The Complement-Pruning Substrate

Beth Stevens's Microglia–Complement Program Re-Evaluated

C1q, C3, CR3 and the Architecture of Synaptic Elimination — A Companion Re-Evaluation under the ONS Methodology

ONS Methodology — Companion Re-Evaluation

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Re-evaluation of Oskar Fischer Prize entrant #158 (Beth Stevens) in dialogue with Homeostatic Microglial Collapse and Convergent Synaptic Collapse.

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This paper is a companion to Homeostatic Microglial Collapse, *Convergent Synaptic Collapse*, and *Bioenergetic Collapse. It evaluates the research program of Oskar Fischer Prize entrant #158, Beth Stevens, through the integrated Collapse framework, with particular attention to complement-mediated synaptic pruning as the effector arm of the homeostatic microglial collapse and the cross-substrate role of SORL1 in microglial lysosomal function.*

Abstract

The Homeostatic Microglial Collapse thesis identifies post-homeostatic microglial behavior as the effector arm whose substrate is the loss of the Butovsky signature. The thesis lists complement-mediated synaptic pruning, MMP release, and cytokine storms as the principal destructive outputs, but it does not yet trace the complement-pruning arm to its primary experimental source. That source is Beth Stevens's laboratory. Stevens, Barres, and colleagues established between 2007 and 2012 that the classical complement cascade — C1q opsonization □ C3 cleavage □ CR3-mediated phagocytosis by microglia — is the developmental program that eliminates redundant synapses during postnatal refinement, and that this same program is *re-activated* in the aging and Alzheimer's brain to eliminate synapses that should not be eliminated.

The Fischer Prize submission framed AD as a "dance battle between human and germ" with neurovascular dysfunction and amyloid-as-antimicrobial-peptide as the central claims. This framing dramatically undersold the actual lab program. The submission's neurovascular and infection-oriented narrative scored at CSC Relevancy 65.3 / TKQ 58.0, which were appropriate for the narrative as written but underweighted the complement-pruning mechanism that is the laboratory's principal output and is one of the most load-bearing single mechanisms in the Collapse trilogy. Stevens's more recent work on **border-associated macrophages (BAMs)** with circadian regulation and on **SORL1 in microglial lysosomal function** further extends her program into the HMC and Bioenergetic substrates

respectively.

Re-scored against the trilogy mechanism registry, the program scores 10/10 on Homeostatic Microglial Collapse tier-1 mechanisms (C1q, C3, CR3, complement pruning, BAMs), 8/10 on Convergent Synaptic Collapse (complement-mediated synapse elimination), and 5/10 on Bioenergetic Collapse (SORL1-lysosomal pathway). The submission–program divergence is large; Stevens's research is arguably the single most important external validation for the HMC framework and warrants a top-of-corpus re-evaluation.

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1. The Strategic Submission vs. the Mechanistic Program

Stevens's Fischer Prize submission centers on a neurovascular/infectious-etiology argument in which amyloid-β and tau function as antimicrobial peptides generated in response to brain infection, and BBB integrity determines whether the antimicrobial response remains protective or becomes pathological. The submission lists border-associated macrophages, SORL1 in microglia, and Bmal1-driven circadian neuroinflammation as ancillary mechanisms but devotes the rhetorical weight to the "dance battle between human and germ" framing.

This framing has two consequences. First, it overlaps with the antimicrobial-peptide hypothesis associated with Moir, Tanzi, and others, and the scoring system did not credit Stevens for novelty on a hypothesis she did not originate. Second, it almost entirely omits her own laboratory's principal output: the 2007 Cell paper (Stevens, Allen et al.) establishing C1q as the developmental synaptic-elimination tag; the 2012 Neuron paper (Schafer, Lehrman et al.) establishing CR3-mediated microglial phagocytosis as the elimination mechanism; the 2016 Science paper (Hong et al.) establishing complement-mediated synapse loss in mouse models of AD; and the subsequent decade of work mapping the complement-pruning mechanism across development, aging, and neurodegeneration.

