The Indifferent Neuron

Caveolin-1, the membrane raft, and the case for treating the platform rather than the pathology — an evaluation of Brian Head's work on Alzheimer's disease

Benjamin Aaron Gustafsson

AdultCognitiveDisease.com

August 2026

A nerve cell's receptors do not work unless they are held together in the right patch of membrane. On that view the failing neuron is not starved of signal — it is deaf to the signal it is already receiving. This is an account of a therapy that leaves every plaque in place and returns the animal to the performance of its healthy littermates.

Contents

Abstract

Almost every therapy ever tested in Alzheimer's disease has been defined by the pathology it removes. The work evaluated here is defined by the pathology it leaves alone.

Brian Head's laboratory has spent sixteen years arguing that the functional unit of a neuron is not the receptor but the patch of membrane the receptor sits in. Neurotrophin receptors, glutamate receptors, the kinases they signal through and the cytoskeletal machinery they pull on are assembled together in cholesterol- and sphingolipid-rich microdomains — membrane lipid rafts — and the scaffolding protein caveolin-1 is what organises them. On this account, the ageing and degenerating brain does not primarily lose its receptors. It loses the platform on which receptors are able to work. A neuron in that state is not starved of signal; it is deaf to the signal it is already receiving.

The therapeutic consequence is a gene therapy, SynCav1, that puts caveolin-1 back into neurons under a neuron-specific promoter. Its signature result, first reported in the 2020 Oskar Fischer Prize submission and published the following year, is a dissociation: in amyloid-bearing mice, one hippocampal injection preserved learning, dendritic arbour, synapse number, presynaptic vesicle density, spine morphology and axonal myelin — and did not reduce plaque burden at all. The disease proceeded; the animal did not decline.

Six years of further work have changed what can be said about that result. Treatment now works when given after deficits have appeared, in two models including the knock-in line the original submission had named as its own principal weakness. The mechanism has moved beyond scaffolding: treated hippocampi show a near-wild-type transcriptome, raised CaMKII and CREB phosphorylation, and preservation of a raft-localised receptor–effector pair, PAC1R and activity-dependent neuroprotective protein. Mitochondrial fission signalling is suppressed. And the same intervention has now been shown to work in a TDP-43 proteinopathy, where the mutant protein turns out to mislocalise *to the rafts themselves* — placing two unrelated proteinopathies on one shared membrane surface. In parallel, the same group has helped build the first mouse in which Alzheimer-type pathology and intact cognition are deliberately uncoupled.

This paper evaluates the theory rather than the therapy. Four conclusions follow. First, the dissociation of pathology from function is the finding, and it is best understood not as a gene therapy result but as an engineered model of cognitive resilience — the laboratory counterpart of the twenty to thirty per cent of older people who carry the pathology and never become demented. Second, the theory's greatest strength, that it does not require knowing what started the disease, is also its sharpest liability: the same intervention improves outcomes in amyloid, TDP-43, superoxide dismutase and traumatic models, and nothing yet published distinguishes a genuine convergence node from a non-specific improvement in neuronal health. Third, the relationship between caveolin-1 and amyloid is genuinely unresolved in the independent

literature — three well-conducted studies report that raising caveolin-1 lowers γ-secretase processing, raises β-secretase processing, and provides the route by which amyloid oligomers enter the neuron. These cannot all be right in the same compartment, and no experiment in the treatment series measures the quantity that would separate them. Fourth, the programme's translational problem is not efficacy but measurement: a therapy that deliberately changes no plaque, no tangle and no fluid biomarker has, at present, nothing to dose against except cognition itself.

The evaluation states what is established, what is inferred, and what is assumed, grades each, and names six experiments that would decide the open questions. What survives is a serious and unusually well-specified answer to a question the field has mostly declined to ask: if the pathology cannot be stopped, can the neuron be made indifferent to it?

1. Introduction: A Therapy Defined by What It Does Not Do

1.1 The programme

Brian P. Head trained as an anesthesiology researcher and works at the University of California San Diego and the VA San Diego Healthcare System, in a group whose original subject was not the brain at all. The caveolins were first interesting to that group because of the heart: cardiac-specific over-expression of caveolin-3 protects the myocardium, and the caveolins were understood there as regulators of stress adaptation — proteins that organise the membrane so that protective signalling can occur (Schilling et al., 2018; Horikawa et al., 2011). The move to the nervous system carried that framing intact. Head's question about the degenerating neuron has always been the question an anesthesiologist asks about a stressed organ: not what is killing it, but what is preventing it from protecting itself.

The line of work that follows has a clear internal logic and a consistent shape:

- **2007–2008.** A conceptual claim, made before any therapy existed: caveolins do things outside caveolae (Head and Insel, 2007). This matters more than it sounds, and it recurs throughout; neurons famously lack the flask-shaped invaginations that define caveolae in endothelium and muscle, so any claim that caveolin-1 is functionally important in a neuron has to be a claim about scaffolding rather than about morphology. The first mechanistic result followed immediately: caveolin-1 expression is required for NMDA-receptor-mediated Src and ERK activation and for the survival of primary neurons under ischaemic stress (Head et al., 2008).
- **2010–2011.** A loss-of-function argument. Caveolin-1 null mice show accelerated neuronal ageing, loss of synapses, raised amyloid-β and phospho-tau, and astrogliosis; the localisation of PSD-95, GluN2A, GluN2B, TrkB and AMPA receptors to rafts falls with age in wild-type hippocampus, and falls early in the null (Head et al., 2010). Then the reciprocal gain-of-function: a synapsin-promoter caveolin-1 construct in primary neurons increased raft formation, receptor expression, NMDA- and BDNF-driven kinase activation, cAMP responsiveness and dendritic growth — and did so *even in the presence of the growth-inhibitory cytokines and myelin-associated inhibitors that normally block neurite extension* (Head et al., 2011).
- **2016–2018.** The claim tested in the intact brain and in the intact animal. Neuron-targeted caveolin-1 delivered to adult and aged mouse hippocampus increased raft-localised TrkB, expanded apical dendritic arbours, and improved contextual fear memory in both age groups

(Mandyam et al., 2017). Ultrastructural and electrophysiological confirmation followed: more presynaptic vesicles per bouton, more type I excitatory synapses, more multiple-synapse boutons, increased myelination, increased long-term potentiation, and increased raft-localised GluN1, GluN2A and GluN2B; immunogold electron microscopy placed caveolin-1 on both sides of the synapse and in the cleft itself (Egawa et al., 2018).

- **2017–2019.** Generality across insults. The same construct improved motor function and preserved memory after controlled cortical impact (Egawa et al., 2017), and extended survival in the $SOD1^{G93A}$ mouse model of amyotrophic lateral sclerosis (Sawada et al., 2019).
- **2020–2021.** The Alzheimer result — submitted to the Oskar Fischer Prize and published the following year (Wang et al., 2021a).
- **2021–2026.** Consolidation and extension: mitochondrial dynamics (Wang et al., 2021b), a translationally realistic spinal delivery route (Wang et al., 2022a), characterisation of a knock-in model (Wang et al., 2022b), symptomatic-stage treatment with transcriptomics (Wang et al., 2025), systemic delivery in a TDP-43 proteinopathy (Wang et al., 2026), and a computationally derived mouse model of pathology without dementia (Jati et al., 2026).

Sixteen years, one molecule, one construct, four diseases. It is unusually coherent for a research programme, and coherence of that kind is both a virtue and a hazard — it is what allows a mechanism to be tested properly, and it is what allows a single unexamined assumption to propagate through everything downstream. Both happen here.

1.2 What kind of claim is this?

It is worth being precise about the sort of theory under evaluation, because the standards differ.

Alzheimer's research is organised around theories of **onset**: what starts the disease. The amyloid cascade hypothesis is exactly such a theory, and was restated as such at its twenty-fifth anniversary (Selkoe and Hardy, 2016). Theories of onset are adjudicated by temporal priority in human tissue, and human tissue offers one frozen frame of a process that runs for two decades or more. This is why so many of them coexist unresolved.

Head's theory is not of that kind, and reading it as though it were produces the wrong verdict. It is a theory of **permissiveness**: a claim about the conditions a neuron must satisfy in order to receive trophic and synaptic signals at all. Its content is that a particular membrane organisation is *necessary* for the transduction of pro-growth and pro-survival signals; that this organisation is degraded by ageing and by several unrelated disease processes; and that restoring it restores signalling competence irrespective of what degraded it.

Claims of that shape are adjudicated by necessity and sufficiency, which are laboratory questions rather than autopsy questions. Nearly all of the evidence in this body of work is of that

kind, and it is the reason the work has produced a candidate therapeutic while much better-powered theories of onset have not.

There is a second, weaker claim entangled with the first: that loss of caveolin-1 is not merely permissive but *contributory* — that falling caveolin-1 is one of the things that makes an ageing brain vulnerable. That claim is a theory of onset, it is the part of the programme with the least secure human evidence, and Section 6 takes it apart.

1.3 What this evaluation asks

Three questions organise what follows.

What does the work establish about how a neuron loses function? Not what initiates the disease — what has to be true of a nerve cell for it to stop responding to the signals that maintain its synapses.

Is the dissociation real, and what is it evidence for? Function preserved, pathology untouched, in model after model. That is either a profound result about resilience or a shallow result about mouse behaviour, and the difference is decidable.

What would it take to believe this in a human being? The programme has a candidate therapy, a patent and no clinical trial. The obstacles are specific and worth naming precisely, because they are not the obstacles the field usually assumes.

Sections 2 to 4 assemble the theory and its central result from the primary work. Section 5 sets out what has been added since the 2020 submission. Sections 6 and 7 test the theory against the independent literature and against itself. Section 8 addresses translation. Sections 9 to 11 grade the evidence, state the weaknesses, and specify what would falsify the account. Section 12 offers a reading of the programme that differs from the one it gives of itself.

2. The Membrane Theory

2.1 The unit of signalling is a patch of membrane, not a receptor

The premise is a piece of cell biology that predates the Alzheimer application and is not seriously disputed in outline. The plasma membrane is not a uniform sheet. Cholesterol and sphingolipids segregate into ordered microdomains — membrane lipid rafts — that are physically distinct from the surrounding bilayer: less fluid, thicker, and, in the operational assay that dominates this literature, buoyant in a sucrose density gradient after carbonate lysis. Rafts concentrate certain proteins and exclude others.

Head's group states the functional consequence in its 2016 review (Egawa et al., 2016): rafts serve as the platform on which signal transduction, cytoskeletal organisation and vesicular trafficking are co-located. Within them sit the caveolins, which are simultaneously scaffolding proteins and cholesterol-binding proteins. Caveolin-1 organises a specific and unusually consequential set of partners:

- **Neurotrophin receptors** — the Trk family, TrkA and TrkB, through which nerve growth factor and BDNF act.
- **Glutamate receptors** — NMDA receptor subunits GluN1, GluN2A, GluN2B, and AMPA receptors.
- **The cyclic-AMP machinery** — G-protein-coupled receptors, adenylyl cyclases, phosphodiesterases.
- **Pro-survival kinases** — Src, and through it ERK1/2 and Akt.
- **Cytoskeletal regulators** — Rho-family GTPases and actin-binding proteins.

The claim that follows is a claim about *sufficiency of components versus sufficiency of arrangement*. A neuron may express normal amounts of TrkB and normal amounts of BDNF may be present, and the signal will still not be transduced if TrkB is not in the raft. Head's group demonstrated the point directly in the null: in caveolin-1 knockout neurons, NMDA- and BDNF-mediated pro-survival kinase activation fails, and re-expressing caveolin-1 restores it (Head et al., 2011). The receptors were there the whole time.

This is the load-bearing idea of the entire programme, and everything else in it — the therapy, the cross-disease generality, the reading of past clinical failures — is downstream of it.

2.2 Caveolin-1 without caveolae

An objection arrives immediately, and the programme met it before it built the therapy.

Caveolae — the 50–100 nm flask-shaped invaginations that give the caveolins their name — are abundant in endothelium, adipocytes, fibroblasts and muscle. Neurons do not have them in any comparable density. If caveolin-1's function were to build caveolae, then caveolin-1 in a neuron would be an orphan.

Head and Insel (2007) argued the opposite case explicitly: caveolins act outside caveolae, as scaffolds that concentrate and organise signalling partners in flat raft domains. The evidence assembled since is consistent with that reading. Immunogold electron microscopy localises caveolin-1 to pre- and postsynaptic membranes and to the synaptic cleft in hippocampus (Egawa et al., 2018), which is not caveolar geography. Caveolin-1 co-immunoprecipitates with DISC1 (Kassan et al., 2017) and with Shisa9 (Wang et al., 2021a) — scaffolding interactions, not vesicular ones. Caveolin-1 phosphorylation is required for axonal growth in human iPSC-derived neurons (Wang et al., 2019), again a signalling role.

But conceding the point has a consequence the programme does not always draw out, and it matters for how the therapy should be understood. If caveolin-1 in neurons is present at low abundance and without caveolae, then SynCav1 is not restoring a neuron to its normal state. It is imposing a membrane organisation more caveolin-rich than any neuron normally has. The independent literature reinforces the concern from the other direction: Bonds et al. (2019), working entirely outside Head's laboratory, describe caveolin-1 flatly as "the endothelial-enriched protein."

This is not a fatal objection — many effective interventions are supraphysiological — but it changes the safety argument, and Section 8.5 returns to it. A therapy that restores a depleted protein to normal levels inherits a presumption of tolerability. A therapy that installs an organising protein at levels no neuron has ever expressed does not.

2.3 The ageing membrane

The bridge from cell biology to disease is a claim about ageing, and it is the part of the theory with the most direct independent support.

Head et al. (2010) compared young, middle-aged and aged mouse hippocampus and reported that raft localisation of PSD-95, GluN2A, GluN2B, TrkB, AMPA receptors and caveolin-1 itself all decline with age. The 2016 review generalises the position: brain cholesterol falls with age, raft abundance falls with it, presynaptic vesicle fusion declines, neurotransmitter release changes, and the composite of these is a substantial part of what is meant by the ageing brain (Egawa et al., 2016).

The distinctive move is what this predicts about therapy. If the ageing neuron has lost the platform rather than the ligand, then supplying ligand should not work. That prediction has been

tested in human beings, expensively, and it failed in the predicted direction — Section 8.3.

2.4 The loss-of-function evidence

The caveolin-1 null mouse is the strongest single piece of evidence for the theory's negative half, and it is worth stating what it actually shows, because the phenotype is broader than a signalling deficit.

