Role of T-cells in a model of tau-mediated neurodegeneration

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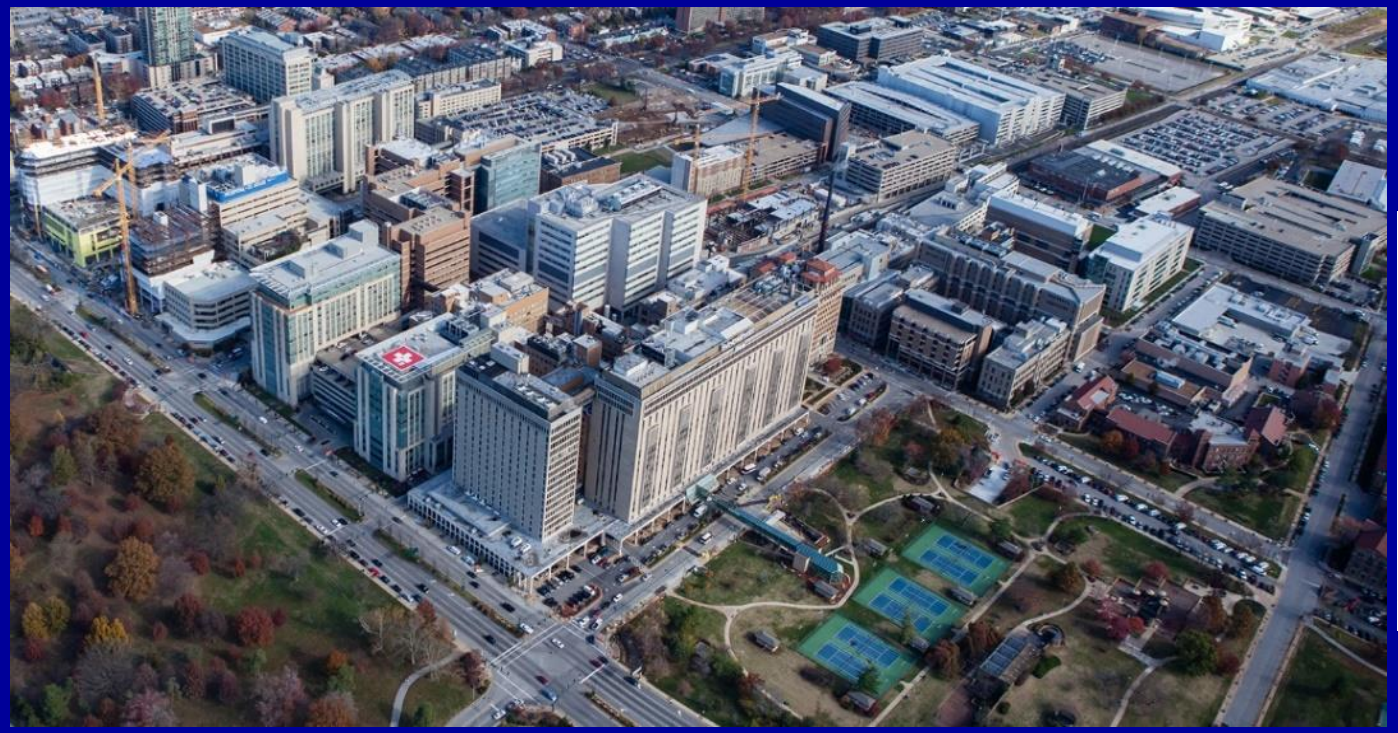

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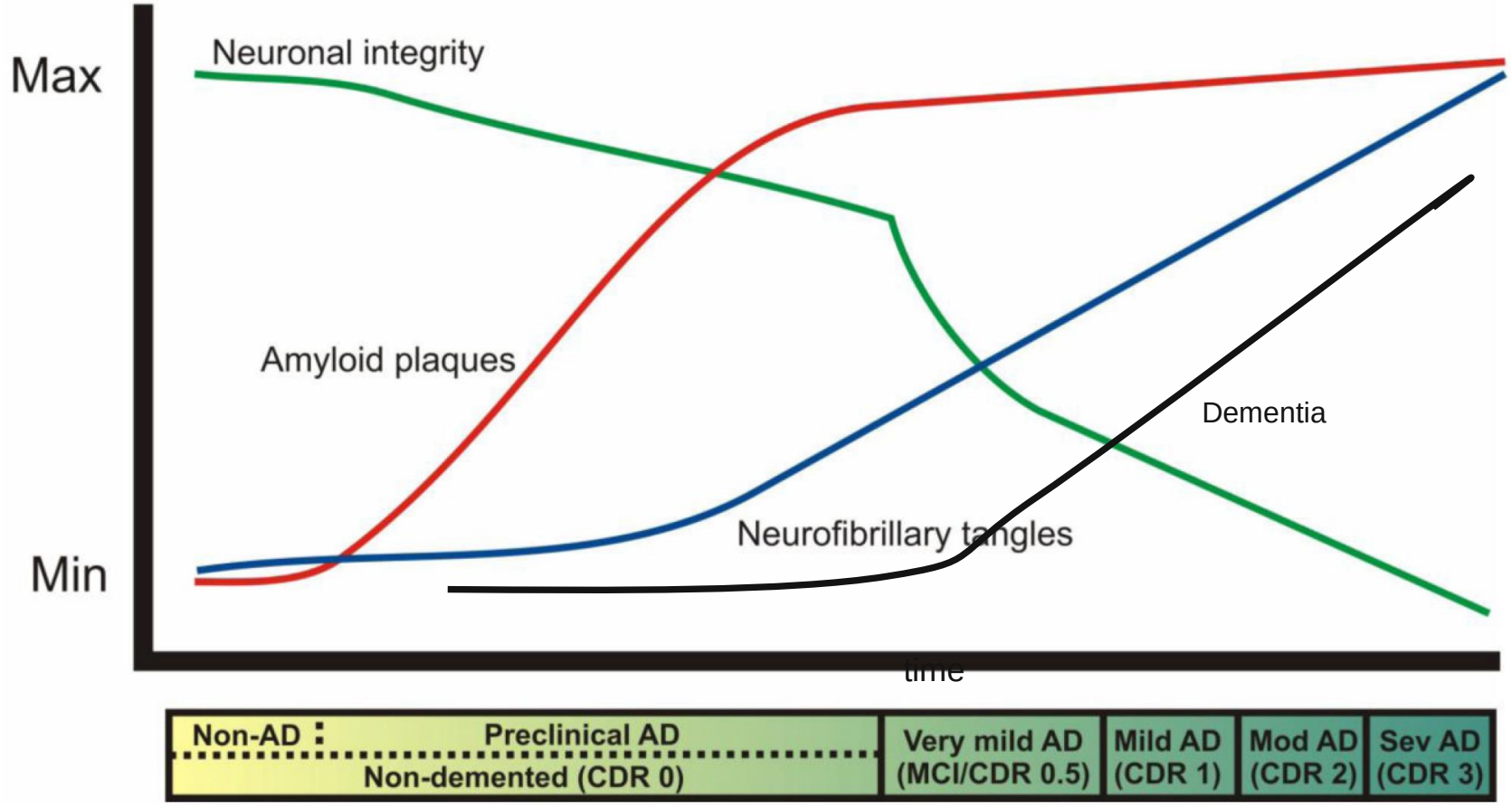
Knight ADRC
Alzheimer's Disease Research Center
WASHINGTON UNIVERSITY ST. LOUIS

Tau pathology and inflammation is critical in the clinical and pathological progression of Alzheimer's disease



Modified from Perrin, Fagan, and Holtzman *Nature*, 2009

P301S mutant tau transgenic mice (PS19)

P301S mutation

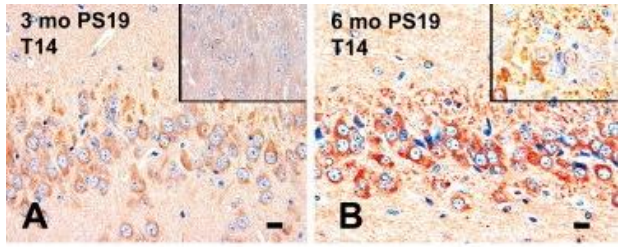
In humans causes early-onset FTDP-17.

P301S tau transgenic mice (express human P301S tau)

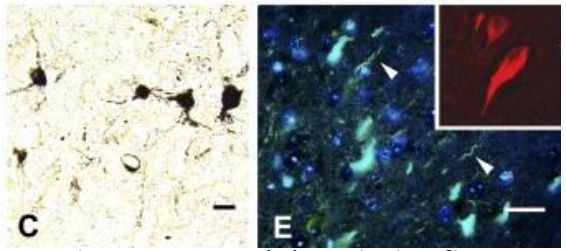
Strong tau positive neuronal staining at 6 months of age.

Strong microglial "activation" coincident with tau accumulation.

