


The Jammed Pump

Load, capacity, and the boundary of convergent clearance failure — what staged human Huntington brain shows, and the narrower claim that survives it



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Every proteinopathy loads the clearance system. Only some of them degrade its capacity. In Alzheimer's disease the accumulating fragment binds the proton pump that is supposed to digest it; in Huntington's disease, in staged human brain, the pump still works and the clock that sets the disease runs in the nucleus.

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Abstract

A widely held account of neurodegeneration holds that the autophagy–lysosomal pathway is the common bottleneck through which diverse upstream insults discharge, so that Alzheimer’s disease, Parkinson’s disease, the ALS–frontotemporal spectrum and Huntington’s disease are variations on a single terminal failure of intracellular clearance. The account is attractive because it is nearly always partly true: a network that handles every internalised molecule, every condemned protein and every damaged organelle will be found abnormal in any disease of cargo, energy, calcium or trophic support, and in normal ageing as well. That ubiquity is the account’s principal evidential weakness, not its strength.

This paper tests the convergence claim at its most exposed point. A recent staged neuropathological study of human Huntington’s disease brain examined autophagy–lysosomal markers in striatum and in the less affected cortex and cerebellum across Vonsattel grades HD2 to HD4, and reported the opposite of what the convergence claim predicts. Lysosomal biogenesis was upregulated; proteolysis was preserved; cargo-loaded autophagosomes and cathepsin-positive autolysosomes were readily observed, implying no significant blockage at autophagosome formation or at autophagosome–lysosome fusion. Substrate clearance failed — but late, at advanced grades, and predominantly in striatum rather than cortex. In Huntington’s disease the clearance machinery is competent while the disease is establishing itself and fails after the disease is under way. That is the reverse of the sequence documented in Alzheimer’s disease, where compartment pathology is the earliest known intraneuronal change, decades ahead of deposition.

I argue that the convergence claim should be narrowed rather than defended, and that the narrowed version is both stronger and more useful. The property that distinguishes Alzheimer’s disease and the tauopathies is not that they load the clearance system — every proteinopathy does that — but that in them the substrate inhibits the machinery that is supposed to degrade it. The β -C-terminal fragment of the amyloid precursor protein binds the V0a1 subunit of the vacuolar H⁺-ATPase and lowers its activity; presenilin 1 is required to deliver that same subunit to the lysosome. The disease therefore closes a loop: undegraded substrate de-acidifies the compartment, the de-acidified compartment degrades less, and more substrate accumulates. Huntington’s disease has no such loop. Its rate-limiting step is a DNA process — somatic expansion of the CAG repeat in striatal projection neurons from an inherited 40–45 to 150 and beyond — and wild-type huntingtin is a scaffold *for* selective autophagy rather than an inhibitor of it, so the mutation subtracts adaptor function instead of jamming the pump.

I therefore propose a four-category taxonomy of clearance involvement — primary lysosomal disease, feedback bottleneck, load without feedback, and bystander disturbance — and place Alzheimer’s disease and the tauopathies in the second, Huntington’s disease in the third, and the progranulin- and glucocerebrosidase-linked disorders in the first. The narrowed claim states that

a self-amplifying substrate–machinery feedback at the terminal, acidification-dependent step of the pathway is a *necessary* feature of the diseases for which clearance failure is causal and early, and that Huntington’s disease lacks it. Twenty-two graded evidence statements, eight predictions and five explicit refutation conditions are supplied. The most important therapeutic consequence is an inversion: in Alzheimer’s disease the machinery must be repaired before flux is induced, because induction into a de-acidified compartment adds undigested cargo; in Huntington’s disease induction is worth attempting early, while the machinery still works, and is likely futile late.

1. Introduction

1.1 A claim that has become difficult to disbelieve

Over the last two decades the endosomal–lysosomal–autophagy network has moved from the periphery of neurodegeneration research to something close to its centre. The reasons are good ones. Neurons are post-mitotic and cannot dilute damaged constituents by division; they are extraordinarily polarised, so that most cargo is generated far from the soma where lysosomal biogenesis is concentrated; and mutations in genes regulating autophagy and lysosomal function cause neurodegenerative disease across the entire age spectrum with a frequency that is out of proportion to the size of that gene set [1,2]. The pathway’s terminal step — acidification-dependent proteolysis — is an active, continuous, ATP-consuming process that ages badly and that many different upstream insults can degrade.

From these premises a strong synthetic claim has been assembled and is now widely repeated in one form or another: that Alzheimer’s disease, Parkinson’s disease, the amyotrophic lateral sclerosis–frontotemporal dementia spectrum and Huntington’s disease are, at bottom, one disease of clearance. On this account the proteins that name the diseases — amyloid- β and tau, α -synuclein, TDP-43 and SOD1, mutant huntingtin — are the visible detritus of a shared underlying failure, and the differences between the diseases reduce to which upstream step is broken and which population of neurons is asked to bear the load.

The claim has real explanatory reach. It accounts for the fact that mixed proteinopathy is the rule rather than the exception in aged brains; it explains why age is the dominant risk factor for conditions with unrelated primary genetics; and it supplies a therapeutic programme — restore clearance capacity — that is indifferent to which protein happens to be accumulating. It also has a serious evidential problem, which is that the network in question touches everything. Every internalised molecule, every condemned protein, every damaged organelle and every recycled receptor in a neuron transits it. Its compartments carry the principal nutrient sensor, a major intracellular calcium store, the receptors whose recycling sets synaptic strength, and the trophic signalling that certain populations depend on for survival. A system with that many functions will be found abnormal in any disease that involves cargo, energy, calcium, receptors or trophic support — which is to say in every neurodegenerative disease, and in ordinary ageing. Finding the pathway disturbed in a disease is therefore very weak evidence that the pathway’s failure *is* the disease.

1.2 The test case

Huntington's disease is the natural place to test the claim, for four reasons.

First, its cause is known and unambiguous: a single expanded CAG repeat in one gene, inherited in a fully dominant fashion, with the length of the longer expanded allele determining the rate of pathogenesis leading to motor onset [3,4]. There is no aetiological heterogeneity to hide behind.

Second, the disease has a validated neuropathological staging system — the Vonsattel grades, based on macroscopic and microscopic severity of striatal involvement and correlating closely with clinical disability [5,6]. Tissue can therefore be ordered along the disease course rather than pooled, which converts a cross-sectional autopsy series into something that can speak to sequence.

Third, mutant huntingtin is an aggregation-prone protein handled by autophagy, and the model literature has for fifteen years reported a specific autophagic lesion in Huntington's disease — a failure of autophagic vacuoles to engulf cytosolic cargo, leaving vesicles that form at normal or enhanced rates but carry little [7]. If that lesion were the primary and early event in the human disease, the convergence claim would have one of its best cases.

Fourth, and decisively, the human tissue study now exists. A staged multiplex confocal and ultrastructural analysis of autophagy-lysosomal functional markers in striatum and in the less affected cortex or cerebellum, across Vonsattel grades HD2 to HD4 and against controls, has been reported [8]. Its findings run against the convergence claim in the specific way that matters: not by showing that the pathway is normal in Huntington's disease, but by showing that it is *competent early and fails late*.

1.3 What this paper argues

I argue three things.

That the convergence claim, in its strong form, is refuted by the Huntington's data and should be narrowed rather than defended. The strong form asserts a shared upstream bottleneck whose failure initiates the diseases. In Huntington's disease the bottleneck is patent while the disease establishes itself and closes only at advanced stages, when substantial striatal neuronal loss has already occurred.

That the narrowing is principled, not ad hoc. The property that distinguishes Alzheimer's disease and the tauopathies from Huntington's disease is not the presence of an aggregating substrate, nor the eventual failure of clearance, but a specific circuit: in Alzheimer's disease the accumulating substrate is itself a direct inhibitor of the machinery that degrades it, at the terminal acidification step, so that load and capacity are not independent variables. Huntington's disease does not have this circuit, and its wild-type gene product is on the machinery's side rather

than against it.

That the narrowed claim is falsifiable and worth trying to falsify. I supply the statement of the narrowed claim, the observations that would refute it, and the experiments that would produce those observations. The narrowed claim is a smaller claim than the one it replaces, and it is a better one, because it can fail.

1.4 What this paper does not argue

It does not argue that autophagy–lysosomal biology is unimportant in Huntington’s disease; the staged human data themselves report progressive accumulation of autophagic vacuole and lipofuscin granules and of huntingtin and p62/SQSTM1 fragments in striatum at advanced grades [8]. It does not argue that clearance-directed therapy is useless in Huntington’s disease; the same data argue the opposite, and specify a window. It does not argue that Alzheimer’s disease is *only* a clearance disease, or that the clearance account is a rival to amyloid-centred thinking rather than a specification of part of it. And it does not attempt to settle Parkinson’s disease or the ALS–frontotemporal spectrum, which are discussed only far enough to show where the narrowed claim would place them and what evidence would be needed to decide.

2. The claim, stated precisely enough to be wrong

2.1 Three readings of “one mechanism”

Statements that several diseases share a mechanism are usually ambiguous between three quite different propositions, only one of which is both interesting and refutable.

Reading A — co-occurrence. The pathway is abnormal in all of these diseases. This is almost certainly true and almost entirely uninformative, for the reason given above: the pathway is abnormal in every chronic neuronal stress and in ageing itself [1]. A claim that can only fail if a disease leaves the lysosome untouched is not doing work.

