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Research review paper

Stem cell-biomaterial interactions for regenerative medicine

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ABSTRACT

The synergism of stem cell biology and biomaterial technology promises to have a profound impact on stem-cell-based clinical applications for tissue regeneration. Biomaterials development is rapidly advancing to display properties that, in a precise and physiological fashion, could drive stem-cell fate both *in vitro* and *in vivo*. Thus, the design of novel materials is trying to recapitulate the molecular events involved in the production, clearance and interaction of molecules within tissue in pathologic conditions and regeneration of tissue/organs.

In this review we will report on the challenges behind translating stem cell biology and biomaterial innovations into novel clinical therapeutic applications for tissue and organ replacements (graphical abstract).

Contents

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1. Stem cell biology

Stem cells are undifferentiated cells characterized by self-renewal and multipotential differentiation. Stem cell self-renewal is the consequence of cell division that takes place within the microenvironment in which stem cells reside (niche). Within the niche the stem cell number is maintained constant by balancing quiescent and activated cells (Carlesso and Cardoso, 2010, Orlacchio et al., 2010a, 2010b). Stem cell division could result in a daughter that remains stem cell and a progenitor daughter (asymmetric division), or in two stem cell daughters (symmetric division) (Cheng et al., 2008; Rusan and Peifer, 2007; Tulina and Matunis, 2001; Yamashita, 2009; Yamashita and Fuller, 2008; Yamashita et al., 2005). In particular, asymmetric stem cell division provides the correct replacement of daughter stem cells inside and outside the niche, and moreover, the replacement of the progenitor cells that generate a differentiated progeny when subjected to specific molecular signals (Cheng et al., 2008; Rusan and Peifer, 2007; Tulina and Matunis, 2001; Yamashita, 2009; Yamashita and Fuller, 2008; Yamashita et al., 2005). Recent studies on the germ stem cell *Drosophila melanogaster*, have described a self-renewal mechanism consisting in the combination of stem cell spindle orientation and signals from the cell niche. Here, the mitotic spindle, organized by the precise positioning of the centrosomes during the interphase (Cheng et al., 2008; Tulina and Matunis, 2001; Yamashita, 2009; Yamashita and Fuller, 2008; Yamashita et al., 2005; Gonzalez, 2007), was perpendicular to the cell hub axis, so that one daughter cell inherited the attachment to the cell hub, while the other was displaced away from it (Cheng et al., 2008; Tulina and Matunis, 2001; Yamashita, 2009; Yamashita et al., 2005; Yerushalmi et al., 2005). Other authors demonstrated a similar spindle organization in the *Drosophila* neuroblast, suggesting that centrosome orientation, within stem cells, could have a general role in asymmetric division (Cowan and Hyman, 2004; Gaziova and Bhat, 2007; Rusan and Peifer, 2007; Segalen and Bellaïche, 2009; Yamashita et al., 2007). In fact, an analogous mechanism has been suggested for the mammalian stem cell division (Cheng et al., 2008).

Generally, the stem cell niche consists of a specific space within the tissue. Two distinct niches supporting hematopoietic stem cells (HSCs) have been identified in the bone marrow: the osteoblastic niche and the vascular niche (Wilson and Trumpp, 2006). In the mammalian brain, stem cell niches are retained in the subventricular zone (SVZ) along the lateral wall of the lateral ventricles and in the subgranular zone (SGZ) of the hippocampal dentate gyrus (Curtis et al., 2007; Mudò et al., 2009, Orlacchio et al., 2010a, 2010b; Rosa et al., 2010).

In adult stem cell niches, a specific cytoarchitectural organization is maintained by the connection between stem cells and somatic cell neighbours (Conover and Notti, 2008; Fuchs et al., 2004). Here, stem cells exhibit different sizes of topographical features which comprise macro- (i.e. bone shape, ligaments, or vessels), micro- (i.e. arrangement, morphology, and projections of other cells) and nanoscale arrangement (such as collagen banding, protein conformation, and ligand presentation). These topographical structures have the potential to influence cell behaviour and functionality by altering morphology, adhesion, motility, proliferation, endocytotic activity, protein abundance, and gene regulation (for a comprehensive review see McNamara et al., 2010). Inside the niche, stem cells are likely exposed to complex, spatially- and temporally-controlled biochemical mixtures of soluble chemokines, cytokines and growth factors, as well as insoluble transmembrane receptor ligands and extracellular matrix (ECM) molecules. The ECM greatly influences cell adhesion, migration, proliferation, differentiation, and survival by: (i) modulating the bioactivities of growth factors and cytokines (ii) sequestering growth factors, or (iii) directly affecting receptor activities (Abbott, 2003; Chen, 2010; Kelleher and Vacanti, 2010; Nili et al., 2003; Santra et al., 2002; Tufvesson and Westergren-Thorsson, 2002), resulting is a "give and take" relationship between cells and the ECM that in turn mediates cell behaviour (Behonick and Werb, 2003).

So far, several molecules have been identified as factors that govern the molecular mechanisms of self-renewal and stem cell proliferation and differentiation (Kochegarov, 2009; Tsiftsoglou et al., 2009). It has been established that Wnt ligand plays a role in stem cell self-renewal and in the differentiation of stem cells into different cell lineages (Angers and Moon, 2009; Fleming et al., 2008; Kikuchi et al., 2007; Zardawi et al., 2009). For instance, the Wnt ligand, produced by osteoblasts within the bone marrow, plays multiple roles in the maintenance of the HSCs function and quiescence, as well as on the growth and differentiation of osteoblasts (Clevers, 2006; Fleming et al., 2008). Moreover, the canonical Wnt signal is also an important regulator of mammalian neural development (Adachi et al., 2007; Bambakidis and Miller, 2004; Hendrickx and Leyns, 2008; Michel et al., 2009; Tsiftsoglou et al., 2009; Yamashita, 2009).

Notch signalling is also involved in the regulation of the self-renewal of adult stem cells and the differentiation of progenitor cells along a particular lineage (Adachi et al., 2007; Angers and Moon, 2009; Borggrefe and Oswald, 2009; Clevers, 2006; Hendrickx and Leyns, 2008; Kikuchi et al., 2007; Zardawi et al., 2009). Notch is required for the selection of neural progenitors both in Drosophila and vertebrates, as well as during the specification of neural progenitors between two different neural subtypes (Cau and Blader, 2009; Tien et al., 2009).

Additionally, stem cell self-renewal, differentiation and identity are maintained by growth factors (i.e. FGF/FGFR, EGF/EGFR), IP3K/Akt, cytokines (De Felici et al., 2009; Ischenko et al., 2008; Klocke et al., 2008), microRNAs (Cao et al., 2006; Chen et al., 2006a, 2006b; Ivey et al., 2008; Judson et al., 2009; Landgraf et al., 2007; Li and Gregory, 2008; Martino et al., 2009a; Visvanathan et al., 2007; Wang et al., 2009), and transcription factors (Amann et al., 2011). It has been demonstrated that soluble growth factors and membrane-anchored receptors generate a network of signals that modulate gene expression through the coordinated action of transcription factors (Amann et al., 2011; Starnes and Sorrentino, 2011). Together these events are under the control of epigenetic mechanisms that orchestrate changes in cell fate through knock-downs of pluripotency gene and activation of genes associated with cell differentiation (Meissner, 2010). In this regard, the polycomb group genes, that encode for chromatin multiprotein complexes, maintain cellular homeostasis (namely stem cell self-renewal and differentiation) by affecting inherited chromatin states that prevent alterations of gene silencing programs (Murr, 2010; Prezioso and Orlando, 2011; Morey and Helin, 2010). Furthermore, histone modifications produced by histone acethyl transpherase enzymes, that are essential for propagation of epigenetic information, are also critical for the activation and maintenance of cellular differentiation (Avvakumov et al, 2011; Park and Luger, 2008). However, it was shown that these events are also governed by a crosstalk between epigenetic modifications and transcription factors (Fukuzawa, 2011).

MicroRNAs have also been implicated in stem cell differentiation (Yi and Fuchs, 2011). This also emerge by observations that stem, progenitors and terminally differentiated cells display distinct microRNA patterns that may be used to identify a cell population (Guo et al., 2011; Liu et al., 2009a; O'Connell et al., 2010). Thus: hsa-miR-130b, hsa-miR-152, hsa-miR-28, hsa-miR-26b, and hsa-miR-193b were found differentially expressed during chondrogenic differentiation of mesenchymal stem cells (Han et al., 2010); the expression of the muscle-specific miRNAs miR-1, miR-133, miR-206 and miR-208 was demonstrated to be essential for the myogenesis as these miRNAs seem to be under the control of a transcriptional network, consisting of the pleiotropic serum response factor, MYOD, and the βHLH transcription factor Twist in cooperation with MEF2 (Braun and Gautel, 2011; Ge and Chen, 2011); the expression of miR-124 was shown to be crucial for neurogenesis (Liu et al., 2011b; Shi et al., 2010).

The combination of cytoarchitectural organization and the overall bioactive molecules generates an interplay of events that maintains stem cells within the niche and controls progenitor cells that migrate outside the niche and differentiate into cell tissues. Thus, the balance between stem cells, self-renewal and differentiation represents the checkpoint for tissue homeostasis.

1.1. Embryonic stem cells

Embryonic stem cells (ESCs) are cells isolated from the inner mass of blastocysts (Fig. 1) (Richards et al., 2004; Trounson, 2006; Unger et al., 2008).

Human ESCs express octamer-binding protein (Oct-4), Nanog, alkaline phosphatase, LIN28, Rex-1, Cripto/TDGF1, DNMT3B, SOX2, EBAF, Thy-1, stage-specific embryonic antigen-3 and −4 (SSEA-3 and −4), tumour-rejection antigen-1-60 and −1-81, high levels of telomerase activity (Chambers and Smith, 2004; Reubinoff et al., 2000). The mechanisms by which ESCs maintain self-renewal and pluripotency are still not yet fully understood. Certainly, Oct3/4, Sox2, and Nanog genes plays a key role in the process of ESCs self-renewal (Mitsui et al., 2003), as well as c-Myc, *Eras*, and Klf4 genes are involved in the maintenance of ESCs pluripotency (Judson et al., 2009; Orlacchio et al., 2010b; Richards et al., 2004; Trounson, 2006; Unger et al., 2008). Other processes such as DNA methylation, the action of other transcription factors, chromatin structure and microRNAs may be required for ESCs regulation (Chen et al., 2006a; Ivey et al., 2008; Judson et al., 2009; Li and Gregory, 2008; Orlacchio et al., 2010b). Many reports highlight the involvement of miRNAs as crucial players in ESCs regulation and ESCs development. In fact ESCs lose their self-renewal differentiation capacity, following alterations in the machinery involved in miRNAs processing, maintenance and activity (Chambers and Smith, 2004; Martino et al., 2009a; Reubinoff et al., 2000; Richards et al., 2004; Trounson, 2006; Unger et al., 2008; Wang et al., 2009). Moreover, it has recently been suggested that miR-134, miR-296 and miR-470 target Oct-4, Nanog and Sox2 mRNAs (Tay et al., 2008).

1.2. Adult stem cells

Compared to ESCs, adult stem cells (ASCs) exhibit similar self-renewal capacity but show a more restricted differentiation potential that gives rise to a specialized tissue-specific cell type (Fig. 1) (Cossu and Bianco, 2003; McKay, 2004; Martino et al., 2009b, 2009c). This restricted potential could be explained by the ASCs maintaining the characteristics of their embryonic layer of origin. In fact, ASCs are generated during ontogeny and persist within the niche in most adult animal tissues and organs (Gritti et al., 2008; Lee and Park, 2009; Lindvall et al., 2004; Ma et al., 2009; Orlacchio et al., 2010b; Uccelli et al., 2008) where they provide cell tissue repopulation under physiological and pathological conditions (Bonner-Weir and Weir, 2005; Brittan and Wright, 2002; Galli et al., 2000; Kim et al., 2005; Tumbar et al., 2004).

Key signals, gap and adherent junctions and miRNAs regulate ASCs behaviour inside the niches (Fuchs et al., 2004; Georgantas et al., 2007; Hirao et al., 2004): for instance, a set of miRNAs, expressed in $CD34^{+}$ASCs, are critical for hematopoiesis (Cheng et al., 2009; Georgantas et al., 2007), whereas, in mammals, miR-124 promotes neuronal differentiation (Cheng et al., 2009; Visvanathan et al., 2007),

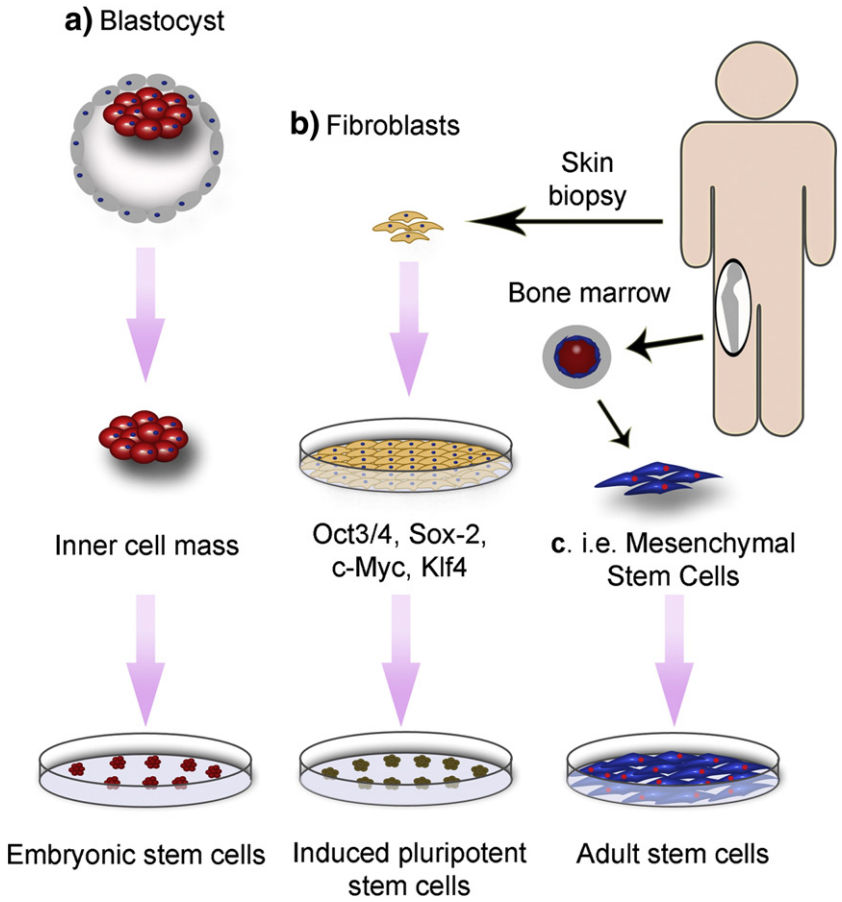

Fig. 1. The cartoon describes stem cell biogenesis. a) Embryonic stem cells, derived from the inner mass of the blastocysts, are pluripotent cells that may differentiate toward all cell types. b) Induced pluripotent stem cells generated *in vitro*, from somatic cells overexpressing Oct3/4, Sox2, c-Myc and Klf4. c) Adult stem cells (ASCs) are created during ontogeny (for example bone marrow mesenchymal stem cells) and persist within the niche in most adult animal tissues and organs.

and miRNAs miR-1 and miR-133 are important for muscle development (Ivey et al., 2008).

