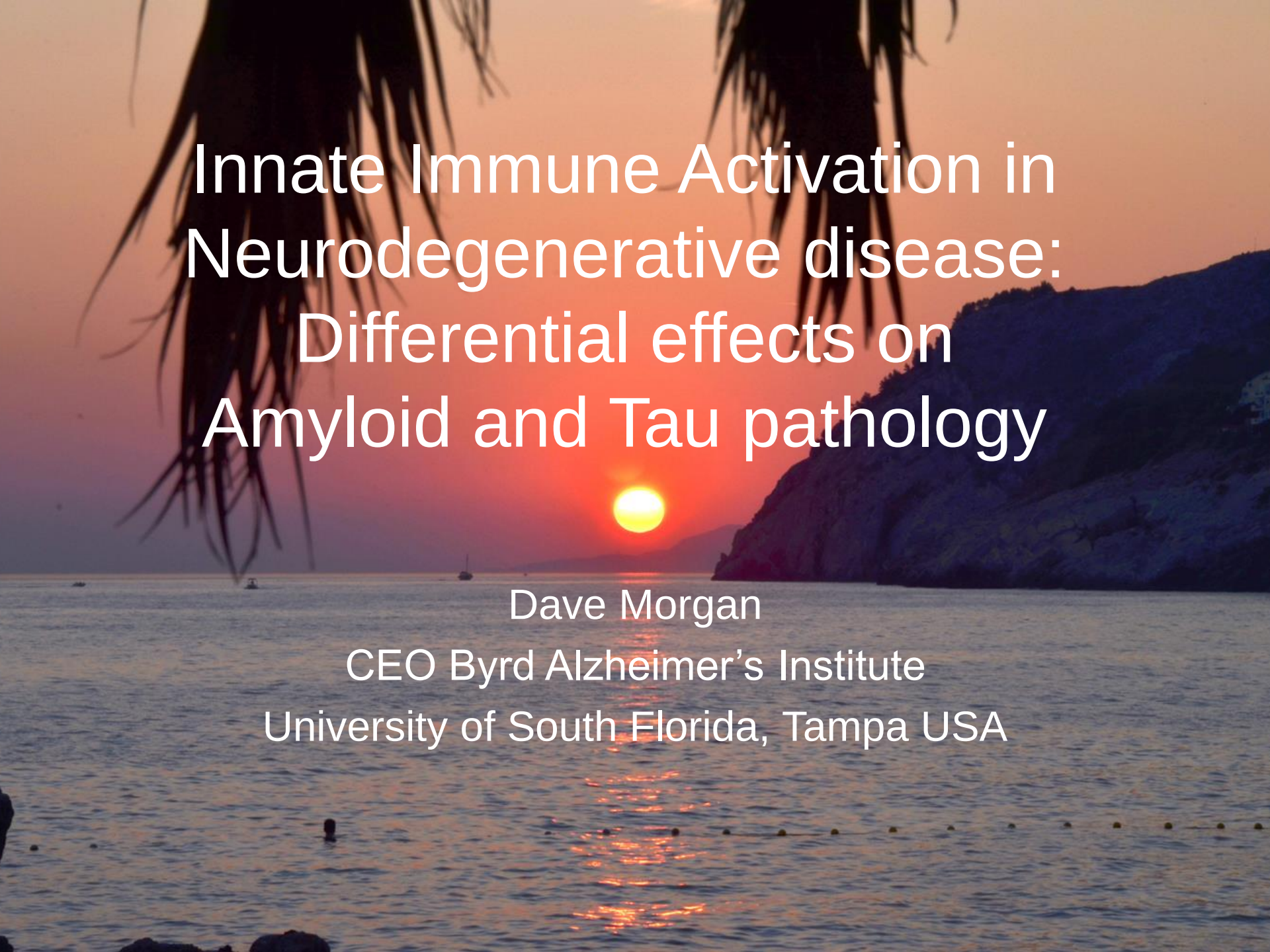
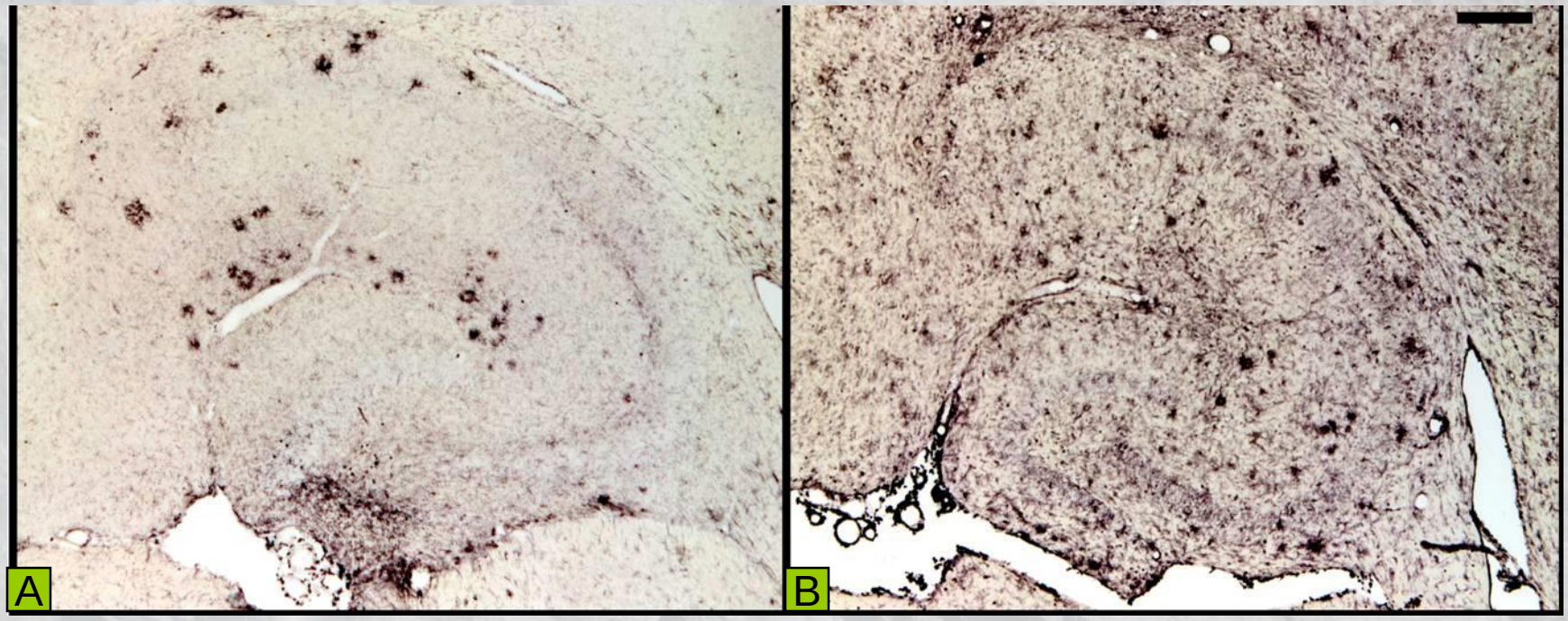


Innate Immune Activation in Neurodegenerative disease: Differential effects on Amyloid and Tau pathology

Dave Morgan
CEO Byrd Alzheimer's Institute
University of South Florida, Tampa USA

