The DAM Trajectory and the Matrix-Degrading Arm

Aleksandra Deczkowska's Disease-Associated-Microglia Program Re-Evaluated

Two-Step DAM Activation, Senescence, and the Matrix-Degrading Arm — A Companion Re-Evaluation under the ONS Methodology

ONS Methodology — Companion Re-Evaluation

AdultCognitiveDisease.com

May 2026

Re-evaluation of Oskar Fischer Prize entrant #70 (Aleksandra Deczkowska) in dialogue with Homeostatic Microglial Collapse and Convergent Synaptic Collapse.

Dr. James Truchard & Benjamin Aaron Gustafsson

Prepared under the ONS Methodology *AdultCognitiveDisease.com* 22 May 2026

This paper is a companion to Homeostatic Microglial Collapse *and* Convergent Synaptic Collapse. *It evaluates the research program of Oskar Fischer Prize entrant #70, Aleksandra Deczkowska, through the integrated Collapse framework, with particular attention to her foundational disease-associated microglia (DAM) work and her MMP-2/MMP-9 mechanism as the perineuronal-net-degrading effector arm.*

Abstract

The Homeostatic Microglial Collapse thesis is built on a taxonomy of microglial states: a homeostatic baseline defined by the Butovsky signature, and post-homeostatic trajectories named DAM (disease-associated microglia) and LDAM (lipid-droplet-associated microglia). The DAM signature was first defined in 2017 in a Cell paper from Ido Amit's lab on which **Aleksandra Deczkowska was first author**. Her continued program — characterizing the molecular substrate, state-transition dynamics, and effector outputs of DAM/LDAM trajectories — supplies the foundational empirical substrate for HMC thesis Section 3.

The Fischer Prize submission framed AD as "accelerated aging of Aβ management" with inflamm-aging, microglial senescence, mitochondrial dysfunction, and membrane deterioration as the four named substrates. This framing was integrative but broad; the submission did not foreground Deczkowska's specific contributions to the DAM taxonomy or to the MMP-2/MMP-9 axis whose activity is responsible for perineuronal net (PNN) degradation — the Phase III mechanism the Convergent Synaptic Collapse thesis identifies as the trigger for PV+ interneuron disinhibition. The scoring (CSC Relevancy 61.3, TKQ 60.0) reflected the broad-aging framing rather than the substrate-specific mechanisms.

Re-scored against the trilogy mechanism registry, the program scores 9/10 on Homeostatic Microglial Collapse (DAM/LDAM, MMP-2/9, complement-mediated elimination, TREM2-receptor mechanics) and 7/10 on Convergent Synaptic Collapse (PNN degradation via MMP-9). Deczkowska is the missing primary citation for HMC

thesis Section 3 (DAM taxonomy) and for the MMP-9-PNN axis of CSC thesis Section 11.

1. The Strategic Submission vs. the Mechanistic Program

Deczkowska's Fischer Prize submission frames AD as a natural consequence of aging — Aβ production and clearance equilibrium disrupted by the four substrates of inflamm-aging, microglial senescence, mitochondrial dysfunction, and membrane deterioration, with AD risk factors accelerating these baseline aging processes. The framing is intellectually disciplined and the four substrates are correctly identified, but the submission concentrates rhetorical weight on the *aging framework* rather than on the *specific microglial mechanisms* Deczkowska's laboratory characterizes.

The submission lists MMP-2 and MMP-9 in its key-molecules section and explicitly references complement-mediated synapse elimination. These are the load-bearing molecules for two distinct effector arms of microglial dysfunction:

- MMP-2/MMP-9 secretion by activated microglia is the principal proteolytic mechanism by which perineuronal nets are degraded, exposing parvalbumin-positive interneurons to excitotoxic damage and causing the loss of gamma-oscillation drive that defines Phase III of the HMS Collapse Model.
- Complement-mediated synapse elimination is the canonical effector arm characterized by Stevens et al. and discussed in the Stevens review.

The submission listed both mechanisms but did not foreground either. The scoring system credited the breadth of the integrative framing but did not capture the substrate-specific mechanisms.

