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Key regulations related to stem cell research

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Abstract

Medicine is an ever-changing science. Stem cell research is nowadays part of the medicine. After developments and trials for decades, in 1988 it was announced that a variety of diseases and injuries would be cured with new stem cell therapy, such as: cancer, diabetes, Parkinson's, spinal cord injuries and many others. After almost 10 years of research in the field, in 2007 other good news and hopes were announced: the possibility to create induced pluripotent stem cells, derived from somatic cells, easily used to establish any disease-specific cell line. And research is going on. In order to find answer to a variety of challenges in this area, a researcher faces the following main question: Which are the legislations and the normative standards to be taken into account when we are supposing to conduct a research on/with stem cells? The purpose of the paper is: (*i*) to familiarize professionals with the current steps in the evolution of stem cell research; (*ii*) to provide main legal orientations related to stem cell research; (*iii*) to indicate limits and explanations on legal regulations related to the research on stem cells.

Keywords: stem cells, pluripotent stem cells, legal regulations.

General considerations on stem cells

Stem cell timeline

According to the *Stedman's Medical Dictionary* [1], the 'stem cell' is a cell with daughter cell that may differentiate into other cell types. It is able to generate all kind – or more kind – of body cells. The history of the stem cells has no certain beginning. The 'stem cell' term was firstly used in 1908 by the Russian histologist Alexander Maksimov (1874–1928) in a congress of the Hematology Society at Berlin [2, 3]. He was referring to hematopoietic stem cells. In the 50's, the initial studies of Leroy C. Stevens and G. Barry Pierce Jr. on teratocarcinoma cells have led to the isolation of the embryonic stem cells (ESCs) [4–6]. Therefore, the first bone marrow transplant took place in 1958. In the 60's, Joseph Altman (1925–2016) and Gopal D. Das (1933–1991) were describing for the first time the neurogenesis [7]. In 1963, Becker *et al.* [8] proved the existence of the stem cells in the mice's bone marrow. In 1968 was registered the first successful curing of the severe immunodeficiency syndrome through a bone marrow transplant [9]. In 1978, the hematopoietic stem cells, mentioned by Maksimov, were discovered in the umbilical cord blood [10]. 1981 represents an important period in the history of the stem cells: M. J. Evans, M. H. Kaufman and G. R. Martin [11] have identified the ESCs on mice. In 1992, the *in vitro* neural stem cells were preserved as neurospheres [12]. In 1997 has been identified the connection between the hematopoietic stem cells and leukemia, thus showing the first case of cancer stem cells [13]. In November 1998, J. A. Thompson with his team isolated the human stem cells [14]. The 2000 were prolific in the research area on adult stem cells. In 2003, Songtao Shi [15] discovered a new source of the adult stem cells in the children's milk (deciduous) teeth. One year later, in 2004–2005, the South-Korean geneticist Woo-Suk Hwang [16] was announcing the first cloning case from unfertilized human oocytes, but he changes his mind, retrieves it and confesses his imposture. In November 2007, it was noted a new important event in the history of the stem cells, the conversion of human skin cells into induced pluripotent stem (iPS) cells [17]. In July 2008, differentiated stem cells were created using skin cells from a patient suffering of lateral amyotrophic sclerosis [18]. And in February 2009, immature sexual cells were created from skin cells/iPS cells [19].

Stem cell types and uses

The stem cells exist in our body as long as we live. These can be grouped in three categories:

(*i*) ESCs, also called totipotent, are the cells prevailed from a few days' old embryo in blastocyst phase and collected in a cell culture;

(*ii*) iPS cells or "reprogrammed" are similar to the embryonic ones but are prevailed from specialized adult cells using a laboratory technique discovered in 2006;

(*iii*) Tissues stem cells are those prevailed from adult tissues and were able to produce a certain number of cellular types.

Through their ability to regenerate the body tissues, they present multiple potential therapeutic applications. The stem cells are a natural reserve of the organism, reestablishing the specialized cells stock of those exhausted or altered. The stem cells activate in the bone marrow to produce 100 000 million of new sanguine cells that we need every day [20]. They have the unique ability to create

copies of themselves every time they divide, as well as other types of specialized cells. These cells are essential for the tissues' preservation, such as the blood, skin, intestine, that are always renewing, as well as the muscles which can develop depending on the needs of the body, as they were affected by the physical efforts [20].

