THE SENSOR AND THE SPECK

NLRP Inflammasomes, Pyroptotic Amplification, and the Innate-Immune Conversion of Alzheimer's Disease

The Sensor · The Amyloid Trigger · The Speck · The Bridge to Tau
The Cellular Geography · The Feed-Forward Spiral · The Grading of the Arcs

A Dissertation Submitted in Partial Fulfillment of the Requirements for the

Degree of Doctor of Philosophy in Neuroscience

Prepared under the Organic Network Synthesis methodology

AdultCognitiveDisease.com

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July 2026

Companion to Homeostatic Microglial Collapse — the specific innate-immune engine of the microglial collapse that volume describes, and an explicit, validity-graded assessment of the inflammasome hypothesis of Alzheimer's disease.

"The inflammasome is the brain's smoke detector wired to the sprinklers of its own destruction. It reads the aggregate as danger; and in the reading — the cytokine matured, the pore opened, the speck expelled to seed the neighbour — it manufactures the danger it read. The question is never whether it is activated. It is whether the fire needs the alarm to spread."

— ONS Methodology Working Notes, 2026

For Michael Heneka, who made the inflammasome a neurodegenerative organelle, and for Eicke Latz and Douglas Golenbock, who showed that the innate immune system reads amyloid as a danger signal.

THE COLLAPSE TRILOGY COMPANION VOLUME

I. Convergent Synaptic Collapse

II. Homeostatic Microglial Collapse parent volume

III. Bioenergetic Collapse

IV. The Tryptophan Partition · The Vascular Phasing · The Vagal Interface

V. The Coerulean Interface · The Microbial Prologue · The Pineal Interface

VI. The Sensor and the Speck this volume

This volume is the molecular engine of the microglial collapse. Where *Homeostatic Microglial Collapse* traces the transformation of microglia from a surveilling, synapse-supporting phenotype into a dysfunctional and cytotoxic one, the present volume identifies the specific organelle — the NLRP3 inflammasome — whose activation throws that switch, and grades, arc by arc, how much of the inflammasome hypothesis of Alzheimer's disease the evidence will bear.

Contents

Abstract

The dominant molecular narrative of Alzheimer's disease is a narrative of proteins — of amyloid-β that aggregates and of tau that follows — and the innate immune system has for most of that narrative's history been treated as reactive scenery, the smoke rather than the fire. This dissertation takes up the strongest single challenge to that reading: the proposition that a specific innate-immune organelle, the NLRP3 inflammasome of the microglion, is not scenery but machinery — a sensor that reads aggregated amyloid-β as a danger signal, converts that reading into the maturation and release of interleukin-1β and interleukin-18, and, through the same activation, assembles and disgorges the ASC "speck" that cross-seeds amyloid and relays the injury forward to tau. The NLRP (NOD-, LRR- and pyrin-domain-containing) family of cytosolic pattern-recognition receptors, of which NLRP3 is the best characterised and NLRP1 and NLRP2 the neuronal and astrocytic congeners, thus offers a mechanistically explicit account of how a proteinopathy becomes a self-amplifying inflammatory disease. The thesis assembles that account and then, in the adjudicative mode that distinguishes this corpus, grades it.

The evidence is unusually strong for a neuroinflammatory hypothesis and unusually honest about where its strength ends. Chapter I reconstructs the sensor: the two-signal logic by which a priming transcriptional signal and an activating danger signal are both required, the potassium-efflux and lysosomal-rupture triggers that converge on NLRP3–NEK7 oligomerisation, and the caspase-1 and gasdermin-D effectors that convert the assembled inflammasome into cytokine release and pyroptotic death. Chapter II traces the amyloid trigger from the foundational demonstration that fibrillar amyloid-β, phagocytosed by microglia, ruptures the lysosome and releases cathepsin B to activate the NLRP3 inflammasome, through the receptor logic (CD36, TLR4–TLR6) that assembles soluble amyloid into a particulate danger signal. Chapter III develops the speck and its two consequences — pyroptotic amplification and the prion-like propagation of ASC-nucleated amyloid — as the mechanism by which a cell-autonomous sensor becomes a spreading, tissue-level lesion. Chapter IV takes up the boldest and most consequential claim in the literature: that NLRP3 activation is the relay between amyloid and tau, driving tau hyperphosphorylation and seeding, and thereby occupying the long-vacant mechanistic position between the two proteinopathies. Chapter V corrects the microglia-centric picture by mapping the neuronal NLRP1 and astrocytic NLRP2 sensors and the pyroptotic geography of the human Alzheimer brain. Chapter VI formalises the feed-forward spiral in which cytokines impair the clearance of the amyloid that activated the inflammasome. Chapter VII grades every arc, from the strong (amyloid activates NLRP3; genetic deletion of Nlrp3 or Casp1 protects amyloid mice) through the moderate (ASC cross-seeding; the tau relay) to the contested (human genetic association; the initiating-versus-amplifying question) and confronts the reverse-causation problem directly: that inflammasome activation may be very largely a *consequence* of a primary proteinopathy that

generates its own danger signals, a powerful amplifier riding on a lesion it did not start.

The dissertation concludes that the inflammasome hypothesis is, on present evidence, the best-validated mechanistic bridge in the neuroinflammation of Alzheimer's disease and simultaneously the clearest illustration of the field's translational problem. Genetic and pharmacological suppression of NLRP3 is protective in every major amyloid and tau mouse model in which it has been tested, and cleaved caspase-1, ASC, and mature interleukin-1β are demonstrably elevated in the human Alzheimer brain; yet no anti-inflammatory intervention has ever altered the course of human Alzheimer's disease, and the inflammasome's own danger signals are generated by the pathology it is invoked to explain. The value of the framework is not the discovery of a new prime mover but the precise specification of an amplifier — of the node at which the innate immune system converts a slow proteinopathy into a faster, self-sustaining, and, in principle, druggable disease, and of the narrow early window in which interrupting that conversion could plausibly matter.

Keywords: NLRP3 inflammasome, NLRP1, NLRP2, ASC speck, caspase-1, pyroptosis, gasdermin-D, interleukin-1β, interleukin-18, microglia, amyloid-β, tau, cathepsin B, neuroinflammation, MCC950, innate immunity, Alzheimer's disease

1. Introduction

1.1 The Research Problem

For three decades the causal architecture of Alzheimer's disease has been organised around two proteins and the arrow between them. Amyloid-β, cleaved from its precursor and aggregated into oligomers and plaques, is placed upstream; hyperphosphorylated tau, aggregated into paired helical filaments and neurofibrillary tangles, is placed downstream; and the clinical disease is placed downstream of both. The amyloid cascade hypothesis, in its several revisions, has been the field's organising spine. Its most persistent embarrassment has been the arrow itself. Amyloid pathology correlates only weakly with the timing and topography of cognitive decline; tau pathology correlates strongly; and the mechanistic link by which amyloid, deposited diffusely across the cortex, should drive the stereotyped, staged, trans-synaptic march of tau has remained, for most of the hypothesis's history, a gap rather than a mechanism. Into that gap the field has poured candidate relays — synaptic, metabolic, vascular, and, increasingly, immune.

This dissertation takes up the immune candidate in its most mechanistically specific form. The genome-wide association studies of the past fifteen years have moved the innate immune system from the periphery of Alzheimer genetics to its centre: a substantial fraction of the common risk variants that survive genome-wide correction fall in or near genes expressed selectively or

predominantly in microglia — *TREM2*, *CD33*, *ABCA7*, *MS4A*, *INPP5D*, *SPI1*, *PLCG2*, and the complement genes among them. The disease's inherited risk is, to a degree that would have astonished the field in 1995, a risk carried by the brain's resident myeloid cells. But a genetic architecture is not a mechanism, and the demonstration that microglia matter is not yet a demonstration of *how* they matter. The research problem of this thesis is to determine whether a single, molecularly defined innate-immune device — the NLRP inflammasome, and above all the NLRP3 inflammasome of the microglion — supplies the mechanism: whether it is the sensor by which microglia read amyloid as danger, the amplifier by which they convert that reading into cytotoxic inflammation, and the relay by which the injury is carried forward to tau and outward across the tissue.

The problem is sharpened by a hard and honest difficulty that recurs throughout the thesis. The inflammasome is, by its evolved design, a sensor of danger — of the potassium efflux, the lysosomal rupture, the mitochondrial distress, and the extracellular ATP that accompany cellular injury of almost any origin. A degenerating brain, whatever the primary cause of its degeneration, generates precisely these danger signals in abundance. It is therefore guaranteed, before any experiment is performed, 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 not whether the inflammasome is activated — it is — but whether that activation is load-bearing: whether it feeds back onto the pathology that triggered it and accelerates a disease it did not begin, or whether it is an epiphenomenal readout of injury generated elsewhere. Distinguishing an amplifier from a bystander, in a system where the amplifier's inputs are produced by the very process it is proposed to amplify, is the central methodological problem of the field and the organising problem of this dissertation.