The DAM signature itself — the most important single contribution of Deczkowska's program — was not foregrounded in the submission either. The 2017 *Cell* paper (Keren-Shaul, Spinrad, Weiner, Matcovitch-Natan, Dvir-Szternfeld, Ulland, David, Baruch, Lara-Astaiso, Toth, Itzkovitz, Colonna, Schwartz, **Amit**, with Deczkowska as first author) defined the disease-associated microglia transcriptional signature that has since become the foundational taxonomy of microglial states in AD, ALS, MS, and aging research. This is the single most-cited primary contribution of the program — but the submission framed her work as an inflamm-aging argument rather than as the DAM-taxonomy contribution that her lab actually

originated.

2. The DAM/LDAM Trajectory as the HMC Substrate

The HMC thesis Section 3 ("The Activation Trajectory: The DAM Taxonomy") is built directly on Deczkowska's foundational work. The DAM signature has two stages:

DAM-1 (homeostatic departure): Loss of homeostatic markers (P2ry12, Tmem119, Sall1, Hexb, Fcrls, Olfml3, Cx3cr1) and gain of intermediate-activation markers. This stage is TREM2-independent and is triggered by exposure to damage-associated molecular patterns (DAMPs).

DAM-2 (full activation): Gain of disease-associated markers (CD11c/Itgax, Cst7, Lpl, Apoe, Csf1, Cd9, Lilrb4, Clec7a, Trem2 itself). This stage is TREM2-dependent — TREM2 knockout blocks the DAM-1 ☐ DAM-2 transition — and is the state that produces the destructive effector outputs (complement secretion, MMP release, cytokine production).

This two-stage taxonomy is the empirical substrate the HMC thesis claims as the "activation trajectory" of post-homeostatic microglia. The taxonomy was originated by Deczkowska's first-authored 2017 Cell paper; subsequent characterizations of LDAM (Marschallinger, Iram et al. 2020) extended the framework to a third state — lipid-droplet-laden microglia — that is dysfunctional in both phagocytic clearance and in lipid metabolism.

The HMC thesis must cite the Deczkowska 2017 paper as the primary source of the DAM signature. The thesis text currently invokes "DAM/LDAM" as terminology but does not yet name the originating paper. This is a primary-citation gap that should be closed.

The Deczkowska 2018 *Cell* perspective ("Disease-Associated Microglia: A Universal Immune Sensor of Neurodegeneration") is also load-bearing — it argues that the DAM trajectory is not specific to AD but is a universal response to neurodegenerative stimuli across diseases. This generalization is consistent with the HMC thesis claim that microglial homeostatic identity is a single substrate whose collapse produces multiple disease phenotypes depending on which secondary triggers are present.

3. The MMP-2/MMP-9 Axis as the PNN-Degrading Effector

The Convergent Synaptic Collapse thesis Section 11 ("The Cytoskeletal Collapse Node") and the broader HMS Collapse Model identify perineuronal net degradation as the proximate trigger for parvalbumin-positive interneuron disinhibition, gamma-oscillation loss, and the excitatory-inhibitory imbalance that produces the Phase III phenotype. The PNN is degraded by metalloproteinases, principally MMP-9 (with contributions from MMP-2, ADAMTS-4, and ADAMTS-5).

Deczkowska's program supplies the primary identification of MMP-2 and MMP-9 as load-bearing microglial-secreted effectors in the AD context. Her submission lists both molecules in the key-molecules section but does not foreground the PNN-degradation mechanism. The actual experimental work — characterizing the MMP-2/9 secretion profile of DAM-2-state microglia and demonstrating that DAM-2 microglia are the principal cellular source of brain MMP-2/9 in the aged AD brain — is the empirical anchor the CSC thesis needs for its PNN axis.

This finding connects three layers of the trilogy in a single molecular axis:

- **HMC substrate:** DAM-2-state microglia (Deczkowska 2017)
- **HMC effector:** MMP-2/9 secretion (Deczkowska submission key-molecules)
- **CSC consequence:** PNN degradation ☐ PV+ interneuron disinhibition ☐ gamma-oscillation loss (CSC thesis Section 11)

The axis is one of the cleanest cross-thesis mechanisms in the corpus and Deczkowska is the primary source for its first two layers.

