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Polymeric thin film technology for neural interfaces: Review and perspectives

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1. Introduction: Thin polymeric film in nanomedicine

An important and exciting direction of research in nanomedicine would be to gain a fundamental understanding of how living cells respond to nanostructures. At this aim, thin film technology plays a key role in helping to understand the cell-surface interactions.
Generally, thin films are deposited onto bulk materials to achieve properties unattainable or not easily attainable in the substrate alone. In particularly, in biomedicine, polymeric thin films are used such as coating to improve the properties of biocompatibility, thus avoiding typical inflammatory response of immunitary system, especially when the system have to be permanently implanted (Jeong *et al.*, 1986).
Various biodegradable polymeric drug delivery devices have been developed for the sustained release of a variety of drugs, which include micro and nanoparticles, films, foams, wafers, discs, and micro- and nanofibers (Jain, 2000) Among them, films have gained growing interest in various applications. (Dorta *et al*., 2002; Jackson *et al.,* 2002; Perugini *et al.*, 2003; Dhanikula *et al.* 2004; Jackson *et al*. 2004; Grant *et al*., 2005; Alexis *et al.* 2005; Westedt *et al*., 2006; Heller *et al*.1980). For example, films for stent applications have been devoleped to prevent early and late complications such as thrombotic closure and restenosis that have been reported with all current metallic stent devices. (Westedt *et al*. 2006; Drachman *et al*. 2000; Alexis *et al* 2004, Hanefeld *et al*. 2006). The surfaces of most metals are electropositively charged and, therefore, are thrombogenic because blood elements are negatively charged. So the drawbacks of metallic stents have encouraged significant efforts to explore other materials as possible stent matrices. Alexis and colleagues studied the *in vitro* release kinetics of two important antirestenosis drugs: paclitaxel and rapamycin from biodegradable stent matrices. The poly(lactic-co-glycolic acid) (PLGA) and poly-DL-lactic acid (PDLLA) were selected in view of their relatively fast degradation rates (Alexis *et al*., 2006).
Many polymer-based implantable film formulations were developed to provide controlled, local release of drug for the treatment of tumors (Ho *et al,* 2005). Local administration of chemotherapeutic agents has been investigated for the treatment of various cancers, such as brain, prostate, esophageal, head and neck, ovarian, and breast cancer (Jeong *et al.*, 1986; Webber *et al.*, 1998; Zhou *et al*., 1998; McCarron *et al*., 2000). The implantation of a polymer-

based device containing anti-cancer drug can provide a high-dose of chemotherapy to a specific area for a prolonged period of time (McCarron *et al.* 2000). The goal of Grant and collaborators, for example, was to develop a delivery system that would benefit from the properties of chitosan and egg phosphatidylcholine lipids, while providing a sustained release of therapeutically effective levels of a hydrophobic agent, paclitaxel, over several months (Grant *et al*., 2005).

The specific combination of chitosan and egg phosphatidylcholine was found to produce films with a minimal degree of swelling and high stability. The chitosan lipid blend serves as the matrix for the delivery system, and the drug is incorporated into nanoparticles that are dispersed throughout the film. This film with high degree of biocompatibility was found to be a promising system for the localized delivery of the highly lipophilic anticancer agent.

Another typical application of thin polymeric film in biomedicine is to prevent post surgical adhesions. Postsurgical adhesions are abnormal tissue attachments that may result from tissue abrasion during surgical procedures. Shi *et al.* studied biodegradable polymeric film formulations for the controlled delivery of paclitaxel as an effective inhibitor of the formation of postsurgical adhesions (Shi *et al*., 2004). The films were intended to provide both a barrier effect to separate traumatized tissues and also to release paclitaxel to inhibit adhesion processes.

2. Neural interfaces and drug delivery system

From the rapid growth in biotechnology, neural engineering has emerged as a new field. The merging of neurophysiology and engineering has resulted in approaches to link brain activity with man-made devices to replace lost sensory and motor function (McGee *et al*., 2009). The excitement in this field is based not only on the prospect of helping a wide range of patients with neural disorders, but also on the certainty that this new technology will make possible to gain scientific insight into the way populations of neurons interact the complex, distributed systems that generate behaviour.

After analytical demonstration of nerve excitation and associated action potential generation by Alan Hodgkin and Andrew Huxley in 1952, the possibility of using electrical phenomenon to cure diseases and to understand the principles of electrical nerve signals have been investigated through implementation of neural interfaces.

Neural prosthetics are devices that link machines to the nervous system with the purpose of restoring lost functions. Two broad approaches are used in this field: neurons are stimulated or inhibited by applied current, or their activity is recorded to intercept motor intention. Stimulation can be used for its therapeutic efficacy, as in deep brain stimulation, to ameliorate the symptoms of Parkinson's disease or to communicate input to the nervous system (for example by transforming sound to neural input with cochlear prosthetics). In contrast, recordings are used to decode ongoing activity for use as a command or input signal to an external device (Schwartz *et al.*, 2006).

A great number of neuro-prostheses use interfaces with peripheral nerves or muscles for neuromuscular stimulation and signal recording. Only in this way, these new artificial devices can be easily incorporated into the natural control strategies of the subjects and can be felt as parts of their own body thanks to the sensory feedback which can be delivered from the sensors embedded in the robotic artefact to the nervous system.

According to Navarro *et al.* 2005, a neural interface can be defined, from an engineering point of view, as a bidirectional transducer that establishes a contact between an artificial device and a neural structure within the body. On the other hand from a biological point of view, an interface is just a "foreign body". These two aspects (the engineering and the biological) must be both taken in high consideration and an optimized invasive neural interface is a compromise between the two requirements.
The biocompatibility is the first and most important requirement for a neural interface. In general, the compatibility between a technical and a biological system can be divided into the structural biocompatibility and the surface biocompatibility (Bronzino *et al.* 1985).

- The structural biocompatibility depends on the mechanical properties of the surrounding tissue and on the adaptation capability of the artificial material structure to the tissue. Device design and material properties should mimicry the biological structure of the target tissue.
- The surface biocompatibility deals with the interaction of the chemical, physical, biological and morphological surface properties of the foreign material and the target tissue with the desired interaction.

Several interfaces have been developed during the past years by many groups, applied both to the central nervous system (CNS, Schwartz 2004) and to the peripheral nervous system (PNS, Navarro *et al.*, 2005).
Notwithstanding the efforts carried out by several groups, the solutions developed so far suffer from several limitations which make very difficult the development of effective bionic systems. For example, cuff – and epineural - electrodes (Tarler *et al.*, 2004) are reliable and robust, imply a reduced invasiveness, can be used to extract interesting information but suffer from a limited selectivity which is a significant drawback especially to deliver a sensory feedback. Intraneural PNS interfaces characterized by needles to be inserted longitudinally (LIFE electrodes, Lawrence *et al*., 2004) or transversally (USEA electrodes, McDonnall *et al*.,2004) into the PNS are very interesting combining a reduced (even if not absent) invasiveness with a good selectivity but their "bandwidth" (*i.e.*, the amount of information which can be exchanged between the natural and artificial systems) is still limited.
Moreover, the use of these devices, and in particular microfabricated neural prostheses, is limited due to an inflammatory tissue reaction following implantation, which quickly degrades the stimulation and recording features of the device (Polikov *et al.*, 2005).
To avoid this phenomenon, several groups addressed their study to novel neuronal interfaces able of promoting neural regeneration. Anyway, the reactive tissue response of the brain to chronically implanted materials remains a formidable obstacle to stable recording from implanted microelectrodes.
Over the course of days and weeks following implantation, a sheath of activated glia forms around the electrode, isolating the implanted device from the neuronal tissue (Szarowski *et al.*, 2003). Studies have reported a "kill zone" around implanted devices where neuronal cell bodies and fibers become severely reduced in density up to 200 μm around the implantation site (Biran *et al*., 2005). The reactive tissue response includes both an acute phase, caused by implantation injury, and a chronic response of the tissue to the implanted material itself (Polikov *et al*., 2005). The tissue response results in a decline in availability of viable neurons

