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AL002c-mediated Reduction in Amyloid β Pathology is Reflected by Changes in Plasma Alzheimer's Disease Biomarkers in 5xFAD Mice

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Background

Microglia and TREM2 in Alzheimer's Disease (AD)

- Microglia play a key role in modulating the response to AD pathology, including the clearance and remodeling of amyloid plaques[1-4]
- Several lines of evidence identify triggering receptor expressed on myeloid cells-2 (TREM2) as a critical regulator of microglial response in AD
  - Microglia with decreased TREM2 function demonstrate altered transcriptional response to AD pathology in both human[5,6] and preclinical studies[6,7]
  - Individuals carrying the hypomorphic missense R47H variant in the *TREM2* gene are at a greatly increased risk for late-onset AD (LOAD)[8]

Targeting TREM2 With AL002 in AD

- AL002 is a novel humanized monoclonal TREM2-activating immunoglobulin G1 (IgG1) antibody and is currently being evaluated in INVOKE-2, a phase 2 trial in participants with early AD (NCT04592874)
- Previously, 5xFAD mice treated with AL002c, a variant of AL002, were shown to have an altered composition of amyloid plaques and a reduced number of dystrophic neurons[9]
- Notably, 5xFAD mice treated with AL002c exhibited reduced neurotoxic filamentous plaque despite no change in total methoxy-X04–positive plaque area or insoluble hippocampal amyloid-beta (Aβ) 42 or Aβ40, consistent with a beneficial remodeling of amyloid plaque by microglia[9]

Fluid Biomarkers of AD

- INVOKE-2 will assess exploratory biomarker endpoints in plasma and cerebrospinal fluid (CSF) to characterize the activity of AL002 in the brain and treatment effects on AD pathology
- Aβ peptides
  - Aβ peptides in plasma or CSF are established biomarkers of amyloid burden in the brain[10]
  - Recent clinical trials with amyloid-lowering therapies[11,12] observe that increases in Aβ42[11] or the Aβ42/40 ratio[13] correlate with the extent of amyloid clearance as measured by amyloid positron emission tomography (PET)
  - Despite the observed correlation between Aβ42/40 and amyloid clearance, it is unknown whether plasma Aβ peptides are an informative marker of amyloid plaque remodeling
- Soluble tau
  - Total tau (t-tau) protein is elevated in AD biofluids, correlates with the rate of cognitive decline, and is believed to reflect the intensity of neuronal degeneration in AD[14,15]
  - Biomarkers of neurodegeneration are hypothesized to reflect a cellular process proximal to cognitive decline and are an important complement to earlier markers of the amyloid cascade, including amyloid pathology

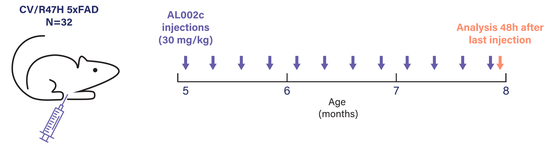
Research Questions

- We sought to establish whether biomarkers of amyloid pathology (Aβ42/40 ratio) or neurodegeneration (t-tau) were sensitive to AL002c treatment effects in 5xFAD mice. Specifically:
  1. Is the plasma Aβ42/40 ratio sensitive to AL002c-induced changes in amyloid plaques in 5xFAD mice, despite no change in total amyloid burden?
  2. Is t-tau an informative biomarker of AL002c-mediated neuroprotection in the 5xFAD model?

