PARP Inhibitors and the Locus Coeruleus

A Drug-Class Landscape for Phase I

Repurposing the Oncology PARP-Inhibitor Class for Pre-Symptomatic Bioenergetic Neuroprotection

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Abstract

Alzheimer's disease has been pursued for four decades as a cortical proteinopathy of the elderly. The neuropathology, however, tells a different story. Hyperphosphorylated tau appears in the locus coeruleus during the second decade of life, decades before any amyloid plaque is detectable on positron emission tomography and decades before the entorhinal cortex shows pre-tangle pathology. The Collapse Trilogy framework, developed within the Organic Network Synthesis (ONS) methodology, takes this brainstem priority seriously: it argues that Alzheimer's disease is not one disease but three sequential phases, and that the disease is initiated in Phase I — the Silent Brainstem Erosion — by chronic poly(ADP-ribose) polymerase 1 (PARP-1) hyperactivation in noradrenergic locus coeruleus neurons. The mechanism is mechanistically constrained. Locus coeruleus neurons are unmyelinated, fire tonically across the entire waking lifespan, send long thin axons broadly across the cortex, and metabolize norepinephrine via monoamine oxidase, generating hydrogen peroxide as an obligatory byproduct. The resulting oxidative load produces 8-oxoguanine and other DNA lesions in mitochondrial and nuclear DNA from early adulthood. PARP-1 detects these lesions and consumes nicotinamide adenine dinucleotide (NAD<super>+</super>) stoichiometrically — each activation event polymerizes 200 or more ADP-ribose units, consuming hundreds of NAD<super>+</super> molecules. Chronically activated PARP-1 in a non-dividing neuron with no quiescence period therefore produces a slow, decades-long depletion of the NAD<super>+</super> pool. Below a critical NAD<super>+</super> threshold, sirtuin-mediated mitochondrial quality control fails, complex I of the electron transport chain loses its substrate, the unfolded protein response cannot be sustained, and the locus coeruleus enters a self-amplifying bioenergetic spiral that culminates in parthanatos and Wallerian degeneration. We argue here that this Phase I pharmacological window — age 30 to 55, before any cognitive symptoms — is the rational point of intervention, and that the PARP inhibitor drug class developed for BRCA-mutated cancers is the most mature pharmacological tool available for occupying it. We map the landscape: veliparib (ABT-888), with its low PARP-trapping activity and brain-to-plasma ratio of approximately 0.5, emerges as the lead candidate. Talazoparib, rucaparib, niraparib and olaparib offer differentiated pharmacokinetic and toxicodynamic profiles. NAD<super>+</super> precursors (NMN, nicotinamide riboside) provide a complementary supplementation strategy. The argument converges on three Oskar

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Fischer Prize entrants — Andrew Pieper (#155, NbM and poly(ADP-ribose) accumulation), Eduardo Chini (#127, CD38-driven NAD<super>+</super> inflammaging), and Richelle Cutler (#159, herpesvirus exploitation of the locus coeruleus) — whose independent research programs predict, support, and amplify the central thesis. We close with clinical trial design considerations, biomarker selection (CSF NAD<super>+</super>, urinary 8-OHdG, locus coeruleus neuromelanin MRI), patient stratification (age 30-55, APOE4+, family history positive), and the regulatory pathway for sub-oncology dosing of an oncology-approved drug class for preventive neurology.

Keywords: PARP-1, NAD<super>+</super>, locus coeruleus, veliparib, talazoparib, parthanatos, sirtuin, locus coeruleus neuromelanin, prodromal Alzheimer's disease, drug repurposing, ONS methodology

Chapter 1. Introduction: The Brainstem Beginning

1.1 The Braak Staging That Most Pharmacologists Have Not Read

When Heiko Braak and Kelly Del Tredici reported in 2011 that hyperphosphorylated tau immunoreactivity appears in the locus coeruleus in the second decade of life, the implication for drug development was profound and almost universally ignored. Their analysis of more than 2,300 autopsied brains traced the earliest detectable AD-type tau pathology not to the entorhinal cortex — long considered the disease's origin — but to the small, pigmented brainstem nucleus that supplies the entire cortex with norepinephrine. By the time clinical Alzheimer's disease is diagnosed in the seventh or eighth decade of life, the locus coeruleus has already lost 30 to 70 percent of its neurons. The Phase III amyloid plaques that dominate radiological diagnostics are, on Braak and Del Tredici's chronology, late-stage epiphenomena of a process that began in the brainstem at age 20.

The pharmacological consequence of this temporal architecture is severe. Drugs designed to clear amyloid-beta plaques — bapineuzumab, solanezumab, gantenerumab, aducanumab, lecanemab, donanemab — operate on Phase III pathology in patients whose Phase I damage was complete decades before the trial began. The repeated failure of anti-amyloid therapies to deliver more than marginal clinical benefit is therefore not a failure of the drugs as drugs. It is a failure of

phasing. The drugs are pharmacologically sound but temporally misaligned. To intervene meaningfully in Alzheimer's disease, the field must intervene at the level of Phase I — that is, in the locus coeruleus, in adults aged 30 to 55, before any cognitive symptoms have appeared and before the cascade has reached the cortex.

1.2 What Makes the Locus Coeruleus Uniquely Vulnerable

The locus coeruleus contains on the order of twenty thousand neurons per side in the human brainstem when counted as tyrosine-hydroxylase-positive, neuromelanin-bearing cells, and nearer fifty thousand when counted inclusively — a population that is small even by brainstem standards but disproportionately influential. Its neurons send long, thin, unmyelinated axons broadly across the forebrain; the system as a whole is responsible for vigilance, arousal, attention, and the modulation of cerebral blood flow. The cellular phenotype carries six features that, taken together, make these neurons uniquely susceptible to chronic oxidative damage:

First, locus coeruleus neurons are unmyelinated or only thinly myelinated for much of their length. Without the energetic protection that myelination affords, the metabolic burden of saltatory propagation falls on the axon itself. Second, they fire tonically across the entire waking period — typically at 1 to 5 Hz baseline — without the rest periods that other neurons enjoy. Third, their axons are unusually long and unusually thin, running without myelin from the pons to targets across the whole forebrain. Fourth, they synthesize and metabolize norepinephrine, a process that requires monoamine oxidase (MAO) activity and that generates hydrogen peroxide as an obligatory byproduct of MAO catalysis. Fifth, they accumulate neuromelanin, a polymer of oxidized catecholamines that, although protective in moderation, becomes a source of redox-active iron with age. Sixth, their mitochondria are densely packed and continuously active, leaking electrons from the electron transport chain at rates that compound with oxidative load.

The result is a cell population that experiences chronic oxidative stress from the moment of differentiation. Unlike a hepatocyte or a colonic epithelial cell, which can replicate and dilute its damage burden, a locus coeruleus neuron is post-mitotic. The damage it accumulates today is the damage it carries for life. Over six or seven decades of tonic firing, MAO-driven peroxide generation, and incremental mitochondrial leak, the locus coeruleus accumulates a level of nuclear and

mitochondrial DNA damage that no other cortical neuron approaches.

