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# Strategies based on stem cells for tissue engineering

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## ABSTRACT

Cell-therapy is a new approach in medical research field. The increased number of patients, which is reported all over the world, has led to the development of innovative solutions capable of improving wound healing. Stem cells, due to their self-renewal and differentiation capacities, gradually replace the traditional medicine used in the past. Even if the risks of using stem cells exists, the promising results they can offer have led to the design of intelligent materials that can make life easier for patients. Stem cells can be classified by many criteria, but the most important are embryonic and adult stem cells. The ability of embryonic stem cells of differentiate into any type of tissue by various strategies makes them an ideal candidate in tissue engineering applications. Ethical problems must be taken into consideration, so the most used in different therapies are adult stem cells. Nowadays, the applications of stem cells are various. They can be used in order to restore the function of soft and hard tissue and to improve the healing time of a wound. Skin problems, osteogenesis, angiogenesis or fracture healing are some examples of tissue disorders that can be restored by using stem cells therapy and nanotechnology.

**Keywords:** *embryonic stem cells, adult stem cells, differentiation, soft tissue engineering, hard tissue engineering***.**

## 1. INTRODUCTION

Over time, the need of healing different parts of the human body has imposed the expansion of medical research by obtaining promising personalized therapies. Nowadays, tissue engineering has an important contribution in healing disorders. Different approaches are used to rebuild a tissue by developing smart biomaterials capable of diminishing the current challenges or to improve tissue function (Sundaramurthi et al., 2014). Stem cells-based materials are used in biomedical applications due to their structure which provides a similarity with extracellular matrix. Their main advantage is the fact that they can act as a template for growth and differentiation of tissues by having the ability to restore the affected function (Marques et al., 2017, O'brien, 2011).

A new approach in materials science is cell therapy. This therapy involves transplantation of cells to the injured area in order to restore the function (Ojeh et al., 2015). Due to their characteristics, stem cells are an appropriate choice in therapies owing to their potential of self-renewal, differentiation and plasticity. The possibilities of stem cells administration involve introducing them in the damaged area of the organ or introducing them in circulatory system (Mollapour Sisakht et al., 2015). The integration of stem cells in nanomedicine seems to have noticeable progress in the medical field. The development of transportable delivery vehicles for cells therapies, therapeutically agents, gene vectors or growth factors is an innovative method to stimulate wound healing (Mofazzal Jahromi et al., 2018).

Stem cells are undifferentiated cells with self-renewal and differentiation capacities that can transform into specific cells, with a specific function for an organ. In medical research, stem cells have the promise to treat and heal various diseases that traditional pharmaceutical therapies cannot cure (Xian et al., 2018). Recent studies have demonstrated that stem cells exist in many organs of the body. The human body, which has some remarkable mechanisms of self-healing, has the ability of producing stem cells in bone marrow, adipose tissue, skin or even liver (Dulak et al., 2015, Dai et al., 2018).

Stem cells-therapy has a lot of advantages for tissue reconstruction. However, this therapy also involves several risks for the patient. Depending on the source of stem cells, autologous or allogenic, the risk of generating teratomas exists. This process can create serious problems for the receptor through a mis directional and inefficient targeting of these cells once introduced into the body (Xian et al., 2018, Suzuki et al., 2013, Amabile et al., 2013).

In order to avoid such medical complications, it is important to determine the compatibility of the donor with the receptor and to perform tests that confirm the efficiency of cell transplantation.

## 2. STEM CELLS SOURCES

Regenerative medicine is used to restore or replace a damaged tissue caused by various factors. Organ transplantation can be also used, but the number of patients who need a new organ is extended while the number of donors is decreasing. To maintain the life of patients in a larger number, regenerative medicine strategies started to include cell therapy and scaffolds seeded with cells (Hipp and Atala, 2008).

To obtain cells for tissue engineering it is necessary to take a small amount of tissue which is processed in a culture. Cells extracted from the tissue are expanding in the culture and after reaching a degree of confluence, they are introduced into a matrix

which is placed into the injured area. The obtained cells can be autologous, provided from the patient or allogenic, extracted from another donor. The main advantage of autologous cells is the fact that they don't cause any internal injuries in the body and they are accepted by the other tissues. Although this approach seems to be an ideal solution, the limited quantity of cells that can be extracted is not sufficient for a complete regeneration of the tissue (Atala et al., 2006, Hipp and Atala, 2008, De Coppi et al., 2007).

Stem cells have two main important functions: the ability of self-renewing for long periods and the capacity to differentiate in various types of cells (Ramalho-Santos and Willenbring, 2007, Chu et al., 2018). Stem cells have high plasticity. A cell can differentiate by conversion from a specific tissue to another type of tissue and to take over the functions of the new tissue formed by accepting the new identity (Fortier, 2005).

