THE PEACEKEEPER'S PARADOX

Regulatory T Cells in Alzheimer's Disease — Whether the Suppression of Immunity Shelters the Brain or Starves It of Repair

The Suppressor Cell · The Two Verdicts · The Choroid-Plexus Gate
The IL-2 Lever · The Timing Problem

A Dissertation Submitted in Partial Fulfillment of the Requirements for the Degree of Doctor of Philosophy in Neuroscience

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An adaptive-immune companion to The Temporal Architecture of Collapse — turning from the brain's innate immunity to the cell that governs it: the Foxp3+ regulatory T cell, the immune system's brake, cast by one camp as the brain's guardian and by another as its saboteur, and graded here as neither — a rheostat whose setting decides whether suppression shelters the brain or starves it of repair.

"Ask whether the fire should be put out or the repair crew let in, and you have asked the whole question. The regulatory T cell answers both at once — which is why one laboratory calls it the guardian of the brain, another the saboteur, and both are holding a true half of the same cell."

— ONS Methodology Working Notes, 2026

For the immunologists who insisted that the brain has an adaptive immune life — and for the two camps who ran the same experiment, drew opposite conclusions, and were each partly right.

THE COLLAPSE TRILOGY IMMUNE COMPANION

I. Convergent Synaptic Collapse

II. Homeostatic Microglial Collapse

III. Bioenergetic Collapse

— The Temporal Architecture of Collapse —

Immune line: The Sensor and the Speck (NLRP inflammasome) · The Tide-Gate (choroid plexus)

Interfaces: The Vagal · The Coerulean · The Pineal · The Microbial Prologue

The Peacekeeper's Paradox — this volume

This volume is the adaptive-immune companion the innate-immune theses presuppose but never name. Where *Homeostatic Microglial Collapse* and *The Sensor and the Speck* follow the brain's resident innate immunity, and *The Tide-Gate* follows the border organ through which the periphery reaches the brain, the present volume turns to the master cell that governs the adaptive response itself — the Foxp3+ regulatory T cell. It sets the field's two opposing verdicts against each other, reconciles them through timing, compartment, and stage, and grades, connection by connection, whether the peacekeeper shelters the brain or starves it of repair.

Contents

Abstract

There is a cell whose whole occupation is to say *no* — to stand down an immune response that has done its work or should never have begun, to enforce the body's tolerance of itself, to keep the peace. It is the regulatory T cell, marked by the transcription factor Foxp3, and it is among the most consequential single cell types the immune system possesses: without it, the body turns on its own tissues and dies of autoimmunity in weeks. This dissertation asks what such a cell does in Alzheimer's disease — and finds, at the centre of the question, a paradox sharp enough to have split the field into two camps that ran the same experiment and drew opposite conclusions.

The paradox is this. Alzheimer's disease involves chronic neuroinflammation, and a peacekeeper that suppresses inflammation might therefore be expected to help. But the disease *also* appears to need a reparative immune response it cannot mount — microglia that should cluster on plaques and clear them, myeloid cells that should be recruited from the blood to sites of damage — and a peacekeeper that suppresses *that* response would hurt. Whether the regulatory T cell is guardian or saboteur thus depends on a prior question the field has not settled: is the immune response in Alzheimer's disease, on the whole, a fire to be put out or a repair crew to be let in? One influential body of work, from the Schwartz laboratory, answered *repair crew*, showed that transiently depleting regulatory T cells opens the choroid-plexus gateway and clears cerebral amyloid, and concluded that the peacekeeper stands in the way of healing. An equally serious body of work, from the Dorothée laboratory and others, answered *fire*, showed that depleting regulatory T cells *accelerates* cognitive decline while amplifying them with low-dose interleukin-2 slows it, and concluded that the peacekeeper protects. Both results are real. Both have been published in the field's best journals. They cannot both be the whole truth.

This dissertation does not pretend to dissolve the paradox by fiat; it grades it. We trace the regulatory T cell through what it is, what each camp actually demonstrated, and how the two verdicts can be reconciled — largely through *timing*, *compartment*, and *disease stage*, the variables that differ across the studies and that turn a protective cell into a permissive one and back. We weigh a human literature that is frankly inconsistent, disagreeing even on whether regulatory T cells are more or fewer in the Alzheimer patient's blood, while converging, tentatively, on the more useful claim that their *suppressive function* is impaired in established disease. And we follow the one thread that has travelled furthest toward the clinic: the amplification of regulatory T cells by low-dose interleukin-2, protective across several independent mouse studies and, as of a 2025 phase-2a trial, safe and cautiously promising in human patients. Our verdict is neither camp's. The regulatory T cell in Alzheimer's disease is best supported not as a simple guardian nor a simple saboteur but as a *context-dependent rheostat* whose net effect, across the preponderance of causal evidence, tilts protective — but whose valence genuinely inverts with the timing and compartment of its action, so that the same intervention can heal or harm depending on when, where, and how long it is applied. That is a more disciplined claim than either verdict alone,

and it is the one the evidence will bear.

I. The Cell That Says No

Every account of Alzheimer's disease that invokes *inflammation* — and nearly all of them now do — makes an implicit assumption about which way the immune system should be pushed. When the field speaks of neuroinflammation as a driver of the disease, of activated microglia strangling synapses, of complement tagging healthy connections for destruction, of a chronic inflammatory tone that accelerates neurodegeneration, the therapeutic implication is that the immune response should be *dampened*. And yet the same field, in the same decade, discovered that the brain's clearance of amyloid depends on immune cells doing their job — on microglia that surround and compact plaques, on monocyte-derived macrophages recruited from the periphery to sites of pathology — and drew the opposite implication: that the immune response should be *supported*. The two implications point in opposite directions, and the tension between them is not a detail. It is the central unresolved question in the immunology of the disease, and it is nowhere posed more sharply than by the cell this dissertation takes as its subject.

The regulatory T cell is the immune system's brake. It is a specialized subset of CD4-positive T lymphocytes, defined by expression of the master transcription factor Foxp3, whose function is not to attack but to *restrain* — to suppress the activation and proliferation of other immune cells, to resolve inflammation once a threat has passed, and, above all, to enforce the body's tolerance of its own tissues. The stakes of this function are not subtle. Human beings and mice that lack functional Foxp3 develop a catastrophic, multi-organ autoimmune syndrome — in humans the fatal disorder IPEX — in which the immune system, released from regulatory restraint, destroys the body's own tissues. The regulatory T cell is, in the most literal sense, what stands between a functioning immune system and self-destruction. It is the peacekeeper, and its peace is not optional.

To ask what such a cell does in Alzheimer's disease is therefore to ask a question whose answer is overdetermined in advance by one's view of the disease. If Alzheimer's is fundamentally a disease of *excess* immune activation — of a brain inflamed to death — then the peacekeeper is a hero, and anything that strengthens it should help. If Alzheimer's is fundamentally a disease of *failed* immune repair — of a brain that cannot summon the cellular help it needs to clear its own waste — then the peacekeeper is an obstacle, and anything that weakens it should help. The literature contains forceful advocates of both positions, each armed with genuine experimental data, and the resulting disagreement is not a matter of one side being sloppy. It is a matter of a cell that does two things at once in a disease that has two faces, and the task of this dissertation is to hold both faces in view without collapsing prematurely into either.

That discipline is the whole point. It would be easy to write a triumphant paper arguing that regulatory T cells protect the brain and that low-dose interleukin-2 is the coming therapy — the evidence for that story is real and, in places, strong. It would be nearly as easy to write the mirror-image paper, arguing that regulatory T cells throttle the brain's reparative immunity and that breaking their tolerance clears amyloid — and that story, too, has real evidence behind it. What is hard, and what the subject demands, is to write the paper that grades both, locates the conditions under which each is true, and states honestly how much of the resulting picture is settled and how much remains a genuine open question at the frontier of neuroimmunology. That is the paper attempted here.

