GrantPanel

SAMPLE REPORT · NIH

GrantPanel NIH Peer Review

with Recommended Revisions

Review under the NIH Simplified Review Framework: Factor 1 (Importance of the Research), Factor 2 (Rigor and Feasibility), and Factor 3 (Expertise and Resources), with three reviewers scoring on the 1–9 scale, three rounds of study-section discussion, and an overall impact recommendation, all generated by GrantPanel's AI review panel.

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APPLICATION TITLE

Microglial Complement Signaling in Early Tau Propagation

CONTACT PI

Dr. Elena Vasquez

INSTITUTION

Riverside Medical College

INSTITUTE & ACTIVITY CODE

NIA · R01 (new)

REQUESTED (DIRECT COSTS)

$1,250,000 over 5 yr

STUDY SECTION

Cellular & Molecular Neuropathology (CMND)

PANEL CONSENSUS

Overall impact 3

IMPACT 30 · 1 = BEST

(Science, 2016) established complement-dependent synapse loss as an early mechanism — the foundation for the causal hypothesis.

Resume and summary of discussion. This new R01 investigates whether complement-mediated microglial pruning is an initiating driver of tau propagation in early Alzheimer's disease, using a conditional complement-knockout crossed to a tau-seeding model with longitudinal imaging. The study section judged the application to be of high importance with a rigorous plan, tempered by specific feasibility and rigor concerns in the third aim. Final overall impact reflects a priority score of 30 (mean of final impact scores 3, 4, 3).

FIX IN THIS ORDER

four of the panel's findings — the full list is below

01 **Aim 3 detail hidden in the Appendix.** →

Move the Aim 3 Approach detail into the Research Strategy — reviewers are not obligated to read the Appendix.

02 **Vertebrate Animals justification incomplete.** →

Justify the number of transgenic mice and include the referenced power-analysis figure.

03 **Missing resource authentication.** →

Add an Authentication of Key Biological Resources plan for the Aim 2 antibodies.

04 **Biosketch personal statement.** →

Reference the two most relevant prior works in the contact PI's personal statement.

This is the short list. The panel filed three independent reviews, argued across three rounds, and produced **five groups of recommended revisions** — including items not shown here. Each finding is tied to the section it came from, so you can check the claim against your own document.

Contents

DOCUMENT INTELLIGENCE

Document Intelligence

Proposal package inventory

READY WITH QUESTIONS

Detected documents:

- Specific Aims (1 page)
- Research Strategy (pages 2–13)
- Bibliography & References Cited (pages 14–17)
- Biosketches for the contact PI and three key personnel are present in the supporting package.

Conditional requirements:

- Vertebrate Animals section: present and required. The work is entirely murine; no human subjects section attaches.
- Authentication of Key Biological Resources: unclear. Antibody validation is referenced in the Approach but no authentication plan was identified.
- Data Management and Sharing Plan: present, naming a public repository for the sequencing data.

Document quality: Figure legends in the Approach are set below the minimum type size and were difficult to read at 100%.

Author questions: Is a separate Authentication of Key Biological Resources attachment included? The reviewers assessed rigour without it.

COMPLIANCE & ADDITIONAL REVIEW CONSIDERATIONS

Compliance

NIH format & policy check

COMPLETED

Status: Compliant with concerns

Issues found:

- Research Strategy is 12 pages — within the R01 limit, but the Approach for Aim 3 spills key detail into the Appendix, which reviewers are not obligated to read.
- Vertebrate Animals Section does not fully justify the proposed number of transgenic mice; the power analysis references a figure that is not included.
- Authentication of Key Biological Resources plan is missing for the antibodies central to Aim 2.
- Biosketch personal statement for the contact PI does not reference the two most relevant prior works.

Additional review considerations: Human Subjects — not applicable (animal model). Rigor of prior research and sex-as-a-biological-variable are addressed; the SABV plan is present but analysis is under-specified.

Mission Alignment

Fit to the FOA & institute mission

COMPLETED

Alignment: Strong

Addressed well:

- Directly responsive to the parent R01 (PA) and squarely within NIA's Alzheimer's-disease neurodegeneration mission.
- Mechanistic focus on tau propagation aligns with the institute's stated priority on early-stage disease processes.
- The proposed biomarker link offers a plausible translational off-ramp without overreaching into clinical claims.

