NARRATIVE REVIEW

Development of stem cell ethics and legislation in the world and in Pakistan; a narrative review

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Abstract

Stem cells can transform into specialized types of cells, and their capability of self-renewal is limitless. The advancements in stem cell therapy have encountered various hurdles. Considering the massive scope of stem cells applications in health, an effective regulation and monitoring system should be implemented. It is important to ensure that stem cell research projects in Pakistan work closely with the ethics committees as respecting human rights are of paramount importance. It is also necessary that the ethics and legislation guidelines are reviewed, updated, and monitored effectively at every evolving step.

Keywords: Stem cells, Research, Transplantation, Legislation, Guidelines.

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Introduction

Stem cells can transform into specialized types of cells and their capability of self-renewal is limitless. They are categorized into Totipotent, Pluripotent, and Multipotent cells. All cell types, including the organism, can emanate from a Totipotent stem cell. Pluripotent stem cells have the potential to differentiate into almost any cell type. They consist of Embryonic Stem Cells (ESCs) and induced Pluripotent Stem Cells (iPSCs) and give rise to all three germ layers (endoderm, mesoderm, and ectoderm). Multipotent stem cells incorporate mature adult cells or somatic cells and they can differentiate into all cell types but are restricted to a specific lineage[1]. The regenerative potential of stem cells has great curative advantages. This uniqueness of stem cells makes it an invaluable research area that brings to light the details regarding human development and can be utilized for therapeutic purposes like tissue repair, transplant, and regeneration.

Stem cells embody various intricate details and enormously impact on medicine and human life. Therefore, it is not surprising that advancements in stem cell therapy (SCT) have raised moral and ethical issues which are often seen as hurdles. For example, ESC therapy is one of the main ethical challenges is since the extraction of the cells is seen as the destruction of an embryo that has prospects of becoming a human. Another area of concern is the continuous proliferation of stem cells and this can incite tumorigenesis which is a detrimental drawback to the otherwise valuable quality of these cells[2,3]. Considering the massive scope that stem cell comprises and an equally broad possibility of potential harm to individuals and society, it is crucial to regulate and monitored it effectively.

Aristotle's keen observation of a lizard growing its tail back led to understanding of the human body's regenerative potential. In the last decade, there was a boom in stem cell research; and the author Roopa R. Nadig believes that stem cells will likely revolutionize healthcare[4]. In the wake of an information explosion on stem cell research, we aim to highlight the advent of stem cell legislation world wide and in Islamic countries and Pakistan while calling attention to the differences in practices amongst the demographics.

Development of stem cell legislation around the world

In 2002, the International Society for Stem Cell Research (ISSCR) was formed to support and promote stem cell science while upholding the ethical principles and guidelines related to research and clinical translation. In 2006 their first set of "Guidelines for the Conduct of Human Embryonic Stem Cell Research" were issued[5]. Subsequent to this "Guidelines for the Clinical Translation of Stem Cells" in 2008[6], and the second version of the "Guidelines for Stem Cell Research and Clinical Translation" in 2016[7] followed bythe third version in 2021 (8). Each publication correlated with the growth and extension of stem cell research and its application in that time frame[9]. The United Nations Educational, Scientific and Cultural Organization (UNESCO) – International Bioethics Committee (IBC) published a report in 2001 on the "Ethical Aspects of Human Embryonic Stem Cell

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Research"[10]. This report was discussed at the Seventh Session of the IBC and consequently finalized. The primary ethical concern was the fate of the human embryos. It was agreed upon that the subject of ethical consideration regarding embryo research is to be handled at the state level since the challenges faced by each state are different. It emphasizes that discussions are carried out at the national level, and all viewpoints and their implications are considered. The state which allows research on ESC should formulate principles and guidelines regarding the same and ensure that they are monitored. The report also states that priority "be given to respect of human dignity and the principles set out in the Universal Declaration of Human Rights (1948) and the Universal Declaration on the Human Genome and Human Rights (1997)"[10]. In 2015, UNESCO-IBC published a report on "Updating Its Reflection on the Human Genome and Human Rights"[11]. This report highlighted iPSCs, a recent finding at that was ethically promising as it could create cells without damaging the embryo[11].