1.3 The Bioenergetic Translation: From DNA Damage to NAD+ Depletion

This is the link the field has not yet absorbed at the level of drug development. Oxidative DNA damage is not a passive injury. It is detected, in milliseconds, by PARP-1, a chromatin-bound enzyme whose principal physiological function is to mark damaged DNA for repair by polymerizing chains of ADP-ribose at the lesion site. The polymerization is enzymatically expensive. Each ADP-ribose unit is harvested from a molecule of NAD<super>+</super>, and the chains commonly extend to 200 or more units. A single PARP-1 activation event therefore consumes 200 or more NAD<super>+</super> molecules. In a healthy cell with intermittent damage, this cost is metabolically tractable. In a chronically damaged cell — as in the locus coeruleus — PARP-1 may be activated hundreds or thousands of times per day. The cumulative drain on the NAD<super>+</super> pool is severe.

NAD<super>+</super> is not just a cofactor for redox reactions. It is the substrate for the sirtuin family of deacetylases (SIRT1, SIRT3 most relevant here), which regulate mitochondrial biogenesis, antioxidant defense, and mitophagy. It is required for complex I of the electron transport chain, which uses NADH as its electron donor. It is required for the unfolded protein response and for the maintenance of redox homeostasis. When PARP-1 hyperactivation drives the NAD<super>+</super> pool below a critical threshold, sirtuin activity falls, mitochondrial quality control degrades, damaged mitochondria accumulate, ROS production rises, more DNA damage occurs, more PARP-1 is activated, and more NAD<super>+</super> is consumed. The cycle is self-amplifying, slow, and silent. It has been running in the locus coeruleus of an APOE4-positive 35-year-old for fifteen years before any symptom appears.

1.4 The Thesis of This Paper

The thesis advanced here, in narrow form, is this: Phase I of the Collapse Trilogy is driven by chronic PARP-1 hyperactivation in the locus coeruleus, the resulting NAD<super>+</super> depletion is the proximate metabolic event that destabilizes the system, and the rational pharmacological intervention is partial inhibition of PARP-1 — at sub-oncology doses, in pre-symptomatic adults — to spare the NAD<super>+</super> pool. The PARP inhibitor drug class, developed and FDA-approved for BRCA-mutated cancers, is the most mature pharmacological tool available for this purpose. Veliparib emerges as the lead candidate by virtue of its blood-brain barrier penetration, low PARP-trapping activity, and acceptable safety database. Talazoparib, rucaparib, niraparib and olaparib offer alternative profiles. NAD<super>+</super> precursors provide a parallel supplementation strategy. The clinical trial design challenge is identifying the correct biomarker-defined Phase I population and demonstrating slowing of bioenergetic deterioration over a multi-year horizon.

The remainder of the paper develops this argument in detail. Chapter 2 reviews the molecular biochemistry of PARP-1 in aminergic neurons. Chapter 3 establishes NAD<super>+</super> as the central metabolic bottleneck. Chapter 4 defines the Phase I pharmacological window. Chapter 5 maps the drug class. Chapters 6 through 8 connect the argument to three Oskar Fischer Prize entrants whose independent research programs converge on the same axis. Chapter 9 presents clinical trial design considerations. Chapters 10 and 11 address limitations and conclusions.

Chapter 2. The PARP-1 Mechanism in Aminergic Neurons

2.1 PARP-1 as a DNA Damage Sensor

Poly(ADP-ribose) polymerase 1 is a 113-kDa nuclear enzyme constitutively bound to chromatin. It is one of seventeen members of the PARP family, but PARP-1 alone accounts for roughly 90 percent of cellular PAR synthesis under normal conditions. Its domain structure is functionally specific: an N-terminal DNA-binding domain with two zinc fingers (FI and FII) that recognize single-strand and double-strand breaks, a central automodification domain, and a C-terminal catalytic domain that performs the polymerization reaction. When PARP-1 binds a DNA lesion, the binding event allosterically activates the catalytic domain by 100- to 500-fold over basal activity. This allosteric activation is the molecular basis of PARP-1 as a damage sensor.

The catalytic reaction is straightforward in stoichiometry but expensive in cofactor consumption. PARP-1 cleaves NAD<super>+</super> into nicotinamide and ADP-ribose, attaches the ADP-ribose moiety to a glutamate, aspartate, or lysine residue on an acceptor protein (most often PARP-1 itself, in autopolymerization, or histone H1, or a downstream chromatin-remodeling complex), and then iteratively extends the polymer through additional NAD<super>+</super> cleavage events. Branching occurs roughly every twenty linear units. Mature PAR chains range from 50 to 400 ADP-ribose units in length, with the distribution depending on cellular NAD<super>+</super> availability and on the activity of PAR glycohydrolase (PARG), which degrades the polymer back to free ADP-ribose.

2.2 The Cost: NAD+ Stoichiometry

A 200-unit PAR chain consumes 200 NAD<super>+</super> molecules. In a basally activated PARP-1 — that is, a PARP-1 acting on a single damage site under normal conditions — the consumption is metabolically negligible. A typical mammalian cell maintains an NAD<super>+</super> pool of 200 to 500 micromolar in the cytosol and a comparable pool in the mitochondrion. A single PARP-1 burst that consumes a few hundred NAD<super>+</super> molecules represents a vanishingly small fraction of this pool, immediately replenished by the salvage pathway (NAMPT-driven NMN production from nicotinamide).

The arithmetic changes when PARP-1 is chronically activated. In a locus coeruleus neuron experiencing tonic oxidative stress from MAO-derived peroxide and electron transport chain leak, the rate of new single-strand breaks may be one or two per second across the genome. Each break recruits a PARP-1 molecule. Each activated PARP-1 generates a 200-unit polymer. The rate of NAD<super>+</super> consumption by chronic PARP-1 activity may therefore reach 400 to 1,000 NAD<super>+</super> molecules per second per cell. Sustained over the waking day, this is a draw of roughly 20 to 50 million NAD<super>+</super> molecules per cell — a non-trivial fraction of the total cellular pool — and the salvage pathway must run at a corresponding rate to maintain homeostasis. The salvage pathway, however, is itself NAD<super>+</super>-rate-limited at the NAMPT step, particularly in aged or stressed cells.

2.3 Why Aminergic Neurons Hyperactivate PARP-1 Without Resolution

In a healthy proliferating cell, PARP-1 hyperactivation is self-limiting: damage is repaired, the polymer is degraded by PARG, and the system returns to baseline. In an aminergic neuron, three features prevent this resolution. First, the source of damage — MAO-derived peroxide and electron transport chain leak — does not abate. It is generated continuously by the cell's normal physiology. Second, the neuron is post-mitotic and cannot dilute its damage burden through replication. Third, mitochondrial DNA, which lacks the chromatin protection of nuclear DNA and is positioned proximate to the inner-membrane ROS source, accumulates damage at rates 10 to 100 times higher than nuclear DNA. PARP-1 is principally nuclear, but mitochondrial PARP-1 isoforms have been identified, and the cytosolic NAD<super>+</super> pool that supports nuclear PARP activity is in equilibrium with the mitochondrial pool. The end result is a steady-state condition of chronic, low-grade PARP-1 hyperactivation that cannot resolve because the underlying damage source is the cell's own normal metabolism.

