The Brake and the Blade

How Alzheimer's disease dismantles the synapse through the system that restrains it — an evaluation of Carla Shatz and Barbara Brott's programme on immune molecules in the brain, twenty-seven years of work, and what its two newest findings change

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A screen for the molecules of developmental plasticity returned a class of protein the brain was not supposed to express. Twenty-seven years later, the receptor that reads them is where Alzheimer's disease delivers its instruction to a synapse to take itself apart. The brake is not faulty. The brake is being pressed by the wrong hand.

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Abstract

In 1998 a screen designed to find genes that developing brain circuits use to refine themselves returned an answer nobody wanted. The messenger RNAs whose levels fell when neural activity was blocked encoded class I major histocompatibility complex molecules — the proteins by which the immune system displays a cell's contents for inspection, and which the brain was believed not to express at all. Carla Shatz's laboratory took the result seriously, and twenty-seven years of work have followed from it. That work has established three things in sequence: that neurons express these immune molecules under the control of their own electrical activity; that a receptor for them, PirB in the mouse and LilrB2 in the human, sits on cortical pyramidal neurons and holds synaptic plasticity down throughout life; and that in Alzheimer's disease this receptor is the point at which two different pathological ligands — soluble amyloid-β oligomers, and now the complement fragment C4d — attach themselves to a neuron and instruct it to take its own dendritic spines apart.

This paper evaluates that programme as a body of work rather than as a set of individual claims, and asks a single question of it: **what does it establish about how synapses are lost, and does that survive the objections?**

The answer assembled here has five parts. **The molecules the programme found are brakes.** Every one of them — the class I MHC ligands H2-K^b and H2-D^b, the receptor PirB, the non-classical ligand Qa-1 — is a restraint. Delete any of them and the mouse gets *more* plasticity: more spines, more functional synapses, better long-term potentiation, faster motor learning, an ocular-dominance critical period that never closes. **The disease is delivered through the brake, not around it.** Amyloid oligomers and C4d bind the same two immunoglobulin domains of the same receptor that binds MHC class I, and the consequence is not a novel injury but the normal restraint programme running without limit. **The transduction is structural and named.** The receptor recruits phosphatases through its inhibitory motifs, cofilin is dephosphorylated past the point where it severs actin and into the range where it bundles it, and the spine's cytoskeleton fails. **The 2025 finding closes a gap in the pruning literature that microglial accounts could not close.** C4d is covalently and durably tethered to the synapse it opsonises, binds LilrB2 at nanomolar affinity, sits on roughly a third of human excitatory synapses, is fourfold elevated in Alzheimer cortex, and — infused into an adult mouse cortex for four days — is *sufficient* to strip dendritic spines, with the loss entirely abolished in PirB-null animals. Synapse elimination in this disease therefore has a neuron-intrinsic arm that requires no microglion at all. **And the receptor has turned out to have more addresses than the programme claimed.** Independent laboratories have since placed the same receptor on microglia, where it inhibits TREM2 signalling; on astrocytes, where it suppresses glutamate transporters; and inside the neuron, where a cleaved cytoplasmic fragment jams Golgi trafficking.

The weaknesses are stated plainly and one of them is serious. In the only standardised head-to-head comparison of the reported amyloid-β receptors, LilrB2 bound synthetic synaptotoxic assemblies but showed **no detectable binding** to soluble oligomers extracted from human Alzheimer brain, while cellular prion protein bound strongly. That result has not been answered. It does not touch the C4d arm, which was established with a different ligand by different methods, and it does not touch the developmental work; but it means the 2013 amyloid-receptor claim should be carried as contested, and this paper carries it that way.

What stands is a mechanism of subtraction: a specific, druggable receptor through which a synapse receives an instruction to disassemble, present at the right anatomical place, engaged by at least one ligand that is demonstrably elevated in the human disease, and already the target of antagonist antibodies that have completed phase 1/2 trials in another field. That is an unusual position for a mechanism in this disease to be in, and the therapeutic argument at the end of this paper turns on it — together with the reason for caution that the same body of work supplies: everything gained by blocking this receptor is gained by removing a restraint the brain evolved to keep.

1. Introduction: A Programme About Restraint

1.1 What was found, and in what order

The chronology matters, because the meaning of the Alzheimer's work depends entirely on what was already known when it arrived.

Between 1998 and 2014 the Shatz laboratory established, in the healthy brain and with no reference to disease, that a set of immune molecules regulates how much a cortical circuit is allowed to change. Class I MHC transcripts are present in neurons and are up- and down-regulated by activity (Corriveau et al., 1998). Mice that cannot put class I MHC on the cell surface fail to refine their retinal projections properly and show distorted synaptic learning rules — enhanced potentiation, absent depression (Huh et al., 2000). A receptor for these molecules, PirB, is expressed on cortical neurons, sits at synapses, and holds the visual cortex's plasticity down at every age (Syken et al., 2006). Two of the fifty-odd class I MHC genes, H2-K^b and H2-D^b, account for most of the phenotype (Datwani et al., 2009), and H2-D^b alone is necessary and sufficient for synapse elimination in the retinogeniculate pathway (Lee et al., 2014).

Only after that structure was in place did the programme turn to Alzheimer's disease. In 2013 it reported that PirB and its human ortholog LilrB2 bind soluble amyloid-β oligomers at nanomolar affinity through the same two immunoglobulin domains that bind MHC class I, and that deleting PirB rescues both synaptic plasticity and memory in an amyloid-overexpressing mouse (Kim et al., 2013). In 2025, with Barbara Brott as first author, it reported a second ligand for the same receptor — C4d, the durable terminal cleavage fragment of complement component 4 — elevated fourfold in Alzheimer cortex and sufficient, on its own, to remove dendritic spines from an adult mouse brain through PirB (Brott et al., 2025).

The order is the argument. The receptor was not discovered by looking for something that amyloid binds. It was discovered by asking why a critical period closes. That gives the disease claim a prior it would not otherwise have: a molecule already known to subtract synapses on purpose was found to be engaged by a molecule that accumulates in the disease.

1.2 The framing problem: brakes are not usually suspects

Mechanistic accounts of Alzheimer's disease are almost always accounts of something breaking. A clearance system fails; an enzyme is lost; a barrier leaks; a cell type turns hostile. The implicit grammar is of a protective apparatus that gives way.

The programme evaluated here has the opposite grammar, and this is what makes it worth a separate treatment. Nothing in it breaks. The molecules involved do in disease precisely what they do in health — they restrain plasticity and eliminate synapses — and the pathology consists in their doing it at the wrong time, in the wrong place, and without a stopping rule. There is no loss-of-function anywhere in the core mechanism. The brake is not faulty. The brake is being pressed by the wrong hand.

This has three consequences that run through the rest of this paper.

The first is interpretive. If the mechanism is a normal programme running long, then the question "what causes Alzheimer's disease" and the question "what removes the synapses" come apart. Anything that raises the concentration of a ligand at the synaptic surface — amyloid oligomers, complement activation, ageing, inflammation — feeds the same machine. The machine does not care which.

The second is therapeutic, and it is uncomfortable. If the target is a brake, then blocking it is not repair; it is disinhibition. The programme's own work shows what disinhibition buys — mice lacking PirB learn a reaching task faster than their wild-type littermates (Albarran et al., 2021) — and it does not show what it costs over a lifetime. Section 14 treats this properly.

The third is evidential. A restraint system that has been conserved and elaborated is presumably there for a reason, and the reason has never been established. This is the largest unexamined space in the programme.

1.3 What this evaluation asks

Three questions organise what follows.

What does the programme establish about the loss of synapses? Not about the cause of the disease — about the mechanism by which a synapse present at age fifty is absent at age eighty. Synapse loss remains the best structural correlate of cognitive impairment in this disease, better than plaque or tangle counts (Terry et al., 1991), which means an account of subtraction is an account of the thing the clinic measures.

Which parts survive adversarial testing? The programme has been tested, unusually directly, by a laboratory with a competing candidate receptor. The result of that test is the single most important fact in this evaluation and is given a section of its own.

What have the last four years changed? Two papers from the laboratory itself — Qa-1 and microglial CD94/NKG2 in 2022, C4d in 2025 — and four from other laboratories that have put the same receptor in places the programme never claimed it. Taken together these have moved the account from a single-ligand, single-cell-type hypothesis to something considerably broader, and, as Section 9 argues, considerably harder to falsify.

Sections 2 to 4 assemble the programme from its primary work. Sections 5 to 7 treat the transduction and the two newest findings. Sections 8 and 9 state the central claim and the convergence around it. Sections 10 to 12 give the weaknesses, the strengths, and the relation to other accounts of synaptic loss. Sections 13 and 14 give the refutation conditions and the therapeutic reading.

2. The Accident: Immune Molecules in Healthy Neurons

2.1 A screen that returned the wrong answer

The founding experiment was not about the immune system and was not about disease.

Before a mammal opens its eyes, waves of spontaneous activity sweep across the retina and drive the developing visual pathway. Blocking that activity prevents the lateral geniculate nucleus from segregating its inputs into eye-specific layers. The question in 1998 was which genes carry the instruction.

