Corruptive Templating of Aβ In Alzheimer's Disease

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Overview

1) The spectrum of proteopathies

2) Cerebral Aβ amyloidosis is inducible in APP-transgenic mice by Aβ-rich brain extracts

3) Aggregated Aβ itself is the seed

4) Aβ seeds travel within, and to, the brain

5) Aβ seeds vary in size

6) *Implications, caveats and open questions*

The spectrum of proteopathies

- Alzheimer's disease (Aβ and tau)
- Prion diseases (PrP)
- Tauopathies (tau)
- Huntington's disease/triplet repeat disorders (polyQ)
- Parkinson's disease/Lewy body disease (α-synuclein)
- Cerebral amyloid angiopathies (Aβ, cystatin, etc.)
- Amyotrophic lateral sclerosis (SOD, TDP43, FUS)
- FTLD ubi+, tau- (TDP43, FUS)
- Familial British Dementia (ABri)
- Familial Danish Dementia (ADan)
- Familial Encephalopathy w/ Neuroserpin Inclusion Bodies (neuroserpin)

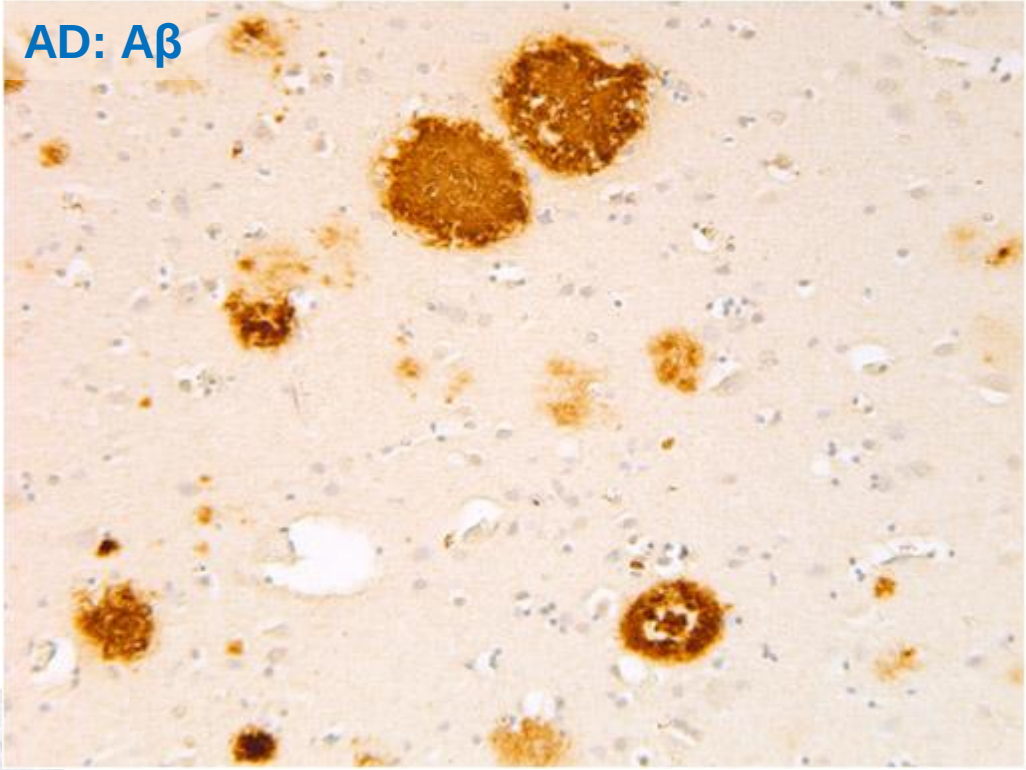
- Systemic amyloidoses (AA, AL, Transthyretin, etc)
- Type II diabetes (amylin)
- Cirrhosis with hepatocytic inclusions (α1-antitrypsin)
- …

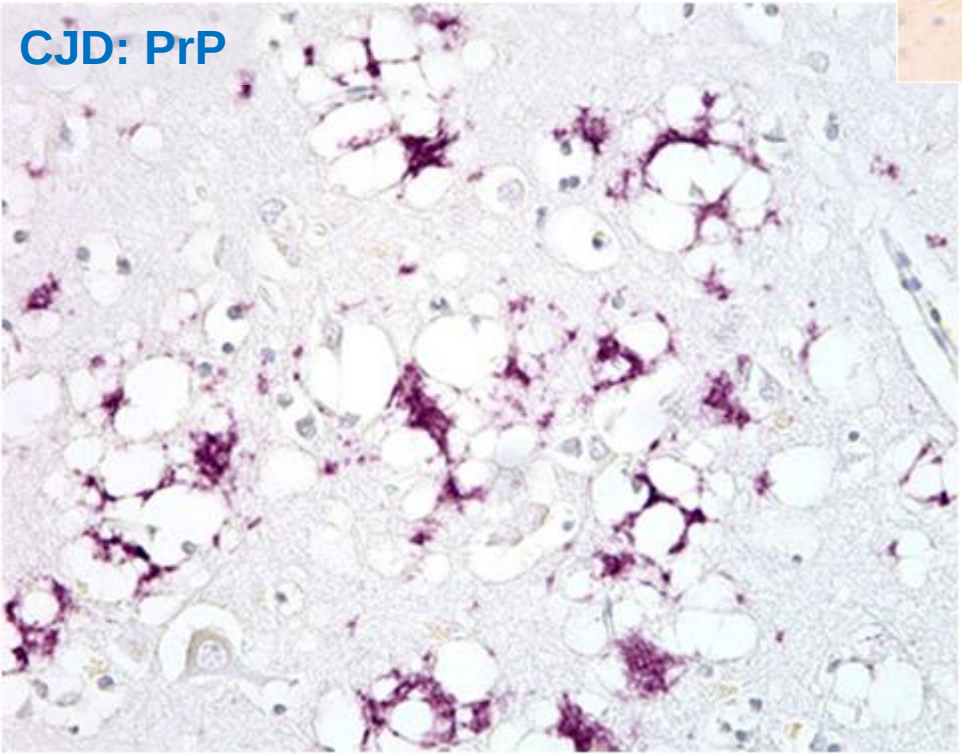
Disease or disease class	Aggregating protein(s)
Alzheimer's disease	Amyloid β peptide (Aβ); Tau protein (see tauopathies)
Cerebral β-amyloid angiopathy	Amyloid β peptide (Aβ)
Retinal ganglion cell degeneration in glaucoma	Amyloid β peptide (Aβ)
Prion diseases (multiple)	Prion protein
Parkinson's disease and other synucleinopathies (multiple)	α-Synuclein
Tauopathies (multiple)	Microtubule-associated protein tau (Tau protein)
Frontotemporal lobar degeneration (FTLD) (Ubi+, Tau-)	TDP-43, FUS
Amyotrophic lateral sclerosis (ALS)	Superoxide dismutase, TDP-43, FUS
Huntington's disease and other triplet repeat disorders (multiple)	Proteins with tandem glutamine expansions
Familial British dementia	ABri
Familial Danish dementia	ADan
Hereditary cerebral hemorrhage with amyloidosis (Icelandic) (HCHWA-I)	Cystatin C
CADASIL	Notch3
Alexander disease	Glial fibrillary acidic protein (GFAP)
Seipinopathies	Seipin
Familial amyloidotic neuropathy, Senile systemic amyloidosis	Transthyretin
Serpinopathies (multiple)	Serpins
AL (light chain) amyloidosis (primary systemic amyloidosis)	Monoclonal immunoglobulin light chains
AH (heavy chain) amyloidosis	Immunoglobulin heavy chains
AA (secondary) amyloidosis	Amyloid A protein
Type II diabetes	Islet amyloid polypeptide (IAPP; amylin)
Aortic medial amyloidosis	Medin (lactadherin)
ApoAI amyloidosis	Apolipoprotein AI
ApoAII amyloidosis	Apolipoprotein AII
ApoAIV amyloidosis	Apolipoprotein AIV
Familial amyloidosis of the Finnish type (FAF)	Gelsolin
Lysozyme amyloidosis	Lysozyme
Fibrinogen amyloidosis	Fibrinogen
Dialysis amyloidosis	Beta-2 microglobulin
Inclusion body myositis/myopathy	Amyloid β peptide (Aβ)
Cataracts	Crystallins
Medullary thyroid carcinoma	Calcitonin
Cardiac atrial amyloidosis	Atrial natriuretic factor
Pituitary prolactinoma	Prolactin
Hereditary lattice corneal dystrophy	Keratoepithelin
Cutaneous lichen amyloidosis	Keratins
Mallory bodies	Keratin intermediate filament proteins
Corneal lactoferrin amyloidosis	Lactoferrin
Pulmonary alveolar proteinosis	Surfactant protein C (SP-C)
Odontogenic (Pindborg) tumor amyloid	Odontogenic ameloblast-associated protein
Seminal vesical amyloid	Semenogelin I
Cystic Fibrosis	cystic fibrosis transmembrane conductance regulator (CFTR) protein
Sickle cell disease	Hemoglobin
Critical illness myopathy (CIM)	Hyperproteolytic state of myosin ubiquitination

