Enhanced Brain Delivery of Sabirnetug in a Mouse Model of Alzheimer's Disease after Fusion with an anti-Transferrin Receptor Antibody Fragment

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Disclosures

Dr. Shughrue is an employee of Acumen Pharmaceuticals and is a minor shareholder.

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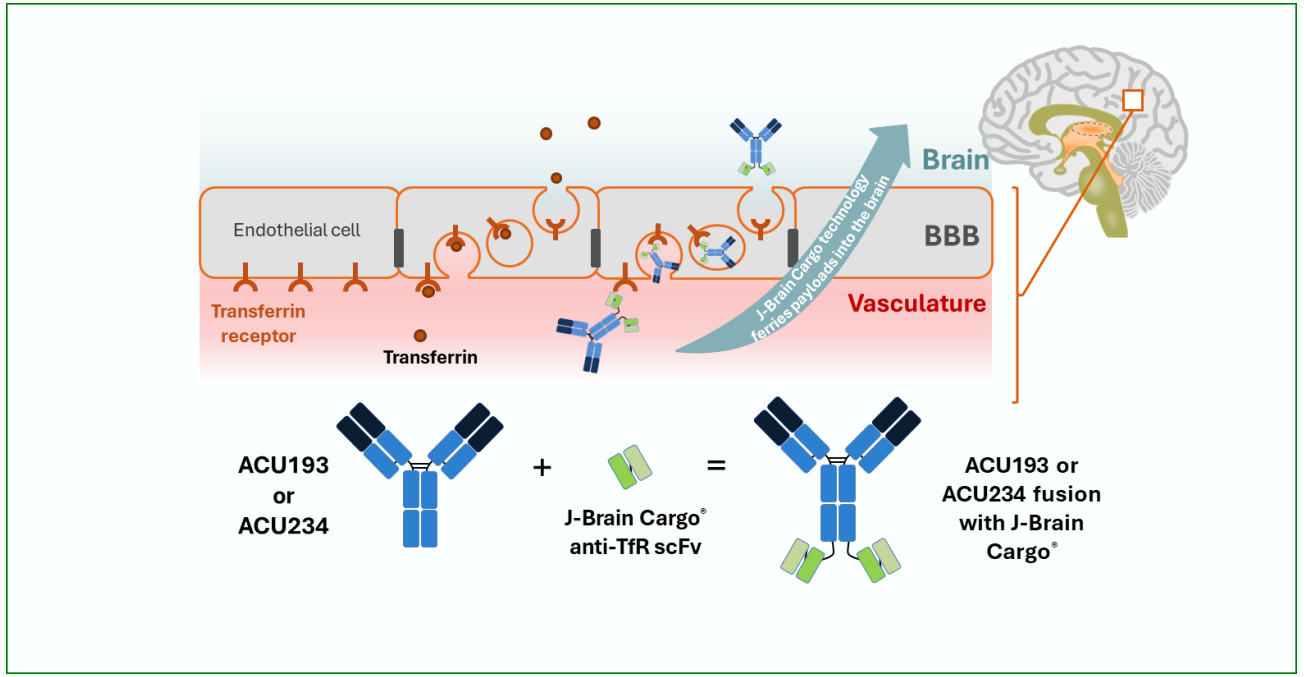
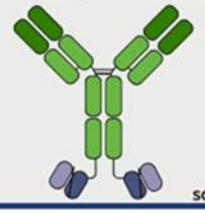
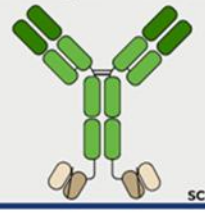
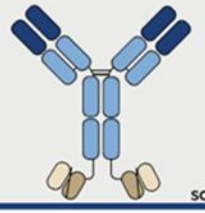
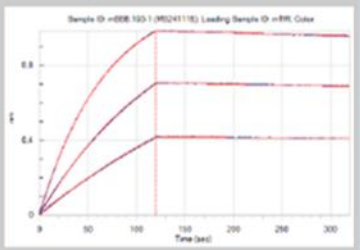
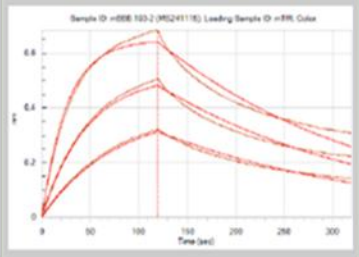
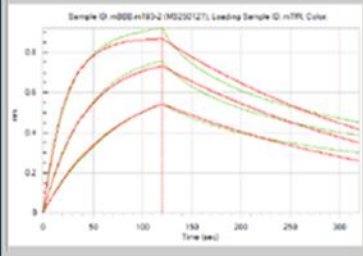
TfR-Mediated Uptake: A Strategy for Enhanced Brain Delivery (EBD) of Immunotherapeutic Agents

- Receptor-mediated transcytosis has been used to enhance brain delivery of molecules including therapeutic antibodies
- JCR has developed a library of J-Brain Cargo fragments (scFv and VHH) that target the transferrin receptor (TfR)
- We used the J-Brain Cargo® technology for enhanced brain delivery of anti-Aβ oligomer mAbs, the candidate AD immunotherapeutic sabirnetug (ACU193) or the non-clinical antibody ACU234.
- The present study evaluated bispecific proteins of ACU193 or ACU234 with scFv fragments targeting the murine TfR for pharmacokinetic and Aβ oligomer binding properties in ARTE10 mouse.



