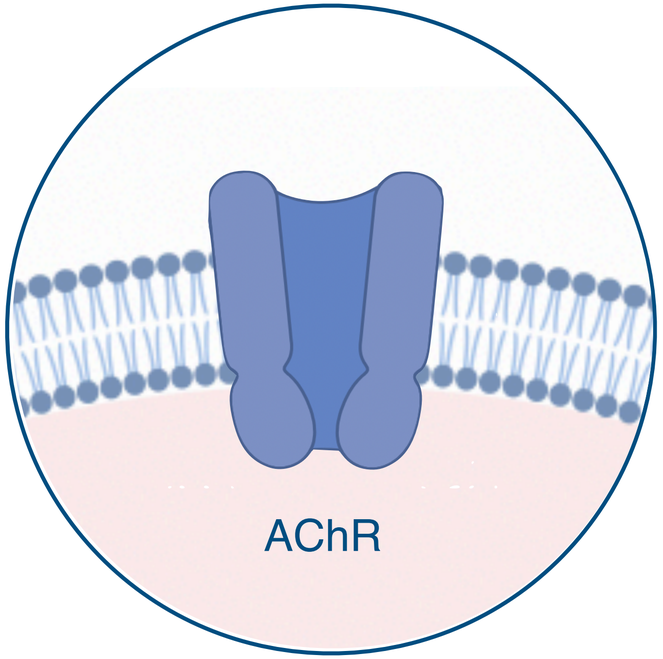
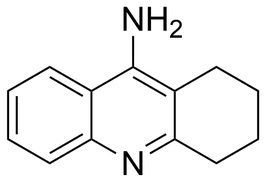



**1993 - 2003**
treating dementia symptoms

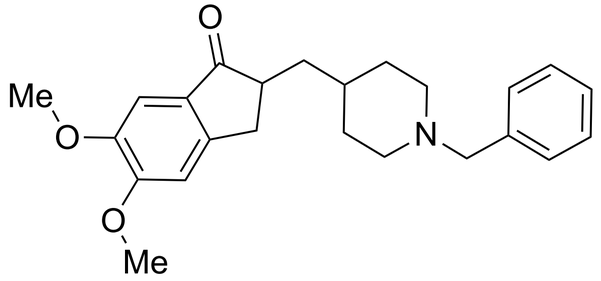
## Cholinesterase Inhibitors (1990s)

manages cognitive decline

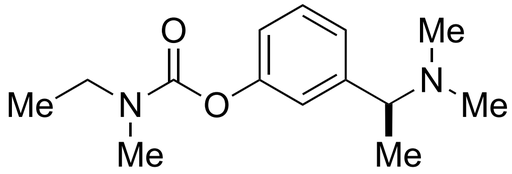
increase levels of acetylcholine (neurotransmitter) deficient in Alzheimer's patients



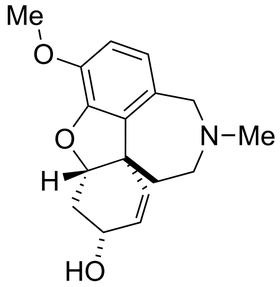

**Tacrine (Cognex) - 1993**




**Donepezil (Aricept) - 1996**



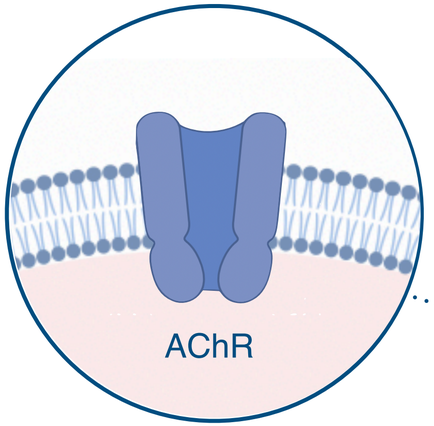

**Rivastigmine (Exelon) - 2000**

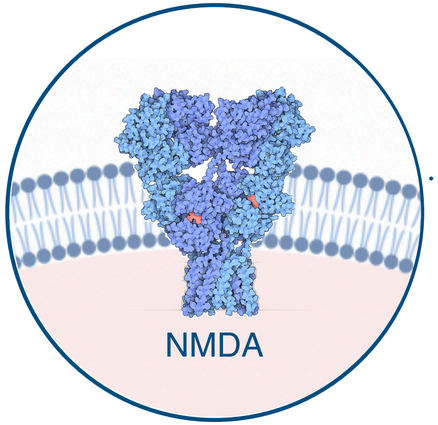


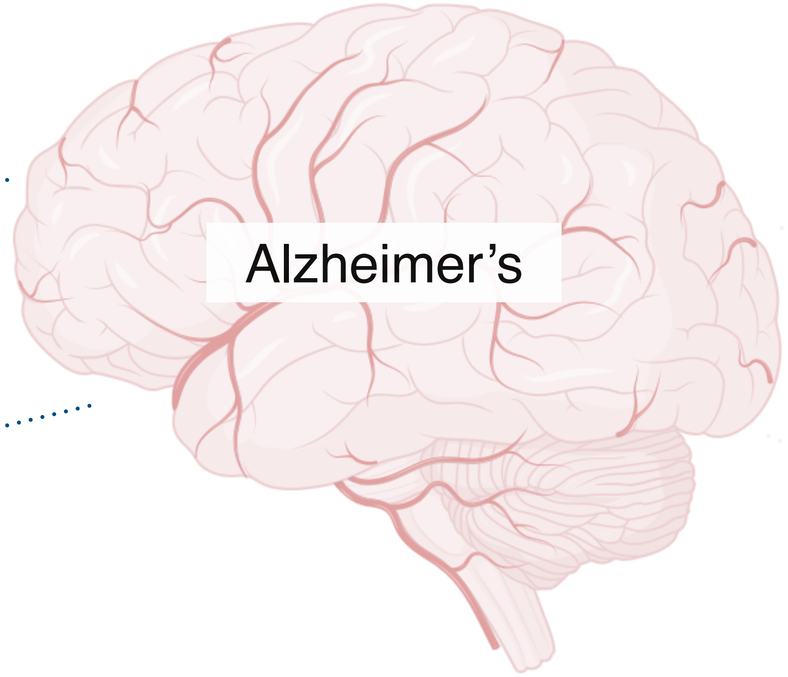

**Galantamine (Razadyne) - 2001**

# Alzheimers treatments & cures

Cognitive symptom management




Disease-modifying treatments (DMTs)







**1993 - 2003**
treating dementia symptoms

→ treatments/cures for Alzheimer’s disease needed

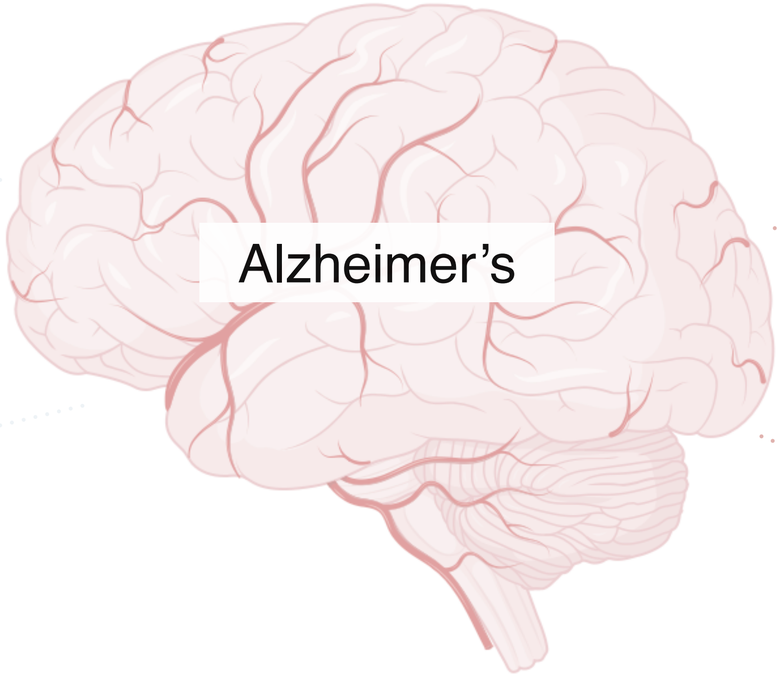
# Alzheimers treatments & cures

Cognitive symptom management

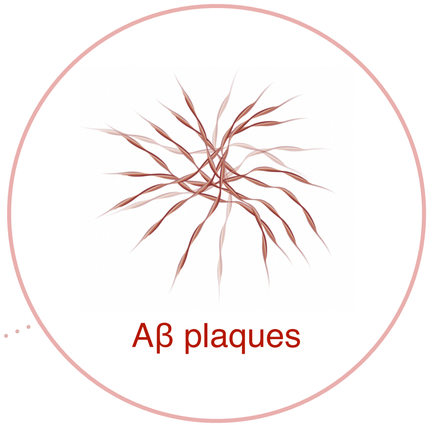


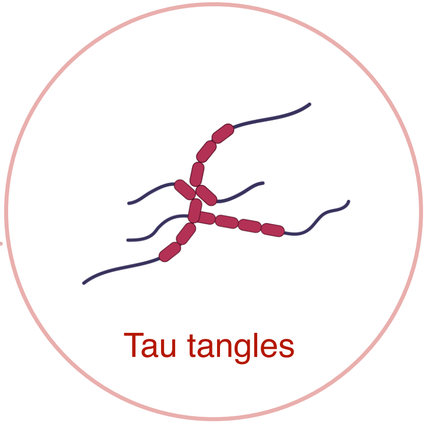







Disease-modifying treatments (DMTs)

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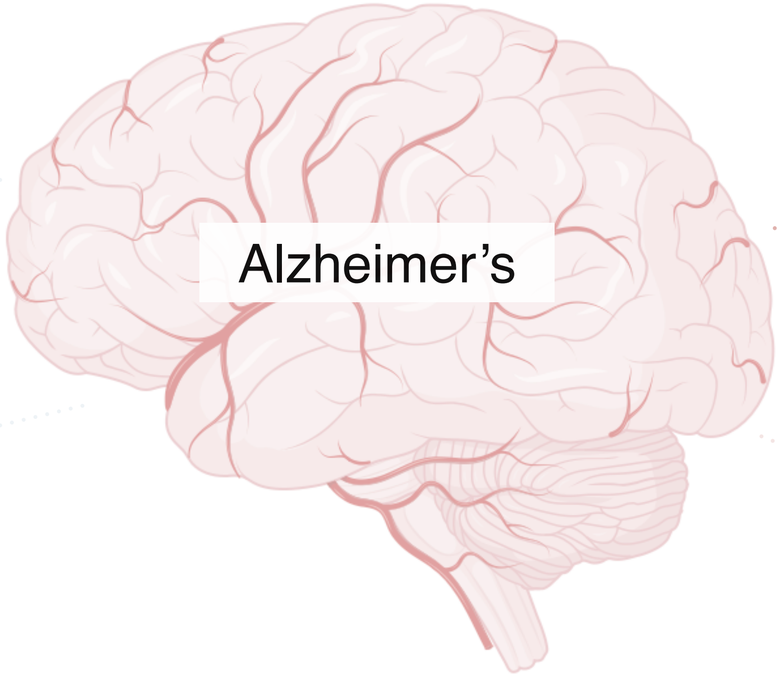


