Ethics of Modern Stem Cell Research and Therapy: Current Critical and Interdisciplinary Perspectives

Ernst R. von Schwarz[1,2,3,4,*], Karine Vartanian[3], Paul Bogaardt[2,3], Aubriana Angel Schwarz[2,3], Laurent Cleenewerck de Kiev[4]

[1]Cedars Sinai Medical Center, Los Angeles, CA

[2]Pacific Heart Medical Group, Murrieta, CA

[3]Dr. von Schwarz Medical Anti-Aging Institute, Los Angeles, CA

[4]Euclid University, Washington, DC

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Corresponding author:

Ernst R von Schwarz, Cedars Sinai Medical Center, Los Angeles, CA, USA

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Abstract

From an academic and clinical point of view, stem cell therapy represents one of the most promising advances in modern medicine, with the ability to partially induce the regeneration of acutely injured or chronically damaged tissues. Stem cell research provides new opportunities for the treatment of various conditions, among them diabetes mellitus, HIV, cardiovascular diseases, and neurodegenerative illnesses. Stem cell therapy is currently not FDA-approved in the US (except for certain blood cancers). While bioethics and religion have mostly discussed the source of cells, i.e., embryonic cells that require the destruction of embryos versus adult tissue for research purposes, we also discuss the controversies with regard to currently offered therapies, and marketing of unapproved procedures from a scientific, clinical, and religious viewpoint.

Introduction

Stem cells have the remarkable potential to develop into many different cell types in the body. These self-renewing precursor cells serve as a sort of repair system and can replenish cells with specialized functions, such as red blood cells, muscle cells, etc. There are diverse sources of stem cells: umbilical cord, placental tissue, bone marrow, amniotic cells, adipose tissue, among other sources. The main types of stem cells of research interest at the present time include embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs), and adult stem cells. Based on the differentiation capacity stem cells can be divided into totipotent, pluripotent, oligo – and unipotent. According to the method of production, there are two groups of stem cells: allogeneic (derived from a donor) and autologous, or person's own cells. Allogenic stem cells might potentially trigger an immune response of likely minor clinical relevance.

Adult stem cells, also known as somatic stem cells, are oligo- or unipotent, which means they can only differentiate into limited types of cells, maintaining the self-repair and tissue homeostasis, making them a weaker alternative compared to embryonic derived stem cell products.

Embryonic stem cells (ESCs) are derived from 4-5 days old pre-implantation embryos (the inner cell mass of the blastocyst), that have been fertilized in vitro and donated for research purposes following informed consent. ESCs are pluripotent and are capable of differentiating into any type of ectodermal, mesodermal, or endodermal cells. The fact that ESCs harvested by the destruction or at least manipulation of the blastocyst, raises ethical issues. Disputes regarding if the 5-day- blastocyst has the same moral considerations as embryos in the post-implantation stage development continue creating controversy surrounding their use. It is difficult to answer the question, from what point of development can a fertilized egg be considered a human being. For some including the Catholic church, life begins with conception, i.e. with fusion of male and female gametes, some consider life from the moment of implantation of the blastocyst to the wall of the uterus, others at a time when the embryo becomes a fetus (around the 8^{th} week after fertilization). In any case, usage of embryonic stem cells does require the destruction or killing of the embryo, which in many cases is considered in surplus embryos, i.e. those considered medical waste from infertility clinics.

One of the potential solutions to the ethical issue of destroying embryos and thus, killing life, was the discovery of induced pluripotent stem cells (iPSCs) by Shinya Yamanaka and Kazutoshi Takahashi, in 2006. iPSCs are a type of pluripotent stem cells that can be lab-generated directly from an adult somatic cell (like a skin cell) and act like ESCs. Induced pluripotent stem cells can be patient-matched, which means that each individual could have their own pluripotent stem cell line. These unlimited supplies of autologous cells could be used to generate histocompatible transplants without the risk of immune rejection. iPCs are typically derived by introducing products of specific sets of pluripotency-associated genes (Myc, Oct3/4, Sox2, Klf4) or reprogramming factors into a given cell type [40].