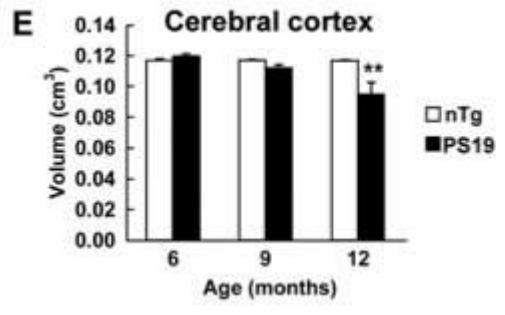
Show neuronal loss ~ 8months of age followed by regional brain atrophy

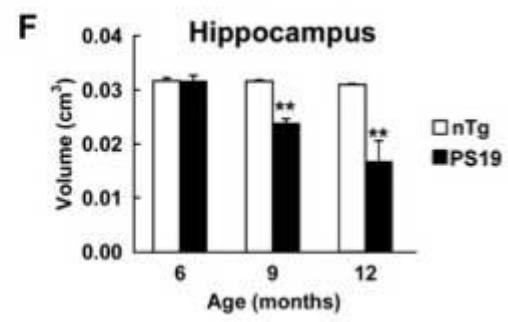


Hippocampus staining of tau



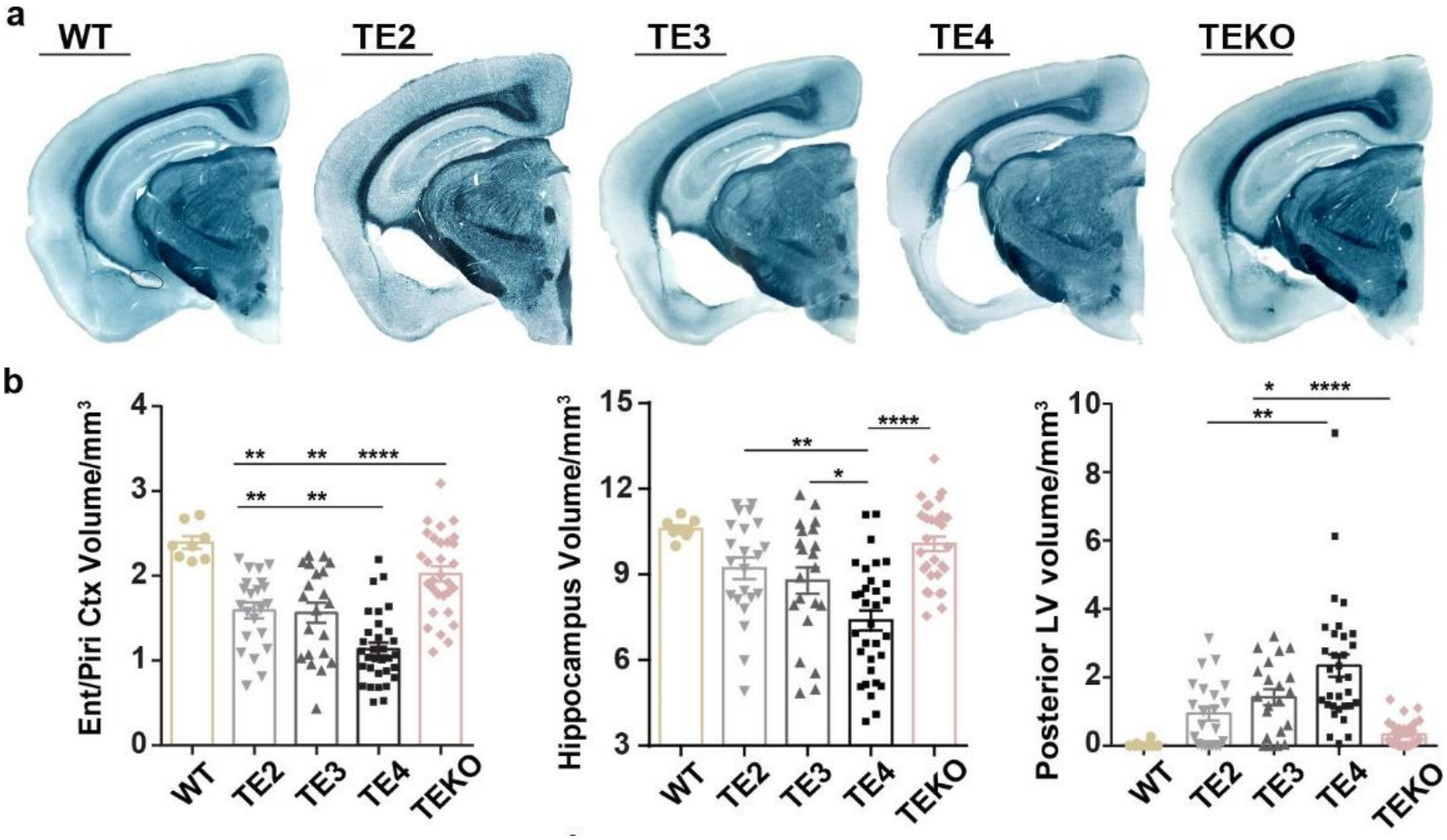
Gallyas silver staining (C) and thioflavin S staining (E)





Yoshiyama *et al.*, Neuron, 2007

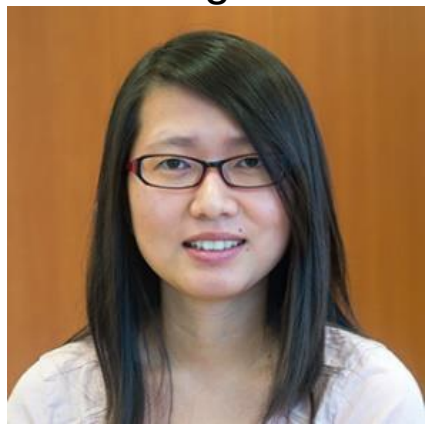
Marked increase in cortical and hippocampal atrophy in P301S/E4 Tau Tg mice at 9 months of age: Little to no injury in the absence of ApoE