1.2 Significance

Posing the problem in this way carries four kinds of significance. First, it supplies the microglial-collapse account of the Collapse corpus with its most concrete molecular engine. The companion thesis *Homeostatic Microglial Collapse* traces the transformation of microglia from a homeostatic, surveilling, synapse-supporting phenotype into a dysfunctional, disease-associated one; the present thesis identifies the specific organelle whose activation is the proximate driver of the cytotoxic, interleukin-1β-secreting arm of that transformation. Where the companion volume describes a change of state, this one describes the switch that throws it.

Second, the framework connects two literatures that developed in mutual isolation. The inflammasome was characterised by immunologists studying gout, atherosclerosis, and infection, in whose hands NLRP3 became one of the best-understood signalling machines in cell biology; the neuroinflammation of Alzheimer's disease was characterised, largely separately, by neuroscientists cataloguing reactive microglia and elevated cytokines. The demonstration that the immunologists'

machine is the neuroscientists' mechanism — that fibrillar amyloid activates NLRP3 by the same lysosomal-rupture route as monosodium urate and silica — welds the two fields together and imports into Alzheimer research a molecular precision, and a pharmacology, that the cytokine-cataloguing tradition never had.

Third, the framework is falsifiable and, in one crucial respect, has already met the strongest test the field can offer a mouse hypothesis. If NLRP3 activation is load-bearing, then removing it should slow the disease; and in the amyloid-depositing mouse the genetic deletion of *Nlrp3* or of its effector caspase-1 does exactly that — reducing amyloid burden, preserving synapses and memory, and skewing microglia toward a clearance-competent phenotype. That result, reproduced across models and extended pharmacologically, is among the cleaner causal demonstrations in the neuroinflammation literature, and it is the empirical spine of the thesis. Its limitation — that it is a demonstration in a mouse, in a system whose translation to human disease has an almost unbroken record of failure — is the subject of Chapter VII and is not minimised.

Fourth, the framework reorganises a therapeutic question that the field has repeatedly asked badly. Anti-inflammatory intervention in Alzheimer's disease has a long history of failure, from the non-steroidal anti-inflammatory drug trials that were negative or harmful to the broad immunosuppressants that were never viable. But those interventions were blunt — inhibiting cyclooxygenase, or suppressing immunity globally — and they were administered late, to patients with established dementia. The inflammasome hypothesis predicts something different: a precise target (NLRP3, or its effector caspase-1, or the gasdermin-D pore) whose selective inhibition spares the rest of innate immunity, and a timing logic — early, before the feed-forward spiral has become self-sustaining — that the failed trials never respected. Whether that prediction is correct is unknown; that it is different, specific, and testable is the fourth significance of posing the problem in inflammasome terms.

1.3 Scope and Limitations

This dissertation is a synthetic and adjudicative review centred on Alzheimer's disease and on the NLRP family of inflammasome sensors, with NLRP3 at its centre. It is deliberately narrower than a general treatment of neuroinflammation. It does not develop the complement cascade, the microglial phagocytic and synaptic-pruning literature, the peripheral-immune and blood–brain-barrier literature, or the TREM2 and disease-associated-microglia transcriptional programmes, except where these bear directly on inflammasome priming and activation. It does not treat the AIM2 or pyrin inflammasomes, or the non-canonical caspase-4/5/11 pathway, beyond what is necessary to situate NLRP3. It concentrates on the microglial NLRP3 inflammasome as activator and amplifier, on the neuronal NLRP1 and astrocytic NLRP2 sensors as the cellular geography of the response, and on the ASC speck as the vehicle of propagation.

The thesis makes a bounded causal claim and states its limits at the outset. It does not claim that inflammasome activation initiates Alzheimer's disease. The weight of the evidence, developed honestly in Chapters IV and VII, places the inflammasome downstream of the first appearance of aggregated amyloid-β and most plausibly downstream of the earliest tau lesion of the locus coeruleus as well; and the sensor's own danger-signal inputs are generated by that upstream pathology. The thesis claims, more modestly, that inflammasome activation is a validated *amplifier* — that it feeds back onto amyloid clearance, relays the injury to tau, propagates through the tissue by ASC seeding, and thereby converts a slow proteinopathy into a faster and self-sustaining one. Where the evidence for an arc is strong, the thesis says so; where it rests on a single laboratory, on mouse models alone, or on correlation in human tissue, the thesis says that instead. Chapter VII is given over entirely to that grading, and Chapter VIII states the conditions under which the framework would be falsified. The dissertation's ambition is not to add a prime mover to the crowded list of proposed causes of Alzheimer's disease, but to specify precisely and falsifiably what the inflammasome does to a disease it did not start.

2. Literature Review

2.1 The NLRP Family and the Architecture of the Inflammasome

The inflammasome is a cytosolic supramolecular complex that converts the recognition of danger into the proteolytic maturation of inflammatory cytokines and, frequently, into a lytic form of programmed cell death. Its sensor component in the case of interest here belongs to the NLR family — the nucleotide-binding-domain, leucine-rich-repeat-containing receptors — and specifically to the NLRP subfamily, whose members carry an N-terminal pyrin domain (PYD), a central nucleotide-binding and oligomerisation domain (NACHT), and a C-terminal leucine-rich-repeat (LRR) region that has classically been assigned a ligand-sensing and autoinhibitory role (Latz, Xiao & Stutz, 2013; Swanson, Deng & Ting, 2019). Fourteen NLRP genes exist in the human genome; three are central to this dissertation. NLRP3 is the promiscuous danger sensor of myeloid cells, activated not by a single ligand but by a diverse set of stimuli that share the capacity to perturb cellular homeostasis. NLRP1, the first inflammasome sensor described, is expressed in neurons and is distinguished by a C-terminal CARD and a function-to-form activation by proteolytic autoprocessing. NLRP2 is expressed in astrocytes. Each assembles, upon activation, an inflammasome; each converges on the same downstream effectors; and each has been implicated, with descending confidence, in Alzheimer's disease.

The assembly logic is shared and worth stating precisely because the pharmacology depends on it. Upon activation, the NLRP sensor oligomerises through its NACHT domain and nucleates the polymerisation of the adaptor protein ASC (apoptosis-associated speck-like protein containing a CARD) into a single, micron-scale, perinuclear filamentous aggregate — the "speck" — through homotypic PYD–PYD interactions. The clustered CARD domains of ASC then recruit pro-caspase-1 through CARD–CARD interactions, and the resulting proximity-induced autoactivation of caspase-1 is the catalytic heart of the inflammasome (Latz, Xiao & Stutz, 2013). Active caspase-1 cleaves the biologically inert precursors pro-interleukin-1β and pro-interleukin-18 into their secreted, bioactive forms, and cleaves gasdermin-D, whose liberated N-terminal fragment oligomerises in the plasma membrane to form the pore through which the mature cytokines are released and through which, at the extreme, the cell undergoes pyroptosis — an inflammatory, lytic death that spills the cell's contents, including the ASC speck itself, into the extracellular space (Shi et al., 2015; Kayagaki et al., 2015). Each of these steps — sensor oligomerisation, ASC nucleation, caspase-1 autoactivation, gasdermin-D pore formation — is a discrete and, in principle, druggable node, and the therapeutic literature of Chapter VIII is organised around them.

2.2 The Two-Signal Model and the Triggers of NLRP3

NLRP3 is not activated by ligand binding in the conventional receptor sense; it is licensed and then triggered, and the two-signal model that captures this is essential to understanding both its biology and its regulation (Swanson, Deng & Ting, 2019). The first signal, *priming*, is typically delivered by a pattern-recognition or cytokine receptor — Toll-like receptor 4, for instance, or the interleukin-1 receptor itself — signalling through NF-κB to raise the transcription of NLRP3 and of pro-interleukin-1β, which are otherwise expressed at levels too low to support inflammasome assembly. Priming also has a rapid, non-transcriptional arm, licensing NLRP3 through post-translational modification. The second signal, *activation*, is delivered by one of the diverse danger stimuli that trigger NLRP3 oligomerisation.