II. What a Regulatory T Cell Is

Before it can be a hero or a villain, the regulatory T cell must be understood as a mechanism, because the whole argument turns on *how* it suppresses and *where*. The modern account, consolidated by Sakaguchi and others over three decades, is of a distinct T-cell lineage whose defining feature is the transcription factor Foxp3 — a molecular switch so central that its forced expression can confer suppressive function on an ordinary T cell, and its loss abolishes the lineage entirely. Regulatory T cells arise by two routes: the majority are generated in the thymus, selected on self-antigens to become a standing, self-tolerant regulatory population; a second population is *induced* in the peripheral tissues from naïve CD4 T cells under the influence of the cytokine transforming growth factor-β and other signals, generated on demand at sites of ongoing immune activity. Both express Foxp3; both suppress; and the distinction between them will matter later, because a disease that alters the peripheral induction of regulatory T cells is doing something different from a disease that alters the standing thymic pool.

How a regulatory T cell suppresses is not one mechanism but a repertoire, and the plurality is itself important, because it means the cell can act at a distance or by contact, on immune cells or on tissue, and can therefore fail — or be enhanced — in more than one way. The best-characterized mechanisms are these. First, *cytokine-mediated suppression*: regulatory T cells secrete the anti-inflammatory cytokines interleukin-10, transforming growth factor-β, and interleukin-35, which dampen the activation of effector T cells, macrophages, and microglia. Second, *contact-dependent inhibition*: regulatory T cells constitutively express the surface molecule CTLA-4, which strips the co-stimulatory ligands CD80 and CD86 from antigen-presenting cells, denying effector T cells the second signal they need to activate. Third, *metabolic disruption*: regulatory T cells express the ectoenzymes CD39 and CD73, which together degrade the pro-inflammatory signal ATP into immunosuppressive adenosine, and they act as a *sink* for interleukin-2, consuming through their

high-affinity receptor the very growth factor that effector T cells depend upon — a mechanism that will prove central to the therapeutics of this dissertation. Fourth, and increasingly appreciated, *direct tissue support*: regulatory T cells resident in non-lymphoid tissues secrete repair factors, most strikingly the epidermal-growth-factor-family ligand amphiregulin, acting not on immune cells at all but on the parenchyma itself.

That last mode deserves emphasis, because it is the one most easily forgotten when regulatory T cells are cast as mere suppressors. Over the past decade it has become clear that regulatory T cells take up residence in specific tissues — visceral fat, skeletal muscle, injured organs — and there acquire specialized, tissue-adapted programs that serve homeostasis and repair rather than immune suppression narrowly construed. The demonstration that most directly concerns the brain came from Ito and colleagues, who showed that after ischaemic stroke, regulatory T cells accumulate in the mouse brain, acquire a distinctive program including expression of the serotonin receptor, and *potentiate neurological recovery* — not by suppressing an immune response but by producing amphiregulin, which restrains the neurotoxic reactive astrogliosis that otherwise worsens injury. A brain regulatory T cell, on this account, is not simply a brake on inflammation; it is a source of trophic and reparative signals directed at the nervous tissue itself. If such cells operate in Alzheimer's disease as they do after stroke, the peacekeeper is also, in part, a repair worker — and the guardian reading gains a mechanism that has nothing to do with putting out a fire.

Two properties of regulatory T cells complete the picture and both bear on aging. The first is that regulatory T cells *accumulate with age*: the frequency of Foxp3-positive regulatory T cells in the blood rises across the human lifespan, part of the broad remodelling of immunity that accompanies senescence. The second is that regulatory T cell *function* — the efficiency of suppression per cell — is separable from frequency and can move independently of it, so that an aged or diseased individual may have more regulatory T cells that each suppress less, or fewer that each suppress more. This separation of number from function is not a technicality. It is, as we shall see, the single most important reason the human data in Alzheimer's disease appear to contradict one another, and any honest reading of that data must keep frequency and function apart.

III. The Paradox in Brief

Before defending it in detail, the argument is worth seeing whole. Read as a question about the direction the immune system should be pushed, the regulatory T cell in Alzheimer's disease presents not one thesis but a confrontation between two, each supported by causal experiments in animals, and a third position that reconciles them. It is useful to state all three at the outset, with their grades,

because the shape of the disagreement is the substance of the subject.

The prosecution — the peacekeeper as saboteur. *The systemic-immunosuppression reading.* On this account, chronic systemic immunosuppression — to which the standing population of regulatory T cells contributes — prevents the brain from recruiting the reparative myeloid cells it needs to clear amyloid. Transiently *lowering* regulatory T cell activity releases that brake, opens the choroid-plexus gateway through which immune cells enter the brain, and permits an influx of amyloid-clearing macrophages, with resulting plaque clearance and cognitive improvement. *Evidential grade: real but narrow. The founding experiments are causal and elegant, but confined largely to one laboratory and one aggressive amyloid model, and the flagship therapeutic corollary — PD-1 checkpoint blockade — failed a rigorous multi-laboratory replication.*

The defense — the peacekeeper as guardian. *The neuroinflammation-restraint-and-repair reading.* On this account, regulatory T cells protect the brain by restraining the chronic, toxic neuroinflammation of the disease and by supporting the *beneficial* arm of microglial function. *Depleting* them accelerates cognitive decline and reduces the recruitment of microglia to plaques; *amplifying* them, most practically with low-dose interleukin-2, increases plaque-associated microglia, reduces amyloid, rescues synapses, and restores memory. *Evidential grade: moderate-to-strong. The direction is reproduced across several independent laboratories and multiple mouse models, is mechanistically coherent, and now has a first, cautiously positive human trial behind it.*

The reconciliation — the peacekeeper as rheostat. *The timing-and-compartment reading.* On this account, both camps are partly right because they manipulated the system at different times, to different depths, in different compartments, and in different models. A *transient, systemic* dip in regulatory T cell tone may trigger a rebound recruitment of reparative cells to the brain (the prosecution's result), while *sustained loss* of regulatory function removes a genuine protection and worsens disease (the defense's result), and *amplification* strengthens that protection. The regulatory T cell is neither purely for nor against the brain; it is a control knob whose optimal setting is neither zero nor maximum, and whose effect depends on the state of the system when it is turned. *Evidential grade: this is the interpretation this dissertation defends, offered as the most parsimonious account of the whole dataset rather than as a separately proven claim.*

The confrontation has one property worth naming in advance, because it governs everything that follows. The disagreement between prosecution and defense is *not*, at bottom, a disagreement about regulatory T cells. It is a disagreement about Alzheimer's disease — specifically, about whether the immune response the disease provokes is, on net, harmful or reparative. The regulatory T cell is simply the instrument through which that deeper question is being asked, which is why grading its role honestly requires grading, alongside it, how much we actually know about what the brain's immune response in Alzheimer's disease is *for*.

IV. The Case for the Prosecution — The Peacekeeper as Saboteur

The most provocative claim in this literature is that regulatory T cells make Alzheimer's disease worse, and that transiently removing them makes it better. The claim is provocative precisely because it runs against the intuitive reading — that suppressing inflammation should help a disease of inflammation — and its authors, principally Michal Schwartz and colleagues at the Weizmann Institute, built it deliberately as a challenge to that intuition. Their argument begins not with regulatory T cells at all but with a reframing of the immune system's relationship to the diseased brain: that the failure in Alzheimer's disease is not too much immune activity but too little of the *right* kind — a deficit of the reparative, myeloid-cell-mediated response that the brain needs to clear amyloid and that chronic systemic immunosuppression prevents it from mounting.

