
The Silencer and the Tether

*Bess Frost's Chromatin Programme, the Elements It Releases,
and the Restraint on cGAS It Would Remove*

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*Relaxing heterochromatin does not only release what it silenced. It loosens what it was
holding.*

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Abstract

In June 2022 the University of Texas at San Antonio awarded four gold Oskar Fischer Prizes of \$500,000 each. One went to Bess Frost, for the proposition that neurodegeneration in Alzheimer's disease and related tauopathies follows from what pathogenic tau does to the three-dimensional packaging of DNA, and from what that in turn does to a neuron's ability to hold its own identity¹. The entry itself was never published. There is no title, no text, no deposited document; the nearest published proxy is a sole-author review written the following year².

This paper takes that thesis seriously enough to test it, and then asks a question it does not ask itself. If pathogenic tau relaxes heterochromatin, two things follow that the programme has treated as one. The first is that silenced repetitive sequence is released, which supplies nucleic acid a cytosolic sensor could read — the *ligand*. The second, entirely separate, is that the nucleosome landscape on which cyclic GMP-AMP synthase sits inert is itself degraded, which would release the enzyme — the *tether*. The programme has pursued the first and has never considered the second, because the second was not known when the programme began: the structural basis of cGAS restraint by the nucleosome was published in 2020³, six years after the founding paper⁴.

We then propose a third element neither arm contains. cGAS-deficient mice age prematurely and show de-repression of LINE-1 elements and a smoothed heterochromatin landscape⁵. If that is right, the enzyme helps maintain the very structure that holds it inactive. Tau relaxes chromatin; chromatin relaxation frees the enzyme; a freed enzyme no longer maintains chromatin; more sequence escapes. We name this the Silencer–Tether loop, state it as a hypothesis with four identified points of failure, and give the experiments that would break it.

Three findings complicate all of this and are stated at the front rather than buried. The only demonstrated sensor for tau-driven element-derived nucleic acid in a mammalian neuron is ZBP1, not cGAS⁶. The direction of the human chromatin change in Alzheimer's disease is disputed, with at least two human studies reporting that the repressive mark H3K9me3 is *increased*^{7, 8}. And no laboratory has ever measured cGAS localisation, chromatin occupancy or nucleosome tethering in a neuron of any species. The tether arm of this paper is therefore a prediction. It is presented as one.

1. A Prize Without a Document

The Oskar Fischer Prize was an unusual instrument. It asked for explanations of Alzheimer's disease rather than for experiments, judged whole theories rather than results, and paid for them. In June 2022 four gold awards of \$500,000 were made, to Carlo Abbate, Estela Area-Gomez, Bess Frost and Ralph Nixon ¹. The awarding institution summarised Frost's submission in one sentence: that neurodegeneration in Alzheimer's disease and related tauopathies results from the consequences of pathogenic forms of tau for the three-dimensional packaging of DNA, and that this restructuring affects the cellular identity of brain cells and drives their death.

That sentence is all there is. The entry was not published, is not indexed, and has no title in the public record. A prize was given for a document nobody outside the committee has read. What exists instead is a published body of work, some of it before the award and some after, and one sole-author review that argues the same thesis at length: that Alzheimer's disease and related tauopathies are disorders of disrupted neuronal identity ². Throughout this paper that review is treated as the best available proxy, and never as the entry itself. Its claims are graded by the primary work beneath them, not by the fact of the prize.

The programme it summarises has four arms, and they were not built in the order in which they are usually presented. The first was chromatin: a 2014 paper reporting that pathogenic tau causes global relaxation of heterochromatin and that restoring heterochromatin in the fly reduces degeneration ⁴. The second was the nuclear lamina, framed as an acquired laminopathy by analogy to progeria ⁹. The third was transposable elements — the sequences that heterochromatin exists to silence — and their release as the toxic consequence of relaxation ^{10, 11}. The fourth was RNA metabolism more broadly ¹². A fifth, therapeutic, arm followed from the third: if the elements are reactivated and reverse-transcribed, a reverse-transcriptase inhibitor should help ¹³.

This paper is about the junction between the third arm and something outside the programme entirely. Alzheimer's disease has a well-documented innate-immune component; cyclic GMP-AMP synthase and its adaptor are

among the most-discussed molecules in that literature^{14, 15, 16}. If tau relaxes chromatin and releases silenced repetitive sequence, then the chromatin programme is producing, as a by-product, exactly the class of molecule that this sensor exists to detect. That connection has been made in outline by third parties¹⁷ and never worked out.

There is a second connection, and it has not been made at all. A word on why we are not starting from the immunology. The downstream signature — interferon-stimulated gene induction — cannot identify the sensor that produced it, because three unrelated adaptors converge on the same transcription factor through the same phosphorylation motif¹⁸. Any argument that runs from an interferon signature backwards to cGAS is invalid on its face. The argument in this paper therefore runs forwards, from chromatin, and is tested at each link rather than at the end.

One further piece of housekeeping. Two attributions circulate in this area and both are wrong. The founding paper is Frost, Hemberg, Lewis and Feany; Michael Hutton was an author on the original fly tauopathy model¹⁹, not on the chromatin paper. And the 2018 human study linking tangle burden to retrotransposon expression across 636 brains is from Joshua Shulman's laboratory²⁰, not Frost's — which makes it one of the most important independent results in the programme's favour, and it is routinely miscredited in a way that erases that independence.

2. The Claim, Stated as a Chain

A theory is easier to assess when it is written as a sequence of links, each of which could be false on its own. The chromatin programme, as its own reviews state it^{2, 21}, is the following chain.

Link 1. Pathogenic tau accumulates and stabilises filamentous actin²².

Link 2. Excess stable actin uncouples the cytoskeleton from the nucleoskeleton, mislocalising lamin and expanding the nucleoplasmic reticulum²³.

Link 3. Nuclear architecture having failed, heterochromatin relaxes: repressive marks are lost and silenced regions open⁴.

Link 4. Sequence that heterochromatin was silencing is transcribed — in particular transposable elements, their silencing further degraded by loss of a small-RNA pathway²⁴.

Link 5. Element transcripts, and any DNA made from them, are toxic; neurons die; cognition follows²⁵.

Each link has a different evidential character, and the differences are large. Link 1 is causal in fly with bidirectional genetic control and observational in mouse. Link 2 is causal in fly. Link 3 is causal in fly, corroborative in mouse, and correlational in human. Link 4 is causal in fly for the small-RNA arm, correlational in human, and — in its strongest independent form — causal in mouse with a different mechanism⁶. Link 5 has no demonstration in Alzheimer's tissue at all.

This paper adds two links the programme does not contain, and it is important to be clear that they are additions rather than readings.

Link 3a — the ligand. If Link 3 holds, the neuron's cytoplasm may acquire repeat-derived nucleic acid. Part II asks whether the measurements that report this are capable of supporting it.

Link 3b — the tether. Independently of Link 4, if Link 3 holds then the nucleosome landscape itself is altered. That matters because cGAS in a resting cell is not a cytosolic sentinel awaiting misplaced DNA; it is predominantly nuclear and held inactive by direct binding to the nucleosome acidic patch^{26, 27}. A change in that landscape is, in principle, a change in the restraint. Part III asks what is actually known about this, and the answer is that a great deal is known in dividing cells and nothing at all in neurons.

Link 3c — the loop. If cGAS itself contributes to maintaining heterochromatin — and the cGAS-null mouse is reported to show de-repressed LINE-1 elements and a smoothed heterochromatin landscape⁵ — then Links 3, 3a and 3b are not a chain but a cycle. Part IV states that cycle and tries to break it.

Two framing decisions follow. First, we do not treat "cGAS-STING is activated in Alzheimer's disease" as a premise. It is a downstream observation with at least four candidate upstream sources, and the interferon readout cannot discriminate between them¹⁸. Second, we do not treat the fly as a weak version of the mouse. The fly is where the causal genetics are, and the causal genetics are the strongest part of the programme; the weakness is that almost

nothing in the mammalian or human arm reproduces the *mechanism*, as opposed to the *phenotype*.

3. Three Facts That Complicate It Before It Is Stated

A synthesis that arranges its inconvenient findings at the end has already decided its conclusion. The three below are placed here, before the argument, because each is capable of defeating a portion of it.

First: the demonstrated sensor is ZBP1, not cGAS. In 2026 a fully independent group — Zhejiang, Xiamen and Tsinghua, with no author from the Frost, Feany, Dubnau or Shulman laboratories — reported the most complete version of this chain that exists in a mammal ⁶. In PS19 mice, tau aggregates bind H3K9me3-marked chromatin and sequester the mark away from HP1, constitutive heterochromatin decondenses, transposable elements are de-repressed, the resulting endogenous Z-form RNAs activate ZBP1, and neurons die. This is a stronger result than anything in the programme's own mammalian work. It independently reproduces the heterochromatin premise, the element-reactivation step, and the nucleic-acid-to-innate-immune-death axis — and the sensor it identifies is not the one this paper is about, and the mechanism of relaxation it identifies is not the one the founding paper proposed. Any argument for cGAS here must explain why a second sensor is needed when one has already been demonstrated, and must accept that Z-RNA sensing is now the incumbent hypothesis rather than the challenger.

Second: the direction of the human chromatin change is disputed. The founding paper reports heterochromatin loss in post-mortem Alzheimer's brain, by immunostaining of H3K9me2 and HP1 with de-repression inferred from bulk transcriptomics ⁴. At least two independent human studies report the opposite for H3K9me3: elevated condensation in sporadic Alzheimer's cortex, supported by chromatin immunoprecipitation sequencing ⁷, and increased global H3K9me3 in orbitofrontal cortex at early stages with loss only late ⁸. A third, in dentate granule cells, finds the same early increase ²⁸. Neither of the first two frames itself as a refutation and neither cites the conflict, which is itself worth noticing. The reconciliations one would reach

for — different marks, different regions, different stages, cell-type heterogeneity, antibody and assay differences, neuronal dilution by glia in bulk tissue — are tested by none of these papers. The most consequential version of this problem is therapeutic: in a tau mouse, the repressive mark H3K9me2 and its methyltransferase are elevated, and an inhibitor that *reduces* repressive marks rescues behaviour²⁹. That is the exact opposite prescription to the one the programme implies.

Third: cGAS tethering has never been measured in a neuron. This is a negative, and it was established by direct search rather than assumed. Every published study of nuclear cGAS tethering used dividing cells — dendritic cells, HeLa, U2OS, embryonic stem cells — or purified components^{26, 30, 3}. Every study that localises cGAS activity in brain places it in microglia or astrocytes³¹. There is no published measurement of cGAS subcellular localisation, chromatin occupancy or nucleosome association in a neuron of any species. The tether arm of this paper is therefore not a re-reading of existing data. It is a prediction about an unmeasured quantity, and it is labelled as one wherever it appears.

Three further negatives belong with these, stated once here and used throughout. No laboratory other than the originating one has reported piwi or piRNA depletion in a tau model or in tauopathy brain²⁴. No study has demonstrated validated somatic element insertions in Alzheimer's neurons; the entire human literature is transcript-, protein- or copy-number-based. And no paper shows DNA or nucleosomes in the cytoplasm of a neuron by any route — not budding³², not nucleophagy³³, not rupture.

4. How Evidence Is Graded Here

Every factual claim in this paper carries one of four labels, applied explicitly at the point of use and collected in the ledger at the end.

Established — demonstrated by direct measurement, with a control that could have produced the opposite result, and reproduced by at least one group with no shared senior author. Example: tau is present in nuclei isolated from human brain ³⁴.

Proposed — asserted by at least one primary study, with the experiment that would confirm it identifiable and not yet done, or done only in a system that cannot answer for the one in question. Example: nuclear-envelope invaginations in tauopathy serve an RNA-export function ³⁵.

Unevidenced — no primary measurement exists in any system relevant to the claim. Example: the chromatin occupancy of cGAS in a neuron. Novel integrations advanced in this paper begin here by definition and are marked as such.

Contradicted — at least one adequately powered study reports a result inconsistent with the claim, and the inconsistency is unresolved. Example: the direction of the H3K9me3 change in human Alzheimer's cortex ⁷.

Three axes are recorded alongside every experimental claim, because in this literature they carry more information than the claim itself.

Species. *Drosophila*, mouse, human post-mortem, human induced neuron, human clinical. The programme's causal architecture is almost entirely invertebrate; its mammalian and human components are almost entirely observational. Both halves of that sentence matter and neither is a criticism on its own.

Cell state. Dividing or post-mitotic. This distinction does more work in this paper than any other. A dividing cell rebuilds its nuclear envelope and re-lays its chromatin at every mitosis; a neuron does neither, and its nuclear pore scaffolds and lamins are among the longest-lived proteins in the body ^{36, 37}. Mechanisms that require replication stress, mitotic missegregation or micronucleus formation are simply unavailable to a neuron, and a large

fraction of the cGAS literature is built on exactly those mechanisms^{38, 39}. Whenever a result is imported from a dividing cell, it is marked D, and the import is argued rather than assumed.

What was measured. Transcript, protein, DNA copy number, integrated insertion, chromatin mark, occupancy, phenotype. The distinction between transcript and insertion, and between copy number and integration, is the hinge of Part II, and the literature blurs it constantly⁴⁰.

Two conventions about negatives. First, a failure to find something in a systematic search is reported as a failure of search, not as proof of absence — but the searches behind the negatives in Chapter 3 were direct and returned nothing, and a claim that cannot be supported after a direct search is not available for use as a premise. Second, negative and contradictory results are given the same prominence as positive ones, in the body rather than in a limitations paragraph. Where a replication failed, it is named⁴¹. Where a correction or erratum exists, it is cited alongside the original^{42, 43, 44, 45}.

Finally, a note on what this paper is not. It is not a review of the Alzheimer's innate-immunity literature, which has been reviewed elsewhere⁴⁶. It is not a defence of the chromatin programme, and it is not an attack on it. It is an attempt to determine which parts of it will bear weight, and to work out what follows if the parts that bear weight are joined to a body of structural biology that the programme has not yet met.

Part I

The Silencer

*The chromatin programme evaluated as a body of evidence:
what each experiment shows, in which species, and what has
been independently reproduced*

5. The Founding Experiment, Arm by Arm

The 2014 paper is the load-bearing document of the whole programme, and it is better than its critics allow and weaker than its citations imply ⁴. It has three arms and they should be read separately, because only one of them is causal.

The fly arm. In *Drosophila* expressing human tau, heterochromatin is lost: repressive marks and HP1 decline, and genes normally held silent are transcribed. The causal work is genetic. Restoring heterochromatin — by manipulating the machinery that establishes it — reduces neurodegeneration. Upstream, the paper places oxidative stress and DNA damage: reactive species generated by tau-driven mitochondrial dysfunction damage DNA, and the damage response relaxes chromatin. That upstream link is not invented for the occasion; it comes from the same laboratory's earlier work showing that excess stabilised actin impairs mitochondrial fission ⁴⁷, and from a parallel paper placing p53 and the DNA-damage response at the centre of tau toxicity in the same model ⁴⁸. As fly genetics this is a coherent, internally controlled argument, and it is the part of the programme that has held up best.

The mouse arm. Tau transgenic mice show the same direction of change in heterochromatin marks. This is corroborative rather than causal: no manipulation restores heterochromatin in the mouse and asks whether degeneration abates. That experiment has still not been done, twelve years later, by anyone.

The human arm. Post-mortem Alzheimer's brain shows reduced H3K9me2 and HP1 by immunostaining, and bulk transcriptomic analysis shows that genes lying in heterochromatically silenced regions are over-represented among those de-repressed. This is the arm that is cited as though it were the finding, and it is the weakest of the three. Immunostaining of post-mortem tissue for a repressive mark is quantitatively fragile; the transcriptomic inference is bulk tissue, in a disease that changes cell composition dramatically; and no manipulation is possible. It is an association, and the paper says so.

What the paper does not do — and this is a point in its favour rather than against it — is claim that the human arm establishes causation. That claim was made later, by the field, in citation.

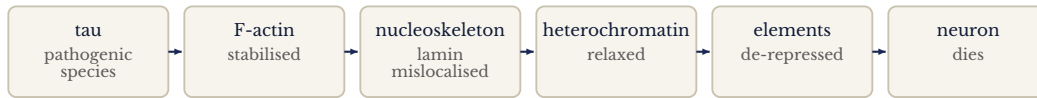
Two other features deserve recording. First, there is no correction, erratum or retraction on this paper, and none on any paper in the programme; the checks were made against comment-and-correction records for every major primary paper. Second, it is heavily cited, and the citations are overwhelmingly affirmative. This matters for a reason that will recur: a claim can be widely believed, never retracted, and still never independently tested in the system that matters.

The strongest independent corroboration of the fly arm comes from a laboratory with no connection to either the Feany or the Frost groups, in India, which reproduced tau-induced heterochromatin relaxation in fly and identified a genetic modifier that suppresses both the relaxation and the degeneration⁴⁹, with a companion result on a second modifier pointing the same way⁵⁰. That is real independent replication of Link 3 — in the fly.

6. What the Fly Carries and What It Cannot

The entire causal architecture of this programme sits on one model organism, and on one paper within it. In 2001 the Feany laboratory showed that expressing human tau in *Drosophila* produces progressive, adult-onset neurodegeneration *without* neurofibrillary tangles¹⁹. That negative result is what licensed everything afterwards: if degeneration does not require the aggregate, then some non-aggregate function of tau must be doing the damage, and the search for it is legitimate.

The chain as the programme states it

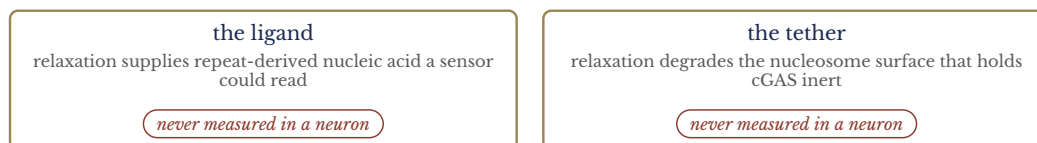


What each link rests on

	fly, causal	mammal, causal	human	independent
tau stabilises F-actin <i>the disease-brain rods are a different object</i>	✓	✗	✗	○
actin uncouples the nucleoskeleton <i>no mammalian test of the mechanism</i>	✓	✗	✗	✗
heterochromatin relaxes <i>two fly replications; human direction disputed</i>	✓	○	○	✓
silencing layer fails (piRNA) <i>unreplicated in eight years</i>	✓	✗	✗	✗
elements are de-repressed <i>measurement cannot exclude passenger reads</i>	✓	✓	○	✓
element nucleic acid kills the neuron <i>shown in mouse — through ZBP1, not cGAS</i>	✓	✓	✗	✓

An open circle marks a single unreplicated study; a cross marks a demonstration the argument needs and no paper supplies.

The two links this paper adds



Neither addition is a reading of existing data. Both are predictions, and both are labelled as such throughout.

Figure 1. The chromatin programme is a sequence of links, each of which can fail on its own. Every causal demonstration in the sequence is invertebrate; every human demonstration is correlational; and the one complete mammalian chain was built by an unconnected laboratory, by a different mechanism, and ends at a different sensor. The two links this paper adds are shown below the sequence, and neither has been measured in any neuron. Sources: 4, 22, 23, 24, 20, 6.

The fly is a genuinely powerful instrument here, and three properties make it so. Neurons in the adult fly brain are post-mitotic, which removes the dividing-cell confound that contaminates most of the chromatin and innate-immunity literature. Genetic manipulation is cheap enough that a claim can be tested bidirectionally — increase the factor, decrease it, and see whether degeneration follows the factor. And lifespan is short enough that

age-dependent processes can actually be observed, which is why the first demonstration that transposable elements activate with age and that this tracks memory loss and lifespan was made in flies, by Dubnau's group, and independently of tau⁵¹. The same laboratory later showed element activation contributing causally to degeneration in a fly model of a different proteinopathy, rescued by pharmacological reverse-transcriptase inhibition⁵² — which is where the therapeutic logic later applied to Alzheimer's actually originates.

The methodological ceiling for fly work in this lineage was set by a 2018 paper that used site-directed insertion to equalise expression across five disease mutations and analysed both sexes⁵³. That is the standard against which a fly causal claim should be read, and not every paper in the programme meets it.

What the fly cannot carry is more specific than "it is not a human". Three things.

It does not have the same silencing machinery. Even in the fly, the brain does not silence transposable elements the way the gonad does: in larval brain the job is done by a small-interfering-RNA and Argonaute pathway, not by piRNAs⁵⁴. A fly result about piwi in neurons therefore does not transfer to the mammalian brain by way of "flies use piRNAs", because in the relevant tissue they largely do not.

It does not have the same elements. The retroelement that propagates degeneration between cells in the fly is an infectious-capable endogenous retrovirus with no direct human counterpart⁵⁵. Findings about it are about a biology humans do not have.

It does not have cGAS. This is decisive for the present argument. Insect innate immunity uses a cyclic-dinucleotide-based system with deep homology to the vertebrate one, but the specific arrangement in which a nucleotidyltransferase sits on nucleosomes and is held inactive is a vertebrate arrangement⁵⁶. Nothing about the tether can be learned in a fly.

The honest summary is that the fly establishes that chromatin relaxation can be causal for neurodegeneration in a post-mitotic neuron. It does not establish that it is causal in a human neuron, and it cannot address the enzyme this paper is about.

7. From Actin to the Nucleoskeleton

Link 1 of the chain is that pathogenic tau stabilises filamentous actin. The source is a 2007 paper showing tau-induced F-actin accumulation and actin-rich rods in fly and mouse tauopathy models, with bidirectional genetic modulation of actin levels modifying degeneration in the expected direction ²². As fly genetics it is strong. Two caveats follow it everywhere and are usually dropped.

The first is that it is from the same laboratory that later produced the chromatin model, so it is not independent corroboration of that model — it is its premise, supplied in-house.

The second is more substantive. The actin rods actually characterised in Alzheimer's brain are cofilin-actin rods, and they are induced by reactive oxygen species, amyloid- β and cytokines through a pathway that does not require tau at all ⁵⁷. Their biochemistry is specific and well described — a roughly one-to-one cofilin-to-actin stoichiometry, disulfide-dependent bundling, induction by oxidative and inflammatory stimuli ⁵⁸. Whether these are the same physical object as the tau-induced F-actin bundles is not established. "Tau causes actin rods" and "there are actin rods in Alzheimer's brain" are two sentences about possibly different things, joined in the literature by a shared noun.

Link 2 is the bridge from cytoskeleton to nucleoskeleton: excess stable actin uncouples the LINC complex, lamin is mislocalised, and the nuclear envelope invaginates into the nucleoplasmic reticulum ²³. The fly genetics here are causal and the human component is post-mortem correlation. The proposed mechanism has independent support of a partial kind: tau does bind and co-organise actin and microtubules, shown by nuclear magnetic resonance and electron microscopy in one independent laboratory ⁵⁹ — a point we note the primary literature establishes in purified systems only.

The mechanical prediction of the model — that pathogenic tau should reduce tension across the nuclear envelope — was tested directly with a fluorescence-resonance tension sensor and confirmed ⁶⁰. That is a real and unusual thing to do: the model made a biophysical prediction and the prediction held. The system was a transformed inducible cell line rather than

a neuron in a brain, and the readout is tension rather than chromatin state, but the logic is the right logic.

The most recent extension identifies emerin, a mechanically sensitive inner-nuclear-membrane protein, as elevated by pathogenic tau, and shows that raising emerin alone is sufficient to produce neurotoxicity, increased F-actin and nuclear invagination in inducible-tau and mutant induced neurons⁶¹. This is the most mechanistically specific result the programme has produced in a human-derived cell, and it is a year old with no in vivo arm and no independent replication.

The status of Link 2, then: proposed, causal in fly, mechanically corroborated in a cell line, with a competing mechanism for the same phenotype described below.

8. The Laminopathy Analogy and Its Load-Bearing Assumption

The framing that gives the programme its rhetorical force is the analogy to progeria: Alzheimer's disease as an *acquired* neurodegenerative laminopathy⁹. The analogy is doing real work, and it rests on an assumption that is correct and on an inference that is not.

