Quo vadis? Bioengineered polysaccharide-based hydrogel scaffolds for damaged central nervous system recovery and regeneration

Isadora C. Carvalho, Herman S. Mansur*

Impairments in the central nervous system (CNS) are a prevalent cause of life-long disabilities worldwide, representing serious health, social, and economic concerns (Doblado et al., 2021). During the last decades, with the population eldering and the increase in the life span, we have experienced an increase in CNS-related disorders, like stroke and neurodegenerative diseases (Jarrin et al., 2021). Paralysis, cognitive function, and sensory losses (Jensen et al., 2020) are among the most predominant outcomes. Regrettably, there is still no effective therapy for CNS repair and regeneration (CNSRR), where most of the current therapeutics can only prevent continued damage in the affected area (Ali and Bhuiyan, 2021). The presence of the blood-brain barrier restricts the permeation of drugs through the circulation, and the difficulty of accessing the damaged regions, which usually demand invasive surgeries, compromise even more the effectiveness of the available treatments (Ojeda-Hernández et al., 2020). Thus, there is an urge to develop an effective therapy for CNSRR. Hopefully, a multidisciplinary strategy has been adopted for designing sophisticated multifunctional platforms based on nature-sourced materials capable of influencing cell fate, delivering therapeutics for the damaged area in a sustained manner, and supporting the adjacent brain parenchyma aiming at CNSRR: the polysaccharides. Here, we do not cover the overall properties of polysaccharide-based materials. Hence, we emphatically recommend the readers resort to state-of-the-art works referenced throughout this paper for further comprehension of the theme (Carvalho et al., 2021; Doblado et al., 2021; Tupone et al., 2021).

Preclinical approaches: The CNS consists of a complex network of nervous cells (e.g., axons, astrocytes, neurons, oligodendrocytes, and microglia) embedded in an extracellular matrix rich in proteins and polysaccharides, composing almost 20% of adults brains (Doblado et al., 2021). Normally, immature cells are regulated by soluble and surface factors, and once properly positioned, neurons grow their axons and dendrites to form synaptic connections (Liu and Hsu, 2020). Following brain damages, however, CNS cells trigger a cascade of self-destroying mechanisms, which hamper the recuperation of the injured area (Carvalho et al., 2021).

Cell therapy emerged as a promising strategy for treating damaged CNS (Tupone et al., 2021). Nevertheless, preclinical and clinical trials revealed that, although with some positive effects, poor cell survival rates critically lower the benefits of the treatments. The lack of a permissive microenvironment capable of assisting cell survival, along with difficulty in integrating the host and the developing tissue, is the main justification for the modest achievements in this field (Ali and Bhuiyan, 2021). To this end, scientists endeavor to improve the viability of implanted cells by combining cell therapy with multifunctional platforms that provide permissive environments to cells for surpassing the harsh conditions found in damaged CNS (Jarrin et al., 2021).

The relevance of using biomaterials for cell transplantation for CNSRR is uncontested. Much evidence has been reported that the same cell type can follow divergent fates upon substrate features. Conversely, different cellular networks can be formed on the same substrate depending on the developmental stage of the implanted cells. Indeed, substrate properties as elastic or compressive *moduli*, viscoelasticity, wettability, and topography highly influence cell mechanotransduction, affecting critical cell activities, including signaling pathways, cytoskeletal rearrangement, and even gene expression (Tupone et al., 2021).

The combination of stem/progenitor cells, neurotrophic factors, and an adaptable polymeric network consists of a singular strategy to deliver cells and therapeutic agents into the injured area (Ali and Bhuiyan, 2021). Hydrogels can offer cells 3D environments that are very similar to those of neural ECM regarding the physicochemical and mechanical features, pore architecture, and electrical cues (Carvalho et al., 2021). Such characteristics are mandatory for a proper restoration of the neural network as mechanical and physicochemical substrate feature influence cell migration, attachment, proliferation, and differentiation. As well, appropriate pore architecture enables a suitable flux of nutrients and cell waste through the substrate. Notably, the presence of electrical cues largely impacts neuron differentiation and communication (Tupone et al., 2021). Considering the complexity of the CNS and the multiplicity of nervous cells, the combination of substrate properties and desired stem cell responses must vary depending on the region, extension, and cause of the injury. Questions as to which lineage stem cells should rather differentiate to achieve a functional network or which cell lines would better perform to attain synaptic integration remain with no answer (Payne et al., 2019). Although further studies are still to be performed, preclinical models have been evidencing that hydrogels hold great potential in reversing the persistent post-injury cavity into a permissive microenvironment for tissue recovery (Tupone et al., 2021).