Stem cells are classified under various categories. One of the criteria takes into account level of organization of the human body. Stem cells can be totipotent, pluripotent, multipotent, and monopotent (Bieniasz et al., 2014). Totipotent cells are capable of forming an entire organism, pluripotent cells are found in the blastocyst, multipotent cells can expend only one specific cell type which can belong to one of the three embryonic layers and monopotent cells are targeted to a specific tissue. The human body is formed from three germ layers. The organism is so complex that only these layers are enough to develop from an embryo an entire body (Shiraki et al., 2009). The ectoderm forms the skin and the neural tissue, the mesoderm forms the muscles, kidneys, blood, stomach, cardiac tissue and the ectoderm forms the lungs, the pancreas and the thyroid.

A very important criterion for the classification of stem cells is based on their origin (Aly, 2015). At this moment, there are four sources of stem cells: stem cells from embryos, stem cells from fetus, stem cells from adults (Lodi et al., 2011) and induced pluripotent stem cells. Among these, the adult stem cells can be extracted from many organs, depending on the disease suffered by the receptor.

### 2.1. Embryonic stem cells

After 5-6 days of fertilization, the blastocyst is formed. Embryonic development begins with a human embryo which contains 50-150 cells when the blastocyst is formed. Embryonic stem cells have the origin in the inner mass of a blastocyst (Hui et al., 2011). Embryonic stem cells have some unique characteristics. They are able to differentiate into various derivates of the three germ layers and they have the capacity to proliferate indefinitely, under certain conditions (Ying et al., 2003).

The advantages of pluripotency and resistance under many conditions have led to cell cultures which can be maintained for several passages. Embryonic stem cells can be cultured, frozen or even transported in different places by maintaining their integrity. A problem that is currently common are ethical considerations which must be considered (Chagastelles and Nardi, 2011).

The first embryonic stem cells extracted was murine. As human cells, murine embryonic stem cells can be cultured for an unlimited propagation (Hanna et al., 2010). To remain undifferentiated, murine cells needs some proteins, like leukemia inhibitory factor or murine embryonic fibroblasts (He et al., 2003). In the medical field, in order to detect and to confirm the source of a stem cell within different populations surface markers are used. In the case of embryonic cells, they include SOX-2, Thy-1, Rex-1, LIN28, SSEA-3 or Oct-4 (Rippon and Bishop, 2004).

Differentiation of embryonic stem cells is variable, and it depends on the conditions of the culture. Studies in the literature describe the possibility of forming neurons, cardiomyocytes, pancreatic cells or endothelium. In order to obtain a specific type of cells, some growth factors and proteins are needed. Another possibility to obtain a certain line is introducing some local factors. For example, the introduction of a population of chondrocytes among embryonic cells could lead to cells that can be used to repair the cartilage (He et al., 2003).

### 2.2. Adult stem cells

Adult stem cells, or somatic stem cells, have the role of maintaining the hematopoiesis, replacing dead cells and restoring the functions of the tissues after various injuries. As embryonic cells, adult stem cells are self-renewable, but this process is hard to prove *in vivo*. They are clonogenic and they have the ability to form different types of tissues (Montagnani et al., 2016). In contrast to embryonic stem cells, adult cells have a lower potential of differentiation and a lower rate of proliferation in culture. The localization of these cells is dynamic and they are capable of generating complex microenvironments when they are connected to offer support and when they are inactivated (Singh et al., 2018). In the case on an injured organ, stem cells migrate from the niche and differentiate in the type of cell which is destroyed in order to maintain the tissue function.

Adult stem cells are divided in two categories. They can be hematopoietic stem cell, which are directed to the blood and mesenchymal stem cells, which are going to the other organs such as muscles, bones and liver. For hematopoietic stem cells, the main sources are bone marrow and blood (Ribeiro et al., 2013, Girlovanu et al., 2015). The main function of these cells is to replace blood cells for short periods of time or even throughout the entire life. They are rare, this being the reason why nowadays transplantation is not a solution all the time. Hematopoietic cells are used for autologous or allogenic transplant for bone marrow. In this case, the specific surface markers are CD34, CD133 and ALDH (Mirabelli et al., 2008, Christ et al., 2007).

Mesenchymal stem cells are pluripotent cells which are found in high amount in the bone marrow stroma (Méndez-Ferrer et al., 2010). Other sources for these cells are adipose tissue (Shiratsuki et al., 2015), cardiac tissue (Mayfield et al., 2014), bones or even neural tissue (Calzolari et al., 2015). Their characteristics include a high rate of proliferation and a rapid chemical or mechanical dissociation. Studies reported in the literature has indicated CD90, CD73 and CD105 as surface markers (Alison and Islam, 2009).