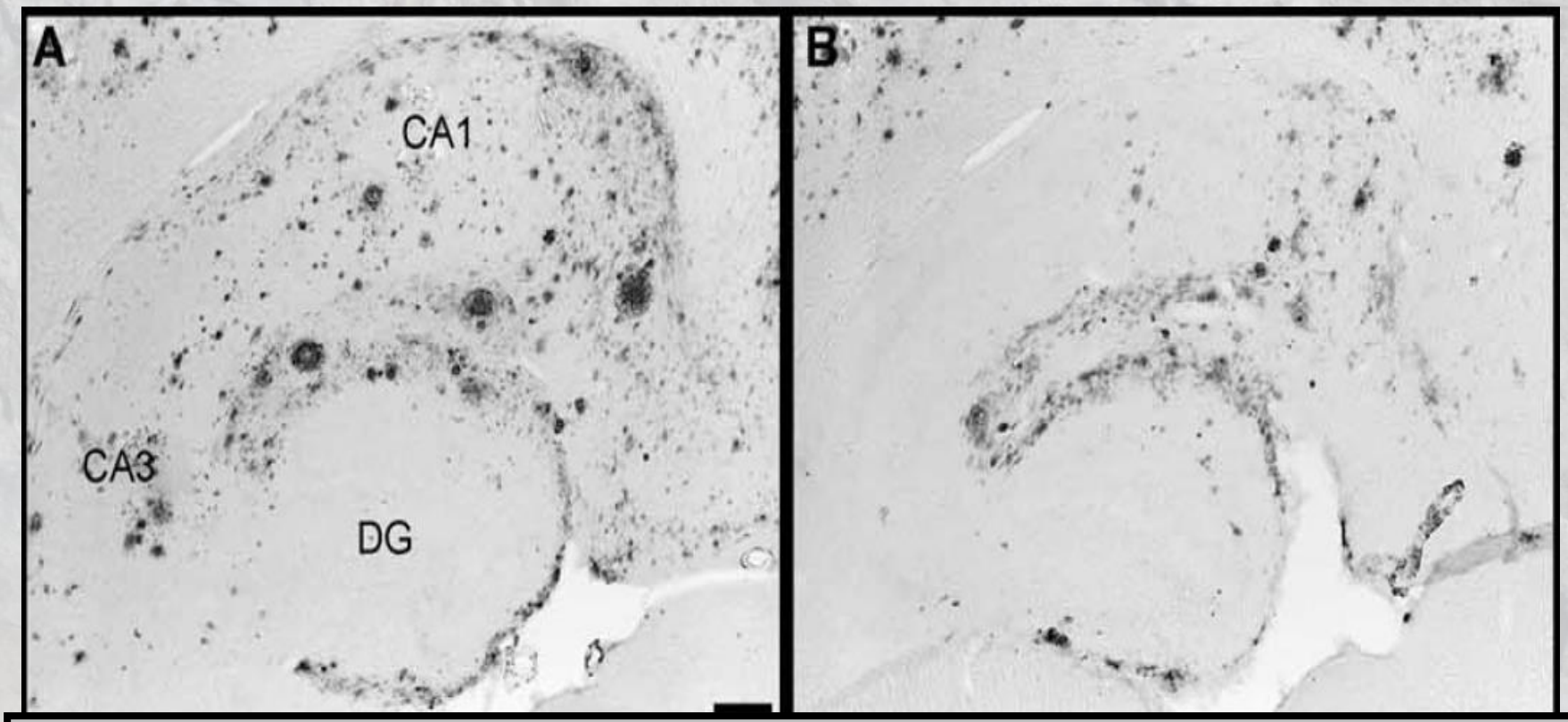
1998: The APP mouse problem; not enough inflammation?

LPS injection into APP mice increases microglial activation



Control, saline injected hippocampus LPS injected hippocampus

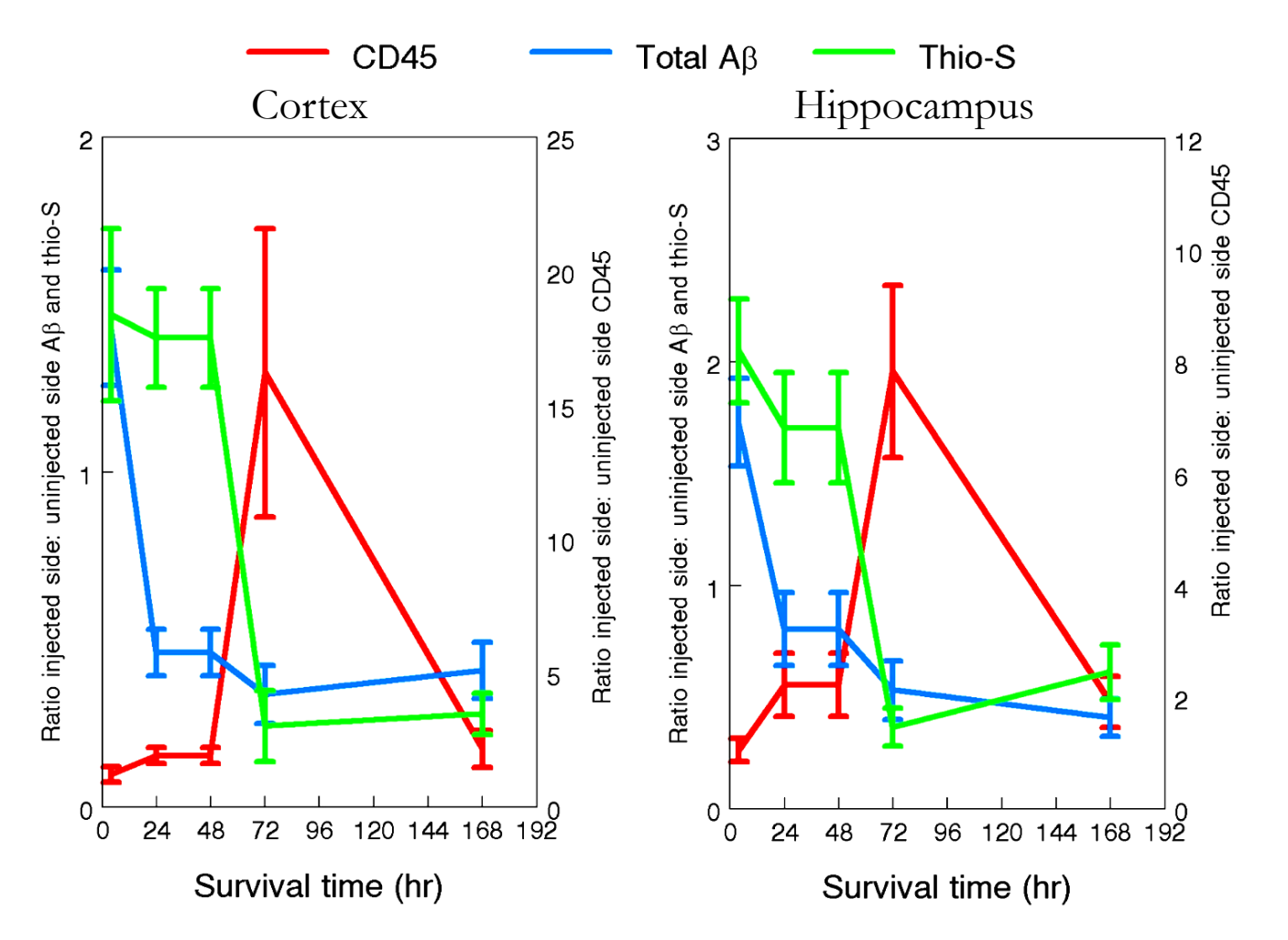
Surprise!
No neurons died and
LPS reduced amyloid.



