Capturing Alzheimer's Disease Using Amyloid Beta Mouse Models in 3D

Identifying detailed spatial distribution and density of β-amyloid plaques and pathological markers of neuroinflammation in transgenic mouse models over time is critical to further our understanding of Alzheimer's disease (AD) and evaluating newtherapeutics. However, these methodologies have previously proven challenging.

As a proof of concept, **Taconic Biosciences and LifeCanvas Technologies** successfully demonstrated *ex vivo* 3D imaging by characterizing distribution and densities of β-amyloid plaques and inflammatory markers in brains of male and female **APPSWE (Tg2576, Taconic model #1349)** and **ARTE10 (APP-PS1, Taconic model #16347)** mice across different ages.

LIFECANVAS TECHNOLOGIES: 3D HISTOLOGY PIPELINE

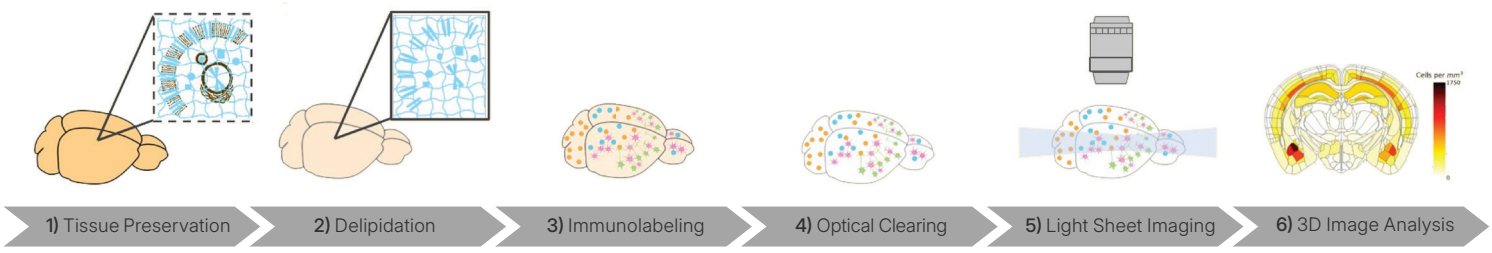


Figure 1. In the LifeCanvas processing pipeline, PFA-fixed brain samples are:

1. Post-fixed with SHIELD reagent for tissue preservation;
2. Delipidated in SmartClear Pro, a device that can delipidate mouse brain samples in 1 day;
3. Immunolabeled with primary and secondary antibodies using SmartBatch+;
4. Optically cleared using EasyIndex refractive index-matching solution (RI= 1.52);
5. Imaged using the SmartSPIM lightsheet microscope with a 3.6x objective; and
6. Analyzed using SmartAnalytics for atlas registration and segmentation analyses of amyloid deposition.

NEUROINFLAMMATORY MARKERS CLUSTER AROUND PLAQUE DEPOSITS IN 6 MONTH-OLD ARTE10 MICE

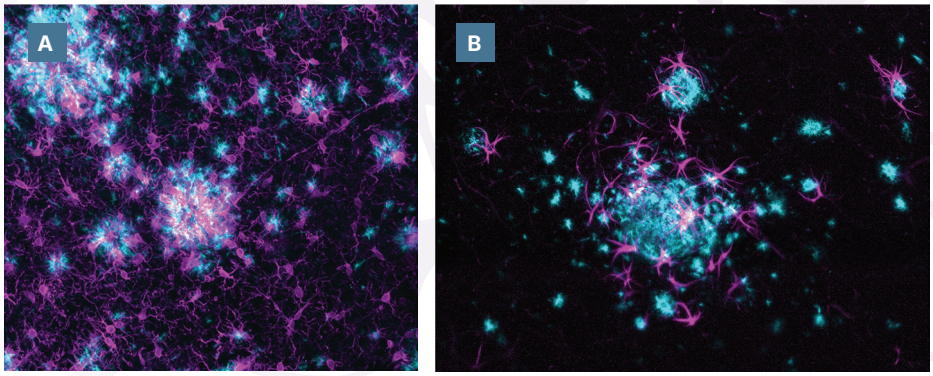
Figure A

- Magenta = microglia (GFAP)
- Cyan = β-amyloid

Figure B

- Magenta = astrocytes (IBA1)
- Cyan = β-amyloid

Clustering of activated microglia **(A)** and astrocytes **(B)** in the hippocampus is in proximity to β-amyloid plaque deposits.



