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Celebrating 25 years of the Sakiyama-Elbert lab: a look back on the evolution of neural biomaterials and future directions for the field

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The field of neural biomaterials has evolved considerably over the past 25 years as new techniques and technologies have been developed for treating the diseases and disorders of both the spinal cord and peripheral nervous system. Here we provide a retrospective of the major advances in this field that correspond to the length of Dr Sakiyama-Elbert's independent research program, which has made seminal contributions to this field. As her former trainees, we also then provide insight into how the field of neural biomaterials can evolve to address the major challenges in treating the diseases and disorders of the nervous system through incorporation into new technologies in tissue engineering and regenerative medicine. This piece provides an important perspective on necessary considerations for clinical and commercial translation to ensure that such novel neural biomaterials are used to their maximum potential.

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1. Introduction

Biomaterials have played an important role in treating injuries and diseases of both the peripheral (PNS) and central nervous system (CNS).[1–6] Initially studies focused on the materials themselves and determined the appropriate scaffold formulations to ensure both biocompatibility and regenerative promoting properties for promoting nervous system repair. Often times these biomaterials would be designed to incorporate drug delivery systems to generate controlled release of factors that promote regeneration directly, such as small molecules and growth factors, or reduce inhibitory effects through the use of enzymes and other factors.[7–9] The incorporation of electrically active materials into such scaffolds has also been evaluated as an effective strategy for promoting regeneration given the importance of electrical signaling in the function of the nervous systems.[6] When developing such biomaterial-based treatments for the nervous system, it is important to distinguish between the peripheral and CNS as they possess very different properties in terms of cellular composition, immune response, and regenerative capacity.[10] The peripheral nervous system has a higher capacity for regeneration while central nervous system and its complexity are notoriously difficult to treat due to its low capacity for regeneration.

Given the complexity of the nervous system, it has become increasingly apparent that additional components must be added into biomaterial-based treatments to address the complexity of diseases and disorders of the nervous system. The technologies include the use of a variety of biological tools, including stem cells for therapeutic application and gene editing for nervous system repair.[11,12] There has also been a large increase in the use of different vectors such as viruses and extracellular vesicles[13] as delivery systems for therapeutic agents for treating the diseased and damaged nervous system. One of the major advantages of these technologies is that they can address the complex pathologies that are associated with the injuries and diseases of the nervous system by replacing lost cellular populations or modulating gene expression to induce significant biological responses. However, the field of biomaterials and tissue engineering needs to evolve to successfully combine these treatments with relevant biological tools in a clinically relevant fashion to address the pathologies of injuries and diseases of the nervous system. Overall, while the biological tools (stem cells, AAVs, gene editing, tools that enable spatial control of biology) have advanced, biomaterials have lagged, particularly with regard to CNS over PNS therapies due to its inherent complexity. There is a clear opportunity to evolve biomaterial strategies to enhance these aforementioned biological tools.

The goal of this commentary is to critically examine the evolution of biomaterial-based strategies for the spinal cord and PNS repair and *in vitro* modeling over the last 25 years, corresponding to the career of the influential neural tissue

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engineer, Dr Shelly Sakiyama-Elbert. Her lab has made seminal contributions to this expanding field, along with use of novel technologies that build upon these advances. Then we discuss how biomaterial-based treatments must evolve in tandem with these aforementioned recent biological innovations to address disease-specific needs in repairing the PNS and CNS. We also discuss with the development of *in vitro* platforms to ensure that these innovations have the appropriate impact for both clinical and translational progress. We have included a section on new technologies that can benefit from advances in neural biomaterials, including organoids, 3D bioprinting, and microfluidic systems. This evolution in approaches to neural tissue engineering has been reflected in the direction and development of Dr Sakiyama-Elbert's research program over the years as well. We then look to the future by analyzing the possibilities of combining emerging technologies with these neural biomaterials.

2. Peripheral nervous system (PNS): gaps in translation

2.1. A historical perspective on 25 years of biomaterials in the PNS

Given the propensity of peripheral nerve to regenerate following injury, the application of biomaterial-based treatments to clinically manage peripheral nerve injuries (PNIs) has had considerable progress even 25 years ago. In the clinic, nerve injuries present on a spectrum, which include damage to individual fascicles and the many axons contained within nerve that may be recoverable, not requiring surgical intervention, or non-recoverable, requiring intervention. For those requiring intervention, while overly simplistic, the range of treatment options can be generally categorized as neurorrhaphy (*i.e.* direct nerve end-to-end repair or nerve transfer), gap reconstruction (*i.e.* nerve gap or neuroma-in-continuity then reconstructed), or when nerve ends cannot be repaired, reconstructed to prevent neuroma formation at the proximal nerve end. For all these interventions, while meaningful levels of recovery can be achieved, no treatment fully restores patient function to their original functioning level. Therefore, there is a desire for adjunct therapies, such as biomaterials or biological tools, which could theoretically overcome this limitation.

During the last 25–50 years, the focus has been on reconstruction of nerve gap injuries, where the utility of biomaterials is most obvious (*i.e.* replace the missing tissue) despite the wide-range of PNIs seen in the clinic. Table 1 provides a summary of the major advances in this area of research. For nerve gap reconstruction, nerve autografts are considered the ''gold standard,'' which involves the harvest of patient's own nerve resulting in subsequent loss of function at this donor site.[14] To supplant the need for autograft in this reconstruction, research began examining alternatives, starting with silicone conduits for bridging the gap in the early 1980s. From that period, biomaterials research advanced to focus on the use of biocompatible synthetic materials (*i.e.* poly(lactic-*co*-glycolic acid) (PLGA), polylactic acid (PLA), and polycaprolactone (PCL)) or naturally derived materials (*i.e.* collagen, fibronectin) that could be used to produce nerve conduits. The first commercial PNI products, a polyglycolic acid (PGA) and a collagen-based conduit for use in nerve gap injury reconstruction, was FDA approved in 1999 (Neurotube®) and 2001 (NeuraGen®), respectively. Moving into the 2000s, there have been at least 13 similar biomaterial-based products that have been approved by the FDA by the end of that decade to treat nerve gap injuries.[14] However, these devices are simplistic by today's standard for the field, where these products consist of empty tubes, ranging from naturally-derived protein-based materials (NeuraGen®) to synthetic polymers (most common are Neurotube®, Neurolac®, and SaluBridge®). Perhaps unsurprising in retrospect, these materials are only indicated to treat nerve gap injuries for short distances between

Table 1 Peripheral nerve injury biomaterial-based treatment advances

Nerve injury type	Key advancement	Ref.
Nerve gap repair	Synthetic nerve conduit as alternative to nerve autograft introduced	Lundborg *et al.*[25] (1979) Lundborg *et al.*[26] (1982)
	Protein-derived nerve conduit	Archibald *et al.*[27] (1991)
	FDA approved nerve conduits	Neurotube® (1999) NeuraGen® (2001)
	Acellular nerve allograft introduced	Hudson *et al.*[20,21](2004)
	FDA approved acellular nerve allograft	Avance® (2007)
	Conduits incorporating drug delivery	Aebischer *et al.*[28] (1989) Fine *et al.*[29] (2002)
	Affinity-based drug delivery system	Sakiyama-Elbert *et al.*[17] (2000) Lee *et al.*[19] (2003)
	Use of drug (GDNF) to overcome long nerve gap limit (>3 cm)	Fadia *et al.*[30] (2020)
	Use of longitudinal structures to overcome long nerve gap limit (>3 cm)	Radtke *et al.*[31] (2011) Smith *et al.*[32] (2022)
	Use of immunomodulation to overcome long nerve gap limit (>1 cm)	Mokarram *et al.*[33] (2012) Mokarram *et al.*[34] (2017)
	Use of human Schwann cells to overcome long nerve gap limit (>3 cm)	Burks *et al.*[35] (2021)
Neurorrhaphy	Polymer wrap with microhooks to repair nerve in clinical use	Eberlin *et al.*[36] (2024)
	Light activated polymer-assisted repair in clinical use	Wlodarczyk *et al.*[37] (2024)
Neuroma	Nerve capping device advancing to clinical trials	Faust *et al.*[38] (2022) Borcherding *et al.*[39] (2025)

nerve ends (*i.e.* ~1–3 cm). Both animal and clinical studies revealed that these products can only promote nerve regeneration up to a 1–3 cm gap length, where repaired gap lengths longer than 1–3 cm fail to promote any nerve regeneration or recovery.[14] This limitation spurred innovation in the decades ahead, including major contributions from Dr Shelly Sakiyama-Elbert.

