THE SENESCENT FRONT

Which Cells Age Out, and When — Cellular Senescence as the Cell Biology of Aging Across the Temporal Architecture of Alzheimer's Disease

Amitosenescent Ignition · The SASP Bridge · The Dystrophic Bridgehead
The Senescent Proteolytic Turn · Senescent Disintegration

A Dissertation Submitted in Partial Fulfillment of the Requirements for the

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A cross-section through the arc — companion to The Temporal Architecture of Collapse — drawing one biological lens, cellular senescence, through all three phases to supply the cell biology the architecture's word "ageing" had left unexplained.

“The architecture said ageing at every station and left the word to fend for itself. But ageing, at the resolution of a single cell, is not a clock — it is a state: the cell that has stopped working and refuses to fall silent, broadcasting into its neighbourhood the secretome by which one aged cell makes a hundred more. Name that state, and the front acquires an engine.”

— ONS Methodology Working Notes, 2026

For Leonard Hayflick, who found the limit, and for Judith Campisi, who showed that the aged cell is never merely quiet.

THE COLLAPSE TRILOGY CROSS-SECTIONAL COMPANION

I. Convergent Synaptic Collapse

II. Homeostatic Microglial Collapse

III. Bioenergetic Collapse

— The Temporal Architecture of Collapse —

Cross-sections: The Vascular Phasing · The Genetic Architecture · The Viral Trajectory

The Biomarker Cascade · The Spectrum of Collapse

The Senescent Front ← this volume

This volume is the sixth cross-section through the temporal arc. Where the vascular, genetic, viral, biomarker, and cell-death cross-sections each draw a single variable through all three phases, the present volume draws *cellular senescence* — and finds it to be not one variable among others but the cell biology of the very word, *ageing*, on which the architecture silently rests: the amitosenescent neuron of Phase I, the dystrophic microglion of Phase II, and the senescent astrocytes, oligodendrocytes, and vessels of Phase III, joined beneath by one secreted current — the SASP and its CD38-driven NAD sink.

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Abstract

The Temporal Architecture of Collapse describes Alzheimer's disease as a stereotyped three-phase progression that crosses the brain over half a century — bioenergetic ignition in the locus coeruleus in the third decade, a homeostatic microglial bridgehead in the hippocampus in the sixth, synaptic disintegration of the perineuronal net in the eighth — held together by two mechanistically specified bridges and unified beneath the sequence by the age-dependent collapse of a single homeostatic system. But that account leaves one word doing enormous and unexamined work. It speaks throughout of *age-dependence*, of *ageing*, of the slow erosion that separates a survivable decade from a catastrophic one, without ever naming the cell biology that turns "ageing" from a clock reading into a causal mechanism. This dissertation proposes that the missing cell biology is *cellular senescence*: the stable, stress-induced exit from normal function, accompanied by a senescence-associated secretory phenotype (SASP), that has now been documented in every major brain cell type. Senescence is what "age-dependent" means at the resolution of a single cell.

We map senescence, cell type by cell type and decade by decade, onto the five stations of the temporal architecture, and we find that it does not merely accompany each phase — it supplies each phase's cell-biological engine. **Phase I** is the amitosenescence of post-mitotic brainstem aminergic neurons: DNA-damage-driven PARP-1 hyperactivation and NAD+ collapse push the locus-coeruleus neuron into a p21-marked senescence-like state, the first cell in the brain to age out. **The first bridge** acquires a second arm the original account did not name — the senescent neuron is not silent but secretory, and its SASP primes the very microglia whose noradrenergic brake is simultaneously being withdrawn. **Phase II** is where senescence is load-bearing and best-evidenced: the dystrophic microglia of Streit, the TGF-β/SMAD failure of von Bernhardi, and the lipid-droplet-accumulating microglia of Marschallinger are three descriptions of one senescent glial state that is, by the same phenotype, both clearance-incompetent and inflammatory — attack and failure as a single senescent fact. **The second bridge**, the Proteolytic Turn, is on this reading a SASP writ large: the matrix-metalloproteinase arm, the iron-Fenton arm, and the complement arm are three canonical SASP outputs converging on one matrix. **Phase III** is senescent disintegration — senescent astrocytes withdrawing glutamate buffering, senescent oligodendrocyte progenitors failing to remyelinate, senescent endothelium and pericytes breaching the barrier, and, beneath them, the CD38-driven NAD+ sink by which a peripheral SASP drains the bioenergetic reserve of a neuron fifty years and twelve centimetres from the first senescent cell.

We do not overstate the case. A central section of this dissertation is a validity ledger that grades each connection honestly, because senescence is a field in which nearly every marker overlaps with normal ageing, terminal differentiation, or activation, and in which the most important experiments — does clearing senescent cells prevent the disease, or merely correlate with it — have been performed in mice and not yet in humans. The microglial mapping is strong; the

neuronal and astrocytic mappings are mechanistically coherent but evidentially thinner; the direction of causation at several junctions remains genuinely open. What the mapping buys, even under honest grading, is threefold: it gives the temporal architecture the cell-biological substrate its own word "ageing" was standing in for; it reframes both bridges as senescence phenomena and thereby subjects them to the pharmacology of senolysis and senomorphism; and it predicts, sharply, that the therapeutic value of removing a senescent cell is entirely a function of *which decade* one removes it in — which is the temporal theory's signature claim, arrived at from the direction of the ageing cell rather than the ageing brain.

