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Review Article

Advances in nerve guidance conduits for peripheral nerve repair and regeneration

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Abstract: Peripheral nerve injury (PNI) can cause partial or total motor and sensory nerve function, leading to physical disability and nerve pain that severely affects patients' quality of life. Autologous nerve transplantation is currently the clinically recognized gold standard, but due to its inherent limitations, researchers have been searching for alternative treatments. Nerve guidance conduits (NGCs) have attracted much attention as a favorable alternative to promote the repair and regeneration of damaged peripheral nerves. In this review, we provide an overview of the anatomy of peripheral nerves, peripheral nerve injury and repair, and current treatment methods. Importantly, different design strategies of NGCs used for the treatment of PNI and their applications in PNI repair are highlighted. Finally, an outlook on the future development and challenges of NGCs is presented.

Keywords: Peripheral nerve injury, nerve guidance conduits, nerve regeneration

Introduction

The nervous system is divided into the central nervous system (CNS) and the peripheral nervous system (PNS) [1]. The CNS is the most complex system in the human body and is responsible for integrating and processing the information transmitted by nerves and directing the responses of different parts of the body organs [2]. And the PNS is an extensive network of neurons that connects muscles, glands, and the CNS throughout the body. Its nerves are responsible for conveying the instructions from the CNS [3, 4]. The CNS and PNS work together to control sensory input, information integration, and motor output, forming a highly specialized body system that mobilizes all parts of the body to respond to multiple changes in the environment [5].

However, PNI is a major health problem worldwide, with more than 1 million PNI occurring annually worldwide [6]. In the United States alone, half a million surgical procedures are performed each year at a cost of up to $1.5 billion [7], resulting in a significant socio-economic burden. CNS disorders are usually caused by trauma, disease, and surgery, which can lead to motor dysfunction, sensory impairment, and neuropathic pain [8, 9]. The CNS injuries do not regenerate spontaneously, and to date, there have been no reports of effective clinical treatment for CNS injury. On the contrary, PNS has the potential to regenerate after injury [10-12]. Autologous transplantation is currently the gold standard for the treatment of PNI [13, 14]; however, it has plenty of limitations, such as donor scarcity, donor size mismatch, and immunological problems [15, 16]. Therefore, new approaches are urgently needed to restore the structure and function of the injured peripheral nervous system.

With the development of tissue engineering techniques, NGCs have emerged as a prospec-

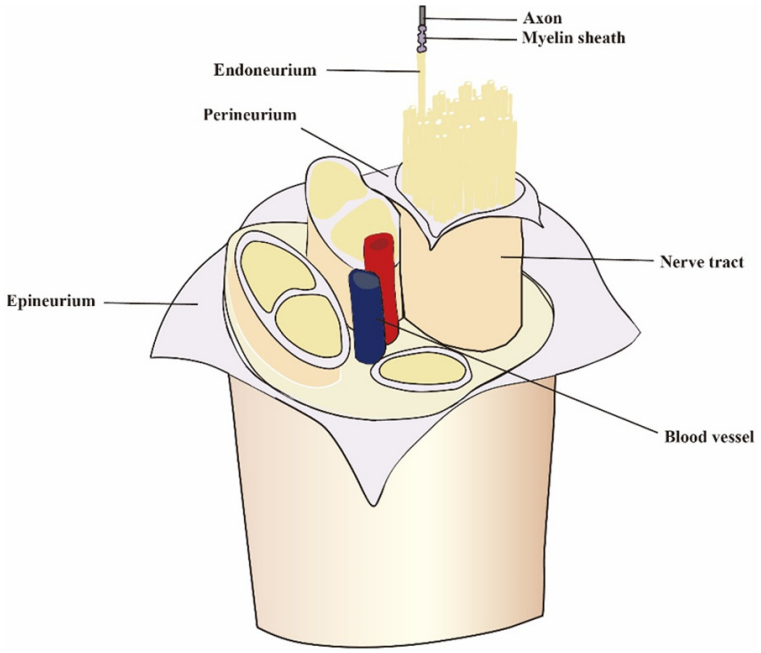

Figure 1. Peripheral nerve anatomy. The three layers of the nerve fiber includes epineurium, perineurium, endoneurium.

tive method to facilitate nerve repair. NGCs are tubular structures that provide a supportive and appropriate microenvironment for nerve regeneration by bridging the severed ends of nerve injuries. In this review, we review the different designs of NGC for nerve regeneration in recent years. What's more, the future research directions and development prospects of NGCs are also discussed.