Basic research into the 2000s developed strategies to treat these gap injuries focused on biomaterials incorporating controlled drug release, tissue engineered scaffolds to fill the conduits, at times including cells (typically Schwann cells or stem cells), and the generation of bioelectric materials to integrate electrical signaling cues to stimulate regeneration.[15,16] Within these strategies, there was a marked focus on directly targeting and stimulating axons to grow to achieve regeneration across long (*i.e.* >1 cm) nerve gaps, to overcome the current commercial conduit limitations. It was during this time that Dr Shelly Sakiyama-Elbert's seminal work with Dr Jeffrey Hubbell introduced an affinity-based drug delivery system (ABDS), which was first targeted at addressing PNIs through the use of axonal-targeting growth factors.[17,18] In contrast to diffusion-based release, ABDSs immobilize drugs within a matrix *via* non-covalent interactions. While diffusion-based drug release is controlled by passive movement of molecules through a medium from a concentration gradient, affinity-based release is mediated by freeing the drug from molecular bonds and interactions. ABDSs improve on diffusion-based systems from using molecular interactions to control drug release, preventing rapid "burst release," stabilizing fragile proteins (like growth factors), and allowing for stimuli-responsive or tailored release profiles, such as axon or cell migration through a matrix.

In their seminal work, Sakiyama-Elbert and Hubbell developed an ABDS that sequestered proteins in a fibrin matrix using non-covalent interactions.[17,18] This system utilized a cleavable bi-domain peptide that incorporates into a fibrin matrix (cleavable portion), while the other domain can non-covalently interact with drugs or other molecules in tandem with drugs. These first studies utilized nerve growth factor (NGF) to promote axon growth within the fibrin-based ABDS to promote nerve regeneration, where this approach was able to promote nerve regeneration across >1 cm nerve gap in rats.[19] This work then expanded to include other neurotrophins and stem cells for CNS application, as discussed in detail in the next section (Section 3).

Perhaps most notable during this time was the development of acellularized scaffolds. Acellular tissue scaffolds are generated using techniques to retain a large portion of native ECM proteins while minimizing cellular debris and undesired immunological response (*i.e.* rejection). A detergent based protocol developed by Hudson *et al.*[20] has been the only processing technique to translate, which would lead to the development of a processed nerve allograft and its commercialization with FDA approval in 2007 (Avance®).[20,21] This product, arguably, has had an outsized impact on patient care in the PNI space, as this product is now used in the majority of nerve gap reconstructions (for gaps <3 cm) over other commercial conduits or even autografts.[22] Despite these advances, the reconstruction of long nerve gaps (*i.e.*, >3 cm), even with the Avance® product which is indicated for up to 7 cm nerve gaps, remains an unmet challenge. In a retrospective analysis, the use of Avance® to repair nerve gap injuries resulted in meaningful motor recovery in 67% of patients with gap lengths <3 cm, but only 38% with gap lengths between 3 and 5 cm, and 10% with gap lengths >5 cm.[23] In a separate study from failed cases of gap repair using[14] ANAs, histology of the reconstruction revealed axons with limited elongation within the ANA, ultimately failing to regenerate across the repaired gap.[24] Thus, there was still a need to advance biomaterials and biological tools to treat PNIs.

2.2. Current state of the art for treating the PNS

The challenge of promoting nerve regeneration across long nerve gap injuries still remains unresolved. For long nerve gap injuries (>3 cm), autografts are still considered the "gold standard" for surgical repair.[14] However, towards biomaterial-based treatments showing great promise, mimicking the internal nerve architecture, primarily the longitudinal nature of peripheral nerve endoneurial structure, has demonstrated considerable progress (Fig. 1a). More recent efforts have demonstrated recapitulating the resolution of this microstructure is critical to success, as early attempts at microchannels on the order of hundreds of microns within a nerve scaffold demonstrated only moderate success.[40] Reducing the scaffolding channels to the precise size of axons, on the order of 1–20 μm, has demonstrated an ability to capture the endogenous architecture of nerve, and will likely be necessary to surpass the nerve autograft in promoting regenerative success.[41] And most importantly, the incorporation of longitudinal structures within nerve conduits has demonstrated the ability to promote nerve regeneration across long nerve gap injuries (>3 cm) in large animal models,[31,32] a major step towards translation of next-generation nerve conduit products.

Additionally, major strides in biomaterial-based treatments moving toward the current era have largely been inspired by an improved understanding of the underlying biology guiding peripheral nerve regeneration. For nerve gap injuries in particular, an improved understanding of how non-neuronal cells, principally macrophages, endothelial cells forming vessels, and Schwann cells act in concert and synergy within a regenerating short gap injury to form an endogenous structural, mechanical, and biochemical microenvironment conducive to promoting nearly complete axonal regeneration across the gap.[42,43] This understanding has resulted in shifting the focus of biomaterials to therapeutic avenues to stimulate these non-neuronal cells, rather than solely targeting the regenerating axons, as a means to overcome the challenge of achieving regeneration across long gap injuries. At the same time, more advanced biomaterials have been generated to construct nerve conduits, ranging from hybrid or composite naturally-derived materials incorporating synthetic fibers or nanomaterials, metal-based biomaterials capable of delivering biofunctional metal ions, to smart-responsive materials that respond to cells as they integrate with the material during ongoing regeneration.[44–46]

Similar to wound repair, peripheral nerve injury and regeneration involves a complex interplay of different immune cells,

