BIOENERGETIC COLLAPSE

The Mitochondrial, Autophagy-Lysosomal, and Metabolic Substrate of Alzheimer's Disease

Nixon · Gouras · Rubinsztein · Heneka · Swerdlow · Picard
Fang/Bohr · Baik · Ulland/Colonna · Youle · Ristow
in dialogue with Butovsky, von Bernhardi, and Marschallinger

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Companion thesis to Convergent Synaptic Collapse *and* Homeostatic Microglial Collapse

Abstract

The two prior Collapse theses identified a single upstream event — loss of the TGF-β/SMAD-maintained homeostatic microglial signature — as the generator of both attack and failure phenotypes in the microglial biology of Alzheimer's disease, and identified the perineuronal net surrounding parvalbumin-positive interneurons as the substrate at which attack and failure become mechanistically identical. Both theses invoked "metabolic fitness," "oxidative senescence," and "failed salvage" as load-bearing variables without specifying the cell-biological machinery whose competence these terms require. This thesis supplies that machinery.

Integrating ten research programs — Nixon on autophagy-lysosomal failure and the PANTHOS inversion of the amyloid cascade, Swerdlow on the mitochondrial cascade hypothesis, Youle on canonical PINK1/Parkin mitophagy, Fang and Bohr on mitophagy failure in Alzheimer's disease and its therapeutic reversal, Baik and colleagues on the empirical collapse of microglial metabolic reprogramming in Alzheimer's disease, Ulland and Colonna on TREM2 as a metabolic fitness gate coupled to OXPHOS and mTOR, Heneka on NLRP3 inflammasome activation as the mitochondrial-ROS-gated effector arm of microglial pathology, Picard on mitochondria as the cellular integrators of allostatic load, Ristow on mitohormesis as the theoretical basis for metabolic therapy, and Rubinsztein on BIN1-mediated autophagosome closure failure and the proteasome-tau feedback loop that connects sporadic LOAD genetics to the quality-control pipeline — this synthesis argues that mitochondrial and autophagy-lysosomal quality-control competence is the single substrate whose age-dependent failure generates the homeostatic microglial collapse described in the prior thesis, the neuronal autophagy-failure pathology described by Nixon, and the systemic metabolic-psychiatric comorbidities described by the emerging metabolic psychiatry literature. Rather than three parallel pathologies, these are three descriptions of one quality-control system failing across cell types, tissues, and disease stages.

The model's genetic grounding now spans both familial and sporadic architecture: presenilin mutations impair the terminal degradation step of the autophagy-lysosomal pipeline (lysosomal acidification via v-ATPase assembly disruption), while BIN1 — the #2 GWAS risk locus for sporadic LOAD — impairs the upstream formation step (autophagosome closure via ESCRT-III/DNM2 coordination), as demonstrated by Rubinsztein's 2025 Cell Reports paper. The two genetic anchors bracket the pipeline at its formation and degradation ends, and both produce the same downstream outcome: accumulation of undegraded autophagic cargo including intraneuronal Aβ and damaged mitochondria. The proteasome-tau feedback loop that Rubinsztein describes further refines the model's third convergence, expanding the sorting variable from mitophagy competence alone to total quality-control competence encompassing both mitophagy and proteasomal capacity, and explaining why dystrophic microglia cluster around pre-tangle tau pathology.

The synthesis advances two original mechanistic claims that occupy documented white space in the literature. The first is that TGF-β/SMAD signaling maintains microglial mitochondrial competence — biogenesis, quality control, and mitophagy capacity — such that age-dependent collapse of the signaling is simultaneously a transcriptional identity collapse and a bioenergetic substrate collapse, not two separable events. The second is that total quality-control competence — of which mitophagy is the dominant component but proteasomal capacity is a significant modifier — is the variable that sorts post-homeostatic microglia into DAM, LDAM, or dystrophic trajectories, such that the apparent trifurcation in the microglial literature reflects graded degrees of a single upstream quality-control failure. These claims generate a concrete experimental program, reframe the NLRP3 inflammasome as the mitochondrial-ROS gate through which failed salvage becomes destructive effector output, and unify five previously distinct therapeutic classes — mitophagy inducers, lysosomal acidification restorers, autophagosome-closure enhancers targeting the BIN1-ESCRT-III-DNM2 axis, TGF-β stabilizers, and metabolic interventions from the ketogenic and GLP-1 literatures — as a single therapeutic class acting on a single substrate. The perineuronal net and PV+ interneuron axis identified in the prior thesis remains the readout by which any such intervention should be measured.

1. Introduction: The Bioenergetic Blind Spot

The two prior theses in the Collapse trilogy arrived at an unusual epistemic position. Convergent Synaptic Collapse identified the perineuronal net and its ensheathed parvalbumin-positive interneuron as the circuit-level substrate whose loss generates the cognitive phenotype of Alzheimer's disease, and Homeostatic Microglial Collapse identified the loss of the TGF-β/SMAD-maintained homeostatic microglial signature as the upstream event whose downstream trajectories produce both the attack and failure phenotypes of the disease-associated microglial literature. Each synthesis was able to explain a considerable share of the experimental findings it integrated, and each generated testable predictions and concrete therapeutic readouts. But each also repeatedly invoked a set of variables whose cell-biological content was left unspecified. "Metabolic fitness," "oxidative senescence," "failed salvage," "exhausted phagocytic capacity," "lipid gridlock," and "cumulative oxidative load" all appear in the prior synthesis as load-bearing terms, and each of them names a phenomenon whose existence is experimentally documented but whose underlying machinery is not. This thesis exists because the Homeostatic Collapse Model is not mechanistically complete until that machinery is supplied, and because the field has been unable to supply it through any of its existing disciplinary divisions.

The blind spot is not that mitochondrial dysfunction has been ignored in the Alzheimer's disease literature. On the contrary: bioenergetic abnormalities in Alzheimer brain tissue were among the first biochemical observations made in the disease, and two decades of sustained work by

Swerdlow, Beal, Lin, Reddy, and others have documented in extensive detail that oxidative phosphorylation is impaired, mitochondrial DNA damage accumulates, electron transport chain complexes are downregulated, and reactive oxygen species production is elevated in affected brain regions. Nor is the problem that autophagy has been ignored: the work of Nixon and colleagues has established over the same period that lysosomal acidification fails, autophagic vacuoles accumulate abnormally in dystrophic neurites, and the autophagy-lysosomal system is compromised well before overt neurodegeneration. The blind spot lies in a different place. It is that these two bodies of work, despite sharing an evident mechanistic proximity, have developed in near-total isolation from the microglial biology of the same disease. The mitochondrial cascade literature has treated Alzheimer's disease primarily as a neuronal bioenergetic failure whose consequences include, incidentally, a neuroinflammatory reaction. The autophagy-lysosomal literature has treated it as a neuronal proteostasis failure whose consequences include, incidentally, microglial engagement with extracellular aggregates. The microglial literature, for its part, has treated "metabolic fitness" as a property cells either have or lack, without asking what organelle-level machinery its presence requires. The three literatures have not been wrong about their respective endpoints. They have been wrong to treat those endpoints as belonging to different diseases.

The consequence of this disciplinary fragmentation is that no existing framework in the field describes Alzheimer's disease as what it increasingly appears to be: a failure of the cellular quality-control machinery that spans mitochondrial homeostasis, mitophagy, and lysosomal degradation in every cell type affected by the disease, manifesting as distinct phenotypes only because different cell types have different downstream options when their quality-control system fails. A neuron whose autolysosomes cannot acidify accumulates autophagic cargo and, as Nixon's 2022 work has now demonstrated, generates extracellular plaques from the inside out through the death and extrusion of autophagy-failed cells. A microglial cell whose mitophagy has failed cannot process the lipid and membrane cargo that surveillance requires it to internalize, and collapses into the gridlocked lipid-droplet phenotype that Marschallinger described. A parvalbumin-positive interneuron whose extraordinary mitochondrial demand cannot be met because its surrounding perineuronal net has been digested by post-homeostatic microglia loses the iron-chelation and diffusion-barrier protections that make its high-firing phenotype energetically tenable, and enters the oxidative failure that precedes its loss. These three cell-type-specific phenotypes share a single substrate failure, and the substrate failure is what the prior theses invoked but did not name. This thesis names it.

A second motivation for the synthesis is that the emerging metabolic psychiatry literature, represented in its most recent form by the 2026 Nature Mental Health review by Sethi, Sarnyai, Picard, and colleagues, has arrived at remarkably similar conclusions from a different direction. The metabolic psychiatry framework argues that systemic metabolic dysfunction — insulin resistance, lipid dysregulation, mitochondrial impairment, and chronic low-grade inflammation — is not a

peripheral comorbidity of psychiatric illness but a central contributor to its pathophysiology, and that the brain's bioenergetic state is bidirectionally coupled to systemic metabolism through mechanisms whose organelle-level substrate is mitochondrial. The allostatic load model of McEwen, the selfish brain theory of Peters, and the mitochondrial allostatic load construct of Picard converge on the claim that mitochondria are the cellular substrate on which chronic stress, metabolic burden, and inflammatory load are integrated and through which they produce their systemic and neuropsychiatric consequences. This framework has been developed with reference to major depressive disorder, bipolar disorder, and schizophrenia, but its mechanistic claims are substrate-general: if mitochondria are the integrator of allostatic load in the neurons of individuals with depression, they are no less the integrator in the microglia of individuals accumulating amyloid. The Homeostatic Collapse Model already implicitly invoked allostatic load through its emphasis on cumulative oxidative and lipid burden across the lifespan. It did not cite the framework that would have given this emphasis its mechanistic vocabulary.

The argument of this thesis can be stated in four propositions whose integration will occupy the sections that follow. First, the autophagy-lysosomal failure that Gouras and Nixon have traced across two decades of work on neuronal Aβ accumulation is not a neuron-specific phenomenon but the neuronal face of a cell-general quality-control collapse, and its microglial face is the loss of homeostatic signature that the prior thesis described. Second, the mitochondrial cascade that Swerdlow has argued is the primum movens of sporadic Alzheimer's disease is not a competing hypothesis to the amyloid cascade but an upstream framing of it, and the Homeostatic Collapse Model is the microglial arm of this upstream framework. Third, the NLRP3 inflammasome program of Heneka and colleagues supplies the mechanistic gate through which failed mitochondrial quality control becomes the destructive microglial effector output that the prior thesis catalogued, such that the complement-mediated synaptic pruning, matrix metalloproteinase release, and cytokine output of post-homeostatic microglia are all downstream of mitochondrial-ROS-gated inflammasome activation. Fourth, the metabolic psychiatry framework, through the construct of mitochondrial allostatic load developed by Picard and McEwen, supplies the bridge by which the cell-autonomous microglial collapse described in the prior thesis becomes continuous with the systemic bioenergetic state of the aging individual, such that cognitive resilience, cognitive decline, and the metabolic comorbidities of aging are all manifestations of the same underlying variable.

This thesis is not an attempt to displace the prior two. It is an attempt to complete them. Where Convergent Synaptic Collapse identified the circuit-level outcome and Homeostatic Microglial Collapse identified the cellular-identity-level mechanism, this thesis identifies the substrate-level generator. The three theses together describe one disease process at three levels of resolution. The implication for therapeutic development is that interventions aimed at any one level — amyloid clearance at the circuit level, complement inhibition at the cellular level, mitochondrial substrate provision at the substrate level — will each capture a partial truth and miss the larger one, and that

the coordinated intervention predicted by the integrated model is neither amyloid-centric, nor microglia-centric, nor neuron-centric, but quality-control-centric. The therapeutic task is to restore the machinery whose failure generates every phenotype, and the measurement of therapeutic success is the preservation of the circuit-level endpoint that the prior thesis identified as the most tractable molecular readout: the perineuronal net and the parvalbumin-positive interneuron it ensheathes.

2. The Autophagy-Lysosomal Axis: Gouras, Nixon, and the Inversion of the Amyloid Cascade

The most consequential recent finding in the cell biology of Alzheimer's disease has not yet been absorbed into the microglial synthesis of the disease, and its absorption is the single largest conceptual adjustment the prior thesis requires. That finding is the demonstration, published by Lee, Yang, Goulbourne, and colleagues in Ralph Nixon's laboratory in 2022, that senile plaques in Alzheimer's disease do not form by extracellular seeding from soluble Aβ that happens to escape neuronal control. They form from the inside out. They originate within individual neurons whose autolysosomes have failed to acidify, whose autophagic cargo has consequently accumulated to the point of organelle rupture, and whose death and extrusion generates the dense-core plaque as the outward manifestation of an intracellular catastrophe that was already complete by the time any extracellular detection technology would have registered its existence. The paper names this process PANTHOS, from the Greek for "all-dying," and documents it in both mouse models and human tissue. Its implications are difficult to overstate and are not yet reflected in how the field describes the amyloid cascade.

But the Nixon finding is not an isolated result dropped into an unprepared literature. It is the mechanistic resolution of a phenomenological observation that Gunnar Gouras and colleagues had been developing for more than two decades before Nixon's paper appeared. In 2000, Gouras, Tsai, Naslund, and a team working at Weill Cornell reported in the American Journal of Pathology that Aβ42 accumulates inside neurons in human Alzheimer brain tissue, and that this intraneuronal accumulation is detectable in neurons of the entorhinal cortex and hippocampus before any extracellular plaque deposition can be identified in the same regions. The finding directly contradicted the prevailing interpretation of the amyloid cascade, which held that Aβ is a secreted peptide whose extracellular accumulation generates the plaques that drive subsequent neurodegeneration. Gouras's observation reversed this temporal ordering: intraneuronal Aβ42 preceded extracellular plaque formation, not the other way around, and the neurons that accumulated it were the same neurons that would eventually degenerate.

Two years later, in 2002, Takahashi, Milner, and Gouras extended the finding with a paper that would prove critical for the integration this thesis attempts. Using immunoelectron microscopy in

both human tissue and transgenic mouse brains, they demonstrated that the intraneuronal Aβ42 accumulation Gouras had identified was not diffuse cytoplasmic deposition but was specifically localized within multivesicular bodies and late endosomal compartments, particularly within neuronal processes and at synaptic sites. The paper further showed that this accumulation was associated with structural pathology at the synapse itself. The significance of the organelle localization was that it placed intraneuronal Aβ squarely within the endolysosomal system — the same cellular machinery whose failure Nixon's group would later demonstrate as the proximate cause of the dense-core plaque. By 2005, Gouras, Almeida, and Takahashi had synthesized the emerging picture into an explicit claim in the title of a review article: that intraneuronal Aβ accumulation is the origin of plaques in Alzheimer's disease, not their consequence.

The Gouras program continued to develop this framework through the subsequent decade. A 2010 Acta Neuropathologica review with Tampellini, Takahashi, and Capetillo-Zarate consolidated the evidence that intraneuronal Aβ accumulation is associated with synaptic pathology, that it precedes plaque formation in every model and tissue in which both have been measured, and that the multivesicular body localization identified in the 2002 paper points specifically at the endolysosomal-autophagy axis as the organellar site at which the critical event occurs. A 2012 Life Sciences review by Gouras, Willén, and Tampellini addressed the technical challenges of detecting intracellular Aβ and pushed back against the field's tendency to dismiss the intraneuronal pool as a minor compartment relative to the extracellular aggregate. And in 2017, a paper from Willén, Edgar, Gouras, and colleagues in Molecular Neurodegeneration closed the mechanistic loop by showing that Aβ accumulation causes multivesicular body enlargement in neurons and that this enlargement can be experimentally modeled by dominant-negative disruption of VPS4A, a component of the ESCRT machinery that governs MVB biogenesis and intraluminal vesicle formation. The 2017 result placed intraneuronal Aβ accumulation inside the endolysosomal quality-control system and demonstrated that it is not merely a passive deposition but an active disruption of organelle function.

The ESCRT-III nexus that connects the Gouras MVB findings to the broader autophagosome-formation machinery has been substantially clarified by the work of David Rubinsztein and colleagues. Their 2025 Cell Reports paper demonstrated that BIN1 (Bridging Integrator 1), the #2 GWAS risk locus for sporadic late-onset Alzheimer's disease after APOE, coordinates autophagosome closure via ESCRT-III and dynamin-2 (DNM2), and that BIN1 overexpression inhibits autophagic clearance. The finding reveals ESCRT-III as a convergent molecular substrate whose dysfunction at two distinct organelles — the multivesicular body (Gouras/Willén via VPS4A disruption) and the forming autophagosome (Rubinsztein via BIN1-mediated closure failure) — both contribute to the intraneuronal Aβ accumulation the Gouras program characterized. At the MVB, ESCRT-III dysfunction impairs intraluminal vesicle formation that would normally sequester Aβ away from the cytoplasm. At the autophagosome, ESCRT-III dysfunction impairs the membrane closure that would seal Aβ-containing cargo within a

compartment deliverable to the lysosome. Both dysfunctions leave Aβ in cellular compartments where it cannot be degraded, and both are connected to the same ESCRT-III molecular machinery whose coordinated function requires components — BIN1 at the autophagosome, VPS4A at the MVB — whose disruption has been independently linked to AD pathology. BIN1's status as the second-largest LOAD genetic risk factor provides the sporadic genetic anchor for this autophagy-lysosomal failure: where presenilin mutations impair the terminal degradation step (lysosomal acidification via v-ATPase assembly disruption), BIN1 risk variants impair an earlier step (autophagosome membrane sealing), and the two genetic anchors bracket the pipeline at its formation and degradation ends.

When the Lee, Yang, Nixon 2022 Nature Neuroscience paper appeared, therefore, it did not arrive at an unprepared field. It arrived at a field that had been told for twenty-two years, by Gouras and collaborators, that Aβ accumulates intraneuronally first, that the accumulation is localized to the endolysosomal compartment, and that it is associated with organelle dysfunction. What the field had not been told was the specific mechanism by which this intraneuronal accumulation progressed from organelle dysfunction to neuronal death to plaque formation. The Nixon paper supplied that mechanism. It demonstrated that in Alzheimer's disease mouse models, autolysosomes in affected neurons fail to acidify sufficiently to activate the hydrolytic enzymes that would ordinarily degrade their autophagic cargo. Aβ, once generated intracellularly, therefore cannot be cleared. It accumulates within the failed autolysosomes, and the resulting organelle expansion gradually engulfs the neuron from within. The affected neurons take on a characteristic morphology that Lee and colleagues termed "flower-like" — the cell body becomes a rosette of expanded autolysosomes filled with undegradable Aβ. Eventually these cells die, and the dense-core plaque that forms at their former location is literally the inside of the cell turned out. The Aβ in the plaque is the Aβ that was accumulating in the intraneuronal multivesicular bodies and autolysosomes Gouras had been describing since 2000.

The mechanistic continuity between the Gouras phenomenology and the Nixon mechanism is not coincidental. It is the same phenomenon observed at different levels of resolution and with different technologies. Gouras used immunohistochemistry and immunoelectron microscopy to establish that Aβ was accumulating inside neurons in an organelle-localized pattern; Nixon used high-resolution live imaging of autolysosomal acidification and a genetic readout of lysosomal function to demonstrate that the organelle in question could not perform its normal degradative duties. Together they constitute a twenty-two-year arc from phenomenology to mechanism, and the arc inverts the amyloid cascade in a specific and testable way. Plaques are not causes of neuronal damage that happen to form in regions of accumulated Aβ. They are gravestones of neurons that died from autophagy-lysosomal failure, and the Aβ they contain is the intracellular cargo that the failed machinery could not clear before organelle rupture and cell death.

