THE CLEARANCE COLLAPSE

Autophagy as the Quality-Control Spine of the Three-Phase Architecture of Alzheimer's Disease — From Mitophagy in the Locus Coeruleus to the Plaque as Gravestone

Macroautophagy · Mitophagy · Autophagosome Closure
Lysosomal Acidification · The Endosomal Interface

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Dr. James Truchard & Benjamin Aaron Gustafsson

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Companion to The Temporal Architecture of Collapse and the Collapse trilogy — tracing the autophagy–lysosomal machinery through all three temporal phases of Alzheimer's disease.

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Abstract

A companion analysis, *The Temporal Architecture of Collapse*, proposed that Alzheimer's disease is best read not as a contest among primary molecules but as a stereotyped three-phase progression that crosses the brain over half a century — bioenergetic ignition in the locus coeruleus in the third decade, microglial collapse in the hippocampus in the sixth, synaptic disintegration of the cortical perineuronal net in the eighth. That account named the phases and specified the two transitions between them. It left open a question that this paper exists to answer: if the disease is a front of failure that changes its substrate as it moves — metabolic, then immunological, then structural — is there any single cellular system that fails *throughout*, beneath all three phases, whose collapse the phases each express in their own idiom? We argue that there is, and that it is autophagy: the machinery by which a cell digests and renews its own contents.

Autophagy is not a step in the Alzheimer cascade. It is the substrate on which the cascade runs. We defend this by tracing the machinery through each phase and showing that what looks like three different diseases is, at the level of self-clearance, one machinery failing in three different cell types under three different loads. In **Phase I**, the load is mitochondrial: the locus-coeruleus neuron, the most metabolically extravagant cell in the brain, depends on mitophagy — the selective autophagy of damaged mitochondria — to survive its own firing, and mitophagy is defeated from both ends, by NAD+ depletion that starves it and by Aβ obstruction of the mitochondrial import channel TOM40 that renders the organelle both unrepairable and unrecognizable. In **Phase II**, the load is lipid: the microglion gorging on myelin debris must clear that lipid by lipophagy, and when lipophagy fails it becomes the lipid-droplet-accumulating cell whose gridlocked metabolism, NAD+ exhaustion through CD38, and TREM2–mTOR decoupling convert it from custodian to effector — and whose ruptured lysosomes arm the NLRP3 inflammasome. In **Phase III**, the load is proteostatic: the endosomal–autophagic interface jams, intraneuronal Aβ accumulates in the multivesicular bodies and late endosomes of cells whose retromer and ESCRT machinery have failed, and the lysosome's proton pump is poisoned by the very lipid-peroxidation aldehydes the disease has been generating since Phase I.

Two structural facts unify the picture. First, the late-onset genetic architecture brackets the autophagy pipeline at both ends: *BIN1*, the second-strongest common risk locus, governs autophagosome closure at the formation end, while presenilin governs lysosomal acidification at the degradation end — and a lesion at either end produces the same outcome, the accumulation of undegraded cargo, which is why two genes acting on opposite ends of one pipeline converge on one disease. Second, the terminal morphology of autophagic failure — the flower-like neuron swollen with un-acidified autolysosomes that Nixon and colleagues named PANTHOS — inverts the amyloid cascade at its root: the plaque is not the cause of the neuron's death but its gravestone, the extruded residue of intracellular compartments that failed to clear their cargo before the cell ruptured. We close by drawing the therapeutic consequence, which is unusually

direct: a disease of failed clearance is treatable in principle by restoring clearance, but only in a phase-matched way — by inducing autophagic flux where the machinery is intact but idling, by feeding the machinery where its substrate has run out, and by protecting the lysosomal pump where reactive aldehydes are poisoning it. Where autophagy fits, in short, is everywhere — and that is precisely why it is the place to intervene.

I. The Question of Where Autophagy Fits

A system, not a step

For most of the past three decades, autophagy entered Alzheimer's discussions as a supporting character — a clearance pathway that, when it underperformed, allowed a little more amyloid or a little more tau to accumulate than it otherwise would. On this reading autophagy is one arrow in the cascade diagram, downstream of the proteins that matter and upstream of the neurons that die. The reading is not wrong so much as it is small. It mistakes a system for a step.

