THE SPECK & THE ARCHITECT

The Inflammasome's Two Outputs — Interleukin-1β, Interleukin-18, the ASC Speck and the Gasdermin Pore — the Cathelicidin Brake Set Above Them, and the Dismantling of the Sulfated Dendritic Interface that Stages Reelin

The Two Locks · The Speck · The Cytokine Arm · The Pore
The Cathelicidin Brake · The Architect · The Two Ends of One Lesion

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The bridge dissertation between two clusters of the corpus that had never been joined: the NLRP3 inflammasome set and the reelin series. It runs the speck's chief output — interleukin-1β — into the aggrecanase secretome that strips the perineuronal net, degrading the same N-sulfated heparan-sulfate bed on which reelin must stand to fire its tau-brake; while the speck's second cytokine, interleukin-18, raises the very kinase the brake restrains. The inflammasome and the failing reelin axis are shown to be one lesion read from two ends — and LL-37 is set above the speck as an honestly graded, context-dependent brake.

"Watch the machine and you will see it make a cytokine; follow the cytokine and you will find it dissolving the floor beneath the one molecule built to keep the tangle from forming. The speck does not build the tangle with its own hands. It builds the tangle by defeating the architect who prevents it."

— ONS Methodology Working Notes, 2026

For those who read the tangle as the work of inflammation or the work of a lost guardian, and so never asked whether the inflammation and the lost guardian were the same event — the amplifier defeating the brake, on one surface, in one act.

THE COLLAPSE FRAMEWORK THE BRIDGE BETWEEN TWO CLUSTERS

The Sensor and the Speck — the NLRP3 machine as amyloid–tau relay

The Net and the Speck — IL-1β, the aggrecanases, and the stripped net

The Architect's Scaffold — reelin secreted into the sulfated matrix

The Architect's Handshake — the three-body clasp reelin–N-sulfated-HS–ApoER2

The Speck and the Architect (the cytokine cuts the weave that stages reelin) — this volume

This volume closes an edge the corpus had left open. On one side stood the inflammasome papers, which followed the NLRP3 machine from amyloid priming through the ASC speck to interleukin-1β, and named that cytokine the commander of the aggrecanases that strip the perineuronal net. On the other stood the reelin papers, which placed reelin inside that same sulfated net and showed it cannot fire its tau-brake without an intact bed of N-sulfated heparan sulfate beneath it. Neither set ever named the other's molecule. This dissertation supplies the missing weld: the cytokine the speck exists to make is the cytokine that dissolves the surface on which the architect must stand, so that the innate-immune amplifier and the gagged guardian become a single lesion read from two ends — the speck lifting reelin's brake on glycogen-synthase-kinase-3β by degrading its stage, while interleukin-18 raises the same kinase from the other side. Above the whole chain it sets LL-37, the sole human cathelicidin, as a possible brake upon the speck — a brake presented in full view of the fact that the same peptide, in the wrong cell, turns the machine on. A brake disabled, unlike a neuron dead, can in principle be restored.

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Abstract

Two literatures on Alzheimer's disease have grown up beside one another without meeting. The first describes an innate-immune machine — the NLRP3 inflammasome — that assembles inside the microglion, nucleates a micron-scale platform called the ASC speck, activates caspase-1, and issues two outputs: a diffusible pair of cytokines, interleukin-1β and interleukin-18, and a membrane conduit, the gasdermin-D pore, through which those cytokines leave and, at the extreme, the cell dies by pyroptosis. The second describes a secreted glycoprotein — reelin — that binds the neuronal lipoprotein receptors ApoER2 and VLDLR, phosphorylates the adaptor Disabled-1, and through that signal holds the tau kinase glycogen-synthase-kinase-3β suppressed, keeping tau off the microtubule-detaching phosphates that build the tangle. The first machine is the best-evidenced amplifier of the disease; the second molecule is one of its best-evidenced protectors, its power confirmed by two human beings who resisted an otherwise deterministic genetic dementia. This dissertation argues that the two literatures describe a single lesion read from opposite ends.

The joint is the extracellular matrix. Reelin does not act in free solution; it is secreted into the perineuronal net and requires an intact bed of N-sulfated heparan sulfate as an obligate co-receptor to cluster ApoER2 and fire Disabled-1 (Pesold and colleagues, 1998; Pan and colleagues, 2025). That same sulfated surface is the standing target of the inflammasome's chief cytokine: interleukin-1β is, across tissue after tissue, the most potent known inducer of the matrix-degrading secretome — the aggrecanases and matrix metalloproteinases that strip the net — and microglia are seen to strip the perineuronal net, in proportion to plaque, in the Alzheimer brain (Crapser and colleagues, 2020). The cytokine the speck exists to make is the cytokine that commands the destruction of the surface on which the architect stands. When that surface falls, three things happen at once on one polymer: the net that armoured the neuron is gone, the sulfated bed that staged reelin is degraded so the tau-brake is lifted, and the remodelled surface admits tau seeds more freely (Holmes and colleagues, 2013). The disinhibited kinase is met from the other side by the inflammasome's second cytokine: interleukin-18 directly raises glycogen-synthase-kinase-3β in human neuron-like cells (Sutinen and colleagues, 2012), and loss of NLRP3 function reduces tau hyperphosphorylation by regulating tau's kinases and phosphatases in vivo (Ising and colleagues, 2019). The speck lifts the brake on GSK-3β by tearing down reelin's bed, and floors the accelerator by cytokine — one kinase, driven from two directions.

Above this chain sits a single, ambivalent regulator. LL-37, the sole human cathelicidin, is a context-dependent rheostat on the very step the thesis turns on — NLRP3-mediated interleukin-1β release. In one setting it *activates* the inflammasome through the P2X7 receptor (Kahlenberg and colleagues, 2013); in another it *suppresses* it, inhibiting LPS/ATP-induced pyroptosis by a dual mechanism, neutralising the priming ligand and blocking the P2X7 trigger (Hu and colleagues, 2014); and independently it binds amyloid-β and retards its fibril assembly

(De Lorenzi and colleagues, 2017). The peptide is therefore, potentially, a brake set above the speck — but a brake graded honestly here as the least secure element in the argument, its suppressor arm shown in peripheral macrophages and never in the human brain.

The verdict is deliberately conservative and inherited from both parent literatures. The inflammasome is a validated amplifier and an unproven initiator; reelin is a resilience modifier, not a trigger; LL-37 is a plausible but unproven modulator. None of the three begins the disease. But the edge that runs from the speck to the architect is, if it holds, the point at which the innate-immune amplifier and the failing tau-brake become the same event — and a point that, unlike the disease's origin, we already possess three ways to interrupt: silence the sensor, spare the sugar, or restore the brake above them both.

I. The Smoke, the Speck, and the Architect

There is a methodological trap that any honest account of inflammation in Alzheimer's disease must disarm before it says anything else. The inflammasome is, by its evolved design, a sensor of danger. A degenerating brain generates danger signals in abundance, whatever the primary cause of its degeneration: extracellular aggregates, ruptured lysosomes, spilled adenosine triphosphate, ionic imbalance, dying cells. It is therefore guaranteed, before any experiment is done, that the inflammasome will be *found activated* in the Alzheimer brain — in the same way that smoke is guaranteed to be found at a fire. The scientific question is never whether the machine is on. It is. The question is whether that activation is load-bearing: whether it feeds back onto the pathology that woke it and accelerates a disease it did not begin, or whether it is an epiphenomenal readout of injury generated somewhere else.

This dissertation adopts, from the outset, the disciplined answer that the machine is an *amplifier* — that it makes the disease worse and faster, that its removal in the mouse makes the disease better, but that it is not the seed and its silencing would not, on present evidence, prevent the disease from beginning. That verdict is not a hedge; it is the load-bearing constraint of the whole argument, and it is defended, not merely asserted, in the Validity Ledger. What the dissertation adds is a specific claim about *where the amplifier does its damage* — a claim that connects the innate-immune literature to a second body of work with which it has never been joined.

