Research America!

Anti-Amyloid Monoclonal Antibodies are Transforming Alzheimer Care and Research

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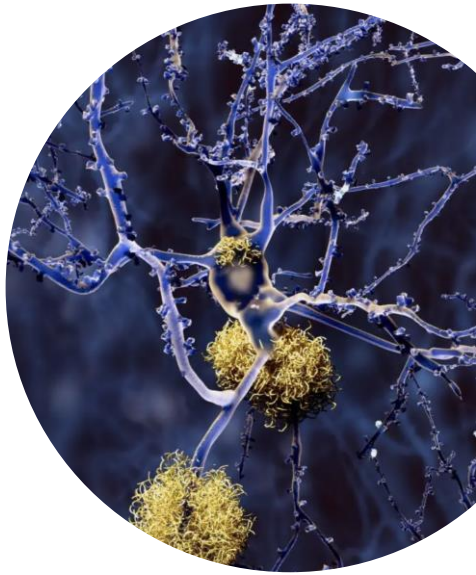

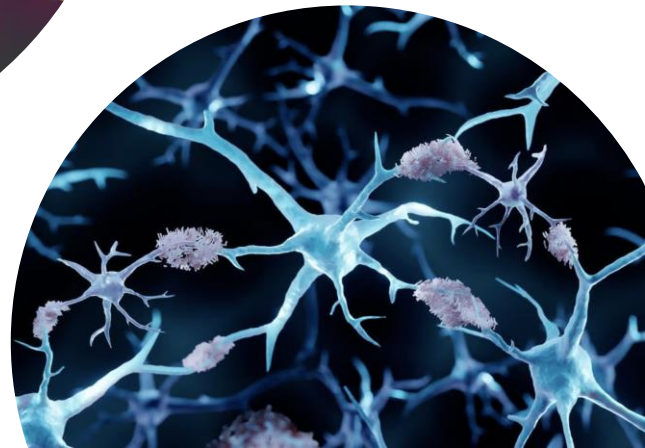

Disclosures / Acknowledgements

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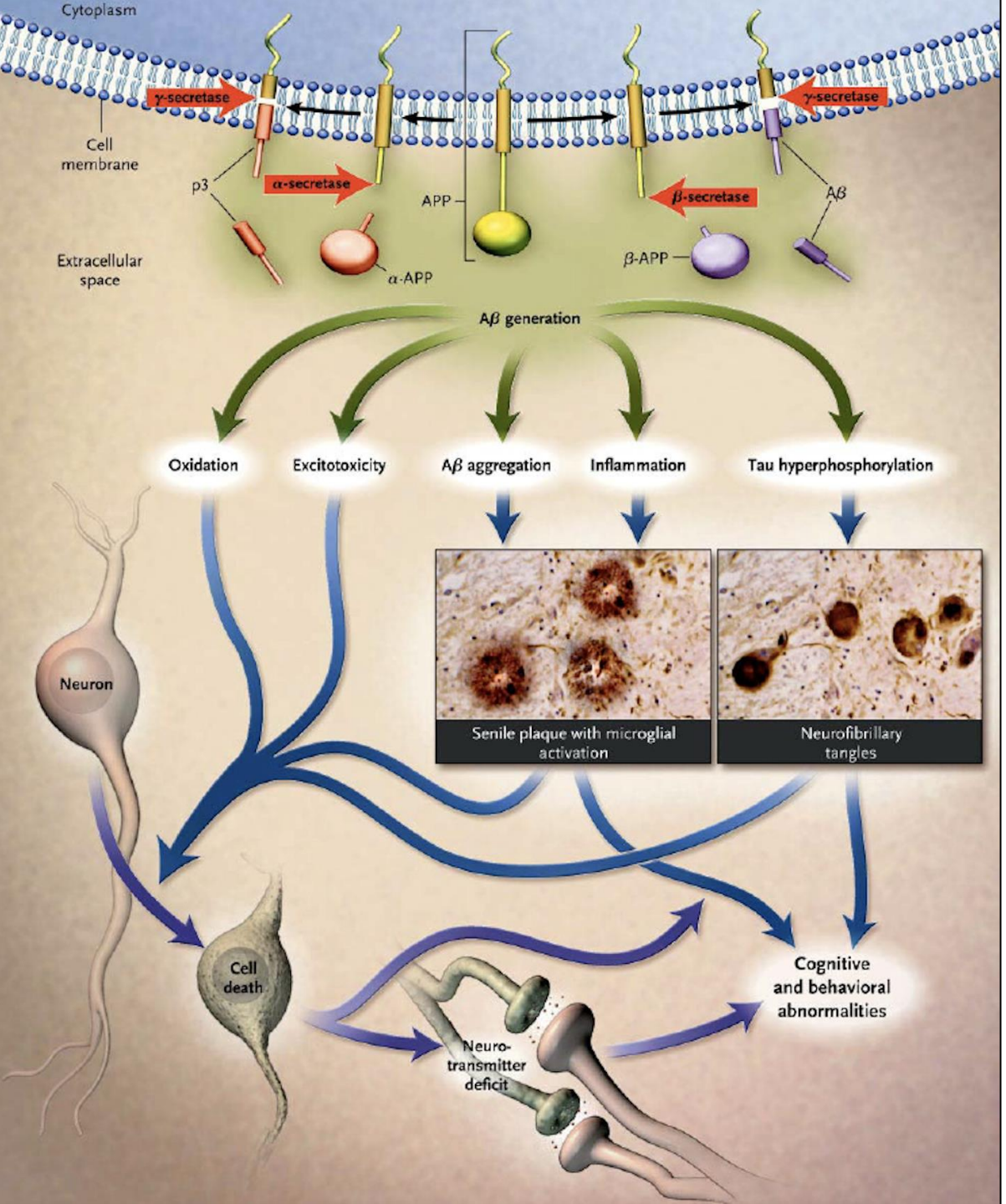
Anti-Amyloid Monoclonal Antibodies are Transforming Alzheimer Care and Research

