Embryonic stem cell research in Iran

COMMENT

Embryonic stem cell research in Iran: status and ethics

MANSOOREH SANIEI[1], RAYMOND DE VRIES[2]

[1]Erasmus Mundus Master of Bioethics Fellow, Departmento di Filosofia, Universita Degli Studi di Padova, Piazza Capitaniato 3, 35100 Padova, ITALY email: saniee50@yahoo.com [2] Bioethics Program, University of Michigan, School of Medicine, 300 North Ingalls Street, Rm 7C27 Ann Arbor, MI 48109-0429 USA e-mail: saniee50@yahoo.com

Abstract

Various successes in regenerative medicine by therapeutic cloning have given rise to expectations that treatments will soon be developed for incurable diseases. But using embryonic stem cells for this purpose raises many ethical dilemmas including those about the beginning of human life. Arguments concerning stem cell research and therapeutic cloning in different countries are influenced by both the religious and bioethical traditions which dominate in these cultures. This article examines how these traditions have influenced stem cell research in Iran through an account of scientific advances and the development of regulations on embryonic stem cell research in Iran.

Introduction

Ethics, religion and culture intersect at one of the most divisive scientific issues: embryonic stem cell (ESC) technology.

Reports published in November 1998 by US scientists regarding their success in isolating and cultivating ESC lines (1, 2), caused an intense debate on the ethical, social and legal implications of human ESC research in many countries, one that continues today. Recent debates have focused on "therapeutic cloning" which holds out the promise of life-changing treatments and possible cures for many degenerative diseases, including Alzheimer's, Parkinson's, diabetes, and cardiomyopathies (3). Proponents and opponents of therapeutic cloning argue about the best and worst case scenarios and the ethical, religious and cultural implications of this scientific breakthrough. Some call it the beginning of the end, and others hail its potential for saving lives. However, different communities have expressed different opinions at the national and international levels. For reaching international consensus on the ESC debate, it is necessary to understand specific national arguments (4) and the perspectives of different cultures and traditions regarding ESC technology. It is the intention of this paper to provide an overview of ESC research in Iran, which has assumed a leadership role in this area in the Middle East, to outline the ethical arguments that are central to this debate, and to identify the ethical reasoning underlying the approval of ESC research in Iran.

The development of ESC research in Iran

Iran has a long history of scientific achievement. Prior to the advent of Islam, it was a leader in mathematics and astronomy. However, like the rest of the Middle East, its scientific power declined as Europe entered the Renaissance period in the early 1300s. Over the next several hundred years, Iran developed slowly and was unable to reach its full potential scientifically (5). It is now starting to invest heavily in science, and major developments are occurring in ESC research with the full support of the government.

In 2002, Iran's supreme leader, Ayatollah Khamenei, publicly supported human embryo research and congratulated the scientists who had produced the stem cells. Iran's clerics and political leaders have also actively promoted science and technology in an attempt to enhance the country's global status (6). According to Iran's Shi`ite religious authorities (the Grand Ayatollahs), stem cell research and therapeutic applications are permissible only in the pre-ensoulment stages of foetal development (7). Due to these positive decrees (religious opinion about whether or not an action is permissible) on the use of ESCs for research and therapeutic purposes, Iran is one of the first Muslim countries to produce ESCs (8).

The Royan Institute, one of the leading institutes for stem cell research in Iran, has expanded its work in investigating the potential for ESCs to differentiate into various cell types, such as cardiomyocytes, __cells and neural cells (9). At the same time other research institutes are involved in regenerative medicine. These include the Iranian Molecular Medicine Network (with 34 research institutes and centres as members), the Iran Polymer and Petrochemical Institute, and Shaheed Beheshti University of Medical Sciences (10, 11). The main goal of this research is to understand human cell specialisation and developmental biology and to create specialised cells to treat a wide range of diseases and conditions (12).

In 2003, the Royan Institute reported the establishment of Iran's first human ESC line named Royan H1 ("royan" in Persian means "embryo") from a blastocyst (9). With this achievement, Iran became the 10th country in the world capable of producing, cultivating and freezing human ESCs (13). Since 2004, scientists at the Royan Institute have established five human ESC lines, named Royan H2 to Royan H6. Royan H2, H5 and H6 had the normal (46,XX and 46,XY) karyotypes and Royan H3 and H4 had the triploid (69,XXY) karyotypes which can differentiate *in vitro* to a variety of cell types (12). This achievement, although not a breakthrough on its own, has enabled scientists to pursue many avenues of research in generating therapeutic cells from these cells (5). For example, recent activities have centred on

differentiating human ESCs into endocrine pancreatic-like cells, hepatocyte-like cells, and so on (14, 15, 16).

In the last few years, other fields of stem cell technology have also progressed in Iran, such as bone marrow stem cell transplantation in the hematopoietic disorders, for chronic myelogenous leukaemia and thalassaemia major (17, 18), multiple sclerosis (19), advanced liver cirrhosis, myocardial infarction (20, 21), and peripheral blood stem cell transplantation for thalassaemia major (22). They are the results of activities in, and collaboration between, research centres where the stem cells were prepared and clinical centres where the patients were selected, treated, and followed.