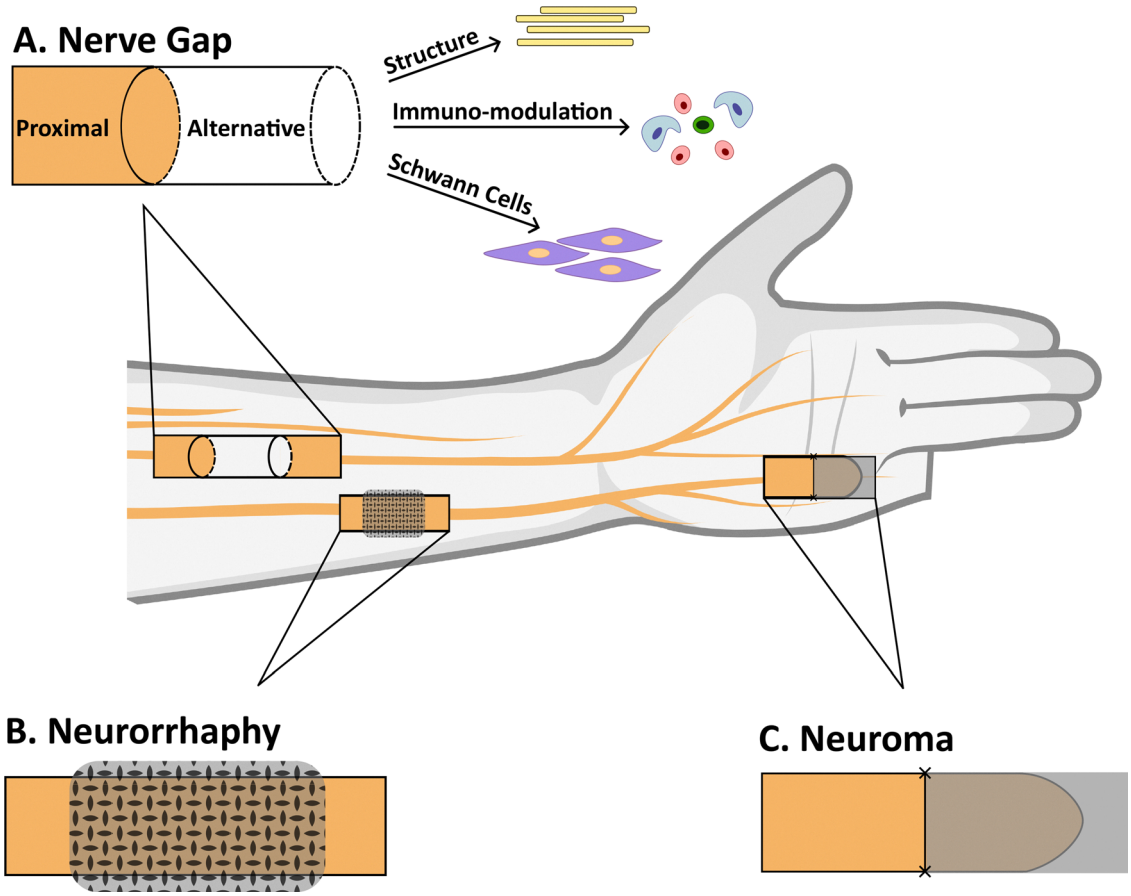

Fig. 1 Schematic showing the architecture of the peripheral nervous system and the different conditions (A) nerve gap, (B) neurorrhapy and (C) (neuroma.) (A) The reconstruction of nerve gap injuries has emphasized the importance of scaffolding with longitudinal structures, as well as therapies targeting immunomodulation and promotion of Schwann cell phenotypes. (B) The direct repair of nerve without a gap (neurorrhapy) has progressed with products addressing suture-less repair. (C) End-neuroma can be treated with a nerve "caps", which leverage knowledge on nerve gap reconstruction to arrest nerve regeneration in a controlled fashion and prevent interaction with the microenvironment.

making immunomodulation a pivotal strategy. The type of immune response, its duration, and the immune cells involved can drastically change the outcome of tissue regeneration, especially upon scaffolds. In the case of nerve gap injuries, initially recruited macrophages primarily repopulate the bridging device, as these cells respond to the hypoxic environment and stimulate angiogenesis, but also respond to the foreign body. The recruitment of macrophage and initiation of angiogenesis is generally considered part of the pro-inflammatory phase to wound healing. This initial pro-inflammatory response, or Type 1 response, is characterized by processes that enhance recruitment of a diverse range of leukocytes, expression of pro-inflammatory cytokines, and polarization of macrophages to a pro-inflammatory (or "M1") phenotype. Following pro-inflammatory signaling, an anti-inflammatory response, or Type 2 response, directly promotes tissue regeneration, characterized by cytokines, such as Interleukins (ILs)-4, IL-10, and IL-13. These cytokines classically promote pro-regenerative immune cell phenotypes, such as the anti-inflammatory (or "M2") macrophage. Given the predominance of macrophages, immunomodulatory approaches to biomaterial design have primarily targeted manipulating macrophage responses (Fig. 1a). Seminal studies from Bellamkonda's lab highlighted how pro-inflammatory signaling reduced nerve regeneration across a gap by delivering pro-inflammatory cytokines from nerve conduits used to repair the gap, while regeneration was improved by delivering anti-inflammatory cytokines.[34,47,48] While these strategies demonstrated regeneration across >1 cm nerve gap injuries in preclinical (rat) models, there have been no follow-on studies to demonstrate capabilities in larger gaps (*i.e.* >3 cm), where the new development of products is needed. As well, there is still a knowledge gap in regards to the role of the diverse range of leukocytes and their responses during nerve regeneration. For example, T cells and eosinophils have been identified within nerve gap injuries during regeneration,[49–51] while significantly lesser in quantity than macrophages ($\sim$1–2% of cells repopulating a nerve gap). These immune cells, compared to macrophages, can respond to the same immunomodulation with distinct effects complicating potential outcomes from immunotherapies. This knowledge gap has arguably slowed translation of immunomodulatory approaches until greater immunobiology is understood.[50]

Alternatively, an increasing number of studies have highlighted the power of harnessing Schwann cells to promote regeneration.[52] Schwann cells are critical to nerve regeneration after injury, as these cells dedifferentiate from myelinating axons

into a "repair" phenotype, proliferate, and produce regeneration-associated factors to promote axon regeneration.[53] The addition of exogenous, cultured Schwann cells can improve nerve regeneration across nerve conduit or acellular nerve allografts repairing a nerve gap.[54] Now, transplantation of Schwann cells has demonstrated success in treating human nerve gap repair.[35,54] However, the difficulty and expertise associated with the isolation and culture of primary Schwann cells has limited wide-spread clinical adoption. Alternatively, promoting an expansion of existing endogenous Schwann cells, either through localized drug delivery from biomaterials[55,56] or through genetic engineering,[57] has yielded success to recapitulate the most important features of the regenerative nerve microenvironment to promote axonal regeneration (Fig. 1a), but with caveats. More research, potentially using advanced genetic tools such as cell engineered genetic circuits, will be required to facilitate capturing the precise timing and effects from phenotypic shifts of Schwann cells. Transitioning from repair to myelinating and mature Schwann cells is critical to avoid undesired effects, as failure to transition from repair phenotype to myelinating impairs recovery.[57] And still within Schwann cells research is the under-researched area of sensory and motor Schwann cell phenotypes,[58] championed by Dr Shelly Sakiyama-Elbert, which may hold unknown keys to improving modality-specific functional recovery (*i.e.* sensory *vs.* motor).

Beyond the treatment of nerve gap injuries, one of the largest shifts in the field in the recent era has been the consideration of technology to address the broader spectrum of PNI management, such as neurorrhaphy reconstruction for injuries without a nerve gap, and neuroma, where nerve repair is not possible. At the start of the 2000s, bioengineering and biomaterials research was focused almost exclusively on treatments for nerve gap injuries. As nerve gap injuries only represent a fraction of PNIs, bioengineering and biomaterial innovations to augment surgical reconstructions had and have only touched the surface of potential improvements. In the case of direct neurorrhaphy repairs (*i.e.* without a gap), biomaterial-based treatments have begun to address suture-less repair with commercial solutions (Fig. 1b). As surgeons have been traditionally limited by mechanical solutions (sutures) to repair nerve, biomaterial-based treatments have been advanced, now either at the clinical trial stage, or FDA approved. Some examples of these solutions include polymer wraps with manufactured microhooks,[36] or light-activated polymer-assisted systems,[37,59] both which avoid deep and damaging penetration of needles within nerve that generate scar impeding axon regeneration.

Building upon the concept of improving neurorrhaphy reconstruction, biomaterials for this purpose (rather than gap repair) incorporating drug release or bioelectric materials are becoming increasingly more poignant. Nerve coaptation devices, wraps, or conduits have been developed to augment repair by targeting axons to increase the growth rate of axons, as overcoming the slow growth of axons (only $\sim$1–3 mm day^{-1}) will be paramount to improving the state of PNI management and patient outcomes.[60] As well, the construction of wraps and conduits capable of the same nerve-repairing features combined with biodegradable, bioelectronically doped materials have been developed for use in nerve reconstructions.[61] Given that operative exogenous electrical stimulation therapies are entering advanced clinical trials for greater wide-spread adoption as a treatment paradigm,[62] and degradable stimulating electrodes with power supplies have already been developed,[63] these technologies could be combined to capture the growth promoting effects for sustained regenerative periods that are required in many severe peripheral nerve injury scenarios.