- History of Alzheimer and amyloid research
- What are anti-amyloid monoclonal antibodies?
- What's next

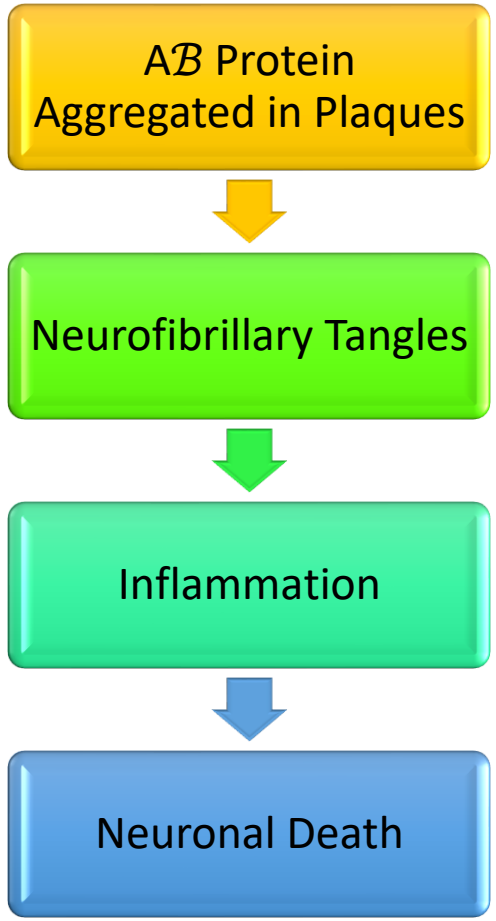
History of Alzheimer and Amyloid Research

- Alois Alzheimer describes neurofibrillary tangles and “miliary foci” (amyloid plaques) in the brain of a woman with early onset dementia (1906)
- Named in honor of Dr. Alzheimer based on this early observation (Kraeplin, 1910)
- Sir Martin Roth discovers that the pathology of “senile dementia” is the same as that of Alzheimer’s disease (previously thought to be characteristic of rare early onset dementia)(1968)
- Robert Katzman notes the aging of the population and the high prevalence of “senile dementia/Alzheimer’s disease” and sees the coming epidemic
- Protein substance found to be amyloid (George Glenner, 1984)
- “Amyloid hypothesis” formulated (Hardy and Allsop, 1991; Hardy and Selkoe and Hardy, 2002)

