THE COMPRESSED ARCHITECTURE

Trisomy 21 as the Whole-Chromosome, Time-Compressed Run of Alzheimer's Three-Phase Collapse

The Congenital Endosome · The Triplicated Tau Kinase · The Interferon Chromosome
The Aggrecanase in Triplicate · The Compressed Clock

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The genetic-forms companion to the corpus's Temporal Architecture. Where that volume lays out the three phases and two bridges of the sporadic disease, this one shows how the gene content of chromosome 21 pre-loads every one of those stations — so that Down syndrome is not early Alzheimer's disease but the whole architecture, pre-installed and run fast.

"An autosomal-dominant mutation runs one gene's experiment across a lifetime. A trisomy runs a whole chromosome's — and if that chromosome happens to carry a factor for every phase of a disease, then the disease it produces is not merely early. It is the entire structure, pre-built and set running on a shortened clock, offered up to be read from ignition to collapse inside a single life."

— ONS Methodology Working Notes, 2026

For the six million who carry the third chromosome, in whom the disease we all fear is written early and plain — and who, by living its whole architecture fast, may teach us to interrupt it in everyone.

THE COLLAPSE CORPUS THE GENETIC-FORMS COMPANION

The Temporal Architecture (the three-phase theory this volume compresses)

The Genetic Architecture of Neurodegeneration (the risk atlas; APP on chromosome 21)

The Biomarker Cascade (which named Down syndrome the 'third reference population')

The Compressed Architecture ← this volume

This volume stands to the corpus as the reading of its one whole-chromosome natural experiment. The Temporal Architecture states the disease as a three-phase progression joined by two bridges; the risk atlas locates *APP* and much of the disease's machinery on chromosome 21; the biomarker volume names Down syndrome, with the autosomal-dominant kindreds, as a population in which the disease's sequence can be read against a known clock. This one draws the three together, laying the gene content of the triplicated chromosome over the phase-map of the architecture, and asks how much of the whole structure a single trisomy pre-loads. The answer — strikingly nearly all of it — is graded, phase by phase, on an explicit scale of strength.

Contents

Abstract

Down syndrome is the most common genetic cause of Alzheimer's disease, and it is usually explained in a single sentence: chromosome 21 carries the amyloid precursor protein gene, a third copy makes more amyloid, and more amyloid brings the disease early. The sentence is true, and it is the cleanest human demonstration in all of neurology that amyloid dosage is causally sufficient to produce Alzheimer's pathology. But it is also, this dissertation argues, a profound under-reading of what trisomy 21 actually is. A person with Down syndrome does not merely carry an extra dose of the disease's first molecule. They carry an extra dose of a molecule at *every* phase of the disease — a chromosome whose gene content, read against the corpus's three-phase Temporal Architecture, loads the bioenergetic ignition, arms both arms of the first bridge, pre-commits the microglial collapse, pre-supplies three of the four arms of the second bridge, and pre-shapes the terminal synaptic substrate. Down syndrome is not early Alzheimer's disease. It is the *entire architecture, pre-installed and run fast* — the corpus's whole syllabus taught in forty years instead of eighty.

The argument proceeds by placing the genes of chromosome 21 into the phase-structure the corpus has already built for the sporadic disease. **Phase I, Bioenergetic Ignition**, appears in the Down brain not in the sixth decade but in the first: *APP* over-dosage acting through its β-cleavage fragment enlarges the early endosome of the Down syndrome neuron in infancy, years before a plaque; *SYNJ1* and *ITSN1* triplication compound the endocytic lesion; and a congenital mitochondrial deficit, with *SOD1* over-expression tilting the redox balance toward hydrogen peroxide, installs the metabolic failure the corpus places at the disease's origin decades ahead of schedule. **The first bridge** — the corpus's locus-coeruleus hand-off, which delivers to the forebrain both the withdrawal of noradrenergic restraint and a stream of templated tau — is, in Down syndrome, genetically armed on both arms at once: the amyloid arm by *APP* dosage, and the tau arm by *DYRK1A*, a chromosome-21 kinase that phosphorylates tau directly and primes it for GSK-3β. **Phase II, the Homeostatic Microglial Bridgehead**, has in trisomy 21 a cause the sporadic disease must wait decades to acquire: the four interferon receptors clustered on chromosome 21 render Down syndrome a constitutive interferonopathy, holding the microglion out of its homeostatic state from birth, with *S100B* and a triplicated *miR-155* pressing in the same direction. **The second bridge**, the Proteolytic Turn, finds three of its arms pre-supplied — the oxidative substrate for Fenton chemistry by *SOD1*, the inflammasome priming by *S100B* and interferon, and — a fact of startling economy — the aggrecan-digesting enzymes themselves, *ADAMTS1* and *ADAMTS5*, encoded on chromosome 21 and therefore dosed up in every Down cell. **Phase III, Synaptic Disintegration**, terminates as the sporadic disease does, on the perineuronal net of the parvalbumin interneuron, but reaches it across a substrate that *DYRK1A* and *OLIG2* have shaped toward excitatory–inhibitory imbalance since before birth.

Two disciplines are imposed throughout. The first is a strength-graded ledger: every gene-to-phase assignment is graded, from the endosomal lesion demonstrated in human Down tissue (established) to the aggrecanase-dosage inference not yet tested in the Down brain (conjectural), so that the architecture's completeness is never mistaken for its proof. The second is the honest naming of the confound that both makes and troubles the thesis: trisomy 21 is present from conception, so much of what the architecture reads as an accelerated *degeneration* is entangled with a lifelong *developmental* difference in how the Down brain is built. This dissertation argues that the entanglement, correctly handled, is the source of Down syndrome's unique evidentiary power rather than a defect in it — that a disease whose every phase is pre-loaded and whose clock runs at half the ordinary length is the fastest available read-out of whether the corpus's temporal ordering, and above all its two bridges, are real. The counterfactual of partial trisomy, which spares *APP* and spares the dementia, keeps the amyloid igniter necessary; the rest of the chromosome, this thesis proposes, sets the tempo and completes the form.

I. The Natural Experiment Already Concluded

There is a version of Down syndrome's relationship to Alzheimer's disease that the field has been able to recite for four decades, and it is worth stating precisely because the aim of this dissertation is to show how much it leaves out. In 1929 Struthers noted the presenile dementia of adults with what was then called mongolism; by the 1980s the neuropathology was unambiguous. Essentially every person with trisomy 21 who lives into their forties develops the full neuropathological picture of Alzheimer's disease — the diffuse and neuritic plaques, the neurofibrillary tangles in the entorhinal and hippocampal and then neocortical fields, the amyloid angiopathy — and the great majority go on, a decade or so later, to a clinical dementia that is now the leading cause of death in the population. The mechanism seemed self-evident the moment the amyloid precursor protein was mapped to chromosome 21: three copies of the gene, roughly one-and-a-half times the protein, a lifelong surfeit of the peptide that aggregates into plaques. Down syndrome became, and remains, Exhibit A for the amyloid cascade hypothesis — the one human population in whom the disease's first molecule is over-produced from conception, and in whom the disease reliably follows.

The corpus does not dispute this reading; it depends on it. The companion volume on the genetic architecture of the disease locates *APP* on chromosome 21 and treats the autosomal-dominant and Down syndrome forms as the cleanest available proofs that amyloid over-production is causally sufficient. The biomarker dissertation goes further and names Down syndrome AD, alongside the autosomal-dominant kindreds of the DIAN cohort, as one of only three reference populations in which the disease's temporal sequence can be read against a known clock — "compressed," it says, "but otherwise comparable." That word, *compressed*, is the seed of this dissertation. It is offered in the biomarker volume as a convenience — Down syndrome runs the same tape faster, and so lets us see the whole of it inside a research career. This volume asks what it would mean to take the compression seriously as a *mechanism* rather than a convenience: to ask not merely that the Down brain runs the ordinary disease quickly, but *why*, and to answer with the specific genes that chromosome 21 carries and the specific phases of the corpus's architecture onto which those genes fall.

The reason the question is worth asking is that the one-sentence account contains a hidden and unexamined claim. If the whole of Down syndrome's dementia were the consequence of *APP* dosage alone, then trisomy 21 would be, mechanistically, nothing more than a third instance of amyloid over-production — biologically identical to an *APP* locus duplication, differing only in the incidental baggage of the rest of the chromosome. That is very nearly how the field has treated it. But a

chromosome is not a gene, and the third copy of chromosome 21 is a third copy of some two hundred and thirty protein-coding genes and a comparable number of regulatory RNAs, many of them dosage-sensitive, several of them — as the following chapters will show — sitting squarely on the molecular machinery that the corpus's Temporal Architecture identifies as load-bearing at each of its three phases and each of its two bridges. The question this dissertation puts is therefore sharp and, to my knowledge, has not been asked in quite this form: *when we place the gene content of chromosome 21 onto the corpus's phase-map of Alzheimer's disease, how much of the architecture does a single trisomy pre-load?* The answer, developed across the chapters that follow, is: strikingly nearly all of it.

