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The Experimental Architecture of Prion-Like Spread: A Critical Evaluation of the Walker–Jucker Research Program

Walker · Jucker

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The Experimental Architecture of Prion-Like Spread: A Critical Evaluation of the Lary Walker and Mathias Jucker Research Program on Seeded Proteinopathy in Mammalian Brain

Abstract

Across a productive two-decade collaboration, Lary Walker (Emory University) and Mathias Jucker (Hertie Institute, Tübingen, and the German Center for Neurodegenerative Diseases, DZNE) supplied the empirical foundation that elevated the prion-like paradigm of neurodegeneration from a theoretical proposal — first articulated for the transmissible spongiform encephalopathies by Stanley Prusiner and extended to the major proteinopathies in his 2012 *Science* synthesis[1] — to a working consensus in the field. This thesis provides an exhaustive critical analysis of the Walker–Jucker program, mapping its evolution from the early 1990s primate seeding experiments[2] through the landmark Kane et al. 2000[3] and Meyer-Luehmann et al. 2006[4] intracerebral inoculation studies, to the decisive 2010 Eisele et al. demonstration that peripherally administered Aβ-containing inoculates could nucleate cerebral β-amyloidosis,[5] and onward to the 2013–2018 synthetic reviews that consolidated the field.[6,7,8]

The central experimental design — intracerebral inoculation of dilute brain extracts from diseased animals or postmortem human tissue into the brains of young, asymptomatic transgenic hosts — reproduces donor pathology with strain-faithful morphology, anatomical specificity, and dose-dependent kinetics. Walker and Jucker established four empirical pillars of the prion-like paradigm: (1) seeded transmission is reproducible across the major proteinopathies (Aβ, tau, α-synuclein, TDP-43, SOD1); (2) the pathology propagates along neuroanatomical projections in stereotyped patterns; (3) discrete conformational "strains" produce reproducibly different pathological signatures; and (4) the propagation is, in principle, blockable. This analysis argues that the Walker–Jucker experimental architecture constitutes the empirical hinge on which modern neurodegeneration research turned. The program supplied Prusiner the proof his 2012 unification required, and supplied Bu, Diamond, and Lee–Trojanowski the methodological scaffolding on which their downstream receptor and circuit-spread work was built. Its legacy is the seeded-inoculation paradigm itself.

> **What remains uncertain:** *Whether the seeded-inoculation paradigm reflects the natural initiating mechanism of sporadic neurodegenerative disease, or whether intracerebral inoculation merely accelerates a process whose physiological onset depends on intracellular, cell-autonomous nucleation events that are reproduced — but not replicated — by exogenous seeding.*

Introduction

By 2010, the field of neurodegeneration faced a conceptual emergency. Two decades of sustained research had established that Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and frontotemporal dementia (FTD) were each characterized by the accumulation of a specific misfolded protein — Aβ and tau in AD, α-synuclein in PD and dementia with Lewy bodies (DLB), TDP-43 in ALS and many FTD cases, SOD1 in familial ALS[1,9] — but the field lacked a unifying mechanistic account of how these proteins propagated through the brain along the stereotyped neuroanatomical pathways that Heiko and Eva Braak had documented at the morphological level a generation earlier.[10,11] The amyloid cascade hypothesis, formulated for AD in 1992 by Hardy and Higgins,[12] offered a causal sequence (Aβ → tau → neurodegeneration) but not a spread mechanism. The dopamine-deficit framework for PD addressed the cellular endpoint but not the staged regional advance of α-synuclein pathology.

The conceptual vacuum was, in principle, ready to be filled by Stanley Prusiner's prion theory, which had received the Nobel Prize in 1997 and which postulated that a single misfolded protein could act as a self-templating infectious particle, inducing native protein in recipient cells to adopt its abnormal conformation.[13] Prusiner's 2012 Science synthesis[1] formally extended the prion concept to AD, PD, ALS, FTD, and Huntington's disease. The argument was rhetorically powerful but theoretically vulnerable on a single critical point: Prusiner's case rested on biophysical analogy and on a small but suggestive body of seeding experiments. The field needed a sustained, reproducible, mammalian-brain experimental program to convert the analogy into demonstrated fact.

That program belongs to Lary Walker and Mathias Jucker. Walker, then at Yerkes Primate Research Center and later at Emory University, had been studying age-related Aβ pathology in non-human primates since the late 1980s and had documented in the early 1990s that brain extracts from aged Aβ-bearing donors could induce Aβ deposition in primate recipients — preliminary data that would lie dormant for nearly a decade before the experimental architecture matured.[2,14] Jucker, trained in Switzerland and at the United States National Institute on Aging, had become a leading developer and user of transgenic mouse models of Aβ pathology, including the APP23 line that would become a workhorse of the seeding field.[15] Their collaboration — formalized in the early 2000s with the establishment of Jucker's group at Tübingen and the Hertie Institute and culminating in two decades of joint papers — produced the experimental architecture that the prion-like paradigm required.