Reading B — common funnel. Many distinct upstream causes converge on this pathway, whose failure then produces the greater part of the downstream phenotype. This is a substantive and probably correct claim about several diseases. It is important to see that it does *not* assert that the pathway’s failure is the origin of any of them. A funnel is where the largest number of causes become one effect. That makes it the most attractive point of therapeutic intervention, because a single agent there has the widest reach. It does not make it the beginning of the story.

Reading C — shared initiating lesion. In each of these diseases, failure of this pathway is an early and causal event, upstream of the protein pathology that names the disease, and the diseases differ chiefly in which neurons are exposed. This is the reading that licenses the slogan “one mechanism, many diseases.” It is the reading that predicts a single clearance-directed intervention should benefit all of them. It is also the only one of the three that can be refuted by staged human tissue.

The remainder of this paper concerns Reading C. Reading B survives everything said here; Reading A survives everything and asserts nothing.

2.2 What Reading C predicts in a staged autopsy series

If clearance failure is early and causal in a disease, then in tissue staged by severity one expects, at the earliest stage at which the disease is recognisable:

1. Evidence of impaired terminal degradation — accumulation of undegraded substrate inside degradative compartments, reduced hydrolase activity, or compartment de-acidification;

2. Either a block at a specific step (formation, transport, fusion, or proteolysis) or a global reduction in flux;
3. Substrate accumulation that *tracks* the clearance deficit rather than preceding it;
4. Involvement that is not confined to the regions that have already lost most of their neurons, since a lesion confined to end-stage tissue cannot be the initiating one;
5. Compensatory biogenesis that is either absent, exhausted, or futile — because a system whose terminal step is broken cannot be rescued by making more of it.

The Alzheimer’s literature satisfies several of these criteria in an unusually direct way, which is why the account was built there. The Huntington’s data satisfy none of them at early grades, and satisfy some at late grades. That difference, and not any general statement about proteostasis, is the substance of this paper.

2.3 A note on what staged human tissue can and cannot show

Post-mortem tissue cannot measure flux. Autophagic flux is a rate, and a rate cannot be read from a fixed specimen; what can be read is the steady-state census of compartments and their contents, the presence and maturation state of hydrolases, and the co-localisation of cargo with compartment markers. From a census one can infer a block — a pile-up of immature compartments upstream of a step, with depletion downstream of it, is strong evidence for a block at that step. One cannot infer the absence of a subtle kinetic slowing that has not yet produced a census abnormality.

This asymmetry cuts in a specific direction, and it should be stated plainly because it is the strongest available objection to the argument of this paper. A finding of *no block* in human tissue is weaker evidence than a finding of a block. The Huntington’s data show cargo-loaded autophagosomes and cathepsin-positive autolysosomes at the stages examined, which argues against significant blockage at formation and at fusion [8]; they do not exclude a reduction in throughput too modest to redistribute the compartment census. I return to this in §8 and grade the relevant claims accordingly.

There is a second limitation of the same kind. The earliest grade examined in the staged human series is HD2, at which, by the grading system’s own counts, roughly half of caudate neurons may already be lost [5]. The series therefore cannot speak to grade 0 and grade 1 tissue, where the earliest cellular changes would be expected. What it can say is that at HD2 — when the neuropathological diagnosis is already secure and the clinical syndrome established — the clearance machinery is comparatively normal. That is a weaker statement than “the machinery is normal before the disease begins,” and I do not make the stronger one.

3. The Alzheimer's case, and what actually makes it strong

To narrow a claim honestly one must first state the case for it at full strength. The Alzheimer's evidence for early, causal clearance failure is the best evidence of its kind in neurodegeneration, and it is much better than the corresponding evidence in any other disease. Five features of it deserve separate statement, because the narrowed claim of §6 is built out of the fifth.

3.1 The compartment changes first

Neuronal early endosomes are markedly enlarged in Alzheimer brain. In the original morphometric study, individual endosomes in human pyramidal neurons displayed volumes up to thirty-two-fold above the normal average, with an average 2.5-fold increase in total endosomal volume per neuron, implying a substantial increase in endocytic activity [9]. The abnormality was present in most pyramidal neurons, detectable at early stages, and absent in several other neurodegenerative disorders examined — an early specificity claim that is rare in this literature.

The follow-up study established the timing more sharply. Endosomal enlargement, together with elevated rab4 and translocation of rabaptin 5, was evident in neocortical pyramidal neurons at preclinical stages of disease, when Alzheimer-type neuropathology was still restricted to the entorhinal region; and in Down syndrome, early endosomes were significantly enlarged in some pyramidal neurons as early as twenty-eight weeks of gestation, decades before classical Alzheimer neuropathology develops [10]. Markers of endocytic activity were only minimally influenced by normal ageing and by the other neurodegenerative diseases studied.

This is the strongest temporal card the clearance account holds in any disease, and it is worth noting exactly what it establishes. In Down syndrome the initiating lesion is a supernumerary chromosome 21 carrying an extra copy of *APP*, so the causal arrow in that condition runs from precursor-protein gene dose to the endosome. The prenatal endosomal change therefore establishes that the compartment responds to precursor-protein biology very early; it does not by itself establish that the compartment is upstream of that biology. The point is a real one and it is conceded here, because the narrowed claim of §6 does not require the compartment to be upstream of *APP*. It requires the compartment and the substrate to be locked together, which is a different and better-supported proposition.

3.2 The lesion is at the terminal step, not at induction

Autophagic vacuoles are uncommon in brains without Alzheimer pathology but abundant in Alzheimer brains, particularly within neuritic processes including synaptic terminals; in dystrophic neurites, autophagosomes, multivesicular bodies, multilamellar bodies and cathepsin-containing autophagolysosomes are the predominant organelles and accumulate in very large numbers [11]. The striking accumulation of *immature* forms in dystrophic neurites suggested, at the time, that transport and maturation to lysosomes were impaired.

Two subsequent studies settled which interpretation was right. In primary cortical neurons, constitutive macroautophagy proved to be highly efficient, with newly formed autophagosomes rapidly cleared by fusion with lysosomes; even after strong induction by mTOR suppression or nutrient deprivation, active cathepsin-positive autolysosomes rather than LC3-II-positive autophagosomes predominated. Selectively impeding the late steps — inhibiting cathepsin-mediated proteolysis within autolysosomes, or disrupting transport on microtubules — reproduced the electron-dense double-membrane compartments seen in Alzheimer dystrophic neurites. The conclusion was that Alzheimer autophagic pathology arises from impaired clearance of autophagic vacuoles rather than from strong induction alone, and that therapeutic modulation must therefore target late steps [12].

The human confirmation came from laser-capture microdissected CA1 pyramidal neurons of early and late-stage Alzheimer subjects. Autophagy-related genes were upregulated more strongly than any other gene-ontology group, reflecting increased autophagosome formation and increased lysosomal biogenesis beginning at early stages — that is, the cell responds correctly to the backlog — while the terminal step nonetheless failed, so that increased induction overburdened failing lysosomes and propelled neuritic dystrophy [13].

This is a distinctive signature and it will matter in §5. In Alzheimer’s disease, biogenesis goes up *and clearance still fails*. Upregulated biogenesis in that setting is a failed compensation. In Huntington’s disease, as will be seen, biogenesis goes up and clearance is maintained, which makes the same observation mean the opposite thing.

3.3 The substrate jams the machine

The feature that distinguishes Alzheimer’s disease from a generic proteostatic overload is that its substrate acts directly on the pump.

Macroautophagy requires presenilin 1. In presenilin-1-null blastocysts, in neurons from hypomorphic mice and in neurons conditionally depleted of the protein, substrate proteolysis and autophagosome clearance during macroautophagy are prevented by a selective impairment of autolysosome acidification and cathepsin activation. The cause is a failure of presenilin-1-dependent targeting of the V0a1 subunit of the vacuolar H⁺-ATPase to lysosomes: N-glycosylation of V0a1,

required for efficient delivery from endoplasmic reticulum to lysosome, depends on selective binding of presenilin-1 holoprotein to the unglycosylated subunit. Presenilin-1 mutations causing early-onset familial Alzheimer's disease produce the same lysosomal and autophagic phenotype in patient fibroblasts [14]. The finding was subsequently extended and the methodology for lysosomal pH quantification examined in detail, with elevated lysosomal pH confirmed across additional cell models of presenilin deficiency, in fibroblasts from patients with presenilin-1 mutations, and in neurons of a presenilin/APP mouse model [15].

The sporadic-disease counterpart is more direct still. The β -C-terminal fragment of the amyloid precursor protein disrupts the vacuolar H^+ -ATPase and lysosomal acidification by a specific mechanism: the phosphorylated YENPTY internalisation motif of APP- β CTF binds selectively within a pocket of the V0a1 cytoplasmic domain and competitively inhibits association of the V1 subcomplex, reducing pump activity. Lowering β CTF tyrosine phosphorylation restores pump and lysosome function in Down syndrome fibroblasts and in the brains of Down syndrome model mice; lowering it below normal constitutive levels boosts holoenzyme assembly and activity, implying that the pump is tonically modulated by phospho- β CTF; and elevated β CTF tyrosine phosphorylation disrupts pump function in two mouse Alzheimer models [16].

Read together, these two results say something that no other neurodegenerative disease can currently say with equal specificity. The gene whose mutations cause the familial disease is required to build the pump. The fragment produced from the other gene whose mutations cause the familial disease jams the pump. Substrate and machinery are not independent.