The Development of Mouse Conjugate Antibodies to Explore Aβ Target Engagement in a Mouse Model of AD

No.	mBBB.193-1	mBBB.193-2	mBBB.234-2	ACU193	ACU234
Candidate Molecules	sabirnetug-scFv #1 bivalent 	sabirnetug-scFv #2 bivalent 	ACU234-scFv #2 bivalent 		
Affinity to mTfR*	0.33 nM	5.34 nM	3.52 nM	N/A	N/A
Sensor gram	Kon (1/Ms): 3.71E+05 Kdis(1/s): 1.24E-04 	Kon (1/Ms): 8.54E+05 Kdis(1/s): 4.56E-03 	Kon (1/Ms): 1.05E+06 Kdis(1/s): 3.68E-03 	N/A	N/A
AβO (K_D)*	0.60 nM	0.45 nM	2.48 nM	2.18 nM	2.39 nM
Monomer (K_D)	6.91 μM	5.87 μM	8.60 μM	3.76 μM	12.73 μM

- ACU193, ACU234, and the bispecific constructs bind Aβ oligomers and monomers with similar affinity

**K_Ds in table from same run (n = 1); Aggregate AβO K_D for all other runs, ACU193 = 0.5 ± 0.2 nM (n = 5); ACU234 = 0.6 ± 0.4 nM (n = 2)*

