The perspective of the use of stem cells in cosmetology according current legal regulations

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Abstract

The cosmetics industry is a branch of the economy, whose characteristic feature is the search for modern and innovative substances and technologies used in the production of cosmetics. The novel substrates in cosmetics include gradually recognized, studied and exploited stem cells. These cells are obtained from plant, animal and human organisms. Because of the potential misuse of human or animal stem cells, all research and development of new cosmetic products is based on biotechnology and plant cell culture technology. Plant stem cells have a high regenerative potential, delay skin aging processes, protect cells from oxidative stress and inflammatory processes. Less than or no tests on animals or humans are needed to study them. Production and marketing of cosmetics based on plant stem cells are regulated by legislative and bioethical regulations. The formal status of stem cells and legal norms regarding their therapeutic use are not unequivocal and still evolve. For stem cells, the following may apply Act on the procurement, storage and transplantation of cells, tissues and organs and the European Parliament Directive 2004/23/EC and the Commission Directives, 2006/17/EC, 2006/86/EC. EU law prohibits the use of stem cells of animal and human origin in cosmetics. Legal provisions contain restrictions aimed at prevention against the uncontrolled possibility of ill-advised, dangerous and harmful to people and the environment the use of stem cells.

Key words:

stem cells, regenarative medicine, legislation, cosmetics

Intoroduction

Stem cells have long fascinated scientists as a subject of scientific research, because of their high potential for regeneration. Embryonic stem cells and induced pluripotent stem cells, and induced pluripotent stem cells that may also be present in the tissues of adult individuals are used in studies [1]. Stem cells are defined by the extent of their potential use, referred to as "development force". Zygote is the most expansive development cell, but is rarely considered a mammalian stem cell, because it splits into blastomers with equal developmental power for up to three cell divisions, and therefore has a very limited self-renewal potential. Zygote and early blastomers form all the tissues of the proper embryo, as well as supporting extracerebral tissue – fetal membranes and placenta. Until now nobody has ever been able to reproduce zygotes or blastomers in cell culture. In contrast, embryonic stem cells (ESCs) can be isolated from the intrinsic mass of blastocysts and grown as immortal cell lines [2].

Among the trending topics in the life sciences, stem cells have received a fair share of attention in the public debate – mostly in connection with their potential for biomedical application and therapies. While the promise of organ regeneration and the end of cancer have captured our imagination, it has gone almost unnoticed that plant stem cells represent the ultimate origin of much of the food we eat, the oxygen we breathe, as well the fuels we burn. Thus, plant stem cells may be ranked among the most important cells for human well-being. Research by many labs in the last decades has uncovered a set of independent stem cell systems that fulfill the specialized needs of plant development and growth in four dimensions. Surprisingly, the cellular and molecular design of these systems is remarkably similar, even across diverse species. In some long-lived plants, such as trees, plant stem cells remain active over hundreds or even thousands of years, revealing the exquisite precision in the underlying control of proliferation, self-renewal and differentiation [3].

Currently, most research focuses on the use of natural cosmetics. Many scientists confirm the potential benefits of using them in body care products. In order to develop an effective cosmetic, it is necessary to know the diversity of plants with different properties and metabolism. OTC products based on plant stem cells are gaining popularity, and the public prefers natural products than those produced through chemical reactions. These products provide the body with nutrients and improve health, while ensuring satisfaction for consumers. In addition, they are free of synthetic and harmful chemicals used in mass-produced cosmetics [4].

In cosmetology, scientists focus their research on adult stem cells found in the skin. They explore the potential of these types of cells, their functioning and aging. These studies help us understand how to protect the skin's stem cells. Two types of adult stem cells have been identified in human skin: epithelial stem cells found in the basal layer of the epidermis and convex stem cells in the hair follicle [6]. Stem cells contain cell growth regulating factors that play a role in the division, development and growth of cells, as well as the production of collagen and proteins. Compared to synthetic low-quality cosmetic products, plant-derived cosmetics are safe to use. Because plant stem cells are made from natural ingredients, their users do not have to worry about skin rashes or pruritus [4].

