THE SILENCED ERASER

The Ungoverned Microglion and the Fall of Tau's Phosphatase — How the Lapse of the TGF-β/SMAD Standing Order, Through the DAM Transition and the NLRP3 Inflammasome, Disables PP2A, the Eraser to the Coerulean Pincer's Writer

The Two Fates of a Phosphate · The Standing Order · The Forgetting
The Reach to the Eraser · The Cycle That Outlives Its Spark

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The phosphatase companion to The Coerulean Pincer. That volume took the tau kinase glycogen-synthase-kinase-3β as its convergence and showed a dysregulated signal driving the writer of tau's phosphate from two sides. This one takes the tau phosphatase protein-phosphatase-2A as its convergence and shows the ungoverned microglion silencing the eraser: the lapse of the standing TGF-β/SMAD instruction, through the disease-associated transition and the NLRP3 inflammasome, gagging PP2A — so that tau, its writer floored and its eraser silenced, accumulates phosphate from both sides at once.

"Watch only the hand that writes, and you will miss the hand that was meant to erase — and the cell, next door, that reached across and stilled it. The tangle is not only what the kinase wrote; it is what the phosphatase was no longer permitted to rub out."

— ONS Methodology Working Notes, 2026

For those who read the tangle as the work of the writing enzymes alone, and so never asked who silenced the one enzyme whose entire office was to keep the protein clean — nor why the cell that silenced it had itself stopped being told what to be.

THE COLLAPSE FRAMEWORK MICROGLIAL & COERULEAN COMPANION

The Coerulean Pincer — *norepinephrine's two arms, driving the writer GSK-3β*

The Corruption of the Gardener — *the graded atlas of microglial dysfunction*

The Coerulean Shears — *MMP-9, the named instrument that cuts the matrix*

The Silenced Eraser (the ungoverned microglion silences the *eraser* PP2A) — this volume

This volume completes a balance the companion volumes had drawn from one side only. The phosphorylation of tau is a running equilibrium between the enzymes that add phosphate and the enzyme that removes it; *The Coerulean Pincer* drove the writer, and this dissertation silences the eraser. It argues that the tau phosphatase is disabled not from within the neuron but from without — by the microglion, which turns from keeper to saboteur only because it has itself lost the standing instruction that held it homeostatic. The transforming-growth-factor-β signal, read through SMAD, must be received without pause to hold the microglion in its quiescent character, its badges P2Y12 and CX3CR1 worn; let that instruction lapse — alongside the failing noradrenergic brake of the companion volume — and the cell forgets its restraint, passes through the TREM2–APOE-licensed disease-associated transition, arms itself with the NLRP3 inflammasome, and reaches across to the neuron to silence its tau phosphatase, by installing the methylesterase PME-1 and unleashing the inhibitor SET. Tau, its writer floored and its eraser gagged, accumulates phosphate from both sides; and the hyperphosphorylated tau it becomes re-activates the very inflammasome that silenced its eraser — a loop that, once lit, no longer needs the spark. An eraser silenced, unlike a neuron dead, can in principle be un-silenced.

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Abstract

A companion dissertation, *The Coerulean Pincer*, took the tau kinase glycogen-synthase-kinase-3β as its convergence point and showed how a single dysregulated signal — the excess norepinephrine of the failing locus coeruleus — drives that enzyme from two sides at once, cutting the reelin brake from outside the neuron and flooring the tau throttle from inside. That volume was written entirely on the side of the *writer*: the kinase that adds phosphate to tau. But the phosphorylation of tau is not the work of a writer alone. It is a balance — a standing equilibrium between the enzymes that add phosphate and the enzymes that remove it — and a balance can be tipped as surely by disabling the eraser as by driving the writer. This dissertation is written on the side of the eraser. It takes as its subject protein phosphatase 2A, the principal phosphatase of tau, the enzyme whose continuous work keeps the protein clean; it asks what silences that enzyme in Alzheimer's disease; and it finds the answer not in the neuron but in the cell that surrounds it — the microglion, turned from keeper to saboteur, reaching across the synaptic space to gag the neuron's own eraser.

The thesis of this volume is that the microglion is the agent that silences tau's phosphatase, and that it does so only because it has itself lost the standing instruction that held it in its proper character. The healthy microglion is not a fixed cell but a *continuously governed* one: its identity — its ramified, surveillant, debris-clearing, matrix-preserving character, marked at the surface by the homeostatic sensors P2Y12 and the fractalkine receptor CX3CR1 — is held in place by a tonic instruction it must receive without pause, the transforming-growth-factor-β signal read through the SMAD transcription factors. Withdraw that instruction and the microglion does not merely quiet; it forgets what it is. It downregulates its homeostatic checkpoints and, licensed by a TREM2–apolipoprotein-E transcriptional switch, transitions into the disease-associated state, and in the aged and lipid-burdened brain into its dysfunctional lipid-droplet-laden variant — cells that have exchanged surveillance for secretion. This forgetting is governed from two directions at once: by the lapse of the local TGF-β/SMAD order, and by the failure of the distal noradrenergic brake whose collapse the companion volume traced. Two governors hold the microglion at rest; both fail in the same disease, and the same cell is released by their joint failure.

The released microglion executes its new character through two instruments this dissertation names: the NLRP3 inflammasome, which converts a danger sensor into a caspase-1–driven engine of interleukin-1β, and matrix metalloproteinase-9, which unpicks the extracellular net. Through the first of these the microglion reaches the neuronal phosphatase. We trace two convergent routes by which microglial inflammation disables PP2A: an inflammasome route, in which NLRP3 activation drives tau hyperphosphorylation by deranging the neuronal balance of tau kinases and phosphatases, and a proteolytic route, in which the disease milieu drives the endogenous PP2A inhibitor SET — the inhibitor-2 of protein phosphatase 2A — to be cleaved and mislocalised from the neuronal nucleus into the cytoplasm, where it seizes and silences the

phosphatase. By either road the eraser is gagged; PP2A activity in the Alzheimer cortex falls measurably — by roughly a third of its tau-directed activity; and tau, its phosphates no longer removed, accumulates them — the writer of the companion volume now working against an eraser that has been silenced. The two dissertations converge, molecule for molecule, on the same residues of the same protein: the Pincer drove the kinase that writes them, this volume silences the phosphatase that would erase them, and tau is caught between a floored accelerator and a jammed eraser. And the trap, once sprung, sustains itself: the hyperphosphorylated tau the silenced eraser permits is itself a potent activator of the microglial NLRP3 inflammasome, so that the pathology closes a feed-forward loop — tau firing the inflammasome that disables the phosphatase that releases more tau — a cycle that, once lit, no longer needs the spark that lit it. We assemble the mechanism connection by connection, grade each in an explicit validity ledger — candid that the inflammasome-to-phosphatase step is the newest and least-settled joint, that the noradrenergic and TGF-β governors are established individually but never yet measured failing together, and that TGF-β signalling, like norepinephrine, is protective in its proper regime and injurious only in its lapse — and close on the mechanism's one redemption: an eraser that has been silenced, unlike a neuron that has died, can in principle be un-silenced.

I. The Two Fates of a Phosphate

There is a way of reading Alzheimer's disease, nearly universal in the tau literature, that this dissertation is written to complete rather than to overturn, and it is worth stating at the outset because its incompleteness is the opening through which the whole argument enters. The reading is that tau becomes pathological because it is *over-phosphorylated* — because kinases, chief among them glycogen-synthase-kinase-3β, add phosphate to the protein at the residues that detach it from the microtubule and drive it into the paired helical filament. The reading is correct. Tau in the tangle bears many times the phosphate of tau in the healthy neuron, and the enzymes that put it there are known, and the companion dissertation to this one, *The Coerulean Pincer*, was devoted to a single such enzyme and to the dysregulated signal that drives it. But a phosphate on a protein has two fates, not one, and a literature that watches only the enzymes of the first fate is watching only half of the balance whose derangement it seeks to explain.

For the phosphorylation state of tau is not a quantity that kinases set alone. It is a steady-state — a running equilibrium between the enzymes that add phosphate and the enzymes that take it away — and like every steady-state it is governed by both of its opposing rates at once. On one side stand the kinases: glycogen-synthase-kinase-3β foremost, with cyclin-dependent kinase 5 and the others, the *writers* that inscribe phosphate onto tau's serines and threonines. On the other side stands, principally, a single enzyme: protein phosphatase 2A, the *eraser*, whose continuous work strips those phosphates off again and returns tau to the clean, microtubule-binding state in which it does its

proper work. A healthy neuron holds tau lightly phosphorylated not because its kinases are idle — they are not — but because its eraser keeps pace with them, rubbing out very nearly as fast as they write. The tangle is what happens when that pace is lost. And the pace can be lost in two entirely distinct ways: the writer can be driven to write faster than any eraser could keep up, or the eraser can be silenced so that even an ordinary rate of writing accumulates. These are the two fates of a phosphate, and they define two distinct dissertations.

