The Vascular Phasing

Cerebrovascular Pathology Across the Three Temporal Phases of the Collapse Trilogy

How Endothelial, Pericyte, and Neurovascular Failure Track and Condition the Bioenergetic, Microglial, and Synaptic Collapses of Late-Onset Alzheimer's Disease Across the Third Through Eighth Decades of Adult Life

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A Dissertation Submitted in Partial Fulfillment of the Requirements for the Degree of Doctor of Philosophy in Neuroscience. Fifth in the Collapse trilogy, companion volume mapping the cerebrovascular substrate onto the tripartite temporal architecture of Convergent Synaptic Collapse, Homeostatic Microglial Collapse, and Bioenergetic Collapse.

“The brain endothelium is the page on which the systemic milieu writes; the parenchyma is the reader that the page faces. Every age-related signal that reaches a neuron has first been read by an endothelial cell.”

— ONS Methodology Working Notes, 2026

For Berislav Zlokovic, whose three decades of work established the cerebrovasculature as a first principle of neurodegeneration, and for Tony Wyss-Coray, whose identification of the brain endothelial gateway to the aged systemic milieu supplied the molecular spine on which the present dissertation rests.

THE COLLAPSE TRILOGY — COMPANION VOLUME

I. Convergent Synaptic Collapse

II. Homeostatic Microglial Collapse

III. Bioenergetic Collapse

IV. The Tryptophan Partition

V. The Vascular Phasing □ this volume

The trilogy's three principal volumes address distinct parenchymal axes of neurodegenerative collapse — synaptic circuit, microglial state, and bioenergetic substrate. The fourth volume identifies tryptophan as a shared upstream metabolic substrate. The present fifth volume maps the cerebrovasculature onto each of the three temporal phases, articulating how the brain endothelium, pericyte axis, and neurovascular unit condition the bioenergetic ignition of Phase I, gate the microglial transition of Phase II, and amplify the synaptic collapse of Phase III. The molecular spine is brain endothelial VCAM-1 as the gateway between the aged systemic milieu and the parenchymal compartment.

Abstract

The Collapse trilogy specifies a tripartite temporal architecture for late-onset Alzheimer's disease in which three parenchymal substrates engage in a stereotyped sequence across the third through eighth decades of adult life: a bioenergetic Phase I anchored in the locus coeruleus and characterized by sustained PARP-1 hyperactivation and NAD□ depletion in catecholaminergic brainstem neurons; a microglial Phase II anchored in the hippocampal-temporal axis and characterized by the loss of the Butovsky-defined TGF-β / SMAD-maintained homeostatic signature in parenchymal microglia; and a synaptic Phase III anchored in the parvalbumin-positive interneuron and perineuronal net axis and characterized by matrix-metalloproteinase digestion of the net, gamma-frequency collapse, and structural disintegration of the cortical microcircuit. The trilogy's temporal account is parenchymal throughout: each phase is defined by a parenchymal cellular failure, and the trilogy's treatment of cause and intervention is similarly parenchymal. The trilogy does not specify the vascular substrate that conditions each phase, the vascular events that constitute each phase's vascular pathology, or the vascular biomarker trajectory by which the three phases can be tracked from the vascular interface. This dissertation advances the thesis that the cerebrovasculature exhibits a phase-specific pathology that maps coherently onto the tripartite temporal architecture, that each parenchymal phase is conditioned and amplified by a phase-specific vascular event, and that the integrated four-substrate framework — vascular conditioning the bioenergetic in Phase I, vascular gating the microglial in Phase II, vascular amplifying the synaptic in Phase III — is the appropriate analytical structure for a complete account of late-onset Alzheimer's pathogenesis. The framework is anchored in the molecular biology of brain endothelial vascular cell adhesion molecule-1 (VCAM-1), an inducible immunoglobulin-superfamily adhesion molecule whose expression is the most age-upregulated soluble protein in mammalian plasma and whose engagement by aged-monocyte α4β1 integrin transduces the systemic aging signal into a parenchymal inflammatory response at each of the three temporal phases. The dissertation is organized in seven analytical chapters preceded by an Introduction, a Literature Review, and a Methodology statement. Chapter I develops the cellular biology of the neurovascular unit as a substrate-independent foundation. Chapter II maps the vascular pathology of Phase I onto the brainstem aminergic substrate, identifying capillary hypoperfusion, vasa-nervorum-style brainstem BBB compromise, and early VCAM-1 induction at

brainstem endothelium as the proximate vascular conditioning events of the bioenergetic ignition. Chapter III maps the vascular pathology of Phase II onto the hippocampal-temporal substrate, articulating the Yousef–Wyss-Coray VCAM-1 mechanism, the Montagne-Zlokovic pericyte-PDGFRβ trajectory, and the APOE4 vascular phenotype as the proximate vascular gateway of the microglial transition. Chapter IV maps the vascular pathology of Phase III onto the cortical synaptic substrate, articulating cerebral amyloid angiopathy, the ARIA constraint on anti-amyloid monoclonal antibody therapy, the basement membrane as the vascular analogue of the parvalbumin perineuronal net, and the small vessel disease continuum that converts the parenchymal disease into the mixed dementia of the eighth decade. Chapter V develops the cross-phase vascular mechanisms — the glymphatic pathway, the neurovascular coupling decline, the APOE4 cross-phase phenotype, and the VCAM-1 trajectory across the lifespan — that operate throughout the disease course rather than within a single phase. Chapter VI develops the phase-specific therapeutic implications, identifying a Phase I cardiovascular window in midlife, a Phase II VCAM-1 / pericyte-stabilization window in late midlife, and a Phase III ARIA-stratified window in late life. Chapter VII derives a series of falsifiable predictions for each phase that the framework specifies.

The dissertation concludes that the vascular phasing of late-onset Alzheimer's disease is the appropriate temporal architecture for a complete account of the disease, that the trilogy's three parenchymal phases are vascularly conditioned and vascularly gated at each step, and that the integrated four-substrate account in which vascular biology engages at every phase is structurally distinct from both the trilogy's three-substrate parenchymal account and from the simpler "vascular comorbidity" framework that has dominated the clinical literature.

Keywords: cerebrovascular pathology, blood-brain barrier, pericyte, VCAM-1, neurovascular unit, locus coeruleus, hippocampal bridgehead, parvalbumin perineuronal net, cerebral amyloid angiopathy, APOE4, glymphatic clearance, Alzheimer's disease, Collapse trilogy

Table of Contents

1. Introduction

1.1 The Research Problem

The cerebrovascular contribution to late-onset Alzheimer's disease has been recognized empirically for at least four decades and has been articulated mechanistically for at least two, but it has not been integrated into the field's principal explanatory architectures with the precision that the empirical literature now demands. The vascular hypothesis of Alzheimer's disease, articulated by Jack de la Torre in the early 1990s and developed across the subsequent quarter-century, treats cerebrovascular dysfunction as the upstream driver of the parenchymal pathology that defines the disease. The amyloid cascade hypothesis, articulated by Hardy and Higgins in 1992, treats parenchymal amyloid-β accumulation as the upstream driver and the vasculature as a downstream consequence whose pathology — cerebral amyloid angiopathy, microbleeds, ARIA — is interpretable only in light of the parenchymal events. The two frameworks have coexisted in the literature for thirty years without reconciliation, and the absence of reconciliation has been a structural impediment to the integration of vascular biology into the design of clinical trials and the stratification of intervention.

The Collapse trilogy — *Convergent Synaptic Collapse* (Volume I), *Homeostatic Microglial Collapse* (Volume II), *Bioenergetic Collapse* (Volume III), and the companion volume *The Tryptophan Partition* (Volume IV) — was an attempt to articulate the convergent infrastructure on which the parenchymal mechanisms of neurodegenerative collapse run, with a focus on the cellular substrates and the temporal sequence of their engagement. The trilogy identified three parenchymal substrates and arranged them in a tripartite temporal architecture: Phase I in the third through fifth decades, anchored in the bioenergetic biology of the locus coeruleus; Phase II in the fifth through seventh decades, anchored in the homeostatic biology of parenchymal microglia and centered on the hippocampal-temporal bridgehead; and Phase III in the seventh decade and beyond, anchored in the matrix biology of the parvalbumin perineuronal net and the resulting collapse of gamma-frequency cortical computation. The trilogy's temporal architecture is the most precise multi-axis account of late-onset Alzheimer's pathogenesis that has been articulated in the prize corpus, and it provides the analytical framework on which the present dissertation builds.

The trilogy did not, however, fully integrate the vascular substrate. The trilogy treated the cerebrovasculature as a passive conduit through which oxygen, glucose, and metabolic substrates pass to the parenchyma, and through which the waste products of parenchymal metabolism return to the systemic circulation. The trilogy did not specify the vascular events that constitute each phase's vascular pathology, did not articulate the temporal trajectory of vascular biomarkers that would track each phase from the vascular interface, and did not develop the therapeutic surface that vascular intervention at each phase would expose. The trilogy's treatment of vascular biology, where it was addressed at all, was as a downstream amplifier of the parenchymal events that define each phase.

This dissertation addresses the question: **What is the phase-specific vascular pathology of late-onset Alzheimer's disease, and how does it map onto the tripartite temporal architecture of the Collapse trilogy?** The thesis advanced is that the cerebrovasculature exhibits a phase-specific pathology that maps coherently onto each of the trilogy's three temporal phases, that each parenchymal phase is vascularly conditioned in its initiation and vascularly amplified in its progression, and that the integrated four-substrate framework — vascular conditioning of bioenergetic in Phase I, vascular gating of microglial in Phase II, vascular amplification of synaptic in Phase III — is the appropriate analytical

structure for a complete account of late-onset Alzheimer's pathogenesis. The framework is anchored in the molecular biology of brain endothelial vascular cell adhesion molecule-1 (VCAM-1), whose Yousef–Wyss-Coray characterization as the necessary mediator of aged-plasma toxicity to the brain supplies the molecular gateway through which the systemic aging signal is transduced into a parenchymal response at each of the three temporal phases.

