Frontiers in Bioscience Landmark

Front. Biosci. (Landmark Ed) **2026**; 31(8): 48402
https://doi.org/10.31083/FBL48402

Review

Mechanism-Targeted Therapeutic Strategies for Traumatic Brain Injury: From Molecular Pathways to Functional Recovery

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Academic Editor: Wei-Lin Jin
Submitted: 20 November 2025 Revised: 8 March 2026 Accepted: 12 March 2026 Published: 18 August 2026

Abstract

Traumatic brain injury (TBI) is characterized by a "translational paradox", where robust preclinical successes rarely achieve clinical efficacy. This review provides a critical appraisal of emerging therapeutics, moving beyond traditional silos to propose a unified, stage-dependent roadmap for neurorestoration. Reflecting on translational insights from past trials, specifically the limitations of standardized timing and phenotypic heterogeneity, we introduce the "Temporal Precision Medicine" framework. Central to this synthesis is the Dual-Axis Theory, which posits that successful emerging modalities, including repurposed agents such as glibenclamide, amantadine, and statins, alongside cell-free biologics and neuromodulation, converge on two shared pathological targets: the Inflammatory Axis (M1-to-M2 microglial polarization) and the Metabolic Axis (restoration of mitochondrial bioenergetics). We operationalize these biological insights into a Triple-Axis Framework, a dynamic clinical roadmap that aligns stage-dependent interventions with phase-specific biomarkers and pathological mechanisms. By integrating these biological signals with bioengineered delivery systems and artificial intelligence (AI)-driven precision phenotyping, the field can transition from acute neuroprotection toward genuine circuit-level regeneration. We conclude with a blueprint for the next generation of TBI trials, emphasizing biomarker-based stratification and multidimensional endpoints to bridge the translational gap.

Keywords: biomarkers, pharmacological; brain injuries, traumatic; drug repurposing; Dual-Axis Theory; neuroinflammatory response; neuroprotection; Temporal Precision Medicine

1. Introduction

Traumatic brain injury (TBI) represents one of the most pervasive and complex challenges in modern medicine. Often referred to as the "silent epidemic", TBI accounts for millions of emergency department visits annually and serves as the leading cause of death and disability among young adults [1,2]. The clinical presentation of TBI is as variable as its etiology. Patients may present across a spectrum of consciousness, ranging from transient confusion and concussion to prolonged coma, vegetative states, or minimally conscious states [3]. Beyond the acute phase, the sequelae of TBI are profound and pervasive. Survivors frequently endure chronic cognitive deficits (impaired memory and executive function) and neuropsychiatric symptoms (depression, anxiety, and personality changes) that severely impact their ability to return to work and overall quality of life [1]. This burden of disease transforms TBI from a singular event into a lifelong chronic condition requiring multidisciplinary management [4,5]. However, characterizing TBI merely by its epidemiology obscures the profound biological and logistical complexities of the disease. Unlike ischemic stroke, which presents a focal vascular occlusion, TBI is a heterogeneous disorder involving diffuse biomechanical forces that trigger a multilayered cascade of cellular and molecular events [1].

The initial mechanical impact sets in motion a secondary injury response characterized by blood–brain barrier (BBB) disruption, excitotoxic glutamate release, mitochondrial failure, and a sterile neuroinflammatory response [6,7,8,9]. While these mechanisms are well understood individually, the clinical translation of therapies targeting them has been disappointing. Over 30 Phase III clinical trials, evaluating agents ranging from progesterone to erythropoietin, have failed to demonstrate benefit in human populations, despite robust efficacy in rodent models [10,11,12]. This "translational gap" suggests that the traditional reductionist approach, targeting a single pathway with a single agent, is insufficient for the multifactorial landscape of human TBI [13]. Current research is therefore pivoting toward a multimodal and precision medicine framework. This paradigm shift recognizes that TBI is not a static event but a dynamic process with distinct temporal windows: an acute phase dominated by a metabolic crisis, a subacute phase of immunomodulation, and a chronic phase of synaptic reorganization.

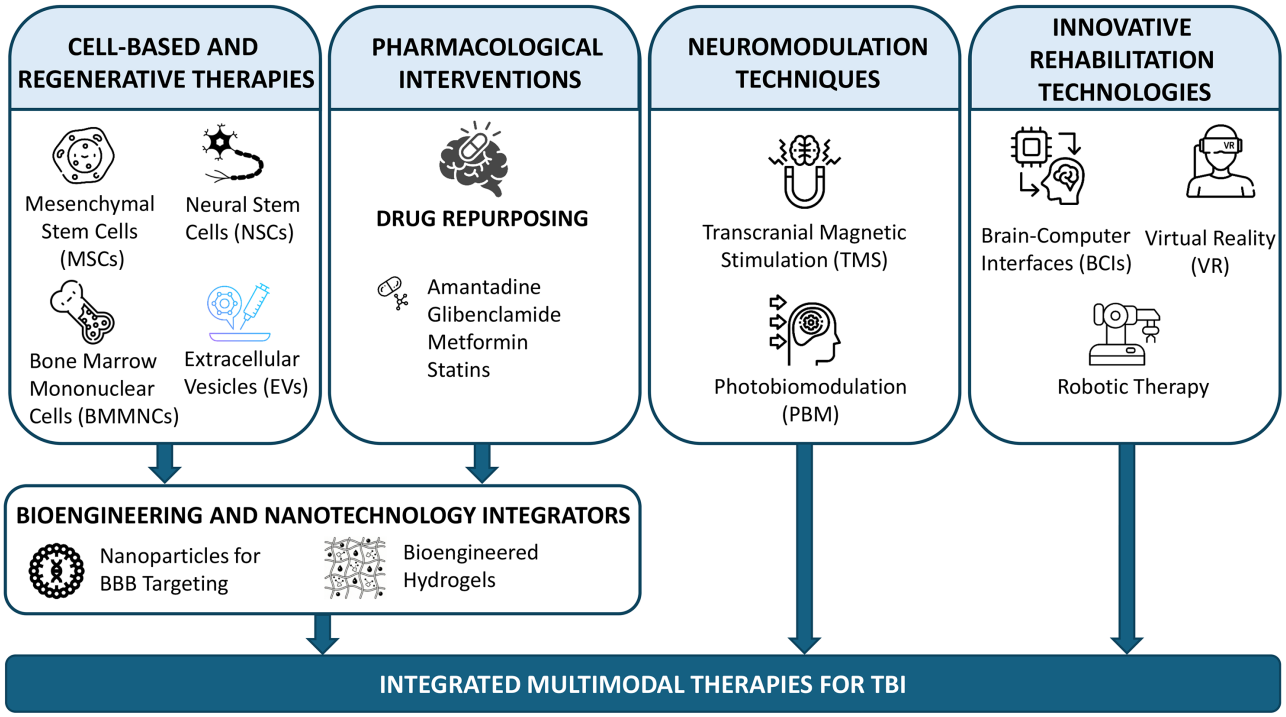

Fig. 1. Conceptual framework for the advancement of traumatic brain injury (TBI) therapeutics. This schematic provides a comprehensive overview of the emerging therapeutic landscape for TBI, categorized by primary modality and delivery mechanism. The framework highlights four distinct pillars of intervention: (1) Cell-Based and Regenerative Therapies: Encompassing MSCs, NSCs, BMMNCs, and EVs. (2) Pharmacological Interventions: Emphasizing drug repurposing strategies for agents such as amantadine, glibenclamide, metformin, and statins. (3) Neuromodulation Techniques: Including TMS and PBM. (4) Innovative Rehabilitation Technologies: Integrating BCIs, VR, and robotic therapy. Central to this model are the Bioengineering and Nanotechnology Integrators, which serve as the essential delivery vehicles and structural scaffolds necessary to bridge the translational gap between biological potential and clinical efficacy. These platforms optimize targeted delivery and localized support of biological and pharmacological agents within the hostile injury environment. Ultimately, the convergence of these individual and engineered approaches aims to establish Integrated Multimodal Therapies for TBI, providing a comprehensive strategy to overcome the "translational paradox" where single-target agents have historically failed to achieve clinical recovery. All figures were manually designed, organized, and rendered using Microsoft PowerPoint. Individual medical icons and vector elements were obtained from Flaticon (https://www.flaticon.com) under a free license for academic publication. Abbreviations: BBB, blood–brain barrier; BCIs, brain-computer interfaces; BMMNCs, bone marrow mononuclear cells; EVs, extracellular vesicles; MSCs, mesenchymal stem cells; NSCs, neural stem cells; PBM, photobiomodulation; TBI, traumatic brain injury; TMS, transcranial magnetic stimulation; VR, virtual reality.

Rationale for a Multidisciplinary Review: Historic therapeutic failures in TBI have often resulted from viewing pharmacological, biological, and engineering strategies in isolation. For instance, the efficacy of stem cell transplantation is increasingly dependent on bioengineered scaffolds for delivery, while neuroprotective drugs are being reimagined through nanoparticle targeting [14]. Therefore, this review deliberately adopts a broad scope, synthesizing advances across regenerative medicine, drug repurposing, and neuro-engineering (Fig. 1). By integrating these distinct domains, we aim to provide a holistic framework that identifies synergistic opportunities for overcoming the translational barriers that have long plagued TBI research.

2. Search Strategy and Selection Criteria

To ensure a rigorous and current synthesis of the literature, we conducted a comprehensive search of the PubMed, Scopus, and Web of Science databases for articles published between January 2000 and February 2026. Priority was given to high-impact studies published in the last five years (2020–2025) to capture the most recent translational advances. Search terms included combinations of keywords such as "Traumatic Brain Injury", "TBI", "Neuroprotection", "Mesenchymal Stem Cells", "Drug Repurposing", "Nanoparticles", "Neuromodulation", and "Bioengineering". Inclusion criteria focused on peer-reviewed references regarding therapeutic mechanisms, preclinical efficacy, and clinical trial outcomes. To capture the most current translational pipeline, we expanded the search to

include clinical trial registry records and preprints. Conversely, we excluded sources focusing solely on epidemiology, purely diagnostic biomarkers without therapeutic relevance, or general biomaterial manufacturing principles unrelated to neurotrauma. Data selection was guided by a critical evaluation framework that prioritized studies addressing the "translational gap", specifically those comparing animal model outcomes with human clinical realities. In total, 113 articles were selected for detailed analysis.

3. The Complexity of Traumatic Brain Injury: A Temporal Framework

Understanding the failure of past therapies requires a deep appreciation of the temporal and spatial heterogeneity of TBI pathology. Rather than a singular event, TBI is an evolving disease process that presents distinct therapeutic targets at different stages [7,15]. To align with contemporary guidelines, we adopt the temporal boundaries established by the recent NIH-NINDS Traumatic Brain Injury Classification and Nomenclature Initiative: acute (0–24 hours), subacute (1–30 days), and chronic (>30 days) [15]. However, while these definitions provide a necessary heuristic scaffold, human TBI pathophysiology remains highly dynamic. Underlying biological cascades, such as neuroinflammation and metabolic dysfunction, rarely adhere to strict timepoints; instead, they are continuous, frequently overlapping processes that vary substantially across individual injury phenotypes.