Corriveau, Huh and Shatz blocked spontaneous action potentials and screened for transcripts whose levels changed. Thirty-two known candidate genes showed nothing. Differential display then returned a decrease in messenger RNAs encoding class I major histocompatibility complex antigens (Corriveau et al., 1998).

Two features of that first paper deserve emphasis, because the whole programme rests on them.

The regulation ran in both directions and in both the immature and mature brain. Visually driven activity regulated class I MHC in the geniculate during the final remodelling of retinal terminals; in the adult hippocampus, kainate-induced seizures *raised* class I MHC transcript levels. This is not a developmental relic. It is an activity-coupled system operating throughout life.

And the pathway's other components were there too. β2-microglobulin, the obligate light chain of the class I MHC heterodimer, was expressed by central neurons. So was CD3ζ, a signalling component of a receptor complex for class I MHC. The finding was not one orphan transcript; it was the outline of a signalling system.

2.2 The functional requirement

A transcript that tracks activity is suggestive. A knockout is evidence.

Huh and colleagues examined mice genetically unable to present class I MHC at the cell surface (β2-microglobulin and TAP1 double mutants) and mice lacking the receptor component CD3ζ (Huh et al., 2000). Three results followed.

Refinement of retinal projections to central targets was incomplete. The developmental sharpening that normally occurs did not occur.

In the adult hippocampus, NMDA-receptor-dependent long-term potentiation was *enhanced* and long-term depression was *absent*. That pairing is the signature of a lost brake. The synapse could still strengthen — more easily than normal — but had lost the capacity to weaken.

And the individual class I MHC genes were expressed by distinct, non-overlapping mosaics of neurons, which raised the possibility, still not resolved, that different members of a fifty-gene family address different circuits.

2.3 Two genes out of fifty

The family's size was a problem. If class I MHC matters for plasticity, which of the fifty-plus mouse genes is doing the work, and is the phenotype in the β2m/TAP1 mice a genuine neuronal effect or a consequence of a systemically broken immune system?

Datwani and colleagues answered the first part by deleting just two genes. Mice lacking H2-K^b and H2-D^b showed enhanced ocular-dominance plasticity — the same phenotype as mice lacking PirB, and, strikingly, the same phenotype as mice lacking all surface class I MHC (Datwani et al., 2009). Two genes accounted for the effect of fifty. The proteins were found not only in visual cortex but in the lateral geniculate nucleus, where their localisation correlated with synaptic markers and with the complement protein C1q — an early and, in hindsight, prophetic observation.

Lee and colleagues answered the second part, and answered it in the way that settles arguments (Lee et al., 2014). In K^bD^b-null mice the developmental decrease in the number of retinal inputs converging on each geniculate neuron failed, and eye-specific layers did not form, despite intact retinal activity and normal basal transmission. Restoring H2-D^b *to neurons alone*, in an animal whose immune system remained compromised, rescued both synapse elimination and eye-specific segregation. The effect is neuronal, not immunological.

The same paper found the mechanism at the level of the learning rule. Using stimulus patterns that mimic endogenous retinal waves, long-term potentiation was intact in the mutants but long-term depression was impaired — because the synapses had an increased complement of calcium-permeable AMPA receptors. Restoring H2-D^b rendered the AMPA receptors calcium-impermeable and restored depression.

This is the most complete causal chain in the entire programme and it has nothing to do with disease: an immune ligand on a neuron sets the subunit composition of a glutamate receptor, which sets whether the synapse can weaken, which sets whether it can be eliminated.

2.4 What the founding decade established

Three propositions, all load-bearing:

- class I MHC molecules are expressed by neurons under the control of neural activity, in both the developing and the adult brain;
- they are required for the elimination of synapses and for the balance between synaptic strengthening and weakening;
- their loss produces a brain with *more* connections and *more* plasticity than normal, not less.

Nothing here concerns Alzheimer's disease. What it supplies is a prior: the brain contains a dedicated molecular apparatus for removing synapses, and that apparatus is built from immune proteins.

3. The Receptor

3.1 A brake with a name

Ligands need receptors. In 2006 Syken and colleagues reported that paired immunoglobulin-like receptor B — PirB, an established MHC class I receptor of the myeloid lineage — is expressed in subsets of neurons throughout the brain, is associated with synapses, and forms complexes with the protein tyrosine phosphatases SHP-1 and SHP-2 (Syken et al., 2006). Soluble PirB fusion protein bound cortical neurons in a manner that depended on MHC class I. And in mice lacking functional PirB, ocular-dominance plasticity was more robust *at all ages*.

That last clause is the important one. The critical period for ocular dominance is the canonical example of a developmental window that closes. In PirB mutants it does not close. The receptor is not a developmental switch that is thrown once; it is a continuous restraint, applied for life.

The phosphatase association identifies the mechanism class. PirB and LilrB2 carry immunoreceptor tyrosine-based inhibitory motifs in their cytoplasmic tails; when the receptor is engaged and those motifs are phosphorylated, SHP-1 and SHP-2 are recruited and dephosphorylate substrates in the vicinity. This is the standard architecture of an inhibitory immune checkpoint (Kang et al., 2016). The neuron, in other words, is running a checkpoint receptor on its dendrites.

3.2 The structural substrate

Between 2013 and 2016 the laboratory established what the brake acts on.

Djurisic and colleagues showed that PirB negatively regulates dendritic spine density and the threshold for adult ocular-dominance plasticity (Djurisic et al., 2013). In PirB-null mice, spine density and spine stability were significantly greater than wild type; miniature synaptic currents were more frequent; long-term potentiation was larger and long-term depression deficient. Monocular deprivation normally produces a robust increase in spine density on layer 5 pyramidal neurons; in the mutants that increase was occluded, because the spines were already there.

Vidal and colleagues then established that the effect is cell-autonomous (Vidal et al., 2016). Using a conditional PirB allele and sparse in-utero electroporation of Cre recombinase, they produced individual layer 2/3 pyramidal neurons lacking PirB in a sea of wild-type neurons and glia. Those individual neurons had elevated spine density and increased miniature excitatory current frequency relative to their untouched neighbours. Dendritic branching and axonal bouton

density were unchanged.

That experiment matters more than its modest presentation suggests. It rules out circuit-level and glial explanations. A single neuron that loses this receptor keeps more of its own synapses. The arithmetic of subtraction is performed inside the cell that loses the contact.

Adelson and colleagues supplied the circuit-level counterpart on the ligand side (Adelson et al., 2016). Mice lacking H2-K^b and H2-D^b had more extensive horizontal cortical connectivity, more highly branched basal dendrites, elevated spine density, elevated axonal bouton density in layer 2/3, and increased miniature current frequency — and enhanced ocular-dominance plasticity persisting into adulthood. The excess connectivity was itself the substrate for the excess plasticity.

3.3 Removing the brake in an adult

The three experiments below are, to this evaluation, the most important in the programme after the C4d work, because they establish that the restraint is *acutely reversible in an adult animal*. A developmental brake that could only be released in a pup would be therapeutically inert.

Bochner and colleagues disrupted PirB function in adulthood two ways: a conditional allele activated late, and minipump infusion of a soluble PirB ectodomain into visual cortex (Bochner et al., 2014). Both enhanced ocular-dominance plasticity in adults. Acute blockade triggered the formation of new functional synapses — miniature excitatory current frequency rose, spine density on layer 5 dendrites rose. And a one-week infusion of the soluble ectodomain *after* the deprivation period allowed recovery from amblyopia, the loss of acuity and spine density produced by long-term monocular deprivation. A structural deficit acquired in development was partially reversed in an adult by blocking one receptor for one week.

Djurisic and colleagues extended the finding to the hippocampus and identified the retrograde messenger (Djurisic et al., 2019). Conditional deletion of PirB from adult pyramidal neurons produced deficient long-term depression across a range of stimulation frequencies with a reciprocal increase in potentiation, and the whole phenotype was explained by disengagement of retrograde endocannabinoid signalling at excitatory synapses. NMDA-receptor-dependent regulation of endocannabinoid signalling was lost; CB1-receptor-dependent and group I mGluR-dependent regulation were intact. Mutant mice performed *better* than wild type in learning and memory tasks.

Albarran and colleagues, working with Jun Ding's laboratory on motor cortex, found the same sign in a different modality (Albarran et al., 2021). PirB-null mice formed more spines, kept more of the new spines formed during learning, and learned a skilled reaching task faster than wild-type littermates. Single-spine glutamate uncaging showed that PirB is required for NMDA-receptor-dependent spine shrinkage — the receptor is part of the machinery that *removes* a spine on cue. Acute inhibition of PirB in the motor cortex of adult wild-type mice increased survival of learning-induced spines and enhanced motor learning.

3.4 The cost that has never been measured

Four independent behavioural and physiological readouts, in three brain regions, all point the same way: less PirB, more synapses, more plasticity, better performance.

This should provoke a question the programme has not answered. If the receptor's removal improves learning at no measured cost, why is it there?

Three candidate answers exist in the programme's own data and none has been tested directly.

The most likely is *stability*. A cortex that cannot close a critical period cannot consolidate. Every measure reported in the PirB-null mice is a measure of acquisition — faster learning, more new spines, larger potentiation, retained plasticity. None is a measure of retention over months, of interference between successively learned tasks, or of the fidelity of a memory recalled long after acquisition. Vidal and colleagues put the hypothesis in a single sentence: PirB may function to co-repress spine density and plasticity, thereby "maintaining headroom" for cells to encode ongoing experience. Headroom is not a quantity anyone has measured.