The assumption is correct. Heterochromatin in a differentiated cell is physically held at the nuclear periphery, and the tether is not incidental. Genetic dissection in mouse tissues established that two tethers operate sequentially — a lamin B receptor tether early, and a lamin A/C tether in terminally differentiated tissue⁶². In a terminally differentiated cell, therefore, peripheral heterochromatin depends on lamin specifically. That a neuron can build and hold a radically non-default chromatin arrangement is not in doubt: rod photoreceptors of nocturnal mammals maintain an inverted nucleus with heterochromatin in the centre⁶³, and Hi-C with polymer modelling shows that heterochromatin self-attraction sets the compartments while lamina attachment converts that into the conventional peripheral arrangement⁶⁴. Lamina attachment is the switch between the two architectures.

What is inferred rather than established is that the progeria mechanism transfers. In Hutchinson–Gilford progeria fibroblasts, mutant lamin A causes lamina thickening, nuclear lobulation and loss of peripheral heterochromatin that worsens with each passage ⁶⁵, and the epigenetic consequences are exactly what the analogy wants: loss of pericentric H3K9me3 and HPI α , with upregulation of satellite repeat transcripts ⁶⁶. Lamin fails, repeats escape. That is the argument.

Three problems.

The cells divide. The passage dependence in the original description is not a detail; it is the mechanism. And when the progeria phenotype was traced to an innate-immune output, the trigger turned out to be replication fork stalling in dividing fibroblasts ⁶⁷. A neuron has no replication forks. This single fact is the most important limit on transferring the progeria story to brain, and it is rarely stated in the reviews that make the transfer.

The sign is not reliable. Prelamin A stabilises a histone methyltransferase and thereby *increases* H3K9me3, and depleting that methyltransferase extends progeroid lifespan by roughly sixty per cent ⁶⁸. So within progeria itself, the relationship between lamin dysfunction and the repressive mark runs in both directions depending on what is measured, and reducing the mark can be beneficial. Any model that treats "more heterochromatin, better" as an axiom has to confront this.

Nobody has looked in a progeria brain. There is no published study of heterochromatin, repeat elements or interferon in progeria neurons or progeria brain tissue. The natural experiment the analogy invokes has not been performed in the tissue the analogy is about.

There is, however, one large-scale human result that supports the lamina–chromatin axis directly and deserves more weight than it usually gets. In 669 human prefrontal cortices, tau burden — and specifically not amyloid — is associated with changes in nearly a quarter of assayed histone-acetylation domains, and the effect size of those changes correlates with how strongly the domain associates with the nuclear lamina ⁶⁹. That is human, large-n, tau-specific, and it says the lamina matters. It is association, it measures acetylation rather than constitutive heterochromatin, and it is bulk tissue. It is still the best human evidence the programme has.

9. The Envelope Arm and Its Three Replications

If one arm of this programme has been independently reproduced, it is this one — and what has been reproduced is the phenotype, not the mechanism.

The programme's own contribution is a fly experiment showing that tau-induced expansion of the nucleoplasmic reticulum traps polyadenylated RNA at the envelope, and that genetic or pharmacological inhibition of RNA export reduces both the trapped RNA and neuronal death³⁵. A companion paper links the same invaginations to depletion of nuclear calcium⁷⁰, and a third to failure of nonsense-mediated decay⁷¹. None of the three has been independently replicated.

The invagination phenotype itself has been replicated three times, by three unconnected groups, and each proposed a different mechanism.

Cambridge and UCL. Human induced cortical neurons carrying tau mutations show nuclear membrane deformation and nucleocytoplasmic transport failure, fully corrected by depolymerising microtubules, with a high incidence of invaginations confirmed in post-mortem frontotemporal dementia cortex⁷². Causal, in a human neuronal system — and the defect is located in microtubules, not actin.

Massachusetts General Hospital. Tau binds nucleoporins directly; transport is impaired in tau mice and in human Alzheimer's tissue; Nup98 mislocalises to tangle-bearing neurons⁷³. The mechanism here is not deformation at all but direct interference with the pore, and the same group later extended the mislocalisation to three other primary tauopathies⁷⁴. Worth noting for priority: nuclear irregularity in Alzheimer's hippocampus, scored by nucleoporin labelling, was described twelve years earlier⁷⁵.

University of Virginia. The most recent and the closest to a direct replication of the lamin work: human post-mortem staging showing lamina disruption from early Braak stages, PS19 mice showing oligomeric tau binding the lamin B receptor with electron-microscopy-confirmed invaginations and chromatin remodelling, and optogenetically induced oligomerisation in human induced

neurons⁷⁶. Concordant phenotype; competing mechanism — the lamin B receptor rather than LINC-complex uncoupling.

Three independent replications of a phenotype with three different proposed mechanisms is a specific epistemic situation, and it is a good one for the phenotype and a poor one for the mechanism. The invaginations are real. Why they are there is unsettled, and the programme's version — mechanical uncoupling through stabilised actin — is one of at least three live accounts, and the only one whose causal demonstration is invertebrate.

One further result belongs here because it points at the repair side. Bidirectional CRISPR screens identify the nuclear-envelope repair machinery — the ESCRT and LEM-domain components — as modifiers of tau aggregation⁷⁷. That is the strongest link between envelope repair and tauopathy in existence, and it was performed in dividing human cell lines. Whether a neuron even expresses enough of that machinery to reseal a rupture over decades is, as far as we can determine, unmeasured. The canonical repair demonstrations are all in dividing, mechanically confined cells⁷⁸, where lamin depletion raises rupture frequency and chromatin is seen herniating through the opening⁷⁹, and the authoritative review of the machinery describes no instance of envelope repair in a neuron⁸⁰.

10. The piRNA Arm and the Pathway That May Not Exist

This is the weakest link in the programme, and it is weak in an unusual way: not contradicted, but unreplicated and resting on a pathway whose existence in the relevant cell is contested.

The claim is that pathogenic tau causes depletion of piwi and piRNAs, that this removes a layer of transposable-element silencing, and that element de-repression then kills neurons²⁴. The causal genetics are in fly and are internally coherent; the human component is expression-level correlation. The claim was received as significant — a research highlight in a major journal asked directly whether tau pathology activates jumping genes⁸¹ — and the fly work was extended to mouse by the same laboratory, showing age- and tau-associated endogenous retrovirus activation at RNA and protein level⁸².

Four problems, in ascending order of severity.

Nobody has replicated it. Systematic search across piRNA, PIWI, Alzheimer's, tauopathy and human brain returns the original paper, reviews citing it, and unrelated work on pathway variants as biomarkers. No other laboratory has reported piwi or piRNA depletion in a tau model or in tauopathy brain. Eight years is a long time for a striking result in a heavily worked field to stand alone.

The mammalian somatic pathway is thinly evidenced. The authoritative review of the field states plainly that piRNAs silence transposons in the germ line of most animals and that somatic piRNA functions have been repeatedly lost, gained and lost again across evolution ⁸³. The mammalian neuronal evidence consists of a limited set of hippocampal small RNAs identified before the misannotation problem was understood ⁸⁴, a survey reporting thousands of "piRNA-like peaks" — the authors' own hedge — using genuine chemical enrichment ⁸⁵, and a knockdown study whose readout is contextual fear memory with no transposon measurement whatsoever ⁸⁶.

A large share of somatic "piRNAs" are misannotated fragments. Reanalysis of small-RNA sequencing against piRNA databases showed that many database piRNAs in somatic non-gonadal tissue, brain included, are piRNA-sized fragments of ribosomal, transfer and small nuclear RNAs, and that these account for the majority of apparent somatic piRNA expression ⁸⁷. The same group then demonstrated the problem concretely, showing that a headline somatic piRNA biomarker was in fact a full-length small nucleolar RNA ⁸⁸. Any measurement of "piRNA depletion" made by counting reads against a piRNA database is exposed to this.

The intuition comes from animals that are not mammals. Much of the rhetorical force of "neuronal piRNAs" derives from *Aplysia*, where a piwi- and piRNA-dependent mechanism methylates a transcription-factor promoter and enhances long-term facilitation ⁸⁹. That is a mollusc, and the mechanism is gene regulation rather than transposon control. And in the fly brain — the system where the tau result was obtained — element silencing runs through Argonaute and small interfering RNAs rather than piRNAs ⁵⁴.

None of this shows the claim is false. It shows that the claim presupposes a mammalian neuronal piRNA-based silencing pathway whose existence is not established, and that no independent group has reproduced the observation. Status: proposed, unreplicated, and dependent on a contested pathway.

What is far better established is the layered silencing that demonstrably does operate in neural cells: KRAB zinc-finger proteins with their corepressor⁹⁰, that corepressor controlling endogenous retroviruses in neural progenitors by histone modification rather than methylation⁹¹, thousands of primate-specific elements serving as its docking platforms in human neural progenitors⁹², the H3K9me3 methyltransferase arm⁹³, and the HUSH–MORC2 corepressor, which becomes load-bearing only where DNA methylation has already failed⁹⁴. If a silencing layer fails in tauopathy, these are the candidates for which mammalian neural evidence actually exists — and none of them is the one the programme names.

11. A Replication Scorecard

Pulling the previous six chapters together produces an uneven picture, and the unevenness is the point. Some claims in this programme have been reproduced by unconnected laboratories in mammals; others have stood alone for a decade; one has been independently reproduced in a mammal with a different mechanism and a different sensor.

Table 1 — The replication scorecard — each claim, who reproduced it, and in what system

Claim	Originating evidence	Independent replication	Species of causal arm	Status
Tau stabilises F-actin	Fly and mouse, bidirectional genetics	Structural binding confirmed in vitro, different lab	Fly	Established for fly; the disease-brain rods are a different object
Actin excess uncouples nucleoskeleton, mislocalises lamin	Fly causal, human correlation	None of the mechanism	Fly	Proposed
Tau reduces nuclear envelope tension	Tension sensor, inducible cell line	None	Cell line	Proposed

Claim	Originating evidence	Independent replication	Species of causal arm	Status
Nuclear envelope invaginates in tauopathy	Fly, mouse, human post-mortem	Three, all independent, three different mechanisms	Human induced neurons, mouse	Established (phenotype); mechanism disputed
Invaginations serve RNA export	Fly causal	None	Fly	Proposed
Tau relaxes heterochromatin	Fly causal, mouse corroborative, human correlation	Fly, twice, independent; mammal once, by mark sequestration	Fly, mouse	Established in fly; contradicted in direction in human
Tau depletes piwi and piRNAs	Fly causal, human correlation	None in eight years	Fly	Proposed, unreplicated
Tau activates transposable elements	Fly, mouse, human	Human n=636 independent; mouse causal independent; several human cohorts	Fly, mouse	Established as association; measurement contested
Element-derived nucleic acid kills neurons	Fly	Mouse, independent, via ZBP1 and Z-RNA	Mouse	Established for ZBP1 route
Tau depletes nuclear calcium	Fly causal, human correlation	None	Fly	Proposed, unreplicated
Tau impairs nonsense-mediated decay	Fly causal, human correlation	None	Fly	Proposed, unreplicated
Emerin links mechanotransduction to tau toxicity	Human induced neurons, causal	None (2026)	Cell	Proposed

Four observations about this table.

First, there is no published dispute. There is no retraction, correction, erratum, Matters Arising, rebuttal letter or published failed replication against any paper in this programme. Searches for letters and comments pairing tau

with chromatin, heterochromatin, lamin or retrotransposon return nothing. What exists instead is a body of work reporting results that point the other way, published without ever naming the programme^{7, 29, 95}. Whether that reflects consensus, disciplinary politeness, or simply that nobody has attempted the direct replication, the record does not say — and the distinction matters, because the three readings have very different implications for how much weight the programme should bear.

Second, the strongest independent result is also the most awkward one. The 2026 mouse study reproduces the heterochromatin premise, the element-reactivation step and the death step — in a mammal, causally, with no shared authorship — and in doing so replaces both the proposed mechanism of relaxation and the proposed sensor⁶.

Third, the human arm of every row is correlational. Not one row has a human causal demonstration. That is not unusual for a neurodegenerative disease and is not a criticism of the laboratory; it is a constraint on what the programme can be said to have shown.

Fourth, the unreplicated rows cluster. Nuclear calcium, nonsense-mediated decay, RNA export through invaginations, piRNA depletion — four proposed downstream consequences, each demonstrated once, in fly, by one laboratory. A programme that generates many mechanisms and independently confirms few is in a specific epistemic position, and it is not the position its citation profile suggests.

Part II

The Ligand

*Whether the elements the programme releases have been
measured well enough to serve as the nucleic acid a sensor
would read*

12. What Was Actually Measured

The programme's central downstream claim is that transposable elements are activated in Alzheimer's disease. Before asking whether that is true, it is worth asking what "activated" has been taken to mean, because the word covers at least five distinct physical quantities and the literature moves between them without marking the transitions.

Transcript. RNA that maps to element sequence. This is what nearly every study in the Alzheimer's literature measures.

Protein. The element-encoded proteins: the RNA-binding ORF1p, and the reverse transcriptase and endonuclease ORF2p.

Extrachromosomal DNA. Complementary DNA made from element RNA that has not integrated. For an innate-immune argument this is the interesting species, because it is DNA and it is in the cytoplasm.

Copy number. Total element-derived DNA per genome, measured by quantitative PCR. It cannot distinguish integrated insertions from unintegrated complementary DNA — which is the single most consequential ambiguity in the field⁴⁰.

Integrated insertion. A completed retrotransposition event, validated at a specific locus with its structural signatures.

The chain from transcript to insertion has five steps, and the evidence thins at each one. In Alzheimer's brain the human literature is entirely transcript-, protein- or copy-number-based. No study has reported validated somatic element insertions in Alzheimer's neurons — not by single-cell sequencing, not by targeted capture, not by any method. That is a gap of a different kind from "the effect size is modest"; it is the absence of any measurement of the quantity the theory's downstream steps require.

The element proteins are worth pausing on, because the programme's therapeutic arm depends on one of them. The reverse transcriptase has proved extraordinarily difficult to detect as a protein. In tumours with hundreds of genetically proven somatic insertions — cells that demonstrably retrotranspose — a rigorous search using mass spectrometry, immunoblot,

immunoprecipitation and immunohistochemistry with five validated monoclonal antibodies could not find it, despite abundant ORF1p⁹⁶. If the enzyme is nearly imperceptible where retrotransposition is proven, inferring its presence in brain from transcript data is not a small extrapolation.

The enzymatic measurement, however, does exist, and it is more interesting than either side of that argument expects. In 2025 a study assayed reverse-transcriptase activity biochemically in cerebral cortex from 31 Alzheimer's and non-diseased brains, alongside targeted long-read sequencing and spatial transcriptomics⁹⁷. Four of its results bear directly on this chapter, and they do not point the same way.

Reverse-transcriptase activity is present in every human brain assayed. The gap the field has worked around for a decade is closed: the activity is real, it is higher in grey matter, and it correlates with neuronal expression of the element open reading frame.

It is lower in Alzheimer's disease than in aged controls. The authors attribute this to neuronal loss in terminal disease, which is a reasonable confound and also exactly the cell-composition problem raised throughout this part. Either way, the direction is the opposite of what a model of disease-driven retroelement reactivation predicts.

Full-length, bicistronic L1 transcripts were essentially absent. They constituted under 0.01 per cent of L1 sequences in most samples, and more than eighty per cent of L1 sequence recovered was non-coding. What is present instead are monocistronic transcripts of the two open reading frames separately. This is the passenger-transcript problem of the next chapter, confirmed in brain tissue by long reads.

And the enzyme is not one enzyme. More than 550 protein-encoding sequence variants of the reverse-transcriptase reading frame were recovered — more than twice the number in the reference genome — spanning a roughly fifty-fold range of activity in overexpression assays. "Reverse-transcriptase activity in brain" is therefore not a single quantity, and an assay that measures its sum is measuring a mixture whose composition can change without its total changing.

The comparable measurement in the neighbouring disease is much weaker and is worth stating for contrast: the only direct enzymatic measurement in an amyotrophic lateral sclerosis cohort is in serum, and its

own internal control undercuts the disease-specific reading, since a large fraction of unaffected blood relatives were also positive — which the authors note is compatible with an inherited endogenous retrovirus rather than a disease process.

The programme is not naive about this. Its own reviews describe the elements as a candidate mechanism rather than a demonstrated one¹⁰, and the laboratory's recent move to long-read sequencing in both human tissue⁹⁸ and fly brain⁹⁹ is a direct response to the measurement problem set out in the next chapter. Long reads span whole transcripts, and spanning a whole transcript is what settles whether a repeat-mapping read is autonomous or a passenger.

13. Ninety-Nine Per Cent Passenger

In 2017 a group combined RNA sequencing with long-range 5-prime RACE and long-read sequencing to ask a simple question: of all the RNA in a cell that maps to L1 sequence, how much actually originates from an L1 promoter? The answer was that at least ninety-nine per cent does not¹⁰⁰. The overwhelming majority of L1-mapping signal is element fragments carried passively inside other cellular transcripts — introns, untranslated regions, read-through — and only a handful of loci produce authentic promoter-driven element transcripts, differing by tissue.

This result is the hinge of the whole field, and it is not a technicality. If a disease changes the expression of genes that happen to contain element fragments, an assay that counts element-mapping reads will report that "element expression is increased" when nothing about the elements has changed at all. The two hypotheses — autonomous element transcription rises, and host genes containing element fragments are more expressed — are observationally indistinguishable under subfamily-level quantification.

The canonical statement of the wider problem is a review that lays out three distinct difficulties: multi-mapping of reads across near-identical copies; insertional and internal sequence polymorphism between individuals; and the need to discriminate autonomous transcripts from chimeric and pervasive transcription¹⁰¹. The mappability component is better than often feared — at common read lengths, between 68 and 88 per cent of annotated elements are

uniquely mappable ¹⁰² — but the residual unmappable fraction is enriched for exactly the young, intact elements the disease claims concern.

Two further results make the picture harder rather than easier. Global DNA demethylation in human neural progenitors activates only evolutionarily young hominoid-specific LIs, while older LIs and other element classes stay silent ¹⁰³: silencing is layered and element-age-specific, so a subfamily-level average blurs together sequences under completely different control. And at single-locus, single-molecule resolution, intronic element methylation turns out to be tied to host-gene transcription, with hypomethylation alone typically insufficient to trigger expression because of redundant silencing ¹⁰⁴. The same conclusion emerges from locus-level chromatin analysis: only a subset of "transitional" loci are responsive to epigenetic dysregulation at all, and hypomethylation predicts expression poorly ¹⁰⁵.

The implication for this paper's argument is specific and it cuts against the argument. If heterochromatin relaxation is to supply a ligand for a cytosolic sensor, it must produce authentic, autonomous transcription of intact elements capable of being reverse-transcribed — not a rise in read counts that could equally reflect host-gene changes at loci that were never silenced by heterochromatin in the first place. Almost none of the Alzheimer's literature can distinguish the two.

14. The Tools, and the One Never Applied Here

The field built tools to address this, and it is worth being precise about what each can and cannot resolve, because the choice of tool determines which claims a dataset can support.

Table 2 — Quantification methods and what each can and cannot resolve

Method	What it resolves	What it cannot resolve	Used in Alzheimer's brain?
Subfamily-level expectation maximisation	Ambiguous read assignment across near-identical copies	Autonomous transcription versus co-transcribed fragments; locus identity	Yes — most published claims rest on it
Locus-level short-read pipelines	Which specific insertion a read came from; transcript type and splicing context	Whether a read spanning only part of an element is autonomous	Occasionally
Bayesian locus-resolved endogenous retrovirus quantification	Specific retroviral insertions	Same short-read span limit	In adjacent diseases
Consensus-specific filtering that excludes exonised fragments	Whether an apparent change reflects host-gene expression	Absolute abundance of genuinely autonomous transcripts	No
Long-read priors inside expectation maximisation	Multi-mapping, with long-read-informed weighting	Requires matched long-read data	No
Direct long-read sequencing of native RNA	Whether a transcript is autonomous or embedded, end to end	Depth; cost; degraded post-mortem RNA	Beginning to be
Single-cell or single-nucleus quantification	Cell type of origin	Three-prime-biased short reads are the worst substrate for the autonomy question	Yes

The first row is where nearly all published Alzheimer's claims sit. The tool that reassigns ambiguously mapped reads by expectation maximisation is excellent at what it was built for, and it aggregates to the element subfamily — which is precisely the resolution at which autonomous and passenger transcription cannot be separated ¹⁰⁶. The first locus-level pipeline demonstrated explicitly that subfamily-level analyses lose differences relating to transcript type, host-gene expression and splicing ¹⁰⁷, and a Bayesian equivalent set the standard for locus-resolved retroviral quantification ¹⁰⁸.

Then there is the fourth row. A tool exists that was built specifically for the objection raised in the previous chapter: it excludes reads deriving from inactive element fragments embedded in canonical transcripts, so that an apparent change in element expression cannot simply reflect a change in host-gene expression¹⁰⁹. As far as we can determine, it has never been applied to an Alzheimer's cohort. Neither has the approach that uses long-read abundance as a prior inside the reassignment step¹¹⁰.

That is the single most actionable finding in this part of the paper. There are published Alzheimer's datasets. There is a tool built for the exact confound those datasets are exposed to. Nobody has run one on the other. Until a headline Alzheimer's result is reproduced under consensus-specific filtering or by long-read sequencing, "transposable element expression is increased in Alzheimer's disease" and "genes containing element fragments are more expressed in Alzheimer's disease" remain the same observation.

Two qualifications, so this is not overstated. First, the programme has begun moving to long reads on its own account, in human tissue and in fly⁹⁸, and that is the right response. Second, a subfamily-level result is not thereby wrong — it is unresolved. The best-powered dataset in the adjacent disease used subfamily-level quantification and produced a finding that is both striking and appropriately modest: across 148 post-mortem cortices, only about one patient in five shows a retrotransposon-high molecular signature¹¹¹. That is what a careful use of a blunt tool looks like.

15. The Baseline Nobody Subtracts

Suppose the measurement problem were solved tomorrow. There would still be a prior question, and it is the one most often skipped: what is the normal amount?

Three results establish that the baseline is high.

Protein. Whole-brain atlas mapping with deep-learning quantification, plus mass spectrometry of endogenous mouse ORF1p, shows widespread, neuron-predominant ORF1p at steady state in normal brain — and that it increases with age¹¹². The human arm is transcript-level and confined to one neuronal population, and the protein measured is ORF1p rather than the

reverse transcriptase. Still: the element-encoded protein is a normal constituent of a normal neuron.

Transcription. Multiomics across developing and adult human brain, with functional testing in cerebral organoids, shows that L1 promoters are physiologically active in normal human brain, generating hundreds of developmentally regulated, cell-type-specific chimeric and regulatory transcripts¹¹³. Element transcription in brain is not an escape; in part it is a function.

Comparative abundance. The healthy brain has the highest retroelement-derived expression of any somatic tissue¹¹⁴.

Put together, these mean that detecting element RNA or ORF1p in an Alzheimer's brain is not a finding. The finding has to be a *difference*, against carefully age-matched controls, measured at locus level, in a defined cell type. And there is at least one careful attempt to do something close to that, which found the difference to be small: comparing young, aged and Alzheimer's post-mortem brain, only one repeat was differentially expressed between aged and young and eight between disease and aged, with a satellite repeat showing the largest change¹¹⁵. That is a modest, well-bounded result, and it is the opposite in spirit to the "storm" framing that circulates.

The storm framing comes from a longitudinal study of twenty-five individuals sampled before and after clinical conversion, reporting 1,790 differentially expressed element transcripts¹¹⁶. The limits are severe and are frequently dropped when it is cited: the tissue is peripheral blood, not brain; the cohort is twenty-five; the pipeline is custom. A related blood study across healthy, mild cognitive impairment and Alzheimer's reports a non-monotonic pattern¹¹⁷ — interesting, and also blood.

There is also a developmental constraint that deserves more weight than it gets. When a corepressor was deleted in vivo in mouse cortical progenitors, endogenous retrovirus transcription rose and produced a genuine inflammatory response — a causal demonstration of exactly the kind the disease argument needs¹¹⁸. But the same study reported that the dynamic, H3K9me3-dependent regulation of those elements operates in proliferating progenitors and *not* in adult neurons. If that generalises, the adult neuron is less poised for de-repression than the model assumes, and the window in which this machinery is load-bearing is developmental.