Autophagy is the process by which a eukaryotic cell consumes and rebuilds itself. It is how a neuron disposes of a depolarized mitochondrion, a misfolded protein aggregate, a surplus of membrane lipid, an exhausted ribosome; it is, in the post-mitotic cell that cannot dilute its damage by dividing, the only route to renewal. A neuron is not a structure that is built once and then maintained; it is a structure that is continuously demolished and rebuilt, and autophagy is the demolition arm of that perpetual renovation. To say that autophagy "contributes" to Alzheimer's disease is therefore like saying that the failure of a city's sanitation contributes to an epidemic. It is true, but it understates the matter: the failure of clearance is not one cause among many but the condition under which the others become lethal.

Why the answer is temporal

If autophagy is a system rather than a step, then the question "where does autophagy fit in Alzheimer's disease?" cannot be answered by pointing to a single box in a diagram. It must be answered temporally — by asking what the machinery is doing, and how it is failing, in each phase of the disease and in each cell that the disease successively recruits. This is the move the companion paper made for the disease as a whole, and it is the move that makes the autophagy question tractable. Autophagy does not fail once, in one way, at one time. It fails first in the mitochondria of brainstem neurons in the third decade, then in the lipid handling of hippocampal microglia in the sixth, then in the endosomal proteostasis of cortical neurons in the eighth — and these are not three failures of three systems but three failures of one system under three loads.

The temporal framing also dissolves an old confusion. The autophagy literature in Alzheimer's has long contained an apparent paradox: some studies find autophagy *suppressed* (too little flux, cargo piling up), others find it *induced* (autophagosomes everywhere, a cell straining to clear what it cannot). Read across a single timepoint these look contradictory. Read across the arc they are sequential: induction is the early compensatory response of a machine still trying, and suppression — more precisely, the failure of completion — is the late state of a machine whose downstream steps have broken. The autophagosomes that accumulate in the Alzheimer brain are not evidence of healthy autophagy but of autophagy arrested at the threshold of degradation, like rubbish trucks queued at a landfill whose gates have rusted shut.

Thesis

This paper advances a single thesis in three parts. First, that autophagy — macroautophagy and its specialized branches, mitophagy and lipophagy, terminating in lysosomal degradation — is the quality-control *spine* of the three-phase architecture: the one cellular system whose age-dependent collapse underlies all three phases, expressed in each as the failure most relevant to that phase's cell and load. Second, that this collapse is bracketed by the disease's own genetics, with *BIN1* failing the pipeline at its formation end and presenilin failing it at its degradation end, both yielding the accumulation of undegraded cargo that the amyloid literature has spent a generation mistaking for a primary cause. Third, that the terminal lesion of autophagic failure — the PANTHOS neuron and the plaque it leaves behind — inverts the causal order of the amyloid cascade, making the plaque a consequence of failed clearance rather than its cause. From these three claims a therapeutic logic follows that is the subject of the paper's final section: restore clearance, but restore it phase by phase.

II. The Machinery of Self-Clearance

Before locating autophagy in the disease it is worth setting out the machinery in working order, because the disease is best understood as the failure of specific, nameable steps within it.

Macroautophagy: from phagophore to autolysosome

Macroautophagy — the principal arm, and the one meant when the word is used without qualification — proceeds as a pipeline. It begins with *initiation*, in which a cup-shaped membrane called the phagophore nucleates around a target, under the control of the ATG gene products and the Beclin-1 complex, with the kinase mTORC1 acting as the master brake: when mTORC1 is active the cell is fed and autophagy is suppressed; when mTORC1 is inhibited, autophagy is licensed. The phagophore elongates and engulfs its cargo, and then must *close* — seal itself into a complete double-membraned autophagosome — a step executed by the ESCRT-III machinery in coordination with dynamin-2 (DNM2) and, critically, the Alzheimer-risk protein BIN1. The closed autophagosome then *fuses* with a lysosome, and the resulting autolysosome *degrades* its contents, a step that depends absolutely on acidification: the vacuolar ATPase (v-ATPase) pumps protons into the lumen to hold the pH near 4.5, the level at which the lysosomal hydrolases activate. Cargo is selected and delivered by adapter proteins — p62/SQSTM1, optineurin, NDP52, TAX1BP1 — that bind ubiquitinated targets at one end and the autophagosomal membrane marker LC3 at the other.