The submission's strategic framing was epistemologically defensible — submitting a synthesis that integrated her work with the antimicrobial-peptide hypothesis was a coherent intellectual choice — but it produced a scoring outcome that does not reflect the magnitude of the laboratory's actual contribution. The

complement-pruning mechanism is the single most experimentally validated post-homeostatic microglial behavior in the AD literature, and it is the principal effector arm the HMC thesis identifies. The score gap between submission and program is among the largest in the corpus.

2. Complement C1q/C3/CR3 as the Effector Arm of Homeostatic Collapse

The Homeostatic Microglial Collapse framework distinguishes between (a) the homeostatic baseline maintained by TGF-β signaling and characterized by the Butovsky signature, and (b) the post-homeostatic states that emerge when this baseline collapses. The post-homeostatic states include the canonical DAM and LDAM trajectories and produce several effector outputs:

- Complement-mediated synaptic pruning
- MMP release with PNN degradation
- Pro-inflammatory cytokine secretion (TNF-α, IL-1β, IL-6)
- NLRP3-driven pyroptotic cytokine amplification

Each of these effector arms has a separate primary literature, and the HMC thesis must cite each by its principal source. For complement-mediated synaptic pruning, that source is Stevens's program. The mechanism the program established is:

- **C1q deposition** marks synapses for elimination. C1q expression in the brain is normally restricted to a developmental window but is re-activated under conditions of aging, neuroinflammation, and Aβ exposure.
- **C1q tagging triggers C3 cleavage** at the synapse, depositing C3 fragments (iC3b/C3b) that serve as opsonins.
- **CR3 (CD11b/CD18) on microglia recognizes opsonized synapses** and initiates phagocytic engulfment.
- **Microglial phagosome-lysosome fusion** then degrades the engulfed synaptic material.

This sequence is the mechanism the HMC thesis Section 5.1 ("Complement-Mediated Synaptic Pruning") should cite as its primary basis. The Convergent Synaptic Collapse thesis Section 12.2 also requires Stevens's program as

the citation for "complement-mediated synapse elimination" as one of the convergent mechanisms producing the synaptic-loss phenotype.

The mechanism also resolves the temporal puzzle of synaptic loss in AD: synaptic loss precedes neuronal loss by years, and the magnitude of synaptic loss is a stronger predictor of cognitive decline than amyloid burden. The complement-pruning mechanism predicts exactly this: a graded, ongoing elimination of synapses by re-activated developmental machinery, with cumulative effects that exceed the threshold for cognitive impairment well before bulk neuronal death.

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3. The Aβ-Induced Re-Activation of the Pruning Program

The Hong et al. 2016 *Science* paper is the load-bearing single experiment. The paper showed that:

- C1q is upregulated in the AD mouse brain before plaque formation
- C1q binds Aβ oligomers
- Aβ-induced C1q deposition tags synapses for elimination
- C3 knockout, CR3 knockout, or C1q knockout each rescue synaptic loss in the AD mouse model
- The rescue is independent of amyloid burden

The independence-of-amyloid-burden result is the key cross-substrate finding. It demonstrates that complement-mediated synapse loss is the *proximate cause* of cognitive decline in AD, not a downstream consequence of amyloid deposition. This is the empirical anchor for the HMC thesis claim that the effector arm of homeostatic microglial collapse is causally upstream of the synaptic phenotype, not downstream of it.

The Hong et al. paper also has therapeutic implications that the HMC thesis Section 11 should reflect. Annexon Biosciences' anti-C1q antibody ANX005 and Roche's anti-C3 antibody program are direct therapeutic spin-offs of this mechanism. ANX005 is in late-stage clinical trials for several neurodegenerative diseases; if it succeeds in AD, it will be the first therapy whose mechanism explicitly targets the post-homeostatic microglial effector arm rather than the upstream amyloid substrate.

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4. Border-Associated Macrophages (BAMs) and Circadian Neuroinflammation

Stevens's more recent program has identified **border-associated macrophages** as a distinct myeloid population residing in the meninges, perivascular spaces, and choroid plexus. BAMs are phenotypically and ontogenically distinct from parenchymal microglia: they derive from a separate yolk-sac lineage, express different transcription factors (including LYVE1, MRC1, CD163), and have distinct functional roles. The HMC thesis Section 7 ("Spatial Compartments: BAMs and Myeloid Ontogeny") requires Stevens's BAM work as its primary source.

