

# Neuroinflammation in preclinical AD: in vivo evidence

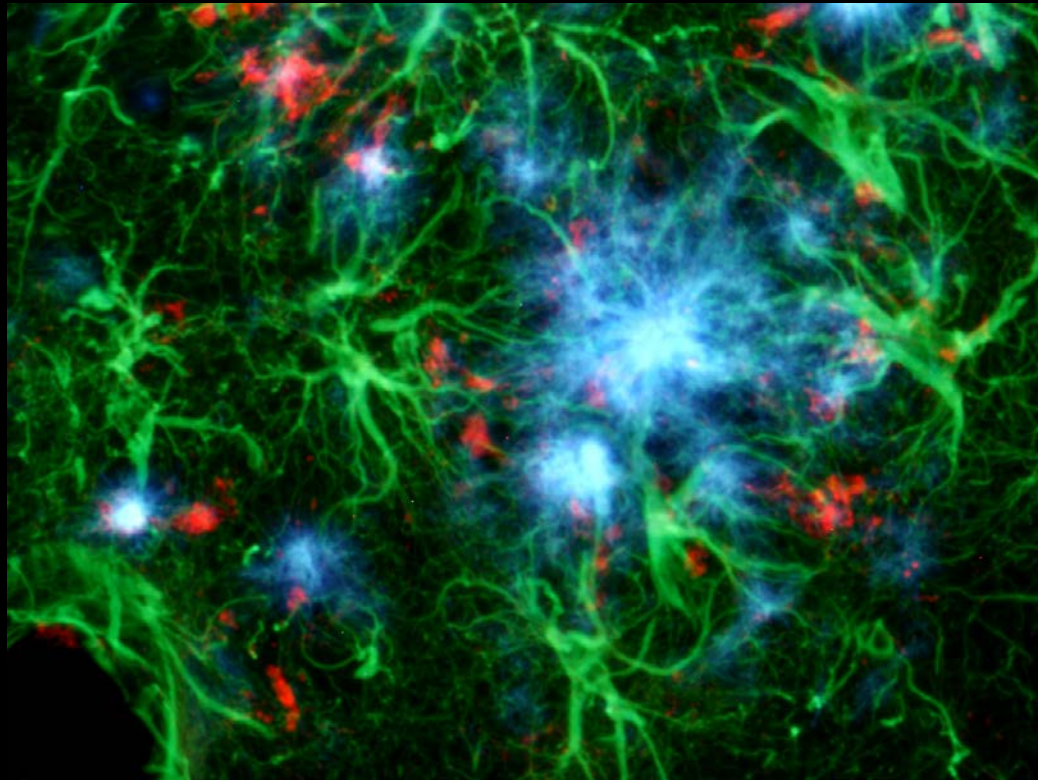
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# Overview

- Background
- Preclinical effects of neuroinflammation
- Future directions

No conflicts of interest.



NFT

Beta-amyloid

Neuronal/synaptic loss

Inflammatory cascade

<http://www.biosensis.com/amylo-amyloid-plaque-stain-reagent-p-1224.html>

# Epidemiological studies



<http://www.sfn.org/~media/SfN/Documents/TheHistoryofNeuroscience/Volume%203/c11.ashx>

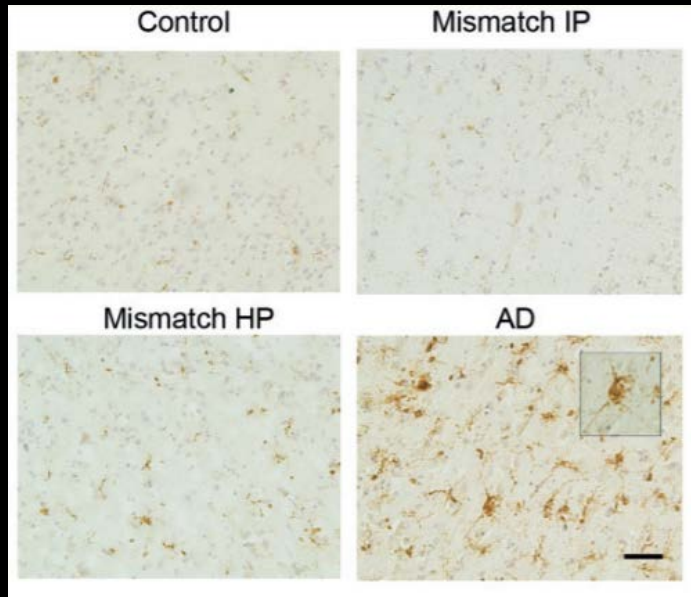
- Prevalence of AD was only 0.4% in arthritis patients
- Rotterdam study, Cache County, BLSA
- 50% decrease in risk for developing AD in NSAID users.

# Animal studies



- LPS induced inflammation in rats will result in a pattern similar to pattern in AD.

