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Tau Strains, the Biosensor Revolution, and the Molecular Biology of Trans-Cellular Tau Propagation

Diamond

Critical Review — Editor Protocol Applied

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A Critical Evaluation of Marc Diamond's Research Program: Tau Strains, the Tau Seeding Assay, and the Molecular Biology of Trans-Cellular Tau Propagation

Abstract

Across two decades of laboratory work, first at Washington University in St. Louis and subsequently at the University of Texas Southwestern Medical Center, where he founded and now directs the Center for Alzheimer's and Neurodegenerative Diseases (CAND, formerly the Center for Alzheimer's and Neurodegenerative Disorders, CSAA), Marc Diamond has become the single most consequential figure in the molecular biology of tau propagation. This thesis offers a doctoral-level critical evaluation of Diamond's research program along four mutually reinforcing axes. The first is the development of the HEK293 tau-RD-CFP/YFP biosensor cell line — the technical innovation that transformed tau seeding from a qualitative phenomenon into an industrially quantifiable assay deployable across cerebrospinal fluid, postmortem brain extract, induced-pluripotent-stem-cell-derived neurons, and high-throughput drug screens.[1,2] The second is the demonstration, through serial cellular passage and inoculation experiments in transgenic mice, that distinct tau conformations — "strains" — are heritably propagated across cell divisions and across animal generations, with each strain producing reproducibly different patterns of cellular pathology, regional vulnerability, and disease progression.[3,4] The third is the identification of heparan sulfate proteoglycans (HSPGs) as the dominant cell-surface co-receptor mediating tau uptake into recipient neurons, a finding that anticipated and now complements Guojun Bu's later identification of the low-density-lipoprotein receptor-related protein 1 (LRP1) as the master internalizing receptor for tau and α-synuclein.[5,6] The fourth is the translation of strain biology into a diagnostic and stratification framework: the recognition, validated by Sjors Scheres's cryo-electron-microscopy structural determinations of patient-derived tau filaments, that Alzheimer's disease, chronic traumatic encephalopathy, progressive supranuclear palsy, corticobasal degeneration, and Pick's disease are not the same disease at different stages but molecularly distinct tauopathies whose fibril folds and therefore therapeutic vulnerabilities differ at the atomic scale.[7,8,9] Together with Bu's LRP1 work, Diamond's program completes the molecular architecture of the prion-like paradigm proposed by Stanley Prusiner and experimentally established by Lary Walker and Mathias Jucker.

> **What remains uncertain:** *Whether the tau strain phenomenon arises principally from the originating cellular environment in which a misfolded tau monomer first templates — implying a developmental-anatomical determinism to tauopathy identity — or from stochastic templating dynamics that can be redirected by therapeutic intervention; and*

> *whether the HSPG-LRP1 co-receptor system is the complete entry mechanism for tau, or whether additional receptors operative in specific cell types (microglia, astrocytes, oligodendrocytes) remain to be uncovered.*

Introduction

For the better part of three decades following its identification as the principal protein component of the neurofibrillary tangle by the laboratories of Inge Grundke-Iqbal, Khalid Iqbal, Michel Goedert, and Virginia Lee, the protein tau was framed almost exclusively in two modes.[10,11] The first was structural: tau was a microtubule-associated protein, encoded by the *MAPT* gene on chromosome 17q21, whose normal function was the stabilization of the neuronal microtubule cytoskeleton, particularly within the axonal compartment.[12] The second was post-translational: tau pathology was understood as the consequence of aberrant phosphorylation, acetylation, ubiquitination, and conformational change of the native protein, which dissociated it from microtubules and rendered it prone to aggregation into paired helical filaments and straight filaments.[13]

What these two framings shared was an essentially cell-autonomous logic. Tau pathology, in the dominant pre-2010 view, was something that happened *inside* a neuron — an internal cytoskeletal collapse driven by kinase dysregulation, oxidative stress, or genetic mutation. The stereotyped anatomical progression of tau pathology that Heiko and Eva Braak had meticulously documented in 1991 — from transentorhinal cortex (Stage I) through entorhinal cortex (Stage II), hippocampus and limbic system (Stages III–IV), into the neocortex (Stages V–VI) — was understood as the sequential awakening of cells with progressively lower thresholds for intrinsic dysfunction.[14] The Braak staging system described *what* happened with remarkable empirical clarity; it did not explain *how*.