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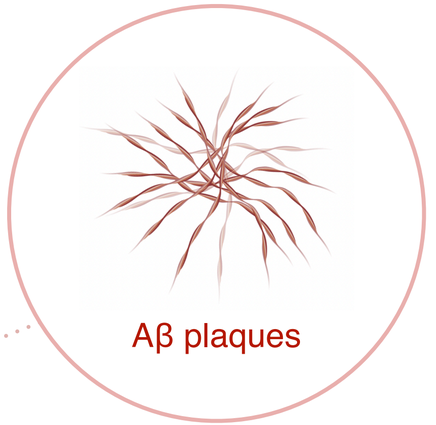
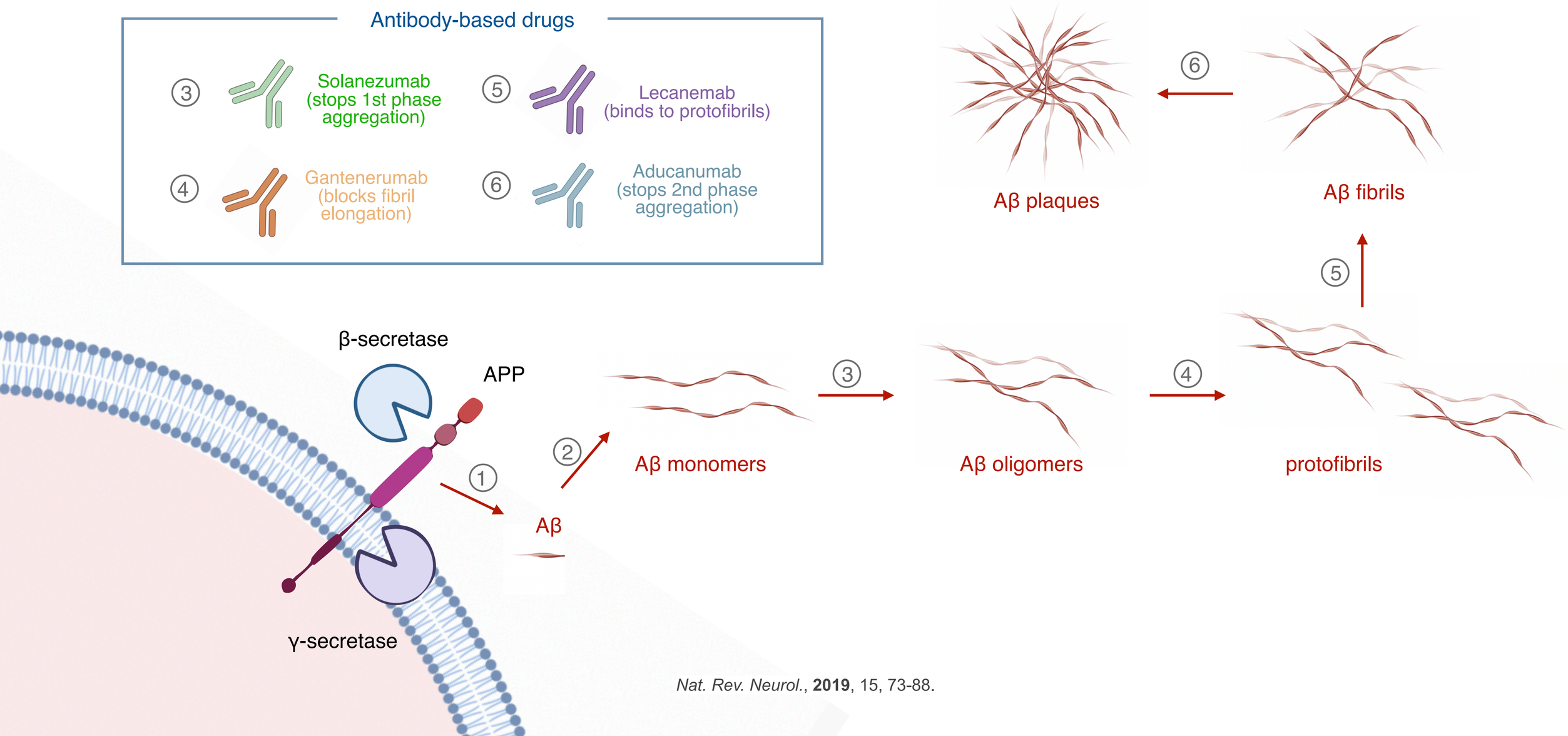
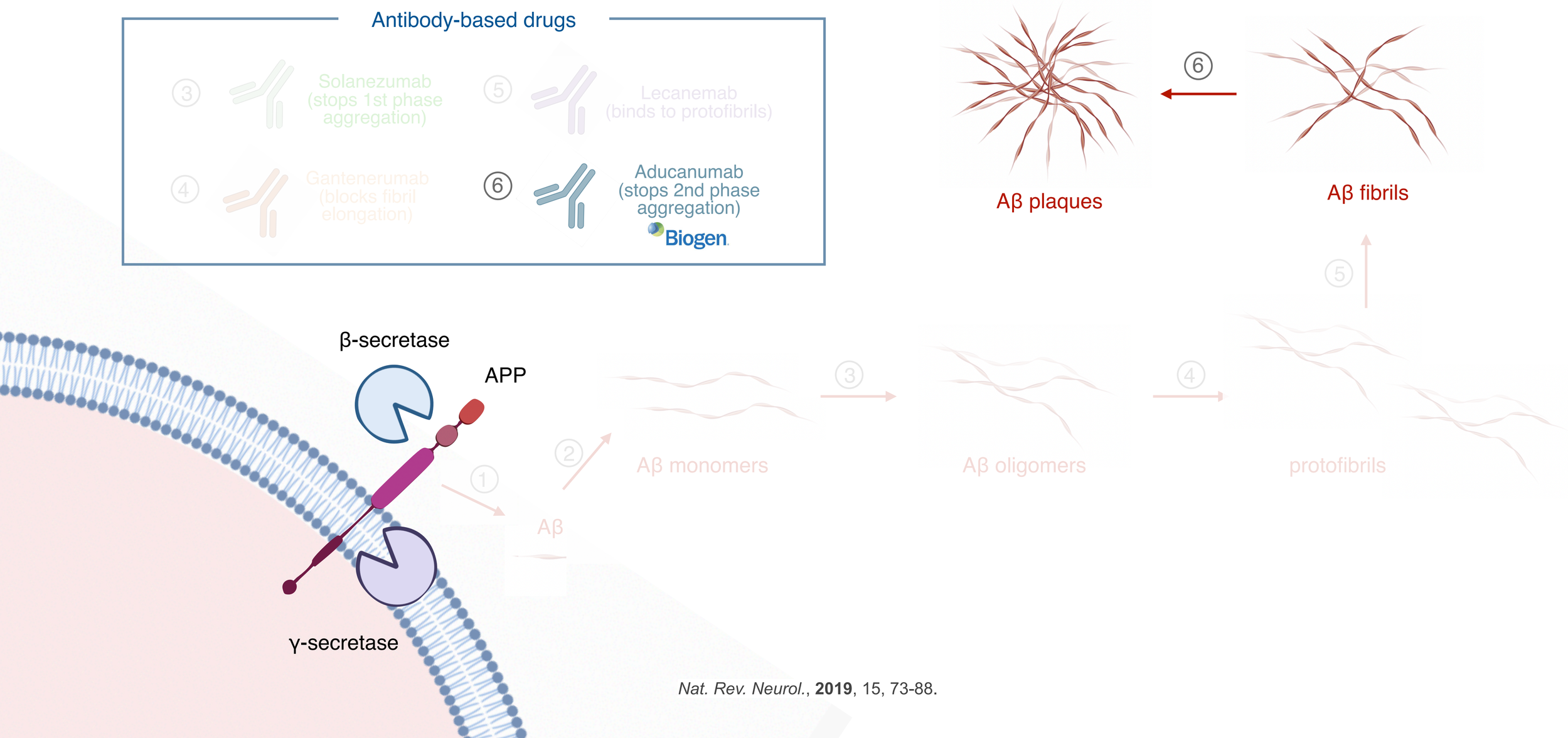


# Alzheimers treatments & cures - Aβ plaques



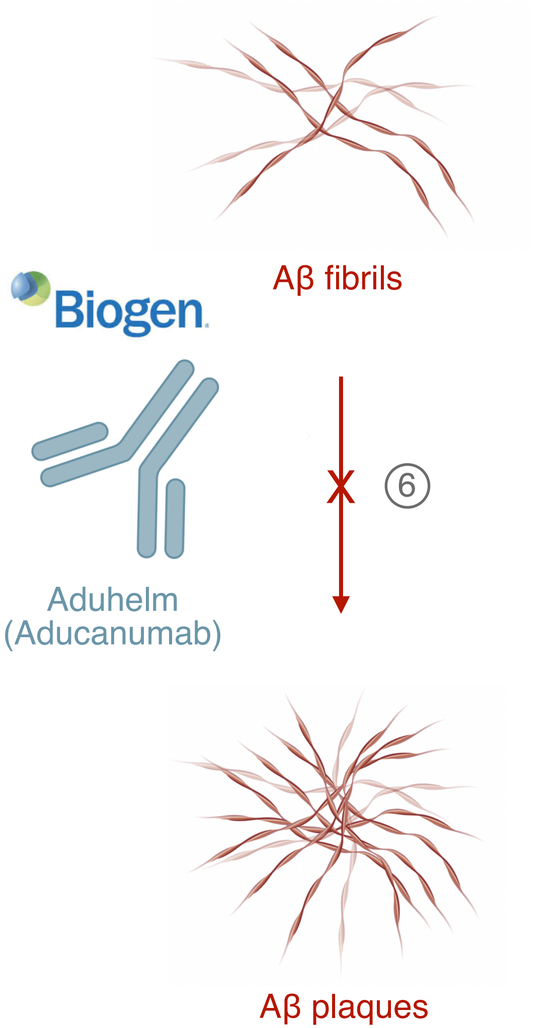

*Nat. Rev. Neurol.*, **2019**, 15, 73-88.

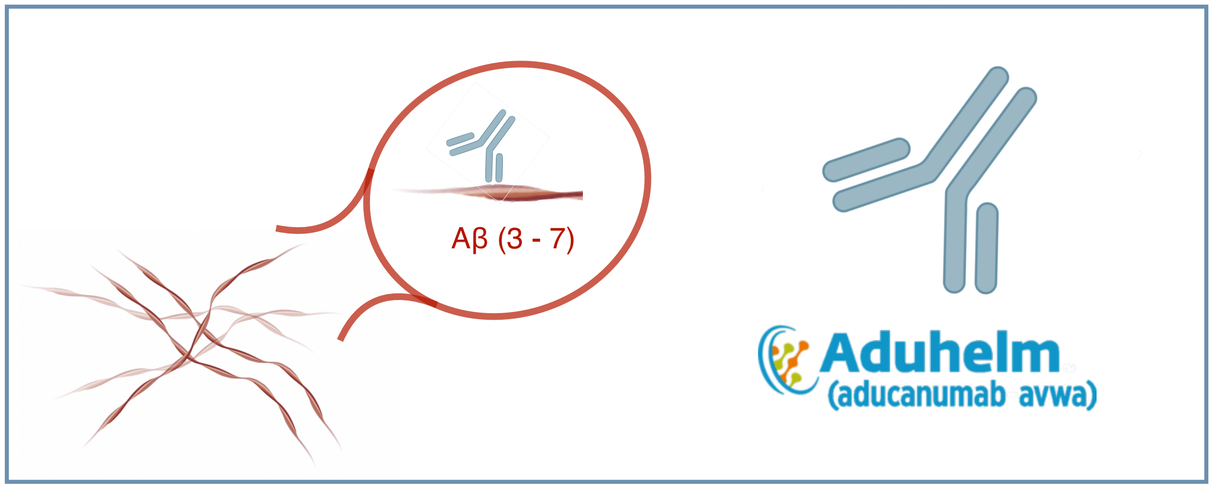
# Alzheimers treatments & cures - Aβ plaques




*Nat. Rev. Neurol.*, **2019**, 15, 73-88.

# Case study - Aducanumab (Aduhelm)




monoclonal AB - FDA approved in 2021

Biogen

- 1st Alzheimer's drug approved in **18 years**
- 1st **disease-modifying** Alzheimer's drug

Predicted to be best-selling drug of all time
($10 billion by 2028)

*Nature*, **2016**, 537, 50-56.

# Case study - Aducanumab (Aduhelm)


Predicted to be best-selling drug of all time
($10 billion by 2028)

# Case study - Aducanumab (Aduhelm)

"FDA Approves Alzheimer’s Drug Aduhelm, the First New Treatment for Disease in Nearly Two Decades"

*The New York Times* (June 2021)

The New York Times

"FDA Approves Aduhelm, First Drug to Target the Root Cause of Alzheimer's"

*Reuters (June 2021)*

REUTERS

"FDA Approval of Aduhelm: A Step Toward Changing the Course of Alzheimer's"

*Washington Post* (June 2021)

The Washington Post

"Aduhelm's Approval Marks Historic Milestone for Alzheimer's Disease"

*NBC News (June 2021)*

NBC NEWS

"Aduhelm Approval Offers New Hope for Alzheimer's Patients"

*CNN (June 2021)*

CNN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# Case study - Aducanumab (Aduhelm)

"FDA Approval of Aduhelm Draws Criticism for Lack of Solid Evidence"

*The New York Times* (June 2021)

The New York Times

"FDA's Approval of Aduhelm Sparks Legal Action and Calls for Reassessment"

*Politico (June 2021)*

POLITICO

"FDA's Approval of Aduhelm Raises Concerns Among Experts"

*The Wall Street Journal* (June 2021)

THE WALL STREET JOURNAL.

"Aduhelm Approval: Growing Rejection Among Medical Community"

*BBC News (June 2021)*

BBC

"Alzheimer's Drug Aduhelm Faces Strong Backlash From Medical Experts"

*The Guardian (June 2021)*

The Guardian

"FDA's Approval of Aduhelm Stirs Concerns Over High Cost and Effectiveness"

*NBC News (June 2021)*

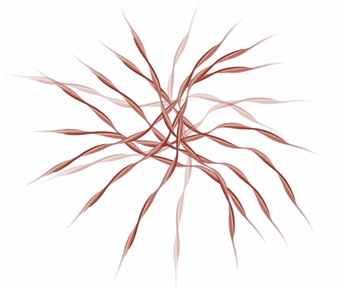
NBC NEWS

# Case study - Aducanumab (Aduhelm)

Aβ fibrils

Biogen

Aduhelm
(Aducanumab)

Aβ plaques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- 1st Alzheimer's drug approved in **18 years**
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absence of evidence in clinical trials that the medication was effective

3 FDA advisers resigned

# Case study - Aducanumab (Aduhelm)

The New York Times

## *Three F.D.A. Advisers Resign Over Agency's Approval of Alzheimer's Drug*

The drug, Aduhelm, a monthly infusion priced at $56,000 per year, was approved this week despite weak evidence that it helps patients.