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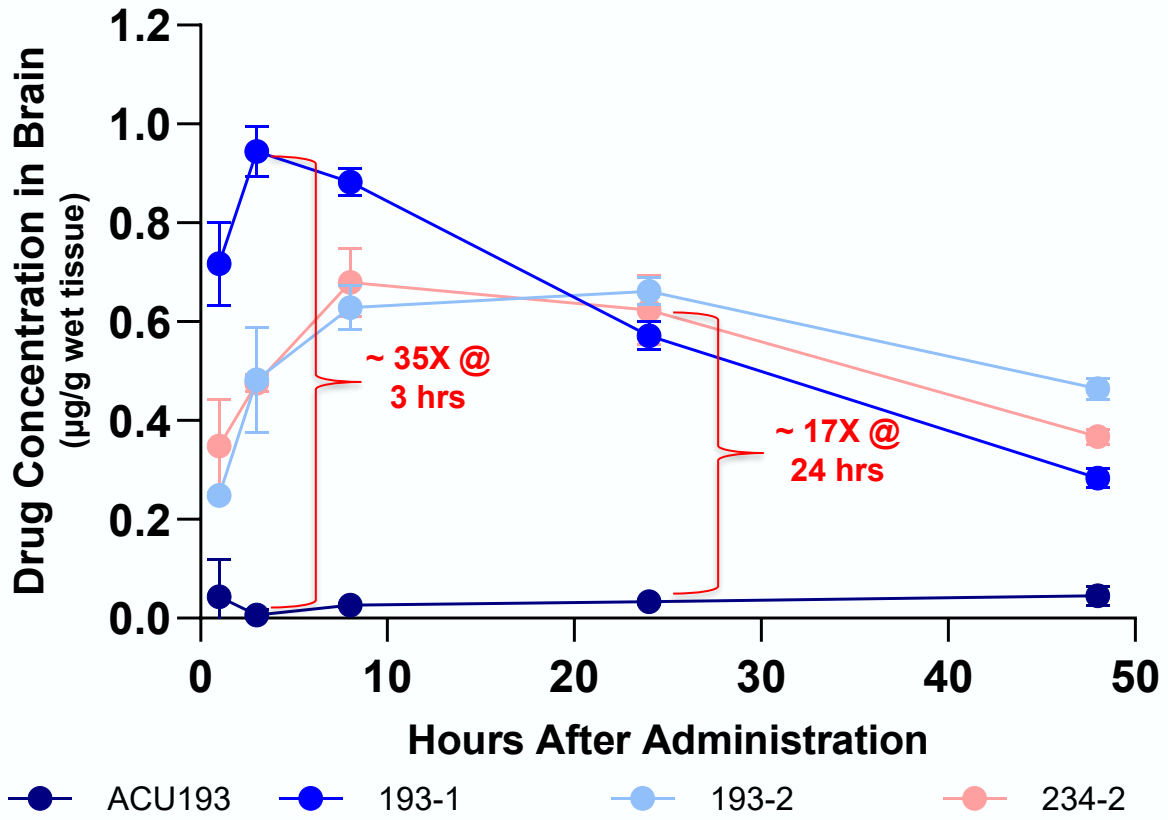
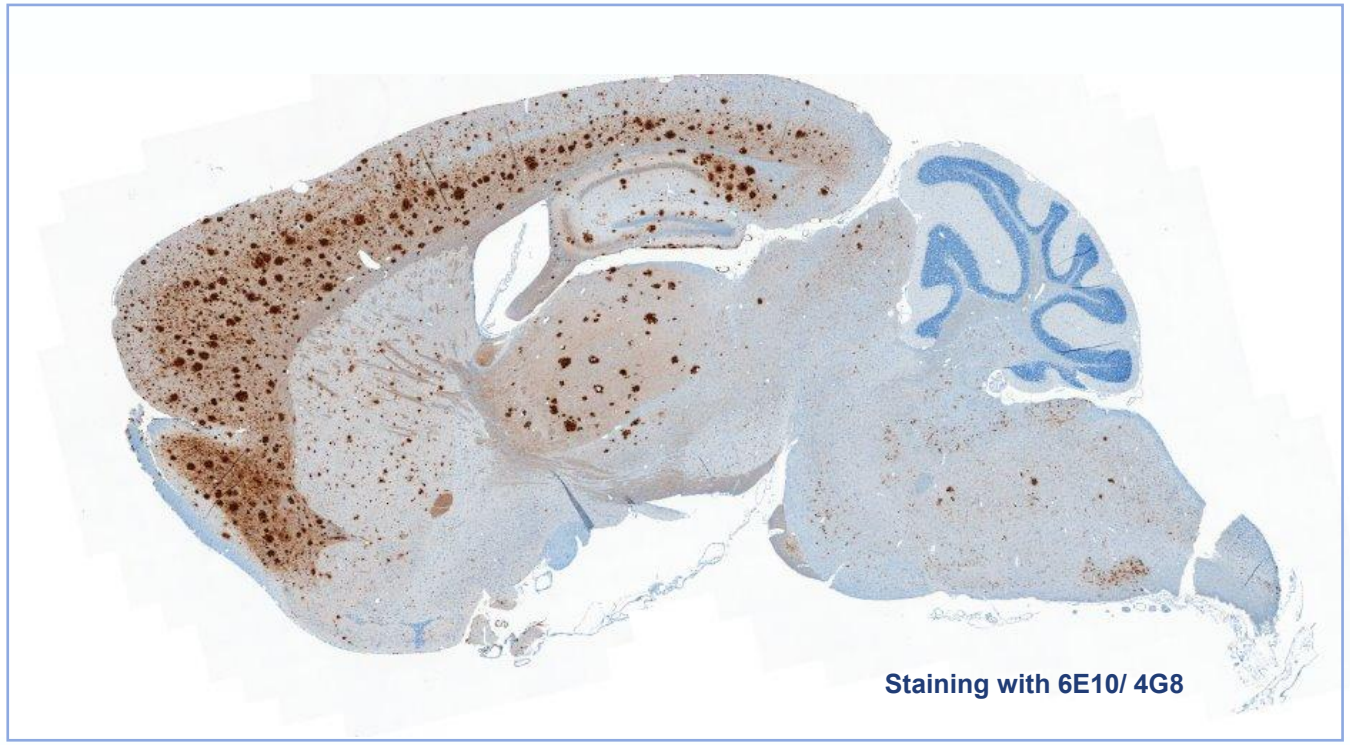
Initial Work in Wild Type Mice Demonstrated that the Mouse Conjugate Antibodies had Enhanced Brain Levels when Compared with ACU193



Animals dosed IV at 2 mg/kg

Use of the ARTE10 AD Mouse Model to Investigate Target Engagement of Bispecific Antibodies

Aβ species in the ARTE10 Mouse Brain



Swedish mutation of the human APP (KM670/671NL) and the M146V mutation (PS1M146V) of human presenilin 1

Study Design:

- Inject 10-month-old male ARTE10 mice (n=9) IV with 2 mg/kg of
  - 193-1
  - 193-2
  - 234-2
  - ACU193
  - ACU234
- 24 hours post injection collect brains and process for histology (n=4) or ECL* (n=5)
- Use ECL or IHC to assess the ability of antibodies to penetrate the BBB and engage Aβ amyloid (target)

