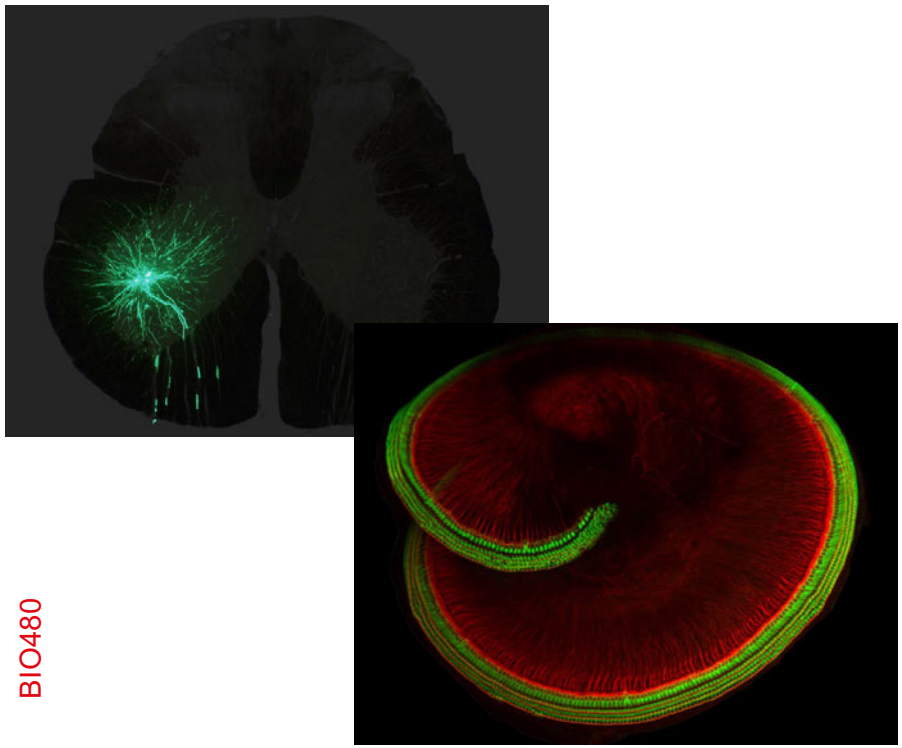
EPFL

Therapeutic applications in neurological and sensory disorders



AD immunotherapy

Gene therapy

BIO480, B. Schneider
December 2025

Novel Therapeutic Approaches for CNS Diseases

- **CNS and Therapy Development**

  General principles

- **Immunotherapy against Alzheimer's Disease**

- **Gene therapy for CNS diseases**

  Example of AAV as gene delivery system for the CNS

  Lipid Storage Diseases – ex vivo gene therapy for MLD

  Motoneuron Diseases – RNAi against SOD1

- **Sensory organs:**

  Blindness functional rescue by optogenetic

  Deafness Rescue of cochlear function

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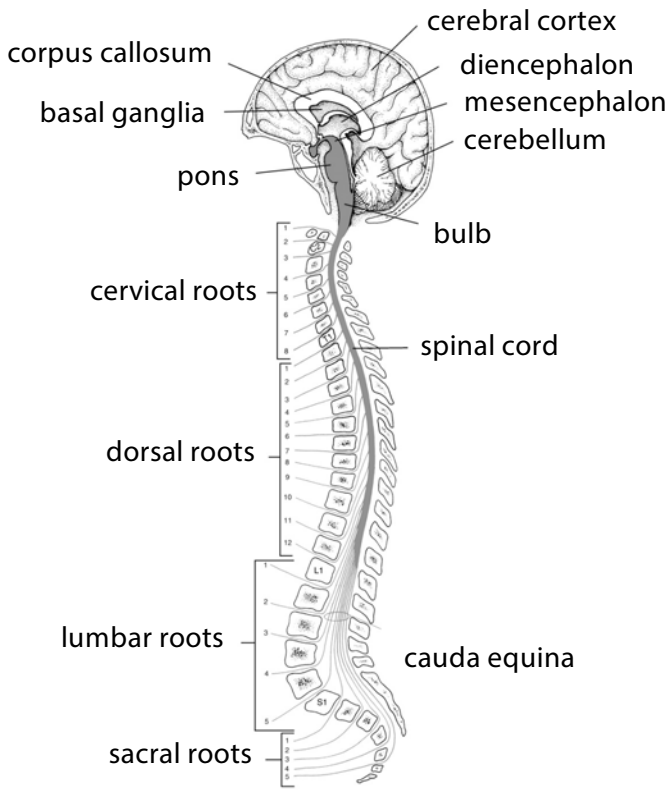
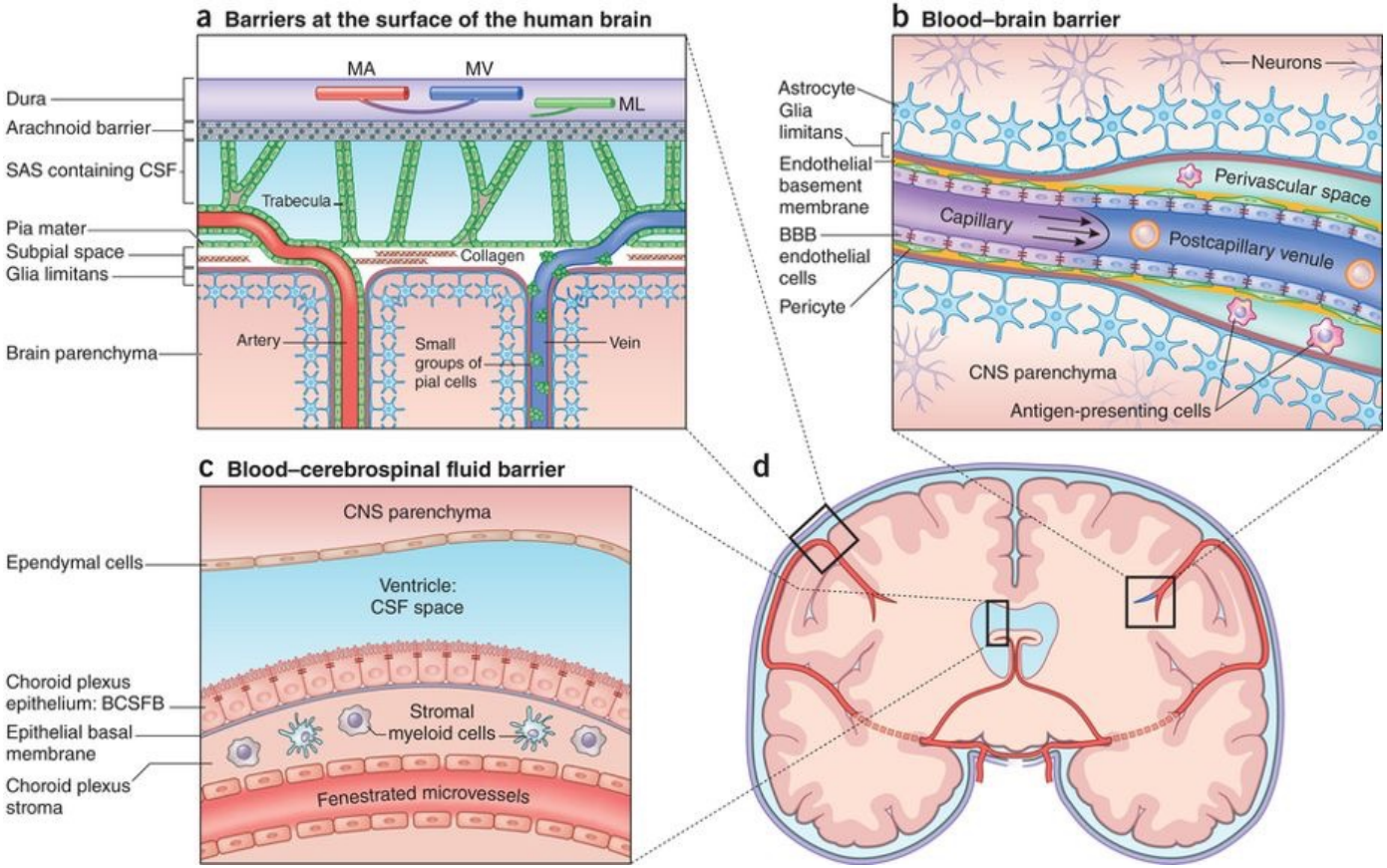
Therapeutics for CNS diseases: a challenging target



- Complex function
- High metabolic demand
- Many sub-populations of cells, mostly post-mitotic
- Connectivity
- Blood-brain barrier
- Large size organ
- Limited access for the immune system
- Little capacity for regeneration
- Aging process

Barriers to the CNS

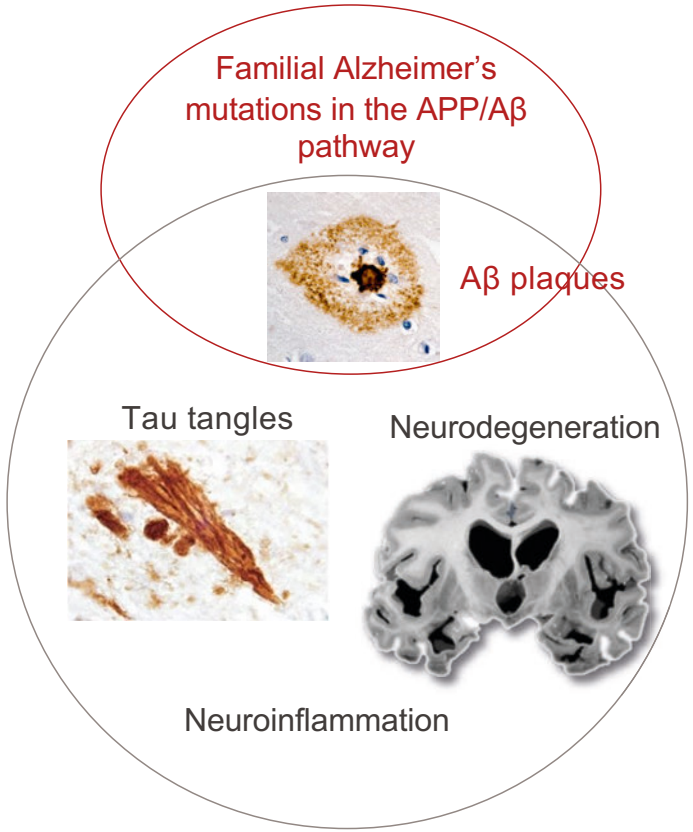
Acellular and cellular brain barriers



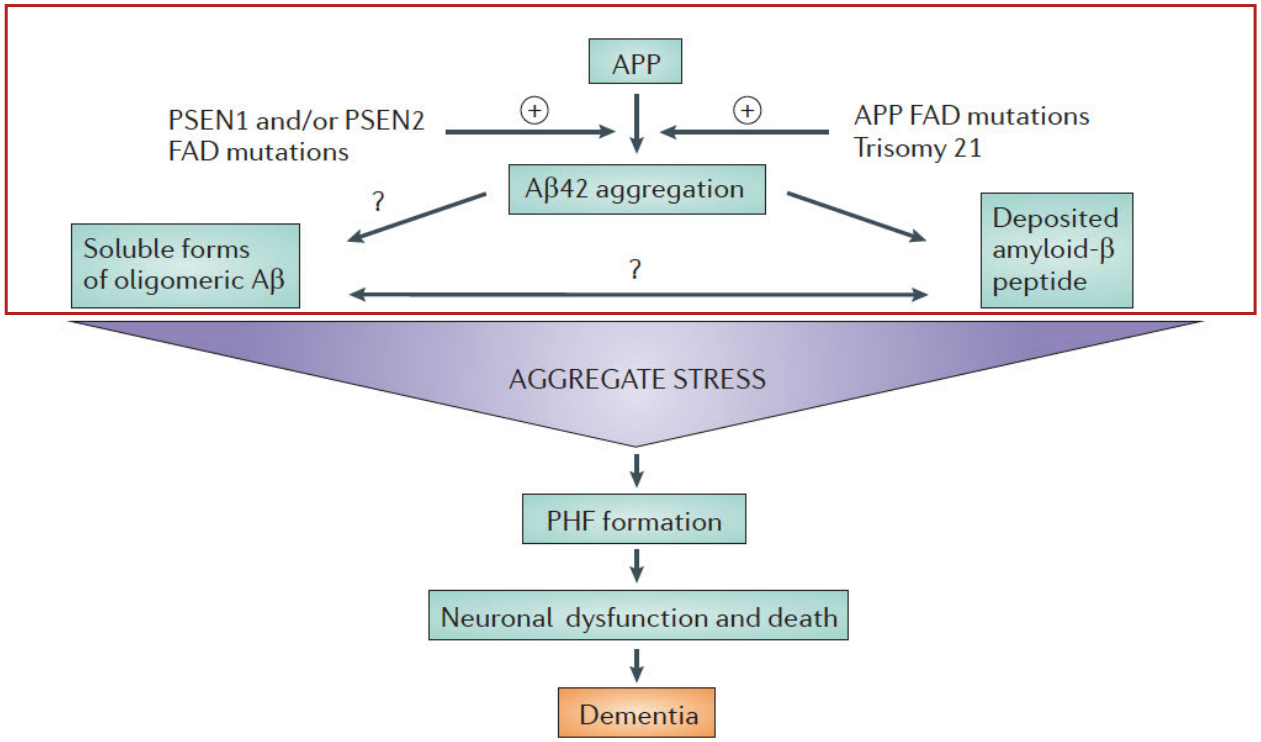
Engelhardt B, Nature Immunology volume 18, pages 123–131 (2017)

Genetic factors for Alzheimer's disease

Genetic causes of AD



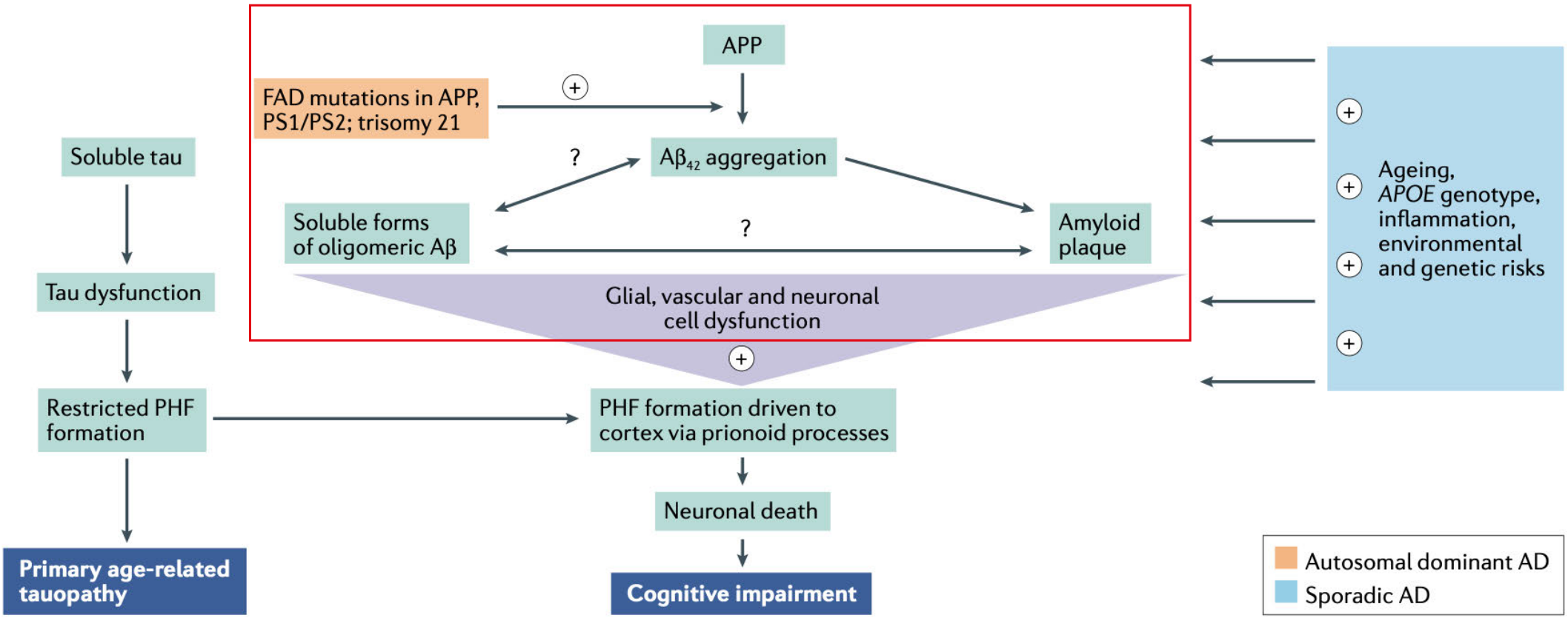
Amyloid β hypothesis



Nature Reviews Drug Discovery 21, pp. 306–318 (2022)

Therapies based on 'β-amyloid cascade hypothesis'

Based on the Aβ hypothesis, this pathway should be the primary target for therapeutic strategies



- *Nature Reviews Drug Discovery 21, pp. 306–318 (2022)*

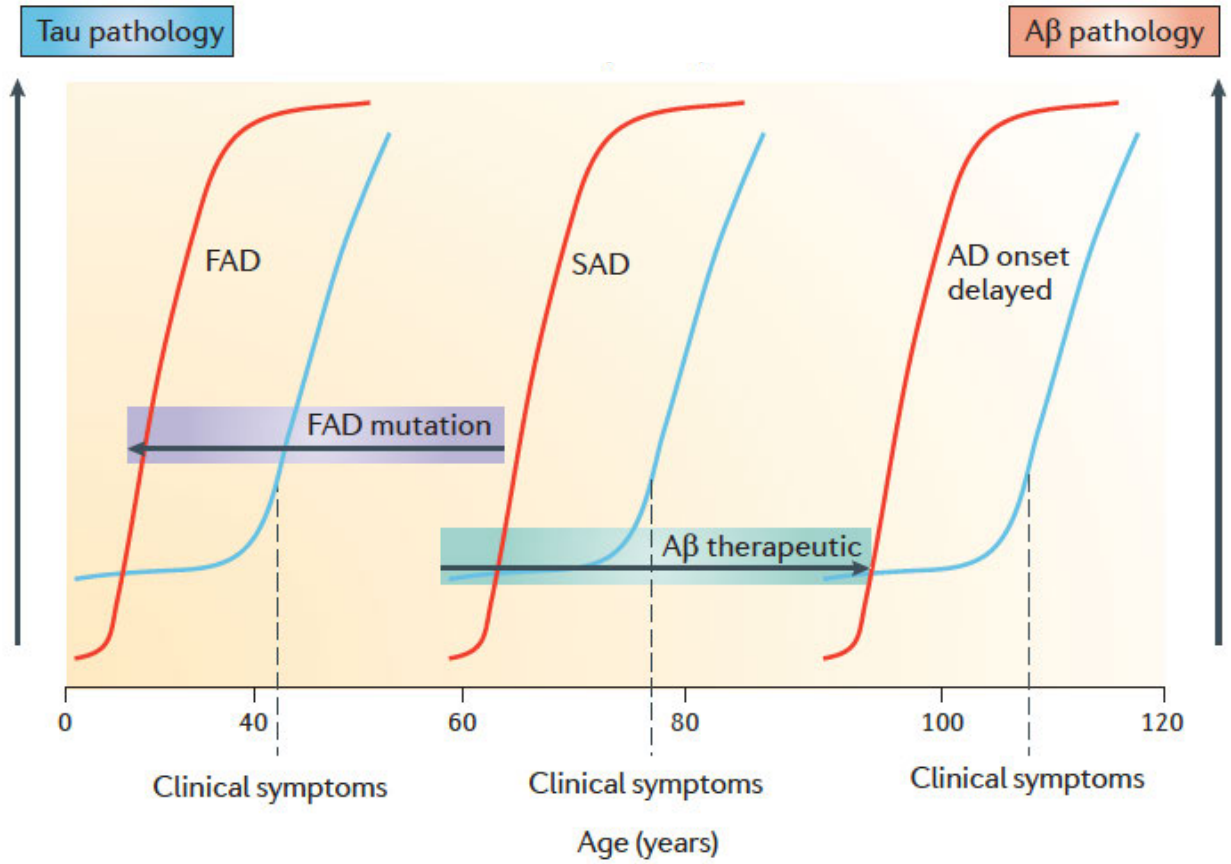
Therapies based on ‘β-amyloid cascade hypothesis’

Rationale for an anti-Aβ treatment:

Assumption:

Aβ-related mechanisms leading to familial early-onset Alzheimer’s disease are similar to sporadic late-onset disease:

→ **therapeutic approach to slow down disease progression?**



Therapeutics targeting Aβ

Inhibitors of Presenilin (PSEN2)

Main issue: on-target side effects

(Notch signaling)

Inhibitors of BACE1 (beta secretase, PSEN1)

Main issue: lack of efficacy

and side effects

Antibodies against various forms of Aβ

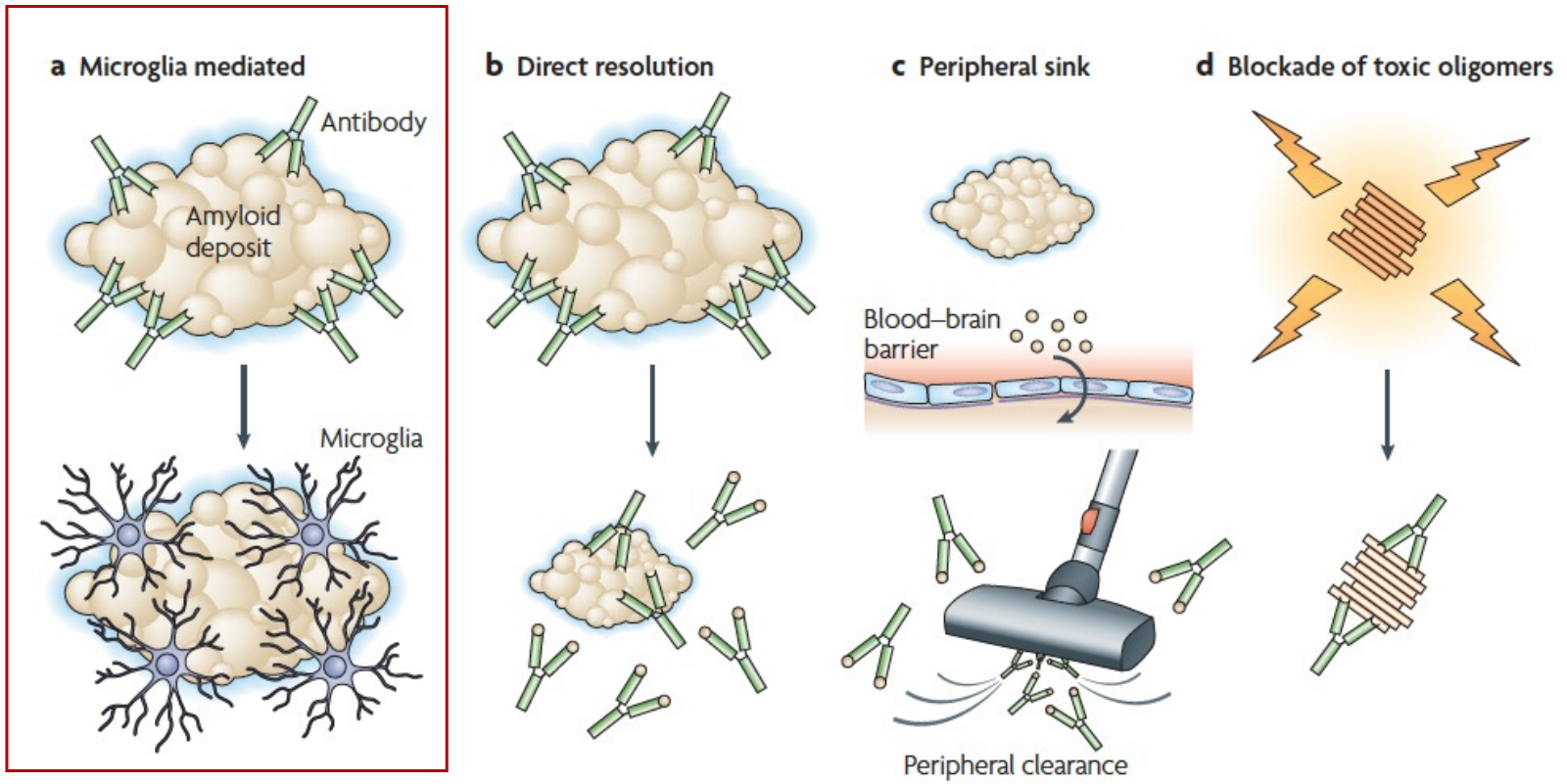
Main issue: lack of efficacy

and side effects (ARIA-E)