Downstream from the nerve injury site, addressing end-organ muscle wasting has begun to see therapeutic solutions; however, only few exist to date. While functional recovery after PNI requires axon regeneration, functional recovery is also limited by progressive atrophy of denervated muscle. Therefore biomaterial-based treatments, such as nanoparticles that provide sustained mitogenic therapy to affected muscle, have demonstrated promise to prevent muscle wasting and thus improve functional recovery following the upstream peripheral nerve injury.[64]

Finally, as a direct divergence from promoting nerve regeneration, instances where nerve regeneration is to be avoided, such as neuroma, have taken lessons learned from nerve gap reconstructions to design so-called nerve "caps" (Fig. 1c). Neuroma is a bulbous mass of tangled axons that can form after peripheral nerve injury and causes chronic pain. Neuroma occurs when regenerating axons cannot reach their target location and instead engage in aberrant, misdirected, and disorganized growth – likely due to pathological interactions between the axons and their surrounding nerve and tissue environment. An estimated 3–5% of all peripheral nerve injuries result in neuroma formation[65–67], while neuroma incidence following extremity amputation is reported to be as high as 48% after lower limb amputation and 25% after upper limb amputation.[68,69] When surgical options to repair nerve (*i.e.* neurorrhaphy or nerve gap reconstruction from removing the neuroma) are not possible, likely due to severe damage or removal of the distal nerve, there is no consensus solution. An approach using a biomaterial solution, such as a nerve cap, has gained traction and has considerable simplicity to implement. These devices are made of biologic or synthetic degradable materials, providing an impermeable closed-ended conduit that prevents the escape of sprouting axons forming at the proximal nerve end, to isolate the transected nerve end from the surrounding environment.[38,39] While nascent technology, the incorporation of controlled drug release as well as other advanced technology already developed for the field of regeneration, could be adapted for this new alternative purpose to prevent or arrest axonal growth and treat pain.

2.3. Outstanding challenges for treating the PNS

Both broad and specific challenges remain to progress treatments for managing peripheral nerve injuries that can potentially be addressed using new technologies. Broadly, balancing new therapeutic solutions and options with regulatory hurdles to commercialization and increased cost to customers is arguably the largest dilemma for the field, as basic options are available to treat a range of management strategies as just presented. Then, more specifically, the greatest need for progress is in the domain

of long nerve gap reconstruction and neuroma prevention/treatment. For example, despite the aforementioned progress in long nerve gap repair, with technologies demonstrating robust axon regeneration, no intervention fully restores patient function to their original levels of function. Perhaps most discouraging, neuroscience understanding that identifies what is missing to achieve full restoration of function has not yet been determined despite robust axon regeneration. Therefore, ongoing research that integrates new findings in neuroscience to biomaterials or biological tools will be needed to continue to advance patient care.

At present, some challenges that remain are within reach to solve. For the reconstruction of nerve gap injuries or capping nerve to prevent neuroma, the continued advancement of biomaterial devices could utilize personalized features that accommodate the tremendous diversity of nerve structural organization that could be encountered during surgery. When nerves are repaired, the individual fascicles are intricately matched by surgeons, as the fascicle or topology of nerve confers important functional information. Individual fascicles are typically sensory and motor, and therefore, mixing fascicles can diminish recovery due to mismatch of regenerating axons to their original end-organ targets (*i.e.* skin or muscle). The number and arrangement of fascicles, as well as their sizes, within each given nerve vary greatly, where existing solutions, whether conduits or processed nerve grafts, are generally "generic" to any nerve with the exception of diameter and length of defect encountered. This enhanced topographical feature is critical for advancement given that nerve fascicular topology is paramount to reconstructive efforts to achieve functional recovery, or limit axon regeneration from axonal misdirection due to fascicle escape in the case of neuroma. Thus, customization in design for these devices is required, either allowing the surgeon to individually repair each fascicle, or the ability to custom "print" conduits containing this fascicular arrangement for each unique scenario of nerve reconstruction (Fig. 2). Additionally, incorporating these changes would improve surgical efficiency, reducing error and time

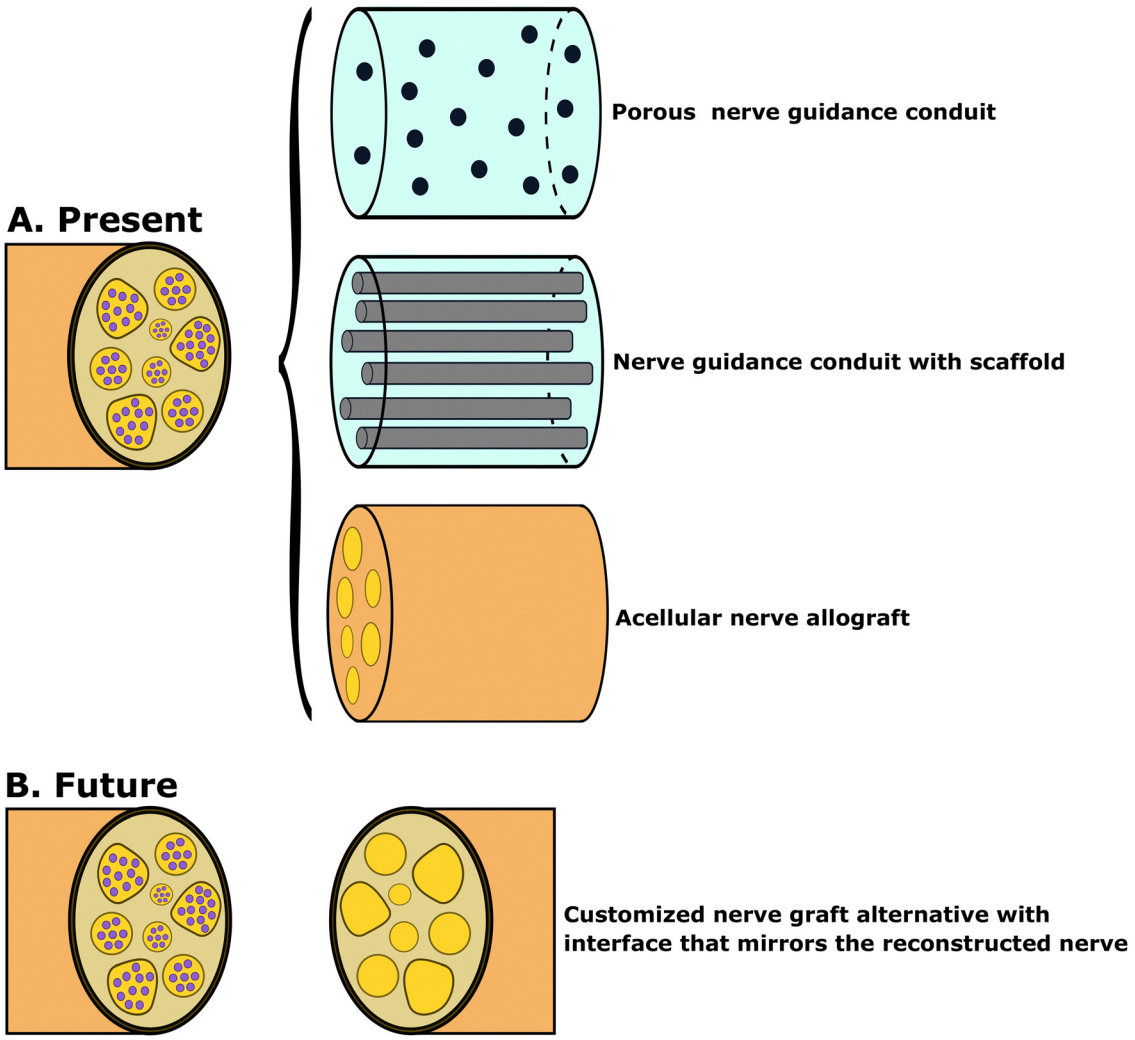

Fig. 2 The past and future of nerve grafts for treating injuries in the PNS. (A) The present shows nerve conduits, with and without scaffolds and longitudinal channels, to mimic neural structure. Alternatively, acellular nerve products, also mimic nerve structure. However, these structures are presently "generic" and do not necessarily match nerve topographically. (B) The future would envision nerve devices that "mirror" the nerve being reconstructed, where topographical information, such as a fascicle sizes, number, and arrangement are precisely matched to the reconstruction.