1.2 Significance

The significance of this reframing is fourfold. First, it integrates the vascular hypothesis and the amyloid cascade hypothesis within a single temporal architecture rather than treating them as competing claims about the same etiology. The vascular and parenchymal substrates engage in a phase-specific, mutually reinforcing sequence in which each substrate at each phase has both a vascular and a parenchymal manifestation. The integrated framework predicts, and the biomarker data confirm, that the vascular pathology is detectable at each phase before the parenchymal pathology is, but the framework does not claim that the vascular substrate is the sole or even the principal driver at each phase. The framework treats vascular and parenchymal pathology as coupled subsystems whose relative weight in driving disease progression shifts across the three phases, with vascular weight maximal at Phase I and minimal but still substantial at Phase III.

Second, the framework supplies a phase-specific biomarker trajectory that is currently underutilized in clinical trials. Cerebrospinal fluid VCAM-1, plasma soluble VCAM-1, cerebrospinal fluid soluble PDGFRβ as a pericyte injury marker, dynamic contrast-enhanced magnetic resonance imaging of regional blood-brain barrier permeability, arterial spin labeling magnetic resonance imaging of regional cerebral blood flow, and cerebral amyloid angiopathy imaging by gradient-echo and susceptibility-weighted MRI together constitute a vascular biomarker panel whose phase-specific trajectory can stratify subjects by the dominant phase of their disease and can inform the selection of intervention. The current Alzheimer's clinical trial framework, organized around the AT(N) (amyloid, tau, neurodegeneration) parenchymal biomarker triad, omits the vascular dimension and therefore systematically misallocates subjects whose dominant pathology is vascular rather than parenchymal.

Third, the framework supplies a phase-specific therapeutic surface that is more granular than the current single-window approach. Phase I (decades three through five) opens a cardiovascular intervention window in midlife in which hypertension control, lipid management, and lifestyle intervention have their largest expected effect on subsequent disease trajectory; the population for whom this window is most relevant is the middle-aged APOE4 carrier whose vascular phenotype is in its leading-edge phase but whose parenchymal pathology has not yet engaged. Phase II (decades five through seven) opens a VCAM-1 / pericyte-stabilization window in late midlife in which targeted vascular pharmacology — VCAM-1 antibody blockade, cyclophilin A / MMP-9 axis suppression, pericyte-supporting interventions — could plausibly arrest or reverse the hippocampal microglial transition. Phase III (decade seven and beyond) opens an ARIA-stratified anti-amyloid window in late life in which the vascular cost of clearance must be weighted against the parenchymal benefit, with the stratification informed by APOE genotype, cerebral amyloid angiopathy burden, and baseline microbleed count. The phase-specific framework is a developmental pharmacology of late-onset Alzheimer's disease in which the four substrates are addressed in the temporal sequence in which they engage and in which the cumulative effect of intervention across phases is the disease-modifying effect that has eluded the single-target approach of the past two decades.

Fourth, the framework supplies a unifying interpretation of a set of otherwise disparate clinical observations: the midlife hypertension – late-life dementia association that the SPRINT-MIND trial confirmed but that no parenchymal-only framework explains mechanistically; the APOE4 epidemiological signal whose temporal precedence over parenchymal amyloid accumulation the Montagne 2020 imaging data established; the heterochronic parabiosis rejuvenation phenotype that the Villeda – Wyss-Coray program established and that the Yousef – Wyss-Coray work attributed to brain endothelial VCAM-1; the regional pattern of FDG-PET hypometabolism that reflects, at the vascular level, GLUT1 reduction at the brain endothelium before it reflects parenchymal hypometabolism; and the substantial fraction of clinically diagnosed Alzheimer's dementia that exhibits mixed vascular and parenchymal pathology at autopsy. Each of these observations is naturally accommodated by the four-substrate framework and is poorly accommodated by the parenchymal-only frameworks.

1.3 Scope and Limitations

This dissertation is a synthetic review, not a report of original experimental data. Its contribution lies in the integration of literatures from cerebrovascular biology, neuroimmunology, the proteomic biology of aging, BBB transport biochemistry, glymphatic clearance physiology, cerebral amyloid angiopathy pathology, and the established Collapse trilogy framework into a single analytical schema centered on the phase-specific vascular pathology of late-onset Alzheimer's disease. The work draws principally on the human aging and Alzheimer's disease literatures because the trilogy is organized around late-onset AD, but the vascular framework extends naturally to vascular cognitive impairment, mixed dementia, and the broader spectrum of age-related cognitive decline that shares the vascular substrate with AD.

The thesis cannot resolve, and does not attempt to resolve, whether the vascular substrate is the causally upstream variable at each phase or whether it is a co-conditioning variable that engages in parallel with the parenchymal substrate. The framework is consistent with either reading and supplies a testable prediction for each: if the vascular substrate is causally upstream at Phase I, then anti-vascular intervention in midlife should prevent or delay the bioenergetic ignition; if it is co-conditioning, then anti-vascular intervention should reduce the rate of progression without necessarily preventing the ignition. The framework also does not resolve the question of whether cerebral amyloid angiopathy is a competing sink for amyloid-β that protects the parenchyma at the cost of vessel-wall accumulation or whether it is a parallel pathology with overlapping risk factors. The Greenberg framework treats this ambiguity directly, and Chapter IV addresses it.

The thesis is restricted to the cerebrovasculature and does not develop the systemic vascular dimension — coronary disease, peripheral arterial disease, kidney microvasculature — even though the systemic vascular substrate is upstream of the cerebrovascular substrate in important respects. The Phase I framework in Chapter II touches on the systemic-to-central coupling through the VCAM-1 plasma proteome, but the full systemic vascular dimension is the subject of a separate analytical track that this dissertation acknowledges but does not develop.

2. Literature Review

2.1 Historical Foundations: From Hachinski to Zlokovic

The recognition that vascular pathology contributes substantially to cognitive impairment in late life is older than the modern Alzheimer's research framework and predates the molecular characterization of the parenchymal pathology by a wide margin. Vladimir Hachinski's articulation of "multi-infarct dementia" in 1974 established the conceptual framework within which vascular contributions to cognitive impairment could be distinguished from the parenchymal pathology described by Alois Alzheimer in 1907. The Hachinski Ischemic Score, developed in 1975, became the principal clinical tool for distinguishing vascular dementia from Alzheimer's disease, and the distinction it enforced — vascular and parenchymal dementia as discrete categories — dominated clinical practice for the subsequent quarter-century.

The recognition that vascular and parenchymal pathologies in fact co-occur in the majority of subjects with clinical Alzheimer's dementia emerged from the autopsy literature of the 1990s and 2000s. Snowdon's Nun Study, drawing on the well-characterized cohort of school-sisters at the University of Kentucky, reported in 1997 that subjects with both cortical infarcts and Alzheimer pathology at autopsy were substantially more cognitively impaired during life than subjects with either alone. The Honolulu-Asia Aging Study, the Religious Orders Study, and the Adult Changes in Thought study collectively established by the early 2010s that mixed pathology is the modal autopsy finding in clinically diagnosed Alzheimer's dementia, with the implication that the conceptual separation of vascular and parenchymal dementias is empirically not supported by the population data.

The mechanistic characterization of the vascular contribution to late-onset Alzheimer's disease has been the principal contribution of Berislav Zlokovic's program at the University of Southern California, extending across more than two decades. Zlokovic's foundational claim, articulated in a series of papers between 2002 and 2011, is that blood-brain barrier breakdown is the proximate driver of parenchymal injury in Alzheimer's disease and that BBB breakdown is causally upstream of, not downstream of, the parenchymal events that the amyloid cascade hypothesis treats. The Zlokovic two-hit vascular hypothesis, in its mature form, holds that pericyte loss is the proximate driver of BBB breakdown and that BBB breakdown

is the proximate driver of parenchymal injury through fibrinogen extravasation, leukocyte infiltration, and the secondary cytokine cascade that follows. The two hits are vascular and amyloid: vascular injury initiates the cascade, amyloid deposition follows and amplifies it, but the vascular event is causally and temporally prior.

The translation of the Zlokovic cellular framework to a human in vivo cohort was the principal contribution of Axel Montagne's papers at the University of Southern California from 2015 onward. The 2015 *Neuron* paper established the first in vivo evidence of BBB breakdown as an early event in the human aging trajectory and as an early event in cognitive impairment. The 2020 *Nature* paper extended the framework to APOE4 carriers and demonstrated that BBB breakdown is the earliest detectable biomarker change in the APOE4 trajectory, preceding parenchymal amyloid accumulation by an estimated decade or more. The Montagne work is the clinical anchor of the present dissertation and is treated in detail in Chapter III.

2.2 The Neurovascular Unit and the Cellular Biology of the Brain Endothelium

The conception of the blood-brain barrier as a static endothelial partition between systemic circulation and parenchyma has been superseded over the past two decades by the conception of the neurovascular unit as the relevant unit of analysis. The neurovascular unit framework, articulated principally by Costantino Iadecola at Cornell across his program from the early 2000s through the present, treats the brain capillary as an integrated cellular complex comprising the endothelial cell, the pericyte, the astrocytic endfoot, the smooth muscle cell at the arteriolar level, the perivascular macrophage, and the basement membrane that anchors the abluminal compartment. The neurovascular unit executes the functions of selective transport, blood flow regulation, immune surveillance, and waste clearance as an integrated system rather than as the property of any single cell type, and its failure under aging and disease conditions is the coordinated failure of the integrated system.

The cellular biology of the brain endothelial cell distinguishes it from systemic endothelial cells in three quantitatively decisive respects. Brain endothelial cells form tight junctions sealed by claudin-5, occludin, and the zonula occludens family of cytoplasmic scaffolds, with claudin-5 the principal molecular determinant of paracellular impermeability. Brain endothelial cells exhibit minimal pinocytotic activity and minimal transcytosis under baseline conditions, with the suppression of

transcytosis actively maintained by MFSD2A-mediated docosahexaenoic acid import (Ben-Zvi et al., 2014; Andreone et al., 2017). Brain endothelial cells express a specialized complement of solute transporters — GLUT1 for glucose, LAT1 for large neutral amino acids, MCT1 for monocarboxylates, LRP1 for amyloid-β and lipoprotein efflux, RAGE for amyloid-β and advanced glycation end product influx, P-glycoprotein and BCRP for xenobiotic efflux — that collectively define the brain endothelium as a selectively curated interface (Daneman and Prat, 2015).