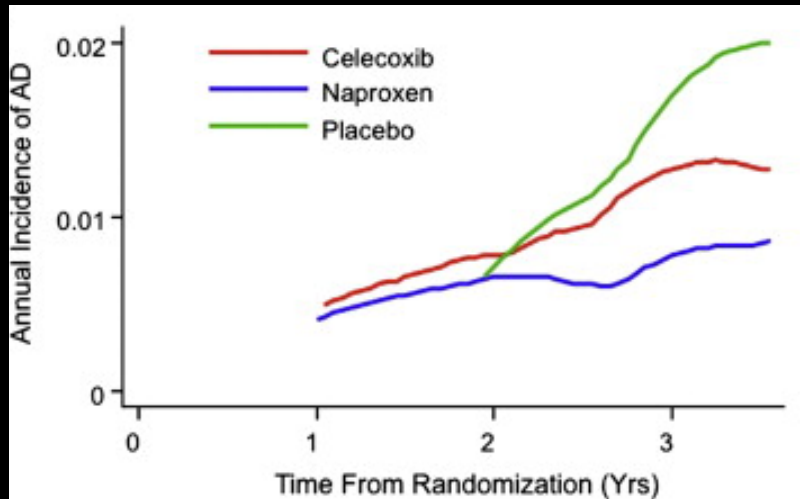
# Human post mortem



- Microglia differentiate symptomatic AD

Perez-Nievas (2013). Brain: 136(Pt 8):2510-26

# Treatment trials in AD

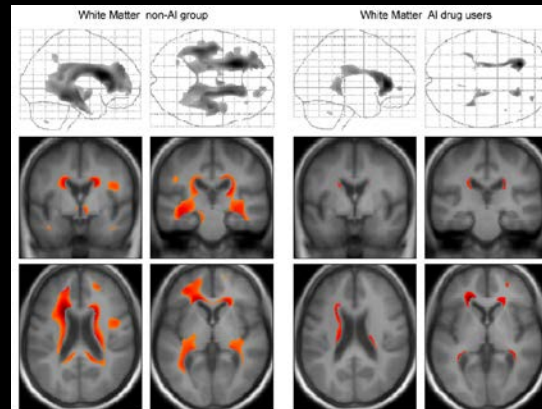
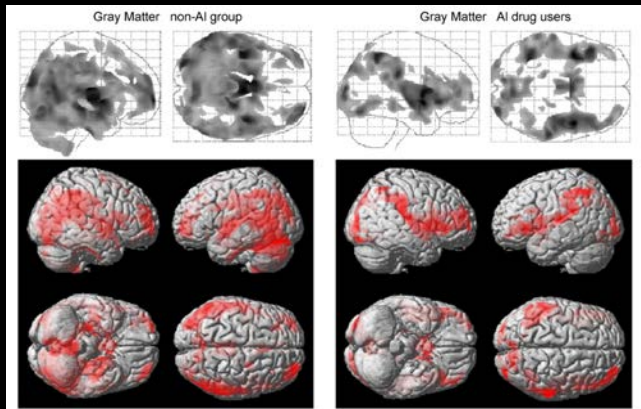


- NSAID trials in dementia
- NSAID trials in MCI
- ADAPT trial discontinued
- Follow-up: reduction in AD incidence among symptomatic enrollees given naproxen

Breitner, 2011, Alzheimer's Dement. 2011

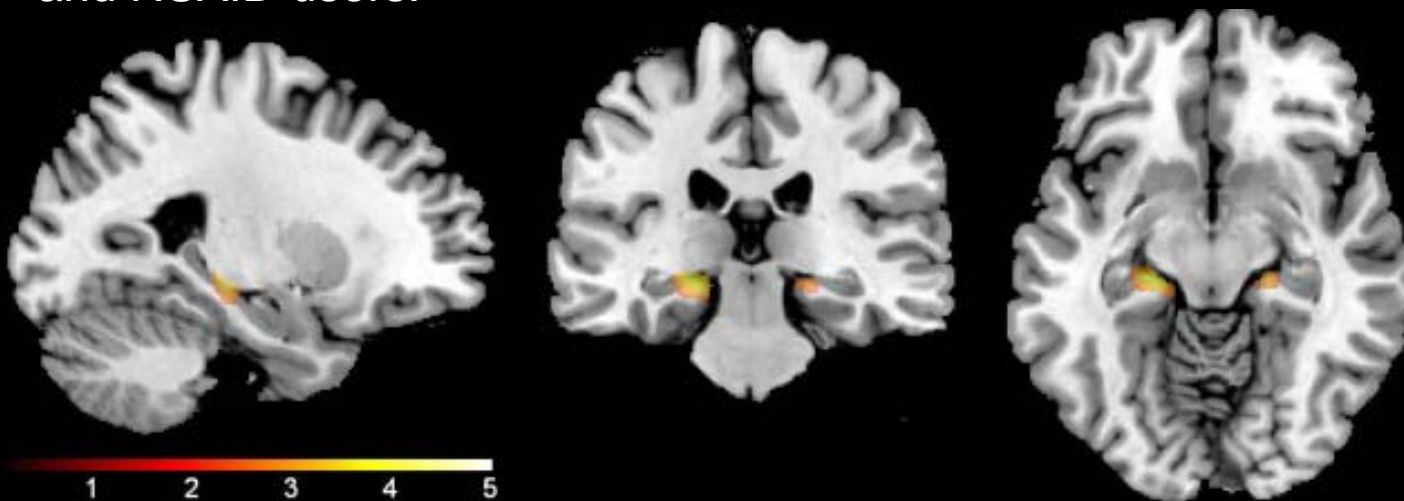
# Anti-inflammatory effects on human brain

- Preserved gray matter volume in RA patients



Walther, Bendlin et al, 2011. *Neurobiology of Aging* 32: 497–505

- and NSAID users.



Bendlin et al, 2010. *Front Aging Neurosci.* 2: 35.



Given that inflammation may play a role in the early stage development of AD...

- . What is the effect of preclinical inflammation on the brain?