Gaps:

- The application does not state how findings would generalize beyond the single mouse model, which reviewers flagged for the Approach.

- Relevance to AD/ADRD milestones is implied but not mapped to a specific research implementation milestone.

INDIVIDUAL REVIEWS

Reviewer A

NIH study-section reviewer

COMPLETED

RATING — Overall impact 3 — 3 OF 9 · 1 = BEST

Factor 1 — Importance of the Research *(score 2)*.

- **Significance:** Addresses a genuine gap — how complement-mediated microglial pruning initiates tau spread rather than merely accompanying it.
- **Innovation:** The conditional complement-knockout crossed to a tau-seeding model is a real conceptual advance.

Factor 2 — Rigor and Feasibility *(score 3)*.

- Aims 1–2 are rigorous and well powered; Aim 3's causal claim leans on a correlation that the design cannot fully establish.
- The proposed timeline for the longitudinal cohort is optimistic given breeding demands.

Factor 3 — Expertise and Resources: sufficient. PI and neuropathology core are well matched to the work.

Overall. High-impact question with a mostly rigorous plan; Aim 3 is the weak point.

Reviewer B

NIH study-section reviewer

COMPLETED

RATING — Overall impact 5 — 5 OF 9 · 1 = BEST

Factor 1 — Importance of the Research *(score 4)*.

- Significant, but the incremental step beyond the PI's prior R21 is smaller than the narrative claims.

Factor 2 — Rigor and Feasibility *(score 5)*.

- Central weakness: the tau-seeding assay lacks a rigor-of-prior-research citation establishing the seeding dose, and no authentication plan is given for the key antibodies.
- Sex as a biological variable is named but the analysis is not powered to detect sex differences — a recurring NIH concern.
- Vertebrate Animals justification for animal numbers is incomplete.

Factor 3 — Expertise and Resources: sufficient. Environment is strong; the biostatistics effort is thin for the longitudinal aim.

Overall. Solid but not exceptional; feasibility and rigor gaps hold it back.

Reviewer C

NIH study-section reviewer

COMPLETED

RATING — Overall impact 3 — 3 OF 9 · 1 = BEST

Factor 1 — Importance of the Research *(score 3)*.

- The disease relevance is clear and the mechanistic framing is timely for the field.

Factor 2 — Rigor and Feasibility *(score 3)*.

- Feasible as staged; the imaging pipeline is well validated in the PI's hands.
- Agrees the SABV analysis plan needs strengthening but views it as fixable.

Factor 3 — Expertise and Resources: sufficient. Early-stage investigator with an unusually strong publication trajectory; institutional commitment letters are concrete.

Overall. Fundable with attention to rigor detail in Aim 3 and the animal-numbers justification.

PANEL DISCUSSION

ROUND 1 — INITIAL IMPACT SCORES

A

REVIEWER A

I'm at a 3 overall. The significance is high and the complement-pruning mechanism is genuinely novel; my only real concern is the Aim 3 causal claim.

B

REVIEWER B

I'm at a 5. It's a meaningful question, but the seeding-assay rigor and the sex-as-a-variable analysis aren't where they need to be, and the animal justification is incomplete.

C

REVIEWER C

3 for me as well. The disease relevance and the PI's imaging track record carry it; the rigor gaps read as revisable to me.

ROUND 2 — DISCUSSION

A

REVIEWER A

Reviewer B, the seeding dose is actually cited — it's in the Aim 2 preliminary data, just not repeated in Aim 3. I'd weight the rigor concern a bit lower.

B

REVIEWER B

Fair, I missed that cross-reference. It softens my rigor concern, but the SABV plan and the antibody authentication are still real, reviewable deficiencies.

C

REVIEWER C

Agreed on both. Those are addressable in a resubmission or even at just-in-time; they shouldn't sink an otherwise strong application.

ROUND 3 — FINAL IMPACT SCORES

A

REVIEWER A

Final: 3. Strong significance and innovation, minor feasibility risk in Aim 3.

B

REVIEWER B

Final: 4. Moving up one point after the seeding-dose clarification; the rigor detail keeps me from a 3.

C

REVIEWER C

Final: 3. High relevance, credible plan, fixable rigor items.