The prion paradigm and Alzheimer pathogenesis

Alzheimer's disease and transmissible virus dementia (Creutzfeldt-Jakob disease). Brown P, Salazar AM, Gibbs CJ Jr, Gajdusek DC. *Ann N Y Acad Sci*. 1982; **396**:131-43

Some speculations about prions, amyloid, and Alzheimer's disease.
Prusiner SB. *N Engl J Med*. 1984; **310**:661-3



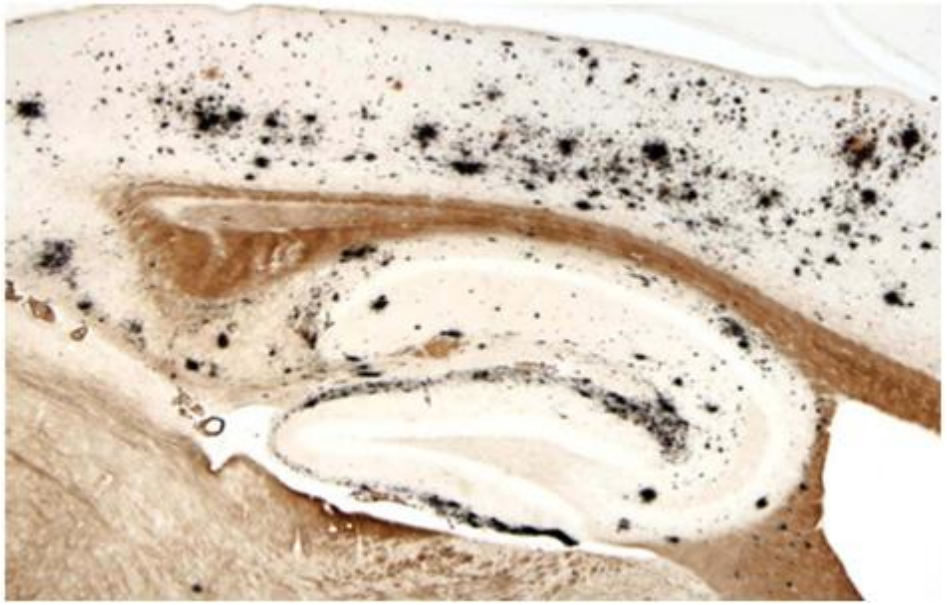


NO:
Evidence for and against the transmissibility of Alzheimer disease
Goudsmit J, Morrow CH, Asher DM, Yanagihara RT, Masters CL, Gibbs CJ Jr, Gajdusek DC. *Neurology* 1980; **30:**945-50

YES:
Induction of beta (A4)-amyloid in primates by injection of Alzheimer's disease brain homogenate. Comparison with transmission of spongiform encephalopathy.
Baker HF, Ridley RM, Duchen LW, Crow TJ, Bruton CJ; *Mol Neurobiol*. 1994; **8**:25-39

APP-transgenic mouse models of Aβ-seeding

Tg2576 mice (Hsiao et al., *Science*, 1996)
[APP23 mice (Sturchler-Pierrat et al., *PNAS* 1997)
APP/PS1 mice (Jankowsky et al., *Biomol. Eng.* 2001)]



21 month old Tg2576 mouse

→ **Aβ plaques usually appear ~between 3 and 9 months of age, depending on the model**

Preparation of the Aβ-seeding extract

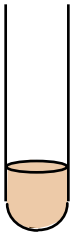
Frozen Aβ-rich brain sample (DONOR)

Homogenize 10% (w/v) in PBS

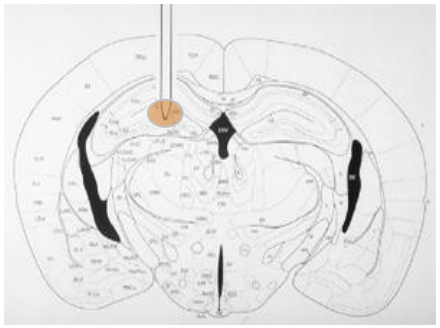
Vortex, Sonicate

Centrifuge 3000 x g 5 minutes

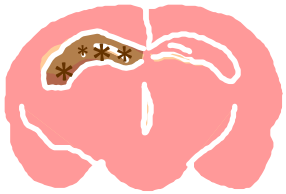
Dilute Supernatant 1:10 in PBS



Brain extract (1:100: ~0.5-10ng Aβ/µl)



Inject brain extract into hippocampus of young APP-transgenic mouse (HOST)