This inversion has profound consequences for the microglial synthesis of the prior thesis, and these consequences are the central reason the Bioenergetic Collapse Model requires a separate treatment rather than a footnote in Homeostatic Microglial Collapse. The prior thesis treated plaques as extracellular substrates whose pathological significance is determined by how microglia engage with them. DAM Stage 2 cells attempt lipid-sensing and phagocytic clearance programs at the plaque periphery; the failure modes of this engagement generate the effector outputs that damage nearby circuitry. Within this framing, microglia are active participants in plaque biology whose success or failure at the plaque determines downstream pathology. The Gouras-Nixon inversion reframes this completely. Microglia arrive at plaques as responders to a pathological event that was already complete when they arrived. The plaque is not an extracellular challenge demanding microglial engagement; it is the extruded remnant of a neuron that died from a quality-control failure entirely internal to the neuron, and microglial engagement with the remnant is necropsy, not defense. The "failed salvage" that the prior thesis attributed to post-homeostatic microglia at the plaque periphery is therefore a second-order quality-control failure — a failed cleanup of a primary quality-control failure — rather than a first-order engagement whose failure drives the pathology.

A further consequence follows. If plaques form from autophagy-failed neurons rather than from extracellular Aβ seeding, then the relationship between amyloid burden and cognitive outcome is not a dose-response curve of extracellular aggregate accumulation but a death count of neurons that have exceeded their autophagy-lysosomal capacity. The resilient individuals described by de Vries and Carulli, who carry symptomatic-AD levels of plaque burden without cognitive decline, become interpretable in a new way. Their plaque counts do not indicate extracellular Aβ that has somehow failed to damage their circuits. Their plaque counts indicate neurons that died from autophagy-lysosomal failure — possibly from a different, less circuit-critical population — while the surviving neurons retained sufficient quality-control competence to continue functioning, and the surrounding microglia retained sufficient homeostatic competence to preserve perineuronal net integrity and PV+ interneuron coverage. Resilience, on this reading, is not the absence of quality-control failure but the preservation of quality-control competence in the cells that matter most for cognition: the parvalbumin-positive interneurons whose perineuronal nets depend on homeostatic microglial function, which in turn depends on mitochondrial and autophagy-lysosomal competence in the microglia themselves.

The Nixon program does not end at PANTHOS. Nixon's earlier work, particularly the 2013 Nature Medicine review and the 2013 European Journal of Neuroscience paper with Wolfe, Lee, and colleagues, established the broader framework within which PANTHOS sits. The 2013 Nature Medicine review articulated the autophagy-lysosomal failure hypothesis as a unifying framework across Alzheimer's, Huntington's, and Parkinson's diseases, arguing that each of these disorders is characterized by a failure of the same basic cellular machinery and that their apparent mechanistic diversity reflects differences in which protein substrates accumulate downstream of the shared

upstream failure. The Wolfe paper established the specific biochemistry of lysosomal acidification failure, tying it to the activity of the vacuolar H+-ATPase and to the interaction between presenilin-1 and the v-ATPase V0a1 subunit that is disrupted in familial Alzheimer's disease. Together these papers establish that autophagy-lysosomal failure in Alzheimer's disease is not a stochastic consequence of age-related proteostasis decline but is mechanistically coupled to the genetics of the disease itself — presenilin mutations impair lysosomal acidification directly, and this impairment is the mechanistic link between familial Alzheimer's genetics and the PANTHOS phenotype.

The genetic grounding of autophagy-lysosomal failure in Alzheimer's disease now spans both familial and sporadic architecture. The presenilin-v-ATPase interaction establishes the familial anchor at the degradation end of the pipeline: presenilin mutations impair lysosomal acidification, preventing completion of autophagic degradation regardless of whether cargo recognition, autophagosome formation, and lysosomal delivery have proceeded normally. The BIN1-ESCRT-III interaction established by Rubinsztein provides the sporadic anchor at the formation end: BIN1 risk variants impair autophagosome closure, preventing the sealed compartment from forming in the first place and therefore blocking all downstream degradative steps regardless of lysosomal competence. The two anchors bracket the autophagy-lysosomal pipeline at its earliest and latest steps, and both produce the same net outcome — accumulation of undegraded cargo including intraneuronal Aβ and damaged mitochondria. That the #1 familial genetic driver and the #2 sporadic genetic risk factor both converge on the same quality-control pipeline, attacking it at different points along its length, is among the strongest available evidence that this pipeline is the mechanistic substrate of the disease rather than one of many contributing pathways.

The implication of this coupling is that autophagy-lysosomal failure is not merely one of many things that goes wrong in Alzheimer's disease. It is the thing that goes wrong first, in at least some cells, as a consequence of the same genetic and biochemical variables that the amyloid cascade has always attributed causal weight to. Presenilin mutations do not cause disease by generating more Aβ; they cause disease by impairing lysosomal acidification, which prevents clearance of whatever Aβ is generated, which drives the PANTHOS phenotype in affected neurons, which produces the plaques that the amyloid cascade interpreted as the disease mechanism. The field's century of work on Aβ generation, aggregation, and toxicity has been work on the downstream consequences of an upstream lysosomal failure, not on the upstream event itself. This is not to dismiss that work — the downstream consequences are real, and they are damaging — but to position it correctly within a cell-biological hierarchy whose upstream node is the quality-control machinery this thesis argues must be restored rather than bypassed.

The Gouras-Nixon axis, then, does two things for the Bioenergetic Collapse Model. First, it establishes that autophagy-lysosomal failure is a documented, mechanistically specified, genetically

coupled upstream event in Alzheimer's disease whose existence the microglial synthesis must accommodate. Second, it establishes that the machinery whose failure is documented in neurons is the same machinery whose failure is invoked, without mechanistic specification, by the microglial synthesis when it describes post-homeostatic microglia as having "exhausted" their phagocytic capacity or as having "failed" their salvage attempts at plaques. The section that follows will argue that the mitochondrial cascade hypothesis of Swerdlow supplies the broader theoretical framing within which both the neuronal Gouras-Nixon axis and the microglial Homeostatic Collapse axis can be understood as manifestations of a single substrate failure, and the subsequent sections will trace that substrate failure across the specific molecular machinery — canonical mitophagy, mitochondrial metabolic reprogramming, NLRP3 inflammasome gating, and mitochondrial allostatic load integration — whose collapse the model asserts as its central claim.

3. The Mitochondrial Cascade: Swerdlow's Upstream Claim

If the Gouras-Nixon axis establishes that autophagy-lysosomal failure is upstream of amyloid pathology in the cell biology of Alzheimer's disease, the mitochondrial cascade hypothesis of Russell Swerdlow establishes that mitochondrial dysfunction is upstream of the autophagy-lysosomal failure itself. Swerdlow and Khan first articulated this claim in a 2004 Medical Hypotheses paper whose explicit title — "A 'mitochondrial cascade hypothesis' for sporadic Alzheimer's disease" — placed mitochondria at the origin of a causal sequence that the field had been accustomed to beginning with Aβ. The original hypothesis proposed that sporadic Alzheimer's disease, which accounts for the overwhelming majority of cases and which has no clear genetic driver, is best understood as a consequence of age-related mitochondrial failure whose downstream effects include the biochemical and cellular changes that the amyloid cascade had placed at its origin. Fourteen years later, in a 2018 Journal of Alzheimer's Disease review, Swerdlow returned to the hypothesis with the benefit of accumulated evidence and articulated an updated version that engaged more directly with the amyloid cascade literature and with the growing body of evidence from postmortem tissue, cellular models, and clinical biomarkers.

The central mechanistic claim of the mitochondrial cascade hypothesis is that mitochondrial DNA, which is inherited maternally and accumulates mutations throughout life at rates far exceeding those of nuclear DNA, reaches by late adulthood a threshold of damage at which mitochondrial function can no longer meet the energetic demands of high-expense cell types. The brain, and particularly neurons with high baseline firing rates and long axonal projections, is the cell population most exposed to this threshold effect because its mitochondrial demand is among the highest in the body and its capacity for mitochondrial turnover is limited by the post-mitotic status of its constituent cells. Once mitochondrial function in these cells falls below the threshold required for homeostatic maintenance, a cascade of downstream consequences unfolds: cellular energy failure, reactive

oxygen species accumulation, impaired ion homeostasis, disrupted proteostasis, activation of stress response pathways, and ultimately the specific biochemical changes — Aβ overproduction or underclearance, tau hyperphosphorylation, synaptic loss — that constitute the diagnostic phenotype of Alzheimer's disease. On this view, the disease is not a proteinopathy that happens to include mitochondrial dysfunction among its many consequences; it is a mitochondrial failure whose proteinopathic manifestations are the field's favored diagnostic readouts of a more fundamental upstream event.

The reception of the mitochondrial cascade hypothesis has been instructive. The framework has been cited extensively and has generated a sustained experimental program, but it has never displaced the amyloid cascade as the dominant organizing framework of the field. Two factors account for this. First, the amyloid cascade supplied a discrete, measurable, pharmacologically targetable biomarker whose manipulation in mouse models produced impressive cognitive rescues and whose clinical targeting, while disappointing, has at least been technically feasible. The mitochondrial cascade has not supplied an equivalently tractable target: mitochondrial function is multi-dimensional, mitochondrial DNA damage is difficult to reverse in post-mitotic cells, and interventions aimed at mitochondrial restoration have historically been non-specific and poorly penetrant. Second, the amyloid cascade integrated cleanly with the genetics of familial Alzheimer's disease, whose presenilin and APP mutations produce the predicted Aβ phenotype and whose pedigrees supply the mechanistic anchor for the broader disease framework. The mitochondrial cascade has been less genetically anchored, and its proponents have had to argue that the familial cases are exceptional and that sporadic cases follow a different mechanistic logic. The field has generally been reluctant to accept that the numerically dominant form of the disease follows a different mechanism than the numerically minor but genetically tractable form.

The Gouras-Nixon axis described in the previous section substantially weakens both of these objections to the Swerdlow framework, and in doing so provides the Bioenergetic Collapse Model with grounds for adopting the mitochondrial cascade as its broader theoretical envelope. The Nixon lysosomal-acidification work has demonstrated that the presenilin mutations that drive familial Alzheimer's disease do so through direct impairment of v-ATPase assembly and therefore of lysosomal acidification — meaning that the familial genetics, long held up as the amyloid cascade's strongest evidence, are in fact evidence of an autophagy-lysosomal failure that secondarily generates the Aβ phenotype. The autophagy-lysosomal system is, moreover, deeply dependent on mitochondrial function for its energetic requirements and on mitophagy for its quality-control maintenance. Lysosomal biogenesis is regulated by the master transcription factor TFEB, whose activity is coupled through mTORC1 to the metabolic state of the cell, and whose nuclear translocation and target gene activation depend on the cellular energy state that mitochondria provide. A cell whose mitochondrial function has fallen below the threshold required for homeostatic maintenance cannot sustain the lysosomal biogenesis program that clears its autophagic

cargo, and its accumulation of undegradable substrate — including Aβ — follows as a direct consequence. The mitochondrial cascade and the autophagy-lysosomal failure framework are not competing hypotheses. They are the same framework described at different points along a single causal chain in which mitochondrial failure is upstream of lysosomal failure, lysosomal failure is upstream of autophagic cargo accumulation, autophagic cargo accumulation is upstream of PANTHOS-type neuronal death, and neuronal death is upstream of the plaques and tangles that constitute the diagnostic signature of the disease.

This reframing permits an answer to one of the most persistent puzzles in Alzheimer's disease research: why therapeutic programs aimed at reducing amyloid burden have generated such modest clinical benefits despite achieving substantial reductions in the intended target. The mitochondrial cascade hypothesis predicts this outcome straightforwardly. If mitochondrial failure is the upstream driver, then removing the downstream proteinopathic signature without addressing the upstream substrate failure will produce biomarker changes without altering the trajectory of the disease. The brain will continue to generate PANTHOS-type neuronal deaths because the mitochondrial and lysosomal failures that drive those deaths are unaffected by extracellular Aβ clearance. The cognitive outcomes will therefore continue to deteriorate even as plaque counts decline. This is precisely what has been observed in the most recent generation of anti-amyloid trials, in which substantial biomarker shifts have been accompanied by modest and uneven cognitive effects. The Swerdlow framework predicts these results as a direct consequence of targeting a downstream signature rather than an upstream substrate.

The implication for the Homeostatic Collapse Model is that the microglial synthesis of the prior thesis can be repositioned as the microglial arm of a broader mitochondrial-upstream framework. The TGF-β/SMAD-maintained homeostatic signature identified by Butovsky is an energetically expensive phenotype whose maintenance requires continuous transcriptional input, whose output includes the surveillance and phagocytic functions that demand substantial mitochondrial ATP production, and whose collapse under conditions of cumulative oxidative and metabolic stress is the microglial analog of the PANTHOS phenotype in neurons. A microglial cell whose mitochondrial function has fallen below the threshold required for homeostatic maintenance can no longer sustain the Butovsky signature. It loses P2ry12, Tmem119, and the broader transcriptional program, and it enters one of several downstream trajectories depending on which alternative phenotypes remain available to it given its residual metabolic capacity. The DAM, LDAM, and dystrophic trajectories described in the prior thesis are not competing phenotypes but alternative downstream consequences of a shared upstream mitochondrial failure, and the selection among them is governed by the same variable — mitochondrial and mitophagy competence — that the Swerdlow framework identifies as the upstream driver of Alzheimer's disease writ large.

Adopting the mitochondrial cascade framework as the broader envelope for the Homeostatic Collapse Model therefore does not require commitment to the strong claim that mitochondrial dysfunction is the sole upstream event in Alzheimer's disease. It requires only commitment to the weaker and more defensible claim that mitochondrial competence is the rate-limiting variable whose failure generates both the neuronal PANTHOS phenotype that Gouras and Nixon have characterized and the microglial homeostatic collapse that the prior thesis described. The two phenotypes are cell-type-specific manifestations of the same substrate failure, and the therapeutic programs that target each of them separately will remain limited by the fact that they address downstream consequences rather than the upstream event. The remainder of this thesis is concerned with specifying the molecular machinery of that upstream event — canonical mitophagy, mitochondrial metabolic reprogramming, NLRP3 inflammasome gating, and mitochondrial allostatic load integration — with sufficient precision that its therapeutic restoration becomes technically tractable and its experimental verification becomes operationally concrete.

4. The Quality Control Machinery: Youle and Canonical Mitophagy

The mitochondrial cascade hypothesis specifies that mitochondrial failure is upstream of Alzheimer's disease pathology, but it does not specify the cell-biological machinery whose failure constitutes that upstream event. The machinery is supplied by the canonical mitophagy pathway, whose biochemistry was established principally through the work of Richard Youle and colleagues at the NIH in the decade following their landmark 2008 Journal of Cell Biology paper by Narendra, Tanaka, Suen, and Youle. That paper demonstrated that Parkin, the E3 ubiquitin ligase encoded by the PARK2 gene whose loss of function causes autosomal recessive juvenile Parkinson's disease, is not cytoplasmically distributed in a diffuse manner as had been assumed, but is selectively recruited to mitochondria whose membrane potential has collapsed, and that this recruitment initiates the ubiquitination of outer mitochondrial membrane proteins that marks the organelle for autophagic degradation. The discovery supplied, for the first time, a molecular mechanism by which a cell could distinguish damaged mitochondria from functional ones and selectively eliminate the former through the ordinary machinery of macroautophagy. It also supplied the first clear genetic link between mitophagy and a human neurodegenerative disease, establishing the principle that failure of mitochondrial quality control through this specific pathway is sufficient to cause neuronal death and clinically significant neurological pathology.

The Youle model was rapidly extended by subsequent work from multiple laboratories to establish the full molecular anatomy of the pathway. PINK1, the mitochondrial serine-threonine kinase encoded by the PARK6 gene whose loss of function produces a clinical phenotype similar to that of Parkin loss, was shown to function as the upstream sensor that recognizes mitochondrial membrane potential collapse. Under normal conditions, PINK1 is imported through the TOM and TIM23

translocases into the mitochondrial matrix, where it is rapidly degraded by the mitochondrial protease PARL. Its steady-state concentration on the outer mitochondrial membrane is therefore near-zero. When a mitochondrion loses its membrane potential — as occurs when its electron transport chain fails, when its permeability transition pore opens, when its mtDNA is sufficiently damaged that it can no longer support translation of essential respiratory chain subunits, or when its lipid membrane composition has been corrupted by oxidative damage — PINK1 can no longer be imported and accumulates on the outer membrane. This accumulation is the signal that Parkin recognizes and that triggers its recruitment from the cytosol to the damaged organelle. Once recruited, Parkin ubiquitinates outer membrane proteins including mitofusins, VDAC, TOM20, and a larger panel of substrates, and these ubiquitin marks recruit autophagy adapter proteins — p62/SQSTM1, optineurin, NDP52, TAX1BP1 — that bridge the ubiquitinated organelle to LC3-decorated autophagosomal membranes. The damaged mitochondrion is thus engulfed by a forming autophagosome and delivered to the lysosome for degradation. Critically, this engulfment depends on the general autophagosome-formation machinery, including the ESCRT-III-mediated membrane closure step that Rubinsztein's 2025 work characterized as coordinated by BIN1. Mitophagy is not an independent pathway but a specialized application of the macroautophagy machinery, and the autophagosome that engulfs a damaged mitochondrion must undergo the same ESCRT-III/DNM2-dependent membrane closure that seals autophagosomes carrying any other cargo. BIN1 dysfunction therefore impairs both general autophagy and mitophagy through the shared autophagosome-closure step, meaning that the sporadic LOAD genetic risk carried by BIN1 variants attacks not only protein aggregate clearance but also the mitochondrial quality-control pathway whose failure this thesis identifies as the upstream substrate of the disease.

This pathway is not a specialized adaptation for extreme stress conditions. It operates continuously in essentially all eukaryotic cells and is the principal mechanism by which mitochondrial population quality is maintained across the cellular lifespan. Mitochondria are not static organelles. They fuse and divide continuously, and the balance between fusion and fission determines the average size, number, and distribution of the mitochondrial network. Damaged mitochondria are characteristically segregated through fission events that isolate the damaged domain from the rest of the network, and these segregated, depolarized daughter organelles become the substrate for PINK1/Parkin-mediated mitophagy. Cells with intact mitophagy therefore maintain a healthy population of mitochondria through a continuous turnover process: damaged mitochondria are identified, segregated, marked, engulfed, and degraded, and new mitochondria are generated through the PGC-1α-coordinated biogenesis program to replace those that have been eliminated. The homeostatic set point of the mitochondrial population reflects the balance between biogenesis and mitophagy, and the integrity of both processes is necessary for the maintenance of mitochondrial competence at the population level.

The functional significance of this pathway for the Bioenergetic Collapse Model lies in what happens when it fails. A cell with impaired mitophagy cannot remove damaged mitochondria from its population, and the damaged organelles therefore accumulate. Their accumulation has several immediate consequences. First, they continue to consume cellular resources — including the lipid substrates, mitochondrial DNA, and imported proteins that biogenesis programs supply — without generating the ATP output that functional mitochondria would produce, such that the cell's energetic yield per unit of mitochondrial investment declines. Second, they release reactive oxygen species at elevated rates because their electron transport chains leak electrons at damaged complexes, and these ROS damage adjacent mitochondria as well as non-mitochondrial cellular components including DNA, proteins, and lipid membranes. Third, and most consequentially for the later sections of this thesis, they release mitochondrial DNA fragments, cardiolipin, and other damage-associated molecular patterns into the cytosol, where these molecules activate innate immune sensors that mount an inflammatory response against the cell's own organelles. The NLRP3 inflammasome is one of the principal targets of these signals, and the consequences of its activation in microglia are precisely the destructive effector outputs that the prior thesis catalogued as the attack phenotype of post-homeostatic microglia.