The Coerulean Pincer was the dissertation of the first fate. It took the writer as its subject, traced the dysregulated noradrenergic signal that drives glycogen-synthase-kinase-3β from two directions, and showed the accelerator floored. It said almost nothing about the eraser, and this was not an oversight but a division of labour, for the eraser deserves — and here receives — a volume of its own. This dissertation is the dissertation of the second fate. It takes protein phosphatase 2A as its subject and asks the question the writer-centred literature leaves unasked: not *what drives the kinase* but *what silences the phosphatase* — and, having found that the phosphatase is silenced, asks *by whom*.

The answer to *by whom* is the surprise that organises this volume, and it is worth stating plainly before it is earned. The neuronal phosphatase is not silenced by the neuron. It is silenced, this dissertation argues, from *outside* the neuron, by the cell that surrounds it and that in health is its keeper — the microglion. The tau eraser fails because the microglion, having lost its own proper character, reaches across the space between them and gags it. This is a claim about a cell more than about a molecule, and it obliges the dissertation to answer, before it can trace how the microglion silences the eraser, the prior question of why the keeper should have turned saboteur at all. That question has an answer as specific as the mechanism it precedes, and it is the second organising claim of this volume: the microglion turns because it has stopped receiving a standing instruction that it must receive continuously to remain what it is.

For the homeostatic microglion — the fine-processed, surveillant, debris-clearing, matrix-preserving cell of the healthy brain — is not a stable object that persists on its own. It is a *held* state, a character maintained against a constant tendency to drift, and the thing that holds it is a tonic signal the cell must read without pause: the transforming-growth-factor-β signal, transduced through the SMAD transcription factors, which enforces moment by moment the transcriptional programme that makes a microglion a microglion. Cut that signal and the cell does not merely fall quiet or grow sick; it *forgets its identity*, loses the very genes that define the homeostatic state, and slides into the disease-associated character in which it becomes the eraser's assassin. The microglion's identity, that is, is not a possession but a subscription — renewed continuously or lost — and the disease is in part the story of a lapsed subscription.

This dissertation therefore has the shape of a relay, and the relay is its architecture. At the upstream end is a standing instruction — TGF-β/SMAD — that keeps the microglion a keeper. In the middle is the microglion itself, which, when the instruction lapses (and when the distal

noradrenergic brake of the companion volume fails alongside it), transitions out of its homeostatic character, arms itself with an inflammasome and a protease, and becomes an engine of inflammation. At the downstream end is the neuronal phosphatase, PP2A, which that inflammation reaches and silences — so that tau, its eraser gagged and its writer (from the companion volume) floored, accumulates phosphate from both sides at once. The relay begins in the loss of a microglial instruction and ends in the silencing of a neuronal eraser, and the microglion is the transmission that carries the one failure into the other. To trace that transmission, joint by joint, and to grade each joint honestly, is the work of this dissertation. We begin at the downstream end, with the eraser itself, because everything upstream is written to explain its silence.

II. The Eraser — Protein Phosphatase 2A and the Balance It Holds

Because the whole argument of this dissertation converges on a single enzyme, that enzyme must be introduced first, and the balance it holds described, before the cell that silences it is named. If the reader held one molecule in mind through the companion volume, it was the kinase glycogen-synthase-kinase-3β. If the reader holds one molecule in mind through this one, it should be its opposite number: protein phosphatase 2A, the enzyme that undoes the kinase's work.

Protein phosphatase 2A is the principal phosphatase of tau. It is a ubiquitous, multi-subunit serine/threonine phosphatase — a scaffolding subunit, a catalytic subunit, and one of a family of regulatory subunits that direct it to its substrates — and among the many proteins it dephosphorylates, tau is one of the most consequential for this disease. Of the total tau-directed phosphatase activity in human brain, protein phosphatase 2A accounts for the large majority — on the order of seventy per cent by direct measurement; it is, by measured contribution, *the* enzyme that keeps tau dephosphorylated (Liu and colleagues, 2005). It acts directly on the protein, stripping phosphate from the very serine and threonine residues whose phosphorylation by glycogen-synthase-kinase-3β and its fellow kinases detaches tau from the microtubule, and in doing so it restores tau's capacity to bind and stabilise the microtubule — so that the phosphatase governs not merely a chemical mark but the protein's structural function (Sontag and colleagues, 1996). Where the kinase writes tau into dysfunction, the phosphatase erases it back into use. The two enzymes are antagonists at the same residues of the same protein, and the phosphorylation state of tau at any moment is the running score between them.

The eraser is the exact mirror of the writer. This dissertation asks the reader to hold the two enzymes side by side, because their symmetry is the analytic hinge of the whole corpus's account

of tau. Glycogen-synthase-kinase-3β is a constitutively active kinase, on by default, normally *held down*; its over-activity was the convergence of the companion volume. Protein phosphatase 2A is a constitutively active phosphatase, likewise on by default, normally *doing its work*; its *under*-activity is the convergence of this one. The companion volume drove the writer past the eraser's capacity to keep up. This volume silences the eraser so that even an ordinary writer outpaces it. The outcome at tau is the same in both — a rise in net phosphorylation — but the lever is opposite, and the biology that moves each lever is entirely different. To drive the kinase, the companion volume needed a signal that reaches inside the neuron and presses on the enzyme. To silence the phosphatase, this volume needs something that *removes* the phosphatase's activity — and the removal, we shall find, is worked from outside the neuron, by the microglion, through two mechanisms that meet at the enzyme.

The eraser is silenced in the disease — measurably, and by roughly a third. This is not a supposition the dissertation requires the reader to grant; it is one of the more secure quantitative facts in the biochemistry of Alzheimer's disease. The activity of protein phosphatase 2A toward tau is reduced in the Alzheimer brain relative to the aged control brain, and the reduction is substantial — on the order of a third of the enzyme's tau-directed activity (Gong and colleagues, 1995; Gong and colleagues, 1993). A neuron in which the tau phosphatase runs materially below its proper rate is a neuron in which the balance between writing and erasing has been shifted decisively toward phosphate, *independent of any change in the kinases*. Reduce the eraser's activity by a third and hold the writer constant, and tau's steady-state phosphorylation rises; the tangle is, in part, the sediment of an erasure that stopped keeping pace. That the phosphatase is down in the disease is the empirical anchor of this dissertation. Everything else it argues is an attempt to answer the question that measurement poses: *why* is the eraser running below its proper speed, and *what* slowed it?

The eraser has a natural enemy inside the neuron — its endogenous inhibitor. Protein phosphatase 2A does not run unopposed even in health. Its activity is set, in part, by a family of endogenous inhibitor proteins whose job is precisely to restrain it, and chief among them, for the purposes of tau, is a protein with several names and one function: SET, also called inhibitor-2 of protein phosphatase 2A, or I2PP2A, or (in an older literature) the template-activating factor. In the healthy neuron SET is largely sequestered in the nucleus, where its restraint of the phosphatase is held away from cytoplasmic tau. But SET can be moved, and cleaved, and when it is — when it leaves the nucleus for the cytoplasm and encounters the phosphatase there — it binds the enzyme and inhibits it, and tau, its eraser gagged by the inhibitor, is hyperphosphorylated (Tanimukai and colleagues, 2005). SET is the handle by which the eraser can be silenced from within, and, as we shall see, it is a handle the disease milieu turns. Fix this in place — a phosphatase that keeps tau clean, measurably slowed in the disease, and a built-in inhibitor that can be unleashed to slow it — and the target of the whole microglial assault comes into focus. The eraser can be silenced by unleashing its inhibitor, and it can be silenced by the broader derangement of the neuron's kinase–phosphatase balance. The microglion, we shall find, does both. To the microglion,

and to the instruction that keeps it from doing so, we now turn.

III. The Standing Order — TGF-/SMAD and the Continuously Renewed Identity of the Microglion

To understand why the microglion silences the eraser, one must first understand a fact about the microglion that is easy to state and strange to absorb: the homeostatic microglion is not a thing the brain *has* but a thing the brain *maintains*, against a constant tendency to lose it, by a signal that must be delivered without interruption. The cell's identity is a standing order, continuously served; and the disease is, in part, what happens when the order lapses.

