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SMART BIOMATERIALS IN CENTRAL NERVOUS SYSTEM REPAIR: FROM BLOOD–BRAIN BARRIER TARGETING TO ARTIFICIAL INTELLIGENCE–GUIDED THERAPEUTIC DESIGN

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Abstract

Central nervous system disorders remain difficult to treat because of limited intrinsic neural regeneration, complex neuroinflammatory responses and the restrictive function of the blood–brain barrier and smart biomaterials have emerged as promising therapeutic platforms capable of combining structural support, controlled drug delivery, cellular modulation and targeted interaction with neural tissue. Through this review we set out to discuss the role of biomaterials in central nervous system repair, with a focus on hydrogel-based scaffolding, decellularized extracellular matrix materials, conductive nanocomposites, nanogels, nanoparticles, and lipid-based delivery systems. Particular attention is paid to strategies to target the blood-brain barrier, including nanoscale carriers designed to improve brain accumulation, therapeutic stability, cell absorption, and controlled release and our review highlights the growing contribution of artificial intelligence to predicting blood-brain barrier permeability, optimizing the properties of biomaterials, and guiding the design of therapeutic systems for the brain. While encouraging preclinical progress, clinical translation remains limited by concerns about safety, reproducibility, biodegradation, immune response, and differences between experimental models and human neurological diseases, and future advances will require integrated biomaterials platforms that combine regenerative, delivery, and computational design strategies.

Keywords: smart biomaterials, central nervous system repair, blood-brain barrier, drug administration, hydrogels, artificial intelligence.

Introduction

Central nervous system (CNS) disorders remain difficult to treat because neural tissue has limited intrinsic regenerative capacity, high structural complexity, and a tightly regulated microenvironment. Unlike many peripheral tissues, the brain and spinal cord have a reduced ability to restore damaged neuronal networks after trauma, ischemia, neurodegeneration, or inflammation, and repair is further restricted by glial scar formation, persistent neuroinflammation, oxidative stress, demyelination, and insufficient axonal regrowth. These pathological mechanisms create a hostile microenvironment that limits neuronal survival, synaptic reconnection, and functional recovery. In this context, biomaterials have evolved from passive scaffolds into biologically active platforms capable of providing structural support, guiding cellular behavior, and modulating the injured neural environment [1,2].

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A central obstacle in CNS therapy is effective drug delivery. The blood–brain barrier (BBB) selectively restricts the passage of most therapeutic agents, thereby limiting drug accumulation in the brain and spinal cord. Although this barrier is essential for maintaining CNS homeostasis, it represents a major pharmacological limitation for neurological therapy. Therefore, current biomaterial-based strategies increasingly combine regenerative support with controlled release, nanoscale delivery, and surface-engineered systems designed to improve BBB interaction, tissue retention, cellular uptake, and therapeutic stability [3,4].

Targeted nanoparticles and nanocarriers are particularly relevant to us because their size, charge, surface chemistry, and ligand functionalization can be optimized to improve transport across CNS barriers, and these systems have been explored for several neurological disorders, including Alzheimer's disease, where disease stage, BBB integrity, and regional pathological changes can influence therapeutic performance [5,6], and nanomaterials, theranostic nanoparticles, and nanogels further expand this approach by integrating drug delivery, imaging potential, controlled release, and disease-specific targeting into multifunctional therapeutic platforms [7-9].

Recent advances in nanotechnology have refined brain-directed delivery by improving particle design, biological functionalization, and developing carriers capable of transporting drugs, genes, proteins, or natural compounds across CNS barriers [10-13]. In parallel, affinity-based delivery systems allow for more precise local targeting by exploiting molecular interactions in neuronal tissues, while combining biomaterials with cell therapies provides an additional regenerative strategy for restoring affected central system microenvironments [14,15].

Neurobiological barriers and smart biomaterial platforms for CNS repair

Central nervous system repair is limited by neuronal loss, axonal disconnection, demyelination, vascular injury, glial scar formation, chronic neuroinflammation, and oxidative stress, and these factors create a non-permissive microenvironment that impairs axonal regrowth, synaptic reconnection, and functional remodeling, and in this context, biomaterial scaffolds have gained relevance because they can support neural stem/progenitor cell survival, differentiation, and integration, and by providing spatial organization, mechanical support, and controlled biological cues, these platforms may improve cell retention and promote more favorable interactions between transplanted cells and host neural tissue [15].

