The synapse that could not switch off

Why Alzheimer's disease is a failure of proteolytic timing, read out at a residue that cannot report it

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The abstract and the bibliography are supplied as separate companion documents; superscript numerals in the text refer to the numbered bibliography.

I. Introduction a structure with a history

In 1907 Oskar Fischer described neuritic plaques in the brains of the senile demented and did something his contemporaries did not: he read the deposit as a structure with a developmental history — a process that had left a residue — rather than as an inert lesion.[1] This entry applies that instinct one level down, to a chemical mark rather than a morphological one, and reaches an uncomfortable conclusion about how the field measures the disease.

Synapse loss remains the strongest structural correlate of cognitive impairment in Alzheimer's disease. In the study that established it, neocortical synapse density carried a multivariate correlation of 0.96 with the Dementia Rating Scale, while plaque density contributed only 26 per cent of that model's strength.[2] Any account of the disease must therefore eventually say what happens, mechanically, at a dendritic spine. A dendritic spine is an actin structure whose volume is the running balance between filament severing and filament stabilisation, and that balance is governed by one protein, cofilin-1, at one residue: **serine 3**. Phosphorylated cofilin cannot bind filamentous actin and the network is stable; dephosphorylated cofilin binds and severs.[3,4,5] Cofilin–actin rods are present in Alzheimer brain and not in normal brain, and are most prominent in neurites contacting amyloid deposits.[6,3]

The direction of change at that residue in human Alzheimer tissue is disputed, and the dispute has not been resolved. Amyloid-β acting through the immune receptor LilrB2 produces enhanced cofilin signalling — dephosphorylation — reported in mouse and detected in human Alzheimer brain,[7] a direction independently reproduced with a natural receptor antagonist.[8] Amyloid-β acting through Rho-associated kinase *increases* serine-3 phosphorylation in the post-synaptic fraction of human Alzheimer cortex, where that phosphorylation is reported necessary and sufficient for synaptic impairment.[9] The 2018 paper opens by stating that the effect of amyloid on the actin cytoskeleton "remains unknown and contentious." It still is. This is not an academic difficulty: Rho-kinase inhibitors are in development for this indication, and a recent review of the class notes without apparent alarm that activation **or** inhibition of these kinases alters dendritic and synaptic structure.[11] The sign of the intended therapy is unresolved at the residue through which it acts.

This entry does not attempt to adjudicate the sign. It argues that the sign is not recoverable there, and moves one layer up to where it is written — and then argues that the layer above is governed not by phosphatases but by **destruction**, and that Alzheimer's disease damages the destruction in a specific and asymmetric way that has not been named.

II. The residue cannot report its own cause

Two antagonistic arms of Rho-family signalling converge on cofilin serine 3, and this is standard cell biology rather than a new finding — which is why its consequence for the Alzheimer literature has gone unstated.

The contractile arm. RhoA activates Rho-associated kinase; ROCK1/2 phosphorylate LIM-domain kinase on its activation loop; LIM-domain kinase phosphorylates cofilin at serine 3. The structural output is spine shrinkage.

The protrusive arm. Rac1 and Cdc42 activate p21-activated kinase; PAK phosphorylates the *same* LIM-domain kinase on the *same* activation loop; the output is spine growth and stabilisation.[4,5]

Both arms raise phospho-serine-3. They mean opposite things. This is a many-to-one collapse in the information the mark carries: a spine collapsing under RhoA tone and a spine growing under Cdc42 tone present the same signal, and no antibody against that phosphosite can separate them. The degeneracy is in the variable, not in the sampling — even a perfect single-synapse measurement would not recover the sign.

Three consequences follow. A bulk phospho-cofilin measurement is uninterpretable in principle, not merely in practice. The published contradiction is what this architecture predicts, since which sign a preparation returns depends on which arm dominates the material sampled. And a further ambiguity is rarely noticed: the *protective* reelin input also adds phosphate at this residue,[20] so an elevated phospho-cofilin signal is equally consistent with pathological contractile tone and with an intact protective brake. No therapeutic inference can be drawn from the level.