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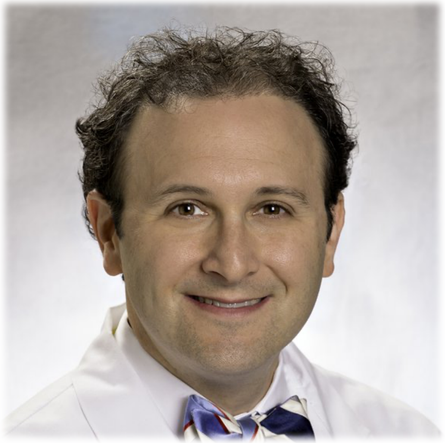
Dr. Aaron Kesselheim, who resigned this week from an F.D.A. advisory committee, speaking at a panel in 2018. "This might be the worst approval decision that the F.D.A. has made that I can remember," he said Thursday. Scott Eisen/Associated Press

By Pam Belluck and Rebecca Robbins

Published June 10, 2021 Updated Sept. 2, 2021

**Prof. Aaron Kesselheim - Harvard**

Harvard - undergraduate 1996
University of Pennsylvania Medicine - M.D. 2002
University of Pennsylvania Law School - J.D. 2002
Harvard - M.P.H. 2007



# Case study - Aducanumab (Aduhelm)

**PORTAL**
**Program On Regulation, Therapeutics, And Law**

**Division of Pharmacoepidemiology and Pharmacoeconomics**
**Harvard Medical School and Brigham & Women's Hospital**
*Aaron S. Kesselheim, M.D., J.D., M.P.H., Director*
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June 10, 2021

Dear Acting Commissioner of Food and Drugs Janet Woodcock, M.D.,

I am hereby resigning from the FDA's Peripheral and Central Nervous System Advisory Committee. I was honored to have served the Committee since 2015 because I believed in the value of Advisory Committees to provide a way for outside experts to provide science-based guidance to the agency on its drug approval decisions. But after my experience on this Advisory Committee for both the eteplirsen and now the aducanumab discussions, it is clear to me that FDA is not presently capable of adequately integrating the Committee's scientific recommendations into its approval decisions.

With eteplirsen, the AdComm and FDA's own scientific staff reported that there was no convincing evidence that the drug worked; both groups were overruled by FDA leadership, which approved the drug based on considerations (including concerns about the sponsor's finances) that were not part of the Advisory Committee's discussions. This week, the aducanumab decision by FDA administrators was probably the worst drug approval decision in recent U.S. history. At the last minute, the agency switched its review to the Accelerated Approval pathway based on the debatable premise that the drug's effect on brain amyloid was likely to help patients with Alzheimer's disease. But this pivotal question was not discussed at the Advisory Committee meeting, and its premise was specifically excluded from discussion, as the FDA said: "We're not using the amyloid as a surrogate for efficacy." At our public meeting, concerns about trial data from one of the FDA's own reviewers were not given adequate time for discussion, and some of the questions FDA asked the Committee to answer were worded in a way that seemed slanted to yield responses that would favor the drug's approval.

For both eteplirsen and aducanumab, the decisions by FDA administrators to ignore the Advisory Committee's clear recommendations led to their approval of two highly problematic drugs that offered little evidence that they would meaningfully benefit patients suffering from these devastating conditions. This will undermine the care of these patients, public trust in the FDA, the pursuit of useful therapeutic innovation, and the affordability of the health care system.

For these reasons, I feel I can no longer make a useful contribution as a member of this Advisory Committee. The aducanumab and eteplirsen debacles demonstrate that the agency needs to reassess its decision-making processes, including how drug candidates are selected for AdComm review, which questions are put to the Committee and how those questions are worded, how anecdotal patient experience with drugs is presented to the committee, and how Committee recommendations are used (or ignored) by FDA officials. When clear AdComm recommendations against a drug are overruled by FDA administrators, as occurred in both these instances, the agency owes it to the nation to provide a detailed justification.

In the future, reforms in these areas could allow outside experts to be better able to provide meaningful input into the FDA approval process. Should this occur, I would look forward to the possibility of rejoining a committee if and when it becomes clear that our input as experts will be fairly sought and help support appropriate decision-making that is truly in patients' best interests.

Sincerely,

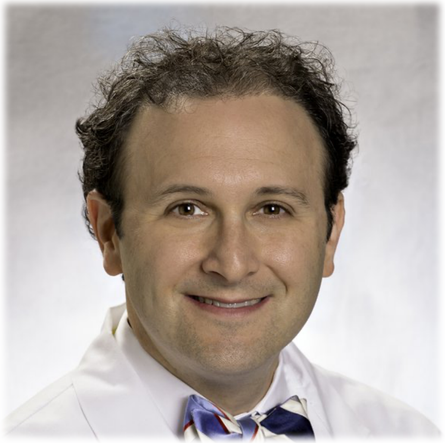
Aaron S. Kesselheim, M.D., J.D., M.P.H.
Professor of Medicine, Brigham and Women's Hospital/Harvard Medical School

Cc: Nathan Fountain, Xavier Becerra

"…the aducanumab decision by FDA administrators was probably the **worst drug approval decision** in recent U.S. history…"

**Prof. Aaron Kesselheim - Harvard**

Harvard - undergraduate 1996
University of Pennsylvania Medicine - M.D. 2002
University of Pennsylvania Law School - J.D. 2002
Harvard - M.P.H. 2007



# Case study - Aducanumab (Aduhelm)


**Prof. Aaron Kesselheim - Harvard**

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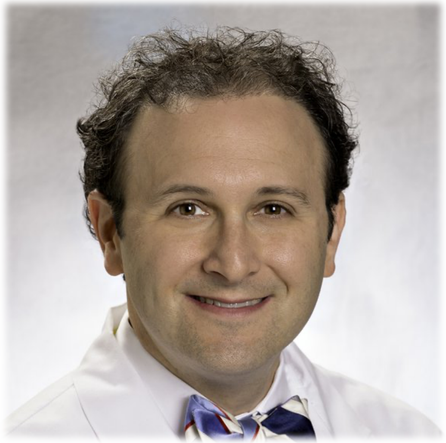
University of Pennsylvania Medicine - M.D. 2002
University of Pennsylvania Law School - J.D. 2002
Harvard - M.P.H. 2007



# Case study - Aducanumab (Aduhelm)

The New York Times

## *Three F.D.A. Advisers Resign Over Agency's Approval of Alzheimer's Drug*

The drug, Aduhelm, a monthly infusion priced at $56,000 per year, was approved this week despite weak evidence that it helps patients.

Share full article 64


Dr. Aaron Kesselheim, who resigned this week from an F.D.A. advisory committee, speaking at a panel in 2018. "This might be the worst approval decision that the F.D.A. has made that I can remember," he said Thursday. Scott Eisen/Associated Press

By Pam Belluck and Rebecca Robbins

Published June 10, 2021 Updated Sept. 2, 2021

**Prof. Aaron Kesselheim - Harvard**

"…the aducanumab decision by FDA administrators was probably the **worst drug approval decision** in recent U.S. history…"

**David Knopman, M.D. - Mayo Clinic neurologist**

"…disappointed at how the advisory committee input was treated by the FDA…"

**Joel Perlmutter, M.D. - Washington University neurologist**

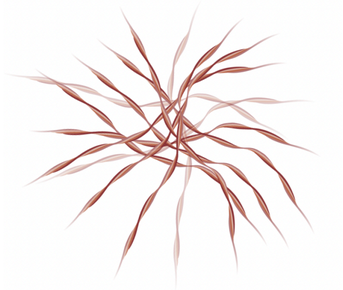
"…ruling by the FDA without further discussion with our advisory committee…"

# Case study - Aducanumab (Aduhelm)

Aβ fibrils

Biogen

Aduhelm
(Aducanumab)

Aβ plaques


phase IV confirmatory trials - 2021

**Biogen CEO Michel Vounatsos**
"…the company has up to nine years to deliver the final results…"

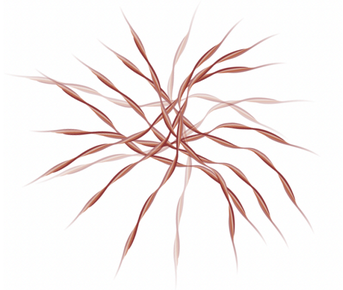
(results in 2030)

# Case study - Aducanumab (Aduhelm)

Aβ fibrils

Biogen

Aduhelm
(Aducanumab)

Aβ plaques


absence of evidence that the medication was effective

# Case study - Aducanumab (Aduhelm)


Biogen

**2015 - Phase III**

2 identical 18-month-long randomized, doubleblind, placebo-controlled, parallel-group studies (EMERGE and ENGAGE)

3,285 participants

348 sites

20 countries

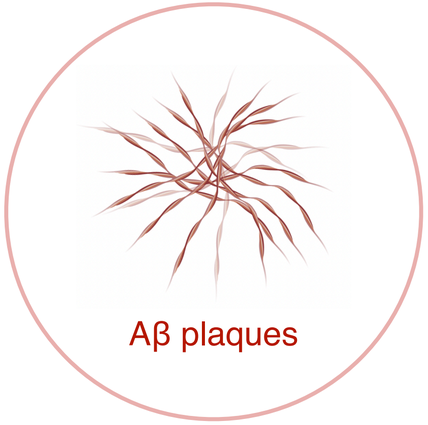
**criteria:** 50-85 years of age, had a diagnosis of early symptomatic AD and were positive for brain amyloid pathology as assessed by PET

# Case study - Aducanumab (Aduhelm)

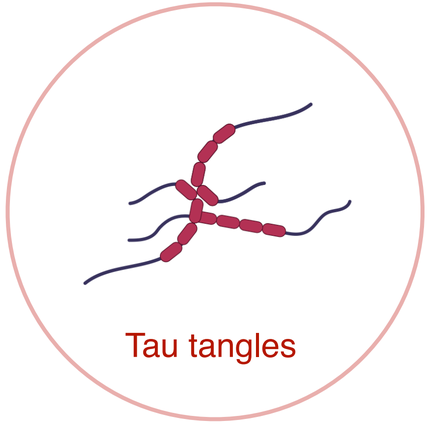

Biogen

**2015 - Phase III**

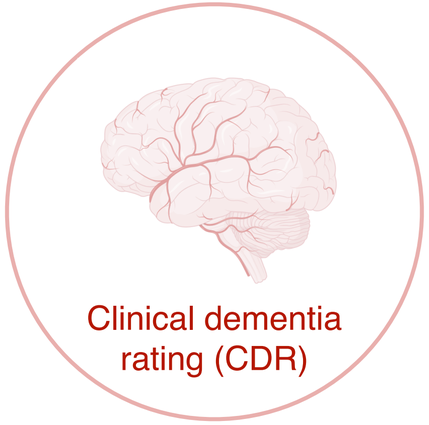
2 identical 18-month-long randomized, doubleblind, placebo-controlled, parallel-group studies (EMERGE and ENGAGE)



Aβ plaques

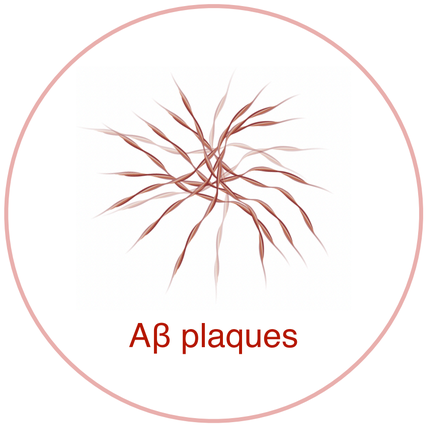


Tau tangles



Clinical dementia rating (CDR)

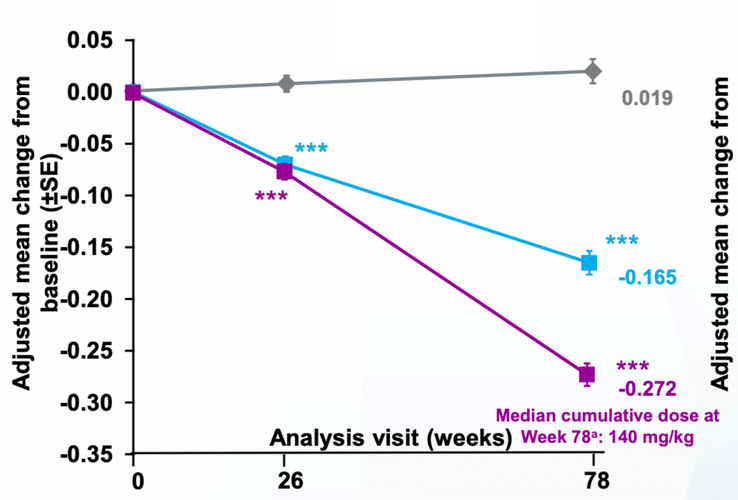
# Case study - Aducanumab (Aduhelm)

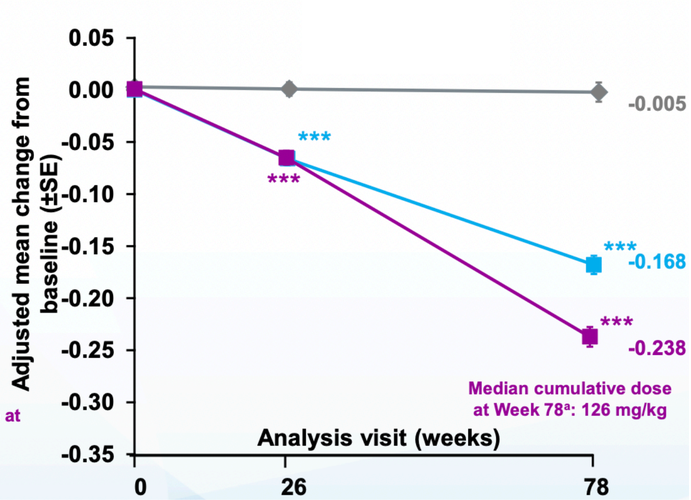

Biogen

**2015 - Phase III**

EMERGE



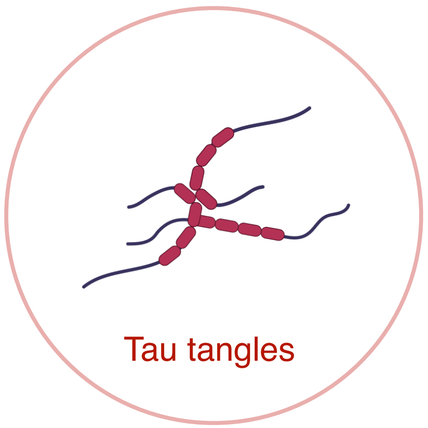

ENGAGE




Placebo
Low dose
High dose

*Biogen clinical trial data slides,* **2019**.

