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Review Paper

Recent advancements in biomaterials and medical devices, aiming to improve consistently the outcomes of therapeutic approaches within spine/cord injury

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We emphasize some implantable "smart", tissue engineering biomaterials and respectively, advanced devices, with important healing potential in spine and/or spinal cord injuries (SCI). There are two main types of such biomaterials: un-resorbable and resorbable, separate in two distinct/ intricate cathegories: acellular and – more recent/ complex – construct scaffolds (polymeric/ gel-type, bioactive or/and self-assembling/ nano-processed). They serve as: continuity („filling the gap")/holding (re)structures, intra-nevraxial neural (re)growth inhibitors' blockers, contains, guides or/and stimulators for neo-forming tissues, delivery vehicles for cells and growth/neuro-protective factors, host immune attack/ reject reactions preventors, cell behavior controllers - including decrease of glial scar formation - or adjunct in bone grafting. Ground-breaking: molding "biological ink" (of micro-inkjet cell aggregates) into 3-D shaped biodegradable polymer gels, to build organs from the ground up (including inside repair/ regeneration). Related reliable trials are on going: they might, in the following about three years, eventually, show consistent improvements of SCI therapy outcomes.

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Keywords: SCI, nevrax, "smart"/ tissue engineering biomaterials, Unresorbable / resorbable (gel-type) implants, Self-assembling/ nano-processed scaffolds, "Biological ink", Organ 3-D printing, Inside repair / regeneration, OFS, RPT

1. Introduction

Biomaterials (metals, alloys, polyester-based materials and also other products useful for tissue repair or/and reconstruction) are different types of substances able to replace or/and harmless interact with living structures. They are meant to substitute some irreversibly damaged anatomical parts and to treat (or hopefully, in the near future, even cure) a great number of severe conditions, all these without being rejected.

A comprehensive definition of modern surgical biomaterials was given recently by Lopez: "*substances and products that not only evade rejection by the body, but that can interact with living tissue. These biomaterials do the job they are meant to perform, and then are either absorbed naturally by the body over time and eliminated by biological processes or become a permanent part of the surrounding tissue*" [1].

Conceptually, biomaterials are meant to do, on one hand, synergistic actions with natural biological processes (ex.: regeneration in wound healing ; even more, to induce cellular responses that might not be normally present, like healing different affected structures in an ill subject or the generation of a new vascular bed in order to receive a cell transplant) and, on the other hand, to block natural phenomena, such as the immune rejection of xeno-transplants or the transmission of growth factor signals that stimulate scar formation. [2]

The main characteristics of the biomaterials domain are: large, extremely complex, intense interdisciplinary, markedly collaborative, rather old - considering their first medical applications -, (but in the same time) very dynamic, continuously expanding, holding recent breakthroughs. Their clinical use in SCI furnished already, some important facilities for the neurosurgical approach and consequently, for the post-operative healthcare/rehabilitation, phases and outcomes. In particular, biomaterials (also) bring major opportunities for efficiently assist/support neural tissue regeneration or/and replacements by homo- or xeno-transplants + (including from inside) reconstruction or/and provide "endogenous" functional electrical stimulation (through neuro-prostheses), making hence possibly some real cures within the Central Nervous System (CNS) / nevraxial pathology. Therefore, the global aim, respectively, the expected results from using biomaterials, is to significantly improve the healing processes, follow-ups, rehabilitation outcomes and thus, overall patients' quality of life (QoL), including and especially for the post SCI ones, as the consequences of a SCI can be devastating and permanent. This represents an important, complicated and still unsolved public health matter.

2. Theory and examples

Surgical biomaterials - generically called implants, actually used in SCI therapeutic approaches, are classified both, by clinical (topographical / custom) and lately, by structural (material and intra-tissue behavior), criteria: I. extra-rahidian (rods and other plate fixation devices, balloon kyphoplasty devices, some bone parts or/and cartilage substitutes, cements, disc/nucleus prostheses - artificial disc-like - spacers for the inner spine channel re-calibration, etc); II. intrarahidian – extra-nevraxial (implantable neural prostheses) and intra-nevraxial (gel-type biomaterials), implants ; A. non-resorbable implants : 1. rods and other devices for vertebrae/spine channel, synthesis or/and plasty (plate fixation devices, balloon kyphoplasty devices, some bone parts or/and cartilage substitutes, cements, disc / nucleus prostheses (artificial disc-like), spacers for the inner spine channel re-calibration); 2. implantable neural prostheses (micro-arrays/electrodes/stimulators, micro and nano-chips: this is a particular type of biomaterials - with character of device too, like for instance and from this point of view, the above mentioned devices - specifically interacting only with neural/muscular structures, for which certain kinds of electrical currents are physiologic/appropriate stimuli; it is a vast, also growing, domain that request (and therefore, will be approached in a distinct paper, except for a device which is already in clinical use / trials – see later); B. resorbable implants: 1.(of) "protected bone regeneration" (PBR) type; 2.organic/polymeric - including gel-type (also, recently: multiple-channel) ones, bio-compatible/bio-active, organic or/and self-assembling / stereospecific, nano-scale processed, scaffolds, to be injected into the lesion/peri-lesion area; they serve mainly as: continuity („filling the gap") / holding (re)structures, intra-nevraxial neural (re)growth inhibitors' blockers, contains, guides or/and stimulators for neo-forming tissues, delivery vehicles for cells and growth/ neuro-protective factors, host immune attack/ reject reactions preventors, cell behavior controllers - including decrease of glial scar formation - or adjunct in bone grafting. These ones prove to be more and more indispensable (also) for rebuilding, intra-lesion, the normal (pre-lesion) cord's micro-structure/ architecture. Hence, in SCI modern therapeutic approaches, bioresorbable implants are conceptually considered and used as both, biologically and biomechanically active, containing complex (micro/ nano) tools for: bone fusion, neural spare / (possibly, also some regrowth / re-wireing facilitation) or/and graft fixation, proving thus, multitargetted useful in treating spine/cord trauma (but also, other diformities or/and diseases of the musculoskeletal system).

It has to be stressed that this dual-criterion and frequently (in practice, as already exemplified) overlapping classification, is quite functional, including for its relative simplicity, but it is neither exhaustive nor determinate, mainly because the very dynamic domain of biomaterials/ tissue engineering is progressing very fast.. Therefore, we consider that, in this still „early" advanced biomaterials' (and biotechnology's) „era" , the more elaborated reviews, the better for this new and complicated, but nevertheless, extremely promising subject-matter. Hence, considering that, to achieve a rather largely accepted classification of biomaterials, generally and in particular of the advanced ones, with significant potential to improve consistently the outcomes in spine/ SCI treatment, different overviews and insights are wellcome.

