Chapter 16

Biomaterials and Stem Cells: Promising Tools in Tissue Engineering and Biomedical Applications

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Additional information is available at the end of the chapter

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Abstract

Biomaterial sciences and tissue engineering approaches are currently fundamental strategies for the development of regenerative medicine. Stem cells (SCs) are a unique cell type capable of self-renewal and reconstructing damaged tissues. At the present time, adult SCs isolated from postnatal tissues are widely used in clinical applications. Their characteristics such as a multipotent differentiation capacity and immunomodulatory activity make them a promising tool to use in patients. Modern material technologies allow for the development of innovative biomaterials that closely correspond to requirements of the current biomedical application. Biomaterials, such as ceramics and metals, are already used as implants to replace or improve the functionality of the damaged tissue or organ. However, the continuous development of modern technology opens new insights of polymeric and smart material applications. Moreover, biomaterials may enhance the SCs biological activity and their implementation by establishing a specific microenvironment mimicking natural cell niche. Thus, the synergistic advancement in the fields of biomaterial and medical sciences constitutes a challenge for the development of effective therapies in humans including combined applications of novel biomaterials and SCs populations.

Keywords: adult stem cells, biomaterials, regenerative medicine, tissue engineering

1. Introduction

Regenerative medicine represents a new interdisciplinary field of clinical science focused on the development and implementation of novel strategies to enhance the process of regeneration of impaired cells, tissues and organs as well as replacing damaged cells with new, fully functional cells of the required phenotype [1, 2].

To improve the effectiveness of such regeneration processes, one of the potential approaches is application of stem cell (SC)-based therapy. In addition, the combination of stem cells with biocompatible materials that may constitute a scaffold for the seeded cells may lead to enforcement of biological activity of stem cells and as such accelerate the process of regeneration or restoration of impaired tissue [3, 4].

2. Therapeutic applications of stem cells

2.1. Classification and characteristics of stem cells (SCs)

Stem cells (SCs) are a unique type of cells characterized by the ability to (i) self-renewal through unlimited cell divisions and (ii) differentiate into other types of specialized cells, including epithelial, muscle, neuronal cells and others [5, 6].

Based on the origin and source of isolation, SCs may be included in two main groups: (i) embryonic SCs (ESCs)—derived from embryos at different stages of development and (ii) adult SCs (ASCs)—isolated from several postnatal and adult tissue sources, including the umbilical cord, cord blood, bone marrow, adipose tissue, central nervous system, retina, skeletal muscle and other mature tissues [7, 8]. The differentiation capacity of embryonic SCs allows them to form any individual organs and fully differentiated cells of the whole body, which corresponds to pluripotency of these SCs. In opposite, most of adult SCs are multipotent and lineage-restricted (monopotent) and generally give rise to certain cell types of one germ layer or cell lineage. They residue in several niches, including bone marrow, liver, muscle, brain and others, where they may be activate towards tissue- or organ-specific cells under certain physiologic or experimental conditions. Moreover, it has been shown that adult SCs may provide efficient regeneration of impaired organs in both preclinical and clinical conditions [7].

Based on the differentiation capacity, SCs populations belong to the following types [5, 9–11]:

- Totipotent SCs (TSCs)—The most developmentally primitive and potent SCs are capable to differentiate into any cell type from three germ layers (mesoderm, ectoderm and endoderm) forming whole organism as well as into extra-embryonic tissues such as placenta; the best examples of TSCs are zygote and first blastomeres [10–13].
- Pluripotent SCs (PSCs)—The cells sustaining the capacity to differentiate into all cell types from three germ layers, but they are not able to give rise to placenta; PSCs are naturally present in developing embryo in stage of morula, in inner cell mass (ICM) of developing blastocyst and in the epiblast of gastrula and in limited number may also be found in adult tissues as remnants from embryonic development [9, 14]; PSCs may also be de novo created via genetic reprogramming of somatic cells and are called 'induced PSCs' (iPS cells) [11, 15].
- Multipotent SCs—The SCs typically capable to give rise to all cell types within one germ layer; the best described examples are mesenchymal SCs (MSCs) isolated from several adult and postnatal tissues [10, 16–18];

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- Unipotent SCs (progenitors)—The cells capable to differentiate into one or two particular types of specialized cell present in particular tissue type; this group includes several population of tissue-committed progenitors such as endothelial progenitor cells, cardiac SCs, satellite cells of skeletal muscles, neural progenitors and others [5, 9, 10].