That cell-autonomous framing collapsed slowly, then quickly. The slow collapse began in 2009 when the laboratory of Markus Tolnay, in collaboration with Florence Clavaguera and Michel Goedert, demonstrated that intracerebral inoculation of brain extract from transgenic mice expressing mutant human P301S tau induced the development of filamentous tau pathology in the brains of wild-type tau-expressing recipients — pathology that propagated along anatomical projections from the injection site over a period of months.[15] The quick collapse came with the recognition that the propagation phenomenon Clavaguera–Tolnay–Goedert had demonstrated *in vivo* was, in principle, reducible to a cellular assay — and that such an assay, if it could be developed at sufficient throughput and quantitative rigor, would transform tau into a tractable molecular target.

This is the methodological vacuum that Marc Diamond entered. The field needed three things it did not have. It needed a quantitative cellular reporter for tau seeding activity; it

needed a structural-biological account of why some tau aggregates seeded efficiently and others did not; and it needed a receptor mechanism by which extracellular tau gained access to the cytoplasm of recipient cells. Across a roughly fifteen-year arc beginning with the 2009 Frost–Jacks–Diamond demonstration of intercellular tau transfer[16] and culminating in the 2021 Shi–Scheres structure-based classification of tauopathies,[9] Diamond's program supplied — or made possible — each of these three deliverables. The present thesis evaluates this program in critical detail, situates it alongside the parallel discoveries of Goedert, Spillantini, Scheres, Bu, and Walker, and considers the therapeutic frontier the synthesis now opens.

Literature Review and Theoretical Positioning

To assess Diamond's program against the appropriate empirical and conceptual background, it is necessary to reconstruct the state of tau biology as Diamond inherited it. The *MAPT* gene on chromosome 17 encodes, through alternative splicing of exons 2, 3, and 10, six major tau isoforms in the adult human central nervous system.[12] Alternative splicing of exon 10 produces isoforms with either three (3R) or four (4R) microtubule-binding repeats — a structural distinction that turns out to be of profound disease relevance, because different tauopathies show distinct 3R/4R ratios.[17] Alzheimer's disease and chronic traumatic encephalopathy display a mixed 3R/4R tau pathology; progressive supranuclear palsy and corticobasal degeneration are predominantly 4R tauopathies; Pick's disease is a predominantly 3R tauopathy.[18]

The genetic linkage of *MAPT* to disease was clinched in 1998, when three independent groups — including those of Mike Hutton, Maria Grazia Spillantini, and Goedert — identified mutations in *MAPT* as the cause of frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17).[19,20] This was a watershed: it established that perturbation of tau alone, in the absence of any amyloid pathology, was sufficient to produce a clinically devastating neurodegenerative disease. The amyloid-centric framing of dementia, in which tau was at best a downstream executor of pre-existing Aβ pathology, was forced into uncomfortable revision.

Throughout the 1990s and 2000s, the tau field maintained a productive but somewhat insular relationship with the dominant amyloid field. Researchers such as Virginia Lee, John Trojanowski, Goedert, Spillantini, and Eva-Maria Mandelkow built a deeply detailed account of tau biochemistry — phosphorylation sites, conformational epitopes recognized by the Alz-50 and MC1 antibodies, the relationship between hyperphosphorylation and microtubule dissociation, the structural transition from random-coil monomer to β-sheet-rich filament.[21,22]

What none of these accounts supplied was a mechanism for the regional progression of pathology that Braak staging had documented with such anatomical precision.

The Clavaguera–Tolnay–Goedert 2009 paper, published in *Nature Cell Biology*, broke the impasse.[15] Its central experiment — intracerebral inoculation of P301S mutant tau brain extract into wild-type human tau transgenic ALZ17 mice, followed months later by detection of filamentous tau pathology that had spread from the injection site along neuroanatomical projections — supplied the missing element. Tau pathology, like the prion pathology Stanley Prusiner had postulated for the transmissible spongiform encephalopathies,[23] was a propagating phenomenon in which a misfolded conformer of a normal cellular protein templated identical misfolding of native protein, and the propagating units spread cell-to-cell along anatomical paths.

The decade following the Clavaguera paper saw rapid empirical confirmation. The laboratories of Karen Duff, Bradley Hyman, Patrick Lewis, and Michel Goedert each contributed inoculation experiments demonstrating that tau spread from injection sites along synaptically connected pathways.[24,25] Lary Walker and Mathias Jucker, who had developed the inoculation paradigm for Aβ amyloidosis a decade earlier,[26] extended their experimental architecture to tau and articulated a unifying prion-like framework for the major proteinopathies.[27] Prusiner formalized the conceptual unification in his 2012 *Science* paper.[28] The field's center of gravity had decisively shifted: tau, like α-synuclein and Aβ, was now a propagating proteinopathy.

Diamond entered this rapidly evolving landscape with a distinct methodological orientation. Where Clavaguera and Walker worked in transgenic mice on the scale of months and years, Diamond was preoccupied with the question of whether tau propagation could be reduced to a cellular assay operating on the scale of days, with quantitative readouts compatible with high-throughput screening. The answer he provided — the tau-RD-CFP/YFP biosensor — would prove to be the single most consequential technical innovation in the molecular biology of tauopathy.