3.4 The loop closes, and it has a morphology

The consequence of substrate–machinery coupling is a self-amplifying cycle, and that cycle has been imaged. Using a neuron-specific transgenic reporter of autophagy and pH, multiplex confocal imaging and correlative light–electron microscopy across five Alzheimer mouse models, autolysosome acidification was found to decline in neurons well before extracellular amyloid deposition, associated with markedly lowered vacuolar H^+ -ATPase activity and with build-up of $A\beta$ and APP- β CTF selectively within enlarged de-acidified autolysosomes. In more compromised but still intact neurons, profuse $A\beta$ -positive autophagic vacuoles pack into large membrane blebs forming perikaryal rosettes — a pattern also present in Alzheimer brains [17].

The morphology matters less than the ordering. De-acidification precedes deposition; substrate accumulates inside the de-acidified compartment; the compartment is the site of the pathology rather than its consequence. Whatever else is true of Alzheimer's disease, the clearance lesion is not a late bystander.

3.5 The genetics point at the organelle

Finally, the human genetics of Alzheimer’s disease is unusually enriched for genes whose primary function is in the endosomal–lysosomal network. The genes that most strongly promote β -amyloidogenesis — *APP*, *PSEN1*, *PSEN2*, *APOE4* — all have primary effects on that network’s function, and mutations in more than thirty-five network-related genes are known to cause familial neurodegenerative disease [18]. Large-scale association analysis across 111,326 clinically diagnosed or proxy cases and 677,663 controls identified 75 risk loci, with pathway analyses confirming amyloid and tau involvement and highlighting microglial implication [19]; a substantial fraction of the prioritised genes act in endocytosis, sorting and vesicular trafficking. The genetic architecture is compatible with an organelle-centred reading and has been used to argue for one.

3.6 The tauopathy extension, and how much weaker it is

The narrowed claim proposed in §7 covers Alzheimer’s disease “and the tauopathies.” That extension deserves to be flagged as the weakest part of the narrowed claim rather than smuggled in.

The direct evidence is that tau is a lysosomal substrate whose handling is disturbed in a self-amplifying way. A large fraction of neuronal tau is degraded by chaperone-mediated autophagy; upon acetylation, tau is preferentially rerouted to macroautophagy and endosomal microautophagy, in part because acetylated tau exerts an inhibitory effect on chaperone-mediated autophagy, with extracellular release as a consequence. Experimental blockage of chaperone-mediated autophagy enhances cell-to-cell propagation of pathogenic tau in a mouse model of tauopathy, and lysosomes isolated from the brains of patients with tauopathies show similar molecular mechanisms leading to chaperone-mediated autophagy dysfunction [20]. This is a substrate that inhibits its own degradative route — the same logical form as the β CTF result, though at a different route and with much weaker human-tissue support.

The acidification link is more tentative. Suppression of a tubulin deacetylase that regulates vacuolar H^+ -ATPase V1 recruitment lowers lysosomal pH, enhances autophagic degradation of both aberrant $A\beta$ and tau in cell models, and on knockdown in the hippocampi of triple-transgenic Alzheimer mice reduces plaque and tangle accumulation and improves cognition; the deacetylase is reported as elevated in Alzheimer model brains and in patients [21]. This supports the proposition that lysosomal acidity is load-bearing for tau as well as for $A\beta$, but it is a cell-and-mouse result with a single-laboratory human component, and it does not distinguish a primary tau–pump interaction from a secondary one.

The honest position is that the tauopathy arm of the narrowed claim is an extrapolation with one good mechanistic anchor and no staged human series of the kind that exists for Huntington’s disease. If the claim is to be tested, the primary tauopathies — progressive supranuclear palsy, corticobasal degeneration, Pick’s disease — are where the test should be run, because they carry tau

pathology without the amyloid precursor protein. I make this a prediction in §9 rather than an assertion here.

4. Huntington's disease: what the model literature established

Before reading the human data it is necessary to state what the model literature had established, because the human study revises it rather than contradicting it outright, and the distinction is where the intellectual content lies.

4.1 The disease

Huntington's disease is caused by an expanded, meiotically unstable CAG repeat in the gene originally designated IT15, on chromosome 4p16.3, encoding a widely expressed protein of approximately 348 kDa unrelated to any then-known gene [22]. Age at motor onset is determined by the length of the longer expanded allele in a completely dominant fashion; the normal allele, the interaction between alleles, and the presence of a second expanded allele do not influence it [3]. Neuropathologically the disease is defined by progressive degeneration of the neostriatum, graded 0 to 4 by macroscopic and microscopic criteria that correlate closely with clinical disability; earliest changes appear in the medial paraventricular caudate, the tail of the caudate and the dorsal putamen, with approximately 50 per cent of caudate neurons lost at grade 1 and 95 per cent at grade 4, and with marked astrocytosis from grade 2 onwards [5]. Later work has extended the pathology to area- and layer-specific neocortical and allocortical neuronal loss, to selected thalamic nuclei, to cerebellar cortex and deep cerebellar nuclei, and to distinct brainstem nuclei [6].

4.2 The cargo-recognition lesion

The autophagic lesion in Huntington's disease was characterised fifteen years ago in cellular and mouse models and in cells from human patients. The primary defect identified was in the ability of autophagic vacuoles to recognise cytosolic cargo: vacuoles formed at normal or even enhanced rates and were adequately eliminated by lysosomes, but failed to efficiently trap cytosolic cargo in their lumen, so that autophagosomes in Huntington's cells contained significantly less cytosolic material than wild-type [7]. The proposal was that inefficient engulfment accounts for slower turnover, functional decay and accumulation.

Two features of this result are routinely lost in secondary accounts and both matter here. First, *the lysosome was not the lesion*: the paper's own statement is that autophagic vacuoles "are adequately eliminated by lysosomes." The Huntington's defect as originally described was upstream of the degradative compartment, at cargo loading, not at proteolysis. Second, the substrate was described as interfering with cargo recognition, not with the hydrolytic machinery. A theory that groups

Huntington's disease with Alzheimer's disease under a single heading of "lysosomal failure" is already at odds with the foundational Huntington's paper it cites.

4.3 Compensation, and the first sign that the machinery holds

A companion result is more telling still. Chaperone-mediated autophagy is constitutively upregulated in cellular and mouse models of Huntington's disease: the lysosome-associated membrane protein type 2A and lysosomal hsc70 are markedly increased, through both stabilisation of LAMP-2A at the lysosomal membrane and transcriptional upregulation of the *lamp-2* splice variant. The interpretation offered was that chaperone-mediated autophagy increases in response to macroautophagic dysfunction early in the disease, with the efficiency of this compensation declining with age [23].

Compensation of this kind is only possible in a competent lysosome. A compartment that cannot acidify or cannot activate its hydrolases gains nothing from more LAMP-2A and more lysosomal hsc70. The result is, read carefully, an early indication that the Huntington's lysosome works — and that the disease's clearance problem is a routing and loading problem in a functioning system rather than a failure of the system itself.

4.4 Huntingtin is on the machinery's side

The final piece of model-organism context inverts the usual framing. Huntingtin functions as a scaffold protein for selective macroautophagy and is dispensable for non-selective macroautophagy. In *Drosophila* it interacts genetically with autophagy pathway components; in mammalian cells it physically interacts with the cargo receptor p62 to facilitate p62's association with LC3 and with Lys-63-linked ubiquitin-modified substrates; and maximal activation of selective autophagy under stress requires huntingtin binding to ULK1, releasing that kinase from mTOR's negative regulation [24].

The implication for disease mechanism is substantial. If wild-type huntingtin is a positive component of selective autophagy, then the polyglutamine expansion can impair autophagy by *subtracting* an adaptor function — a loss-of-function effect on cargo recognition, which is precisely the lesion the model literature described [7]. It does not require, and there is no evidence for, a gain-of-function inhibition of the degradative machinery analogous to β CTF's action on the V0a1 subunit. The two diseases damage the pathway in mechanistically opposite senses: Alzheimer's disease adds an inhibitor of the terminal step; Huntington's disease removes a facilitator of an earlier step.

4.5 Aggregation as coping, not as choking

One further model result constrains any account in which mutant huntingtin overwhelms the clearance system. Longitudinal single-neuron imaging with an automated microscope that returns to the same neuron over time showed that neurons die in a manner dependent on mutant huntingtin dose and polyglutamine length but independent of time; that many neurons die without ever forming an inclusion body; that the amount of *diffuse* intracellular huntingtin predicts whether and when inclusion formation or death occurs; and that inclusion body formation predicts improved survival and is followed by decreased mutant huntingtin elsewhere in the neuron [25]. Inclusion formation functions as a coping response.

If sequestration into inclusions were an index of clearance failure, it should predict death. It predicts survival. The toxic species is the diffuse fraction, and the cell's handling of it — including by aggregation — is protective within limits. This is not the behaviour of a system whose degradative capacity is the binding constraint.

5. What the staged human brain shows

5.1 The design

The human study examined autophagy–lysosomal functional markers in relation to mutant huntingtin aggresome pathology, using multiplex confocal and ultrastructural immunocytochemical analyses, in striatum and in the less affected cortex or cerebellum of Huntington brains staged from grade HD2 to HD4 by Vonsattel criteria, compared with controls [8].

Three features of that design should be registered. It is human tissue, not a model. It is *staged*, so that findings can be ordered along the disease course rather than pooled into a single “Huntington versus control” contrast. And it carries an internal regional control — cortex and cerebellum in the same brains, where degeneration is far less severe than in striatum — which allows the disease-severity axis and the tissue-identity axis to be separated to a degree that a striatum-only design cannot achieve.

5.2 What was found

The findings, taken in the order the paper reports them, are as follows.