Alois Alzheimer



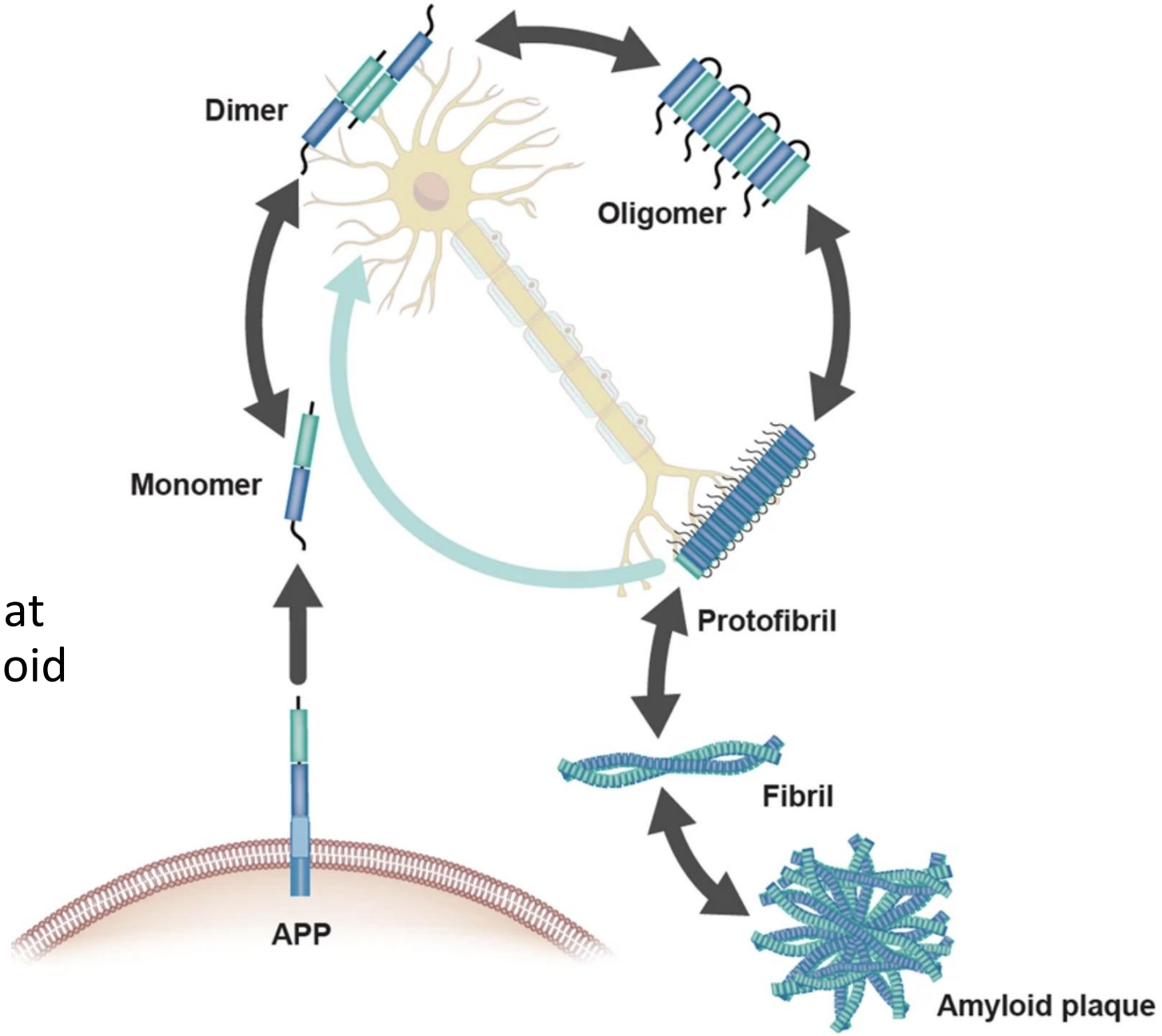
The Amyloid Cascade Hypothesis



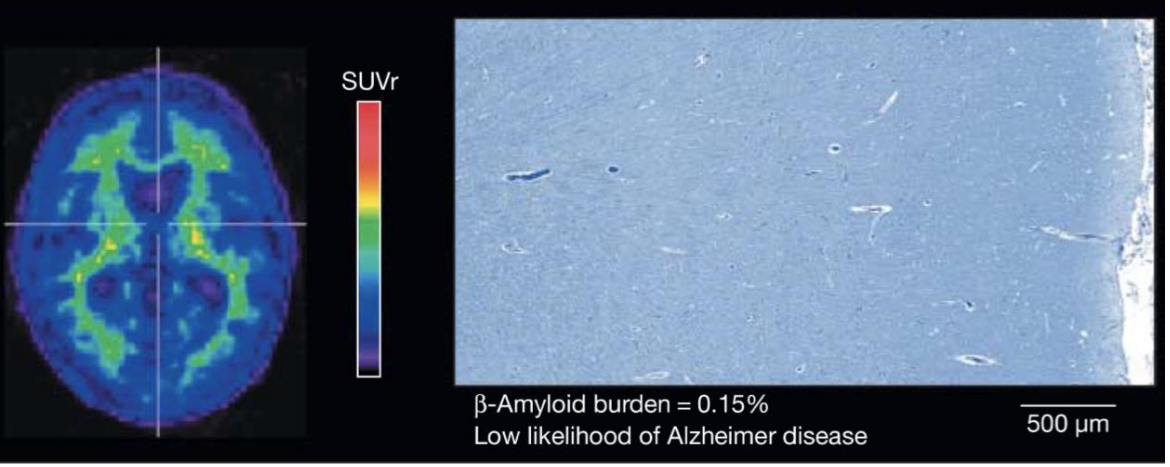
Cummings J. N Eng J Med 2004; 351: 56-67