The second body of work concerns reelin, and it is not a story about inflammation at all. Reelin is a large secreted glycoprotein, known first as the architect of the layered cortex — the molecule that tells migrating neurons where to stop during development. But the architect does not leave when the building is finished. It takes up residence in the adult brain as a tonic guardian of the synapse: it signals through the neuronal lipoprotein receptors ApoER2 and VLDLR, it enhances

long-term potentiation, and — the fact that matters here — it holds the tau kinase glycogen-synthase-kinase-3β suppressed, keeping tau in its normal microtubule-binding state (Hiesberger and colleagues, 1999). Two human beings have now shown the world how much that guardianship is worth: each carried a deterministic autosomal-dominant Alzheimer's mutation and each should have been demented in their forties, and each instead resisted for decades, one through a variant in the reelin receptor pathway's competitor APOE and one through a gain-of-function variant in reelin itself (Arboleda-Velasquez and colleagues, 2019; Lopera and colleagues, 2023). Reelin is, on the strongest human evidence in the entire field, a genuine brake on the disease.

The claim of this thesis is that these two literatures — the speck and the architect — are not merely both true of the Alzheimer brain but *mechanically continuous*. The inflammasome's principal output is a cytokine whose defining systemic function is to command the destruction of the extracellular matrix. Reelin's signal is staged on precisely that matrix — it cannot fire without an intact bed of sulfated sugar. The amplifier and the guardian meet on one surface, and when the amplifier degrades that surface it does not merely inflame the neighbourhood: it unstages the architect, lifts the brake on the kinase, and, on the very same polymer, opens the gate to the tau seed. The name of this dissertation is the name of the meeting: the speck, which is the physical heart of the inflammasome, and the architect, which is reelin. The chapters that follow build the machine, name its two outputs, set a possible brake above it, describe the architect and the surface that stages it, and then weld the two together at the joint where the cytokine cuts the weave.

We begin with the machine.

II. The Two Locks Priming and the Trigger

The NLRP3 inflammasome is built to be difficult to fire. It is a two-signal device, guarded by two locks that must be opened in sequence, and the sequence is not incidental — it is the cell's insurance against detonating its most inflammatory weapon by accident. Understanding the two locks is necessary because the therapeutic and regulatory logic of the entire thesis — including where LL-37 might act — depends on which lock is being turned.

The first lock is **priming**, and it is transcriptional. In the resting microglion the components of the machine are held at levels too low to assemble, and the cytokine it will eventually mature does not yet exist in usable form. Priming raises both. In the Alzheimer setting the priming ligand is fibrillar and oligomeric amyloid-β itself, sensed at the cell surface through a receptor complex organised around the scavenger receptor CD36 with Toll-like receptors 4 and 6, signalling through

the canonical innate pathway to the transcription factor NF-κB. The output of priming is a raised transcription of the sensor protein NLRP3 and, critically, of the inactive precursor pro-interleukin-1β, which has no signal peptide and cannot be secreted or activated until the second lock is turned. A chronically amyloid-laden parenchyma keeps the microglion perpetually primed; this is the sense in which amyloid is upstream of the machine, and it is one of the reasons the machine cannot honestly be called the initiator. The device is loaded by the proteinopathy it will later help to spread.

The second lock is **activation**, and it is post-translational and fast. Where priming is a matter of hours and transcription, activation is a matter of minutes and protein conformation. Three convergent triggers open it, and the elegance of the modern account is that they converge on one final common event. The first trigger is **potassium efflux**: a drop in the cytosolic concentration of potassium is the single perturbation shared by nearly every NLRP3 activator, from bacterial pore-forming toxins to extracellular adenosine triphosphate acting through the P2X7 receptor to crystalline and particulate matter, and reduction of intracellular potassium is by itself sufficient to activate the sensor (Muñoz-Planillo and colleagues, 2013). Downstream of that efflux the mitotic kinase NEK7 is an essential mediator, licensing the oligomerisation of NLRP3 (He and colleagues, 2016). The second trigger is the one most specific to Alzheimer's disease: **lysosomal rupture**. When the microglion phagocytoses fibrillar amyloid-β it cannot fully digest, the engorged and destabilised phagolysosome ruptures and releases the protease cathepsin B into the cytosol — the mechanism by which insoluble material, from silica to urate to amyloid, is read as danger (Halle and colleagues, 2008). The third trigger is **mitochondrial**: damaged mitochondria leak reactive oxygen species and oxidised mitochondrial DNA that further license assembly. The synthesis of these routes into a coherent regulatory picture is the achievement of the modern inflammasome field (Swanson and colleagues, 2019).

The two-lock architecture explains a fact that will matter for the therapeutics of the final chapters: the machine can be intercepted at either lock, and interception at the two locks has entirely different consequences for host defence. To block priming is to lower the ceiling on every downstream event but also to blunt legitimate immunity broadly; to block the trigger — as the specific inhibitor MCC950 does, and as the amyloid-relevant cathepsin-B route invites — is to leave priming and general immunity intact and disarm only the detonation (Coll and colleagues, 2015). And it explains where a bifunctional regulator would be most interesting: a molecule that could touch *both* the priming ligand and the potassium-efflux trigger would be acting on the two locks at once. We will meet exactly such a molecule, LL-37, in Chapter VII — and find that whether it opens or closes the locks depends on the cell it is standing in.

For now, the two locks are open. The sensor is oligomerised. What happens next is the assembly of the platform that gives this dissertation half its title.

III. The Speck Nucleation of a Signalling Platform

When both locks are turned, the sensor protein NLRP3 does not act alone; it cannot, because it has no catalytic activity of its own. It is a nucleator. Through its central NACHT domain the activated sensor oligomerises, and the oligomer presents a corona of pyrin domains (PYD). These recruit, by homotypic PYD–PYD contact, the adaptor that is the true protagonist of this chapter: **ASC** — apoptosis-associated speck-like protein containing a caspase-recruitment domain. ASC is a two-domain molecule, a pyrin domain married to a caspase-recruitment domain (CARD), and it is built to polymerise. Seeded by the sensor's pyrin corona, ASC assembles into long helical filaments, and those filaments condense into a single, dense, micron-scale perinuclear structure — one per cell, a full-stop visible under the microscope. This is the **ASC speck**, and it is not a by-product of inflammasome activation. It *is* the active inflammasome, made large.

The speck's function is to be a signalling platform, and it works by the logic of proximity-induced enzyme activation. The condensed CARD domains of the polymerised ASC present a second homotypic surface — CARD–CARD — that recruits the inactive zymogen pro-caspase-1. Concentrating many pro-caspase-1 molecules onto the platform forces their autoproteolytic maturation into active caspase-1, the protease that will perform every downstream act in this thesis. The speck is, in other words, a device for converting a danger signal into a burst of protease activity by the simple expedient of bringing the enzyme's molecules into contact with one another. Its geometry is its mechanism.

Two properties of the speck take it beyond the boundary of the cell that made it, and both matter for Alzheimer's disease. The first is that the speck is **released and remains active outside the cell**. When the microglion dies — as, at the extreme of its own activation, it will (Chapter V) — the speck is expelled intact into the extracellular space, where it continues to recruit and mature pro-interleukin-1β, and where it can be phagocytosed by a neighbouring macrophage, rupture that cell's lysosome, and nucleate a fresh round of ASC polymerisation in the recipient. The speck behaves, in short, as a **prionoid**: a self-propagating protein conformation that carries the inflammatory signal from cell to cell (Franklin and colleagues, 2014). Inflammation, on this account, is not only a diffusible cytokine gradient; it is a transmissible protein structure.