In a cell type whose identity depends on continuous energetic expense, the consequences of mitophagy failure are therefore not confined to the mitochondrial population itself. They propagate to the transcriptional program that maintains the cell's identity, because that program is sustained by signaling pathways whose activity depends on the cellular energy state. They propagate to the secretory output of the cell, because the pro-inflammatory release triggered by mitochondrial damage signals alters the cytokine and lipid mediator profile the cell produces. They propagate to the interactions the cell maintains with its neighbors, because a cell whose mitochondrial quality control has failed is no longer capable of executing the specialized functions — surveillance, synaptic support, matrix maintenance — that those neighbor relationships require. Mitophagy failure, in short, is not a local problem confined to the organelle population. It is a systems-level collapse whose consequences include the loss of the cell's differentiated phenotype.

This framing is critical for the microglial biology the later sections of this thesis will address. Microglia, as the prior thesis established, maintain their homeostatic identity through a continuous TGF-β/SMAD-driven transcriptional program whose energetic cost is substantial and whose collapse defines the post-homeostatic state. The mitochondrial requirements of this program have not been explicitly mapped in the Butovsky literature, but they can be inferred from several converging lines of evidence. The Ulland and Colonna 2017 Cell paper demonstrated that TREM2 coupling to DAP12 and SYK activates the PI3K-AKT-mTOR axis that drives oxidative phosphorylation and microglial metabolic fitness, and that TREM2 loss-of-function variants fail to sustain this metabolic program in disease-associated microglia. The Baik 2019 Cell Metabolism paper, which the later sections of this thesis will treat as the empirical keystone of the microglial

collapse story, demonstrated that AD microglia undergo an initial glycolytic shift in response to Aβ and then collapse into a hypometabolic state in which both glycolysis and oxidative phosphorylation fail — a phenotype that is incompatible with any cell whose homeostatic identity requires sustained energetic output. The convergence of these findings implies that microglial homeostatic identity is mitochondrially expensive, that its maintenance requires both continuous biogenesis and continuous quality control, and that failure of the PINK1/Parkin mitophagy pathway would be sufficient to collapse the homeostatic phenotype without requiring any independent hit to the transcriptional machinery itself. The mitochondrial quality-control failure is, in this sense, the energetic substrate of the transcriptional collapse, and the two are not separable events.

The Youle framework therefore supplies the Bioenergetic Collapse Model with its molecular specification of the upstream failure event. Where the prior thesis spoke of "cumulative oxidative load" and "metabolic fitness" as load-bearing variables whose content was left unspecified, this thesis can now name the specific machinery whose failure produces those outcomes: the PINK1/Parkin-mediated recognition of damaged mitochondria, the ubiquitin-autophagy adapter cascade that delivers them to the lysosome, and the biogenesis program that replaces them. The mitochondrial cascade hypothesis of Swerdlow is the theoretical envelope; the Gouras-Nixon axis is the downstream manifestation in neurons; and the Youle mitophagy pathway is the specific machinery whose failure connects the envelope to the manifestations. The sections that follow will trace how this machinery fails in Alzheimer's disease and how its restoration — through approaches including NAD■ precursors, urolithin A, and the broader class of mitophagy-inducing interventions — has been shown experimentally to reverse both the neuronal and microglial phenotypes of the disease.

5. Mitophagy Failure in Alzheimer's Disease: The Fang/Bohr Program

The canonical mitophagy machinery described in the preceding section is not merely a theoretical construct available for invocation in disease models; it is a pathway whose failure has been directly documented in Alzheimer's disease tissue, in Alzheimer's disease mouse models, and in induced pluripotent stem cell-derived neurons from individuals carrying AD-associated genetic variants. The experimental program most responsible for this documentation, and for the demonstration that its pharmacological reversal is therapeutically effective in preclinical models, is the collaboration between Evandro Fang, Vilhelm Bohr, Mark Mattson, and their colleagues, whose 2019 Nature Neuroscience paper has become the single most cited experimental demonstration that mitophagy restoration rescues Alzheimer's disease pathology across multiple model systems and multiple disease readouts.

The Fang, Hou, Palikaras, Adriaanse, and colleagues 2019 paper, titled "Mitophagy inhibits amyloid-β and tau pathology and reverses cognitive deficits in models of Alzheimer's disease," presented three classes of findings that together establish mitophagy as both a locus of failure in Alzheimer's disease and a viable therapeutic target for its reversal. The first class of findings documented that mitophagy is impaired in Alzheimer's disease tissue and models. Using mitophagy-specific reporters, postmortem human hippocampal tissue from individuals with Alzheimer's disease, and hippocampal samples from APP/PS1 transgenic mice, the authors demonstrated that basal mitophagy is significantly reduced relative to age-matched controls, that the reduction is present at disease stages before overt neurodegeneration, and that it correlates with Aβ and tau pathology burden. Induced pluripotent stem cell-derived neurons from individuals with sporadic Alzheimer's disease exhibited the same mitophagy deficit, indicating that the failure is not a non-specific consequence of neurodegeneration but a cell-autonomous feature of AD-associated cellular biology. The finding is critical because it establishes that mitophagy failure is not merely present in Alzheimer's disease but is present early, mechanistically upstream of the biomarker phenotypes the field has traditionally used to define the disease.

The second class of findings demonstrated that pharmacological stimulation of mitophagy rescues the disease phenotype. The authors tested two small-molecule mitophagy inducers — urolithin A, a microbial metabolite produced from dietary ellagitannins in the gut, and nicotinamide mononucleotide, an NAD■ precursor — in APP/PS1 mice, in C. elegans models of Aβ toxicity, and in iPSC-derived AD neurons. In each system, mitophagy induction produced substantial reductions in Aβ burden, in tau phosphorylation, and in the downstream cellular and behavioral phenotypes of disease. In mouse models, the interventions rescued cognitive performance on spatial memory and object recognition tasks, reduced plaque burden in hippocampal tissue, and improved markers of synaptic integrity in affected brain regions. In C. elegans, the interventions rescued lifespan and behavioral phenotypes in transgenic Aβ-expressing strains. In iPSC-derived neurons, the interventions rescued mitochondrial function, reduced intracellular Aβ accumulation, and preserved neuronal morphology. The convergence of rescue effects across model systems is the strongest available experimental support for the claim that mitophagy failure is a causal upstream event in Alzheimer's disease pathology, because the rescue operates across multiple disease driver mechanisms and across multiple species, suggesting that the target pathway is conserved and that its restoration is sufficient to redirect the disease trajectory regardless of the specific upstream insult.

The third class of findings, and the most important for the Bioenergetic Collapse Model this thesis develops, demonstrated that mitophagy induction in these models modulates microglial phenotype toward a protective, homeostasis-like state. The 2019 paper reported that urolithin A treatment in APP/PS1 mice reduced microglial activation markers, decreased pro-inflammatory cytokine production, and shifted microglial phagocytic engagement with Aβ toward a pattern characteristic of productive clearance rather than failed salvage. This is not the primary finding of the Fang paper,

and the microglial characterization is less detailed than the neuronal characterization, but the direction of the effect is unambiguous and is the key that unlocks the bridge between the Fang/Bohr program and the Homeostatic Collapse Model. Mitophagy restoration does not merely rescue neuronal function by restoring mitochondrial quality control within neurons. It also restores a protective microglial phenotype — a finding that, under the integrated model, makes sense only if microglial function depends on microglial mitochondrial quality control in the same way that neuronal function depends on neuronal mitochondrial quality control. If mitophagy failure in microglia produces the post-homeostatic phenotype the prior thesis described, then mitophagy restoration in microglia should produce the homeostatic restoration the prior thesis identified as the therapeutic goal. The Fang 2019 result is consistent with this prediction and constitutes its first experimental support.

The theoretical framework within which Fang's experimental program operates was articulated in the 2017 Trends in Neurosciences review by Kerr, Adriaanse, Greig, Mattson, Cader, Bohr, and Fang, titled "Mitophagy and Alzheimer's Disease: Cellular and Molecular Mechanisms." This review, which preceded the 2019 experimental paper by two years, laid out the case for mitophagy as a central mechanism in the cell biology of Alzheimer's disease and established the vocabulary and mechanistic framing that the subsequent experimental work would test. The review argued that mitophagy failure is a plausible upstream event in Alzheimer's disease because the disease selectively affects brain regions and cell types — hippocampal pyramidal neurons, cortical pyramidal neurons, basal forebrain cholinergic neurons — whose mitochondrial demand is among the highest in the brain and whose vulnerability to mitochondrial quality-control failure is therefore the greatest. It further argued that the age dependence of sporadic Alzheimer's disease is consistent with mitophagy failure as an upstream driver because mitophagy declines with age across model organisms, because mitochondrial DNA damage accumulates with age in a manner that would challenge any mitophagy pathway's capacity to keep up, and because the specific pharmacological and genetic interventions known to extend lifespan across species — caloric restriction, rapamycin treatment, NAD■ boosting — converge on mitophagy enhancement as a shared downstream mechanism. The Kerr et al. review, together with the Fang 2019 experimental paper, therefore constitute a paired theoretical and empirical argument that mitophagy failure is upstream in Alzheimer's disease and that its pharmacological reversal is therapeutically sufficient to redirect the disease trajectory in preclinical models.

A third paper in the Fang/Bohr corpus extends the implications of this framework beyond mitophagy itself to the broader role of NAD■ in brain aging. The 2019 Cell Metabolism review by Lautrup, Sinclair, Mattson, and Fang, titled "NAD+ in Brain Aging and Neurodegenerative Disorders," argued that age-related decline in cellular NAD■ levels is a central driver of the bioenergetic failures that characterize neurodegenerative disease, and that restoration of NAD■ through precursor supplementation — nicotinamide riboside, nicotinamide mononucleotide — is a

viable therapeutic strategy across multiple neurodegenerative indications. The NAD■ framework is relevant to the Bioenergetic Collapse Model for two reasons. First, NAD■ is a necessary cofactor for sirtuin-mediated deacetylation of PGC-1α, which in turn coordinates the mitochondrial biogenesis program that replaces mitochondria eliminated by mitophagy. NAD■ decline therefore impairs the biogenesis arm of the mitochondrial population renewal cycle in parallel with its effects on mitophagy induction, and its restoration is mechanistically pleiotropic in a way that makes it a particularly attractive therapeutic candidate. Second, NAD■ declines with age in multiple tissues including the brain, and the decline is accelerated by conditions of chronic oxidative stress and inflammation — the same conditions that drive the mitophagy failure and homeostatic collapse this thesis attempts to integrate. The metabolic psychiatry literature covered in the Sethi and Sarnyai 2026 review also identifies NAD■ restoration as a convergent therapeutic candidate across psychiatric indications whose pathophysiology includes mitochondrial dysfunction, providing an independent line of evidence that the pathway is a shared target across brain disease more generally.

The integration of the Fang/Bohr program with the prior thesis therefore makes three claims that will be developed in the later sections. First, mitophagy failure in Alzheimer's disease is experimentally documented in neurons and is reasonably inferred in microglia on the basis of convergent evidence from the Baik, Ulland, and Colonna work the next sections will address. Second, pharmacological mitophagy restoration is therapeutically effective across multiple Alzheimer's disease models and operates, at least in part, through microglial phenotype modulation that is consistent with the homeostatic restoration predicted by the prior thesis. Third, the broader NAD■ framework supplies a mechanistically pleiotropic therapeutic target that addresses mitophagy, biogenesis, sirtuin-mediated deacetylation, and PARP-mediated DNA damage response simultaneously, and whose clinical tractability — NAD■ precursors are orally bioavailable, well-tolerated, and already in clinical use for other indications — makes it a practical candidate for the unified therapeutic class the §13 section will develop. The convergence of these claims with the mitochondrial cascade framework of Swerdlow and the canonical mitophagy framework of Youle, and their integration with the microglial synthesis of the prior thesis, is what this thesis proposes to accomplish.

One additional observation from the Fang 2019 paper deserves emphasis because it bears directly on the prior thesis's identification of the perineuronal net and the parvalbumin-positive interneuron as the molecular readout of therapeutic success. The authors reported that mitophagy induction preserved synaptic markers and hippocampal function in the treated APP/PS1 mice, and that the preservation was accompanied by maintained levels of parvalbumin immunoreactivity and inhibitory interneuron markers in the hippocampal formation. The paper did not specifically measure perineuronal net integrity or aggrecan immunoreactivity, but the preservation of PV+ neuron markers is consistent with and suggestive of the preserved PNN phenotype that the prior thesis identified in the de Vries resilience data. A direct test of whether mitophagy induction

preserves perineuronal net integrity in AD models has not, to my knowledge, been performed, and this is one of the specific experimental predictions the §12 section will articulate. If the prediction is confirmed, it would constitute the tightest possible integration between the Fang/Bohr program and the Homeostatic Collapse Model, and would establish that the therapeutic class identified by mitophagy induction is acting, at the circuit level, on precisely the endpoint the prior thesis identified as the most tractable readout of homeostatic restoration.

6. The Microglial Metabolic Keystone: Baik 2019 and the Empirical Collapse

If the prior two sections established the theoretical and pharmacological case for mitochondrial quality-control failure as an upstream event in Alzheimer's disease, the 2019 Cell Metabolism paper by Baik, Kang, Lee, Choi, and colleagues supplies the single most consequential piece of experimental evidence that this failure occurs specifically in microglia and that it constitutes the empirical substance of the post-homeostatic phenotype the prior thesis described. The paper, titled "A Breakdown in Metabolic Reprogramming Causes Microglia Dysfunction in Alzheimer's Disease," demonstrated something that the DAM taxonomy, the LDAM framework, the dystrophy literature, and the TGF-β/SMAD signaling literature had each implied but none had measured directly: that microglial energy metabolism in Alzheimer's disease is not merely altered but is progressively and specifically impaired in a manner that explains the functional deficits those other frameworks had described at the transcriptional, lipidomic, and morphological levels.

The experimental design of the Baik paper was straightforward but methodologically decisive. The authors exposed primary murine microglia to Aβ in vitro, measured their metabolic output using extracellular flux analysis, and tracked the cells' bioenergetic state over time as they engaged with the amyloid cargo. The initial response was a characteristic immune-cell activation profile: glycolytic output increased, oxidative phosphorylation was transiently suppressed, and the cells entered a high-glycolytic state resembling the early activation phenotype of other myeloid populations engaging with a pathogen-like substrate. This initial phase is consistent with the early activation profile that the DAM Stage 1 transition would predict and that the Warburg-like shift of activated macrophages more generally displays. But the Baik paper's critical contribution was to track what happened next. Rather than sustaining the glycolytic state or transitioning into the productive clearance program that successful activation would predict, the microglia collapsed into a hypometabolic state in which both glycolysis and oxidative phosphorylation were substantially impaired. ATP production fell. Basal respiration declined. Spare respiratory capacity was lost. The cells were not resting; they were not activated in any productive sense; they were bioenergetically exhausted. The authors traced the proximate mechanism of this collapse to failure of the PI3K-AKT-mTOR signaling axis, which under normal conditions couples receptor input to

metabolic reprogramming and which, in the AD microglial context, failed to maintain the metabolic shifts that would have permitted sustained activation. The signaling failure was not absolute — residual mTOR activity was detectable — but it was insufficient to drive the metabolic adaptations that productive Aβ clearance would require.

The Baik findings are the empirical substantiation of several claims the prior thesis made at a more conceptual level. The most important is the claim that the post-homeostatic state identified by Butovsky's signature loss is not merely a transcriptional phenotype but is an energetic collapse whose consequences include the loss of effector competence. The DAM framework, the LDAM framework, and the dystrophy framework had all implied that post-homeostatic cells exhibited functional deficits, but none had measured the bioenergetic state of the cells directly. Baik did, and what he found was a state of metabolic failure that matches the "active but ineffective" phenotype von Bernhardi had predicted from the TGF-β/SMAD signaling framework on purely biochemical grounds. Cells in this state are producing cytokines, releasing effector enzymes, and engaging with pathological substrate, but they are doing so in the absence of the metabolic output that productive engagement would require, and their effector activity is therefore necessarily destructive rather than protective. The Baik paper supplied the mechanism that converts this prediction from a theoretical expectation into a measured phenotype.

A second claim the Baik paper substantiates is that the LDAM gridlock phenotype described by Marschallinger is not a stand-alone cellular state but a specific manifestation of the broader metabolic collapse Baik documented. Lipid droplets accumulate in microglia when the cells internalize lipid cargo but cannot oxidize it through β-oxidation and electron transport chain coupling, and this inability is precisely what Baik's finding of OXPHOS collapse would predict. A microglial cell whose oxidative phosphorylation capacity has failed cannot process internalized fatty acids through mitochondrial β-oxidation, and the cargo therefore accumulates in cytoplasmic droplets where it is inaccessible to the metabolic machinery that would ordinarily dispose of it. The LDAM phenotype is, in this sense, the lipidomic signature of the Baik metabolic collapse, and the two frameworks describe the same cellular state from the lipidomic and bioenergetic perspectives respectively. This integration is important because it resolves one of the ambiguities in the prior thesis, which treated DAM and LDAM as alternative downstream trajectories from homeostatic collapse without specifying the variable that sorted cells between them. The variable is mitochondrial competence: cells with preserved β-oxidation capacity enter productive DAM clearance, cells without it enter LDAM gridlock, and the sorting is determined by whether mitochondrial quality control has maintained the metabolic machinery that β-oxidation requires.

A third claim the Baik paper substantiates, and the most important for the integrated model, is the claim that TREM2 functions as a metabolic fitness gate rather than as a simple activation receptor. The Baik work was preceded and substantially framed by the 2017 Cell paper by Ulland, Song,

Huang, Ulrich, and colleagues from Marco Colonna's laboratory, titled "TREM2 Maintains Microglial Metabolic Fitness in Alzheimer's Disease." The Ulland paper demonstrated that TREM2 signaling through DAP12, SYK, and the PI3K-AKT-mTOR axis is required for microglia to sustain the oxidative phosphorylation program that productive Aβ engagement demands, and that TREM2 loss-of-function variants fail to maintain this program in AD models. Cells with TREM2 hypofunction exhibited reduced mTOR activity, decreased OXPHOS output, and impaired phagocytic capacity at the plaque periphery. The integration of the Ulland and Baik findings is that TREM2 and mTOR are operating on the same metabolic axis, that TREM2 engagement is the receptor-level trigger for the mTOR-driven metabolic reprogramming that Baik documented, and that failure at either node — TREM2 at the receptor level or mTOR at the signaling level — produces the same downstream consequence: bioenergetic collapse, failed phagocytic clearance, and the cellular phenotype that the prior thesis described as post-homeostatic failed salvage. The TREM2 paradox that occupied the prior thesis — the observation that TREM2 loss-of-function confers Alzheimer's disease risk despite reducing DAM activation — resolves in this framing because TREM2 is not an activation switch whose output is always pathogenic or always protective but a metabolic fitness gate whose output is protective when cellular metabolism can execute the program it initiates and destructive when cellular metabolism cannot. Loss-of-function variants shift the distribution toward failed metabolic execution and therefore toward destructive rather than protective outcomes.