Young caveolin-1 knockout mice show (Head et al., 2010): reduced hippocampal synapse number; reduced PSD-95, GluN2A and GluN2B in synaptosomes; failure to be protected against cerebral ischaemia–reperfusion injury; elevated amyloid-β; elevated phospho-tau; astrogliosis; and reduced cerebrovascular volume. The authors' summary is that caveolin-1 loss constitutes "a non-mutational model for Alzheimer's disease."

Independent work agrees on the behavioural half. Gioiosa et al. (2008), from a separate group, reported altered emotionality, impaired spatial memory and cholinergic dysfunction in caveolin-1 null mice. Niesman et al. (2014) showed that both caveolin-1 and caveolin-3 nulls sustain larger lesions and mount larger cytokine responses after controlled cortical impact.

Two cautions belong with this evidence and are not always attached to it.

First, the global knockout deletes caveolin-1 everywhere, including in the endothelium where it is most abundant. Reduced cerebrovascular volume in the null is a vascular phenotype, and a vascular phenotype is sufficient by itself to produce cognitive impairment, raised amyloid and astrogliosis. The null therefore cannot cleanly support a *neuronal* caveolin-1 claim. It is Head's own neuron-specific gain-of-function work, not the null, that carries that weight.

Second, "a non-mutational model for Alzheimer's disease" is a strong phrase for a mouse with more amyloid, more phospho-tau, fewer synapses and worse memory. Many manipulations produce that quartet. The claim that would distinguish caveolin-1 from the rest is that its loss is *upstream* of the others, and the knockout does not establish that.

3. From Scaffold to Therapy: The Construct

3.1 What SynCav1 is, and why the promoter is the design

The therapeutic agent is deliberately simple: the human caveolin-1 coding sequence under the control of a neuron-specific synapsin promoter, packaged in adeno-associated virus. Two design decisions carry almost all of the reasoning.

The promoter is a containment strategy, not a targeting convenience. Caveolin-1 is most abundant in brain endothelium, and there its function is one you emphatically do not want to amplify: caveolae-mediated transcytosis is the vesicular route across the blood–brain barrier, and the barrier's integrity depends on that route being *suppressed*. Andreone et al. (2017) showed that CNS endothelial cells maintain barrier function through a lipid environment, established by the transporter Mfsd2a, that inhibits caveolae formation. A construct that raised caveolin-1 in endothelium would be expected to open the barrier. The synapsin promoter is what makes the therapy coherent with its own cell biology, and it deserves more credit in descriptions of the work than it usually gets.

The gene is small. Caveolin-1 is a 178-amino-acid protein; its coding sequence is comfortably within the roughly 4.7 kilobase packaging capacity of AAV, with room for a full-length promoter. This is not a trivial advantage. Several of the most attractive protective targets in neurodegeneration — reelin at 3,461 amino acids being the extreme case — cannot be delivered by AAV at all. Caveolin-1's tractability as cargo is one of the underrated reasons this programme has a candidate and other resilience programmes do not.

3.2 The healthy brain first

The sequence in which the work was done is unusual and, in retrospect, is what makes the disease results interpretable.

Before touching a disease model, the group established what the construct does to a normal hippocampus. In adult (6-month) and aged (20-month) mice, hippocampal SynCav1 increased caveolin-1 expression, raft abundance, and raft-localised caveolin-1 and TrkB; expanded apical dendritic arbours in CA1 and dentate granule neurons; and improved contextual fear memory. The structural effect was smaller in aged animals but present (Mandyam et al., 2017).

Egawa et al. (2018) then supplied the ultrastructure and the physiology. In adult mouse hippocampus, SynCav1 increased presynaptic vesicles per bouton, total type I excitatory synapses, same-dendrite multiple-synapse boutons, myelination, long-term potentiation, and raft-localised GluN1, GluN2A and GluN2B.

The importance of this ordering is that it fixes the direction of interpretation for everything that follows. SynCav1 is not an anti-amyloid agent that happens to help synapses. It is a synaptogenic and myelinating agent whose effects were characterised in the absence of disease, and then applied to disease. When a treated Alzheimer mouse has more synapses than an untreated one, the parsimonious reading is not that the disease was blocked; it is that the same synaptogenic programme ran on top of it. The programme's own framing — "preservation" — slightly obscures this. Some of what is measured is very likely addition rather than preservation, and Section 11 treats that as a real interpretive weakness rather than a quibble.

3.3 The submission

The 2020 Oskar Fischer Prize submission — *Synapsin-promoted caveolin-1 gene therapy preserves hippocampal function in a mouse model of Alzheimer's Disease* — reports the following experiment, published the following year in expanded form (Wang et al., 2021a).

APPswe/PS1ΔE9 mice, which carry mutant amyloid precursor protein and presenilin-1 and develop hippocampal learning and memory deficits at 9 and 11 months, received a single bilateral hippocampal injection of AAV9-SynCav1 or a control AAV9-SynRFP vector at 3 months of age — before symptoms. Animals were assessed at 9 and 11 months.

The design has one feature worth flagging as a strength: the control is not saline but an identical vector expressing red fluorescent protein under the same promoter. Whatever the surgery, the capsid, the promoter and the act of over-expressing a protein in neurons do on their own, both groups received it.

4. The Dissociation

4.1 What was preserved

At 9 months, treated Alzheimer mice acquired fear learning normally where untreated Alzheimer mice did not. At 11 months, untreated animals showed the expected deficit in contextual memory recall; treated animals were indistinguishable from wild-type. Open-field testing showed no differences in locomotion or anxiety-like behaviour among groups, which matters because it rules out the most common artefactual explanation for a freezing-based readout.

Structurally, at 9 and 11 months, treated animals showed:

- Preserved hippocampal and cortical caveolin-1, and preserved MAP2 — the dendritic marker whose loss in CA1, CA3 and dentate granule neurons the authors note resembles what is seen in post-mortem human tauopathy and chronic traumatic encephalopathy.
- Preserved full-length TrkB and LRP1, in whole homogenate and specifically in the buoyant raft fractions. Raft-localised synaptobrevin was unchanged across all groups, which is the internal control establishing that the fractionation itself was not simply shifted.
- Increased total type I excitatory synapses and presynaptic vesicles per bouton in CA1 stratum radiatum by electron microscopy.
- Preserved spine geometry. Untreated animals showed the stubby, thick-necked, short spines reported in human Alzheimer biopsy material and in transgenic models (Androuin et al., 2018); treated animals retained neck diameter, spine length and total spine area.
- Preserved myelin. G-ratio — axon lumen diameter divided by total fibre diameter, an inverse index of myelination — rose in untreated CA3 Schaffer collaterals at both time points, and the rise was due to thinner myelin sheaths rather than to larger axons. Treated animals had lower G-ratios and thicker sheaths.
- Preserved infrapyramidal mossy fibre area at 11 months, assessed by synaptoporin. The suprapyramidal bundle was unaffected — a regional specificity that is more interesting than it is usually made to sound, since the infrapyramidal projection is the one that correlates with spatial learning.
- Preserved apical dendritic arborisation by Golgi-Cox, from 60 to 270 μm from the soma, with greater soma-to-tip distance and more spines.

Proteomics of the raft fractions found 2,417 quantifiable proteins. In untreated Alzheimer mice versus wild-type, 65 were up and 52 down. The most strongly down-regulated protein in the disease state was **Shisa9** (log2 = −5.9), an AMPA-receptor auxiliary subunit — the protein also known as CKAMP44, which shapes short-term plasticity in the dentate gyrus (von Engelhardt et al., 2010; Karataeva et al., 2014). In treated versus untreated animals, caveolin-1 was the most up-regulated protein, as it must be; Shisa9 was the second. Caveolin-1 immunoprecipitation pulled down Shisa9, and did so most strongly in treated animals.

That last observation is the most mechanistically specific thing in the submission. It proposes a chain: caveolin-1 organises the raft; the raft holds Shisa9; Shisa9 stabilises AMPA receptors at the postsynaptic density; AMPA receptor stability underwrites the dentate and CA1 function that fear conditioning measures. It is a plausible chain, it is supported by an interaction and by concordant directionality, and it has not been tested by manipulating Shisa9 — a gap that remains open six years later.

A second, quieter thread runs through the same proteomic dataset and closes a loop in the theory. Among the proteins down-regulated in diseased rafts and restored by treatment was KIAA1468, subsequently characterised as RELCH — a Rab11-binding protein that tethers recycling endosomes to the trans-Golgi network and, in doing so, controls where cholesterol goes inside the cell (Sobajima et al., 2018). Depleting it disrupts cholesterol delivery to the Golgi. This matters because cholesterol binds caveolin-1 in the trans-Golgi network, and that binding is required for caveolin-1 to oligomerise and reach the raft. The implication, which the submission states carefully as a possibility rather than a result, is that the therapy may partly restore the neuron's own cholesterol handling — and if so, the relationship between caveolin-1 and cholesterol is not one-directional support but a loop, in which each is required to position the other. Whether falling caveolin-1 causes the trafficking defect or results from it is described in the submission as unknown, and it still is.

Two further proteins from the same dataset deserve mention because they connect this work to the wider cell biology of the disease: Ap2b1, a subunit of the clathrin adaptor complex that governs endocytosis, and synaptojanin 2, a phosphoinositide phosphatase acting on synaptic vesicle recycling. Both fell in disease and rose with treatment. Endosomal abnormality is among the earliest cellular changes described in Alzheimer neurons, and a treatment that normalises adaptor and phosphatase levels at the membrane is acting in that territory whether or not it was designed to.

4.2 What was not touched

Amyloid plaque burden did not change. Astrogliosis did not change (Wang et al., 2021a). This has held in every subsequent Alzheimer experiment from the group, including the symptomatic-stage study in two independent models (Wang et al., 2025). In the ALS work, survival was extended without any change in expression of the mutant SOD1 protein driving the disease (Wang et al., 2022a).

The authors present this as a virtue, and in the argumentative sense it is: it establishes that the cognitive benefit cannot be an amyloid-clearance effect in disguise. But the same fact is a liability in every other sense, and the programme has been slower to say so. Section 8.4 develops the point; in brief, a therapy that moves no measurable pathology is a therapy with no target-engagement biomarker, and target engagement is what early-phase human trials are for.

4.3 Why the dissociation is the result

It is worth being explicit about why this experiment matters more than its individual measurements.

The central epidemiological fact about Alzheimer's disease pathology is that it is *not sufficient* for dementia. Somewhere between a fifth and a third of cognitively intact older people carry substantial amyloid and tau at autopsy (Dubois et al., 2016; Jati et al., 2026). Synapse loss, not plaque burden, is the structural measure that tracks cognitive decline — a result established in biopsy material by DeKosky and Scheff (1990), confirmed in autopsy series by Terry et al. (1991), and localised to CA1 in mild disease and mild cognitive impairment by Scheff et al. (2007). These are among the most reproduced findings in the field, and the therapeutic programme built on them is small.

What SynCav1 does is produce that dissociation on demand. The pathology is present and unchanged; the synapse is held; the animal performs. Whatever else it is, that is a laboratory instantiation of the human phenomenon of asymptomatic Alzheimer's disease, and it is one of very few.

The comparison worth drawing is not to anti-amyloid antibodies but to the human resilience genetics. The Christchurch variant of *APOE3*, homozygous in a woman who carried the *PSEN1* E280A mutation and an extraordinary amyloid burden yet remained cognitively intact until her seventies (Arboleda-Velasquez et al., 2019), and the *RELN*-COLBOS variant in a man from the same kindred who was similarly protected (Lopera et al., 2023), are natural experiments with the same logical structure: full pathology, preserved function. Head's own submission reaches for exactly this comparison, citing the Christchurch case as evidence that "proteins involved in regulating brain cholesterol homeostasis may in part contribute to some form of neuronal resilience against amyloid plaques."

That is the right frame, and it is a better frame than the one the work usually receives. Section 12 argues that it should be adopted explicitly.

5. What Has Been Added Since

Six years separate the prize submission from the present. The additions are not decorative; three of them change what can be claimed, and one of them closes the submission's own stated weakness. They are set out here roughly in order of how much they alter the standing of the theory.

5.1 Treatment after symptoms — the entry's own limitation, closed

The 2020 submission ends with a candid statement of its principal weakness, and it is not the one most reviewers would have chosen. The authors flag the model — APPswe/PS1ΔE9 over-expresses mutant precursor protein and therefore generates non-physiological quantities of precursor fragments alongside amyloid-β — and name the remedy: the knock-in lines developed by Saito and Saido (2014), in which the endogenous mouse gene is humanised and mutated in place, so that the protein is expressed at normal levels.

A second and larger weakness is present but unstated: the treatment was given at 3 months, six months before the earliest deficit. Presymptomatic delivery is the easiest possible test of a neuroprotective agent and the least informative about clinical utility, because the human beings who would receive such a therapy will already be symptomatic when they are identified.

Both were addressed in 2025 (Wang et al., 2025). The design:

- **Two models.** PSAPP as before, and the $App^{NL\text{-}G\text{-}F}$ knock-in — the clinically relevant line the 2020 paper had named.
- **Delivery after deficits appear.** AAV9-SynCav1 into hippocampus at 6 months in PSAPP and 8 months in the knock-in; behaviour tested at 12 months in both.
- **Result.** Contextual memory recall was preserved in treated animals of both models, in males and females of the knock-in line. Cued memory was not rescued in either. Open-field performance was unaffected.
- **Pathology.** Plaque load unchanged, as before.

The failure of cued recall to respond is not a footnote and should not be read as one. Contextual fear memory is hippocampus-dependent; cued fear memory is substantially amygdala-dependent. A hippocampally injected therapy that rescues the hippocampal task and not the extra-hippocampal one is behaving exactly as an anatomically restricted intervention should. That internal consistency is a point in the work's favour. It is also a hard ceiling: the authors state it themselves, noting that hippocampus-restricted expression "constrains the ability to combat global brain atrophy exhibited

in late-stage AD."

One caveat belongs on the word *symptomatic*. The PSAPP animals treated at 6 months are described in the paper's own supplementary data as lacking plaques and astrogliosis at that age. "Early symptomatic" is accurate; "symptomatic" invites a reading of late-stage disease that the experiment does not support. The knock-in animals treated at 8 months, with fear-learning deficits documented from 6 months in the group's own characterisation (Wang et al., 2022b), are the better instance of the claim.