3.1 Current Clinical Management: The Standard of Care

Despite the proliferation of experimental therapies, the current standard of care for TBI remains largely supportive, adhering to evidence-based guidelines established by the Brain Trauma Foundation [16].

3.1.1 Emergency and Acute Management

The primary objective in the acute setting is the prevention of secondary injury by maintaining adequate cerebral perfusion pressure (CPP) and controlling intracranial pressure (ICP). Standard interventions include osmotherapy (mannitol or hypertonic saline) to reduce cerebral edema, sedation (e.g., propofol) to lower metabolic demand, and surgical decompressive craniectomy for refractory hypertension [17]. Continuous multimodality monitoring, tracking ICP, brain tissue oxygenation ($PbtO_2$), and cerebral blood flow is critical for guiding these clinical decisions, yet no pharmacological agent is currently approved to directly treat the neural injury itself [18].

3.1.2 Rehabilitation and Long-Term Care

Once medical stabilization is achieved, management shifts toward functional recovery. Standard physical and occupational therapies focus on restoring motor skills and adaptability. However, the management of chronic sequelae remains challenging. Mood and behavioral disorders are treated symptomatically; selective serotonin reuptake inhibitors (SSRIs) are commonly prescribed for depression and anxiety, while beta-blockers or mood stabilizers may be used to manage post-traumatic agitation and aggression [19,20]. Despite these interventions, a significant proportion of survivors suffer from persistent cognitive and emotional deficits, underscoring the urgent need for the disease-modifying therapies discussed in the following sections.

3.2 The Acute Phase: Mechanical Shearing and Metabolic Crisis (0–24 Hours)

The primary injury involves the direct mechanical tearing of axons and blood vessels. This immediate structural damage is largely irreversible [6]. However, it triggers a rapid "secondary injury" cascade characterized by massive depolarization and the release of excitatory neurotransmitters, primarily glutamate. This excitotoxicity leads to an influx of intracellular calcium, activating proteases that degrade the cytoskeleton and initiate apoptotic pathways [7,9]. Simultaneously, the physical disruption of the BBB allows peripheral immune cells to infiltrate the parenchyma, exacerbating cerebral edema and raising ICP [9,21]. Therapies in this phase must be neuroprotective and rapid. The goal is to stabilize the BBB, scavenge free radicals, and prevent the spread of necrosis. This explains the historical focus on agents like progesterone and hypothermia, which aim to dampen this acute metabolic storm [22].

3.3 The Subacute Phase: The Neuroinflammatory Transition (1–30 Days)

As the acute metabolic crisis subsides, the brain's resident immune cells, microglia, become the dominant actors. In the subacute phase, microglia can adopt either a pro-inflammatory (M1-like) phenotype, releasing cytokines that kill injured neurons, or a reparative (M2-like) phenotype that clears debris and releases neurotrophic factors [23,24]. This phase represents a critical "window of opportunity" for immunomodulatory therapies. Treatments such as mesenchymal stem cells (MSCs) or repurposed statins are theoretically most effective here, not by replacing lost neurons, but by steering the microglial response toward repair and preventing chronic neurodegeneration [25,26].

3.4 The Chronic Phase: Circuit Dysfunction and Neurodegeneration (>30 Days)

Long-term disability in TBI is often driven by diffuse axonal injury (DAI) that disrupts the functional connectivity of neural networks. Over months, this can evolve into chronic traumatic encephalopathy (CTE) or Alzheimer's-like dementia [6,27]. At this stage, acute neuroprotectants are ineffective. Instead, therapeutic strategies must focus on neuroplasticity and regeneration. Technologies such as Transcranial Magnetic Stimulation (TMS) and Photobiomodulation (PBM) aim to retrain damaged circuits and promote synaptic reorganization [28,29].

Table 1. Comprehensive summary of emerging TBI therapies.

Intervention	Primary axis & category	Target pathway	Route & timing	Clinical evidence	Key outcomes & limitations	References
MSCs	Inflammatory. Cell-Based Therapy	M1 → M2 microglial shift	IV; Subacute	Phase I/II (e.g., MATRIx)	Mixed: Safe but inconsistent efficacy. Limit: Pulmonary first-pass effect.	[30,31,34,35,36,37,38]
BMMNCs	Inflammatory. Cell-Based Therapy	Immunomodulation; growth factor secretion	IV; Ultra-acute → Subacute (<48 h)	Phase II (Pediatric)	Promising: Preserved white matter; reduced Intensive Care Unit (ICU) stay. Limit: Invasive harvesting.	[39,40,41]
Statins (e.g., Atorvastatin)	Inflammatory & Metabolic. Drug Repurposing	Anti-inflammatory; cerebral blood flow augmentation	PO; Subacute	Phase II (e.g., APT-TBI-01)	Improve GCS and survival; Healthy user bias; Need RCTs to confirm causality.	[52,53,54,55]
Glibenclamide	Inflammatory & Metabolic. Drug Repurposing	SUR1-TRPM4 Inhibition; BBB stability	IV; Acute → Subacute (<72 h)	Phase II (e.g., ASTRAL)	Promising: Reduces cytotoxic edema and midline shifts. Limit: Risk of hypoglycemia.	[59,60,61,62]
Extracellular vesicles (EVs)	Inflammatory. Cell-free Biologics	miRNA/Protein cargo transfer	IV/IN; Acute → Subacute	Preclinical/Phase I	Next-Gen: High BBB permeability; low immunogenicity. Limit: Lack of standardized isolation.	[32,33,45,46,47,48,49,50,51]
Metformin	Metabolic. Drug Repurposing	AMPK activation; mitochondrial repair	PO; Subacute	Phase II	Promising: Reduced S100B/NSE levels; metabolic recovery. Limit: GI side effects.	[56,57,58]
PBM (Light)	Metabolic. Neuromodulation	Mitochondrial ATP (cytochrome c oxidase)	Transcranial; Chronic	Small controlled studies and case series	Promising: Improved executive function and ATP production. Limit: Lack of standardized dosing.	[28,69,70,71]
Amantadine	Metabolic. Inflammatory & Restorative. Drug Repurposing	NMDA Antagonism; Dopaminergic stimulation	PO/NG; Subacute → Chronic	Phase III (Historic); Phase II (MR-301)	Benchmark: Increased rate of functional improvement (DRS). Limit: Limited effect on focal pathology.	[63,64,65,66,67]
TMS (rTMS)	Restorative. Neuromodulation	Cortical excitability; LTP promotion	Non-invasive; Chronic	Phase II	Promising: "Re-recruits" dormant pathways; improves processing speed. Limit: High phenotypic variability	[28,29,68]
NSCs	Inflammatory & Restorative. Cell-Based Therapy	Neuronal/Glial differentiation	Intracerebral; Subacute → Chronic	Investigational	Potential: True tissue replacement. Limit: Survival <5% without scaffolds.	[42,43,44]
Hydrogels/Scaffolds	Restorative. Bioengineering	Physical matrix provision; ECM mimicry	Surgical; Subacute	Preclinical	Structural: Supports NSC survival; bridging of necrotic cavities. Limit: Requires invasive craniotomy.	[76,77,78,79]
Nanoparticles	Integrator. Nanotechnology	BBB crossing; Targeted delivery; "Trojan Horse" strategy	IV; Acute	Preclinical	Experimental: Superior delivery of payloads. Limit: Long-term neurotoxicity concerns.	[72,73,74,75]

Abbreviations: AMPK, AMP-activated protein kinase; BBB, blood–brain barrier; BMMNCs, bone marrow mononuclear cells; DRS, disability rating scale; ECM, extracellular matrix; EVs, extracellular vesicles; GCS, Glasgow Coma Scale; IN, intranasal; IV, intravenous; LTP, long-term potentiation; MSCs, mesenchymal stem cells; NG, nasogastric; NMDA, N-methyl-D-aspartate; NSCs, neural stem cells; NSE, neuron-specific enolase; PBM, photobiomodulation; PO, *Per Os* (by mouth); RCTs, randomized controlled trials; rTMS, repetitive transcranial magnetic stimulation; S100B, S100 calcium-binding protein B.

4. Emerging TBI Treatments: Mechanisms and Translation

The therapeutic landscape for TBI is shifting from a search for "silver bullets" to a nuanced application of multimodal interventions. This section critically evaluates emerging strategies, categorized by their primary modality, while explicitly assessing the discrepancy between preclinical mechanisms and clinical realities. To provide a comprehensive overview of this complex landscape, we summarize the mechanism of action, preclinical evidence, clinical status, and key limitations of each therapeutic class in Table 1 (Ref. [28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79]).

4.1 Cell-Based and Regenerative Therapies

Regenerative cell therapies represent the idealized standard for addressing the complex pathology of TBI. However, the conceptual framework has evolved significantly: the initial goal of direct neuronal replacement has largely been superseded by the "bystander effect" hypothesis, where transplanted cells act as "living drug factories" to modulate the hostile injury microenvironment.

4.1.1 Mesenchymal Stem Cells (MSCs)

MSCs are multipotent stromal cells isolated from bone marrow, adipose tissue, or umbilical cord blood. They remain the most widely studied cell type in TBI research due to their low immunogenicity and ethical ease of access [80].

Preclinical Mechanisms: In preclinical models, their efficacy operates through a distinct mechanism: unlike neural stem cells, MSCs rarely differentiate into functional neurons *in vivo*. Instead, they function as "drugstores" for the injured brain, secreting a secretome cocktail of trophic factors (brain-derived neurotrophic factor [BDNF], vascular endothelial growth factor [VEGF], nerve growth factor [NGF]) and extracellular vesicles (EVs) [30,31,32]. Mechanistically, MSCs modulate the M1/M2 microglial axis, shifting the immune response from a pro-inflammatory state to a reparative one [33,34]. Consequently, rodent studies consistently demonstrate that intravenous (IV) MSC administration reduces lesion volume and improves spatial memory, even when cell engraftment is minimal [35,81].

Clinical Translation & Limitations: Despite these robust preclinical mechanisms, clinical translation has proven complex. While Phase I and early Phase II trials have successfully confirmed the safety, feasibility, and low immunogenicity of intravenous MSC infusions in severe TBI patients, efficacy data remain mixed and largely exploratory. While some small clinical cohorts have demonstrated encouraging trends toward improved motor scores and altered inflammatory cytokine profiles, definitive Phase III efficacy is currently hindered by major physical delivery barriers [36]. A critical limitation is the "Pulmonary First-Pass Effect", where the majority of IV-infused MSCs become trapped in the lung capillaries, preventing them from reaching the brain [37]. This failure of delivery suggests that future trials must pivot toward alternative routes (e.g., intranasal, intrathecal) or utilize cell-free exosomes to bypass size constraints. To address these variables, modern clinical efforts, such as the adaptive Phase II MATRIx trial, are now shifting focus toward dose-optimization and utilizing fluid biomarkers like neurofilament light chain (NfL) to definitively track *in vivo* target engagement and neurorestoration, rather than relying solely on blunt clinical scales [38].