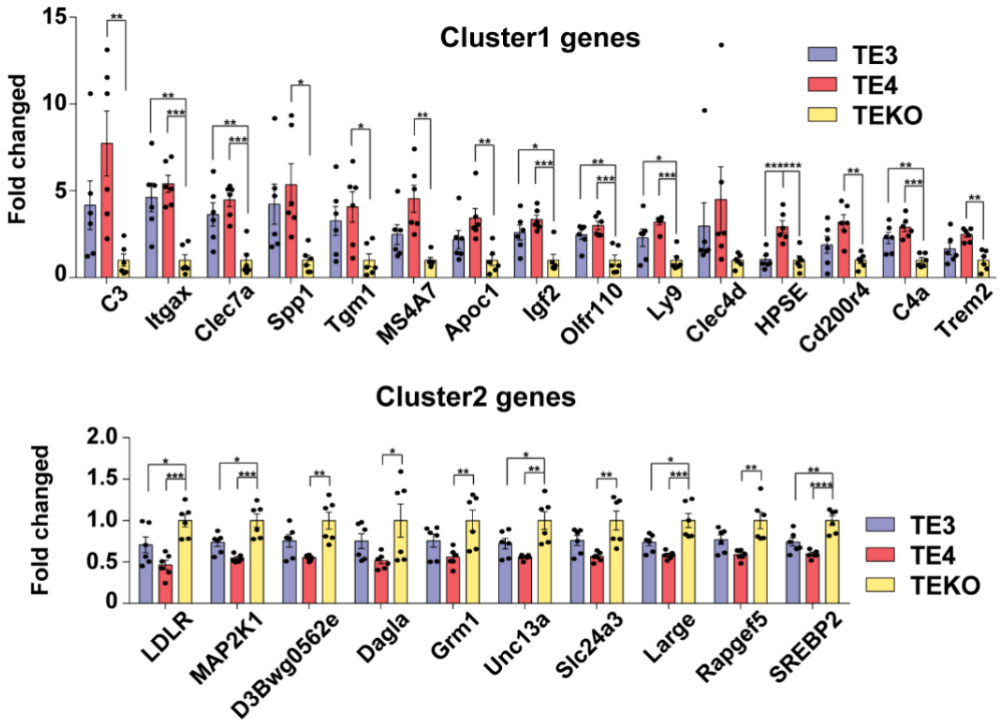
TE: P301S/ApoE
WT: Non-tau transgenic

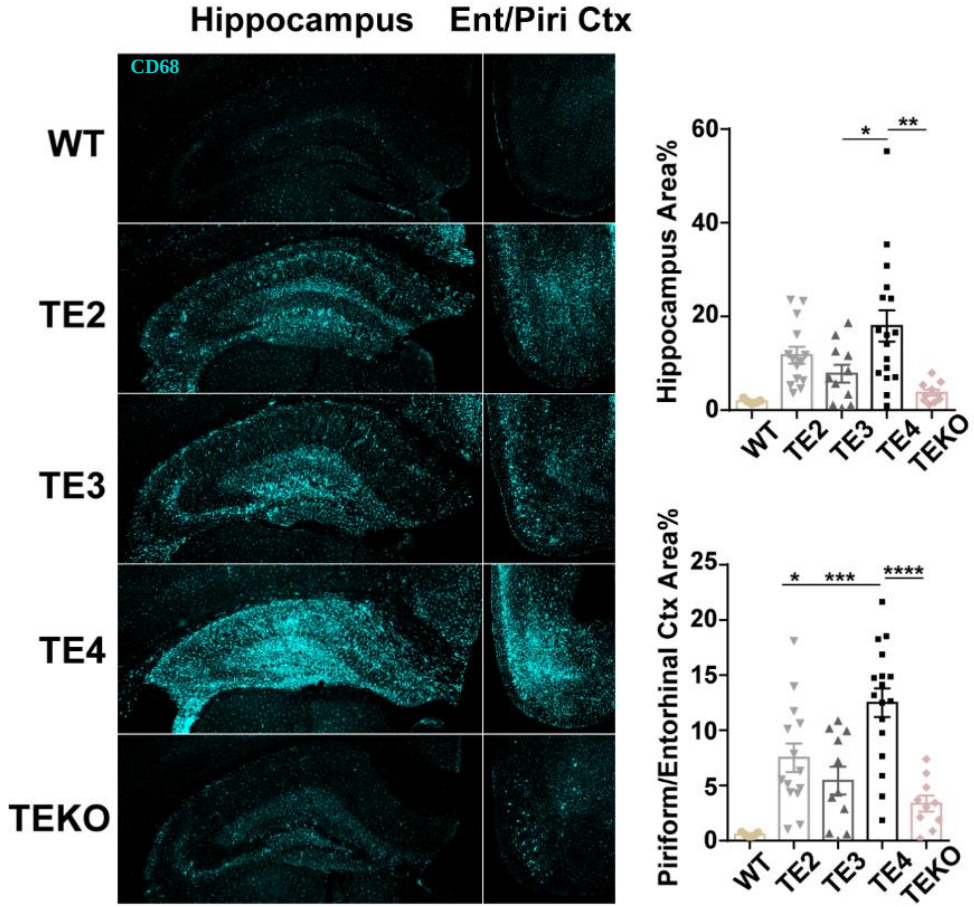
Shi et al. Nature 2017. Sep 28;549(7673):523-527.

Yang Shi



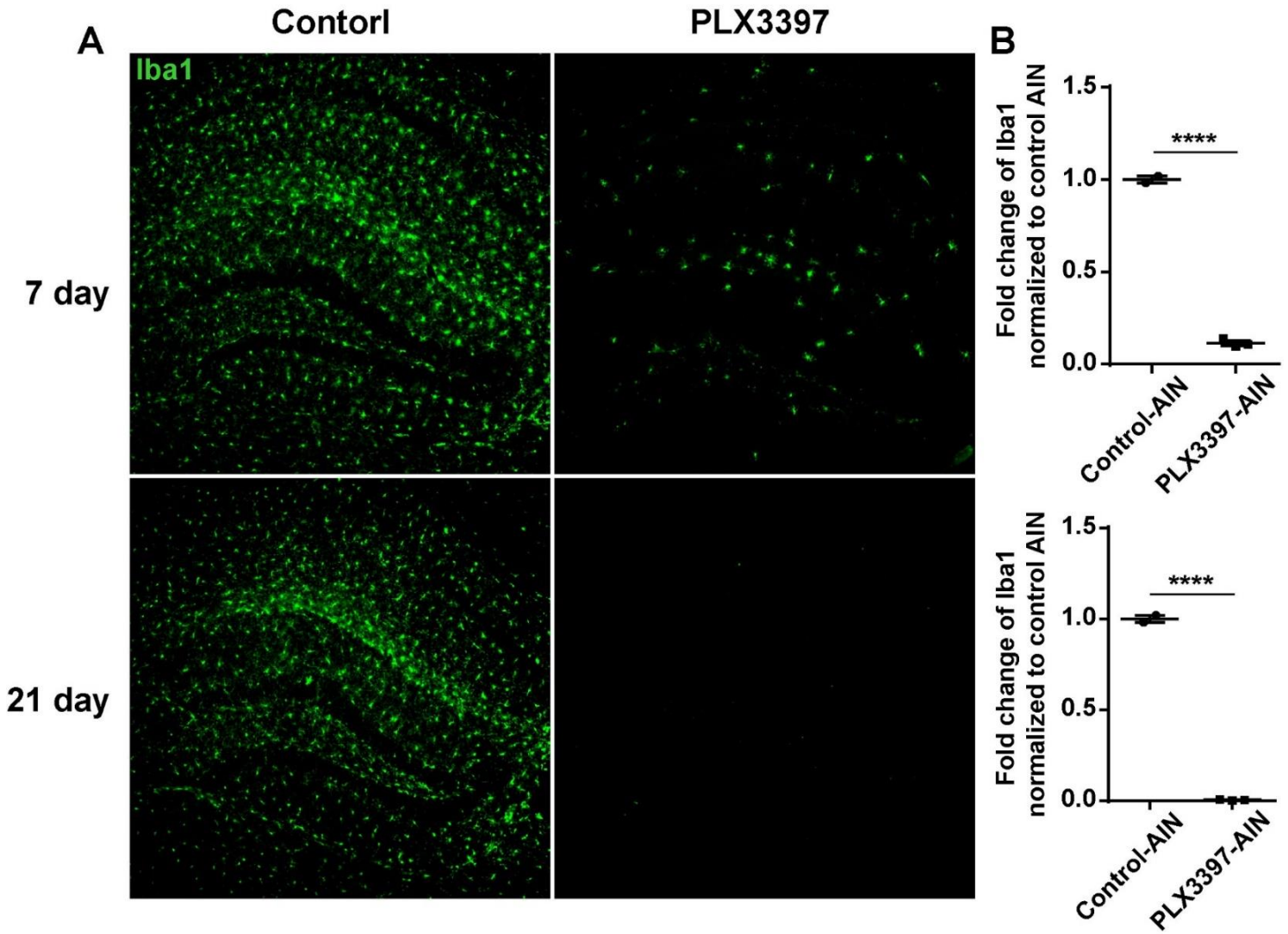
Marked increase in inflammatory microglial genes and down regulation of microglial homeostatic genes in P301S Tau Tg mice expressing human apoE4



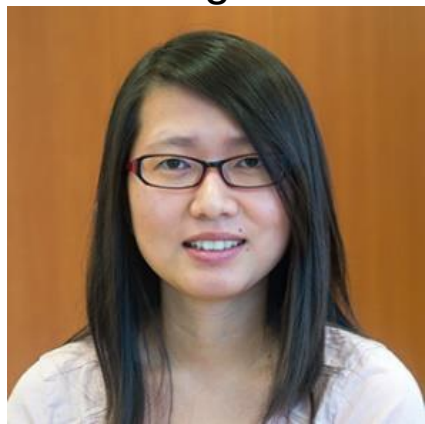


Shi *et al, Nature*, 2017

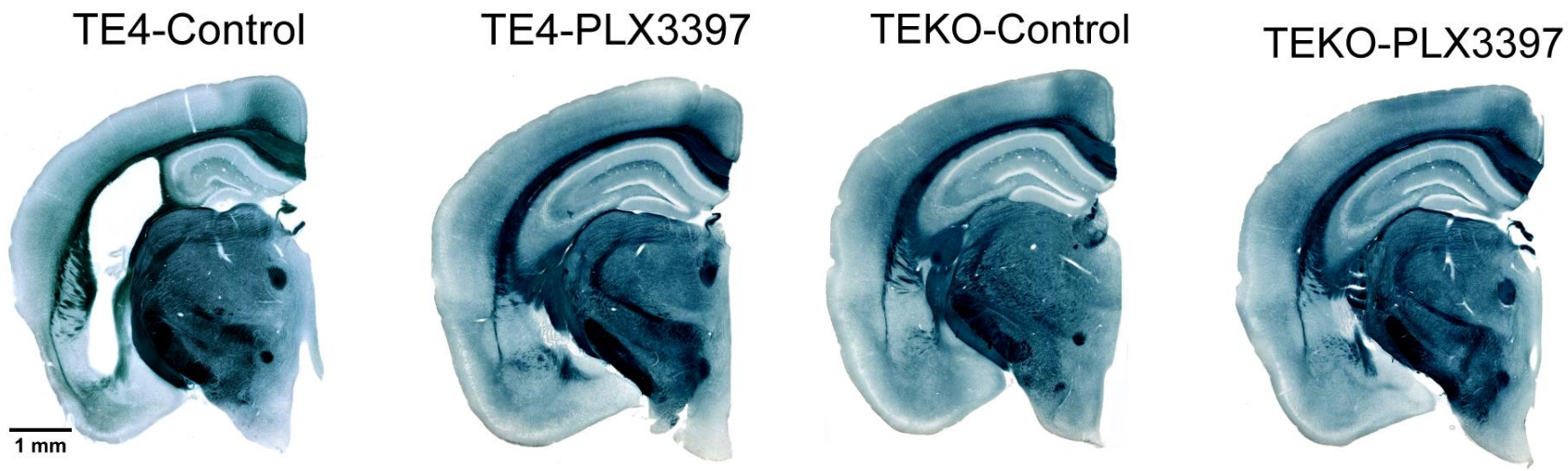
ChoPLX3397 (500 mg/kg) virtually ablates virtually all microglia by 21 days



Yang Shi



Microglia drive APOE-dependent neurodegeneration in a tauopathy model



Shi Y et al. J Exp Med. 2019 Nov 4;216(11):2546-2561. doi: 10.1084/jem.20190980

Similar results reported in:

Mancuso R, et al. Brain. 2019 Oct 1;142(10):3243-3264. doi: 10.1093/brain/awz241.