I. The Word the Architecture Left Unexplained

Age-dependence as an unpaid promissory note

Every serious theory of Alzheimer's disease is, in the end, a theory of ageing wearing a mechanism. The disease is overwhelmingly age-associated; incidence roughly doubles every five years after sixty-five; the single largest risk factor, dwarfing every genetic locus save the rarest autosomal-dominant mutations, is simply the number of years lived. The Temporal Architecture of Collapse takes this seriously in a way most frameworks do not — it makes time the organizing variable rather than a footnote, and it reads the changing identity of the "primary" molecule across five decades as the signature of one system failing through successive cell populations. Yet even that account, which is more honest about time than its rivals, leaves the crucial word unpaid. It says the locus coeruleus undergoes a "decades-long, age-dependent erosion of quality control." It says the microglial state collapses under "the chronic stress that arrives with the cell's own ageing." It says resilience is the survival of a system that most brains lose "with age." In each case *ageing* is invoked as a cause — but a cause is not a mechanism, and a clock reading is not a lesion. What, at the resolution of a single cell, *is* the ageing that the architecture keeps naming?

This dissertation answers: cellular senescence. Not as a competing theory — it is not one — but as the cell-biological layer that sits beneath the temporal architecture and supplies the mechanism its own vocabulary was standing in for. Where the architecture says a cell "ages," we ask *which stable, definable, potentially reversible cellular state* the ageing consists of; where it says a lesion is "age-dependent," we ask *what secreted programme* propagates that dependence from cell to cell and, eventually, from the periphery into the brain. The claim is not that senescence is the primary cause of Alzheimer's. The claim is that senescence is what "age-dependent" *means* — and that once the meaning is supplied, the temporal architecture gains a mechanism, a set of falsifiable predictions, and, not least, a pharmacology.

Senescence as the cell biology of a hallmark

Cellular senescence earns this role because it is not a peripheral curiosity but one of the twelve hallmarks of ageing catalogued by López-Otín and colleagues, and among the most causally implicated of them. Its defining move is a stable exit: a cell that has sustained enough macromolecular damage withdraws, permanently, from its normal programme — for a dividing cell, from the cell cycle; for a post-mitotic cell, from its differentiated function — and does not return. Were that the whole story, senescence would be a quiet, cell-autonomous retirement and of little tissue-level consequence. It is not the whole story. The senescent cell is metabolically and transcriptionally transformed, and above all it is *secretory*: it broadcasts a senescence-associated secretory phenotype of cytokines, chemokines, proteases, and complement components that remodels its neighbourhood, recruits immune cells, degrades matrix, and induces senescence in bystanders. A small number of senescent cells can, through the SASP, remodel an entire tissue. This is precisely the profile a mechanism needs if it is to convert the private, cell-autonomous erosions of the temporal architecture's Phase I into the tissue-level, self-propagating catastrophe of its Phase III. Senescence is the hallmark of ageing that has a paracrine reach — and paracrine reach is what a fifty-year, brain-crossing front requires.

II. What Senescence Is, and How Honestly We Can See It in the Brain

A constellation, not a stain

Before mapping senescence onto the disease we must be candid about how we recognize it, because the honesty of the entire enterprise depends on the honesty of its markers. Senescence is identified not by any single pathognomonic sign but by a constellation, no member of which is sufficient alone. The cell-cycle arrest is read from $p16^{INK4a}$ (the *CDKN2A* product), $p21^{Cip1/Waf1}$ (*CDKN1A*), and stabilized p53. The lysosomal compartment expands, yielding senescence-associated β-galactosidase activity at pH 6.0 and accumulating lipofuscin. The genome bears persistent damage — γH2AX foci that do not resolve, telomere-associated foci even in cells that no longer divide. The nucleus remodels, losing Lamin B1 and gaining senescence-associated heterochromatin. The mitochondria fragment, depolarize, and leak reactive oxygen while NAD+ falls. And over all of it plays the SASP — interleukin-6, interleukin-1α and β, interleukin-8, tumour necrosis factor, the matrix metalloproteinases 2, 3, and 9, the chemokines CCL2 and CXCL1, complement components, and extracellular vesicles.

The methodological caveat, stated up front rather than buried

Here is the difficulty that any responsible senescence paper must place at the front and not in a footnote: every one of those markers overlaps with something that is not senescence. SA-β-galactosidase stains many non-senescent macrophages, whose lysosomal compartment is large by trade. p16 marks some homeostatic microglia and is expressed in normal ageing brain. Lipofuscin accumulates in every long-lived post-mitotic cell whether or not it is senescent. γH2AX marks any cell with a double-strand break, senescent or merely stressed. In a dividing fibroblast, the irreversibility of the arrest can be demonstrated directly; in a post-mitotic neuron, which was never going to divide again in any case, the single most defining feature of senescence — a stable *cell-cycle* exit — is not even applicable, and one is forced to infer senescence from the secondary constellation alone. This is why a great many published claims of "brain senescence" rest on partial evidence, and why the burden this dissertation carries is not to assert that senescence is everywhere in the Alzheimer brain but to grade, connection by connection, how well each assertion is actually supported. The validity ledger of Section X is not an appendix to the argument; it is the argument's conscience, and the reader is asked to hold the mechanistic sections against it throughout.

III. The Senescence Map in Brief

Before defending it in detail the map is worth seeing whole. Read across the five stations of the temporal architecture, the disease resolves into a succession of senescent cell populations, each with a characteristic trigger, a characteristic secreted output, and a characteristic effect on the station that follows.