*ECL = electrochemiluminescence

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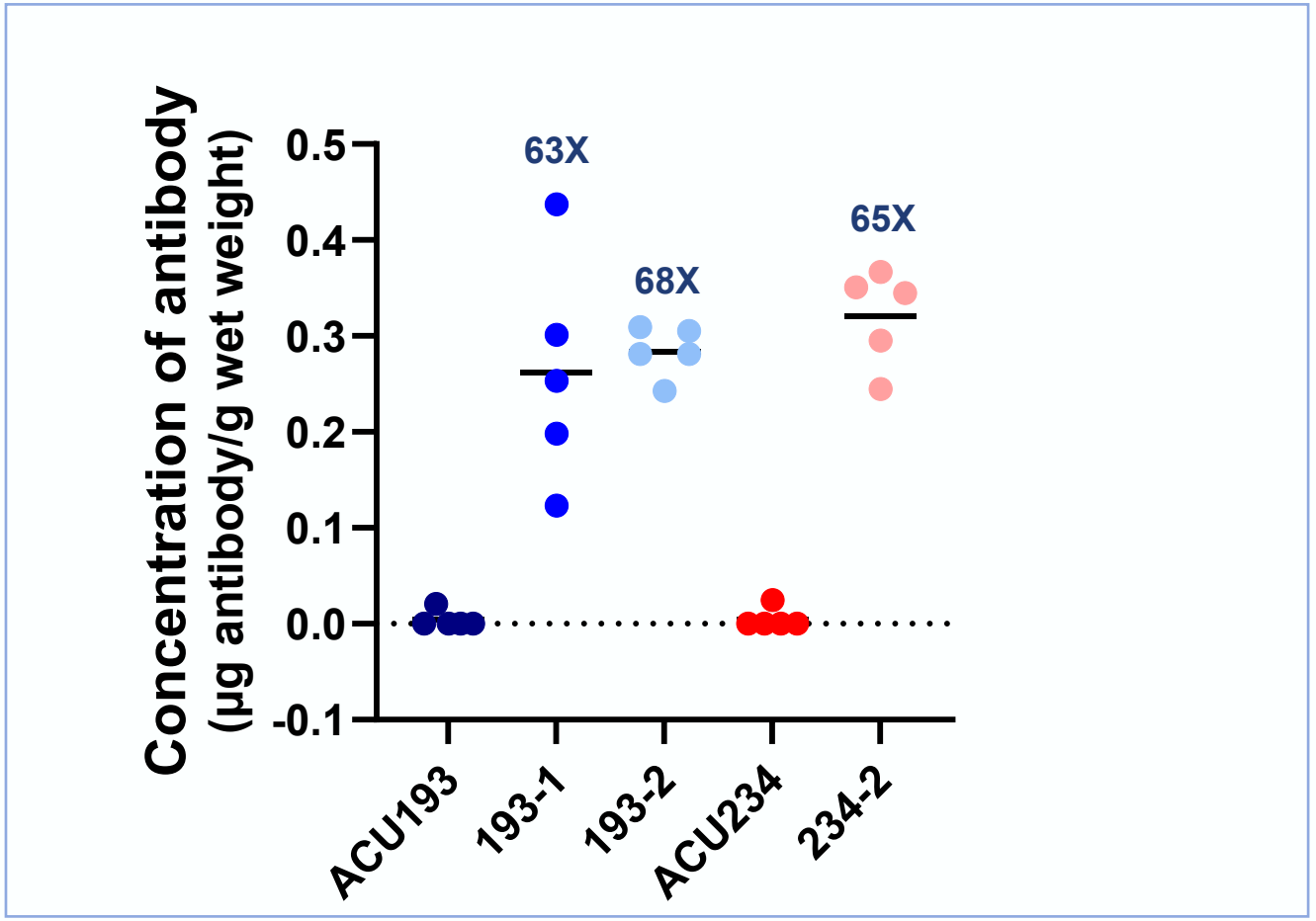
Bispecific Antibodies Show Enhanced Delivery to the ARTE10 Mouse Brain when Compared with ACU193 or ACU234



- Results from the ARTE10 mice suggest that antibodies with different PK properties show similar target engagement in the brain