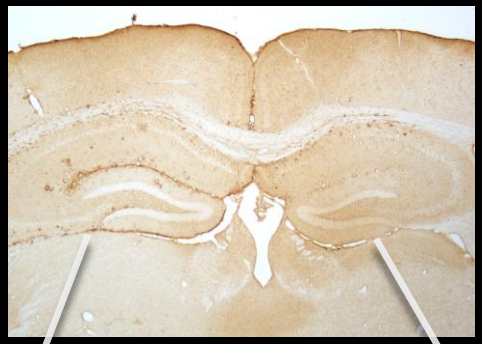


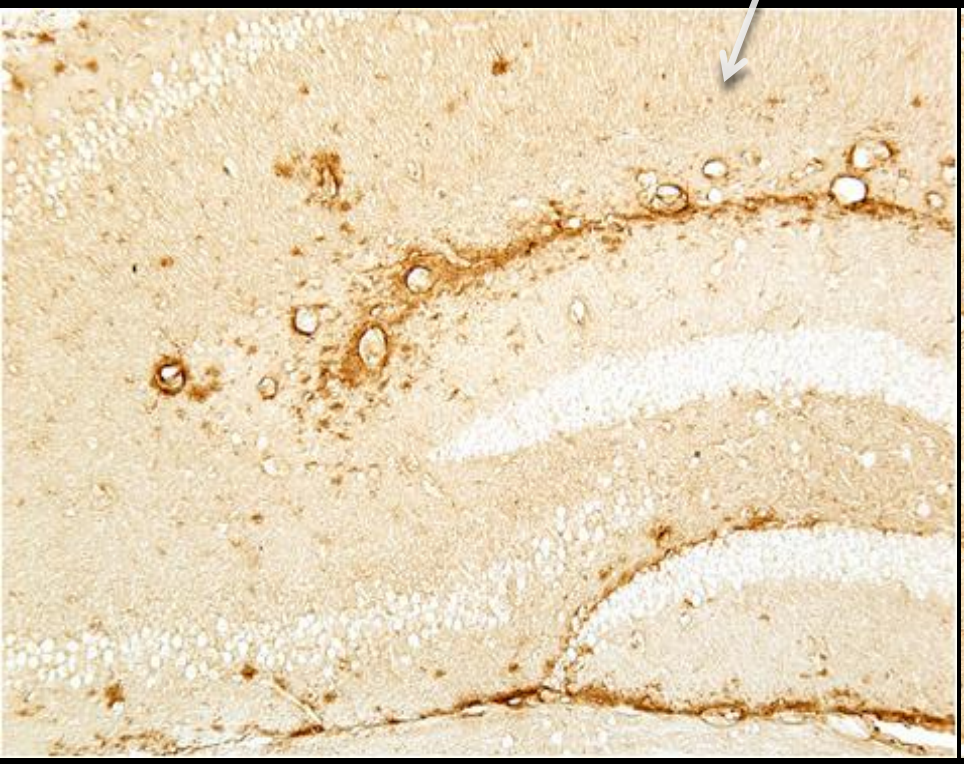
Analyze after incubation

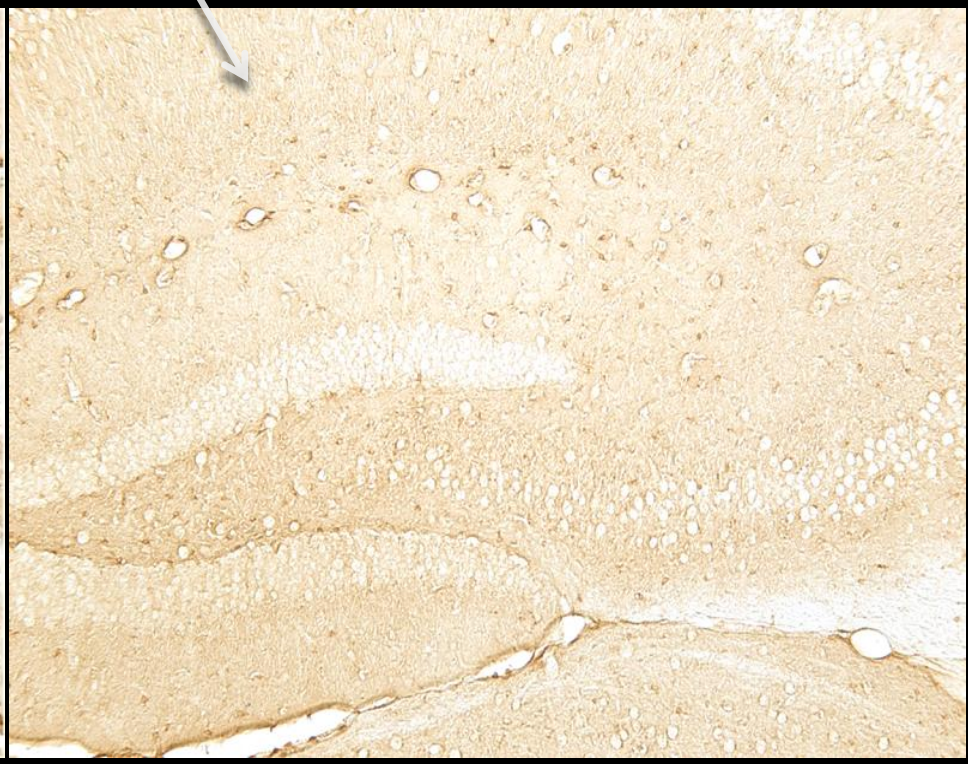
Kane et al., *J Neurosci* 2000

Five month incubation (3-8 months)