Anatomy and injury of peripheral nerves

Peripheral nerve anatomy

The peripheral nervous system includes a collection of the nerves stemming from the brain and spinal cord, as well as the ganglia associated with them. The nerves that derive from the brain and spinal cord are called cranial and spinal nerves, respectively, and consist of nerve fiber bundles [5]. The nerve fiber bundles consist of multiple longitudinal arrangements of axons and are covered by three layers of connective tissue. These layers play an important role in the movement of nerve fibers in the body. On the one hand, they protect nerve bundles from stretching and compression. On the other hand, it contains blood vessels (neurovessels) that provide nutritional support for nerve fibers [17].

From the inside out, nerve fibers and connective tissue consist of three layers, which are shown in **Figure 1**. The innermost layer is the endoneurum, including loose collagenous matrix, nerve fibers, Schwann cells (SCs), fibroblasts, endothelial-like cells, mastocytes, and so on, which protect these cells from mechanical forces. The second layer is the perineurium, which contains epithelium-like cells and collagen fibers and will wrap each fascicle individually, providing strong mechanical protection for the nerve bundle. The outermost layer is the epineurium, which contains blood vessels that flush nerves and some fatty tissue. It plays an important role in isolating the external environment and providing mechanical protection [18]. The most basic cells in PNS include endothelial cells, macrophages, mastoid cells, and neurons. In addition, other supportive cells have been found in the PNS, including macrophages, satellite glial cells, and SCs, which are critical to axonal regeneration. Specifically, macrophages have a strong ability to phagocytose foreign bodies, contributing to endocytosis of damaged nerve fibers and myelin fragments [19-21]. Satellite glial cells play an important role in regulating the external microenvironment, thereby promoting axonal regeneration of peripheral nerves [22-24]. SCs produce extracellular matrix (ECM), neurotrophic factors, cell adhesion molecules, and other molecules conducive to nerve regeneration to provide a supportive environment for cells in tissue. SCs are divided into two types: myelinated SCs encircle large diameter axons one by one in the myelin sheath, while unmyelinated SCs surround multiple small diameter axons without producing myelin.

Peripheral nerve injuries

PNI can cause damage to the sensory and motor nerves, resulting in partial or complete loss of function and even disability, which seriously affects the quality of life of patients [25-27]. The higher the degree of injury, the more

complete the loss of function and the more difficult the repair. According to the severity of the injury, nerve injury is divided into five grades [28]. Grade I PNI is the mildest, caused by ischemia or focal demyelination due to traction or mild compression. For grade II injury, only the axons are damaged with the rest of the structure is intact. For grade III injury, the axons are damaged and the nerve lining is destroyed. For grade IV injury, the epineurium is the only intact structure, and the axons, endoneurum, internal nerves, and nerve bundles are all damaged. Finally, the grade V injury is complete damage to the entire nerve trunk [29]. After axon damage, both myelinated and unmyelinated SCs undergo extensive reprogramming to promote and guide axonal repair. These SCs then secrete chemical molecules including cytokines and neurotrophic factors, to support the survival of injured neurons, promote axon regeneration, and guide the regenerated axons to reconnect with their original targets [30-32].

Current treatment methods

Although the peripheral nervous system has the ability to self-repair and regenerate, it cannot fully recover due to scattered axonal growth, scarring, and neuroma obstruction. Unfortunately, direct suturing is limited by the loss of nerve tissue and the tension on the sutured nerve [33]. Therefore, microsurgery implantation of replacements is required for larger interstitial nerve injuries to achieve nerve regeneration and functional recovery. Current treatments for PNI can be divided into two types: surgical treatments and non-surgical treatments. Electrostimulation [34-39], magnetic stimulation [40-42], laser therapy [43], as well as the introduction of growth factor [44, 45] are the main approaches for accelerating nerve repair and regeneration. Benefiting from these non-surgical treatments, short gaps of injured peripheral nerves can regenerate to some extent. However, the disadvantages of these methods should also be considered. For example, the frequency range and duration of electrical stimulation must be carefully selected, as higher frequencies and prolonged stimulation may aggravate nerve injury [5]. Although many studies have reported a variety of applications of magnetic stimulation in nerve regeneration [46-48], which can efficiently facilitate axonal regeneration and functional repair, some studies have questioned the application of variable magnetic fields in nerve repair [49]. Walker et al. used 3 different modes of magnetic stimulation on rats with sciatic nerve injury, and unfortunately, they did not observe any difference in functional recovery [50]. Moreover, the success rate of non-surgical treatment for PNI is unclear [5].