Methods

- As described previously,[16] CV-KO-5xFAD and R47H-KO-5xFAD mice were generated by introducing either common variant (CV) or R47H human *TREM2* (*hTREM2*) into mouse *Trem2* (*mTrem2*)–deficient mice and crossing them with the 5xFAD mouse model of AD, in which amyloid deposition begins at 2 months[17]
- Five-month-old CV-KO-5xFAD and R47H-KO-5xFAD mice (N=32, n=6-13 per group) received weekly intraperitoneal injections of 30-mg/kg AL002c or a control mouse IgG1 for 12 weeks and were sacrificed 48 hours after the last injection (**Figure 1**)
- Levels of plasma Aβ42, Aβ40, and t-tau were quantified using the Simoa® Neurology 3-Plex A Advantage Kit (Quanterix)
- Group differences in Aβ42/40 ratios were analyzed using Student's t-tests
- Mann Whitney U tests were used to analyze plasma t-tau data
- All statistical tests were conducted using GraphPad Prism
- Significance level was set to 0.05

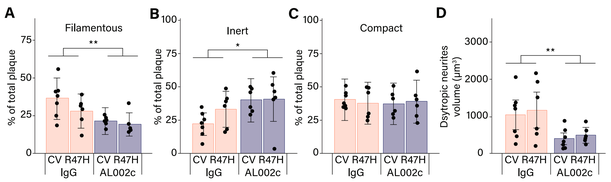
Figure 1. Timeline of AL002c Treatment in CV/R47H 5xFAD Mice



Results

- Wang et al previously showed that, in 5xFAD mice, AL002c treatment reduced the proportion of neurotoxic filamentous Aβ plaques and increased the proportion of inert plaques (**Figure 2A-B**), while compact plaque area (**Figure 2C**) and total brain Aβ42 and Aβ40 levels remained constant[9]
- AL002c-treated mice also exhibited reduced neurite dystrophy (**Figure 2D**) and reversal of a behavioral phenotype observed in 5xFAD mice, consistent with the reduction in neurotoxic pathology[9]

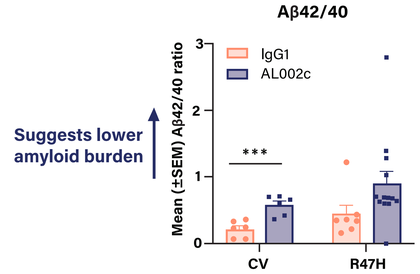
Figure 2. AL002c Shifts Composition of Aβ Plaques and Reduces Neurite Dystrophy



Data are presented as mean ± SEM. *, $p < 0.05$; **, $p < 0.01$ by two-way ANOVA.

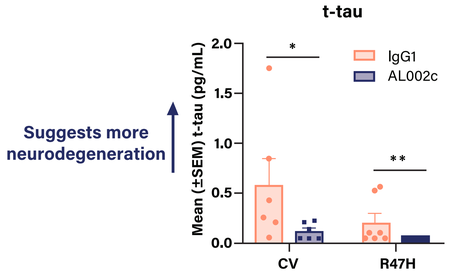
- Here, we show that AL002c-treated CV-5xFAD mice had a higher plasma Aβ42/40 ratio compared with IgG1-treated CV-5xFAD mice ($p < 0.001$; **Figure 3**), while this difference did not achieve significance for R47H-5xFAD mice ($p = 0.056$)
- Pooled AL002c-treated mice had a higher plasma Aβ42/40 ratio compared with IgG1-treated mice (pooled CV and R47H-5xFAD $p < 0.01$)
- AL002c-treated mice exhibited lower plasma t-tau compared with their respective control-treated mice (**Figure 4**; CV-5xFAD $p < 0.05$; R47H-5xFAD $p < 0.01$; pooled CV and R47H-5xFAD $p < 0.001$)
- No differences were observed between R47H and CV genotypes in plasma Aβ42/40 ratio or t-tau

Figure 3. AL002c Treatment Increases Plasma Aβ42/40 Ratio



Note: The dilution-adjusted limit of detection (LOD) was 0.98 pg/mL for Aβ40 and 0.225 pg/mL for Aβ42. An Aβ42/40 ratio could not be calculated for 1 mouse for which Aβ40 data were unavailable. CV-KO-5xFAD, AL002c, n=6; CV-KO-5xFAD, IgG1, n=6; R47H-KO-5xFAD, AL002c, n=12; R47H-KO-5xFAD, IgG1, n=7. Each symbol represents data from 1 mouse. ***, $p < 0.001$

