

Chapter 43

Biomaterials, spinal cord injury, and rehabilitation: A new narrative

Elisa Lacroce^a, Giuseppe Perale^{b,c}, and Filippo Rossi^a

^aDepartment of Chemistry, Materials and Chemical Engineering “Giulio Natta”, Politecnico di Milano, Milan, Italy; ^bFaculty of Biomedical Sciences, University of Southern Switzerland (USI), Lugano, Switzerland; ^cLudwig Boltzmann Institute for Experimental and Clinical Traumatology, Vienna, Austria

List of abbreviations

AEMA	2-aminoethyl methacrylate
BBB	Basso, Beattie, Bresnahan score
BDNF	brain-derived neurotrophic factor
BSCB	blood–spinal cord barrier
CNS	central nervous system
ECM	extracellular matrix
HA	hyaluronic acid
HP	hydroxyphenyl
MOEAA	[2-(methacryloyloxy)ethoxy]acetic acid
MOETA+	[2-(methacryloyloxy)ethyl]trimethylammonium chloride
MSCs	mesenchymal stem cells
NFs	nanofibers
NPs	nanoparticles
NTs	nanotubes
NT-3	neurotrophin-3
NWs	nanowires
PCL	poly(<i>ε</i> -caprolactone)
PEG	polyethylene glycol
PEI	polyethyleneimine
PHEMA	poly(2-hydroxyethyl methacrylate)
PHPMA	poly(N-(2-hydroxypropyl)-methacrylamide)
PLA	polylactic acid
PLGA	poly(lactic- <i>co</i> -glycolic acid)
RGD	Arg-Gly-Asp
SC	spinal cord
SCI	spinal cord injury
SC-ECM	spinal cord extracellular matrix
SEM	scanning electron microscopy
SIKVAV	ser-Ile-Lys-Val-Ala-Val
UB-ECM	urinary bladder extracellular matrix
UC-ECM	umbilical cord extracellular matrix

Introduction

Spinal cord injury (SCI) is a lesion of the spinal cord which leads to the permanent loss of sensory and motor functions below the injury site. The traumatic effect of SCI is due to the low regenerative capability of the tissue, which is in contrast

with the fast inflammatory response that occurs in the first minutes after the injury and starts the secondary injury in the following hours. The latter is characterized by demyelination and the formation of a glial scar tissue which represents a physical barrier to the growth of axons. Nowadays, there are no effective clinical treatments able to regenerate the nervous tissue and restore the motor functions, so new strategies are being developed by researchers in order to overcome these limitations. One strategy is represented by scaffolds able to provide a structure that mimics the extracellular matrix (ECM) and at the same time supports the cellular attachment, growth and differentiation. The scaffolds must be biocompatible, non-toxic and have mechanical and morphological properties suitable for the tissue regeneration. In addition, they can chemically bind or physically entrap one or more drugs and release them in a controlled manner. The materials used for scaffold development can be synthetic or natural. Examples of the most used chemically synthesized materials are aliphatic polyesters such as polylactide, polyglycolide, and polycaprolactone (Pires & Pêgo, 2015). Synthetic materials present the advantage of being able to be controlled and modified from the point of view of chemistry, mechanical and structural properties in order to mimic as much as possible the ECM. In contrast, natural scaffolds are more similar in composition to ECM because some of the molecules are already present in the ECM, such as e.g., collagen, fibronectin, and hyaluronic acid but they have some differences in composition depending on their origin and previous treatments. Other natural materials such as alginate, agarose, and chitosan are widely used too. In addition, also the mechanical properties of the scaffold should be similar to the target biological tissue in order to avoid adverse effects. For the treatment the SCI, a stiff scaffold is not suitable because it is not able to support flexible movements of spinal cord without further lesioning other surrounding tissues. In addition, it was demonstrated that a stiff material promotes astrocyte growth (Georges, Miller, Meaney, Sawyer, & Janmey, 2006) and causes glial cell activation which leads to inflammation response and formation of a fibrotic tissue. Hence, soft scaffold, such as hydrogel, better matches the mechanical properties of the nervous tissue. Hydrogels are suitable for this purpose not only because of their flexibility, but also because of their bioadhesive and swelling properties, which confer the ability to stay localized in situ and to exchange metabolites with the surrounding tissue fluids. Other factors can influence the tissue regeneration, such as the pore sized distribution of the scaffold which has to guarantee the possibility for cells and fluids to enter inside the scaffold. The topography, the charge, the composition of the surface and the orientation of the fibers influence actin cytoskeleton and hence cell adhesion, spreading and differentiation.

In the case of nerve tissue regeneration, fibers arranged in a longitudinal way and pore size of 50 to 100 μm enhance nerve regeneration (Jurga et al., 2011; Yuan et al., 2014). Moreover, scaffold can be made of non-degradable or degradable materials. In the first case, the scaffold remains inside the body so the tissue can partially regenerate occupying the space between the fibers, whereas in the second case, it is necessary that the rate of degradation of the scaffold matches tissue regeneration speed.

Hydrogels and scaffolds

Synthetic-based hydrogels

Among synthetic non-biodegradable hydrogel used for SCI repair poly(N-(2-hydroxypropyl)-methacrylamide) (PHPMA) is very promising. The research group of Woerly et al. developed a hydrogel made of PHPMA, obtained by a radical polymerization of the monomer HPMA with the use of a divinyl cross-linking agent (Woerly et al., 1999), functionalized by a synthetic peptide which includes RGD sequence (Woerly, Pinet, De Robertis, Van Diep, & Bousmina, 2001). The implantation of the hydrogel into the neonatal and adult spinal cord reveals a good infiltration of cells and blood vessels and the following implantation of the hydrogel seeded with rat mesenchymal stem cells (MSCs) in rats results in better Basso, Beattie, Bresnahan (BBB) score than the control group without the implantation (Hejčl et al., 2010). Another investigated polymer in nerve tissue regeneration is the biocompatible and hydrophilic poly(2-hydroxyethyl methacrylate) (HEMA). As previously said, the charge and the structure of the hydrogel can influence the behavior of cells and the ingrowth of the new tissue. A study by Hejčl et al. (Hejčl et al., 2010) was conducted to compare the different effects of the surface charge and structure of HPMA and HEMA hydrogels on tissue regeneration. Specifically, four different hydrogels were prepared and seeded with rat MSCs: one HPMA-RGD hydrogel by using heterophase separation (HPMA-HS-RGD), which resulted in a structure characterized by microparticles, two HPMA hydrogels by using a solid porogen, one functionalized by RGD peptide (HPMA-SP-RGD), and one without functionalization (HPMA-SP), which resulted in network structures, and the last hydrogel made by positively charged copolymers of HEMA with [2-(methacryloyloxy)ethyl]trimethylammonium chloride (MOETA⁺). After successful in vitro studies, hydrogels were implanted into rat SCI hemisection model. The best results in terms of in vitro adhesiveness and in vivo survival of MSC was found in the positively charged HEMA-MOETA⁺ hydrogel, whereas the best results in terms of axonal ingrowth and vascularization was found in the HPMA-SP-RGD

hydrogel demonstrating the higher efficacy of the network architecture respect to the globular ones. With respect to the influence of the RGD peptide, it increases the vascularization but has no effect the growth of axons.

Hydrogel functionalization with cell-adhesive peptides

The presence of cell-adhesive peptides on hydrogels, such as the laminin-derived peptide sequence SIKVAV [Ser-Ile-Lys-Val-Ala-Val] and fibronectin-derived peptide RGD [Arg-Gly-Asp], can enhance cell adhesion, migration on the scaffold, proliferation, and differentiation (Rossi & van Griensven, 2014). The research group of Kubinova et al. functionalized a copolymer-based hydrogel of HEMA and 2-aminoethyl methacrylate (AEMA) with the laminin-derived Ac-CGGASIKVAVS-OH peptide by disulfide bridges (Kubinová et al., 2010). The functionalization with SIKVAV and RGD (Macková et al., 2016) was made on the same type of hydrogel also through the maleimide-thiol coupling reaction. All the functionalized hydrogels guarantee the adhesion and proliferation of rat MSCs maintaining their multi-lineage potential. In addition, in vivo studies results shown a higher connective tissue and vascularization on fibronectin-modified HEMA hydrogel compared to the non-functionalized one (Hejčl et al., 2018). Other molecules such as serotonin can be used as neurotransmitter and can improve neuronal differentiation of implanted or endogenous neuronal progenitor precursors. Despite promising in vitro results, in vivo model studies on implanted PHEMA functionalized with serotonin showed a migration of seeded neural progenitor out from the polymer leading to a fail in proving a long-term effect on nerve tissue reconstruction (Růžicka et al., 2013).

Porosity orientation

The orientation of fibers is important for tissue regeneration because it provides preferential lines along with the cells growth and proliferation. In addition, adequate porosity and mechanical properties have to support the movements of the organ and the regeneration of the new tissue. Hence, in the case of scaffolds for nervous tissue regeneration, the best one has to be characterized by parallel guiding channels and pores. The group of Kubinová et al. (2015) developed SIKVAV-modified PHEMA hydrogels with parallel oriented pores prepared by a salt-leaching method with ammonium oxalate needle-like crystals, and added 8%, 4%, and 0% (wt%) of [2-(methacryloyloxy)ethoxy]acetic acid (MOEAA) obtaining three hydrogels with 57%–77% porosity, pore diameter of ~60 nm, and an elastic modulus of 6.7, 27.4, and 45.3 kPa along the pore axis and 2.9, 3.6, and 11 kPa in a perpendicular direction. After 2 months of implantation the results showed that the softest hydrogel collapses because of the thinness of walls causing a sparse axonal growth inside the hydrogel, whereas the stiffest hydrogel supported axonal ingrowth into the pore guides but cyst formed at the tissue-scaffold interface because of difference in mechanical properties between the two components. The best results in terms of axonal ingrowth, presence of blood vessels and Schwann cells are obtained using the hydrogel with the moderate elasticity modulus of 27.4 kPa along the pores. Unfortunately, the use of the moderate scaffold seeded with MSCs was not able to promote a sufficient axonal growth.

Indeed, the rate of axonal growth resulted very slow and after 6 months from the implantation only few axons were able to cross the hydrogel and infiltrate the caudal stump (Hejčl et al., 2018). Therefore, other factors are necessary in order to promote axonal regeneration. For example, the presence of MSCs overexpressing of an NT-3 receptor (Zeng et al., 2015) or brain-derived neurotrophic factor (BDNF) (Gao et al., 2013) on the scaffold can be added in order to enhance axonal growth and recovery of motor functions.

Natural-based hydrogels

This type of hydrogels may be made by ECM derived components such as collagen or hyaluronic acid. Hyaluronic acid (HA) is a natural biocompatible polymer, biodegradable and non-toxic, but it does not favor the attachment of cells. A possible overcoming solution is represented by the use of the hydroxyphenyl derivative of HA which is able to covalently crosslink in situ, forming a hydrogel in presence of horseradish peroxidase enzyme and hydrogen peroxidase (Kučera et al., 2015). Moreover, the RGD peptide can be linked to the HA-PH derivative (Zaviskova et al., 2018) in order to favor the attachment of cells on (HP-HA) hydrogel. Human Wharton's jelly derived mesenchymal stem cells (hWJ-MSCs) were encapsulated in the hydrogel, which then was injected in the sub-acute spinal cord hemisection. In situ crosslinking had no cytotoxic effect or negative effect on cells. HA-PH-RGD hydrogel was able to favor axonal ingrowth and the presence of hWJ-MSCs increases the effect. However, there were no improvements of motor function probably due to the low quantity of cells encapsulated inside the gel.

Extracellular matrix-based hydrogels

Another type of natural-based hydrogel is represented by decellularized ECM: it is suitable for tissue regeneration because of its biocompatibility, biomolecular and complex chemical composition which characterize it and distinguish it from other scaffolds. Decellularization is performed by different chemical, physical or enzymatic method and then the decellularized ECM is transformed in a liquid phase using pepsin solubilization at $\text{pH} < 2$ in order to be injected into the site of injury. The physiological temperature and pH favor its crosslinking in situ, leading to its original structure. The research group of Kubinova tried to use ECM-based hydrogels derived from CNS, such as porcine spinal cord (SC-ECM), and non-CNS derived, such as human umbilical cord tissue (UB-ECM) and porcine urinary bladder (UB-ECM). After implantation into injured spinal cord they stimulated nerve tissue regeneration and no differences on biological response were seen between the use of CNS and non-CNS-derived ECM (Kočí et al., 2017; Medberry et al., 2013). However, a critical problem was represented by the fast degradation rate of the scaffold, which was due to the infiltration of resident cells present in the site of lesion.

Therefore, inadequate structure was provided to the new tissue and a correct regeneration of the tissue was compromise. In order to decrease the rate of degradation it was necessary to increase the number of crosslinks. This can be done using crosslinking agents such as genipin, which is able to bridge free amino groups present in the ECM. Its use on the UC-ECM hydrogel did not increase in vivo inflammatory response (Výborný et al., 2019), moreover the lack of ethical problems and the allogeneic source leads to consider promising the use of umbilical cord in neural tissue regeneration.

Nanomaterials

Nanotechnology and nanomedicine

Nanotechnology is the synthesis and characterization of nanosystems and their application in different fields, from the research to the industrial practice. When nanotechnology is applied in medicine and healthcare, it is called nanomedicine. Nanomedicine covers different medical fields such as prevention, diagnosis and treatment. It uses nanomaterials in the range of 10–1000 nm for interacting with biological systems at the molecular level. In addition, the resulting high surface area per unit volume favors a higher number of interactions with biological systems. Thanks to the binding with specific cellular receptors nanosystems can also deliver drugs and molecules in specific site without damaging the surrounding healthy tissue. Nanomedicine developed a lot of structures such as nanoparticles, nanotubes, nanorods, nanogels, quantum dots, etc., but the most used in SCI field are nanoparticles, nanogels, and nanotubes.