Tg2576 mouse



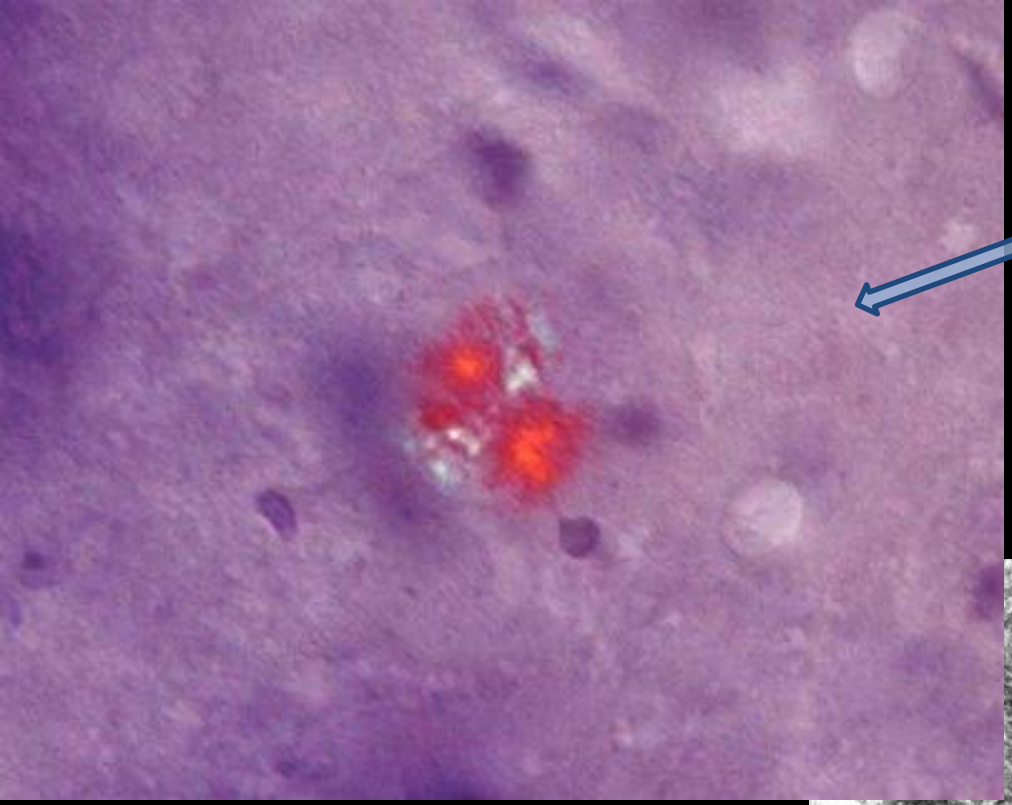




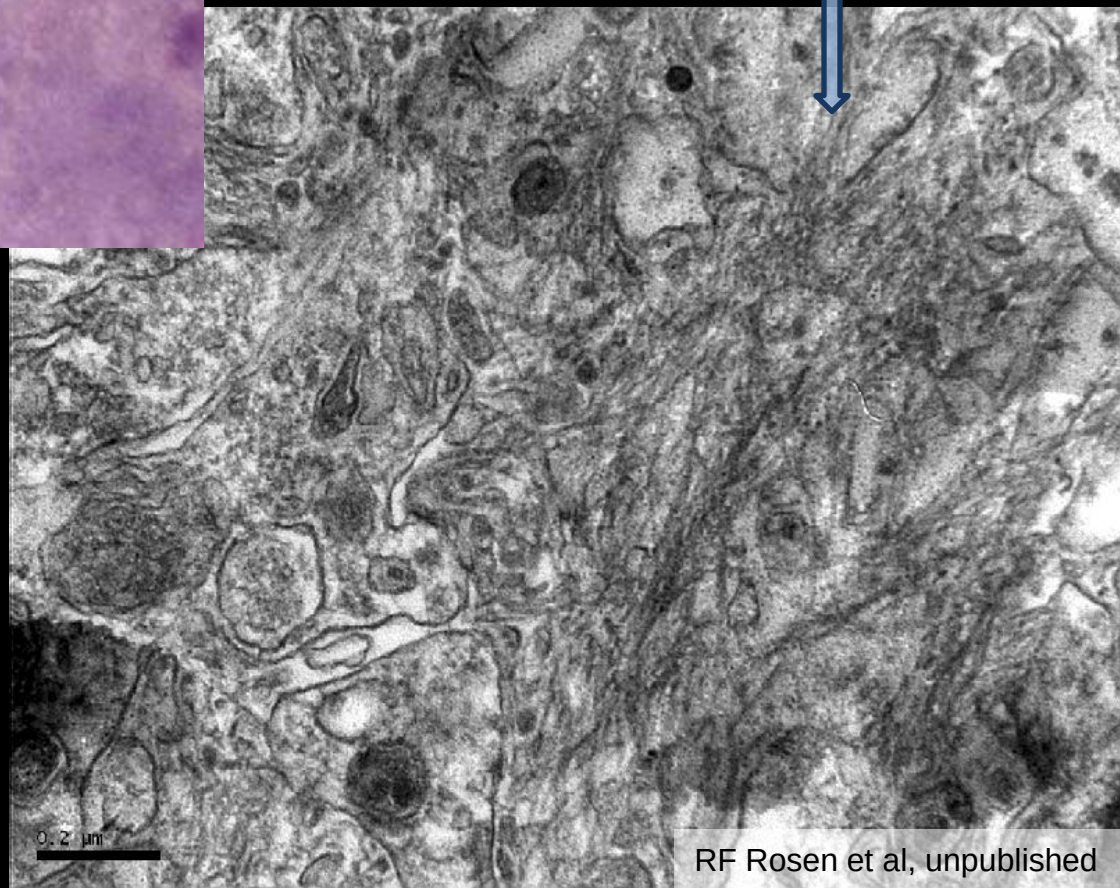
Ipsilateral: AD brain extract

Contralateral: Control extract

Kane et al., *J Neurosci* 2000

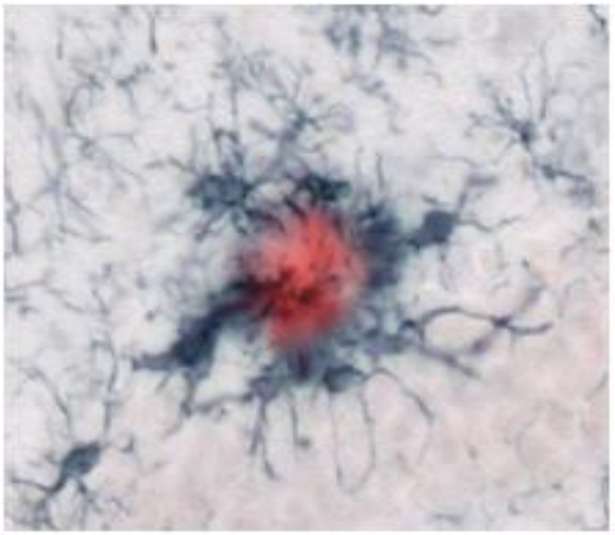


Seeding yields congophilic and fibrillar deposits

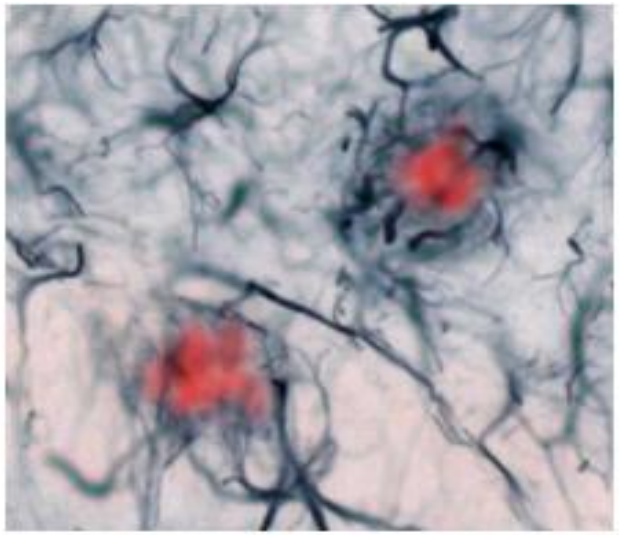


RF Rosen et al, unpublished

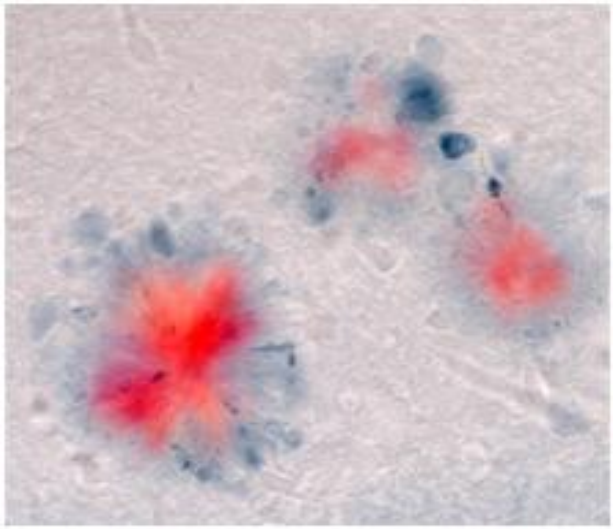
Seeded Aβ lesions evoke glial and neuritic reactivity



Activated microglia
(Iba1)



Reactive Astrocytes
(GFAP)

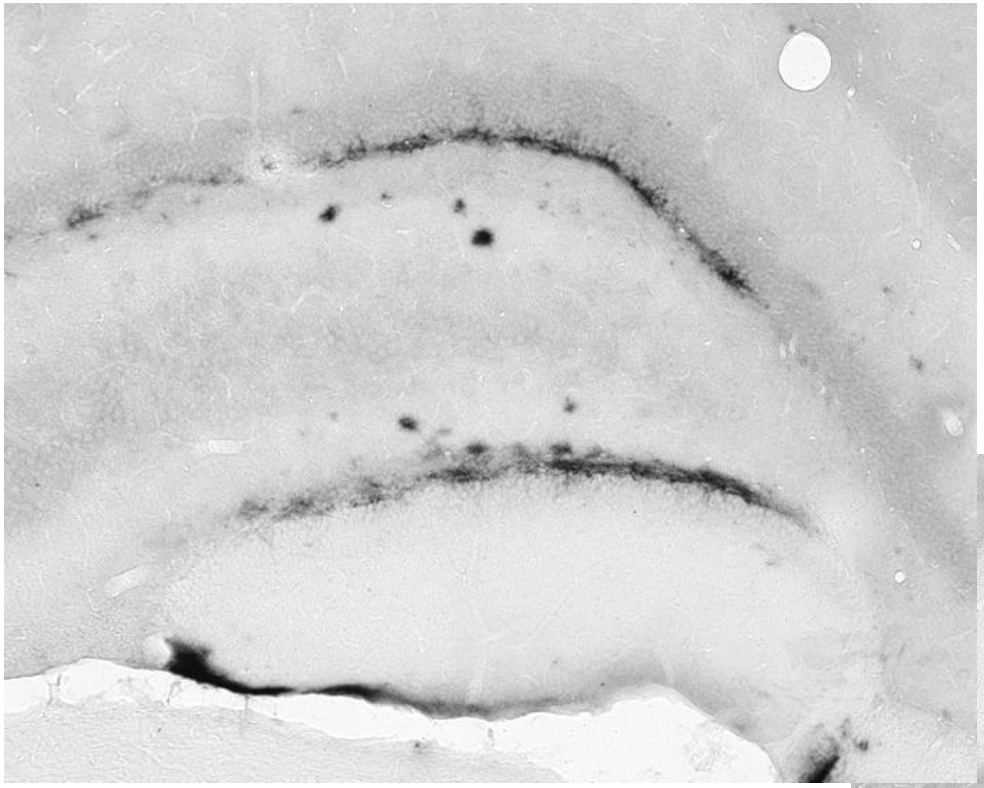


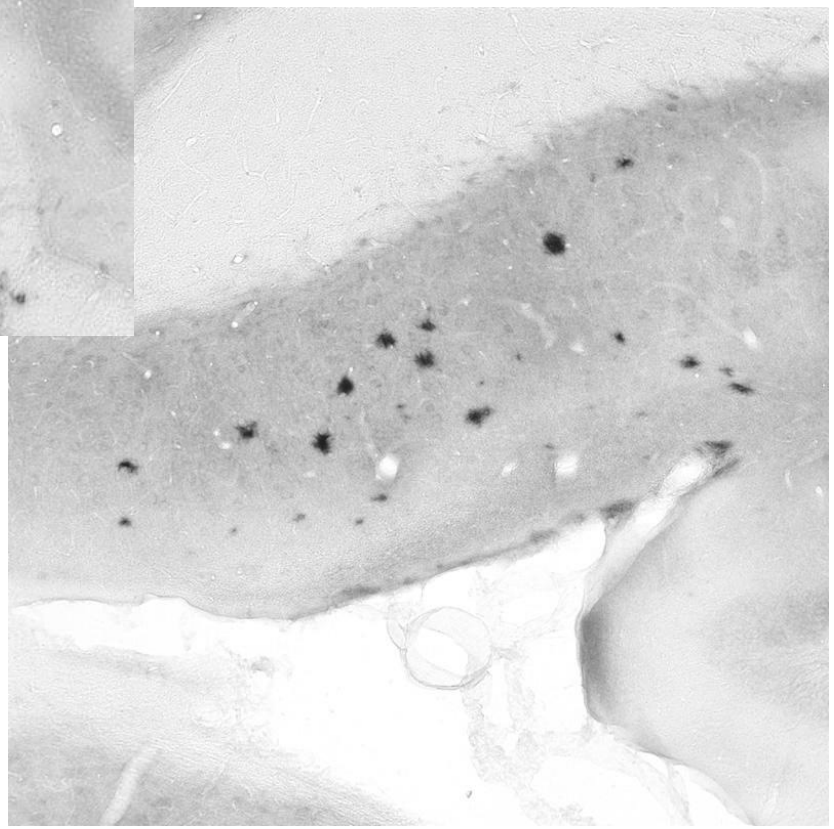
Dystrophic boutons
(APP)

Langer et al *J Neurosci* 2011

Seeded Aβ in a refractory host: APP21 rat

9 month incubation (12 months of age)