The second is *metabolic*. Synapses are the brain's dominant energy expense. A cortex with systematically elevated spine density is a cortex with a systematically elevated bill, and the animals in these experiments are young.

The third is *injury*. Adelson and colleagues found that mice lacking either the MHC class I ligands or PirB had smaller infarcts and better motor recovery after middle cerebral artery occlusion, and that this held in hippocampal slice cultures lacking any peripheral immune system (Adelson et al., 2012). Removing the brake was protective in acute injury too. This is the one place where the programme has looked for a cost and found a benefit instead.

The absence of a demonstrated cost is not evidence that there is none. It is a gap, and Section 14 argues that the gap is where the therapeutic risk lives.

4. The Turn to Alzheimer's Disease

4.1 The 2013 result

Kim and colleagues reported that PirB and LilrB2 are receptors for soluble amyloid-β oligomers with nanomolar affinity; that the interaction is mediated by the first two extracellular immunoglobulin domains — the same D1D2 module that binds MHC class I; that engagement leads to enhanced cofilin signalling, which was also observed in human Alzheimer brain; that the deleterious effect of amyloid oligomers on hippocampal long-term potentiation required PirB; and that in an amyloid-overexpressing transgenic mouse, PirB contributed to adult memory deficits and mediated the loss of synaptic plasticity in juvenile visual cortex (Kim et al., 2013).

Set the amyloid question aside for a moment and note the architecture of the claim. It is not "amyloid is toxic and here is another thing it touches." It is "the pathological ligand engages a receptor whose known function is to subtract synapses, at the same site the physiological ligand uses." If true, the disease does not need to invent a mechanism of synapse loss. It borrows one.

4.2 What "receptor" is doing in that sentence

The word carries four distinct claims, which have different evidentiary status and are worth separating, because the challenge in Section 10 attacks only one of them.

Binding. Amyloid-β oligomers bind PirB and LilrB2 with nanomolar affinity in cell-based and biochemical assays. Independent structural and computational work has since modelled the interface, characterising the conformation and size of the Aβ42 oligomers that target LilrB2 and proposing a tetracoordinated arrangement for the recognition (Mei et al., 2023; Ma et al., 2022). These are models, not structures, and should be read as such.

Sufficiency of the receptor for the effect. The oligomer-induced impairment of long-term potentiation required PirB — it did not occur in the null.

Contribution in a disease model. PirB deletion rescued memory deficits in an amyloid-overexpressing transgenic mouse.

Human relevance. Enhanced cofilin signalling was reported in human Alzheimer brain, and LilrB2 is present in human brain.

The first claim — binding, specifically binding to the amyloid species that are actually present in human Alzheimer brain — is the one that has been directly challenged, and it is the one on which

the other three rest.

4.3 A prior clue from 2012

One year before the receptor paper, William and colleagues — with Bradley Hyman's group at Massachusetts General Hospital and with Shatz as a co-author — showed something that is easy to overlook and is arguably a cleaner result than the 2013 paper (William et al., 2012).

They took the canonical *systems-level* assay of cortical plasticity, ocular dominance, and applied it to amyloid-overexpressing mice. Following monocular deprivation during the critical period, mice expressing mutant APP with presenilin-1, and mice expressing mutant APP alone, showed **no ocular-dominance plasticity**. The defect was evident by two independent methods, Arc induction and intrinsic-signal optical imaging in awake animals.

The significance is this. Amyloid overexpression does not merely damage synapses; it abolishes the brain's capacity for the specific form of experience-dependent structural change that PirB and MHC class I regulate. Two systems that had been studied separately — the developmental plasticity apparatus and the amyloid literature — were shown to be operating on the same variable before anyone knew they shared a receptor.

4.4 What the 2013 paper licensed and what it did not

It licensed: LilrB2/PirB is a candidate mediator of amyloid's synaptotoxicity, with a plausible mechanism inherited from developmental biology.

It did not license: LilrB2 is *the* amyloid receptor; the pathway accounts for a defined fraction of human synapse loss; or blocking it in a human being would preserve cognition. Those claims require human causal evidence that does not exist for any candidate amyloid receptor.

The programme has generally been careful about this. The 2013 abstract says the findings "imply that LilrB2 contributes to human AD neuropathology," which is the right strength. Secondary literature has not always been as careful.

5. Transduction: Cofilin, and the Skeleton of the Spine

5.1 The switch

A dendritic spine is a bag of actin. Its shape, its capacity to hold receptors, and its ability to enlarge or shrink on demand are all properties of a filamentous actin network under continuous turnover.

Cofilin regulates that network, and it is regulated in turn by phosphorylation on a single residue, serine 3. Phosphorylated cofilin is inactive and the filament network is stable. Dephosphorylated cofilin severs filaments, increasing turnover; brief, local activation of cofilin is a normal and necessary part of synaptic plasticity. LIM kinase phosphorylates the residue; the slingshot phosphatases remove the phosphate.

The 2013 paper's mechanistic claim is that ligand binding to the D1D2 domains of PirB/LilrB2 recruits phosphatase activity through the receptor's inhibitory motifs and drives cofilin dephosphorylation past the physiological range.

5.2 From severing to bundling

What happens beyond that range is the part of the story that explains structural collapse rather than merely functional weakening, and it comes from outside the programme.

Minamide and colleagues showed that a range of neurodegenerative stimuli induce persistent rods composed of ADF/cofilin and actin, which form within neurites and disrupt distal neurite function (Minamide et al., 2000). At high concentrations of active cofilin the protein's behaviour inverts: instead of severing filaments it saturates and bundles them into a rigid, insoluble, one-to-one cofilin–actin lattice. Bamburg and colleagues have reviewed the biology of these rods and their multiple modes of regulation in neuronal development and degeneration (Bamburg et al., 2021).

The consequence for a spine is mechanical rather than biochemical. A rod occupying a spine neck occludes it. Cargo cannot pass. Receptors cannot be delivered; mitochondria cannot be delivered; the spine is functionally disconnected before it is anatomically absent.

This gives the pathway a property that most accounts of synaptic dysfunction lack: it predicts a structure, and the structure is observable.

5.3 Independent corroboration that the cofilin axis is dysregulated in the disease

Rush and colleagues, working independently of the programme, showed that synaptotoxicity in Alzheimer's disease involves dysregulation of actin cytoskeletal dynamics through cofilin 1 phosphorylation (Rush et al., 2018). This is corroboration of the *node*, not of the receptor: it establishes that the cofilin switch is disturbed in the disease without establishing which receptor disturbs it.

That distinction runs through this whole section, and it is worth stating as a rule for reading the programme. **The cofilin endpoint is well evidenced and multiply sourced. The attribution of that endpoint to LilrB2 rests on the programme's own work and on the LOTUS experiments discussed in Section 9.4.**

5.4 A note on directionality

One further observation belongs here, and it is a juxtaposition rather than a finding.

Reelin — the extracellular glycoprotein that guides cortical lamination and, in the adult, restrains tau phosphorylation through the lipoprotein receptors ApoER2 and VLDLR — acts on the same residue of the same protein, in the opposite direction. Chai and colleagues showed that reelin signalling, via ApoER2, Disabled-1, Src-family kinases and PI3-kinase, induces serine-3 phosphorylation of n-cofilin, rendering it unable to depolymerise F-actin and thereby stabilising the cytoskeleton (Chai et al., 2009).

So two receptor systems on the same neuron converge on serine 3 of cofilin with opposite signs. Reelin, through ApoER2, phosphorylates it and stabilises the actin network. Amyloid, through LilrB2, dephosphorylates it and destabilises the network. One is a guardian of structure and the other an instruction to dismantle, and they are writing to the same address.

This has not been demonstrated in a single experiment and is offered here as an inference from two literatures that do not cite one another. It is the most tractable untested prediction in this paper, and Section 13 states it as a falsifier: if reelin signalling and LilrB2 signalling are co-manipulated in the same neurons, they should show measurable antagonism at serine 3, and if they do not, the convergence is coincidental.

6. The Second Ligand

6.1 C4d: from inert marker to ligand

The classical complement pathway is initiated by the C1 complex. C1s cleaves C4 into soluble C4a and surface-depositing C4b; factor I then cleaves membrane-bound C4b into C4c, which is released, and C4d, which remains **covalently attached to the surface where the cascade fired**.

Clinically, C4d has been used for decades as a durable footprint of complement activation — in transplant rejection, in particular, where it marks antibody-mediated injury. Biologically it was an orphan: a stable residue with no known receptor and no known signalling function in the central nervous system.

Brott and colleagues report that C4d is a high-affinity ligand for LilrB2 and PirB, that it marks human excitatory synapses, that it rises with age and further in Alzheimer's disease, and that it is sufficient to remove dendritic spines from an adult mouse cortex through PirB (Brott et al., 2025).

6.2 The binding

Surface plasmon resonance gave a dissociation constant of about 3 nM for C4d binding to LilrB2 in the cell-free measurement. Binding to LilrB1, the closely related family member, was not detected — the interaction is selective within the family. Cell-based measurements gave weaker but still high affinities: about 37 nM on LilrB2-expressing HEK293 cells and about 56 nM for murine PirB.