The 2024–2025 work showing that **Bmal1 deletion in BAMs worsens plaque burden** identifies a circadian regulatory axis whose disruption is sufficient to accelerate AD pathology in mouse models. This finding is consequential for two reasons:

- It identifies BAMs as a separate intervention target — distinct from parenchymal microglia — whose function is genetically distinguishable.
- It identifies circadian disruption as a mechanism with direct mechanistic consequences for AD pathology, supplying empirical support for the epidemiological observation that sleep disruption is a risk factor for AD.

The HMC thesis Section 7 should be updated to include the Stevens BAM/Bmal1 work as the source of the circadian-neuroinflammation axis. The current thesis text mentions BAMs but does not yet anchor them in this specific empirical finding.

5. SORL1 in Microglial Lysosomal Function — Cross-Substrate Bridge to Bioenergetic Collapse

Stevens's program also includes recent (2025) work on **SORL1 in microglial lysosomal function**. SORL1 is the #3 LOAD GWAS locus (after APOE and BIN1) and was previously characterized principally as an endosomal sorting receptor in neurons. Stevens's group demonstrated that SORL1 is also expressed on microglia and that microglial SORL1 regulates lysosomal trafficking of phagocytosed amyloid. SORL1 risk variants in microglia produce a phagocytosis-without-degradation phenotype in which engulfed material accumulates in dysfunctional lysosomes — exactly the mechanism the Bioenergetic Collapse thesis identifies as the autophagy-lysosomal collapse, but operating in the microglial compartment.

This finding is cross-substrate. It connects:

- The Homeostatic Microglial Collapse framework (microglial state)
- The Bioenergetic Collapse framework (lysosomal function)
- The endosomal-nexus convergence node (SORL1 as the canonical retromer-pathway gene)
- The sporadic genetic architecture (SORL1 as a LOAD risk locus)

The Bioenergetic Collapse thesis Section 7 (NLRP3) and Section 11 (Bioenergetic Collapse Model) should be updated to reflect that SORL1 risk variants produce microglial lysosomal failure that is mechanistically continuous with the neuronal lysosomal failure described by Nixon/Gouras. The Rubinsztein review's identification of BIN1 as the sporadic anchor of Convergence 1 (neuronal autophagosome closure) has a natural complement in Stevens's identification of SORL1 as the sporadic anchor of the microglial arm of the same substrate collapse.

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6. The Stevens Triad and the Cross-Substrate Architecture

The three arms of Stevens's program — complement pruning, BAMs, and microglial SORL1 — form a triad that maps onto three distinct substrate failures:

No other single laboratory in the AD corpus supplies primary evidence for three substrate failures spanning two trilogy theses. This is the strongest case in the audit for a comprehensive re-evaluation.

7. Ten Key Questions Re-Evaluation

8. CSC Re-Evaluation with Trilogy-Relevance Overlay

Revised relevancy score: 82.0/100 (vs original 65.3).

The score gap of +16.7 is the largest of any entrant in the Tier-1 audit and confirms the audit's classification of Stevens as a **framing-mismatch** blindspot. The submission's narrative obscured the substrate-level mechanism that is the largest single contribution of any laboratory in the corpus to the HMC thesis.

9. Integration Recommendations for the Trilogy

Recommendation 1 — HMC Thesis §5.1 needs Stevens as primary source

The current Section 5 ("Effector Arms") of the HMC thesis describes complement-mediated synaptic pruning but does not yet have Stevens's program as the explicit primary citation. The section should be rewritten to position the C1q/C3/CR3 mechanism as the principal effector arm of homeostatic microglial collapse, with Stevens, Hong et al. 2016 *Science*, and the Schafer/Stevens 2012 *Neuron* paper as the load-bearing citations.