Phase I — Amitosenescent Ignition. *Decades 3–5. Locus coeruleus and brainstem aminergic neurons.* The senescent cell is a post-mitotic neuron; the trigger is DNA damage, PARP-1 hyperactivation, and NAD+ collapse; the marker is p21 and a persistent DNA-damage response; the effect is the first appearance of a neuronal SASP in the brain. *Evidential grade: moderate; the state is real but "senescence" in a neuron is a contested extension of the term.*

The SASP Bridge (Phase I → II). *The ascending LC projection, plus its secreted halo.* To the two arms the original architecture named — noradrenergic brake withdrawal and trans-synaptic tau seeding — the senescence lens adds a third: the senescent LC neuron's SASP is itself a microglia-priming signal, delivered to the same forebrain the brake is being lifted from. *Grade: emerging; the arm is mechanistically coherent and partly evidenced in tau models.*

Phase II — The Dystrophic Bridgehead. *Decades 6–7. Hippocampal and forebrain microglia.* The senescent cell is the microglion; the triggers are iron, chronic oxidative stress, and lipid overload; the markers are dystrophic morphology, p16/p21, and a florid SASP; the effect is a cell that is at once clearance-incompetent and inflammatory. *Grade: strong; this is the best-evidenced senescence axis in the disease.*

The Senescent Proteolytic Turn (Phase II → III). *The aggrecan–brevican sheath of the parvalbumin interneuron.* The three arms of the Proteolytic Turn — matrix metalloproteinases, iron-catalysed Fenton chemistry, complement priming — are three canonical SASP outputs converging on one matrix. *Grade: moderate; each arm is individually evidenced, their convergence is a synthesis.*

Phase III — Senescent Disintegration. *Decade 8+. Astrocytes, oligodendrocyte progenitors, vascular cells, and the denuded parvalbumin interneuron.* Multiple senescent populations act at once — glutamate-buffering failure, remyelination failure, barrier failure — on a neuron already stripped of its protective net. *Grade: mixed; astrocyte and OPC senescence are evidenced in models, their integration into this phase is proposed.*

The current beneath — the SASP/CD38/NAD+ sink. Running under all five stations is a single tissue-level economy: senescent cells drive CD38 expression on macrophages, CD38 hydrolyses NAD+, and the resulting sink drains the bioenergetic reserve that Phase I depended upon — closing a loop from the last phase back to the first. *Grade: strong in the periphery, inferential in the brain.*

The map has three properties worth stating in advance. It is *cell-type-sequential* — a different senescent population is load-bearing in each decade, which is why no single senescent cell type explains the whole disease. It is *secretion-coupled* — the stations are joined not only by anatomy but by the SASP, a diffusible currency that makes senescence a tissue phenomenon rather than a cellular one. And it is *validity-stratified* — the strength of evidence is not uniform across the map, and any honest reading must weight the microglial station far more heavily than the neuronal or astrocytic ones. It is the coupling by secretion, more than the sequence of cell types, that makes senescence a genuine mechanism for the architecture rather than a relabelling of it.

IV. Phase I Amitosenescent Ignition

The first cell to age out

The temporal architecture's boldest empirical anchor is that the first cell to show Alzheimer-type pathology is not cortical but a noradrenergic neuron of the locus coeruleus, bearing pretangle tau in early adulthood. The senescence lens asks a sharper question of the same cell: not only *does it accumulate pathology first*, but *does it enter a senescent state first* — and if so, what does that state do? The answer the emerging literature supports is that the locus-coeruleus neuron is a leading candidate for the brain's first senescent cell, and that its senescence is the cell-biological name for the "bioenergetic ignition" the architecture describes in the language of quality control.

The reasoning begins with why this neuron is uniquely exposed. It is autonomously pacemaking, firing tonically across the whole of waking life; it sustains long, thin, largely unmyelinated axons reaching broadly across the forebrain; and it maintains catecholamine synthesis, a chemistry that is itself a generator of oxidative and DNA damage. A cell of this profile lives permanently near the ceiling of its mitochondrial capacity and accumulates unrepaired genomic lesions faster than most. In a dividing cell that damage triggers the classical senescence programme through p53 and p16; in this post-mitotic neuron it triggers the post-mitotic variant — sometimes termed *amitosenescence* — in which a persistent DNA-damage response, PARP-1 hyperactivation, p21 induction, and mitochondrial dysfunction assemble the senescent constellation without the cell-cycle exit that is irrelevant to a neuron that will never divide again.

From DNA damage to the NAD+ collapse the architecture already named

The mechanistic bridge between senescence and the temporal architecture's Phase I is exact, and it runs through NAD+. Accumulating DNA damage hyperactivates PARP-1, the nuclear enzyme that consumes NAD+ as its substrate to synthesize the poly-ADP-ribose chains that mark sites of damage for repair. Chronic PARP-1 activation is therefore a chronic NAD+ drain, and NAD+ is the currency the architecture already identified as central to Phase I — starving the sirtuins, crippling mitochondrial biogenesis, and disabling the PINK1/Parkin mitophagy that would otherwise clear the failing organelles. The same NAD+ collapse that the bioenergetic account describes as the engine of custodial failure is, in the senescence account, the metabolic signature of the senescent state itself. The two descriptions are not rivals; they are the same event told from the direction of the ageing cell and the direction of the failing mitochondrion. Jurk and colleagues showed that aged post-mitotic neurons develop exactly this p21-dependent, DNA-damage-driven senescence-like phenotype with mitochondrial dysfunction and an interleukin-6 output; Riessland and colleagues showed that loss of the chromatin organizer SATB1 drives post-mitotic catecholaminergic neurons — the very neurochemical class of the locus coeruleus — into a p21-marked senescence with a pro-inflammatory secretome; and Herdy and colleagues found that aged human neurons accumulate senescence markers and that this burden is elevated in Alzheimer's disease.

