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# The Prion Theory and Its Extension to the Major Proteinopathies: A Critical Evaluation of Stanley Prusiner's Unifying Synthesis

Prusiner

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# The Prion Theory and Its Extension to the Major Proteinopathies: A Critical Evaluation of Stanley Prusiner's Unifying Synthesis in Neurodegenerative Disease

## Abstract

In 1982, Stanley B. Prusiner published in *Science* a single-author paper proposing that the transmissible spongiform encephalopathies (TSEs) were caused by a novel infectious entity composed solely of protein — a "prion" — devoid of any nucleic acid genome.[1] The hypothesis violated the central dogma of molecular biology, was met with sustained and sometimes vitriolic skepticism for more than a decade, and was ultimately validated by a body of biochemical, genetic, and structural evidence sufficient to earn Prusiner the 1997 Nobel Prize in Physiology or Medicine.[2] Thirty years after the original proposal, in 2012, Prusiner published a second discipline-altering paper, again in *Science*, titled *"A unifying role for prions in neurodegenerative diseases,"*[3] in which he extended the prion concept to encompass Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), and Huntington's disease (HD) — eight distinct proteinopathies unified by a single biophysical mechanism of templated misfolding.

This doctoral-level critical evaluation traces the prion concept from its origin in the scrapie investigations of the 1960s and 1970s through Prusiner's 1982 biochemical isolation of PrP, the conformational mechanism elucidated in the 1990s, the 1997 Nobel, and the 2012 unifying synthesis. It then evaluates the reception of the 2012 synthesis — the institutional resistance from the Alzheimer's and Parkinson's research communities, the gradual accumulation of seeded-transmission evidence by Walker, Jucker, Diamond, Lee, and Trojanowski, and the eventual consolidation of the prion-like paradigm as the dominant model of neurodegenerative disease progression. The analysis closes by assessing the therapeutic frontier the synthesis has opened: anti-prion antisense oligonucleotides, structural-targeting strategies, selective propagation blockade, and the recent identification by Bu and Diamond of LRP1 and heparan sulfate proteoglycans as the receptors that mediate the propagation step. Prusiner's legacy is a unified mechanistic framework that reorganized neurodegeneration research and made tractable a class of diseases that had previously appeared etiologically heterogeneous.

> **What remains uncertain:** *Whether the prion mechanism applies uniformly across all eight templating proteins, or whether the kinetics, strain biology, and cellular receptor logic differ in ways that demand disease-specific therapeutic strategies; and whether the initiating misfolding event in sporadic disease arises stochastically, environmentally, or as a*

> *consequence of upstream cellular dysfunction that the prion framework does not itself explain.*

## Introduction

The transmissible spongiform encephalopathies have occupied a peculiar position in the history of neurology since their first systematic description in the early twentieth century. Scrapie in sheep — recognized as a distinct disease entity in the British Isles for at least two hundred years — Creutzfeldt-Jakob disease (CJD) in humans, kuru in the Fore people of Papua New Guinea, and bovine spongiform encephalopathy (BSE) in cattle share a constellation of pathological features (spongiform vacuolation of the neuropil, neuronal loss, astrogliosis, absence of inflammatory infiltrate) that distinguishes them from every other category of neurological disease.[4] They also share a property that for decades resisted biological explanation: experimental transmissibility. Brain homogenate from a diseased animal, inoculated into a healthy one, reliably induced the same disease after a long incubation period.

The mechanism of this transmission was the central question of the field for forty years. In 1959, William Hadlow noted the pathological similarities between scrapie and kuru, suggesting that kuru — then under intensive investigation by D. Carleton Gajdusek among the Fore — might be experimentally transmissible.[5] Gajdusek pursued the suggestion and in 1966 demonstrated that kuru could be transmitted to chimpanzees by intracerebral inoculation, a finding for which he received the 1976 Nobel Prize.[6] Gajdusek termed the responsible agent a "slow virus," a deliberately agnostic placeholder reflecting the agent's exceptionally long incubation period and the absence of any evidence of a conventional virus. Throughout the 1960s and 1970s, the slow-virus hypothesis was the working consensus, even as repeated efforts to isolate viral nucleic acid from infectious preparations consistently failed.

The most consequential challenge to the slow-virus hypothesis came in 1967 from Tikvah Alper and colleagues at the Hammersmith Hospital in London. Alper demonstrated that the scrapie agent was extraordinarily resistant to inactivation by ultraviolet and ionizing radiation at doses that would readily destroy any nucleic acid genome of conventional size.[7] In the same year, the mathematician J. S. Griffith published in *Nature* a brief theoretical paper proposing three possible models for a protein-only infectious agent, the third of which — that the agent was a protein capable of catalyzing its own conformational replication — anticipated the prion hypothesis by fifteen years.[8] Neither Alper's radiation data nor Griffith's theoretical proposal was sufficient to dislodge the slow-virus consensus, in part because no candidate protein had been isolated and characterized.

That isolation was the achievement of Stanley B. Prusiner. Trained as a neurologist at the University of California, San Francisco, Prusiner encountered a CJD patient as a resident in

1972 and was struck by the absence of any known therapeutic approach to a disease whose etiology was, at the time, completely opaque.[2] Over the subsequent decade, working with hamster brain as a source of scrapie agent and developing increasingly refined fractionation protocols, Prusiner's laboratory progressively purified the infectious activity to a single protein. In 1982, in a single-author paper in *Science* titled *"Novel proteinaceous infectious particles cause scrapie,"* he proposed the term "prion" — for "proteinaceous infectious particle" — and laid out the protein-only hypothesis.[1] The hypothesis violated the central dogma of molecular biology, which had since the 1958 formulation by Crick been understood to require nucleic acid as the substrate of all biological self-replication. The reception was bitter and protracted.

What makes Prusiner's career a fit subject for the Organic Network Synthesis is not the prion discovery alone but the extension. In 2012, three decades after the original proposal, Prusiner published *"A unifying role for prions in neurodegenerative diseases,"*[3] arguing that the same biophysical mechanism he had elucidated for PrP^Sc — self-templated conformational conversion, propagation along anatomical pathways, strain phenomena — applied with full generality to Aβ in Alzheimer's disease, α-synuclein in Parkinson's disease and Lewy body dementia, tau in the tauopathies, TDP-43 in ALS and FTD, SOD1 in familial ALS, huntingtin in Huntington's disease, and the polyglutamine repeat proteins of the spinocerebellar ataxias. The 2012 synthesis is the conceptual hinge of modern neurodegeneration research. It is the move from eight distinct diseases to one mechanism. The remainder of this evaluation assesses the prion concept's empirical foundation, the 2012 unification, the long contestation that followed, and the therapeutic frontier the synthesis has opened.

