neuroglia

MDPI

Perspective

Glia-Targeted Therapeutics

Parisa Gazerani [1,2,*], Nielsen Santos Pereira [3,4] and Marcos Fabio Henriques dos Santos [3,4,5,6]

[1] Department of Life Sciences and Health, Faculty of Health Sciences, Oslo Metropolitan University, 0167 Oslo, Norway
[2] ADvanced hEalth Intelligence and Brain-insPired Technologies (ADEPT), Faculty of Technology, Art and Design (TKD), Oslo Metropolitan University, 0167 Oslo, Norway
[3] Laboratório de Morfogênese Celular (LMC), Instituto de Ciências Biomédicas (ICB), Universidade Federal do Rio de Janeiro (UFRJ), Rio de Janeiro 21941-902, Brazil
[4] Programa de Pós-Graduação em Medicina (Anatomia Patológica), Universidade Federal do Rio de Janeiro (UFRJ), Rio de Janeiro 21941-902, Brazil
[5] Programa de Pós-Graduação em Neurociência Translacional (PGNET), Instituto de Ciências Biomédicas (ICB), Universidade Federal do Rio de Janeiro (UFRJ), Rio de Janeiro 21941-902, Brazil
[6] Programa de Pós-Graduação em Medicina (Radiologia), Universidade Federal do Rio de Janeiro (UFRJ), Rio de Janeiro 21941-902, Brazil
* Correspondence: parisaga@oslomet.no

Abstract

Despite remarkable advances in glial biology, the development of effective glia-targeted therapeutics has lagged behind. Accumulating evidence has established glial cells as dynamic regulators of neuroimmune communication, synaptic function, metabolic homeostasis, tissue repair, and disease progression. Advances in single-cell and spatial transcriptomics, molecular profiling, functional imaging, and human-relevant experimental models have revealed remarkable diversity among central and peripheral glial populations, highlighting context-dependent functional states and complex communication networks involving neurons, vascular cells, immune cells, and other glia. These discoveries have expanded therapeutic opportunities while challenging conventional pharmacological strategies that broadly target individual glial cell types or isolated inflammatory pathways. Although numerous pharmacological interventions intentionally or unintentionally modulate glial function, clinical translation has remained limited, highlighting the need for a more integrated therapeutic framework. In this perspective, we critically examine the current landscape of glia-targeted therapeutics through the concept of glial pharmacology, presented as a conceptual framework for understanding how pharmacological interventions modulate glial cells, their functional states, and multicellular communication networks to influence nervous system homeostasis and disease. Rather than providing an exhaustive review, we synthesize the lessons learned from existing therapeutic strategies, discuss the major biological and translational challenges limiting clinical success, and propose guiding principles for the rational development of next-generation glia-targeted therapeutics. We argue that future progress will depend on moving beyond broad cell-specific modulation toward context-dependent therapeutic strategies informed by glial biology, multicellular communication networks, biomarker-guided target engagement, and disease context.

Keywords: glia-targeted therapeutics; glial pharmacology; glial heterogeneity; neuroimmune crosstalk; microglia; astrocytes; neuropharmacology; biomarker-guided therapeutics; precision medicine; translational neuroscience; neuroimmune signaling

Check for updates

Academic Editors: Héctor Romo-Parra, Carmen Rubio and Norma Serrano-García

Received: 16 July 2026
Revised: 7 August 2026
Accepted: 9 August 2026
Published: 11 August 2026

Copyright: © 2026 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license.

1. Introduction

Despite remarkable advances in glia science in recent decades, the translation of these discoveries into effective therapeutics has lagged behind [1–3]. Pharmacological strategies targeting glial cells have expanded considerably, driven by growing recognition of their central roles in neuroimmune crosstalk, synaptic regulation, metabolic homeostasis, tissue repair, and disease progression across a broad spectrum of neurological disorders [4–7]. However, despite encouraging experimental findings and increasing therapeutic interest, relatively few glia-targeted interventions have demonstrated consistent clinical benefit [8,9]. This translational gap reflects not only the inherent complexity of nervous system disorders but also a rapidly evolving understanding of glia that has challenged many of the assumptions underlying traditional pharmacological approaches.

Technological advances, including single-cell and spatial transcriptomics, high-dimensional molecular profiling, advanced imaging, and human-relevant experimental models, have substantially expanded our understanding of glial function [10–13]. Rather than representing relatively homogeneous cell populations, microglia, astrocytes, oligodendrocytes, and peripheral glial cells exhibit remarkable molecular, functional, and regional diversity that continuously adapts to developmental stage, aging, environmental exposures, and disease [4,13,14]. Glial responses are now recognized as dynamic and context-dependent, operating within complex multicellular communication networks involving neurons, vascular cells, peripheral immune cells, and other glial populations [12,15,16]. These discoveries challenge therapeutic strategies that broadly suppress or activate glial cell types without considering their functional states, biological context, or network interactions.

At the same time, accumulating evidence indicates that many established therapeutics influence glial function through mechanisms that were either intentionally targeted or only recognized after clinical or experimental use [17–20]. Conversely, several highly promising glia-directed interventions have produced disappointing or inconsistent outcomes despite compelling preclinical evidence [6,8,21]. Collectively, these observations suggest that successful therapeutic modulation of glia depends on more than identifying individual molecular targets; it requires understanding when, where, and how pharmacological interventions interact with dynamic glial systems. This shift moves the focus from targeting glial cells as isolated entities toward understanding pharmacological modulation of integrated neuroimmune networks that determine nervous system function in health and disease [22,23].

Although discussion of glia-targeted therapeutics has largely focused on central glial populations, a comprehensive pharmacological framework should also encompass peripheral glia, including satellite glial cells (SGCs) and Schwann cells, which are increasingly recognized as active regulators of neuronal excitability, inflammatory signaling, neuroimmune communication, and pain-related plasticity [13,24–26]. Considering peripheral glia broadens the translational scope of glia-targeted therapeutics beyond the central nervous system while revealing common pharmacological principles across glial populations. At the same time, glial responses can be modulated by numerous non-pharmacological approaches, including exercise, diet, sleep, microbiome-derived signals, and other environmental interventions [27–30]. Although these complementary strategies represent an important and rapidly evolving area of investigation, we focus specifically on pharmacological modulation because of its central role in therapeutic development, drug discovery, and clinical translation.

In this perspective, we propose glial pharmacology as a conceptual framework informed by principles of systems and network pharmacology [31,32] for understanding how pharmacological interventions intentionally or unintentionally modulate glial cells,

their functional states, and their communication networks to influence nervous system homeostasis and disease. Although the term glial pharmacology has previously been used to broadly describe pharmacological research involving glia and glia-directed therapeutics [17], the present framework extends this concept from the pharmacological study or targeting of glial cells toward an integrated approach to therapeutic discovery and translation. Its incremental contribution lies not in identifying glia as pharmacological targets per se, but in organizing contemporary understanding of glial biology around five interrelated principles: targeting dynamic functional states rather than cell identity alone; considering multicellular communication networks as therapeutic substrates; incorporating biological context as a determinant of therapeutic efficacy; preserving physiological glial functions while correcting maladaptive responses; and integrating biomarkers and precision approaches into therapeutic development.

Within this framework, glia-targeted therapeutics extend beyond drugs specifically designed to act on glial cells. They also encompass pharmacological interventions whose therapeutic efficacy, adverse effects, or disease-modifying properties are mediated, wholly or in part, through glial mechanisms. Rather than providing an exhaustive review of glia or individual molecular targets, we critically examine the current landscape of glia-targeted therapeutics, discuss the major biological and translational challenges limiting clinical success, and propose guiding principles to support the rational development of next-generation glia-targeted therapeutics.

2. The Current Landscape of Glia-Targeted Therapeutics

The expanding landscape of glia-targeted therapeutics reflects a fundamental shift in pharmacological thinking about nervous system disorders. For decades, therapeutic development in neurology was largely centered on neuronal receptors, neurotransmitters, and ion channels, with glial cells considered primarily as passive support elements or secondary responders to neuronal dysfunction [8,33]. Accumulating evidence now demonstrates that many pharmacological agents exert clinically relevant effects on glial biology, either intentionally or as previously unrecognized contributors to their therapeutic efficacy, disease-modifying actions, or adverse effects [6,34–37]. Concurrently, advances in glial biology have stimulated the development of interventions specifically designed to target glial signaling pathways, neuroimmune communication, metabolic homeostasis, and tissue repair [6,35,38]. Together, these developments have expanded therapeutic strategies beyond traditional neuron-centric pharmacology and established glial biology as a central determinant of pharmacological response.

Importantly, glia-targeted therapeutics do not represent a single class of drugs. Rather, they encompass a continuum of pharmacological strategies that have evolved alongside advances in glial biology, molecular technologies, and translational neuroscience. This evolution can be conceptualized as progressing from incidental glial modulation, in which glial effects were recognized only after therapeutic development, toward mechanism-informed glial targeting, and more recently toward precision glial pharmacology, where therapeutic interventions are designed to account for the heterogeneity, functional states, and multicellular communication networks of glia (Figure 1). This transition is further facilitated by emerging computational approaches that are transforming modern drug discovery and development [39]. Artificial intelligence (AI), machine learning, systems pharmacology, network pharmacology, and computational modeling increasingly complement experimental neuroscience by integrating multidimensional biological data to identify novel therapeutic targets, predict drug–target interactions, prioritize drug repurposing opportunities, and support biomarker-guided patient stratification [40]. As these approaches continue to mature, they are expected to accelerate the rational development of glia-targeted therapeutics

by enabling more precise and context-aware pharmacological strategies that account for the complexity of glial biology and multicellular neuroimmune interactions.