Since 1984, the European Union has provided funding for scientific research through a series of "framework programs for research and technological development" [5]. From 2002 to 2006, under the Sixth Framework Program, the EU provided funding for research using embryonic stem cells, although it did not finance the actual act of destroying the embryos to derive the stem cells [6]. More recently, a legal battle over whether stem cell techniques can be patented may alter the research landscape, as the removal of the legal protections provided by the patent system might greatly dampen incentives for stem cell research in the EU [7].

Plant and animal stem cells – minirewiev

Stem cell research is a rapidly developing field, and it is enjoying an unprecedented level of public

interest owing to its therapeutic potential, such as in human tissue replacement and drug discovery. Plant stem cells, as in animals, are defined by their ability to both renew themselves and to generate daughter cells to produce new tissues. They share several common features as they are both maintained in specialized microenvironments, which are known as stem cell niches, where local signals from an organizer act to maintain the adjacent stem cells [8]. As a milestone breakthrough of stem cell and regenerative medicine in recent years, somatic cell reprogramming has opened up new applications of regenerative medicine by breaking through the ethical shackles of embryonic stem cells. However, induced pluripotent stem (iPS) cells are prepared with a complicated protocol that results in a low reprogramming rate. To obtain differentiated target cells, iPS cellsand embryonic stem cells still need to be induced using step-by-step procedures. The safety of induced target cells from iPS cells is currently a further concerning matter. More broadly conceived is lineage reprogramming that has been investigated since 1987. Adult stem cell plasticity, which triggered interest in stem cell research at the end of the last century, can also be included in the scope of lineage reprogramming [9].

Stem cells are self-renewing cells that can differentiate into specialized cell type(s). Pluripotent stem cells, i.e. embryonic stem cells (ESC) or induced pluripotent stem cells (iPSC) differentiate into cells of all three embryonic lineages. Multipotent stem cells, like hematopoietic stem cells (HSC), can develop into multiple specialized cells in a specific tissue. Unipotent cells differentiate only into one cell type, like e.g. satellite cells of skeletal muscle. There are many examples of successful clinical applications of stem cells. Over million patients worldwide have benefited from bone marrow transplantations performed for treatment of leukemias, anemias or immunodeficiencies. Skin stem cells are used to heal severe burns, while limbal stem cells can regenerate the damaged cornea. Pluripotent stem cells, especially the patient-specific iPSC, have a tremendous therapeutic potential, but their clinical application will require overcoming numerous drawbacks. Therefore, the use of adult stem cells, which are multipotent or unipotent, can be at present a more achievable strategy. Noteworthy, some studies ascribed particular adult stem cells as pluripotent. However, despite efforts, the postulated pluripotency of such events like "spore-like cells", "very small embryonic-like stem cells" or "multipotent adult progenitor cells" have not been confirmed in stringent independent studies. Also plasticity of the bone marrow-derived cells which were suggested to differentiate e.g. into cardiomyocytes, has not been positively verified, and their therapeutic effect, if observed, results rather from the paracrine activity [10].

New advances in cell reprogramming, and particularly in obtaining iPS cells, have represented a promising possibility for avoiding the use of human embryonic cells in experimental research and clinical medicine, use which is ethically unacceptable, as obtaining these cells requires the destruction of human embryos. The road travelled to arrive at the discovery of iPS cells, and especially the ethical assessment of each of the steps taken to that end, are evaluated in this paper. The ethical judgement merited by the various uses that can be made of iPS cells is also examined, because just when it seemed that iPS cells could resolve the ethical problems inherent to the use of embryonic stem cells, new possibilities for using iPS cells, especially related with human reproduction, have opened up expectations for using these cells that are far removed from the most fundamental ethical standards [11].