## Literature Review and Theoretical Positioning

The historical literature on the transmissible spongiform encephalopathies divides cleanly into four eras, each characterized by a dominant theoretical model and a corresponding experimental program. Tracking the prion concept through these eras illuminates both the resistance Prusiner encountered and the gradual epistemological displacement that culminated in the 2012 synthesis.

The first era, extending from the early twentieth century through approximately 1965, was dominated by the assumption that the transmissible spongiform encephalopathies were caused by a slow-acting virus of conventional construction. Scrapie was studied primarily as an agricultural problem in the United Kingdom and as a comparative-pathology curiosity in the laboratories of Gordon and Pattison.[4] Creutzfeldt and Jakob's original case descriptions from the 1920s had identified the spongiform pathology but offered no mechanistic interpretation. Gajdusek's epidemiological investigation of kuru — beginning in 1957 and culminating

in the 1966 chimpanzee-transmission demonstration[6] — established the transmissibility of a human TSE and earned the slow-virus framework its dominant position.

The second era, from approximately 1967 through 1982, was the era of incipient challenge. Alper's radiation-resistance data[7] and Griffith's theoretical protein-only model[8] introduced the possibility that the infectious agent was unconventional, but the absence of a purified candidate molecule prevented these ideas from displacing the slow-virus consensus. Throughout this period, Prusiner's laboratory at UCSF pursued the biochemical purification of the scrapie agent, encountering the methodological obstacles inherent in fractionating an agent whose only readout was a year-long bioassay in hamsters.[9] The 1982 publication of "Novel proteinaceous infectious particles cause scrapie"[1] opened the third era.

The third era, from 1982 through approximately 2000, was the era of consolidation of the prion concept within TSE research and its initial empirical validation. The cloning of the prion protein gene (*PRNP*) in 1985 by Bruce Chesebro and the demonstration that PrP^C and PrP^Sc are encoded by the same gene[10] established that the prion mechanism could not depend on a hidden nucleic acid genome encoded by the agent itself. The generation of *Prnp*-null mice by Charles Weissmann's laboratory in 1992, and the demonstration that these mice were completely resistant to scrapie infection,[11] closed the genetic case: without PrP^C, no prion disease. The 1997 Nobel Prize[2] formalized the field's acceptance of the prion concept as applied to the TSEs. Throughout this era, however, the prion framework was understood by most of the neurodegeneration research community to apply narrowly to the spongiform encephalopathies and to have no bearing on the major proteinopathies — Alzheimer's, Parkinson's, ALS — that occupied the bulk of clinical attention.

The fourth era, from approximately 2000 through the present, has been the era of the prion-like paradigm's extension and contestation. Three experimental programs were decisive. First, Mathias Jucker and Lary Walker, in a series of papers beginning with the 2006 demonstration that intracerebral inoculation of Aβ-containing extract could nucleate amyloid pathology in young APP-transgenic mice,[12] established that seeded transmission was a real biological phenomenon for Aβ. Their 2010 *Science* paper, *"Peripherally applied Aβ-containing inoculates induce cerebral β-amyloidosis,"*[13] extended the finding to peripheral routes of administration. Second, John Trojanowski and Virginia Lee at the University of Pennsylvania, working with α-synuclein, demonstrated that synthetic α-synuclein preformed fibrils introduced into cultured neurons or injected into wild-type mouse brain could nucleate widespread Lewy-pathology-like inclusions that propagated along anatomical projections.[14] Third, Marc Diamond, then at Washington University and later at UT Southwestern, developed cellular biosensor assays for tau seeding activity and demonstrated that tau aggregates released from one cell could be taken up by another and template the misfolding of native cytoplasmic tau.[15]

By the time of Prusiner's 2012 synthesis,[3] these three experimental programs had established that the templated-misfolding mechanism was empirically demonstrable for Aβ, α-synuclein, and tau. The synthesis itself articulated what the experimental evidence was beginning to imply: that the major proteinopathies were not eight diseases but one mechanism. Subsequent reviews by Walker and Jucker,[16,17,18] by Soto,[19] by Aguzzi and Calella,[20] and by Goedert[21] have consolidated the framework, and the 2020–2022 identification by Bu of LRP1 as the neuronal receptor mediating tau and α-synuclein uptake[22,23] supplied the molecular machinery the synthesis had implied.

## Analytical Framework and Methodology

This evaluation employs a critical-historiographical and biological framework, integrating the primary biochemical, genetic, and structural literature with the institutional and rhetorical history of the prion concept's reception. The analysis draws principally on peer-reviewed primary papers and on the Nobel Lecture[24] in which Prusiner himself laid out the empirical case as he understood it in 1997. Methodologically, four experimental paradigms structure the assessment.

The first is biochemical purification. Prusiner's 1982 paper rested on a years-long protocol that progressively enriched scrapie infectivity through detergent extraction, sucrose gradient sedimentation, and protease treatment, ultimately yielding a preparation in which infectivity co-purified with a single protease-resistant protein, subsequently named PrP.[1,9] The methodological discipline of co-purification — the requirement that infectivity track with the candidate molecule across orthogonal fractionation methods — was the core epistemological move that distinguished the prion hypothesis from the slow-virus alternatives.

The second is genetic ablation. The Weissmann laboratory's 1992 generation of *Prnp*-null mice, and the subsequent demonstration that these animals were completely resistant to scrapie inoculation while developing normally,[11] provided the genetic complement to the biochemical case. No PrP^C substrate, no disease. The genetic logic was reinforced by the identification of *PRNP* mutations causing familial CJD, Gerstmann–Sträussler–Scheinker disease (GSS), and fatal familial insomnia,[25] establishing that genetic alterations to the prion protein itself were sufficient to cause disease.

The third is conformational and structural assay. The biophysical distinction between PrP^C (predominantly α-helical, protease-sensitive, soluble) and PrP^Sc (β-sheet-enriched, protease-resistant, aggregation-prone) was established by circular dichroism and Fourier-transform infrared spectroscopy in the early 1990s.[26] More recently, cryo-electron microscopy structures of authentic *ex vivo* prion fibrils have provided atomic-resolution images of the

templating conformation,[27] resolving in concrete molecular detail what was for decades an inferential argument.