The honest statement of the baseline problem: the normal brain is full of element-derived RNA and protein, that amount rises with normal ageing, at least one silencing layer is developmental rather than adult, and the disease-associated increment — when measured carefully, at locus level, against age-matched controls — may be single-digit.

16. A Laboratory Against Itself

The most instructive result in this literature is a contradiction produced by one group, working carefully, in two directions.

In 2025, single-nucleus transcriptome and accessibility data from Alzheimer's prefrontal cortex showed element transcripts broadly increased across cell types, with the largest retrotransposon increases in excitatory neurons and element loci more accessible in disease ¹¹⁹. This is the best cell-type-resolved evidence in the field and it supports the programme's claim in the right cell.

In 2026, the same laboratory reanalysed RNA sequencing from *isolated* human and mouse microglia and found element transcripts stable across most of the human lifespan, minimal change in Alzheimer's versus age-matched controls, and — in transgenic mice — pathology-associated *decreases* ¹²⁰. The authors state the contrast with whole-tissue results explicitly.

Two readings are possible and they have different consequences.

The charitable reading for the programme is that the two results are consistent: elements rise in neurons and not in microglia, which is what a neuron-intrinsic chromatin mechanism predicts. That reading is available and it is the one we would adopt if the assays were equivalent.

They are not equivalent. Single-nucleus data are three-prime-biased short reads — the worst possible substrate for distinguishing autonomous element transcription from intronic read-through — and they are computationally deconvolved from a tissue whose cell composition is dramatically altered by the disease. The isolated-microglia data are physically sorted. A whole-tissue or nucleus-deconvolved increase is exactly what a shift in cell proportions would produce, and Alzheimer's brain loses neurons and gains reactive glia.

Two studies from a laboratory sympathetic to the hypothesis, using different designs, give opposite answers in the cell type they overlap on. That is a cell-composition confound demonstrated rather than merely hypothesised.

The independent cohorts do not resolve it. A large study across three brain biobanks identified 26,188 element expression quantitative trait loci and a causal element modulating a complement gene in induced neurons ¹²¹ — impressive scale, still bulk. A second from the same group offers an alternative upstream driver entirely, reporting herpesvirus-associated element activation in ageing brain with two large post-mortem cohorts and an antiviral alleviating element activation in a tau cell model ¹²². That is a friendly rival hypothesis for the same downstream phenomenon and should be treated as one.

And one well-designed independent study points at a different cell altogether: elevated L1 in Alzheimer's, with ORF1p immunoreactivity in *microglia*, and causal activation in human induced microglia altering morphology, cytokine secretion and phagocytosis ¹²³. Concordant on element activation, divergent on the cell of origin — and the programme's causal claims are neuronal.

The state of the evidence is therefore: element activation in Alzheimer's brain is repeatedly reported, has never been measured with a method that can exclude the passenger-transcript confound, has a demonstrated cell-composition confound, and is attributed to different cell types by different well-designed studies.

17. From Transcript to Insertion

Even granting every transcript measurement, the programme's downstream steps require something transcript data cannot supply. Reverse transcription must happen, and complementary DNA must accumulate somewhere a sensor can reach it, and — for the mutational version of the argument — insertions must occur.

The rate of somatic insertion in the normal human brain is the subject of the field's defining dispute, and it is unresolved.

The high estimate comes from single-cell retrotransposon capture sequencing of human hippocampal neurons: 13.7 somatic L1 insertions per neuron ¹²⁴. Bulk-tissue capture had earlier reported thousands of putative somatic insertions across hippocampus and caudate ¹²⁵.

The low estimate comes from single-neuron sequencing with rigorous internal controls — genome-wide insertion profiling of 300 neurons with better than eighty per cent recovery of known germline insertions as a validity check — giving fewer than 0.6 unique somatic insertions per neuron, with most neurons having none ¹²⁶.

The dispute was made formal in 2016, when a reanalysis of the high-estimate data identified single-cell amplification chimeras, bioinformatic errors and validation failures, concluded that thousands of apparent somatic mutations were artefacts, and revised the rate to roughly 0.2 events per neuron — about fifty-fold lower than claimed ¹²⁷. That reanalysis has not been withdrawn and the discrepancy has not been resolved. Any argument that invokes somatic retrotransposition in disease inherits it.

The most rigorous positive result available is instructive precisely because of how modest it is: combining locus-level methylation analysis with three independent single-cell genomic approaches across 24 hippocampal neurons, one somatic insertion was characterised and validated with its transduction signature ¹²⁸. One event, from twenty-four neurons, validated to a standard nothing else in the field meets.

Three further constraints.

Not every element-associated change is an insertion. Machine-learning analysis of single-cell sequencing identified somatic L1-associated variants, a substantial fraction of which are *deletions* produced by element endonuclease cutting rather than insertions¹²⁹. "L1-associated genomic change" and "retrotransposition" are different categories, routinely merged downstream.

The permissiveness results use engineered elements. The founding demonstrations of neuronal retrotransposition used a codon-optimised, highly active engineered reporter in neural stem cells and transgenic mice¹³⁰, extended to human neural progenitors with an endogenous copy-number arm¹³¹, and later shown to work in non-dividing human neurons¹³². These establish that the cell is permissive for a hot engineered element. They do not measure endogenous activity.

Somatic mosaicism in neurons is real and is mostly something else. Single-cell sequencing of cortical neurons shows substantial somatic mutation, dominated by transcription-associated single-nucleotide variants rather than retrotransposition¹³³. The genome of a neuron does change with age. Retroelements are a minor contributor.

The closest disease precedent is schizophrenia, where element copy number was reported increased in sorted prefrontal neurons¹³⁴ — and copy number carries the unintegrated-complementary-DNA ambiguity, which a principal of the high-rate camp has himself proposed may account for most such signals in neurological disease⁴⁰.

For the innate-immune argument, there is a saving grace and it should be stated. If the cytosolic DNA is what matters, then unintegrated complementary DNA is the *desirable* species, not an artefact. The ambiguity that ruins the mutational argument is irrelevant to the sensing argument. What is needed for the sensing argument is a direct measurement of cytoplasmic element-derived DNA in a neuron — and that has been done in one system: in a nuclease-deficiency model, human induced neural cells accumulate element-derived cytosolic single-stranded DNA, secrete interferon, and are rescued by reverse-transcriptase inhibition¹³⁵. A monogenic model, with the interferon coming from astrocytes and the sensor inferred rather than proven — but it is the strongest causal chain from element complementary DNA to neuroinflammation in a human neural system that exists.

18. The Precedent Next Door

Amyotrophic lateral sclerosis reached this juncture fifteen years earlier, and what happened there is the single most useful guide to what should be expected here.

The originating claim was that an endogenous retrovirus, HERV-K, is expressed in patient brain and contributes to motor neuron disease: transcript and protein detection in autopsy tissue, neurite retraction in human neurons, and progressive motor dysfunction in mice transgenic for the viral envelope¹³⁶. It was a strong, multi-arm paper in a major journal.

In 2019 an independent group attempted a direct replication of the brain-expression component, using standards-compliant quantitative PCR of three viral genes in premotor cortex from 34 cases and 23 controls with two reference genes, and found no difference⁴¹. The original authors replied that control selection and methodology explained the discrepancy¹³⁷, and the replicating authors responded¹³⁸. The exchange closed without resolution. No retraction, no correction, no agreed answer — a disagreement conducted through correspondence and left standing.

Meanwhile the clinical programme proceeded. An open-label, single-arm phase 2a study of combination antiretroviral therapy in forty patients reported a 21.8 per cent reduction in the rate of functional decline¹³⁹. That number is routinely cited as though it were evidence of benefit. Its 95 per cent confidence interval runs from -4.8 to 48.6 per cent: it crosses zero. There was no placebo arm, and the survival comparison used a model-based historical expectation rather than randomisation. The trial was a safety and tolerability study and it succeeded as one. It is not evidence of efficacy, and the phase 3 successor has no published result.

Two other results from that field carry directly across. Machine-learning stratification of 148 post-mortem cortices found that only about one patient in five has a retrotransposon-high molecular signature¹¹¹ — a reminder that even where the phenomenon is real it may be a subtype rather than a mechanism of the disease. And the strongest design anyone has used on this question anywhere: FACS-sorted disease-affected neuronal nuclei from human brain, assayed for transcript, chromatin accessibility and element DNA

content, showing element decondensation where the nuclear protein is lost¹⁴⁰. That is the experiment the Alzheimer's field has not done, in the tissue it has not done it in.

The lesson is not that the Alzheimer's claim will fail. It is that the Alzheimer's claim has not yet been subjected to the test the equivalent claim next door failed. There has been no blinded, standards-compliant, independent attempt to replicate a headline element finding in Alzheimer's brain. There is no dedicated methodological critique of Alzheimer's-specific element analyses as a standalone paper; the nearest thing is a negative result in isolated microglia¹²⁰ and the generic methodological literature^{100, 101}.

A parallel note on a second sensing route that competes with everything in this paper. Knockdown of the RNA-editing enzyme ADAR1 in human astrocytes raises both interferon signalling and element transcripts, with the enzyme declining across human brain ageing and disease¹⁴¹. If element-derived nucleic acid matters in Alzheimer's brain, double-stranded RNA sensing is a live route to the same endpoint — and, like the Z-RNA route, it does not require cGAS.

Status of Part II. That repeat-derived RNA is abundant in normal brain and rises with age: established. That it is further increased in Alzheimer's brain: proposed, repeatedly reported, never measured with a method that excludes the passenger confound, and with a demonstrated cell-composition confound. That element-derived complementary DNA accumulates in Alzheimer's neurons: unevidenced. That completed somatic insertions occur in Alzheimer's neurons: unevidenced. That reverse-transcriptase activity is present in human brain: established — and reported *lower* in Alzheimer's than in aged controls, with full-length element transcripts essentially absent⁹⁷, which is a problem for the model rather than a support for it.

Part III

The Tether

*Where cGAS actually sits, what holds it inactive, and why
nothing in that literature has ever been examined in a neuron*

19. The Enzyme Is Mostly Nuclear and Mostly Off

The account of cyclic GMP-AMP synthase that circulates in the disease literature is a switch: DNA appears in the cytosol where it should not be, the enzyme binds it, makes a second messenger, and an interferon response follows. Every element of that account is true of something the enzyme does. It is not a description of where the protein is or what most of it is doing.

The biochemistry is well settled. The enzyme was identified by fractionation and mass spectrometry as the cytosolic activity that produces a second messenger in response to double-stranded DNA¹⁴, the messenger itself was characterised¹⁵, and crystal structures showed that DNA binding produces an activating conformational change¹⁴² in a protein belonging to the nucleotidyltransferase family⁵⁶. Activation is not simple binding: it requires DNA-induced oligomerisation¹⁴³, is steeply length-dependent¹⁴⁴, and proceeds through the formation of protein–DNA ladders¹⁴⁵. The human enzyme has an additional DNA-binding interface that enhances activation^{146, 147}, and the intrinsically disordered amino terminus contributes non-specific DNA binding that promotes activation¹⁴⁸. Above a threshold, enzyme and DNA undergo liquid-like phase separation into condensates that are the actual catalytic compartment¹⁴⁹. The messenger has unusual mixed-linkage chemistry and high affinity for its adaptor¹⁵⁰.

None of this is in dispute. What is in dispute — or rather, what is settled and then ignored — is the resting distribution of the protein.

In 2019 two groups reported, independently, that cGAS is predominantly nuclear in resting cells and is held there tightly²⁶. Tight nuclear tethering, the first group argued, is essential for preventing autoreactivity: an enzyme that is in the nucleus with the genome and is not constantly firing must be actively restrained. The molecular basis of that restraint was worked out the following year²⁷. And a chromatin immunoprecipitation study with a tagged knock-in mouse showed that nuclear cGAS is not distributed at random: it is enriched on centromeric satellite DNA and, to a lesser degree, on LINE elements^{30, 44}.

That last detail should be read twice in the context of this paper. The enzyme sits preferentially on the repetitive, heterochromatic sequence that the chromatin programme says is de-repressed in tauopathy. Nobody has connected those two facts, because the two literatures do not overlap.

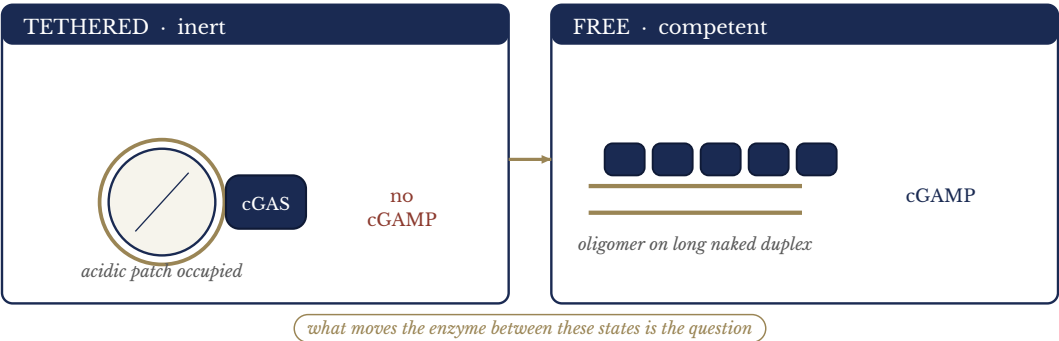
The nuclear enzyme is not idle, either. It suppresses DNA repair and promotes tumorigenesis¹⁵¹; chromatin-bound, it inhibits repair and accelerates genome destabilisation¹⁵²; it decelerates replication forks¹⁵³; it restricts one end-joining subpathway by suppressing poly-ADP-ribosylation¹⁵⁴ and regulates the balance between two others through a complex with Ku80¹⁵⁵. It promotes mitotic cell death¹⁵⁶. Reviews of this nuclear arm now exist^{157, 158}, and the recurring observation is that these functions require DNA binding and oligomerisation but *not* catalysis — which is the property every inhibitor in development targets.

For the present argument, one consequence dominates. If most cGAS is nuclear and held inactive on nucleosomes, then the question "does cGAS become active in tauopathy?" is not primarily a question about DNA appearing in the cytosol. It is a question about whether the restraint is still holding.

20. The Structural Basis of the Restraint

Between March and September 2020, five independent groups published cryo-electron microscopy structures of cGAS bound to the nucleosome, and they agreed^{3, 159, 160, 161}. The enzyme's DNA-binding surface docks onto the nucleosome acidic patch — the negatively charged groove formed by histones H2A and H2B on the nucleosome face — and that engagement is mutually exclusive with the binding mode required for activation. The nucleosome is not merely a poor substrate. It is a competitive inhibitor that occupies the very surface the enzyme needs in order to oligomerise on free DNA.

The resting state: nuclear, docked, and off



Events that would release it, and events that would not

✗	loss of H3K9 methylation	a tail mark; the octamer and the patch remain
✗	HP1 displacement from the mark	the mechanism shown in mouse tauopathy
○	higher-order decompaction	changes access, not occupancy; untested
✓	nucleosome eviction or displacement	would remove the patch; never measured in a neuron
✓	competition for the acidic patch	any factor binding the same surface
✓	nuclease-mediated liberation	demonstrated for MRE11 in a tumour context
✗	mitotic phosphorylation lifted	a neuron never enters mitosis

Every row above was established in a dividing cell. None has been measured in a neuron of any species.

Figure 3. In a resting cell most of this enzyme is nuclear, docked on the nucleosome acidic patch in a pose that is mutually exclusive with the one activation requires, and concentrated on satellite and LINE sequence. The lower panel separates events that would release it from events that would not: losing a histone methyl mark leaves the octamer, and the patch, in place. Every row of the upper panel was established in a dividing cell, and no row has been measured in a neuron of any species. Sources: ^{26, 27, 3, 159, 30, 162, 164}

This is an elegant solution to a real problem. A cell that keeps a DNA sensor in the same compartment as three billion base pairs of its own DNA needs that sensor to be off by default, and switched off by the DNA itself. Chromatinised DNA holds the enzyme inert; naked or fragmented DNA does not. One of the

five structural papers has since been corrected ⁴⁵, and the correction is cited here alongside the original rather than left implicit.

The restraint has a specific and testable dependency: it depends on the nucleosome. Not on the nucleus, not on a compartment barrier, but on the physical presence of an intact nucleosome surface presenting an accessible acidic patch. That dependency is what makes the connection to the chromatin programme worth making at all.

There is a second structural detail that matters here and is easy to miss. The strength of the tether is not uniform along the genome. Occupancy mapping places the enzyme preferentially on centromeric satellite and, secondarily, LINE sequence ³⁰ — that is, on exactly the compartment where nucleosome density, repressive marks and higher-order compaction are highest. Whatever the tether is, it is concentrated in constitutive heterochromatin.

Two inferences follow, and they point in opposite directions. The first is that the enzyme is anchored where the genome is most tightly packaged, which is the most secure place for it to be. The second is that the security of that anchoring is a function of the packaging — and the packaging is precisely what the chromatin programme claims is degraded in tauopathy.

It is worth being explicit about what would and would not follow from relaxation. Loss of a repressive histone mark does not remove a nucleosome. H3K9 methylation is a modification on a histone tail, not the histone itself, and an unmethylated nucleosome still presents an acidic patch. A model in which "heterochromatin relaxes, therefore cGAS is released" is too fast by at least one step. What would matter is nucleosome *eviction* or *displacement* — loss of octamer occupancy, not loss of a mark — or a change in the higher-order packing that alters the accessibility of the patch, or competition for the patch by another factor.

Whether tau-associated chromatin relaxation involves nucleosome eviction, as opposed to mark loss and decompaction with the octamers still in place, has not been measured in any system. The independent 2026 mouse work is the most suggestive datum available, and it is suggestive in a specific way: what tau aggregates are reported to do there is *sequester the H3K9me3 mark away from HP1*, decondensing heterochromatin ⁶. That is mark redistribution and loss of a reader, not octamer loss. On the structural

argument set out above, that mechanism would not by itself release a nucleosome-tethered enzyme.

This is the first place where the tether argument gets harder rather than easier, and it is stated here rather than in a caveat at the end.

21. The Other Restraints

The nucleosome is not the only thing holding this enzyme off its own genome, and the other restraints are worth tabulating because each has a different relationship to the neuron.

Table 3 — The restraints on nuclear cGAS, and what is known about each in a neuron

Restraint	Mechanism	Where demonstrated	Available to a neuron?	Measured in a neuron?
Nucleosome acidic patch	Competitive occlusion of the DNA-binding surface	Five cryo-EM structures; dividing cells and purified components	Yes, in principle	No
Barrier-to-autointegration factor	Outcompetes the enzyme for nuclear DNA	Dividing cells	Yes, in principle	No
Mitotic phosphorylation	Aurora-B-dependent phosphorylation plus tethering during mitosis	Dividing cells	No — requires mitosis	Not applicable
Nuclease clearance of free DNA	Cytosolic and lysosomal nucleases degrade the ligand before sensing	Mouse genetics, human disease	Yes	Partially
Ligand length threshold	Short DNA fails to nucleate the ladder or condensate	Purified components	Yes	No
Release by nuclease processing	Liberation from nucleosome sequestration during tumorigenesis	Dividing cells	Unknown	No

The barrier-to-autointegration factor competes with the enzyme for nuclear DNA and restricts it, a genuinely separate layer from the nucleosome tether¹⁶². During mitosis, when the envelope dissolves and the enzyme meets condensed chromosomes wholesale, phosphorylation plus tethering keeps it inactive¹⁶³ — a restraint a neuron never needs and never uses. Release is also regulated: the MRE11 nuclease liberates the enzyme from nucleosome sequestration in a tumour context¹⁶⁴, which is proof of principle that the tether can be opened by a defined biochemical event rather than only by

chromatin collapse. And what determines whether the enzyme is recruited to a ruptured micronucleus turns out to be the antecedent chromatin organisation of the chromosome inside it ¹⁶⁵ — chromatin state, again, determining enzyme behaviour.

The nuclease layer is the one with the most human evidence behind it, and it is not about chromatin at all. Loss-of-function mutations in the cytosolic exonuclease TREX1 cause a severe interferonopathy ¹⁶⁶; the mouse phenotype is cGAS-dependent ¹⁶⁷; and the whole logic of self-DNA tolerance is that free DNA is destroyed before it accumulates ¹⁶⁸. Oxidised DNA resists that destruction ¹⁶⁹, which is a mechanistically specific way for an oxidatively stressed neuron to acquire a more durable ligand. And in brain specifically, loss of the lysosomal nuclease DNase II causes neuronal double-stranded DNA accumulation and drives tau pathology ¹⁷⁰.

Now the column that matters. Of the six restraints in the table, one is unavailable to a neuron because it requires mitosis. Of the remaining five, the nuclease layer has partial neuronal evidence. The other four have none: not one has been examined in a neuron of any species.

That is the state of the field, and it is worth saying plainly why it happened. The structural and cell-biological work on nuclear cGAS was done by structural biologists and cancer biologists, in the cells those fields use — HeLa, U2OS, dendritic cells, embryonic stem cells, purified histones. The brain work on cGAS was done by neuroimmunologists, who found the enzyme where their methods look, which is in microglia. Neither community had a reason to ask what a nucleosome-tethered enzyme does inside a cell that never divides and never rebuilds its chromatin. The question falls between two literatures, and it has therefore not been asked.

22. What a Relaxed Landscape Would Do to a Tethered Enzyme

This chapter states a prediction. It is labelled unevidenced throughout, in the sense defined in Chapter 4: no primary measurement exists in any system relevant to the claim.

Start from what is distinctive about the neuronal nucleus. Its chromatin is maintained without replication, by continuous nucleosome turnover rather than by replication-coupled reassembly¹⁷¹. Its nuclear pore scaffolds and lamins are among the longest-lived proteins in the body and are never replaced³⁶, so damage accumulates³⁷. Its silencing is not passive: conditional deletion of a repressive complex in post-mitotic neurons causes de-repression and progressive fatal neurodegeneration¹⁷², which means the packaging is actively held rather than inherited. And in the one organism where a genome-wide heterochromatin map of actual neurons exists, lamina-associated domains and HP1 domains coincide in neurons in a way they do not in dividing cells¹⁷³ — neuronal heterochromatin is organised differently from the dividing-cell case that every lamina-domain map is built on^{174, 175}.

A neuron is therefore a cell that holds a fixed, actively maintained, never-rebuilt chromatin structure for eighty years. If a sensor is tethered to that structure, the tether is a contract with a surface that is never renewed.

The prediction has four parts.

(i) The enzyme should be there. Nuclear cGAS sits preferentially on centromeric satellite and LINE sequence³⁰. In a neuron, that compartment is lamina-associated and long-lived. Prediction: neuronal cGAS is predominantly nuclear and enriched in constitutive heterochromatin, in proportions at least as extreme as in dividing cells, because a neuron has no mitosis during which the distribution is reset. Unevidenced.

(ii) The restraint should be more load-bearing, not less. A dividing cell gets a clean re-tether at each mitosis; its chromatin errors are diluted. A neuron gets one. Prediction: the consequences of a failure of tethering are more

severe, and more cumulative, in a neuron than in any cell in which it has been studied. Unevidenced.

(iii) What would release it is nucleosome loss, not mark loss. As set out in Chapter 20, demethylation does not remove an octamer. The releasing events, in order of plausibility: eviction or displacement of nucleosomes at specific loci; competition for the acidic patch by another factor; proteolytic or nuclease-mediated liberation of the kind demonstrated for MRE11¹⁶⁴; or physical separation of the enzyme from chromatin altogether.

(iv) And the threshold is a ligand-quality threshold, not a switch. Activation requires oligomerisation on DNA above a length threshold^{144, 143}, and proceeds by condensation¹⁴⁹. A partially released enzyme in a nucleus full of long chromatinised DNA is not necessarily an active enzyme. The prediction is graded, not binary: relaxation shifts the equilibrium between tethered-inert and free-competent pools, and whether that shift crosses the threshold depends on how much free, long, protein-poor DNA is available. In a neuron under oxidative stress, with nuclease-resistant oxidised DNA¹⁶⁹ and physiological activity-induced double-strand breaks that are repaired more slowly with age^{176, 177}, the free-DNA pool is not zero.