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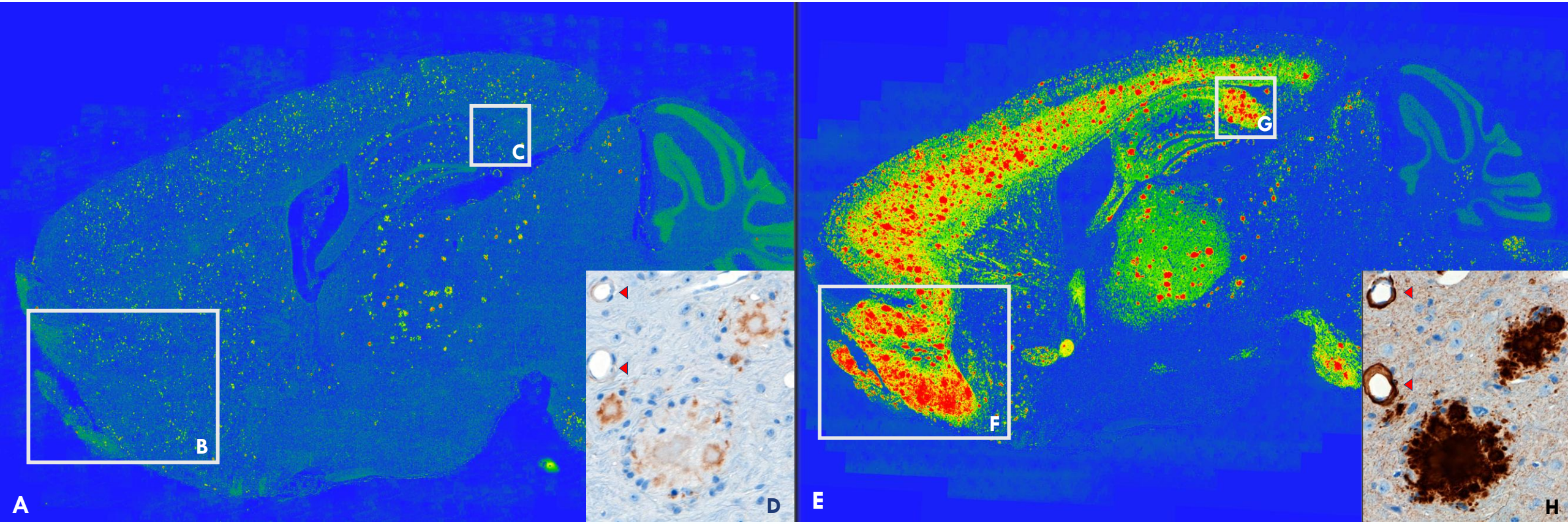
Immunohistochemical Localization of Bispecific Constructs in the ARTE10 Mouse Brain 24 hours after IV dosing

Immunodetection of human IgG2 (193.2)

Total Aβ (6E10/4G8)



- Note the dramatically reduced dense core plaque staining (white boxes, D vs. H) with fusion antibodies