Binding mapped to the N-terminal D1D2 immunoglobulin domains: the same module that binds MHC class I and the same module reported to bind amyloid oligomers.

That single structural fact carries most of the paper's conceptual weight. **The receptor is not acquiring a new function in disease. It is receiving a new ligand at an existing site.** Whatever the neuron does when a class I MHC molecule engages D1D2 is what it will do when C4d engages D1D2.

6.3 The human anatomy

The colocalisation work used array tomography — ultrathin serial sectioning with immunofluorescence, which resolves individual synapses without the axial blurring that defeats conventional confocal microscopy at this scale. The technique is well suited to the question and Kristina Micheva, one of its developers, is an author.

In human cortex, nearly 60% of excitatory synapses carried C4 or LilrB2 immunostaining, and about 30% carried explicit C4d signal. Colocalisation at inhibitory synapses was roughly threefold lower.

Two things follow. First, this is not a rare event confined to the neighbourhood of plaques: a third of excitatory synapses in human cortex carry the ligand. Second, the excitatory selectivity is a real anatomical prediction, and it matches the pathology — excitatory synapse loss dominates the structural picture in Alzheimer cortex.

The quantities also rise where the theory says they should. C4 and LilrB2 messenger RNA increase in human cortex from around 24 years of age and plateau at about 40. C4 protein was elevated and C4d protein about fourfold higher in Alzheimer prefrontal cortex than in age-matched controls. In the APP/PS1 mouse, C4 message and C4d protein were both elevated relative to wild type at 13–16 months. In Alzheimer brains, C4d–LilrB2 colocalisation was enriched near amyloid plaques, and oligomeric amyloid, LilrB2 and C4d were frequently found together at individual synapses.

6.4 The causal test

Correlation in human tissue plus a mouse experiment is the standard structure, and here the mouse experiment is unusually clean.

Recombinant C4d was infused into the cortex of adult mice (from postnatal day 70) by osmotic minipump — approximately 10 µg total, delivered at 0.25 µL/h over four days. Dendritic spine density on layer 5 pyramidal neurons fell significantly in wild-type animals, within roughly 800 µm of the infusion site. In PirB-null mice, spine density after C4d infusion was indistinguishable from BSA-infused controls.

Read the result precisely, because its precision is what makes it valuable:

- **Sufficiency.** A single complement fragment, applied to an otherwise normal adult brain with no amyloid, no tau, no inflammation and no transgene, removes dendritic spines.
- **Necessity of the receptor.** The effect is entirely PirB-dependent. Not attenuated — abolished.
- **Adult.** This is not a developmental window phenomenon.
- **Locality.** The 800 µm radius corresponds roughly to the diffusion field, which is what one expects of a ligand acting where it lands.

6.5 What this changes about the pruning debate

The literature on synapse elimination in Alzheimer's disease has, since 2007, been largely a literature about microglia. Stevens and colleagues established that C1q, the initiating protein of the classical cascade, is expressed by postnatal neurons and tags synapses for elimination in the developing visual system (Stevens et al., 2007). Hong and colleagues showed that in Alzheimer mouse models C1q is increased and associated with synapses before overt plaque deposition, that inhibiting C1q, C3, or the microglial complement receptor CR3 reduces early synapse loss, and that microglia engulf synaptic material in a CR3-dependent manner when exposed to soluble amyloid oligomers (Hong et al., 2016).

That account has a structural feature worth naming: **every step of it requires a microglion**. The opsonin is a flag; the flag must be read by a phagocyte; the phagocyte does the removing.

The C4d result adds a second arm with a different topology. C4d is generated by the same cascade at the same synapse — but instead of, or in addition to, flagging the synapse for an external eater, it binds a receptor on the postsynaptic neuron and instructs that neuron to disassemble its own spine. No phagocyte is required for the spine to be lost.

Three consequences follow.

It resolves an evidentiary awkwardness. Direct human evidence for microglial complement-dependent synapse engulfment in Alzheimer tissue has been harder to obtain than the mouse literature would suggest, and the mechanisms demonstrated in human tissue have not always been complement-dependent. A neuron-intrinsic arm is more tractable in fixed human material, because it requires colocalisation rather than a caught-in-the-act phagocytic event. The array tomography in Brott and colleagues is exactly that kind of evidence.

It changes the therapeutic arithmetic. Anti-C1q and anti-CR3 strategies act on the glial arm. If the neuronal arm operates in parallel, blocking the glial arm alone leaves the synapse being dismantled from within. Conversely, blocking the receptor leaves the opsonin in place, and the phagocyte can still act.

It reframes complement's role. In the microglial account, complement is a tagging system. In this account complement is also a *signalling* system, with a durable, covalently tethered ligand and a neuronal receptor — a considerably more consequential position for it to occupy.

6.6 What the paper does not show

The evaluation is only as good as the caveats, and there are several.

The array tomography was performed on a small number of human specimens: fresh resected temporal cortex from a 60-year-old, and superior frontal gyrus from a 70-year-old Alzheimer donor. Western blot comparisons used Alzheimer donors aged 81 and 85 against two age-matched 85-year-old controls. These are small numbers, which the anatomical detail justifies but which do not support population-level inference. The fourfold C4d elevation is a real measurement in a small cohort and should be read as such.

The minipump concentration is high relative to anything a synapse plausibly sees in vivo. Sufficiency at a supraphysiological dose does not establish that endogenous C4d contributes materially to synapse loss at endogenous concentrations. That is the single largest inferential gap in the paper.

Residual C4d binding persisted in PirB-null tissue, which the authors attribute to additional putative C4d receptors known in immune cells — neuropilin is named. The receptor is dominant for the spine phenotype, but it is not the only binding site.

No new cofilin data are presented. The mechanistic link from C4d engagement to spine collapse is carried over from the 2013 amyloid work by analogy at the shared D1D2 site. It is a reasonable inference and it is an inference.

And the human data are cross-sectional and post-mortem. C4d rises with age and rises further in disease. Whether it rises *before* synapse loss in a given human brain is not addressed and, with post-mortem tissue, cannot be.

7. The Other Recent Finding: Qa-1 and the Microglial Reader

7.1 The result

The programme's other publication of the last four years is easily overlooked next to the C4d paper and points somewhere quite different (Marin et al., 2022).

Qa-1 is a non-classical MHC class I molecule — the mouse counterpart of human HLA-E. Marin and colleagues found it expressed in the healthy brain by layer 6 corticothalamic neurons. In visual cortex its expression begins during the critical period for ocular-dominance plasticity and is regulated by neuronal activity. In mice lacking Qa-1, ocular-dominance plasticity is perturbed.

The receptor, though, is not on a neuron. Qa-1's cognate immune receptor is the CD94/NKG2 heterodimer, and in cortex CD94/NKG2 is expressed by **microglia**. Selectively targeting the Qa-1/CD94-NKG2 interaction phenocopied the plasticity defect of the Qa-1 knockouts, and microglia underwent activity-dependent changes in morphology in a Qa-1-dependent manner.

7.2 A neuron speaking to a microglion in immune vocabulary

Read structurally, this is the mirror image of everything else in the programme.

In the PirB axis, a ligand in the extracellular space engages a receptor on the neuron and the neuron acts on itself. In the Qa-1 axis, the neuron *is the ligand-bearing cell* and the microglion carries the receptor. Layer 6 neurons display an activity-regulated MHC class I molecule that microglia read, and the reading changes microglial morphology and the plasticity of the circuit.

The general form is a class of signal that the field has come to call "don't-eat-me" or, more accurately, "restrain yourself" signalling — a neuron-expressed ligand that suppresses a microglial effector function. CD47 acting on microglial SIRPα is the best-known example; HLA-E acting on CD94/NKG2 is the classical inhibitory pair in natural-killer-cell biology, and its appearance in cortex is genuinely unexpected.

Salminen's recent review makes the point that the brain in Alzheimer's disease is unusually rich in ligands for inhibitory checkpoint receptors — LILRB2-4, the Siglecs, PD-1, SIRPα — and argues that inappropriate inhibitory checkpoint signalling contributes to the disease by suppressing microglial function (Salminen, 2025). The Qa-1 finding sits squarely in that frame and precedes

most of it.

7.3 Why it matters for the disease account

Two reasons, one direct and one structural.

Directly: the Qa-1 paper establishes that the same molecular family the programme has been studying operates at the neuron–microglia interface as well as inside the neuron. Any full account of synapse elimination in this brain has to include both, and they can have opposite signs — one arm restrains the microglion, the other instructs the neuron.

Structurally: it is the clearest demonstration that this programme's central object is not a molecule but a *vocabulary*. The brain has repurposed the immune system's language of self-presentation and restraint for the negotiation of which synapses stay. That is the programme's real claim, and Section 8 states it precisely.

8. The Central Claim: Development's Machinery, Reused

8.1 Stating it precisely

The claim implicit across twenty-seven years, and stated explicitly in the programme's own review of the field (Shatz, 2009) and in its lectures, has three parts.

One. The mammalian brain removes synapses during development by a dedicated molecular programme built out of immune-system components — MHC class I ligands, their neuronal receptors, and the classical complement cascade.

