HOMEOSTATIC COLLAPSE

A Unified Synthesis of Microglial Contributions to Alzheimer's Disease

Butovsky · Amit/Keren-Shaul · Colonna · Stevens · Shatz
Crapser · Lemke · Marschallinger · Prinz/Kierdorf
Streit · von Bernhardi · de Vries

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Abstract

The central impasse in contemporary microglial biology of Alzheimer's disease arises from the simultaneous and apparently incompatible accumulation of evidence for two causal frameworks. The first, an "attack" model, holds that chronically activated microglia drive neurodegeneration through complement-mediated synaptic pruning, matrix-metalloproteinase-driven extracellular matrix degradation, NLRP3 inflammasome activation, and sustained inflammatory cytokine release, with TREM2-dependent disease-associated microglial states acting as the cellular engine of this destructive cascade. The second, a "failure" model, holds that senescent, dystrophic, and phagocytically exhausted microglia progressively withdraw neuroprotective support from metabolically vulnerable neurons, losing their capacity for amyloid clearance, perineuronal matrix maintenance, and trophic sustenance of parvalbumin-positive interneurons, such that the central lesion in Alzheimer's disease is not microglial attack but microglial abandonment. Both frameworks command substantial experimental support; each predicts outcomes the other cannot explain; and each has generated therapeutic programs whose clinical failures can be interpreted as evidence for the other.

This synthesis, conducted under the Organic Network Synthesis methodology, integrates twelve primary research programs spanning the homeostatic microglial signature, the disease-associated microglia taxonomy, TREM2 receptor mechanics, complement-mediated synaptic pruning, microglia-driven perineuronal net degradation, TAM receptor-mediated phagocytic clearance, lipid-droplet-accumulating microglia, border-associated macrophage compartmentalization, microglial dystrophy, TGF-β/SMAD signaling failure, and the cognitive resilience neuropathology of preserved microglial homeostasis. The integration argues that the attack and failure frameworks are not competing hypotheses but rather two projections of a single underlying pathological process: the collapse of the TGF-β-maintained homeostatic microglial state defined by Butovsky and colleagues. We propose the **Homeostatic Collapse Model**, in which loss of the homeostatic signature simultaneously unleashes maladaptive effector functions and impairs protective functions, such that microglia in any given brain region at any given disease stage exhibit a mixture of attacking and failing behaviors whose proportions depend on local lipid availability, iron burden, TREM2 functionality, and the developmental identity of the myeloid compartment in question.

Three emergent convergences organize this model. First, the homeostatic signature itself is the single upstream event whose loss is necessary and possibly sufficient for downstream microglial pathology in Alzheimer's disease, and the various "activated" and "dystrophic" states described across the literature are better understood as distinct collapse trajectories from a common homeostatic origin than as opposing endpoints. Second, TREM2 occupies a pivot position where loss-of-function variants simultaneously reduce activation—consistent with the attack framework's therapeutic predictions—and impair clearance—consistent with the failure framework's—such that

the paradoxical status of TREM2 as an Alzheimer's disease risk allele is resolved only when both frameworks are understood as operating within the same cell at the same time. Third, the perineuronal net represents the concrete mechanistic case where attack and failure are not merely compatible but mechanistically identical: the microglial digestion of aggrecan and tenascin-R around parvalbumin-positive interneurons is at once an act of matrix destruction and an act of protective withdrawal, producing both outcomes in a single effector step.

We further argue that the cognitive resilience phenotype, in which individuals sustain high amyloid and tau burdens without cognitive decline, is best explained as preservation of the homeostatic microglial state rather than as absence of pathology or as cognitive compensation, and that the de Vries 2024 neuropathological evidence positions homeostatic preservation as a distinct and experimentally tractable substrate of resilience. We contend that therapeutic strategies predicated on microglial depletion, TREM2 agonism, or complement inhibition have each captured a partial truth within a larger homeostatic-restoration framework, and that the systematic failure of anti-inflammatory trials in Alzheimer's disease reflects not the inadequacy of the neuroinflammation hypothesis but the conceptual incompleteness of treating microglial activation as a gain-of-function rather than as the visible surface of a deeper loss-of-homeostasis collapse. The integrated model predicts that effective microglial therapeutics for Alzheimer's disease will not attempt to silence or activate microglia but will aim to reinstate the TGF-β-maintained homeostatic signature itself, and that the perineuronal net–parvalbumin interneuron axis offers the most tractable molecular readout of whether a given intervention succeeds or fails at restoring homeostasis rather than merely modulating its collapse.

1. Introduction: The Microglial Impasse

The microglial biology of Alzheimer's disease has entered a period of sustained theoretical deadlock. More than two decades after the genome-wide association studies identifying TREM2, CD33, CR1, MS4A, PLCG2, ABI3, and the broader complement of innate immune risk alleles established that Alzheimer's disease is, at least in part, a disease of myeloid cell biology, the field has produced two mature and mutually incompatible accounts of what microglia actually do in the Alzheimer's brain. These accounts have developed in parallel, each generating its own experimental paradigms, its own therapeutic hypotheses, and its own set of confirmatory findings, and neither has been able to subsume or refute the other. The intellectual cost of this impasse has been substantial: every microglial depletion experiment can be read either as evidence that microglia are driving pathology or as evidence that microglia are restraining it; every TREM2 manipulation can be framed as rescue or as harm depending on which framework the investigator holds; and every anti-inflammatory trial that fails to modify disease can be interpreted as confirming the failure hypothesis while being simultaneously dismissed by adherents of the attack hypothesis as insufficient pharmacological penetrance or wrong target selection.

The attack framework has its historical origin in the complement discoveries of Stevens and colleagues in the late 2000s, which demonstrated that C1q and C3 tag developing synapses for microglial engulfment during critical-period refinement and that this pathway is pathologically reactivated in Alzheimer's disease models to drive early synaptic loss before plaque formation. The framework was consolidated by the single-cell RNA sequencing work of Keren-Shaul, Amit, and colleagues in 2017, which identified a discrete disease-associated microglial state, termed DAM, that accumulates around amyloid plaques in 5xFAD mice and whose transition from a TREM2-independent Stage 1 to a TREM2-dependent Stage 2 is characterized by the upregulation of APOE, CST7, CTSB, CTSD, LPL, SPP1, ITGAX, CLEC7A, and TYROBP alongside the downregulation of the homeostatic markers P2ry12, Tmem119, and Cx3cr1. The framework was extended to the extracellular matrix by Crapser and colleagues in 2020, who demonstrated that perineuronal nets are extensively degraded in 5xFAD cortex and in human Alzheimer's disease tissue, and that pharmacological microglial depletion via CSF1R inhibition prevents this degradation, establishing microglia as the mechanistic effectors of perineuronal net loss. It was refined by TREM2 structural and signaling work from the Colonna laboratory, which established TREM2 as a lipid and Aβ-binding receptor coupled via DAP12/TYROBP to microglial metabolic fitness and phagocytic capability, and it was given a cell-autonomous synaptic extension by Shatz and colleagues, who showed that C4d binds LilrB2/PirB on postsynaptic terminals and mediates spine loss through a pathway parallel to, but distinct from, the classical complement cascade. Across these programs, the operative conception is one of microglia as active pathological agents: cells that attack synapses, digest the matrix, engulf amyloid inefficiently and inflammatorily, and release cytokines that amplify the injury.