Based on their properties, when ASCs are transplanted they are able to recognize and respond to signals within the host tissue, this phenomenon leads to the preservation of ASCs stem-properties even in tissues of different embryonic origin (Cossu and Bianco, 2003; Galli et al., 2000; Lee and Park, 2009; Ortiz-Gonzalez et al., 2004). Hence, under specific stimuli, HSCs – that in physiological conditions generate cells of hematopoietic origin – were also able to generate non-hematopoietic cells (Goldman, 2005; Lee and Park, 2009). Similarly, bone marrow derived mesenchymal stem cells, known to differentiate into different mesenchymal cell types including osteoblasts, chondrocytes, and adipocytes (Goldman, 2005; Ortiz-Gonzalez et al., 2004; Pittenger et al., 1999; Uccelli et al., 2008), are also able to differentiate into other cell lineage types, such as skeletal myoblasts, endothelial cells, hepatocytes, and neuron-like cells when subjected to specific stimuli (Cossu and Bianco, 2003; Galli et al., 2008; Lee and Park, 2009; Ma et al, 2009; Ortiz-Gonzalez et al., 2004; Seale et al., 2000; Uccelli et al., 2008; Zuk et al., 2001). Adult neural stem/precursor cells, that are able to generate new neural cells throughout their lifetime (Gritti et al., 2008; Ma et al., 2009), under specific stimuli, are also capable of generating muscle cells (Galli et al., 2000).

1.3. Induced pluripotent stem cells

Takahashi and Yamanaka (2006) demonstrated that the over expression of Oct3/4, Sox2, c-Myc, and Klf4 genes in somatic cells can directly generate pluripotent cells with embryonic-like properties. These induced pluripotent stem (iPS) cells are a new class of stem cells generated *in vitro* from somatic differentiated cells (Fig. 2).

Presently, many laboratories are investigating the generation of iPS cells from different cell sources, ASCs and/or somatic differentiated cells, whilst improving the experimental procedure (Chambers and Smith, 2004; Judson et al., 2009; Liu et al., 2010; Mitsui et al., 2003; Rodolfa and Eggan, 2006; Sendtner, 2009). In this context it has been demonstrated that miR-291-3p, miR-294 and miR-295 increase the efficiency of reprogramming by Oct4, Sox2 and Klf4, but not by these factors combined with c-Myc. The researchers explained these findings by stating that those genes are downstream effectors of the c-Myc during reprogramming, whereas c-Myc binds miRNAs promoter (Judson et al., 2009).

To minimize genome modification in iPS cells and to eliminate the exogenous reprogramming factors, a system has been developed consisting of a piggyBac transposon/transposase that only requires the inverted terminal repeat flanking sequences and the transient expression of the transposase enzyme to catalyse insertion or excision events (Kaji et al., 2009; Woltjen et al., 2009).

With this aim, Mátés et al. (2009), have generated hyperactive transposases derived from Sleeping Beauty, and demonstrated that these hyperactive transposases resulted in superior gene transfer efficiencies and expression in mesenchymal and muscle stem/progenitor cells, consistent with higher expression levels of therapeutically relevant proteins including coagulation factor IX. Hence, this hyperactive transposon system represents an attractive nonviral gene transfer platform with broad implications for regenerative medicine, cell and gene therapy (Belay et al., 2010).

2. Biomaterial properties

Currently, a plethora of ingenious biomaterial platforms have been generated for biomedical applications. The biomaterials have to provide informative microenvironments mimicking a physiological niche, allowing stem cells to interpret the biomaterial instructions and modify their fate accordingly. In particular based on its composition and structure, biomaterial will transmit specific signals to cells that will decode these into biochemical signals. Hence, topography, chemistry and physical properties of biomaterials are critical parameters for directing cell fate (Kumari et al., 2010).

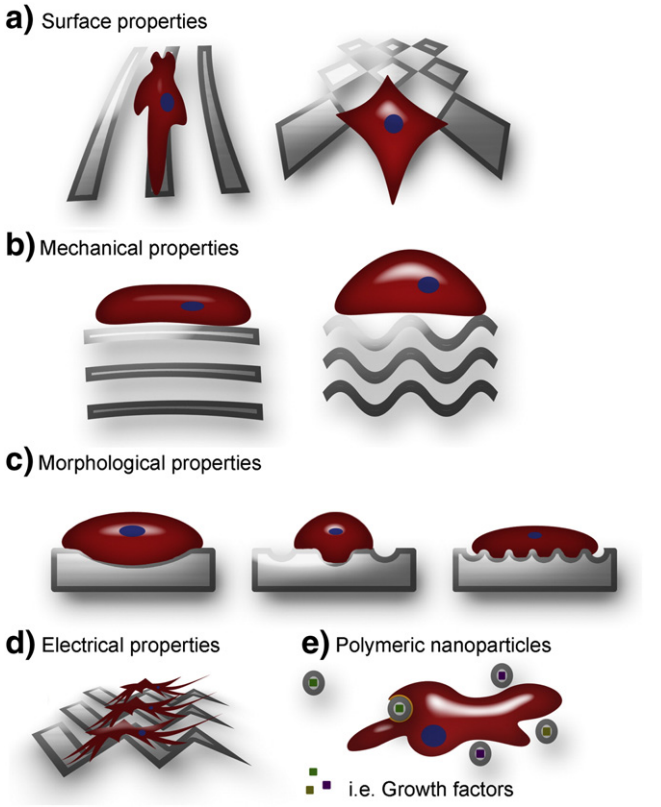

Fig. 2. Scaffold properties. a) Surface properties. The surface topography could drive cell adhesion, proliferation, migration and differentiation. b) Mechanical properties. Stem cells respond to the mechanical properties of the substrate on which they are growing, thus changing their fate. c) Morphological properties. Scaffold morphologies for stem cell biomaterial interaction may vary in terms of interconnectivity, pore-size and shape. d) Electrical properties. Electrical properties of the substrates are important issues in biomaterial-cell interaction. e) Polymeric nanoparticles. Different smart nanosystems, nanoparticles and nanoshells can be developed based on biodegradable polymers. Biodegradable nanosystems allow improvement of the therapeutic value of several water soluble/non soluble bioactive molecules by improving bioavailability, solubility and retention time.

Based on these concerns, in this review we will focus on the properties of biomaterials that are known to influence stem cell fate (Fig. 2). Examples of biomaterial designs, in terms of surface topography squares (a) and grooves (b), biodegradable polymeric scaffolds (c, d), polymeric (e) and composite electrospun mats (f), are reported in Fig. 3.

2.1. Surface properties

Harrison (1911) first reported the influence of the substratum surface on cell migration, showing that embryonic cells cultured on a spider web followed the fibers of the web. To date several groups have demonstrated that surface topography (random/ordered reliefs, patterns, etc.) and surface chemical composition could drive cell adhesion, proliferation, migration and differentiation (D'Angelo et al., 2010; Kilian et al., 2010; Martino et al., 2009c; McPhee et al., 2010). Therefore, many surface engineering approaches have been followed in order to introduce useful surface characteristics to the polymer without changing bulk properties for activating specific biological responses (Anselme et al., 2000; Croll et al., 2006; Tan and Saltzman, 2002). Plasma processes, for example, may easily modify the chemical properties of surfaces with different coatings of biomedical interest (e.g. adhesion, immobilization of biomolecules, non-fouling) but can also change the surface morphology (e.g. micro-/nanostructured

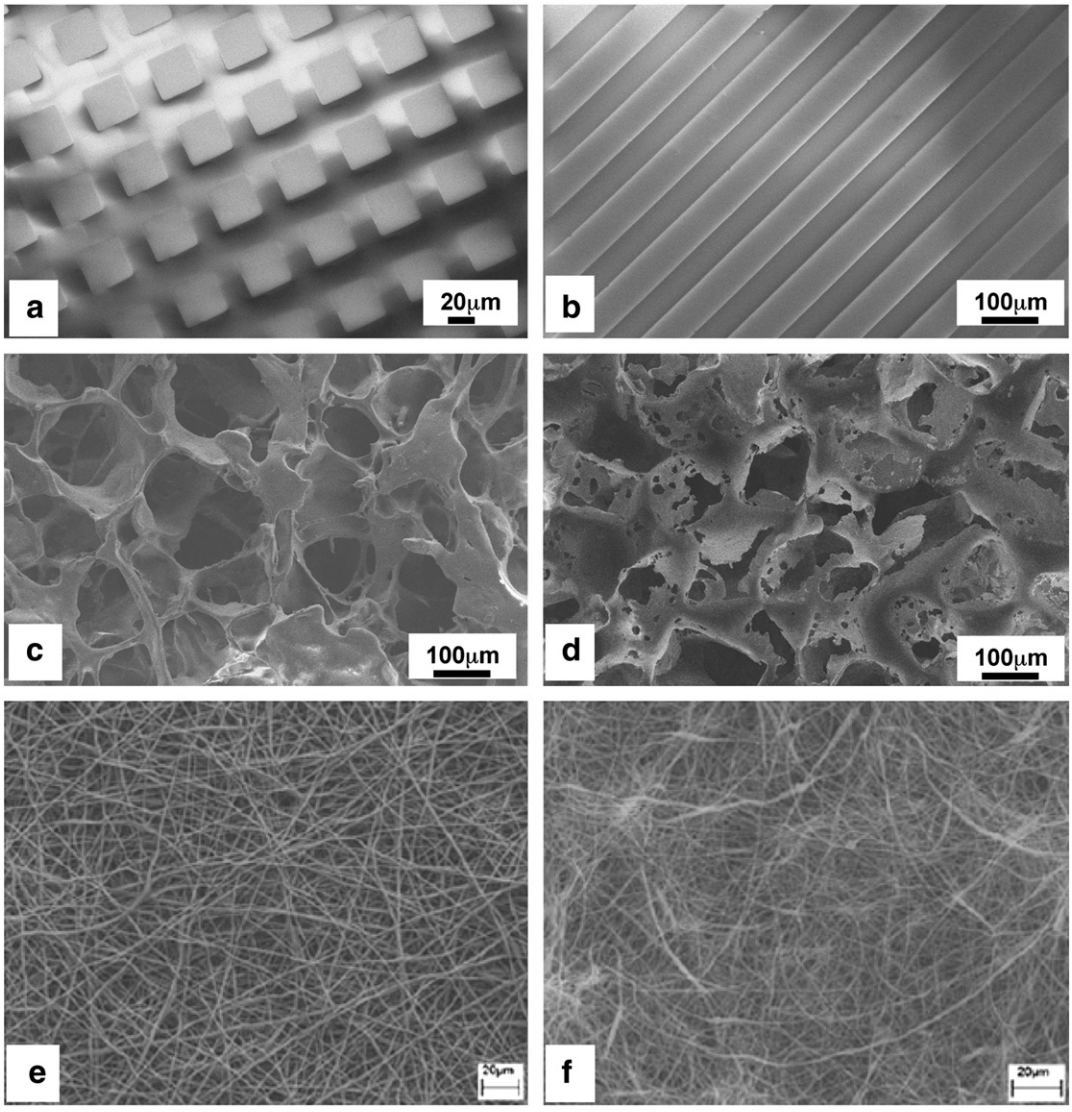

Fig. 3. Examples of biomaterial designs. Surface topography: squares (a) and grooves (b), biodegradable polymeric scaffolds (c, d) and polymeric and composite electrospun mats (e, f). Part of the figure is from references: Martino et al., 2009a and Armentano et al., 2009b.

coatings with tuneable roughness and shape of structures, or with etching processes, possibly combined with masking techniques like Colloidal Lithography) (Di Mundo et al., 2010). In this context we have reported that radiofrequency oxygen plasma treatment was effective in changing the surface properties of Polylactide (PLLA) scaffolds. The treatment functionalized the surface of the PLLA homogeneously without affecting its bulk properties, changing wettability, roughness and the interaction of proteins with the surface of PLLA polymer, thus improving the stem cell attachment (Armentano et al., 2009a; Di Mundo et al., 2010; Sardella et al., 2008).

Different types of surface topographies may be easily generated. Features comprise: scale (micro- and nanometer scale), type (e.g. ridges and grooves) (Clark et al., 1991; den Braber et al., 1996; Flemming et al., 1999; Lim et al., 2005) and distribution (randomly or regularly distributed such as pits or spikes) (Curtis et al., 2001; Martines et al., 2004; Muller et al., 2001; Wan et al., 2005). Cells have been found to sense micro- and nano-meter topography with uniform chemical properties as well as aligning and orienting themselves along grooves. In some cases, the dimensions of these structures could also induce the neural differentiation of stem cells (Christopherson et al., 2009; Yang et al., 2005; Yim et al., 2007). Recently, we demonstrated that human bone marrow mesenchymal stem cells responded to different nanopattern designs with specific changes of their microtubule organization. In particular, we observed that the groove pattern exerted a more dynamic effect, associated with stem cell alignment, elongation (Martino et al., 2009c) and with the neuronal-like cell differentiation in the case of surface topography featuring grooves with width/spacing of 40/30 μm (D'Angelo et al., 2010; Biggs et al., 2010).