The Directive 2004/23/EC[12] of the European Parliament and of the Council focuses on the need to safeguard and maintain the standard of human tissues and cells. According to the Directive, Member states must ensure that trained professionals carry out the testing related to tissues and cells. The authorities ensure that the procurement, handling, storage, and distribution of tissues and cells are as per the guidelines[12]. Regulation (EU) 2021/695[13] of the European Parliament and the Council promulgated that funding for the research on adult and embryonic stem cells will be permitted depending on its constituents and the legislative regime of that Member State. It also mentions that an Ethical Assessment shall be carried out on all the activities related to stem cell research[13]. Consequently, there is no well-defined set of rules and regulations for stem cell research and States have been given the authority to make their guidelines.

Development of stem cell legislation in the Islamic world

In Islamic countries, stem cell research has made noticeable progress. This is attributed to the fact that many Muslim countries have been funding the development of high-caliber research institutes. These include Tajikistan, Kazakhstan, the Kyrgyz Republic, and the Aga Khan Development Network which together formed the University of Central Asia[14]. Formation of the First Stem Cell Bank in the UAE is currently in progress. It aims to build stem cell tourism in UAE. According to the Market Data Forest, the size of the stem cell market in the Middle East and Africa is estimated to reach around US$2.85 billion by the end of 2026[15]. Recently, the Abu Dhabi Stem Cell Center developed a possible game-changing treatment for coronavirus by devising an approach that regenerates lung cells and inhibits the overactivity of the immune system[16].

Arguments in various countries regarding stem cell research have been made on religious and socio-cultural grounds. These grounds heavily influence the formation of ethical and legislative guidelines. Iran, a Muslim country, does not allow the creation of an embryo for research purposes. It will enable only supernumerary in vitro fertilization (IVF) embryos, aborted embryos, iPSCs, and cord blood or placenta of a newborn for stem cell research. Donated embryos cannot be implanted in the uterus of a woman or any animal and any judgment regarding abortion should have no link to obtaining stem cells from the fetus. The legislation seeks respect for human life and selfless concern for the welfare of all beings[17].

In multi-religious countries like Malaysia, the formation of unified legislation and ethical guidelines for stem cell therapy is challengingt. Each faith has its school of thought and viewpoint related to the production and use of stem cells. The National Fatwa Declaration Committee in 2002 and the Mufti Department of Selangor in 2006 laid out the basis on which stem cell research can be conducted: Stem cells can be derived from adult stem cells, placenta or umbilical cord of the baby with the parent's consent and the process should cause no harm. It can also be extracted from spare embryos stored for IVF or from a spontaneous abortion or miscarriage due to a medical procedure as long as it is per the Sharia Law. The use of stem cells is allowed as long as it follows the Sharia Law[18]. Cloning humans for any cause is not permitted. Contrary to this, according to the views of Christianity in Malaysia, new cells can be created to make new organs and extract the needed DNA. As stated by Buddhism in Malaysia, embryogenesis on the 4th-5th day of post-fertilization is not considered a living thing. In 2009, the revised guidelines for Stem Cell Research and Therapy impelled to include the perspective of other religions in making policies for stem cell research and therapy. However, reaching a consensus was difficult especially related to the 14-day rule that was not approved by Catholics but eventually, it reached a middle ground as in other countries. In Asian countries like Malaysia, India, Pakistan, Singapore, and Indonesia, etc. policy making related to stem cell research will always be dependent on the religious outlook since religion is a component of their constitution[18,19].

Islamic countries that allow research on human embryos

apply the 14-day post-fertilization rule. Some Muslim countries allow for the research to be according to international standards. However, it may not be acceptable to some other Muslim researchers. Therefore, the formation of a uniform legislation internationally, addressing the viewpoints and beliefs of all Muslim nations, must be taken into consideration. Aga Khan University has made such an effort to incorporate and represent everyone to connect and unite science, ethics, law, and medicine scholars from several countries made by to share their ideas with a focus on the Islamic perspective. This effort resulted in the emergence of "The Lisbon Statement" (Thinking Group on Regenerative Medicine, 2019)[14,20]. According to this Statement, a fundamental objective should be made based on the set multi-cultural guidelines similar to ISSCR. This should include the representation of different groups in discussions involving the current practices in science, ethical concerns, and developments in research. It aims at encouraging the involvement of different communities and enhancing international collaboration. Organizations from the United Arab Emirates, Iran, and Malaysia have also contributed to The Thinking Group funded by Aga Khan University[14].