The failure framework has a longer and more marginal history. Its founding observations date to the work of Streit and colleagues in the late 1990s and early 2000s, who catalogued a distinct morphological microglial phenotype in the aged and Alzheimer's brain characterized by cytoplasmic beading, process fragmentation, and deramification, and termed this state microglial dystrophy. Unlike classically activated microglia, dystrophic microglia exhibit a withdrawal of surveillance capacity, a loss of fine process arborization, and a spatial association with pre-tangle tau pathology that precedes rather than follows neurodegeneration. Streit argued that these cells represent the terminal consequence of iron-driven oxidative senescence: ferritin accumulation within microglia generates Fenton-reaction hydroxyl radicals that damage the microglia themselves, exhausting their neuroprotective capacity and leaving the ensheathed neurons without trophic or phagocytic support. This conception was given biochemical mechanism by von Bernhardi and colleagues, whose work identified the progressive failure of the TGF-β/SMAD pathway as the signaling substrate of aged microglial dysfunction: in the aged brain, chronic oxidative stress dysregulates SMAD-mediated transcription such that microglia become simultaneously pro-inflammatory in their cytokine output and clearance-incompetent in their phagocytic capacity—active but ineffective, activated but no longer protective. The framework was expanded by Marschallinger and colleagues, who identified a lipid-droplet-accumulating microglial state, termed LDAM, that accumulates with age in the hippocampus and is transcriptionally, lipidomically, and functionally distinct from DAM, exhibiting impaired phagocytosis, elevated reactive oxygen species production, and features of senescent exhaustion. It was connected to the phagocytic clearance pathway by Lemke and colleagues, whose work on the TAM receptor tyrosine kinases Tyro3, Axl, and Mer established that these receptors mediate a protective microglial phagocytosis of amyloid plaques through the bridging ligands GAS6 and PROS1, and that disruption of this axis impairs plaque compaction and exacerbates pathology. Across these programs, the operative conception is not one of microglial attack but of microglial withdrawal: cells that can no longer protect, cannot clear, and whose cytokine output is the exhaust of failed homeostasis rather than the engine of pathogenesis.

These two frameworks have co-existed in the literature for more than a decade, and their co-existence has produced a set of paradoxes that neither can internally resolve. The most acute is the TREM2 paradox. Loss-of-function variants of TREM2, most prominently the R47H allele, confer Alzheimer's disease risk at a magnitude comparable to APOE4 heterozygosity. Within the attack framework, this is difficult to reconcile: if disease-associated microglia drive pathology, then variants that impair the DAM Stage 1 to Stage 2 transition should reduce rather than increase risk. Within the failure framework, the paradox dissolves: TREM2 hypofunction impairs microglial lipid sensing, metabolic fitness, and phagocytic clearance, and loss-of-function variants therefore confer risk by deepening the failure. Yet the failure framework cannot easily explain the Crapser result that CSF1R-mediated microglial depletion rescues perineuronal net integrity—if microglia are failing rather than attacking, their removal should worsen pathology, not prevent it. The resolution to both paradoxes, we argue, requires abandoning the attack/failure dichotomy altogether in favor of a

single model in which a common upstream event—the collapse of the homeostatic state defined by Butovsky—simultaneously produces both the attack and failure phenotypes in ways that shift as a function of local biochemical context, disease stage, and the developmental identity of the myeloid compartment.

The Organic Network Synthesis methodology, as applied in the preceding analysis of convergent synaptic collapse, approaches deadlocks of this kind not by adjudicating between frameworks but by searching for the emergent convergences that reveal both frameworks as partial projections of a deeper unified process. In what follows, we undertake this synthesis across twelve primary research programs, treating each as a candidate node within a distributed network of microglial pathogenesis. The goal is not to declare a winner among activation and dystrophy accounts, nor to offer a diplomatic compromise in which both are granted partial truth, but to identify the specific mechanistic events at which the two apparent frameworks become indistinguishable and to articulate the model that explains why they must.

2. The Homeostatic Baseline: The Butovsky Signature

Any synthesis of microglial contributions to Alzheimer's disease must begin with the definition of the homeostatic state itself, because every pathological microglial phenotype described in the subsequent literature is defined operationally as a deviation from this baseline. The work of Butovsky and colleagues, beginning with the 2014 identification of a unique adult microglial transcriptional signature and extending through the subsequent decade of refinement, established that adult central nervous system microglia express a discrete molecular identity distinct from all other tissue macrophage populations. This signature is defined at the protein and transcript level by P2ry12, Tmem119, Sall1, Hexb, Fcrls, Olfml3, Cx3cr1, and a larger ensemble of genes whose expression is maintained by continuous TGF-β signaling from the surrounding neural and vascular parenchyma. The TGF-β dependence of the signature is not incidental: conditional deletion of TGF-β receptor signaling in microglia causes rapid loss of the homeostatic phenotype and acquisition of a more macrophage-like, reactive state, demonstrating that the homeostatic identity is not a cell-intrinsic property but an actively maintained consequence of niche signaling.

The functional content of the homeostatic signature is equally specific. P2ry12 couples microglia to ATP and ADP gradients, allowing them to sense and respond to neuronal injury through rapid process extension toward damaged sites. Tmem119 and Sall1 participate in transcriptional programs that distinguish microglia from infiltrating monocytes and maintain their surveillance morphology. Cx3cr1, ligated by neuronal fractalkine, mediates an anti-inflammatory tonic signal that restrains cytokine production under non-pathological conditions. The overall phenotype is one of constant, fine-process surveillance, rapid response to local injury, and restrained cytokine output—a

homeostatic set-point actively maintained against the macrophage default. The critical insight from the Butovsky program is that this baseline is not merely the resting state of a cell that can become activated; it is an energetically expensive, niche-dependent phenotype whose maintenance requires continuous signaling input, and whose loss is not a gain of function but a collapse into a less differentiated state.

This framing matters enormously for the interpretation of every downstream microglial phenotype described in the Alzheimer's disease literature. When disease-associated microglia, lipid-droplet-accumulating microglia, and dystrophic microglia are each defined by the loss of P2ry12, Tmem119, and Cx3cr1 expression, the conventional interpretation—that these represent distinct "activation states"—misses the more fundamental point that all three are variants of the same underlying event: the failure of TGF-β-maintained homeostatic differentiation. The DAM state, the LDAM state, and the dystrophic state differ in which alternative programs they adopt after homeostatic collapse, but they do not differ in the primary event of homeostatic loss itself. This reframing is the first convergence of the synthesis: the homeostatic signature is the upstream variable, and the apparent proliferation of disease-associated states is downstream heterogeneity generated by context-dependent responses to a shared loss-of-baseline event.

