Hertie Institute
for Clinical Brain Research

DZNE
Deutsches Zentrum für Neurodegenerative Erkrankungen
in der Helmholtz-Gemeinschaft

Prion Disease and Their Intersection with AD: Aβ seeds

Mathias Jucker

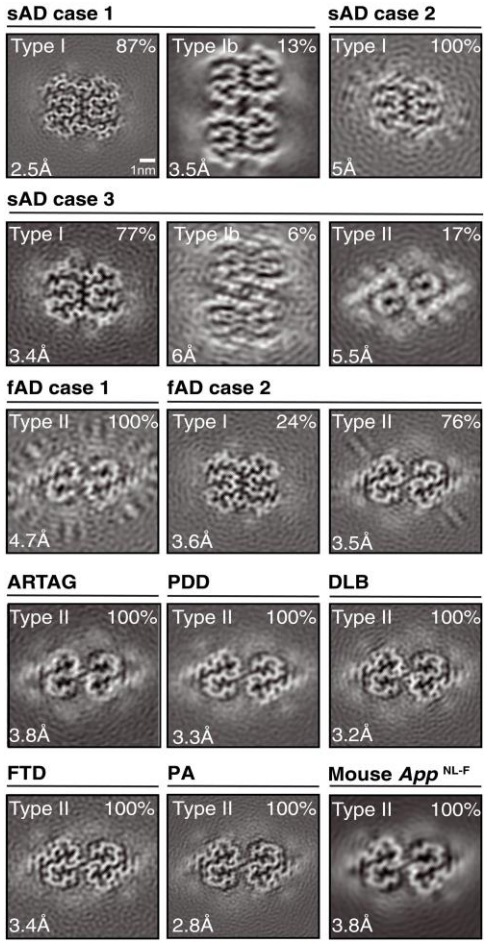
Hertie-Institute for Clinical Brain Research (HIH),
German Center for Neurodegenerative Diseases (DZNE),
Tübingen, Germany

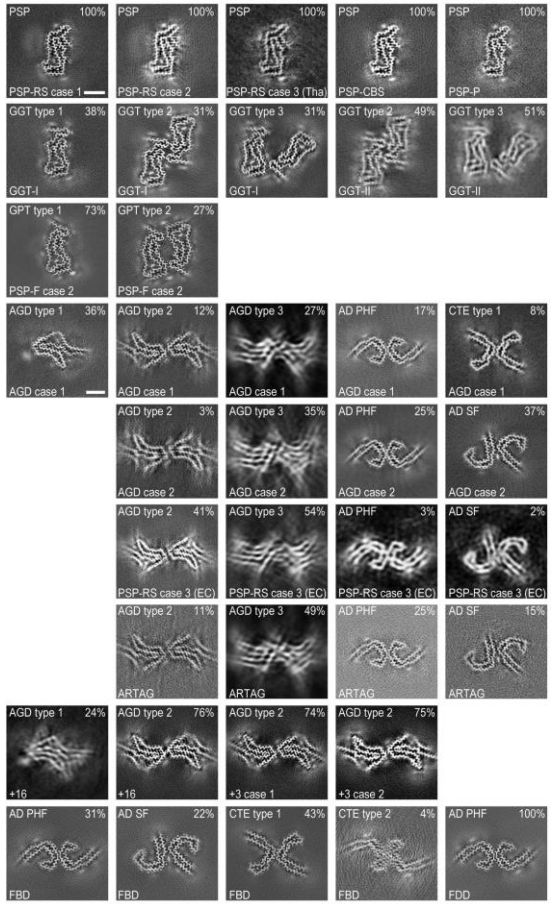
CH

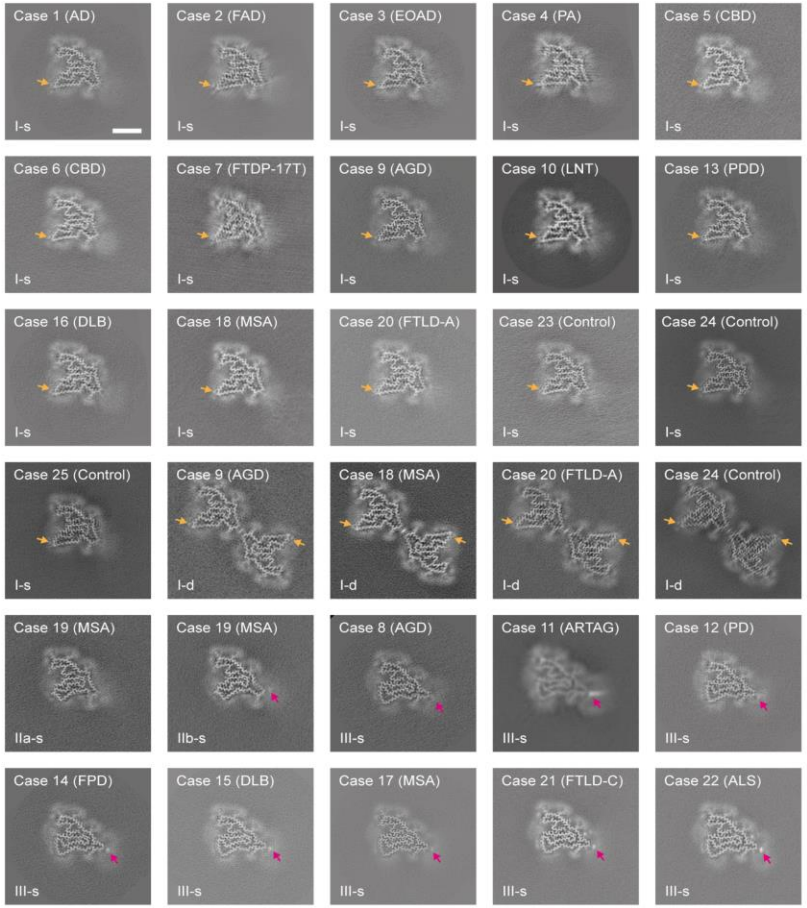
What is a proteopathic seed?

A proteopathic seed refers to an abnormal form of a protein that has the ability to induce other normal proteins to fold into the same abnormal shape. These misfolded proteins can accumulate in the brain and cause various neurodegenerative disorders such as Alzheimer's, Parkinson's, and Huntington's disease

Proteopathic lesion structure

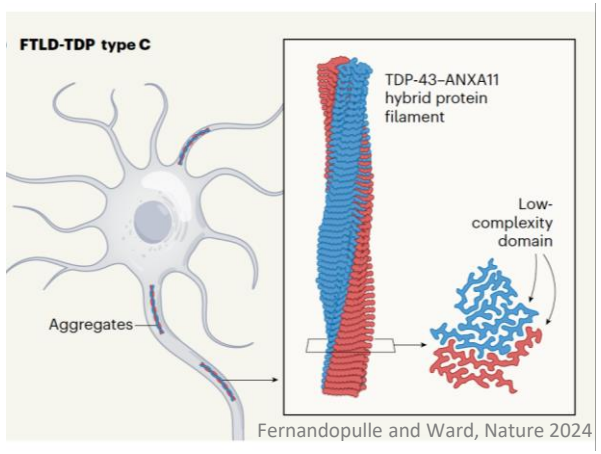






Shi et al., Nature 2021; Yang et al., Science 2022; Schweighauser et al., Nature 2022

Heteromeric Aβ seeds, cross-seeding ?



Fernandopulle and Ward, Nature 2024

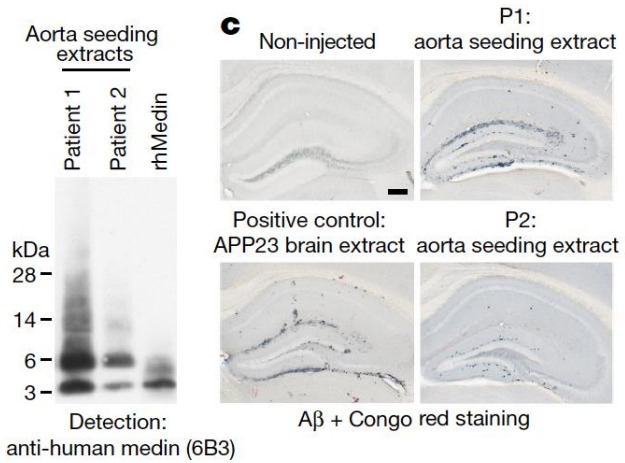
Article

Heteromeric amyloid filaments of ANXA11 and TDP-43 in FTLD-TDP type C

https://doi.org/10.1038/s41586-024-08024-5
Received: 14 June 2024
Accepted: 5 September 2024
Published online: 11 September 2024
Open access
Check for updates

Diana Arseni[1], Takashi Nonaka[2], Max H. Jacobsen[3], Alexey G. Murzin[1], Laura Cracco[3], Sew Y. Peak-Chew[1], Holly J. Garringer[3], Ito Kawakami[2], Hisaomi Suzuki[4], Misumoto Onaya[4], Yuko Saito[5], Shigeo Murayama[5], Changiz Geula[6], Ruben Vidal[3], Kathy L. Newell[3], Marsel Mesulam[6], Bernardino Ghetti[3], Masato Hasegawa[2] & Benjamin Ryskeldi-Falcon[1]✉

Neurodegenerative diseases are characterized by the abnormal filamentous assembly of specific proteins in the central nervous system[1]. Human genetic studies have established a causal role for protein assembly in neurodegeneration[2]. However, the underlying molecular mechanisms remain largely unknown, which is limiting