# Case study - Aducanumab (Aduhelm)

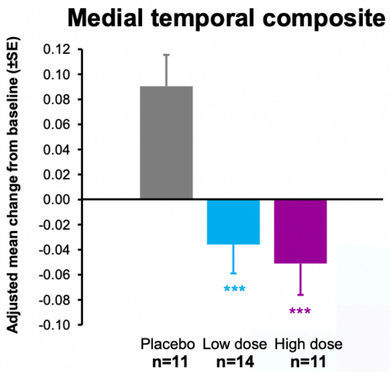




Biogen

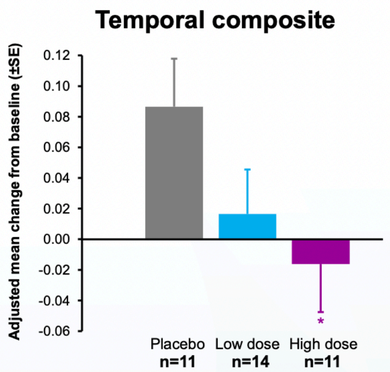
**2015 - Phase III**

EMERGE

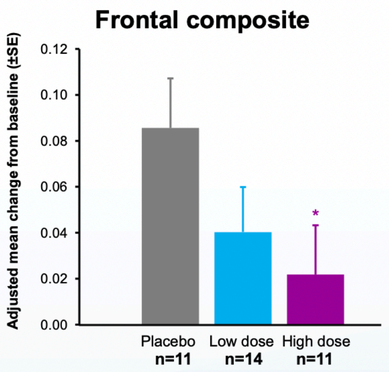
ENGAGE




HIPPOCAMPUS
PARAHIPPOCAMPAL
TEMPORAL LOBE ANTERIOR MEDIAL
(includes Entorhinal and Amygdala)
TEMPORAL LOBE ANTERIOR LATERAL




TEMPORAL LOBE Comprised of:
SUPERIOR, POSTERIOR, MIDDLE INFERIOR
POSTERIOR, SUPERIOR ANTERIOR,
FUSIFORM GYRUS




FRONTAL LOBE Comprised of:
MIDDLE, PRECENTRAL, STRAIGHT GYRUS
INFERIOR, SUPERIOR
ORBITOFRONTAL CORTEX Comprised of:
ANTERIOR, MEDIAL, LATERAL, POSTERIOR

Placebo
Low dose
High dose

*Biogen clinical trial data slides,* 2019.

# Case study - Aducanumab (Aduhelm)

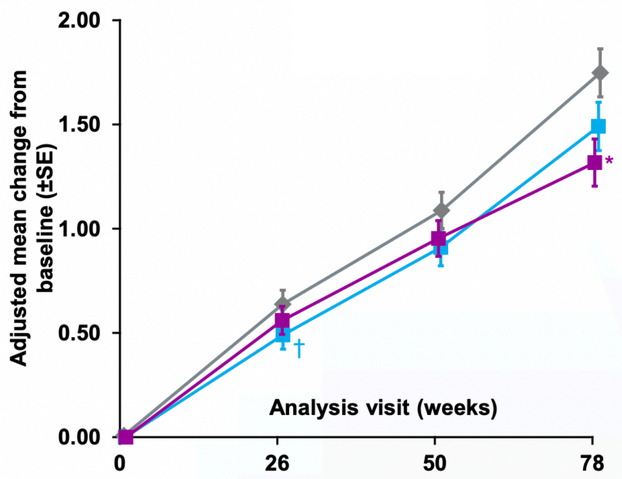
Biogen

Biogen Aduhelm (aducanumab avwa)

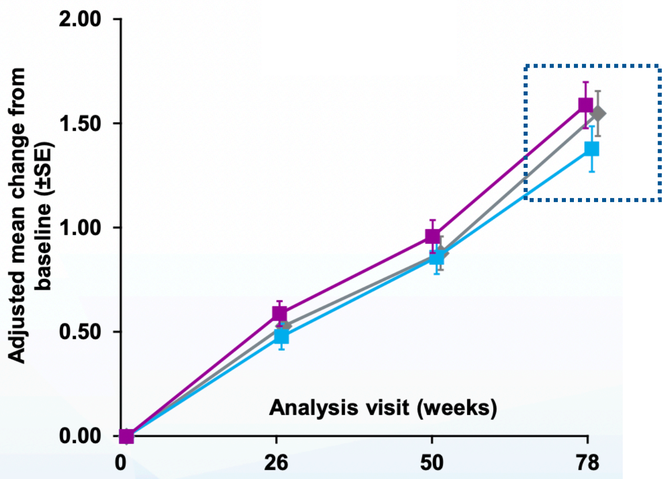
Clinical dementia rating (CDR)

**2015 - Phase III**

EMERGE




ENGAGE



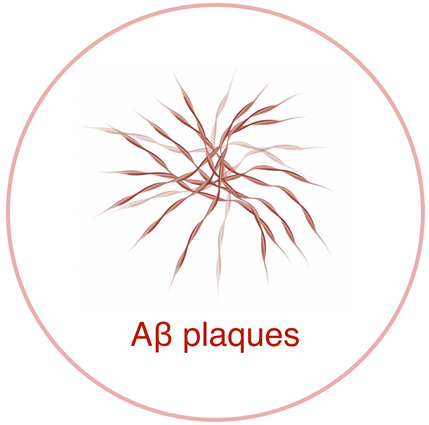

Placebo
Low dose
High dose

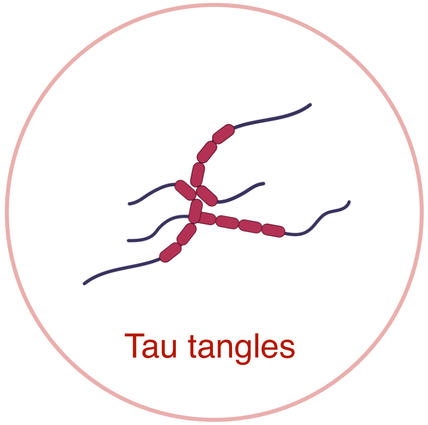
*Biogen clinical trial data slides,* **2019**.

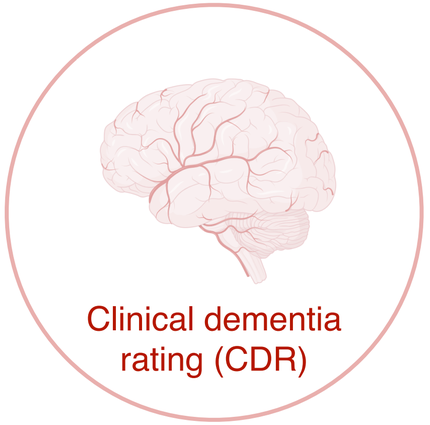
# Case study - Aducanumab (Aduhelm)


Biogen

**2015 - Phase III**




| | | | |
|---|---|---|---|
| EMERGE | ✓ | ✓ | ~ |
| ENGAGE | ✓ | ✓ | ✗ |

# Case study - Aducanumab (Aduhelm)


Biogen

**2015 - Phase III**

**March 2019**

**March 2019** - Biogen stopped development of Aduhelm

**Biogen** spent **$2.4 billion** on Alzheimer's-related research toward **Aduhelm**

# Case study - Aducanumab (Aduhelm)


Biogen

**2015 - Phase III**

**March 2019**


**- US$100 billion**

**March 2019** - Biogen stopped development of Aduhelm

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# Case study - Aducanumab (Aduhelm)


Biogen

**2015 - Phase III**

**March 2019**

**October 2019**


**- US$100 billion**

**October 2019** - announcement for FDA approval

# Case study - Aducanumab (Aduhelm)


Biogen

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**March 2019**

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# Case study - Aducanumab (Aduhelm)

Biogen

Biogen Aduhelm (aducanumab avwa)

**2015 - Phase III**

**March 2019** **October 2019**

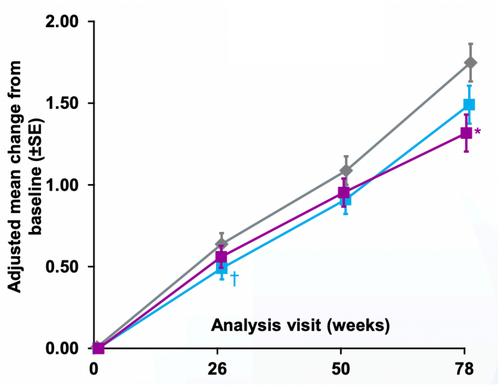

**October 2019** - announcement for FDA approval

**- US$100 billion** **+ US$60 billion**

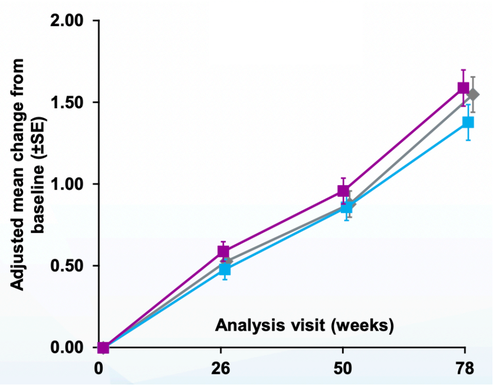
# Case study - Aducanumab (Aduhelm)

Biogen

EMERGE

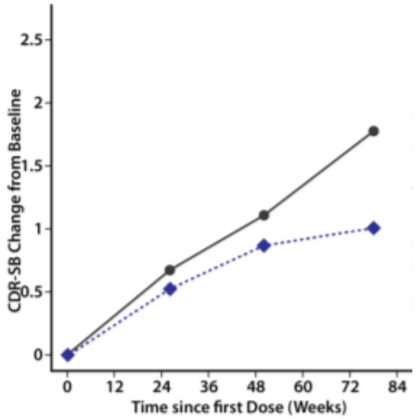



ENGAGE




Placebo
Low dose
High dose

EMERGE

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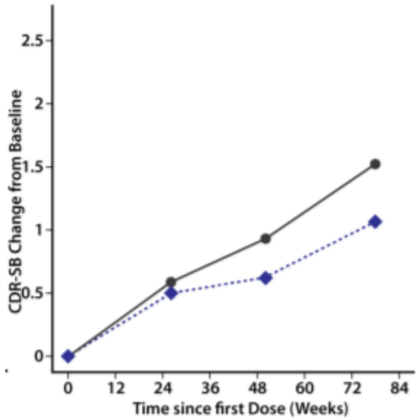



Clinical dementia rating (CDR)

# Case study - Aducanumab (Aduhelm)


Biogen


**FDA accelerated approval** - approval June 2021

IV every 4 weeks

US$56,000 a year

# Case study - Aducanumab (Aduhelm)

The New York Times

## *Three F.D.A. Advisers Resign Over Agency's Approval of Alzheimer's Drug*

The drug, Aduhelm, a monthly infusion priced at $56,000 per year, was approved this week despite weak evidence that it helps patients.

Share full article 64


Dr. Aaron Kesselheim, who resigned this week from an F.D.A. advisory committee, speaking at a panel in 2018. "This might be the worst approval decision that the F.D.A. has made that I can remember," he said Thursday. Scott Eisen/Associated Press

By Pam Belluck and Rebecca Robbins

Published June 10, 2021 Updated Sept. 2, 2021

"FDA Approval of Aduhelm Draws Criticism for Lack of Solid Evidence"

*The New York Times* (June 2021)

The New York Times

"FDA's Approval of Aduhelm Raises Concerns Among Experts"

*The Wall Street Journal* (June 2021)

THE WALL STREET JOURNAL.