This thesis evaluates the Walker–Jucker program along four axes: methodological rigor, conceptual contribution, empirical reach (which proteinopathies and which model systems), and translational consequence. It situates the program against the conceptual pre-

requisites supplied by Prusiner, the parallel tau and α-synuclein seeding work pursued by Michel Goedert, Markus Tolnay, Florence Clavaguera,[16] Virginia Lee, John Trojanowski, Kelvin Luk, and Laura Volpicelli-Daley,[17,18] and the downstream receptor-level mechanism subsequently identified by Guojun Bu (LRP1) and Marc Diamond (heparan sulfate proteoglycans). The thesis argues that Walker and Jucker supplied the empirical hinge: the seeded-inoculation paradigm that converted prion-like behavior from a theoretical proposal into a working consensus, and that the field's subsequent diagnostic and therapeutic ambitions — seed amplification assays, propagation-blocking antibodies, early-intervention trial designs — all derive from the methodological template they established.

Literature Review and Theoretical Positioning

The historiography of seeded transmission in non-prion proteinopathies begins, paradoxically, in the prion field itself. Throughout the 1980s and early 1990s, the painstaking demonstrations by Prusiner, Carleton Gajdusek, and others that scrapie, Creutzfeldt-Jakob disease (CJD), and kuru could be transmitted to laboratory animals by intracerebral inoculation of brain homogenate[13,19] established both the conceptual template and the technical methodology that Walker and Jucker would later adapt. The intracerebral-inoculation paradigm — small-volume injection of dilute homogenate into a defined cortical or subcortical site, followed by long incubation and immunohistochemical analysis — was native to the prion field. Adapting it to the non-transmissible proteinopathies required only one conceptual move: the willingness to treat Aβ and, eventually, tau and α-synuclein, as candidate templating substrates.

That move was anticipated by a small handful of papers in the late 1980s and early 1990s. In 1989, Daniel Carleton Gajdusek and colleagues had speculated explicitly that the aggregation of Aβ might share mechanistic similarities with prion replication.[20] Walker and his colleague Harry LeVine had reported in the early 1990s that aged squirrel monkey brain extracts injected into the cerebral parenchyma of young squirrel monkeys could induce Aβ deposition at the injection site within a span of months.[2,14] The primate work was methodologically demanding, ethically constrained, and largely overlooked at the time — a function of the field's preoccupation with the elucidation of the amyloid cascade and with the still-controversial reception of the prion hypothesis itself.

The 2000s witnessed the maturation of transgenic mouse models that displayed reliable, dense, age-dependent Aβ pathology — Tg2576 (Karen Hsiao Ashe, 1996),[21] APP23 (Sturchler-Pierrat, Jucker et al., 1997),[15] APPPS1 (Radde, Jucker et al., 2006),[22] and eventually 5xFAD (Oakley et al., 2006).[23] These models supplied something the primate work had lacked: a tractable, statistically powered, anatomically reproducible host system in

which seeded induction could be tested with the rigor the field demanded. The Kane et al. 2000 paper[3] — published in the Journal of Neuroscience and authored by Mary Jo Kane, William Lipinski, Michael Callahan, Walker, and colleagues — was the first formal demonstration in transgenic mice that intracerebral infusion of postmortem AD brain extract could nucleate cortical β-amyloidosis in young APP-overexpressing recipients that would not otherwise have developed pathology at the time of analysis. The paper supplied the foundational proof of concept for the entire downstream program.

The methodological refinements of the mid-2000s — most notably the Meyer-Luehmann et al. 2006 Science paper, "Exogenous induction of cerebral β-amyloidogenesis is governed by agent and host"[4] — established three additional empirical pillars: dose-dependence (seeding required a minimum quantity of Aβ-containing material), agent-dependence (different donor preparations produced morphologically distinct deposits), and host-dependence (recipient APP genotype determined permissiveness). These three findings collectively foreclosed the alternative explanation that injection itself, or non-specific brain trauma, was sufficient to nucleate amyloid pathology. The seeded-induction phenomenon was specific, dose-dependent, and conformationally faithful.

By the late 2000s, parallel programs were emerging for tau and α-synuclein. Florence Clavaguera, working with Tolnay and Goedert at Tübingen and the MRC Laboratory of Molecular Biology in Cambridge, published in 2009 in Nature Cell Biology the first demonstration that brain extract from a P301S tauopathy mouse, injected into the brain of a wild-type human tau-expressing recipient, could induce filamentous tau pathology that propagated to anatomically connected regions over six to twelve months.[16] The α-synuclein parallel emerged in 2011–2012 with the Volpicelli-Daley et al. and Luk et al. demonstrations that pre-formed α-synuclein fibrils could induce Lewy body–like pathology in vitro and in vivo with stereotyped anatomical propagation.[17,18] By 2013, when Jucker and Walker published their synthetic Nature review, "Self-propagation of pathogenic protein aggregates in neurodegenerative diseases,"[6] the empirical case for cross-proteinopathy prion-like behavior was robust enough to consolidate.

The theoretical positioning of the Walker–Jucker program rests on a single load-bearing claim: that the templated-misfolding mechanism Prusiner had postulated for the TSEs operated also for Aβ, tau, α-synuclein, TDP-43, and SOD1, and that this operation could be experimentally demonstrated in mammalian brain by intracerebral or even peripheral inoculation of dilute seeded material into appropriate transgenic hosts. The Walker–Jucker contribution was to supply the experimental architecture by which this claim could be tested rigorously, reproducibly, and across multiple proteinopathies. By 2018, when their Nature Neuroscience review[8] synthesized a decade of cross-laboratory work, the prion-like framework had become the dominant model of neurodegenerative disease progression — and the receptor-level work of Bu, Diamond, and others[24,25] was rapidly identifying

the molecular machinery that mediated the spread Walker and Jucker had phenomenologically established.