Human-animal chimeras contain cells from both animals and humans, they are offering potential innovation in stem cell research, but also bringing up ethical concerns. “Chimera” has been defined as an organism, that derives from two or more zygotes and therefore contains cells of different genotypes. Commonly used techniques to acquire interspecies chimeras include injecting human pluripotent stem cells into animal embryos with further development of human tissues, removing the nucleus from an animal egg, and replacing it with a human cell nucleus. Human-animal chimeras provide the ability for disease modeling, organ growth, and drug testing. The most obvious advantage of chimera organs is that they would provide an inexhaustible source of organs for transplantation with a low risk of immune rejection. However, crossing the species boundaries between humans and animals also remains a major ethical issue. Creating chimeras with significant human brain development could lead to concerns regarding the dissolution of the distinction between humans and animals. According to ISSCR guidelines, “to avoid unpredictable and widespread chimerism, researchers should endeavor to use targeted chimerism strategies to limit chimerism to a particular organ system or region of the gestating chimeric animal” (ISSCR, 2021). Animals may develop structural and physiological abnormalities due to the implantation of human stem cells, raising concerns regarding anticruelty animal rights. Researchers are committed to improve techniques and investigate alternatives to minimize animal suffering. ISSCR guidelines for the transfer of human pluripotent stem cells and their direct derivatives into animal hosts provide guidance for designing and conducting stem cell research, considering animal welfare (ISSCR, 2021). Further discussions and guidelines are required, as this field of stem cell research progresses.

Studies applying microfluidic technology,“organ-in-a-dish” and 3D bioprinting using stem cells have been published, revealing new opportunities for disease modeling, drug development, and regenerative

medicine [11]. Organoids are in vitro-generated 3D structures that mimic the function and organization of real organs, that resembles an organ of interest in a relatively simplified form. Being a more complex and realistic model of human tissues compared to traditional 2D cell cultures, organoids may not fully represent features like vascularization, the immune system, the elimination system for removal of metabolic waste, and other aspects of a whole organ. Countless organoid systems have been created for the brain, heart, lung, liver, etc., revolutionizing stem cell research and providing a powerful tool to study disease modeling, potential therapies and pharmacodynamics, gene editing, and regenerative medicine. However, researchers should be aware of ethical issues that may arise in the future as organoid models become more complex through long-term maturation or through the assembly of multiple organoids.

This debate includes the research use of induced pluripotent stem cells, which have tremendous potential in regenerative medicine, but for which long-term outcomes remain unknown at this time [10, 31]. In addition, the use of so-called 'medical waste' for the extraction of stem cells from different tissues including embryonic tissue remains understandably controversial [22]. However, this long-term issue is eroding as with appropriate manipulation, cells such as skin cells can now be induced to be like and act like embryonic stem cells, i.e., pluripotent cells that can develop into any tissue to repair damage and thus, enhance the concept of translational regenerative medicine [25].

In this review, we aim to describe the current state of affairs on stem cell research and federal regulations in the United States, followed by a critical discussion about ethical, moral and religious issues that might be of concern to the general public.

Even though stem cell research is still in its early stages of clinical investigations, lacking a significant amount of reproducible data from large scale controlled studies, stem cell therapy has gained widespread attention among the public in recent years due to anecdotal reports of healing of paralysis or cure from HIV or improvements of injuries and chronic degenerative diseases.

Despite the fact that stem cell therapy is not approved by the FDA in the US or elsewhere, there are hundreds of clinics offering unapproved therapies for cash worldwide for a multitude of diseases, oftentimes using marketing of false claims of cure of incurable diseases to attract desperate patients. On the other hand, however, the vast majority of studies conducted so far using stem cell have shown benefits and many patients report anecdotal improvements of chronic debilitating diseases such as heart diseases or neurodegenerative diseases, among others.

Still, ethical issues and public concerns surround stem cell research and therapy, which is widely considered one of the most socially controversial areas of modern science [35].

A literature review was conducted to identify publications related to the ethics of modern stem cell research and therapy. PubMed, JSTOR, Scopus and Google Scholar databases were used.

Clinical Stem Cell Research

For about two decades, credible studies have demonstrated the potential benefits of stem cells for the regeneration of damaged tissue, in particular regarding clinical benefits in patients with cardiovascular and neurodegenerative diseases. In and around the year 2000, several landmark studies were conducted and published that demonstrated promising results using stem cell therapy to obtain measurable improvements of mobility and symptoms in patients with Parkinson's disease [16, 29, 41]. The same applies to patients with cardiovascular diseases after heart attacks [24, 34, 44] or with congestive heart failure [7, 13, 6, 5, 14]. As of this writing, there is a consensus among scientists that stem cell therapy

represents a milestone for regenerative therapy, which at least in part challenges the old dogma of irreversible tissue damage after ischemia with the possibility to achieve repair and reverse degeneration caused by trauma, hypoxia, or aging.