Two features of this pipeline matter for everything that follows. It is *directional* — formation precedes closure precedes fusion precedes degradation — so a lesion at any stage halts the whole line. And it is *bracketed by acidification*: nothing the upstream machinery accomplishes counts unless the autolysosome can finally acidify, because un-acidified cargo is cargo undegraded.

Mitophagy: the specialized branch

Mitophagy is macroautophagy aimed specifically at mitochondria, and it is the branch that matters most in Phase I. Its canonical pathway is the PINK1/Parkin system: when a mitochondrion's membrane potential collapses — the signature of a damaged organelle — the kinase PINK1 accumulates on its outer membrane rather than being imported and degraded, and recruits the E3 ligase Parkin, which writes ubiquitin chains on outer-membrane proteins. Those chains are read by the same adapters — p62, optineurin, NDP52 — that consign the tagged mitochondrion to an autophagosome. Mitophagy thus shares its entire downstream half with macroautophagy: the mitophagosome is an autophagosome, closed by the same BIN1–ESCRT-III–DNM2 machinery and degraded in the same acid-dependent autolysosome. This sharing is the reason a single lesion in the common machinery defeats both general proteostasis and mitochondrial quality control at once.

The two anchors: BIN1 and presenilin

The strongest evidence that autophagy is causal in Alzheimer's, rather than merely correlated with it, comes from the disease's own genetics, which happen to mark the autophagy pipeline at both of its ends. At the *formation* end sits BIN1 — after APOE, the second-strongest common genetic risk locus for late-onset disease — whose role in coordinating ESCRT-III and dynamin-2 to close the autophagosome was characterized by Rubinsztein and colleagues. A BIN1 risk variant is a variant that impairs the sealing of the autophagosome. At the *degradation* end sits presenilin, whose familial mutations are textbook causes of early-onset disease: beyond its famous role in γ-secretase, presenilin-1 is required for the delivery and assembly of the v-ATPase that acidifies the lysosome, so that presenilin mutations impair lysosomal acidification, as Wolfe, Nixon, and colleagues established.

The two anchors make a structural argument that neither makes alone. They act on opposite ends of one pipeline — one cannot close the bag, the other cannot dissolve its contents — and they produce the *same* downstream outcome: the accumulation of undegraded autophagic cargo, including damaged mitochondria and intraneuronal Aβ. When two independent genetic findings, at opposite ends of one machine, converge on one disease, the machine is not incidental to the disease. It is the disease's substrate.

Transcriptional command: TFEB, mTORC1, and the NAD+ link

Autophagy is not only a pipeline but a programme, governed transcriptionally by TFEB, the master regulator of the lysosomal and autophagic gene network. TFEB is held inactive in the cytoplasm by mTORC1 phosphorylation; when energy or nutrients run short and mTORC1 releases it, TFEB translocates to the nucleus and drives the biogenesis of new lysosomes and autophagy components. This places the whole system under metabolic command — and it is here that autophagy couples to the bioenergetic lesion of Phase I. NAD+, the central redox currency of the cell, declines with age and is further drained by PARP-1 hyperactivation and by CD38; its fall cripples the sirtuins that coordinate mitochondrial biogenesis and, through the mTORC1–TFEB axis, the lysosomal biogenesis on which clearance depends. A cell low on NAD+ and high on mTORC1 stress is a cell that cannot manufacture the very machinery it most needs. Autophagy, in other words, is not only a victim of the energy crisis; it is downstream of it by design.