The fourth is amplification and detection assay. The development of protein misfolding cyclic amplification (PMCA) by Claudio Soto in 2001[28] provided an *in vitro* system that recapitulated the templated conversion of PrP^C to PrP^Sc, dramatically reducing the time required to assay prion activity and providing an experimental framework adaptable to other proteinopathies. The real-time quaking-induced conversion (RT-QuIC) assay developed by Byron Caughey[29] further refined the detection of prion seeding activity to clinically useful sensitivities, enabling diagnostic application to sporadic CJD and, increasingly, to α-synucleinopathies and tauopathies via the seed-amplification assays that have been developed since 2018.[30] The methodological lineage from PMCA to modern α-synuclein seed amplification assays represents the direct biological inheritance of Prusiner's framework.

## Chapter 1: Scrapie, CJD, and the Original Prion Diseases

The empirical foundation of the prion concept lies in the transmissible spongiform encephalopathies, a small but pathologically distinctive family of neurodegenerative diseases that have been observed in humans, sheep, cattle, deer, elk, mink, and several other mammalian species. The TSEs share a triad of features: spongiform vacuolation of the neuropil, neuronal loss without inflammatory infiltrate, and the accumulation of protease-resistant aggregates of the prion protein. They also share the property — unique in neurology — of experimental transmissibility by intracerebral, intraperitoneal, oral, or, under some conditions, peripheral inoculation. This chapter traces the empirical history of the original prion diseases that supplied Prusiner with the experimental substrate from which the broader concept would later be extrapolated.

### 1.1 Scrapie: The Foundational Substrate

Scrapie has been recognized in British sheep and goats since at least the eighteenth century. Affected animals develop a progressive neurological syndrome characterized by intense pruritus (the eponymous "scrape" against fenceposts), gait ataxia, weight loss, and death over a course of weeks to months.[4] The disease was the subject of veterinary investigation for two centuries before its transmissibility was definitively established by Cuillé and Chelle in 1936, who demonstrated experimental transmission to healthy sheep by intraocular inoculation of brain extract.[31] This early transmission work established the existence of an infectious agent but did not resolve its nature, and for thirty years thereafter the agent was assumed to be a conventional virus of unusual properties.

The methodological breakthrough that opened the modern era was the adaptation of scrapie to laboratory rodents — first mice by Chandler in 1961,[32] then hamsters by Marsh and Kimberlin in the 1970s.[33] The hamster-adapted strain (specifically the 263K strain) became the workhorse of Prusiner's biochemical fractionation program, in part because of its relatively short incubation period (approximately 70 days at terminal titer) and its high concentration of infectious activity per gram of brain tissue. The hamster scrapie model is the substrate from which prions, as a biochemical entity, were ultimately isolated.[1,9]

### 1.2 Kuru and the Gajdusek Lineage

Kuru — a Fore-language word meaning "to tremble" — was identified in the late 1950s as a fatal cerebellar ataxia of high prevalence among the Fore people of the Eastern Highlands of Papua New Guinea. The Australian patrol officer J. R. McArthur and the medical officer Vincent Zigas first brought the disease to international attention in 1957.[34] D. Carleton Gajdusek, then at the U.S. National Institutes of Health, conducted extensive field investigations from 1957 onward and established that kuru's transmission was tied to the Fore practice of ritualistic mortuary endocannibalism, in which female and child relatives of the deceased consumed brain tissue as a mark of respect.[5] When the practice was suppressed by the Australian colonial administration in the late 1950s, the incidence of kuru in birth cohorts born after the suppression dropped to zero, providing definitive epidemiological evidence of the transmission route.

The 1966 experimental transmission of kuru to chimpanzees by intracerebral inoculation, achieved by Gajdusek, Gibbs, and Alpers,[6] earned Gajdusek the 1976 Nobel Prize in Physiology or Medicine and established the conceptual category of "unconventional slow virus infections of the central nervous system." Within the slow-virus framework, kuru, scrapie, and CJD were understood to be caused by related but distinct conventional viral agents of exceptionally long incubation period. The framework was the dominant interpretive lens within which Prusiner's 1982 protein-only hypothesis would have to assert itself.

### 1.3 Creutzfeldt-Jakob Disease: Sporadic, Familial, and Iatrogenic

Creutzfeldt-Jakob disease, first described in independent case reports by Hans Gerhard Creutzfeldt in 1920 and Alfons Maria Jakob in 1921, presents clinically as a rapidly progressive dementia accompanied by myoclonus, cerebellar ataxia, and characteristic periodic sharp-wave complexes on electroencephalography.[35] The disease was for decades regarded as a sporadic neurological curiosity of unknown etiology, with an incidence of approximately one case per million per year worldwide. The 1968 demonstration by Gibbs and Gajdusek that CJD could be experimentally transmitted to chimpanzees[36] placed it within the slow-virus family alongside kuru and scrapie.

Three distinct etiological categories of human prion disease are now recognized. Sporadic CJD (sCJD), which accounts for approximately 85 percent of human cases, arises in the absence of any known exogenous exposure or familial history; its initiating event remains one of the central unsolved questions of prion biology. Familial prion diseases (familial CJD, GSS, fatal familial insomnia) account for approximately 10–15 percent of cases and are caused by autosomal dominant mutations in the *PRNP* gene.[25] Iatrogenic CJD has been documented following the use of cadaveric dura mater grafts, contaminated neurosurgical instruments, and — most consequentially — the administration of cadaveric pituitary-derived human growth hormone to short-statured children, an episode that produced more than two hundred deaths worldwide before the practice was abandoned in the mid-1980s in favor of recombinant hormone.[37]

### 1.4 BSE, vCJD, and the British Crisis

The most consequential public-health episode in the history of prion biology was the bovine spongiform encephalopathy (BSE) epidemic in the United Kingdom in the late 1980s and 1990s. BSE arose in British cattle in the mid-1980s and was traced to the practice of feeding cattle with meat-and-bone meal that had been rendered from the carcasses of sheep (and, eventually, of BSE-infected cattle themselves).[38] The change in rendering protocols in the early 1980s — specifically the abandonment of organic solvent extraction steps that had previously inactivated the scrapie agent — is the most plausible proximate cause. By 1992, the annual incidence of BSE in British cattle had reached approximately 37,000 cases, and the cumulative epidemic ultimately exceeded 180,000 confirmed cases with a much larger number of subclinical infections in the slaughter cohort.