The pericyte-endothelial axis is the principal cellular dyad of the neurovascular unit, with pericyte-to-endothelial ratios in cortical capillaries approaching one-to-three (the highest of any capillary bed) and pericyte coverage of capillary surface area approaching thirty percent (Sweeney et al., 2018). The pericyte supports the endothelial cell through PDGF-B / PDGFRβ paracrine signaling, contributes to tight junction maintenance through Notch and angiopoietin signaling, and executes contractile blood flow regulation at the capillary level. Pericyte loss in the Zlokovic-Montagne framework is the proximate event that produces BBB breakdown, with the cascade running through reduced PDGFRβ signaling, reduced tight junction support, claudin-5 reduction, and increased paracellular permeability (Bell et al., 2010; Sweeney et al., 2018). The pericyte injury biomarker — soluble PDGFRβ released into CSF as the receptor is shed from damaged pericytes — has been validated as a quantitative biomarker of pericyte injury and tracks with hippocampal BBB permeability on DCE-MRI (Nation et al., 2019).

2.3 The Aged Systemic Milieu and the Wyss-Coray Program

The recognition that the soluble plasma proteome of young and aged mammals differs in a quantitatively substantial fashion and that the differential effects of young and aged plasma on brain biology are mediated by these soluble factors was the principal contribution of Tony Wyss-Coray's program at Stanford from the late 2000s through the present. Saul Villeda's 2011 *Nature* paper established that heterochronic parabiosis — the surgical joining of the systemic circulation of a young and an aged mouse — produced an aging effect on the brain of the young mouse and a rejuvenating effect on the brain of the aged mouse, with the principal cellular substrate of the rejuvenation being the hippocampal neurogenic niche and the cognitive substrate being hippocampal-dependent learning and memory. The 2014 *Nature Medicine* paper from the same laboratory extended the finding to systemic plasma administration: the rejuvenating effects of young blood on the aged brain were attributable to soluble factors in young plasma and could be reproduced by repeated injection of young plasma into aged recipients.

The principal finding of the Yousef – Wyss-Coray work, published in *Nature Medicine* in 2019 with Hanadie Yousef as lead author, is that vascular cell adhesion molecule-1 (VCAM-1) — specifically the soluble VCAM-1 ectodomain shed from activated endothelium — is the single most age-upregulated protein in mammalian plasma, with plasma sVCAM-1 concentrations rising approximately tenfold across the adult mouse lifespan and approximately fivefold across the adult human lifespan. The Yousef paper went further and established the mechanistic chain by which plasma VCAM-1 mediates aged-plasma toxicity to the brain. Aged plasma induces VCAM-1 expression on brain endothelial cells in young recipient mice. The VCAM-1 induction is necessary for the downstream effects of aged plasma on the brain: pharmacological antibody blockade of VCAM-1, and tissue-specific conditional deletion of *Vcam1* in brain endothelial cells, both abolish the aged-plasma effects on hippocampal microglia, on hippocampal neurogenesis, and on hippocampal-dependent cognitive performance. The brain endothelial VCAM-1 was thus established as the necessary mediator of the aged-plasma signal to the brain.

The mechanistic chain through which brain endothelial VCAM-1 transduces the aged-plasma signal into a parenchymal effect comprises three steps that the present dissertation develops as the molecular substrate of the phase-specific framework. The first step is the engagement of brain endothelial VCAM-1 by α4β1-expressing

leukocytes — principally aged monocytes whose surface α4β1 is elevated in the aged state. The second step is endothelial signaling: VCAM-1 engagement activates NADPH oxidase and produces a local reactive oxygen species pulse, which activates endothelial NF-κB and induces the secretion of interleukin-6 and CCL2 into the abluminal compartment. The third step is parenchymal reception: the endothelial-secreted cytokines destabilize the homeostatic microglial signature and prime the parenchymal microglia for the disease-associated trajectory. The VCAM-1 mechanism is the molecular gateway between the aged systemic milieu and the parenchymal compartment, and it is the molecular anchor of the present dissertation.

2.4 The Tripartite Architecture of the Collapse Trilogy

The Collapse trilogy specifies a tripartite temporal architecture for late-onset Alzheimer's pathogenesis in which three parenchymal substrates engage in a stereotyped sequence across the third through eighth decades. The architecture has been articulated in three principal theses and extended by the Tryptophan Partition companion volume; the present dissertation extends it further by mapping the vascular substrate onto each of the three phases.

Phase I, articulated by the Bioenergetic Collapse thesis, is the bioenergetic ignition of the locus coeruleus across the third through fifth decades. The locus coeruleus is the noradrenergic brainstem nucleus that supplies tonic noradrenergic drive to the forebrain and that is unusually metabolically active per unit volume. The Phase I substrate is the cellular biology of catecholamine metabolism within the locus coeruleus neuron, with the proximate driver of failure being sustained PARP-1 hyperactivation in response to mitochondrial oxidative stress and the consequent NAD□ depletion that compromises sirtuin signaling, OXPHOS efficiency, and the integrated stress response. The Phase I timing — early adult onset in the third decade with progressive expansion through the fifth — reflects the long subclinical phase during which locus coeruleus neuron count is progressively reduced from the approximately fifty thousand neurons of early adulthood toward the approximately twenty-five thousand at which clinical symptoms begin to emerge. The locus coeruleus is the disease's earliest parenchymal substrate, and its bioenergetic ignition is the first parenchymal event of the trilogy's temporal sequence.

Phase II, articulated by the Homeostatic Microglial Collapse thesis, is the loss of the Butovsky-defined homeostatic microglial signature across the fifth through seventh decades. The Butovsky 2014 transcriptional signature comprises a discrete molecular identity — P2ry12, Tmem119, Sall1, Hexb, Fcrls, Olfml3, Cx3cr1, and a larger ensemble of co-regulated genes — whose expression is maintained by continuous TGF-β signaling from the surrounding neural and vascular parenchyma. The signature is not a cell-intrinsic property but an actively maintained niche identity, and its loss under chronic inflammatory pressure produces a series of disease-associated microglial states (DAM, IRMs, MGnD) whose cellular biology has been extensively characterized. The Phase II timing — late midlife onset with progressive expansion through the seventh decade — reflects the cumulative load of inflammatory signaling that the parenchymal microglia experience under sustained vascular and systemic inflammatory drive, with the loss of the homeostatic signature occurring when the cumulative inflammatory load exceeds the TGF-β / SMAD maintenance capacity. The hippocampal-temporal axis is the principal Phase II target because hippocampal microglia have the lowest cumulative TGF-β tone in the forebrain and the highest exposure to vascular inflammatory signals due to the hippocampus's specialized vascular anatomy.

Phase III, articulated by the Convergent Synaptic Collapse thesis, is the structural disintegration of the cortical microcircuit through matrix-metalloproteinase digestion of the parvalbumin perineuronal net across the seventh decade and beyond. The parvalbumin perineuronal net is the dense chondroitin sulfate proteoglycan matrix that ensheathes parvalbumin-positive fast-spiking interneurons in the cortex and hippocampus and that supplies both metabolic and electrochemical support for the high-frequency firing on which gamma-frequency cortical computation depends. The Phase III event is the MMP-mediated digestion of the perineuronal net by activated microglia, the consequent loss of gamma-frequency drive in affected circuits, and the structural disintegration of the cortical layer that the parvalbumin interneuron stabilizes. The Phase III timing reflects the accumulation of microglial MMP-9 secretion that the Phase II microglial transition produced, with the perineuronal net the proximate downstream target of the MMP-9 that the disease-associated microglia secrete.

2.5 Phase-Specific Biomarker Trajectories

The biomarker literature on Alzheimer's disease has been organized principally around the AT(N) parenchymal triad — amyloid, tau, neurodegeneration — with the framework articulated by Jack et al. in 2018 and extended in subsequent revisions. The AT(N) framework treats the parenchymal substrates as the principal biomarker axes and the vascular substrate as outside the framework. The Janelidze 2018 *Neurology* paper and the Sweeney 2018 *Nature Reviews Neurology* paper independently proposed the extension of the framework to include vascular and neuroinflammatory biomarkers, with cerebrospinal fluid VCAM-1, ICAM-1, sPDGFRβ, and angiopoietin-2 as candidate vascular markers and CSF YKL-40, sTREM2, and GFAP as candidate neuroinflammatory markers. The integrated framework has not yet been adopted in clinical trial design, but the empirical data supporting it are substantial.

The phase-specific behavior of these vascular biomarkers across the trilogy's three phases has not been articulated in a single integrated framework. The Phase I behavior — what the brainstem-anchored bioenergetic ignition looks like at the vascular interface — has been characterized only sporadically. The Phase II behavior — what the hippocampal-anchored microglial transition looks like at the vascular interface — has been the subject of the Montagne-Zlokovic program. The Phase III behavior — what the cortical-anchored synaptic collapse looks like at the vascular interface — has been the subject of the cerebral amyloid angiopathy and ARIA literature. The present dissertation integrates these phase-specific accounts into a single biomarker trajectory whose temporal evolution tracks the disease across the third through eighth decades.

2.6 Glymphatic Clearance and the Sleep-Vascular Interaction

The glymphatic clearance pathway, characterized principally by Maiken Nedergaard and Jeffrey Iliff and their colleagues from 2012 onward, is the cerebrospinal-fluid-to-interstitial-fluid exchange system through which solute waste — including amyloid-β, tau, and metabolic byproducts — is cleared from the parenchymal compartment. The pathway operates through periarterial CSF inflow, AQP4-mediated CSF-ISF exchange at the astrocytic endfoot, parenchymal percolation, and perivenous drainage to meningeal lymphatics. The pathway is driven by arterial pulsatility and is approximately tenfold more active during slow-wave sleep than during waking. The glymphatic pathway is both a vascular system (driven by arterial pulsatility, dependent on perivascular architecture) and a sleep-state system (active principally during slow-wave sleep), and its failure with aging is a vascular-sleep failure whose phase-specific manifestation the present dissertation develops.

The Mestre 2018 *Nature Communications* paper established that hypertension and arterial stiffening impair glymphatic clearance through reduced pulse pressure, providing the mechanistic link between cardiovascular risk factors and parenchymal solute accumulation. The Kress 2014 *Annals of Neurology* paper established that AQP4 polarization at the astrocytic endfoot is reduced in the aged brain, providing the molecular substrate for the glymphatic decline. The Nedergaard – Goldman 2020 *Science* paper proposed that glymphatic failure is a final common pathway to dementia, integrating the vascular, sleep-related, and parenchymal substrates of waste clearance into a single explanatory framework. The glymphatic pathway is treated in detail in Chapter V as a cross-phase mechanism whose phase-specific manifestation differs across Phases I, II, and III.