Personalized medicine as a novel field of medicine refers to the prescription of specific therapeutics procedure for an individual. This approach has established based on pharmacogenetic and pharmacogenomic information and data. The terms precision and personalized medicines are sometimes applied interchangeably. However, there has been a shift from "personalized medicine" towards "precision medicine". Although personalized medicine emerged from pharmacogenetics, nowadays it covers many fields of healthcare. Accordingly, regenerative medicine and cellular therapy as the new fields of medicine use cell-based products in order to develop personalized treatments. Different sources of stem cells including mesenchymal stem cells, embryonic stem cells and induced pluripotent stem cells (iPSCs) have been considered in targeted therapies which could

give many advantages. iPSCs as the novel and individual pluripotent stem cells have been introduced as the appropriate candidates for personalized cell therapies. Cellular therapies can provide a personalized approach. Because of person- to- person and population differences in the result of stem cell therapy, individualized cellular therapy must be adjusted according to the patient specific profile, in order to achieve best therapeutic results and outcomes [12].

Legislation of stem cells

Cosmetics containing human stem cells or their ecstracts were not introduced to the market due to legal, ethical and safety concerns. However, plant stem cells, which avoid these problems, are highly valued in the cosmetics industry and improved in their breeding technology.

In European Union countries using cells, tissues or products of human origin in cosmetics is prohibited [13]. Changing the direction of basic stem cell research for routine therapies is a complex and multistep process. This process involves managing the expected therapeutic benefits and potencial threats, while respecting applicable regulations. Regulatory boundaries for "stem cell-based products" in EU are defined in several regulations of European Union [14].

Legislation on cell therapy in EU is based on three directives:

1. Directive 2003/63/EC (amending Directive 2001/83/EC), which defines cell therapy products as clinical products and includes their specific requirements.
2. Directive 2001/20/EC, which emphasizes that CTs are mandatory for such cell therapy products and describes the special requirements for approval of such trials.
3. Directive 2004/23/EC, which establishes the standard quality, donation safety, harvesting, tests, processing, preservation, storage, and distribution of human tissues and cells [15].

The EU directives recognize that conventional nonclinical pharmacology and toxicological studies may be different for cell-based drugs, but should be strictly necessary for predicting response in humans. The EU regulation (1394/2007) on Advanced Therapy Medicinal Products (ATMPs) became effective from December 2008 and is binding in its entirety and directly applicable in all Member States of the European Parliament and of the council. ATMPs include gene therapy medicinal products, somatic cell therapy products (as defined in Directive 2001/83/EC), and tissue engineered products. Cells fall under this regulation, in case they have been subjected to substantial manipulation, resulting in a change of their biological characteristics, physiological functions or structural properties relevant for the intended therapeutic application. The Committee for Advanced Therapies (CAT) within European Medicines Agency (EMA) is responsible, among other tasks, for preparing a draft opinion on the quality, safety, and efficacy of ATMPs that follow the centralized marketing authorization (MA) procedure. Yet, no MA has been granted for any stem cell based medical product (SCBPM) in the EU [16].

Somatic cell therapies, including iPSCs and MSCs, are regulated as advanced therapy medicinal products (ATMPs). All ATMPs are subject to a centralised marketing authorisation procedure involving a 210-day assessment for quality, safety and efficacy by the CAT (Committee for Advanced Therapies). EU regulation allows member states to authorise hospitals on a national scale to use ATMPs without marketing authorisation, known as the "hospital exemption" clause [17]. The basis of such an exemption is to allow non-commercial ATMPs with enough evidence for therapeutic use to be received by an individual patient under the exclusive responsibility of a medical practitioner. A public consultation into ATMP regulation in Europe deemed the high requirements of the regulation as responsible for the disappearance of innovative products as well as discouraging to new development [18]. In 2006, as the European Union was debating whether to fund human ES cell research the Sejm, the lower house of the Polish parliament, passed a resolution declaring that human ES cell research is "inconsistent with Polish law," in that it violates the article in Poland's constitution ensuring "the legal protection of the life of every human being" [13]. The resolution went on to