Two. That programme is not dismantled when development ends. It runs, under activity control, for life, and is what sets the ceiling on adult plasticity.

Three. In Alzheimer's disease, pathological ligands engage that programme's receptors, and synapse loss is the programme executing without its normal constraints.

The three parts have very different evidentiary status and should never be quoted as a unit. Part one is established. Part two is established for PirB specifically and by strong inference for the ligands. Part three is a hypothesis supported by mouse causal experiments and human anatomical correlation.

8.2 The schizophrenia parallel

The strongest external support for the general shape of the claim comes from a different disease.

Sekar and colleagues showed that schizophrenia's strongest population-level genetic association, at the MHC locus, arises in substantial part from structurally diverse alleles of the complement component 4 genes; that these alleles generate widely varying C4A and C4B expression in brain; that each common allele associates with schizophrenia in proportion to its tendency to generate greater C4A expression; that human C4 protein localises to neuronal synapses, dendrites, axons and cell bodies; and that in mice C4 mediates synapse elimination during postnatal development (Sekar et al., 2016).

The inference the field drew is that schizophrenia involves excessive synaptic pruning during adolescence, when the prefrontal cortex is normally pruned.

If that is right, then the same developmental elimination programme is implicated in two disorders, at two different ages, in two different cortical regions, by two different mechanisms of over-engagement: in schizophrenia by inherited over-expression of the ligand-generating cascade, in Alzheimer's disease by age-related and pathology-driven accumulation of the ligand.

This is a genuine and substantial argument, and it is worth being clear about what it is an argument *for*. It supports the claim that the pruning programme is a real, shared, disease-relevant target. It does not, on its own, support any specific claim about LilrB2, because the schizophrenia work implicates C4 without implicating a neuronal receptor.

What the 2025 C4d paper adds is precisely the missing link: it names a neuronal receptor for a C4 product. If that holds, the two diseases converge not only on a cascade but on a receptor.

8.3 The strong version and the weak version

The claim admits two readings and they are very different theories.

The strong version. Synapse loss in Alzheimer's disease *is* developmental pruning, re-run. The critical-period machinery is reactivated; the disease is a developmental process out of time.

The weak version. Synapse loss in Alzheimer's disease *uses* components of the developmental pruning machinery, among other mechanisms, without being that process.

The strong version is more interesting and less supported. It predicts things that have not been observed: a coordinated developmental transcriptional programme re-expressed in ageing cortex; competition between inputs as the selection rule for which synapses go; a restored capacity for the kind of large-scale structural reorganisation critical periods permit. None is established in Alzheimer tissue.

The weak version is what the evidence supports, and it is not a small claim. It says that the disease's most clinically consequential lesion is executed by a normal, conserved, receptor-mediated programme with an identified ligand, an identified receptor, an identified second messenger and an identified structural endpoint. That is more mechanistic specificity than most accounts of synapse loss in this disease can offer.

8.4 One asymmetry worth noting

There is an asymmetry between the developmental and disease arms that the programme does not dwell on.

Developmental pruning is *selective*: it removes the inputs that lose a competition and keeps those that win, and the selection rule — correlated activity — is well characterised. The ligands are activity-regulated, and that regulation is the mechanism of selection.

The disease arm as described has no comparable selection rule. C4d is deposited where complement fires; amyloid oligomers accumulate where they accumulate. The receptor executes on whatever synapse the ligand reaches.

That difference is the strongest reason to prefer the weak version. Developmental pruning is *sculpting*. What the disease arm describes is *erosion*. The molecules are shared; the logic is not.

9. One Receptor, Several Addresses

Between 2022 and 2026, laboratories with no connection to the programme placed the same receptor in three places the programme never claimed, and identified an endogenous molecule that blocks it. These findings are what the phrase "recent progress" most directly refers to, and they change the shape of the account.

Table 1 — Reported ligands of LilrB2/PirB relevant to the nervous system

Ligand	Source	Site on receptor	Status
MHC class I (H2-K^{b}, H2-D^{b}; HLA class I)	Neuron, activity-regulated	D1D2	Established; the physiological ligand (Syken et al., 2006)
Nogo, MAG, OMgp	Myelin	Ectodomain	Established; PirB is a high-affinity receptor for all three (Atwal et al., 2008)
Amyloid-β oligomers	Pathological	D1D2	Contested — see §10.1 (Kim et al., 2013; Smith et al., 2019)
C4d	Complement activation at the synapse	D1D2	New; Kd ≈ 3 nM cell-free (Brott et al., 2025)
Angiopoietin-like proteins	Systemic	Ectodomain	Established outside the CNS (Zheng et al., 2012)
Phosphatidylserine	Apoptotic/stressed membranes	—	Reported as a shared LILRB2/TREM2 ligand (Zhao et al., 2022)
LOTUS	Endogenous antagonist	Blocks Aβ site	Blocks Aβ binding to PirB and LilrB2 (Kawaguchi et al., 2022)

9.1 The microglial address

Zhao and colleagues reported that LILRB2 is expressed, together with TREM2, on human brain microglia, and that co-ligation of the two receptors by a shared ligand — amyloid oligomers or phosphatidylserine — significantly inhibits TREM2 signalling (Zhao et al., 2022). They raised antagonist antibodies against LILRB2 with sub-nanomolar potency. In human iPSC-derived microglia, blocking LILRB2 rescued TREM2 signalling, enhanced phagocytosis of amyloid oligomers, increased migration, and restored cytokine responses. In 5XFAD mice grafted with human microglia, the antibody increased microglial clustering around plaques and markedly increased plaque phagocytosis.

The importance of this for the present evaluation is hard to overstate, for two reasons.

It puts the receptor on the other principal cell type in the disease, with the *same sign*: LILRB2 is a brake there too, and blocking it releases the brake. Given that loss-of-function variation in TREM2 is among the largest genetic risk factors for Alzheimer's disease, a receptor that pharmacologically suppresses TREM2 signalling is a significant object.

And it means that a single antagonist would act at two places at once — protecting the spine from a disassembly instruction and licensing the microglion to clear. It is rare for one target to have two beneficial addresses in this disease. It is also, as Section 14 notes, a reason for caution rather than only for optimism.

9.2 The astrocytic address

Zhang and colleagues reported that astrocytes express PirB and that it governs glutamate handling (Zhang et al., 2026). Inhibiting astrocytic PirB — with a soluble PirB extracellular peptide, with the small molecule fluspirilene, or by knockdown — raised expression of the excitatory amino-acid transporters EAAT1 and EAAT2, activated mTOR signalling, and reduced neuronal apoptosis in neuron–astrocyte co-culture; overexpression did the reverse. Mice with astrocyte-specific conditional PirB deletion, injected intrahippocampally with amyloid oligomers, showed better working memory, higher EAAT expression, and less hippocampal neuronal loss than floxed controls.

Glutamate reuptake is the astrocyte's principal protective function in this disease. If amyloid suppresses it through PirB, the receptor is also an excitotoxicity node. This is one paper, in one model, using intrahippocampal oligomer injection — a model with well-known limitations — and should be carried as preliminary. But its direction is consistent with everything else: the receptor restrains a protective function, and blocking it restores that function.

9.3 The intracellular address

The most surprising of the recent findings is Han and colleagues' report that PirB is proteolytically cleaved upon amyloid exposure, in Alzheimer patients and in mouse models, and that the resulting C-terminal fragment does damage from inside the cell (Han et al., 2026).

Proteomic screening of human cerebrospinal fluid identified cleaved membrane proteins; the cleavage was then validated in post-mortem Alzheimer brain, primary neurons and APP/PS1 mice. The C-terminal fragment accumulates in the Golgi apparatus by retrograde transport and binds the GAT domain of GGA3, disrupting Golgi transport, impairing lysosomal maturation, and compromising anterograde synaptic vesicle transport. Inhibiting the cleavage, or over-expressing the GGA3-GAT domain, restored Golgi function, reduced plaque burden and tau phosphorylation, and rescued memory deficits.

If this replicates, it means the receptor has a second, non-canonical mode: engaged by the pathological ligand, it is cut, and its tail becomes an intracellular saboteur of the trafficking system. That mode is not a checkpoint at all, and it is not something the developmental framework anticipated.

It also has a specific therapeutic implication that differs from everything else in this paper: if the damage is done by the fragment, blocking the ligand at the ectodomain and blocking the *cleavage* are different interventions, and the second might matter more.

9.4 The endogenous antagonist

Kawaguchi and colleagues had previously identified LOTUS (lateral olfactory tract usher substance) as an endogenous antagonist of the type-1 Nogo receptor and of PirB. They then showed that LOTUS inhibits the binding of amyloid to PirB in a heterologous expression system; that in cultured hippocampal neurons from LOTUS-overexpressing transgenic mice, amyloid-induced dephosphorylation of cofilin and amyloid-induced loss of PSD-95 were both suppressed; that the amyloid-induced fall in dendritic spine density was improved in those neurons; and that human LOTUS inhibits amyloid binding to human LilrB2 in the same way (Kawaguchi et al., 2022).

This is important as corroboration rather than as therapy. It is an independent laboratory, using a different tool — a natural competitive antagonist rather than a knockout — reproducing the specific mechanistic chain the programme proposes: block the ligand at the receptor, and the cofilin dephosphorylation, the PSD-95 loss and the spine loss are all prevented. That is the strongest external replication the amyloid arm has.