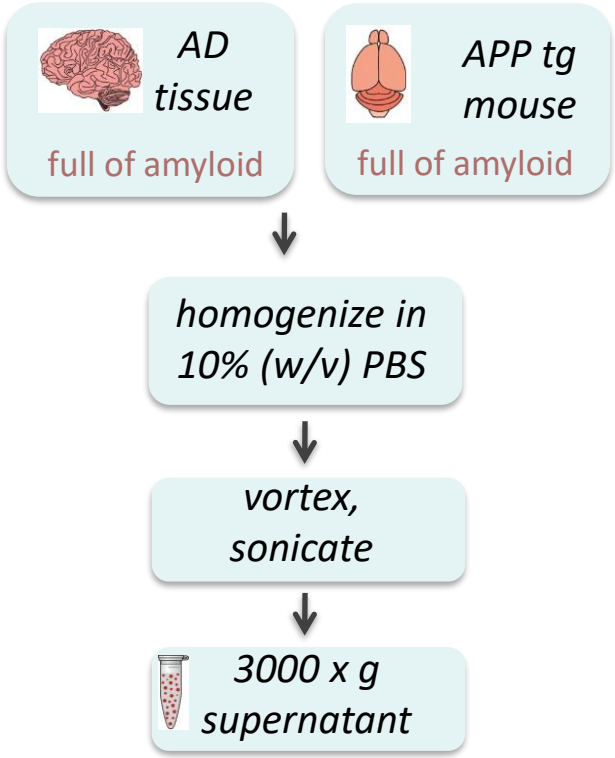


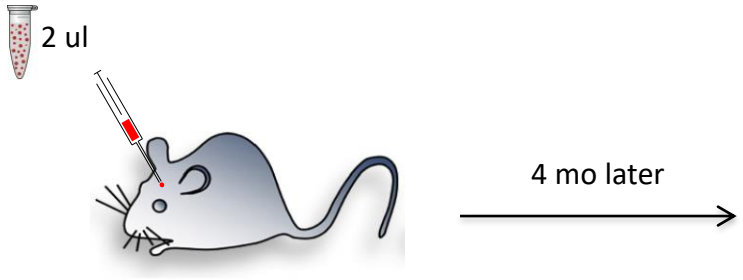
Medin co-aggregates with vascular amyloid-β in Alzheimer's disease

https://doi.org/10.1038/s41586-022-05440-3
Received: 8 February 2021
Accepted: 12 October 2022
Published online: 16 November 2022
Open access

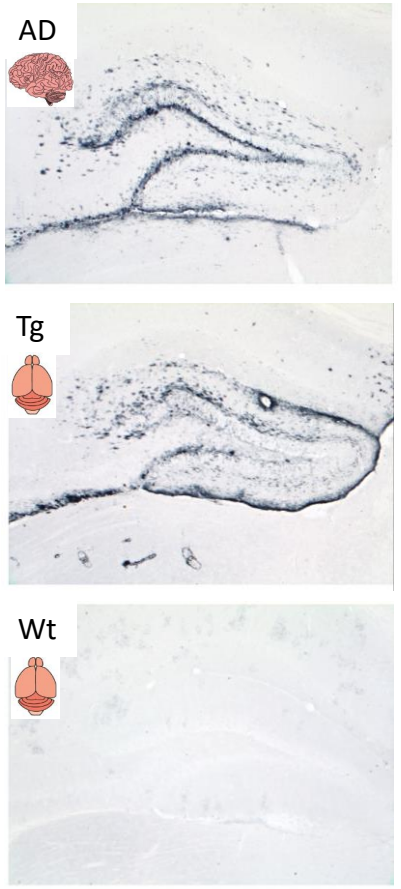
Jessica Wagner[1,2,3,17], Karoline Degenhardt[1,2,3,17], Marleen Veit[1,2,3], Nikolaos Louros[4,5], Katerina Konstantoulea[4,5], Angelos Skodras[1,2], Katleen Wild[1], Ping Liu[1,2,3], Ulrike Obermüller[2], Vikas Bansal[1], Anupriya Dalmia[1], Lisa M. Häsler[1,2], Marius Lambert[1,2], Matthias De Vleeschouwer[4,5], Hannah A. Davies[6,7], Jillian Madine[7,8], Deborah Kronenberg-Versteeg[1,2], Regina Feederle[9,10], Domenico Del Turco[11], K. Peter R. Nilsson[12], Tammaryn Lashley[13,14], Thomas Deller[11], Marla Gearing[15], Lary C. Walker[16], Peter Heutink[1], Frederic Rousseau[4,5], Joost Schymkowitz[4,5], Mathias Jucker[1,2] & Jonas J. Neher[1,2]✉

Injection of Aβ seed-containing brain extract into APP tg mice



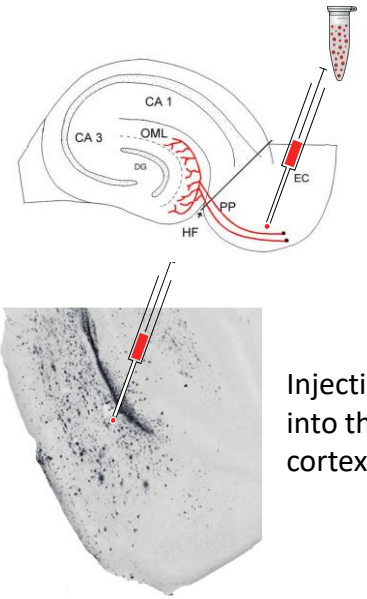


Intracerebral injection in young APP tg mice

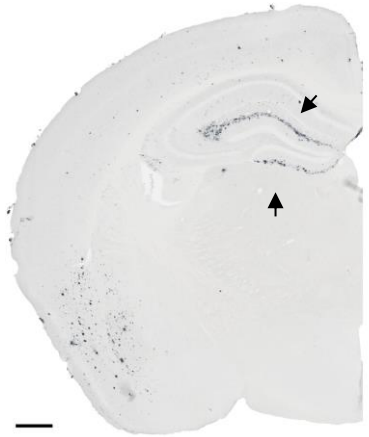


Meyer-Lühmann *et al.*, Science 2006

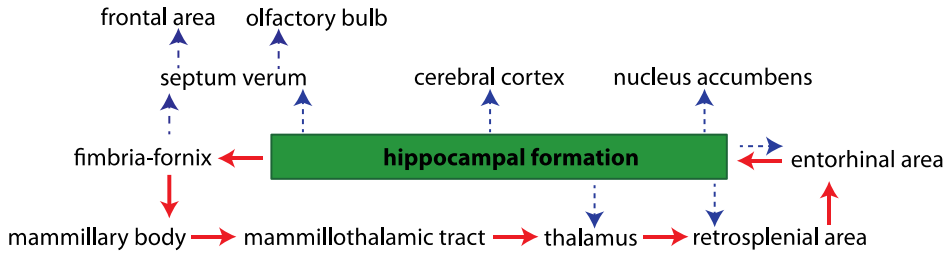
Spreading of amyloid between brain regions

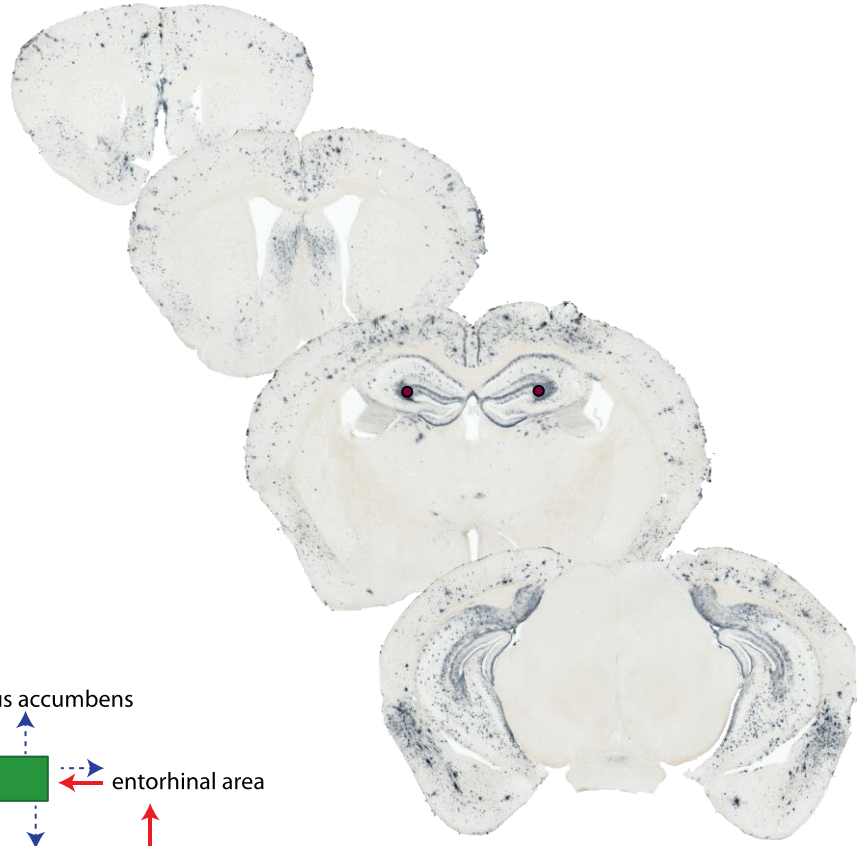


Injection of brain extract into the entorhinal cortex .....



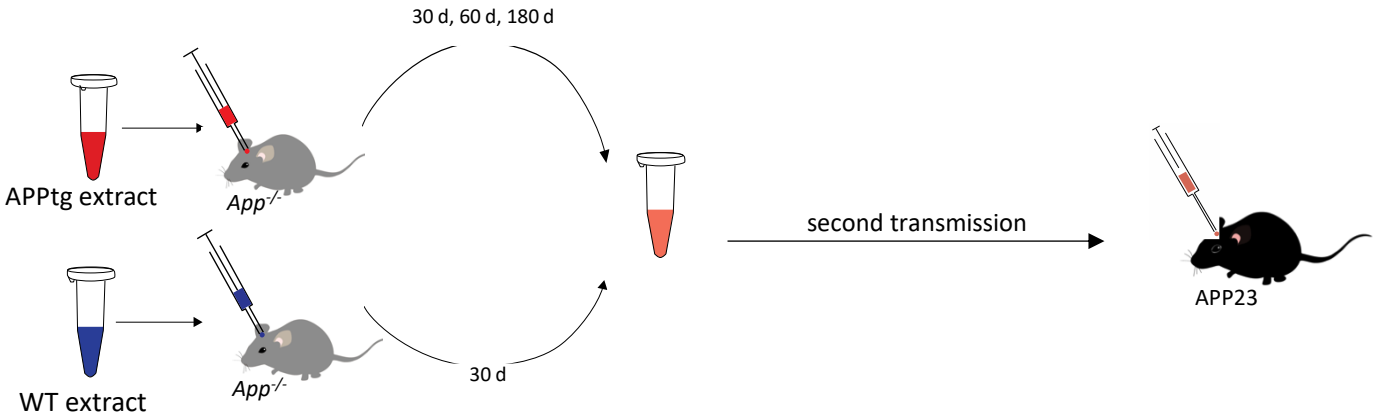
... induces amyloid in the outer molecular layer of the dentate gyrus.