Properties of nanomaterials

The treatment of SCI with drugs administrated by oral, intravenous or intra-arterial ways is not effective due to the filtrating action of the blood–spinal cord barrier (BSCB) which prevents the passage of foreign and immunological substance from bloodstream to the SC parenchyma. Nanomaterials can be developed by top-down, bottom-up or hybrid methods. The first method consists in transforming a bulk material to a nanosized material, the second one consists in forming a nanomaterial starting from molecular arrangements and interactions whereas the last method is based on mixing the previous two. Nanocarriers have to correspond to specific size in order to favor their migration across the biological barrier of spinal cord and the target the desired tissue. Smaller particles are more suitable for this purpose and the possible presence of ligands on their surface can bind to receptor molecule of neural cells favoring the activation of specific cellular response. The drawback of using small particles is the limited control on modification in a batch-to-batch synthesis approach (Saraiva et al., 2016). Furthermore, the shape of the nanovectors influences their behavior inside biological environments and their cellular uptake too.

Specifically, in the case of nervous system, nanorods characterized by targeting peptides are considered more able than nanoparticles in accumulating in specific vascular environment without activating immune clearance (Kolhar et al., 2013) or, for example, biconcave nanoparticles enhance the release of drug respect to spherical or tubular particles (Zuidema, Gilbert, & Osterhout, 2016). Finally, surface charge has a key role with respect to the final aim of particles. In general, positively charged nanoparticles are better internalized by cells (Xiao et al., 2011; Yue et al., 2011) but the modification with chemical groups or peptides can change the surface charge leading to a different aim such as to target a specific area or avoid activation of immune systems. As for the composition of hydrogels, also nanomaterials can be made by synthetic or natural materials. Natural nanomaterials are in general biocompatible, non-toxic and very similar in composition and chemical features with the biological environment allowing a weak immune response, but it is difficult to achieve a good

reproducibility during their development and production. On the other hand, synthetic nanomaterials guarantee a high reproducibility and possibility to modify their chemical, physical and morphological properties adapting them to the final purpose, but their immunogenicity is higher compared to the natural ones. Natural materials used for developing nanoparticles are collagen, lipids, albumin, fibrin, silicone, alginate, agarose, hyaluronic acid, chitosan, cellulose, heparin and chondroitin sulfate, whereas synthetic materials used are polyethylene glycol (PEG), polyethyleneimine (PEI), polylactic acid (PLA), poly(lactic-co-glycolic acid) (PLGA), polyglycolic derivatives, polymethacrylate, polyacrylates, polycyanoacrylates, and poly(ϵ -caprolactone) (PCL). Fig. 1 represents a summary of natural and synthetic polymers.

Nanoparticles

Nanoparticles are colloidal systems made of polymer chains from which is possible to obtain nanospheres or nanocapsules (Fig. 2). Nanosphere are systems with a size of 100–200 nm composed of a solid matrix with physically or chemically entrapped drug (Liu, Xiao, & Allen, 2004). They can be covered at their surface with surfactants or hydrophilic polymers which avoid opsonization and subsequent internalization from immune cells. Nanocapsules are nanosystems composed by an external polymeric layer which surround a lipophilic core.

These systems are very useful in encapsulating hydrophobic drugs in the core of nanoparticle and releasing them in situ. Generally, they are made of PLA, PLGA or PCL surrounded by hydrophilic PEG in order to avoid the activation of immune system. Finally, polymersomes are nanocapsules made of an aqueous core able to encapsulate hydrophilic drugs. In this case the aqueous core is enclosed by amphiphilic copolymers which expose hydrophilic segments in the core and external surface, whereas hydrophobic segment in the middle.

There are different techniques used to synthesize nanoparticles:

- Emulsion: it consists in emulsifying an oil phase containing hydrophobic monomers with a water phase containing surfactants. The polymerization of hydrophobic monomers starts after the addition of oil-soluble initiators forming polymeric particles inside an aqueous phase. In order to avoid opsonization and aggregation between nanoparticles, surfactants bind to the surface of particles by a polycondensation reaction between the two monomers present in the oil and in the aqueous phase or by the presence of initiators. The drug can be encapsulated during the polymerization process or absorbed at the end of the polymerization.
- Nanoprecipitation: it consists in desolvation of polymers dissolved in the solvent solution after the addition of it to the non-solvent solution.
- Solvent evaporation: emulsifying agents dissolved in water phase are added to an organic phase containing drug and polymer dissolved. The formation of oil/water emulsions is followed by solvent evaporation by using temperature or low pressure obtaining the nanoparticles.
- Salting out: the organic solution containing the polymer is added to an aqueous phase containing an emulsifier and a high concentration of salts. Then, pure water is added to promote the diffusion of organic solvent into water phase forming nanoparticles.
- Controlled gelification: gel nanospheres can be formed by using sodium alginate and calcium chloride.
- Desolvation: this method can be used only on natural polymers which are dissolved in aqueous environment. The following drip of a desolvating agent, such as ethanol or acetone, containing active molecule and the addition of cross-linking molecules in polymeric solution allow to obtain nanoparticles.
- Coacervation: coacervates are formed by electrostatic interactions between cargo aqueous phase and polymer.

As regard to nanocapsules, they are formed by mixing an oil-containing lipophilic surfactants with an aqueous phase miscible with organic solvent containing polymeric chains and therapeutic molecules. Under stirring, oil droplets are forming in the aqueous phase and polymers interact with the two phases exposing the hydrophobic chain toward the oil component and the hydrophilic one toward the aqueous phase. A method recently developed is based on following addition of water to the system favoring the passage of solvent from the center of nanoparticles to the external phase. Finally, polymersomes are formed starting from a copolymers dissolved in an organic solvent. Then the solvent evaporates leading to the formation of a polymeric layer and water is added to rehydrate polymers.

The following sonication and extrusion of solution lead to the formation of polymersomes. In the case the therapeutic molecule is a protein, some steps such as the use of organic solvent or sonication can denature the protein leading to its inactivation. In this case, the addition of natural salts or alcohols can affect its 3D structure favoring aggregates with polymer chains. At last, the use of glutaraldehyde can stabilize the nanoparticles.

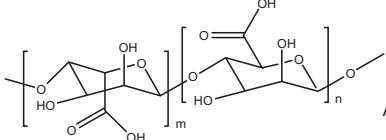
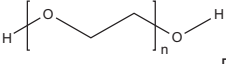
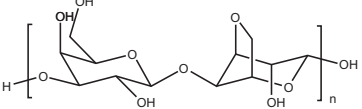
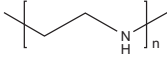
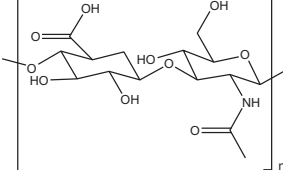
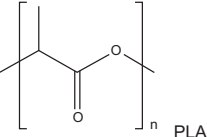
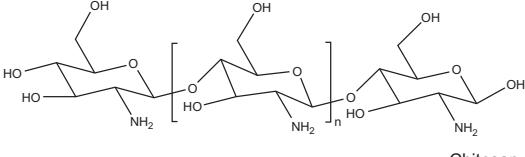
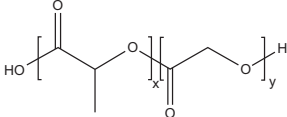
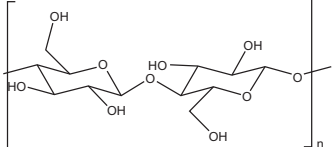
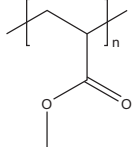
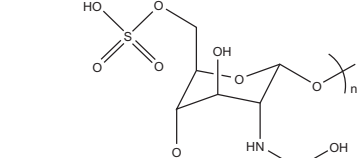
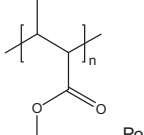
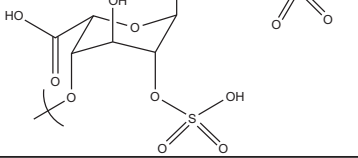
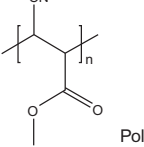
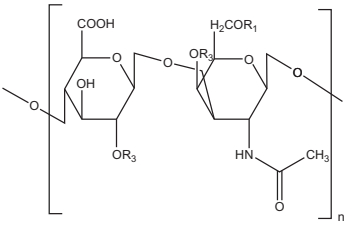
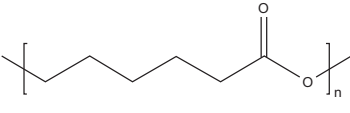
NATURAL POLYMERS	SYNTHETIC POLYMERS
 <p style="text-align: right;">Alginate</p>	 <p style="text-align: right;">PEG</p>
 <p style="text-align: right;">Agarose</p>	 <p style="text-align: right;">PEI</p>
 <p style="text-align: right;">Hyaluronic acid</p>	 <p style="text-align: right;">PLA</p>
 <p style="text-align: right;">Chitosan</p>	 <p style="text-align: right;">PLGA</p>
 <p style="text-align: right;">Cellulose</p>	 <p style="text-align: right;">Polyacrylate</p>
 <p style="text-align: right;">Heparin</p>	 <p style="text-align: right;">Polymethacrylate</p>
 <p style="text-align: right;">Heparin</p>	 <p style="text-align: right;">Polycyanoacrylate</p>
 <p style="text-align: right;">Chondroitin sulfate</p>	 <p style="text-align: right;">PCL</p>

FIG. 1 Polymers for NPs. Chemical structure of natural and synthetic polymers used for developing NPs.

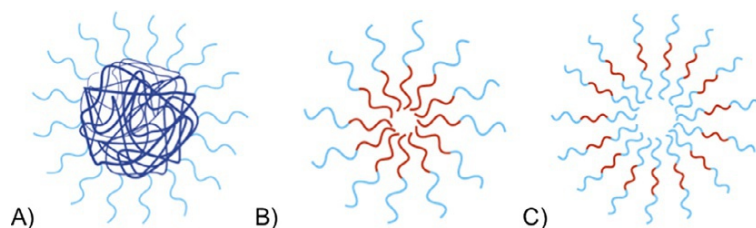


FIG. 2 Different NPs. Structure of (A) nanospheres, (B) nanocapsules, and (C) polymersomes.

Functionalization of nanoparticles

Nanoparticle functionalization is needed in order to increase its half-life and favor its interaction with the targeted cells. In case of SCI it is important that nanoparticles are able to pass across the BSCB and reach the site of injury providing neuroprotective and/or neuro-regenerative effect. The functionalization can consist in addition of surfactants, biomolecule, dyes (for in vitro and in vivo tracking) and peptides by linking them to functional polymer groups such as hydroxyl, amine, carboxylic or alkyl groups. For example the presence of antioxidant enzyme superoxide dismutase on the surface of nanoparticles induces neuroprotective action (Varma et al., 2013) or the release of encapsulated fibroblast growth factor-2 inside PLGA nanoparticles reduces vasoconstriction in SCI during primary injury and favors angiogenesis (Kang, Baumann, Tator, & Shoichet, 2012). Reactions with functional groups such as the carboxyl group can link chitosan to a PEG grafting biotin able to attract monoclonal antibody OX26 leading to a decrement of neuronal cell death in injured spinal cord (Aktaş et al., 2005). The functionalization can be performed also on cation polymers such as PEI or chitosan. The most common methods to functionalize amine groups are making a reaction with thiol or maleimide group forming a disulfide bond.

The effects of encapsulated neurotrophin

Neurotrophin is a protein that induces axonal regeneration and can be used as therapeutic molecule in case of SCI. The research group of Elliot Donaghue et al. was able to encapsulate neurotrophin-3 (NT-3) inside PLGA 220 nm nanoparticles through a double emulsion-solvent evaporation method, and then to entrap nanoparticles inside a hyaluronan/methyl cellulose matrix in order to have a more confined and controlled release of NT-3 (Elliott Donaghue, Tator, & Shoichet, 2015). In particular, the diffusion of NT-3 outside the matrix lasted 50 days in in vitro studies and 28 days in in vivo studies, leading to consider this system as a possible solution in order to limit the number of dosing. In addition, a higher locomotor recovery and axonal growth was seen in mouse model study after the treatment with PLGA NPS loaded with NT-3, compared to the controls.

Nanogels

Nanogels are innovative nanoparticles with hydrophilic properties and high colloidal stability. They are characterized by swelling behavior which gives them the unique ability to exchange ions and biological molecules with the surrounding environment maintaining an equilibrium of metabolites between the internal and external parts. In addition, their deformability allows an easy passage through biological barrier and this characteristic, together with the swelling behavior, allows considering nanogels soft materials because of their similar properties to hydrogels. Nanogels can be developed starting from monomers of low molecular weight or from polymeric precursors. In the first case, monomers polymerize thanks to a controlled living radical polymerization using an initiator molecule from which the polymerization starts and propagates forming the nanoparticle, whereas in the second case the process is characterized by an inter-polymer interactions. Particularly, functional groups of polymer precursors chemically interact each other forming covalent bonding between polymer chains. Another possible technique is based on physical interactions between polymer chains such as hydrogen bonding, electrostatic interactions, Van der Waals forces or hydrophilic/hydrophobic interactions. In this case, the final nanogel has a low stability and its structure can be easily compromised by temperature, pH or external forces. A new strategy that can be used to produce nanogels is represented by the non-wetting templates (PRINT) technology. It is a lithographic technique that uses non-wetting elastomeric templates inside which nanogels are formed allowing a high reproducibility. Another new approach is represented by molecular imprinting, although its use is very difficult in nanogel developing. It consists in a linkage of a chosen protein on a functional monomer in order to form a template molecule. Then the polymerization starts

using cross-linking agent and the protein is detached. The remaining polymer will present a cavity complementary to the protein and it will be used for selective cell targeting during the treatment of SCI.