# Preclinical

- Participants with risk
- Parental FH
- APOE4

# In vivo markers

- MRI
  - Volumetric
  - Microstructure
  - Blood flow
  - Functional
  
  - PET
  - FDG
  - PiB
  - PBR28
- CSF
  - A $\beta$ 42, sAPP $\beta$
  - T-Tau, P-Tau, NFL
  - IL6, IL8, TNFalpha
  - MCP-1, YKL-40
  
  - Plasma
  - IL6, IL8, IL10, IL1 $\beta$ , HS-CRP, TNFalpha

# In vivo markers

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- Volumetric
- Microstructure
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- PET

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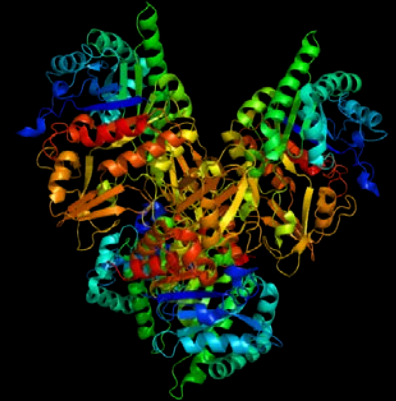
- CSF

- A $\beta$ 42, sAPP $\beta$
- T-Tau, P-Tau, NFL
- IL6, IL8, TNFalpha
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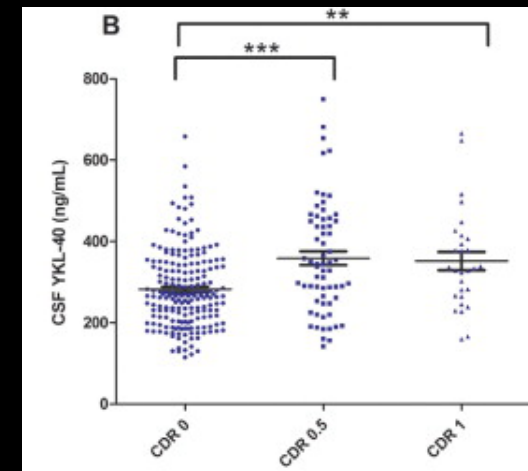
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# CSF markers



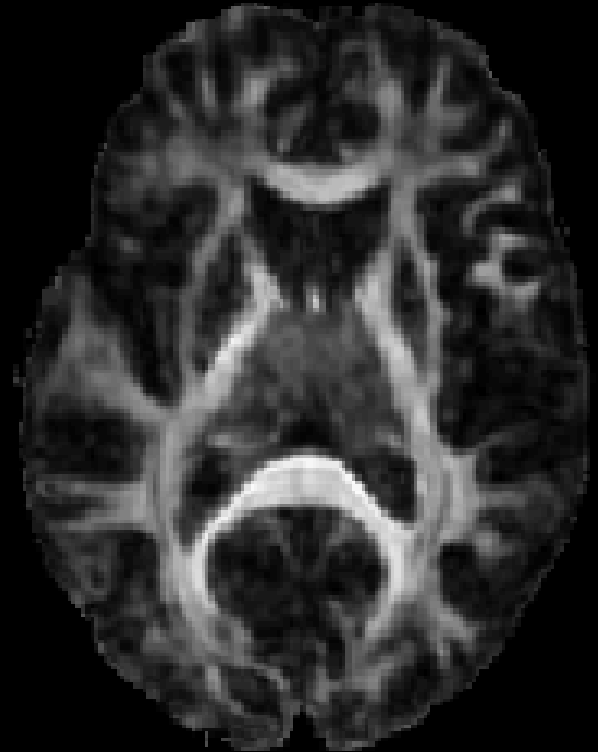
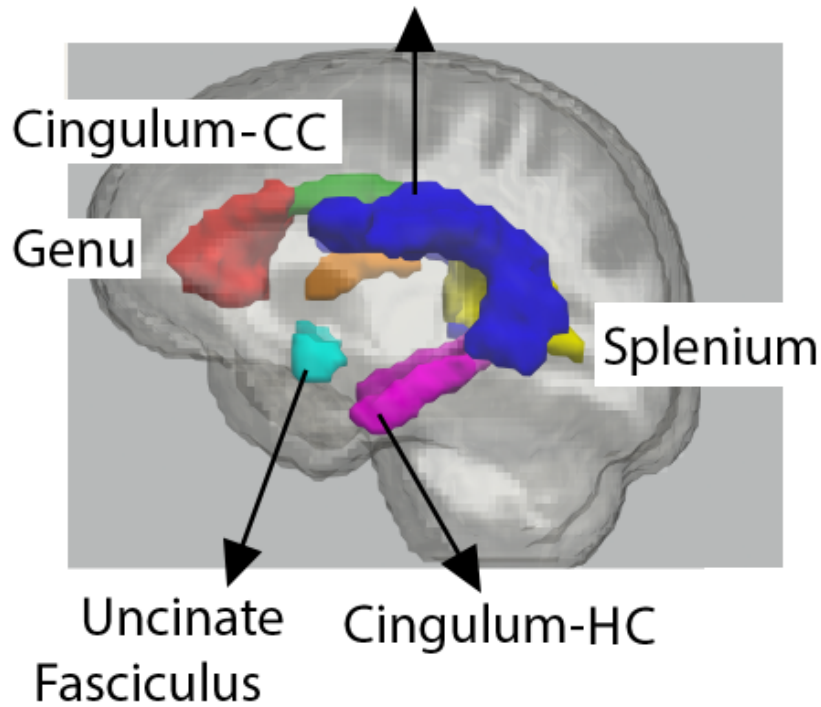
<http://en.wikipedia.org/wiki/CHI3L1>

- YKL-40 secreted by activated microglia
- Increased CSF YKL-40 described in early-stage AD (Craig-Schapiro et al. 2010).
- YKL-40 obtained using ELISA (Zetterberg)
- A $\beta$ 42 obtained via X-MAP
- Complementary markers included MCP-1, sAPP $\beta$ , T-Tau, and P-Tau181)



Biol Psychiatry. 2010; 68(10): 903–912.  
doi:10.1016/j.biopsych.2010.08.025.

