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# A Paradigm Shift in Molecular Neurodegeneration: The LRP1 Receptor and the Mechanism of Prion-Like Propagation

Bu · Prusiner · Walker

Critical Review — Revised Edition, Prion-Like Integration

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# A Paradigm Shift in Molecular Neurodegeneration: A Critical Assessment of Guojun Bu's Research on LRP1, Proteostasis, and the Neurovascular Unit — with Integration of the Prusiner–Walker Prion-Like Paradigm

## Abstract

The low-density lipoprotein receptor-related protein 1 (LRP1) has historically occupied a highly specialized niche in the molecular biology of neurodegenerative disease, primarily conceptualized as a vital conduit for the clearance of amyloid-beta (Aβ) peptides from the central nervous system. Over the past three decades, the research trajectory of Guojun Bu — spanning tenures at Washington University in St. Louis, the Mayo Clinic, the Hong Kong University of Science and Technology, and SciNeuro Pharmaceuticals — has fundamentally redefined the epistemological framework surrounding LRP1 and its associated apolipoproteins. This doctoral-level thesis provides an exhaustive, critical analysis of Bu's contributions to molecular neuroscience, mapping the evolution of LRP1 from a simple endocytic clearance receptor to a central, pleiotropic modulator of brain proteostasis, lipid homeostasis, and neurovascular integrity.

Through a rigorous synthesis of primary molecular data, transgenic in vivo models, and clinical transcriptomics, this analysis demonstrates how Bu's laboratory engineered a paradigm shift in the understanding of apolipoprotein E (APOE) receptors. Initially establishing the precise cellular kinetics of LRP1-mediated Aβ degradation within the brain parenchyma across neurons and glia, Bu's subsequent investigations revealed a paradoxical dual nature to the receptor. Recent seminal discoveries indicate that LRP1 actively facilitates the prion-like cellular uptake and inter-neuronal propagation of pathological tau and α-synuclein.

This revised edition integrates Bu's molecular findings with the broader prion-like paradigm pioneered by Stanley Prusiner — whose 2012 *Science* paper "A unifying role for prions in neurodegenerative diseases"[59] reframed Alzheimer's, Parkinson's, and related disorders as templated-misfolding diseases — and by Lary Walker and Mathias Jucker, whose seeded-transmission experiments[61,62,63] supplied the empirical proof. Where Prusiner and Walker established *that* misfolded proteins propagate through the brain along anatomical networks, Bu's LRP1 work establishes the molecular mechanism by which they do so. This thesis argues that the three programs constitute a single integrated framework: neurodegeneration is not merely a failure of clearance mechanisms, but a catastrophic, evolutionary subversion of the brain's homeostatic lipid and protein receptor network. The report concludes by evaluating the translational implications of these discoveries, specifically assessing the challenges

and promise of targeting LRP1's ligand promiscuity for novel neurotherapeutics and blood-brain barrier shuttling platforms in 2026 and beyond.

> **What remains uncertain:** *Whether selective pharmacological blockade of LRP1's interaction with tau and α-synuclein — without compromising its Aβ-clearance and APOE-transport functions — is structurally achievable; and whether the prion-like spread mechanism applies uniformly across the eight known templating proteins or admits cell-type-specific exceptions.*

## Introduction

The pathogenesis of Alzheimer's disease (AD) and related neurodegenerative disorders has long been dominated by the amyloid cascade hypothesis, a framework which posits that the accumulation, oligomerization, and subsequent deposition of amyloid-beta (Aβ) peptides serve as the primary nucleating events driving downstream synaptic dysfunction, neuroinflammation, and irreversible neuronal apoptosis.[1] However, the repeated failure of early clinical trials targeting the overproduction of Aβ via secretase inhibition forced a critical re-evaluation of the mechanisms governing brain proteostasis.[4] It has become increasingly evident that sporadic, late-onset AD — which accounts for the vast majority of clinical cases — is driven less by the anomalous overproduction of pathogenic proteins than by a systematic, age-related failure in their clearance, coupled with cascading disruptions in lipid metabolism, vascular integrity, and trans-neuronal transmission of misfolded protein assemblies.[1,61]

At the absolute center of this mechanistic pivot is the low-density lipoprotein receptor-related protein 1 (LRP1). Structurally, LRP1 is a massive, 600-kDa transmembrane endocytic receptor belonging to the LDL receptor (LDLR) family.[7] Comprising a 515-kDa extracellular α-chain containing multiple distinct ligand-binding domains and an 85-kDa transmembrane and cytoplasmic β-chain responsible for endocytosis and intracellular signal transduction, LRP1 is ubiquitously expressed across the neurovascular unit.[5] Its presence spans neurons, astrocytes, microglia, and brain capillary endothelial cells. LRP1 exhibits an extraordinary degree of ligand promiscuity, binding to more than forty distinct molecules including apolipoprotein E (APOE), $\alpha_2$-macroglobulin, Aβ, tissue plasminogen activator, and various extracellular matrix components.[1]

To understand the multifaceted roles of LRP1 in neurodegeneration is to trace the scientific lineage of Guojun Bu. Receiving his Ph.D. in biochemistry from Virginia Tech in 1990, Bu subsequently completed postdoctoral training and served as a Professor of Cell Biology and Neuroscience at the Washington University School of Medicine in St. Louis.[11] He later became the Chair of the Department of Neuroscience at the Mayo Clinic, and currently serves as the Lo Ka Chung Charitable Foundation Professor of Science at the Hong Kong University

of Science and Technology (HKUST), alongside his role as Chief Scientific Officer at SciNeuro Pharmaceuticals.[11] Bu's research has systematically dismantled the reductionist view of LRP1 as a mere biochemical "garbage disposal" for amyloid plaques.[11]

The primary research problem addressed in this analysis is the inherent biological paradox of LRP1, a contradiction thoroughly mapped by Bu's laboratory: How can a receptor that is absolutely vital for the protective clearance of neurotoxic Aβ and the maintenance of essential neuronal lipid homeostasis simultaneously act as the primary pathological vector for the intercellular spread of tau and α-synuclein? This paradox sits at the bleeding edge of molecular neurodegeneration. Bu's extensive deployment of conditional knockout mouse models and human induced pluripotent stem cell (iPSC) lines has provided the empirical foundation required to resolve this contradiction.[14]

The paradox cannot be evaluated, however, without first situating Bu's molecular findings within the broader theoretical revolution that made the question askable in the first place. That revolution belongs to Stanley Prusiner, whose Nobel-recognized prion theory of transmissible spongiform encephalopathies[58] was extended in 2012 to encompass the full spectrum of neurodegenerative proteinopathies,[59] and to Lary Walker and Mathias Jucker, whose meticulous seeded-inoculation experiments[61,62,63] demonstrated that the prion-like behavior Prusiner postulated was experimentally reproducible for Aβ, tau, and α-synuclein in mammalian brain.