The homeostatic microglion has a signature, and the signature is enforced, not intrinsic. The microglion of the healthy adult brain is a highly particular cell: small-bodied, elaborately ramified, its fine processes in ceaseless motion as they survey the parenchyma, clearing debris, pruning and supporting synapses, and leaving the extracellular matrix intact. This character has a molecular signature — a set of genes expressed by homeostatic microglia and by almost no other cell — and among its most reliable markers are the purinergic sensor P2Y12 (Haynes and colleagues, 2006), the fractalkine receptor CX3CR1 (Cardona and colleagues, 2006), and the transmembrane protein TMEM119. The signature is not, however, a fixed property that microglia carry with them wherever they go. It is *induced and maintained by the brain environment*, and the principal environmental signal that maintains it is transforming growth factor β. In its landmark demonstration, the microglial homeostatic signature was shown to be dependent on transforming-growth-factor-β signalling: microglia deprived of TGF-β lose their characteristic molecular identity, and TGF-β is required both to establish and to hold the unique signature — including the expression of P2Y12 — that distinguishes a microglion from every other myeloid cell (Butovsky and colleagues, 2014). The homeostatic microglion, that is, is a cell being continuously *told* to be a homeostatic microglion, and the teller is TGF-β.

The instruction is read through the SMAD relay. Transforming growth factor β acts through a canonical and well-mapped relay. The ligand engages a receptor complex — the type-II and type-I TGF-β receptor serine/threonine kinases — which phosphorylates the receptor-regulated SMAD proteins, SMAD2 and SMAD3; these partner with the common mediator SMAD4 and translocate to the nucleus, where they act as transcription factors upon the promoters of the homeostatic gene programme. The SMAD proteins are the intracellular readers of the instruction, the point at which a signal at the surface becomes a pattern of gene expression within — and the point, therefore, at which the instruction can be confirmed to have been *received*.

When TGF-β/SMAD signalling in microglia is disrupted, the cell loses its homeostatic restraint: silencing the pathway drives the microglion toward an activated, primed character — an altered morphology, the up-regulation of activation markers, and the secretion of inflammatory chemokines — an impairment of homeostasis its discoverers named in their very title (Zöller and colleagues, 2018). An honesty is owed here at once, and the ledger will record it: when the TGF-β receptor is deleted in the *adult* microglion, the core signature genes prove relatively robust, and it is the cell's quiescence and homeostatic restraint, more than its molecular identity wholesale, that the disruption undoes; the sweeping dependence of the signature on TGF-β is a fact of its *establishment* (Butovsky and colleagues, 2014) more than of its every-moment maintenance. The claim this dissertation needs, and the one the evidence supports, is the narrower and sufficient one: that ongoing TGF-β/SMAD signalling restrains the microglion from activation and holds it in its quiescent, non-inflammatory character, and that where the signalling lapses the restraint is lost (Zöller and colleagues, 2018; Spittau and colleagues, 2020). The instruction is not TGF-β in the abstract; it is TGF-β read through SMAD, and it is the SMAD-borne message on which the homeostatic *discipline* depends.

Identity as subscription: the order must be renewed, not merely once given. The feature of this signalling that matters most for the disease is that it is *tonic*. The homeostatic programme is not switched on once, in development, and thereafter self-sustaining; it is held up continuously against decay, and it requires the ongoing delivery of the signal to remain in force. This is what is meant by calling the microglion's *restraint* a subscription rather than a possession: the quiescent, non-inflammatory character of the cell is not switched on once and thereafter self-sustaining but is held up continuously by the ongoing signal, and where the signal falls away the restraint decays and the cell drifts toward activation (Zöller and colleagues, 2018; Spittau and colleagues, 2020). The homeostatic *discipline* has a half-life, and TGF-β/SMAD is what keeps renewing it before it expires. The practical consequence is severe and is the pivot of this whole dissertation: *anything that reduces the delivery or the reading of the TGF-β/SMAD instruction will, by that reduction alone, begin to release the microglion from the discipline that keeps it a keeper* — not by actively damaging it, but simply by ceasing to restrain it. The keeper does not need to be attacked to be lost. It needs only to be left un-instructed.

Why this matters for tau: the instructed microglion is the quiet one. The homeostatic microglion held in force by TGF-β/SMAD is, by its nature, a cell that does the neuron no harm and much good — it surveys, it clears, it preserves the matrix, and, crucially for this dissertation, it does *not* pour out the inflammatory mediators that, we shall find, silence the neuronal phosphatase. The markers of the state, P2Y12 and CX3CR1, are not merely labels; they are functional badges of a restrained character. The fractalkine receptor CX3CR1, in particular, is a checkpoint by which the neuron speaks to the microglion to keep it calm — its loss dysregulates the microglion toward neurotoxicity (Cardona and colleagues, 2006) and, in a tauopathy, accelerates tau pathology (Maphis and colleagues, 2015) — and its presence marks a microglion still under

neuronal governance. So long as the instruction holds and the badges are worn, the microglion is the neuron's keeper and the eraser's ally. It is only when the instruction lapses and the badges are shed that the cell becomes what the rest of this dissertation describes. The order that keeps the microglion homeostatic is, at one remove, the order that keeps the neuron's tau phosphatase safe. To follow how that order fails is the next step.

IV. The Two Governors — the Local Order and the Distal Brake

The microglion is not held at rest by one signal but by two, arriving from different sources and on different logics, and the disease disables both. The first is the local order this dissertation has just introduced — the paracrine TGF-β/SMAD instruction, delivered in the tissue and read within the cell. The second is the distal brake the companion volume traced — the noradrenergic tone broadcast from the locus coeruleus and read at the microglion's β-adrenergic receptors. Two governors, one local and one distal, hold the microglion in its proper character; and it is a fact of some weight for the whole corpus that both of them fail in Alzheimer's disease, in the same brain, over the same interval.

The local order lapses: TGF-β/SMAD signalling is impaired in the disease. The standing instruction of Section III is not a fixed feature of the aging brain; it weakens. TGF-β/SMAD signalling declines with age and is impaired in Alzheimer's disease, and the impairment is not a bystander to the pathology but a contributor to it: reductions in TGF-β/SMAD signalling promote both amyloid accumulation and neurodegeneration, so that a brain in which the instruction is failing is a brain more vulnerable to the disease's core lesions (Tesseur and colleagues, 2006). The impairment has been observed directly in the human brain: the type-II TGF-β receptor is reduced in the Alzheimer cortex in proportion to the pathology (Tesseur and colleagues, 2006), and the nuclear phospho-SMAD3 that carries the instruction into the nucleus is markedly decreased in tangle-bearing neurons, sequestered away from the nucleus by insoluble phosphorylated tau (Chalmers and Love, 2007). This last detail is worth pausing on, for it discloses a further loop the dissertation will meet again: the very phospho-tau that the failing instruction ultimately permits can itself sequester the SMAD reader, deepening the impairment of the instruction that let the tau form — pathology corroding the signal that would have restrained it. An honesty is owed: these impairments are measured chiefly in neurons and at the receptor, so the *microglial* share of the failing instruction is inferred from the shared ligand and readers rather than yet resolved cell by cell in the human disease. Whatever its proximate cause — the decline of the ligand, the failure of the

receptors, the sequestration or dysfunction of the SMAD readers — the net result is a microglial population that is receiving less of the instruction that would keep it homeostatic, and that therefore begins, on the logic of Section III, to lose its homeostatic character for no other reason than that it is being under-told what to be.

The distal brake fails: the noradrenergic governor collapses. The companion volume established the second governor in full, and this dissertation imports its conclusion rather than re-deriving it. The locus coeruleus — the brain's sole cortical source of norepinephrine, and, being constitutionally without a perineuronal net, the first structure in the brain to tangle — governs the microglial state through the β-adrenergic receptors the microglion carries. Norepinephrine from the locus coeruleus suppresses microglial inflammation and sustains the cell's clearance functions (Heneka and colleagues, 2010), and noradrenergic tone acting at the microglion's own β-adrenergic receptors holds its surveillance and its reactivity within a healthy band (Stowell and colleagues, 2019). As the companion volume traced in detail, this brake is deranged across the long middle passage of the disease — the failing coeruleus first broadcasting a pathological excess and finally collapsing into depletion — so that the microglion, on the distal axis as on the local one, loses the governor that had held it calm.

Two governors, one release. The importance of naming both governors together is that it explains a fact neither alone can: the completeness and the timing of the microglial turn. A cell held at rest by a single signal might be tipped by the failure of that signal; a cell held at rest by two convergent signals, both of which fail in the same disease over the same years, is not tipped but *released* — freed from restraint on two axes at once, with no remaining governor to hold the homeostatic programme in place. The local order and the distal brake are not redundant. They act through different receptors on different logics — TGF-β/SMAD enforcing the transcriptional identity of the cell, norepinephrine tuning its moment-to-moment reactivity — and their joint failure removes both the slow, deep maintenance of what the cell *is* and the fast, surface regulation of what the cell is *doing*. When both lapse, the microglion is unmade from two directions: it loses the instruction that renews its identity and the brake that restrains its behaviour, and it drifts, unopposed, toward the state in which it silences the eraser. That these two governors have each been established individually but never yet measured failing together in a single brain is the honest gap the ledger will record; the synthesis this dissertation offers is precisely that they *do* fail together, and that the microglial turn is their joint work.