5.2 A model worth treating

The knock-in experiment was possible because the group first spent a paper characterising the line (Wang et al., 2022b), and that paper is more useful to the field than its citation count suggests.

$App^{NL\text{-}G\text{-}F}$ mice carry humanised Swedish, Iberian and Arctic mutations at the endogenous locus. The time course established: fear learning deficits at 6 months, contextual memory deficits at 12 months; mild amyloidosis with microgliosis by 3 months, progressing with astrocytosis at 6 and 12; hippocampal mitochondria normal at 3 months, but by 7 months showing reduced ATP production, raised membrane potential, increased reactive oxygen species, enlarged volume and reduced mitofusin-2; by 12 months, reduced total oxygen consumption rate.

The finding worth extracting is the ordering. Mitochondrial dysfunction is present at 7 months, ahead of the contextual memory deficit at 12, in a model that expresses precursor protein at physiological levels. That is a bioenergetic lesion that cannot be dismissed as an artefact of over-expression, and it arrives before the cognitive one.

5.3 From scaffold to programme

The most substantial conceptual advance since 2020 is that the mechanism is no longer purely structural.

The 2025 study profiled hippocampal transcriptomes and found that treated PSAPP animals resembled age-matched wild-type mice — not partially, but as an overall profile. Against untreated disease controls, 133 genes were up and 337 down. Gene ontology enrichment ran in coherent directions: up in learning or memory, cognition, synaptic structure and activity, and neurotransmitter secretion; down in the neurodegenerative-disease pathways — Alzheimer's, Parkinson's, Huntington's, amyotrophic lateral sclerosis — and in multiple synaptic dysfunction terms.

Two mechanistic threads were pulled from it.

Activity. In transfected primary cortical neurons, SynCav1 raised phosphorylated CaMKII and phosphorylated CREB. These are the canonical readouts of activity-dependent transcription —

the pathway through which a neuron converts synaptic use into the gene expression that consolidates it. If SynCav1 raises them, then the intervention is not merely holding receptors in place; it is raising the throughput of the activity-to-transcription loop.

PAC1R and ADNP. Treated animals showed raised hippocampal activity-dependent neuroprotective protein (ADNP), and — specifically in the raft fraction, with whole-cell levels unchanged — raised PAC1R, the type I receptor for pituitary adenylate cyclase-activating polypeptide and a known regulator of ADNP expression.

The internal logic of this pair is good. PAC1R is a G-protein-coupled receptor; caveolin-1 organises GPCR–adenylyl cyclase signalling; the effect is raft-specific rather than expression-level, which is precisely the signature the scaffolding theory predicts. ADNP is not a minor protein: it is essential for brain formation (Pinhasov et al., 2003), its haploinsufficiency causes a human neurodevelopmental syndrome, and its active fragment NAP reduces tau hyperphosphorylation and improves learning in transgenic mice (Vulih-Shultzman et al., 2007).

It is worth attaching the cautionary history. That fragment became davunetide, and davunetide failed a phase 2/3 trial in progressive supranuclear palsy on both co-primary endpoints (Boxer et al., 2014). The failure does not impugn ADNP biology, but it does establish that raising ADNP-pathway activity by exogenous peptide is not by itself therapeutic in a human tauopathy. If ADNP is genuinely the effector, the programme has inherited a target with a negative clinical precedent, and the difference between the two approaches — sustained, cell-autonomous, receptor-level elevation versus intermittent peptide administration — becomes the thing that has to be argued rather than assumed.

5.4 Energy

Two papers place caveolin-1 on the bioenergetic axis, and this is the least anticipated development in the programme.

In PSAPP mice, hippocampal SynCav1 mitigated mitochondrial damage and loss and improved respiration. Mechanistically, untreated animals showed increased phosphorylation of DRP1, the dynamin-related GTPase that executes mitochondrial fission, with consequent excessive fragmentation; treated animals had lower phospho-DRP1 and higher mitofusin-1, restoring the fission–fusion balance (Wang et al., 2021b). In the TDP-43 model five years later, the same signature reappeared: SynCav1 lowered phospho-DRP1 at serine 616, lowered phosphorylated mitochondrial fission factor, reduced Fis1, and preserved mitochondrial length and cristae density (Wang et al., 2026).

That the same fission-suppression signature appears in two unrelated proteinopathies is the strongest internal evidence the programme has for a genuine convergence node rather than a model-specific effect.

How a plasma-membrane scaffolding protein controls mitochondrial fission is not established here, and the papers do not overclaim it. Three routes are available in the wider literature and none is excluded: caveolin traffics to mitochondria under stress (Fridolfsson et al., 2012); caveolin-1 regulates cellular metabolism in non-neuronal cells and raises mitochondrial respiration in microglia when elevated (Niesman et al., 2013); and DRP1 phosphorylation is downstream of the same kinases — ERK, Akt, CaMKII — that the raft organises. The third is the most parsimonious and would make the mitochondrial effect a consequence of the signalling effect rather than a parallel one. It is testable and untested.

5.5 Beyond amyloid: the shared surface

The 2026 study is, in theoretical terms, the most important paper the group has published since the submission (Wang et al., 2026).

TDP-43^{A315T} transgenic mice — a model of the proteinopathy that defines most frontotemporal dementia and amyotrophic lateral sclerosis, and that occurs as a co-pathology in a large fraction of Alzheimer brains under the name of limbic-predominant age-related TDP-43 encephalopathy (Nelson et al., 2019) — received AAV-PHP.eB-SynCav1 by retro-orbital intravenous injection at 2 months, 5×10^{11} vector genomes per animal. Contextual freezing rose from 32.6% to 60.3%; cued fear extinction, absent in controls, was restored.

The mechanistic finding is the one that matters, and it was not predicted by the theory as previously stated. Roughly 15% of the mutant TDP-43 was found mislocalised **to the membrane lipid rafts**. Raft-associated GluN2A fell in untreated animals. SynCav1 reduced the mislocalisation, preserved raft GluN2A, and preserved synaptic ultrastructure.

This reframes the theory. Until 2026 the raft was a *victim* — an organisation degraded by ageing and by disease, whose restoration helped. In the TDP-43 result the raft is a *site of pathology*: the surface to which a misfolded protein goes, and on which it does its damage. If that generalises, then the membrane microdomain is not merely the platform whose loss permits degeneration; it is a shared failure surface on which mechanistically unrelated proteinopathies converge.

There is independent reason to take this seriously rather than as a one-model curiosity. Amyloidogenic processing of the precursor protein occurs in rafts (Ehehalt et al., 2003); targeting β-secretase exclusively to rafts increases β-site cleavage (Cordy et al., 2003); the raft localisation of the secretases is a well-developed literature in its own right (Vetrivel and Thinakaran, 2010). And caveolin-1 is itself the route by which amyloid-β oligomers are internalised: knocking it out reduces intracellular oligomer uptake (da Silva Correia et al., 2024). Three proteinopathic processes — amyloid production, amyloid entry, TDP-43 mislocalisation — all transact at the same membrane compartment.

Two limitations are stated in the paper and should travel with the result. The study used **female mice only**, because male TDP-43^{A315T} animals die suddenly at around 3 to 3.5 months from gastrointestinal dysmotility. And phospho-TDP-43 fell in treated animals, which the authors explicitly decline to interpret: whether this is direct biochemical inhibition or a secondary consequence of preserved neuronal health "remains an area of active investigation." That is the correct posture, and it is worth noting because the alternative — claiming a proteinopathy-modifying effect — would have been available and was not taken.

5.6 Resilience discovered, not only engineered

The last addition comes from a different direction and is not a caveolin paper at all.

Working with a computational group, Head's collaborators trained Boolean implication networks on large human cortical RNA-sequencing datasets, extracted an invariant Alzheimer gene signature that stratified disease states across independent cohorts, and reverse-translated it into mouse models. The signature identified a dissociation in chromogranin A-deficient PS19 mice: males showed Alzheimer-like transcriptomic and neuropathological features in prefrontal cortex while learning and memory remained intact; females were more resilient still, with suppressed tau aggregation and preserved synaptic ultrastructure (Jati et al., 2026).

The claim is a validated murine model of asymptomatic Alzheimer's disease — pathology present, cognition intact, by design.

Set beside SynCav1, this is the same phenomenon approached from the opposite end. SynCav1 engineers the dissociation by intervening downstream at the synapse. The chromogranin A model discovers a dissociation by removing an upstream neuroendocrine node. Both produce an animal that has the disease and does not have the dementia. A laboratory that can produce that state two independent ways is in a position to ask the question the field has struggled to formulate: what is the minimal set of conditions under which a brain tolerates Alzheimer pathology?

5.7 A biomarker for the myelin claim

One further addition deserves mention because it repairs a specific gap.

Myelin thinning in CA3 Schaffer collaterals, measured by G-ratio in electron micrographs, has been part of the disease phenotype and part of the treatment effect since the submission. G-ratio is a destructive, terminal, laborious measurement — useless as a longitudinal endpoint and impossible in a human being.

Ultrashort echo time magnetisation transfer imaging now provides a non-invasive equivalent. In App^{NL-G-F} knock-in mice at ~14 months, the imaging ratio was significantly reduced relative to wild-type in both corpus callosum and hippocampus; histological Luxol fast blue staining confirmed

the reduction in the same regions; and in corpus callosum the imaging and histological measures correlated at r = 0.82 (Wang J. et al., 2026). The same animals showed impaired fear learning and contextual and cued recall.

This is a supporting paper rather than a central one, but it converts a claim that could only be made post mortem into one that could in principle be tracked in a living human on a clinical scanner. Section 8.4 returns to why that matters more for this programme than for most.

6. The Independent Literature: Corroboration and Contradiction

A programme this internally consistent has to be checked against work done by people who are not in it. The results are mixed in an instructive way: the loss-of-function claim has strong independent support, the direction-of-change claim in human tissue is contradicted, and the relationship to amyloid processing is genuinely unresolved.

6.1 The diabetic brain — independent corroboration

The strongest external support comes from Bonds et al. (2019), from Orly Lazarov's and Richard Minshall's groups in Chicago. Head is a co-author but not a senior one, and the model, the construct and the readouts are not his.

The findings: caveolin-1 is reduced in the brains of type 2 diabetes patients relative to healthy ageing, and inversely correlated with amyloid-β. The depletion is recapitulated in db/db diabetic mice, which show recognition memory deficits together with up-regulated precursor protein and BACE1, a trend toward a higher Aβ42/40 ratio, and hyperphosphorylated tau. Restoring caveolin-1 by viral over-expression rescued the learning and memory deficits *and reduced the pathology* — precursor protein, BACE1 and phospho-tau all fell. In HEK cells expressing the Swedish mutant, caveolin-1 knockdown raised precursor protein, its C-terminal fragments and amyloid-β; restoration normalised the processing.

Three things follow.

First, this is independent human tissue evidence for caveolin-1 depletion in a condition that is a major risk factor for late-onset Alzheimer's disease. It is the best human data the theory has.

Second, it goes further than Head's own results in a way that ought to be uncomfortable rather than reassuring. Bonds et al. changed the pathology. SynCav1 never has, in any model, at any age. Either the two constructs are doing different things, or the two models differ in whether amyloid processing is caveolin-sensitive, or the neuron-specific promoter is the relevant difference — Bonds et al. used an untargeted adenoviral vector, so their effect may be endothelial, glial or global rather than neuronal. All three are plausible. None has been tested.

Third, and least comfortably: if restoring caveolin-1 can lower BACE1 and phospho-tau in one hands, then the absence of any such effect in SynCav1 experiments is a discrepancy in the theory's own house, not merely a design choice.

6.2 The direction problem

The theory's premise is that caveolin-1 falls in the ageing and degenerating brain. Two independent studies of human tissue report that it rises.

Gaudreault et al. (2004), from Judes Poirier's group, measured hippocampal caveolin protein and frontal cortex caveolin mRNA in autopsy-confirmed Alzheimer cases against age-matched controls, and found both **up-regulated approximately two-fold**. They also reported increases in hippocampal tissue from apolipoprotein E-deficient mice and in aged wild-type mice, and interpreted the increase as a response to disturbed transbilayer cholesterol distribution.

Kang et al. (2006) reported caveolin-1 **up-regulated in all regions of the aged rat brain and in elderly human cerebral cortex**, co-localised with the precursor protein in detergent-insoluble fractions.

These are not fringe results. They are direct measurements in human tissue, from two groups, published in reputable journals, and they contradict the premise as usually stated. The programme's own human-tissue claim — that caveolin-1 and its associated signalling components are decreased "in degenerating neurons in postmortem human brains" — rests principally on studies of chronic traumatic encephalopathy and cholinergic basal forebrain neurons (Mufson et al., 2018; Tiernan et al., 2018) rather than on a systematic quantification in Alzheimer cortex.

Four reconciliations are available, and they are not equally good.

Cell type. Bulk hippocampal homogenate is dominated by endothelium and glia, where caveolin-1 is most abundant. Vascular pathology and reactive gliosis both increase in Alzheimer's disease; an increase in bulk caveolin-1 could reflect vascular and glial expansion while neuronal caveolin-1 falls. This is the strongest reconciliation, it is entirely consistent with Bonds et al. calling caveolin-1 "endothelial-enriched," and it is directly testable by single-cell or single-nucleus measurement. It has not been done.

Compartment. Total protein and raft-localised protein are different quantities, and the programme's own data separate them: in the submission, whole-homogenate and raft-fraction caveolin-1 both fell, but the emphasis throughout is on *localisation*. A neuron could contain more caveolin-1 and have less of it correctly positioned. This too is testable and untested.

Stage. An early compensatory rise followed by a late fall would produce either result depending on when tissue was sampled. Kang et al. report the rise in *senescent* neurons and in aged brain — which is to say, in the condition the theory says precedes the loss. There is no cross-sectional human series that resolves this.

Species and model. The mouse data are Head's; the contradicting human data are not. This reconciliation is available but is the weakest, since it concedes that the human premise is

unestablished.

The honest statement of the position is this: **the claim that neuronal caveolin-1 falls in the human Alzheimer brain is not established.** It is plausible, it is consistent with the mouse data and with the diabetes data, and it is contradicted by the only two direct measurements of bulk human tissue. Nothing in the therapeutic argument actually requires it — a gain-of-function that works does not need to be a restoration — but the programme presents it as settled, and it is not.