This document posits that Bu's work, when read alongside the Prusiner–Walker paradigm, represents a fundamental historiographical and biological paradigm shift within neuroscience. By systematically decoupling the distinct compartmental functions of LRP1, Bu has demonstrated that the receptor functions as the central node in the brain's extracellular proteostasis network[18] — and that this same node is the molecular gateway through which prion-like proteinopathies advance across neural circuits. The ensuing chapters will critically assess this argument through a chronological and thematic deconstruction of the laboratory's findings. Following a review of the historical literature and analytical frameworks, Chapter 1 examines the canonical Aβ clearance paradigm. Chapter 2 transitions to the critical role of LRP1 in lipid homeostasis and APOE signaling. Chapter 3 — newly added in this revised edition — establishes the Prusiner–Walker prion-like paradigm as the conceptual prerequisite for understanding what Bu's LRP1 discoveries actually explain. Chapter 4 then critically evaluates Bu's groundbreaking demonstration that LRP1 is the receptor mediating the propagation Prusiner and Walker had described at the disease level. Chapter 5 analyzes the translational potential of these findings, assessing the viability of LRP1 as a pharmacological target and drug delivery vector.

## Literature Review and Theoretical Positioning

To properly contextualize the magnitude of Guojun Bu's interventions in the field, one must trace the historiography of LRP1 within molecular neuroscience. The receptor was initially cloned and characterized in the late 1980s and early 1990s, predominantly recognized by Joachim Herz and colleagues as a hepatic scavenger receptor responsible for the systemic clearance of chylomicron remnants and $\alpha_2$-macroglobulin.[7] By the late 1990s and early 2000s, as the amyloid hypothesis reached its zenith, researchers began searching for the specific biological machinery responsible for regulating Aβ levels in the central nervous system, shifting the focus of LRP1 from the liver to the brain.[7]

The early 2000s witnessed the emergence of the "amyloid sink" hypothesis, heavily championed by Berislav Zlokovic and his colleagues. Zlokovic's models posited that LRP1 expressed at the abluminal surface of brain capillary endothelial cells was the primary engine for the transcytosis of Aβ across the blood-brain barrier (BBB) into the systemic circulation, where it was subsequently cleared by hepatic LRP1 or bound by soluble LRP1 (sLRP1) circulating in the plasma.[5] In this vascular-centric model, sLRP1 acts as a peripheral "sink," sequestering 70 to 90% of plasma Aβ and preventing its reentry into the central nervous system.[8] Simultaneously, David Holtzman's laboratory established the critical linkage between APOE — the strongest genetic risk factor for late-onset AD — and Aβ clearance, demonstrating that APOE isoforms differentially influence the rate at which Aβ is removed from the brain.[2]

It was within this intellectual milieu that Guojun Bu began his most consequential theoretical positioning. Prior to Bu's rigorous cellular profiling, the field largely viewed LRP1-mediated clearance through the vascular lens of the BBB efflux model.[24] Bu introduced a crucial theoretical and empirical correction: he recentered the focus onto the brain parenchyma. Bu argued that while BBB efflux is critical, the cellular clearance of Aβ by neurons and glia via LRP1-mediated endocytosis is an equally, if not more, vital component of local Aβ homeostasis.[15]

Furthermore, Bu's group challenged prevailing notions regarding the precise interactions between APOE, Aβ, and LRP1. Early literature frequently assumed that APOE directly bound Aβ to facilitate its clearance.[22] However, subsequent refinements by Bu, alongside Holtzman and Philip Verghese, demonstrated through stoichiometric measurements at physiological concentrations that APOE and Aβ exhibit very little direct interaction. Instead, they proposed a competitive mechanism: APOE and Aβ compete for the same binding domains on the LRP1 receptor. This provided a compelling mechanistic explanation for why elevated levels of the APOE4 isoform, which binds receptors tightly but supports clearance poorly, exacerbates Aβ accumulation.[2] More recently, the field has evolved to recognize that while LRP1 is central, other receptors like the very-low-density lipoprotein receptor (VLDLR) specifically mediate

the clearance of certain APOE4-Aβ complexes, adding layers of complexity to the clearance network.[3]

The literature regarding LRP1 evolved significantly after 2010. The receptor's physiological mandate expanded far beyond Aβ when it was discovered that LRP1 is essential for brain lipid metabolism, cholesterol transport, and the maintenance of synaptic stability.[27] However, the most disruptive theoretical positioning in the recent literature occurred between 2020 and 2022. As the field increasingly recognized — following Prusiner's 2012 synthesis and the Walker–Jucker experimental program — that neurodegenerative diseases propagate through the brain in a stereotypical, prion-like manner along anatomical networks, the search for the cellular receptor mediating this uptake became paramount. Bu's laboratory shattered the existing consensus by identifying LRP1 as the master receptor regulating the cellular internalization and trans-synaptic spread of both tau[29] and α-synuclein.[14] This shifted the historiographical narrative of LRP1 from a strictly protective scavenger to a hijacked mediator of pathogenesis, establishing a completely new frontier in the study of proteinopathies and supplying the molecular substrate that the Prusiner–Walker paradigm had been awaiting for a decade.

## Analytical Framework and Experimental Paradigms

This analysis employs a critical, synthetic framework, integrating molecular biology, genetics, and translational pharmacology to assess the impact of Guojun Bu's research program in conjunction with the prion-like paradigm of Prusiner and Walker. The analysis relies on a thorough examination of peer-reviewed primary literature, highly cited foundational papers, comprehensive review articles, and recent clinical trial disclosures associated with Bu's academic laboratories and his commercial ventures at SciNeuro Pharmaceuticals.

The disciplinary approach is deeply rooted in molecular and cellular neuroscience, specifically evaluating the experimental rigor of the transgenic and in vitro models utilized to derive findings regarding LRP1. Bu's methodological brilliance often lay in his use of advanced genetic ablation techniques. Because global *Lrp1* gene knockout is embryonic lethal in mice, studying its physiological function in the adult mammalian brain required highly sophisticated conditional knockout strategies. The analysis heavily weights data derived from *Cre/loxP* recombination systems. By driving Cre recombinase expression under specific promoters, Bu's team created neuronal *Lrp1* conditional knockout (Lrp1-nKO) mice using the synapsin-I promoter, and vascular mural cell-specific knockouts (smLrp1−/−) using the sm22-α promoter.[15] These in vivo models allowed Bu to effectively isolate the cell-specific functions of LRP1 within the highly complex, interacting microenvironments of the neurovascular unit.