In this respect, we present, in two attached hereto tables, a (just concerning) scaffold's design, concentrating the data from a recent - submitted to be published in about the same time with this (our) work's abstract for the International Conference BiomMedD'2006 - exhaustive and well documented, mainly descriptive, overview on the related tissue engineering. We choose to reproduce most accurate the scaffolds' afferent concepts within Samadikuchaksaraei's paper - including the main referencs citated by him - so that, overall, the use of advanced biomaterials in the complicated and still unsolved domain of SCI to be as complete as possible emphasized. On this occasion, there will also be observed differences between our and his vision, concerning this subject's structure [3].

As announced in the abstract, this paper will approach only breakthrough novelties in the field, so that rather older biomaterials or/and devices (mainly those belonging to the non-resorbable implants domain) will be, most of them, only mentioned.

As already briefly anticipated above, the neurosurgical use of appropriate biomaterials, means: easier and quicker achievement of a maximal possible morphological and functional post-operative regain , sooner attempt of a minimal necessary healing level for starting the rehabilitation process, better opportunities for patient's management (including some follow-up procedures) and subsequently, better global medical and QoL outcomes.

But, the use of biomaterials is not exonerated of troubles. A major such a problem is the "foreign body reaction" (FBR): a host-driven reaction that develops in response to the implantation of almost all biomaterials. Its severity is of various degrees and can be detrimental to the biomaterials' function, in certain conditions, possibly leading even to implant failure. The formation of foreign body giant cells (FBGC), which damage the surface of biomaterials, may be considered a real hallmark of this immune-mediated reaction. FBGC derive from blood-borne monocytes. In response to the release of local chemotactic signals, FBGC enter the implantation site after surgery, indicating, in the same time, that the key cell type within FBR might be the macrophages: they seem to be implicated including/ mainly (?) in the development of fibrosis, by providing profibrotic signals to fibroblasts. Fortunately, FBR can be counteracted by modulating some important molecular agents, such as hydrophilic and anionic substrates - these increase macrophage apoptosis[4]. - and also by targeting („blocking giants") key immune molecules (possibly including, directly or indirectly, FBCG): this solution could prevent rejection and damage of implants. Hence, at the contact point between tissue and implants, it has been recently targeted a

molecule, called CC chemokine ligand (CCL)-2 [old: (MCP)-1], that is thought to recruit precursors of the foreign body giant cells (FBGC) [5]. As regards the prevention of the implant's surface damage - comprising also strategies to limit FBGC formation - biodegradable materials may thus, in addition, also be effective for the biological control of the biomaterials' degradation rate.

Bioresorbable polymer implants are basically made from a chemical family known as alpha esters, i.e.: polylactic acid (PLA) and polyglycolic acid (PGA), successfully used as suture material over the past 30 years. But, as for the scaffolding – an extremely complex, cutting-edge domain – there have been / are used / tested also a rather large variety of biomaterials (see Appendix I).

Bioresorbable polymer implants, comparing to no-resorbable, are safer and have some important advantages : they offer application versatility, as they can be designed either for hard (bone - in these situations, acting very similar to traditional metallic devices) or for soft tissues, their endurance being easily contoured intra-operatively, to closely match targeted anatomy. Permanent metal or nonresorbable implants remain in the body after healing takes place, unless they are surgically removed, metallic implant materials presenting additionally, risk of osteoporosis (stress shielding - the weakening of healing bone, resulting from excessively rigid fixation over prolonged periods of time), whereas bioresorbable implants (including/especially the PLA ones), made from molecules similar to those in the human body (see further), resorb after the tissue is healed, thus eliminating the need for secondary surgeries (sometimes very complicated and risky) that may be required to remove a metallic device; in the mean time, they present a significantly reduced risk of stress shielding. Bioresorbable implants do not obscure radiographs or MRI / CT scans, allowing for more accurate evaluation (including for follow-up / tracks) during the healing process.

PLA, essentially contains the same lactic acid molecular building blocks that occur naturally in the human body, produced in the muscles, during strenuous activity; its longer molecular polymer (/co-polymer) chains are created by combining lactic acid derivatives, known as lactides, respectively polilactides (also named PLA). Having strong / intimate similarities with the naturally lactic acid molecules in the body, PLA copolymers, once implanted, first do the "jobs" they have been set-up for and then - better and better controlled, lately - they start a physiologic-like degradation process - the PLA degradation circle (Fig.1) :

Furthermore, within clinical use, numerous scientific evaluations, including for safety and bio-compatibility, have shown, comparing PLA vs. PGA properties, differences in tissue reactions. The main difference consists in the intensity of inflammatory tissue reactions: one study reports that PGA initiates an inflammatory tissue response even double than of PLA's [6].

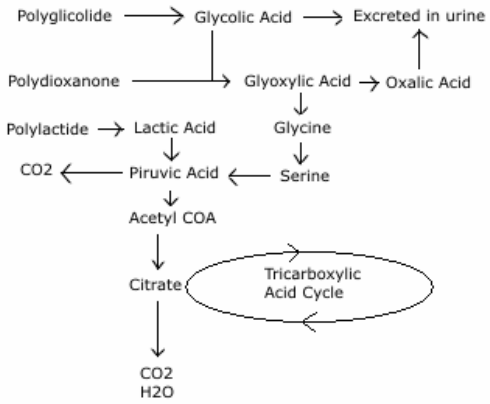

Fig. 1. The PLA degradation circle.

Appendix I

Table 1. Acellular scaffolds/ "cell-free bioscaffolds" (adapted after Samadikuchaksaraei).

Active substance	Basic physical / chemical characteristic(s)	Main therapeutic action(s)	Study(ies) / Trial(s)	Comment(s)	Main citated reference(s)
Collagen	-major constituent of extracellular matrix	-fill the gap and seems to support axonal regeneration -effects are depending on the contents in inhibitory or trophic factors - supports neural cells attachment and respectively, growth factors	-on SCI animal models	-also considered a component of inhibitory glial scar, possibly inhibitting nerve growth -but collagen might not be inhibitory to axonal regeneration per se -marketed as NeuraGen™ Nerve Gide	-Harley BA, Spilker MH, Wu JW, Asano K, Hsu HP, Spector M et al.: Optimal degradation rate for collagen chambers used for regeneration of peripheral nerves over long gaps. Cells Tissues Organs 2004, 176: 153-165. -Tsai EC, Dalton PD, Shoichet MS, Tator CH: Matrix inclusion within synthetic hydrogel guidance channels improves specific supraspinal and local axonal regeneration after complete spinal cord transection. Biomaterials 2006, 27: 519-533. -Klapka N, Müller HW: Collagen matrix in spinal cord injury. J Neurotrauma 2006, 23: 422-435. -Yoshii S, Oka M, Shima M, Akagi M, Taniguchi A: Bridging a spinal cord defect using collagen filament. Spine 2003, 28: 2346-2351. -Yoshii S, Oka M, Shima M, Taniguchi A, Taki Y, Akagi M: Restoration of function after spinal cord transection using a collagen bridge. J Biomed Mater Res A 2004, 70: 569-575.
Alginate	-an extracellular matrix derived from the brown seaweed -a sponge developed by	-IT PROMOTED AXONAL ELONGATION AND LED TO FUNCTIONAL	- in vitro -on SCI young rats -electrophysiological	-THE AXONS ESTABLISHED ELECTROPHYSIOLOGICALLY FUNCTIONAL	-Kataoka K, Suzuki Y, Kitada M, Ohnishi K, Suzuki K, Tanihara M *et al.*: **Alginate, a bioresorbable material derived from brown seaweed, enhances**