While the scientific world is enthusiastic about the potential of regenerative medicine, the demand for medical care among the public, especially for incurable chronic diseases, has created a sizable business offering unapproved stem cell therapies outside randomized clinical trials for cash [15]. While many providers report anecdotal success stories using stem cell therapies for a variety of conditions from arthritis to HIV to neurodegenerative diseases, there remains a lack of large-scale reliable scientific data from controlled clinical studies supporting the beneficial concept as well as the risk-benefit ratio.

Politics and Federal Stem Cell Research Funding

Due in part to the political leadership and stance of the federal administration in the United States, stem cell research is either merely tolerated or, at times, promoted. The Dickey-Wicker Amendment is the appropriation to a bill passed by the United States Congress in 1995 and signed by former President Bill Clinton, which prohibits the United States Department of Health and Human Services (HHS) from using appropriated funds for the creation of human embryos for research purposes in which human embryos are destroyed. It is important to mention that the Dickey-Wicker Amendment defines the use of federal funding for human embryo research, but not the experimentation itself.

In 2001, President George W. Bush (Republican) announced that the federal government would only support research on the currently 64 existing lines of human embryonic stem cells but did not allow the creation of new cell lines from human embryos. However, there was a significant increase in state-level funding of stem-cell research in response to the Bush federal limitations. This surge in state-level funding partially counterbalanced a limitation imposed by the federal government and helped to maintain and advance stem cell research in the US. California, New York, New Jersey, and Massachusetts were among the frontrunners in providing state funding for stem cell research. California, for example, created CIRM in response to the Bush restrictions; and that state creation has since funded nearly $4 billion in stem cell research, including 68 clinical trials in humans.

The National Institutes of Health Guidelines for Research Using Human Stem Cells (effective on July 7, 2009) set federal regulatory policy. The document designated the definition of human embryonic stem cells (hESCs) and the eligible sources of hESCs, postulated that individuals donating embryos for research purposes should do so freely, with voluntary and informed consent.

In 2009, President Barack Obama (Democrat) removed barriers for responsible scientific research involving human stem cells, and federal funding for stem cell research increased to $200 million per year.

The Stem Cell Therapeutic and Research Reauthorization Act of 2015 provided five additional years of funding for the US national network of cord blood banks and for the associated registry, patient aide programs, and outcomes monitoring.

During the presidency of Donald J. Trump (Republican), the Department of Health and Human Services spent approximately $115 million on embryonic tissue research. Further, a mandatory review by an ethics advisory board was initiated to evaluate all fetal tissue research applications. In April 2021, the administration under current President Joe R. Biden (Democrat) completely reversed prior restrictions, deleted the ethics review for grant applications, and re-instated intramural fetal tissue research by the National Institutes of Health.

In summary, we can emphasize that no federal law ever did ban stem cell research in the United States, but only placed restrictions on funding and use. Although, there are certain restrictions on stem cell research implemented by several states [3].

The FDA on Stem Cell Therapy

Whereas stem cell research usually does not directly affect patient care directly, the business of offering unapproved stem cell therapies to patients for different conditions falls under the US Food and Drug Administration (FDA) as a regulatory federal agency whose main task is to protect the consumer/ patient from harm. Despite the relatively large number of small studies supporting the concept of stem cell regeneration, there is no FDA approval for any stem cell product for any disease at the current time (with the exception of stem cell transplantation for certain forms of blood cancer). In contrast, the FDA publicly warns against unapproved therapies using stem cell products. Nevertheless, there are over 7600 clinical trials of stem cell treatments posted on different websites including clinicaltrials.gov for a large variety of different conditions, including many that are considered incurable.

Ethical Issues of Stem Cell Research

Among the general public, there is a common but inaccurate belief that all stem cell research and therapy require the destruction of human embryos. For many, this would create a conflict due to moral, ethical, cultural, and religious convictions.