Furthermore, this report evaluates Bu's necessary transition into human-derived in vitro models. To circumvent the translational limitations of murine models — which frequently express Aβ peptides that differ structurally from human forms and do not naturally develop full-spectrum Alzheimer's pathology[33] — Bu's later work heavily utilized human induced pluripotent stem cells (iPSCs). By utilizing CRISPR/Cas9 gene-editing technology to generate isogenic LRP1-knockout iPSC-derived neurons (iPSNs), Bu achieved unprecedented molecular resolution. For instance, in his foundational α-synuclein studies, guide RNAs were designed to target exon 6 of the human *LRP1* gene, resulting in a 191 base-pair deletion that caused a frameshift and a premature stop codon, ensuring complete receptor ablation.[14]

These models were paired with rigorous biochemical assays. To map specific molecular interactions, Bu extensively utilized the Receptor-Associated Protein (RAP), a known physiological LRP1 binding antagonist, to prove competitive inhibition.[31] To track protein spread in vivo, his laboratory engineered adeno-associated viruses (AAVs) designed to distinguish between the initial site of protein expression and its subsequent neuroanatomical spread following stereotaxic injection into the mouse hippocampus[31] — methodologically extending the inoculation paradigms first systematized by Walker and Jucker in their cerebral amyloidosis induction experiments.[63] The analytical framework of this document evaluates these findings not in isolation, but as a continuous, evolving network of discoveries. It interrogates the causal relationships between LRP1 expression, lipid transport, Aβ degradation, and pathological protein seeding, uncovering the precise biomechanical vulnerabilities that allow LRP1 to be exploited by neurodegenerative diseases.

## Chapter 1: The Aβ Clearance Paradigm and the Cellular Distribution of LRP1

The foundational pillar of Guojun Bu's research portfolio rests on elucidating the exact mechanisms by which the brain protects itself from the toxic accumulation of amyloid-beta. While the earliest iterations of the amyloid hypothesis focused almost exclusively on the over-activation of β- and γ-secretases generating excess Aβ, the realization that late-onset Alzheimer's disease is predominantly a clearance defect shifted the global research focus to cellular degradation pathways.[1] Within this context, Bu's investigations into LRP1 fundamentally altered the understanding of which cells are responsible for this clearance, dismantling the rigid dichotomy between Aβ-producing neurons and Aβ-clearing glia.

### 1.1 The Dual Role of Neurons in Amyloid Dynamics

Prior to Bu's critical interventions, neurons were primarily conceptualized as the victims and originators of AD pathology — the primary source of Aβ generation via amyloid precursor

protein (APP) cleavage. Clearance was largely assumed to be the domain of microglia, astrocytes, and the efflux machinery of the blood-brain barrier.[24] In a landmark 2013 study published in the *Journal of Neuroscience*, Bu and Kanekiyo utilized conditional forebrain neuronal *Lrp1* knock-out mice to demonstrate that neurons themselves possess a highly active, LRP1-dependent Aβ clearance mechanism.[15]

Through rigorous in vivo microdialysis, Bu's team directly measured the interstitial fluid (ISF) of the living mouse brain and found that Aβ clearance from the ISF was profoundly impaired in the absence of neuronal LRP1.[16] Crucially, the genetic deletion of LRP1 did not alter the mRNA transcription levels of major Aβ-degrading enzymes such as neprilysin or insulin-degrading enzyme (IDE), nor did it affect the baseline production of Aβ.[16] This isolated the metabolic defect specifically to receptor-mediated endocytosis.

To prove the pathological relevance of this defect, Bu crossed these *Lrp1* knock-out mice with the established APP/PS1 amyloid transgenic mouse model. The resulting offspring demonstrated a massive, selective exacerbation of amyloid plaque deposition in the cortex.[15] This finding forced a paradigm shift: neurons are not merely passive producers of toxic proteins; they are actively engaged in a delicate, continuous autocrine and paracrine loop of clearance, critically dependent on the high expression of LRP1.[16]

### 1.2 Glial Clearance and Receptor Chaperones

Bu's laboratory successfully expanded this cellular clearance paradigm to the glial compartments. In astrocytes, LRP1 was shown to modulate not only direct Aβ uptake but also the expression of various Aβ-degrading enzymes and broader cellular degradation pathways, acting as a master regulatory switch for astrocytic phagocytosis.[36] Similarly, in microglia — the resident immune macrophages of the CNS — Bu utilized fluorescence-activated cell sorting (FACS) and high-resolution confocal microscopy to prove that LRP1-mediated endocytosis directs internalized Aβ precisely to the acidic lysosomal compartments for definitive degradation.[35]

To further dissect the biochemical mechanics of this clearance, Bu explored the structural interactions of LRP1 utilizing the Receptor-Associated Protein (RAP). RAP is a specialized endoplasmic reticulum chaperone that binds tightly to LRP1 during its synthesis, preventing premature intracellular ligand interaction. Bu's group made the unexpected and highly consequential discovery that RAP itself binds directly to both Aβ40 and Aβ42, forming stable complexes that significantly enhance cellular internalization across multiple cell types.[34] This suggested that LRP1 does not act in a vacuum; it operates within a highly complex microenvironment of co-receptors and chaperones. Heparan sulfate proteoglycans (HSPGs), for instance, were shown to act as essential co-receptors, capturing Aβ at the cell surface and

handing it off to LRP1 for internalization, a process that could be blocked by heparinase treatment.[34]

### 1.3 Resolving the Sink Hypothesis

While Bu confirmed the critical importance of peripheral clearance — where soluble LRP1 (sLRP1) in the plasma acts as a peripheral "sink" to sequester circulating Aβ and draw it out of the brain — his work added critical physiological nuance to Zlokovic's vascular models.[8] Bu demonstrated that the parenchymal clearance by neurons and glia acts as the first, and perhaps most vital, line of defense. If parenchymal LRP1 is overwhelmed by toxic oligomers, or genetically down-regulated as naturally occurs during human aging, the BBB transcytosis mechanisms alone are insufficient to prevent plaque nucleation.[8] This comprehensive body of work established LRP1 as the universal orchestrator of Aβ dynamics, simultaneously governing local cellular degradation, transcytosis across the BBB, and ultimate systemic clearance by the liver.[5]