for recording, and a reduction in signal to noise ratio over time, which reduces or eliminates the ability to effectively collect recordings (Vetter *et al*., 2004).
Two strategies are possible for improving the tissue response to invasive neural interfaces: to increase the structure biocompatibility and/or the surface biocompatibility.
The first aspect can be achieved by the introduction of flexible interfaces. The inflammation at the implantation sites is thought to be aggravated by the mechanical mismatch between the stiff interface and the soft biological tissue. Their different mechanical properties induce relative drifts between the interface and the tissue encouraging the formation of a glial scar, which can encapsulate or break the probe with time (Cheung *et al.* 2006). Among the other materials, the polyimide has been having a great success for the development of neural interfaces as substrate for metal active sites and tracks. Because of its high flexibility (Young's modulus between 4 and 10 GPa). If compared with silicon and silicon insulation (SiO2, Si3N4), it got a similar insulation resistance and dielectric strength at a lower. Polyimide is proved as a non-toxic material in biomedicine (Richardson et al. 1993) In addition, polyimide-based neural interfaces can be processed by thin film technologies which ensure high precision and repeatability, allows a variety of designs suitable for implantation in different nerves and anatomical regions, and a higher number of active sites can be positioned within a small surface (Stieglitz *et al.* 2005). As an example, polyimide-based regenerative electrodes with a thin film structure have been allowed for much better regeneration than silicon dice (Lago et al. 2005) while the tf-LIFE (thin film LIFE base on polyimide) demonstrated a good compromise between invasiveness and selectivity (Lago *et al*. 2007).
From the other hand, alternative strategies are focusing also on the enhancement of surface biocompatibility. Local drug delivery to the region surrounding the implant as a means to avoid tissue response phenomena is actively pursued by several groups. The basic idea is to release bioactive components from a polymer coating on the electrode to the damaged neurons in order to induce adhesion and regeneration.
Cue *et al.* used electrochemical polymerization to optimize the surface of the metal electrode sites. Poly(3,4-ethylenedioxythiophene) (PEDOT)/poly(styrene sulfonate) (PSS) was electrochemically deposited on the microelectrodes of neural probes (Cue *et al*., 2003). The PEDOT/PSS coating decreases the impedance modulus and, moreover, in comparison to a previous study on polypyrrole, PEDOT demonstrated much better electrochemical stability (Cui *et al*, 2001). A bioactive peptide was incorporated in the PEDOT film during the electrochemical polymerization to be released during the *in vitro* tests. The coated probes were cultured with rat glial cells that grew on the coating area of the probes and high quality acute neural recordings were obtained through the coated electrodes.
One of the limits of the use of polymer surface coating is the increasing of dimensions of the device, potentially adding a layer to the surface that could range from tens to hundreds of micrometers in thickness. The high surface area-to-volume ratio of the coatings may reduce the ability for sustained delivery over long periods of time, which could minimize its potential for limiting the chronic neuroinflammatory response.
To overcome these disadvantages, Williams *et al.,* presented a method for targeted microscale drug delivery, based on micromachined "wells" fabricated into the substrate of a MEMS (micro-electro-mechanical systems)- based chronic implant (Williams *et al*., 2005). These wells are holes that extend through the device thickness and allow for the integration of matrices (*i.e*., hydrogels) infused with bioactive substances.

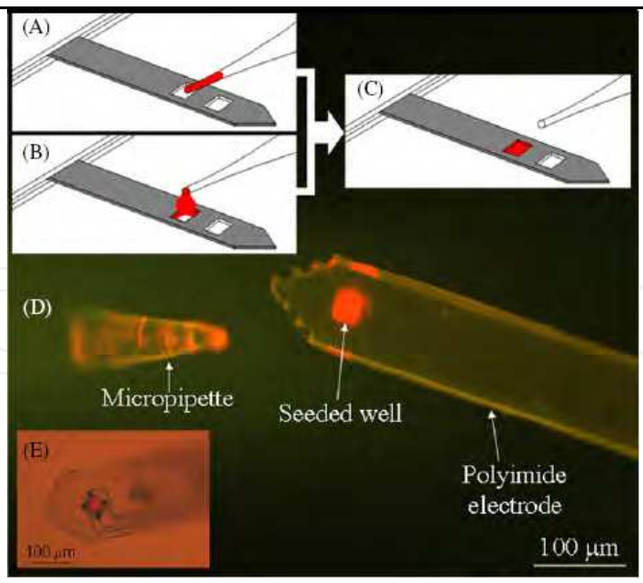

Fig. 1. Illustration of electrode well seeding technique. Schematics of the device and pipette depicting the injection and the droplet deposition methods prior to gel loading are given in (A) and (B), respectively, (C) schematic of a device with a filled well, (D) fluorescent image of probe immediately after the gel loading and subsequent withdrawal of pipette tip. The edges of the probe appear red due to internal reflection of the fluorescent DiI emanating from the well through the polyimide substrate. The volume of gel contained within the well is approximately 9 pL based on the well dimensions and (E) shows a polyimide based electrode with a seeded well in the middle of a tetrode arrangement of recording sites.

Since the matrices replace the substrate instead of adding to it, the device footprint is not increased. The lower surface area-to-volume ratio lends the technique to extended time release periods. Another benefit arises from the possibility of inducing cellular growth through the holes, which, if achievable, may serve to physically anchor the implant into the surrounding tissue. Particularly for electrically-based probes, any reduction of device movement post-implantation would aid in the localization of electrical signals and their subsequent assignment to individual cells.

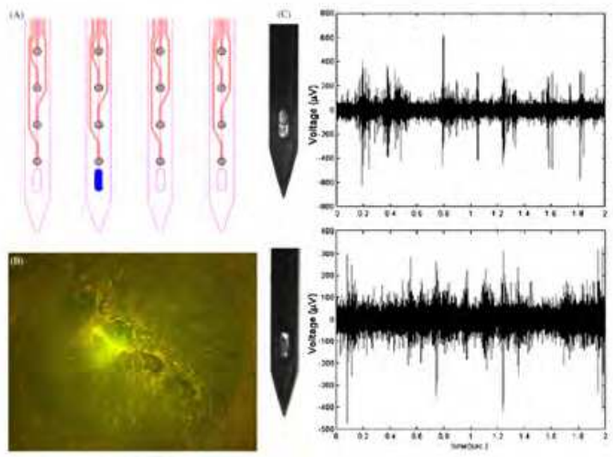

Fig. 2. Wells seeded with NGF. The upper left schematic (A) illustrates the layout of an implanted microelectrode array, showing the relative position of the NGF-seeded well in relation to a recording site. In this four-shank implant, only one of the shanks has an NGF-seeded well. The implanted animal was sacrificed after 40 days, sectioned at the level of the NGF-seeded well, and immunohistochemically stained with antibodies against GFAP and the extracellular matrix protein, laminin. (B) is a histological image from this implant. The site that contained the NGF-seeded well (second from the left in this image) showed increased levels of matrix deposition versus the unseeded electrode shank sites. (C) shows the electrophysiological recordings taken from two individual electrode sites closest to two different seeded wells, each at 40-days post-implantation.

Qualitative observations depicted in Fig. 2B show a notable tissue response in the form of laminin deposition, seen as a green "cloud" over and adjacent to the site of NGF release from the gel. Additionally, an increased level of GFAP expression (yellow stained cells) can be seen around the implant sites. These results are typical for the sites of NGF seeding, but noticeably different from the well sites without NGF, which all showed a relatively normal response. A two-second sample of the extracellular recordings taken from two different recording sites, each located 15 µm from two different seeded wells is given in Fig. 2 C. These recordings demonstrate that the sites near the NGF-seeded wells remain electrically viable following implantation. The recordings are typical for the sites adjacent to the NGF-seeded wells, although not statistically different from the other sites in the array. In all animals implanted with functioning electrodes (n = 4, 48 hours and 40 days), neural signals were recorded from the sites adjacent to the wells that had been seeded with bioactive molecules. Qualitatively, the electrodes were able to record unit activity with acceptable signal amplitude.