In the case of mesenchymal stem cells, adipose tissue is a source that can be easily accessed. Adipose tissue contains various

types of molecules including mature adipocytes in a high percentage and the stromal vascular fraction, in which fibroblasts, endothelial cells, monocytes, macrophages, lymphocytes and adipose stem cells are found. Several studies have demonstrated that a culture based on adipose stem cells can form a homogenous population of mesodermal. By comparison with bone marrow derived stem cells, the adipose cells present a high capacity of proliferation. In cell therapy some factors are determinants. One of them is the age of donor, as the younger the donor is, the greater the chances for the transplant to be successful are. Additionally, culture conditions, location, color or patient conditions are factors that can affect the process (Mizuno et al., 2012).

Adipose-derived stem cells are used in regenerative medicine. They seem to be promising in allogenic cell therapies and in organ transplants in order to restore the structure and function of the tissue. They can secrete some growth factors which can be used for an optimal differentiation. A group of researchers have shown adipose stem cells potential to be involved in angiogenesis. The growth factors produced, such as vascular endothelial growth factor, basic fibroblast growth factor, or angiopoietin-1/2 can induce the cardiac regeneration after a myocardial infarction (Cai et al., 2009, Klar et al., 2017). These results are encouraging for the medical research field because cardiac muscle is the tissue that heals in the lowest percentage from the human body.

## 3. STRATGIES FOR STEM CELLS DIFFERENTIATION

The process of differentiation of stem cells can be influenced by the culture conditions. Pluripotent stem cells are maintained in a media which contains specific growth factors in order to assure cell pluripotency or to induce cellular differentiation. There are three approaches for stem cell differentiation. The development of a co-culture, with other cell types, the formation of embryoid bodies, which are directing the differentiation and monolayer differentiation (Efthymiou et al., 2014).

In a co-culture, specific cells are used, which are called feeder cells, with the role of assuring the external factors that are needed in stem cells differentiation. A problem about this strategy is the lack of control. Having a high number of cells and diversity between them, it is difficult to establish the purity of the differentiation process. Embryoid bodies in suspension act as a support for pure stem cells by mimicking the real embryogenesis. The monolayer system involves the introduction of stem cells in a media supplied with certain proteins or growth factors (Khatiwala and Cai, 2016, Efthymiou et al., 2014).

Another strategy to differentiate stem cells is the use of extracellular matrix. The extracellular matrix maintains the structural integrity of a tissue. It is composed of many proteins, such as collagen, elastin, fibronectin, but it also contains other biological molecules. The use of an extracellular matrix in a culture of stem cells increases the chances of having a directed differentiation of stem cells. For example, the use of a matrix based on collagen can induce the formation of a population of cardiomyocytes. One important aspect is the source of the matrix, as it is important to assure a similarity between the cells and the matrix support, so that the culture has a high purity (Heng et al., 2004).

Developmental programming is a strategy based on directing the embryonic stem cells toward definitive endoderm in order to obtain a specific population of cells, such as hepatocytes or cardiomyocytes. Some recent studies have shown that small molecules can be used to target this differentiation. The cell culture is extremely important, as it is fundamental to have substances that can mimic the real structure of the body or even have some proteins extracted from the host. The addition of Activin A can be used to induce the endoderm. Activin A acts as a natural ligand, named Nodal, which has the role of transforming growth factor-beta signaling so it can begin the endodermal differentiation. With this method, various types of tissue can be obtained. Skin, liver or pancreatic tissues are some of the *in vitro* models presented in the literature (Bernstein and Hyun, 2012, Hou et al., 2013, Burridge et al., 2012).

Engineering micropatterned surfaces of a polymer can be also considered a long-term strategy to direct the human neural stem cells and to modify the differentiation rate (Béduer et al., 2012).

## 4. BIOMEDICAL APPLICATIONS OF STEM CELLS

### 4.1. Soft tissue engineering

The evolution of biomedical engineering has shown promising results for the future of patients worldwide. The design of materials with innovative properties is important for an optimal rate of healing. Nowadays, the technology allows for the fabrication of biomaterials which are tolerated by the human body and which improve the regeneration of organs by offering support.