"Alzheimer's Drug Aduhelm Faces Strong Backlash From Medical Experts"

*The Guardian (June 2021)*

The Guardian

# Case study - Aducanumab (Aduhelm)


Biogen

**2015 - Phase III** — **March 2019** — **October 2019** — **FDA approval** — **June 2021**

**2022** - total sales $2.8 million
(predicted to be +$1 billion)

IV every 4 weeks

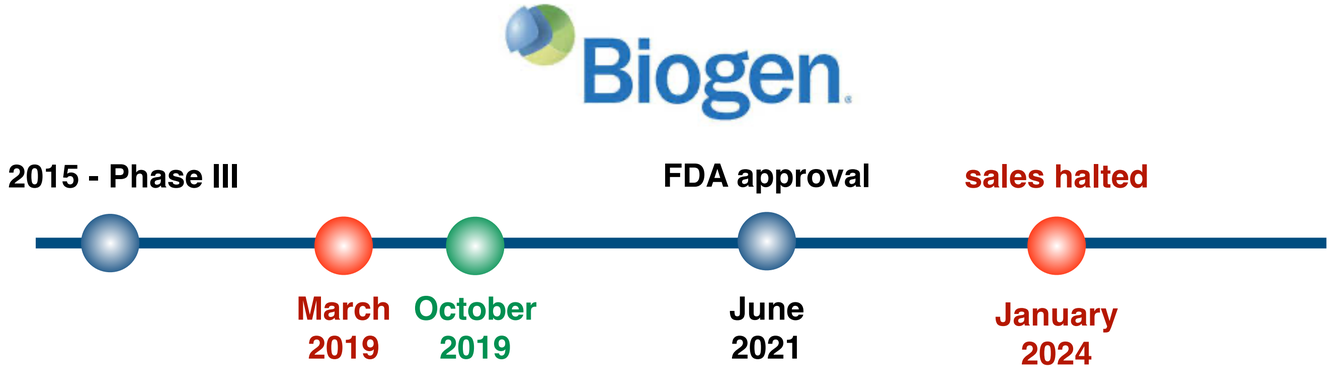
US$56,000 a year

social media

**safety concerns**

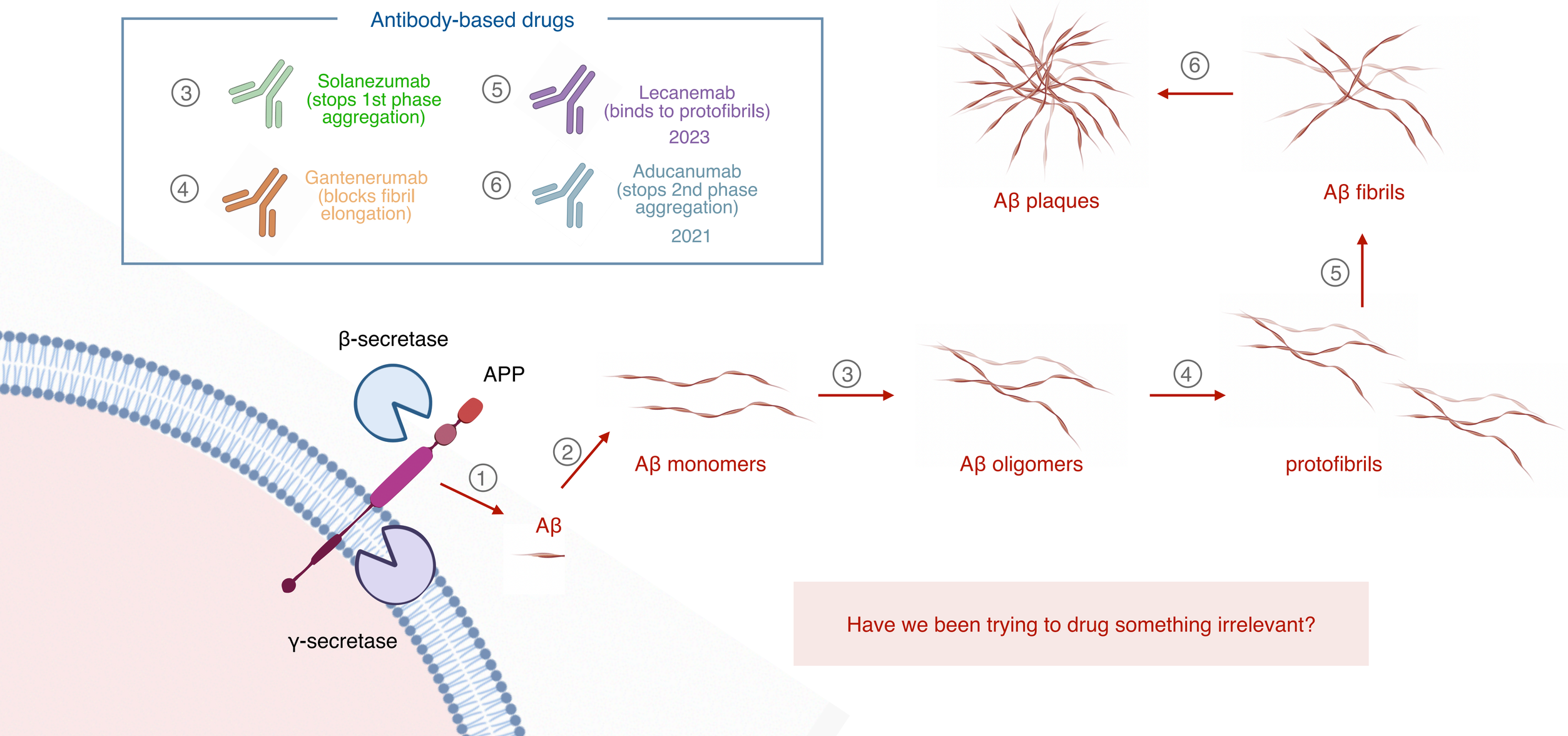
ARIA-E (Edema) - brain swelling

# Case study - Aducanumab (Aduhelm)


**January 2024** - Biogen removed Aduhelm from the market

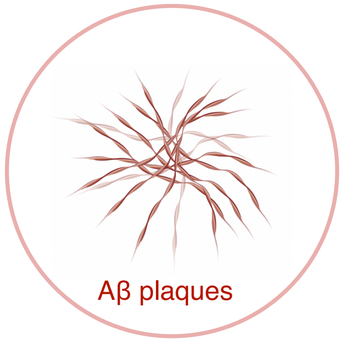
# Alzheimers treatments & cures - Aβ plaques



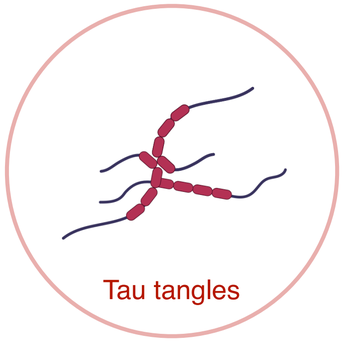

Have we been trying to drug something irrelevant?

# Alzheimers treatments & cures - Aβ plaques

Aβ plaques:
“Correlation vs Causality”

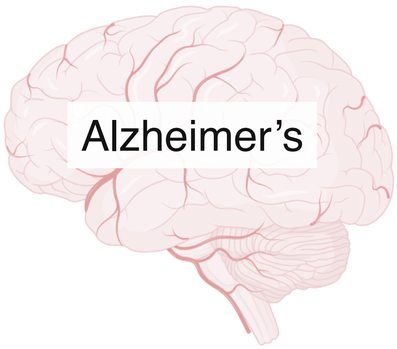


Aβ plaques



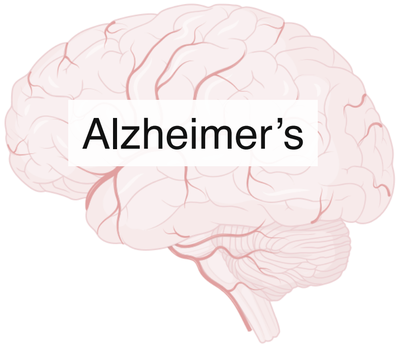
Tau tangles

causes

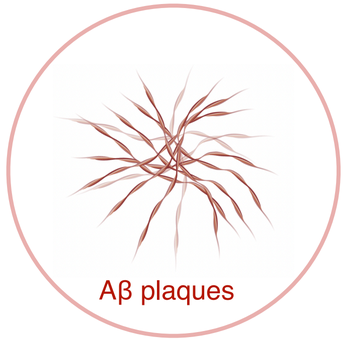


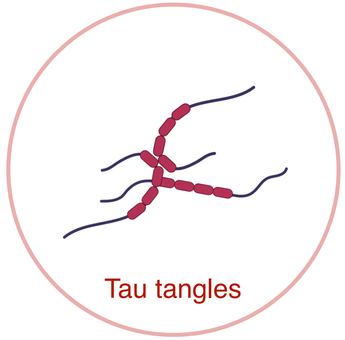
# Alzheimers treatments & cures - Aβ plaques

Aβ plaques:
“Correlation vs Causality”



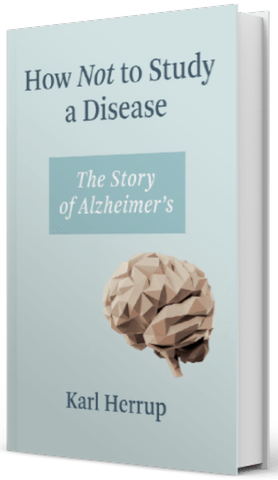

causes



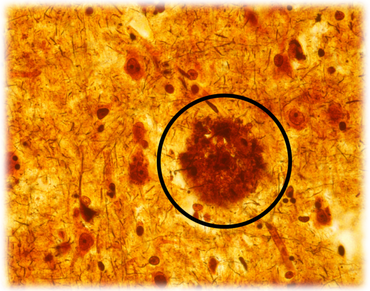



# Where has Alzheimer's research gone wrong?


Karl Herrup
(neurobiologist)




"Alzheimer's research direction likely went wrong right back at the very beginning, in **1906 with Auguste Deter**"



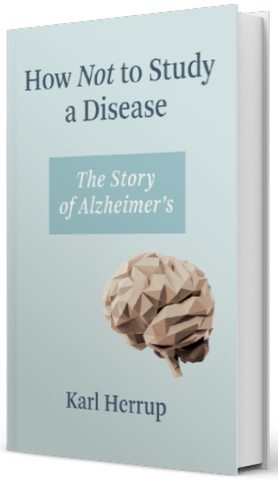
"…when **two things occur together,** it doesn't necessarily mean that **one causes the other**…"

"…in confusing correlation with causality, the field has been trapped into this model of the disease…"

(we may have gone down a big rabbit hole!)

# Where has Alzheimer's research gone wrong?


Karl Herrup
(neurobiologist)




NIH
National Institute on Aging

"…decided they had to do something to **attract the funding dollars**, and they realized that the idea of aging is not really scary…"

"…they needed a **boogeyman**, and they decided that, of all the diseases of aging, **dementia was probably the most feared**…"

"…what was argued by the founders of the NIA was that, well, if you look at the brains of anyone with **dementia**, you can find these **plaques**…"

"…the **pharmaceutical industry** stands to make **so much money**, if they can have proprietary rights on a drug…"

NOVARTIS Pfizer Eisai Biogen Lilly

# Alzheimers treatments & cures - Aβ plaques

Antibody-based drugs

Biogen

③ Solanezumab (stops 1st phase aggregation)

⑤ Lecanemab (binds to protofibrils)

④ Gantenerumab (blocks fibril elongation)

⑥ Aducanumab (stops 2nd phase aggregation)

2021

Aβ plaques

⑥

Aβ fibrils

⑤

β-secretase

APP

① Aβ

② Aβ monomers

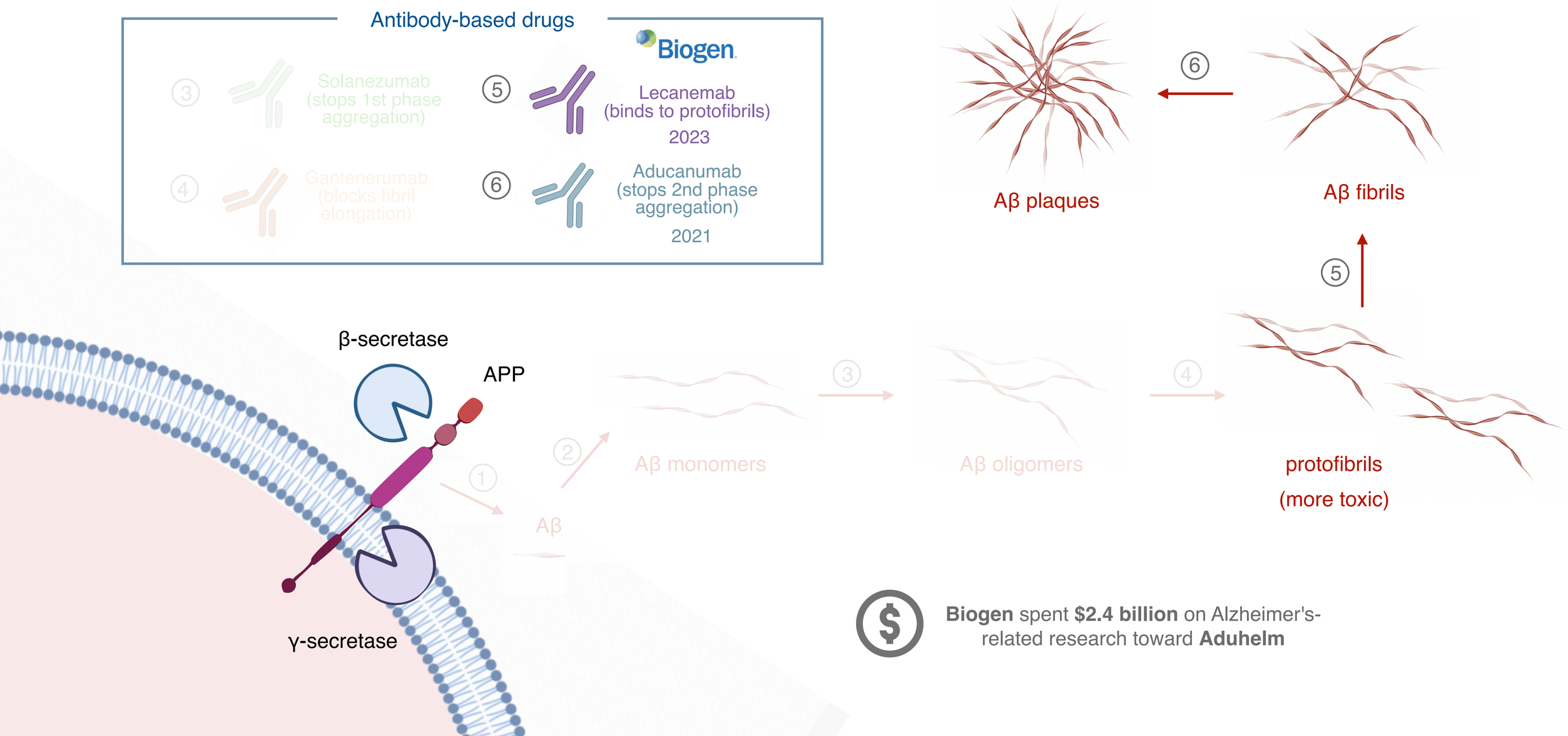
③ Aβ oligomers

④ protofibrils

γ-secretase

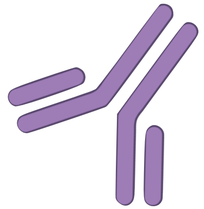
**Biogen** spent **$2.4 billion** on Alzheimer's-related research toward **Aduhelm**