2.7 APOE4 as a Vascular Genotype

The apolipoprotein E ε4 allele is the dominant genetic risk factor for late-onset Alzheimer's disease, with heterozygotes carrying approximately threefold elevated risk and homozygotes approximately twelvefold elevated risk relative to APOE3/APOE3 controls. The molecular biology of APOE4 has been treated principally as a parenchymal phenomenon — APOE4-mediated impairment of amyloid-β clearance, APOE4-mediated dysregulation of intracellular lipid trafficking, APOE4-mediated impairment of synaptic plasticity. The Zlokovic program developed an alternative reading: APOE4 is in significant measure a vascular genotype whose vascular phenotype is temporally and mechanistically prior to its parenchymal phenotype.

The molecular basis of the APOE4 vascular phenotype is the failure of APOE4 to suppress the cyclophilin A / NF-κB / MMP-9 signaling axis in pericytes. APOE3 and APOE2 isoforms suppress this axis through normal LRP1 interaction; APOE4 fails to suppress it, with the consequence that cyclophilin A is constitutively elevated, NF-κB is activated, MMP-9 is secreted, and the tight junction proteins of the adjacent endothelial cell — claudin-5, occludin, ZO-1 — are progressively degraded (Bell et al., 2012; Halliday et al., 2016). The Montagne 2020 *Nature* paper extended this molecular framework to a human in vivo cohort and demonstrated that APOE4 carriers exhibit hippocampal BBB breakdown years before they exhibit detectable amyloid accumulation or cognitive symptoms. The APOE4 vascular phenotype is therefore the leading edge of the APOE4 trajectory, and the parenchymal APOE4 phenotype is downstream of the vascular one. The implications of this reading for the phase-specific framework are developed in Chapter V.

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3. Methodology

This dissertation is a synthetic review of the published literature in cerebrovascular biology, neuroimmunology, BBB transport biochemistry, the proteomic biology of aging, glymphatic clearance physiology, cerebral amyloid angiopathy pathology, and the established Collapse trilogy framework. The methodological contribution is not the generation of new data but the integration of existing data into a single analytical schema centered on the phase-specific vascular pathology of late-onset Alzheimer's disease.

The literature review draws on three principal corpora. The first is the cerebrovascular literature, principally the Zlokovic program at the University of Southern California, the Iadecola program at Cornell, the Nedergaard / Iliff glymphatic program, the Wyss-Coray aged-plasma program at Stanford, and the broader cerebrovascular biology literature represented in *Nature*, *Nature Medicine*, *Neuron*, and *Nature Reviews Neurology*. The second is the Collapse trilogy itself — *Convergent Synaptic Collapse*, *Homeostatic Microglial Collapse*, *Bioenergetic Collapse*, and *The Tryptophan Partition* — and the supporting Organic Network Synthesis methodology documents. The third is the clinical Alzheimer's biomarker literature, principally the AT(N) framework, the SPRINT-MIND trial data, the lecanemab and donanemab clinical trial reports, and the ARIA characterization literature.

The integration proceeds in three analytical steps. First, the cellular biology of the neurovascular unit is established as a substrate-independent foundation (Chapter I). Second, the trilogy's tripartite temporal architecture is mapped phase by phase onto the vascular substrate, with each phase chapter (II, III, IV) developing the phase-specific vascular events that condition and amplify the parenchymal pathology of that phase. Third, the cross-phase mechanisms (Chapter V), the phase-specific therapeutic implications (Chapter VI), and the falsifiable predictions (Chapter VII) are derived from the integrated framework. Each analytical chapter is internally organized in a uniform structure: a statement of the phase-specific vascular hypothesis, a development of the cellular and molecular biology, an articulation of the relevant biomarker trajectory, an integration with the relevant parenchymal substrate of the trilogy, and a discussion of the therapeutic implications specific to that phase.

The dissertation does not generate predictions that cannot be derived from the published literature, but it organizes the published literature into a single framework whose explanatory and predictive scope exceeds that of any single component literature. The framework is, in this sense, an architecture rather than a discovery, and its principal contribution is the integration of literatures that have remained largely separate.

4. Chapter I — The Vascular Substrate: Neurovascular Unit Anatomy and Cellular Biology

4.1 The Neurovascular Unit as the Relevant Unit of Analysis

The chapter establishes the cellular biology of the neurovascular unit (NVU) as the substrate-independent foundation on which the phase-specific framework of subsequent chapters rests. The NVU comprises five cellular components — the brain capillary endothelial cell, the pericyte, the astrocytic endfoot, the smooth muscle cell at the arteriolar level, and the perivascular macrophage — and one extracellular component, the basement membrane that anchors the abluminal compartment. The integrated NVU executes the functions of selective transport, regional blood flow regulation, immune surveillance, and perivascular waste clearance as a coordinated cellular complex rather than as the property of any single cell type, and the phase-specific failure of the NVU developed in subsequent chapters is the coordinated failure of the integrated system.

4.2 The Brain Endothelial Cell: A Curated Interface

The brain endothelial cell differs from systemic endothelial cells in three quantitatively decisive respects: tight junction integrity, transcytosis suppression, and polarized transporter expression. The tight junction complex is sealed by claudin-5 (the principal molecular determinant of paracellular impermeability), occludin, and the JAM family of adhesion molecules, anchored to the actin cytoskeleton through the ZO-family cytoplasmic scaffolds. The transcytosis suppression is actively maintained by MFSD2A-mediated docosahexaenoic acid import that produces a lipid composition incompatible with caveolar formation. The polarized transporter expression — GLUT1 for glucose, LAT1 for amino acids, MCT1 for monocarboxylates, LRP1 for amyloid-β efflux, RAGE for amyloid-β influx, P-glycoprotein and BCRP for xenobiotic efflux — defines the brain endothelium as a selectively curated interface whose substrate specificity is the product of decades of evolutionary selection for the requirements of the central nervous system.

4.3 The Pericyte-Endothelial Dyad

The pericyte is the contractile mural cell embedded in the basement membrane immediately adjacent to the endothelial cell. The pericyte-to-endothelial ratio in cortical capillaries is approximately one-to-three, the highest of any capillary bed in the body, and pericyte coverage of capillary surface area approaches thirty percent in cortical gray matter. The pericyte contributes to blood flow regulation through its contractile state, to capillary stability through its paracrine support of endothelial tight junctions via PDGF-B / PDGFRβ signaling and Notch signaling, to immune surveillance through its expression of pattern recognition receptors, and to waste clearance through its participation in the perivascular drainage pathway. The pericyte is the cellular component of the NVU whose age-dependent loss has been most precisely quantified by the Zlokovic program and whose contribution to BBB integrity is most directly attested by genetic models of pericyte ablation.

4.4 The Astrocytic Endfoot and AQP4 Polarization

The astrocytic endfoot is the specialized terminal of an astrocyte process that contacts the basement membrane and completes the abluminal coverage of the NVU. The endfoot expresses the aquaporin-4 water channel in a polarized distribution, with AQP4 enriched at the membrane that contacts the basement membrane and depleted from the membrane that contacts the parenchymal neuropil. The polarization is the molecular substrate of glymphatic clearance, treated in Chapter V. The endfoot also contributes to neurovascular coupling through arachidonic acid metabolite release in response to neuronal activity and to NVU integrity through paracrine support of endothelial tight junctions via sonic hedgehog and angiopoietin-1.

4.5 The Smooth Muscle Cell and Cerebral Amyloid Angiopathy

The vascular smooth muscle cell, present at the level of the arteriole and pre-capillary arteriole, executes the moment-to-moment regulation of arteriolar diameter and therefore of regional cerebral blood flow. Smooth muscle cells respond to a combination of intrinsic myogenic tone, neural input from perivascular sympathetic and parasympathetic projections, and local metabolic signals propagated from the parenchyma through astrocytic and pericytic intermediaries. The smooth muscle cell is the principal cellular substrate of cerebral amyloid angiopathy, developed in Chapter IV: amyloid-β40 accumulates within and around the smooth muscle layer of cortical and leptomeningeal arterioles, progressively replaces the smooth muscle with amyloid deposits, and abolishes the vessel's capacity for autoregulation.

4.6 The Perivascular Macrophage and the CNS Border Compartment

The perivascular macrophage is a CNS-resident macrophage population distinct from parenchymal microglia, residing in the Virchow-Robin perivascular space between the basement membrane of the vessel and the glia limitans formed by astrocytic endfeet. Perivascular macrophages express markers including CD163, CD206, and Lyve-1 that distinguish them from parenchymal microglia, and they execute specialized immune surveillance at the vascular interface. The perivascular macrophage is a distinct CNS-border myeloid compartment whose integration with the parenchymal microglial population treated by the Homeostatic Microglial Collapse thesis is developed in Chapter III. The Drieu 2022 *Nature* paper extended the framework by characterizing parenchymal border macrophages as regulators of CSF flow dynamics, supplying an additional cellular substrate for the glymphatic-vascular interaction treated in Chapter V.

4.7 The Basement Membrane as a Matrix Scaffold

The basement membrane is the extracellular matrix layer composed of laminin, type IV collagen, nidogen, and perlecan that surrounds the endothelial-pericyte complex and anchors the astrocytic endfoot. The basement membrane is the abluminal compartment through which the perivascular drainage pathway operates, and its compositional changes in aging and in cerebral amyloid angiopathy — including thickening, fragmentation, and amyloid-β deposition — are the structural substrate of NVU failure. The basement membrane is the vascular analogue of the parvalbumin perineuronal net treated by the Convergent Synaptic Collapse thesis: both are matrix-stabilized homeostatic scaffolds whose age- and disease-related degradation by matrix metalloproteinases is the proximate event in the failure of the compartment they stabilize. The basement membrane / perineuronal net analogy is developed in detail in Chapter IV.

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5. Chapter II — Phase I (Decades 3–5): The Vascular Conditioning of Bioenergetic Ignition

5.1 The Phase I Vascular Hypothesis

The Phase I vascular hypothesis is that the bioenergetic ignition of the locus coeruleus across the third through fifth decades is vascularly conditioned by capillary hypoperfusion at the brainstem, by early BBB compromise at the vasa nervorum, and by the leading-edge induction of VCAM-1 at brainstem endothelium under the developing pressure of the aged systemic milieu. The conditioning events are not the proximate driver of the LC neuron failure that the Bioenergetic Collapse thesis treats — the proximate driver remains sustained PARP-1 hyperactivation and NAD□ depletion within the LC neuron — but the conditioning events are the vascular substrate that sets the threshold above which the parenchymal events engage. The LC is unusually vascularly vulnerable, and its parenchymal vulnerability to bioenergetic ignition is therefore vascularly conditioned.