## Superior Longitudinal Fasciculus



- Inflammation may cause neuronal damage
- Amyloid deposition is toxic to neurons
- $A\beta_{42}$  aggregates into oligomers along microtubules of neuronal processes
- AD involves hyperphosphorylation of tau protein, resulting in axonal abnormalities

# Study Summary

- Participants with risk (Parental FH, APOE4)
- Underwent brain imaging and lumbar puncture
- CSF sample were assayed for markers related to A $\beta$  and microglia
- Overarching hypothesis: greater microglial activation, altered microstructure

# Models

- . Regression
- . Main effects: YKL-40
- . YKL-40 x risk (APOE4 & FH)
- . YKL-40 x amyloid ( $A\beta$ 42)
- . Covariates: Age, sex
- . Indices of microstructure: FA & MD

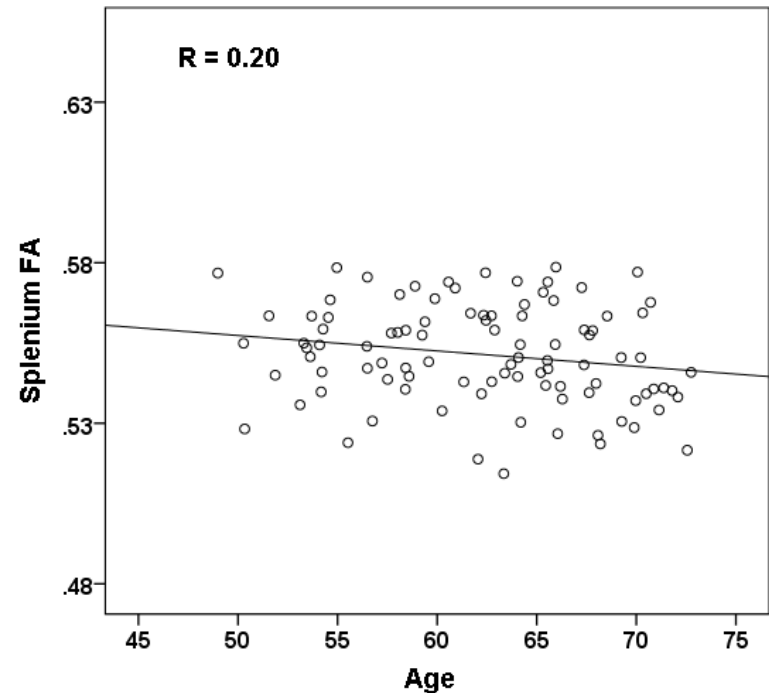
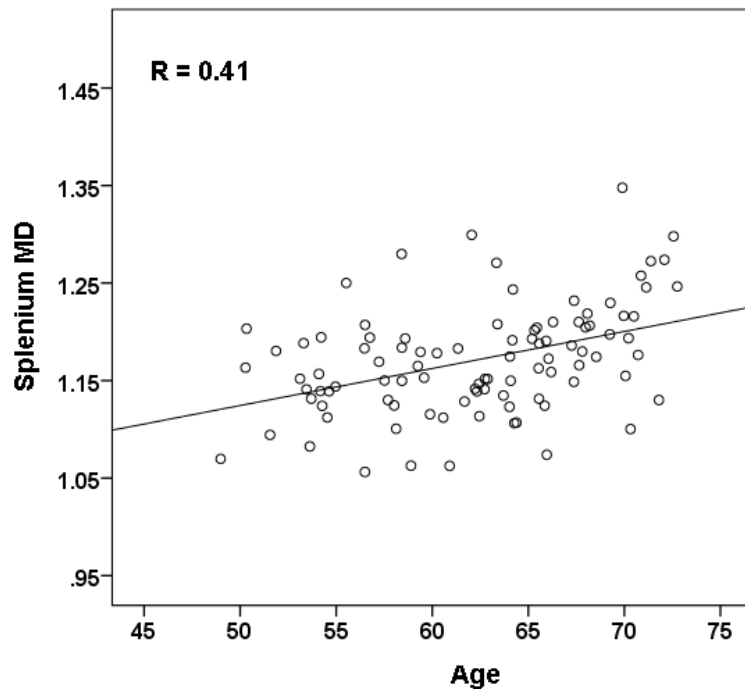


# Demographics

- N = 97 (cog. healthy, MMSE mean = 29.36)
- age range = 49 – 72 years
- mean = 62 years
- 36% APOE4+
- 72% FH+
- 64 women, 33 men

# Results: DTI and Age

- Effect of age on 12/14 measures
- (all but cingulum-HC FA & SLF MD)



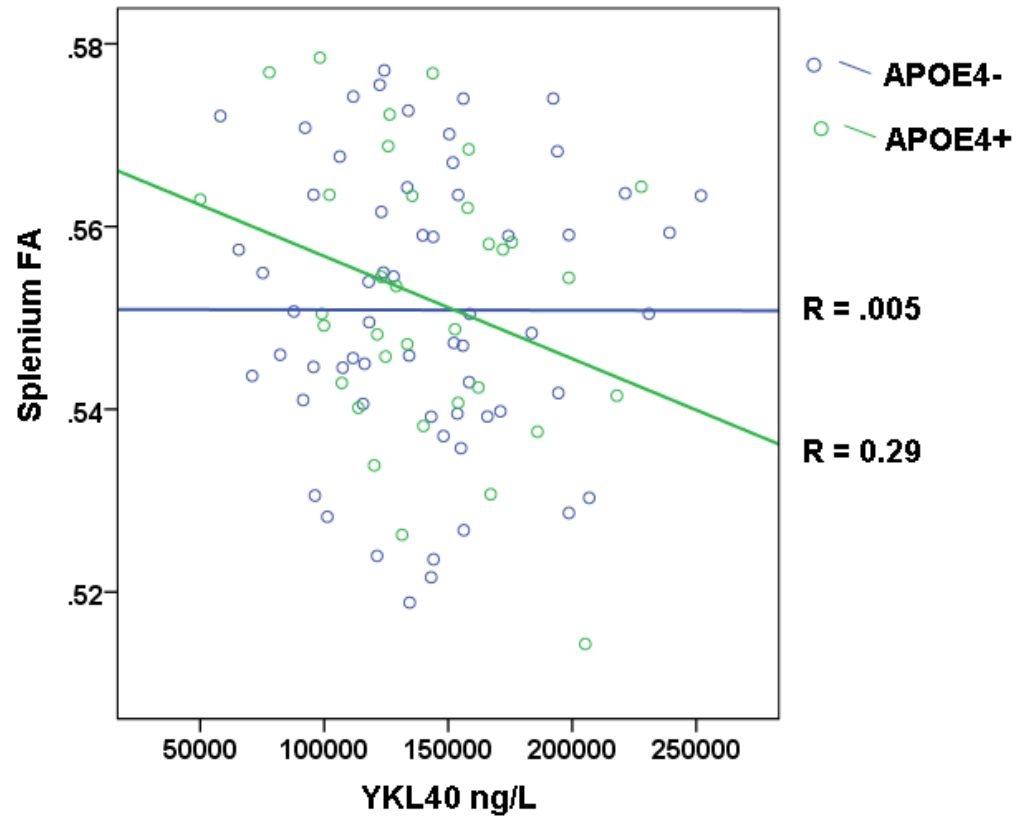
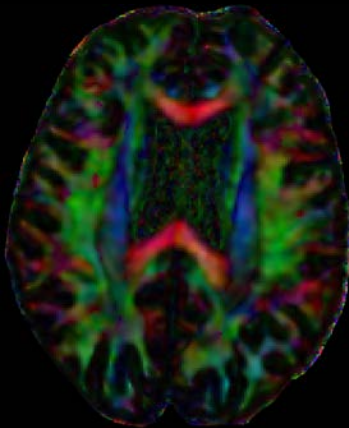
# Results: YKL-40, risk and A $\beta$