state that experimentation on human embryos would violate the Polish penal code and medical ethics code [13]. **Research with human embryonic stem cells (hESC):** Law of 1 July 2005 on the collection, preservation and transplantation of cells, tissues and organs [Ustawa z dnia 1 lipca 2005 r. o pobieraniu, przechowywaniu i przeszczepianiu komórek, tkanek i narządów] (Journal of Laws of 2005 n. 169 item 1411) does not refer to the collection of embryonic stem cells and gonads, embryonic and foetal tissue, as well as blood. Polish legal rules do not include separate regulations with respect to the human embryo and human embryo stem cells. There is also no legal definition for the embryonic stage of life. Regulations referring to legal protection and conduct rules in the pre-birth stage of human life are included in the Act of 7 January 1993 on Family Planning, Protection of Human Foetus and Admissible Conditions for an Abortion (Journal of Laws of 1993 n. 17 item 78) [unified text in Polish]. In accordance with the article 26 of the Act on the Medical Profession of 5 December 1996 (Journal of Laws of 1997 n. 28 item 152, unified text published in Journal of Laws of 2008 n. 136 item 857) [unified text in Polish], unborn children cannot participate in scientific experiments, which means indirectly that the participation of unborn children in therapeutic experiments is permissible, although there is no regulation on this issue [19].

Cell therapies have specific features compared to other medicinal products. The reflection paper is useful and provides an important guide for the interpretation of the Regulation (EC) No 1394/2007. Good surgical practise using manipulated cells as "concurrent treatment" is not defined in EU legislation. Regulation 1394/2007 was established to ensure that patients are not put into undue risk and that products without proven safety and efficacy are not used to treat patients. Substantial manipulation is defined as any processing that alters the original relevant biological, physiological or structural characteristics of cells or tissues. Tissue dissociation to a single cell state usually requires several steps including collagenase treatment (to digest extracellular matrix) and when needed, broad-specificity proteases (e.g. trypsin) to disperse tightly associated cells. These stable cell-cell interactions through gap junctions, tight junctions, adherent junctions and desmosomes play crucial role for the biological activity or structural characteristics of cells or tissues. These types of intercellular interactions are distinguished from those between cells and the extracellular matrix and need specific proteases to cleave them. That being said, we have to keep in mind that recombinant collagenase used to digest extracellular matrix are contaminated with trypsin-like-activity due likely to copurification of clostripain which is responsible for most if not all this activity since it is difficult to separate clostripain from collagenase because of its charge heterogeneity. In addition, enzyme-digested tissues might also induce cleavage of a wide variety of cell membrane receptors leading to alteration of cell biological activities [20].

The law rules and policy governance concerning the sources, research and uses in treatment and managing of stem cells in humans. The law regulations are very often the source of much controversy and vary significantly by country around the world. There are large differences between countries in relation to the law and control of research on plant and human stem cells.

Perspectives and censequences for cosmetology

Significant interest in stem cells in cosmetology is connected, among others, with constant striving to increasing the life expectancy and slowing down or reversing the harmful effects of aging. Therefore, functional cosmetics based on stem cell technology, that combine the anti-aging concept with advanced technology, is a new trend in the cosmetics industry. Stem cells are self-renewing and they have ability to differentiated that's why these cells are the most important skin cells, as a source of continuous regeneration of the epidermis. Development of stem cell cosmetics is based on stem cell technology, that includes use extracts or culture media of stem cells. [21]. Consumers are interested in more and more naturally prepared cosmetics. Scientific research

confirms the beneficial effects of extracts such as antioxidant capacity, tyrosinase inhibition and antibacterial activity [4].

Several plant stem cell extracts are known and used commercially as a source of regenerative therapy for human cells in the field of cosmetics. The most common example of the use of stem cells of plant origin in cosmetics is currently used in the skin care of a Swiss apple cell *Uttwiler Spätlauber* [22].