Year	Drug	Company	Mechanism of action	Target	Patient population	Outcome	Observations
2007	Tramiprosate	Neurochem	Unclear; may interact with Aβ oligomers	Soluble Aβ/Aβ oligomers	Mild to moderate AD	Lack of efficacy	–
2009	Tarenflurbil	Myriad Genetics/ Lundbeck	γ-Secretase modulator	Soluble Aβ	Mild AD	Lack of efficacy	Unlikely to have achieved adequate target engagement in the brain
2011	Semagacestat	Eli Lilly	γ-Secretase inhibitor	Soluble Aβ	Mild to moderate AD	Toxicity and lack of efficacy	Increases cognitive decline/no lowering of brain amyloid
2012	Bapineuzumab	Elan/Pfizer/ Johnson & Johnson	Anti-Aβ mAb	Soluble Aβ and plaque	Mild to moderate AD	Lack of efficacy	No significant removal of amyloid
2013	Gammagard	Baxter	Unclear; IVIG may bind soluble Aβ	Soluble Aβ	Mild to moderate AD	Lack of efficacy	–
2013	Solanezumab	Eli Lilly	Anti-Aβ mAb	Soluble Aβ	Mild to moderate AD	Lack of efficacy	No removal of amyloid
2016	Gantenerumab	Hoffman La Roche	Anti-Aβ mAb	Plaque	Mild AD	Lack of efficacy	Converted into an open-label study
2016	Solanezumab	Eli Lilly	Anti-Aβ mAb	Soluble Aβ	Mild AD	Lack of efficacy	No removal of amyloid
2016	Solanezumab	Eli Lilly	Anti-Aβ mAb	Soluble Aβ	Prodromal AD	Trial halted	–
2016	Verubecestat	Merck	BACE inhibitor	Soluble Aβ	Mild to moderate AD	Lack of efficacy	Increases cognitive decline/modest lowering of brain amyloid (~20 CL)
2018	Verubecestat	Merck	BACE inhibitor	Soluble Aβ	Prodromal AD	Lack of efficacy	Increases cognitive decline
2018	Atabecestat	Janssen	BACE inhibitor	Soluble Aβ	Asymptomatic at risk of AD	Toxicity	Increases cognitive decline
2018	Lanabecestat	AstraZeneca/Eli Lilly	BACE inhibitor	Soluble Aβ	Early AD	Lack of efficacy	Increases cognitive decline
2018	Lanabecestat	AstraZeneca/Eli Lilly	BACE inhibitor	Soluble Aβ	Mild AD	Lack of efficacy	Increases cognitive decline
2019	Crenezumab	AC Immune/ Hoffman La Roche	Anti-Aβ mAb	Soluble Aβ	Prodromal to mild AD	Lack of efficacy	–
2019	Elenbecestat	Biogen/Eisai	BACE inhibitor	Soluble Aβ	Prodromal to MCI due to AD	Lack of efficacy	Increases cognitive decline
2019	Umibecestat	Amgen/Novartis	BACE inhibitor	Soluble Aβ	Asymptomatic at risk of AD	Lack of efficacy	Increases cognitive decline
2019	Amilomotide	Novartis	Vaccine	Aβ	Asymptomatic at risk of AD	Trial halted	–
2020	Aducanumab	Biogen/Eisai	Anti-Aβ mAb	Plaque	MCI to early dementia	Evidence of efficacy	BLA given accelerated approval by the FDA but rejected by the CHMP of the EMA

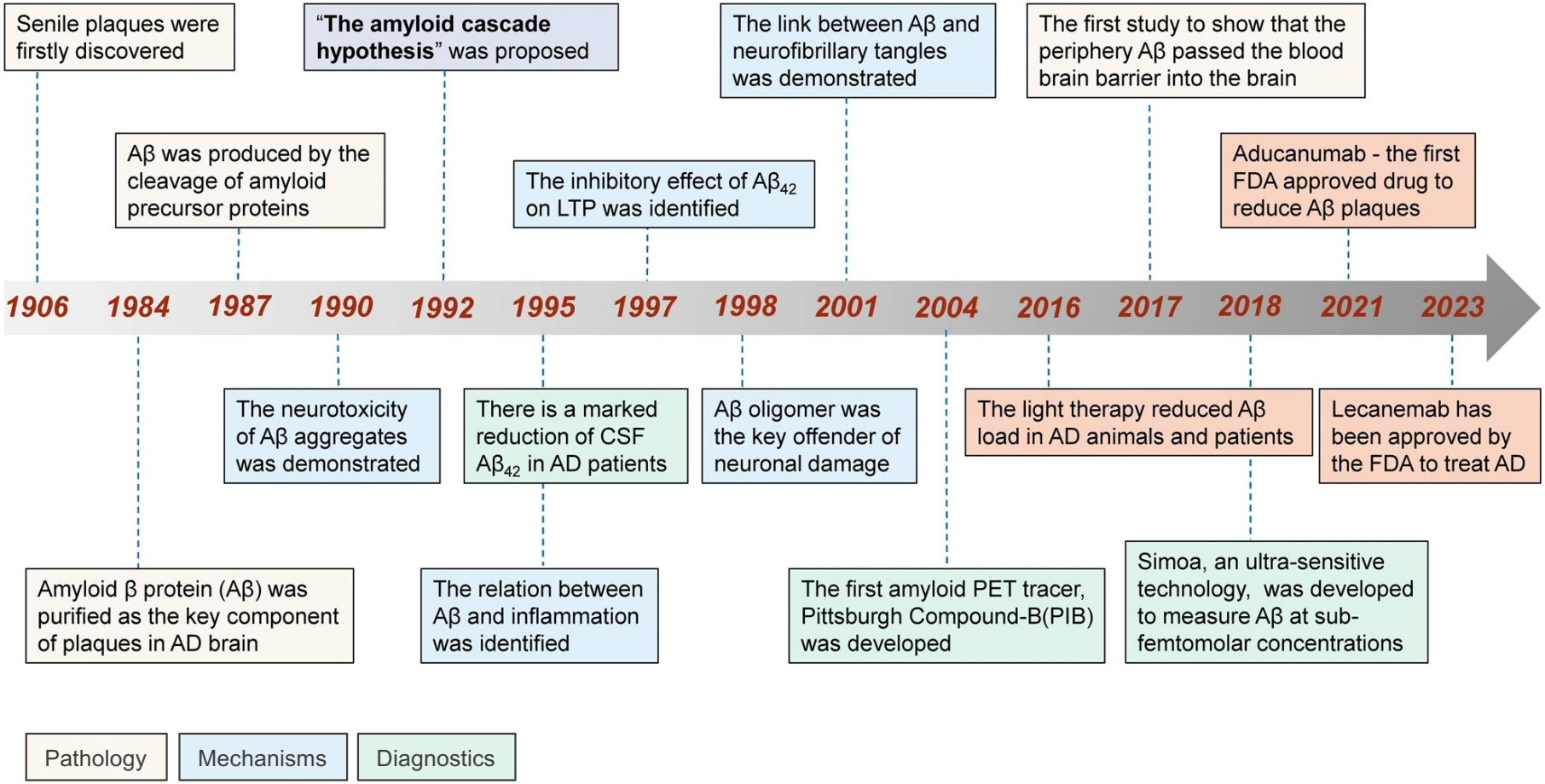
Antibody-mediated clearance of Amyloid β pathology

Passive immunization with anti-Aβ antibodies: proposed mechanisms



The most accepted mechanism

Immunotherapy against Amyloid β pathology: historical perspective

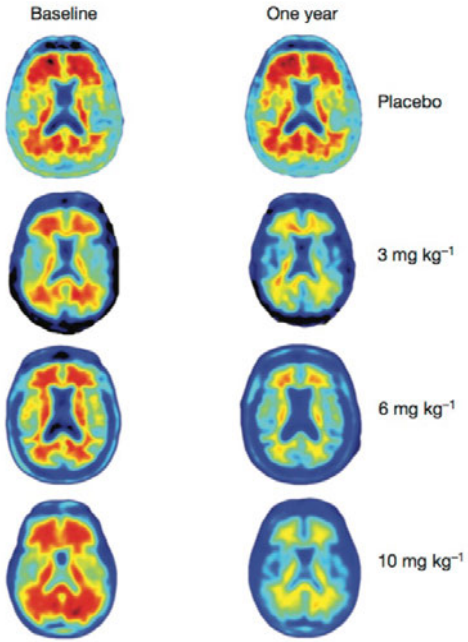


Sig Transduct Target Ther **8**, 248 (2023)

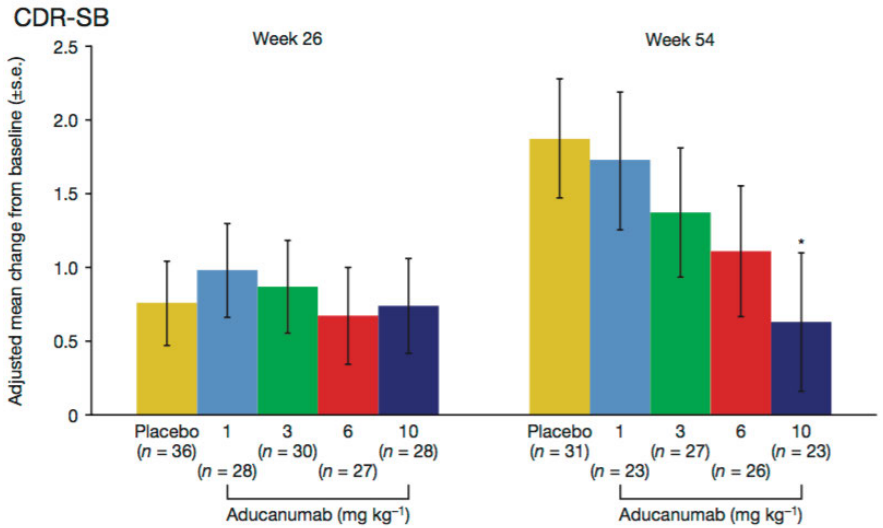
Anti-amyloid β therapy: antibody-mediated clearance

Phase 1b trial with Aducanumab in prodromal or mild AD

amyloid PET imaging at baseline and week 54



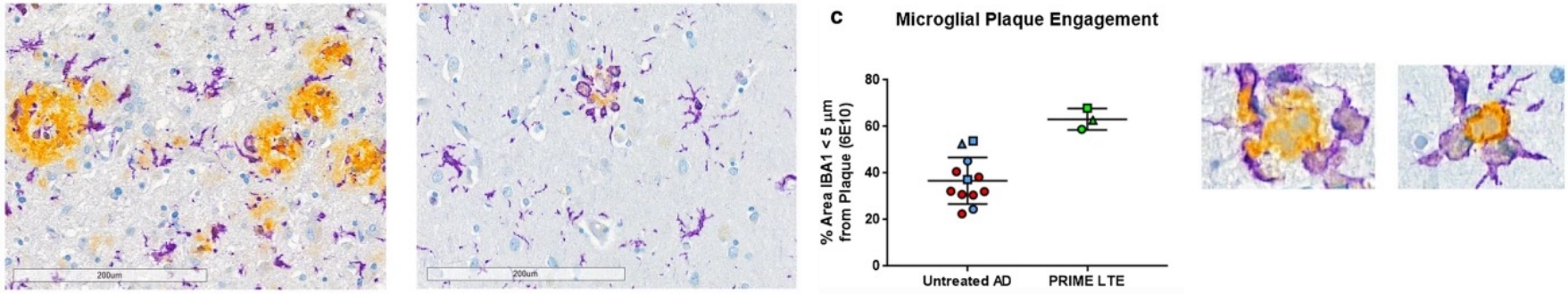
Effect on Clinical Dementia Rating (CDR-SB)



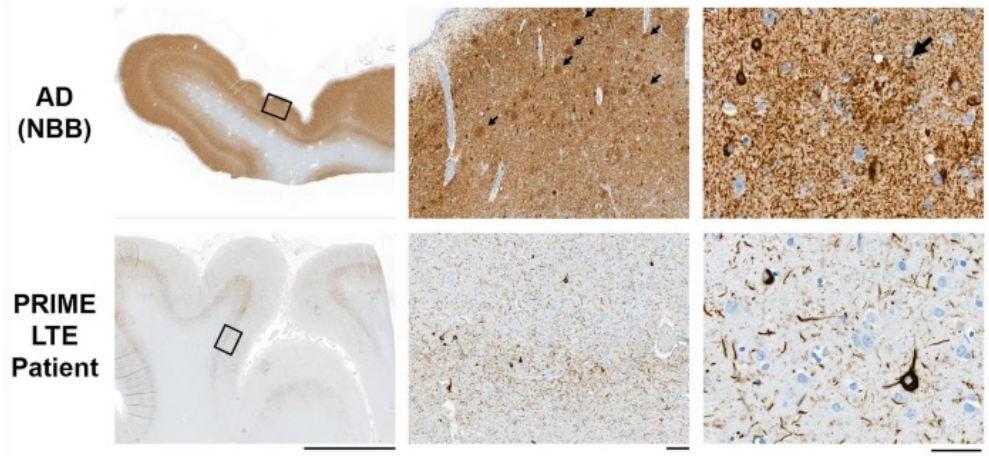
Sevigny J et al, Nature 537, 2016

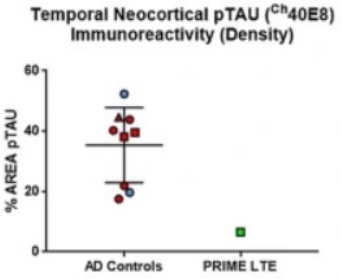
Alzheimer's pathology in a patient treated with Aducanumab (32-months treatment) shows reduction of Aβ plaque pathology

Microglia surrounding amyloid plaques



Phospho-tau pathology





Acta Neuropathologica vol 144, pp 143–153 (2022)

The ups and downs of a ‘promising’ anti-Aβ treatment

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

March 21 2019

Shock revelation sees Biogen erase its aducanumab losses

Oct 22 2019

Biogen Asks FDA To Approve Aducanumab

July 8 2020

Data for Biogen's Alzheimer's hopeful aducanumab 'highly persuasive': FDA briefing documents

Nov 4 2020

Biogen’s Alzheimer’s drug candidate takes a beating from FDA advisers

Nov 6 2020

Biogen

FDA grants accelerated approval for ADUHELM™ as the first and only Alzheimer's disease treatment to address a defining pathology of the disease

June 7 2021

Biogen, with sales falling sharply, posts 'obviously disappointing' Aduhelm sales of $300K, CEO Vounatsos says

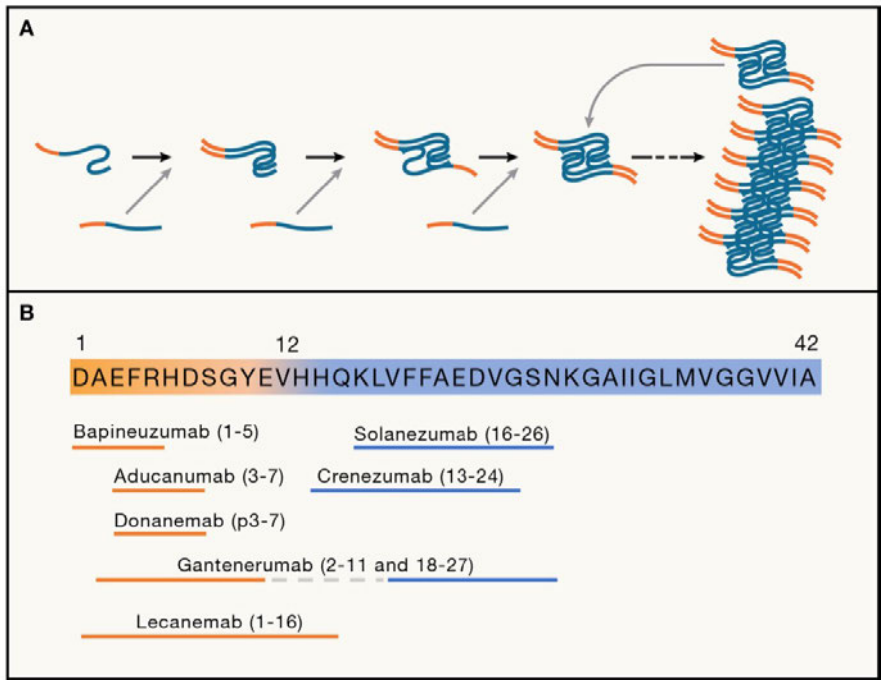
October 20 2021

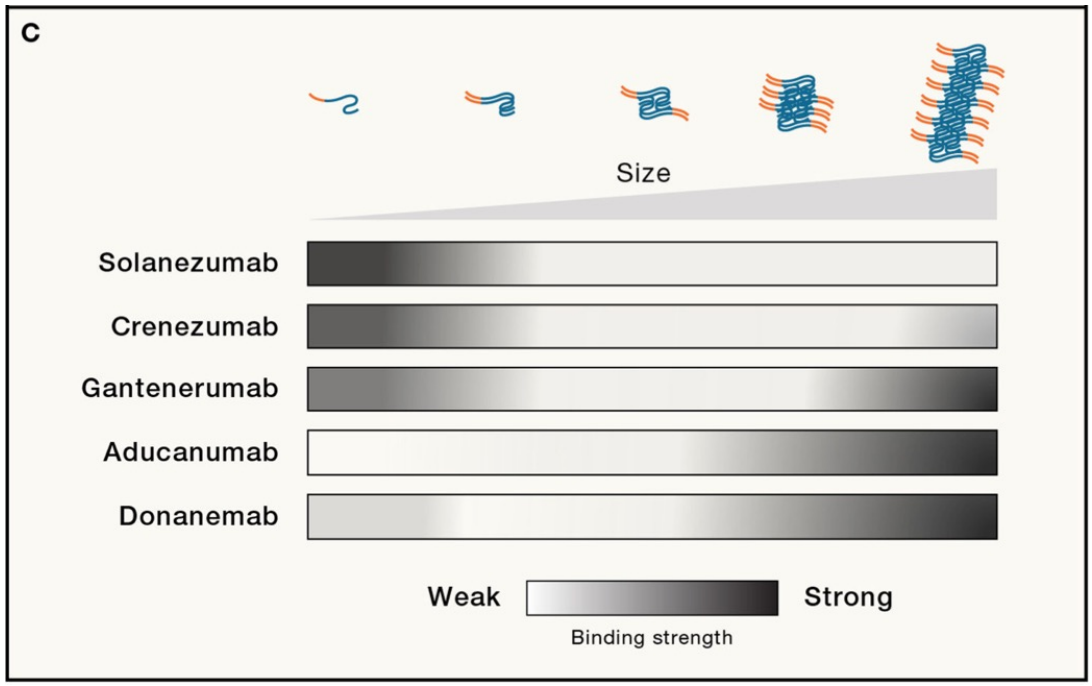
EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Aduhelm: Withdrawal of the marketing authorisation application Share

Antibody-mediated clearance of Amyloid β pathology

Aβ epitopes of monoclonal antibodies tested in clinical trials for Alzheimer disease

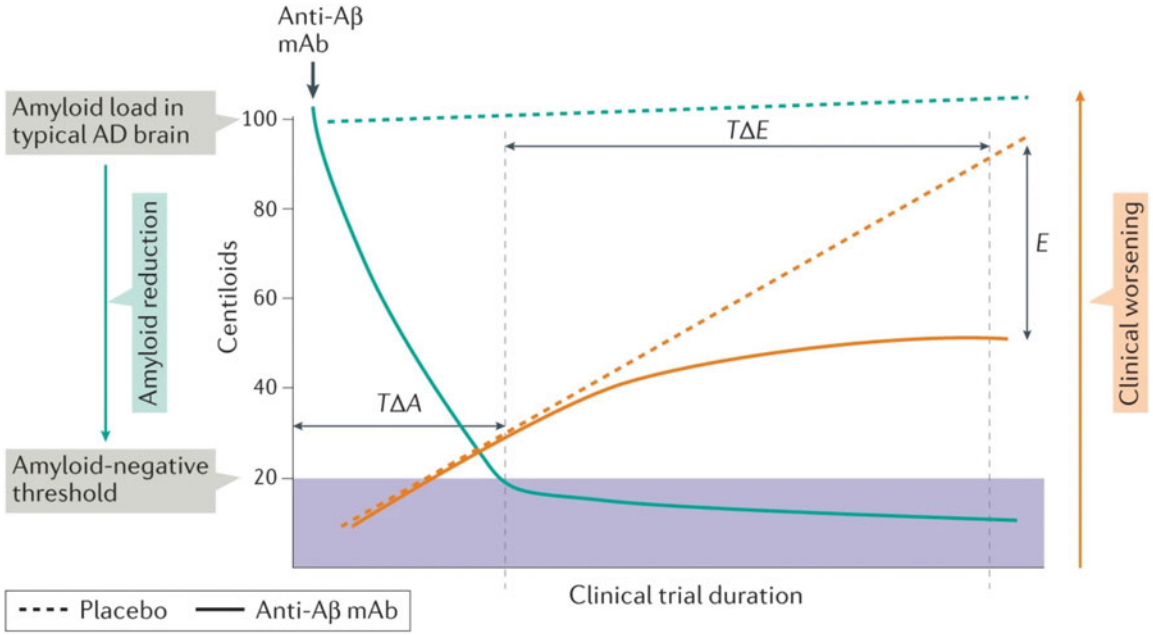


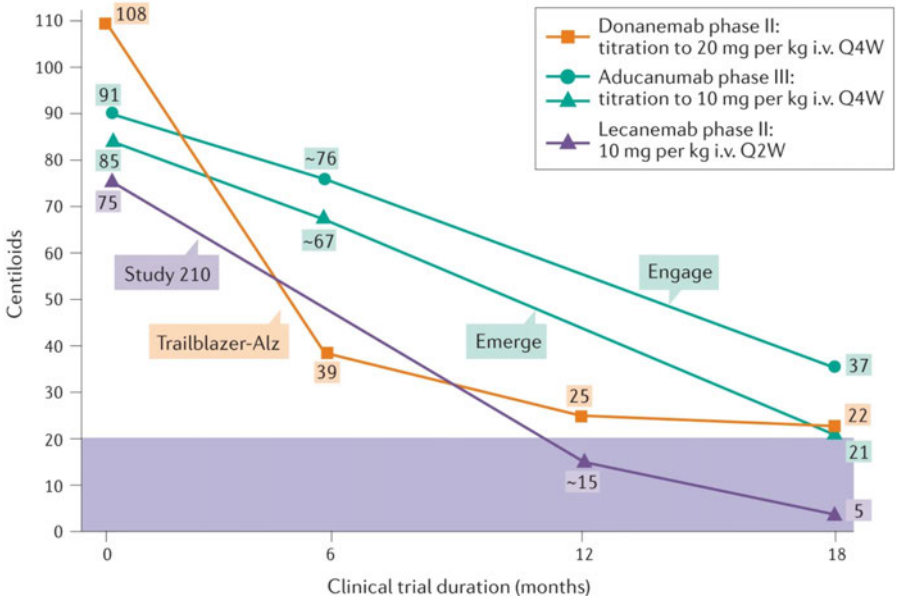


Cell, Vol. 186(20), (2023), pp. 4260-4270
Nature Reviews Drug Discovery volume 21, pages 306–318 (2022)
Nature Structural & Molecular Biology volume 27, pages 1125–1133 (2020)

Aβ immunotherapy: evaluation of efficacy

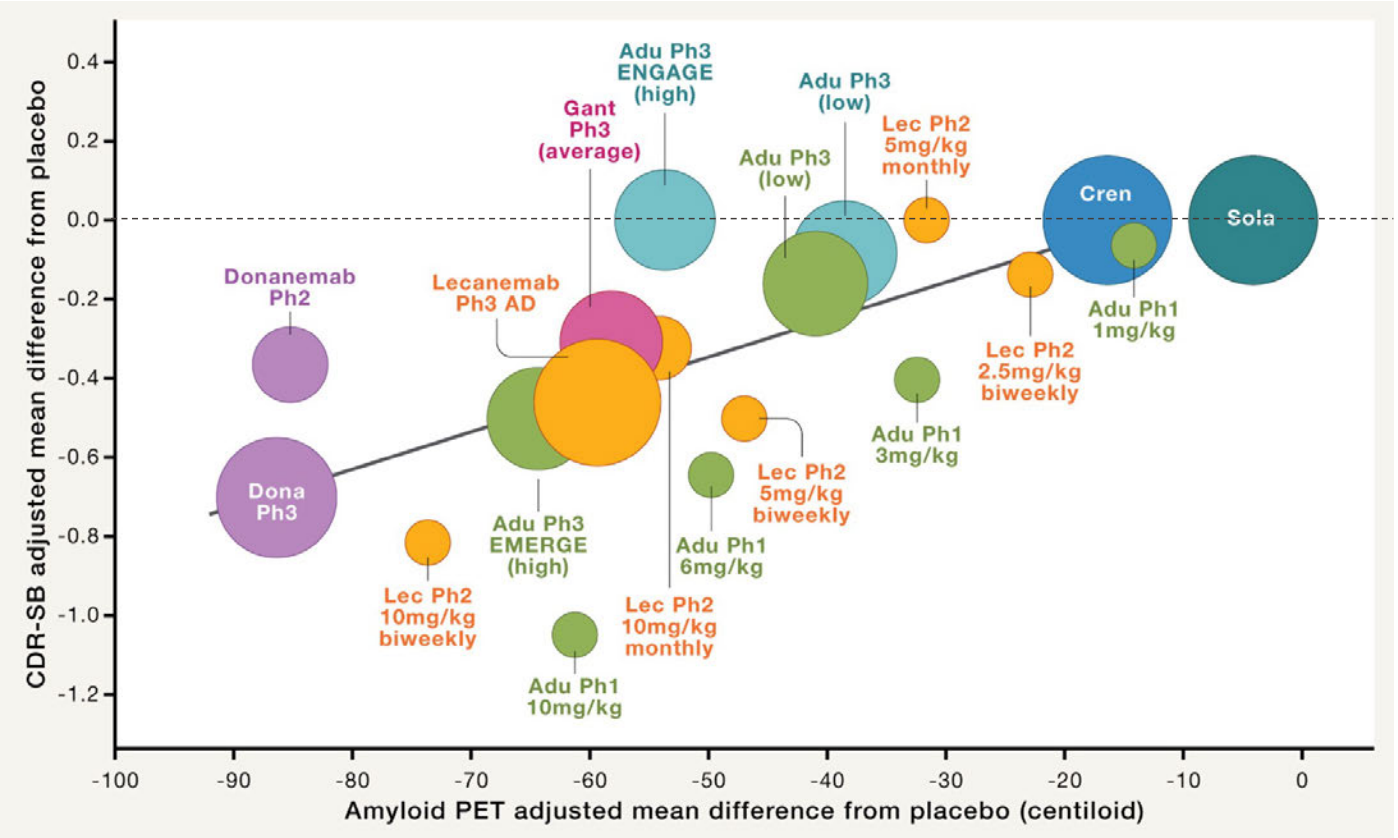
PET imaging of amyloid β load in the brain





Nature Reviews Drug Discovery volume 21, pages 306–318 (2022)

Aβ immunotherapy: evaluation of efficacy of the different antibodies

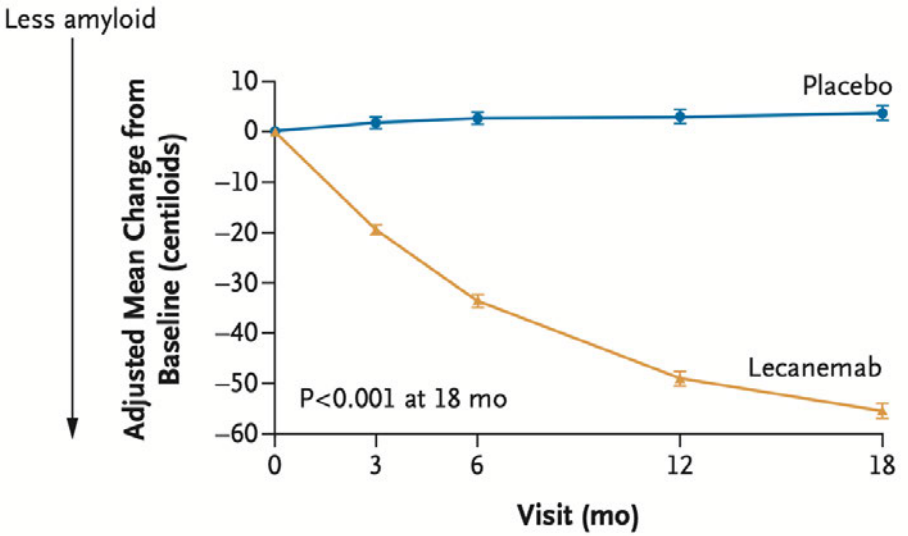


Variable outcome of anti-Aβ antibody treatments.