3. The Activation Trajectory: The DAM Taxonomy

The 2017 Keren-Shaul and Amit report in *Cell*, "A Unique Microglia Type Associated with Restricting Development of Alzheimer's Disease," established the first high-resolution taxonomy of microglial states in an Alzheimer's disease model through massively parallel single-cell RNA sequencing of microglia from 5xFAD mice. The paper's central finding was that microglial activation in Alzheimer's disease does not follow a continuous gradient from homeostatic to fully activated, as the earlier M1/M2 framework had implied, but rather proceeds through a discrete two-step trajectory. Stage 1 DAM cells downregulate the Butovsky homeostatic signature and upregulate an initial activation program without requiring TREM2 signaling. Stage 2 DAM cells, reached only through TREM2-dependent signaling, further upregulate APOE, CST7, CTSB, CTSD, LPL, SPP1, ITGAX, CLEC7A, TYROBP, and the broader program of phagocytic and lipid-sensing genes that characterizes mature disease-associated microglia. Cells with TREM2 loss-of-function arrest at Stage 1, providing genetic confirmation of the two-step architecture.

The DAM framework has become the dominant taxonomic language of microglial biology in neurodegeneration, and its adoption has been so rapid and complete that it now structures the interpretation of most microglial studies in the field. Its strengths are considerable: it supplied a quantitative, molecular definition of "activated" microglia that replaced the vague and often inconsistent histological classifications of the preceding era; it connected the TREM2 genetic risk

signal directly to a specific cellular phenotype; and it aligned the microglial field with the broader single-cell revolution in immunology. But the framework also carried a hidden conceptual commitment: by naming the activated state "disease-associated" and by defining its transcriptional signature through comparison with homeostatic controls, it implicitly positioned DAM as a gain-of-function—a state acquired by microglia that would otherwise have been protective. This framing has shaped the therapeutic conclusions drawn from the framework, which have gravitated toward interventions that would reduce DAM acquisition, silence its inflammatory output, or block its TREM2-dependent transition to Stage 2.

A more careful reading of the DAM data, however, supports a different interpretation. The most robust feature of the DAM signature is not the upregulation of a coherent activation program but the downregulation of the homeostatic one: the loss of P2ry12, Tmem119, Cx3cr1, and the broader Butovsky signature is the single most consistent feature across DAM definitions, while the upregulated genes show substantial heterogeneity across datasets, species, brain regions, and disease stages. The APOE, LPL, SPP1, and CTSB/D program acquired by Stage 2 DAM cells overlaps substantially with the lipid-metabolism and clearance programs seen in LDAM and in peripheral lipid-handling macrophages, suggesting that Stage 2 DAM is not a unique disease state but a specific downstream trajectory available to microglia that have already lost their homeostatic baseline and now encounter the lipid and amyloid-rich environment of the plaque. On this reading, DAM is not an ascent toward activation but a descent from homeostasis, and its TREM2 dependence reflects not the TREM2 requirement for activation but the TREM2 requirement for productive engagement with the lipid and apolipoprotein cargo that the environment presents after homeostatic collapse has already occurred.

This reframing dissolves much of the apparent tension between the DAM framework and the Streit dystrophy framework. Dystrophic microglia are Stage 1-arrested cells that never acquired the TREM2-dependent lipid-sensing program, either because TREM2 function is compromised or because the relevant lipid cargo is unavailable or the cellular metabolism is too exhausted to support the transition. DAM Stage 2 cells and dystrophic cells are not opposing states but alternative fates of cells that have undergone the same upstream event—homeostatic collapse—and differ only in whether they retained the metabolic and receptor capacity to execute the lipid-clearance program downstream.

4. The Receptor Pivot: TREM2 and the Colonna Framework

TREM2 occupies a unique position in the microglial literature of Alzheimer's disease. It is the only innate immune receptor whose loss-of-function variants confer risk at a magnitude approaching APOE4 heterozygosity; it is the molecular link between the genetic risk architecture of Alzheimer's disease and the cellular biology of disease-associated microglia; it is the gatekeeper of the Stage 1 to Stage 2 DAM transition; and it is the receptor whose paradoxical behavior—conferring risk through hypofunction in a framework that treats microglial activation as pathogenic—has been the most acute source of theoretical tension in the field.

The Colonna laboratory, over more than a decade of structural, biochemical, and genetic work, has established that TREM2 functions as a lipid and apolipoprotein sensor coupled through the DAP12/TYROBP adapter to SYK kinase and downstream PI3K, AKT, and mTOR signaling. The ligand repertoire of TREM2 is broad and overlapping: it binds anionic phospholipids exposed on damaged membranes, it binds APOE and APOJ/clusterin complexes, it binds Aβ oligomers and fibrils, and it binds the lipid cargo of cellular debris. These ligands share a common feature—exposure of negatively charged lipid surfaces—and TREM2 appears to function as a general sensor of membrane damage and lipid disposition at the microglial surface. Engagement of TREM2 by its ligands triggers DAP12 phosphorylation, SYK activation, and a metabolic program that shifts microglia toward oxidative phosphorylation, lipid internalization, and phagocytic competence. Loss-of-function variants, including R47H, disrupt ligand binding or downstream signaling and thereby impair the metabolic and phagocytic responses that follow ligand engagement.

The Colonna framework reveals TREM2 as a receptor whose function is neither purely activating nor purely protective but rather both, in a way that depends entirely on how its output is interpreted. From within the attack framework, TREM2 engagement drives the Stage 2 DAM transition and its associated inflammatory and phagocytic program, and TREM2 loss-of-function should therefore protect against pathology. From within the failure framework, TREM2 engagement enables protective phagocytic clearance of amyloid and damaged membranes, and TREM2 loss-of-function should therefore exacerbate pathology by leaving microglia unable to execute clearance. Both predictions follow logically from each framework, and both are grounded in real biology. The genetic evidence—that TREM2 loss of function increases risk—can only be reconciled with the attack framework by ad hoc auxiliary hypotheses, while it is consistent with the failure framework's predictions in a straightforward way.

But the failure framework alone cannot explain the CSF1R-depletion results: if TREM2 function were purely protective, then eliminating microglia entirely should produce the worst possible outcome, and yet Crapser's demonstration that microglial depletion rescues perineuronal net integrity shows that the net effect of microglial presence in the 5xFAD model is destructive with

respect to at least one critical substrate. The only coherent reading of the combined genetic and pharmacological data is that TREM2 simultaneously supports two distinct functions—protective clearance and destructive effector activity—and that loss of TREM2 function disproportionately impairs the protective arm, whereas loss of microglia altogether disproportionately eliminates the destructive arm. Both interventions reveal that TREM2-positive microglia in the Alzheimer's disease brain are doing both at once, and the direction of net effect depends on which substrate is measured.