Compared with non-surgical treatment, surgical treatment is more commonly used in the treatment of PNI. Generally, surgical treatments mainly focus on transplantation, including allografts, autografts, and tissue engineering grafts [5, 51]. As with other organ transplants, nerve allografts require systemic immunosuppression. However, the widespread use of nerve allografts has been limited by problems associated with immunomodulatory therapy [52]. Despite the problems of immunosuppression, nerve allografts still appeal to scientists. This is due to the fact that the immunosuppression can be prevented by adding host Schwann cells to the nerve allograft [53]. Moreover, Safa et al. reported a meaningful recovery in 82% of patients when the peripheral nerve repair gap was 70 mm, which is comparable to those of autologous nerve transplantation [54]. In addition, the advantages of allografts also include the absence of donor site morbidity and the small wounds caused by surgery, which make it possible to reduce postoperative pain [55].

Autologous nerve transplantation is considered to be the most reliable clinical treatment for PNI [56, 57]. One of the advantages of autologous transplantations is their ability to revascularization, which is an essential regeneration process for damaged tissues [58]. Revascularization reduces oxygen deprivation at the damaged site and promotes the delivery of nutrients and cells for nerve regeneration [59]. However, there are several critical and unavoidable drawbacks in the application of autologous nerve transplantation, including the damage of donor site, insufficient supply of donor nerves, and mismatch between donor and recipient nerves [60, 61]. Therefore, researchers have been exploring better methods to treat PNI that overcome the limitations of autologous transplantation. Tissue-engineered grafts have been a hot research topic for the treatment of PNI in recent years. NGCs synthe-

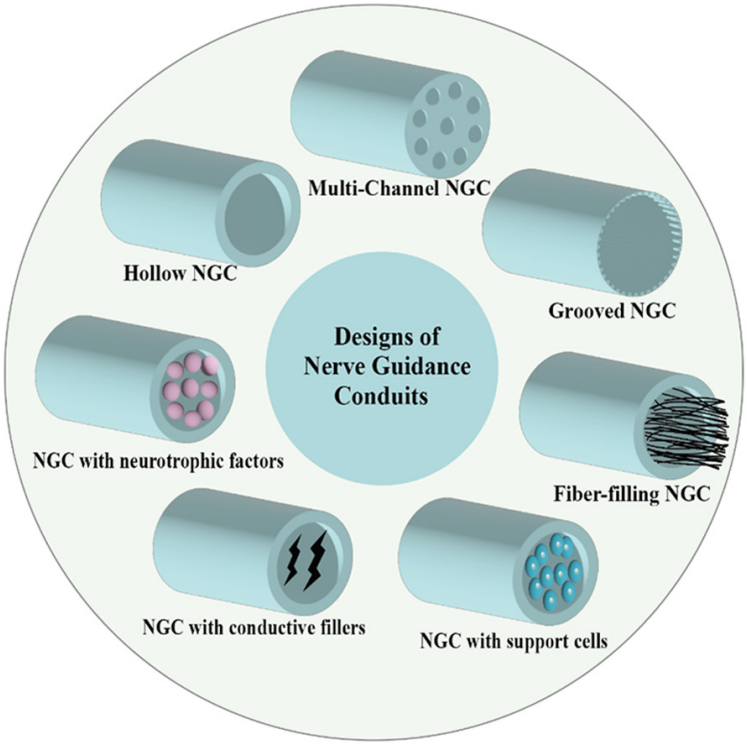

Figure 2. Different designs of NGC include hollow NGC, multi-channel NGC, grooved NGC, fiber-filling NGC, and NGC loaded with neurotrophic factor, conductive fillers and support cells.

sizing various cues have even received more and more researchers' attention and extensive studies (**Figure 2**).