Development of stem cell legislation in Pakistan

From the commencement of the first stem cell transplant SCT by Dr. Tahir Shamsi and his team in 1995 for AML at Ziauddin Hospital[21], developments in stem cell research and transplant facilities in Pakistan have been going on at a slower but steady pace compared to other countries in the region. In the first decade, only 3 centers were established and almost 350 bone marrow transplants (BMTs) were performed. By the end of the second decade, 9 centers were registered with the Human Organ Transplant Authority (HOTA) but there were only 4 active centers, and around 1500 BMTs were performed. Economic challenges were identified as the biggest obstacle in Pakistan's progress of stem cell research and bone marrow transplants. [21,22].

Pakistan's National Bioethics Committee has formulated Protocols/Guidelines for Stem Cell Research/Regulation which the HOTA has aopted. These guidelines were congruous with the religious sentiments and social norms of Pakistan. Comprehensive and elaborate guidelines were constructed to protect patients and bone marrow donors from potential damage. According to the Protocols, all stem cell research and transplant centres need to be registered with and authorized by HOTA and their policies must be approved by it. HOTA oversees the ethical and legal aspects of SCT and research, including the SCT procedure's technicalities. The HOTA is commissioned to visit the stem cell research and transplant field and monitor and collect reports on the projects[23].

The HOTA guidelines state that the use of adult stem cells for particular hematologic conditions is allowed.However, the commercial sale of adult stem cells is prohibited. Acquiring stem cells from a fetus by terminating a pregnancy is also forbidden. It is important to ensure that no harm occurs to the fetus during the of extraction of cord blood stem cells and the precise time of umbilical cord clamping is also determined. Informed consent entailing the risks and benefits related to the procedure should be attained from the parents; in case of any conflict maternal wishes will be prioritized[23].

The HOTA guidelines also state that an embryo cannot be created exclusively for acquiring stem cells; only the extra embryos can be used after seeking permission from the couple in the IVF clinics. Using human ESCs and fetal/adult cells for in vitro exploration is admissible. In vitro culture of any embryo for more than 14 days or when primitive streaks appear is not allowed. Although in vivo investigations shall only be permitted on non-primate animals, reproduction of animals that arise from these studies is not allowed. Human cloning and insertion of human embryos in the uterus after alteration at any stage are strictly prohibited[23].

Pakistan is a lower middle-income country with the 5th largest population of about 225,199,929 people according to the World Bank data 2021[24]. There is a massive scarcity of resources compared to the need for SCT and transplants in Pakistan. SCT is hopeful for millions of Pakistanis suffering from thalassemia, leukemia, type 1 diabetes, and other diseases. Therefore, there is a dire need for investments in Stem cell centers and cord blood banks in the government. With the expansion of BMT centers, national donor registration, and advancements in stem cell research, the number of transplants per year is expected to increase[23]. Along with these developments, it is important to ensure that stem cell research projects in Pakistan work closely with the ethics committee, and respecting human rights is of paramount importance. Ethics and legislation guidelines should be reviewed, updated, and monitored effectively at every evolving step. Collaboration with International Stem Cell Research Centers and Organizations is imperative for the growth of SCT in Pakistan. It is important that all trained professionals work in unison to handle any ethical or legal conflict that may arise regarding SCT.

This article is the only comprehensive review from Pakistan that compares the ethical barriers and guidelines

in Pakistan on stem cell research and therapy with other countries. However, we believe that further analysis is required to expand on the implementation of the legislation in Pakistan and its implications. This article does not present an in-depth interpretation of stem cell ethics and legislation in Islamic countries. However, it includes various up-to-date articles and studies from the Muslim World and Asia.

Conclusion

Even though there has been great progress in stem cell research, it is still the tip of the iceberg. Utilizing the immense potential of stem cells will be a game changer. . The progression in stem cell research and therapy has also given rise to a discussion on its ethicality; as the ethics are usually based on the morals of the region. Currently, there is no well-defined set of rules and regulations for stem cell research and States have been given the authority to make their own guidelines. We believe an unambiguous, clear, and unanimously accepted legislation is needed that is also revised regularly to keep up with the pace at which research in stem cells is advancing. With global advancements, we must focus on an international body that can form widely accepted legislation that strictly regulates the ethical aspect of stem cell research and therapy and addresses the religious and cultural concerns of all groups.

Acronyms

- Embryonic Stem Cells – ESCs
- Induced Pluripotent Stem Cells – iPSCs
- International Society for Stem Cell Research – ISSCR
- United Nations Educational, Scientific and Cultural Organization – UNESCO
- International Bioethics Committee – IBC
- Human Organ Transplant Authority – HOTA
- Bone marrow transplant – BMT
- Stem cell therapy – SCT

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