Polysaccharide hydrogels for CNS repair and regeneration: Strong evidence has been reported to support that the main strategy for CNSRR relies on the combination of cell therapy and tissue engineering (Doblado et al., 2021). Thus, multidisciplinary professionals have to design platforms that serve as protecting substrates for cell transplantation, sustained-release devices of therapeutic biomolecules, and physical barriers that protected engrafted cells against embroidered immune responses. Both synthetic and natural-based polymers are suitable for reaching such goals, each class presenting pros and cons considering the required set of properties (Carvalho et al., 2021). Aiming at CNSRR, the use of materials from natural sources had been revealed to be more interesting owing to the amalgamation of biophysical features, comprehensive biological information, and biodegradability (Jensen et al., 2020). Particularly, polysaccharides are current trends in biomaterials as they offer advantages as degrading into nontoxic monosaccharides when compared to other soft matter alternatives such as proteins (Luo et al., 2021). Hyaluronic acid (HA), chitosan, alginate, gellan gum, cellulose, and their derivatives are undoubtedly the most applied polysaccharides for CNS applications. Nevertheless, agarose, dextran, starch, and heparan sulfate are also reported to be potential candidates, alone or blended with other polysaccharides or synthetic polymers (Carvalho et al., 2021).

Polysaccharides applied for CNSRR hold benefits that go beyond their easy processability: many of them are naturally bioactive and act in different front lines considering tissue regeneration. Notably, assorted polysaccharide structures encompass intrinsic anti-inflammatory, antioxidant, and immune regulatory activities (Carvalho et al., 2021). Moreover, they can be naturally remodeled by neural cells (e.g., HA) following the implantation, preventing the formation of glial scar (e.g., HA), embedding antibiotic and mucoadhesive features (e.g., chitosan) to the implant site, serving as sustained therapeutic delivery agents (e.g., alginate), or can even stimulating electric neuron activity (e.g., cellulose). Additionally, most of them can spontaneously interact with chemokines, growth factors, and signaling molecules (Ojeda-Hernández et al., 2020). Although some polysaccharides are not compliant enough for engendering bioactive substrates alone, as alginate and gellan gum, they are useful components for CNS applications following structural manipulation/blending with other biomaterials due to properties as viscoelastic and physicochemical behaviors.

Polysaccharides can be modified with relative easiness to present a diversity of desired chemical functionalities, as carboxymethyl and thiol, that serve as both anchoring sites to graft drugs or peptide motifs and as cell-substrate communication points. Yet, the latter function is not entirely unveiled because there is no consensus of the biological activities attained through their modification. Along with chain functionalization, the combination of different polysaccharides or polysaccharides with synthetic polymers is a current strategy to overcome some limitations of natural-based raw materials, such as batch-to-batch variations and limited mechanical strength (Luo et al., 2021).

Following the disclosure of important nervous ECM properties, the use of polysaccharides as base materials for building multifunctional platforms for CNSRR has been exponentially increasing. Well-designed studies revealed that the brain follows a complex viscoelastic behavior, showing important anisotropic properties and various compressive, elastic, and shear *moduli* depending on the analyzed region (Carvalho et al., 2021). Importantly, by modifying polysaccharide structure regarding the chemical functionalities, surface charge, and crosslinking density, it is possible to create substrates with tunable properties to match the intrinsic features of specific damaged sites inside the CNS. According to earlier reports, if the injured area locates within the gray matter that is mainly composed of neurons, the use of softer substrates (0.1–1 kPa) can induce better neuronal differentiation. On the other hand, if the damaged cavity belongs to white matter, which is rich in glial cells, the use of stiffer substrates (3–10 kPa) should be considered (Liu and Hsu, 2020; Carvalho et al., 2021).

When hydrated, polysaccharides can form hydrogels, mimicking the physicochemical and mechanical properties of nervous ECM, befitting the cell-material interface to regulate immunological responses and neural cell fate (Carvalho et al., 2021). Moreover, polysaccharide chemical structures can be modified to carry biochemical cues to help guide tissue recovery, as adhesion motifs, growth factors, chemoattractants, and proneural mnemonics. Along with the physicochemical and mechanical features, such structural versatility elucidates the potential of polysaccharides in CNSRR (Jensen et al., 2020; Tupone et al., 2021).