Matrix-based decellularized extracellular biomaterials are particularly relevant to us because they retain tissue-like biochemical and structural cues that can support cell adhesion, migration, and remodeling, and their native composition can provide matrix proteins, adhesion motifs, and three-dimensional architecture that are difficult to reproduce using fully synthetic systems, and in CNS repair these features observed by us can help recreate an environment It is permissive for neuronal and glial interactions, and their translation depends on several critical factors, including source variability, decellularization efficiency, residual immunogenicity, batch-to-batch reproducibility, degradation behavior, and mechanical stability[16].

Since neuroinflammation is a major barrier to repair, modern biomaterials are also designed to regulate microglial, macrophage, and astrocytic responses. Following CNS injury, excessive activation of these cells contributes to secondary damage, cytokine release, oxidative stress, and glial scar formation, and immunomodulatory biomaterials may reduce secondary injury by controlling inflammatory cell activation, promoting reparative phenotypes, and limiting chronic scar-associated inhibition and this function is essential because successful regeneration requires not only structural support but also a biological environment that permits axonal extension, cellular migration, and tissue integration [17].

Hydrogels are among the most adaptable platforms for CNS regeneration, and their high water content, adjustable stiffness, and injectable properties allow them to fill lesion cavities, deliver trophic factors, and provide a soft matrix for axonal growth because their mechanical

properties can be adjusted to resemble neural tissue, hydrogels can reduce mechanical mismatch, and improve local compatibility, as they can also be designed to control porosity, degradation rate, molecular release, and cell-material interactions, making them suitable for both acellular and cell-charged regenerative strategies [18].

This concept has been extended by adding electrical functionality, which can support the extension of hydrogel neurites with conductive nanocomposites, neuronal differentiation and electroactive communication in regenerating tissues. Because neuronal tissue depends on electrical signaling, conductive platforms can provide a more relevant physiological microenvironment, especially when combined with stimulation-based approaches, and multifunctional hydrogels further integrate conductivity, adhesion, elasticity, self-healing behavior, and interface compatibility, making them useful for both regenerative scaffolding and neural biointerfaces. Observing these properties we realized that they are particularly important for advanced neural interfaces, where long-term integration requires mechanical compliance, signal stability, and reduced tissue reactivity [19,20].

AI-validated brain-targeted lipid nanoparticles illustrate how smart biomaterials can be optimized for neuronal tropism and CNS specificity, supporting a transition toward data-guided therapeutic design. Although lipid nanoparticles are primarily delivery systems rather than structural scaffolds, their integration into the broader field of smart biomaterials is important because they demonstrate how nanoscale engineering, biological targeting, and computational validation can be combined to improve CNS-directed therapy, and together, these platforms indicate that future CNS repair strategies will likely depend on hybrid biomaterial systems capable of integrating scaffold function, immunomodulation, electroactivity, controlled delivery, and computationally guided optimization [21]. We have made a comparative synthesis of the main smart biomaterials platforms discussed in this section, including their functional roles in CNS repair and their specific relevance for regenerative or delivery-oriented strategies, which are presented in Table 1.

Table 1. Smart biomaterial platforms for CNS repair and their functional relevance

Biomaterial platform	Main role in CNS repair	Relevance to the review	Ref.
Biomaterials combined with neural stem/progenitor cells	Support cell survival, differentiation and integration	Neural regeneration and spinal cord repair	[15]
Decellularized extracellular matrix-based biomaterials	Provide native-like structural and biochemical cues	Biomimetic scaffold for tissue remodeling	[16]
Immunomodulatory biomaterials	Modulate microglial, macrophage and reactive astrocytic responses	Reduction of neuroinflammation and glial scarring	[17]
Hydrogels	Fill lesion cavities, deliver trophic factors and support axonal growth	Core platform for neuroregeneration	[18]
Conductive hydrogels	Add electroactive functionality	Support neuronal signaling and differentiation	[19]
Multifunctional hydrogels	Integrate adhesion, conductivity, elasticity and biointerface compatibility	Regeneration and advanced neural interfaces	[20]
AI-validated lipid nanoparticles	Enable neuronal targeting and computational optimization	Link between smart biomaterials and AI-guided design	[21]