Analytical Framework and Experimental Paradigms

This analysis employs a critical, methodologically focused framework, evaluating the Walker–Jucker program as a sustained experimental architecture rather than as a sequence of isolated discoveries. The analysis relies on primary peer-reviewed papers from the Walker, Jucker, and joint Walker–Jucker laboratories from 1993 through 2024, augmented by the synthetic reviews of 2013, 2015, and 2018,[6,7,8] and by parallel and downstream contributions from the Goedert–Tolnay–Clavaguera, Lee–Trojanowski–Luk, and Bu laboratories that situate the Walker–Jucker work in its broader field context.

The central methodological apparatus of the Walker–Jucker program is the intracerebral inoculation protocol. In its mature form, the protocol comprises six operational components. First, donor material is prepared from either postmortem AD brain tissue or from aged transgenic mouse brain, homogenized in cold buffer, and clarified by low-speed centrifugation to yield a dilute supernatant containing seed-competent material — typically denominated by total protein concentration and by Aβ ELISA quantification, though the precise relationship between bulk Aβ content and seeding activity has remained a subject of methodological refinement.[4,26] Second, the homogenate is delivered by stereotaxic injection (typically 2.5 µl or less, at a slow infusion rate) into the hippocampus or overlying cortex of young, asymptomatic transgenic hosts — APP23, Tg2576, APPPS1, or 5xFAD mice in the Aβ studies, P301S or ALZ17 mice in the tau studies, M83 or A53T mice in the α-synuclein studies.[4,15,16,18] Third, the inoculated animals are aged for a defined incubation period — typically four to eight months for Aβ, six to twelve months for tau, two to six months for α-synuclein. Fourth, animals are euthanized and brains processed for immunohistochemistry using antibodies specific to the templating protein and, in later iterations, to conformation-specific epitopes that distinguish strain variants. Fifth, the pathology is scored quantitatively by stereological estimation of plaque or tangle burden across defined anatomical regions, with attention to whether the pathology has spread beyond the injection site along known neuroanatomical projections. Sixth, dilution series and biochemical depletion experiments establish dose-dependence and confirm that the seeding activity tracks with the misfolded protein rather than with bulk homogenate.[4,5]

Three methodological refinements distinguish the mature Walker–Jucker program from the earlier 1990s primate work. First, the use of inbred transgenic mouse lines supplied statistical power and genetic uniformity that the squirrel monkey work could not provide. Second, the development of conformation-specific antibodies (most notably the OC and

A11 antibodies developed by Charles Glabe and others) permitted differentiation of seeded morphologies that would have appeared indistinguishable by bulk amyloid staining alone.[27] Third, the integration of dot-blot conformational profiling and, later, solid-state NMR fingerprinting allowed the field to demonstrate that distinct seed preparations carried distinct conformational signatures that were faithfully reproduced in recipient tissue — the operational definition of "strain" in the prion-like context.[28,29]

The analytical framework of this document evaluates the Walker–Jucker findings not as isolated experimental demonstrations but as a continuous, methodologically evolving program whose successive iterations progressively tightened the empirical case for prion-like behavior in non-TSE proteinopathies. The thesis interrogates the causal relationships among inoculum preparation, host permissiveness, incubation kinetics, anatomical spread, and conformational fidelity, and assesses whether the program's collective experimental output is sufficient to support the strong theoretical claim — that prion-like templated misfolding is the dominant mechanism of pathological spread in the major proteinopathies — or whether weaker claims, in which intracerebral inoculation accelerates a process whose physiological onset depends on additional intracellular machinery, are more empirically defensible.

Chapter 1: The Original Seeding Experiments (1990s–2009)

The empirical lineage of the Walker–Jucker program begins not in a transgenic mouse colony but in the marmoset and squirrel monkey colonies of the Yerkes Primate Research Center in the late 1980s and early 1990s. Walker's first independent contributions to the seeding literature exploited an empirical curiosity: aged primates, like aged humans, accumulate Aβ-positive cortical deposits, and brain extracts from heavily Aβ-laden donors might therefore carry seeding-competent material that could be detected by intracerebral transfer into younger primate recipients.[2,14]

1.1 The Walker Primate Studies (1993–1998)

In a series of papers published between 1993 and 1998, Walker and his collaborators documented that intracerebral injection of postmortem brain homogenate from aged Aβ-bearing squirrel monkeys or from AD patients into the brains of younger primate recipients could induce localized Aβ deposition at the injection site within months — a timescale dramatically shorter than the years required for de novo age-related Aβ accumulation in the same recipient species.[2,14] The primate work was methodologically painstaking, and the resulting data sets were small. The papers were nonetheless theoretically suggestive: they reported localized Aβ induction with morphological features that

recapitulated the donor pathology, and they established that the phenomenon was not confined to laboratory rodents.

The primate work was, however, limited by three structural constraints. First, the small sample sizes intrinsic to primate research foreclosed the statistical power required to demonstrate dose-dependence and host-genotype-dependence with rigor. Second, the long natural lifespans of primates made comprehensive incubation-period studies impractical. Third, the ethical and logistical constraints of primate research foreclosed the kind of cross-laboratory replication that the field would eventually demand. The primate work was a proof of principle; the demonstration required a tractable mammalian model.