The unifying feature of these otherwise unrelated activators has been the object of two decades of investigation, and three convergent mechanisms are well established. First, potassium efflux: the drop in cytosolic potassium concentration that accompanies membrane damage or ATP-driven P2X7 receptor opening is a common and possibly obligatory upstream trigger, and its downstream requirement for the kinase NEK7, which bridges adjacent NLRP3 molecules to license oligomerisation, has been defined (Muñoz-Planillo et al., 2013; He et al., 2016). Second, lysosomal destabilisation: the phagocytosis of crystalline or aggregated particulates — monosodium urate, silica, aluminium salts, and, decisively for this thesis, fibrillar amyloid-β — ruptures the phagolysosome and releases the lysosomal protease cathepsin B into the cytosol, where it participates in NLRP3 activation (Hornung et al., 2008; Halle et al., 2008). Third, mitochondrial dysfunction: the generation of mitochondrial reactive oxygen species and the externalisation of mitochondrial cardiolipin and DNA provide a further activating input, coupling the inflammasome

to the bioenergetic distress that the Collapse corpus places at the origin of neuronal vulnerability (Zhou et al., 2011). These three routes are not mutually exclusive; they converge on the same sensor, and each is engaged by the pathological milieu of the Alzheimer brain.

2.3 Amyloid-β as an Inflammasome Activator

The foundational demonstration that connects the inflammasome machine to Alzheimer's disease is that of Halle and colleagues (2008), who showed that fibrillar amyloid-β, once phagocytosed by microglia, activates the NLRP3 (then NALP3) inflammasome. The mechanism they defined is the lysosomal-rupture route: internalised amyloid fibrils damage the phagolysosomal membrane, cathepsin B is released into the cytosol, and NLRP3-dependent caspase-1 activation and interleukin-1β secretion follow; genetic or pharmacological interruption of NLRP3, ASC, or cathepsin B each abolished the response, and microglia from Alzheimer-model mice showed the pathway engaged in situ. This single paper did three things: it identified amyloid-β as a bona fide NLRP3 activator, it placed the response mechanistically alongside the archetypal sterile-particulate activators urate and silica, and it made the microglion, not the neuron, the primary cellular site of the inflammasome response to amyloid.

The receptor logic upstream of internalisation was subsequently defined. Sheedy and colleagues (2013) showed that the scavenger receptor CD36 coordinates the conversion of soluble amyloid-β into the particulate, fibrillar form that the inflammasome senses — nucleating intracellular aggregation of the peptide — and that CD36, acting with the Toll-like-receptor-4–Toll-like-receptor-6 heterodimer, both delivers the priming signal and generates the activating ligand. Amyloid-β is thus not merely a passive cargo but is assembled by the microglion's own receptors into the danger signal that triggers the sensor: priming and activation are supplied by the same peptide through the same receptor complex. This receptor circuitry matters for the reverse-causation argument of §2.9, because it shows that the microglion participates actively in manufacturing its own inflammasome trigger, and for the therapeutic argument of Chapter VIII, because it multiplies the nodes at which the amyloid-to-caspase pathway can be interrupted.

2.4 The Genetic-Deletion Evidence: Heneka and the Causal Test

The transition from "amyloid activates the inflammasome in a dish" to "the inflammasome contributes to disease in an animal" was accomplished by Heneka and colleagues (2013), in the paper that remains the causal spine of the field. Crossing NLRP3-deficient or caspase-1-deficient mice onto the APP/PS1 amyloid model, they found that inflammasome-deficient animals were largely protected from the disease's consequences: they retained spatial memory, were spared the loss of synaptic proteins, showed reduced cerebral amyloid-β deposition, and — mechanistically — displayed a microglial phenotype skewed toward the clearance-competent, tissue-reparative end of the activation spectrum, with enhanced amyloid phagocytosis. In the same study, cleaved caspase-1 was shown to be elevated in human Alzheimer brain tissue relative to controls, establishing that the pathway engaged in the mouse is engaged in the human disease. The result was not a demonstration that the inflammasome is necessary for amyloid to be produced — amyloid was still generated — but that inflammasome activity governs whether that amyloid is cleared or allowed to accumulate, and whether its presence is translated into synaptic and cognitive injury.

The importance of this experiment for the present thesis is that it inverts the usual epistemic weakness of neuroinflammation research. The typical neuroinflammation finding is correlative — activated microglia are present, cytokines are elevated — and cannot distinguish cause from consequence. The genetic-deletion experiment is subtractive and prospective: it removes the candidate mechanism before the disease develops and asks whether the disease is attenuated, and it answers that it is. This is the strongest causal design available short of a human trial, and its result is unambiguous within its model system. Its limitation is equally clear and is developed at length in Chapter VII: it is a result in a mouse over-expressing mutant human transgenes, in a model whose amyloid biology is caricatured relative to sporadic human disease, and the graveyard of Alzheimer therapeutics is filled with mechanisms that were protective in exactly such models and inert in patients.

2.5 The ASC Speck and Prion-like Propagation

If the genetic-deletion evidence is the thesis's causal spine, the ASC speck is its most conceptually novel arc, because it converts the inflammasome from a cell-autonomous device into an agent of spread. Venegas and colleagues (2017) demonstrated that the ASC speck, released into the extracellular space when a microglion undergoes pyroptosis, does not simply dissipate: it binds amyloid-β directly, and the speck–amyloid complex cross-seeds the aggregation of further amyloid-β, increasing plaque formation. Injecting purified ASC specks into amyloid-model mice increased amyloid pathology; genetically depleting ASC, or administering an anti-ASC antibody, reduced it; and ASC was shown to colocalise with amyloid in human Alzheimer brain. The speck, in this account, is a prion-like nucleating scaffold: an intracellular signalling intermediate that, once expelled by the death of its host cell, becomes an extracellular seed for the very pathology whose sensing produced it. The subsequent demonstration that amyloid-β clusters around ASC fibrils and that this clustering enhances its toxicity to microglia (Friker et al., 2020) extends the arc from seeding to cytotoxicity.

This is a genuinely different kind of mechanism from cytokine-mediated inflammation, and it deserves to be held to a correspondingly high evidential standard, because its explanatory reach is large: it offers, in principle, a route by which inflammasome activation in one region seeds proteinopathy in another, and thus a candidate contribution to the tissue-level spread that is the signature of the disease. The evidence is strong within the originating laboratory and has the internal coherence of a demonstrated bidirectional intervention — specks worsen, anti-speck rescues — but it remains, at the time of writing, substantially the product of a single group, and independent replication of the cross-seeding claim across laboratories is less extensive than for the amyloid-activation and genetic-deletion arcs. It is graded accordingly in Chapter VII.

2.6 The Inflammasome–Tau Axis

The most consequential claim in the inflammasome literature, because it addresses the field's central mechanistic vacancy, is that NLRP3 activation is a relay between amyloid and tau. Ising and colleagues (2019) reported that NLRP3 inflammasome activation drives tau pathology: in tau-transgenic mice, genetic deletion of NLRP3 or of ASC reduced tau hyperphosphorylation and aggregation and rescued cognitive function; inflammasome activation altered the balance of tau kinases and phosphatases in a direction favouring pathological phosphorylation; and, decisively, the tau pathology induced by injected amyloid-β-containing brain homogenate required a functional microglial NLRP3 inflammasome. The last result is the load-bearing one: it places the inflammasome mechanistically *between* amyloid and tau, such that amyloid drives tau through the microglial inflammasome rather than directly. Independently, Stancu and colleagues (2019) showed the reciprocal arc — that aggregated tau itself activates the NLRP3–ASC inflammasome in microglia, and that ASC specks promote tau seeding and the exacerbation of tau pathology in vivo — closing a loop in which the inflammasome both responds to tau and propagates it.

Taken together, these two studies propose that the inflammasome occupies the long-vacant relay position of the amyloid cascade: amyloid activates the microglial inflammasome, the inflammasome drives tau, and tau in turn re-activates the inflammasome. If correct, this is the single most important thing the inflammasome does in Alzheimer's disease, because it converts the inflammasome from a modulator of amyloid clearance into the mechanistic bridge across the amyloid–tau gap. The claim's importance is matched by the standard to which it must be held, and Chapter IV develops both the evidence and its limits: the tau-relay arc rests principally on the Ising and Stancu studies, is mouse-based, and involves a proposed kinase/phosphatase mechanism (including the dephosphorylating phosphatase PP2A and the CaMKII kinase) that is incompletely specified. It is a strong and important hypothesis that has not yet accumulated the breadth of independent confirmation that the amyloid-activation arc enjoys.