The second property is the one that welds the inflammasome to the proteinopathy it is embedded in. The extracellular ASC speck **binds amyloid-β directly and cross-seeds it**. In the Alzheimer brain, released microglial specks associate rapidly with amyloid-β, increase the formation of amyloid-β oligomers and aggregates, and act as an inflammation-driven cross-seed for

amyloid pathology; injecting specks spreads amyloid pathology in a susceptible mouse, and depleting the adaptor, or blocking it with an antibody, prevents that spread (Venegas and colleagues, 2017). Here the amplifier logic becomes concrete: the machine that amyloid primes produces a structure that seeds more amyloid. The speck is not the origin of the plaque, but it is a mechanism by which the plaque propagates — the arsonist who did not light the fire but carries embers to the next room.

The speck, then, is the physical heart of the machine: a platform that turns danger into protease, a prionoid that carries inflammation between cells, and a cross-seed that spreads the aggregate. Everything the rest of this dissertation describes flows from the protease the speck activates. That protease has two substrates, and therefore the machine has two outputs. The first is a pair of cytokines. The second is a pore. We take them in turn.

IV. The Cytokine Arm The Two Interleukins

The first and defining output of the speck is a pair of cytokines that the activated caspase-1 cleaves from their inactive precursors: **interleukin-1β** and **interleukin-18**. These are the reason the machine exists. Both are members of the interleukin-1 family, the cytokine family most tightly bound to the innate immune response — so tightly that the cytoplasmic domain of the interleukin-1 receptor is homologous to the cytoplasmic domains of the Toll-like receptors, meaning that the cell's response to interleukin-1 and its response to a bacterial pattern run through the same intracellular grammar (Dinarello, 2009). To understand the inflammasome's downstream reach is to understand what these two cytokines command, and the argument of this dissertation is that what they command, in the brain, is the destruction of the surface on which reelin stands and the direct disinhibition of the kinase reelin restrains.

Interleukin-1β is the more studied of the two and the more consequential for the matrix. It is synthesised as an inactive precursor, pro-interleukin-1β, which — lacking a secretory signal peptide — is trapped in the cytosol until caspase-1 cleaves it to its mature, active, releasable form. Once released it signals through the interleukin-1 receptor type I and the adaptor MyD88 to NF-κB, and among the most reliable consequences of that signalling, across system after system, is the induction of the matrix-catabolic secretome: the matrix metalloproteinases and, above all, the aggrecanases of the ADAMTS family that degrade the large chondroitin-sulfate proteoglycans of the extracellular matrix. This is a general property of the cytokine, established most thoroughly in cartilage biology, and it is the hinge on which Chapter X will turn. For the present it is enough to fix the identity: interleukin-1β is the inflammasome's diffusible instruction to dissolve the matrix.

That interleukin-1β is genuinely engaged in the human Alzheimer brain, and not merely in mouse models, is among the oldest findings in the field. Interleukin-1 immunoreactivity is elevated many-fold in Alzheimer brain tissue and in Down syndrome, concentrated in microglia, decades before the modern inflammasome was described (Griffin and colleagues, 1989). The modern work has closed the loop back to the machine: the NLRP3 and NLRP1 inflammasomes are demonstrably assembled and active in Alzheimer patients, with co-localisation of the sensor, the adaptor, and caspase-1, and significantly increased production of both interleukin-1β and interleukin-18 (Saresella and colleagues, 2016). The cytokine that the century-old histology saw is the output of the platform the recent structural work described.

Interleukin-18 is the quieter member of the pair, and for this thesis it is the more surgically important, because it reaches the tau kinase directly. Like interleukin-1β it is cleaved to its active form by caspase-1 on the speck. Unlike interleukin-1β its most consequential action in the neuron is not on the matrix but on the intracellular machinery of tau. In human neuron-like cells, interleukin-18 increases the amyloidogenic processing of the amyloid precursor protein — raising the β-secretase BACE-1 and shifting the cell toward amyloid-β production — but it does something else in the same experiment that matters more here: it increases the expression of **glycogen-synthase-kinase-3β** and of cyclin-dependent kinase 5, the two kinases most responsible for the pathological hyperphosphorylation of tau (Sutinen and colleagues, 2012). This is the single most important pharmacological fact for the architecture of this dissertation, and it deserves to be stated in isolation: *the inflammasome's second cytokine raises the very kinase that reelin's signal exists to suppress.* The speck, through interleukin-18, pushes up the accelerator on tau. Reelin, through Disabled-1, holds down the brake. They act on the same enzyme, from opposite directions. When Chapter X removes reelin's brake, interleukin-18 will already be leaning on the throttle.

The cytokine arm, then, is not a generic inflammatory nuisance. It is two specific instructions issued by one platform: interleukin-1β to dissolve the matrix that stages the guardian, and interleukin-18 to raise the kinase the guardian restrains. The relevance of the inflammasome to Alzheimer's disease as a therapeutic target rests substantially on this arm (White and colleagues, 2017). But the cytokines cannot leave the cell through the conventional secretory route — pro-interleukin-1β has no signal peptide, and neither cytokine can cross an intact membrane. Their release requires the machine's second output. It requires a pore.

V. The Pore Gasdermin-D and the Two Deaths

For two decades the field knew that inflammasome activation released interleukin-1β and killed the cell by a lytic, inflammatory death called pyroptosis, but it did not know how — because the cytokine has no signal peptide and cannot be conventionally secreted, and because the death did not look like apoptosis. The missing piece, identified in 2015, is the second substrate of caspase-1 and the second output of the machine: **gasdermin-D**. Its discovery reorganised the whole downstream picture, and it supplies the second half of this dissertation's account of how the speck does its damage.

Gasdermin-D is a two-domain protein held in an autoinhibited state: an amino-terminal domain with intrinsic membrane-disrupting activity, restrained by a carboxy-terminal domain that folds back and silences it. The inflammatory caspases — caspase-1 in the canonical pathway, and caspase-4, -5, and -11 in the non-canonical pathway that senses cytosolic lipopolysaccharide directly — cleave the linker between the two domains, and that single cut is both necessary and sufficient for pyroptosis (Shi and colleagues, 2015; Kayagaki and colleagues, 2015). The cleavage releases the amino-terminal fragment from its intramolecular restraint. The freed fragment then does what its structure was built to do: it travels to the plasma membrane, binds the acidic membrane lipids — phosphoinositides and cardiolipin — on the inner leaflet, and oligomerises into a large transmembrane pore. The pore is a defined structure, not a vague breach: most gasdermin pores contain sixteen protomers arranged in a ring with an inner diameter of roughly ten to fourteen nanometres (Ding and colleagues, 2016). The autoinhibition is conserved across the whole gasdermin family; the specificity of gasdermin-D is only that it is the family member the inflammatory caspases are built to cut.

The pore is the conduit that resolves both mysteries at once, and its dual role is the reason this dissertation treats the cytokine arm and the pore arm as one coupled device rather than two independent fates. First, the gasdermin-D pore is the **route of cytokine release**: the mature but signal-peptide-less interleukin-1β leaves the cell through this pore. Gasdermin-D is required for interleukin-1β secretion — in gasdermin-D-deficient cells the cytokine is processed normally by caspase-1 but cannot get out (He and colleagues, 2015). The pore is not merely a wound; it is the door through which the cytokine arm is delivered. A cell can, under limited activation, open enough pores to release cytokine while surviving — "hyperactivation" without death — but as the pores multiply the second consequence follows.

Second, at sufficient density the pores overwhelm the cell's capacity to repair its membrane, and the cell undergoes **pyroptosis**: it swells, its membrane ruptures, and it spills its entire cytosolic contents — including, crucially, the intact ASC speck, which then continues its prionoid and cross-seeding career in the extracellular space (Chapter III). Pyroptosis is thus the mechanism that converts a single activated microglion into both a bolus of released cytokine and a released, propagating speck. The two outputs of the machine are delivered by the same door, and the more the door opens the more certainly the cell dies and seeds its neighbours.