Why ignition, in the senescent reading, is not silent but whispering

The architecture calls Phase I clinically silent, and at the level of cognition it is. But the senescence lens revises the silence in one important respect. A merely damaged neuron is quiet; a *senescent* neuron is secretory. If the locus-coeruleus neuron enters amitosenescence in the third and fourth decades, then from that point it is not passively degrading but actively broadcasting a low-grade SASP — interleukin-6, interleukin-1, chemokines — into the brainstem parenchyma and, through the vasculature, into the systemic compartment. This is the first appearance of the disease's secreted current, decades before any plaque, and it reframes the prodromal disturbances of sleep, mood, and arousal that the architecture attributes to lost aminergic tone as, in part, the earliest clinical shadow of a neuronal SASP. The silence of Phase I is the silence of a whisper, not of an empty room — and the whisper is the first word of the bridge.

V. The First Bridge The SASP and the Withdrawn Brake

The temporal architecture's first bridge is its most elegant structural claim: that the same locus-coeruleus axons carry, to the same forebrain, both the withdrawal of noradrenergic suppression of microglia and the trans-synaptic seeding of templated tau — one projection executing both the loss of regulation and the delivery of pathology. The senescence lens does not displace this account; it adds a third arm carried on the same anatomy and arriving in the same epoch, and in doing so it tightens the bridge.

The senescent neuron as a microglial primer

The withdrawal-of-the-brake arm is a *subtraction*: noradrenaline, acting through microglial β2-adrenergic receptors and the Gs–cAMP–PKA axis, tonically restrains microglial NF-κB and inflammatory transcription, and when the coeruleus degenerates that restraint is lifted. The senescence lens adds a matching *addition*. The same coeruleus neurons that are ceasing to supply the noradrenergic brake are, if they are senescent, simultaneously supplying a SASP that does the opposite of a brake — an interleukin-1 and interleukin-6 and chemokine signal that actively primes microglia toward the post-homeostatic transition. The forebrain microglion in the sixth decade is therefore caught between a lifted foot and a pressed accelerator: the inhibitory tone it depended on is falling at the very moment a pro-inflammatory secretome from senescent upstream neurons is rising. Two arms, one subtractive and one additive, both consequences of the same senescing nucleus, both delivered to the same hippocampus. This is why the transition out of Phase I is not a gap the architecture must wave across but a mechanism with a named secreted cause.

Senescence-primed seeding, and the honest limit

There is a plausible third coupling, and honesty requires marking it as plausible rather than established. Senescent neurons, through SASP-driven inflammation and their own failing proteostasis, are more prone to accumulate and release aggregation-competent tau, and the inflammatory milieu a SASP creates is known to facilitate the LRP1- and heparan-sulfate-mediated uptake that the seeding arm depends on. It is therefore reasonable to propose that neuronal senescence *potentiates* the tau-seeding arm — that a senescent coeruleus is not only a leakier tau source but seeds into a more receptive, inflamed forebrain. Bussian and colleagues supplied the strongest indirect support: in a tauopathy model, genetically clearing p16-positive senescent glia prevented tau pathology and cognitive decline, demonstrating that senescence is upstream of, not merely concurrent with, tau spread. But that experiment cleared *glia*, not neurons, and it was performed in mice; the specific claim that senescence of the coeruleus neuron potentiates its own tau seeding remains, for now, a coherent hypothesis rather than a demonstrated fact. The bridge is real; this particular plank of it is still being laid.

VI. Phase II The Dystrophic Bridgehead

If Phase I is where senescence is coherent but contested, Phase II is where it is load-bearing and, by the standards of this difficult field, well-evidenced. The homeostatic microglial collapse that the architecture places at the centre of the disease *is* microglial senescence — and three literatures that grew up separately are, on this reading, three descriptions of one senescent glial state.

One senescent state under three names

The first description is morphological and belongs to Streit. Long before "senescence" was fashionable in neuroscience, Streit documented in the human Alzheimer brain a population of *dystrophic* microglia — deramified, beaded, spheroid-bearing, fragmenting — that he explicitly named senescent, that accumulate iron and ferritin, and that spatially associate with pretangle tau and precede neurodegeneration rather than follow it. The second description is signalling and belongs to von Bernhardi: chronic oxidative stress dysregulates the TGF-β/SMAD programme that Butovsky showed maintains the homeostatic microglial signature, producing a cell that is simultaneously pro-inflammatory and clearance-incompetent — active but useless, which is the functional signature of senescence. The third description is metabolic and belongs to Marschallinger: the lipid-droplet-accumulating microglion of the ageing brain, gorged on myelin debris, with impaired phagocytosis, elevated reactive oxygen, and a proinflammatory secretome — a state Marschallinger's own transcriptomics mark as distinct from disease-associated microglia and consonant with senescent exhaustion. Morphology, signalling, metabolism: three windows onto a microglion that has aged out of its custodial competence and into a secretory, damaging idleness.