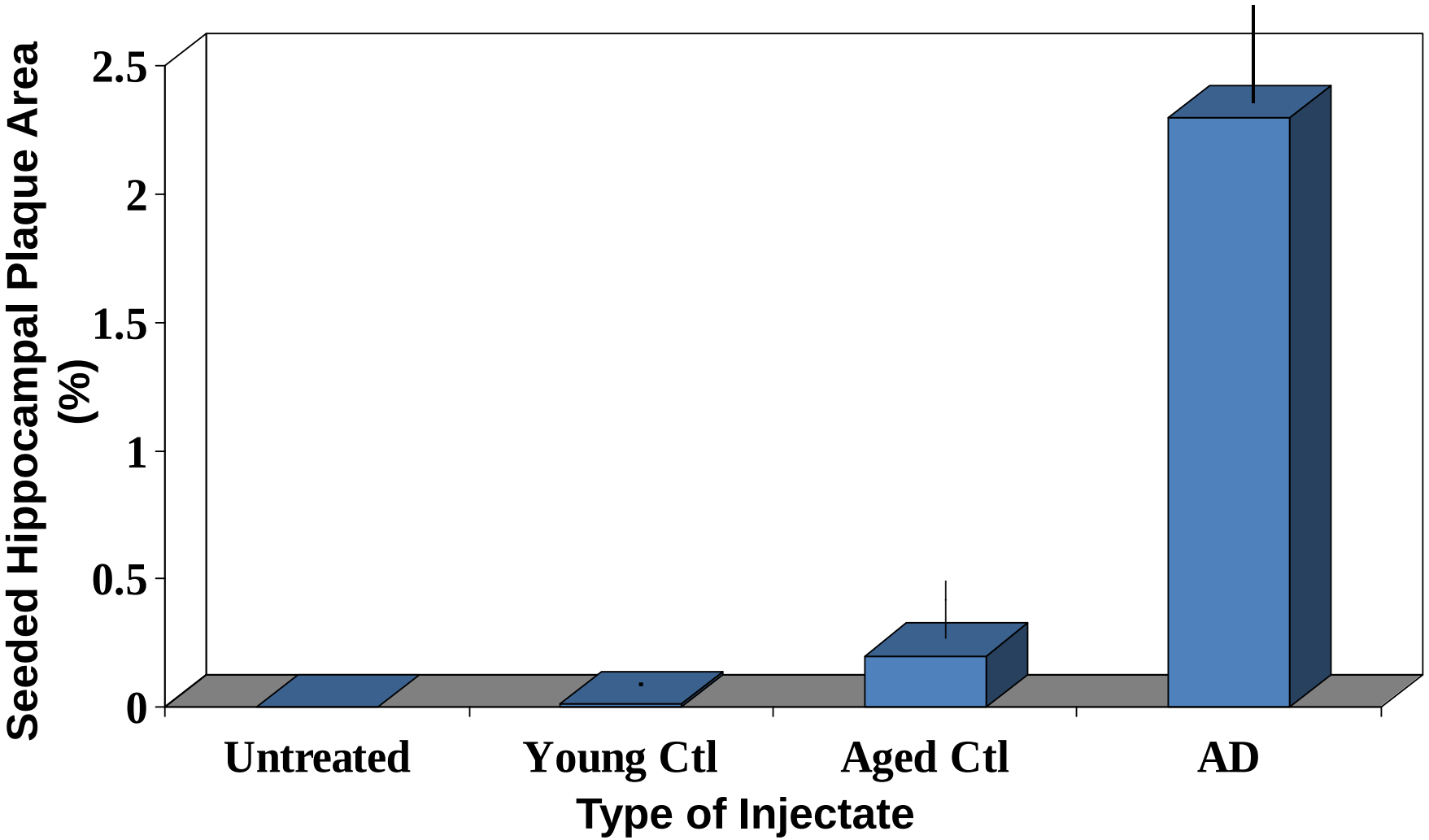




Rosen, Fritz et al., *J Neurochem* 2012

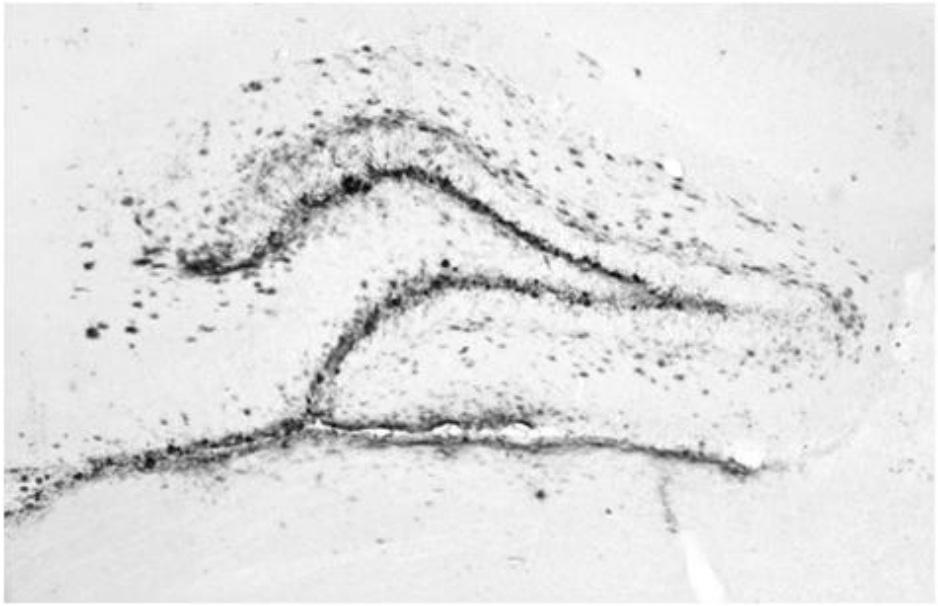
Evidence that aggregated Aβ itself is the seed