III. Autophagy in Phase I The Substrate Lesion

Why the locus coeruleus fails first

The companion paper located the disease's origin in the locus coeruleus, the small noradrenergic nucleus of the pons whose pretangle tau appears in early adulthood. The autophagy account explains *why* this cell, of all cells, is first. The locus-coeruleus neuron is autonomously pacemaking, fires tonically throughout waking life, sustains one of the most extensively branched axonal trees in the brain, and runs a catecholamine chemistry that is itself a source of oxidative load. A cell with this profile lives permanently near the ceiling of its mitochondrial capacity, which means it depends, more than almost any other neuron, on flawless mitophagy to retire its damaged mitochondria before their reactive-oxygen output accumulates. It has no reserve. The cell that most needs mitophagy is therefore the cell in which any age-dependent erosion of mitophagy first crosses from compensated to catastrophic — and that is the neuropathological definition of where Alzheimer's begins.

NAD+ depletion and the starving of mitophagy

The first blow to mitophagy in Phase I is energetic. Mitophagy is an ATP-expensive process layered on top of the very metabolism it polices, and it is gated by NAD+-dependent signalling. As NAD+ falls with age — drained by the PARP-1 response to accumulating DNA damage and consumed by the rising CD38 of an inflammaging milieu — the sirtuins fall silent, mitochondrial biogenesis falters, and the TFEB-driven manufacture of lysosomal capacity slows. The cell is asked to clear more damaged mitochondria precisely as its capacity to clear them contracts. Fang and colleagues demonstrated the inverse directly and consequentially: restoring mitophagy — pharmacologically, with NAD+ precursors or the mitophagy inducer urolithin A — reduces amyloid and tau pathology and reverses cognitive deficits in disease models, establishing that the mitophagy deficit is not a bystander but a lever.

TOM40 obstruction: the un-repairable mitochondrion

The second blow is structural, and it is where amyloid first enters the autophagy story — not as plaque but as a saboteur of mitochondrial maintenance. The replacement of a mitochondrion's proteome depends on the import of nuclear-encoded proteins through the translocase of the outer membrane, whose central channel is TOM40. Devi and colleagues showed that Aβ binds and obstructs TOM40, throttling import — the same lesion that α-synuclein inflicts on TOM20 in Parkinson's disease, as Di Maio and colleagues demonstrated. A mitochondrion that cannot import new proteins cannot be repaired. Worse, because PINK1's recognition of damage depends on its own handling at the import machinery, an import-obstructed mitochondrion may be both unrepairable and imperfectly flagged for disposal. The cell is thus left with a growing population of failing organelles it can neither fix nor fully clear — and the reactive-oxygen output of that population gates the NLRP3 inflammasome, priming the inflammatory tinder that will catch in Phase II.

PANTHOS and the plaque as gravestone

The terminal morphology of Phase I autophagic failure is the most consequential observation in this entire account, because it inverts the amyloid cascade at its root. Lee, Yang, Goulbourne, Nixon, and colleagues characterized neurons in which autolysosomes fail to acidify and swell into a rosette of un-degraded, Aβ-filled compartments — a flower-like figure they named PANTHOS (from the Greek for "all" and the poisonous bloom). These neurons are not responding to external plaque; they are accumulating their own undegraded intracellular cargo because their clearance machinery has failed. When such a neuron finally ruptures and dies, the dense Aβ it could not digest is extruded into the parenchyma, where it condenses into the dense-core plaque that pathology has read for a century as the cause of the disease.

Nixon's inference reorders everything: the plaque is the *gravestone* of a neuron that died of autophagic-lysosomal failure, not the weapon that killed it. The Aβ in the plaque is intracellular cargo that failed machinery could not clear before the cell came apart. This is consonant with the inside-out tradition of Gouras and colleagues, who showed that intraneuronal Aβ42 accumulates in multivesicular bodies and late endosomes years before plaques appear and is associated with synaptic pathology from the start. On this reading, four decades of therapeutic effort aimed at clearing extracellular plaque have been aimed at the headstone rather than the disease — and the disease, the failure of clearance, was upstream and intracellular all along.