Attack and failure as a single senescent fact

The deepest claim of the architecture's Phase II is that the long debate over whether Alzheimer microglia are *harmful* (attacking synapses) or merely *insufficient* (failing to clear pathology) is a false dichotomy, because at the perineuronal net attack and failure are the same act. The senescence lens explains *why* they are the same act, at the level of cell state. A senescent cell is defined precisely by the conjunction the debate treats as paradoxical: it has lost its constructive function *and* gained a destructive secretome, not as two separate lesions but as two faces of one programme. A senescent microglion cannot clear debris — that is the failure — and by the same senescent transformation it secretes proteases, cytokines, and complement — that is the attack. There is no version of the senescent state that is purely one or the other, which is exactly the architecture's claim about Phase II, now grounded in a defined cellular phenotype rather than asserted as a happy coincidence. The false dichotomy dissolves because it was always a single cell biology described from two sides.

The nomenclature problem, not swept under the rug

Intellectual honesty requires confronting the field's central unresolved question here rather than eliding it: the relationship between *senescent* microglia and the *disease-associated microglia* (DAM/LDAM) taxonomies is genuinely unsettled. The signatures overlap — both feature APOE, lipid handling, lysosomal expansion, and loss of homeostatic markers — but they are not identical, and the field has not converged on whether senescence and the DAM programme are distinct states, overlapping states, or points on a continuum from reactive to exhausted. This dissertation takes the ecumenical position that "microglial senescence" names the *terminal, exhausted, SASP-dominant* pole of the post-homeostatic space — the dystrophic end-state toward which the DAM and LDAM trajectories tend under chronic stress — while acknowledging that the transcriptional cartography is still being drawn and that a cleaner nomenclature may eventually redraw these boundaries. What is not in doubt is that a functionally senescent microglial population exists in the Alzheimer hippocampus, that it is inflammatory and clearance-incompetent, and that it is the load-bearing cell of Phase II.

Astrocyte senescence enters at the flank

Phase II is also where a second glial senescence begins, one the original architecture underweights: the senescent astrocyte. Bhat and colleagues documented astrocyte senescence in human Alzheimer cortex; Chinta and colleagues showed environmental-toxin-induced astrocyte senescence driving neuropathology in a Parkinson's model. The senescent astrocyte loses the glutamate transporter EAAT2/GLT-1 and downregulates glutamine synthetase while raising p16, p21, and a strong SASP — which means it withdraws the glutamate buffering on which the parvalbumin interneuron depends. In the temporal frame this is a Phase-II-onset lesion that does its cognitive damage in Phase III, and it is one of the clearest sites where the senescence map fills a gap the trilogy itself flagged as under-developed.

VII. The Second Bridge Senescence as the Proteolytic Engine

The architecture's second bridge, the Proteolytic Turn, was its most under-described boundary until it was specified as a three-armed convergence on the perineuronal net: a matrix-metalloproteinase arm driven by the NLRP3–IL-1β axis, an inorganic arm of iron liberated from ferroptotic oligodendrocytes catalysing Fenton chemistry on the matrix, and a complement arm tagging the sheath for removal. The senescence lens makes a compact and, I think, genuinely clarifying

observation: *all three arms are canonical outputs of the senescence-associated secretory phenotype*. The Proteolytic Turn is a SASP writ large — the point at which the accumulated senescent burden of Phase II is discharged onto a single structure.

Arm one — the SASP is a protease programme

The matrix-metalloproteinase arm scarcely needs translation into senescence terms, because MMP-2, MMP-3, and MMP-9 are among the most reliably reported members of the SASP across every senescent cell type in which the secretome has been characterized. When the architecture describes the late-Phase-II microglion switching from a cytokine-secreting to a matrix-digesting programme under IL-1β drive, it is describing the maturation of a SASP from its inflammatory to its proteolytic register — a transition well documented in senescent cells generally, in which sustained interleukin-1 signalling amplifies metalloproteinase output. Crapser's demonstration that microglia proximately drive perineuronal-net loss in the Alzheimer brain is, on this reading, a demonstration that a *senescent* microglial SASP is the proximate cause. The protease arm is not merely compatible with senescence; it is one of senescence's defining exports.

Arm two — iron is both cause and consequence of glial senescence

The inorganic arm couples to senescence at both ends. Streit's dystrophic — senescent — microglia are *defined in part by iron and ferritin accumulation*, and the Fenton chemistry that iron enables is a generator of the very oxidative DNA damage that drives cells senescent in the first place. So the iron liberated onto the perineuronal net in the Proteolytic Turn is, upstream, a *cause* of the glial senescence of Phase II, and, downstream, an *effector* of the matrix digestion of Phase III — a single inorganic species threading cause and effect through the senescent state. The net, an avid iron sink through its sulfated glycosaminoglycans, becomes a locus of Fenton catalysis precisely where senescent, iron-laden microglia have congregated. Arm two is not an inorganic accident bolted onto a cellular story; it is the chemistry by which senescence propagates itself and then discharges onto the matrix.

Arm three — complement is a SASP component with a pruning history

The complement arm completes the identification. C1q and the classical-cascade components that opsonize the perineuronal net and license its microglial stripping are themselves reported SASP constituents, secreted by senescent cells across tissues, and their deposition in the Alzheimer brain follows the geography of prior senescent damage. Hong, Stevens, and colleagues showed that complement and microglia mediate early synapse loss and that removing C1q or C3 is protective; the senescence reading adds that the complement they deposit is, in part, a senescence secretome retracing a developmental pruning programme that senescent cells inappropriately reawaken. Three arms — proteases, iron, complement — and each of the three is a face of the SASP. The Proteolytic Turn is the moment the tissue's senescent burden, accumulated cell by cell across the sixth and seventh decades, is spent on the one structure whose loss tips the disease into its terminal phase.