Functionalization of nanogels

The functionalization of nanogels with drug, peptides, proteins, enzymes, dyes, etc. can be performed using different types of reactions (Fig. 3): formation of amide bond from an ester bond, esterification, ring opening and Schiff base reactions,

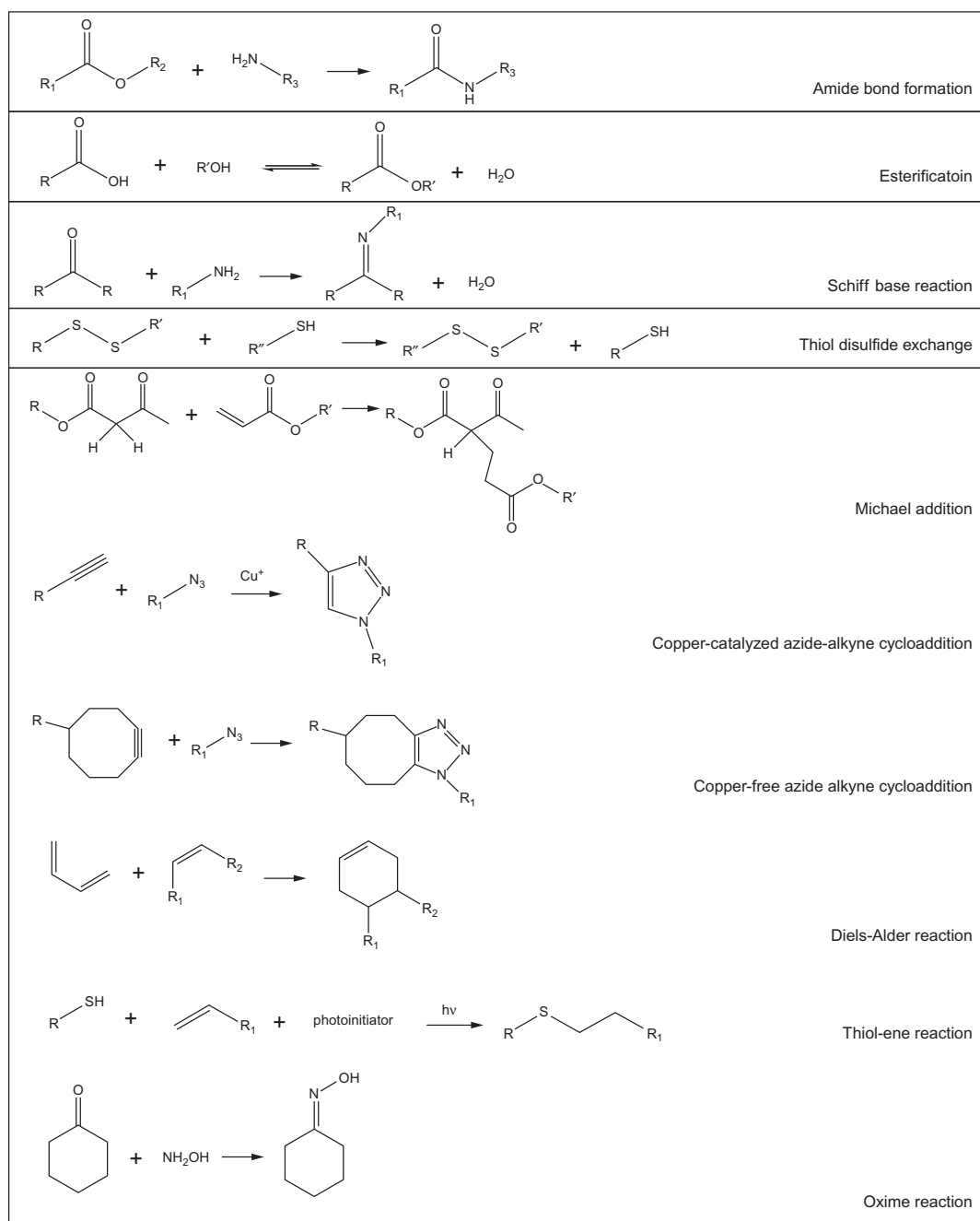


FIG. 3 Polymer functionalization. Different strategies of polymer functionalization.

thiol disulfide exchange and finally click chemistry which includes Michael type addition, copper-catalyzed and copper-free azide-alkyne cycloaddition, Diels–Alder reaction, thiol-ene reaction or oxime reaction. Depending on the type of chemical bond, the *cargo* can be released according to a change of temperature, pH, the presence of enzymes or other external stimuli able to break the bond. For example, redox-responsive NGs are able to accumulate in the target tissue and release the cargo only when redox stimulus is applied (Ghorbani & Hamishehkar, 2019).

In another study, the research group of Mauri et al. (2017) developed nanogels able to be internalized by microglia cells and release the therapeutic *cargo* only in the cytosol. In this case, the fast release in biological fluids that characterizes the hydrophilic drugs and the following rapid clearance from the body is avoided. The drug mimetic, rhodamine, was linked to PEG using the thiol chemistry forming a disulfide bond that can be broken in the cytosol by glutathione or cysteines, whereas the Cy5 dye was linked to the PEI by copper-catalyzed alkyne-azide cycloaddition. Finally, carbamate bonds formed the final nanogel. In vitro studies showed fluorescent signals inside the cytosol demonstrating the internalization of nanogels from microglia and the release of drug in the cytosol after 4 days. The functionalization can also be non-covalent if other interactions occur. This is the case of PEI functionalization in which electrostatic attraction between genes, peptide or growth factor and protonated amine on polymer chains is used to functionalize the nanogel.

Nanochannels, nanotubes, nanowires, and conduits

It is worth mentioning other nanostructures that are used in SCI repair: tubular particles such as nanotubes (NTs), nanowires (NWs), and nanofibers (NFs) can guide axonal regeneration and limit the local inflammation at the same time.

Nanotubes are cylinders with a diameter in the order of nanometers, made of graphene. These structures are similar to cytoskeletal elements in neurons, signaling proteins and ion channels, so their presence does not activate immune or inflammatory responses. Their flexibility, electrical conductivity, and durability allow their implantation in the spinal cord for a long time. In addition, they can be functionalized with active molecules, such as 4-hydroxynonenal which promotes neurons spatial orientation and interconnections (Mattson, Haddon, & Rao, 2000), neurotrophic factors which provide neuroprotective effect or chemical groups which confers superficial charge to stimulate axonal growth. In vivo studies about the injection of NTs during the secondary injury phase showed a reduction of injured site, an increment of neurofilament-positive fibers and a partial recovery of locomotor functions (Roman, Niedzielko, Haddon, Parpura, & Floyd, 2011).

Nanowires are structures similar in shape with that on nanotubes but in this case the length is much longer than the diameter. In addition, they are generally made with metals, semiconductors, insulators or polymers with electric properties. They can be used for SCI repair in order to provide cell adhesion, proliferation, and electric stimulation as made by Bechara and coworkers (Bechara, Wadman, & Popat, 2011) with PCL NWs linked with polypyrrole, an electroconductive polymer.

Nanofibers (NFs) are the third most common nanosystems used for nerve regeneration. Their spatial orientation and diameter are able to positively influence cell behavior and differentiation. In particular, cell aggregation decreases and cell proliferation increases as the diameter of NFs decreases, whereas aligned NFs results in higher rate of neural stem cell differentiation than NFs oriented in random way (Xie et al., 2009; Yang, Xu, Kotaki, Wang, & Ramakrishna, 2004). Also in this case, NFs can be functionalized at their surface with specific chemical groups or molecules which confers surface charges, such as Rolipram in PLGA NFs (Zhu et al., 2010), able to improve axonal growth and reduce inflammatory response in the site of injury.

Conduits are cylindrical systems used to cover nerve gap and provide a guide for nerve regeneration. Promising conduits are made of PLGA-chitosan or PCL because of their effect in promoting remyelination of axons. Even if their use has positive effects on nerve repair, their implantation is invasive causing infections, inflammation and other permanent damages, making the risk/benefit balance unfavorable.

Case study: Agarose–carbomer-based hydrogels

Even if the polymers used for biomaterials preparation are biocompatible, this does not ensure they promote a correct cell viability; functional compounds are hence needed in order to provide an interaction between the cells and the polymeric scaffold. RGD peptide, for example, can be used for scaffold functionalization because of its ability to bind to the receptors present on the surface of cell membrane and activate a cell adhesion response. The research group of Perale and Rossi (Caron et al., 2016; Papa et al., 2018) proved the extremely promising results obtained with functionalized poly-acrylic acid (PAA) and polyethylene glycol (PEG) with RGD peptide by using a click chemistry strategy. In particular, PAA polymer was previously functionalized with an alkyne group (Fig. 4) (Mauri et al., 2018). Then, CuAAC click reaction between RGD azide and alkyne polymers was conducted at 50°C–60°C forming the triazole. Finally, the hydrogel was synthesized by microwave-assisted polycondensation between mixed RGD-functionalized polymers and agarose.

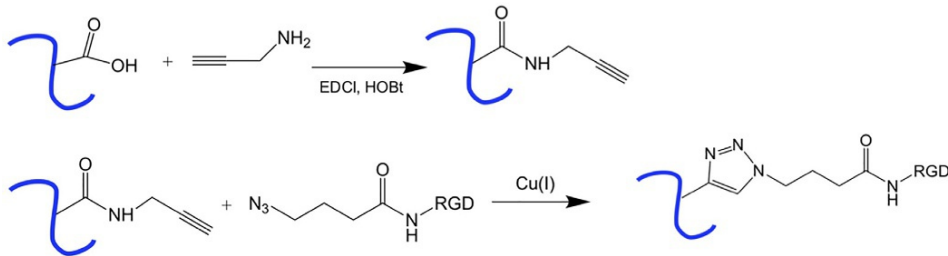
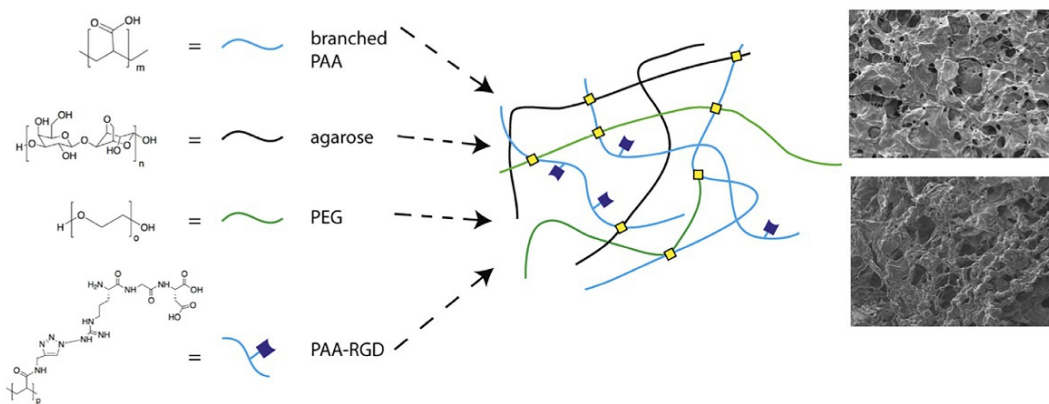
Polymer functionalization**Hydrogel synthesis**

FIG. 4 Agarose–Carbomer-based hydrogels. Schematic representation of RGD-functionalized (HG-RGD) hydrogels. (Adapted from Mauri, E., Sacchetti, A., Vicario, N., Peruzzotti-Jametti, L., Rossi, F., & Pluchino, S. (2018). Evaluation of RGD functionalization in hybrid hydrogels as 3D neural stem cells culture systems. *Biomaterials Science*, 6(3), 501–510. doi:10.1039/c7bm01056g, with permission from the Royal Society of Chemistry.)

From SEM analysis of the final hydrogel, there were not differences in polymer network and porous structure compared to the non-functionalized one, and adequate mechanical and morphological properties result from physical and chemical characterization. The system is highly biocompatible, can remain localized in the lesion site, can maintain the stemness of the loaded cells (Fig. 5) *in vitro* and *in vivo* improving the locomotor performances of mice (Fig. 6).

Applications to other areas of neuroscience

SCI remains one of the most devastating conditions in neurological diseases. Most of the post traumatic degeneration of the tissue is caused by a multifactorial secondary injury including several interconnected processes. Relevant is the involvement of acute and chronic inflammation, represented mostly by inflammation that contributes to the cascade of harmful events during the secondary injury, in the end leading to spreading and chronicity of SCI. An unresolved inflammation is a pathological hallmark of many neuropathologies and microglial cells can play a relevant role in these scenarios. The current view suggests that under normal physiological condition the acute inflammatory response is a transitory process, aiming at eliminating many potential toxic stimuli, which is followed by resolution of the inflammation and a return to homeostasis. Hence, an acute neuro-inflammatory response is considered generally beneficial to the CNS, since it tends to limit the damages and contributes to the repair of injured tissue. However, in many neuropathologies, an over-activation and an accumulation of microglial cells occurs, due to persistent insults or triggered by factors released in the damaged environment by dead cell. Indeed, a sustained release of pro-inflammatory mediators can propagate the inflammatory reaction, promoting microglia proliferation and further releasing pro-inflammatory factors that feed an uncontrolled response. Therefore, a prolonged and unresolved chronic inflammation due to over-activation of microglial cells can have neurotoxic consequences that could lead to the exacerbation of the pathology.