That this lytic death is not a mouse-only artefact but a feature of the human Alzheimer brain is now established at the level of tissue. Cleaved gasdermin-D — the activated, pore-forming fragment — is detectable in the human Alzheimer medial temporal lobe, in microglia expressing the full NLRP3 machine, in astrocytes, and in a subset of pyramidal neurons; the number of cells bearing the cleaved effector is increased in Alzheimer's disease relative to control, and cleaved-gasdermin-D-positive neurons in the hippocampal CA1 field are associated with local neuronal loss (Moonen and colleagues, 2023). The pore, in other words, is not only how the cytokine leaves and how the speck escapes; in the neuron it is a direct execution mechanism, a way for the inflammatory cascade to kill a nerve cell outright. The machine's second output is, at its terminus, a form of neuronal death.

We now have the whole machine. Two locks, one platform, two outputs — a diffusible cytokine pair and a membrane pore that delivers them and, at the extreme, lyses the cell. Before we take this machine to the architect, we pause to make explicit what has been implicit: that these two outputs are not alternatives but a single coupled device.

VI. One Speck, Two Outputs The Coupled Device

It is tempting, and it is a mistake, to picture the inflammasome as choosing between two fates — to release cytokines *or* to die by pyroptosis, the cytokine arm *or* the pore arm. The molecular facts of the preceding two chapters forbid the disjunction. The two outputs share a substrate-generating enzyme, share a delivery structure, and reinforce one another. They are one device with two ends, and stating their coupling plainly is necessary before the bridge is built, because the bridge inherits both ends at once.

Consider the shared dependencies. Both outputs originate at the same platform: it is caspase-1, matured on the ASC speck, that cleaves pro-interleukin-1β, cleaves pro-interleukin-18, *and* cleaves gasdermin-D. One protease, activated by one geometry, generates all three products. There is no branch point at which the cell decides between cytokine and pore; the same enzymatic burst produces the mature cytokines and the pore-forming fragment simultaneously. And the two outputs are then mechanically interdependent in the manner established in Chapter V: the pore is the route by which the cytokines are released (He and colleagues, 2015), so the cytokine arm is *delivered through* the pore arm rather than beside it. Cytokine release is not an alternative to pore formation; it is a low-intensity setting of it.

Consider, next, the way the two ends amplify one another across cells. When pore density crosses the threshold into pyroptosis, the dying cell releases not only its cytokine load but the intact ASC speck, which cross-seeds amyloid (Venegas and colleagues, 2017) and nucleates fresh inflammasomes in recipient cells (Franklin and colleagues, 2014). Those recipient cells, primed by the ambient amyloid and now seeded by the incoming speck, assemble their own platforms and open their own pores. The pore arm thus propagates the entire device — cytokine arm included — to the next cell. A single detonation becomes a travelling wave, and each station of the wave issues both a cytokine bolus and a released speck.

This coupling is what licenses the dissertation's central structural move. When Chapter X sends the inflammasome's output into the reelin axis, it does not send one output; it sends both, and they arrive on the same target from complementary directions. The cytokine arm dissolves the matrix that stages reelin and, through interleukin-18, raises the kinase reelin restrains. The pore arm kills the very interneurons whose perineuronal nets and reelin secretion are at issue — for the neurons most reliably wrapped in perineuronal nets, and among the richest sources of reelin secreted into those nets, are the parvalbumin-positive and GABAergic interneurons that Chapter IX will place at the centre of the sulfated interface. The device that dissolves the guardian's stage is the same device that can lyse the cells that build the stage. One speck; two outputs; a single coordinated assault on one surface.

Before we reach that surface, we ask whether anything stands above the speck to restrain it — whether the chain has a brake set upstream of the platform itself. There is a candidate, and it is the most ambivalent actor in the whole account.

VII. The Cathelicidin Brake LL-37 Above the Speck

Every chapter so far has described a machine running forward. This one asks whether the brain carries an endogenous molecule capable of running it backward — of suppressing NLRP3-mediated interleukin-1β release at or above the level of the speck. The candidate is **LL-37**, the sole human cathelicidin, the mature antimicrobial peptide cleaved from the precursor encoded by the CAMP gene: thirty-seven amino acids, strongly cationic, amphipathic, α-helical, expressed across epithelia and myeloid cells and inducible by vitamin D and by the microbial-fermentation product butyrate. LL-37 is a genuine and important regulator of the inflammasome. It is also, and this must be said before anything else, a Janus-faced one — and the honesty of this dissertation depends on presenting both faces before pressing the one the title implies.

The activating face. In the classical myeloid setting LL-37 is not a brake on the inflammasome but a trigger for it. Externalised on neutrophil extracellular traps and abundant at sites of sterile inflammation, LL-37 activates caspase-1 in human and murine macrophages and drives the release of active interleukin-1β and interleukin-18, and it does so through exactly the trigger described in Chapter II — potassium efflux driven by the P2X7 receptor (Kahlenberg and colleagues, 2013). In lupus this is a feed-forward loop: the peptide activates the machine, the machine's interleukin-18 stimulates more trap formation, and more traps externalise more peptide. Any claim that LL-37 suppresses the inflammasome must be made in full view of this literature, in which the same peptide, in a closely related cell, does the opposite.

The suppressing face. And yet, in a different configuration, LL-37 demonstrably *inhibits* the inflammasome, and it does so at both of the locks defined in Chapter II. In macrophages stimulated with lipopolysaccharide and adenosine triphosphate — the standard priming-plus-trigger protocol — LL-37 inhibits the induction of interleukin-1β, the activation of caspase-1, the assembly of the inflammasome, and the resulting pyroptotic death, by a **dual mechanism**: it neutralises the lipopolysaccharide so that the priming signal is blunted, and it directly inhibits the P2X7 response to adenosine triphosphate so that the potassium-efflux trigger is dampened (Hu and colleagues, 2014). This is a remarkable specificity. The one molecule touches the two locks — the priming ligand and the trigger receptor — that the entire regulatory architecture of the machine turns on. Where a synthetic inhibitor like MCC950 blocks the sensor, LL-37 in this configuration blocks the two inputs. If the brain could be persuaded to hold LL-37 in this configuration, it would be braking the speck from above.

The amyloid face. Independent of the inflammasome, LL-37 engages the disease's other pole. It binds amyloid-β directly, with the interaction shown by surface plasmon resonance, and it retards amyloid-β fibril assembly — preventing the peptide from adopting its β-sheet secondary structure and from forming the long straight fibrils characteristic of the disease — while the microglial toxicity of amyloid-β is greatly attenuated when the two peptides are co-incubated before exposure (De Lorenzi and colleagues, 2017). This places LL-37 in a suggestive relationship to amyloid-β that runs deeper than chance, because amyloid-β is itself an antimicrobial peptide, active against bacteria and fungi at physiological concentrations (Soscia and colleagues, 2010). The two peptides are, on this reading, players in the same innate-immune game: one the professional cathelicidin, the other an amyloid that behaves like one. LL-37 may therefore sit above the speck twice over — braking the priming ligand at the machine, and binding the priming aggregate before it can prime.

Now the discipline. Every claim in this chapter about LL-37 as a suppressor rests on peripheral cells — macrophages, monocytes, neutrophils — and none of it has been demonstrated in the microglion of the human brain. The suppressor experiment (Hu and colleagues, 2014) is a macrophage experiment; the amyloid experiment (De Lorenzi and colleagues, 2017) is in vitro

biophysics and cell lines; the concentration of LL-37 actually achieved in the Alzheimer parenchyma is not established, and the activating face (Kahlenberg and colleagues, 2013) warns that in the wrong configuration the same peptide would *worsen* everything this dissertation describes. LL-37 is therefore introduced here as the argument's most speculative element and graded accordingly in the Ledger: a plausible, mechanistically specific, and therapeutically tempting brake set above the speck — and an unproven one. It is the hypothesis the thesis would most like to be true and has the least right to assume. What it offers, even at this grade, is a third interruption point: not silencing the sensor, not sparing the sugar, but restraining the two locks before they turn.