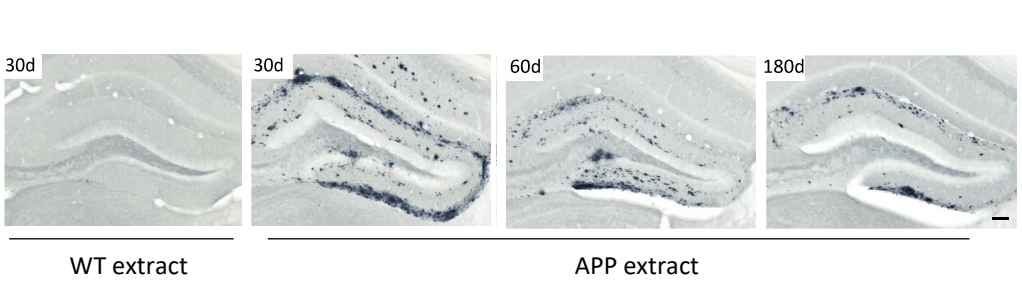


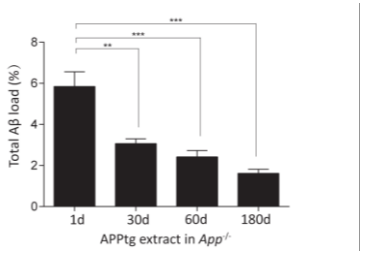


Eisele *et al.*, PNAS 2009; Hamaguchi et al., Acta Neuropathol 2012

Durability of Aβ seeds





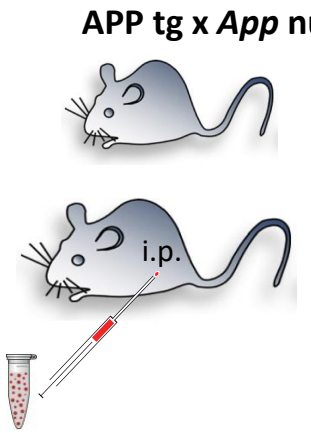


→ Aβ seeds can persist for months in brain at levels below routine detection

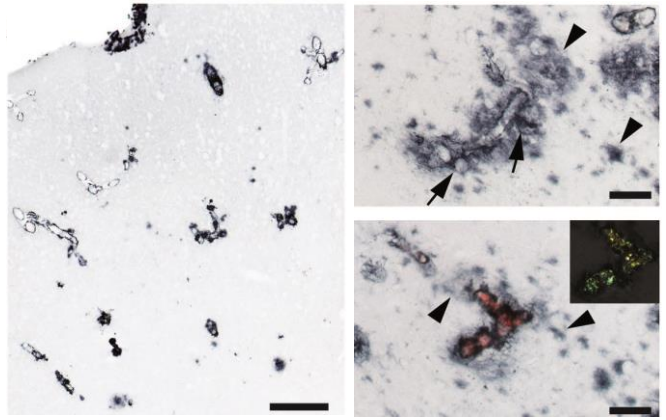
→ Aβ seeds regain propagation and pathogenicity when Aβ becomes available

Ye et al., Nature Neuroscience 2015

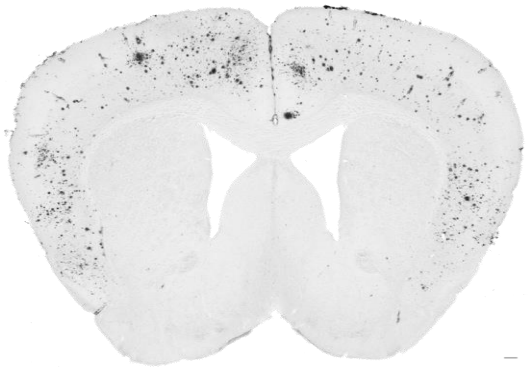
Amyloid-induction after peripheral application of Aβ seeds



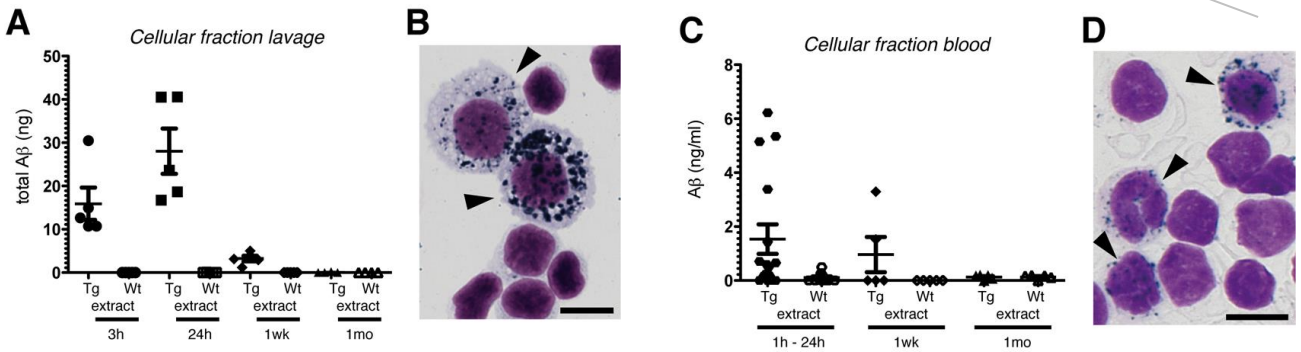
Transport /Mechanism ?



Eisele *et al*., Science 2010;



Eisele *et al*., J Neurosci 2014;



Morales *et al. acta neuropathol commun* (2020) 8:213
https://doi.org/10.1186/s40478-020-01087-1

Acta Neuropathologica Communications

RESEARCH Open Access

Infusion of blood from mice displaying cerebral amyloidosis accelerates amyloid pathology in animal models of Alzheimer's disease

Rodrigo Morales[1,2*†], Claudia Duran-Aniotz[1,3†], Javiera Bravo-Alegria[1,4], Lisbell D. Estrada[5], Mohammad Shahnawaz[1], Ping-Ping Hu[1,6], Carlos Kramm[1,4], Diego Morales-Scheihing[1,4], Akihiko Urayama[1] and Claudio Soto[1,4*]

Properties of Prions and Aβ seeds

Properties	PrP-prions	Aβ seeds
β-strand-rich secondary structure	Yes	Yes
Potential to form amyloid	Yes	Yes
Seeds initiate pathology	Yes	Yes
Long incubation period	Yes	Yes
Spread within and to the brain	Yes	Yes
Synthetic seeds are less potent	Yes	Yes
Multiple distinct strains	Yes	Yes
Protease-resistant & -sensitive forms	Yes	Yes
Resistance to high temperature	Yes	Yes
Resistance to formaldehyde	Yes	Yes
Serial transmissibility in mice	Yes	Yes
Transmissibility in humans	Yes	?

Elementary – Season 1, Episode 17

Possibility Two

Iatrogenic CAA (iCAA) and Alzheimer (iAD)

Banerjee G, *et al. J Neurol Neurosurg Psychiatry* 2022;**93**:693–700. doi:10.1136/jnnp-2022-328792

Cerebrovascular disease

Review

Iatrogenic cerebral amyloid angiopathy: an emerging clinical phenomenon

Gargi Banerjee ,[1] Kiran Samra ,[2] Matthew E Adams,[3] Zane Jaunmuktane,[4,5] Adrian Robert Parry-Jones,[6,7] Joan Grieve,[8] Ahmed K Toma,[8] Simon F Farmer,[9] Richard Sylvester,[9] Henry Houlden ,[5] Peter Rudge,[1] Simon Mead ,[1] Sebastian Brandner,[1,2,4] Jonathan M Schott ,[2] John Collinge,[1] David J Werring [10]

Clinical Picture

Intracerebral haemorrhage caused by iatrogenic cerebral amyloid angiopathy in a patient with a history of neurosurgery 35 years earlier

Simon Fandler-Höfler, Markus Kneihsl, Markus Beitzke, Christian Enzinger, Thomas Gattringer

Lancet 2023; 402: 411

Department of Neurology (S Fandler-Höfler PhD, M Kneihsl PhD, M Beitzke MD, Prof C Enzinger MD, Prof T Gattringer PhD) and Division of Neuroradiology, Vascular and Interventional Radiology, Department of Radiology (M Kneihsl, T Gattringer), Medical University of Graz, Graz, Austria

Correspondence to: Dr Simon Fandler-Höfler, Department of Neurology, Medical University of Graz, Graz A-8036, Austria
simon.fandler@medunigraz.at

A 40-year-old man reporting difficulties reading and a headache over the left occipital region, which he said began the day before, attended our emergency department.

On general examination he was well; his blood pressure was slightly raised at 150/95 mm Hg and other vital signs were within normal limits. Neurological examination showed a defect in the patient's right visual field; we found no meningism, cranial nerve abnormalities, sensorimotor deficits, or pyramidal tract signs.

A brain CT showed a small acute intracerebral haemorrhage in the left occipital lobe as well as evidence of a previous craniotomy and a defect in the parenchyma of the right occipital lobe (figure). The patient was admitted to the stroke unit for close monitoring and antihypertensive medication.

On further enquiry about his medical history, the patient reported previous neurosurgery after a severe traumatic brain injury in his early childhood. A brain MRI, on the day after admission, showed multiple lobar cerebral microbleeds and confluent white matter hyperintensities in a multi-spot pattern (figure), indicating cerebral amyloid angiopathy.

A review of the medical records confirmed that the patient, aged 5 years, had neurosurgery where cadaveric dura had been used.

Genetic testing excluded hereditary forms of cerebral amyloid angiopathy: no mutations or duplications were present in the amyloid precursor protein (*APP*), presenilin 1 (*PSEN1*), or presenilin 2 (*PSEN2*) genes.

PET-CT confirmed increased beta-amyloid deposition in the brain and cerebrospinal fluid analysis showed reduced levels of 42-amino acid β amyloid (Aβ42) and 40-amino acid β amyloid (Aβ40), consistent with cerebral amyloid angiopathy.

Over a follow-up period of 3 years, the patient had two further intracerebral haemorrhages in the right and left frontal lobes. Repeated MRIs showed pronounced progression of cerebral microbleeds, white matter hyperintensities, and disseminated cortical superficial siderosis.

Iatrogenic cerebral amyloid angiopathy is a relatively recently described brain disease; the underlying pathophysiological processes are thought to be caused by transmission of amyloid beta protein by neurosurgery or neurointervention using cadaveric dura, with similarities to more established prion-associated diseases such as iatrogenic Creutzfeldt-Jakob disease. Reported latency periods between exposure and symptom onset range from 25 to 45 years. Iatrogenic cerebral amyloid angiopathy, compared with sporadic cerebral amyloid angiopathy, is associated with earlier disease onset—typically in the third, fourth, or fifth decades of life—although onset in older ages is possible. A diagnosis of iatrogenic cerebral amyloid angiopathy should be considered in patients presenting with lobar intracerebral haemorrhage and a history of neurosurgery which was done many years before. Typical MRI findings of cerebral amyloid angiopathy—such as lobar intracerebral haemorrhage, convexal subarachnoid haemorrhage, lobar cerebral microbleeds, cortical superficial siderosis, white matter hyperintensities in a multi-spot pattern, and enlarged perivascular spaces in the centrum semiovale—and onset at less than 55 years of age should further raise suspicion.