The crisis acquired its global significance in 1996 when the UK government acknowledged a probable link between BSE and a novel form of human prion disease, variant CJD (vCJD), which presented at unusually young ages with a distinctive clinical phenotype and a characteristic "florid plaque" neuropathology.[39] The link was confirmed in subsequent years by molecular strain-typing experiments demonstrating that the prion strain causing vCJD was indistinguishable from that causing BSE.[40] Although the eventual vCJD epidemic was limited — fewer than two hundred and forty cases worldwide as of 2026 — the episode established the principle of cross-species prion transmission as a matter of public-health urgency and provided the political and scientific context within which Prusiner's 1997 Nobel was awarded.

### 1.5 Chronic Wasting Disease and the Contemporary Frontier

Chronic wasting disease (CWD), a TSE of cervids (deer, elk, moose, reindeer), was first identified in captive mule deer in Colorado in 1967 and has since spread across the wild cervid populations of North America and, in 2016, was identified in Norwegian reindeer.[41] CWD differs from the other TSEs in its high transmissibility through environmental contami-

nation — prions are shed in saliva, urine, and feces, and persist in soil for extended periods — and in the absence, to date, of any documented case of human transmission. The ongoing geographic expansion of CWD represents the contemporary frontier of TSE epidemiology and the principal residual public-health concern within the prion field. The experimental and surveillance frameworks deployed against CWD are direct lineal descendants of Prusiner's biochemical methodology.

## Chapter 2: PrP^C and PrP^Sc — The Conformational Template Mechanism

The biophysical core of the prion concept is the assertion that a single polypeptide sequence can adopt two stable conformations — one benign and ubiquitous, one pathogenic and self-templating — and that the pathogenic conformation can catalyze the conversion of the benign conformation to its own state. This chapter examines the molecular biology of this assertion: the protein PrP itself, the conformational distinction between PrP^C and PrP^Sc, the templating mechanism, the strain phenomenon, and the species barrier.

### 2.1 The Prion Protein: Sequence, Structure, and Cellular Biology

The prion protein is encoded by the single-copy gene *PRNP*, located on the short arm of chromosome 20 in humans. The mature human PrP polypeptide is 209 amino acids in length, generated from a 253-residue precursor by removal of an N-terminal signal peptide and a C-terminal hydrophobic sequence that is replaced by a glycosylphosphatidylinositol (GPI) anchor.[42] The mature protein is trafficked through the secretory pathway, glycosylated at two N-linked sites, and displayed on the outer leaflet of the plasma membrane via its GPI anchor. PrP^C is expressed most abundantly in the central nervous system, particularly at the presynaptic terminal, and at lower levels in lymphocytes, cardiomyocytes, and several other peripheral cell types.[43]

The native conformation of PrP^C, as determined by solution NMR by Wüthrich and colleagues in the mid-1990s, comprises a disordered N-terminal region of approximately 100 residues followed by a structured C-terminal globular domain containing three α-helices and a short two-stranded antiparallel β-sheet.[44] The cellular function of PrP^C remains, three decades after the cloning of the gene, only partially understood. Proposed functions include copper binding via the N-terminal octapeptide repeat region, neuroprotection against oxidative stress, modulation of synaptic transmission, and contribution to myelin maintenance in the peripheral nervous system.[45] Notably, *Prnp*-null mice are viable, fertile, and largely normal in their behavior and neurological function,[11] a phenotype that places a ceiling on the in-

dispensability of PrP^C for normal life and creates a permissive context for therapeutic strategies that lower PrP expression.

### 2.2 The Conformational Distinction

The biophysical distinction between PrP^C and PrP^Sc is the central biological claim of the prion hypothesis. The two forms have identical amino acid sequences and identical post-translational modifications; they differ exclusively in their three-dimensional fold. PrP^C is dominated by α-helical secondary structure (approximately 42 percent α-helix, 3 percent β-sheet by FTIR), is soluble in mild detergents, and is fully degraded by proteinase K. PrP^Sc is dominated by β-sheet secondary structure (approximately 30 percent α-helix, 43 percent β-sheet), forms insoluble aggregates, and resists proteinase K digestion except for an N-terminal truncation of approximately 67 residues that yields the characteristic "PrP 27–30" fragment originally purified by Prusiner.[26,46]

The conformational difference is the substrate for the templating mechanism. In the "heterodimer" or "refolding" model originally proposed by Prusiner, a monomer of PrP^Sc binds a monomer of PrP^C and catalyzes its refolding into the β-sheet-enriched conformation, generating two PrP^Sc molecules that can each templare further conversion.[9] In the "nucleated polymerization" model favored by subsequent kinetic analysis, PrP^Sc exists as oligomeric or fibrillar nuclei to which PrP^C monomers add, undergoing conformational conversion as they incorporate; fragmentation of the growing fibril generates new nuclei and produces the exponential amplification observed experimentally.[47] The nucleated polymerization model is now the dominant interpretation and underlies both the PMCA and RT-QuIC assays.

### 2.3 The Strain Phenomenon

The single most theoretically demanding observation in prion biology is the existence of strains. Distinct prion strains — propagated through inbred mouse lines of identical PrP sequence — produce reproducibly different incubation periods, anatomical distributions of pathology, and biochemical signatures (glycosylation patterns of the protease-resistant fragment, conformational stability profiles).[48] Because the strains are inherited from one biological passage to the next without any nucleic acid intermediate, the strain information must be encoded in the conformation of PrP^Sc itself. The empirical existence of strains thus demonstrates that a single polypeptide sequence can adopt multiple distinct β-sheet-enriched conformations, each capable of templating its own propagation with fidelity.

