

# Exploring the Role of Endothelial Cldn5 Expression in Alzheimer's Disease Pathology

Emily A. Groom<sup>1</sup>, Molly R. Batchelder<sup>1</sup>, Riane Richard<sup>1</sup>, Kasey M. Belanger-Mayer<sup>1</sup>, Rachel M. Smith<sup>1</sup>, Qingfen Li<sup>2</sup>, Bryce A. Thibodeau<sup>2</sup>, Ramon Bossardi Ramos<sup>3</sup>, Christina A. Thrasher<sup>1</sup>, \*Kevin Pumiglia<sup>2</sup>, \*Kristen L. Zuloaga<sup>1</sup>

1: Department of Neuroscience & Experimental Therapeutics, Albany Medical College, Albany, NY 12208 2: Department of Regenerative and Cancer Cell Biology, Albany Medical College, Albany, NY 12208 3: Department of Molecular and Cellular Physiology, Albany Medical College, Albany, NY 12208

## BACKGROUND

Cerebrovascular pathology is observed in up to 84% of **Alzheimer's disease (AD)** cases, yet less than 10% of dementia research examines these vascular contributions to AD<sup>1-4</sup>

**Vascular dysfunction & neuroinflammation** are observed early in AD, preceding cognitive decline<sup>5-8</sup>

**Cldn5** is a tight junction protein that regulates the blood-brain barrier integrity<sup>9</sup>

Studies have shown that Cldn5 levels are decreased in human post-mortem brains of AD patients<sup>10</sup>

The **Tg-SwDI mouse model of AD** exhibits vascular pathology accompanied by a reduction in Cldn5

## HYPOTHESIS

*Reduced Cldn5 expression exacerbates vascular contributions to cognitive impairment and dementia*

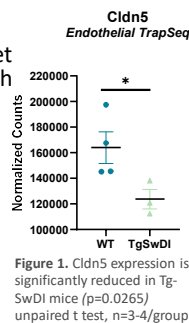
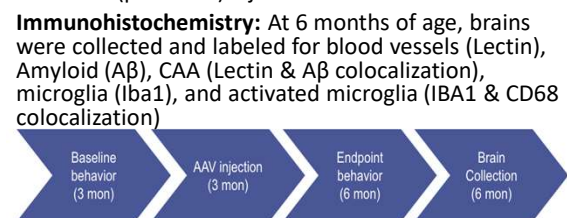
## METHODS

**Mice:** We used male and female Tg-SwDI mice on a C57BL/6J background. Tg-SwDI mice develop amyloid beta plaques in the brain parenchyma and the cerebral microvasculature (cerebral amyloid angiopathy; CAA). This is accompanied by a pronounced increase in activated microglia by 6 months of age.

**AAV Injection:** To modify endothelial Cldn5 levels in the brain, mice received a retroorbital BR1-AAV injection at 3 months of age to knockdown (KD) Cldn5. Control (Ctrl) mice received an empty vector.

**Behavioral Testing:** The Y-maze test was used to assess working memory at 3 months (pre-AAV injection) and 6 months (post-AAV) injection.

**Immunohistochemistry:** At 6 months of age, brains were collected and labeled for blood vessels (Lectin), Amyloid (A $\beta$ ), CAA (Lectin & A $\beta$  colocalization), microglia (Iba1), and activated microglia (IBA1 & CD68 colocalization)