- . YKL-40: range: 49.99-320.30 ng/mL, mean = 144.57 ng/mL
- . YKL-40 did not differ between FH or APOE4 risk groups
- . YKL-40 was positively correlated with sAPP $\beta$  ( $r = .54$ ,  $p < .001$ ) and A $\beta$ 42 ( $r = .37$ ,  $p < .001$ )\*
- . No main effects of YKL-40 on the DTI measures

\* Controlling for age

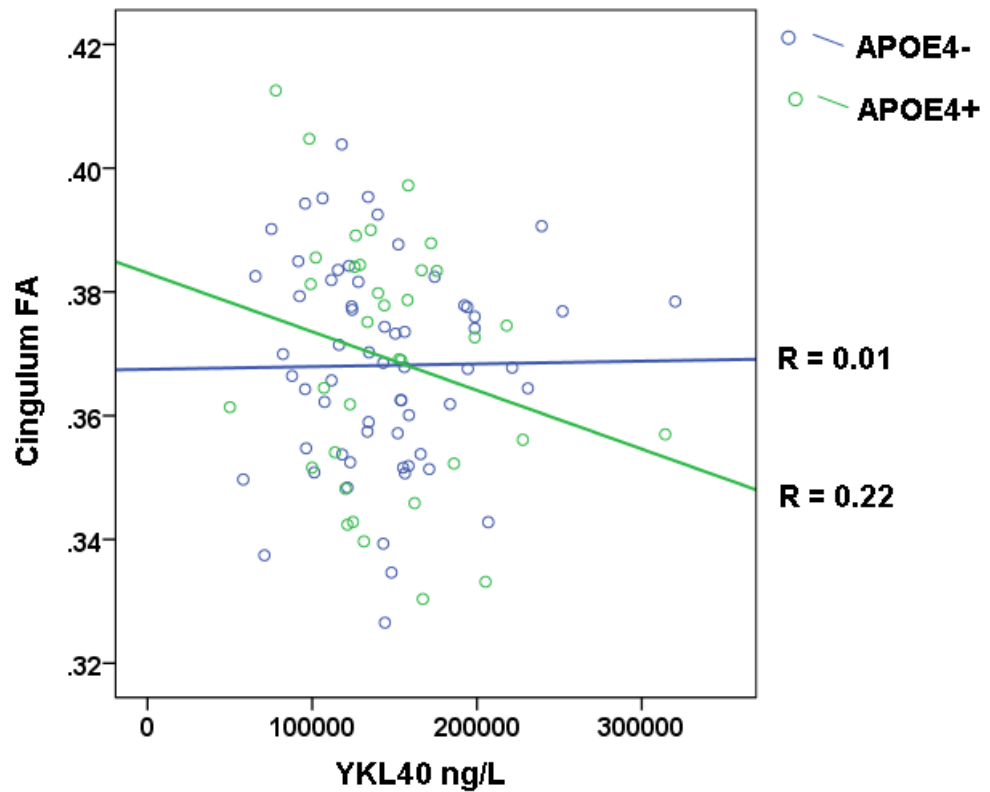
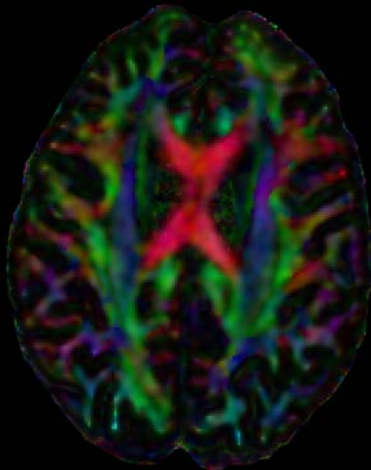
# YKL-40 interacts with APOE4