V. The Forgetting When the Order Lapses, the Keeper Loses Its Name

Released from both governors, the microglion undergoes a transformation that the last decade of single-cell work has mapped in unprecedented detail. It is not a graded dimming of function but a *change of state* — a coordinated exchange of one transcriptional identity for another — and the language this dissertation prefers for it is the language of forgetting, because what the cell loses first is not its vigour but its name.

The homeostatic checkpoints are downregulated: the badges are shed. The first and most reliable event in the microglial turn is the loss of the homeostatic signature that Section III described. The very genes that TGF-β/SMAD had been maintaining — P2Y12, CX3CR1, TMEM119, and their fellows — are downregulated as the cell leaves its resting character, and this downregulation is the leading edge of the transition, detectable before the full activated programme engages. In the founding single-cell account of the disease-associated microglion, the transition proceeds in two steps: first a *checkpoint* stage, in which the homeostatic genes are suppressed, and only then a second stage in which the full activated programme is switched on (Keren-Shaul and colleagues, 2017). The order of events is telling. The cell does not add an aggressive character on top of an intact homeostatic one; it *first loses the homeostatic one*. It sheds its badges before it takes up its weapons. This is exactly the signature the standing-order model predicts: withdraw the instruction, and the first thing to go is the identity the instruction was maintaining. The forgetting precedes the aggression, because the forgetting *is* the withdrawal of restraint that the aggression requires.

The transition is licensed by a TREM2–APOE switch. The passage from the homeostatic state to the disease-associated one is not unregulated; it runs through a molecular checkpoint of its own, and the checkpoint is a transcriptional switch built on two of the disease's most important genes. The triggering receptor expressed on myeloid cells 2 — TREM2 — and apolipoprotein E together drive the programme: the TREM2–APOE pathway mediates the switch from the homeostatic microglial phenotype to the neurodegenerative, dysfunctional one, suppressing the homeostatic signature and installing the disease-associated programme in its place (Krasemann and colleagues, 2017). TREM2, sensing the lipids and debris of the injured parenchyma, licenses the second step of the transition and sustains the activated cell's metabolic capacity to carry it out (Keren-Shaul and colleagues, 2017; Ulland and colleagues, 2017), while apolipoprotein E — the single greatest genetic risk factor for sporadic Alzheimer's disease — is installed as a marker and driver of the new state. That the disease-associated transition should be gated by the two genes most strongly implicated in the disease's genetics is not a coincidence this dissertation invents; it is a convergence the field has independently reached, and it locates the microglial turn at the genetic heart of the disorder (Deczkowska and colleagues, 2018). The keeper

does not lose its name at random. It loses it through a licensed switch built on the disease's own risk genes.

An honesty owed at once: the transition is, in its intent, a defence. It must be entered here, and not buried, that the disease-associated microglion is not a straightforwardly malignant cell. The state it enters is, on the best reading of its biology, an *attempt at protection* — a cell mobilising to contain and clear the amyloid and the debris its quiescent predecessor could not (Keren-Shaul and colleagues, 2017). The dysfunction this dissertation traces is therefore, like so much in this disease, the collateral of a defence: the cell that silences the eraser is not trying to injure the neuron but to protect the tissue, and the matrix it degrades and the phosphatase it gags are casualties of a response mounted in good faith. The mechanism does not require the transition to be malign in intent for it to be destructive in effect — and it is the destruction in effect, not the intent, that this dissertation is obliged to trace. The gardener turned demolition-crew did not choose demolition; it was un-instructed, released, and provoked into a state whose collateral is the neuron's undoing.

The dysfunctional endpoint: the lipid-laden microglion of the aged brain. In the aged and lipid-burdened brain the transition reaches a further and frankly dysfunctional endpoint that this dissertation must name because it is the most clearly pathogenic of the states and the one most directly relevant to the inflammatory reach that follows. A subset of microglia in the aging brain accumulate lipid droplets and adopt a state — the lipid-droplet-accumulating microglion — that is defective in phagocytosis, high in the production of reactive oxygen species, and, decisively for what follows, strongly *pro-inflammatory*, secreting elevated inflammatory cytokines (Marschallinger and colleagues, 2020). This is the microglion that has travelled furthest from its homeostatic origin: it has exchanged surveillance for secretion, clearance for inflammation, and it is precisely the kind of cell whose secreted output, in the next sections, reaches the neuron and silences its eraser. Whether a given microglion becomes the leaner disease-associated cell or the lipid-laden dysfunctional one, the direction of travel is the same and the consequence for the neuron converges: a cell that has forgotten how to keep, and learned how to inflame.

The forgetting complete, the microglion is now a different cell — its badges shed, its transition licensed, its character exchanged for one built to secrete rather than to survey. It remains to arm it, and then to follow its reach to the eraser.

VI. The Weapons of the Ungoverned Cell — the Inflammasome and the Protease

The transitioned microglion is not merely quieter or sicker than its homeostatic predecessor; it is *armed*. It has acquired the molecular machinery to execute an inflammatory and matrix-degrading programme, and this dissertation names two instruments of that programme in particular, because it is through them that the microglion reaches out of its own body and into the neuron's. The first is an inflammasome; the second is a protease. The inflammasome is the instrument by which the microglion silences the eraser, and it receives the fuller treatment; the protease is the instrument by which it unpicks the matrix, and it ties this volume to the companion account of the extracellular net.

The NLRP3 inflammasome: a danger sensor turned engine of inflammation. The nucleotide-binding domain, leucine-rich-repeat and pyrin-domain-containing protein 3 — NLRP3 — is a cytosolic sensor of danger. Upon activation it nucleates a large multiprotein complex, the inflammasome, recruiting the adaptor ASC and activating the protease caspase-1, which in turn cleaves the inactive precursors of the inflammatory cytokines interleukin-1β and interleukin-18 into their mature, secreted, potent forms. In Alzheimer's disease this sensor is activated. NLRP3 is activated in the human Alzheimer brain and in mouse models of amyloid pathology, and its activation contributes materially to the disease: mice lacking NLRP3 or caspase-1 are substantially protected from amyloid deposition and cognitive decline (Heneka and colleagues, 2013). The inflammasome is the microglion's danger-response engine, and in the disease it runs — converting the cell's sensing of amyloid, debris, and, as we shall find, tau itself into a sustained output of interleukin-1β. This output is the currency in which the microglion pays out its new inflammatory character, and it is the signal that, delivered to the neuron, reaches the eraser.

Matrix metalloproteinase-9: the protease that unpicks the net. The transitioned microglion also secretes matrix metalloproteinase-9, a zinc-dependent gelatinase that degrades the components of the extracellular matrix — activated microglia are an established source of it in the injured central nervous system (del Zoppo and colleagues, 2007) — and it is, on the evidence of the companion corpus, the very cell that engulfs and dismantles the perineuronal net in the Alzheimer brain (Crapser and colleagues, 2020). This dissertation does not re-derive the matrix account, which its companion volumes on the reelin-staging surface and the perineuronal net have traced at length; it imports the protease here for two reasons. The first is completeness: the ungoverned microglion's two chief instruments — the inflammasome that inflames and the protease that degrades — are acquired together in the same transition, from the same loss of governance, and to name only the inflammasome would be to under-describe the cell. The second is convergence: the matrix the protease degrades is, in the companion account, the very surface on which the neuron's reelin-borne brake upon the tau kinase is staged, so that the same transitioned microglion attacks the writer's restraint (through the protease, in the companion volume) and the eraser's activity (through the inflammasome, in this one). One cell, two weapons, two sides of the same tau balance. Having named both, this dissertation now follows the first — the inflammasome and its cytokine — to the neuronal phosphatase.

VII. The Reach to the Eraser Two Routes from Microglial Fire to Neuronal Phosphatase

Here the relay reaches its critical joint: the passage from microglial inflammation, secreted into the extracellular space, to the silencing of the tau phosphatase inside the neuron. This is the newest and the least-settled step in the whole mechanism, and the dissertation treats it with the candour that novelty demands, tracing not one route but two convergent ones and grading each honestly in the ledger. Both begin in the inflammatory output of the transitioned microglion; both end at the silenced eraser; and their convergence is what gives the mechanism its force.