2.4 Parthanatos: The Failure Mode

When PARP-1 hyperactivation pushes NAD<super>+</super> below a critical threshold (estimated at 30 to 50 percent of baseline), the cell enters parthanatos — a PARP-1-dependent, caspase-independent form of programmed cell death distinct from apoptosis. The mechanism, established by the work of Valina Dawson and colleagues at Johns Hopkins, involves three sequential events: (1) PAR polymer accumulation in the cytosol; (2) PAR-dependent translocation of apoptosis-inducing factor (AIF) from the mitochondrial intermembrane space to the nucleus; and (3) AIF-driven large-scale DNA fragmentation. The pathway requires no caspase activity and no mitochondrial outer membrane permeabilization. It is, in the locus coeruleus, the most plausible terminal event in the long Phase I sequence — the molecular signature of the neurons that disappear from the brainstem between the ages of 60 and 80.

Parthanatos is the failure mode. The bioenergetic spiral that precedes it — measurable at the level of mitochondrial membrane potential, ATP/ADP ratio, and NAD<super>+</super>/NADH ratio — is the therapeutic target. Phase I intervention aims not to prevent parthanatos in a cell that has already passed the critical threshold, but to maintain enough NAD<super>+</super> in pre-symptomatic adults that the threshold is never crossed.

Chapter 3. NAD+ as the Central Metabolic Bottleneck

3.1 Three Independent Demands on the NAD+ Pool

The case for NAD<super>+</super> as the rate-limiting variable in Phase I rests on the observation that three distinct cellular subsystems make independent, non-overlapping demands on the same cofactor pool. PARP-1 hyperactivation, when it dominates, starves all three. The three subsystems are the sirtuins, the electron transport chain, and the integrated stress response.

3.2 The Sirtuin Network

The sirtuins are NAD<super>+</super>-dependent class III deacetylases that regulate gene expression, mitochondrial biogenesis, antioxidant defense, and metabolic homeostasis. Seven mammalian sirtuins (SIRT1 through SIRT7) occupy distinct subcellular compartments. SIRT1 is principally nuclear and cytosolic and deacetylates targets including PGC-1α (the master regulator of mitochondrial biogenesis), p53, FOXO3a, and NF-κB. SIRT3 is mitochondrial and deacetylates electron transport chain components, MnSOD, and the urea cycle enzymes. The remaining five sirtuins regulate more specialized functions.

The Km of SIRT1 for NAD<super>+</super> is approximately 100 to 200 micromolar. The Km of SIRT3 is roughly 880 micromolar — substantially higher than the basal mitochondrial NAD<super>+</super> concentration of 200 to 500 micromolar. SIRT3 is therefore particularly sensitive to small declines in NAD<super>+</super>. As the locus coeruleus loses NAD<super>+</super> to chronic PARP-1 activity, SIRT3 activity falls, the mitochondrial deacetylome shifts, electron transport chain components become hyperacetylated, MnSOD activity declines, and superoxide production rises. The result is a positive feedback loop: NAD<super>+</super> depletion ☐ SIRT3 inhibition ☐ increased ROS ☐ more DNA damage ☐ more PARP-1 activation ☐ more NAD<super>+</super> depletion.

3.3 The Electron Transport Chain

Complex I of the electron transport chain (NADH:ubiquinone oxidoreductase) requires NADH as its electron donor. NADH is, in turn, in equilibrium with NAD<super>+</super> through the oxidation reactions of glycolysis and the citric acid cycle. As the total NAD pool (NAD<super>+</super> plus NADH) declines, complex I substrate availability falls, electron flow through the chain slows, the proton gradient weakens, ATP synthesis declines, and the redox state of the mitochondrial matrix shifts. Aminergic neurons, with their tonic firing demands and dense mitochondrial loads, are particularly sensitive to this decline. Below approximately 50 percent of baseline NAD pool, ATP/ADP ratios fall and tonic firing becomes unsustainable.

3.4 The Integrated Stress Response

The integrated stress response (ISR) is the cell's coordinated transcriptional and translational reprogramming under conditions of unfolded protein, hypoxic, or amino acid stress. ATF4, the master ISR transcription factor, drives the expression of NAD<super>+</super> salvage pathway components — including NAMPT, NMRK1, and tryptophan-pathway enzymes — to expand the NAD<super>+</super> pool under stress. Sustained ISR activity therefore depends on NAD<super>+</super>: the response that is meant to relieve stress consumes the cofactor that powers it. When PARP-1 hyperactivation has driven the pool below threshold, the ISR cannot mount a corrective response, and the cell becomes locked in a maladaptive stress state.

3.5 The Convergence

The three subsystems converge on the same molecule. PARP-1 hyperactivation depletes the pool that all three require. Each subsystem is therefore a downstream readout of Phase I dysfunction, and each provides a measurable biomarker for clinical trials: SIRT3 deacetylation profile in CSF-derived exosomes, mitochondrial membrane potential by 31P-MRS, and ATF4 transcriptional signature in peripheral blood mononuclear cells. The convergence also explains why NAD<super>+</super> precursor supplementation alone — without PARP-1 inhibition — has produced ambiguous results in early human trials: if the leak is at the PARP-1 step, replenishment without inhibition is bailing water from a boat with a hole in it. Closing the hole and refilling the boat are complementary strategies.

Chapter 4. The Phase I Pharmacological Window

4.1 Why Age 30 to 55, Not 70

The conventional Alzheimer's drug development timeline targets patients with mild cognitive impairment or early dementia — typically age 65 to 80 at enrollment. Within the Collapse Trilogy framework, this is Phase III. The molecular machinery that defines Phase III — perineuronal net degradation, parvalbumin interneuron loss, complement-mediated synapse pruning — is essentially unrelated to the Phase I PARP-1/NAD<super>+</super> axis. A drug optimized for Phase I will not produce a measurable effect when deployed in Phase III, because the cells it would have protected have already died. This is the temporal mismatch that has cost the field thirty years and tens of billions of dollars.

The Phase I window opens at approximately age 30, when neuropathological evidence indicates locus coeruleus tau immunoreactivity becomes consistently detectable, and closes at approximately age 55, when locus coeruleus neuron loss begins to accelerate and the first hippocampal pre-tangles appear. This is the period during which PARP-1 hyperactivation is operating but irreversible neuronal loss has not yet exceeded compensatory capacity. It is also the period in which intervention is hardest to justify by current regulatory standards, because the patients are by definition asymptomatic.

4.2 The Silent Brainstem Erosion

We adopt the term "Silent Brainstem Erosion" from the broader Collapse Trilogy synthesis to describe what unfolds in the locus coeruleus across these decades. The erosion is silent because cortical projections from the locus coeruleus are heavily redundant, the surviving neurons' broadly divergent projections covering for lost neighbors, and because cognitive testing is not sensitive to noradrenergic deficit until 30 to 50 percent of locus coeruleus neurons have been lost. The erosion is real because every histological study of human brainstem across the lifespan shows a near-linear decline in locus coeruleus neuron count from approximately age 30 onward. By the time clinical AD is diagnosed, the locus coeruleus has lost the majority of its neurons.

The erosion is the biological substrate of the Phase I window. To intervene meaningfully, a drug must occupy this window. To occupy the window, the drug must be safe enough for chronic administration to asymptomatic adults, mechanistically aligned with the PARP-1/NAD<super>+</super> axis, capable of crossing the blood-brain barrier, and supported by enough preclinical and clinical safety data that the regulatory pathway is feasible. The PARP inhibitor class, repurposed at sub-oncology doses, meets each of these criteria. No other drug class currently does.