NGCs with mechanical cues for PNI

The most typical tissue engineering strategy is to construct NGCs by natural, synthetic, or semi-synthetic biopolymers to repair nerve injury, which may contain biochemical cues to promote nerve regeneration and repair [7, 62]. Importantly, NGCs can address the problems of donor site disease, limited supply, and the secondary incision of autografts [5]. The US Food and Drug Administration (FDA) has approved the construction of NGCs based on collagen, polyglycolic acid, and polylactide-ε-caprolacton [33], which have shown good performance in PNI repair, suggesting that artificial NGCs may be a promising solution for PNI regeneration. NGCs with different morphological and mechanical cues have attracted much attention. The main designs of NGCs include hollow design, multi-channel design, grooved design, and NGCs with fillers [63].

Hollow NGCs

Due to the approval of the FDA, hollow NGCs are more clinically acceptable compared to other types of NGCs [64]. Studies have shown that the hollow NGCs can prevent the infiltration of fibroblasts and allow the accumulation of neurotrophic factors (NTFs), thus providing clues for nerve regeneration. It can also prevent the formation of neuromas and scarring at the wound site, promote axial sprouting, and prevent the invasion of fibroblasts [65]. The most commonly used techniques for preparing hollow NGCs include electrospinning, solvent casting, cross-linking, physical film winding, melt extrusion, and weaving [66]. NGCs can also be prepared by selecting a certain method based on the desired properties [67]. However, hollow NGCs still have limitations in that they can lead to incomplete nerve regeneration due to the axonal dispersion and innervation of the regenerated nerves [68].

Multi-channel NGCs

Multi-channel conduits achieve neural orientation by restricting the space for axonal regeneration by sub-channels, preventing the dispersion of biochemical signals and providing topographical guidance [69, 70]. Therefore, many researchers have studied the application of multi-channel NGCs in nerve repair. Lee et al. designed a multi-channel NGC based on the functional Arg-Gly-Asp. They performed a 10 mm sciatic nerve transection in a rat model and evaluated the effectiveness of the NGCs after 8 weeks. The results showed a significant improvement in nerve electrophysiological activity of NGC-guided regenerated nerve compared to autologous nerve grafts. Furthermore, NGCs were comparable to autologous nerve grafts in terms of functional recovery and target muscle [71]. In another study, Frost et al. prepared electrospun multi-channel NGCs using polycaprolactone (PCL) or poly-L-lactic acid

(PLLA) and used them to bridge a 10 mm defect in the rat sciatic nerve to study their repair effects. It was demonstrated that these multichannel NGCs could promote axonal regeneration in vivo [72]. Zhang L et al. developed an extrusion-stretching method to prepare multichannel NGCs without the use of solvents and electric fields, which avoids the potential effects of traditional preparation methods on cells or tissues. The prepared multi-channel NGCs loaded with multi-walled carbon nanotubes (MWCNTs) have improved flexibility and multifunctionality, which can enhance the axonal growth and promote the formation of anisotropic tissue [73].

Grooved NGCs

Grooved NGCs have anisotropic groove structures on their inner walls which can provide topographic cues for cell migration and neurite extension [74, 75]. The material topology plays a significant role in nerve regeneration, and the simulation of this structure will facilitate the directional growth of nerve axons [76, 77]. Wang Z et al. prepared polyacrylonitrile NGCs by the dry-spraying and wet-spinning method and incorporated microgroove structures on their inner surface to repair PNI in Sprague Dawley (SD) rats. It was found that the repair ability of the prepared NGCs was similar to that of autologous transplantation. In another study, researchers designed a composite NGC by filling decellularized rat nerves or kidneys into poly(lactic-hydroxyglycolic acid) (PLGA) grooved conduit and introducing biochemical signals. The obtained NGCs were then transplanted to repair sciatic nerve injury in rats for 16 weeks, the results showed that decellularized nerves promoted nerve regeneration more effectively than decellularized kidneys. Moreover, compared with the simple decellularized tissue, the decellularized tissue combined with grooved PLGA conduit was significantly more effective in repairing PNI [78]. These findings provide support for the design of NGCs and provide guidance for improving neural tissue engineering strategies.