2.2. Types of SCs with potential clinical application

Recently, more attention has been directed to potential utilization of SCs in clinical applications in patients. Due to the legal and ethical restrictions, the employment of embryonic SCs, which possess the largest spectrum of differentiation capacity, is controversial and prohibited in many countries. Moreover, SCs with pluripotent characteristics may lead to adverse side effects following their injection including teratoma formation [19, 20]. Therefore, the therapies employing adult SCs play a major role in human treatment as safe and effective approaches. Transplantations of autologous SCs isolated from mobilized peripheral blood or bone marrow are currently widely used in haematological patients with malignancies such as leukaemia and lymphoma [21]. Moreover, haematopoietic stem cells (HSCs) residing predominantly in adult bone marrow are widely used for bone marrow reconstitution in patients suffering from several genetic and autoimmune diseases, blood cancers and haematopoietic defects [5, 7].

Current growing expectations for further advancements in regenerative medicine are highly focused on mesenchymal stem/stromal cells (MSCs) belonging to adult SCs isolated from several tissue types [16, 18, 22, 23]. MSCs are multipotent, non-haematopoietic cells, which can be isolated from various sources including bone marrow, adipose tissue, cord blood, umbilical cord, Wharton's jelly and other tissues of the adult organism [22, 24]. Isolation of this type of cells does not raise any ethical concerns and is a relatively easy procedure. Moreover, MSCs are characterized by low immunogenicity with simultaneous immunomodulatory effect, and after transplantation, teratoma formation does not occur in the recipient organism [16, 18, 22, 23, 25]. Furthermore, potential regenerative applicability of MSCs is also enhanced by their paracrine activity related to several molecules released to their environment that may impact on other neighbouring cells affecting their functions [22, 25]. MSCs produce and release bioactive molecules, including multitude growth factors (e.g. TGF-β1, bFGF, BMP-4), anti-inflammatory factors (e.g. IL-10, PGE2, HGF) and cytoprotective agents (e.g. IL-6, MCP-1, IGF-1), which promote resident cells to divide and remodel the damaged tissue [26]. All these listed features make MSCs as promising tool for biomedical research.

MSCs possess a robust proliferation capacity as well as a potential to differentiate into several lineages of mesodermal origin, including bone, cartilage and adipose tissue [23]. Moreover, they have been also shown to give rise to other cell types, such as endothelial, cardiac or liver cells, which may also be utilized in tissue regeneration [16, 27]. These unique biological values may be utilized for the development of personalized treatment strategy for several diseases and provide the progress in establishing modern cell-based therapy. Cell-based therapy represents a promising perspective of treatment directed at the regeneration of damaged tissues or organs using stem cells or progenitor cells both in the autologous and allogeneic system [16, 28–30].

According to the current U.S. National Institutes of Health database including clinical trials conducted worldwide, there are currently more than 240 clinical trials being conducted in the world employing MSCs in patients [31]. Examples of the application of MSCs isolated from different sources in the treatment of selected diseases are shown in **Table 1**.

One of the great new opportunities in medical science is the possibility of obtaining the induced pluripotent SCs (iPS cells) by genetic reprogramming of mature cells into the stage of pluripotency [15]. Due to the discovery of this phenomenon, professor Shinya Yamanaka was honoured with the Nobel Prize in medicine and physiology in 2012. Since then, iPS cells constitute an excellent model for *in vitro* studies of molecular mechanisms associated with the development and progression of several diseases, including Parkinson's disease [32], Huntington disease [33], Down syndrome [34] and others. Moreover, dozens of laboratories are questing for optimal utilization of these cells in tissue regeneration. However, due to the possibility of teratoma formation after iPS transplantation, their applications in medicine are still limited.

Thus, despite the fact that several new rising SCs types are being examined and optimized for future applications, the most commonly applicable SCs in cell therapies of distinct human diseases are adult stem cells including predominantly MSCs derived from bone marrow, adipose tissue and umbilical cord as well as HSCs harvested from bone marrow, mobilized peripheral blood and cord blood [16, 18, 28–30].