Article

Microglia-mediated T cell infiltration drives neurodegeneration in tauopathy

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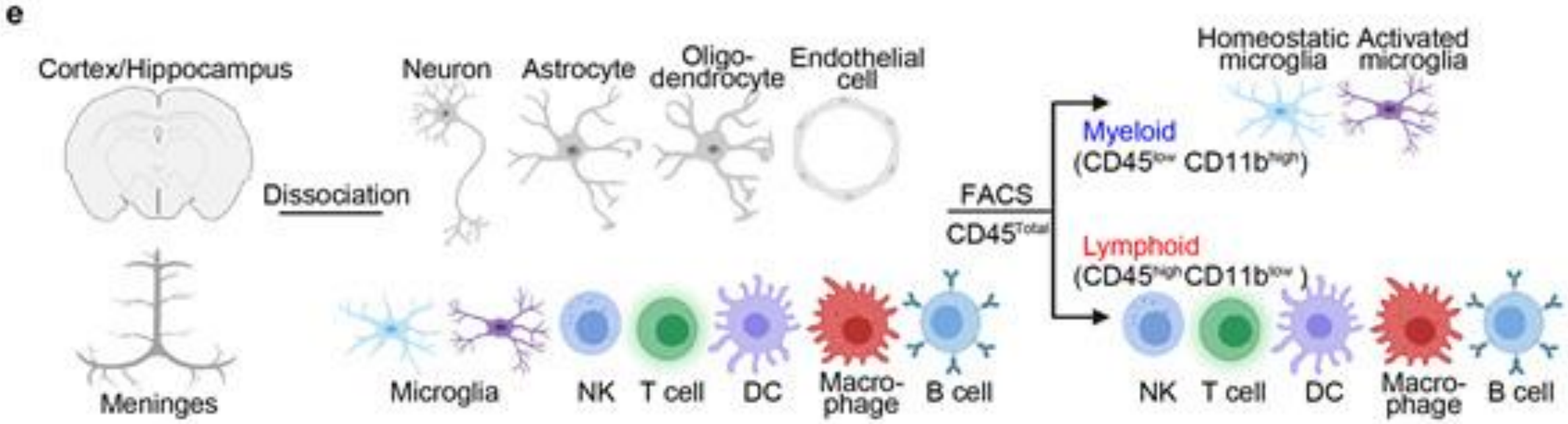
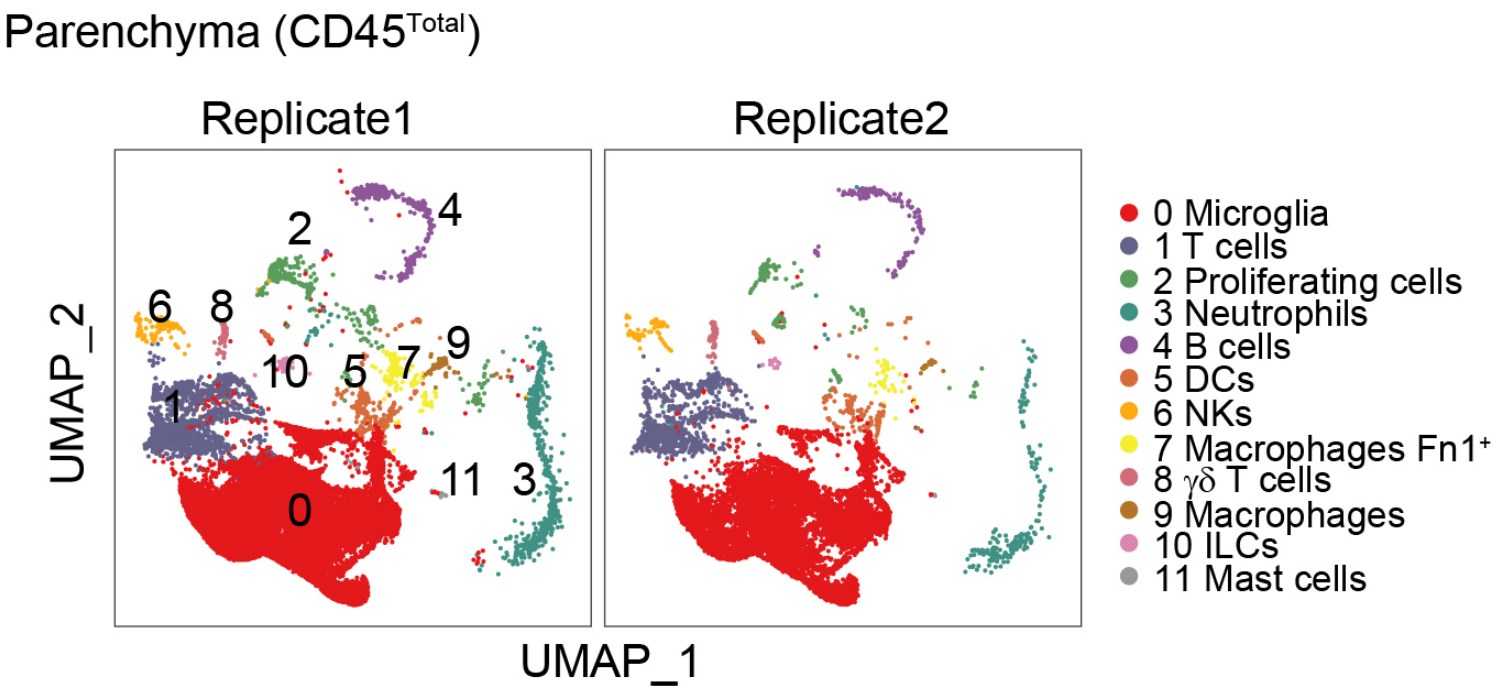
Xiaoying Chen[1], Maria Firulyova[2], Melissa Manis[1], Jasmin Herz[3,4], Igor Smirnov[3,4], Ekaterina Aladyeva[3], Chanung Wang[1], Xin Bao[1], Mary Beth Finn[1], Hao Hu[1], Irina Shchukina[3], Min Woo Kim[3,4], Carla M. Yuede[1], Jonathan Kipnis[1,3,4], Maxim N. Artyomov[3], Jason D. Ulrich[1] & David M. Holtzman[1,4]✉

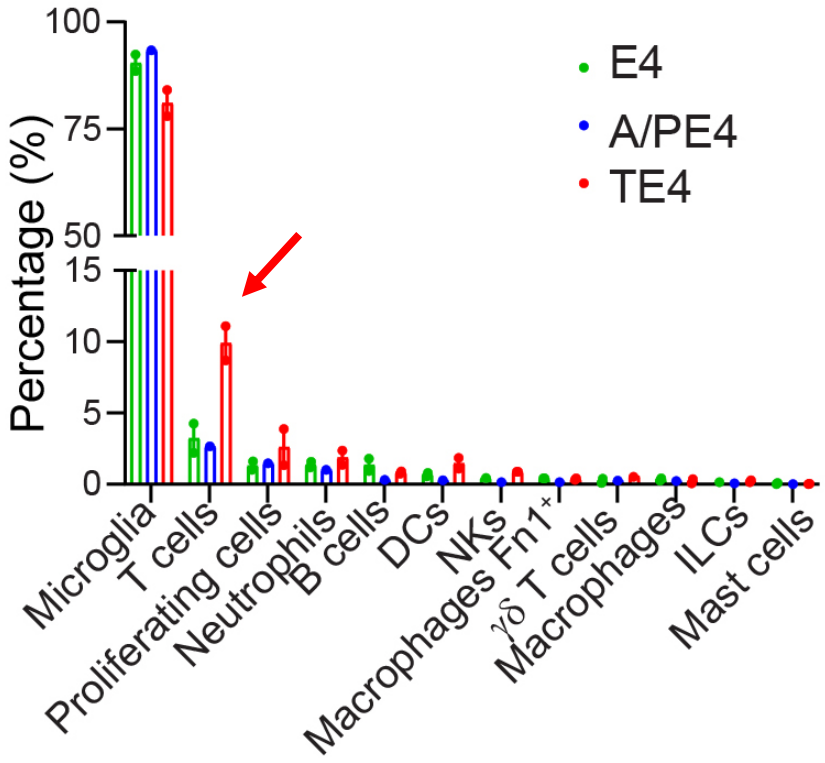
Nature. 2023 Mar 8. doi: 10.1038/s41586-023-05788-0. Online ahead of print. PMID: 36890231

What happens more globally to the immune cell populations in the presence of amyloid vs. in the setting of tau-mediated neurodegeneration?

