DAY 4
ABSTRACT 4

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Establishing glial responses to anti-Aβ immunotherapy through single-cell RNAseq to gain insights into mechanisms of ARIA

Abstract:

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Background:

While anti-Aβ immunotherapies effectively clear Aβ plaques, mouse and human data show consistent and significant cerebrovascular adverse events of this treatment approach. Anti-Aβ immunotherapies have been plagued in clinical trials by the occurrence of amyloid-related imaging abnormalities (ARIA), signifying cerebrovascular disruptions of the edema (ARIA-E) or hemorrhagic (ARIA-H) type in the brain. Despite these cerebrovascular adverse effects, the FDA granted accelerated approval to aducanumab and lecanemab. *However, our mechanistic understanding underlying ARIA remains minimal. Elucidating the mechanism(s) by which anti-Aβ antibodies cause ARIA is critical towards improving safety of these therapies for AD.*

Method:

In the current study, we aimed to determine the glial responses to anti-Ab antibodies with the hypothesis that astrocytes and microglia have temporal cellular shifts that contribute to cerebrovascular dysfunction after acute anti-Aβ antibody administration. To identify changes in glial gene expression in response to acute anti-Aβ antibody we performed a single cell sequencing and digital spatial profiling (DSP) on 14mo Tg2576 APP mice (Fig. 1). We observed differences in size of clusters between anti-Aβ (6E10) and IgG control (IgG1) intracranial injections after 24hr and 3days, suggesting some clusters of cells respond to anti-Aβ in a time-dependent or antibody manner (Fig. 2).

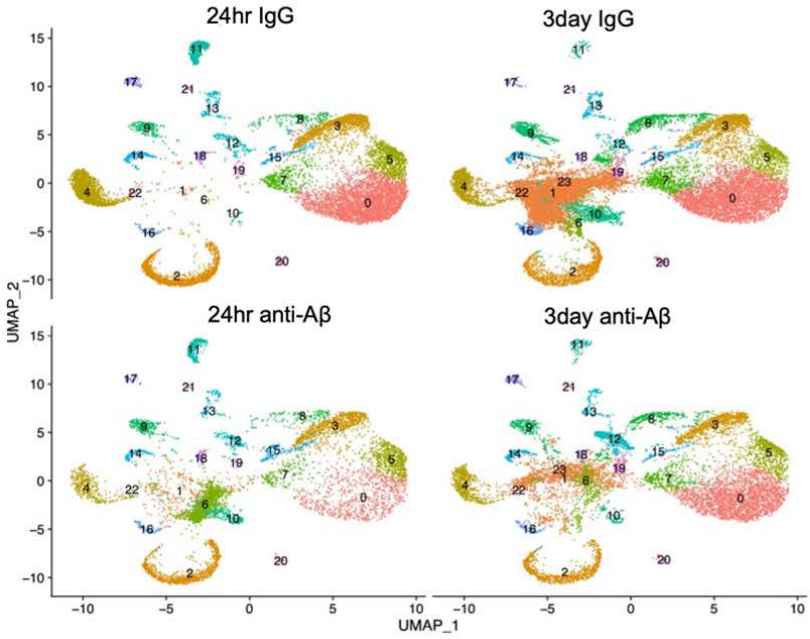
Result:

Preliminary data identified some of the clusters as microglia (Cx3cr1) and astrocytes (Aldoc), as well as oligodendrocytes (Plp). Apoe was increased in multiple cell types. DSP on these mice is ongoing, however we aim

to further characterize the transcriptional profile of glia at the vasculature, and in the vicinity of Aβ plaques and cerebral amyloid angiopathy (CAA). Contralateral hemispheres are utilized for downstream validation studies.

Conclusion:

Our work will elucidate the mechanisms of anti-Aβ antibody-induced glial response and establish the role of astrocytes and microglia in cerebrovascular dysfunction and ARIA. This work is critical to improve safety and increase generalizability of these therapies.



Cluster	% of 24hr IgG cells	% of 3day IgG cells	% of 24hr Anti-Aβ	% of 3day Anti-Aβ
0	31.4%	21.4%	10.6%	23.4%
1	0.5%	33.6%	3.9%	15.4%
2	12.9%	5.7%	12.0%	8.1%
3	11.2%	6.6%	11.5%	8.3%
4	13.5%	5.1%	4.9%	5.7%
6	0.2%	2.5%	18.7%	6.1%