1. Donor brain extract must contain aggregated Aβ

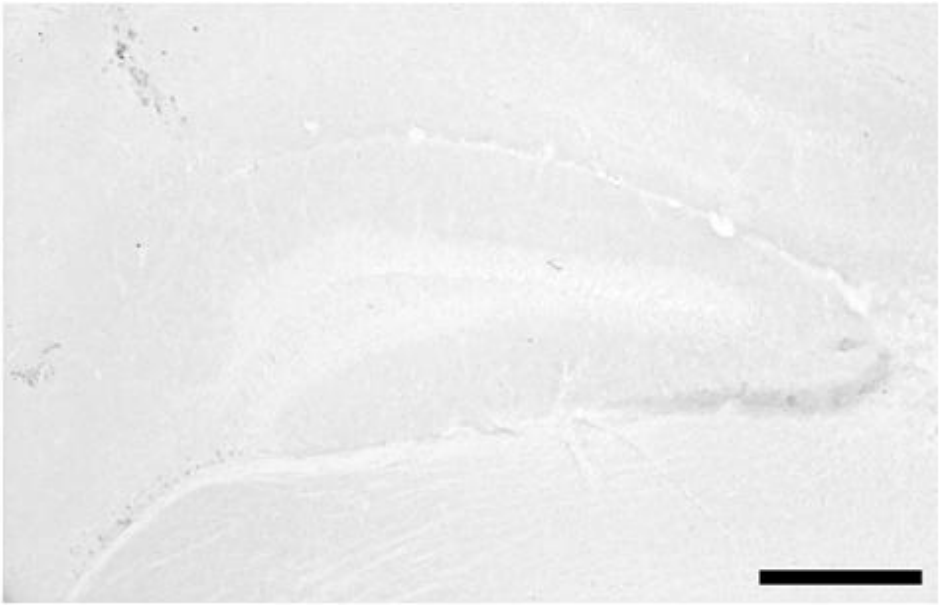


Kane et al., *J Neurosci* 2000

2. The seeded host must generate human-type Aβ



APP23 Host

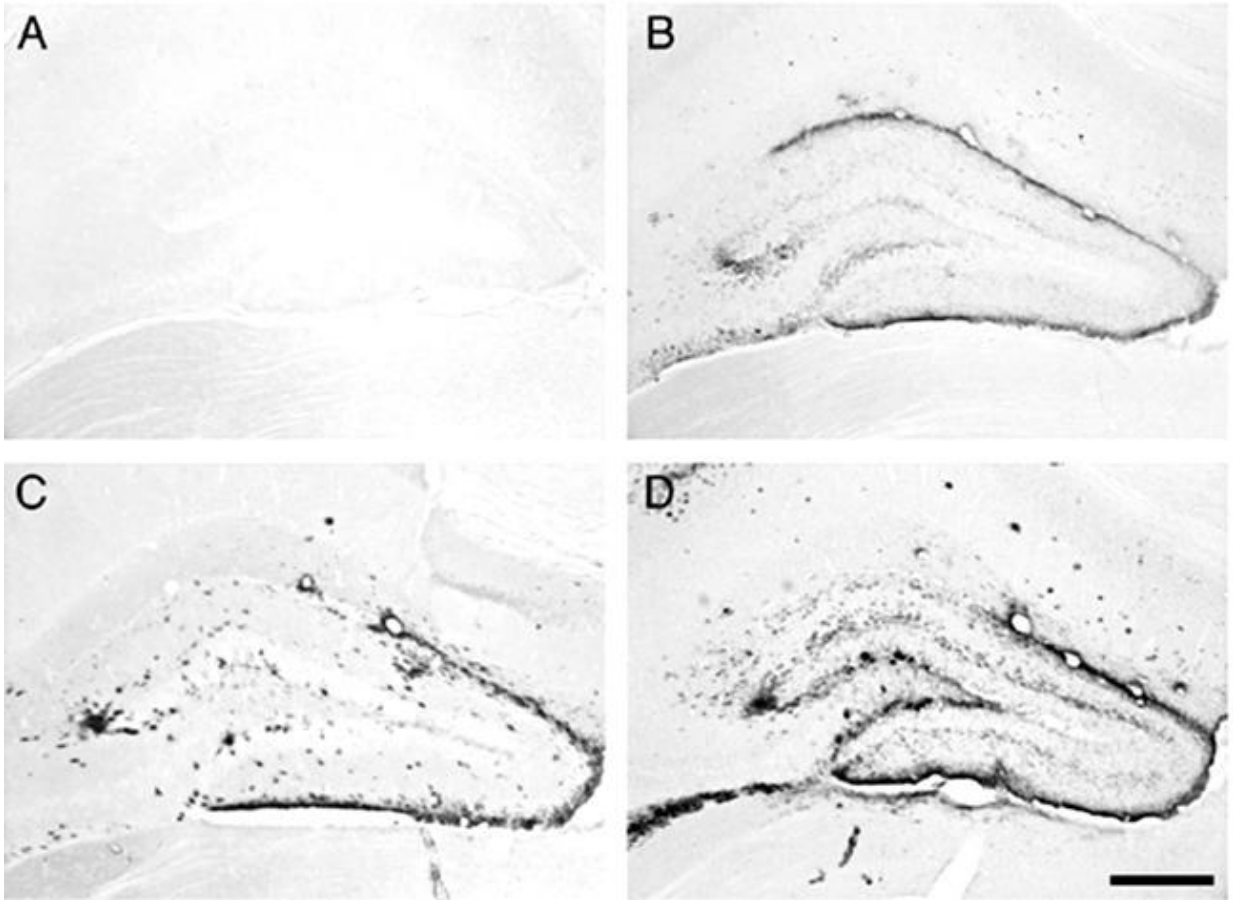


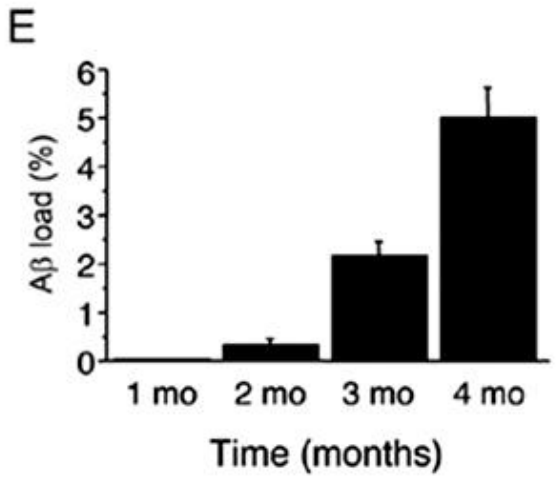
Non-Tg Host

Meyer-Luehmann et al., *Science* 2006

3. The immunoreactive material is not the injectate

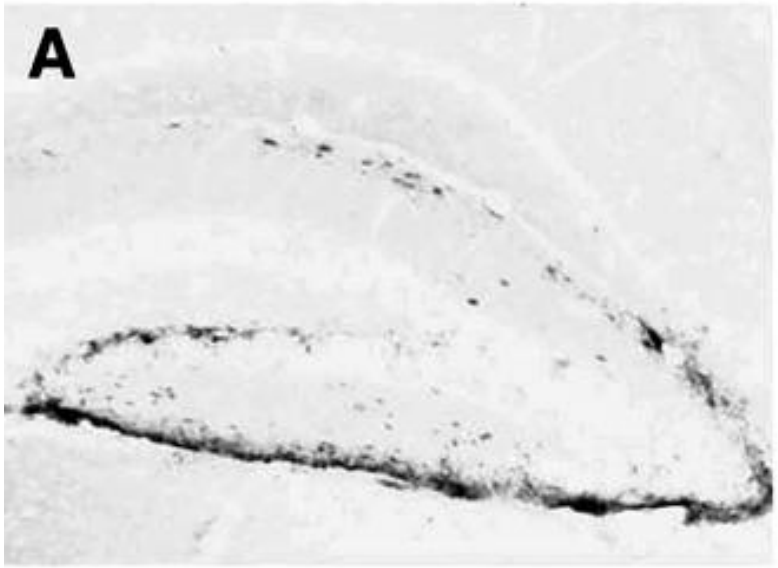
(Aβ deposition follows a lag period)