Cell, Volume 186, Issue 22, 2023, Pages 4757-4772

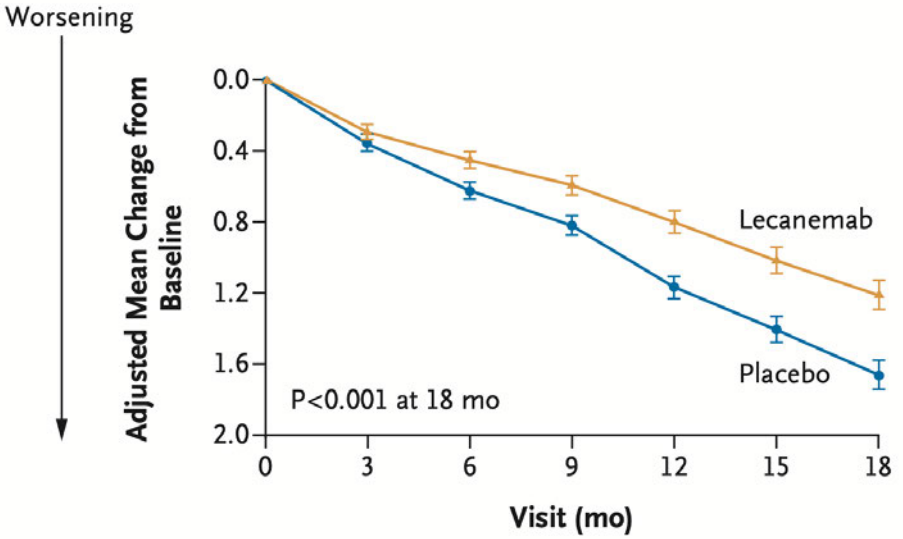
Aβ immunotherapy: *lecanemab* efficacy

Amyloid Burden on PET



No. of Participants					
Lecanemab	354	296	275	276	210
Placebo	344	303	286	259	205

CDR-SB Score

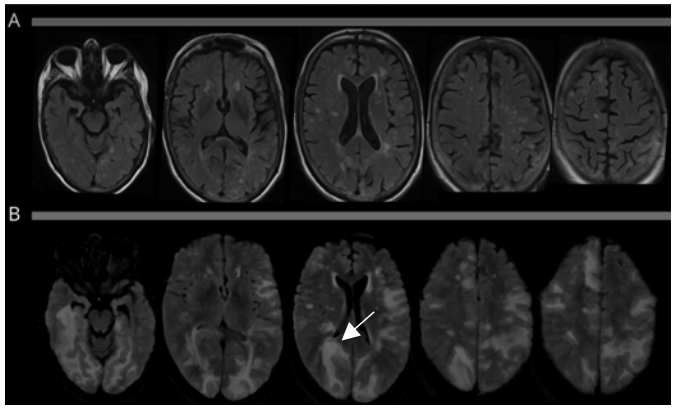


No. of Participants							
Lecanemab	859	824	798	779	765	738	714
Placebo	875	849	828	813	779	767	757

- *N Engl J Med 2023;388:9-21. DOI: 10.1056/NEJMoa2212948*

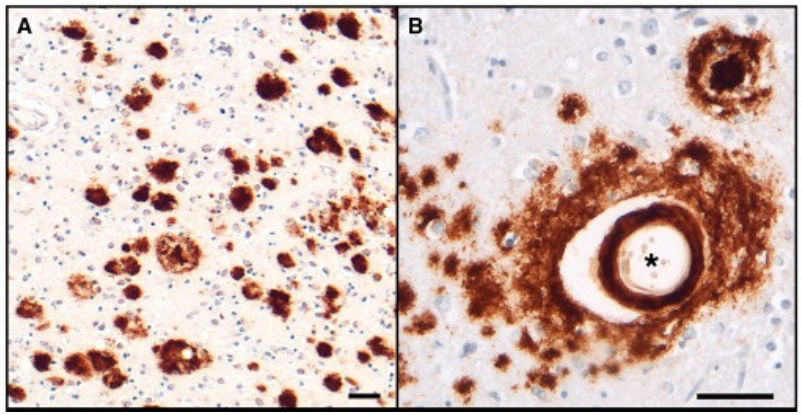
Side-effects associated with anti-Aβ immunotherapy

- Amyloid-related imaging abnormalities (ARIA= edema/effusion) linked to pre-existing Aβ deposition (especially CAA).
- Changes in brain volume.

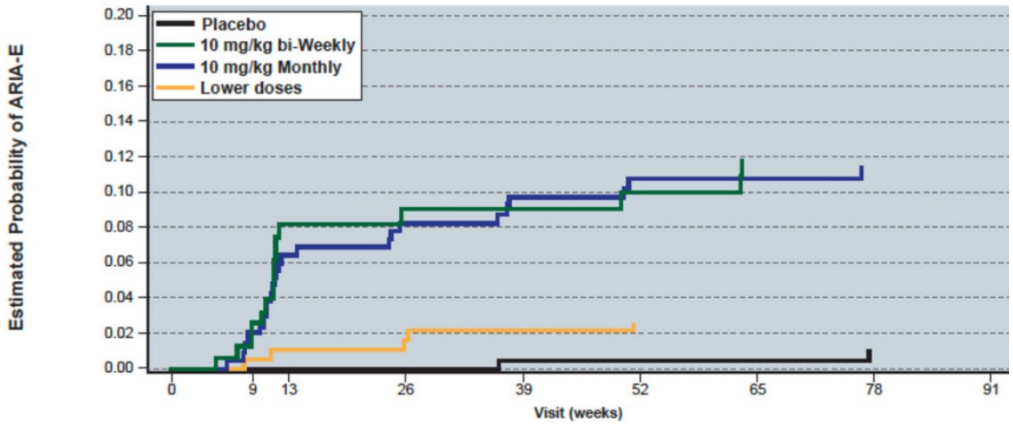


Amyloid plaques in the brain parenchyma

Cerebral β-amyloid angiopathy (CAA)



Frequency of ARIA in lecanemab-treated AD patients

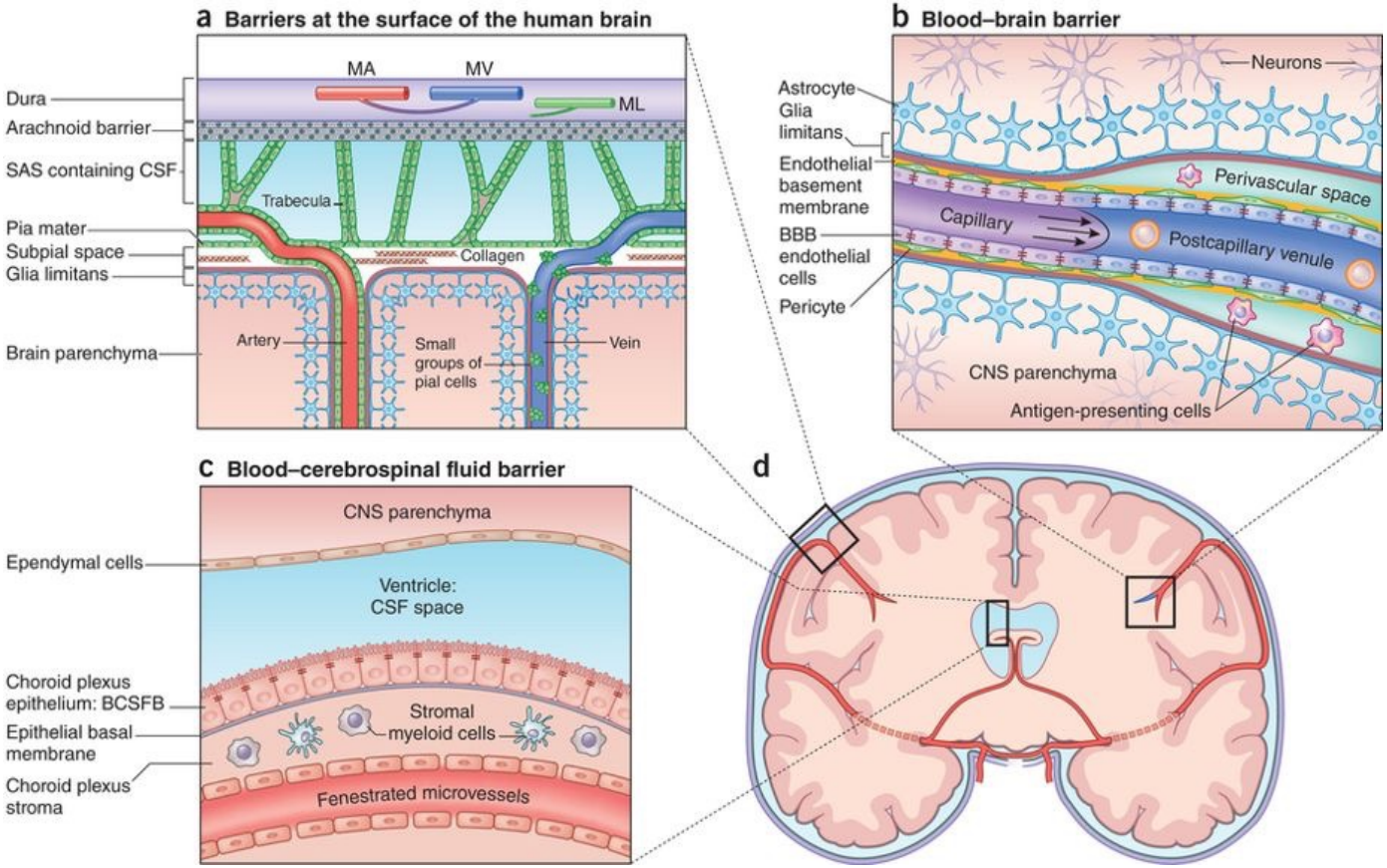


BIO480

- *Cell, Vol. 186, Issue 20, 2023, pp. 4260-4270*

Barriers to the CNS

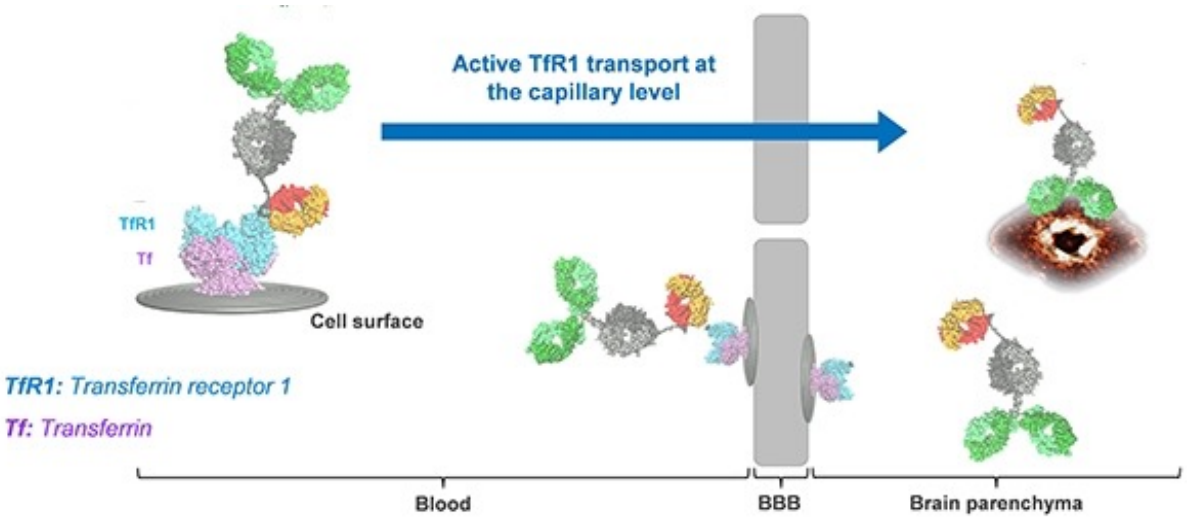
Acellular and cellular brain barriers

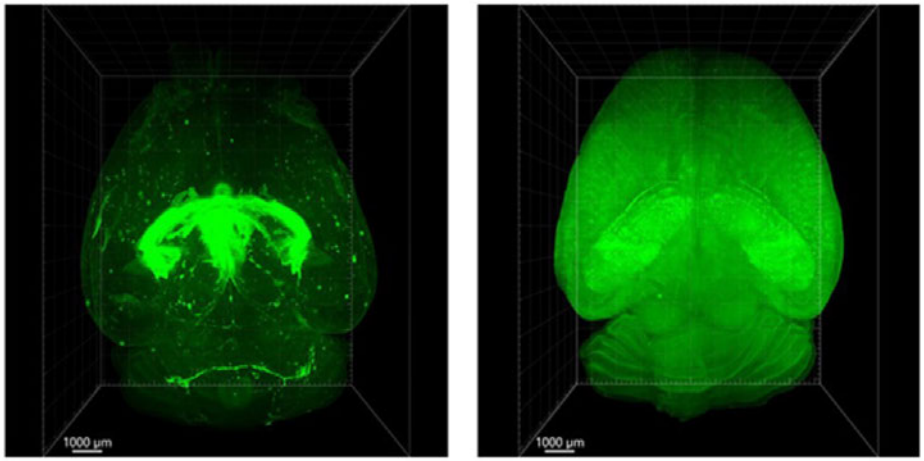


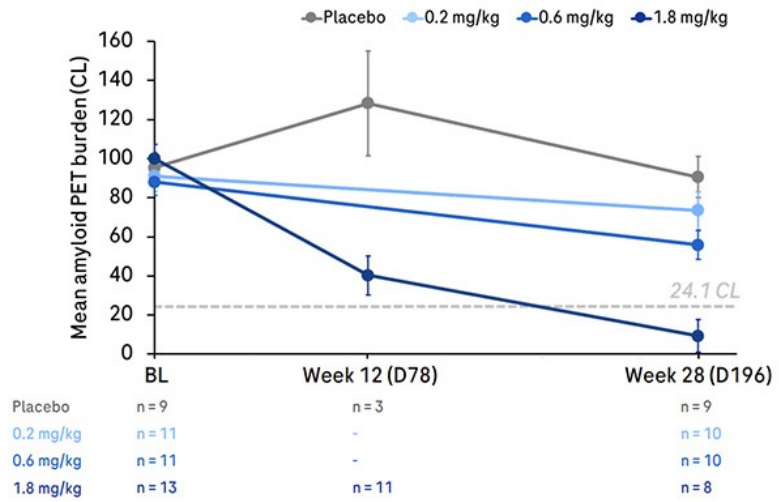
Engelhardt B, Nature Immunology volume 18, pages 123–131 (2017)

Engineering of anti-Aβ antibodies to cross the blood-brain barrier

- Antibody is designed to bind the transferrin receptor to induce shuttling through the BBB.







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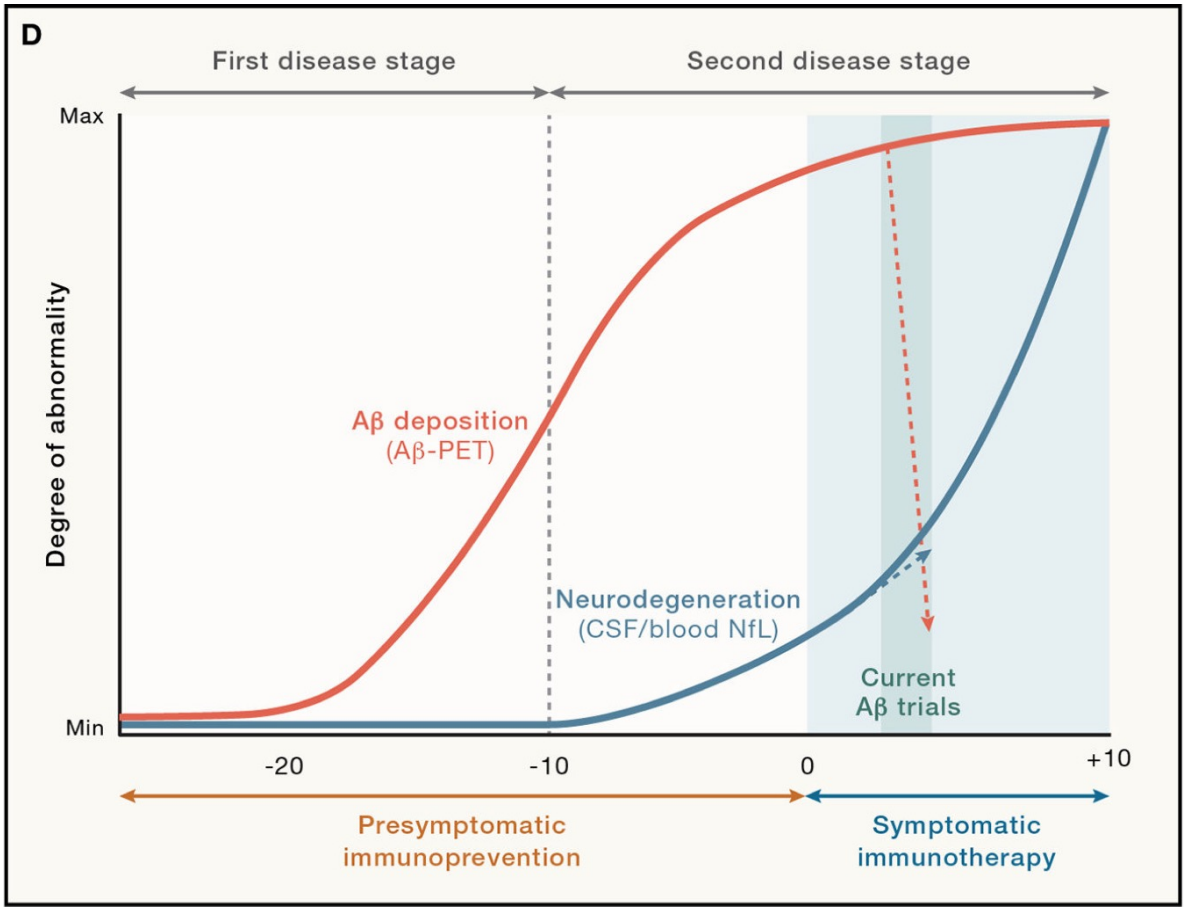
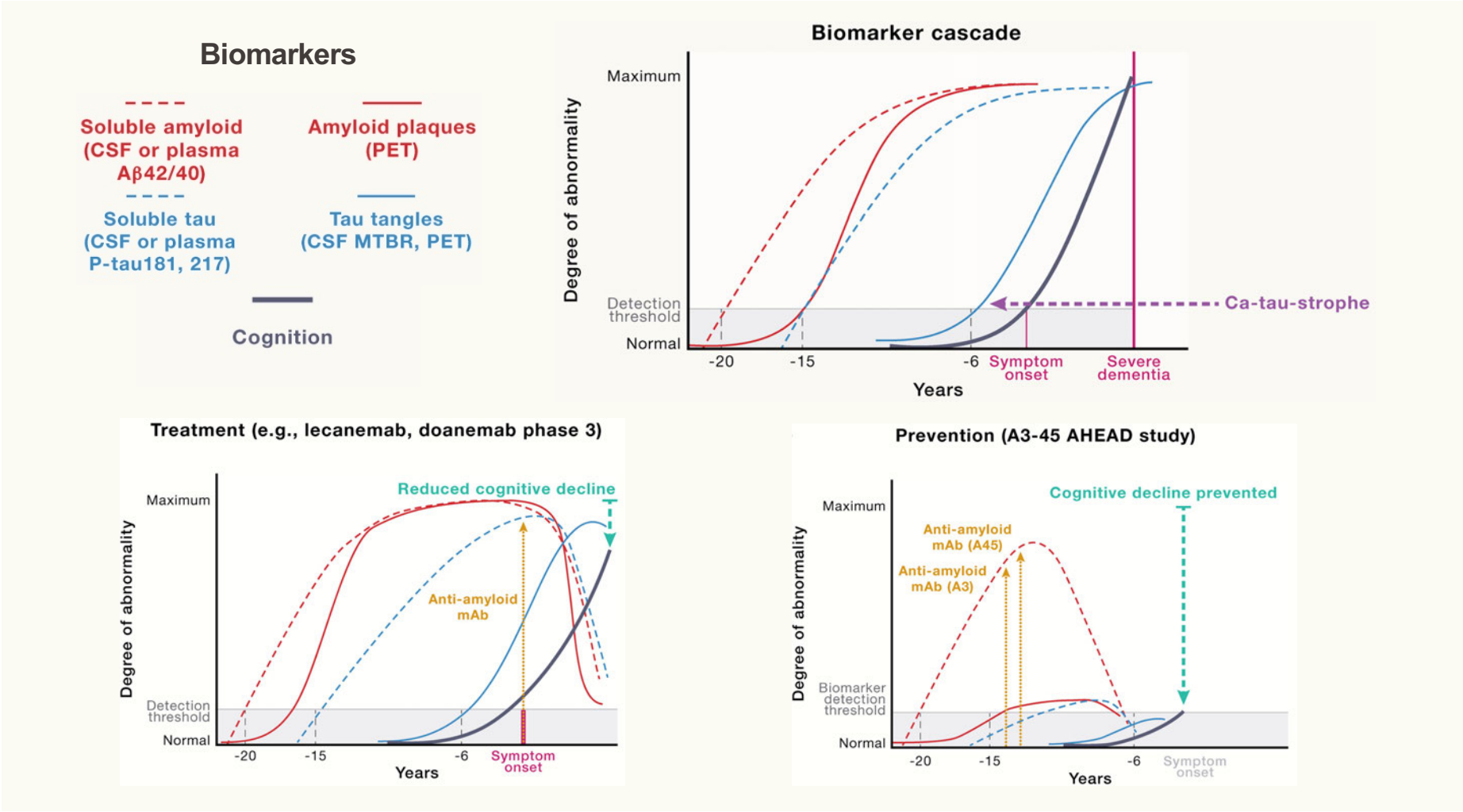
DOI: 10.1016/j.neuron.2013.10.061

Aβ immunotherapy: the importance of therapeutic window



Cell, Vol. 186, Issue 20, 2023, pp. 4260-4270

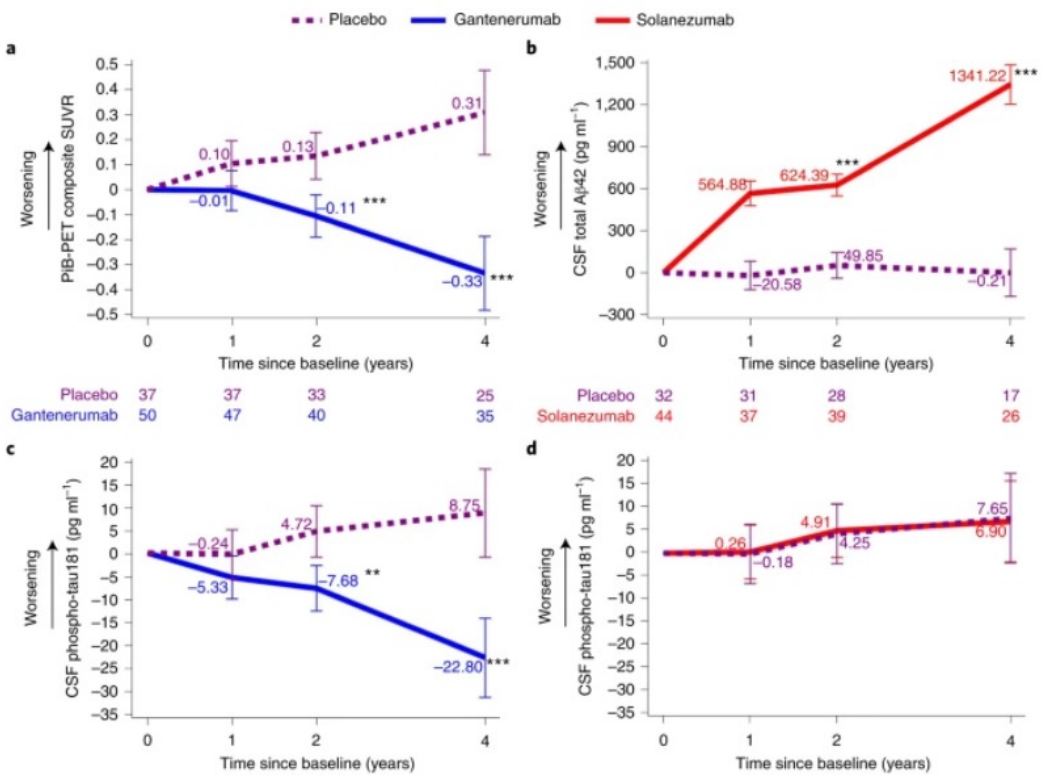
Aβ immunotherapy: towards prevention ?