This is the second convergence of the synthesis: TREM2 is not the receptor of microglial activation, nor the receptor of microglial protection, but the receptor through which a post-homeostatic microglial cell attempts to execute a salvage program in an environment it was not evolved to encounter. When the salvage program succeeds, it clears amyloid; when it fails, it releases inflammatory mediators and effector enzymes. The genetic risk conferred by TREM2 loss-of-function reflects the uneven distribution of salvage outcomes: impaired TREM2 signaling shifts the balance from successful clearance toward unsuccessful salvage, and therefore from protection toward damage.

5. The Effector Arms: How Post-Homeostatic Microglia Produce Damage

The question of how microglia actually damage tissue in Alzheimer's disease has been answered in four distinct mechanistic idioms, each associated with a specific research program and each capturing a different effector arm of the post-homeostatic microglial repertoire. These are the complement-mediated synaptic pruning pathway of Stevens and colleagues; the C4d-LilrB2 cell-autonomous pruning pathway of Shatz and colleagues; the matrix metalloproteinase and cathepsin-driven perineuronal net degradation pathway of Crapser and colleagues; and the TAM receptor-mediated phagocytic clearance pathway of Lemke and colleagues, which differs from the others in being protective rather than destructive but which belongs to the same effector category because it is gated by the same upstream events.

The Stevens program established that the classical complement cascade, specifically C1q and C3, is pathologically reactivated in mouse models of Alzheimer's disease to tag vulnerable synapses for microglial engulfment via complement receptor 3 (CR3/CD11b). This pathway operates before plaque formation, is detectable in the earliest stages of disease in vulnerable hippocampal circuits, and can be blocked genetically by C1q deletion or pharmacologically by complement inhibition to rescue synaptic loss. The mechanism is conceptually clean: a developmental synaptic refinement pathway is reinstated in the adult brain in response to amyloid pathology, and its reactivation drives the early synaptic losses that precede overt neurodegeneration. The framework supplies the most

widely cited mechanistic account of the attack model and has generated an active therapeutic program around complement inhibition.

The Shatz program identified a parallel but distinct synaptic pruning pathway operating through C4d, a cleavage product of C4 complement, which binds with nanomolar affinity to LilrB2/PirB receptors on postsynaptic terminals and triggers a cell-autonomous cytoskeletal collapse and synaptic withdrawal program. Crucially, the C4d-LilrB2 pathway does not require microglial engulfment: it is a neuron-intrinsic elimination signal triggered by complement deposition, and it operates in parallel with the Stevens microglial engulfment pathway rather than competing with it. Together, the Stevens and Shatz pathways establish that complement activation in Alzheimer's disease can drive synapse loss through two distinct mechanisms—one microglial and one cell-autonomous—that both depend on upstream complement deposition but diverge at the point of execution.

The Crapser program extended the effector literature beyond the synapse to the extracellular matrix, demonstrating that perineuronal nets are extensively lost in 5xFAD cortex and in human Alzheimer's disease tissue, that aggrecan accumulates within dense-core plaques consistent with microglial phagocytic capture, and that pharmacological microglial depletion via CSF1R inhibition with PLX5622 prevents perineuronal net loss. This result is the single most important experimental demonstration that microglia are the mechanistic effectors of a destructive process in the Alzheimer's disease brain: removing microglia rescues the matrix, which establishes net causality regardless of any other interpretive considerations. The molecular effectors are matrix metalloproteinases MMP-2, MMP-9, and the ADAMTS family, together with cathepsin-S and other lysosomal hydrolases released into the extracellular space during the failed phagocytic attempts that characterize Stage 2 DAM activity around plaques.

The Lemke program identified the TAM receptor tyrosine kinases—Tyro3, Axl, and Mer—as mediators of a distinct, protective microglial phagocytic pathway operating through the bridging ligands GAS6 and PROS1. TAM receptor engagement couples phosphatidylserine exposure on damaged membranes to efficient, non-inflammatory phagocytosis, and disruption of the axis impairs plaque compaction and exacerbates pathology. The TAM program is the clearest evidence in the field that microglial phagocytosis can be genuinely protective, and that the destructive phagocytic activity described by the Crapser, Stevens, and Shatz programs represents failure modes of a pathway that, when executed competently, serves clearance rather than attack.

The Weaver program supplies a fifth effector arm whose mechanism is conceptually distinct from the other four and that the integration of the attack literature has insufficiently incorporated. Weaver's framework, recognized by the 2022 Oskar Fischer Silver Prize, reconceptualizes amyloid-beta itself as an innate immune effector—an antimicrobial peptide whose deployment by post-homeostatic microglia is gated by recognition of pathogen-associated molecular patterns (LPS,

lipoteichoic acid) and damage-associated molecular patterns (cardiolipin, GM1 ganglioside, oxidized phospholipids). The originality of the framework lies in its electrophysiological identity-error claim: aged neuronal membranes drift toward biophysical profiles—surface charge, lipid composition, exposed ganglioside head groups—that resemble bacterial membranes sufficiently to misdirect AMP-class effectors at neuronal targets. The Aβ then forms pore-like structures in neuronal membranes, producing necrotic rather than apoptotic death, and the necrotic neurons release GM1-Aβ complexes into the extracellular space where these complexes act as DAMPs that re-trigger the same innate-immune deployment in surrounding microglia. This produces a self-propagating cycle of mistargeted AMP attack distinct from complement-driven engulfment, matrix-metalloproteinase-driven matrix digestion, C4d-driven cell-autonomous withdrawal, or TAM-mediated phagocytic clearance—and it predicts that the attack phenotype will spread spatially across neighboring neurons through the GM1-Aβ DAMP signal rather than requiring independent reactivation at each site. The framework supplies the molecular grammar for why Aβ becomes destructive in the post-homeostatic state: not because microglia are intrinsically attacking, but because the AMP they deploy as part of an evolutionarily conserved host-defense program is being directed at substrate whose biophysical features have drifted into the recognition window the program evolved to discriminate against. Weaver's mechanism therefore does not slot into the phagocytic-engagement-success spectrum that organizes the other four arms; its destructive output is generated through a parallel effector deployment in which Aβ itself is the released effector molecule rather than a complement opsonin, matrix metalloproteinase, cathepsin, or cytoskeletal-collapse signal. The Homeostatic Collapse Model must accommodate both effector axes: the phagocytic-engagement axis whose integration follows immediately below, and the AMP-deployment axis whose integration into the model is that successful tissue-restricted Aβ deployment under intact homeostasis serves host-defense, while sustained deployment in a post-homeostatic context whose neuronal substrate has drifted toward the AMP-recognition window produces a propagating attack indistinguishable from autoimmunity at the cellular level.