- Splenium FA
- $p = .022$



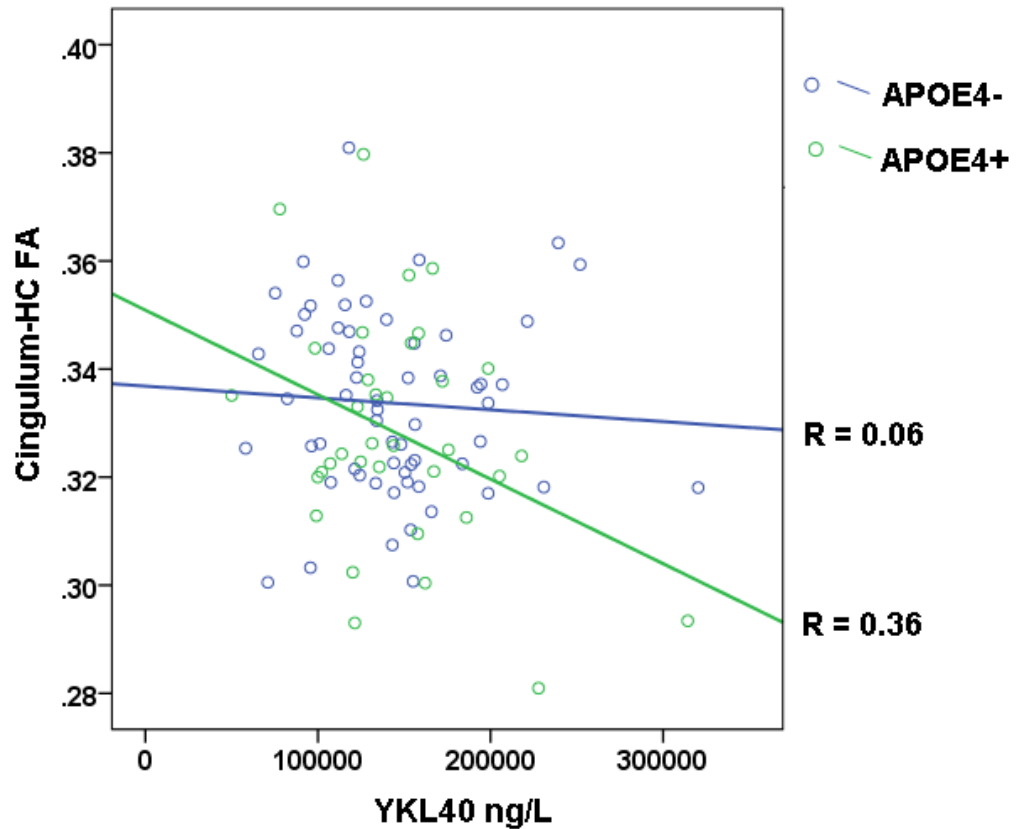
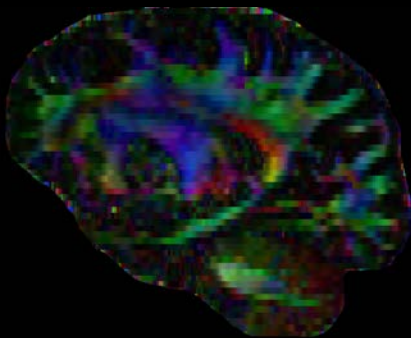
# YKL-40 interacts with APOE4

- Cingulum FA
- $p = .011$



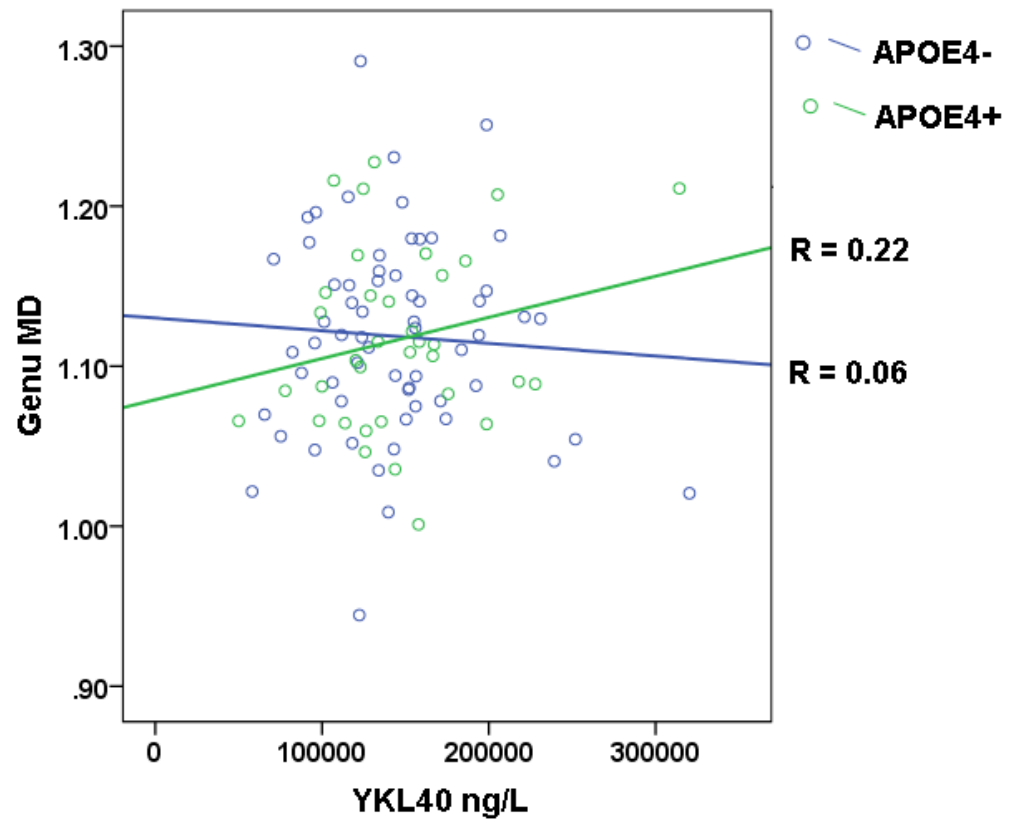
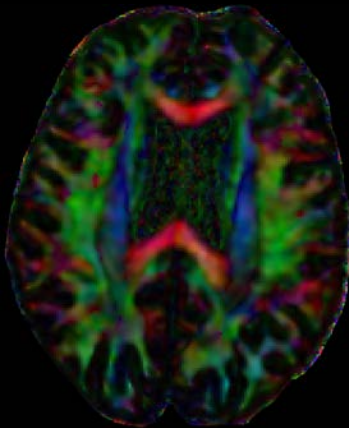
# YKL-40 interacts with APOE4

