



SAA mice exhibit characteristics of CAA and vascular deficits across AD progression

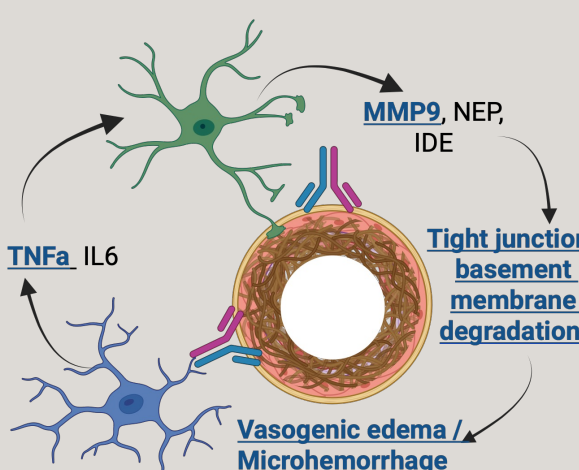
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Background:

- Cerebral amyloid angiopathy (CAA) is a common neuropathological feature of AD characterized by heavy build-up of amyloid-beta proteins along the walls of arteries and arterioles in the brain.

Cerebral amyloid angiopathy (CAA)



- CAA can induce microhemorrhages and local inflammation, and recent trials have shown that anti-amyloid antibody therapies can induce Amyloid-Related Imaging Abnormalities (ARIA)
 - ARIA subtypes:
 - ARIA-E: Edema/Effusion
 - ARIA-H: Hemorrhage
- It is critical to understand the temporal relationship between vascular amyloid deposition and vascular damage in CAA in preclinical models in order to identify mechanisms and targets.
- ARIA is not well understood and there are no current treatments to reduce ARIA incidence.

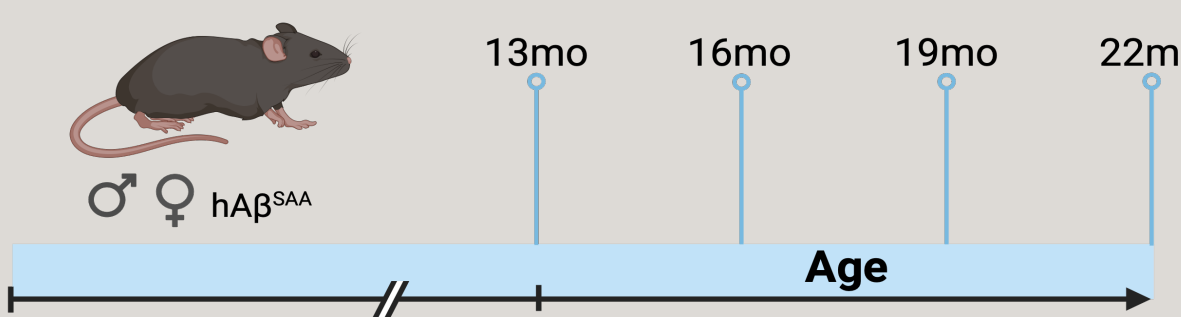
Why characterize this model?

- When characterizing a model, it is important to include timepoints that represent advanced age as this is the biggest risk factor for Alzheimer's disease and dementia.
- It is important to fully characterize new models in all capacities
 - We focused on characterizing the overall build up of CAA, plaques, and vasculature as the model ages