## Cell-Type Specific Functions of LRP1 in the Neurovascular Unit

| CELL TYPE | PRIMARY LRP1 FUNCTION | IMPACT OF LRP1 DELETION | RELEVANCE TO DISEASE |
|---|---|---|---|
| **Neurons** | Facilitates receptor-mediated endocytosis and clearance of amyloid-β (Aβ). Essential for maintaining brain lipid homeostasis. | Significant increase in brain interstitial Aβ. Induces global lipid metabolism defects (reduced cholesterol, sulfatide). Reduced NMDA and Glu receptor levels. | Exacerbates amyloid plaque deposition. Drives age-dependent progressive dendritic spine and synapse loss, neuroinflammation, memory loss, and eventual neurodegeneration. |
| **Astrocytes** | Modulates Aβ-degrading enzymes and acts as a critical cellular degradation pathway for Aβ clearance in the brain. | Significantly impairs critical brain Aβ clearance mechanisms. | Identifies specific astrocytic clearance pathways that may establish new targets for Alzheimer's disease prevention and therapy. |
| **Microglia** | Mediates Aβ phagocytosis and actively targets internalized Aβ into lysosomal compartments for degradation. | Decreases Aβ42 cellular uptake and severely suppresses overall phagocytic capacity. | Contributes to Alzheimer's pathogenesis by compromising the essential Aβ clearance functions of the brain's resident immune cells. |
| **Vascular Mural Cells (Pericytes & Smooth Muscle)** | Modulates cerebrovasculature integrity and blood-brain barrier (BBB) maintenance in an APOE genotype-dependent manner. | Disrupts BBB integrity, triggers excess paravascular glial activation, and visibly reduces cerebrovascular collagen IV. | Impairs spatial memory (particularly in APOE4 models) and fundamentally drives Vascular Cognitive Impairment and Dementia (VCID) alongside Alzheimer's disease. |

*Summary of LRP1 functionalities across distinct cell types within the central nervous system. Bu's conditional knockout studies demonstrated that LRP1 is not a monolithic receptor; its deletion triggers distinct pathological cascades depending on the cellular compartment.*

## Chapter 2: Lipid Homeostasis, APOE Isoforms, and the Cerebrovasculature

While the clearance of Aβ established LRP1's prominence in AD research, focusing solely on amyloid severely restricts the biological scope of the receptor. Guojun Bu's most profound conceptual leap was recognizing that neurodegeneration is inextricably linked to the collapse of brain lipid metabolism. Because the brain is the most lipid-rich organ in the body — comprising roughly 20% of total body cholesterol despite representing only 2% of body

mass — the precise transport and metabolism of these lipids are paramount for maintaining the structural integrity of synaptic membranes.[39]

### 2.1 The Cholesterol Conduit and Synaptic Degeneration

Cholesterol cannot cross the blood-brain barrier; therefore, the CNS must rely entirely on *de novo* synthesis, a process managed primarily by astrocytes. This newly synthesized cholesterol is packaged into lipoprotein particles and delivered to neurons to support membrane turnover, dendrite formation, and synaptic vesicle release.[39] The primary carriers of these essential lipids are the apolipoproteins, predominantly APOE.

Bu hypothesized that if LRP1 is a major receptor for APOE, its absence should trigger profound lipid dyshomeostasis. In a pivotal 2010 study published in the *Journal of Neuroscience*, Bu's group analyzed the forebrain of neuronal *Lrp1* knock-out mice and discovered a catastrophic, global defect in brain lipid metabolism. The genetic ablation of LRP1 resulted in severely decreased levels of cholesterol, sulfatide, galactosylceramide, and triglycerides across the cortical parenchyma.[27]

The second-order biological insights derived from this discovery are profound: the reduction in structural lipids led to a physical deterioration of the neuronal architecture. Through histological analysis, Bu observed progressive, age-dependent dendritic spine degeneration, massive synapse loss, and profound memory deficits on rotarod and spatial memory paradigms.[27] Furthermore, these lipid deficits specifically reduced the membrane localization of critical glutamate receptor subunits, such as NMDA receptor 1 and GluR1, fundamentally impairing synaptic transmission.[28] This definitively proved that LRP1 is not merely an AD-specific clearance protein, but a fundamental pillar of basal neuronal survival. It strongly suggested that long before Aβ begins to aggregate, age-related declines in LRP1 expression may starve neurons of the cholesterol required to maintain their synaptic connections, preconditioning the brain to subsequent amyloid toxicity and neurodegeneration.[28]

### 2.2 The APOE4 Conundrum and the ApoE Christchurch Variant

The intersection of LRP1 and APOE forms the absolute nexus of genetic risk for Alzheimer's disease. The ε4 allele of the APOE gene (APOE4) is the strongest genetic risk factor for late-onset AD, while APOE2 is highly protective.[11] Bu dedicated a significant portion of his career to unraveling the precise biochemical nature of the APOE4 enigma.

Bu's research detailed how APOE and its receptors modulate multiple pathogenic pathways simultaneously. As noted in the literature review, Bu's work clarified that APOE and Aβ actually compete for binding sites on the LRP1 receptor.[2] In physiological conditions, high concentrations of APOE4 — which is known to bind receptors with different kinetics than APOE3

— can effectively saturate LRP1, blocking the receptor and preventing the clearance of Aβ, leading to extracellular accumulation.[22] This dynamic is further complicated by recent findings that the APOE4–Aβ complex is preferentially cleared not by LRP1, but by the very-low-density lipoprotein receptor (VLDLR), whereas protective APOE2–Aβ and APOE3–Aβ complexes utilize both LRP1 and VLDLR at a significantly faster internalization rate.[3]

Further highlighting the importance of APOE-receptor interactions, recent high-profile research has focused on the APOE3-Christchurch (R136S) mutation, an incredibly rare genetic variant that confers profound resilience against autosomal dominant Alzheimer's disease.[41] Bu and colleagues have been instrumental in interpreting how this mutation functions. The R136S mutation sits precisely in the receptor-binding domain of APOE. It heavily reduces the binding affinity of APOE to LDLR and LRP1, which paradoxically protects the brain by altering lipoprotein-particle uptake, thereby reducing intracellular lipid peroxidation and the accumulation of toxic lipofuscin.[41] This demonstrates that *dampening* specific APOE-LRP1 interactions can yield massive therapeutic benefits — an observation that anticipates the central therapeutic puzzle the Bu–Prusiner–Walker synthesis poses: which LRP1 interactions to amplify, and which to selectively block.

### 2.3 Vascular Integrity and VCID

More recently, Bu expanded this investigation to the neurovascular unit, investigating how APOE4 impacts the structural integrity of the blood-brain barrier. Utilizing vascular mural cell-specific *Lrp1* knockout mice (smLrp1−/−) crossed with human APOE3 or APOE4 knock-in mice, Bu demonstrated that LRP1 deficiency in pericytes and vascular smooth muscle cells leads to severe spatial memory impairments exclusively in the APOE4 background.[32] This disruption was characterized by a loss of cerebrovascular collagen IV, excess paravascular glial activation, and catastrophic BBB breakdown.[32] This research cemented the concept that peripheral and vascular APOE pools interact with LRP1 to dictate the structural integrity of the brain's vasculature, highlighting vascular cognitive impairment and dementia (VCID) as a co-pathology inherently linked to LRP1 dysfunction.[32]

## Chapter 3: The Prion-Like Paradigm — Prusiner, Walker, and the Conceptual Prerequisite

Before Bu's molecular receptor discoveries can be interpreted in their full theoretical weight, a more fundamental paradigm shift must be acknowledged: the recognition that neurodegenerative diseases are not regional collapses arising independently in vulnerable brain areas, but instead spreading proteinopathies whose pathological signatures advance through neuroanatomical networks by templated misfolding. This reconceptualization belongs pri-

marily to two research lineages, separated by three decades but unified by a single biological insight: Stanley Prusiner's prion theory, and Lary Walker and Mathias Jucker's experimental seeding program.