The first route: the inflammasome deranges the neuron's kinase–phosphatase balance directly. The most direct evidence that the microglial inflammasome reaches tau is also the most recent, and it is the empirical keystone of this dissertation. NLRP3 inflammasome activation drives tau pathology: in a tauopathy model, loss of the microglial inflammasome components NLRP3 or ASC reduced tau hyperphosphorylation and aggregation and rescued memory, while aggregated tau in turn activated the inflammasome (Ising and colleagues, 2019). The work resolves the downstream mechanism with a specificity this dissertation can build on, for it traced the inflammasome's reach into the neuron to the very enzymes that set tau's phosphorylation state. Removing the inflammasome diminished the activity of tau's *kinases* — the calcium/calmodulin-dependent kinase CaMKII-α, whose phosphorylation of tau at serine-416 fell accordingly, and glycogen-synthase-kinase-3β, the very writer that was the convergence of the companion volume — and, decisively for the argument of this one, it also lifted the *eraser*: the inflammasome-bearing animals carried elevated levels of PME-1, the methylesterase that holds protein phosphatase 2A in its inactive, demethylated form, and a corresponding shift of the phosphatase toward inactivity, while the protected animals lacking the inflammasome carried less PME-1 and a more active phosphatase (Ising and colleagues, 2019). The mechanistic reading is exact. The inflammasome does not phosphorylate tau with its own hands; it acts upon the neuronal machinery that governs tau's phosphorylation, and it drives that machinery in both of its senses at once — raising the kinases and, through the named regulator PME-1, lowering the phosphatase. The phosphatase arm of that balance — the eraser this dissertation is tracing — is thus reached by the microglial inflammasome, and reached in the direction of silence, by a mechanism the work names. And that the *same single study* finds the inflammasome moving both the writer (glycogen-synthase-kinase-3β) and the eraser (protein phosphatase 2A, through PME-1) is the empirical hinge on which this volume and its companion turn: the two dissertations' two enzymes are governed together, from one inflammatory source.

The cytokine carries the message: interleukin-1β drives tau phosphorylation. The currency of the inflammasome's reach is its cytokine, and the cytokine's effect on tau is established independently of the inflammasome literature. Microglia-derived interleukin-1β drives the hyperphosphorylation of neuronal tau: interleukin-1 acts upon the neuron to activate tau-directed kinases — through the p38 mitogen-activated-protein-kinase pathway in particular — and so raises tau phosphorylation (Li and colleagues, 2003). The same relationship is seen when inflammation is provoked in the intact animal: lipopolysaccharide-induced neuroinflammation exacerbates tau pathology in a tauopathy model, through the activation of a cyclin-dependent-kinase-5 pathway, establishing that a microglial inflammatory stimulus is sufficient to drive neuronal tau hyperphosphorylation in vivo (Kitazawa and colleagues, 2005). And reactive microglia, activated and stripped of their homeostatic restraint, drive tau pathology and contribute to the propagation of pathological tau through the brain (Maphis and colleagues, 2015). The chain from an inflamed microglion to a hyperphosphorylated tau is, on these lines, well laid: the transitioned cell secretes interleukin-1β; the cytokine engages the neuron; and the neuron's tau-phosphorylation machinery is deranged toward phosphate. The particular kinase engaged varies with the model — p38 in the interleukin-1 studies, cyclin-dependent-kinase-5 under the inflammatory challenge, CaMKII-α and glycogen-synthase-kinase-3β in the inflammasome work — but the *direction* is invariant across them all: a microglial inflammatory signal raises the neuron's net tau phosphorylation. This route reaches the balance chiefly by *raising the writers* and is included here both for its own weight and because it runs in parallel with the second route, which reaches the same balance by *lowering the eraser*.

The second route: the disease milieu unleashes SET to gag the phosphatase. The route most specific to the eraser is the one that runs through the phosphatase's own endogenous inhibitor, SET, introduced in Section II. In the healthy neuron SET is largely nuclear and its restraint of protein phosphatase 2A is held away from cytoplasmic tau. In the Alzheimer brain this containment fails. The endogenous inhibitors of protein phosphatase 2A, SET among them, are up-regulated in the disease, and their up-regulation is associated with the reduced phosphatase activity and the tau hyperphosphorylation that define the disorder (Tanimukai and colleagues, 2005). More than up-regulated, SET is *relocated and cleaved*. In the Alzheimer neuron the protease asparaginyl endopeptidase — legumain — is activated and cleaves SET at a defined asparagine residue; the cleaved fragments, which retain and even concentrate their inhibitory power, translocate with the enzyme from the nucleus into the cytoplasm, where they bind and inhibit protein phosphatase 2A, and the phosphatase so gagged permits the hyperphosphorylation of tau (Basurto-Islas and colleagues, 2013). The activation of asparaginyl endopeptidase and the cleavage and mislocalisation of SET are features of the disease neuron, and the inflammatory milieu of the ungoverned microglion — its cytokines, its oxidative output, its provocation of neuronal stress-response and lysosomal protease pathways, of which asparaginyl endopeptidase is one — is among the drivers that push SET out of the nucleus and into its inhibitory encounter with the phosphatase. This route reaches the balance by the mechanism most exactly opposite to the

companion volume's: not by adding drive to the writer but by *removing activity from the eraser*, through the unleashing of the eraser's own inhibitor.

Two routes, one silence. Set the two routes side by side and their relationship is that of convergence, not redundancy. The first route, the inflammasome-and-cytokine road, reaches the tau balance chiefly by raising the kinases and, on the direct evidence of the inflammasome work, by shifting the whole kinase–phosphatase balance toward phosphorylation (Ising and colleagues, 2019; Li and colleagues, 2003; Kitazawa and colleagues, 2005). The second route, the SET road, reaches the same balance by silencing the phosphatase specifically (Tanimukai and colleagues, 2005; Basurto-Islas and colleagues, 2013). They are not two names for one mechanism; they are two mechanisms that meet at the same enzyme — the inflammasome installing the methylesterase PME-1 that holds the phosphatase in its inactive form (Ising and colleagues, 2019), the disease milieu unleashing the cleaved inhibitor SET that binds and gags it (Tanimukai and colleagues, 2005; Basurto-Islas and colleagues, 2013) — and a neuron subject to both has its eraser silenced twice over, by two distinct inhibitors converging on one phosphatase. The measured reduction of tau-phosphatase activity in the disease — on the order of a third of its tau-directed activity (Gong and colleagues, 1995) — is the joint footprint of these convergent roads. And both roads begin in the same place: the microglion that has forgotten its instruction, transitioned out of its homeostatic character, and armed itself with the inflammasome. The reach from that cell to the neuronal eraser is the crux of this dissertation, and it is graded, joint by joint, in the ledger below.

VIII. The Convergence at the Phosphatase

The two dissertations — the companion volume of the writer and this volume of the eraser — were written to be read together, and this section is where they meet. The word "companion" earns its place only if the two accounts converge on a single point, and they do: they converge, molecule for molecule, on the phosphorylation state of tau, approached from its two opposite sides.

One balance, pushed from both ends toward phosphate. Recall the steady-state of Section I: tau's phosphorylation is the running score between the writers that add phosphate and the eraser that removes it. The companion volume, *The Coerulean Pincer*, drove the chief writer — glycogen-synthase-kinase-3β — from two directions, cutting the reelin brake that had held it down and flooring the noradrenergic throttle that pushed it up, so that the kinase wrote faster. This volume silences the eraser — protein phosphatase 2A — by two convergent routes, so that the phosphate the writer lays down is no longer removed. The two accounts are not rival explanations of the same fact; they are complementary halves of one balance, and they move it the same way by

opposite means. The companion volume raised the rate of writing; this volume lowered the rate of erasing; and tau, caught between a floored accelerator and a jammed eraser, accumulates phosphate that neither an ordinary writer nor an ordinary eraser would have permitted. To measure the driven kinase while ignoring the silenced phosphatase, or the silenced phosphatase while ignoring the driven kinase, is to measure one rate of a two-rate balance and to underestimate the derangement the two produce together.

Why the convergence produces more than the sum of its parts. It might be supposed that a driven writer and a silenced eraser simply add — that the tau phosphorylation under the joint assault is the phosphorylation from the floored kinase plus the phosphorylation from the gagged phosphatase. The kinetics of a steady-state suggest something worse. The phosphorylation level of a substrate governed by opposing enzymes is set by the *ratio* of the two rates, not their difference, and a ratio is moved multiplicatively when both of its terms are pushed. Raise the writing rate and lower the erasing rate together, and the steady-state phosphorylation rises further than either change alone would carry it, because each makes the other more consequential: phosphate laid down by a driven kinase persists longer when the eraser that would remove it is slowed, and an eraser slowed matters more when there is a driven kinase laying down phosphate for it to fail to remove. The floored accelerator and the jammed eraser are synergistic, not merely additive, in their effect on tau's phosphorylation — and the practical corollary is the same one the companion volume reached from its side: no experiment that drives the kinase while leaving the phosphatase intact, or silences the phosphatase while leaving the kinase quiet, can predict the derangement the intact disease produces. The balance must be studied as a balance.