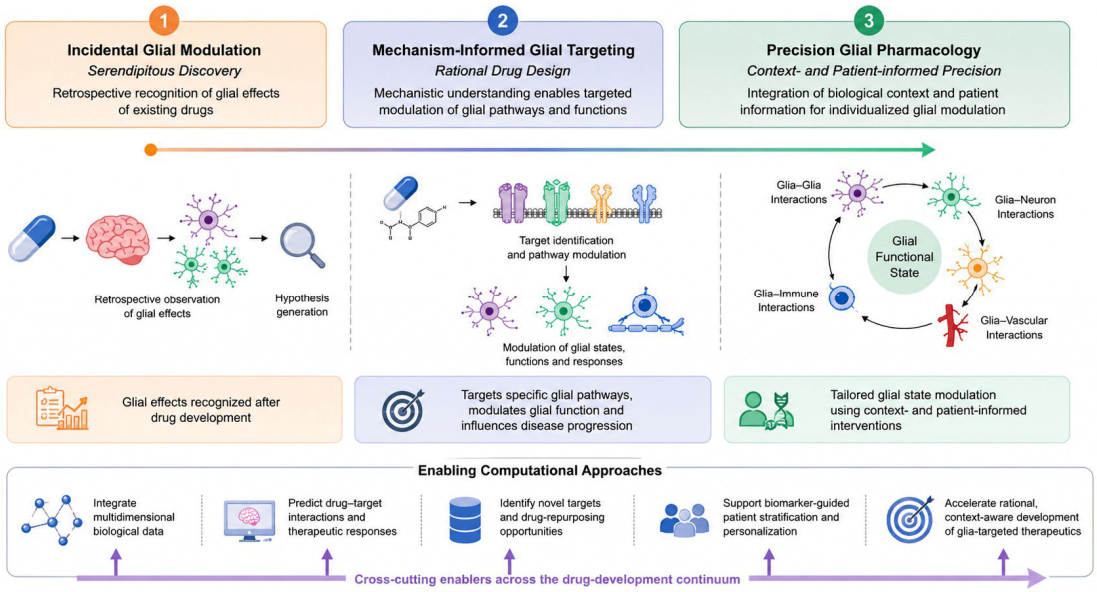


Figure 1. Conceptual evolution of glia-targeted therapeutics from incidental glial modulation to precision glial pharmacology. The framework illustrates the progression from retrospective recognition of glial effects of existing drugs, through mechanism-informed targeting of specific glial pathways, toward context- and patient-informed precision glial pharmacology. Computational approaches increasingly support this evolution by integrating multidimensional biological data, predicting drug–target interactions and therapeutic responses, identifying novel targets and drug-repurposing opportunities, and enabling biomarker-guided patient stratification. These tools therefore act as cross-cutting enablers across the drug-development continuum rather than representing a separate stage of glia-targeted therapeutic development.

2.1. Incidental Glial Modulation

Recognition of the therapeutic relevance of glial modulation emerged initially through observations that numerous pharmacological agents developed for unrelated indications unexpectedly influenced glial biology [8,41,42]. In many instances, these effects were identified only after extensive experimental or clinical use, revealing previously unrecognized contributions of glial cells to therapeutic efficacy, disease modification, or adverse effects, including those associated with minocycline, fingolimod, and ceftriaxone [43–48]. Such observations helped to broaden pharmacological thinking beyond purely neuronal mechanisms and demonstrated that glial modulation has long been an integral, albeit frequently overlooked, component of pharmacotherapy.

Importantly, these discoveries established a fundamental principle that continues to shape therapeutic development today: pharmacological modulation of glial biology often preceded mechanistic understanding of glial function itself [49–51]. Rather than being deliberately designed to target glia, many successful therapeutic agents were later found to influence neuroimmune signaling, inflammatory responses, glutamate homeostasis, or myelin biology through glial mechanisms. Recognition of these unintended yet biologically relevant actions provided the first evidence that glial cells represent therapeutically meaningful regulators of nervous system function rather than passive participants in disease [52–54].

2.2. Mechanism-Informed Glial Targeting

As understanding of glial biology expanded, therapeutic development progressively shifted from serendipitous observations toward mechanism-informed pharmacological

strategies. Rather than viewing glia as passive responders to neuronal pathology, emerging interventions increasingly target molecular pathways regulating microglial activation, astrocytic glutamate transport, purinergic signaling, neuroimmune communication, oligodendrocyte differentiation, remyelination, and metabolic homeostasis. Representative examples include P2X7, CSF1R, TREM2 [55], GLT-1, and connexins [56–62]. These advances have substantially broadened the pharmacological repertoire and generated encouraging experimental and early clinical findings across neurological disorders.

Nevertheless, translation into clinical practice has remained inconsistent. Therapeutic responses frequently vary according to anatomical region, disease stage, biological sex, aging, systemic inflammatory and metabolic status, and the local tissue microenvironment, reflecting the remarkable heterogeneity and context-dependent behavior of glial cells [3,4,63]. Furthermore, interventions that successfully suppress maladaptive inflammatory responses may simultaneously compromise physiological functions essential for synaptic regulation, immune surveillance, metabolic support, vascular homeostasis, or tissue repair. These observations indicate that successful glia-targeted therapeutics require selective modulation of pathological processes while preserving beneficial glial functions.

2.3. Precision Glial Pharmacology: An Emerging Therapeutic Paradigm

Rather than targeting individual glial populations or isolated signaling pathways, emerging therapeutic strategies increasingly aim to modulate dynamic glial functional states within complex multicellular communication networks involving neurons, vascular cells, peripheral immune cells, and other glial populations. This paradigm has been enabled by advances in single-cell and spatial transcriptomics, high-dimensional molecular profiling, and systems pharmacology, which have revealed previously unrecognized glial heterogeneity, disease-associated cellular states, and intercellular signaling networks [4,10,11,64,65]. These approaches, together with molecular biomarkers and patient-specific biological characteristics, provide opportunities to develop more precise pharmacological interventions that account for disease stage, multicellular communication, and biological context while preserving physiological homeostasis. Selective delivery across the blood–brain barrier and preferential targeting of specific glial populations remain major pharmacological challenges that must be addressed to maximize therapeutic efficacy while minimizing off-target effects.

Importantly, this evolving paradigm extends beyond identifying novel molecular targets. It recognizes that therapeutic efficacy depends on understanding which glial populations should be modulated, when intervention should occur, where within the nervous system modulation is required, and how pharmacological interventions reshape integrated neuroimmune systems. This perspective also encompasses peripheral glial populations, including SGCs and Schwann cells, whose emerging roles in neuronal excitability, inflammatory signaling, neuroimmune communication, and pain-related plasticity broaden the translational landscape of glia-targeted therapeutics [13,24,66,67].

Collectively, the evolution of glia-targeted therapeutics demonstrates that progress has been driven not only by the discovery of new molecular targets but also by a progressive shift in pharmacological thinking, from broad modulation of glial activity toward selective modulation of context-dependent glial biology. Representative pharmacological strategies currently investigated or applied across neurological disorders are summarized in Table 1. Importantly, these examples include both therapies intentionally developed to modulate glial biology and pharmacological agents whose glial mechanisms were recognized only after therapeutic development. Viewed together, they highlight both the expanding therapeutic opportunities and the persistent translational challenges that motivate the broader conceptual framework of glial pharmacology proposed in the following section.

Table 1. Representative pharmacological strategies illustrating the evolution of glia-targeted therapeutics and their implications for glial pharmacology.

Pharmacological Strategy	Representative Example(s)	Primary Molecular Target	Predominant Glial Cell(s)	Principal Glial Mechanism	Major Neurological Application(s)	Pharmacological Insight
Broad anti-inflammatory modulation	Minocycline	Multiple inflammatory pathways	Microglia	Suppresses pro-inflammatory activation and cytokine production	Neuropathic pain, stroke, neurodegenerative disorders	Broad microglial inhibition alone does not consistently translate into clinical benefit, emphasizing the importance of biological context.
Multi-target glial modulation	Ibudilast	PDE4, MIF	Microglia, astrocytes	Modulates neuroinflammation and glial activation	Chronic pain, multiple sclerosis, ALS	Simultaneous modulation of multiple glial pathways may provide greater therapeutic benefit than single-target approaches.
Antioxidant and immunometabolic modulation	Dimethyl fumarate	Nrf2 pathway	Astrocytes, microglia	Enhances antioxidant defenses and immunomodulation	Multiple sclerosis	Restoring glial homeostasis may be as important as suppressing inflammation.
Sphingosine-1-phosphate receptor modulation	Fingolimod	S1P receptors	Astrocytes, oligodendrocytes, microglia	Regulates neuroimmune signaling and supports remyelination	Multiple sclerosis	Therapeutic efficacy extends beyond peripheral immune modulation to include direct actions on glial biology.
Purinergic signaling modulation	P2X7 receptor antagonists	P2X7 receptor	Microglia	Inhibits ATP-dependent inflammasome activation	Neuropathic pain, neurodegeneration	Therapeutic efficacy depends strongly on disease stage, target engagement, and biological context.

Table 1. *Cont.*

Pharmacological Strategy	Representative Example(s)	Primary Molecular Target	Predominant Glial Cell(s)	Principal Glial Mechanism	Major Neurological Application(s)	Pharmacological Insight
Microglial state modulation	CSF1R inhibitors; TREM2 modulators	CSF1R; TREM2	Microglia	Regulates microglial survival, phagocytosis, metabolism, and disease-associated functional states	Neurodegenerative disorders, brain injury	Functional state may represent a more meaningful therapeutic target than glial cell identity alone.
Astrocytic glutamate homeostasis	Ceftriaxone	EAAT2/GLT-1	Astrocytes	Restores glutamate uptake and excitatory homeostasis	ALS, epilepsy, neuropathic pain	Preserving physiological astrocyte function represents a valuable therapeutic strategy.
Glial network modulation	Connexin-43 modulators	Connexin-43	Astrocytes	Modulates gap-junction communication and intercellular signaling	Pain, ischemia	Intercellular glial communication represents a pharmacological target in its own right.
Remyelination-promoting therapies	Clemastine; anti-LINGO-1 strategies	Multiple pathways	Oligodendrocyte lineage cells	Promotes oligodendrocyte differentiation and myelin repair	Multiple sclerosis and demyelinating disorders	Repair and regeneration should complement immunomodulation in glia-targeted therapeutics.
Gene-, RNA-, and cell-based therapies	Gene editing, RNA therapeutics, stem cell approaches	Multiple molecular targets	Multiple glial populations	State-specific modulation, gene correction, and regenerative approaches	Multiple neurological disorders	Future therapeutics may increasingly rely on selective modulation of glial functional states rather than broad suppression or activation.

Table 1. *Cont.*

Pharmacological Strategy	Representative Example(s)	Primary Molecular Target	Predominant Glial Cell(s)	Principal Glial Mechanism	Major Neurological Application(s)	Pharmacological Insight
Peripheral glia-targeted strategies	Purinergic modulators; connexin modulators; extracellular vesicle-based approaches	Multiple signaling pathways	Satellite glial cells, Schwann cells	Modulates neuron–glia communication, inflammatory signaling, and peripheral neuroimmune interactions	Neuropathic pain, craniofacial pain, peripheral nerve disorders	Peripheral glia broaden the scope of glial pharmacology beyond the CNS and represent an emerging frontier for therapeutic development.