### 3.1 Prusiner's Prion: From Scrapie to a Unifying Paradigm

In 1982, Stanley Prusiner published in *Science* a paper that would alter the field of neurodegeneration permanently: *"Novel proteinaceous infectious particles cause scrapie."*[58] The discovery — that the transmissible spongiform encephalopathies (TSEs), including scrapie, Creutzfeldt-Jakob disease (CJD), and bovine spongiform encephalopathy (BSE), were caused not by viruses or viroids but by self-templating misfolded protein particles he termed "prions" — was met with vigorous skepticism. The infectious unit appeared to lack nucleic acid, violating central dogma. The mechanism, however, was eventually validated: pathogenic prion protein (PrP^Sc) acted as a conformational template, inducing native cellular prion protein (PrP^C) to adopt the misfolded conformation, which propagated cell-to-cell and host-to-host. Prusiner was awarded the Nobel Prize in Physiology or Medicine in 1997.

For two decades, the prion framework was considered to apply narrowly to the TSEs. The dominant view held that Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis (ALS), and frontotemporal dementia (FTD) were fundamentally distinct disorders driven by independent biochemical pathways. Prusiner himself argued otherwise. In his 2012 *Science* paper, *"A unifying role for prions in neurodegenerative diseases,"*[59] he laid out a comprehensive theoretical case that all major neurodegenerative diseases share a common prion-like mechanism: a self-propagating misfolded protein that templates the conversion of its native counterpart and that physically spreads through the brain along anatomical networks. The argument extended the prion concept to Aβ, tau, α-synuclein, TDP-43, SOD1, huntingtin, and the polyglutamine repeat proteins — eight distinct templating proteins, each defining its associated proteinopathy through the same underlying biophysical mechanism.

The 2012 synthesis was contested. The term "prion" carried unwelcome epidemiological baggage from BSE and the concomitant variant-CJD crisis, and the AD and PD fields had institutional and rhetorical reasons to resist the assimilation. The synthesis nonetheless prevailed — not because the rhetoric softened, but because the experimental evidence accumulated at a rate the resistance could not match. That evidence belongs primarily to Walker and Jucker.

### 3.2 Walker and Jucker: The Experimental Architecture of Spread

Lary Walker (Emory University) and Mathias Jucker (German Center for Neurodegenerative Diseases, Tübingen) have, across a productive collaboration spanning two decades, supplied the empirical foundation that elevated the prion-like paradigm from theoretical proposal

to working consensus. Their central experimental design — intracerebral inoculation of dilute brain extracts from diseased animals or postmortem human tissue into the brains of young, asymptomatic transgenic hosts — has been adapted and replicated across laboratories worldwide.

The Eisele et al. 2010 paper, *"Peripherally applied Aβ-containing inoculates induce cerebral β-amyloidosis,"* published in *Science*,[63] demonstrated that intracerebral and even peripheral inoculation of Aβ-containing brain homogenate could nucleate cortical amyloidosis in transgenic mice that would not otherwise have developed pathology at the time of analysis. The Aβ "seeds" recapitulated the morphology and distribution of the donor pathology, providing the first decisive evidence that Aβ aggregation in vivo is a templated, transmissible event rather than a stochastic concentration-driven precipitation.

Subsequent work by the Walker-Jucker collaboration extended this finding across the spectrum of proteinopathies. The 2013 *Nature* paper, *"Self-propagation of pathogenic protein aggregates in neurodegenerative diseases,"*[61] synthesized seeding evidence for Aβ, tau, α-synuclein, and TDP-43, arguing that prion-like mechanisms were not merely possible but were demonstrably operative in the major proteinopathies. The 2015 *Annual Review of Neuroscience* paper, *"Neurodegenerative diseases: expanding the prion concept,"*[60] consolidated the molecular and cell-biological evidence into a unified theoretical framework that the field could no longer credibly resist. By the time of the 2018 *Nature Neuroscience* review, *"Propagation and spread of pathogenic protein assemblies in neurodegenerative diseases,"*[62] the prion-like framework had become the dominant model of neurodegenerative disease progression.

The Walker-Jucker program established four empirical pillars that any complete account of neurodegeneration must address: (1) misfolded protein aggregates from one brain can nucleate identical pathology when introduced to another; (2) the pathology spreads from the inoculation site along neuroanatomical projections in a stereotyped, network-respecting pattern; (3) different "strains" of the same protein produce reproducibly different pathological signatures; and (4) the spread is, in principle, blockable — though no clinically deployable blocker has yet been validated.

### 3.3 The Missing Mechanism: The Receptor Question

For the decade between 2010 and 2020, the prion-like framework rested on a critical empirical gap. The Walker-Jucker seeding experiments had established *that* misfolded protein aggregates moved from cell to cell. The Prusiner synthesis had established *why* such movement was biologically consequential. But the question of *how* — by what cellular machinery extracellular protein aggregates gained access to the cytoplasm of recipient neurons — remained unresolved. Multiple receptor candidates were proposed during this interval: he-

paran sulfate proteoglycans (HSPGs), members of the LDL receptor family, scavenger receptors, and clathrin-independent endocytic machinery were all implicated to varying degrees. None unified the data across cell types and protein species.

This is the empirical vacuum that Bu's 2020–2022 work filled. By identifying LRP1 as the master neuronal receptor for both tau[29] and α-synuclein[14] uptake — and demonstrating that this same receptor mediates trans-synaptic propagation in vivo — Bu supplied the molecular machinery for the disease-level phenomenon that Prusiner had theorized and Walker had experimentally demonstrated. The three programs, read together, constitute a single causal architecture: conceptual framework (Prusiner) → empirical seeding evidence (Walker–Jucker) → molecular receptor mechanism (Bu).

### 3.4 The Stakes of the Synthesis

The integration of these three frameworks fundamentally alters the therapeutic landscape of neurodegeneration. If late-onset AD is — in addition to a clearance failure and a lipid disorder — a propagating proteinopathy whose progression depends on a specific molecular receptor, then disease modification requires interventions that operate at all three levels simultaneously. Conventional anti-amyloid antibodies (lecanemab, donanemab) operate downstream of all three: they clear deposited Aβ without restoring clearance capacity, without rectifying the lipid disorder, and without blocking trans-neuronal propagation. The modesty of their clinical benefit is precisely what the integrated framework predicts.