Control, saline injected hippocampus LPS injected hippocampus

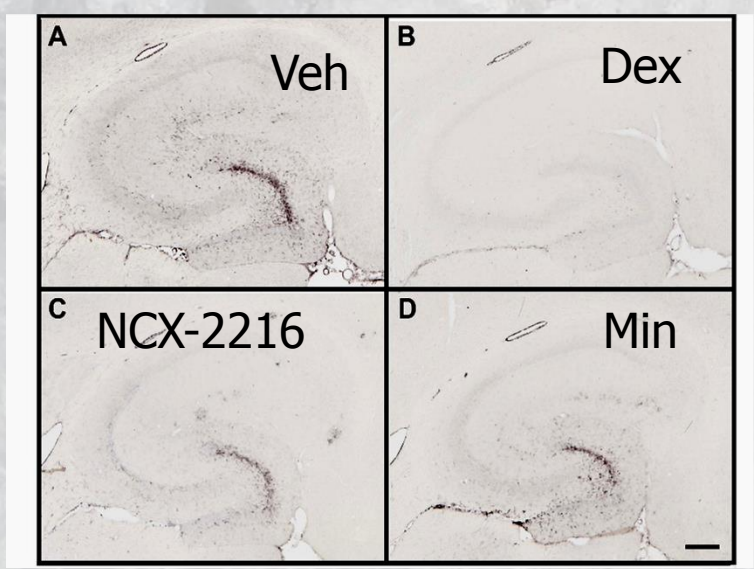
Aβ Immunohistochemistry. 3d post LPS injection

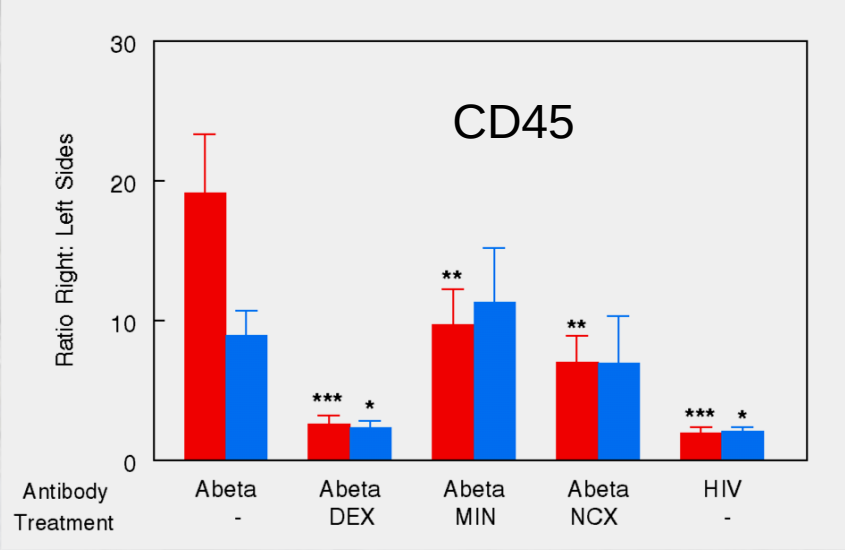
Intracranial Anti-Aβ Antibody Injections Decrease Amyloid and Activate Microglia

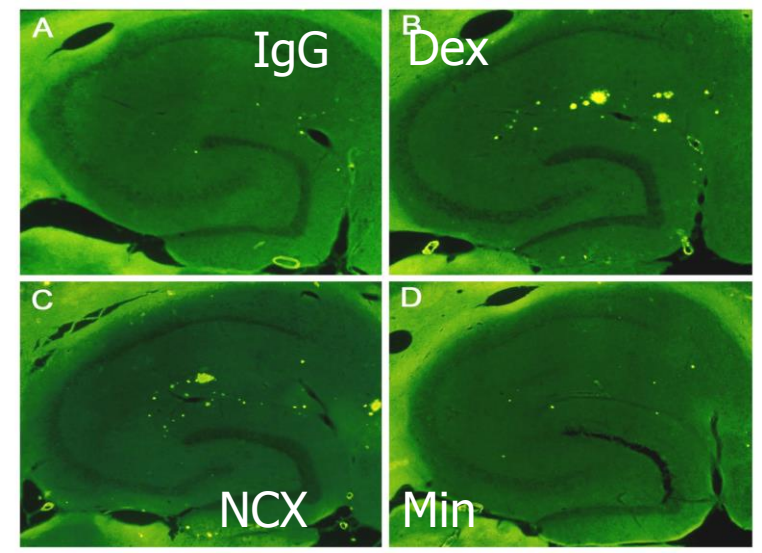


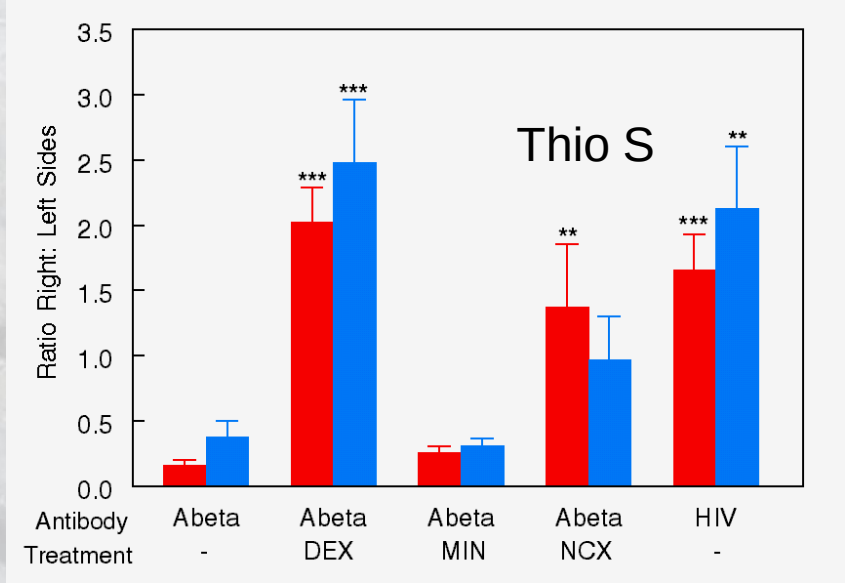
Wilcock et al, J. Neurosci (2003) 23:3745

Antibody-mediated amyloid clearance blocked when microglial activation suppressed with Dexamethasone









Review: Experimental manipulations of microglia in mouse models of Alzheimer's pathology