Analytical Framework and Experimental Paradigms

This thesis evaluates Diamond's research program through an integrated methodological lens drawn from molecular cell biology, structural biology, and translational neurology. The analysis weights the primary peer-reviewed literature produced by Diamond's group and collaborators between 2009 and 2026, the structural-biology contributions of Sjors Scheres and Michel Goedert that validated and extended the strain hypothesis at atomic resolution, and the clinical-trial and translational-development literature produced by the various biotechnology programs that have built upon Diamond's tools.

The central experimental apparatus of Diamond's program is the tau biosensor cell line. Briefly, HEK293 cells are stably transfected to express the four-repeat microtubule-binding region of tau (tau-RD, residues 244–372) bearing the disease-associated P301S mutation, fused to cyan fluorescent protein (CFP) in one population and yellow fluorescent protein (YFP) in another, with both fusion constructs co-expressed in the same cell.[1] In the absence of seeding activity, the tau-RD monomers remain diffusely cytoplasmic and the CFP and YFP fluorophores are sufficiently separated that no fluorescence resonance energy transfer (FRET) occurs. When a tau seed is introduced into the cell — via lipofection of brain extract, treatment with synthetic preformed fibrils, or natural uptake of a tauopathy-derived sample — the cytoplasmic tau-RD monomers are recruited into seeded aggregates, the CFP and YFP fluorophores are brought into FRET proximity, and a quantitative FRET signal becomes detectable by fluorescence-activated cell sorting (FACS) or by automated microscopy.[1,29] The assay is fast (signal develops within 24–48 hours), is highly quantitative across orders of magnitude of seeding input, and is compatible with multi-well screening formats.

For strain characterization, Diamond's group developed a serial-passage protocol in which seeded biosensor cells are lysed and the lysate used to seed naive biosensor cells, with the cycle repeated across multiple passages. Cloning of individual seeded cells permits the isolation of cell lines that propagate distinct tau conformations stably across hundreds of cell divisions; these lines can then be characterized by their morphological inclusion patterns, by their seeding behavior in mice when re-introduced, and by their atomic structure when sufficient material can be purified.[3,4] Combinatorial panels of strain-specific monoclonal antibodies further permit conformational fingerprinting at single-cell resolution.[30]

For mechanistic dissection of tau uptake, Diamond's group has deployed genome-wide RNA-interference screens, CRISPR/Cas9 knockout screens, biochemical competition assays using soluble heparin and enzymatic digestion of cell-surface glycosaminoglycans by heparinase, and structural studies of tau–heparin complexes.[5,31] For in vivo validation, the laboratory has extensively used stereotaxic injection of seeds into both wild-type and tauopathy transgenic mice (including the PS19 P301S line and the rTg4510 model), with quantitative biosensor-based detection of seeding activity in dissected regions at terminal time points serving as the primary readout for trans-synaptic spread.[2,32]

Chapter 1: The Tau Biosensor and the Industrialization of Seeding Assays

Diamond's earliest contribution to the propagation literature was the 2009 Frost–Jacks–Diamond *Journal of Biological Chemistry* paper, which used a cell-culture co-culture model to demonstrate that aggregated tau released from one cell could be internalized by an adja-

cent cell and could there template the aggregation of native tau monomers.[16] This was, in essence, the cellular minimum-viable-experiment for tau prion-like behavior, predating the Clavaguera *in vivo* demonstration by a few months and converging with it conceptually. But the 2009 paper, while important as a proof of principle, did not yet supply a quantitative assay. The seeded-aggregation signal was detected microscopically and was not amenable to high-throughput deployment.

1.1 The 2014 Holmes–Furman–Diamond Biosensor Paper

The breakthrough came in 2014, with the publication in *PNAS* of Holmes, Furman, Mahan and colleagues' paper "Proteopathic tau seeding predicts tauopathy in vivo."[1] The paper introduced the tau-RD-CFP/YFP HEK293 biosensor cell line in essentially the form it is still used today. The technical achievement was substantial. By fusing the tau microtubule-binding region — the minimal aggregation-prone fragment of tau, comprising the residues that form the core of mature paired helical filaments — to spectrally compatible CFP and YFP variants, and by ensuring high enough expression that diffuse cytoplasmic concentration was just below the spontaneous aggregation threshold, Diamond's group created a cell that was on the knife-edge of aggregation, requiring only a small templating input to trigger a robust, FRET-detectable response.