during surgery for reconstruction. These accommodations at present seem best-suited to advances in imaging to visual the needed nerve structure to mimic, combined with 3D printing technologies, as remarkable customization is facilitated by this manufacturing process.[70,71] While this specific topographic customization within nerve has not yet been demonstrated, the complex branching of nerve has been custom printed with a nerve conduit incorporating complex internal scaffold cues to promote regeneration across long regenerative distances.[72]

3. Spinal cord biomaterials: supporting regenerative biologic therapies

3.1. A historical perspective on 25 years of biomaterials in the CNS

Inspired by the daunting challenge of regenerating the CNS, the body's most architecturally intricate and inhospitable microenvironment, neural biomaterials research over the past 25 years has spawned waves of innovations in scaffolds, drug delivery vehicles, and cell–support systems. We focus here on the spinal cord, reflecting Dr Sakiyama-Elbert's specific interests and contributions to the field; however, many concepts discussed share thematic similarities with other CNS regions. Table 2 shows the key advances in biomaterials for regenerating the CNS. Early studies in the 2000s, including Dr Sakiyama Elbert's pioneering use of fibrin matrices for controlled neurotrophin delivery, highlighted the potential of biomaterials to provide both structural support and bioactive cues for endogenous tissue remodeling.[17,18,73–75] Her lab was among the first to combine biomaterials with controlled growth factor release with co-deliver growth factor release and cell transplantation to promote differentiation and survival,[76–78] and their fibrin scaffolds have been successfully used by others for human neural stem cell transplants for over a decade. This choice has proven prescient: fibrin remains one of the most widely used materials for CNS transplantation,[79] demonstrating long-standing efficacy in preclinical models and a more favorable safety profile than many synthetic materials in the path to FDA approval. Strategies at the forefront combine the intrinsic advantages of natural materials—such as biocompatibility and bioactivity—with engineered structural features designed to guide regeneration.[80,81] For example, injectable biomaterials developed to conform to the delicate and irregular spaces of CNS injuries without exerting additional pressure or damage emulates consideration for the fragile microenvironment of the brain and spinal cord.[82,83] A major focus has been fabrication of three-dimensional architectures: aligned fibers, patterned conduits, and microchannel scaffolds have been designed to direct neurite extension along preferred pathways, mimicking the guidance cues of developing neural tissue.[84,85] Meanwhile, the development of sophisticated drug delivery systems capable of releasing both pro-regenerative and anti-inhibitory factors highlights the field's ingenuity in combining diverse synthesis techniques and materials to meet the complex demands of CNS repair in the harsh post-injury microenvironment.[78,86–89]

Despite myriad advances, the efficacy of biomaterials as standalone interventions for spinal cord regeneration has not been realized. Limited intrinsic regeneration, persistent inflammation, and complex inhibitory signaling hinder repair on the timescales needed to exploit transient pro-regenerative windows. These challenges are compounded in humans by much greater lesion distances, larger tissue voids, and significant anatomical differences in the spinal cord compared with rodent models.[90–92] Even combinatorial biomaterial approaches designed to support transplanted cells, despite promising preclinical data, have rarely advanced beyond early-phase clinical trials. Closer examination reveals that the choice and quality of cell populations have often been suboptimal. For example, the idea of mesenchymal stem cells as valuable trophic support for CNS repair persists in the

Table 2 Spinal cord injury biomaterial-based treatment advances

Key advancement	Ref.
Fibrin glue used to restore function in an SCI model	Cheng *et al.*[98] (1996)
Development of affinity-based drug delivery systems (ABDS) for controlled release of neurotrophins	Taylor *et al.*[73] (2004), Taylor *et al.*[99] (2006), Johnson *et al.*[100](2009)
Development of injectable poly(ethylene glycol) hydrogels for controlled release of neurotrophins	Piantano *et al.*[101](2006)
Development of agarose hydrogels for controlled release of neurotrophins	Jain *et al.*[102] (2006)
Development of injectable hyaluronan and methylcellulose hydrogels for SCI	Gupta *et al.*[103] (2006), Khaing *et al.*[104] (2011)
Templated scaffolds filled with different ECM proteins (matrigel, fibrinogen, collagen) promote regeneration post SCI	Tsai *et al.*[105] (2006)
Combining fibrin-based ABDS with neural progenitors to treat SCI	Johnson *et al.*[74] (2010), Johnson *et al.*[76] (2010)
Controlled delivery of anti-NogoA from biomaterial scaffolds for SCI repair	Stanwick *et al.*[106] (2012)
Combining fibrin scaffolds with human neural progenitors to treat SCI	Lu *et al.*[107] (2012)
Aligned biomaterial channels for SCI repair	Tuinstra *et al.*[108] (2012) Pawar *et al.*[109] (2015)
Controlled delivery of chondroitinase from methylcellulose scaffolds promote SCI regeneration	Pakulska *et al.*[110] (2013)
Combining hyaluronan-based gels with neural progenitors to treat SCI	Mothe *et al.*[111] (2013)
Combining fibrin-based ABDS with engineered progenitor motor neurons for SCI repair	McCreedy *et al.*[77] (2014), Wilems *et al.*[78] (2015)
Decellularized nerve-based hydrogels for SCI repair	Cerqueira *et al.*[112] (2018), Lin *et al.*[113] (2018), Cornelison *et al.*[114] (2018)
Combining hyaluronic acid scaffolds with engineered V2a interneurons for treating SCI	Thompson *et al.*[115] (2018)
Combining injectable PEG-based hydrogel with hiPSC-derived neural progenitors for SCI repair	Doulames *et al.*[116] (2024)
Granular hydrogels for stem cell delivery for treating SCI	Tigner *et al.*[117] (2024)
3D bioprinted scaffolds containing stem cells for SCI repair	Han *et al.*[118] (2025)

literature,[93] even though similar effects can occur with nonviable cells,[94] and neuroscientists increasingly emphasize the importance of neuronal relay mechanisms for functional recovery.[95] Perhaps the integration of rigorous neurobiology with biomaterials research has been underemphasized, a challenge that is both technically demanding and costly for classically trained materials scientists. Many technologies are still developed for rodent cell populations or experimental models that repeatedly fail to translate,[96,97] rather than being designed around human cells closer to GMP standards and severe injury paradigms. As a result, each new effort requires reinvention and reoptimization, diverting limited resources toward approaches unlikely to succeed. Meanwhile, the fields of stem cell biology, gene therapy, and synthetic biology are accelerating, bringing human stem cell-derived products and genetic interventions into the clinic for CNS diseases once presumed uncurable.

This landscape suggests that the future of biomaterials in CNS repair lies not in isolated use but as synergistic platforms supporting proven regenerative modalities. Reflecting on past limitations and aligning biomaterial development with therapies that are already achieving clinical impact may help the field reclaim relevance and accelerate meaningful outcomes for patients.