# Alzheimers treatments & cures - Aβ plaques



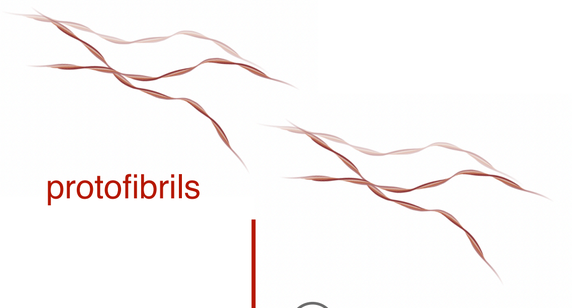

**Biogen** spent **$2.4 billion** on Alzheimer's-related research toward **Aduhelm**

# Case study - Lecanemab (Leqembi)



Leqembi
(2023)

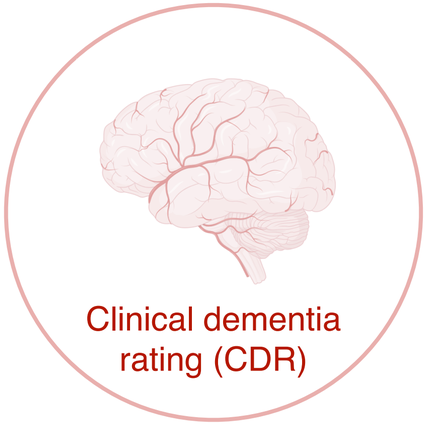
Eisai Biogen



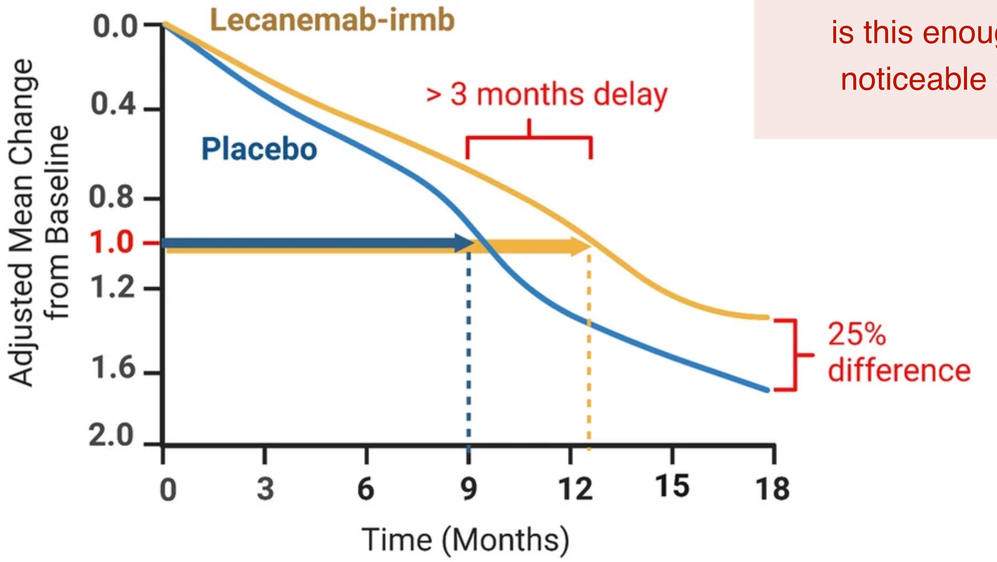
protofibrils

⑤

Aβ fibrils



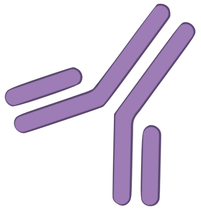
Clinical dementia
rating (CDR)




is this enough to make it a noticeable difference… ?

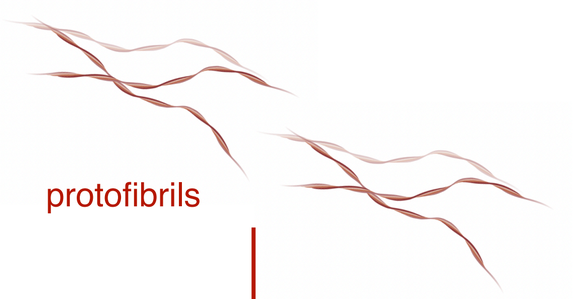
*N. Engl. J. Med.*, **2023**, 388:9-21.

# Case study - Lecanemab (Leqembi)



Leqembi
(2023)

Eisai Biogen



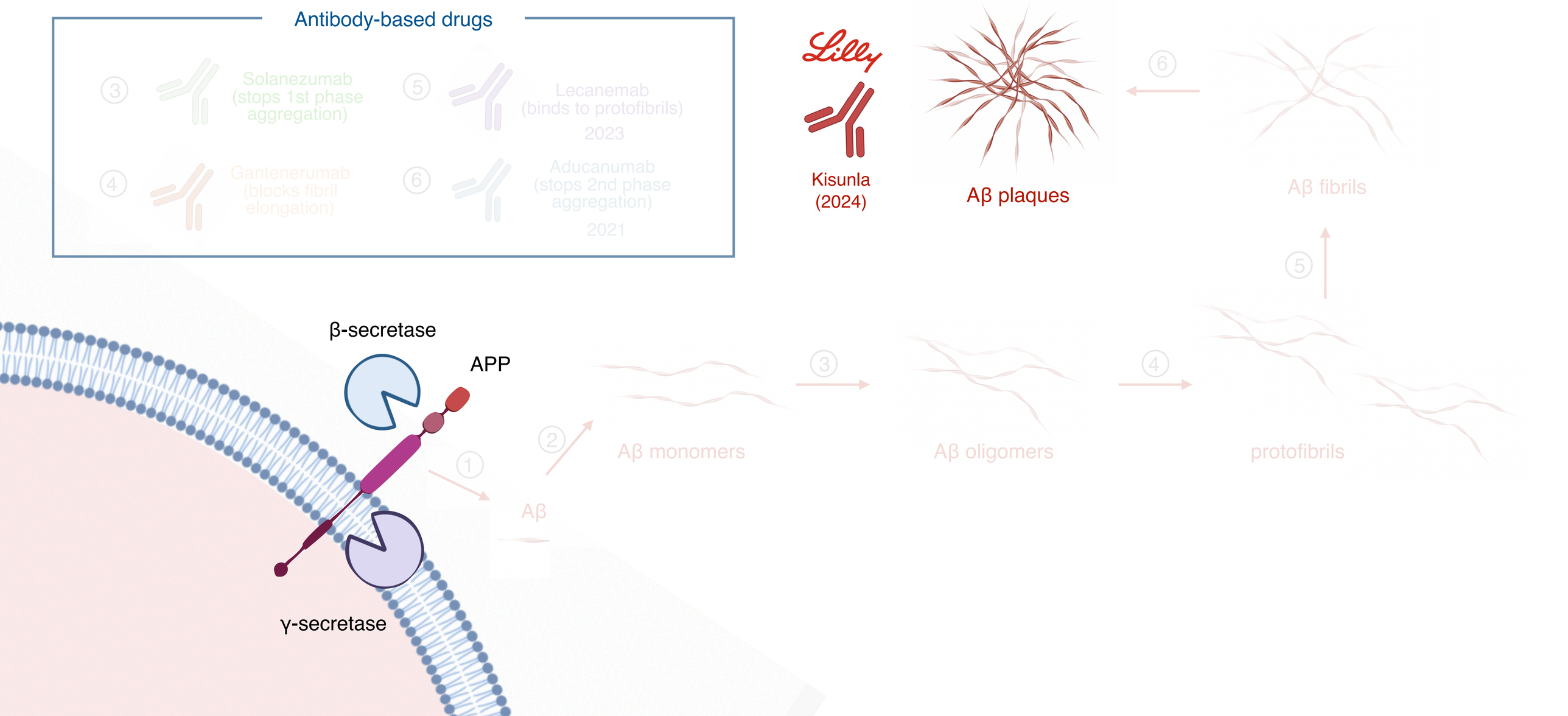

Aβ fibrils

**2024** - Leqembi total sales $280 million

**(sales expected to decline in 2025)**

*N. Engl. J. Med.*, **2023**, 388:9-21.

# Alzheimers treatments & cures - Aβ plaques



# Case study - Donanemab (Kisunla)

Kisunla
(2024)

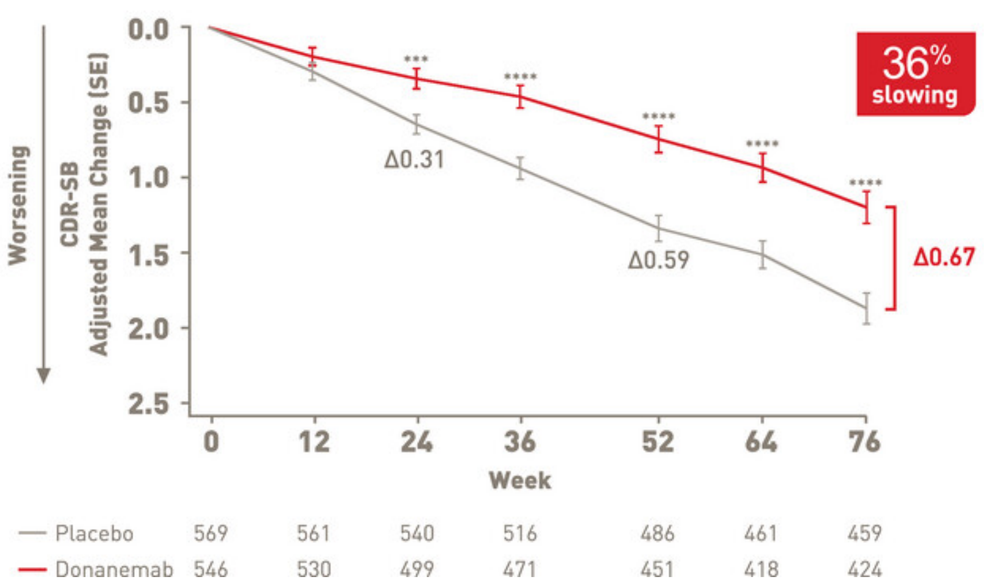
Lilly

pyroglutamate
(Aβ3pE-42)

more selective
(better safety profile)

Aβ plaques

Clinical dementia
rating (CDR)

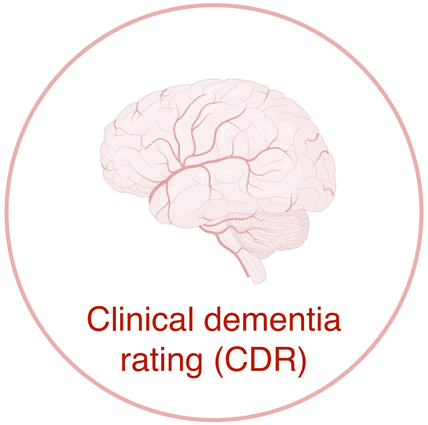


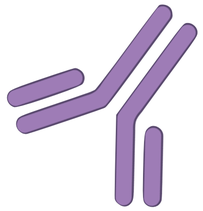

*JAMA*., **2023**, 330(6):512-527.

# Alzheimers treatments & cures - Aβ plaques

Kisunla
(2024)

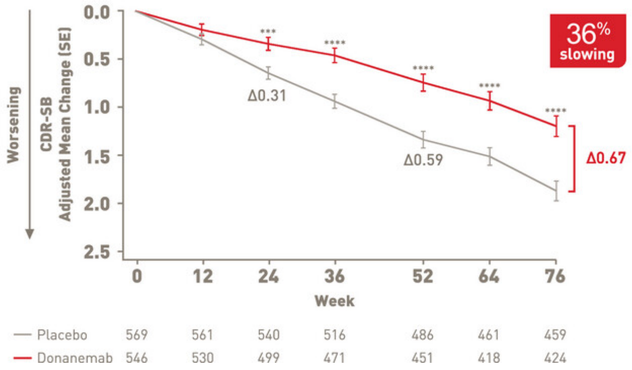
Lilly



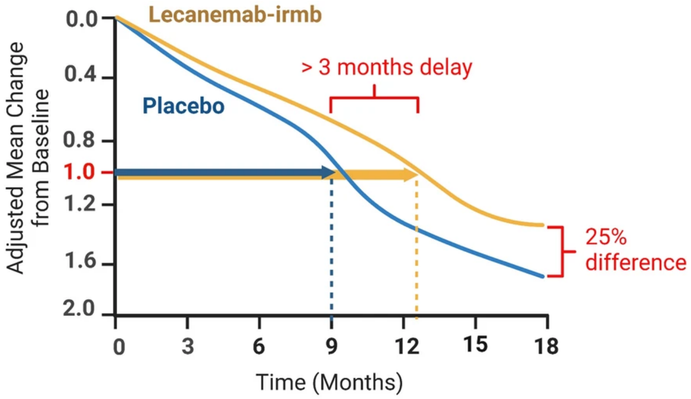



Leqembi
(2023)

Eisai Biogen




Clinical trials have not been entirely satisfactory…



# Talk outline

**Part I**

- History of Alzheimer’s - Alois Alzheimer
- Alzheimer’s disease causing hypotheses

**Part II**

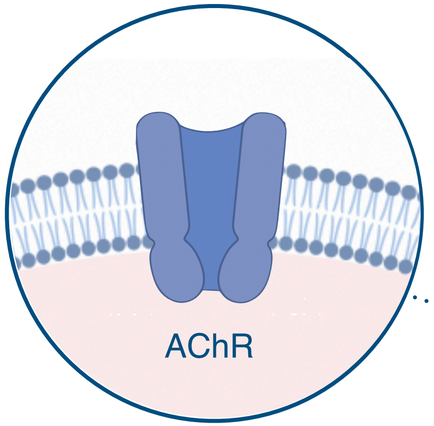
- Alzheimer’s drug treatment strategies
- Clinical case studies (controversial FDA approvals)