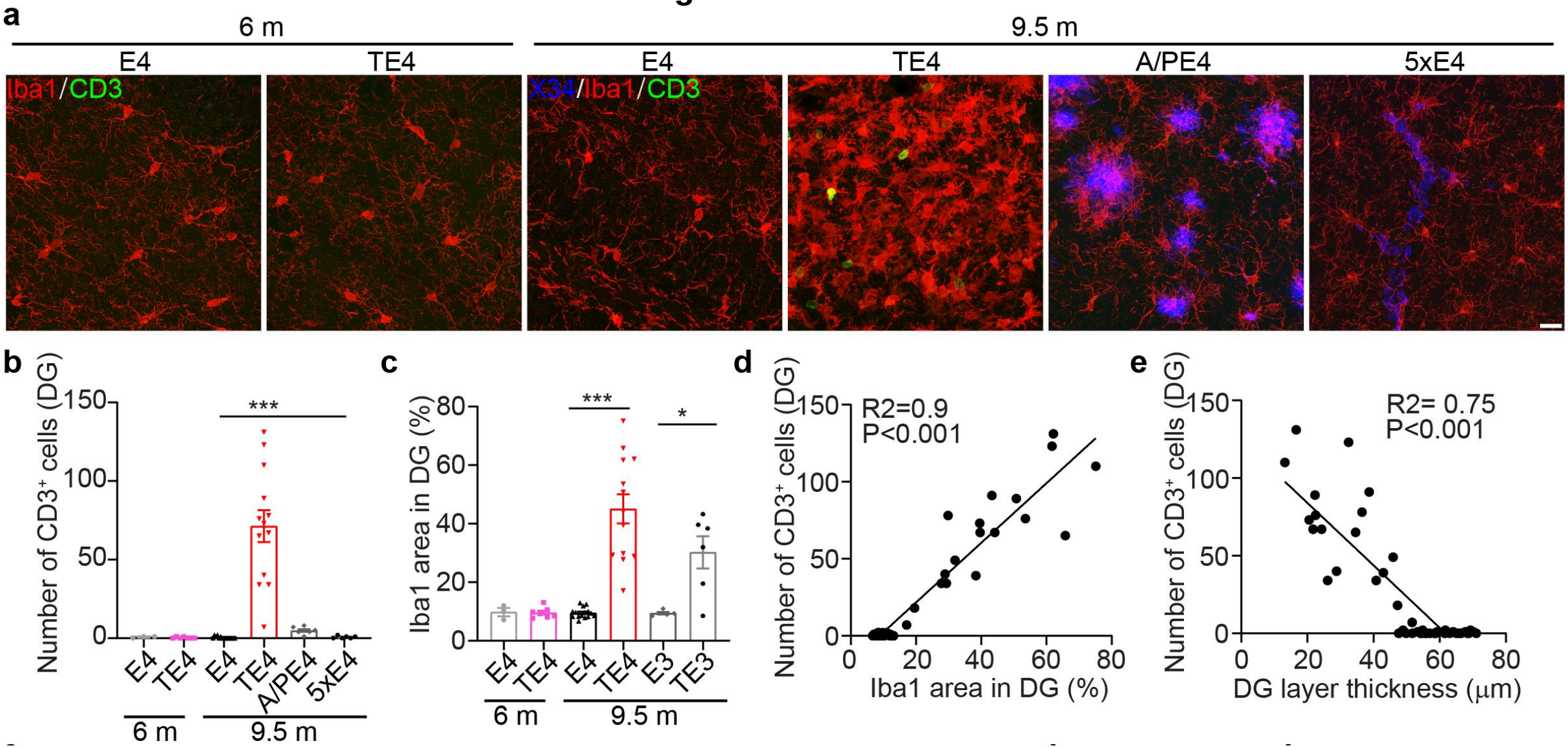


Single immune cell RNA profiling reveals large increase in T cells in the presence of tau but not amyloid pathology

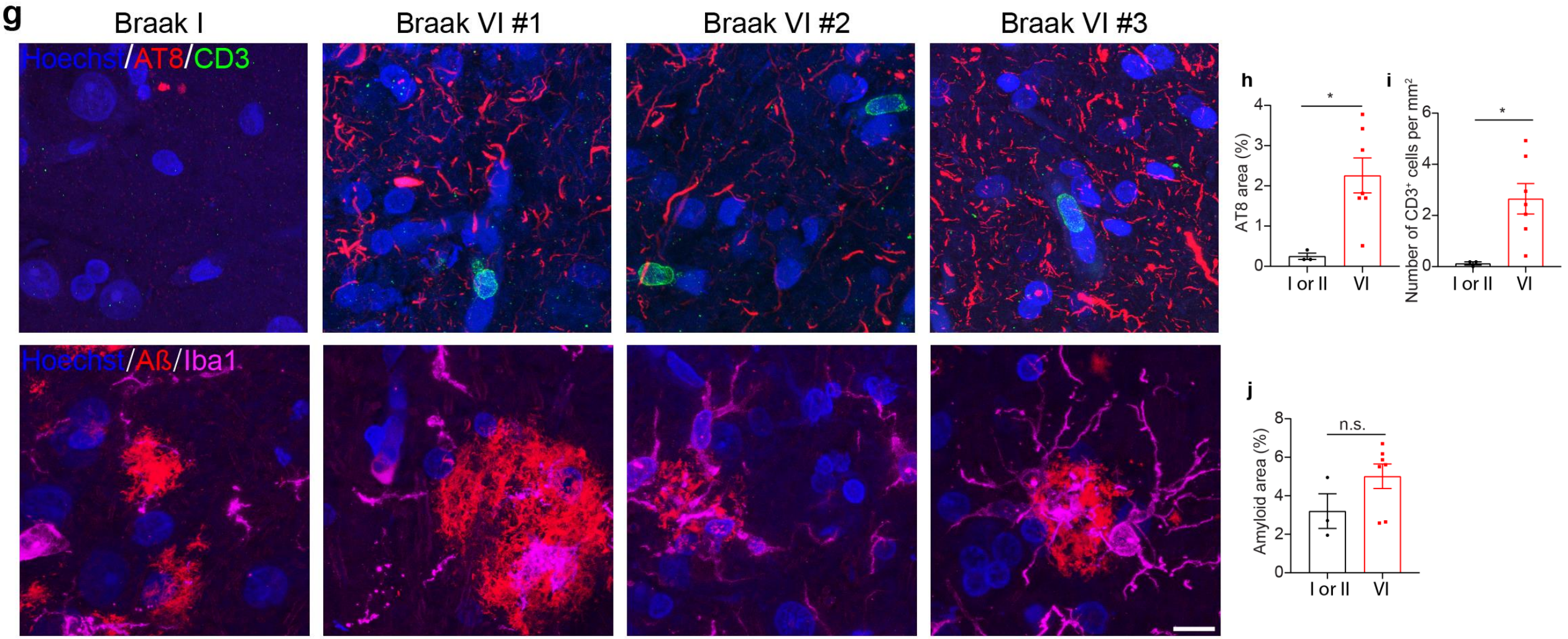




Increase in T-cells in hippocampus of P301S Tau mice correlates with reactive microglia and neuronal loss



Increase in CD3-positive T-cells in areas of the AD brain with a large burden of tauopathy



T cells enter the brain in the presence of tauopathy

Neuro–degenerative Diseases

Brief Communication

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Extravascular CD3+ T Cells in Brains of Alzheimer Disease Patients Correlate with Tau but Not with Amyloid Pathology: An Immunohistochemical Study

BRAIN
A JOURNAL OF NEUROLOGY

Hippocampal T cell infiltration promotes neuroinflammation and cognitive decline in a mouse model of tauopathy