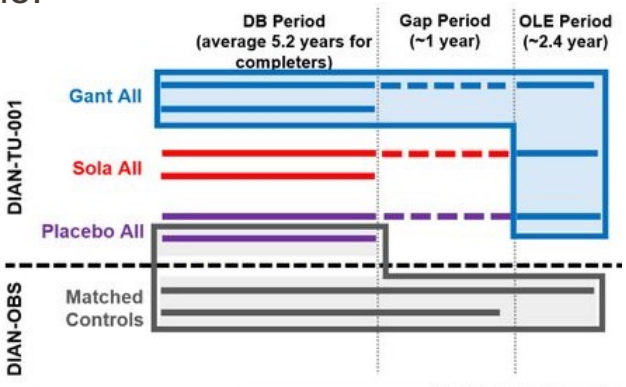


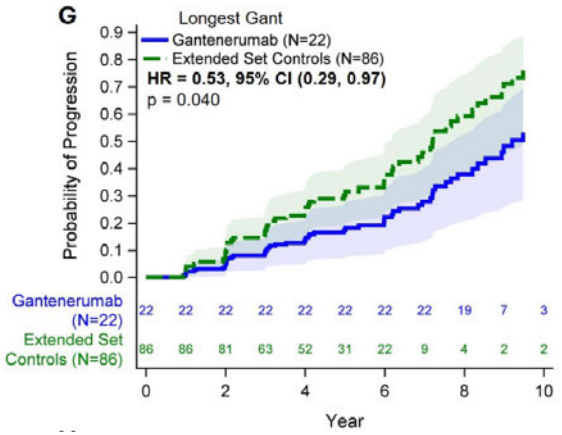
Cell, Volume 186, Issue 22, 2023, Pages 4757-4772

DIAN-TU preventive trial for Alzheimer's disease

- **Autosomal dominant AD** caused by mutations in APP, Presenilin 1 or Presenilin 2.
- Treatment initiated at **pre-symptomatic and mild symptomatic stages**.
- DIAN–TU-001: testing gantenerumab (anti-fibrillar Aβ) and solanezumab (anti-soluble Aβ).
- 2015: 4-years treatment trial started to slow or prevent cognitive decline.



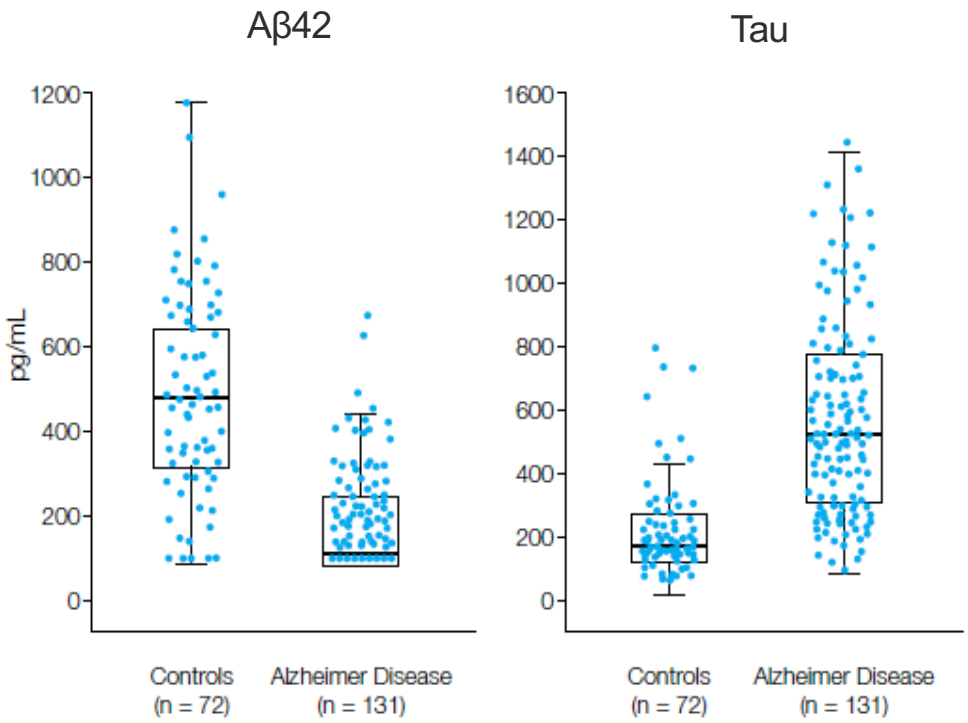




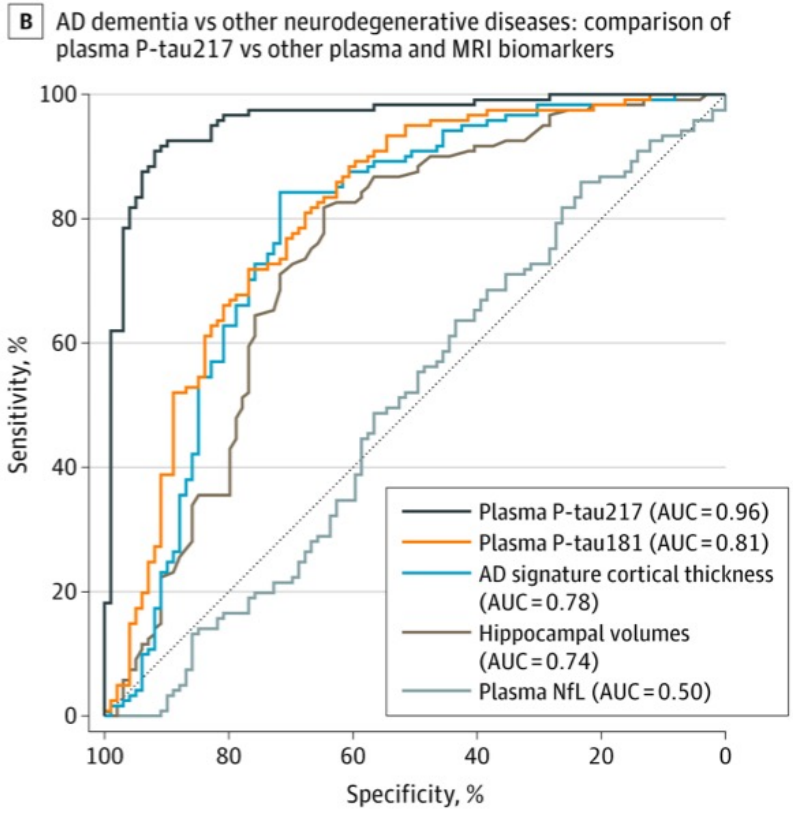
doi: https://doi.org/10.1101/2024.10.29.24316289

Biomarkers for Alzheimer's disease

CSF Tau and Aβ levels

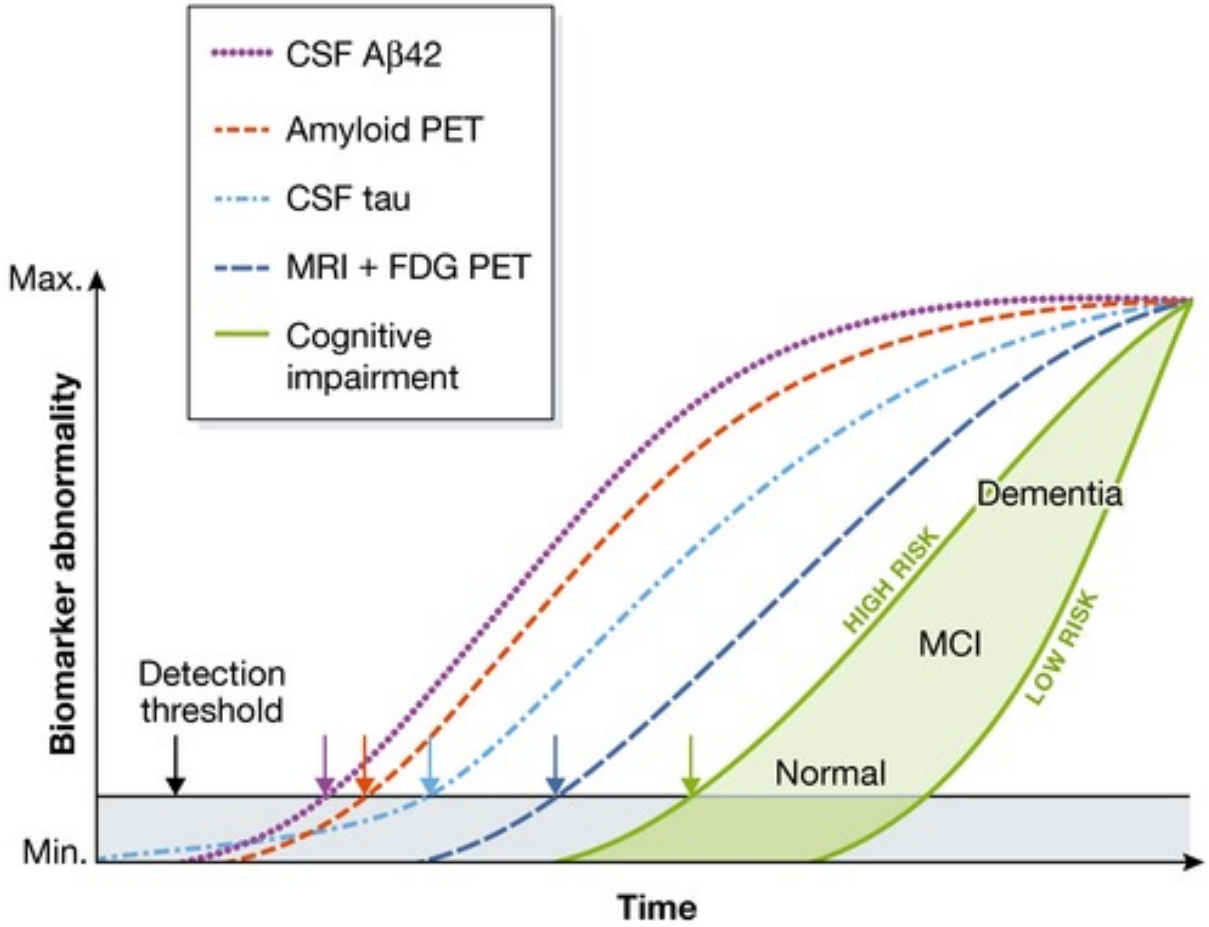


Plasma phospho-tau levels



Sunderland T et al., JAMA 289 (2003)
Palmqvist S et al., JAMA. 2020;324(8):772-781

Biomarkers for Alzheimer's disease



EMBO Mol Med 8(6) p595 2016

Therapies based on 'β-amyloid cascade hypothesis'

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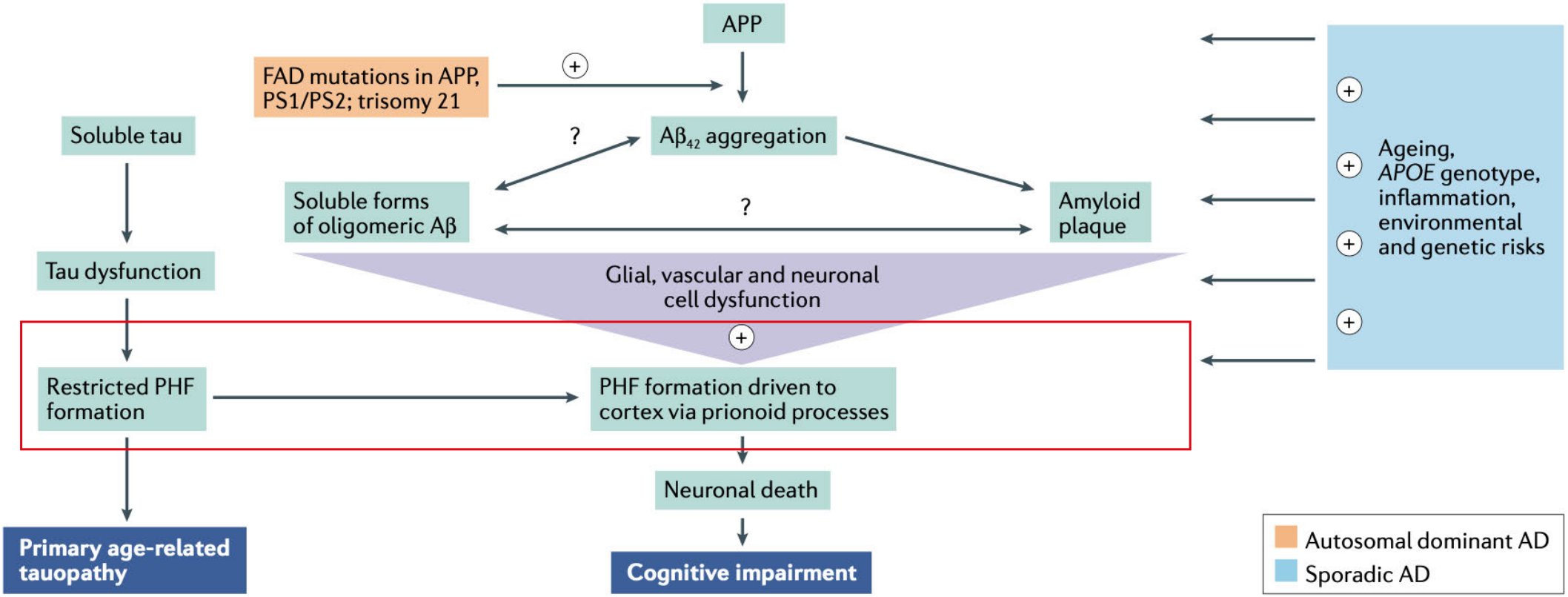
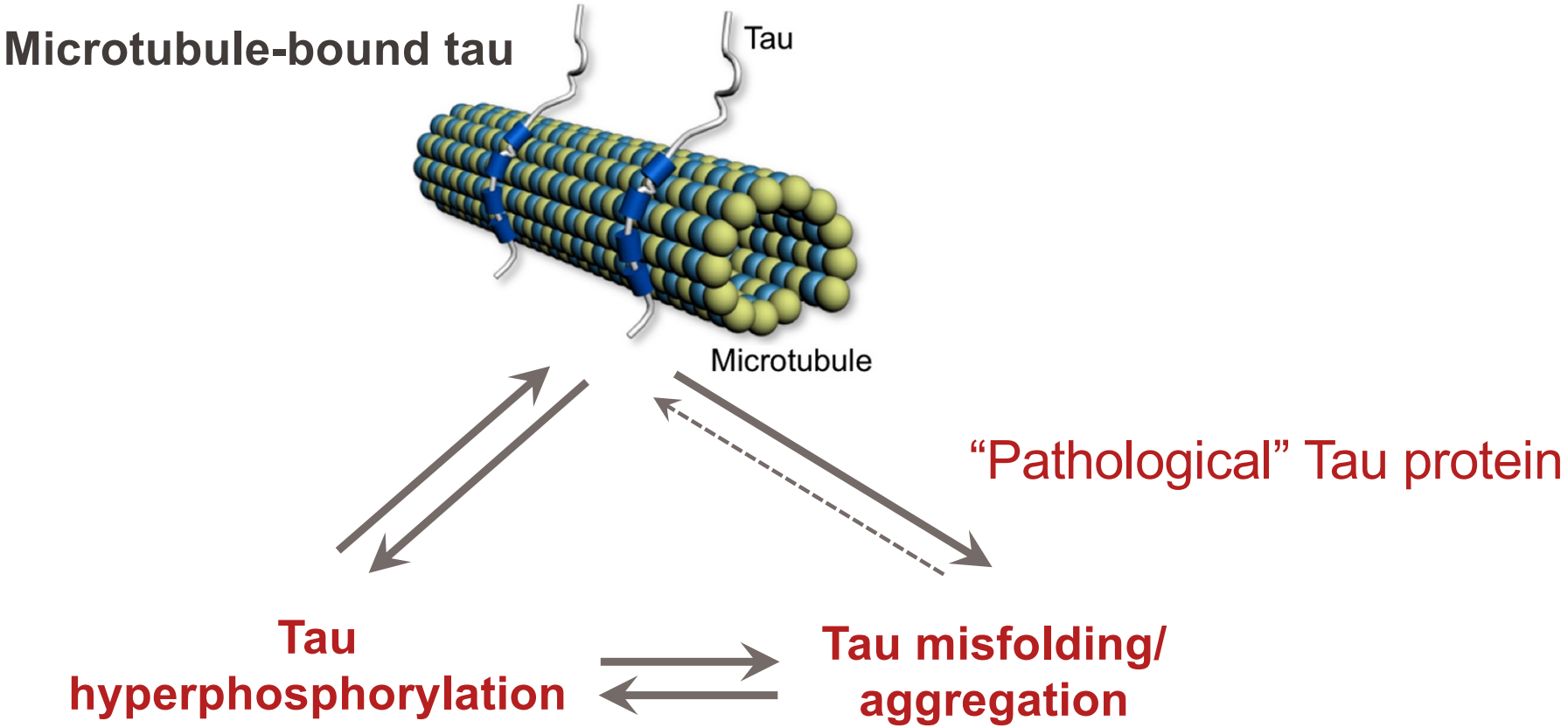


- *Nature Reviews Drug Discovery 21, pp. 306–318 (2022)*

Tau pathology in Alzheimer's disease: therapeutic target



Brain imaging with Tau PET ligands reveals spread of Tau pathology

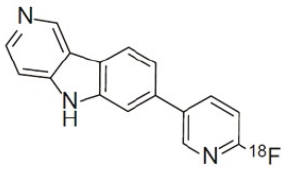
Tau PET imaging: Tau pathology as a function of age and amyloid pathology

Neuron
Article

PET Imaging of Tau Deposition in the Aging Human Brain

Michael Schöll,[1,2,6] Samuel N. Lockhart,[1,6] Daniel R. Schonhaut,[3] James P. O'Neil,[4] Mustafa Janabi,[4] Rik Ossenkoppele,[1,3,5] Suzanne L. Baker,[4] Jacob W. Vogel,[1] Jamie Faria,[4] Henry D. Schwimmer,[1] Gil D. Rabinovici,[1,3,4] and William J. Jagust[1,4,*]

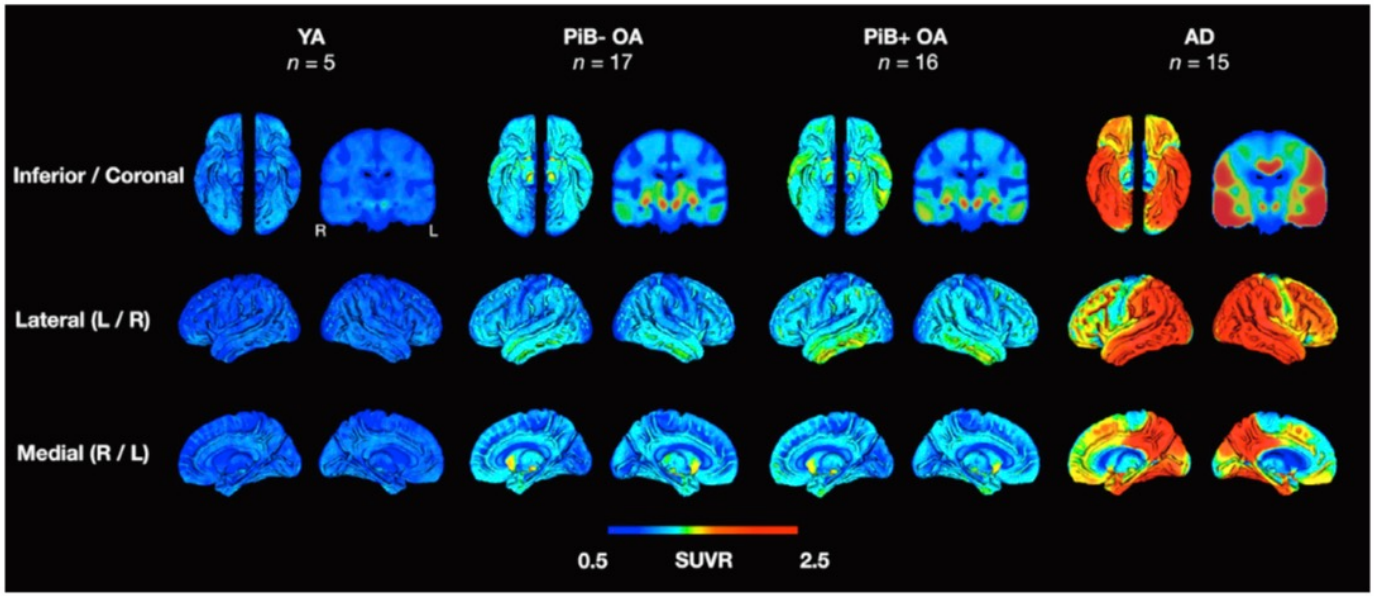
2016



^{18}F-AV1451(T807)

Tau PET ligand: high affinity for paired-helical filaments (PHFs), insoluble fibers composed of hyper-phosphorylated tau

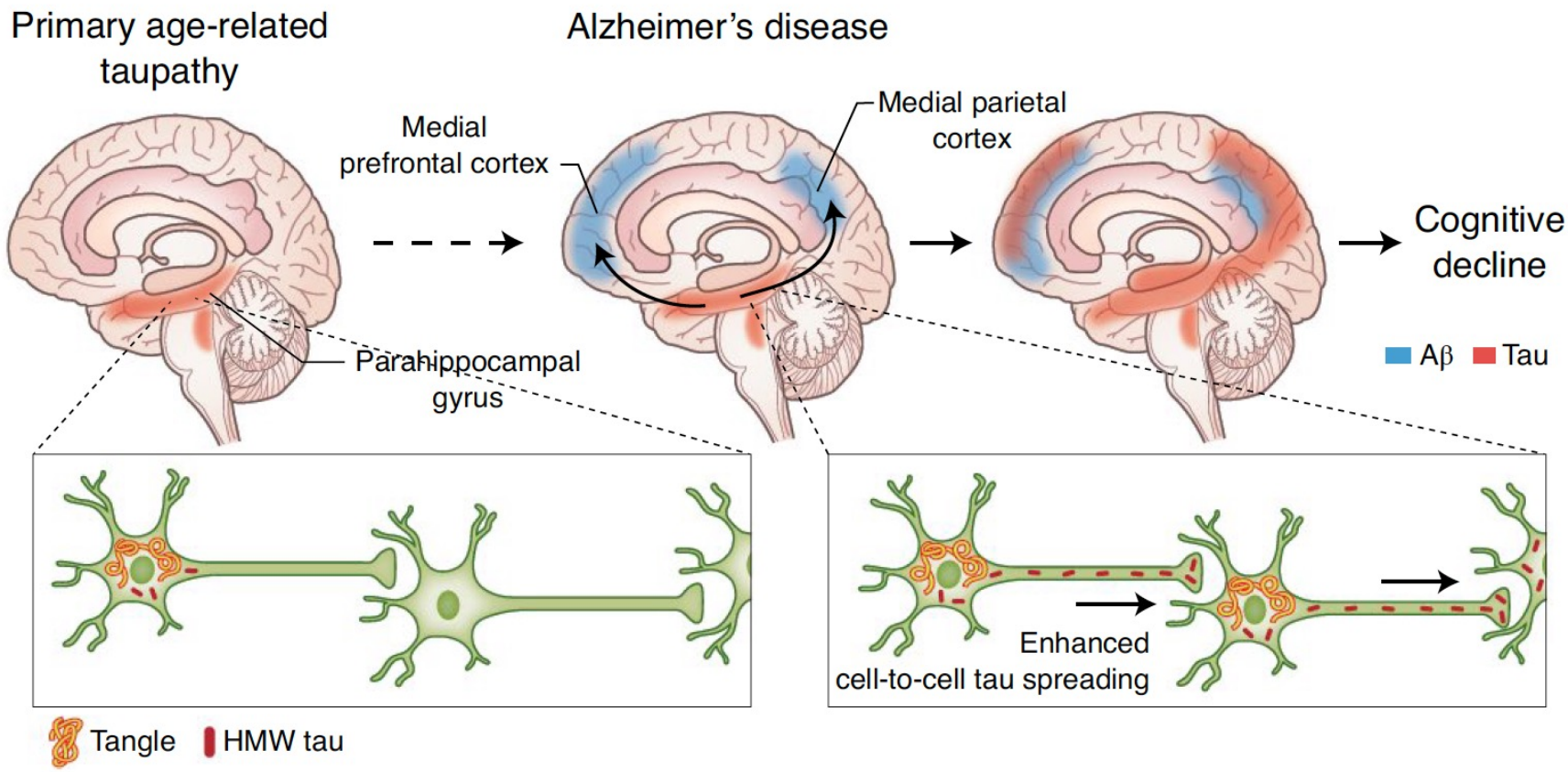
Young adults (20-26y.) Old adults (64-90y.) Alzheimer's (53-77y.)