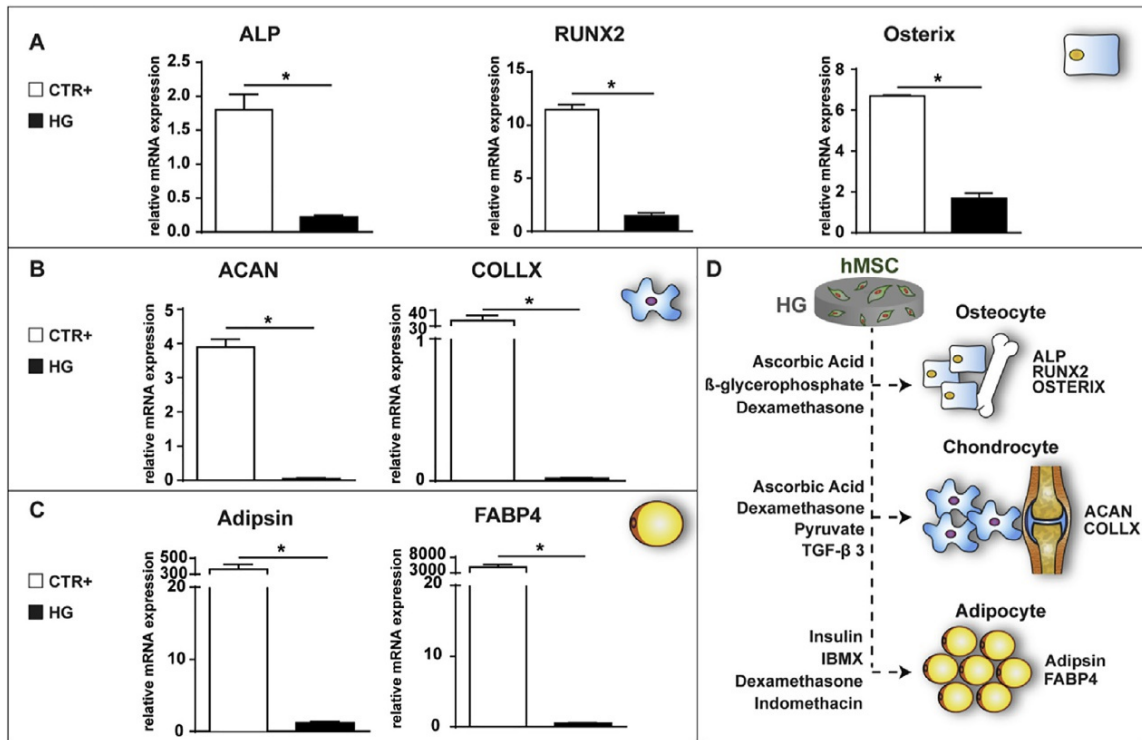


FIG. 5 mRNA analysis of hMSCs encapsulated within biomimetic scaffold. Graphs representing the expression of specific genes related to three differentiation lineages: alkaline phosphatase (ALP), runt-related transcription factor 2 (RUNX2) and osterix for osteogenic differentiation; aggrecan (ACAN) and collagen type X (COL1X) for chondrogenic differentiation and adipsin and fatty acid binding-protein 4 (FABP4) for adipogenic differentiation. hMSCs encapsulated within HG for 21 days are compared to the positive control represented by hMSCs loaded in HG and treated with specific differentiating media for 21 days. (Reprinted with permission from Caron, I., Rossi, F., Papa S., Aloe, R., Sculco, M., Mauri, E., Sacchetti, A., et al. (2016). A new three dimensional biomimetic hydrogel to deliver factors secreted by human mesenchymal stem cells in spinal cord injury. *Biomaterials*, 75(1), 135–147. doi:10.1016/j.biomaterials.2015.10.024, Elsevier.)

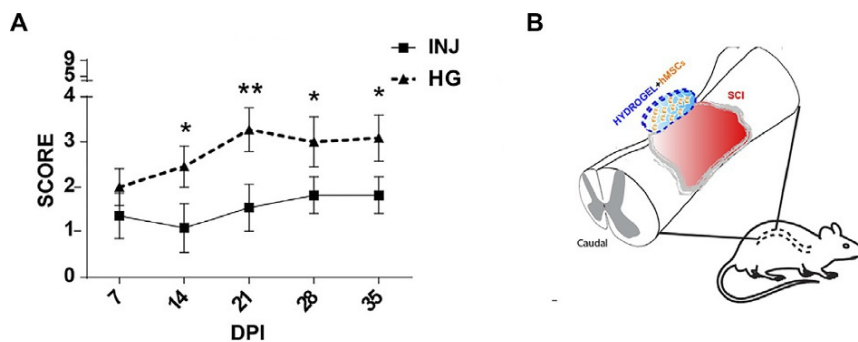


FIG. 6 HG ability to improve locomotor performance in SCI mice. In vitro HG ability to improve locomotor performance in SCI mice: (A) untreated SCI mice (INJ) or treated (HG) 1 DPI examined weekly starting 7 days post treatment, using the Basso Mouse Scale-BMS (score 0, complete paralysis, 9 complete mobility, referred to healthy mice). (C) Positioning of the hydrogel + cells in the SCI mouse model. (Reprinted with permission from Papa, S., Vismara, I., Mariani, A., Barilani, M., Rimondo, S., De Paola, M., et al. (2018). Mesenchymal stem cells encapsulated into biomimetic hydrogel scaffold gradually release CCL2 chemokine in situ preserving cytoarchitecture and promoting functional recovery in spinal cord injury. *Journal of Controlled Release*, 278(10), 49–56. doi:10.1016/j.jconrel.2018.03.034, Elsevier.)

Several neurodegenerative CNS disorders, including traumatic brain injury, spinal cord injury, stroke, amyotrophic lateral sclerosis, Alzheimer's disease, Parkinson's disease, epilepsy and multiple sclerosis are associated with chronic neuro-inflammation and high levels of several cytokines. For these reasons, new therapeutic approaches able to modulate activated microglial cells are needed. In recent years, new evidences, from both in vitro and in vivo studies, suggest that nanoparticles can be selectively internalized by a specific phagocytic activity of macrophages, exploiting them as Trojan horses to selectively treat these cells. This delivery approach represents a promising strategy to develop tailored treatment during the inflammatory response.

Mini-dictionary of terms

Colloids: system composed by a disperse phase with a size range between 1 and 1000 nm dissolved in an incompatible continuous phase.

Drug delivery system: engineered materials able to load and deliver drugs with a controlled kinetics, maintaining the pharmacological activity during time.

Emulsion: thermodynamically unstable colloid constituted by two immiscible liquids.

Functionalization: chemical reaction between two reactive sites with consequent formation of covalent chemical bond.

Hydrogel: network of cross-linked hydrophilic polymeric chains able to absorb an extremely large amount of water (dispersion medium).

Nanogels: nanoparticle, usually in the tens to hundreds of nanometers in diameter, composed of a cross-linked hydrophilic polymer network composed of synthetic polymers or biopolymers chemically or physically cross-linked.

Nanomedicine: medical applications of nanomaterials that range from biological devices, to nanoelectronics biosensors, molecular nanotechnology such as biological machines.

Nanoparticles: particles of matter with size range between 1 and 100 nm (nm) in terms of diameter.

Polymer: substance constituted by very large molecules, or macromolecules, composed of many repeating subunits and that can be synthesized by step-growth or chain-growth mechanisms.

Tissue engineering: biomedical engineering discipline that uses a combination of cells, engineering, materials methods, and suitable factors to maintain, restore or replace different types of biological tissues.

Key facts of “Biomaterials, spinal cord injury, and rehabilitation: A new narrative”

- SCI is the most frequent disabling spinal injury, estimated 2.5 million people worldwide live with SCI
- SCI is a multifactorial where most of the medical problems are caused by cascade of events (secondary injury)
- A winning therapeutic strategy is represented by the possibility to work against different pathological mechanisms.
- Hydrogels, three-dimensional polymeric networks thanks to their water affinity to maintain cells viable and able to restore the damaged tissue.
- Nanoparticles, thanks to their ability to be cell selective, can carry and deliver drugs into specific cells working as Trojan horses.

Summary points

- SCI is a debilitating condition caused by damage to the spinal cord.
- More than 130,000 new spinal cord injuries are reported every year.
- Hydrogel can restore the tissue carrying cells within the damage site.
- Scaffold can drive axonal growth across their ordered pores.
- Nanoparticles can selectively deliver drugs within cells reducing secondary injury issues.

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Support in spinal cord injury: A focus on robotics

Angel Gil-Agudo^{a,b} and Guillermo Asín-Prieto Eng^{b,c}

^aNeurorehabilitation and Biomechanics Unit (HNP-SESCAM), Associate Unit CSIC, Physical Medicine and Rehabilitation Department, National Hospital for Paraplegics, SESCAM, Toledo, Spain; ^bNeurorehabilitation and Biomechanics Unit (HNP-SESCAM), Associate Unit CSIC, Biomechanics and Technical Aids Department, National Hospital for Paraplegics, SESCAM, Toledo, Spain; ^cGogoa Mobility Robots, S.L., Abadío, Vizcaya, Spain

List of abbreviations

ADL	activity of daily living
AIS	ASIA impairment scale
ARTIC	advance robotic therapy integrated centers
ASIA	American Spinal Injury Association
CNS	central nervous system
CPG	central pattern generator
FES	functional electrical stimulation
SCI	spinal cord injury

Introduction

The incorporation of robotics in the field of neurorehabilitation is taking place rapidly, both in research and in its clinical applications, and is presented as a very promising tool that is changing therapeutic paradigms. In the late 1980s and early 1990s, basic research findings constituted a major change in therapeutic intervention in neurorehabilitation. One of most relevant was that in experimental models with cats subjected to a spinal cord injury (SCI), the subsequent training of the locomotor function applied to them offered good results. In fact, it was shown that these cats with SCI walked effectively when placed on a treadmill with partial weight support (Barbeau & Rossignol, 1987). The suggested mechanism is the activation of the basic neuronal circuitries sufficient to generate efficient stepping patterns and independent standing. Indeed, the operations underlying the elaboration of motor patterns for walking and standing are essentially achieved by the neuronal networks embedded within the lumbosacral segments of the spinal cord (Grillner & Zangger, 1984). These findings led to the concept of spinal learning via activity-dependent plasticity. Following this concept, it was found that locomotor activity can be activated in patients with severe SCI via passive activation of the legs on a treadmill (Barbeau, Danakas, & Arsenault, 1993). Synchronous reciprocal movements of both legs, simulating normal walking are required to activate the locomotor centers in the spinal cord. The repetitive and simultaneous activation of certain sensory and motor pathways with task-specific training can select and reinforce those spinal circuits improving the ability to perform the practiced movement successfully. Thus, functional rehabilitation (i.e., walking) had to be intensive and task-oriented. Intensive and task-oriented are the two pillars of the motor learning neuroplasticity-based neurorehabilitation concepts that also justify the development of robotic therapy (Cai et al., 2006; Edgerton, Courtine, Gerasimenko, et al., 2008).

Although these interventions appear promising, in order to translate them into clinical practice in humans, a great effort is needed to standardize the assessments of the therapies applied (Curt, Schwab, & Dietz, 2004). Gait training using partial weight bearing systems on treadmills in patients who had suffered a stroke or SCI was extended in the early 1990s following motor learning principles. This therapy initially presented high costs in terms of personnel and effort, as it required the participation of at least two physiotherapists to mobilize the paralyzed lower extremities of the patient with the intention of reproducing the treadmill walking cycle (Dietz & Harkema, 2004). The great effort that this activity demanded from the physiotherapists limited the duration of the treatment sessions. This limitation led to the idea that a robotic device could

serve as an alternative to manual treatment and that such a device could cover the demands of functional training (Colombo, Joerg, Schreier, & Dietz, 2000). This led to the first robotic systems for walking training with weight suspension on treadmills.

These robotic assistive devices enable to start a functional and task-oriented training as soon as possible after the injury and allow an intensive application of adequate afferent feedback and a high number of repetitions of functional movements (Wirz & Rupp, 2012).

Furthermore, the outcome of rehabilitation is better if the patient is more motivated and involved in the treatment (Weber & Stein, 2018). All these without forgetting one of the most evident shortcomings of conventional systems, which is the need to incorporate sensors that provide objective variables of the patient's condition or of the execution of the task, need to be trained. These issues are satisfactorily addressed by robotic devices. This therapy can be applied alone or in combination with other new technologies such as functional electrical stimulation (FES) or virtual reality.

Robotic therapy has experienced a huge boom in the last 15 years. In fact, different clinical guidelines approved its use as a complementary element to conventional therapy in the rehabilitation of patients with upper limb deficits after suffering a stroke (Department of Veterans Affairs et al., 2010). Robotic devices are appropriately adapted to the need to assist limb movements based on their ability to perform simple, repetitive tasks in a consistent manner that facilitates functional recovery and adaptive plasticity (Edgerton & Roy, 2009). There are two main categories: distal end effector devices and exoskeleton-type devices. Distal end effectors were the first to appear and are characterized by the fact that they use a single distal point of contact to guide the movement of the entire limb. In the upper extremity, it can make contact in the hand or forearm, facilitating the movements of the elbow and shoulder. They produce combined movements being difficult to isolate pure simple movements. The operation of exoskeletons is different. They are structures located in parallel to the different parts of the extremities with more than one point of interaction with the person. They provide direct control over each segment of the limb by incorporating individualized motors, also called actuators, which coincide with the anatomical axis of each joint. Thus, each actuator triggers the movement of each joint on which it is located. The design of exoskeletons seems to be more suitable than that of distal effector systems to achieve large joint paths (Krebs, Conroy, Bever, & Hogan, 2012).