The methodological attraction of Down syndrome is, at bottom, the same as the attraction the companion dissertation found in the protective alleles, and it is worth being explicit about it because it justifies the whole enterprise. Human genetics offers its strongest inferences when a fixed change is present from conception, because the arrow of time then excludes reverse causation: whatever follows the change cannot have caused it. A person with trisomy 21 has carried the full triplication since the first division of the zygote. Everything that unfolds in their brain across the subsequent five or six decades unfolds *downstream* of a genetic perturbation that was complete before the nervous system existed. If the corpus's architecture is right — if the disease really does proceed from a bioenergetic ignition through a microglial bridgehead to a synaptic disintegration, joined by two specifiable bridges — then a population in whom every one of those stations is genetically pre-loaded should traverse the whole sequence, in order, on a foreshortened clock. Down syndrome is the experiment that trisomy already ran. This dissertation is an attempt to read its result against the architecture the corpus built for everyone else.

> *Down syndrome has been read for forty years as the proof that too much amyloid brings the disease. This dissertation reads it as something larger: the proof that a single chromosome can pre-load the whole disease — and the fastest natural test of whether the architecture the corpus proposes is real.*

II. The Architecture to Be Compressed

Because the argument of this dissertation is that trisomy 21 compresses a specific structure, that structure must be stated before it can be compressed. The corpus's flagship theory holds that Alzheimer's disease is not, at its deepest level, a contest between molecules — amyloid versus tau, the plaque versus the tangle — but a stereotyped progression in *time*, in which the identity of the primary lesion changes as the disease moves through the decades of a life and across the anatomy of a brain. The theory names three phases and, more importantly, two bridges between them, and it is the bridges, far more than the phases, that make it a falsifiable theory rather than a list of stations.

Phase I is Bioenergetic Ignition, and in the sporadic disease it occupies the third through fifth decades in near-total clinical silence. Its seat is the locus coeruleus and the brainstem aminergic nuclei — the most metabolically extravagant and earliest-failing neurons in the human brain — and its substrate is not a protein but a process: the slow failure of the machinery by which a neuron disposes of its own damaged components. Mitophagy fails as NAD+ is depleted and PARP-1 is hyperactivated; the import of new proteins into the mitochondrion is obstructed; the autophagy–lysosomal system silts up; and the terminal morphology is the flower-like, autolysosome-swollen neuron that Nixon named PANTHOS, whose rupture leaves a plaque behind as its gravestone. The defining feature of Phase I is that it produces no dementia. It is a metabolic disease of a few tens of thousands of brainstem cells, and its only outward signs are the prodromal disturbances of sleep, mood, and arousal that precede memory loss by decades.

The first bridge, the Locus Coeruleus Bridge, carries the disease from a private brainstem affair into a forebrain disease. The same coeruleus axons that have begun to fail deliver, along one anatomical arbor and in the same epoch, two things at once: the withdrawal of the noradrenergic signal that normally restrains microglia across the forebrain, and a stream of templated tau seeds that propagate trans-synaptically into the limbic system. One projection executes both the loss of regulation and the delivery of the pathology. This dual-pressure arrival on the hippocampus is what converts a metabolic disease into an immune one.

Phase II is the Homeostatic Microglial Bridgehead, occupying the sixth and seventh decades in the hippocampus. Its lesion is the collapse of the TGF-β/SMAD-maintained homeostatic identity of the microglion — the transcriptional programme (P2RY12, TMEM119, CX3CR1, and their companions) that keeps the brain's resident immune cell in its surveying, supporting, restrained state. Under the chronic stress of the released noradrenergic brake, the tau seeds, and the cell's own ageing, that programme fails, and the microglion exits into post-homeostatic states in which — this is the deepest claim of the Phase II thesis — its protective withdrawal and its destructive attack are

no longer separable acts. The brain does not acquire a harmful cell type; it loses the governor on a cell type it has always had.

The second bridge, the Proteolytic Turn, is the disease's most intricate transition, and because its target is no longer a cell but a structure — the perineuronal net — it requires three converging arms rather than two. The first arm is a change in the microglial secretory programme, in which lipid-laden post-homeostatic microglia assemble the NLRP3 inflammasome, cleave IL-1β, and are driven by it to transcribe the matrix metalloproteinases and aggrecanases (MMP-9, MMP-3, ADAMTS-4/5) — the conversion of a cytokine-secreting cell into a matrix-digesting one. The second arm is inorganic: iron liberated from ferroptotic oligodendrocytes loads the net's sulfated glycosaminoglycans and catalyses Fenton chemistry, generating hydroxyl radicals that fragment the proteoglycan and make it a better substrate for the enzymes of the first arm. The third arm is complement: C1q deposited on the net activates the classical cascade, C4d opsonins mark the matrix, and CR3-bearing microglia strip it. The three arms meet on one structure.

Phase III is Synaptic Disintegration, the decade of clinical dementia. The perineuronal net surrounding the parvalbumin-positive fast-spiking interneuron — the cell that paces cortical computation and generates the gamma rhythms of working memory and attention, and the most metabolically exposed neuron in the cortex — is digested. Stripped of the net that was at once its structural scaffold and its antioxidant buffer, the interneuron loses its inhibitory competence, excitatory–inhibitory balance collapses, gamma rhythms degrade, and the network failure experienced as dementia ensues.

Three properties of this architecture matter for what follows. It is *anatomically directional*, the front moving from brainstem to limbic system to cortex in the same rostral order Braak documented for tau. It is *substrate-shifting*, the primary lesion being metabolic in Phase I, immunological in Phase II, and structural in Phase III — which is exactly why no single-molecule theory ever fit the whole disease. And it is *bridged*: the transitions are mechanisms in their own right, each with named molecular arms and a named anatomical substrate. To compress this architecture is to run all three substrate-shifts and both bridges on a shortened clock. The claim of this dissertation is that trisomy 21 does precisely that, and does it not by accelerating an external clock but by carrying, on the triplicated chromosome, a genetic pre-load at every station.

III. A Grammar of Dosage

Before the genes of chromosome 21 can be placed onto the architecture, three things must be made precise: what "dosage" does, how a developmental perturbation is to be told apart from a degenerative one, and on what scale the gene-to-phase assignments of this dissertation are to be graded. Without these, a catalogue of chromosome-21 genes falling on Alzheimer pathways would be a party trick rather than an argument.

What a third copy does, and does not, do

The elementary fact of trisomy is that three copies of a gene yield, to a first approximation, one-and-a-half times its product. For most genes this 50 percent surfeit is buffered — by feedback, by degradation, by the redundancy of networks — and produces no discernible phenotype. The genes that matter to Down syndrome are the *dosage-sensitive* ones, those whose function scales with their abundance across the relevant range and whose 1.5-fold over-expression therefore shifts a biological set-point rather than being absorbed. *APP* is the paradigm: its product is cleaved by mass-action-sensitive secretases, so more precursor yields proportionally more of every cleavage fragment, and the phenotype scales. Not every chromosome-21 gene is dosage-sensitive, and a disciplined argument must not treat mere physical location on the triplicated chromosome as equivalent to a demonstrated dosage effect. Throughout this dissertation the distinction is kept: a gene earns a place in the architecture not by being on chromosome 21 but by carrying evidence that its over-expression shifts the specific biology the corpus assigns to a specific phase.

There is a second subtlety the grammar must hold. A gene's 50 percent surfeit is present in every cell, at every age, from conception. Its consequences, however, need not be. A dosage-sensitive gene can produce a phenotype that is fully expressed in development (a mis-built circuit), or one that accrues slowly across life (a metabolic debt that compounds), or one that is latent until an age-dependent second factor arrives (a primed inflammasome that waits for its trigger). The same 1.5-fold input can therefore read as developmental, degenerative, or conditional depending on the biology it feeds. This is not a complication to be apologised for; it is the very structure that lets a single trisomy load different phases of a time-ordered disease in different temporal modes, and Chapter X returns to it as the thesis's central honesty.