1.2 The Kane et al. 2000 Paper

The decisive transition to the transgenic mouse era was effected by the 2000 Kane et al. paper, "Evidence for seeding of β-amyloid by intracerebral infusion of Alzheimer brain extracts into young Tg2576 mice."[3] The paper reported that intracerebral infusion of AD postmortem brain extract into the hippocampi of young Tg2576 mice — which would not otherwise have developed amyloid pathology for many months — produced detectable Aβ deposition at the injection site within five months. Critically, infusion of age-matched non-AD control brain produced no comparable deposition. The 2000 paper supplied the foundational evidence that the seeding phenomenon was specific to AD-derived material, host-permissive (requiring APP-overexpressing recipients), and operationally tractable in a model system that could support the comprehensive dose-response and conformation-specificity studies the field would subsequently demand.

The 2000 paper was, by the standards of the field, a quiet publication. Its methodological implications would take six years to be fully realized in the literature. But the experimental architecture it established — postmortem donor material, dilute intracerebral infusion, defined incubation, anatomical scoring — would become the standard against which all subsequent seeding experiments were compared.

1.3 The Meyer-Luehmann et al. 2006 Paper

The 2006 Meyer-Luehmann et al. paper, "Exogenous induction of cerebral β-amyloidogenesis is governed by agent and host," published in Science,[4] represented the consolidation of the seeded-induction paradigm into a mature empirical framework. The paper, with Mathias Jucker and Walker as senior authors, reported four interlocking findings. First, intracerebral injection of brain extract from aged APP23 transgenic mice into young APP23 recipients robustly induced cortical Aβ deposition, recapitulating the donor pathology in morphology and anatomical distribution. Second, the seeded induction exhibited a clear dose-response relationship, with dilution series demonstrating a defined threshold below

which seeding was undetectable. Third, the seeded morphology was determined by both the donor preparation (the "agent") and the recipient genotype (the "host"): different donor inocula produced distinguishable plaque morphologies, and recipients of different APP transgenes exhibited differential permissiveness. Fourth, the seeding activity was protein-based — protease digestion or formic acid denaturation of the inoculum abolished its activity, while nucleic acid digestion did not.

The 2006 paper supplied the empirical foundation for the subsequent prion-like framing. By demonstrating that the seeded pathology preserved morphological and conformational features of the donor material — and that this preservation was protease-sensitive in the manner expected of a misfolded-protein template — the paper closed the methodological case that the phenomenon was consistent with templated misfolding rather than with non-specific induction of de novo amyloid aggregation. The methodological refinements introduced in the 2006 paper — careful titration of inoculum concentration, attention to recipient age and genotype, rigorous anatomical scoring, and biochemical depletion controls — would become the standard methodological repertoire of the field. By 2009, when Clavaguera et al.[16] reported the first comparable demonstration for tau, the methodological template was sufficiently mature that the extension to a second proteinopathy required only adaptation rather than innovation of the basic experimental architecture.

Chapter 2: The 2010 Eisele Paper — Peripheral Inoculation and Long-Distance Spread

If the 2006 Meyer-Luehmann paper consolidated the intracerebral seeding paradigm into a mature empirical framework, the 2010 Eisele et al. paper, "Peripherally applied Aβ-containing inoculates induce cerebral β-amyloidosis,"[5] published in Science, decisively shattered one of its constraining assumptions. The paper, with Walker and Jucker as senior authors and Yvonne Eisele as first author, reported that intraperitoneal injection of Aβ-containing brain extract into APP23 transgenic mice could nucleate cortical β-amyloidosis — that the seeding activity could traverse from the peripheral compartment to the central nervous system and produce histologically detectable cerebral pathology. The methodological and conceptual consequences of this finding were profound and remain incompletely resolved a decade and a half later.

2.1 The Experimental Design

The Eisele experiments employed a methodologically conservative protocol that maximized the credibility of the central claim. Young APP23 transgenic mice, four to six weeks of age, received intraperitoneal injections of brain extract prepared from aged APP23

mice with established cortical amyloidosis. Control mice received either age-matched non-transgenic brain extract or vehicle alone. After incubation periods of four to seven months — significantly longer than the months required for intracerebral seeding — the brains were processed for Aβ immunohistochemistry and quantitative stereological analysis.

The results were striking. Mice that had received peripheral inoculation of Aβ-bearing material exhibited cortical and hippocampal amyloid deposits at significantly elevated frequency and density compared to vehicle-treated controls. The deposits were morphologically indistinguishable from those produced by intracerebral seeding and from those that would have arisen spontaneously many months later in untreated APP23 mice. Critically, peripheral inoculation of brain extract from non-transgenic mice produced no comparable effect, and protease-digested or denatured inoculum was inactive — establishing that the seeding activity required intact Aβ-containing material.

2.2 The Conceptual Consequences

The Eisele finding broke the strict intracerebral-only requirement that had constrained the prion-like framework for Aβ. The 2010 paper implied that Aβ seeds were, in principle, capable of traversing biological barriers — the gut wall, the blood-brain barrier, or both — in quantities sufficient to nucleate cortical pathology. The mechanistic route by which this traversal occurred remained, and remains, unresolved. Three possibilities have been entertained in the subsequent literature. First, that intact seeds may cross the blood-brain barrier directly, exploiting receptor-mediated transcytosis or transient barrier breaches. Second, that seeds may be transported retrogradely along peripheral nerves, in particular the vagus nerve, in a fashion analogous to the proposed gut-to-brain spread of α-synuclein in Parkinson's disease.[30] Third, that peripheral inoculation may produce a low-level systemic seeding effect that ultimately nucleates cerebral amyloidosis through indirect mechanisms.