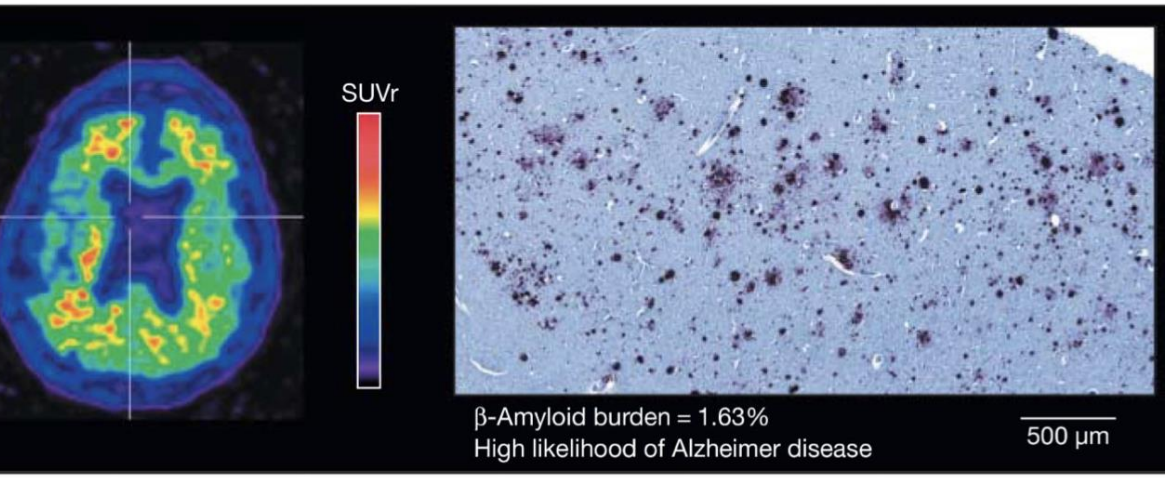
2003-2016

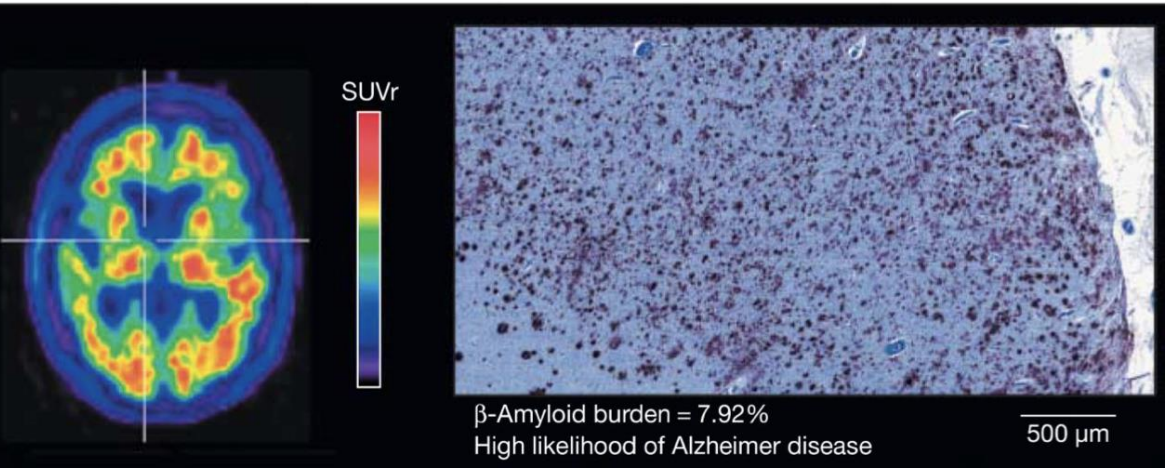
- All clinical trials were negative
  - A$\mathcal{B}$-directed
  - Non-A$\mathcal{B}$-directed
- Enormous learnings about A$\mathcal{B}$ were accruing
- Molecular biology studies showed that there were several “species” of amyloid
- Species have different toxicities and different treatment implications



Hampel H, et al. Mol Psychiatry 2021; 26: 5481-5503







Amyloid Brain Imaging: A Major Technological Advance

- First published 2005[1]
- First amyloid PET approved by FDA 2012[2]
- 2 more types of amyloid PET approved since
- All show amyloid plaque, not other species of amyloid

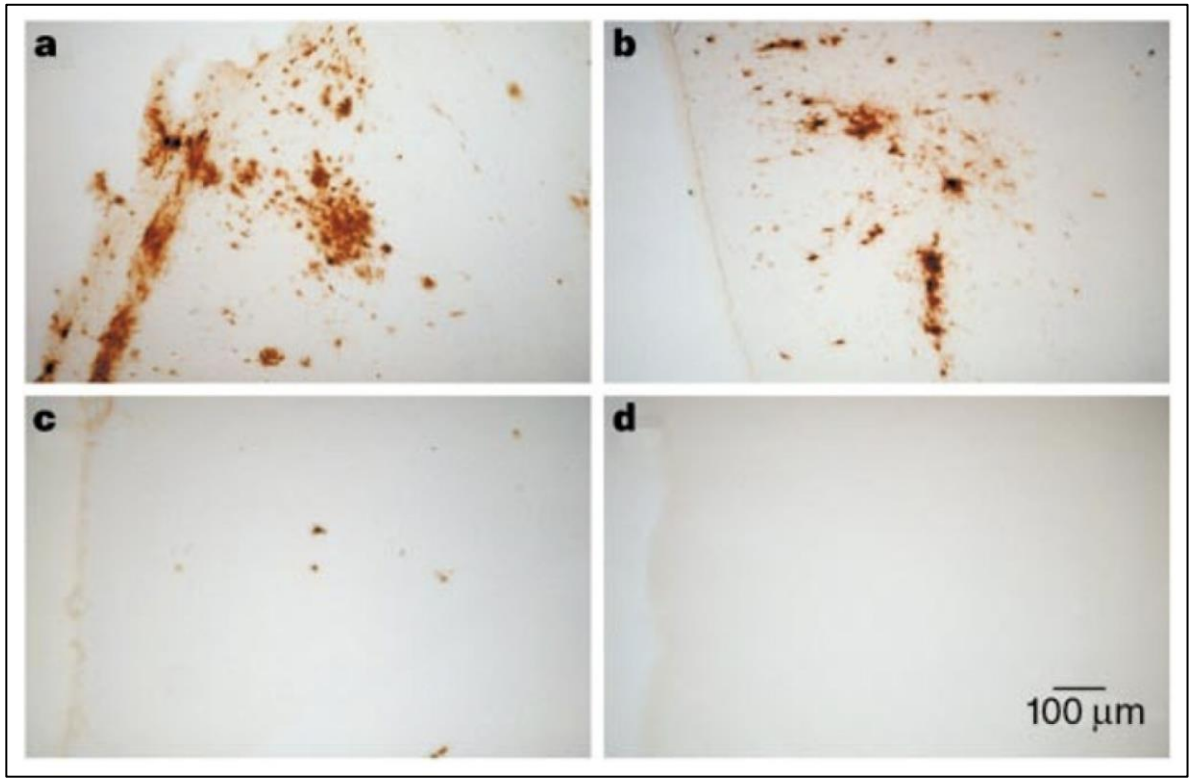
[1]Klunk W, et al. J Neurosci 2005; 25: 10598-10606; [2]Clark C, et al. JAMA 2011; 305: 275-283