Stem cell research, as a human-subject research, necessitates strict ethical guidelines to protect participants. Fundamental ethical principles that govern it, include respect of human dignity, autonomy, beneficence and justice. In 1974 the National Research Act provided guidelines for human subject research to regulate the use of human experimentation in medicine (National Research Service Award Act of 1974). The resulting Belmont Report, published in 1978, further summarized ethical principles and guidelines for human subject research (The Belmont Report, 1979). These principles remain the basis for the United States Department of Health and Human Services (HHS) human subject protection regulations. Applications of these principles to conduct research require fulfillment of informed consent, assessment of risk and beneficence, and selection of human subjects in research. Institutional review boards (IRBs) have the federally mandated responsibility to review research involving human subjects to ensure that a proposed protocol meets the appropriate ethical guidelines before subjects may be enrolled in the study [43].

Whether stem cell research involves embryonic material or might create or worsen malignancies or could even interfere with the natural biology of the course of life from conception to natural death, such are among the ethical, cultural, and religious controversies associated with stem cell research and therapy.

Scientific Professional Society Guidelines

The International Society for Stem Cell Research (ISSCR) was formed in 2002 as a 501(c)(3) nonprofit organization. The society published its first guidelines in 2006 entitled “Guidelines for the Conduct of Human Embryonic Stem Cell Research,” (ISSCR guidelines, 2007) with the addition of “Guidelines for the Clinical Translation of Stem Cells” in December 2008 (ISSCR guidelines, 2009). The ISSCR Guideline Updates Task Force published a revised guideline in May 2016 (“Guidelines for Stem Cell Research and Clinical Translation,” [21]) followed by a subsequent revision in 2021 [23]. In its original version, the guidelines proposed that research institutions should create Stem Cell Research Oversight Committees. Also, an Embryo Research Oversight process was suggested in the 2016 guidelines. The

updated 2021 guidelines covered the culture of human embryos and stem cell-derived models of embryonic development, together with more robust clinical translation guidance. The guidelines also include categories that are considered unsafe or unethical, such as genome editing for reproductive reasons or human reproductive cloning. The ISSCR also recommends "to forcefully caution against the premature commercialization of unproven stem cell-based interventions."

First proposed in 1979, the international ethical standard, the 14-day rule limited the development of human embryos in a laboratory setting to a maximum of 14 days after fertilization. Some researchers challenged the 14-day limit to further study human embryo development, while opponents argued about crossing moral boundaries and unintended consequences from manipulating human development at this stage. "It is currently not technically feasible to culture human embryos beyond the formation of a primitive streak or 14 days post-fertilization. However, culture systems are evolving, making this a possibility in the near future." (ISSCR, 2021, 12-13). In 2021, the International Society for Stem Cell Research (ISSCR) removed the 14-day rule from its guidelines. According to recommendation 2.2.2.1, the ISSCR now encourages a case-by-case review process with stricter oversight for research exceeding 14 days. As stem cell research continues to evolve, ongoing regulations are necessary to balance scientific innovations with ethical concerns.

Religious Issues and Stem Cell Research

Contrary to what is often assumed, most religions (including the Roman Catholic Church) do not oppose stem cell research and therapy. A recent report from the United States Conference of Catholic Bishops stated that any research using stem cells is supported, with the exception of using embryonic-derived stem cells if this means the destruction of a human embryo. Even if the embryonic blastocytes are considered medical waste since they are not meant to be implanted into a uterus but destroyed and wasted (as in the case of IVF-created embryos that are no longer to be used), the Catholic Church strictly opposes the destruction of any embryo since life begins with conception in a traditional Christian view. As early as August 2000, the Vatican's Pontifical Academy for Life had issued a statement strictly opposing embryonic stem cell retrieval while even now financially supporting the use of adult stem cells for research and therapeutic purposes, as declared in 2010 [42].

Besides this, several publications have addressed the ethical issues from the Catholic point of view on the appropriate performance of stem cell research. A position paper from 2006 by Prieur et al. examined how such research could be conducted legitimately in a Catholic institution by using an ethical analysis involving a narrative context, the nature of the moral act, and the principle of material cooperation, along with references to significant ethical assessments [32].

Only a few studies addressed the issues of ethical viewpoints. As an example, a small study from Malaysia used face-to-face interviews among religious leaders to evaluate their position on embryonic stem cell research which revealed that representatives of Hinduism and Buddhism did permit embryonic stem cell research with some reservations as long as a viable rationale is provided for the purpose of alleviating pain and suffering. By contrast, Catholics opposed embryonic stem cell research on the basis of the protection and inviolability of human life, and even oppose if the source of the embryonic stem cells is from infertility treatments that otherwise would be discarded [39, 38].