6.3 Caveolin-1 and amyloid processing: three results that cannot all hold

If caveolin-1 organises the rafts in which the secretases act, it should affect amyloid production. Three independent studies say it does, in three different directions.

Study	Manipulation	Effect on amyloid processing
Kang et al., 2006	Caveolin-1 over-expression, neuroblastoma cells	β-secretase processing **increased**, via PKC down-regulation
Kapoor et al., 2010	Caveolin-1 knockdown / over-expression, cell lines	Knockdown **increased** γ-secretase processing of precursor protein and Notch; over-expression **decreased** it, by shifting γ-secretase between caveolar and clathrin-coated compartments
da Silva Correia et al., 2024	Caveolin-1 knockout neurons	Intracellular amyloid oligomer uptake **significantly reduced**; caveolin-1 binds both cellular prion protein and amyloid peptides
Bonds et al., 2019	Caveolin-1 knockdown / restoration, HEK-APPswe and db/db mice	Knockdown **increased** precursor protein, C-terminal fragments and amyloid; restoration normalised, and lowered BACE1 in vivo

Read together: raising caveolin-1 should increase β-cleavage (Kang), decrease γ-cleavage (Kapoor), decrease β-cleavage (Bonds), and increase oligomer internalisation (da Silva Correia).

Some of this is reconcilable. β- and γ-secretase are different enzymes in different membrane environments, so opposite effects on the two cuts are not contradictory; Kang and Kapoor may both be right. Cell type differs — neuroblastoma, HEK, primary neuron. Direction of manipulation differs. And the four studies measure four different things: secreted βAPP, γ-secretase activity, intracellular oligomer, and steady-state protein levels.

What is not reconcilable is the therapeutic silence. If caveolin-1 elevation had any of these effects in a neuron in vivo, SynCav1 should have moved amyloid in some direction in at least one of six experiments across two models and two delivery routes. It has not moved it in any.

Three readings of that are possible, and they have quite different implications.

1. **The effects are small relative to the driving over-expression.** In a mouse making mutant precursor protein at many times the physiological rate, a modest shift in secretase geography would be invisible against plaque load. This is likely and would mean the effects are real but therapeutically irrelevant in these models — and possibly relevant in a human brain, where the driving force is far smaller.
2. **The effects cancel.** Increased β-cleavage and decreased γ-cleavage would partly offset. This is testable by measuring the fragments, which no SynCav1 paper does.
3. **Plaque load is the wrong measure.** The most consequential species — soluble oligomers and the intraneuronal pool — are not what an anti-amyloid immunostain reports. Given da Silva Correia et al.'s finding that caveolin-1 is the entry route for oligomers, this is the possibility that should worry the programme most, and it is the one no experiment addresses.

This is the single most important untested question in the work. A SynCav1-treated neuron might be internalising more amyloid-β oligomer than an untreated one, and doing well anyway. If so, the therapy is even more interesting than claimed — it would be preserving function *against a higher intracellular burden*. If the reverse, the mechanism is partly an amyloid-handling mechanism after all, and the "independent of amyloid" framing needs qualifying. Section 11 lists the experiment.

6.4 The endothelium, where the same protein is a hazard

One asymmetry deserves emphasis because it is the clearest case in which the programme's design choices are vindicated by outside work.

Caveolae-mediated transcytosis is the vesicular route across the blood–brain barrier, and barrier integrity depends on its suppression. Andreone et al. (2017) established the mechanism: lipids transported by Mfsd2a create an endothelial membrane environment that inhibits caveolae vesicle formation, and it is this inhibition that keeps CNS endothelium unusually impermeable.

Raising caveolin-1 in brain endothelium would therefore be expected to increase transcytosis and degrade the barrier. Any systemically delivered, ubiquitously expressed caveolin-1 construct would do exactly that. SynCav1 does not, because the synapsin promoter confines expression to neurons — and the 2026 study, which is the first to deliver the vector systemically, is the first in which this containment does real work rather than notional work.

The same asymmetry sharpens the interpretation of the human tissue disagreement in Section 6.2. If bulk caveolin-1 rises in the Alzheimer brain because vascular and glial caveolin-1 rises, then the human data are not evidence against the theory; they are evidence that the compartment matters, which is the theory's own central claim.

6.5 The field has moved toward the membrane

The last piece of independent context is not about caveolin-1 at all, and it changes the standing of the programme more than any single experiment.

In 2025, *Annual Review of Biochemistry* published "A Lipid-Raft Theory of Alzheimer's Disease" (Rappoport, 2025). The argument runs, in outline: the resolution of competition between synaptic candidates for long-term enhancement depends on the formation of plasma-membrane lipid rafts; raft formation requires astrocyte-produced cholesterol; sporadic Alzheimer's disease is caused by impaired raft formation, which prevents conversion of short- to long-term memory and yields excessive tau phosphorylation, intracellular cholesterol accumulation, synaptic dysfunction and neurodegeneration; amyloid production is promoted by cholesterol during the switch to competition resolution.

This was developed independently of Head's programme and reaches the same causal position from the direction of plasticity theory rather than of therapeutics. Its existence does not make either account correct. What it does is change the burden of argument. In 2020, a submission proposing that membrane organisation is the tractable lesion in Alzheimer's disease was making an unusual claim in an amyloid-dominated field. In 2026, the membrane has an independent, comprehensive, high-profile theoretical statement behind it, and Head's programme is the only one that has built a therapy on it.

The concordance is not total, and the difference is worth naming. Rappoport's theory locates the primary failure in astrocytic cholesterol supply. Head's locates it in the neuronal scaffolding protein that organises what the cholesterol builds. These are complementary — supply and assembly — and they generate a joint prediction that neither makes alone: that a neuron with abundant caveolin-1 should be less sensitive to a shortfall in astrocytic cholesterol delivery than a neuron without it. That is a clean, cheap experiment, and nobody has run it.

7. The Specificity Question

7.1 One intervention, four diseases

The same construct, in the same laboratory, has now improved outcomes in:

Model	Disease	Delivery	Principal result
APPswe/PS1ΔE9	Amyloid	Hippocampal AAV9, 3 m	Learning and memory preserved at 9 and 11 m; synapses, spines, arbour, myelin preserved; plaques unchanged
App^{NL-G-F} knock-in	Amyloid, physiological expression	Hippocampal AAV9, 8 m	Contextual memory preserved at 12 m; transcriptome near wild-type; plaques unchanged
SOD1^{G93A} mouse and rat	Motor neuron disease	Transgenic cross; subpial spinal AAV9	Onset delayed, motor function and neuromuscular junctions preserved, survival extended ~10%; mutant protein unchanged
TDP-43^{A315T}	TDP-43 proteinopathy	Systemic AAV-PHP.eB, 2 m	Contextual memory nearly doubled; raft mislocalisation of TDP-43 reduced; mitochondrial fission suppressed
Controlled cortical impact	Traumatic brain injury	Hippocampal AAV9	Motor function improved, memory preserved

Five models, four aetiologies, no shared upstream molecule. Amyloid precursor protein, superoxide dismutase 1, TDP-43 and mechanical impact have essentially nothing in common except that each ends in the failure of neurons.

This is the programme's most striking fact and its most serious interpretive problem, and the two are the same fact.

7.2 Two readings

The convergence reading. Membrane raft organisation is a shared downstream node. Whatever the upstream insult, a neuron under stress loses raft integrity, and with it the ability to transduce the trophic signals that would sustain it. Restoring the platform restores that capacity regardless of what degraded it. Under this reading, the cross-disease generality is precisely the evidence for the theory: a genuine convergence node *should* work in unrelated diseases, and its doing so is a prediction confirmed rather than an anomaly explained.

The non-specific reading. SynCav1 is a synaptogenic, pro-arborisation, pro-myelination intervention that improves neuronal health in any model where neurons are unhealthy. It works in four diseases the way exercise, enriched environment, or reduced stress work in four diseases — by raising the substrate that disease consumes, not by engaging disease mechanism. Under this reading, the generality is evidence of *lack* of mechanism, and the effect size in each model should be roughly proportional to how much slack the model has.

Neither reading is refuted by anything currently published, and the programme's own framing does not distinguish them. Both readings predict everything observed so far.

7.3 What separates them

Three discriminating observations exist, and two of them are available now.

First, the ceiling test. The non-specific reading predicts that SynCav1 should help healthy animals as much as, or more than, diseased ones — a healthy neuron has as much to gain from more synapses as a sick one. The convergence reading predicts a larger relative effect in disease, because the disease has created a deficit that the intervention specifically fills.

The data here run against the non-specific reading, though not decisively. In healthy adult and aged mice, SynCav1 improved contextual fear memory (Mandyam et al., 2017) — so it is not disease-specific in the strict sense. But the aged animals gained less structurally than the adult ones, which is the wrong direction for a simple "more substrate is better" account and the right direction for a "restore what is lost" account applied to an already-degraded membrane. This is suggestive and under-analysed; a properly powered comparison of effect size in wild-type versus disease at matched ages has never been reported.

Second, the mislocalisation test. This is the strongest available evidence for convergence, and it comes from the 2026 study. Mutant TDP-43 mislocalises to rafts, and SynCav1 reduces that mislocalisation. A non-specific health-improving intervention has no reason to change where a mutant protein goes. If that finding replicates — and it currently rests on a single experiment in one sex of one line — it establishes that the intervention engages the disease process at the membrane rather than merely compensating for it downstream.

Third, the dose–response test, which has not been done. If the mechanism is raft restoration, then benefit should track raft-localised protein rather than total caveolin-1 expression, and should saturate once raft occupancy is restored. If the mechanism is non-specific trophic support, benefit should track total expression and continue to rise. Every published experiment uses a single vector dose. This is the cheapest of the three experiments and the most informative.

7.4 A note on how the question should be framed

There is a temptation to treat "non-specific" as a criticism, and it is worth resisting.

If a single, deliverable, well-tolerated intervention raises the synaptic and myelin substrate of the brain such that four unrelated neurodegenerative diseases produce less disability, that is not a failure of mechanism; it is a description of cognitive reserve, delivered pharmacologically. Reserve is real, it is the best-established protective factor in the epidemiology, and nobody has a molecule for it.

What the distinction changes is not whether the therapy is worth developing but *how it should be developed and against what it should be measured*. A convergence-node therapy is developed against mechanism: dose to raft occupancy, measure raft-localised receptor, expect effect in the specific disease. A reserve therapy is developed against capacity: dose to tolerability, measure structural substrate, expect effect across diseases and expect it to be larger the earlier it is given. Those are different trials. The programme currently proceeds as though the first were established while its evidence base is equally compatible with the second, and that ambiguity is a strategic liability rather than merely an intellectual one.

8. Translation

8.1 Three delivery routes, and what each was for

The delivery work is more sophisticated than the therapeutic literature usually notices, and reading the three routes as a sequence clarifies what has and has not been solved.

Stereotactic hippocampal AAV9 (2021, 2025). Bilateral injections, three sites per hemisphere, roughly 3 μL per hemisphere at 2×10^{10} genome copies per μL. This is the research route: maximal control, maximal local expression, minimal translatability. Its value is that it isolates the biology from the delivery problem entirely. Its ceiling is anatomical, and the authors state it — hippocampus-restricted expression cannot address global atrophy.

Subpial spinal AAV9 (2022a). Developed with Martin Marsala's group, this route places vector under the pia of the spinal cord and achieves broad segmental transduction. In $SOD1^{G93A}$ mice, lumbar subpial delivery delayed onset, preserved α-motor neuron morphology and neuromuscular junction integrity, improved running-wheel performance, and extended survival by about 10%. Cervical delivery in $SOD1^{G93A}$ rats preserved forelimb grip strength and motor evoked potentials.

This is the most translationally serious delivery work in the programme, because subpial injection is a real neurosurgical procedure with a real path to human use, and because the rat result demonstrates the route scales beyond mouse anatomy. It is also, notably, the experiment in which the mutant protein was explicitly unchanged — the dissociation reproduced in a second disease.

Systemic AAV-PHP.eB (2026). Retro-orbital intravenous injection, 5×10^{11} vector genomes, crossing the blood–brain barrier to transduce neurons throughout the brain. This solves, at a stroke, the anatomical ceiling that limits every hippocampal experiment.

In mice.

8.2 The LY6A problem

AAV-PHP.eB was engineered by directed evolution in mice (Deverman et al., 2016; Chan et al., 2017), and its remarkable central nervous system tropism — 69% of cortical neurons after intravenous delivery — depends on a receptor that human beings do not have.

Hordeaux et al. (2018) showed that the neurotropic properties of the parent capsid PHP.B are limited to C57BL/6J mice and are absent in other strains and in non-human primates. Huang et al.

(2019) identified the reason: LY6A, a glycosylphosphatidylinositol-anchored protein expressed on mouse brain endothelium, is the receptor. Disrupting it abolishes PHP.eB transduction of mouse brain endothelial cells; ectopically expressing it raises transduction of otherwise non-permissive cells more than thirty-fold. *LY6A* has no human orthologue.

The consequence is unambiguous and needs stating plainly, because the 2026 paper's framing — "systemic delivery" — invites the wrong inference. **The 2026 TDP-43 result is a biology experiment, not a delivery experiment.** It demonstrates that widely distributed neuronal caveolin-1 expression is beneficial and tolerated in a proteinopathy model. It demonstrates nothing about whether such expression can be achieved in a human brain by intravenous injection, and the capsid used cannot do it.

This is not a criticism of the choice — PHP.eB is the correct tool for asking whether brain-wide expression helps, and asking that question was the right thing to do. It is a criticism of how the result is likely to be read. The honest translational statement is that the programme has one route with a plausible human path (subpial, for spinal cord), one route with a partial human path (stereotactic, for hippocampus, as used in existing Alzheimer gene therapy trials), and no route at all for the brain-wide expression that its own anatomical argument says is needed.

8.3 What AAV2-NGF taught, and what this theory says about it

The most instructive precedent for this programme is a failure, and the programme's relationship to it is unusually direct.

Nerve growth factor gene therapy for Alzheimer's disease ran from a phase 1 trial of ex vivo fibroblast delivery (Tuszynski et al., 2005) through demonstration of trophic responses in treated human neurons (Tuszynski et al., 2015) to a randomised, sham-surgery-controlled phase 2 trial of AAV2-NGF delivered stereotactically to the nucleus basalis of Meynert. The phase 2 trial was negative on all cognitive and functional endpoints (Rafii et al., 2018).