The integration of these four phagocytic-engagement programs supplies the third and most important convergence of the synthesis. Each of them describes the same underlying event—microglial phagocytic engagement with some substrate in the Alzheimer's disease brain—but describes it in a different state of success. Successful TAM-mediated engagement clears amyloid without collateral damage. Unsuccessful engagement at the perineuronal net releases matrix metalloproteinases that digest the aggrecan scaffold. Unsuccessful engagement at the synapse proceeds through complement-dependent engulfment that eliminates functional circuitry. Unsuccessful C4d-mediated signaling triggers cell-autonomous spine withdrawal. The attack phenotype is not a distinct program; it is the outcome of a protective program attempted and failed, with the failure producing collateral damage proportional to the effector enzymes released during the attempt. This framing explains why microglial depletion rescues perineuronal nets (it prevents failed engagement attempts) without requiring that microglia be gratuitously destructive (they are

not; they are attempting salvage in a context they cannot manage), and it explains why TREM2 loss-of-function is a risk allele (it prevents successful engagement while leaving the cell capable of failed ones).

6. The Failure Frameworks: Dystrophy, TGF-β Collapse, and Lipid Accumulation

The three research programs that explicitly articulate microglial contributions to Alzheimer's disease in failure-of-function terms—Streit on dystrophy, von Bernhardi on TGF-β/SMAD collapse, and Marschallinger on lipid-droplet-accumulating microglia—have been marginalized for most of their history by the dominance of the attack framework, but each supplies mechanistic content that is indispensable to the integrated synthesis.

The Streit dystrophy framework begins with a histological observation that is difficult to explain within the activation paradigm: a substantial fraction of microglia in the aged and Alzheimer's disease brain exhibit cytoplasmic beading, process fragmentation, deramification, and spheroid formation—a morphology that is neither the ramified surveillance phenotype of homeostatic microglia nor the amoeboid, process-retracted phenotype of classically activated ones. Streit argued that this dystrophic morphology represents the terminal consequence of cellular senescence driven by iron accumulation: microglia phagocytose iron and ferritin as part of their normal surveillance and clearance function, and over decades of life this cargo accumulates intracellularly, generating Fenton-reaction reactive oxygen species that damage the microglial cytoskeleton, lysosomal membranes, and mitochondrial networks. The resulting dystrophic cells are phagocytically incompetent, transcriptionally exhausted, and spatially associated with pre-tangle tau pathology—appearing in regions destined for neurodegeneration before neuronal loss occurs.

The Streit framework's significance is not that it displaces the attack framework but that it identifies a necessary condition for the Alzheimer's disease microglial phenotype that the attack framework cannot generate on its own: aging. Classical activation is not an age-dependent process; young microglia can become activated by acute stimuli and return to homeostasis afterward. Dystrophy is an age-dependent process, generated by the accumulated oxidative and phagocytic load of decades, and it is only in aged microglia that the post-homeostatic state becomes committed rather than reversible. The Streit framework therefore supplies the temporal dimension the attack framework lacks: it explains why Alzheimer's disease is an age-dependent disorder of microglial biology rather than a stochastic consequence of amyloid accumulation that could in principle occur at any age.

The von Bernhardi framework supplies the signaling substrate of microglial aging. Chronic oxidative stress progressively dysregulates the TGF-β/SMAD pathway, which—as Butovsky established—is the master regulator of the homeostatic microglial signature. With age, SMAD2 and

SMAD3 signaling become uncoupled from TGF-β receptor engagement, SMAD7 inhibitory feedback becomes elevated, and the transcriptional program that maintains P2ry12, Tmem119, and the broader homeostatic signature cannot be sustained. The result is a microglial population that has lost its homeostatic baseline, not through acute activation, but through cumulative failure of the signaling pathway that maintains it. Simultaneously, the pro-inflammatory program is disinhibited, producing a cellular state that von Bernhardi characterized as "active but ineffective": high cytokine output combined with impaired phagocytic clearance, the worst of both worlds. The von Bernhardi framework is the crucial mechanistic bridge between Butovsky's homeostatic biology and Streit's dystrophic outcome: it identifies the specific pathway whose age-dependent failure generates the post-homeostatic state, and it explains why that state exhibits simultaneously elevated inflammatory output and impaired protective function.

The Marschallinger program, with its identification of lipid-droplet-accumulating microglia as a distinct and functionally impaired state of aged microglia, supplies the lipidomic dimension of the failure framework. LDAM cells accumulate intracellular lipid droplets, exhibit impaired phagocytosis of Aβ and apoptotic debris, elevated reactive oxygen species production, and a distinct transcriptional signature characterized by PLIN2, DGAT2, and ACSL1 upregulation. Critically, LDAM is transcriptionally distinct from DAM despite sharing the downregulation of the Butovsky homeostatic signature, and it represents a state that is reached through an alternative post-homeostatic trajectory: where DAM Stage 2 cells attempt lipid processing through the TREM2/APOE/LPL program, LDAM cells accumulate lipid droplets without processing them, trapped in a state of metabolic gridlock. The Marschallinger framework connects the lipid biology of the APOE/TREM2 genetic risk signal to a specific dysfunctional cellular phenotype, and it suggests that the failure of lipid handling in aged and Alzheimer's-vulnerable microglia is a distinct axis of dysfunction not fully captured by DAM-centric models.

Taken together, the three failure frameworks describe three convergent manifestations of the same underlying event: the age-dependent failure of homeostatic maintenance, generating microglial states that lack the capacity for productive engagement with amyloid and damaged neural substrates, and that respond to such engagement through maladaptive enzymatic release, lipid trapping, or terminal dystrophy rather than through protective clearance. The integration with the attack framework is immediate once the Homeostatic Collapse Model is articulated: the attack phenotype and the failure phenotype are the same cells doing the same thing, viewed from different angles.

7. The Spatial Compartments: BAMs and Myeloid Ontogeny

The work of Prinz and Kierdorf on border-associated macrophages (BAMs) and the developmental ontogeny of central nervous system myeloid populations supplies a dimension that the attack and failure frameworks alike have systematically underweighted: the spatial and developmental heterogeneity of CNS myeloid cells. The central insight of the Prinz program is that "microglia" as a category has been applied with insufficient precision across the neurodegeneration literature, and that the CNS contains multiple distinct myeloid populations—parenchymal microglia, meningeal macrophages, perivascular macrophages, and choroid plexus macrophages—each with separate yolk-sac developmental origins, separate transcriptional identities, separate functional roles, and separate relationships to Alzheimer's disease pathology. The BAM populations express markers such as Lyve1, CD206, CD163, and MRC1 that distinguish them from parenchymal microglia, and they mediate distinct functions including cerebrovascular amyloid clearance, glymphatic flow regulation, and peripheral immune surveillance at the CNS border.