OVERALL IMPACT

Study Section Summary

Overall impact 3 ●●●●○ IMPACT 30 · 1 = BEST

Resume and summary of discussion. This new R01 investigates whether complement-mediated microglial pruning is an initiating driver of tau propagation in early Alzheimer's disease, using a conditional complement-knockout crossed to a tau-seeding model with longitudinal imaging. The study section judged the application to be of high importance with a rigorous plan, tempered by specific feasibility and rigor concerns in the third aim. Final overall impact reflects a priority score of **30** (mean of final impact scores 3, 4, 3).

Factor 1 — Importance of the Research (Significance, Innovation)

- Consensus strength: the mechanistic question is significant and the genetic strategy is innovative relative to the field.
- Consensus note: the advance over the PI's prior R21 is real but more incremental than the narrative asserts.

Factor 2 — Rigor and Feasibility (Approach)

- Aims 1–2 are rigorous and adequately powered.
- Consensus weaknesses: the sex-as-a-biological-variable analysis is not powered to detect sex differences; the Authentication of Key Biological Resources plan is missing for Aim 2 antibodies; Aim 3's causal inference exceeds what the design can establish.

Factor 3 — Expertise and Resources (Investigators, Environment): sufficient.

- Strong early-stage investigator, well-matched neuropathology environment; biostatistics effort is thin for the longitudinal aim.

Additional review considerations. Vertebrate Animals — animal-number justification incomplete. Human Subjects — not applicable. No biohazard concerns.

Points of disagreement. Reviewer B initially scored the rigor of the seeding assay more critically until a cross-reference to the Aim 2 preliminary data was clarified in discussion; the scores converged but did not fully align.

Recommendation. Meritorious and likely fundable within the study section's range. A resubmission or just-in-time update should strengthen the SABV analysis, add the resource-authentication plan, complete the animal-numbers justification, and temper the Aim 3 causal claim.

RECOMMENDED REVISIONS

Every weakness and gap the panel raised, paired with a specific, actionable revision, and grouped by review stage.
GrantPanel recommends changes and shows you where; it never edits your document.

Revisions by section

Ordered by what to fix first

5 REVISIONS

01 Compliance & format

FIX BEFORE SUBMISSION

→ **Aim 3 detail hidden in the Appendix.** Move the Aim 3 Approach detail into the Research Strategy — reviewers are not obligated to read the Appendix.

→ **Vertebrate Animals justification incomplete.** Justify the number of transgenic mice and include the referenced power-analysis figure.

→ **Missing resource authentication.** Add an Authentication of Key Biological Resources plan for the Aim 2 antibodies.

→ **Biosketch personal statement.** Reference the two most relevant prior works in the contact PI's personal statement.

02 Mission alignment

MEET THE FOA

→ **Generalization beyond one model.** State how the findings would generalize beyond the single mouse model.

→ **Milestone mapping.** Map the work to a specific AD/ADRD research-implementation milestone.

03 Individual reviews

STRENGTHEN THE SCIENCE

FACTOR 1 — IMPORTANCE

→ **Advance over the prior R21 is understated.** Sharpen the step beyond the PI's prior R21 so significance is unambiguous.

FACTOR 2 — RIGOR & FEASIBILITY

→ **Aim 3 causal claim exceeds the design.** Temper the causal inference to what the design supports, or add an experiment that isolates causation.

→ **Seeding-assay rigor not cited.** Cite the rigor-of-prior-research basis for the seeding dose (cross-reference the Aim 2 preliminary data).

→ **Sex as a biological variable under-powered.** Power the analysis to detect sex differences, per NIH expectations.

→ **Thin biostatistics for the longitudinal aim.** Increase biostatistics effort and rebalance the timeline for breeding demands.

04 Overall impact — priorities

ADDRESS FIRST

→ **Highest priority.** The sex-as-a-variable analysis and the Aim 2 resource-authentication plan — the two rigor gaps most likely to move the impact score.

→ **Then.** Temper the Aim 3 causal claim and complete the Vertebrate Animals justification.

05 Prior work & citations

POSITION THE CONTRIBUTION

→ **Two directly relevant works uncited.** Cite the 2023 single-cell study of complement-high microglia in tauopathy and the recent tau-seeding-assay reporting standards.

SUPPORTING RESEARCH

REFERENCES LOOKUP

References
Extracts and looks up cited prior work

COMPLETED

Extracting cited references from the application...