The founding experiment appeared in 2015. Working in the 5XFAD mouse, an aggressive model that deposits amyloid early and heavily, Baruch and colleagues showed that *transient depletion* of Foxp3-positive regulatory T cells — or transient pharmacological inhibition of their activity — was followed by clearance of amyloid-β plaques, mitigation of the neuroinflammatory response, and reversal of cognitive decline. Crucially, they traced a mechanism through the border organ this series has examined elsewhere: transient regulatory T cell depletion acted on the brain's choroid plexus, the selective gateway for immune-cell trafficking into the central nervous system, and was associated with the subsequent recruitment of immunoregulatory cells — monocyte-derived macrophages, and, notably, regulatory T cells themselves — to the cerebral sites of plaque pathology. The interpretation was that systemic immunosuppression, maintained in part by regulatory T cells, holds the choroid-plexus gate shut; that briefly lifting that suppression opens the gate; and that through the open gate flows the reparative myeloid response the brain has been unable to summon.

The mechanism is worth pausing on, because it is more subtle than the slogan "deplete Tregs to clear amyloid" suggests, and the subtlety will matter for the reconciliation. Note that in Baruch's own account, the cells recruited to the plaques *after* transient depletion include regulatory T cells — the peacekeeper returns, in the brain, as part of the reparative wave. What is being manipulated is not the mere presence of regulatory T cells but the *systemic tone* of immunosuppression at a particular moment, and the benefit may depend as much on the rebound that follows the dip as on the dip itself. This is not how the result is usually summarized, but it is what the data show, and it is the seam along which the two camps can eventually be sewn together.

The prosecution's second and more consequential paper extended the logic from regulatory T cells to the molecular brake that helps define them. In 2016, Baruch and colleagues reported that blockade of the PD-1 immune checkpoint — the inhibitory receptor whose engagement exhausts T cells and whose blockade, in oncology, unleashes anti-tumour immunity — evoked an interferon-γ-dependent systemic immune response, drove recruitment of monocyte-derived macrophages to the brain, cleared cerebral amyloid, and improved memory in Alzheimer mouse models, with the caveat that repeated treatment sessions were required to sustain the benefit. The arc was elegant and, for a field starved of mechanistically novel therapies, electrifying: rejuvenate the exhausted peripheral immune system, break the tolerance that holds the brain's gate shut, and let reparative immunity in. Checkpoint blockade, the tool that had transformed cancer therapy, might transform Alzheimer's disease.

It did not survive contact with replication. In 2018, Latta-Mahieu and colleagues — a consortium spanning three pharmaceutical companies — attempted to reproduce the anti-PD-1 benefit across a range of amyloid transgenic models, using the same anti-PD-1 isotype and two mouse-chimeric variants to control for the possibility that the original result depended on an immune reaction to a xenogeneic antibody. Although PD-1 blockade did stimulate systemic activation of the peripheral immune system, monocyte-derived macrophage infiltration into the brain was *not* detected, and the progression of brain amyloid pathology was *not* altered. Negative results were obtained in additional models at additional institutions. The authors concluded, with unusual bluntness, that inhibition of PD-1 signalling by itself is not sufficient to reduce amyloid pathology, and that animal-model data did not support further clinical evaluation of the approach. This is not a minor footnote. It is a multi-laboratory, industrial-scale failure to replicate the prosecution's flagship therapeutic claim, and it must weigh heavily in any honest grading.

Where, then, does the prosecution stand? Its foundational observation — that transient manipulation of systemic immunosuppression can, in an aggressive amyloid model, open the choroid-plexus gate and recruit reparative myeloid cells with benefit to pathology and cognition — is a real and causally supported result, and it introduced a genuinely important reframing of immune failure in the disease. But it is narrow: concentrated in one laboratory, leaning heavily on the 5XFAD model, and crowned by a therapeutic corollary that a rigorous replication effort could not confirm. The prosecution has established that the immune response in Alzheimer's disease has a reparative arm worth recruiting; it has not established that regulatory T cells are, on balance, the enemy of that recruitment. As we turn to the defense, the evidence will pull the other way.

V. The Case for the Defense The Peacekeeper as Guardian

Against the prosecution stands a body of work, developed principally by Guillaume Dorothée and colleagues in Paris and corroborated by several independent groups, that reaches the opposite conclusion by, in part, the opposite experiment. Where the prosecution transiently depleted regulatory T cells and found benefit, the defense depleted them and found *harm*; where the prosecution broke tolerance, the defense *amplified* it and found benefit. The symmetry is striking, and the fact that careful investigators manipulating the same cell type reached opposite conclusions is the empirical core of the paradox.

The defense's central paper appeared in 2016, the same year as the prosecution's PD-1 report, in the journal *Brain*. Dansokho and colleagues studied spontaneous disease progression in the APPPS1 mouse — a slower amyloid model than 5XFAD — and manipulated regulatory T cells in both directions. *Early transient depletion* of regulatory T cells accelerated the onset of cognitive deficits, and did so *without altering amyloid-β deposition* — an important detail, because it dissociates the cognitive effect from the plaque burden and points to a mechanism operating on the brain's response to amyloid rather than on amyloid itself. That mechanism, they found, was microglial: depletion reduced the recruitment of microglia toward amyloid deposits and shifted the disease-related gene-expression profile unfavourably. Conversely, *amplification* of regulatory T cells through peripheral low-dose interleukin-2 treatment increased the number of plaque-associated microglia and restored cognitive function. The conclusion was the mirror of Schwartz's: regulatory T cells play a beneficial role, slowing disease progression and supporting — not obstructing — the microglial response to amyloid.

Notice that both camps agree on something crucial, and it is easy to miss in the noise of their disagreement: *both hold that recruiting immune cells to plaques is good*. Schwartz's benefit comes from recruiting monocyte-derived macrophages through the choroid-plexus gate; Dansokho's harm comes from *losing* the microglial recruitment that regulatory T cells support. The disagreement is not about whether the brain needs reparative myeloid cells at the plaque — both say it does — but about whether regulatory T cells *help or hinder* that recruitment. Schwartz's model casts regulatory T cells as gatekeepers holding the border shut; Dansokho's casts them as facilitators helping microglia do their job. This is a resolvable disagreement, and locating its resolution is the work of the next section.

The defense does not rest on one laboratory. Baek and colleagues, working in the 3xTg-AD model in 2016, provided an independent and unusually complete test by manipulating regulatory T cells in both directions with different tools. Adoptive transfer of purified regulatory T cells into 3xTg-AD mice improved cognitive function and reduced amyloid-β plaque deposition, whereas transfer of effector T cells worsened behaviour — a clean demonstration that the regulatory subset,

specifically, carries the benefit. In the opposite direction, transient depletion of regulatory T cells over four months markedly aggravated spatial-learning deficits, decreased cerebral glucose metabolism on FDG-PET imaging, and *increased* the deposition of amyloid plaques and the accumulation of microglia and macrophages in the hippocampus. Here depletion worsened amyloid, where in Dansokho's hands it had not touched it — a discrepancy that itself reflects model and timing differences — but the direction of the cognitive effect was identical: less regulatory T cell activity, worse disease.

The defense's most translationally important thread runs through interleukin-2, and it deserves its own paragraph because it is the cleanest and most reproducible line in the whole literature. Interleukin-2, at low doses, preferentially expands and activates regulatory T cells, exploiting their high-affinity receptor to stimulate the brake without unleashing effector immunity. Alves and colleagues, in 2017, treated APP/PS1 mice with established Alzheimer pathology using a single administration of an interleukin-2 gene-therapy vector and followed them for five months. The treatment expanded regulatory T cells both systemically and in the brain; in the hippocampus it recruited astrocytes around amyloid plaques, decreased the amyloid-β42/40 ratio and the plaque load, improved synaptic plasticity, rescued dendritic spine density, and — the outcome that matters — recovered memory deficits in the Morris water maze. They further reported that interleukin-2 levels are themselves *decreased* in hippocampal biopsies of Alzheimer patients, suggesting the pathway they were augmenting is one the disease depletes. Three independent laboratories, three models, one direction: amplifying regulatory T cells, whether by adoptive transfer, by anti-CD25-free expansion, or by low-dose interleukin-2, protects the brain.