Tissue engineering is based on biology and engineering and was developed to simplify the patient's life by offering biological substitutions in the case of an injured tissue (Sundaramurthi et al., 2014). Scaffolds, the polymeric biomaterials that are used in regenerative medicine, present the properties necessary for healing. Scaffolds are used for retention and delivery of cells or proteins to the injured area. Acting as a template, they guide the formation of a new tissue (Baino and Vitale-Brovarone, 2011, Alaribe et al., 2016). Scaffolds together with cells and growth factors are the key components of tissue engineering. These materials can be seeded with cells and introduced in a bioreactor, a device that assures the chemical and mechanical conditions for biomaterials (Martin et al., 2004). There are two possibilities to heal a damaged tissue. The cell-seeded scaffolds can be cultured *in vitro* to obtain the tissue which is introduced in a final form in the body or the cell-seeded scaffolds can be brought at the injured site allowing the body to induce

regeneration (O'brien, 2011, Chaudhari et al., 2016). Soft tissue engineering is addressed to skin problems. Skin, an important organ with an extended area (Lai-Cheong and McGrath, 2009), has some important functions. It protects us from external factors (Kolarsick et al., 2011), acts as a barrier to prevent the loss of necessary fluids from the body and creates an isothermal barrier (Varkey et al., 2015, Zomer and Trentin, 2018). Many factors can destroy the skin. In order to reduce the wounds, stem cells seeded in scaffolds can be used.

Stem cells-scaffolds can be made of various polymers. Natural polymers have the advantages of not inducing a response of the immune system once implanted in the body (Debels et al., 2015). Collagen is used in such applications due to the specific characteristics. It is biocompatible, non-toxic, offers similarity with the extracellular matrix and it is easy to extract, comparing to other natural polymers (Dong and Lv, 2016, Parenteau-Bareil et al., 2010, Gómez-Guillén et al., 2011). Many other polymers can be used such us alginate, silk or chitosan. These suggestions are confirmed by the high number of biomaterials reported in literature. According to Mohajeri et al., a collagen sponge reinforced with polypropylene blend fibers was successfully used as a scaffold for stem cells which, after the *in vitro* tests, have shown a high rate of proliferation and differentiation (Mohajeri et al., 2010).

### 4.2. Hard tissue engineering

In hard tissue engineering the main subject is the bone. Bone is a complex organ, so the characteristics of a biomaterial are important. Bone regeneration includes the migration, proliferation and differentiation of osteoprogenitor cells, the entire process finalizing with bone remodeling (Li et al., 2013). In medical research, some new techniques were employed in order to obtain a better cellular integration without producing any inflammation. Over time, for hard tissue engineering were used metals. To obtain a better and faster healing, researchers have introduced the polymeric materials capable of offering support, but also of being seeded with stem cells (Liu et al., 2013). For osteoporosis, natural materials such as green tea can be used for differentiation and guidance of bone marrow thus decreasing the bone resorption (Ortiz et al., 2018). Laser surface micro structuring is a method that, according to some recent studies, can promote osteogenesis by modifying the surface topography of a biomaterial which includes stem cells. Pores, grooves or pits can induce the transformation of mesenchymal stem cells into a tissue with specific properties (Béduer et al., 2012, Khang et al., 2012, Ortiz et al., 2018).

Bone scaffolds can be made of porous polymers which can offer a better integration of body cells. The main problem of a medical device implanted in the body is the angiogenesis. It is very important that new blood vessel can form for an optimal healing. To produce osteogenesis and angiogenesis, proteins, growth factors and stem cells can be used (Bose et al., 2012, Bramfeld et al., 2010). According to Zhang et al, an innovative scaffold based on silk loaded with stem cells was used as an implantable device. The role of this biomaterial was to support and transport the stem cells to the wounded tissue. *In vitro* and *in vivo* tests have shown potential regarding these materials by determining a better osteogenesis and a high rate of cell proliferation (Zhang et al., 2014).

Bone regeneration involves also the nanotechnology which can assure superior properties of the material. Magnetic nanoparticles can be used in applications for bone tissue engineering due to the fact that cells react to magnetic and mechanical stimulation (Chen et al., 2013). According to Xia Y. et al (2018), magnetic field can be used to improve the properties of a stem-cell scaffold by allowing a better integration in the tissue. Superparamagnetic iron oxide nanoparticles provide an effective strategy for cell-targeted therapies. Magnetic field and nanoparticles can support the osteogenesis by placing the cells distribution at a control pattern. By controlling the distribution and the density of cells and by modifying the intensity of magnetic field, regeneration of bone can be easily accomplished (Xia et al., 2018).

Stem cells are also used in muscle or cartilage tissue engineering by being introduced in the body through a porous scaffold or an implantable device. According to Fuoco C. et al. (2016), mesenchymal stem cells are capable of differentiate into skeletal muscle tissue. Recent studies have proved that differentiation can occur *in vivo* by assuring an optimal microenvironment with a high amount of oxygen. In case of skeletal muscle tissue, it is necessary to accomplish the mechanical properties and to have an interconnectivity of the tissues (Fuoco et al., 2016). Biomaterials used for this type of scaffolds must offer a support, but also be biocompatible and accepted by the areas around the wound or the fracture.