ESCs are more undifferentiated than the adult stem cells. They create all the cellular types of an organism. *In vitro*, they contribute in the creation of pluripotent cellular lines and used to regenerate different parts of the body affected by a disease, an accident or by the aging process. Using the stem cells, we have the opportunity to analyze the process of stem differentiation, to study *in vitro* the effect of the new drugs and especially new treatments of cellular transplant can be done [20].

The use of human stem cells is part of the actual medical therapy. Nowadays, the most frequent treatment is the hematopoietic stem cells transplant from bone marrow, blood or placental blood. This cellular transplant is an efficient treatment for multiple hematological diseases or cancers (leukemia). The stem cells have an important role also in the intestinal or skin transplant, in which the stem cells for these elements are indispensable for the maintenance of a function mostly depending on the regeneration ability [21].

The stem cells transplant techniques continue to develop and to multiply. Nowadays, the technical limits in the transplant of organs, tissues or cells lead the researchers to imagine new intervention methods through artificial prosthesis, xenotransplantation, human stem cells. Through their regeneration property, stem cells hold great promises in the area of medical research. Due to these cells, various therapeutic applications of a not only repairing, but also regenerative medicine occur, the development of new therapies for many serious human diseases [21].

Stem cell regulations in domestic and international normative standards

In this section, we will discuss about the principal legal internal and international regulations on the research on stem cells to which we should refer when starting the construction of the design of the a research or of a project in this area.

Romanian legal framework related to stem cell research

Nowadays, Romania does not have a body of specific laws in this area of research. It has not been yet adopted a framework law to regulate the medically assisted reproduction methods and the research on the excess of human embryos [22]. Although, Romania as member state of the European Union (EU), of the European Council (EC) and of other international institutions that have adopted regulations in this area, has to respect the law principles, as well as the European and international norms which it has ratified and signed. As internal legislation, we can take into account the regulations on the research on the human being and the stipulations on the transplant of hematopoietic stem cells. Internal legal norms related to this field are the Law No. 95/2006 on Health Reform, the new project of transplantation law, in public debate, and the *Code of Medical Deontology*.

Law No. 95/2006, in the section on the transplant of hematopoietic stem cells, Article 145 states the conditions in which organs removal, tissues and cells from potential minor donors, as follows: only with the consent of the minor, if he is 14 years old and with the written consent of the legal representative, parents, tutor or curator. If the minor is under the age of 14, the removal can be done with the consent of the legal representative.

Regarding the 14 years old donor, his consent has to be written or verbal and expressed in front of the President of the Court of the territorial division the center is caring out the transplant, after a mandatory investigation by the competent tutelary authority. The refusal of the minor cancels any removal.

The *Code of Medical Deontology*, updated in 2016, in force from 2017, explicitly prohibits the creation of human embryos for research (Article 49), in the chapter about the limits of the medical research. However, no legal act in Romania regulates directly and explicitly the research on stem cells.

International and European legal framework regarding stem cell research

There are some legal frameworks related to stem cell research at European level, provided by various European and international institutions. In the following sections, we will present the current orientations in this area.

World Health Organization (WHO)

WHO adopted, in May 8, 1997, the Act entitled *Cloning in Human Reproduction* [23]. Article 9 states that "the accelerated development and growing complexity of industrial and biomedical technology and the globalization of trade emphasize the need for worldwide harmonization and regulation of policies and practices. New biomedical technology has to be assessed in the light of health risks of this kind as well as for potential benefits (...)".

United Nations Educational, Scientific and Cultural Organization (UNESCO) – International Bioethics Committee (IBC)

UNESCO – IBC proposed, on April 6, 2001, a document on *The Use of Embryonic Stem Cells in Therapeutic Research* [24]. The document states: the right and the obligation of each individual society to discuss this question in its own right; governments should promote free and informed public debates in all countries, at national level; in countries where the research on embryos is allowed, it should be subject to state regulation in order to ensure adequate respect of the ethical principles; the use of so-called "surplus" embryos for stem cell research should be tied to the free and informed consent of the donors and research projects should be reviewed by ethics committees; the careful assessment of the advantages and risks of alternative methods of stem cell derivation.

The same IBC presented, on October 2, 2015, a *Report on Updating its Reflection on the Human Genome and Human Rights* [25], which states that ESC research should be "non-controversial" and the "use of induced

pluripotent stem cells instead of embryonic stem cells is a step in this direction".