Active substance	Basic physical / chemical characteristic(s)	Main therapeutic action(s)	Study(ies) / Trial(s)	Comment(s)	Main citated reference(s)
	cross-linking of its fibers with covalent bonds -ALGINATE-BASED ANISOTROPIC CAPILLARY HYDROGEL (ACH)	IMPROVEMENTS		PROJECTIONS -COMPARED WITH COLLAGEN, ALGINATE REDUCED GLIAL SCAR FORMATION AT THE CONSTRUCT-TISSUE INTERFACE -STRONG BOOST OF AXONS' LONGITUDINALLY DIRECTED REGENERATIVE INGROWTH INTO THIS IMPLANT	**elongation of amputated axons of spinal cord in infant rats.** *J Biomed Mater Res* 2001, **54:** 373-384. -Suzuki K, Suzuki Y, Ohnishi K, Endo K, Tanihara M, Nishimura Y: **Regeneration of transected spinal cord in young adult rats using freezedried alginate gel.** *Neuroreport* 1999, **10:** 2891-2894. -Kataoka K, Suzuki Y, Kitada M, Hashimoto T, Chou H, Bai H *et al*.: **Alginate enhances elongation of early regenerating axons in spinal cord of young rats.** *Tissue Eng* 2004, **10:** 493-504. -Prang P, Muller R, Eljaouhari A, Heckmann K, Kunz W, Weber T *et al*.: **The promotion of oriented axonal regrowth in the injured spinal cord by alginate-based anisotropic capillary hydrogels.** *Biomaterials* 2006, **27:** 3560-3569.
Poly(α-hydroxy acids)	- synthetic biodegradable polymers - excellent bio-compatibility - possible skipping some of their characteritics, mainly of mechanical and/or degradation rate, kind, by alteration of the composition and distribution of their repeating units - advantages of synthetic scaffolds vs. natural ones: lower batch-to-batch variation, more predictable/reproductible physical properties, higher potential for control of material impurities -A BETTER 3-DIMENSIONAL CONSTRUCT: MACROPOROUS SCAFFOLDS (FOAMS) MADE OF POLY(D,L-LACTIC ACID) (PDLLA) CONTAINING POLY(ETHYLENE OXIDE)-BLOCK-POLY(D,L-LACTIDE) (PELA) COPOLYMER (PDLLA-PELA FOAMS)	**- POLY(D,L-LACTIC-CO-GLYCOLIC ACID) 50:50 (PLA25GA50) PROOVED GOOD MECHANICAL PROPERTIES AND TO PROMOTE AXONAL REGROWTH**	on SCI/transected rats	-THE FOAMS WERE MOLDED INTO SMALL DIAMETER RODS AND 14-20 RODS WERE ASSEMBLED USING ACIDIC FIBROBLAST GROWTH FACTOR (AFGF)-CONTAINING FIBRIN GLUE AND USED TO BRIDGE THE TRANSECTED RAT SPINAL CORD -WHEN ADDED BDNF TO THE SAME FOAM (EMBEDDED IN FIBRIN GLUE CONTAINING AFGF), THE SCAFFOLD APPEARED EASIER HANDLING, FLEXIBLE AND SUPPORTING THE FORMATION OF BLOOD VESSELS AND MIGRATION OF ASTROCYTES, SCHWANN CELLS AND AXONS, BUT WITH NO FUNCTIONAL IMPROVEMENT	-Wu L, Ding J: In vitro degradation of three-dimensional porous poly(D,Llactide-co-glycolide) scaffolds for tissue engineering. Biomaterials 2004, 25: 5821-5830. -Maquet V, Martin D, Scholtes F, Franzen R, Schoenen J, Moonen G *et al*.: **Poly(D,L-lactide) foams modified by poly(ethylene oxide)-block poly(D,Llactide) copolymers and a-FGF: in vitro and in vivo evaluation for spinal cord regeneration.** *Biomaterials* 2001, **22:** 1137-1146. -Blacher S, Maquet V, Schils F, Martin D, Schoenen J, Moonen G *et al*.: **Image analysis of the axonal ingrowth into poly(D,L-lactide) porous scaffolds in relation to the 3-D porous structure.** *Biomaterials* 2003, **24:**1033-1040. -Patist CM, Mulder MB, Gautier SE, Maquet V, Jerome R, Oudega M: **Freezedried poly(D,L-lactic acid) macroporous guidance scaffolds impregnated with brain-derived neurotrophic factor in the transected adult rat thoracic spinal cord.** *Biomaterials* 2004, **25:** 1569-1582.
Synthetic hydrogels	-nonbiodegradable materials -crosslinked networks of hydrophilic co-polymers (able to retain substantial amount of water with respect to the network density) swelling in water and providing three-dimensional substrates, proper for cell attachment and growth and/or suitable for carryng small molecules -low interfacial tension with biological fluids and possibly resembling mechanical properties to the spinal cord structure	-advantage over the biodegradable materials: they do not expose the tissues to the intermediary breakdown products, which may negatively meddle the regenerative process -POSSBILITY TO INFILTRATED BY BLOOD VESSELS, GLIAL CELLS AND REGENERATING DESCENDING SUPRASPINAL AXONS, WITH DIFFERENT DEGREES of locomotor improvements - degrees glial scar formation - adhesion-mediated cell migration needed for tissue (re)construction [PHPMA-RGD(Arg-Gly-Asp) hydrogel/ NeuroGel]	on SCI/transected cats, respectively rats	-POLY[N-2-(HYDROXYPROPYL) METHACRYLAMIDE] (PHPMA) **-HYDROGEL (NEUROGEL™)** -POLY(2-HYDROXYETHYL METHACRYLATE-CO-METHYL-METHACRYLATE) (PHEMA-MMA) **-MARKETED AS** NEUROGEL™	-Woerly S: Restorative surgery of the central nervous system by means of tissue engineering using NeuroGel implants. Neurosurg Rev 2000, 23: 59-77. -Tsai EC, Dalton PD, Shoichet MS, Tator CH: Synthetic hydrogel guidance channels facilitate regeneration of adult rat brainstem motor axons after complete spinal cord transection. J Neurotrauma 2004, 21: 789-804. -Bakshi A, Fisher O, Dagci T, Himes BT, Fischer I, Lowman A: Mechanically engineered hydrogel scaffolds for axonal growth and angiogenesis after transplantation in spinal cord injury. J Neurosurg Spine 2004, 1: 322-329. -Dalton PD, Flynn L, Shoichet MS: Manufacture of poly(2-hydroxyethyl methacrylate-co-methyl methacrylate) hydrogel tubes for use as nerve guidance channels. Biomaterials 2002, 23: 3843-3851. -Woerly S, Doan VD, Sosa N, de Vellis J, Espinosa A: Reconstruction of the transected cat spinal cord following NeuroGel implantation: axonal tracing, immunohistochemical and ultrastructural studies. Int J Dev Neurosci 2001, 19: 63-83. - Woerly S, Doan VD, Sosa N, de Vellis J, Espinosa-Jeffrey A: Prevention of gliotic scar formation by NeuroGel allows partial endogenous repair of transected cat spinal cord. J Neurosci Res 2004, 75: 262-272. - Woerly S, Pinet E, de Robertis L, Van Diep D, Bousmina M: Spinal cord repair with PHPMA hydrogel containing RGD peptides (NeuroGel). Biomaterials 2001, 22: 1095-1111.
Polyethylene glycol (PEG)	-water-soluble surfactant polymer	-in SCI, in situ seals/repairs cell membrane breaches, (re)establishing the anatomical continuity and thus cord function - reduces cystic cavitation and the extent of the injury -reverses the pathological membrane consecutive permeabilization -global antioxidant effects -non-toxic: intravenous administration of the	-on SCI/ severed guinea pigs -on complete paraplegic dogs	-aqueous solution -prolonged application can induce conduction block - marketed (still) as antifreeze fluid for cars; not (yet?) clinical use	-Shi R, Borgens RB: Anatomical repair of nerve membranes in crushed mammalian spinal cord with polyethylene glycol. J Neurocytol 2000, 29:633-643. -Shi R, Borgens RB: Acute repair of crushed guinea pig spinal cord by polyethylene glycol. J Neurophysiol 1999, 81: 2406-2414. -Luo J, Borgens R, Shi R: Polyethylene glycol immediately repairs neuronal membranes and inhibits free radical production after acute spinal cord injury. J Neurochem 2002, 83: 471-480. - Luo J, Shi R: Diffusive oxidative stress following acute spinal cord injury in guinea pigs and its inhibition by polyethylene glycol. Neurosci Lett 2004, 359: 167-170. -Luo J, Borgens R, Shi R: Polyethylene glycol improves function and reduces oxidative stress in synaptosomal preparations following spinal cord injury. J Neurotrauma 2004, 21: 994-1007. -Shi R, Borgens RB, Blight AR: Functional reconnection