We turn now from the machine and its possible brake to the second protagonist — the architect the machine will be shown to dismantle.

VIII. The Architect Reelin and the Dendritic Interface

Reelin enters this dissertation not as a victim of inflammation — nothing in its own literature mentions the inflammasome — but as an independently established guardian of neuronal homeostasis, and it is precisely because its protective credentials were earned in a separate field that the bridge, when built, will carry weight. This chapter states the reelin axis and its interface with the synapse on reelin's own terms.

The signalling axis is linear and well-mapped. Secreted reelin binds two neuronal members of the low-density-lipoprotein-receptor family, **ApoER2** and **VLDLR**, on the postsynaptic surface. Receptor engagement clusters the intracellular adaptor **Disabled-1** and drives its tyrosine phosphorylation by Src-family kinases, chiefly Fyn. From phosphorylated Disabled-1 the signal descends through phosphatidylinositol-3-kinase and Akt to the inhibitory phosphorylation of **glycogen-synthase-kinase-3β**. That kinase is the principal enzyme that hyperphosphorylates tau; a live reelin signal keeps it suppressed and tau in its normal, microtubule-binding state, while the loss of reelin signalling releases the kinase and permits tau to be pathologically modified. This chain — reelin to the receptors to Disabled-1 to the suppression of the kinase to the protection of tau — was demonstrated directly when it was shown that reelin binds the ectodomains of VLDLR and ApoER2, that blocking the receptors abolishes reelin-induced Disabled-1 phosphorylation, and that mice lacking either reelin or both receptors exhibit hyperphosphorylation of tau (Hiesberger and colleagues, 1999). This is the tau brake, and it is the reason reelin belongs in a dissertation about tangles.

The interface at which reelin exerts this protection is the **dendrite and the synapse**, and here reelin is not merely a passive brake but an active tuner of neurotransmission. ApoER2 sits in the postsynaptic density in a complex with the NMDA-type glutamate receptor; reelin signalling through it potentiates NMDA-receptor currents, enhances long-term potentiation, and thereby raises synaptic gain. Critically for a disease defined by synaptic failure, reelin *antagonises amyloid-β at the synapse*: it prevents the suppression of long-term potentiation and of NMDA-receptor function that pathological concentrations of amyloid-β would otherwise impose, in a manner dependent on Src-family kinase activation — but only up to a concentration ceiling, above which amyloid-β wins and reelin's protection collapses (Durakoglugil and colleagues, 2009). This is the homeostatic reading of the disease that reelin's own field has arrived at: amyloid-β and reelin are opposing hands on synaptic gain, and Alzheimer's disease is, in part, the collapse of that balance rather than the intrusion of a foreign poison — a reframing crystallised in the recent characterisation of amyloid-β as a physiological synaptic modulator whose adaptive brake becomes maladaptive with age and inflammation (Herz, 2025).

That reelin's guardianship is real, and not an artefact of mouse genetics, is established by the strongest kind of evidence the field possesses: human resistance to a deterministic dementia. Two individuals carrying autosomal-dominant Alzheimer's mutations that should have caused early dementia instead resisted for decades. The first was homozygous for the **Christchurch variant of APOE**, which impairs the binding of apolipoprotein E — reelin's competitor at the same receptors — and who, despite an extreme amyloid burden, had limited tau tangle spread and preserved cognition into her seventies (Arboleda-Velasquez and colleagues, 2019). The second was heterozygous for a gain-of-function variant in reelin itself, **RELN-COLBOS (H3447R)**, who remained cognitively intact until his late sixties despite the same mutation and an extreme amyloid burden, and whose variant reelin showed an enhanced ability to activate Disabled-1 and to reduce tau phosphorylation in a knock-in mouse (Lopera and colleagues, 2023). These two cases are the empirical spine of reelin's claim to matter: a stronger reelin signal, or a weaker competitor at reelin's receptors, buys decades of resistance to a genetically inevitable disease — with the resistance appearing specifically as limited *tau* spread on a background of undiminished amyloid, exactly the signature the tau brake predicts.

Reelin does not fail in Alzheimer's disease by disappearing. It fails by being **gagged** — a distinction that will matter for the bridge and for therapy. In the diseased brain reelin protein and messenger RNA actually *rise* with advancing pathology, yet reelin-induced Disabled-1 phosphorylation *falls*: amyloid-β co-aggregates with secreted reelin and traps it, and the receptor's downstream response is deadened, so that the brain has more reelin protein and less reelin signal (Cuchillo-Ibáñez and colleagues, 2016). This is the phenomenon of **reelin resistance**, analogous to insulin resistance — a rising ligand and a falling effect — and it dissolves an apparent paradox in the biomarker literature by showing that the guardian has not left its post; it has been silenced at it. Consistent with the brake's causal reality, experimentally reducing reelin expression accelerates

amyloid plaque formation and tau pathology in a transgenic model (Kocherhans and colleagues, 2010).

The architect, then, is a tonic guardian of the dendritic interface, a brake on the tau kinase, a proven modifier of human disease, and — in the diseased brain — a guardian more gagged than gone. The question this dissertation exists to answer is *how* it is gagged. Reelin's own literature attributes the gagging to amyloid-β trapping the ligand. This dissertation adds a second, converging mechanism, and to see it we must look not at the ligand but at the surface on which the ligand must stand.

IX. The Sulfated Interface Where the Architect Is Staged

The decisive fact about reelin, for the purposes of joining it to the inflammasome, is that it does not act in free solution. It acts on a surface, and the surface is made of sulfated sugar. This chapter establishes the surface; the next sends the inflammasome against it.

Reelin is, physically, a **tenant of the perineuronal net**. In the adult cortex and hippocampus reelin is preferentially synthesised and secreted by a specific class of GABAergic interneurons, and it is secreted not diffusely but *into the perineuronal net* — the dense, lattice-like extracellular matrix of chondroitin-sulfate and heparan-sulfate proteoglycans that ensheathes certain neurons, where reelin non-synaptically modulates the enwrapped cell (Pesold and colleagues, 1998). The architect lives in the wall. This co-location is not decorative: it places reelin's site of action within the very structure that the inflammasome's cytokine is built to dissolve.

The reason the co-location is load-bearing, rather than merely anatomical, was established only recently, and it is the keystone of the whole bridge. Reelin **requires N-sulfated heparan sulfate as an obligate co-receptor** to fire its signal. Full-length reelin binds heparan sulfate with high affinity, and this binding is not incidental to receptor activation but necessary for it: heparan sulfate acts as a co-receptor for reelin-induced clustering of ApoER2, and degrading the cell-surface heparan sulfate with heparinase, or knocking out the key N-sulfation enzyme NDST1, sharply reduces reelin's attachment and its ability to dimerise its receptor — while N-desulfated heparin, lacking the N-sulfate groups, fails to support the interaction, pinning the requirement specifically on N-sulfation (Pan and colleagues, 2025). Reelin, in other words, cannot cluster ApoER2 and cannot fire Disabled-1 without an intact bed of correctly N-sulfated heparan sulfate beneath it. The sugar is not a passive scaffold; it is a functional part of the receptor. That the resilience-conferring RELN-COLBOS variant of Chapter VIII binds heparan sulfate *even more tightly* than wild-type reelin

ties the protective human genetics directly to this sulfated interface: the variant that resists dementia is the variant that grips the sugar harder.