The defense's mechanism is now visible in outline, and it is richer than "suppress inflammation." Regulatory T cells appear to protect the Alzheimer brain along at least three routes: by restraining the chronic, toxic neuroinflammation — the effector-T-cell and pro-inflammatory-microglial activity — that drives neurodegeneration; by *supporting* the beneficial, plaque-clustering arm of the microglial response, so that their loss reduces protective microgliosis rather than increasing it; and, plausibly, by the direct tissue-reparative signalling — amphiregulin and its relatives — that brain regulatory T cells were shown to provide after stroke. The guardian, on this reading, is not merely a fire-fighter but a foreman: it puts out the wrong fires while keeping the useful crews at work. This is the more strongly and broadly evidenced of the two verdicts. But it is not the whole story, because the prosecution's data are also real, and a theory that cannot explain why *both* sets of experiments came out as they did has not earned its verdict.

VI. Reconciling the Verdicts — The Timing Problem

Two careful laboratories transiently depleted regulatory T cells in amyloid mice and reported opposite outcomes. This is the kind of contradiction that either indicts one party's competence or reveals that a hidden variable governs the system — and in this case the hidden variables are not hidden at all once one lays the studies side by side. They differ in model, in the timing and duration and depth of the manipulation, in the compartment emphasized, and in the readout. The reconciliation this dissertation defends is that the regulatory T cell is a *rheostat* whose effect on the Alzheimer brain is not fixed in sign, and that the studies disagree because they turned the knob at different times, by different amounts, in different animals.

Consider first the *model*. The prosecution's foundational result came in 5XFAD, an aggressive model in which amyloid accumulates early and overwhelmingly and in which the reparative capacity of resident microglia is quickly outstripped; the defense's came in APPPS1 and 3xTg-AD, slower models in which the endogenous microglial response has more room to matter. In a brain drowning in amyloid faster than its microglia can respond, importing an external myeloid workforce — by opening the choroid-plexus gate — may be the dominant lever, and briefly lowering systemic immunosuppression to do so may help. In a brain accumulating amyloid slowly, the *quality and persistence* of the endogenous microglial response may be the dominant lever, and regulatory T cell support of that response may be what matters. The same cell can be a net obstacle in the first regime and a net asset in the second without any contradiction in its biology.

Consider next *timing and duration*, which is the crux. The prosecution's benefit followed a *transient* dip in regulatory T cell activity — a brief perturbation whose downstream effect included, on Schwartz's own showing, a rebound recruitment of immunoregulatory cells (macrophages *and* regulatory T cells) to the brain. A transient dip is not the same intervention as a sustained loss. It is entirely coherent that briefly lowering systemic immunosuppression triggers a reparative wave — a controlled, self-limited immune activation that floods the brain with clearance-competent cells and then resolves — while *chronically* lowering regulatory T cell function removes a standing protection and lets toxic inflammation run. Baek's depletion ran for four months and worsened disease; Dansokho's early transient depletion accelerated deficits; Schwartz's transient depletion, in a different model with different kinetics, helped. The variable that best separates benefit from harm is not the direction of the manipulation but its *temporal structure*: a pulse may recruit repair, a chronic reduction may unleash damage. The regulatory T cell, in other words, may be like many homeostatic controllers — one whose brief release triggers an adaptive response but whose sustained failure is pathogenic.

Consider next *compartment*. The prosecution's mechanism is fundamentally *peripheral and systemic*: it concerns the tone of immunosuppression in the blood and the state of the choroid-plexus gate,

and its effector cells are monocyte-derived macrophages imported from outside the brain. The defense's mechanism is increasingly *central and local*: it concerns microglial recruitment to plaques, astrocytic behaviour, and — by extension from the stroke literature — regulatory T cells resident in the brain parenchyma providing trophic support. Peripheral regulatory T cell tone and central regulatory T cell action are not the same quantity, and an intervention that lowers the first while a disease has already lowered the second could produce net benefit even if central regulatory T cells are protective. The choroid-plexus gateway is the hinge between these compartments — the same border organ whose failure this series has examined in *The Tide-Gate* — and it is precisely at that hinge that the systemic and central readings of the regulatory T cell meet and can be told apart.

Finally, consider the *readout*. Dansokho's transient depletion worsened cognition *without changing amyloid*; Baek's prolonged depletion worsened cognition *and increased* amyloid; Schwartz's transient depletion *cleared* amyloid. That amyloid burden and cognitive outcome dissociate across these studies is itself informative: it tells us the regulatory T cell acts substantially on the brain's *response* to amyloid — the microglial, inflammatory, and synaptic response that determines cognition — rather than only on the plaque load, and that studies foregrounding plaque clearance and studies foregrounding cognition are, in part, measuring different things. A cell that protects synapses and cognition while leaving plaques untouched, and a manipulation that clears plaques while doing uncertain things to the reparative-inflammatory balance, can both be reported accurately and read as opposite verdicts by readers who equate amyloid with disease.

The reconciliation, then, is not a fudge but a specific empirical claim: that the sign of the regulatory T cell's effect on the Alzheimer brain depends on when in the disease it is manipulated, for how long, in which compartment, and against which readout — and that the preponderance of the *causal* evidence, weighted for reproducibility across laboratories and models, favours a net-protective role for regulatory T cell *function*, realized especially through the low-dose interleukin-2 amplification that three independent groups found beneficial, while granting the prosecution its genuine and important finding that a transient, systemic lowering of immunosuppression can, in the right model at the right time, recruit reparative immunity to the brain. The peacekeeper is a rheostat, and the field's disagreement is a disagreement about where the knob was set.

VII. What the Human Blood Shows and Doesn't

Mouse experiments can be causal; human studies of Alzheimer's disease, for the most part, cannot. Nearly the entire human literature on regulatory T cells in the disease consists of cross-sectional

comparisons — counting and phenotyping the regulatory T cells in the blood of patients and controls at a single point in time — and such studies can establish association but not direction, and are exquisitely sensitive to how the cells are defined, which stage of disease is sampled, and how small the cohort is. The result is a human literature that is, to be honest, inconsistent, and the discipline this subject requires is to report that inconsistency rather than to cherry-pick the studies that flatter one's preferred verdict.

The disagreement begins with the most basic question: are there more regulatory T cells in the Alzheimer patient's blood, or fewer? Rosenkranz and colleagues, in 2007, found that regulatory T cell frequency *increases* with age and is accompanied by *intensified* suppressive activity in both Alzheimer's and Parkinson's disease — more regulatory T cells, each suppressing harder. Saresella and colleagues, in 2010, likewise found regulatory T cells *increased* in both mild cognitive impairment and Alzheimer's disease, with an important stage-dependent nuance to which we return. But Ciccocioppo and colleagues, in 2019, using a refined flow-cytometric definition, found the *total* and *resting* regulatory T cells *decreased* in Alzheimer's disease relative to healthy subjects. And Oberstein and colleagues, in 2018, found the proportion of regulatory T cells *unchanged* between groups, while noting that it correlated positively with the neurodegeneration markers total tau and phospho-tau in the Alzheimer patients. Increased, decreased, unchanged: the frequency literature does not converge, and anyone who tells you it clearly shows regulatory T cells rising or falling in Alzheimer's disease is overreading it.