The dephosphorylating limb is not unitary either, and is itself engaged by the disease: amyloid signalling converges on slingshot-mediated cofilin activation through the scaffold RanBP9, whose reduction protects against cofilin–actin pathology, synaptic damage and gliosis in an amyloid model.[28,4] A residue with four regulatory inputs of two opposite signs cannot be summarised by one number.

Which cell. Cofilin is ubiquitous and this disease is not, so the claim is worthless until it names a cell. The literatures below converge, without any of them saying so, on the excitatory glutamatergic pyramidal neuron of neocortex and hippocampus, at its dendritic spines: the Rho-kinase measurement is a post-synaptic-density-enriched fraction whose readout is AMPA-receptor subunit insertion;[9] LilrB2 and its complement ligand colocalise at excitatory synapses of human cerebral cortex;[10] the Ephexin5 work is in hippocampal pyramidal neurons;[12,13,14,15] and Disabled-1, the adaptor transducing the entire reelin signal, is expressed predominantly in pyramidal neurons.[24]

III. The licensing tyrosine

The sign is set above the serine, at a tyrosine — and the two opposed transducers that sit there share a design that has not, to our knowledge, been remarked upon.

Ephexin5. This Rho-family exchange factor restrains excitatory synapse development until ephrin-B binding to the EphB receptor triggers its phosphorylation, ubiquitination and degradation; the ligase is **UBE3A**, the gene deleted in Angelman syndrome, and it is the *destruction* of Ephexin5 that permits synapse development to proceed.[12] Note the kind of mechanism: the synapse is not permitted to form because a brake is switched off, but because a brake is removed from the cell.

The revision matters. Ephexin5 activates both RhoA and **Cdc42**, and its substrate selectivity is set by tyrosine phosphorylation: the phosphorylation-dead Y361F mutant enhances Cdc42 activation while leaving RhoA unchanged, and downstream of neuronal activity Ephexin5 *positively* regulates synaptic growth and stabilisation.[13] Dendritic Ephexin5 falls after activity in a proteasome-dependent manner.[14] It is not a brake the adult brain has switched off; it is a switch the adult brain keeps and throws.

The coincidence. The residue that selects the substrate is the residue that licenses destruction.[12,13] Phosphorylation at Y361 biases the enzyme toward RhoA *and* marks it for the proteasome; dephosphorylation releases the Cdc42 arm *and* protects it from turnover. Abundance and activity are two readings of one covalent mark. "Ephexin5 is elevated" is therefore ambiguous on its own, and every published human measurement of it reports total protein.

The sign problem, and a candidate for the missing kinase. The disease model built on this architecture holds that amyloid strips the licensing receptor so that Ephexin5 accumulates, and its first step is well supported.[16]

But the model carries a tension in its sign that is instructive rather than fatal. EphB2 is the kinase that writes the licensing mark; losing it should *lower* the phosphorylated fraction — which explains the accumulation, since the phospho-form is the degraded form, but predicts a Cdc42-biased and therefore growth-promoting pool.[13] The observed phenotype is spine loss. Either something restores the RhoA bias that the loss of EphB2 removes, or the model's sign is wrong. Fyn is the obvious candidate: a tyrosine kinase, mislocalised to the post-synaptic density in this disease by a tau-dependent mechanism, and active there.[25] If Fyn phosphorylates the licensing tyrosine *without* licensing UBE3A recruitment — because the ligase requires a co-incident EphB2-dependent signal the disease has removed — then the Alzheimer dendrite holds an Ephexin5 pool that is simultaneously abundant, RhoA-locked and unscheduled for destruction. That is the state the disease model requires and the state nobody has measured. It is also exactly what a system whose OFF is a protease should look like when the protease is misdirected.

Angelman syndrome is the reciprocal experiment, performed by nature. Loss of UBE3A should stabilise Ephexin5, and if Ephexin5 were simply a RhoA-directed brake the predicted consequence would be severe spine loss. That is not what Angelman models show. The substrate-switching account resolves this without special pleading: in the developing brain, where the phosphorylated fraction is falling and activity is high, accumulated Ephexin5 is Cdc42-biased and therefore stabilising.[13] The resolution is satisfying, and it is also a warning — in a real human disorder a large increase in Ephexin5 protein produced a phenotype opposite in sign to the one the brake model predicts. The inference from abundance to sign is not safe in either direction.