Average global retention

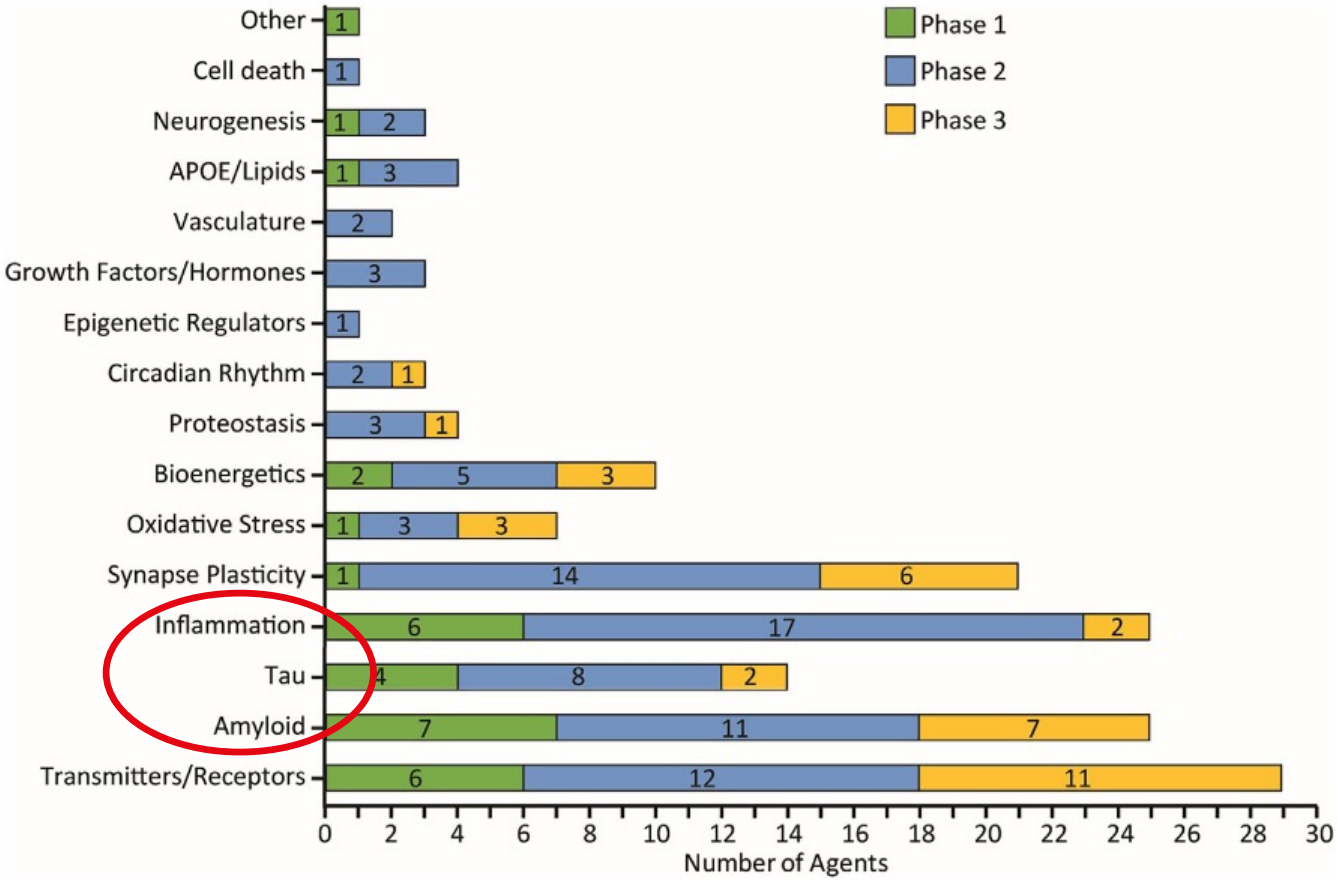
Model of Tau / Aβ interaction in Alzheimer's disease

Aβ pathology triggers spreading of Tau tangles in Alzheimer's disease



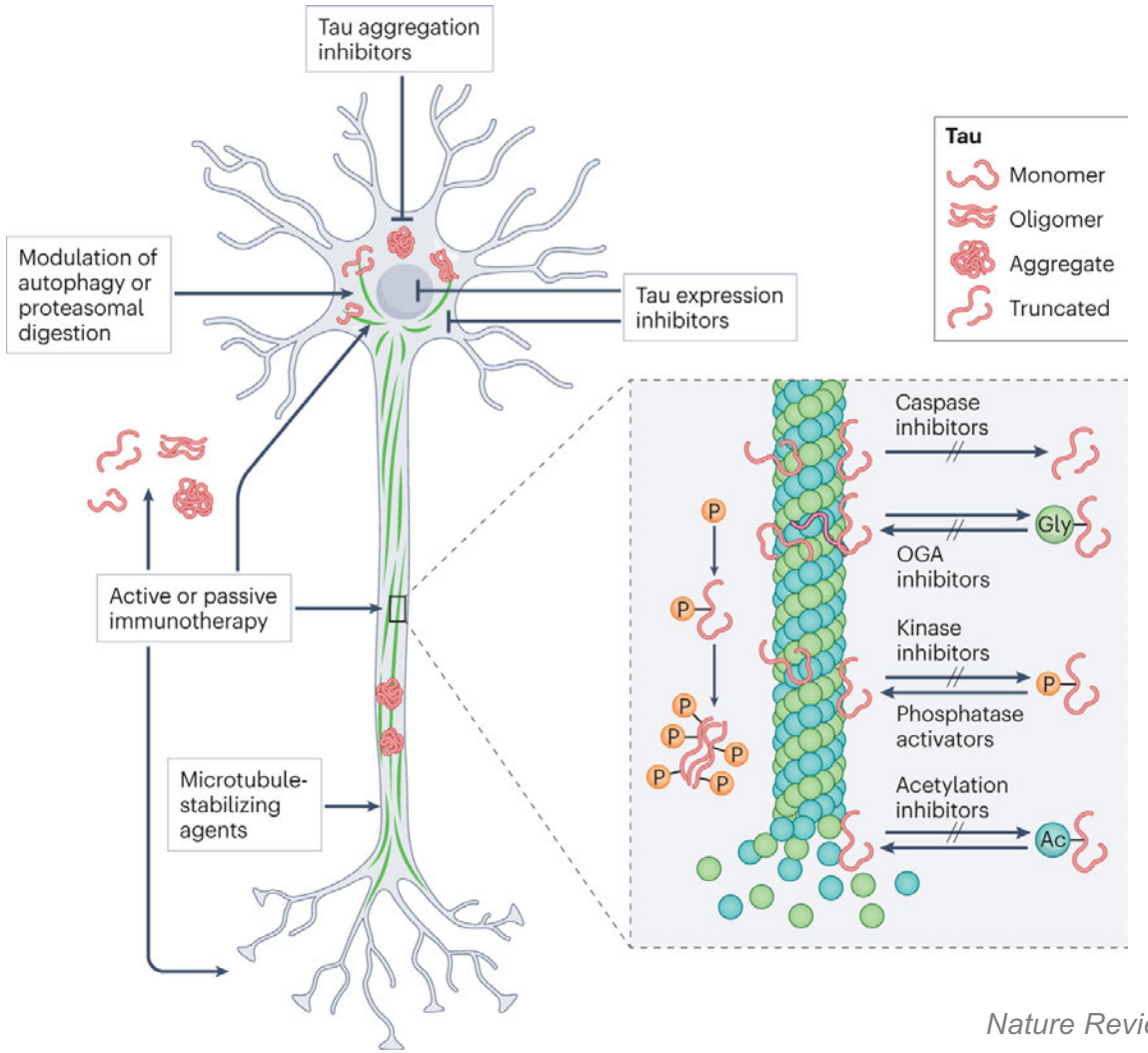
Molecular Psychiatry 26, pp 5481–5503 (2021)

Mechanisms of action of the AD drugs under clinical trial



Cummings et al., 2023

AD Treatments Targeting the Tau Pathology: Mechanisms of Action

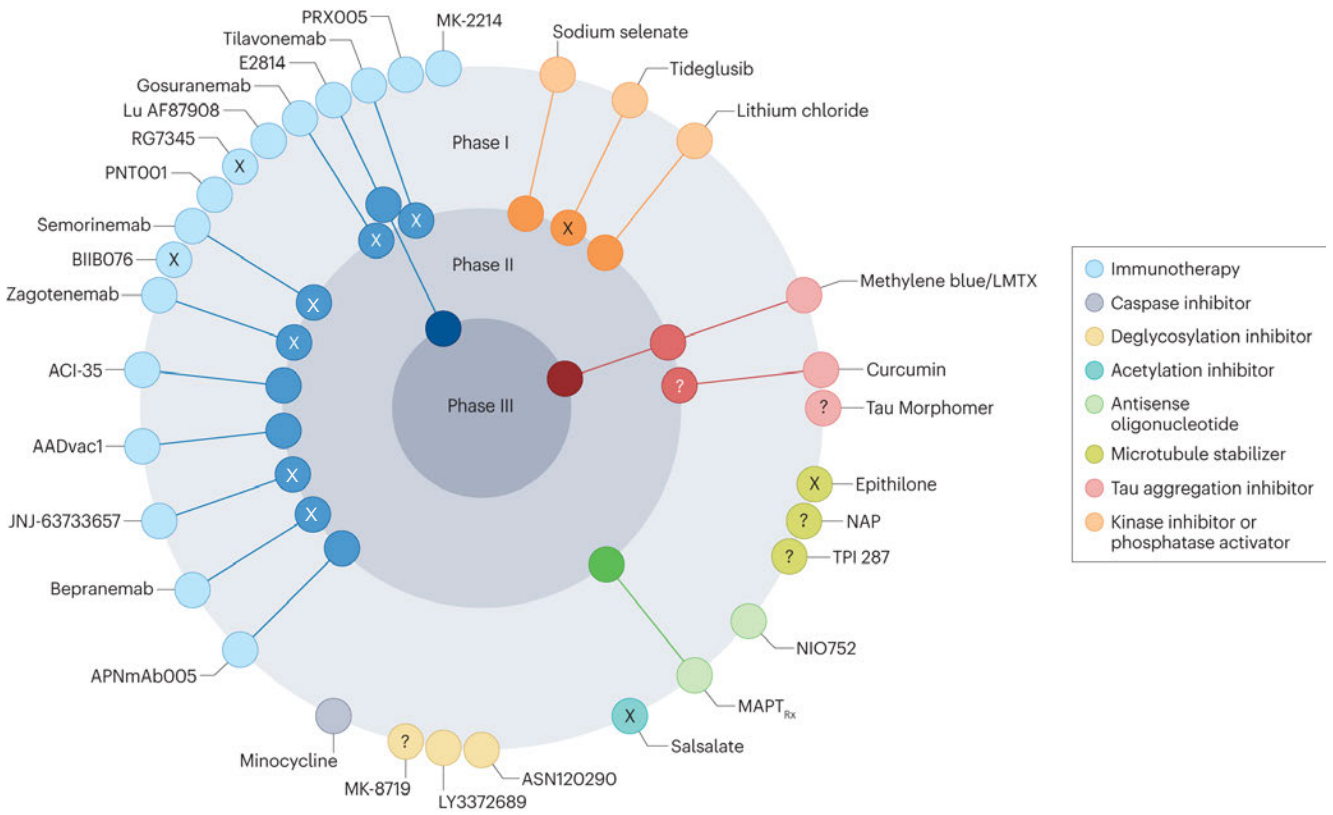


Nature Reviews Neurology vol. 19, pp. 715–736 (2023)

AD Treatments Targeting Tau: Current Clinical Trials

Drug	Company	Target	Status
Bepranemab	UCB	Mid-region epitope	Phase II failed
Etalanetug	Eisai	Mid-region epitope	Phase III[a]
BMS-986446	BMS	Mid-region epitope	Phase II
Posdinemab	J&J	Mid-region epitope	Phase II
VY-TAU01	Voyager	C-terminal epitope	Phase I
Semorinemab	Roche	N-terminal epitope	Discontinued
Gosuranemab	Biogen	N-terminal epitope	Discontinued
Tilavonemab	AbbVie	N-terminal epitope	Discontinued
Zagotenemab	Eli Lilly	Conformational epitope[b]	Discontinued
BIIB076	Biogen	Mid-region epitope	Discontinued
Lu AF87908	Lundbeck	C-terminal epitope	Discontinued
RG7345	Roche	C-terminal epitope	Discontinued

[a]Being tested in combination with anti-amyloid lecanemab. [b]Includes the N-terminal.



- *Nature Reviews Neurology vol. 19, pp. 715–736 (2023)*

Novel Therapeutic Approaches for CNS Diseases

- **CNS and Therapy Development**

  General principles

- **Immunotherapy against Alzheimer's Disease**

- **Gene therapy for CNS diseases**

  Example of AAV as gene delivery system for the CNS

  Lipid Storage Diseases – ex vivo gene therapy for MLD

  Motoneuron Diseases – RNAi against SOD1

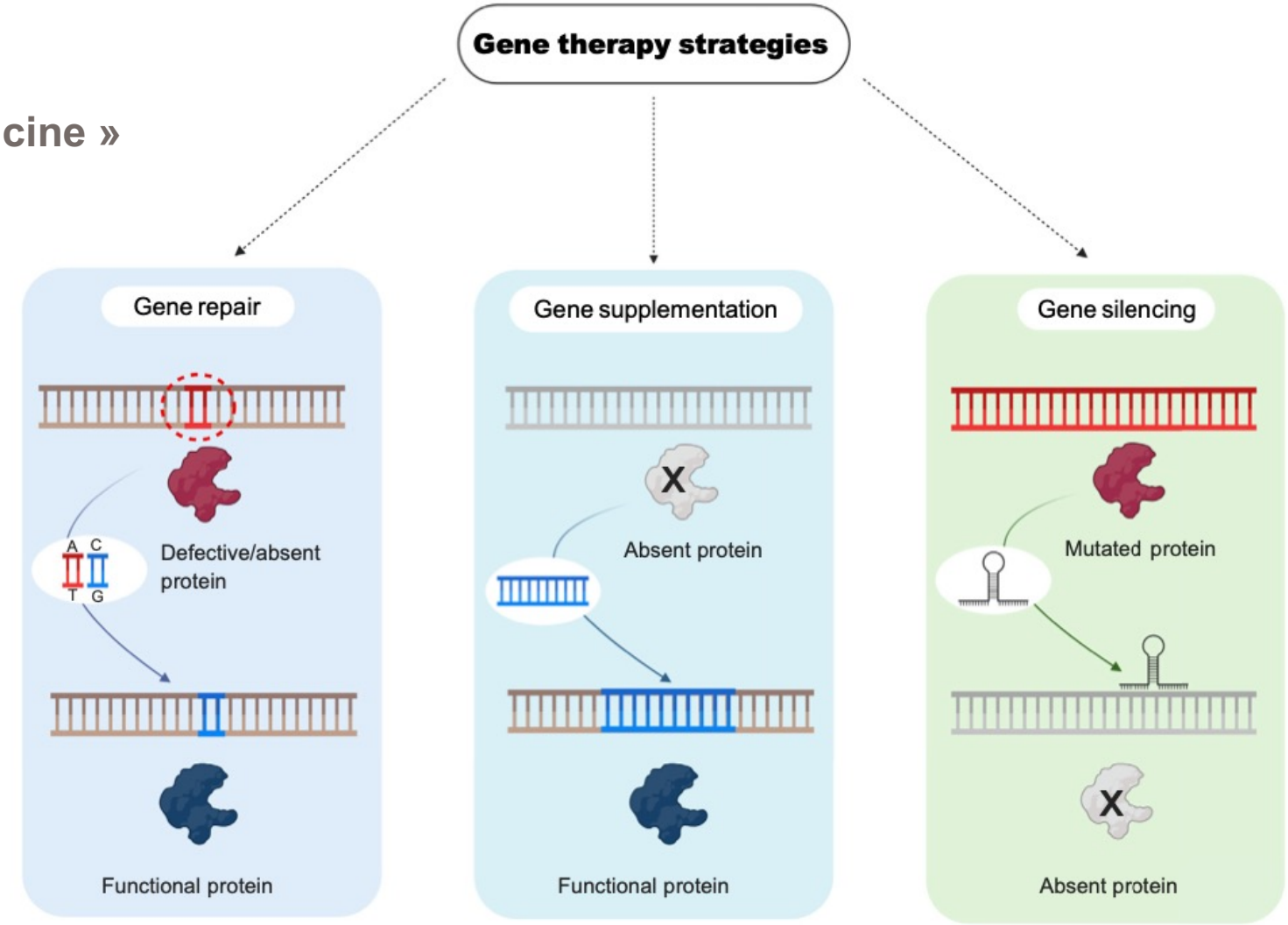
- **Sensory organs:**

  Blindness functional rescue by optogenetic

  Deafness Rescue of cochlear function

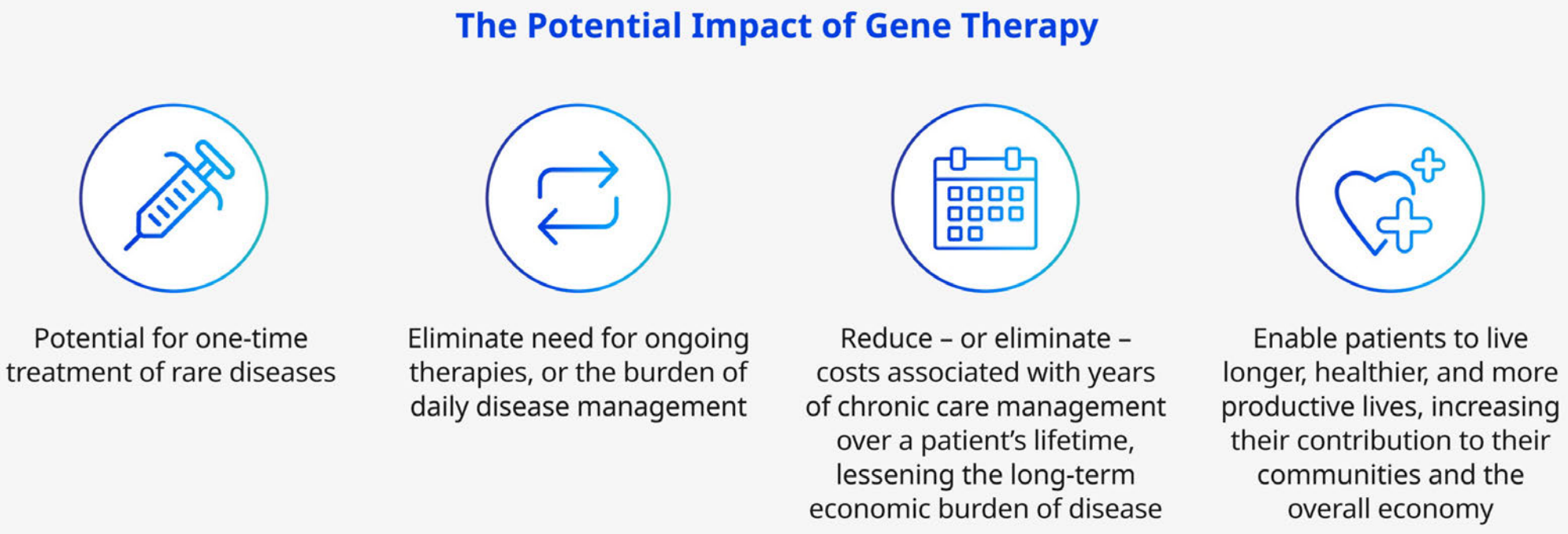
Gene therapy: nucleic acids as therapeutic modality

« Precision medicine »



JHEP Reports 2021 vol. 3

The potential impact of gene therapy



Bhatia, Sonal et al.
Molecular Therapy Methods & Clinical Development, Volume 32, Issue 2, 101220

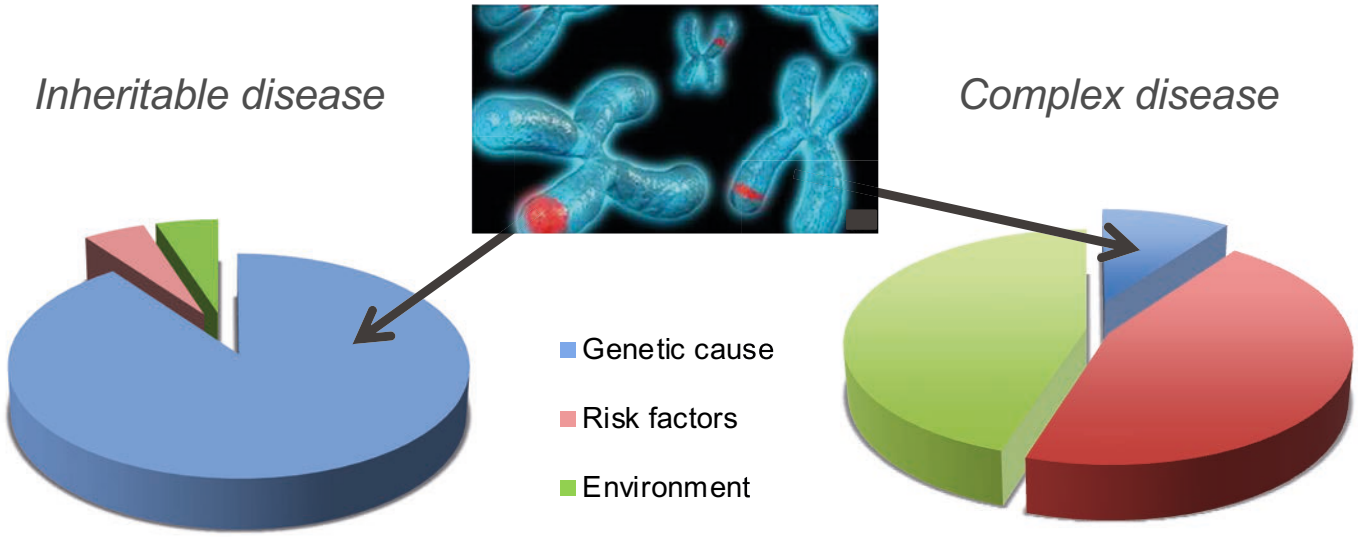
Gene therapy emerges as a therapeutic modality for inheritable rare diseases

- Defective genes account for ~80% of the total of more than 7,000 diseases known to date
- Rare diseases affect **300 mio people.**
- **95%** with no approved treatment.

- **>1100** rare **neurological** disorders
- **>350** hereditary **eye** diseases
- **>400** genetic causes of **deafness**

Genetics: rare monogenic diseases versus complex diseases

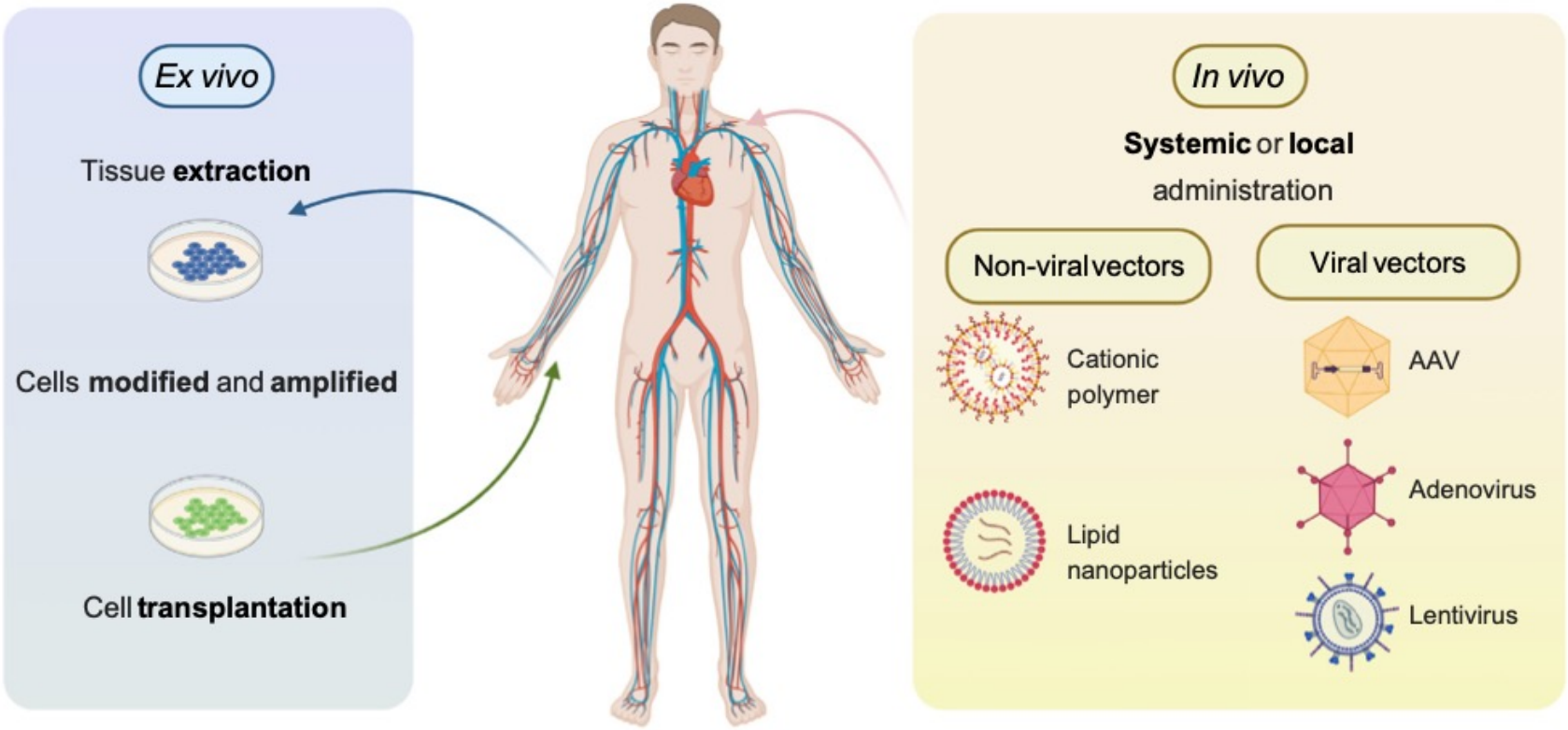
« Rare diseases » with genetic cause



Huntington's disease
Spinal Muscular Atrophy (SMA)
Adrenoleukodystrophy

Alzheimer's disease
Parkinson's disease
Amyotrophic Lateral Sclerosis (ALS)

Gene therapy: nucleic acids as therapeutic modality



Development path:

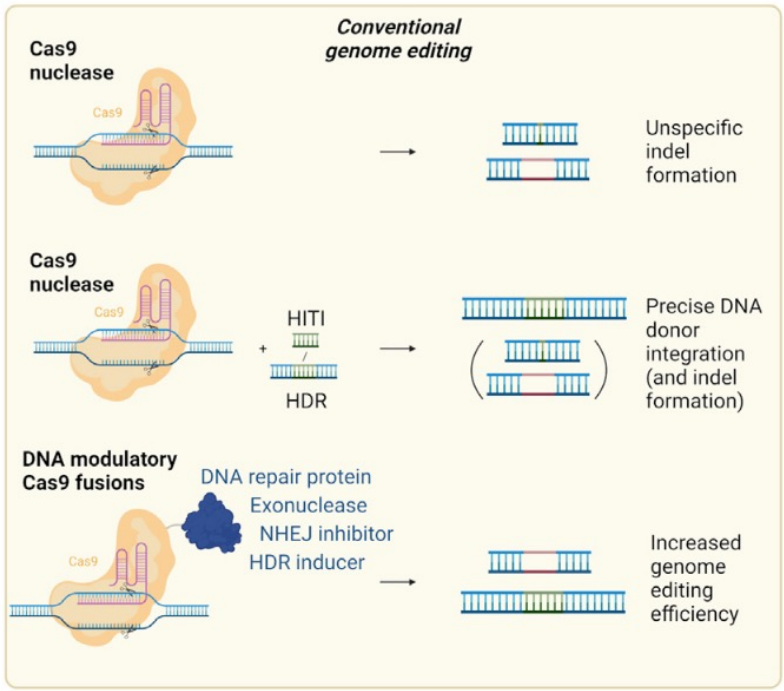
1- Disease model
2- Biodistribution
3- Safety/toxicity
4- Manufacturing