Blood–brain barrier targeting and controlled delivery strategies

The blood-brain barrier (BBB) is a major limitation in the treatment of central nervous system disorders, as it restricts the passage of most therapeutic agents and limits the efficient accumulation of drugs in patients' neural tissue, and its selective permeability is essential for maintaining central nervous system homeostasis, but also prevents many drugs, proteins, nucleic acids and conventional therapeutic molecules from reaching concentrations effective in the brain and spinal cord. Therefore, targeting the BBB has become a central goal in the design of smart biomaterials for CNS repair. Modern delivery systems aim not only to cross or modulate BBB, but also to improve therapeutic stability, tissue retention, cell absorption, and controlled release. In this context, biomaterial-based delivery platforms are increasingly designed as multifunctional systems that interact with biological barriers while preserving therapeutic activity and reducing systemic toxicity [3,4].

Nanoparticles and nanocarriers are among the most extensively investigated platforms because their size, surface charge, hydrophobicity, and ligand functionalization can be adapted to enhance brain targeting, and by modifying these physicochemical parameters, nanosystems may improve circulation time, avoid premature degradation, and increase the probability of interaction with endothelial transport mechanisms. These systems may exploit receptor-mediated transport, adsorptive interactions, or disease-associated changes in BBB permeability, with applications in neurodegenerative diseases, brain injury, and other CNS pathologies. In Alzheimer’s disease and other chronic neurological disorders, targeted nanoparticles may be particularly relevant because disease progression, BBB dysfunction, and regional pathological changes can influence delivery efficiency and therapeutic response [5-7].

Theranostic nanoparticles, nanogels, and brain-targeted nanosystems further expand this approach by combining drug delivery with imaging, controlled release, and disease-specific therapeutic functions, and heranostic systems are especially important because they may allow simultaneous diagnosis, monitoring, and treatment, which is highly relevant in complex CNS disorders where lesion localization and therapeutic distribution are difficult to assess and nanogels offer additional functional advantages through their hydrated structure, tunable swelling behavior, and capacity for sustained or stimuli-responsive drug release. These properties support prolonged therapeutic exposure and may reduce the need for repeated administration [8-10].

Additional strategies observed by us include targeted brain delivery through biologically functionalized nanoparticles, natural compound-mediated BBB modulation, and affinity-based delivery systems designed for local and precise molecular interactions in neural tissue and surface functionalization with biological ligands can improve tissue specificity and cellular absorption, while BBB modulation approaches can transiently enhance therapeutic access without permanently disrupt the integrity of the barrier. Affinity-based systems are also promising because they exploit molecular recognition to keep therapeutic agents close to relevant neural targets, improving local accuracy and reducing off-target exposure [11-13].

More recently, AI-validated lipid nanoparticles and deep learning models for BBB permeability prediction have introduced a computational dimension to CNS delivery, and these approaches can support rational optimization of biomaterial properties, molecular candidates, and delivery strategies prior to extensive experimental testing. By predicting BBB permeability and validating neural targeting, computationally guided platforms can reduce empirical trial and error and accelerate the development of CNS-specific therapeutic systems. Overall, targeted and controlled delivery strategies to BBB represent a central component of intelligent biomaterials design, linking nanoscale engineering, biological specificity, therapeutic release, and data-guided optimization for CNS repair [21,22].

We have summarized the main targeted and controlled delivery strategies for BBB discussed in this section, along with their functional roles and their relevance to CNS repair in Table 2.

Table 2. BBB-targeted and controlled delivery strategies for CNS applications

Strategy	Main function	Relevance to CNS repair	Ref.
BBB-targeting nanoparticles	Improve transport across CNS barriers	Enhance brain accumulation and therapeutic specificity	[4-7]
Theranostic nanoparticles	Combine delivery and imaging	Support diagnosis-guided treatment	[8]
Nanogels	Enable controlled and sustained drug release	Improve local therapeutic retention	[9]
Nanotechnology-enhanced brain delivery	Optimize nanoscale drug transport	Applicable to multiple brain diseases	[10]
Functionalized targeted nanoparticles	Improve cellular and tissue specificity	Support targeted brain drug delivery	[11]
BBB permeability modulation	Enhance access of therapeutic agents	Useful for brain-directed delivery strategies	[12]
Affinity-based delivery systems	Use molecular interactions for local targeting	Enable precise CNS drug release	[13]
AI-guided lipid nanoparticles / BBB prediction	Optimize targeting and permeability	Link delivery design with computational prediction	[21,22]