The counterfactual that disciplines the whole

The strongest constraint on any account of Down syndrome and Alzheimer's disease is the counterfactual supplied by partial trisomy 21. A small number of individuals carry a triplication of only part of chromosome 21, and in the rare cases whose triplicated segment *excludes* the *APP* locus, the lifelong over-dosage of scores of other chromosome-21 genes does not produce Alzheimer's dementia or its neuropathology. Reciprocally, duplication of the *APP* locus *alone* — a microduplication involving no other chromosome-21 gene — is sufficient to cause an autosomal-dominant early-onset Alzheimer's disease with prominent amyloid angiopathy. Read together, these two natural experiments deliver a verdict that this dissertation accepts without reservation: *APP* dosage is necessary, and *APP* dosage alone is sufficient to cause the disease. Any thesis that made the other chromosome-21 genes into co-equal causes of the dementia would founder on the partial-trisomy cases.

The argument of this dissertation is therefore carefully not that. It is not that the non-*APP* genes *cause* the Down syndrome dementia; the counterfactual forbids it. It is that they *shape* it — that they set the tempo at which the *APP*-ignited disease traverses the architecture, pre-commit the phases through which it must pass, and determine the completeness and the particular form of the collapse. An igniter is necessary and can be sufficient to burn a building; it does not follow that the building's construction, its wiring, and its stored fuel are irrelevant to how fast and how completely it burns. The remainder of this dissertation is the case that chromosome 21 is a building pre-wired and pre-fuelled at every one of the architecture's stations, and that this — not the amyloid dose alone — is what "compression" names.

The grading scale

No gene-to-phase assignment in this dissertation is asserted without a grade, and the grades are defined once, here, and applied uniformly in the ledger of Chapter VIII. The scale answers a single question: *how firmly is this chromosome-21 gene's over-dosage tied, in Down syndrome specifically, to the phase of the architecture onto which this dissertation places it?*

Tier	Name	The bar it must clear
I	Established	The dosage effect on this phase's biology is demonstrated in human Down syndrome tissue or fluid, or robustly across Down syndrome models with direct human corroboration, and the mechanism is at least partly worked out.
II	Well-supported	The dosage effect is demonstrated in Down syndrome models with mechanistic clarity and partial human corroboration, and the direction of effect on the phase is secure.
III	Emerging	The mechanism is compelling and the gene's over-dosage plausibly drives the phase, but the evidence in Down syndrome specifically is thin, indirect, or inferred largely from non-trisomic model systems.
IV	Conjectural	The phase-assignment is a reasoned inference from the gene's known biology and its position on the triplicated chromosome, worth stating for the architecture it completes, but not yet tested in the Down brain.

Two flags are carried alongside the tier, because the temporal mode of a lesion is as important to this thesis as its strength. A **congenital** flag (▲) marks an effect present from development, part of how the Down brain is built; a **degenerative** flag (▼) marks an effect that manifests as an age-related decline; and a lesion may carry both, being installed in development and compounding with age. The flags are not decoration. They are the instrument by which Chapter X separates the developmental confound from the degenerative architecture, and they are the reason the ledger can be read as a timeline as well as a table.

IV. Phase I Pre-Loaded — The Congenital Bioenergetic Lesion

The corpus places the origin of Alzheimer's disease in a metabolic and custodial failure — the collapse of mitochondrial and autophagy–lysosomal quality control — that in the sporadic disease takes three decades of adult life to declare itself. The first and most consequential fact about Down syndrome, read through the architecture, is that this Phase I lesion is not a late acquisition of the Down brain but a congenital feature of it. The machinery the corpus identifies as failing first is, in trisomy 21, dysregulated from infancy.

The endosome that is enlarged before the plaque

The single most important observation in this chapter is one of the oldest and most robust in the Down syndrome literature, and its significance is transformed when it is read against the corpus's Phase I. In the brains of individuals with Down syndrome, the neuronal early endosome is abnormally enlarged — and it is enlarged *early*, in the first years of life, decades before a single amyloid plaque appears, and indeed before the age at which diffuse amyloid begins to accumulate at all. Cataldo and Nixon showed that this endosomal enlargement, the earliest known cytopathology of Alzheimer's disease, is present in Down syndrome neurons in infancy and is shared, in attenuated form, with the sporadic disease, where it likewise precedes amyloid deposition. The lesion is not a consequence of the plaque; it is upstream of it.

Crucially, the driver of the enlarged endosome is not the amyloid peptide but an earlier product of the same precursor. The endosomal phenotype is driven by *APP* gene dosage acting through the β-cleaved carboxy-terminal fragment, βCTF (C99) — the membrane-bound stub that remains after β-secretase has cut the precursor and before γ-secretase releases the peptide. βCTF, over-produced in proportion to the tripled precursor, dysregulates the small GTPase Rab5 and the endosomal fusion machinery, and the endosome swells. This is a Phase I lesion in the corpus's precise sense: a failure of the endosomal–lysosomal trafficking and quality-control apparatus, driven by an *APP* fragment that is not the plaque-forming peptide, appearing before and independently of amyloid deposition. The Down brain enters the world with the disease's first cytological lesion already present, and it is present because the chromosome is tripled.

Two further chromosome-21 genes compound the endocytic failure, and their presence on the triplicated chromosome is not incidental to it. *SYNJ1*, encoding the phosphoinositide phosphatase synaptojanin-1, is triplicated in Down syndrome, and its over-dosage dysregulates the $PI(4,5)P_2$ pool on which endocytosis and autophagosome formation depend; Cossec and colleagues showed that

trisomy for *SYNJ1* alone reproduces features of the endosomal phenotype, and the corpus's own external-scientist review flags synaptojanin-1 as a shared therapeutic node across Alzheimer's, Down syndrome, and epilepsy. *ITSN1*, encoding intersectin-1, a scaffold of the endocytic machinery, is likewise triplicated and likewise contributes to endosomal enlargement. Three chromosome-21 genes — *APP* through its βCTF, *SYNJ1*, and *ITSN1* — thus converge on a single Phase I lesion, the failing endosome, and all three are dosed up together in every neuron of the Down brain from the beginning. The corpus's Phase I insight was that quality-control failure, not any single protein, is the true origin lesion, identified by the convergence of formation-failure and degradation-failure on one phenotype. Down syndrome supplies that convergence genetically, at three loci at once, from birth.

The mitochondrion in deficit from the first division

The second pillar of Phase I is mitochondrial. The corpus locates the disease's ignition in the failure of mitochondrial quality control and the depletion of the cell's energetic currency, and here again Down syndrome presents the lesion congenitally rather than as an age-dependent acquisition. Mitochondrial dysfunction is a consistent and early feature of trisomy 21, demonstrable in fetal tissue and in cells that have never aged: reduced complex I activity, a lowered mitochondrial membrane potential, diminished ATP synthesis, elevated reactive-oxygen production, and a fragmented mitochondrial network. Helguera and Busciglio described this as an *adaptive downregulation* of mitochondrial function in Down syndrome — the trisomic cell throttling its own oxidative metabolism, a state the corpus would recognise as the metabolic hibernation of a neuron conserving against a substrate it cannot safely burn. The chromosome-21 contribution is partly specific — *RCAN1* (DSCR1), a triplicated regulator of calcineurin, disturbs mitochondrial dynamics and the calcineurin–PGC-1α axis of mitochondrial biogenesis; *NRIP1* (RIP140) represses the same biogenic programme — and partly the summed burden of many genes, but the phenotype is unambiguous and it is present from the start.

Onto this metabolic deficit chromosome 21 adds a specific redox distortion whose importance the later chapters will compound. *SOD1*, encoding copper–zinc superoxide dismutase, sits on chromosome 21 and is over-expressed by the expected half-again in Down syndrome. Superoxide dismutase converts the superoxide radical into hydrogen peroxide; when it is over-dosed without a matched increase in the downstream enzymes — catalase, glutathione peroxidase — that dispose of hydrogen peroxide, the result is not less oxidative stress but a shifted one, an accumulation of hydrogen peroxide, the substrate of the hydroxyl-radical-generating Fenton reaction. The Down brain therefore carries, from birth, a redox economy tilted toward exactly the peroxide that Chapter VII will show feeds the second bridge. The oxidative-stress literature on Down syndrome, reviewed by Perluigi and Butterfield as "a route toward Alzheimer-like dementia," documents the lipid peroxidation and protein oxidation that this tilted economy produces, detectable long before dementia.

The terminal morphology of Phase I, the autolysosome-swollen PANTHOS neuron, has been observed in Down syndrome brains, as the corpus's own concept note on autophagic collapse records — the end-stage of the same endosomal–autophagic failure, now advanced to the point of neuronal lysis, appearing in the Down brain as it does in the sporadic disease but reached across a foreshortened span. The Phase I picture in Down syndrome is thus complete and congenital: the endosome enlarged in infancy by three converging chromosome-21 genes, the mitochondrion in deficit from fetal life, the redox balance tilted toward peroxide by *SOD1*, and the autophagic collapse waiting at the end of the same road the sporadic disease travels more slowly.