Type of MSCs	Condition	ClinicalTrials.gov identifier
Umbilical cord-derived MSCs	Hepatic cirrhosis	NCT02652351
	Aplastic anaemia	NCT03055078
	Stroke	NCT02580019
	Pneumoconiosis	NCT02668068
	Rheumatoid arthritis	NCT02643823
	Sweat gland diseases	NCT02304562
Bone marrow-derived MSCs	Acute myocardial infarction	NCT01652209
	Chronic myocardial ischaemia	NCT02460770
	Acute respiratory distress syndrome	NCT02097641
	Middle cerebral artery infarction	NCT01461720
	Prostate cancer	NCT01983709
	Stroke	NCT02564328
Adipose-derived MSCs	Infantile spinal muscular atrophy	NCT02855112
	Multiple sclerosis	NCT02326935
	Hair restoration	NCT02865421

Source: Ref. [31].

Table 1. The application of MSCs in selected clinical trials.

2.3. Utilization of SC derivatives as a potential alternative to cell-based therapy

Immunomodulatory properties of SCs are important features involved in tissue repair, which are directly related to their paracrine activity. Despite the directly released molecules, mammalian cells, including SCs, are able to produce extracellular vesicles (EVs) carrying bioactive factors, which may additionally be involved in the modulation of the repair process of damaged tissues [35]. EVs represent heterogeneous population of small, circular structures surrounded with the protein-lipid membrane that are released by cells including SCs. Importantly, the size and molecular composition of EVs are different and unique depending on the cell type of origin and the mechanism of their biogenesis. Depending on the size of EVs, they may be distinguished in apoptotic bodies (1–5 μm), microparticles (100 nm–1 μm) and exosomes (30–100 nm) fractions [36, 37].

Several recent scientific reports indicate that EVs express surface markers characterizing the cells from which they are released, along with EV-specific antigens including tetraspanins (CD9, CD63 and CD81), endosome or membrane-binding proteins (TG101), signal transduction or scaffolding proteins (syntenin) [36, 37]. Importantly, EVs may also include various types of bioactive components (e.g. mRNA, miRNA and enzymes), as well as receptors, adhesion or signalling proteins [38, 39]. Importantly, the contents of EVs can be effectively transferred to the target cells, change their function and impact in the regeneration of impaired tissues. Moreover, the presence of protein-lipid membrane on the surface of EVs can protect their bioactive content from extracellular enzymes and therefore the cargo may be delivered in a fully functional form into targeted cells [38, 40]. Thus, EVs are recognized as mediators of intercellular communication and constitute an alternative or reinforcement of a standard cell-based therapy.

The biological relevance of EVs has been established in different experimental settings. Depending on the origin and content of EVs, they may enhance immune system, endorse anti-tumour responses and thus may provide important tools for novel anti-tumour therapies, such as melanoma treatment [41]. EVs may also be utilized as drug delivery vehicles [42], in regenerative medicine [43] and immune therapy [44]. Recently, our study also indicated that SC-derived EVs may be utilized as a novel tool for regenerative therapies of ischemic tissue including in heart repair [38, 40].

However, further studies are required for comprehensive analysis of the mechanisms of EVs action and potential clinical applications of these promising SC derivatives.

3. Medical application of selected natural and synthetic biomaterials

3.1. Material requirements for biomaterials

Biomaterial by definition is a 'substance (other than a drug), synthetic or natural, that can be used as a system or part of a system that treats, augments, or replaces any tissue, organ, or function of the body' [45]. Thus, according to the definition biomaterials are progressively

used in tissue engineering. They may be utilized for the construction of implants to replace lost or damaged organs or tissues and may also constitute a scaffold for enhanced stem cells to reconstruct not fully functional tissue [45, 46].

Due to the wide range of potential applications of biomaterials in regenerative medicine, their physical and chemical properties may be different [45, 47]. However, in order to use a biomaterial in medical application, it should follow relevant requirements such as biocompatibility and biofunctionality [45, 47]:

- Biocompatibility is the ability to integrate with the recipient's cells in a safe manner and without adverse side effects.
- Biofunctionality is the ability to perform a specific biological function, based on the relevant parameters of the physical and mechanical properties.