4.1.2 Bone Marrow Mononuclear Cells (BMMNCs)

BMMNCs are a heterogeneous population containing MSCs, hematopoietic progenitor cells, and endothelial progenitor cells. Their primary translational advantage is autologous feasibility; unlike pure MSCs that require weeks of culture, BMMNCs can be harvested and reinfused within hours of injury. Preclinical evidence suggests this rapid intervention stabilizes the blood–brain barrier (BBB) and promotes angiogenesis [39,40].

Clinical Evidence: Clinically, a Phase II pediatric trial demonstrated that acute autologous BMMNC transplantation in children with severe TBI [Glasgow Coma Scale (GCS) score 3–8] was not only safe but was associated with preserved white matter volume and reduced time in intensive care [39,41]. This success in pediatric populations, which possess higher intrinsic neuroplasticity, highlights the importance of patient stratification in clinical trial design. However, a critical limitation of these early phase studies is the lack of direct correlation between this radiological preservation and long-term functional recovery (e.g., Glasgow Outcome Scale-Extended [GOS-E] scores) [39]. Future trials must demonstrate that structural sparing translates into tangible cognitive or motor benefits to justify the invasive nature of the procedure.

4.1.3 Neural Stem Cells (NSCs)

NSCs are uniquely capable of differentiating into neurons, astrocytes, and oligodendrocytes, offering the potential for true tissue replacement [42].

Translational Challenge: The hostile, necrotic cavity of a TBI lesion limits the survival of transplanted NSCs (often <5% survival rate) [36,43]. Without a supportive bioengineered scaffold (discussed in Section 4.4), direct injection of NSCs often results in cell death or failure to integrate into existing neural circuits. Consequently, NSCs remain largely investigational compared to the more clinically advanced MSCs. Furthermore, while traditionally viewed through the lens of chronic tissue replacement, NSC therapy also serves a critical role during the subacute phase. When administered in this earlier window, NSCs act primarily along the inflammatory axis, secreting factors that dampen the inflammatory cascade, stabilize the BBB, and

provide early neuroprotection before permanent glial scarring is established [44].

4.1.4 Cell-Free Biologics: Extracellular Vesicles (EVs)

Rationale and Mechanism: Recent paradigm shifts in regenerative medicine suggest that the therapeutic efficacy of stem cells is largely mediated by paracrine signaling rather than cell replacement. EVs, particularly exosomes (30–150 nm), represent the bioactive "cargo" of this secretome, transporting microRNAs, lipids, and proteins that drive neurorepair [45,46]. Unlike whole cells, EVs can cross the BBB more efficiently and carry negligible risk of tumorigenesis or immune rejection [47].

Translational Status: Preclinical studies from 2020–2025 have demonstrated that MSC-derived exosomes significantly reduce neuroinflammation and improve functional recovery in TBI models [48,49]. However, clinical translation is currently hindered by a lack of standardization. The heterogeneity of EV cargo, which varies based on the donor cell's culture conditions, creates a major manufacturing hurdle. Rather than relying on the inconsistent natural secretome, future efforts should prioritize the engineering of vesicles for targeted delivery of miRNAs or growth factors, ensuring these modifications do not interfere with the particles' low immunogenicity and non-oncogenic nature [50,51].

4.2 Pharmacological Interventions: The Era of Drug Repurposing

Given the high cost and failure rate of developing novel neuroprotective drugs, the field has pivoted toward "drug repurposing", identifying existing Food and Drug Administration (FDA)-approved agents with pleiotropic neuroprotective properties [10].

4.2.1 Statins (HMG-CoA Reductase Inhibitors)

Mechanism: Beyond cholesterol lowering, statins (e.g., atorvastatin, simvastatin) exert powerful anti-inflammatory effects by inhibiting the isoprenylation of Rho GTPases. In TBI, upregulation of RhoA contributes to axonal growth cone collapse and apoptosis. By blocking this pathway, statins preserve cytoskeletal integrity and improve endothelial function [52,53].

Clinical Status: Observational studies indicate that patients on pre-injury statins have improved survival rates and higher GCS scores. However, randomized controlled trials (RCTs) are needed to rule out the "healthy user bias" often present in these retrospective analyses [54,55].

4.2.2 Metformin

Mechanism: Traditionally a diabetes drug, metformin is a potent activator of AMP-activated protein kinase (AMPK). In the context of TBI, AMPK activation serves as a "metabolic master switch", restoring mitochondrial bioenergetics and reducing oxidative stress [56,57]. Furthermore, metformin has been shown to inhibit the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) inflammatory pathway [56].

Clinical Status: A small pilot RCT (n = 30) demonstrated that metformin administration in the subacute phase reduced serum levels of S100 calcium-binding protein B (S100B) and neuron-specific enolase (NSE) (biomarkers of neuronal injury) [58]. While promising, the therapeutic window is debated, as early AMPK activation can arguably be detrimental if metabolic substrates are scarce.

4.2.3 Progesterone: A Lesson in Failure

The clinical evaluation of progesterone serves as a paradigmatic case study in the challenges of TBI translation.

Disconnect: In rodents, progesterone dramatically reduced edema and apoptosis [82]. Yet, two massive Phase III trials (PROTECT III and SYNAPSE) failed to show any benefit in human mortality or functional recovery [12,83,84].

Critical Analysis: This failure highlights the heterogeneity problem. The trials enrolled "all-comer" TBI patients rather than selecting those specifically with DAI or specific hormonal profiles. Furthermore, the dosing window effective in rats (who metabolize drugs rapidly) did not translate linearly to human pharmacokinetics, underscoring the limitations of standard scaling models [13,85].

4.2.4 Glibenclamide: Targeting Vascular Integrity and Edema

Mechanism: Beyond direct neuroprotection, emerging repurposing strategies increasingly target the neurovascular unit to prevent secondary edema. Glibenclamide (Glyburide), a sulfonylurea used in diabetes, has shown promise in preventing contusion expansion by inhibiting the SUR1-TRPM4 channel, a key driver of cytotoxic edema [59,60].

Clinical Status: The Operation Brain Trauma Therapy (OBTT) consortium recognized the drug as a 'top performer' for its robust ability to limit cerebral edema and lesion volume across multiple preclinical models [59,61]. Clinically, the translation of glibenclamide (formulated as intravenous BIIB093) advanced to the ASTRAL Phase II trial (NCT03954041). This trial was specifically designed to evaluate its efficacy in preventing contusion expansion and mitigating secondary cerebral edema in patients with moderate-to-severe TBI. While early clinical evaluations demonstrated an encouraging safety profile and biological plausibility for reducing midline shift, the definitive clinical path to market has been complicated. Although these targeted TBI programs showed significant clinical potential, their currently inactive status is largely a result of corporate portfolio prioritization rather than a demonstrated lack of clinical efficacy [62]. Similarly, inhibition of Matrix Metalloproteinases (MMPs), specifically MMP-9, has been

shown to preserve BBB tight junctions and reduce hemorrhagic conversion in preclinical models, though clinical translation remains in early stages [86].

4.2.5 Amantadine: The Benchmark for Dopaminergic Reactivation

Mechanism: Amantadine is a multi-target agent that exerts significant influence over early-stage pathological processes through anti-inflammatory action (downregulating microglial activation) and metabolic regulation (reducing oxidative stress), while simultaneously providing neurotrophic support [63]. Although clinically initiated during the subacute phase, the recommended administration window of 4 to 16 weeks means its restorative dopaminergic effects actively bridge the transition into the chronic phase of recovery [64].

Clinical Status: A landmark multicenter randomized controlled trial demonstrated that a four-week regimen significantly increased the rate of functional improvement on the Disability Rating Scale (DRS). While its precise mechanism is multifaceted, involving the upregulation of aromatic L-amino acid decarboxylase (AADC) and modulation of neuroinflammation, its success underscores the importance of targeting circuit-level arousal rather than just cellular survival [65,66,67].

4.3 Neuromodulation: Rewiring the Injured Brain

For patients in the chronic phase of TBI, where the primary pathology is circuit dysfunction rather than acute cell death, neuromodulation offers a non-invasive avenue for recovery.

4.3.1 Transcranial Magnetic Stimulation (TMS)

Mechanism: Repetitive TMS (rTMS) uses magnetic fields to induce electrical currents in the cortex. High-frequency stimulation (>5 Hz) promotes long-term potentiation (LTP), strengthening synaptic connections, while low-frequency stimulation (<1 Hz) induces long-term depression (LTD) [29]. In TBI, where DAI disrupts network connectivity, rTMS is used to "re-recruit" dormant pathways.

Emerging Data: Recent studies suggest rTMS also exerts neuroprotective effects by reducing oxidative stress and downregulating pro-inflammatory cytokines, suggesting a dual mechanism of action that addresses both the molecular and circuit-level pathologies of the injury [28,29,68].

4.3.2 Photobiomodulation (PBM)

Mechanism: PBM (Low-Level Light Therapy) utilizes near-infrared light to penetrate the skull. The primary chromophore is cytochrome c oxidase within the mitochondria. Photon absorption boosts electron transport chain efficiency, increasing ATP production and reducing reactive oxygen species (ROS) [28].

Clinical Utility: Small RCTs and case series have shown PBM improves executive function and cerebral blood flow in chronic TBI patients [69,70]. However, the field is plagued by a lack of standardization in dosimetry (wavelength, irradiance, and pulse frequency), making cross-study comparisons difficult [71].

4.4 Bioengineering and Nanotechnology

Bioengineering serves as the "integrator", providing the delivery vehicles necessary to make biological and pharmacological agents effective.

4.4.1 Nanoparticles for BBB Targeting

Challenge: The BBB prevents 98% of small-molecule drugs from entering the brain [72].

Solution: Recent advances in nanotechnology focus on "Trojan Horse" strategies. Polymeric (poly(lactic-co-glycolic acid) [PLGA]) and lipid-based nanoparticles can be surface-modified with ligands (e.g., transferrin) that bind to receptors on the brain endothelium, facilitating receptor-mediated transcytosis [73,74].

Critical Assessment: While engineered nanoparticles demonstrate significantly higher brain accumulation than free drugs in rodent models, concerns regarding long-term neurotoxicity and clearance (the "retention" problem) remain significant hurdles for FDA approval [75].

4.4.2 Bioengineered Hydrogels: From Passive Scaffolds to Active Therapeutics

Addressing the Mechanical Mismatch: Standard pharmaceutical interventions fail to address the physical reality of severe TBI: the formation of a fluid-filled necrotic cavity that acts as a physical barrier to axonal regeneration. Injectable hydrogels address this by mimicking the brain's native extracellular matrix (ECM) [76]. Unlike rigid implants, modern hydrogels are designed with specific viscoelastic and stress-relaxing properties that closely match the stiffness of native brain tissue, thereby minimizing mechanical stress on fragile, regenerating neural networks [76,77].