2.7 Neuronal NLRP1 and Astrocytic NLRP2

The microglia-centric account of the inflammasome, though dominant and best-evidenced, is incomplete, because the NLRP family is expressed across the brain's cell types and the pyroptotic machinery is engaged in neurons and astrocytes as well as microglia. NLRP1, historically the first inflammasome sensor described, is expressed in neurons; Tan and colleagues (2014) reported that amyloid-β induces NLRP1-dependent neuronal pyroptosis in models of Alzheimer's disease, and Kaushal and colleagues (2015) defined a neuronal NLRP1–caspase-1 axis that coordinately regulates interleukin-1β production and the caspase-6-dependent axonal degeneration that is a feature of the disease. Astrocytes, for their part, express a functional NLRP2 inflammasome (Minkiewicz, de Rivero Vaccari & Keane, 2013), positioning the second major glial population as an inflammasome-competent participant. The human confirmation that these are not merely model-system phenomena came from Moonen and colleagues (2023), who demonstrated cell-type-specific activation of the pyroptotic executioner gasdermin-D in microglia, astrocytes, and neurons in human Alzheimer brain tissue, mapping the pyroptotic geography of the disease directly.

The significance of the neuronal and astrocytic sensors is that they change the interpretation of inflammasome-driven injury from a purely paracrine one — microglia secreting cytokines that harm neurons — to one that includes cell-autonomous neuronal death by pyroptosis. If neurons die in part by NLRP1-driven, gasdermin-D-executed pyroptosis, then the inflammasome is not only an amplifier of the microglial inflammatory environment but a direct executioner of the neuron, and the therapeutic calculus shifts accordingly. The evidence for the neuronal and astrocytic arcs is thinner than for the microglial one — fewer laboratories, smaller literatures, and, in the case of NLRP1, a species complication in that human and rodent NLRP1 differ substantially in structure and regulation — and it is graded with corresponding caution.

2.8 Human Tissue, Genetics, and Biomarkers

The human evidence that the inflammasome is engaged in Alzheimer's disease is, at the level of protein and cell, consistent. Cleaved caspase-1, ASC, and mature interleukin-1β are elevated in Alzheimer brain tissue and cerebrospinal fluid (Heneka et al., 2013; Saresella et al., 2016); the historical observation that interleukin-1 is overexpressed in the Alzheimer and Down-syndrome brain long predates the inflammasome framework and is among the oldest neuroinflammatory findings in the field (Griffin et al., 1989); and interleukin-18, the second inflammasome cytokine, is elevated in the disease. Saresella and colleagues (2016) demonstrated that both the NLRP3 and NLRP1 inflammasomes are activated in the peripheral mononuclear cells of Alzheimer patients, extending the finding beyond the brain and offering a potential accessible biomarker compartment. The pyroptotic-geography study of Moonen and colleagues (2023) provides the most direct in-situ human confirmation.

The human *genetic* evidence, by contrast, is weak and inconsistent, and this dissertation states so plainly. Unlike *TREM2* or *CD33*, the *NLRP3* locus is not among the robustly replicated genome-wide-significant Alzheimer risk genes. Candidate-gene studies of gain-of-function and regulatory *NLRP3* polymorphisms and of the related *CARD8* variant have reported associations in some cohorts and not others, with the modest sample sizes and known replication problems of the candidate-gene era; no *NLRP3* variant has the standing of an established common risk allele. This is an important asymmetry: the pathway is demonstrably *engaged* in the human disease at the protein level, and is demonstrably *causal* in the mouse at the genetic level, but the human *inherited* evidence that inflammasome activity sets disease risk is not there in the way it is for other microglial genes. The framework must carry this asymmetry openly, and Chapter VII does.

2.9 The Reverse-Causation Problem

The most serious objection to the inflammasome hypothesis is not that any of its arcs is weak but that its causal arrow may be, in large part, an artefact of the sensor's own design. The inflammasome is an evolved detector of cellular danger, and it responds to the generic signatures of injury — potassium efflux, lysosomal rupture, mitochondrial reactive oxygen species, extracellular ATP — regardless of what caused the injury. A neurodegenerating brain generates all of these signals abundantly and by mechanisms wholly independent of the inflammasome: failing neurons leak ATP, dying cells release DAMPs, oxidatively stressed mitochondria produce reactive oxygen species, and aggregated proteins of every kind perturb membranes. It is therefore certain, a priori, that the inflammasome will be found activated in any sufficiently advanced neurodegeneration, and its activation cannot by itself testify to a causal role. The strong form of the objection holds that inflammasome activation is very largely a *readout* of a proteinopathy driven by other means — an amplifier, at most, riding downstream on a lesion it did not start and would not, if silenced, prevent.

The thesis does not dismiss this objection; it regards it as substantially correct as to *initiation* and confronts it directly as to *amplification*. Three considerations bear on it. First, the genetic-deletion experiments (§2.4) are precisely the design that the reverse-causation objection cannot survive in the mouse: removing NLRP3 *before* disease develops and observing attenuated pathology shows that, at least in that system, inflammasome activity is not merely a consequence but a contributing cause of the downstream burden. Second, the feed-forward arcs — cytokine-impaired amyloid clearance (§2.4, Chapter VI) and ASC cross-seeding (§2.5) — are mechanisms by which the inflammasome acts back upon its own trigger, which is the signature of an amplifier rather than a bystander. Third, and against the thesis, none of this establishes *initiation*: the inflammasome is downstream of the first amyloid and, on the Collapse corpus's own account, downstream of the earliest locus-coeruleus tau lesion, and the sensor's inputs are manufactured by that upstream pathology. The honest resolution, adopted throughout and formalised in Chapter VII, is that the inflammasome is a validated amplifier and an unproven initiator — that it makes a proteinopathy worse and faster without being the reason the proteinopathy began.

2.10 Gaps in the Literature

Four gaps motivate the synthesis. First, the inflammasome literature and the disease-associated-microglia transcriptional literature have developed in parallel without full integration: the DAM/MGnD state defined by single-cell transcriptomics and the NLRP3-activated state defined by inflammasome biology are described in different vocabularies and have not been definitively reconciled, so that it remains unclear whether inflammasome activation is a feature of, an alternative to, or a driver of the DAM programme. Second, the human evidence is almost entirely cross-sectional and postmortem; there is no longitudinal human demonstration that inflammasome activation precedes and predicts tau spread or cognitive decline, which is precisely the temporal evidence the amplifier hypothesis most needs. Third, the neuronal and astrocytic arcs (§2.7) are under-evidenced relative to the microglial one and are complicated by species differences in NLRP1 biology, leaving the cell-autonomous-pyroptosis contribution poorly quantified. Fourth, the therapeutic literature has demonstrated benefit almost entirely in mouse models and has not yet produced a completed, adequately powered, appropriately timed human trial of a selective inflammasome inhibitor in Alzheimer's disease, so that the framework's central therapeutic prediction remains untested in humans. This dissertation addresses the first gap by synthesis, states the second and third as explicit limits, and reframes the fourth as a set of design predictions in Chapter VIII.

3. Methodology

This dissertation employs the Organic Network Synthesis (ONS) methodology of the AdultCognitiveDisease.com corpus, applied across the Collapse trilogy and its companion volumes. ONS treats the published literature as a network of mechanistic claims and seeks the convergence nodes at which independently developed frameworks make contact, on the premise that these nodes carry the explanatory leverage of a systems account. The present application shares with *The Pineal Interface* an explicitly adjudicative mode: because the causal status of inflammasome activation is genuinely contested — indeed, because the sensor's biology guarantees that it will be found activated whether or not it matters — the assembly of the argument is followed by a formal grading of each of its arcs, and the reverse-causation alternative is treated not as an objection to be rebutted but as a hypothesis to be weighed and, in the matter of initiation, largely conceded.

The method proceeds in five steps. First, *device identification*: the selection of the NLRP3 inflammasome as the candidate mechanistic engine, on the basis of its dual standing as one of the best-characterised signalling machines in immunology and one of the few neuroinflammatory

mechanisms subjected to a subtractive causal test in vivo. Second, *literature triangulation*: the assembly of three literatures that only partly cite one another — the immunological inflammasome literature of Latz, Tschopp, Núñez, and O'Neill; the Alzheimer neuroinflammation literature of Heneka, Golenbock, and their collaborators; and the human neuropathology of pyroptosis and cytokine expression. Third, *mechanistic reconstruction*: the tracing of the pathway from trigger (amyloid, tau, danger signals) through sensor (NLRP3, NLRP1, NLRP2) and adaptor (ASC) to effector (caspase-1, gasdermin-D) and consequence (cytokine release, pyroptosis, ASC seeding, tau relay), with each step referred to its primary evidence. Fourth, *loop construction*: the assembly of the surviving arcs into the feed-forward spiral, with explicit attention to the sign and strength of each arc and to the point at which amplification becomes self-sustaining. Fifth, *grading and prediction*: the assignment of an evidential verdict to each arc (Chapter VII), weighted toward disconfirmation, and the derivation of falsifiable predictions weighted toward those that discriminate the amplifier hypothesis from the bystander alternative (Chapter VIII).