Immunotherapy Emerges

- Vaccination with A$\mathcal{B}$ produces marked reduction of brain amyloid plaques[1]

Upper panels; amyloid deposition in mouse model of Alzheimer's (no vaccination)

Lower panels; amyloid deposition in mouse model of Alzheimer's (vaccinated)



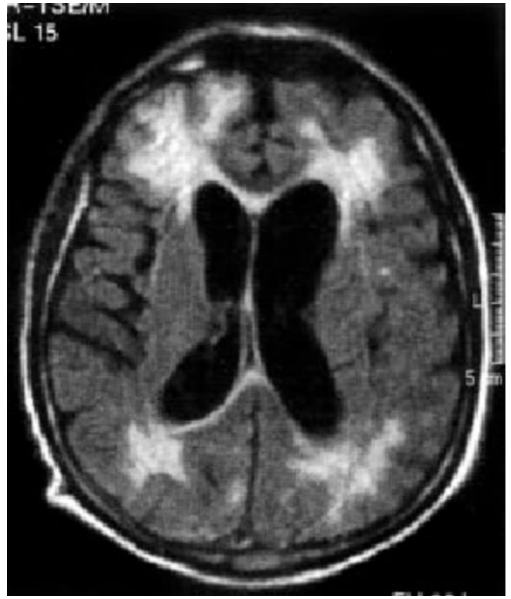
Dale Schenk (1957-2016)

[1]Schenk D. et al. Nature 1999; 400: 173-177;

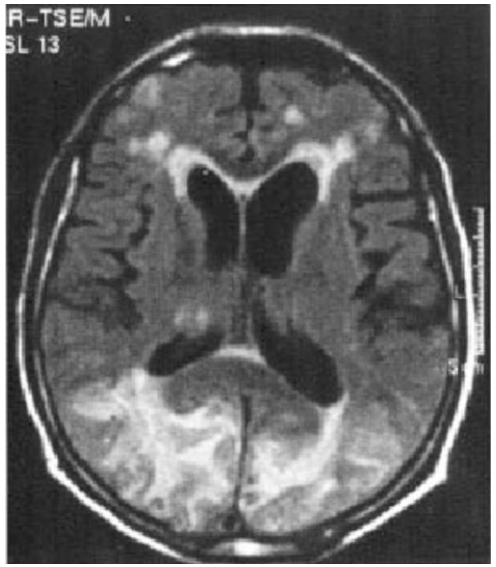
Human Immunotherapy Trials: A Learning Process

- First human vaccination study (AN1792) is terminated early; 6% of patients develop an immune encephalitis[1]
- Passive immunotherapy (with monoclonal antibodies targeting A$\mathcal{B}$) trial with bapineuzumab is negative[2]
- Other antibodies fail to show a drug-placebo difference in trials, none are directed at amyloid plaques or protofibrillar species of amyloid[3,4,5]
- Study observations suggests the dose of the monoclonal antibodies is too low and that plaque reduction is important[6,7]

AN1792



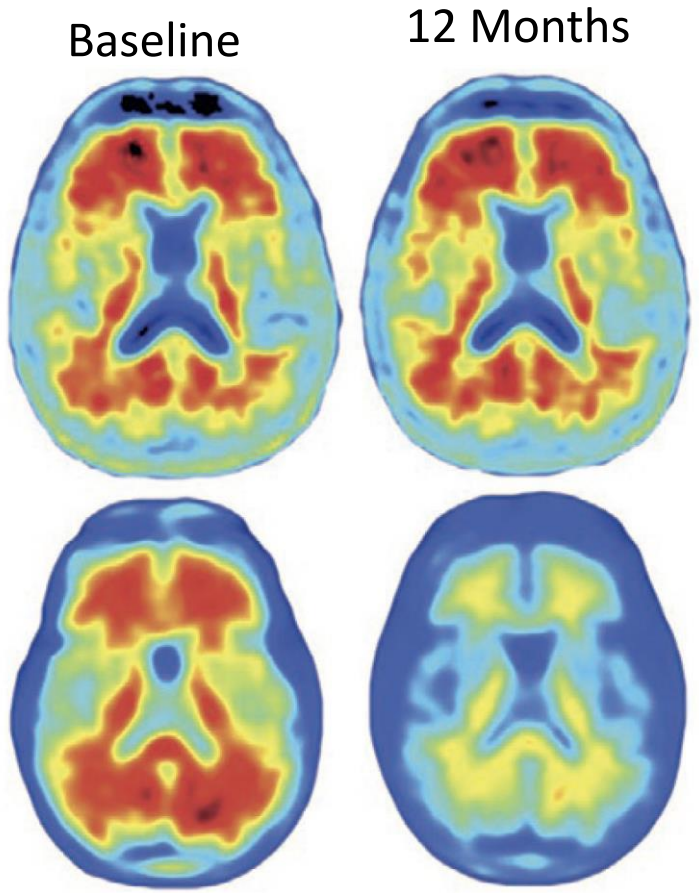
AN1792



[1]Gilman S, et al. Neurol 2005; 64: 1553-1562; [2]Salloway S, et al. N Engl J Med 2014; 370: 322-333;
[3]Honig L, et al. N Engl J Med 2018l 378: 321-330; [4]Cummings J, et al. 2018; 90: 1889-1897;
[6]Ostrowitzki S, et al. Alz Res & Therapy 2107; 9: 96-110; [7]Rinne J, et al. Lancet Neurol 2010; 9: 363-372