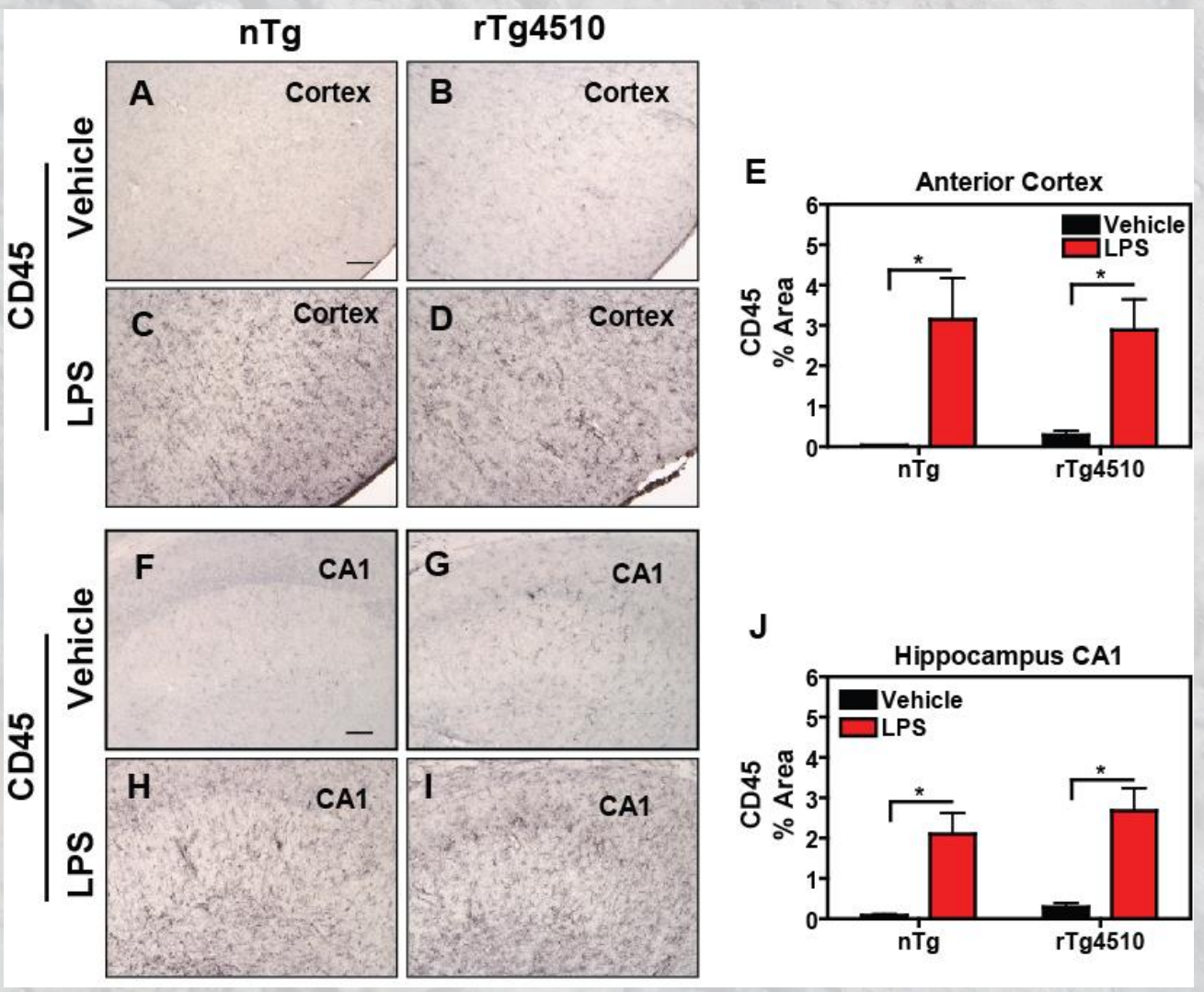
D. C. Lee*†, J. Rizer*‡, J. B. Hunt*†, M.-L. B. Selenica*†, M. N. Gordon*‡ and D. Morgan*‡

Neuropathology and Applied Neurobiology (2013), **39**, 69–85

Table 5. Manipulation of cytokine signalling in models of amyloid deposition

Experimental manipulation	*Plaque microglial response*	*Effect on amyloid load*
IL-1 increase	↑	↓
TNF increase	↑	↓
TNF receptor null	↓	↑
IFN-γ increase	↑	↓
IFN receptor null	↓	↓
IL-6 increase	↑	↓
IL-4 increase	↑	↓
TGFβ increase	↑	↓
G-CSF increase	↑	↓
GM-CSF increase	↑	↓

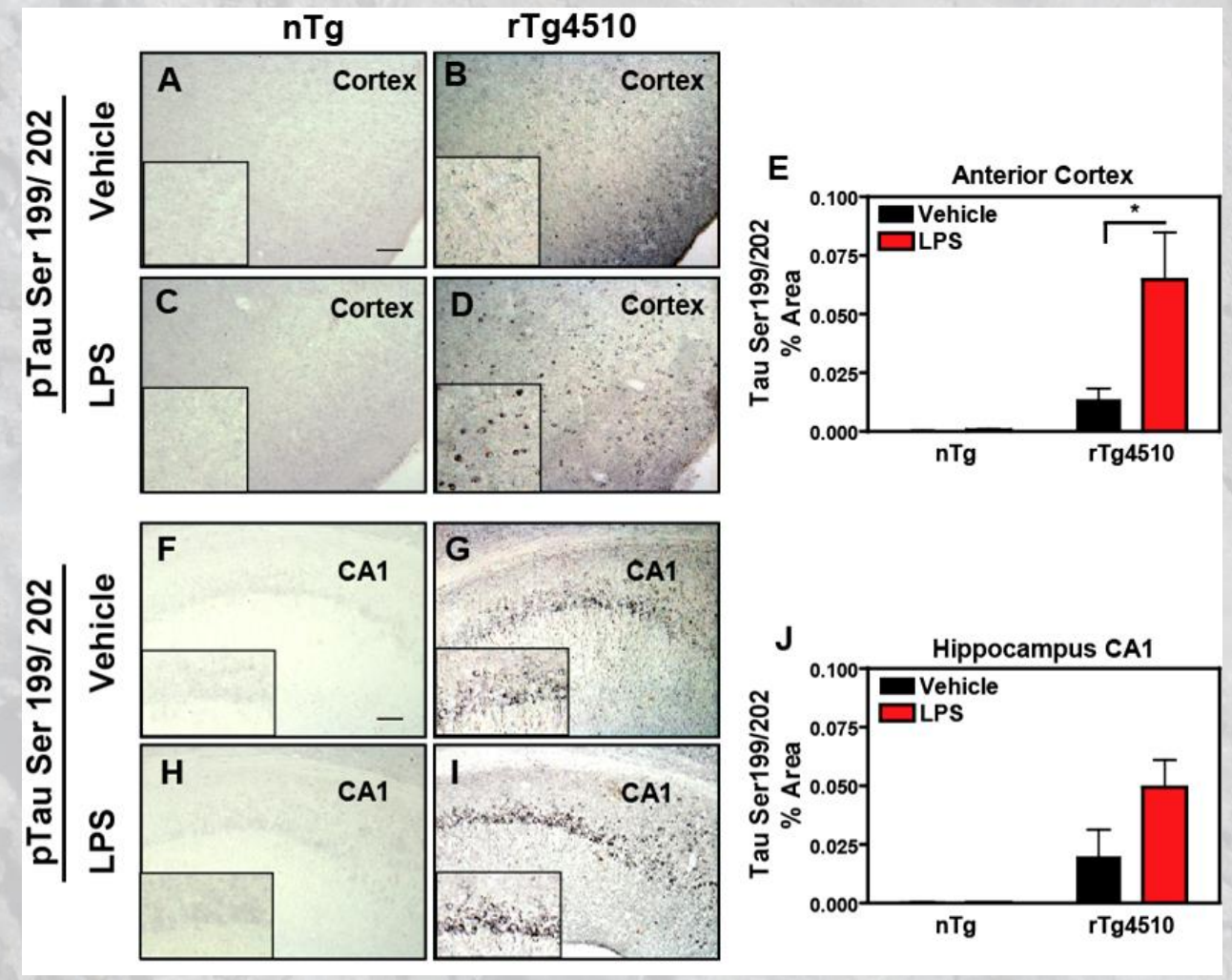
LPS (10 µg) into Hippocampus and Cortex increases CD45 in Tg4510 mice



Mice are 4.5 mo old. 7 day survival.