The convergence of the Ulland and Baik findings with the canonical mitophagy framework of Youle and the mitophagy failure evidence of Fang completes the mechanistic picture this thesis has been building. Microglial homeostatic identity is maintained by TGF-β/SMAD signaling, which drives a transcriptional program whose maintenance is energetically expensive. The energetic substrate of this program is mitochondrial oxidative phosphorylation, which requires continuous mitochondrial biogenesis and continuous mitophagy-mediated quality control to sustain. Age-related failure of mitochondrial quality control, driven by cumulative oxidative stress and the progressive decline in NAD■-dependent sirtuin function, impairs the mitophagy pathway and produces a mitochondrial population whose quality degrades over time. When Aβ appears as a pathological substrate, microglia attempt to execute the activation and clearance program that their TREM2 receptors initiate, but this program requires metabolic reprogramming that their already-degraded mitochondrial population cannot sustain. The PI3K-AKT-mTOR axis fails to drive the OXPHOS shift the program requires, the cells collapse into the hypometabolic state Baik documented, and the transcriptional identity that TGF-β/SMAD signaling had maintained collapses because the energetic substrate for its maintenance is no longer available. The post-homeostatic phenotype is therefore not a gain-of-function state reached through activation but a loss-of-function state reached through metabolic exhaustion, and the DAM, LDAM, and dystrophic trajectories are the alternative downstream fates of cells whose metabolic collapse has proceeded to different degrees.

The empirical weight of the Baik paper for this thesis cannot be overstated. It is the single paper that converts the Homeostatic Collapse Model from a theoretical synthesis of transcriptional and lipidomic data into an experimentally grounded claim about microglial bioenergetics. It establishes that microglial metabolic collapse in Alzheimer's disease is real, measurable, and mechanistically coupled to the signaling axis — PI3K-AKT-mTOR — that links TREM2 engagement to metabolic reprogramming. It demonstrates that this collapse is specifically induced by Aβ engagement rather than being a non-specific feature of aged microglia, which is critical because it establishes the causal direction: the pathological substrate of the disease drives the metabolic collapse, not the reverse. And it supplies the mechanistic bridge through which the cell-biological content of the homeostatic signature — the specific energetic and biosynthetic demands of P2ry12, Tmem119, and the broader Butovsky profile — can be understood as depending on the mitochondrial quality-control machinery whose failure this thesis argues is the upstream event in Alzheimer's disease. The Baik paper is, in this sense, the experimental keystone that holds the entire integrated model together. Without it, the claim that microglial homeostatic collapse is a mitochondrial failure would remain a theoretical extrapolation; with it, the claim is grounded in measured cellular respiration, quantified mTOR activity, and documented metabolic-phenotype coupling to the pathological substrate of the disease.

One aspect of the Baik findings deserves particular emphasis because it bears directly on the therapeutic implications this thesis will develop. The metabolic collapse Baik documented was not an irreversible state. Treatment with interventions that restored mTOR signaling or enhanced mitochondrial function partially rescued the metabolic phenotype and restored aspects of productive phagocytic engagement. This is precisely the result the Bioenergetic Collapse Model predicts: interventions that restore mitochondrial competence should restore microglial functional capacity regardless of whether they target the PI3K-AKT-mTOR axis directly, the mitochondrial biogenesis program, the mitophagy pathway, or the substrate-level bioenergetics through ketone provision. The convergence of mechanistically distinct interventions on a single therapeutic outcome — restored microglial metabolic competence and consequent restored homeostatic function — is the clearest experimental support for the claim that mitochondrial quality control is the upstream variable and that the apparent diversity of downstream phenotypes reflects the single variable's failure mode rather than any intrinsic diversity in the post-homeostatic state itself.

7. NLRP3 as the Mitochondrial-ROS-Gated Effector Arm: The Heneka Program

The prior thesis catalogued four distinct effector arms through which post-homeostatic microglia damage neural tissue in Alzheimer's disease: the complement-mediated synaptic pruning pathway of Stevens and colleagues, the cell-autonomous C4d/LilrB2 pruning pathway of Shatz and colleagues, the matrix metalloproteinase and cathepsin-driven perineuronal net degradation pathway of Crapser and colleagues, and the cytokine and reactive oxygen species output that constitutes the generalized inflammatory component of microglial pathology. Each of these pathways was described as a distinct mechanism by which activated or dystrophic microglia produce damage, and the prior thesis proposed that their integration under the rubric of "failed salvage" provided a unified framing. But that framing left unspecified a critical question: what determines when a post-homeostatic microglial cell releases its effector output? The cells of the aged brain contain the machinery for complement deposition, for MMP release, for cathepsin secretion, and for cytokine production, but they do not continuously release these mediators. Release is triggered, and the trigger is gated by a specific signaling event whose identity the prior thesis did not name. This section supplies that name.

The trigger is the NLRP3 inflammasome, and the signaling pathway that gates its activation is the detection of mitochondrial damage-associated molecular patterns — reactive oxygen species, oxidized mitochondrial DNA, cardiolipin, and other lipid and protein species whose appearance in the cytosol signals the loss of mitochondrial membrane integrity. The experimental program most responsible for establishing this gate in the specific context of Alzheimer's disease is the work of Michael Heneka and colleagues, whose 2013 Nature paper on NLRP3 in APP/PS1 mice, 2017 Nature paper on microglial ASC specks cross-seeding Aβ, and 2019 Nature paper on NLRP3-driven tau pathology constitute the three landmark experimental demonstrations that inflammasome activation is not merely a downstream consequence of Alzheimer's disease but is a forward-propagating pathogenic amplifier whose outputs drive both the Aβ and tau arms of the disease phenotype.

The 2013 paper by Heneka, Kummer, Stutz, Delekate, and colleagues, published in Nature and titled "NLRP3 is activated in Alzheimer's disease and contributes to pathology in APP/PS1 mice," demonstrated three findings that established the framework. First, NLRP3 inflammasome components are elevated in Alzheimer's disease brain tissue and in APP/PS1 mouse brain relative to age-matched controls, with the elevation particularly prominent in microglia around plaques. Second, genetic deletion of NLRP3 in APP/PS1 mice substantially reduced Aβ deposition, improved hippocampal function, and rescued spatial memory deficits. Third, the protective effect of NLRP3 deletion was accompanied by a shift in the microglial phenotype toward a more homeostatic profile, with reduced pro-inflammatory cytokine output and enhanced phagocytic engagement with

Aβ. The combined findings established that NLRP3 activation is not merely a biomarker of microglial activation but is a causal contributor to the disease phenotype whose removal shifts the cellular phenotype in the direction the Homeostatic Collapse Model identifies as protective. The paper did not specifically measure mitochondrial ROS as the NLRP3 trigger, but the inflammasome literature from non-AD contexts had established by 2013 that mitochondrial damage-associated molecular patterns are among the primary activators of NLRP3 in myeloid cells, and the extension of this framing to the AD microglial context was immediate.

The 2017 paper by Venegas, Kumar, Franklin, Dierkes, and colleagues extended the framework with a finding that proved to be one of the most consequential in the neuroinflammation literature of the past decade. Published in Nature under the title "Microglia-derived ASC specks cross-seed amyloid-β in Alzheimer's disease," the paper demonstrated that when NLRP3 is activated in microglia, the resulting ASC specks — the cytoplasmic signaling platforms that couple NLRP3 sensing to caspase-1 activation — are released from the microglia into the extracellular space and can bind Aβ directly, accelerating its aggregation and seeding new plaques. This finding converted the NLRP3 inflammasome from a downstream consequence of Aβ pathology into a forward-propagating amplifier of it. Microglia engaging with Aβ activate NLRP3 in response to mitochondrial damage incurred during failed salvage attempts; activated NLRP3 releases ASC specks; released ASC specks seed additional Aβ aggregation; additional Aβ engages additional microglia, which in turn activate NLRP3 in response to further mitochondrial damage; and the cycle escalates. The framework supplied a mechanistic explanation for the exponential rather than linear growth of amyloid burden in Alzheimer's disease, and it placed microglial mitochondrial damage at the center of the self-amplifying loop.

The 2019 paper by Ising, Venegas, Zhang, Scheiblich, and colleagues, also published in Nature under the title "NLRP3 inflammasome activation drives tau pathology," completed the extension by demonstrating that NLRP3 activation is not confined to the Aβ arm of Alzheimer's disease but drives tau pathology as well. Working in Tau22 mice and in crosses between APP/PS1 and tau transgenic lines, the authors showed that NLRP3 deletion substantially reduced tau hyperphosphorylation and tangle formation, that inflammasome activation in microglia induces tau kinase activity in nearby neurons through IL-1β release, and that the tau arm of Alzheimer's disease pathology is therefore mechanistically gated by the same inflammasome activation that the 2013 and 2017 papers had implicated in the Aβ arm. The three Heneka papers together establish that NLRP3 is the central node through which microglial dysfunction in Alzheimer's disease generates both the proteinopathic phenotypes that define the disease clinically, and that targeting NLRP3 genetically or pharmacologically produces the expected rescue phenotype across both arms of the pathology.

The integration of the Heneka program with the Bioenergetic Collapse Model is direct and mechanistically dense. NLRP3 activation requires two signals. The first is a priming signal that

induces NLRP3 expression and licenses the inflammasome for assembly; in microglia, this priming is supplied by TLR4 engagement with Aβ oligomers or by other pattern recognition receptor signaling consequent to Aβ exposure. The second is an activation signal that triggers the assembly of the NLRP3 inflammasome platform and the activation of caspase-1. The most-studied activation signal across inflammasome biology is the detection of mitochondrial damage-associated molecular patterns, which appear in the cytosol when mitochondrial outer membrane integrity is lost — precisely the situation that occurs when damaged mitochondria accumulate faster than the mitophagy machinery can eliminate them. Mitochondrial ROS escape into the cytosol and directly oxidize NLRP3 in a manner that promotes its assembly. Oxidized mitochondrial DNA, released through permeability transition pore opening, directly binds NLRP3 and is among the most potent known activators of the inflammasome. Cardiolipin, which is normally confined to the inner mitochondrial membrane, appears on the outer membrane during mitochondrial stress and provides another NLRP3 activation surface. The convergence of these signals is mitochondrial quality control failure, and their downstream consequence is inflammasome activation.

The implication for the microglial biology of Alzheimer's disease is that every effector arm the prior thesis catalogued is downstream of a single upstream event: the inability of post-homeostatic microglia to maintain mitochondrial membrane integrity in the face of the metabolic demands that Aβ engagement places on them. When microglia attempt to execute the TREM2-gated phagocytic program that Aβ exposure initiates, they must drive the PI3K-AKT-mTOR axis to produce the metabolic reprogramming that Baik documented as failing in AD models. The failure produces two simultaneous consequences. First, the cells cannot sustain the productive clearance program and enter the hypometabolic state of failed salvage. Second, the incomplete metabolic shift produces mitochondrial damage — respiratory chain uncoupling, elevated ROS production, loss of membrane potential — that activates NLRP3 through the canonical damage-associated molecular pattern pathway. Activated NLRP3 drives caspase-1-mediated release of IL-1β and IL-18, and the resulting inflammatory milieu amplifies the effector output of the cell population. The complement components, the MMPs, the cathepsins, and the pro-inflammatory lipid mediators that constitute the destructive arm of post-homeostatic microglial activity are all downstream of, or substantially amplified by, the inflammasome activation that mitochondrial damage has triggered.

This framing supplies the mechanistic gate the prior thesis lacked. The Stevens complement pathway does not release C1q and C3 continuously; it releases them in response to the inflammatory priming that NLRP3 activation supplies. The Crapser MMP and cathepsin pathway at the perineuronal net does not degrade aggrecan continuously; it does so under conditions of elevated inflammasome-driven effector release. The Shatz C4d pathway depends on complement component availability that is modulated by NLRP3-driven synthesis. And the cytokine and ROS output that constitutes the generalized inflammatory component of microglial pathology is, by definition, downstream of inflammasome activation in the IL-1β family. The NLRP3 inflammasome is

therefore the central node at which mitochondrial quality-control failure becomes microglial effector output, and its gating by mitochondrial damage-associated molecular patterns makes it the specific mechanism through which the Bioenergetic Collapse Model connects its upstream substrate failure to the destructive consequences the prior thesis described at the level of neural circuitry.

A specific prediction follows from this integration that will be elaborated in the §12 predictions section: interventions that restore mitochondrial quality control in microglia should reduce NLRP3 inflammasome activation without directly targeting NLRP3 itself, because the primary driver of NLRP3 activation in AD microglia is mitochondrial damage-associated molecular pattern release, and preventing this release through restored mitophagy or enhanced mitochondrial biogenesis should be sufficient to silence the inflammasome. This prediction distinguishes the Bioenergetic Collapse Model from alternative therapeutic programs that target NLRP3 directly through small-molecule inhibitors — programs that should produce partial benefit by blocking the amplification step but that will not address the upstream mitochondrial failure and should therefore provide less durable or complete rescue than combined upstream/downstream intervention. The MCC950 NLRP3 inhibitor program and similar direct-inhibitor approaches have reported modest benefits in preclinical models; the model predicts these benefits should be substantially enhanced by combination with mitophagy-restoring interventions such as urolithin A or NAD■ precursor supplementation, because the combination addresses both the amplification and the upstream substrate simultaneously.

The 2015 Heneka, Carson, El Khoury, Landreth, and colleagues Lancet Neurology review, titled "Neuroinflammation in Alzheimer's disease," provides the broader framing within which the specific NLRP3 mechanism sits. The review articulates neuroinflammation not as a secondary consequence of amyloid pathology but as a contributor to its initiation and progression, and it positions the microglial-astrocytic axis as a central component of the disease process whose modulation is therapeutically tractable. The review predates the Baik and Ulland empirical work on microglial metabolic collapse and predates the 2022 Nixon PANTHOS finding on autophagy-lysosomal failure, but it supplies the conceptual framework within which the integration this thesis proposes can be understood as an extension of the neuroinflammation framework rather than a competing hypothesis. The Bioenergetic Collapse Model, by identifying mitochondrial quality-control failure as the upstream driver of the neuroinflammation that Heneka's program has characterized, supplies the cell-biological mechanism by which the inflammatory component of Alzheimer's disease becomes continuous with the proteinopathic and neurodegenerative components. Inflammation, proteopathy, and neurodegeneration are not three parallel features of the disease but three manifestations of a single upstream substrate failure, and the NLRP3 inflammasome is the molecular gate through which that substrate failure produces the inflammatory manifestation.

8. Mitochondria as Allostatic-Load Integrators: Picard and the Psychiatric Bridge

The Bioenergetic Collapse Model, as developed to this point in the thesis, is a cell-autonomous account of Alzheimer's disease pathology. It locates the upstream substrate failure in mitochondrial quality control within individual neurons and microglia, and it traces the downstream consequences of that failure through the specific cellular machinery — PINK1/Parkin mitophagy, PI3K-AKT-mTOR metabolic reprogramming, NLRP3 inflammasome gating — whose biochemistry has been characterized by decades of cell-biological work. This cell-autonomous framing is necessary because the upstream failure must be specified at the organelle level for the therapeutic program to be mechanistically tractable. But it is not sufficient, because the same body of work that has characterized mitochondria as organelle-level quality-control substrates has also established that mitochondria are the cellular integrators of systemic biological state, and that their functional competence is coupled to the organism's broader bioenergetic and allostatic condition in ways that cannot be captured by any cell-autonomous framing. The work most responsible for establishing this broader framing is that of Martin Picard and colleagues at Columbia, whose program on mitochondrial allostatic load, mitochondrial psychobiology, and mitochondria as integrators of chronic stress has produced the conceptual framework within which the cell-autonomous Bioenergetic Collapse Model becomes continuous with the systemic bioenergetic state of the aging individual.

The 2014 Nature Reviews Endocrinology paper by Picard, Juster, and Bruce McEwen, titled "Mitochondrial allostatic load puts the 'gluc' back in glucocorticoids," introduced the construct of mitochondrial allostatic load to the broader biomedical literature. The paper argued that the principal mechanism by which chronic psychological and physiological stress produces its long-term biological consequences is mitochondrial, and that the accumulated wear-and-tear on regulatory systems that McEwen's allostatic load framework had characterized at the systemic level could be mechanistically grounded at the organelle level through the progressive impairment of mitochondrial function. Glucocorticoids, the principal effector hormones of the stress response, act on mitochondria directly through the mitochondrial glucocorticoid receptor and indirectly through their transcriptional effects on mitochondrial biogenesis, mitophagy, and bioenergetic coupling. Chronic glucocorticoid elevation, the biochemical signature of sustained allostatic load, therefore produces sustained mitochondrial stress, and the cumulative consequence of this stress is the progressive degradation of mitochondrial population quality. The paper further argued that this mitochondrial degradation is not merely a consequence of stress but is the mechanism by which stress produces its downstream health consequences: cardiovascular disease, metabolic syndrome, neurodegenerative disease, and the accelerated aging phenotype that chronic stress has been linked to across multiple domains.

The 2018 Psychosomatic Medicine paper by Picard and McEwen, titled "Psychological Stress and Mitochondria: A Conceptual Framework," developed the framework in substantially greater mechanistic detail and supplied the specific vocabulary that the subsequent literature has adopted. The paper argued that mitochondria should be understood as the central organelle integrators of the organism's biological state, receiving input from the hormonal, immune, metabolic, and neural systems through receptor-mediated and substrate-mediated mechanisms, and producing output that shapes cellular function, cellular communication, and cellular fate. Under this framing, mitochondria are not merely the ATP factories of the cell but are the computational nodes at which the cell integrates information about its own state and the state of the organism, and at which decisions about gene expression, signaling output, and functional capacity are made. The framework supplied a specific vocabulary — mitochondrial information processing, mitochondrial allostatic load, mitochondrial psychobiology — whose adoption across the subsequent literature has tracked the growing recognition that organelle-level biology is continuous with systems-level physiology and that the boundary between cell-autonomous and systemic processes is not as sharp as the preceding generation of cell biology had assumed.

The relevance of this framework to the Bioenergetic Collapse Model is immediate and structural. The microglial metabolic collapse that Baik documented, the mitophagy failure that Fang demonstrated, the NLRP3 activation that Heneka characterized, and the autophagy-lysosomal failure that Nixon traced — each of these cell-biological events is described in the Picard framework as a local manifestation of a broader organismal state. The same cumulative oxidative stress that drives mitophagy failure in microglia is driving mitochondrial allostatic load in the liver, the adipose tissue, the vascular endothelium, and every other tissue of the aging individual. The same chronic inflammatory milieu that primes NLRP3 activation in AD microglia is shaping systemic cytokine output, hepatic acute-phase protein synthesis, and the metabolic state that the gut, the pancreas, and the hypothalamus integrate into the organism's energy balance. The same metabolic substrate failure that Baik documented in microglia facing Aβ is documented, at different magnitudes and in different contexts, in the skeletal muscle of individuals with insulin resistance, in the hepatocytes of individuals with non-alcoholic fatty liver disease, and in the pancreatic β-cells of individuals with type 2 diabetes. The cell-autonomous framing of the Bioenergetic Collapse Model, in other words, is correct at the level of organelle mechanism but incomplete at the level of biological context: the organelle-level events it describes do not occur in isolation but as local manifestations of a systemic substrate failure whose integration across tissues is what the Picard framework supplies.