It also identifies a candidate endogenous resilience factor. If LOTUS levels vary between people, they are a plausible modifier of how much synaptic damage a given amyloid burden produces — which is the variable that the resilience literature in human tissue keeps landing on

(Perez-Nievas et al., 2013).

9.5 A receptor that explains too much

Table 2 — Where the receptor has been placed, and with what confidence

Location	Function reported	Consequence of blocking	Confidence
Cortical/hippocampal pyramidal neuron	Restrains spine density, plasticity, LTD; transduces Aβ and C4d to cofilin	More spines, more plasticity, better learning; spine loss prevented	High for the physiological role; contested for the Aβ ligand
Microglion	Inhibits TREM2 signalling on shared-ligand co-ligation	Restored TREM2 signalling, phagocytosis, migration	Moderate — one laboratory, strong design
Astrocyte	Suppresses EAAT1/2 via mTOR	Restored glutamate uptake, less neuronal death	Low–moderate — single study, one model
Golgi (cleaved cytoplasmic fragment)	Binds GGA3-GAT, jams trafficking	Restored Golgi and lysosomal function	Low — single study, 2026, not replicated
Axon (myelin inhibitor receptor)	Mediates Nogo/MAG/OMgp inhibition of regeneration	Partial release from myelin inhibition	High (Atwal et al., 2008)

Two readings of this table are possible and honesty requires stating both.

The generous reading: an inhibitory receptor family that evolved to hold immune effectors in check has been recruited by several cell types in the brain to hold *their* effector functions in check, and one antagonist would release all of them.

The sceptical reading: a receptor that appears in every cell type, binds every ligand tried, and whose blockade improves every outcome measured, is a receptor whose literature is running ahead of its evidence. Fields that report only positive findings for a single target tend to be corrected later. The Expression of Concern issued in 2025 over an unrelated 2012 PirB paper on hypoxic-ischaemic injury, following image-duplication concerns to which the authors did not respond, is a reminder that the wider PirB literature is uneven in quality and should not be read as a uniform body.

This paper's position is that the neuronal and microglial addresses are well enough evidenced to build on, and that the astrocytic and intracellular addresses should be regarded as interesting and unreplicated.

10. Where the Programme Is Weak

10.1 The head-to-head binding failure

This is the most serious challenge to the programme and it must be stated in full rather than in summary.

Smith, Kostylev, Lee and Strittmatter set out to compare the reported amyloid-β receptors under standardised conditions — the same assays, the same amyloid preparations, controlled and confirmed cell-surface expression (Smith et al., 2019). Of fifteen reported receptors surveyed, only three showed direct binding to synaptotoxic assemblies of synthetic amyloid: cellular prion protein, Nogo receptor 1, and LilrB2. So far this is a partial vindication: LilrB2 is one of three survivors out of fifteen.

The problem is what happened with human material. Binding studies using soluble amyloid oligomers extracted from human Alzheimer brain revealed strong affinity for cellular prion protein, weak affinity for NgR1, and **no detectable affinity for LilrB2**. And hippocampal neurons lacking both NgR1 and LilrB2 showed a smaller reduction in oligomer binding than neurons lacking prion protein alone.

Three points about how to read this.

It is a serious, well-designed challenge. The whole point of the study was to remove the between-laboratory variability that makes this field difficult, and it is the only such comparison that exists. Its result on human-derived material directly contradicts the claim that most needs human support.

The competing-interest structure should be visible but not used to dismiss it. The senior author is the founder of a company developing NgR1-targeted therapeutics and is an inventor on a patent covering prion-protein antagonism for Alzheimer's therapy; both are disclosed in the paper. That is a reason to want independent replication. It is not a reason to discount a negative result obtained under controlled conditions, and no independent replication of the comparison has appeared in the seven years since.

Its scope is narrower than it first appears. The study tested binding of amyloid species to receptors. It says nothing about C4d, which was not known to be a ligand in 2019 and was measured by different methods with a defined recombinant protein. It says nothing about the developmental work. It does not address whether LilrB2 engagement, however achieved, produces

the downstream cofilin and spine phenotypes — which the LOTUS experiments independently support. And amyloid extracted from post-mortem brain is a heterogeneous and partly aggregated material whose relationship to the species present at a living synapse is itself uncertain.

The honest conclusion is that the amyloid arm of the programme is **contested on its central biochemical claim, and unresolved**, and that the complement arm is not affected by the challenge. This evaluation carries it that way throughout.

10.2 Amyloid-receptor pluralism, and what it does to the arithmetic

Even taking the 2013 binding data at face value, the field the claim enters is crowded. Prion protein (Laurén et al., 2009), NgR1, EphB2, the α7 nicotinic receptor, RAGE, the insulin receptor and a dozen others have been proposed as amyloid receptors. Amin and Harris have argued that this multiplicity is not simply a failure of rigour: several receptors recognise shared molecular features displayed by fibril ends and by neurotoxic oligomers, which would explain why so many different proteins bind the same material (Amin and Harris, 2021).

If that is right, the question changes from "which is the receptor" to "what fraction of the synaptotoxicity does each carry, in a human brain, at endogenous concentrations." Nobody has answered that for any candidate, and the experiment that would answer it — a controlled comparison of single and combined receptor deletions against a defined human-derived amyloid preparation, measuring synapse loss rather than binding — has not been done.

It also weakens the therapeutic case for targeting any one of them. A pathway with five parallel receptors is a pathway in which blocking one changes little.

10.3 The evidence is mouse-heavy where it matters most

Every causal experiment in the programme is a mouse experiment. Every human experiment is anatomical or biochemical correlation.

That is not a criticism of the laboratory — it is the structure of the field, and the array tomography work is among the better human anatomy in the synapse-loss literature. But it should be named clearly, because the mouse models used are amyloid-overexpressing transgenics, which produce amyloid at concentrations and on timescales that do not correspond to human sporadic disease. The rescues obtained in those animals establish that the receptor mediates *that model's* phenotype.

The C4d minipump experiment is a partial exception and is the more valuable for it: it uses no transgene at all, applying a defined human-relevant ligand to a normal adult brain. It is the closest thing the programme has to a clean causal demonstration, and the reason it is clean is that it dispenses with the model.

10.4 The genetics do not point cleanly

If LILRB2 were a major executor of synapse loss, one might expect its common variation to influence risk.

The picture is genuinely mixed. Large European genome-wide studies have expanded the risk locus catalogue substantially (Bellenguez et al., 2022), and the LILRB cluster has entered the discussion, but not as a large-effect locus. The most informative recent work is a cross-ancestry study in East Asians which establishes LILRB2-LILRB5 as an Alzheimer's susceptibility locus with **ethnic-specific effects**: the lead variant rs587709-T is associated with decreased risk and increased LILRB5 expression in Europeans, and with *increased* risk and increased LILRB2 expression in East Asians (Cao et al., 2026).

That is a real association and a genuinely interesting one — the direction inverts with ancestry, and the gene whose expression tracks the variant differs. But a locus whose effect direction flips between populations is not a locus that establishes a mechanism, and a candidate-gene study in a Chinese Han cohort found no association at rs1761461/LILRB2 (Yan et al., 2024).

The fair summary: the genetics are consistent with the locus mattering, are not consistent with it mattering greatly or simply, and cannot at present be used to support the mechanism.

10.5 What the programme has not addressed

Four absences are worth naming.

Tau. The programme has essentially nothing to say about tau, which is the pathology that tracks the topography and timing of neurodegeneration most closely. The 2026 cleavage paper reports reduced tau phosphorylation when PirB cleavage is inhibited, which is the first connection of any kind, and it comes from another laboratory.

Regional selectivity. Nothing in the mechanism explains why the entorhinal cortex and hippocampus fail first. C4 and LilrB2 expression rise with age across cortex. A mechanism with a uniform substrate does not by itself produce a regionally ordered disease.

The age curve. C4 and LilrB2 messenger RNA rise from the mid-twenties and plateau at about forty. Symptomatic disease begins decades later. Whatever converts a longstanding elevated ligand-and-receptor state into synapse loss is not in the account.

Excitatory-inhibitory balance. The colocalisation is threefold lower at inhibitory synapses. If the mechanism preferentially removes excitatory contacts, it should shift the excitatory-inhibitory balance of the cortex in a specific direction, with consequences for network function that are measurable and have not been measured.

10.6 A note on secondary presentation

One recurring problem is not the laboratory's but the field's. The 2013 title — "Human LilrB2 is a β-amyloid receptor" — has been widely quoted as though the definite article were settled, and the 2025 C4d finding has already been summarised in places as demonstrating that complement drives synapse loss in Alzheimer's disease, which is a stronger statement than a four-day minipump infusion in a mouse supports. The primary papers are more careful than their reception. This evaluation has tried to cite the papers rather than the reception.

11. Where the Account Is Strong

Against those weaknesses, five things stand.

The prior is genuine and was established first. The receptor's synapse-eliminating function was characterised over fifteen years, in health, before any disease claim was made. Most proposed mediators of synaptic damage in Alzheimer's disease are molecules found by looking for damage. This one was found by asking why a critical period ends. The disease claim is therefore constrained by an independent body of work in a way that most are not.