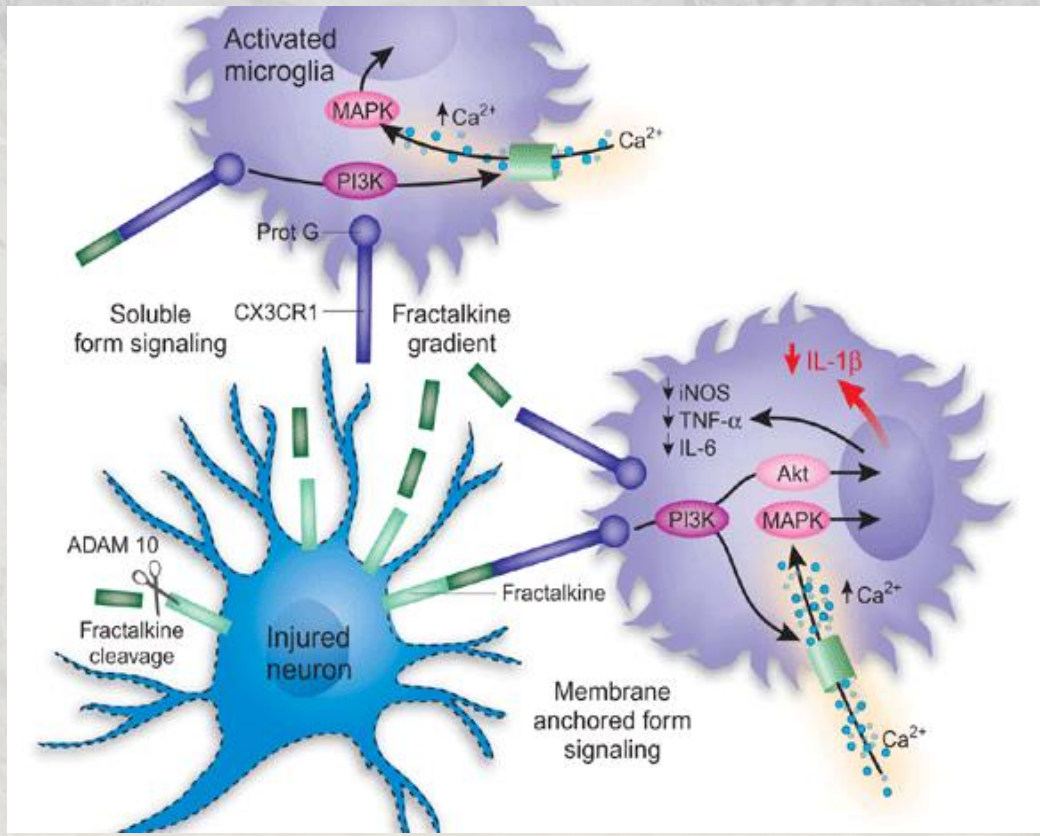
Lee et al (2010), J Neuroinflammation. 16; 56

LPS Injections Increase Phospho-tau Ser 199/202 within 7 days



Fractalkine (CX3CL1) signaling in CNS

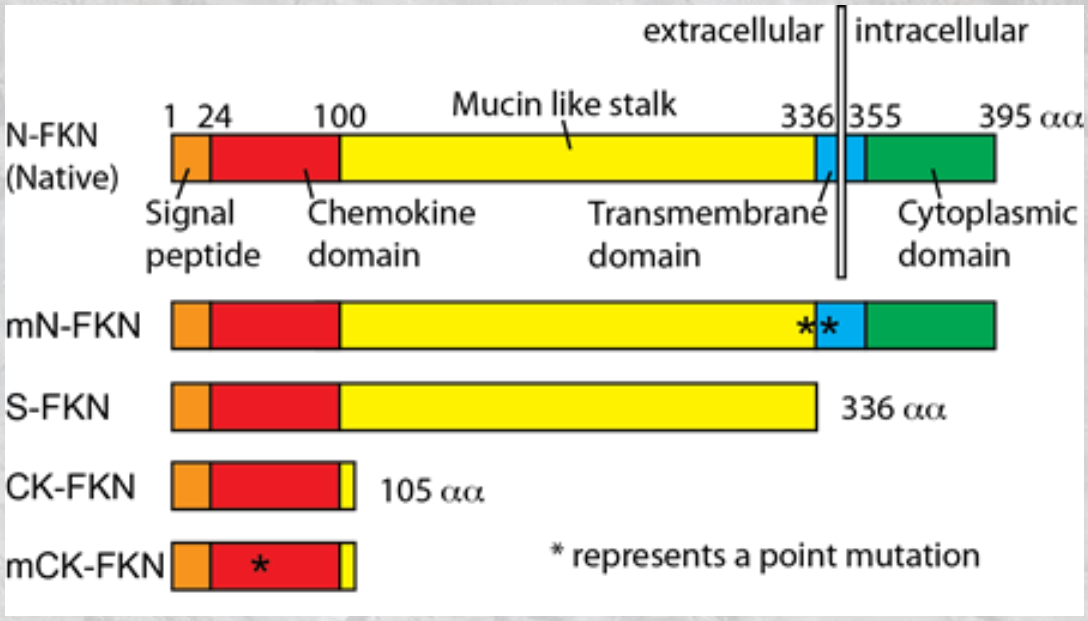
- Fractalkine is a neuronal protein that is cleaved by ADAM 10 to release a soluble peptide.
- Both soluble and membrane associated fractalkine can interact with the fractalkine receptor on microglia to induce quiescence.
- A single mutation can render FKN uncleavable and permanently membrane bound