The strain phenomenon has profound implications for the broader proteinopathies. If different conformational variants of PrP^Sc produce different clinical phenotypes and pathological distributions, then it becomes plausible that the heterogeneity within the major pro-

teinopathies — for instance, the distinction between Alzheimer's-type tauopathy and the tauopathies of progressive supranuclear palsy, corticobasal degeneration, and Pick's disease — reflects analogous conformational strain differences in the templating tau aggregates. This hypothesis has been substantially borne out by the cryo-EM work of Goedert, Scheres, and colleagues, who have demonstrated that the tau filaments of distinct tauopathies have reproducibly distinct atomic-resolution structures.[49]

### 2.4 Species Barriers and Transmission Efficiency

The transmission of prions between species is generally inefficient, with long incubation periods and incomplete attack rates that diminish further when the donor and recipient species differ substantially in PrP sequence. This "species barrier" was demonstrated empirically in the 1960s in mouse-to-hamster scrapie transmission and is now understood to reflect the requirement for sequence and structural compatibility between the templating PrP^Sc and the substrate PrP^C.[50] Transgenic experiments in which mice express PrP from a heterologous species typically abolish the species barrier for that source, confirming the PrP^C substrate-compatibility interpretation.

The species barrier has practical consequences beyond its theoretical interest. The relative inefficiency of cross-species transmission of BSE to humans — yielding fewer than 240 cases of vCJD against an exposure of millions during the British crisis — is interpretable as a species-barrier effect. The relative efficiency of CWD transmission within cervids and the apparent absence to date of CWD transmission to humans is, similarly, a species-barrier observation whose stability cannot be guaranteed indefinitely. The molecular logic of the species barrier — sequence and structural compatibility between template and substrate — generalizes to the broader prion-like proteinopathies, where the question of whether α-synuclein from one species can seed pathology in another, or whether tau strains from one tauopathy can cross-seed another, are matters of active investigation.[51]

> **What remains uncertain:** *The molecular event that initiates PrP^Sc formation in sporadic CJD remains unidentified. The familial mutations destabilize PrP^C and presumably increase the probability of spontaneous misfolding; the iatrogenic and BSE-linked cases originate in transmitted seed; but the origin of the initiating seed in the 85 percent of human prion disease that is sporadic is a fundamental gap. Whether sporadic CJD arises through stochastic spontaneous misfolding, through cryptic exposure, or through a cellular-stress-driven misfolding event that exceeds proteostatic capacity is unresolved, and the answer matters profoundly for the generalization of the prion concept to the major proteinopathies.*

# Chapter 3: The 2012 Unifying Synthesis — Extending Prions to AD, PD, ALS, HD, FTD

In May 2012, Stanley Prusiner published in *Science* a brief but theoretically explosive paper titled *"A unifying role for prions in neurodegenerative diseases."*[3] The paper argued that the biophysical mechanism Prusiner had elucidated for PrP^Sc — self-templating misfolding, propagation through tissue, strain phenomena, cellular toxicity — applied with full generality to the major proteinopathies. The eight templating proteins enumerated in the 2012 paper (PrP itself, plus Aβ, tau, α-synuclein, TDP-43, SOD1, huntingtin, and the polyglutamine repeat proteins of the spinocerebellar ataxias) were to be understood as variations on a single molecular theme. The proteinopathies, on this view, were not eight diseases but one mechanism manifesting in eight protein contexts. This chapter examines the empirical grounds on which Prusiner constructed the 2012 synthesis and assesses the conceptual leap involved in the move from eight diseases to one mechanism.

## 3.1 The Empirical Substrate for the Synthesis

By 2012, the empirical case for prion-like behavior in the major proteinopathies had accumulated to a critical threshold. Three independent lines of evidence converged on the templated-misfolding interpretation.

The first line was the seeding experiments of Walker and Jucker. Beginning with the 2006 demonstration that intracerebral inoculation of Aβ-containing brain extract from AD patients or transgenic mice into young APP-transgenic recipient mice nucleated robust amyloid deposition at the inoculation site,[12] the Walker-Jucker program extended through the 2010 demonstration that the seeding effect extended to peripheral routes of administration[13] and was reproducible across multiple transgenic lines. The seeded pathology recapitulated the morphology and distribution of the donor pathology, demonstrating both transmissibility and a degree of strain memory.

The second line was the α-synuclein seeding experiments of Lee, Trojanowski, and colleagues at Penn. Their 2011–2012 work demonstrated that synthetic α-synuclein preformed fibrils, generated entirely in vitro from recombinant protein, could nucleate Lewy-pathology-like inclusions when introduced into cultured primary neurons or injected into the striatum of wild-type mice.[14] The inclusions were composed of hyperphosphorylated endogenous α-synuclein and propagated along anatomical projections from the injection site to interconnected brain regions, recapitulating the topographical staging that Braak had described from human autopsy material.[52]

The third line was the tau seeding work of Marc Diamond and of the Tolnay-Goedert collaboration. Diamond's cellular biosensor system, in which two tau-fluorescent-protein fusions re-

port aggregation by fluorescence resonance energy transfer (FRET), demonstrated that tau aggregates released from one cell could be taken up by another and template the misfolding of the recipient cell's native cytoplasmic tau.[15] Clavaguera, Tolnay, and Goedert demonstrated in transgenic mice that inoculation of tau from human tauopathy brain or from mouse models could nucleate widespread, propagating tauopathy in regions remote from the injection site.[53]

By 2012, the experimental templated-misfolding case was empirically secure for Aβ, α-synuclein, and tau. The Prusiner synthesis extrapolated the same mechanism to TDP-43, SOD1, huntingtin, and the polyglutamine repeat proteins on the basis of in vitro biochemical evidence of self-templating fibril formation, and on the basis of the morphological similarity of the resulting pathological inclusions to the prion archetype.

### 3.2 The Conceptual Leap: From Eight Diseases to One Mechanism

The 2012 synthesis effected a reorganization of the conceptual taxonomy of neurodegeneration. Prior to the synthesis, the major proteinopathies were classified by clinical phenotype (dementia of the AD type, movement disorder of the PD type, motor neuron disease of the ALS type) and by the predominant pathological protein (Aβ plus tau for AD, α-synuclein for PD/LBD, TDP-43 or SOD1 for ALS, tau for FTD-tauopathy, huntingtin for HD, polyglutamine for the SCAs). The eight proteins were understood as eight distinct biochemical accidents, each demanding its own mechanistic explanation.

The Prusiner synthesis proposed that this taxonomy was the wrong one. The unifying feature of the proteinopathies, on the synthesis, was not the identity of the misfolded protein but the mechanism of its misfolding and propagation. All eight proteins, despite their disparate native functions and amino acid sequences, exhibited the same biophysical behavior: each could adopt a self-templating misfolded conformation; each propagated through the brain along anatomical pathways; each exhibited strain-like conformational variation that produced distinct phenotypes; each was associated with stereotyped clinical progression that tracked the anatomical spread of the pathology. The unifying concept demanded a single therapeutic strategy: blockade of the propagation step.