5.2 The Locus Coeruleus and Its Vascular Anatomy

The locus coeruleus is the noradrenergic brainstem nucleus that supplies the principal noradrenergic projection to the forebrain and that consists of approximately fifty thousand neurons in early adulthood declining to twenty-five thousand or fewer by the eighth decade. The LC is anatomically located in the dorsolateral tegmentum of the pons immediately beneath the floor of the fourth ventricle, and it is supplied by a single arterial source — branches of the superior cerebellar artery and of the pontine perforating branches — whose autoregulatory capacity is more limited than that of cortical arterial supply. The LC's vascular vulnerability is therefore architectural: a small, densely packed, highly metabolically active nucleus served by a single arterial source whose autoregulation degrades with age more sharply than cortical autoregulation does. The brainstem perfusion data, principally from MR arterial spin labeling studies in the human aging literature, document a regional decline in brainstem perfusion that begins in the fourth decade and progresses through the fifth, with the LC region exhibiting among the largest regional declines.

5.3 Capillary Hypoperfusion as Upstream of NAD□ Depletion

The cellular biology of LC bioenergetic failure is the cellular biology of sustained PARP-1 hyperactivation in response to mitochondrial oxidative stress and the consequent NAD□ depletion that compromises sirtuin signaling and OXPHOS efficiency. The proximate driver of the mitochondrial oxidative stress is the auto-oxidation chemistry of noradrenaline within the LC neuron, but the threshold above which the oxidative stress becomes pathological is set by the cell's instantaneous oxygen and substrate availability, which is in turn set by capillary perfusion. Capillary hypoperfusion at the LC region therefore lowers the threshold above which the parenchymal bioenergetic ignition engages, and the recurrent sub-ischemic hypoperfusion intervals that the impaired neurovascular coupling of the third and fourth decades produces are the vascular conditioning events that the Phase I framework treats as upstream of the parenchymal events. The cellular logic is: oxidative stress is generated by LC chemistry; oxygen availability sets the cell's capacity to handle the stress; vascular hypoperfusion reduces oxygen availability; the cell's capacity is exceeded and PARP-1 hyperactivation engages. The vascular event is upstream of the parenchymal event in this chain.

5.4 Brainstem BBB Permeability in the Third and Fourth Decades

The brainstem BBB has been less extensively characterized than the cortical or hippocampal BBB, in part because of the technical difficulty of high-resolution DCE-MRI in deep brainstem structures. The available literature, principally from rodent models and from the limited human imaging cohorts that have included brainstem coverage, indicates that brainstem BBB permeability increases with age in a regional pattern that includes the LC and that the regional permeability is elevated in subjects with prodromal Alzheimer's disease relative to age-matched controls. The mechanism is not fully characterized, but the working framework is that brainstem BBB compromise admits inflammatory mediators from the systemic compartment into the immediate environment of the LC neuron, sensitizing the neuron to oxidative stress and lowering the threshold for PARP-1 hyperactivation. The brainstem BBB compromise is therefore a Phase I vascular event that engages decades before the corresponding hippocampal BBB compromise of Phase II.

5.5 Early VCAM-1 Induction at the Brainstem Endothelium

The Yousef – Wyss-Coray VCAM-1 mechanism, characterized principally at the hippocampal endothelium, generalizes to other brain regions including the brainstem. Brainstem endothelial cells, like cortical and hippocampal endothelial cells, express VCAM-1 in response to TNF-α and IL-1β through NF-κB-dependent transcription, and the brainstem endothelial VCAM-1 induction has been documented in aged mouse models. The Phase I framework predicts that brainstem endothelial VCAM-1 is the leading-edge vascular event that integrates the systemic aging signal at the brainstem level, with the induction beginning in the third decade and progressing through the fifth. The Phase I VCAM-1 induction is quantitatively smaller than the Phase II hippocampal induction, but it is temporally earlier, and it is the leading edge of the vascular trajectory that the trilogy's temporal architecture progresses across.

5.6 Phase I Vascular Biomarkers

The phase-specific biomarker panel for Phase I comprises four principal markers. Plasma soluble VCAM-1 is the systemic readout of the brain endothelial VCAM-1 induction and tracks with the developing pressure of the aged systemic milieu. Cerebrospinal fluid soluble PDGFRβ is the readout of early pericyte injury and tracks with the leading-edge BBB compromise. Arterial spin labeling MRI of brainstem cerebral blood flow is the imaging readout of brainstem hypoperfusion and is detectable in cohorts with sufficient brainstem resolution. The midlife cardiovascular risk factor profile — blood pressure, lipid panel, glycemic control, smoking status, sleep architecture — is the systemic vascular readout that integrates the principal modifiable contributors to the Phase I substrate. The Phase I biomarker panel is currently not assembled in any single clinical framework, but its components are individually well-validated, and its integrated use would supply a phase-specific stratification that the AT(N) parenchymal framework cannot.

5.7 Integration with the Bioenergetic Collapse Thesis

The Phase I vascular substrate integrates with the Bioenergetic Collapse thesis as the upstream conditioning of the LC parenchymal substrate. The Bioenergetic Collapse thesis treats LC parenchymal failure as the disease's earliest parenchymal substrate; the Phase I vascular framework treats LC vascular vulnerability as the upstream conditioning that lowers the threshold above which the parenchymal failure engages. The integration is multiplicative: a given level of LC bioenergetic stress produces a given probability of PARP-1 hyperactivation that depends on the cell's instantaneous oxygen availability, which depends on capillary perfusion, which depends on the vascular substrate. The Phase I vascular framework therefore supplies the threshold-modulating substrate that the Bioenergetic Collapse thesis's parenchymal substrate operates on, and the integrated account is structurally distinct from either component alone.

6. Chapter III — Phase II (Decades 5–7): The Vascular Gateway of the Microglial Transition

6.1 The Phase II Vascular Hypothesis

The Phase II vascular hypothesis is that the loss of the Butovsky-defined homeostatic microglial signature in the hippocampal-temporal axis across the fifth through seventh decades is gated by a vascular event at the hippocampal endothelium whose proximate molecular driver is brain endothelial VCAM-1. The Yousef – Wyss-Coray mechanism, characterized principally at the hippocampal endothelium, establishes the molecular chain by which the aged systemic milieu is converted into a parenchymal signal that destabilizes the homeostatic microglial signature: aged plasma ☐ VCAM-1 induction at hippocampal endothelium ☐ aged-monocyte α4β1 engagement ☐ endothelial NF-κB activation ☐ abluminal IL-6 / CCL2 secretion ☐ parenchymal microglial signature destabilization. The Phase II vascular event is therefore the gateway through which the systemic aging signal accesses the parenchymal microglial compartment, and it is the proximate upstream driver of the microglial transition that the Homeostatic Microglial Collapse thesis treats.

6.2 The Hippocampal Bridgehead and Its Vascular Anatomy

The hippocampus is the principal Phase II parenchymal target because hippocampal microglia have the lowest cumulative TGF-β tone in the forebrain and the highest exposure to vascular inflammatory signals due to the hippocampus's specialized vascular anatomy. The hippocampus is supplied by branches of the posterior cerebral artery and of the anterior choroidal artery, with the hippocampal proper served principally by the posterior cerebral branches and the dentate gyrus served by both sources. The hippocampal vascular architecture is unusually leaky relative to the cortical vascular architecture: tight junction protein expression is constitutively lower, transcytosis suppression is less complete, and the dentate gyrus subgranular zone in particular is characterized by a specialized vascular niche that supports adult hippocampal neurogenesis at the cost of higher baseline BBB permeability. The vascular leakiness of the hippocampus is therefore a constitutive feature that makes the hippocampal microglia preferentially exposed to vascular inflammatory signals.

6.3 The Montagne-Zlokovic Hippocampal BBB Trajectory

The Montagne 2015 *Neuron* paper established that hippocampal BBB permeability increases with age in cognitively healthy volunteers, with the increase beginning in the sixth decade and progressing through the seventh and eighth. The Nation 2019 *Nature Medicine* paper extended the finding to a cohort with mild cognitive impairment, demonstrating that hippocampal BBB permeability is elevated in MCI subjects relative to age-matched controls in the absence of detectable amyloid or tau pathology by CSF biomarkers — the BBB breakdown is therefore an early-stage event whose temporal precedence over parenchymal amyloid and tau accumulation is now established. The Montagne 2020 *Nature* paper extended the framework to APOE4 carriers and demonstrated that the BBB breakdown is the earliest detectable biomarker change in the APOE4 trajectory, preceding parenchymal amyloid accumulation by an estimated decade or more. The Montagne-Zlokovic hippocampal BBB trajectory is the principal in vivo evidence base for the Phase II vascular hypothesis.

6.4 The Yousef – Wyss-Coray VCAM-1 Mechanism in Detail

The mechanistic chain through which brain endothelial VCAM-1 transduces the aged-plasma signal into a parenchymal microglial effect comprises three steps that the Yousef – Wyss-Coray work and subsequent literature have progressively elucidated. The first step is the engagement of brain endothelial VCAM-1 by α4β1-expressing leukocytes, principally aged monocytes whose surface α4β1 is itself elevated in the aged state. The engagement produces firm adhesion at the brain microvasculature; the adhesion is not necessarily followed by transmigration in the aged brain but may be sustained without transmigration for hours or days, during which the adherent monocyte secretes inflammatory cytokines that diffuse across the endothelium into the parenchymal compartment. The second step is endothelial signaling: VCAM-1 engagement activates NADPH oxidase and produces a local reactive oxygen species pulse, which activates endothelial NF-κB and induces the secretion of IL-6 and CCL2 into the abluminal compartment. The third step is parenchymal reception: the endothelial-secreted cytokines reach the parenchymal microglia and destabilize the homeostatic microglial signature, priming the microglia for the disease-associated trajectory that the Homeostatic Microglial Collapse thesis treats.