## 5. CONCLUSIONS AND FUTURE PERSPECTIVES

Cell therapy is a new approach in tissue engineering which is continuously used in the medical field. The advantages of having some biological structures have led to the design of various biomaterials seeded with stem cells. Depending on the possibilities and on the organ that must be replaced, researchers can use hematopoietic stem cells or mesenchymal stem cells. The ethical problems must be taken into consideration because, even if it seems that the embryonic stem cells are better than adult cells, there are some rules to be respected. Nowadays, stem cells therapy, along with biotechnology and tissue engineering, is in continuous development.

As future perspectives, the possibilities of using stem cells should involve easier processing and extraction methods in order to develop novel innovative biomaterials. These materials will be capable of eliminating the risks that exist from transplants between patients.

## 6. REFERENCES


Alaribe, F.N., Manoto, S.L. & Motaung, S.C. **(2016)**. Scaffolds from biomaterials: Advantages and limitations in bone and tissue engineering. *Biologia,* 71**,** 353-366.

Alison, M. & Islam, S. **(2009)**. Attributes of adult stem cells. *The Journal of Pathology: A Journal of the Pathological Society of Great Britain and Ireland,* 217**,** 144-160.

Aly, L.a.A. **(2015)**. Stem cells: Sources, and regenerative therapies in dental research and practice. *World journal of stem cells,* 7**,** 1047-1053.

Amabile, G., Welner, R.S., Nombela-Arrieta, C., D'alise, A.M., Di Ruscio, A., Ebralidze, A.K., Kraytsberg, Y., Ye, M., Kocher, O., Neuberg, D.S., Khrapko, K., Silberstein, L.E. & Tenen, D.G. **(2013)**. In vivo generation of transplantable human hematopoietic cells from induced pluripotent stem cells. *Blood,* 121**,** 1255-1264.

Atala, A., Bauer, S.B., Soker, S., Yoo, J.J. & Retik, A.B. **(2006)**. Tissue-engineered autologous bladders for patients needing cystoplasty. *The lancet,* 367**,** 1241-1246.

Baino, F. & Vitale-Brovarone, C. **(2011)**. Three-dimensional glass-derived scaffolds for bone tissue engineering: Current trends and forecasts for the future. *Journal of Biomedical Materials Research Part A,* 97A**,** 514-535.

Béduer, A., Vieu, C., Arnauduc, F., Sol, J.-C., Loubinoux, I. & Vaysse, L. **(2012)**. Engineering of adult human neural stem cells differentiation through surface micropatterning. *Biomaterials,* 33**,** 504-514.

Bernstein, H.S. & Hyun, W.C. **(2012)**. Strategies for enrichment and selection of stem cell-derived tissue precursors. *Stem cell research & therapy,* 3**,** 17.

Bieniasz, M., Chmura, A. & Kwiatkowski, A. **(2014)**. Stem cells–general characteristic and sources. *MEDtube Science Jun,* 2**,** 8-14.

Bose, S., Roy, M. & Bandyopadhyay, A. **(2012)**. Recent advances in bone tissue engineering scaffolds. *Trends in biotechnology,* 30**,** 546-554.

Bramfeld, H., Sabra, G., Centis, V. & Vermette, P. **(2010)**. Scaffold vascularization: A challenge for three-dimensional tissue engineering. *Current medicinal chemistry,* 17**,** 3944-3967.

Burridge, P.W., Keller, G., Gold, J.D. & Wu, J.C. **(2012)**. Production of de novo cardiomyocytes: Human pluripotent stem cell differentiation and direct reprogramming. *Cell stem cell,* 10**,** 16-28.

Cai, L., Johnstone, B.H., Cook, T.G., Tan, J., Fishbein, M.C., Chen, P.S. & March, K.L. **(2009)**. Ifats collection: Human adipose tissue-derived stem cells induce angiogenesis and nerve sprouting following myocardial infarction, in conjunction with potent preservation of cardiac function. *Stem cells,* 27**,** 230-237.

Calzolari, F., Michel, J., Baumgart, E.V., Theis, F., Götz, M. & Ninkovic, J. **(2015)**. Fast clonal expansion and limited neural stem cell self-renewal in the adult subependymal zone. *Nature neuroscience,* 18**,** 490.

Chagastelles, P.C. & Nardi, N.B. **(2011)**. Biology of stem cells: An overview. *Kidney International Supplements,* 1**,** 63-67.

Chaudhari, A., Vig, K., Baganizi, D., Sahu, R., Dixit, S., Dennis, V., Singh, S. & Pillai, S. **(2016)**. Future prospects for scaffolding methods and biomaterials in skin tissue engineering: A review. *International journal of molecular sciences,* 17**,** 1974.

Chen, J., Rungsiyakull, C., Li, W., Chen, Y., Swain, M. & Li, Q. **(2013)**. Multiscale design of surface morphological gradient for osseointegration. *Journal of the Mechanical Behavior of Biomedical Materials,* 20**,** 387-397.