The corpus placed the disease's ignition in a bioenergetic and custodial failure that takes the sporadic brain thirty years to reach. The Down brain is born inside it. Phase I is not accelerated in trisomy 21; it is congenital.

V. The First Bridge, Genetically Armed

The corpus's first bridge is its most elegant single idea: the locus coeruleus, failing in Phase I, delivers to the forebrain along one axonal arbor both the withdrawal of noradrenergic restraint on microglia and a stream of templated tau seeds — the same projection that regulates the forebrain becoming the projection that poisons it. The bridge has two arms, an amyloid-and-regulation arm and a tau-seeding arm, and its power in the corpus's telling is that a single anatomical event drives both. In Down syndrome, uniquely, *both arms are genetically armed*, and by two different chromosome-21 genes.

The coeruleus fails early in the Down brain

The anatomical premise of the bridge holds in Down syndrome, and holds early. The locus coeruleus and the noradrenergic system are affected in the neuropathology of Down syndrome AD, with loss of coeruleus neurons and depletion of forebrain noradrenergic markers, and the cholinergic and aminergic systems degenerate as the disease advances — the same brainstem-first, aminergic vulnerability the corpus places at the head of the sporadic disease. Iulita and Cuello's work on the dysmetabolism of nerve growth factor in Down syndrome adds a mechanistic layer that the corpus would read as bridge-relevant: the trophic support on which the basal forebrain depends is disrupted early, weakening precisely the aminergic and cholinergic projections whose integrity the first bridge concerns. The Down brain therefore supplies the bridge's anatomical substrate and supplies it on the compressed clock — the coeruleus that the sporadic disease erodes across three silent decades is, in trisomy 21, pressured from both the congenital Phase I lesion beneath it and the developmental trophic deficit around it.

The amyloid arm, by APP dosage

The first arm of the bridge — the withdrawal of noradrenergic suppression that raises the inflammatory set-point of forebrain microglia, coupled to the amyloid burden that the failing, LC-innervated forebrain accumulates — is armed in Down syndrome by the same *APP* dosage that defines the syndrome's relationship to the disease. But the architecture lets us read that dosage more precisely than the amyloid-cascade sentence allows. The amyloid in Down syndrome is not merely abundant; it arrives in a spatial and temporal pattern that the bridge predicts. Amyloid PET in adults with Down syndrome shows the earliest deposition in the striatum — the striatum-first pattern shared with autosomal-dominant *APP*-driven disease — and then a stereotyped spread, with the sequence of biomarker change (amyloid, then tau, then neurodegeneration, then cognitive decline) following the ordered trajectory that Fortea and colleagues mapped in their large cross-sectional cohort and that mirrors, on a compressed timeline, the DIAN sequence in autosomal-dominant disease. The amyloid arm of the bridge, in other words, is not only armed in Down syndrome but *legible* there, its output following the ordered course the architecture requires.

The tau arm, by DYRK1A

It is the second arm of the bridge that Down syndrome arms in a way no other population does. The corpus's bridge delivers templated tau; the rate-limiting event in generating a seed-competent tau is its hyperphosphorylation. Chromosome 21 carries *DYRK1A*, the dual-specificity tyrosine-phosphorylation-regulated kinase 1A, and *DYRK1A* is a tau kinase. Over-dosed by half again in every Down cell, DYRK1A phosphorylates tau directly — at threonine-212 and other sites — and, critically, primes tau for subsequent phosphorylation by glycogen synthase kinase-3β, so that its over-activity accelerates the whole hyperphosphorylation cascade rather than a single step. DYRK1A additionally phosphorylates the amyloid precursor itself and regulates the alternative splicing of tau's own transcript, shifting the 3R:4R isoform ratio in a direction that favours pathology. Wegiel and colleagues documented DYRK1A's over-expression and its co-localisation with neurofibrillary pathology in the Down syndrome brain, tying the triplicated kinase directly to the tangles.

The consequence for the architecture is exact and, so far as I know, has not been stated before in these terms. In the sporadic disease, the first bridge's two arms — the amyloid-and-regulation arm and the tau-seeding arm — are driven by a single anatomical event, the coeruleus's failure, and the tau arm's rate is set by whatever slow, stochastic, age-dependent processes hyperphosphorylate tau in an ageing brainstem. In Down syndrome, the tau arm is not left to those slow processes. It is *genetically accelerated*, because the chromosome that over-produces the amyloid substrate of the first arm *also* over-produces the kinase that generates the tau seed of the second. The bridge that the sporadic brain must build slowly, arming each arm by degrees, the Down brain crosses on a span pre-armed at both ends: *APP* on the amyloid side, *DYRK1A* on the tau side, both triplicated, both

present from conception. This is the single clearest instance in the whole dissertation of what compression means at the level of mechanism — not a faster clock, but a bridge whose two arms are each independently pre-loaded by the same trisomy.

> *The corpus's first bridge delivers amyloid and tau along one failing projection. Trisomy 21 arms both arms of it by gene dosage — the amyloid arm by APP, the tau arm by the kinase DYRK1A — so that the hand-off the sporadic brain assembles across a decade is, in the Down brain, genetically pre-built.*

VI. Phase II Pre-Loaded — The Interferon Chromosome

If Chapter IV's claim was that Down syndrome is born inside Phase I, this chapter's is stronger still: that trisomy 21 supplies the cause of Phase II — the collapse of homeostatic microglial identity — that the sporadic disease must wait six decades to acquire, and supplies it as a constitutive, lifelong state written into the immune biology of the chromosome. This is, in my judgement, the most important and the most under-appreciated point of contact between Down syndrome and the corpus's architecture, because it identifies a *specific molecular driver* for a phase the corpus otherwise reaches by the accumulated stress of ageing.

Down syndrome is a constitutive interferonopathy

The decisive fact is one that the Down syndrome field has established only in the last decade, and its implications for the corpus's Phase II have not been drawn. Chromosome 21 carries a cluster of four interferon receptor genes — *IFNAR1* and *IFNAR2* (the type I interferon receptor subunits), *IFNGR2* (a type II interferon receptor subunit), and *IL10RB* (a shared receptor chain) — and their triplication renders the entire trisomic organism hypersensitive to interferon. Sullivan, Espinosa, and colleagues showed that trisomy 21 *consistently activates the interferon response*: across cell types and individuals, the Down syndrome transcriptome is dominated by a constitutive interferon signature, as though the whole system were mounting a chronic, low-grade antiviral response to nothing. Waugh and colleagues extended this to the whole immune system with mass cytometry, describing a global immune remodelling with multi-lineage hypersensitivity to type I interferon. Down syndrome is, in the modern reading, a genetically determined *interferonopathy* — and the interferon it over-signals is one of the most potent known drivers of microglial activation.

Read against the corpus, this is not a fact about the immune system that happens to co-occur with the dementia. It is a Phase II mechanism, pre-installed. The corpus defines Phase II as the loss of the TGF-β/SMAD-maintained homeostatic microglial programme — the exit of the microglion from its surveying, restrained state into the post-homeostatic states in which attack and failure become one act. Type I interferon is precisely an antagonist of microglial homeostasis: chronic interferon signalling drives microglia out of the homeostatic P2RY12/TMEM119 signature and into interferon-responsive activated states, opposing the TGF-β programme that holds them quiescent. A brain whose every microglion carries a triplicated interferon-receptor cluster is a brain in which the homeostatic set-point is chronically pushed toward collapse *from birth*. Where the sporadic disease reaches Phase II by the slow arrival of the released noradrenergic brake and the tau

seeds upon an ageing microglial population, the Down brain begins life with its microglia already biased out of homeostasis by a constitutive interferon tone. The interferon chromosome does not cause the dementia — the counterfactual of Chapter III forbids that — but it pre-commits the microglial collapse that the dementia requires, and it does so decades early.

The corroborating dosage: S100B and miR-155

Two further chromosome-21 factors press the microglion in the same direction, and their independent presence on the triplicated chromosome is part of the point: Phase II, like Phase I, is loaded in Down syndrome at more than one locus. *S100B*, encoding the astrocytic calcium-binding protein, sits on chromosome 21 and is over-expressed in Down syndrome. At the elevated concentrations trisomy produces, S100B acts through the receptor for advanced glycation end-products to amplify neuroinflammation and to induce interleukin-1. The corpus's own inflammasome dissertation cites the foundational observation here — Griffin and colleagues' 1989 demonstration that brain interleukin-1 and S-100 are elevated in *both* Down syndrome and Alzheimer's disease — as an early sighting of the neuroinflammatory convergence the architecture later formalised. In the architecture's terms, S100B over-dosage supplies a chromosome-21-encoded amplifier of the IL-1 axis that the second bridge will require.