From Passive Support to Active Therapy: While currently restricted to preclinical rodent models, hydrogels have demonstrated efficacy as "active" depots that prevent drug washout and ensure sustained local delivery. Scaffolds loaded with dexamethasone have significantly reduced glial scarring and lesion volume by mitigating acute inflammation [87,88]. Similarly, hydrogels incorporating antioxidants like curcumin or neurotrophic factors like BDNF have successfully neutralized reactive oxygen species (ROS) and promoted neurite outgrowth in animal studies, preventing the neuronal atrophy typical of the chronic phase [89,90,91].

Next-Generation Functionalities: Emerging designs include conductive hydrogels that restore electrical signaling to guide reinnervation, as well as matrices that protect encapsulated Neural Stem Cells (NSCs) or exosomes from the hostile host environment [78,79]. Looking forward, the field is pivoting toward "stimuli-responsive" materials ca-

pable of releasing payloads in response to specific injury signals, while utilizing artificial intelligence (AI) to optimize scaffold porosity and degradation rates for eventual human translation [92,93].

5. Current Challenges and Future Outlook

While the therapeutic arsenal for TBI is expanding, the transition from bench to bedside remains fraught with obstacles. This section synthesizes the technological, biological, and methodological challenges defining the current landscape and proposes a strategic roadmap for the future.

5.1 Innovative Rehabilitation Technologies

As survival rates for severe TBI continue to improve, the burden of care is shifting from acute stabilization toward the complex challenges of long-term rehabilitation. In this context, the focus has moved beyond traditional physical therapy to advanced neurotechnologies that actively engage the brain's remaining capacity for change. Brain-Computer Interfaces (BCIs) have evolved from simple assistive tools into active rehabilitative instruments. While early BCIs focused on bypassing damaged neural pathways to grant patients control over external devices through electroencephalogram (EEG) signals, recent "closed-loop" systems represent a significant leap forward [94,95]. By delivering real-time feedback or direct cortical stimulation in response to specific brain activity, these systems aim to promote Hebbian plasticity, strengthening the synaptic connections between spared neural ensembles through repeated, synchronized activation.

Complementing this, Virtual Reality (VR) provides an immersive and enriched environment that is particularly well-suited for cognitive rehabilitation [96]. Unlike static, paper-and-pencil exercises, VR allows for the precise and dynamic manipulation of sensory input within a safe, controlled setting. This ecologically valid approach enables patients to practice real-world activities, such as navigating a virtual town or performing multi-step kitchen tasks, which facilitates the retraining of executive function and spatial memory. By integrating BCIs with these immersive VR scenes, researchers are creating high-engagement "neurofeedback" loops that offer superior sensory feedback, potentially accelerating the recovery of complex brain functions [97].

5.2 Artificial Intelligence (AI) and Precision Medicine

The promise of AI in neurotrauma lies in its capacity to decipher the immense heterogeneity of TBI. As the field moves beyond traditional statistics, machine learning algorithms trained on multidimensional datasets, spanning genomics, high-resolution neuroimaging, and real-time intensive care unit (ICU) vitals, are beginning to identify nonlinear correlations that were previously undetectable [98]. This shift is fundamentally transforming prognosis, moving the clinical focus away from broad, often inadequate categorizations like mild or severe, and toward "precision phenotyping". Such granularity enables a predictive approach to care, allowing clinicians to determine with greater accuracy which specific patients are likely to benefit from high-stakes interventions, such as decompressive craniectomy. Despite this potential, the integration of AI into the clinical workflow requires a cautious and critical assessment. A primary barrier to adoption is the 'black box' phenomenon, in which the lack of interpretability in algorithmic decision-making limits clinical trust [99]. Furthermore, these models are prone to overfitting; algorithms trained on narrow, single-center data frequently struggle with poor generalizability [100]. Before AI can truly become a standard of care, the field must address these interpretability gaps and the ethical concerns surrounding data bias to ensure that machine learning serves as a reliable partner in the neurointensive care unit.

5.3 Mechanistic Convergence: Unifying Pathways of Repair

Although this review categorizes therapies by modality, a critical synthesis reveals that successful interventions invariably converge on two shared pathological axes.

The Inflammatory Axis serves as a primary point of convergence; modalities as diverse as MSCs, vagus nerve stimulation (VNS), and statins all target a shared biological endpoint: the promotion of a reparative immune environment. This shift suggests that future combinatorial strategies should prioritize the synergistic dampening of the inflammatory cascade rather than the targeting of isolated receptors [10,101,102].

Simultaneously, the Metabolic Axis acts as a vital target for bioenergetic restoration. Approaches like PBM and metformin utilize distinct vectors to resolve the energetic crisis common across diverse TBI endotypes [28,56,103]. In this framework, Bioengineering acts as the essential integrator rather than a standalone therapy. Technologies like hydrogels and nanoparticles serve as the sophisticated "delivery vehicles" that allow these convergent biological signals to cross the blood–brain barrier and sustain their effects within the hostile injury environment.

5.4 The Translational Dilemma: Analyzing Past Failures

A foundational cause of this translational failure lies in the intrinsic biological limitations of preclinical animal models. The vast majority of preclinical success is derived from rodent models, which present severe anatomical and pharmacokinetic discrepancies when compared to human patients [13]. Because the rodent brain is lissencephalic (smooth) and possesses a significantly different white-to-gray matter ratio, the biomechanical forces of experimental impacts do not accurately replicate the complex, widespread diffuse axonal injury (DAI) characteristic of severe human TBI. Furthermore, rodents possess a vastly accelerated basal metabolic rate; consequently, the pharma-

cokinetic timelines for drug metabolism and the secondary injury cascades are highly compressed [85]. An acute therapeutic window that proves highly effective in a rodent model frequently fails to scale linearly to the complex, protracted pathophysiology of human injury, resulting in therapies that are fundamentally misaligned with human clinical timelines [13,85].

Beyond these preclinical challenges, as noted in the Introduction, the historical failure of trials like PROTECT III and SYNAPSE stems from three structural flaws [12,83,84]. First, phenotypic heterogeneity remains a significant hurdle; historic trials have often treated TBI as a monolithic entity rather than a collection of distinct injury endotypes [1,104]. Consequently, a drug specifically targeting axonal repair will inevitably fail in a patient cohort dominated by ischemic mass lesions, ultimately diluting the statistical signal of efficacy. Second, a "one-size-fits-all" timing mismatch often precludes therapeutic success. Because secondary injury cascades evolve at different rates depending on the nature of the primary insult, administering neuroprotective agents at fixed time points often misses the optimal therapeutic window for the individual patient. Finally, the field's reliance on insensitive endpoints, particularly the GOS-E, remains problematic [105]. As a coarse functional measure, the GOS-E frequently fails to capture subtle but clinically meaningful improvements in cognition, mood, or quality of life; this often leads to the abandonment of potentially beneficial drugs simply because they do not move the needle on a global, non-specific scale.

5.5 Temporal Precision: A Stage-Dependent Framework

To move forward, emerging therapies must be mapped onto the dynamic pathophysiological state of the brain, a concept we propose as "Temporal Precision Medicine". This framework recognizes that the success of an intervention depends entirely on its alignment with the evolving injury environment. In the Acute Phase (0–24 hours), the therapeutic priority is strictly neuroprotection. During this narrow window, targets such as excitotoxicity and BBB disruption are paramount. Drug repurposing strategies (e.g., glibenclamide or memantine) serve as the acute, rapid-response defense, targeted at stabilizing the neurovascular unit, blunting the immediate metabolic crisis, and mitigating early secondary damage [106,107]. As the injury transitions into the Subacute Phase (1–30 days), the clinical priority shifts toward immunomodulation and debris clearance. Stem cell therapies and cell-free biologics (e.g., MSCs, BMMNCs, and EVs) function as the subacute bridge. They are strategically deployed to leverage their paracrine secretome, operating primarily along the Inflammatory Axis to steer the microglial response and shift the hostile microenvironment from a state of secondary injury toward active repair [39,45,53]. Finally, in the Chronic Phase (months to years), the objective becomes regeneration and functional restoration. The pathological targets at this late stage are synaptic plasticity and large-scale network reorganization. Modalities like neuromodulation (rTMS and PBM) and technology-driven rehabilitation (e.g., BCIs and robotics) serve as the chronic restorative engines. They are utilized here to stimulate endogenous repair, engaging the remaining neural architecture to drive long-term synaptic plasticity and circuit-level recovery [28,29].

By strictly aligning therapeutic mechanisms with this biological timing, clinicians can finally avoid the "right drug, wrong time" failures that have historically plagued TBI clinical trials. It is this precise, stage-dependent sequencing of modalities that defines the practical utility of our proposed framework.

5.6 Strategic Roadmap: Actionable Strategies for Future Trials

To overcome the structural barriers that have historically stifled TBI research, future clinical trials must adopt a more sophisticated and dynamic methodology. Central to this evolution is biomarker-based stratification, which moves beyond the clinical limitations of the GCS [108]. The critical evolution in our approach lies in the operationalization of the Dual-Axis Theory into the Triple-Axis Framework. While the Dual-Axis Theory serves as the mechanistic foundation, positing that diverse therapeutic modalities converge on the Inflammatory and Metabolic axes to prevent secondary injury, the Triple-Axis Framework provides the actionable clinical roadmap. By integrating three vertical dimensions, Biomarker Signals (Axis 1), Pathological Mechanisms (Axis 2), and Interventions (Axis 3), this framework transforms static biological theory into a dynamic strategy for stage-dependent patient management.

In this clinical model, the 'Biomarker-Pivot' acts as the primary navigation tool. Acute elevations of glial fibrillary acidic protein (GFAP) and ubiquitin carboxyl-terminal hydrolase L1 (UCH-L1) act as a molecular 'stopwatch' for Phase I interventions, where the mechanism-target is the stabilization of the neurovascular unit and prevention of early secondary injury [109]. Subsequently, a rising lactate/pyruvate ratio acts as a critical metabolic signal, indicating the transition to Phase II. During this subacute window, the framework addresses the convergence of the Inflammatory and Metabolic axes, utilizing combined strategies like MSCs and metformin to achieve bioenergetic restoration and M2 microglial polarization [110]. Finally, the emergence of NfL and BDNF signals the transition to Phase III, identifying the precise moment the cerebral environment becomes receptive to restorative and plasticity-oriented therapies such as rTMS and intensive cognitive rehabilitation [111]. By timing interventions to these biological signals rather than fixed chronological days post-injury, researchers can significantly reduce the 'noise' of patient heterogeneity that has historically plagued Phase III trials (summarized in Fig. 2).