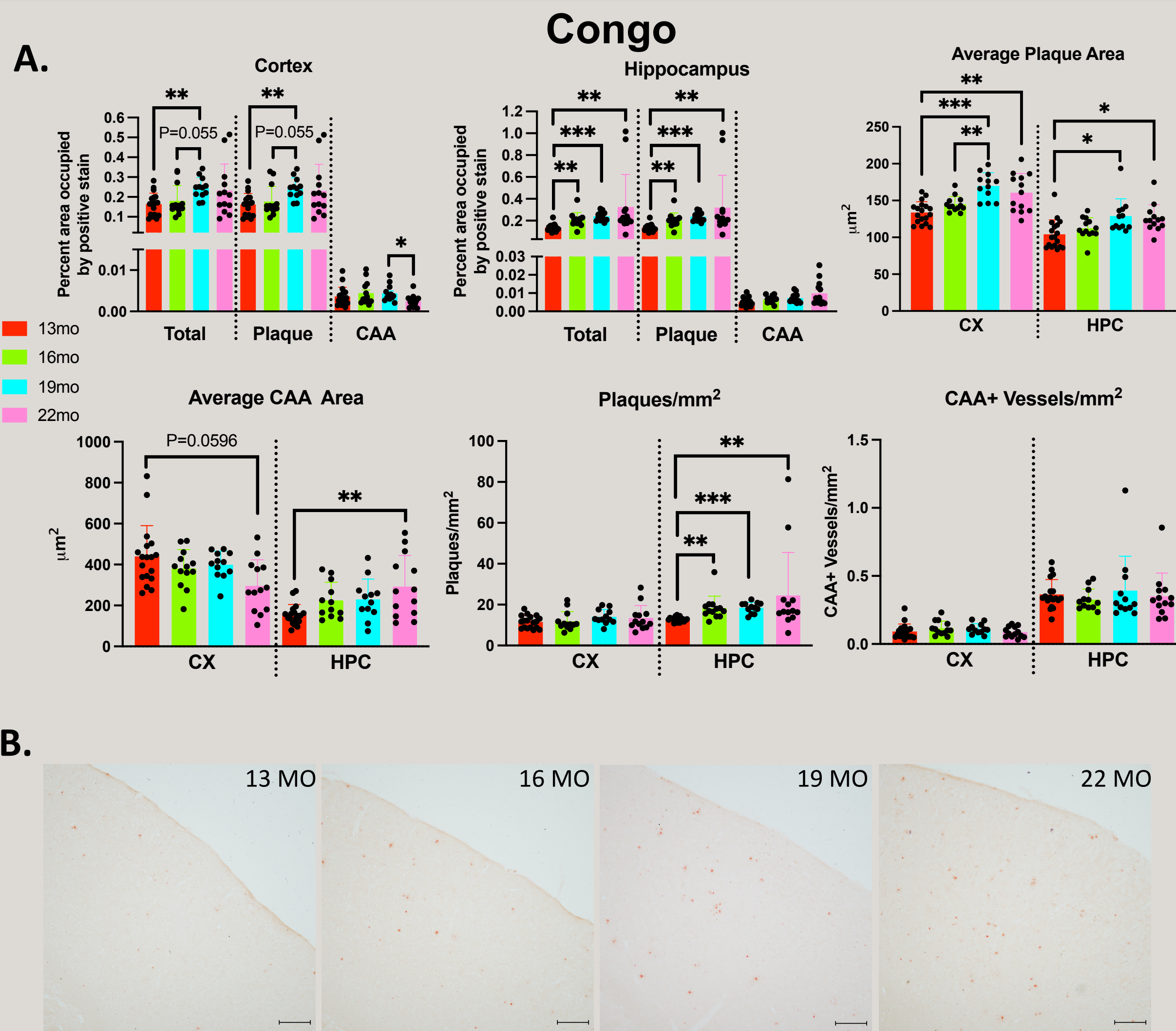
Methods:

Model: APP^{SAA} humanized Aβ knock-in mouse model with Swedish, Arctic, Austrian mutations