## RESULTS

### Cldn5 KD Impairs Working Memory

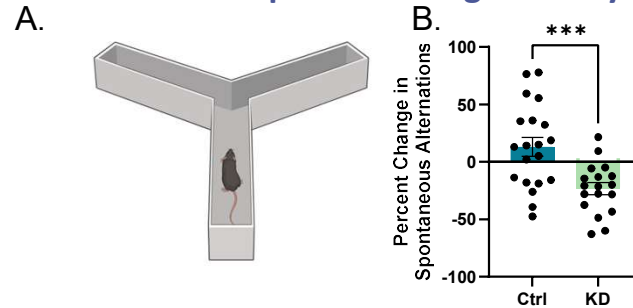
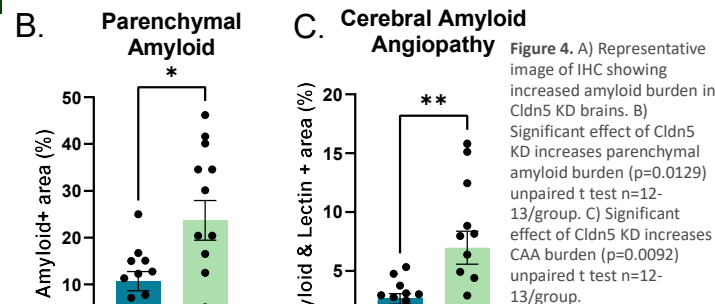
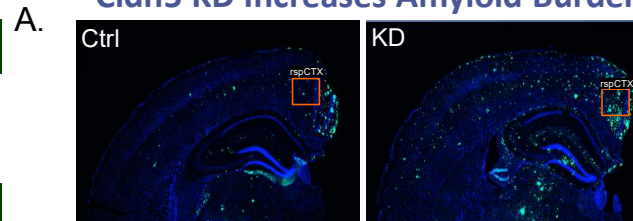
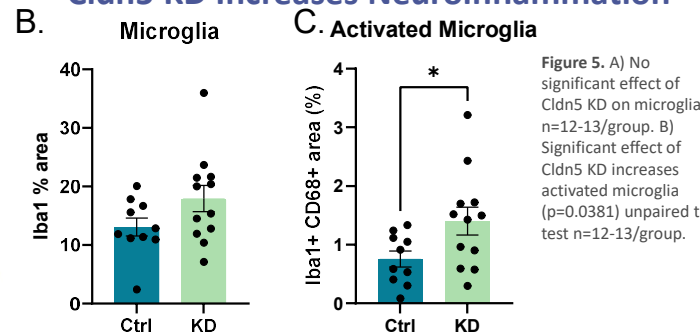


Figure 3. A) Schematic of the Y-maze test. B) Cldn5 KD significantly decreases performance in the Y-maze test (p=0.0122) Welch's t test n=17-18/group.

### Cldn5 KD Increases Amyloid Burden



### Cldn5 KD Increases Neuroinflammation



## CONCLUSIONS

The tight junction protein Cldn5 is essential for BBB integrity and **Cldn5 is reduced in the Tg-SwDI mouse model of AD.**

Cldn5 KD AAV significantly decreased Cldn5 expression

Cldn5 KD impaired performance in the Y-maze test suggesting **working memory deficits**

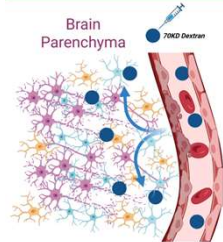
Cldn5 KD increased both **parenchymal amyloid burden** and **cerebral amyloid angiopathy**

Cldn5 KD did not increase microglia area covered but did **increase activated microglia** suggesting increased neuroinflammation

**Damage to the cerebral vasculature can exacerbate AD pathology**

## FUTURE DIRECTIONS

Future studies will investigate the functional consequence of Cldn5 KD via blood-brain barrier integrity assays and measure brain pro-inflammatory cytokine levels



## REFERENCES

1) Attems *BMC medicine* 2014 2) Brun *Annals of neurology* 1986 3) Fernando *Journal of the neurological sciences* 2004 4) Nichols *The lancet healthy longevity* 2023 5) Van de Haar *Neurobiology of aging* 2016 6) Korte *Acta neuropathologica* 2020 7) Noe *Frontiers in aging neuroscience* 2020 8) Sweeny *Nature Neuroscience* 2018 9) Hashimoto *Fluids barriers CNS* 2023 10) Jakel *Brain pathol* 2024

## ACKNOWLEDGEMENTS

Funded by the **American Heart Association** (25PRE1374600, EG), the **Alzheimer's Association** (AARG-849204; KLZ), **NIA** U01 AG07264 (KZ, KP) and **NINDS** R01 NS110749 (KLZ).