Abbreviations: ALS, amyotrophic lateral sclerosis; CSF1R, colony-stimulating factor 1 receptor; EAAT2/GLT-1, excitatory amino acid transporter 2/glutamate transporter 1; MIF, macrophage migration inhibitory factor; Nrf2, nuclear factor erythroid 2-related factor 2; PDE4, phosphodiesterase-4; S1P, sphingosine-1-phosphate; TREM2, triggering receptor expressed on myeloid cells 2. Note: Representative examples are provided for illustrative purposes and do not constitute an exhaustive list of pharmacological agents or therapeutic indications.

3. From Glia-Targeted Therapeutics to Glial Pharmacology

The evolution of glia-targeted therapeutics outlined in the previous section demonstrates that identifying glial molecular targets alone is insufficient for successful therapeutic development. As our understanding of glial biology has expanded, so too has the realization that pharmacological interventions influence complex, dynamic, and highly interconnected neuroimmune systems rather than isolated cell populations. Consequently, effective therapeutic modulation requires consideration not only of molecular target engagement but also of glial functional states, multicellular communication networks, biological context, and preservation of physiological homeostasis.

This conceptual shift raises a fundamental pharmacological question: how should glial biology be incorporated into the rational discovery, evaluation, and translation of therapeutics? We propose that this question is best addressed through the framework of glial pharmacology. Rather than redefining neuropharmacology, glial pharmacology expands its perspective by recognizing that therapeutic efficacy frequently emerges from coordinated modulation of integrated neuroimmune systems rather than from isolated molecular targets alone. This framework provides a biologically informed foundation for understanding why some glia-targeted therapies succeed, why others fail, and how future therapeutic development may become more precise, context-dependent, and translationally relevant.

3.1. Defining Glial Pharmacology

Although the term glial pharmacology has previously appeared in the literature to broadly describe pharmacological research involving glial biology and glia-directed therapeutics [17], it has not been explicitly defined as an integrated framework for therapeutic discovery and translation.

In this perspective, we propose glial pharmacology as a framework that integrates contemporary knowledge of glial biology with pharmacological principles to guide the rational discovery, evaluation, optimization, and clinical translation of glia-targeted therapeutics. Rather than focusing exclusively on molecular targets or individual glial cell types, this framework considers how pharmacological interventions modulate glial biology across multiple levels of biological organization, from intracellular signaling pathways to multicellular communication networks and system-level regulation [32,68].

Within this framework, a glia-targeted therapeutic is not defined solely by its primary molecular target but by whether modulation of glial biology meaningfully contributes to its therapeutic efficacy, disease-modifying actions, or adverse effects. Accordingly, glial pharmacology encompasses both pharmacological agents intentionally designed to target glial mechanisms and drugs whose clinically relevant actions are mediated, wholly or in part, through glial modulation. This broader definition recognizes that many established therapeutics influence glial biology despite having originally been developed to target neuronal, vascular, or immune pathways, whereas newer therapeutic strategies increasingly exploit glial-specific mechanisms to restore nervous system function (e.g., minocycline; fingolimod; dimethyl fumarate; GLT-1; P2X7; CSF1R; TREM2).

A defining feature of glial pharmacology is the recognition that glial cells function as dynamic participants within integrated neuroimmune systems rather than isolated pharmacological targets. Therapeutic interventions therefore influence not only intracellular signaling but also reciprocal interactions among glial populations, neurons, vascular cells, peripheral immune cells, and the extracellular microenvironment. These interactions occur within well-recognized biological structures and communication networks, including the tripartite synapse, the gliovascular unit, the neurovascular unit, and peripheral sensory ganglia, where satellite glial cells and Schwann cells actively regulate neuronal excitability, inflammatory signaling, and tissue homeostasis and repair [13,69,70]. Con-

sequently, therapeutic efficacy and safety emerge from coordinated biological responses across interconnected cellular systems rather than from the modulation of single receptors or individual cell populations alone.

This systems-oriented perspective also acknowledges that identical pharmacological interventions may produce markedly different biological and clinical outcomes depending on glial functional state, anatomical location, disease stage, biological sex, aging, genetic background, systemic inflammatory and metabolic status, and local tissue microenvironment [4,10,11,63,71]. Successful therapeutic modulation therefore depends not only on identifying appropriate molecular targets but also on determining which glial populations should be modulated, when intervention should occur, where within the nervous system modulation is required, and how pharmacological interventions reshape integrated neuroimmune systems while preserving essential physiological functions. The proposed framework also intersects with established concepts in systems and network pharmacology, which emphasize multiscale interactions and interconnected biological targets, and with precision neurology, which seeks to account for interindividual biological variability in disease characterization and therapeutic decision-making [31,32,68,72]. Glial pharmacology builds on these perspectives but places the distinctive pharmacological properties of glial biology—including dynamic functional states, context-dependent responses, and reciprocal interactions within multicellular networks—at the center of therapeutic discovery and translation.

Glial pharmacology should therefore be viewed as a complementary framework within neuropharmacology rather than as a separate or competing discipline. Traditional neuropharmacology has historically emphasized pharmacological modulation of neuronal receptors, neurotransmitter systems, ion channels, and defined molecular pathways. Glial pharmacology shifts the analytical focus toward how pharmacological interventions influence dynamic glial functional states and their interactions within multicellular networks. Accordingly, therapeutic effects are considered not only in terms of molecular target engagement but also in relation to biological context, network-level consequences, and preservation of physiological glial functions. These distinctions provide the conceptual basis for the five principles outlined below and are summarized comparatively in Table 2.

Table 2. Comparison of conventional target-based pharmacology and the proposed framework of glial pharmacology.

Core Principle	Conventional Target-Based Perspective	Glial Pharmacology Perspective	Implication for Therapeutic Development
1. Therapeutic targets are functional states rather than cell identity	Therapeutic strategies are commonly organized around defined molecular targets, pathways, or cell populations.	Emphasizes dynamic glial functional states and state transitions rather than glial cell identity alone.	Identify and selectively modulate disease-associated states while preserving physiological glial functions.
2. Glial communication networks represent therapeutic substrates	Drug effects are often evaluated primarily through target- or pathway-specific mechanisms.	Considers glia–neuron, glia–glia, glia–vascular, and glia–immune interactions as therapeutically relevant networks.	Evaluate how interventions reshape multicellular communication and system-level responses, rather than only individual pathways.
3. Biological context determines therapeutic efficacy	Biological context may be considered during preclinical or clinical translation but is not necessarily intrinsic to target definition.	Disease stage, anatomical location, biological sex, aging, systemic state, and the local microenvironment are integral determinants of pharmacological response.	Incorporate biological context into target validation, experimental design, patient stratification, and therapeutic timing.

Table 2. *Cont.*

Core Principle	Conventional Target-Based Perspective	Glial Pharmacology Perspective	Implication for Therapeutic Development
4. Homeostasis should be preserved while pathology is corrected	Therapeutic strategies frequently emphasize inhibition or activation of disease-associated targets or pathways.	Seeks selective correction of maladaptive glial states while preserving homeostatic, protective, and reparative functions.	Design state-selective interventions and assess preservation of physiological glial functions alongside therapeutic efficacy.
5. Translation requires biomarkers and precision pharmacology	Translation commonly emphasizes target engagement, dose–response relationships, safety, and clinical efficacy.	Integrates glial-state biomarkers, target engagement, biological context, and patient-specific characteristics into therapeutic development.	Use multimodal biomarkers and computational approaches for patient stratification, response monitoring, and precision therapeutic adaptation.

3.2. Core Principles of Glial Pharmacology

The framework proposed here is founded on five interrelated principles that distinguish glial pharmacology from conventional target-based approaches (Figure 2; Table 2). Together, these principles provide a biologically informed framework for the rational discovery, evaluation, and translation of next-generation glia-targeted therapeutics.