Winter *et al.*, have investigated the use of biodegradable, neurotrophin-eluting hydrogels *(i.e.*, poly(ethylene glycol)-poly(lactic acid), PEGPLA) as a means of attracting neurites to the surface of stimulating electrodes. PEGPLA hydrogels with release rates ranging from 1.5 to 3 weeks were synthesized (Winter *et al,* 2007). PEGPLA was selected because of the unique properties of the individual components. PEG has been shown to improve immune response to implanted elements and has been used to increase the circulation time of drugs. Thus PEG as a hydrogel component may reduce immune reaction to the implanted prosthesis and increase the circulation time of released neurotrophins associated with degrading PEG

molecules. The PLA portion of the polymer provides biodegradability, allowing for eventual elimination of the polymer from the array. Additionally, the degradation rate can be used to regulate neurotrophin release through variations of the PEGPLA ratio. These hydrogels were applied to multielectrode arrays with sputtered iridium oxide charge-injection sites. PC12 cell cultures were exposed to NGF-releasing boluses, suspended in trans well inserts for 5/14 days, and compared to a positive control receiving 50 ng/mL of NGF, to a negative control receiving no NGF, and a to sham receiving BSA-releasing boluses.

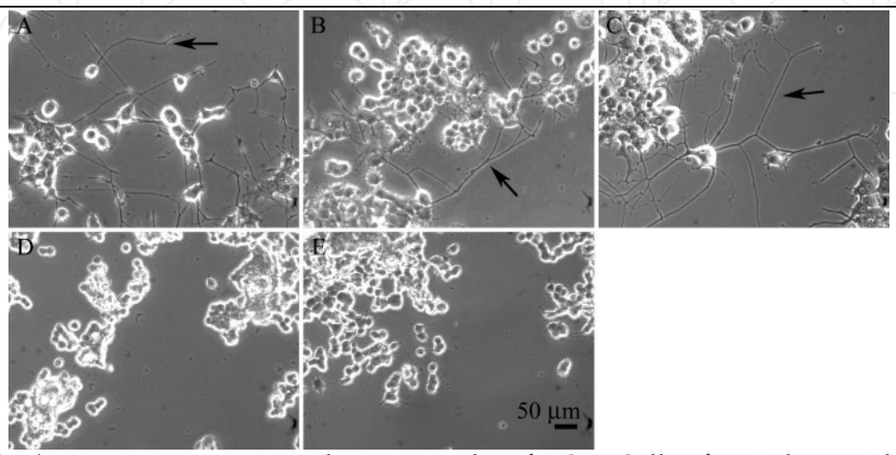

Fig. 3. (A-E) Representative optical micrographs of PC12 Cells after 5 days with boluses in culture. (A) Positive control receiving 50 ng/mL NGF, (B) and (C) substrates display large numbers of neurites (arrows), whereas (D) negative control receiving 0 ng/mL NGF and (E) sham, BSA-releasing bolus display only few, short neurites.

The results of this work show that PEGPLA polymers can produce controlled, sustained release of neurotrophins, and that these neurotrophins produce neurite extension in a neuronal cell culture model.

It was also verified that these hydrogels can be applied to electrically stimulating neural prostheses, and do not impede the function of these devices. Thus, neurotrophin-eluting hydrogels provide one possible means to attract neurites to an electrical prosthesis surface, potentially lowering electrical stimulation thresholds. If lower thresholds can be achieved, larger numbers of electrodes could be driven with the same power requirements, increasing pixel density. These high density devices will lead to greatly improved fidelity in electrically evoked sensory and functional responses.

Recently, Pierce *et al* used another approach to mitigate the reactive tissue response of the brain to chronically implanted materials. A bioactive coating in the form of an ultra-porous silica sol–gel was applied on the surface of silicon-based microelectrodes (Pierce *et al*., 2009). The sol–gel technique allows for application of thin films of ultraporous silica, the morphology of which is characterized as a flat surface with pore size and surface features <25nm (Jedlicka *et al*., 2005). The films have a thickness of approximately 100 nm. These ultra-porous sol–gel thin films have been shown to be excellent substrates for neuronal growth (Jedlicka *et al*., 2006, 2007a).

In Pierce's study the attention was centred on two features of the microelectrode: the adherence of the coating and the resultant changes in electrical properties. Sol–gel presence

and uniformity on the probes were assessed by the preparation of a fluorescently labelled coating that was revealed by fluorescence micrographs.

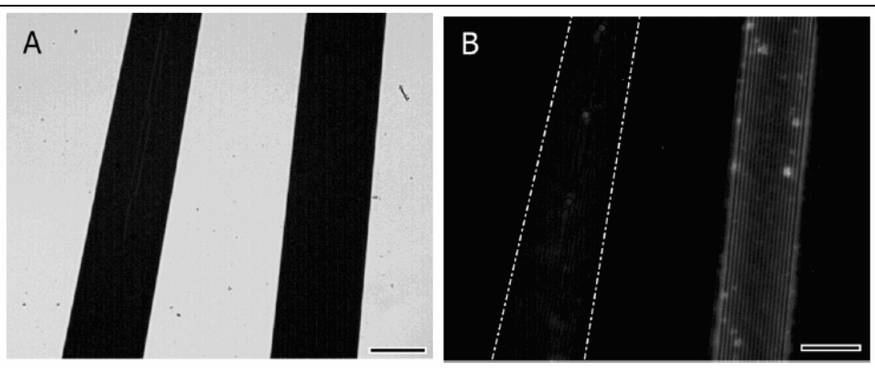

Fig. 4. Microscopy confirms the adherence of sol–gel coatings to microelectrodes. (A) Bright field image of probes shows their location. (B) Fluorescent micrograph of coated probes. For the right probe, fluorescein salt was added to the precursor sol and was encapsulated throughout the coating. The left probe was coated in an unlabeled sol–gel as a control. The fluorescence of the right probe confirms coating adhesion. These images demonstrate that the silica sol–gels can be successfully applied to silicon-based microelectrodes and Winter confirm the ability to encapsulate molecules in the TMOS precursor to enable drug delivery to the implantation site.

To evaluate the stability of the coating an established agarose brain model was used: the coating appeared unaltered after insertion into the model, demonstrating adherence of the coating to the probe that experiences similar mechanical stresses during surgical insertion.
Another important evaluation concerns the electrical properties of the microelectrode. Without favourable electrical properties, a coating designed to mitigate the reactive tissue response would be of little value. The cyclic voltammetry study demonstrated that the dip-coated, ambient-dried thin film silica sol–gel coatings do not adversely affect the electrical characteristics of the implantable electrodes, and it may in fact provide beneficial electrical properties. A major advantage of the sol–gel produced silica is a wide versatility for biofunctionalization. All together, these features will allow the sol–gel silica coatings to be used as a platform material for the mitigation of the chronic phase of the reactive tissue response, without causing significant detriment to the functionality of the probes.
Green *et al* led a study on modified laminin peptides DEDEDYFQRYLI and DCDPGYIGSR used to dope poly(3,4-ethylenedioxythiophene) (PEDOT) electrodeposited on platinum (Pt) electrodes (Green *et al*, 2008).
DCDPGYIGSR was chosen due to positive results reported by Cui *et al*. (Cui *et al*, 2003) DEDEDYFQRYLI, a peptide which has not previously been incorporated into conducting polymers, was also assessed. This peptide contains the active sequence YFQRYLI, identified by Tashiro *et al*. and reported to mediate cell attachment and promote neurite outgrowth in both PC12 cells and cerebellar microexplant cultures (Tashiro *et al*, 1998). The effect of a large biomolecule dopant on conducting polymer physico- chemical properties was established with comparison to conventionally doped PEDOT/paratoluene sulfonate (pTS).