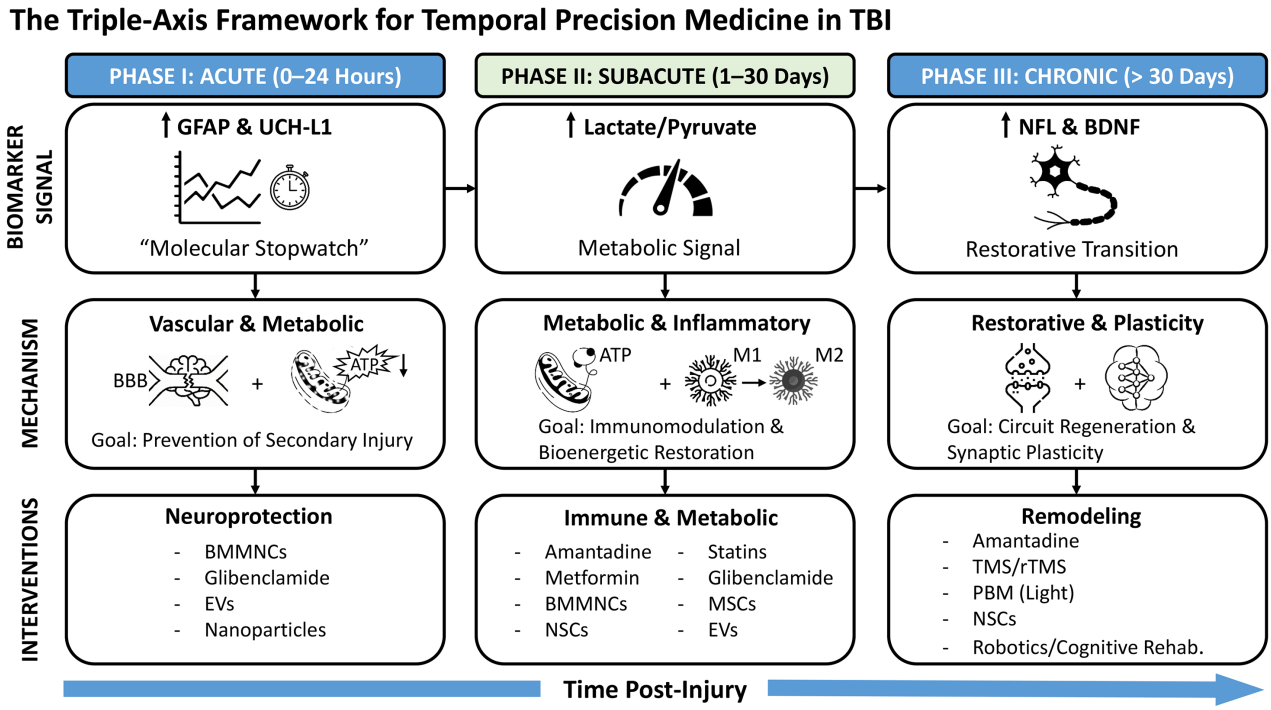

Fig. 2. The Triple-Axis Framework for Temporal Precision Medicine in traumatic brain injury (TBI). This schematic illustrates the operationalization of the Triple-Axis Framework, a dynamic clinical roadmap that aligns stage-dependent interventions with phase-specific biological signals and pathological mechanisms. The framework is structured across three chronological windows: Phase I (Acute, 0–24 hours), Phase II (Subacute, 1–30 days), and Phase III (Chronic, >30 d). Axis 1 (Biomarker Signal): Represents the "Biomarker-Pivot", identifying stage-specific indicators used to navigate therapeutic transitions. It highlights the progression from the acute "Molecular Stopwatch" (GFAP and UCH-L1) to subacute metabolic signals (Lactate/Pyruvate) and chronic restorative markers (NfL and BDNF). Axis 2 (Mechanism): Details the evolving pathophysiology and corresponding therapeutic goals. This axis maps the transition from preventing secondary injury (addressing BBB disruption and mitochondrial bioenergetic collapse) to achieving subacute immunomodulation (M1 to M2 polarization) and finally promoting chronic circuit regeneration and synaptic plasticity. Axis 3 (Interventions): Categorizes multimodal therapies by their optimal window of biological efficacy. Neuroprotective strategies (e.g., glibenclamide, BMMNCs) are prioritized in the acute phase, while Immune and Metabolic modulators (e.g., amantadine, metformin, MSCs) bridge into the subacute phase. Remodeling efforts in the chronic phase utilize neuromodulation and innovative rehabilitation technologies to drive long-term recovery. The vertical arrows indicate the alignment of phase-specific biomarkers with the underlying mechanism-target, while the horizontal arrow represents the temporal continuum of the "Temporal Precision Medicine" approach. The upward (↑) and downward (↓) arrows within the small panels indicate upregulation or elevation, and downregulation or reduction in expression levels, respectively. Abbreviations: ATP, adenosine triphosphate; BBB, blood-brain barrier; BDNF, brain-derived neurotrophic factor; BMMNCs, bone marrow mononuclear cells; GFAP, glial fibrillary acidic protein; MSCs, mesenchymal stem cells; NfL, neurofilament light chain; NSCs, neural stem cells; PBM, photobiomodulation; rTMS, repetitive transcranial magnetic stimulation; TBI, traumatic brain injury; UCH-L1, ubiquitin carboxyl-terminal hydrolase L1.

However, the successful implementation of this biomarker-pivot framework relies heavily on overcoming significant logistical barriers within the ICU [18]. Currently, the practical feasibility of real-time patient stratification is limited by assay turnaround times; point-of-care platforms capable of delivering rapid quantitative readouts for markers like GFAP and UCH-L1 are urgently needed to guide acute Phase I interventions [109]. Furthermore, standardizing sample collection, processing, and assay calibration across multicenter platforms remains a critical hurdle to ensure that dynamic metabolic signals, such as the lactate/pyruvate ratio, are interpreted with high fidelity and minimal inter-institutional variability [18,110].

Additionally, the rigid structure of traditional trials should give way to adaptive trial designs. By implementing adaptive platform trials, researchers can evaluate multiple therapies simultaneously and utilize interim data to drop ineffective arms or refine dosing regimens in real time [55]. This flexibility not only maximizes statistical power but also accelerates the identification of viable treatments.

Finally, the definition of clinical success must be expanded through the use of multidimensional endpoints. Rather than relying on a single global function score, future assessments should integrate high-resolution neuroimaging, such as Diffusion Tensor Imaging (DTI), with sensitive cognitive batteries like the NIH Toolbox and patient-reported outcomes [112,113]. This composite approach ensures that subtle but critical improvements in neural connectivity and cognitive quality of life are no longer overlooked.

6. Conclusion

TBI remains a formidable clinical challenge, yet the therapeutic landscape is undergoing a fundamental transformation. We are moving away from the reductionist search for a single "neuroprotective" agent and toward a multimodal, precision medicine approach. The integration of bioengineering with regenerative medicine and pharmacology offers new hope for bridging the translational gap. However, success depends on a critical pivot in research methodology. We must abandon the "one-size-fits-all" model in favor of the Triple-Axis Framework, which respects the heterogeneity of the injury and the temporal dynamics of recovery. By combining biomarker-driven patient stratification with mechanisms targeted to the inflammatory, metabolic, and restorative phases, the field will be better positioned to bridge the translational gap and advance the promise of preclinical science into meaningful clinical recovery.

Abbreviations

AADC, aromatic L-amino acid decarboxylase; AI, artificial intelligence; AMPK, AMP-activated protein kinase; BBB, blood–brain barrier; BCI, brain-computer interface; BDNF, brain-derived neurotrophic factor; BMMNCs, bone marrow mononuclear cells; CPP, cerebral perfusion pressure; CTE, chronic traumatic encephalopathy; DAI, diffuse axonal injury; DRS, disability rating scale; DTI, diffusion tensor imaging; ECM, extracellular matrix; EEG, electroencephalogram; EPO, erythropoietin; EVs, extracellular vesicles; FDA, U.S. Food and Drug Administration; GCS, Glasgow Coma Scale; GFAP, glial fibrillary acidic protein; GOS-E, Glasgow Outcome Scale-Extended; HMG-CoA, 3-hydroxy-3-methylglutaryl-coenzyme A; ICP, intracranial pressure; ICU, Intensive Care Unit; IN, intranasal; IV, intravenous; LTD, long-term depression; LTP, long-term potentiation; MMP, matrix metalloproteinase; MSC, mesenchymal stem cell; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NfL, neurofilament light chain; NG, nasogastric; NGF, nerve growth factor; NIH, National Institutes of Health; NMDA, N-methyl-D-aspartate; NSC, neural stem cell; NSE, neuron-specific enolase; OBTT, Operation Brain Trauma Therapy; PBM, photobiomodulation; $PbtO_2$, brain tissue oxygen tension; PLGA, poly(lactic-co-glycolic acid); PO, *Per Os* (by mouth); RCT, randomized controlled trial; RhoA, ras homolog family member A; ROS, reactive oxygen species; rTMS, repetitive transcranial magnetic stimulation; S100B, S100 calcium-binding protein B; SSRI, selective serotonin reuptake inhibitor; TBI, traumatic brain injury; TMS, transcranial magnetic stimulation; UCH-L1, ubiquitin carboxyl-terminal hydrolase L1; VEGF, vascular endothelial growth factor; VNS, vagus nerve stimulation; VR, virtual reality.

Availability of Data and Materials

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

Author Contributions

Conceptualization, AC, SDB; investigation, WW, SD, ER, BB, SG, AC; writing—original draft preparation, WW, SD, ER, BB, SG, AC; writing—review and editing, WW, SD, AC; visualization, SD; supervision, AC, SG, SDB; project administration, SD, AC. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Funding

This research received no external funding.

Conflicts of Interest

The authors declare no conflicts of interest.

References

[1] Maas AIR, Menon DK, Manley GT, Abrams M, Åkerlund C, Andelic N, et al. Traumatic brain injury: progress and challenges in prevention, clinical care, and research. The Lancet. Neurology. 2022; 21: 1004–1060. https://doi.org/10.1016/S1474-4422(22)00309-X

[2] Weil ZM, Karelina K. Lifelong consequences of brain injuries during development: From risk to resilience. Frontiers in Neuroendocrinology. 2019; 55: 100793. https://doi.org/10.1016/j.yfrne.2019.100793

[3] Sandsmark DK. Clinical Outcomes after Traumatic Brain Injury. Current Neurology and Neuroscience Reports. 2016; 16: 52. https://doi.org/10.1007/s11910-016-0654-5

[4] Guan B, Anderson DB, Chen L, Feng S, Zhou H. Global, regional and national burden of traumatic brain injury and spinal cord injury, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. BMJ Open. 2023; 13: e075049. https://doi.org/10.1136/bmjopen-2023-075049

[5] Masel BE, DeWitt DS. Traumatic brain injury: a disease process, not an event. Journal of Neurotrauma. 2010; 27: 1529–1540. https://doi.org/10.1089/neu.2010.1358