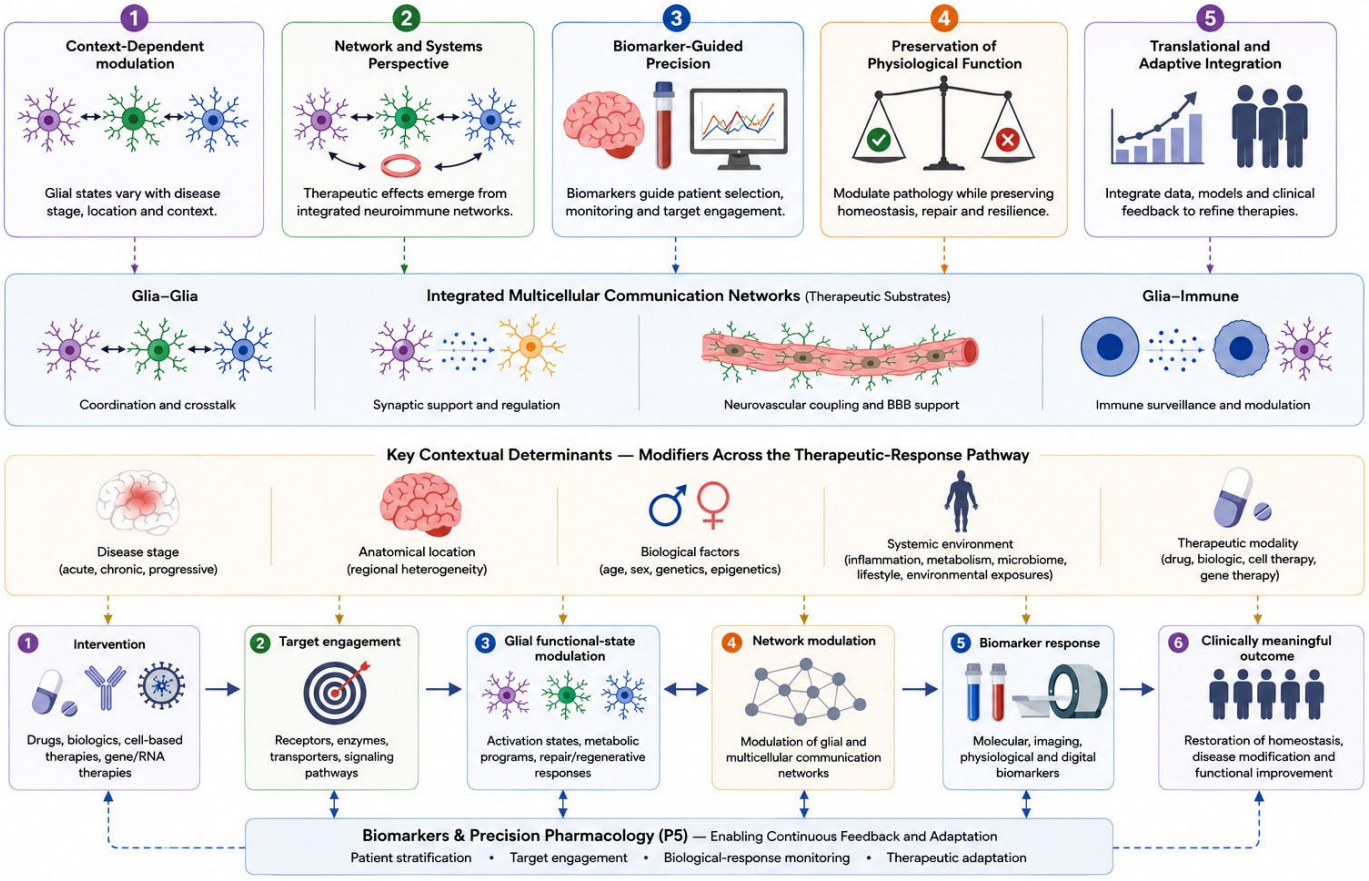


Figure 2. Integration of the five core principles of glial pharmacology across the therapeutic-response pathway. The five principles are linked to a therapeutic continuum extending from pharmacological intervention and molecular target engagement to glial functional-state modulation, multicellular network regulation, biomarker response, and clinically meaningful outcomes. Integrated glia–glia, glia–neuron, glia–vascular, and glia–immune communication networks represent key therapeutic substrates. Contextual determinants—including disease stage, anatomical location, biological factors,

systemic environment, and therapeutic modality—modify responses across the pathway rather than representing sequential stages. Biomarkers and precision pharmacology support patient stratification, assessment of target engagement and biological response, response monitoring, and therapeutic adaptation, thereby enabling continuous feedback across the therapeutic pathway. Arrows and connections indicate functional and reciprocal relationships within the framework rather than a strictly unidirectional biological sequence.

Principle 1. *Therapeutic targets are functional states rather than cell identity.*

Glial populations cannot be adequately classified as uniformly beneficial or detrimental. Microglia, astrocytes, oligodendrocyte lineage cells, SGCs, and Schwann cells exhibit remarkable phenotypic plasticity that varies across development, aging, and disease stages; anatomical regions; and local tissue microenvironments [42]. Consequently, pharmacological interventions should aim to selectively modulate pathological functional states while preserving or restoring physiological functions, rather than indiscriminately suppressing or activating entire glial populations. This shift from targeting cell identity to targeting cellular state represents one of the most important conceptual advances in contemporary glial biology and provides a foundation for precision glia-targeted therapeutics.

Principle 2. *Glial communication networks represent therapeutic substrates.*

Glial cells operate within highly interconnected communication networks involving neurons, vascular cells, peripheral immune cells, extracellular matrix components, and other glial populations [73]. These interactions underpin key biological interfaces such as the tripartite synapse, the neurovascular unit, and peripheral sensory ganglia, where SGCs and Schwann cells actively regulate neuronal excitability, inflammatory signaling, tissue repair, and neuroimmune communication [7]. Therapeutic responses, therefore, emerge from the coordinated regulation of multicellular communication rather than from the modulation of isolated molecular pathways. Pharmacological interventions should consequently be evaluated according to their influence on glia–neuron, glia–glia, glia–vascular, and glia–immune interactions, recognizing that restoration of communication network homeostasis may ultimately be more therapeutically meaningful than modifying individual signaling molecules.

Principle 3. *Biological context determines therapeutic efficacy.*

The pharmacological consequences of glial modulation are inherently context-dependent. Disease stage, anatomical location, biological sex, aging, genetic background, systemic inflammatory and metabolic status, environmental exposures, and local tissue microenvironment all influence glial functional states and their responses to pharmacological intervention [74,75]. Consequently, therapeutic strategies that are beneficial in one disease, disease stage, or patient population may prove ineffective, or even detrimental, in another. Context-dependent pharmacology should therefore become an integral component of therapeutic discovery and clinical development rather than a secondary consideration during late-stage translation.

Principle 4. *Homeostasis should be preserved while pathology is corrected.*

Unlike many conventional pharmacological targets, glial cells cannot simply be inhibited without risking disruption of essential physiological functions [76]. They regulate synaptic activity, metabolic support, neurotransmitter homeostasis, myelin maintenance, immune surveillance, vascular integrity, and tissue repair and regeneration [50]. Therapeutic interventions should therefore avoid indiscriminate suppression of glial activity and instead seek to selectively restore physiological homeostasis while limiting maladaptive responses. Preserving beneficial glial functions is likely to be as important as reducing

pathological processes, emphasizing that successful therapy should rebalance rather than simply inhibit glial biology.

Achieving such selectivity will require therapeutic strategies capable of distinguishing maladaptive glial states from physiological glial functions. Potential approaches include targeting receptors, signaling pathways, or molecular signatures that are preferentially expressed or functionally altered in disease-associated glial states; exploiting spatial or temporal differences in target availability; and developing delivery systems that increase drug exposure within relevant glial populations or pathological microenvironments. Advances in single-cell and spatial profiling may facilitate identification of molecular signatures that distinguish disease-associated from homeostatic glial states and thereby support more selective pharmacological intervention [10,11,65]. Importantly, such strategies should aim to modulate pathological state-associated signaling rather than eliminate entire glial populations, with preservation of immune surveillance, metabolic support, and tissue-repair functions incorporated as explicit measures of therapeutic selectivity.

TREM2-directed approaches provide an illustrative example of this principle: rather than broadly suppressing microglial activity, modulation of TREM2-associated signaling may offer opportunities to influence disease-associated microglial functions while seeking to preserve essential homeostatic and immune-surveillance activities [55,60]. However, the extent to which TREM2-directed interventions can achieve such state-selective modulation in humans remains to be established.

Principle 5. *Translation requires biomarkers and precision pharmacology.*

Successful translation of glia-targeted therapeutics requires reliable approaches for identifying appropriate patients, monitoring target engagement, and evaluating biological responses. Molecular biomarkers, functional neuroimaging, extracellular vesicles, fluid biomarkers, spatial transcriptomics, physiological monitoring, and multimodal computational approaches provide increasingly powerful opportunities to characterize glial biology in vivo [77–79]. In parallel, AI, systems pharmacology, network pharmacology, and computational modeling are beginning to transform drug discovery by integrating multidimensional biological datasets, identifying novel therapeutic targets, predicting drug responses, supporting drug repurposing, and enabling biomarker-guided patient stratification [80,81]. Integrating these technologies with pharmacological development will facilitate precision glial therapeutics tailored to disease stage, biological context, and individual patient characteristics. Future digital twin frameworks may further integrate multimodal biomarkers, longitudinal clinical data, and pharmacological responses to enable individualized prediction of glial dynamics and therapeutic outcomes.

Collectively, these principles establish the conceptual foundation of glial pharmacology and shift the emphasis from isolated molecular target engagement toward biologically integrated therapeutic regulation. Ultimately, the success of glial pharmacology should be judged not simply by target engagement, but by its capacity to restore adaptive glial function and improve clinically meaningful outcomes. Their integration across the therapeutic-response pathway is illustrated in Figure 2.

3.3. Applying the Framework: Fingolimod as an Illustrative Example

The practical application of the five principles can be illustrated retrospectively using fingolimod. Fingolimod was not developed according to the framework proposed here; nevertheless, its pharmacology illustrates how an established therapeutic can be reconsidered through a glial pharmacology perspective. First, its actions extend beyond a single glial cell identity, as sphingosine-1-phosphate receptor signaling can influence multiple glial populations and their functional responses [47]. Second, these effects occur within broader neuroimmune communication networks rather than through an isolated

glial pathway. Third, the consequences of such modulation depend on biological context, including cellular state, anatomical compartment, and the surrounding inflammatory environment. Fourth, potential therapeutic benefits must be considered alongside preservation of physiological immune and glial functions. Finally, biomarkers capable of characterizing relevant biological states and monitoring target engagement and response would be required to translate such mechanistic complexity toward more precise therapeutic use. Viewed retrospectively, fingolimod therefore illustrates how the five principles can provide a structured approach for interrogating a glia-relevant therapeutic beyond a conventional target–drug relationship.

4. Translating Glial Pharmacology into Therapeutic Innovation

The framework of glial pharmacology extends beyond redefining how glial biology is interpreted; it also provides practical guidance for the discovery, development, evaluation, and clinical translation of next-generation therapeutics. As summarized in Figure 3, successful implementation will require coordinated advances across drug discovery, experimental modeling, biomarker development, precision pharmacology, and emerging computational technologies. Together, these advances provide a translational roadmap for developing glia-targeted therapeutics that account for glial heterogeneity, dynamic functional states, multicellular communication, and patient-specific biological context.