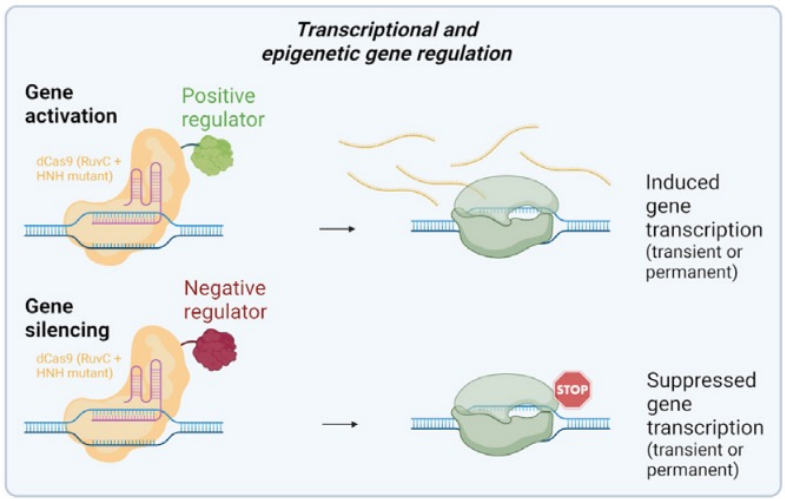
→ **Therapeutic efficacy (clinical trial)**

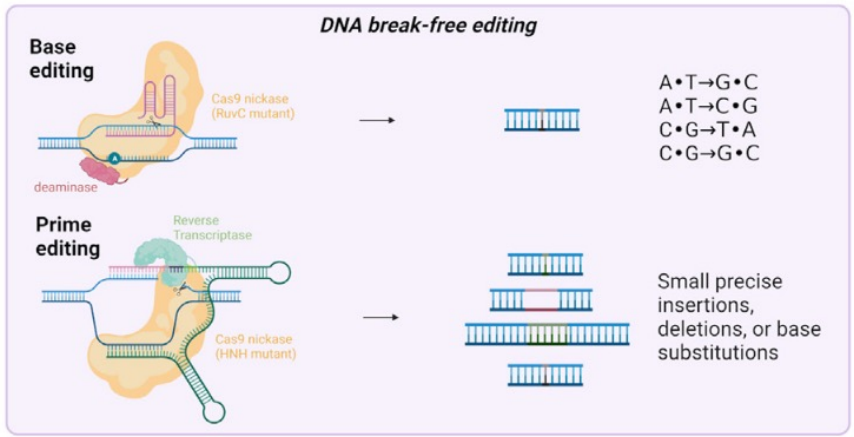
JHEP Reports 2021 vol. 3

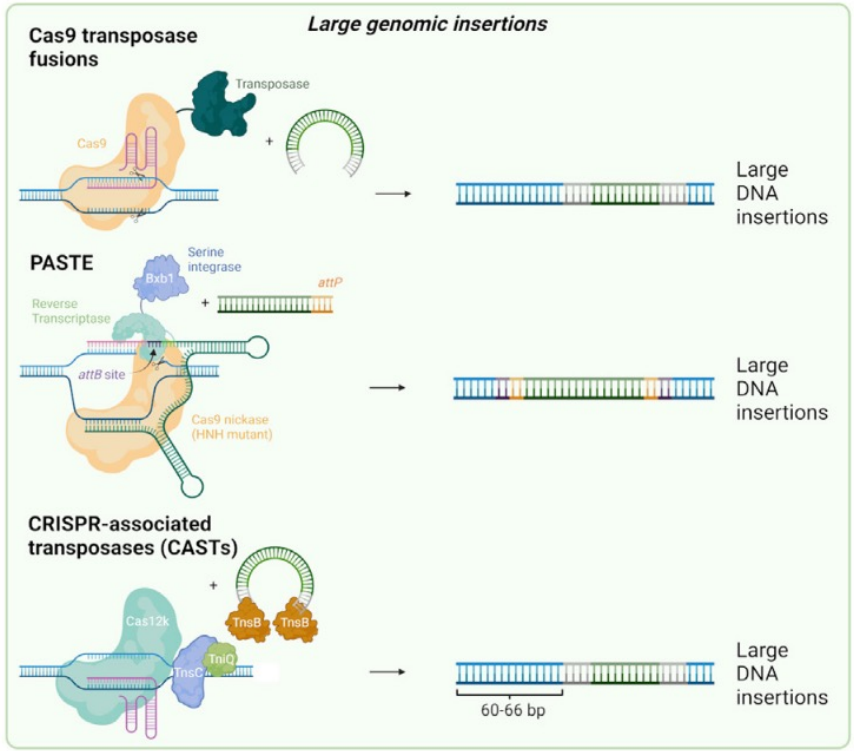
EPFL

Gene Editing Technologies





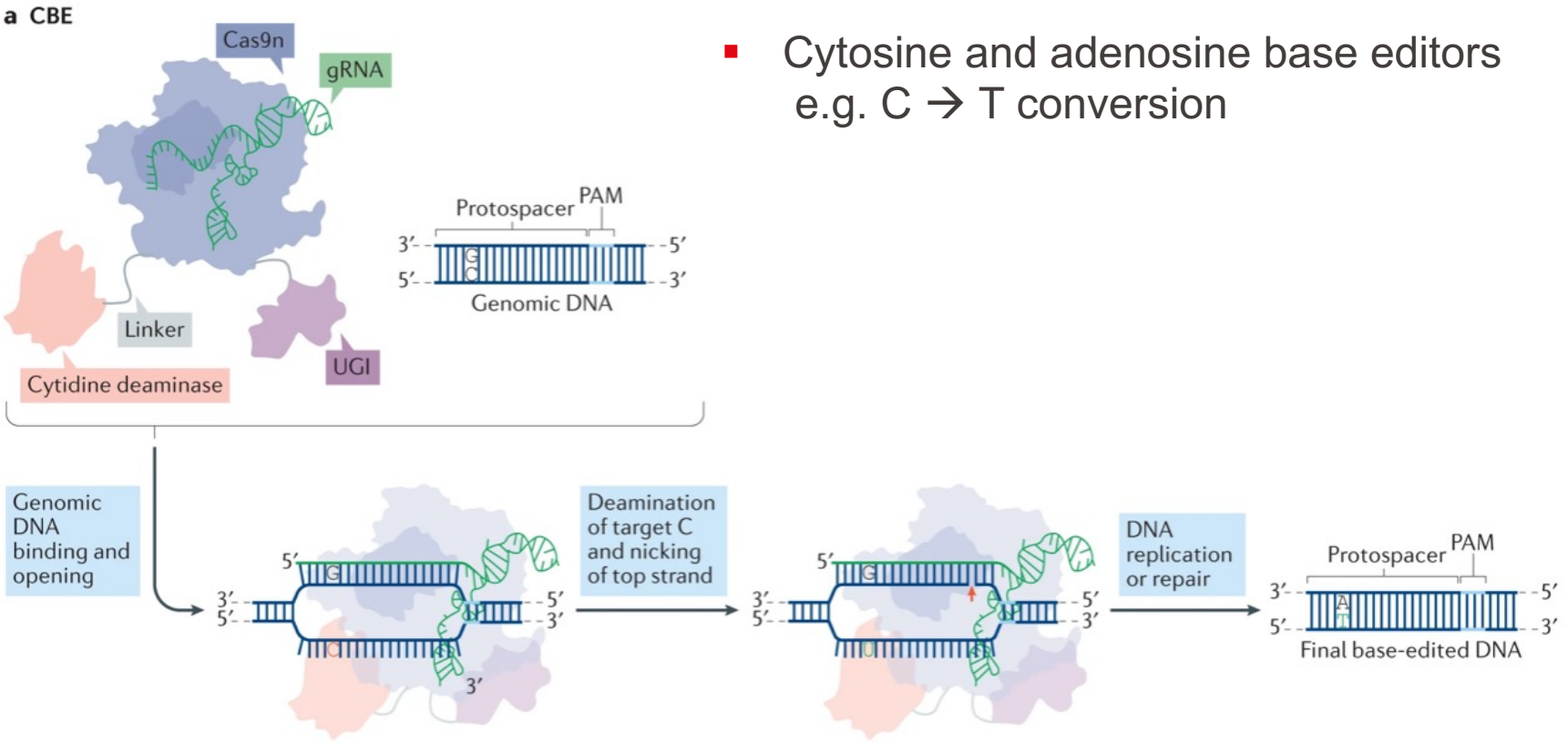




BIO480

https://doi.org/10.1016/j.omtn.2023.102066

Base editing

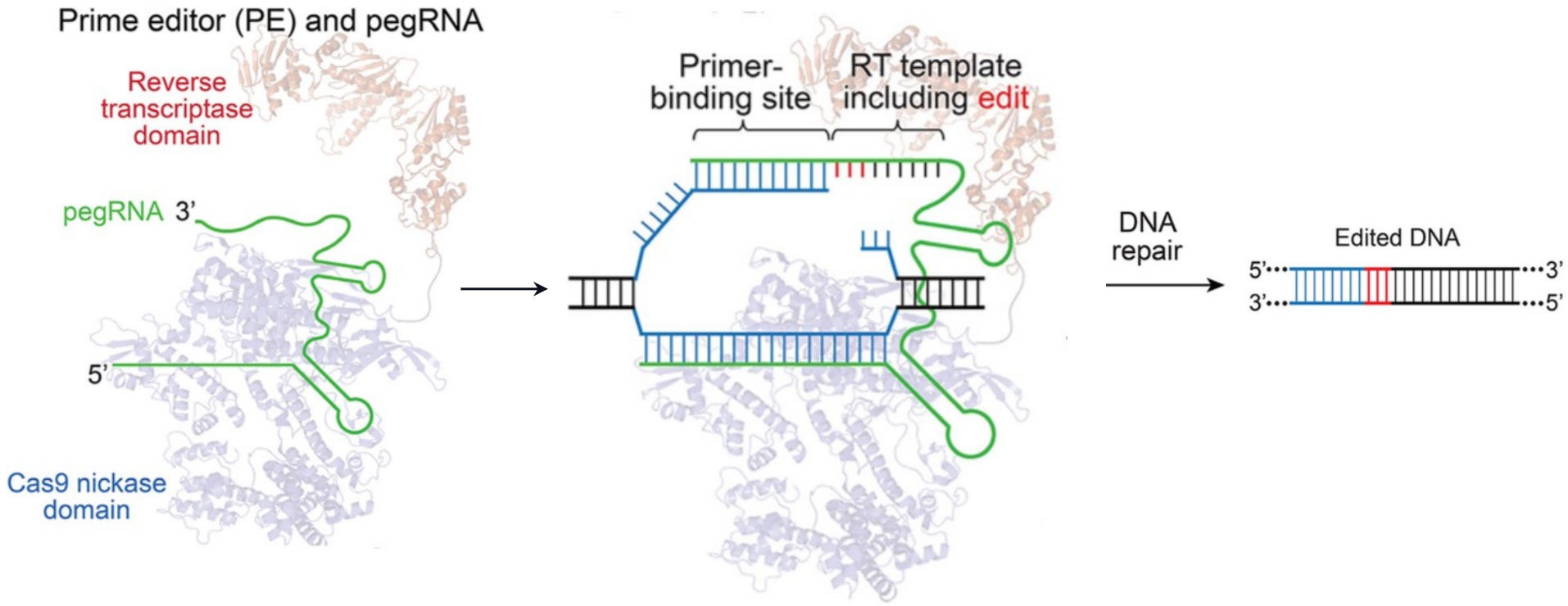


- Cytosine and adenosine base editors
  e.g. C → T conversion

- Porto, E.M., et al. Nat Rev Drug Discov 19, 839–859 (2020)

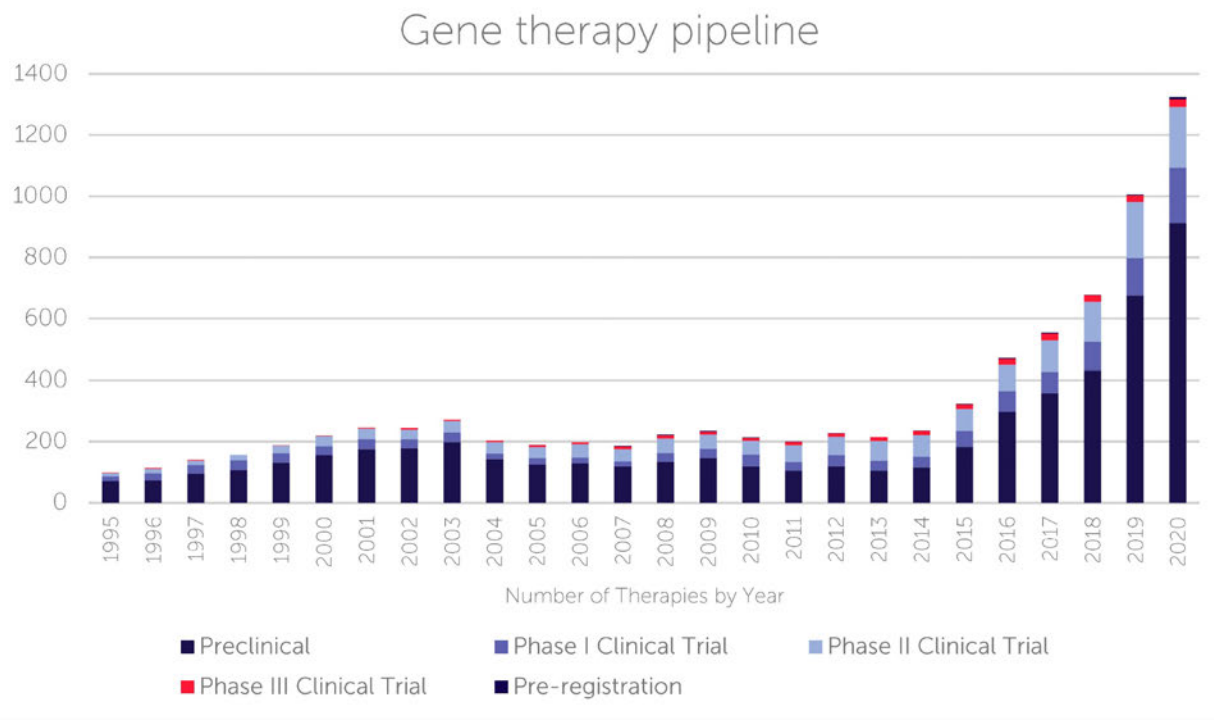
Next generation of gene editing : « prime editing »

Genome editing without double-strand breaks or donor DNA



Anzalone, A.V., et al. Nature (2019) doi:10.1038/s41586-019-1711-4

Gene therapy: pipeline



Global Status	Q3 2022	Q4 2022	Q1 2023	Q2 2023	Q3 2023
Preclinical	1,480	1,515	1,493	1,539	1,522
Phase I	264	254	245	240	256
Phase II	249	248	247	260	267
Phase III	32	30	30	30	30
Pre-registration	6	6	7	6	7
Total	**2,031**	**2,053**	**2,022**	**2,075**	**2,082**

- 2021: 'FDA anticipates approving **10–20 /yr** cell and gene therapies by 2025'
- ⇒ **this has not been achieved.**

report 2021

Gene therapy: initial failures leading to a more robust technology

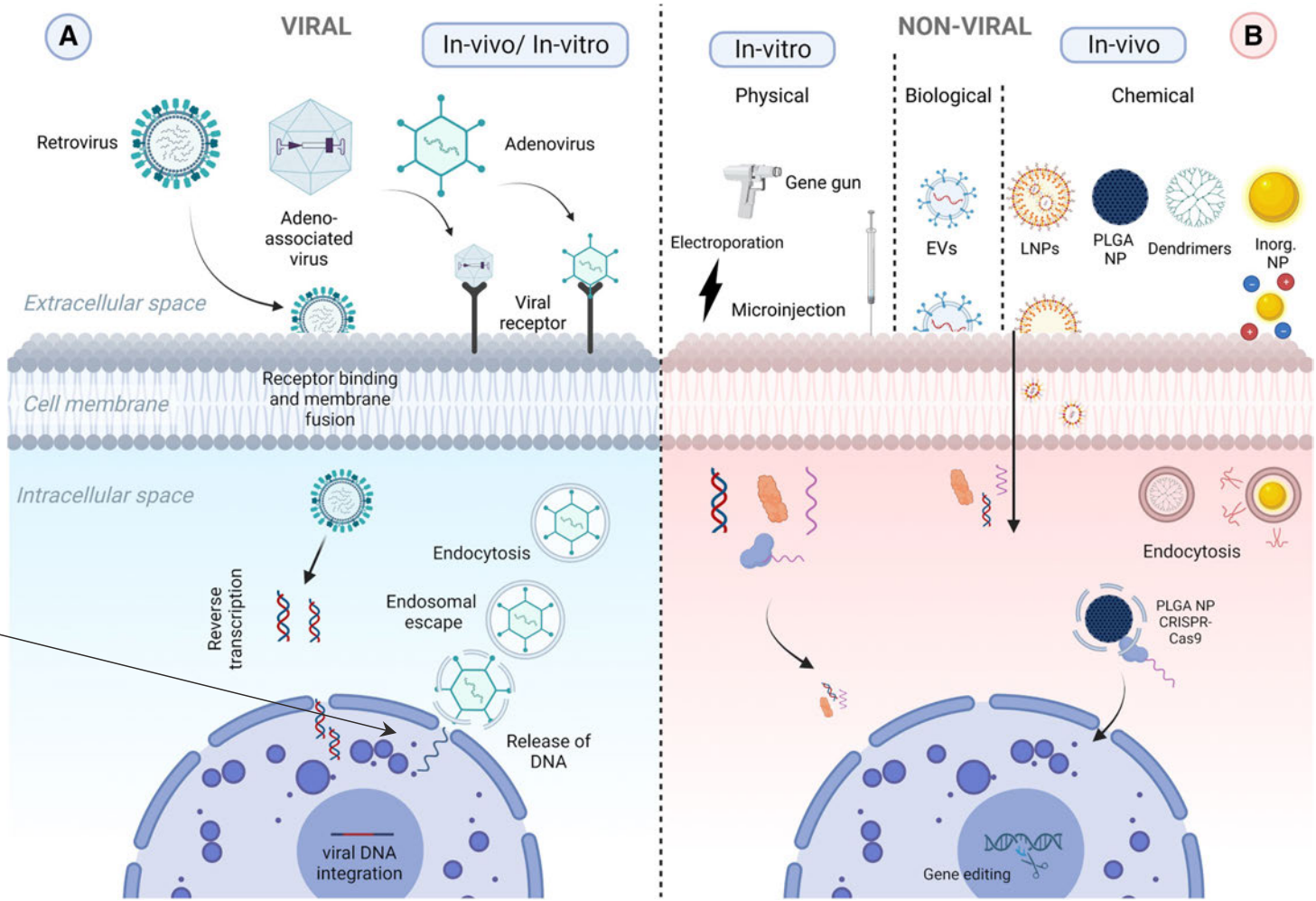
- 1972: Science paper describing the concept
- 1990: first therapeutic gene transfer for SCID patients with immune deficits due to adenosine deaminase (ADA) deficiency
- Major issues in gene therapy
  - 1999: Gene therapy is fatal for Jesse Gelsinger (ornithine transcarbamylase deficiency syndrome, Ad5 vector)

    ➔ **FDA halts gene therapy trials**
  - 2002, Alain Fischer: successful trial for SCID immunodeficiency leads to a fatal leukemia case caused by insertional mutagenesis

    ➔ **FDA halts gene therapy trials, questioning the risk of insertional mutagenesis**
- 2020/2021 Gene therapy is successfully used for the development of vaccines against COVID-19

Gene therapy: vectors

The three main challenges of gene therapy: **delivery, delivery** and **delivery**.



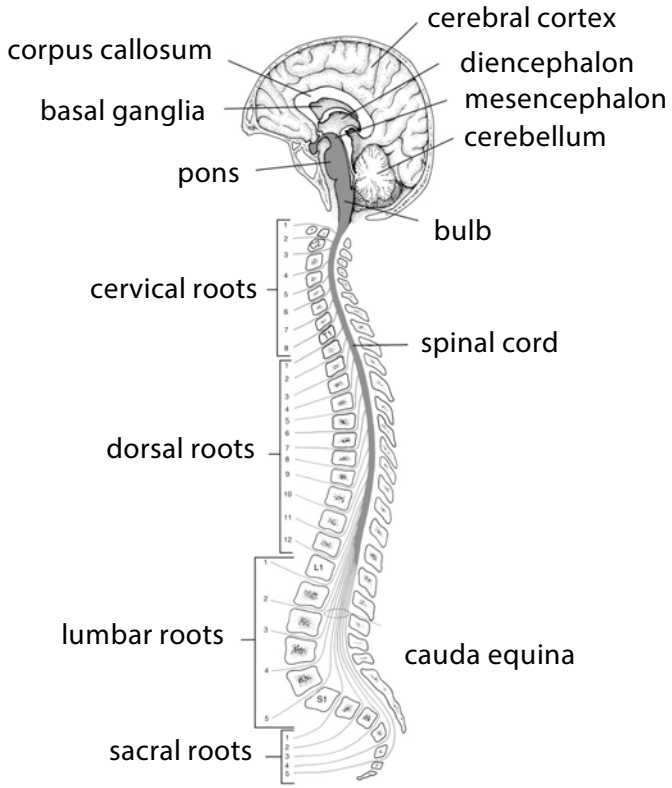
Viral vectors are particularly efficient at delivering a transgene into the nuclear compartment of post-mitotic cells.

https://doi.org/10.1016/j.omtn.2023.102066

Gene therapy: modalities

	Advantage	Disadvantage	Application	Main obstacle
Antisense oligonucleotide	Manufacturability	Need for repeated administration	Gene silencing, splicing modifier	Cell targeting not controlled
mRNA	Manufacturability	Transient expression	Gene replacement, (vaccine), editing	Delivery
Viral vector	Long-term expression, efficacy	Dose finding is difficult, toxicity	Gene silencing, editing, gene replacement	Dose finding, manufacuring, immunity
Nanoparticles	Capacity, manufacturability	Toxicity	Gene silencing, editing, gene replacement	Delivery, efficacy in non-dividing cells
Genetically modified cells	Long-term effects, quality control	Manufacturability	Gene replacement, editing	Delivery, approach not compatible for neurons

Gene therapy in the CNS: a challenging target

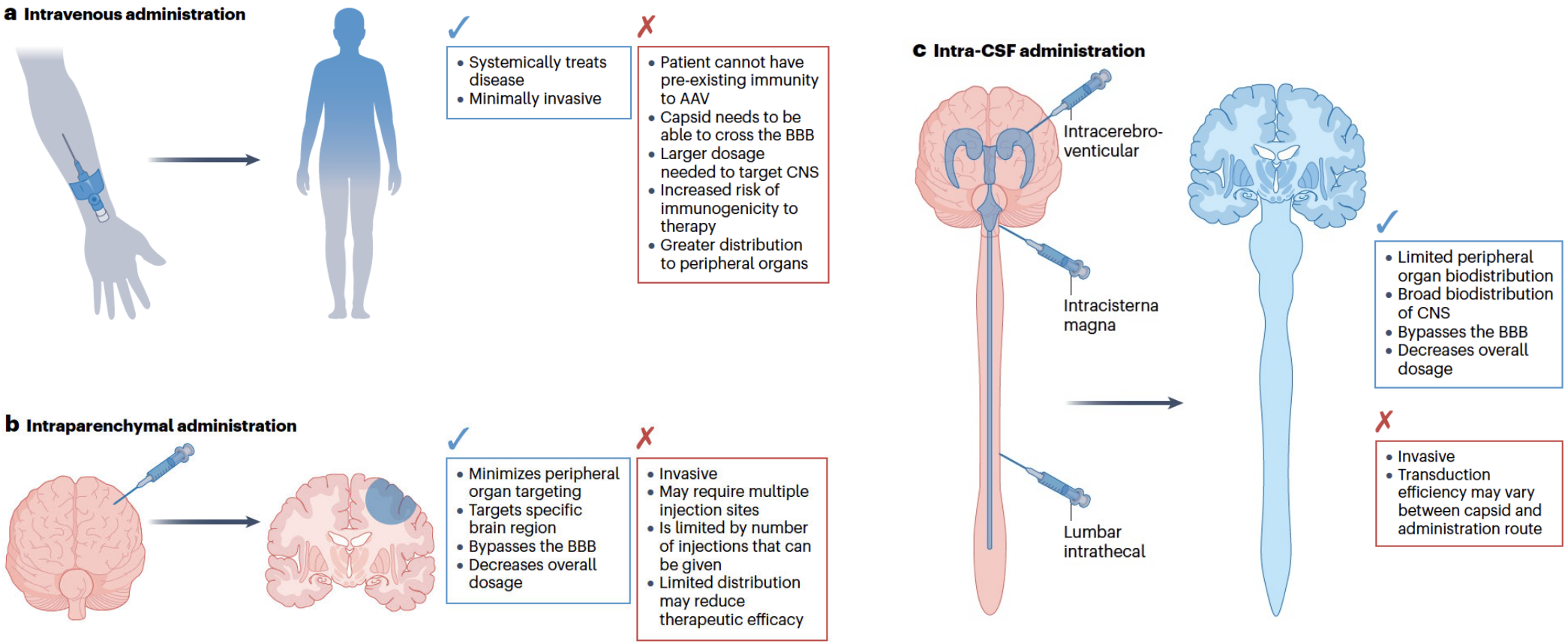


- **Several populations of cells, mostly post-mitotic**
- **Connectivity**
- **Poorly accessible, large-sized organ**
- **Complex function**
- **Specific DNA repair mechanisms**

Specific aspects for gene therapy applications

- Delivery and route of administration are critical.
- ***In vivo* gene therapy** is preferred over *ex vivo* approaches.
- Gene editing is challenging (DNA repair mechanisms).
- Off-target effects need to be carefully controlled.
- Cell-type specific targeting is often essential for efficacy.