Active substance	Basic physical / chemical characteristic(s)	Main therapeutic action(s)	Study(ies) / Trial(s)	Comment(s)	Main citated reference(s)
		polimer is safe and with extremely rapid beneficial effects			of severed mammalian spinal cord axons with polyethylene glycol. J Neurotrauma 1999, 16: 727-738. -Duerstock BS, Borgens RB: Three-dimensional morphometry of spinal cord injury following polyethylene glycol treatment. J Exp Biol 2002, 205: 13-24. -Borgens RB, Shi R: Immediate recovery from spinal cord injury through molecular repair of nerve membranes with polyethylene glycol. FASEB J 2000, 14: 27-35. -Borgens RB, Shi R, Bohnert D: Behavioral recovery from spinal cord injury following delayed application of polyethylene glycol. J Exp Biol 2002, 205: 1-12. -Cole A, Shi R: Prolonged focal application of polyethylene glycol induces conduction block in guinea pig spinal cord white matter. Toxicol In Vitro 2005, 19: 215-220. - Laverty PH, Leskovar A, Breur GJ. A preliminary study of intravenous surfactants in paraplegic dogs: polymer therapy in canine clinical SCI. J Neurotrauma 2004; 21: 1767-77.
Fibrin	-derived from blood -major component of clots	-bridging and localazing molecule (many cells directly bind to the fibrin via their surface receptors, to the site of injury) for many types of cell-cell interactions -fibrin gel, engineered to release neurotrophin-3 after degradation by the invading cells, provided vigorous cellular infiltration of the fibrin and diminished formation of the glial scar.		-in the treatment of SCI, usually enriched with acidic fibroblast growth factor (aFGF) and is used in conjunction with other modalities	-Laurens N, Koolwijk P, de Maat MP: Fibrin structure and wound healing. J Thromb Haemost 2006, 4: 932-939. -Taylor SJ, McDonald JW, III, Sakiyama-Elbert SE: Controlled release of neurotrophin-3 from fibrin gels for spinal cord injury. J Control Release, 2004, 98: 281-294.
Matrigel	-an extracellular matrix extracted from the Engelbreth Holm Swarm (EHS) sarcoma and contains laminin, fibronectin, and proteoglycans, with laminin predominating	-stimulates cell proliferation and preserves the typical morphological features of olfactory Olfactory Ensheathing Glial (OEG), Schwann and bone marrow stromal in culture; - A REGULAR SCAFFOLD FOR CONSTRUCTION OF SCHWANN CELLS MADE BRIDGES AND ALSO FOR DELIVERY OF HUMAN ADULT OLFACTORY neuroepithelial-derived progenitors	-in vitro -on SCI rats	-implantation of Matrigel alone does not increase regenerative activities in the spinal cord - matrigel combined with vascular endothelial growth factor (VEGF) decreases degeneration of corticospinal tract and respectively increases axonal regenerative activities	-Novikova LN, Mosahebi A, Wiberg M, Terenghi G, Kellerth JO, Novikov LN: Alginate hydrogel and matrigel as potential cell carriers for neurotransplantation. J Biomed Mater Res A 2006, 77: 242-252. -Freshney RI: Culture of Animal Cells: a Manual of Basic Technique, 4th edn. New York: Wiley-Liss; 2000. -Xiao M, Klueber KM, Lu C, Guo Z, Marshall CT, Wang H et al.: Human adult olfactory neural progenitors rescue axotomized rodent rubrospinal neurons and promote functional recovery. Exp Neurol 2005, 194: 12-30.
Fibronectin (Fn)	-glycoprotein found in many extracellular matrices and in plasma - PLASMA FIBRONECTIN FIBROUS AGGREGATES CAN BE USED TO MAKE fibronectin (in a single direction oriented pores) mats	-involved in cell attachment and migration due to its interaction with cell surfaces -combination of fibronectin with alginate hydrogel supports OEG cells proliferation	-in vitro -on SCI rats	-cell proliferation rate: significantly lower than what was observed on Matrigel -FAILURE OF AXONS OUTGROWTH FROM THE MAT TO THE SURROUNDING TISSUE: attributed to the astrocytosis and glial scar formation around the implant	-Novikova LN, Mosahebi A, Wiberg M, Terenghi G, Kellerth JO, Novikov LN: Alginate hydrogel and matrigel as potential cell carriers for neurotransplantation. J Biomed Mater Res A 2006, 77: 242-252. -King VR, Henseler M, Brown RA, Priestley JV: Mats made from fibronectin support oriented growth of axons in the damaged spinal cord of the adult rat. *Exp Neurol* 2003, 182: 383-398. - King VR, Phillips JB, Hunt-Grubbe H, Brown R, Priestley JV: Characterization of non-neuronal elements within fibronectin mats implanted into the damaged adult rat spinal cord. Biomaterials 2006, 27:485-496.
Agarose	-polysaccharide derived from seaweed -a freeze-dried agarose scaffold with uniaxial linear pores extending through its full length was manufactured: it is biocompatible and able to function as a depot for growth factors -such scaffolds retain their microstructure without the use of chemical cross-linkers	-retain their guidance capabilities within the spinal cord for at least 1 month -in association with BDNF, it was observed within implant: ORGANIZED AND LINEAR axonal growth into the agarose, which did not evoke fibrous tissue encapsulation in host tissue.	-in vitro -on SCI rats	- THE IMPLANT WAS ALSO PENETRATED WITH SCHWANN CELLS, blood vessels and macrophages	-Stokols S, Tuszynski MH: The fabrication and characterization of linearly oriented nerve guidance scaffolds for spinal cord injury. Biomaterials 2004, 25: 5839-5846. - Stokols S, Tuszynski MH: Freeze-dried agarose scaffolds with uniaxial channels stimulate and guide linear axonal growth following spinal cord injury. Biomaterials 2006, 27: 443-451.