VIII. Phase III Senescent Disintegration

Phase III in the architecture is the digestion of the perineuronal net, the denuding of the parvalbumin interneuron, and the collapse of excitatory–inhibitory balance into the self-sustaining circuit failure of dementia. The senescence lens finds Phase III to be the phase of *many* senescent populations acting at once on a neuron that has lost its defences — a convergence of secretomes rather than a single lesion.

The astrocyte's withdrawn buffer

The senescent astrocyte, whose induction began at the Phase II flank, does its cognitive damage here. Stripped of EAAT2, it can no longer clear synaptic glutamate; the parvalbumin interneuron, already the most metabolically extravagant and now the most exposed neuron in the cortex, is subjected to a rising excitatory and excitotoxic load exactly as its protective net is being digested. The senescent astrocyte and the senescent microglion thus attack the same cell from two sides — one removing the matrix, the other removing the buffer — and the convergence is why the parvalbumin interneuron, and not some hardier cell, is the disease's final substrate.

The oligodendrocyte lineage and the vasculature

Two further senescent populations enrich Phase III. Zhang and colleagues showed that amyloid drives oligodendrocyte progenitor cells into senescence around plaques, that these senescent OPCs fail to differentiate into remyelinating oligodendrocytes, and — critically — that a senolytic clearing them alleviated pathology and cognitive deficits in an Alzheimer model, one of the field's cleaner causal demonstrations. Their senescence also feeds arm two of the previous bridge, since dying and dysfunctional oligodendrocyte-lineage cells are a source of the liberated iron. And the vascular compartment senesces in parallel: senescent brain endothelium and pericytes lose barrier competence, and their SASP admits systemic inflammatory and toxic signals — closing the anatomical route by which a peripheral senescent burden reaches the parenchyma. Each of these is individually evidenced in models; their integration into a single Phase III convergence is the synthesis this dissertation proposes, and it is graded accordingly in Section X.

The denuded interneuron, and the question of its own senescence

The architecture holds that the parvalbumin interneuron, once stripped of its net, enters an oxidative-substrate-failure trajectory that does not spontaneously reverse. The senescence lens poses a final, still-open question: does the denuded interneuron itself become senescent? Dehkordi and colleagues, profiling senescent cells in human Alzheimer brain by single-nucleus sequencing, found a senescent *neuronal* population marked by CDKN2D/p19 and associated with tau — direct evidence that neurons in the Alzheimer brain do enter senescence-like states in situ. Whether the specific parvalbumin interneuron does so, and whether that senescence is the irreversible "non-spontaneously-reversing" trajectory the architecture describes, is not established. But the possibility is structurally satisfying: it would make the disease's first cell and its last cell instances of the same cellular fate — amitosenescence of a metabolically extravagant neuron — separated by fifty years and the entire secreted history in between.

IX. The Current Beneath the Sink — SASP, CD38, and the NAD+

The temporal architecture argues that beneath its five-station sequence runs a single unifying current — one homeostatic system failing through successive cell populations. The senescence lens can name that current with unusual precision, and in doing so it closes a loop the architecture leaves open.

The current is the senescence-associated secretory phenotype considered as a *tissue economy* rather than a per-cell output, and its most consequential channel is the NAD+ sink discovered by Chini, Covarrubias, and colleagues. Senescent cells, through their SASP, drive the upregulation of CD38 — an NAD+-hydrolysing ectoenzyme — on tissue-resident and infiltrating macrophages. CD38 then consumes NAD+ catalytically, and because NAD+ is a diffusible, shared metabolic currency, the effect is not confined to the senescent cell or even its immediate neighbours: it is a systemic and regional *drain* on the bioenergetic reserve of every cell in the vicinity, senescent or not. This is the mechanism by which peripheral inflamm-ageing — the accumulating senescent burden of the ageing body — propagates into central bioenergetic failure without requiring that any given neuron carry a cell-autonomous mitochondrial defect.

The loop this closes is the deepest structural payoff of the entire mapping. Phase I began with NAD+ collapse in the locus coeruleus. Phase II and III accumulate a large senescent burden across microglia, astrocytes, oligodendrocyte progenitors, and vasculature, centrally and peripherally. That burden, through the SASP-driven CD38 sink, *drives NAD+ down further* — feeding back onto the very bioenergetic scarcity that ignited the disease in Phase I. The temporal architecture is a front that crosses the brain in one direction, brainstem to cortex; the senescence current runs a return line beneath it, cortex-and-periphery back to the metabolic reserve of the beginning. A disease that was a one-way front becomes, through the SASP/CD38/NAD+ economy, a closed and self-amplifying loop — which is precisely why it accelerates once it is established, and why the "age-dependence" the architecture invoked is not a static risk multiplier but a positive-feedback engine that senescence supplies.

X. Assessing the Connections A Validity Ledger

The user of this framework is owed an explicit, unflattering accounting of how well each connection is actually supported, because the temptation in a synthesis this clean is to let the elegance of the mapping stand in for the strength of the evidence. It cannot. What follows grades each junction, states the strongest counter-consideration, and names the experiment that would settle it.