IV. Autophagy in Phase II The Microglial Variant

Lipophagy and the lipid-gridlocked microglion

When the disease moves from the brainstem to the hippocampus it also moves from one cell type to another, and the autophagy lesion changes its cargo accordingly. The microglion of Phase II is not failing to clear mitochondria so much as failing to clear *lipid*. A microglion that repeatedly phagocytoses myelin debris and apoptotic membrane must dispose of the ingested lipid through lipophagy — the selective autophagy of lipid droplets — and the lysosomal acid lipase that depends on it. When that disposal cannot keep pace, the cell fills with lipid droplets and becomes the lipid-droplet-accumulating microglion (LDAM) described by Marschallinger and colleagues: a dysfunctional, pro-inflammatory state with impaired phagocytosis and a metabolism gridlocked by the very material it failed to clear. The LDAM is, at bottom, a cell that drowned in its own undigested cargo — the microglial counterpart of the PANTHOS neuron.

TREM2–mTOR and the cost of metabolic incompetence

The microglial autophagy lesion is governed by the receptor that governs everything else in Phase II: TREM2. Ulland and colleagues showed that TREM2 sustains microglial metabolic fitness by maintaining mTOR signalling and ATP supply, and that when TREM2 function is lost, mTOR signalling is disrupted and the cell shifts into a maladaptive, energy-starved autophagy — autophagy not as healthy renewal but as the stress response of a metabolically failing cell, rescuable in their experiments by replenishing cellular ATP. This is the microglial echo of the neuronal lesson: autophagic competence is downstream of metabolic competence, and a cell whose energy state has collapsed cannot run the clearance machinery that energy state commands, even as the demand for clearance rises.

CD38, NAD+, and the autophagy–homeostasis coupling

The metabolic thread that runs from Phase I reappears here in a microglia-specific form. Activated microglia upregulate CD38, an NAD+-consuming ectoenzyme, and the resulting local NAD+ depletion — documented in the aging brain by Lautrup, Sinclair, Mattson, and Fang, and mechanistically tied to age-related decline by Camacho-Pereira and colleagues — starves the sirtuin-dependent programmes that support both mitochondrial quality control and the homeostatic transcriptional signature itself. Autophagic competence and homeostatic identity are thus coupled through a shared NAD+ budget: the same depletion that disables the microglion's clearance machinery helps tip it out of its homeostatic state. The post-homeostatic microglion is, in part, a microglion that can no longer afford to clean.

Lysosomal rupture, DAMPs, and the arming of NLRP3

The final move of the Phase II autophagy lesion is the one that connects failed clearance to active harm. A microglion engorged with undigested lipid and damaged organelles is a microglion whose lysosomal membranes are destabilized; when those membranes rupture, they spill cathepsins and release the mitochondrial and lipid damage-associated molecular patterns that are the canonical second signal for the NLRP3 inflammasome. Heneka and colleagues showed that NLRP3 is activated in Alzheimer's disease and drives pathology in disease models. The causal chain is therefore complete and, in retrospect, inevitable: failed lipophagy produces the lipid-gridlocked cell, the gridlocked cell's lysosomes rupture, the rupture arms NLRP3, and the armed inflammasome licenses the IL-1β and downstream proteases that, in the companion architecture, execute the Proteolytic Turn onto the perineuronal net. The microglial clearance failure is not a quiet insufficiency. It is the trigger of the effector phase.

V. Autophagy in Phase III The Endosomal Interface

Retromer, multivesicular bodies, and the traffic jam upstream of autophagy

In the cortical and entorhinal neurons of Phase III the autophagy lesion takes its third form, fused now with the endosomal system that feeds it. Autophagy does not run in isolation; it shares membranes, adapters, and lysosomes with the endosomal sorting pathway, and a jam in one becomes a jam in the other. Small and colleagues placed retromer dysfunction — the failure of the VPS35/VPS26/VPS29 complex and its receptor SORLA to sort and recycle endosomal cargo — at the upstream origin of the trafficking failure, and the consequence is the accumulation of cargo, including Aβ, in swollen endosomal compartments. The enlarged early endosome is one of the earliest cytopathological signs of Alzheimer's disease, visible before plaques, and it marks a cell whose sorting and clearance systems have begun to seize together.