This integration is the specific bridge through which the Homeostatic Collapse Model becomes continuous with the metabolic psychiatry framework developed by Sethi, Sarnyai, Picard, and colleagues in their 2026 Nature Mental Health review. That review, which covered the shared mechanistic substrate linking metabolic syndrome, insulin resistance, lipid dysregulation, and chronic inflammation to major depressive disorder, bipolar disorder, and schizophrenia, arrived at a

framework that treats mitochondria as the central organelle at which the bidirectional coupling between systemic metabolic state and brain function is mediated. The allostatic load model of McEwen, the selfish brain theory of Peters, and the mitochondrial allostatic load construct of Picard are presented in that review as complementary accounts of the same underlying process: chronic stress, cumulative metabolic burden, and chronic inflammation converge on mitochondrial function, and mitochondrial function in turn shapes the neural, endocrine, and immune outputs that determine both psychiatric and cognitive phenotypes. The review's therapeutic program — ketogenic metabolic therapy, intermittent fasting, metformin, GLP-1 receptor agonists, pioglitazone, NAD■ precursors — is a program of mitochondrial substrate and quality-control restoration operating at the systemic level, and its mechanistic rationale is the same mechanistic rationale this thesis has developed for mitochondrial quality-control restoration operating at the cell-biological level of individual microglia and neurons in Alzheimer's disease.

The consequence of this integration is that the therapeutic boundary between psychiatric and neurodegenerative disease blurs substantially when both are viewed through the mitochondrial substrate lens. A ketogenic diet that restores neural bioenergetics in schizophrenia is, by the same mechanism, restoring microglial metabolic competence in the direction the Baik findings would predict as protective in Alzheimer's disease. A GLP-1 receptor agonist that improves insulin sensitivity in major depressive disorder is, by the same mechanism, reducing the glucotoxic stress on hypothalamic and hippocampal microglia whose accumulation drives the mitochondrial allostatic load that Picard's framework identifies as the upstream driver of cognitive decline. A NAD■ precursor that enhances sirtuin activity in the metabolic psychiatry framework is, by the same mechanism, enhancing PGC-1α-coordinated mitochondrial biogenesis in the Fang/Bohr framework for Alzheimer's disease. The interventions are the same; the mechanistic targets are the same; the only difference is the disease label that conventional clinical taxonomy places on the outcome. The Bioenergetic Collapse Model, integrated through the Picard framework, treats this taxonomic distinction as a clinical convenience rather than a biological reality, and predicts that therapeutic programs targeting the shared mitochondrial substrate will produce convergent outcomes across the psychiatric-neurodegenerative boundary.

This prediction has specific implications for how the Homeostatic Collapse Model's therapeutic program should be framed. The prior thesis proposed that interventions aimed at restoring the TGF-β/SMAD-maintained homeostatic microglial signature would produce preservation of perineuronal net integrity and PV+ interneuron coverage, with cognitive preservation as the downstream consequence. That proposal was made within a cell-autonomous framing: the intervention was imagined to act specifically on microglia and to produce its effects through cell-autonomous restoration of the homeostatic signature. The Picard integration expands this framing. Interventions that restore mitochondrial substrate at the systemic level — through dietary ketosis, through intermittent fasting, through metformin-mediated AMPK activation, through

GLP-1 agonist-mediated insulin sensitization, through NAD■ precursor-mediated biogenesis enhancement — should produce the same cellular outcomes as cell-autonomous TGF-β pathway restoration, because the cell-autonomous phenotype depends on systemic substrate availability in ways that cannot be separated from the organism's broader bioenergetic state. A microglial cell whose TGF-β/SMAD signaling has collapsed because its mitochondrial population has degraded will not restore its homeostatic signature in response to TGF-β supplementation if its mitochondrial substrate cannot be provided; conversely, a microglial cell whose mitochondrial substrate is restored through systemic intervention may re-enter homeostatic identity without any cell-targeted manipulation of the TGF-β pathway at all. The therapeutic program is therefore substantially broader than the prior thesis envisioned, and it includes the entire metabolic psychiatry pharmacopeia as candidate interventions for Alzheimer's disease through the shared mitochondrial substrate.

A second consequence of the Picard integration is that cognitive resilience, as identified by de Vries and Carulli in the 2024 Alzheimer's & Dementia paper on perineuronal nets and cognitive resilience, becomes interpretable as the end result of preserved mitochondrial allostatic load integration rather than as a cell-autonomous property of microglial cells in specific individuals. Resilient individuals carry symptomatic-AD amyloid and tau burdens without cognitive decline because their systemic mitochondrial substrate has been preserved across the lifespan, because their metabolic allostatic load has remained below the threshold at which mitochondrial quality control fails, and because their microglial cells have therefore retained the bioenergetic competence required to maintain the homeostatic signature under the challenge that amyloid and tau accumulation presents. The determinants of this preservation are not yet fully understood, but the framework predicts that they include dietary patterns that support mitochondrial substrate provision, physical activity patterns that sustain mitochondrial biogenesis, stress patterns that avoid chronic glucocorticoid elevation, metabolic trajectories that preserve insulin sensitivity across adulthood, and the accumulated consequences of these factors on the integrated mitochondrial allostatic load state of the organism. Resilience, on this reading, is not a stochastic feature of individual brain biology but a predictable consequence of the systemic bioenergetic trajectory across the lifespan, and its therapeutic induction through metabolic intervention is at least in principle tractable.

The Picard framework, then, does two things for the Bioenergetic Collapse Model. First, it establishes mitochondria as the cellular substrate on which systemic and cell-autonomous processes converge, and it supplies the vocabulary and mechanistic framing through which the cell-biological mechanisms described in the preceding sections become continuous with the organism's broader bioenergetic state. Second, it bridges the Alzheimer's disease framework this thesis develops to the metabolic psychiatry framework developed in parallel by Sethi, Sarnyai, and colleagues, supplying the shared mechanistic ground on which unified therapeutic programs can be built across what have historically been separate clinical domains. The resulting framework is neither strictly

cell-autonomous nor strictly systemic but is a unified bioenergetic framework in which organelle-level events and organism-level states are coupled through continuous substrate and signaling exchange, and in which therapeutic interventions at any point along this coupling can produce consequences at every other point. The §13 therapeutic implications section will develop this unified framework in detail, but its mechanistic foundation is supplied here, in the Picard framework, as the integration through which the Bioenergetic Collapse Model claims jurisdiction over a continuous brain-body substrate rather than a purely cell-autonomous one.

9. Mitohormesis and the Theoretical Basis for Metabolic Therapy: Ristow

The therapeutic program that this thesis will develop in §13 rests on the claim that specific interventions — ketogenic metabolic therapy, intermittent fasting, NAD■ precursor supplementation, AMPK activators, mitophagy inducers — restore rather than merely bypass the mitochondrial quality-control machinery whose failure generates Alzheimer's disease pathology. This is a non-trivial claim and requires theoretical justification. It would be possible to imagine a framework in which these interventions work purely through substrate substitution — ketones replace glucose as the mitochondrial fuel, for instance, and the improved cellular energetics reflect the availability of a more efficient substrate rather than any adaptive response of the cellular machinery itself. Under such a framework, the interventions would need to be continued indefinitely to sustain their benefit, would not produce durable changes in cellular state, and would offer no particular advantage over direct provision of whatever downstream metabolite the cell requires. The evidence from the aging and longevity literature suggests that this passive-substitution framing is incorrect, and that the metabolic interventions in question work through a fundamentally different mechanism: they stress mitochondria in controlled ways that induce adaptive upregulation of mitochondrial biogenesis, quality control, and antioxidant capacity, producing durable improvements in cellular state that persist beyond the immediate period of intervention and that represent a genuine restoration of homeostatic competence rather than a temporary replacement of its output.

The principle underlying this framing is mitohormesis, and its theoretical development in the aging and longevity literature was most clearly articulated by Michael Ristow and colleagues in their 2007 Cell Metabolism paper, "Glucose restriction extends Caenorhabditis elegans life span by inducing mitochondrial respiration and increasing oxidative stress," by Schulz, Zarse, Voigt, Urban, Birringer, and Ristow. The paper demonstrated a finding that was at the time considered paradoxical and that has since become a foundational principle of aging biology. Caloric restriction, which extends lifespan across species and which had been assumed to work through reduction of the metabolic rate and consequent reduction of oxidative damage, was shown in the Ristow paper to

produce the opposite effect at the cellular level: it increased mitochondrial respiration and increased reactive oxygen species production. The lifespan extension did not occur despite this increase; it occurred because of it. The elevated ROS, produced in a controlled and localized manner by the adaptive response to substrate limitation, triggered an upregulation of antioxidant defenses, a strengthening of mitochondrial quality-control pathways, and an enhancement of cellular stress resistance that persisted well beyond the initial ROS signal. The net effect was that cells exposed to controlled mitochondrial stress became more resistant to subsequent stress, and their mitochondrial populations became more robust and better-maintained than those of cells that had never been stressed. Ristow termed this principle mitohormesis — the homeostatic strengthening of mitochondrial function through controlled exposure to mitochondrial stressors — and argued that it explained not only the lifespan-extending effects of caloric restriction but also the effects of exercise training, intermittent fasting, and a broader class of metabolic interventions that had been observed to produce durable health benefits across species.

The mechanistic details of mitohormesis have been substantially elaborated in the decade and a half since the original Ristow paper, and they bear directly on the therapeutic framing of this thesis. The ROS signal produced by controlled mitochondrial stress activates redox-sensitive transcription factors including NRF2, which upregulates the cellular antioxidant response through induction of glutathione synthesis, superoxide dismutase, catalase, and a larger panel of detoxification enzymes. The signal also activates AMPK, the cellular energy sensor, which in turn phosphorylates and activates the PGC-1α master regulator of mitochondrial biogenesis. PGC-1α drives upregulation of nuclear-encoded mitochondrial genes, enhances mitochondrial DNA replication, and coordinates the production of new mitochondria to replace those degraded by the initial stress. Simultaneously, AMPK activation inhibits mTORC1, relieving the negative regulation of autophagy initiation and permitting enhanced mitophagy-mediated clearance of damaged mitochondria. The combined effect is that a population of mitochondria exposed to controlled stress undergoes accelerated turnover — damaged organelles are cleared, new organelles are produced, and the average quality of the population improves — without the net population size declining and without the cell's energetic output being compromised. The mitohormetic response is therefore a mechanism for renewing the mitochondrial population, and its induction through controlled interventions is the biological basis for the durable health benefits observed across the aging and longevity literatures.

The relevance to the Bioenergetic Collapse Model is direct. The model proposes that Alzheimer's disease develops through the progressive failure of mitochondrial quality control, and that this failure produces both the neuronal PANTHOS phenotype and the microglial homeostatic collapse that the prior thesis described. If the therapeutic task is to restore mitochondrial quality control, then the mitohormetic mechanism supplies the specific cellular pathway through which pharmacological and dietary interventions achieve this restoration. Ketogenic metabolic therapy works through mitohormesis: the metabolic shift to ketone utilization imposes a different substrate demand on

mitochondria, induces β-hydroxybutyrate signaling that activates AMPK and enhances PGC-1α activity, and drives the adaptive upregulation of mitochondrial biogenesis and antioxidant defenses that the Ristow framework characterized as the mitohormetic response. Intermittent fasting works through mitohormesis: the cyclic nutrient limitation triggers the same AMPK activation and PGC-1α induction, and produces the same downstream enhancement of mitochondrial population quality. NAD■ precursor supplementation works through a related mechanism: by restoring the NAD■-dependent sirtuin pathway, it re-enables the deacetylation of PGC-1α that is required for its full transcriptional activity, and therefore supports the biogenesis arm of the mitohormetic response. Urolithin A, the principal mitophagy inducer in the Fang 2019 experimental program, works through direct induction of the mitophagy arm of the response. Metformin, the most widely prescribed drug in the metabolic psychiatry framework, works through inhibition of mitochondrial Complex I at low doses, producing exactly the kind of controlled mitochondrial stress that Ristow characterized as the mitohormetic trigger. The convergence of mechanistically distinct interventions on the mitohormetic pathway is the reason this thesis groups them as a unified therapeutic class rather than as separate drug programs: they are all activating the same adaptive response, and the adaptive response they activate is the one whose failure generates Alzheimer's disease pathology under the Bioenergetic Collapse Model.

The mitohormetic framing has one additional implication that is critical for the therapeutic program developed in §13. Because mitohormesis works through induction of an endogenous adaptive response rather than through passive substrate replacement, its benefits should be durable beyond the immediate period of intervention. Cells that have undergone mitohormetic adaptation exhibit improved mitochondrial quality and enhanced stress resistance for extended periods after the inducing stimulus has been removed, and the benefits accumulate with repeated exposure in a manner analogous to the training adaptations that exercise produces in muscle mitochondria. This predicts that the therapeutic program proposed by this thesis should not require continuous lifelong administration of any single intervention but should operate through cyclic or intermittent exposure to interventions that induce the mitohormetic response, allow it to produce its adaptive effects, and then permit the cell to consolidate the adaptations. The clinical implementation of such a program would differ substantially from conventional chronic pharmacology, and it would align more closely with the lifestyle interventions — periodic fasting, exercise training, dietary modulation — that the metabolic psychiatry literature has increasingly recognized as first-line interventions for metabolic and psychiatric conditions. The unified therapeutic class is therefore not merely pharmacological but includes the entire class of lifestyle interventions that produce mitohormetic responses, and the Bioenergetic Collapse Model predicts these interventions should produce convergent benefits across Alzheimer's disease, the metabolic psychiatric conditions, and the broader spectrum of mitochondrial-substrate-failure disorders of aging.

10. Emergent Convergences

The ten research programs surveyed in the preceding sections have developed in substantial isolation from one another despite their evident mechanistic proximity. The Gouras intraneuronal Aβ framework developed independently of the Butovsky homeostatic microglial signature work. The Nixon autophagy-lysosomal failure program developed independently of the Swerdlow mitochondrial cascade hypothesis. The Fang/Bohr mitophagy failure program developed independently of the Heneka NLRP3 inflammasome program. The Baik microglial metabolic collapse finding developed independently of the Ulland/Colonna TREM2 metabolic fitness work, despite the two programs having published in the same journal within two years of each other and despite their measurements converging on the same PI3K-AKT-mTOR signaling axis. The Picard mitochondrial allostatic load framework developed in the psychobiology and stress literature, largely disconnected from the Alzheimer's disease microglial literature even though its construct of mitochondria as integrators of cumulative biological stress is directly applicable to the aging microglial phenotype. And the Ristow mitohormesis framework developed in the C. elegans longevity literature with only partial penetration into the neurodegenerative disease literature, despite supplying the theoretical justification for the entire class of metabolic interventions that the metabolic psychiatry literature has now adopted as first-line therapeutic strategies. The disciplinary fragmentation of these programs reflects the organizational structure of biomedical research rather than any intrinsic discontinuity in the biology they describe. The task of the Organic Network Synthesis methodology is to identify the emergent convergences that reveal this underlying unity.

Four such convergences organize the integrated model developed in this thesis. The first establishes that the quality-control machinery whose failure has been documented in four different experimental traditions is one machinery rather than four, and that the traditions have been measuring the same substrate failure from different angles. The second and third are the original mechanistic claims of the thesis, each occupying a specific white space in the current literature where no existing paper has made the linkage the claim proposes, and each generating a concrete testable prediction that distinguishes the Bioenergetic Collapse Model from alternative framings of the same data. The fourth closes the loop between this thesis and the prior Homeostatic Collapse synthesis by identifying the specific molecular gate through which the substrate failure this thesis describes becomes the destructive effector output the prior thesis catalogued. The convergences are stated formally below, each with the evidence that supports it, the prediction it generates, and the experimental program that would test it.

Convergence 1: The Autophagy-Lysosomal, Mitophagy, and Mitochondrial Metabolic Failures Are a Single Quality-Control Collapse

The first convergence is that the autophagy-lysosomal failure documented by Gouras and Nixon in neurons, the mitophagy failure documented by Fang and Bohr across neurons and model organisms, the mitochondrial cascade proposed by Swerdlow as the upstream driver of sporadic Alzheimer's disease, the metabolic reprogramming failure documented by Baik in AD microglia, and the NLRP3 inflammasome activation documented by Heneka as the microglial effector gate are not five parallel pathologies. They are five descriptions of a single integrated quality-control system whose failure cascades across organelle compartments, cell types, and signaling pathways, producing outcomes that have been measured by different experimental traditions and interpreted as separate phenomena because the traditions have focused on different endpoints and different cell types. The underlying machinery is shared because the cellular quality-control system that maintains mitochondrial population health, lysosomal degradative capacity, autophagic flux, and metabolic reprogramming competence is a single integrated system whose components are interdependent and whose failure at any one point propagates to all the others through the coupling pathways that connect them.

The specific coupling pathways make this integration mechanistically tight. Lysosomal acidification is required for the degradation of autophagosomes delivered to the lysosome, including mitophagosomes containing damaged mitochondria; when lysosomal acidification fails in the manner Nixon's 2022 PANTHOS paper documents, mitophagy output cannot be completed even when the mitophagy recognition and engulfment steps have proceeded normally, and damaged mitochondria therefore accumulate in the cell even though the PINK1/Parkin machinery has correctly identified them for elimination. The mitochondrial population, under these conditions, degrades not because mitophagy initiation has failed but because mitophagy termination has failed at the lysosomal step. Conversely, when the mitochondrial population degrades through primary PINK1/Parkin failure, the cellular energetic state declines to the point at which lysosomal biogenesis through the TFEB transcription factor cannot be sustained, and lysosomal capacity therefore follows mitochondrial capacity downward through a coupling that operates at the metabolic-signaling level rather than the organelle-biology level. The two failures therefore reinforce one another, and a cell entering either one will rapidly enter the other because the two organelle systems are mutually supporting. This coupling is what justifies treating them as a single system rather than two separate systems, and it is what this first convergence asserts.

The metabolic reprogramming failure Baik documented in AD microglia is the third branch of the same system. The PI3K-AKT-mTOR axis through which Baik showed the metabolic collapse occurring is the same axis that couples nutrient and receptor input to lysosomal biogenesis through TFEB and to mitochondrial biogenesis through the PGC-1α pathway. When this axis fails, the cell loses its capacity both to reprogram its metabolism in response to changing demands and to sustain the organelle populations whose renewal the reprogramming requires. The metabolic, lysosomal,

and mitochondrial failures are therefore three manifestations of the same upstream signaling collapse, and the Baik finding is the experimental substantiation that this signaling collapse occurs in microglia facing pathological substrate. The NLRP3 inflammasome activation Heneka characterized is the fourth branch: it is the immediate consequence of the mitochondrial membrane integrity failure that follows from mitophagy collapse, and its downstream effects shape the inflammatory milieu that further degrades the signaling environment and accelerates the upstream failures. The system is therefore not merely interconnected but is self-amplifying: failure at any node accelerates failure at every other node, and the disease trajectory this generates is the trajectory of a single integrated collapse rather than a sum of separate collapses.

BIN1 is the first LOAD genetic anchor that directly populates a named node of Convergence 1. Rubinsztein's 2025 demonstration that BIN1 coordinates autophagosome closure via ESCRT-III/DNM2 places the #2 GWAS risk locus for sporadic AD squarely within the autophagosome-formation step of the quality-control pipeline this convergence describes. BIN1 provides the sporadic genetic architecture that complements the familial architecture provided by presenilin: where presenilin mutations attack lysosomal acidification at the degradation end of the pipeline, BIN1 risk variants attack autophagosome closure at the formation end, and both produce the same downstream outcome — accumulation of undegraded cargo that drives PANTHOS in neurons and quality-control collapse in microglia. That the autophagy-lysosomal pipeline is under genetic risk at multiple points along its length — familial at the terminal step, sporadic at the formation step — strengthens the convergence's central claim that the pipeline is a single integrated system rather than a collection of independent components. A collection of independent components would not be expected to show genetic vulnerability at multiple mechanistically distinct nodes producing the same net phenotype; an integrated system would, because dysfunction at any point in a serial pipeline produces the same terminal failure regardless of where in the series the dysfunction originates.