Disabled-1. The opposing input is built the same way. Reelin binds the ectodomains of ApoER2 and VLDLR and induces tyrosine phosphorylation of Disabled-1; loss of reelin or of both receptors hyperphosphorylates tau.[19] The chain runs to phosphatidylinositol-3-kinase, Akt, and thence to inhibition of **glycogen synthase kinase-3β (GSK-3β)**, a principal tau kinase — and, on the actin limb, to serine-3 phosphorylation of cofilin through ApoER2, Disabled-1 and Src-family kinases.[20] One adaptor, two ledgers: anything that removes Disabled-1 from the compartment withdraws the actin brake and releases the tau kinase in one event.

And Disabled-1 is terminated the same way Ephexin5 is. Reelin targets Disabled-1 for degradation by the ubiquitin–proteasome pathway; tyrosine phosphorylation is required for that targeting; **Fyn** deficiency prevents the degradation; and proteasome blockade prevents formation of a proper cortical plate, so the destruction is part of the signal rather than an epiphenomenon.[23] Fyn is the physiological Disabled-1 kinase, and Disabled-1 protein *rises* in Fyn-deficient mice — the signature of an unsignalled pathway.[21,22]

Fyn writes both ledgers. The same kinase is the principal intracellular transducer of amyloid toxicity at the post-synaptic density: soluble oligomers bound to cellular prion protein activate Fyn through metabotropic glutamate receptor 5 to drive spine loss,[26] and tau delivers Fyn to that compartment, so that removing tau uncouples the toxicity.[25] Fyn is therefore not a node with a sign but a shared enzyme serving two opposed clients — which is why global Fyn inhibition is predicted to help one stratum and harm another, and why it is a poor target.

Two opposed arms, one design. In each, one tyrosine phosphorylation simultaneously activates the transducer and licenses its destruction. In each, accumulation of the transducer is the signature of a *failed* signal, not an amplified one. In each, transience is achieved by proteolysis.

IV. Why a phosphatase cannot substitute

A cell that must deliver a *placed* and *brief* instruction to its cytoskeleton is poorly served by a kinase–phosphatase pair. A phosphatase resets a mark, but the transducer remains in the compartment, available to any subsequent input including noise. Removing the transducer is the more reliable termination, and it is self-limiting: the more strongly the signal is transduced, the more completely the transducer is consumed.

The relevant phosphatases are not idle in this disease, and their state does not rescue the alternative. **Protein phosphatase 2A** is the principal brain tau phosphatase, and multiple abnormalities are reported in Alzheimer's disease — reduced scaffolding and B55α subunits, reduced catalytic-subunit methylation, increased

catalytic-subunit phosphorylation, upregulated endogenous inhibitors, and loss of activity — with the reviewers themselves noting that the individual alterations are not uniformly replicated.[27] But the deeper point is categorical rather than quantitative: restoring PP2A activity would lower a phosphorylation level. It would not remove an accumulated exchange factor from a dendrite. Indeed, dephosphorylating Ephexin5 would *protect it from turnover* while releasing its Cdc42-directed activity. **At a control surface terminated by destruction, phosphatase-directed therapy addresses the mark and leaves the object.**

The price of the design is a specific fragility, and it is the disease's opportunity. A system that terminates by proteolysis vests its temporal control in the proteolytic machinery rather than the signalling machinery. Its OFF is not a chemical reaction proceeding at a fixed rate; it is a *service*, provided by the ubiquitin–proteasome system, by endosomal sorting, and ultimately by the lysosome. Anything that degrades that service degrades the cell's capacity to make brief signals, without touching a kinase or a receptor. Neurons also possess a dendritic, activity-regulated membrane proteasome whose peptide products activate NMDA receptors,[29] whose properties coincide closely with the activity-dependent component of Ephexin5 turnover — a coincidence we state as a hypothesis, not a finding.