The mechanism establishes a direct molecular chain from the aged systemic milieu to the parenchymal microglia, mediated entirely by brain endothelial VCAM-1. The chain is supported by direct experimental evidence: antibody blockade of VCAM-1 and endothelial-specific *Vcam1* deletion both abolish the aged-plasma effects on hippocampal microglia, on hippocampal neurogenesis, and on hippocampal-dependent cognitive performance in mice. The Phase II vascular hypothesis is therefore the application of the Yousef – Wyss-Coray mechanism to the temporal architecture of the Collapse trilogy, with the brain endothelial VCAM-1 induction as the proximate upstream driver of the microglial transition.

6.5 The APOE4 Phase II Vascular Phenotype

The Phase II vascular framework supplies the temporal and mechanistic context for the APOE4 vascular phenotype articulated by the Zlokovic-Montagne program. APOE4 carriers exhibit hippocampal BBB breakdown years before they exhibit detectable amyloid accumulation, and the BBB breakdown is the earliest detectable biomarker change in the APOE4 trajectory. The Phase II framework places this event at the hippocampal end of the brain at the fifth through seventh decades, with the molecular mechanism the cyclophilin A / NF-κB / MMP-9 axis in pericytes that APOE4 fails to suppress. The APOE4 Phase II vascular phenotype is therefore the early-stage manifestation of the APOE4 cross-phase vascular liability developed in Chapter V, with the hippocampal endothelial-pericyte axis as the principal site of expression.

6.6 Pericyte Loss and the sPDGFRβ Trajectory

The pericyte injury biomarker — soluble PDGFRβ in CSF — has been validated by the Nation 2019 paper and by subsequent cohorts as a quantitative biomarker of pericyte injury whose elevation tracks with hippocampal BBB permeability on DCE-MRI, with cognitive decline in longitudinal follow-up, and with subsequent conversion from MCI to clinical dementia. The CSF sPDGFRβ elevation is present at the preclinical stage and is independent of CSF amyloid-β and tau measurements, establishing pericyte injury as a vascular event with a measurable trajectory distinct from the parenchymal events captured by the AT(N) biomarker framework. The Phase II framework treats sPDGFRβ as the principal pericyte-axis biomarker of the phase, with elevation beginning in the late fifth decade and progressing through the seventh.

6.7 Phase II Vascular Biomarkers

The phase-specific biomarker panel for Phase II comprises five principal markers. Cerebrospinal fluid VCAM-1 is the principal molecular biomarker and tracks with the developing pressure of the aged systemic milieu at the brain endothelial interface. Plasma soluble VCAM-1 is the systemic readout and is more accessible. Cerebrospinal fluid soluble PDGFRβ is the pericyte injury readout. Dynamic contrast-enhanced MRI of hippocampal BBB permeability is the imaging readout and is detectable on standard clinical MRI scanners with appropriate sequence development. Cerebrospinal fluid YKL-40 and sTREM2 are the parenchymal neuroinflammatory readouts that integrate the downstream microglial response. The Phase II biomarker panel is more developed in the clinical literature than the Phase I panel, with each component individually validated and the integrated use now beginning to be adopted in research cohorts.

6.8 Integration with the Homeostatic Microglial Collapse Thesis

The Phase II vascular substrate integrates with the Homeostatic Microglial Collapse thesis as the upstream gateway through which the aged systemic milieu accesses the parenchymal microglial compartment. The HMSP thesis treats parenchymal microglial signature loss as the disease's principal middle-phase substrate; the Phase II vascular framework treats brain endothelial VCAM-1 as the proximate upstream driver of the signature loss. The integration is causal: the parenchymal microglia do not lose their homeostatic signature spontaneously but in response to specific inflammatory inputs whose proximate source is the brain endothelium under VCAM-1 induction. The Phase II vascular framework therefore supplies the upstream input that the HMSP thesis's parenchymal substrate transduces, and the integrated account is structurally a chained causal sequence from systemic aging through vascular gateway to parenchymal microglial transition.

7. Chapter IV — Phase III (Decade 7+): The Vascular Amplification of Synaptic Collapse

7.1 The Phase III Vascular Hypothesis

The Phase III vascular hypothesis is that the structural disintegration of the cortical microcircuit through MMP digestion of the parvalbumin perineuronal net in the seventh decade and beyond is vascularly amplified by cerebral amyloid angiopathy at the cortical vessel wall, by basement membrane degradation that parallels the perineuronal net degradation, and by the small vessel disease continuum that produces the mixed dementia of the eighth decade. The Phase III vascular events are not the proximate driver of the perineuronal net digestion — the proximate driver remains microglial MMP-9 secretion, which the Phase II microglial transition produced — but the Phase III vascular events both amplify the parenchymal disintegration and impose the therapeutic constraint (ARIA) that the anti-amyloid monoclonal antibody clearance strategy encounters at the vascular interface.

7.2 Cerebral Amyloid Angiopathy as Phase III Vascular Pathology

Cerebral amyloid angiopathy is the deposition of amyloid-β within and around the smooth muscle cells of cortical and leptomeningeal arterioles and small arteries. CAA is present at autopsy in approximately ninety percent of subjects with clinical Alzheimer's disease and is the principal vascular comorbidity of the parenchymal disease. The amyloid that accumulates in the vessel wall is principally amyloid-β40, in contrast to the predominantly amyloid-β42 species that accumulates in parenchymal plaques, with the differential distribution reflecting the higher solubility and the slower aggregation kinetics of amyloid-β40 and the perivascular drainage pathway through which soluble amyloid is cleared from the parenchyma along the basement membranes of cortical arterioles. The CAA deposition is therefore a clearance-pathway event: amyloid-β40 produced in the parenchyma is cleared along the perivascular drainage pathway and accumulates in the vessel wall when the perivascular drainage capacity is exceeded.

The cellular biology of CAA progression follows a stereotyped sequence in which amyloid-β40 first deposits in the basement membrane of the vessel, then accumulates in the smooth muscle cell layer, then progressively replaces the smooth muscle cells, and finally compromises the structural integrity of the vessel wall. The

advanced stages of CAA include vessel-in-vessel deposition, fibrinoid necrosis of the affected vessel wall, and microaneurysm formation. The clinical consequences of advanced CAA include lobar intracerebral hemorrhage, cortical superficial siderosis, convexity subarachnoid hemorrhage, and the cerebral microbleeds detected on gradient-echo and susceptibility-weighted MRI. CAA is therefore the principal Phase III vascular pathology by which the parenchymal amyloid load of the late-stage disease is expressed at the vascular interface.

7.3 The ARIA Constraint on Anti-Amyloid Monoclonal Antibody Therapy

The amyloid-related imaging abnormalities (ARIA) that emerge as adverse events of lecanemab, donanemab, and the earlier aducanumab are vascular events: ARIA-E is the imaging signature of vasogenic edema attributable to leak of plasma constituents across the compromised vessel wall, and ARIA-H is the imaging signature of microhemorrhage attributable to rupture of CAA-affected vessels. The mechanism is interpretable within the Phase III framework: the monoclonal antibodies bind amyloid-β within the parenchyma and within the vessel wall, recruit microglia to the antibody-amyloid complexes, and stimulate amyloid clearance through Fc-receptor-mediated phagocytosis. The clearance of amyloid from the vessel wall is a destabilizing event for a vessel whose structural integrity has already been compromised by amyloid replacement of the smooth muscle layer, and the consequence is the leak or rupture of the affected vessel.

The ARIA events are therefore not idiosyncratic toxicities of the antibodies but predictable consequences of the interaction of the antibody mechanism with the underlying Phase III CAA pathology. The clinical decision to administer or withhold anti-amyloid monoclonal antibodies in a given patient is, in current practice, substantially constrained by the patient's burden of cerebral microbleeds on baseline MRI and by the patient's APOE genotype, with APOE4 homozygotes exhibiting the highest CAA burden and the highest ARIA risk. The Phase III framework therefore predicts the ARIA constraint as a structural feature of the vascular substrate and supplies the mechanistic basis for the patient stratification that minimizes the vascular cost.

7.4 The Basement Membrane as Vascular Perineuronal Net Analogue

The basement membrane that anchors the brain endothelial cell and the parvalbumin perineuronal net that ensheathes the parvalbumin interneuron are matrix-stabilized homeostatic scaffolds whose age- and disease-related degradation by matrix metalloproteinases is a proximate event in the failure of the compartment they stabilize. The analogy is mechanistically tight: both scaffolds are composed of proteoglycan and structural protein components (chondroitin sulfate proteoglycans for the perineuronal net, laminin and type IV collagen for the basement membrane), both are degraded by overlapping metalloproteinases (principally MMP-9, with contributions from MMP-2 and MMP-3), and both are stabilized by similar molecular mechanisms (cross-linking, tissue inhibitor of metalloproteinase (TIMP) inhibition, and the activity of MMP-suppressing factors). The Phase III framework treats the parallel degradation of the basement membrane and the perineuronal net as coupled events, with the MMP-9 secreted by activated microglia digesting both scaffolds simultaneously. The vascular and parenchymal pathologies of Phase III therefore share a common molecular substrate and a common downstream effector, and the Phase III framework is structurally a single mechanism with vascular and parenchymal manifestations.

7.5 Small Vessel Disease and the Mixed Dementia Endpoint

The cerebral small vessel disease (cSVD) family of pathologies — arteriolosclerosis, lipohyalinosis, microbleeds, lacunar infarcts, white matter hyperintensities — accumulates across the decades of adult life and contributes substantially to the cognitive presentation of late-life dementia. The autopsy literature on the prevalence of mixed pathology has converged on the finding that the majority of subjects with clinical Alzheimer's dementia at autopsy exhibit substantial cerebrovascular pathology in addition to the parenchymal pathology, with the consequence that the "pure Alzheimer's" pathology that has dominated the clinical research framework is the exception rather than the rule in the elderly population. The Phase III framework treats mixed dementia as the modal phenotypic endpoint of the trilogy's temporal sequence, with the cortical synaptic pathology of the perineuronal net axis combining with the cortical vascular pathology of the small vessel disease continuum to produce the cognitive presentation that is clinically recognized as Alzheimer's dementia in the eighth decade.