[6] Blennow K, Brody DL, Kochanek PM, Levin H, McKee A, Ribbers GM, et al. Traumatic brain injuries. Nature Reviews. Disease Primers. 2016; 2: 16084. https://doi.org/10.1038/nrdp.2016.84
[7] Capizzi A, Woo J, Verduzco-Gutierrez M. Traumatic Brain Injury: An Overview of Epidemiology, Pathophysiology, and Medical Management. The Medical Clinics of North America. 2020; 104: 213–238. https://doi.org/10.1016/j.mcna.2019.11.001
[8] Lamade AM, Anthonymuthu TS, Hier ZE, Gao Y, Kagan VE, Bayır H. Mitochondrial damage & lipid signaling in traumatic brain injury. Experimental Neurology. 2020; 329: 113307. https://doi.org/10.1016/j.expneurol.2020.113307
[9] Freire MAM, Rocha GS, Bittencourt LO, Falcao D, Lima RR, Cavalcanti JRLP. Cellular and Molecular Pathophysiology of Traumatic Brain Injury: What Have We Learned So Far? Biology. 2023; 12: 1139. https://doi.org/10.3390/biology12081139
[10] Ghiam MK, Patel SD, Hoffer A, Selman WR, Hoffer BJ, Hoffer ME. Drug Repurposing in the Treatment of Traumatic Brain Injury. Frontiers in Neuroscience. 2021; 15: 635483. https://doi.org/10.3389/fnins.2021.635483
[11] Loane DJ, Faden AI. Neuroprotection for traumatic brain injury: translational challenges and emerging therapeutic strategies. Trends in Pharmacological Sciences. 2010; 31: 596–604. https://doi.org/10.1016/j.tips.2010.09.005
[12] Cheong S, Gupta R, Kadaba Sridhar S, Hall AJ, Frankel M, Wright DW, et al. Progesterone for Traumatic Brain Injury, Experimental Clinical Treatment III Trial Revisited: Objective Classification of Traumatic Brain Injury With Brain Imaging Segmentation and Biomarker Levels. Critical Care Explorations. 2025; 7: e1306. https://doi.org/10.1097/CCE.0000000000001306
[13] Frangogiannis NG. Why animal model studies are lost in translation. The Journal of Cardiovascular Aging. 2022; 2: 22. https://doi.org/10.20517/jca.2022.10
[14] Lynch DG, Narayan RK, Li C. Multi-Mechanistic Approaches to the Treatment of Traumatic Brain Injury: A Review. Journal of Clinical Medicine. 2023; 12: 2179. https://doi.org/10.3390/jcm12062179
[15] Conklin J, Lev MH. A New Multimodal Classification and Nomenclature System for Acute Traumatic Brain Injury From the NIH-NINDS. AJR. American Journal of Roentgenology. 2025; 225: e2533684. https://doi.org/10.2214/AJR.25.33684
[16] Hawryluk GWJ, Rubiano AM, Totten AM, O'Reilly C, Ullman JS, Bratton SL, et al. Guidelines for the Management of Severe Traumatic Brain Injury: 2020 Update of the Decompressive Craniectomy Recommendations. Neurosurgery. 2020; 87: 427–434. https://doi.org/10.1093/neuros/nyaa278
[17] Schizodimos T, Soulountsi V, Iasonidou C, Kapravelos N. An overview of management of intracranial hypertension in the intensive care unit. Journal of Anesthesia. 2020; 34: 741–757. https://doi.org/10.1007/s00540-020-02795-7
[18] Sharma R, Tsikvadze M, Peel J, Howard L, Kapoor N, Freeman WD. Multimodal monitoring: practical recommendations (dos and don'ts) in challenging situations and uncertainty. Frontiers in Neurology. 2023; 14: 1135406. https://doi.org/10.3389/fneur.2023.1135406
[19] Szeleszczuk Ł, Frączkowski D. Propranolol versus Other Selected Drugs in the Treatment of Various Types of Anxiety or Stress, with Particular Reference to Stage Fright and Post-Traumatic Stress Disorder. International Journal of Molecular Sciences. 2022; 23: 10099. https://doi.org/10.3390/ijms231710099
[20] Khalili H, Ahl R, Paydar S, Sjolin G, Cao Y, Abdolrahimzadeh Fard H, et al. Beta-Blocker Therapy in Severe Traumatic Brain Injury: A Prospective Randomized Controlled Trial. World Journal of Surgery. 2020; 44: 1844–1853. https://doi.org/10.1007/s00268-020-05391-8
[21] Sivandzade F, Alqahtani F, Cucullo L. Traumatic Brain Injury and Blood-Brain Barrier (BBB): Underlying Pathophysiological Mechanisms and the Influence of Cigarette Smoking as a Premorbid Condition. International Journal of Molecular Sciences. 2020; 21: 2721. https://doi.org/10.3390/ijms21082721
[22] Cutler SM, Cekic M, Miller DM, Wali B, VanLandingham JW, Stein DG. Progesterone improves acute recovery after traumatic brain injury in the aged rat. Journal of Neurotrauma. 2007; 24: 1475–1486. https://doi.org/10.1089/neu.2007.0294
[23] Giordano KR, Saber M, Green TRF, Rojas-Valencia LM, Ortiz JB, Murphy SM, et al. Colony-Stimulating Factor-1 Receptor Inhibition Transiently Attenuated the Peripheral Immune Response to Experimental Traumatic Brain Injury. Neurotrauma Reports. 2023; 4: 284–296. https://doi.org/10.1089/neur.2022.0092
[24] Marino Lee S, Hudobenko J, McCullough LD, Chauhan A. Microglia depletion increase brain injury after acute ischemic stroke in aged mice. Experimental Neurology. 2021; 336: 113530. https://doi.org/10.1016/j.expneurol.2020.113530
[25] Liu Y, Zeng R, Wang Y, Huang W, Hu B, Zhu G, et al. Mesenchymal stem cells enhance microglia M2 polarization and attenuate neuroinflammation through TSG-6. Brain Research. 2019; 1724: 146422. https://doi.org/10.1016/j.brainres.2019.146422
[26] Bagheri H, Ghasemi F, Barreto GE, Sathyapalan T, Jamialahmadi T, Sahebkar A. The effects of statins on microglial cells to protect against neurodegenerative disorders: A mechanistic review. BioFactors (Oxford, England). 2020; 46: 309–325. https://doi.org/10.1002/biof.1597
[27] Lucke-Wold BP, Turner RC, Logsdon AF, Bailes JE, Huber JD, Rosen CL. Linking traumatic brain injury to chronic traumatic encephalopathy: identification of potential mechanisms leading to neurofibrillary tangle development. Journal of Neurotrauma. 2014; 31: 1129–1138. https://doi.org/10.1089/neu.2013.3303
[28] Hamblin MR. Photobiomodulation for traumatic brain injury and stroke. Journal of Neuroscience Research. 2018; 96: 731–743. https://doi.org/10.1002/jnr.24190
[29] Philip NS, Ramanathan D, Gamboa B, Brennan MC, Kozel FA, Lazzeroni L, et al. Repetitive Transcranial Magnetic Stimulation for Depression and Posttraumatic Stress Disorder in Veterans With Mild Traumatic Brain Injury. Neuromodulation : Journal of the International Neuromodulation Society. 2023; 26: 878–884. https://doi.org/10.1016/j.neurom.2022.11.015
[30] Naji A, Eitoku M, Favier B, Deschaseaux F, Rouas-Freiss N, Suganuma N. Biological functions of mesenchymal stem cells and clinical implications. Cellular and Molecular Life Sciences : CMLS. 2019; 76: 3323–3348. https://doi.org/10.1007/s00018-019-03125-1
[31] Gupta A, Singh S. Potential Role of Growth Factors Controlled Release in Achieving Enhanced Neuronal Trans-differentiation from Mesenchymal Stem Cells for Neural Tissue Repair and Regeneration. Molecular Neurobiology. 2022; 59: 983–1001. https://doi.org/10.1007/s12035-021-02646-w
[32] Delila L, Nebie O, Le NTN, Timmerman K, Lee DY, Wu YW, et al. Neuroprotective effects of intranasal extracellular vesicles from human platelet concentrates supernatants in traumatic brain injury and Parkinson's disease models. Journal of Biomedical Science. 2024; 31: 87. https://doi.org/10.1186/s12929-024-01072-z
[33] Wang J, Xia J, Huang R, Hu Y, Fan J, Shu Q, et al. Mesenchymal stem cell-derived extracellular vesicles alter disease outcomes via endorsement of macrophage polarization. Stem Cell Research & Therapy. 2020; 11: 424. https://doi.org/10.1186/s13287-020-01937-8

[34] Liu X, Wei Q, Lu L, Cui S, Ma K, Zhang W, et al. Immunomodulatory potential of mesenchymal stem cell-derived extracellular vesicles: Targeting immune cells. Frontiers in Immunology. 2023; 14: 1094685. https://doi.org/10.3389/fimmu.2023.1094685

[35] Terada K, Sasaki M, Nagahama H, Kataoka-Sasaki Y, Oka S, Ukai R, et al. Therapeutic efficacy of intravenous infusion of mesenchymal stem cells in rat perinatal brain injury. Pediatric Research. 2023; 94: 1921–1928. https://doi.org/10.1038/s41390-023-02717-9

[36] Mohamed GA, Lench DH, Grewal P, Rosenberg M, Voeks J. Stem cell therapy: a new hope for stroke and traumatic brain injury recovery and the challenge for rural minorities in South Carolina. Frontiers in Neurology. 2024; 15: 1419867. https://doi.org/10.3389/fneur.2024.1419867

[37] Ferrini E, Stellari FF, Franceschi V, Macchi F, Russo L, Murgia A, et al. Persistency of Mesenchymal Stromal/Stem Cells in Lungs. Frontiers in Cell and Developmental Biology. 2021; 9: 709225. https://doi.org/10.3389/fcell.2021.709225

[38] Zanier ER, Pischiutta F, Rulli E, Vargiolu A, Elli F, Gritti P, et al. MesenchymAl stromal cells for Traumatic bRain Injury (MATRIx): a study protocol for a multicenter, double-blind, randomised, placebo-controlled phase II trial. Intensive Care Medicine Experimental. 2023; 11: 56. https://doi.org/10.1186/s40635-023-00535-1

[39] Cox CS, Jr, Notrica DM, Juranek J, Miller JH, Triolo F, Kosmach S, et al. Autologous bone marrow mononuclear cells to treat severe traumatic brain injury in children. Brain : a Journal of Neurology. 2024; 147: 1914–1925. https://doi.org/10.1093/brain/awae005

[40] Wang J, Fu X, Jiang C, Yu L, Wang M, Han W, et al. Bone marrow mononuclear cell transplantation promotes therapeutic angiogenesis via upregulation of the VEGF-VEGFR2 signaling pathway in a rat model of vascular dementia. Behavioural Brain Research. 2014; 265: 171–180. https://doi.org/10.1016/j.bbr.2014.02.033

[41] Bou Najm D, Alame S. Therapeutic potential of stem cells in pediatric neurology: Insights from clinical trials. Neuroprotection (Chichester, England). 2025; 3: 303–321. https://doi.org/10.1002/nep3.70022

[42] Weber RZ, Rust R, Tackenberg C. How neural stem cell therapy promotes brain repair after stroke. Stem Cell Reports. 2025; 20: 102507. https://doi.org/10.1016/j.stemcr.2025.102507

[43] Li X, Sundström E. Stem Cell Therapies for Central Nervous System Trauma: The 4 Ws-What, When, Where, and Why. Stem Cells Translational Medicine. 2022; 11: 14–25. https://doi.org/10.1093/stcltm/szab006