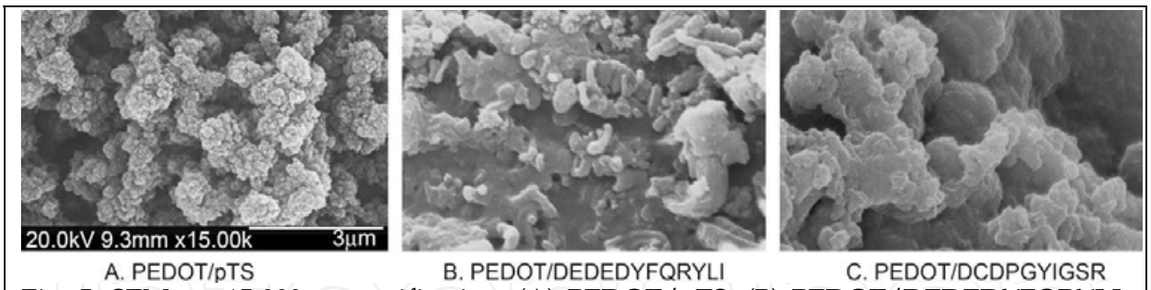

Fig. 5. SEMs at 15,000x magnification: (A) PEDOT/pTS; (B) PEDOT/DEDEDYFQRYLI; (C) PEDOT/DCDPGYIGSR

The resulting film was less homogeneous in microscopic appearance than the control PEDOT/pTS film. Doping PEDOT with laminin peptides, DEDEDYFQRYLI and DCDPGYIGSR, resulted in altered formation of the polymer during electrodeposition.

The use of large synthetic peptides as anionic dopants produced a softer interface with improved impedance characteristics, especially in the low frequency, biologically significant, region. However, reduced polymer electrochemical stability and lower adherence of the films to the Pt electrode was observed when compared to the conventionally doped pTS control. The larger DEDEDYFQRYLI dopant was shown to reduce the efficiency of electropolymerisation and consequently this polymer presented lower mechanical adherence than the DCDPGYIGSR-doped PEDOT.

The effect of peptide doped polymers on mammalian cell interactions and the cell response to peptides containing specific bioactive ligands was assessed using the neural-like PC12 cell line.

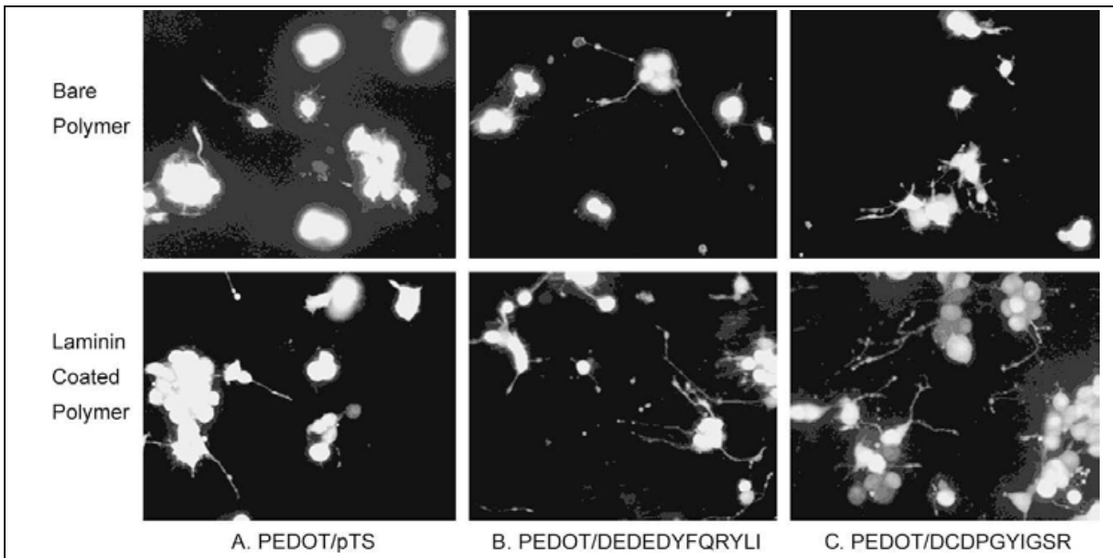

Fig. 6. Sample images of PC12 neurite outgrowth on PEDOT at 96 h post-plating with bare polymer (top) and adsorbed whole laminin coated polymer (bottom): A. PEDOT/pTS; B. PEDOT/DEDEDYFQRYLI; C. PEDOT/DCDPGYIGSR.

Uncoated DEDEDYFQRYLI-doped PEDOT appears to support higher neurite outgrowth per cell than both PEDOT/pTS and PEDOT/DCDPGYIGSR despite having the lowest density of attached cells. PEDOT/ DCDPGYIGSR also presented a greater neurite outgrowth per cell than the PEDOT/pTS control. All polymers showed a significant improvement in cell attachment and growth compared to the conventional Pt electrode.

3. A case study: alginate coated CNT array

Carbon nanotubes (CNTs) are molecular-scale tubes of graphitic carbon with outstanding properties. They are among the stiffest and strongest fibers known, and have remarkable electronic properties and many other unique characteristics. For these reasons they have attracted huge academic and industrial interest, with thousands of papers on nanotubes being published every year (Ciofani *et al.*, 2009).

More recently, nanotubes formed from conductive polymers have been applied to electrode sites, both reducing site impedance and providing a platform for controlled drug release (Abidian *et al.*, 2006; Abidian and Martin, 2008). Although many of these methods are promising, none have emerged as a definitive solution to the problem of reactive tissue response.

The case study presented in this Section is a combination of a polymer technology and carbon nanotubes array for the development of a drug delivery system at cellular level. Starting from these preliminary results, it is possible obtain innovative neural interface that combine the electrical properties of carbon nanotubes with the advantage of a drug delivery system, to avoid the typical response of the immunitary system.

Recently, the use of carbon nanotubes (Tasis *et al,* 2006) attracted significant attention of several groups for the development of novel neuronal interfaces (Nguyen *et al.*, 2007 Nguyen *et al.,* 2006, Gabay *et al.,* 2007). Composite materials containing multi-walled CNTs have shown the ability to limit astrocyte production of glial scarring, while maintaining good neuronal connections (McKenzie *et al.*, 2004).

Nguyen and collaborators found that PC12 cells cultured on PPy-coated CNT arrays (treated with a thin layer of collagen to promote cell adhesion) can form extended neural network upon differentiation. Starting from these considerations, in our laboratory we have proposed a combination of drug delivery system with such CNT array, exploiting a thin film of calcium alginate as drug reservoir embedded into the platform.

Two *in vitro* assays have been performed to validate the protein release on two cell lines: CrFK and PC12 cell, a cell line derived from a transplantable rat pheochromocytoma that respond reversibly to NGF by inducing a neuronal phenotype. In its presence, these cells undergo a dramatic change in phenotype whereby they acquire most of the characteristic properties of sympathetic neurons. The polymeric film embedded in the CNT array is described and characterized in terms of release kinetics using bovine serum albumin as drug model.

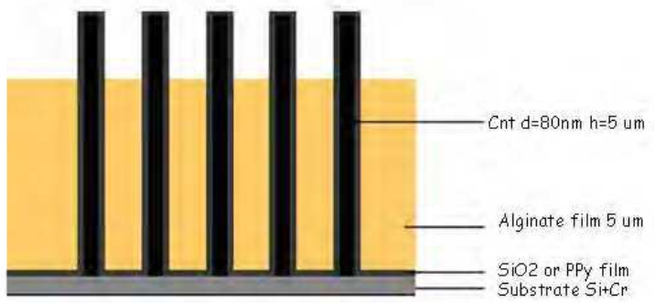

Fig. 7. Schematic illustration of the proposed CNT based system

Figure 7 represents the scheme of the proposed system. The main structure is composed by the CNT array, embedded with a thin film of alginate entrapping the drug.