The causal experiments are bidirectional and acute. Delete the receptor and the injury does not occur; block it acutely in an adult and plasticity returns; supply the ligand and spines are lost; supply the ligand to a receptor-null animal and nothing happens. Add the independent LOTUS experiments, where a natural antagonist prevents the cofilin dephosphorylation, the PSD-95 loss and the spine loss, and the pathway has been manipulated from four directions.

The mechanism terminates in a structure. Most accounts of synaptic dysfunction terminate in a functional measurement. This one terminates in actin: a named residue on a named protein, a switch with a known inversion at high activity, and a rod that physically occludes a spine neck. That is a mechanism one can look for in tissue.

The anatomy is human and quantitative. A third of human excitatory synapses carrying the ligand, a threefold excitatory-over-inhibitory selectivity, a fourfold elevation in disease, and colocalisation with amyloid at individual distressed synapses is more than most mechanisms in this field have.

It is a mechanism of subtraction. The clinical variable in Alzheimer's disease is loss — of synapses, of function, of self. Accounts built on accumulation must add a step to reach loss. This one begins there.

12. Relation to Other Accounts of Synaptic Loss

12.1 The microglial-engulfment account

Complementary, not rival. Stevens' and Hong's work establishes that complement tags synapses and that microglia remove them; Brott's work establishes that a downstream product of the same cascade instructs the neuron to remove the spine itself. Both arms are fed by the same upstream event. The correct picture is a cascade with two effector limbs — one cellular, one cell-intrinsic — and the open question is their relative contribution, which nobody has measured.

The prediction that separates them is straightforward: microglial depletion or CR3 blockade should abolish the glial arm and leave the neuronal arm intact. A C4d minipump experiment in a microglia-depleted cortex would settle it in a fortnight.

12.2 The intraneuronal-amyloid account

Gouras and colleagues have argued for two decades that amyloid accumulates inside vulnerable human neurons, in the endosomal compartments that also traffic glutamate receptors, and that a loaded compartment damages the synapse from within.

The two accounts sit on opposite sides of the same membrane and are not in conflict. One describes a signal arriving at the postsynaptic surface; the other describes cargo accumulating in the compartment behind it. They even predict an interaction: a receptor that is chronically engaged and internalised will traffic through the same endosomal system that the intraneuronal account says is already overloaded. The 2026 finding that a cleaved PirB fragment reaches the Golgi and jams GGA3-dependent transport is, if it holds, exactly that interaction.

12.3 The cofilin convergence with reelin signalling

Set out in §5.4 and restated here because it is the sharpest testable link between this programme and a separate literature. Reelin, through ApoER2 and Dab1, phosphorylates n-cofilin at serine 3 and stabilises the actin cytoskeleton (Chai et al., 2009). Amyloid, through LilrB2, drives dephosphorylation of the same residue and destabilises it (Kim et al., 2013). One residue, two receptors, opposite signs, both on the dendrites of the same cortical pyramidal neurons.

If that antagonism is real, then reelin signalling is a candidate endogenous buffer against LilrB2-mediated spine collapse, and the loss of reelin signalling that accompanies apolipoprotein E4

carriage would be expected to lower the threshold at which a given ligand load produces structural damage. Neither literature has tested this. It is a two-experiment question.

12.4 The matrix

One further connection deserves a sentence, since it bears on which synapses are reachable at all. Perineuronal nets — the condensed, highly sulfated extracellular matrix that encases subsets of cortical interneurons — physically restrict synaptic remodelling and are, like PirB, a brake on plasticity whose removal reopens critical periods. Two independent brakes on the same process, one molecular and one structural, both implicated in the closure of developmental windows, is a coincidence worth someone's attention: a synapse buried in matrix may be inaccessible to a diffusing complement fragment, which would predict that net-ensheathed synapses are spared the C4d-LilrB2 mechanism and lost by some other route. The array tomography needed to check this has already been done for other purposes.

12.5 Where amyloid sits in this account

Worth stating explicitly, because the programme is often filed under "amyloid".

In the strong reading of the 2013 paper, amyloid is the ligand and the mechanism is a limb of the amyloid cascade (Selkoe and Hardy, 2016). In the reading this evaluation prefers — following the 2025 work and the challenge in §10.1 — amyloid is *one* ligand for a receptor that has several, and the receptor's engagement by complement products is at present better evidenced in human tissue than its engagement by human-derived amyloid.

That is an unusual position and it is worth naming plainly: **the newer arm of this programme is the better-evidenced arm**, and it is not an amyloid arm.

13. What Would Refute It

A mechanism worth taking seriously states its failure conditions. These are ordered from most to least decisive.

One. Demonstrate, in human tissue with adequate numbers, that C4d deposition at synapses does not precede synapse loss — that it marks synapses already lost rather than synapses about to be. C4d is a durable footprint, and a footprint can be left after the event. This is the single most important open question about the 2025 result and it is answerable with staged post-mortem cohorts.

Two. Show that PirB deletion does not protect synapses in a model that does not over-express amyloid — a knock-in model, or an aged wild-type animal. Every protection result to date comes from over-expressing transgenics.

Three. Repeat the standardised binding comparison (Smith et al., 2019) with independent hands and independent human amyloid preparations. If LilrB2 again fails to bind human-derived oligomers, the 2013 claim should be withdrawn as stated, whatever the C4d arm shows.

Four. Show that C4d's spine-stripping effect requires supraphysiological concentrations — that it disappears at concentrations matching those measured in human cortex. Sufficiency at 10 µg over four days does not establish contribution at endogenous levels.

Five. Test the reelin antagonism directly. Co-manipulate ApoER2/Dab1 signalling and LilrB2 signalling in the same neurons and measure serine-3 phosphorylation of cofilin. If the two do not interact at that residue, the convergence proposed in §5.4 and §12.3 is coincidental and should be dropped.

Six. Deplete microglia and repeat the C4d infusion. If the spine loss disappears, the mechanism is not cell-intrinsic and the principal novelty of the 2025 paper fails.

Seven. Show that blocking LILRB2 in an aged animal produces cognitive or structural harm over a long horizon. Every reported blockade result is short-term. A brake whose removal is beneficial at three months and harmful at eighteen is a brake, not a target.

14. Therapeutic Reading

14.1 The precedent is unusually strong

Most mechanisms in this disease reach the therapeutic section as speculation. This one arrives with two pieces of prior evidence that are rare in combination.

Blocking the receptor acutely, in an adult mammalian brain, with a soluble decoy delivered locally for one week, restored a structural and functional deficit that had been established months earlier (Bochner et al., 2014). Amblyopia is not Alzheimer's disease, but it is a demonstration that this receptor's blockade can recover lost spines and lost function in an adult.

And antagonist antibodies against human LILRB2 exist and have been through clinical trials — in oncology, where the receptor is an immune checkpoint on tumour-associated macrophages. JTX-8064, a humanised IgG4 antagonist that blocks LILRB2's binding to classical and non-classical MHC class I, completed a phase 1/2 programme as monotherapy and in combination with a PD-1 inhibitor in advanced solid tumours (NCT04669899). Separately, Zhao and colleagues generated sub-nanomolar LILRB2 antagonists specifically to interrogate the microglial pathway (Zhao et al., 2022).

The toxicology, manufacture and human pharmacology of blocking this receptor systemically are therefore partly known, which removes several years from any development path.

14.2 Why the oncology programme is not a neurology programme

Four reasons, and they are not trivial.

The antibodies were designed to act on peripheral myeloid cells, and no meaningful brain exposure should be assumed; conventional IgG reaches the central nervous system at roughly a thousandth of its plasma concentration. Any CNS programme needs a transport strategy — a transferrin-receptor shuttle, an intrathecal route, or a different modality entirely.

The oncology intent is to *activate* immunity by removing a myeloid checkpoint. In the brain the intent would be partly the same (release TREM2 signalling) and partly different (protect a neuron from a disassembly signal). These are not the same pharmacology and may not have the same dose-response.

Chronic dosing in an ageing population is a different safety problem from time-limited dosing in advanced cancer. Removing an inhibitory checkpoint chronically is the mechanism by which

checkpoint inhibitors cause autoimmune toxicity.

And the epitope may matter. An antibody that blocks MHC-class-I binding will not necessarily block C4d binding or amyloid binding, even though all three engage D1D2. Which ligands a given antagonist displaces is an empirical question that has not been asked for any existing molecule.

14.3 The double edge

This is the part of the therapeutic argument that the programme's own data make unavoidable.

Every reported consequence of blocking this receptor is an increase in plasticity: more spines, more functional synapses, larger potentiation, deficient depression, faster learning, an unclosing critical period. In a young mouse over weeks this reads as benefit. In an ageing human over years it might read as something else — a cortex that cannot stop changing, that cannot weaken a synapse, that cannot consolidate.

Long-term depression is not a defect. It is half of the mechanism by which a circuit stores anything. Every genetic and pharmacological manipulation in this programme impairs it.

There is also the specific risk that follows from §9.1. If LILRB2 blockade releases microglial TREM2 signalling and enhances phagocytosis, and if the same receptor on the neuron protects spines when blocked, then a single antagonist changes the setting of *both* effectors at once. That is the argument for it and the argument against it. A brain in which microglia are more phagocytic and neurons hold more spines is not obviously a brain in equilibrium.