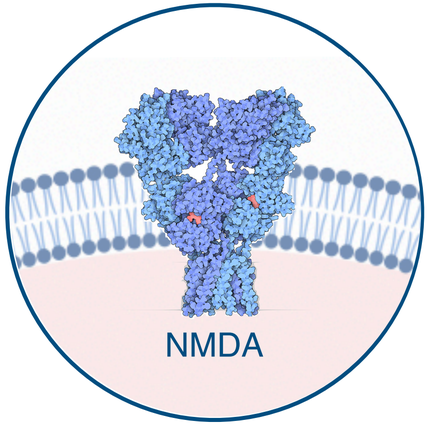
**Part III**

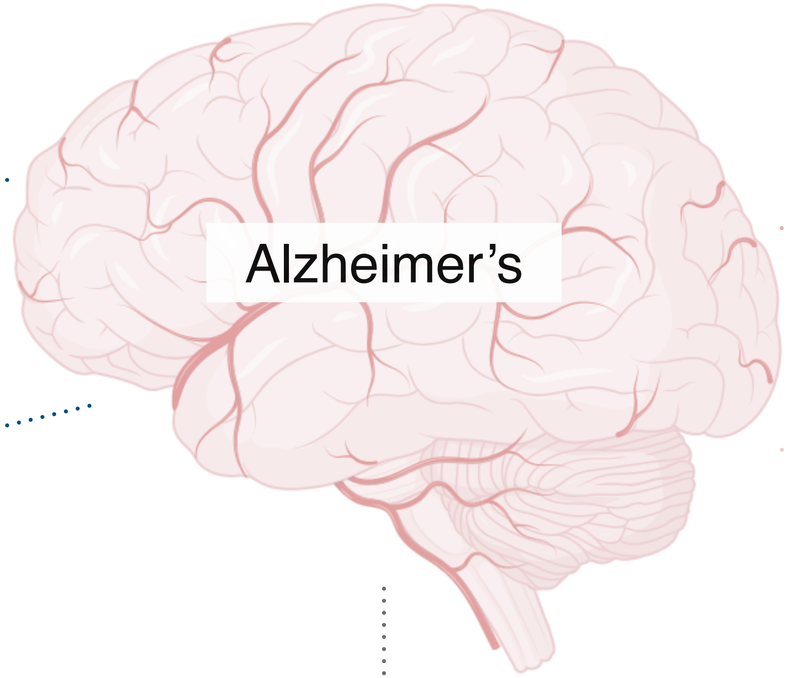
- Outlook & future directions - how are Pharma companies tackling Alzheimer’s

# Alzheimers treatments & cures

Cognitive symptom management

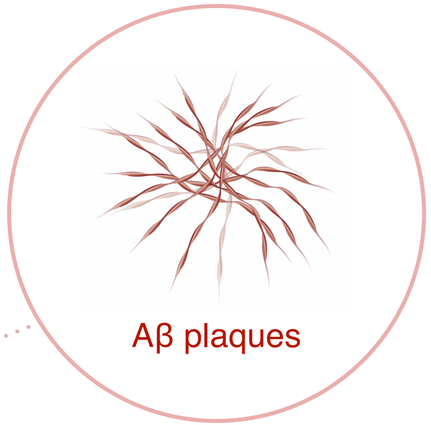


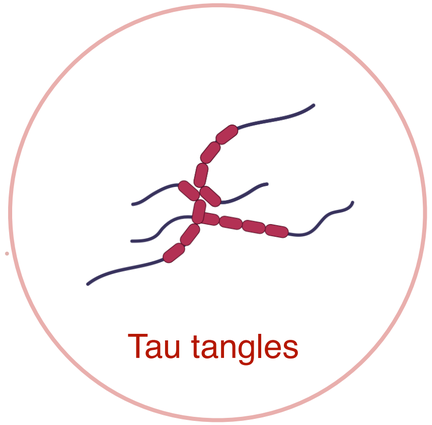




Alternative treatment strategies?

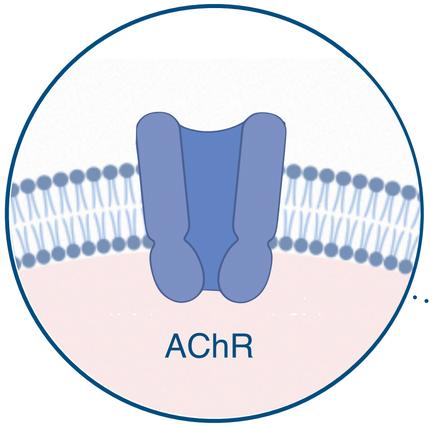
Disease-modifying treatments

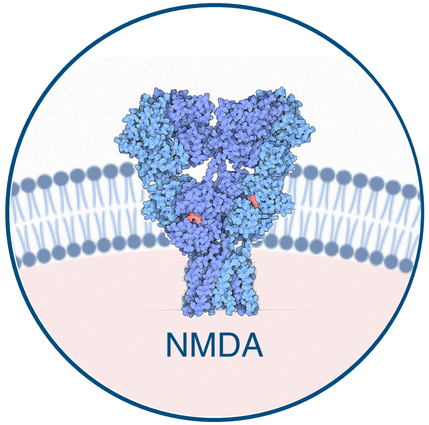


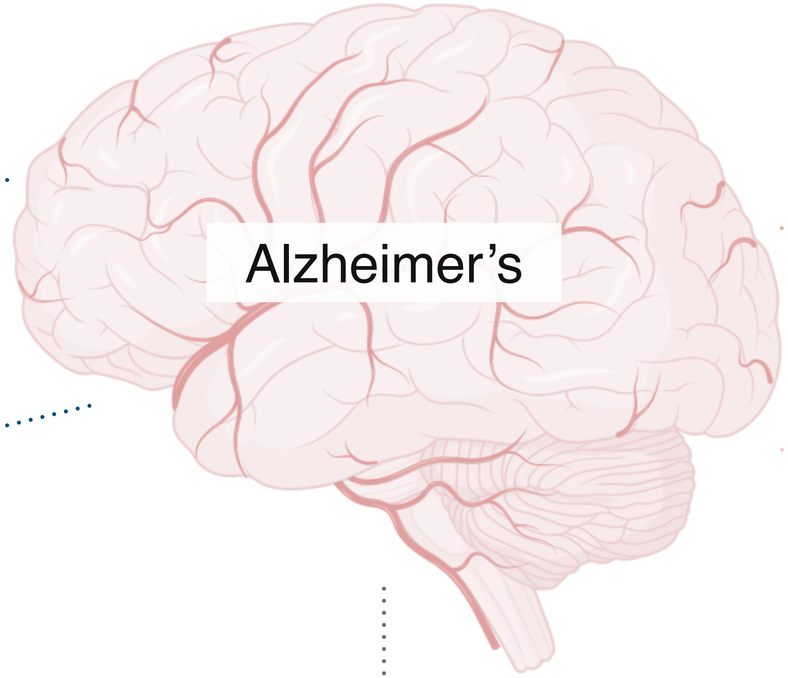



# Alzheimers treatments & cures

Cognitive symptom management

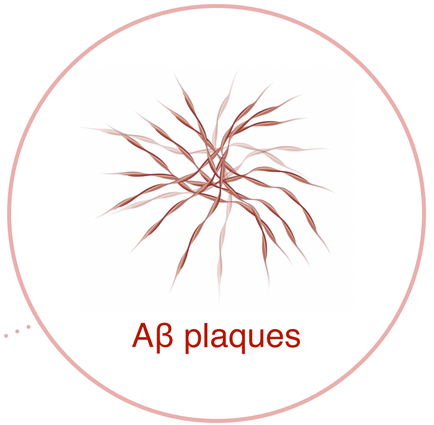


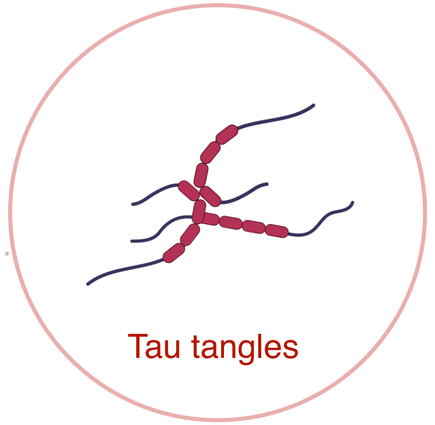





Disease-modifying treatments

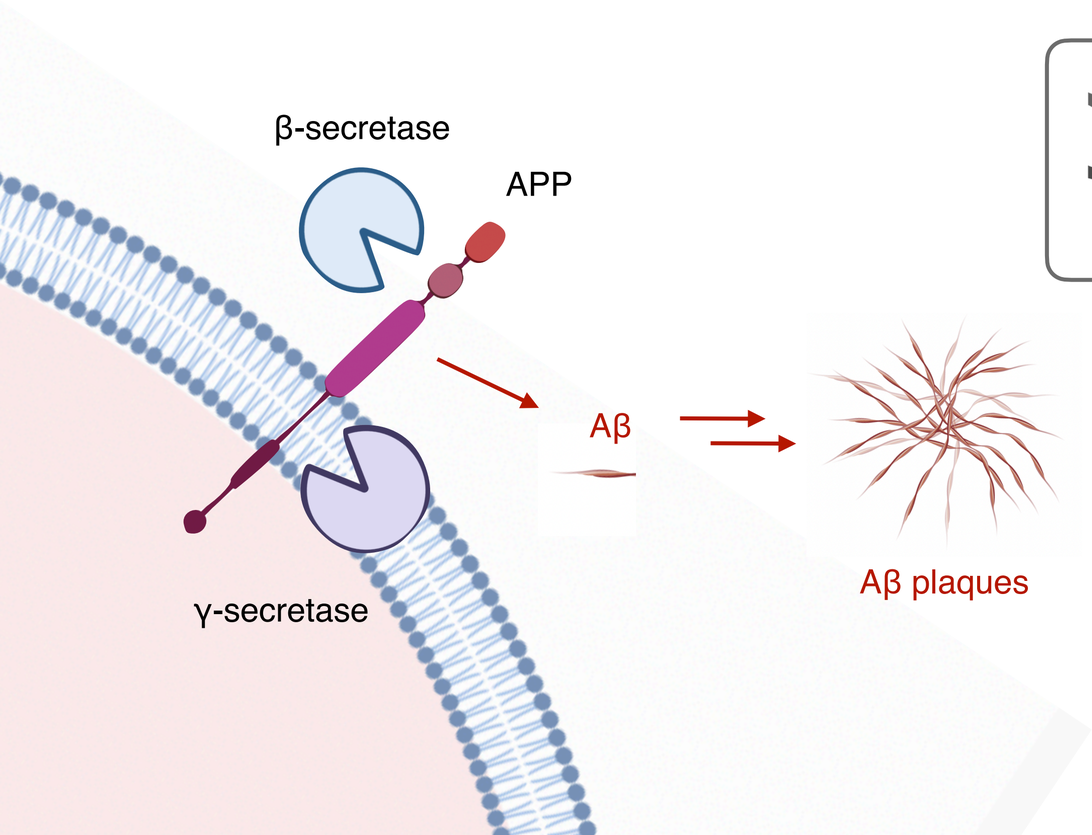


## Familial Alzheimer’s Disease (fAD)

inherited genetic mutations

APP
β-secretase (BACE)
γ-secretase (PSEN1 & PSEN2)





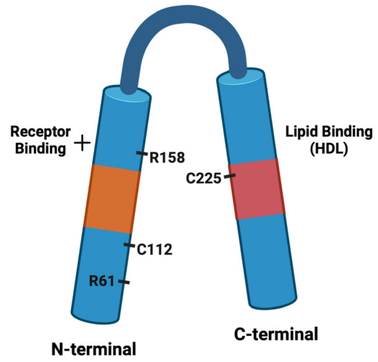

Aβ plaques

Genetic factors

## Sporadic Alzheimer's Disease (sAD)

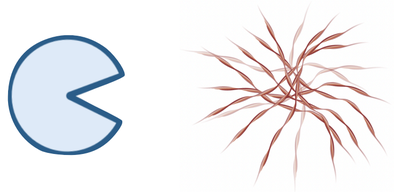
random genetic mutations

APOE




lipid transport

cellular uptake of cholesterol & lipoproteins



search for other sAD Aβ modifying proteins

*Front. Genet.,* **2017**, 8:58.