The significance of the BAM decomposition for the synthesis is twofold. First, it reveals that several experimental results previously interpreted as findings about "microglia" are in fact findings about specific myeloid subpopulations whose behavior and regulation differ substantially from parenchymal microglia. CSF1R-mediated depletion, for example, eliminates not only microglia but also the meningeal and perivascular macrophage compartments, and the interpretation of Crapser's perineuronal net rescue must accommodate the possibility that some portion of the rescue effect reflects BAM removal rather than microglial removal alone. Second, it supplies the spatial framework within which the Homeostatic Collapse Model operates: homeostatic collapse is not a uniform process across the brain but varies across myeloid compartments, such that parenchymal microglia around plaques may be in DAM Stage 2, microglia in adjacent regions may be dystrophic, perivascular macrophages at the amyloid-laden vasculature may be in an LDAM-like state, and meningeal macrophages may remain homeostatic. The spatial and developmental heterogeneity of the CNS myeloid compartment explains why bulk transcriptomic studies have produced inconsistent signatures across cohorts and why single-cell analyses reveal multiplicity of states within a single specimen.

The integration with the preceding framework is direct: the Homeostatic Collapse Model predicts that different compartments will collapse along different trajectories depending on their baseline transcriptional programs, their developmental origin, their lipid and amyloid exposure, and their tissue niche signaling context. Parenchymal microglia around plaques collapse into DAM trajectories; aged parenchymal microglia distant from plaques collapse into LDAM or dystrophic trajectories; perivascular macrophages collapse into states that reflect their specialized role in cerebrovascular amyloid handling. The apparent diversity of microglial states in Alzheimer's disease is the predictable consequence of homeostatic collapse occurring in multiple distinct niches with

multiple distinct downstream options.

8. The Resilience Evidence: Homeostatic Preservation as Substrate

The de Vries and Carulli neuropathological study of 2024 provides the most theoretically consequential human tissue evidence in the contemporary microglial literature of Alzheimer's disease. By comparing post-mortem brains from three groups—age-matched controls, symptomatic Alzheimer's disease, and "resilient" individuals who had carried AD-level amyloid and tau pathology without exhibiting cognitive decline during life—the study demonstrated that resilient brains differ from symptomatic brains not in the burden of Aβ or tau pathology but in the preservation of perineuronal net integrity around parvalbumin-positive interneurons and in the homeostatic, rather than pathological, profile of the microglial matrix remodeling activity. Resilient individuals showed intact synaptic contacts onto PV+ interneurons, preserved aggrecan and tenascin-R immunostaining, and microglial transcriptional signatures lacking the MMP-2, MMP-9, and cathepsin-S upregulation that characterizes symptomatic Alzheimer's disease.

The significance of the de Vries finding is that it separates cognitive resilience from cognitive reserve—the capacity to withstand neural injury through alternative circuitry or compensation—and identifies it as a distinct biological substrate grounded in the preservation of specific cellular and molecular features. Crucially, the feature being preserved is not amyloid absence or tau absence but microglial homeostasis itself. Resilient individuals accumulated amyloid and tau to symptomatic-disease thresholds, but their microglia did not collapse into the destructive post-homeostatic state, and their perineuronal nets therefore remained intact, and their PV+ interneurons therefore retained functional coverage, and their inhibitory circuitry therefore sustained excitation-inhibition balance, and they therefore did not develop dementia despite carrying the pathological hallmarks.

This result is the strongest human evidence available for the Homeostatic Collapse Model. It establishes that the pathological significance of amyloid and tau is contingent on whether they trigger microglial homeostatic collapse, that resilient individuals are those in whom this collapse does not occur or is resisted, and that the molecular substrate of resilience is the preserved TGF-β-maintained homeostatic signature itself rather than any particular downstream effector. It also supplies the experimental readout for therapeutic development: an intervention that restores microglial homeostasis in Alzheimer's disease patients should produce a phenotype resembling the resilient state, with preserved perineuronal nets, intact PV+ interneuron coverage, and preserved cognition, regardless of whether it affects amyloid or tau burden directly.

9. Emergent Convergences

Across the twelve research programs surveyed, three emergent convergences organize the integrated model, each of which reframes a long-standing tension in the field and each of which generates testable predictions that neither the attack nor the failure framework alone could produce.

Convergence 1: Homeostatic Collapse as the Single Upstream Event

The first convergence is that the loss of the TGF-β-maintained homeostatic signature is the single upstream event common to every pathological microglial phenotype described in the Alzheimer's disease literature. DAM Stage 1 cells, DAM Stage 2 cells, lipid-droplet-accumulating microglia, dystrophic microglia, and complement-activated pruning microglia all share, as their most robust and reproducible feature, the downregulation of P2ry12, Tmem119, Cx3cr1, and the broader Butovsky signature. They differ in which downstream programs they adopt after the collapse, but they do not differ in the collapse itself. This convergence has immediate interpretive consequences: it implies that the field's proliferation of microglial activation states is not evidence of distinct pathogenic programs but evidence of a single upstream collapse with multiple downstream trajectories, and it implies that therapeutic strategies aimed at specific downstream states will fail whenever the upstream collapse continues to generate new post-homeostatic cells at rates exceeding those at which the intervention silences the downstream effectors.

The mechanistic content of this convergence is supplied by the von Bernhardi program: TGF-β/SMAD signaling failure, driven by chronic oxidative stress and the age-dependent accumulation of inhibitory feedback, is the specific pathway through which homeostatic maintenance fails. This failure is gradual and cumulative, occurring over decades of life and accelerated by amyloid-related oxidative load. Once the signaling collapses, the microglial population loses its niche-maintained identity and defaults into a macrophage-like state whose subsequent behavior depends on local context. The therapeutic implication is that upstream stabilization of the TGF-β/SMAD pathway, rather than downstream modulation of any particular effector, is the target class most likely to restore homeostatic function.

Convergence 2: TREM2 as the Collision Point

The second convergence is that TREM2 is the receptor at which the attack and failure frameworks collide mechanistically, and that its paradoxical genetic status as a risk allele despite its role in activation is resolved only when both frameworks are understood as operating simultaneously within the same cell. TREM2 gates the execution of the lipid-sensing and phagocytic program that post-homeostatic microglia attempt in order to clear amyloid and damaged membranes. When the program succeeds, it produces protective clearance with minimal collateral damage. When the program fails—because TREM2 function is impaired, because the lipid cargo is excessive, because the phagocytic competence is compromised by LDAM or dystrophic features, or because the cellular metabolism cannot sustain the energetic cost—it releases effector enzymes, cytokines, and complement components into the extracellular space, producing the attack phenotype as a consequence of failed salvage rather than as a gain-of-function.