Huntingtin localises to autophagy–lysosomal compartments. Immunolabelling revealed localisation of huntingtin and mutant huntingtin in vesicular compartments of the pathway labelled by the adaptor proteins p62/SQSTM1 and ubiquitin, and by cathepsin D, as well as in huntingtin-positive inclusions [8]. The substrate is where it should be if the pathway is engaging it.

At HD2 the pathway is comparatively normal. Neurons at the earliest grade examined were described as comparatively normal; the abnormalities that follow are described as emerging at later stages [8].

At later stages compartments enlarge and cluster, and this is progressive and regionally graded. Neurons at later grades exhibited progressive enlargement and clustering of cathepsin-D-immunoreactive autolysosomes and lysosomes, and, ultrastructurally, autophagic vacuole and lipofuscin granules accumulated progressively, more prominently in striatum than in cortex [8].

Substrate and adaptor fragments rise in striatum but not cortex. These changes were accompanied by rises in the levels of huntingtin/mutant huntingtin and of p62/SQSTM1 — particularly of their fragments — in striatum but not in cortex [8]. The regional dissociation is important: it aligns the biochemical abnormality with the region that is degenerating, not with the

presence of the mutation, which is uniform across the brain.

Lysosomal biogenesis is upregulated. LAMP1 and LAMP2 RNA and LAMP1 protein increased [8]. This is a transcriptional and protein-level expansion of lysosomal capacity, and it echoes at the human-tissue level the compensatory LAMP-2A upregulation found in models [23].

There is no significant blockage at formation or at fusion. Cargo-loaded autophagosomes and cathepsin-positive autolysosomes were readily observed, implying a lack of significant blockage in autophagosome formation and in autophagosome–lysosome fusion [8].

The authors’ own conclusion. Upregulated lysosomal biogenesis and preserved proteolysis maintain autophagic clearance in early-stage Huntington’s disease, while the progressive huntingtin build-up and autolysosome accumulation at advanced stages may signify a failure in autophagy substrate clearance. The therapeutic corollary they draw is that stimulation of the pathway applied at early disease stages, when the clearance machinery is fully competent, could yield benefit [8].

5.3 What this does and does not overturn

It does not overturn the cargo-recognition result [7]. If anything it is consistent with it: cargo-loaded autophagosomes are formed and cleared, which is what the earlier work reported, and the earlier work located the deficit in *efficiency* of engulfment rather than in vesicle formation or lysosomal elimination. Nor does it overturn the observation that autophagy–lysosomal pathology exists in Huntington’s disease; the paper documents that pathology in detail.

What it overturns is the ordering. The convergence claim in its strong form requires the clearance lesion to be present early and to drive substrate accumulation. The staged human data report the reverse arrangement: biogenesis up, proteolysis preserved, no formation or fusion block, and substrate clearance failing only at advanced stages, in the region that is already the most severely degenerated. In Huntington’s disease the clearance failure looks like a consequence of advanced disease rather than its cause.

5.4 The evidential status of the study, stated fairly

One staged autopsy series is not a literature. Its principal limitations are those identified in §2.3 — a fixed-tissue census cannot exclude a kinetic slowing, and grade HD2 is not early disease in any biological sense, only early in the range of tissue available. There are two further limitations worth stating.

First, control tissue in any human autopsy series carries agonal and post-mortem variability that bears on labile markers, and hydrolase activity inferred from immunoreactivity is not the same as hydrolase activity measured.

Second, the study comes from a laboratory that has been the principal architect of the clearance account in Alzheimer's disease [8,11,14,16,17]. This is worth naming explicitly, and it cuts in the direction of credibility rather than against it: a result that constrains the reach of a framework, reported by the framework's own authors, is not a result produced by motivated reasoning in the convenient direction. The measurement platform is also the same one on which the Alzheimer's findings were built, which makes the cross-disease comparison unusually clean — the contrast between a competent Huntington lysosome and a de-acidified Alzheimer autolysosome is not an artefact of different laboratories using different assays.

The appropriate evidential grade for the central Huntington finding is therefore *probable* rather than *established*, and it is graded so in §8. What it is not is negligible, and a framework that asserts convergence cannot leave it unaddressed.

6. Why Huntington’s disease runs the other way

Having established the divergence, the question is why. Four asymmetries between the two diseases, taken together, explain it, and the fourth generates the narrowed claim.

6.1 The rate-limiting step in Huntington’s disease is a DNA process

The single most important development in Huntington’s disease biology over the last decade is the discovery that the inherited repeat is not the proximate toxic entity, and that the interval between conception and midlife degeneration is occupied by a process operating on DNA rather than on protein.

Unbiased genome-wide association analysis of age at neurological onset identified loci that accelerate or delay onset by years, with association at *MLH1* and pathway analysis implicating DNA handling and repair mechanisms in altering the course of the disease [26]. The subsequent literature validated mismatch-repair and interstrand-crosslink-repair components — notably *MSH3* and *FAN1* — as modifiers whose mechanism is somatic CAG instability, supported by the protective effect of CAA interruptions within the CAG tract [27]. A more recent analysis comparing genome-wide association studies of somatic expansion in blood with expansion-driven clinical phenotypes confirmed that somatic expansion is driven by a mismatch-repair-related process with cell-type-specific genetic modification, and identified shared modifiers (*MSH3*, *PMS2*, *FAN1*) alongside distinct ones, including a synonymous CAG-adjacent variant that dramatically hastens motor onset without increasing somatic expansion [28].

Single-cell measurement then supplied the mechanism in human tissue. Measuring repeat length alongside genome-wide RNA expression in single cells showed that the repeat expands somatically in striatal projection neurons from an inherited 40–45 to 100–500 or more; that expansion from 40 to 150 had no apparent cell-autonomous effect; and that neurons with 150–500+ repeats lost first positive and then negative features of neuronal identity, de-repressed senescence and apoptosis genes, and were lost. The conclusion drawn was that expansion beyond roughly 150 repeats causes striatal projection neurons to degenerate quickly and asynchronously, so that at any one time most neurons carry an innocuous but unstable gene, and pathogenesis is a DNA process for almost all of a neuron’s life [4]. Complementary work using nuclear sorting and deep molecular profiling found expansions arising at mutant *HTT* in striatal medium spiny neurons, cholinergic interneurons and cerebellar Purkinje neurons — and at mutant *ATXN3* in medium spiny neurons from spinocerebellar ataxia type 3 donors — with expansion in medium spiny

neurons associated with higher MSH2 and MSH3 levels, and supporting a model in which expansion is necessary but may not be sufficient for cell death [29].

The implication for the convergence claim is direct and, I think, decisive. If most of the disease interval is occupied by repeat expansion in a neuron that is otherwise functionally normal, and if the neuron becomes acutely vulnerable only after crossing a somatic threshold, then the proteostatic load is *not* the rate-limiting variable for most of the disease course. It is downstream of a clock that runs in the nucleus. A clearance lesion cannot be the initiating event in a disease whose initiating event is a polymerase or repair-complex error, and whose timing is set by the kinetics of that error.

The biomarker data are consistent with this picture. In young adult premanifest gene carriers a mean 23.6 years from predicted onset, there was no significant evidence of cognitive or psychiatric impairment and no group difference in brain imaging measures beyond slightly smaller putamen volumes, while cerebrospinal-fluid and plasma neurofilament light and cerebrospinal-fluid YKL-40 were already elevated [30]. A very long latency with minimal functional consequence, terminating in relatively rapid regional loss, is the signature of a threshold process, not of a slowly closing bottleneck.

6.2 The substrate does not jam the machine

In Alzheimer's disease the accumulating species has an identified, structurally specified inhibitory action on the terminal step: the phosphorylated internalisation motif of APP- β CTF binds a pocket in the V0a1 cytoplasmic domain and competitively inhibits V1 association [16], and the gene required to deliver that same subunit to the lysosome is the gene whose mutations cause the dominant familial disease [14].

No comparable action has been demonstrated for mutant huntingtin. The lesion attributed to it in models is interference with cargo recognition and with the association between p62 and the autophagosome formation site [7] — an event upstream of the lysosome, at the loading dock rather than at the incinerator. Consistently, the human staged data report preserved proteolysis, readily observed cathepsin-positive autolysosomes, and upregulated lysosomal biogenesis [8]: a machine that is working, and being built more of.

This is the load-versus-capacity distinction, and it is the hinge of the whole argument. Every proteinopathy adds load. Only some of them degrade capacity. A theory that treats “the clearance pathway is involved” as equivalent across diseases has conflated the two.

6.3 The wild-type protein is a component of the pathway

Because wild-type huntingtin scaffolds selective macroautophagy — bridging p62 to LC3 and to Lys-63-linked ubiquitinated substrates, and binding ULK1 to release it from mTOR's negative regulation [24] — the polyglutamine expansion acts on the pathway partly by impairing a component of it. This gives Huntington's disease a partial loss-of-adaptor phenotype rather than a gain-of-inhibitor phenotype.

The two produce different system behaviours. Loss of an adaptor reduces the selectivity and efficiency of cargo capture while leaving degradative capacity intact, which is compensable: the cell can raise biogenesis, recruit an alternative route such as chaperone-mediated autophagy [23], and maintain clearance for a long time. Gain of an inhibitor at the terminal step is not compensable in the same way, because every compensatory route ends at the same de-acidified compartment. This is exactly why increased induction in Alzheimer's disease overburdens failing lysosomes and worsens neuritic dystrophy [13], while increased biogenesis in Huntington's disease maintains clearance [8].

