

HUMAN EMBRYONIC STEM CELLS WHERE TO DRAW THE LINE

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Abstract

Introduction: Human-embryonic stem cells (hESC) are derived from very early stages of the human embryo. These cells have immense plasticity and can be conditioned to develop into any type of cell of the human body. Despite all their promising utility, hESC researches have recently been the subject of fervent debate.

Objective: This paper explores the implications of hESC therapy from a bio-ethical perspective.

Method: Published literature with strict inclusion and exclusion criteria was extensively reviewed through use of general and meta search engines to elucidate the applications and implications of hESC.

Discussion: Studies indicate that the potential of hESC in reconstructive and regenerative medicine is undisputable but complex social and moral issues are hopelessly intertwined beneath the pleasant facade. hESC offer endless possibilities in understanding bio-molecular disease patterns, supplying readymade healthy organs, interpreting aging and organogenesis at the cellular level. The use of hESC is well established in leukemia and scientists anticipate diverse applications in a wide range of congenital and acquired medical conditions. However, many dilemmas arise in context of their biomedical usage because of the destruction of donor human embryos in producing stem cells, adverse transplant reactions, teratogenicity, phenotypic / genotypic abnormalities, non-standardized research laws, logistic issues and the possibility of eternal life and humanoid chimeras.

Conclusion: The wisdom to choose between 'mindful utilization' and 'senseless exploitation' lies with us. The large scale commercialization of human life or the killing of viable embryos cannot be justified by any means. A neutral approach with increased involvement of uncontroversial progenitors should be adopted.

Keywords: Embryo, stem cell, research ethics

Introduction

Despite its significant advancements, modern medicine still offers an incomplete solution to many health issues facing mankind. Many people in need of therapeutic transplants are forced to wait months, and perhaps even years, to receive these services. There are many medical conditions that are still untreatable. There are congenital or familial disorders that are yet unpreventable. These are just some examples of

the types of challenges that patients and their families may confront in the modern health care setting due to lack, scarcity or unavailability of medical resources, substitutes and solutions.

The promise of human embryonic stem cells: Human Embryonic stem cells (hESC) are undifferentiated pluripotent cells derived from early stage human embryos. hESC can differentiate into all three embryonic germ layers, and finally into more than 150 specialized somatic cell types. Through the utilization of hESC, scientists dream of harvesting its immense plasticity in regenerative and reconstructive medicine. Stem cell researches promise a better understanding of the ageing and organogenesis phenomenon, genetic trends of familial or congenital disorders and the bio-molecular patterns of diseases. There is likelihood of using such cells for drug development, toxicity testing, study of developmental processes, gene control, trauma repair, rejection free auto-transplantation and developing an inexhaustible array of specific therapeutic cells for use with bone marrow, nerves, heart muscles and pancreatic islets. Today, stem cell therapy is well established in leukemia and scientists anticipate diverse applications in a wide range of medical conditions like parkinsonism, spinal cord injury, myelopathy, sclerosis, diabetes, renal and lung cancers, birth defects etc^{1,2}. In a nutshell, the stem cell revolution aspires to offer a permanent intervention at the cellular level to alleviate most of man's ailments.

Human embryonic stem cells- An ongoing debate: In spite of their vast therapeutic potential, the most critical issue in hESC based researches is the source of stem cells themselves; the human embryo, which is invariably killed /destroyed during the production of stem cells. Presently, two schools of thought have emerged; the humanitarian traditionalists who regard stem cell oriented studies a source of callous feticide that is equivalent to genocide and the utilitarian modernists who enthusiastically advocate the immense biomedical value of stem cells³. At this intersection, it may well be asked: Can the killing of human embryos for stem cell genesis be justified? And if so, to what extent can we validate depriving a 'growing person' the right to live and contribute socially and intellectually to humanity? This paper elucidates some ethical, moral, social and regulatory issues that are hopelessly intertwined with hESC.

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Methods and Materials

An extensive review of published literature was done through use of general and meta search engines (google scholar, pubmed, ovid, science direct) to harvest prominent medical database (medline, embase, cochraine). The search strategies used were 'Mesh' (key terms used were: embryo, stem cell, research ethics etc), 'Text word' searching, 'Reference list harvesting' and 'Related articles' feature. Strict inclusion and exclusion criteria were applied to include 75 articles ranging from the year 2000 through 2011, based on context relevance. Key journals from Jazan medical library were hand searched for further information.

Discussion

hESC are derived from the inner cell mass of a developing blastocyst. (the early stage of a human embryo). Embryos created for the sole purpose of research may either be produced by fusion of donated gametes (therapeutic / reproductive cloning) or by somatic cell nuclear transfer / (SCNT) / non reproductive cloning. Surplus or unused embryos can also be obtained from infertility treatment clinics, for use in stem cell laboratories. hESC lineages can also be cultured from tissues of 8 to 10 week old aborted fetuses.