The resolution of this apparent chaos lies in the distinction insisted upon earlier — *frequency versus function*, and *stage*. Two studies point the way. Saresella's stage-resolved analysis found that the most suppressive subset of regulatory T cells was elevated specifically in mild cognitive impairment, where amyloid-stimulated T-cell proliferation was correspondingly reduced and regulatory suppression was more efficient — a picture of a compensatory regulatory response mounted early, in the prodromal stage, and *lost* by the time of full dementia. Faridar and colleagues, in 2020, went directly at function: they found that the *suppressive capacity* of regulatory T cells — their actual ability to restrain responder-T-cell proliferation and to quell pro-inflammatory macrophages — was specifically compromised at the Alzheimer dementia stage, relative to mild cognitive impairment and controls, and that this dysfunction could be *reversed* by ex vivo expansion. The reconciling reading is that early in the disease the regulatory compartment may be intact or even up-regulated as a compensatory brake, and that as the disease advances the brake *fails functionally* — the cells may still be counted, but they no longer suppress as they should. On this reading the frequency studies disagree partly because they sampled different stages and defined the cells differently, while the functional studies converge on a more useful claim: that regulatory T cell *function* is impaired in established Alzheimer's disease.

That claim, if it holds, is the human literature's most important contribution, because it is the premise on which the whole therapeutic program rests. If regulatory T cells were simply

overabundant and overactive in Alzheimer's disease, the prosecution's logic — remove the brake — would be the rational human strategy. If instead the regulatory compartment is functionally *insufficient* by the dementia stage, then the defense's logic — restore and amplify the brake — is the rational strategy, and the low-dose interleukin-2 approach is its natural instrument. Faridar's finding, that regulatory T cell function is compromised in Alzheimer's disease and restorable by expansion, is the human hinge on which the therapeutics turn, and it points toward amplification, not depletion.

But the grade must remain honest. This is cross-sectional human data, in small cohorts, with inconsistent cell definitions and no capacity to establish direction. It cannot tell us whether the regulatory dysfunction it observes is a *cause* of the disease's progression or a *consequence* of the same neurodegenerative and inflammatory milieu that damages everything else — whether the failing brake is helping to drive the car off the road or is merely one more thing the crash has broken. And a further hazard shadows all of it: the adaptive immune system's involvement in Alzheimer's disease, real as it is, may be a bystander phenomenon. Gate and colleagues showed, in a landmark 2020 study, that clonally expanded CD8 T cells patrol the cerebrospinal fluid in Alzheimer's disease and that some are specific for Epstein-Barr virus antigens — evidence that the intrathecal T-cell response is antigen-experienced and real, but also a reminder that much of what the adaptive immune system is doing in and around the Alzheimer brain may reflect age-related immune remodelling and latent-virus surveillance rather than a disease-specific program that regulatory T cells could be expected to govern. The human data establish that the adaptive immune system is *present and altered* in Alzheimer's disease; they do not, by themselves, establish that regulatory T cells are a lever on its course.

VIII. Mechanisms in the Brain — How a Regulatory T Cell Would Act

If regulatory T cells matter in Alzheimer's disease, they must act somewhere, on something, by some molecule — and the plausibility of the whole account depends on whether coherent mechanisms exist to carry the effects the mouse experiments report. They do, and it is worth assembling them, because a graded verdict should rest on mechanism as well as outcome. Four routes of action are supported, in ascending order of specificity to the brain.

The first and most generic is *suppression of effector and helper T cells*. The adaptive immune response in Alzheimer's disease is not neutral: effector CD4 T cells specific for amyloid-β can be pathogenic, as the history of amyloid immunotherapy made vivid, and the balance between pro-inflammatory

helper subsets and regulatory T cells appears skewed in the disease. Oberstein and colleagues found the pro-inflammatory Th17 subset increased in the early, mild-cognitive-impairment stage of Alzheimer's disease — a shift in the helper-T-cell balance toward inflammation. Regulatory T cells are the physiological counterweight to exactly this shift: by suppressing Th17 and other effector responses through CTLA-4, interleukin-10, and their other mechanisms, they hold the adaptive immune response to amyloid within safe bounds. The clinical stakes of that restraint are not hypothetical. When Alzheimer patients were actively immunized against amyloid-β in the AN1792 trial, roughly six percent developed a subacute meningoencephalitis attributed to T-cell and microglial activation — a near-catastrophe that halted the trial and that stands as the field's starkest demonstration that an unrestrained anti-amyloid T-cell response can devastate the brain. Regulatory T cells are what normally prevent that response from arising. A cell that stands between the amyloid brain and autoimmune meningoencephalitis is not lightly cast as the enemy.

The second route is *modulation of microglia*, and it is the one both camps converge upon. Regulatory T cells shape microglial phenotype, and the direction they push it appears, on the defense's evidence, to be toward the reparative, plaque-clustering, amyloid-clearing program and away from the chronically activated, neurotoxic one. Dansokho's finding that regulatory T cell depletion *reduced* microglial recruitment to plaques, and Baek's that depletion *increased* an accumulation of microglia and macrophages that accompanied worsened disease, are not as contradictory as they look: the first concerns the beneficial clustering of microglia in a productive response, the second an accumulation in the context of failed clearance and rising amyloid. What regulatory T cells appear to modulate is not the *quantity* of microglia but the *quality* of their response — a distinction that maps onto the broader recognition, developed in this series' *Homeostatic Microglial Collapse*, that microglia in Alzheimer's disease can be protective or destructive depending on their programmed state. Regulatory T cells, on this account, are one of the peripheral signals that help set that state, and Faridar's demonstration that expanded human regulatory T cells suppress pro-inflammatory macrophages through a contact-dependent mechanism gives the modulation a concrete molecular form.

The third route is *direct tissue support of the nervous parenchyma*, extrapolated from the stroke literature but mechanistically specified. Ito and colleagues showed that brain-resident regulatory T cells suppress neurotoxic reactive astrogliosis and potentiate neurological recovery by secreting amphiregulin, acting on astrocytes rather than on immune cells. Reactive astrogliosis is a prominent feature of the Alzheimer brain, and Alves and colleagues, tellingly, found that interleukin-2-driven regulatory T cell expansion recruited astrocytes around amyloid plaques in a pattern associated with reduced amyloid and improved synaptic function — a hint that the regulatory-T-cell-to-astrocyte axis operates in the amyloid brain as it does after stroke. If it does, then regulatory T cells protect the brain not only by governing immunity but by directly restraining and redirecting the astrocytic response, a mechanism that owes nothing to the fire-versus-repair-crew framing and that would make the guardian reading robust to how one resolves the inflammation question.

The fourth route is *action at the choroid-plexus gateway* — the systemic-to-central hinge the prosecution built its case upon. The choroid plexus, as *The Tide-Gate* argued at length, is the selective gate through which peripheral immune cells reach the cerebrospinal fluid, and its permissiveness is regulated by the systemic immune state, including the interferon balance that Baruch and colleagues placed at the centre of brain aging. Regulatory T cell tone is one input to that gate. Here the mechanism is genuinely double-edged: by keeping systemic immunosuppression high, regulatory T cells may hold the gate relatively shut, limiting the influx of reparative macrophages (the prosecution's harm); by restraining a chronic, damaging peripheral inflammation, they may protect the brain from a maladaptive flood (the defense's benefit). The gateway is the one place in the whole account where the regulatory T cell's effect is most credibly *bidirectional at the level of a single mechanism*, and it is therefore the place where the rheostat metaphor is most literally true. Whether opening the gate helps or harms depends on what comes through it, and that depends on the state of the system — which returns us, once more, to timing and stage.

Two honest gaps remain in the brain-mechanism picture. First, the *localization* of regulatory T cells in the human Alzheimer brain is not well established: whether, and where, and how many regulatory T cells actually reside in or traffic through the diseased human parenchyma, as opposed to acting from the blood and the borders, is not firmly known, and much of the local-action account is extrapolated from mice and from other diseases. Second, the *quantitative weight* of each route — how much of the observed benefit flows through T-cell suppression versus microglial modulation versus astrocytic support versus gateway effects — has not been dissected. The mechanisms exist and are plausible; their relative contributions in the human disease are inferred, not measured, and the verdict must be graded accordingly.