There is still no consensus regarding the decisive medical procedure to deal with CNS injuries, which represents an imperative challenge in designing future devices for CNSRR. Nonetheless, it is a unanimous opinion that such systems should be conceived in a way that can be implanted through minimally invasive surgeries. The versatility of polysaccharides allows for the *in situ* formation of multifunctional 3D structures, as reported for chitosan-based, HA-based, and cellulose-based hydrogels (Carvalho et al., 2021). Such materials can be injected into the injured cavity by very thin needles capable of achieving regions that could not be accessed by other surgical methods owing to the complexity and fragility of the nervous tissue (Jensen et al., 2020). Moreover, injectable hydrogels can better fill irregular voids in the injured cavity, providing an axonal growth-permissive environment and appropriate structural support to the surrounding tissue, which is mandatory in case of large trauma or surgical removal of tumors (Liu and Hsu, 2020). A trending approach for developing injectable hydrogels for CNSRR is the exploration of polysaccharide networks with dynamic crosslinks with shear-thinning and self-healing properties, commonly referred to as "*4D systems*" (Jensen et al., 2020). Compared to those containing covalent crosslinking, these hydrogels offer advantages as punctual remodulation of the surface by localized disruption of inter/intrachain bonds by cell activity. Such strategy allows for a deeper interaction between cell and substrate, leading to complex cellular responses and the consequent differentiation into diverse CNS cell types (Jensen et al., 2020).

The future leads to personalized solutions: Owing to the miscellaneous nature of CNS damage, heterogeneity of phenomena involved in each CNS injury, and the complexity of the neural network and synaptic architecture, it is judicious to believe that it would never be a single set of joined components (e.g., biomaterial, cell type, and maturation state, released therapeutic molecule) capable of fully complying the requirements and functions to promote CNSRR. Thus, when designing devices for CNSRR, one must take into consideration a group of specificities of the brain lesion so that the newly formed tissue would mimic as much as possible the native environment. Hence, it will be conceivable to build a platform able to support gradual tissue ingrowth by offering host and/or implanted cells a microenvironment with appropriate biochemical, biophysical, topological, and mechanical signals for developing a multifunctional tissue while fighting against specific difficulties found in the damaged area, such as exaggerated inflammatory responses and deficient vascularization.

CNS tissue engineering is expected to become gradually more personalized in terms of lesion type, site and scale of the injury, and even patient age due to natural changes in tissue through life. Thus, the more adaptable a system is to fulfill lesion demands, the higher the probability of being translated to clinical stages. In such a context, polysaccharides hold great potential once they are susceptible to being manipulated with easiness for supplying the host region with the required features without reducing their intrinsic properties. Lastly, we expect the next generation of biomaterials for CNSRR to act also as monitoring agents, providing information regarding the neuronal network formation and sensing the microenvironment conditions, including pH changes, oxygen levels, and, depending on lesion nature, the presence of toxic substances or specific signaling molecules. **Figure 1** summarizes the main features of polysaccharide-based platforms for CNSRR, evidencing the pros and cons of the use of the most applied polysaccharides, the desirable substrate properties, the expected results regarding cell differentiation, and the future trends of such systems.

To date, no polysaccharide or synthetic-based platform for CNSRR has been tested in human subjects. Much effort is still to be endeavored for achieving adequate success in the preclinical stages before translating such devices into the medical clinic, although no doubt it will be accomplished!

The present work was supported by the research funding support from Brazilian Agencies: CAPES, FAPEMIG, CNPq, and FINEP (to HSM).