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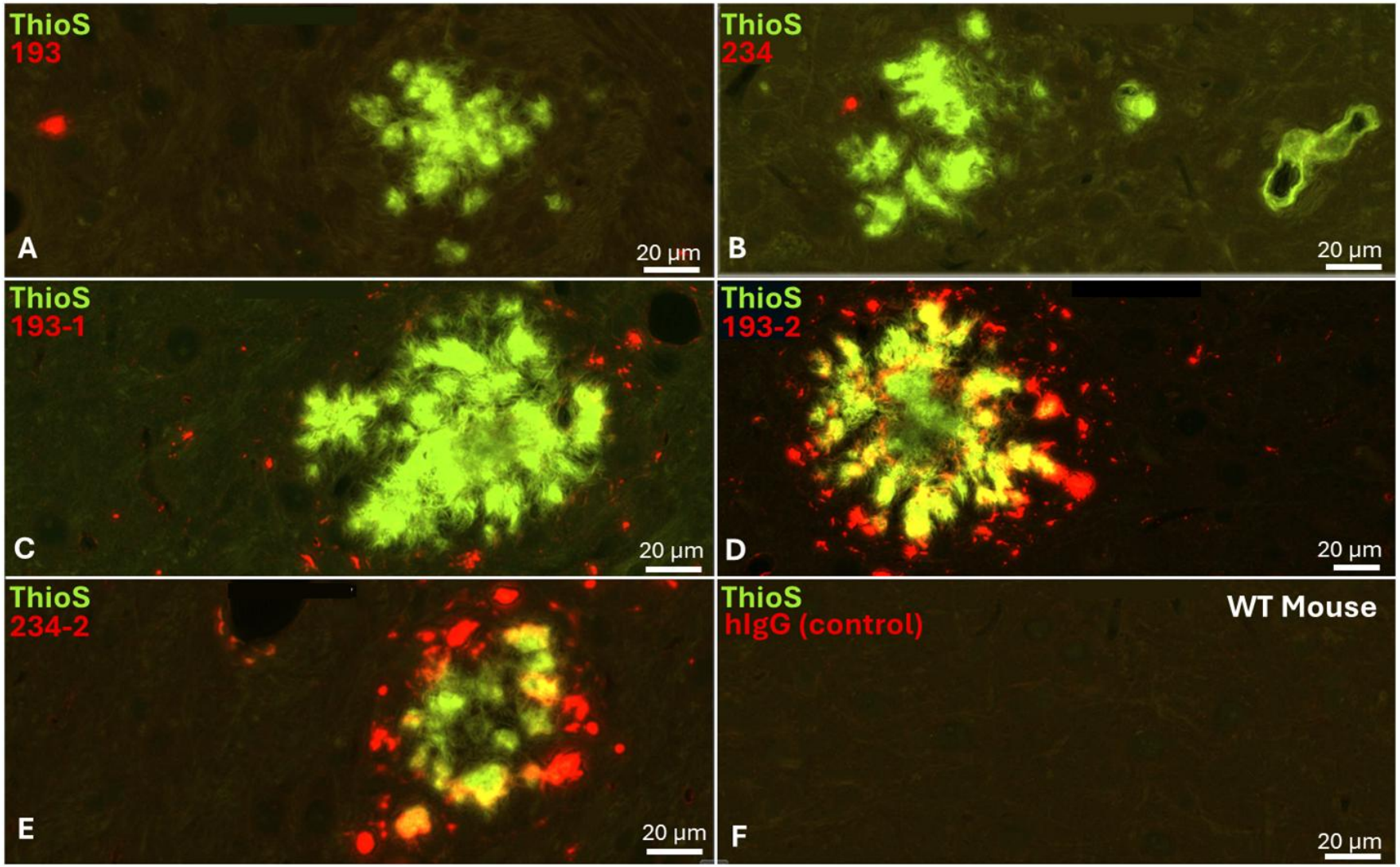
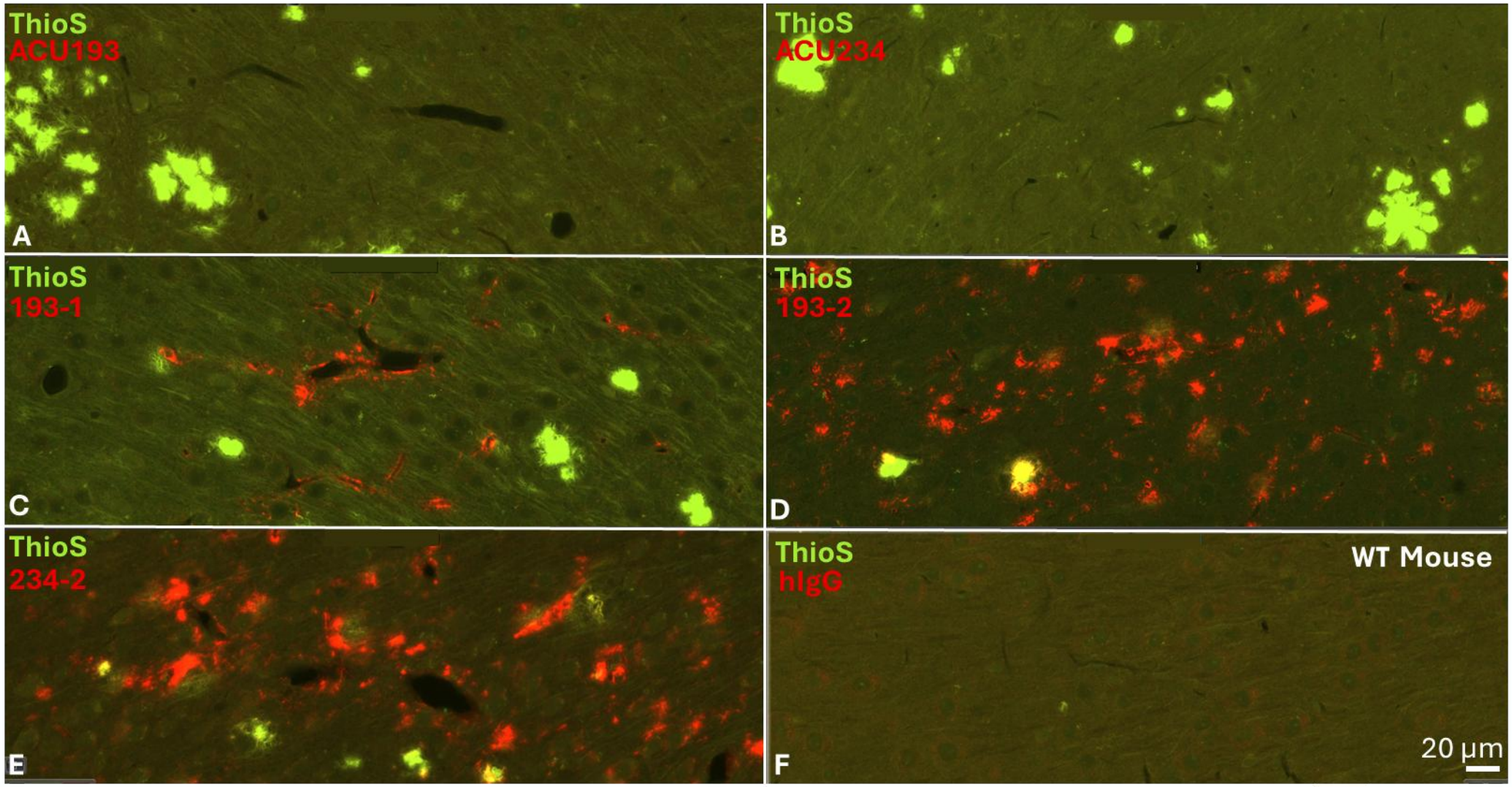