6.4 Sequestration is protective, and the failure is late and regional

Inclusion formation in Huntington's disease predicts improved survival and reduces mutant huntingtin elsewhere in the neuron [25]; the diffuse fraction is the toxic one. And in staged human tissue, the biochemical evidence of failing clearance — rising huntingtin and p62 fragments, accumulating autophagic vacuole and lipofuscin granules — is confined to the striatum and to advanced grades, absent from the cortex of the same brains [8].

A lesion that appears only in the region that has already lost most of its neurons, and only at the stage at which it has lost them, has the distribution of a consequence.

6.5 The asymmetries, tabulated

Table 1 — Five asymmetries between Alzheimer’s disease and Huntington’s disease in the clearance pathway

Property	Alzheimer’s disease	Huntington’s disease
Earliest detectable intraneuronal change	Endosomal enlargement in pyramidal neurons at preclinical stages; prenatal in trisomy 21 [9,10]	Somatic CAG expansion in striatal projection neurons, with no apparent cell-autonomous effect below ~150 repeats [4,29]
Relation of substrate to machinery	β CTF binds V0a1 and inhibits v-ATPase assembly; PSEN1 required to deliver V0a1 [14,16]	Mutant huntingtin impairs cargo recognition; wild-type huntingtin is itself a selective-autophagy scaffold [7,24]
Terminal proteolysis	Impaired; autolysosomes de-acidified before deposition [15,17]	Preserved at the stages examined; cathepsin-positive autolysosomes readily observed [8]
Meaning of upregulated biogenesis	Failed compensation — induction overburdens failing lysosomes and propels dystrophy [13]	Successful compensation — biogenesis up, clearance maintained [8,23]
Timing of clearance failure relative to neuronal loss	Before deposition, before loss [10,17]	At advanced grades, in the region already most degenerated [8]

7. The narrowed claim

7.1 Statement

I propose the following replacement for the strong convergence claim.

> **Narrowed claim.** In a subset of neurodegenerative diseases — Alzheimer’s disease and, provisionally, the primary tauopathies — failure of the autophagy–lysosomal pathway is early and causal, because in these diseases the accumulating substrate directly inhibits the terminal, acidification-dependent step of the pathway that is required to degrade it. This substrate–machinery feedback, and not proteostatic load as such, is what makes clearance failure causal rather than consequential. In diseases that impose proteostatic load without such feedback — of which Huntington’s disease is the clearest human example — clearance failure is late, regional, and a consequence of degeneration rather than its driver.

The claim is deliberately narrower in three respects. It names a *mechanism* (feedback at the acidification step) rather than a *location* (the lysosome). It is restricted to diseases for which that mechanism is demonstrated rather than assumed. And it makes a definite negative assertion — that Huntington’s disease does not belong — which is the part that can most easily be shown to be wrong.

7.2 The discriminating property

The discriminating property is best stated in the language of system dynamics. Let load be the rate at which substrate requiring degradation is generated, and capacity the maximum rate at which the pathway can degrade it. Every proteinopathy raises load. The question that separates the diseases is whether capacity is an *independent* variable.

Where capacity is independent of load, raising load produces a linear backlog with a fixed ceiling, and compensatory expansion of capacity — more lysosomes, more LAMP protein, recruitment of a parallel route — genuinely helps. The system degrades gracefully until load exceeds the expanded ceiling.

Where capacity is a decreasing function of accumulated load — where the substrate jams the machine — the system has positive feedback. Backlog reduces capacity, which increases backlog. Compensation is not merely insufficient but can be counterproductive, because inducing more autophagosome formation delivers more cargo to a compartment that cannot digest it. This is precisely what is observed in Alzheimer’s disease, where autophagy-related gene expression rises

more than any other gene-ontology group while clearance still fails and neuritic dystrophy is propelled [13].

On this reading, Alzheimer’s disease is a feedback disease and Huntington’s disease is a load disease. The two require different theories, different biomarkers and different drugs, and calling them the same disease obscures all three differences.

7.3 A taxonomy of clearance involvement

The load/feedback distinction generalises into four categories, which I offer as a replacement for the undifferentiated “clearance is involved.”

Table 2 — Four categories of autophagy-lysosomal involvement in neurodegenerative disease

Category	Definition	Diagnostic signature	Examples
I. Primary lysosomal disease	The causal mutation is in a lysosomal gene; degradative capacity is reduced from the outset, independently of any aggregating substrate	Storage material; capacity deficit measurable before and independent of disease-specific protein pathology	Biallelic <i>GRN</i> mutation causing neuronal ceroid lipofuscinosis type 11 [31]; the lysosomal storage disorders generally
II. Feedback bottleneck	The accumulating substrate inhibits the terminal degradative step, so capacity falls as load rises	Compartment de-acidification preceding deposition; compensatory biogenesis that fails; induction worsens pathology	Alzheimer’s disease [14,16,17]; provisionally the primary tauopathies [20,21]
III. Load without feedback	Substrate load rises but degradative capacity is preserved; compensation works, and fails only when the cell is already dying	Preserved proteolysis and successful compensatory biogenesis at early stages; clearance failure confined to end-stage, degenerating regions	Huntington’s disease [8,23,25]
IV. Bystander disturbance	Pathway abnormality is present but neither causal nor rate-limiting; it reflects general cellular stress	Pathway markers abnormal without a demonstrated capacity deficit or feedback loop; abnormality not specific to the disease	Normal ageing; much of the “pathway is abnormal in disease X” literature [1]

Two remarks on the taxonomy. First, the categories are about *mechanism*, not severity: a category III disease can be more lethal than a category II one. Second, a disease can move between categories over its course — Huntington’s disease arguably enters category II or IV late, once striatal neurons are dying — which is exactly why staging matters and why pooled autopsy contrasts mislead.

7.4 Where Parkinson’s disease and the ALS–frontotemporal spectrum sit

I place neither with confidence, and the reason is instructive: the evidence needed to place them is the evidence that exists for Alzheimer’s disease and now for Huntington’s disease, and it has not been assembled for either.

For Parkinson’s disease there is a strong genetic argument for at least partial category I membership. Mutations in *GBA*, which in biallelic form cause Gaucher’s disease, are associated with Parkinson’s disease with an odds ratio above five across sixteen centres and 5,691 patients, with earlier presentation and more atypical features in carriers [32]. That is a primary lysosomal-enzyme deficit conferring risk for a synucleinopathy. Whether α -synuclein additionally inhibits the degradative machinery in a way that closes a feedback loop — which would make sporadic Parkinson’s disease category II — is plausible but not established with the specificity available for β CTF. The observation that recombinant pro-cathepsin D enhances α -synuclein degradation and restores endo-lysosomal and autophagic function in patient-derived neurons and in cathepsin-D-deficient mice [33] is consistent with capacity being load-bearing, but does not by itself demonstrate substrate-driven capacity loss.

For the ALS–frontotemporal spectrum, heterozygous *GRN* mutations cause frontotemporal dementia with TDP-43 inclusions while homozygous mutations cause a lysosomal storage disease, and the neuropathology of a homozygous carrier showed hallmarks of neuronal ceroid lipofuscinosis with an absence of TDP-43 cytoplasmic inclusions — suggesting a dose-dependent shift between lysosomal and TDP-43 pathologies [31]. That is a remarkable natural experiment and it argues that progranulin-linked disease is category I at full dose and something else at half dose. It does not settle the category of sporadic TDP-43 proteinopathy.

The honest summary is that these two are unplaced, that placing them requires staged human tissue of the kind that now exists for Huntington’s disease, and that the convergence claim’s habit of asserting membership without that evidence is the practice this paper is arguing against.

7.5 What the narrowing costs and what it buys

It costs the slogan. “One mechanism, many diseases” is a better sentence than anything proposed here, and giving it up means giving up the implication that a single clearance-directed agent would benefit four diseases at once.

It buys three things.

Falsifiability. The narrowed claim makes a specific negative assertion about Huntington’s disease and a specific mechanistic assertion about the tauopathies, and §10 lists the observations that would refute each.

Credit for the predictions that were right. A framework advertised as explaining everything gets no credit for explaining anything, and this one has predicted several things correctly that its rivals did not: that the fragment rather than the peptide would prove the pathogenic species; that autophagic pathology in Alzheimer’s disease would prove to be a clearance problem rather than an induction problem [12]; that inducing autophagy without repairing the terminal step would not help. Those predictions are buried when they sit alongside a hundred post-hoc accommodations.

A therapeutic rule with a sign. The undifferentiated claim implies “enhance clearance” everywhere. The narrowed claim implies opposite prescriptions in the two diseases — repair before inducing in category II; induce early, while the machinery is competent, in category III — and it is the second of these that the staged human Huntington data explicitly recommend [8].

8. Strength of evidence

The argument above rests on load-bearing claims of very unequal quality. They are graded here on a four-level scale: **established** (multiple independent groups, human or definitive experimental evidence, no serious contrary literature); **probable** (good direct evidence, single principal source or limited replication); **inferred** (follows from established findings but not directly tested); **speculative** (proposed here, or supported only by indirect argument).