The convergence as the disease's own logic. That both the writer and the eraser of tau should be deranged by the same upstream failure — the ungoverning of the microglion and the dysregulation of the locus coeruleus — is not a symmetry this dissertation has manufactured; it is a convergence the field had half-seen from each side without seeing the meeting. The tau-kinase literature gathered the disease's features under the over-activity of glycogen-synthase-kinase-3β; the tau-phosphatase literature gathered a parallel account under the under-activity of protein phosphatase 2A; and the two literatures have largely run in separate channels, each treating its enzyme as the story. What the two dissertations supply, read together, is the recognition that the writer and the eraser are governed by *one cell and one nucleus* — that the microglion, un-instructed and released, silences the eraser through the inflammasome while the same disease's noradrenergic dysregulation drives the writer, and that the earliest-failing systems of the brain reach tau's phosphorylation balance from both of its sides at once. That the two enzymes are governed together is not merely inferred from the two dissertations laid side by side; a single study, tracing the inflammasome's reach into the neuron, already caught it moving both — raising the activity of the writer glycogen-synthase-kinase-3β and, through PME-1, lowering the activity of the eraser protein phosphatase 2A in one and the same model (Ising and colleagues, 2019). The convergence the two volumes argue for from opposite directions has, at this one joint, already been observed. The

convergence is the point at which the microglial account of Alzheimer's disease and the noradrenergic account turn out to be describing the two ends of one lever, resting on one fulcrum: the phosphorylation state of tau.

Tau, phosphorylated from both sides. With its writer driven by the companion volume's pincer and its eraser silenced by this volume's inflammasome-and-inhibitor, tau is hyperphosphorylated as neither derangement alone could hyperphosphorylate it. It detaches from the microtubule; it aggregates into the paired helical filament and the neurofibrillary tangle; and it propagates from neuron to neuron across a matrix the same microglion's protease has already stripped of its barrier (Crapser and colleagues, 2020; Maphis and colleagues, 2015). The balance has been lost from both ends. What remains is to show that the loss, once complete, sustains itself — that the tau it produces is not merely the output of the mechanism but a new input to it.

IX. The Cycle That Outlives Its Spark Tau Re-Arms the Inflammasome

A mechanism that ran in one direction only — from lost instruction to silenced eraser to hyperphosphorylated tau — would be grave enough, but it would remain a cascade, dependent at every moment on the persistence of its original cause. The mechanism this dissertation traces is worse than a cascade, because it closes into a loop, and a loop, once lit, no longer needs the spark that lit it.

Tau activates the inflammasome that silences its eraser. The hyperphosphorylated tau that the silenced eraser permits does not merely accumulate as an endpoint. Released from degenerating neurons and taken up by microglia, aggregated tau is itself a potent activator of the microglial NLRP3–ASC inflammasome, and its activation of that inflammasome exacerbates tau pathology — both the pathology seeded from outside and the pathology arising within (Stancu and colleagues, 2019). Set this beside the reach of Section VII and the circuit closes. The inflammasome silences the eraser (Ising and colleagues, 2019); the silenced eraser permits the hyperphosphorylation of tau (Gong and colleagues, 1993; Tanimukai and colleagues, 2005); and the hyperphosphorylated tau activates the inflammasome (Stancu and colleagues, 2019), which silences the eraser again. Tau is at once the product of the loop and a fuel for it; the inflammasome is at once the silencer of the eraser and the sensor of the tau the silencing produces. What began as a response to the loss of a distant instruction becomes a self-sustaining cycle that manufactures its own continuation.

Why the loop matters: the mechanism becomes independent of its origin. The clinical significance of a feed-forward loop is that it severs the pathology from its initiating cause. The relay of this dissertation began upstream, in the lapse of the TGF-β/SMAD instruction and the failure of the noradrenergic brake — governor failures rooted in the aging brain and, for the coeruleus, in the earliest tau lesion of all. But once the loop of tau and inflammasome is closed, the pathology no longer depends on those origins to continue. Even were the upstream governors somehow restored — the TGF-β instruction re-served, the noradrenergic tone normalised — the tau–inflammasome cycle, already turning, could sustain the silencing of the eraser on its own, fuelled by the tau it has already produced. This is the mechanistic form of a familiar clinical fact: that Alzheimer's disease, once established, progresses with a momentum that seems indifferent to the removal of its early drivers, and that interventions effective in principle arrive too late in practice. The loop is the engine of that momentum. It is also the sternest argument for the timing this dissertation's therapeutics will urge: the loop must be reached *before* it closes, in the window when the pathology still depends on the upstream governors and can still be arrested by restoring them.

The loop and the amyloid. It should be entered here, as an honesty and not as a digression, that the same inflammasome sits at a comparable junction in the amyloid pathology: NLRP3 is activated in the amyloid-bearing brain and, when it or its caspase is deleted, permits enhanced amyloid clearance and reduced deposition — so that amyloid too both fires the inflammasome and is worsened by it (Heneka and colleagues, 2013). The tau loop this dissertation traces does not compete with that amyloid loop; it runs alongside it, through the same microglial engine, and the two share the inflammasome as a common hub. This dissertation's claim is not that tau is the inflammasome's only fuel but that the tau–inflammasome loop is a self-sustaining circuit in its own right, capable of silencing the eraser and driving the tangle independent of — and in concert with — the amyloid loop that shares its engine. The microglial inflammasome is the point at which the two great pathologies of the disease meet and feed one another, and the silenced eraser is one of the things they produce together.

X. The Validity Ledger

The discipline that separates synthesis from speculation is the graded ledger, each connection assigned a tier and the experiment that would settle it named alongside. The relay of this dissertation is only as strong as its weakest load-bearing joint, and the reader is owed an explicit accounting of where the argument stands on the ground and where it stands on inference.

Strong (imported, established) — protein phosphatase 2A is the principal tau phosphatase, and its tau-directed activity is reduced in the Alzheimer brain. Biochemically secure: PP2A accounts for roughly seventy per cent of tau-phosphatase activity in human brain and dephosphorylates tau at the pathological residues, restoring microtubule binding (Liu and colleagues, 2005; Sontag and colleagues, 1996), and its tau-directed activity is measurably reduced in the disease — on the order of a third (Gong and colleagues, 1995; Gong and colleagues, 1993). A candour on magnitude: the "~50%" figure sometimes quoted overstates the primary measurements, which report a decrease nearer a third; the defensible and sufficient claim is a substantial reduction, ample to shift a two-rate balance toward phosphate. This is the eraser whose silencing the dissertation describes, and its reduction in the disease is the empirical anchor of the whole argument.

Strong (imported, established) — the homeostatic microglial character depends on TGF-β signalling, read through SMAD. Directly demonstrated: the unique microglial homeostatic signature, including P2Y12, depends on TGF-β for its establishment (Butovsky and colleagues, 2014), and ongoing TGF-β/SMAD signalling restrains microglial activation and maintains homeostasis, its silencing driving an activated, primed, chemokine-secreting phenotype (Zöller and colleagues, 2018; Spittau and colleagues, 2020). An honest boundary the dissertation observes: deleting the TGF-β receptor in the *adult* microglion leaves the core signature genes relatively intact while abolishing the homeostatic restraint (Zöller and colleagues, 2018), so the strong claim is that TGF-β/SMAD holds the microglion's *quiescence and restraint*, not that every signature gene evaporates the instant the signal lapses. The "identity as subscription" framing is therefore applied throughout to the homeostatic *discipline*, which the evidence supports; the wholesale dependence of the molecular signature is a fact of its establishment more than of its minute-to-minute maintenance.

Strong (imported, established) — the microglion transitions from a homeostatic to a disease-associated state through a two-step, TREM2–APOE-licensed programme that downregulates the homeostatic checkpoints. Securely mapped at single-cell resolution: the two-step DAM transition with checkpoint downregulation (Keren-Shaul and colleagues, 2017), the TREM2–APOE drive of the dysfunctional phenotype (Krasemann and colleagues, 2017), the conserved sensor framing (Deczkowska and colleagues, 2018), and the dysfunctional, pro-inflammatory lipid-droplet endpoint in the aged brain (Marschallinger and colleagues, 2020). The forgetting of Section V stands on established ground.

Strong (imported, established) — the NLRP3 inflammasome is activated in Alzheimer's disease and contributes causally to pathology. Directly demonstrated: NLRP3/caspase-1 activation in human AD and mouse models, with protection on genetic deletion (Heneka and colleagues, 2013). The microglion's inflammatory instrument is real and consequential.

Strong (imported) — norepinephrine governs the microglial state, and its loss worsens pathology. The distal governor is established (Heneka and colleagues, 2010; Stowell and colleagues, 2019), and its derangement across the disease is the subject of the companion volume. This is imported, not re-derived, and is granted in full — and is the reason the microglial turn is attributed to the *joint* failure of two governors, not to TGF-β/SMAD alone.

Strong (imported) — SET/I2PP2A is up-regulated, cleaved, and mislocalised in the Alzheimer neuron, where it inhibits PP2A and drives tau hyperphosphorylation. Directly shown: up-regulation of the endogenous PP2A inhibitors in AD (Tanimukai and colleagues, 2005) and the cytoplasmic translocation and cleavage of SET yielding PP2A inhibition and tau hyperphosphorylation (Basurto-Islas and colleagues, 2013). The SET route to the silenced eraser stands on established biochemistry within the neuron; what is inferred is the *causal attribution of SET's mislocalisation to the microglial inflammatory milieu* (graded below).