ESCRT-III at two addresses: one machinery, two failures

The deepest unity within Phase III — and one of the strongest arguments that autophagy and the endosomal system are a single clearance problem — is the recurrence of ESCRT-III at two distinct organellar addresses. Willén, Edgar, Gouras, and colleagues showed that Aβ accumulation enlarges the multivesicular body and that this is reproduced by a dominant-negative form of the ESCRT-III ATPase VPS4A: ESCRT-III failure at the *endosome*. Rubinsztein and colleagues showed that BIN1 coordinates ESCRT-III to close the *autophagosome*: ESCRT-III failure at the autophagic membrane. The same molecular machinery, failing at two locations, produces the same result — the failure to sequester and clear Aβ — which means that what the field has described as separate "endosomal" and "autophagic" defects are two presentations of one machinery's collapse. This is the cell-biological core of the claim that autophagy is a spine and not a step: even within a single phase, the lesion refuses to stay in one compartment.

4-HNE and the poisoning of the proton pump

Phase III also closes a loop that runs all the way back to Phase I, and it does so through the lysosome's acid pump. The lipid-peroxidation cascade that the companion architecture places at the heart of synaptic collapse — driven by iron, by APOE4-associated lipid vulnerability, and by the oxidative stress that has been mounting since the brainstem — generates reactive aldehydes, chief among them 4-hydroxynonenal (4-HNE). These aldehydes form covalent adducts on susceptible proteins, and among their targets are the subunits of the v-ATPase and of ATP synthase. A 4-HNE-adducted v-ATPase is a proton pump that cannot fully acidify the lysosome — which means that the lipid peroxidation of Phase III reproduces, by a chemical route, the same acidification failure that presenilin mutations cause genetically and that defines the PANTHOS lesion of Phase I. The disease thus manufactures, in its late phase, the poison for the very machinery whose early failure began it: a feed-forward loop in which oxidative damage disables clearance, and disabled clearance permits more oxidative damage. It is this loop, more than any single lesion, that makes the late disease self-sustaining.

Autophagy at the synapse

Finally, autophagy has a local role at the synapse itself, the structure on which Phase III converges. Synaptic terminals depend on local autophagy to turn over synaptic-vesicle proteins and damaged components far from the cell body, and the axonal transport of autophagosomes to the soma for degradation is itself vulnerable to the trafficking failures and intraneuronal Aβ that define the phase. A synapse whose local clearance fails is a synapse that cannot maintain its proteostasis under the excitatory and oxidative load of a disinhibited, perineuronal-net-stripped cortex — which is to say that the autophagy lesion is present even at the disease's terminal anatomical address, the last and smallest compartment in which the cell's failure to clear itself is expressed.

VI. One Machinery, Three Failures

The unifying claim

The three phases of Alzheimer's disease present, at the level of cells and molecules, as three different diseases: a metabolic failure of brainstem neurons, an immunological failure of hippocampal microglia, a structural failure of cortical synapses. The autophagy account shows that beneath these three presentations runs one machinery, failing three times. The cargo differs — mitochondria in Phase I, lipid in Phase II, protein and endosomal cargo in Phase III — and the cell differs, and the load differs, but the lesion is the same lesion: the failure of regulated self-clearance, halted at one or another step of a single directional pipeline that ends, in every case, at an acid-dependent lysosome. Mitophagy, lipophagy, and the endosomal–autophagic interface are not three systems that happen to fail in sequence; they are three faces of macroautophagy, sharing closure machinery (BIN1–ESCRT-III) and degradation machinery (the v-ATPase-acidified lysosome), and it is the shared machinery that makes them fail together.

Why "which protein is primary" was the wrong question

This is why the long argument over the primary molecule has been so inconclusive. Amyloid, tau, and the activated microglion are each real, and each is genuinely central to the phase in which it is load-bearing — but none is primary across the disease, because the thing that is constant across the disease is not a protein but a *process*, and the proteins are, in large part, the cargo that the failed process could not clear. Intraneuronal Aβ accumulates because autophagy cannot degrade it; the plaque forms because the autolysosome could not acidify; tau pathology is restrained by mitophagy and unleashed by its failure; the microglial effector state is, in part, the state of a cell that can no longer clean. To ask which of these is primary is to ask which piece of uncollected rubbish caused the strike. The autophagy account reframes the question from *what* accumulated to *why nothing was cleared*, and the answer to the second question is the same in every phase.