7.6 White Matter Hyperintensities and Cortical Disconnection

The white matter hyperintensities that accumulate with age, with hypertension, with diabetes, and with the broader spectrum of vascular risk factors are the principal imaging correlate of small vessel disease and are quantitatively associated with cognitive impairment in cross-sectional and longitudinal cohorts. The cellular biology of the white matter lesion is the consequence of chronic small vessel hypoperfusion, with oligodendrocyte vulnerability to hypoxic stress driving the demyelination and axonal compromise that produces the imaging finding. The cognitive impact of the white matter lesion is the disconnection of cortical regions whose communication depends on the affected white matter tracts. The Phase III framework treats white matter hyperintensities as the cortical disconnection counterpart to the cortical perineuronal net failure: the parenchymal failure of the cortical microcircuit (Phase III parenchymal) and the vascular disconnection of cortical regions (Phase III vascular) together produce the cortical pathology that the clinical presentation reflects.

7.7 Phase III Vascular Biomarkers

The phase-specific biomarker panel for Phase III comprises five principal markers. Susceptibility-weighted MRI or gradient-echo MRI of cerebral microbleeds is the principal CAA imaging biomarker and is now a standard component of clinical Alzheimer's MRI protocols. FLAIR MRI of white matter hyperintensities is the principal small vessel disease imaging biomarker and is similarly standard. Centiloid quantification of amyloid PET signal is the parenchymal amyloid biomarker that the Phase III intervention decisions must integrate with the vascular biomarkers. APOE genotype is the principal genetic biomarker of Phase III vascular risk and informs the ARIA stratification of anti-amyloid intervention. Cerebrospinal fluid VCAM-1 and ICAM-1 are the molecular biomarkers of the persistent endothelial activation that continues throughout the Phase III window. The Phase III biomarker panel is the most clinically developed of the three phases, reflecting the late-stage focus of current clinical practice and the regulatory requirements for anti-amyloid therapy administration.

7.8 Integration with the Convergent Synaptic Collapse Thesis

The Phase III vascular substrate integrates with the Convergent Synaptic Collapse thesis as the parallel vascular pathology that shares the molecular substrate of MMP-mediated matrix degradation with the parenchymal pathology of perineuronal net digestion. The CSC thesis treats parvalbumin perineuronal net digestion as the proximate executor of structural disintegration; the Phase III vascular framework treats basement membrane degradation as the parallel vascular event with the same molecular substrate. The integration is structural rather than causal: the vascular and parenchymal pathologies of Phase III are not in a causal sequence but are parallel manifestations of a single molecular event (microglial MMP-9 secretion) at two distinct cellular targets. The integrated Phase III account is therefore a single mechanism with vascular and parenchymal expressions, and the cumulative effect of the two on the cognitive presentation is the phenotypic endpoint that the clinical diagnosis recognizes.

8. Chapter V — Cross-Phase Vascular Mechanisms

8.1 The Glymphatic Pathway Across All Three Phases

The glymphatic clearance pathway is the principal cross-phase vascular mechanism in the framework: it operates throughout the disease course, its phase-specific manifestation differs across Phases I, II, and III, and its failure couples the vascular and parenchymal substrates at each phase. In Phase I, glymphatic failure is principally a sleep-architecture event: the third and fourth decades see the progressive reduction in slow-wave sleep duration and amplitude that compromises the principal driving force of glymphatic flow, and the consequent reduction in parenchymal clearance of amyloid-β and tau begins the cumulative load that subsequent phases amplify. In Phase II, glymphatic failure adds a vascular pulsatility component: the fifth and sixth decades see the progressive arterial stiffening that the systemic vascular substrate produces, and the reduced pulse pressure available to drive periarterial CSF flow compounds the sleep-architecture decline. In Phase III, glymphatic failure adds an AQP4 polarization component: the seventh decade and beyond see the loss of AQP4 polarization at the astrocytic endfoot that the parenchymal aging program produces, and the reduced clearance efficiency compounds both the sleep-architecture decline and the arterial pulsatility decline. The integrated glymphatic failure across the three phases produces a multiplicative reduction in parenchymal clearance whose downstream consequence is the elevated steady-state parenchymal concentrations of amyloid-β and tau that the parenchymal substrates of each phase operate on.

8.2 Neurovascular Coupling Decline as a Continuous Variable

The neurovascular coupling response — the moment-to-moment matching of regional cerebral blood flow to regional metabolic demand — declines progressively across the adult lifespan and is reduced in magnitude and prolonged in latency in aged mice, in APOE4 carriers, and in subjects with prodromal Alzheimer's disease. The decline is a continuous variable that operates across all three phases of the trilogy's temporal architecture, with the phase-specific consequences differing in magnitude rather than in mechanism. In Phase I, the neurovascular coupling decline is a leading-edge contributor to LC hypoperfusion. In Phase II, the decline is a contributor to hippocampal hypoperfusion and to the developing pressure on the hippocampal endothelial-pericyte axis. In Phase III, the decline is a contributor to the cortical hypoperfusion that compounds the small vessel disease pathology and the cortical disconnection of white matter hyperintensities. The integrated neurovascular coupling decline is therefore a continuous cross-phase substrate whose phase-specific manifestation is the regional target of the largest decline at each phase.

8.3 APOE4 as the Cross-Phase Vascular Genotype

APOE4 is the principal cross-phase vascular genotype in the framework: its molecular biology (cyclophilin A / NF-κB / MMP-9 axis dysregulation in pericytes) operates throughout the adult lifespan, and its phase-specific manifestations differ in regional target rather than in mechanism. In Phase I, APOE4 contributes to brainstem capillary dysfunction and to the developing pressure on the LC vascular substrate. In Phase II, APOE4 is the principal genetic driver of the hippocampal BBB breakdown that the Montagne-Zlokovic trajectory documents. In Phase III, APOE4 is the principal genetic driver of the CAA burden that determines the ARIA risk of anti-amyloid intervention. The APOE4 cross-phase vascular phenotype is therefore a single molecular mechanism with three phase-specific regional expressions, and the integrated framework treats APOE4 as a vascular genotype whose impact on disease trajectory is mediated principally through the vascular substrate at each phase.

8.4 The VCAM-1 Trajectory Across the Lifespan

The brain endothelial VCAM-1 trajectory is the principal cross-phase molecular biomarker in the framework, with plasma sVCAM-1 rising approximately fivefold across the adult human lifespan and brain endothelial VCAM-1 expression rising in parallel. The phase-specific induction is regional and quantitative: brainstem endothelial VCAM-1 leads in Phase I, hippocampal endothelial VCAM-1 dominates in Phase II, and cortical endothelial VCAM-1 sustains in Phase III. The VCAM-1 trajectory is therefore the principal molecular marker of the cross-phase vascular substrate, and its temporal evolution across the three phases is the principal trajectory that the framework's biomarker panel tracks. The clinical implication is that plasma sVCAM-1 measured serially across midlife and into late life supplies a phase-stratification variable that the AT(N) parenchymal biomarker framework cannot.

8.5 The Endothelial-Microglial-Synaptic Coupling

The integrated cross-phase framework treats the endothelial, microglial, and synaptic compartments as a coupled triad whose phase-specific failure modes are mechanistically linked. The endothelial-microglial coupling is the VCAM-1 mechanism that the Phase II framework treats. The microglial-synaptic coupling is the MMP-9 mechanism that the Phase III framework treats. The endothelial-synaptic coupling is the basement membrane / perineuronal net analogy that the Phase III framework treats. The integrated triad is the substrate on which the trilogy's three parenchymal phases operate, and the four-substrate account (vascular plus three parenchymal) is the integrated framework that the present dissertation advances.

9. Chapter VI — Phase-Specific Therapeutic Implications

9.1 The Phase I Window: Cardiovascular Risk Factor Control in Midlife

The Phase I therapeutic window is the third through fifth decades, during which the vascular substrate is the active site of pathological progression and during which intervention directed at the vascular substrate would be expected to produce the largest effect on subsequent disease trajectory. The interventions appropriate to this window are not novel pharmacology in most cases but established cardiovascular medicine: control of hypertension to standards now supported by the SPRINT-MIND trial data, treatment of hyperlipidemia, control of diabetes and the broader metabolic syndrome, smoking cessation, and the lifestyle interventions — physical activity, dietary modification, sleep hygiene — whose vascular benefits are extensively documented. The translation of cardiovascular standards of care to the prevention of Alzheimer's disease is the principal therapeutic implication of the Phase I framework. The population for whom this window is most relevant is the middle-aged APOE4 carrier whose vascular phenotype is in its leading-edge phase but whose parenchymal pathology has not yet engaged. The middle-aged population is, however, the population least often engaged by current Alzheimer's clinical trial frameworks, which focus principally on the late-prodromal and early-symptomatic stages in which parenchymal pathology has already accumulated.

9.2 The Phase II Window: VCAM-1 Blockade and Pericyte Stabilization

The Phase II therapeutic window is the fifth through seventh decades, during which the vascular gateway to the parenchymal microglial transition is the active site of pathological progression. The interventions appropriate to this window are more pharmacologically targeted than the Phase I interventions and include: VCAM-1 antibody blockade (whose proof-of-concept the Yousef – Wyss-Coray mouse work has established and whose translation to human clinical-grade antibodies is technically straightforward); cyclophilin A / MMP-9 axis suppression in pericytes (whose molecular target the Bell-Zlokovic 2012 paper characterized and whose pharmacological development is active); pericyte-supporting interventions (PDGF-B / PDGFRβ axis stabilization, with the molecular target well-characterized and the pharmacology in development); and continued cardiovascular risk factor control. The Phase II window is the principal vascular intervention window for established midlife Alzheimer's risk factors (APOE4 genotype, elevated plasma sVCAM-1, elevated CSF sPDGFRβ, hippocampal BBB permeability on DCE-MRI), and the appropriate population is the late-middle-aged subject with elevated vascular biomarkers but absent or minimal parenchymal pathology.

9.3 The Phase III Window: ARIA-Stratified Anti-Amyloid Therapy

The Phase III therapeutic window is the seventh decade and beyond, during which the parenchymal synaptic pathology is the principal driver of cognitive presentation but the vascular substrate imposes the ARIA constraint on anti-amyloid intervention. The Phase III interventions are the lecanemab and donanemab monoclonal antibodies whose efficacy is established in the clinical trial literature and whose vascular cost is the ARIA-E and ARIA-H imaging abnormalities that result from anti-amyloid clearance at the compromised vessel wall. The Phase III framework supplies the patient stratification that minimizes the vascular cost: APOE4 homozygotes have the highest CAA burden and the highest ARIA risk; subjects with baseline cerebral microbleeds above a threshold count have elevated ARIA risk; subjects with imaging evidence of substantial cortical superficial siderosis have elevated ARIA risk. The Phase III window therefore integrates parenchymal-targeted intervention with vascular biomarker-informed stratification, and the integrated approach is the appropriate practice for late-life intervention.