The synthesis also offered an explanation for several long-standing puzzles of neurodegeneration. The stereotyped anatomical staging of pathology in AD (Braak tau staging, Thal Aβ staging) and PD (Braak α-synuclein staging) had been treated as descriptive epidemiology without mechanistic interpretation; the synthesis explained the staging as the spatial signature of prion-like propagation along defined neuronal projection systems. The long latency between molecular onset and clinical presentation — a feature shared by all the major proteinopathies — was explained as the kinetic signature of the seeded-amplification process.

The age-relatedness of all the proteinopathies was explained as the consequence of cumulative spontaneous misfolding events whose probability rises with the duration of cellular life.

### 3.3 The Eight Templating Proteins in Detail

**Aβ.** The amyloid-β peptide, cleaved from the amyloid precursor protein (APP) by β- and γ-secretases, aggregates into β-sheet-rich fibrils that compose the senile plaques of Alzheimer's disease. The seeded-transmission evidence of Walker and Jucker[12,13] established the templated-misfolding behavior of Aβ in vivo. Iatrogenic transmission of cerebral Aβ amyloidosis through cadaveric pituitary-derived growth hormone has subsequently been documented in human recipients,[54] providing a CJD-analogous demonstration of cross-individual Aβ transmissibility.

**Tau.** The microtubule-associated protein tau, when abnormally hyperphosphorylated, dissociates from microtubules and assembles into paired helical filaments (in AD) or into the structurally distinct filaments of the non-AD tauopathies. The cryo-EM work of Goedert, Scheres, and colleagues has demonstrated that the filament structures of distinct tauopathies are reproducibly distinct,[49] validating the strain interpretation at atomic resolution. The Diamond and Clavaguera-Goedert work[15,53] establishes seeded propagation.

**α-Synuclein.** The presynaptic protein α-synuclein composes the Lewy bodies and Lewy neurites of Parkinson's disease, Lewy body dementia, and multiple system atrophy (where it forms glial cytoplasmic inclusions of a structurally distinct conformation). The Lee-Trojanowski preformed-fibril work[14] and subsequent *in vivo* propagation studies, along with the recent identification by Bu of LRP1 as the neuronal receptor mediating α-synuclein uptake,[23] place α-synuclein squarely within the prion-like framework.

**TDP-43.** The DNA/RNA-binding protein TDP-43 is the principal aggregating protein in approximately 97 percent of ALS cases and approximately 45 percent of FTD cases.[55] Seeded propagation has been demonstrated in cell-culture and mouse models, with evidence of strain-like conformational variation distinguishing ALS-TDP from FTD-TDP.

**SOD1.** Superoxide dismutase 1, mutated in approximately 20 percent of familial ALS, forms aggregates that exhibit templated-misfolding behavior in cellular and mouse models, with cell-to-cell propagation documented in transgenic systems.[56]

**Huntingtin.** The huntingtin protein, when its polyglutamine tract is expanded beyond approximately 36 repeats, undergoes conformational misfolding and forms intranuclear and cytoplasmic aggregates whose templated-misfolding behavior has been documented in cell-culture and animal models.[57]

**Polyglutamine repeat proteins.** The same polyglutamine expansion logic that operates in huntingtin operates in the eight protein contexts of the spinocerebellar ataxias and in spinobulbar muscular atrophy (Kennedy disease), unified by the common biophysical behavior of expanded polyQ tracts and supporting the synthesis as applied to a wider class than the eight headline disorders.

## Chapter 4: The Resistance, the Reception, and the Consolidation

The 2012 synthesis did not achieve immediate acceptance. The Alzheimer's and Parkinson's research communities, in particular, resisted the assimilation of their disorders into the prion framework for reasons that were partly scientific and partly institutional. This chapter examines the structure of the resistance, the empirical evidence that progressively overcame it, and the contemporary state of consensus within the field.

### 4.1 The Sources of Resistance

The scientific objections to the 2012 synthesis fell into three principal categories. First, the absence of demonstrated interpersonal transmissibility of AD, PD, and ALS was contrasted with the demonstrated transmissibility of CJD, kuru, and BSE. The argument held that whatever templated-misfolding behavior could be elicited under experimental conditions, the epidemiological absence of disease clusters and the historical absence of iatrogenic transmission demonstrated that the relevant proteins were not "prions" in any clinically meaningful sense. Second, the absence of an evident infectious vector — no documented disease-spreading particle in saliva, feces, or other biological fluids — distinguished AD and PD from the TSEs in a way that the synthesis appeared to elide. Third, the heterogeneity of the templating proteins themselves (Aβ, tau, α-synuclein, TDP-43, SOD1, huntingtin, polyQ) and of their cellular contexts was argued to defeat any single unifying mechanism.

The institutional and rhetorical objections were arguably more decisive in the short run. The term "prion" carried, by 2012, two decades of accumulated epidemiological alarm — the BSE crisis, the variant-CJD episode, the suppression of cadaveric growth hormone — that the AD and PD research communities had no interest in importing. To recharacterize Alzheimer's disease as a prion disease was to invite public misinterpretation of the contagiousness of the disorder, with potential consequences for blood donation, surgical practice, and the long-term care of dementia patients. The resistance to the terminology was real and politically defensible even when the underlying biology was conceded. Walker and Jucker, in their major reviews, have argued for the term "prion-like" rather than "prion" precisely to acknowledge the biological isomorphism without inviting the epidemiological implication.[16,17]

### 4.2 The Empirical Erosion of the Resistance

The resistance eroded over the decade following the 2012 synthesis primarily under the accumulated weight of seeded-transmission experiments. The Eisele et al. 2010 demonstration of cerebral β-amyloidosis induction by peripheral inoculation,[13] the Jaunmuktane et al. 2015 documentation of iatrogenic Aβ amyloidosis in recipients of cadaveric growth hormone treated decades earlier,[54] the Luk et al. 2012 demonstration of α-synuclein propagation following preformed-fibril injection in wild-type mice,[14] the Clavaguera et al. tau-propagation studies,[53] and the cryo-EM strain structures of Goedert and Scheres[49] collectively transformed the synthesis from a contested hypothesis into a working consensus. By approximately 2018, the prion-like framework had become the dominant interpretive lens within which neurodegenerative disease progression was discussed at major scientific meetings, even when the terminology of "propagation," "spread," or "templated misfolding" was preferred to the historically loaded "prion."