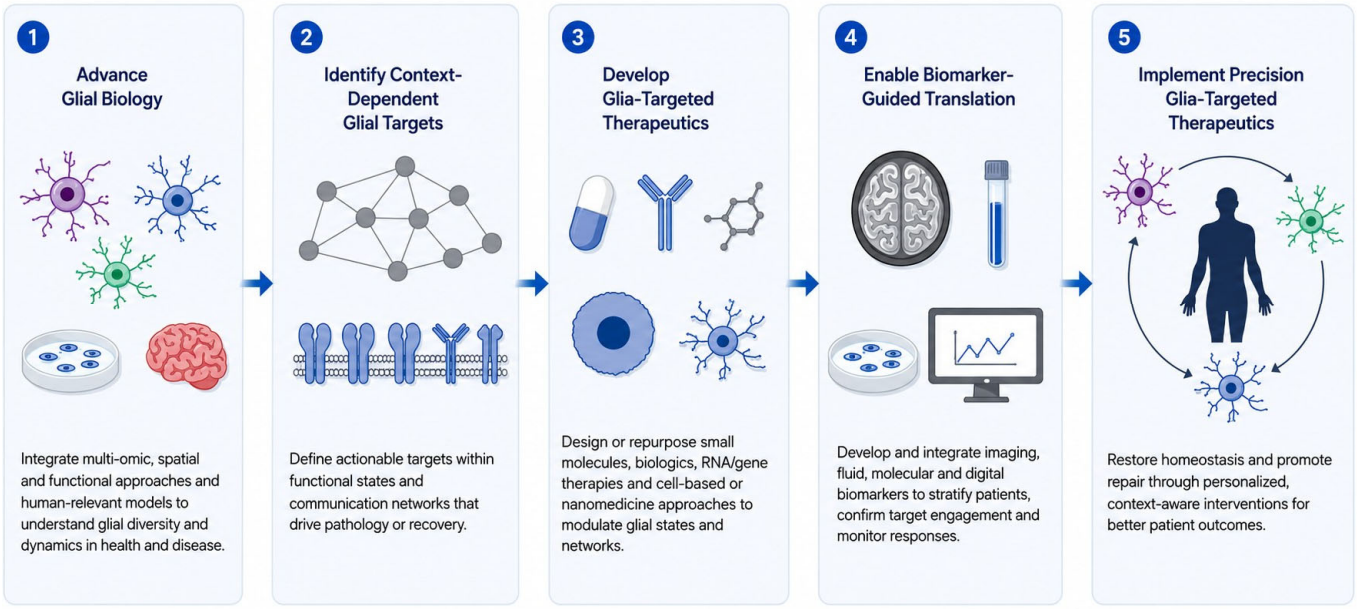


Figure 3. Translational roadmap for implementing glial pharmacology in therapeutic development. The framework illustrates the progression from advances in glial biology to precision glia-targeted therapeutics, integrating biological discovery, identification of context-dependent glial targets, therapeutic development, biomarker-guided translation, and precision clinical implementation.

4.1. Rethinking Drug Discovery for Glia-Targeted Therapeutics

Traditional drug discovery has largely focused on identifying single molecular targets whose modulation produces predictable therapeutic effects [82]. However, the complexity of glial biology challenges this reductionist paradigm. Glial cells integrate multiple signaling pathways simultaneously while continuously adapting to changes in their local microenvironment, making therapeutic responses highly context-dependent [6]. Future therapeutic discovery should therefore prioritize modulation of biological networks and functional states rather than isolated receptors or signaling molecules.

An important opportunity within this framework is drug repurposing [83]. Many established therapeutics, including minocycline, fingolimod, ceftriaxone, dimethyl fumarate, and ibudilast, were initially developed for mechanisms unrelated to glial biology but were subsequently shown to exert clinically relevant glial-modulating effects [8,84–87]. Systematic identification of previously unrecognized glial mechanisms among existing therapeutics may therefore accelerate clinical translation while reducing the time and cost associated with conventional drug development.

Emerging computational approaches are expected to further accelerate this process. AI, machine learning, systems pharmacology, and network pharmacology increasingly integrate multidimensional biological datasets to identify novel therapeutic targets, predict drug–target interactions, optimize drug repurposing, and prioritize candidate compounds for experimental validation [88,89]. Rather than replacing experimental neuroscience, these approaches complement mechanistic investigation by improving hypothesis generation and supporting rational therapeutic design.

4.2. Human-Relevant Experimental Models

One of the major obstacles to successful translation has been the limited ability of conventional experimental models to capture the complexity and diversity of human glial biology. Species differences, simplified cellular environments, and inadequate representation of disease progression contribute to the frequent discrepancy between encouraging preclinical findings and disappointing clinical outcomes.

Recent advances in induced pluripotent stem cell (iPSC) technology, brain organoids, assembloids, organ-on-chip platforms, and spatial transcriptomics provide increasingly sophisticated opportunities to investigate human glial biology under physiologically relevant conditions [90–92]. These platforms enable investigation of multicellular interactions, disease-specific phenotypes, and patient-derived biological variability while facilitating more predictive evaluation of candidate therapeutics [93].

Despite these advances, human-derived models remain imperfect representations of dynamic glial disease biology. iPSC-derived cultures, brain organoids, assembloids, and related platforms can reproduce selected cellular, molecular, and multicellular features of human nervous system disorders, but they do not necessarily capture the temporal transitions of glial functional states that occur during disease initiation, progression, treatment, and recovery. Limitations in cellular maturation, vascularization, immune-system integration, systemic influences, and long-term microenvironmental interactions may further constrain their ability to reproduce context-dependent glial responses [91–93]. Consequently, human-relevant models for glial pharmacology should be evaluated not only according to their cellular composition or human origin, but also according to their capacity to reproduce disease-relevant glial state transitions and pharmacological responses over time. Combining these models with longitudinal molecular profiling, functional analyses, and controlled perturbations may therefore provide more informative platforms for evaluating state-selective glia-targeted therapeutics.

4.3. Biomarkers and Target Engagement

Successful translation of glia-targeted therapeutics requires reliable methods to identify appropriate patients, demonstrate pharmacological target engagement, and monitor biological response. One of the major challenges in glial drug development is distinguishing failure to adequately modulate the intended biological target from failure of the underlying therapeutic hypothesis [8,94,95]. Biomarkers should therefore support diagnosis, patient stratification, pharmacodynamic target engagement, and longitudinal therapeutic monitoring [96,97].

Candidate biomarkers include molecular signatures, cerebrospinal fluid and blood biomarkers, extracellular vesicles, functional neuroimaging, spatial molecular profiling, and physiological monitoring. Integration of multimodal biomarkers may enable more accurate assessment of glial functional states, disease progression, therapeutic response, and patient stratification [98–100].

Ultimately, biomarker-guided pharmacology has the potential to transform glia-targeted therapeutics from empirically selected interventions into mechanism-informed precision treatments.

4.4. Precision Glial Therapeutics

Recognition of glial heterogeneity [101] naturally aligns with the principles of precision medicine. Rather than assuming that individual neurological disorders share uniform glial pathology, therapeutic strategies should increasingly account for disease stage, anatomical localization, biological sex, aging, genetic background, systemic physiology, and environmental exposures.

Future clinical trials may therefore benefit from biomarker-guided patient selection, adaptive trial designs, and longitudinal assessment of glial functional states [102]. Such approaches may improve therapeutic efficacy while reducing unnecessary exposure to ineffective treatments.

4.5. Emerging Technologies and Future Perspectives

Several emerging technologies are expected to substantially influence the future of glial pharmacology. RNA-based therapeutics [103], gene editing, targeted nanomedicine, regenerative medicine, extracellular vesicle engineering, and advanced drug-delivery systems offer new opportunities [104,105] to selectively modulate glial biology with increasing precision. Overcoming challenges associated with selective delivery across the blood–brain barrier and preferential targeting of specific glial populations will remain essential for maximizing therapeutic efficacy while minimizing off-target effects.

AI, multimodal computational modeling, and digital health technologies are likely to further transform therapeutic development by integrating molecular, imaging, physiological, and clinical datasets across multiple biological scales [106,107]. These approaches may facilitate the identification of novel therapeutic targets, the optimization of drug discovery pipelines, the prediction of treatment response, and the design of adaptive clinical trials [108].

AI may also support therapeutic discovery through molecular docking, prediction of absorption, distribution, metabolism, excretion, and toxicity (ADMET), and generative approaches for candidate identification and optimization [109].

Looking further ahead, digital twin frameworks [110] may provide individualized computational representations of glial biology by integrating multimodal biomarkers, disease trajectories, environmental exposures, and therapeutic responses into continuously evolving disease models. Although these technologies remain at an early stage, they illustrate how glial pharmacology may ultimately evolve from population-based therapeutic strategies toward continuously adaptive, personalized pharmacological interventions.

Collectively, these developments indicate that the future of glial pharmacology will depend not only on identifying new therapeutic targets but also on integrating advances in molecular neuroscience, computational biology, biomarker science, and precision medicine into a unified translational framework.

5. Conclusions

The expanding recognition of glial cells as active regulators of neuroimmune communication, synaptic function, metabolism, tissue repair, and disease progression has fundamentally reshaped contemporary neuroscience. At the same time, advances in molecular profiling, human-relevant experimental models, biomarker science, and computational biology have revealed that glial biology is considerably more dynamic, heterogeneous, and context-dependent than previously appreciated. These discoveries have created unprecedented opportunities for therapeutic innovation while simultaneously exposing the limitations of pharmacological strategies that broadly target individual glial populations or isolated signaling pathways.

In this perspective, we propose glial pharmacology as a conceptual and translational framework that builds on established developments in neuropharmacology, precision neurology, systems pharmacology, and network pharmacology. These approaches have established the importance of patient heterogeneity, biological networks, and multiscale interactions in therapeutic response and provide an important foundation for the present framework. Glial pharmacology does not seek to duplicate or replace these approaches. Its incremental value lies in integrating their principles around pharmacological challenges that are particularly relevant to glial biology: dynamic and context-dependent functional states, reciprocal interactions among glia, neurons, vascular and immune cells, and the need to correct maladaptive responses while preserving essential homeostatic, protective, and reparative functions. By linking these features with biomarker-guided target engagement and therapeutic development, the framework provides a glia-centered structure connecting contemporary glial biology with pharmacological discovery and translation.

Importantly, this framework is intended to complement rather than replace established principles of neuropharmacology. Its purpose is to provide a common conceptual language that connects advances in glial biology with therapeutic development across the central and peripheral nervous systems. Several limitations of the proposed framework should nevertheless be acknowledged. Its implementation depends on capabilities that remain incompletely developed, particularly the ability to identify, monitor, and selectively modulate dynamic glial functional states in humans. Current molecular, imaging, fluid, and computational biomarkers provide incomplete and often indirect representations of glial activity, making longitudinal assessment of state transitions and treatment responses challenging. Therapeutic delivery represents an additional constraint, particularly for central nervous system targets, where blood–brain barrier permeability, regional distribution, and cell-specific drug exposure may limit effective modulation. Moreover, the heterogeneity and context dependence that motivate the framework also complicate its experimental validation and clinical implementation. Glial pharmacology should therefore currently be regarded as a conceptual and translational framework whose utility will require prospective validation alongside advances in human-relevant models, drug-delivery technologies, dynamic biomarkers, and longitudinal monitoring approaches.

The future development of glia-targeted therapeutics will therefore depend not simply on identifying additional molecular targets, but on determining how, when, and in whom glial biology can be modulated to produce meaningful therapeutic benefit. Advances in human-relevant models, dynamic biomarkers, computational approaches, and precision pharmacology will be essential for testing and refining the framework proposed here. By organizing these developments around the distinctive biology of glial cells, glial pharmacology provides a foundation for moving from increasingly detailed descriptions of glial complexity toward more rational, selective, and clinically translatable therapeutic strategies.