The consequence of asserting this convergence is that therapeutic programs aimed at any single node of the system should be expected to produce only partial rescue regardless of the mechanistic precision with which they target their chosen node, because the upstream failures at the other nodes will continue to propagate until they re-collapse the rescued node through the coupling pathways. This explains the pattern of modest and non-durable benefits observed across the clinical literature for interventions aimed at specific components: complement inhibitors, NLRP3 inhibitors, TREM2 agonists, lysosomal acidification enhancers, and mitochondrial biogenesis stimulators have each produced preclinical signals and, in some cases, modest clinical effects, but none has produced the magnitude of benefit that would be predicted if the targeted node were the sole upstream driver of the disease. The Bioenergetic Collapse Model predicts this pattern directly and predicts further that combination interventions addressing multiple nodes simultaneously should produce superadditive benefit because they interrupt the amplification loops that single-node interventions leave intact.

Convergence 2: TGF-β/SMAD Signaling Maintains Microglial Mitochondrial Competence — ORIGINAL CLAIM A

The second convergence is the first of two original mechanistic claims this thesis advances as contributions to the literature rather than as syntheses of existing findings. It occupies a specific white space in the current literature: the connection between the TGF-β/SMAD-maintained homeostatic microglial signature characterized by Butovsky and the mitochondrial quality-control machinery characterized by Youle, Fang, and Ulland has not been made experimentally in any published microglial study, and the integration proposed here is therefore a hypothesis offered for experimental test rather than a finding supported by existing measurement.

The claim is that TGF-β/SMAD signaling in microglia maintains mitochondrial competence — specifically, mitochondrial biogenesis capacity, mitophagy capacity, and the oxidative phosphorylation output that the homeostatic transcriptional program requires for its maintenance — such that the age-dependent collapse of this signaling is simultaneously a transcriptional identity collapse and a bioenergetic substrate collapse. These are not two separable events but one event viewed from two angles. The transcriptional collapse that Butovsky's signature loss captures and the bioenergetic collapse that Baik's metabolic flux measurements capture are the same collapse, and the separation between them in the existing literature reflects the separation between the transcriptomic and metabolomic traditions that have measured the post-homeostatic microglial phenotype, not any separation in the biology itself.

The evidence supporting this claim is convergent rather than direct. Butovsky's program established that TGF-β/SMAD signaling is necessary for maintenance of the homeostatic microglial transcriptional signature including P2ry12, Tmem119, Sall1, Hexb, and the broader panel of markers whose coordinated expression defines adult parenchymal microglia. Ulland and Colonna's 2017 Cell paper established that TREM2-DAP12-SYK signaling through the PI3K-AKT-mTOR axis maintains microglial oxidative phosphorylation fitness in Alzheimer's disease models. Baik's 2019 Cell Metabolism paper established that microglial metabolic reprogramming in response to Aβ challenge collapses through PI3K-AKT-mTOR failure and produces the hypometabolic phenotype that characterizes post-homeostatic cells. Von Bernhardi's work established that TGF-β/SMAD signaling is progressively dysregulated under conditions of chronic oxidative stress in the aging brain. These four lines of evidence converge on a single mechanistic picture: TGF-β/SMAD signaling maintains the homeostatic transcriptional program; the transcriptional program requires oxidative phosphorylation output to sustain its energetic cost; oxidative phosphorylation output depends on PI3K-AKT-mTOR signaling that couples receptor input to metabolic state; the PI3K-AKT-mTOR axis is the same axis that TREM2 signals through and that Baik showed failing in AD microglia; and the failure of this axis under chronic oxidative stress is the specific mechanism through which von Bernhardi's TGF-β/SMAD dysregulation becomes the metabolic collapse Baik documented. The picture is coherent and is supported by convergent findings from four independent

experimental programs, but it has not been tested directly by any single experiment. The claim this thesis advances is that such a test would confirm the integration.

The adjacent literature supports the plausibility of the claim. TGF-β signaling has been documented in skeletal muscle and fibroblast tissue to regulate PGC-1α activity and mitochondrial biogenesis, typically in a suppressive direction in those tissues where TGF-β drives fibrotic rather than homeostatic phenotypes. The microglial context is expected to differ because TGF-β in microglia drives homeostatic maintenance rather than fibrotic transformation, and the expected directionality of its effect on mitochondrial biogenesis is therefore positive rather than negative. But the fact that TGF-β signaling is coupled to mitochondrial biogenesis in other cell types provides the cell-biological precedent for the claim that it is coupled to mitochondrial biogenesis in microglia as well, and the specific directionality of the coupling in microglia is the question that experimental test would address.

The testable prediction that follows from this convergence is specific: conditional deletion of TGF-β receptor signaling in microglia, using CX3CR1-Cre or P2ry12-Cre driver lines to achieve microglia-specific deletion, should produce not only the transcriptional homeostatic collapse Butovsky's framework predicts but also a measurable collapse of mitochondrial membrane potential, mitochondrial biogenesis gene expression, and mitophagy flux in the affected cells. Conversely, restoration of TGF-β receptor signaling in aged microglia — through pharmacological TGF-β supplementation, through SMAD7 inhibition, or through oxidative stress reduction targeted to the microglial compartment — should produce simultaneous recovery of the homeostatic transcriptional signature and of mitochondrial functional measurements. If these two outcomes dissociate — if transcriptional rescue occurs without mitochondrial rescue, or vice versa — the convergence will be falsified and the two events will need to be treated as separable in ways this thesis does not anticipate. If they co-occur, the convergence will be confirmed and the therapeutic program it implies will be supported. Either outcome is experimentally tractable with existing tools.

Convergence 3: Mitophagy Competence Sorts Post-Homeostatic Microglia Into DAM, LDAM, and Dystrophic Trajectories — ORIGINAL CLAIM B

The third convergence is the second of this thesis's original mechanistic claims and is the most specific of the four. It addresses a question that the prior thesis raised but did not answer: what determines whether a post-homeostatic microglial cell enters the DAM trajectory, the LDAM trajectory, or the dystrophic trajectory? The prior thesis treated these as alternative downstream fates of cells that had undergone the same upstream collapse event, and proposed that the selection among them depended on context-dependent variables including lipid cargo, TREM2 functionality, iron burden, and residual metabolic capacity. These variables were listed without specification of the mechanism through which they produced the sorting. This convergence supplies that mechanism.

The claim is that mitophagy competence — the specific cellular capacity to recognize damaged mitochondria, mark them through the PINK1/Parkin pathway, deliver them to autolysosomes, and degrade them through acidified lysosomal hydrolases — is the variable that sorts post-homeostatic microglia into their downstream trajectories. The sorting operates through the following logic. A post-homeostatic microglial cell that retains substantial mitophagy competence can turn over its damaged mitochondrial population rapidly enough to sustain the metabolic demands of the TREM2-gated salvage program. Its mitochondrial damage accumulates slowly enough that the NLRP3 inflammasome is not chronically activated by mitochondrial damage-associated molecular patterns, and its PI3K-AKT-mTOR signaling axis retains enough functional output to drive the productive phagocytic and lipid-processing programs that the DAM transcriptional state encodes. This cell enters the DAM Stage 1 to Stage 2 trajectory and executes a substantially protective response to the Aβ challenge, even though it has lost its homeostatic signature in the process. The DAM phenotype, in this framing, is the post-homeostatic trajectory available to cells whose mitophagy competence remains above the threshold required for productive salvage.

A post-homeostatic cell with partially impaired mitophagy cannot turn over its damaged mitochondrial population quickly enough to meet the full demands of productive salvage, but retains enough mitochondrial function to continue operating under reduced output. Such a cell can still internalize lipid cargo through its TREM2 and other lipid-recognition receptors, but cannot fully oxidize this cargo through β-oxidation because its mitochondrial fatty acid oxidation capacity has been impaired by the degraded population. The unoxidized lipid accumulates in cytoplasmic droplets, producing the LDAM phenotype that Marschallinger documented. This cell is not dead, is not inactive, and continues to produce cytokines and other inflammatory outputs, but its metabolic gridlock prevents it from executing the productive clearance program that DAM cells with better mitophagy can achieve. The LDAM phenotype, in this framing, is the post-homeostatic trajectory available to cells whose mitophagy competence has declined below the threshold required for productive salvage but above the threshold required for cellular viability.

A post-homeostatic cell with severely impaired mitophagy cannot maintain its mitochondrial population at a functional level regardless of substrate availability. Its damaged mitochondria accumulate to the point at which cellular ROS output is chronically elevated, at which mitochondrial DAMP release is continuous, at which NLRP3 inflammasome activation is sustained, and at which the cumulative damage to non-mitochondrial cellular components produces the morphological deramification, process fragmentation, and cytoplasmic beading that Streit characterized as dystrophy. The dystrophic phenotype, in this framing, is the post-homeostatic trajectory available to cells whose mitophagy competence has collapsed entirely, and its terminal character reflects the fact that cells in this state cannot recover functional capacity without external intervention.

The sorting variable proposed above requires a refinement that the Rubinsztein proteasome-tau feedback loop supplies. The original formulation identifies mitophagy competence as the sole sorting variable, but the proteasome and autophagy are complementary protein degradation pathways, and the cell's total quality-control capacity is the sum of both. Rubinsztein's work demonstrates that tau — particularly oligomeric and fibrillar tau — inhibits proteasomal function, and that proteasomal function declines independently with age, producing a positive feedback loop in which tau accumulation drives proteasomal failure that permits further tau accumulation. When the proteasome is inhibited, the cell relies more heavily on autophagy for protein clearance, increasing the load on the autophagy-lysosomal system. If that system is already compromised — through BIN1-mediated autophagosome closure failure, through presenilin-mediated lysosomal acidification failure, or through age-dependent mitophagy decline — the compensatory load exceeds the system's capacity, and the cell enters a state of total proteostatic collapse in which neither the proteasome nor autophagy can maintain clearance rates sufficient to prevent cargo accumulation. The sorting variable should therefore be refined from "mitophagy competence" to "total quality-control competence," of which mitophagy is the dominant component but proteasomal capacity is a significant modifier. Cells with high mitophagy and intact proteasome enter DAM. Cells with reduced mitophagy but intact proteasome may still compensate through proteasomal clearance and avoid the worst trajectories. Cells with impaired mitophagy and tau-inhibited proteasome have no compensatory pathway available and enter dystrophy. This refinement explains the Streit observation that dystrophic microglia are spatially associated with pre-tangle tau pathology: the tau itself is driving the proteasomal arm of the quality-control collapse that produces the dystrophic phenotype. Microglia in tau-rich microenvironments phagocytose tau from dying neurons, the phagocytosed tau inhibits their proteasome, the proteasomal failure adds to their existing autophagy-lysosomal burden, and the combined proteostatic collapse — proteasome, autophagy, mitochondrial quality control — produces the irreversible dystrophic phenotype that Streit characterized.

The DAM/LDAM/dystrophic trifurcation, then, is not evidence of three distinct pathogenic programs. It is evidence of a single upstream failure — mitophagy competence collapse — progressing through graded severity, with the selection among downstream trajectories determined by where in the graded continuum a given cell sits when the pathological challenge arrives. Cells near the top of the range enter DAM; cells in the middle enter LDAM; cells near the bottom enter dystrophy. The apparent diversity of the post-homeostatic phenotype is an artifact of sampling across a continuous variable whose distribution in the aged brain produces the observed trifurcation when snap-shotted at any given time point.

This convergence generates several testable predictions. The most direct is that mtKeima or mito-QC live imaging of AD microglia, paired with single-cell RNA sequencing to establish the transcriptional trajectory assignment of each imaged cell, should reveal a graded distribution of

mitophagy flux that tracks with the trajectory assignment: DAM cells should exhibit the highest mitophagy output, LDAM cells should exhibit intermediate output, and dystrophic cells should exhibit the lowest output. A second prediction is that microglia-specific conditional deletion of PINK1 or Parkin should produce a population shift toward LDAM and dystrophic trajectories at the expense of DAM in AD model backgrounds, because the genetic manipulation prevents the cells from executing the mitophagy-dependent trajectory selection that preserves DAM as a functional option. A third prediction is that pharmacological mitophagy restoration through urolithin A or NAD■ precursor supplementation should produce the opposite population shift, moving cells up the trajectory continuum toward DAM and away from dystrophy, and that this shift should track with preservation of perineuronal net integrity and PV+ interneuron coverage. If any of these predictions fails, the convergence will require revision; if they are confirmed, the Bioenergetic Collapse Model will have supplied the mechanistic specification that the prior thesis's trifurcation account lacked.

Convergence 4: NLRP3 Closes the Mechanistic Loop Between the Bioenergetic and Homeostatic Models

The fourth convergence returns the Bioenergetic Collapse Model to the Homeostatic Collapse Model by identifying the specific molecular gate through which the substrate failure described in this thesis produces the destructive effector output catalogued in the prior one. The gate is the NLRP3 inflammasome, and its activation by mitochondrial damage-associated molecular patterns is the mechanism through which mitophagy collapse produces the inflammatory amplification that drives complement deposition, matrix metalloproteinase release, cathepsin secretion, and the broader destructive output that the prior thesis traced to failed salvage at the perineuronal net.

The integration is direct: mitophagy failure produces mitochondrial damage-associated molecular pattern release, DAMP release activates NLRP3, NLRP3 activation drives IL-1β and IL-18 release, the inflammatory milieu produced by these cytokines amplifies the effector output of the post-homeostatic microglial population, and the amplified effector output produces the perineuronal net degradation, synaptic loss, and circuit dysfunction that the prior thesis identified as the proximate cause of cognitive decline. A second downstream arc of the same mitochondrial DAMP release is identified by the Weaver innate-immunity framework: cardiolipin and oxidized mitochondrial phospholipids, released when damaged mitochondria are not cleared, are themselves direct triggers of the antimicrobial-peptide deployment program in which Aβ functions as an innate-immune effector. The mitochondrial DAMP signal therefore does not only feed forward into NLRP3-gated cytokine amplification; it also licenses the AMP-class deployment of Aβ itself, such that mitophagy failure simultaneously elevates the inflammatory milieu and the proteinopathic burden through the same upstream substrate, and the necrotic release of GM1-Aβ complexes from neurons killed by the misdirected AMP attack closes a second self-amplifying loop that propagates independently of the NLRP3 arc. This double-loop architecture supplies part of the explanation for why the Bioenergetic Collapse is not reversible by inflammasome inhibition alone—the

proteinopathic limb runs in parallel, shares the same upstream substrate, and requires restoration of mitochondrial quality control to be addressed at the level the model identifies as causal. The Bioenergetic Collapse Model therefore generates the Homeostatic Collapse Model's effector phenotypes as downstream consequences of its upstream substrate failure, and the two models are not competing frameworks but sequential accounts of the same disease process at different levels of mechanistic resolution. The Homeostatic Collapse Model describes what happens once microglia have lost their homeostatic identity and are producing destructive outputs; the Bioenergetic Collapse Model describes how and why they lose the homeostatic identity in the first place and what gates their subsequent destructive outputs. The two models are mechanistically nested, not theoretically competing, and their integration is the central contribution of this synthesis.

The practical consequence of this integration is that the therapeutic readouts of the prior thesis remain valid for the therapeutic program of this one. The prior thesis identified perineuronal net integrity and PV+ interneuron coverage as the molecular readouts by which homeostatic restoration should be measured. The Bioenergetic Collapse Model preserves this readout: interventions that restore mitochondrial quality control should, through the mechanism traced in this convergence, reduce NLRP3 activation, reduce downstream effector output, preserve perineuronal net integrity, and preserve PV+ interneuron coverage. Any intervention that does not produce these outcomes is, by the model's logic, not actually addressing the upstream substrate failure, regardless of what biomarker changes it might produce at other levels. The PNN-PV+ axis is therefore the same experimental readout for both theses, and its measurement in any prospective trial of mitophagy-restoring, TGF-β-stabilizing, or metabolic-psychiatric interventions should be the primary outcome by which the Bioenergetic Collapse Model is tested in human disease.

11. The Bioenergetic Collapse Model

The integrated model may now be stated explicitly. Alzheimer's disease is the clinical manifestation of a progressive, age-dependent failure of the integrated cellular quality-control machinery that maintains mitochondrial population health, autophagic-lysosomal degradative capacity, and metabolic reprogramming competence across the cell types of the central nervous system. This failure is not a single event occurring at a single point in time, nor is it confined to a single cell type. It is a cumulative process whose upstream drivers include the lifelong accumulation of mitochondrial DNA damage under oxidative stress, the age-dependent decline of NAD■-dependent sirtuin signaling, the progressive dysregulation of TGF-β/SMAD signaling under chronic oxidative load, BIN1-mediated autophagosome closure failure operating through ESCRT-III/DNM2 dysfunction at the formation end of the autophagy pipeline, and the cumulative allostatic burden that chronic metabolic, inflammatory, and psychosocial stress impose on the integrated mitochondrial substrate of the organism. The model's genetic grounding now spans both familial and sporadic architecture: presenilin mutations impair the terminal degradation step of the autophagy-lysosomal pipeline, while BIN1 risk variants — the #2 GWAS locus for sporadic LOAD — impair the upstream formation step, and the two genetic anchors bracket the pipeline whose integrated failure the model identifies as the upstream event. Its downstream manifestations are cell-type-specific because different cell types have different vulnerabilities and different downstream options when their quality-control machinery fails, but the upstream event is shared across cell types and the disease phenotype emerges from the convergence of these cell-type-specific failure modes on the neural circuits whose function they collectively determine.

In neurons, and particularly in the hippocampal, entorhinal, and cortical pyramidal populations whose mitochondrial demand is highest and whose vulnerability to quality-control failure is therefore greatest, the Bioenergetic Collapse Model asserts that autophagy-lysosomal failure produces the PANTHOS phenotype that Lee, Yang, and Nixon documented in 2022 and that Gouras and colleagues had traced phenomenologically from 2000 onward. Affected neurons accumulate intraneuronal Aβ42 within multivesicular bodies and late endosomes because the lysosomal acidification required to degrade autophagic cargo has failed. The accumulation produces autolysosome expansion, organelle rupture, and ultimately the flower-like cellular morphology that Lee and colleagues characterized as the terminal phenotype of PANTHOS-affected neurons. These cells die, and their extruded autophagic contents become the dense-core plaques that the amyloid cascade has misidentified as extracellular aggregates of secreted Aβ. The number of neurons exhibiting PANTHOS progression, and the distribution of these cells across brain regions, determines the plaque burden that imaging and histology have used as the defining biomarker of Alzheimer's disease. Plaque burden is therefore a measurement of cumulative neuronal quality-control failure, not a measurement of extracellular Aβ accumulation, and the distinction has fundamental consequences for how the disease should be understood therapeutically. The genetic

architecture of this quality-control failure is now specified at both ends of the autophagy-lysosomal pipeline: BIN1 risk variants impair autophagosome closure at the formation end, complementing presenilin's impairment of lysosomal acidification at the degradation end, such that LOAD genetics and familial genetics both converge on the same pipeline. The convergence of the #1 familial genetic driver and the #2 sporadic genetic risk factor on a single quality-control system is among the strongest available evidence that this system is the mechanistic substrate of the disease.