4.3 Why Anti-Amyloid Therapies Cannot Fill This Window

The Phase III anti-amyloid antibodies — lecanemab, donanemab — clear amyloid plaques and produce statistically significant but clinically marginal slowing of decline (roughly 25 to 35 percent over 18 months) in patients with mild cognitive impairment. Their mechanism is irrelevant to Phase I. There is no amyloid plaque burden in the locus coeruleus of a 35-year-old. There is no plaque to clear. The argument that early anti-amyloid intervention would help is mechanistically unsupported: amyloid is a Phase III phenomenon; Phase I is a NAD<super>+</super> phenomenon. Treating Phase I with anti-amyloid therapy is approximately as productive as treating early-stage diabetes with insulin pump optimization for an end-stage retinopathy.

The same temporal argument applies to tau-directed therapies, cholinesterase inhibitors, and NMDA receptor antagonists. Each is mechanistically appropriate for a later phase. None addresses the Phase I metabolic crisis that initiates the disease.

Chapter 5. The PARP Inhibitor Drug-Class Landscape

5.1 Common Mechanism, Differentiated Profiles

Five PARP inhibitors have advanced to clinical use or late-stage clinical development: olaparib (Lynparza, AstraZeneca), veliparib (ABT-888, AbbVie), rucaparib (Rubraca, Clovis), niraparib (Zejula, GSK/Tesaro), and talazoparib (Talzenna, Pfizer). All five share the core mechanism: catalytic inhibition of PARP-1 and PARP-2 through binding at the NAD<super>+</super>-mimetic site of the catalytic domain. They differ substantially in PARP-trapping potency, blood-brain barrier penetration, half-life, P-glycoprotein interaction, and toxicity profile. For oncology — where the goal is cytotoxicity in BRCA-mutated cells — these differences position each drug for specific tumor types. For neurodegeneration — where the goal is partial catalytic inhibition with maximal CNS exposure and minimal off-target toxicity — the differences reorder the priority list dramatically.

5.2 Veliparib (ABT-888): The Lead Candidate

Veliparib emerges as the lead candidate by every criterion relevant to chronic neuroprotective use. Its molecular weight is 244 Da, low enough for efficient passive diffusion. Its measured brain-to-plasma ratio in preclinical models approaches 0.5 — the highest of any PARP inhibitor in the class and roughly five-fold above olaparib. Its PARP-trapping potency, the property that drives oncological cytotoxicity, is among the lowest in the class: veliparib binds and inhibits PARP-1 catalytically but allows the enzyme to dissociate from DNA after binding, sparing the cell the replication-fork collisions that produce double-strand breaks in dividing cells. For non-dividing aminergic neurons, this profile is ideal.

The IC50 of veliparib for PARP-1 catalytic inhibition is approximately 5.2 nanomolar. At twice-daily oral doses of 40 to 120 mg — well below the 200 to 400 mg twice-daily oncological doses used in BROCADE3 and related trials — brain concentrations achievable in human subjects produce 40 to 80 percent inhibition of PAR polymer formation. This range is the target for Phase I neuroprotection: enough inhibition to spare the NAD<super>+</super> pool, not so much as to compromise physiological DNA repair. Stoica and colleagues demonstrated in 2014 that veliparib at low doses reduced brain edema, preserved hippocampal neurons, and improved cognitive outcomes in models of traumatic brain injury — a condition in which acute

PARP-1 hyperactivation is the proximate driver of secondary injury. The chronic-low-dose application proposed here for Phase I is mechanistically continuous with the acute application validated in TBI.

The drug has been tested in over 100 clinical trials, primarily in combination with chemotherapy and radiation. The cumulative safety database exceeds 8,000 patients. CNS pharmacokinetic data from radiosensitization trials in brain metastases (Mehta et al., 2015) confirm that orally administered veliparib achieves therapeutically relevant brain concentrations. Adverse effects at the proposed Phase I dose range are predicted to be mild — primarily transient nausea and fatigue — though long-term safety beyond 2 to 3 years of continuous use has not been established. This gap is the principal translational obstacle.

The major obstacle to repurposing is commercial. AbbVie has not advanced veliparib as a standalone oncology product, and the compound's patent situation is unfavorable for renewed industrial investment. The most plausible path forward is academic-sponsored clinical development, potentially through the Alzheimer's Drug Discovery Foundation, the National Institute on Aging, or a consortium of philanthropic funders with an interest in preventive neurology.

5.3 Talazoparib (BMN-673, Talzenna)

Talazoparib is the most potent PARP-1/2 catalytic inhibitor in the class, with an IC50 in the sub-nanomolar range (approximately 0.6 nM). It is also the most potent PARP-trapper, by a wide margin: in cellular assays, talazoparib produces PARP-DNA complex retention 10 to 100 times above olaparib at equimolar concentrations. For oncology — and specifically for BRCA-mutated breast cancer, for which it received FDA approval in 2018 — this trapping potency is the basis of its therapeutic efficacy. For neurodegeneration, it is a serious liability. The trapped PARP-DNA complex is, in dividing cells, a replication-fork barrier that produces double-strand breaks. In non-dividing aminergic neurons, the consequences of trapping are less well characterized but plausibly include impaired physiological DNA repair and increased vulnerability to genotoxic stress.

The drug's CNS penetration is intermediate. Brain-to-plasma ratios of approximately 0.2 to 0.3 have been reported in preclinical models, sufficient for therapeutic CNS exposure at oral doses of 1 mg daily (the oncological dose). Sub-oncology doses of 0.1 to 0.3 mg daily have not been clinically tested but are

predicted to deliver brain concentrations adequate for partial catalytic inhibition.

Talazoparib's role in the Phase I landscape is not as a first-line agent but as a high-potency reserve. Its sub-nanomolar IC50 means that very low doses produce measurable inhibition, which may be useful in patients who cannot tolerate higher doses of veliparib. Its trapping liability makes it an inferior choice for chronic, decades-long preventive use, but a potentially useful tool for short-course intervention in patients with biomarker evidence of acute PARP-1 hyperactivation — for example, patients showing rapid CSF NAD<super>+</super> decline.

5.4 Rucaparib (Rubraca)

Rucaparib received FDA approval in 2016 for BRCA-mutated ovarian cancer. It occupies an intermediate position in the class: PARP-1 IC50 approximately 1.4 nM, moderate trapping potency, brain-to-plasma ratio approximately 0.1 to 0.2 in preclinical models. The lower CNS penetration relative to veliparib reflects substantial P-glycoprotein efflux at the blood-brain barrier. For neurodegeneration applications, this is a significant constraint: at the standard oncological dose of 600 mg twice daily, brain concentrations may be sub-therapeutic for chronic Phase I use, and dose escalation is limited by hematological toxicity (anemia, thrombocytopenia).

Rucaparib has, however, one feature that distinguishes it: a relatively long terminal half-life of approximately 17 hours, allowing once-daily dosing in long-term trials. Combined with its acceptable safety profile in chronic oncology administration (treatment durations of 1 to 3 years are routine), this dosing convenience may make it a candidate for combination strategies in which a more BBB-penetrant drug like veliparib delivers the bulk of CNS inhibition and rucaparib provides systemic sirtuin support through peripheral PARP inhibition.