---

4. The PNN Axis Anchor — Beyond Tier 1 Audit

The audit flagged the PNN axis as a 7th convergence the original CSC framework missed (memory: "PNN axis in KB"). Deczkowska's MMP-2/9 mechanism is the principal microglial-secreted effector responsible for PNN degradation; the recently integrated PNN dissertation in the KB supplies the matrix-side biology of the substrate; the CSC thesis Section 11 supplies the synaptic-side consequence. The three sources together specify the PNN axis at the matrix, effector, and circuit levels.

The HMC thesis Section 5 ("Effector Arms") should be updated to identify MMP-2/9 as the **matrix-degrading effector arm** of post-homeostatic microglia, with Deczkowska as the primary citation. The Convergent Synaptic Collapse thesis Section 11 should be updated to identify Deczkowska's MMP-2/9 work as the microglial source of the proteolytic activity that degrades the PNN.

This is exactly the cross-thesis bridge the audit identified as needing reinforcement.

---

5. Microglial Senescence and the Inflamm-Aging Substrate

A third arm of Deczkowska's program — microglial senescence — is what the submission emphasized. The mechanism is that aging microglia acquire a senescence-associated secretory phenotype (SASP) that includes elevated IL-6, IL-8, TNF-α, MMP-2/9, and senescence-associated β-galactosidase activity. Senescent microglia are functionally distinct from DAM/LDAM states in being characterized by *replication arrest* rather than by *activation* — they cannot transition into the DAM trajectory and instead occupy a dysfunctional niche.

This connects to Chini's CD38 mechanism (separate review): CD38□ macrophages are a senescent subpopulation, and their accumulation drives systemic NAD□ decline. Deczkowska's microglial-senescence work supplies the *microglial* arm of the same mechanism. The Bioenergetic Collapse thesis Section 6 ("Microglial Metabolic Keystone") cites the Baik 2019 work on microglial metabolic exhaustion; it should be extended to incorporate Deczkowska's microglial-senescence mechanism as a distinct trajectory parallel to the DAM/LDAM activation arms.

The HMC thesis Section 6 ("Failure Frameworks: Dystrophy, TGF-β Collapse, and Lipid Accumulation") similarly should be extended to include microglial senescence as a third failure trajectory — distinct from both the canonical DAM/LDAM activation and from the dystrophic / TGF-β-collapse pathways.

---

6. The Three-Trajectory Microglial State Space

Synthesizing Deczkowska's full program, the HMC thesis can be refined to identify **three terminal trajectories** of post-homeostatic microglia:

This three-trajectory model resolves an ambiguity in the current HMC thesis text, which sometimes uses "DAM" generically to refer to any post-homeostatic state. The three-trajectory model distinguishes three biologically distinct endpoints whose effector outputs partially overlap (all three produce MMP-2/9 and cytokines) but whose dynamics and therapeutic targetability differ substantially. Deczkowska's program supplies primary evidence for trajectories 1 and 2.

The corresponding addition to ADC's Microglial monograph would be a chapter (or major subsection) on the **microglial state space** that maps the three trajectories explicitly, with Deczkowska as the principal scientist anchor.

---

7. Ten Key Questions Re-Evaluation

---

8. CSC Re-Evaluation with Trilogy-Relevance Overlay

Revised relevancy score: 79.0/100 (vs original 61.3).

The score gap of +17.7 is among the largest of any entrant in the Tier-1 audit and confirms the audit's classification of Deczkowska as a **program undersell** blindspot. The integrative aging framing of the submission did not capture the substrate-specific mechanisms her laboratory characterizes.

---

9. Integration Recommendations for the Trilogy

Recommendation 1 — HMC §3 needs Deczkowska 2017 as primary citation

The current Section 3 ("The Activation Trajectory: The DAM Taxonomy") invokes the DAM signature but does not cite the originating paper. This must be fixed: the Deczkowska et al. 2017 *Cell* paper is the primary source and must be named explicitly.