The prion-like paradigm also implies a critical reframing of clinical trial design. Pathology that has already propagated through the cortex cannot be reversed by interventions that block further uptake. The therapeutic window for receptor-blocking strategies is necessarily early — before the propagation cascade has saturated the cortical network. This places a high premium on early biomarkers and on identifying the originating "seed sites" from which propagation initiates. Walker has argued specifically that the entorhinal cortex and locus coeruleus are likely seed sites for tau, with downstream propagation along well-mapped projection pathways — a hypothesis that converges with the temporal pharmacology argument the broader Organic Network Synthesis has been advancing.

> **What remains uncertain:** *Whether the Bu–Prusiner–Walker synthesis applies uniformly across the eight known templating proteins, or whether the LRP1 mechanism is partial — operative for tau and α-synuclein but supplemented by alternative receptors (HSPGs, members of the LDLR family) for other proteinopathies. The structural promiscuity of LRP1 suggests breadth; the cell-type specificity of certain proteinopathies (e.g., motor-neuron selectivity in ALS) suggests additional receptor logic remains to be uncovered.*

## Chapter 4: LRP1 as the Receptor for Prion-Like Spread — The Double-Edged Sword

Chapter 3 has established the conceptual framework and experimental architecture within which Bu's LRP1 receptor discoveries acquire their full theoretical weight. This chapter examines the molecular discoveries themselves — the experimental program by which Bu's laboratory identified the receptor that mediates the prion-like propagation Prusiner and Walker had described at the disease level.

The most revolutionary paradigm shift in recent neurodegenerative research, as Chapter 3 detailed, is the prion-like hypothesis. For years, the specific biochemical mechanism by which large, highly insoluble protein aggregates exited one neuron and gained entry into an adjacent healthy neuron remained a profound mystery. In a series of groundbreaking papers published between 2020 and 2022, Guojun Bu's laboratory, operating at the vanguard of the field, identified LRP1 as the primary neuronal surface receptor mediating the internalization and subsequent spread of both pathogenic tau and α-synuclein.[29]

## The Paradox of LRP1: Protective Clearance vs. Pathogenic Propagation

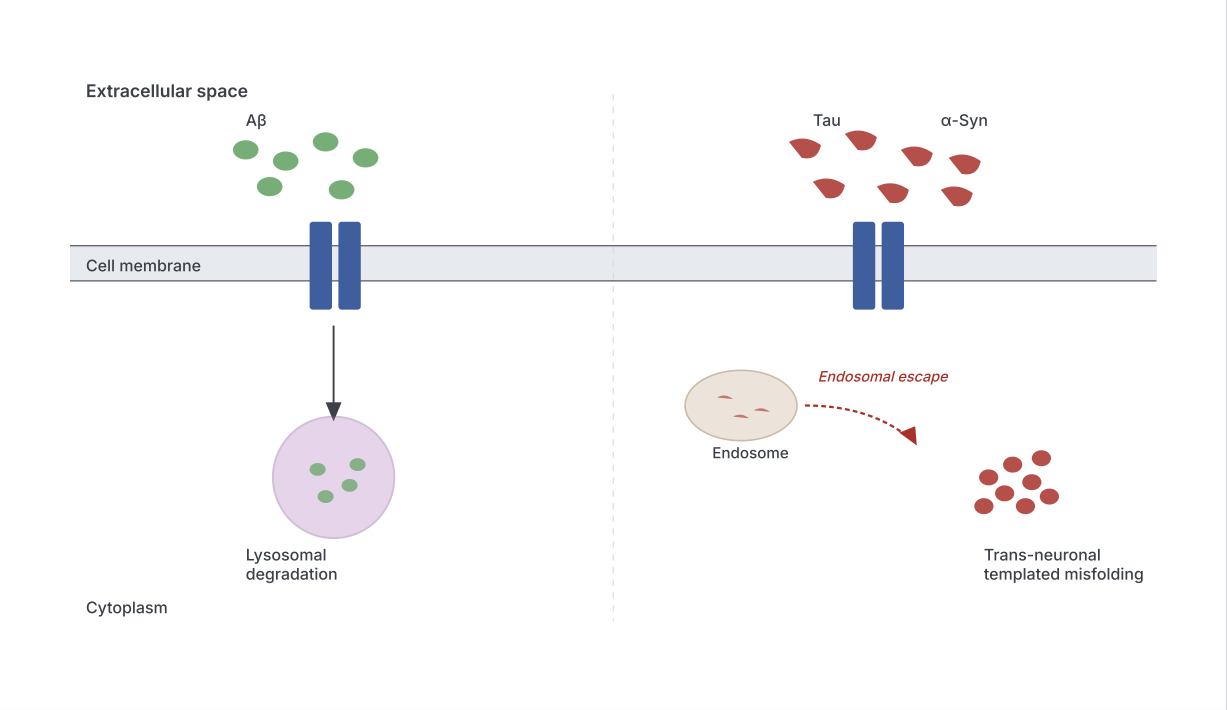


Illustration of LRP1's dual role in proteostasis. **Left:** LRP1 mediates the protective clearance of Aβ by directing it to the lysosome for degradation, supporting the parenchymal clearance arm of the brain's proteostasis network (Bu et al., 2013). **Right:** Pathogenic proteins such as tau and α-synuclein hijack the same receptor, gaining intracellular access through endosomal escape and subsequently templating misfolding of native cytoplasmic protein in the recipient neuron — the molecular mechanism underlying the prion-like spread described by Prusiner (2012) and experimentally demonstrated by Walker and Jucker (2010, 2013).

### 4.1 The Propagation of Tauopathies

Tau is a highly soluble microtubule-associated protein that, when abnormally hyperphosphorylated, dissociates from the cytoskeleton and aggregates to form the neurofibrillary tangles (NFTs) characteristic of AD, progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), and frontotemporal dementia (FTD).[30] In 2020, Bu and his collaborators demonstrated that LRP1 acts as the master regulator of tau endocytosis.[29]

Through in vitro assays, Bu's group showed that the targeted knockdown of LRP1 in H4 neuroglioma cells and iPSC-derived neurons significantly and specifically reduced the cellular uptake of tau. The molecular mechanism relies on a highly specific structural interaction: tau binds directly to LRP1 via specific lysine residues located within its microtubule-binding region (MTBR). When researchers applied chemical blockade to these specific lysine residues, tau endocytosis was completely abrogated.[29] Moving to an in vivo murine model designed to study tau spread, the researchers proved that down-regulating LRP1 effectively halted the

propagation of mutant human tau from transduced neurons to adjacent, interconnected healthy neurons.[29] This established LRP1 as the absolute gatekeeper of tau pathology — and supplied the molecular receptor for the trans-synaptic spread Walker and Jucker had demonstrated phenomenologically.