The 2020–2022 identification by Bu of LRP1 as the neuronal receptor mediating tau[22] and α-synuclein[23] uptake closed the remaining major mechanistic gap. The templated-misfolding framework had described the disease-level phenomenon (propagation along anatomical pathways), the molecular event (templated conversion of native protein), and the cellular intermediate (uptake and release by neurons), but had not identified the molecular machinery responsible for the uptake step. The Bu identification of LRP1, complemented by Diamond's identification of heparan sulfate proteoglycans as a co-receptor system for tau,[58] supplied the receptor mechanism. The synthesis is now empirically complete in the sense that each major step of the templating-and-propagation cycle has identified molecular substrate.

### 4.3 The Contemporary Consensus

As of 2026, the prion-like paradigm is the dominant model of neurodegenerative disease progression within the academic neurodegeneration community, with the qualifier "prion-like" preferred to "prion" in most contexts to acknowledge the absence of interpersonal transmissibility under ordinary conditions. The Jucker-Walker 2018 *Nature Neuroscience* review, *"Propagation and spread of pathogenic protein assemblies in neurodegenerative diseases,"*[18] is now the canonical statement of the framework as applied to the major proteinopathies. Goedert's 2015 *Science* review, *"Alzheimer's and Parkinson's diseases: The prion concept in relation to assembled Aβ, tau, and α-synuclein,"*[21] is the canonical statement of the framework as applied to the assembled-protein structures of those two disorders.

The translation of the consensus into clinical practice and clinical-trial design has proceeded more slowly than the basic-science consolidation. The anti-amyloid antibody campaign that culminated in the approval of lecanemab (2023) and donanemab (2024) was conceived

within the older "clearance failure" framework and operates by removing deposited Aβ rather than by blocking propagation. The modest clinical benefit of these agents — measurable but well short of disease arrest — is precisely what the prion-like framework predicts: removal of existing pathology in a disease whose progression is dominated by ongoing propagation can yield only proportionate clinical benefit. The next generation of therapeutic candidates, designed within the prion-like framework, target propagation directly. The Ionis-Biogen antisense oligonucleotide against PRNP (IONIS-PrP, now ION717) is the most direct lineal descendant of Prusiner's work and is, as of 2026, in early clinical trial.[59]

## Chapter 5: Therapeutic Implications and Open Questions

The therapeutic implications of the prion theory and its proteinopathy extension are substantial but, as of 2026, only beginning to be realized in clinical practice. This chapter examines the four principal therapeutic axes that follow from the prion framework, assesses the historical record of anti-prion therapeutic development, and identifies the open mechanistic questions whose resolution conditions the next generation of interventions.

### 5.1 PrP-Lowering Antisense Oligonucleotides

The cleanest therapeutic implication of the prion concept is that lowering the substrate PrP^C expression should arrest disease progression. The genetic basis for this strategy is unambiguous: *Prnp*-null mice are resistant to scrapie inoculation and develop normally;[11] heterozygous animals show delayed disease onset proportionate to the reduction in substrate expression. The therapeutic strategy is to deliver an antisense oligonucleotide (ASO) that degrades *PRNP* mRNA, lowering PrP^C protein expression in the central nervous system and thereby starving the propagation cycle of substrate.

The Ionis Pharmaceuticals program (originally IONIS-PrP, now ION717) has, in preclinical mouse models, demonstrated substantial extension of survival when administered prior to or shortly after prion inoculation.[60] The clinical program is being pursued in collaboration with Biogen and is, as of 2026, in early clinical evaluation in genetic-prion-disease patients (familial CJD, GSS, fatal familial insomnia carriers) where the genetic case for the intervention is unambiguous. Whether the PrP-lowering strategy will translate to sporadic CJD, where treatment can typically only begin after the rapidly progressive clinical syndrome is already manifest, is an open question of immediate clinical importance.

### 5.2 Small-Molecule Anti-Prion Compounds

The history of small-molecule anti-prion development has been one of repeated disappointment. The most prominent example is quinacrine, an antimalarial drug identified in the early

2000s as having anti-prion activity in cell-culture screens, which underwent multiple clinical trials in sporadic CJD without demonstrable efficacy.[61] Subsequent candidates — pentosan polysulfate, tetracycline derivatives, polyene macrolide antibiotics — have similarly failed to demonstrate clinical benefit in human prion disease. The history suggests that small-molecule blockade of the conformational conversion event is biophysically difficult, and that the broad-spectrum cellular toxicity of compounds active in vitro generally exceeds the therapeutic window in vivo.

More recent efforts have shifted toward structural targeting informed by the cryo-EM structures of *ex vivo* prion fibrils.[27] Knowledge of the atomic-resolution structure of the templating fibril enables rational design of compounds that stabilize the native PrP^C conformation, that destabilize the templating fibril, or that occupy the templating interface. This work is in early stages and has not yet produced clinical candidates, but it represents the most plausible path to a small-molecule anti-prion agent.

### 5.3 Passive Immunization and Anti-Aggregate Antibodies

The success of anti-amyloid passive immunization (lecanemab, donanemab) in lowering brain Aβ burden in AD has prompted the development of analogous strategies for other proteinopathies. Anti-tau, anti-α-synuclein, and anti-PrP monoclonal antibodies are at various stages of clinical investigation. The mechanism of action is most plausibly the clearance of extracellular aggregate species during the trans-synaptic transit between donor and recipient neurons — that is, blockade of the propagation step itself. The Aducanumab/lecanemab/donanemab clinical data, with modest but measurable slowing of cognitive decline, are interpretable as proof of principle that propagation-blocking interventions can yield clinical benefit. Whether the same logic will succeed for tau-targeting antibodies (currently in trial: gosuranemab, semorinemab, tilavonemab, zagotenemab — most of which have failed in Phase 2) and α-synuclein-targeting antibodies (prasinezumab, cinpanemab) remains to be determined.[62]

### 5.4 Selective Receptor-Mediated Propagation Blockade

The most recent therapeutic frontier, opened by the Bu identification of LRP1 as the neuronal receptor for tau and α-synuclein uptake,[22,23] is selective blockade of the receptor-mediated propagation step. Conceptually, a molecule that selectively occupies the LRP1 binding domain engaged by misfolded tau or α-synuclein — without disturbing the receptor's binding to Aβ or APOE, both of which are required for normal brain function — would, in principle, arrest the propagation cascade at whatever stage it had reached at the time of administration. Existing pathology would not be reversed, but its further spread to spared cortical regions would stop. For diseases whose clinical course is determined by the extent of cortical spread, such an intervention could be transformative.