AI-guided optimization, translational challenges, and future perspectives

Artificial intelligence is becoming increasingly relevant to the development of smart biomaterials for central nervous system repair, as it can support the rational design, screening, and optimization of complex therapeutic platforms and in CNS applications, biomaterials must simultaneously address biocompatibility, controlled degradation, mechanical compatibility, blood–brain barrier interaction, cellular targeting, and therapeutic release. These requirements are difficult to optimize using conventional empirical approaches because small changes in particle size, surface charge, ligand density, matrix stiffness, porosity, or degradation kinetics can substantially affect biological performance. AI-assisted strategies may therefore help identify optimal combinations of material properties, drug cargo, surface functionalization, and delivery routes, reducing trial-and-error experimentation and improving translational predictability [1].

A particularly important direction is the application of computational models to brain-targeted delivery and since BBB permeability strongly influences therapeutic success, deep learning-based prediction of molecular transport may guide the selection, modification, or exclusion of candidate compounds before experimental validation. Such models can support early-stage decision-making by estimating whether a molecule or carrier system is likely to reach the CNS in therapeutically relevant concentrations. Similarly, AI-validated lipid nanoparticles with neuronal tropism illustrate how data-driven approaches can optimize nanoscale carriers to enhance CNS specificity, biological targeting, and therapeutic efficacy [21,22].

In our opinion, AI-guided optimization can be valuable for regenerative biomaterials, including hydrogels, conductive nanocomposites, decellularized matrices, and cell support scaffolds, and these platforms require precise control of mechanical and biological parameters to match the neural microenvironment and support cell survival, axonal extension, immunomodulation, and tissue integration. Computational approaches could help predict how stiffness, degradation profile, conductivity, and biochemical functionalization influence neuronal and glial responses, and this is particularly relevant for CNS repair, where excessive inflammatory response, mechanical mismatch, or poor integration with host tissue can compromise therapeutic outcomes [14,15,17-20].

Despite these advances, there are several challenges for smart biomaterials designed for CNS repair, which must demonstrate long-term safety, controlled biodegradation, minimal neurotoxicity, reproducible production, and stable biological performance, and nanoparticles, nanogels, hydrogels, and conductive platforms require careful evaluation of immune activation, tissue accumulation, elimination, mechanical mismatch, and potential interference with neural signaling [7-10,17-20]. Furthermore, many promising findings are still coming from preclinical models, while human CNS disorders show greater biological heterogeneity, variable BBB integrity, disease-stage-dependent responses, and complex interactions between neurodegeneration, vascular dysfunction, inflammation, and impaired repair mechanisms [3-6].

Another key limitation we observed is the availability and quality of data used for AI-guided biomaterials design where predictive models depend on standardised, reproducible and biologically significant datasets, but biomaterials studies often differ in experimental protocols, outcome measures, animal models, material characterisation and reporting standards, and without harmonised datasets and external validation, AI models can generate predictions that appear computationally robust but remain difficult to translate biologically. Therefore, future studies should integrate material characterization, biological response profiling, BBB transport data, and therapeutic outcome measures into interoperable datasets suitable for machine learning analysis [1,21,22].

Future progress will likely depend on integrating biomaterials engineering, BBB targeted delivery, regenerative biology, and AI-guided modeling into unified therapeutic systems, where such platforms can enable personalized CNS repair strategies by combining controlled release, cell modulation, neuroinflammatory regulation, neural targeting, and computationally optimized design, and successful clinical translation will require standardized datasets, robust validation, scalable manufacturing, regulatory clarity, and closer alignment between experimental models and patient-specific neurological pathology [1,14,15,21,22].

Conclusions

Smart biomaterials represent a promising strategy for central nervous system repair by integrating structural support, controlled therapeutic delivery, targeting of the blood-brain barrier and modulation of the neural microenvironment, and hydrogels, nanocarriers, decellularized matrices, conductive platforms and lipid nanoparticles provide complementary mechanisms to promote regeneration, reduce neuroinflammation and improve CNS-specific delivery, and we have noticed that the incorporation of artificial intelligence adds a new dimension, enabling predictive optimization of biomaterial properties, BBB permeability, and therapeutic targeting. However, clinical translation remains limited by safety, reproducibility, biodegradation, immune response, and the difference between preclinical models and human pathology. Future progress will depend on integrated, validated and patient-oriented biomaterial systems.

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