Human embryonic stem cells- some dilemmas to wrestle:

Legal framework: a patchy piecemeal: The laws on hESC are not comprehensive or homogeneous. There are variations in the policy models not only across countries but even across states in some countries. Table I shows the hESC research policies of different countries of the world. While some countries permit production of hESC by reproductive cloning, others ban it. Some countries permit embryo genesis

only by sexual methods. Others legalize use of donated embryos from willing persons and infertility clinics^{4,5}.

Research ethics committees adopt varied review policies for hESC based studies. While some authorities claim it to fall under human subject research (if egg/sperm/somatic cell donors are identifiable); others state it to fall under animal subject research (if cloning with animal cells is involved). Still other authorities suggest that it is cellular biologics and falls under none of the categories mentioned above. Hence, one can well imagine the extent of legal haziness around the issue of hESC. A potential challenge for key stake holders lies in developing standardized benchmark guidelines for hESC creation and usage. This lack of standardization often leads to abuse and malpractice in researches when cell lines are unlawfully obtained or cultured or unregistered lineages are used for the sake of convenience.

Moral status: Is the embryo a human equivalent? For many stakeholders, commitment to stem cell research is a commitment to 'business as usual' in the medical community, where the benefits of hESC outweigh the odds of embryo killings. But the question still lurks in the background: "What is the moral status of the embryo that needs to be sacrificed?" In broad terms, an embryo is described as 'anything beyond a fertilized egg'. Staunch idealists like Eisenberg⁶ opinion that "one may not set aside one person's (embryo) life for the sake of another." Hence we can infer the moral status of an embryo as equivalent to any other alive individual⁷. A new wave of research suggests that from a very early stage of intrauterine development, the fetus can feel, dream and even enjoy rhymes⁸. As early as the first trimester, it yawns, sucks, smiles, swallows as well as smells.

Table-I: World stem cell map showing the policies of different countries in human embryonic stem cell research

Stem cell policy: World stem cell map		
Permissive	Flexible	Restrictive policy or no established policy
Permit use of various embryonic stem cell derivation techniques including somatic cell nuclear transfer (SCNT), also called research or therapeutic cloning. SCNT is the transfer of a cell nucleus from a somatic or body cell into an egg from which the nucleus has been removed.	Stem cell derivations from fertility clinic donations only, excluding SCNT, and often under certain restrictions. "Research is permitted only on remaining or unused embryos no longer needed for reproduction."	Restrictive policies range from outright prohibition of human embryo research to permitting research on imported embryonic stem cell lines only to permitting research on a limited number of previously established stem cell lines.
Countries in this category include Australia, Belgium, China, India, Israel, Japan, Singapore, South Korea, Sweden, the United Kingdom and others. All except the U.S. have banned by law human reproductive cloning. These countries represent a global population of more than 2.7 billion people	Countries in this category include Brazil, Canada, France, Iran, South Africa, Spain, The Netherlands, Taiwan, and others. These countries represent a global population of more than 1 billion people.	Countries with a restrictive policy include Austria, Germany, Ireland, Italy, Norway, and Poland.

☆ Adapted from Bioethics committee study guides; Anatolia college model; 2008; United Nations. <http://www.stemcelldilemma.com/worldstemcellmap.html>

Researches indicate that the roots of human behavior begin to develop quite early-just weeks after conception. In fact, well before a woman realizes she is pregnant, her embryo; the organ that looks like a lumpy dough, has already embarked on the most spectacular feat of human development; that will eventually allow the 'growing person' to move, think, feel and behave in a human way. Can we take away the 'right to live' from this 'growing human' who is so much similar to us in almost all aspects? And if we think qualitatively in terms of man power, talent scales and brain power, we might also be depriving humanity of some real time Einsteins, Darwins, Mozarts and Michelangelos.

End of life for whom? Scientists anticipate hESC to provide an unending array of 'ready to use', 'rejection proof' transplant organs. But this scenario raises some questions under certain circumstances. A person who has lived his / her life to the prime, and is now on death bed, requiring urgent organ transplantation; may willfully undergo the procedure as a life saving, medically and ethically valid intervention. However, if acquiring such an intervention includes the need for sacrificing a human embryo, is it morally justified? To what extent can we validate borrowing one person's life for the sake of another one's longevity? The deliberate creation and then destruction of an embryo for stem cell harvest is the primary source of controversy for pro-life supporters. The human embryo is not merely a clump of cells; it is a 'sacred' clump of cells, with a potential that is unbelievable. In destroying potential human babies, are we taking into our hands the divine power to decide about life and death? Along a wider picture, there is a bigger issue associated with the 'embryonic stem cell concept'.