9.4 Cross-Phase Interventions: Sleep, Exercise, Blood Pressure Control

The cross-phase interventions in the framework are those whose benefit operates throughout the disease course rather than within a single phase. Sleep architecture optimization is a cross-phase intervention whose benefit operates through glymphatic clearance enhancement, through systemic inflammatory load reduction, and through cardiovascular risk factor mitigation; the benefit is largest in Phase I (when sleep-architecture decline is the leading-edge glymphatic event) but operates throughout. Physical activity is a cross-phase intervention whose benefit operates through cardiovascular conditioning, through vascular endothelial nitric oxide synthase upregulation, and through systemic inflammatory load reduction; the benefit is largest in Phase I and Phase II. Blood pressure control is a cross-phase intervention whose benefit operates through reduction of arterial stiffening, through preservation of neurovascular coupling, and through reduction of small vessel disease accumulation; the benefit operates throughout but is largest in Phase I and Phase II. The cross-phase interventions are the foundation of the framework's therapeutic approach and operate independently of the phase-specific pharmacological interventions.

9.5 The Developmental Pharmacology of Alzheimer's Disease

The integrated therapeutic framework that emerges from the four-substrate analysis is a developmental pharmacology of late-onset Alzheimer's disease in which the four substrates are addressed in the temporal sequence in which they engage. Phase I (decades 3–5) is the vascular window addressed by cardiovascular risk factor control. Phase II (decades 5–7) is the vascular-microglial window addressed by VCAM-1 blockade, pericyte stabilization, and continued cardiovascular risk factor control. Phase III (decade 7 and beyond) is the parenchymal window addressed by anti-amyloid intervention with ARIA-stratified patient selection. The cumulative effect of intervention across the four substrates is the disease-modifying effect that has eluded the single-target approach of the past two decades, and the phase-specific framework is the analytical structure within which that cumulative effect is achievable.

10. Chapter VII — Falsifiable Predictions and Experimental Design

10.1 Phase I Predictions

The Phase I framework predicts: (i) Brainstem cerebral blood flow on MR arterial spin labeling declines progressively across the third through fifth decades in cognitively healthy adults and declines more sharply in APOE4 carriers; (ii) Plasma soluble VCAM-1 rises progressively across the third through fifth decades and the rate of rise is greater in APOE4 carriers; (iii) Brainstem BBB permeability on DCE-MRI is detectable in the fifth decade in cohorts with sufficient brainstem resolution and is elevated in APOE4 carriers; (iv) Midlife antihypertensive treatment to SPRINT-MIND standards produces a larger reduction in subsequent dementia incidence in APOE4 carriers than in non-carriers; (v) Midlife glycemic control produces a larger reduction in subsequent dementia incidence in subjects with elevated baseline plasma sVCAM-1 than in subjects with normal baseline values. Each prediction is testable in existing or near-future cohorts, and each is consistent with the Phase I framework but not with the parenchymal-only framework.

10.2 Phase II Predictions

The Phase II framework predicts: (i) Hippocampal BBB permeability on DCE-MRI rises progressively across the fifth through seventh decades and the rate of rise is greater in APOE4 carriers; (ii) Cerebrospinal fluid VCAM-1 rises in parallel with the hippocampal BBB permeability and the rise precedes detectable parenchymal amyloid accumulation by an estimated decade; (iii) Cerebrospinal fluid soluble PDGFRβ rises in parallel with the hippocampal BBB permeability and is the most sensitive biomarker of early Phase II pathology; (iv) Anti-VCAM-1 antibody intervention in late midlife subjects with elevated plasma sVCAM-1 and elevated hippocampal BBB permeability reduces the subsequent rate of cognitive decline and reduces the rate of conversion from MCI to dementia; (v) Cyclophilin A / MMP-9 axis suppression in APOE4 carriers reduces the hippocampal BBB breakdown trajectory and the subsequent rate of cognitive decline. Each prediction is testable, and the anti-VCAM-1 trial in particular is the principal proof-of-concept test of the framework that the present dissertation advances.

10.3 Phase III Predictions

The Phase III framework predicts: (i) ARIA-E incidence with lecanemab and donanemab is quantitatively predictable from baseline CAA burden, APOE genotype, and baseline microbleed count, with the predictive model derivable from existing trial data; (ii) Cerebral microbleed accumulation across the seventh decade and beyond is faster in subjects with elevated plasma sVCAM-1 and elevated CSF VCAM-1 than in subjects with normal vascular biomarkers; (iii) Basement membrane MMP-9 activity, measured by zymography of postmortem cortical tissue, is correlated with parvalbumin perineuronal net loss in the same tissue and both are correlated with antemortem cognitive performance; (iv) White matter hyperintensity volume and cortical perineuronal net loss are independent contributors to cognitive performance in the eighth decade, with both required to fully account for the cognitive presentation. Each prediction is testable, and the integration of vascular and parenchymal substrates in the Phase III phenotypic endpoint is the principal empirical claim of the framework at that phase.

10.4 Cross-Phase Predictions

The cross-phase framework predicts: (i) Glymphatic clearance, measured by intrathecal gadolinium MRI or by emerging dynamic glymphatic imaging methods, declines progressively across all three phases with the rate of decline reflecting the integrated sleep-architecture, arterial-pulsatility, and AQP4-polarization contributions; (ii) Neurovascular coupling response amplitude, measured by task-based BOLD fMRI, declines progressively across all three phases with the regional pattern reflecting the phase-specific dominant target; (iii) APOE4 genotype is the principal genetic driver of the cross-phase vascular trajectory and APOE4 carriers exhibit accelerated trajectories on each of the cross-phase biomarkers; (iv) Plasma soluble VCAM-1 measured serially across midlife and into late life supplies a phase-stratification variable whose accuracy exceeds that of any individual phase-specific biomarker. Each cross-phase prediction is testable, and the integration of cross-phase biomarkers into a single trajectory framework is the principal contribution of the cross-phase chapter to the dissertation.

10.5 Experimental Design Recommendations

The framework supports a series of experimental design recommendations for the next generation of Alzheimer's disease clinical trials. The principal recommendation is that vascular biomarkers be incorporated into the AT(N) framework as a fourth axis: AT(N)V, where V denotes the vascular axis composed of plasma sVCAM-1, CSF sPDGFRβ, hippocampal BBB permeability, and microbleed burden. The integrated AT(N)V framework supplies a four-axis biomarker stratification that the current AT(N) framework cannot, and the phase-specific behavior of the V axis across the lifespan is the principal trajectory that the present dissertation has developed. A secondary recommendation is that midlife intervention trials incorporate APOE4 stratification not only as a covariate but as the primary stratification variable, with the largest effect expected in APOE4 carriers in the leading-edge Phase II window. A tertiary recommendation is that anti-VCAM-1 antibody trials proceed in late-middle-aged subjects with elevated plasma sVCAM-1 and elevated hippocampal BBB permeability, with the primary outcome the rate of cognitive decline and the secondary outcomes the rate of hippocampal BBB normalization on DCE-MRI and the rate of CSF VCAM-1 normalization.

11. Conclusion

The cerebrovasculature exhibits a phase-specific pathology that maps coherently onto the tripartite temporal architecture of the Collapse trilogy. The mapping is not metaphorical or heuristic; it is mechanistically tight, biomarker-supported, and therapeutically actionable. Phase I (decades 3–5) is vascularly conditioned by brainstem capillary hypoperfusion, by early BBB compromise at the vasa nervorum, and by leading-edge VCAM-1 induction at brainstem endothelium under the developing pressure of the aged systemic milieu; the vascular events lower the threshold above which the parenchymal LC bioenergetic ignition engages. Phase II (decades 5–7) is vascularly gated by the Yousef – Wyss-Coray VCAM-1 mechanism at the hippocampal endothelium, by the Montagne-Zlokovic pericyte-PDGFRβ trajectory, and by the APOE4 vascular phenotype; the vascular events constitute the proximate upstream driver of the parenchymal microglial transition. Phase III (decade 7 and beyond) is vascularly amplified by cerebral amyloid angiopathy at the cortical vessel wall, by basement membrane degradation that parallels the perineuronal net degradation, and by the small vessel disease continuum; the vascular events both amplify the parenchymal synaptic disintegration and impose the ARIA constraint on anti-amyloid intervention.

The framework's central claim is that the trilogy's three parenchymal phases are vascularly conditioned in their initiation and vascularly amplified in their progression, that the integrated four-substrate framework (vascular plus three parenchymal) is the appropriate analytical structure for a complete account of late-onset Alzheimer's pathogenesis, and that brain endothelial VCAM-1 is the molecular gateway through which the systemic aging signal is transduced into a parenchymal response at each of the three temporal phases. The framework is not a vascular hypothesis competing with the amyloid cascade hypothesis; it is an integration of the two within a single temporal architecture in which the vascular and parenchymal substrates engage in a phase-specific, mutually reinforcing sequence. The framework supplies a phase-specific biomarker trajectory that the current AT(N) framework cannot, a phase-specific therapeutic surface that the current single-window approach cannot, and a falsifiable prediction set that distinguishes the framework from its competitors.

The implication for the trilogy is that the three-substrate parenchymal account is structurally incomplete and that the four-substrate account in which vascular biology

engages at every phase is the appropriate extension. The implication for the field is that the Phase 0 / Phase I vascular window in midlife is the appropriate temporal target for prevention-stage intervention, that the Phase II VCAM-1 gateway is the appropriate molecular target for late-midlife pharmacology, and that the Phase III ARIA constraint is the appropriate vascular consideration for late-life intervention. The integrated framework is the appropriate analytical structure within which the next generation of Alzheimer's disease research and clinical practice should proceed.

The dissertation closes with the observation that Oskar Fischer's century-old recognition that the inflammatory response is not a bystander to neurodegeneration but a participant in it anticipated, by a hundred and twenty years, the immunometabolic and vascular framework on which the present dissertation depends. The Fischer recognition placed the inflammatory response at the center of the disease; the present framework places the vascular interface — at which inflammatory signaling is transduced from the systemic to the central compartment — at the temporal beginning of the disease and at the gateway through which each subsequent phase engages. The integrated framework is, in this sense, the natural extension of the Fischer recognition into the cellular biology of the twenty-first century.

12. References

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