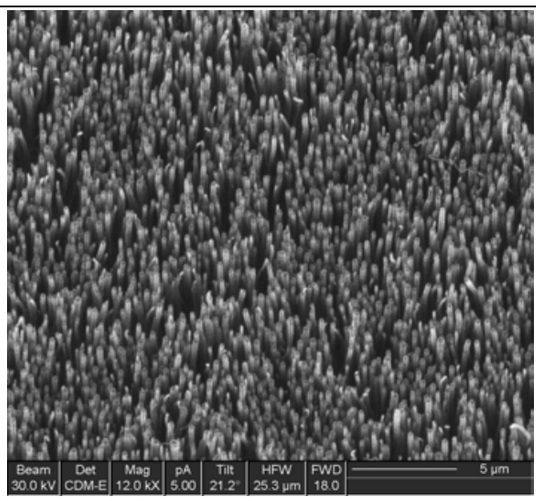

Fig. 8. FIB image of the as-grown CNT array

The as-grown CNT array is not stable when treated in liquid environments: during the drying process, CNTs irreversibly stick together to form microbundles, driven by the capillary force of water droplets (Figure 8). In order to avoid this phenomenon, a double approach was followed: SiO_2 film was deposited *via* sputtering in order to prevent the CNT sticking in a liquid environment, and to improve mechanical features of CNTs. A thin layer of a conductive polymer, polypirrole, was deposited by electrochemical deposition in order to reduce the impedance of the system and to improve the recording.

This phenomenon is completely avoided by performing a SiO_2 coating. The SiO_2 thin film, in fact, improves CNT mechanical features against the capillary force of water droplets during the drying process, thus preserving vertically alignment (Fig. 9b). The thin film of polypirrole partially avoided the problem, but it was not found satisfactory.

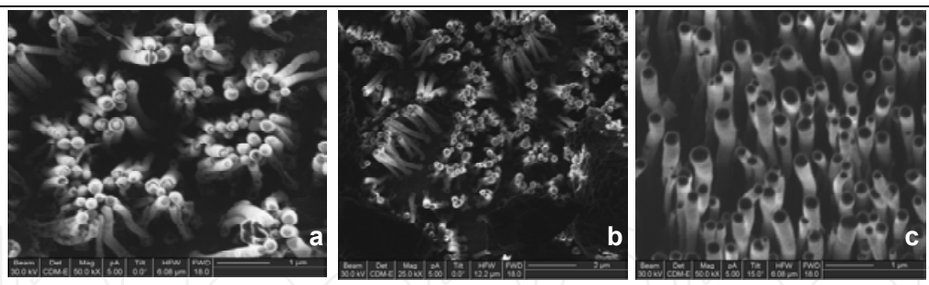

Fig. 9. Bare (a), PPy-coated (b), and SiO_2-coated (c) CNT array (samples dipped in water and dried in air before the imaging)

Among polymers, alginate has several unique properties that have allowed using it as a matrix for the entrapment and/or delivery of a variety of biological agents (Chretien *et al.*, 2005). It is a co-polymer extracted from some types of brown algae, and it is made up of two uronic acids: D-mannuronic acid and L-guluronic acid. Polyvalent cations are responsible for interchain and intrachain reticulations because they are tied to the polymer when two guluronic acid residuals are close (Mikkelsen *et al.*, 1995). The reticulation process consists of the simple substitution of sodium ions with calcium ions (Gombotz *et al.*, 1998). The relatively mild gelation process has enabled not only proteins (Ciofani *et al.*, 2008) but also cells (Murtas *et al.*, 2005) and DNA (Kimberly *et al.*, 2006) to be incorporated into alginate matrices with full retention of the biological activity.

For drug release kinetics investigation, BSA entrapped in the film was used as "protein model", as its molecular weight is similar to that one of NGF and its concentration can be much more easily evaluated concentration in the release bulk *via* spectrophotometry.

Crosslinking was thus performed with a 30% $CaCl_2$ solution, gently stirred and quickly removed (Simpson *et al.*, 2004).

In order to define a thickness of the film polymer comparable to the height of CNTs, different alginate solutions at several concentrations were tested, producing films on Si clean surface. Subsequently, *via* FIB analysis, the film thickness for the different conditions was measured, and finally the alginate concentration corresponding to a film thickness of approximately 5 μm was chosen.

The typical temporal trend of the protein release from the alginate thin film is reported in Figure 10.

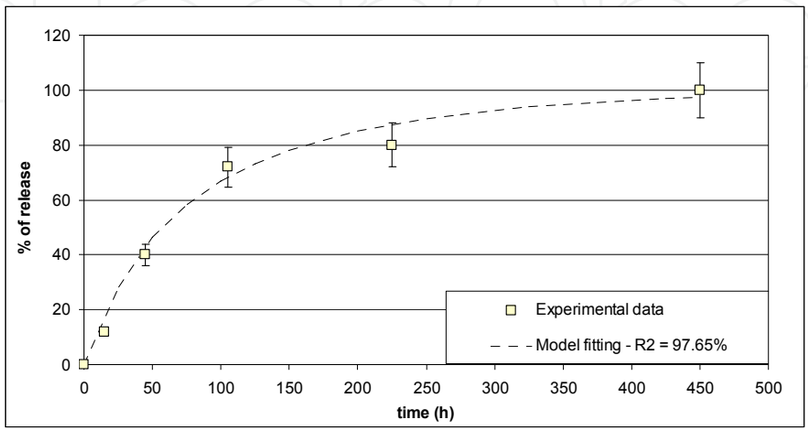

Fig. 10. Alginate release profile: experimental data and model fitting (n =3).

Protein amount is given as percentage of the initial amount entrapped into the film (200 μg per cm^3 of film). The trend is well fitted (R^2 =97,65%) with a bi-exponential curve as already reported for alginate fibers (Ciofani *et al*. 2008a) and microspheres (Ciofani *et al*., 2008b) and described by the following expression:

$$C_2(t) = \frac{C_{10}}{1+\frac{V_2}{V_1}} \cdot (1 - e^{-h \cdot S \cdot (\frac{1}{V_1}+\frac{1}{V_2}) \cdot t}) + \frac{S \cdot C_{s0}}{V_2} \cdot (1 - e^{-2 \cdot k_S \cdot t}) \quad (1)$$

where C_2 is the protein in the bulk, C_{10} is the concentration inside the gel, S and V_1 are, respectively, the surface and the volume of film, V_2 is the volume of the bulk, h is the massive exchange coefficient, C_{s0} is the protein concentration on the surface of the film and finally k_s is the desorption rate constant.

Substituting known values and by fitting the experimental data with the mathematical model of equation (1), the h value results 10^{-9} m/s, in agreement with data given in the literature for alginate microsphere (Laca *et al*., 1999).

In vitro experiments were carried out on two cell lines: in preliminary assays feline nephritic fibroblasts (CrFK) were used just to validate the diffusion of the drug in the bulk and the up-take by the cells. Other salient responses to NGF include cessation of proliferation, generation of long neurites, acquisition of electrical excitability, hypertrophy and a number of changes in composition associated with acquisition of a neuronal phenotype (Greene *et al*., 1998)

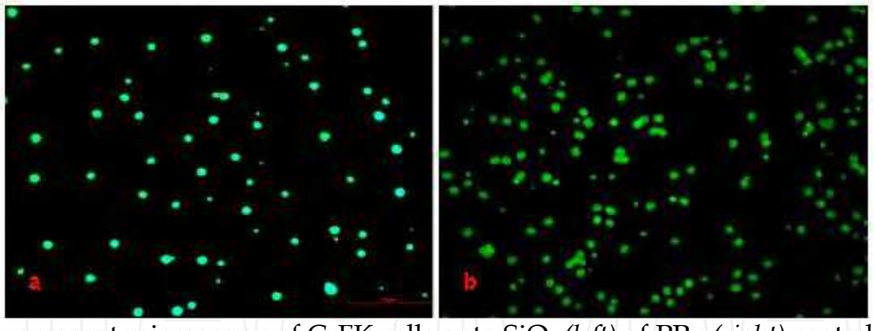

Fig. 11. Fluorescent microscopy of CrFK cells onto SiO_2 *(left)* of PPy *(right)* coated CNT interface entrapping fluoscent BSA coniugate after six hours of incubation

Figure 11 shows fluorescent microscopy images of CrFK cells after six hours of incubation onto CNT array coated with SiO_2 and PPy, respectively. These results demonstrate that the FITC-BSA, embedded in the alginate film, is efficiently released and internalized by the cells.