- Cingulum-HC FA
- $p = .005$



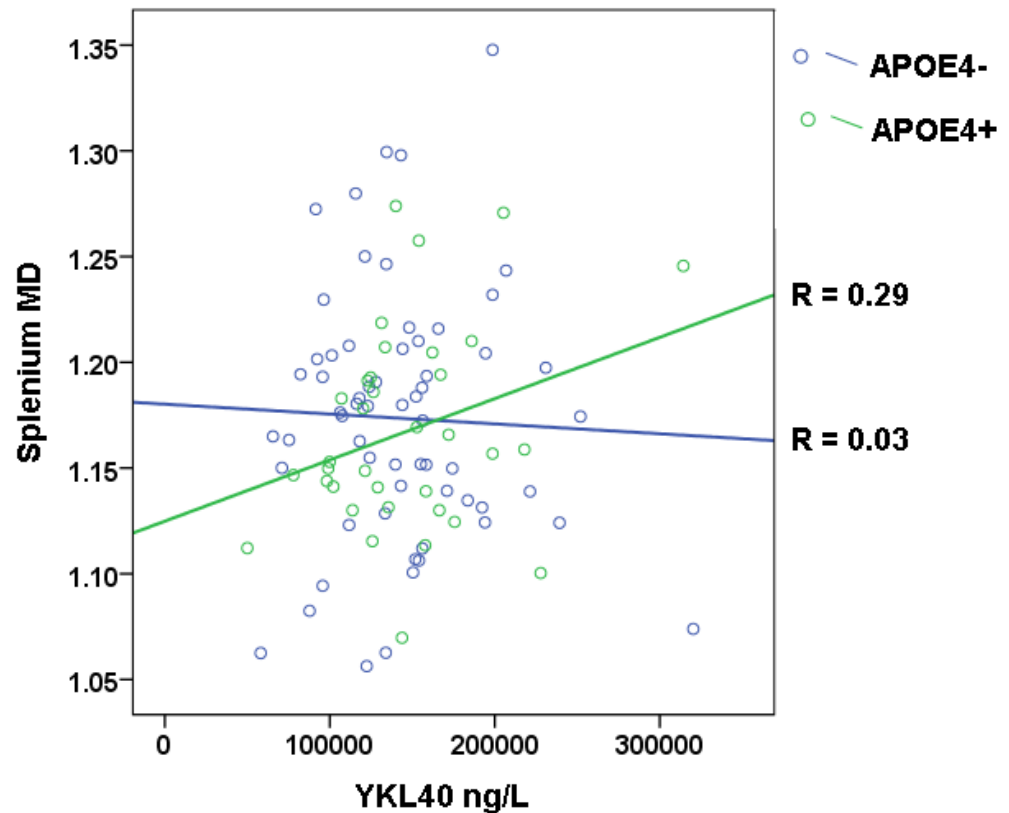
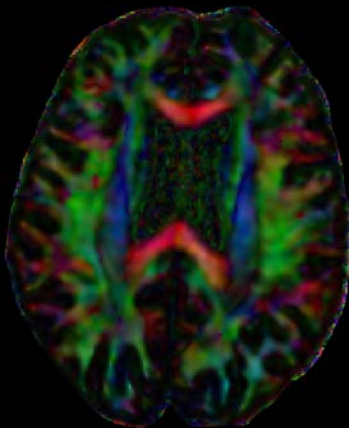
# YKL-40 interacts with APOE4

- Genu MD
- $p = .046$



# YKL-40 interacts with APOE4

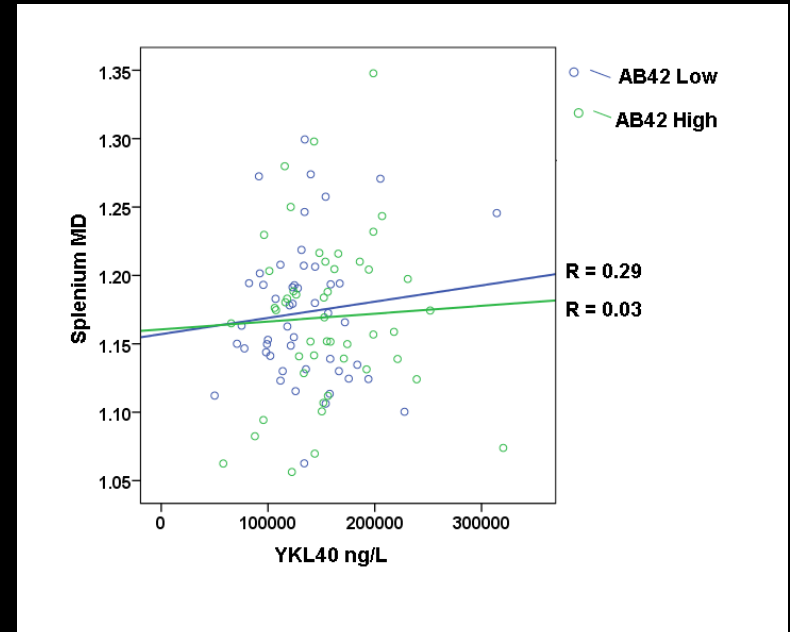
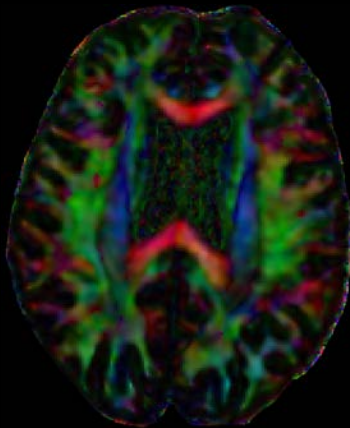
- Splenium MD
- $p = .013$