Other important properties of biomaterials, which are affecting the potential application in medicine, include [45, 48, 49] the following:

- Biodegradation—Decomposition of the material in a natural way, when degradation products remain in the human body but without adverse side effects.
- Bioresorbability—Decomposition of the material in a natural way at a certain period of time after implantation. Non-toxic-degraded products are removed from the body *via* metabolic pathways (hydrolytic or enzymatic degradation).
- Non-toxicity—From the surface or porous of the material does not elute any toxic components, such as surfactants, stabilizers, catalysts, pigments and UV absorbents, which were used during production and that are incompatible with living organisms.
- Mechanical properties—Biomaterial should possess particular mechanical properties consistent with the anatomical site into which it will be implanted.

3.2. Applications of biomaterials

Several biomaterials useful for distinct applications in medical sciences, including in tissue repair and organ reconstruction, have already been developed over the last few decades [45, 47]. The biomaterial sciences are currently one of the highly advancing fields, which also closely cooperate with biotechnological and medical studies. Recent advancement in regenerative medicine strongly requires such strong support from biomaterial sciences, which may provide novel solutions for tissue repair [4, 49].

Among the biomaterials recognized and developed for potential medical purposes, here are multitude materials commonly present in natural sources or *de novo* designed and created for such purposes.

3.2.1. Naturally derived biomaterials

Natural materials commonly present in nature such as agarose, collagen, alginate, chitosan, hyaluronate or fibrin fully cooperate with living tissues of the recipient and possess low

cytotoxicity [47, 48]. Moreover, they may exhibit specific protein-binding sites that improve integration with cells after transplantation [48]. Thus, they are considered predominantly interesting for tissue engineering applications.

One of the most common natural biomaterials is collagen—an important component of connective tissue, including bones, tendons, ligaments and skin [46, 50]. Collagen is simply absorbed into the body, is non-toxic and exhibits a low immune response and as such is a perfect biocompatible material with an adequate mechanical strength and flexibility for several applications. Moreover, collagen enhances cell adhesion to such surface, stimulates also biological interactions between cells and facilitates restoration of the natural microenvironment of cell niche and thereby may support the reconstruction of several damaged tissues [46, 48, 50].

Collagen may be employed for tissue engineering in the form of sponges, gels, hydrogels and sheets. It may also be chemically crosslinked in order to enhance or alter the rate of degradation of the fibres [51]. Currently, collagen preparations are used predominantly in wound healing and cartilage regeneration. Injectable form of collagen is used for cosmetic and aesthetic medicine as a tissue filler. In addition, collagen-based membranes are used in the periodontal treatment as a barrier preventing the migration of epithelial cells. It also forms a favourable microenvironment for stem cells to facilitate reconstruction of the damaged area [50, 51].

3.2.2. Synthetic biomaterials

Synthetic materials are considered as an alternative to natural materials. Due to their defined chemical composition and the ability to control the mechanical and physical properties, they are extensively used in therapeutic applications and basic biological studies [48, 52–55].

Due to distinct variants of polymerization reaction and formation of co-polymers, multiple synthetic polymers with wide range of physical and chemical properties may be achieved in chemical laboratories. Moreover, novel technologies in the synthesis and formation of more complex structures allow for the production of advanced composites [54]. Synthetic polymers, such as poly(ethylene) (PE), polyurethanes (PUR), polylactides (PLA) and poly(glycolide) (PGA), are widely employed as implants and components of medical devices [56]. Moreover, polymers may constitute suitable scaffold for cell propagation and enhance their biological activity, including neural stem cells, retinal progenitor cells or smooth muscle cells [55, 57, 58]. Thus, this group of biomaterials is currently in a special focus of scientists working on combined approaches using biocompatible scaffolds and stem cells for tissue repair [55, 57, 58].

Biodegradable polymers, including polyhydroxycarboxylic acids, such as PGA, PLA, poly(3-hydroxybutyrate), poly(4-hydroxybutyrate) and poly(∈-caprolactone) (PCL) are of wide interest in the development of novel technologies [56]. One of their potential applications is utilization in the treatment of cardiovascular diseases. Our recent studies have shown the positive impact of both PCL and PLA scaffolds on proliferation, migration and proangiogenic potential of mesenchymal SCs derived from umbilical cord tissue *in vitro*, suggesting the possible applications of these materials in cardiovascular repair *in vivo* (unpublished data) [59].

Synthetic polymers may also be used in biodegradable stents implanted after a heart attack and greatly contribute to patient recovery [56]. Importantly, the material should have suitable decomposition kinetics. Too long decomposition time (i.e. in the case of PLA or PGA) may lead to late stent thrombosis or blockages [56, 60]. One of a possible solution of this problem is to use rapidly biodegradable polymer stents coated with SCs to help rebuild damaged tissue and additionally stimulate resident cells to grow.