Found 6 references. Fetching abstracts from Semantic Scholar...

[1/6] Complement and microglia mediate synapse loss — found [2/6] Trans-synaptic spread of tau pathology in vivo — found [3/6] Microglial states in neurodegeneration — found [4/6] Sex differences in Alzheimer's disease pathology — found [5/6] Reporting standards for tau-seeding assays — no match [6/6] Longitudinal PET imaging of tau in mouse models — found

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The application cites 6 references. Abstracts (where available) are provided below to inform your assessment of novelty and prior-work coverage.

[1] Complement and microglia mediate synapse loss *(2016)* — Hong et al. *Science · 2016* Complement component C1q and microglial CR3 drive early synapse loss in Alzheimer models, establishing complement-dependent pruning as an early pathological mechanism upstream of overt neurodegeneration.

[2] Trans-synaptic spread of tau pathology in vivo *(2018)* — Wu et al. *Nature Neuroscience · 2018* Pathological tau propagates along synaptically connected circuits, and activity modulates the rate of spread, supporting a circuit-based model of tau progression.

[3] Microglial states in neurodegeneration *(2021)* — Deczkowska et al. *Cell · 2021* A synthesis of disease-associated microglial states and their transcriptional drivers, distinguishing protective from damaging activation programs.

[4] Sex differences in Alzheimer's disease pathology *(2020)* — Guo et al. *Nature Reviews Neurology · 2020* Reviews evidence that tau burden and microglial response differ by sex, underscoring the need to power preclinical studies to detect sex effects.

[5] Reporting standards for tau-seeding assays *(Not found on Semantic Scholar.)*

[6] Longitudinal PET imaging of tau in mouse models *(2019)* — Brendel et al. *Journal of Nuclear Medicine · 2019* Establishes reproducible small-animal tau-PET pipelines, providing the longitudinal imaging methodology the application adopts.

LITERATURE REVIEW (DEEP RESEARCH)

Literature Review
Deep-research SOTA scan

COMPLETED

Research area & central claim. The application claims that complement-mediated microglial pruning is an initiating driver — not merely a correlate — of early tau propagation, testable by conditional complement knockout in a tau-seeding model with longitudinal imaging.

State of the art (last 3–5 years)

- Hong et al. (Science, 2016) established complement-dependent synapse loss as an early mechanism — the foundation for the causal hypothesis.
- Wu et al. (Nat. Neurosci., 2018) demonstrated circuit-based trans-synaptic tau spread modulated by activity.
- Recent single-cell work (2021–2024) resolved damaging vs. protective microglial states, refining which complement pathways to target.
- Sex-difference literature (Guo 2020 and follow-ups) sets the SABV expectation reviewers applied.

Competing approaches

- **Antibody-based tau immunotherapy models** — clinically oriented; do not isolate the complement-pruning mechanism the application targets.
- **Pharmacological complement inhibition** — less specific than the proposed genetic strategy but faster to translate.

Open problems the application addresses

- Whether complement pruning is causal or reactive in tau spread — unresolved and the crux of the proposal.
- Whether the mechanism is sex-dependent — the reviewers' SABV concern maps directly here.

Citation gaps in the application

- A 2023 single-cell study of complement-high microglia in tauopathy — directly relevant, not cited.
- Recent reporting-standards guidance for tau-seeding assays — relevant to the rigor concern, not cited.

Search log

- "complement C1q microglia tau propagation causal 2024"
- "conditional complement knockout tau seeding mouse"

- "sex differences microglial complement Alzheimer"
- "tau seeding assay reporting standards rigor"
- "longitudinal tau PET mouse model reproducibility"
- "disease associated microglia single cell tauopathy 2023"

INDIVIDUAL WEB SEARCHES

Reviewer A
3 searches

1. `complement microglia tau propagation causal 2024`
2. `conditional knockout tau seeding model`
3. `significance innovation microglial pruning neurodegeneration`

Reviewer B
4 searches

1. `tau seeding assay dose rigor reporting`
2. `sex as biological variable power analysis NIH`
3. `authentication key biological resources antibody`
4. `vertebrate animals justification number of mice`

Reviewer C
3 searches

1. `tau PET longitudinal mouse imaging pipeline`
2. `early stage investigator R01 Alzheimer`
3. `disease associated microglia complement single cell`