Council of Europe

The Council of Europe adopted, on April 4, 1997, the *Convention for the Protection of Human Rights and Dignity of the Human Being* with regard to the *Application of Biology and Medicine*: *Convention on Human Rights and Biomedicine* [26] – Oviedo Convention. The Article 18.2 of the Convention states that "the creation of human embryos for research purposes is prohibited" and Member States are at liberty to undertake the conditional authorization of research with "surplus" embryos.

On January 12, 1998, the Council adopted an *Additional Protocol* to the *Convention for the Protection of Human Rights and Dignity of the Human Being* with regard to the *Application of Biology and Medicine, on the Prohibition of Cloning Human Beings* [27]. Article 1 of the *Protocol* prohibits "any intervention seeking to create a human being genetically identical to another human being alive or dead". Article 2 excludes exemption from this prohibition (*e.g.*, for reasons of public safety, prevention of crime, protection of public health or the protection of the rights and freedoms of others). The *Protocol* leaves the domestic laws of the States to define the scope of the term "human being".

European Union

In July 6, 1998, it was adopted the *Directive 98/44/EC of the European Parliament and of the Council on the legal protection of biotechnological inventions* [28]. The Article 6 states that "Inventions shall be considered not patentable where their commercial exploitation would be contrary to order public or morality; (...) On the basis of paragraph 1, the following, in particular, shall be considered not patentable: processes for cloning human beings; processes for modifying the germ line genetic identity of human beings; uses of human embryos for industrial or commercial purposes; (...)".

On March 31, 2004, EU presented the *European Tissue and Cell Directive*, Directive 2004/23/EC [29]. This Directive is not against the decisions adopted by the member states on the use or disuse of a certain type of human cells, inclusively of the germinal and ESCs. However, if a use of these cells is authorized in a member state, the Directive imposes the application of all necessary dispositions for the public health protection, taking into account the risks presented by these cells according to the scientific knowledge and their special nature, as well as the guaranty of respecting the fundamental rights.

On November 13, 2007, the *Regulation (EC) No. 1394/2007 of the European Parliament and of the Council on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No. 726/2004* [30]. This Act states, in the Article 7, that the regulation of advanced therapy medicinal products at Community level should not interfere with decisions made by member states on whether to allow the use of any specific type of human cells, such as ESCs, or animal cells. It should also not affect the application of national legislation prohibiting or restricting the sale, supply or use of medicinal products consisting of or derived from these cells.

European Court of Justice

The European Court of Justice, on October 18, 2011, gave the final decision in the *Case of Oliver Brüstle v. Greenpeac*e [31]. Judges state that the use of the human embryos as therapy or as diagnosis can be patented, but their use for research is not patentable. The Court also quoted the *Directive 98/44/EC*: "Although it seeks to promote investment in the field of biotechnology, use of biological material originating from humans must be consistent with regard for fundamental rights and, in particular, the dignity of the person".

European Medicines Agency (EMA)

EMA adopted, on February 2011, a *Reflection paper on stem cell-based medicinal products* [32]. Developers of stem cell-based medicines need to pay close attention to the way the medicines are manufactured, to ensure that the final medicine is as consistent and reproducible as possible. Preclinical and clinical testing also need to take account of the cells' properties, ensuring that the possible risks of tumor development and rejection by the body are studied adequately and balanced against their benefits for patients.

International Society for Stem Cell Research (ISSCR)

ISSCR proposed three different Guidelines on the research on and with stem cells. The first one was presented on December 21, 2006 – *Guidelines for the Conduct of Human Embryonic Stem Cell Research* [33]. The second one, adopted on December 3, 2008 – *Guidelines on the Clinical Translation of Stem Cells* [34], highlights the scientific, clinical, regulatory, ethical, and social issues that should be addressed so that basic stem cell research is responsibly translated into appropriate clinical applications for treating patients. The last one, adopted on May 12, 2016 – *Guidelines for Stem Cell Research and Clinical Translation* [35], updates the current advances in science and the scientific enterprise around the world.