Christ, O., Lucke, K., Imren, S., Leung, K., Hamilton, M., Eaves, A., Smith, C. & Eaves, C. **(2007)**. Improved purification of hematopoietic stem cells based on their elevated aldehyde dehydrogenase activity. *haematologica,* 92**,** 1165-1172.

Chu, G.-Y., Chen, Y.-F., Chen, H.-Y., Chan, M.-H., Gau, C.-S. & Weng, S.-M. **(2018)**. Stem cell therapy on skin: Mechanisms, recent advances and drug reviewing issues. *Journal of Food and Drug Analysis,* 26**,** 14-20.

Dai, R., Hua, W., Xie, H., Chen, W., Xiong, L. & Li, L. **(2018)**. The human skin-derived precursors for regenerative medicine: Current state, challenges, and perspectives. *Stem cells international.*

De Coppi, P., Bartsch Jr, G., Siddiqui, M.M., Xu, T., Santos, C.C., Perin, L., Mostoslavsky, G., Serre, A.C., Snyder, E.Y., Yoo, J.J., Furth, M.E., Soker, S. & Atala, A. **(2007)**. Isolation of amniotic stem cell lines with potential for therapy. *Nature Biotechnology,* 25**,** 100.

Debels, H., Hamdi, M., Abberton, K. & Morrison, W. **(2015)**. Dermal matrices and bioengineered skin substitutes: A critical review of current options. *Plastic and reconstructive surgery Global open,* 3.

Dong, C. & Lv, Y. **(2016)**. Application of collagen scaffold in tissue engineering: Recent advances and new perspectives. *Polymers,* 8**,** 42.

Dulak, J., Szade, K., Szade, A., Nowak, W. & Józkowicz, A. **(2015)**. Adult stem cells: Hopes and hypes of regenerative medicine. *Acta Biochimica Polonica,* 62.

Efthymiou, A.G., Chen, G., Rao, M., Chen, G. & Boehm, M. **(2014)**. Self-renewal and cell lineage differentiation strategies in human embryonic stem cells and induced pluripotent stem cells. *Expert opinion on biological therapy,* 14**,** 1333-1344.

Fortier, L.A. **(2005)**. Stem cells: Classifications, controversies, and clinical applications. *Veterinary Surgery,* 34**,** 415-423.

Fuoco, C., Petrilli, L.L., Cannata, S. & Gargioli, C. **(2016)**. Matrix scaffolding for stem cell guidance toward skeletal muscle tissue engineering. *Journal of orthopaedic surgery and research,* 11**,** 86.

Girlovanu, M., Susman, S., Soritau, O., Rus-Ciuca, D., Melincovici, C., Constantin, A.-M. & Mihu, C.M. **(2015)**. Stem cells-biological update and cell therapy progress. *Clujul medical,* 88**,** 265.

Gómez-Guillén, M., Giménez, B., López-Caballero, M.A. & Montero, M. **(2011)**. Functional and bioactive properties of collagen and gelatin from alternative sources: A review. *Food hydrocolloids,* 25**,** 1813-1827.

Hanna, J., Cheng, A.W., Saha, K., Kim, J., Lengner, C.J., Soldner, F., Cassady, J.P., Muffat, J., Carey, B.W. & Jaenisch, R. **(2010)**. Human embryonic stem cells with biological and epigenetic characteristics similar to those of mouse escs. *Proceedings of the National Academy of Sciences of the United States of America,* 107**,** 9222-9227.

He, Q., Li, J., Bettiol, E. & Jaconi, M.E. **(2003)**. Embryonic stem cells: New possible therapy for degenerative diseases that affect elderly people. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences,* 58**,** M279-M287.

Heng, B.C., Haider, H.K., Sim, E.K.-W., Cao, T. & Ng, S.C. **(2004)**. Strategies for directing the differentiation of stem cells into the cardiomyogenic lineage in vitro. *Cardiovascular research,* 62**,** 34-42.

Hipp, J. & Atala, A. **(2008)**. Sources of stem cells for regenerative medicine. *Stem cell reviews,* 4**,** 3-11.

Hou, P., Li, Y., Zhang, X., Liu, C., Guan, J., Li, H., Zhao, T., Ye, J., Yang, W. & Liu, K. **(2013)**. Pluripotent stem cells induced from mouse somatic cells by small-molecule compounds. *Science***,** 1239278.

Hui, H., Tang, Y., Hu, M. & Zhao, X. **(2011)**. Stem cells: General features and characteristics. *Stem cells in clinic and research.* InTech.