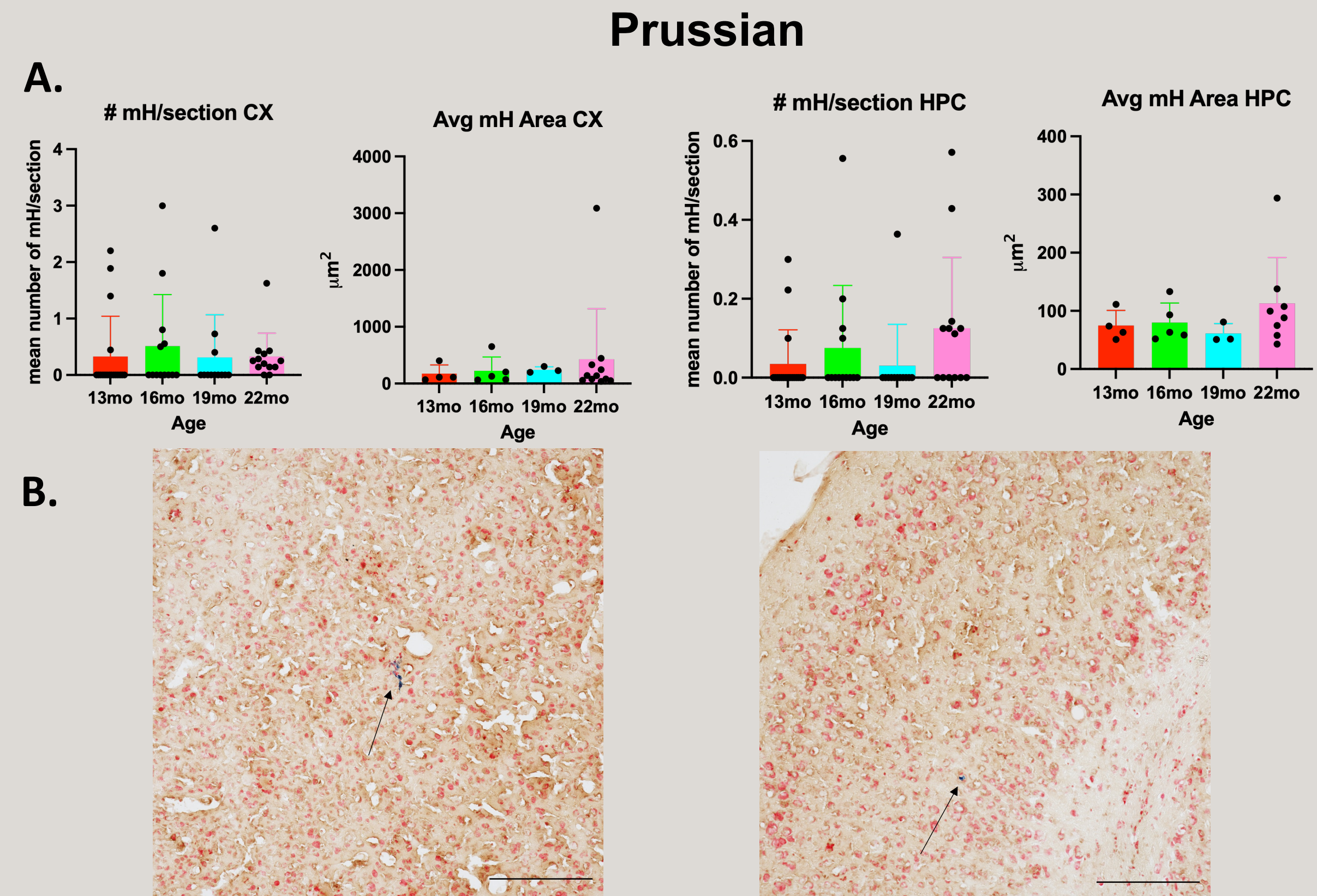
- N=57 total, ~9 males and ~5 females per group