Contributors
SF-H wrote the first draft of the manuscript; all other authors critically revised it. We were all involved in the patient's treatment. Written consent for publication was obtained from the patient.

Declaration of interests
We declare no competing interests.

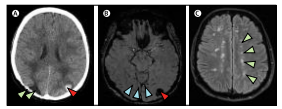


Figure: Intracerebral haemorrhage caused by iatrogenic cerebral amyloid angiopathy from neurosurgery 35 years earlier
(A) Brain CT shows small acute intracerebral haemorrhage in the left occipital lobe (red arrow). (A) craniotomy, and parenchymal defect in the right occipital lobe (green arrows). (B) Susceptibility-weighted MRI shows several lobar cerebral microbleeds (blue arrows) and acute haemorrhage (red arrow). (C) T2-fluid attenuated inversion recovery sequence MRI shows white matter hyperintensities in a multi-spot pattern (green arrows).

nature medicine

Article

https://doi.org/10.1038/s41591-023-02729-2

Iatrogenic Alzheimer's disease in recipients of cadaveric pituitary-derived growth hormone

Received: 3 October 2023

Accepted: 17 November 2023

Published online: 29 January 2024

Gargi Banerjee [1,2], Simon F. Farmer[3], Harpreet Hyare[4,5], Zane Jaunmuktane [6,7], Simon Mead [1,2], Natalie S. Ryan[8,9], Jonathan M. Schott [8,9], David J. Werring [10,11], Peter Rudge[1,2] & John Collinge [1,2]

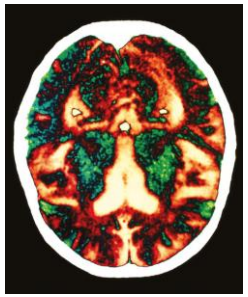
Nature | Vol 626 | 8 February 2024 |

'TRANSMISSIBLE' ALZHEIMER'S HINTS SEEN IN BRAINS FOR FIRST TIME

The findings support a controversial hypothesis that proteins related to the disease can be transferred.

By Carissa Wong

disease can be contagious.

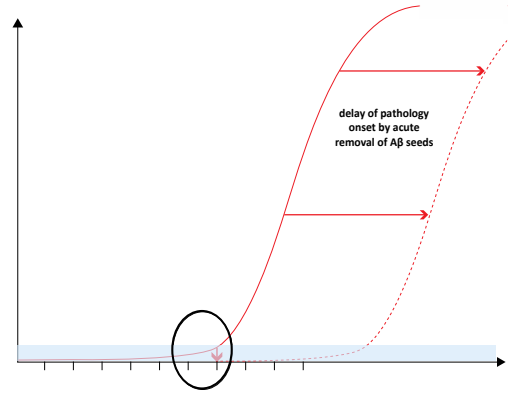


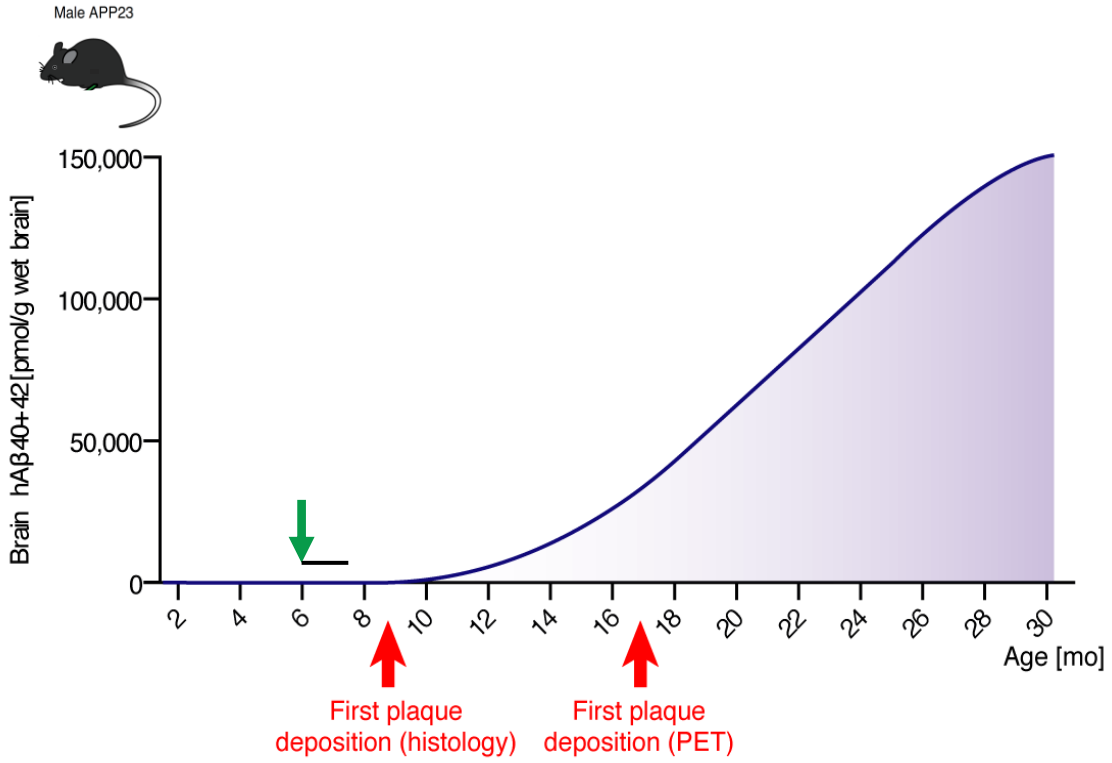
Current research directions:

- Inactivation of Aβ seeds

- How does Aβ **mediate toxicity**?

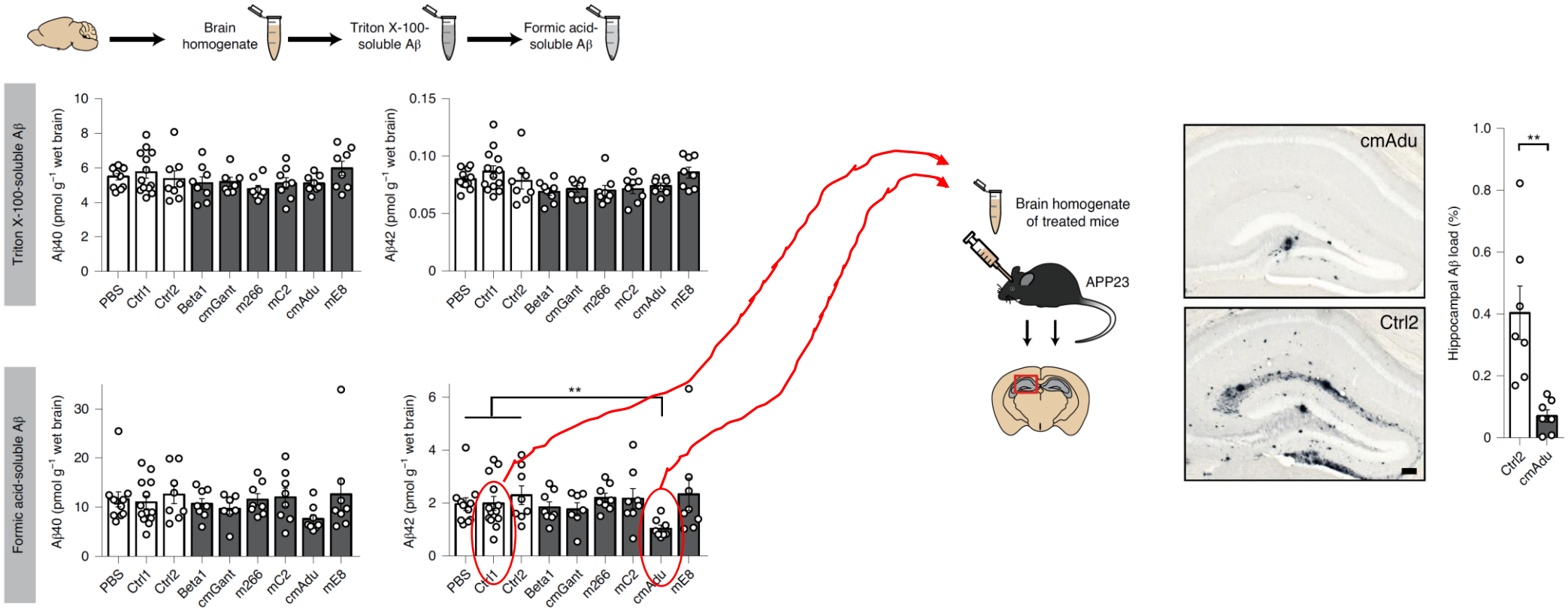
Acute targeting of pre-amyloid Aβ seeds

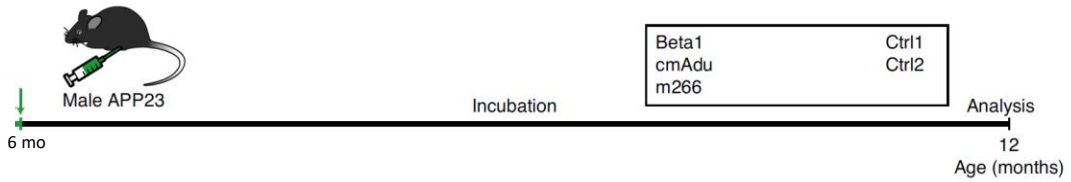


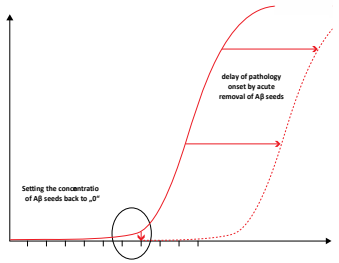


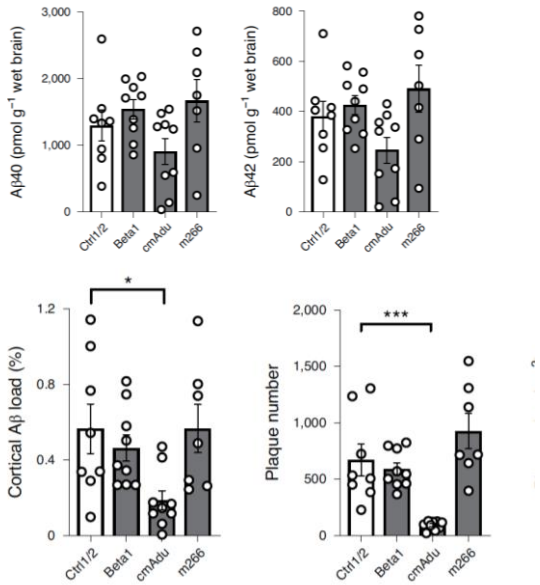
Clinical antibody	Mouse antibody	IgG subclass	Linear Aβ epitope
Aducanumab®	*cm*Aducanumab	IgG2a	3-7
Solanezumab®	m266	IgG2a	16-26
Gantenerumab®	*cm*Gantenerumab	IgG1	3-7; 18-27
Crenezumab®	mC2	IgG2a	13-24
Donanemab®	mE8	IgG2a	pE3
	Beta1	IgG2a	3-6
	anti-wheat auxin, Control 1	IgG2a	-
	P1.17; unknown antigen, Control 2	IgG2a	-