Fiber-filling NGCs

Unfilled NGCs have enough space to allow free nerve growth and to reconnect with their proper targets. In contrast, NGCs with fillings provide physical and biological support to direct cell growth and extension [65]. Therefore, in order to achieve long-gap PNI repair, the internal filling of NGCs may be a decisive factor. Many types of nanofibers have attracted special attention due to their properties similar to natural ECM and have been used to fill the NGCs [79].

Jeon J et al. prepared porous patterned NGC filled with aligned fibers (PA-NGC) with microgrooves on the inner surface of the lumen. The prepared NGCs were then implanted into a 10 mm deficient rat sciatic nerve model to investigate their ability to support nerve regeneration. The findings indicated that the growth rate of neurofilament in the PA-NGC group was significantly better than that the group of NGCs filled with random fibers. It also displayed the best performance on electrophysiology, muscle wet weight, and muscle fiber diameter [80]. In another study, the researchers designed an original spiral-shaped NGC with an array of nanofibers and wrapped with outer nanofiber tubes. In vivo application in a 10 mm model of sciatic nerve defect in SD rats showed that the novel spiral NGC promoted nerve regeneration. The results of gait analysis, electrophysiological examination, histological evaluation, and gastrocnemius measurements indicated that the constructed NGCs offered a more ideal microenvironment for peripheral nerve regeneration than conventional NGC [81]. The results of this study have important implications for improving tissue engineering strategies for PNI treatment.

NGCs with biochemical cues for PNI

In addition to physical cues, it is also important to create a microenvironment with high biological attractiveness that is suitable for nerve growth through biochemical cues. The electrical conductivity and neurotrophic capacity of NGCs are also crucial for the repair of PNI.

NGC with conductive fillers

Except for some fundamental properties of NGC, such as biocompatibility and biodegradability, electrical conductivity is one of the crucial properties that promote nerve regeneration [82-84]. The biological processes of wound healing, muscle contraction, and nerve signaling in the human body are greatly impacted by the presence of bioelectricity. Therefore, the

introduction of conductive materials to NGCs helps to facilitate tissue regeneration by establishing connections for the natural flow of bioelectricity within the body [85, 86].

In one study, researchers fabricated electrically conductive NGCs using a mixture of PCL and polypyrrole - polycaprolactone conductive block copolymer (PPy-b-PCL) by a novel 3D printing technique of electrohydrodynamic jetting. The technique overcomes the difficulties of controlling pore size, porosity, fiber size, and orientation during electrospinning. The authors investigated the effects of the prepared NGCs on the growth and differentiation of human embryonic stem cell-derived neural crest stem cells (hESC-NCSCs). The results showed that hESC-NCSCs could attach to and differentiate into peripheral neurons on conduits containing PCL and PCL/PPy. Furthermore, NGCs containing higher PCL/PPy content were more effective in promoting the growth and maturation of nerve cells and [87]. Hu et al. prepared conductive topological scaffolds by modifying *Morpho* butterfly wings with reduced graphene oxide nanosheets and brain-derived neurotrophic factor and manually curling into NGCs for PNI repair. Their results suggested that the modified wings could facilitate the growth and orientation of nerve cells. Additionally, the obtained conductive NGCs showed a great performance in repairing rat sciatic nerve 10 mm defects [88]. In conclusion, these findings show that the conductive NGCs have potential clinical application value for PNI repair and regeneration.

NGCs with neurotrophic factors

NTFs can bind to cell receptors to regulate and direct cellular activities. Meanwhile, NTFs can promote neuronal survival, axonal regeneration, and SC migration [89-91]. Therefore, the introduction of NTFs in NGCs can further promote the regeneration and repair of injured nerves. By combing various therapies for promoting peripheral nerve regeneration, Chang et al. designed a naturally degradable multi-channel scaffold with oriented electrospun nanofibers and a neurotrophic gradient (MC/AN/NG). In vitro results suggested that the neural stem cell differentiated cells extended their neurites along the aligned nanofibers. What's more, the cell density was higher in areas with higher nerve growth factor concentrations, and the neurotrophic factors significantly improved myelination. When transplanted into rabbit sciatic nerve injuries for repair, the results showed that their fabricated MC/AN/NG NGCs exhibited better performance in nerve and muscle functional recovery than autologous nerve grafts [92]. In a study by Carvalho et al., they prepared fibroin protein-based NGCs capable of controlled release of growth factors for PNI repairing. They implanted fibroin NGCs loaded with neurotrophic factor derived from glial cell lines at 10 mm of sciatic nerve defect in rats. The results showed better performance in nerve repair compared with autografts and free fibroin conduits [93]. These studies demonstrated that NGCs loaded with neurotrophic factors is one of the most promising and prominent possibilities for promoting nerve regeneration.