Castle et al. (2020) then did the thing that is almost never done: they obtained post-mortem tissue from trial participants and asked where the vector had gone. The answer was that it had not gone far enough. Transduction was confined to a small fraction of the intended target, and the paper's title states the conclusion — the trial identified "a need for improved vector delivery."

Head's submission offers a different and mechanistically prior explanation for the same failure, and it was written before Castle's analysis was published. The argument: neurotrophin therapy depends on neurotrophin receptor function, receptor function depends on raft localisation, and raft localisation is exactly what is lost in the degenerating neurons the therapy targets. On this reading, AAV2-NGF was pouring ligand onto receptors that could not transduce it, and better delivery would have produced better transduction of the same non-functional signalling.

These two explanations are not mutually exclusive and both may be right. But they are distinguishable, and the distinction has practical consequence: if Castle is right, the fix is a better vector; if Head is right, the fix is to restore the receiving apparatus first, or instead.

There is a detail here that is easy to miss and worth stating. **Matthew Castle is a co-author on Head's 2026 systemic delivery paper.** The person who established that the field's previous Alzheimer gene therapy failed on delivery geometry is now working on the delivery of this one. That is the correct people talking to each other, and it is a better sign for the programme's translational seriousness than any single result.

The submission's own version of the argument is worth quoting for its restraint: "The lack of MLR-localized NTR in previous therapies may provide a mechanistic explanation for the failed multicenter phase 2 clinical trial." *May provide.* It is offered as a hypothesis, and it remains one — no experiment has tested whether SynCav1 pre-treatment rescues the response to exogenous neurotrophin in a degenerating neuron. That experiment is listed in Section 11, and it is the one that would convert a plausible post-hoc reading of a clinical failure into a testable therapeutic strategy.

8.4 The measurement problem

This is, in the author's assessment, the most serious obstacle to human development of SynCav1, and it is not the one usually raised.

Every Alzheimer therapeutic programme that has reached the clinic in the last decade has had a target-engagement biomarker. Anti-amyloid antibodies clear amyloid, and amyloid PET measures it: lecanemab and donanemab were both developed against a readout that shows, in weeks to months, whether the drug is doing the thing it was designed to do (van Dyck et al., 2023; Sims et al., 2023). The recent secondary analysis of TRAILBLAZER-ALZ 2, which stratified participants by post-treatment amyloid level and examined the relationship to clinical outcome and to plasma phospho-tau 217, glial fibrillary acidic protein and neurofilament light, is possible only because such readouts exist (Lu et al., 2025).

SynCav1 has, by design, none of this. It does not change plaque. It does not change tangle. Nothing in the published work suggests it would change plasma phospho-tau 217 or amyloid ratios, and the one relevant measurement — TDP-43 phosphorylation in the 2026 study — the authors explicitly decline to interpret as target engagement.

A first-in-human trial of this therapy would therefore face a specific difficulty: after a single irreversible injection of a vector at a chosen dose, there would be no way to know within the first year whether the therapy had engaged its target, short of waiting for a cognitive endpoint in a disease whose cognitive endpoints require hundreds of patients and eighteen months. Dose selection would be guesswork. Futility analysis would be impossible.

Three partial solutions are visible in the recent work, and it is worth noting that the programme appears to be assembling them without describing them as such.

Transcriptomic signature. The 2025 finding that treated hippocampi approach a wild-type transcriptome is, in principle, the beginning of a pharmacodynamic readout. It is not accessible in a living human brain, but its plasma-detectable shadow — if one exists — would be.

ADNP and PAC1R. A receptor–effector pair whose raft localisation changes with treatment is exactly the shape of thing that could become a measurable target-engagement marker if any of it appears in cerebrospinal fluid. ADNP is measurable in human blood and cerebrospinal fluid. Nobody has asked whether it moves with this intervention in a large animal.

Myelin imaging. Ultrashort echo time magnetisation transfer imaging detects the myelin deficit in the knock-in model non-invasively, and correlates with histology (Wang J. et al., 2026). Myelin content in CA3 Schaffer collaterals has been a treatment-responsive endpoint since the 2020 submission. Of the three, this is the only one that is already a human-scanner measurement, and it is the most promising and least developed.

The recommendation that follows is concrete: **the programme's highest-value next investment is not another efficacy model but a pharmacodynamic readout.** Efficacy in a sixth model adds little to a body of work that already shows efficacy in five. A biomarker that moves with dose would change what is possible.

8.5 Safety, honestly stated

Three specific concerns attach to this therapy and are not adequately addressed in the published record.

It is a gain of function, not a restoration. As Section 2.2 established, neurons are not caveolin-rich cells and do not have caveolae. SynCav1 installs an organising protein at levels no neuron normally expresses. The usual safety inference — "we are only restoring what was lost" — is unavailable, and the human tissue disagreement in Section 6.2 makes it more unavailable, not less: if bulk caveolin-1 is *raised* in the Alzheimer brain, then a therapy that raises it further needs an argument.

Caveolin-1 elevation has known adverse phenotypes in the brain. The clearest is behavioural. Avchalumov et al. (2021) delivered a caveolin-1-expressing lentivirus to rat dorsal striatum and found that it *enhanced* methamphetamine self-administration, shifted the dose–response curve upward, and produced a drug-vulnerable phenotype; knockdown produced the opposite. Sucrose responding was unaffected, so the effect was specific to the drug rather than a general change in motivation. The mechanism proposed — caveolin-1 regulation of dopamine D1 receptor function and CaMKII phosphorylation in the striatum — is the same mechanism, in a different

circuit, that the Alzheimer work regards as therapeutic.

This is not a reason to abandon the therapy. It is a reason the synapsin promoter is insufficient on its own as a containment strategy, since synapsin is expressed by striatal neurons too. A brain-wide systemically delivered SynCav1 would raise caveolin-1 in the striatum, and the one experiment that has tested what that does found an addiction-vulnerability phenotype. The stereotactic hippocampal route does not have this problem. The systemic route, which is the direction of travel, does. It should be measured.

It is irreversible. AAV expression in post-mitotic neurons is effectively permanent. There is no discontinuation. Any adverse effect that emerges — including one that emerges after a decade — cannot be withdrawn. This is true of all AAV gene therapy and is not specific to this programme, but it interacts badly with the measurement problem in Section 8.4: a therapy that cannot be dosed to a biomarker and cannot be stopped is one in which the first human dose selection is a high-stakes, essentially irreversible guess.

8.6 Where it would sit alongside anti-amyloid therapy

The therapeutic landscape changed after the submission was written, and the change is favourable to this programme rather than otherwise.

Lecanemab and donanemab both slowed decline in early symptomatic Alzheimer's disease, and both left the great majority of decline intact (van Dyck et al., 2023; Sims et al., 2023). The most recent analysis of the donanemab trial confirms a relationship between depth of amyloid removal and clinical outcome, and confirms that removing amyloid does not stop the disease (Lu et al., 2025).

That is precisely the gap Head's argument identifies. The submission states it in one sentence: "removal of toxic amyloid species alone will not restore neuronal and synaptic plasticity in the neurodegenerative brain." Six years later, that is not a contrarian position; it is what the trials show.

The combination hypothesis follows and is explicitly left open in the submission — "we have not tested whether SynCav1 in combination with amyloid-lowering drugs could work together." It remains untested six years later, and it is the most obvious experiment in the whole programme: an anti-amyloid antibody plus SynCav1 in a knock-in mouse, with the antibody removing the driver and the gene therapy holding the synapse. Two arms of a mechanism that address different halves of the same disease, in an era when the first arm is licensed. There is no technical obstacle.

9. Strength of Evidence

The claims of the programme differ enormously in how well they are supported, and the differences are not visible from the way the work is usually summarised. The table below grades each principal claim. The scale is deliberately plain:

- **Established** — demonstrated by direct experiment, with the effect reproduced across models, laboratories, or both.
- **Well supported** — demonstrated by direct experiment, reproduced within one laboratory, not independently replicated.
- **Supported** — demonstrated once, or by indirect evidence consistent across several studies.
- **Inferred** — a reasonable interpretation of the data that has not been tested as such.
- **Assumed** — required by the argument, and not demonstrated.
- **Contested** — direct evidence exists on both sides.

#	Claim	Grade	Basis, and what is missing
1	Membrane rafts organise neurotrophin and glutamate receptor signalling; disrupting them disrupts signalling	Established	Broad independent cell-biological literature; Head et al., 2008, 2011 in neurons specifically
2	Caveolin-1 is required for NMDA- and BDNF-driven pro-survival signalling in neurons	Well supported	Loss and rescue in the null; single laboratory (Head et al., 2008, 2011)
3	Raft localisation of synaptic receptors declines with age in rodent hippocampus	Well supported	Head et al., 2010; consistent with the age-related membrane literature (Egawa et al., 2016)
4	Caveolin-1 loss produces a neurodegenerative phenotype in mice	Established	Head et al., 2010; independently in Gioiosa et al., 2008 and Niesman et al., 2014. Confounded by the vascular phenotype of the global null
5	Neuron-targeted caveolin-1 increases synapses, dendritic arbour, myelin and LTP in healthy hippocampus	Well supported	Mandyam et al., 2017; Egawa et al., 2018 — ultrastructure and electrophysiology, single laboratory

#	Claim	Grade	Basis, and what is missing
6	SynCav1 preserves hippocampal-dependent memory in amyloid models	Well supported	Two models, presymptomatic and early-symptomatic delivery, vector-matched controls (Wang et al., 2021a, 2025). No independent replication
7	It does so without reducing amyloid plaque load	Established	Reproduced in every relevant experiment, and the negative is the easier result to trust
8	The benefit generalises across unrelated proteinopathies	Well supported	Amyloid, SOD1, TDP-43, trauma (Sawada et al., 2019; Wang et al., 2022a, 2026; Egawa et al., 2017)
9	Mutant TDP-43 mislocalises to membrane rafts, and SynCav1 reduces this	Supported	Single experiment, one line, female mice only (Wang et al., 2026). High value; needs replication
10	SynCav1 restores mitochondrial fission–fusion balance	Well supported	Two models, concordant molecular signature (Wang et al., 2021b, 2026). Mechanism connecting membrane to mitochondrion not established
11	Neuronal caveolin-1 is decreased in the human Alzheimer brain	Contested	Reduced in type 2 diabetes brain (Bonds et al., 2019); increased in bulk Alzheimer hippocampus and cortex (Gaudreault et al., 2004; Kang et al., 2006). Cell-type resolution would settle it
12	Shisa9 mediates the synaptic benefit	Inferred	Co-immunoprecipitation and concordant direction (Wang et al., 2021a). Never manipulated
13	PAC1R–ADNP mediates the neuroprotective effect	Inferred	Raft-specific PAC1R change plus ADNP elevation (Wang et al., 2025). Neither manipulated; ADNP pathway has a negative clinical precedent (Boxer et al., 2014)
14	Raft loss explains the failure of neurotrophin gene therapy in humans	Inferred	Mechanistically coherent, competes with a delivery explanation supported by post-mortem data (Castle et al., 2020). Directly testable, untested
15	The mechanism is disease-mechanism engagement rather than non-specific trophic support	Inferred	Best evidence is the TDP-43 mislocalisation result. No dose–response, no matched healthy-versus-disease effect-size comparison
16	Elevating neuronal caveolin-1 does not increase amyloid burden inside the neuron	Assumed	Plaque load unchanged, but intraneuronal and oligomeric amyloid never measured — and caveolin-1 is the oligomer entry route (da Silva Correia et al., 2024)

#	Claim	Grade	Basis, and what is missing
17	The therapy is safe at supraphysiological expression, brain-wide, for life	Assumed	No long-term safety study; a striatal caveolin-1 elevation produced an addiction-vulnerability phenotype (Avchalumov et al., 2021)
18	Systemic delivery is achievable in humans	Assumed	The capsid used depends on a mouse-specific receptor with no human orthologue (Hordeaux et al., 2018; Huang et al., 2019)

The shape of this table is the shape of the programme. The cell biology is strong. The animal efficacy is strong within one laboratory and unreplicated outside it. The human premise is contested. The mechanism at the level of specific effectors is inferred rather than demonstrated. And the three assumptions — no intraneuronal amyloid cost, long-term safety, human deliverability — are the three things a development programme would have to establish first.

10. Weaknesses

Stated plainly, and separated from the questions in Section 11, which are questions the evidence could answer.

10.1 No independent replication of the treatment effect

Every published experiment showing that SynCav1 benefits a disease model comes from Head's laboratory or from collaborations in which his group provides the construct and the framing. Bonds et al. (2019) is genuinely independent and supports the underlying caveolin-1 biology, but it uses a different vector, a different promoter, a different model and reports a different outcome profile — it changed the pathology, which SynCav1 never does.

For a body of work sixteen years old with a patented therapeutic and a stated ambition to reach clinical trials, this is the most consequential gap. It is not an accusation of anything; it is a structural feature of how single-construct programmes develop, and it is fixable by distributing the vector.

10.2 One behavioural paradigm

Fear conditioning carries nearly the entire behavioural argument. It appears in the 2020 submission, the 2021 paper, the 2022 characterisation, the 2025 symptomatic study and the 2026 TDP-43 study. Open-field testing is used, correctly, to exclude motor and anxiety confounds, but it is a control rather than an endpoint.

Contextual fear conditioning is a good hippocampal task and its interpretation here is disciplined — the repeated failure of cued recall to respond is evidence that the readout is anatomically meaningful rather than a general arousal effect. But a single paradigm cannot distinguish memory from learning rate, or hippocampal encoding from consolidation, and it is not the task on which the rest of the field's data rest. Spatial navigation, novel object recognition, and any test of cognitive flexibility are essentially absent.

10.3 "Symptomatic" is early

The 2025 study is presented as establishing efficacy at the symptomatic stage, and it is a genuine advance over presymptomatic dosing. But the PSAPP animals treated at 6 months are documented in the paper's own supplementary material as lacking plaques and astrogliosis at the time of treatment, and the knock-in animals at 8 months are two months past deficit onset in a line whose contextual deficit arrives at 12.

Human beings present for treatment years after synapse loss has begun. Nothing in this programme has tested delivery into an animal with established synapse loss and established gliosis, which is the condition the therapy would actually meet.

10.4 Preservation or addition?

Because SynCav1 increases synapse number, spine density, dendritic arbour and myelination in *healthy* hippocampus (Mandyam et al., 2017; Egawa et al., 2018), a treated diseased animal with more synapses than an untreated one is not thereby shown to have lost fewer. It may have lost the same number and started from a higher count.