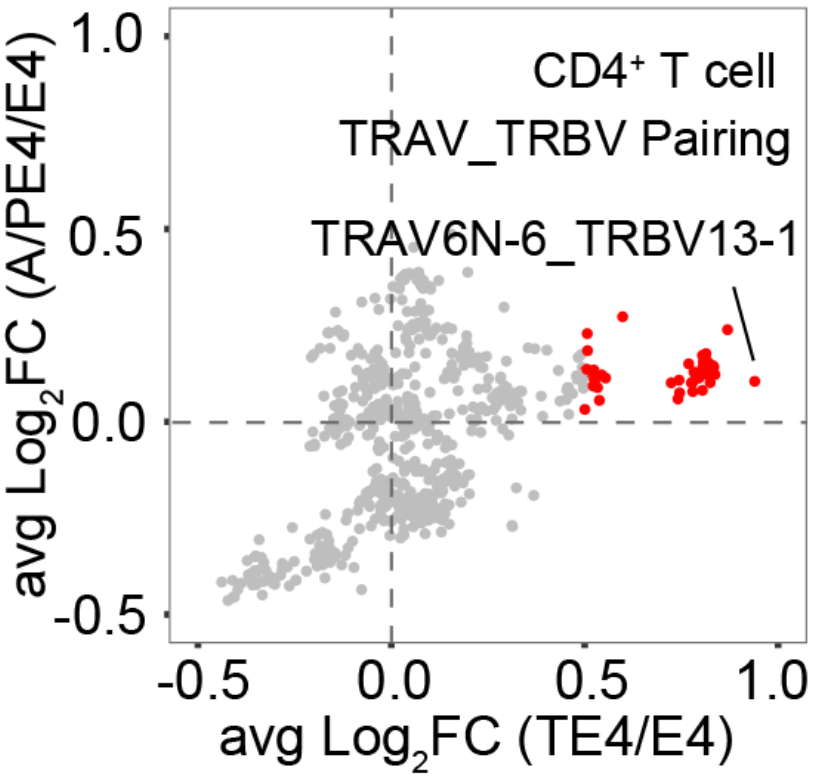
Cyril Laurent,[1] Guillaume Dorothée,[2,3,*] Stéphane Hunot,[4,5,6,7,*] Elodie Martin,[4,]
Yann Monnet,[4,5,6,7] Marie Duchamp,[2,3] Yuan Dong,[2,3] François-Pierre Légeron,[4,5,]
Antoine Leboucher,[1] Sylvie Burnouf,[1] Emilie Faivre,[1] Kévin Carvalho,[1] Raphaëlle C
Nadège Zommer,[1] Dominique Demeyer,[1] Nathalie Jouy,[1,8] Veronique Sazdovitch
Susanna Schraen-Maschke,[1] Cécile Delarasse,[4,5,6,7] Luc Buée[1,#] and David Blum[1,]

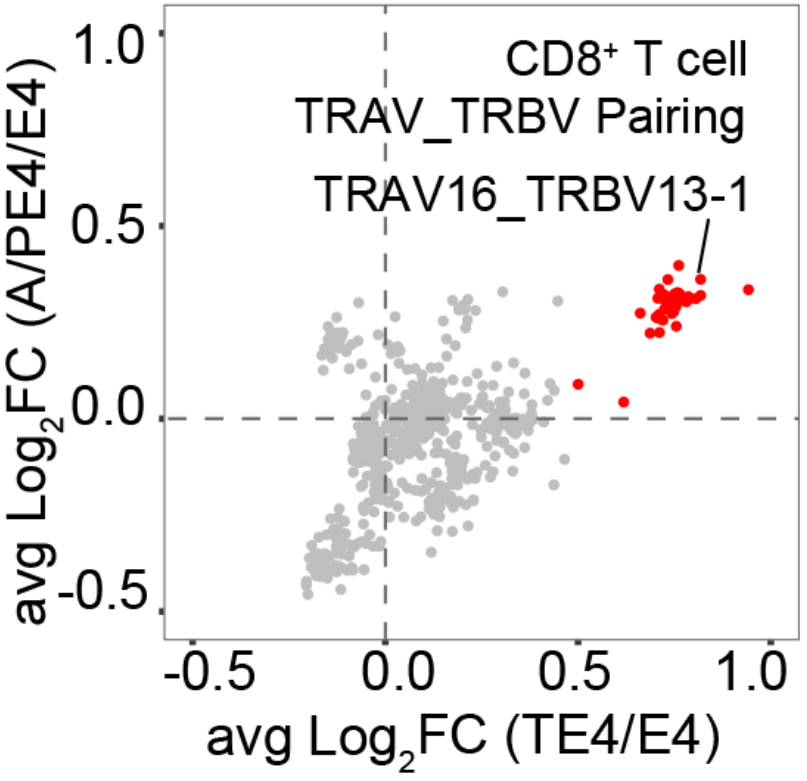
Nature. 2020 January ; 577(7790): 399–404. doi:10.1038/s41586-019-1895-7.

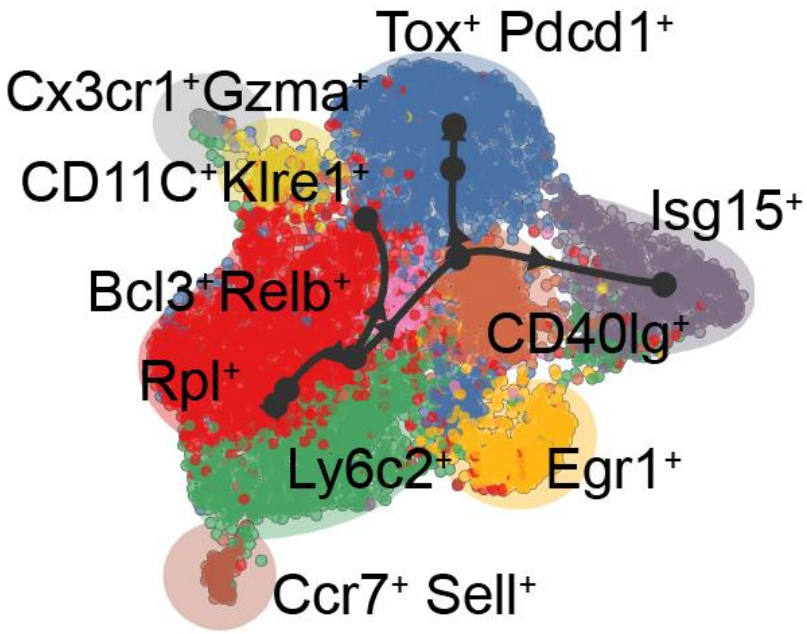
Clonally expanded CD8 T cells patrol the cerebrospinal fluid in Alzheimer's disease

David Gate[1,2,*], Naresha Saligrama[3], Olivia Leventhal[1], Andrew C. Yang[4,5], Michael S. Unger[6,7], Jinte Middeldorp[1,2,8], Kelly Chen[1], Benoit Lehallier[1,2], Divya Channappa[1], Mark B. De Los Santos[1], Alisha McBride[1,2], John Pluvinage[1,9,10], Fanny Elahi[11], Grace Kyin-Ye Tam[1,12], Yongha Kim[1,12], Michael Greicius[1,12], Anthony D. Wagner[13,14], Ludwig Aigner[6,7], Douglas R. Galasko[15], Mark M. Davis[3,16,17], Tony Wyss-Coray[1,2,5,14,18,*]

Shift of T cells from activated to exhausted states with unique TCR clonal expansion in tauopathy

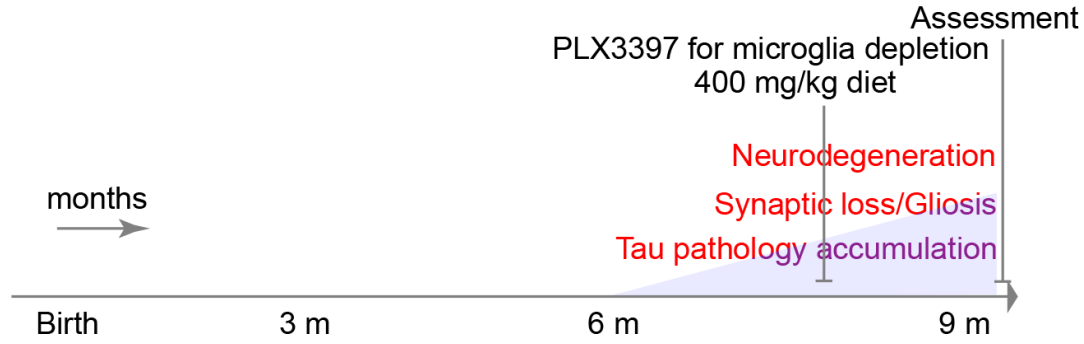


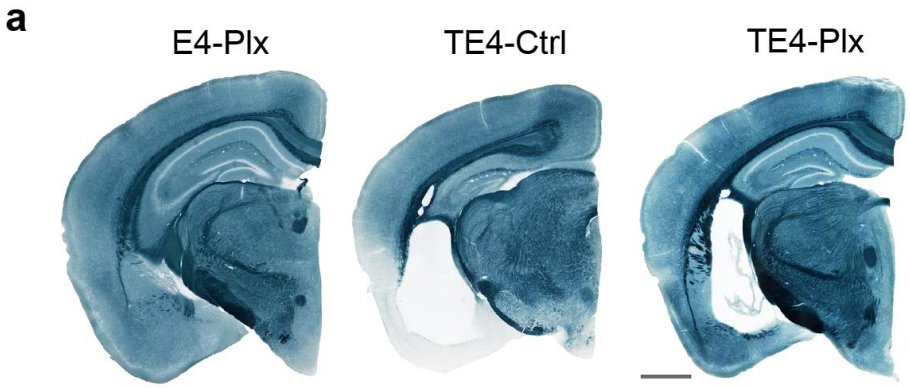


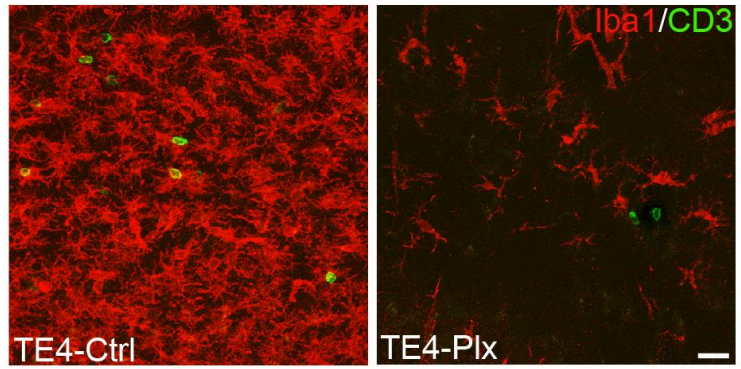


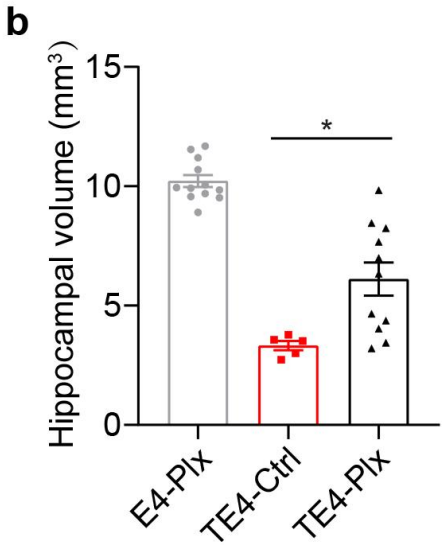
Activated microglia recruit T cells into the brain parenchyma