NGCs with support cells for PNI

Cell-based therapy has become a potential method to promote the repair of nerve injury [94]. In the field of tissue engineering, a variety of cells have been used for PNI repair, mainly including SCs and stem cells.

Schwann cells

SCs are known as natural seed cells because they are the main glial cells of the peripheral nervous system and are key cells for peripheral nerve regeneration [95]. Therefore, SC-based NGCs are ideal scaffolds for PNI repair. The role of SCs in nerve regeneration is undisputed, so how to better transplant autologous or allogeneic SCs into injury sites has become the focus of many researchers. For example, Salehi's team [96] constructed biodegradable and conductive NGCs by combining polylactic acid, MWCNTs, and gelatin nanofibers. In addition, they used chitosan nanoparticles coated with recombinant human erythropoietin for transplantation of SCs. The results showed that the NGC successfully delivered SCs to the site of the sciatic nerve defect in rats and demonstrated a regenerative capacity comparable to that of autologous nerve transplantation. In another study, Jahromi et al. prepared NGCs using PLLA and surface-modified MWCNT as carriers, filled with SCs and nanocurcumin, which reduced apoptosis of SCs. It was found that the number of nerve fibers at the injured site of the rat sciatic nerve increased significantly, suggest-

ing that this NGC is an appropriate method to promote nerve regeneration after PNI [97]. Although SCs are known as the gold standard for neural bridging [96], their disadvantages such as limited supply, long culture cycles, and immune rejection problems have limited their wide application.

Stem cells

Researchers have turned their attention to undifferentiated stem cells because of their potential to self-renew and differentiate. There have been various types of stem cells used for nerve regeneration, such as bone marrow stromal cells (BMSCs) [98], neural stem cells [99, 100], adipose-derived stem cells [101], mesenchymal stem cells [8, 102], and embryonic stem cells [103]. Studies have shown that the combination of stem cells and NGCs has a remarkable therapeutic effect on PNI repair. It has been reported that rat BMSCs were used as supporting cells to fill silk fibroin-based NGCs, which were then implanted into the rat sciatic nerve defects to bridge the 10 mm-long space. The finding of research demonstrated that the scaffold up-regulated the expression of multiple growth factor genes and significantly improved the outcome of nerve regeneration and functional recovery [95]. In summary, stem cells have significant potential for clinical application as seed cells to construct cell-based NGCs.

Conclusion and perspective

In recent years, due to the outstanding performance of NGCs in PNI repair, it has been increasingly recognized as the next gold standard that can replace autologous nerve grafts. In this review, the repair effects of NGCs designed with different strategies on PNI were reviewed from the perspectives of mechanical cues, biochemical cues, and supporting cells. The NGCs with different mechanical cues including hollow NGCs, multi-channel NGCs, grooved NGCs, and fiber-filling NGCs. They all have certain limitations. Regenerated nerve axons are dispersed in hollow NGCs, making them less likely to connect with the target. The production processes of multi-channel NGC and grooved NGC are complicated. Fiber-filling NGCs require the development of more easily degradable fibers to avoid secondary surgery removal of the conduit. Therefore, more materials or fillers that are more suitable for guiding nerve growth need to be designed in the future. Furthermore, the application of 3-dimensional or 4-dimensional printing techniques for the preparation of NGCs allows for customized nerve repair approaches for each PNI patient. Moreover, NGCs combined with multiple physical and biochemical cues may surpass the efficacy of autologous nerve transplantation and has the potential to be developed into clinical applications in the future. Nerve regeneration is an extremely complicated process in which axons can grow in response to topological, electrical, or biochemical cues and supporting cells that guide their directed growth. Therefore, future design strategies for NGCs should focus on composite scaffolds that synthesize various cues. In conclusion, although new technologies are emerging in the field and other alternative treatments for PNI are being investigated, further research and more attention are needed to overcome the barriers to translating these technologies into the clinic.

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Disclosure of conflict of interest

None.

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