We say explicitly what this argument does not establish. It does not establish that the tether fails in tauopathy. It does not establish that relaxation of the kind the chromatin programme describes is sufficient to release a nucleosome-bound enzyme, and Chapter 20 gives a specific reason to doubt it. What it establishes is that the question is well-posed, mechanistically specific, and answerable with existing methods — and that nobody has asked it.

23. The Measurement That Has Never Been Made

It is worth stating the negative precisely, because a precise negative is an experimental programme.

There is no published measurement of cGAS subcellular localisation in a neuron. Not by fractionation, not by imaging with a validated antibody, not with a tagged knock-in. There is no measurement of its chromatin occupancy in a neuron. There is no measurement of its association with nucleosomes in a neuron. These are not difficult experiments; the tagged knock-in mouse that produced the occupancy map in dendritic cells already exists³⁰.

What does exist is expression data, and it is the reason the question was dropped. Human protein and transcript atlases place the enzyme predominantly in myeloid and vascular populations¹⁷⁸, purified-cell transcriptomics of brain assigns most of the signal to microglia rather than neurons¹⁷⁹, and single-cell atlases of the human brain are consistent^{180, 181}. Every study that localises cGAS *activity* in brain places it in microglia or astrocytes³¹.

Three things should be said about that.

First, it is good evidence and it is the main reason to be sceptical of a neuron-intrinsic mechanism. If the enzyme is largely absent from neurons, the tether argument has nothing to act on. That possibility is live and this paper does not dismiss it.

Second, low expression is not absence, and the relevant question for a tether is not abundance but occupancy. An enzyme present at a tenth the microglial level, concentrated in heterochromatin, in a cell that never resets, is not obviously irrelevant. Transcript-level atlases are also a poor instrument for a protein whose function depends on where it is rather than how much of it there is.

Third, and most importantly: the absence of the measurement is not evidence about its result. "cGAS has not been found in neurons" and "cGAS has not been looked for in neurons with a method capable of finding it where it

would be" are different statements, and the literature contains the second, not the first.

Two related negatives complete the picture, and they constrain the ligand side as much as the tether side.

Heterochromatin loss has never been linked to innate immune activation in brain. No study manipulates a heterochromatin factor in neurons and reads out cGAS, its adaptor, or interferon. The nearest approaches are all indirect or use a different sensor: the tau-to-element-to-ZBP1 route in mouse neurons ⁶; tau-to-heterochromatin-to-element transcription with no immune readout ^{20, 24}; heterochromatin-factor loss producing element-driven interferon in non-neuronal cells ^{182, 183}; and cGAS–STING in ageing brain driven by mitochondrial DNA in microglia ³¹. The link is assembled from non-overlapping pieces, and this paper does not pretend otherwise.

No DNA has been shown to leave a neuronal nucleus. Envelope budding in neurons is established ¹⁸⁴ and ribonucleoprotein export by budding is established ³²; nucleophagy captures nuclear material in degenerating neurons ³³; envelope rupture in neurons has been demonstrated ¹⁸⁵ and integrity declines with age in neurons themselves ¹⁸⁶. No paper shows DNA or nucleosomes in the neuronal cytoplasm by any of these routes. Nor are there micronuclei: inflammatory stimulation does not induce them in primary neurons cell-autonomously ¹⁸⁷, and the mitotic route that generates them elsewhere ^{38, 39, 188} is unavailable to a cell that does not divide — a point reinforced by the single-cell sequencing showing no elevated aneuploidy in Alzheimer's neurons ^{189, 43}, and by the fact that even the strongest cell-cycle-re-entry evidence stops at DNA replication rather than mitosis ^{190, 191}.

Status of Part III. That cGAS is predominantly nuclear and tethered to nucleosomes in dividing cells: established. That the tether is competitive occlusion of the acidic patch: established. That nuclear cGAS is enriched on repetitive heterochromatic sequence: established in one dividing-cell system. That any of this holds in a neuron: unevidenced, and never tested. That tau-associated chromatin relaxation would release a tethered enzyme: unevidenced, with a specific structural reason for doubt.

Part IV

The Loop

*The enzyme helps maintain the structure that restrains it —
stated as a named hypothesis, with the four points at which it
would break*

24. The Enzyme Maintains the Chromatin That Restrains It

The argument so far has been linear: tau relaxes chromatin, chromatin relaxation releases sequence and might release an enzyme. A 2026 result makes that linearity untenable, and it is the empirical foundation of everything in this part.

Mice lacking cGAS age prematurely, and the ageing phenotype is associated with de-repression of LINE-1 elements and a flattened, smoothed heterochromatin landscape ⁵. The enzyme is not only restrained by heterochromatin. It participates in maintaining it. A companion analysis describes a dual role for the enzyme in shaping cellular and organismal responses to genomic instability ¹⁹², which is the same observation from the other side: this protein is a chromatin factor that also happens to be an immune sensor, and the two roles are not separable by compartment.

This should not be as surprising as it is. The nuclear functions of the enzyme are all chromatin functions. It suppresses repair ¹⁵¹, inhibits repair from a chromatin-bound position ¹⁵², decelerates replication forks ¹⁵³, and is required for cellular senescence ¹⁹³ — a state defined in part by a wholesale reorganisation of heterochromatin ¹⁹⁴. A protein with that portfolio was always going to have a maintenance role. What the null mouse adds is direction: without it, silencing degrades and repeats escape.

Three qualifications before this is used.

It is one paper, and it is 2026. No independent replication exists. The result is load-bearing for the loop hypothesis and should be the first thing anyone tries to reproduce.

The mouse is not a neuron. The phenotype is organismal; the de-repression is not cell-type-resolved in a way that isolates post-mitotic neurons.

The direction of the maintenance effect is the opposite of the naive expectation. One might have assumed that a DNA sensor, if anything, would be activated by de-repressed repeats and would then act against them. Here its absence

causes the de-repression. The enzyme is upstream of silencing, not merely downstream of its failure.

There is a second line that converges on the same place from the lamina. Nuclear lamina erosion has been shown to resurrect endogenous retroviruses, and to underlie neuronal ageing and neurodegeneration¹⁹⁵. That is the programme's Link 2 and Link 4 joined in one mammalian experiment, by a group outside the programme. And a 2026 study reports that cytoplasmic DNA sensing links L1 expression to neuronal senescence in Alzheimer's disease¹⁹⁶ — in directly induced human neurons, the system that preserves donor age¹⁹⁷. These are the two closest things in existence to the chain this paper is assembling, and neither of them is about tau.

The senescence literature supplies the mechanism by which chromatin fragments become a ligand in dividing cells: cytoplasmic chromatin fragments pinch off from intact nuclei of senescent cells and activate the enzyme to drive the inflammatory secretory phenotype¹⁹⁸, an independent group showed the same¹⁹⁹, and the enzyme is required for senescence itself¹⁹³. Whether neurons do anything equivalent is unknown; neuronal senescence is a marker constellation^{200, 201, 202} rather than a demonstrated programme, and senescence-associated heterochromatic foci have never been reported in a neuron¹⁹⁴.

25. The Silencer–Tether Loop

We now state the integration. It is unevidenced in the sense of Chapter 4 — it is a novel proposal, not a reading of existing data — and it is stated in a form designed to be broken.

> The Silencer–Tether loop. In a post-mitotic neuron, cGAS is tethered to nucleosomes in constitutive heterochromatin, where it is catalytically inert and contributes to the maintenance of that heterochromatin. Pathogenic tau degrades heterochromatin. Degradation reduces the tethered fraction of the enzyme. A reduced tethered fraction means reduced chromatin maintenance, which degrades heterochromatin further, releasing more repetitive sequence and more of the enzyme. The loop is self-amplifying, has no mitotic reset available to it, and runs on a timescale of decades.

The Silencer–Tether loop

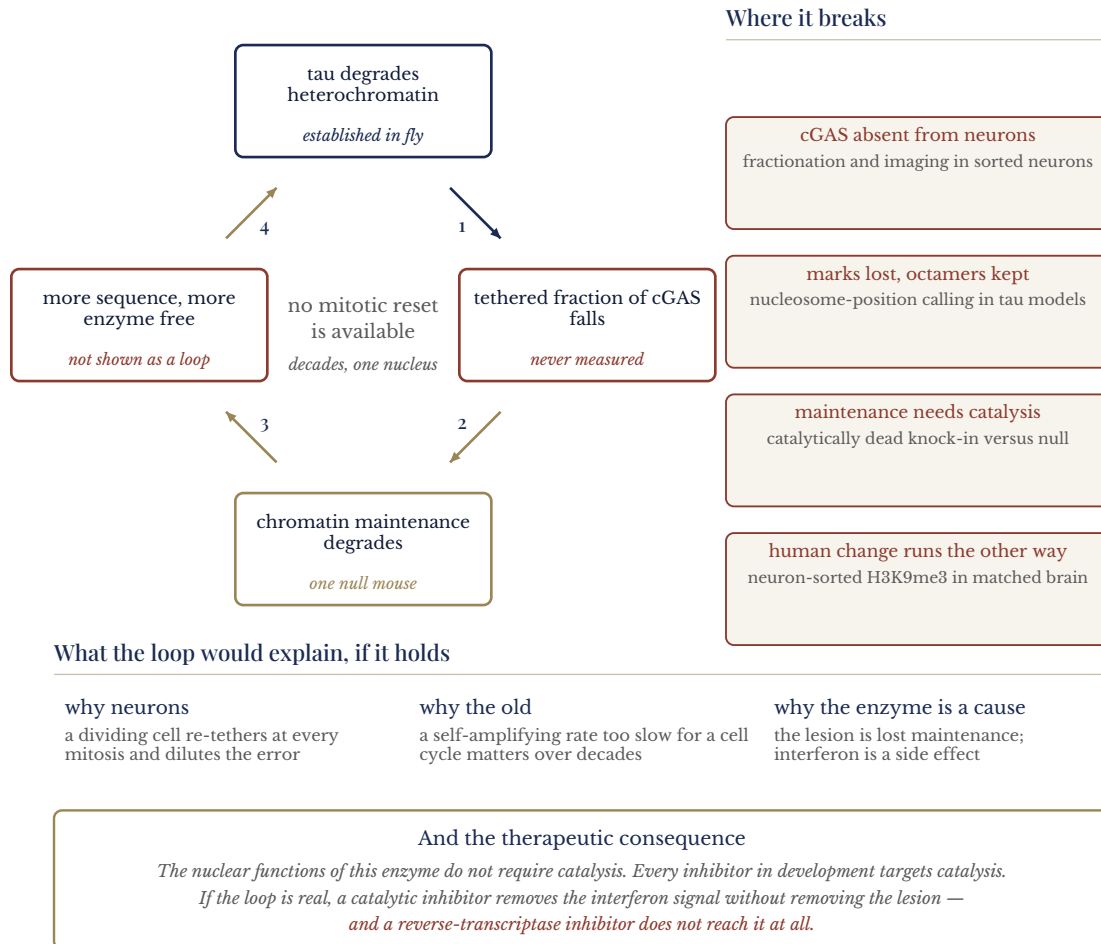


Figure 4. The proposal in one diagram. Tau degrades heterochromatin; degradation reduces the tethered fraction of the enzyme; the untethered enzyme no longer maintains heterochromatin; more sequence and more enzyme are released. The loop has no mitotic reset available to it, which is why it would matter in a neuron and nowhere else. Four break points are marked with the experiment that tests each; one of the four is already contradicted in human tissue. Sources: ^{4, 5, 192, 6, 7, 195}.

The four steps, with the status of each:

Step 1 — tau degrades neuronal heterochromatin. *Established in fly* ^{4, 49}; *established in mouse by a different mechanism* ⁶; *contradicted in direction in human* ^{7, 8}.

Step 2 — degradation reduces the tethered fraction of the enzyme. *Unevidenced*. Requires nucleosome eviction or patch occlusion, not merely mark loss (Chapter 20). No measurement in any neuron.

Step 3 — the untethered enzyme no longer maintains heterochromatin. *Proposed*, on one mouse null phenotype^{5, 192}. The null mouse shows that absence of the protein degrades silencing; it does not show that untethering the protein has the same effect as deleting it, which is a distinct and testable claim.

Step 4 — further degradation releases more sequence and more enzyme. *Unevidenced* as a loop; each half has partial support^{195, 196}.

Three properties make this worth proposing rather than merely speculating.

It explains why the disease is of the old and of neurons. A dividing cell resets the tether at every mitosis; errors are diluted across daughters. A neuron holds one chromatin structure, maintained by turnover rather than replication, for a lifetime. A self-amplifying loop that runs at a rate too slow to matter over a cell cycle is exactly the kind of loop that matters over eighty years. This is also why the mechanism cannot be tested in the systems where the enzyme has been studied.

It makes the enzyme a cause rather than a consequence. The entire disease literature on this pathway treats the enzyme as a responder: something goes wrong, DNA appears, the sensor fires. Here, partial loss of a chromatin-maintenance function is itself a lesion, and interferon is a side effect rather than the mechanism. That reframing has a direct therapeutic consequence, developed in Chapter 30.

It is precedented, in a different organism and a different protein. A mutually reinforcing element-and-protein feedback loop driving the spread of degeneration has been demonstrated in fly⁵⁵. The topology is not invented.

And four properties make it fragile, which is the subject of the next chapter.

One further consequence deserves stating because it changes what the interferon data mean. If the loop operates, the neuronal contribution is *chromatin maintenance failure*, and the interferon that the field measures may be coming from somewhere else entirely — from microglia sensing

mitochondrial DNA ³¹, or from neurons exporting micronuclei to microglia ²⁰³, ²⁰⁴. Those are not competing explanations of the loop; they are compatible with it, and they would make the loop invisible to every assay the field currently uses.

26. Where the Loop Breaks

A hypothesis worth stating is one whose failure modes can be named in advance. There are four, and any one of them is sufficient.

Table 4 — Four points at which the proposed loop would break

Failure point	The claim it kills	The experiment that tests it	Current evidence
cGAS is absent from neurons, or present at levels too low to matter	The whole loop	Tagged knock-in or validated imaging with fractionation in mouse and human neurons	Expression atlases place it in myeloid and vascular cells; no neuronal measurement exists
Tau-associated relaxation loses marks but not octamers	Step 2	Neuron-sorted micrococcal nuclease or ATAC with nucleosome-position calling, tau versus control	The one mammalian mechanism described is mark sequestration, not eviction
The maintenance function requires catalysis, or requires the cytosolic pool	Step 3	Catalytically dead knock-in versus null; tether-deficient knock-in versus null	Nuclear functions generally do not require catalysis, but this one has not been separated
The human chromatin change runs the other way	Steps 1 and 2, and the whole programme	Neuron-sorted H3K9me3 profiling in age-matched Alzheimer's and control brain	Two human studies report increase; the founding study reports decrease; no neuron-sorted dataset exists

The first is the most likely to be fatal and the easiest to test. If the enzyme is simply not in neurons in meaningful amounts, the tether and the loop are both empty, and the correct account of innate immunity in this disease is the microglial one that the field already has ³¹, ²⁰⁵.

The second is the most interesting. As Chapter 20 established, an unmethylated nucleosome still presents an acidic patch, and the best-described mammalian mechanism of tau-driven decondensation is sequestration of a mark away from its reader ⁶ — which would leave the octamers, and therefore the tether, in place. If chromatin relaxation in tauopathy is mark redistribution without nucleosome loss, Step 2 fails and the ligand arm survives without the tether arm.

The third is a clean genetics question that nobody has asked. The enzyme's nuclear functions generally require DNA binding and oligomerisation rather than catalysis ¹⁵², ¹⁵³, and its release from sequestration can be driven by a nuclease ¹⁶⁴. Whether heterochromatin maintenance belongs in the non-catalytic column is unknown, and it is exactly the kind of question a catalytically dead knock-in answers in one experiment.

The fourth is not specific to this paper's proposal; it is the central unresolved empirical dispute in the whole programme, and it is the subject of Chapter 29.

A fifth possibility should be named although it is not a failure so much as a redirection. The loop might be real and irrelevant — operating, but contributing so little to neuronal death compared with the ZBP1 route ⁶, the microglial route ²⁰⁵, or plain accumulated DNA damage ²⁰⁶ that it is not worth targeting. Effect size is a separate question from existence, and nothing in this paper speaks to it.

27. The Nearest Existing Demonstrations

Rather than leave the loop as a diagram, it is worth setting out precisely how close the existing literature gets to each step, because the gaps are smaller than they look in three places and larger in one.

Closest to Step 1 in a mammal. Tau aggregates binding H3K9me3-marked chromatin and sequestering the mark from HP1, with element de-repression and neuronal death following, in PS19 mice ⁶. This is a complete demonstration of chromatin-to-element-to-death in a mammalian neuron. It is also the strongest evidence *against* the specific mechanism the founding

paper proposed, since it operates by mark sequestration rather than oxidative-stress-driven relaxation.

Closest to lamina-driven element release in a mammal. Nuclear lamina erosion resurrecting endogenous retroviruses, framed as underlying neuronal ageing and neurodegeneration¹⁹⁵. This is the programme's Link 2 joined to its Link 4, by an outside group, in a mammal.

Closest to element-to-sensing in a human neuron. Cytoplasmic DNA sensing linking L1 expression to neuronal senescence in Alzheimer's disease, in directly induced neurons¹⁹⁶. And, in a monogenic model, element-derived cytosolic DNA in human neural cells producing interferon and rescued by reverse-transcriptase inhibition¹⁸⁵.

Closest to heterochromatin-failure-to-sensing in any mammal. Loss of a heterochromatin-associated factor producing cytoplasmic element complementary DNA and a cGAS-dependent interferon response, improved by reverse-transcriptase inhibitors in vivo¹⁸³, and element de-repression in senescence driving interferon through the same route¹⁸². Neither has a neuronal arm.

Closest to the sensing step in a neuron of any kind. Nothing. In a neural context, the micronucleus-to-enzyme route is documented only in ataxia-telangiectasia organoids²⁰⁷, and genome instability without interferon signalling has been shown to drive neuropathology in a separate model²⁰⁸ — which is a reminder that the damage and the interferon can come apart.

That last gap is the real one. Everything upstream has a mammalian demonstration somewhere. The step at which a neuron's own chromatin failure is read by a neuron's own cGAS has no demonstration at all, in any species, in any model.

Two further pieces of context bound how much a neuron could plausibly contribute. Neuronal DNA damage in Alzheimer's is real and substantial: double-strand breaks accumulate early in disease²⁰⁹, the genomic landscape of those breaks in post-mortem brain has been mapped²¹⁰, and breaks arise physiologically from neuronal activity¹⁷⁶ and are repaired more slowly with age and pathology¹⁷⁷. So the free-DNA supply is not hypothetical. But neurons also export nuclear material rather than only accumulating it: neuronal micronuclei propagate to microglia and alter microglial characteristics²⁰³, and this transfer increases with age²⁰⁴. If a neuron's route

for dealing with escaped nuclear material is to hand it to a phagocyte, then the sensing cell need not be the suffering cell — and the entire signature the field measures could be microglial even if the lesion is neuronal.

Status of Part IV. That cGAS contributes to heterochromatin maintenance: proposed, on one mouse study. That lamina erosion releases endogenous retroviruses in a mammalian brain: established in one system. That element expression links to cytoplasmic DNA sensing in human Alzheimer's neurons: proposed, one 2026 study. That the Silencer–Tether loop operates: unevidenced, with four named failure points and the experiments that test them.

Part V

Assessment

*The competing sensors, the unresolved direction of the human
chromatin change, what the clinical programme actually tests,
and a ledger*

28. Four Sensors for One Signature

Alzheimer's brain has an interferon signature. Type I interferon signalling drives neuroinflammation and synapse loss in mouse models, with receptor blockade rescuing microgliosis and synapse loss, and with correlative human post-mortem support²¹¹; concerted interferon signalling across microglia and other neural cells impairs memory²¹². Components of the cGAS pathway are altered in mouse cortex and hippocampus in Alzheimer's models²¹³, and the adaptor and p53 repair pathways are reported compromised in human disease²¹⁴. None of this identifies a sensor, for the reason given in Chapter 1: three unrelated adaptors converge on the same transcription factor through the same motif¹⁸.

At least four sensors, with four different ligands, have primary evidence behind them.

Table 5 — Four sensors proposed for one downstream signature

Proposed sensor	Ligand	Cell	Strongest evidence	Problem for it
ZBP1	Z-form RNA from de-repressed elements	Neuron	PS19 mouse, causal, independent, complete chain	Very recent; limited human validation
cGAS	Mitochondrial DNA	Microglia	Ageing brain, causal, with genetic and pharmacological arms	Ligand is not element-derived; cell is not the dying one
cGAS	Extracellular tau protein, via PQBP1	Microglia	Microglia-specific inducible depletion in vivo	Ligand is a protein, not a nucleic acid
MDA5 or PKR	Double-stranded RNA	Astrocyte	Editing-enzyme knockdown raises elements and interferon	Sensor not tested by loss of function

ZBP1 is the incumbent. The 2026 mouse study is the only complete demonstration of element-derived nucleic acid killing a mammalian neuron

through an innate sensor, and the sensor is ZBP1 responding to Z-RNA⁶. Any cGAS argument in this space is now a challenger, and should be written as one.

The mitochondrial route is the best-evidenced cGAS route. In ageing brain, cGAS–STING drives inflammation and neurodegeneration, with the cytosolic DNA in old microglia identified as mitochondrial rather than retroelement-derived³¹. In tauopathy specifically, genetic ablation and pharmacological inhibition of cGAS both rescue synaptic integrity and memory without changing tau load — and the trigger is again mitochondrial DNA leakage²⁰⁵. Disease-risk alleles elevate microglial cGAS-associated senescence and interferon signalling in a tauopathy model²¹⁵, blockade of adaptor activation alleviates microglial dysfunction and a broad spectrum of pathology²¹⁶, activation of the pathway contributes to pathogenesis²¹⁷, and microglial deletion of the enzyme preserves intercellular communication and alleviates amyloid pathology²¹⁸. This is a substantial, internally consistent, mostly microglial body of work, and it is the reason to doubt a neuron-intrinsic mechanism.

The protein-ligand route removes nucleic acid from the argument altogether. Tau activates microglia through a PQBP1–cGAS–STING axis in which the trigger is extracellular tau protein, not DNA²¹⁹. If that is the dominant route, chromatin has nothing to do with it.

The double-stranded-RNA route competes directly with the element argument. Suppression of an RNA-editing enzyme in human astrocytes raises interferon signalling and element transcripts together, and that enzyme declines across human brain ageing and disease¹⁴¹. Elements could matter without cGAS mattering.

Two further observations complicate the cell-assignment question rather than settling it. Neurons do express and use this machinery in some settings: neuronal STING orchestrates an inflammatory stress response in multiple sclerosis models²²⁰, neuronal STING activation occurs in amyotrophic lateral sclerosis and frontotemporal dementia²²¹, and a related sensor drives neuron-specific interferon signalling and neurodegeneration in a genetic ALS model²²². And a striking recent result runs in the opposite direction from everything above: an anti-herpetic function of tau is reported to *preserve* neurons through the cGAS–STING–TBK1 pathway²²³, while a protective APOE3 variant confers resilience against tau pathology partly by inhibiting this pathway^{224, 225}.

The honest position: the interferon signature is real, at least four sensors have primary evidence, the best-evidenced cGAS route is microglial and mitochondrial, the best-evidenced element route is neuronal and non-cGAS, and a third-party assessment of how the element work connects to innate immunity has already noted that the connection is programmatic rather than demonstrated¹⁷.

29. The Direction-of-Effect Dispute

This is the central unresolved empirical problem, and it has two halves: which way the chromatin change runs, and whether nuclear tau is present to cause it.