### 4.2 The Synucleinopathy Connection

Building upon the monumental tau discoveries, Bu's laboratory launched an exhaustive investigation into Parkinson's disease (PD) and Lewy body dementia (LBD), which are characterized by the aggregation and trans-synaptic spread of α-synuclein (α-Syn).[14] Published in *Molecular Neurodegeneration* in 2022 by Chen et al., Bu hypothesized that if LRP1 mediates tau spread, its structural promiscuity might allow it to serve as a universal receptor for the propagation of diverse proteinopathies — a direct mechanistic test of the unification Prusiner had proposed a decade earlier.

The methodological rigor of this study was extraordinary. As discussed, Bu's team utilized CRISPR/Cas9 to create isogenic LRP1-knockout human iPSCs, differentiating them into mature neurons.[14] Using flow cytometry, they treated these neurons with fluorescently labeled α-Syn in three distinct forms: monomers, oligomers, and highly pathogenic pre-formed fibrils (PFFs). The data were unequivocal: the rapid uptake of both monomeric and highly toxic oligomeric α-Syn was significantly reduced in the absence of LRP1, confirming that the receptor is not specific to tau.[31]

To map the exact biochemical interaction at an atomic level, Bu's team capped the amines of the lysine residues on α-Syn using sulfo-NHS acetate.[14] Just as with tau, masking these lysine residues — as well as deleting the N-terminus of the protein — effectively blocked LRP1-mediated cellular uptake. To prove the physiological relevance of this in vitro data, the lab generated adeno-associated viruses (AAVs) to express α-Syn, injecting them stereotaxically into the hippocampi of six-month-old neuronal *Lrp1* conditional knockout mice. Three months post-injection, the trans-synaptic spread of α-Syn to remote cortical regions was massively attenuated in the LRP1-deficient mice compared to wild-type controls.[31] A 2025 follow-up by an independent laboratory[45] reproduced and extended the finding to the striatum-to-substantia-nigra projection in a Parkinson's disease model, confirming that the mechanism is general across α-synuclein-vulnerable circuits.

### 4.3 The Double-Edged Sword Hypothesis

These cumulative discoveries solidify the "Double-Edged Sword" hypothesis of LRP1. On one hand, LRP1 is absolutely required to bind extracellular Aβ and route it safely to the lysosome for protective destruction.[1] On the other hand, pathogenic tau and α-synuclein have evolutionarily hijacked this exact same surface receptor to gain entry into the neuronal endo-

somal system. Once inside the endosome, these specific pathogenic proteins manage to escape into the cytoplasm before lysosomal fusion occurs, allowing them to seed further aggregation and exert massive neurotoxicity through the templated-misfolding mechanism Prusiner postulated.[29,59]

This biological reality drastically alters the therapeutic landscape. One cannot simply design a drug to upregulate LRP1 globally to clear amyloid plaques, as doing so might simultaneously accelerate the cortical spread of tau and α-synuclein, thereby precipitating a rapid worsening of clinical dementia.[3] The receptor's utility relies entirely on the precise compartmentalization of its ligands and on the differential biochemical signatures by which Aβ and the propagating proteinopathies engage its multiple binding clusters. The lysine-residue dependence Bu identified for both tau and α-synuclein uptake provides the structural opening through which selective therapeutic intervention may eventually be threaded.

> **What remains uncertain:** *Whether the endosomal-escape step — the moment at which internalized tau or α-synuclein evades lysosomal fusion and templates cytoplasmic native protein — is itself receptor-mediated, or whether it depends on alternative cellular machinery (Rab GTPase activity, ESCRT dysfunction, lipid composition of the endosomal membrane). If the escape step is mechanistically separable from the uptake step, it represents a distinct therapeutic target whose blockade would defang the propagation without disturbing LRP1's clearance function.*

## Chapter 5: Translational Neuropharmacology and the Blood-Brain Barrier Shuttle

The ultimate objective of molecular neuroscience is the translation of basic biological mechanisms into disease-modifying therapeutics. Guojun Bu's transition from strict academia to the pharmaceutical industry — specifically his role as Chief Scientific Officer at SciNeuro Pharmaceuticals — highlights the commercial and clinical urgency of targeting LRP1 and its associated proteostasis networks.[11] However, the therapeutic manipulation of LRP1 presents formidable pharmacological challenges that require highly innovative bioengineering.

### 5.1 Ligand Promiscuity and the Specificity Challenge

As established in previous chapters, LRP1 is highly pleiotropic. It is essential for systemic Aβ clearance, but it also binds over 40 diverse physiological ligands, regulating vital biological processes ranging from blood coagulation (binding to tissue plasminogen activator) to lipid metabolism (APOE) and cellular growth signaling.[1] Because of this profound ligand promiscuity, designing a broad-spectrum LRP1 agonist or antagonist is clinically untenable. A non-

specific LRP1 activator might enhance Aβ clearance but inadvertently trigger massive tau propagation or disrupt hepatic lipid metabolism, leading to severe, possibly fatal, systemic toxicity.[3]

Therefore, the future of LRP1-targeted therapeutics lies in structural precision. Research has demonstrated that LRP1 possesses multiple distinct extracellular domains (Clusters I through IV), each responsible for interacting with specific families of ligands.[47] By utilizing advanced structural biology and monoclonal antibody technology, it is theoretically possible to develop subtype-selective regulatory tools. For example, designing a sterically hindered molecule that specifically blocks the interaction between LRP1 and the lysine residues of α-synuclein — without disrupting the receptor's ability to bind APOE or Aβ — could effectively halt the spread of Parkinsonian pathology while maintaining basal lipid homeostasis.[5] Bu's in vitro success using sulfo-NHS acetate to cap these exact residues provides a highly compelling biochemical proof-of-concept for this targeted approach.[31]

### 5.2 Exploiting LRP1 for BBB Penetrance

While targeting LRP1 directly to halt neurodegeneration is exceedingly complex, SciNeuro Pharmaceuticals and others are successfully exploiting LRP1 for a completely different purpose: serving as a universal drug delivery vector. One of the greatest historical hurdles in treating central nervous system disorders is the impenetrable nature of the blood-brain barrier, which prevents over 98% of small-molecule drugs and nearly 100% of large-molecule biologic drugs (such as monoclonal antibodies) from reaching the brain parenchyma at therapeutic concentrations.[5]