The 2010 paper was deliberately cautious about ascribing a specific mechanism. The empirical claim was nonetheless decisive: peripheral compartment inoculation was sufficient to nucleate central pathology, and the proper theoretical framework for understanding Aβ pathology therefore had to accommodate this systemic dimension. The implications for human disease were sobering: if peripheral exposure to Aβ-containing material was, in principle, capable of nucleating cerebral amyloidosis, the iatrogenic transmission risks suggested by case reports of cadaveric dura mater grafts and pituitary hormone preparations[31,32] acquired a more rigorous empirical basis.

2.3 The Follow-Up Architecture (2014–2017)

The 2014 Eisele et al. follow-up extended the analysis with a series of refinements that addressed objections raised against the original report.[33] The follow-up demonstrated that the peripherally induced cerebral amyloidosis exhibited the morphological hallmarks of seeded — rather than spontaneous — pathology, that the effect required Aβ-containing donor material, and that the effect persisted across multiple host APP transgenes. Subsequent work by the Jucker group documented the route of peripheral-to-central transfer with increasingly refined biochemical and anatomical methods.[34]

The 2017 Purro et al. paper from John Collinge's laboratory at the MRC Prion Unit,[32] reporting evidence of Aβ pathology in younger-than-expected human subjects who had received cadaver-derived growth hormone preparations decades earlier, supplied an independent line of evidence that the peripheral-to-central transfer the Eisele paper had demonstrated in mice could, under specific iatrogenic circumstances, operate in human beings as well. The convergence of the Walker–Jucker mouse work and the Collinge human observational data established the empirical foundation for the contemporary regulatory framework around surgical instrument decontamination and cadaveric tissue preparation — a translational consequence that had not been anticipated by the original 2010 design.

Chapter 3: Strain Diversity and Conformational Variants

The concept of conformational "strain" — distinct biochemical variants of the same primary-sequence protein that produce distinguishable pathological phenotypes — is the load-bearing theoretical lift of the prion-like paradigm. The strain concept had been established in the TSE field decades earlier: distinct PrP^Sc conformations produce CJD subtypes with characteristic incubation periods, neuroanatomical distributions, and lesion profiles.[13,35] The question of whether the strain phenomenon extended to Aβ, tau, and α-synuclein was, throughout the late 2000s and early 2010s, the methodological frontier of the Walker–Jucker program.

3.1 The Stöhr Synthetic Aβ Prions (2012)

The 2012 Stöhr et al. paper from Stanley Prusiner's laboratory, "Purified and synthetic Alzheimer's amyloid beta (Aβ) prions,"[36] published in PNAS, supplied the foundational demonstration that synthetic Aβ fibrils — generated by in vitro polymerization of recombinant Aβ peptide in the absence of any biological seed — could nucleate cerebral amyloidosis when intracerebrally inoculated into transgenic mouse recipients. The Stöhr work established that the seeded-induction phenomenon required only the misfolded Aβ tem-

plate itself, with no contribution from accessory molecules present in postmortem brain homogenate. It also opened the methodological possibility of systematically varying the conformation of the inoculum to test whether different conformational preparations produced distinguishable pathological outputs in recipients.

3.2 The Heilbronner Strain Demonstration (2013)

The 2013 Heilbronner et al. paper from the Jucker laboratory, "Seeded strain-like transmission of β-amyloid morphotypes in APP transgenic mice,"[37] published in EMBO Reports, supplied the decisive demonstration that distinct donor inocula produced distinct seeded morphologies in genetically identical recipients. The paper compared brain extracts from APP23 and APPPS1 transgenic mice — two well-characterized lines that exhibit characteristic differences in their cortical Aβ pathology, with APP23 producing predominantly dense-cored plaques and APPPS1 producing predominantly diffuse plaques. When these distinct donor inocula were injected into a common APP23 host background, the recipient pathology faithfully recapitulated the donor morphology: APP23-derived inoculum produced dense-cored deposits, APPPS1-derived inoculum produced diffuse deposits, even in genetically identical recipient brains.

The Heilbronner result was the operational definition of "strain" applied to a non-TSE proteinopathy. It demonstrated that the seeded morphology was determined not by the recipient genotype alone — which would have predicted uniform pathology in genetically identical hosts — but by the conformational signature of the donor seed, which was preserved through templated propagation. The 2013 finding was conceptually momentous: it established that the conformational information carried by an Aβ seed was sufficient to specify the morphological output, in the manner postulated for PrP^Sc strains in the TSE field. The strain concept had now been formally extended from the prion field to a non-TSE proteinopathy.

3.3 The 2014 Watts–Prusiner Conformational Variants

The 2014 Watts et al. paper from Prusiner's laboratory, "Serial propagation of distinct strains of Aβ prions from Alzheimer's disease patients,"[38] extended the strain demonstration to human-derived material. The Watts paper reported that brain extracts from clinically and pathologically distinct AD patients — including subjects with rapidly progressing variants and with vascular-predominant pathology — could be serially passaged through transgenic mouse hosts, with the passaged material reproducibly recapitulating the donor strain in subsequent passages. The serial-passage architecture was directly analogous to the methodology by which TSE strains had been characterized in the prion field.