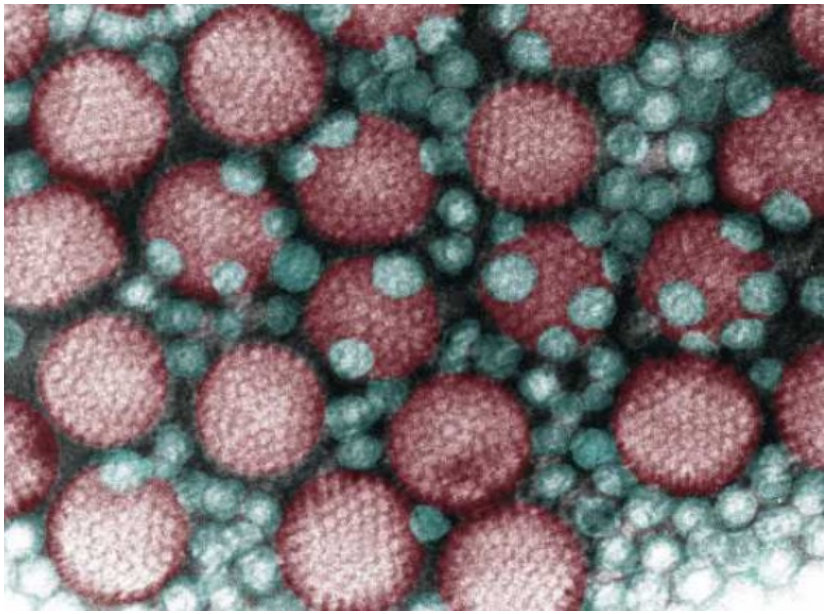
Central nervous system: routes of administration



https://doi.org/10.1038/s41573-023-00766-7

Adeno-Associated Virus: from a defective virus to an effective vector

- **Non-pathogenic**
- 4.75 kb genome
- 20 nm diameter protein capsid, stable
- **“Gutless” viral vector**
- **Vector remains mostly episomal (rare genomic integration).**
- Depends on ’helper’ virus co-infection for replication.



AAV particles (blue) contaminating an adenovirus suspension.

Key Elements in AAV Design for Gene Therapy

- **AAV capsid design / AAV receptor**

  ⇒ **cell and tissue tropism**

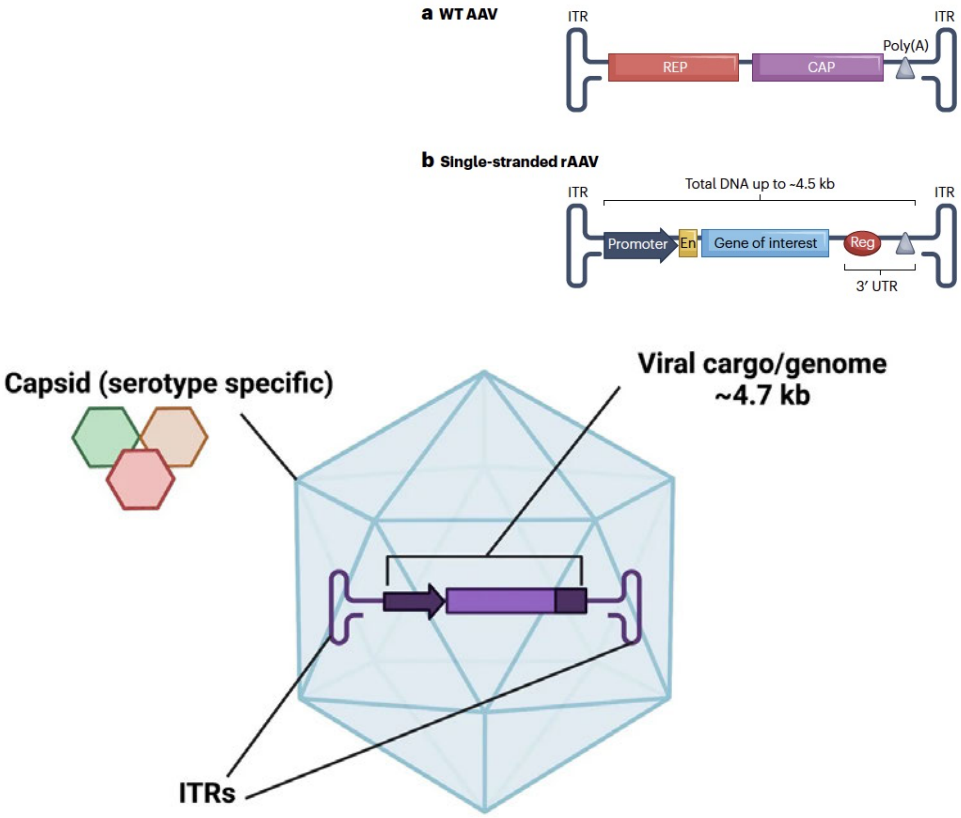
- **Vector genome**

  - promoter activity in specific cell types, regulation
  - RNA processing elements (enhancers, pA)
  - inverted terminal repats
  - coding sequence

  ⇒ **transgene expression**

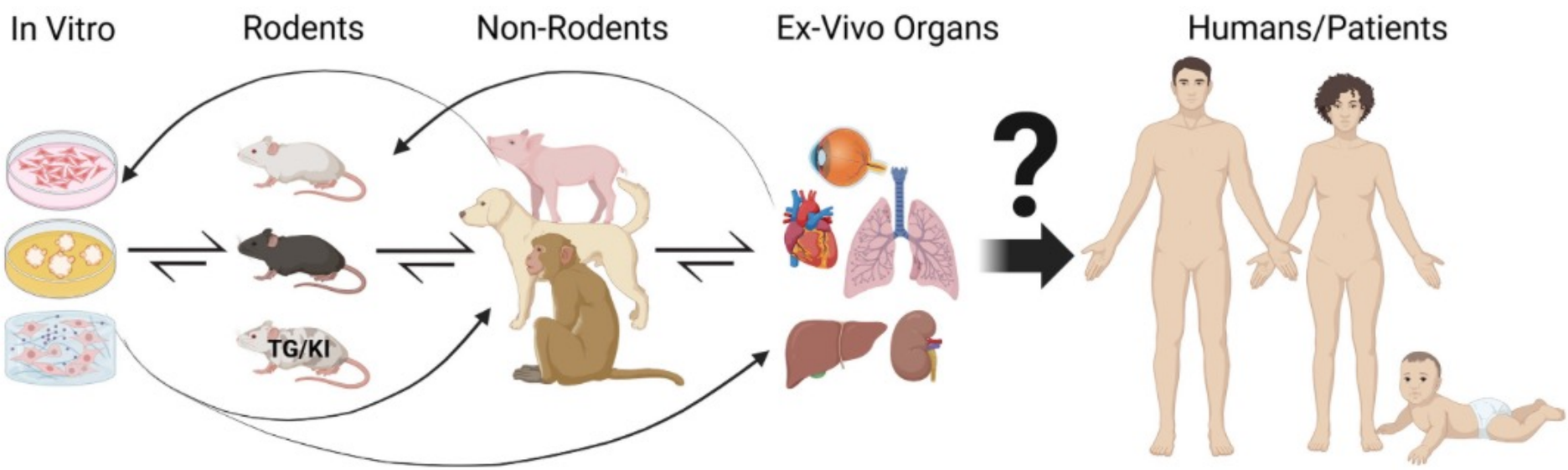
- **Route of administration**

  ⇒ **biodistribution**

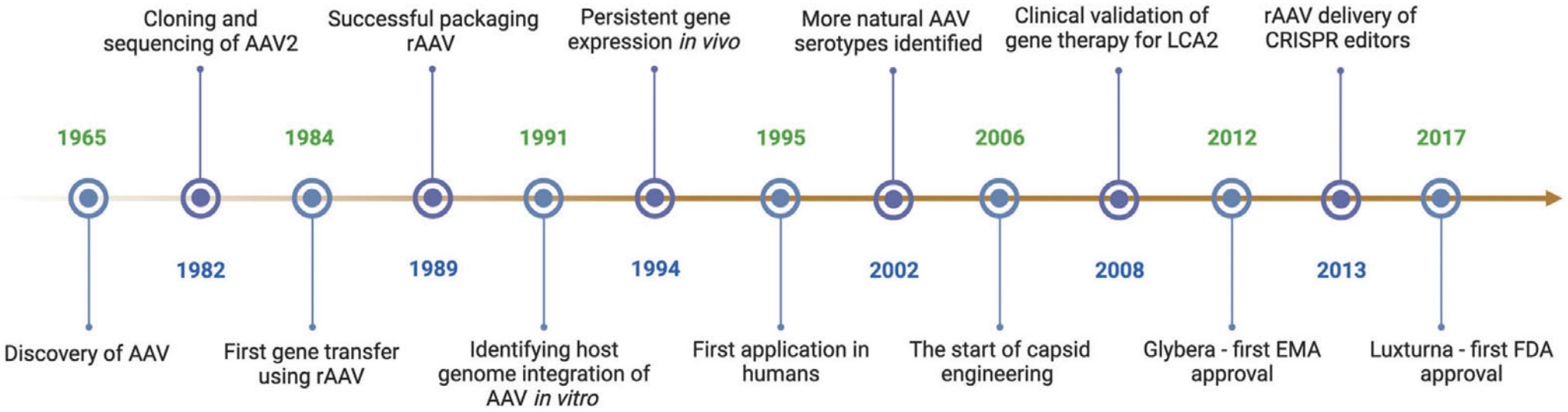


The Challenge of Predicting Vector Biodistribution in Humans/Patients

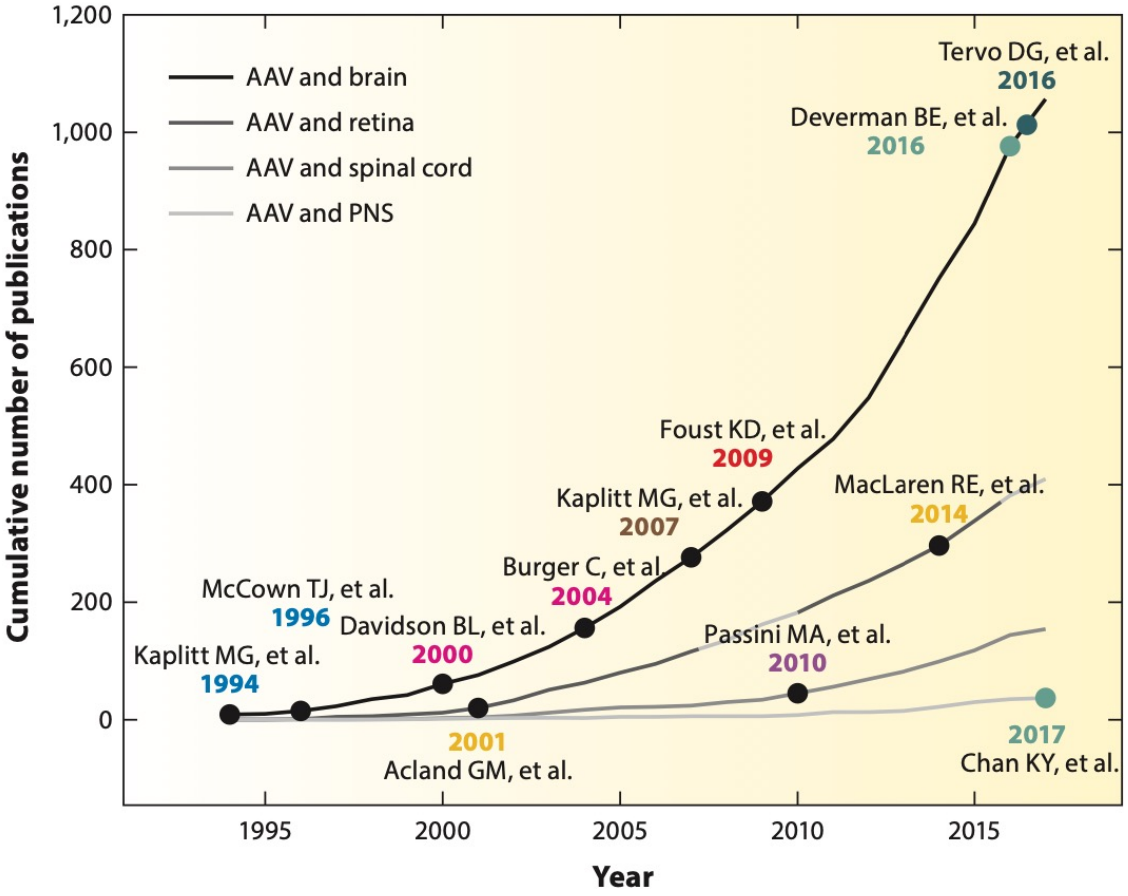
Preclinical models to assess vector biodistribution and transgene expression



Historical milestones in AAV biology research and gene therapy development



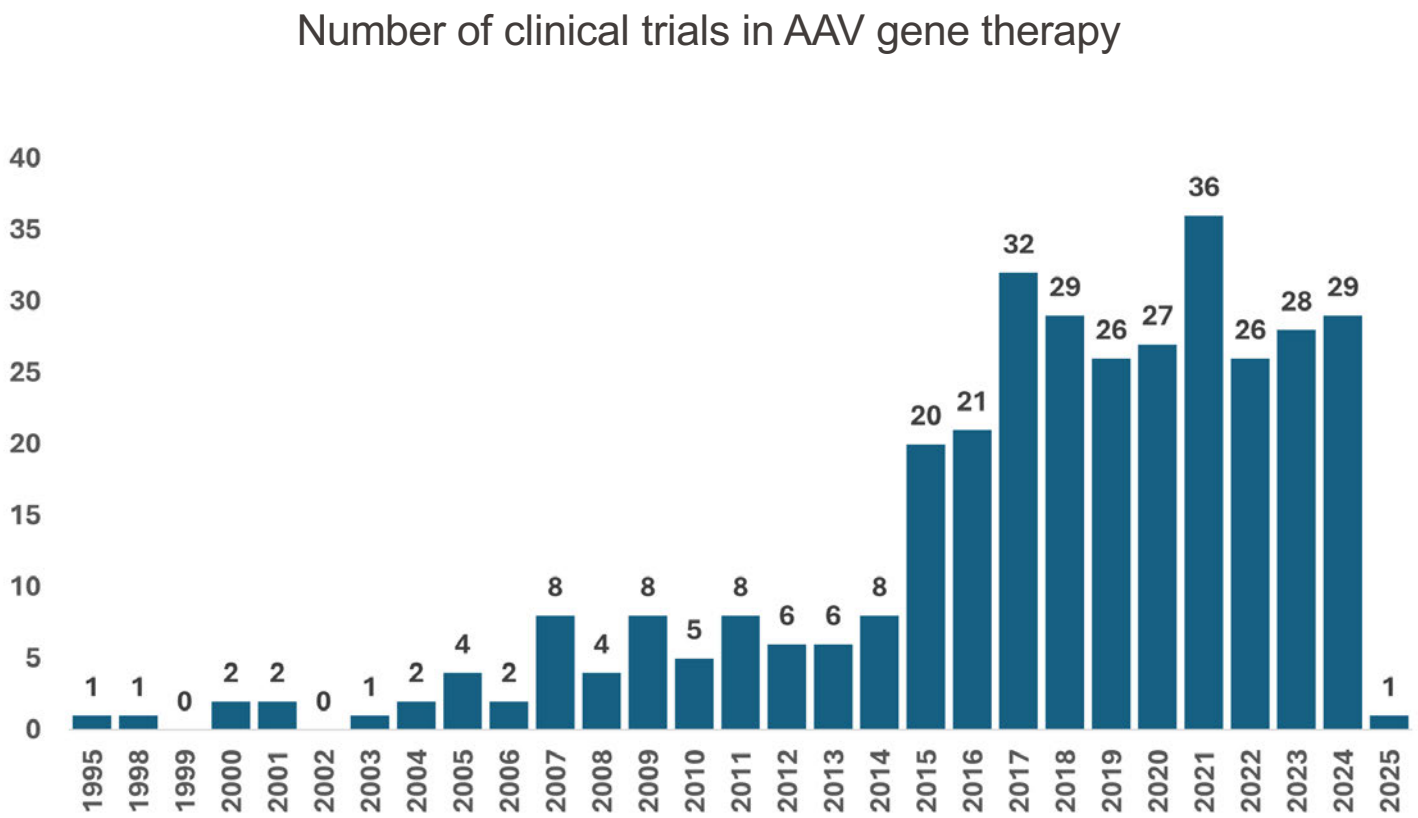
AAV-based gene therapy: applications in the CNS and sensory organs



1. First demonstrations of rAAVs in the brain
2. Comparison of rAAV serotypes' gene transfer, tropism, and distribution in the CNS
3. Phase I trial: AAVs for Parkinson's disease
4. CNS-wide transduction via systemic injection of AAV into neonatal mice
5. Retinal gene therapy
6. Spinal cord gene therapy
7. Designer rAAVs for systemic delivery to the CNS and PNS: rAAV-PHP.B, rAAV-PHP.eB, and rAAV-PHP.S
8. Designer rAAV for efficient retrograde trafficking: rAAV2-retro

Annu. Rev. Neurosci. 2018. 41:323–48

AAV: clinical trials



Molecular Therapy Vol. 33 No 5 May 2025

Examples of AAV-based Technologies for Human Medical Applications

- **Blindness**: gene rescue for RPE65 (Leber Congenital Amaurosis), functional replacement by **optogenetic.**
- **Familial deafness**: gene rescue of otoferlin using a **2-vector approach** (DNFB9).
- **Neuromuscular disease**: gene rescue of SMN (SMA) **in the CNS using systemic AAV9 injection**.
- **Muscular disease**: rescue of dystrophin function **using a minigene** (Duchenne).
- **Hemophilia**: gene replacement of coagulation FVIII (hemophilia A) and FIX (hemophilia B) using **liver-directed expression**.

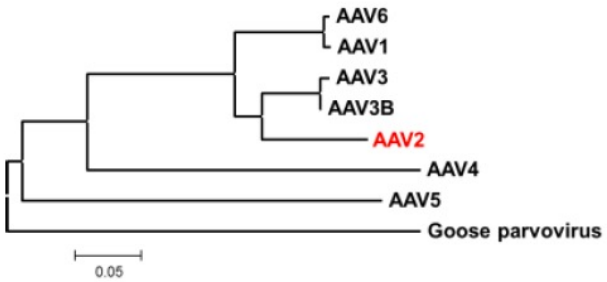
AAV vectors: approved therapies

AAV-based gene therapy treatments that reached market approval:

Product	Company	Description	Indication
GLYBERA	UniQure	AAV1-LPL(S447X)	Lipoprotein lipase deficiency
LUXTURNA	Spark	AAV2-RPE65	Inherited RPE65 retinal diseases
ZOLGENSMA	Novartis (Avexis)	AAV9-SMN1	Spinal muscular atrophy
UPSTAZA	PTC	AAV2-AADC	AADC deficiency
ROCTAVIAN	BioMarin	AAV5-FVIII	Hemophilia A
HEMGENIX	CSL/UniQure	AAV5-FIX	Hemophilia B
ELEVIDYS	Sarepta/Roche	AAVrh74-µDys	Duchenne
BEQVEZ	Pfizer	AAVrh74-FIX	Hemophilia B

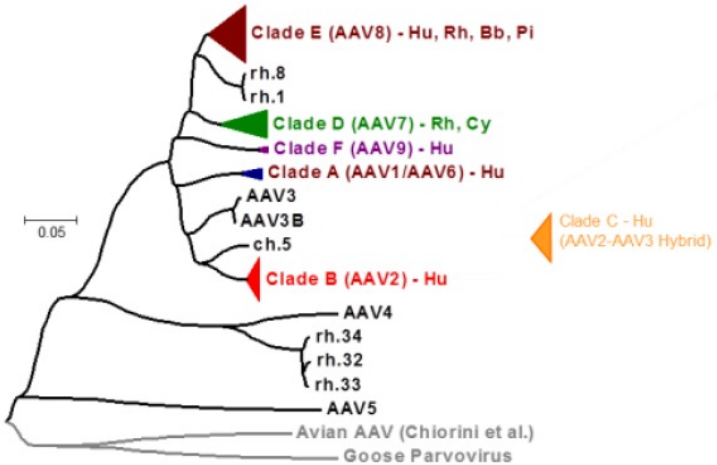
Gene therapy: generating more effective AAV vectors

AAV 1.0



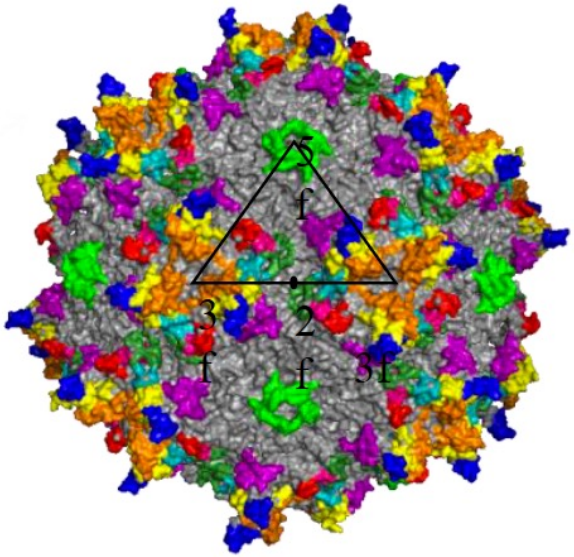
Initial AAV serotypes
(isolated in th 60's-70's)

AAV 2.0



Expanded repertoire of **natural serotypes**
(identified from natural sources)
Most used in recent clinical trials

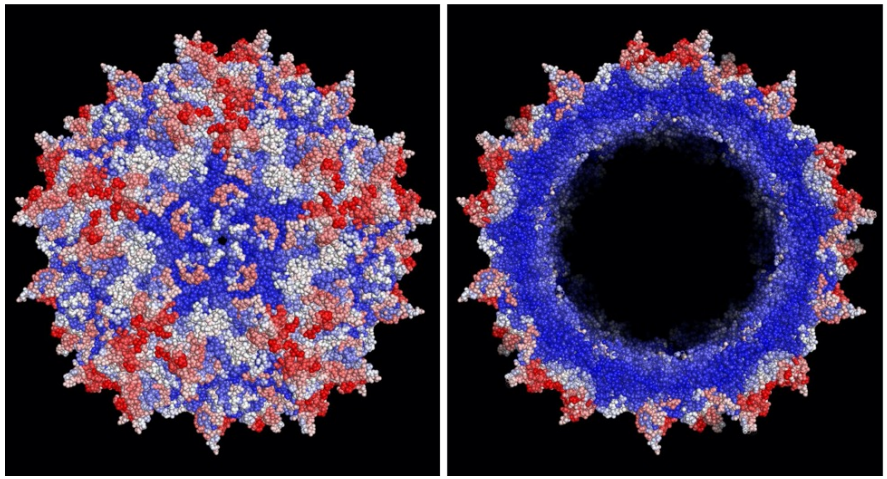
AAV 3.0



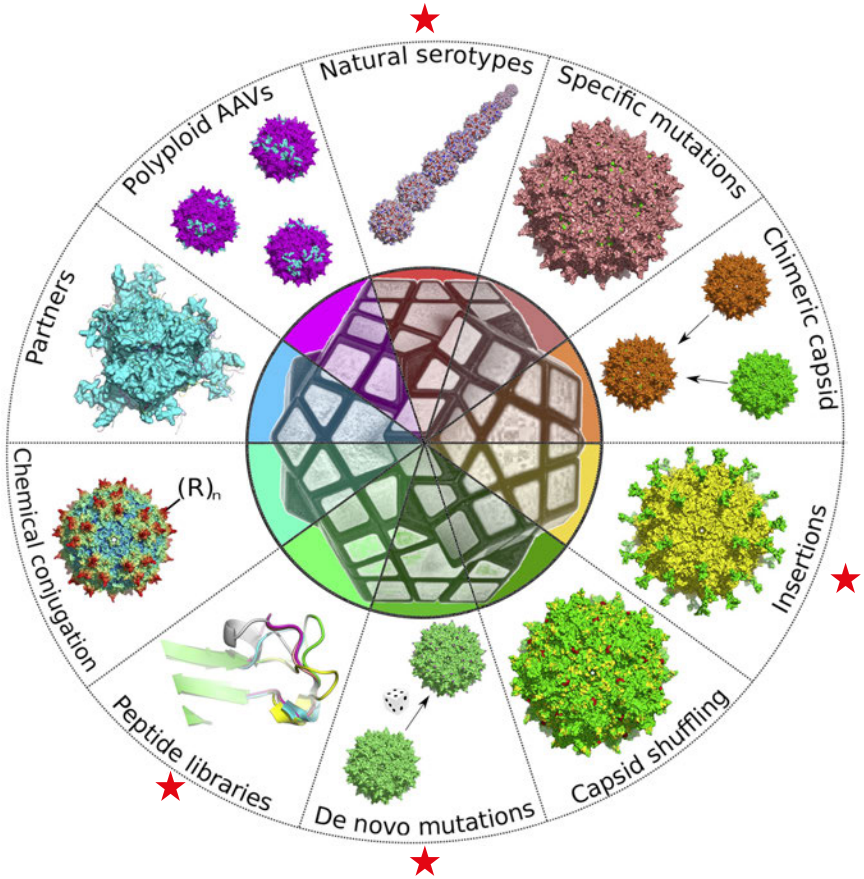
Engineered serotypes
Libraries: >1x10^6 variants
Directed evolution