The Holmes 2014 paper did three things at once. First, it characterized the biosensor analytically — establishing its specificity for tau (it did not respond to α-synuclein or polyglutamine seeds), its quantitative range, its FACS-based readout protocol, and its serial-passage stability.[1] Second, it demonstrated that the biosensor could detect tau seeding activity in human brain extracts from Alzheimer's disease cases at dilutions far below those at which any conventional biochemical assay could detect aggregated tau, opening the door to seeding-activity quantification in cerebrospinal fluid, blood, and small-volume biopsy samples. Third, and most consequentially, it demonstrated that biosensor-detected seeding activity in mouse brain regions predicted the subsequent development of tau pathology at those sites — establishing the assay as a prospective predictor, not merely a retrospective detector, of tauopathy progression.[1]

1.2 Methodological Revolution and Downstream Deployment

The Holmes biosensor cell line was rapidly distributed to laboratories worldwide through the American Type Culture Collection (ATCC), an act of methodological generosity whose impact is difficult to overstate. Within a few years, tau seeding activity was being measured in human cerebrospinal fluid as a candidate biomarker for early Alzheimer's disease,[33] in post-mortem brain extracts from cases spanning the full spectrum of tauopathies,[4] in iPSC-derived cortical neurons differentiated from patients carrying *MAPT* mutations,[34] and in plasma from athletes with histories of repetitive head impact as a candidate biomarker for CTE.[35]

The biosensor enabled the first large-scale screens for small-molecule inhibitors of tau seeding[36] and the first quantitative comparisons of seeding potency across tauopathies.[4]

Refinements followed. The v2 biosensor, introduced by Furman and colleagues, incorporated additional mutations to the tau-RD construct that sharpened the dynamic range and reduced background.[29] A live-cell imaging version permitted the kinetics of templated aggregation to be tracked in real time in individual cells, revealing that the seeded-aggregation event in any given recipient cell is essentially binary — once a critical nucleus forms, the aggregation propagates rapidly to consume the available monomer pool.[37] Variants were developed for α-synuclein, TDP-43, and prion protein seeding assays by other groups working from the same conceptual blueprint,[38] a sign of the platform's generalizability.

1.3 Critical Assessment of the Biosensor Paradigm

The biosensor's methodological power is undeniable. It is the first tool that turned tau seeding into something one can *count* across orders of magnitude with reproducibility and statistical rigor. But the assay also has limitations that the field has had to learn to navigate. The HEK293 cellular environment is not a neuron; the tau-RD construct lacks the full-length protein's projection domain, post-translational-modification landscape, and physiological microtubule-binding interactions; and the lipofection step used to potentiate seed uptake in many protocols bypasses the natural receptor-mediated uptake pathway whose biology Diamond's later work would elucidate. The biosensor measures the *capacity* of a sample to seed templated aggregation under permissive conditions; it does not, by itself, measure the in vivo bioavailability or the cell-type-specific uptake efficiency that determine pathology in the intact brain. These caveats notwithstanding, the biosensor has performed precisely the function its designers intended: it has converted tau seeding from an art into an industry.

Chapter 2: Tau Strains and Conformational Diversity

The biosensor was a tool. The strain framework was the conceptual revolution it enabled. The recognition that the same primary amino acid sequence of tau can fold into multiple distinct, heritable, pathology-defining conformations is, in the author's judgment, the single most consequential conceptual contribution of Diamond's program — surpassing even the biosensor's methodological impact in its long-term scientific implications.

2.1 The 2014 Sanders–Diamond *Neuron* Paper

The strain hypothesis was first formalized for tau in the 2014 *Neuron* paper by Sanders, Kaufman, DeVos and colleagues, "Distinct tau prion strains propagate in cells and mice and define different tauopathies."[3] The experimental architecture was elegant. Beginning from a

homogeneous biosensor cell population, Sanders introduced different sources of seeding material — synthetic preformed fibrils made under different aggregation conditions, brain extracts from different tauopathy cases, lysates from previously seeded biosensor lines — and cloned out individual cells that had been stably seeded. The clonal lines so derived stably propagated their seeded tau conformation across hundreds of cell divisions, and the conformations were morphologically distinguishable: some clones displayed dense, juxtanuclear, mulberry-like inclusions; others displayed dispersed speckled inclusions; still others displayed filamentous threads filling the entire cytoplasm. When lysates from these morphologically distinct lines were used to seed naive biosensor cells, the resulting cells reproduced the morphology of the donor — that is, the morphological signature was heritable through the seeding process, evidence of structural information transfer.[3]

To prove that the cellular strains were not artifacts of the biosensor environment, Sanders and colleagues injected strain-defined lysates into the brains of PS19 mice and characterized the resulting pathology after several months. Different strains produced different pathology: different patterns of neuronal versus glial deposition, different regional distributions, different rates of progression.[3] The conclusion was unavoidable. The same tau protein, in the same recipient organism, produced reproducibly different diseases depending on the templating conformation introduced. This was prion-like behavior in the formal sense Prusiner had defined for the TSEs: distinct strains of a single protein producing distinct, heritable disease phenotypes.