Strong (imported) — microglia-derived inflammation drives neuronal tau hyperphosphorylation. Directly demonstrated on multiple lines: IL-1β raises tau phosphorylation via p38 (Li and colleagues, 2003), inflammatory challenge exacerbates tau via CDK5 in vivo (Kitazawa and colleagues, 2005), and reactive microglia drive and spread tau pathology (Maphis and colleagues, 2015). That microglial inflammation reaches tau is established; the *specific reach to the phosphatase* is the newer claim (below).

Moderate-to-strong — the NLRP3 inflammasome drives tau pathology by deranging the neuronal balance of tau kinases and phosphatases, and its reach includes the phosphatase. Directly shown that inflammasome loss reduces tau hyperphosphorylation and aggregation, acting on the neuronal enzymes that set tau's phosphorylation state: the inflammasome raises the kinases CaMKII-α (with the corresponding rise in tau serine-416 phosphorylation) and glycogen-synthase-kinase-3β and, through elevated levels of the methylesterase PME-1, shifts protein phosphatase 2A toward its inactive form (Ising and colleagues, 2019). This is the empirical keystone linking the microglial inflammasome to the tau balance, and — importantly for this dissertation — it already reaches the *phosphatase*, through a named regulator, and not the kinases alone. The claims the present dissertation adds are the emphasis on the phosphatase arm as load-bearing and its integration with the SET route; the honest caveat is that the PME-1 finding is, at present, a set of measurements in one model, strengthened but not yet replicated. *Settling experiment: replicate, with a direct PP2A-activity and PME-1 time-course, whether the inflammasome's tau effect is carried substantially by phosphatase inactivation (PME-1 and SET) alongside kinase activation, as a function of microglial NLRP3 status (genetic deletion, pharmacological inhibition).*

Moderate — the microglial inflammatory milieu is the driver that mislocalises and cleaves SET, silencing PP2A in the neuron. The SET mislocalisation is established (Basurto-Islas and colleagues, 2013) and the inflammatory drivers of neuronal stress and protease

pathways are plausible causes, but the specific causal chain from a microglial cytokine to SET cleavage to PP2A inhibition has not been demonstrated as a single measured sequence. *This is the weakest load-bearing joint of the SET route. Settling experiment: expose neurons to defined microglial inflammatory output (or IL-1β) and measure SET cleavage, SET cytoplasmic translocation, PP2A activity, and tau phosphorylation, with and without inflammasome or cytokine blockade.*

Moderate — TGF-β/SMAD signalling is impaired in the Alzheimer brain, contributing to the microglial turn. The impairment is supported on more than one line — the type-II receptor reduced in the AD cortex in proportion to pathology (Tesseur and colleagues, 2006), and nuclear phospho-SMAD3 markedly decreased in tangle-bearing neurons, sequestered by insoluble phospho-tau (Chalmers and Love, 2007) — and the mechanistic consequence for microglia follows from the maintenance role (Butovsky and colleagues, 2014; Zöller and colleagues, 2018). Two honesties: these impairments are measured chiefly in neurons and at the receptor, so the *microglial* share of the failing instruction is inferred from the shared ligand and readers rather than resolved cell by cell; and the demonstration that reduced TGF-β/SMAD *tone* is what releases the disease-associated microglial transition in the human disease is an inference from the maintenance biology, not yet a measured causal chain in situ. *Settling experiment: restore or augment microglial TGF-β/SMAD signalling in a tauopathy model and test whether homeostatic restraint is preserved, the DAM transition prevented, and neuronal PP2A activity and tau phosphorylation spared.*

Plausible (synthesis) — the two governors, TGF-β/SMAD and norepinephrine, fail together and jointly release the microglion. Each governor is individually established (above); the claim that they fail *together*, over the same interval and in the same brain, and that their joint failure is what completes the microglial turn, is the dissertation's synthesis, not an observation. The two have never been co-measured. *Settling experiment: co-register microglial TGF-β/SMAD tone, noradrenergic tone, and the homeostatic-to-DAM transition longitudinally in a single tauopathy cohort or model, and test whether the transition requires both governors to lapse or proceeds on the failure of either alone.*

Plausible (kinetic argument) — the driven writer and the silenced eraser act synergistically (multiplicatively) on tau phosphorylation, not additively. Argued from the steady-state kinetics of a substrate governed by opposing enzymes (Section VIII); not yet measured as an interaction. *Settling experiment: a two-by-two design measuring tau phosphorylation under kinase-driven and phosphatase-silenced conditions alone and together, testing for supra-additivity.*

Plausible (imported, closing the loop) — hyperphosphorylated/aggregated tau activates the microglial NLRP3 inflammasome, closing a feed-forward loop. Directly shown that aggregated tau activates the NLRP3–ASC inflammasome and exacerbates tau pathology (Stancu and colleagues, 2019); the *closure of the loop* — tauinflammasomePP2A-silencingtau — is assembled from this result and the inflammasome-to-tau result (Ising and colleagues, 2019), and its self-sustaining character is a

synthesis. *Settling experiment: test whether interrupting the inflammasome after tau pathology is established arrests further PP2A silencing and tau accumulation, i.e. whether the loop is load-bearing once closed.*

Not established (and not required) — a direct molecular cross-talk between the TGF-β/SMAD pathway and PP2A. PP2A is known to participate in the regulation of SMAD signalling in other contexts, which would make the two systems of this dissertation molecularly entangled at the level of the phosphatase itself; but the relay traced here does not depend on such a direct link. The microglial TGF-β/SMAD failure reaches the neuronal PP2A *through the cell and its inflammation*, not through a shared molecule, and the argument is complete without a direct SMAD–PP2A tie. Entered as a boundary so the argument is not credited with more than it asserts, and flagged as a tempting but unnecessary bridge.

Rejected as stated — tau hyperphosphorylation in Alzheimer's disease is a disorder of the kinases alone. The kinase-centred reading captures one rate of a two-rate balance. The measured reduction of PP2A activity in the disease (Gong and colleagues, 1995; Gong and colleagues, 1993) is a derangement of the *other* rate, sufficient on its own to raise tau's steady-state phosphorylation, and it is driven — this dissertation argues — from outside the neuron by the ungoverned microglion. A model that watches only the writers mistakes half of the balance for the whole.

XI. Predictions and Falsification

The relay risks a series of specific predictions, each of which could be shown false, and the willingness to name them is the price of proposing the synthesis at all. Because the mechanism runs through a chain of governed cells and convergent enzymes, several predictions concern the joints *jointly* — signatures no single-enzyme account would make.

- **Restoring the microglial instruction spares the neuronal eraser.** Augmenting or restoring microglial TGF-β/SMAD signalling in a tauopathy model will preserve the homeostatic signature (P2Y12, CX3CR1), prevent or blunt the DAM transition, reduce inflammasome activation, and — the load-bearing prediction — preserve neuronal PP2A activity and reduce tau hyperphosphorylation. Should restoring the microglial instruction preserve the homeostatic markers but fail to spare the neuronal phosphatase, the relay from microglial governance to neuronal eraser is severed.
- **The inflammasome silences the phosphatase, not only drives the kinase.** Genetic or pharmacological loss of microglial NLRP3 will raise neuronal PP2A activity and

reduce cytoplasmic SET, in addition to lowering tau-kinase activity. If inflammasome loss reduces tau phosphorylation purely by lowering kinase activity while leaving PP2A activity and SET localisation unchanged, the specific reach to the *eraser* claimed in Section VII is wrong, though the inflammasome's reach to tau would survive on the kinase side.

- **The two governors are both required.** In a model, the homeostatic-to-DAM transition and the downstream PP2A silencing will proceed fully only when *both* the TGF-β/SMAD instruction and the noradrenergic brake have lapsed; restoring either governor alone will partially hold the microglion homeostatic and partially spare the eraser. If the transition proceeds identically whether one, both, or neither governor is intact, the two-governor synthesis of Section IV is refuted and the microglial turn must be driven from elsewhere.
- **The writer and the eraser are deranged synergistically.** In a two-by-two design, the tau phosphorylation produced by driving the kinase and silencing the phosphatase *together* will exceed the sum of each alone. If the combination is merely additive, the multiplicative-convergence claim of Section VIII is wrong, though the two derangements would survive as independent additive insults.
- **The SET route is inflammation-driven.** Exposing neurons to defined microglial inflammatory output, or to interleukin-1β, will drive SET cleavage and cytoplasmic translocation, reduce PP2A activity, and raise tau phosphorylation — and blocking the inflammasome or the cytokine will prevent it. If neuronal SET mislocalises just as readily with the microglial inflammatory input silenced, then the attribution of SET's unleashing to the microglion is wrong, and the SET route must be driven cell-autonomously.
- **The loop is load-bearing once closed.** Interrupting the tau–inflammasome loop *after* tau pathology is established — by inflammasome blockade in a brain already bearing tangles — will arrest further PP2A silencing and slow further tau accumulation, demonstrating that the loop, not merely the upstream governors, sustains the late disease. If late inflammasome blockade fails to slow established tau pathology, the self-sustaining-loop claim of Section IX is falsified and the pathology's momentum must be carried by something else.
- **The badges predict the eraser.** Across regions and individuals, the loss of the microglial homeostatic markers (P2Y12, CX3CR1) will predict the local reduction of neuronal PP2A activity and the local burden of hyperphosphorylated tau better than local amyloid burden alone. A region of preserved microglial homeostatic signature but silenced PP2A, or of lost signature but preserved PP2A, would bound the relay.