Aftermath on donors: There are emotional repercussions on the mother who undergoes egg/embryo donation. Studies indicate that females who give up their 'would-be-babies' are prone to some degree of psychological discomfort upon the severing of an emotional bond^{9,10}. The feeling of losing a 'potential baby' or destining it to the 'test tubes and scalpels of a stem cell lab' may take its toll in the form of anxiety, guilt and post decision regrets. According to Dipietro JA¹⁰ "The earliest relationship does not begin with birth. Pregnant women construct mental representations of the fetus, and feelings of affiliation or maternal-fetal attachment generally increase over the course of gestation". In light of the former statement, can humanity permit such a sacrifice; as this is not only the sacrifice of one yet 'unborn person', but also the sacrifice of a mother's emotions. While it may be permissible to use life-saving tissue from spontaneously aborted/dead fetuses for hESC production, there is always a fear of encouraging or condoning abortion in such circumstances.

Autonomy and beneficence issues: Often, complex autonomy, traceability or identifier issues and conflict of interests arise over egg/sperm/somatic cell donor informed

consents, ownership rights and patents in case of stem cell lineage production, registry, commercialization or transplantation¹¹.

Considering the fetus to be a growing human person; is it ethically valid to borrow its 'piece of flesh' or even 'a whole life' for research purposes without an efficient consent process? And whose consent must be taken in this case; the growing person (human embryo) or the guardian parent (sperm, egg or somatic cell donor)? There are identifier/ tagging issues; regarding the extent upto which the hESC researcher or biological material recipient is entitled to seek information about the original source or donor. Federal grant funding issues often arise regarding the cell lineages used in research, where cell line origin and cell generation methods are not properly known/exposed. Often, registered cell lines are practically un-usable and those that are viable are unregistered.

While the risk benefit assessment is crucial in stem cell research, it is also more difficult, due to existing knowledge gaps and variable intents. Unfortunately, the current hESC framework is prone to many loopholes and ill defined perspectives.

Regulatory issues: These include the possibility of exploitation or undue coercion of certain vulnerability groups or populations in case of commercialization of egg donors, egg banks or human cell banks. Presently, more than a third of the registered cell lines are of Caucasian origin which depicts the racial imbalance in stem cell harvesting resources. A study by Klitzman and Sauer¹¹. on the payment of egg donors in USA found that most women were unwilling to donate eggs because of absence of payment, rather than ethical concerns. Also, there was a general ignorance regarding research policies among the participants of the study. In such situations, the question is not just 'whether to pay', but also 'who to pay', how much to pay' and 'when to pay'. This holds especially true in resource limited nations where illiteracy, poverty and over population can victimize the less privileged.

Other issues associated with hESC therapy include social stratification, probable person hood alterations among users, therapeutic exceedence and higher expectation induced dissatisfaction and regret. Research personnel and public education is still not sufficient for the proper understanding and awareness of these issues.

Systems barriers: hESC treatment modalities are resource intensive and sophisticated. They require prolonged and specialized trainings for practitioners and evidence regarding the extent of their therapeutic affectivity is not yet fully established in many medical conditions. There are organizational barriers like potential cost of new technologies incurred on health systems, feasibility issues around 'who' is to gain access to these technologies, trust in scientific establishment and regulatory systems, consumer acceptance, user motivation problems and shared responsibility issues of hESC teams. In resource

starved and poor nations, adoption of hESC therapy may even be considered an unnecessary extravagance. Hence, at this point in time, they cannot be made universally available or applicable in the average hospital setting for the common man. Presently, hESC therapy seems to be a privilege that only the elite can afford.

Medical concerns: hESC are associated with some serious medical concerns like the possibility of uncontrolled proliferation in transplants, outright rejections, adverse immune reactions, gross phenotypic and genotypic abnormalities, teratogenicity etc.

Descent into an unknown world of designer therapy? The hESC, with its immense plasticity and unlimited regenerative capacity, tempts us towards futuristic notions like ready-made, inexhaustible chains of organs, surrogate biological systems, duplicate individuals, a-temporal existence and eternal life beyond the physical barriers of time, age and disease. The revolutionary idea of servile clones and chimeras (human-animal mutant transgressions) inspires hopes as well as fears. Yet, we are currently in a realm of fascinating speculation and will require many more years of intensive research to determine the true potential that stem cells hold for us.

Conclusion and Recommendation

hESC promises alluring benefits like creating new evidence based medical knowledge, designing earlier and more effective interventions and improving overall health care. While the uses of hESC are too many and undisputable; ultimately, the wisdom to choose wisely lies with us. The sense-less 'large scale production' or 'deliberate killings' of viable human embryos for stem cell genesis cannot be justified by any means.

A neutral approach should be adopted, to promote application of induced pluripotent cell linings that can resort to an 'embryonic state' without involving any form

of destructive feticide. Also, the embryos created in infertility clinics should be judiciously donated for stem cell researches. Optimized techniques for multiple re-use of the 'source embryo' can further alleviate our moral burden. Uncontroversial progenitors like amniotic fluid, cord blood and adult somatic cells should be advocated in stem cell labs. Such a conscientious approach will incur a minimal loss of human lives. The need of the hour is a structured, standardized and transparent biomedical framework that can optimize use and limit abuse of embryonic stem cells.

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