2.2 The 2016 Kaufman–Sanders–Diamond Strain Library

The 2016 follow-up paper by Kaufman, Sanders and colleagues, also in *Neuron*, extended the strain framework into a systematic catalogue.[4] The group generated a library of eighteen tau prion strains by cloning seeded biosensor cells from a wide range of human tauopathy brain extracts — Alzheimer's disease, progressive supranuclear palsy, corticobasal degeneration, Pick's disease, chronic traumatic encephalopathy, and argyrophilic grain disease. Each strain was inoculated into PS19 mice and the resulting pathology characterized in detail. The findings were striking: each strain produced a reproducibly distinct combination of (1) cell-type-specific pathology (neuronal versus astrocytic versus oligodendroglial), (2) regional distribution, and (3) progression rate. Strains derived from PSP cases produced glial-predominant pathology resembling PSP; strains derived from AD cases produced neuronal-predominant pathology; strains derived from Pick's disease produced morphologically distinct "Pick body"-like inclusions.[4]

The implication of these findings was paradigm-redefining. The tauopathies are not a single disease at different anatomical stages; they are distinct molecular diseases whose differences are encoded in the conformations of the templating tau aggregate. The clinical diagnostic problem of distinguishing PSP from CBD from AD-tau in vivo was, at the molecular

level, a problem of distinguishing tau conformations. The therapeutic problem of intervening in any one tauopathy was, at the molecular level, a problem of selectively targeting the relevant conformer.

2.3 Cryo-EM Confirmation: Goedert–Scheres and the Structural Vindication

The strain hypothesis as Diamond articulated it was a functional, cellular-level claim. Its definitive structural vindication came from a different laboratory — that of Sjors Scheres at the MRC Laboratory of Molecular Biology in Cambridge, working in close collaboration with Michel Goedert. Beginning in 2017, Scheres and Goedert published a series of papers in *Nature* and *Acta Neuropathologica* reporting cryo-electron-microscopy structures of tau filaments purified directly from human postmortem brain.[7,8,39] The structural findings were extraordinary: tau filaments from Alzheimer's disease cases, regardless of which case, adopted a single common fold (the "Alzheimer fold"); tau filaments from chronic traumatic encephalopathy adopted a different, characteristic fold; tau filaments from corticobasal degeneration adopted yet another; tau filaments from Pick's disease adopted a third; tau filaments from progressive supranuclear palsy and from other 4R tauopathies each adopted their own structurally distinct folds.[7,8,9]

The 2021 Shi–Scheres–Goedert paper "Structure-based classification of tauopathies," published in *Nature*, formalized the finding into a structural taxonomy: every characterized human tauopathy has a distinct tau-fibril fold; the fold is reproducible across patients with the same disease; and the fold is, in the Scheres group's strong claim, the molecular signature of the disease itself.[9] This was a remarkable convergence with the Diamond strain framework. What Diamond had inferred from cellular morphology, seeding behavior, and in vivo pathology, Scheres confirmed at atomic resolution: distinct tauopathies are distinct structural entities.

2.4 The Origin-of-Strain Question

The strain framework, however, raises a question it does not by itself answer: how do strains arise in the first place? Two broad hypotheses divide the field. The first holds that strain identity is determined by the originating cellular environment — the specific intracellular milieu in which a tau monomer first misfolds, including the local concentration of chaperones, the post-translational-modification status of the monomer, the membrane lipid composition, and the cell-type-specific proteome — and that once a strain is templated, it propagates with high fidelity from cell to cell.[40] The second holds that strain identity is determined by the templating dynamics themselves — that subtle structural variations in the initial misfolding event are amplified through serial templating into the macroscopically distinct folds observed in disease.[41] The two hypotheses are not mutually exclusive, and the resolution of their relative contributions is among the most active questions in the contemporary tau field.