In this chapter, we will focus on upper limb robots, stationary and ambulatory lower limb exoskeletons.

Upper limb robots

Cervical SCI can result in partial or complete tetraplegia. Each small improvement in motor control of the upper extremity can translate to significant ameliorations in function and increases independence for the individual. As mentioned above, this type of therapy offers new possibilities in the rehabilitation not only for the lower limbs but also for the upper limbs. The robotic devices allow the application of high-intensity sessions during longer periods of time, remaining invariable certain physical parameters such as speed, strength, or precision (Page, Hill, & White, 2013; Takahashi, Der-Yeghiaian, Le, Motiwala, & Cramer, 2008). There is evidence that suggests task-based therapy specifically designed to deal with lost abilities produce better results than resistance strengthening exercises (Teasell & Kaira, 2004). This task should be performed by the patient as far as possible. That's why the devices should be equipped with a controller that provides the least assistance needed to accomplish the movement (assist as needed) and reproducible treatment protocols.

Some studies point out that by focusing the improvement of robotic therapy more on the proximal recovery of the upper limb (shoulder and elbow), it does not translate into improvement of the functional ability that depends on hand control. However, the best results seem to be found by adding the application of both types of therapies (Bayona, Bitensky, Salter, & Teasell, 2005). Despite the low number of studies, results from these studies suggest that robotic training protocols are feasible and well tolerated and have a positive impact on improving arm and hand functions in selected patients with cervical SCI, but the results must be interpreted with caution (Mehrholz, Platz, Kugler, & Pohl, 2009). In any case, studies with larger samples are needed, especially those that analyze the distal region of the upper limb, in order to have solid conclusions about the effectiveness of these devices.

Most of the current devices include a virtual reality module with visual or haptic feedback to improve sensory feedback, as well as patient motivation and engagement. They also have the capability to obtain movement kinematics that can provide precise information about movement quality that otherwise is not included in functional assessments (Esquenazi & Talaty, 2019).

Although there is a number of different robotic devices currently used for neurorehabilitation of the upper extremities following SCI (Fig. 1), we will now focus on the most commonly used:

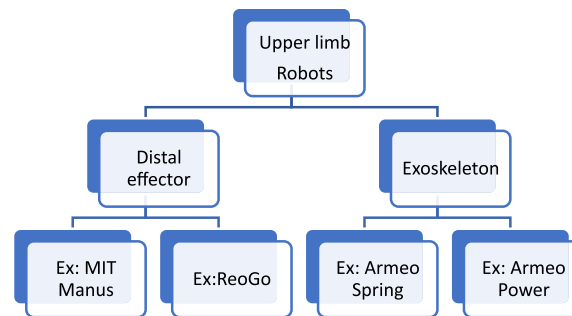


FIG. 1 Types of upper limb robots.

MIT MANUS

It was designed to provide high-intensity and reproducible upper limb rehabilitation in adults and older children. This modular distal effector system consists of a series of proximal and distal components that can be used individually or together for upper extremity training. It comprises two modules and 5 degrees of freedom, two for elbow and forearm motion, and three for wrist motion and allows patients to perform reaching movements in horizontal plane. The robot can move, guide, or perturb the movement of a patient's upper limb and record quantities, such as position, velocity, and force. The operating paradigm is the so-called "assist as needed." Thanks to motion sensors, the mobility of the joint segments can always be monitored. The patient-robot interface consists of video games for elbow, shoulder, and wrist exercises that can be used to increase the quality of therapy sessions as well as keep the user engaged (Krebs, Hogan, Aisen, & Volpe, 1998). It has initially been used in the rehabilitation of the upper limb of stroke patients, proving effective in the sub-acute and chronic phases by reducing motor deficits, improving function and bringing about a lasting change (Bayón-Calatayud et al., 2014; Fasoli et al., 2004). The commercialized version of MIT-MANUS, INMOTION (Bionik Laboratories Corp., Toronto, Canada), has been used in patients with SCI to a limited extent although one study demonstrated that after a training protocol, significant improvements in quality of movement were found with no changes in upper extremity strength, pain, or spasticity (Cortés et al., 2013).

ReoGo

The ReoGo system (Motorika Medical, Caesarea, Israel) is a stationary fixed based end-effector arm rehabilitation robot, which facilitates the mobilization of the upper limb on a support that allows a wide range of movements in the 3 dimensions of space. The Reo-Go allows for movements at the shoulder, elbow, and wrist. It also uses a real-time visual feedback monitor to display games for the subject to perform. Although it has primarily been used for stroke patients, it has also been applied in SCI. Reo-Go was incorporated into an acute incomplete SCI patient therapy protocol. The subject demonstrated remarkable improvements in muscle strength, active range of motion and functional assessment (Siedziewski, Schaaf, & Mount, 2012).

Armeo

Armeo devices (Hocoma AG, Volketswil, Switzerland) were the first unilateral upper extremity exoskeletons marketed for upper limb rehabilitation. This range of devices includes the Armeo Power for the most affected patients, the Armeo Spring, the Armeo Spring for children and the Armeo Senso for those less affected.

The Armeo system is a well-documented device and is the only device shown to offer better functional results after stroke compared to traditional therapy. Two studies showed the utility of this device for upper limbs in SCI subjects focusing on the potential of these devices in performing upper limb assessment (Rudhe, Albisser, Starkey, Curt, & Bolliger, 2012; Zariffa et al., 2012). The Armeo Power is one of the most advanced active exoskeletons for upper extremity rehabilitation. It is based on the ARMin device, which consists of an exoskeleton covering the upper limb and allowing anthropometric adaptations. It provides support for the weight of the patient's upper limb and features different modes of use, such as mobilization mode, 2D and 3D games and functional training of daily life activities. ARMin provides three actuated degrees of freedom for the shoulder and one for the elbow joint. It offers three different therapy modes: the movement therapy, the game therapy and the ADL (activity of daily living) training mode. Like the MIT-MANUS, Armeo



FIG. 2 Armeo Spring. Upper limb device that works through a system of springs that eliminate the weight of the body as an enabler.

Power uses an “assist as needed” mode of operation, allowing the clinician to adapt the difficulty of the task to the degree of recovery. There are studies that demonstrate its usefulness in patients with SCI (Rudhe et al., 2012). An earlier version is the Armeo Spring that manages to cover the shoulder and elbow, and also works the wrist flexo-extension and manual gripping. It is a passive exoskeleton (Fig. 2). It works through a system of springs that eliminate the weight of the body instead of using motors to assist movement as the Armeo Power does. Both feature a monitor with motivational games to encourage repetitive movements. The software allows the clinician to select the task and its degree of difficulty by defining the required joint path and the rhythm of the selected game.

Other devices

There are other devices on the market such as the DIEGO (Tyromotion, Graz, Austria) which uses a wiring system to support and mobilize the limb, the Bi-Manu-Track (RehaStim, Germany) which facilitates the treatment of both upper limbs simultaneously. There are devices that focus on the individual mobility of each finger but allow practice in gripping by controlling the performance of each finger. This would be the case of AMADEO (Tyromotion, Graz, Austria), HAND-CARE 2 and RUTGERS-MASTER II (Rutgers University, USA), although the latter excludes the treatment of the fifth finger. It is not common but in some cases two robotic devices have been used in combination, such as the Armeo Power and the Amadeo, using the first for the shoulder, elbow, and carpal and the second for the shoulder, elbow, and carpal.

Stationary lower limb robots

Thoracic and lower SCIs can result in partial to complete paralysis of the lower extremities. Independent mobility for many can only be achieved at a wheelchair level, although walking oftentimes remains a priority (Dittuno, Patrick, Stineman, & Dittuno, 2008). Lower limb robots have emerged as potential upright mobility devices for those with lower limb paralysis. Locomotor training focuses on retraining the motor function via plastic change (Morawietz & Moffat, 2013; Nam et al., 2017), and the neurophysiological mechanism underlying the restoration of human restoration after SCI involve enhancing the afferent input to the spinal cord and activating CPG (central pattern generator) embedded within the lumbosacral spinal cord (Dietz, Wirz, & Curt, 1998). Plastic changes can be induced in both the spinal cord level and sensory motor cortex via intensive locomotor training, mainly in incomplete SCI subjects (Hubli & Dietz, 2013).

As it has been previously referred, to manually replicate a normal walking pattern with the patient in body weight-supported on a treadmill two or three therapists are needed to control and move lower limbs. This is a strenuous and exhausting task for therapist, so sophisticated automated electromechanical devices have been developed (Tefertiller, Pharo, Evans, & Winchester, 2011) that offers several advantages, including the ability to increase the intensity and total duration of training while maintaining a physiological gait pattern.

TABLE 1 Types of lower limb robots.

Lower limb robots		
Stationary robots		Ambulatory exoskeletons
Distal effector	Stationary exoskeletons	Ex: Ekso Bionics, Rewalk, Indego, etc.
Ex: Gait Trainer	Ex: Lokomat	

As in the case of the upper limbs, in the lower limb robots we also find, depending on their structure, distal effectors and exoskeletons (Table 1). Among lower limb robotic exoskeletons, we can distinguish the stationary and the ambulatory ones. In this section we will discuss the stationary ones, and the ambulatory will be analyzed in the following section.

End effector devices

End-effector-based systems work like conventional elliptical trainers: the subject's feet are strapped to two footplates moving along a gait-like trajectory, as in an elliptical trainer, moving the entire lower limb. They work based on a constraint at the distal end of the kinetic chain that specifies the trajectory there and the proximal joints can simply move as the body geometry and articulations dictate. The footplates generate the stance and swing phases in most instances with symmetric motion. The main difference compared with exoskeletons with a treadmill is that the feet are always in contact with the moving platform, simulating the gait phases but not necessarily generating true swing and stance phases. The trajectories of the footplates, as well as the vertical and horizontal movements of the center of mass, are programmable. The end-effector design lends itself to gait retraining and stair climbing (Hesse, Waldner, & Tomelleri, 2010). Examples of end-effector devices include Gait Trainer GT1 (Reha-Stim, Berlin, Germany), G-EO (Reha Technologies, Switzerland) and Lokohelp. In relation to SCI patients, 3-dimensional data were obtained with Lokomat and G-EO. Their kinematic data were compared when devices were used by SCI or traumatic brain injury patients. The results confirmed a more controlled and repetitive gait pattern when using Lokomat and the G-EO system provided a gait pattern that had more variability of motion for the hips and knees, with slightly reduced knee motion, and the gait pattern differed slightly from that observed during overground walking (Esquenazi & Talaty, 2019).

Stationary exoskeletons

Stationary exoskeletons have a device that surrounds the patient's legs, which may be suspended from an overhead guide rail, supported by a metal frame on wheels, or the exoskeleton can even be directly supported by a mobile robot. They are usually connected directly to the ground through a rigid frame or bolted to a wall, enhancing and ensuring total safety. Stationary exoskeletons can have a large and powerful motors and controllers. They often involve walking on a treadmill. These devices are less complex in their engineering requirements and more stable and safer than ambulatory exoskeletons that allow overground walking due to the elimination of fall risk. They are less accommodating of individual gait variations, such as changes of speed or direction. This group of stationary exoskeletons includes the Lokomat, Walk-Trainer, LOPES or ReoAmbulator.

The Lokomat (Hocoma AG, Volketswil, Switzerland) is the most clinically implanted and studied robot on the market. The Lokomat is a bilaterally driven gait orthosis that is used in conjunction with a body support system (Colombo et al., 2000). It is essentially a robotic implementation of the treadmill walking training system with partial weight support and manual mobilization of the patient by physiotherapists. This system consists of a treadmill, a partial weight support system and a bilateral exoskeleton that provides action on the hips and knees with the ankle being passively supported by a spring to facilitate dorsiflexion of the swing phase of walking (Riener, 2012). The Lokomat moves the patient legs through the gait cycle mainly in the sagittal plane (Fig. 3). The device's hip and knee are actuated by linear drives integrated into an exoskeleton structure. There is no actuator on the ankle and dorsal flexion during the swing phase is achieved passively by means of springs. The lower limb motion can be controlled with highly repeatable predefined hip and knee joint trajectories on the basis of a conventional position control strategy. The exoskeleton is fixed to the rigid frame of the body weight support system and the patient is fixed to the exoskeleton with straps around the waist, thighs and shanks.

The hip and knee joint trajectories can be manually adjusted to the individual patient by changing amplitude and offsets. Signals obtained from force sensors may be used to determine the interactions torques between the patient and the device,



FIG. 3 Lokomat. Lokomat system with a spinal cord-injured patient.

which inform about the voluntary muscle effort produced by the patient (Riener, 2012). The device allows some anthropometrical adaptation to the lower limb segments size via telescopic bars so that the exoskeleton can be used by subjects with different shank and thigh lengths. The width of the hip exoskeleton may also be adjusted by changing the distance between the two lower limbs.

The body weight support system consists of a harness worn by the patient, ropes and pulleys and a counterweight used to partial unload the patient. A patient-cooperative control strategy has been developed that recognize the patient's movement intention and motor ability by monitoring muscular efforts and adapt the robotic assistance to the patient's contribution (Riener et al., 2005). It is recommended that the control and strategies should do the same as a human therapist assisting the patient's movement only as much as needed and informing the patient how to optimize voluntary muscle efforts.