Other types of common synthetic materials useful for biomedical applications are ceramics. It has been well described that ceramic scaffolds, such as, for example, hydroxyapatite (HA) and tri-calcium phosphate (TCP), are characterized by biocompatibility, high mechanical stiffness (Young's modulus), very low elasticity and a hard brittle surface [49]. Due to their chemical and structural similarity to the mineral phase of native bone, these materials may enhance osteoblast proliferation and therefore they are widely utilized in bone regeneration [61, 62]. Moreover, ceramics may be exploited in dental and orthopaedic procedures to fill bone defects or as a bioactive coating material for implants to increase their integration after transplantation [63, 64]. However, their clinical applications are still limited due to the difficulties with the ability to change the shape of the material dedicated for transplantation and controlling time of their degradation rate [49, 65].

Similarly, titanium (Ti)-based metallic materials have been widely optimized for bone repair due to their mechanical properties and resistance to corrosion following the transplantation [66–68]. It has been shown that titanium scaffolds are effectively colonized by osteoblasts responsible for bone formation and this process may be enhanced *via* additional modifications of the scaffold surface by its roughening, coating with HA or graphene oxide (GO), as well as its biofunctionalization with bioactive molecules such as heparin and bone morphogenetic protein 2 (BMP-2) [69–72].

Importantly, graphene in its different forms is currently being considered as a potential new promising material for biomedical applications including tissue repair [73, 74]. This 2D carbon biocompatible material exhibits great electrical, conductive and physical properties, which make it interesting for potential applications for drug delivery and scaffold coating in regenerative therapies [74, 75]. It has been shown that graphene may enhance osteogenic differentiation of SCs [72, 73]. Moreover, our recent data also suggest the beneficial impact of graphene oxide (GO) on proliferative capacity, viability and differentiation potential of umbilical cord tissue-derived MSCs, which confirms the possibility of future graphene employment in tissue repair [76].

3.2.3. Hydrogels

Hydrogels are frequently used biomaterials in the biomedical applications and represent systems consisting of two or more compartments comprising a three-dimensional (3D) network of polymer chains and water that fills the spaces between the macromolecules [77, 78]. The main characteristics of hydrogels include the biocompatibility and ability to swell in solution until they reach a state of equilibrium. These allow them to be injected into the body in a non-invasive manner [77, 78].

Hydrogels demonstrate transparency and bioadhesive properties and they are widely used in the pharmaceutical and dermatological industries by local administration or filling the defects caused by injury [77]. They may also be utilized as an injectable material for bone and cartilage tissue engineering, which may be combined with appropriate cell injection [53, 78, 79]. It has been shown that *in situ* implementation of hydrogels promotes osteoblast differentiation [53, 79]. Therefore, injectable therapy constitutes a promising approach for non-invasive technique of transplantation, where also cell-based component may be added to enhance tissue repair.

3.2.4. Smart materials

Smart materials represent a new generation of biomaterials, exceeding the functionality of the currently widely used construction materials. Smart materials are characterized by the ability to alter their physical characteristics in a controlled manner including changing the shape, colour, stiffness or stickiness in response to several external stimuli, such as temperature, hydrostatic pressure, electric and magnetic field or radiation [80]. These changes are related to the revealing or eliciting the new functionality of the material and may be utilized in biomedical applications. Through the common connection between the internal sensor, the activator and a specific control mechanism, smart materials are able to respond to external stimuli. Importantly, these mechanisms are also responsible for the return to the original state, when a stimulant disappeared [80, 81].

Smart materials include several types such as listed below [52, 80, 82–84]:

- **Colour changing materials**—Materials that change colour in a reversible manner, depending on electrical, optical or thermal changes. These types of materials are exploited, for example, in optoelectronic components, lenses, lithium batteries, ferroelectric memory, temperature sensors or as the indicators of battery consumption [80, 81].
- **Light-emitting materials**—Materials emitting visible or invisible light, as a result of external stimuli such as short wavelength radiation (e.g. X-rays, ultraviolet light), temperature and electric voltage. They are utilized in electronics, filters for glasses, devices that detect UV rays, in criminology and in geology to identify minerals and rocks. They may also be exploited as a component of protective clothing, safety elements and warning materials [80, 81].
- **Shape memory materials**—Metal alloys that change shape as a result of temperature increase or decrease, respectively, to the set value. The reversibility of the process is to return to its original shape by changing the temperature or under the influence of the applied motion (the effect of pseudoelasticity). These materials are used in temperature sensors, electronics, robotics, telecommunications and production of medical devices (micro-pump, surgical clamps, orthodontic wire, long- and short-term implants, suture tightening on a stiffen wound, orthopaedic devices, bone nails, clamps, surgical instruments and others) [83, 84].
- **Self-assembling materials**—Materials that exhibit the intrinsic ability to spontaneously connect individual elements into an ordered 2D or 3D structure. In addition, they can also

have the ability to bind metal atoms, ions, molecules or semiconductors. They are widely used in biological research and nanotechnology, that is, in the tissue regeneration, as components for the storage of drugs, crystal engineering, as artificial proteins with pH-sensitive structure, as semi-permeable membrane as well as for the production of electronic processors and displays [52, 82].

- **Self-repairing materials**—Structural damage of this type of material is automatically and autonomously recovered by inducing a change in the shape or the self-assembly of the molecules. This process is not a method of complete repair of the impaired material; however, it may be used in the military, automotive, aviation and electronics industries [52, 82].

4. Novel aspects of the application of stem cells and biomaterials in tissue engineering and regenerative medicine

4.1. Biomaterials approaches for enhancement of SCs-based therapy

Modern approaches in current regenerative medicine include developing biocompatible scaffolds and combining them with living cell of selected type and bioactive molecules, in order to enhance the regeneration process of damaged tissues and organs [47].

Growing evidence indicate different populations of stem cells as a promising tool that may be utilized in tissue engineering and repair. Importantly, despite the regenerative properties of SCs, the restoration processes in damaged tissue are long and may not often be fully effective for functional recovery of damaged tissue. On the other hand, appropriate stimulation of reparative capacity of SCs may be achieved by modulation of chemical and physical properties of optimized biomaterials [47, 70, 77]. Therefore, simultaneous application of optimized and well-combined SCs and biomaterials may open new perspectives for the synergistic effective cooperation of both such components to improve the efficiency of the regeneration process [77]. Biomaterials may enhance the biological activity of SCs by establishing a specific niche related to their native microenvironment. This type of cell-biomaterial interactions leads to stimulation of cell adhesion, proliferation and directed differentiation of the cells implemented at the injured site [47, 70, 77]. Therefore, therapy based on biomaterials and SCs opens new possibilities for the development of innovative medicine [47, 77].

Currently, growing evidence is focused on encapsulation of native SCs prior to their transplantation [47, 85]. Cells encapsulation technique is based on the immobilization of cells in a semi-permeable membrane, which protects cells against mechanical damage and immune system response. Notably, the construction of the microcapsules allows bidirectional diffusion of nutrients, oxygen and wastes and therefore provides appropriate conditions for cell development [47, 85].

Encapsulated cells may be subjected to transplantation and directed differentiation. The material used to construct the microcapsules should possess particular physical properties,

such as biocompatibility, mechanical stability, permeability, appropriate size, strength and durability [47]. One of the most common encapsulation materials is alginate. Due to the fact that the procedure for cell encapsulation using alginate can be performed under physiological conditions (physiological temperature and pH) and using isotonic solutions, it is widely distributed through clinical and industrial applications. Moreover, this natural biodegradable polymer that mimics the extracellular matrix and promotes cell functions and metabolism has been established in cartilage regenerative approaches [86, 87]. Microencapsulation technology represents a novel cell culture system that allows maintaining cell viability and differentiation of interested cell lines. It also may support the extracellular matrix production and cell organization in reconstructed tissue [86].

5. Conclusions

Significant advancement of regenerative medicine, nanomedicine and biomaterials engineering offers extended possibilities to obtain novel, effective achievements, which may be utilized in biomedical applications. The effect of interdisciplinary activity resulted in the development of bioactive scaffolds that promote cell propagation and enhance their biological activity. However, some difficulties in biomaterial- and cell-based therapy are still unclear and need to be addressed for widespread investigations. Nevertheless, integrative research in biomaterials and medicine fields is a challenge to develop effective therapies for cancer, civilization diseases and provide further development of tissue engineering.

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