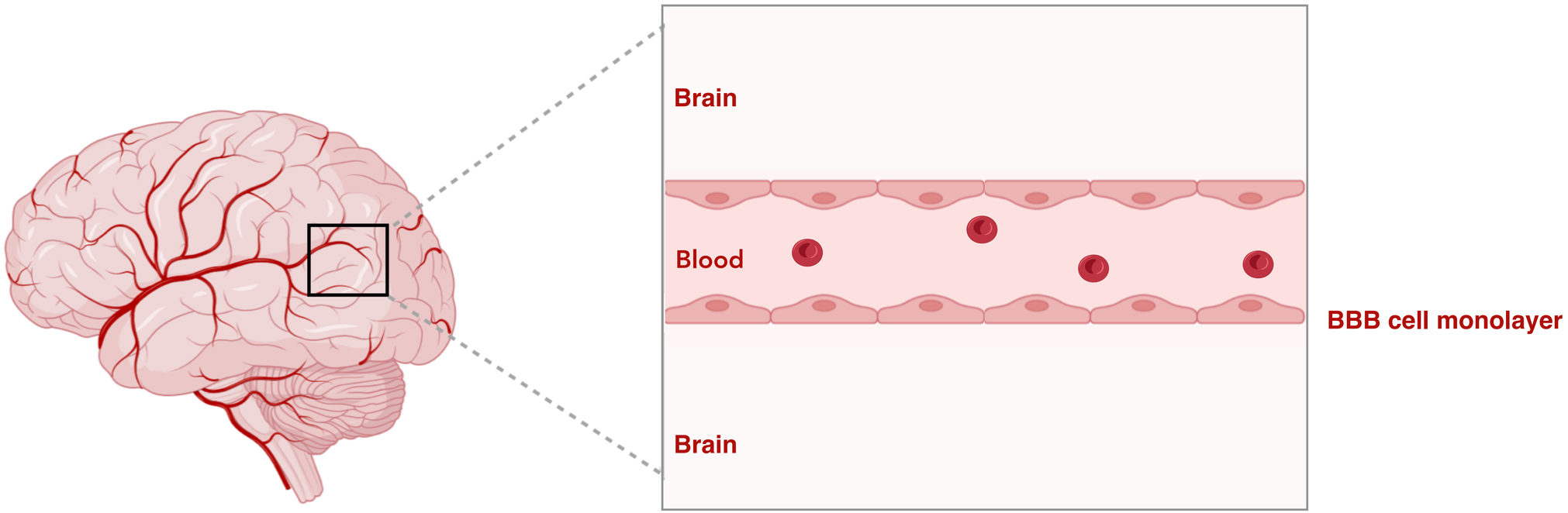
# Bottleneck in brain drug development: the BBB

"…>98% of all small molecule drugs do not cross the BBB, and ~100% of biologic drugs do not cross the BBB…"

By 2025, pharmaceutical companies are expected to invest over $2 - $3 billion annually in **BBB delivery mechanisms**…

Pardridge, W.M., et al., *NeuroRx.* 2005, 2, 3–14.

# The Blood-Brain Barrier (BBB)



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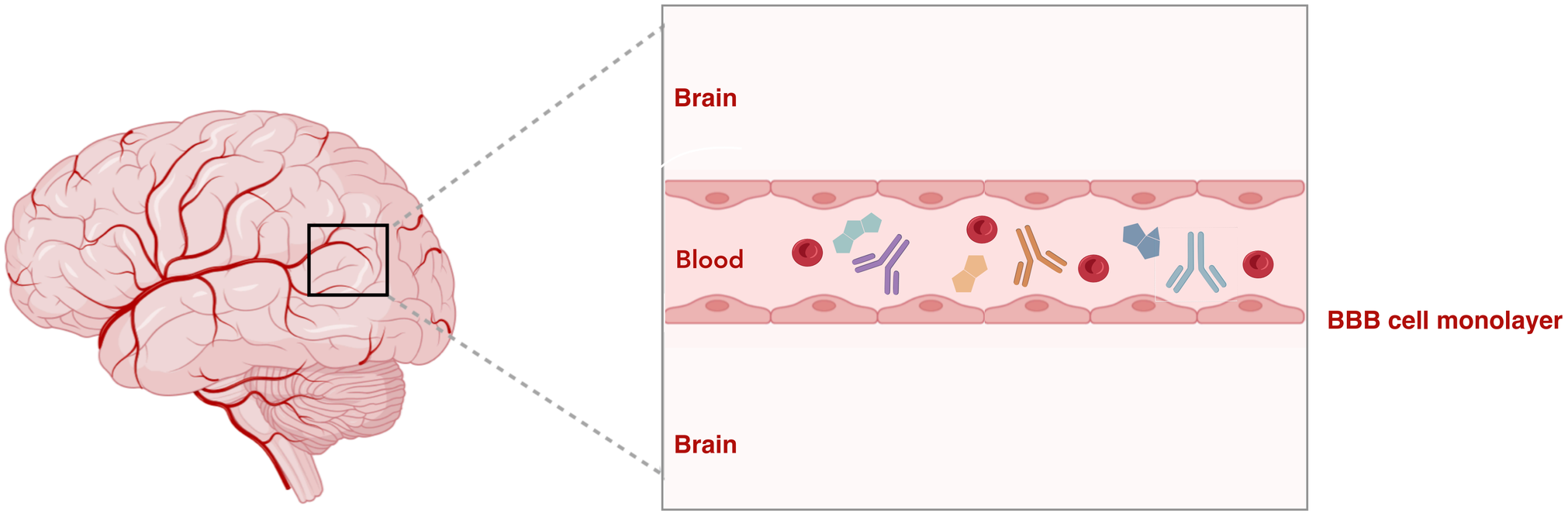

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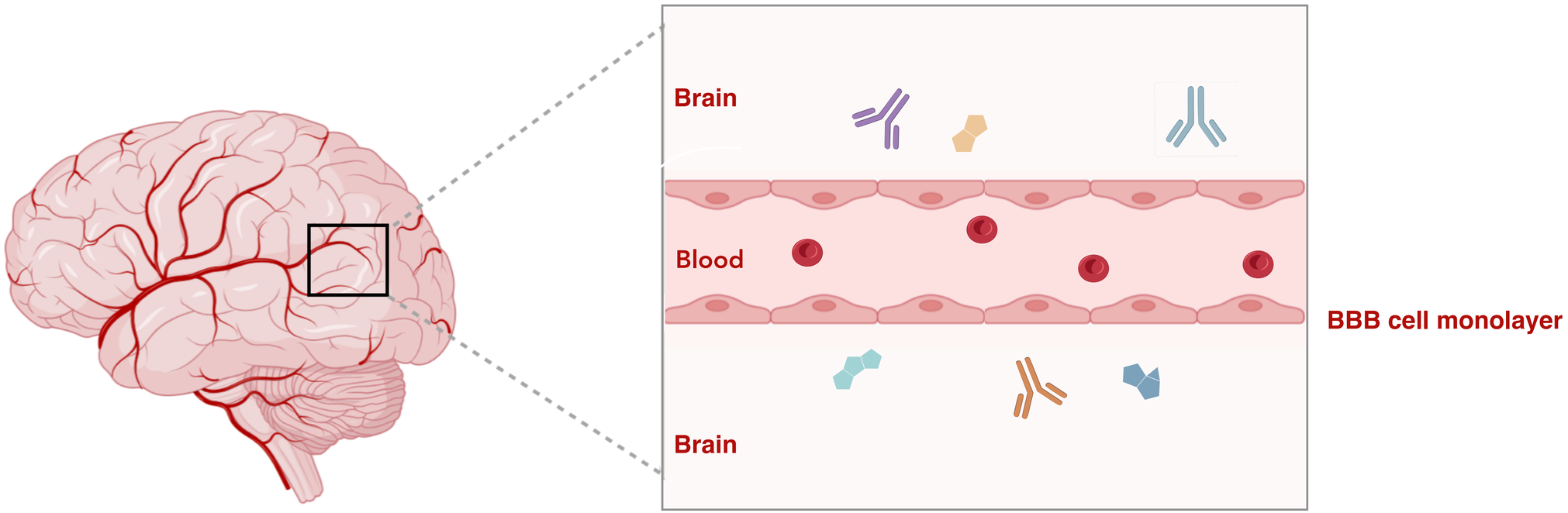


# Strategies to overcome the BBB

rigidity

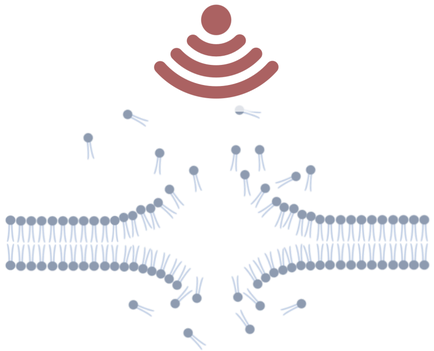
lipophilicity



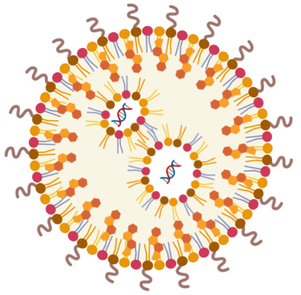
Chemical Alterations

Antibody-Engineering

Cranial Injections



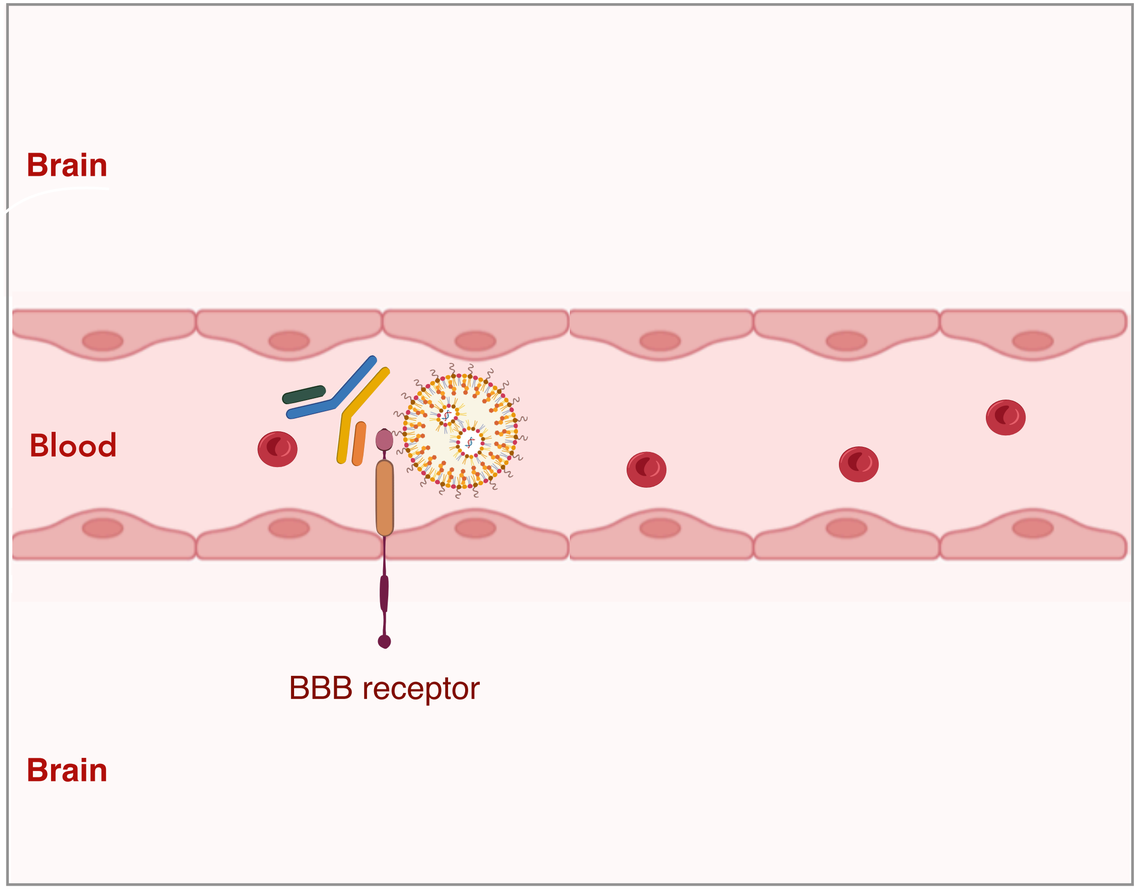
Focused Ultrasound
(FUS)

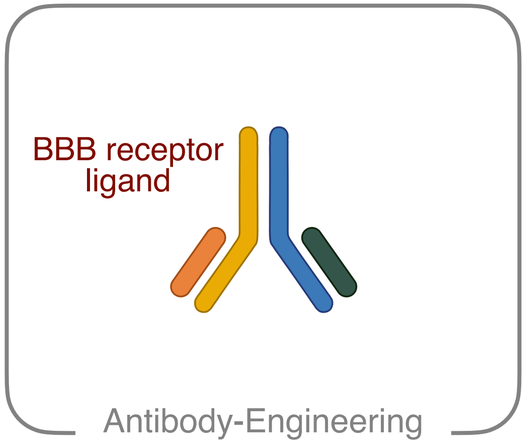


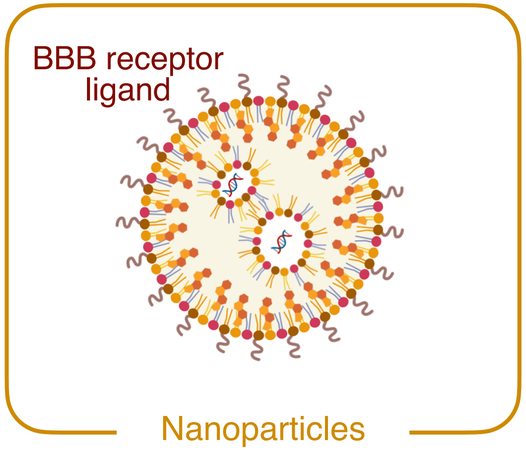
Nanoparticles
(NPs)

*Eur. J. Med. Res.*, 2024, *29:*313.

# Strategies to overcome the BBB




*Eur. J. Med. Res.*, 2024, *29*:313.

# Outlook

## Alternative treatment strategies

Genetic factors

## Tackling the BBB

Antibody engineering

## Early detection

brain imaging

## Disease-modifying treatments (DMTs)

Clinical dementia rating (CDR)

Aduhelm (2021)

Biogen

Leqembi (2023)

Biogen

Eisai

Donanemab (2024)

Lilly

Aβ plaques:
Correlation vs Causality

Thank you!

Any Questions?