3.2 Current state of the art in spinal cord biomaterials

Numerous high-quality reviews have comprehensively described the use of biomaterials for spinal cord repair,[2,119–122] therefore, this section only highlights major themes underlying what we see as the most successful approaches in recent years. Historically, a diverse range of both natural and synthetic polymers has been explored, including extracellular matrix (ECM)–derived materials such as collagen, laminin, fibronectin, and hyaluronic acid (HA), as well as polysaccharides like agarose, chitosan, cellulose, and methylcellulose, alongside synthetic systems including polyesters (PLGA, PGA, PLLA), methacrylate-based polymers (PMMA, PHEMA), silicones such as polydimethylsiloxane (PDMS), polyethersulfone (PES), polyethylene terephthalate (PET), polycarbonates, and polyurethanes. Despite extensive investigations, the limited success of many of these materials has progressively narrowed the field toward biomaterials that are injectable and can be precisely tuned to recapitulate the mechanical and biochemical properties of the native spinal cord ECM. Also, given the complexity of SCI, the best biomaterial candidates have often demonstrated feasibility for supporting hPSC-derived populations. HA-based hydrogels have received particular attention due to their abundance in the CNS, roles in cell–cell and cell–matrix signaling, and compatibility with injectable delivery.[103,104,123,124] Similarly, multi-arm polyethylene glycol (PEG) platforms have enabled the development of injectable hydrogel[116,125,126] or granular microgel scaffolds[117] that support cell transplantation and tissue integration. Scaffolds incorporating decellularized spinal cord-derived components have also gained traction because these hybrid systems unite the tunability of synthetic or semi-synthetic matrices with cell-instructive biochemical cues of native extracellular matrix, preserving adhesion ligands, growth factor-binding domains, and matrix-bound signaling molecules.[115,127–129] Notably, work from the Sakiyama-Elbert group combined ECM derived from mouse embryonic stem cells (mESC)-derived astrocytes with HA hydrogels and showed that ECM from pro-regenerative, but not fibrous, astrocytes reduced glial scarring and improved neuronal integration,[130] underscoring the importance of cell-type-specific, non-generic ECM in spinal cord regeneration. This study also highlights the need for sophisticated biomaterials that mimic the region specific properties of tissues like the spinal cord.

Collectively, the most promising scaffold designs share common features: they are functionalized, tunable, and injectable, support host and transplanted cell survival and growth, and minimize harmful inflammatory host responses. However, challenges remain, including scalable and reproducible scaffold fabrication, sourcing of materials, particularly xenogeneic ECM components—and, for cell-instructive scaffolds, incorporating clinically translatable human cell types and conducting preclinical studies that demonstrate benefit beyond cell transplantation alone.

3.3 Emerging areas in spinal cord repair

Over the past 25 years, stem cell technology has transformed from an aspirational concept into a realistic therapeutic platform for spinal cord repair. Dr Sakiyama-Elbert lab has been a pioneer in this space, particularly in the differentiation and transplantation of mESCs for SCI. In 2010, Johnson *et al.* showed that transplanting mESC-derived neural progenitors within a fibrin scaffold after SCI improved behavioral function, but excessive proliferation of the graft emphasized the need to purify cell populations for translation. This observation guided the next decade of research in the Sakiyama-Elbert laboratory, establishing them as leaders in developing developmental biology–inspired methods to generate discrete spinal cord interneuron types[131–138] and astrocytes[139] from mESCs cells for transplantation. Dr Sakiyama-Elbert hypothesized that certain cell types would be more critical than others for recovery, and mESC-based resources provided an ideal system to test this systematically without the complications of human–rodent xenotransplantation. These studies have been foundational for subsequent efforts to differentiate human PSC-derived spinal cord cell types; in particular, V2a interneurons[140–142] which have been identified as cell lineage critical for functional recovery after SCI.[143] Recent rodent fetal graft studies have shown that both cell phenotype (dorsal *vs.* ventral)[144,145] and regional identity (brain *vs.* spinal)[146] shape graft integration and interneuronal relay formation *vs.* long-tract regeneration, highlighting the need for complimentary biomaterials and cell therapy strategies that recreate the host's physical, biochemical, and cellular composition.

The derivation of human embryonic stem cells (hESCs) and later human induced pluripotent stem cells (hIPSCs) in 2007[147] established the possibility of scalable, patient-specific cell production for transplantation. The initial surge of enthusiasm sparked by the hope that stem cells could overcome the limited regenerative capacity of the CNS faltered during the early years[148,149] but is now being rekindled as the field achieves tangible clinical milestones. These early efforts were hindered by suboptimal stem cell isolation techniques, lack of standardized benchmarking, and

inadequate quality control of desired cell populations. Such limitations contributed to the underwhelming outcomes of initial clinical trials, such as the Asterias/Geron trial for oligodendrocyte precursor cell (OPC) transplantation for spinal cord myelination which failed to progress for both financial and biological reasons.[150] Since then, advances in iPSC generation, cryopreservation, and standardized quality control have led to the production of GMP-quality cell banks that are now in use across the industry.[151,152] Improved neural differentiation methods have been marked by the shift away from animal-derived materials such as serum and Matrigel toward chemically defined media formulations. In cases where embryoid body differentiation was once considered essential to guide neural development, the discovery of dual SMAD inhibitors for 2D adherent culture[153] has increased speed, yield, reproducibility, and control over neural cell fate. Coupled with the identification of key morphogens, these improvements have enabled precise, region-specific differentiation and high-purity cell populations. Clinical-grade differentiation protocols for hPSCs now produce neurons for Parkinson's disease,[154–156] epilepsy,[157] retinal degeneration,[158–160] and SCI[161] as well as glial progenitors for stroke[162] and ALS.[163] This specificity not only correlates strongly with functional outcomes but also enhances quality control needed for regulatory compliance. Multiple Phase I and Phase II clinical trials are underway internationally, providing critical insights into the challenges and requirements for next-generation therapies.

In parallel to stem cell technologies, advances in gene editing driven by the development of CRISPR/Cas9[164,165] in 2012 have driven two complementary research trajectories pertinent to CNS regeneration: the use of gene editing to generate human neural populations for *in vitro* modeling, and the use of synthetic biology to engineer transplanted or endogenous cells as therapeutic delivery systems. The Sakiyama-Elbert laboratory was ahead of its time in applying synthetic biology to spinal cord modeling and repair,[166] using BAC recombineering in the early 2010s to generate mESC lines that produced pure progenitor[77,132] and post-mitotic motor neurons[131] *via* antibiotic selection. The advent of CRISPR democratized gene editing, accelerating these efforts and enabling the production of pure V0v,[137] V2a,[134] and V3[133] interneuron populations using similar strategies. While effective in mESCs, where differentiation efficiencies were high, these approaches are less practical for hPSCs, as inserting long transgenes into transcriptionally active sites is more challenging, differentiation is slower, yields are often lower, gene silencing can occur, and regulatory requirements make translation particularly difficult.

Direct reprogramming *via* transcription factor upregulation has become a preferred strategy for generating near-pure populations from hPSCs for translational applications. Since the discovery of the BAM factors in 2012 to rapidly reprogram human neurons, the field has advanced significantly.[167] Researchers can now rapidly generate neurons (*e.g.*, *via* NGN2[168]) and glia (*e.g.*, *via* SOX9/NFIA[169]) populations using lentiviral, transposon-based, or transgenic systems on virtually any genetic background. This makes relevant human cell populations more accessible than ever to laboratories without extensive expertise in human cell culture, improving the reproducibility of disease models and enabling deeper preclinical assessment of translational potential. Ongoing efforts are exploring new gene combinations to generate highly specific cell lineages, such as the NGN2-LHX3-ISL1 cassette for lower motor neurons,[167] and developing hybrid differentiation strategies that combine small-molecule approaches with direct reprogramming to produce region-specific populations, including ventral spinal interneurons and motor neurons.[170] As the FDA and other regulatory agencies increasingly request data with human cells to better predict clinical outcomes,[171] integrating these approaches into tissue engineering approaches using biomaterials will be essential to remain translationally relevant. However, at this time, direct reprogramming strategies are currently best suited for *in vitro* applications and may have limited utility for spinal cord transplantation, as they focus on post-mitotic cells that are unlikely to survive the stress of transplantation, and synthetic genetic materials pose additional immunogenic and regulatory hurdles. *In vivo* editing of astrocytes and other scar components remains of interest but is technically difficult, a potential area where biomaterials could aid in targeting and improving outcomes.