Table 2. Cell-scaffold constructs/ "cell-seeded bioscaffolds" (adapted after Samadikuchaksaraei).

Active substance(s) / construct	Basic physical / chemical characteristic(s)	Main therapeutic action(s)	Study(ies)/ Trial(s)	Comment(s)	Main citated reference(s)
Matrigel constructs	-purified Schwann cells mixed with Matrigel and inserted in semipermeable non-degradable 60/40 polyacrylonitrile/polyvinylchloride (PAN/PVC) copolymer guidance channels **-combined by infusion of BDNF or NT-3 to the distal cord stump** -a combination of SC/Matrigel cable inside PAN/PVC channels with implantation of OEGs in the distal and proximal cord stumps and infusion of chondroitinase ABC to the SC bridge/host spinal cord interface	- used as both, a bridge for filling a transection hole and a scaffold for in vivo delivery of Schwann cells (including derived from human bone marrow stromal cells in an ultra-filtration membrane - Millipore – tube) **- penetration of the implanted bridge by myelinated axons, blood vessels, macrophages and fibroblasts** **- axonal growth from the implant into the distal host spinal cord stump was effectively promoted for several cord segments**	**- on SCI transected rats** **- electro-physiological (evoked cord potentials)** -histological	**- functionality of regenerating axons but for only a few of them (uncombined with BDNFor NT-3)** **-addition of BDNF** to the SC/Matrigel cable inside the PAN/PVC guidance channels and GDNF added, reduced, increased growth of regenerating axons into the construct and also reduced the reactive gliosis and cystic cavitation at the graft-host interface, with significant improvement in hind limb function -the same with OEGs and chondroitinase infusion and respectively, with Schwann cells derived from human bone marrow stromal cells in an ultra-filtration membrane - Millipore - tube	**-Pinzon A, Calancie B, Oudega M, Noga BR: Conduction of impulses by axons regenerated in a Schwann cell graft in the transected adult rat thoracic spinal cord. J Neurosci Res 2001, 64: 533-541.** **-**Bamber NI, Li H, Lu X, Oudega M, Aebischer P, Xu XM: **Neurotrophins BDNF and NT-3 promote axonal re-entry into the distal host spinal cord through Schwann cell-seeded mini-channels.** *Eur J Neurosci* 2001, **13:** 257-268. -Iannotti C, Li H, Yan P, Lu X, Wirthlin L, Xu XM: **Glial cell line-derived neurotrophic factor-enriched bridging transplants promote propriospinal axonal regeneration and enhance myelination after spinal cord injury.** *Exp Neurol* 2003, **183:** 379-393. - Fouad K, Schnell L, Bunge MB, Schwab ME, Liebscher T, Pearse DD: **Combining Schwann cell bridges and olfactory-ensheathing glia grafts with chondroitinase promotes locomotor recovery after complete transection of the spinal cord.** *J Neurosci* 2005, **25:** 1169-1178. -Kamada T, Koda M, Dezawa M, Yoshinaga K, Hashimoto M, Koshizuka S *et al*.: **Transplantation of bone marrow stromal cell-derived Schwann cells promotes axonal regeneration and functional recovery after complete transection of adult rat spinal cord.** *J Neuropathol Exp Neurol* 2005, **64:** 37-45.
Collagen construct	-Cortical neonatal rat astrocytes were embedded in collagen type I gel and transplanted	**- allows precise application of the cells to the injured site** - prevents migration of astrocytes into the host tissue	**- on SCI hemisected rats**	**-ease of manipulation of collagen into various shapes, but:** **-**modest and temporary locomotor recovery	-Joosten EA, Veldhuis WB, Hamers FP: **Collagen containing neonatal astrocytes stimulates regrowth of injured fibers and promotes modest locomotor recovery after spinal cord injury.** *J Neurosci Res* 2004, **77:** 127-142.
Alginate constructs	- adult neural progenitor cells harvested from rats cervical spine can be mounted on an alginate-based anisotropic capillary hydrogel **(ACH)** - neurospheres prepared from fetal rat hippocampus injected into the alginate sponge, and implanted **- microencapsulation of fibroblasts producing brain-derived neurotrophic factor (BDNF) in alginate-poly-L-ornithine** **-**neonatal Schwann cells seeded on alginate and fibronectin-coated poly-β-hydroxybutyrate (PHB) fibers	**-construct supporting axonal regeneration** - aginate increased the survival of neurospheres after transplantation and supported **their migration, differentiation and integration to the host spinal cord** **- promoted growth of regenerating axons into the cellular matrix that developed between the capsules, leading to improvement of the function of the affected limbs**	**-on SCI injured rats**	**-microcapsules protect fibroblasts from the host immune response and eliminate the need for immunosuppressive therapy** **-PHB** supported ingrowth of regenerating axons, along the entire length of the graft	-Prang P, Muller R, Eljaouhari A, Heckmann K, Kunz W, Weber T et al.: The promotion of oriented axonal regrowth in the injured spinal cord by alginate-based anisotropic capillary hydrogels. Biomaterials 2006, 27: 3560-3569. -Wu S, Suzuki Y, Kitada M, Kitaura M, Kataoka K, Takahashi J et al.: Migration, integration, and differentiation of hippocampus-derived neurosphere cells after transplantation into injured rat spinal cord. Neurosci Lett 2001, 312: 173-176. -Tobias CA, Dhoot NO, Wheatley MA, Tessler A, Murray M, Fischer I: Grafting of encapsulated BDNF-producing fibroblasts into the injured spinal cord without immune suppression in adult rats. J Neurotrauma 2001, 18: 287-301. -Tobias CA, Han SS, Shumsky JS, Kim D, Tumolo M, Dhoot NO et al.: Alginate encapsulated BDNF-producing fibroblast grafts permit recovery of function after spinal cord injury in the absence of immune suppression. Neurotrauma 2005, 22: 138-156. -Novikov LN, Novikova LN, Mosahebi A, Wiberg M, Terenghi G, Kellerth JO: **A novel biodegradable implant for neuronal rescue and regeneration after spinal cord injury.** *Biomaterials* 2002, **23:** 3369-3376.
Fibrin constructs	-fibrin is frequently used to enhance the effects of cell-scaffold constructs **- fibrin containing** acidic fibroblast growth factor	**- increased sprouting of corticospinal tracts in rats**	**-on SCI transected rats**	**- basic fibroblast growth factor (bFGF) is not efficient** -SC/fibrin clot has	**-Guest JD, Hesse D, Schnell L, Schwab ME, Bunge MB, Bunge RP: Influence of IN-1 antibody and acidic FGF-fibrin glue on the response of injured corticospinal tract axons to human**