Author Contributions: Conceptualization, P.G.; writing—original draft, P.G.; writing—review and editing, P.G., N.S.P. and M.F.H.d.S. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: No new data were created or analyzed in this study. Data sharing is not applicable to this article.

Acknowledgments: During the preparation of this manuscript, the authors used Microsoft 365 Copilot, Grammerly Version. 1.2.91.1461, and Gamma version 1.0.2 on iOS. All scientific concepts, interpretations, and conclusions were developed, critically evaluated, and approved by the authors, who take full responsibility for the content of this perspective.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Kettenmann, H.; Verkhratsky, A. Glial Cells. In *Neuroscience in the 21st Century: From Basic to Clinical*; Pfaff, D.W., Ed.; Springer: New York, NY, USA, 2013; pp. 475–506.
2. Verkhratsky, A.; Nedergaard, M. Physiology of Astroglia. *Physiol. Rev.* **2018**, *98*, 239–389. [CrossRef] [PubMed]
3. Salter, M.W.; Stevens, B. Microglia emerge as central players in brain disease. *Nat. Med.* **2017**, *23*, 1018–1027. [CrossRef] [PubMed]
4. Escartin, C.; Galea, E.; Lakatos, A.; O'Callaghan, J.P.; Petzold, G.C.; Serrano-Pozo, A.; Steinhäuser, C.; Volterra, A.; Carmignoto, G.; Agarwal, A.; et al. Reactive astrocyte nomenclature, definitions, and future directions. *Nat. Neurosci.* **2021**, *24*, 312–325. [CrossRef] [PubMed]
5. Kettenmann, H.; Verkhratsky, A. Neuroglia: The 150 years after. *Trends Neurosci.* **2008**, *31*, 653–659. [CrossRef] [PubMed]
6. García-Domínguez, M. Glial Cell Dynamics in Neuroinflammation: Mechanisms, Interactions, and Therapeutic Implications. *Biomedicines* **2026**, *14*, 115. [CrossRef] [PubMed]
7. Guo, X.; Liu, H.; Song, Y.J.; Wang, J.H.; Liu, D.; Zheng, Z.W.; Li, J.J.; Li, B.; Song, A.; He, W.; et al. Neuro-Immune Crosstalk: Molecular Mechanisms, Biological Functions, Diseases, and Therapeutic Targets. *MedComm* **2026**, *7*, e70497. [CrossRef] [PubMed]
8. Vishnumukkala, T.; Che Mohd Nassir, C.M.N.; Hein, Z.M.; Kalerammana Gopalakrishna, P.; Karikalan, B.; Alkatiri, A.; Jagadeesan, S.; Naik, V.R.; Thomas, W.; Mohd Moklas, M.A.; et al. Glial Cells as Emerging Therapeutic Targets in Neurodegenerative Diseases: Mechanistic Insights and Translational Perspectives. *Cells* **2025**, *14*, 1497. [CrossRef] [PubMed]
9. Gao, C.; Jiang, J.; Tan, Y.; Chen, S. Microglia in neurodegenerative diseases: Mechanism and potential therapeutic targets. *Signal Transduct. Target. Ther.* **2023**, *8*, 359. [CrossRef] [PubMed]
10. Hammond, T.R.; Dufort, C.; Dissing-Olesen, L.; Giera, S.; Young, A.; Wysoker, A.; Walker, A.J.; Gergits, F.; Segel, M.; Nemesh, J.; et al. Single-Cell RNA Sequencing of Microglia throughout the Mouse Lifespan and in the Injured Brain Reveals Complex Cell-State Changes. *Immunity* **2019**, *50*, 253–271.e6. [CrossRef] [PubMed]
11. Masuda, T.; Sankowski, R.; Staszewski, O.; Prinz, M. Microglia Heterogeneity in the Single-Cell Era. *Cell Rep.* **2020**, *30*, 1271–1281. [CrossRef] [PubMed]
12. Allen, N.J.; Lyons, D.A. Glia as architects of central nervous system formation and function. *Science* **2018**, *362*, 181–185. [CrossRef] [PubMed]
13. Hanani, M.; Spray, D.C. Emerging importance of satellite glia in nervous system function and dysfunction. *Nat. Rev. Neurosci.* **2020**, *21*, 485–498. [CrossRef] [PubMed]
14. Sofroniew, M.V.; Vinters, H.V. Astrocytes: Biology and pathology. *Acta Neuropathol.* **2010**, *119*, 7–35. [CrossRef] [PubMed]
15. Kim, H.Y.; Kim, S.; Akaydin, A.N.; Kim, S.; Hyeon, S.J.; Lee, J.; Ryu, H. The rise of astrocytes: Are they guardians or troublemakers of the brain disorder? *Exp. Mol. Med.* **2026**, *58*, 301–318. [CrossRef] [PubMed]
16. McQuaid, C.; Sewell, M.; Montagne, A. Friend or foe? Glial–vascular interactions in health and neurodegenerative disease. *Pharmacol. Rev.* **2026**, *78*, 100143. [CrossRef] [PubMed]
17. Koizumi, S. Glial pharmacology in Asia & Beyond. *Pharmacol. Res. Perspect.* **2021**, *9*, e00881. [CrossRef] [PubMed]
18. Tsuda, M.; Shigemoto-Mogami, Y.; Koizumi, S.; Mizokoshi, A.; Kohsaka, S.; Salter, M.W.; Inoue, K. P2X4 receptors induced in spinal microglia gate tactile allodynia after nerve injury. *Nature* **2003**, *424*, 778–783. [CrossRef] [PubMed]
19. Coull, J.A.; Beggs, S.; Boudreau, D.; Boivin, D.; Tsuda, M.; Inoue, K.; Gravel, C.; Salter, M.W.; De Koninck, Y. BDNF from microglia causes the shift in neuronal anion gradient underlying neuropathic pain. *Nature* **2005**, *438*, 1017–1021. [CrossRef] [PubMed]

20. Heneka, M.T.; Carson, M.J.; El Khoury, J.; Landreth, G.E.; Brosseron, F.; Feinstein, D.L.; Jacobs, A.H.; Wyss-Coray, T.; Vitorica, J.; Ransohoff, R.M.; et al. Neuroinflammation in Alzheimer's disease. *Lancet Neurol.* **2015**, *14*, 388–405. [CrossRef] [PubMed]
21. Ferreira, A.F.F.; Santos-Silva, A.C.; Muratori, B.G.; Britto, L.R. The impact of CSF1R inhibitor-mediated microglial depletion in rodent models of Alzheimer's and Parkinson's disease: A systematic review and meta-analysis. *Front. Aging Neurosci.* **2026**, *18*, 1733682. [CrossRef] [PubMed]
22. Reardon, C.; Murray, K.; Lomax, A.E. Neuroimmune Communication in Health and Disease. *Physiol. Rev.* **2018**, *98*, 2287–2316. [CrossRef] [PubMed]
23. Krsek, A.; Ostojic, L.; Zivalj, D.; Baticic, L. Navigating the Neuroimmunomodulation Frontier: Pioneering Approaches and Promising Horizons—A Comprehensive Review. *Int. J. Mol. Sci.* **2024**, *25*, 9695. [CrossRef] [PubMed]
24. Gazerani, P. Satellite Glial Cells in Pain Research: A Targeted Viewpoint of Potential and Future Directions. *Front. Pain Res.* **2021**, *2*, 646068. [CrossRef] [PubMed]
25. McKenzie, A.; Dombrower, R.; Theeraphapphong, N.; McKenzie, S.; Hijazin, M.A. Glial Activation, Neuroinflammation, and Loss of Neuroprotection in Chronic Pain: Cellular Mechanisms and Emerging Therapeutic Strategies. *Biomedicines* **2026**, *14*, 58. [CrossRef] [PubMed]
26. Wawrzyniak, A.; Krawczyk-Marć, I.; Żuryń, A.; Kłosowicz, M.; Walocha, J.; Wysiadecki, G.; Balawender, K. Unveiling significance of peripheral nervous system glia: Implications for nervous system disorders and therapeutic interventions. *Folia Morphol.* **2025**, *84*, 493–500. [CrossRef] [PubMed]
27. Belaya, I.; Ivanova, M.; Sorvari, A.; Ilicic, M.; Loppi, S.; Koivisto, H.; Varricchio, A.; Tikkanen, H.; Walker, F.R.; Atalay, M.; et al. Astrocyte remodeling in the beneficial effects of long-term voluntary exercise in Alzheimer's disease. *J. Neuroinflamm.* **2020**, *17*, 271. [CrossRef] [PubMed]
28. Mee-Inta, O.; Zhao, Z.W.; Kuo, Y.M. Physical Exercise Inhibits Inflammation and Microglial Activation. *Cells* **2019**, *8*, 691. [CrossRef] [PubMed]
29. Hablitz, L.M.; Nedergaard, M. The Glymphatic System: A Novel Component of Fundamental Neurobiology. *J. Neurosci.* **2021**, *41*, 7698–7711. [CrossRef] [PubMed]
30. Erny, D.; Hrabě de Angelis, A.L.; Jaitin, D.; Wieghofer, P.; Staszewski, O.; David, E.; Keren-Shaul, H.; Mahlakoiv, T.; Jakobshagen, K.; Buch, T.; et al. Host microbiota constantly control maturation and function of microglia in the CNS. *Nat. Neurosci.* **2015**, *18*, 965–977. [CrossRef] [PubMed]
31. Vicini, P.; van der Graaf, P.H. Systems pharmacology for drug discovery and development: Paradigm shift or flash in the pan? *Clin. Pharmacol. Ther.* **2013**, *93*, 379–381. [CrossRef] [PubMed]
32. Hopkins, A.L. Network pharmacology. *Nat. Biotechnol.* **2007**, *25*, 1110–1111. [CrossRef] [PubMed]
33. Volonté, C.; Hu, G.; Shaw, C.A.; Viegas, C., Jr.; dos Santos, J.A.; Vaz, S.H.; Sebastião, A.M.; Balcar, V.J.; Mozley, P.D.; Verde, F.; et al. Neuroprotection beyond neurons: Integrated biomarker-based and astroglia- or microglia-targeted approaches to combat neurodegenerative diseases. *Explor. Neuroprotective Ther.* **2026**, *6*, 1004136. [CrossRef]
34. Jeong, S.H.; Shin, J.Y.; Lee, P.H. Drug repurposing for disease-modifying effects in multiple system atrophy. *Transl. Neurodegener.* **2026**, *15*, 15. [CrossRef] [PubMed]
35. Suk, K. Neuroglia in traumatic brain injury: Pathophysiology and therapeutic targeting. *Brain Netw. Disord.* **2026**, *2*, 93–107. [CrossRef]
36. Scarante, F.F.; Ribeiro, M.A.; Almeida-Santos, A.F.; Guimarães, F.S.; Campos, A.C. Glial Cells and Their Contribution to the Mechanisms of Action of Cannabidiol in Neuropsychiatric Disorders. *Front. Pharmacol.* **2021**, *11*, 618065. [CrossRef] [PubMed]
37. Wang, X.; Zhao, M.; Liu, Z. The dual effects of anesthetics on glial cells: A review of neuroprotection and neurotoxicity. *Front. Pharmacol.* **2026**, *17*, 1724695. [CrossRef] [PubMed]
38. Jubair, H. Glial cells in dementia: From cellular dysfunction to therapeutic frontiers. *Cell Transpl.* **2026**, *35*, 9636897251414216. [CrossRef] [PubMed]
39. Tutone, M.; Almerico, A.M. Computational Strategies Reshaping Modern Drug Discovery. *Molecules* **2026**, *31*, 200. [CrossRef] [PubMed]
40. Singh, S.; Kumar, R.; Payra, S.; Singh, S.K. Artificial Intelligence and Machine Learning in Pharmacological Research: Bridging the Gap Between Data and Drug Discovery. *Cureus* **2023**, *15*, e44359. [CrossRef] [PubMed]
41. Ralay Ranaivo, H.; Craft, J.M.; Hu, W.; Guo, L.; Wing, L.K.; Van Eldik, L.J.; Watterson, D.M. Glia as a therapeutic target: Selective suppression of human amyloid-beta-induced upregulation of brain proinflammatory cytokine production attenuates neurodegeneration. *J. Neurosci.* **2006**, *26*, 662–670. [CrossRef] [PubMed]
42. Haywood, R.E. Glial cells of the central and peripheral nervous systems: An overview of existing research. *J. Appl. Neurosci.* **2024**, *3*, 13. [CrossRef]
43. Gilron, I.; Xiao, M.Z.X.; Carley, M.; Salter, M.W.; Hutchinson, M.R.; Moulin, D.E.; Moore, R.A.; Ross-White, A. Glial-modulating agents for the treatment of pain: A systematic review. *Pain* **2025**, *166*, 1030–1049. [CrossRef] [PubMed]