IX. The Validity Ledger

The preceding sections have graded their claims in passing; this section gathers the grading into one place, because the honesty of the whole enterprise depends on its being auditable. Three failure modes threaten every connection drawn in this dissertation. The first is *reverse causation and bystander status*: the human evidence is cross-sectional, and an altered regulatory T cell compartment in Alzheimer's disease may be a consequence of the disease, or an epiphenomenon of age-related immune remodelling, rather than a lever on its course. The second is *model dependence*: the causal animal evidence lives in transgenic amyloid mice whose relationship to human sporadic Alzheimer's disease is imperfect, and whose differences from one another generate part of the very disagreement we are grading. The third is *the direction-of-manipulation confound*: transient versus sustained, systemic versus central, early versus late — interventions that share a name ("Treg depletion") but differ in

temporal and spatial structure, and that cannot be pooled as if they were the same experiment.

Moderate-to-strong — regulatory T cell amplification (low-dose interleukin-2) is protective in animal models. This is the ledger's most robust causal thread. Three independent laboratories, using three tools (adoptive transfer, ex-vivo expansion, and low-dose interleukin-2) across at least three mouse models (APPPS1, 3xTg-AD, APP/PS1), found that increasing regulatory T cell number or function improved cognition, and in most cases reduced amyloid and supported a beneficial microglial or astrocytic response. Convergent direction across independent groups and models is the strongest structure observational biology offers short of a human trial. *Settling experiment (now partly done): a randomized human trial of regulatory-T-cell amplification with disease-relevant endpoints — which, as of 2025, exists in preliminary form and is discussed below.*

Moderate — regulatory T cell function is impaired in established human Alzheimer's disease. The functional human data (Faridar) converge where the frequency data (Rosenkranz, Saresella, Oberstein, Ciccocioppo) diverge, and the stage-resolved picture — compensatory early, failing late — is coherent. But the studies are small, cross-sectional, and cannot establish direction. *Settling experiment: longitudinal measurement of regulatory T cell suppressive function across the preclinical-to-dementia transition, correlated with subsequent cognitive decline, in cohorts large enough to separate cause from consequence.*

Real but narrow — transient systemic reduction of immunosuppression can recruit reparative immunity and clear amyloid. The prosecution's foundational result is causal and important, and it established a genuine reparative arm of brain immunity worth recruiting. But it is concentrated in one laboratory and one aggressive model, and its temporal structure (a transient pulse, with a regulatory-cell rebound) is not equivalent to "regulatory T cells are harmful." *Settling experiment: independent replication of the choroid-plexus-gateway benefit of transient Treg reduction, in multiple models and laboratories, with the rebound dynamics explicitly dissected.*

Weak / refuted as a therapeutic corollary — PD-1 checkpoint blockade reduces amyloid pathology. The original positive report did not survive a rigorous, multi-company, multi-model replication effort, which found no macrophage infiltration and no change in amyloid. This corollary should be held as unproven at best and likely negative as a monotherapy. *Settling experiment: already substantially conducted, and negative; further pursuit requires a fundamentally new rationale.*

Weak — regulatory T cells act locally within the human Alzheimer brain. That brain-resident regulatory T cells provide tissue-reparative support (amphiregulin, astrocyte modulation) is well demonstrated after stroke and plausibly extended to Alzheimer's disease by the Alves astrocyte findings, but the presence, location, and quantitative role of regulatory T cells in the human Alzheimer parenchyma are not established. *Settling experiment: rigorous spatial mapping of Foxp3-positive cells in human Alzheimer brain across disease stages, with functional characterization.*

Uncertain — the human adaptive immune changes are disease-specific rather than bystander. The clonal CD8 expansion in cerebrospinal fluid (Gate) and the shifted helper/regulatory balance are real, but their EBV-specificity and age-relatedness leave open how much reflects a disease-driving program regulatory T cells could govern. *Settling experiment: demonstration that the adaptive-immune alterations track disease progression independent of age and latent-virus status, and are modifiable by regulatory T cell manipulation with cognitive benefit.*

Rejected — regulatory T cells are, on balance, harmful in Alzheimer's disease. The strong form of the prosecution's claim is not supported by the weight of the causal evidence, which favours net protection by regulatory T cell function; the narrow, timing-specific benefit of transient systemic reduction does not generalize to a harmful verdict. This claim is not made in this dissertation.

The ledger's shape is its message. One moderate-to-strong protective thread reproduced across laboratories, one moderate human functional claim, one real-but-narrow finding on the other side, one refuted therapeutic corollary, and several honest uncertainties. This is not the profile of a villain, nor of an unambiguous hero. It is the profile of a context-dependent controller whose net causal effect, as best the evidence shows, is protective — the rheostat the previous sections described, arrived at here from the direction of the graded evidence.

X. Where the Regulatory T Cell Sits Guardian, Saboteur, or Rheostat

This is the question on which the value of the entire account turns, and it must be answered without flinching. Is the regulatory T cell, in Alzheimer's disease, a friend of the brain, an enemy, or something more conditional? The two camps have each staked a simple answer, and the temptation is to declare a winner. The evidence does not support a simple answer, and forcing one would repeat the error this dissertation was written to avoid.

Consider what it would take for the regulatory T cell to be a straightforward *saboteur*, as the strong prosecution reading holds. Its removal would have to reliably improve the disease, across models and laboratories and — eventually — in humans. It does not. Removal accelerates cognitive decline in APPPS1 mice, aggravates learning deficits and worsens amyloid and metabolism in 3xTg-AD mice, and its checkpoint-inhibition corollary failed multi-laboratory replication. The saboteur reading survives only in a narrow, timing-specific form — transient systemic reduction, in an aggressive model, recruiting a self-limited reparative wave — and even there the benefit involves

regulatory cells returning to the brain. The unqualified saboteur is not the cell the evidence describes.

Consider, at the other extreme, the regulatory T cell as an unqualified *guardian*, whose amplification is simply good. This is closer to the weight of the evidence, and it is the reading this dissertation leans toward — but "simply good" is too strong, and the prosecution's genuine finding is why. There exist conditions — a particular model, a particular moment, a transient and systemic manipulation — under which lowering regulatory T cell tone helps the brain by opening it to reparative immunity. A cell whose amplification is beneficial in most tested conditions but whose transient reduction is beneficial in others is not an unqualified guardian; it is a controller with an optimum that is neither zero nor maximum. To call it simply a guardian is to ignore real data, and this account does not.

What remains is the defensible middle, and it is the position this dissertation adopts: the regulatory T cell is a *context-dependent rheostat* whose net causal effect on the Alzheimer brain, integrated across the reproducible evidence, is *protective* — realized above all through the low-dose interleukin-2 amplification that three independent laboratories found beneficial and that a first human trial has now cautiously supported — but whose sign genuinely inverts under specific, identifiable conditions of timing, duration, compartment, and disease stage. This verdict has a specific structure. It holds that regulatory T cell *function* is a genuine protection, plausibly failing as the disease advances, whose restoration is the rational therapeutic direction. It holds that the prosecution's benefit is real but is a statement about a *transient systemic perturbation in an overwhelmed brain*, not about the cell's standing role. And it holds that the two are reconciled not by declaring one side mistaken but by recognizing that a homeostatic controller can help when strengthened and also help when briefly released, because "briefly released" and "chronically weakened" are different interventions with different downstream dynamics. The regulatory T cell sits where a rheostat sits: not as friend or foe in the abstract, but as a setting that can be turned the right way or the wrong way, and whose right setting the field is only beginning to find.