The distinction matters for what is being claimed. "Neuroprotection" implies that the loss process was slowed. "Compensation" implies it was outpaced. Only the first is a claim about disease mechanism; the second is a claim about reserve. The published experiments cannot distinguish them, because the treated wild-type arm — SynCav1 in a non-diseased animal, aged in parallel — is absent from the disease studies even though the group has run exactly that experiment separately.

10.5 Small groups for the mechanistic measurements

Behaviour is well powered — 15 to 20 animals per group in the submission, with a stated power calculation. The mechanistic work is not: 3 to 5 animals per group for raft isolation, immunoblot, immunofluorescence, Golgi-Cox and electron microscopy. This is conventional for such assays and is not misreported, but it means the proteomic and ultrastructural findings — including the Shisa9 result on which the mechanistic story rests — are generated from a handful of animals and have not been reproduced in an independent cohort.

10.6 The programme's own signalling readout failed

An honest weakness, and one the submission reports rather than hides. If SynCav1 works by preserving raft-localised TrkB, then TrkB activation should be measurable. It was not: phospho-TrkB and phospho-Src were highest in treated animals but did not reach significance because of within-group variance.

The explanation offered is reasonable — receptor abundance is not receptor activation without ligand, and activation kinetics are 15 to 60 minutes, which is not a window one catches by sacrificing an animal months after gene transfer. But the consequence stands: the central mechanistic step of the theory, that restored receptor localisation produces restored receptor signalling, has been demonstrated in vitro and not in vivo, and the in vivo attempt was negative.

10.7 Sex, and the models' own limits

The 2026 TDP-43 study used females only, for a stated and legitimate reason. The 2025 study reports both sexes in the knock-in line, which is an improvement. But sex is emerging as a first-order variable in exactly this territory — the asymptomatic model paper from the same group reports that female chromogranin A-deficient PS19 mice are markedly more resilient than males (Jati et al., 2026) — and a resilience-focused programme that runs single-sex experiments is leaving its most interesting variable unmeasured.

11. What Would Settle the Open Questions

Six experiments. Each is technically available now, each addresses a claim graded *Inferred*, *Assumed* or *Contested* in Section 9, and each has a clearly interpretable negative result.

1. Measure intraneuronal and oligomeric amyloid in treated animals. *Addresses claim 16.* Caveolin-1 is the route by which amyloid oligomers enter neurons (da Silva Correia et al., 2024). Every SynCav1 experiment measures plaque and none measures the intracellular pool. Quantify intraneuronal amyloid-β and soluble oligomer in treated and untreated hippocampus by the standard sequential-extraction and oligomer-specific assays. *If oligomer uptake is increased and function is preserved anyway*, the therapy is more remarkable than claimed and the resilience framing is vindicated. *If uptake is decreased*, the mechanism is partly amyloid-handling and the "amyloid-independent" description needs qualifying. Either result is informative; the current absence of the measurement is the single largest hole in the account.

2. Dose–response against raft occupancy. *Addresses claim 15.* Deliver three vector doses spanning an order of magnitude. Measure total caveolin-1, raft-localised caveolin-1, raft-localised TrkB and GluN2A, and behaviour. *If benefit tracks raft occupancy and saturates*, the mechanism is raft restoration and the convergence reading is supported. *If benefit tracks total expression monotonically*, the effect is trophic and non-specific, and the therapy should be developed as a reserve intervention rather than a mechanism-targeted one.

3. Caveolin-1 in human brain, at cell-type resolution. *Addresses claim 11.* The disagreement between Head's premise and the human data of Gaudreault et al. (2004) and Kang et al. (2006) is entirely attributable to bulk measurement. Single-nucleus RNA sequencing of Alzheimer and control cortex, stratified by cell type and by Braak stage, would settle in one dataset whether neuronal *CAV1* falls while endothelial and astrocytic *CAV1* rises. Much of the necessary data already exists in public repositories. *If neuronal caveolin-1 does not fall*, the therapy is a pure gain of function and should be argued as one — which is a defensible position, but a different one.

4. Test the neurotrophin-rescue hypothesis directly. *Addresses claim 14.* The claim that the AAV2-NGF trial failed because degenerating neurons cannot transduce neurotrophin signal is the programme's most interesting reading of clinical evidence, and it has never been tested. Deliver SynCav1 or control to aged or diseased animals, then challenge with exogenous BDNF or a TrkB agonist, and measure receptor phosphorylation, downstream kinase activation and structural response. *If SynCav1 restores the response to ligand in cells that had lost it*, the programme has a second, and

arguably more clinically tractable, therapeutic strategy: caveolin-1 as an enabling co-therapy for the neurotrophin approaches that have already failed alone. *If it does not*, an attractive explanation of a real clinical failure should be retired.

5. Manipulate the proposed effectors. *Addresses claims 12 and 13.* Shisa9 and the PAC1R–ADNP axis are currently correlative. Knock down Shisa9 in SynCav1-treated animals; block PAC1R or reduce ADNP in the same design. If the behavioural benefit survives the loss of a proposed mediator, that mediator is a marker rather than a mechanism.

6. Combination with amyloid removal, and a treated healthy control. *Addresses claims 6 and 15, and weakness 10.4.* A four-arm study in the knock-in model — vehicle, anti-amyloid antibody, SynCav1, both — with wild-type animals receiving SynCav1 and ageing in parallel. This answers three questions at once: whether the two mechanisms are additive, whether the treated diseased brain differs from a treated healthy brain in the way "preservation" implies, and whether the therapy's benefit is proportional to the deficit it is supposed to fill.

A seventh, outside the programme but implied by it: **test whether caveolin-1 elevation protects neurons against a shortfall in astrocyte-derived cholesterol.** Rappoport's (2025) theory locates the primary failure in supply; Head's in assembly. If assembly can compensate for supply, the two accounts join into one, and the joint theory makes predictions neither makes alone.

12. Reading the Programme

12.1 It is not best described as a gene therapy

The work is presented, by its authors and by the coverage it receives, as a gene therapy for Alzheimer's disease. That description is accurate and unhelpful, because it invites comparison with the class of interventions this therapy is least like.

Gene therapies in neurodegeneration are usually replacement or suppression strategies aimed at a known causal molecule: supply the missing enzyme, silence the toxic transcript, deliver the trophic factor the tissue lacks. Every one of them is defined by a relationship to a specific upstream lesion, and every one of them is evaluated by whether it corrects that lesion.

SynCav1 has no such relationship, in any of the five models where it works. It corrects no lesion. In amyloid models the amyloid remains; in SOD1 models the mutant protein remains; in the TDP-43 model the proteinopathy is present and the authors decline to claim they modified it. What the therapy does is change the terms on which the neuron meets the lesion.

The right comparison class is not gene therapy. It is **resilience**.

12.2 The resilience frame, stated properly

Three human observations define the phenomenon.

Between a fifth and a third of cognitively intact older people carry substantial amyloid and tau pathology at autopsy (Dubois et al., 2016). Synapse density, not plaque burden, is what tracks cognition (DeKosky and Scheff, 1990; Terry et al., 1991; Scheff et al., 2007). And in at least two documented cases, a single genetic variant has held cognition intact against an amyloid burden that should have been overwhelming — the *APOE3* Christchurch homozygote (Arboleda-Velasquez et al., 2019) and the *RELN*-COLBOS carrier (Lopera et al., 2023), both from the Colombian presenilin-1 kindred.

These are the same phenomenon at three levels of description: population, tissue and gene. Together they say that Alzheimer pathology is a hazard whose translation into dementia is *modifiable*, and that the modifier acts at the synapse.

SynCav1 is the most developed pharmacological instance of that modifier. Set against the genetic cases, it has a specific and underappreciated profile:

	Christchurch *APOE3*	*RELN*-**COLBOS**	**SynCav1**
Acts on	Lipoprotein receptor binding, heparan sulfate interaction	Reelin signalling to the tau kinase cascade	Membrane platform assembly
Requires knowing the cause	No	No	No
Position	Upstream of tau spread	Upstream of tau phosphorylation	Downstream, at the synapse
Pathology changed	Tau spread limited	Tau limited locally	None
Deliverable	Not by AAV (protein-level variant)	Not by AAV (3,461 residues)	**Yes — 178 residues**

The last row is the point. The two human resilience alleles that the field most wants to phenocopy cannot be delivered as genes: one is a point substitution in a protein that would have to be edited in situ, the other encodes a protein far beyond AAV's packaging capacity. Caveolin-1 is 178 amino acids. Whatever else is true of this programme, it is the resilience strategy that fits in the vector.

12.3 The membrane as a shared failure surface

The 2026 TDP-43 result suggests a stronger claim than the programme has yet made, and it is worth stating in its own right because it may outlive the therapy.

Assemble what is now known about what happens at the neuronal membrane raft in neurodegeneration:

- Amyloidogenic processing of the precursor protein occurs there (Ehehalt et al., 2003), and forcing β-secretase into rafts increases β-site cleavage (Cordy et al., 2003).
- γ-secretase partitions between caveolar and non-caveolar membrane, and caveolin-1 controls the partition (Kapoor et al., 2010).
- Amyloid oligomers enter the neuron by a caveolin-1-dependent route, in complex with cellular prion protein (da Silva Correia et al., 2024).
- Mutant TDP-43 mislocalises to rafts, and raft-associated glutamate receptor subunits fall as it does (Wang et al., 2026).
- Neurotrophin receptors require raft localisation to signal, and lose it with age (Head et al., 2010; Egawa et al., 2016).
- Raft formation depends on astrocyte-supplied cholesterol, and its failure has been proposed as the primary lesion of sporadic Alzheimer's disease (Rappoport, 2025).

Six independent lines, four laboratories, three diseases, one compartment. The membrane raft is where the precursor protein is cut, where the product re-enters, where a second proteinopathy deposits, where trophic signal is received, and where age takes its earliest measurable structural toll on a neuron.

If that is right, then the theory worth extracting from this work is larger than caveolin-1 and larger than any therapy built on it: **the neuronal membrane microdomain is a shared failure surface on which mechanistically unrelated neurodegenerative processes converge, and it is the surface on which a neuron's capacity to defend itself is either present or absent.** Caveolin-1 is one handle on that surface. It is unlikely to be the only one.

12.4 What the programme should say about itself

Three adjustments would strengthen how this work is presented, at no cost to what it claims.

Lead with the dissociation, not the gene. The result that matters is function preserved against unchanged pathology, reproduced in five models. That is a statement about the disease, not about a vector, and it is what makes the work interesting to people who will never care about caveolin-1.

Stop asserting the human premise. The claim that neuronal caveolin-1 falls in the Alzheimer brain is contested by the only direct human measurements, and the therapy does not need it. A gain-of-function that confers resilience is a complete and defensible argument. Presenting a contested premise as settled invites a reviewer to reject the whole for the part.

Name the specificity problem before someone else does. The cross-disease generality is currently presented as unambiguous strength. It is a strength *and* an unresolved question, and the programme has the tools to resolve it. Section 11's second experiment would do it in one study.

13. Conclusions

Brian Head's work makes a claim about neurons that is easy to state and hard to test: that a nerve cell's ability to be sustained depends less on what is available to it than on whether it is organised to receive it. The receptors for the trophic and synaptic signals that maintain a neuron do not work unless they are held together in a particular kind of membrane, and that membrane degrades with age and with disease. On this account the failing neuron is not starved. It is deaf.

The therapy that follows — a small scaffolding protein delivered to neurons under a neuron-specific promoter — has produced, across sixteen years and five disease models, one result of real substance: memory, dendritic architecture, synapse number, spine geometry, myelin and mitochondrial integrity preserved while the pathology proceeds untouched. That dissociation has now been reproduced under presymptomatic and early-symptomatic dosing, in a physiologically expressing knock-in as well as an over-expressing transgenic, in a motor neuron disease and in a TDP-43 proteinopathy, and by three delivery routes.

What that result is evidence *for* is the open question, and it admits two answers that the published work does not distinguish: a genuine convergence node at the membrane, engaged by the therapy; or a general elevation of synaptic and myelin substrate that leaves less for any disease to consume. The best evidence for the first is that mutant TDP-43 mislocalises to the very compartment the therapy restores — a finding one year old, from one experiment, in one sex of one mouse line, and the most important thing in the programme to replicate.

The theory's weakest link is not its animal data but its human premise. Whether neuronal caveolin-1 actually falls in the Alzheimer brain is contested by the only direct measurements available, and the disagreement is almost certainly a matter of which cells were measured — a question that existing public datasets could settle. The programme does not need the premise; a gain of function that confers resilience is a complete argument. But it asserts it, and asserting a contested claim is a liability the work does not have to carry.

The largest untested question is more specific and more interesting. Caveolin-1 is the route by which amyloid oligomers enter a neuron. No experiment in this programme has measured the intraneuronal amyloid pool in a treated animal. A SynCav1 neuron may be functioning well while carrying *more* internal amyloid than an untreated one — which would make the resilience claim stronger than its authors have made it — or it may be handling amyloid better, which would qualify the amyloid-independence that is the programme's signature. One experiment separates these.

And the largest practical obstacle is not efficacy. It is that a therapy defined by leaving the pathology alone has, by construction, no target-engagement biomarker: nothing to dose against, nothing to read at three months, nothing to stop for. The programme is quietly assembling candidates — a transcriptomic signature, a raft-localised receptor–effector pair, and a myelin measurement that already runs on a clinical scanner. Of these the imaging is the nearest and the least developed, and developing it would do more for this therapy's prospects than efficacy in a sixth model.

What stands, and stands well, is this. The field has spent thirty years asking how to stop the pathology, and has recently learned — from the first drugs that genuinely remove it — that stopping the pathology slows the disease and does not arrest it. The complementary question is what makes a brain tolerate what it cannot remove. That question has three good human answers, all of them observational: the fifth to a third of older people who carry the pathology without the dementia, and two individuals in one Colombian family who carried it with a protective variant. Head's programme is the most developed attempt to produce that state deliberately, in an animal, by an intervention that fits in a vector.

Whether it becomes a medicine is uncertain and depends on questions of delivery, dose and measurement that remain unsolved. Whether it has already changed what should be regarded as a therapeutic endpoint in this disease is not uncertain at all. A treatment that leaves every plaque in place and returns an animal to the performance of its healthy littermates is a demonstration that the plaque was never the thing that had to be moved.

References

All references were verified against the PubMed record. PMIDs are given for traceability.