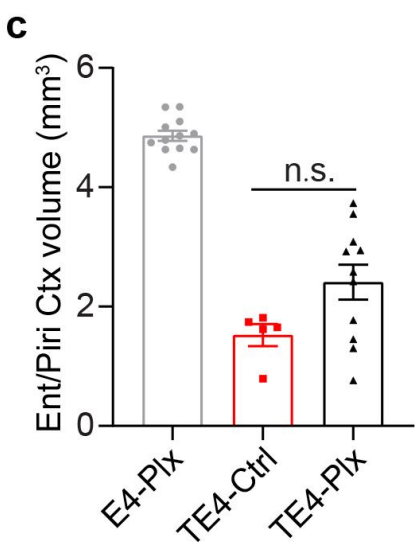
Activated microglia → T cells

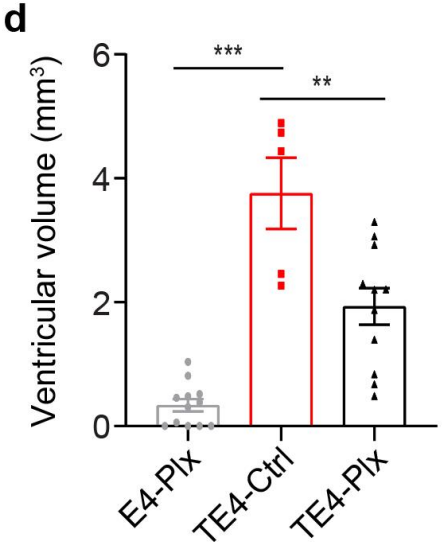


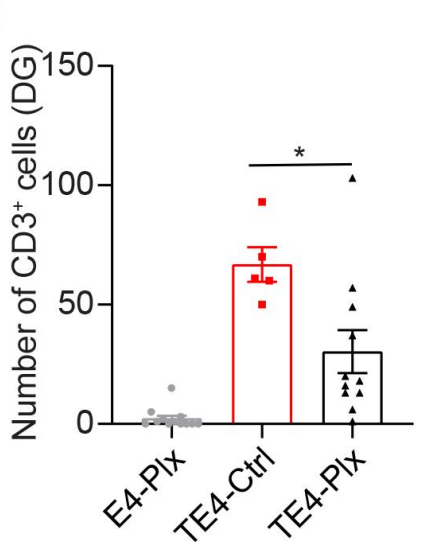




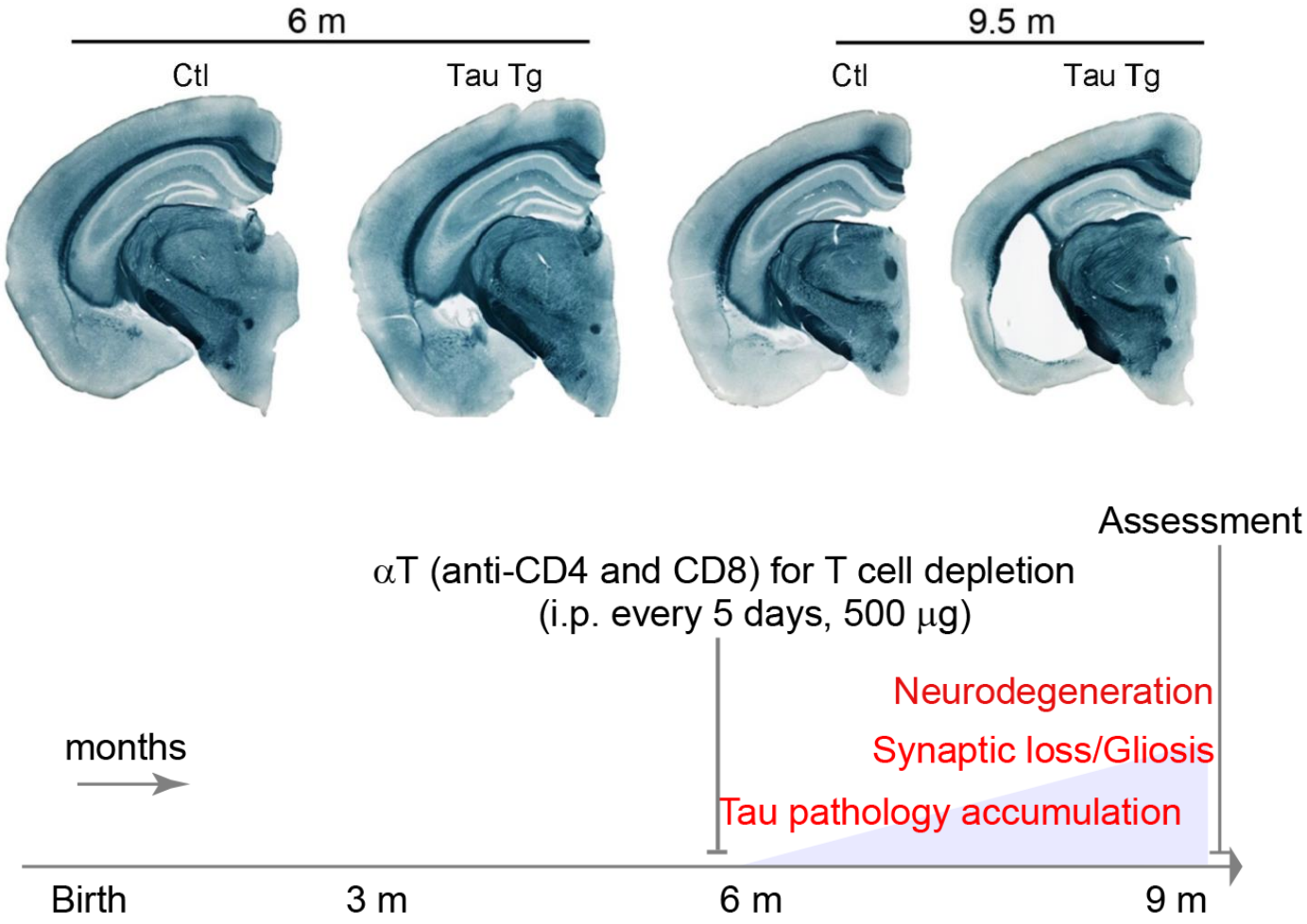




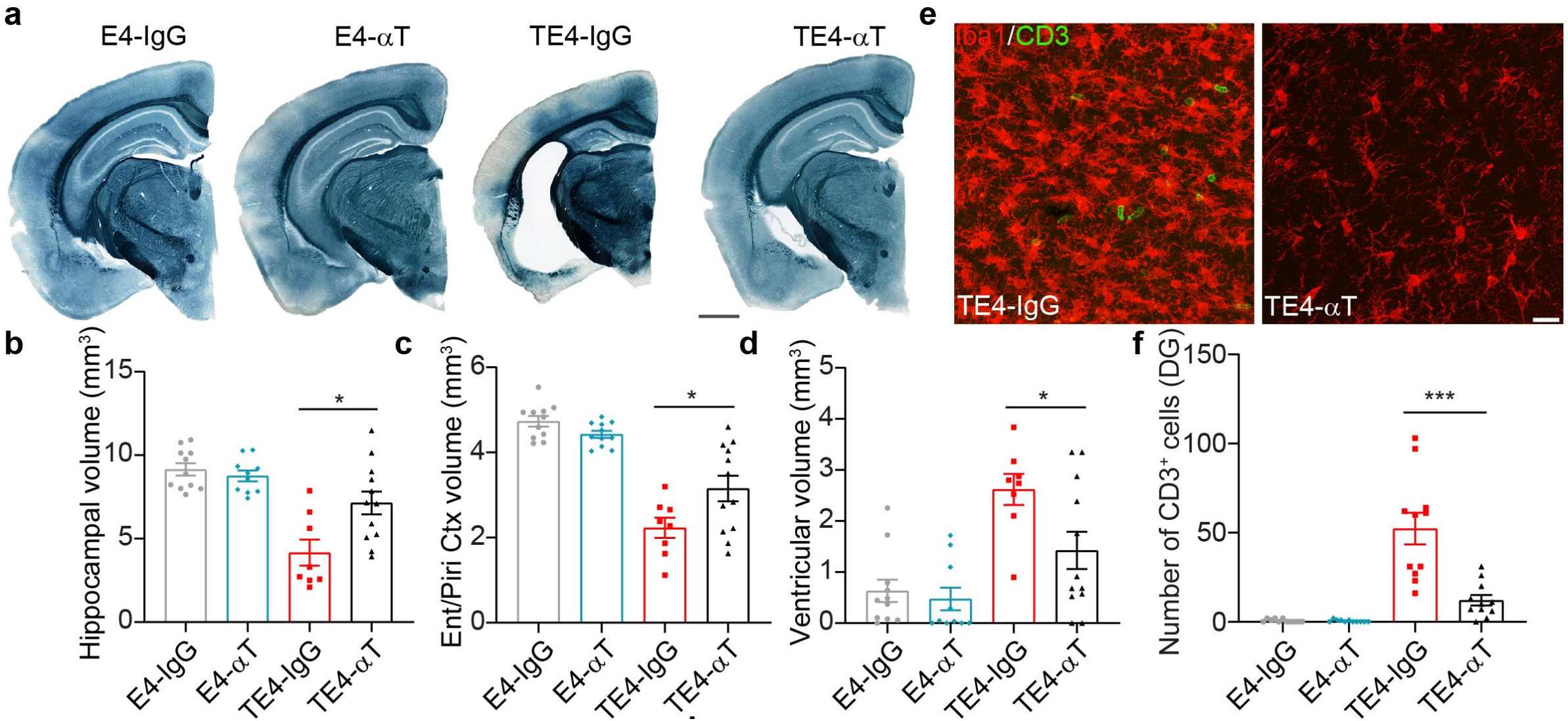




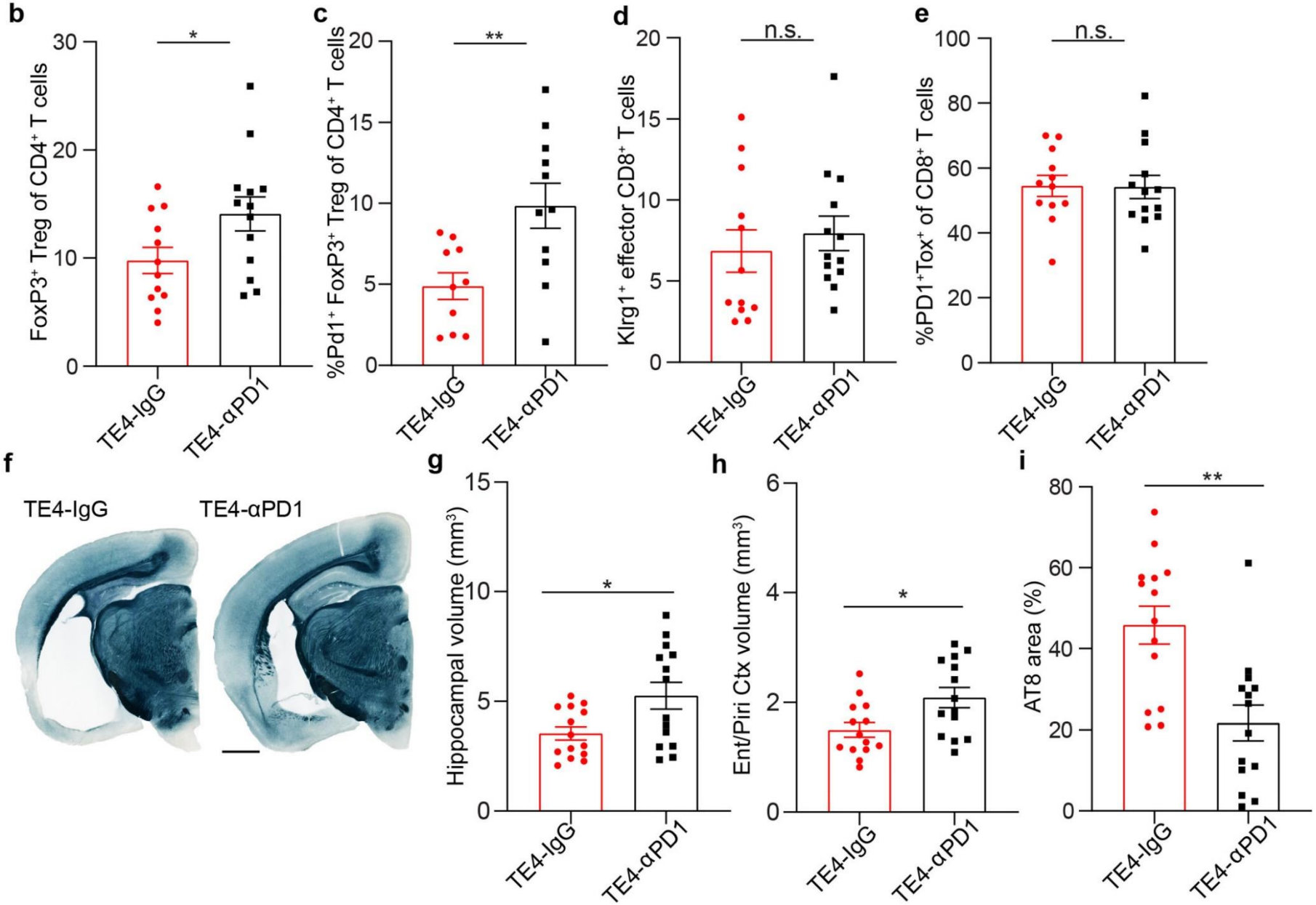
Does infiltration of T cells directly lead to neurodegeneration?

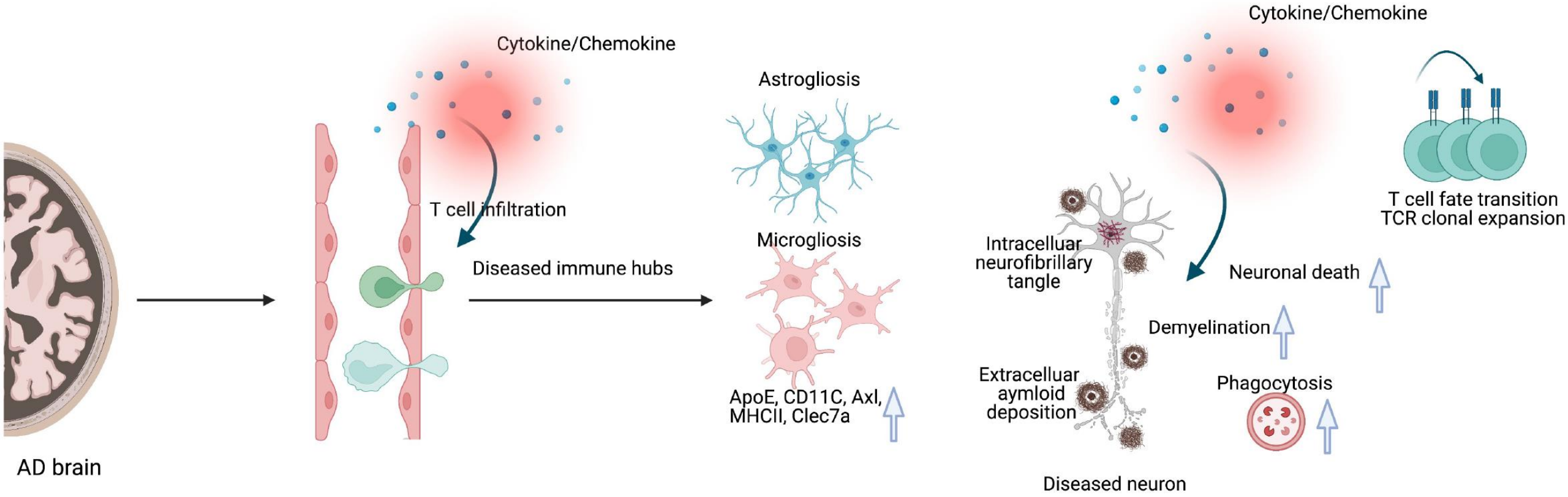


T cell depletion protects against brain atrophy



Anti-PD1 antibody increases T regs in brain and decreases Tau-mediated neurodegeneration





Summary

- ✓ T cells increase in areas with tauopathy in AD brain.
- ✓ T cells have a unique TCR clonal expansion.
- ✓ T cells interact with activated microglia.
- ✓ T cell depletion protects against tauopathy

Some of many Future Questions

- ➢ How do T cells contribute to neurodegeneration?
- ➢ Do ApoE isoforms enable differential T-cell response to antigen?
- ➢ Which cells are antigen presenting?
- ➢ What are the antigens?

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