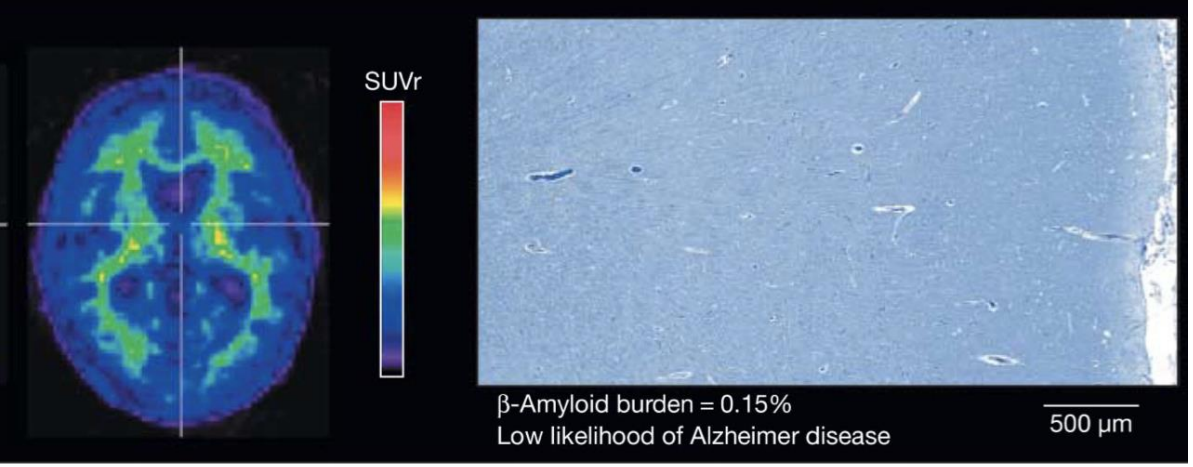
Aducanumab (Aduhelm®): The Turning Point[1,2]

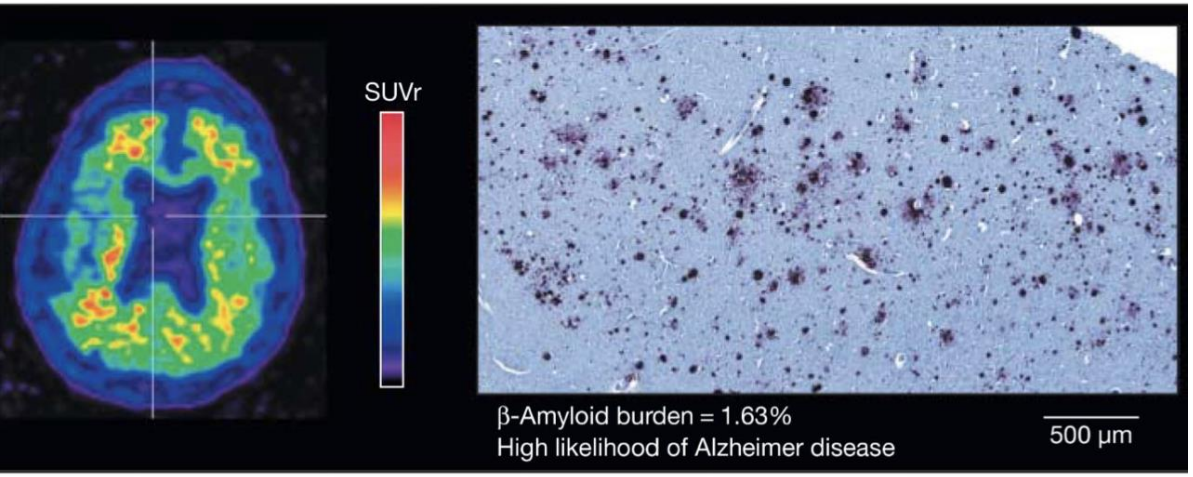
- Plaque focused
- Dose range explored to high dose
- Phase 1
  - High dose produced marker A$\mathcal{B}$ reduction
  - Clinical measures supported disease slowing
- Phase 3
  - Trials prematurely terminated for erroneous interpretation of futility
  - Marked A$\mathcal{B}$ plaque reduction
  - Clinical benefit in 1 study (Emerge) not the other (Engage)
- Controversial accelerated approval by the FDA