The same sulfated surface has a second, darker office, and it is the one that makes its degradation doubly consequential. Heparan-sulfate proteoglycans are the **gateway for the cellular uptake and propagation of tau seeds**. Pathological tau, like several proteopathic proteins, enters cells and templates its misfolding by first binding cell-surface heparan sulfate; blocking or removing the heparan sulfate blocks the internalisation and propagation of tau (Holmes and colleagues, 2013). This yields a surface with a divided character. In its intact, correctly sulfated state the heparan-sulfate bed is protective on two counts: it stages reelin's tau-brake, and — as the aggrecan-rich perineuronal net — it physically armours the neuron, net-bearing neurons carrying notably lower tangle burden. But the same chemistry that stages reelin can, when the surface is remodelled, present the docking site for tau's entry. The surface is a shield and a gate written in one polymer.

Here, then, is the interface the whole dissertation has been converging on. One sulfated extracellular surface performs three offices for the neuron at once: it *armours* the cell as the perineuronal net, it *stages* the reelin signal that brakes the tau kinase, and — when intact — it withholds the *gate* through which tau seeds enter. All three offices depend on the integrity of the sulfated matrix. Degrade that matrix and you strip the armour, unstage the guardian, and open the gate, in a single act, on a single polymer. What remains is to identify the agent that degrades it — and to show that the agent is the inflammasome's own output.

X. The Cytokine Cuts the Weave The Bridge

This is the chapter the dissertation exists to write. The two edifices are built: on one side the inflammasome, a coupled device whose speck issues a cytokine arm and a pore arm; on the other the architect, a tonic tau-brake staged on a sulfated surface that also armours the neuron and withholds the tau gate. The claim now is that the first dismantles the second, and that the dismantling explains, mechanically, how the architect is gagged.

The bridge is a single molecular fact carried across a single anatomical junction. The molecular fact is that **interleukin-1β is among the most potent known inducers of the matrix-catabolic secretome** — the matrix metalloproteinases MMP-3 and MMP-9 and, above all, the aggrecanases ADAMTS-4 and ADAMTS-5, the enzymes that cleave the aggrecan core of the perineuronal net. This is not a neural speculation; it is a general and heavily replicated property

of the cytokine, foundational to the biology of inflammatory joint disease, and it is the reason the inflammasome's chief product functions, wherever it is released, as an instruction to dissolve the chondroitin-sulfate matrix. The anatomical junction is that in the Alzheimer brain the cells that carry the machine and the cells whose nets are stripped are neighbours: **microglia facilitate the loss of perineuronal nets in the Alzheimer brain**, engulfing and degrading net material in proportion to plaque burden, in both mouse models and human cortical tissue — and, decisively, depleting microglia prevents the net loss even though plaques persist, and activating microglia with lipopolysaccharide is sufficient to elicit the net loss in wild-type animals (Crapser and colleagues, 2020). The net is stripped, the strippers are microglia, and the microglia are running the machine this dissertation has spent nine chapters describing.

Assemble the chain. Amyloid-β primes and triggers the microglial NLRP3 inflammasome (Chapters II–III). The speck matures caspase-1, which issues interleukin-1β and interleukin-18 through the gasdermin-D pore (Chapters IV–VI). Interleukin-1β induces the aggrecanases and metalloproteinases, and the activated microglion degrades the perineuronal net and, with it, the sulfated heparan-sulfate bed on which that net is built (Crapser and colleagues, 2020). Now the three offices of the sulfated surface (Chapter IX) fail together, on one polymer, in one act:

- The **armour** is stripped: the aggrecan net that lowered the enwrapped neuron's tangle burden is gone, and the parvalbumin interneurons it protected are exposed.
- The **stage** is degraded: with the N-sulfated heparan-sulfate bed dissolved, reelin loses its obligate co-receptor and can no longer cluster ApoER2 or phosphorylate Disabled-1 (Pan and colleagues, 2025). The tau-brake is lifted. This is a second, independent route to the **reelin resistance** of Chapter VIII — not the amyloid trapping the ligand (Cuchillo-Ibáñez and colleagues, 2016) but the cytokine dissolving the ligand's stage. The guardian is gagged not only by having its mouth stopped but by having the floor pulled from under it.
- The **gate** is opened: the remodelled heparan-sulfate surface presents the docking site through which tau seeds enter and propagate (Holmes and colleagues, 2013), so the same act that unbrakes tau's phosphorylation also admits tau's templated spread.

And the disinhibited kinase does not wait alone. The moment reelin's brake is lifted from glycogen-synthase-kinase-3β, the inflammasome's *second* cytokine is already pushing the same kinase up: interleukin-18 raises glycogen-synthase-kinase-3β directly in human neurons (Sutinen and colleagues, 2012). The speck therefore converges on one enzyme from two directions at once — lifting reelin's foot off the brake by degrading its sulfated stage, and leaning on the accelerator by cytokine. This is the deepest form the bridge takes: not a chain but a pincer, closing on GSK-3β.

The convergence is corroborated at the level of whole-animal genetics by the most important single experiment for this thesis. Loss of NLRP3 inflammasome function **reduces tau hyperphosphorylation and aggregation by regulating tau's kinases and**

phosphatases, and fibrillar amyloid-β induces tau pathology in an NLRP3-dependent manner — placing the inflammasome squarely on the causal path between amyloid and tau, acting through the very phospho-regulatory machinery reelin controls (Ising and colleagues, 2019). And the relationship is reciprocal, which closes the loop into a self-sustaining cycle: aggregated tau itself activates the NLRP3–ASC inflammasome and exacerbates tau pathology (Stancu and colleagues, 2019). Once the speck has torn down reelin's stage and raised the kinase, the tau it helps to build re-activates the speck. The amplifier, having disabled the brake, is fed by the very pathology the disabled brake permits.

Two disciplines must be imposed on this bridge, and both are honoured in the Ledger. First, the **parallel-effects** caveat: amyloid-β independently drives both arms of the pincer — it primes the inflammasome *and* it traps reelin directly (Cuchillo-Ibáñez and colleagues, 2016) — so the inflammasome route and the direct-amyloid route are not mutually exclusive, and the inflammasome's share of the observed reelin resistance is not yet quantified. Second, the **companion-driver** caveat: the enzymatic degradation of reelin's sulfated stage has already been argued, in a sibling dissertation, to be driven by the noradrenergic control of matrix proteases downstream of the locus coeruleus. The inflammasome-cytokine route developed here does not displace that noradrenergic route; it stands beside it as a second hand on the same protease output — two upstream commanders, one matrix-catabolic secretome, one degraded surface. The bridge claims that the inflammasome is *a* cause of the unstaging, load-bearing and specific, not the only one.

With the bridge built, the two literatures are one. The speck and the architect are the same lesion, read from two ends.

XI. The Two Ends of One Lesion — Convergence on One Kinase

Stand back from the molecules and look at the shape. This dissertation began with two literatures that had never been introduced: an innate-immune machine studied by immunologists, and a developmental glycoprotein studied by neuroscientists of the synapse. It ends with a single object seen from two sides. The object is the phosphorylation state of one kinase, glycogen-synthase-kinase-3β, and the two sides are the two literatures.

From the immunological side, the kinase is *pushed up*. The speck matures interleukin-18, which raises glycogen-synthase-kinase-3β directly (Sutinen and colleagues, 2012); the speck's interleukin-1β

dissolves the sulfated matrix; and loss of the whole machine reduces tau phosphorylation by acting on tau's kinases and phosphatases (Ising and colleagues, 2019). From the neuroscientific side, the same kinase is *held down* — by reelin, staged on the sulfated matrix, signalling through Disabled-1 (Hiesberger and colleagues, 1999), its power measured in the decades of dementia-resistance it buys a human being who signals it harder (Lopera and colleagues, 2023). The disease is what happens when the hand that pushes up strengthens while the hand that holds down is knocked away — and the argument of Chapter X is that they are not two independent misfortunes but one, because the very act that strengthens the push (inflammasome activation, cytokine release) is the act that removes the restraint (degradation of reelin's sulfated stage). One event; two ends; one kinase.