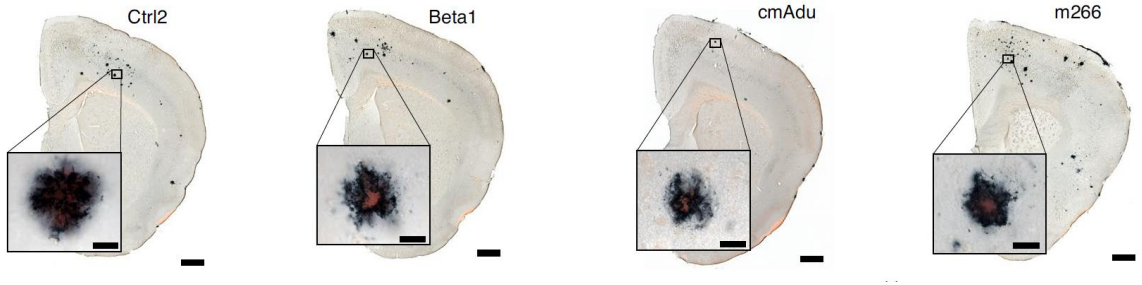
Uhlmann et al., Nature Neuroscience 2020


Brain homogenate
Triton X-100-soluble Aβ
Formic acid-soluble Aβ
Triton X-100-soluble Aβ
Formic acid-soluble Aβ
Aβ40 (pmol g−1 wet brain)
Aβ42 (pmol g−1 wet brain)
PBS
Ctrl1
Ctrl2
Beta1
cmGant
m266
mC2
cmAdu
mE8
**
Brain homogenate of treated mice
APP23
cmAdu
Ctrl2
Hippocampal Aβ load (%)
**
Ctrl2
cmAdu

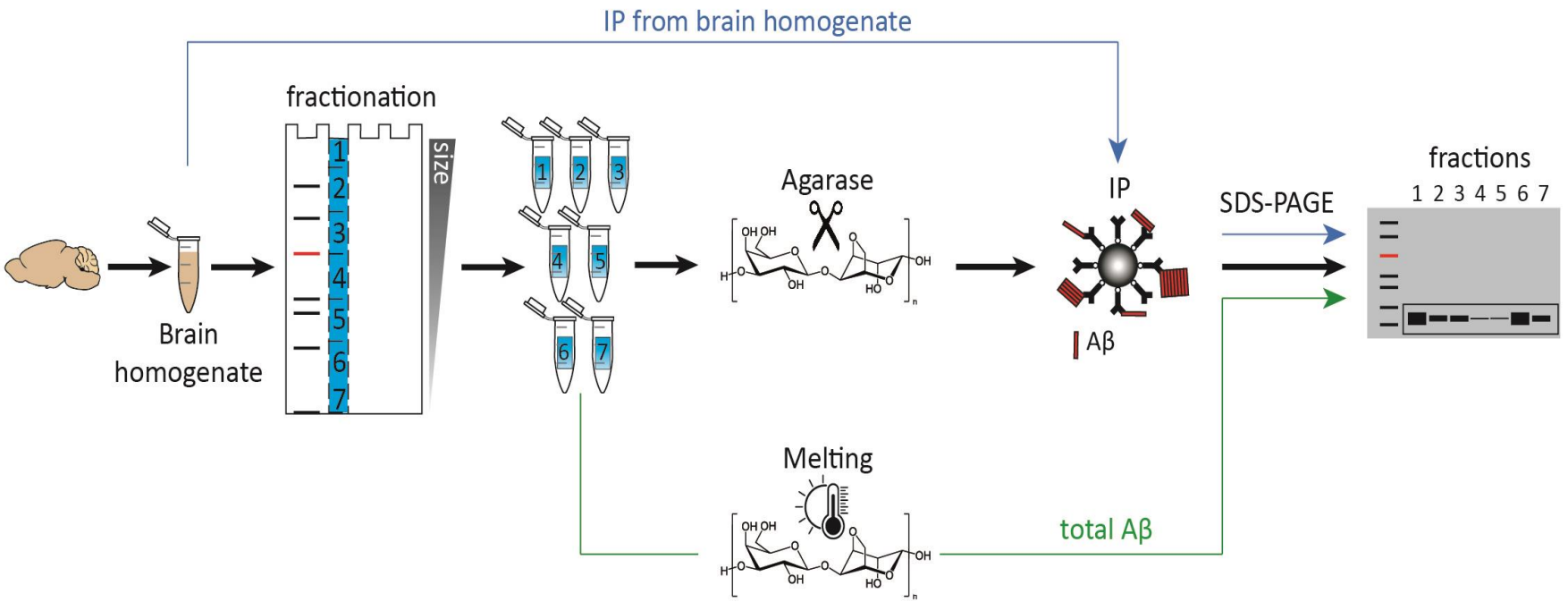

Male APP23
6 mo
Incubation
Beta1
cmAdu
m266
Ctrl1
Ctrl2
Analysis
12
Age (months)

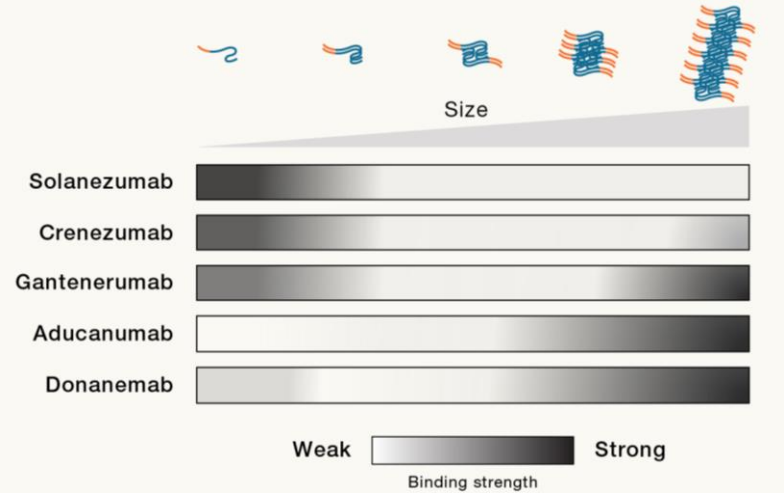

delay of pathology onset by acute removal of Aβ seeds
Setting the concentratio of Aβ seeds back to „0"

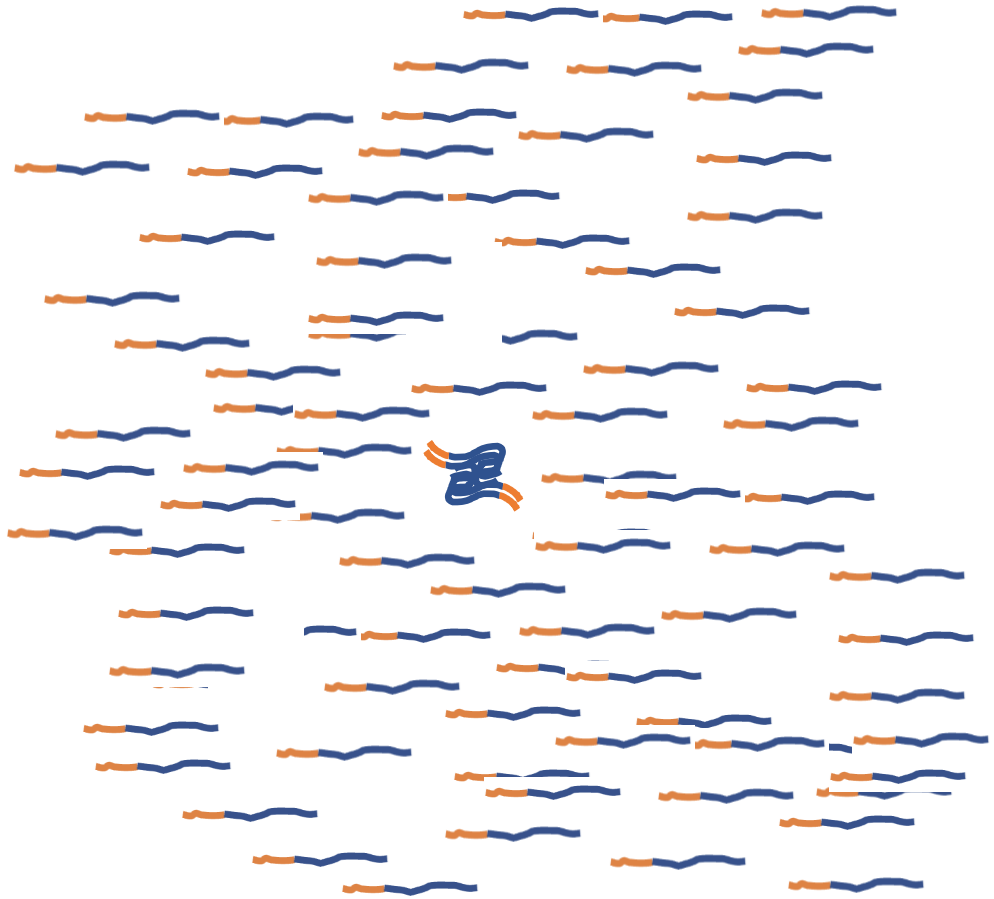

Aβ40 (pmol g⁻¹ wet brain)
Aβ42 (pmol g⁻¹ wet brain)
Cortical Aβ load (%)
Plaque number
Ctrl1/2
Beta1
cmAdu
m266
*
***


Ctrl2
Beta1
cmAdu
m266

Aβ-assembly-recognition-profiling for antibodies (ARPA)