Chapter 3: HSPG-Mediated Uptake — The Receptor Question Before Bu

If tau pathology spreads cell-to-cell, then there must exist a cellular machinery by which extracellular tau aggregates gain access to the cytoplasm of recipient neurons. This is the receptor question. Diamond's contribution to the receptor question, articulated principally in the 2013 Holmes–DeVos–Kfoury paper in *PNAS*, was the identification of heparan sulfate proteoglycans (HSPGs) as the dominant cell-surface molecule mediating tau uptake.[5]

3.1 The 2013 Holmes–Diamond HSPG Paper

The Holmes 2013 paper, "Heparan sulfate proteoglycans mediate internalization and propagation of specific proteopathic seeds," was methodologically rigorous and conceptually ambitious.[5] The experimental program had three pillars. First, biochemical competition: pre-incubation of tau seeds with soluble heparin — a structural analogue of the heparan-sulfate side chains decorating HSPG core proteins — abolished cellular uptake of the seeds in the biosensor assay. Second, enzymatic ablation: treatment of recipient cells with heparinase (which enzymatically degrades cell-surface heparan sulfate chains) similarly abolished uptake. Third, genetic confirmation: cells with genetically engineered deficiencies in heparan-sulfate biosynthesis (e.g., loss-of-function mutations in *EXT1*, *EXT2*, and *NDST1*) showed dramatic reductions in tau seed internalization.[5]

The implications were significant. HSPGs are ubiquitous cell-surface molecules whose biological function in healthy tissue is the binding and presentation of a wide range of extracellular ligands — growth factors, morphogens, cytokines, and structural extracellular-matrix components. Their hijacking by tau seeds (and, as the same paper demonstrated, by α-synuclein seeds) suggested that prion-like proteinopathies were exploiting a fundamental, evolutionarily ancient cell-surface receptor system rather than relying on a tauopathy-specific receptor. The therapeutic implication followed directly: small molecules or biologics that interfered with the HSPG–tau interaction might block propagation across the spectrum of tauopathies (and potentially synucleinopathies).[5]

3.2 Subsequent HSPG Findings and Therapeutic Concepts

Subsequent work from Diamond's group and others has refined the HSPG-tau interaction at structural and biochemical resolution. The 6-O-sulfated heparan-sulfate motifs appear to be particularly important for tau binding;[42] particular sulfation patterns may show preferential affinity for specific tau strains, contributing to cell-type tropism;[43] and small molecules designed to block tau-HSPG binding have shown proof-of-concept efficacy in cellular assays.[44] Heparinoid drugs already in clinical use for other indications have been explored

for repurposing potential, although their systemic anticoagulant effects complicate translation.[45]

3.3 The Bu Synthesis: HSPGs as Co-Receptors, LRP1 as Internalizer

In 2020 the receptor question was given a further critical refinement by Guojun Bu's laboratory at Washington University and the Mayo Clinic. In a series of papers culminating in the Rauch–Bu 2020 demonstration that LRP1 is the master regulator of tau uptake and spread,[6] and the Chen–Bu 2022 extension to α-synuclein,[46] Bu identified the low-density-lipoprotein-receptor-related protein 1 (LRP1) as the principal high-affinity neuronal receptor mediating the trans-cellular spread of both tau and α-synuclein. Critically, the LRP1 finding does not contradict Diamond's HSPG finding; the two are mechanistically complementary. The contemporary synthesis holds that HSPGs serve as low-affinity, high-density "capture" molecules that bind extracellular tau at the cell surface and concentrate it within the glycocalyx, and that LRP1 then serves as the high-affinity internalizing receptor that carries the captured tau into the endosomal compartment.[47] The model is structurally analogous to the established two-step capture-and-internalization paradigm for many other receptor systems, including the entry of certain viruses into cells.[48]

The Diamond HSPG framework and the Bu LRP1 framework, taken together, supply the molecular machinery of tau propagation in its full architecture: extracellular release of tau (mechanisms still under active investigation, with both exosomal and free-tau pathways implicated)[49] → HSPG-mediated capture and surface concentration → LRP1-mediated internalization into the endosomal compartment → endosomal escape (the most mechanistically obscure step) → cytoplasmic templated seeding. Each step is, in principle, a therapeutic target. The HSPG and LRP1 layers are the ones for which the most direct molecular handles are currently available.

> **What remains uncertain:** *Whether the HSPG–LRP1 capture-and-internalization system is exhaustive for tau entry into all relevant cell types, or whether additional receptor systems operate specifically in microglia (where scavenger receptors and CD33-family receptors may dominate), in astrocytes (where lipoprotein-receptor family members other than LRP1 may contribute), and in oligodendrocytes (which become tau-pathology-bearing in PSP and CBD but whose tau-uptake receptor biology remains poorly characterized).*

Chapter 4: From Bench to Bedside — Diagnostic and Stratification Applications

The translation of strain biology from a laboratory finding into a clinical framework is among the most active translational programs in contemporary neurodegenerative medicine. The clinical promise is clear. If different tauopathies are molecularly distinct entities whose differences are encoded at the structural level of the tau fibril, then the differential diagnosis of tauopathies in vivo — a problem that has historically required postmortem neuropathology to resolve definitively — should in principle become tractable through strain-specific molecular imaging and biofluid biomarkers.