Alginate film coated on the CNT array and entrapping NGF was finally tested on PC12 cells monitoring their differentiation. An alginate solution entrapping 2 nM of NGF was casted on the CNT array and thereafter crosslinked with a 30% $CaCl_2$ solution as previously reported. PC12 cells were seeded on an *ad hoc* polystyrene substrate, fabricated with high

precision milling machine, at a density of 50,000/cm². The substrate was thereafter placed on the CNT array system and the cells were grown in differentiating medium.
Figure 12 shows clearly differentiated PC12 cells after incubation on the CNT array coated with the releasing film. The microscope analysis was carried out up to three days of incubation, and, specifically, after 8 (Figure 12a), 24 (Figure 12b), 48 (Figure 12c) and finally after 72 hours (Figure 12d). Number of differentiated cells incremented during the time: at the third day of culture, the PC12 cells generate a neural network, that is a clear demonstration that the NGF is released from the film and still maintained its bioactivity.

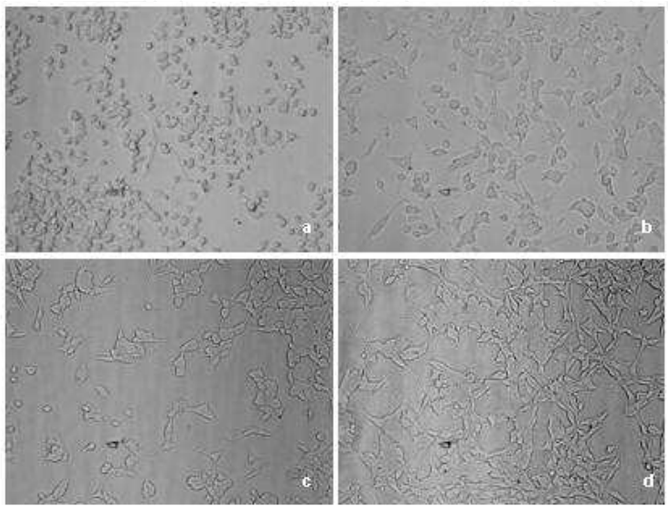

Fig. 12. Differentiating PC12 cells after 8 (a), 24 (b), 48 (c) and 72 h (d)

Fig. 13a and 13b show, respectively, the percentage of differentiated cells and the neurite length at the different time points. Figure 6a shows that already after eight hour, a non negligible number of cells, about the 10%, are differentiated. After 24 h there is a spread of the number of differentiated cells, about the 85% of the total cells. In the second day, the number increased up to 90% and, in the third day, about 96% of the cells presented well developed neurites. Figure 6b reports the trend of neurite length in the time: already after 24 hours, the mean length of the neurite is 30 ±17.9 μm and after 72 hours the length increases up to 28 ±15.9 μm.

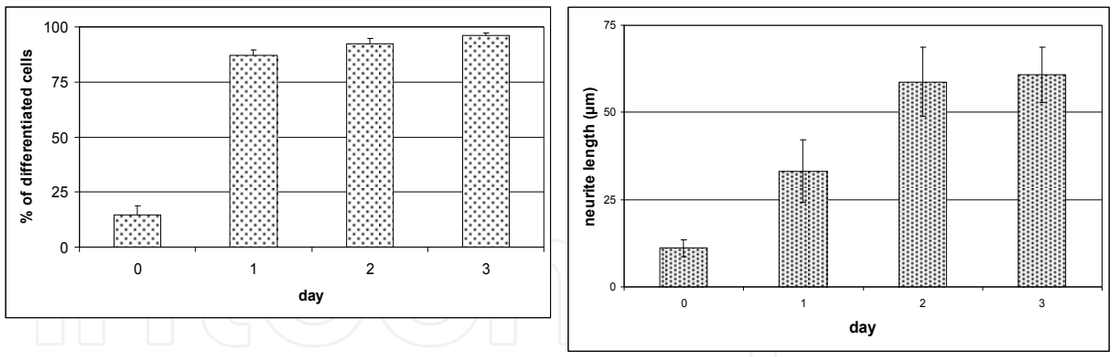

Fig. 13. Percentage of differentiated cells (a) and neurite length (b) *vs*. time (n = 3)

These data do not significantly differ (p > 0.1, Student's t-test) from control tests performed with "free" NGF (80 ng/ml in the culture medium) where, after three days of incubation, almost 95% of cell were differentiated with an average neurite length of about 30 µm.

4. Conclusion

Drug delivery to the central nervous system (CNS) remains a challenge despite advances in understanding the mechanisms involved in the development of neurodegenerative disorders and the actions of neuroactive agents. Drug accessibility to the CNS is limited by the blood-brain barrier; moreover the systemic administration of neuroactive biomolecules to support neuronal regeneration has several intrinsic problems, including the toxicity and poor stability associated with many bioactive factors (Maysinger *et al*., 1997).

A variety of techniques to deliver therapeutics to the CNS has been established, including osmotic pumps (Lewin *et al*., 1997) and silicone reservoirs. However, pumps frequently become clogged, thus limiting their ability to sustain effective concentrations; moreover these methods are often associated to highly invasive drawbacks, including device failure and higher potentials for inflammation and infection due to their non degradable components. Polymeric delivery systems have the potential to maintain therapeutic levels of a drug, to reduce side effects and to facilitate the delivery of drugs with short in vivo half-lives.

In this Chapter we have outlined different applications of polymers, usually intended as agent acted to improve the biodistribution of the desired drugs. Namely, we have highlighted the huge possibilities offered by the thin film technology applied to the concepts of "drug delivery" and "drug targeting". After a summary of the most relevant examples in the literature, we described the ongoing work in our lab, aimed at obtaining an efficient combination of physical and chemical features of an innovative neuronal interface based on a carbon nanotubes array.

The achieved results indicate that polymer technology could be efficiently embedded in CNT array (Hind *et al*., 2004) acting as drug delivery system at cellular level. The implication of this study open several perspectives in particular in the field of neurointerfaces, combining several functions into a single platform (Navarro *et al*., 1998; Navarro *et al*., 2005).

5. References

Abidian MR.; Kim DH.; Martin DC. (2006). Conducting-polymer nanotubes for controlled drug release. *Advanced Materials*; vol.18, pp. 405–9.

Abidian MR.; Martin DC. (2008). Experimental and theoretical characterization of implantable neural microelectrodes modified with conducting polymer nanotubes. *Biomaterials* vol. 29, pp. 1273–83.

Alexis F.; Venkatraman SS.; Rath SK.; Boey F. (2004). In vitro study of release mechanisms of paclitaxel and rapamycin from drug-incorporated biodegradabile stent matrices. *Journal of Control release* vol. 98, pp. 67–74.

Biran R.; Martin DC.; Tresco PA. (2005). Neuronal cell loss accompanies the brain tissue response to chronically implanted silicon microelectrode arrays. *Experimental Neurology* vol. 195 pp. 115–26.

Bronzino JD.; (1995). Biomedical Engineering Handbook, CRC Press, pp., 2000.IEEE Press, Boca Raton.

Chen J. (1997). A multichannel neural probe for selective chemical delivery at the cellular level *IEEE Trans. Biomed.* vol. 44 pp. 760–69.

Cheung KC.; Renaud P.; Tanila H.; Djupsund K. (2007). Flexible polyimide microelectrode array for in vivo recordings and current source density analysis. *Biosensors and Bioelectronics* 22, 1783-1790

Chretien C., Chaumeil. JC. (2005). Release of a macromolecular drug from alginate-impregnated particles. *International Journal of Pharmaceutics* vol. 304, pp. 18–28.

Ciofani G.; Cascone MG.; Serino LP.; Lazzeri L. (2008). Urease loaded alginate microspheres for blood purification. *Journal of Microencapsulation* vol. 25, pp. 569–576.

Ciofani G.; Raffa V.; Pizzorusso T.; Menciassi A; Dario P. (2008). Characterization of an alginate based drug delivery system for neurological applications. *Medical Engeenering and Physics* vol. 30, pp. 848–855.