2.2. Mechanical properties

Stem cells respond to the mechanical properties of the substrate on which they are growing (Discher et al., 2005; Engler et al., 2006). The interaction between nanostructures and polymer matrix represents the basis for enhanced mechanical and functional properties of the polymers. The nanocomposite approach has emerged in the last two decades as an efficient strategy to upgrade the structural and functional properties of synthetic polymers (Bianco et al., 2010), by the combination of polymers and organic/inorganic fillers (Armentano et al., 2011; Gorrasi et al., 2008; Tjong, 2006). In particular, the novel bio-nanocomposites allow both local and bulk modulation of the material mechanical properties (Baker et al., 2009). Moreover, these bio-nanocomposites provided quantitative information about the

forces that are sensed and exerted by the cells (Plant et al., 2009). Design and preparation of multi-component polymer systems represents a viable strategy in order to develop innovative multi-functional biomaterials. Aliphatic polyesters, such as poly-glycolic (PGA), poly-lactic (PLA) and poly-caprolactone (PCL) acids, are the most widely used degradable synthetic polymers for biomedical devices.

The mechanical properties of these biodegradable polymers may be modulated using nanometric engineered structures taking advantage of the inherent high surface area-volume ratio of nanomaterials (Qiao and Brinson, 2009).

Several microstructural parameters, such as the matrix properties and distribution of the fillers, the interfacial binding, and the synthesis or processing methods can affect this process. In particular the interface adhesion between nanoparticles and polymer matrix is the major factor that affects the nanocomposite mechanical properties. The interfaces may also affect the effectiveness of the load transfer from the polymer matrix to nano-structures (Armentano et al., 2010; Hong et al., 2005).

Thus, surface modification of nanostructures is needed to promote the dispersion of fillers and to enhance the interfacial adhesion between the matrix and the nanophase (Hong et al., 2004; Li et al., 2008). As an example, HA nanoparticles, grafted with PLA, are easily dispersed in the PLA matrix to form a PLA-g-HA/PLA composite. The composite showed a uniform dispersion of HA and exhibited improved mechanical properties compared to corresponding HA/PLA composite and the pristine PLA (Wutticharoenmongkol et al., 2007).

2.3. Electrostrictive properties

Electrostrictive or electroactive properties are referred to as polymers change in size or shape, following stimulations with electric inputs (Smela, 2003). A response to these stimuli is a basic phenomenon in living systems (Furth et al., 2007). Electroactive polymers (EAPs) become an intriguing research matter once electrical charges were shown to play important roles in stimulating either the proliferation or differentiation of various cell types (Basser, 1994; Kerns et al., 1991). EAPs have useful actuation properties, such as sizable active strains and/or stresses, large compliance, low density, low power consumption and ease of processing, thereby suggesting a potential, not yet fully elucidated, to configure biomaterials with intrinsic actuation capabilities. The greatest promise of this technology relies on its high versatility, compliance, lightness and scalability, as well as low cost (Smela, 2003). Recently, Huang et al. (2008) developed a new biodegradable and electroactive polymer as a scaffold for tissue engineering, through the condensation and polymerization of hydroxyl-capped poly(L-lactide) (PLA) and carboxyl-capped aniline pentamer (AP). The copolymer exhibited excellent electroactivity, solubility and biodegradability and under electrical stimulations, was capable to enhance rat neuronal pheochromocytoma PC-12 cell differentiation (Huang et al., 2008).

Stimuli-responsive polymer actuators have the ability to respond to external stimuli and as a consequence exert mechanical work. For example, Li et al. (2011) have developed novel electrospun cellulose acetate-fullerenol nanofibrous actuators leading to. more than a 3-fold increase under either continuous (DC) or alternate (AC) current conditions and beneficial effects of minute concentrations of fullernols on structural and electroactive performance of cellulose acetate nanoporous biocompatible actuators (Li et al., 2011).

2.4. Electrical properties

The electrical properties of the substrates could be a relevant topic for biomaterial-cell interaction. Currently, the effect on cell adhesion, migration, and orientation in response to electrical stimuli has been documented using a 2D culture system (Wang et al., 2003). Electrical properties of the polymers could be modulated by introducing conductive nanostructures, such as metal nanoparticles (e.g. silver, gold) and carbon nanostructures (e.g. nanotubes, graphene, nanofibers) (Sun et al., 2006). The latter can be classified based on their structure and nanoscale dimensions such as zero-dimensional structures (fullerenes, diamond clusters), one-dimensional (carbon nanotubes, carbon nanofibers, diamond nanorods), two-dimensional (graphite sheets, diamond nanoplatelets) and three-dimensional structures (nanocrystalline diamond films, fullerite) (Dottori et al., 2011; Dresselhaus et al., 1996; Harrison and Atala, 2007). In this regard, carbon nanotubes (CNT) are considered to be the ideal reinforcing agents for high-strength polymer composites, because of their mechanical strength, high electrical conductivity, and high aspect ratio (Bianco et al., 2010; Dottori et al., 2011). On the other hand, electrically conductive nanocomposites provide the possibility to establish electrical conductivity and good mechanical properties. Conjugate polymers, as polypyrrole (PPy), were also used alone or in combination with biopolymers. This allows tailoring of the level of conductivity in a controlled manner. Due to their versatile functional properties, PPy-based conducting polymers could contribute to a new generation of biomaterials (Rivers et al., 2002).

The combination of different nanostructures represents a valuable strategy to integrate the functions of components in multi-hybrid systems in order to obtain multifunctional materials (Fortunati et al., 2011). Misra et al. (2007) incorporated multi-walled carbon nanotubes (MWCNT) in a novel bioresorbable/bioactive composite, for the first time, developing a ternary nanocomposite scaffold combining three different materials. The addition of MWCNTs to bioactive composite materials makes a new highly conductive material, since it produces a three-dimensional electrical conducting network. The MWCNT composites obey Ohm's law and exhibit classic ohmic conduction.

Together these results suggest that the combination of two different nanostructures allows the development of multifunctional biomaterials with tailored bioactivity, structural and mechanical integrity as well as electrical conductivity of porous scaffolds.

2.5. Morphological properties

Scaffold morphology, in terms of interconnectivity, pore-size and shape is another crucial point for stem cell-biomaterial interaction. Scaffolds might be defined as an artificial structure that should mimic morphologic structure and function of the surrounding tissue. Scaffolds allow cell attachment and migration, deliver and retain cells and biochemical factors, enable diffusion of vital cell nutrients and expressed products. High porosity and adequate pore-size are key requisites to increase the surface area available for cell attachment and tissue in-growth, in order to facilitate the uniform distribution of cells and the adequate transport of nutrients. For instance, some pores sized between 2 and 5 μm, dispersed on the walls of the scaffolds, would be helpful for fibro-vascular colonization and nutrient transportation. Small pores on the macropore surface of the scaffolds may also be helpful to improve the biological performance of the porous scaffolds and promote favourable bioresorption of the material (Yuan et al., 1999).

Thus, the development of novel biomaterials with different fabrication techniques could be critical for the success of tissue engineering. Nanocomposite 3D scaffolds based on biodegradable polymers have been developed by using different nano-structures and processing methods. These techniques mainly include solvent casting and particulate leaching, gas foaming, emulsion freeze-drying, electrospinning, rapid prototyping and thermally induced phase separation (Grodzinski, 2006; Ma, 2004; Ma and Langer, 1995; Wei and Ma, 2004; Zhang and Ma, 2001). Fig. 3(c-f) shows polymeric and composite scaffold developed by solvent casting particulate leaching and electrospinning processes.

2.6. Polymeric nanoparticles

Different smart nanosystems, nanoparticles and nanoshells can be developed based on biodegradable polymers. Biodegradable nanosystems allow improving the therapeutic value of several water soluble/non soluble bioactive molecules by improving bioavailability, solubility, and retention time (Teixeira et al., 2005). Degradation and consequently the releasing mechanism can be modulated by the polymer properties such as molecular weight, copolymer composition and crystallinity (Kumari et al., 2010). Smart polymeric nanosystems show large conformational changes in response to small environmental stimuli such as temperature, ionic strength, pH, light or electromagnetic field and the ability to carry numerous active drugs (Astete et al., 2007). Therefore, smart polymeric nanosystems may offer promises of revolutionary improvements in tissue engineering, diagnosis and targeted drug delivery systems.

3. Stem cell-biomaterial applications

The ultimate goal of regenerative medicine and tissue engineering is the generation of functional tissue or organs. In this section we report some translational research examples showing how the new technologies in biomaterial development and the knowledge of stem cell biology can benefit patients with regenerative medical applications.

3.1. Stem cell niche

Damaged tissues often lose deeper layers as well, that contain stem cell niches. In such cases biomaterials could be useful tools for re-establishing the niches' functionality (Lutolf et al., 2009). Artificial niches would need to incorporate appropriate 'homing' signals able to attract and localize endogenous stem cells by means of known cell–cell or cell–matrix adhesive interactions (see Section 1 for details). Thus, the development of an artificial niche requires parameters including the dynamic control of soluble and surface-bound cytokines, ECM, cell-cell interactions, mechanical forces and physico-chemical cues (Dickinson et al., 2011; Peerani and Zandstra, 2010).

Despite accessibility to a plethora of ingenious biomaterial platforms with which to analyze the influence on the stem-cell niches, these platforms have only just begun to be applied with the aim of directing stem-cell fate.

Interesting perspectives on modelling bone marrow niches using scaffold-based 3D culture systems have recently been proposed by Di Maggio et al. (2011). Compared to standard 2D culture systems, a 3D scaffold-based model would facilitate a spatial distribution of the different cells, resulting in a structural organization which could better resemble the *in vivo* counterpart. Nichols et al. (2009) described the development of an *in vitro* artificial bone marrow, based on a 3D scaffold with inverted colloidal crystal (ICC) geometry mimicking the structural topology of actual bone marrow matrix. ICC scaffolds were capable of supporting expansion of $CD34^+$ HSCs with B-lymphocyte differentiation (Nichols et al., 2009).

A smart approach has also been recently described by Gilbert et al. (2010). Using a bioengineered substrate in conjunction with a highly automated single-cell tracking algorithm, the authors showed that substrate elasticity is a potent regulator of muscle stem cells' (MuSC) fate in culture. In fact, MuSCs cultured on soft hydrogel substrates, that mimic the elasticity of muscle self-renewal *in vitro*, contribute extensively to muscle regeneration when subsequently transplanted into mice. This study has provided novel evidence, showing that recapitulating physiological tissue rigidity allows the propagation of adult muscle stem cells (Gilbert et al., 2010).

3.2. Bone tissue

The World Health Authority has declared the last decade as *"The Bone and Joint Decade"*. Current bone therapies include *i*) auto-grafts, considered as the *'golden standard'* for the best clinical success. It involves the harvesting of healthy bone from one location of the patient's body and its transplantation into the damaged part of the same patient (Chen and Jin, 2010; Kneser et al., 2006; Szpalski et al., 2010); *ii*) allografts, which involves the harvesting and processing of bone from a cadaver and its transplantation into the patient (Brannen and Patterson, 2010; Dhawan et al., 2010; Smith et al., 2010); *iii*) synthetic materials such as metals, plastics and various ceramic materials (Arinzeh, 2005; Arvidson et al., 2010; Döbelin et al., 2010; Henricson and Rydholm, 2010; Reichert et al., 2010); *iv*) growth factors (bone morphogenetic proteins, parathyroid hormones) and drugs (e.g. bisphosphonates) (Chen et al., 2004; Cosman, 2005; Kaji and Sugimoto, 2005; Khan and Lane, 2004; Laflamme and Rouabhia, 2011; Lambrinoudaki et al., 2006).

Unfortunately, auto-graft and allograft therapy have several drawbacks consisting of the surgical costs, infection, harvested site morbidity, immunogenicity and disease transmittance. Therefore, researchers are developing cell-based bone tissue engineering as an alternative tool for bone substitutes and skeletal related disorders.

The paradigm of bone tissue engineering procedures consists in the isolation and expansion of mesenchymal stem cells (MSCs) from the patients and their seeding onto porous biodegradable matrices (scaffolds). During the *in vitro* culture period, stem cells are generally exposed to signalling molecules (e.g. growth factors and other osteo-inductive molecules), supplied as soluble factors and/or released by the scaffold, to drive MSCs toward the osteogenic lineage differentiation. This engineered tissue is implanted into the damaged site to regenerate the new bone as the scaffold degrades (Salgado et al., 2004).

The selection of the most appropriate material to produce a scaffold represents one of the crucial steps for bone tissue engineering (Gomes et al., 2002). In this context, alloplastic bone substitutes (synthetic substances including hydroxyapatite, other ceramics and polymers) have been processed for clinical bone applications.

Hydroxyapatite (HA) (Ca10(PO4)6(OH)2) is the major mineral component (69 wt.%) of human hard tissues, it could be natural or synthetic. HA have several potential clinical applications. These include the filling of bony defects, the retention of alveolar ridge form following tooth extraction and the capacity as a bone expander when combined with autogenous bone during ridge augmentation and sinus grafting procedures (Develioglu et al., 2010; Fu et al., 2010; Herath et al., 2010; Timperley et al., 2010; Venugopal et al., 2011). Although the use of HA enables the elimination of the donor site morbidity, the tendency for granular migration and incomplete resorption has become a long-term difficulty (Gentile et al., 2010; Kawase et al., 2010; Matsuo et al., 2010; Roohani-Esfahani et al., 2010; Zhang et al., 2010).

Other types of ceramics are tricalcium phosphate (TCP), bioglasses, and calcium sulphate (McLaren, 2004; Schwartz et al., 2008). TCP is similar to HA with a different stoichiometric profile. TCP has been formulated into several formats, but the disadvantage of the unpredictable rate of bioresorption is still unresolved (McLaren, 2004; Schwartz et al., 2008).