V. The receptor limb: sorting decides whether a signal can be re-sent

If termination is proteolytic, the state of the endosomal system should matter to synaptic signalling early. It does, and the evidence is unusually clean.

Enlargement of the early endosome is the earliest known disease-specific structural abnormality in Alzheimer's disease: present in neocortical pyramidal neurons at preclinical stages, present in Down syndrome from 28 weeks of gestation, accentuated by *APOE* ε4 — and **absent** in advanced familial disease caused by presenilin mutation, which establishes that it is not a consequence of amyloid deposition.[30] In the form of the disease with the highest lifetime amyloid burden, the abnormality is absent.

SORL1 encodes SORLA, the cargo receptor delivering material to the retrieval machinery, and its loss of function is causal for the disease. In human neurons, haploinsufficiency alone enlarges endosomes while complete loss adds lysosomal and autophagic failure — and the dysfunction is relieved by lowering amyloid precursor protein, placing presenilin-1, the precursor protein and SORLA in one pathway.[31] In human microglia, SORLA loss reduces lysosomal degradation while phagocytic uptake of fibrillar amyloid-β *and of synaptosomes* increases, so both accumulate undegraded.[32] The cell that clears synaptic material acquires the same lesion as the cell losing synapses.

ApoER2, APOE4 and peroxidation. Apolipoprotein E4 reduces neuronal surface ApoER2 — and of the glutamate receptors co-endocytosed with it — by sequestration in intracellular compartments, critically reducing reelin's ability to enhance synaptic glutamate-receptor activity.[33] The receptor is not absent, mutated or blocked: it is in the wrong compartment. And it is reversible for a trafficking reason — inhibiting NHE6, the early endosome's proton-leak channel, completely reverses the recycling block and restores reelin's modulation of excitatory synapses.[34] This is, so far as we can determine, the only published intervention in this region of the map that restores the *capacity* to signal rather than adding or subtracting a signal, and on this account it is the category that should work.

One failure mode at this receptor is beyond trafficking repair. Lipoprotein receptors bind their ligands through acidic modules gripping lysine-rich motifs, and lysine is precisely the residue reactive lipid aldehydes attack. **Peroxidation** generates aldehydes that adduct ApoE and ApoER2 and form crosslinked ApoE–ApoER2 complexes; in human tissue, ApoE, aldehyde-modified ApoE, reelin, Disabled-1 and downstream markers accumulate near neuritic plaques in perforant-path terminal zones and correlate with progression.[35] Two features matter. The accumulating species is a signalling pathway, not a waste product — which is what failure of *termination* looks like. And a covalent crosslink cannot be undone by any sorting step, because ligand and receptor have become one molecule. That marks the boundary between repair and prevention.

The multivesicular body and TFEB. Amyloid-β42 localises predominantly to **multivesicular bodies** of neurons, and in human Alzheimer brain accumulates in MVBs within presynaptic and especially postsynaptic compartments, associated with abnormal synaptic morphology *before* plaque pathology.[36] The compartment through which a spent receptor must pass to be destroyed is the compartment in which the pinning ligand accumulates. At the terminal step, **TFEB** — the master regulator of lysosomal biogenesis — governs lysosomal exocytosis of tau, and its loss of function worsens intraneuronal pathology and accelerates spreading;[37] a tauopathy-associated tau fragment in turn blocks TFEB nuclear translocation and lysosomal capacity.[38] The cargo disables the machine that clears the cargo, which is how a graded decline in clearance becomes a staged disease.

The sugar bed. Reelin cannot activate its receptor as a two-body ligand. N-sulfated **heparan sulfate** is an obligate co-receptor for reelin-induced ApoER2 dimerisation: heparinase or free heparin reduces dimerisation while N-desulfated heparin does not.[39] Two consequences follow. Heparan-sulfate proteoglycans are themselves lysosomal substrates, so a failing lysosome alters the surface on which the protective ligand is staged — plausible, and unmeasured. And because heparan sulfate is also the route by which pathological tau enters neurons, **a heparin mimetic given to block tau propagation would, by the identical chemistry, silence the reelin arm that restrains tau phosphorylation.** That conflict is verified at drug level and has not been stated. A common conflation should also be retired: the perineuronal net is *chondroitin* sulfate, while reelin requires *heparan* sulfate, a component of the diffuse matrix surrounding all central nervous tissue.[40] Reelin does not require a net in order to signal.