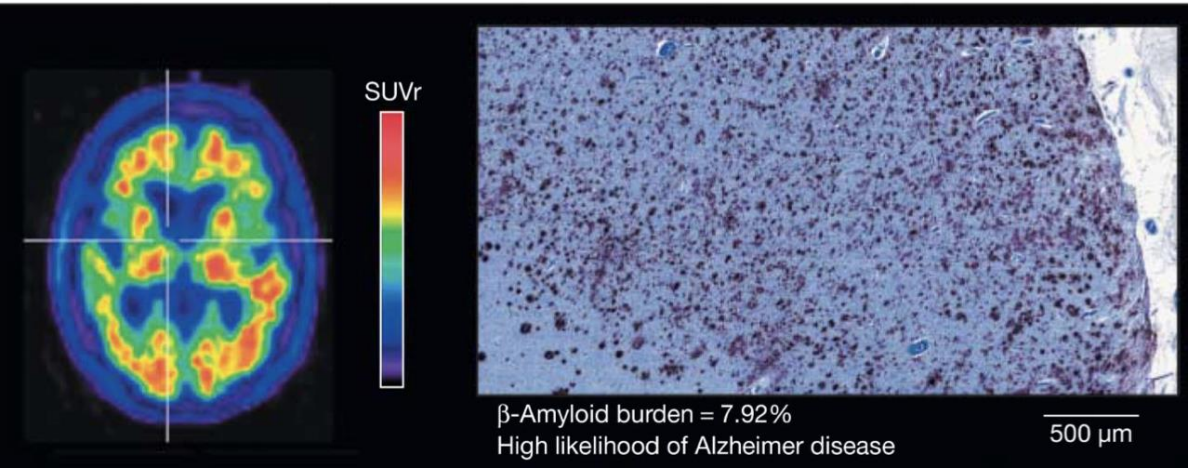


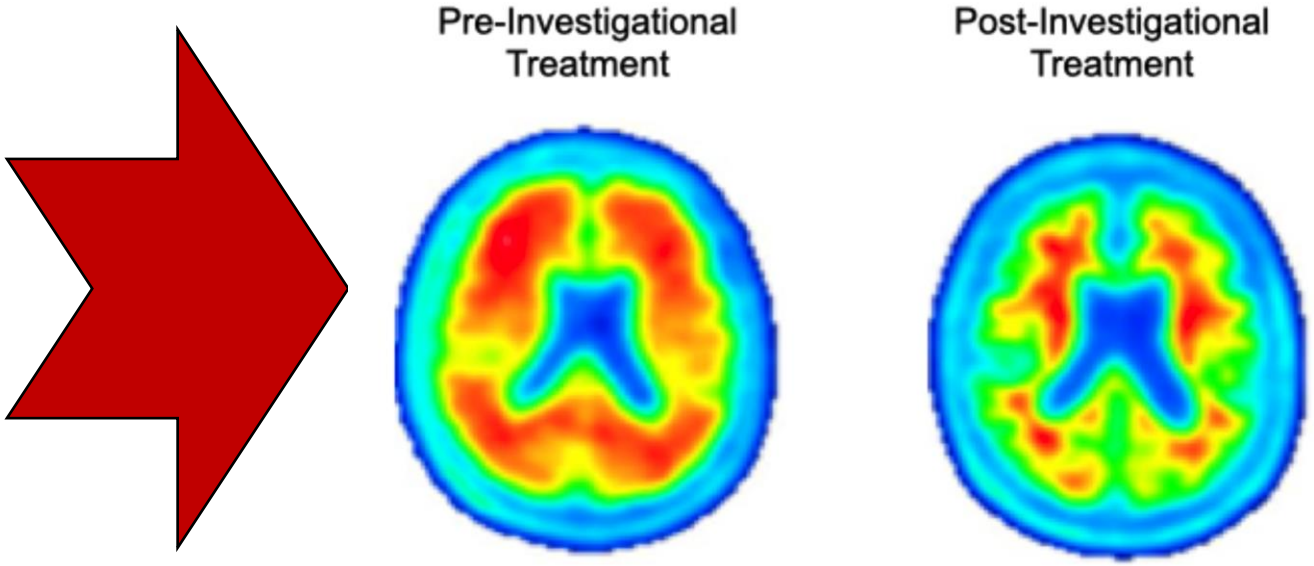
[1]Sevigny J, et al. Nature 2016; 537; 50-56; [2]Budd Haeberlein S, et al. J Prev Alzheimers Dis 2022; 9: 197-210

Consider This!









Clark C, et al. JAMA 2011; 305: 275-283; Klunk W, et al. J Neurosci 2005; 25: 10598-10606; figure courtesy of A3,45

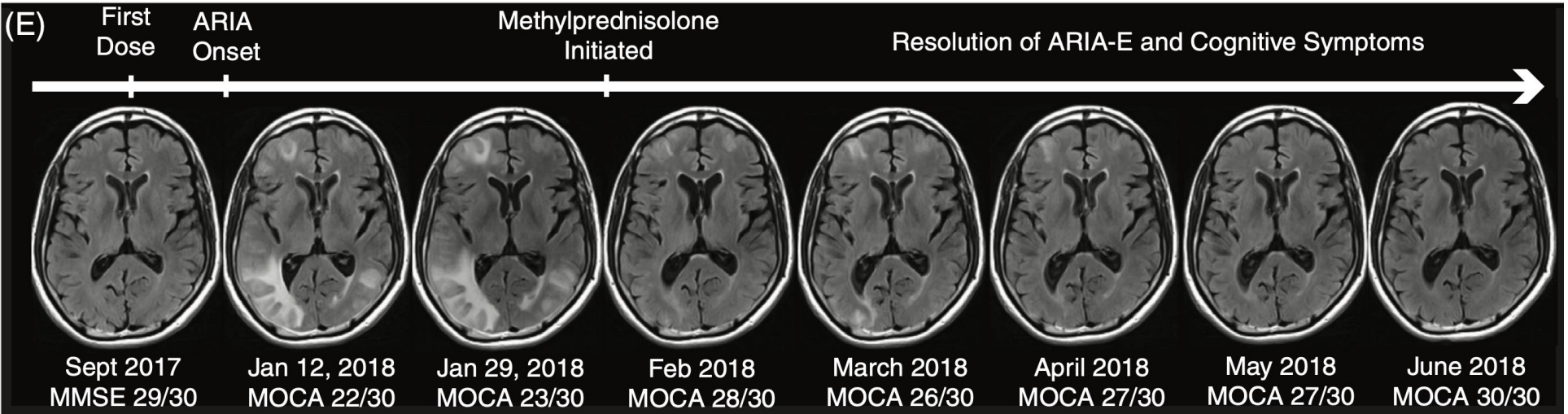
Lecanemab (Leqembi®) and Donanemab Confirm the Relationship Between Amyloid Lowering and Slowing of Clinical Decline