Because LRP1 is highly expressed on the luminal surface of brain capillary endothelial cells — where it natively binds ligands in the blood and actively transports them across the barrier via transcytosis — it serves as an ideal molecular Trojan horse. SciNeuro has developed a proprietary "BBB shuttle platform" that links therapeutic antibodies or small molecules to an LRP1-binding moiety.[48] When injected systemically, the shuttle binds to endothelial LRP1, is actively internalized into transport vesicles, and is safely released into the brain interstitial fluid on the abluminal side, achieving dramatically elevated CNS drug concentrations compared to passive diffusion.[49]

This platform is currently being integrated with SciNeuro's robust clinical pipeline, which includes assets like SNP318, an oral, CNS-penetrant Lp-PLA2 (lipoprotein-associated phospholipase A2) inhibitor that recently completed Phase 1 trials.[51,52] By targeting Lp-PLA2, SNP318 aims to dampen the severe vascular inflammation and BBB permeability deficits that Bu's earlier research identified as downstream consequences of APOE4 and LRP1 dysfunction.[32] This represents the apotheosis of Bu's research trajectory: translating the fundamen-

tal biology of neurovascular lipid receptors into clinically actionable, BBB-penetrating therapeutics aimed at preserving the physical integrity of the aging brain.

### 5.3 Gene Therapy and the Peripheral Sink

Beyond direct pharmacological modulation, gene therapy utilizing adeno-associated viruses (AAV) is rapidly emerging as a method to upregulate specific components of the clearance network.[5] Preclinical models have demonstrated that selective restoration of LRP1 expression in brain endothelial cells via AAV can reinstate the normal export function of Aβ-LRP1 complexes, significantly reducing amyloid burden in transgenic mice.[5]

Furthermore, strategies to boost the peripheral "sink" — specifically soluble LRP1 (sLRP1) circulating in the plasma, which naturally sequesters 70–90% of plasma Aβ — are being aggressively explored. This strategy aims to draw toxic proteins out of the brain along a concentration gradient without risking the severe neuroinflammatory side effects (such as ARIA) frequently associated with direct, brain-penetrant anti-Aβ monoclonal antibodies.[8] As Bu highlighted in a 2026 paper published in *Nature Reviews Neurology* titled "Alzheimer disease protection from the periphery,"[54] manipulating systemic LRP1 and hepatic clearance pathways may offer a safer, highly scalable avenue for disease modification. Additionally, exploring off-target benefits of existing drugs, such as the angiotensin receptor blockers telmisartan and candesartan — which have shown efficacy in reducing Aβ and tau aggregates in preclinical models by indirectly modulating receptor networks — represents a parallel avenue for enhancing proteostasis.[57]

### 5.4 The Open Therapeutic Frontier: Selective Propagation Blockade

The most consequential therapeutic frontier opened by the Bu–Prusiner–Walker synthesis is the prospect of selective propagation blockade. If pathology spreads through the cortex by LRP1-mediated trans-synaptic uptake of misfolded tau and α-synuclein, then a molecule that selectively occupies the LRP1 binding domain engaged by these proteins — without disturbing the binding domains engaged by Aβ or APOE — would, in principle, freeze the disease at whatever stage it has reached at the time of administration. The patient's existing pathology would not be reversed; but its further advance into spared cortical regions would be arrested. For a disease whose clinical progression is largely determined by the extent of cortical spread, such an intervention could be transformative even in the absence of any clearance-enhancing effect.

The structural prerequisite for this approach is the resolution of LRP1's binding-domain architecture at sufficient atomic detail to permit rational design of cluster-specific antagonists. This work is underway in multiple structural biology laboratories. The clinical prerequisite is the development of biomarkers that detect propagation in vivo, since the proposed therapy

halts progression rather than removing existing burden. Until then, the staging tools currently available (Braak staging by autopsy; Aβ-PET and tau-PET by imaging) will need to be supplemented by spread-trajectory measures that can serve as trial endpoints.

## Conclusion

The vast body of work produced by Guojun Bu and his collaborators over the past two decades constitutes one of the most significant advancements in the molecular understanding of neurodegenerative disease. By rigorously interrogating the LRP1 receptor using advanced conditional knockout models and human iPSC technologies, Bu dismantled the simplistic, monolithic models of the early 2000s, replacing them with a highly nuanced, system-level understanding of brain homeostasis and cellular interconnectivity.

This thesis has demonstrated that LRP1 can no longer be viewed merely as an amyloid sink. Bu's research unequivocally proved that LRP1 is the master regulator of brain lipid metabolism, essential for synaptic integrity and baseline neuronal survival.[27] More profoundly, Bu's discovery that LRP1 directly mediates the cellular uptake and trans-synaptic spread of both pathogenic tau and α-synuclein forces a massive paradigm shift in how the scientific community conceptualizes disease progression in Alzheimer's and Parkinson's diseases.[29] This "Double-Edged Sword" hypothesis perfectly encapsulates the tragic biological irony of neurodegeneration: the very receptors the brain relies upon for protection and systemic clearance are the exact physical avenues exploited by misfolded proteins to enact their destruction.

The revised edition has positioned Bu's discoveries within the broader prion-like paradigm pioneered by Stanley Prusiner and experimentally established by Lary Walker and Mathias Jucker. Read together, the three programs constitute a single integrated causal architecture: the conceptual reframing of neurodegeneration as templated-misfolding disease (Prusiner, 2012); the experimental demonstration that this reframing is empirically correct across the major proteinopathies (Walker–Jucker, 2010–2018); and the molecular identification of LRP1 as the receptor that mediates the propagation step (Bu, 2020–2022). What was for a decade a paradigm without a mechanism is now a paradigm with one — and the therapeutic implications follow directly from the integration.

The contributions of Bu's laboratory have permanently altered the translational therapeutic landscape. Future research directions must focus heavily on the structural biology of LRP1 ligand binding. If precision therapeutics can be engineered to selectively block the binding of pathogenic tau and α-synuclein to specific lysine residues without impeding the life-sustaining transport of APOE and the clearance of Aβ, it would represent a monumental breakthrough in neuropharmacology — and the first clinical intervention to act on the propagation

mechanism the Prusiner–Walker–Bu synthesis has identified as central to disease progression. Until that level of structural precision is achieved, leveraging the extraordinarily high expression of LRP1 at the blood-brain barrier as a molecular shuttle for delivering novel biologic therapeutics — as currently pioneered by SciNeuro Pharmaceuticals — stands as the most immediate and promising clinical translation of Guojun Bu's foundational discoveries.[49] In successfully synthesizing lipid metabolism, protein clearance, and pathological propagation under the overarching umbrella of a single mega-receptor — and in supplying the molecular machinery for the prion-like spread that defines modern neurodegeneration — Bu has provided the molecular blueprint required to eventually halt the progression of neurodegenerative disease.

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