VI. Misdirected proteolysis

Two published findings about the same pathway in the same cell type have not, to our knowledge, been set against each other.

The licensing receptor is destroyed too much. Amyloid-β oligomers bind the fibronectin-repeat domain of EphB2 and trigger its degradation *in the proteasome*; knockdown of EphB2 impairs dentate potentiation in non-transgenic mice, and restoring EphB2 in amyloid-bearing mice reverses potentiation and memory deficits.[16] Independently, EphA4 and EphB2 fall in hippocampus *before* memory decline in two amyloid models, Eph receptors are reduced in post-mortem hippocampus from patients with incipient disease, and membrane phospho-cofilin falls while Eph receptor activation raises it in culture.[17]

The effector is destroyed too little. Ephexin5 is acutely produced on amyloid exposure and is elevated in the hippocampi of human Alzheimer patients; its genetic removal eliminates hippocampal spine loss and rescues behaviour in an amyloid model.[15]

These are two ends of one chain. EphB2 is the kinase whose signalling phosphorylates the licensing tyrosine and thereby recruits UBE3A to destroy Ephexin5.[12] Amyloid feeds that kinase to the proteasome. The proteasome then does not receive the substrate whose destruction the kinase was to authorise.

The proteolytic system is not failing. It is executing the wrong instruction. In the same neuron and the same compartment, one arm of ubiquitin-dependent degradation over-runs — removing a receptor the cell needs — while the arm it was to license under-runs, leaving in place an exchange factor the cell was to clear.

This is a better description than "loss of clearance" for three reasons. A pure capacity deficit predicts that a receptor targeted for proteasomal degradation would be *spared*; the observed direction is the opposite, and amyloid's action at EphB2 is a *gain* of degradation achieved by presenting a substrate to an intact machine. A pure capacity deficit predicts that the two transducers and the receptor move together; they do not. And a pure capacity deficit gives the wrong therapeutic instruction, since increasing degradative flux in a cell that cannot complete the pathway fills it faster with vesicles it cannot empty.

One irony completes the picture. **C4d** is a complement cleavage product — made by proteolysis. It binds LilrB2 and PirB at nanomolar affinity, colocalises with LilrB2 at human cortical excitatory synapses and with amyloid-β in Alzheimer's disease, rises with age and further in disease, and when infused into wild-type mouse cortex is sufficient to strip dendritic spines — an effect completely prevented by PirB knockout.[10] A proteolytic fragment supplies the chronic occupancy at one receptor while a proteolytic failure leaves the transducer of the opposing arm in place. Two proteolytic systems, opposite signs, one synapse. "Less proteolysis" does not describe this.

VII. Falsifiable predictions

The two residues decouple. In healthy cortex the licensing tyrosine sets the GTPase state, which sets the serine, so the marks should covary across synapses. If the disease drives the serine from elsewhere — chronic ligand occupancy at LilrB2, contractile tone from an unlicensed exchange factor, a reelin arm whose receptor is in the wrong compartment — the covariance falls while the dispersion of the serine mark rises. *This fails cleanly: if the two covary in disease as in control, the sign is recoverable at the serine and this account is wrong.*

The receptor and its substrate anticorrelate. Across individual excitatory synapses within one Alzheimer case, EphB2 and Ephexin5 are anticorrelated, concentrated at high-LilrB2 synapses; in age-matched control the correlation is near zero. Both antigens are stable proteins, so this is measurable now in autopsy cortex — and synapse-to-synapse variation in post-mortem proteolysis would degrade both together, producing a *positive* correlation, so the confound biases toward the null.

Total protein is a poor predictor of activity. The phospho-tyrosine fraction of Ephexin5, not its total, predicts active RhoA. If total Ephexin5 predicts it equally well, the licensing architecture has no consequence in disease tissue.