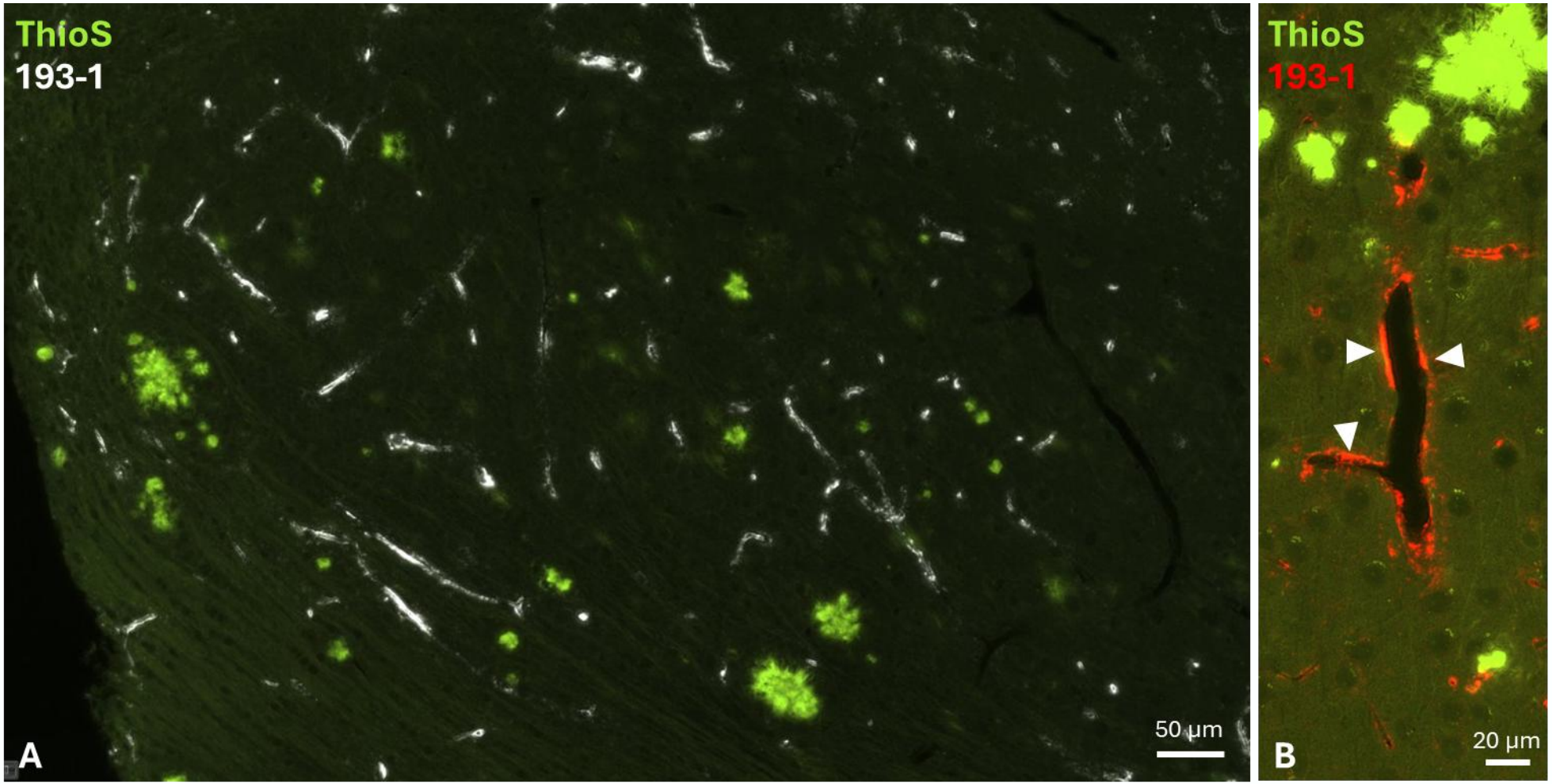
Differential Staining of Aβ Structures in the ARTE10 Mouse Thalamus 24 hours after IV Dosing of Bispecific Antibodies