[44] Yang Y, Hu X, Qin Q, Kong F, Peng X, Zhao J, et al. Optimal therapeutic conditions for the neural stem cell-based management of ischemic stroke: a systematic review and network meta-analysis based on animal studies. BMC Neurology. 2022; 22: 345. https://doi.org/10.1186/s12883-022-02875-z

[45] Chen J, Chopp M. Exosome Therapy for Stroke. Stroke. 2018; 49: 1083–1090. https://doi.org/10.1161/STROKEAHA.117.018292

[46] Kalluri R, LeBleu VS. The biology, function, and biomedical applications of exosomes. Science (New York, N.Y.). 2020; 367: eaau6977. https://doi.org/10.1126/science.aau6977

[47] Dong X, Dong JF, Zhang J. Roles and therapeutic potential of different extracellular vesicle subtypes on traumatic brain injury. Cell Communication and Signaling : CCS. 2023; 21: 211. https://doi.org/10.1186/s12964-023-01165-6

[48] Yarahmadi A, Dorri Giv M, Hosseininejad R, Rezaie A, Mohammadi N, Afkhami H, et al. Mesenchymal stem cells and their extracellular vesicle therapy for neurological disorders: traumatic brain injury and beyond. Frontiers in Neurology. 2025; 16: 1472679. https://doi.org/10.3389/fneur.2025.1472679

[49] Li P, Sun S, Zhu X, Liu X, Yin R, Chen Y, et al. Intranasal delivery of engineered extracellular vesicles promotes neurofunctional recovery in traumatic brain injury. Journal of Nanobiotechnology. 2025; 23: 229. https://doi.org/10.1186/s12951-025-03181-9

[50] Che Shaffi S, Hairuddin ON, Mansor SF, Syafiq TMF, Yahaya BH. Unlocking the Potential of Extracellular Vesicles as the Next Generation Therapy: Challenges and Opportunities. Tissue Engineering and Regenerative Medicine. 2024; 21: 513–527. https://doi.org/10.1007/s13770-024-00634-4

[51] Chen L, Xiong Y, Chopp M, Zhang Y. Engineered exosomes enriched with select microRNAs amplify their therapeutic efficacy for traumatic brain injury and stroke. Frontiers in Cellular Neuroscience. 2024; 18: 1376601. https://doi.org/10.3389/fncel.2024.1376601

[52] Sultan W, Sapkota A, Khurshid H, Qureshi IA, Jahan N, Went TR, et al. Statins' Effect on Cognitive Outcome After Traumatic Brain Injury: A Systematic Review. Cureus. 2021; 13: e16953. https://doi.org/10.7759/cureus.16953

[53] Sánchez-Aguilar M, Tapia-Pérez JH, Sánchez-Rodríguez JJ, Viñas-Ríos JM, Martínez-Pérez P, de la Cruz-Mendoza E, et al. Effect of rosuvastatin on cytokines after traumatic head injury. Journal of Neurosurgery. 2013; 118: 669–675. https://doi.org/10.3171/2012.12.JNS121084

[54] Susanto M, Pangihutan Siahaan AM, Wirjomartani BA, Setiawan H, Aryanti C, Michael. The neuroprotective effect of statin in traumatic brain injury: A systematic review. World Neurosurgery: X. 2023; 19: 100211. https://doi.org/10.1016/j.wnsx.2023.100211

[55] University of California SF. Multi-Arm Multi-Stage Adaptive Platform Trial (APT) for the Acute Treatment of Traumatic Brain Injury (APT-TBI-01). NLM identifier: NCT05826912. 2023. Available at: https://clinicaltrials.gov/study/NCT05826912 (Accessed: 15 February 2026).

[56] Underwood EL, Redell JB, Maynard ME, Kobori N, Hylin MJ, Hood KN, et al. Metformin Reduces Repeat Mild Concussive Injury Pathophysiology. eneuro. 2022; 9: ENEURO.0421–21.2021. https://doi.org/10.1523/ENEURO.0421-21.2021

[57] Fan YY, Wang YJ, Guo J, Wu MN, Zhang MS, Niu BL, et al. Delayed metformin treatment improves functional recovery following traumatic brain injury via central AMPK-dependent brain tissue repair. Brain Research Bulletin. 2020; 164: 146–156. https://doi.org/10.1016/j.brainresbull.2020.08.021

[58] Taheri A, Emami M, Asadipour E, Kasirzadeh S, Rouini MR, Najafi A, et al. A randomized controlled trial on the efficacy, safety, and pharmacokinetics of metformin in severe traumatic brain injury. Journal of Neurology. 2019; 266: 1988–1997. https://doi.org/10.1007/s00415-019-09366-1

[59] Jha RM, Simard JM. Glibenclamide for Brain Contusions: Contextualizing a Promising Clinical Trial Design that Leverages an Imaging-Based TBI Endotype. Neurotherapeutics : the Journal of the American Society for Experimental NeuroTherapeutics. 2023; 20: 1472–1481. https://doi.org/10.1007/s13311-023-01389-x

[60] Jha RM, Bell J, Citerio G, Hemphill JC, Kimberly WT, Narayan RK, et al. Role of Sulfonylurea Receptor 1 and Glibenclamide in Traumatic Brain Injury: A Review of the Evidence. International Journal of Molecular Sciences. 2020; 21: 409. https://doi.org/10.3390/ijms21020409

[61] Jha RM, Mondello S, Bramlett HM, Dixon CE, Shear DA, Dietrich WD, et al. Glibenclamide Treatment in Traumatic Brain Injury: Operation Brain Trauma Therapy. Journal of Neurotrauma. 2021; 38: 628–645. https://doi.org/10.1089/neu.2020.7421

[62] Remedy Pharmaceuticals I. A Multicenter, Double-Blind, Mul-

tidose, Placebo-Controlled, Randomized, Parallel-Group, Phase 2 Study to Evaluate the Efficacy and Safety of Intravenous BIIB093 for Patients With Brain Contusion. NLM identifier: NCT03954041. 2019. Available at: https://clinicaltrials.gov/study/NCT03954041 (Accessed: 15 February 2026).

[63] Ossola B, Schendzielorz N, Chen SH, Bird GS, Tuominen RK, Männistö PT, et al. Amantadine protects dopamine neurons by a dual action: reducing activation of microglia and inducing expression of GDNF in astroglia [corrected]. Neuropharmacology. 2011; 61: 574–582. https://doi.org/10.1016/j.neuropharm.2011.04.030

[64] Dekundy A, Pichler G, El Badry R, Scheschonka A, Danysz W. Amantadine for Traumatic Brain Injury-Supporting Evidence and Mode of Action. Biomedicines. 2024; 12: 1558. https://doi.org/10.3390/biomedicines12071558

[65] Hadgu RM, Borghol A, Gillard C, Wilson C, Elqess Mossa S, McKay M, et al. Evaluation of Outcomes in Patients Receiving Amantadine to Improve Alertness After Traumatic Brain Injury. Hospital Pharmacy. 2021; 56: 486–494. https://doi.org/10.1177/0018578720920803

[66] Loggini A, Tangonan R, El Ammar F, Mansour A, Goldenberg FD, Kramer CL, et al. The role of amantadine in cognitive recovery early after traumatic brain injury: A systematic review. Clinical Neurology and Neurosurgery. 2020; 194: 105815. https://doi.org/10.1016/j.clineuro.2020.105815

[67] SHINKEI Therapeutics I. Multicenter, Double-blind, Randomized, Placebo Controlled, Study to Assess the Safety of Amantadine Hydrochloride (HCl) Intravenous (IV) Solution (MR-301), in Patients With Severe Traumatic Brain Injury (TBI). NLM identifier: NCT06253923. 2024. Available at: https://clinicaltrials.gov/study/NCT06253923 (Accessed: 15 February 2026).

[68] Rodrigues PA, Zaninotto AL, Ventresca HM, Neville IS, Hayashi CY, Brunoni AR, et al. The Effects of Repetitive Transcranial Magnetic Stimulation on Anxiety in Patients With Moderate to Severe Traumatic Brain Injury: A *Post-hoc* Analysis of a Randomized Clinical Trial. Frontiers in Neurology. 2020; 11: 564940. https://doi.org/10.3389/fneur.2020.564940

[69] Chan ST, Mercaldo N, Figueiro Longo MG, Welt J, Avesta A, Lee J, et al. Effects of Low-Level Light Therapy on Resting-State Connectivity Following Moderate Traumatic Brain Injury: Secondary Analyses of a Double-blinded Placebo-controlled Study. Radiology. 2024; 311: e230999. https://doi.org/10.1148/radiol.230999

[70] Hipskind SG, Grover FL, Jr, Fort TR, Helffenstein D, Burke TJ, Quint SA, et al. Pulsed Transcranial Red/Near-Infrared Light Therapy Using Light-Emitting Diodes Improves Cerebral Blood Flow and Cognitive Function in Veterans with Chronic Traumatic Brain Injury: A Case Series. Photobiomodulation, Photomedicine, and Laser Surgery. 2019; 37: 77–84. https://doi.org/10.1089/photob.2018.4489

[71] Lim L. Traumatic Brain Injury Recovery with Photobiomodulation: Cellular Mechanisms, Clinical Evidence, and Future Potential. Cells. 2024; 13: 385. https://doi.org/10.3390/cells13050385

[72] Wu D, Chen Q, Chen X, Han F, Chen Z, Wang Y. The blood-brain barrier: structure, regulation, and drug delivery. Signal Transduction and Targeted Therapy. 2023; 8: 217. https://doi.org/10.1038/s41392-023-01481-w

[73] Lei K, Zhou L, Dan M, Yang F, Jian T, Xin J, et al. Trojan Horse Delivery Strategies of Natural Medicine Monomers: Challenges and Limitations in Improving Brain Targeting. Pharmaceutics. 2025; 17: 280. https://doi.org/10.3390/pharmaceutics17030280

[74] Romero-Ben E, Goswami U, Soto-Cruz J, Mansoori-Kermani A, Mishra D, Martin-Saldaña S, et al. Polymer-based nanocarriers to transport therapeutic biomacromolecules across the blood-brain barrier. Acta Biomaterialia. 2025; 196: 17–49. https://doi.org/10.1016/j.actbio.2025.02.065

[75] Xuan L, Ju Z, Skonieczna M, Zhou PK, Huang R. Nanoparticles-induced potential toxicity on human health: Applications, toxicity mechanisms, and evaluation models. MedComm. 2023; 4: e327. https://doi.org/10.1002/mco2.327

[76] Aqel S, Al-Thani N, Haider MZ, Abdelhady S, Al Thani AA, Kobeissy F, et al. Biomaterials in Traumatic Brain Injury: Perspectives and Challenges. Biology. 2023; 13: 21. https://doi.org/10.3390/biology13010021

[77] Sarma S, Deka DJ, Rajak P, Laloo D, Das T, Chetia P, et al. Potential injectable hydrogels as biomaterials for central nervous system injury: A narrative review. Ibrain. 2023; 9: 402–420. https://doi.org/10.1002/ibra.12137

[78] Chen T, Xia Y, Zhang L, Xu T, Yi Y, Chen J, et al. Loading neural stem cells on hydrogel scaffold improves cell retention rate and promotes functional recovery in traumatic brain injury. Materials Today. Bio. 2023; 19: 100606. https://doi.org/10.1016/j.mtbio.2023.100606

[79] Wu C, Liu A, Chen S, Zhang X, Chen L, Zhu Y, et al. Cell-Laden Electroconductive Hydrogel Simulating Nerve Matrix To Deliver Electrical Cues and Promote Neurogenesis. ACS Applied Materials & Interfaces. 2019; 11: 22152–22163. https://doi.org/10.1021/acsami.9b05520

[80] Tręda C, Włodarczyk A, Rieske P. The hope, hype and obstacles surrounding cell therapy. Journal of Cellular and Molecular Medicine. 2024; 28: e18359. https://doi.org/10.1111/jcmm.18359

[81] Shahror RA, Linares GR, Wang Y, Hsueh SC, Wu CC, Chuang DM, et al. Transplantation of Mesenchymal Stem Cells Overexpressing Fibroblast Growth Factor 21 Facilitates Cognitive Recovery and Enhances Neurogenesis in a Mouse Model of Traumatic Brain Injury. Journal of Neurotrauma. 2020; 37: 14–26. https://doi.org/10.1089/neu.2019.6422

[82] Li X, Zhang J, Zhu X, Wang P, Wang X, Li D. Progesterone reduces inflammation and apoptosis in neonatal rats with hypoxic ischemic brain damage through the PI3K/Akt pathway. International Journal of Clinical and Experimental Medicine. 2015; 8: 8197–8203.