Bioactive glasses are silico-phosphate chains that have been used in the treatment of periodontal bone defects (Miliauskaite et al., 2007; Sculean et al., 2007). These materials have the ability to bind chemically with the bone. Same bioactive glasses may have osteo-inductive properties and have been tested in animal trials (Clokie and Sàndor, 2001).

Based on their intrinsic nature, polymers can be fashioned in seemingly endless configurations (Ahern et al., 2010; Mazzonetto

et al., 2010). Combinations of polyglycolic acid (PGA) and polylactic acid (PLA) have been successfully used as bioresorbable sutures for many years (Cosman, 2005) and more recently, as bioresorbable fixation materials (Changoor et al., 2006; Hile et al., 2005). All of them are approved by the Food and Drug Administration (USA).

Many authors have reported that electrospun hybrid scaffolds based on bioresorbable polymers and hydroxyapatite allowed osteoblast proliferation and differentiation (Kim et al., 2006; Venugopal et al., 2008; Wutticharoenmongkol et al., 2007). In this context, because of its similarity to biological apatites (high bioresorption degree and immediate precipitation of apatite on its surface when immersed in physiological solution), Ca-deficient-hydroxyapatite (d-HAp) is being widely investigated (Bianco et al., 2010; Durucan and Brown, 2000; LeGeros et al., 2003; Okuda et al., 2008; Siddharthan et al., 2005). Recently, Meng et al. (2010) generated a promising therapeutic application consisting of a paramagnetic nanofibrous composite with poly-lactide, hydroxyapatite and γ-Fe(2)0(3) nanoparticles that significantly enhanced the proliferation, differentiation and ECM secretion by osteoblasts under a static magnetic field. Moreover, nanofibrous (NF)-gelatin/apatite composite scaffolds have been created to mimic both the physical architecture and chemical composition of natural bone ECM. The biomimetic NF-gelatin/apatite scaffolds allowed a higher expression of bone sialo-protein and osteocalcin compared to NF-gelatin scaffold (Liu et al., 2009b).

Promising results have also emerged from the work of Liu et al. (2011a). Researchers incorporated akermanite (AK) (Ca(2) MgSi (2) O(7)) into Poly(lactide-co-glycolide) (PLGA) beads to PLGA in order to improve the physiochemical, drug-delivery and biological properties of PLGA beads. The incorporation of AK into PLGA beads altered the anisotropic micro-porosity in the homogenous structure; improved their compressive strength and apatite-formation ability in simulated body fluids; neutralized the acidic products from PLGA beads; led to a sustainable and controllable release of bovine serum albumin hence enhancing the proliferation and alkaline phosphatase activity of BMSCs (Liu et al., 2011a).

Bioactive HA, with addition of silicon (Si) in the crystal structure (silicon-doped hydroxyapatite (SiHA)), has become a highly attractive alternative to conventional HA in bone replacement leading to a significant improvement in *in vivo* bioactivity and osteoconductivity. Munic et al. (2011) synthesized a nanometre-scaled SiHA which closely resembles the size of bone mineral. Thus, addition of silicon provides an extra chemical signal to stimulate and enhance bone formation for new generation coatings and to improve cellular adhesion and proliferation by controlling cell alignment with the addition of metallic implantation design.

The future of bone regeneration could lie with this class of synthetic materials (Clokie and Sàndor, 2001). These materials could be better utilized for their resorption ability at variable rates, and for their compatibility with the new bioactive agents. The emerging idea is the generation of completely synthetic bio-implants with predictable degradation and innate osteocompetent potential (Clokie and Sàndor, 2001; Horan et al., 2005).

3.3. Nervous tissue

The treatment of nerve tissue repair, in particular in spinal cord injury, requires new medical therapy, because axons do not regenerate appreciably in their native environment. Currently, the *gold standard* for treating large nerve defects consists of nerve autograft transfers. This strategy is unfortunately limited by the donor site morbidity, the shortage of donor nerve and inadequate functional recovery (Chen et al., 2006b; Meek and Coert, 2002). Alternatively, the therapy consists of the use of a nerve guidance conduit that could provide a pathway for nerve out-growth and also promote nerve regeneration.

Therefore, neural tissue engineering could represent a promise for nerve tissue regeneration.

Despite the fact that neural tissue engineering lacks standard material and fabrication techniques to facilitate directional nerve outgrowth, a number of synthetic or natural biopolymers able to generate aligned support, such as PLLA, PLGA, PCL, collagen and chitosan, have been utilized to produce a nerve guidance conduit for nerve repair (Bellamkonda, 2006; Bini et al., 2004; Chew et al., 2007; Ciardelli and Chiono, 2006; Huang and Huang, 2006; Yang et al., 2010). Recently, Chun-Yang Wang et al. (2011) demonstrated that the aligned silk fibroin blended with PLLA-PCL nanofibrous scaffolds, promoted peripheral nerve regeneration significantly better than the aligned PLLA-PCL alone.

Recently, we have investigated how the design of surface topography may stimulate stem cell differentiation towards a neural lineage (D'Angelo et al., 2010). To this end, hydrogenated amorphous carbon (a-C:H) groove topographies with width/spacing ridges ranging from 80/40 μm, 40/30 μm and 30/20 μm and depths of 24 nm were used as a single mechanotransducer stimulus to generate neural cells from hBM-MSCs *in vitro* (D'Angelo et al., 2010). Despite the simultaneous presence of a-C:H, micropatterned nanoridges and soluble BDNF resulted in the highest percentage of neuronal-like differentiated cells, our findings demonstrate that the surface topography with micropatterned nanoridge width/spacing of 40/30 μm (single stimulus) induced hBM-MSCs to acquire neuronal characteristics in the absence of differentiating agents. On the other hand, the alternative a-C:H ridge dimensions tested failed to induce stem cell differentiation towards neuronal properties, thereby suggesting the occurrence of a mechanotransducer effect exerted by optimal nano/microstructure dimensions on the hBM-MSCs responses (D'Angelo et al., 2010).

Microfabricated electrodes for stimulating and recording signals from individual neurons that have facilitated direct electrical connections with living tissue is another important application (Nicolelis et al., 2003; Rousche and Normann, 1998). Conducting polymers deposited onto the electrode surfaces reduce the impedance of the electrodes and provide a mechanical buffer between the hard device and the soft tissue. Furthermore, it is also possible to incorporate and deliver pharmacological agents such as anti-inflammatory drugs and neurotrophic factors. *In vivo* studies have shown that these coatings improve the long-term recording performance of cortical electrodes (Ludwig et al., 2006; Orive et al., 2009; Chaterji et al., 2007). In recent years, due to their unique properties CNTs have sparked interest for their use in biomedical applications, in particular for neural cell growth research (Armentano et al., 2010; Bianco et al., 2010; Harrison and Atala, 2007). Either pristine or functionalized with various chemical groups, CNTs are biocompatible with neuronal cell adhesion and growth. Functionalized CNTs can modulate neuronal growth, in fact, positively charged CNTs promote greater neurite outgrowth of hippocampal neurons in culture than cells grown on neutral or negatively charged CNTs (Lee and Parpura, 2009). Conductivity and mechanical properties of CNTs have been shown to affect neuronal morphology as well (Lee and Parpura, 2009). Other neural cells, such as stem and glial cells can also be successfully grown on CNT substrates. While the acute toxicity of pristine CNTs is currently considered to be comparable to that of other forms of carbon, long-term exposure limits need to be established in order to use these materials as neural prosthesis. Nonetheless, accumulating data in support of the use of CNTs as a biocompatible and permissive substrate/scaffold for neural cells is of great importance since such application holds great potential in biomedicine (Lee and Parpura, 2009).

3.4. Skeletal and cardiac muscle

Traumatic injuries can interrupt muscle contraction by damaging the skeletal muscle and/or the peripheral nerves. The healing process results in scar tissue formation that impedes muscle function. Therefore, a scaffold is needed that will trigger muscle cell elongation, orientation, fusion and striation. McKeon-Fischer and Freeman (2011) generated a three composite scaffold made of PLLA and electrospun gold (Au) nanoparticles (Nps) named 7% Au-PLLA, 13% Au-PLLA and 21% Au-PLLA. The scaffold's conductivity increased with the presence of (Au) Nps. The low cell proliferation on all three of the Au-PLLA scaffolds was not due to Au Nps toxicity, but to myotube differentiation and fusion (McKeon-Fischer and Freeman, 2011).

Other authors are trying to develop novel biomaterials for muscle repair using electrospun chitosan microfibers. So far, chitosan microfibers have been shown to support the attachment and viability of rat muscle-derived stem cells and their subcutaneous implantation (Kang et al., 2010).

During the last decade myocardial tissue engineering has taken advantage of the development of new biomaterials and a clearer understanding of the processes that are involved in cardiac tissue growth. Cardiac tissue engineering aims to repair damaged myocardial tissues by applying heart patches created *in vitro*. To this aim the combination of two matrix-attached peptides, the adhesion peptide G(4)RGDY and heparin-binding peptide G(4)SPPRRARVTY (HBP) could have a role in cardiac tissue regeneration. In the study by Sapir et al. (2011) neonatal rat cardiac cells were seeded into unmodified, single peptide or double peptide-attached alginate scaffolds, all having the same physical features of porosity, hydrogel forming and matrix stiffness. The cardiac tissue developed in the HBP/RGD-attached scaffolds revealed the best features of functional muscle tissue (Sapir et al., 2011).

Classical porous scaffolds have proven to be inadequate because they are not able to reproduce the typical myocardial environment. Given the importance of topography in this process, one approach in order to increase functionality of the cardiac tissue-engineered constructs, relies on the attempts to mimic the microarchitecture of natural tissues (Biggs et al., 2010; Kantawong et al., 2010). For this purpose, samples of pig myocardium were de-cellularized, embedded in paraffin wax and analyzed under an optical microscope, in order to evaluate the geometrical features of the cardiac ECM. On the basis of these data, a simplified model of the cardiac ECM microarchitecture was designed. Microfabricated scaffolds were created with the Soft Lithography technique, using a bioartificial blend, based on alginate, gelatin and a novel poly(N-isopropylacrylamide)-based copolymer. The microfabricated scaffolds showed anisotropic mechanical properties of adult human left ventricular myocardium and promoted myoblast alignment in the absence of external stimuli (Rossellini et al., 2010).

4. Conclusions

The combination of stem cells and biomaterial nanotechnology offers promising perspectives in clinical practice.

In spite of successful tissue engineering scaffolds having been developed for skin, bone, vasculature, heart, cornea, and nervous system (Table 1), the state of the art for stem-cell biomaterial clinical trials is still limited and the relevant functional outcomes are not completely satisfactory.

However, impressive advances have been made for clinic bone replacement. Subbaiah and Thomas (2011) successfully evaluated the additional efficacy of a bioactive alloplast (PerioGlas) for the treatment of a case of aggressive periodontitis (Miliauskaite et al, 2007; Sculean et al., 2007). Other clinical studies have been based on the combination of mesenchymal stem cells either with HAp/β-tricalcium phosphate particles for posterior maxillary sinus augmentation (Shayesteh et al., 2008), or with Hap particles for the reconstruction of bony jaw defects prior to dental implant placement (Meijer et al., 2008).

Cochlear implants for hearing (Haynes et al., 2009; Moore and Shannon, 2009) and retinal prostheses for vision are also under development (Chen et al., 2006b). While special sense prostheses have been generated, somatosensory restoration has only recently been attempted (Dhillon and Horch, 2005; Heming et al., 2010). Some commercially available neural scaffolds that are made of biodegradable and bioabsorbable polymers have been approved by the U.S. FDA or Conformit Europe (EC), such as Neurotube™ PGA nerve guidance conduit, NeuraGen™ collagen nerve guidance conduit, and Neurolac™ poly(DLLA-epsilon-CL) nerve guidance conduit and have now entered clinical trials (Gu et al., 2011).

In conclusion, the future of regenerative medicine is based on the fabrication of innovative micro/nano-scale devices combined with

Table 1
Stem cell-biomaterial-based applications. Representative examples of stem cell-biomaterial interactions for tissue engineering applications.

Stem cell-biomaterial-based applications			
Stem cells	Biomaterials	Applications	References
• Mesenchymal stem cells	• Chitosan: poly(butylene terephthalate adipate) • Electrospun polycaprolactone nanofiber meshes • Polyhydroxyalkanoate (PHA) scaffolds coated with PHA granule binding protein PhaP fused with RGD peptide	Cartilage tissue engineering	Alves da Silva et al. (2010a, 2010b), You et al. (2011)
	• Poly(ethylene glycol) hydrogels • Poly[(L-lactide)-co-(epsilon-caprolactone)]/gelatin nanofibers	Bone tissue engineering	Parekh et al. (2011), Rim et al. (2009)
	• Elastomeric poly(1,8-octanediol-co-citrate) based thin films	Urinary bladder tissue engineering	Sharma et al. (2010)
	• Nanopatterned hydrogenated amorphous carbon films	Neural engineering	D'Angelo et al. (2010)
	• Fibronectin and poly(lactic-co-glycolic acid)	Heart tissue engineering	Tay et al. (2010)
	• bFGF-releasing ultrafine PLGA fibres • collagen-based scaffolds	Ligament/tendon tissue engineering	Sahoo et al. (2010), Butler et al. (2010)
• Human circulating myogenic precursor	• Cluster-assembled nanostructured titanium dioxide	Muscle tissue engineering	Belicchi et al. (2010)
• Embryonic stem cells	• Poly(glycerol sebacate • Electrospun poly(glycolic acid) (PGA) collagen composites fibers	Heart tissue engineering	Chen Q.Z. et al. (2010); Hosseinkhani et al, 2010
• hESC-derived mesenchymal stem cells (hESC-MSCs)	• Knitted silk-collagen sponge scaffold	Ligament/tendon tissue engineering	Chen J.L. et al. (2010a)
• Neural precursor/stem cell	• Magnetic nanoparticles • Pro-neural rat interferon-γ (rIFN-γ) and methacrylamide chitosan	Neural tissue engineering	Pickard et al. (2011), Leipzig et al. (2011)
• Dental pulp stem cells	• Titanium surface textures • Nanofibrous PCL/gelatin/nHA scaffolds	Bone tissue engineering	Mangano et al. (2010); Yang et al. (2010)
• Adipose-mesenchymal stem cell	• Trabecular titanium scaffolds • Poly(L-lactic acid)/tricalcium phosphate scaffolds	Bone tissue engineering	Gastaldi et al. (2010); McCullen et al. (2009)

spatial distribution of molecules that define the physical and chemical stimulation and drive stem cells towards specific differentiation lineages and tissue/organ reconstitution.