Table 3 — Strength of evidence for the load-bearing claims

#	Claim	Grade	Basis and principal limitation
1	The autophagy–lysosomal pathway is disturbed in a wide range of neurodegenerative diseases and in ageing	Established	Reviewed across diseases [1,2]; the claim’s weakness is its near-universality, not its truth
2	Neuronal early endosomes are enlarged in Alzheimer brain at preclinical stages, and prenatally in trisomy 21	Established	Morphometry in human tissue, with specificity against other neurodegenerative diseases [9,10]
3	Alzheimer autophagic pathology reflects impaired clearance of autophagic vacuoles rather than induction alone	Established	Neuronal models reproducing the human morphology by selective late-step inhibition [12]; human CA1 transcriptomics and protein data [13]; consistent human ultrastructure [11]
4	Presenilin 1 is required to deliver the v-ATPase V0a1 subunit to lysosomes, and familial mutations impair autolysosome acidification	Established	Multiple genetic backgrounds plus patient fibroblasts [14]; independent pH quantification [15]
5	APP- β CTF directly inhibits the v-ATPase by competitive interference with V1 association	Probable	Structurally specified binding, rescue by lowering tyrosine phosphorylation in cells and in vivo [16]; single principal laboratory
6	Autolysosome de-acidification precedes extracellular amyloid deposition in Alzheimer models	Probable	Five mouse models with a pH-sensitive neuronal reporter and correlative microscopy [17]; mouse evidence with human morphological corroboration
7	Alzheimer genetic risk is enriched for endosomal–lysosomal genes	Established	Large-scale association study [19]; enumeration of network genes causing familial neurodegeneration [18]

#	Claim	Grade	Basis and principal limitation
8	Tau is degraded by chaperone-mediated autophagy, and acetylated tau inhibits that route and is rerouted, promoting propagation	Probable	Mouse and human lysosome data [20]; inhibition demonstrated, human tissue component limited
9	Lysosomal acidity is load-bearing for tau pathology as well as for A β	Inferred	Single-laboratory knockdown study in cells and 3 $\times$ Tg-AD mice [21]; no primary human tauopathy series
10	Huntington's disease is caused by an expanded CAG repeat whose longer allele fully determines age at motor onset	Established	Gene identification [22]; 4,068-subject regression [3]
11	Huntington neuropathology is graded by striatal severity, with ~50% caudate neuron loss already at grade 1	Established	Original 163-case series [5]; subsequent extension [6]
12	In Huntington models the primary autophagic defect is cargo recognition, with lysosomal elimination of vacuoles adequate	Established	Cellular and mouse models plus human patient cells; the paper's own statement that vacuoles are adequately eliminated by lysosomes [7]
13	Chaperone-mediated autophagy is compensatorily upregulated in Huntington models	Probable	Cellular and mouse models, transcriptional and protein-stability mechanisms identified [23]
14	Wild-type huntingtin is a scaffold for selective macroautophagy	Probable	Genetic interaction in <i>Drosophila</i> , physical interactions with p62, LC3 and ULK1 in mammalian cells [24]
15	Inclusion body formation in Huntington neurons predicts improved survival; the diffuse fraction is toxic	Established	Longitudinal single-neuron survival analysis [25]
16	In staged human Huntington brain, lysosomal biogenesis is upregulated and proteolysis preserved, without significant block at formation or fusion	Probable	Single staged human series with internal regional control [8]; fixed tissue cannot exclude kinetic slowing, and HD2 is not early disease
17	In staged human Huntington brain, substrate clearance failure appears at advanced grades and predominantly in striatum	Probable	Same series; regional dissociation of huntingtin and p62 fragment accumulation between striatum and cortex [8]
18	Somatic CAG expansion in striatal projection neurons, not inherited repeat length per se, is the proximate driver of their degeneration	Probable	Single-cell repeat measurement with transcriptomics [4]; cell-type-specific expansion and MutS β /FAN1 mechanism [29]; modifier genetics [26,27,28]

#	Claim	Grade	Basis and principal limitation
19	Clearance failure in Huntington's disease is therefore consequential rather than initiating	Inferred	Follows from 16, 17 and 18 taken together; not directly tested by an intervention experiment in human tissue
20	Substrate-driven inhibition of the terminal acidification step, not proteostatic load, is what makes clearance failure causal	Speculative	The paper's own proposal; assembled from 4, 5, 6, 12, 14 and 16; no experiment has yet been designed to test the general form
21	Huntington's disease belongs to a "load without feedback" category distinct from Alzheimer's disease	Speculative	Follows from 20; the category boundary is proposed here and the tauopathy membership is untested
22	Clearance-directed therapy should be applied early in Huntington's disease and preceded by repair of acidification in Alzheimer's disease	Inferred	The early-window recommendation is the staged study's own [8]; the repair-before-induce rule follows from 3, 4, 5 and 6 and is supported by re-acidification results in other contexts [33,34]

9. Predictions

The narrowed claim is worth stating only if it constrains future observation. Eight predictions follow; each is stated so that a contrary result would count against the claim.

P1 — Lysosomal pH in Huntington neurons is normal at pre-degenerative stages.

In patient-derived induced pluripotent stem cell medium spiny neurons carrying expanded repeats, and in Huntington model neurons before overt degeneration, lysosomal pH measured with a ratiometric probe validated for lysosomal compartments [15] will not differ from isogenic controls, whereas the same measurement in presenilin-mutant or β CTF-elevated neurons will show elevation [14,15,16].

P2 — Induction helps early in Huntington models and not late. mTOR inhibition or an equivalent inducer, applied to Huntington models before the appearance of autolysosome and lipofuscin accumulation, will reduce diffuse mutant huntingtin and improve outcome, as reported historically [35]; applied after that accumulation, it will not, and may worsen compartment pathology. The same intervention in an Alzheimer model with demonstrated autolysosome de-acidification will increase autophagic vacuole burden [12,13].

P3 — Re-acidification helps in Alzheimer’s disease and not in Huntington’s disease before late stage. Restoring lysosomal acidity — by acidic nanoparticles [34], by enzyme supplementation [33], or by genetic or pharmacological restoration of v-ATPase assembly [16,21] — will reduce substrate burden in Alzheimer models and will have no effect on mutant huntingtin burden in Huntington models at pre-degenerative stages, because there is nothing to restore.

P4 — Suppressing somatic expansion will alter the Huntington clearance phenotype; enhancing clearance will not alter expansion. An intervention that slows somatic CAG expansion will delay or prevent the late striatal autolysosome and lipofuscin accumulation, because that accumulation is downstream of neuronal decompensation [4,8]. Conversely, an intervention that enhances clearance will not measurably alter the somatic expansion trajectory, because expansion is a DNA-repair process with no known dependence on autophagic flux.

P5 — The regional dissociation will replicate in an independent Huntington cohort. Rising huntingtin and p62 fragments and progressive autophagic vacuole and lipofuscin accumulation will again be found in striatum and not in cortex of the same brains, and will again scale with Vonsattel grade [8]. Failure to replicate the regional dissociation would be the most

economical way to overturn the argument of §6.4.

P6 — Primary tauopathies will show a terminal-step lesion that non-tau degenerations do not. In progressive supranuclear palsy, corticobasal degeneration and Pick’s disease — tauopathies without amyloid precursor protein involvement — staged tissue will show evidence of terminal degradative failure (de-acidified compartments, undegraded substrate within cathepsin-positive compartments) at stages before regional neuronal loss. If instead these disorders resemble Huntington’s disease, with preserved proteolysis and successful compensatory biogenesis until late, then the tauopathy arm of the narrowed claim fails and the claim should contract to Alzheimer’s disease alone.

P7 — Compensatory biogenesis will have opposite predictive value in the two categories. Across diseases, upregulation of lysosomal biogenesis markers will correlate with *maintained* substrate clearance in category III diseases and with *failing* clearance in category II diseases. The same measurement therefore means opposite things depending on category, which is a testable and unusual prediction.

P8 — Clearance-directed agents will show disease-specific rather than pan-neurodegenerative efficacy. If a clearance-enhancing agent enters trials in more than one of these diseases, its effect sizes will not be correlated across them, and specifically an agent effective in Alzheimer’s disease by repairing acidification will be inert in Huntington’s disease. A single agent showing comparable benefit across Alzheimer’s, Parkinson’s and Huntington’s disease would be strong evidence for the strong convergence claim and against this paper.

10. What would refute the narrowed claim

Five results would refute it, in descending order of decisiveness.

R1 — Demonstration of a direct inhibitory interaction between mutant huntingtin (or an N-terminal fragment of it) and the v-ATPase or another component of the terminal degradative step, with the specificity established for APP- β CTF at V0a1. This would place Huntington's disease in category II and destroy the load/feedback distinction as a disease boundary. The experiment is a binding and functional assay of the kind already performed for β CTF [16], run with huntingtin exon 1 fragments of pathogenic and non-pathogenic repeat length.

R2 — A staged human Huntington series, including grade 0 and grade 1 tissue, showing compartment de-acidification or hydrolase inactivation before striatal neuronal loss. This would reverse the ordering on which §5 and §6.4 depend. Grade 0 and 1 tissue is rare but not unobtainable, and the study would be the natural extension of the existing series [5,8].

R3 — Demonstration that clearance enhancement alters the somatic expansion trajectory, or that expansion is autophagy-dependent. If the DNA clock proved to run through the degradative pathway — for example if mismatch-repair component turnover were autophagy-controlled in a way that set expansion rate — then clearance would be upstream of the rate-limiting step after all, and the argument of §6.1 would fail.

R4 — Failure of the regional and stage dissociation to replicate, such that clearance markers in Huntington brain prove abnormal in cortex as well as striatum and at the earliest available grades.

R5 — A clearance-directed intervention producing comparable, mechanism-consistent clinical benefit across Alzheimer's disease and Huntington's disease. This is the therapeutic form of the strong convergence claim, and it is the result the strong claim predicts. It has not been observed; it has also not been properly tested, and that should be conceded.

Two clarifications about what would *not* refute the claim, since the distinction is where most confusion in this literature lies. Finding further autophagy-lysosomal abnormalities in Huntington's disease would not refute it — the claim already concedes that the pathway fails in Huntington's disease, and specifies only when. Nor would demonstrating that clearance enhancement benefits

Huntington models refute it; the staged human data themselves predict benefit, provided it is applied early [8].