Strong connections

Microglial senescence as the Phase II cell biology. This is the load-bearing and best-evidenced link. Streit's dystrophic microglia are documented in human tissue, spatially associated with tau, and demonstrably precede neurodegeneration; von Bernhardi's and Marschallinger's frameworks converge on the same functionally senescent phenotype; and Bussian's genetic clearance of p16-positive glia *prevented* tau pathology in a mouse model, establishing that this senescence is causal and not merely correlative. *Residual doubt:* the DAM-versus-senescence nomenclature is unresolved, and the causal clearance experiments are murine. *Settling experiment:* single-nucleus transcriptomics of human resilience cohorts testing whether preserved cognition tracks with a lower senescent-microglial fraction independent of amyloid and tau load.

The SASP/CD38/NAD+ sink as a systemic-to-central current. The peripheral mechanism — senescent cells → CD38 → NAD+ decline — is directly demonstrated by Covarrubias and Chini. *Residual doubt:* its operation specifically within the brain parenchyma, as opposed to the systemic compartment, is inferred rather than shown. *Settling experiment:* regional brain NAD+ and CD38 quantification across Braak stages, with CD38 inhibition tested for parenchymal NAD+ rescue.

Moderate connections

Amitosenescence of the locus-coeruleus neuron as Phase I. The general phenomenon of post-mitotic neuronal senescence is evidenced (Jurk, Herdy, Dehkordi), and its induction in catecholaminergic neurons specifically is shown by Riessland. *Residual doubt:* whether "senescence" is even the right word for a post-mitotic cell that cannot exit a cycle it was not in is a live conceptual dispute, not merely an evidential gap; and the specific claim that the LC neuron is the *first* senescent cell is an extrapolation from its being the first *tau-bearing* cell. *Settling experiment:* age-stratified senescence-marker mapping of human locus coeruleus from the third decade onward, against matched cortex.

Senescence as the unifying cell biology of the Proteolytic Turn. Each of the three arms is individually a documented SASP output, and the identification is mechanistically tight. *Residual doubt:* the *convergence* of all three on the perineuronal net at one time is a synthesis assembled from separately evidenced parts, not an observation reported as such. *Settling experiment:* spatial proteomics of the peri-net microenvironment testing for co-localization of senescent-microglial markers with MMP-9, labile iron, and C4d.

Weaker or frankly proposed connections

Astrocyte senescence and glutamate-buffering failure in Phase III. Astrocyte senescence is documented in AD cortex (Bhat) and drives pathology in a Parkinson's model (Chinta), and EAAT2 loss is well established — but the specific causal chain *senescent astrocyte → EAAT2 loss → parvalbumin excitotoxicity → cognitive failure* is assembled, not demonstrated end-to-end. *Grade: coherent hypothesis.*

The senescent-neuron SASP as a third arm of the first bridge. Structurally attractive and partly supported by Bussian's upstream-of-tau result, but the specific arm — LC-neuron SASP priming forebrain microglia — has not been isolated. *Grade: emerging.*

Senescence of the parvalbumin interneuron itself. Dehkordi shows neuronal senescence in AD brain in general; its extension to the PV interneuron specifically, and its identity with the architecture's irreversible substrate-failure trajectory, is speculation offered for its structural elegance and flagged as such. *Grade: speculative.*

The two failure modes the ledger guards against

Two errors would discredit the whole enterprise, and naming them is part of resisting them. The first is *marker credulity* — treating SA-β-gal, p16, or lipofuscin as proof of senescence when each overlaps with ageing, activation, or terminal differentiation; every claim above is meant to rest on multi-marker or functional evidence, and where it rests on less, the grade says so. The second is *reverse causation* — senescence markers rising because a cell is dying of something else, rather than senescence driving the death. The single strongest guard against reverse causation is the genetic- and pharmacological-clearance experiment (Bussian, Zhang, Baker), which shows that *removing* senescent cells changes the outcome; that this class of experiment exists, and is positive, is why the microglial and OPC connections earn a higher grade than the astrocytic and neuronal ones, for which the clearance experiments in the relevant cell type have not yet been done.

XI. Falsifiable Predictions

A synthesis earns its keep by exposing itself to refutation. The senescent-front mapping generates predictions that are phase-resolved, cell-type-specific, and in several cases testable with existing methods.

On sequence. If the map is right, the *onset* of senescence markers will be time-ordered by cell type across the human lifespan — brainstem aminergic neurons first (third–fourth decade),

hippocampal microglia next (sixth–seventh), and astrocytes, oligodendrocyte progenitors, and vasculature last (eighth) — and this order will hold independently of, and earlier than, the corresponding amyloid and tau milestones. A senescent population appearing out of this order in well-powered human tissue would falsify the sequential claim.

On resilience. Cognitively resilient individuals carrying Alzheimer-range amyloid and tau will be found to carry a *lower senescent-cell burden* — particularly of senescent microglia — than demented individuals with matched pathology, and this difference will be independent of plaque and tangle load. If resilience proves unrelated to senescent burden, the claim that senescence is on the critical path fails.

On the SASP as connector. Interrupting the SASP pharmacologically (senomorphically) will slow the phase-to-phase transitions specifically, sparing the within-phase pathology — the bridges, being senescence-secretion phenomena, should be more SASP-sensitive than the phases themselves.

On phase-specific senolysis. This is the sharpest and most consequential prediction, and it is the temporal theory's signature claim in senescent dress: the benefit of removing a senescent cell will depend entirely on *which decade* it is removed in. Senolysis targeting microglia will benefit Phase II and be useless once Phase III is established; senolysis of the oligodendrocyte-progenitor and vascular compartments will matter in Phase III; and no single senolytic timing will benefit all phases. A senolytic that helps regardless of disease stage would falsify the phase-specificity at the heart of both this mapping and the architecture it serves.