Khang, D., Choi, J., Im, Y.-M., Kim, Y.-J., Jang, J.-H., Kang, S.S., Nam, T.-H., Song, J. & Park, J.-W. **(2012)**. Role of subnano-, nano- and submicron-surface features on osteoblast differentiation of bone marrow mesenchymal stem cells. *Biomaterials,* 33**,** 5997-6007.

Khatiwala, R. & Cai, C. **(2016)**. Strategies to enhance the effectiveness of adult stem cell therapy for ischemic heart diseases affecting the elderly patients. *Stem Cell Reviews and Reports,* 12**,** 214-223.

Klar, A.S., Zimoch, J. & Biedermann, T. **(2017)**. Skin tissue engineering: Application of adipose-derived stem cells. *BioMed research international,* 2017.

Kolarsick, P.A., Kolarsick, M.A. & Goodwin, C. **(2011)**. Anatomy and physiology of the skin. *Journal of the Dermatology Nurses' Association,* 3**,** 203-213.

Lai-Cheong, J.E. & Mcgrath, J.A. **(2009)**. Structure and function of skin, hair and nails. *Medicine,* 37**,** 223-226.

Li, X., Wang, L., Fan, Y., Feng, Q., Cui, F.Z. & Watari, F. **(2013)**. Nanostructured scaffolds for bone tissue engineering. *Journal of Biomedical Materials Research Part A,* 101**,** 2424-2435.

Liu, Y., Lim, J. & Teoh, S.-H. **(2013)**. Development of clinically relevant scaffolds for vascularised bone tissue engineering. *Biotechnology advances,* 31**,** 688-705.

Lodi, D., Iannitti, T. & Palmieri, B. **(2011)**. Stem cells in clinical practice: Applications and warnings. *Journal of experimental & clinical cancer research : CR,* 30**,** 9-9.

Marques, C., Suzuki, D. & Marques, J. **(2017)**. Tissue engineering and regenerative medicine in skin wound healing: What has been done recently-a mini review. *Advances in Tissue Engineering and Regenerative Medicine,* 2**,** 219-221.

Martin, I., Wendt, D. & Heberer, M. **(2004)**. The role of bioreactors in tissue engineering. *Trends in biotechnology,* 22**,** 80-86.

Mayfield, A.E., Tilokee, E.L. & Davis, D.R. **(2014)**. Resident cardiac stem cells and their role in stem cell therapies for myocardial repair. *Canadian Journal of Cardiology,* 30**,** 1288-1298.

Méndez-Ferrer, S., Michurina, T.V., Ferraro, F., Mazloom, A.R., Macarthur, B.D., Lira, S.A., Scadden, D.T., Ma'ayan, A., Enikolopov, G.N. & Frenette, P.S. **(2010)**. Mesenchymal and haematopoietic stem cells form a unique bone marrow niche. *nature,* 466**,** 829.

Mirabelli, P., Di Noto, R., Lo Pardo, C., Morabito, P., Abate, G., Gorrese, M., Raia, M., Pascariello, C., Scalia, G., Gemei, M., Mariotti, E. & Del Vecchio, L. **(2008)**. Extended flow cytometry characterization of normal bone marrow progenitor cells by simultaneous detection of aldehyde dehydrogenase and early hematopoietic antigens: Implication for erythroid differentiation studies. *BMC physiology,* 8**,** 13-13.

Mizuno, H., Tobita, M. & Uysal, A.C. **(2012)**. Concise review: Adipose-derived stem cells as a novel tool for future regenerative medicine. *Stem cells,* 30**,** 804-810.

Mofazzal Jahromi, M.A., Sahandi Zangabad, P., Moosavi Basri, S.M., Sahandi Zangabad, K., Ghamarypour, A., Aref, A.R., Karimi, M. & Hamblin, M.R. **(2018)**. Nanomedicine and advanced technologies for burns: Preventing infection and facilitating wound healing. *Advanced Drug Delivery Reviews,* 123**,** 33-64.

Mohajeri, S., Hosseinkhani, H., Golshan Ebrahimi, N., Nikfarjam, L., Soleimani, M. & Kajbafzadeh, A.-M. **(2010)**. Proliferation and differentiation of mesenchymal stem cell on collagen sponge reinforced with polypropylene/polyethylene terephthalate blend fibers. *Tissue Engineering Part A,* 16**,** 3821-3830.

Mollapour Sisakht, M., Kheirkhah, M.S., Sharifzad, F. & Nilforoushzadeh, M.A. **(2015)**. Skin stem cells in skin cell therapy. *J Skin Stem Cell,* 2.

Montagnani, S., Rueger, M.A., Hosoda, T. & Nurzynska, D. **(2016)**. Adult stem cells in tissue maintenance and regeneration. *Stem cells international***,** 7362879-7362879.

O'brien, F.J. **(2011)**. Biomaterials & scaffolds for tissue engineering. *Materials today,* 14**,** 88-95.