In current times, for innovative cosmetic scientists, the goal is to connect the evidence from ancient practices to evidence in modern science and see where the application of plants in cosmetics can improve the delivery to the skin in a more effective, safer and targeted way [23]. Plant science research in herbal biotechnology and physiologic effects on the skin by plant stem cells give a new chances in future cosmetology.

In recent years, there have been many "stem cell clinics," both in the United States and around the world, that offer various "stem cell treatments" that are not scientifically proven and not regulated by the US Food and Drug Administration (FDA). These clinics mostly claim to use stem cells from one's own body fat, bone marrow, and blood, although some use cells from amniotic fluid, placental tissue, umbilical cord tissue, and even unknown sources of cells from other donors. It is unknown whether the cells used are actually stem cells. These clinics tend to engage in false marketing to the public, with promises that stem cell treatments can improve cosmetic appearance as well as help a variety of conditions ranging from arthritis to autism. The FDA is currently in the process of developing guidelines to more strictly regulate these clinics [24].

Regenerative medicine refers to a multidisciplinary field that develops methods to regenerate, repair, improve or replace cells, organs, and tissues that have been damaged due to aging, diseases, chronic diseases or congenital abnormalities. Regenerative medicine aims to develop new therapies in order to heal structure and biological function following tissue injury and delay the progression of the diseases. This field presents novel treatment approaches including tissue engineering, cell biology, and biomaterials [25; 26; 27; 28; 29]. Regenerative medicine involves the use of stem cells from different sources. The study of these isolated stem cells compromises the foundation of regenerative medicine which contributing cellular therapy [27; 28; 29; 30; 31]. Regenerative medicine is likely to involve the implantation of new tissue in patients with damaged or diseased organs. A substantial obstacle to the success of transplantation of any cells, including stem cells and their derivatives, is the immune-mediated rejection of foreign tissue by the recipient's body. In current stem cell transplantation procedures with bone marrow and blood, success can hinge on obtaining a close match between donor and recipient tissues and on the use of immunosuppressive drugs, which often have severe and life-threatening side effects. To ensure that stem cell-based therapies can be broadly applicable for many conditions and individuals, new means to overcome the problem of tissue rejection must be found. Although ethically controversial, somatic cell nuclear transfer, a technique that produces a lineage of stem cells that are genetically identical to the donor, promises such an advantage. Other options for this purpose include genetic manipulation of the stem cells and the development of a very large bank of embryonic stem cell lines. In conjunction with research on stem cell biology and the development of stem cell therapies, research on approaches that prevent immune rejection of stem cells and stem cell-derived tissues should be actively pursued [32].

Therefore, personalized medicine as the most promising method to customize health care in order to improve the quality of medical services can shed light on the treatment of patients according to individual differences [12]. The combination of poor quality science, unclear funding models, unrealistic hopes, and unscrupulous private clinics threatens regenerative medicine's social licence to operate. If regenerative medicine is to shift from mostly small-scale bespoke experimental interventions into routine clinical practice, substantial rethinking of the social contract that supports such research and clinical practice in the public arena will be required [33].

High-quality, publicly funded research is the wellspring of medical breakthroughs. Although private, for-profit research plays a critical role in translating the fruits of basic research into medical advances

that are broadly available to the public, stem cell research is far from the point of providing therapeutic products. Without public funding of basic research on stem cells, progress toward medical therapies is likely to be hindered. In addition, public funding offers greater opportunities for regulatory oversight and public scrutiny of stem cell research. Stem cell research that is publicly funded and conducted under established standards of open scientific exchange, peer review, and public oversight offers the most efficient and responsible means of fulfilling the promise of stem cells to meet the need for regenerative medical therapies [32].