44. Kaur, T.; Dushyant; Yadav, N.; Saini, V.; Devi, R.; Dhingra, A.K. Neuroinflammatory and Synaptic Roles of Glial Cells in Autism Spectrum Disorder. *CNS Neurol. Disord. Drug Targets* 2026, *in press*. [PubMed]
45. Paudel, Y.N.; Angelopoulou, E.; Kulkarni, S.; Blair, R.E.; Deshpande, L.S. Microglia in Epilepsy: From Molecular Mechanism to Therapeutic Strategy. *Cells* **2026**, *15*, 835. [CrossRef] [PubMed]
46. Eshrati, S.; Nikbakhtzadeh, M.; Arezoomandan, R.; Fattahi, A. Efficacy of minocycline in substance use disorder: A systematic review of preclinical and clinical studies. *Pharmacol. Biochem. Behav.* **2025**, *250*, 173982. [CrossRef] [PubMed]
47. Li, W.; Xu, H.; Testai, F.D. Mechanism of Action and Clinical Potential of Fingolimod for the Treatment of Stroke. *Front. Neurol.* **2016**, *7*, 139. [CrossRef] [PubMed]
48. Zhi, H.; Wang, X.; Chen, Y.; Cai, Z.; Li, J.; Guo, D. Ceftriaxone affects ferroptosis and alleviates glial cell activation in Parkinson's disease. *Int. J. Mol. Med.* **2025**, *55*, 85. [CrossRef] [PubMed]
49. Verkhratsky, A.; Ho, M.S.; Parpura, V. Evolution of Neuroglia. *Adv. Exp. Med. Biol.* **2019**, *1175*, 15–44. [CrossRef] [PubMed]
50. Wawrzyniak, A.; Krawczyk-Marć, I.; Żuryń, A.; Walocha, J.; Balawender, K. Diversity, Functional Complexity, and Translational Potential of Glial Cells in the Central Nervous System. *Int. J. Mol. Sci.* **2025**, *26*, 9080. [CrossRef] [PubMed]
51. Rasband, M.N. Glial Contributions to Neural Function and Disease. *Mol. Cell Proteom.* **2016**, *15*, 355–361. [CrossRef] [PubMed]
52. Verkhratsky, A.; Li, B.; Niu, J.; Lin, S.-S.; Su, Y.; Jin, W.-N.; Li, Y.; Jiang, S.; Yi, C.; Shi, F.-D.; et al. Neuroglial Advances: New Roles for Established Players. *J. Neurochem.* **2025**, *169*, e70080. [CrossRef] [PubMed]
53. Dar, N.J.; Bhat, J.A.; John, U.; Bhat, S.A. Neuroglia in Neurodegeneration: Exploring Glial Dynamics in Brain Disorders. *Neuroglia* **2024**, *5*, 488–504. [CrossRef]
54. Sharma, A.; Parekh, B.; Patil, V.; RJ, S.; Nayak, P.P.; Singh, G.; Al-Hasnaawei, S. Astrocytes and Microglia in Alzheimer's Disease: Friends, Foes, or Both? *Dev. Neurobiol.* **2026**, *86*, e23015. [CrossRef] [PubMed]
55. Li, Y.; Xu, H.; Wang, H.; Yang, K.; Luan, J.; Wang, S. TREM2: Potential therapeutic targeting of microglia for Alzheimer's disease. *Biomed. Pharmacother.* **2023**, *165*, 115218. [CrossRef] [PubMed]
56. Bhattacharya, A.; Biber, K. The microglial ATP-gated ion channel P2X7 as a CNS drug target. *Glia* **2016**, *64*, 1772–1787. [CrossRef] [PubMed]
57. Pajarillo, E.; Rizor, A.; Lee, J.; Aschner, M.; Lee, E. The role of astrocytic glutamate transporters GLT-1 and GLAST in neurological disorders: Potential targets for neurotherapeutics. *Neuropharmacology* **2019**, *161*, 107559. [CrossRef] [PubMed]
58. Giaume, C.; Naus, C.C.; Sáez, J.C.; Leybaert, L. Glial Connexins and Pannexins in the Healthy and Diseased Brain. *Physiol. Rev.* **2021**, *101*, 93–145. [CrossRef] [PubMed]
59. Franklin, R.J.M.; Ffrench-Constant, C. Regenerating CNS myelin—From mechanisms to experimental medicines. *Nat. Rev. Neurosci.* **2017**, *18*, 753–769. [CrossRef] [PubMed]
60. George, J. TREM2 as an evolving therapeutic target in Alzheimer's disease. *Neural Regen. Res.* **2023**, *18*, 2680–2681. [CrossRef] [PubMed]
61. Peng, L.; Fang, Z.; Zhang, W.; Rao, G.W.; Zheng, Q. Recent advances in colony stimulating factor-1 receptor (CSF1R) inhibitors. *Biochem. Pharmacol.* **2025**, *242*, 117187. [CrossRef] [PubMed]
62. Lubetzki, C.; Zalc, B.; Williams, A.; Stadelmann, C.; Stankoff, B. Remyelination in multiple sclerosis: From basic science to clinical translation. *Lancet Neurol.* **2020**, *19*, 678–688. [CrossRef] [PubMed]
63. Hanamsagar, R.; Bilbo, S.D. Sex differences in neurodevelopmental and neurodegenerative disorders: Focus on microglial function and neuroinflammation during development. *J. Steroid Biochem. Mol. Biol.* **2016**, *160*, 127–133. [CrossRef] [PubMed]
64. Rao, Y.; Bai, Y.; Li, X.; Du, B.; Peng, B. The evolution of microglia replacement: A new paradigm for CNS disease therapy. *Cell Stem Cell* **2025**, *32*, 1807–1832. [CrossRef] [PubMed]
65. Deczkowska, A.; Keren-Shaul, H.; Weiner, A.; Colonna, M.; Schwartz, M.; Amit, I. Disease-Associated Microglia: A Universal Immune Sensor of Neurodegeneration. *Cell* **2018**, *173*, 1073–1081. [CrossRef] [PubMed]
66. Campana, W.M. Schwann cells: Activated peripheral glia and their role in neuropathic pain. *Brain Behav. Immun.* **2007**, *21*, 522–527. [CrossRef] [PubMed]
67. Jessen, N.A.; Munk, A.S.; Lundgaard, I.; Nedergaard, M. The Glymphatic System: A Beginner's Guide. *Neurochem. Res.* **2015**, *40*, 2583–2599. [CrossRef] [PubMed]
68. van der Graaf, P.H.; Benson, N. Systems pharmacology: Bridging systems biology and pharmacokinetics-pharmacodynamics (PKPD) in drug discovery and development. *Pharm. Res.* **2011**, *28*, 1460–1464. [CrossRef] [PubMed]
69. Araque, A.; Parpura, V.; Sanzgiri, R.P.; Haydon, P.G. Tripartite synapses: Glia, the unacknowledged partner. *Trends Neurosci.* **1999**, *22*, 208–215. [CrossRef] [PubMed]
70. Joan Abbott, N. Are glial cells excitable after all? *Trends Neurosci.* **1985**, *8*, 141–142. [CrossRef]
71. Demmings, M.D.; da Silva Chagas, L.; Traetta, M.E.; Rodrigues, R.S.; Acutain, M.F.; Barykin, E.; Datusalia, A.K.; German-Castelan, L.; Mattera, V.S.; Mazengenya, P.; et al. (Re)building the nervous system: A review of neuron-glia interactions from development to disease. *J. Neurochem.* **2025**, *169*, e16258. [CrossRef] [PubMed]
72. Small, S.L. Precision neurology. *Ageing Res. Rev.* **2025**, *104*, 102632. [CrossRef] [PubMed]