3.4 Tau and α-Synuclein Strains

The strain concept was extended to tau in a series of papers by the Lee–Trojanowski group, the Diamond laboratory, and others, demonstrating that distinct conformational preparations of recombinant or brain-derived tau produced reproducibly distinct pathological signatures and that these signatures correlated with clinically and pathologically distinct tauopathies — AD-type tau, PSP-type tau, CBD-type tau, and the Pick's disease morphotype.[39,40] The extension to α-synuclein was effected by the Lee group and the Melki laboratory, with demonstrations that distinct α-synuclein strain preparations produced PD-like, multiple system atrophy (MSA)-like, or DLB-like pathology in appropriate recipient models.[41,42]

The strain framework now constitutes the dominant explanatory architecture for the clinical heterogeneity of the major proteinopathies. The classical neuropathological observation that AD, PSP, CBD, Pick's disease, PD, MSA, and DLB are distinguishable by characteristic morphological and anatomical features — features that have historically been catalogued by the Braak staging systems and refined by successive iterations of neuropathological criteria[10,11] — is now interpretable as the macroscopic signature of distinct conformational strains of the underlying templating proteins. The Walker–Jucker contribution to this framework was the methodological architecture by which strain identity could be operationally defined and experimentally demonstrated.

> **What remains uncertain:** *Whether the strain concept, as operationally defined by passage faithfulness in mammalian inoculation models, captures the full molecular complexity of the conformational variability observed in human disease, or whether human proteinopathies exhibit additional layers of conformational diversity (post-translational modification, lipid envelope, accessory protein binding) that are flattened by the experimental passage paradigm. The convergence of solid-state NMR and cryo-EM structural data with the operational passage definitions of strain is, as of 2026, still in progress.*

Chapter 4: Extension Across the Proteinopathies — Tau, α-Synuclein, TDP-43, SOD1

The Walker–Jucker program, while centered on Aβ, supplied the methodological template that was rapidly extended to the other major proteinopathies of neurodegeneration. The cross-proteinopathy extension was effected in part by direct collaboration and in part by parallel laboratories that adopted the Walker–Jucker experimental architecture. By 2013, when Jucker and Walker published their synthetic Nature review,[6] the seeded-inoculation

paradigm had been demonstrated for Aβ, tau, α-synuclein, TDP-43, and SOD1, with strong empirical evidence for prion-like behavior in each case.

4.1 Tau: The Clavaguera–Tolnay–Goedert Lineage

The decisive demonstration of seeded tau pathology was effected by Florence Clavaguera, working with Markus Tolnay at Basel and with Michel Goedert at the MRC Laboratory of Molecular Biology in Cambridge. The 2009 Clavaguera et al. paper, "Transmission and spreading of tauopathy in transgenic mouse brain,"[16] published in Nature Cell Biology, reported that brain extract from P301S tauopathy mice — which develop dense filamentous tau pathology — injected into the brains of ALZ17 mice expressing wild-type human tau, induced filamentous tau pathology that propagated to anatomically connected regions over six to fifteen months. The 2009 paper supplied the foundational demonstration that the seeded-induction paradigm extended to tau, and it set the methodological template for the rapid expansion of the tau seeding field over the subsequent decade.

Subsequent work by the Goedert–Tolnay–Clavaguera consortium and by independent laboratories — including the Marc Diamond group at UT Southwestern, which developed the FRET-based tau seeding biosensor cell line that has become a standard quantitative assay for tau seed activity[43] — established that tau seeding propagated trans-synaptically along well-defined anatomical projections,[44] that distinct tau strains produced reproducibly distinct pathological phenotypes,[39,40] and that brain-derived tau seeds carried discrete conformational signatures detectable by biochemical and structural methods.[45] The cumulative body of tau seeding work supplied the experimental foundation for the contemporary view that tau pathology in AD, PSP, CBD, and FTD-tau spreads through the brain by templated misfolding along anatomical circuits — a view that converges with the Braak staging observations of three decades earlier[10] and that has critical implications for the design of anti-tau immunotherapies currently in clinical trials.

4.2 α-Synuclein: The Volpicelli-Daley and Luk Demonstrations

The α-synuclein seeding paradigm was established in two interlocking papers from the Lee–Trojanowski laboratory at the University of Pennsylvania in 2011–2012. The 2011 Volpicelli-Daley et al. paper, "Exogenous α-synuclein fibrils induce Lewy body pathology leading to synaptic dysfunction and neuron death,"[17] published in Neuron, supplied the foundational in vitro demonstration that pre-formed α-synuclein fibrils, applied to primary neuronal cultures, were internalized and induced endogenous wild-type α-synuclein to misfold and aggregate into structures phenotypically identical to authentic Lewy bodies. The 2012 Luk et al. paper, "Pathological α-synuclein transmission initiates Parkinson-like neurodegeneration in nontransgenic mice,"[18] published in Science, extended the demonstration to wild-type mouse brain, showing that intrastriatal injection of pre-formed α-

synuclein fibrils induced α-synuclein pathology that propagated along anatomical projections to the substantia nigra and that produced progressive dopaminergic neuron loss and motor deficits over months.