XI. Therapeutic Corollaries

A rheostat is worth treating precisely because its setting can be adjusted, and the therapeutic question in Alzheimer's disease is not whether to engage the regulatory T cell but in which direction, at what stage, and by how much. Four directions follow from the account, each inheriting the grade of the mechanism it targets, and one inversion warning runs through all of them.

The first, and best-grounded, is **amplifying regulatory T cell function, principally with low-dose interleukin-2**. Because the protective thread is the account's most reproducible, and because interleukin-2 preferentially expands regulatory T cells through their high-affinity receptor, low-dose interleukin-2 is the most rational regulatory-T-cell-directed strategy, and it is the one that has travelled furthest toward the clinic. The preclinical case is strong: Dansokho, Alves, and others found low-dose or gene-delivered interleukin-2 protective across models. And as of 2025, the first controlled human evidence exists. Faridar and colleagues reported a phase-2a, randomized, double-blind, placebo-controlled trial of low-dose interleukin-2 in thirty-eight patients with mild-to-moderate Alzheimer's disease: the treatment was safe and well tolerated, with no serious adverse events; it expanded regulatory T cell numbers and suppressive function; and, in the more effective dosing arm, it improved a cerebrospinal-fluid marker of amyloid, stabilized a marker of neurodegeneration that rose in the placebo group, favourably shifted plasma inflammatory mediators, and produced a trend toward slower cognitive decline. These are early, small, partly exploratory findings, and their authors frame them as a foundation for further investigation rather than a demonstration of efficacy — but they are the first human data to show that amplifying the regulatory T cell in Alzheimer patients is feasible, safe, and biologically active in the predicted direction. This direction earns the account's highest therapeutic grade: *promising, and now in human testing.*

The second is **restoring regulatory T cell function directly, by ex vivo expansion or adoptive transfer**. Faridar's 2020 demonstration that the impaired suppressive function of Alzheimer patients' regulatory T cells can be restored by ex vivo expansion, and Baek's that adoptive transfer of regulatory T cells protects mice while transfer of effector T cells harms them, together motivate a cell-therapy approach: expand a patient's own regulatory T cells to functional competence and return them. This is more complex and less mature than low-dose interleukin-2, and its human evidence is a step behind, but it targets the same protective mechanism and its grade is *moderate*.

The third is **the timing discipline** — less a drug than a principle drawn from the reconciliation. If the sign of the regulatory T cell's effect depends on disease stage and on the temporal structure of the manipulation, then *when* an intervention is given may matter as much as *what* it is. The functional-insufficiency reading suggests amplification is most rational at the stage where regulatory function is failing — established disease and perhaps late prodrome — while the compensatory-early picture cautions against blunting a regulatory response that may be doing useful work in the earliest stages. The prosecution's finding, conversely, warns that *chronic* immunosuppression is not the goal and that there may be a role, in specific circumstances, for transient and controlled immune activation. The clinical corollary is that regulatory-T-cell therapeutics should be developed with explicit attention to stage and dynamics, not as a fixed dose given regardless of where the patient sits on the disease trajectory. Its grade is *a principle, not a proven protocol.*

The fourth is a **caution against the opposite strategy**: the therapeutic *reduction* of regulatory T cells, or checkpoint blockade to break tolerance. The account gives this direction a low grade. Its flagship instance, PD-1 blockade, failed multi-laboratory replication; its rationale depends on a saboteur reading the weight of evidence does not support; and its central hazard is the one the AN1792 trial made unforgettable — that unleashing anti-amyloid adaptive immunity can produce autoimmune meningoencephalitis. Removing the brake that prevents that catastrophe is not a step to take on the strength of a narrow, model-specific benefit. This direction is *not recommended on current evidence.*

The inversion warning that runs through all four is the one this series has learned to state explicitly for any molecule or cell that reads in two directions. The regulatory T cell is a double-edged instrument: the same amplification that restrains toxic neuroinflammation may, if pushed too far or applied at the wrong stage, over-suppress the reparative immunity the brain also needs; the same reduction that might transiently recruit repair may, if sustained, unleash the damage regulatory T cells hold back. There is no setting of the rheostat that is safe in all conditions, and the therapeutic task is not to maximize or minimize regulatory T cell activity but to find and hold its optimum — a task that presupposes the staging and monitoring tools the field is only now developing. The peacekeeper can be strengthened into a censor or weakened into an accomplice, and the art of the therapy is the setting in between.

XII. Predictions and Falsification

A frame earns its keep by the predictions it makes and the observations that would sink it. The rheostat account of the regulatory T cell commits to the following, each stated so that its failure would count against the frame.

It predicts that **amplifying regulatory T cells benefits patients at the stage of functional insufficiency**. In patients with established Alzheimer's disease — where regulatory T cell function appears impaired — amplification by low-dose interleukin-2 or cell therapy should slow cognitive decline and shift inflammatory and neurodegenerative biomarkers favourably, as the 2025 phase-2a trial's trends suggest. If adequately powered trials show no benefit of regulatory T cell amplification at any stage, the protective thread — the account's strongest — is wrong, and with it the whole verdict.

It predicts a **stage dependence of the effect**. Because the account holds that regulatory function is compensatory early and failing late, the benefit of amplification should be *greater* in

patients further along the functional-insufficiency curve, and interventions that *reduce* regulatory T cell tone should be more hazardous, not more helpful, as disease advances. A flat or inverted stage response would falsify the timing reconciliation.

It predicts that **the two camps' results are conditions of one system, not contradictions**. A single study that manipulates regulatory T cells across a matrix of timing (transient versus sustained), compartment (systemic versus central), and model (aggressive versus slow) should recover *both* the prosecution's and the defense's outcomes as functions of those variables. If, instead, regulatory T cell reduction proves uniformly beneficial or uniformly harmful across that matrix, the rheostat account is wrong and one simple verdict is right after all.

It predicts **a functional, not merely numerical, human signature**. Longitudinal human study should find that declining regulatory T cell *suppressive function* — more than frequency — precedes and predicts cognitive decline. If frequency, not function, turns out to be the operative variable, or if neither predicts anything longitudinally, the human premise of the therapeutic program weakens.

And it predicts, as its clearest falsifier, that **regulatory T cell function is causally upstream of the response to amyloid, not merely a bystander**. If regulatory T cell alterations in Alzheimer's disease prove to be pure consequences of age-related immune remodelling and latent-virus surveillance — modifiable without any effect on the disease's course — then the regulatory T cell is a spectator, the therapeutic program is misconceived, and this account is substantially wrong. The frame is built to be broken on this point, which is the mark of a claim worth making.

XIII. Coda The Setting of the Knob

The history of immunology in Alzheimer's disease is a history of the field changing its mind about which way to push. For a generation the instinct was to suppress — to treat the disease as an inflammation and reach for the brake. Then came the recognition that the brain needs its immune cells, that microglia clear as well as harm, that the failure might be too little repair rather than too much attack, and the instinct reversed. The regulatory T cell has been caught in the middle of that reversal, cast as hero by one reading and villain by the other, and the temptation has been to resolve the tension by choosing a side.

The disciplined resolution is that neither side owns the cell. The regulatory T cell is the immune system's rheostat, and in Alzheimer's disease it controls a response that is itself two-faced — part fire,

part repair crew — so that the same cell that shelters the brain from a toxic, self-directed inflammation also stands, at the border, between the brain and the reparative flood it sometimes needs. Turn the knob down chronically and the fire spreads; turn it down briefly, in the right brain at the right moment, and the repair crew arrives; turn it up, especially where the cell has failed, and the fire is banked while the useful crews keep working. The weight of the causal evidence says that, for the patient who already has the disease, the useful direction is *up* — restore and strengthen the failing peacekeeper — and the first human trial has begun, cautiously, to bear that out. But the deeper lesson is the one the paradox taught: that there is no setting of this knob that is right in all conditions, and that the science of the regulatory T cell in Alzheimer's disease is, in the end, the science of finding its optimum. The peacekeeper's paradox is not that the cell is contradictory. It is that the brain it guards needs peace and repair at once, and asks the same cell to supply both.