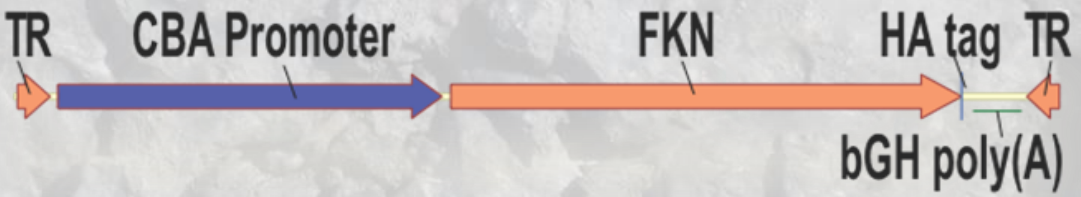


Re & Przedborski, 2006, Nat. Neurosci. 9:859

Does Fractalkine Over Expression Modify Alzheimer Pathology

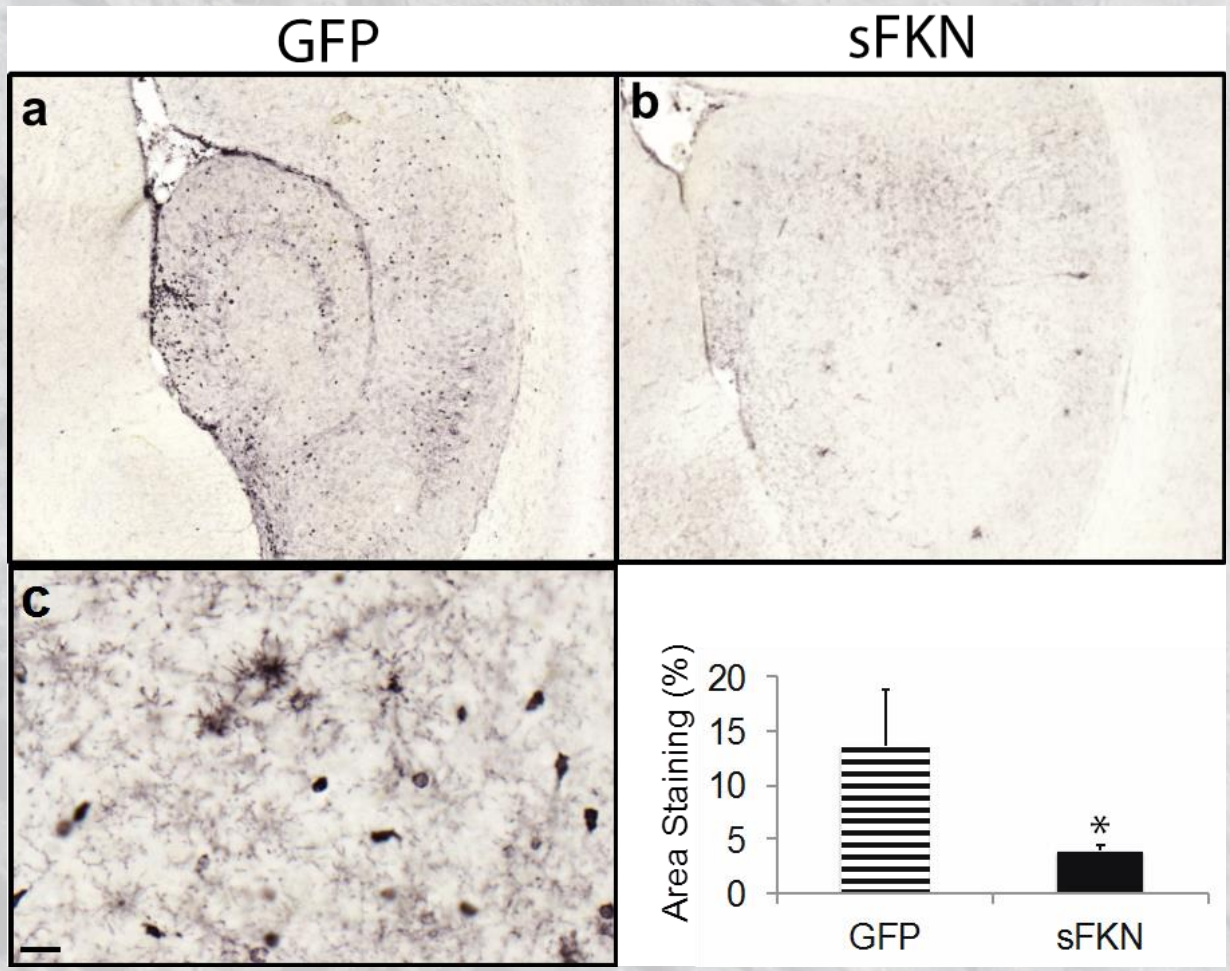
Kevin Nash, PhD



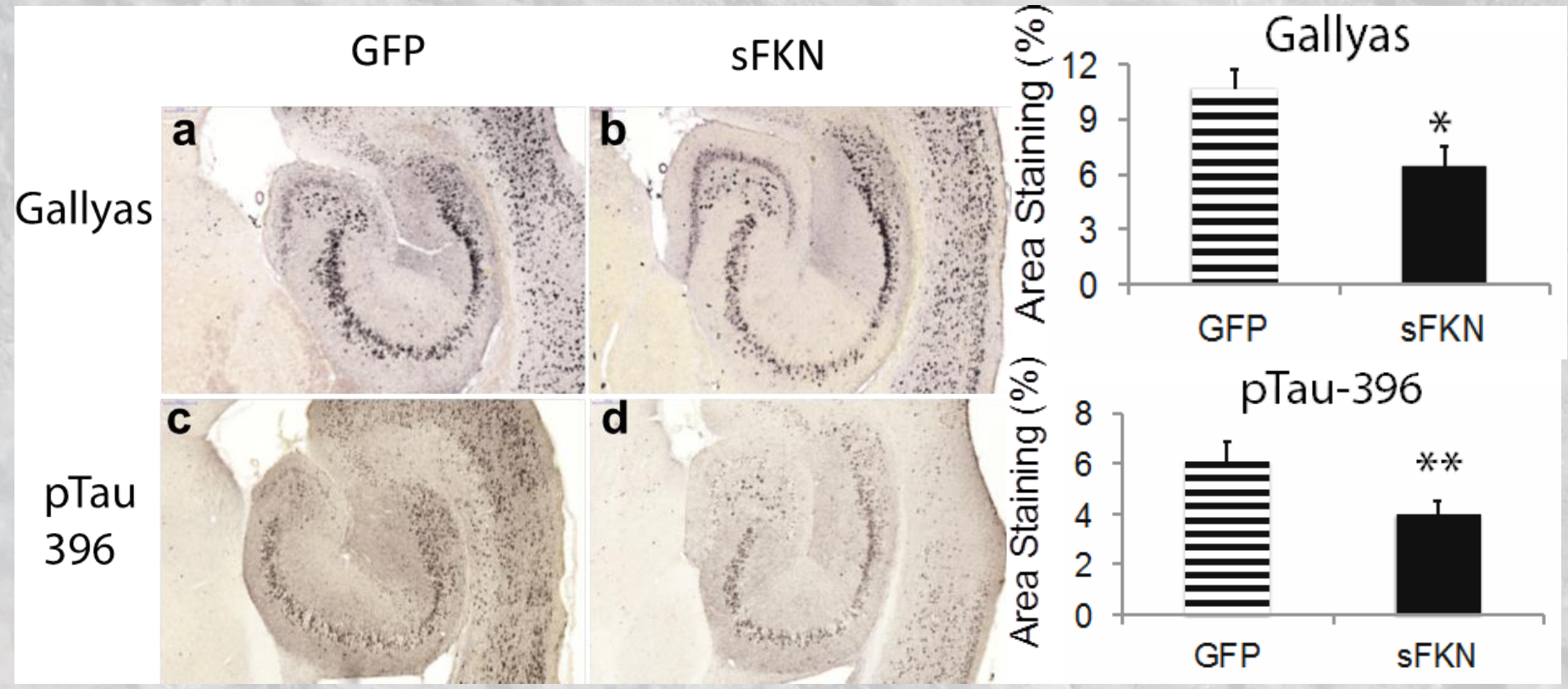


- rAAV9 vector expressing a soluble form of fractalkine (aa 1-336) injected bilaterally into hippocampus of both Tg4510 tau depositing mice (3mo-6 mo) and APP+PS1 amyloid depositing mice.

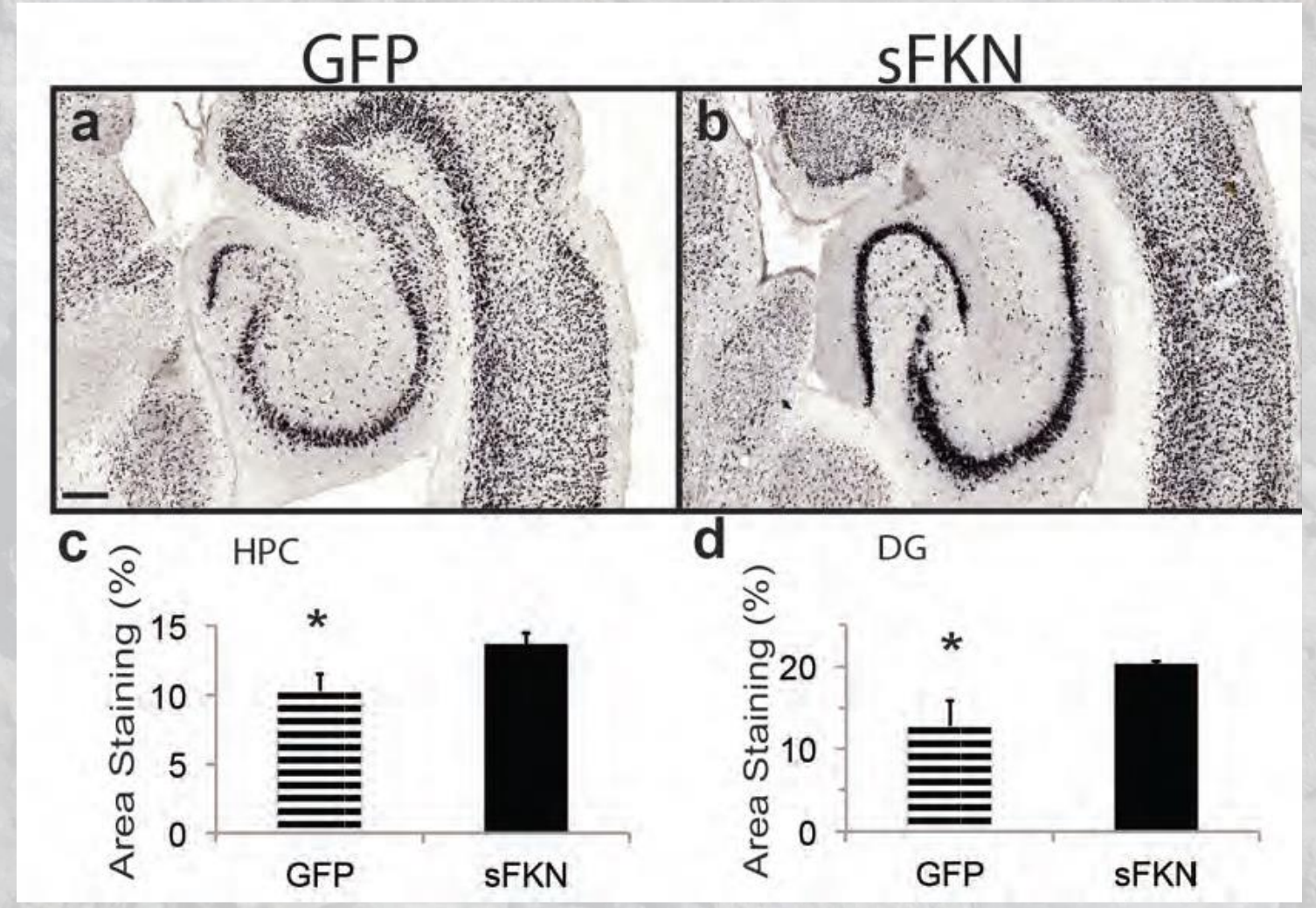
Fractalkine reduced microglial activation detected by CD45 staining