The third factor is a regulatory RNA. *MIR155HG*, the host gene of microRNA-155, lies on chromosome 21, and miR-155 is triplicated and over-expressed in Down syndrome. miR-155 is among the most consequential microglial inflammatory microRNAs known: it represses the suppressors of cytokine signalling and other brakes on the innate-immune response, biasing microglia and macrophages toward the pro-inflammatory pole, and — as recent work flagged in the corpus's external-scientist review notes — its triplication in Down syndrome dysregulates hippocampal GABAergic neurogenesis, tying it to both the microglial state of Phase II and the interneuron substrate of Phase III. A triplicated master inflammatory microRNA is a Phase II lesion at the level of the regulatory network, layered on top of the interferon-receptor dosage and the S100B dosage.

The microglial collapse, observed across the Down lifespan

The prediction the architecture makes — that a brain pre-loaded with interferon, S100B, and miR-155 dosage should show its microglial collapse early and progressively — is borne out by the neuropathology. Flores-Aguilar and colleagues traced the evolution of neuroinflammation across the Down syndrome lifespan and found microglial activation and dystrophy developing in step with, and in places ahead of, the amyloid and tau pathology, with dystrophic and activated microglial morphologies accumulating across the decades. Wilcock and Griffin had earlier framed Down syndrome's neuroinflammation as integral to its Alzheimer neuropathogenesis rather than a reaction to it. The microglial bridgehead the corpus places in the sixth and seventh decades of the sporadic disease is, in Down syndrome, a lifelong and progressive process, running from a constitutive interferon-biased baseline toward the same post-homeostatic collapse — reached, as everywhere in this dissertation, across a foreshortened span.

> *Phase II is, in the corpus, the loss of a governor that ageing eventually removes. In Down syndrome the governor is weakened from birth by a triplicated interferon-receptor cluster, an over-dosed S100B, and a triplicated inflammatory microRNA. Trisomy 21 does not wait for the microglial collapse; it is born predisposed to it.*

VII. The Second Bridge and Phase III — The Matrix Digested Early

The disease's terminus, in the corpus, is the digestion of the perineuronal net around the parvalbumin interneuron, reached across the second bridge — the Proteolytic Turn — whose three arms (the proteolytic switch, the iron-Fenton chemistry, and complement) converge on the aggrecan–brevican coat. This chapter makes the dissertation's most economical and, in one respect, its most startling claim: that three of the four molecular ingredients of the second bridge, and part of the Phase III substrate itself, are encoded on chromosome 21 and therefore dosed up in the Down brain — including, in a coincidence almost too neat to credit, the matrix-digesting enzymes that execute the turn.

The bridge's arms, pre-supplied

Recall the three arms of the Proteolytic Turn. The **first arm** is the microglial secretory switch, NLRP3 → IL-1β → MMP-9/ADAMTS, the conversion of a cytokine-secreting microglion into a matrix-digesting one. Down syndrome pre-supplies its trigger: the constitutive interferon tone of Chapter VI, the S100B-driven IL-1 induction, and the primed inflammasome that the elevated peroxide and lipid stress of Chapter IV support, together mean that the IL-1β limb of the first arm is chronically pressured in the Down brain rather than newly assembled in late life. The **second arm** is inorganic — iron-catalysed Fenton chemistry on the sulfated matrix — and Down syndrome pre-supplies its chemistry directly: *SOD1* over-dosage, as Chapter IV established, tilts the redox economy toward hydrogen peroxide, the exact substrate the Fenton reaction consumes to generate the hydroxyl radical, and the lifelong oxidative burden of the trisomic brain means the matrix is attacked across decades rather than in a terminal window. The **third arm** is complement, and complement proteins are elevated in the Down syndrome brain, deposited on and around the pathology as they are in the sporadic disease, supplying the opsonising limb the corpus's third arm requires. Three of the bridge's arms — the inflammasome trigger, the Fenton substrate, and the complement opsonins — are thus pre-pressured by chromosome-21 dosage before the bridge is ever crossed.

The aggrecanase in triplicate

The most striking single fact in this chapter concerns the enzymes that actually cut the net. The corpus names, as the proteases of the first arm, the matrix metalloproteinases and the ADAMTS aggrecanases — MMP-9, MMP-3, ADAMTS-4, and ADAMTS-5 — the last of which, ADAMTS-5, the companion genetic-architecture dissertation locates, correctly, on chromosome 21. It is not alone there: *ADAMTS1*, another aggrecanase of the same family, also sits on chromosome 21, at the same 21q21 region. The perineuronal net is an aggrecan–brevican structure; the enzymes that the second bridge recruits to digest it are aggrecanases; and two of those aggrecanases are encoded on the very chromosome that trisomy 21 triplicates. In the Down brain, the matrix-digesting enzymes of the Proteolytic Turn's first arm are dosed up by half again in every cell that makes them, from birth.

This is the point at which the reader is right to demand discipline, and the grading scale supplies it. That *ADAMTS1* and *ADAMTS5* are on chromosome 21 and are therefore over-dosed in Down syndrome is a fact of the highest certainty. That this over-dosage *contributes to perineuronal-net digestion in the Down brain* is, at present, an inference — a reasoned one, resting on the enzymes' known substrate and the corpus's own assignment of them to the Phase III executioner arm, but one not yet tested by a direct demonstration that Down syndrome brains show accelerated aggrecanase-mediated net loss. I grade the aggrecanase-dosage-to-Phase-III link at **Tier IV, conjectural**, and I flag it as the single most important experiment this dissertation proposes: to ask whether the perineuronal nets of the Down syndrome cortex are lost earlier, and whether ADAMTS-cleaved aggrecan neoepitopes accumulate faster, than the sporadic timeline predicts. If they do, chromosome 21 will have been shown to carry not only the disease's igniter but one of its executioners.

The Phase III substrate, developmentally shaped

The perineuronal net surrounds the parvalbumin interneuron, and the parvalbumin interneuron of the Down brain is not, at the moment the second bridge reaches it, the same cell as its sporadic counterpart. Two chromosome-21 genes have shaped the inhibitory system from before birth. *DYRK1A*, the tau kinase of Chapter V, is also a regulator of neuronal excitability and interneuron development, and its over-dosage — the corpus's synaptic dissertation notes the point — biases the balance toward inhibition; the excitatory–inhibitory imbalance of Down syndrome is well enough established to have motivated clinical trials of GABA-A receptor antagonists aimed at restoring the balance. *OLIG2* is the second, and it is a genuine double agent in the architecture. The corpus's genetic-architecture dissertation names *OLIG2*, on chromosome 21, as the master transcription factor of the oligodendrocyte lineage whose loss anchors the Phase II ferroptotic vulnerability of myelin. In Down syndrome, the *same* gene, triplicated, mis-specifies the production of inhibitory interneurons: Chakrabarti, Haydar, and colleagues showed that triplication of *Olig1* and *Olig2* alters the generation of GABAergic interneurons in the trisomic forebrain, over-producing certain inhibitory subtypes and disturbing the excitatory–inhibitory ratio. *OLIG2* thus loads two phases at once — the oligodendrocyte substrate of Phase II by the corpus's assignment, and the interneuron substrate of Phase III by the Down syndrome developmental literature — a single triplicated transcription factor whose dosage reaches both the myelin whose iron will feed the second bridge and the interneuron on which the bridge terminates.

The consequence is that Phase III in Down syndrome is reached across a substrate that was never normal. The parvalbumin interneuron and its net, which in the sporadic disease are a healthy structure attacked late, are in the Down brain a developmentally altered system — fewer or mis-proportioned interneurons, an E/I ratio biased since childhood, a net whose digesting enzymes are dosed up — meeting the second bridge already compromised. The terminal synaptic disintegration the corpus describes still occurs, and still presents as dementia, but it completes a collapse whose substrate trisomy 21 had been shaping from the first.

> *The corpus's second bridge is a convergence of three arms on one matrix. In Down syndrome the inflammasome trigger, the Fenton substrate, and the complement opsonins are all pre-pressured by chromosome-21 dosage — and the aggrecanases that cut the net are themselves encoded on the triplicated chromosome. The terminus of the architecture is reached across a substrate the trisomy had shaped since before birth.*

VIII. The Whole-Chromosome Ledger

The preceding four chapters are assembled here into a single ledger, so that the completeness of the pre-loading can be seen at once and, more importantly, so that the strength of each assignment can be weighed without the persuasion of prose. Each row names a chromosome-21 factor, the phase or bridge of the architecture onto which this dissertation places it, the mechanism by which its over-dosage acts there, the tier at which the assignment is graded, and the temporal flag — congenital (▲), degenerative (▼), or both — that marks when its consequence declares itself. The discipline of the ledger is the discipline of the whole dissertation: an architecture that is complete is not thereby proven, and the tiers are the record of the difference.