Strategies Applied for the Development of Novel AAV Capsid Variants

Capsid 'fitness' for AAV production

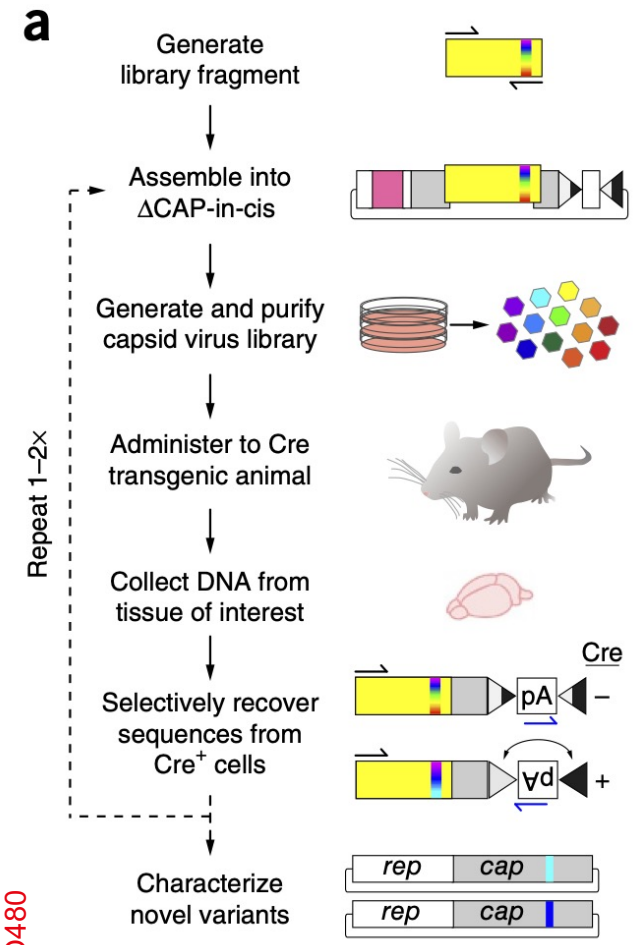


Evaluation of individual a.a. residues in the AAV2 capsid
(red color = "fit for insertion")

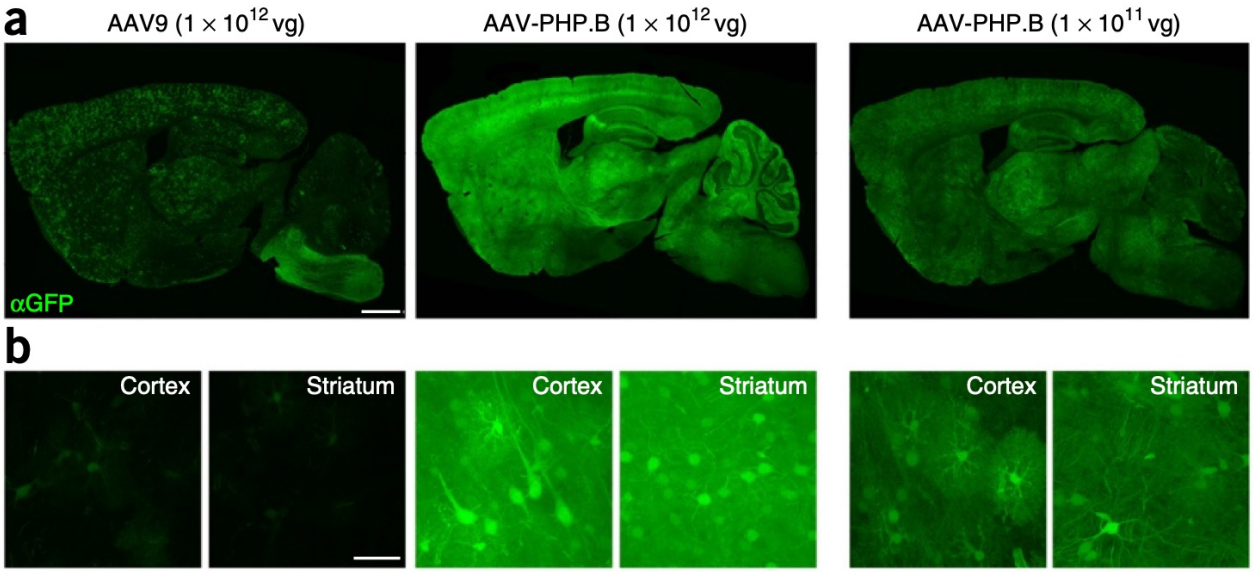


Molecular Therapy, Volume 30, Issue 12, 3515 – 3541
Science 2019: 366 (6469), pp.1139-1143

Directed evolution of AAV able to pass the blood-brain barrier: AAV-PHP vectors



- Screening of AAV9 Cap variants.
- 7-mer random peptide inserted in loop VIII of AAV9 VP1.

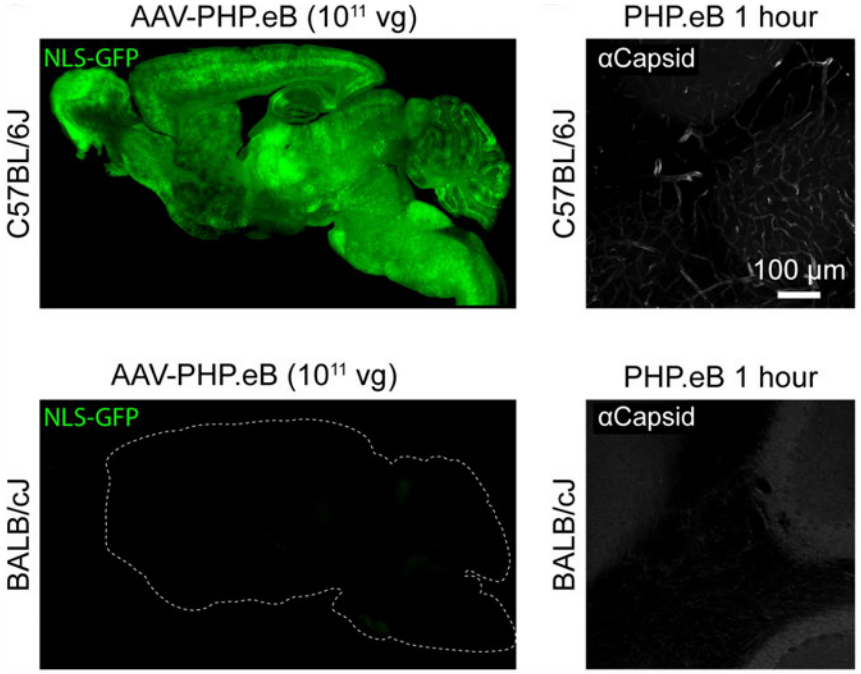


BIO480

Nature Biotechnology volume 34, pages 204–209 (2016)

Directed evolution of AAV vectors: the limit of the mouse species

AAV-PHP.eB variant selected for transport across the BBB binds the LY6A receptor expressed in the mouse endothelial cells of **C57BL/6 mice** (**no homologue in primates…**).



Delivering genes across the blood-brain barrier: LY6A, a novel cellular receptor for AAV-PHP.B capsids

Qin Huang, Ken Y. Chan, Isabelle G. Tobey, Yujia Alina Chan, Tim Poterba, Christine L. Boutros, Alejandro B. Balazs, Richard Daneman, Jonathan M. Bloom, Cotton Seed, Benjamin E. Deverman

Molecular Therapy
Original Article

AMERICAN SOCIETY of GENE & CELL THERAPY

The GPI-Linked Protein LY6A Drives AAV-PHP.B Transport across the Blood-Brain Barrier

Juliette Hordeaux,[1,4] Yuan Yuan,[1,4] Peter M. Clark,[1] Qiang Wang,[1] R. Alexander Martino,[1] Joshua J. Sims,[1] Peter Bell,[1] Angela Raymond,[2,3] William L. Stanford,[2,3] and James M. Wilson[1]

Human Gene Therapy, Vol. 31, No. 1-2 | Research Articles

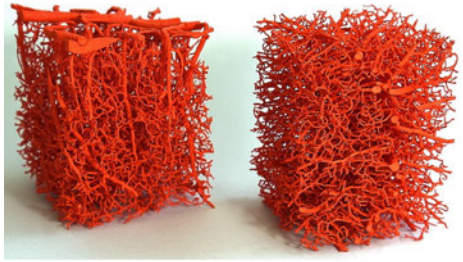
Full Access

***Ly6a* Differential Expression in Blood–Brain Barrier Is Responsible for Strain Specific Central Nervous System Transduction Profile of AAV-PHP.B**

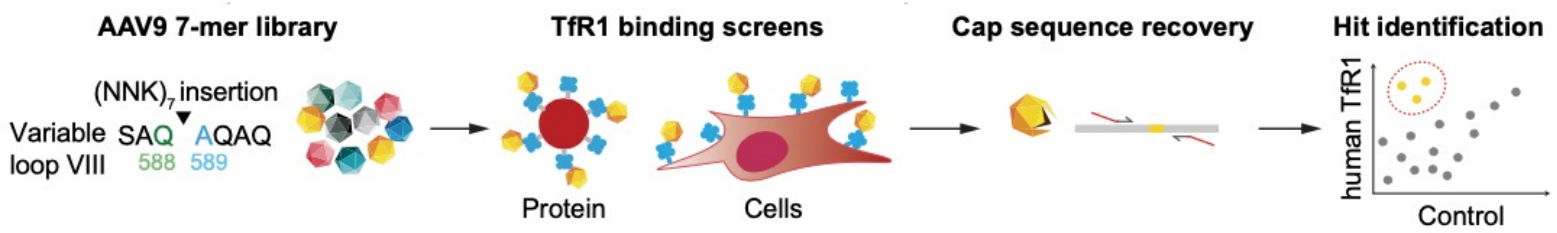
Ana Rita Batista, Oliver D. King, Christopher P. Reardon, Crystal Davis, Shankaracharya, Vivek Philip, Heather Gray-Edwards, Neil Aronin, Cathleen Lutz, John Landers, and Miguel Sena-Esteves

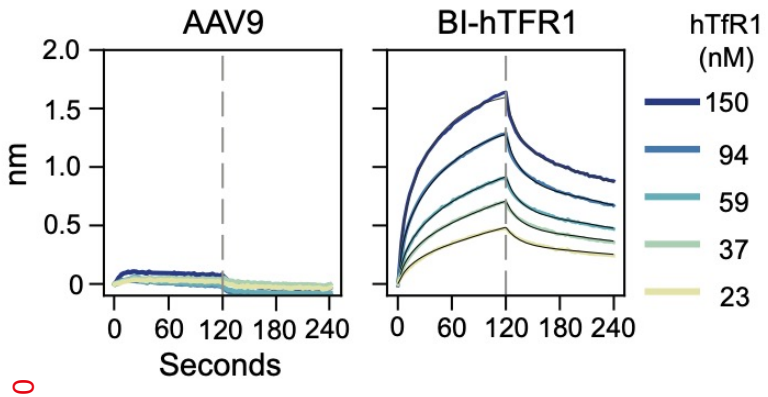
AAV Binding the Transferrin Receptor for Gene Delivery to the Brain

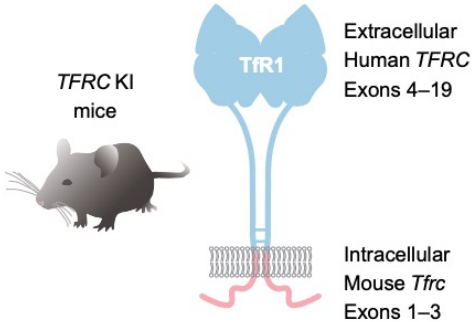
AAV capsid modified for binding the TfR1 receptor to pass the blood-brain barrier.

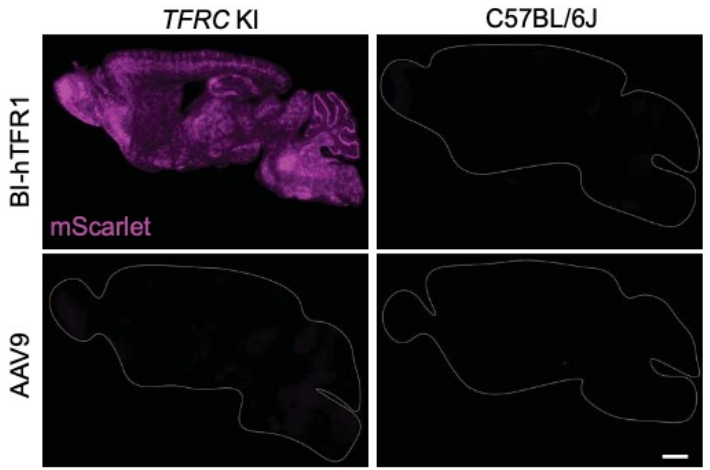


Brain vasculature









Huang et al., Science 384, 1220–1227 (2024)

Novel Therapeutic Approaches for CNS Diseases

- **CNS and Therapy Development**

  General principles

- **Aβ immunotherapy against Alzheimer's Disease**

- **Gene therapy for CNS diseases**

  Example of AAV as gene delivery system for the CNS

  Lipid Storage Diseases – ex vivo gene therapy for MLD

  Amyotrophic Lateral Sclerosis – RNAi against SOD1

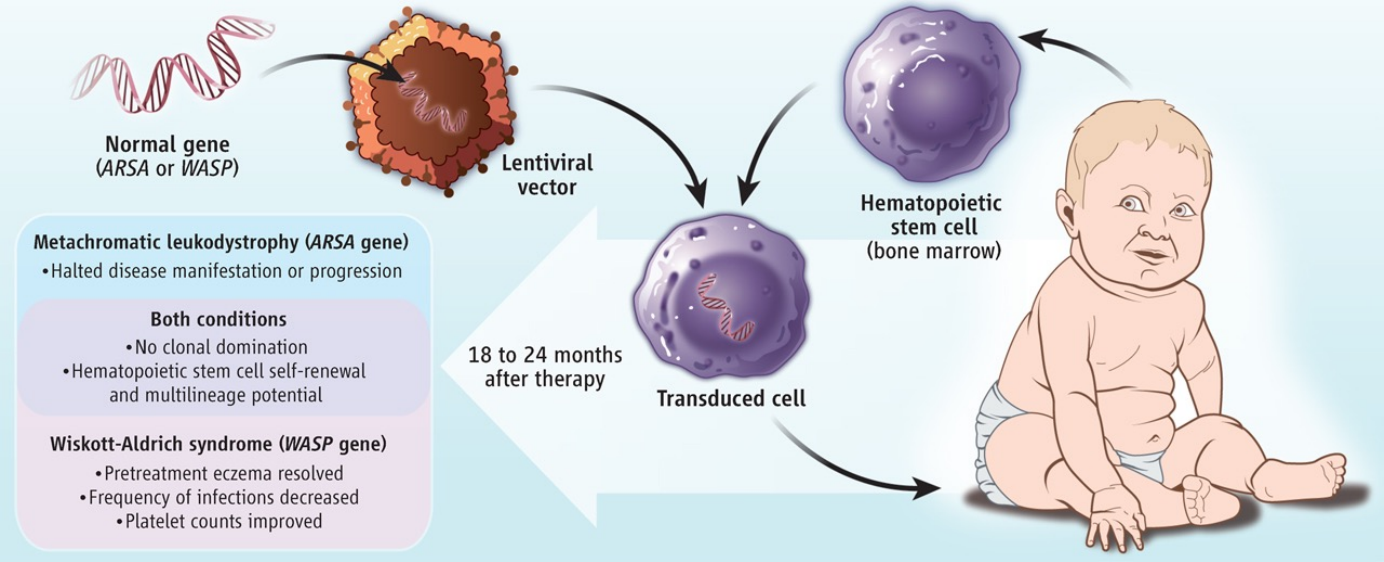
- **Sensory organs:**

  Blindness functional rescue by optogenetic

  Deafness Rescue of cochlear function

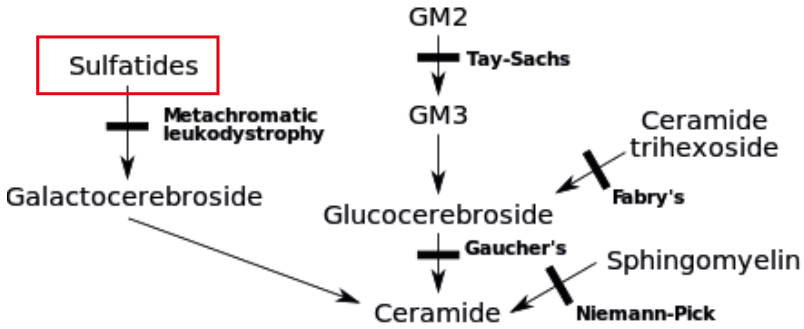
Ex vivo gene therapy for lipid storage disorders

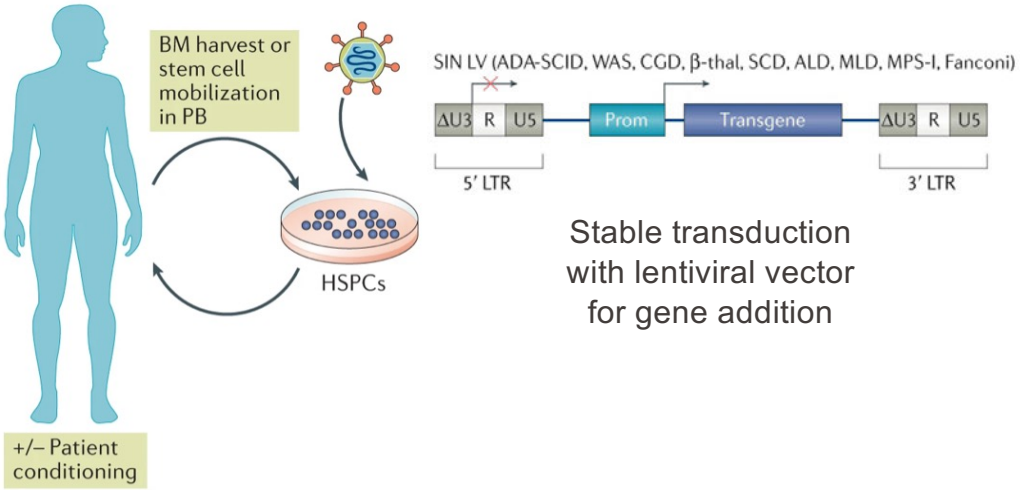
- Leukodystrophies: genetic CNS disorders → progressive neurologic deterioration
- Metachromatic leukodystrophy (MLD) is caused by mutations leading to a deficiency of the lysosomal enzyme arylsulfatase A (ARSA)
- Build-up of sulfatides → cerebral demyelination and loss of neurons
- Affects both oligodendrocytes and Schwann cells (PNS and CNS)
- Most common late infantile form (accounting for 50% of cases): onset at 2 yrs of age, fatal within a few years
- Seizures, impaired swallowing, muscle wasting, paralysis, and dementia



Ex vivo gene therapy for lipid storage disorders

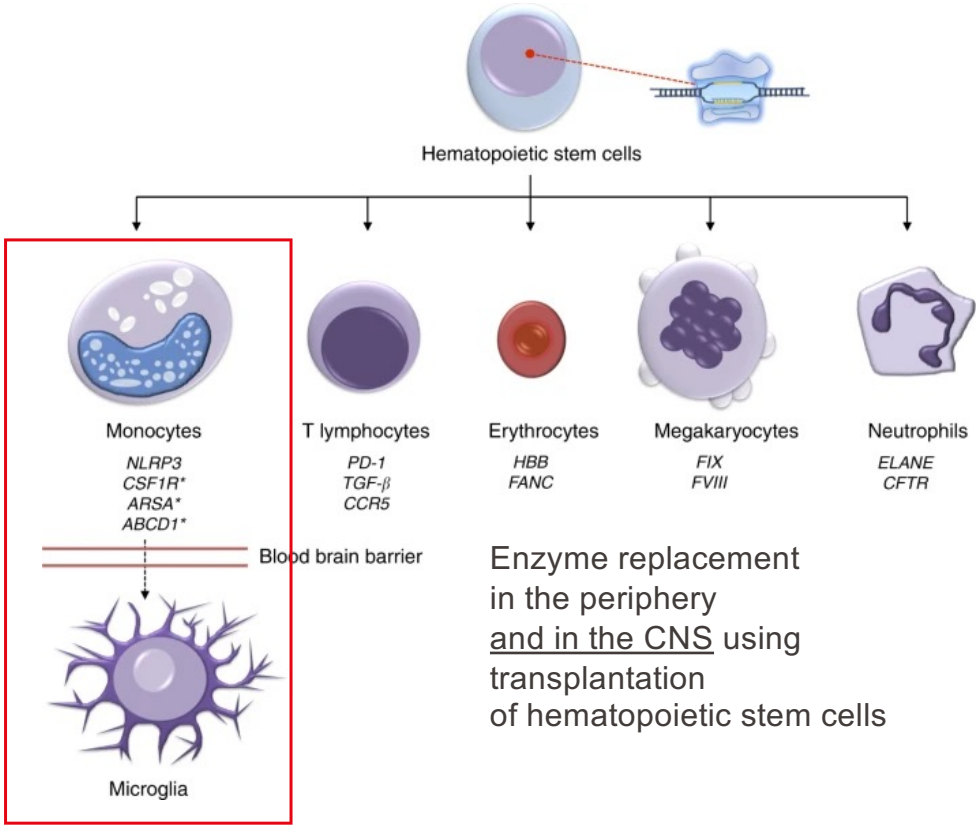
Metabolism of sphingolipids





Stable transduction with lentiviral vector for gene addition

Future: accurate gene editing by guided nuclease and corrected cell selection

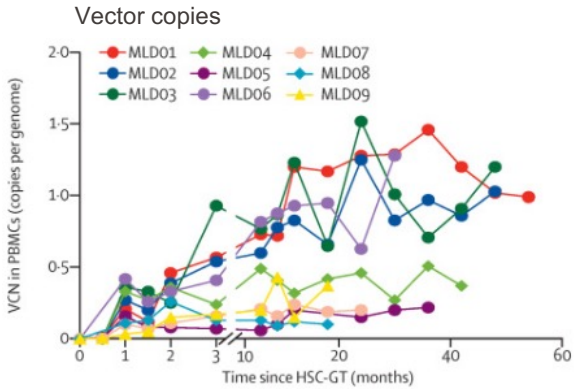


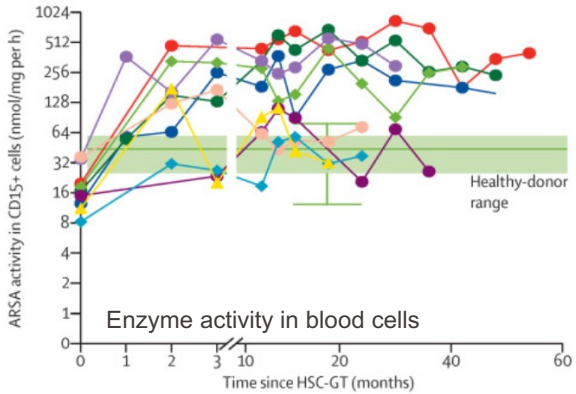
Enzyme replacement in the periphery and in the CNS using transplantation of hematopoietic stem cells

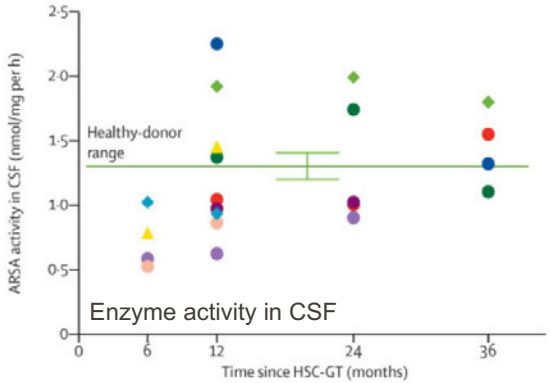
- *Cavazzana, M. et al. Nat Rev Drug Discov 18, 447–462 (2019)*
  Daniel-Moreno, A. et al. Bone Marrow Transplant 54, 1940–1950 (2019)

Ex vivo gene therapy for lipid storage disorders

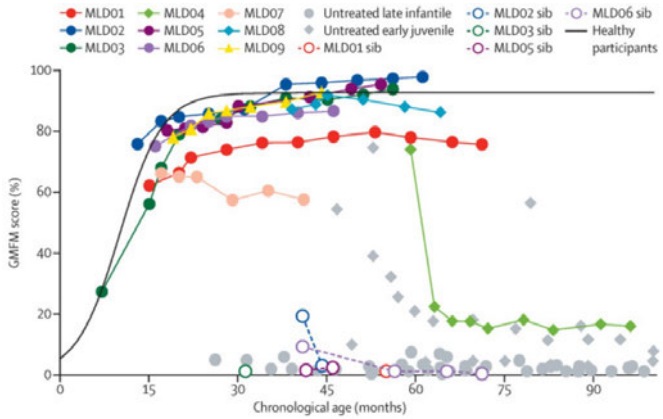
- Engraftment of LV transduced progenitors in the bone marrow in patients treated by hematopoietic stem cell gene therapy
- ↑ ARSA activity in granulocytes and in the CSF





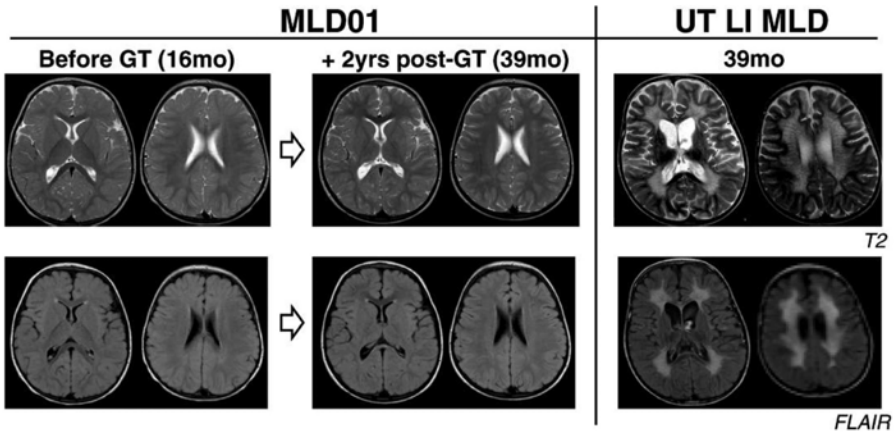


- Improvement of the Gross Motor Function Measure [GMFM]



- *Sessa M et al, The Lancet 2016*
  Biffi A et al, Science 2013

- Correction of extensive and severe demyelination in MLD patient



- Abnormal hyperintensities (tigroid signal)
- Abnormal white matter signal, atrophy