Future directions will involve: *i*) elucidation of molecular mechanisms by which biomaterials topography and stiffness influence stem cells behavior, thereby, the availability of micro/nano-scale culture devices could be useful to standardize the huge amount of data on mechanotransduction studies from many groups in the world; *ii*) bench to bedside translation of these scientific data to clinical applications. To this end, collaborative efforts between cell biologists and materials scientists are critical for answering key biological questions and promoting interdisciplinary stem-cell research in directions of clinical relevance.

5. Abbreviations

a-C:H	hydrogenated amorphous carbon
AK	akermanite
Au-PLLA	Poly(lactic acid) and electrospun gold
c-Myc	c-myc protein
CNT	Carbon Nano Tubes
Cripto/TDGF1	Cripto/Teratocarcinoma-Derived Growth Factor 1
DNMT3B	DNA (cytosine-5-)-methyltransferase 3 beta
EBAF	Endometrial bleeding associated factor
ECM	Extra Cellular Matrix
EGF	Epidermal Growth Factor
EGFR	Epidermal Growth Factor Receptor
Eras	ES cell expressed Ras
FGF	Fibroblast Growth Factor
FGFR	Fibroblast Growth Factor Receptor
HA	hydroxyapatite
HBP	heparin-binding peptide
HSCs	Hematopoietic Stem Cells
IP3K/Akt	Phosphatidil Inositolo 3 phosphate Kinase/ serine-threonine protein kinase
Klf4	Kruppel-like factor 4
LIN28	Lin-28 homolog
MWCNT	multi-walled carbon nanotubes
NSC	Neural Stem Cells
PCL	poly-caprolactone HA
PGA	poly-glycolic acid
PLGA	Poly(lactide-co-glycolide)
PLLA	Poly(lactic acid)
PPy	Polypyrrole
SGZ	Sub-Granular Zone
SOX2	SRY (sex determining region Y)-box 2
SVZ	SubVentricular Zone
TCP	tricalcium phosphate
Thy-1	Cluster of Differentiation 90
Wnt	Wingless-type

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References

Abbott A. Cell culture: biology's new dimension. Nature 2003;424:870–2.
Adachi K, Mirzadeh Z, Sakaguchi M, Yamashita T, Nikolcheva T, Gotoh Y, et al. Beta-catenin signalling promotes proliferation of progenitor cells in the adult mouse subventricular zone. Stem Cells 2007;25:2827–36.
Ahern BJ, Harten RD, Gruskin EA, Schaer TP. Evaluation of a fiber reinforced drillable bone cement for screw augmentation in a sheep model-mechanical testing. Clin Transl Sci 2010;3:112–5.
Alves da Silva ML, Martins A, Costa-Pinto AR, Correlo VM, Sol P, Bhattacharya M, et al. Chondrogenic differentiation of human bone marrow mesenchymal stem cells in chitosan-based scaffolds using a flow-perfusion bioreactor. J Tissue Eng Regen Med 2010 Dec 29. [Electronic publication ahead of print].
Alves da Silva ML, Martins A, Costa-Pinto AR, Costa P, Faria S, Gomes M, et al. Cartilage tissue engineering using electrospun PCL nanofiber meshes and MSCs. Biomacromolecules 2010b;11:3228–36.
Amann PM, Eichmüller SB, Schmidt J, Bazhin AV. Regulation of gene expression by retinoids. Curr Med Chem 2011;18:1405–12.
Angers S, Moon RT. Proximal events in Wnt signal transduction. Nat Rev Mol Cell Biol 2009;10:468–77.
Anselme K, Linez P, Bigerelle M, Le Maguer D, Le Maguer A, Hardouin P, et al. The relative influence of the topography and chemistry of TiAl6V4 surfaces on osteoblastic cell behaviour. Biomaterials 2000;21:1567–77.
Arinzeh TL. Mesenchymal stem cells for bone repair: preclinical studies and potential orthopedic applications. Foot Ankle Clin 2005;10:651–65.
Armentano I, Ciapetti G, Pennacchi M, Dottori M, Devescovi V, Granchi D, et al. Role of PLLA Plasma Surface Modification in the Interaction with Human Marrow Stromal Cells. J Appl Polym Sci 2009a;114:3602–11.
Armentano I, Del Gaudio C, Bianco A, Dottori M, Nanni F, Fortunati E, Kenny JM. Processing and properties of poly(e-caprolactone)/carbon nanofibre composite mats and films obtained by electrospinning and solvent casting. J Mat Sci 2009b;44:4789–95.
Armentano I, Dottori M, Fortunati E, Mattioli S, Kenny JM. Biodegradable polymer matrix nanocomposites for tissue engineering: A review. Polym Degrad Stab 2010;95:2126–46.
Armentano I, Marinucci L, Dottori M, Balloni S, Fortunati E, Pennacchi M, et al. Novel poly(L-lactide) PLLA/SWNTs nanocomposite for biomedical applications: material characterization and biocompatibility evaluation. J Biomater Sci Polym Ed 2011;22:541–56.
Arvidson K, Abdallah BM, Applegate LA, Baldini N, Cenni E, Gomez-Barrena E, et al. Bone regeneration and stem cells. J Cell Mol Med 2010. doi:10.1111/j.1582-4934.2010.01224.x. Dec 3.
Astete CE, Kumar CSSR, Sabliov CM. Size control of poly(d,l-lactide-co-glycolide) and poly(d,l-lactide-co-glycolide)-magnetite nanoparticles synthesized by emulsion evaporation technique. Colloids Surf A: Physiochem Eng Aspects 2007;299:209–16.
Avvakumov N, Nourani A, Côté J. Histone chaperones: modulators of chromatin marks. Mol Cell 2011;41:502–14.
Baker SC, Rohman G, Southgate J, Cameron NR. The relationship between the mechanical properties and cell behaviour on PLGA and PCL scaffolds for bladder tissue engineering. Biomaterials 2009;30:1321–8.
Bambakidis NC, Miller RH. Transplantation of oligodendrocyte precursors and sonic hedgehog results in improved function and white matter sparing in the spinal cords of adult rats after contusion. Spine J 2004;4:16–26.
Basser PJ. Focal magnetic stimulation of an axon. IEEE Trans Biomed Eng 1994;41:601–6.
Behonick DJ, Werb Z. A bit of give and take: the relationship between the extracellular matrix and the developing chondrocyte. Mech Dev 2003;120:1327–36.
Belay E, Mátrai J, Acosta-Sanchez A, Ma L, Quattrocelli M, Mátés L, et al. Novel hyperactive transposons for genetic modification of induced pluripotent and adult stem cells: a nonviral paradigm for coaxed differentiation. Stem Cells 2010;28:1760–71.
Belicchi M, Erratico S, Razini P, Meregalli M, Cattaneo A, Jacchetti E, et al. Ex vivo expansion of human circulating myogenic progenitors on cluster-assembled nanostructured TiO_2. Biomaterials 2010;31:5385–96.
Bellamkonda RV. Peripheral nerve regeneration: an opinion on channels, scaffolds and anisotropy. Biomaterials 2006;27:3515–8.
Bianco A, Del Gaudio C, Baiguera S, Armentano I, Bertarelli C, Dottori M, et al. Microstructure and cytocompatibility of electrospun nanocomposites based on poly(ε-caprolactone) and carbon nanostructures. Int J Artif Organs 2010;33:271–82.
Biggs MJ, Richards RG, Dalby MJ. Nanotopographical modification: a regulator of cellular function through focal adhesions. Nanomedicine 2010;6:619–33.
Bini T, Gao SJ, Tan TC, Wang S, Lim A, Hai LB, et al. Electrospun poly(l-lactide–co-glycolide) biodegradable polymer nanofibre tubes for peripheral nerve regeneration. Nanotechnology 2004;15:1459–64.
Bonner-Weir S, Weir GC. New sources of pancreatic beta-cells. Nat Biotechnol 2005;23:857–61.
Borggrefe T, Oswald F. The Notch signalling pathway: transcriptional regulation at Notch target genes. Cell Mol Life Sci 2009;66:1631–46.
Brannen H, Patterson P. Help in evaluating bone allografts. OR Manager 2010;26:8–10.
Braun T, Gautel M. Transcriptional mechanisms regulating skeletal muscle differentiation, growth and homeostasis. Nat Rev Mol Cell Biol 2011;12:349–61.
Brittan M, Wright NA. Gastrointestinal stem cells. J Pathol 2002;197:492–509.
Butler DL, Gooch C, Kinneberg KR, Boivin GP, Galloway MT, Nirmalanandhan VS, et al. The use of mesenchymal stem cells in collagen-based scaffolds for tissue-engineered repair of tendons. Nat Protoc 2010;5(5):849–63.
Cao X, Yeo G, Muotri AR, Kuwabara T, Gage FH. Noncoding RNAs in the mammalian central nervous system. Annu Rev Neurosci 2006;29:77–103.