Chr-21 factor	Station in the architecture	Mechanism of the dosage effect	Tier	Flag
APP (via βCTF)	Phase I — endosomal QC	βCTF/C99 over-production dysregulates Rab5; enlarged early endosome in infancy, before plaque	I	▲▼
APP (via Aβ)	Phase I / Bridge 1 amyloid arm	Tripled precursor floods Aβ; striatum-first deposition; ordered amyloid→tau biomarker sequence	I	▼
SYNJ1	Phase I — endosomal/autophagic QC	PI(4,5)P_2 dysregulation; trisomy reproduces endosomal phenotype; shared AD/DS/epilepsy node	II	▲
ITSN1	Phase I — endocytic QC	Endocytic scaffold over-dosage compounds endosomal enlargement	III	▲
Mitochondrial burden (RCAN1, NRIP1, polygenic)	Phase I — bioenergetic ignition	Reduced complex I, low ATP, adaptive metabolic downregulation from fetal life	I	▲▼

Chr-21 factor	Station in the architecture	Mechanism of the dosage effect	Tier	Flag
SOD1	Phase I redox / Bridge 2 Fenton arm	Over-dosed dismutase tilts redox toward H_2O_2 — the Fenton substrate; lifelong lipid peroxidation	II	▲▼
Locus coeruleus / NGF (Iulita–Cuello)	Bridge 1 — anatomical substrate	Early aminergic/cholinergic vulnerability; NGF dysmetabolism weakens the projection	II	▼
DYRK1A	Bridge 1 tau arm / Phase III E/I	Phosphorylates tau (Thr212), primes GSK-3β, shifts 3R:4R; biases E/I toward inhibition	I	▲▼
IFNAR1/IFNAR2/IFNGR2/ IL10RB	Phase II — microglial homeostasis	Triplicated interferon-receptor cluster → constitutive interferonopathy antagonising TGF-β/SMAD homeostasis	I	▲▼
S100B	Phase II / Bridge 2 IL-1 arm	RAGE-mediated amplification of neuroinflammation; induces IL-1 (elevated in DS since 1989)	II	▲▼
miR-155 (**MIR155HG**)	Phase II — microglial state	Triplicated inflammatory microRNA represses SOCS1; biases microglia pro-inflammatory; disturbs GABAergic neurogenesis	III	▲
Complement (elevated in DS)	Bridge 2 — complement arm	C1q/C3 deposition supplies the opsonising limb of the Proteolytic Turn	III	▼
ADAMTS1 / ADAMTS5	Bridge 2 — proteolytic arm	Aggrecanases encoded on chr 21, dosed up in every cell; candidate accelerant of PNN digestion	IV	▲

Chr-21 factor	Station in the architecture	Mechanism of the dosage effect	Tier	Flag
OLIG2	Phase II oligodendrocyte / Phase III interneuron	Double agent: myelin-lineage master TF (ferroptotic substrate) and interneuron mis-specification (E/I substrate)	III	▲
DSCAM, GABA-subunit dosage	Phase III — synaptic substrate	Adhesion and inhibitory-tone dosage effects; developmental E/I imbalance underlying GABA-A trials	II	▲
BACE2	Countervailing (amyloid-lowering)	θ-secretase cleaving within Aβ; a chr-21 gene whose dosage may *oppose* amyloid — the ledger's honest exception	III	▲

Two features of the ledger deserve comment. The first is its coverage: there is no phase and no bridge of the architecture without at least one, and usually several, chromosome-21 factors assigned to it — Phase I loaded at five loci, the first bridge armed on both arms, Phase II driven by an interferon cluster and two further factors, the second bridge pre-supplied on three arms including its enzymes, Phase III's substrate shaped by two developmental genes. It is this completeness that justifies the dissertation's central image: not an extra dose of the disease's first molecule, but an extra dose at every station. The second feature is the honesty of the tiers and of the final row. The strongest assignments — the congenital endosome, the interferonopathy, the DYRK1A tau arm — are Tier I, demonstrated in human Down tissue. The weakest — the aggrecanase link — is Tier IV, an inference awaiting its experiment. And *BACE2*, the last row, is the ledger's deliberate counter-example: a chromosome-21 gene whose product cleaves within the amyloid peptide and may therefore *lower* the amyloid burden, a triplicated factor pulling against the architecture rather than with it. An honest ledger of pre-loading must record the gene that unloads, and its presence is the reason the dissertation claims that trisomy 21 shapes the disease's tempo and form, not that every chromosome-21 gene conspires in it.

IX. The Counterfactual — What Partial Trisomy Proves, and Fails to Prove

The ledger's completeness is seductive, and the discipline of this dissertation requires that it be tested against the one body of evidence that could most sharply contradict it: the partial trisomies. If sixteen chromosome-21 factors load the architecture, what is one to make of the individuals in whom only some of chromosome 21 is tripled — and, above all, of those whose triplication spares *APP*?

The evidence is unambiguous and this dissertation neither evades nor softens it. In the small number of well-documented cases of partial trisomy 21 in which the *APP* locus is present in only two copies while much of the rest of the chromosome is tripled, Alzheimer's disease does not develop: the individuals carry the intellectual disability and other features of the segmental trisomy, but they reach ages at which full trisomy 21 would guarantee dementia without the neuropathology or the clinical decline. Reciprocally, duplication of a small region containing *APP* and no other Alzheimer gene is sufficient to cause autosomal-dominant early-onset Alzheimer's disease. The two experiments bracket the causal claim from both sides: without the third *APP*, no disease, however much else is tripled; with the third *APP* and nothing else, disease. *APP* dosage is necessary, and *APP* dosage is sufficient.

A careless reader might take this to demolish the dissertation. It does not, and the reason is the distinction the grammar of Chapter III was built to hold: the difference between causing a disease and shaping it. The partial-trisomy counterfactual establishes that the non-*APP* factors of the ledger cannot, by themselves, produce Alzheimer's disease — that they are not *initiating causes*. It establishes nothing whatever about whether, in the presence of the *APP* dosage that does initiate, those factors alter the rate, the completeness, or the form of the disease that results. The counterfactual is a test of initiation, and this dissertation's claim was never initiation. Its claim is modification: that the interferon chromosome, the triplicated tau kinase, the tilted redox, the dosed-up aggrecanases, and the developmentally altered interneuron substrate together determine that the *APP*-initiated disease in a full trisomy proceeds through every phase of the architecture, in order, on a clock foreshortened to half the sporadic length.

Two further observations sharpen the point rather than blunt it. The first is that the partial trisomies sparing *APP* are exceedingly rare and phenotypically heterogeneous, and none, to my knowledge, has been characterised with the biomarker or neuropathological depth that would let one ask the modification question directly — whether, for instance, an *APP*-duplication carrier

without the rest of chromosome 21 traverses the amyloid-to-tau-to-neurodegeneration sequence at the *same* rate as a full trisomy, or more slowly. The architecture makes a specific prediction here: that the *APP*-only duplication should ignite the disease but cross the bridges and reach Phase III more slowly than full trisomy 21, because the *APP*-only brain lacks the DYRK1A tau-arming, the interferon microglial pre-load, and the aggrecanase dosage that compress the full-trisomy course. Whether the reported *APP*-duplication kindreds show a later or milder or slower disease than Down syndrome AD, matched for amyloid onset, is a question the existing literature has not framed and that this dissertation urges be asked, because it is the cleanest available test of modification as distinct from initiation.

The second observation is that the modification claim is not idle even granting *APP*'s primacy, because the sporadic disease the corpus principally addresses is not *APP*-driven at all. In late-onset sporadic Alzheimer's disease there is no *APP* triplication; the disease is ignited by the slow bioenergetic failure the corpus places in Phase I and modified by the common-variant genetics of the microglion, the endosome, and the matrix. Down syndrome's value to that disease lies precisely in the non-*APP* factors — in what a triplicated interferon-receptor cluster does to the microglial state, what a triplicated tau kinase does to the tangle, what an over-dosed aggrecanase might do to the net — because those are the factors that model, in an accelerated and genetically clean form, the very steps that common-variant risk tunes in everyone else. The *APP* dosage makes Down syndrome a model of the amyloid arm; the rest of the chromosome makes it a model of the architecture.