The TREM2 paradox dissolves under this reading. Loss-of-function variants increase risk because they shift the balance of attempted salvage from successful clearance toward unsuccessful release, increasing the collateral damage per engagement attempt without reducing the number of attempts. Pharmacological TREM2 agonism should therefore be protective only in individuals whose microglial metabolism is capable of executing the enhanced clearance program without tipping into failed salvage—a population that overlaps poorly with clinical trial populations in whom amyloid burden is high, lipid handling is already compromised, and the downstream metabolic capacity is exhausted. The repeated failures of TREM2 agonist trials in advanced disease populations are entirely predicted by the Homeostatic Collapse Model: boosting the receptor does not help when the cell no longer has the metabolic capacity to execute the program the receptor initiates.

Convergence 3: The PNN as Mechanistic Reconciliation

The third convergence—and the most concrete and therapeutically actionable—is that the perineuronal net represents the specific substrate at which microglial attack and microglial failure become mechanistically indistinguishable. When post-homeostatic microglia release MMP-2, MMP-9, ADAMTS-4, and cathepsin-S into the perineuronal space, they simultaneously perform an act of matrix destruction (attack) and an act of protective withdrawal from the ensheathed parvalbumin-positive interneuron (failure). The destruction of aggrecan and tenascin-R removes the iron-chelation and diffusion-barrier functions that protect the high-firing PV+ interneuron from oxidative injury; this is simultaneously damage to the matrix and removal of protection from the cell. No distinction between attack and failure can be drawn at the level of the single effector act, because a single enzymatic release performs both functions in one step.

This is the deepest convergence in the synthesis because it demonstrates that the attack and failure frameworks were never describing different phenomena: they were describing the same phenomenon from the perspectives of the substrate and the protected cell respectively. The Crapser

demonstration that microglial depletion rescues perineuronal nets is not, in this framing, a refutation of the failure framework—it is the expected consequence of preventing the salvage attempts that fail at the PNN. The de Vries demonstration that resilient individuals preserve perineuronal nets and PV+ synaptic contacts despite high pathology is not a refutation of the attack framework—it is the expected consequence of preserving the homeostatic state that prevents the failed salvage from occurring in the first place. The PNN is where the synthesis becomes concrete: any therapeutic intervention that preserves perineuronal net integrity in the Alzheimer's disease brain is, by that fact, restoring homeostasis, and any intervention that does not preserve PNN integrity is, by that fact, insufficient to the task regardless of what other endpoints it modifies.

10. The Homeostatic Collapse Model

The integrated model may now be stated explicitly. Alzheimer's disease involves a progressive, age-dependent collapse of the TGF-β/SMAD-maintained homeostatic microglial signature across the parenchymal, perivascular, and other CNS myeloid compartments. This collapse is driven by the cumulative effect of oxidative stress, iron and ferritin accumulation, chronic amyloid exposure, and the age-dependent failure of the signaling pathways that maintain the homeostatic state. Once collapse occurs in a given microglial cell, the cell enters a post-homeostatic condition whose subsequent trajectory depends on its metabolic fitness, its lipid cargo, its TREM2 functionality, its position within the CNS myeloid compartment, and the density and type of pathological substrate it encounters.

Cells with intact TREM2 function and sufficient metabolic capacity enter the DAM trajectory and attempt to execute lipid-sensing and phagocytic clearance programs. When these programs succeed, the outcome is protective: amyloid is cleared, damaged membranes are phagocytosed, and collateral damage is minimized. When they fail, the same programs release effector enzymes and cytokines that damage the synapse, matrix, and ensheathed neurons. Cells with impaired TREM2 function arrest at DAM Stage 1 and contribute to pathology through sustained inflammatory output without productive clearance. Cells whose metabolism has been compromised by lipid accumulation enter the LDAM trajectory and are functionally gridlocked, unable to execute clearance but still producing cytokines. Cells whose cumulative oxidative load has exceeded their capacity for homeostatic return enter the dystrophic trajectory described by Streit and lose surveillance capacity entirely, withdrawing neuroprotective support from the neurons in their vicinity.

The attack phenotype and the failure phenotype are not distinct states but alternative manifestations of post-homeostatic cells encountering different local conditions and producing different local consequences. Both phenotypes generate the same net pathological outcome—the loss of neural circuit function—through mechanistically overlapping pathways. The Crapser result, the Stevens

result, the Shatz result, and the Lemke result all describe specific effector arms of the post-homeostatic repertoire; the Streit result, the von Bernhardi result, and the Marschallinger result all describe specific failure modes of the same repertoire; and the de Vries result demonstrates that preservation of the upstream homeostatic state prevents the entire downstream cascade regardless of amyloid or tau burden.

Within this model, the cognitive resilience phenotype becomes interpretable as the preservation of homeostatic microglial identity in the face of amyloid and tau accumulation. The resilience substrate is not any particular downstream protective mechanism but the upstream TGF-β/SMAD-maintained homeostatic state itself. The therapeutic implication is that effective microglial interventions for Alzheimer's disease must aim to reinstate this state rather than to modulate its downstream collapse products, and that the perineuronal net–PV+ interneuron axis offers the most concrete molecular readout of whether a given intervention restores homeostasis or merely redirects its collapse.

11. Therapeutic Implications

The Homeostatic Collapse Model carries specific and non-trivial implications for the design of microglial therapeutics in Alzheimer's disease. First, interventions aimed at silencing microglial activation—through anti-inflammatory drugs, cytokine blockade, or complement inhibition—address the downstream collapse products rather than the upstream collapse event, and are predicted to produce modest and unsustainable benefits proportional to the rate at which new post-homeostatic cells are generated. The sustained failure of NSAID trials and the modest effect sizes of complement inhibitor programs are consistent with this prediction.

Second, interventions aimed at activating microglia—through TREM2 agonism, CSF1R modulation, or engineered activation—presume that the cells are capable of executing productive salvage programs and will fail whenever the cellular metabolism, lipid handling, or phagocytic competence has been sufficiently compromised that enhanced receptor signaling leads to failed rather than successful engagement. The clinical disappointments of TREM2 agonist programs in advanced disease populations are consistent with this prediction.

Third, interventions aimed at depleting microglia through CSF1R inhibition prevent both the destructive and protective outputs of post-homeostatic cells, producing net benefit when the cells' behavior is predominantly destructive (as Crapser demonstrated for the perineuronal net in 5xFAD) but predicted to produce net harm when applied in contexts where TAM-mediated phagocytic clearance is the dominant activity. Depletion is a blunt intervention that should be timed and targeted with great care and that should not be expected to generalize across disease stages, brain regions, or patient populations.

Fourth, and most consequentially, interventions aimed at restoring the TGF-β/SMAD-maintained homeostatic signature—through enhanced TGF-β signaling, SMAD7 inhibition, oxidative stress reduction targeted to microglia, or niche-signaling restoration—address the upstream collapse event and are predicted to produce durable benefit by reducing the generation of post-homeostatic cells rather than by modulating their downstream activity. This therapeutic class has not been systematically explored in the Alzheimer's disease literature, in part because the homeostatic signature was not widely appreciated until the Butovsky work became established, and in part because the field's therapeutic imagination has been captured by the downstream effector pathways. The model predicts that this class of interventions should be developed as a matter of priority, and that their success or failure should be measured by the preservation of perineuronal net integrity and PV+ interneuron coverage rather than by bulk amyloid or tau readouts.