By comparison to the Catholic view, contemporary Judaism defines an individual as a human being with a separate existence, by contrast to the human embryo, which is still directly dependent on the mother. Thus, an embryo is not strictly speaking "a person" but a potentiality that should not be considered a mere object to be used [33]. On the other hand, treatment with embryonic cells is tolerated

in Judaism as a clear preference for live and self-sustaining individual over 'a cluster of cells' [2].

Islam is typically not presented as having an overall or official doctrine on the use of embryonic stem cell research. According to Islamic teachings, an embryo in the early stage of pregnancy does not have a soul, while other scholars argue that the termination of an embryo at any stage of pregnancy is morally impermissible [4]. Several discussions, however, are ongoing with different opinions on stem cell research and the permissibility of using embryonic tissue.

Besides embryonic stem cells, other tissues have stem cells that can be more easily retrieved without ethical religious concerns, such as adipose tissues or cells obtained from bone marrow biopsies from the patient (as autologous material). Besides this, donor-provided stem cells from Wharton's jelly, umbilical cord blood and placenta tissue are in use for allogenic stem cell research and therapy within the frame of clinical studies.

The creation of induced pluripotent stem cells from adult (skin) cells offers an alternative to embryonic tissue. However, potential harmful issues of immunogenicity and mutagenesis (cancerogenicity) are yet to be evaluated.

Discussion

The more people are educated, the higher the likelihood for a broader acceptance of stem cell research in general, as long as ethical and religious boundaries are kept. A recent Japanese survey explored the public versus the scientific communities' view on stem cell research with 2,160 public responses and 1,115 responses from members of the Japanese Society for Regenerative Medicine. Whereas the public was more interested in practical questions such as treatment costs and risk, the researchers were more intrigued by scientific outcomes [36].

A survey from Saudi Arabia revealed a high degree of misconception regarding whether stem cell therapies are approved and officially recommended [1]. This article overstates a "high risk of cancer with stem cell therapies," which is a controversial position. In contrast, there is a potential for stem cells to be beneficial for different types of cancer (besides allogenic stem cell transplantation for certain blood cancers,) [37] such as mesenchymal-derived stem cells for pancreatic cancer, and the possible effects on prostate cancer [20] and glioblastoma are under investigation [9, 8, 30].

Due to the lack of objective information coupled with an overwhelming amount of advertising and marketing materials on the web, the general public can be described as misled rather than informed about the pros and cons of the current stages of stem cell research and therapy.

For many researchers, there are no major ethical issues in conducting stem cell research, while some in the medical research fields argue it might even be unethical not to try to find ways to alleviate suffering from different diseases if there are potential ways to use regenerative technologies. As someone argued about placebo whether it is unethical to use it or unethical not to use it [12], stem cell proponents might have similar thoughts that it is unethical not to study and discover what nature offers by exploring the body's own cells and their properties and how to use them to repair the damage, considering the medical consensus that it is acceptable to use chemicals (drugs) or external forces (radiation) to manipulate and hopefully treat our bodies.

Even though stem cell therapy is not currently FDA-approved, there are public, scientific, and even ethical expectations to conduct pre-clinical and clinical studies to evaluate the safety, tolerability, and efficacy of stem cells for certain diseases. It should be prohibited to market false claims of cure for

incurable diseases, which result in false hopes in desperately sick patients. Within the framework of approved clinical trials, however, the effects and safety profiles of stem cell therapies need to be further evaluated.

In view of the enormous disease burden, costs, social isolation, frailty and poor outcomes of age-related diseases such as heart failure, arthritis, and dementia among others, an informed claim can be made that active stem cell research is ethical and needed considering the common higher good and the need to alleviate suffering for patients as we search for regenerative modalities to increase not only health span but also to improve mobility as well as physical and mental functionality with improved quality of life.

A brief review of the ethical issues surrounding stem cell research and therapy can purely stimulate more questions and discussions in order to educate the public rather than providing answers and solutions. In view of the current practice of unapproved stem cell therapies offered by hundreds of clinics in the US and elsewhere - oftentimes outside the academic world of controlled clinical trials -caution is advised regarding non-scientific approaches and deceiving marketing claims of cures of incurable diseases. On the other hand, however, the vital quest to further evaluate methods of regenerative medicine to relieve suffering, reduce pain and inflammation, and provide some degree of regeneration of damaged tissue undoubtedly has a promising future in modern medicine and anti-aging therapy ahead, is unopposed by all major religions, and demands more public, philanthropic, and industrial support.

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