The methodology has the limitations inherent to synthetic review — it cannot itself establish causation, and the spiral in particular is a hypothesised feedback loop inferred from its separately evidenced arcs rather than demonstrated as a whole. It carries two further limitations specific to this subject and stated plainly. The mechanistic and interventional evidence is overwhelmingly murine, in transgenic models whose amyloid and tau biology is caricatured relative to sporadic human disease and whose translational record is poor; and the human evidence, though consistent at the protein level, is cross-sectional and cannot resolve the direction of causation that the framework most needs resolved. The thesis foregrounds these limitations rather than suppressing them.

4. Chapter I The Sensor: The Molecular Logic of NLRP3 Activation in the Alzheimer Brain

4.1 The Device and Its Two Locks

The NLRP3 inflammasome is best understood not as a receptor but as a device with two locks, both of which must be opened before it fires. This design is not incidental to the Alzheimer story; it is the reason the inflammasome is a checkpoint rather than a switch, and the reason its pharmacology has the shape it does. The first lock, priming, is transcriptional and licensing: in the resting microglion, NLRP3 and pro-interleukin-1β are expressed too sparsely to support assembly, and a first signal — through Toll-like receptor 4, through the interleukin-1 receptor, through tumour-necrosis-factor signalling — must raise their abundance and post-translationally license the sensor before it can respond (Swanson, Deng & Ting, 2019). The second lock, activation, is the danger signal proper: the perturbation of cytosolic homeostasis that drives NLRP3 to oligomerise, recruit NEK7, nucleate ASC, and activate caspase-1.

The two-lock design matters for Alzheimer's disease because the disease supplies both keys, and supplies them through the same pathology. Amyloid-β, acting through the CD36–TLR4–TLR6 receptor complex, delivers the priming signal; amyloid-β, phagocytosed and delivered to the lysosome, delivers the activating signal by rupturing the lysosomal membrane (Sheedy et al., 2013; Halle et al., 2008). A chronically inflamed brain, moreover, is a chronically primed brain: the standing elevation of interleukin-1β and tumour-necrosis-factor that characterises the Alzheimer parenchyma keeps the first lock open, so that the microglion is held in a state of readiness in which any subsequent danger signal is sufficient to fire the device. This is the cellular basis of the feed-forward spiral of Chapter VI: the cytokine output of one round of activation is itself the priming signal for the next.

4.2 The Convergent Triggers

The remarkable feature of NLRP3 is the diversity of its activators and the narrowness of the mechanisms through which they act. Three convergent triggers, each engaged in the Alzheimer brain, license activation. Potassium efflux, the drop in cytosolic potassium below a threshold, is the most general; it is driven in the diseased brain by membrane damage and by the ATP-gated P2X7 receptor, whose activation by the ATP released from injured neurons couples neuronal death to microglial inflammasome activation, and it requires the kinase NEK7 to bridge NLRP3 monomers into the active oligomer (Muñoz-Planillo et al., 2013; He et al., 2016). Lysosomal destabilisation, the rupture of the phagolysosome and release of cathepsin B, is the trigger most specific to the amyloid story and is developed in Chapter II (Hornung et al., 2008; Halle et al., 2008). Mitochondrial distress — the production of mitochondrial reactive oxygen species and the externalisation of oxidised mitochondrial DNA and cardiolipin — supplies the third input and is the node at which the inflammasome connects to the bioenergetic collapse that the Collapse corpus places at the origin of neuronal vulnerability (Zhou et al., 2011).

That these three triggers converge on one sensor is the key to the sensor's role as an integrator. The Alzheimer brain does not present the microglion with a single insult but with a milieu — aggregated amyloid, released ATP, oxidative stress, damaged mitochondria, and, later, aggregated tau — and NLRP3 is the device that integrates this heterogeneous danger into a single, stereotyped, cytotoxic output. This integrative property is why the inflammasome is a more attractive therapeutic target than any individual trigger: to inhibit NLRP3 is to close the funnel through which many insults are channelled, rather than to plug one of many inlets.

4.3 The Effectors: Cytokines and the Pore

The output of the assembled inflammasome is delivered by two proteolytic effectors, and the distinction between them structures the therapeutic landscape. Caspase-1, autoactivated on the ASC scaffold, cleaves pro-interleukin-1β and pro-interleukin-18 to their mature forms; these cytokines, once released, prime further inflammasomes, activate neuronal stress kinases, impair long-term potentiation, and — as Chapter VI develops — impair the microglial clearance of amyloid. Caspase-1 also cleaves gasdermin-D, whose N-terminal fragment inserts into the plasma membrane and oligomerises into a pore. The gasdermin-D pore is both the conduit through which the mature cytokines exit the cell and, when formed in sufficient number, the lesion that lyses it: pyroptosis, the inflammatory programmed death that releases the cell's entire contents, including the ASC speck, into the extracellular space (Shi et al., 2015; Kayagaki et al., 2015).

This bifurcation of the output — soluble cytokine on one branch, membrane pore and lytic death on the other — is the reason the pyroptotic geography of the human disease (Moonen et al., 2023) matters as much as the cytokine measurements do, and the reason the effector nodes offer distinct therapeutic surfaces. An inhibitor of caspase-1 blocks both branches; an inhibitor of the gasdermin-D pore blocks pyroptosis and cytokine release while sparing the intracellular functions of caspase-1; an antibody against the released ASC speck (§2.5) blocks the propagation branch alone. The multiplicity of effectors, like the multiplicity of triggers, is what makes the inflammasome a rich rather than a brittle target, and it is developed in Chapter VIII.

5. Chapter II The Amyloid Trigger: From Fibril to Caspase

5.1 The Lysosomal Route

The mechanistic core of the amyloid–inflammasome connection is the lysosomal-rupture route defined by Halle and colleagues (2008), and it is worth tracing in full because its specificity is the source of both its evidential strength and its therapeutic tractability. A microglion encountering fibrillar amyloid-β phagocytoses it; the fibrils are delivered to the phagolysosome; there, by a mechanism shared with other rigid, crystalline, or fibrillar particulates, they damage the lysosomal membrane; the membrane damage releases the lysosomal cysteine protease cathepsin B into the cytosol; and cathepsin B participates, with the potassium efflux that accompanies the same membrane perturbations, in the activation of NLRP3. The demonstration was subtractive at every step: inhibition of phagocytosis, of cathepsin B, of NLRP3, or of ASC each abolished the amyloid-driven interleukin-1β response, and microglia lacking NLRP3 did not respond to fibrillar amyloid. The route places amyloid-β firmly among the sterile particulate activators of NLRP3, alongside monosodium urate (gout) and silica (silicosis), and this is more than an analogy: it means that the extensive pharmacology developed against particulate-driven NLRP3 activation in those diseases is, in principle, transferable to Alzheimer's disease.

5.2 The Manufacture of the Trigger

A subtle but important elaboration of the amyloid-trigger arc is that the microglion does not merely encounter a pre-formed danger signal; it participates in manufacturing one. Sheedy and colleagues (2013) showed that CD36 nucleates the intracellular conversion of soluble amyloid-β into the fibrillar, particulate form that the inflammasome senses, so that the receptor that recognises the peptide also assembles it into the ligand that triggers the sensor. The conformational specificity matters: soluble amyloid-β monomer is a weak activator, oligomeric and fibrillar amyloid a strong one, and the microglion's receptors bias the peptide toward the aggregated, activating conformations. This has two implications. Mechanistically, it means that inflammasome activation is not a passive consequence of ambient amyloid concentration but an actively assembled response, dependent on the microglion's receptor repertoire — which connects the inflammasome to the *TREM2*, *CD33*, and scavenger-receptor genetics of the disease. Therapeutically, it opens the upstream nodes — CD36, the TLR4–TLR6 heterodimer — to intervention, though at the cost of specificity, since these receptors serve many functions beyond inflammasome priming.

5.3 The Coupling to Bioenergetic and Oxidative Collapse

The amyloid trigger does not act on a healthy cell in isolation; it acts on a microglion embedded in the oxidative and bioenergetic milieu that the Collapse corpus places at the origin of the disease, and the mitochondrial arm of NLRP3 activation is the point of contact. Mitochondrial reactive oxygen species and oxidised mitochondrial DNA are activating inputs to NLRP3 (Zhou et al., 2011); the bioenergetic distress that the *Bioenergetic Collapse* thesis traces in the vulnerable neuron is mirrored in the microglion, whose metabolic reprogramming toward glycolysis on activation is itself a determinant of inflammasome output. The inflammasome is, in this reading, not merely a sensor of amyloid but a sensor of the *convergence* of amyloid with oxidative and bioenergetic stress — which is to say, a sensor tuned to fire precisely in the conditions the diseased brain provides. This coupling is the mechanistic seam between the present thesis and the bioenergetic and homeostatic-microglial volumes of the corpus: the same mitochondrial oxidant stress that renders the locus-coeruleus neuron vulnerable renders the microglion inflammasome-prone, so that the two collapses are triggered by a shared upstream chemistry.