II. Therapeutic consequences

11.1 The rule has a sign, and the sign differs by category

In a category II disease, inducing autophagic flux without first restoring the terminal step delivers more cargo to a compartment that cannot process it. This is not a theoretical hazard: increased autophagosome formation and lysosomal biogenesis are already present in Alzheimer CA1 neurons at early disease stages and overburden failing lysosomes, propelling neuritic dystrophy [13]. The prescription is *repair, then induce* — restore v-ATPase assembly or lysosomal acidity, verify the restoration with a pH measurement, and only then consider enhancing flux. Proofs of principle that acidity can be restored exist in other contexts: acidic poly(lactide-co-glycolide) nanoparticles lower lysosomal pH, rescue chloroquine-induced toxicity, restore function in toxin and genetic cellular models and attenuate degeneration in vivo [34]; recombinant pro-cathepsin D is endocytosed, correctly targeted, matured, and restores endo-lysosomal and autophagic function while reducing insoluble substrate [33]; and reducing a tubulin deacetylase that governs V1 recruitment lowers lysosomal pH and reduces both A β and tau pathology in mice [21]. None of these is a clinical agent. All of them address the correct step.

In a category III disease, the machinery is intact and induction is the rational intervention — but only while it is intact. The staged human data make this recommendation explicitly: stimulation applied at early stages, when the clearance machinery is fully competent, could yield therapeutic benefit [8]. The corresponding negative prediction is that the same intervention applied at grade 3 or 4, into striatum already carrying accumulated autophagic vacuole and lipofuscin granules, will do little. The historical demonstration that mTOR inhibition reduces polyglutamine toxicity in fly and mouse models [35] was performed in young animals — that is, in the early window the human data now identify — which is consistent rather than coincidental.

11.2 The limit of clearance therapy in Huntington's disease

There is a harder implication that follows from §6.1 and that should be stated even though it is unwelcome. If the rate-limiting step in Huntington's disease is somatic repeat expansion in striatal projection neurons, and if neurons become acutely vulnerable only after crossing a somatic threshold near 150 repeats [4], then no clearance-directed intervention can address the disease's driver. It can at best raise the threshold at which a given somatic repeat length becomes lethal, or extend the interval over which an expanding neuron remains functional. That may be a substantial clinical benefit — extending the pre-threshold interval is precisely what a disease-modifying therapy for Huntington's disease would need to do — but it is a modifier's benefit, not a cure's, and it should be presented as such.

The same logic explains why huntingtin-lowering is the more direct strategy and why its difficulty has been in execution rather than in concept. The phase 3 evaluation of the antisense oligonucleotide tominersen in manifest Huntington's disease was stopped early after the drug failed to show benefit over placebo and, at the highest dose, was associated with worse outcomes [36,37]. Whatever the explanation — dose, the consequences of lowering wild-type huntingtin, which is itself a selective-autophagy scaffold [24], or intervention at too late a stage — the episode is a caution against the assumption that acting on the named protein is automatically the right move, and it is an argument for interventions timed against the somatic-expansion clock rather than against clinical onset.

11.3 Why a pan-neurodegenerative clearance drug is not implied

The strong convergence claim's most attractive corollary was that a single agent acting on clearance would benefit four diseases. The narrowed claim withdraws that corollary and replaces it with something more modest and more defensible: agents that *restore degradative capacity* should benefit category I and category II diseases and should be inert in category III until late; agents that *increase flux* should benefit category III early and should be neutral or harmful in category II. Trials designed on the undifferentiated claim — a flux enhancer taken into a de-acidified Alzheimer brain, or a re-acidifier taken into a competent Huntington striatum — would be predicted to fail for reasons that have nothing to do with the compounds.

12. Limitations

A single staged series carries the central negative finding. The Huntington evidence rests principally on one human study [8]. Its stage range begins at HD2, its measurements are made on fixed tissue, and its inference of preserved proteolysis rests on the presence of cathepsin-positive autolysosomes and cargo-loaded autophagosomes rather than on a direct rate measurement. A second, independent staged series — ideally including grade 0 and 1 tissue — is the most important missing piece, and the argument here should be regarded as provisional until it exists.

Absence of a block is weaker evidence than presence of one. This has been stated in §2.3 and is repeated because it is the strongest objection. A modest reduction in throughput that has not yet redistributed the compartment census would be invisible to this design, and would soften — though not reverse — the ordering argument.

The category boundaries are proposed, not derived. The four-category taxonomy of §7.3 is an organising proposal of this paper. It is graded speculative in Table 3 and should not be treated as an established classification. Its value is that it generates the predictions of §9 and the refutation conditions of §10; if those fail, the taxonomy should be discarded.

Parkinson’s disease and the ALS–frontotemporal spectrum are not placed. I have deliberately declined to assign them. The evidence needed is staged human tissue with the same regional-internal-control design, and it does not exist for either.

The tauopathy arm is an extrapolation. It rests on one strong mechanistic result about chaperone-mediated autophagy and acetylated tau [20] and one single-laboratory acidification result [21]. It is the part of the narrowed claim most likely to require revision, and P6 is the prediction on which it stands or falls.

Some evidence is assessed from abstracts and published summaries. The tominersen outcome is taken from the trial correspondence [36] and a review of genetically targeted trials [37] rather than from full supplementary data.

The historical literature is uneven. The autophagic phenotype of Huntington’s disease has been studied far more in models than in staged human tissue, while the Alzheimer’s phenotype has been studied in both. Some of the apparent asymmetry between the two diseases may reflect an asymmetry of effort rather than of biology, and the argument would be strengthened by a Huntington literature of comparable depth.

13. Conclusion

The proposition that neurodegenerative diseases converge on a single failure of intracellular clearance has been useful and is partly true. Its strong form — that clearance failure is the early, causal, shared lesion across Alzheimer’s, Parkinson’s, the ALS–frontotemporal spectrum and Huntington’s disease — does not survive contact with staged human Huntington brain, in which lysosomal biogenesis is upregulated, proteolysis is preserved, autophagosome formation and fusion are not significantly blocked, and substrate clearance fails only at advanced stages and predominantly in the striatum that has already lost most of its neurons [8].

The correct response is to narrow the claim rather than to defend it, and the narrowing is principled. What makes clearance failure causal in Alzheimer’s disease is not that the disease produces a difficult substrate — every proteinopathy does that — but that the substrate binds and jams the pump that is supposed to degrade it, at the terminal acidification step, while the gene required to build that pump is the gene whose mutations cause the dominant familial form [14,16]. Load and capacity are therefore coupled, the system has positive feedback, and compensatory biogenesis fails because every compensatory route ends at the same de-acidified compartment. Huntington’s disease has no such coupling. Its wild-type gene product is a scaffold for the very pathway in question [24]; its mutation subtracts cargo-recognition efficiency rather than adding an inhibitor [7]; its compensations work [23]; its aggregation is protective [25]; and its rate-limiting step is a DNA process in the nucleus that clearance biology does not touch [4,29].

The narrowed claim is a smaller thing than the slogan it replaces. It covers one disease securely and a family of tauopathies provisionally. It makes a definite negative assertion about the disease most often cited as its fourth pillar. It predicts that the same measurement — upregulated lysosomal biogenesis — means opposite things in the two categories. And it can be refuted, most directly by demonstrating a huntingtin–v-ATPase interaction with the specificity already established for the amyloid precursor protein fragment, or by finding compartment de-acidification in grade 0 and grade 1 Huntington striatum.

A framework that explains four diseases without being able to fail is worth less than one that explains one and a half and can. The staged Huntington data were produced by the laboratory that built the clearance account, and they constrain it. That is how the boundary of a theory is supposed to be found.

References

1. Nixon RA, Rubinsztein DC. Mechanisms of autophagy-lysosome dysfunction in neurodegenerative diseases. *Nature Reviews Molecular Cell Biology*. 2024;25(11):926–946. PMID 39107446.
2. Nixon RA. The role of autophagy in neurodegenerative disease. *Nature Medicine*. 2013;19(8):983–997. PMID 23921753.
3. Lee JM, Ramos EM, Lee JH, Gillis T, Mysore JS, Hayden MR, Warby SC, Morrison P, et al. CAG repeat expansion in Huntington disease determines age at onset in a fully dominant fashion. *Neurology*. 2012;78(10):690–695. PMID 22323755.
4. Handsaker RE, Kashin S, Reed NM, Tan S, Lee WS, McDonald TM, Morris K, Kamitaki N, Mullally CD, Morakabati NR, Goldman M, Lind G, Kohli R, Lawton E, Hogan M, Ichihara K, Berretta S, McCarroll SA. Long somatic DNA-repeat expansion drives neurodegeneration in Huntington’s disease. *Cell*. 2025;188(3):623–639.e19. PMID 39824182.
5. Vonsattel JP, Myers RH, Stevens TJ, Ferrante RJ, Bird ED, Richardson EP. Neuropathological classification of Huntington’s disease. *Journal of Neuropathology and Experimental Neurology*. 1985;44(6):559–577. PMID 2932539.
6. Rüb U, Vonsattel JPV, Heinsen H, Korf HW. The neuropathology of Huntington’s disease: classical findings, recent developments and correlation to functional neuroanatomy. *Advances in Anatomy, Embryology and Cell Biology*. 2015;217:1–146. PMID 26767207.
7. Martinez-Vicente M, Talloczy Z, Wong E, Tang G, Koga H, Kaushik S, de Vries R, Arias E, Harris S, Sulzer D, Cuervo AM. Cargo recognition failure is responsible for inefficient autophagy in Huntington’s disease. *Nature Neuroscience*. 2010;13(5):567–576. PMID 20383138.
8. Berg MJ, Veeranna, Rosa CM, Kumar A, Mohan PS, Stavrides P, Darji S, Marchionini DM, Yang DS, Nixon RA. Pathobiology of the autophagy-lysosomal pathway in the Huntington’s disease brain. *Acta Neuropathologica Communications*. 2025;13(1):228. PMID 41204380.
9. Cataldo AM, Barnett JL, Pieroni C, Nixon RA. Increased neuronal endocytosis and protease delivery to early endosomes in sporadic Alzheimer’s disease: neuropathologic evidence for a mechanism of increased β -amyloidogenesis. *Journal of Neuroscience*. 1997;17(16):6142–6151. PMID 9236226.