The Luk et al. 2012 paper was the α-synuclein analog of the Kane et al. 2000 Aβ paper and the Clavaguera et al. 2009 tau paper: it established that the seeded-induction paradigm operated for α-synuclein in mammalian brain, that the resulting pathology recapitulated the anatomical and morphological hallmarks of human PD, and that the methodological template was now operative across three of the major proteinopathies. The subsequent decade saw the α-synuclein seeding paradigm extended to gut-to-brain propagation models,[30] to MSA versus PD strain comparisons,[41,42] and to the development of α-synuclein seed amplification assays that now constitute the most sensitive available antemortem biomarker for synucleinopathies.[46]

4.3 TDP-43 and SOD1

The extension to TDP-43 — the principal aggregating protein in ALS and in the majority of FTLD cases — was effected in a series of papers in the mid-2010s. The 2014 Smethurst et al. paper from the Hanger laboratory[47] and the 2018 Porta et al. paper from the Lee group[48] demonstrated that pre-formed TDP-43 fibrils or brain-derived TDP-43 seeds induced TDP-43 pathology in recipient neurons in culture and in transgenic mouse models. The SOD1 extension was effected by the Brännström and Marklund laboratories, demonstrating seeded SOD1 aggregation in transgenic ALS mouse models with stereotyped spinal cord propagation patterns.[49]

The TDP-43 and SOD1 demonstrations have remained, by comparison with the Aβ, tau, and α-synuclein bodies of work, methodologically more contested. The aggregation kinetics of TDP-43 are sensitive to post-translational modification and to liquid-liquid phase separation dynamics that complicate the interpretation of seeded-induction experiments,[50] and the SOD1 seeding work has been largely confined to familial-mutation transgenic models whose relationship to sporadic ALS pathology remains uncertain. The cross-proteinopathy generality of the prion-like framework is therefore robust for Aβ, tau, and α-synuclein, and provisional for TDP-43 and SOD1.

4.4 The 2013 Synthesis

The 2013 Jucker–Walker Nature review, "Self-propagation of pathogenic protein aggregates in neurodegenerative diseases,"[6] consolidated the cross-proteinopathy seeding evidence into a unified theoretical framework. The review argued that the prion-like behavior demonstrated for Aβ, tau, α-synuclein, TDP-43, and SOD1 was sufficient to support the strong claim that templated misfolding was the dominant mechanism of pathological

spread in the major neurodegenerative diseases. The 2015 Walker–Walker review in Annual Review of Neuroscience, "Neurodegenerative diseases: expanding the prion concept,"[7] further refined the theoretical case and addressed the principal objections — most notably the question of whether the prion-like terminology was appropriate for proteins whose pathological spread, while templated, did not appear to constitute interpersonal infectious transmission in the manner of the classical TSEs. The 2018 Jucker–Walker Nature Neuroscience review[8] consolidated the developing literature on receptor-mediated cellular uptake — the work of Guojun Bu identifying LRP1[24] and of Marc Diamond identifying heparan sulfate proteoglycans[25] — and integrated the molecular-mechanism findings into the broader prion-like framework.

> **What remains uncertain:** *Whether the empirical generality of the prion-like framework across five major templating proteins reflects a unified molecular mechanism — common cellular uptake machinery, common endosomal escape kinetics, common templating biophysics — or whether the apparent generality conceals a multiplicity of distinct cellular mechanisms whose phenomenological outputs converge on a similar seeded-induction architecture. The receptor-level work of Bu and Diamond suggests partial convergence, but the cell-type-specific vulnerabilities of each proteinopathy (motor neurons in ALS, dopaminergic neurons in PD, entorhinal cortex in AD) point toward additional receptor or uptake logic that the unified framework has not yet captured.*

Chapter 5: Therapeutic and Diagnostic Implications

The translational consequences of the Walker–Jucker experimental program have been substantial in two principal domains: the development of seed-amplification diagnostic assays, and the conceptual reframing of disease-modifying therapeutic strategy. The 2018 Jucker–Walker Nature Neuroscience review[8] articulated both translational frontiers, and the subsequent five years have seen substantial empirical progress in each.

5.1 Seed-Amplification Assays as Diagnostic Tools

The methodological logic of the seeded-induction paradigm — that misfolded protein seeds, when supplied with substrate, will template the conversion of native protein into the misfolded conformation — was directly translatable into in vitro diagnostic assays. The protein misfolding cyclic amplification (PMCA) assay, originally developed by Claudio Soto for prion detection,[51] was adapted in the 2010s for Aβ, tau, and α-synuclein detection. The real-time quaking-induced conversion (RT-QuIC) assay, originally developed by

Byron Caughey for prion detection,[52] was similarly adapted for the major non-TSE proteinopathies.

The α-synuclein adaptation has been the most clinically consequential. The 2017 Fairfoul et al. RT-QuIC assay[53] and the subsequent refinements by the Soto laboratory and the Caughey group[46] demonstrated that cerebrospinal fluid samples from clinically diagnosed PD and DLB patients contained α-synuclein seeds detectable at sensitivities of >90% with specificities approaching 95%. The α-synuclein seed amplification assay (SAA) is, as of 2026, the most sensitive available antemortem biomarker for synucleinopathies, and the Michael J. Fox Foundation's Parkinson's Progression Markers Initiative has integrated the assay into the contemporary biomarker-driven definition of PD itself.[54] The diagnostic frontier represents one of the most concrete and clinically deployable translations of the Walker–Jucker experimental program — albeit one effected by adjacent laboratories rather than by Walker and Jucker directly.

5.2 Implications for Disease-Modifying Trial Design

The therapeutic implications of the prion-like framework are subtler and, as of 2026, more contested. If neurodegenerative pathology spreads through the brain by templated misfolding along anatomical circuits, then disease modification requires interventions that block the propagation step — and such interventions must be deployed before the propagation cascade has saturated the cortical network. The therapeutic window for propagation-blocking strategies is necessarily early, before symptomatic onset or in the earliest prodromal phases. This places a high premium on early biomarker detection — which the seed amplification assays now begin to supply — and on identifying the originating "seed sites" from which propagation initiates.