AGE-DEPENDENT INCREASE IN Aβ PLAQUES AND U-SHAPE EFFECT OF MICROGLIA ASSOCIATED WITH PLAQUES OVER TIME

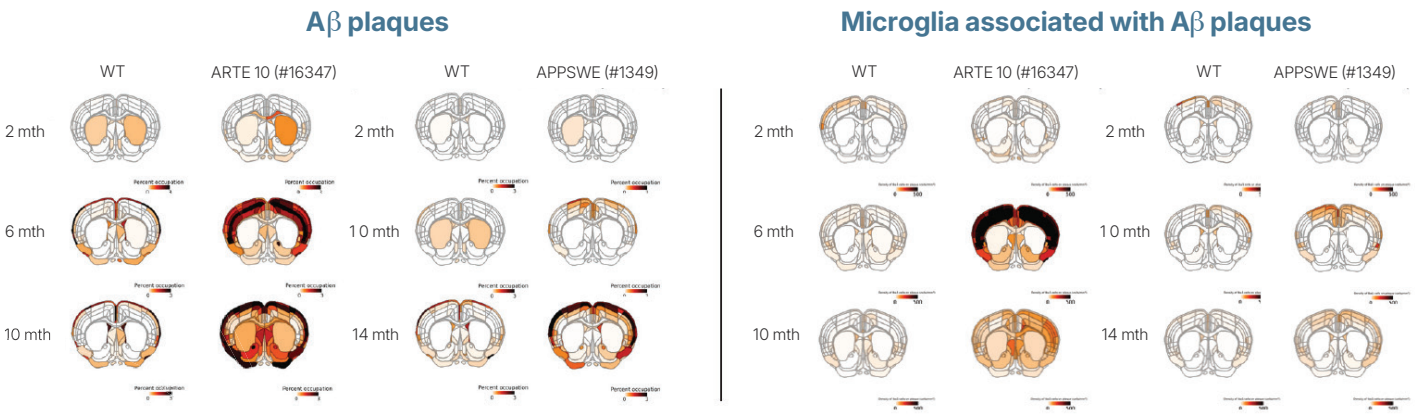


Figure 1. Heatmaps (25 m sections) generated from image registration to the Allen Brain Atlas and segmentation analyses of plaque deposition (SmartAnalytics) for control wild type (WT) and APPSWE and ARTE10 transgenic mice highlight increased plaque deposition in cortical regions in ARTE10 mice >6 mo and at >14 mo in the APPSWE mice. Similar findings were found in the hippocampus.

β-AMYLOID PLAQUE DEPOSITION AND MICROGLIA OVERLAP IN HIPPOCAMPUS

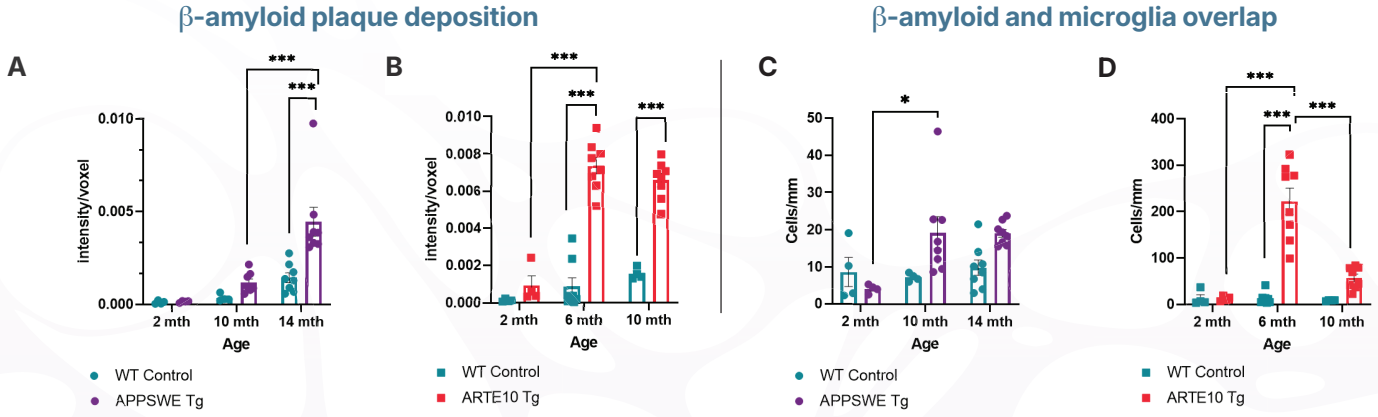


Figure 2. Intensity of plaques per voxel **(A and B)** and density of microglia cells on plaques **(C and D)** calculated for entire hippocampus per animal (n=4-8 per group) for the APPSWE model **(A and C)** and ARTE10 model **(B and D)**. Plaque deposition was significantly increased relative to wild type (WT) controls by 6 months of age for ARTE10 mice **(B)**, whereas plaques were not significantly increased in the APPSWE mice until 14 months of age **(A)**. Microglia overlap with plaques differently in the APPSWE and ARTE10 models, following a U shape function in the ARTE10 mice specifically **(D)**. Similar findings were found in the cerebral cortex.

CONCLUSION

Whole tissue clearing, staining and light sheet imaging results in more robust, unbiased, and high-resolution data with improved characterization than currently possible using traditional 2D immunohistochemistry. **APPSWE** and **ARTE10** mice display progressive Aβ plaque formation, with more aggressive development in the **ARTE10** model. Brain-wide neuroinflammation involvement via both microglia and astrocytes is demonstrated for the first time in both **ARTE10**and **APPSWE** transgenic models.

Alzheimer's Disease in 3D: Characterization of Plaques and Neuroinflammation within AD Mouse Models Using Innovative Tissue Clearing and Imaging Techniques.

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