[83] Skolnick BE, Maas AI, Narayan RK, van der Hoop RG, MacAllister T, Ward JD, et al. A clinical trial of progesterone for severe traumatic brain injury. The New England Journal of Medicine. 2014; 371: 2467–2476. https://doi.org/10.1056/NEJMoa1411090

[84] Ma J, Huang S, Qin S, You C, Zeng Y. Progesterone for acute traumatic brain injury. The Cochrane Database of Systematic Reviews. 2016; 12: CD008409. https://doi.org/10.1002/14651858.CD008409.pub4

[85] Risling M, Smith D, Stein TD, Thelin EP, Zanier ER, Ankarcrona M, et al. Modelling human pathology of traumatic brain injury in animal models. Journal of Internal Medicine. 2019; 285: 594–607. https://doi.org/10.1111/joim.12909

[86] Sunny A, James RR, Menon SR, Rayaroth S, Daniel A, Thompson NA, et al. Matrix Metalloproteinase-9 inhibitors as therapeutic drugs for traumatic brain injury. Neurochemistry International. 2024; 172: 105642. https://doi.org/10.1016/j.neuint.2023.105642

[87] Jones C, Elliott B, Liao Z, Johnson Z, Ma F, Bailey ZS, et al. PEG hydrogel containing dexamethasone-conjugated hyaluronic acid reduces secondary injury and improves motor function in a rat moderate TBI model. Experimental Neurology. 2023; 369: 114533. https://doi.org/10.1016/j.expneurol.2023.114533

[88] Jones CE, Elliott B, Ma F, Bailey Z, Gilsdorf J, Scultetus AH, et al. Point-of-Injury Treatment with Hydrogel Containing Dexamethasone Improves Cognitive Function and Reduces Secondary Injury Response After TBI. Gels (Basel, Switzerland). 2025; 11:

600. https://doi.org/10.3390/gels11080600

[89] Han Y, Weng W, Zhang Y, Feng Q, Ma Y, Quan A, et al. Intraoperative application of intelligent, responsive, self-assembling hydrogel rectifies oxygen and energy metabolism in traumatically injured brain. Biomaterials. 2024; 306: 122495. https://doi.org/10.1016/j.biomaterials.2024.122495

[90] He Z, Zang H, Zhu L, Huang K, Yi T, Zhang S, et al. An anti-inflammatory peptide and brain-derived neurotrophic factor-modified hyaluronan-methylcellulose hydrogel promotes nerve regeneration in rats with spinal cord injury. International Journal of Nanomedicine. 2019; 14: 721–732. https://doi.org/10.2147/IJN.S187854

[91] Shi W, Huang CJ, Xu XD, Jin GH, Huang RQ, Huang JF, et al. Transplantation of RADA16-BDNF peptide scaffold with human umbilical cord mesenchymal stem cells forced with CXCR4 and activated astrocytes for repair of traumatic brain injury. Acta Biomaterialia. 2016; 45: 247–261. https://doi.org/10.1016/j.actbio.2016.09.001

[92] Da Silva K, Kumar P, van Vuuren SF, Pillay V, Choonara YE. Three-Dimensional Printability of an ECM-Based Gelatin Methacryloyl (GelMA) Biomaterial for Potential Neuroregeneration. ACS Omega. 2021; 6: 21368–21383. https://doi.org/10.1021/acsomega.1c01903

[93] Li Z, Song P, Li G, Han Y, Ren X, Bai L, et al. AI energized hydrogel design, optimization and application in biomedicine. Materials Today. Bio. 2024; 25: 101014. https://doi.org/10.1016/j.mtbio.2024.101014

[94] Hettick M, Ho E, Poole AJ, Monge M, Papageorgiou D, Takahashi K, et al. The Layer 7 Cortical Interface: A Scalable and Minimally Invasive Brain–Computer Interface Platform. bioRxiv. 2024. https://doi.org/10.1101/2022.01.02.474656 (preprint)

[95] Tonin A, Semprini M, Kiper P, Mantini D. Brain-Computer Interfaces for Stroke Motor Rehabilitation. Bioengineering (Basel, Switzerland). 2025; 12: 820. https://doi.org/10.3390/bioengineering12080820

[96] Popa LL, Chira D, Strilciuc Ș, Mureșanu DF. Non-Invasive Systems Application in Traumatic Brain Injury Rehabilitation. Brain Sciences. 2023; 13: 1594. https://doi.org/10.3390/brainsci13111594

[97] Gray SN. An Overview of the Use of Neurofeedback Biofeedback for the Treatment of Symptoms of Traumatic Brain Injury in Military and Civilian Populations. Medical Acupuncture. 2017; 29: 215–219. https://doi.org/10.1089/acu.2017.1220

[98] Calderone A, Latella D, Bonanno M, Quartarone A, Mojdehdehbaher S, Celesti A, et al. Towards Transforming Neurorehabilitation: The Impact of Artificial Intelligence on Diagnosis and Treatment of Neurological Disorders. Biomedicines. 2024; 12: 2415. https://doi.org/10.3390/biomedicines12102415

[99] Huang X, Gu L, Sun J, Eils R. Bridging the gaps: Overcoming challenges of implementing AI in healthcare. Med (New York, N.Y.). 2025; 6: 100666. https://doi.org/10.1016/j.medj.2025.100666

[100] Badar M, Younis R, Sikdar S, Nejdl W, Fisichella M. FedFUEL: fairness and utility enhancing agnostic federated learning framework. Data Mining and Knowledge Discovery. 2025; 39: 84. https://doi.org/10.1007/s10618-025-01152-0

[101] Vay SU, Flitsch LJ, Rabenstein M, Rogall R, Blaschke S, Kleinhaus J, et al. The plasticity of primary microglia and their multifaceted effects on endogenous neural stem cells in vitro and in vivo. Journal of Neuroinflammation. 2018; 15: 226. https://doi.org/10.1186/s12974-018-1261-y

[102] Zhang H, Li CL, Qu Y, Yang YX, Du J, Zhao Y. Effects and neuroprotective mechanisms of vagus nerve stimulation on cognitive impairment with traumatic brain injury in animal studies: A systematic review and meta-analysis. Frontiers in Neurology. 2022; 13: 963334. https://doi.org/10.3389/fneur.2022.963334

[103] Daines SA. The Therapeutic Potential and Limitations of Ketones in Traumatic Brain Injury. Frontiers in Neurology. 2021; 12: 723148. https://doi.org/10.3389/fneur.2021.723148

[104] Wilson L, Stewart W, Dams-O'Connor K, Diaz-Arrastia R, Horton L, Menon DK, et al. The chronic and evolving neurological consequences of traumatic brain injury. The Lancet. Neurology. 2017; 16: 813–825. https://doi.org/10.1016/S1474-4422(17)30279-X

[105] Bodien YG, McCrea M, Dikmen S, Temkin N, Boase K, Machamer J, et al. Optimizing Outcome Assessment in Multicenter TBI Trials: Perspectives From TRACK-TBI and the TBI Endpoints Development Initiative. The Journal of Head Trauma Rehabilitation. 2018; 33: 147–157. https://doi.org/10.1097/HTR.0000000000000367

[106] MacLean MA, Muradov JH, Greene R, Van Hameren G, Clarke DB, Dreier JP, et al. Memantine inhibits cortical spreading depolarization and improves neurovascular function following repetitive traumatic brain injury. Science Advances. 2023; 9: eadj2417. https://doi.org/10.1126/sciadv.adj2417

[107] Li ZM, Xiao YL, Zhu JX, Geng FY, Guo CJ, Chong ZL, et al. Recombinant human erythropoietin improves functional recovery in patients with severe traumatic brain injury: A randomized, double blind and controlled clinical trial. Clinical Neurology and Neurosurgery. 2016; 150: 80–83. https://doi.org/10.1016/j.clineuro.2016.09.001

[108] Ghaith HS, Nawar AA, Gabra MD, Abdelrahman ME, Nafady MH, Bahbah EI, et al. A Literature Review of Traumatic Brain Injury Biomarkers. Molecular Neurobiology. 2022; 59: 4141–4158. https://doi.org/10.1007/s12035-022-02822-6

[109] Thelin EP, Zeiler FA, Ercole A, Mondello S, Büki A, Bellander BM, et al. Serial Sampling of Serum Protein Biomarkers for Monitoring Human Traumatic Brain Injury Dynamics: A Systematic Review. Frontiers in Neurology. 2017; 8: 300. https://doi.org/10.3389/fneur.2017.00300

[110] Carpenter KLH, Jalloh I, Hutchinson PJ. Glycolysis and the significance of lactate in traumatic brain injury. Frontiers in Neuroscience. 2015; 9: 112. https://doi.org/10.3389/fnins.2015.00112

[111] Burke E, Cramer SC. Biomarkers and predictors of restorative therapy effects after stroke. Current Neurology and Neuroscience Reports. 2013; 13: 329. https://doi.org/10.1007/s11910-012-0329-9

[112] PRACTICAL, PANTHER, TRAITS, INCEPT, and REMAP-CAP investigators. The Rise of Adaptive Platform Trials in Critical Care. American Journal of Respiratory and Critical Care Medicine. 2024; 209: 491–496. https://doi.org/10.1164/rccm.202401-0101CP

[113] Nelson LD, Ranson J, Ferguson AR, Giacino J, Okonkwo DO, Valadka AB, et al. Validating Multi-Dimensional Outcome Assessment Using the Traumatic Brain Injury Common Data Elements: An Analysis of the TRACK-TBI Pilot Study Sample. Journal of Neurotrauma. 2017; 34: 3158–3172. https://doi.org/10.1089/neu.2017.5139