Fifth, the model predicts that effective microglial therapeutics will need to be compartment-specific, distinguishing between parenchymal microglia, perivascular macrophages, and other border-associated populations, because the collapse trajectories and therapeutic requirements differ across compartments. Current pharmacology lacks this resolution, and the development of compartment-selective interventions is a necessary technical prerequisite for the successful implementation of the homeostatic restoration program.

Finally, the model predicts that the combination of homeostatic restoration with amyloid-lowering therapies should produce superadditive benefit, because reducing the substrate load that drives homeostatic collapse should lower the rate of post-homeostatic cell generation, while restoring homeostatic signaling should directly preserve the cells that remain. This combination has not been tested in clinical trials, and the model suggests it should be a priority for combination therapy design.

12. Conclusion

The contemporary microglial biology of Alzheimer's disease has been organized around a false dichotomy between attack and failure frameworks, each of which has accumulated substantial experimental support while being unable to explain the findings of the other. The twelve research programs integrated in this synthesis—spanning the homeostatic signature, the DAM taxonomy, TREM2 receptor mechanics, complement-mediated synaptic pruning, matrix-driven perineuronal net degradation, TAM-mediated phagocytic clearance, lipid-droplet-accumulating microglia, border-associated macrophage compartmentalization, microglial dystrophy, TGF-β/SMAD collapse, and the resilience neuropathology of preserved homeostasis—together support a unified model in which the attack and failure phenotypes are two projections of a single underlying event: the age-dependent collapse of the TGF-β-maintained homeostatic microglial state.

Under the Homeostatic Collapse Model, the microglial contribution to Alzheimer's disease begins with the cumulative, decades-long failure of the signaling pathway that maintains homeostatic identity. Post-homeostatic cells enter one of several downstream trajectories—DAM, LDAM, dystrophic, or other—whose apparent diversity reflects context-dependent responses to a shared upstream event rather than distinct pathogenic programs. These cells attempt salvage programs that produce protective outcomes when they succeed and destructive outcomes when they fail, and the balance of success and failure at any given brain region and disease stage determines whether the dominant phenotype appears as attack or as exhaustion. TREM2 is the receptor at which this balance is gated, which is why loss-of-function variants confer risk and why receptor agonism has produced disappointing clinical results. The perineuronal net is the substrate at which attack and failure become mechanistically indistinguishable, which is why it is the most promising molecular readout of therapeutic success. The cognitive resilience phenotype is the human demonstration that preserving the upstream homeostatic state is sufficient to prevent the downstream cascade regardless of amyloid or tau burden, which is why homeostatic restoration should be the dominant therapeutic strategy of the next decade of microglial research.

The epistemological lesson of the synthesis is that the Alzheimer's disease research field has, in its microglial chapter as in its amyloid chapter, repeatedly mistaken the visible surface of pathology for the underlying process that generates it. DAM is the surface; homeostatic collapse is the process. Complement-mediated pruning is the surface; failed salvage at the synapse is the process. Dystrophy is the surface; TGF-β/SMAD failure is the process. The Organic Network Synthesis methodology, by refusing to adjudicate between surface descriptions and searching instead for the process that unites them, makes this lesson visible. The model it produces is neither an attack framework nor a failure framework but a framework in which attack and failure are the same thing seen from different angles, and in which the therapeutic task is neither to silence microglia nor to activate them but to reinstate the homeostatic state whose collapse generated both phenotypes in the first place.

The work ahead is to test these predictions experimentally, to develop the pharmacology of homeostatic restoration, to establish perineuronal net integrity as a biomarker of therapeutic success, and to reinterpret the existing anti-inflammatory and microglial-modulatory clinical literature in light of the unified model. The microglial contribution to Alzheimer's disease is neither an attack nor a failure; it is a collapse, and the therapeutic task is restoration.

References

A full reference list compiled from the twelve primary research programs surveyed, the Organic Network Synthesis knowledge base, and the supporting literature will accompany the final version of this thesis. Key foundational references include:

Butovsky, O., et al. (2014). Identification of a unique TGF-β-dependent molecular and functional signature in microglia. *Nature Neuroscience*, 17(1), 131–143.

Keren-Shaul, H., Spinrad, A., Weiner, A., ..., Amit, I. (2017). A unique microglia type associated with restricting development of Alzheimer's disease. *Cell*, 169(7), 1276–1290.e17.

Stevens, B., Allen, N. J., Vazquez, L. E., et al. (2007). The classical complement cascade mediates CNS synapse elimination. *Cell*, 131(6), 1164–1178.

Werneburg, S., ..., Shatz, C. J. (2025). C4d, a high-affinity LilrB2 ligand, is elevated in Alzheimer's disease and mediates synapse pruning. *Proceedings of the National Academy of Sciences*, 122.

Crapser, J. D., Spangenberg, E. E., ..., Green, K. N. (2020). Microglia facilitate loss of perineuronal nets in the Alzheimer's disease brain. *EBioMedicine*, 58, 102919.

Ulland, T. K., Song, W. M., Huang, S. C., ..., Colonna, M. (2017). TREM2 maintains microglial metabolic fitness in Alzheimer's disease. *Cell*, 170(4), 649–663.

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

Huang, Y., Happonen, K. E., Burrola, P. G., ..., Lemke, G. (2021). Microglia use TAM receptors to detect and engulf amyloid β plaques. *Nature Immunology*, 22(5), 586–594.

Prinz, M., Masuda, T., Wheeler, M. A., Quintana, F. J. (2021). Microglia and central nervous system–associated macrophages—from origin to disease modulation. *Annual Review of Immunology*, 39, 251–277.

Kierdorf, K., Erny, D., Goldmann, T., et al. (2013). Microglia emerge from erythromyeloid precursors via Pu.1- and Irf8-dependent pathways. *Nature Neuroscience*, 16(3), 273–280.

Streit, W. J., Braak, H., Xue, Q. S., Bechmann, I. (2009). Dystrophic (senescent) rather than activated microglial cells are associated with tau pathology and likely precede neurodegeneration in Alzheimer's disease. *Acta Neuropathologica*, 118(4), 475–485.

von Bernhardi, R., Eugenín-von Bernhardi, L., Eugenín, J. (2015). Microglial cell dysregulation in brain aging and neurodegeneration. *Frontiers in Aging Neuroscience*, 7, 124.

de Vries, L. E., Jongejan, A., Monteiro Fortes, J., ..., Carulli, D. (2024). Perineuronal nets and cognitive resilience in Alzheimer's disease. *Alzheimer's & Dementia*, 20.

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