The largest body of scientific is for Lokomat when used by individuals with SCI or stroke. However, there is no consensus of whether and how it affects outcomes in comparison with conventional therapies (Alcobendas-Maestro et al., 2012; Ucar, Parker, & Bugdayci, 2014; Westlake & Patten, 2009) although a recent review provide evidence that acute SCI patients treated with Lokomat showed significantly greater improvement in gait distance and functional level of mobility and independence, and chronic SCI patients a significantly greater improvement in speed and balance were observed than in the group with no intervention (Nam et al., 2017). The Advance Robotic Therapy Integrated Centers (ARTIC) network has recently been set up to collect a large amount of data in order to obtain results with statistical significance. The database includes almost 600 patients not only with SCI but with other neurological conditions with gait deficits who used the Lokomat as part of their rehabilitation (Van Hedel et al., 2018). Other devices, such as the ReoAmbulator (Motorika, New Jersey, USA) have very limited published reports with inconclusive results (Mantone, 2006). A report on LOPES (University of Twente, the Netherlands) showed improved walking ability, as well as gait quality, in subjects with incomplete SCI after an 8 weeks treatment program, with slower walking subjects showing greater benefits (Fleerkotte et al., 2014).

Ambulatory exoskeletons

Ambulatory exoskeletons are used as a powerful tool in the clinical environment and promoting gait training. Both patients with complete and incomplete SCI can use these exoskeletons but with different aim. Patients with incomplete injuries present an improvement prognosis considering the exoskeletons as a rehabilitation tool. In those cases of complete SCI in which recovery is not foreseeable, its use is intended with the aim of permitting the patient to gain a standing up position, walking short distances and replacing the wheelchair as a means of movement in the community in the future.

They adapt to the lower limbs and have electric motors or other kind of powered actuators that mobilize the joints to produce an automatic overground gait. Furthermore, they offer different approaches on the intelligence of the system, from merely healthy normal gait pattern repetition to EMG-based actuation, passing through error augmentation (Marchal-Crespo & Reinkensmeyer, 2009). These robotic systems make it possible for subjects with SCI to perform the action of walking over ground without the need of partial weight support, harnesses, or the treadmill.

Probably the most popular of these robotic exoskeletons for ambulatory walking is the ReWalk (ReWalk Robotics, Inc., Marlborough, MA, USA). It is a lower limb exoskeleton with two active joints (knee and hip), intended to be used with patients with SCI from T4 to L5 and allowing standing up, sitting down, walking, climbing and descending stairs. There are two versions: for personal use and for rehabilitation. Both exoskeletons are composed of a metallic structure that is adjusted by means of tapes or straps, a pelvic support and motors at the hip and knee joints. The difference between both versions is that the exoskeleton for personal use is customized to the dimensions of the user, whereas, in the case of rehabilitation version, the hip and lateral components are replaceable. It offers several levels of assistance and starts ambulation thanks to a sensor that detects the forwards-leaning of the trunk as a signal to start walking.

The different modes of action (walking forward, going from sitting to standing, stopping, going from standing to sitting) are controlled by a control unit located on the patient's wrist. The device has also a "manual" mode (only in sitting position), where the user can control each joint from its local control system (interface at each joint), useful mode for hazards such as spasticity.

Another lower limb exoskeleton is the Vanderbilt exoskeleton, marketed as Indego (Parker Hannifin Corp., Cleveland, OH, USA), with a modular design that facilitates its adaptation. This product is intended to be used with patients with SCI or stroke. As other commercial exoskeletons, the hip and knee are motorized. On the other hand, the knee joints consist of an electromechanical brake that blocks the motor in the event of a power failure, to avoid the fall of the patient. This exoskeleton allows gaits at a speed of up to 0.8 km/h (with a battery life of up to an hour). The control of this product is based on postural information and is composed of three detachable elements facilitating the donning and doffing of the user. It can be used in patients with level of injury C7 to L5 in rehabilitation facilities.

Like the previous two, the Ekso (Ekso Bionics, Richmond, CA, USA) has actuators on the hips and knees and has a backpack that contains the batteries and controllers. Ekso Bionics mainly commercializes two lower limb exoskeletons: Hulc (Human Universal Load Carrier) and Ekso (eLEGS at the start). The first one is a hydraulic exoskeleton intended to be used for the transport and handling of loads, not a medical device, thus falling outside of the focus of this short review. Ekso, on the other hand, was introduced by the company to allow paraplegics to stand up and walk using crutches or a walker. This exoskeleton is made up of force and movement sensors, which collect information and transfer it to movement. The approximate weight of this product is 20 kg and it can reach a speed of 3.2 km/h with a battery life of up to 6 h. Its software allows the clinician to adjust the amount of assistance provided at each limb and. The control of the device is performed by the therapist accompanying the patient. Patients with level of injury from T4 to L5 can use this exoskeleton or even from C7 if AIS (ASIA Impairment Scale) D (Mekki, Delgado, Fry, Putrino, & Huang, 2018).

HAL (Hybrid Assistive Limb) developed by the Japanese company Cyberdyne was initially developed to assist older adults with muscle weakness in walking (Kawamoto & Sankai, 2002) although it is also used for gait rehabilitation in patients with SCI. It consists of a modular design that provides uni- or bilateral actuation at the hip and/or knee joints. The system allows automatic and voluntary control thanks to the activation of certain muscles whose signal is collected by EMG electrodes.

Currently marketed HAL exoskeleton version is intended to be used for different applications, namely rehabilitation, work that requires force, rescue work and even entertainment. There are currently different versions but HAL-5 is full-body exoskeleton for paraplegic users. Both the hip and the knee function actively; however, the ankle is a passive joint.

These four exoskeletons are approved by the FDA, ReWalk and Indego for use in clinical centers and in the community, while Ekso is only for clinical use with medical supervision.

Unlike already described exoskeletons, Hank (Gogoa Mobility Robots, Guipúzcoa, Spain) has six actuated joints including the two ankles to avoid the effect of foot drop during gait (Asín-Prieto, Intxaurburu Sarasua, Fernández Seco, & Fernández Isoird, 2020). It is based on Exo-H2 (Technaid S.L., Madrid, Spain) (Bortole et al., 2015). Hank is intended for patients with incomplete SCI. Its operating system is also based on the "assist as needed" mode and allows a certain deviation from the ideal gait pattern before applying the correcting force (Fig. 4). It presents an open control architecture to be able to make it compatible with other neural interfaces such as brain computer interfaces (BCI) or brain-machine interface systems, or other technologies that facilitate the recovery process such as functional electrical stimulation (FES). The control modes range from rigid trajectory tracking, to transparent mode, passing through adjustable assistance per joint. The trajectory is tuned depending on the selected speed and can also be adjusted to user constraints. The device can also perform sit to stand and stand to sit actions.

The first exoskeleton marketed that has its own balance system is the REX (REX Bionics, New Zealand), freeing the patient from using crutches for use, as is the case with other devices. In this way, its use is preferably reserved to treat alterations in postural balance although it also allows walking. It is also the first device intended to be used without any help, as a substitute of the wheelchair, in a daily environment.

As is to be expected due to the novelty of its appearance, the experiences registered with exoskeletons that have been carried out so far present small samples that make it difficult to obtain significant results. Several studies on specific

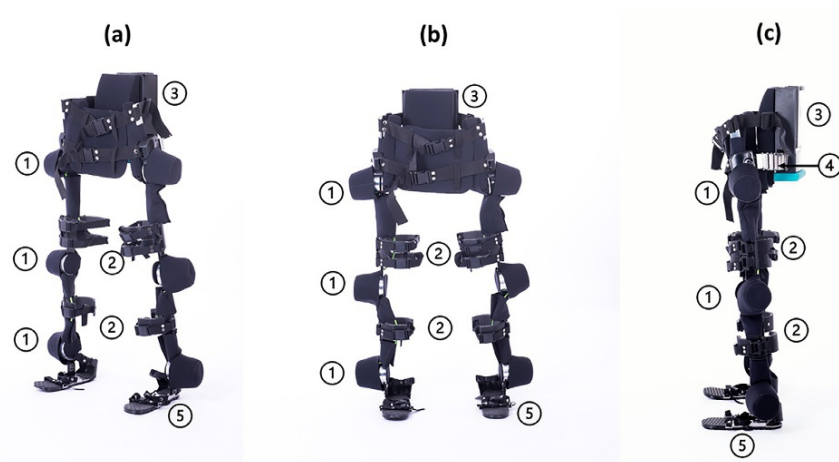


FIG. 4 HANK exoskeleton. HANK exoskeleton; (A) oblique view, (B) frontal view, (C) lateral view; (1) actuators, (2) attachment and fitting, (3) backpack containing battery, main microprocessor and the communication electronics connects, (4) flexible arm for adaptation to pelvis, (5) force-sensing-resistors for measuring foot-floor contact.

exoskeletons and feasibility have been conducted and they have found to be practical for use (Bach Baunsgaard et al., 2018; Benson, Hart, Tussler, & van Middentrop, 2016; Esquenazi, Talaty, Packel, & Saulino, 2012; Tefertiller et al., 2018). There are some studies that compare different exoskeletons systems as tools for rehabilitation in the chronic SCI population (Contreras-Vidal et al., 2016). The benefits that have been reported to date include strengthening the muscles, increasing speed and gait efficiency, as well as improvements in aspects of SCI such as spasticity, pain, cardiovascular and metabolism, in the control of intestinal rhythm, in osteoporosis and in quality of life (Winchester et al., 2005) and benefits also in the budget for the recovery (Pinto et al., 2020).

Applications to other areas of neuroscience

In this chapter we have presented the new features of robotic-based treatments from the point of view of neuroplasticity and their application in therapy. There is an increasing evidence to support the concept for reorganization and plasticity of the injured central nervous system (CNS). The potential for reorganization is particularly high after CNS injury but also possible at later stages. Reorganization in a functionally meaningful way seems to depend on motor activity as executed during rehabilitative training and followed by functional improvements. The science behind exercise in CNS disorders is supported by the therapy concept of increased dosage effect. Task oriented, high repetition movements based on the principles of motor learning can improve muscle strength, motor control, and movement coordination in patients with neurological impairments. All these findings are also applied not only after a SCI but also after brain damage (ictus, traumatic brain injury, cerebral palsy). Robots enhance the rehabilitation process and may improve therapeutic outcomes and have the potential to support clinical evaluation by allowing instrumented measurement of physiological and performance parameters, precisely control and measure the therapeutic interventions, implement novel forms of mechanical manipulation impossible for therapists to provide and supply different forms of feedback, thereby increasing patient's motivating and improving outcomes.

Mini-dictionary of terms

Neuroplasticity: Ability of the Central Nervous System to make functional changes after injury and adapt to new situation.

Task-oriented training: Training focused on recovering a specific task such as walking.

Robotic device: Device that use robotic technology in rehabilitation programs.

Functional electrical stimulation (FES): Type of electrotherapy aimed at achieving a functional improvement (such as walking) and not the analytical stimulation of a muscle group without having a functional objective.

Virtual reality: It is an environment of scenes or objects of real appearance. The most common meaning refers to an environment generated by computer technology, which creates in the user the sensation of being immersed in it.

Distal end effector devices: Distal end effectors are characterized by the fact that they use a single distal point of contact to guide the movement of the entire limb.

Exoskeleton-type devices: They are structures located in parallel to the different parts of the extremities with more than one point of interaction with the person. They provide direct control over each segment of the limb by incorporating individualized motors.

Actuators: This term is synonymous with motors.

Haptic: Haptic perception is based on the forces experienced during contact with the robotic device, this has allowed the creation of virtual haptic sensations with different qualities of perception.

Degrees of freedom: It refers to the number of planes in which a joint can be moved.

Assist as needed: This term refers to the robotic control strategy in which the actuators act to complete a certain joint path that the patient cannot perform.

Swing phase: This term refers to the gait cycle phase in which the foot is not in contact with the ground and allows the limb to move forward.

Stance phase: This term refers to the phase of the walking cycle in which the foot is in contact with the ground giving stability to the limb.

Key facts of functional recovery

- It is based on the concept of spinal learning via activity-dependent plasticity.
- The training effects of any motor task depend on the provision of sufficient and appropriate stimuli.
- Locomotor activity can be activated in patients with severe SCI via passive activation of the legs on a treadmill.
- Functional rehabilitation (i.e., walking) had to be intensive and task-oriented.
- Gait training using partial weight support systems on treadmills is based on the principles of functional recovery.
- Robotic therapy allows task-oriented treatments and intensive.

Summary points

- New technologies in neurorehabilitation represents a huge change in treatment protocols for spinal cord injuries
- The training effects depend on the provision of sufficient and appropriate stimuli
- Training must be task-oriented
- Training must be intensive
- Partial body weight support systems on treadmills is based on the principles of functional recovery
- Robotic therapy allows task-oriented and intensive treatment
- Robots offers objective data of patient performance
- There are robots for upper limb and lower limbs
- Robots be classified in distal end effector devices, stationary exoskeletons and ambulatory exoskeletons

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Section F

Resources

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Recommended resources and sites for the neuroscience of spinal cord injury

Rajkumar Rajendram^{a,b,c}, Vinood B. Patel^d, and Victor R. Preedy^e

^aCollege of Medicine, King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia; ^bDepartment of Medicine, King Abdulaziz Medical City, King Abdullah International Medical Research Center, Ministry of National Guard Health Affairs, Riyadh, Saudi Arabia; ^cStoke Mandeville Hospital, Buckinghamshire Healthcare NHS Trust, Aylesbury, United Kingdom; ^dUniversity of Westminster, School of Life Sciences, Department of Biomedical Science, London, United Kingdom; ^eDiabetes and Nutritional Sciences Research Division, Faculty of Life Science and Medicine, King's College London, London, United Kingdom

List of Abbreviation

SCI Spinal cord injury

Introduction

Any insult to the spinal cord temporarily or permanently affecting its function can be defined as a spinal cord injury (SCI). Motor vehicle incidents are currently the most common reason for SCI (Chen, Tang, Vogel, & Devivo, 2013). Approximately, a third of all new SCI is attributable to this single preventable cause (Chen et al., 2013). This is particularly upsetting because, depending on the location (i.e., level) and severity of insult, SCI may significantly impair autonomic, sensory, and/or motor function. As such, SCI often afflicts young people and results in permanent, life-changing, and devastating disabilities.