The main objective is the need for expansion of stem cell characteristics to maximize stem cell efficacy (i.e. the proper selection of a stem cell) and the efficacy (maximum effect) and safety of stem cell derived drugs. Other considerations to take into account in cell therapy will be the suitability of infrastructure and technical staff, biomaterials, production costs, biobanks, biosecurity, and the biotechnological industry. The general objectives in the area of stem cell research in the next few years, are related to identification of therapeutic targets and potential therapeutic tests, studies of cell differentiation and physiological mechanisms, culture conditions of pluripotent stem cells and efficacy and safety tests for stem cell-based drugs or procedures to be performed in both animal and human models in the corresponding clinical trials [34].

Summary

Scientific research to develop, evaluate and use plant stem cells in cosmetic preparations, which meet the requirements of consumers, lead to conclusions, that natural products are mild and biodegradable, showing low toxicity and no side effects. Therefore, plant stem cells produced in biotechnology processes are closed in order to obtain better properties. These cells are compatible with human skin and support skin stem cells that protect the skin, including against UV damage [4]. There is a growing number of consumers concerned about such components as against UV damage synthetic chemicals, mineral oils and others. They demand more natural products with identifiable and more natural ingredients free of harmful chemicals [35].

There are several regulatory issues that relate to the safety, efficacy, and quality of SCBPs to be considered while preparing a cell- and tissue-based therapy for clinical and commercial use. Initially, safety testing is critical, including assays for potential microbial, fungal, endotoxin, mycoplasma, and viral contamination; karyotype testing; and enrichment for the required cell population. Once safety has been established, the product must pass *in vitro* functional assays designed to act as surrogate measures for clinical effectiveness [36].

Unproven stem cell therapies increase the risk of therapeutic misestimation (where patients incorrectly estimate the probability of benefit or risk [37], jeopardises the reputation of legitimate therapies which are yet to be commercialised and fans misconceptions regarding the current state of scientific and clinical developments. Whilst a political consensus exists around tighter regulation, the market for unproven therapies appears to be expanding. In Australia, the number of private stem cell clinics has exponentially increased from two to over 40 since 2011 [38], under a medical practice exemption clause which enables autologous stem cell therapies for individual patients to be outside of the remit of the Therapeutic Goods Administration (TGA) [39]. Similar exemptions in the EU include "compassionate use" programmes in which a patient with life-threatening, long-lasting or debilitating illness who cannot be treated by an authorised medical product accesses an investigational drug outside of a clinical trial [41]. We conclude that the ethical debate on cell reprogramming and particularly on the experimental and clinical use of induced pluripotent stem cells (iPSC) remains open [11]. The intractability of the ethical debate is double edged: legislators not only have placed tighter restrictions on certain stem cell therapies, but do so in favour of less controversial cells which will have worse outcomes for patients. It is by considering this relationship between the politics, ethics and science of stem cells that the reasons for the currently limited clinical significance of stem cell therapies be realized [40]. In the case

of embryonic stem cell research, it is impossible to respect both moral principles. To obtain embryonic stem cells, the early embryo has to be destroyed. This means destroying a potential human life. But embryonic stem cell research could lead to the discovery of new medical treatments that would alleviate the suffering of many people. So which moral principle should have the upper hand in this situation? The answer hinges on how we view the embryo. Does it have the status of a person? [42]. Conflicting ethical perspectives surround the use of embryonic stem cells in medical research, particularly where the moral and legal status of human embryos is concerned. The use of embryonic stem cells is not the first biomedical research activity to raise ethical and social issues among the public. Restrictions and guidelines for the conduct of controversial research have been developed to address such concerns in other instances [32]. A regulatory framework will be required to ensure patient accessibility to products and governmental assistance for their regulation and control. Bioethical aspects will be required related to the scientific and therapeutic relevance and cost of cryopreservation over time, but specially with respect to embryos which may ultimately be used for scientific uses of research as source of embryonic stem cells, in which case the bioethical conflict may be further aggravated [33].