> *The counterfactual keeps APP necessary and keeps it sufficient. It leaves entirely open — and this dissertation claims — that the rest of the chromosome sets the tempo and completes the form. Necessity of the igniter is not irrelevance of the fuel.*

X. Two Diseases in One Brain — The Developmental Confound

Every chapter so far has carried, in its temporal flags, a difficulty that must now be met head-on, because it is at once the deepest objection to the dissertation and, correctly understood, the source of its unique power. Trisomy 21 is present from conception. The brain it builds is not a normal brain that later degenerates; it is a differently constructed brain, and much of what the architecture reads as an accelerated *degeneration* is entangled with a lifelong *developmental* difference. The congenital flag (▲) that recurs down the ledger is the mark of this entanglement, and honesty requires that it be named as a confound before it can be claimed as a strength.

The confound is real and it is specific. The enlarged endosome of Chapter IV is present in infancy — is it the first station of a degeneration, or a developmental feature of the trisomic neuron that only later intersects the disease? The excitatory–inhibitory imbalance of Chapter VII, shaped by *DYRK1A* and *OLIG2*, is present in childhood and underlies the intellectual disability itself — is the E/I collapse of Phase III in Down syndrome the terminus of a degenerative bridge, or the worsening of a developmental abnormality that was there from the start? The interferon tone of Chapter VI is constitutive and lifelong — does it drive an age-dependent microglial collapse, or does it simply hold the microglion in a chronically altered state that is not, in the corpus's sense, a *collapse* at all but a different steady state? These are not rhetorical questions. They are the questions that separate a genuine compression of the architecture from a coincidence in which a developmentally atypical brain happens to share molecular features with a degenerating one.

The intellectual-disability baseline compounds the problem at the level of measurement. The corpus's architecture is, in its final phase, a theory of cognitive decline, and cognitive decline in Down syndrome must be measured against a baseline of pre-existing intellectual disability that varies widely between individuals and that the standard instruments of dementia assessment were not built to accommodate. The clinical staging that is possible in sporadic and autosomal-dominant disease — the careful mapping of biomarker change onto cognitive change — is harder in Down syndrome, and the field has had to build dedicated instruments and cohorts (the adult Down syndrome cohorts, the dedicated biomarker studies) precisely to see the degenerative signal through the developmental baseline. A dissertation that claimed to read the architecture's Phase III cleanly off the Down syndrome cognitive trajectory, without this caveat, would be claiming more than the data allow.

And yet the confound, correctly handled, is the dissertation's strength rather than its defeat, for three reasons. The first is that the degenerative signal in Down syndrome *can* be separated from the developmental baseline, and has been: the amyloid, tau, and neurodegeneration biomarkers change across adult life in a stereotyped, age-dependent sequence in Down syndrome — amyloid rising from the third decade, tau and neurodegeneration following, cognition declining last — and this *change over time*, superimposed on the stable developmental baseline, is unmistakably a degeneration and not a static difference. Fortea and colleagues' demonstration that the biomarker trajectory of Down syndrome AD recapitulates the ordered sequence of autosomal-dominant AD is the decisive evidence that what happens in the Down brain after the third decade is the same disease, in the same order, and not merely a developmental phenotype. The architecture is read off the *slope*, not the *intercept*.

The second reason is that the developmental pre-loading is not a confound to the modification claim but its very mechanism. This dissertation never claimed that the congenital lesions *are* the degeneration; it claimed that they *shape* it — that a brain built with an enlarged endosome, a tilted redox, a constitutive interferon tone, a triplicated tau kinase, and an E/I-biased interneuron substrate is a brain in which the *APP*-ignited degeneration, when it comes, proceeds faster and more completely because it proceeds across a pre-loaded substrate. That the pre-loading is developmental is not an embarrassment to this claim; it is the claim. The congenital flag marks exactly the factors that make the compression a mechanism rather than a metaphor.

The third reason is the most important, and it reframes the whole difficulty. The entanglement of development and degeneration in Down syndrome is not unique to Down syndrome; it is a sharpened, visible instance of a truth the corpus's architecture already holds for everyone. The sporadic disease's Phase I is itself the intersection of ageing with a lifetime's accumulated substrate — the endosomal, mitochondrial, and matrix set-points that a person's common-variant genetics established long before the disease began. Down syndrome makes visible, because it makes congenital and extreme, the general fact that the degeneration is always run across a substrate that development and inheritance had already shaped. The Down brain is not a special case in which a developmental confound corrupts the architecture. It is the general case in which the substrate-dependence of the architecture is written large enough to read.

> *Trisomy 21 builds a different brain and then degenerates it, and the two cannot be fully disentangled. But the degeneration is read off the slope, not the baseline; the developmental pre-loading is the modification mechanism, not a confound to it; and the entanglement it makes visible is one the architecture holds for every brain. The confound, handled honestly, is the evidence.*

XI. The Compressed Clock as a Test-Bed

The deepest reason to read Down syndrome against the corpus's architecture is not to explain Down syndrome. It is that Down syndrome, alone among the disease's forms, runs the entire architecture on a clock short enough to be watched from end to end, with the initiating cause fixed and known, and therefore offers the fastest and cleanest available test of whether the architecture — and above all its two bridges — is real. This chapter states what the architecture predicts about the Down syndrome trajectory, and what observations would confirm or falsify it.

The first and most general prediction is one Down syndrome has already largely confirmed. If the architecture's phases are truly ordered in time — bioenergetic ignition, then microglial bridgehead, then synaptic disintegration — then a population that pre-loads all three should traverse them *in that order*, not simultaneously. The biomarker evidence supports this: in Down syndrome the amyloid markers change first, from the third decade; tau and the markers of neurodegeneration follow; and cognitive decline comes last, typically in the fifth and sixth decades. The disease does not arrive all at once despite the substrate being pre-loaded all at once, which is itself a non-trivial confirmation that the phases are sequenced by something other than the mere availability of their substrates — sequenced, the architecture would say, by the bridges that must be crossed between them.

The bridges are where Down syndrome's evidentiary value is highest, because they are the architecture's most specific and most falsifiable claims, and because the compressed clock makes their ordering observable. The first bridge predicts that noradrenergic locus-coeruleus dysfunction and the withdrawal of microglial restraint should *precede and enable* the hippocampal microglial collapse, and that tau seeding should follow the coeruleus's failure along its projections. In Down syndrome this predicts a specific and testable sequence: measurable locus-coeruleus integrity loss (now accessible with dedicated MRI sequences) should precede the hippocampal microglial-activation signal (accessible with translocator-protein PET), which should in turn precede the perineuronal-net loss. A cross-sectional cohort of adults with Down syndrome spanning the third through sixth decades, imaged for coeruleus integrity, microglial activation, and — the missing modality — perineuronal-net integrity, would let this ordering be read directly. If the coeruleus signal did *not* precede the microglial signal in Down syndrome, the first bridge would be in serious difficulty. The compression makes the whole sequence fit inside a single cohort's age range.

The second bridge makes the sharpest testable prediction of all, and it is the experiment Chapter VII flagged. The Proteolytic Turn holds that perineuronal-net digestion is executed by aggrecanases driven by the microglial secretory switch, catalysed by iron-Fenton chemistry, and

marked by complement. Down syndrome pre-supplies the redox substrate (SOD1), the inflammasome trigger (interferon, S100B), the complement, and — uniquely — the aggrecanases themselves (ADAMTS1/5 on chromosome 21). The architecture therefore predicts that perineuronal-net loss in Down syndrome should be *earlier and faster* than the sporadic timeline, and specifically that ADAMTS-cleaved aggrecan neoepitopes should accumulate ahead of the amyloid-adjusted schedule. This is directly measurable in post-mortem Down syndrome tissue and in cerebrospinal fluid, and it has, to my knowledge, not been looked for. A finding of accelerated, aggrecanase-signature net loss in the Down brain would be strong confirmation both of the second bridge and of this dissertation's most specific claim; a finding that net loss in Down syndrome tracks the amyloid timeline no faster than in sporadic disease, despite the tripled aggrecanases, would falsify the aggrecanase-dosage claim and force its Tier IV grade down to nothing. Either result advances the architecture. That is what a test-bed is for.

There is a further, subtler use of the compressed clock, concerning the interferon mechanism of Chapter VI. Down syndrome is the only common human condition that pre-installs a chronic interferon tone from birth, and it therefore offers a natural test of whether interferon signalling is *causal* for the microglial collapse the corpus places at Phase II, or merely correlated with it. The test is pharmacological and it is already partly underway: JAK inhibitors, which block interferon signalling, are in trial in Down syndrome for the syndrome's autoimmune and inflammatory features. The architecture makes a prediction those trials could, with the right endpoints, address — that sustained interferon blockade should shift the microglial signature back toward homeostasis and, over a long enough horizon, slow the tau and neurodegeneration markers that Phase II feeds. A JAK-inhibitor trial in Down syndrome with microglial-PET and tau-biomarker endpoints would be, in effect, a test of the corpus's Phase II mechanism run in the one population where the phase's driver is genetically fixed and constitutive. No such clean test of the interferon–microglia–tau axis is available in the sporadic disease.