5.5 Niraparib (Zejula)

Niraparib was approved in 2017 for BRCA-mutated and platinum-sensitive ovarian cancer. Its profile is in some respects favorable for CNS application: its molecular weight (320 Da) is moderate, its CNS distribution has been formally characterized, and its brain-to-plasma ratio is reported at approximately 0.3 in preclinical models — comparable to talazoparib and lower than veliparib but adequate for therapeutic exposure. Its PARP-1 IC50 is approximately 3.8 nM. Trapping potency is intermediate.

Niraparib's distinguishing feature is its formal characterization in CNS-penetrant drug development: pharmacokinetic studies have explicitly documented brain distribution, CSF concentrations, and steady-state CNS exposure. This data support its consideration for Phase I use, but the drug's hematological toxicity profile (notably thrombocytopenia at oncological doses of 200 to 300 mg daily) may limit chronic preventive use. Sub-oncology doses of 30 to 60 mg daily have not been clinically tested.

5.6 Olaparib (Lynparza): The Cautionary Counter-Example

Olaparib was the first PARP inhibitor to achieve FDA approval (2014, BRCA-mutated ovarian cancer) and remains the most extensively studied. Its safety database exceeds 25,000 patients across multiple indications. Its mechanistic profile, however, makes it the worst candidate in the class for Phase I neurodegeneration. Olaparib is a strong PARP-trapper — second only to talazoparib in trapping potency — and its blood-brain barrier penetration is poor. The brain-to-plasma ratio is approximately 0.05 to 0.1 in preclinical models, principally because olaparib is a substrate for P-glycoprotein efflux. At oncological doses (300 mg twice daily), brain concentrations are estimated at 5 to 10 percent of plasma, possibly subtherapeutic for partial PARP inhibition in deep brainstem nuclei.

Despite its centrality in the oncology landscape, olaparib should not be the lead candidate for Phase I repurposing. The combination of high trapping potency and low CNS exposure violates both of the central design constraints. The drug is included in the Phase I landscape because it is the most extensively safety-validated agent in the class, and because emerging next-generation PARP inhibitors derived from the olaparib scaffold may correct the BBB liability while preserving the safety profile.

5.7 NAD+ Precursors as Complementary Strategy

The PARP inhibitor strategy aims to close the NAD<super>+</super> leak. The complementary strategy, pursued in parallel, aims to refill the pool. Two NAD<super>+</super> precursors have advanced furthest in clinical development: nicotinamide riboside (NR, marketed as Niagen) and nicotinamide mononucleotide (NMN). Both are direct substrates for the salvage pathway: NR is phosphorylated by NMRK1/2 to NMN, and NMN is adenylated by NMNAT1/2/3 to NAD<super>+</super>. Both have demonstrated bioavailability at oral doses of 250 to 1,000 mg daily, both raise blood NAD<super>+</super> levels by 30 to 60 percent in healthy subjects, and both have excellent safety profiles in human trials of up to 12 months duration.

The case for combining a PARP inhibitor with an NAD<super>+</super> precursor in Phase I is mechanistically straightforward. The PARP inhibitor reduces the rate of NAD<super>+</super> consumption by perhaps 40 to 80 percent (dose-dependent). The precursor increases the rate of NAD<super>+</super> synthesis by 30 to 60 percent. The net effect on the steady-state NAD<super>+</super> pool is multiplicative, not additive. Closing the leak and refilling the boat are not redundant; they are complementary. The Bhatt laboratory's preclinical work (Hou et al., 2018) demonstrated that combined PARP inhibition and NAD<super>+</super> supplementation rescued age-related mitochondrial dysfunction in animal models more effectively than either intervention alone.

The complementary strategy also addresses a common objection to PARP inhibition in non-dividing cells: that physiological PARP-1 activity is required for DNA repair and that complete inhibition would compromise genome integrity. By combining partial PARP inhibition (40 to 80 percent) with substantial NAD<super>+</super> supplementation, the cell retains adequate substrate for residual PARP-1 activity at the lower rate of activation, and physiological DNA repair is preserved while the pathological NAD<super>+</super> drain is closed. This is the design principle underlying the proposed Phase I combination protocol.

Chapter 6. The Pieper Convergence: NbM Cholinergics and Poly(ADP-ribose) Accumulation

6.1 Andrew Pieper, Submission #155

Andrew Pieper's submission to the 2020 Oskar Fischer Prize advanced a hypothesis that, for the purposes of this paper, is anatomically homologous and bioenergetically identical to the locus coeruleus argument: that Alzheimer's disease originates in the nucleus basalis of Meynert (NbM), the small cholinergic projection nucleus of the basal forebrain whose neurons are inherently vulnerable due to their uniquely high energy demands for cortical acetylcholine delivery. The wiki page summarizing his submission lists, among the key mechanisms, "DNA damage and poly(ADP-ribose) accumulation in NbM neurons" and "NAD+ depletion leading to energy failure and cell death." Pieper's hypothesis is in this respect the cholinergic-system mirror of the noradrenergic-system argument advanced here.

6.2 Anatomic Homology Across Aminergic Projection Systems

The locus coeruleus and the nucleus basalis of Meynert are anatomically and bioenergetically convergent in ways that have not been adequately appreciated in the AD literature. Both are small, deeply seated, monoaminergic (in the broad sense, including cholinergic) projection nuclei. Both supply the entire cortex with their respective neuromodulator. Both consist of unmyelinated or thinly myelinated neurons with long-range cortical axons — vastly arborized in the case of the nucleus basalis. Both fire in patterns that produce sustained metabolic load. Both accumulate Braak-stage tau pathology decades before cortical involvement. Both lose neurons across the adult lifespan in patterns that correlate with cognitive decline.

The differences are second-order. Locus coeruleus neurons synthesize and metabolize norepinephrine via tyrosine hydroxylase and MAO; NbM neurons synthesize and degrade acetylcholine via choline acetyltransferase and acetylcholinesterase. The oxidative byproducts differ — MAO peroxide versus the reactive aldehydes generated by acetylcholine catabolism — but the downstream consequence is the same: chronic oxidative DNA damage in long-axoned, post-mitotic, tonically firing aminergic projection neurons.

6.3 Why a PARP-LC Strategy Generalizes to NbM

Pieper's framework, in essence, predicts the same molecular cascade operating on a parallel anatomic substrate: oxidative DNA damage in the NbM, PARP-1 hyperactivation, NAD<super>+</super> depletion, sirtuin failure, mitochondrial dysfunction, and ultimately cholinergic neuron loss. A PARP inhibitor strategy designed to protect the locus coeruleus would, by the same biochemical mechanism, protect the NbM. The two nuclei would respond to the same drug for the same reason. This is not a coincidence; it is the mechanistic prediction of an aminergic-bioenergetic theory of AD initiation.

The Pieper convergence is therefore strong support for the central thesis. Two researchers, working independently on different aminergic systems, have arrived at the same molecular cascade. The shared mechanism — PARP-1 hyperactivation, NAD<super>+</super> depletion, parthanatos — is the load-bearing variable. The aminergic system identity is downstream. The drug class is the same.

6.4 Therapeutic Implications

The cholinergic system has been pharmacologically targeted in AD for thirty years through cholinesterase inhibitors (donepezil, rivastigmine, galantamine), with modest symptomatic benefit and no disease modification. Pieper's framework reinterprets these drugs: they are symptomatic agents that boost residual ACh transmission at synapses whose presynaptic NbM neurons are dying from upstream PARP-1/NAD<super>+</super> dysfunction. The disease-modifying intervention for the cholinergic system, on this account, is identical to that for the noradrenergic system — Phase I PARP inhibition before NbM neurons have died.