	(aFGF) – and fibrin cloths, as well - applied to both ends of Schwann cells (SC)/Matrigel cables in PAN/PVC guidance channels, including for bridging transection holes			been inserted in PAN/PVC guidance, bridge a transected SCI rats, combined (BDNF) or NT-3, a combined treatment led to significant improvement of hind limb function	**Schwann cell grafts. J Neurosci Res 1997, 50: 888-905.** -Meijs MF, Timmers L, Pearse DD, Tresco PA, Bates ML, Joosten EA et al.: Basic fibroblast growth factor promotes neuronal survival but not behavioral recovery in the transected and Schwann cell implanted rat thoracic spinal cord. J Neurotrauma 2004, 21: 1415-1430. -Blits B, Oudega M, Boer GJ, Bartlett BM, Verhaagen J: **Adeno-associated viral vector-mediated neurotrophin gene transfer in the injured adult rat spinal cord improves hind-limb function.** *Neuroscience* 2003, **118:** 271-281.
Poly(α-hydroxy acids)-construct	-two-component blend scaffold, of a 50:50 poly(lactic-co-glycolic acid) (PLGA) (75%) and a block copolymer of poly(lactic-co-glycolic acid)-polylysine **(25%)** -scaffold's inner portion emulated the gray matter via a porous polymer layer -scaffold's outer portion emulated the white matter with long, axially oriented pores, for axonal guidance and radial porosity (to allow fluid transport while inhibiting ingrowth of scar tissue)	**-long-term functional improvement accompanied by reduction of epidural and glial scar formation and growing of regenerating corticospinal tract fibers through the construct**	**-on SCI hemisected adult rats**	**- inner layer was seeded with a clonal multipotent neural precursor cell line, derived from neonatal mouse cerebellum**	**-Teng YD, Lavik EB, Qu X, Park KI, Ourednik J, Zurakowski D et al.: Functional recovery following traumatic spinal cord injury mediated by a unique polymer scaffold seeded with neural stem cells. Proc Natl Acad Sci U S A 2002, 99: 3024-3029.**

This explains why PLA implants are, at present, more used in the clinical practice than the PGA ones, although, very recently, there are studies - tightly connected to our subject - that emphasizes the (even more) valuable use of their combination. It is the case of a multiple-channel - a plurality of distinct channels running parallel along the length of the - scaffold, to promote spinal cord axonal regeneration, made of Poly lactic / co-glycolic acid - PLGA - copolymer ratio = 85:15. Such scaffolds, seeded by injection molding with rapid solvent evaporation, degraded in vitro over a period of 30 weeks, with a time-sustained delivery of a surrogate drug, observed for 12 weeks. Primary, Schwann cells were distributed in the channels of the scaffold ; then, Schwann-cell containing scaffolds were implanted into transected adult rat spinal cords, were proved - by 3-D reconstruction of serial histological sections - to contain regenerating axons at one month post-operation [7].

In the last few years, it became technically available to make nanofibre tubes, by electrospunning : through maintaining the needle tip of a syringe, that contains a fluid jet of a 7 wt% solution of poly L-lactide-*co*-glycolide (PLGA, with a copolymer ratio of 10:90), in hexafluoroisopropanol, at a voltage of 12 kV, and respectively, an aluminium collection grid (kept) 10 cm away, at a negative voltage. The nanofibres of copolymer could then be used as nanofibre nerve-guide conduits, able to improve the nerve regeneration by incorporating Schwann cells or nerve growth factors into the copolymer nanofibre tubes. Initially tested into rats' sectioned sciatic nerves, these copolymer nanofibre tubes showed to be flexible enough not to break, also biodegradable and did not cause any inflammation [8].

Within PBR sub-domain, bioresorbable polymer implants are used to maintain the relative position of weak bony tissue, such as bone grafts or bone graft substitutes, as well as bioresorbable thin films for soft tissue applications. Recent examples are represented by some bioresorbable lumbar spine especially manufactured cages, used for spine graft containment (the OS Spine™ System/ implants designed for bone grafts or fragments, as well as a protective barrier for graft harvest sites) and/or different bioresorbable screws and tacks [9].

Prosthetic Disc Nucleus [PDN(R)] - to be used with its patented surgical instrumentation - technology ("Method and Apparatus for Dilation of Spinal Disc Annulus"): it is a device comprised of a hydrogel material - designed to partially or completely replace, the morphology and function of a failed spinal disc nucleus [10]. Furthermore, in 2004, Poly (Vinyl Alcohol) Hydrogel - a prosthetic replacement for the nucleus pulposus, begun to be tested (implants) on primates) [11].

As emphasized before, resorbable biomaterials are overall, better than non-resorbable ones but an important property of the latter type scaffolds (i.e. mechanical compatibility with host tissues) must not be neglected. Hence, a nonbiodegradable hydrogel : poly (2-hydroxyethylmethacrylate - PHEMA), was engineered using thermally initiated free radical solution polymerization. In preclinical study, rats underwent a partial cervical hemisection injury, followed by implantation of either PHEMA or PHEMA soaked in 1 μg of brain-derived neurotrophic factor (BDNF) : the mechanically engineered PHEMA was found to be well accepted by host tissues and might be useful as a platform for sustained drug delivery, to promote axonal growth and

functional recovery after SCI [12]. Recently, there are reported very interesting and promising results - yet in tissue cultures and on animals - related to the use of a special kind of silk fibers as biomaterials that help cells to bind, acting as a scaffold on which nerve cells could grow. The benefit of the silk was that it could be assembled into complex tubes designed to fit the nerves or the length of the gap that needed bridging, in peripheral nerves, but also in post SCI cord repair [13].