4.1 Strain-Specific PET Tracers

The first generation of tau-PET tracers — flortaucipir (Tauvid, AV-1451) approved by the FDA in 2020,[50] followed by the second-generation tracers MK-6240, PI-2620, RO948, and PM-PBB3[51] — was developed in the pre-strain era and was optimized for binding to Alzheimer's-disease tau fibrils. The clinical experience with these tracers has been instructive. They reliably detect AD-tau pathology with sufficient sensitivity and specificity for both clinical use and trial enrichment; their performance on the non-AD tauopathies (PSP, CBD, PiD), however, has been distinctly more variable, with off-target binding to monoamine oxidase B and to neuromelanin in the basal ganglia confounding interpretation in the very disorders where 4R-tau pathology is most clinically relevant.[52]

The strain framework predicts — and the cryo-EM structures of Scheres and colleagues confirm — that the failure of first-generation tracers on the 4R tauopathies reflects the structural differences between AD-tau fold and 4R-tau folds, which present different surface chemistry and different small-molecule binding pockets. The next generation of tau tracers, currently in development, is being designed explicitly against the cryo-EM-resolved structures of the 4R-tauopathy folds.[53] Strain-specific PET, if achieved, would transform tauopathy clinical care: the differential diagnosis of PSP versus CBD versus AD-tau versus PiD could be made at the molecular level in living patients, enabling stratified clinical trial enrollment and, eventually, strain-targeted therapeutics.

4.2 CSF and Plasma Biomarkers of Seeding Activity

The biosensor assay itself has been adapted as a candidate biomarker. Multiple groups have demonstrated that tau seeding activity is detectable in cerebrospinal fluid from AD patients at levels that correlate with disease progression and that may be detectable earlier than conventional fluid biomarkers such as p-tau181 and p-tau217.[33,54] Plasma-based detection remains technically more challenging owing to the lower seed concentrations and the more

complex biofluid matrix, but proof-of-concept demonstrations have been reported in CTE-relevant populations.[35]

The clinical use case is best framed as complementary to, not competitive with, the now well-established phosphorylated-tau plasma assays developed by the laboratories of Oskar Hansson, Kaj Blennow, and Henrik Zetterberg.[55] Phosphorylated tau measures the burden of a specific post-translational modification associated with tau pathology; seeding activity measures the propagation capacity of tau in the sample. The two measures are biologically distinct, and trials enrolling on both endpoints are now in design.

4.3 Strain-Specific Therapeutic Antibodies

The most direct therapeutic implication of the strain framework is in the design of conformation-selective monoclonal antibodies. The first wave of anti-tau immunotherapies — tilavonemab (ABBV-8E12, formerly C2N-8E12) and gosuranemab (BIIB092) — failed in Phase II trials for PSP and AD respectively, with both programs discontinued by 2022.[56] A standard retrospective explanation invokes pharmacokinetic and target-engagement failures, but the strain framework supplies an additional, more uncomfortable explanation: the antibodies may have been targeting tau epitopes that were either inaccessible in the disease-specific fold or were shared across propagation-competent and propagation-incompetent tau conformers, blunting their selective efficacy.[57]

The next generation of tau antibodies is being designed explicitly against strain-specific conformational epitopes — antibodies that recognize only the AD-tau fold, or only the PSP-tau fold, with the goal of selective targeting of the disease-relevant conformer while sparing physiological tau pools.[58] Several such programs are in early clinical development, although none has yet reached pivotal trial reporting.

Chapter 5: Therapeutic Frontier and Open Questions

The therapeutic landscape opened by Diamond's program, viewed in 2026, is at once promising and humbling. The biology is now understood at a level of mechanistic resolution that would have seemed unimaginable in 2009. The clinical translation of that biology into disease-modifying therapy has proven harder than the underlying mechanistic clarity might have predicted.

5.1 Tau-Lowering Antisense Oligonucleotides

The most direct therapeutic strategy — reducing the total tau substrate available for seeded aggregation — is being pursued by tau-lowering antisense oligonucleotides, of which the

Ionis–Biogen agent BIIB080 (formerly IONIS-MAPT*Rx*) is the most clinically advanced.[59] Phase I/II data in mild Alzheimer's disease patients have demonstrated dose-dependent reductions in cerebrospinal-fluid total tau and phosphorylated tau of approximately 50% sustained over months,[60] with manageable safety profiles. Phase II efficacy readouts are anticipated in 2027–2028. The clinical hypothesis is that lowering the tau substrate will slow disease progression by reducing the monomer pool available for templated incorporation into propagating aggregates.