Most of the countries from the EU have adopted legal regulations on the research on stem cells. These can be found, especially, on legal documents related to the techniques of medically assisted reproduction [36]. The explanation lies on the fact that the initial debate on the research on stem cells was directly connected with the one referring to the status of the human embryo, as the focus was on the research on ESCs. From 2012, a new alignment of the legislation of the EU member states occurs on behalf of the research on ESCs. Therefore, the Netherlands (2002), Belgium (2003) and Sweden (2005) have aligned to the Great Britain (1990) legislation, authorizing the research on human embryos within 14 days of fertilization [37]. The Czech Republic, Denmark, Finland, France, Greece and Spain dispose of legislations that authorize ESCs derivation. Estonia, Hungary, Latvia and Slovenia have no specific regulations on ESCs but tolerate certain researches on supernumerary embryos. Germany and Italy have restrictive regulations on the research on

ESCs, thus the researchers cannot derive new lines of stem cells, but they can import them. Five member states are opposing radically to this type of research: Austria, Lithuania, Malta, Slovakia and Poland [38].

Limits of legal regulations and possible explanations

As it can be seen, the reference legal documents in the area of stem cells research do not establish clear and stable limits of this type of research, but leave the member states to define and to classify this type of research. The only explicit interdiction is the creation of human embryos for research purpose stated by Oviedo Convention [26]. The other documents are limited only to recommendations, showing, thus, the direction to follow when researches enroll in research projects in this domain. The explanation consists on that the legal regulations in the medical biotechnologies' domain are characterized by a double particularity: (*i*) the *principle of subsidiarity* – the research on stem cells is a domain that concerns the member states; (*ii*) *ethical pluralism* – the European policy is adapted to the national identities and is not imposing measures against the consciousness and the types of national acts, after the same principle as the policy on culture [39, 40].

Principle of subsidiarity

This principle expresses the desire of the individual or of the member states (...) to depend on state or on the central authorities only when needing their help [41]. It is stated in Article 5 align. (3) of the *Treaty on European Union* the following: "Under the principle of subsidiarity, in areas which do not fall within its exclusive competence, the Union shall act only if and in so far as the objectives of the proposed action cannot be sufficiently achieved by the Member States, either at central level or at regional and local level, but can rather, by reason of the scale or effects of the proposed action, be better achieved at Union level" [42]. This principle is also stated in the legal documents presented in the above section. Therefore, the member states have the liberty to decide how to classify this type of research, and if an internal legislation is missing in the research protocols and projects on stem cells will be taken into account the legal international orientations and the law principles contained.

Ethical pluralism

The *ethical pluralism* was defined by David J. Roy as "the search of the social, juridical and traditionally religious consensus regarding the moral values" [43], in a multicultural context. In the process of enactment, the consensus of the participants is important. However, in a democratic community is impossible to exist a consensus, hardly can be negotiated a majority, on respecting the protected social values. The European identity was constructed on four fundamental values: the principles of the representative democracy, compliance with the law, social justice and compliance on human rights [44]. The diversity of the national positions prevents and delay the process of the adoption and regulation of a unitary position at the EU level. The debate regarding the *ethical pluralism* should not be understood as an exigency of "unification" of the behaviors, but of finding some fundaments able to justify the knowledge of good and of bad. Finding an agreement between different groups seems impossible to realize, the consent is achieved according to the democratic rule of the vote of the majority. This rule is often contested and the plurality of opinions and arguments creating confusions in the public opinion, however no solution seems to be found, therefore, this rule is the only one to take into account in present. Therefore, the European Commission acts as a convergence facilitator between the member states [40] respecting the sensible points of each state. A consent of the hierarchy of values accepted by all member states is impossible to realize, and if realized, the democracy will be questioned. The solution adopted is to inform the population, through public debate and dialog with the civil society.

Concluding remarks

At the question what law or legal orientations a researcher has to respect when starting a research or when it structures the design of a research project on stem cells, the answer is not unitary: there is a series of legal regulations, but none of them refers to the research itself in this domain. In Romania, we do not have a specific regulation to frame this type of research and to take into account the last evolutions on stem cell research. According to the general law principles, *everything which is not forbidden is allowed* [45] from Latin *nulla poena sine lege* ("no penalty without a law"). However, even if Romania has not yet adopted a specific legislation in this domain, the researchers have to consider all legal norms and the European legislative orientations, our country being member of all the structures that regulated orientations in this area, such as WHO, UN, EC and the EU. In the end, we can affirm that the research on stem cells is possible but respecting the general law principles and the legal regulations in force presented in this article. It would be preferable to exist an internal specific legislation on the topic based on our country's social and cultural context, on the principles of the internal law, and in the international orientations in matter.

Conflict of interests

The authors declare that they have no conflict of interests.

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