Autophagic competence as a determinant of resilience

The reframing makes a prediction about resilience that complements the one the companion architecture made. If cognitive resilience is, as the neuropathology of resilient individuals suggests, the preservation of function despite Alzheimer-level protein burden, then on the autophagy account resilience should track *clearance capacity* — the maintained ability to digest cargo — more closely than it tracks cargo itself. A brain that clears well tolerates amyloid and tau because it is continuously disposing of damaged components and never crosses into the self-sustaining loop of failed acidification and mounting oxidative damage. A brain that clears poorly succumbs at the same protein burden because its cargo is not cargo-in-transit but cargo-accumulating. Resilience, in this light, is not the absence of the disease's proteins but the presence of the machinery that keeps them moving — and autophagic competence, sustained by NAD+, by metabolic fitness, and by an un-poisoned lysosome, is its substrate.

VII. The Therapeutic Logic of Restored Clearance

A disease of failed clearance has an unusually direct therapeutic implication: restore clearance. But the autophagy account also explains why this is harder than it sounds and why past attempts have been blunt — because the pipeline fails at different steps in different phases, and an intervention that helps at one step is useless or harmful at another. The rational programme is therefore not "enhance autophagy" in the abstract but three distinct manoeuvres, matched to where in the pipeline, and in which phase, the lesion lies.

Inducing flux: the mTORC1–AMPK–TFEB axis

Where the machinery is intact but idling — held down by an over-active mTORC1 in a cell that cannot sense its own need to clear — the manoeuvre is to induce flux by lifting the brake. This is the logic of the classical autophagy inducers: direct mTORC1 inhibition by rapamycin, and the AMPK-activating, caloric-restriction-mimetic strategies that the ONS pharmacology series has developed around the bioenergetic phase. The ATP-synthase modulator J147, in Goldberg and colleagues' account, partially restrains ATP synthase to activate AMPK, suppress mTORC1, and drive TFEB-dependent lysosomal biogenesis; the FASN inhibitor CMS121, in Ates and colleagues' account, engages the same AMPK–mTORC1–TFEB axis from the lipid-substrate side while reducing the 4-HNE that poisons the lysosome. Spermidine and trehalose belong to the same geroneuroprotective class. The shared principle is to manufacture clearance capacity in a cell that has stopped manufacturing it — and the shared caution is that flux induction helps only where the downstream degradation step still works.

Feeding the machine: NAD+ restoration and mitophagy induction

Where the machinery is starved rather than idling — the Phase I and Phase II lesion of NAD+ depletion — the manoeuvre is to restore the substrate. NAD+ precursors (nicotinamide riboside, nicotinamide mononucleotide), paired where appropriate with CD38 inhibition to stop the leak, refill the budget on which the sirtuins, mitochondrial biogenesis, and TFEB-driven lysosomal renewal depend. Fang and colleagues' demonstration that NAD+ precursors and the direct mitophagy inducer urolithin A reduce amyloid and tau and reverse cognitive deficits is the proof of principle that feeding the machine is not merely supportive but disease-modifying in models. This is the manoeuvre with the clearest mechanistic claim to act early, in the silent decades of Phase I, where the lesion is energetic and the machinery is still structurally whole.

Protecting the pump: defending lysosomal acidification

Where the machinery is being actively poisoned — the Phase III lesion of 4-HNE adduction of the v-ATPase — neither inducing flux nor feeding substrate suffices, because the problem is at the irreplaceable final step, acidification. Here the manoeuvre is to defend the pump: to suppress the lipid-peroxidation cascade that generates the aldehydes (iron chelation or compartmentalization, GPX4 preservation, the antioxidant strategies the ONS iron–GPX4 and FASN analyses develop) so that the lysosome can continue to acidify and the autolysosome can continue to degrade. Protecting acidification is the manoeuvre most specific to the late disease and the one most likely to interrupt the self-sustaining loop, because the loop runs through the poisoned pump.