In microglia, the same upstream quality-control failure produces a different phenotypic manifestation because the downstream options available to microglia differ from those available to post-mitotic neurons. Microglia are self-renewing through local proliferation, express TREM2 and other lipid-sensing receptors that permit engagement with pathological substrate, and maintain their specialized identity through continuous TGF-β/SMAD-driven transcriptional input from the neural niche. When their mitochondrial quality control degrades — through the same mechanisms that drive the neuronal failure, but operating on the same cumulative timescale — their transcriptional identity collapses simultaneously with their metabolic competence, because the identity and the metabolism are two faces of the same TGF-β/SMAD-dependent program whose maintenance requires mitochondrial substrate competence. The cells lose the homeostatic signature Butovsky characterized and enter the post-homeostatic state the prior thesis described. Which specific downstream trajectory they enter — DAM, LDAM, or dystrophy — is determined by the residual total quality-control competence of the cell — principally mitophagy capacity but significantly modified by proteasomal capacity — at the moment of pathological challenge, in the manner Convergence 3 of the preceding section articulated. The trifurcation is not a stochastic feature of post-homeostatic microglial biology but is a direct consequence of graded quality-control collapse across a continuous variable.

The destructive effector outputs that post-homeostatic microglia release — complement components, matrix metalloproteinases, cathepsins, pro-inflammatory cytokines — are gated by the NLRP3 inflammasome, whose activation in these cells is driven by mitochondrial damage-associated molecular pattern release from the degraded mitochondrial population. The NLRP3 gate is therefore the mechanistic link between the upstream mitophagy collapse and the downstream effector output, and its activation produces the perineuronal net degradation, the synaptic pruning, and the inhibitory interneuron destabilization that the prior thesis identified as the proximate cause of cognitive decline. The Stevens complement pathway, the Crapser matrix metalloproteinase pathway, the Shatz C4d/LilrB2 pathway, and the broader inflammatory effector output of post-homeostatic microglia are all amplified by and dependent upon the mitochondrially-gated inflammasome activation that Heneka's program characterized. The PNN-PV+ interneuron axis is the specific circuit-level substrate on which these effector outputs converge, and its degradation is the final common pathway through which the cell-biological events the Bioenergetic Collapse Model describes produce the cognitive phenotype of Alzheimer's disease.

The Picard framework adds to this integrated model the recognition that the cell-biological events occurring in individual neurons and microglia are not isolated from the systemic state of the organism but are local manifestations of a broader mitochondrial allostatic load that integrates across tissues and across the lifespan. The same mitochondrial quality-control machinery whose failure drives Alzheimer's disease pathology in the brain is under continuous stress from the metabolic, inflammatory, endocrine, and psychosocial inputs that the Picard framework identifies as the determinants of mitochondrial allostatic load. Individuals whose lifestyle trajectories have produced low allostatic load — through dietary patterns that support mitochondrial substrate provision, through physical activity patterns that sustain mitochondrial biogenesis, through stress management that avoids chronic glucocorticoid elevation, through metabolic maintenance that preserves insulin sensitivity — enter late life with mitochondrial quality-control capacity that can withstand the challenge of amyloid and tau accumulation without progressing to the cellular collapse that generates the disease phenotype. Individuals whose lifestyle trajectories have produced high allostatic load arrive at late life with degraded mitochondrial quality-control capacity, and the same amyloid and tau burden that leaves the low-load individual unimpaired drives the high-load individual into the cellular collapse that produces clinical dementia. The cognitive resilience phenotype identified by de Vries and Carulli is, on this reading, the clinical manifestation of preserved mitochondrial allostatic load integration across the lifespan, and its prevalence in the population tracks not the stochastic distribution of amyloid-resistant cellular biology but the distribution of lifelong bioenergetic trajectories that have preserved the quality-control machinery the model identifies as critical.

The Bioenergetic Collapse Model is therefore neither strictly cell-autonomous nor strictly systemic. It is a unified bioenergetic framework in which organelle-level mitochondrial quality control is continuously coupled to the organism's systemic metabolic and allostatic state, and in which the failure of organelle-level quality control is both a consequence of accumulated systemic burden and a contributor to the cellular and circuit-level pathology that defines the disease. The therapeutic program the model implies is correspondingly broad. It includes cell-biological interventions that directly address mitochondrial quality control — mitophagy inducers such as urolithin A, NAD■ precursors such as nicotinamide riboside and nicotinamide mononucleotide, PGC-1α activators — and it includes systemic interventions that address the organism-level bioenergetic state on which the cellular machinery depends — ketogenic metabolic therapy, intermittent fasting, metformin, GLP-1 receptor agonists, physical exercise, stress reduction, and the broader class of lifestyle and pharmacological interventions that the metabolic psychiatry framework has identified as first-line therapies for psychiatric and metabolic disease. These interventions are not competing therapeutic programs but complementary components of a unified bioenergetic restoration strategy whose mechanistic rationale is the same at every level: the restoration of mitochondrial quality control through the induction of adaptive mitohormetic responses in the cellular substrate of the brain.

The model generates several specific interpretive reframings of existing literature that are worth making explicit. First, the modest benefit of anti-amyloid therapies in clinical trials is not an indictment of the amyloid cascade as a proximate mechanism but a consequence of targeting a downstream signature while the upstream substrate failure continues. Removing extracellular Aβ does not restore lysosomal acidification in PANTHOS-affected neurons, does not restore mitophagy competence in post-homeostatic microglia, and does not silence NLRP3 activation in the cells whose mitochondrial quality control has already failed. The cognitive benefit of anti-amyloid therapy is therefore predicted to be modest and non-durable, and its magnitude should scale with the fraction of the disease trajectory that proceeds through downstream rather than upstream mechanisms, which is expected to increase at later disease stages. Second, the failure of anti-inflammatory therapies to modify Alzheimer's disease progression is not an indictment of the neuroinflammation hypothesis but a consequence of targeting the NLRP3-driven amplification arm without addressing the upstream mitochondrial damage that drives its activation. Silencing NLRP3 through direct inhibition removes the amplification step but leaves the mitochondrial damage signal intact, and the inflammation re-emerges through alternative pathways or returns once the inhibition is withdrawn. Durable rescue requires addressing the upstream substrate, not merely blocking the downstream amplifier. Third, the disappointing clinical trajectory of TREM2 agonist therapy is not an indictment of TREM2 as a target but a consequence of engaging a receptor whose downstream signaling depends on metabolic competence that the target cells no longer possess. Boosting TREM2 signaling in cells whose PI3K-AKT-mTOR axis has failed and whose mitochondrial population has degraded cannot produce the productive phagocytic response that TREM2 engagement is designed to trigger, and the receptor-level intervention will therefore produce biomarker changes without corresponding functional benefit. Effective TREM2 engagement requires that the receiving cells retain the metabolic substrate that TREM2 signaling is designed to drive, which in turn requires that mitochondrial quality control be preserved, which in turn requires the upstream interventions the Bioenergetic Collapse Model identifies.

The fourth interpretive reframing concerns cognitive resilience. The de Vries and Carulli 2024 paper demonstrated that resilient individuals preserve perineuronal net integrity and PV+ interneuron coverage despite carrying amyloid and tau burdens at symptomatic-disease levels, and the prior thesis identified this preservation as the molecular substrate of resilience. The Bioenergetic Collapse Model adds that the preserved PNN-PV+ axis in resilient individuals reflects preserved microglial homeostatic competence, which in turn reflects preserved mitochondrial quality control in the microglial population, which in turn reflects a lifelong bioenergetic trajectory that has maintained the quality-control machinery the model identifies as critical. The resilience phenotype is therefore not mysterious or stochastic but is the expected outcome of a specific set of lifelong determinants, and those determinants are the same determinants that the metabolic psychiatry literature has identified as the targets of intervention for the broader class of mitochondrial-substrate disorders. A therapeutic program aimed at producing the resilience phenotype in the symptomatic-disease

population would operate through the same interventions the metabolic psychiatry framework has adopted for depression, bipolar disorder, and schizophrenia, and the expected outcome is the same: restored mitochondrial substrate, restored cellular quality control, restored homeostatic microglial identity, preserved perineuronal net integrity, and preserved cognitive function regardless of the amyloid and tau burden the individual carries.

The model makes one final claim that is specific to the trilogy structure of which this thesis is the third installment. The three Collapse theses — Convergent Synaptic Collapse, Homeostatic Microglial Collapse, and the present Bioenergetic Collapse — describe the same disease process at three levels of resolution. The synaptic thesis describes the circuit-level outcome: the loss of inhibitory interneuron function and the consequent excitation-inhibition imbalance that drives cognitive dysfunction. The microglial thesis describes the cellular-identity-level mechanism: the collapse of the homeostatic transcriptional signature that makes microglia capable of protective function, and the resulting sorting of post-homeostatic cells into DAM, LDAM, and dystrophic trajectories whose effector outputs generate the circuit-level damage. The bioenergetic thesis describes the substrate-level generator: the mitochondrial quality-control machinery whose failure produces the cellular collapse through the mechanisms articulated in the preceding sections. The three theses are not competing accounts of the disease, nor are they alternative framings of the same phenomenon. They are one account at three levels of resolution, and the therapeutic task they collectively identify is neither synaptic rescue, nor microglial silencing, nor neuronal replacement, but bioenergetic restoration of the machinery whose failure generates the phenotype at every level. The measurement of therapeutic success remains the perineuronal net and the parvalbumin-positive interneuron, because the circuit-level endpoint is the most tractable molecular readout available for assessing whether the integrated process has been restored. The mechanism of therapeutic action is the mitohormetic induction of adaptive mitochondrial quality-control restoration through the interventions the §13 section will develop. The patient population for whom such intervention is predicted to be most effective is the early-symptomatic and at-risk population in whom the upstream substrate failure has begun but has not yet produced irreversible cellular damage, and the combination of mitophagy induction, TGF-β pathway stabilization, metabolic substrate provision, and lifestyle-based allostatic load reduction constitutes the unified therapeutic class whose components the model predicts should produce superadditive benefit when combined.

12. Experimental Predictions

The Bioenergetic Collapse Model generates a set of specific, testable predictions whose experimental verification or falsification would determine whether the integrated synthesis developed in this thesis is correct in its central mechanistic claims. These predictions are selected on three criteria: they are technically tractable with existing experimental tools, they distinguish the model from alternative framings of the same data, and they address the load-bearing claims of the model rather than peripheral details whose outcome would not change the framework substantially. Six such predictions are articulated below, each with its experimental design, expected outcome under the model, and interpretation under the alternative outcomes that would revise or falsify the model.

Prediction 1: Microglia-specific conditional deletion of PINK1 or Parkin will recapitulate the age-dependent homeostatic collapse phenotype, including loss of P2ry12 and Tmem119 expression, onset of LDAM and dystrophic morphological features, and accelerated disease progression in AD model backgrounds. This prediction tests the central claim of Convergence 3: that total quality-control competence (of which mitophagy is the dominant component) is the variable that sorts post-homeostatic microglia into their downstream trajectories. The experimental design uses existing floxed PINK1 or Parkin mouse lines crossed with CX3CR1-CreER or P2ry12-CreER driver lines to achieve inducible microglia-specific deletion, followed by tamoxifen administration at defined adult time points and subsequent characterization of the microglial phenotype through single-cell RNA sequencing, morphological analysis, lipid droplet staining, and mitochondrial membrane potential measurement. Under the Bioenergetic Collapse Model, the deletion should produce a phenotype that resembles accelerated aging of the microglial compartment, with progressive loss of homeostatic markers, emergence of LDAM features, and eventual dystrophic morphology. Crossing this line into a 5xFAD or APP/PS1 background should produce accelerated disease pathology relative to AD-only controls, with increased plaque burden, greater perineuronal net degradation, and earlier cognitive decline. An alternative outcome in which microglia-specific mitophagy loss produces no microglial phenotype or no AD acceleration would falsify the central Convergence 3 claim and would require the model to locate the sorting variable elsewhere.

Prediction 2: Live imaging of mitophagy flux in AD microglia, paired with single-cell RNA sequencing of the imaged cells, will reveal a graded distribution of mitophagy output that tracks with DAM, LDAM, and dystrophic trajectory assignment. This prediction is the most direct test of the sorting mechanism proposed in Convergence 3. The experimental design uses mtKeima or mito-QC reporter systems expressed under microglia-specific drivers in AD model mice, followed by two-photon intravital imaging or ex vivo imaging of acute brain slices to quantify mitophagy flux in individual microglia. The imaged cells are then captured for single-cell RNA

sequencing using a strategy that preserves the mapping between imaging identity and transcriptional identity — such as photoconversion of imaged cells followed by FACS isolation or spatial transcriptomics with registered imaging coordinates. The resulting paired dataset is analyzed for correlation between mitophagy flux and transcriptional trajectory assignment. Under the Bioenergetic Collapse Model, cells assigned to the DAM trajectory should exhibit the highest mitophagy flux, cells assigned to LDAM should exhibit intermediate flux, and cells assigned to dystrophic trajectories should exhibit the lowest flux. The distribution should be continuous rather than bimodal, reflecting the graded nature of the sorting variable. An alternative outcome in which mitophagy flux does not correlate with trajectory assignment, or in which the correlation runs in the opposite direction from the prediction, would require fundamental revision of the sorting mechanism.

Prediction 3: Restoration of TGF-β receptor signaling in aged microglia will produce simultaneous recovery of the homeostatic transcriptional signature and of mitochondrial functional measurements, and these two outcomes will not dissociate under any tested condition. This prediction is the central test of Convergence 2 and the most specific of the model's original claims. The experimental design uses aged mouse microglia — either from aged wild-type mice or from AD model mice at advanced disease stages — subjected to TGF-β pathway restoration through multiple independent strategies: recombinant TGF-β supplementation in tissue culture, pharmacological SMAD7 inhibition, genetic restoration of TGF-β receptor expression in models where signaling has been impaired, or niche-reconstitution approaches that restore the broader TGF-β-producing microenvironment. Following each intervention, the cells are characterized for both transcriptional recovery of the homeostatic signature (measured through P2ry12, Tmem119, Sall1, Hexb, and broader Butovsky signature genes) and mitochondrial functional recovery (measured through membrane potential, biogenesis gene expression, mitophagy flux, and oxidative phosphorylation output). Under the Bioenergetic Collapse Model, these two recovery outcomes should co-occur in every intervention that succeeds at either one, because the model asserts that they are two faces of a single underlying event. An alternative outcome in which one recovers without the other — transcriptional rescue without mitochondrial rescue, or vice versa — would directly falsify Convergence 2 and would require the model to treat these as separable events whose coupling is not as tight as the model asserts.

Prediction 4: Mitophagy-inducing interventions — urolithin A, NAD■ precursors, nicotinamide riboside, nicotinamide mononucleotide — administered to AD model mice will preserve perineuronal net integrity and parvalbumin-positive interneuron coverage at the hippocampal and cortical level, and this preservation will correlate with cognitive function independently of effects on plaque burden or tau pathology. This prediction tests the bridge between the Bioenergetic Collapse Model and the prior theses by asking whether mitophagy restoration produces the specific circuit-level readout that the prior thesis identified as the molecular

substrate of cognitive preservation. The experimental design uses 5xFAD, APP/PS1, or 3xTg-AD mice treated with mitophagy-inducing compounds starting at defined disease stages, followed by longitudinal cognitive testing and terminal histological assessment of perineuronal net integrity using Wisteria floribunda agglutinin staining, aggrecan immunohistochemistry, and tenascin-R immunohistochemistry. PV+ interneuron density, somatic PV intensity, and inhibitory synapse markers are measured in parallel. The correlation analysis tests whether cognitive preservation in treated animals tracks with PNN preservation rather than with plaque or tau burden reduction. Under the Bioenergetic Collapse Model, the PNN-PV+ readout should track cognitive outcome more tightly than any amyloid or tau biomarker, because the model asserts that circuit preservation occurs through microglial homeostatic restoration which operates on the PNN directly rather than through amyloid or tau clearance. A dissociation in which plaque burden decreases without PNN preservation, or in which PNN is preserved without cognitive benefit, would require revision of either the Bioenergetic Collapse Model's therapeutic mechanism or the prior thesis's identification of PNN integrity as the circuit-level readout.

Prediction 5: Postmortem brain tissue from resilient individuals — those carrying high amyloid and tau burden without clinical dementia, as identified in the de Vries and Carulli cohort and equivalent cohorts — will show preserved mitophagy markers, preserved mitochondrial DNA integrity, and preserved microglial metabolic gene expression relative to symptomatic-AD brains matched for amyloid and tau burden. This prediction tests the Bioenergetic Collapse Model's interpretation of resilience as preservation of mitochondrial quality-control competence. The experimental design uses banked postmortem tissue from resilient individuals — those whose neuropathological burden met AD diagnostic criteria without corresponding clinical impairment — compared to matched symptomatic-AD tissue and non-demented low-pathology controls. The comparison focuses on microglial mitophagy markers (BNIP3L/NIX, OPTN, NDP52), mitochondrial biogenesis markers (PGC-1α, TFAM, NRF1, NRF2), mitochondrial DNA copy number and damage, and metabolic gene expression including the PI3K-AKT-mTOR axis components Baik identified as load-bearing for microglial metabolic competence. Under the Bioenergetic Collapse Model, resilient individuals should show preserved values across these markers relative to the symptomatic comparison group, and the preservation should be most pronounced in the microglial population where it matters most for the homeostatic collapse mechanism. The analysis can be performed using single-nucleus RNA sequencing to achieve cell-type-specific resolution, or using laser capture microdissection of microglia for targeted molecular analysis. An alternative outcome in which resilient individuals do not differ from symptomatic individuals in mitochondrial quality-control markers would be strong evidence against the model's interpretation of resilience and would require the mechanism of resilience to be located elsewhere — possibly in specific genetic variants affecting amyloid toxicity, in cognitive reserve mechanisms unrelated to microglial biology, or in factors not yet identified.

Prediction 6: Gene-gene interactions between BIN1, TREM2, APOE, and presenilin-adjacent LOAD risk variants should produce worse outcomes than single-locus risk, because these loci hit different nodes of the same quality-control pipeline. This prediction operationalizes Rubinsztein's gene-gene interaction framework within the specific mechanistic scaffold of the Collapse model's coupling-pathway architecture. BIN1 risk variants impair autophagosome closure; TREM2 risk variants impair the metabolic reprogramming that Baik showed failing in AD microglia; APOE ε4 drives amyloid deposition that increases the cargo load on an already-compromised pipeline. A BIN1 × TREM2 double-risk genotype should produce more severe quality-control collapse than either alone, because BIN1 impairs the formation step while TREM2 impairs the metabolic substrate that both formation and degradation steps require. A BIN1 × APOE ε4 combination should produce worse outcomes than APOE-driven amyloid load would produce in individuals with intact BIN1-mediated clearance. A BIN1 × presenilin-adjacent variant combination should produce complete pipeline failure spanning formation and degradation ends, generating the most severe PANTHOS phenotype. These predictions are directly testable in existing LOAD cohorts with genome-wide genotyping and longitudinal cognitive data: individuals carrying risk variants at multiple quality-control-pipeline loci should show earlier onset, faster progression, or both, relative to individuals carrying either alone. The predictions have not been tested and represent one of the most immediately tractable clinical-genetic tests the integrated framework generates. If confirmed, they would demonstrate that the coupling pathways Convergence 1 describes have population-level genetic reality and are not merely cell-biological abstractions.

These six predictions collectively test every load-bearing claim of the Bioenergetic Collapse Model. Prediction 1 tests the causal role of mitophagy in microglial homeostatic collapse. Prediction 2 tests the sorting mechanism of Convergence 3 at the level of individual cells. Prediction 3 tests the TGF-β/mitochondrial coupling that constitutes Convergence 2 and the model's most specific original claim. Prediction 4 tests the therapeutic bridge to the circuit-level readout identified by the prior thesis, which is the clinical translation point of the entire framework. Prediction 5 tests the model's interpretation of resilience as preserved mitochondrial substrate competence. Prediction 6 tests whether the coupling pathways of Convergence 1 have population-level genetic reality through gene-gene interactions at different pipeline nodes. If all six predictions are confirmed, the Bioenergetic Collapse Model will have been substantially validated as a framework for understanding Alzheimer's disease and for designing therapeutic interventions. If any are falsified, the framework will require revision in ways that this section has attempted to anticipate. Either outcome advances the field, because the predictions are sharp enough that their experimental resolution is informative regardless of which way the resolution goes.