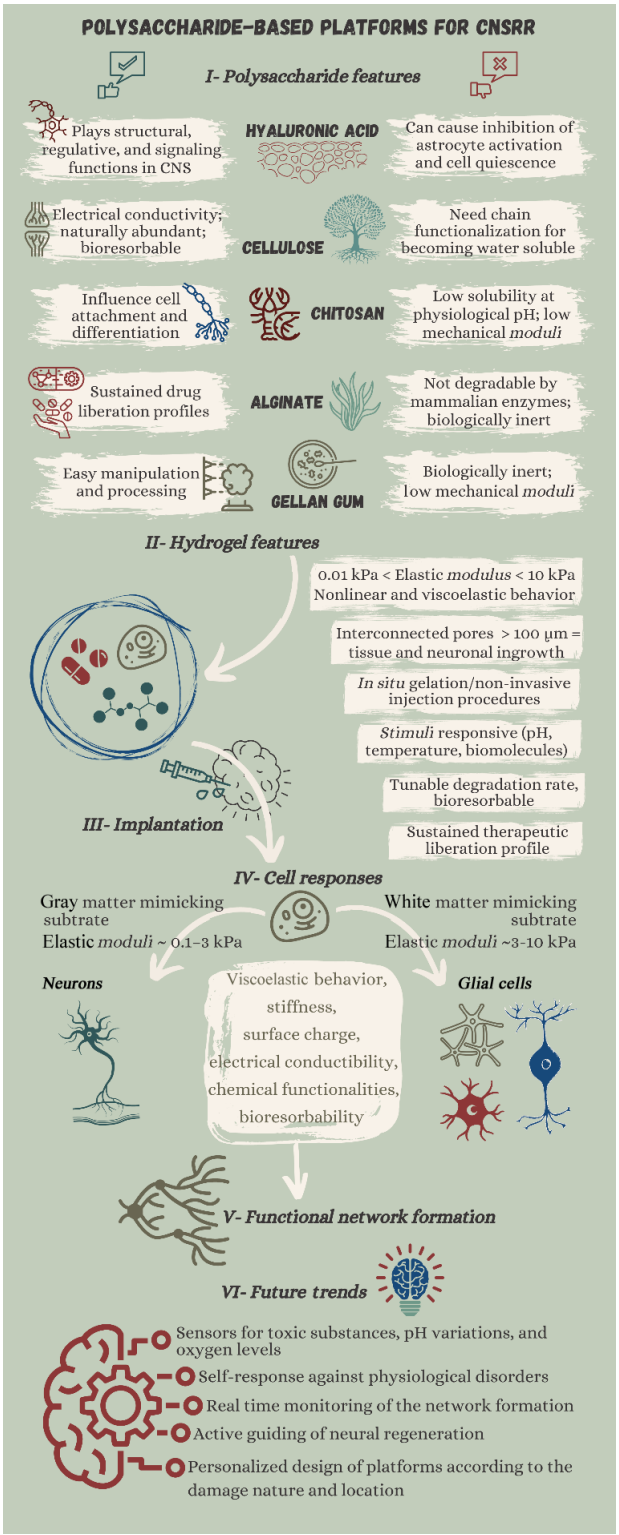

Figure 1 | **Current approach and future trends of polysaccharide-based platforms for central nervous system repair and regeneration (CNSRR).**
All reference values are presented based on the best-achieved results reported in the consulted literature.

Isadora C. Carvalho, Herman S. Mansur*
Center of Nanoscience, Nanotechnology and Innovation- CeNano2I, Department of Metallurgical and Materials Engineering, Federal University of Minas Gerais, Belo Horizonte, MG, Brazil
***Correspondence to:** Herman S. Mansur, PhD, hmansur@demet.ufmg.br.
https://orcid.org/0000-0002-3032-495X (Herman S. Mansur)
Date of submission: June 15, 2021
Date of decision: August 4, 2021
Date of acceptance: August 25, 2021
Date of web publication: December 10, 2021

https://doi.org/10.4103/1673-5374.330599
How to cite this article: *Carvalho IC, Mansur HS (2022) Quo Vadis? Bioengineered polysaccharide-based hydrogel scaffolds for damaged central nervous system recovery and regeneration. Neural Regen Res 17(7):1478-1480.*

Plagiarism check: *Checked twice by iThenticate.*
Peer review: *Externally peer reviewed.*

Open peer reviewer: *Patricia Setton-Avruj, Universidad de Buenos Aires, Argentina.*
Additional file: *Open peer review report 1.*

References

Ali MA, Bhuiyan MH (2021) Types of biomaterials useful in brain repair. Neurochem Int 146:105034.

Carvalho IC, Mansur HS, Leonel AG, Mansur AAP, Lobato ZIP (2021) Soft matter polysaccharide-based hydrogels as versatile bioengineered platforms for brain tissue repair and regeneration. Int J Biol Macromol 182:1091-1111.

Doblado LR, Martínez-Ramos C, Pradas MM (2021) Biomaterials for neural tissue engineering. Front Nanotechnol doi: 10.3389/fnano.2021.643507.

Jarrin S, Cabré S, Dowd E (2021) The potential of biomaterials for central nervous system cellular repair. Neurochem Int 144:104971.

Jensen G, Holloway JL, Stabenfeldt SE (2020) Hyaluronic acid biomaterials for central nervous system regenerative medicine. Cells 9:2113.

Liu Y, Hsu SH (2020) Biomaterials and neural regeneration. Neural Regen Res 15:1243-1244.

Luo M, Zhang X, Wu J, Zhao JL (2021) Modifications of polysaccharide-based biomaterials under structure-property relationship for biomedical applications. Carbohydr Polym 266:118097.

Ojeda-Hernández DD, Canales-Aguirre AA, Matias-Guiu J, Gomez-Pinedo U, Mateos-Díaz JC (2020) Potential of chitosan and its derivatives for biomedical applications in the central nervous system. Front Bioeng Biotechnol doi: 10.3389/fbioe.2020.00389.

Payne SL, Tuladhar A, Obermeyer JM, Varga BV, Teal CJ, Morshead CM, Nagy A, Shoichet MS (2019) Initial cell maturity changes following transplantation in a hyaluronan-based hydrogel and impacts therapeutic success in the stroke-injured rodent brain. Biomaterials 192:309-322.

Tupone MG, D'Angelo M, Castelli V, Catanesi M, Benedetti E, Cimini A (2021) A state-of-the-art of functional scaffolds for 3d nervous tissue regeneration. Front Bioeng Biotechnol doi: 10.3389/fbioe.2021.639765.

P-Reviewer: Setton-Avruj P; C-Editors: Zhao M, Liu WJ, Qiu Y; T-Editor: Jia Y