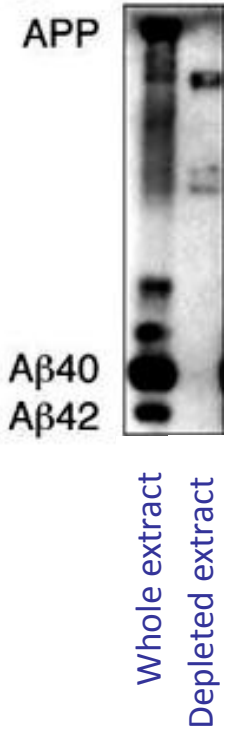
Meyer-Luehmann et al., 2006

4. Seeding is reduced by immunodepletion of Aβ



Whole extract

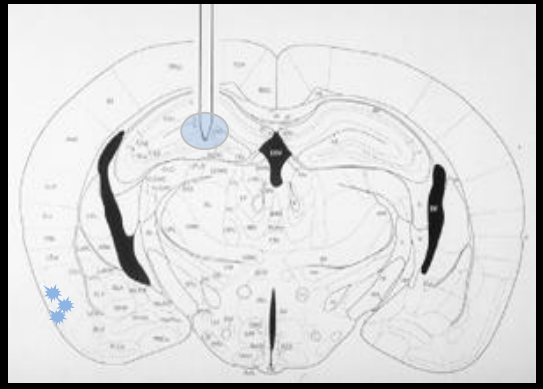
Immunodepleted extract

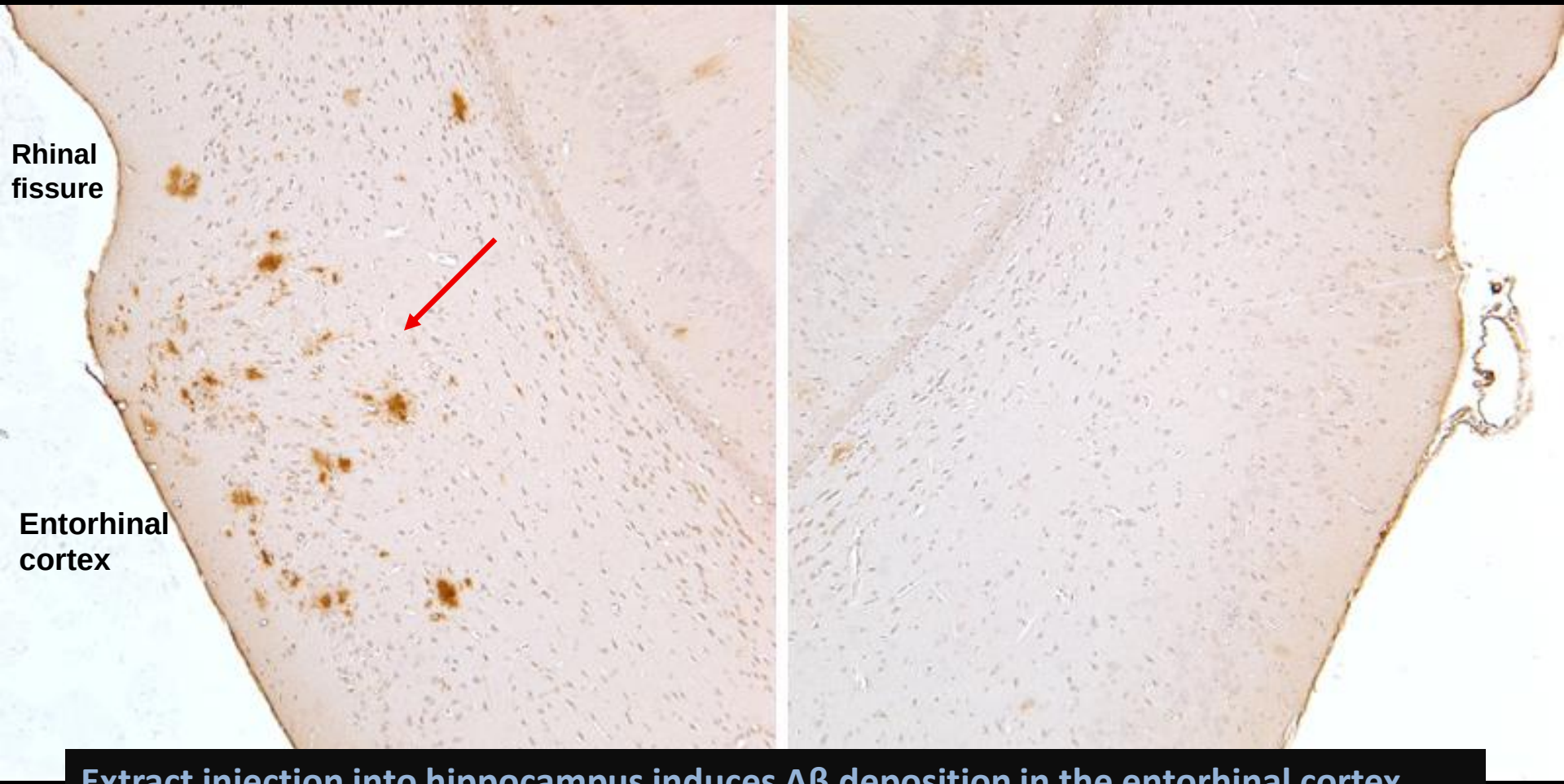


Meyer-Luehmann et al., 2006

Aβ seeds travel within, and to, the brain

Spread of seeded pathology within the brain: Neuronal transport?

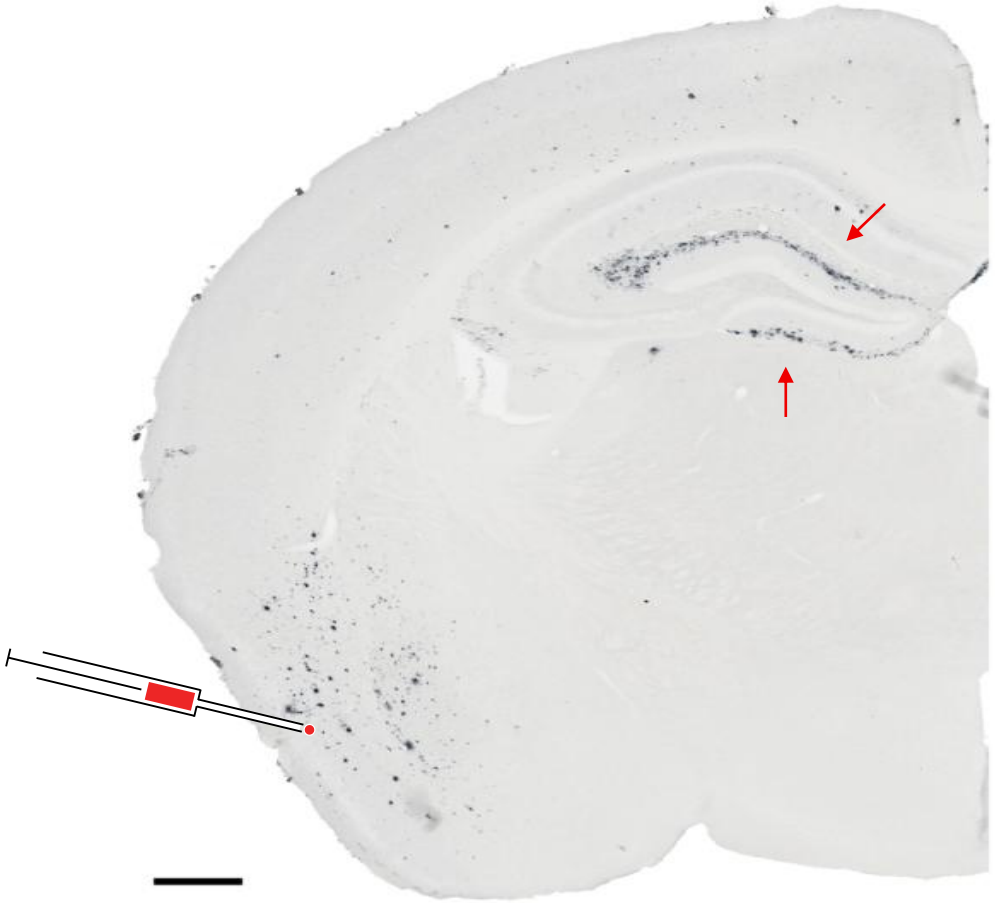




Extract injection into hippocampus induces Aβ deposition in the entorhinal cortex…

Walker et al., *Peptides* 2002

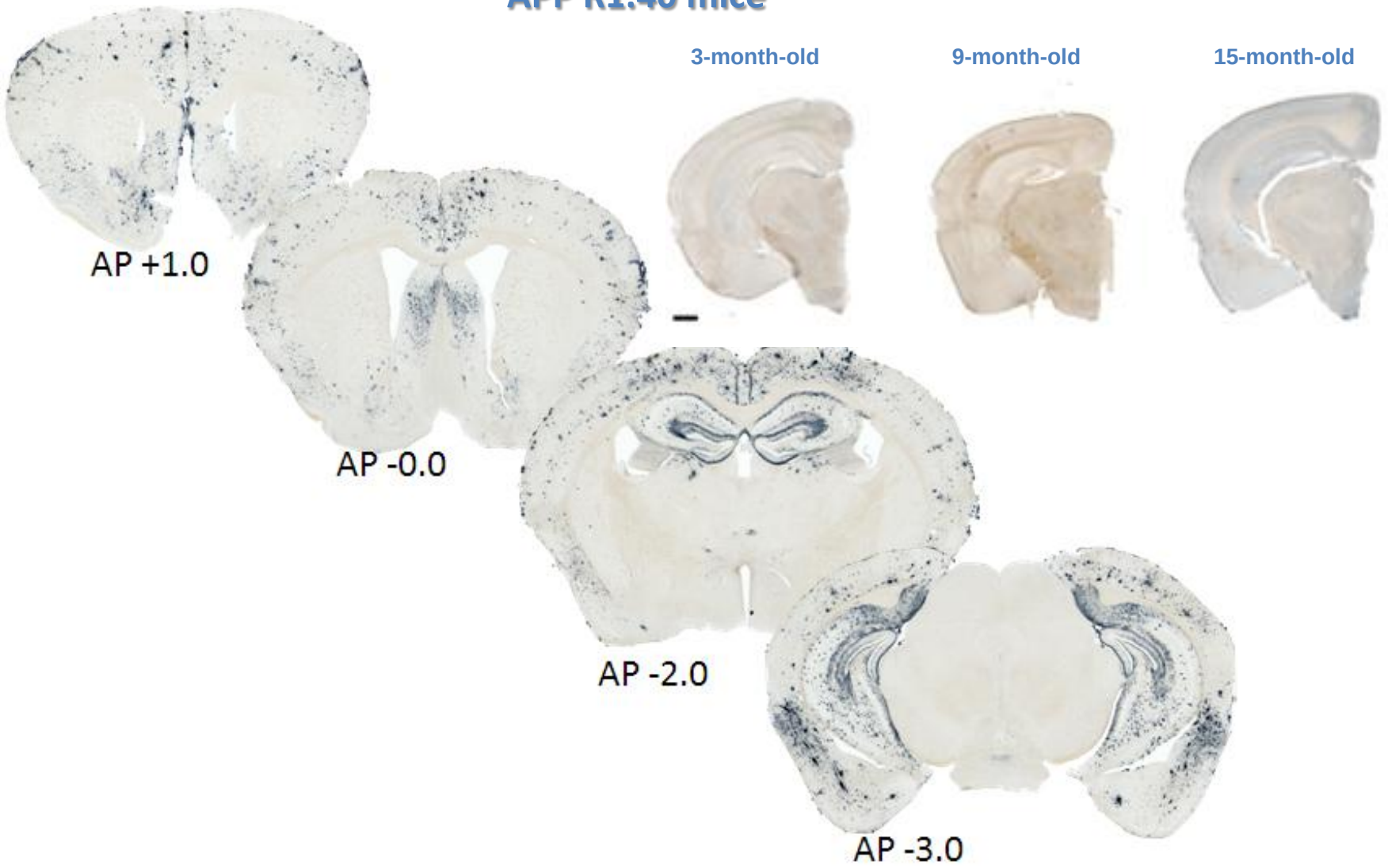
…injection into entorhinal cortex induces Aβ deposition in the hippocampus