Ciofani G.; Raffa V. (2009). Mini-Reviews in *Medicinal Chemistry*, in press Chemically Functionalized Carbon Nanotubes: Emerging Vectors for Cell Therapy.

Cui XY.; (2001). Surface modification of neural recording electrodes with conducting polymer/biomolecule blends *Journal of Biomedical Materarials Research,* vol. 56, pp. 261–72.

Cui XY.; Hetke JF.; Wiler JA.; Anderson DJ.; Martin DC. (2001). Electrochemical deposition and characterization of conducting polymer polypyrrole/PSS on multichannel neural probes. *Sensor and Actuators A: Physics,* vol. 93, pp. 8–18.

Cui X.; Lee VA.; Raphael Y.; Wiler JA.; Hetke JF.; Anderson DJ. (2001). Surface modification of neural recording electrodes with conducting polymer/biomolecule blends. *Journal of Biomedical Materials Research*; vol. 56, pp. 261–72.

Cui X.; Wiler J.; Dzaman M.; Altschuler RA.; Martin DC.; (2003) In vivo studies of polypyrrole/ peptide coated neural probes. *Biomaterials*; 24:777–87.

Cui X.; David C.; Martin. (2003). Electrochemical deposition and characterization of poly(3,4-ethylenedioxythiophene) on neural microelectrode array *Sensors and actuators*. vol. 89, pp. 92-102.

Cui X.; (2003).In vivo studies of polypyrrole/peptide coated neural probes *Biomaterials,* vol. 24, pp. 777–87.

Dhanikula AB.; Panchagnula R. (2004). Developmentand characterization of biodegradable chitosan films for local delivery of paclitaxel. *AAPS J* vol. 6, pp. 1–12.

Dorta, MJ.; Oliva, A.; Mungula O., Llabres M.; Farina JB. (2002). In-vitro release of fluoropyrimidines fromPLGA film implants. *Journal of Pharmacy and Pharmacology* vol. 54, pp. 757–763.

Drachman DE.; Edelman ER.; Seifert P.; Groothuis AR.; Bornstein DA.; Kamath KR.; Palasis M.; Yang D.; Nott SH.; Rogers C. (2000). Neointimal thickening after stent delivery of paclitaxel: Change in compositionand arrest of growth over six months. *Journal of the American College of Cardiology,* vol. 36, pp. 2325–2332.

Hanefeld P.; Westedt U.; Wombacher R.; Kissel T.; Schaper A.; Wendorff JH.; Greiner A. (2006). Coating of poly(p-xylylene) by PLA-PEO-PLA triblock copolymers with excellent polymer-polymer adhesion for stent applications. *Biomacromolecules* vol. 7, pp. 2086–2090.

Heller PF.; Jenkins GM.; Cheng L.; Leong K.; Shao W.; Brinker J.; Hope E.; Nater C.; Lakatta E.; Froelich JP. (1995). The sustained release of galardin and taxol from gelatin chondroitin sulfate coacervate films. *Materials Research Society Symposia Proceedings* vol. 395, pp. 55–60.

Hinds; Chopra N.; Rantell T.; Andrews R.; Gavalas V.; Bachas LG. (2004). Aligned multiwalled carbon nanotube membranes, *Science*, vol. 303, pp. 62-65.

Ho EA.; Vassileva V.; Allen C.; Piquette-Miller M. (2005). In vitro and in vivo characterizations of a novel biocompatible polymer-lipid implant system for the sustained delivery of paclitaxel. *Journal of Control Release* vol. 104, pp. 181–191.

Gabay T Ben-David M.; Kalifa I.; Sorkin R.; Abrams Z.R.; Ben-Jacob E.; Hanein Y. (2007). Electro-chemical and biological properties of carbon nanotube-based multi-electrode arrays. *Nanotechnology* col. 6, pp.1–6.

Gombotz WR.; Wee SF. (1998). Protein release from alginate matrices. *Advanced Drug Delivery Reviews* vol. 31, pp. 267–285.

Grant J.; Blicker.; Piquette-Miller M.; Allen C. (2005). Hybrid films from blends of chitosan and egg phosphatidylcholine for localized delivery of paclitaxel. *Journal of Pharmaceutical Science* vol. 94, pp. 1512–1527.

Greene LA.; Farinelli SE.; Cunningham ME.; Park DS. (1998). in Culture and experimental use of the PC12 rat pheochromocytoma cell line *Culturing Nerve Cells.*

Green A.; Lovell NH.; Poole-Warren LA.; (2009) Cell attachment functionality of bioactive conducting polymers for neural interfaces *Biomaterials* vol. 30, pp. 3637–3644.

Jackson JK.; Skinner JC.; Burgess L.; Sun T.; Hunter WL.; Burt HM. (2002). Paclitaxel-loaded crosslinked hyaluronic acid films for the prevention of post surgical adhesions. *Pharmaceutical Research* vol. 19, pp. 411–417.

Jackson JK.; Smith J.; Letchford K.; Babiuk KA.; Machan L.; Signore P.;Hunter WL.; Wang K.; Burt HM. (2004). Characterization of perivascular poly (lactic-co-glycolic acid) films containing paclitaxel. *International Journal of Pharmaceutics* vol. 283, pp.97–109.

Jedlicka S.; Leavesley SJ.; Little KM.; Robinson JP.; Nivens DE.; Rickus JL.; (2006) Interactions between chemical functionality and nanoscale surface topography impact fibronectin conformation and neuronal differentiation on model sol–gel silica substrates. *Materials Research Society Proceedings*.

Jedlicka SS.; Little KM.; Nivens DE.; Zemlyanov D.; Rickus JL.; (2007) Peptide ormosils as cellular substrates. *Journal of Materials Chemistry*; 17:5058–67.

Jedlicka SS.; McKenzie JL.; Leavesley SJ.; Little KM.; Webster TJ.; Robinson JP,(2006). Sol–gel derived materials as substrates for neuronal differentiation: effects of surface features and protein conformation. *Journal of Materials Chemistry*; 16:3221–30.

Jeong, S.Y.; Kim, S.W.; (1986). Biodegradable polymeric drug delivery systems. *Arch. Pharm. Res*. 9, 63-73.

Jones LL.; Tuszynski MH. (2001). Chronic intrathecal infusions after spinal cord injury cause scarring and compression, *Microscopy Research and Technique*, pp. 317–324.

Kato Y.; Nishino M.; I Saito, Suzuki T.; Mabuchi K. (2006). Flexible Intracortical Neural Probe with Biodegradable Polymer for Delivering Bioactive *Components Proceedings of International Conference on Microtechnologies in Medicine and Biology*.

Kimberly L.; Douglas CA.; Piccirillo; Tabrizian M. (2006). Effects of alginate inclusion on the vector properties of chitosan-based nanoparticles. *Journal of Control Release* vol. 115, pp. 354–361.

Laca A.; Garcia LA.; Argueso F.; Diaz M. (1999). Protein diffusion in alginate beads monitored by confocal microscopy, The application of wavelets for data reconstruction and analysis. *Journal of Industrial Microbioogy and. Biotechnology* vol. 23, pp. 155–165.

Lago N.; Ceballos D.; Rodrıguez FJ.; Stieglitz T.; Navarro X. (2005). Long term assessment of axonal regeneration through polyimide regenerative electrodes to interface the peripheral nerve.. *Biomaterials,* 26, 2021-2031

Langer R.; (1998) Drug delivery and targeting, *Nature,* vol. 392, pp. 5–10.

Lewin SL.; Utley DS.; Cheng ET.; Verity AN.; Terris DJ. (1997). Simultaneous treatment with BDNF and CNTF after peripheral nerve transection and repair enhances rate of functional recovery compared with BDNF treatment alone, *Laryngoscope*, vol. 107, pp. 992–999.

Maysinger D.; Morinville A. (1997). Drug delivery to the nervous system, *Trends Biotechnology* vol.15, pp. 410–18.

McCarron PA.; Woolfson AD.; Keating SM.; (2000). Sustained release of 5-fluorouracil from polymeric nanoparticles. *Journal of Pharmacy and Pharmacology* vol. 52, pp. 1451-1459.