Walker has argued specifically that the entorhinal cortex and the locus coeruleus are likely seed sites for tau in AD, with downstream propagation along well-mapped projection pathways.[8] The hypothesis converges with the Braak staging observation that the earliest detectable tau pathology in AD is found in the entorhinal cortex and the brainstem nuclei,[10] and it implies that propagation-blocking interventions deployed in cognitively normal individuals with detectable early-stage tau seeding may, in principle, arrest disease advance before the cortical propagation cascade has spread to functionally critical regions.

The currently approved anti-amyloid antibody therapeutics — lecanemab and donanemab — operate not on the propagation mechanism but on the clearance of deposited Aβ.[55,56] The clinical benefit of these agents is modest, consistent with the prion-like framework's prediction that pathology that has already propagated through the cortex cannot be reversed by interventions that remove existing burden without blocking further uptake. The

next generation of anti-amyloid and anti-tau immunotherapies — including the propagation-blocking conformation-specific antibodies currently under preclinical evaluation — may, if deployed sufficiently early in the disease course, achieve the disease modification that the clearance-based agents have not.

5.3 The Receptor-Targeting Frontier

The downstream molecular-mechanism work of Guojun Bu identifying LRP1 as the master neuronal receptor for tau and α-synuclein uptake,[24] and of Marc Diamond identifying heparan sulfate proteoglycans as obligatory co-receptors,[25] has opened a second therapeutic frontier: selective pharmacological blockade of the uptake step itself. If propagation depends on receptor-mediated internalization of extracellular seeds, then a molecule that selectively blocks the receptor's binding to the misfolded ligand — without disturbing the receptor's binding to its physiological ligands — would, in principle, halt the propagation cascade without disrupting normal physiology. The structural prerequisites for this approach — atomic-resolution mapping of the receptor's binding-domain architecture, identification of the specific epitopes engaged by misfolded versus physiological ligands — are under active investigation in multiple structural biology laboratories.

The Walker–Jucker experimental architecture supplied both the demonstration that propagation occurs and the methodological platform on which the receptor-level work could be built. The seeded-inoculation models are now standard preclinical platforms for testing propagation-blocking interventions, and the strain-faithful passage paradigms developed in the 2013 Heilbronner work[37] and the 2014 Watts work[38] have become the standard against which candidate therapeutic interventions are evaluated for their ability to block strain-specific propagation in vivo.

Conclusion

The two-decade experimental program of Lary Walker and Mathias Jucker constitutes the empirical hinge on which modern neurodegeneration research turned. The conceptual move that Prusiner had articulated in his 2012 Science synthesis[1] — that the major proteinopathies of neurodegeneration share a common prion-like mechanism of templated misfolding and trans-cellular spread — required, to be more than a theoretical proposal, a sustained mammalian-brain experimental program capable of demonstrating the phenomenon rigorously, reproducibly, and across multiple proteinopathies. Walker and Jucker supplied that program.

The methodological architecture they established — intracerebral inoculation of dilute brain extract into young, asymptomatic transgenic hosts, with quantitative anatomical

scoring of seeded pathology, dose-response titration, biochemical depletion controls, and conformational profiling — has become the standard preclinical platform for the seeded-induction field. The 2000 Kane paper,[3] the 2006 Meyer-Luehmann paper,[4] the 2010 Eisele peripheral inoculation paper,[5] the 2013 Heilbronner strain demonstration,[37] and the three synthetic reviews of 2013, 2015, and 2018[6,7,8] together constitute the foundational empirical literature on which the contemporary prion-like framework rests.

The cross-proteinopathy extension — to tau by Clavaguera–Tolnay–Goedert, to α-synuclein by Lee–Trojanowski–Luk–Volpicelli-Daley, to TDP-43 and SOD1 by adjacent laboratories — adopted the Walker–Jucker methodological template and validated its generality. The downstream molecular-mechanism work of Bu (LRP1) and Diamond (HSPGs) supplied the receptor-level architecture that the phenomenological seeding work had previously lacked. The diagnostic translation — RT-QuIC and PMCA seed amplification assays for α-synuclein, tau, and Aβ — has converted the Walker–Jucker experimental logic into clinically deployable antemortem biomarkers that are now reshaping the operational definition of synucleinopathy itself.[54]

The Walker–Jucker legacy is the seeded-inoculation paradigm. It supplied Prusiner the proof his unification required, supplied Bu the methodological platform on which receptor identification could be effected, supplied the field the experimental architecture by which propagation-blocking therapeutics may yet be developed, and supplied the conceptual reframing under which the staged regional advance of neurodegenerative pathology — the phenomenon Heiko Braak had documented morphologically a generation earlier[10,11] — finally acquired a mechanistic interpretation consistent with its empirical regularities. The contemporary view that neurodegenerative diseases are propagating proteinopathies, whose progression depends on templated misfolding and trans-cellular spread along anatomical circuits, is the view Walker and Jucker established. Whether the propagation-blocking therapeutic strategies that this view implies will, over the next decade, deliver the disease modification that clearance-focused agents have not, is the next empirical question the field will answer — on a methodological platform that Walker and Jucker built.

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