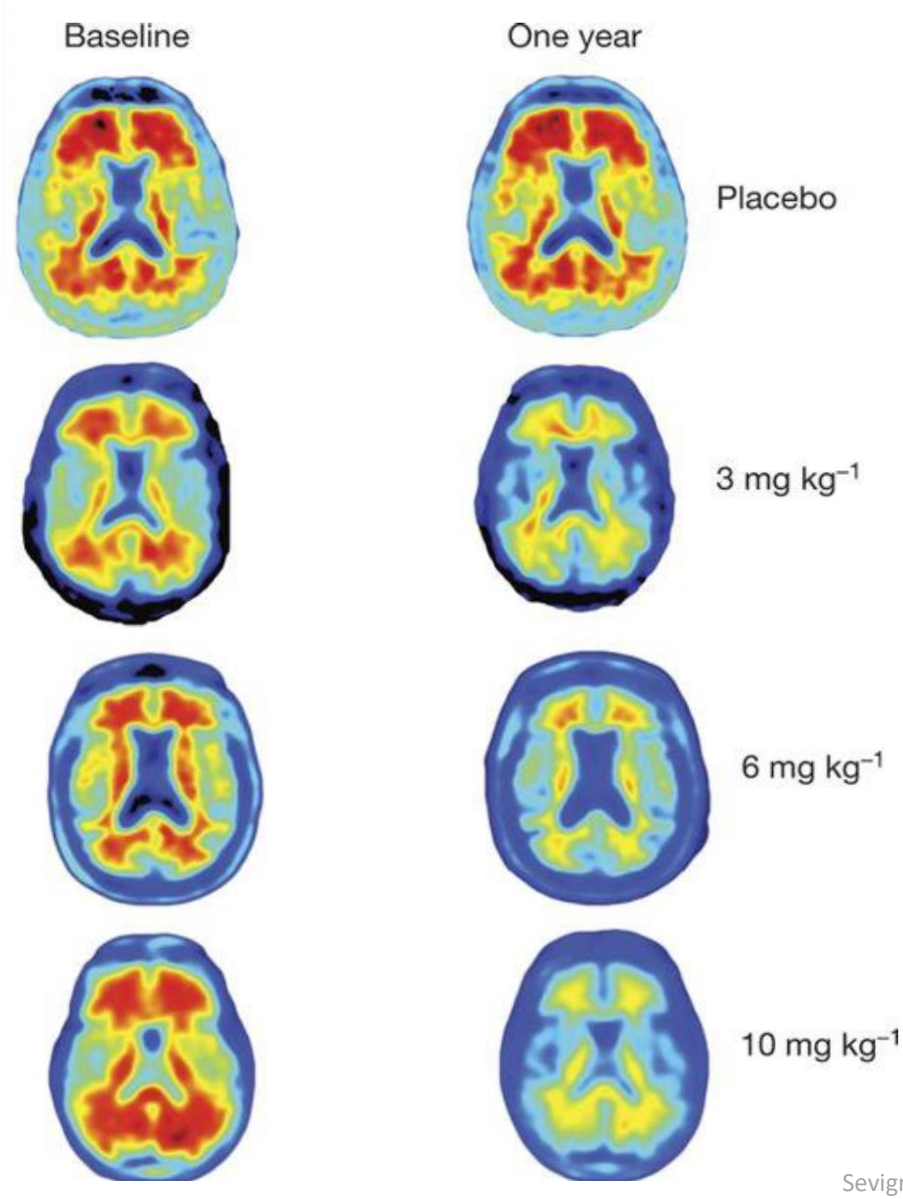
Jucker and Walker, Cell 2023

Current research directions:

- **Inactivation** of Aβ seeds

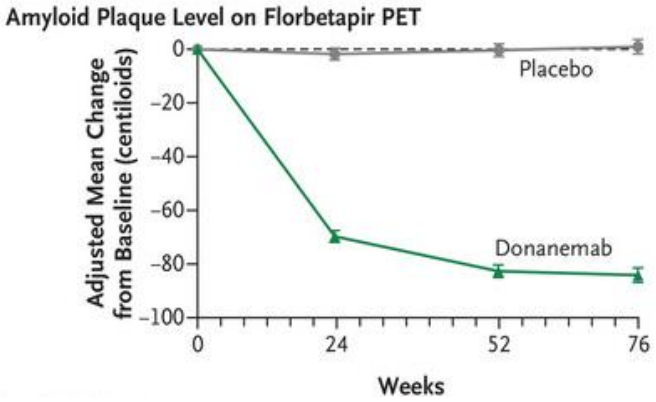
- How does Aβ **mediate toxicity**?

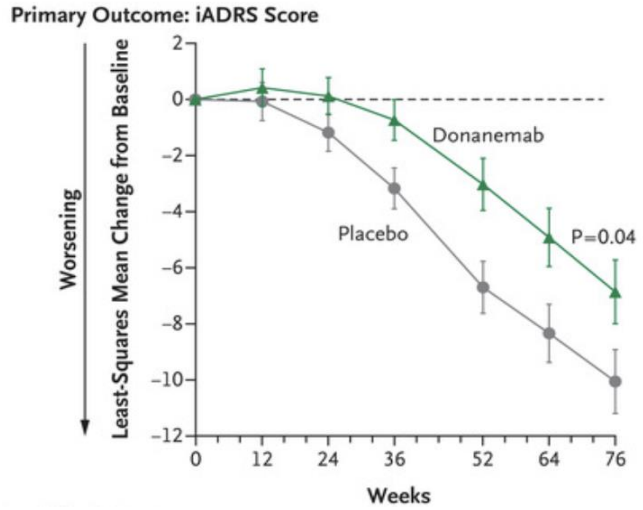
Aβ Immunotherapy

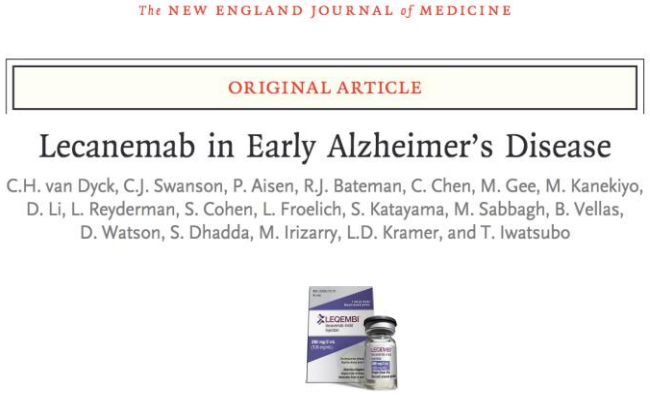


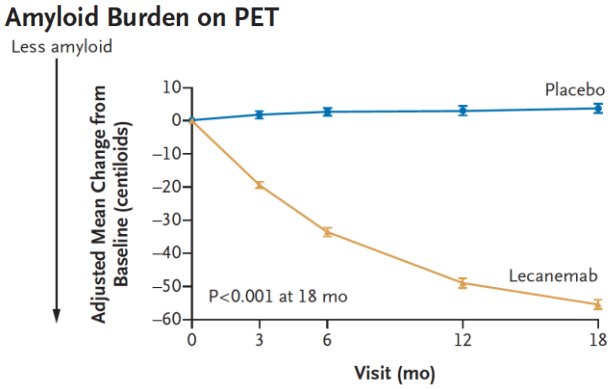
Sevigny et al., Nature 2016

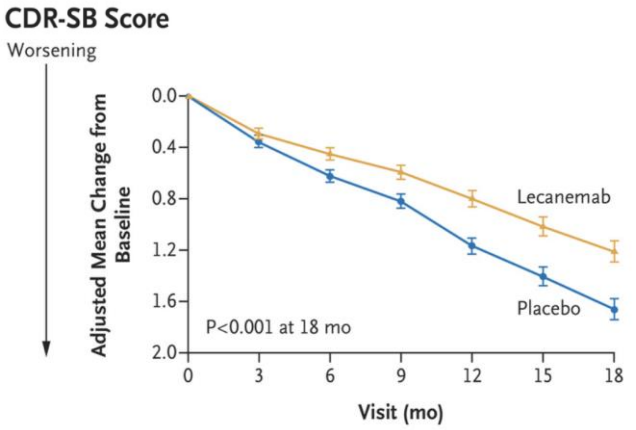
Aβ Immunotherapy in humans



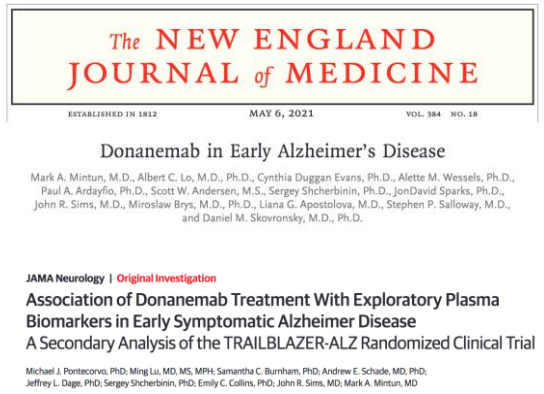








Aβ Immunotherapy in humans



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 6, 2021 VOL. 384 NO. 18

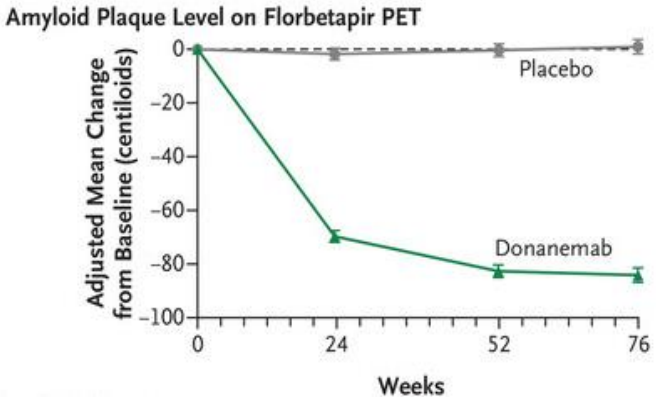
Donanemab in Early Alzheimer's Disease

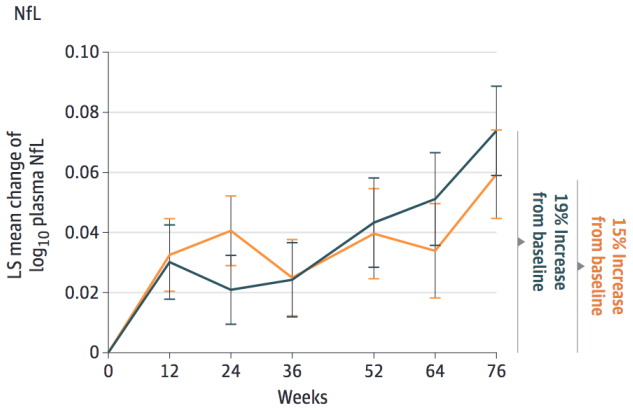
Mark A. Mintun, M.D., Albert C. Lo, M.D., Ph.D., Cynthia Duggan Evans, Ph.D., Alette M. Wessels, Ph.D., Paul A. Ardayfio, Ph.D., Scott W. Andersen, M.S., Sergey Shcherbinin, Ph.D., JonDavid Sparks, Ph.D., John R. Sims, M.D., Miroslaw Brys, M.D., Ph.D., Liana G. Apostolova, M.D., Stephen P. Salloway, M.D., and Daniel M. Skovronsky, M.D., Ph.D.