6. Chapter III The Speck: Pyroptosis, ASC Cross-Seeding, and Propagation

6.1 The Two Fates of an Activated Microglion

When the inflammasome fires, the microglion has, in effect, two possible fates, and both propagate the disease. In the first, sub-lytic fate, the gasdermin-D pore forms in modest numbers, the mature cytokines are released, and the cell survives to be primed and to fire again — a secretory phenotype that sustains the chronic cytokine elevation of the disease. In the second, lytic fate, the pore load is sufficient to rupture the cell, and the microglion undergoes pyroptosis, spilling its contents — cytokines, cellular DAMPs, and, critically, the ASC speck — into the extracellular space (Shi et al., 2015). The demonstration by Moonen and colleagues (2023) that gasdermin-D is activated in a cell-type-specific manner across microglia, astrocytes, and neurons in the human Alzheimer brain establishes that this second, lytic fate is not a model-system artefact but a feature of the human disease. Pyroptosis converts the inflammasome from a device that harms its neighbours by secretion into a device that harms them by disintegration, releasing a bolus of pro-inflammatory and pro-aggregatory material at the moment of the host cell's death.

6.2 The Speck as Seed

The released ASC speck is the most consequential item in that bolus, because it does not merely inflame — it seeds. Venegas and colleagues (2017) demonstrated that extracellular ASC specks bind amyloid-β and cross-seed its aggregation, that injected specks increase amyloid pathology, and that depleting ASC or neutralising the speck with an antibody reduces it. This is a propagation mechanism of a fundamentally different character from cytokine diffusion. A cytokine acts transiently and is cleared; a nucleating seed acts catalytically and persists, templating the conversion of soluble amyloid into aggregate wherever it lodges. The speck thus supplies a candidate mechanism by which inflammasome activation contributes not only to the intensity of local inflammation but to the spatial *spread* of amyloid pathology — a microglial contribution to the prion-like propagation that is otherwise discussed almost entirely in terms of the misfolded proteins themselves. The subsequent finding that amyloid clustering around ASC fibrils increases the peptide's toxicity to microglia (Friker et al., 2020) adds a cytotoxic dimension: the speck–amyloid complex is not only a seed but a poison.

6.3 The Weight the Arc Can Bear

The speck arc is the thesis's most novel and, correspondingly, its most carefully graded. Its internal evidence is strong and bidirectional — the intervention that adds specks worsens pathology and the intervention that removes them rescues it — which is the logical structure of a causal demonstration. But two cautions temper it. First, the arc is, at the time of writing, substantially the product of a single laboratory and its collaborators, and the cross-seeding claim has not been replicated across the field with the breadth that the amyloid-activation arc (§2.3) enjoys; extraordinary mechanisms warrant ordinary amounts of independent confirmation, and that confirmation is still accumulating. Second, the quantitative contribution of speck-mediated seeding to the total amyloid burden of the human disease is unknown: that specks can seed amyloid, demonstrated, is not the same as that speck-seeding accounts for a material fraction of human plaque, which is not demonstrated. The arc is therefore graded in Chapter VII as moderate-to-strong in mechanism and unquantified in human magnitude — a real and important mechanism whose disease-level weight remains to be established.

7. Chapter IV The Bridge to Tau: The Inflammasome as the Amyloid Tau Relay

7.1 The Vacancy the Bridge Fills

The amyloid cascade hypothesis has always had a hole at its centre. Amyloid is upstream and tau is downstream, but the mechanism by which cortical amyloid deposition should drive the anatomically distinct, trans-synaptically propagating, tightly cognition-correlated accumulation of tau has never been specified to the field's satisfaction. This vacancy is the reason the amyloid hypothesis has been simultaneously dominant and unsatisfying: it names the endpoints of the cascade without naming the relay between them. The inflammasome hypothesis's boldest claim is that it names the relay — that the microglial NLRP3 inflammasome is the device that converts the presence of amyloid into the acceleration of tau.

7.2 The Evidence for the Relay

The claim rests principally on Ising and colleagues (2019). In tau-transgenic mice, genetic loss of NLRP3 or of ASC reduced tau hyperphosphorylation and aggregation and rescued cognition, establishing that inflammasome activity is required for the full development of tau pathology in that model. Mechanistically, inflammasome activation was shown to shift the balance of the enzymes that regulate tau phosphorylation — reducing the activity of the principal tau phosphatase, PP2A, and engaging tau kinases — so that the net effect of inflammasome signalling is a more heavily phosphorylated, more aggregation-prone tau. Decisively, the experiment tested the relay directly: tau pathology seeded by the injection of amyloid-β-containing brain homogenate required a functional microglial NLRP3 inflammasome, such that removing the inflammasome uncoupled amyloid from its ability to drive tau. This is the result that places the inflammasome *between* the two proteinopathies rather than merely alongside each. The reciprocal arc — that aggregated tau itself activates the NLRP3–ASC inflammasome, and that ASC specks seed tau as they seed amyloid — was established by Stancu and colleagues (2019), closing the loop: amyloid drives tau through the inflammasome, and tau drives the inflammasome that drives more tau.

7.3 The Weight the Bridge Can Bear

The tau-relay arc is the single most important and the single most carefully qualified claim in this dissertation, and the two facts are related. It is the most important because, if correct, it does what the amyloid hypothesis has failed to do for thirty years: it supplies a specific, molecular, druggable mechanism for the amyloid-to-tau transition, and it explains why anti-amyloid interventions might fail — because they leave the relay, and therefore the tau pathology, intact once the spiral is self-sustaining. It is the most carefully qualified because its evidential base, though of high quality, is narrow: it rests principally on the Ising and Stancu studies, is entirely murine, and turns on a proposed kinase/phosphatase mechanism that is incompletely specified and not yet independently reconstructed in detail. The arc has not accumulated the breadth of confirmation that the amyloid-activation and genetic-deletion arcs enjoy, and the models in which it was demonstrated carry the usual caution that murine tau biology, like murine amyloid biology, is an imperfect surrogate for the human disease. The thesis therefore advances the tau relay as its most valuable *hypothesis* while declining to advance it as an established *fact*, and Chapter VII grades it as strong-in-quality but narrow-in-breadth — precisely the profile of a claim that most urgently requires, and most would reward, independent replication.

8. Chapter V Beyond Microglia: The Cellular Geography of the Inflammasome

8.1 The Neuron as Inflammasome-Competent

The microglion is the protagonist of the inflammasome story, but it is not the only inflammasome-competent cell in the brain, and the geography matters because it determines whether inflammasome-driven injury is entirely paracrine or partly cell-autonomous. Neurons express NLRP1, the founding member of the inflammasome sensor family, and the neuronal NLRP1 inflammasome can be activated in Alzheimer models by amyloid-β to drive a caspase-1-dependent neuronal pyroptosis (Tan et al., 2014). Kaushal and colleagues (2015) defined the downstream architecture of the neuronal response, showing that neuronal NLRP1–caspase-1 activation coordinately regulates both interleukin-1β production and the caspase-6-dependent axonal degeneration that is a feature of the disease. If neurons die in part by their own inflammasomes, then the inflammasome is not only the microglial device that inflames the neuron's environment but a death programme resident within the neuron itself — a shift in interpretation with therapeutic consequences, since a purely paracrine mechanism would be addressed by silencing microglia, whereas a cell-autonomous one requires reaching the neuron.

8.2 The Astrocyte and the Pyroptotic Map

Astrocytes complete the geography. They express a functional NLRP2 inflammasome (Minkiewicz, de Rivero Vaccari & Keane, 2013), positioning the brain's most numerous glial population as an inflammasome-competent participant in the response. The human synthesis of this distributed picture is the pyroptotic map of Moonen and colleagues (2023), who demonstrated cell-type-specific gasdermin-D activation in microglia, astrocytes, and neurons in Alzheimer brain tissue — the most direct human evidence that the pyroptotic machinery is engaged across all three major cell types, not merely in microglia. The picture that emerges is of a brain in which the inflammasome response is distributed: microglia sense and amplify, astrocytes participate, and neurons die in part by their own pyroptotic programmes.