Another conceptual and technical important breakthrough, which seems to have valuable consequences towards our subject too, is the possibility of using an ink jet printer to write patterns of biomaterials ; termed *"organ printing"* - one of several approaches to directly write biological systems – such a work is a combination of engineering with developmental biology [14]. The groundbreaking principle is the use of a (micro)-inkjet printer, to print a "biological ink" (resorbable "bio-ink"), composed of cell aggregates, into a 3-D, biodegradable polymer gel. But, to do this, are necessary : very complex (hi-tech) collaborative work, highly qualified and dedicated researchers / specialists, multidisciplinary teams within multicentric, excellence researches and technologies.

Within the past century, there have been achieved some successes in building organs from the ground up, using a desktop printing advanced technology. Still, the major problem of 3-D printing is that the method could not yet produce large tissues (that needs complex blood vessels networks - a key condition for viable and functional coax to the host living tissue), i.e. could not yet form three-dimensional, multi-tissue, organ structures : when seeding a *prebuilt scaffold*, cells will penetrate only a few millimeters beyond its surface and then *crust* around the scaffold, where the cells adhere themselves and afterwards they take a very long time to fill the interior [15].

The (morphological) "epicenter" of SCI is represented by a central hemorrhagic necrosis, surrounded by surviving axons, with a centrifugal distribution. The basic, mechanical for this fact, consists in the 'boundary' layer's viscoelastic properties of the tissue flow within the meningeal tube [16] assimilated to the mechanical events occurring in a compressed toothpaste tube [17]. A hopefully, suggestive and comprehensive related graph, is represented below (Fig. 2):

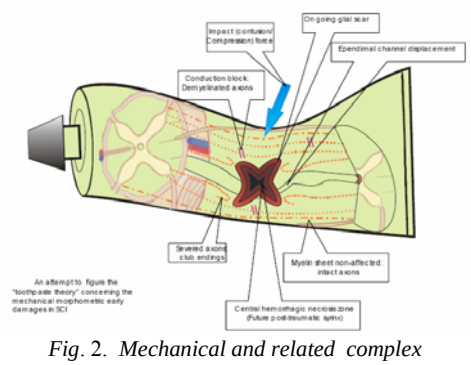

Fig. 2. Mechanical and related complex events/ damages, within SCI.

Additionally, the axiom "a chain is as strong as its weakest link" may explain in what consists the apparently paradoxical vulnerability of the large, myelinated axons, to trauma: the myelinated portions of these axons are stiff and do not stretch well when quickly elongated ; almost all of the stretch and shear evoked forces concentrate on the nodes of Ranvier - the weakest link -, which can easily break down. Severed axons tend to retract, forming club endings ; thus, these mechanical events contribute to the intimate basis' achievement of the mainly irreversible damages, within SCI. Finally and globally, considering also the "secondary lesions'" cascade of events (the secondary injury processes that occur after the initial injury in the CNS), all these result mostly in paralysis or/and other severe, peculiar related spine/ SC-I conditions.

Especially in the last years, it became obvious that CNS/cord post-traumatic scars are a principal and redoubtable - mostly mechanical - barrier against regeneration, preventing the injured nevraxial fibres from growing again : following CNS injuries, by-products of many of the pathways events' cascade reactions (also) stimulate the glial cells (first of all the astrocytes) to emit "signaling" molecules (to) proliferate, in attempt to replace / repair the destroyed neural tissue; this results mainly, in gliosis and collagen, fibrous scars [18].

A seeming, rather simple but very efficient neuroprotective method, for acute SCI, is the so-called "fusion technology", based on polyethylene glycol (PEG). As it will be noticed farther, according to an idea enunciated above, the use of PEG in SCI is one of the therapeutic - still experimental - approaches, difficult to be classified, because it prooved some really important preventive effects against the secondary injury lesions (reactive oxygen species - ROS/ free toxic radicals - scavenging/ anti membranes lipid peroxidation (LPO) protecting, cell/ tissue mechanical sparing and reparing properties) in local and systemic administration, as well: "the behavioral responses to injected and topically applied PEG in various models of neurotrauma are consistently positive" [19].

This technique was initially developed as a therapy for traumatic peripheral nerve injuries. A sticky solution of PEG - a non-toxic (? - o.n.) hydrophylic polymer - applied to the damaged nerve axon for one or two minutes and then washed off, it was observed that basically removes water from the cell membranes, allowing them to fuse together. Within a few seconds-minutes after, nerve endings are rejoined and conduction of electrical signals across the previously damaged area is re-established [20].

In a more recent study, PEG in sterile saline solution, was injected intravenously within 72 hours of the initial spinal cord injury, in complete paraplegic dogs. The functional recovery was impressive and inexpectedly rapid, compared to the control group. The study also proved that the intravenous administration of the polimer is safe, i. e. non-toxic [21].

A very modern, complex and promising approach to be, hopefully, soon introduced in clinical use, is the Regeneration Promoting Treatment (RPT) is a neuro-

protective/therapeutic method preventing the formation of such regeneration inhibiting scars. The first product, of a series to be completely available in the next years, is Cordaneurin and will enter clinical trials in 2007: it is meant to prevent the scar formation in acute CNS damage (up to 3 days post injury), thus enabling the traumatized nerves to extensively regenerate over long distances in their natural nerve tract [22]. To fully exploit the potential of this product, there is, in preclinical phase - for treating (also) chronic SCI patients - a complex therapeutic system (CordaChron : Cordaneurin in combination with Chemokine SDF-1γ - one of the CNS development key modulators, i.e. a special type of immune modulator blocking substance which inhibit the neuron's growth following a damage, with neurosurgery of the collagen scar / "refreshment" of the lesion at the point of injury and respectively, with implantation of bio-absorbable biomaterials channels, to bridge far distance lesions).

As already mentioned, following CNS, including spinal cord injuries, the body can produce glial cells, especially astrocytes, leading, by proliferation and biochemical signals, to scarring and hinder injury repair; another awesome, cutting-edge advanced biomaterials research, lead to the production of a scaffold that can direct post injury cell differentiation, so that neural progenitor (stem) cells become neurons and not astrocytes. The scaffold contains nanofibers made of molecules called peptide amphiphiles. Normally, the molecules repel each other and remain liquid, but positively charged molecules, such as the calcium in living tissue, cause them to clump together such as they can self-assemble into porous tubes about five nanometers wide and several hundred nanometers long [23].