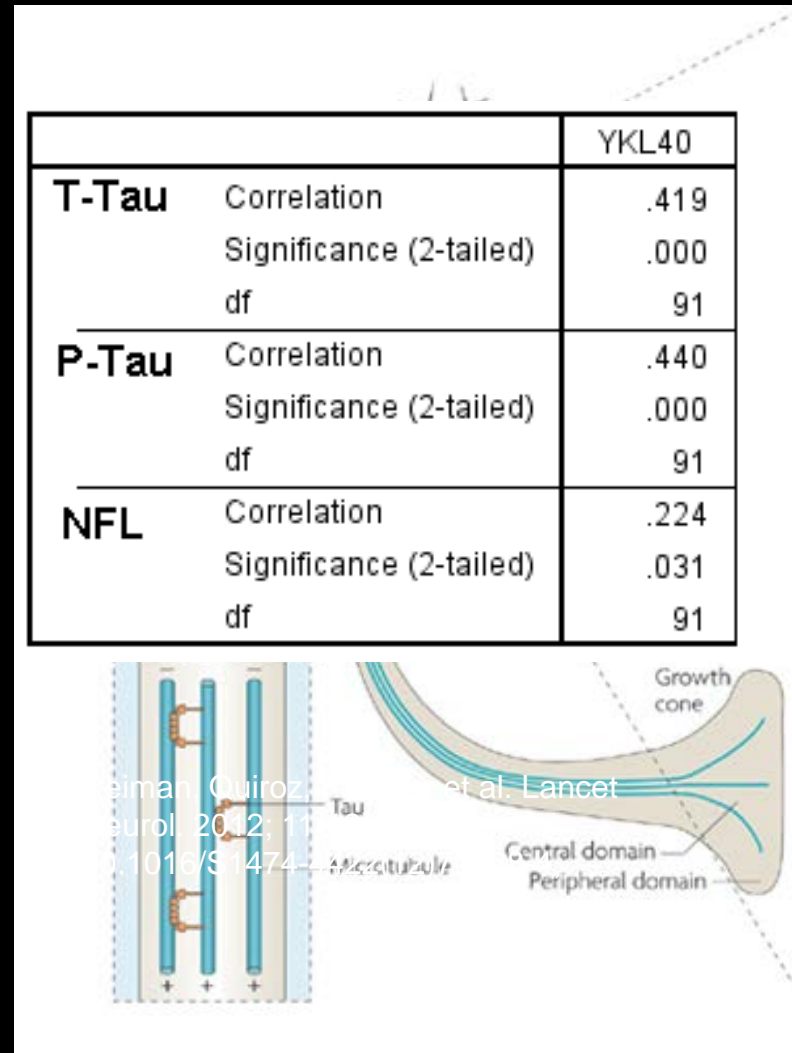
# YKL-40 and A $\beta$ 42...

- Weak trend
- Low A $\beta$ 42+higher YKL-40 = higher diffusivity
- Splenium MD (p = .089)



# Summary

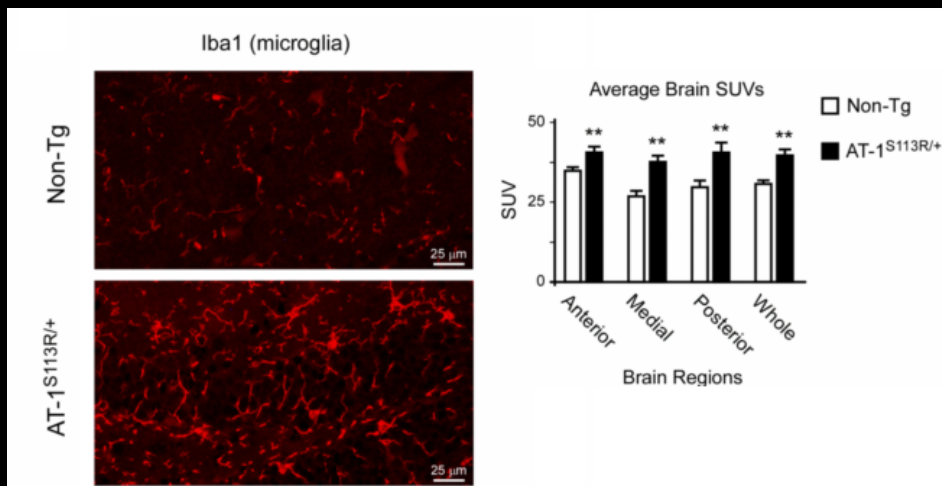
- YKL-40 levels did not differ by FH or APOE4 risk groups
- YKL-40 was related to markers of amyloid (sAPP $\beta$ , A $\beta$ 42)
- APOE4 + microglia was associated with altered microstructure
- Vulnerability due to APOE4
- Axonal loss in presence of inflammation?



Axons have tau-bound microtubules.

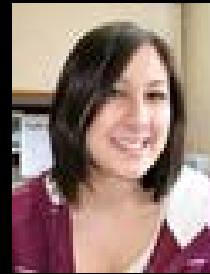
# Conclusion & Future Directions

- Evidence for preclinical relationship
- Timing is important: dampen inflammation or exploit immune response?
- Future: additional participants, markers, longitudinal data
- Regional pattern of inflammation: [11C]PBR28





Wisconsin ADRC  
CSF Working Group



National Institute on Aging  
R01 AG037639 [BBB]  
R01 AG027161 [MAS]  
ADRC P50 AG033514 [SA]  
R01 AG021155 [SCJ]



UW ICTR/CTSA 1UL1RR025011  
NICHD P30 HD003352-45

[www.brainmap.wisc.edu](http://www.brainmap.wisc.edu)

GRECC/ William S. Middleton Memorial Veterans Hospital, Madison, WI.