Ojeh, N., Pastar, I., Tomic-Canic, M. & Stojadinovic, O. **(2015)**. Stem cells in skin regeneration, wound healing, and their clinical applications. *International journal of molecular sciences,* 16**,** 25476-25501.

Ortiz, R., Aurrekoetxea-Rodríguez, I., Rommel, M., Quintana, I., Vivanco, M. & Toca-Herrera, J. **(2018)**. Laser surface microstructuring of a bio-resorbable polymer to anchor stem cells, control adipocyte morphology, and promote osteogenesis. *Polymers,* 10**,** 1337.

Parenteau-Bareil, R., Gauvin, R. & Berthod, F. **(2010)**. Collagen-based biomaterials for tissue engineering applications. *Materials,* 3**,** 1863-1887.

Ramalho-Santos, M. & Willenbring, H. **(2007)**. On the origin of the term "stem cell". *Cell Stem Cell,* 1**,** 35-38.

Ribeiro, A., Laranjeira, P., Mendes, S., Velada, I., Leite, C., Andrade, P., Santos, F., Henriques, A., Grãos, M., Cardoso, C.M.P., Martinho, A., Pais, M., Da Silva, C.L., Cabral, J., Trindade, H. & Paiva, A. **(2013)**. Mesenchymal stem cells from umbilical cord matrix, adipose tissue and bone marrow exhibit different capability to suppress peripheral blood b, natural killer and t cells. *Stem cell research & therapy,* 4**,** 125-125.

Rippon, H.J. & Bishop, A.E. **(2004)**. Embryonic stem cells. *Cell Proliferation,* 37**,** 23-34.

Shiraki, N., Higuchi, Y., Harada, S., Umeda, K., Isagawa, T., Aburatani, H., Kume, K. & Kume, S. **(2009)**. Differentiation and characterization of embryonic stem cells into three germ layers. *Biochemical and Biophysical Research Communications,* 381**,** 694-699.

Shiratsuki, S., Terai, S., Murata, Y., Takami, T., Yamamoto, N., Fujisawa, K., Burganova, G., Quintanilha, L.F. & Sakaida, I. **(2015)**. Enhanced survival of mice infused with bone marrow-derived as compared with adipose-derived mesenchymal stem cells. *Hepatology Research,* 45**,** 1353-1359.

Singh, A., Yadav, C.B., Tabassum, N., Bajpeyee, A.K. & Verma, V. **(2018)**. Stem cell niche: Dynamic neighbor of stem cells. *European Journal of Cell Biology*.

Sundaramurthi, D., Krishnan, U.M. & Sethuraman, S. **(2014)**. Electrospun nanofibers as scaffolds for skin tissue engineering. *Polymer Reviews,* 54**,** 348-376.

Suzuki, N., Yamazaki, S., Yamaguchi, T., Okabe, M., Masaki, H., Takaki, S., Otsu, M. & Nakauchi, H. **(2013)**. Generation of engraftable hematopoietic stem cells from induced pluripotent stem cells by way of teratoma formation. *Molecular therapy : the journal of the American Society of Gene Therapy,* 21**,** 1424-1431.

Varkey, M., Ding, J. & Tredget, E. **(2015)**. Advances in skin substitutes—potential of tissue engineered skin for facilitating anti-fibrotic healing. *Journal of functional biomaterials,* 6**,** 547-563.

Xia, Y., Sun, J., Zhao, L., Zhang, F., Liang, X.-J., Guo, Y., Weir, M.D., Reynolds, M.A., Gu, N. & Xu, H.H.K. **(2018)**. Magnetic field and nano-scaffolds with stem cells to enhance bone regeneration. *Biomaterials,* 183**,** 151-170.

Xian, W., Duleba, M., Yamamoto, Y., Vincent, M. & Mckeon, F. **(2018)**. Biobanking organoids or ground-state stem cells? *Journal of Clinical Medicine,* 7**,** 555.

Ying, Q.-L., Nichols, J., Chambers, I. & Smith, A. **(2003)**. Bmp induction of id proteins suppresses differentiation and sustains embryonic stem cell self-renewal in collaboration with stat3. *Cell,* 115**,** 281-292.

Zhang, W., Zhu, C., Ye, D., Xu, L., Zhang, X., Wu, Q., Zhang, X., Kaplan, D.L. & Jiang, X. **(2014)**. Porous silk scaffolds for delivery of growth factors and stem cells to enhance bone regeneration. *PloS one,* 9**,** e102371.

Zomer, H.D. & Trentin, A.G. **(2018)**. Skin wound healing in humans and mice: Challenges in translational research. *Journal of dermatological science,* 90**,** 3-12.

## 7. CONFLICTS OF INTEREST

The author declares no conflict of interest.