Carlesso N, Cardoso AA. Stem cell regulatory niches and their role in normal and malignant hematopoiesis. Curr Opin Hematol 2010;17:281–6.
Cau E, Blader P. Notch activity in the nervous system: to switch or not switch? Neural Dev 2009;4:36.
Chambers I, Smith A. Self-renewal of teratocarcinoma and embryonic stem cells. Oncogene 2004;23:7150–60.
Changoor A, Hurtig MB, John Runciman R. Osteochondral graft fixation using a bioresorbable bone cement. J Biomech 2006;39:2887–92.
Chaterji S, Kwon IK, Park K. Smart polymeric gels: redefining the limits of biomedical devices. Prog Polym Sci 2007;32:1083–122.
Chen XD. Extracellular matrix provides an optimal niche for the maintenance and propagation of mesenchymal stem cells. Birth Defects Res C Embryo Today 2010;90:45–54.
Chen FM, Jin Y. Periodontal tissue engineering and regeneration: current approaches and expanding opportunities. Tissue Eng Part B Rev 2010;16:219–55.
Chen D, Zhao M, Mundy GR. Bone morphogenetic proteins. Growth Factors 2004;22: 233–41.
Chen JF, Mandel EM, Thomson JM, Wu Q, Callis TE, Hammond SM, et al. The role of microRNA-1 and microRNA-133 in skeletal muscle proliferation and differentiation. Nat Genet 2006a;38:228–33.
Chen MB, Zhang F, Lineaweaver WC. Luminal fillers in nerve conduits for peripheral nerve repair. Ann Plast Surg 2006b;57:462–71.
Chen JL, Yin Z, Shen WL, Chen X, Heng BC, Zou XH, et al. Efficacy of hESC-MSCs in knitted silk-collagen scaffold for tendon tissue engineering and their roles. Biomaterials 2010a;31:9438–51.
Chen QZ, Ishii H, Thouas GA, Lyon AR, Wright JS, Blaker JJ, et al. An elastomeric patch derived from poly(glycerol sebacate) for delivery of embryonic stem cells to the heart. Biomaterials 2010b;31:3885–93.
Cheng J, Türkel N, Hemati N, Fuller MT, Hunt AJ, Yamashita YM. Centrosome misorientation reduces stem cell division during ageing. Nature 2008;456: 599–604.
Cheng LC, Pastrana E, Tavazoie M, Doetsch F. miR-124 regulates adult neurogenesis in the subventricular zone stem cell niche. Nat Neurosci 2009;12:399–408.
Chew SY, Mi RF, Hoke A, Leong KW. Aligned protein–polymer composite fibers enhance nerve regeneration: a potential tissue-engineering platform. Adv Funct Mater 2007;17:1288–96.
Christopherson GT, Song H, Mao HQ. The influence of fiber diameter of electrospun substrates on neural stem cell differentiation and proliferation. Biomaterials 2009;30:556–64.
Ciardelli G, Chiono V. Materials for peripheral nerve regeneration. Macromol Biosci 2006;6:13–26.
Clark P, Connolly P, Curtis AS, Dow JA, Wilkinson CD. Cell guidance by ultrafine topography in vitro. J Cell Sci 1991;99:73–7.
Clevers H. Wnt/beta-catenin signalling in development and disease. Cell 2006;127: 469–80.
Clokie CML, Sàndor GKB. Bone: present and future. In: Babush C, editor. Dental implants: The art and science, 5. Philadelphia: W.B. Saunders Company; 2001. p. 59–84.
Conover JC, Notti RQ. The neural stem cell niche. Cell Tissue Res 2008;331:211–24.
Cosman F. Anabolic therapy for osteoporosis: parathyroid hormone. Curr Osteoporos Rep 2005;3:143–9.
Cossu G, Bianco P. Mesoangioblasts vascular progenitors for extravascular mesodermal tissues. Curr Opin Genet Dev 2003;13:537–42.
Cowan CR, Hyman AA. Asymmetric cell division in *C. elegans*: cortical polarity and spindle positioning. Annu Rev Cell Dev Biol 2004;20:427–53.
Croll TI, O'Connor AJ, Stevens GW, Cooper-White JJ. A blank slate? Layer-by-layer deposition of hyaluronic acid and chitosan onto various surfaces. Biomacromolecules 2006;7:1610–22.
Curtis AS, Casey B, Gallagher JO, Pasqui D, Wood MA, Wilkinson CD. Substratum nanotopography and the adhesion of biological cells. Are symmetry or regularity of nanotopography important? Biophys Chem 2001;94:275–83.
Curtis MA, Faull RL, Eriksson PS. The effect of neurodegenerative diseases on the subventricular zone. Nat Rev Neurosci 2007;8:712–23.
D'Angelo F, Armentano I, Mattioli S, Crispoltoni L, Tiribuzi R, Cerulli GG, et al. Micropatterned hydrogenated amorphous carbon guides mesenchymal stem cells towards neuronal differentiation. Eur Cell Mater 2010;20:231–44. Oct 5.
De Felici M, Farini D, Dolci S. In or out stemness: comparing growth factor signalling in mouse embryonic stem cells and primordial germ cells. Curr Stem Cell Res Ther 2009;4:87–97.
den Braber ET, de Ruijter JE, Smits HT, Ginsel LA, von Recum AF, Jansen JA. Quantitative analysis of cell proliferation and orientation on substrata with uniform parallel surface micro-grooves. Biomaterials 1996;17:1093–9.
Develioglu H, Saraydin S, Kartal U, Taner L. Evaluation of the long-term results of rat cranial bone repair using a particular xenograft. J Oral Implantol 2010;36: 167–73.
Dhawan S, Dhawan R, Gill AS, Sikri P. Comparison of the regenerative potential of an allograft used alone and that in conjunction with an immunosuppressive drug in the treatment of human periodontal infrabony defects: a clinical and radiological study. Indian J Dent Res 2010;21:557–63.
Dhillon GS, Horch KW. Direct neural sensory feedback and control of a prosthetic arm. IEEE Trans Neural Syst Rehabil Eng 2005;13:468–72.
Di Maggio N, Piccinini E, Jaworski M, Trumpp A, Wendt DJ, Martin I. Toward modeling the bone marrow niche using scaffold-based 3D culture systems. Biomaterials 2011;32:321–9.
Di Mundo R, Gristina R, Sardella E, Intranuovo F, Nardulli M, Milella A, et al. Micro-/nanoscale structuring of cell-culture substrates with fluorocarbon plasmas. Plasma Process Polym 2010;7:212–23.
Dickinson LE, Kusuma S, Gerecht S. Reconstructing the differentiation niche of embryonic stem cells using biomaterials. Macromol Biosci 2011;1:36–49.
Discher DE, Janmey P, Wang YL. Tissue cells feel and respond to the stiffness of their substrate. Science 2005;310:1139–43.
Döbelin N, Luginbühl R, Bohner M. Synthetic calcium phosphate ceramics for treatment of bone fractures. Chimia (Aarau) 2010;64:723–9.
Dottori M, Armentano I, Fortunati E, Kenny JM. Production and properties of solvent-cast poly(ε-caprolactone) composites with carbon nanostructures. J Appl Polym Sci 2011;19:3544–52.
Dresselhaus MS, Dresselhaus G, Eklund PC. Science of fullerenes and carbon nanotubes. San Diego: Academic Press; 1996.
Durucan C, Brown PW. Low temperature formation of calcium-deficient hydroxyapatite-PLA/PLGA composites. J Biomed Mater Res 2000;51:717–25.
Engler AJ, Sen S, Sweeney HL, Discher DE. Matrix elasticity directs stem cell lineage specification. Cell 2006;126:677–89.
Fleming HE, Janzen V, Lo Celso C, Guo J, Leahy KM, Kronenberg HM, et al. Wnt signaling in the niche enforces hematopoietic stem cell quiescence and is necessary to preserve self-renewal in vivo. Cell Stem Cell 2008;2:274–83.
Flemming RG, Murphy CJ, Abrams GA, Goodman SL, Nealey PF. Effects of synthetic micro- and nano-structured surfaces on cell behavior. Biomaterials 1999;20: 573–88.
Fortunati E, D'Angelo F, Martino S, Orlacchio A, Kenny JM, Armentano I. Carbon nanotubes and silver nanoparticles for multifunctional conductive biopolymer composites. Carbon 2011;49:2370–9.
Fu Q, Rahaman MN, Fu H, Liu X. Silicate, borosilicate, and borate bioactive glass scaffolds with controllable degradation rate for bone tissue engineering applications. I. Preparation and in vitro degradation. J Biomed Mater Res A 2010;95:164–71.
Fuchs E, Tumbar T, Guasch G. Socializing with the neighbors: stem cells and their niche. Cell 2004;116:769–78.
Fukuzawa M. Control of prestalk-cell differentiation by transcription factors. Dev Growth Differ 2011;53:538–47.
Furth ME, Atala A, Van Dyke ME. Smart biomaterials design for tissue engineering and regenerative medicine. Biomaterials 2007;28:5068–73.
Galli R, Borello U, Gritti A, Minasi MG, Bjornson C, Coletta M, et al. Skeletal myogenic potential of human and mouse neural stem cells. Nat Neurosci 2000;3: 986–91.
Galli R, Gritti A, Vescovi AL. Adult neural stem cells. Methods Mol Biol 2008;438:67–84.
Gastaldi G, Asti A, Scaffino MF, Visai L, Saino E, Cometa AM, et al. Human adipose-derived stem cells (hASCs) proliferate and differentiate in osteoblast-like cells on trabecular titanium scaffolds. J Biomed Mater Res A 2010;94:790–9.
Gaziova I, Bhat KM. Generating asymmetry: with and without self-renewal. Prog Mol Subcell Biol 2007;45:143–78.
Ge Y, Chen J. MicroRNAs in skeletal myogenesis. Cell Cycle 2011;10:441–8.
Gentile P, Chiono V, Boccafoschi F, Baino F, Vitale-Brovarone C, Vernè E, et al. Composite films of gelatin and hydroxyapatite/bioactive glass for tissue-engineering applications. J Biomater Sci Polym Ed 2010;21:1207–26.
Georgantas III RW, Hildreth R, Morisot S, Alder J, Liu CG, Heimfeld S, et al. CD34+ hematopoietic stem-progenitor cell microRNA expression and function: a circuit diagram of differentiation control. Proc Natl Acad Sci USA 2007;104:2750–5.
Gilbert PM, Havenstrite KL, Magnusson KE, Sacco A, Leonardi NA, Kraft P, et al. Substrate elasticity regulates skeletal muscle stem cell self-renewal in culture. Science 2010;329:1078–81.
Goldman S. Stem and progenitor cell-based therapy of the human central nervous system. Nat Biotechnol 2005;23:862–71.
Gomes ME, Salgado AJ, Reis RL. Polymer based systems on tissue engineering, replacement and regeneration. 1st edition. Dordrecht, The Netherlands: Kluwer; 2002. 221 pp.
Gonzalez C. Spindle orientation, asymmetric division and tumour suppression in *Drosophila* stem cells. Nat Rev Genet 2007;8:462–72.
Gorrasi G, Vittoria V, Murariu M, Ferreira ADS, Alexandre M, Dubois P. Effect of filler content and size on transport properties of water vapor in PLA/calcium sulfate composites. Compos Sci Technol 2008;9:627–32.
Gritti A, Galli R, Vescovi AL. Clonal analyses and cryopreservation of neural stem cell cultures. Methods Mol Biol 2008;438:173–84.
Grodzinski JJ. Polymers for tissue engineering, medical devices, and regenerative medicine. Concise general review of recent studies. Polym Adv Technol 2006;17: 395–418.
Gu X, Ding F, Yang Y, Liu J. Construction of tissue engineered nerve grafts and their application in peripheral nerve regeneration. Prog Neurobiol 2011;2:204–30.
Guo L, Zhao RC, Wu Y. The role of microRNAs in self-renewal and differentiation of mesenchymal stem cells. Exp Hematol 2011;39:608–16.
Han J, Yang T, Gao J, Wu J, Qiu X, Fan Q, et al. Specific microRNA expression during chondrogesis of human mesenchymal stem cells. Int J Mol Med 2010;25:377–84.
Harrison RG. On the stereotropusm of embryonic cells. Science 1911;34:279–81.
Harrison BS, Atala A. Review, carbon nanotube applications for tissue engineering. Biomaterials 2007;28:344–53.
Haynes DS, Young JA, Wanna GB, Glasscock III ME. Middle ear implantable hearing devices: an overview. Trends Amplif 2009;13:206–14.
Heming E, Sanden A, Kiss ZH. Designing a somatosensory neural prosthesis: percepts evoked by different patterns of thalamic stimulation. J Neural Eng 2010;7:064001.
Hendrickx M, Leyns L. Non-conventional Frizzled ligands and Wnt receptors. Dev Growth Differ 2008;50:229–43.
Henricson A, Rydholm U. Use of a trabecular metal implant in ankle arthrodesis after failed total ankle replacement. Acta Orthop 2010;81:745–7.
Herath HM, Di Silvio L, Evans JR. Biological evaluation of solid freeformed, hard tissue scaffolds for orthopedic applications. J Appl Biomater Biomech 2010;8:89–96.