Beyond modeling, gene editing and gene delivery strategies are being used therapeutically. The first gene therapy for spinal muscular atrophy, which employs an adeno-associated virus (AAV) vector to deliver SMN1,[172] has transformed patient outcomes allowing children who would not have survived beyond age two to live into their second decade.[173–175] While side effects continue to be studied, the success of a single-dose gene therapy has catalyzed a surge of other approaches, including antisense oligonucleotides (ASOs) and RNA therapies, to modulate gene expression for a wide range of CNS conditions, including rare diseases. The idea of cells as drug delivery vehicles is also gaining momentum. For example, new clinical trials for amyotrophic lateral sclerosis (ALS) are testing glial cells engineered to overexpress GDNF, leveraging astrocytes' intrinsic ability to migrate, integrate into surviving neural networks, and persist far longer than traditional biomaterial systems.[163] At the same time, efforts to create universal stem cell lines by knocking out human leukocyte antigen (HLA) proteins for "off-the-shelf" products aim to reduce or eliminate the need for immunosuppression.[176]

Collectively, these advances represent first-pass approaches to repairing the CNS that already show efficacy without biomaterials, prompting a crucial question for the field: how can we build on 25 years of biomaterials innovation to integrate these new modalities? Thoughtful combinations of biomaterials with gene- and cell-based therapies could enable more reproducible manufacturing, improved cell survival, enhanced spatial control, and ultimately better clinical outcomes.

3.4. Outstanding challenges for treating the CNS

Despite advances in experimental therapies at the bench, patients with SCI continue to face a substantial gap in clinical care, with no curative options that restore function or promote long-term repair. Designing biomaterials with intervention timing in mind is critical and should be reevaluated in light of new basic science insights into differential cell responses

and plasticity mechanisms. Early acute-stage strategies should focus on glial remodeling,[177] microglial response,[178] and inflammation reduction during decompression surgery,[179] whereas chronic-stage approaches may emphasize corticospinal tract repair,[92,180] and neurostimulation[181–184] to promote endogenous rewiring of host networks. Moving beyond the vision of biomaterials as standalone solutions for SCI, research should focus on overcoming translational challenges in biologic therapies with emerging clinical success, including biomanufacturing, immunomodulation, and complementary drug delivery. Repurposing existing biomaterials for these applications can deliver immediate clinical impact by enhancing the delivery, efficacy, and consistency of nascent therapies beyond what biology alone can achieve.

Biomanufacturing of high-quality, clinically relevant neural cell populations remains a formidable challenge, as each biological product requires unique conditions for expansion, differentiation, and storage.[185] Material substrates could be leveraged to scale up production, improve reproducibility, and streamline differentiation processes, thereby generating consistent, GMP-grade cells for transplantation or *in vitro* modeling. This progression is already happening in the cellular agriculture space, which is translating lessons learned from biomedical scale-up principles to food production and distribution,[186] and for adoptive cell therapies.[187] While efforts are underway to develop hydrogels for scaling hPSCs,[188–190] rodent neural populations[191,192] and organoids,[193,194] meaningful clinical impact will require an immediate shift toward expanding spinal cord-specific cell populations with GMP compatibility, as failure to do so risks necessitating redevelopment of scale-up strategies at later translational stages. 3D biomaterials-based scale-up of some brain types has begun,[195,196] but efficiencies remain lower than in 2D, posing a significant challenge for meeting regulatory requirements for controlled, reproducible cell production. Biomaterials also offer opportunities in process development, acting as transplant vehicles designed to improve cell viability, promote self-organization *in vivo* and/or reduce handling errors for surgeons. Novel cryoprotectants[197] for cell suspensions or even intact 3D tissues could minimize stress and apoptosis in fragile populations and preserve engineered architectures for off-the-shelf use. Incorporating bioelectrical properties into materials[198,199] may also accelerate the maturation of neural populations, which remains slow due to the inhospitable environment of the injured CNS, although such strategies will require careful balancing with potential toxicity.

Immunomodulation continues to be an urgent priority when developing implantable therapies. Despite the historical view of the CNS as immune privileged, disruption of the blood-brain or blood-spinal cord barrier—whether by injury or regenerative intervention—elicits acute and chronic immune responses that can jeopardize transplanted cells and devices.[200] As cell therapies advance through clinical trials, the long-term consequences of tapering immunosuppressive regimens, including the risk of graft rejection, remain unresolved. Engineered cell products may introduce immunological burdens beyond allogeneicity, as viral delivery systems, synthetic transgenes, and biomanufacturing byproducts[201] can elicit additional adaptive or innate immune responses. Because autologous cell therapies are still distant and universal cell lines or HLA banks may not be sufficient, biomaterials should be designed to address distinct objectives: dampening the initial immune response *versus* promoting long-term tolerance.[202]

Finally, drug delivery remains a powerful complementary approach. Targeted delivery of small molecules, biologics, or gene-editing tools can support neurogenesis, enhance regeneration, and reduce the inhibitory environment. For example, emerging anti-Nogo antibody therapies are showing promise in clinical trials for promoting corticospinal tract recovery[203] after SCI, and biomaterials should be engineered to accommodate such biologics. Future platforms may also integrate thermostable or engineered proteins that require only short-term expression, aligning with the temporal needs of regeneration and reducing chronic exposure risks.[204,205] Ultimately biomaterials strategies for CNS repair must move beyond static scaffolds toward dynamic, multifunctional systems amenable to scalable production, precise delivery, immune protection, and enhanced integration of advanced cell and gene therapies.

4. Shifting from animal models to human-based systems for evaluating treatments for the nervous system

A notable shift has occurred in fundamental and applied research in recent years with the movement away from using animals to model diseases and test potential drugs. This shift reflects both the ethical issues with performing such studies, as well as their translational limitations. An additional argument can be made that such humanized models reduce the impact on the environment due to using less resources and generating less waste in comparison to animal models. This shift reflects that the human biology associated with neurological diseases and disorders cannot be recapitulated in animal models due to limitations in their biology. Recent legislation in the United States has eliminated applications to the National Institutes of Health that focus only on animal studies – indicating the transition to more humanized models of the nervous system for studying the nervous system and analyzing the effect of potential disease modifying treatments. The invention of induced pluripotent stem cells in 2006 opened up a world of possibility as these stem cells generated by reprogramming patient derived cells provided unprecedented ways to model the human biology of disease.[206,207] This impact was particularly profound for neuroscience as the human central nervous system has a much higher degree of complexity in comparison to animal models and many neurodegenerative diseases have genetic components. These cells provide an important way to model such diseases and they provide significant insight into the variation that occurs in these diseases[208,209] (Fig. 3). The next section will discuss recent advances in using such cells to model the nervous system. In particular, we have chosen to focus on neural organoids, microphysiological systems and 3D bioprinting as these three technologies stand to benefit from