Recommendation 2 — HMC Thesis §7 needs Stevens BAM/Bmal1 work

The current Section 7 ("Spatial Compartments: BAMs and Myeloid Ontogeny") should be updated to include the Bmal1-deletion □ worsened-plaque-burden finding as the empirical anchor for the circadian-neuroinflammation axis.

Recommendation 3 — Bioenergetic Thesis §11 needs Stevens SORL1-microglial work

The Bioenergetic Collapse Model section should add SORL1 as the sporadic genetic anchor of the **microglial arm** of the autophagy-lysosomal collapse, complementing Rubinsztein's BIN1 (sporadic anchor of the neuronal arm) and presenilin mutations (familial anchor of the terminal degradation step).

Recommendation 4 — CSC Thesis §12.2 needs Stevens as primary source

The CSC thesis Section 12 (Neuroimmune Interface) currently cites complement-pruning but should be updated to explicitly anchor this on Stevens's program. The Hong et al. 2016 amyloid-independence-of-rescue finding is the empirical anchor for the claim that synaptic loss is causally upstream of the cognitive phenotype.

Recommendation 5 — ADC website integration

The Microglial monograph on the ADC site (chapters 1–5) anchors on Butovsky, Heneka, and the homeostatic-vs-DAM trajectory. A dedicated chapter or major subsection on the **complement-pruning effector arm** is the missing piece. Stevens is the natural "scientist pair" for one of the chapters — in the same way that the Synaptic monograph pairs Fischer (1907) with Gouras (2005), the Microglial monograph could pair Butovsky (homeostatic identity) with Stevens (effector pruning), making the conceptual arc *identity* ☐ *activation* ☐ *effector damage*. The Hong et al. 2016 result is the kind of single-figure proof point the ADC monographs use as chapter pivots.

The ANX005 / pegcetacoplan / SORL1-microglial trio also gives the Microglial monograph a clinically translatable therapeutic finale — a missing element relative to the Bioenergetic monograph's PARP-inhibitor finale and the Synaptic monograph's MMP-9-inhibitor finale.

10. Conclusion

Beth Stevens's research program is arguably the most under-scored single program in the Fischer Prize corpus. The submission's neurovascular-infection framing obscured a laboratory whose principal output is the most experimentally validated post-homeostatic microglial effector arm in the AD literature: complement C1q/C3/CR3-mediated synaptic pruning. The triad of complement pruning, BAM/Bmal1 circadian regulation, and microglial SORL1-lysosomal function maps onto three distinct trilogy substrate failures and supplies the HMC thesis with its principal effector mechanism, its spatial compartment, and its cross-substrate bridge to the Bioenergetic framework.

The score gap of +16.7 (from 65.3 to 82.0) is the largest in the Tier-1 audit. Stevens warrants a top-of-corpus re-evaluation, an explicit scientist-pair slot in the ADC Microglial monograph, and three separate thesis integrations (HMC §5.1, HMC §7, Bioenergetic §11) across two of the three trilogy theses.

References

• Stevens B, Allen NJ, Vazquez LE, et al. The classical complement cascade mediates CNS synapse elimination. *Cell* 2007;131(6):1164–1178.

• Schafer DP, Lehrman EK, Kautzman AG, et al. Microglia sculpt postnatal neural circuits in an activity and complement-dependent manner. *Neuron* 2012;74(4):691–705.

• Hong S, Beja-Glasser VF, Nfonoyim BM, et al. Complement and microglia mediate early synapse loss in Alzheimer mouse models. *Science* 2016;352(6286):712–716.

• Stevens lab (Van Hove et al. and follow-up papers) on BAM heterogeneity and Bmal1-circadian regulation, *Nature Neuroscience* / *Cell* (2024–2025).

• Stevens lab work on SORL1 in microglial lysosomal function (2025).

• Audit: Submission-Program Divergence Blindspots, kb/wiki/meta/audit*submission*program_blindspots.md (2026-04-17).

• Companion thesis: ONS*HomeostaticCollapse*Thesis.md.

• Companion thesis: ONS*SynapticCollapse*Thesis.md.

• Companion thesis: ONS*BioenergeticCollapse*Thesis.md.