13. Therapeutic Implications

The therapeutic program implied by the Bioenergetic Collapse Model is both more specific and more expansive than the therapeutic programs generated by any of the frameworks it integrates. It is more specific because it identifies a single mechanistic target — the mitochondrial quality-control machinery whose failure constitutes the upstream event in the disease — and judges all candidate interventions by their capacity to restore that target rather than by their effects on downstream biomarkers or individual pathway components. It is more expansive because it recognizes that the target can be addressed from multiple directions simultaneously, and that interventions traditionally siloed into separate therapeutic categories — cell-biological, pharmacological, dietary, lifestyle — are in fact complementary components of a unified restoration strategy whose effects on the common target are additive and potentially superadditive. This section develops the therapeutic program in detail, organized around the six intervention classes that the model identifies as mechanistically convergent and around the experimental and clinical strategies through which their combination should be tested.

The first intervention class comprises direct mitophagy inducers — small molecules and dietary compounds whose mechanism of action is the stimulation of the PINK1/Parkin-mediated recognition, engulfment, and degradation of damaged mitochondria. Urolithin A, the microbial metabolite produced from dietary ellagitannins by gut bacteria, is the most studied member of this class and has been demonstrated in multiple preclinical models to induce mitophagy, improve mitochondrial function, and produce measurable cognitive and muscular benefits in aging and disease models. The Fang 2019 paper demonstrated its efficacy in APP/PS1 mice and in C. elegans Aβ models, and subsequent work has extended these findings across additional model systems. Urolithin A is orally bioavailable, has passed early-phase clinical trials for sarcopenia and metabolic indications, and is commercially available as a dietary supplement under the Mitopure trade name, making it the most clinically tractable direct mitophagy inducer currently available. The model predicts that urolithin A should produce measurable cognitive and biomarker benefits in early Alzheimer's disease populations, with the magnitude of benefit scaling with the degree of remaining mitochondrial substrate at the time of intervention — patients at earlier disease stages, whose microglial populations retain substantial mitophagy-competent cells, should show greater benefit than patients at advanced stages where the cellular substrate has already been exhausted.

NAD■ precursors — nicotinamide riboside and nicotinamide mononucleotide — constitute a related class of mitophagy-enhancing interventions whose mechanism operates through restoration of the NAD■-dependent sirtuin pathway that couples mitochondrial biogenesis to mitophagy. NAD■ declines with age in multiple tissues including the brain, and its decline impairs sirtuin-mediated deacetylation of PGC-1α and other mitochondrial regulatory proteins. Precursor supplementation restores cellular NAD■ levels, which in turn restores the sirtuin-mediated

regulatory program that the Fang 2019 paper implicated as the mechanism of mitophagy induction. Lautrup, Sinclair, Mattson, and Fang's 2019 Cell Metabolism review articulated the NAD■ framework for brain aging and neurodegenerative disease in detail, and the subsequent clinical literature has produced early evidence of tolerability and pharmacokinetic feasibility in human populations. The model predicts that NAD■ precursor supplementation should produce effects mechanistically convergent with urolithin A — both should enhance mitochondrial quality control, both should restore microglial metabolic competence, and both should preserve the PNN-PV+ axis that the prior thesis identified as the therapeutic readout — and that the combination of the two may produce superadditive benefit because they target different nodes of the mitochondrial quality-control system simultaneously.

The second intervention class comprises lysosomal acidification restorers — interventions that directly address the autophagy-lysosomal failure that the Nixon program characterized and that the PANTHOS paper established as the proximate mechanism of plaque formation. This class is currently less pharmacologically mature than the mitophagy inducer class, but candidate approaches exist including v-ATPase assembly enhancers, TRPML1 agonists that promote lysosomal calcium signaling and downstream lysosomal biogenesis, and TFEB activators that drive the transcriptional program for lysosomal renewal. Preclinical work on these approaches has demonstrated that lysosomal function can be enhanced pharmacologically and that the enhancement produces cellular benefits in models of autophagy-lysosomal dysfunction. The model predicts that lysosomal restoration should be particularly effective in combination with mitophagy induction, because the mitophagy pathway depends on lysosomal degradative capacity to complete its function, and enhancing mitophagy induction without addressing lysosomal bottlenecks may produce limited benefit if the damaged mitochondria recognized by PINK1/Parkin cannot be degraded once delivered to the lysosome. The combination of urolithin A or NAD■ precursors with a lysosomal-restoring agent is therefore predicted to produce larger benefit than either alone, and represents one of the most promising combination strategies the model identifies.

The third intervention class comprises autophagosome-closure enhancers — interventions that address the formation-end bottleneck that BIN1 risk variants create in the autophagy-lysosomal pipeline. Rubinsztein's 2025 demonstration that BIN1 overexpression inhibits autophagosome closure via ESCRT-III/DNM2 identifies a specific molecular axis whose modulation could restore the formation step that BIN1 variants impair. If elevated BIN1 expression is the mechanism through which LOAD risk variants produce autophagosome closure failure, then interventions that reduce BIN1 expression toward normal levels, or that enhance ESCRT-III or DNM2 function at the autophagosomal membrane to compensate for BIN1-mediated inhibition, could address the formation-end bottleneck without requiring any manipulation of the downstream lysosomal or mitophagy machinery. This class is pharmacologically immature — no clinical-stage autophagosome-closure enhancer has been developed — but the molecular target is now specified

with sufficient precision to support drug discovery programs, and the BIN1-ESCRT-III-DNM2 axis represents a druggable scaffold amenable to small-molecule or antisense-oligonucleotide intervention. The model predicts that autophagosome-closure enhancement should be particularly effective in combination with lysosomal acidification restoration, because the two classes address the two ends of the same pipeline: closure enhancers ensure that autophagosomes form and seal correctly, while lysosomal restorers ensure that the sealed autophagosomes can be degraded once delivered. Additionally, Rubinsztein's onset-vs-progression distinction implies that different intervention classes may be optimal at different disease stages: autophagosome-closure enhancement may be most effective in the pre-symptomatic and early-symptomatic phases when the formation-end bottleneck is the rate-limiting failure, while proteasome-supporting interventions may be more effective in the progression phase when the tau-driven proteasomal feedback loop has become the dominant accelerator.

The fifth intervention class comprises TGF-β/SMAD pathway stabilizers — interventions aimed at restoring the specific signaling pathway that maintains the homeostatic microglial signature and, under the original Convergence 2 claim of this thesis, maintains the mitochondrial competence that underlies the signature. The prior thesis proposed TGF-β pathway restoration as a therapeutic strategy without specifying the mechanism through which it would act on microglial biology. This thesis sharpens the proposal by asserting that TGF-β pathway restoration acts simultaneously on the transcriptional identity and the mitochondrial substrate of microglia, and that its effects on these two dimensions should be non-separable. Candidate interventions include recombinant TGF-β delivery to the brain through localized administration, pharmacological SMAD7 inhibition to relieve the inhibitory feedback that accumulates under chronic oxidative stress, and small-molecule enhancers of TGF-β receptor signaling that have been developed for other indications. These approaches are less clinically mature than the mitophagy inducer class but supply a mechanistically distinct target whose combination with mitophagy induction would test whether the two mechanisms converge on a shared downstream outcome, as the model predicts they should. A specific clinical prediction is that the combination of a TGF-β pathway stabilizer with a mitophagy inducer should produce greater benefit than either alone, and that the benefit should be measurable as simultaneous recovery of the Butovsky signature and of mitochondrial functional markers in accessible microglial populations.

The sixth intervention class is the largest and the most clinically mature: it comprises the bioenergetic substrate interventions drawn from the metabolic psychiatry framework developed by Sethi, Sarnyai, Picard, and colleagues. These include ketogenic metabolic therapy, intermittent fasting, metformin, GLP-1 receptor agonists such as semaglutide and liraglutide, pioglitazone, and the broader class of interventions that enhance insulin sensitivity, restore mitochondrial substrate availability, and activate AMPK-mediated biogenesis programs. The Bioenergetic Collapse Model predicts that each of these interventions should produce benefit in Alzheimer's disease through the

same mechanism by which it produces benefit in the psychiatric indications for which it was developed: by restoring mitochondrial substrate competence at the systemic level, which in turn supports the cell-autonomous quality-control machinery that the other intervention classes address more directly. The clinical tractability of this class is substantial — these interventions are FDA-approved for other indications, have established safety profiles, have orally bioavailable formulations, and in several cases have existing clinical infrastructure for delivery and monitoring. The barrier to their use in Alzheimer's disease is not pharmacological but conceptual: the field has not yet recognized that interventions targeting systemic metabolic state should be expected to modify the cell-biological trajectory of a neurodegenerative disease. The Bioenergetic Collapse Model, through the Picard integration developed in §8, supplies the conceptual framework within which this expectation becomes principled rather than opportunistic.

A specific sub-recommendation within this class deserves particular emphasis because it is the intervention for which the preclinical and early clinical evidence is most suggestive: ketogenic metabolic therapy. The ketogenic diet produces sustained elevation of β-hydroxybutyrate as a metabolic substrate, drives the mitohormetic adaptive response characterized by Ristow, activates AMPK and PGC-1α through multiple convergent mechanisms, and has been demonstrated in pilot trials to produce cognitive benefits in individuals with Alzheimer's disease and in related conditions. The Sethi pilot trial in bipolar disorder and schizophrenia, covered in the 2026 Nature Mental Health review, produced measurable psychiatric and metabolic improvements. The model predicts that ketogenic metabolic therapy in Alzheimer's disease populations should produce convergent benefits across cognitive, metabolic, and biomarker readouts, and that its effects should be mechanistically additive with direct mitophagy induction through urolithin A or NAD■ precursors. A clinical trial testing this specific combination — ketogenic metabolic therapy plus urolithin A or nicotinamide riboside supplementation in early Alzheimer's disease — would be one of the most direct tests of the integrated therapeutic program this thesis proposes, and would be technically feasible with existing infrastructure.

The integration of these six intervention classes into a unified therapeutic strategy requires attention to sequencing, combination, and patient selection. The model predicts that the therapeutic benefit of any given intervention should scale with the degree of remaining mitochondrial substrate at the time of intervention, which implies that earlier intervention is expected to produce greater benefit than later intervention, and that the target population for maximum effect is the at-risk and early-symptomatic population rather than the advanced-disease population where most current AD trials have been conducted. The combination of interventions should be additive across mechanistically distinct classes — mitophagy induction plus lysosomal restoration plus autophagosome-closure enhancement plus TGF-β stabilization plus systemic bioenergetic substrate provision — and should avoid redundant targeting within a single class where the added benefit is expected to be modest. The specific combination the model predicts as most effective for

early-symptomatic Alzheimer's disease is: ketogenic metabolic therapy or cyclic intermittent fasting as the systemic substrate intervention; urolithin A or nicotinamide riboside as the direct mitophagy inducer; metformin or a GLP-1 receptor agonist as the AMPK-activating pharmacological adjunct; and physical exercise as the mitohormetic stimulus for endogenous biogenesis induction. This combination addresses multiple nodes of the integrated quality-control system simultaneously, is pharmacologically and clinically tractable with existing tools, and has a plausible path to clinical trial within the current regulatory framework.

The measurement of therapeutic success under this program should follow the prior thesis's identification of the perineuronal net and parvalbumin-positive interneuron axis as the circuit-level readout. Direct measurement in human populations requires imaging modalities that can assess PNN integrity and PV+ interneuron function non-invasively, and these are less well-developed than amyloid and tau imaging but are within the technical reach of current and near-future methodology. Magnetic resonance spectroscopy of GABA and of metabolic substrates including β-hydroxybutyrate and lactate supplies one approach. Advanced diffusion imaging of inhibitory circuit integrity supplies another. Positron emission tomography tracers targeting perineuronal net components are in development and may provide a direct readout within the next several years. Pending these advances, surrogate readouts including cognitive performance on tasks specifically sensitive to inhibitory interneuron function, electrophysiological measurements of gamma oscillations that depend on PV+ interneuron activity, and biomarker measurements of NLRP3 inflammasome output can supply reasonable intermediate endpoints for clinical trial design.

The final point this section will make concerns the relationship between the unified therapeutic program the model proposes and the existing anti-amyloid and anti-tau programs that dominate current Alzheimer's disease drug development. The Bioenergetic Collapse Model does not predict that anti-amyloid or anti-tau interventions are useless, but it predicts that they are partial and that their benefit will be limited by their failure to address the upstream substrate failure. The combination of anti-amyloid therapy with the bioenergetic restoration program this thesis proposes should produce substantially greater benefit than either alone, because the anti-amyloid arm addresses the downstream burden while the bioenergetic arm addresses the upstream machinery. Such a combination approach represents the most pragmatic pathway to clinical deployment of the integrated framework, because it preserves the investment the field has made in anti-amyloid development while correcting the framework's central limitation. The specific prediction is that adding a mitophagy inducer, a metabolic substrate intervention, or a combination of both to an approved anti-amyloid monoclonal antibody should produce cognitive benefit substantially greater than the monoclonal alone, and should produce this benefit while simultaneously reducing the inflammatory and metabolic adverse effects that have complicated the monoclonal programs. This prediction is testable within existing trial infrastructure and represents the most direct clinical test of the Bioenergetic Collapse Model's practical relevance.

14. Conclusion

The Collapse trilogy, of which this thesis is the third and final installment, has been an attempt to apply the Organic Network Synthesis methodology to one of the most theoretically fragmented domains of contemporary biomedical research. Alzheimer's disease has generated, over the past century of investigation, a research literature whose volume and technical sophistication rivals that of any other disease in the biomedical canon, and whose therapeutic failure rivals that of any major clinical target the pharmaceutical industry has attempted. The disconnect between the field's scientific productivity and its clinical return on investment is not a consequence of insufficient effort, insufficient funding, or insufficient mechanistic detail. It is a consequence of theoretical fragmentation: the disease has been approached by a dozen different research communities each operating within its own conceptual framework, measuring its own endpoints, targeting its own molecular substrates, and interpreting its results within the assumptions of its own discipline. The frameworks have each captured real features of the disease, and the therapies each framework has generated have each produced modest signals, but no framework has been able to subsume the others, and no therapy has been able to produce the transformative clinical benefit that the field's mechanistic understanding of the disease should, in principle, have enabled.

The three Collapse theses propose a different approach. Rather than treating the existing frameworks as competing hypotheses whose adjudication would identify the correct one, the ONS methodology treats them as partial projections of a single underlying process whose unified description has been obscured by the disciplinary organization of research rather than by any intrinsic feature of the biology. Convergent Synaptic Collapse took the inhibitory interneuron and its perineuronal net as the circuit-level substrate on which the disease produces its cognitive phenotype, and argued that the diversity of circuit-level findings in the literature — excitation-inhibition imbalance, gamma oscillation disruption, hippocampal-cortical disconnection, PV+ interneuron vulnerability — are projections of a single circuit-level collapse whose molecular substrate is the perineuronal net itself. Homeostatic Microglial Collapse took the TGF-β/SMAD-maintained homeostatic microglial signature as the cellular-identity-level substrate whose failure generates the disease-associated microglial phenotypes, and argued that the apparent conflict between the attack and failure frameworks of microglial biology dissolves when both are recognized as downstream manifestations of a single homeostatic collapse whose trifurcation into DAM, LDAM, and dystrophic trajectories reflects graded severity rather than distinct programs. The present thesis, Bioenergetic Collapse, takes the integrated mitochondrial and autophagy-lysosomal quality-control machinery as the substrate-level generator whose failure produces both the neuronal PANTHOS phenotype that Gouras and Nixon characterized and the microglial homeostatic collapse the prior thesis described, and it argues that this machinery is the upstream target whose restoration should be the central aim of therapeutic development.

The three theses are not three accounts of the disease. They are one account at three levels of mechanistic resolution, and their integration produces a framework in which the circuit-level outcome, the cellular-identity-level mechanism, and the substrate-level generator are continuously coupled through the specific molecular pathways that connect them. The therapeutic task this framework implies is neither circuit-level rescue through synaptic pharmacology, nor cellular-level silencing through microglial modulation, nor substrate-level replacement through metabolite provision. It is restoration of the integrated quality-control machinery whose failure generates the disease phenotype at every level. The interventions that accomplish this restoration are drawn from the mitophagy induction, NAD■ restoration, autophagy-lysosomal enhancement, autophagosome-closure enhancement, TGF-β pathway stabilization, and metabolic psychiatry classes developed in the preceding sections, and their combination is predicted to produce superadditive benefit because each class targets a different node of the same integrated system. The measurement of therapeutic success is the preservation of the perineuronal net and the parvalbumin-positive interneuron, because the circuit-level endpoint is the final common pathway through which all upstream interventions must act if they are to produce cognitive benefit.

The epistemological lesson of the Collapse trilogy is one that the field of Alzheimer's disease research has been slow to internalize. The most damaging intellectual move in biomedical research is the mistake of treating the visible surface of a pathology for the mechanism that generates it. The amyloid plaque is the visible surface; autophagy-lysosomal failure is the mechanism. The activated microglial cell is the visible surface; homeostatic collapse is the mechanism. The lost synapse is the visible surface; quality-control failure is the mechanism. The mitochondrial dysfunction that neuroimaging can detect is itself the visible surface; the specific failure of PINK1/Parkin mitophagy under the conditions of cumulative oxidative and allostatic load is the mechanism. Each step in the hierarchy mistakes a downstream signature for an upstream event, and each therapeutic program built on that mistake targets the signature rather than the event. The Collapse trilogy is an attempt to descend the hierarchy to its actual generator and to build a therapeutic program on that foundation rather than on any of the intermediate projections the field has misidentified as the target.

The work ahead is empirical. The six predictions developed in §12 test the load-bearing claims of the model, and their experimental resolution will determine whether the integrated framework is correct, partially correct, or in need of fundamental revision. The unified therapeutic program developed in §13 is testable in clinical populations with existing tools and existing regulatory pathways, and its evaluation through combination trials of mitophagy inducers, metabolic substrate interventions, and lifestyle approaches is within reach of current clinical research infrastructure. The PNN-PV+ circuit-level readout can be measured with developing imaging modalities and with surrogate electrophysiological and cognitive endpoints, and its integration into trial designs would supply the specific endpoint the Bioenergetic Collapse Model predicts should track most tightly with therapeutic benefit. The outcome of these experimental and clinical programs will determine

whether the Collapse trilogy has identified the correct framework for understanding Alzheimer's disease or whether its contribution will be limited to clarifying the questions that the next framework will need to answer. Either outcome advances the field. The microglial contribution to Alzheimer's disease is neither an attack nor a failure nor a mystery. It is the downstream face of a quality-control collapse whose origin is mitochondrial, whose propagation is through autophagy-lysosomal and metabolic failure, whose gate is the NLRP3 inflammasome, and whose circuit-level endpoint is the perineuronal net. The therapeutic task is restoration, not suppression, activation, or replacement. The measurement is cognitive, and the pathway is bioenergetic. The work ahead is the work of testing whether the restoration approach produces the clinical benefit the framework predicts, and the next decade of Alzheimer's disease research will either confirm the framework or supply the evidence that corrects it.

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