73. De Luca, C.; Colangelo, A.M.; Virtuoso, A.; Alberghina, L.; Papa, M. Neurons, Glia, Extracellular Matrix and Neurovascular Unit: A Systems Biology Approach to the Complexity of Synaptic Plasticity in Health and Disease. *Int. J. Mol. Sci.* **2020**, *21*, 1539. [CrossRef] [PubMed]
74. García-Domínguez, M. Interplay Between Aging and Glial Cell Dysfunction: Implications for CNS Health. *Life* **2025**, *15*, 1498. [CrossRef] [PubMed]
75. Müller, L.; Di Benedetto, S.; Müller, V. Influence of biological sex on neuroinflammatory dynamics in the aging brain. *Front. Aging Neurosci.* **2025**, *17*, 1670175. [CrossRef] [PubMed]
76. Liu, Y.C.; Eyo, U.B.; Lu, T.Y. Dynamic glia in the living brain: Insights into glial physiology and function from in vivo imaging. *J. Neurophysiol.* **2026**, *135*, 11–27. [CrossRef] [PubMed]
77. Ahmad, S.; Srivastava, R.K.; Singh, P.; Naik, U.P.; Srivastava, A.K. Role of Extracellular Vesicles in Glia-Neuron Intercellular Communication. *Front. Mol. Neurosci.* **2022**, *15*, 844194. [CrossRef] [PubMed]
78. Guido, G.; Preziosa, P.; Filippi, M.; Rocca, M.A. TSPO PET in multiple sclerosis: Emerging insights into pathophysiology, prognosis, and treatment monitoring. *Mult. Scler. Relat. Disord.* **2025**, *100*, 106546. [CrossRef] [PubMed]
79. Martinez-Perez, D.A.; McGlothan, J.L.; Rodichkin, A.N.; Abilmouna, K.; Bursac, Z.; Lopera, F.; Villegas-Lanau, C.A.; Guilarte, T.R. Amyloid-β plaque-associated microglia drive TSPO upregulation in Alzheimer's disease. *Acta Neuropathol.* **2025**, *150*, 6. [CrossRef] [PubMed]
80. Pathak, A.; Theagarajan, R.; Rizqi, M.M.; Nugraha, A.S.; Boruah, T.; Pratiksha; Kumar, H.; Naik, B.; Yadav, S.; Jha, A.K.; et al. AI-enabled drug and molecular discovery: Computational methods, platforms, and translational horizons. *Discov. Mol.* **2025**, *2*, 32. [CrossRef]
81. Correale, J. Glial Plasticity and Dysfunction: Mechanistic Insights and Therapeutic Opportunities in Neurodegeneration. *J. Neurochem.* **2026**, *170*, e70414. [CrossRef] [PubMed]
82. Medina-Franco, J.L.; Giulianotti, M.A.; Welmaker, G.S.; Houghten, R.A. Shifting from the single to the multitarget paradigm in drug discovery. *Drug Discov. Today* **2013**, *18*, 495–501. [CrossRef] [PubMed]
83. Kulkarni, V.S.; Alagarsamy, V.; Solomon, V.R.; Jose, P.A.; Murugesan, S. Drug Repurposing: An Effective Tool in Modern Drug Discovery. *Russ. J. Bioorg Chem.* **2023**, *49*, 157–166. [CrossRef] [PubMed]
84. Schwartz, E.K.C.; De Aquino, J.P.; Sofuoglu, M. Glial modulators as novel therapeutics for comorbid pain and opioid use disorder. *Br. J. Clin. Pharmacol.* **2024**, *90*, 3054–3066. [CrossRef] [PubMed]
85. Jones, J.D. Potential of Glial Cell Modulators in the Management of Substance Use Disorders. *CNS Drugs* **2020**, *34*, 697–722. [CrossRef] [PubMed]
86. Gilron, I.; Xiao, M.Z.X.; Balanaser, M.; Carley, M.; Ghasemlou, N.; Salter, M.W.; Hutchinson, M.R.; Moulin, D.E.; Moore, R.A.; Ross-White, A. Glial-modulating agents for the treatment of pain: Protocol for a systematic review. *BMJ Open* **2022**, *12*, e055713. [CrossRef] [PubMed]
87. Afridi, R.; Tsuda, M.; Ryu, H.; Suk, K. The Function of Glial Cells in the Neuroinflammatory and Neuroimmunological Responses. *Cells* **2022**, *11*, 659. [CrossRef] [PubMed]
88. Serrano, D.R.; Luciano, F.C.; Anaya, B.J.; Ongoren, B.; Kara, A.; Molina, G.; Ramirez, B.I.; Sánchez-Guirales, S.A.; Simon, J.A.; Tomietto, G.; et al. Artificial Intelligence (AI) Applications in Drug Discovery and Drug Delivery: Revolutionizing Personalized Medicine. *Pharmaceutics* **2024**, *16*, 1328. [CrossRef] [PubMed]
89. Verma, V.; Kumar, D. Artificial intelligence and machine learning in drug discovery: From lead discovery to clinical validation (2020–2025). *Lett. Drug Des. Discov.* **2025**, *22*, 100341. [CrossRef]
90. Wang, J.; Sun, Z.; Zhou, Y.; Wang, L.; Liu, J. Advances in the pathophysiological study of brain development: Application of cerebral organoid combined with Spatial omics technology. *Stem Cell Res. Ther.* **2026**, *17*, 88. [CrossRef] [PubMed]
91. Pazzin, D.B.; Previato, T.T.R.; Budelon Gonçalves, J.I.; Zanirati, G.; Xavier, F.A.C.; da Costa, J.C.; Marinowic, D.R. Induced Pluripotent Stem Cells and Organoids in Advancing Neuropathology Research and Therapies. *Cells* **2024**, *13*, 745. [CrossRef] [PubMed]
92. Papamichail, L.; Koch, L.S.S.; Veerman, D.; Broersen, K.; van der Meer, A.D. Organoids-on-a-chip: Microfluidic technology enables culture of organoids with enhanced tissue function and potential for disease modeling. *Front. Bioeng. Biotechnol.* **2025**, *13*, 1515340. [CrossRef] [PubMed]
93. Cuní-López, C.; Stewart, R.; Oikari, L.E.; Nguyen, T.H.; Roberts, T.L.; Sun, Y.; Guo, C.C.; Lupton, M.K.; White, A.R.; Quek, H. Advanced patient-specific microglia cell models for pre-clinical studies in Alzheimer's disease. *J. Neuroinflamm.* **2024**, *21*, 50. [CrossRef] [PubMed]
94. Möller, T.; Boddeke, H.W. Glial cells as drug targets: What does it take? *Glia* **2016**, *64*, 1742–1754. [CrossRef] [PubMed]
95. Chen, K.; Stieger, K.C.; Kozai, T.D. Challenges and opportunities of advanced gliomodulation technologies for excitation-inhibition balance of brain networks. *Curr. Opin. Biotechnol.* **2021**, *72*, 112–120. [CrossRef] [PubMed]
96. Garden, G.A.; Campbell, B.M. Glial biomarkers in human central nervous system disease. *Glia* **2016**, *64*, 1755–1771. [CrossRef] [PubMed]

97. Zeng, W.; Wu, H.; Huang, Y. Multiple sclerosis: Glial cell activation—Biomarker advances and their translational significance. *Sci. Prog.* **2025**, *108*, 368504251390710. [CrossRef] [PubMed]
98. Noh, M.Y.; Kwon, H.S.; Kwon, M.S.; Nahm, M.; Jin, H.K.; Bae, J.S.; Kim, S.H. Biomarkers and therapeutic strategies targeting microglia in neurodegenerative diseases: Current status and future directions. *Mol. Neurodegener.* **2025**, *20*, 82. [CrossRef] [PubMed]
99. Türkegün Şengül, M.; Nemutlu Samur, D. Glial biomarkers improve classification of cognitive impairment: An explainable artificial intelligence study using CSF biomarkers. *Front. Neurol.* **2026**, *17*, 1787915. [CrossRef] [PubMed]
100. Huang, H.; He, W.; Tang, T.; Qiu, M. Immunological Markers for Central Nervous System Glia. *Neurosci. Bull.* **2023**, *39*, 379–392. [CrossRef] [PubMed]
101. Bezzi, P.; Magnaghi, V.; Paolicelli, R.C.; Hornung, J.P. Editorial: Glial heterogeneity: Impact on neuronal function and dysfunction. *Front. Neuroanat.* **2023**, *17*, 1249919. [CrossRef] [PubMed]
102. Li, Y.; Lai, D.; Li, R.; Chen, H.; Huang, X.; Ning, J. A Biomarker Signature-Guided Clinical Trial Design for Precision Medicine. *Stat. Med.* **2025**, *44*, e70103. [CrossRef] [PubMed]
103. Makkar, S.K. Advances in RNA-based therapeutics: Current breakthroughs, clinical translation, and future perspectives. *Front. Genet.* **2025**, *16*, 1675209. [CrossRef] [PubMed]
104. Mehdizadeh, S.; Mamaghani, M.; Hassanikia, S.; Pilehvar, Y.; Ertas, Y.N. Exosome-powered neuropharmaceutics: Unlocking the blood-brain barrier for next-gen therapies. *J. Nanobiotechnol.* **2025**, *23*, 329. [CrossRef] [PubMed]
105. Zhou, L.; Kodidela, S.; Godse, S.; Thomas-Gooch, S.; Kumar, A.; Raji, B.; Zhi, K.; Kochat, H.; Kumar, S. Targeted Drug Delivery to the Central Nervous System Using Extracellular Vesicles. *Pharmaceuticals* **2022**, *15*, 358. [CrossRef] [PubMed]
106. Khan, S.N.; Danishuddin; Khan, M.W.A.; Guarnera, L.; Akhtar, S.M.F. Multi-modal AI in precision medicine: Integrating genomics, imaging, and EHR data for clinical insights. *Front. Artif. Intell.* **2025**, *8*, 1743921. [CrossRef] [PubMed]
107. Alharthi, S. AI-powered in silico twins: Redefining precision medicine through simulation, personalization, and predictive healthcare. *Saudi Pharm. J.* **2025**, *34*, 1. [CrossRef] [PubMed]
108. Seyhan, A.A.; Carini, C. Artificial Intelligence in drug discovery and development: Current landscape, challenges, and future perspectives. *Crit. Rev. Oncol./Hematol.* **2026**, *226*, 105461. [CrossRef] [PubMed]
109. Ekins, S.; Lane, T.R. Applications of artificial intelligence in drug discovery for neurological diseases. *Neurotherapeutics* **2025**, *22*, e00624. [CrossRef] [PubMed]
110. Gazerani, P. Toward a Digital Twin-Inspired Framework for Studying Trigeminal Satellite Glial Cell Dynamics in Craniofacial Pain: A Hypothesis. *Neuroglia* **2026**, *7*, 7. [CrossRef]

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.