Andreone BJ, Chow BW, Tata A, Lacoste B, Ben-Zvi A, Bullock K, Deik AA, Ginty DD, Clish CB, Gu C. Blood-brain barrier permeability is regulated by lipid transport-dependent suppression of caveolae-mediated transcytosis. *Neuron*. 2017;94(3):581–594.e5. PMID 28416077.

Androuin A, Potier B, Nägerl UV, Cattaert D, Danglot L, Thierry M, Youssef I, Triller A, Duyckaerts C, El Hachimi KH, Dutar P, Delatour B, Marty S. Evidence for altered dendritic spine compartmentalization in Alzheimer's disease and functional effects in a mouse model. *Acta Neuropathologica*. 2018;135(6):839–854. PMID 29696365.

Arboleda-Velasquez JF, Lopera F, O'Hare M, Delgado-Tirado S, Marino C, Chmielewska N, Saez-Torres KL, Amarnani D, Schultz AP, Sperling RA, Leyton-Cifuentes D, Chen K, Baena A, Aguillon D, Rios-Romenets S, Giraldo M, Guzmán-Vélez E, Norton DJ, Pardilla-Delgado E, Artola A, Sanchez JS, Acosta-Uribe J, Lalli M, Kosik KS, Huentelman MJ, Zetterberg H, Blennow K, Reiman RA, Luo J, Chen Y, Thiyyagura P, Su Y, Jun GR, Naymik M, Gai X, Bootwalla M, Ji J, Shen L, Miller JB, Kim LA, Tariot PN, Johnson KA, Reiman EM, Quiroz YT. Resistance to autosomal dominant Alzheimer's disease in an APOE3 Christchurch homozygote: a case report. *Nature Medicine*. 2019;25(11):1680–1683. PMID 31686034.

Avchalumov Y, Kreisler AD, Trenet W, Nayak M, Head BP, Piña-Crespo JC, Mandyam CD. Caveolin-1 expression in the dorsal striatum drives methamphetamine addiction-like behavior. *International Journal of Molecular Sciences*. 2021;22(15):8219. PMID 34360984.

Bonds JA, Shetti A, Bheri A, Chen Z, Disouky A, Tai L, Mao M, Head BP, Bonini MG, Haus JM, Minshall RD, Lazarov O. Depletion of caveolin-1 in type 2 diabetes model induces Alzheimer's disease pathology precursors. *Journal of Neuroscience*. 2019;39(43):8576–8583. PMID 31527120.

Boxer AL, Lang AE, Grossman M, Knopman DS, Miller BL, Schneider LS, Doody RS, Lees A, Golbe LI, Williams DR, Corvol JC, Ludolph A, Burn D, Lorenzl S, Litvan I, Roberson ED, Höglinger GU, Koestler M, Jack CR Jr, Van Deerlin V, Randolph C, Lobach IV, Heuer HW, Gozes I, Parker L, Whitaker S, Hirman J, Stewart AJ, Gold M, Morimoto BH; AL-108-231 Investigators. Davunetide in patients with progressive supranuclear palsy: a randomised, double-blind, placebo-controlled phase 2/3 trial. *Lancet Neurology*. 2014;13(7):676–685. PMID 24873720.

Castle MJ, Baltanás FC, Kovacs I, Nagahara AH, Barba D, Tuszynski MH. Postmortem analysis in a clinical trial of AAV2-NGF gene therapy for Alzheimer's disease identifies a need for improved vector delivery. *Human Gene Therapy*. 2020;31(7–8):415–422. PMID 32126838.

Chan KY, Jang MJ, Yoo BB, Greenbaum A, Ravi N, Wu WL, Sánchez-Guardado L, Lois C, Mazmanian SK, Deverman BE, Gradinaru V. Engineered AAVs for efficient noninvasive gene delivery to the central and peripheral nervous systems. *Nature Neuroscience*. 2017;20(8):1172–1179. PMID 28671695.

Cordy JM, Hussain I, Dingwall C, Hooper NM, Turner AJ. Exclusively targeting beta-secretase to lipid rafts by GPI-anchor addition up-regulates beta-site processing of the amyloid precursor protein. *Proceedings of the National Academy of Sciences USA*. 2003;100(20):11735–11740. PMID 14504402.

da Silva Correia A, Schmitz M, Fischer AL, da Silva Correia S, Simonetti FL, Saher G, Goya-Maldonado R, Arora AS, Fischer A, Outeiro TF, Zerr I. Cellular prion protein acts as mediator of amyloid beta uptake by caveolin-1 causing cellular dysfunctions in vitro and in vivo. *Alzheimer's & Dementia*. 2024;20(10):6776–6792. PMID 39212313.

DeKosky ST, Scheff SW. Synapse loss in frontal cortex biopsies in Alzheimer's disease: correlation with cognitive severity. *Annals of Neurology*. 1990;27(5):457–464. PMID 2360787.

Deverman BE, Pravdo PL, Simpson BP, Kumar SR, Chan KY, Banerjee A, Wu WL, Yang B, Huber N, Pasca SP, Gradinaru V. Cre-dependent selection yields AAV variants for widespread gene transfer to the adult brain. *Nature Biotechnology*. 2016;34(2):204–209. PMID 26829320.

Dubois B, Hampel H, Feldman HH, Scheltens P, Aisen P, Andrieu S, Bakardjian H, Benali H, Bertram L, Blennow K, Broich K, Cavedo E, Crutch S, Dartigues JF, Duyckaerts C, Epelbaum S, Frisoni GB, Gauthier S, Genthon R, Gouw AA, Habert MO, Holtzman DM, Kivipelto M, Lista S, Molinuevo JL, O'Bryant SE, Rabinovici GD, Rowe C, Salloway S, Schneider LS, Sperling R, Teichmann M, Carrillo MC, Cummings J, Jack CR Jr; Proceedings of the Meeting of the International Working Group and the American Alzheimer's Association on "The Preclinical State of AD". Preclinical Alzheimer's disease: definition, natural history, and diagnostic criteria. *Alzheimer's & Dementia*. 2016;12(3):292–323. PMID 27012484.

Egawa J, Pearn ML, Lemkuil BP, Patel PM, Head BP. Membrane lipid rafts and neurobiology: age-related changes in membrane lipids and loss of neuronal function. *Journal of Physiology*. 2016;594(16):4565–4579. PMID 26332795.

Egawa J, Schilling JM, Cui W, Posadas E, Sawada A, Alas B, Zemljic-Harpf AE, Fannon-Pavlich MJ, Mandyam CD, Roth DM, Patel HH, Patel PM, Head BP. Neuron-specific caveolin-1 overexpression improves motor function and preserves memory in mice subjected to brain trauma. *FASEB Journal*. 2017;31(8):3403–3411. PMID 28450301.

Egawa J, Zemljic-Harpf A, Mandyam CD, Niesman IR, Lysenko LV, Kleschevnikov AM, Roth DM, Patel HH, Patel PM, Head BP. Neuron-targeted caveolin-1 promotes ultrastructural and functional hippocampal synaptic plasticity. *Cerebral Cortex*. 2018;28(9):3255–3266. PMID 28981594.

Ehehalt R, Keller P, Haass C, Thiele C, Simons K. Amyloidogenic processing of the Alzheimer beta-amyloid precursor protein depends on lipid rafts. *Journal of Cell Biology*. 2003;160(1):113–123. PMID 12515826.

Fridolfsson HN, Kawaraguchi Y, Ali SS, Panneerselvam M, Niesman IR, Finley JC, Kellerhals SE, Migita MY, Okada H, Moreno AL, Jennings M, Kidd MW, Bonds JA, Balijepalli RC, Ross RS, Patel PM, Miyanohara A, Chen Q, Lesnefsky EJ, Head BP, Roth DM, Insel PA, Patel HH. Mitochondria-localized caveolin in adaptation to cellular stress and injury. *FASEB Journal*. 2012;26(11):4637–4649. PMID 22859372.

Gaudreault SB, Dea D, Poirier J. Increased caveolin-1 expression in Alzheimer's disease brain. *Neurobiology of Aging*. 2004;25(6):753–759. PMID 15165700.

Gioiosa L, Raggi C, Ricceri L, Jasmin JF, Frank PG, Capozza F, Lisanti MP, Alleva E, Sargiacomo M, Laviola G. Altered emotionality, spatial memory and cholinergic function in caveolin-1 knock-out mice. *Behavioural Brain Research*. 2008;188(2):255–262. PMID 18083242.

Head BP, Insel PA. Do caveolins regulate cells by actions outside of caveolae? *Trends in Cell Biology*. 2007;17(2):51–57. PMID 17150359.

Head BP, Patel HH, Tsutsumi YM, Hu Y, Mejia T, Mora RC, Insel PA, Roth DM, Drummond JC, Patel PM. Caveolin-1 expression is essential for N-methyl-D-aspartate receptor-mediated Src and extracellular signal-regulated kinase 1/2 activation and protection of primary neurons from ischemic cell death. *FASEB*

Journal. 2008;22(3):828–840. PMID 17905724.

Head BP, Peart JN, Panneerselvam M, Yokoyama T, Pearn ML, Niesman IR, Bonds JA, Schilling JM, Miyanohara A, Headrick J, Ali SS, Roth DM, Patel PM, Patel HH. Loss of caveolin-1 accelerates neurodegeneration and aging. *PLoS One*. 2010;5(12):e15697. PMID 21203469.

Head BP, Hu Y, Finley JC, Saldana MD, Bonds JA, Miyanohara A, Niesman IR, Ali SS, Murray F, Insel PA, Roth DM, Patel HH, Patel PM. Neuron-targeted caveolin-1 protein enhances signaling and promotes arborization of primary neurons. *Journal of Biological Chemistry*. 2011;286(38):33310–33321. PMID 21799010.

Hordeaux J, Wang Q, Katz N, Buza EL, Bell P, Wilson JM. The neurotropic properties of AAV-PHP.B are limited to C57BL/6J mice. *Molecular Therapy*. 2018;26(3):664–668. PMID 29428298.

Horikawa YT, Panneerselvam M, Kawaraguchi Y, Tsutsumi YM, Ali SS, Balijepalli RC, Murray F, Head BP, Niesman IR, Rieg T, Vallon V, Insel PA, Patel HH, Roth DM. Cardiac-specific overexpression of caveolin-3 attenuates cardiac hypertrophy and increases natriuretic peptide expression and signaling. *Journal of the American College of Cardiology*. 2011;57(22):2273–2283. PMID 21616289.

Huang Q, Chan KY, Tobey IG, Chan YA, Poterba T, Boutros CL, Balazs AB, Daneman R, Bloom JM, Seed C, Deverman BE. Delivering genes across the blood-brain barrier: LY6A, a novel cellular receptor for AAV-PHP.B capsids. *PLoS One*. 2019;14(11):e0225206. PMID 31725765.

Jati S, Taheri S, Kal S, Sinha SC, Head BP, Mahata SK, Sahoo D. AI guided discovery of a murine model of asymptomatic Alzheimer's disease. *Acta Neuropathologica Communications*. 2026;14(1):110. PMID 41935326.

Kang MJ, Chung YH, Hwang CI, Murata M, Fujimoto T, Mook-Jung IH, Cha CI, Park WY. Caveolin-1 upregulation in senescent neurons alters amyloid precursor protein processing. *Experimental & Molecular Medicine*. 2006;38(2):126–133. PMID 16672766.

Kapoor A, Hsu WM, Wang BJ, Wu GH, Lin TY, Lee SJ, Yen CT, Liang SM, Liao YF. Caveolin-1 regulates γ-secretase-mediated AβPP processing by modulating spatial distribution of γ-secretase in membrane. *Journal of Alzheimer's Disease*. 2010;22(2):423–442. PMID 20847442.

Karataeva AR, Klaassen RV, Ströder J, Ruiperez-Alonso M, Hjorth JJ, van Nierop P, Spijker S, Mansvelder HD, Smit AB. C-terminal interactors of the AMPA receptor auxiliary subunit Shisa9. *PLoS One*. 2014;9(2):e87360. PMID 24498314.

Kassan A, Egawa J, Zhang Z, Almenar-Queralt A, Nguyen QM, Lajevardi Y, Kim K, Posadas E, Jeste DV, Roth DM, Patel PM, Patel HH, Head BP. Caveolin-1 regulation of disrupted-in-schizophrenia-1 as a potential therapeutic target for schizophrenia. *Journal of Neurophysiology*. 2017;117(1):436–444. PMID 27832597.

Lopera F, Marino C, Chandrahas AS, O'Hare M, Villalba-Moreno ND, Aguillon D, Baena A, Sanchez JS, Vila-Castelar C, Ramirez Gomez L, Chmielewska N, Oliveira GM, Littau JL, Hartmann K, Park K, Krasemann S, Glatzel M, Schoemaker D, Gonzalez-Buendia L, Delgado-Tirado S, Arevalo-Alquichire S, Saez-Torres KL, Amarnani D, Kim LA, Mazzarino RC, Gonzalez H, Ortiz-Cardona J, Aguirre-Acevedo DC, Pantoja AF, Yepes Y, Bocanegra Y, Cardenas-Aguayo MDC, Aristizabal-Rojas H, Estrada-Lopez K, Ruiz-Duque L, Sepulveda-Falla D, Quiroz YT, Arboleda-Velasquez JF. Resilience to autosomal dominant Alzheimer's disease in a Reelin-COLBOS heterozygous man. *Nature Medicine*. 2023;29(5):1243–1252. PMID 37188781.

Lu M, Kim MJ, Collins EC, Shcherbinin S, Ellinwood AK, Yokoi Y, Brooks DA, Hansson O, Knopman DS, Sims JR, Mintun MA. Posttreatment amyloid levels and clinical outcomes following donanemab for early symptomatic Alzheimer disease: a secondary analysis of the TRAILBLAZER-ALZ 2 randomized clinical trial. *JAMA Neurology*. 2025;82(12):1251–1256. PMID 41082199.

Mandyam CD, Schilling JM, Cui W, Egawa J, Niesman IR, Kellerhals SE, Staples MC, Busija AR, Risbrough VB, Posadas E, Grogman GC, Chang JW, Roth DM, Patel PM, Patel HH, Head BP. Neuron-targeted caveolin-1 improves molecular signaling, plasticity, and behavior dependent on the hippocampus in adult and aged mice. *Biological Psychiatry*. 2017;81(2):101–110. PMID 26592463.