Figure 4. AL002c Decreases Plasma Total Tau Levels



Note: The dilution-adjusted LOD was 0.095 pg/mL. Measurements that were below the LOD were assigned a value of half of the LOD, 0.0475 pg/mL. CV-KO-5xFAD, AL002c, n=6; CV-KO-5xFAD, IgG1, n=6; R47H-KO-5xFAD, AL002c, n=13; R47H-KO-5xFAD, IgG1, n=7. Each symbol represents data from 1 mouse. *, $p < 0.05$; **, $p < 0.01$.

Conclusions

- Treatment with AL002c, a TREM2-agonistic antibody, resulted in an increase in plasma Aβ42/40 ratio and a decrease in plasma t-tau in 5xFAD mice
- AL002c-induced changes in plasma Aβ42/40 levels suggest that the Aβ42/40 ratio can reflect remodeling of amyloid plaques without a reduction in total methoxy-X04–positive plaque or insoluble Aβ42 or Aβ40 burden in 5xFAD mice
- AL002c-induced changes in plasma t-tau suggest that AL002c improves biomarkers of neurodegeneration in 5xFAD mice, consistent with the decrease in dystrophic neurites seen with AL002c treatment[9]
- These results lend further support to the clinical utility of plasma Aβ42/40 as a marker for the reduction of neurotoxic amyloid plaques and t-tau as a marker of neurodegeneration in clinical trials with AL002
- A phase 2 trial (INVOKE-2; NCT04592874) and long-term extension study (NCT05744401) are ongoing to evaluate the efficacy and safety of AL002 in slowing disease progression in participants with early AD

References

1. Casali BT, et al. *Neurobiol Dis*. 2020;142:104956.
2. Karch CM, Goate AM. *Biol Psychiatry*. 2015;77:43-51.
3. Lambert JC, et al. *Nat Genet*. 2013;45:1452-1458.
4. Song WM, Colonna M. *Nat Immunol*. 2018;19:1048-1058.
5. Mathys H, et al. *Nature*. 2019;570:332-337.
6. Zhou Y, et al. *Nat Med*. 2020;26:131-142.
7. Keren-Shaul H, et al. *Cell*. 2017;169:1276-1290 e1217.
8. Jonsson T, et al. *N Engl J Med*. 2013;368:107-116.
9. Wang S, et al. *J Exp Med*. 2020;217.
10. Doecke JD, et al. *Neurology*. 2020;94:e1580-e1591.
11. Bittner T, et al. Graduate I and II results: effect of subcutaneous gantenerumab on fluidbiomarkers of AD pathology and neurodegeneration. Poster presented at ADPD; March 2023; Gothenburg, Sweden.
12. van Dyck CH, et al. *N Engl J Med*. 2023;388:9-21.
13. McDade E, et al. *Alzheimers Res Ther*. 2022;14:191.
14. Jack CR, Jr, et al. *Alzheimers Dement*. 2018;14:535-562.
15. Samgard K, et al. *Int J Geriatr Psychiatry*. 2010;25:403-410.
16. Song WM, et al. *J Exp Med*. 2018;215:745-760.
17. Oakley H, et al. *J Neurosci*. 2006;26:10129-10140.

Disclosures

This work was supported by the National Institutes of Health (RF1 AG05148501, R21 AG059176, and RF1 AG059082) and the Cure Alzheimer's Fund. Biomarker quantification was funded by Alector, Inc. BB, AI, BS, and IT are employees of Alector, LLC, and may have an equity interest in Alector, Inc.

Acknowledgments

Medical writing services were provided by Scient Healthcare Communications, in accordance with Good Publication Practices (GPP 2022), and were funded by Alector, Inc., South San Francisco, CA.

Presented at the Alzheimer's Association International Conference | July 16-20, 2023 | Amsterdam, Netherlands