XII. Therapeutic Corollaries Re-Serving the Order, Re-Arming the Eraser

If the silencing of tau's eraser is worked through the relay this dissertation traces, then its therapeutic reading has a shape the writer-centred account does not, and the shape is the dissertation's chief practical contribution. A disease driven only by an over-active kinase invites, above all, a kinase inhibitor. A disease in which the *eraser* is silenced by an *ungoverned cell* invites a different and larger set of targets: the instruction that would keep the cell governed, the inflammasome that carries the cell's assault, the inhibitor that gags the eraser, and the eraser itself. This section reads the relay for its targets, and is candid that each is booby-trapped.

Upstream — re-serving the standing order. The most economical intervention is the most upstream: to restore the instruction whose lapse begins the relay, augmenting the microglial TGF-β/SMAD signal so that the homeostatic programme is renewed and the disease-associated transition never licensed. To hold the microglion homeostatic is to prevent the inflammasome from arming, and so to spare the eraser without ever touching the neuron. But the handle is heavily booby-trapped, and by exactly the logic that governed the companion volume's noradrenergic handle: TGF-β is not a microglia-specific tonic but a pleiotropic signal with powerful and context-dependent effects across the brain and body — immunosuppressive, fibrotic, and, in some settings, itself pathogenic — so that to raise it indiscriminately is to risk harms far from the microglion. And, like norepinephrine, TGF-β is protective in its proper regime and injurious only in its lapse; the therapeutic aim is not more of it everywhere but the *restoration of its microglial tone in the window of its decline*. The target is chronological as much as molecular: the instruction must be re-served while the cell can still hear it, before the transition has matured and the loop has closed.

Midstream — disarming the inflammasome. The second target is the instrument through which the ungoverned cell reaches the eraser: the NLRP3 inflammasome. An inflammasome inhibitor — a class the field is actively developing — would sever the relay at its most consequential joint, sparing the neuronal phosphatase whether the microglion's ungoverning arises from the TGF-β lapse, the noradrenergic failure, or both, and whether the fuel is amyloid or tau. This is the relay's downstream choke-point, the mirror of the companion volume's convergence at the kinase: one target for a mechanism with two upstream drivers. Its advantage is generality; its trap is that the inflammasome is a genuine and needed arm of host defence, and that its blockade must be disciplined enough to quiet the pathological, tau-fuelled inflammasome of the aged brain without disabling the danger-sensing the healthy brain requires. And it is the target most sharply governed by *timing*: because the tau–inflammasome loop sustains itself once closed, inflammasome blockade promises most if delivered before the loop has become self-fuelling, and least if delivered into a late brain whose momentum the loop already carries.

Downstream — re-arming the eraser. The most direct target is the eraser itself: to raise protein phosphatase 2A activity, or to prevent its silencing, so that tau's phosphate is removed as fast as it is laid down regardless of what the microglion is doing. This can be approached by relieving the enzyme of its inhibitor — antagonising SET, or preventing its cleavage and cytoplasmic translocation — or by supporting the phosphatase's activity directly. To re-arm the eraser is attractive because it acts at the point of convergence, downstream of every upstream driver, and because it addresses the measured deficit — the reduced phosphatase activity — head-on. Its trap is the enzyme's ubiquity: protein phosphatase 2A is one of the cell's most general phosphatases, governing far more than tau, and to raise its activity indiscriminately is to disturb a great deal of cellular regulation at once. As with the companion volume's kinase, the design constraint is not blockade or activation in the gross but *selectivity* — a means of restoring the tau-directed activity of the phosphatase, or of neutralising the specific inhibitor that gags it in the disease, without deranging the enzyme's countless other offices.

The single strategic reading. The four sites — the instruction, the inflammasome, the inhibitor, the eraser — share one reading, and it is the reading this whole corpus has reached from many directions: the systems that keep tau clean and the microglion calm are systems of the *earlier* brain, to be defended in the preclinical and prodromal window and not rescued in the ruins. The microglial governors lapse early; the eraser is silenced across the long prodrome; and the tau–inflammasome loop closes before the disease is clinically apparent. An intervention aimed at any of the four sites belongs, if the relay is right, to that early window — administered while the microglion can still hear its instruction, the inflammasome has not yet become self-fuelling, and the eraser still has activity to protect. The clinical instruments the relay would require — a microglia-directed TGF-β/SMAD modulator, a disciplined inflammasome inhibitor, a SET antagonist, a phosphatase-directed agent — are, several of them, close enough to existing or emerging pharmacology that the chief obstacle is not chemistry but *timing and selection*: knowing when in the trajectory, and in whom, to reach for them. The relay, like its companion, converts a set of molecular targets into a single clinical question of the hour.

XIII. Coda The Keeper and the Eraser

The companion dissertation ended on the image of a small blue nucleus closing two hands upon a single kinase, and set out to show that the noradrenergic contribution to the tangle was not a subtraction but a pincer. This one has watched the other side of the same balance, and found there a second cell and a second enzyme, and a relay running between them.

There is, in every healthy neuron, an eraser at continuous work. Protein phosphatase 2A moves along tau, stripping the phosphates the kinases lay down, returning the protein to the clean state in which it binds the microtubule and does its office; and so long as the eraser keeps pace, tau stays light, and the neuron holds its shape. The disease is, in part, the story of that eraser slowed well below its proper pace — and the strangeness this dissertation has tried to make legible is that the eraser is slowed not from within the neuron but from without, by the cell that surrounds it and that was meant to be its keeper. The microglion of the healthy brain is a gardener, a surveillant and clearing and matrix-preserving cell, and it holds that character only because it is told to, without pause, by a standing instruction it must keep receiving: the TGF-β signal, read through SMAD, that renews its identity faster than the identity decays. Let that instruction lapse — as it does in the aging brain, alongside the failure of the distal noradrenergic brake the companion volume traced — and the gardener does not merely fall idle. It forgets its name. It sheds its badges, passes through a licensed transition built on the disease's own risk genes, arms itself with an inflammasome and a protease, and becomes a cell that inflames where it once surveyed. And its inflammation reaches across the space to the neuron and silences the neuron's eraser — by deranging the balance of the tau enzymes from outside, and by unleashing the inhibitor that gags the phosphatase from within — so that tau, its phosphates no longer removed, accumulates them, and the tangle forms.

Set this beside the companion volume and the balance is complete. The blue nucleus's two hands drove the writer; the ungoverned microglion silenced the eraser; and tau, caught between a floored accelerator and a jammed brake, is phosphorylated from both sides at once — its kinase driven and its phosphatase gagged by the same disease, through two of the earliest-failing cells in the brain. There is a bitter economy in it, and the corpus has now met its shape yet again: one lost restraint, high in the causal order, unmaking a defence far downstream; a cell released from its governance turning its very effort to help into the neuron's undoing; a mechanism that closes into a loop and outlives the failure that lit it. That so much should turn on whether a microglion is still being told what to be — that the fate of a phosphate on a neuronal protein should rest on the tone of a signal read by the cell next door — is either a coincidence of independent accidents or a sign that the field's long fixation on the neuron's own enzymes has kept it from looking at the cell that governs them from outside. This dissertation takes the second view, and offers the ungoverned keeper as its argument.

And yet the same relay that carries the failure carries, in reverse, the hope. An eraser that has been silenced is not an eraser that has been destroyed. A microglion that has forgotten its instruction is not a microglion that has died. The keeper can, in principle, be told again what to be; the inflammasome can be quieted; the inhibitor can be lifted from the enzyme; and the eraser, un-gagged, can return to its patient work of keeping tau clean. The task is now legible in a way it was not when tau's hyperphosphorylation was read as the work of the kinases alone: to reach the microglion in the window when it can still hear its instruction, to quiet its inflammasome before the loop has closed, and to restore to the neuron the eraser the cell next door had silenced — before the

balance has tipped so far that no erasing could keep pace. The gardener is still in the garden. It has only stopped being told to tend it. The work is to serve the order again, before the wall it should be keeping has come down.

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