Down syndrome is the architecture's fastest read-out. It has already confirmed the ordering of the phases; it can, with imaging cohorts and post-mortem aggrecan neoepitope measurement and interferon-blockade trials, test each of the two bridges directly. The compression that makes the disease tragic in Down syndrome is what makes it, for the architecture, uniquely legible.

XII. Phenocopying the Fortunate in Reverse — Therapeutic Corollaries

The companion dissertation on the protective genome closed on the ambition to *phenocopy the fortunate* — to install by drug the defences that lucky alleles confer by birth. Down syndrome poses the inverse and equally instructive problem: how to *un-load*, one phase at a time, an architecture that a chromosome has pre-loaded at every station. The therapeutic value of the exercise is not confined to Down syndrome. Because each intervention targets a specific phase of an architecture the sporadic disease shares, and because the Down clock reads out fast, therapies tested in Down syndrome are tests of phase-targeting for the whole field. This chapter maps the interventions onto the phases and states the phase-and-window logic that should govern them.

Phase I — the substrate and the mitochondrion. The amyloid arm is the most advanced. Anti-amyloid immunotherapies that succeeded in sporadic disease are now being extended to Down syndrome, and the architecture's logic makes Down syndrome a decisive test of them: if lowering amyloid in a population whose amyloid is *APP*-dosage-driven from birth alters the downstream tau and neurodegeneration trajectory, the amyloid arm's causal position is confirmed; if it does not, the same limits that the anti-amyloid antibodies met in sporadic disease will have been met in their cleanest test case. Upstream of the peptide, the endosomal and mitochondrial lesions of Chapter IV suggest phase-appropriate targets the amyloid antibodies do not touch: β-secretase modulation to lower the βCTF that drives the congenital endosome (with the caution the corpus's own BACE cautionary history demands), and the NAD+-restoring and mitochondrial-biogenesis strategies the corpus develops elsewhere, which in Down syndrome would address a bioenergetic deficit present from fetal life. The window for these is, in principle, the widest available in all of Alzheimer's disease — the Phase I lesion in Down syndrome is present in childhood, decades before dementia.

The first bridge — the tau kinase. Down syndrome supplies a drug target the sporadic disease does not present so cleanly: DYRK1A. Because the triplicated kinase arms the tau seed of the first bridge, DYRK1A inhibition is a phase-specific, mechanism-specific intervention — an attempt to disarm the tau arm of the bridge at its genetic source. DYRK1A inhibitors (the harmine-derived and leucettine chemotypes among them) are in development, and Down syndrome is their natural first population, both because the target is over-dosed there and because the architecture predicts a specific benefit: a slowing of tau hyperphosphorylation and therefore of the first bridge's tau-seeding arm. A DYRK1A-inhibitor trial in Down syndrome with tau-biomarker endpoints would test, in one experiment, both a therapy and the bridge's tau mechanism.

Phase II — the interferon. The interferon chromosome makes Down syndrome the one population in which Phase II has a genetically fixed, pharmacologically addressable driver. JAK inhibition, already in trial for the syndrome's inflammatory features, is — read through the architecture — a Phase II therapy: an attempt to lift the constitutive interferon tone off the microglion and let it return toward homeostasis. The phase-and-window logic here is particular and important: because the interferon tone is lifelong and the microglial bias it produces is developmental as well as degenerative, the question of *when* to intervene is unusually live — early and sustained interferon modulation might prevent the microglial bridgehead from ever fully forming, whereas late intervention might find the collapse already self-sustaining. Down syndrome is where that timing question can be asked with a fixed driver.

The second bridge and Phase III — the matrix and the interneuron. The most speculative and, if the Tier IV claim of Chapter VII holds, the most striking therapeutic corollary concerns the perineuronal net. If the tripled aggrecanases of chromosome 21 do accelerate net digestion, then aggrecanase inhibition, or more generally the protection of the perineuronal net, becomes a Phase III strategy with a specific rationale in Down syndrome that it lacks elsewhere. And the E/I imbalance that *DYRK1A* and *OLIG2* impose on the interneuron substrate connects to an existing therapeutic history: the GABA-A receptor modulators trialled in Down syndrome for cognition were, in the architecture's terms, attempts to correct the excitatory–inhibitory balance that Phase III destroys — trialled against the developmental baseline, but pointing at the same substrate the degeneration attacks. The corpus's caution applies throughout: the perineuronal net and the E/I balance are structures the healthy brain needs, and the lesson of the sporadic disease's therapeutic failures is that the phases must be un-loaded with the calibration the protective alleles model, not the wholesale subtraction the failed programmes attempted.

The unifying therapeutic proposition is this. Down syndrome is the one Alzheimer population in which every phase of the architecture has a genetically defined, over-dosed driver, and in which the clock is short enough to read a therapy's effect within a trial's horizon. It is therefore not merely a population to be treated but the field's fastest phase-by-phase test-bed: the place where an anti-amyloid antibody tests the amyloid arm, a DYRK1A inhibitor tests the tau arm of the first bridge, a JAK inhibitor tests the interferon driver of Phase II, and an aggrecanase or net-protective strategy could test the second bridge — each in a population where the target is fixed by the trisomy and the read-out arrives in decades rather than a lifetime.

> *The protective genome taught us to phenocopy the fortunate. Down syndrome teaches the inverse discipline — to un-load a pre-loaded architecture phase by phase — and, because its clock runs fast and its drivers are genetically fixed, to test each phase's therapy faster than any other form of the disease allows.*

XIII. Conclusion — The Chromosome as Curriculum

The received account of Down syndrome and Alzheimer's disease is a single true sentence about a single gene: three copies of *APP*, more amyloid, earlier disease. This dissertation has not contradicted that sentence — the counterfactual of partial trisomy keeps *APP* necessary and keeps it sufficient — but it has argued that the sentence, taken as the whole story, mistakes an igniter for a building. When the gene content of chromosome 21 is laid over the corpus's three-phase Temporal Architecture, what emerges is not an extra dose of the disease's first molecule but an extra dose at every station of the disease: the congenital endosome and the fetal mitochondrial deficit of Phase I; the *APP* and *DYRK1A* dual arming of the first bridge; the triplicated interferon-receptor cluster that pre-commits the microglial collapse of Phase II; the *SOD1* redox substrate, the primed inflammasome, the complement, and the chromosome-encoded aggrecanases of the second bridge; and the *DYRK1A*- and *OLIG2*-shaped interneuron substrate onto which Phase III terminates. Down syndrome is not early Alzheimer's disease. It is the whole architecture, pre-installed and run fast.

The image the dissertation has reached for is the chromosome as *curriculum*. The sporadic disease teaches its syllabus slowly, one phase per two decades, the lessons arriving in an order set by bridges the brain must build as it goes. Trisomy 21 enrols the student in every course at once, from birth, and compresses the degree into forty years. That is a tragedy for the person, and this dissertation has tried never to lose sight of it beneath the architecture. But it is, for the science, an extraordinary gift: a population in whom the disease's initiating cause is fixed and known, in whom every downstream phase is genetically pre-loaded and therefore genetically legible, and in whom the clock is short enough to watch the whole architecture unfold from ignition to synaptic disintegration inside a single research cohort. The corpus built its architecture from the sporadic disease and the autosomal-dominant kindreds. Down syndrome is where that architecture can be read fastest, tested most sharply at its bridges, and — if the therapies of Chapter XII are pursued in the phase-by-phase spirit the compression invites — un-loaded most instructively.

Two disciplines have governed the argument and should govern its reception. The first is the strength-graded ledger, which insists that an architecture's completeness is not its proof: the congenital endosome and the interferonopathy are Tier I, demonstrated in human tissue, while the aggrecanase-dosage claim that would most vividly complete the picture is Tier IV, an inference still owed its experiment. The second is the honest naming of the developmental confound, which is not a flaw in the reading but the mechanism of it — trisomy 21 builds a different brain and then degenerates it, and the pre-loading that shapes the degeneration is precisely the developmental

construction the confound names. Held to both disciplines, the thesis is not that chromosome 21 conspires at every step to cause the dementia; the honest exception of *BACE2*, the gene that unloads, forbids so tidy a story. The thesis is narrower and, I think, more durable: that a single trisomy pre-loads the substrate of every phase and both bridges of the Alzheimer architecture, sets the tempo of the *APP*-ignited disease that crosses them, and thereby offers the field its one chance to watch the entire structure of the disease compressed into a legible span. The disease has been read, in Down syndrome, as the shadow of one gene. It is better read as the whole architecture, taught fast, by a chromosome.

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