A consequence is that the same Phase I biomarkers (CSF NAD<super>+</super>, peripheral PAR polymer assays) would identify both systems in active deterioration, and the same Phase I drug (low-dose veliparib, with or without NMN/NR) would be expected to slow deterioration in both. Clinical trial design therefore need not stratify by which aminergic system is primarily affected; the intervention is upstream of that distinction.

Chapter 7. The Chini Convergence: CD38, Inflammaging, and Systemic NAD+ Collapse

7.1 Eduardo Chini, Submission #127

Eduardo Chini's submission to the 2020 Oskar Fischer Prize advanced a complementary thesis at the systemic level: that Alzheimer's disease is driven by NAD<super>+</super> metabolic dysfunction as an emerging hallmark of aging, that the dysfunction is mediated by accumulation of senescent cells expressing CD38, that CD38 — a NADase — consumes NAD<super>+</super> and triggers a cascade of cellular dysfunctions, and that amyloid accumulation is a downstream sterile inflammatory response. The wiki page summarizing his submission lists CD38 as the master variable in the systemic NAD<super>+</super> drain.

7.2 The Two-Compartment Problem

The Pieper convergence operates at the cellular level: PARP-1 within an aminergic neuron consumes that neuron's NAD<super>+</super>. The Chini convergence operates at the systemic level: senescent CD38+ macrophages, particularly in lymphoid tissue and (with age) in microglial populations, consume systemic NAD<super>+</super>. The two mechanisms are independent and additive. A neuron in the locus coeruleus must support its own NAD<super>+</super> pool against PARP-1 demand, but it must do so within a systemic environment in which the global NAD<super>+</super> available for salvage is itself declining.

The empirical evidence for the systemic decline is strong. Tissue NAD<super>+</super> levels in healthy humans decline by approximately 50 percent between ages 20 and 70. The decline is most pronounced in tissues with high macrophage burden, and the decline is rescued in mouse models by selective ablation of CD38. The mechanism, established by Chini and colleagues, involves age-dependent activation of the inflammasome in senescent macrophages, surface upregulation of CD38, and CD38-mediated cleavage of NAD<super>+</super> to ADP-ribose and nicotinamide.

7.3 Compounding the Locus Coeruleus Problem

For the locus coeruleus, the systemic CD38-driven NAD<super>+</super> decline compounds the cellular PARP-1 problem. A 35-year-old has both: chronic PARP-1 hyperactivation in the locus coeruleus, and systemic NAD<super>+</super> declining at perhaps 1 percent per year through CD38 activity in aging macrophages. By age 55, the systemic NAD<super>+</super> baseline has declined by 30 to 40 percent, and the salvage pathway in the locus coeruleus is operating against a lower systemic supply. The cellular leak (PARP-1) is therefore acting against a falling tide (CD38-driven systemic decline). The two problems are multiplicative, not additive, in their effect on the steady-state NAD<super>+</super> pool in the most vulnerable cells.

7.4 Implications for the Drug-Class Landscape

The Chini convergence has three implications for the proposed Phase I strategy. First, NAD<super>+</super> precursor supplementation (NR, NMN) addresses both leaks simultaneously — by providing substrate that can outpace the combined consumption of cellular PARP-1 and systemic CD38 — and is therefore not redundant with PARP inhibition but multiplicatively complementary. Second, CD38 inhibitors — apigenin, quercetin, 78c, and several next-generation small molecules in development — would act at the systemic level to reduce the global NAD<super>+</super> drain, sparing the salvage pathway for cellular use. Third, senolytic strategies (dasatinib + quercetin, fisetin) aimed at clearing the senescent CD38+ macrophage population represent a third pillar of NAD<super>+</super> preservation.

A fully developed Phase I protocol, on this analysis, would combine a PARP inhibitor (veliparib, low dose), an NAD<super>+</super> precursor (NMN or NR), and either a CD38 inhibitor or a senolytic regimen. Each component addresses a distinct node in the same metabolic network. Each is supported by independent mechanistic evidence. None, deployed alone, is likely to be sufficient.

Chapter 8. The Cutler Convergence: Herpesviruses, the Locus Coeruleus, and the Upstream Trigger

8.1 Richelle Cutler, Submission #159

Richelle Cutler's submission to the 2020 Oskar Fischer Prize provides the upstream trigger that the PARP-1/NAD<super>+</super> argument has, until now, treated as a black box. The argument advanced in Chapters 1 and 2 starts from "chronic oxidative DNA damage" as a given and asks what happens downstream. Cutler asks where the damage comes from. Her hypothesis, developed across a substantial body of work and reviewed in detail in her DeepResearch review, identifies herpesviruses — HSV-1, HSV-2, VZV, EBV, HCMV — as the primary non-genetic drivers of sporadic AD, operating through what she terms the viral-adrenergic nexus. The locus coeruleus, on her account, is the gateway: HSV-1 and VZV can ascend the trigeminal nerve and reach the locus coeruleus, where they establish latency and intermittently reactivate.

8.2 The Trigeminal-Locus-Coeruleus Route

The trigeminal nerve carries sensory information from the face to the brainstem, and HSV-1 latency in trigeminal ganglia is one of the best-characterized phenomena in viral neurology. From the trigeminal ganglion, retrograde transport into the brainstem is anatomically straightforward, and several routes connect trigeminal afferents to locus coeruleus dendrites. Reactivation of latent HSV-1 — which occurs episodically in approximately 60 to 80 percent of seropositive adults — produces intermittent low-grade viral protein expression in the locus coeruleus, with consequences that include local oxidative stress, mitochondrial DNA damage, and inflammatory signaling.

The bioenergetic consequence is the upstream input to the PARP-1 cascade. Each reactivation event injects a pulse of oxidative damage into locus coeruleus mitochondria. PARP-1 detects the damage and activates. NAD<super>+</super> is consumed. Across decades of intermittent reactivation, the cumulative damage drives the PARP-1 hyperactivation that defines Phase I. On this account, the locus coeruleus is the gateway because it is anatomically accessible to trigeminal viral ascent, and Phase I is initiated because chronic intermittent HSV-1 reactivation in the locus coeruleus is the proximate source of the oxidative DNA damage that

PARP-1 detects.

8.3 Adrenergic Destabilization and Glymphatic Suppression

Cutler's framework extends beyond the gateway argument. She proposes that locus coeruleus dysfunction produces adrenergic destabilization — chronic norepinephrine hyperactivity followed by depletion — and that the resulting hyperadrenergic vasoconstriction suppresses glymphatic flow. The glymphatic system is the brain's principal route of metabolic waste clearance, and its suppression in turn impairs the clearance of soluble amyloid-beta and damaged proteins. The Phase I bioenergetic crisis therefore initiates a Phase II proteostatic crisis through this adrenergic-glymphatic mechanism.

The implication for the drug-class landscape is significant. A successful Phase I PARP inhibitor strategy would, by preserving locus coeruleus function, also preserve adrenergic stability and glymphatic flow — and thereby slow the Phase II progression. The intervention is upstream not only of NbM cholinergic loss (Pieper) but also of cortical proteinopathy (the Phase II amyloid/tau cascade). PARP inhibition in Phase I is, by this argument, a single intervention with cascading downstream protective effects across all three Collapse phases.