Eisele, Jucker et al unpublished

Long-term incubation (3-15 months of age) leads to widespread Aβ deposition in brain

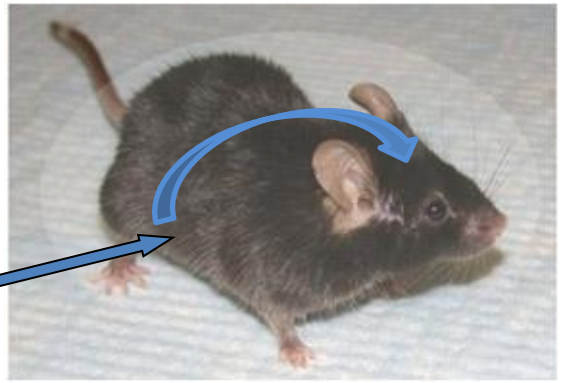
APP R1.40 mice



Hamaguchi et al., *Acta Neuropath* 2012

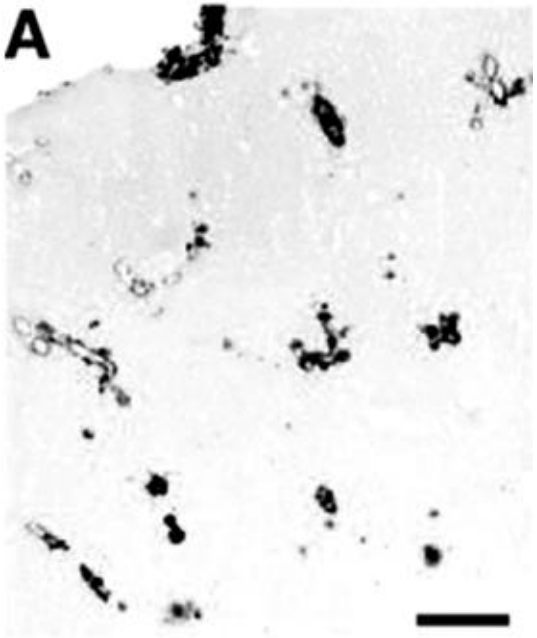
Aβ seeds can travel from periphery to brain

Dilute Tg Mouse Brain extract



Inject brain extract i.p. into 2 month-old βAPP-transgenic mice (2 injections, 100ul each)

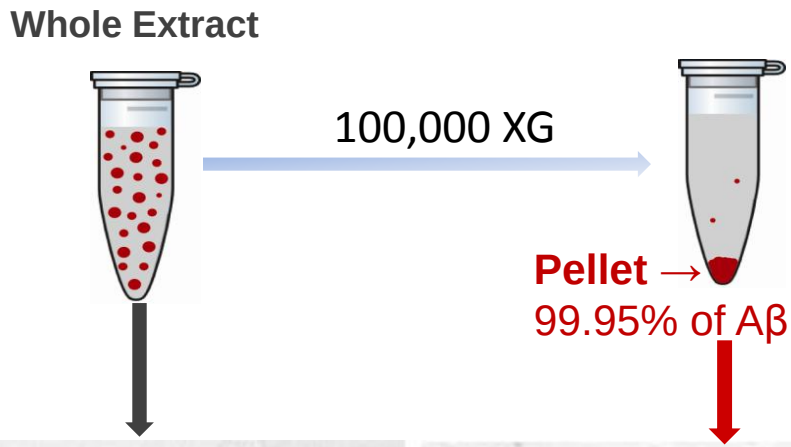
6-8 month incubation

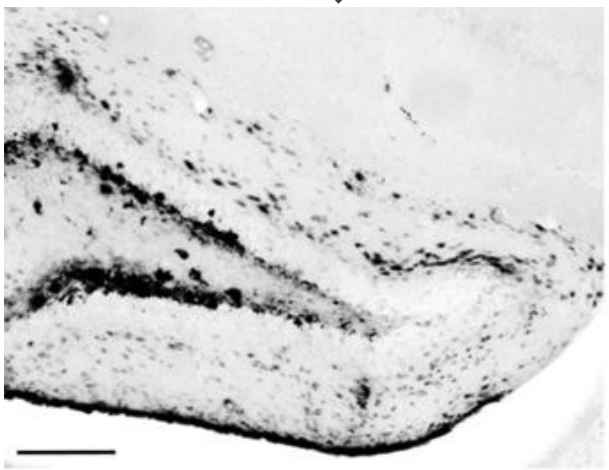


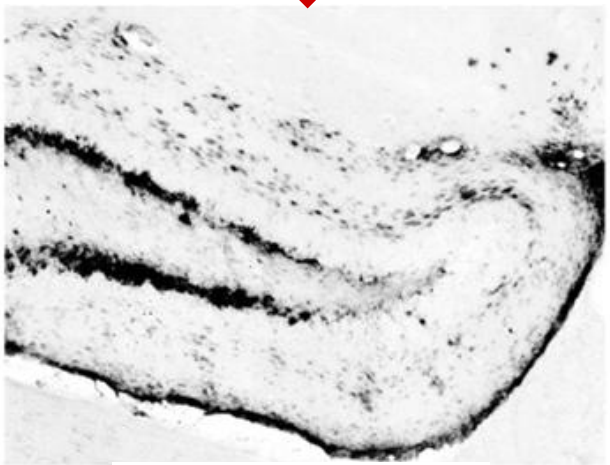
Eisele et al., *Science* 2010

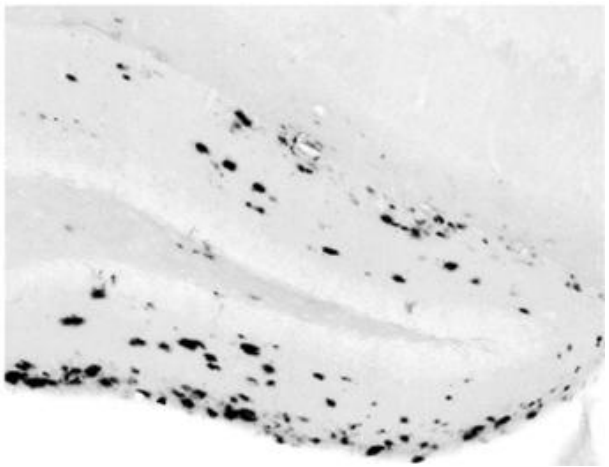
Aβ seeds vary in size

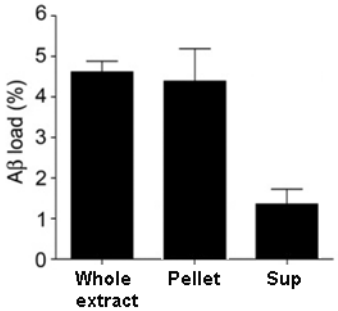
Seeding by TBS-soluble and insoluble fractions:
Soluble Aβ seeds are superproportionally active











Protease K-sensitive soluble seeds!

Langer, et al., *J Neurosci* 2011

Implications, caveats and open questions

1. Aβ-amyloidosis, *not* AD
2. How do seeds form *in vivo*?
3. Why are they not cleared?
4. How do they transfer from cell to cell?
5. Are all seeds the same? (the strain problem)
6. Can we seed toxic oligomers?
7. Are some seeded aggregates *protective*, e.g. by binding oligomers?
8. Is there cross-seeding between proteins, or between non-protein seeds and proteins *in vivo*?
9. Can seeds be targeted therapeutically?

Jucker and Walker *Ann Neurol* 2011