The structural prerequisite for this approach is high-resolution characterization of the LRP1 binding domains engaged by tau and α-synuclein, work that is underway in multiple structural biology laboratories. The clinical prerequisite is the development of biomarkers for in vivo propagation that can serve as trial endpoints, since the proposed intervention halts spread rather than removing existing burden. Tau-PET imaging, α-synuclein seed-amplification assays in cerebrospinal fluid and skin biopsies,[30] and emerging blood-based biomarkers (phospho-tau 217, glial fibrillary acidic protein, neurofilament light chain) collectively constitute the biomarker infrastructure on which such trials will be conducted.

### 5.5 Open Questions

Three principal mechanistic questions remain unresolved and condition the next decade of anti-prion therapeutic development. First, which conformational species of misfolded protein are seed-competent? The classical prion hypothesis was framed around the protease-resistant fibrillar species, but kinetic evidence increasingly suggests that small oligomeric intermediates are the most active seeding species, with mature fibrils representing relatively inert end-products of the aggregation pathway.[63] The conformational target of seed-amplification-blocking therapeutics must be these intermediates, not the mature fibrils, with consequences for both small-molecule and antibody design.

Second, what initiates the original misfolding event in sporadic disease? In familial prion disease, the destabilizing mutation in PrP itself supplies the initiating perturbation. In iatrogenic disease, the inoculated seed supplies the perturbation. But in sporadic CJD, sporadic AD, sporadic PD, sporadic ALS — together comprising the overwhelming majority of clinical neurodegeneration — the initiating event is unknown. Stochastic spontaneous misfolding, cellular-stress-driven loss of proteostatic capacity, cryptic environmental exposure, and upstream cellular dysfunction (mitochondrial, lysosomal, endoplasmic reticulum) have all been proposed. The question matters profoundly for prevention: only the proximate initiating perturbation, if it can be identified, can be averted prophylactically.

Third, what protective factors prevent uptake or templating in individuals who, despite age and accumulated cellular wear, do not develop disease? The genetic resistance alleles identified at *PRNP* (the M129V polymorphism, the E219K variant in Japanese populations) provide proof of principle that natural variation in the substrate confers resistance.[64] Analogous protective variants in the major proteinopathies — the APOE2 allele in AD, the APOE3-Christchurch variant, GBA1 variants protective against PD — suggest that the same logic operates more broadly. Mapping the molecular basis of these protective effects is the inverse of mapping the disease mechanism, and may identify therapeutic strategies that recapitulate naturally occurring resistance.

> **What remains uncertain:** *Whether the therapeutic blockade of receptor-mediated propagation will yield durable clinical benefit in disorders whose pathology is well-established at the time of diagnosis. The prion-like framework predicts that propagation-blocking interventions are most efficacious when administered early, before the propagation cascade has saturated the cortical network. The clinical infrastructure for early diagnosis of pre-symptomatic neurodegeneration — biomarker panels, imaging protocols, screening programs — is still incomplete. The next decade will test whether the therapeutic logic of the synthesis can be operationalized within a clinical timeline that captures the appropriate disease stage.*

## Conclusion

Stanley Prusiner's 1982 discovery of prions and his 2012 extension of the prion concept to the major proteinopathies together constitute one of the most consequential theoretical achievements in the history of neurodegeneration research. The 1982 paper established the existence of a class of infectious agents composed solely of protein, in violation of the central dogma; the discovery was contested for more than a decade and was ultimately validated by a body of biochemical, genetic, and structural evidence sufficient to earn the 1997 Nobel Prize. The 2012 paper extended the same biophysical mechanism — self-templating conformational misfolding, propagation along anatomical pathways, strain phenomena — to Aβ, tau, α-synuclein, TDP-43, SOD1, huntingtin, and the polyglutamine repeat proteins. The extension was contested in turn and has been validated over the subsequent decade by the seeded-transmission experiments of Walker, Jucker, Lee, Trojanowski, Diamond, and Clavaguera-Goedert, by the cryo-EM strain structures of Scheres and colleagues, and by the recent identification of LRP1 and heparan sulfate proteoglycans as the molecular receptors mediating the propagation step.

The synthesis effected a fundamental reorganization of the conceptual taxonomy of neurodegeneration. The major proteinopathies, previously understood as eight distinct biochemical disorders, are now understood as variations on a single mechanism. The unifying feature is not the identity of the misfolded protein but the biophysics of its misfolding and propagation. The therapeutic implications follow directly: propagation-blocking interventions, applied early in the disease course, should arrest progression even when existing pathology cannot be reversed. This therapeutic strategy is the direct lineal descendant of Prusiner's 1982 insight, and the Ionis-Biogen anti-PrP antisense oligonucleotide program now in early clinical evaluation is its most immediate clinical embodiment.

The recent receptor identifications by Bu (LRP1) and Diamond (HSPGs) close the major remaining mechanistic gap and complete the empirical infrastructure of the prion-like frame-

work. What was for three decades a synthesis without a receptor mechanism is now a synthesis with one. The therapeutic frontier of selective propagation blockade — molecules that occupy the receptor binding domain engaged by misfolded tau and α-synuclein without disturbing the receptor's clearance and lipid-transport functions — is the direct beneficiary of this closure. The structural biology required to design such molecules is underway; the biomarker infrastructure required to test them in pre-symptomatic populations is partially in place; the clinical-trial designs required to demonstrate propagation blockade as a therapeutic endpoint are being developed in real time.

Prusiner's legacy, ultimately, is the demonstration that the neurodegenerative diseases are a tractable class. They are not a heterogeneous collection of biochemical accidents but variations on a single mechanism whose components have now been identified at the conceptual (Prusiner), experimental (Walker–Jucker–Lee–Trojanowski–Diamond), structural (Goedert–Scheres), and molecular-receptor (Bu–Diamond) levels. The integration of these programs supplies the framework within which the major proteinopathies may finally yield to disease-modifying therapy. The remaining work is implementation.

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