8.4 The Antiviral Adjunct

Cutler's framework also suggests an adjunct strategy beyond the PARP inhibitor / NAD<super>+</super> precursor / CD38 inhibitor combination. Antiviral suppression of HSV-1 reactivation — through valacyclovir, acyclovir, or famciclovir — would reduce the upstream oxidative damage burden, lowering the chronic PARP-1 activation rate at its source. The Itzhaki laboratory's work on valacyclovir for AD provides a partial proof-of-concept: a small randomized trial (the VALAD trial) demonstrated that 18 months of valacyclovir was safe and produced biomarker signals consistent with reduced viral burden. The combination of antiviral suppression, PARP inhibition, NAD<super>+</super> precursor, and CD38 inhibition would address the Phase I cascade at four sequential nodes: viral reactivation, oxidative damage, PARP-1 activation, NAD<super>+</super> consumption, and systemic NAD<super>+</super> drain.

Chapter 9. Clinical Trial Design Considerations

9.1 The Population Problem

The principal challenge in designing a Phase I PARP inhibitor trial is the population. The mechanistic argument requires enrollment of asymptomatic adults aged 30 to 55 — patients by definition without measurable cognitive decline, without amyloid PET positivity, and without any current basis for clinical concern. The trial must demonstrate slowing of a process that, in untreated controls, will not produce a clinical endpoint for 20 to 40 years. Conventional cognitive endpoints (MMSE, MoCA, ADAS-Cog) are unsuitable because they are insensitive to Phase I dysfunction. Conventional imaging endpoints (amyloid PET, tau PET, hippocampal volume) are unsuitable because Phase I pathology is sub-threshold for these modalities. A new biomarker framework is required.

9.2 Phase I Biomarkers

Three biomarker categories appear feasible for Phase I trials:

CSF NAD<super>+</super> and metabolite panels. Direct measurement of NAD<super>+</super>, NADH, NMN, and nicotinamide in cerebrospinal fluid by LC-MS provides a CNS-specific readout of the metabolic state being targeted. Preliminary work from several groups suggests that CSF NAD<super>+</super> declines measurably with age and is further reduced in MCI patients. A Phase I trial would enroll patients with CSF NAD<super>+</super> below an age-adjusted threshold and would track NAD<super>+</super> stabilization or recovery over the trial period. Lumbar puncture is invasive but feasible at trial entry, midpoint (12 months), and trial end (24 to 36 months).

Urinary 8-OHdG and oxidative DNA damage markers. 8-hydroxy-2-deoxyguanosine, the predominant oxidative DNA lesion targeted by PARP-1, is excreted in urine and can be quantified by ELISA or LC-MS. Urinary 8-OHdG is non-invasive, reproducible across laboratories, and serves as a peripheral readout of total-body oxidative DNA damage. Locus-coeruleus-specific damage is not directly measured, but the systemic measure tracks the underlying biology.

Locus coeruleus neuromelanin MRI. Neuromelanin-sensitive MRI sequences (typically T1-weighted with magnetization transfer or specific sequences

such as MT-T1-FLASH at 3T or 7T) directly visualize the locus coeruleus and quantify its neuromelanin signal. Several research groups have demonstrated that LC neuromelanin signal declines with age, declines further in MCI and AD, and is reduced in APOE4 carriers. Neuromelanin MRI is the only existing imaging modality that directly visualizes the Phase I target tissue, and it is feasible to repeat at 6- to 12-month intervals across a multi-year trial.

A composite endpoint combining all three measurements — CSF NAD<super>+</super> stabilization, urinary 8-OHdG reduction, and LC neuromelanin signal preservation — provides a mechanistic readout sensitive enough to detect Phase I drug effects within a 24- to 36-month trial. None of these individual biomarkers has been validated for Phase III approval, but each is sufficient to support proof-of-concept and dose-finding studies.

9.3 Patient Selection

Three risk-enrichment criteria narrow the trial population to those most likely to show Phase I activity within the trial timeframe:

Age 30 to 55. This is the Phase I window. Younger patients show insufficient pathological progression; older patients have crossed into Phase II.

APOE4 positivity. APOE4 heterozygotes have approximately 3-fold elevated AD risk; APOE4 homozygotes have approximately 12-fold elevated risk and earlier mean onset (roughly age 65 vs 80). Genotype enrichment compresses the timeline of expected progression.

Family history positive for early-onset AD. First-degree relative diagnosis before age 70 substantially elevates risk and is a feasible enrollment criterion.

A trial enrolling APOE4-positive adults aged 40 to 55 with first-degree family history would have, on the most plausible mechanistic models, an annualized rate of CSF NAD<super>+</super> decline of approximately 2 to 4 percent. A drug effect of 50 percent slowing — modest by the standards of active Phase I PARP inhibition — would be detectable at 24 months with sample sizes in the range of 200 to 400 patients per arm.

9.4 Dosing Strategy

The dosing strategy departs from oncology conventions. Oncology uses PARP inhibitors at the maximum tolerated dose (MTD) to achieve maximum cytotoxicity in BRCA-mutated cells. Neurodegeneration prevention uses PARP inhibitors at the minimum effective dose (MED) to achieve partial catalytic inhibition with maximum safety margin for chronic administration. The MED for veliparib is estimated, on the basis of preclinical data and CNS pharmacokinetics from radiosensitization trials, at 10 to 40 mg twice daily — roughly an order of magnitude below the oncological MTD. A dose-finding trial with three arms (10 mg, 20 mg, 40 mg twice daily) plus placebo would establish the dose-response relationship.

The minimum trial duration is 24 months, with an optional 12-month extension. Shorter trials would be insufficient to detect the slow biomarker changes characteristic of Phase I. Longer trials face attrition, regulatory complexity, and the question of whether observed biomarker effects translate to clinical benefit on the multi-decade Phase I timeline.

9.5 Regulatory Pathway

The regulatory pathway for repurposing an oncology-approved PARP inhibitor for AD prevention is non-trivial. The FDA's 2018 draft guidance on early Alzheimer's disease drug development opened a pathway for biomarker-supported approvals in pre-symptomatic populations, but the specific application to a PARP inhibitor at sub-oncology dose has not been tested. A regulatory dialogue that combines preclinical efficacy data, CNS pharmacokinetic data from existing oncology trials, and biomarker-validated proof-of-concept data from a small Phase IIa would be the natural prelude to a larger Phase IIb dose-finding trial. A Phase III prevention trial, on conventional designs, would require 3,000 to 5,000 patients followed for 5 to 7 years and is not realistic for an academic-sponsored development program. The most feasible path to approval is therefore biomarker-supported accelerated approval based on Phase IIb data, with confirmatory Phase IV cognitive outcomes data accumulating over the post-approval period.

Chapter 10. Limitations and Open Questions

10.1 Long-Term PARP Inhibition in Non-Dividing Cells

The principal mechanistic concern with chronic PARP inhibition in aminergic neurons is that physiological PARP-1 activity is required for some forms of DNA repair, particularly base excision repair and the resolution of single-strand breaks. Complete inhibition of PARP-1 in non-dividing cells could, in principle, allow unresolved damage to accumulate and to be converted to double-strand breaks during transcription. This concern is mitigated by three considerations: first, the proposed Phase I strategy uses partial inhibition (40 to 80 percent) rather than complete blockade; second, alternative DNA repair pathways (XRCC1-mediated SSB repair, mismatch repair) remain functional; third, the combination strategy with NAD<super>+</super> precursors preserves substrate for residual PARP-1 activity. Nonetheless, long-term safety beyond 3 to 5 years of continuous use is not established, and post-approval pharmacovigilance would be essential.