- Lecanemab (Phase 3)[1]
  - Marked amyloid plaque lowering
  - Positive on primary clinical trial outcome (slowing of decline as measured by Clinical Dementia Rating Scale Sum or Boxes (CDR-SB))
  - Positive on all secondary outcomes (cognition, function)
  - Accelerated approval based on Phase 2; standard approval to be considered by FDA
- Donanemab (Phase 2)[2]
  - Marked amyloid plaque lowering
  - Positive on primary clinical trial outcome (slowing of clinical decline as measured by integrated Alzheimer's Disease Rating Scale (iADRS)
  - Phase 3 positive; details on yet published

[1]van Dyck C, et al. New Engl J Med 2022; 388: 9-21; [2]Mintun M, et al. New Engl Med 2021; 384: 1691-1704

ARIA: A Challenge that Must Be Managed

ARIA: amyloid related imaging abnormalities	Thought to result from amyloid removal from the blood vessel	Leakage of fluid or blood into the brain	15-30% of patients
Symptoms in 3-5% of patients	Rarely can be serious or fatal	80-90% recover and treatment can be continued	Must be monitored with periodic MRI



VandeVrede L, et al. Alz & Dem: DADM 2020; 12: e12101

Immunotherapies are Unprecedented Therapies that Make New Demands on Health Care

Early Alzheimer's: must be recognized and diagnosed

Alzheimer's must be confirmed with lumbar puncture/spinal fluid studies or amyloid PET

Patients must have MRI prior to treatment to ensure they do not have excessive brain vascular disease

Treatments are given intravenously 1/m (donanemab) or 2/m (lecanemab)

MRI must be obtained periodically in first 6-12 months

ARIA can occur

Reimbursement by CMS is uncertain

Where are We Now?

- Anti-amyloid monoclonal antibodies slow the progression of AD!
- These agents are the first disease-modifying therapies for AD
- These drugs are approved by FDA for the treatment of early AD confirmed to have brain amyloid
- Monoclonal antibodies require infusion and MRI monitoring
- Monoclonal antibodies have rare but important side effects (ARIA)
- Reimbursement of treatment with monoclonal antibodies is uncertain

What's Coming Next?

- Monoclonal antibodies
  - Subcutaneous administration (to avoid IV requirement)
  - Diagnosis by blood test (to avoid lumbar puncture or amyloid PET)
  - Likely 2-3 year time frame
- Other types of treatment
  - Anti-tau ASO (administered through spinal tap every 3-6 months)
  - Anti-inflammatory agents
  - Synaptic agents
  - Metabolic agents

Some Larger Points

- Great demonstration of research and discovery leading to new therapies
- Illustration of the importance of breakthrough technology (amyloid PET)
- Reveals the need for health care system planning to incorporate unprecedented therapies for new (previously untreatable) patient populations
- Science forward!

Thank you

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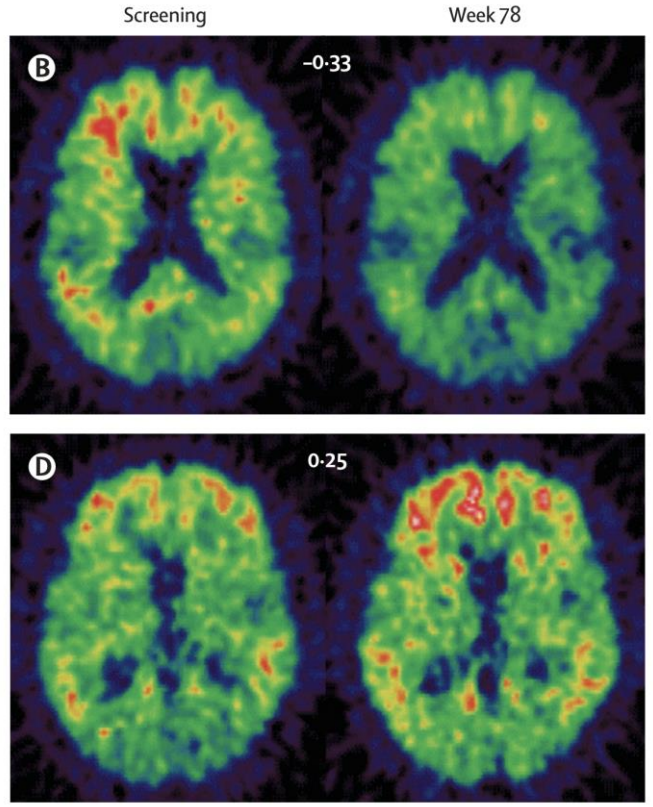

Bapineuzumab

Placebo

2 mg/kg (now use 10 mg/kg for tx)7

[1]Gilman S, et al. Neurol 2005; 64: 1553-1562; [2]Salloway S, et al. N Engl J Med 2014; 370: 322-333; [3]Honig L, et al. N Engl J Med 2018l 378: 321-330; [4]Cummings J, et al. 2018; 90: 1889-1897; [6]Ostrowitzki S, et al. Alz Res & Therapy 2107; 9: 96-110; [7]Rinne J, et al. Lancet Neurol 2010; 9: 363-372