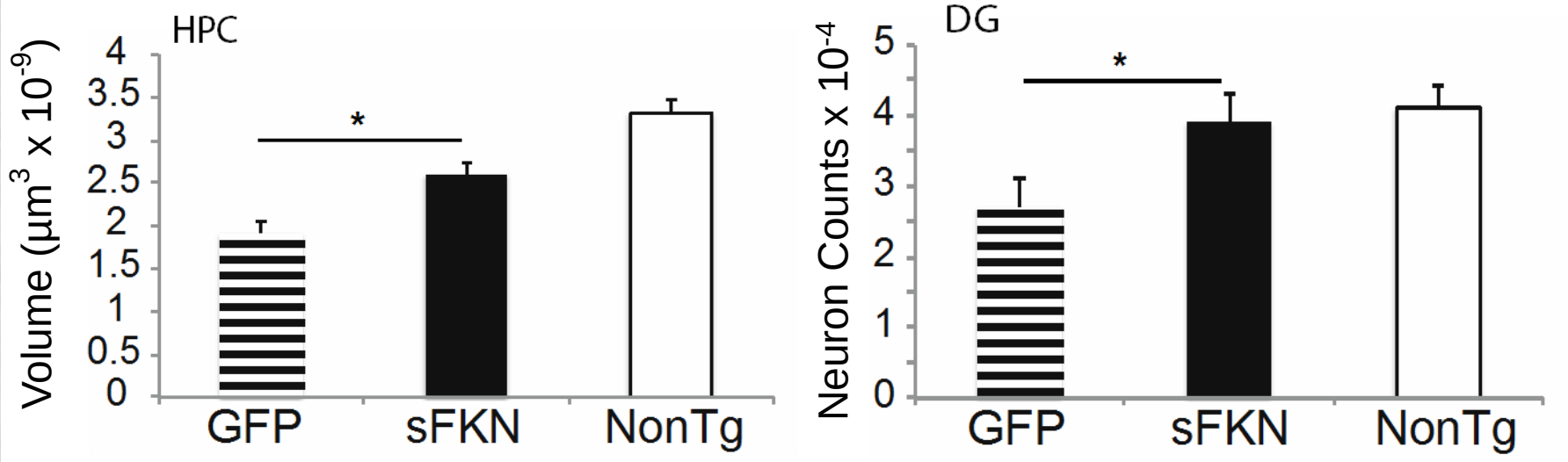
Fractalkine expression reduces tau pathology



Fractalkine expression preserves neuronal staining (NeuN) in hippocampus



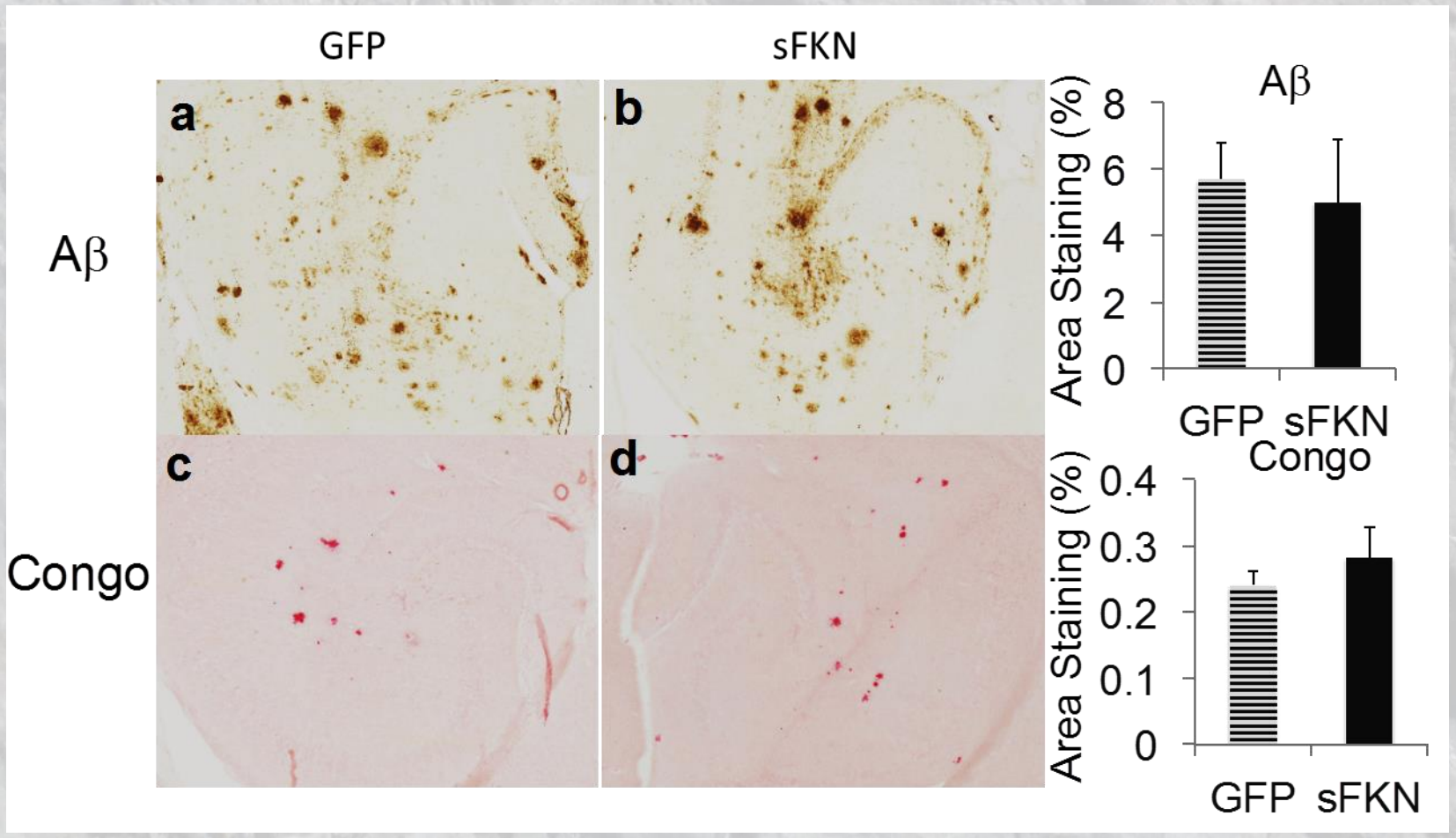
Fractalkine expression diminishes hippocampal atrophy and rescues dentate gyrus neuron loss (Nissl stain)



Hippocampal Atrophy

Stereology Counts

APP+PS1 mice were injected with Fractalkine at 6 mo and tissue collected at 10 mo of age. No change was found in any measure