The first documented reports of patients with SCI are contained in the Edwin Smith Papyrus which arises from around 2500 years BC (Hughes, 1988). Indeed, it is important to note that this seminal document states that SCI is “an ailment not to be treated” (Donovan, 2007; Hughes, 1988). Nearly 5000 years ago, most SCI was probably related to injuries sustained in combat (Donovan, 2007). In that setting, it was probably appropriate to triage the scarce resources available on the battlefield to those patients with injuries which would not prevent a return to active military service (Donovan, 2007). Yet, regrettably, in the 21st century, besides those few specialists in neurorehabilitation, many clinicians still approach SCI with a significant degree of therapeutic nihilism.

Until relatively recently, the limited clinical literature on SCI focused purely on the feasibility and appropriateness of surgical intervention (Donovan, 2007). This was in part because developments in the field of anesthesia facilitated surgery for SCI. Regardless, technological advances such as advanced orthotic devices (To, Kirsh, Kobetic, & Triolo, 2005) and powered wheelchairs (Algood, Cooper, Fitzgerald, Cooper, & Boninger, 2005) allow those who are managed conservatively (i.e., without surgery) to have a good quality of life.

Perhaps the most internationally renowned clinician for the rehabilitation of patients with SCI was Sir Ludwig Guttmann (Donovan, 2007). He is most widely recognized as the founder of the Stoke-Mandeville Games which subsequently became the Paralympics (Donovan, 2007). Yet his contribution to improving the outcomes of SCI is equally important. A neurosurgeon appointed to lead the SCI unit at Stoke-Mandeville Hospital, Buckinghamshire, England in 1944; he advocated a holistic approach to this cohort and highlighted the importance of their physicians focusing on rehabilitation rather than acting as single organ “ologists” (Donovan, 2007; Guttmann, 1976). The National Spinal Injuries Centre (NSIC) at Stoke-Mandeville Hospital became a role-model for the handful of centers which subsequently blossomed worldwide.

The NSIC continues to advocate for this complex cohort. It is important to prevent insidious neglect from the misconception that the outcomes of patients with SCI are poor. Indeed, a recent series of patients with SCI admitted to the intensive care unit at Stoke-Mandeville Hospital found that survival to hospital discharge is very good (78%; Adam, Rouse, Ali, & Rajendram, 2019). Thus, although, as yet, there is no cure for SCI, therapeutic nihilism is unwarranted.

The inability of victims of SCI to regain neurological function has been thought (for over 100 years) to be due to the failure of the neurons of the central nervous system to regenerate (Cajal, 1928). Thus, considerable resources have focused

on attempts to stimulate neuronal regeneration. As a consequence, novel tools for the study of SCI have recently become available. Our understanding of the neuroscience of SCI has advanced, although more slowly than desired. Importantly, the neurons of the central nervous system have been shown to have greater plasticity and greater capacity to regenerate than originally thought (Barnabe-Heider & Frisen, 2008).

Although the promise of being able to initiate neuronal regeneration looms elusively on the horizon, extensive further research is required for SCI to become an ailment that can be cured. Regardless, it even experienced scientists struggle to remain up to date. To assist colleagues who are interested in understanding more about the neuroscience of spinal cord injury, we have therefore produced tables containing up-to-date resources in this chapter. The experts who assisted with the compilation of these tables of resources are acknowledged below.

Resources

Tables 1–5 list the most up-to-date information on the regulatory bodies (Table 1), journals (Table 2), books (Table 3), professional societies (Table 4), research groups, and centers emerging technologies, platforms, and other resources (Table 5) that are relevant to an evidence-based approach to the neuroscience of spinal cord injury. Some organizations are listed in more than one table as they occasionally fulfill more than one role.

TABLE 1 Regulatory bodies and relevant organizations.	
American Spinal Injury Association (ASIA)	https://asia-spinalinjury.org/
American Society for Surgery of the Hand (ASSH)	https://www.assh.org/hand/s/tetraplegia
Asociación de personas con lesión medular y otras discapacidades física (ASPAYM)	https://www.aspaym.org
Associação Brasileira de Fisioterapia Neurofuncional	https://abrafin.org.br/
Associazione Aspal Paratetraplegici Liguria	www.associazione-paratetraplegici-liguria.it
Associazione Gruppo Animazione Lesionati Midollari (GALM)	www.galm.it
Associazione Il Melograno Organizzazione di Volontariato	http://www.ilmelogranooodv.org/
Associazione Medullolesi Siciliana	http://www.ass-medullolesi.org/
Associazione Paraplegici di Roma e del Lazio	www.apromaelazio.it
Associazione Paraplegici Lombardia - Onlus	www.apl-onlus.it
Associazione Paraplegici Marche	https://www.apmarche.org/
Associazione Paraplegici Toscana	http://www.atponlus.org
Associazione Paratetraplegici Nord Est	http://www.paratetraplegicinordest.it
Associazione Spina Bifida Italia	www.spinabifidaitalia.it;
Associazione Tetra-Paraplegici Friuli Venezia Giulia Onlus	http://www.paraplegicifvg.it/
Associazione Voglia di Vivere	https://www.vdvpistoia.org/
Australian Spinal Injury Alliance	https://spinalinjuryalliance.com.au/
Canadian Spinal Cord Injury Rehabilitation Association	https://cscira.ca/
Canadian Spinal Research Organization	https://www.csro.com/
Centre for the Rehabilitation of the Paralysed (CRP) Bangladesh	https://www.crp-bangladesh.org/
Christopher and Dana Reeve Foundation	https://www.christopherreeve.org/
Comitato Paralimpico Italiano	http://www.comitatoparalimpico.it/
Craig H Neilsen Foundation	https://chnfoundation.org/
elearnSCI	http://www.elearnsoci.org/
European Commission	https://ec.europa.eu/info/index_en

TABLE 1 Regulatory bodies and relevant organizations—cont'd

European Network on Independent Living	www.enil.it
European Paralympic Committee	https://www.europaralympic.org/
European Spinal Cord Injury Federation	http://www.escif.org/
Federation of European Societies for Surgery of the Hand (FESSH)	https://fessh.com/
Federazione Associazioni Italiane Paratetraplegici	http://www.faiponline.it/drupal/
Fundación Lesionado Medular	www.medular.org
International Group for Research into Spinal Cord Injury (SCI-Research Group)	https://sites.hss.univr.it/npsy-labvr/spinal-cord-injury-research-center/
International Spinal Cord Society	https://www.iscos.org.uk/
International Spinal Research Trust	https://spinal-research.org/
Japan Spinal Cord Foundation	http://www.jscf.org/
Life Rolls On	Liferollson.org
Ministério da Saúde Ministry of Health of Brazil	https://www.gov.br/saude/pt-br
National Council on Independent Living (NCIL)	https://ncil.org
National Institute for Health and Care Excellence	https://www.nice.org.uk/guidance/ng41
National Institute of Neurological Disorders and Stroke	https://www.commondataelements.ninds.nih.gov/Spinal%20Cord%20Injury
National Spinal Cord Injury Association of Illinois	https://sci-illinois.org/
Paralyzed Veterans of America	https://www.pva.org/
Reeve Foundation (also known as Christopher & Dana Reeve Foundation)	https://www.christopherreeve.org/
Rick Hansen Foundation	https://www.rickhansen.com/
Sarah Network Rehabilitation Hospitals	www.sarah.br
Sheperd Center. Rehabilitation Hospital	https://www.shepherd.org/
Spinal Cord Injuries Australia	https://scia.org.au/
Spinal Cord Injuries: Clinical Trials	https://stemcellportal.com/clinical_trials_spinal_cord_injuries
Spinal Cord Injury Alberta	https://sci-ab.ca/
Spinal Cord Injury British Columbia	https://sci-bc.ca/
Spinal Cord Injury Research Program- Mayo Clinic	https://www.mayo.edu/research/centers-programs/spinal-cord-injury-research-program
Spinal injuries association	https://www.spinal.co.uk/
SpinalCord-ItalianLab	https://spinalcord-italianlab.it/
The Community Research and Development Information Service (CORDIS)	https://cordis.europa.eu/article/id/89878-spinal-cord-injury-treatment-and-rehabilitation
The International Spinal Cord Society	https://www.iscos.org.uk/
The National Spinal Cord Injury Foundation	www.spinalcord.org
Unite2fight paralysis	https://u2fp.org
United Spinal Association	https://unitedspinal.org/
United States Food and Drug Administration (FDA)	https://www.fda.gov/home
World Health Organization	https://www.who.int

This table lists the regulatory bodies and organizations involved with the neuroscience of spinal cord injury and associated specialties or interests. The links were accurate at the time of going to press but may move or alter. In these cases, the use of the "Search" tabs should be explored at the parent address or site. See also Table 4.

TABLE 2 Relevant journals publishing original research and review articles related to the neuroscience of spinal cord injury.

Spinal Cord
Journal of Spinal Cord Medicine
World Neurosurgery
Journal of Neurotrauma
Neural Regeneration Research
Archives of Physical Medicine and Rehabilitation
Experimental Neurology
Scientific Reports
Spinal Cord Series and Cases
PLoS One
Topics in Spinal Cord Injury Rehabilitation
Chinese Journal of Tissue Engineering Research
Spine
Neuroscience Letters
International Journal of Molecular Sciences
Journal of Neurosurgery Spine
Disability and Rehabilitation
European Spine Journal
Neurourology and Urodynamics
Journal of Neuroscience
Spine Journal
Molecular Neurobiology
Neuroscience
Frontiers in Neuroscience
Journal of Neuroinflammation
Frontiers in Neurology
Global Spine Journal
Frontiers in Cellular Neuroscience
American Journal of Physical Medicine and Rehabilitation
Medicine United States
Journals publishing original research and review articles related to the neuroscience of spinal cord injury. Included in this list are the top 30 journals which have published the most number of articles on spinal cord injury over the past 5 years. Data derived from Scopus.

Application to other areas of neuroscience

The pathophysiology and management of spinal cord injuries are similar to traumatic injuries to the other components of the nervous system. These include the brain and the peripheral nervous system. Thus, the contents of this chapter are also relevant to the understanding of traumatic brain injuries and peripheral neuropathies.

TABLE 3 Relevant books.

Book title	Authors or editors	Publisher	Year
AACD Reabilitação	Fernandes AC, Ramos ACR, Morais Filho MC, Ares MJJ	Manole	2014
AOSpine Masters Series, Volume 7: Spinal Cord Injury and Regeneration	Vialle LR, Fehlings M, Weidner N	Thieme	2016
CNS Regeneration: Basic Science and Clinical Advances	Tuszynski MH, Kordower J	Elsevier	1999; 2007
Critical Care in Spinal Cord Injury	Fehlings M	Future Medicine LTD	2013
Delisa's Physical Medicine and Rehabilitation: Principles and Practice	Delisa JA	Lippincott Williams & Wilkins	2010
Diagnostic Imaging: Spine	Ross JS, Moore R	Elsevier	2020
Diseases of the Spinal Cord	Hattingen, E	Springer	2015
Diseases of the Spinal Cord: Novel Imaging, Diagnosis and Treatment	Hattingen, EHattingen E, Weidauer S, Setzer M, Klein JC, Vrionis F	Springer	2013
Essentials of Spinal Cord Injury. Basic Research to Clinical Practice	Fehlings MG, Vaccaro AR, Boakye M, Rossignol S, Dituno JF Jr., Burns AS	Thieme Medical Publishers	2012
Essentials of the Adult Neurogenic Bladder	Corcos J, Karsenty G, Kessler T, Ginsberg D,	Taylor & Francis Group	2015
Functional Electrical Stimulation: Standing and Walking After Spinal Cord Injury	Kralj AR, Bajd T	CRC Press	1989
Hand Function A Practical Guide to Assessment	Duruöz MT	Springer	2019
Incontinence 6th edition	Abrams P, Cardozo L, Wagg A, Wein A	International Consultation on Urological Diseases	2017
Ischemic and Traumatic Brain and Spinal Cord Injuries Mechanisms and Potential Therapies	Farooqui A	Academic Press	2018
Lesión medular. Enfoque multidisciplinar	Esclarin de Ruz A	Panamericana	2020
Living with Spinal Cord Injury: A Wellness Approach	Cristian A	Demos Medical Publishing	2010
Management and Rehabilitation of Spinal Cord Injuries	Ko HY	Springer	2019
Management of Spinal Cord Injuries: A Guide for Physiotherapists	Harvey L	Elsevier	2008
Manual de Medicina Física y Rehabilitación	Frontera WR, Silver JK, Rizzo T	Elsevier España	2020
Medicina e Reabilitação: Princípios e Práticas	Fernandes AC, Ramos ACR, Casilis MEP, Herbert SK	Artes Médicas	2013
Neurological Aspects of Spinal Cord Injury	Weidner N, Rupp R, Tansey K	Springer	2017
Neurotrauma: A Comprehensive Textbook on Traumatic Brain Injury and Spinal Cord Injury	Wang K	Oxford University Press	2018
Programa de Atualização em Fisioterapia Neurofuncional (PROFISIO)	Faria C, Leite H	Artmed	2021
Recovery of Motor Function Following Spinal Cord Injury	Fuller, H	IntechOpen	2016
Rehabilitation in Spinal Cord Injuries	Reznik J, Simmons J	Elsevier	2020