This is why the title pairs the speck with the architect and not, say, the speck with the tangle. The tangle is the outcome; the architect is the antagonist whose defeat produces the outcome. The inflammasome does not build the tangle with its own hands. It builds the tangle by defeating the molecule whose entire homeostatic office was to prevent it — by dissolving the sulfated floor on which that molecule must stand to work, while simultaneously raising the kinase that molecule exists to restrain. The lesion is the defeat of the architect, and the speck is the instrument of the defeat.

The framing also disciplines the causal claim in a way both parent literatures demand. Neither the speck nor the architect *initiates* Alzheimer's disease. Amyloid-β is upstream of the inflammasome — it is the priming and triggering ligand — and amyloid-β is upstream of reelin resistance — it traps the ligand directly. The inflammasome and the reelin axis are both, in the vocabulary this corpus has settled on, **modifiers**: the one an amplifier, the other a resilience factor. What the convergence establishes is not a new initiator but a new *mechanism of amplification* — a specific, physical account of how the innate-immune amplifier does a large part of its damage, namely by disabling the disease's most powerful endogenous brake at the surface where that brake is anchored. The convergence makes two well-evidenced modifiers into one mechanism, and in doing so it makes both more consequential than either was alone: the inflammasome matters more because it explains reelin resistance, and reelin matters more because it explains what the inflammasome destroys.

One lesion, then, read from two ends. The remaining question is the practical one — whether an account that names the lesion also names a place to intervene.

XII. The Therapeutic Knife-Edge

A synthesis earns its keep by the interventions it implies and by the honesty with which it names their dangers. The convergence of this dissertation offers three points of interruption, arranged from

the best-evidenced to the most speculative, and each carries a specific hazard that the mechanism itself predicts.

Silence the sensor. The most direct and best-evidenced intervention is to inhibit the inflammasome upstream of both its outputs. The specific small-molecule NLRP3 inhibitor MCC950 blocks the sensor and, in Alzheimer models, promotes the non-inflammatory clearance of amyloid and reduces pathology (Coll and colleagues, 2015); the whole rationale for inflammasome-directed therapy in Alzheimer's disease rests on this arm (White and colleagues, 2017). In the framework built here, silencing the sensor is attractive precisely because it interrupts *both* ends of the pincer at their common origin: no active caspase-1 means no interleukin-18 to raise the kinase and no interleukin-1β to dissolve reelin's stage. The hazard is the one every anti-inflammatory strategy carries into a disease of the aged brain: the inflammasome is a genuine arm of host defence, and chronic systemic blockade risks infection and blunts legitimate immunity. Targeting the trigger rather than the priming lock, and delivering to the brain rather than the body, are the levers by which that hazard is managed.

Spare the sugar. The bridge chapter localises the damage to a specific surface — the N-sulfated heparan-sulfate bed that stages reelin — and thereby predicts a subtle and non-obvious therapeutic trap. Because the *same* heparan-sulfate surface both stages reelin (protective) and admits tau seeds (harmful), the intuitive strategy of blocking heparan sulfate to stop tau propagation (Holmes and colleagues, 2013) would, if it worked by degrading or masking the sulfated bed, *also silence reelin* (Pan and colleagues, 2025) — curing the gate by demolishing the stage. This is a genuine knife-edge, and the mechanism sharpens it into a design rule: an anti-tau therapy aimed at heparan sulfate must discriminate between the sulfation codes that stage reelin (N-sulfation) and those that admit tau, and must tune the surface rather than abolish it. The correct therapeutic verb is not *block* but *preserve*: protect the sulfated bed from the aggrecanases, and both offices — the staging and the withholding of the gate — are kept intact together.

Restore the brake above the speck. The most speculative intervention is the one Chapter VII introduced. If LL-37 can be held in its suppressing configuration, it brakes NLRP3-mediated interleukin-1β release at both locks (Hu and colleagues, 2014) and binds amyloid-β before it can prime (De Lorenzi and colleagues, 2017), and because LL-37 is inducible — by vitamin D, by butyrate — this arm is, in principle, reachable by the diet and the microbiome rather than the pharmacy. But this is the point of maximum hazard in the whole account, and the mechanism itself supplies the warning: the same peptide, in the wrong cellular configuration, *activates* the inflammasome through P2X7 (Kahlenberg and colleagues, 2013), and LL-37 carries independent pro-inflammatory and pro-autoimmune liabilities in other diseases. To raise LL-37 blindly is as likely to turn the machine on as off. This arm is offered as a hypothesis to be tested, not a therapy to be prescribed, and it is graded accordingly.

Three interruptions, then — the sensor, the sugar, the brake — arranged along a descending gradient of evidence and an ascending gradient of risk. The disease's origin remains beyond all three; none of these interventions is claimed to prevent Alzheimer's disease from beginning. What they share is that they target the *amplification* — the point at which the innate-immune machine defeats the endogenous brake — which is the one part of the causal chain this dissertation claims we already know three ways to interrupt.

XIII. The Validity Ledger

Every load-bearing claim of this dissertation is entered below at its true evidentiary weight, with the experiment that would settle it. Two standing caveats govern the entire ledger. The **translational discount**: much of the decisive causal evidence — inflammasome knockout, gasdermin biology, reelin-reduction, the aggrecanase induction — is murine or in vitro, and its transfer to the human brain is assumed, not shown. The **parallel-effects caveat**: amyloid-β independently drives most of the arcs described here, so demonstrating that a mechanism *can* operate is not demonstrating the *share* of the human pathology it accounts for.

Strong (imported, established) — the NLRP3 inflammasome is a two-signal device whose speck matures IL-1β and IL-18 and cleaves gasdermin-D. The two-signal architecture, the potassium-efflux trigger, NEK7, the ASC speck as caspase-1-activating platform, and gasdermin-D as the pore-forming pyroptosis effector are established across independent laboratories (Muñoz-Planillo and colleagues, 2013; He and colleagues, 2016; Shi and colleagues, 2015; Kayagaki and colleagues, 2015; Ding and colleagues, 2016; He and colleagues, 2015). This is the machine, and rejecting it requires deliberate misreading. *Settling experiment: none required; this is textbook.*

Strong (imported, established) — the inflammasome is active in the human Alzheimer brain and contributes causally to pathology in models. Elevated IL-1 in Alzheimer tissue (Griffin and colleagues, 1989), assembled NLRP3/NLRP1 inflammasomes in patients (Saresella and colleagues, 2016), cleaved gasdermin-D in human Alzheimer microglia, astrocytes and neurons (Moonen and colleagues, 2023), NLRP3/caspase-1 knockout protection in APP/PS1 mice (Heneka and colleagues, 2013), and speck cross-seeding of amyloid (Venegas and colleagues, 2017) together establish an active, contributory machine. *Settling experiment: an inflammasome inhibitor trial in humans with a tau-imaging endpoint.*

Strong (imported, established) — reelin is a tau-braking synaptic guardian and a genuine human resilience factor. The reelinApoER2/VLDLRDab1GSK-3βtau axis (Hiesberger and colleagues, 1999), synaptic antagonism of amyloid-β (Durakoglugil and colleagues, 2009), and above all two human resistance cases (Arboleda-Velasquez and colleagues, 2019; Lopera and colleagues, 2023) place reelin's protective reality beyond reasonable doubt. *Settling experiment: none required for the guardianship itself.*

Strong (imported) — reelin requires an intact N-sulfated heparan-sulfate bed to signal, and that bed also gates tau uptake. The heparan-sulfate co-receptor requirement (Pan and colleagues, 2025) and the heparan-sulfate tau-entry gate (Holmes and colleagues, 2013) are directly demonstrated. This is the keystone of the bridge. *Settling experiment: show, in human Alzheimer tissue, that regions of aggrecanase-degraded matrix co-localise with lost Dab1 phosphorylation.*