Human chromatin measurements in Alzheimer's brain

	mark	tissue	direction of the change	neuron-sorted
Frost 2014	H3K9me2, HP1	cortex, bulk	▼ <i>toward open</i>	×
Lee 2020	H3K9me3	cortex, bulk	▲ <i>toward closed</i>	×
Alves 2023	H3K9me3	orbitofrontal	▲ <i>toward closed</i>	×
Gil 2022	H3K9me3	dentate gyrus	▲ <i>toward closed</i>	×
Pietrzak 2011	rDNA methylation	cortex, bulk	▲ <i>toward closed</i>	×
Hernández-Ortega 2016	H3K9me2	CA1	▼ <i>toward open</i>	×
Calderón 2020	H3K9me2/me3 lost	mixed nuclei	▼ <i>toward open</i>	×
Nativio 2018	H4K16ac lost	temporal lobe	▲ <i>toward closed</i>	×
Nativio 2020	H3K27ac, H3K9ac gained	temporal lobe	▼ <i>toward open</i>	×
Klein 2019	H3K9ac, n = 669	prefrontal, bulk	<i>reorganised, not directional</i>	×
Marzi 2018	H3K27ac	entorhinal	<i>reorganised, not directional</i>	×

Not one of these measurements is neuron-sorted. Acetylation rows are scored by what the change implies for accessibility, not by the sign of the mark.

The reconciliations nobody has tested

*different marks behave differently · the change is biphasic, compacting early · the direction differs by region
or the whole signal is cell composition in a disease that loses neurons and gains glia*

Figure 2. Each row is a published measurement of chromatin state in human Alzheimer's brain. The column records which way the change ran. No row is neuron-sorted, every row is bulk tissue or mixed nuclei in a disease that loses neurons and gains glia, and no study quantifies the effect of post-mortem interval on these marks. The founding observation of heterochromatin loss and the three reports of increased H3K9me3 have never been reconciled, or cited against one another. Sources: ^{4, 7, 8, 28, 69, 228, 29}.

The chromatin half. The founding paper reports reduced H3K9me2 and HP1 in post-mortem Alzheimer's cortex ⁴. Against it: H3K9me3-mediated heterochromatin condensation is reported *elevated* in sporadic Alzheimer's cortex, with chromatin immunoprecipitation sequencing and transcriptomics ⁷; global H3K9me3 is reported *increased* in orbitofrontal cortex at early stages and lost only late ⁸; and H3K9me3 is reported *increased* in early-stage dentate granule cells ²⁸, in a cohort whose companion study also

ties lamina redistribution and nuclear tau loss together across Braak stages ²²⁶. Ribosomal DNA promoters are *hypermethylated* in mild cognitive impairment and Alzheimer's ²²⁷ — silencing increased, at the locus where nuclear tau is supposed to act.

The acetylation literature does not settle it either, because it is mark-specific rather than directional. H4K16ac is gained in normal ageing and dramatically lost in Alzheimer's ²²⁸; two other active marks are *gained* in Alzheimer's, with a fly model showing that increasing them worsens degeneration ^{229, 42}; an independent entorhinal cortex study finds thousands of differential acetylation peaks enriched for disease heritability without attributing them to tau ²³⁰; and the largest study, in 669 cortices, finds tau-specific effects whose magnitude scales with lamina association ⁶⁹. One environmental study reports reduced repressive marks with increased DNA damage in exposed young brains, in mixed nuclei and not a case-control design ²³¹.

The therapeutic version of the dispute is the sharpest form of it. In a tau mouse, the repressive mark H3K9me2 and its methyltransferase are elevated, and an inhibitor that reduces repressive marks rescues behaviour ²⁹. If heterochromatin loss were the toxic event, that drug should have made the animals worse.

Nobody has done the experiment that would resolve this. There is no neuron-sorted H3K9me3 profiling — no CUT&RUN, no chromatin immunoprecipitation sequencing on sorted neuronal nuclei — comparing Alzheimer's and age-matched control brain. Every human measurement above is bulk tissue or immunostaining of mixed nuclei, in a disease that loses neurons and gains glia. The plausible reconciliations are all untested: different marks behave differently; the change is biphasic, compacting early and relaxing late; the direction differs by region; or the whole thing is cell composition. And there is no quantitative study of post-mortem interval or agonal state on heterochromatin marks in human brain, which leaves an unquantified confound under every one of these results.

The nuclear-tau half. For tau to relax chromatin directly, it must be in the nucleus. It is: nuclear tau isoforms were identified at nucleolar organiser regions in 1990 ²³² — in primate cells only, a species caveat usually dropped — and all isoforms were subsequently detected in nuclei isolated from human frontal cortex ³⁴. It binds DNA directly, in the minor groove, with an AT-rich

preference²³³, localises to AT-rich satellite heterochromatin²³⁴, and occupies defined genomic regions in neurons under normal and stress conditions²³⁵.

But the functional literature on nuclear tau runs against the toxic-gain-of-function reading with striking consistency. Tau *loss* disrupts pericentromeric H3K9me3 and HP1 α clustering, and nuclear tau overexpression rescues it⁹⁵. Tau-deficient neurons are *more* vulnerable to stress-induced DNA damage, rescued by human tau²³⁶, in vitro and in vivo²³⁷. Tau associates with a regulator of heterochromatin stability and ribosomal DNA silencing, and tau depletion *increases* ribosomal transcription and *decreases* heterochromatin²³⁸. Four independent lines, all assigning nuclear tau a silencing-supportive role.

And the human tissue data are worse still for the model. Nuclear tau *declines* in CA1 and dentate gyrus in Alzheimer's and virtually disappears from tangle-bearing neurons²³⁹. If nuclear tau is the effector, it is leaving exactly the cells that are dying.

There is also a well-supported nuclear tau pathology that is simply not chromatin relaxation: tau aggregates are RNA-protein assemblies that mislocalise nuclear speckle components, shown in cells, mouse brain and human Alzheimer's, frontotemporal dementia and corticobasal tissue²⁴⁰.

Finally, the causal ordering is contestable at its origin. The founding mechanism routes through oxidative stress and DNA damage — but oxidative damage in Alzheimer's neurons is greatest *before*, and reduced *within*, tangle-bearing cells²⁴¹; double-strand breaks alone reorganise the three-dimensional genome without tau²⁰⁶; breaks drive tau accumulation rather than the reverse in one system²⁴²; a fully non-cell-autonomous route produces neuronal breaks through HMGB1 and Ku70²⁴³; and nucleolar stress alone is sufficient to kill hippocampal neurons²⁴⁴. Any of these can generate the observed correlation. The general heterochromatin-loss-with-ageing model that frames all of this²⁴⁵ has its strongest direct support in the fly²⁴⁶ and remains, in mammals, an inference.

30. The Therapeutic Reading

The programme has a clinical arm, and it is the only part of this literature that has reached a patient. It also tests a different link from the one this paper is about, and the distinction matters.

The logic is stated in the programme's own reviews: if elements are reactivated and reverse-transcribed, a reverse-transcriptase inhibitor should reduce the resulting complementary DNA^{11, 247}. The preclinical support in mice is real: lamivudine prevents neuropathology in a tau model²⁴⁸, ameliorates pathology in an amyloid model with coordinated pathway inhibition²⁴⁹, and rescues cognitive deficits in a further model²⁵⁰. An epidemiological association between nucleoside reverse-transcriptase inhibitor exposure and reduced Alzheimer's risk has been reported²⁵¹, and a study of lamivudine effects on cognitive-impairment biomarkers and interferon-stimulated gene expression has been published²⁵².

One result complicates the rationale before the trial is even discussed. When reverse-transcriptase activity was measured biochemically in human cortex, it was present in every brain and *lower* in Alzheimer's than in aged controls, and full-length bicistronic element transcripts were essentially absent⁹⁷. A drug that inhibits an enzyme whose activity is already reduced in the target tissue is not obviously well matched to the lesion. The authors attribute the reduction to neuronal loss in terminal disease, which may be right — but it is the same cell-composition confound that undermines the transcript measurements, and it has not been corrected for in either direction.

The clinical test itself is a twelve-patient, open-label, single-arm, twenty-four-week safety and feasibility study of 300 mg daily lamivudine in early Alzheimer's disease¹³. It met its primary endpoints, which were safety and feasibility. The reported reduction in cerebrospinal-fluid GFAP and rise in the plasma amyloid ratio are exploratory biomarker findings in twelve uncontrolled participants; they are not efficacy, and describing them as efficacy is the same error that the neighbouring field made with an uncontrolled forty-patient study whose confidence interval crossed zero¹³⁹. No placebo-controlled trial of any reverse-transcriptase inhibitor in Alzheimer's disease has been published.

Now the distinction that this paper exists to draw. A reverse-transcriptase inhibitor tests the ligand arm. It does not test the tether arm, and under the loop hypothesis it cannot.

If the lesion is that de-repressed elements are reverse-transcribed into cytosolic DNA that a sensor reads, then blocking the polymerase removes the ligand, and the drug is mechanistically apt. If the lesion is that a chromatin-maintenance factor has been untethered — Steps 2 and 3 of the loop — then no amount of reverse-transcriptase inhibition touches it, because the damage is happening in the nucleus, upstream of any complementary DNA, and interferon is a side effect rather than the mechanism. The two hypotheses predict the same biomarker movements and different clinical outcomes.

The same logic applies, with more force, to inhibiting cGAS itself. A substantial medicinal-chemistry effort exists: early tool compounds^{253, 254}, human-specific inhibitors²⁵⁵, and orally bioavailable series developed by structure-based design²⁵⁶, with reviews now written specifically around neurological indications^{257, 46}. Every one of these targets catalysis. But the nuclear functions of this enzyme — repair suppression¹⁵², fork deceleration¹⁵³, and, on the evidence of the null mouse, heterochromatin maintenance⁵ — generally do *not* require catalysis. A catalytic inhibitor would therefore leave the loop running while silencing the interferon readout by which anyone would detect it. If the loop is real, catalytic inhibition is the worst of both worlds: it removes the signal without removing the lesion.

Two boundary conditions from human genetics are worth keeping in view. Gain-of-function mutations in the adaptor cause a severe vasculopathy²⁵⁸, so this pathway is not one to activate; a common human hypomorphic allele appears to be a null and is carried without evident harm²⁵⁹, so partial loss is tolerated; and interferon-score methodology for this class of disease is established²⁶⁰, which means a central pharmacodynamic readout is at least conceivable.

And the negative prior for anti-inflammatory intervention in this disease is heavy and should not be forgotten: hydroxychloroquine failed²⁶¹, the non-steroidal prevention trial failed²⁶², and etanercept was negative²⁶³. A new mechanism does not exempt a drug from that history. Nor should the programme's own non-element interventions be forgotten as evidence that the laboratory tests other routes too: biotin rescues mitochondrial dysfunction

and neurotoxicity in the fly model ²⁶⁴, and an elevation in translation rate in early disease is framed by the same group as adaptive rather than toxic ²⁶⁵ — a more careful posture than the headline claims usually adopt.

31. A Staged Experimental Programme

The experiments below are ordered by the cost of being wrong: the earliest are cheap and capable of killing the whole proposal, the latest are expensive and only worth doing if the earlier ones survive.

Stage 1 — is there anything to argue about? (months, existing reagents)

1. *Localise the enzyme in a neuron.* Subcellular fractionation plus imaging with a validated antibody, and ideally the existing tagged knock-in mouse ³⁰, in sorted cortical and hippocampal neurons from young and old mice and in human post-mortem neuronal nuclei. Read out: nuclear versus cytosolic fraction, and chromatin association. A negative here ends the tether and loop arms.
2. *Map its occupancy in a neuron.* Chromatin immunoprecipitation or CUT&RUN for cGAS in sorted neuronal nuclei. Prediction: enrichment on satellite and LINE sequence, as in dendritic cells ³⁰. A flat profile falsifies Step 2 in advance.
3. *Settle the direction of the human chromatin change.* Neuron-sorted H3K9me3 CUT&RUN in age-matched Alzheimer's and control brain, with glial nuclei profiled in parallel from the same tissue, and post-mortem interval recorded and modelled. This single experiment addresses the field's central dispute ^{7, 8, 4} and is overdue by a decade.
4. *Reanalyse what already exists.* Run consensus-specific filtering ¹⁰⁹ and long-read-informed reassignment ¹¹⁰ on published Alzheimer's element datasets ^{119, 121}. Read out: how much of the reported signal survives. This costs compute and nothing else.

Stage 2 — does relaxation release the enzyme? (one to two years)

5. *Ask whether marks or octamers are lost.* Neuron-sorted micrococcal-nuclease digestion with nucleosome-position calling, plus accessibility profiling, in

tau mice and human tissue. If octamers persist, Step 2 fails and the tether arm should be abandoned ⁶.

6. *Perturb the tether directly.* Acidic-patch mutants, and the tether-deficient enzyme variants already characterised ²⁷, expressed in neurons; read out chromatin association, element transcripts and interferon.
7. *Separate catalysis from maintenance.* Catalytically dead knock-in versus null, scored for heterochromatin state and element de-repression. If the maintenance function survives catalytic inactivation, catalytic inhibitors will not touch the loop ⁵.
8. *Reproduce the null-mouse chromatin phenotype independently, in neurons.* The single most important replication in this paper ^{5, 192}.

Stage 3 — does it matter? (two to four years)

9. *Neuron-restricted deletion.* Conditional deletion of the enzyme in excitatory neurons of a tauopathy mouse, compared against microglial deletion in the same background ^{205, 218}. Read out: chromatin state, element transcripts, interferon, synapse density, behaviour. This is the experiment that assigns the phenotype to a cell.
10. *Sensor competition.* Cross the same tauopathy model to ZBP1-null animals and to cGAS-null animals, in parallel, with identical readouts ⁶. Read out: which deletion rescues, and whether the effects are additive. Without this, the field will keep arguing about which sensor matters using non-comparable experiments.
11. *Find the cytosolic species.* Immunoprecipitate the enzyme from brain and sequence the DNA bound to it. No enzyme-bound DNA has ever been recovered from brain tissue in any species, and until it is, every ligand argument in this literature — including this paper's — is inference.

Stage 4 — what would change practice

12. *A central pharmacodynamic readout.* Interferon scoring in cerebrospinal fluid, using established methodology ²⁶⁰, in a tauopathy cohort, with the element measurements made by a method that can survive the passenger confound.
13. *A controlled trial.* The existing clinical evidence is twelve uncontrolled patients ¹³. Whatever the mechanism, the next study should be

randomised and placebo-controlled, and should measure both element transcripts and a chromatin readout, so that a null result is interpretable rather than merely disappointing.

Two experiments are conspicuously absent from this list because they cannot be done. Nothing about the tether can be learned in *Drosophila*, which lacks the enzyme. And no human causal experiment is possible, which means the human arm will remain correlational, and the burden falls on getting the human measurements right rather than on getting more of them.

32. The Ledger

Table 6 — The ledger — every load-bearing claim and its status

Claim	Status	Strongest evidence	What is missing
Tau is present in human neuronal nuclei and binds DNA	Established	Human tissue; in vitro minor-groove binding	Nothing; but the import route is unknown
Tau relaxes heterochromatin in fly neurons	Established	Causal genetics, replicated independently twice	Nothing in fly
Tau relaxes heterochromatin in human neurons	Contradicted	Two human studies report the opposite for H3K9me3	Neuron-sorted profiling in age-matched tissue
Nuclear tau is a chromatin-protective factor	Proposed, and inconvenient	Four independent loss-of-function lines	Reconciliation with the gain-of-function model
Nuclear envelope invaginates in tauopathy	Established	Three independent replications, human and mouse	Agreement on mechanism
Invaginations export RNA	Proposed	Fly causal, one laboratory	Any independent test

Claim	Status	Strongest evidence	What is missing
Tau depletes piwi and piRNAs	Proposed, unreplicated	Fly causal, one laboratory, eight years	Independent replication; evidence the pathway exists in mammalian neurons
Element transcripts rise in Alzheimer's brain	Proposed	Multiple cohorts, several designs	A method that excludes the passenger confound; control for cell composition
Element complementary DNA accumulates in Alzheimer's neurons	Unevidenced	None in Alzheimer's tissue	Direct measurement
Completed somatic insertions occur in Alzheimer's neurons	Unevidenced	None	Single-cell insertion profiling in disease tissue
Reverse-transcriptase activity is present in human brain	Established	Enzymatic assay in 31 cortices — and lower in disease	Cell-composition-corrected comparison
Element-derived nucleic acid kills mammalian neurons	Established, via ZBP1	PS19 mouse, causal, independent	Human validation
cGAS is nuclear and nucleosome-tethered	Established, in dividing cells	Five concordant structures	Any measurement in a neuron
Nuclear cGAS occupies repetitive heterochromatin	Established, in one dividing-cell system	Tagged knock-in occupancy map	Any measurement in a neuron
cGAS is present in neurons at functionally relevant levels	Unevidenced	Expression atlases argue against	Fractionation and imaging in sorted neurons
Chromatin relaxation releases tethered cGAS	Unevidenced	None	Nucleosome-occupancy measurement in tau models
cGAS maintains heterochromatin	Proposed	One 2026 null-mouse study	Independent replication; neuronal arm
The Silencer–Tether loop operates	Unevidenced	Novel proposal	Four named failure points, Chapter 26

Claim	Status	Strongest evidence	What is missing
cGAS–STING is activated in Alzheimer's brain	Established	Multiple models and human tissue	Which sensor, which ligand, which cell
That activation is microglial and mitochondrial	Established for the ageing brain	Two conditional knockouts plus pharmacology	Whether it accounts for all of the signature
Reverse-transcriptase inhibition benefits patients	Unevidenced	Twelve uncontrolled patients	A placebo-controlled trial

What would have to be true. For the thesis of this paper to be right — for the chromatin programme to connect to cGAS at all — five things must hold, and each is currently unmeasured or disputed. cGAS must be present in neurons in functionally relevant amounts, and nuclear. It must be tethered to heterochromatic nucleosomes there, as it is in dividing cells. Tau-associated relaxation must involve nucleosome displacement and not merely loss of a mark. The untethered enzyme must lose its maintenance function, not merely change compartment. And the human chromatin change must run in the direction the founding paper reports, which two independent human studies deny.

That is five conditions, of which one is contradicted and four are unevidenced. This paper does not claim the loop is real. It claims that the question is well-posed, that the experiments are cheap and specified, and that the reason nobody has done them is that the two literatures involved have never been read together.

What the prize was given for. The proposition that neurodegeneration follows from what tau does to the three-dimensional packaging of DNA, and from what that does to a neuron's ability to hold its identity¹. Read narrowly — as a claim about fly neurons — it is established and independently replicated. Read as a claim about human neurons, it is an association whose direction is disputed. Read as a claim about mechanism, its most complete mammalian demonstration was produced by an unconnected laboratory and works by a different mechanism with a different sensor⁶.

The programme's other proposed consequences of relaxation — nuclear calcium depletion, nonsense-mediated decay failure, an element-derived gag-like protein as an effector²⁶⁶, actin overstabilisation driving cell-cycle

activation ²⁶⁷ — are each demonstrated once, in fly, by one laboratory. A programme that generates many mechanisms and independently confirms few is not thereby wrong. It is unfinished, and the commentary that accompanied its founding paper said as much at the time, in asking what the therapy would target ²⁶⁸.

The endpoint that all of it must eventually explain has not changed since 1991: synapse loss is what tracks cognition ²⁵. Nothing in this paper, and nothing in the programme it examines, has yet connected a chromatin measurement in a human neuron to a synapse.

References and Source Notes

References are numbered in order of first citation in the main text. Primary studies support the mechanistic discussion; official gene records establish nomenclature and orthology, and trial records establish development status only. Corrections, failed replications and disputed detections are identified explicitly, both here and at the point of use. Proposed integrations, the ledger and the experimental programme are original analytical synthesis.

- [1] The University of Texas at San Antonio. Alzheimer's researchers awarded \$4M in Oskar Fischer Prizes from UTSA. *UTSA Today*. 2022. Source.
- [2] Frost B. Alzheimer's disease and related tauopathies: disorders of disrupted neuronal identity. *Trends in Neurosciences*. 2023. doi:10.1016/j.tins.2023.07.006.
- [3] Michalski S, de Oliveira Mann CC, Stafford CA, et al. Structural basis for sequestration and autoinhibition of cGAS by chromatin. *Nature*. 2020. doi:10.1038/s41586-020-2748-0.
- [4] Frost B, Hemberg M, Lewis J, Feany MB. Tau promotes neurodegeneration through global chromatin relaxation. *Nature Neuroscience*. 2014. doi:10.1038/nn.3639.
- [5] Martinez JC, Morandini F, Rechsteiner C, et al. cGAS-deficient mice display premature aging associated with derepression of LINE1 elements and inflammation. *Nature Aging*. 2026. doi:10.1038/s43587-026-01206-y.
- [6] Liu W, Wu SA, Zhang BX, Guo SH, Li L, Sun W, Han J, Mo W. Tau aggregates cause reactivation of transposable DNA elements, leading to Z-RNA-ZBP1-mediated neuronal death. *Nature Neuroscience*. 2026. doi:10.1038/s41593-026-02299-9.
- [7] Lee MY, Lee J, Hyeon SJ, Cho H, Hwang YJ, Shin JY, McKee AC, Kowall NW, Kim JI, Stein TD, Hwang D, Ryu H. Epigenome signatures landscaped by histone H3K9me3 are associated with the synaptic dysfunction in Alzheimer's disease. *Aging Cell*. 2020. doi:10.1111/accel.13153.
- [8] Alves VC, Figueiro-Silva J, Ferrer I, Carro E. Epigenetic silencing of OR and TAS2R genes expression in human orbitofrontal cortex at early stages of sporadic Alzheimer's disease. *Cellular and Molecular Life Sciences*. 2023. doi:10.1007/s00018-023-04845-1.
- [9] Frost B. Alzheimer's disease: an acquired neurodegenerative laminopathy. *Nucleus*. 2016. doi:10.1080/19491034.2016.1183859.
- [10] Frost B, Dubnau J. The role of retrotransposons and endogenous retroviruses in age-dependent neurodegenerative disorders. *Annual Review of Neuroscience*. 2024. doi:10.1146/annurev-neuro-082823-020615.
- [11] Ochoa Thomas E, Zuniga G, Sun W, Frost B. Awakening the dark side: retrotransposon activation in neurodegenerative disorders. *Current Opinion in Neurobiology*. 2020. doi:10.1016/j.conb.2020.01.012.