References

All references below were retrieved and verified via PubMed; digital object identifiers are provided for each. Attribution: bibliographic metadata for the works cited was confirmed against the PubMed database.

1. Sakaguchi S, Yamaguchi T, Nomura T, Ono M. Regulatory T cells and immune tolerance. *Cell*. 2008;133(5):775–787. DOI: 10.1016/j.cell.2008.05.009

2. Orgogozo JM, Gilman S, Dartigues JF, Laurent B, Puel M, Kirby LC, Jouanny P, Dubois B, Eisner L, Flitman S, Michel BF, Boada M, Frank A, Hock C. Subacute meningoencephalitis in a subset of patients with AD after Aβ42 immunization. *Neurology*. 2003;61(1):46–54. DOI: 10.1212/01.wnl.0000073623.84147.a8

3. Rosenkranz D, Weyer S, Tolosa E, Gaenslen A, Berg D, Leyhe T, Gasser T, Stoltze L. Higher frequency of regulatory T cells in the elderly and increased suppressive activity in neurodegeneration. *Journal of Neuroimmunology*. 2007;188(1–2):117–127. DOI: 10.1016/j.jneuroim.2007.05.011

4. Saresella M, Calabrese E, Marventano I, Piancone F, Gatti A, Calvo MG, Nemni R, Clerici M. PD1 negative and PD1 positive CD4+ T regulatory cells in mild cognitive impairment and Alzheimer's disease. *Journal of Alzheimer's Disease*. 2010;21(3):927–938. DOI: 10.3233/JAD-2010-091696

5. Baruch K, Deczkowska A, David E, Castellano JM, Miller O, Kertser A, Berkutzki T, Barnett-Itzhaki Z, Bezalel D, Wyss-Coray T, Amit I, Schwartz M. Aging-induced type I interferon response at the choroid plexus negatively affects brain function. *Science*. 2014;346(6205):89–93. DOI: 10.1126/science.1252945

6. Baruch K, Rosenzweig N, Kertser A, Deczkowska A, Sharif AM, Spinrad A, Tsitsou-Kampeli A, Sarel A, Cahalon L, Schwartz M. Breaking immune tolerance by targeting Foxp3+ regulatory T cells mitigates Alzheimer's disease pathology. *Nature Communications*. 2015;6:7967. DOI: 10.1038/ncomms8967

7. Baruch K, Deczkowska A, Rosenzweig N, Tsitsou-Kampeli A, Sharif AM, Matcovitch-Natan O, Kertser A, David E, Amit I, Schwartz M. PD-1 immune checkpoint blockade reduces pathology and improves memory in mouse models of Alzheimer's disease. *Nature Medicine*. 2016;22(2):135–137. DOI: 10.1038/nm.4022

8. Dansokho C, Ait Ahmed D, Aid S, Toly-Ndour C, Chaigneau T, Calle V, Cagnard N, Holzenberger M, Piaggio E, Aucouturier P, Dorothée G. Regulatory T cells delay disease progression in Alzheimer-like pathology. *Brain*. 2016;139(Pt 4):1237–1251. DOI: 10.1093/brain/awv408

9. Baek H, Ye M, Kang GH, Lee C, Lee G, Choi DB, Jung J, Kim H, Lee S, Kim JS, Lee HJ, Shim I, Lee JH, Bae H. Neuroprotective effects of CD4+CD25+Foxp3+ regulatory T cells in a 3xTg-AD Alzheimer's disease model. *Oncotarget*. 2016;7(43):69347–69357. DOI: 10.18632/oncotarget.12469

10. Alves S, Churlaud G, Audrain M, Michaelsen-Preusse K, Fol R, Souchet B, Braudeau J, Korte M, Klatzmann D, Cartier N. Interleukin-2 improves amyloid pathology, synaptic failure and memory in Alzheimer's disease mice. *Brain*. 2017;140(3):826–842. DOI: 10.1093/brain/aww330

11. Latta-Mahieu M, Elmer B, Bretteville A, Wang Y, Lopez-Grancha M, Goniot P, Moindrot N, Ferrari P, Blanc V, Schussler N, Brault E, Roudières V, Blanchard V, Yang ZY, Barneoud P, Bertrand P, Roucourt B, Carmans S, Bottelbergs A, Mertens L, Wintmolders C, Larsen P, Hersley C, McGathey T, Racke MM, Liu L, Lu J, O'Neill MJ, Riddell DR, Ebneth A, Nabel GJ, Pradier L. Systemic immune-checkpoint blockade with anti-PD1 antibodies does not alter cerebral amyloid-β burden in several amyloid transgenic mouse models. *Glia*. 2018;66(3):492–504. DOI: 10.1002/glia.23260

12. Oberstein TJ, Taha L, Spitzer P, Hellstern J, Herrmann M, Kornhuber J, Maler JM. Imbalance of circulating Th17 and regulatory T cells in Alzheimer's disease: a case control study. *Frontiers in Immunology*. 2018;9:1213. DOI: 10.3389/fimmu.2018.01213

13. Ito M, Komai K, Mise-Omata S, Iizuka-Koga M, Noguchi Y, Kondo T, Sakai R, Matsuo K, Nakayama T, Yoshie O, Nakatsukasa H, Chikuma S, Shichita T, Yoshimura A. Brain regulatory T cells suppress astrogliosis and potentiate neurological recovery. *Nature*. 2019;565(7738):246–250. DOI: 10.1038/s41586-018-0824-5

14. Ciccocioppo F, Lanuti P, Pierdomenico L, Simeone P, Bologna G, Ercolino E, Buttari F, Fantozzi R, Thomas A, Onofrj M, Centonze D, Miscia S, Marchisio M. The characterization of regulatory T-cell profiles in Alzheimer's disease and multiple sclerosis. *Scientific Reports*. 2019;9(1):8788. DOI: 10.1038/s41598-019-45433-3

15. Gate D, Saligrama N, Leventhal O, Yang AC, Unger MS, Middeldorp J, Chen K, Lehallier B, Channappa D, De Los Santos MB, McBride A, Pluvinage J, Elahi F, Tam GK, Kim Y, Greicius M, Wagner AD, Aigner L, Galasko DR, Davis MM, Wyss-Coray T. Clonally expanded CD8 T cells patrol the cerebrospinal fluid in Alzheimer's disease. *Nature*. 2020;577(7790):399–404. DOI: 10.1038/s41586-019-1895-7

16. Faridar A, Thome AD, Zhao W, Thonhoff JR, Beers DR, Pascual B, Masdeu JC, Appel SH. Restoring regulatory T-cell dysfunction in Alzheimer's disease through ex vivo expansion. *Brain Communications*. 2020;2(2):fcaa112. DOI: 10.1093/braincomms/fcaa112

17. Machhi J, Kevadiya BD, Muhammad IK, Herskovitz J, Olson KE, Mosley RL, Gendelman HE. Harnessing regulatory T cell neuroprotective activities for treatment of neurodegenerative disorders. *Molecular Neurodegeneration*. 2020;15(1):32. DOI: 10.1186/s13024-020-00375-7

18. Faridar A, Gamez N, Li D, Wang Y, Boradia R, Thome AD, Zhao W, Beers DR, Thonhoff JR, Nakawah MO, Román GC, Volpi JJ, Toledo JB, George M, Davis CS, Pascual B, Grundman M, Masdeu JC, Appel SH. Low-dose interleukin-2 in patients with mild to moderate Alzheimer's disease: a randomized clinical trial. *Alzheimer's Research & Therapy*. 2025;17(1):146. DOI: 10.1186/s13195-025-01791-x