8.3 The Caution the Geography Requires

The distributed picture is attractive because it is comprehensive, and comprehensiveness is a reason for caution as much as for confidence. The neuronal and astrocytic arcs are supported by markedly thinner literatures than the microglial one, and the NLRP1 arc carries a specific and serious complication: human and rodent NLRP1 differ substantially in their gene structure, their domain organisation, and their mode of activation, so that the extrapolation of rodent neuronal-NLRP1 findings to human neurons is less secure than for the more conserved NLRP3. The gasdermin-D activation demonstrated in human neurons by Moonen and colleagues is strong evidence that *some* pyroptotic machinery is engaged in human neurons, but it does not by itself establish that neuronal NLRP1 is the sensor driving it, nor does it quantify the contribution of neuronal pyroptosis to total neuronal loss. The geography is therefore best held as a well-motivated map whose microglial territory is well-surveyed and whose neuronal and astrocytic territories are sketched — real, but not yet drawn to scale.

9. Chapter VI The Feed-Forward Spiral

9.1 The Loop Stated

The arcs of the preceding chapters, assembled, describe a loop rather than a line, and the loop is the thesis's central systems claim. Aggregated amyloid-β activates the microglial NLRP3 inflammasome (Chapter II). The activated inflammasome does four things, each of which feeds back to worsen the trigger. It releases interleukin-1β and interleukin-18, which prime further inflammasomes and impair the microglion's own capacity to clear amyloid, so that amyloid accumulates (§9.2). It releases ASC specks, which cross-seed amyloid and template new aggregation (Chapter III). It drives tau pathology through the amyloid–tau relay (Chapter IV), and the resulting aggregated tau is itself an inflammasome activator (Stancu et al., 2019), adding a second trigger to the loop. And it executes pyroptosis, releasing DAMPs that prime and activate neighbouring inflammasomes. Each output returns as an input; the loop is positive; and a positive loop, once its gain exceeds unity, is self-sustaining independent of the initial stimulus.

9.2 The Clearance Arc

The most important feedback arc, because it operates on the trigger most directly, is the impairment of amyloid clearance by the inflammasome's own cytokine output. The genetic-deletion evidence of Heneka and colleagues (2013) established the arc by subtraction: removing NLRP3 or caspase-1 not only reduced inflammation but *increased* amyloid clearance and reduced amyloid burden, because the inflammasome-deficient microglion adopts a more phagocytic, clearance-competent phenotype. The reciprocal was shown by Tejera and colleagues (2019), who demonstrated that systemic inflammation impairs microglial amyloid clearance through the NLRP3 inflammasome, coupling peripheral inflammatory events to central amyloid accumulation. The arc is mechanistically decisive for the amplifier hypothesis: it shows the inflammasome acting *back upon its own trigger*, converting the presence of amyloid into the reduced clearance of amyloid, which is the defining signature of a feed-forward amplifier and the clearest refutation, within the mouse, of the pure-bystander reading.

9.3 The Asymmetry and the Tipping Point

The spiral is not symmetric in its arms, and the asymmetry carries the thesis's central timing prediction. Early in the disease, the loop's gain is low: amyloid is sparse, priming is intermittent, and the inflammasome fires transiently and clears its trigger between firings. As amyloid accumulates, tau enters the loop as a second trigger, cytokine priming becomes chronic rather than intermittent, pyroptosis releases standing pools of DAMPs, and ASC specks accumulate as persistent seeds — and the loop's gain rises past the point at which it is self-sustaining. Beyond that tipping point, the inflammasome no longer requires the original stimulus, because its own outputs supply its inputs; and beyond that point, an intervention against the initial trigger — anti-amyloid therapy, for instance — can no longer arrest the disease, because the disease is now driven by the loop rather than by the trigger. This is the mechanistic reading of the clinical observation that anti-amyloid interventions have their best (though still modest) effects early and little effect late, and it is the basis of the timing prediction that recurs throughout the Collapse corpus: the inflammasome is interruptible only before its spiral becomes self-sustaining, which is early, and before much of the pathology that the spiral will produce has appeared.

10. Chapter VII An Assessment of Validity: Grading the Arcs

10.1 The Purpose of an Explicit Grading

The inflammasome literature is, by the standards of neuroinflammation, unusually strong, and precisely for that reason it invites the uncritical adoption of its whole as though every arc were as well-evidenced as its best. This chapter resists that by grading each arc explicitly, weighting the assessment toward disconfirmation, and stating for each not merely whether it is supported but by what kind of evidence, in what species, and from how many independent laboratories. The grading is the adjudicative core of the dissertation and the honest counterweight to the accumulative argument of the preceding chapters.

10.2 The Strong Arcs

Four arcs are strong. That fibrillar amyloid-β activates the NLRP3 inflammasome through lysosomal rupture and cathepsin B release is established, mechanistically specific, subtractively demonstrated, and consistent with the archetypal particulate activators of NLRP3 (Halle et al., 2008; Hornung et al., 2008); it has been reproduced widely. That genetic deletion of *Nlrp3* or *Casp1* protects amyloid-model mice — reducing amyloid burden, preserving synapses and memory, and enhancing clearance — is the field's cleanest causal test and has been extended pharmacologically (Heneka et al., 2013; Dempsey et al., 2017). That the inflammasome pathway is engaged in the human Alzheimer brain, with elevated cleaved caspase-1, ASC, interleukin-1β, interleukin-18, and cell-type-specific gasdermin-D activation, is established at the protein and tissue level across independent studies (Griffin et al., 1989; Heneka et al., 2013; Saresella et al., 2016; Moonen et al., 2023). And that the inflammasome acts back upon amyloid clearance — that its cytokine output reduces the microglial phagocytosis of amyloid — is subtractively demonstrated and is the mechanistic basis of the amplifier claim (Heneka et al., 2013; Tejera et al., 2019). These four arcs, taken together, justify the thesis's central claim that the inflammasome is a validated amplifier of amyloid pathology in the mouse and is demonstrably engaged in the human disease.

10.3 The Moderate Arcs

Three arcs are moderate: real in mechanism, narrower in breadth or unquantified in human magnitude. The ASC-speck cross-seeding arc (Venegas et al., 2017; Friker et al., 2020) is bidirectionally demonstrated within its originating laboratory but is not yet broadly replicated across the field, and its quantitative contribution to human amyloid burden is unknown. The amyloid–tau relay (Ising et al., 2019; Stancu et al., 2019) is of high individual quality and, if correct, of the highest importance, but it rests on a narrow murine evidence base and an incompletely specified kinase/phosphatase mechanism, and it awaits independent replication commensurate with its ambition. The pharmacological-inhibition arc — that selective NLRP3 inhibitors such as MCC950 and OLT1177 reproduce the genetic protection — is consistent and reproduced across compounds and models (Dempsey et al., 2017; Lonnemann et al., 2020) but is, like all of the interventional evidence, murine, and its translation is untested. These arcs are load-bearing for the thesis's *hypotheses* but not yet for its *facts*.

10.4 The Contested and Under-Evidenced Arcs

Three arcs are contested or thin. The human genetic evidence that inflammasome activity sets inherited disease risk is weak: no *NLRP3* or *CARD8* variant has the replicated, genome-wide standing of *TREM2* or *CD33*, and the candidate-gene associations are inconsistent (§2.8). The neuronal-NLRP1 and astrocytic-NLRP2 arcs are supported by thin literatures and, in the case of NLRP1, complicated by substantial human–rodent species differences that weaken the extrapolation (Tan et al., 2014; Kaushal et al., 2015; Minkiewicz et al., 2013). And the reconciliation of the inflammasome-activated microglial state with the disease-associated-microglia transcriptional programme is unresolved: whether NLRP3 activation is a feature of, an alternative to, or a driver of the DAM/MGnD state is not established. These arcs are advanced as motivated possibilities, not as pillars.

10.5 The Reverse-Causation Problem and What Survives It

The framework's central vulnerability is that the inflammasome's activation is guaranteed by its design in any advanced neurodegeneration, so that its presence testifies to injury rather than to a causal role (§2.9). The thesis concedes this as to *initiation*: the inflammasome is downstream of the first aggregated amyloid and, on the corpus's own account, downstream of the earliest locus-coeruleus tau lesion; it is not the reason the proteinopathy begins, and no evidence places it there. What survives the concession is *amplification*, and it survives on two grounds that the pure-bystander reading cannot accommodate. The genetic-deletion experiments remove the inflammasome *before* disease and observe attenuated pathology, which a bystander could not produce; and the feed-forward arcs — impaired clearance, ASC seeding, the tau relay — are mechanisms by which the inflammasome acts upon its own trigger, which a bystander does not do. The defensible position, adopted as the thesis's conclusion, is that the inflammasome is a validated amplifier and an unproven initiator: it makes the disease worse and faster, and its removal in the mouse makes the disease better, but it is not the seed of the disease and its silencing would not, on present evidence, prevent the disease from beginning.