- [12] Zuniga G, Frost B. Selective neuronal vulnerability to deficits in RNA processing. *Progress in Neurobiology*. 2023. doi:10.1016/j.pneurobio.2023.102500.
- [13] Sullivan AC, Zuniga G, Ramirez P, Fernandez R, Wang CP, Li J, Davila L, Pelton K, Gomez S, Sohn C, Gonzalez E, Lopez-Cruzan M, Gonzalez DA, Parker A, Zilli E, de Erausquin GA, Seshadri S, Espinoza S, Musi N, Frost B. A Phase IIa clinical trial to evaluate the effects of anti-retroviral therapy in Alzheimer's disease (ART-AD). *npj Dementia*. 2025. doi:10.1038/s44400-024-00001-z.
- [14] Sun L, Wu J, Du F, Chen X, Chen ZJ. Cyclic GMP-AMP synthase is a cytosolic DNA sensor that activates the type I interferon pathway. *Science*. 2013. doi:10.1126/science.1232458.
- [15] Wu J, Sun L, Chen X, et al. Cyclic GMP-AMP is an endogenous second messenger in innate immune signaling by cytosolic DNA. *Science*. 2013. doi:10.1126/science.1229963.
- [16] Ishikawa H, Barber GN. STING is an endoplasmic reticulum adaptor that facilitates innate immune signalling. *Nature*. 2008. doi:10.1038/nature07317.
- [17] Evering TH, Marston JL, Gan L, Nixon DF. Transposable elements and Alzheimer's disease pathogenesis. *Trends in Neurosciences*. 2023. doi:10.1016/j.tins.2022.12.003.
- [18] Liu S, Cai X, Wu J, et al. Phosphorylation of innate immune adaptor proteins MAVS, STING, and TRIF induces IRF3 activation. *Science*. 2015. doi:10.1126/science.aaa2630.
- [19] Wittmann CW, Wszolek MF, Shulman JM, Salvaterra PM, Lewis J, Hutton M, Feany MB. Tauopathy in *Drosophila*: neurodegeneration without neurofibrillary tangles. *Science*. 2001. doi:10.1126/science.1062382.
- [20] Guo C, Jeong HH, Hsieh YC, Klein HU, Bennett DA, De Jager PL, Liu Z, Shulman JM. Tau activates transposable elements in Alzheimer's disease. *Cell Reports*. 2018. doi:10.1016/j.celrep.2018.05.004.
- [21] Frost B, Götz J, Feany MB. Connecting the dots between tau dysfunction and neurodegeneration. *Trends in Cell Biology*. 2015. doi:10.1016/j.tcb.2014.07.005.
- [22] Fulga TA, Elson-Schwab I, Khurana V, Steinhilb ML, Spires TL, Hyman BT, Feany MB. Abnormal bundling and accumulation of F-actin mediates tau-induced neuronal degeneration in vivo. *Nature Cell Biology*. 2007. doi:10.1038/ncb1528.
- [23] Frost B, Bardai FH, Feany MB. Lamin dysfunction mediates neurodegeneration in tauopathies. *Current Biology*. 2016. doi:10.1016/j.cub.2015.11.039.
- [24] Sun W, Samimi H, Gamez M, Zare H, Frost B. Pathogenic tau-induced piRNA depletion promotes neuronal death through transposable element dysregulation in neurodegenerative tauopathies. *Nature Neuroscience*. 2018. doi:10.1038/s41593-018-0194-1.
- [25] Terry RD, Masliah E, Salmon DP, et al. Physical basis of cognitive alterations in Alzheimer's disease: Synapse loss is the major correlate of cognitive impairment. *Annals of Neurology*. 1991. doi:10.1002/ana.410300410.
- [26] Volkman HE, Cambier S, Gray EE, Stetson DB. Tight nuclear tethering of cGAS is essential for preventing autoreactivity. *eLife*. 2019. doi:10.7554/eLife.47491.

- [27] Zhao B, Xu P, Rowlett CM, et al. The molecular basis of tight nuclear tethering and inactivation of cGAS. *Nature*. 2020. doi:10.1038/s41586-020-2749-z.
- [28] Gil L, Chi-Ahumada E, Niño SA, Capdeville G, Méndez-Torres AM, Guerrero C, Rebolledo AB, Olazabal IM, Jiménez-Capdeville ME. Pathological nuclear hallmarks in dentate granule cells of Alzheimer's patients: a biphasic regulation of neurogenesis. *International Journal of Molecular Sciences*. 2022. doi:10.3390/ijms232112873.
- [29] Wang W, Cao Q, Tan T, Yang F, Williams JB, Yan Z. Epigenetic treatment of behavioral and physiological deficits in a tauopathy mouse model. *Aging Cell*. 2021. doi:10.1111/acer.13456.
- [30] Gentili M, Lahaye X, Nadalin F, et al. The N-terminal domain of cGAS determines preferential association with centromeric DNA and innate immune activation in the nucleus. *Cell Reports*. 2019. doi:10.1016/j.celrep.2019.01.105.
- [31] Gulen MF, Samson N, Keller A, et al. cGAS-STING drives ageing-related inflammation and neurodegeneration. *Nature*. 2023. doi:10.1038/s41586-023-06373-1.
- [32] Speese SD, Ashley J, Jokhi V, Nunnari J, Barria R, Li Y, Ataman B, Koon A, Chang YT, Li Q, Moore MJ, Budnik V. Nuclear envelope budding enables large ribonucleoprotein particle export during synaptic Wnt signaling. *Cell*. 2012. doi:10.1016/j.cell.2012.03.032.
- [33] Baron O, Boudi A, Dias C, Schilling M, Nölle A, Vizcay-Barrena G, Rattray I, Jungbluth H, Scheper W, Fleck RA, Bates GP, Fanto M. Stall in canonical autophagy-lysosome pathways prompts nucleophagy-based nuclear breakdown in neurodegeneration. *Current Biology*. 2017. doi:10.1016/j.cub.2017.10.054.
- [34] Brady RM, Zinkowski RP, Binder LI. Presence of tau in isolated nuclei from human brain. *Neurobiology of Aging*. 1995. doi:10.1016/0197-4580(95)00023-8.
- [35] Cornelison GL, Levy SA, Jenson T, Frost B. Tau-induced nuclear envelope invagination causes a toxic accumulation of mRNA in *Drosophila*. *Aging Cell*. 2019. doi:10.1111/acer.12847.
- [36] Toyama BH, Savas JN, Park SK, Harris MS, Ingolia NT, Yates JR, Hetzer MW. Identification of long-lived proteins reveals exceptional stability of essential cellular structures. *Cell*. 2013. doi:10.1016/j.cell.2013.07.037.
- [37] D'Angelo MA, Raices M, Panowski SH, Hetzer MW. Age-dependent deterioration of nuclear pore complexes causes a loss of nuclear integrity in postmitotic cells. *Cell*. 2009. doi:10.1016/j.cell.2008.11.037.
- [38] Mackenzie KJ, Carroll P, Martin CA, et al. cGAS surveillance of micronuclei links genome instability to innate immunity. *Nature*. 2017. doi:10.1038/nature23449.
- [39] Harding SM, Benci JL, Irianto J, et al. Mitotic progression following DNA damage enables pattern recognition within micronuclei. *Nature*. 2017. doi:10.1038/nature23470.
- [40] Faulkner GJ, Billon V. L1 retrotransposition in the soma: a field jumping ahead. *Mobile DNA*. 2018. doi:10.1186/s13100-018-0128-1.
- [41] Garson JA, Usher L, Al-Chalabi A, Huggett J, Day EF, McCormick AL. Quantitative analysis of human endogenous retrovirus-K transcripts in postmortem premotor

- cortex fails to confirm elevated expression of HERV-K RNA in amyotrophic lateral sclerosis. *Acta Neuropathologica Communications*. 2019. doi:10.1186/s40478-019-0698-2.
- [42] Nativio R, Lan Y, Donahue G, et al. Author Correction: An integrated multi-omics approach identifies epigenetic alterations associated with Alzheimer's disease. *Nature Genetics*. 2020. doi:10.1038/s41588-020-00733-7.
- [43] van den Bos H, Spierings DCJ, Taudt AS, et al. Erratum to: Single-cell whole genome sequencing reveals no evidence for common aneuploidy in normal and Alzheimer's disease neurons. *Genome Biology*. 2016. doi:10.1186/s13059-016-1015-z.
- [44] Gentili M, Lahaye X, Nadalin F, et al. Erratum: The N-terminal domain of cGAS determines preferential association with centromeric DNA and innate immune activation in the nucleus. *Cell Reports*. 2019. doi:10.1016/j.celrep.2019.03.049.
- [45] Pathare GR, Decout A, Gluck S, et al. Author Correction: Structural mechanism of cGAS inhibition by the nucleosome. *Nature*. 2026. doi:10.1038/s41586-026-10959-w.
- [46] Feng W, Aikeda A, Sinha SC, Gan L. Expanding roles of cGAS-STING signaling in neuroinflammation. *Journal of Clinical Investigation*. 2026. doi:10.1172/JCI204550.
- [47] DuBoff B, Götz J, Feany MB. Tau promotes neurodegeneration via DRP1 mislocalization in vivo. *Neuron*. 2012. doi:10.1016/j.neuron.2012.06.026.
- [48] Merlo P, Frost B, Peng S, Yang YJ, Park PJ, Feany M. p53 prevents neurodegeneration by regulating synaptic genes. *Proceedings of the National Academy of Sciences*. 2014. doi:10.1073/pnas.1419083111.
- [49] Chanu SI, Sarkar S. Targeted downregulation of dMyc suppresses pathogenesis of human neuronal tauopathies in *Drosophila* by limiting heterochromatin relaxation and tau hyperphosphorylation. *Molecular Neurobiology*. 2017. doi:10.1007/s12035-016-9858-6.
- [50] Nisha, Sarkar S. Downregulation of glob1 mitigates human tau mediated neurotoxicity by restricting heterochromatin loss and elevating the autophagic response in *Drosophila*. *Molecular Biology Reports*. 2022. doi:10.1007/s11033-022-07498-8.
- [51] Li W, Prazak L, Chatterjee N, Grüniger S, Krug L, Theodorou D, Dubnau J. Activation of transposable elements during aging and neuronal decline in *Drosophila*. *Nature Neuroscience*. 2013. doi:10.1038/nn.3368.
- [52] Krug L, Chatterjee N, Borges-Monroy R, Hearn S, Liao WW, Morrill K, Prazak L, Rozhkov N, Theodorou D, Hammell M, Dubnau J. Retrotransposon activation contributes to neurodegeneration in a *Drosophila* TDP-43 model of ALS. *PLoS Genetics*. 2017. doi:10.1371/journal.pgen.1006635.
- [53] Bardai FH, Wang L, Mutreja Y, Yenjerla M, Gamblin TC, Feany MB. A conserved cytoskeletal signaling cascade mediates neurotoxicity of FTDP-17 tau mutations. *Journal of Neuroscience*. 2018. doi:10.1523/JNEUROSCI.1550-17.2017.
- [54] Olenkina OM, Simonov RA, Ivannikova AY, Abramov YA, Sivkina AL, Ulianov SV, Shevelyov YY. Ago2-mediated recruitment of HPIa on transposable elements in *Drosophila* brain. *Cells*. 2025. doi:10.3390/cells14171361.

- [55] Chang YH, Dubnau J. Endogenous retroviruses and TDP-43 proteinopathy form a sustaining feedback driving intercellular spread of *Drosophila* neurodegeneration. *Nature Communications*. 2023. doi:10.1038/s41467-023-36649-z.
- [56] Kranzusch PJ, Lee ASY, Berger JM, Doudna JA. Structure of human cGAS reveals a conserved family of second-messenger enzymes in innate immunity. *Cell Reports*. 2013. doi:10.1016/j.celrep.2013.05.008.
- [57] Minamide LS, Striegl AM, Boyle JA, Meberg PJ, Bamburg JR. Neurodegenerative stimuli induce persistent ADF/cofilin-actin rods that disrupt distal neurite function. *Nature Cell Biology*. 2000. doi:10.1038/35023579.
- [58] Bamburg JR, Bernstein BW. Actin dynamics and cofilin-actin rods in Alzheimer disease. *Cytoskeleton*. 2016. doi:10.1002/cm.21282.
- [59] Cabrales Fontela Y, Kadavath H, Biernat J, Riedel D, Mandelkow E, Zweckstetter M. Multivalent cross-linking of actin filaments and microtubules through the microtubule-associated protein Tau. *Nature Communications*. 2017. doi:10.1038/s41467-017-02230-8.
- [60] Sohn C, Ma J, Ray WJ, Frost B. Pathogenic tau decreases nuclear tension in cultured neurons. *Frontiers in Aging*. 2023. doi:10.3389/fragi.2023.1058968.
- [61] Sohn C, Pardo S, Molleur D, Paduri SR, Lambert M, Uttke Z, Sohn EJ, Thomas MG, Weintraub ST, Frost B. Elevation of the mechanically-sensitive protein emerin links nuclear mechanotransduction to tau-induced cytoskeletal remodeling in neurons. *Nucleus*. 2026. doi:10.1080/19491034.2026.2697135.
- [62] Solovei I, Wang AS, Thanisch K, Schmidt CS, Krebs S, Zwerger M, Cohen TV, Devys D, Foisner R, Peichl L, Herrmann H, Blum H, Engelkamp D, Stewart CL, Leonhardt H, Joffe B. LBR and lamin A/C sequentially tether peripheral heterochromatin and inversely regulate differentiation. *Cell*. 2013. doi:10.1016/j.cell.2013.01.009.
- [63] Solovei I, Kreysing M, Lancôt C, Kösem S, Peichl L, Cremer T, Guck J, Joffe B. Nuclear architecture of rod photoreceptor cells adapts to vision in mammalian evolution. *Cell*. 2009. doi:10.1016/j.cell.2009.01.052.
- [64] Falk M, Feodorova Y, Naumova N, Imakaev M, Lajoie BR, Leonhardt H, Joffe B, Dekker J, Fudenberg G, Solovei I, Mirny LA. Heterochromatin drives compartmentalization of inverted and conventional nuclei. *Nature*. 2019. doi:10.1038/s41586-019-1275-3.
- [65] Goldman RD, Shumaker DK, Erdos MR, Eriksson M, Goldman AE, Gordon LB, Gruenbaum Y, Khuon S, Mendez M, Varga R, Collins FS. Accumulation of mutant lamin A causes progressive changes in nuclear architecture in Hutchinson-Gilford progeria syndrome. *Proceedings of the National Academy of Sciences*. 2004. doi:10.1073/pnas.0402943101.
- [66] Shumaker DK, Dechat T, Kohlmaier A, Adam SA, Bozovsky MR, Erdos MR, Eriksson M, Goldman AE, Khuon S, Collins FS, Jenuwein T, Goldman RD. Mutant nuclear lamin A leads to progressive alterations of epigenetic control in premature aging. *Proceedings of the National Academy of Sciences*. 2006. doi:10.1073/pnas.0602569103.

- [67] Kreienkamp R, Graziano S, Coll-Bonfill N, Bedia-Diaz G, Cybulla E, Vindigni A, Dorsett D, Kubben N, Batista LFZ, Gonzalo S. A cell-intrinsic interferon-like response links replication stress to cellular aging caused by progerin. *Cell Reports*. 2018. doi:10.1016/j.celrep.2018.01.090.
- [68] Liu B, Wang Z, Zhang L, Ghosh S, Zheng H, Zhou Z. Depleting the methyltransferase Suv39h1 improves DNA repair and extends lifespan in a progeria mouse model. *Nature Communications*. 2013. doi:10.1038/ncomms2885.
- [69] Klein HU, McCabe C, Gjonneska E, Sullivan SE, Kaskow BJ, Tang A, Smith RV, Xu J, Pfenning AR, Bernstein BE, Meissner A, Schneider JA, Mostafavi S, Tsai LH, Young-Pearse TL, Bennett DA, De Jager PL. Epigenome-wide study uncovers large-scale changes in histone acetylation driven by tau pathology in aging and Alzheimer's human brains. *Nature Neuroscience*. 2019. doi:10.1038/s41593-018-0291-1.
- [70] Mahoney R, Ochoa Thomas E, Ramirez P, Miller HE, Beckmann A, Zuniga G, Dobrowolski R, Frost B. Pathogenic tau causes a toxic depletion of nuclear calcium. *Cell Reports*. 2020. doi:10.1016/j.celrep.2020.107900.
- [71] Zuniga G, Levy S, Ramirez P, De Mange J, Gonzalez E, Gamez M, Frost B. Tau-induced deficits in nonsense-mediated mRNA decay contribute to neurodegeneration. *Alzheimer's & Dementia*. 2022. doi:10.1002/alz.12653.
- [72] Paonessa F, Evans LD, Solanki R, Larrieu D, Wray S, Hardy J, Jackson SP, Livesey FJ. Microtubules deform the nuclear membrane and disrupt nucleocytoplasmic transport in tau-mediated frontotemporal dementia. *Cell Reports*. 2019. doi:10.1016/j.celrep.2018.12.085.
- [73] Eftekharzadeh B, Daigle JG, Kapinos LE, Coyne A, Schiantarelli J, Carlomagno Y, Cook C, Wegmann S, Rothstein JD, Hyman BT. Tau protein disrupts nucleocytoplasmic transport in Alzheimer's disease. *Neuron*. 2018. doi:10.1016/j.neuron.2018.07.039.
- [74] Dickson JR, Frosch MP, Hyman BT. Altered localization of nucleoporin 98 in primary tauopathies. *Brain Communications*. 2022. doi:10.1093/braincomms/fcac334.
- [75] Sheffield LG, Miskiewicz HB, Tannenbaum LB, Mirra SS. Nuclear pore complex proteins in Alzheimer disease. *Journal of Neuropathology & Experimental Neurology*. 2006. doi:10.1097/01.jnen.0000195939.40410.08.
- [76] Yuan S, Essepian N, Roberts R, Sherman E, Wang Q, Erisir A, Jiang L. Tau oligomerization induces nuclear lamina invagination and chromatin remodeling in Alzheimer's disease. *Acta Neuropathologica*. 2026. doi:10.1007/s00401-026-03018-1.
- [77] Prissette M, Fury W, Koss M, Racioppi C, Fedorova D, Dragileva E, Clarke G, Pohl T, Dugan J, Ahrens D, Chukwurah E, Zheng S, Bouffard J, Caballero A, Chiao E, Droguett G, Yancopoulos GD, Murphy AJ, Adler C, Ni M, Wei Y, Zambrowicz B, Jaquish D, Adams NC, Friendewey D, Poueymirou W. Disruption of nuclear envelope integrity as a possible initiating event in tauopathies. *Cell Reports*. 2022. doi:10.1016/j.celrep.2022.111249.
- [78] Raab M, Gentili M, de Belly H, Thiam HR, Vargas P, Jimenez AJ, Lautenschlaeger F, Voituriez R, Lennon-Duménil AM, Manel N, Piel M. ESCRT III repairs nuclear envelope ruptures during cell migration to limit DNA damage and cell death. *Science*. 2016. doi:10.1126/science.aad7611.

- [79] Denais CM, Gilbert RM, Isermann P, McGregor AL, te Lindert M, Weigelin B, Davidson PM, Friedl P, Wolf K, Lammerding J. Nuclear envelope rupture and repair during cancer cell migration. *Science*. 2016. doi:10.1126/science.aad7297.
- [80] Vietri M, Radulovic M, Stenmark H. The many functions of ESCRTs. *Nature Reviews Molecular Cell Biology*. 2020. doi:10.1038/s41580-019-0177-4.
- [81] Ridler C. Does tau pathology activate jumping genes?. *Nature Reviews Neurology*. 2018. doi:10.1038/s41582-018-0056-1.
- [82] Ramirez P, Zuniga G, Sun W, Beckmann A, Ochoa E, DeVos SL, Hyman B, Chiu G, Roy ER, Cao W, Orr M, Buggia-Prevot V, Ray WJ, Frost B. Pathogenic tau accelerates aging-associated activation of transposable elements in the mouse central nervous system. *Progress in Neurobiology*. 2022. doi:10.1016/j.pneurobio.2021.102181.
- [83] Ozata DM, Gainetdinov I, Zoch A, O'Carroll D, Zamore PD. PIWI-interacting RNAs: small RNAs with big functions. *Nature Reviews Genetics*. 2019. doi:10.1038/s41576-018-0073-3.
- [84] Lee EJ, Banerjee S, Zhou H, Jammalamadaka A, Arcila M, Manjunath BS, Kosik KS. Identification of piRNAs in the central nervous system. *RNA*. 2011. doi:10.1261/rna.2565011.
- [85] Perera BPU, Tsai ZT, Colwell ML, Jones TR, Goodrich JM, Wang K, Sartor MA, Faulk C, Dolinoy DC. Somatic expression of piRNA and associated machinery in the mouse identifies short, tissue-specific piRNA. *Epigenetics*. 2019. doi:10.1080/15592294.2019.1600389.
- [86] Leighton LJ, Wei W, Marshall PR, Ratnu VS, Li X, Zajackowski EL, Spadaro PA, Khandelwal N, Kumar A, Bredy TW. Disrupting the hippocampal Piwi pathway enhances contextual fear memory in mice. *Neurobiology of Learning and Memory*. 2019. doi:10.1016/j.nlm.2019.04.002.
- [87] Tosar JP, Rovira C, Cayota A. Non-coding RNA fragments account for the majority of annotated piRNAs expressed in somatic non-gonadal tissues. *Communications Biology*. 2018. doi:10.1038/s42003-017-0001-7.
- [88] Tosar JP, García-Silva MR, Cayota A. Circulating SNORD57 rather than piR-54265 is a promising biomarker for colorectal cancer: common pitfalls in the study of somatic piRNAs in cancer. *RNA*. 2021. doi:10.1261/rna.078444.120.
- [89] Rajasethupathy P, Antonov I, Sheridan R, Frey S, Sander C, Tuschl T, Kandel ER. A role for neuronal piRNAs in the epigenetic control of memory-related synaptic plasticity. *Cell*. 2012. doi:10.1016/j.cell.2012.02.057.
- [90] Ecco G, Imbeault M, Trono D. KRAB zinc finger proteins. *Development*. 2017. doi:10.1242/dev.132605.
- [91] Fasching L, Kapopoulou A, Sachdeva R, Petri R, Jönsson ME, Männe C, Turelli P, Jern P, Cammas F, Trono D, Jakobsson J. TRIM28 represses transcription of endogenous retroviruses in neural progenitor cells. *Cell Reports*. 2015. doi:10.1016/j.celrep.2014.12.004.
- [92] Brattås PL, Jönsson ME, Fasching L, Nelander Wahlestedt J, Shahsavani M, Falk R, Falk A, Jern P, Parmar M, Jakobsson J. TRIM28 controls a gene regulatory network based on

- endogenous retroviruses in human neural progenitor cells. *Cell Reports*. 2017. doi:10.1016/j.celrep.2016.12.010.
- [93] Fukuda K, Shinkai Y. SETDB1-mediated silencing of retroelements. *Viruses*. 2020. doi:10.3390/v12060596.
- [94] Pandiloski N, Horváth V, Karlsson O, Koutounidou S, Dorazehi F, Christoforidou G, Matas-Fuentes J, Gerdes P, Garza R, Jönsson ME, Adami A, Atacho DAM, Johansson JG, Englund E, Kokaia Z, Jakobsson J, Douse CH. DNA methylation governs the sensitivity of repeats to restriction by the HUSH-MORC2 corepressor. *Nature Communications*. 2024. doi:10.1038/s41467-024-50765-4.
- [95] Mansuroglu Z, Benhelli-Mokrani H, Marcato V, Sultan A, Violet M, Chauderlier A, Buée L, Galas MC, Bonnefoy E. Loss of Tau protein affects the structure, transcription and repair of neuronal pericentromeric heterochromatin. *Scientific Reports*. 2016. doi:10.1038/srep33047.
- [96] Ardeljan D, Wang X, Oghbaie M, Taylor MS, Husband D, Deshpande V, Steranka JP, Gorbounov M, Yang WR, Sie B, Larman HB, Jiang H, Molloy KR, Altukhov I, Li Z, McKerrow W, Fenyö D, Burns KH, LaCava J. LINE-1 ORF2p expression is nearly imperceptible in human cancers. *Mobile DNA*. 2019. doi:10.1186/s13100-019-0191-2.
- [97] Nicodemus J, Liu CS, Ransom L, Tan V, Romanow W, Jimenez N, Chun J. Sequence diversity and encoded enzymatic differences of monocistronic L1 ORF2 mRNA variants in the aged normal and Alzheimer's disease brain. *Journal of Neuroscience*. 2025. doi:10.1523/JNEUROSCI.2298-24.2025.
- [98] Ramirez P, Sun W, Dehkordi SK, Zare H, Pascarella G, Carninci P, Fongang B, Bieniek KF, Frost B. Long-read sequencing reveals genomic and epigenomic variation in the dark genome of human Alzheimer's disease. *Alzheimer's & Dementia*. 2025. doi:10.1002/alz.70852.
- [99] Ramirez P, Zuniga G, Ochoa E, Frost B. Long-read sequencing-based analyses of the adult *Drosophila* brain transcriptome in physiological and pathological settings. *BMC Genomics*. 2025. doi:10.1186/s12864-025-12111-w.
- [100] Deininger P, Morales ME, White TB, Baddoo M, Hedges DJ, Servant G, Srivastav S, Smither ME, Concha M, DeHaro DL, Flemington EK, Belancio VP. A comprehensive approach to expression of L1 loci. *Nucleic Acids Research*. 2017. doi:10.1093/nar/gkw1067.
- [101] Lanciano S, Cristofari G. Measuring and interpreting transposable element expression. *Nature Reviews Genetics*. 2020. doi:10.1038/s41576-020-0251-y.
- [102] Sexton CE, Han MV. Paired-end mappability of transposable elements in the human genome. *Mobile DNA*. 2019. doi:10.1186/s13100-019-0172-5.
- [103] Jönsson ME, Ludvik Brattås P, Gustafsson C, Petri R, Yudovich D, Pircs K, Verschuere S, Madsen S, Hansson J, Larsson J, Månsson R, Meissner A, Jakobsson J. Activation of neuronal genes via LINE-1 elements upon global DNA demethylation in human neural progenitors. *Nature Communications*. 2019. doi:10.1038/s41467-019-11150-8.
- [104] Lanciano S, Philippe C, Sarkar A, Pratella D, Domrane C, Doucet AJ, van Essen D, Saccani S, Ferry L, Defossez PA, Cristofari G. Locus-level L1 DNA methylation profiling