The honest position: blocking a brake to treat a disease of excessive braking is coherent, and it is not the same as repairing something broken. The therapeutic window is a window between too little restraint and too much, and nobody has measured either edge.

14.4 Four routes, ranked

Ligand blockade rather than receptor blockade. Prevent C4d or amyloid from reaching D1D2 while leaving MHC class I engagement intact. LOTUS is the proof of principle that this is chemically possible (Kawaguchi et al., 2022), and it is the route that preserves the physiological brake. This is the most attractive option and the least developed.

Cleavage inhibition. If the 2026 result holds, the damage from the neuronal arm may be done substantially by the cleaved cytoplasmic fragment rather than by surface signalling (Han et al., 2026). Blocking the protease, or the PirB-CTF/GGA3-GAT interface, would spare all normal receptor function. It is a cleaner target than the receptor. It rests on one unreplicated paper.

Upstream complement modulation. If C4d is the ligand that matters, then reducing classical-pathway activation reduces the ligand without touching the receptor at all. Anti-C1q

strategies already in clinical development for other indications would do this, and — importantly — would act on the glial and neuronal arms simultaneously, which nothing else on this list does.

Receptor antagonism. The fastest route, the best-precedented, and the bluntest. It should be reserved for a defined disease window rather than given chronically.

14.5 What to measure

C4d is the programme's most immediately useful contribution to human research, quite apart from whether the mechanism is right.

It is a covalent, durable footprint of complement activation at the synapse. It rises with age and rises further in disease. It is measurable in tissue by established methods, and its clinical measurement in other organs is routine — C4d immunostaining has been standard in transplant pathology for two decades.

The obvious study is a staged one: C4d burden at synapses across Braak stages, in the same specimens as synapse density, asking whether deposition precedes loss. That is the experiment named as the first refutation condition in Section 13, and it is a study that requires no new technology.

Whether C4d can be measured usefully in cerebrospinal fluid is a separate and largely unaddressed question. The one relevant prior report is old and small. Given that the fragment's defining property is that it stays covalently attached to the surface where it was generated, a fluid assay may be measuring the wrong pool.

15. The Ledger

A body of work spanning twenty-seven years does not have a single evidentiary status, and summarising it as though it did is the commonest way of misreading it. What follows grades each load-bearing claim on one scale. **Tier I** is demonstrated: direct experimental evidence, bidirectional where the design permits, replicated or internally cross-checked. **Tier II** is supported: consistent evidence from a single laboratory, a single model, or a single method, with no contradicting result. **Tier III** is inference: a reasonable reading of two or more established findings that has not itself been tested.

Table 3 — Graded ledger of the programme's claims

Claim	Principal evidence	Tier	Where it is vulnerable
Neurons express class I MHC under activity control, in development and adulthood	Differential display, activity blockade, seizure induction; multiple genes and both chains (Corriveau et al., 1998)	I	None material; replicated widely since
Class I MHC is required for synapse elimination and for balanced learning rules	β2m/TAP1 and CD3ζ mutants; K^bD^b double null; neuronal rescue in an immune-compromised animal (Huh et al., 2000; Datwani et al., 2009; Lee et al., 2014)	I	The neuronal rescue is the load-bearing control and rests on one paper
PirB/LilrB2 is a lifelong brake on cortical plasticity and spine density	Null and conditional alleles, cell-autonomous sparse deletion, acute ectodomain infusion; four regions, four readouts (Syken et al., 2006; Djurisic et al., 2013, 2019; Vidal et al., 2016; Bochner et al., 2014; Albarran et al., 2021)	I	Nothing contradicts it; the *purpose* of the brake is untested
The brake is acutely reversible in an adult brain	Soluble PirB ectodomain, one week, recovery from amblyopia (Bochner et al., 2014)	I	Single laboratory; visual cortex only

Claim	Principal evidence	Tier	Where it is vulnerable
LilrB2/PirB binds amyloid-β oligomers and transduces their synaptotoxicity	Nanomolar binding and PirB-dependent LTP impairment (Kim et al., 2013); independent antagonist replication of the downstream chain (Kawaguchi et al., 2022)	**Contested**	No detectable binding to human-brain-derived oligomers in the only standardised comparison (Smith et al., 2019); unanswered for seven years
C4d is a high-affinity LilrB2 ligand at the same D1D2 site	Surface plasmon resonance, Kd ≈ 3 nM cell-free; no binding to LilrB1; domain mapping (Brott et al., 2025)	I	Single laboratory; recombinant protein
C4d marks a large fraction of human excitatory synapses and rises in disease	Array tomography, ~30% of excitatory synapses; ~3-fold excitatory selectivity; fourfold protein elevation (Brott et al., 2025)	II	Very small cohorts; post-mortem; cross-sectional
C4d is sufficient to strip spines in an adult brain, through PirB	Osmotic minipump, four days, wild type versus PirB null (Brott et al., 2025)	I for sufficiency	Supraphysiological dose; says nothing about endogenous contribution
Synapse elimination in this disease has a neuron-intrinsic arm requiring no microglion	Follows from the above; not tested against microglial depletion	III	The decisive experiment (§13, refutation six) has not been done
The transduction runs through cofilin serine 3 to the actin skeleton	Programme's cofilin data; independent human dysregulation (Rush et al., 2018); rod biology (Minamide et al., 2000; Bamburg et al., 2021); antagonist rescue of the exact chain (Kawaguchi et al., 2022)	II	The node is well evidenced; its attribution to this receptor is not independent of the programme
Qa-1 on layer 6 neurons restrains microglia via CD94/NKG2	Knockout, interaction blockade phenocopy, microglial morphology (Marin et al., 2022)	II	One paper; no disease data of any kind
LILRB2 inhibits microglial TREM2 signalling	Antagonist antibodies, human iPSC microglia, grafted microglia in 5XFAD (Zhao et al., 2022)	II	One laboratory, strong design, not replicated
Astrocytic PirB suppresses glutamate transport	Peptide, small molecule, knockdown, conditional knockout with oligomer injection (Zhang et al., 2026)	II–III	Single study; oligomer-injection model

Claim	Principal evidence	Tier	Where it is vulnerable
A cleaved PirB fragment jams Golgi trafficking from inside the neuron	CSF proteomics, human tissue validation, RUSH assays, rescue by cleavage inhibition (Han et al., 2026)	III	Single 2026 study, unreplicated; largest claim on thinnest support
Reelin/ApoER2 and amyloid/LilrB2 antagonise at cofilin serine 3	Juxtaposition of Chai et al., 2009 with Kim et al., 2013	III	Proposed here; never tested in one system
Common variation at *LILRB2* influences Alzheimer risk	Cross-ancestry association with opposite effect directions (Cao et al., 2026)	II for association, III for mechanism	Direction inverts with ancestry; a candidate-gene study was null (Yan et al., 2024)
Synapse loss in this disease *is* developmental pruning re-run	—	Not supported	No re-expressed developmental programme, no competitive selection rule observed in Alzheimer tissue (§8.3)

Read down the right-hand column and the shape of the programme is clear. Its developmental core is as securely established as anything in systems neuroscience. Its complement arm is new, well designed, and thinly sampled. Its amyloid arm is the part most often quoted and the part in the worst evidentiary condition. And its most expansive recent claims — the astrocyte, the Golgi fragment — belong to other laboratories and have not been checked by anyone.

16. Conclusion

Twenty-seven years ago a screen for the molecules of developmental plasticity returned a class of protein the brain was not supposed to express, and the laboratory that found it did the unusual thing of believing the result. What followed was a slow reconstruction of how a cortex decides which of its connections to keep: activity-regulated immune ligands on neurons, an inhibitory receptor on their dendrites, phosphatases recruited to a cytoplasmic motif, a switch on a single serine of an actin-severing protein, and a spine that shrinks on command.

None of this was about Alzheimer's disease and all of it turned out to bear on it. A disease that removes synapses was found to be doing so through the apparatus the brain built to remove synapses on purpose. Two pathological ligands have now been described at the same site on the same receptor, and the second — the complement fragment C4d, covalently welded to the synapse where the cascade fired, present on a third of human excitatory synapses, fourfold elevated in Alzheimer cortex, and sufficient on its own to strip spines from an adult brain in four days through PirB and nothing else — is the better evidenced of the two.

The account is not complete and one part of it is contested. LilrB2's binding to amyloid extracted from human brain has been directly tested and directly failed, and that has not been answered in seven years. The causal evidence remains mouse evidence. The genetics do not point cleanly, and where they point they point in different directions in different populations. Nothing in the mechanism explains why the entorhinal cortex goes first, or what converts a ligand-and-receptor state present since the fourth decade into a disease in the eighth.

What stands is a specific, anatomically situated, structurally terminating, druggable mechanism for the loss of synapses — the lesion that correlates with the clinical disease better than any other — with the unusual property that antagonists of its central target have already been through human trials. And what stands alongside it is the reason for restraint: everything this mechanism offers, it offers by removing a restraint. The brain kept this brake for a reason. The programme has never found out what the reason is, and until someone does, every therapeutic proposal in this area is a proposal to take away a system whose purpose we have not yet established.

That is not an argument against pursuing it. It is an argument for measuring the cost before, rather than after.

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