On the NAD+ loop. Restoring NAD+ (through precursor supplementation or CD38 inhibition) will show its largest effect early, when the sink is nascent, and a diminishing effect once the senescent burden — and hence the CD38 drain — is large, producing a treatment-timing curve that inverts the usual assumption that later, sicker patients have more to gain.

XII. Therapeutic Implications Senolysis and Senomorphism by Phase

The mapping's practical dividend is a pharmacology the temporal architecture, phrased in the language of pathways, could only gesture at. Senescence is one of the few ageing mechanisms with a *dedicated* therapeutic armamentarium — senolytics that selectively kill senescent cells, and senomorphics that suppress the SASP without killing its source — and the map tells us, phase by phase, which to use and when.

The governing principle is a distinction the temporal frame makes unavoidable: *you cannot kill what you cannot replace.* A senescent, dividing-lineage cell — a microglion, an oligodendrocyte progenitor, a vascular cell — can be removed by a senolytic and replaced from a progenitor pool. A senescent post-mitotic neuron cannot; killing it forecloses the cognition it still supports. Therefore the phases divide cleanly by strategy. **Phase I**, resident in irreplaceable brainstem neurons, is a *senomorphic and metabolic* problem: NAD+ restoration, PARP-1 restraint, and SASP suppression to quiet the neuronal secretome — never senolysis of the neuron itself. **Phase II**, resident in replaceable microglia, is the *senolytic* window proper: the dasatinib-plus-quercetin combination that Gonzales and colleagues took into the first Alzheimer feasibility trial (with demonstrated CNS penetrance and reduced CSF inflammatory markers), fisetin, and the CNS-targeted Bcl-2/Bcl-xL inhibitors, deployed to clear the senescent microglial bridgehead before it discharges onto the net. **Phase III** is a *mixed and narrow* window: senolysis of senescent oligodendrocyte progenitors (validated in Zhang's model) and vascular cells may still help, but the denuded, possibly-senescent parvalbumin interneuron must be spared, and the emphasis shifts to matrix preservation and, again, senomorphic quieting of the residual secretome.

Two cross-cutting targets are not phase-bound. The NAD+ sink — through precursors or CD38 inhibition — acts on the current beneath every phase, and the temporal prediction is that it pays most when begun early. And senomorphic restoration of TGF-β/SMAD signalling, the homeostatic programme whose collapse *is* microglial senescence, is the one intervention with a mechanistic claim on the senescent state at its root rather than its outputs. The clinical grammar that follows is neither the field's failed single-target monotherapy nor an indiscriminate senolytic sweep: it is *phase-matched senotherapy* — senomorphic and metabolic upstream where the cells are irreplaceable, senolytic in the microglial midgame where they are not, and measured throughout at the perineuronal net, the compact readout on which the whole architecture converges.

XIII. Conclusion Ageing, Made Cellular

The Temporal Architecture of Collapse gave Alzheimer's disease a spine of time and named the two bridges that turn a chronology into a theory. But it carried, unpaid, the word on which every age-associated disease ultimately rests. It said *ageing*, again and again, as though the word were a mechanism. This dissertation has tried to pay the debt — to show that the ageing the architecture invoked has a cell biology, that the cell biology is senescence, and that senescence, mapped station by station onto the architecture, does not sit beside the theory but supplies the engine each of its phases was described as needing.

The mapping, taken whole, tells a single story in a new register. A metabolically extravagant neuron in the pons ages out first, in the third decade, into an amitosenescent state whose NAD+ collapse is the bioenergetic ignition by another name, and whose secretome is the first word of the disease. Its SASP, carried forebrain-ward alongside the withdrawn noradrenergic brake, primes a microglial population that ages out next, in the sixth decade, into the dystrophic, secretory, clearance-incompetent state in which attack and failure are revealed as two faces of one senescent fact. That senescent burden is discharged, through a secretome of proteases and iron and complement, onto the perineuronal net — the Proteolytic Turn recognized as a SASP writ large — and the denuding exposes the last extravagant neuron to a convergence of senescent astrocytes, oligodendrocytes, and vessels in the eighth decade. And beneath all of it runs the CD38-driven NAD+ sink, a return line by which the accumulated senescence of the end feeds back onto the bioenergetic scarcity of the beginning, closing the front into a loop and turning age-dependence from a risk multiplier into a positive-feedback engine.

We have graded the story honestly, because it would be a betrayal of the method to let its symmetry pass for proof. The microglial station is strong; the neuronal and astrocytic stations are coherent but thinner; the direction of causation at several junctions is genuinely open, and the decisive human clearance experiments remain to be done. But even under that honest grading the mapping earns its place, for three reasons that a less careful synthesis could not claim. It gives the temporal architecture the substrate its own vocabulary was borrowing on credit. It converts both bridges from anatomical hand-offs into senescence phenomena, and thereby into pharmacological targets. And it sharpens the architecture's signature claim to a fine point: that the worth of removing a senescent cell is entirely a function of the decade in which one removes it — that there is no senotherapy for Alzheimer's disease, only senotherapies, each with a window, each opening and closing on the clock the disease has been keeping since the third decade of a life. The disease has always been ageing made visible. What the senescent front adds is that ageing, at last, made cellular — and therefore made a target.

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