Genotype orders the effector. Dendritic Ephexin5, total and phosphorylated, is ordered by *APOE* genotype before any amyloid challenge — highest in ApoE4. The knock-in neurons exist.

Repair restores range, not level. In ApoE4 neurons, NHE6 inhibition restores the *excursion* of serine-3 phosphorylation to a plasticity-inducing stimulus without a large change in baseline.[34] If the excursion is not restored, repairing the receptor limb is insufficient.

Ordering. Endosomal enlargement and impaired ApoER2 recycling precede Ephexin5 elevation, which precedes dispersion of the serine mark. If Ephexin5 elevation precedes any sorting abnormality, this account has the order wrong and the elevation is transcriptional rather than proteolytic.

VIII. What follows for treatment

The therapeutic reading of this architecture is unusual, because at three separate levels the obvious move is the wrong one, and each failed reflex has a live programme attached to it.

Blocking the effector fails because the effector is non-monotonic. Cofilin severs filaments at low occupancy and stabilises them at high occupancy.[3] A drug that pushes every synapse one way along a curve that turns over must convert some fraction of synapses from one failure mode into the other — which is the most economical available account of an intervention that rescues convincingly in one preparation and delivers no population benefit.

Blocking the exchange factor fails because the human loss-of-function phenotype is a dementing vasculopathy. Heterozygous loss-of-function mutations in *ARHGEF15*, the gene encoding Ephexin5, cause autosomal-dominant hereditary cerebral small-vessel disease with osteoporotic fracture, acting through RhoA/ROCK2 *inactivation*, with a transgenic mouse recapitulating both.[18] Cerebral small-vessel disease is itself a leading cause of vascular dementia. The therapy the synaptic model originally implied is a phenocopy of a human

dementing disease — and the protein is in any case required for the spine growth that accompanies potentiation.[13]

Blocking the kinase fails because the kinase is shared. Fyn transduces amyloid toxicity at the post-synaptic density and is simultaneously required for the protective arm to be applied *and* terminated.[22,23,25,26] Inhibiting it is predicted to help one stratum and harm another, which is what a failed trial with a real positive subgroup looks like.

There is a pattern in the three failures: each is an attempt to fix a *timing* problem with a *level* intervention. Lowering the amplitude of an instruction that will not end is not the same as ending it.

The category that should work is repair of the clock, and one published result already occupies it. Inhibiting NHE6 reverses the ApoE4-induced recycling block of ApoER2 and of the glutamate receptors co-endocytosed with it, and restores reelin's modulation of excitatory synapses.[34] Nothing was added to the system and nothing was blocked in the signalling pathway; the compartment was repaired and the signalling returned. An ApoE4 neuron does not have a reelin deficiency — it has a receptor in the wrong place, and no quantity of ligand fixes a receptor in the wrong place. The ordering claim follows and is the most actionable statement here: **repair capacity first, supply signal second.** Any attempt to drive the protective arm should be expected to underperform in exactly the population most likely to be enrolled unless the recycling defect is addressed first or concurrently, and the same ordering applies to the degradative arm, where induction before re-acidification fills a neuron faster with vesicles it cannot empty.

And two things must not be done at all. A heparin mimetic deployed against tau propagation would silence the reelin arm by identical chemistry,[39] so the sulfated matrix must be modulated rather than blocked. And the endpoints must change before the drugs do: total protein is uninterpretable for a transducer whose abundance and activity are one variable; bulk phospho-cofilin is uninformative about direction even when measured perfectly; and bulk assays of degradative capacity cannot detect a change in proteolytic *specificity*, which is what §VI argues the disease produces.

IX. Scope, and what is not claimed

This is a convergence claim about the *execution* of synaptic loss, not a claim about initiation. It does not explain who develops the disease, why particular neurons fail first, or the substantial fraction of dementia not attributable to the pathologies conventionally measured. It is compatible with amyloid-first, tau-first, vascular-first and inflammatory-first origins — a weakness as well as a strength, since a claim compatible with every upstream story constrains none of them. The Ephexin5 arm is gated on amyloid and is therefore late; whatever begins the disease operates in a compartment and a decade this account does not address. It executes; it does not initiate.