Why timing decides everything

The three manoeuvres are not interchangeable, and their non-interchangeability is the autophagy account's sharpest therapeutic claim. Feeding the machine helps most in Phase I and is largely wasted in a Phase III cell whose pump is already adducted; protecting the pump is decisive in Phase III and beside the point in a Phase I cell whose lesion is energetic; inducing flux helps wherever the downstream steps survive and harms wherever they do not — for an autophagy inducer applied to a cell that cannot acidify its lysosomes merely fills it faster with autophagosomes it cannot complete, accelerating the PANTHOS trajectory rather than relieving it. This last point is not hypothetical caution; it is the predictable consequence of inducing formation upstream of a blocked degradation step, and it is the most likely reason that indiscriminate "autophagy enhancement" has disappointed. The lesson is the companion architecture's lesson in a new register: the disease is a process in time, and clearance, like everything else, must be restored at the step and in the phase where it is actually failing.

VIII. Falsifiable Predictions

The autophagy account generates predictions that are sharp, mechanistic, and in several cases testable with existing tools.

On the locus coeruleus. Mitophagy markers will be found to fail earliest and most severely in locus-coeruleus and other brainstem aminergic neurons, before cortical involvement and before plaque, in proportion to those cells' metabolic load — and restoring mitophagy in these neurons in model systems will delay the downstream phases more effectively than clearing amyloid.

On the two anchors. BIN1 and presenilin risk variants will be shown to produce the same cargo-accumulation phenotype by failing opposite ends of the pipeline — closure and acidification respectively — and a cell carrying both lesions will accumulate cargo no faster than a cell carrying the more severe single lesion, because the pipeline is already halted.

On the plaque as gravestone. High-resolution longitudinal pathology will confirm that dense-core plaques form predominantly at the sites of PANTHOS neuronal death rather than seeding independently in the extracellular space, and that intraneuronal autolysosomal Aβ accumulation precedes local plaque formation.

On the poisoned pump. Lysosomal acidification, measured directly, will be found to fail in late-phase neurons in proportion to 4-HNE adduction of the v-ATPase, and suppressing lipid peroxidation will preserve acidification independently of any effect on amyloid.

On therapy and timing. Autophagy-flux inducers will help in cells and phases where lysosomal degradation is intact and will *worsen* outcomes where acidification has failed; NAD+ restoration will show its largest effect when administered presymptomatically; and only an intervention that protects acidification will interrupt the late self-sustaining loop. Each prediction is stated so that a single experiment could refute it.

IX. Conclusion The Cell That Could Not Clear Itself

The companion architecture proposed that Alzheimer's disease is a fifty-year front of failure that crosses the brain from brainstem to cortex, changing its substrate as it goes. This paper has asked what fails *beneath* that front, in every phase, and has found a single answer: the cell's capacity to clear and renew itself. Autophagy is not a contributor to Alzheimer's disease in the way a risk factor contributes to a statistic. It is the system whose collapse the disease *is*, expressed as a mitochondrial failure in the brainstem neuron, a lipid failure in the hippocampal microglion, and an endosomal–proteostatic failure in the cortical synapse — one machinery, three cargoes, three cells, one half-century.

To see the disease this way is to see why its proteins have been so difficult to defeat. Amyloid in the plaque is the gravestone of a neuron that could not digest its own contents; intraneuronal Aβ is cargo the autophagosome could not seal or the lysosome could not dissolve; the effector microglion is, in part, a cell that drowned in undigested lipid; the late, self-sustaining loop is the disease manufacturing, through lipid peroxidation, the very poison that disables the pump on which all clearance ends. The proteins are real and each matters in its phase, but they are, to a degree the

field has been slow to accept, the visible residue of an invisible failure of housekeeping — and a therapy aimed at the residue rather than the housekeeping addresses the symptom of the lesion rather than the lesion.

Where autophagy fits, then, is not in one box of the diagram but along its entire length. It is the spine on which the temporal architecture stands. And because it is a spine — a continuous system rather than a single step — it offers what no single-protein target can: a place to intervene in every phase of the disease, provided only that the intervention is matched to the step that is failing and the decade in which it fails. The cell that could not clear itself is the cell at the centre of Alzheimer's disease. Teaching it to clear again, phase by phase and early enough to matter, is the therapeutic programme that a temporal theory of clearance makes not only conceivable but specific.

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