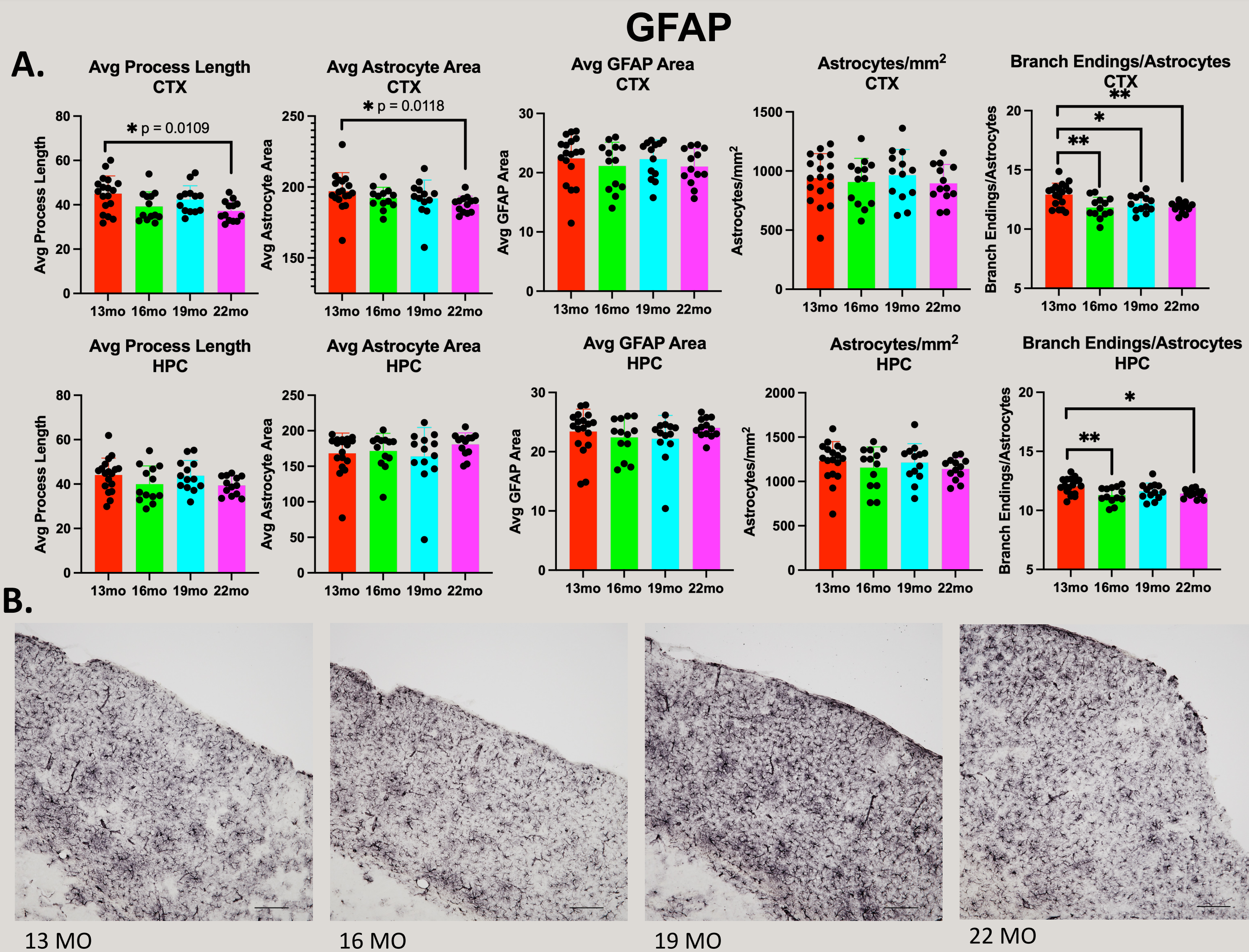
- Intervals: 13, 16, 19, and 22 months
- Immunohistochemistry/Histology
 - Congo Red, Prussian Blue (microhemorrhages), and GFAP (astrocytes)



A) Quantification of Congo red staining in 13, 16, 19 and 22mo hAβ^{SAA} cortex (CX) and hippocampus (HPC). Tukey-post hoc or Steel Dwass tests for multiple comparisons were performed depending on distribution of data. * indicates P<0.05, ** indicates P<0.01, *** indicates P<0.0001. B) Representative images of Congo red staining at 10x magnification. Scale bar in all images = 200μm.



A) Quantification of Prussian blue staining in 13, 16, 19 and 22mo hAβ^{SAA} cortex (CX) and hippocampus (HPC). Tukey-post hoc or Steel Dwass tests for multiple comparisons were performed depending on distribution of data. * indicates P<0.05, ** indicates P<0.01, *** indicates P<0.0001. B) Representative images of Prussian blue positive hemorrhages at 20x magnification. Scale bar in all images = 200μm.



A) Quantification of GFAP staining in 13, 16, 19 and 22mo hAβ^{SAA} cortex (CX) and hippocampus (HPC). Tukey-post hoc or Steel Dwass tests for multiple comparisons were performed depending on distribution of data. * indicates P<0.05, ** indicates P<0.01, *** indicates P<0.0001. B) Representative images of GFAP at 10x magnification. Scale bar in all images = 200μm.

Future Directions and Conclusions

- IBA 1 staining
 - We would like to see microglial activation in the tissue.
- DP71 staining
 - As a marker for astrocyte end feet, we would like to do this stain to see how the vascular morphology of the model changes over time.
- Targeted transcriptomics
 - Earlier studies indicated that this mouse model is prone to ARIA when given immunotherapies without a high CAA burden. We would like to further explore the vascular and inflammatory responses as the model ages.
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