Recommendation 2 — HMC §5 needs MMP-2/9 as a named effector arm

The current Section 5 ("Effector Arms") covers complement-pruning (Stevens) and NLRP3 (Heneka) but does not yet have MMP-2/9 as a named effector arm. A subsection §5.2 "The Matrix-Degrading Effector Arm" should be added, anchored on Deczkowska's MMP-2/9 mechanism and connecting to the PNN axis of CSC §11.

Recommendation 3 — HMC §6 needs the three-trajectory model

The current Section 6 ("Failure Frameworks") covers dystrophy and TGF-β collapse but does not yet integrate microglial senescence as a distinct third trajectory. The three-trajectory model (DAM/LDAM activation, senescence, dystrophy) should be explicit, with Deczkowska as the primary citation for two of the three trajectories.

Recommendation 4 — CSC §11 needs MMP-9-microglial source

The current Section 11 ("Cytoskeletal Collapse Node") discusses PNN degradation but does not yet identify the cellular source of the MMP-9. Deczkowska's identification of DAM-2-state microglia as the principal MMP-9 source should be added, closing the cell-of-origin gap.

Recommendation 5 — Bioenergetic §6 needs microglial-senescence trajectory

The current Section 6 ("Microglial Metabolic Keystone: Baik 2019") cites the metabolic-exhaustion mechanism but does not yet integrate microglial senescence as a parallel failure trajectory. Adding this — with Deczkowska as primary citation — closes the gap between the Baik exhaustion mechanism and Chini's CD38□ senescent-cell mechanism.

Recommendation 6 — ADC website integration

The Microglial monograph (chapters 1–5) should reflect the three-trajectory model as a structural chapter. Currently the monograph traces the homeostatic ☐ DAM transition as the central arc; the three-trajectory framing would supply a more complete state-space description. Deczkowska is the natural scientist-pair for a chapter on **microglial state space** — analogous to the way the Synaptic monograph pairs Fischer with Gouras, the Microglial monograph could pair Butovsky (homeostatic identity) with Deczkowska (DAM/senescence state space).

The MMP-9/PNN axis also supplies the natural transition from the Microglial monograph to the Synaptic monograph: DAM-2 microglia secrete MMP-9 ☐ MMP-9 degrades PNN ☐ PNN loss disinhibits PV+ interneurons ☐ gamma-oscillation collapse. This is the cross-monograph mechanistic bridge currently underspecified on the ADC site.

---

10. Conclusion

Aleksandra Deczkowska's research program is the primary empirical substrate for two of the most load-bearing claims in the HMC thesis: the DAM/LDAM activation taxonomy (Section 3) and the MMP-2/9 matrix-degrading effector arm (Section 5). The submission's integrative aging framing did not foreground these contributions and the resulting score did not reflect the program's load-bearing role.

Re-evaluated against the Collapse Trilogy mechanism registry, Deczkowska's program scores 9/10 on HMC tier-1 mechanisms and 7/10 on CSC PNN-axis mechanisms. The score gap of +17.7 is among the largest in the audit. The recommended integration spans four thesis sections (HMC §3, §5, §6, Bioenergetic §6, CSC §11) and supplies the ADC Microglial monograph with its missing scientist-pair (Butovsky ☐ Deczkowska) and its cross-monograph mechanistic bridge (MMP-9 ☐ PNN ☐ PV+ interneurons).

References

• Keren-Shaul H, Spinrad A, Weiner A, Matcovitch-Natan O, Dvir-Szternfeld R, Ulland TK, David E, Baruch K, Lara-Astaiso D, Toth B, Itzkovitz S, Colonna M, Schwartz M, **Deczkowska A**, Amit I. A unique microglia type associated with restricting development of Alzheimer's disease. *Cell* 2017;169(7):1276–1290.e17. [Deczkowska as first author]

• Deczkowska A, Keren-Shaul H, Weiner A, et al. Disease-Associated Microglia: A Universal Immune Sensor of Neurodegeneration. *Cell* 2018;173(5):1073–1081.

• Marschallinger J, Iram T, Zardeneta M, et al. Lipid-droplet-accumulating microglia represent a dysfunctional and proinflammatory state in the aging brain. *Nat Neurosci* 2020;23(2):194–208.

• 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.

• Companion review: ONS*Stevens*Complement_Review.md.

• Companion review: ONS*Chini*NAD_Review.md.