Moderate — IL-1β degrades the perineuronal net / sulfated matrix in the Alzheimer brain via the microglial aggrecanase secretome. That IL-1β induces ADAMTS aggrecanases and MMPs is strong general biology; that microglia strip the perineuronal net in the Alzheimer brain, plaque-dependently and reversibly on microglial depletion, is directly shown (Crapser and colleagues, 2020). The specific step that IL-1β *is the cytokine* commanding the observed net loss in the Alzheimer brain is inferred from the convergence, not measured in situ. *This is the weakest load-bearing joint on the inflammasome side. Settling experiment: conditional deletion of IL-1 signalling, or IL-1 receptor antagonism, and quantification of perineuronal-net preservation and Dab1-phosphorylation rescue in an Alzheimer model.*

Moderate — IL-18 raises GSK-3β in neurons, converging with reelin-unstaging on one kinase. The IL-18GSK-3β result is demonstrated in human neuron-like cells (Sutinen and colleagues, 2012), and NLRP3 loss reduces tau phosphorylation by regulating tau kinases/phosphatases in vivo (Ising and colleagues, 2019). The claim that the cytokine push and the reelin-brake release act on the *same molecular pool* of GSK-3β in the same neuron is a synthesis. *Settling experiment: in a single neuronal system, show additive tau hyperphosphorylation from IL-18 exposure plus heparan-sulfate-bed degradation, abolished by GSK-3β inhibition.*

Plausible (synthesis) — inflammasome-driven matrix degradation is a load-bearing route to reelin resistance, parallel to direct amyloid trapping. Reelin resistance is established (Cuchillo-Ibáñez and colleagues, 2016); that a substantial share of it proceeds through inflammasome-cytokine-driven degradation of reelin's sulfated stage, rather than through amyloid trapping the ligand, is this dissertation's novel and unproven claim. *Settling experiment: dissociate the two routes — inhibit the inflammasome in a model where amyloid-reelin trapping is held constant, and measure the recovered reelin signal.*

Plausible (kinetic/therapeutic argument) — sparing the N-sulfated bed preserves the reelin stage while an anti-tau strategy would demolish it. Follows directly

from the shared-surface fact (Pan and colleagues, 2025; Holmes and colleagues, 2013); untested as a therapeutic discrimination. *Settling experiment: a sulfation-code-selective agent that blocks tau uptake without impairing reelin-induced ApoER2 clustering.*

Contested / thinly evidenced (and honestly the argument's most speculative element) — LL-37 is an endogenous suppressor of NLRP3-mediated IL-1β release relevant to the brain. The suppressor arm is real but peripheral (Hu and colleagues, 2014); the amyloid-binding arm is in vitro (De Lorenzi and colleagues, 2017); and an activating arm exists in the same peptide (Kahlenberg and colleagues, 2013). No demonstration exists in human microglia, and the parenchymal concentration is unmeasured. *Settling experiment: measure LL-37 in Alzheimer parenchyma and test, in human microglia, whether it suppresses or activates the amyloid-primed NLRP3 inflammasome.*

Not established (and not required) — that any element here initiates Alzheimer's disease. Amyloid-β is upstream of both the inflammasome and reelin resistance; the whole account is of amplification and resilience-failure, not initiation. This is a boundary, deliberately drawn.

Rejected as stated — "reelin loss initiates the disease" and "the inflammasome initiates the disease." Both are rejected by the same logic the parent literatures rejected them: reelin is a modifier whose failure is downstream of amyloid trapping and matrix degradation, and the inflammasome is a sensor guaranteed to be found active at any neurodegeneration. Neither is the seed. Both are load-bearing amplifiers of a fire lit elsewhere.

XIV. Falsifiable Predictions

The synthesis is worth stating only if it can be shown to be wrong. The following predictions are ordered from the most discriminating — those whose failure would most damage the thesis — to the least.

1. Spatial coincidence of matrix loss and unstaged reelin. In human Alzheimer tissue, regions of aggrecanase-degraded perineuronal net and reduced N-sulfated heparan sulfate will co-localise with regions of reduced Disabled-1 phosphorylation and increased active (non-inhibited) glycogen-synthase-kinase-3β, on a background of preserved or elevated total reelin protein. *If reelin signal falls where the sulfated bed is intact, the staging mechanism is wrong.*

2. Inflammasome inhibition rescues the reelin signal, not merely inflammation. Silencing NLRP3 or antagonising the interleukin-1 receptor in an Alzheimer model will preserve the perineuronal net and *recover reelin-induced Disabled-1 phosphorylation*, and the tau-protective effect of inflammasome inhibition will be attenuated when reelin signalling is independently blocked. *If inflammasome inhibition protects tau with reelin signalling clamped off, the brake-disabling route is not load-bearing.*

3. Two-hit convergence on GSK-3β. In a neuronal system, interleukin-18 exposure and degradation of the heparan-sulfate bed will produce additive tau hyperphosphorylation that a glycogen-synthase-kinase-3β inhibitor abolishes — demonstrating that the cytokine push and the reelin-brake release converge on one kinase. *If the two hits are not additive on GSK-3β, the pincer is two separate stories.*

4. Sulfation-selective dissociation of stage and gate. An agent selective for the sulfation motifs that admit tau, sparing those that stage reelin, will reduce tau uptake without reducing reelin-induced ApoER2 clustering. *If the two functions cannot be pharmacologically separated, the "spare the sugar" therapeutic is unreachable, though the mechanism may still hold.*

5. LL-37 configuration determines direction in microglia. In human amyloid-primed microglia, LL-37 will suppress NLRP3-mediated interleukin-1β release under conditions favouring lipopolysaccharide-neutralisation and P2X7 blockade, and activate it under conditions favouring P2X7 engagement — with the parenchymal concentration determining which face dominates in vivo. *If LL-37 only ever activates the microglial inflammasome, the brake-above-the-speck hypothesis fails, and only the amyloid-binding arm survives.*

6. Interneuron-selective vulnerability. The neurons that both bear perineuronal nets and secrete reelin into them — the parvalbumin-positive and GABAergic interneurons — will show earlier and disproportionate loss of net, reelin signal, and, via the pore arm, pyroptotic markers, relative to net-poor neurons. *If net-bearing interneurons are not preferentially affected, the coupled-device assault on the sulfated interface is overstated.*

XV. Coda The Brake, the Blade, and the Wall

The dissertation set out to join two things that had never been introduced: a machine and an architect. The machine is the inflammasome — a two-locked device that assembles a speck, activates a protease, and issues two outputs, a pair of cytokines and a pore. The architect is reelin — a developmental glycoprotein that stayed on as the adult synapse's guardian, holding the tau kinase down, its power proven by the human beings it has saved. Between them lay a wall of sulfated sugar,

and on that wall three things were written at once: the armour that shielded the neuron, the stage on which the architect stood to work, and the withheld gate through which the tangle spreads.

The argument was that the machine dismantles the wall, and that in dismantling it the machine defeats the architect. Its chief cytokine, interleukin-1β, is across all of biology the instruction to dissolve the matrix, and the microglia that carry the machine are seen to dissolve exactly this matrix in the Alzheimer brain. When the wall comes down the armour is stripped, the stage is degraded so the architect can no longer signal, and the gate is opened to the seed — three losses on one polymer, in one act. And the kinase the architect had restrained is met, the instant its brake is lifted, by the machine's second cytokine leaning on it from the other side. The speck lifts the brake and floors the accelerator, and the two are the same event.

None of this begins the disease; the fire is lit elsewhere, by the amyloid that primes the machine and traps the architect alike. What the synthesis claims is narrower and, perhaps, more useful: that the point where the innate-immune amplifier does much of its damage is a nameable surface, and that we already hold three ways to defend it — silence the sensor, spare the sugar, restore the brake set above the speck. The wall can, in principle, be kept standing. The architect has not left the building; it has only lost the floor beneath its feet. The work is to keep the floor intact long enough for the architect to matter.

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