Continued

TABLE 3 Relevant books—cont'd

Book title	Authors or editors	Publisher	Year
Spinal Cord Injuries Management and Rehabilitation	Sisto SA, Druin E, Sliwinski MM	Elsevier	2008
Spinal cord injury	Holtz A, Levi R	Oxford University Press.	2010
Spinal Cord Injury (SCI) Repair Strategies	Giuseppe P, Filippo R	Elsevier Health Sciences	2019
Spinal Cord Injury: A guide for patient and families (American Academy of Neurology)	Selzer M, Dobkin B	Demos Health	2008
Spinal Cord Injury: Management and Rehabilitation	Sisto SA, Druin E, Sliwinski MM	Mosby-Elsevier	2009
Spinal Cord Medicine	Kirshblum S, Campagnolo DI	Lippincott Williams & Wilkins	2011
Spinal Cord Medicine, 3rd Edition	Kirshblum S, Vernon WL	Springer	2018
Spinal Trauma: Imaging, Diagnosis and Management	Schwaartz ED, Flanders AE	Lippincott Williams & Wilkins	2006
Spine and Spinal Cord Trauma	Vaccaro A, Fehlings M, Dvorak M	Thieme Medical Publishing	2011
Textbook of neurogenic bladder Third edition	Corcos J, Ginsberg D, Karsenty G	Taylor & Francis Group	2015
The art of healthy living with physical impairments	Lagerstrom A-C, Wahman K	Spinalis	2014
The Physiology of Exercise in Spinal Cord Injury	Taylor JA	Springer	2017
Therapeutic Strategies to Spinal Cord Injury	Jendelova P	MDPI	2018
Traumatic Brain and Spinal Cord Injury. Challenges and Developments	Morganti-Kossmann C, Raghupathi R, Maas A	Cambridge	2012
Urologic management of the spinal cord injured patient	Elliott S, Gomez R	SIU Academy	2017
Vascular Anatomy of the Spinal Cord	Thron AK	Springer	2016

This table lists books on the neuroscience of spinal cord injury.

TABLE 4 Professional societies and other organizations.

Society name	Web address
Academy of Spinal Cord Injury Professionals	https://www.academyscipro.org/
Academy of Spinal Cord Injury Professionals (ASCIP)	https://www.academyscipro.org/
American Academy of Physical Medicine and Rehabilitation (AAPM&R)	https://www.aapmr.org/
American Congress of Rehabilitation Medicine (ACRM)	https://acrm.org/
American Spinal Cord Injury Association (ASIA)	https://asia-spinalinjury.org/
AO Spine Knowledge Forum Spinal Cord Injury	https://aospine.aofoundation.org
Asian Spinal Cord Network (ASCoN)	https://ascon.info/
Asociación Española de Enfermería especializada en Lesión Medular	www.aselme.com
ASSH (American Society for Surgery of the Hand)	https://www.assh.org/hande/s/tetraplegia
Association of Academic Physiatrists (AAP)	https://www.physiatry.org/

TABLE 4 Professional societies and other organizations—cont'd

Society name	Web address
Australian and New Zealand Spinal Cord Society	https://anzscos.org/
Canadian Spinal Cord Injury Rehabilitation Association	https://cscira.ca/
Christopher & Dana Reeve Foundation	www.christopherreeve.org
European Spinal Cord Injury Federation (ESCIF)	http://www.escif.org/
Federation of European Societies for Surgery of the Hand (FESSH)	https://fessh.com/
Fehlings Lab Twitter	www.twitter.com/DrFehlings
Fehlings Lab Website	www.drfehlings.ca
International Continence Society	https://www.ics.org
International Neuro-Urology Society	https://www.neuro-uro.org
International Society of Physical Medicine and Rehabilitation (ISPRM)	https://www.isprm.org/
International Spinal Cord Society (ISCoS)	https://www.iscos.org.uk/
Korean Spinal Cord Society	http://www.koscoss.kr/
National Organization For Rare Disorders (NORD)	https://rarediseases.org/organizations/national-spinal-cord-injury-association/
North American Spine Society	https://www.spine.org/
Praxis Spinal Cord Institute	www.praxisinstitute.org
Protection Center of Spinal Cord Disabilities of Iran	www.irannokhaa.ir (not viable at the time of going to press)
Sheperd Center. Rehabilitation Hospital	https://www.shepherd.org/
Shirley Ryan Hability Lab	https://www.sralab.org/conditions/spinal-cord-injury
Sociedad Española de Paraplejia	www.sociedaddeparaplejia.com
Società Italiana Chirurgia della Mano (SICM)	https://www.sicm.it/
Society for neuroscience	https://www.sfn.org
Spinal Cord Injury Associations & Organizations (USA)	https://www.sci-info-pages.com/spinal-cord-injury-organizations/
Spinal Cord Injury Canada	https://sci-can.ca/about-us
Spinal Cord Injury Ontario	https://sciontario.org/
Spinal Cord Injury Research Evidence (SCIRE)	https://scireproject.com/
Spinal Cord Society-Indian Chapter	http://www.scs-isic.com/
Spinal Injuries Association	https://www.spinal.co.uk/
The Academy of Spinal Cord Injury Professionals	https://www.academyscipro.org/
The Asian Spinal Cord Network	https://ascon.info/
The Canadian Spinal Research Organization (CSRO)/American Spinal Research Organization (ASRO)	https://www.csro.com/
The International Spinal Cord Society	https://www.iscos.org.uk/
The Nordic Spinal Cord Society	http://noscos.org/
United Spinal Association	https://unitedspinal.org/

This table lists some societies and organizations devoted to understanding the neuroscience of spinal cord injury. Please note, occasionally the location of the websites or web address changes. Not viable at the time of going to press indicates that the site has changed or is the process of being changed. See also Table 1.

TABLE 5 Emerging techniques, platforms, and other sites of interest relevant to the neuroscience of spinal cord injury.

Organization or company or society name	Web address
Acreditando	https://www.acreditando.com.br/
American Society for Surgery of the Hand (ASSH)	https://www.assh.org/hande/s/tetraplegia
American Spinal Injury Association (ASIA)-e Learning Center	https://asia-spinalinjury.org/learning/
Association for Assistance of Disabled Children (AACD)	https://aacd.org.br/centro-de-reabilitacao
Avery biomedical devices	https://www.averybiomedical.com/spinal-cord-injury-treatments/
California Institute for Regenerative Medicine (CIRM)	https://www.cirm.ca.gov
Christopher & Dana Reeve Foundation	https://www.christopherreeve.org/
Clinical Trials. Gov	https://clinicaltrials.gov
Dalhousie University Faculty of Medicine Wheelchair Skills Program (WSP)	https://wheelchairskillsprogram.ca/en/
Elearning-SCI	http://www.elearnsoci.org
European Multicenter Study about Spinal Cord Injury (EMSCI)	https://www.emsci.org
facing disability	https://facingdisability.com/resources/assistive-technology
Federation of European Societies for Surgery of the Hand (FESSH)	https://fessh.com/
Gaylord Speciality Healthcare	https://www.gaylord.org/Patients-Families/Conditions-Services/Spinal-Cord-Injury-Program
inspire neurocare	https://www.inspireneurocare.co.uk/
Instituto de Medicina Física e Reabilitação (Rede Lucy Montoro)	https://www.redelucymontoro.org.br/site/programa-de-reabilitacao.html
Instituto Novo Ser	http://www.novoser.org.br/index.html
International Collaboration on Repair Discoveries (ICORD)	https://icord.org/
International Group for Research into Spinal Cord Injury (SCI-Research Group)	https://sites.hss.univr.it/npsy-labvr/spinal-cord-injury-research-center/
International Society of Spinal Cord Injury	www.iscos.org.uk
Kentucky Spinal Cord Injury Research Center	https://louisville.edu/kscirc
Kessler Foundation	https://kesslerfoundation.org/
Mayo Foundation for Medical Education and Research	https://www.mayo.edu/research/centers-programs/spinal-cord-injury-research-program
Miami Project to Cure Paralysis	https://www.themiamiproject.org/
Model System Knowledge Translation Center (MSKTC)	https://msktc.org/sci
National Institute of Neurological Disorders and Stroke: SCI	https://www.ninds.nih.gov/Disorders/Patient-Caregiver-Education/Hope-Through-Research/Spinal-Cord-Injury-Hope-Through-Research
Ontario Neurotrauma Foundation	https://spauldingrehab.org/
Physiopedia (Assistive Devices for Spinal Cord Injury)	https://www.physio-pedia.com/Assistive_Devices_for_Spinal_Cord_Injury
Praxis Spinal Cord Institute	https://praxisinstitute.org/

TABLE 5 Emerging techniques, platforms, and other sites of interest relevant to the neuroscience of spinal cord injury—cont'd

Organization or company or society name	Web address
ProBed	https://www.pro-bed.com/blog/info/top-10-spinal-cord-research-organizations
PropelPhysiotherapy	https://propelphysiotherapy.com/spinal-cord-injury/assistive-devices-sci-rehabilitation
Rede SARAH (Specialized assistance in rehabilitation)	https://www.sarah.br/especialidades/neurorreabilitacao-em-lesao-medular/
ReWalk	https://rewalk.com/
Shepherd Center	https://www.shepherd.org/resources-healthcare-professionals/research/spinal-cord-injury/current
Società Italiana Chirurgia Della Mano (SICM)	https://www.sicm.it/
Spaulding Rehabilitation Network	https://onf.org/knowledge-mobilization/spinal-cord-injury-2/knowledgemobilization-sci-networkssummits/
Spinal Cord Injury Adaptive Equipment And Assistive Technology	https://www.sci-info-pages.com/adaptive-equipment/
Spinal Cord Injury and You (SCI-U)	http://sci-u.ca/
Spinal Cord Injury Research Evidence	https://scireproject.com/
Spinal Cord Injury Trials Finder	https://scitrialsfinder.net
Spinal Cord Outcomes Partnership Endeavor	https://scope-sci.org/
Spinal Cord Research Centre	https://scrc.umanitoba.ca/wp/
Spinal Research	https://spinal-research.org/
Spinal Research Institute	https://www.thesri.org/spinal-cord-research-hub/
SpineUniverse	https://www.spineuniverse.com/
The American Trauma Society	https://www.amtrauma.org/
The Big Idea	https://reevebigidea.org/
Transforming Research and Clinical Knowledge in Spinal Cord Injury (TRACK-SCI)	https://spinalcordinjury.ucsf.edu
Unite 2 Fight Paralysis	https://u2fp.org/
United Spinal Association	https://askus-resource-center.unitedspinal.org/index.php?pg=kb.book&id=32

This table lists some emerging technologies and platforms relevant to the neuroscience of spinal cord injury. Please note, occasionally the location of the websites or web address changes.

Mini-dictionary of terms

Orthotic device: A support/brace for the spine or limbs.

Neuronal plasticity: The ability of neural networks to adapt and/or change by reorganization and/or growth.

Neuronal regeneration: The repair/regrowth of neurons by the formation of new axons, synapses neurons, or glia.

Neurorehabilitation: The process which aims to restore function to patients who have sustained a neurological insult such as stroke or spinal cord injury.

Therapeutic nihilism: The perception that it is impossible to improve the outcome of a patient with a specific condition.

Key facts of spinal cord injury

- Any insult to the spinal cord temporarily or permanently affecting, its function can be defined as a spinal cord injury.
- Spinal cord injury often afflicts young people and results in permanent, life-changing, and devastating disabilities.

- Following spinal cord injury, therapeutic nihilism is unwarranted as survival to discharge home is good and technological advances have greatly improved quality of life.
- Lack of functional recovery post spinal cord injury is thought to be due to failure of central neurons to regenerate.
- Despite great advances, vast amounts must still be learned about the neuroscience of spinal cord injury before this devastating condition can be cured.

Summary points

- Patients with spinal cord injury often survive to be discharged at home, and their quality of life has been improved by technological advances.
- Although there is currently no cure for spinal cord injury, prognostic pessimism is unwarranted.
- There is significant interest in stimulating neuronal regeneration to promote functional recovery after spinal cord injury.
- Recent advances have suggested that central neurons have greater plasticity than previously thought. This seed plants the hope that the ability to control neuronal regeneration is on the horizon.
- The expansion of the knowledge and understanding of the neuroscience of spinal cord injury has been slow but steady. It is becoming increasingly difficult for those interested in this field to remain up to date.

Acknowledgements (in alphabetical order)

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DIAGNOSIS AND TREATMENT OF SPINAL CORD INJURY

THE NEUROSCIENCE OF SPINAL CORD INJURY

EDITED BY

RAJKUMAR RAJENDRAM, VICTOR R. PREEDY, AND COLIN R. MARTIN

Diagnosis and Treatment of Spinal Cord Injury will enhance readers' understanding of the complexities of the diagnosis and management of spinal cord injuries. Featuring chapters on drug delivery, exercise, and rehabilitation, this volume discusses in detail the impact of the clinical features, diagnosis, management, and long-term prognosis of spinal cord injuries on the lives of those affected. The book has applicability for neuroscientists, neurologists, clinicians, and anyone working to better understand spinal cord injuries.

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