10.6 The Translational Discount

A final and overarching qualification applies to the entire interventional case and is stated as a discount rather than as a footnote. Every demonstration that suppressing the inflammasome slows Alzheimer's disease is a demonstration in a mouse, in a transgenic model whose amyloid and tau biology is caricatured and whose predictive record for human therapeutics is close to unbroken failure. Anti-inflammatory strategies in particular have failed repeatedly in human Alzheimer's disease — the non-steroidal anti-inflammatory drug prevention trials were negative or harmful, and no immunomodulatory approach has altered the disease course. The inflammasome hypothesis is distinguished from those failures by its molecular specificity and by its timing logic, but it is not exempted from the base rate: the prior probability that a mechanism protective in these models will prove protective in patients is low, and the thesis's therapeutic claims must be read against that prior. This discount does not negate the framework; it calibrates it, and it is the reason Chapter VIII is written as a set of falsifiable predictions rather than as a set of recommendations.

11. Chapter VIII Therapeutic Implications and Falsifiable Predictions

11.1 The Therapeutic Surface

The inflammasome offers an unusually rich therapeutic surface because its pathway is a chain of discrete, druggable nodes. The sensor itself is targeted by the selective small-molecule NLRP3 inhibitors, of which MCC950 (CRID3) is the prototype: it blocks NLRP3 oligomerisation, and in amyloid-model mice it promotes non-phlogistic amyloid clearance and rescues cognition (Coll et al., 2015; Dempsey et al., 2017). A second-generation inhibitor, OLT1177 (dapansutrile), an orally bioavailable compound already in human trials for inflammatory disease, similarly rescues cognition in an Alzheimer model (Lonnemann et al., 2020), and further selective NLRP3 inhibitors have entered clinical development for neurological indications. The effector caspase-1 is targeted by inhibitors such as VX-765 (belnacasan), which alleviates cognitive impairment and neuropathology in Alzheimer models (Flores et al., 2018). The gasdermin-D pore, the ASC speck (targetable by neutralising antibody; Venegas et al., 2017), and the upstream P2X7 and NEK7 nodes each offer additional surfaces. The pathway is, in short, one of the most tractable in neurodegeneration — richly druggable, with tool compounds and clinical-stage molecules already in hand.

11.2 The Timing Logic and the Selectivity Requirement

The framework makes two design demands that the failed anti-inflammatory trials of the past did not respect. The first is timing: because the inflammasome is an amplifier whose spiral becomes self-sustaining past a tipping point (§9.3), its inhibition can only arrest the disease before that point — early, in preclinical or prodromal disease, before the loop is independent of its initial trigger. A trial that administers an inflammasome inhibitor to patients with established dementia is testing the hypothesis in the population least able to confirm it, exactly as the melatonin trials of the companion volume tested a protective agent after the nucleus it protects had already degenerated. The second is selectivity: the failed anti-inflammatory trials used blunt instruments — cyclooxygenase inhibition, global immunosuppression — that suppressed protective as well as pathological immunity. The inflammasome hypothesis demands the opposite: a selective inhibitor of NLRP3 or of gasdermin-D that closes the pathological amplifier while sparing the rest of innate immunity, including the microglial phagocytosis that clears amyloid — a phagocytosis that, per §9.2, inflammasome inhibition actually *enhances*. This last point is the framework's most attractive therapeutic feature: selective inflammasome inhibition is predicted not to suppress amyloid clearance but to restore it.

11.3 Falsifiable Predictions

The framework is falsifiable, and its value depends on stating the predictions that would confirm or refute it. Six are advanced, ordered from the most to the least discriminating.

Prediction 1 — The timing-conditional trial. A selective NLRP3 or gasdermin-D inhibitor, administered in preclinical or prodromal Alzheimer's disease (amyloid-positive, tau-low, cognitively intact or minimally impaired), will slow tau accumulation and cognitive decline; the

same agent administered in established dementia will not. A trial that shows benefit late as readily as early, or benefit in neither, falsifies the amplifier-with-a-tipping-point reading.

Prediction 2 — The clearance signature. Selective inflammasome inhibition in humans will be accompanied by *enhanced*, not suppressed, amyloid clearance on PET, distinguishing it mechanistically from blunt immunosuppression; if inflammasome inhibition reduces amyloid clearance, the murine clearance arc (§9.2) does not translate.

Prediction 3 — The tau relay in humans. If the amyloid–tau relay is correct, then inflammasome inhibition will attenuate the amyloid-to-tau transition specifically — reducing new tau-PET accumulation in amyloid-positive individuals — rather than acting on amyloid or tau independently. Failure of inflammasome inhibition to affect tau accumulation in amyloid-positive individuals falsifies the relay as a human mechanism.

Prediction 4 — The biomarker precedence. Longitudinal measurement of inflammasome-pathway biomarkers (cerebrospinal-fluid or plasma ASC, interleukin-18, cleaved caspase-1) will show their rise *preceding* and *predicting* subsequent tau accumulation and cognitive decline, as an amplifier engaging before its downstream effects. If these markers rise only concurrently with or after tau, the amplifier's temporal priority is not supported.

Prediction 5 — The peripheral compartment. Because inflammasome activation is demonstrable in peripheral mononuclear cells in Alzheimer's disease (Saresella et al., 2016), a peripheral inflammasome-activation signature will track central disease and offer an accessible pharmacodynamic biomarker for inflammasome-directed trials; its failure to track would confine the mechanism to the brain and complicate its clinical development.

Prediction 6 — The convergence with bioenergetic and microglial collapse. Because the mitochondrial arm of NLRP3 activation couples the inflammasome to oxidative and bioenergetic stress (§5.3), interventions that relieve microglial bioenergetic distress will reduce inflammasome output, and the protective effect of inflammasome inhibition will be greatest where oxidative stress is greatest — predicting an interaction, rather than mere additivity, between inflammasome-directed and bioenergetic interventions.

11.4 The Honest Therapeutic Summary

The therapeutic promise of the inflammasome is real and is the strongest in the neuroinflammation field, but it must be stated with the translational discount of §10.6 applied. The pathway is richly druggable, the preclinical evidence is consistent across compounds and models, and clinical-stage selective inhibitors exist. Against this stands the near-unbroken failure of anti-inflammatory strategies in human Alzheimer's disease and the low prior that a mouse-validated mechanism will translate. The framework's contribution is not the promise itself but the specification of the conditions under which the promise could be fairly tested — selectively, early, with clearance and tau-relay biomarkers as the readouts — conditions that no completed trial has yet met. Until such a trial is run, the inflammasome hypothesis remains the best-motivated untested therapeutic proposition in the disease.

12. Conclusion

This dissertation set out to determine whether the NLRP inflammasome is scenery or machinery in Alzheimer's disease, and it concludes that it is machinery of a specific and bounded kind: not the prime mover of the disease, but its principal innate-immune amplifier — the device by which a slow proteinopathy is converted into a faster, self-sustaining, and, in principle, druggable one. The evidence supports this reading with a strength unusual for neuroinflammation. Fibrillar amyloid-β activates the microglial NLRP3 inflammasome by the same lysosomal-rupture mechanism as the archetypal sterile particulates; the genetic deletion of the sensor or its effector protects amyloid-model mice and enhances their clearance of amyloid; the pathway is demonstrably engaged in the human brain at the protein and cellular level; and the inflammasome acts back upon its own trigger, impairing amyloid clearance, seeding amyloid through released ASC specks, and — in the boldest and most consequential of its arcs — relaying the injury to tau across the very gap the amyloid cascade has never filled.

The dissertation is equally clear about the limits of this reading. The inflammasome is downstream of the pathology it amplifies; its activation is guaranteed by its design in any advanced neurodegeneration, so that its presence cannot testify to a causal role; the strongest arcs are murine, in models whose translational record is poor; the human genetic evidence that inflammasome activity sets disease risk is weak; the tau-relay and ASC-seeding arcs, though of high quality, rest on narrow evidence bases awaiting independent replication; and every anti-inflammatory strategy tried in human Alzheimer's disease has failed. The framework does not overturn these facts; it is disciplined by them. Its value is not the addition of a new cause to the crowded list of proposed

causes of Alzheimer's disease, but the precise specification of an amplifier — of the node at which the innate immune system reads amyloid as danger and, in reading it, makes it worse; of the loop by which that reading becomes self-sustaining; and of the narrow, early, and testable window in which interrupting the reading might still matter. The sensor and the speck are not the fire, but they are the mechanism by which the fire spreads, and that mechanism, unlike the fire's origin, we already know how to interrupt.

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