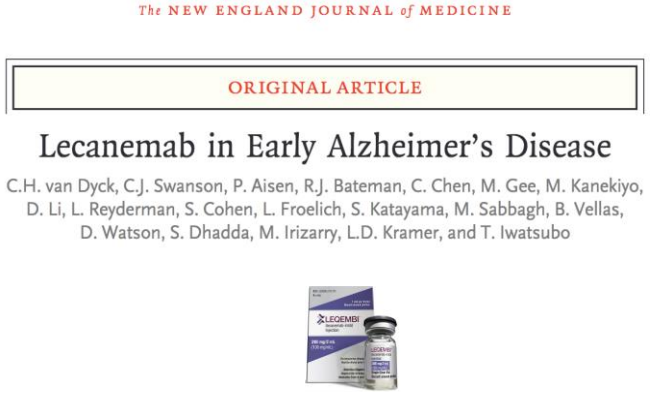
JAMA Neurology | Original Investigation

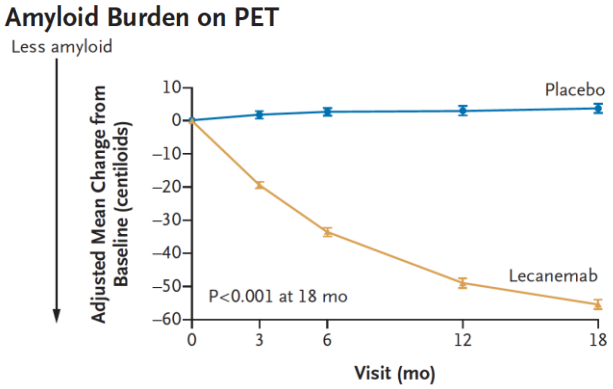
Association of Donanemab Treatment With Exploratory Plasma Biomarkers in Early Symptomatic Alzheimer Disease
A Secondary Analysis of the TRAILBLAZER-ALZ Randomized Clinical Trial

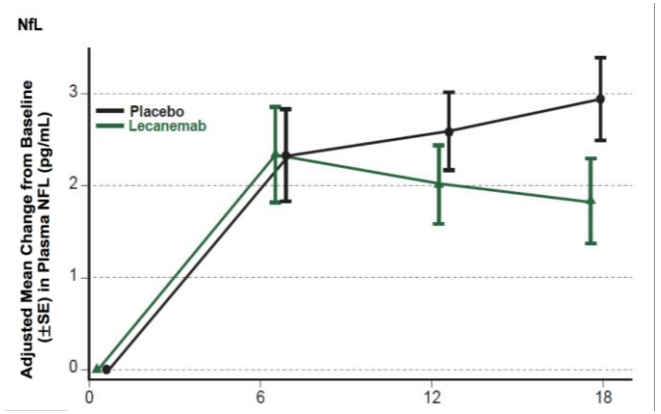
Michael J. Pontecorvo, PhD; Ming Lu, MD, MS, MPH; Samantha C. Burnham, PhD; Andrew E. Schade, MD, PhD; Jeffrey L. Dage, PhD; Sergey Shcherbinin, PhD; Emily C. Collins, PhD; John R. Sims, MD; Mark A. Mintun, MD