Mufson EJ, He B, Ginsberg SD, Carper BA, Bieler GS, Crawford F, Alvarez VE, Huber BR, Stein TD, McKee AC, Perez SE. Gene profiling of nucleus basalis tau containing neurons in chronic traumatic encephalopathy: a Chronic Effects of Neurotrauma Consortium study. *Journal of Neurotrauma*. 2018;35(11):1260–1271. PMID 29338612.

Nelson PT, Dickson DW, Trojanowski JQ, Jack CR, Boyle PA, Arfanakis K, Rademakers R, Alafuzoff I, Attems J, Brayne C, Coyle-Gilchrist ITS, Chui HC, Fardo DW, Flanagan ME, Halliday G, Hokkanen SRK, Hunter S, Jicha GA, Katsumata Y, Kawas CH, Keene CD, Kovacs GG, Kukull WA, Levey AI, Makkinejad N, Montine TJ, Murayama S, Murray ME, Nag S, Rissman RA, Seeley WW, Sperling RA, White CL 3rd, Yu L, Schneider JA. Limbic-predominant age-related TDP-43 encephalopathy (LATE): consensus working group report. *Brain*. 2019;142(6):1503–1527. PMID 31039256.

Niesman IR, Zemke N, Fridolfsson HN, Haushalter KJ, Levy K, Grove A, Schnoor R, Finley JC, Patel PM, Roth DM, Head BP, Patel HH. Caveolin isoform switching as a molecular, structural, and metabolic regulator of microglia. *Molecular and Cellular Neuroscience*. 2013;56:283–297. PMID 23851187.

Niesman IR, Schilling JM, Shapiro LA, Kellerhals SE, Bonds JA, Kleschevnikov AM, Cui W, Voong A, Krajewski S, Ali SS, Roth DM, Patel HH, Patel PM, Head BP. Traumatic brain injury enhances neuroinflammation and lesion volume in caveolin deficient mice. *Journal of Neuroinflammation*. 2014;11:39. PMID 24593993.

Pinhasov A, Mandel S, Torchinsky A, Giladi E, Pittel Z, Goldsweig AM, Servoss SJ, Brenneman DE, Gozes I. Activity-dependent neuroprotective protein: a novel gene essential for brain formation. *Brain Research. Developmental Brain Research*. 2003;144(1):83–90. PMID 12888219.

Rafii MS, Tuszynski MH, Thomas RG, Barba D, Brewer JB, Rissman RA, Siffert J, Aisen PS; AAV2-NGF Study Team. Adeno-associated viral vector (serotype 2)-nerve growth factor for patients with Alzheimer disease: a randomized clinical trial. *JAMA Neurology*. 2018;75(7):834–841. PMID 29582053.

Rappoport A. A lipid-raft theory of Alzheimer's disease. *Annual Review of Biochemistry*. 2025;94:387–416. PMID 39476407.

Saito T, Matsuba Y, Mihira N, Takano J, Nilsson P, Itohara S, Iwata N, Saido TC. Single App knock-in mouse models of Alzheimer's disease. *Nature Neuroscience*. 2014;17(5):661–663. PMID 24728269.

Sawada A, Wang S, Jian M, Leem J, Wackerbarth J, Egawa J, Schilling JM, Platoshyn O, Zemljic-Harpf A, Roth DM, Patel HH, Patel PM, Marsala M, Head BP. Neuron-targeted caveolin-1 improves neuromuscular function and extends survival in $SOD1^{G93A}$ mice. *FASEB Journal*. 2019;33(6):7545–7554. PMID 30894019.

Scheff SW, Price DA, Schmitt FA, DeKosky ST, Mufson EJ. Synaptic alterations in CA1 in mild Alzheimer disease and mild cognitive impairment. *Neurology*. 2007;68(18):1501–1508. PMID 17470753.

Schilling JM, Head BP, Patel HH. Caveolins as regulators of stress adaptation. *Molecular Pharmacology*. 2018;93(4):277–285. PMID 29358220.

Selkoe DJ, Hardy J. The amyloid hypothesis of Alzheimer's disease at 25 years. *EMBO Molecular Medicine*. 2016;8(6):595–608. PMID 27025652.

Sims JR, Zimmer JA, Evans CD, Lu M, Ardayfio P, Sparks J, Wessels AM, Shcherbinin S, Wang H, Monkul Nery ES, Collins EC, Solomon P, Salloway S, Apostolova LG, Hansson O, Ritchie C, Brooks DA, Mintun M, Skovronsky DM; TRAILBLAZER-ALZ 2 Investigators. Donanemab in early symptomatic Alzheimer disease:

the TRAILBLAZER-ALZ 2 randomized clinical trial. *JAMA*. 2023;330(6):512–527. PMID 37459141.

Sobajima T, Yoshimura SI, Maeda T, Miyata H, Miyoshi E, Harada A. The Rab11-binding protein RELCH/KIAA1468 controls intracellular cholesterol distribution. *Journal of Cell Biology*. 2018;217(5):1777–1796. PMID 29514919.

Terry RD, Masliah E, Salmon DP, Butters N, DeTeresa R, Hill R, Hansen LA, Katzman R. Physical basis of cognitive alterations in Alzheimer's disease: synapse loss is the major correlate of cognitive impairment. *Annals of Neurology*. 1991;30(4):572–580. PMID 1789684.

Tiernan CT, Ginsberg SD, He B, Ward SM, Guillozet-Bongaarts AL, Kanaan NM, Mufson EJ, Counts SE. Pretangle pathology within cholinergic nucleus basalis neurons coincides with neurotrophic and neurotransmitter receptor gene dysregulation during the progression of Alzheimer's disease. *Neurobiology of Disease*. 2018;117:125–136. PMID 29859871.

Tuszynski MH, Thal L, Pay M, Salmon DP, U HS, Bakay R, Patel P, Blesch A, Vahlsing HL, Ho G, Tong G, Potkin SG, Fallon J, Hansen L, Mufson EJ, Kordower JH, Gall C, Conner J. A phase 1 clinical trial of nerve growth factor gene therapy for Alzheimer disease. *Nature Medicine*. 2005;11(5):551–555. PMID 15852017.

Tuszynski MH, Yang JH, Barba D, U HS, Bakay RA, Pay MM, Masliah E, Conner JM, Kobalka P, Roy S, Nagahara AH. Nerve growth factor gene therapy: activation of neuronal responses in Alzheimer disease. *JAMA Neurology*. 2015;72(10):1139–1147. PMID 26302439.

van Dyck CH, Swanson CJ, Aisen P, Bateman RJ, Chen C, Gee M, Kanekiyo M, Li D, Reyderman L, Cohen S, Froelich L, Katayama S, Sabbagh M, Vellas B, Watson D, Dhadda S, Irizarry M, Kramer LD, Iwatsubo T. Lecanemab in early Alzheimer's disease. *New England Journal of Medicine*. 2023;388(1):9–21. PMID 36449413.

Vetrivel KS, Thinakaran G. Membrane rafts in Alzheimer's disease beta-amyloid production. *Biochimica et Biophysica Acta*. 2010;1801(8):860–867. PMID 20303415.

von Engelhardt J, Mack V, Sprengel R, Kavenstock N, Li KW, Stern-Bach Y, Smit AB, Seeburg PH, Monyer H. CKAMP44: a brain-specific protein attenuating short-term synaptic plasticity in the dentate gyrus. *Science*. 2010;327(5972):1518–1522. PMID 20185686.

Vulih-Shultzman I, Pinhasov A, Mandel S, Grigoriadis N, Touloumi O, Pittel Z, Gozes I. Activity-dependent neuroprotective protein snippet NAP reduces tau hyperphosphorylation and enhances learning in a novel transgenic mouse model. *Journal of Pharmacology and Experimental Therapeutics*. 2007;323(2):438–449. PMID 17720885.

Wang D, Li X, Li W, Duong T, Wang H, Kleschevnikova N, Patel HH, Breen E, Powell S, Wang S, Head BP. Nicotine inhalant via E-cigarette facilitates sensorimotor function recovery by upregulating neuronal BDNF-TrkB signalling in traumatic brain injury. *British Journal of Pharmacology*. 2024;181(17):3082–3097. PMID 38698493.

Wang D, Chernov AV, Lam R, Wang H, Li W, Li X, Duong T, Wang S, Head BP. Neuron-targeted caveolin-1 overexpression attenuates cognitive loss and pathological transcriptome changes in symptomatic Alzheimer's disease models. *Signal Transduction and Targeted Therapy*. 2025;10(1):172. PMID 40425572.

Wang D, Ta V, Wang H, Ju J, Wang C, Chehadeh C, Torreblanca-Zanca A, Magaña Y, Castle MJ, Wang S, Head BP. Systemic delivery of synapsin-promoted caveolin-1 overexpression ameliorates pathological TDP-43-induced cognitive decline and neurodegenerative changes. *Alzheimer's & Dementia*. 2026;22(1):e71450. PMID 42187024.

Wang J, Athertya JS, Cheng X, Patel A, Chan NR, Liu B, Tang Q, Chang EY, Wang S, Ma Y, Head BP, Tang G, Du J. Ultrashort echo time magnetization transfer imaging of myelin in APP knock-in mice. *NeuroImage*.

2026;337:122040. PMID 42252040.

Wang S, Zhang Z, Almenar-Queralt A, Leem J, DerMardirossian C, Roth DM, Patel PM, Patel HH, Head BP. Caveolin-1 phosphorylation is essential for axonal growth of human neurons derived from iPSCs. *Frontiers in Cellular Neuroscience*. 2019;13:324. PMID 31379509.

Wang S, Leem JS, Podvin S, Hook V, Kleschevnikov N, Savchenko P, Dhanani M, Zhou K, Kelly IC, Zhang T, Miyanohara A, Nguyen P, Kleschevnikov A, Wagner SL, Trojanowski JQ, Roth DM, Patel HH, Patel PM, Head BP. Synapsin-caveolin-1 gene therapy preserves neuronal and synaptic morphology and prevents neurodegeneration in a mouse model of AD. *Molecular Therapy Methods & Clinical Development*. 2021a;21:434–450. PMID 33981778.

Wang S, Ichinomiya T, Terada Y, Wang D, Patel HH, Head BP. Synapsin-promoted caveolin-1 overexpression maintains mitochondrial morphology and function in PSAPP Alzheimer's disease mice. *Cells*. 2021b;10(9):2487. PMID 34572135.

Wang S, Ichinomiya T, Savchenko P, Wang D, Sawada A, Li X, Duong T, Li W, Bonds JA, Kim EJ, Miyanohara A, Roth DM, Patel PM, Patel HH, Tadokoro T, Marsala M, Head BP. Subpial delivery of adeno-associated virus 9-synapsin-caveolin-1 (AAV9-SynCav1) preserves motor neuron and neuromuscular junction morphology, motor function, delays disease onset, and extends survival in $hSOD1^{G93A}$ mice. *Theranostics*. 2022a;12(12):5389–5403. PMID 35910808.

Wang S, Ichinomiya T, Savchenko P, Devulapalli S, Wang D, Beltz G, Saito T, Saido TC, Wagner SL, Patel HH, Head BP. Age-dependent behavioral and metabolic assessment of $App^{NL\text{-}G\text{-}F/NL\text{-}G\text{-}F}$ knock-in (KI) mice. *Frontiers in Molecular Neuroscience*. 2022b;15:909989. PMID 35966019.

Appendix: The 2020 Submission in Summary

For readers who wish to compare the account above with the primary submission, the essentials are set out here without commentary.

Title. *Synapsin-promoted caveolin-1 gene therapy preserves hippocampal function in a mouse model of Alzheimer's Disease: Implications for human intervention.*

Design. APPswe/PS1ΔE9 mice and wild-type controls received bilateral hippocampal AAV9 at 3 months of age — SynCav1 in the treatment group, SynRFP in both control groups — delivered stereotactically at three sites per hemisphere, 1.5 µL at 10^9 genome copies per µL, at 0.5 µL per minute. Three groups: WT-SynRFP, AD-SynRFP, AD-SynCav1. Behaviour at 9 and 11 months, followed by tissue analysis. Behavioural cohorts of 15–20 per group by prior power calculation; 3–5 per group for biochemistry, immunofluorescence, Golgi-Cox and electron microscopy. Randomised and double-blinded.

Behavioural findings. At 9 months, treated animals acquired fear learning normally where untreated animals did not; no group difference in contextual or cued recall. At 11 months, untreated animals were impaired in contextual recall while treated animals were indistinguishable from wild-type. Open-field testing showed no differences in locomotion or anxiety-like behaviour at either age.

Biochemical findings. Caveolin-1, full-length TrkB and LRP1 were reduced in untreated hippocampus, in whole homogenate and in buoyant raft fractions, and preserved with treatment. Raft-associated synaptobrevin was unchanged across groups. Phospho-TrkB (Y814) and phospho-Src (Y416) were highest in treated raft fractions but did not reach significance.

Proteomics. 2,417 quantifiable proteins in raft fractions. Disease versus wild-type: 65 up, 52 down; Shisa9 most strongly down (log2 = −5.9). Treatment versus disease: 80 up, 88 down; caveolin-1 most up (log2 = 7.8), Shisa9 second (log2 = 5.9). Caveolin-1 immunoprecipitation recovered Shisa9, most abundantly in treated animals. Ap2b1, cofilin-2, CCT-5, FXYD, KIAA1468, MAN2C1, NDRG4, synaptojanin 2 and Prdx6 were down in disease and up with treatment.

Structural findings. Increased total type I excitatory synapses and presynaptic vesicles per bouton in CA1 stratum radiatum at 9 and 11 months; preserved spine neck diameter, greater spine length and total spine area; reduced G-ratio with thicker myelin sheaths in CA3 Schaffer collaterals at both ages; preserved infrapyramidal mossy fibre area at 11 months with no change in the suprapyramidal bundle; preserved CA1 apical dendritic arborisation from 60 to 270 µm from the soma, greater soma-to-tip distance and more spines.

Unchanged. Amyloid plaque burden. Astrogliosis.

Stated limitation. The APPswe/PS1ΔE9 model over-expresses mutant precursor protein, "which contains intrinsic problems and may induce artificial symptoms"; the authors name the $App^{NL\text{-}F/NL\text{-}F}$ knock-in as the appropriate next model.

Stated open question. Whether SynCav1 combined with amyloid-lowering drugs or biologics would improve higher brain function further — "a hypothesis that will require further studies."

The work was published in expanded form the following year as Wang et al. (2021a).