It calls for an examination of the scientific benefits of such research to inform debate on the question, and argues for the need to take genuine account of the public's views on this matter [43]. After several decades of experiments, stem cell therapy is becoming a magnificent game changer for medicine. With each experiment, the capabilities of stem cells are growing, although there are still many obstacles to overcome. Regardless, the influence of stem cells in regenerative medicine and transplantology is immense. Currently, untreatable neurodegenerative diseases have the possibility of becoming treatable with stem cell therapy. Induced pluripotency enables the use of a patient's own cells. Tissue banks are becoming increasingly popular, as they gather cells that are the source of regenerative medicine in a struggle against present and future diseases. With stem cell therapy and all its regenerative benefits, we are better able to prolong human life than at any time in history [44].

Stem cells give possibility for new therapies, but their use in research has been now debated. Each countries have chosen to regulate stem cell research in very different ways. Stem cell research is helping scientists to understand how an organism develops from a single cell and how healthy cells come to replace defective cells in people and animals organisms. Current and future research create hope for wide usage stem cells in understanding cancer, regenerative medicine, therapies, drug development and more.

References

1. Bhartiya D. Pluripotent Stem Cells in Adult Tissues: Struggling To Be Acknowledged Over Two Decades. Stem Cell Rev. 2017 Dec;13(6):713-724.
2. Daley GQ. Stem cells and the evolving notion of cellular identity. Philos Trans R Soc Lond B Biol Sci. 2015;370(1680):20140376.
3. Greb T, Lohmann JU. Plant Stem Cells. Curr Biol. 2016;26(17):R816-21.
4. Jha M. Phyto-Stem Cell: New Door in Cosmetology. Biotechnology Products in Everyday Life. 2019. pp187-197.
5. European Commission Community Research and Development Information Services (CORDIS), "What is FP7?".
6. Barthel R, Aberdam D. (2005) Epidermal stem cells. J Eur Acad Dermatol Venereol. 19:405–413. 5.
7. Gwennaël Joliff-Botrel and Pascale Perrin, eds., "European Research Projects Involving Stem Cells in the 6th Framework Programme," European Commission Directorate General for Research: Life Sciences, Genomics and Biotechnologies for Health
8. Sablowski R. Plant and animal stem cells: conceptually similar, molecularly distinct? Trends Cell Biol. 2004;14:605–611.
9. Zhou J, Yue W, Pei X. Advances in cell lineage reprogramming. Sci China Life Sci. 2013;56(3):228-33.
10. Dulak J, Szade K, Szade A, Nowak W, Józkowicz A. Adult stem cells: hopes and hypes of regenerative medicine. Acta Biochim Pol. 2015;62(3):329-37.
11. Aznar Lucea J, Martínez M. [Ethical reflections on cell reprogramming]. Cuad Bioet. 2012;23(78):287-299.