Conclusions

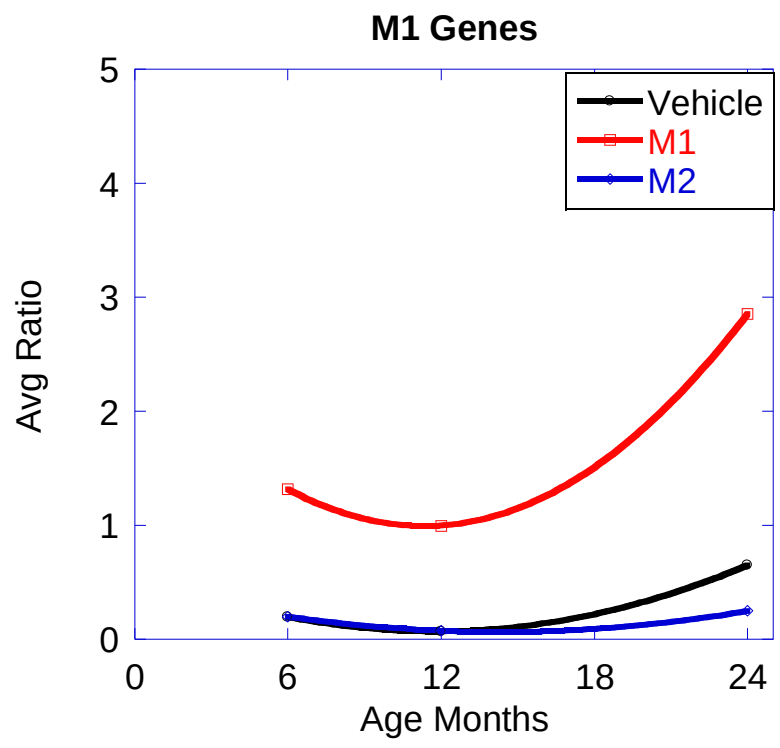
- Overexpressing fractalkine in Tg4510 mice rescues the tau histological phenotype, as predicted from knockout studies.
- Continued memory deficits in Tg4510 likely are due to tauopathy in extrahippocampal regions.
- Overexpressing fractalkine in a rat model of synucleinopathy protects from nigral neuron loss.
- Only secreted fractalkine is effective. Native and mutant (membrane only) fractalkine exhibit no protection.

Conclusions

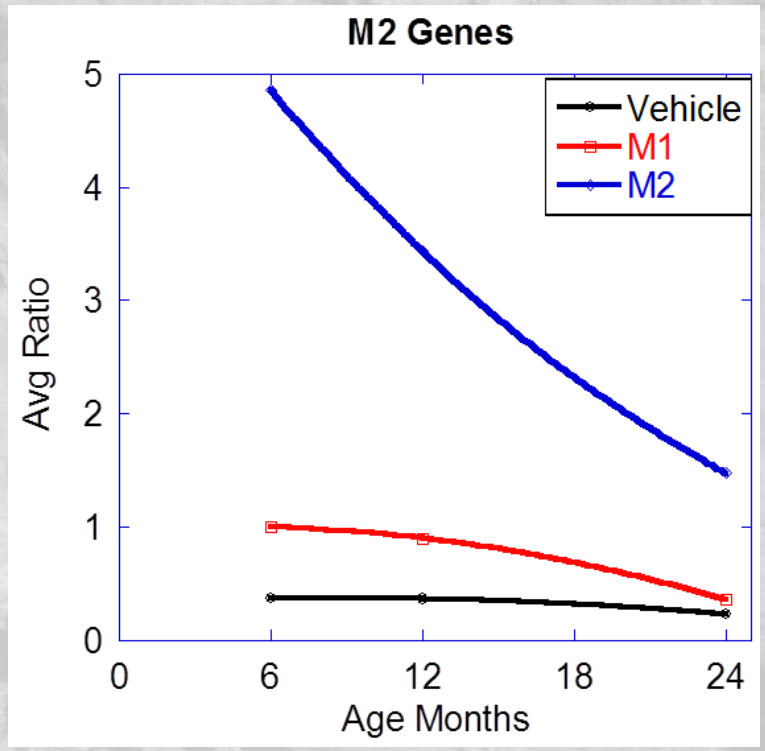
- Lipopolysaccharide induces changes in microglia which enhance degradation of amyloid deposits in APP mouse brain
- Similar injections in mice depositing tau leads to exacerbation of some pathology
- Similar observations of treatments with opposing effects on amyloid versus tau pathology have been observed regarding fractalkine receptor regulation of microglial activation (B. Lamb) and IL-1 regulation of neuroinflammation (K. O'Banion) and systemic LPS (F. LaFerla)
- Whats good for amyloid may be bad for tau with respect to regulation of microglial activation

Aging increases sensitivity to proinflammatory cytokines and decreases sensitivity to alternative activation cytokines

Inflammatory CKs; IL-1, TNF, IL-12
Intrahippocampal, 3d survival



Alternative CKs; IL-4, IL-13
Intrahippocampal, 3d survival



M1 Genes

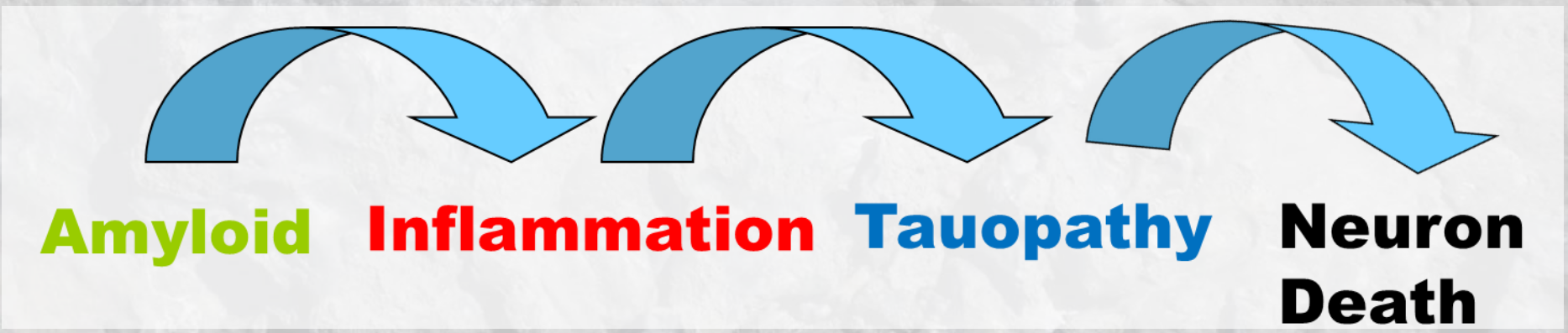
- **CCL5 (Rantes), CXCL13**
- **MARCO, Calgranulin A**
- **Calgranulin B, TIMP1**

M2 Genes

EAR11, Ch3l3 (YM1)
Renla (Fizz1), Arginase 1
IGF-1, Erdr1

Emerging View of Alzheimer's Pathology

- Because of age, life events and/or genetics, amyloid deposits form within the brain over decades (before disease)
- Amyloid can affect memory, but alone does not destroy neurons or the connections between them, synapses. At some point, amyloid initiates the formation of tau filaments (tangles) within neurons
- Either the tau filaments or other changes they cause leads to loss of synapses, neuronal function and ultimately neuron death.



Research Partners

Alzheimer Lab - USF

Marcia Gordon
Kevin Nash
Daniel Lee
Maj-Linda Selenica
Aurelie Joly-Amado
Milene Lara
Sulana Schroeder
Jerry Hunt
Karissa Serraneau
Dylan Finneran
Amber Tetlow

USFCollaborators

Chuanhai Cao
Jun Tan
Paula Bickford
Linella Gemma
Chad Dickey
Joshua Morganti

Supported By

NIA
Benjamin Foundation
Alzheimer's Association

...until Alzheimer's is a memory™