- reveals the epigenetic and transcriptional interplay between LIs and their integration sites. *Cell Genomics*. 2024. doi:10.1016/j.xgen.2024.100498.
- [105] Freeman B, White T, Kaul T, Stow EC, Baddoo M, Ungerleider N, Morales M, Yang H, Deharo D, Deininger P, Belancio VP. Analysis of epigenetic features characteristic of LI loci expressed in human cells. *Nucleic Acids Research*. 2022. doi:10.1093/nar/gkac013.
- [106] Jin Y, Tam OH, Paniagua E, Hammell M. TETranscripts: a package for including transposable elements in differential expression analysis of RNA-seq datasets. *Bioinformatics*. 2015. doi:10.1093/bioinformatics/btv422.
- [107] Yang WR, Ardeljan D, Pacyna CN, Payer LM, Burns KH. SQuIRE reveals locus-specific regulation of interspersed repeat expression. *Nucleic Acids Research*. 2019. doi:10.1093/nar/gky1301.
- [108] Bendall ML, de Mulder M, Iñiguez LP, Lecanda-Sánchez A, Pérez-Losada M, Ostrowski MA, Jones RB, Mulder LCF, Reyes-Terán G, Crandall KA, Ormsby CE, Nixon DF. Telescope: characterization of the retrotranscriptome by accurate estimation of transposable element expression. *PLoS Computational Biology*. 2019. doi:10.1371/journal.pcbi.1006453.
- [109] Ansaloni F, Gualandi N, Esposito M, Gustincich S, Sanges R. TEspeX: consensus-specific quantification of transposable element expression preventing biases from exonized fragments. *Bioinformatics*. 2022. doi:10.1093/bioinformatics/btac526.
- [110] Lee S, Barbour JA, Tam YM, Yang H, Huang Y, Wong JWH. LocusMasterTE: integrating long-read RNA sequencing improves locus-specific quantification of transposable element expression. *Genome Biology*. 2025. doi:10.1186/s13059-025-03522-9.
- [111] Tam OH, Rozhkov NV, Shaw R, Kim D, Hubbard I, Fennessey S, Propp N, Fagegaltier D, Harris BT, Ostrow LW, Phatnani H, Ravits J, Dubnau J, Gale Hammell M. Postmortem cortex samples identify distinct molecular subtypes of ALS: retrotransposon activation, oxidative stress, and activated glia. *Cell Reports*. 2019. doi:10.1016/j.celrep.2019.09.066.
- [112] Bonnifet T, Sinnassamy S, Massiani-Beaudoin O, Mailly P, Monnet H, Loew D, Lombard B, Servant N, Joshi RL, Fuchs J. Steady-state neuron-predominant LINE-1 encoded ORF1p protein and LINE-1 RNA increase with aging in the mouse and human brain. *eLife*. 2025. doi:10.7554/eLife.100687.
- [113] Garza R, Atacho DAM, Adami A, Gerdes P, Vinod M, Hsieh P, Karlsson O, Horvath V, Johansson PA, Pandiloski N, Matas-Fuentes J, Quaegebeur A, Kouli A, Sharma Y, Jönsson ME, Monni E, Englund E, Eichler EE, Hammell MG, Barker RA, Kokaia Z, Douse CH, Jakobsson J. LINE-1 retrotransposons drive human neuronal transcriptome complexity and functional diversification. *Science Advances*. 2023. doi:10.1126/sciadv.adh9543.
- [114] Evans TA, Erwin JA. Retroelement-derived RNA and its role in the brain. *Seminars in Cell & Developmental Biology*. 2021. doi:10.1016/j.semcdb.2020.11.001.
- [115] Turan E, Çeltik B, Dağlar G, Kaya I, Tüfekçi M, Yandım C. Comparisons between young, aged, and Alzheimer's brains reveal specific expression patterns for a subset of transposons and satellite repeats. *Journal of Biosciences*. 2025. Source.

- [116] Macciardi F, Bacalini MG, Miramontes R, Boattini A, Taccioli C, Modenini G, Malhas R, Anderlucci L, Gusev Y, Gross TJ, Padilla RM, Fiandaca MS, Head E, Guffanti G, Federoff HJ, Mapstone M. A retrotransposon storm marks clinical phenoconversion to late-onset Alzheimer's disease. *GeroScience*. 2022. doi:10.1007/s11357-022-00580-w.
- [117] Cavalier AN, Smith ME, McWilliams GT, McEntee CM, Bettcher BM, Coughlan C, LaRocca TJ. Epigenetic dysregulation of transposable elements in cognitive impairment and Alzheimer's disease. *GeroScience*. 2025. doi:10.1007/s11357-025-01765-9.
- [118] Jönsson ME, Garza R, Sharma Y, Petri R, Södersten E, Johansson JG, Johansson PA, Atacho DAM, Pircs K, Madsen S, Yudovich D, Ramakrishnan R, Holmberg J, Larsson J, Jern P, Jakobsson J. Activation of endogenous retroviruses during brain development causes an inflammatory response. *EMBO Journal*. 2021. doi:10.15252/embj.2020106423.
- [119] McEntee CM, LaRocca TJ. Single-cell transcriptome patterns of transposable elements in Alzheimer's disease. *Molecular Neurobiology*. 2025. doi:10.1007/s12035-025-05140-9.
- [120] Grant RA, Doser RL, LaRocca TJ. Distinct transposable element transcript patterns in microglia across aging and Alzheimer's disease. *Aging Cell*. 2026. doi:10.1111/ace1.70653.
- [121] Feng Y, Yang X, Hou Y, Zhou Y, Leverenz JB, Eng C, Pieper AA, Goate A, Shen Y, Cheng F. Widespread transposable element dysregulation in human aging brains with Alzheimer's disease. *Alzheimer's & Dementia*. 2024. doi:10.1002/alz.14164.
- [122] Feng Y, Cao SQ, Shi Y, Sun A, Flanagan ME, Leverenz JB, Pieper AA, Jung JU, Cummings J, Fang EF, Zhang P, Cheng F. Human herpesvirus-associated transposable element activation in human aging brains with Alzheimer's disease. *Alzheimer's & Dementia*. 2025. doi:10.1002/alz.14595.
- [123] Roy N, Haq I, Ngo JC, Bennett DA, Teich AF, De Jager PL, Olah M, Sher F. Elevated expression of the retrotransposon LINE-1 drives Alzheimer's disease-associated microglial dysfunction. *Acta Neuropathologica*. 2024. doi:10.1007/s00401-024-02835-6.
- [124] Upton KR, Gerhardt DJ, Jesuadian JS, Richardson SR, Sánchez-Luque FJ, Bodea GO, Ewing AD, Salvador-Palomeque C, van der Knaap MS, Brennan PM, Vanderver A, Faulkner GJ. Ubiquitous L1 mosaicism in hippocampal neurons. *Cell*. 2015. doi:10.1016/j.cell.2015.03.026.
- [125] Baillie JK, Barnett MW, Upton KR, Gerhardt DJ, Richmond TA, De Sapio F, Brennan PM, Rizzu P, Smith S, Fell M, Talbot RT, Gustincich S, Freeman TC, Mattick JS, Hume DA, Heutink P, Carninci P, Jeddloh JA, Faulkner GJ. Somatic retrotransposition alters the genetic landscape of the human brain. *Nature*. 2011. doi:10.1038/nature10531.
- [126] Evrony GD, Cai X, Lee E, Hills LB, Elhosary PC, Lehmann HS, Parker JJ, Atabay KD, Gilmore EC, Poduri A, Park PJ, Walsh CA. Single-neuron sequencing analysis of L1 retrotransposition and somatic mutation in the human brain. *Cell*. 2012. doi:10.1016/j.cell.2012.09.035.
- [127] Evrony GD, Lee E, Park PJ, Walsh CA. Resolving rates of mutation in the brain using single-neuron genomics. *eLife*. 2016. doi:10.7554/eLife.12966.
- [128] Sanchez-Luque FJ, Kempen MHC, Gerdes P, Vargas-Landin DB, Richardson SR, Troskie RL, Jesuadian JS, Cheetham SW, Carreira PE, Salvador-Palomeque C, García-Cañadas M, Muñoz-Lopez M, Sanchez L, Lundberg M, Macia A, Heras SR,

- Brennan PM, Lister R, Garcia-Perez JL, Ewing AD, Faulkner CJ. LINE-1 evasion of epigenetic repression in humans. *Molecular Cell*. 2019. doi:10.1016/j.molcel.2019.05.024.
- [129] Erwin JA, Paquola ACM, Singer T, Gallina I, Novotny M, Quayle C, Bedrosian TA, Alves FIA, Butcher CR, Herdy JR, Sarkar A, Lasken RS, Muotri AR, Gage FH. L1-associated genomic regions are deleted in somatic cells of the healthy human brain. *Nature Neuroscience*. 2016. doi:10.1038/nn.4388.
- [130] Muotri AR, Chu VT, Marchetto MCN, Deng W, Moran JV, Gage FH. Somatic mosaicism in neuronal precursor cells mediated by L1 retrotransposition. *Nature*. 2005. doi:10.1038/nature03663.
- [131] Coufal NG, Garcia-Perez JL, Peng GE, Yeo GW, Mu Y, Lovci MT, Morell M, O'Shea KS, Moran JV, Gage FH. L1 retrotransposition in human neural progenitor cells. *Nature*. 2009. doi:10.1038/nature08248.
- [132] Macia A, Widmann TJ, Heras SR, Ayllon V, Sanchez L, Benkaddour-Boumzaouad M, Muñoz-Lopez M, Rubio A, Amador-Cubero S, Blanco-Jimenez E, Garcia-Castro J, Menendez P, Ng P, Muotri AR, Goodier JL, Garcia-Perez JL. Engineered LINE-1 retrotransposition in nondividing human neurons. *Genome Research*. 2017. doi:10.1101/gr.206805.116.
- [133] Lodato MA, Woodworth MB, Lee S, Evrony GD, Mehta BK, Karger A, Lee S, Chittenden TW, D'Gama AM, Cai X, Luquette LJ, Lee E, Park PJ, Walsh CA. Somatic mutation in single human neurons tracks developmental and transcriptional history. *Science*. 2015. doi:10.1126/science.aab1785.
- [134] Bundo M, Toyoshima M, Okada Y, Akamatsu W, Ueda J, Nemoto-Miyauchi T, Sunaga F, Toritsuka M, Ikawa D, Kakita A, Kato M, Kasai K, Kishimoto T, Nawa H, Okano H, Yoshikawa T, Kato T, Iwamoto K. Increased L1 retrotransposition in the neuronal genome in schizophrenia. *Neuron*. 2014. doi:10.1016/j.neuron.2013.10.053.
- [135] Thomas CA, Tejwani L, Trujillo CA, Negraes PD, Herai RH, Mesci P, Macia A, Crow YJ, Muotri AR. Modeling of TREX1-dependent autoimmune disease using human stem cells highlights L1 accumulation as a source of neuroinflammation. *Cell Stem Cell*. 2017. doi:10.1016/j.stem.2017.07.009.
- [136] Li W, Lee MH, Henderson L, Tyagi R, Bachani M, Steiner J, Campanac E, Hoffman DA, von Geldern G, Johnson K, Maric D, Morris HD, Lentz M, Pak K, Mammen A, Ostrow L, Rothstein J, Nath A. Human endogenous retrovirus-K contributes to motor neuron disease. *Science Translational Medicine*. 2015. doi:10.1126/scitranslmed.aac8201.
- [137] Garcia-Montojo M, Li W, Nath A. Technical considerations in detection of HERV-K in amyotrophic lateral sclerosis: selection of controls and the perils of qPCR. *Acta Neuropathologica Communications*. 2019. doi:10.1186/s40478-019-0753-z.
- [138] Garson JA, Usher L, Al-Chalabi A, Huggett J, Day EF, McCormick AL. Response to the Letter from Garcia-Montojo and colleagues concerning our paper entitled, Quantitative analysis of human endogenous retrovirus-K transcripts in postmortem premotor cortex fails to confirm elevated expression of HERV-K RNA in amyotrophic lateral sclerosis. *Acta Neuropathologica Communications*. 2019. doi:10.1186/s40478-019-0756-9.

- [139] Gold J, Rowe DB, Kiernan MC, Vucic S, Mathers S, van Eijk RPA, Nath A, Garcia Montojo M, Norato G, Santamaria UA, Rogers ML, Malaspina A, Lombardi V, Mehta PR, Westeneng HJ, van den Berg LH, Al-Chalabi A. Safety and tolerability of Triumeq in amyotrophic lateral sclerosis: the Lighthouse trial. *Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration*. 2019. doi:10.1080/21678421.2019.1632899.
- [140] Liu EY, Russ J, Cali CP, Phan JM, Amlie-Wolf A, Lee EB. Loss of nuclear TDP-43 is associated with decondensation of LINE retrotransposons. *Cell Reports*. 2019. doi:10.1016/j.celrep.2019.04.003.
- [141] McEntee CM, Cavalier AN, LaRocca TJ. ADAR1 suppression causes interferon signaling and transposable element transcript accumulation in human astrocytes. *Frontiers in Molecular Neuroscience*. 2023. doi:10.3389/fnmol.2023.1263369.
- [142] Civril F, Deimling T, de Oliveira Mann CC, et al. Structural mechanism of cytosolic DNA sensing by cGAS. *Nature*. 2013. doi:10.1038/nature12305.
- [143] Li X, Shu C, Yi G, et al. Cyclic GMP-AMP synthase is activated by double-stranded DNA-induced oligomerization. *Immunity*. 2013. doi:10.1016/j.immuni.2013.10.019.
- [144] Luecke S, Holleufer A, Christensen MH, et al. cGAS is activated by DNA in a length-dependent manner. *EMBO Reports*. 2017. doi:10.15252/embr.201744017.
- [145] Andreeva L, Hiller B, Kostrewa D, et al. cGAS senses long and HMGB/TFAM-bound U-turn DNA by forming protein-DNA ladders. *Nature*. 2017. doi:10.1038/nature23890.
- [146] Xie W, Lama L, Adura C, et al. Human cGAS catalytic domain has an additional DNA-binding interface that enhances enzymatic activity and liquid-phase condensation. *PNAS*. 2019. doi:10.1073/pnas.1905013116.
- [147] Zhou W, Whiteley AT, de Oliveira Mann CC, et al. Structure of the human cGAS-DNA complex reveals enhanced control of immune surveillance. *Cell*. 2018. doi:10.1016/j.cell.2018.06.026.
- [148] Tao J, Zhang XW, Jin J, et al. Nonspecific DNA binding of cGAS N terminus promotes cGAS activation. *Journal of Immunology*. 2017. doi:10.4049/jimmunol.1601909.
- [149] Du M, Chen ZJ. DNA-induced liquid phase condensation of cGAS activates innate immune signaling. *Science*. 2018. doi:10.1126/science.aat1022.
- [150] Zhang X, Shi H, Wu J, et al. Cyclic GMP-AMP containing mixed phosphodiester linkages is an endogenous high-affinity ligand for STING. *Molecular Cell*. 2013. doi:10.1016/j.molcel.2013.05.022.
- [151] Liu H, Zhang H, Wu X, et al. Nuclear cGAS suppresses DNA repair and promotes tumorigenesis. *Nature*. 2018. doi:10.1038/s41586-018-0629-6.
- [152] Jiang H, Xue X, Panda S, et al. Chromatin-bound cGAS is an inhibitor of DNA repair and hence accelerates genome destabilization and cell death. *EMBO Journal*. 2019. doi:10.15252/emboj.2019102718.
- [153] Chen H, Chen H, Zhang J, et al. cGAS suppresses genomic instability as a decelerator of replication forks. *Science Advances*. 2020. doi:10.1126/sciadv.abb8941.

- [154] Yang H, Gao B, Wu B, et al. cGAS restricts PARP1-mediated microhomology-mediated end joining by suppressing poly-ADP-ribosylation. *Cell Death and Differentiation*. 2025. doi:10.1038/s41418-025-01637-x.
- [155] Zhang H, Jiang L, Du X, et al. The cGAS-Ku80 complex regulates the balance between two end joining subpathways. *Cell Death and Differentiation*. 2024. doi:10.1038/s41418-024-01296-4.
- [156] Zierhut C, Yamaguchi N, Paredes M, et al. The cytoplasmic DNA sensor cGAS promotes mitotic cell death. *Cell*. 2019. doi:10.1016/j.cell.2019.05.035.
- [157] Bai J, Liu F. Nuclear cGAS: sequestration and beyond. *Protein and Cell*. 2021. doi:10.1007/s13238-021-00869-0.
- [158] Cho MG, Gupta GP. Unveiling cGAS mechanisms: insights into DNA damage and immune sensing in cancer. *DNA Repair*. 2025. doi:10.1016/j.dnarep.2025.103868.
- [159] Kujirai T, Zierhut C, Takizawa Y, et al. Structural basis for the inhibition of cGAS by nucleosomes. *Science*. 2020. doi:10.1126/science.abd0237.
- [160] Boyer JA, Spangler CJ, Strauss JD, et al. Structural basis of nucleosome-dependent cGAS inhibition. *Science*. 2020. doi:10.1126/science.abd0609.
- [161] Pathare GR, Decout A, Gluck S, et al. Structural mechanism of cGAS inhibition by the nucleosome. *Nature*. 2020. doi:10.1038/s41586-020-2750-6.
- [162] Guey B, Wischniewski M, Decout A, et al. BAF restricts cGAS on nuclear DNA to prevent innate immune activation. *Science*. 2020. doi:10.1126/science.aaw6421.
- [163] Li T, Huang T, Du M, et al. Phosphorylation and chromatin tethering prevent cGAS activation during mitosis. *Science*. 2021. doi:10.1126/science.abc5386.
- [164] Cho MG, Kumar RJ, Lin CC, et al. MRE11 liberates cGAS from nucleosome sequestration during tumorigenesis. *Nature*. 2024. doi:10.1038/s41586-023-06889-6.
- [165] MacDonald KM, Nicholson-Puthenveedu S, Tageldeen MM, et al. Antecedent chromatin organization determines cGAS recruitment to ruptured micronuclei. *Nature Communications*. 2023. doi:10.1038/s41467-023-36195-8.
- [166] Crow YJ, Hayward BE, Parmar R, et al. Mutations in the gene encoding the 3'-5' DNA exonuclease TREX1 cause Aicardi-Goutieres syndrome at the AGS1 locus. *Nature Genetics*. 2006. doi:10.1038/ng1845.
- [167] Gray EE, Treuting PM, Woodward JJ, Stetson DB. Cutting edge: cGAS is required for lethal autoimmune disease in the Trex1-deficient mouse model of Aicardi-Goutieres syndrome. *Journal of Immunology*. 2015. doi:10.4049/jimmunol.1500969.
- [168] Stetson DB, Ko JS, Heidmann T, Medzhitov R. Trex1 prevents cell-intrinsic initiation of autoimmunity. *Cell*. 2008. doi:10.1016/j.cell.2008.06.032.
- [169] Gehrke N, Mertens C, Zillinger T, et al. Oxidative damage of DNA confers resistance to cytosolic nuclease TREX1 degradation and potentiates STING-dependent immune sensing. *Immunity*. 2013. doi:10.1016/j.immuni.2013.08.004.

- [170] Li LJ, Sun XY, Huang YR, et al. Neuronal double-stranded DNA accumulation induced by DNase II deficiency drives tau phosphorylation and neurodegeneration. *Translational Neurodegeneration*. 2024. doi:10.1186/s40035-024-00427-8.
- [171] Maze I, Wenderski W, Noh KM, Bagot RC, Tzavaras N, Purushothaman I, Elsässer SJ, Guo Y, Ionete C, Hurd YL, Tamminga CA, Halene T, Farrelly L, Soshnev AA, Wen D, Rafii S, Birtwistle MR, Akbarian S, Buchholz BA, Blitzer RD, Nestler EJ, Zhou MM, Tarakhovsky A, Dewell S, Allis CD. Critical role of histone turnover in neuronal transcription and plasticity. *Neuron*. 2015. doi:10.1016/j.neuron.2015.06.014.
- [172] von Schimmelmann M, Feinberg PA, Sullivan JM, Ku SM, Badimon A, Duff MK, Wang Z, Lachmann A, Dewell S, Ma'ayan A, Han MH, Tarakhovsky A, Schaefer A. Polycomb repressive complex 2 (PRC2) silences genes responsible for neurodegeneration. *Nature Neuroscience*. 2016. doi:10.1038/nn.4360.
- [173] Pindyurin AV, Ilyin AA, Ivankin AV, Tselebrovsky MV, Nenasheva VV, Mikhaleva EA, Pagie L, van Steensel B, Shevelyov YY. The large fraction of heterochromatin in Drosophila neurons is bound by both B-type lamin and HP1a. *Epigenetics & Chromatin*. 2018. doi:10.1186/s13072-018-0235-8.
- [174] Guelen L, Pagie L, Brasset E, Meuleman W, Faza MB, Talhout W, Eussen BH, de Klein A, Wessels L, de Laat W, van Steensel B. Domain organization of human chromosomes revealed by mapping of nuclear lamina interactions. *Nature*. 2008. doi:10.1038/nature06947.
- [175] Peric-Hupkes D, Meuleman W, Pagie L, Bruggeman SW, Solovei I, Brugman W, Gräf S, Flicek P, Kerkhoven RM, van Lohuizen M, Reinders M, Wessels L, van Steensel B. Molecular maps of the reorganization of genome-nuclear lamina interactions during differentiation. *Molecular Cell*. 2010. doi:10.1016/j.molcel.2010.03.016.
- [176] Madabhushi R, Gao F, Pfenning AR, et al. Activity-induced DNA breaks govern the expression of neuronal early-response genes. *Cell*. 2015. doi:10.1016/j.cell.2015.05.032.
- [177] Suberbielle E, Sanchez PE, Kravitz AV, et al. Physiologic brain activity causes DNA double-strand breaks in neurons, with exacerbation by amyloid-beta. *Nature Neuroscience*. 2013. doi:10.1038/nn.3356.
- [178] Karlsson M, Zhang C, Mear L, et al. A single-cell type transcriptomics map of human tissues. *Science Advances*. 2021. doi:10.1126/sciadv.abh2169.
- [179] Zhang Y, Chen K, Sloan SA, et al. An RNA-sequencing transcriptome and splicing database of glia, neurons, and vascular cells of the cerebral cortex. *Journal of Neuroscience*. 2014. doi:10.1523/JNEUROSCI.1860-14.2014.
- [180] Siletti K, Hodge R, Mossi Albiach A, et al. Transcriptomic diversity of cell types across the adult human brain. *Science*. 2023. doi:10.1126/science.add7046.
- [181] Mathys H, Davila-Velderrain J, Peng Z, et al. Single-cell transcriptomic analysis of Alzheimer's disease. *Nature*. 2019. doi:10.1038/s41586-019-1195-2.
- [182] De Cecco M, Ito T, Petrashen AP, et al. L1 drives IFN in senescent cells and promotes age-associated inflammation. *Nature*. 2019. doi:10.1038/s41586-018-0784-9.