Another but synergistic direction was also studied within biomaterials/SCI therapeutic approaches, in respect to capabilities of delivering neurotrophic factors: Neurotrophin-3 is an already well-known neurotrophic factor, which, expressed in situ (in adult rats), induces axonal plasticity in the injured spinal cord [24]. Thus, recent studies aim to find more appropriate means of delivering NT-3 to the injured site, such as using biomaterials : fibrin gels, allowing slow diffusion of NT-3, mediated by cell degradation of fibrin, proved some good results [25].

In a very recent study on advanced biomaterials [26] a hydrogel-type polymeric hollow fiber membrane transplant - porous poly (2-hydroxyethyl methacrylate-co-methyl methacrylate) tubes - synthesized by a novel centrifugal casting process [27, 28], was implanted immediately following spinal cord transection, inside the lesion. For the ends of the tubes remained attached to the spinal cord, special, standard manufactured tisseel, was applied to the ends of the spinal cord and porous tube, as an adhesive. The minute and respectively, the gross physical properties of the channels - soft and flexible, similar in feel to those of contact lenses - served mainly to reduce the scar tissue post-trauma formation (this appeared to be the more plausible neuro-protective/ therapeutic mechanism) and as a nerve guidance channel. The results of the study emphasized significantly improvements in hindlimb locomotor function and skeletal muscle oxidative potential, after 28 days, in adult rats. There was also apparent connection re-establishment of rostal and caudal ends of the spinal cord [26].

In the end of the examples' presentation, it is to be mentioned a related, advanced medical device, too, especially considering that it is already in (for the moment, still limited) clinical use [29] Thus, the application of an oscillating (in which the polarity was inversed every 15 minutes), low-voltage, direct current of electricity - that generates an electrical field mimicking the polarity guidance into areas above and below a SCI area - stimulates the surrounding neural fibers to grow across the lesion site. The oscillating field is generated by a battery-powered device, atached to the vertebrae.

Such an application/device has been tested on dogs with acute SCI, for a rather long period [30] and recently, the quite same team of researchers, also conducted a preliminary phase 1 clinical trial with the so-called "Oscillating Field Stimulator" device (OFS) in patients with complete SCI, following the opinion and initial approval of the Food and Drug Administration (FDA) of the USA [29].

The device has 2 sets of 3 electrodes each, attached at a distance of 1-2 disk segments above the area of injury and respectively, at a distance of 1-2 disk segments below it. The device was implanted within 18 days of injury and explanted at 15 weeks. Additionally to the control of the surgical wound healing process, the patients were reassessed at 6 months and 1 year. Results: the neurological, clinical - sensation and respectively, motor function testing - and Somato-Sensory Evoked Potentials (SSEP) scores, were better, statisticallysignificant, compared with baseline (according to the statistical methods used). There was only 1 case - successfully treated - of wound infection after the OFS device explantation.

Based on these data, the FDA has given the permission for the enrollment of another 10 patients, the researchers aiming - if the results.obtained will be as compelling as the reported ones - a future randomized controlled trial. The industrial producer of the (already trade marketed) OFS - "Andara™ "- device, has filed an application for Humanitarian Use Device status from the FDA and, if the application would be successful, the device could be marketed commercially, in late 2007 [31].

At present, the aforementioned researchers are investigating too, in animals other novel approaches, that appear synergistic with OFS. The Andara™ OFS™ therapy, will be used in combination with a wide range of growth factors and unlike the indication of the existent OFS device, the new, so-called "Andara™ OFS™ PLUS™ System", has been designed for the complex therapeutic approach of SCI lesions that are months or years old. Actually, a preclinical study using this new device that, as reported, has supplementary - including pharmacological - therapeutic properties, is currently being conducted in naturally injured dogs [31].

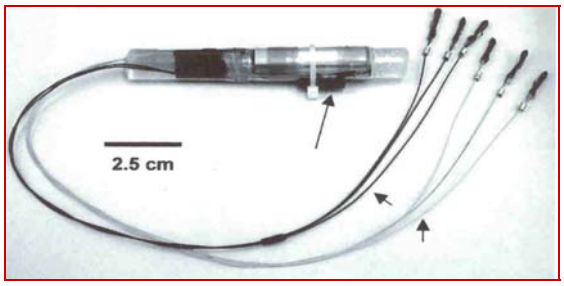

Fig. 3. An OFS device; body has 1 cm in diameter, is outfitted with a magnet - to keep the reed switch open, for deactivating the device's functioning - and also equipped with 6 - three white and three black - electrodes (see arrows).

3. Discussion and conclusions

The afore presented data, strongly support the idea that regeneration of CNS/cord injuries (resulting in attending one of the most difficult but also challenging nowadays issue: healing paralysis with all its many and severe complications, that are social/professional excluding), being so difficult, needs very complex and elaborated strategies. For instance in the past decade there were still hoping that just the stem cells, in addition with growth and neurotrophic factors could heal CNS lesions. At present, it became obvious that this is not enough: being the most elaborated functional structure within Universe, CNS is an up-most example for deepest connection between functioning and morphological infrastructures.

Therefore, the cells and related small molecules supposed to promote CNS regeneration couldn't do this only by themselves, but only if/ when properly seeded within the former, pre-lesion tissue architecture; and here comes the great role biomaterials may have and hopefully, will be able to play: a nano-scale, adequate scaffolding, capable to reproduce and re-integrate the cell graft into the local, initial-normal, CNS/cord structure.

If they will be able to in situ: self-assembling, support, conduct the graft accommodation at cellular/molecular level and eventually, vanish/resorb, this will mean that biomaterials worth the great and growing importance shown to them.

Only in this way it becomes possible to achieve the sine qua non support and guidance for neural / axonal re-growth and re-connection ("bridging" the gap represented by the cord lesion level) or/and for a local, viable repopulation by cell (need to be, ab initio, correctly seeded) transplants. This regards also stem cells (which are not that "smart", to do all by themselves: perfectly sense the biochemical signals from a seriously damaged area, migrate right to that place and differentiate (qualitative and quantitative) strictly only into the tissues necessary to be replaced - as they have been thought to do, until a few years ago) ; hence, a post SCI real functionally repair couldn't, to date, be achieved simply by using / locally introducing stem cells (alones or with different adjuncts, such as growth or /and neurotrophic factors, scar scavengers, inhibiting proteins blockers, ligands, etc.). This emphasizes and supports, conceptually and practically, the irreplaceable role of smart scaffolding, implantable biomaterials, for an effective, real CNS cord injuries healing.

At present, almost all of the studies were done in cell/tissue cultures or/and animals. Reliable trials, in the next about three years, are/will be on going. For the first time, they might show consistent improvements of SCI complex therapeutic approaches' clinical outcomes, including those based on advanced biomaterials.

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