McKenzie JL.; Waid MC.; Shi R.; Webster TJ.; (2004). Decreased functions of astrocytes on carbon nanofiber materials, *Biomaterials*, 25, 1309-1317,

Mikkelsen A., Eigsaeter A., (1995) Density distribution of calcium induces alginate gels: a numerical study *Biopolymers* vol. 36, pp. 17–41.

Murtas G.; Capuani M.; Dentini; Manetti C.; Masci G.; Massimi M.; Miccheli A.; Crescenzi V.; (2005). Alginate beads as immobilization matrix for hepatocytes perfused in a bioreactor. *Journal of Biomaterial Science Polymer Edition*. vol. 16, pp. 829–846.

Navarro CS.; Rodriguez CA.; Blau C.; Buti M.; Valderrama E.; Meyer JU; Stieglitz T. (1998). Stimulation and recording from regenerated peripheral nerves through polyimide sieve electrodes, *Journal of Peripheral Nervous System*, vol. 3, pp. 91-101.

Navarro X.; Krueger, TB.; Lago N.; Micera S.; Stieglitz T.; Dario P.; (2005) A critical review of interfaces with the peripheral nervous system for the control of neuroprostheses and hybrid bionic systems *Journal of the Peripheral Nervous System.*

Nguyen T.D. Vu; H. Chen; A.M. Cassell; Andrews R.J.; Meyyappan M.; J. Li, (2007) Vertically aligned carbon nanofiber architecture as a multifunctional 3-D neural electrical interface. *IEEE Transaction Biomedical Engeenering* vol. 54, pp. 1121–1128.

Nguyen-Vu T.D., Chen H.; Cassell AM.; Andrews R.; Meyyappan M.; Li J.; (2006). Vertically aligned carbon nanofiber arrays: an advance toward electrical-neural interfaces. *Small* vol. 2, pp. 89–94.

Perugini P.; Genta I.; Conti B.; Modena T.; Pavanetto F. (2003). Periodontal delivery of ipriflavone: Newchitosan/PLGA film delivery system for a lipophilicdrug. *International Journal of Pharm*aceutics vol. 252, pp. 1–9.

Piercea A L.; Sommakiaa S.; Rickus JL.; Ottoa KJ. (2009). Thin-film silica sol–gel coatings for neural microelectrodes, *Journal of Neuroscience Methods.*

Polikov VS, Tresco PA, Reichert WM. (2005) Response of brain tissue to chronically implanted neural electrodes. *Journal of Neuroscience Methods*;vol. 148, pp. 1–18.

Radin S.; Ducheyne P. (2007). Controlled release of vancomycin from thin sol–gel films on titanium alloy fracture plate. *Biomaterials* vol. 28, pp. 1721–9.

Rajeev AJ. (2000). The manufacturing techniques of various drug loaded biodegradable poly(lactide-*co*-glycolide) (PLGA) devices *Biomaterials*, vol. 21, pp. 2475-2490.

Retterer ST; (2004), Model neural prostheses with integrated microfluidics: a potential intervention strategy for controlling reactive cell and tissue responses *IEEE Transaction of Biomedical Engeneering,* vol. 51, pp. 2063–73.

Richardson RR.; Miller JA.; Reichert WM. (1993). Polyimides as Biomaterials: Preliminary Biocompatibility Testing. *Journal of Biomaterials.* 14, 627-63.

Santos X.; Rodrigo J.; Hontanilla B.; Bilbao G. (1998). Evaluation of peripheral nerve regeneration by nerve growth factor locally administered with a novel system, *Journal of Neuroscience Method*, vol. 85, pp.119–27.

Schmidt CE.; Leach LB. (2003). Neural tissue engineering: Strategies for Repair and Regeneration, *Annual Review of Biomedical Engeneering*, vol. 5, pp. 293–347.

Schwartz AB. (2004). Cortical Neural Prosthetics, *Annual Review of Neuroscience*, vol. 27, pp. 487-507.

Schwartz AB.; Cui X.; Douglas J.; Weber and Daniel W. Moran (2006). Brain-Controlled Interfaces: Movement Restoration with Neural Prosthetics *Neuron.*

Shi R.; Burt HM.; (2004). Amphiphilic dextran-graftpoly(epsilon-caprolactone) films for the controlledrelease of paclitaxel. *Int J Pharm* 271:167–179.

Simpson N.E.; Stabler CL.; Simpson, C.P.; Sambanis A. I. Constantinidis, (2004) The role of the CaCl2-guluronic acid interaction on alginate encapsulated betaTC3 cells. *Biomaterials* 25, 2603–2610.

Stieglitz T.; Scuettler M.; Koch KP. (2005). Implantable Biomedical Microsystems for Neural Prostheses. *IEEE Biomimetic Systems* 58 -64

Szarowski DH.; (2003). Brain Responses to micro-machined silicon devices, *Brain Research*, vol. 983, pp. 23-35.

Szarowski DH.; Andersen MD.; Retterer S.; Spence AJ.; Isaacson M.; Craighead HG. (2003). Brain responses to micro-machined silicon devices. *Brain Research*; vol. 983, pp. 23–35.

Tashiro K, Nagata I.; Yamashita N.; Okazaki K.; Ogomori K.; Tashiro N. (1994). A synthetic peptide deduced from the sequence in the cross-region of laminin A chain mediates neurite outgrowth, cell attachment and heparin binding. *Biochemical Journal;* vol. 302, pp. 39–45.

Tasis D.; N. Tagmatarchis, A. Bianco, M. Prato (2006). Chemistry of carbon nanotubes. *Chemical Review* vol. 106, pp. 1105–1136.

Vadim S.; Polikov PA.; Tresco and William M. Reicher; (2009). Bioelectronics and Implanted Devices EM McGee Medical Enhancement and Posthumanity, *Journal of Neuroscience Methods*, pp 1-18

Vetter RJ.; Williams JC., Hetke JF.; Nunamaker EA.; Kipke DR. (2004) Chronic neural recording using silicon-substrate microelectrode arrays implanted in cerebral cortex. *IEEE Transactions on Biomedical Engineering;* vol. 51, pp. 896–904.

Wand He.; Bellamkonda RV.; (2005) Nanoscale neuro-integrative coatings for neural implants *Biomaterials* vol. 26, pp. 2983–90.

Westedt U.; Wittmar M, Hellwig M, Hanefield P, Greiner A, Schaper AK, Kissel T. (2006). Coating of poly(p-xylylene) by PLA-PEO-PLA triblock copolymers with excellent polymer-polymer adhesion for *Journal of Control Release* vol. 111, pp. 235–245.

Webber.; W.L., Lago, F., Thanos, C., Mathiowitz, E., (1998). Characterization of soluble, salt-loaded degradable PLGA films and their release of tetracycline. *J. Biomed. Res.* 41, 18_/29

Williams JC.; Holecko MM; Massia SP; (2005). Neurotrophin-eluting hydrogel coatings for neural stimulating electrodes *Journal of Neural Enginnering,*

Winter JO.; Cogan SF.; Rizzo JF.; (2007) III - Journal of Biomedical Materials Research Part B.

Zhou, T.; Lewis, H., Foster, RE., Schwendeman, SP., (1998). Development of a multiple-drug delivery-implant for intraocular management of proliferative vitreoretinopathy. *Journal of Control Release* vol. 55, pp. 281-295

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This book provides a timely overview of a current state of knowledge of the use of polymer thin film for important technological applications. Polymer thin film book covers the scientific principles and technologies that are necessary to implement the use of polymer electronic device. A wide-ranging and definitive coverage of this emerging field is provided for both academic and practicing scientists. The book is intended to enable readers with a specific background, e.g. polymer nanotechnology, to become acquainted with other specialist aspects of this multidisciplinary field. Part A of the book covers the fundamental of the key aspect related to the development and improvement of polymer thin film technology and part B covers more advanced aspects of the technology are dealt with nano-polymer layer which provide an up-to-date survey of current research directions in the area of polymer thin film and its application skills.

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