- [183] Simon M, Van Meter M, Ablueva J, et al. LINE1 derepression in aged wild-type and SIRT6-deficient mice drives inflammation. *Cell Metabolism*. 2019. doi:10.1016/j.cmet.2019.02.014.
- [184] Tanabe LM, Liang CC, Dauer WT. Neuronal nuclear membrane budding occurs during a developmental window modulated by torsin paralogs. *Cell Reports*. 2016. doi:10.1016/j.celrep.2016.08.044.
- [185] Li Y, Huang H, Gao J, Lu J, et al. A TLK2-mediated calcium-driven cell death pathway links neuronal degeneration to nuclear envelope disruption. *Nature Communications*. 2025. doi:10.1038/s41467-025-58737-y.
- [186] Gasset-Rosa F, Chillon-Marinhas C, Goginashvili A, Atwal RS, Artates JW, Tabet R, Wheeler VC, Bang AG, Cleveland DW, Lagier-Tourenne C. Polyglutamine-expanded huntingtin exacerbates age-related disruption of nuclear integrity and nucleocytoplasmic transport. *Neuron*. 2017. doi:10.1016/j.neuron.2017.03.027.
- [187] Yano S, Akiyama K, Tsuchiya R, et al. A MATLAB-based program for three-dimensional quantitative analysis of micronuclei reveals that neuroinflammation induces micronuclei formation in the brain. *Scientific Reports*. 2021. doi:10.1038/s41598-021-97640-6.
- [188] Hatch EM, Fischer AH, Deerinck TJ, Hetzer MW. Catastrophic nuclear envelope collapse in cancer cell micronuclei. *Cell*. 2013. doi:10.1016/j.cell.2013.06.007.
- [189] van den Bos H, Spierings DCJ, Taudt AS, Bakker B, Porubský D, Falconer E, Novoa C, Halsema N, Kazemier HG, Hoekstra-Wakker K, Guryev V, den Dunnen WFA, Foijer F, Colomé-Tatché M, Boddeke HWGM, Lansdorp PM. Single-cell whole genome sequencing reveals no evidence for common aneuploidy in normal and Alzheimer's disease neurons. *Genome Biology*. 2016. doi:10.1186/s13059-016-0976-2.
- [190] Yang Y, Geldmacher DS, Herrup K. DNA replication precedes neuronal cell death in Alzheimer's disease. *Journal of Neuroscience*. 2001. doi:10.1523/JNEUROSCI.21-08-02661.2001.
- [191] Herrup K, Yang Y. Cell cycle regulation in the postmitotic neuron: oxymoron or new biology?. *Nature Reviews Neuroscience*. 2007. doi:10.1038/nrn2124.
- [192] Bergman M, Goshtchevsky U, Atlan T, et al. A dual role for cGAS in shaping cellular and organismal responses to genomic instability. *Genes and Development*. 2026. doi:10.1101/gad.352760.125.
- [193] Yang H, Wang H, Ren J, Chen Q, Chen ZJ. cGAS is essential for cellular senescence. *PNAS*. 2017. doi:10.1073/pnas.1705499114.
- [194] Narita M, Nunez S, Heard E, Narita M, Lin AW, Hearn SA, Spector DL, Hannon CJ, Lowe SW. Rb-mediated heterochromatin formation and silencing of E2F target genes during cellular senescence. *Cell*. 2003. doi:10.1016/s0092-8674(03)00401-x.
- [195] Zhang H, Li J, Yu Y, et al. Nuclear lamina erosion-induced resurrection of endogenous retroviruses underlies neuronal aging. *Cell Reports*. 2023. doi:10.1016/j.celrep.2023.112593.

- [196] Herdy JR, Taylor EE, Karbacher L, et al. Cytoplasmic DNA sensing links LINE-1 expression to neuronal senescence in Alzheimer's disease. *bioRxiv*. 2026. doi:10.64898/2026.07.27.740588.
- [197] Herdy JR, Traxler L, Agarwal RK, Karbacher L, Schlachetzki JCM, Boehnke L, Zangwill D, Galasko D, Glass CK, Mertens J, Gage FH. Increased post-mitotic senescence in aged human neurons is a pathological feature of Alzheimer's disease. *Cell Stem Cell*. 2022. doi:10.1016/j.stem.2022.11.010.
- [198] Dou Z, Ghosh K, Vizioli MG, et al. Cytoplasmic chromatin triggers inflammation in senescence and cancer. *Nature*. 2017. doi:10.1038/nature24050.
- [199] Gluck S, Guey B, Gulen MF, et al. Innate immune sensing of cytosolic chromatin fragments through cGAS promotes senescence. *Nature Cell Biology*. 2017. doi:10.1038/ncb3586.
- [200] Jurk D, Wang C, Miwa S, Maddick M, Korolchuk V, Tzolou A, Gonos ES, Thrassivoulou C, Saffrey MJ, Cameron K, von Zglinicki T. Postmitotic neurons develop a p21-dependent senescence-like phenotype driven by a DNA damage response. *Aging Cell*. 2012. doi:10.1111/j.1474-9726.2012.00870.x.
- [201] Dehkordi SK, Walker J, Sah E, Bennett E, Atrian F, Frost B, Woost B, Bennett RE, Orr TC, Zhou Y, Andhey PS, Colonna M, Sudmant PH, Xu P, Wang M, Zhang B, Zare H, Orr ME. Profiling senescent cells in human brains reveals neurons with CDKN2D/p19 and tau neuropathology. *Nature Aging*. 2021. doi:10.1038/s43587-021-00142-3.
- [202] Musi N, Valentine JM, Sickora KR, Baeuerle E, Thompson CS, Shen Q, Orr ME. Tau protein aggregation is associated with cellular senescence in the brain. *Aging Cell*. 2018. doi:10.1111/accel.12840.
- [203] Yano S, Asami N, Kishi Y, et al. Propagation of neuronal micronuclei regulates microglial characteristics. *Nature Neuroscience*. 2025. doi:10.1038/s41593-024-01863-5.
- [204] Maeda C, Kishi Y, Takeda I, et al. Age-associated neuronal micronuclei formation and transfer to microglia. *Frontiers in Aging Neuroscience*. 2026. doi:10.3389/fnagi.2026.1787252.
- [205] Udeochu JC, Amin S, Huang Y, et al. Tau activation of microglial cGAS-IFN reduces MEF2C-mediated cognitive resilience. *Nature Neuroscience*. 2023. doi:10.1038/s41593-023-01315-6.
- [206] Dileep V, Boix CA, Mathys H, Marco A, Welch GM, Meharena HS, Loon A, Jeloka R, Peng Z, Bennett DA, Kellis M, Tsai LH. Neuronal DNA double-strand breaks lead to genome structural variations and 3D genome disruption in neurodegeneration. *Cell*. 2023. doi:10.1016/j.cell.2023.08.038.
- [207] Aguado J, Chaggar HK, Gomez-Inclan C, et al. Inhibition of the cGAS-STING pathway ameliorates the premature senescence hallmarks of Ataxia-Telangiectasia brain organoids. *Aging Cell*. 2021. doi:10.1111/accel.13468.
- [208] Aditi, Downing SM, Schreiner PA, et al. Genome instability independent of type I interferon signaling drives neuropathology caused by impaired ribonucleotide excision repair. *Neuron*. 2021. doi:10.1016/j.neuron.2021.09.040.

- [209] Shanbhag NM, Evans MD, Mao W, et al. Early neuronal accumulation of DNA double strand breaks in Alzheimer's disease. *Acta Neuropathologica Communications*. 2019. doi:10.1186/s40478-019-0723-5.
- [210] Zhang X, Liu Y, Huang M, et al. Landscape of double-stranded DNA breaks in postmortem brains from Alzheimer's disease and non-demented individuals. *Journal of Alzheimer's Disease*. 2023. doi:10.3233/JAD-230316.
- [211] Roy ER, Wang B, Wan YW, et al. Type I interferon response drives neuroinflammation and synapse loss in Alzheimer disease. *Journal of Clinical Investigation*. 2020. doi:10.1172/JCI133737.
- [212] Roy ER, Chiu G, Li S, et al. Concerted type I interferon signaling in microglia and neural cells promotes memory impairment associated with amyloid beta plaques. *Immunity*. 2022. doi:10.1016/j.immuni.2022.03.018.
- [213] Passarella S, Kethiswaran S, Brandes K, et al. Alteration of cGAS-STING signaling pathway components in the mouse cortex and hippocampus during healthy brain aging. *Frontiers in Aging Neuroscience*. 2024. doi:10.3389/fnagi.2024.1429005.
- [214] Nelson TJ, Xu Y. Sting and p53 DNA repair pathways are compromised in Alzheimer's disease. *Scientific Reports*. 2023. doi:10.1038/s41598-023-35533-6.
- [215] Carling GK, Fan L, Foxe NR, et al. Alzheimer's disease-linked risk alleles elevate microglial cGAS-associated senescence and neurodegeneration in a tauopathy model. *Neuron*. 2024. doi:10.1016/j.neuron.2024.09.006.
- [216] Chung S, Jeong JH, Park JC, et al. Blockade of STING activation alleviates microglial dysfunction and a broad spectrum of Alzheimer's disease pathologies. *Experimental and Molecular Medicine*. 2024. doi:10.1038/s12276-024-01295-y.
- [217] Xie X, Ma G, Li X, et al. Activation of innate immune cGAS-STING pathway contributes to Alzheimer's pathogenesis in 5xFAD mice. *Nature Aging*. 2023. doi:10.1038/s43587-022-00337-2.
- [218] He S, Li X, Mittra N, et al. Microglial cGAS deletion preserves intercellular communication and alleviates amyloid-beta-induced pathogenesis of Alzheimer's disease. *Advanced Science*. 2025. doi:10.1002/advs.202410910.
- [219] Jin M, Shiwaku H, Tanaka H, et al. Tau activates microglia via the PQBP1-cGAS-STING pathway to promote brain inflammation. *Nature Communications*. 2021. doi:10.1038/s41467-021-26851-2.
- [220] Woo MS, Mayer C, Binkle-Ladisch L, et al. STING orchestrates the neuronal inflammatory stress response in multiple sclerosis. *Cell*. 2024. doi:10.1016/j.cell.2024.05.031.
- [221] Marques C, Held A, Dorfman K, et al. Neuronal STING activation in amyotrophic lateral sclerosis and frontotemporal dementia. *Acta Neuropathologica*. 2024. doi:10.1007/s00401-024-02688-z.
- [222] Naumann M, Wierschin TM, Kretschmer S, et al. RIG-I mediated neuron-specific IFN type 1 signaling in FUS-ALS induces neurodegeneration and offers new biomarker-driven individualized treatment options for (FUS-)ALS. *Advanced Science*. 2026. doi:10.1002/advs.202417135.

- [223] Hyde VR, Zhou C, Fernandez JR, et al. Anti-herpetic tau preserves neurons via the cGAS-STING-TBK1 pathway in Alzheimer's disease. *Cell Reports*. 2025. doi:10.1016/j.celrep.2024.115109.
- [224] Naguib S, Lopez-Lee C, Torres ER, et al. The R136S mutation in the APOE3 gene confers resilience against tau pathology via inhibition of the cGAS-STING-IFN pathway. *Immunity*. 2025. doi:10.1016/j.immuni.2025.05.023.
- [225] Arboleda-Velasquez JF, Lopera F, O'Hare M, et al. Resistance to autosomal dominant Alzheimer's disease in an APOE3 Christchurch homozygote: a case report. *Nature Medicine*. 2019. doi:10.1038/s41591-019-0611-3.
- [226] Gil L, Niño SA, Chi-Ahumada E, Rodríguez-Leyva I, Guerrero C, Rebolledo AB, Arias JA, Jiménez-Capdeville ME. Perinuclear lamin A and nucleoplasmic lamin B2 characterize two types of hippocampal neurons through Alzheimer's disease progression. *International Journal of Molecular Sciences*. 2020. doi:10.3390/ijms21051841.
- [227] Pietrzak M, Rempala G, Nelson PT, Zheng JJ, Hetman M. Epigenetic silencing of nucleolar rRNA genes in Alzheimer's disease. *PLoS One*. 2011. doi:10.1371/journal.pone.0022585.
- [228] Nativio R, Donahue G, Berson A, Lan Y, Amlie-Wolf A, Tuzer F, Toledo JB, Gosai SJ, Gregory BD, Torres C, Trojanowski JQ, Wang LS, Johnson FB, Bonini NM, Berger SL. Dysregulation of the epigenetic landscape of normal aging in Alzheimer's disease. *Nature Neuroscience*. 2018. doi:10.1038/s41593-018-0101-9.
- [229] Nativio R, Lan Y, Donahue G, Sidoli S, Berson A, Srinivasan AR, Shcherbakova O, Amlie-Wolf A, Nie J, Cui X, He C, Wang LS, Garcia BA, Trojanowski JQ, Bonini NM, Berger SL. An integrated multi-omics approach identifies epigenetic alterations associated with Alzheimer's disease. *Nature Genetics*. 2020. doi:10.1038/s41588-020-0696-0.
- [230] Marzi SJ, Leung SK, Ribarska T, Hannon E, Smith AR, Pishva E, Poschmann J, Moore K, Troakes C, Al-Sarraj S, Beck S, Newman S, Lunnon K, Schalkwyk LC, Mill J. A histone acetylome-wide association study of Alzheimer's disease identifies disease-associated H3K27ac differences in the entorhinal cortex. *Nature Neuroscience*. 2018. doi:10.1038/s41593-018-0253-7.
- [231] Calderón-Garcidueñas L, Herrera-Soto A, Jury N, Maher BA, González-Maciél A, Reynoso-Robles R, Ruiz-Rudolph P, van Zundert B, Varela-Nallar L. Reduced repressive epigenetic marks, increased DNA damage and Alzheimer's disease hallmarks in the brain of humans and mice exposed to particulate urban air pollution. *Environmental Research*. 2020. doi:10.1016/j.envres.2020.109226.
- [232] Loomis PA, Howard TH, Castleberry RP, Binder LI. Identification of nuclear tau isoforms in human neuroblastoma cells. *Proceedings of the National Academy of Sciences*. 1990. doi:10.1073/pnas.87.21.8422.
- [233] Wei Y, Qu MH, Wang XS, Chen L, Wang DL, Liu Y, Hua Q, He RQ. Binding to the minor groove of the double-strand, tau protein prevents DNA from damage by peroxidation. *PLoS One*. 2008. doi:10.1371/journal.pone.0002600.

- [234] Sjöberg MK, Shestakova E, Mansuroglu Z, Maccioni RB, Bonnefoy E. Tau protein binds to pericentromeric DNA: a putative role for nuclear tau in nucleolar organization. *Journal of Cell Science*. 2006. doi:10.1242/jcs.02907.
- [235] Benhelli-Mokrani H, Mansuroglu Z, Chauderlier A, Albaud B, Gentien D, Sommer S, Schirmer C, Buée L, Lefebvre B, Galas MC, Souès S, Bonnefoy E. Genome-wide identification of genic and intergenic neuronal DNA regions bound by Tau protein under physiological and stress conditions. *Nucleic Acids Research*. 2018. doi:10.1093/nar/gky929.
- [236] Sultan A, Nessler F, Violet M, Bégar S, Loyens A, Talahari S, Mansuroglu Z, Marzin D, Sergeant N, Humez S, Colin M, Bonnefoy E, Buée L, Galas MC. Nuclear tau, a key player in neuronal DNA protection. *Journal of Biological Chemistry*. 2011. doi:10.1074/jbc.M110.199976.
- [237] Violet M, Delattre L, Tardivel M, Sultan A, Chauderlier A, Caillierez R, Talahari S, Nessler F, Lefebvre B, Bonnefoy E, Buée L, Galas MC. A major role for Tau in neuronal DNA and RNA protection in vivo under physiological and hyperthermic conditions. *Frontiers in Cellular Neuroscience*. 2014. doi:10.3389/fncel.2014.00084.
- [238] Maina MB, Bailey LJ, Wagih S, Biasetti L, Pollack SJ, Quinn JP, Thorpe JR, Doherty AJ, Serpell LC. The involvement of tau in nucleolar transcription and the stress response. *Acta Neuropathologica Communications*. 2018. doi:10.1186/s40478-018-0565-6.
- [239] Hernández-Ortega K, Garcia-Esparcia P, Gil L, Lucas JJ, Ferrer I. Altered machinery of protein synthesis in Alzheimer's: from the nucleolus to the ribosome. *Brain Pathology*. 2016. doi:10.1111/bpa.12335.
- [240] Lester E, Ooi FK, Bakkar N, Ayers J, Woerman AL, Wheeler J, Bowser R, Carlson GA, Prusiner SB, Parker R. Tau aggregates are RNA-protein assemblies that mislocalize multiple nuclear speckle components. *Neuron*. 2021. doi:10.1016/j.neuron.2021.03.026.
- [241] Nunomura A, Hofer T, Moreira PI, Castellani RJ, Smith MA, Perry G. RNA oxidation in Alzheimer disease and related neurodegenerative disorders. *Acta Neuropathologica*. 2009. doi:10.1007/s00401-009-0508-1.
- [242] Asada-Utsugi M, Uemura K, Ayaki T, Uemura MT, Minamiyama S, Hikami R, Morimura T, Shodai A, Ueki T, Takahashi R, Kinoshita A, Urushitani M. Failure of DNA double-strand break repair by tau mediates Alzheimer's disease pathology in vitro. *Communications Biology*. 2022. doi:10.1038/s42003-022-03312-0.
- [243] Tanaka H, Kondo K, Fujita K, Homma H, Tagawa K, Jin X, Jin M, Saito T, Saido T, Murayama S, Okazawa H. HMGB1 signaling phosphorylates Ku70 and impairs DNA damage repair in Alzheimer's disease pathology. *Communications Biology*. 2021. doi:10.1038/s42003-021-02671-4.
- [244] Kiryk A, Sowodniok K, Kreiner G, Rodriguez-Parkitna J, Sönmez A, Górkiewicz T, Bierhoff H, Wawrzyniak M, Janusz AK, Liss B, Konopka W, Schütz G, Kaczmarek L, Parlato R. Impaired rRNA synthesis triggers homeostatic responses in hippocampal neurons. *Frontiers in Cellular Neuroscience*. 2013. doi:10.3389/fncel.2013.00207.
- [245] Villeponteau B. The heterochromatin loss model of aging. *Experimental Gerontology*. 1997. doi:10.1016/s0531-5565(96)00155-6.

- [246] Wood JG, Hillenmeyer S, Lawrence C, Chang C, Hosier S, Lightfoot W, Mukherjee E, Jiang N, Schorl C, Brodsky AS, Neretti N, Helfand SL. Chromatin remodeling in the aging genome of *Drosophila*. *Aging Cell*. 2010. doi:10.1111/j.1474-9726.2010.00624.x.
- [247] Orr ME, Sullivan AC, Frost B. A brief overview of tauopathy: causes, consequences, and therapeutic strategies. *Trends in Pharmacological Sciences*. 2017. doi:10.1016/j.tips.2017.03.011.
- [248] Valles-Saiz L, Avila J, Hernandez F. Lamivudine (3TC), a nucleoside reverse transcriptase inhibitor, prevents the neuropathological alterations present in mutant tau transgenic mice. *International Journal of Molecular Sciences*. 2023. doi:10.3390/ijms241311144.
- [249] Zhang Y, Zhang X, Huang J, Sun Z. Lamivudine ameliorates neuropathology in 5xFAD mice via coordinated inhibition of the cGAS-STING pathway with enhancement of mitophagy. *Brain Research Bulletin*. 2026. doi:10.1016/j.brainresbull.2026.112014.
- [250] Martinez de Lagran M, Elizalde-Torrent A, Paredes R, Clotet B, Dierssen M. Lamivudine, a reverse transcriptase inhibitor, rescues cognitive deficits in a mouse model of down syndrome. *Journal of Cellular and Molecular Medicine*. 2022. doi:10.1111/jcmm.17411.
- [251] Magagnoli J, Ambati M, Cummings TH, et al. Association of nucleoside reverse transcriptase inhibitor use with reduced risk of Alzheimer's disease. *Alzheimer's and Dementia*. 2025. doi:10.1002/alz.70180.
- [252] Fundacion FLS de Lucha Contra el Sida; ClinicalTrials.gov. Effect of lamivudine on neurocognitive impairment biomarkers and type-I interferon-stimulated genes in the plasma of patients with mild cognitive impairment — NCT06519357. *ClinicalTrials.gov study registration*. 2026. Source.
- [253] Hall J, Brault A, Vincent F, et al. Discovery of PF-06928215 as a high affinity inhibitor of cGAS enabled by a novel fluorescence polarization assay. *PLoS ONE*. 2017. doi:10.1371/journal.pone.0184843.
- [254] Vincent J, Adura C, Gao P, et al. Small molecule inhibition of cGAS reduces interferon expression in primary macrophages from autoimmune mice. *Nature Communications*. 2017. doi:10.1038/s41467-017-00833-9.
- [255] Lama L, Adura C, Xie W, et al. Development of human cGAS-specific small-molecule inhibitors for repression of dsDNA-triggered interferon expression. *Nature Communications*. 2019. doi:10.1038/s41467-019-08620-4.
- [256] Cyr P, Fader LD, Burch JD, et al. Discovery of potent and orally bioavailable pyrimidine amide cGAS inhibitors via structure-guided hybridization. *ACS Medicinal Chemistry Letters*. 2024. doi:10.1021/acsmedchemlett.4c00471.
- [257] Alarcon-Esposito J, Nagiri RK, Gan L, Sinha SC. Identification and development of cGAS inhibitors and their uses to treat Alzheimer's disease. *Neurotherapeutics*. 2025. doi:10.1016/j.neurot.2025.e00536.
- [258] Liu Y, Jesus AA, Marrero B, et al. Activated STING in a vascular and pulmonary syndrome. *New England Journal of Medicine*. 2014. doi:10.1056/NEJMoal312625.

- [259] Patel S, Blaauboer SM, Tucker HR, et al. The common R71H-G230A-R293Q human TMEM173 is a null allele. *Journal of Immunology*. 2017. doi:10.4049/jimmunol.1601585.
- [260] Rice GI, Forte GM, Szykiewicz M, et al. Assessment of interferon-related biomarkers in Aicardi-Goutieres syndrome associated with mutations in TREX1, RNASEH2A, RNASEH2B, RNASEH2C, SAMHD1, and ADAR: a case-control study. *Lancet Neurology*. 2013. doi:10.1016/S1474-4422(13)70258-8.
- [261] Van Gool WA, Weinstein HC, Scheltens P, Walstra GJ. Effect of hydroxychloroquine on progression of dementia in early Alzheimer's disease: an 18-month randomised, double-blind, placebo-controlled study. *Lancet*. 2001. doi:10.1016/s0140-6736(01)05623-9.
- [262] ADAPT Research Group; Lyketsos CG, Breitner JC, Green RC, et al. Naproxen and celecoxib do not prevent AD in early results from a randomized controlled trial. *Neurology*. 2007. doi:10.1212/01.wnl.0000260269.93245.d2.
- [263] Butchart J, Brook L, Hopkins V, et al. Etanercept in Alzheimer disease: a randomized, placebo-controlled, double-blind, phase 2 trial. *Neurology*. 2015. doi:10.1212/WNL.0000000000001617.
- [264] Lohr KM, Frost B, Scherzer C, Feany MB. Biotin rescues mitochondrial dysfunction and neurotoxicity in a tauopathy model. *Proceedings of the National Academy of Sciences*. 2020. doi:10.1073/pnas.1922392117.
- [265] Zuniga G, Katsumura S, De Mange J, Ramirez P, Atrian F, Morita M, Frost B. Pathogenic tau induces an adaptive elevation in mRNA translation rate at early stages of disease. *Aging Cell*. 2024. doi:10.1111/accel.14245.
- [266] Schulz L, Ramirez P, Lemieux A, Gonzalez E, Thomson T, Frost B. Tau-induced elevation of the activity-regulated cytoskeleton associated protein Arc1 causally mediates neurodegeneration in the adult Drosophila brain. *Neuroscience*. 2022. doi:10.1016/j.neuroscience.2022.04.017.
- [267] Beckmann A, Ramirez P, Gamez M, Gonzalez E, De Mange J, Bieniek KF, Ray WJ, Frost B. Moesin is an effector of tau-induced actin overstabilization, cell cycle activation, and neurotoxicity in Alzheimer's disease. *iScience*. 2023. doi:10.1016/j.isci.2023.106152.
- [268] Soukup SF, Verstreken P. PIWIL1 protein power targets tau therapy. *Nature Neuroscience*. 2014. doi:10.1038/nn.3659.