5.2 Passive Tau Immunotherapy: Failures and Recalibration

The Phase II failures of tilavonemab and gosuranemab in 2019–2021 prompted significant strategic recalibration across the tau immunotherapy field.[56] A new generation of antibodies has been engineered against more selective epitopes — the strain-specific conformational antibodies discussed in Chapter 4, antibodies against post-translational modifications enriched on pathological tau, and antibodies against the microtubule-binding-region core that is sequestered within the fibril fold and exposed only in conformations relevant to propagation.[61] Several such candidates are in early-to-mid-stage clinical development. Whether the increased selectivity translates into superior clinical outcomes will be the central question of the next several years of tau-antibody development.

5.3 HSPG and LRP1 Blockade

The receptor-blockade strategy — interfering with the HSPG-mediated capture or LRP1-mediated internalization steps to halt propagation — remains at the preclinical proof-of-concept stage. The challenges are formidable. HSPGs and LRP1 are both ubiquitous receptors with extensive physiological functions; the goal must be selective inhibition of the tau-binding interface without disruption of physiological ligand binding. The structural-biology prerequisites are being assembled, but the development of selective small-molecule or biologic blockers is at an early stage.[62] If achievable, propagation blockade would have the conceptual advantage of arresting disease progression without depending on the clearance of existing pathology — a fundamentally different therapeutic mode from current anti-amyloid approaches.

5.4 Open Questions

The largest unresolved questions are interlocking. Where does tau pathology initiate? The Braak system places Stage I in the transentorhinal cortex, but more recent work from Heiko Braak's group and from Per Andersen and others has implicated the locus coeruleus — the brainstem nucleus that sends noradrenergic projections throughout the cortex — as the earliest detectable site of abnormal tau in cognitively unimpaired individuals.[63] If the locus coeruleus is the true initiating site, the therapeutic window for early intervention is shifted

significantly earlier in life and the targeting strategy must accommodate brainstem accessibility. How do strains arise — the conformational origin question discussed in Chapter 2 — remains unresolved at the mechanistic level. Whether the in vivo trans-synaptic spread mechanism involves predominantly soluble oligomeric tau, fibrillar tau, exosome-packaged tau, or some combination is still being characterized.[49] Each of these questions is the subject of active investigation; none has a settled answer.

Conclusion

Marc Diamond's research program has, across two decades, transformed the molecular biology of tauopathy from a field of qualitative observations and untested propagation hypotheses into a structured, mechanistically tractable, and increasingly clinically actionable enterprise. The biosensor cell line provided the assay that the field needed to make tau seeding a quantitative phenomenon. The strain framework provided the conceptual architecture that united the disparate clinical tauopathies under a single molecular logic while simultaneously establishing why they are distinct diseases requiring distinct interventions. The HSPG receptor identification provided the first molecular mechanism for the trans-cellular uptake step that the prion-like paradigm had postulated but not previously explained.

Read alongside the parallel programs of Guojun Bu (whose LRP1 work complements the HSPG framework with the high-affinity internalizing receptor), Lary Walker and Mathias Jucker (whose seeding experiments supplied the in vivo demonstration of trans-cellular spread for the major proteinopathies), Stanley Prusiner (whose 2012 unifying synthesis reframed neurodegeneration as a templated-misfolding family of diseases), and Sjors Scheres and Michel Goedert (whose cryo-EM structures supplied atomic-resolution confirmation of the strain framework), Diamond's contributions complete the molecular architecture of contemporary tau biology. Tau is no longer a microtubule-associated protein gone awry. It is a propagating, strain-faithful, receptor-mediated proteinopathy whose biology is now mechanistically tractable across the full scale from atomic structure to clinical syndrome.

The therapeutic translation of this biology has been more difficult than the mechanistic clarity might have predicted. Two large passive immunotherapy programs have failed in Phase II. The first generation of tau-PET tracers performs well on AD but poorly on the 4R tauopathies. The receptor-blockade strategies remain preclinical. The tau-lowering antisense program is the most clinically advanced and may report pivotal efficacy data within the decade. The strain-specific antibody and PET-tracer programs are positioned to enter mid-stage development across the same horizon. Whether any of these programs will deliver clinical benefit on the scale that the underlying biology suggests should be possible is the central open question.

What is no longer in serious doubt is the framework within which the question must be asked. Tauopathies are distinct molecular diseases, defined by distinct tau-fibril folds, propagating through the brain by receptor-mediated trans-cellular spread, amenable in principle to intervention at the levels of substrate reduction, conformer-selective immunotherapy, and receptor-mediated propagation blockade. The molecular blueprint is in hand. The clinical execution remains to be completed. Diamond's program has supplied the blueprint with a thoroughness and methodological rigor that is rare in any field of contemporary biomedicine, and its imprint on the next generation of tau therapeutics will be foundational.

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