12. Arjmand B, Goodarzi P, Mohamadi-Jahani F, Falahzadeh K, Larijani B. Personalized Regenerative Medicine. Acta Med Iran. 2017;55(3):144-149.
13. Christine Mummery, "Advocate-general's recommendation could undermine European biotechnology sector," EuroStemCell, April 28, 2011.
14. Schultz G. "Polish Parliament Adopts Resolution Against Human Embryonic Research," Life Site News, July 24, 2006.
15. George B. Regulations and guidelines governing stem cell based products: Clinical considerations. Perspect Clin Res. 2011;2(3):94–99.
16. Antonio L. Future research and therapeutic applications of human stem cells: General, regulatory, and bioethical aspects. J Transl Med. 2010;8:131
17. Committee for Advanced Therapies and CAT Scientific Secretariat. Use of unregulated stem-cell based medicinal products. Lancet. 2010;376:514.
18. Article 28. Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004.
19. European Commission: Regulation (EC) No. 1394/2007 on Advanced Therapy Medicinal Products. Summary of the response to the public consultation 2013.
20. Raposio E, Ciliberti RG. Clinical use of adipose-derived stem cells: European legislative issues. Ann Med Surg (Lond). 2017;24:61–64.
21. www.freedomofresearch.org/ Research-and-Self-Determination-Index/
22. Choi SH, Yun J, Kwon SM. Study of functional cosmetics based on stem cell technology. Tissue Eng Regen Med. 2015;12(2):78-83.
23. Trehan S, Michniak-Kohn B, Beri K. Plant stem cells in cosmetics: current trends and future directions. Future Sci OA. 2017;3(4):FSO226.
24. Jin J. Stem Cell Treatments. JAMA. 2017;317(3):330.
25. Nelson TJ, Behfar A, Terzic A. Strategies for therapeutic repair: The "R(3)" regenerative medicine paradigm. Clin Transl Sci 2008;1:168-71.
26. Atala A. Regenerative medicine strategies. J Pediatr surg 2012;47:17-28.
27. Buckler RL. Opportunities in regenerative medicine. BioProcess Int 2011;9:1419.
28. Harris DT. Stem cell banking for regenerative and personalized medicine. Biomedicines 2014;2:50-79.
29. Hipp J, Atala A. Sources of stem cells for regenerative medicine. Stem Cell Rev. 2008;4:3-11.
30. Mahla RS. Stem Cells Applications in Regenerative Medicine and Disease Therapeutics. Int J Cell Biol 2016;2016:6940283.
31. Fisher MB, Mauck RL. Tissue engineering and regenerative medicine: recent innovations and the transition to translation. Tissue Eng Part B Rev 2013;9:1-13.
32. National Research Council (US) and Institute of Medicine (US) Committee on the Biological and Biomedical Applications of Stem Cell Research. Washington (DC): National Academies Press (US); 2002. Stem Cells and the Future of Regenerative Medicine.
33. Cossu G, Birchall M, Brown T, et al. Lancet Commission: Stem cells and regenerative medicine. Lancet. 2018;391(10123):883-910.
34. Liras A. Future research and therapeutic applications of human stem cells: general, regulatory, and bioethical aspects. J Transl Med. 2010;8:131.
35. Pavlović M., Radotić K. (2017) Cultured Plant Stem Cells as a Source of Plant Natural Products. In: Animal and Plant Stem Cells. Springer, Cham. pp 211-216.
36. Escamilla M., Ferre A., Hidalgo C., Fuentes N., Kaps R.: Revision of european ecolabel criteria for soaps, shampoos and hair conditioners. Joint Res. Centre Eur. Comm. pp. 1-40 (2012).
37. Rayment EA, Williams DJ. Concise Review: Mind the gap: Challenges in characterizing and quantifying cell- and tissue-based therapies for clinical translation. Stem Cells. 2010;28:996–1004.
38. Pentz RD, White M, Harvey RD, Farmer ZL, Liu Y, Lewis C, Khuri FR. Therapeutic misconception, misestimation, and optimism in participants enrolled in phase 1 trials. Cancer. 2012;118(18):4571–8.
39. Munsie M, Pera M. Regulatory loophole enables unproven autologous cell therapies to thrive in Australia. Stem Cells Dev. 2014;23(S1):34–38. 20.Therapeutic Goods Administration. Therapeutic Goods (Excluded Goods) Order No. 1. 2011
40. Committee for Medicinal Products for Human Use (CHMP). Guideline on compassionate use of medicinal products, pursuant to article 83 of regulation (EC) No 726/2004. 2007; 2-3.
41. Poulos J. The limited application of stem cells in medicine: a review. Stem Cell Res Ther (2018);9:1.

42. https://www.eurostemcell.org/embryonic-stem-cell-research-ethical-dilemma.
43. Bahadur G, Iqbal M, Malik S, Sanyal A, Wafa R,Noble R. Admixed human embryos and stem cells: legislative, ethical and scientific advances. RBMO, 2008;17(1):25-32.
44. Zakrzewski W, Dobrzyński M, Szymonowicz M, Rybak Z. Stem cells: past, present, and future. Stem Cell Research & Therapy, 2019;10:68.