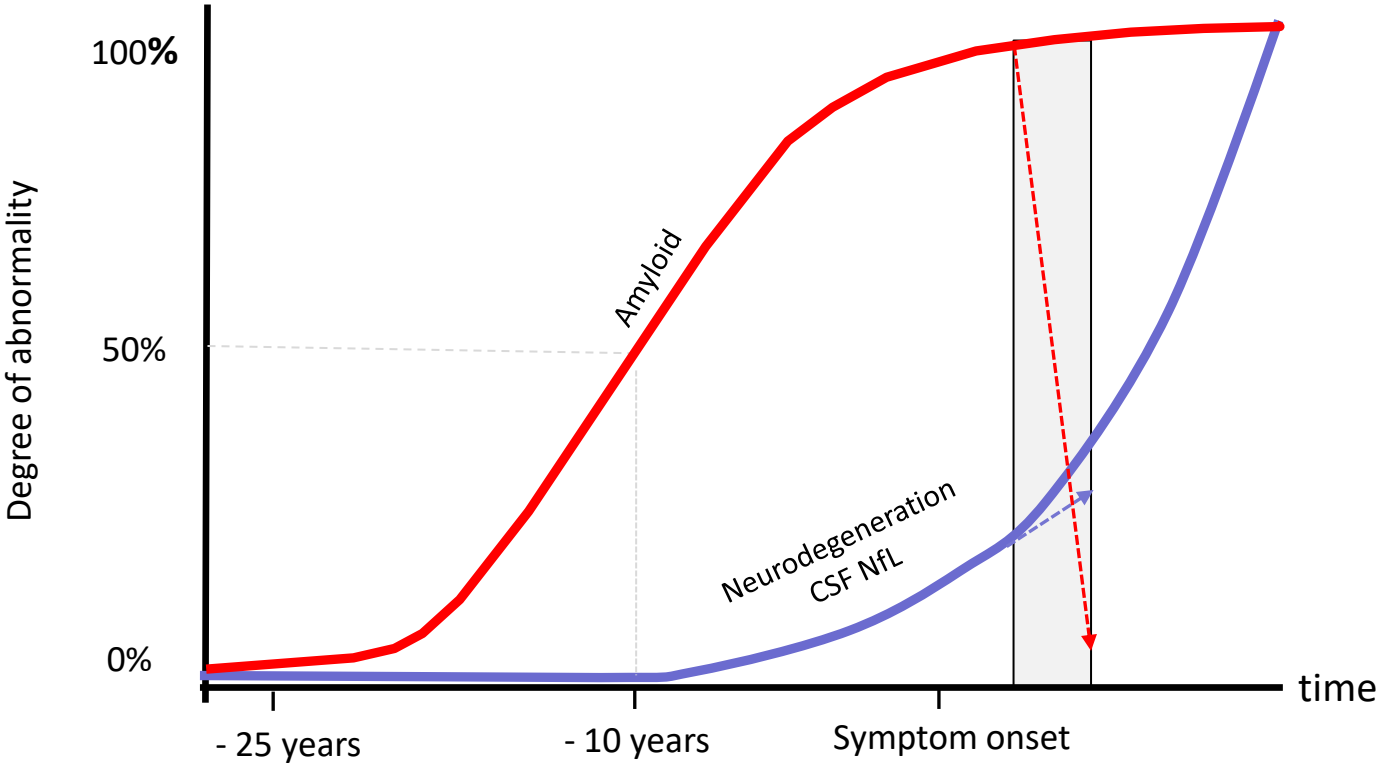


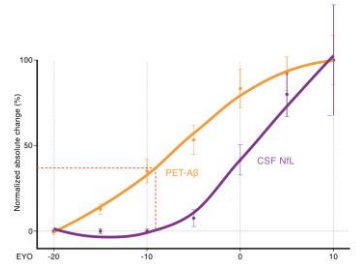




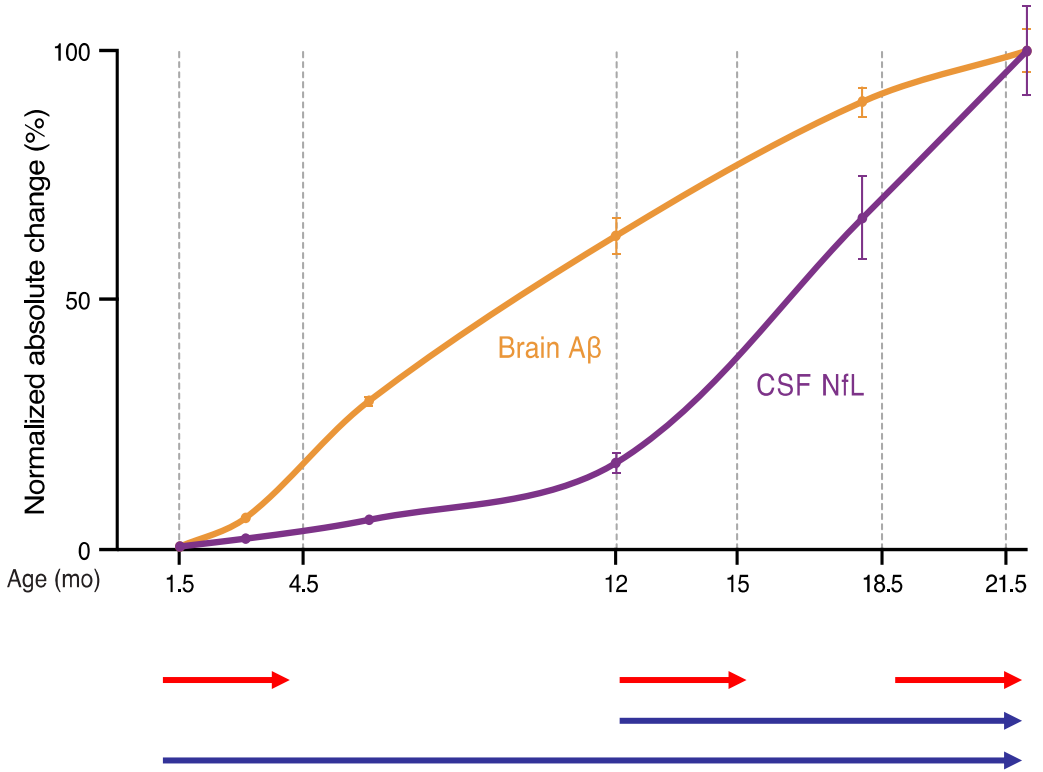
DIAN

Dominantly Inherited Alzheimer Network



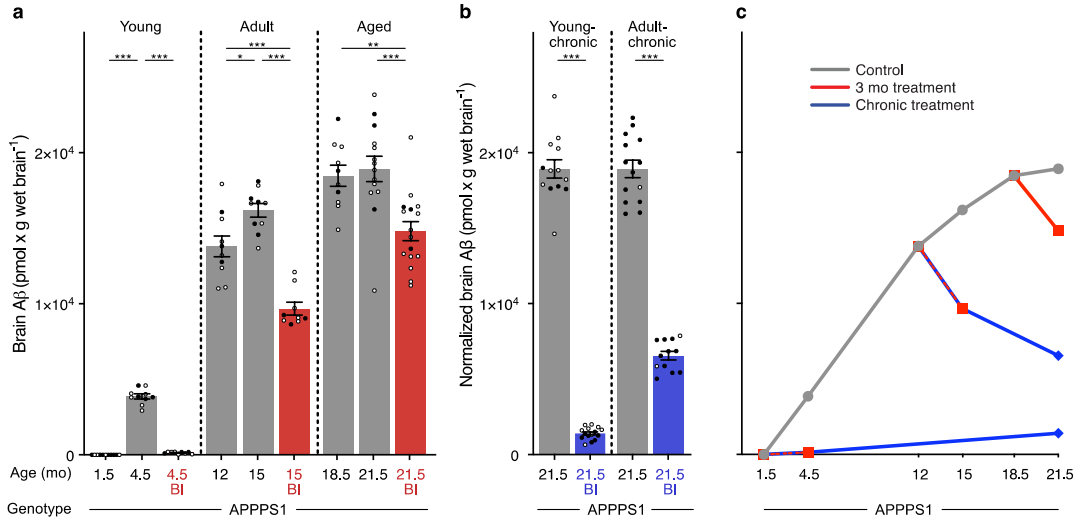


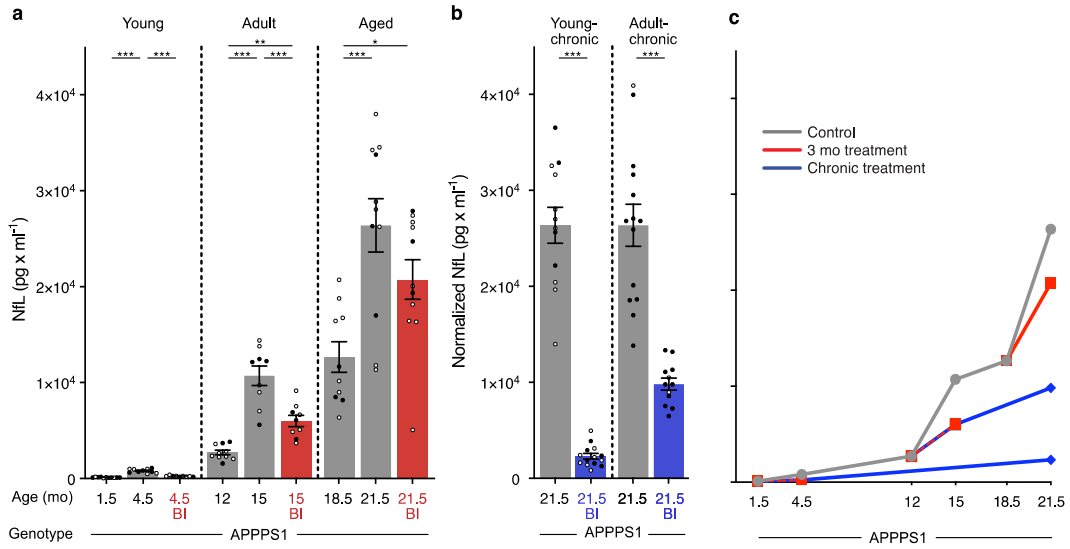
Neurodegeneration (NfL levels in CSF) in response to cerebral β-amyloidosis



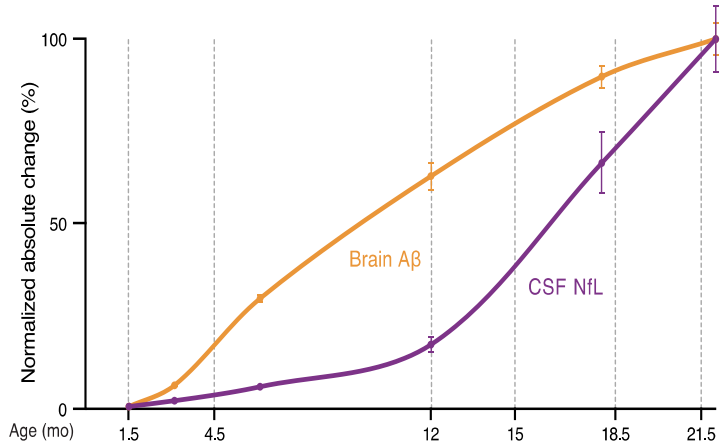
Rother et al., Nature Comm 2022

Temporal uncoupling of brain Aβ and neurodegeneration





How does Aβ mediate toxicity?



LETTER

doi:10.1038/nature09768

Prion propagation and toxicity *in vivo* occur in two distinct mechanistic phases

Malin K. Sandberg[1], Huda Al-Doujaily[1], Bernadette Sharps[1], Anthony R. Clarke[1] & John Collinge[1]

540 | NATURE | VOL 470 | 24 FEBRUARY 2011

Conclusion 1

Aβ seeds are present well before amyloid formation becomes detectable.

Acute inactivation of such early seeds causes robust delay of β-amyloidosis.

Targeting such pre-amyloid seeds maybe necessary to achieve effective primary prevention of Alzheimer´s Disease

We need to better understand how aggregated Aβ relates to neurodegeneration

Thanks to my lab members and to the many co-workers!

DZNE
Deutsches Zentrum für Neurodegenerative Erkrankungen
in der Helmholtz-Gemeinschaft

Hertie Institute
for Clinical Brain Research

Current lab members:

Carina Bergmann
Angelos Skodras
Ulrike Obermüller
Lisa M. Häsler
Anna Hofmann
Marc Welzer
Jörg Odenthal
Antonia Keller
Vasiliki Panagiotakopoulou
Marius Lambert
Ying Xu
Anika Bühler
Stephan A. Kaeser
Sinja Bucher
Matthias Staufenbiel

Stephan A. Müller, DZNE Munich
Stefan F. Lichtenthaler, DZNE Munich
Jonas Neher, LMU and DZNE Munich

Thierry Bussiere, Biogen, Cambridge, Ma
Derya Shimshek, Novartis, Basel, Switzerland
Clara Theunis, Janssen, Beerse, Belgium

Lary C. Walker, Emory, Atlanta

Stephanie A. Schulz, Harvard, Boston
Jasmeer P. Chhatwal, Harvard, Boston

DIAN
Dominantly Inherited
Alzheimer Network

www.hih-tuebingen.de/cn/

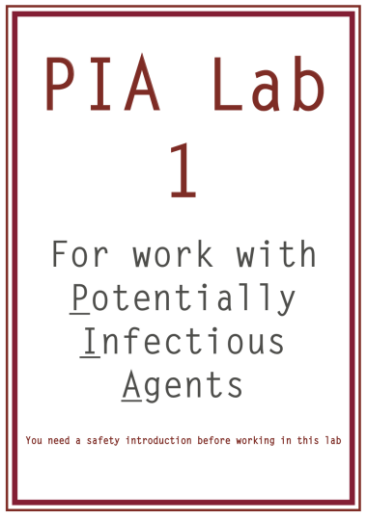
@MathiasJucker

Precautions

Lancet Neurol 2020; 19: 872–78

Potential human transmission of amyloid β pathology: surveillance and risks

Elsa Lauwers, Giovanna Lalli*, Sebastian Brandner, John Collinge, Veerle Compernolle, Charles Duyckaerts, Gustaf Edgren, Stéphane Haïk, John Hardy, Adel Helmy, Adrian J Ivinson, Zane Jaunmuktane, Mathias Jucker, Richard Knight, Robin Lemmens, I-Chun Lin, Seth Love, Simon Mead, V Hugh Perry, James Pickett, Guy Poppy, Sheena E Radford, Frederic Rousseau, Carol Routledge, Giampietro Schiavo, Joost Schymkowitz, Dennis J Selkoe, Colin Smith, Dietmar R Thal, Tom Theys, Pierre Tiberghien, Peter van den Burg, Philippe Vandekerckhove, Clare Walton, Hans L Zaaijer, Henrik Zetterberg, Bart De Strooper*



PIA Lab

Labs for work with Potentially Infectious Agents (PIA)

Misfolded proteins such as Aβ, α-Synuclein und Tau have infectious properties at the molecular level (Jucker and Walker, Nature, 2013). These infectious properties are reminiscent of the properties of prions. Although there is currently no evidence that such misfolded proteins can induce neurodegenerative diseases in humans, precautions are warranted (Leuwers *et al.*, Lancet Neurology, 2020).

There are currently no mandatory safety regulations for working with such misfolded proteins in our laboratory. Nevertheless, as a department we have decided that work with misfolded proteins that are potentially infectious is to be done in two designated laboratories of the HIH (FORS) (**PIA 1, room 1.204;** and **PIA 2, room 3.113**).

What kind of work is handled in the PIA labs?

1) Native human material
2) Native mouse tissue that contains misfolded Aβ, α-Synuclein and Tau (or any other potentially infectious amyloid)
3) Recombinant, synthetic, lyophilized Aβ, α-Synuclein and Tau

Note: Once the tissue is fixed we do no longer handle the tissue in the PIA labs, although precaution is still warranted since also fixed misfolded proteins may keep some residual infectivity.

Additional rules (beyond the common S1 rules) when working in the PIA lab

1) Get an introduction about "potentially infectious agents" from Mathias Jucker before working the first time in a PIA lab.
2) Doors of the PIA labs must always be closed. Wear a lab coat, shoe protection and gloves (preferentially double) at all times.
3) Lab coats used in the PIA lab stay in the PIA lab. (Once no longer needed or dirty move them to the laundry collection bag in the PIA lab for autoclaving and washing).
4) Equipment in the PIA lab stays in the PIA lab. If equipment used in a PIA lab must be moved outside the lab, see Anika Bübler or Uli Obermüller for decontamination and cleaning.
5) Always use an absorbing bench cover for your bench work. After you've finished, trash the bench cover. If there are spillovers clean the bench with 1% SDS (preferentially wetted for 1 hour) in order to inactivate misfolded proteins.
6) Any waste produced from a PIA lab must be collected in double-layered autoclaving bags. Close waste bags after you finished your work, but leave them in the PIA lab. They will be collected when autoclaving is done directly from the PIA lab.
7) As in any other lab, but in particular in the PIA lab, avoid production of aerosols. Wear a mask and goggles if aerosol generating work has to be done outside the hood, e.g. when cutting on the cryostat. Also wear cut-protective gloves when working with the cryostat. Use filter tips for pipetting.