Hile DD, Kowaleski MP, Doherty SA, Lewandrowski KU, Trantolo DJ. An injectable porous poly(propylene glycol-co-fumaric acid) bone repair material as an adjunct for intramedullary fixation. Biomed Mater Eng 2005;15:219–27.
Hirao A, Arai F, Suda T. Regulation of cell cycle in hematopoietic stem cells by the niche. Cell Cycle 2004;3:1481–3.
Hong ZK, Qiu XY, Sun JR, Deng MX, Chen XS, Jing XB. Grafting polymerization of L-lactide on the surface of hydroxyapatite nano-crystals. Polymer 2004;45:6705–13.
Hong Z, Zhang P, He C, Qiu X, Liu A, Chen L, et al. Nano-composite of poly(L-lactide) and surface grafted hydroxyapatite: mechanical properties and biocompatibility. Biomaterials 2005;26:6296–304.
Horan RL, Antle K, Collette AL, Wang Y, Huang J, Moreau JE, et al. In vitro degradation of silk fibroin. Biomaterials 2005;26:3385–93.
Hosseinkhani H, Hosseinkhani M, Hattori S, Matsuoka R, Kawaguchi N. Micro and nano-scale in vitro 3D culture system for cardiac stem cells. J Biomed Mater Res A 2010;94:1–8.
Huang YC, Huang YY. Biomaterials and strategies for nerve regeneration. Artif Organs 2006;30:514–22.
Huang L, Zhuang X, Hu J, Lang L, Zhang P, Wang Y, et al. Synthesis of biodegradable and electroactive multiblock polylactide and aniline pentamer copolymer for tissue engineering applications. Biomacromolecules 2008;9:850–8.
Ischenko I, Seeliger H, Schaffer M, Jauch KW, Bruns CJ. Cancer stem cells: how can we target them? Curr Med Chem 2008;15:3171–84.
Ivey KN, Muth A, Arnold J, King FW, Yeh RF, Fish JE, et al. MicroRNA regulation of cell lineages in mouse and human embryonic stem cells. Cell Stem Cell 2008;2:219–29.
Judson RL, Babiarz JE, Venere M, Blelloch R. Embryonic stem cell-specific microRNAs promote induced pluripotency. Nat Biotechnol 2009;27:459–61.
Kaji H, Sugimoto T. Treatment of osteoporosis with parathyroid hormone: evidence and perspective. Clin Calcium 2005;15:611–5.
Kaji K, Norrby K, Paca A, Mileikovsky M, Mohseni P, Woltjen K. Virus-free induction of pluripotency and subsequent excision of reprogramming factors. Nature 2009;458:771–5.
Kang YM, Lee BN, Ko JH, Kim GH, Kang KN, Kim da Y, et al. In vivo biocompatibility study of electrospun chitosan microfiber for tissue engineering. Int J Mol Sci 2010;11:4140–8.
Kantawong F, Burgess KE, Jayawardena K, Hart A, Riehle MO, Oreffo RO, et al. Effects of a surface topography composite with puerariae radix on human STRO-1-positive stem cells. Acta Biomater 2010;6:3694–703.
Kawase T, Okuda K, Kogami H, Nakayama H, Nagata M, Sato T, et al. Human periosteum-derived cells combined with superporous hydroxyapatite blocks used as an osteogenic bone substitute for periodontal regenerative therapy: an animal implantation study using nude mice. J Periodontol 2010;81:420–7.
Kelleher C, Vacanti JP. Engineering extracellular matrix through nanotechnology. J R Soc Interface 2010;7:S717–29.
Kerns JM, Fakhouri AJ, Weinrib HP, Freeman JA. Electrical stimulation of nerve regeneration in the rat: the early effects evaluated by a vibrating probe and electron microscopy. Neuroscience 1991;40:93–107.
Khan SN, Lane JM. The use of recombinant human bone morphogenetic protein-2 (rhBMP-2) in orthopaedic applications. Expert Opin Biol Ther 2004;4:741–8.
Kikuchi A, Yamamoto H, Kishida S. Multiplicity of the interactions of Wnt proteins and their receptors. Cell Signal 2007;19:659–71.
Kilian KA, Bugarija B, Lahn BT, Mrksich M. Geometric cues for directing the differentiation of mesenchymal stem cells. Proc Natl Acad Sci USA 2010;107:4872–7.
Kim CF, Jackson EL, Woolfenden AE, Lawrence S, Babar I, Vogel S, et al. Identification of bronchioalveolar stem cells in normal lung and lung cancer. Cell 2005;121:823–35.
Kim HW, Lee HH, Knowles JC. Electrospinning biomedical nanocomposite fibers of hydroxyapatite/poly(lactic acid) for bone regeneration. J Biomed Mater Res A 2006;79:643–9.
Klocke R, Kuhlmann MT, Scobioala S, Schäbitz WR, Nikol S. Granulocyte colony-stimulating factor (G-CSF) for cardio- and cerebrovascular regenerative applications. Curr Med Chem 2008;15:968–77.
Kneser U, Schaefer DJ, Polykandriotis E, Horch RE. Tissue engineering of bone: the reconstructive surgeon's point of view. J Cell Mol Med 2006;10:7–19.
Kochegarov A. Small molecules for stem cells. Expert Opin Ther Pat 2009;19:275–81.
Kumari A, Kumar Yadav S, Yadav SC. Biodegradable polymeric nanoparticles based drug delivery systems. Review. Colloids Surf B Biointerfaces 2010;75:1–18.
Laflamme C, Rouabhia M. A medical device for prefabrication of large bone grafts in modern medicine. Med Hypotheses 2011;4:489–91.
Lambrinoudaki I, Christodoulakos G, Botsis D. Bisphosphonates. Ann N Y Acad Sci 2006;1092:397–402.
Landgraf P, Rusu M, Sheridan R, Sewer A, Iovino N, Aravin A, et al. Mammalian microRNA expression atlas based on small RNA library sequencing. Cell 2007;129:1401–14.
Lee PH, Park HJ. Bone marrow-derived mesenchymal stem cell therapy as a candidate disease-modifying strategy in Parkinson's disease and multiple system atrophy. J Clin Neurol 2009;5:1–10.
Lee W, Parpura V. Carbon nanotubes as substrates/scaffolds for neural cell growth. Prog Brain Res 2009;180:110–25.
LeGeros RZ, Lin S, Rohanizadeh R, Mijares D, LeGeros JP. Biphasic calcium phosphate bioceramics: preparation, properties and applications. J Mater Sci Mater Med 2003;14:201–9.
Leipzig ND, Wylie RG, Kim H, Shoichet MS. Differentiation of neural stem cells in three-dimensional growth factor-immobilized chitosan hydrogel scaffolds. Biomaterials 2011;32:57–64.
Li Q, Gregory RI. MicroRNA regulation of stem cell fate. Cell Stem Cell 2008;2:195–6.
Li J, Lu XL, Zheng YF. Effect of surface modified hydroxyapatite on the tensile property improvement of HA/PLA composite. Appl Surf Sci 2008;255:494–7.
Li J, Vadahanambi S, Kee CD, Oh IK. Electrospun fullerenol-cellulose biocompatible actuators. Biomacromolecules 2011. doi:10.1021/bm2004252. May 5.
Lim JY, Hansen JC, Siedlecki CA, Hengstebeck RW, Cheng J, Winograd N, et al. Osteoblast adhesion on poly(L-lactic acid)/polystyrene demixed thin film blends: effect of nanotopography, surface chemistry, and wettability. Biomacromolecules 2005;6:3319–27.
Lindvall O, Kokaia Z, Martinez-Serrano A. Stem cell therapy for human neurodegenerative disorders-how to make it work. Nat Med 2004;10(Suppl):S42–50.
Liu SP, Fu RH, Yu HH, Li KW, Tsai CH, Shyu WC, et al. MicroRNAs regulation modulated self-renewal and lineage differentiation of stem cells. Cell Transplant 2009a;18:1039–45.
Liu X, Smith LA, Hu J, Ma PX. Biomimetic nanofibrous gelatin/apatite composite scaffolds for bone tissue engineering. Biomaterials 2009b;30:2252–8.
Liu J, Verma PJ, Evans-Galea MV, Delatycki MB, Michalska A, Leung J, et al. Generation of induced pluripotent stem cell lines from Friedreich ataxia patients. Stem Cell Rev 2010 Dec 22. [Electronic publication ahead of print].
Liu G, Wu C, Fan W, Miao X, Sin DC, Crawford R, et al. The effects of bioactive akermanite on physiochemical, drug-delivery, and biological properties of poly(lactide-co-glycolide) beads. J Biomed Mater Res B Appl Biomater 2011a;96:360–8.
Liu K, Liu Y, Mo W, Qiu R, Wang X, Wu JY, et al. MiR-124 regulates early neurogenesis in the optic vesicle and forebrain, targeting NeuroD1. Nucleic Acids Res 2011b;39:2869–79.
Ludwig KA, Uram JD, Yang J, Martin DC, Kipke DR. Chronic neural recordings using silicon microelectrode arrays electrochemically deposited with a poly(3,4-ethylenedioxythiophene) (PEDOT) film. J Neural Eng 2006;3:59–70.
Lutolf MP, Doyonnas R, Havenstrite K, Koleckar K, Blau HM. Perturbation of single hematopoietic stem cell fates in artificial niches. Integr Biol (Camb) 2009;1:59–69.
Ma PX. Scaffold for Tissue Engineering. Mater Today 2004;7:30–40.
Ma PX, Langer R. Degradation, structure and properties of fibrous poly(glycolic acid) scaffolds for tissue engineering. In: Mikos AG, et al, editor. Polymers in Medicine and Pharmacy. PA: Materials Research Society; 1995. p. 99.
Ma DK, Bonaguidi MA, Ming GL, Song H. Adult neural stem cells in the mammalian central nervous system. Cell Res 2009;19:672–82.
Mangano C, De Rosa A, Desiderio V, d'Aquino R, Piattelli A, De Francesco F, et al. The osteoblastic differentiation of dental pulp stem cells and bone formation on different titanium surface textures. Biomaterials 2010;31:3543–51.
Martines E, McGhee K, Wilkinson C, Curtis A. A parallel-plate flow chamber to study initial cell adhesion on a nanofeatured surface. IEEE Trans Nanobioscience 2004;3:90–5.
Martino S, D'Angelo F, Armentano I, Tiribuzi R, Pennacchi M, Dottori M, et al. Hydrogenated amorphous carbon nanopatterned film designs drive human bone marrow mesenchymal stem cell cytoskeleton architecture. Tissue Eng Part A 2009a;15:3139–49.
Martino S, di Girolamo I, Orlacchio A, Datti A, Orlacchio A. MicroRNA implications across neurodevelopment and neuropathology. J Biomed Biotechnol 2009b;2009:654346.
Martino S, di Girolamo I, Tiribuzi R, D'Angelo F, Datti A, Orlacchio A. Efficient siRNA delivery by the cationic liposome DOTAP in human hematopoietic stem cells differentiating into dendritic cells. J Biomed Biotechnol 2009c;2009:410260.
Mátés L, Chuah MK, Belay E, Jerchow B, Manoj N, Acosta-Sanchez A, et al. Molecular evolution of a novel hyperactive Sleeping Beauty transposase enables robust stable gene transfer in vertebrates. Nat Genet 2009;41:753–61.
Matsuo A, Chiba H, Takahashi H, Toyoda J, Abukawa H. Clinical application of a custom-made bioresorbable raw particulate hydroxyapatite/poly-L-lactide mesh tray for mandibular reconstruction. Odontology 2010;98:85–8.
Mazzonetto R, Klüppel LE, Neto HD, Chessa JG, Nascimento FF. Reconstruction of severely resorbed maxilla with biodegradable polylactide screws: case series. Int J Oral Maxillofac Implants 2010;25:821–5.
McCullen SD, Zhu Y, Bernacki SH, Narayan RJ, Pourdeyhimi B, Gorga RE, et al. Electrospun composite poly(L-lactic acid)/tricalcium phosphate scaffolds induce proliferation and osteogenic differentiation of human adipose-derived stem cells. Biomed Mater 2009;4:035002.
McKay RD. Stem cell biology and neurodegenerative disease. Philos Trans R Soc Lond B Biol Sci 2004;359:851–6.
McKeon-Fischer KD, Freeman JW. Characterization of electrospun poly(L-lactide) and gold nanoparticle composite scaffolds for skeletal muscle tissue engineering. J Tissue Eng Regen Med 2011;7:560–8.
McLaren AC. Alternative materials to acrylic bone cement for delivery of depot antibiotics in orthopaedic infections. Clin Orthop Relat Res 2004;427:101–6.
McNamara LE, McMurray RJ, Biggs MJ, Kantawong F, Oreffo RO, Dalby MJ. Nanotopographical control of stem cell differentiation. J Tissue Eng 2010;2010:120623.
McPhee G, Dalby MJ, Riehle M, Yin H. Can common adhesion molecules and microtopography affect cellular elasticity? A combined atomic force microscopy and optical study. Med Biol Eng Comput 2010;48:1043–53.
Meek MF, Coert JH. Clinical use of nerve conduits in peripheral-nerve repair: review of the literature. J Reconstr Microsurg 2002;18:97–109.
Meijer GJ, de Bruijn JD, Koole R, van Blitterswijk CA. Cell based bone tissue engineering in jaw defects. Biomaterials 2008;29:3053–61.
Meissner A. Epigenetic modifications in pluripotent and differentiated cells. Nat Biotechnol 2010;28:1079–88.
Meng J, Zhang Y, Qi X, Kong H, Wang C, Xu Z, et al. Paramagnetic nanofibrous composite films enhance the osteogenic responses of pre-osteoblast cells. Nanoscale 2010;2:2565–9.
Michel F, Lévesque TN, Rezak M. Therapeutic microinjection of autologous adult human neural stem cells and differentiated neurons for Parkinson's disease: five-year post-operative outcome. Open Stem Cell J 2009;1:20–9.
Miliauskaite A, Selimovic D, Hannig M. Successful management of aggressive periodontitis by regenerative therapy: a 3-year follow-up case report. J Periodontol 2007;78:2043–50.