10.2 NAD+ Supplementation vs. PARP Blockade

A legitimate alternative strategy is NAD<super>+</super> supplementation alone, without PARP inhibition. NMN and NR have favorable safety profiles, are available as supplements, and produce measurable increases in tissue NAD<super>+</super> at recommended doses. The case for combining the two interventions, made in Chapter 5, depends on the assumption that the rate-limiting step is the PARP-1 leak rather than the salvage pathway capacity. If the salvage pathway can be driven sufficiently fast by precursor supplementation alone, PARP inhibition becomes unnecessary. Empirically, the question is unresolved: NAD<super>+</super> precursor monotherapy has produced ambiguous biomarker signals in early human trials. The combination strategy is rational on first principles but unvalidated in human Phase I populations.

10.3 The Regulatory Challenge of Preventive Pharmacology

The deepest obstacle is regulatory rather than scientific. The current FDA framework for Alzheimer's drug approval is built around symptomatic and disease-modifying therapies for diagnosed disease. The framework for true preventive pharmacology — drugs administered to asymptomatic adults to prevent the onset of disease — exists in cardiovascular medicine (statins, antihypertensives) but not in neurology. The path to a preventive AD drug therefore requires not only clinical evidence but also regulatory innovation: the development of biomarker-based approval pathways that accept slowing of pre-symptomatic progression as evidence of clinical benefit. This is an active area of FDA dialogue but remains underdeveloped.

10.4 The Disease-Modifying vs. Preventive Distinction

Related but distinct is the question of how to position a Phase I PARP inhibitor in the existing AD drug taxonomy. It is not symptomatic (it does not improve cognition in established disease). It is not disease-modifying in the conventional sense (it does not act on amyloid plaques or tau tangles). It is preventive — it acts on the molecular cascade decades before the disease is clinically manifest. The closest analogy is to statin therapy in cardiovascular medicine, where lipid-lowering pre-symptomatic intervention prevents myocardial infarction in patients at elevated risk. The Phase I PARP inhibitor would occupy an analogous position: NAD<super>+</super>-preserving pre-symptomatic intervention to prevent neurodegeneration in patients at elevated risk. The regulatory and clinical category of "neuroprotective preventive pharmacology" does not yet formally exist but is the natural home of the proposed strategy.

10.5 Open Questions

Several questions remain underdetermined by current evidence and would benefit from targeted study:

The exact threshold of NAD<super>+</super> depletion below which the Phase I cascade becomes self-sustaining is not known.

The relative contributions of nuclear vs. mitochondrial PARP-1 to the locus coeruleus NAD<super>+</super> drain are not characterized.

The dose-response relationship between veliparib and CSF NAD<super>+</super> stabilization in human subjects has not been established.

The interaction between PARP inhibition and NAD<super>+</super> precursor supplementation has been studied in animal models but not in human Phase I populations.

The role of APOE4 in modulating PARP-1 activity is suggested by indirect evidence (APOE4 carriers show greater oxidative damage burden) but has not been directly tested.

The contribution of HSV-1 reactivation to the chronic oxidative damage burden in the locus coeruleus, central to Cutler's framework, awaits direct biomarker validation.

Each of these questions is tractable. None is resolved.

Chapter 11. Conclusion

Phase I of the Collapse Trilogy demands a drug that protects NAD<super>+</super> pools in pre-symptomatic adults. The pharmacology required is partial catalytic inhibition of PARP-1 at sub-oncology dose, deployed chronically across the Phase I window of age 30 to 55. The drug class developed for BRCA-mutated cancers — veliparib, talazoparib, rucaparib, niraparib, olaparib — is the most mature pharmacological tool currently available for this purpose. Veliparib emerges as the lead candidate by virtue of its low PARP-trapping potency, its blood-brain barrier penetration, and its acceptable safety database. The complementary strategy of NAD<super>+</super> precursor supplementation (NMN, NR) addresses the salvage-pathway side of the same metabolic equation. CD38 inhibition and antiviral suppression of HSV-1 reactivation provide additional adjuncts at distinct upstream and systemic nodes.

The argument converges with three independent research programs in the Oskar Fischer Prize corpus. Andrew Pieper's nucleus basalis of Meynert framework predicts the same PARP-1/NAD<super>+</super> cascade in the parallel cholinergic projection system. Eduardo Chini's CD38-driven inflammaging program identifies a systemic NAD<super>+</super> drain that compounds the cellular leak. Richelle

Cutler's herpesvirus-locus coeruleus framework provides the upstream trigger for the chronic oxidative damage that initiates PARP-1 hyperactivation. Each program has been developed independently. Each converges on the same metabolic axis. The convergence is the strongest available evidence that the axis is real, that the cascade is the load-bearing mechanism, and that intervention at this point of the cascade is the rational therapeutic strategy.

The barriers to clinical translation are not principally scientific. Veliparib is a mature drug with extensive safety data. CSF NAD<super>+</super>, urinary 8-OHdG, and locus coeruleus neuromelanin MRI are mature biomarkers. APOE4 and family history provide adequate enrichment criteria. The Phase I window is anatomically and temporally well-defined. The barriers are commercial — the patent landscape for veliparib is unfavorable for industrial development — and regulatory — the framework for true preventive pharmacology in neurology does not yet formally exist. These are obstacles to be navigated, not reasons to abandon the strategy.

Alzheimer's disease has resisted pharmacological intervention for three decades because the field has been treating Phase III pathology in patients whose Phase I damage was complete decades before the trial began. The history of cardiovascular medicine offers an instructive parallel: the development of statins as preventive therapy for asymptomatic adults at elevated cardiovascular risk transformed a major cause of mortality from a death sentence into a manageable risk factor. Phase I PARP inhibition is the closest available analog in neurology. The drug class is FDA-approved, the mechanism is established, the biomarkers are mature, the population is identifiable, and the scientific case is strong. What remains is to do the trials.

The Collapse Trilogy frames Alzheimer's disease as three sequential pathologies, each with its own dominant molecular machinery and its own therapeutic window. Phase I — the Silent Brainstem Erosion — is the phase that has been ignored. PARP inhibitors, repurposed at sub-oncology dose for chronic administration to pre-symptomatic adults, are the load-bearing drug class. The locus coeruleus is the load-bearing tissue. NAD<super>+</super> is the load-bearing metabolite. The next decade of AD drug development will, on this analysis, succeed or fail based on whether the field accepts the temporal architecture of the disease and reorients its pharmacology accordingly.

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This paper is part of the Collapse Trilogy series of doctoral working papers prepared under the Organic Network Synthesis (ONS) methodology at AdultCognitiveDisease.com. Companion papers address Phase II (Hippocampal Bridgehead) and Phase III (Excitatory/Inhibitory Collapse) interventions. The

argument advanced here is theoretical and grounded in mechanism; none of the Phase I strategies described has been validated in clinical trials designed around the Collapse Trilogy framework. This document is a research reference, not clinical guidance.