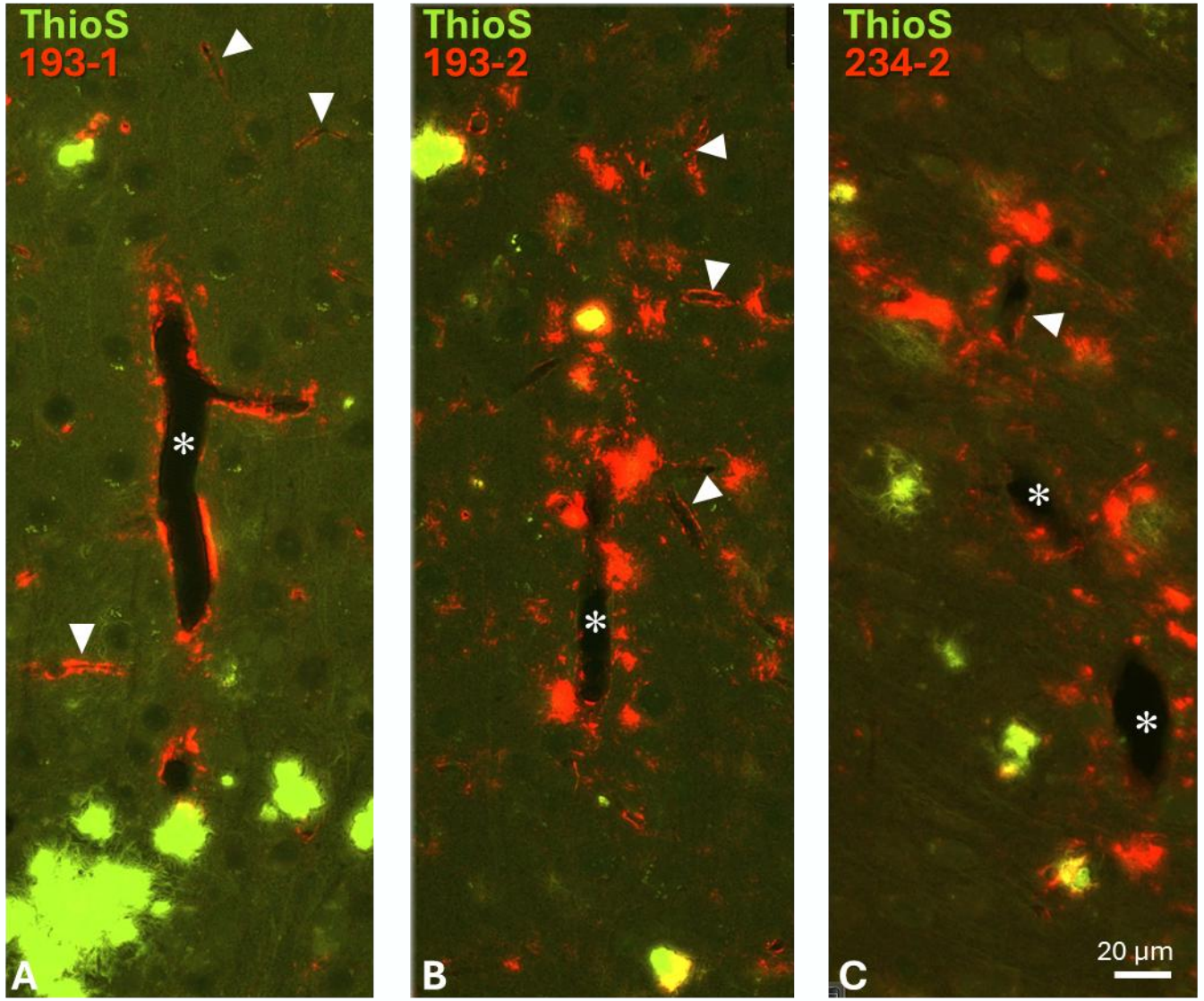
Localization of Bispecific Antibodies in the ARTE10 Mouse Cerebral Cortex



Staining for 193-1 in the Cortex Suggests that Antibody is Localized to the Capillary Wall and Not in the Parenchyma



A Comparison of Capillary Staining Among the Three Bispecific Antibodies



* capillary lumen

► capillary wall

Summary

- Bispecific constructs of ACU193 or ACU234 with a mouse anti-TfR scFv retain their ability to bind the TfR and to selectively bind Aβ oligomers
- Studies in wild type mice demonstrated that all mouse bispecific antibody constructs had enhanced brain delivery (17-35X), as compared to ACU193 and ACU234
- In the ARTE10 mouse, bispecific antibody constructs were detected in brain using ECH, with antibody levels 63-69X higher than ACU193 or ACU234
- Analysis of the regional and cellular distribution of antibodies revealed that both mBBB.193-2 and mBBB.234-2 stained Aβ structures of interest, demonstrating target engagement, while mBBB.193-1 was largely localized to the capillary walls
- Since mBBB.193-1 had the highest affinity for the mouse TfR, 330 pM as compared with 5.34 nM (mBBB.193-2) and 3.52 nM (mBBB.234-2), it is possible that the mBBB.193-1 antibody construct was unable to release from the TfR on the capillary wall to enter the brain

Thank you!

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