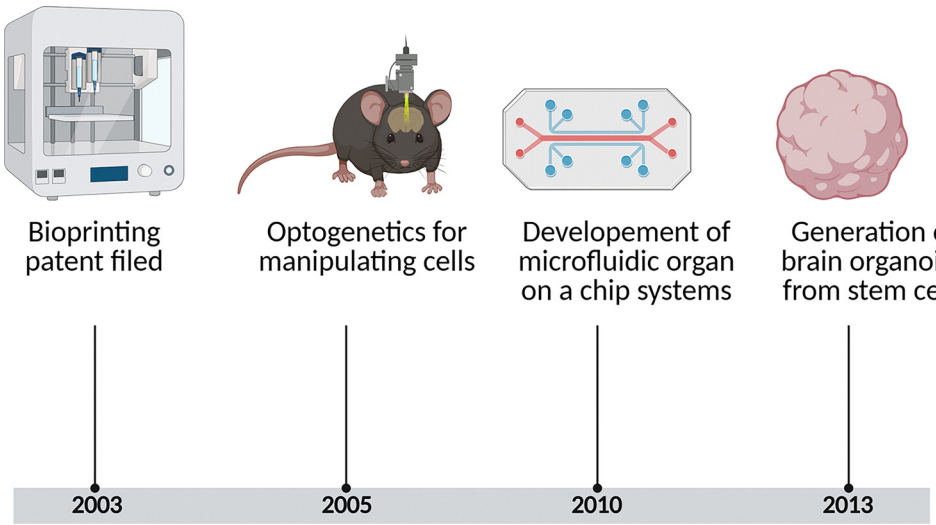

Fig. 3 Timeline of development for emerging technologies for replacing animal models include organoids, microphysiological systems, and 3D bioprinting which can be paired with advances in biotechnology such as optogenetics. Created in Biorender.

advances in neural biomaterials to better replicate the physiological properties of the nervous system.

4.1. Enabling technologies for treating the nervous system

Recent advances in biotechnology have generated ways to use human cells to replicate the microenvironment found *in vivo*, providing key advantages over traditional 2D cell culture. Technologies, including organoids, microphysiological systems, and bioprinting, have emerged as the main contenders for replacing the use of animals to study neurodegenerative diseases and injuries to the nervous systems. Organoids – tissue structures that form based on the intrinsic properties of the stem cells from which they are derived – have become an increasing popular way to model the structures found in the brain.[210] Organoids from different regions of the brain and spinal cord can be joined together to study their interactions and these complex structures are referred to as assembloids.[211,212] Organoids can also be generated to mimic peripheral nerves as well, providing a way to probe their activity in a humanized system.[213] There are some drawbacks to using organoids as they require extensive labor to be produced, limiting throughput, and they also suffer from reproducibility due to relying on the intrinsic properties of the stem cells used. The use of biomaterials can enhance the reproducibility of the organoids as well as generate region specific organoids as these protocols often require the use of biomaterials like Matrigel and collagen to ensure appropriate differentiation. For example, the ability to generate microstructures and apply chemical and electrical gradients can promote consistency during the organoid production process.[214] Biomaterial scaffolds can also be used as carriers to enable scale-up production of neural organoids as well, which can address current limitations when using neural organoids as an alternative to animal models. However, these challenges can be addressed as this technology continues to mature.

Another popular technology for studying the nervous system is the use of microphysiological systems (MPS).[215,216] These microfluidic based systems are often referred to as a ''lab-on-a-chip'' and they use small volumes of liquids and cells to mimic human tissues, including those found in the central and peripheral nervous system. Dr Sakiyama-Elbert's research has taken advantage of these neural system on a chip models to study transport in healthy and diseased neurons[217,218] as well as the effects of GDNF.[219] Additionally, these tissue chips can be linked together to create multi-organ systems. They can also be combined with neural organoids to study the healthy and diseased nervous system.[220] Many MPS have been translated commercially through companies like Emulate which sells a popular MPS for modeling the blood brain barrier. As with any system containing multiple cells types, ensuring the media formulation is appropriate to keep all the cells alive and functioning is challenging. Biomaterials can also be used in combination with MPS as a way to ensure cell survival and function inside of these systems as they provide a 3D microenvironment that mimics the conditions found *in vivo*.[221] The presence of such materials in MPS systems can also be used to direct cell behavior depending on their architecture and microstructural properties. Also, the small scale of these systems can make it difficult to study diseases and disorders that have complex pathology.

3D bioprinting neural tissues has also gained popularity in recent years as a tool for studying the nervous system.[222] It is an additive manufacturing process where a 3D structure is produced using cell laden bioinks based on the instructions contained in a computer aided design file. A recent cell stem cell study detailed how this technology has advanced showing how to model complex neural interactions between neurons and astrocytes in both healthy and diseased neural tissues, indicating the power of this technique.[223] This process is often more reproducible than organoid generation. However, it does require significant amounts of cells to produce physiologically relevant phenotypes and bioinks for printing are often expensive. Biomaterials play a crucial role in this process as they serve as the platform for developing bioinks. A wide variety of

bioinks have been evaluated for use in 3D bioprinting neural tissues.[222] Fibrin-based bioinks have become increasingly popular as a tool for bioprinting neural tissue as this biomaterial has been used in several studies to produce functional and complex neural tissues. 3D bioprinting of functional neural tissue will also benefit from recent trends in the field towards using smart bioinks and machine learning to optimize these processes.[224,225] An additional benefit of being able to control the shape of the construct means that this technology lends itself well to the production of nerve guidance conduits.[226] This technology can also be used to generate a large number of constructs for high throughput screening of potential drug targets.

All of these systems have the potential to incorporate human immune cells to further expand their relevance for modeling diseases. For example, microglia play an important role in regulating the immunity of both the healthy and diseased nervous system[227] and these important cells can be included in the aforementioned models of the human nervous system. Additionally, these systems can also be probed using newer molecular biology tools, such as single cell-omics, including spatial RNA-seq to determine cellular composition of complex multicellular structures, live imaging, and optogenetics to provide insight into the structure and function of these human tissue models. There are some caveats when working with such systems, including the ethics of making chimeric systems that incorporate human cells into animal models[228] and concerns about the use of human neural organoids given their potential for generating thought.[229] Overall, these technologies provide important ways to advance the field of neural biomaterials and tissue engineering.

5. Conclusions

As described in this commentary, biomaterials have played a key role in advancing the field of neural tissue engineering over the past 25 years that correspond to Dr Sakiyama-Elbert's career and her important work in advancing this field forward. Building upon this strong foundation of work as we look to the future of this field, it is essential for biomaterials to become more accessible to biologists and clinicians to fully integrate these technologies being developed by the materials engineers as treating disorders of the nervous systems requires an interdisciplinary approach given their complexity. For example, the journal cell stem cell has recently began publishing articles focused on technologies as a way to bridge this technological gap between engineers and biologists, showing the importance of interdisciplinary collaboration.[230] This process will require a shift towards developing such technologies through a user centric approach where the needs of the end user – whether it is a lab scientist, clinician or patient – and their associated human factors needs are being considered. Additional factors to consider when developing the next generation of biomaterials include figuring out how to make such systems adaptable for high throughput screening when looking for potential therapeutics by considering the cost, standardization of the materials, and reproducibility. These same considerations also apply to other reagents like cell culture media and biologics given how complicated it can be to keep the sensitive cells of the nervous system alive and functioning both *in vitro* and *in vivo*. All these factors will help to ensure that the highest quality research is being achieved.

Author contributions

All the authors came up with conceptual framework and contributed to the writing and revision of this manuscript.

Conflicts of interest

Dr Willerth is the C. E. O. of Axolotl Biosciences, a biotechnology company that sells bioinks for 3D printing tissue models. Dr Wood is a co-founder of Tissuelock, LLC, a biotechnology company that develops wound and tissue plane closure devices for reconstructive operations.

Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.

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