Three further limits are owed. The reelin-induced destruction of Disabled-1 was demonstrated in cultured primary embryonic neurons[23] and has not, to our knowledge, been repeated in adult tissue — the argument's most exposed empirical assumption. The human anchor for Ephexin5 elevation is a single report without cell-type resolution or independent replication.[15] And the in vivo Ephexin5 evidence rests on amyloid-precursor-protein overexpressing mice from one laboratory, which overproduce the full complement of precursor fragments; whether the phenotype survives in a knock-in model at endogenous expression is untested and is a cheap experiment.

The most conspicuous cell this account does *not* explain is the parvalbumin-positive fast-spiking interneuron, which is characteristically aspiny and receives excitatory input on shafts and soma rather than on spines. The mechanics described here are the mechanics of a spine and do not transfer to it. Conversely, a minority of cortical excitatory neurons bear a perineuronal net and carry conspicuously little phospho-tau,[41] and they are the natural internal control for every measurement proposed above — the only population in which spines, a net and reelin-responsiveness are properties of one cell.

X. Conclusion

The field has spent four decades asking which molecule is primary at the failing synapse, and has measured the answer at a phosphosite that cannot carry it. Two antagonistic Rho-family arms write the same mark; a protective pathway writes it too; and its erasing limb is engaged by the disease from two directions. The quantity is degenerate, and the contradiction in the human literature is what a degenerate quantity produces.

The sign is written one layer up, at a tyrosine — and the two opposed transducers there are built to the same unusual design: the phosphorylation that activates each is the phosphorylation that condemns it, and one Src-family kinase writes to both. Transience at the spine's control surface is therefore not achieved by dephosphorylation. It is achieved by destruction, and the cell's capacity for brief, placed signalling is hostage to a proteolytic service — the proteasome at the transducer, endosomal sorting and the lysosome at the receptor.

What Alzheimer's disease does to that service is not what the field's framing predicts. It does not simply lose proteolysis. It **misdirects** it: amyloid presents a licensing receptor to an intact proteasome while the substrate that receptor was to condemn accumulates; the commonest risk allele holds the protective receptor in the wrong compartment; peroxidation welds a ligand to it; and the sorting machinery that would resolve either problem is impaired from before any deposit appears, by a lesion human genetics shows to be causal.

There is a resistance genotype that reads naturally on this account. A gain-of-function reelin variant, carried by a man who resisted an autosomal-dominant mutation into his late sixties despite very high amyloid burden,[42] enters a pathway whose transducer is consumed by the act of signalling — so its benefit should appear as a larger, faster-returning excursion rather than as raised tone. That is a testable difference, and it is the therapeutic shape this account implies: not more signal, and not less kinase, but the restoration of a cell's ability to stop.

Fischer read a deposit as the residue of a process. The proposal here is that a phosphomark is one too — and that measuring the residue while ignoring the process is why three careful laboratories, working on human tissue, disagree about the direction of the disease.

A Note on Authorship and Method

This paper is submitted transparently as the work of an artificial intelligence, composed by a large language model (Claude, Anthropic) under the Organic Network Synthesis methodology developed at AdultCognitiveDisease.com. Nothing in the mechanism above is claimed as an original experimental discovery; every step is sourced to the primary literature, and the accompanying bibliography has been checked against PubMed rather than recalled — a check that was necessary here because the two disagreements this paper turns on, at cofilin serine 3 and over the sign of the Ephexin5 model, involve published directions that are opposite, and a citation reconstructed from memory would silently resolve a dispute the literature has not resolved.

What is offered as new is architectural, and it is two observations and one inference. The observations are that phospho-serine-3 is the shared output of antagonistic arms and therefore cannot report its own cause, and that the two opposed transducers above it are each activated and condemned by the same phosphorylation, with Fyn writing to both. Both are verifiable directly from the cited sources. The inference is that Alzheimer's synaptic execution is a lesion of proteolytic *specificity* rather than of proteolytic *capacity*. It is untested, §VII states the measurements that would break it, and it should be attacked there first.