Misra SK, Watts PCP, Valappil SP, Silva SRP, Roy I, Boccaccini AR. Poly(3-hydroxybutyrate)/Bioglass composite films containing carbon nanotubes. Nanotechnology 2007;18:075701–8.
Mitsui K, Tokuzawa Y, Itoh H, Segawa K, Murakami M, Takahashi K, et al. The homeoprotein Nanog is required for maintenance of pluripotency in mouse epiblast and ES cells. Cell 2003;113:631–42.
Moore DR, Shannon RV. Beyond cochlear implants: awakening the deafened brain. Nat Neurosci 2009;12:686–91.
Morey L, Helin K. Polycomb group protein-mediated repression of transcription. Trends Biochem Sci 2010;35:323–32.
Mudò G, Bonomo A, Di Liberto V, Frinchi M, Fuxe K, Belluardo N. The FGF-2/FGFRs neurotrophic system promotes neurogenesis in the adult brain. J Neural Transm 2009;116:995–1005.
Muller B, Riedel M, Michel R, De Paul SM, Hofer R, Heger D, et al. Impact of nanometer-scale roughness on contact-angle hysteresis and globulin adsorption. J Vac Sci Technol B 2001;19:1715–20.
Munic G, Koller G, Di Silvio L, Edirisinghe MJ, Bonfield W, Huang J. The pathway to intelligent implants: osteoblast response to nano silicon-doped hydroxyapatite patterning. J R Soc Interface 2011;58:678–88.
Murr R. Interplay between different epigenetic modifications and mechanisms. Adv Genet 2010;70:101–41.
Nichols JE, Cortiella J, Lee J, Niles JA, Cuddihy M, Wang S, et al. In vitro analog of human bone marrow from 3D scaffolds with biomimetic inverted colloidal crystal geometry. Biomaterials 2009;30:1071–9.
Nicolelis MA, Dimitrov D, Carmena JM, Crist R, Lehew G, Kralik JD, et al. Chronic, multisite, multielectrode recordings in macaque monkeys. Proc Natl Acad Sci U S A 2003;100:11041–6.
Nili N, Cheema AN, Giordano FJ, Barolet AW, Babaei S, Hickey R, et al. Decorin inhibition of PDGF-stimulated vascular smooth muscle cell function: potential mechanism for inhibition of intimal hyperplasia after balloon angioplasty. Am J Pathol 2003;163:869–78.
O'Connell RM, Chaudhuri AA, Rao DS, Gibson WS, Balazs AB, Baltimore D. MicroRNAs enriched in hematopoietic stem cells differentially regulate long-term hematopoietic output. Proc Natl Acad Sci USA 2010;107:14235–40.
Okuda T, Ioku K, Yonezawa I, Minagi H, Gonda Y, Kawachi G, et al. The slow resorption with replacement by bone of a hydrothermally synthesized pure calcium-deficient hydroxyapatite. Biomaterials 2008;29:2719–28.
Orive G, Anitua E, Pedraz JL, Emerich DF. Biomaterials for promoting brain protection, repair and regeneration. Nat Rev Neurosci 2009;10:682–92.
Orlacchio A, Bernardi G, Orlacchio A, Martino S. Stem cells and neurological diseases. Discov Med 2010a;9:546–53.
Orlacchio A, Bernardi G, Orlacchio A, Martino S. Stem cells: an overview of the current status of therapies for central and peripheral nervous system diseases. Curr Med Chem 2010b;17:595–608.
Ortiz-Gonzalez XR, Keene CD, Verfaillie CM, Low WC. Neural induction of adult bone marrow and umbilical cord stem cells. Curr Neurovasc Res 2004;1:207–13.
Parekh SH, Chatterjee K, Lin-Gibson S, Moore NM, Cicerone MT, Young MF, et al. Modulus-driven differentiation of marrow stromal cells in 3D scaffolds that is independent of myosin-based cytoskeletal tension. Biomaterials 2011;9:2256–64.
Park YJ, Luger K. Histone chaperones in nucleosome eviction and histone exchange. Curr Opin Struct Biol 2008;18:282–9.
Peerani R, Zandstra PW. Enabling stem cell therapies through synthetic stem cell-niche engineering. J Clin Invest 2010;120:60–70.
Pickard MR, Barraud P, Chari DM. The transfection of multipotent neural precursor/stem cell transplant populations with magnetic nanoparticles. Biomaterials 2011;9:2274–84.
Pittenger MF, Mackay AM, Beck SC, Jaiswal RK, Douglas R, Mosca JD, et al. Multilineage potential of adult human mesenchymal stem cells. Science 1999;284:143–7.
Plant AL, Bhadriraju K, Spurlin TA, Elliott JT. Review Cell response to matrix mechanics: focus on collagen. Biochim Biophys Acta 2009;1793:893–902.
Prezioso C, Orlando V. Polycomb proteins in mammalian cell differentiation and plasticity. FEBS Lett 2011;13:2067–77.
Qiao R, Brinson LC. Simulation of intherphase percolation and gradients in polymer nanocomposites. Compos Sci Technol 2009;69:491–9.
Reichert JC, Wullschleger ME, Cipitria A, Lienau J, Cheng TK, Schütz MA, et al. Custom-made composite scaffolds for segmental defect repair in long bones. Int Orthop 2010 Dec 7. [Electronic publication ahead of print].
Reubinoff BE, Pera MF, Fong CY, Trounson A, Bongso A. Embryonic stem cell lines from human blastocysts: somatic differentiation in vitro. Nat Biotechnol 2000;18:399–404.
Richards M, Tan SP, Tan JH, Chan WK, Bongso A. The transcriptome profile of human embryonic stem cells as defined by SAGE. Stem Cells 2004;22:51–64.
Rim NG, Lee JH, Jeong SI, Lee BK, Kim CH, Shin H. Modulation of osteogenic differentiation of human mesenchymal stem cells by poly[(L-lactide)-co-(epsilon-caprolactone)]/gelatin nanofibers. Macromol Biosci 2009;9:795–804.
Rivers TJ, Hudson TW, Schmidt CE. Synthesis of a novel, biodegradable electrically conducting polymer for biomedical applications. Adv Funct Mater 2002;12:33–7.
Rodolfa KT, Eggan K. A transcriptional logic for nuclear reprogramming. Cell 2006;126:652–5.
Roohani-Esfahani SI, Nouri-Khorasani S, Lu Z, Appleyard R, Zreiqat H. The influence hydroxyapatite nanoparticle shape and size on the properties of biphasic calcium phosphate scaffolds coated with hydroxyapatite-PCL composites. Biomaterials 2010;31:5498–509.
Rosa AI, Gonçalves J, Cortes L, Bernardino L, Malva JO, Agasse F. The angiogenic factor angiopoietin-1 is a proneurogenic peptide on subventricular zone stem/progenitor cells. J Neurosci 2010;30:4573–84.
Rossellini E, Vozzi G, Barbani N, Giusti P, Cristallini C. Three-dimensional microfabricated scaffolds with cardiac extracellular matrix-like architecture. Int J Artif Organs 2010;33:885–94.
Rousche PJ, Normann RA. Chronic recording capability of the Utah Intracortical Electrode Array in cat sensory cortex. J Neurosci Methods 1998;82:1–15.
Rusan NM, Peifer M. A role for a novel centrosome cycle in asymmetric cell division. J Cell Biol 2007;177:13–20.
Sahoo S, Toh SL, Goh JC. A bFGF-releasing silk/PLGA-based biohybrid scaffold for ligament/tendon tissue engineering using mesenchymal progenitor cells. Biomaterials 2010;31:2990–8.
Salgado AJ, Coutinho OP, Reis RL. Bone tissue engineering: state of the art and future trends. Macromol Biosci 2004;4:743–65.
Santra M, Reed CC, Iozzo RV. Decorin binds to a narrow region of the epidermal growth factor (EGF) receptor, partially overlapping but distinct from the EGF-binding epitope. J Biol Chem 2002;277:35671–81.
Sapir Y, Kryukov O, Cohen S. Integration of multiple cell-matrix interactions into alginate scaffolds for promoting cardiac tissue regeneration. Biomaterials 2011;7:1838–47.
Sardella E, Detomaso L, Gristina R, Senesi GS, Agheli H, Sutherland DS, et al. Nanostructured cell-adhesive and cell-repulsive plasma-deposited coatings: chemical and topographical effects on keratinocyte adhesion. Plasma Processes Polym 2008;5:540–51.
Schwartz Z, Doukarsky-Marx T, Nasatzky E, Goultschin J, Ranly DM, Greenspan DC, et al. Differential effects of bone graft substitutes on regeneration of bone marrow. Clin Oral Implants Res 2008;19:1233–45.
Sculean A, Pietruska M, Arweiler NB, Auschill TM, Nemcovsky C. Four-year results of a prospective-controlled clinical study evaluating healing of intra-bony defects following treatment with an enamel matrix protein derivative alone or combined with a bioactive glass. J Clin Periodontol 2007;34:507–13.
Seale P, Sabourin LA, Girgis-Gabardo A, Mansouri A, Gruss P, Rudnicki M. A. Pax7 is required for the specification of myogenic satellite cells. Cell 2000;102:777–86.
Segalen M, Bellaïche Y. Cell division orientation and planar cell polarity pathways. Semin Cell Dev Biol 2009;20:972–7.
Sendtner M. Stem cells: tailor-made diseased neurons. Nature 2009;457:269–70.
Sharma AK, Hota PV, Matoka DJ, Fuller NJ, Jandali D, Thaker H, et al. Urinary bladder smooth muscle regeneration utilizing bone marrow derived mesenchymal stem cell seeded elastomeric poly(1,8-octanediol-co-citrate) based thin films. Biomaterials 2010;31:6207–17.
Shayesteh YS, Khojasteh A, Soleimani M, Alikhasi M, Khoshzaban A, Ahmadbeigi N. Sinus augmentation using human mesenchymal stem cells loaded into a β-tricalcium phosphate/hydroxyapatite scaffold. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2008;106:203–9.
Shi Y, Zhao X, Hsieh J, Wichterle H, Impey S, Banerjee S, et al. Kosik KMicroRNA regulation of neural stem cells and neurogenesis. J Neurosci 2010;30:14931–6.
Siddharthan A, Seshadri SK, Sampath Kumar TS. Rapid synthesis of calcium deficient hydroxyapatite nanoparticles by microwave irradiation. Trends Biomater Artif Organs 2005;18:110–3.
Smela E. Conjugated polymer actuators for biomedical applications. Adv Mater 2003;15:481–94.
Smith KE, Huang Z, Ma T, Irani A, Lane Smith R, Goodman SB. Molecular profile of osteoprogenitor cells seeded on allograft bone. J Tissue Eng Regen Med 2010 Dec 30. [Electronic publication ahead of print].
Starnes LM, Sorrentino A. Regulatory circuitries coordinated by transcription factors and microRNAs at the cornerstone of hematopoietic stem cell self-renewal and differentiation. Curr Stem Cell Res Ther 2011;6:142–61.
Subbaiah R, Thomas B. Efficacy of a bioactive alloplast, in the treatment of human periodontal osseous defects-a clinical study. Med Oral Patol Oral Cir Bucal 2011;16:e239–44.
Sun S, Titushkin I, Cho M. Regulation of mesenchymal stem cell adhesion and orientation in 3D collagen scaffold by electrical stimulus. Bioelectrochemistry 2006;69:133–41.
Szpalski C, Barr J, Wetterau M, Saadeh PB, Warren SM. Cranial bone defects: current and future strategies. Neurosurg Focus 2010;29:E8.
Takahashi K, Yamanaka S. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. Cell 2006;126:663–76.
Tan J, Saltzman WM. Topographical control of human neutrophil motility on micropatterned materials with various surface chemistry. Biomaterials 2002;23:3215–25.
Tay Y, Zhang J, Thomson AM, Lim B, Rigoutsos I. MicroRNAs to Nanog, Oct4 and Sox2 coding regions modulate embryonic stem cell differentiation. Nature 2008;455:1124–8.
Tay CY, Yu H, Pal M, Leong WS, Tan NS, Ng KW, et al. Micropatterned matrix directs differentiation of human mesenchymal stem cells towards myocardial lineage. Exp Cell Res 2010;316:1159–68.
Teixeira M, Alonso MJ, Pinto MMM, Barbosa CM. Development and characterization of PLGA nanospheres and nanocapsules containing xanthone and 3-methoxyxanthone. Eur J Pharm Biopharm 2005;59:491–500.
Tien AC, Rajan A, Bellen HJ. A Notch updated. J Cell Biol 2009;184:621–9.
Timperley AJ, Nusem I, Wilson K, Whitehouse SL, Buma P, Crawford RW. A modified cementing technique using BoneSource to augment fixation of the acetabulum in a sheep model. Acta Orthop 2010;81:503–7.
Tjong SC. Structural and mechanical properties of polymer nanocomposites. Mater. Sci. Eng. R 2006;53:73–197.
Trounson A. The production and directed differentiation of human embryonic stem cells. Endocr Rev 2006;27:208–19.
Tsiftsoglou AS, Bonovolias ID, Tsiftsoglou SA. Multilevel targeting of hematopoietic stem cell self-renewal, differentiation and apoptosis for leukemia therapy. Pharmacol Ther 2009;122:264–80.

Tufvesson E, Westergren-Thorsson G. Tumour necrosis factor-alpha interacts with biglycan and decorin. FEBS Lett 2002;530:124–8.
Tulina N, Matunis E. Control of stem cell self-renewal in *Drosophila* spermatogenesis by JAK-STAT signaling. Science 2001;294:2546–9.
Tumbar T, Guasch G, Greco V, Blanpain C, Lowry WE, Rendl M, et al. Defining the epithelial stem cell niche in skin. Science 2004;303:359–63.
Uccelli A, Moretta L, Pistoia V. Mesenchymal stem cells in health and disease. Nat Rev Immunol 2008;8:726–36.
Unger C, Skottman H, Blomberg P, Dilber MS, Hovatta O. Good manufacturing practice and clinical-grade human embryonic stem cell lines. Hum Mol Genet 2008;17: R48–53.
Venugopal J, Low S, Choon AT, Kumar AB, Ramakrishna S. Electrospun-modified nanofibrous scaffolds for the mineralization of osteoblast cells. J Biomed Mater Res A 2008;85:408–17.
Venugopal JR, Giri Dev VR, Senthilram T, Sathiskumar D, Gupta D, Ramakrishna S. Osteoblast mineralization with composite nanofibrous substrate for bone tissue regeneration. Cell Biol Int 2011;35:73–80.
Visvanathan J, Lee S, Lee B, Lee JW, Lee SK. The microRNA miR-124 antagonizes the anti-neural REST/SCP1 pathway during embryonic CNS development. Genes Dev 2007;21:744–9.
Wan Y, Wang Y, Liu Z, Qu X, Han B, Bei J, et al. Adhesion and proliferation of OCT-1 osteoblast-like cells on micro- and nano-scale topography structured poly(L-lactide). Biomaterials 2005;26(21):4453–9. Jul.
Wang E, Zhao M, Forrester JV, McCaig CD. Bi-directional migration of lens epithelial cells in a physiological electrical field. Exp Eye Res 2003;76:29–37.
Wang Y, Keys DN, Au-Young JK, Chen C. MicroRNAs in embryonic stem cells. J Cell Physiol 2009;218:251–5.
Wang CY, Zhang KH, Fan CY, Mo XM, Ruan HJ, Li FF. Aligned natural-synthetic polyblend nanofibers for peripheral nerve regeneration. Acta Biomater 2011;7 (2):634–43. Feb.
Wei G, Ma PX. Structure and properties of nano-hydroxyapatite/polymer composite scaffolds for bone tissue engineering. Biomaterials 2004;25:4749–57.
Wilson A, Trumpp A. Bone-marrow haematopoietic-stem-cell niches. Nat Rev Immunol 2006;6:93–106.
Woltjen K, Michael IP, Mohseni P, Desai R, Mileikovsky M, Hämäläinen R, et al. piggyBac transposition reprograms fibroblasts to induced pluripotent stem cells. Nature 2009;458:766–70.
Wutticharoenmongkol P, Pavasant P, Supaphol P. Osteoblastic phenotype expression of MC3T3-E1 cultured on electrospun polycaprolactone fiber mats filled with hydroxyapatite nanoparticles. Biomacromolecules 2007;8:2602–10.
Yamashita YM. The centrosome and asymmetric cell division. Prion 2009;3:84–8.
Yamashita YM, Fuller MT. Asymmetric centrosome behavior and the mechanisms of stem cell division. J Cell Biol 2008;180:261–6.
Yamashita YM, Fuller MT, Jones DL. Signaling in stem cell niches: lessons from the *Drosophila* germline. J Cell Sci 2005;118:665–72.
Yamashita YM, Mahowald AP, Perlin JR, Fuller MT. Asymmetric inheritance of mother versus daughter centrosome in stem cell division. Science 2007;315:518–21.
Yang F, Murugan R, Wang S, Ramakrishna S. Electrospinning of nano/microscale poly(L-lactic acid) aligned fibers and their potential in neural tissue engineering. Biomaterials 2005;26:2603–10.
Yang X, Yang F, Walboomers XF, Bian Z, Fan M, Jansen JA. The performance of dental pulp stem cells on nanofibrous PCL/gelatin/nHA scaffolds. J Biomed Mater Res A 2010;93:247–57.
Yerushalmi R, Scherz A, van der Boom ME, Kraatz HB. Stimuli responsive materials: new avenues toward smart organic devices. J Mater Chem 2005;15:4480–7.
Yi R, Fuchs E. MicroRNAs and their roles in mammalian stem cells. J Cell Sci 2011;124: 1775–83.
Yim EKF, Pang SW, Leong KW. Synthetic nanostructures inducing differentiation of human mesenchymal stem cells into neuronal lineage. Exp Cell Res 2007;313: 1820–9.
You M, Peng G, Li J, Ma P, Wang Z, Shu W, et al. Chondrogenic differentiation of human bone marrow mesenchymal stem cells on polyhydroxyalkanoate (PHA) scaffolds coated with PHA granule binding protein PhaP fused with RGD peptide. Biomaterials 2011;9:2305–13.
Yuan HP, Kurashina K, de Bruijn JD, Li YB, de Groot K, Zhang XD. Preliminary study on osteoinduction of two kinds of calcium phosphate ceramics. Biomaterials 1999;20: 1799–806.
Zardawi SJ, O'Toole SA, Sutherland RL, Musgrove EA. Dysregulation of Hedgehog, Wnt and Notch signalling pathways in breast cancer. Histol Histopathol 2009;24: 385–98.
Zhang R, Ma PX. Processing of polymer scaffolds: phase separation. In: Atala A, Lanza R, editors. Methods of Tissue Engineering. San Diego: Academic Press; 2001. p. 715.
Zhang JC, Lu HY, Lv GY, Mo AC, Yan YG, Huang C. The repair of critical-size defects with porous hydroxyapatite/polyamide nanocomposite: an experimental study in rabbit mandibles. Int J Oral Maxillofac Surg 2010;39:469–77.
Zuk PA, Zhu M, Mizuno H, Huang J, Futrell JW, Katz AJ, et al. Multilineage cells from human adipose tissue: implications for cell-based therapies. Tissue Eng 2001;7: 211–28.