10. Cataldo AM, Peterhoff CM, Troncoso JC, Gomez-Isla T, Hyman BT, Nixon RA. Endocytic pathway abnormalities precede amyloid β deposition in sporadic Alzheimer's disease and Down syndrome: differential effects of APOE genotype and presenilin mutations. *American Journal of Pathology*. 2000;157(1):277–286. PMID 10880397.
11. Nixon RA, Wegiel J, Kumar A, Yu WH, Peterhoff C, Cataldo A, Cuervo AM. Extensive involvement of autophagy in Alzheimer disease: an immuno-electron microscopy study. *Journal of Neuropathology and Experimental Neurology*. 2005;64(2):113–122. PMID 15751225.
12. Boland B, Kumar A, Lee S, Platt FM, Wegiel J, Yu WH, Nixon RA. Autophagy induction and autophagosome clearance in neurons: relationship to autophagic pathology in Alzheimer's disease. *Journal of Neuroscience*. 2008;28(27):6926–6937. PMID 18596167.
13. Bordi M, Berg MJ, Mohan PS, Peterhoff CM, Alldred MJ, Che S, Ginsberg SD, Nixon RA. Autophagy flux in CA1 neurons of Alzheimer hippocampus: increased induction overburdens failing lysosomes to propel neuritic dystrophy. *Autophagy*. 2016;12(12):2467–2483. PMID 27813694.
14. Lee JH, Yu WH, Kumar A, Lee S, Mohan PS, Peterhoff CM, Wolfe DM, Martinez-Vicente M, et al. Lysosomal proteolysis and autophagy require presenilin 1 and are disrupted by Alzheimer-related PS1 mutations. *Cell*. 2010;141(7):1146–1158. PMID 20541250.
15. Wolfe DM, Lee JH, Kumar A, Lee S, Orenstein SJ, Nixon RA. Autophagy failure in Alzheimer's disease and the role of defective lysosomal acidification. *European Journal of Neuroscience*. 2013;37(12):1949–1961. PMID 23773064.
16. Im E, Jiang Y, Stavrides PH, Darji S, Erdjument-Bromage H, Neubert TA, Choi JY, Wegiel J, Lee JH, Nixon RA. Lysosomal dysfunction in Down syndrome and Alzheimer mouse models is caused by v-ATPase inhibition by Tyr-phosphorylated APP β CTF. *Science Advances*. 2023;9(30):eadg1925. PMID 37494443.
17. Lee JH, Yang DS, Goulbourne CN, Im E, Stavrides P, Pensalfini A, Chan H, Bouchet-Marquis C, et al. Faulty autolysosome acidification in Alzheimer's disease mouse models induces autophagic build-up of A β in neurons, yielding senile plaques. *Nature Neuroscience*. 2022;25(6):688–701. PMID 35654956.
18. Nixon RA. Amyloid precursor protein and endosomal–lysosomal dysfunction in Alzheimer's disease: inseparable partners in a multifactorial disease. *FASEB Journal*. 2017;31(7):2729–2743. PMID 28663518.
19. Bellenguez C, Küçükali F, Jansen IE, Kleindam L, Moreno-Grau S, Amin N, Naj AC, Campos-Martin R, et al. New insights into the genetic etiology of Alzheimer's disease and related dementias. *Nature Genetics*. 2022;54(4):412–436. PMID 35379992.

20. Caballero B, Bourdenx M, Luengo E, Diaz A, Sohn PD, Chen X, Wang C, Juste YR, et al. Acetylated tau inhibits chaperone-mediated autophagy and promotes tau pathology propagation in mice. *Nature Communications*. 2021;12(1):2238. PMID 33854069.
21. Ge C, Wang K, Tang H, Ke Y, Wang H, Fu Q, Xiu Y, Guo Y, Jia YF, Long Z, He G, Tang Q. NDS1 suppresses lysosomal acidification and ameliorates amyloid- β and MAPT/tau pathology in Alzheimer's disease. *Translational Neurodegeneration*. 2026;15(1). PMID 42015299.
22. The Huntington's Disease Collaborative Research Group. A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. *Cell*. 1993;72(6):971–983. PMID 8458085.
23. Koga H, Martinez-Vicente M, Arias E, Kaushik S, Sulzer D, Cuervo AM. Constitutive upregulation of chaperone-mediated autophagy in Huntington's disease. *Journal of Neuroscience*. 2011;31(50):18492–18505. PMID 22171050.
24. Rui YN, Xu Z, Patel B, Chen Z, Chen D, Tito A, David G, Sun Y, Stimming EF, Bellen HJ, Cuervo AM, Zhang S. Huntingtin functions as a scaffold for selective macroautophagy. *Nature Cell Biology*. 2015;17(3):262–275. PMID 25686248.
25. Arrasate M, Mitra S, Schweitzer ES, Segal MR, Finkbeiner S. Inclusion body formation reduces levels of mutant huntingtin and the risk of neuronal death. *Nature*. 2004;431(7010):805–810. PMID 15483602.
26. Genetic Modifiers of Huntington's Disease (GeM-HD) Consortium. Identification of genetic factors that modify clinical onset of Huntington's disease. *Cell*. 2015;162(3):516–526. PMID 26232222.
27. Maiuri T, Hung CLK, Stuart C, Begeja N, Barba-Bazan C, Peng Y, Savic N, Wong T, Truant R. DNA repair in Huntington's disease and spinocerebellar ataxias: somatic instability and alternative hypotheses. *Journal of Huntington's Disease*. 2021;10(1):165–173. PMID 33579859.
28. Genetic modifiers of somatic expansion and clinical phenotypes in Huntington's disease highlight shared and tissue-specific effects. *Nature Genetics*. 2025;57(6):1426–1436. PMID 40490511.
29. Mätlik K, Baffuto M, Kus L, Deshmukh AL, Davis DA, Paul MR, Carroll TS, Caron MC, Masson JY, Pearson CE, Heintz N. Cell-type-specific CAG repeat expansions and toxicity of mutant huntingtin in human striatum and cerebellum. *Nature Genetics*. 2024;56(3):383–394. PMID 38291334.

30. Scahill RI, Zeun P, Osborne-Crowley K, Johnson EB, Gregory S, Parker C, Lowe J, Nair A, et al. Biological and clinical characteristics of gene carriers far from predicted onset in the Huntington's disease Young Adult Study (HD-YAS): a cross-sectional analysis. *Lancet Neurology*. 2020;19(6):502–512. PMID 32470422.
31. Huin V, Barbier M, Bottani A, Lobrinus JA, Clot F, Lamari F, Chat L, Rucheton B, et al. Homozygous GRN mutations: new phenotypes and new insights into pathological and molecular mechanisms. *Brain*. 2020;143(1):303–319. PMID 31855245.
32. Sidransky E, Nalls MA, Aasly JO, Aharon-Peretz J, Annesi G, Barbosa ER, Bar-Shira A, Berg D, et al. Multicenter analysis of glucocerebrosidase mutations in Parkinson's disease. *New England Journal of Medicine*. 2009;361(17):1651–1661. PMID 19846850.
33. Prieto Huarcaya S, Drobny A, Marques ARA, Di Spiezio A, Dobert JP, Balta D, Werner C, Rizo T, et al. Recombinant pro-CTSD (cathepsin D) enhances SNCA/ α -synuclein degradation in α -synucleinopathy models. *Autophagy*. 2022;18(5):1127–1151. PMID 35287553.
34. Bourdenx M, Daniel J, Genin E, Soria FN, Blanchard-Desce M, Bezard E, Dehay B. Nanoparticles restore lysosomal acidification defects: implications for Parkinson and other lysosomal-related diseases. *Autophagy*. 2016;12(3):472–483. PMID 26761717.
35. Ravikumar B, Vacher C, Berger Z, Davies JE, Luo S, Oroz LG, Scaravilli F, Easton DF, Duden R, O'Kane CJ, Rubinsztein DC. Inhibition of mTOR induces autophagy and reduces toxicity of polyglutamine expansions in fly and mouse models of Huntington disease. *Nature Genetics*. 2004;36(6):585–595. PMID 15146184.
36. McColgan P, Thobhani A, Boak L, Schobel SA, Nicotra A, Palermo G, Trundell D, Zhou J, et al. Tominersen in adults with manifest Huntington's disease. *New England Journal of Medicine*. 2023;389(23):2203–2205. PMID 38055260.
37. Imbimbo BP, Triaca V, Imbimbo C, Nisticò R. Investigational treatments for neurodegenerative diseases caused by inheritance of gene mutations: lessons from recent clinical trials. *Neural Regeneration Research*. 2023;18(8):1679–1683. PMID 36751779.