The rapid progress in stem cell technology forced the government to put in place appropriate ethical and scientific supervision of stem cell research and therapeutic applications to make sure that these advances are used responsibly, fairly and humanely. In 2005, the Ministry of Health and Tehran University of Medical Sciences jointly developed a set of guidelines regarding research on gametes and embryos which permitted the use of human embryos for stem cell research and therapy under certain circumstances (7, 23, 24). According to these guidelines, National and Regional Ethical Committees in universities and research centres should supervise ESC research and therapeutic cloning adhering to these guidelines as well as the Ethical Guidelines for Genetic Research (7). The principles behind the Ethical Guidelines for Gamete and Embryo Research are given in brief below:

1. Respect for human dignity and human rights
2. Voluntary and informed participation in research which will not affect the patient's treatment
3. Respect for privacy and confidentiality
4. Equitable distribution of benefits and harms, especially in research, includes clinical treatment
5. Minimisation of risk for the embryo or the future child and maximisation of benefit for individuals and society
6. Prohibition of the production of hybrids using humans and animals
7. Prohibition of eugenics
8. Prohibition of the production of human embryos for research purposes
9. Use of only surplus IVF embryos, below 14 days, for research which includes destruction of the embryo
10. Responsible persons for the embryo are the donor, her partner and recipients
11. All information regarding research and clinical cares of the embryo is available to responsible persons.

However, Iran's approach is currently based on guidelines, not parliamentary legislation (24) and the guidelines are still open for public examination and debate.

Ethical arguments

Most scientists believe that stem cell research will lead to stem cell-based therapies only if scientists can derive new ESC lines. ESCs are needed since their ability to live indefinitely in tissue culture and the wide range of cell types to which they give rise make them unique. Therefore, the most important ethical problem regarding the source and use of ESCs is the moral status of the human embryos which are used to derive stem cell lines. This moral problem brings into tension two fundamental moral principles that we highly value: the duty to respect the value of human life and the duty to prevent or alleviate suffering (25). Now, the question is: shall we destroy one life to save another one or should we ignore the potential of life-saving treatments out of respect for the potential life of the embryo? For the protection of human life and dignity, we should first determine when life begins and the foetus is considered a person.

Scientists' point of view

Scientists, respecting scientific evidence and ethical reasoning, have argued for using human ESCs for treatment, saying that the risks outweighed the benefits. They have stated that, first, ESCs gave hope of treatment or cure for many diseases. Second, the embryos they would work on would be at a very early stage of development. Third, ethics bodies already allow research on embryos up to 14 days for the improvement of IVF (26). Finally, ESC research provides a new tool for basic science, with broad potential applications in genetics and developmental biology (27). From this viewpoint, early embryos have little moral significance. Therefore, there is *not* sufficient reason *not* to proceed with treating embryos as a research resource. Some ethicists have presented a utilitarian argument, that if the products of ESC research *might* potentially treat diseases such as Alzheimer's, or prevent the birth of disabled children, the decision weighed more heavily in favour of proceeding than not proceeding (28). Of course, this is not a strong ethical argument in itself.

Opponents are concerned about the "slippery slope" of this debate, which is that devaluation of human embryos at the very beginning of their life would encourage a policy of sacrificing the vulnerable for the benefit of others. The instrumental use of embryos may increase society's toleration for the loss of life and also make it easier for society to accede to currently more controversial practices involving the ending of life. This, in turn, could put persons with disabilities and the aged at risk (29). According to this argument, even if we do not regard research on embryos as wrong, it may still open the way to dehumanising practices such as embryo farms, "reproductive cloning", "designer babies", the use of foetuses for spare parts, and the commodification of human life (30, 31).

This is a powerful critique - that research on embryos could lead to completely objectifying and commodifying human life. In addition, the religious critique questions when human life begins - at conception, at 14 days, at viability, or at the development of consciousness (32). The debate on research involving human embryos, abortion and IVF existed from the late 1970s, but human ESC research introduced subtle but

important changes into this ongoing debate. However, ethics, religion and culture rightly or wrongly feel threatened by new knowledge and new technology.

Islamic point of view

In Iran embryo research is influenced by the religious belief that full human life with its attendant rights begins only after the "ensoulment" of the foetus (33). Islam is unique among world religions in that the embryological development of humans has been extensively discussed and described in the divine scripture, the Qur`an, and commented on in detail by Prophet Mohammad and the Imams, exemplary teachers who are descendents of the Prophet (34). Ensoulment is generally believed by Muslim scholars to take place at 120 days after conception [although a minority belief indicates ensoulment takes place 40 days after conception (35).] However, a majority of the Shi`ite and some Sunni jurists have exercised caution in making such a distinction[MSOffice1] because they regard the embryo in the pre-ensoulment stages as alive and its eradication as a sin. Based on theological and ethical considerations derived from the Qur`anic passages that describe the embryonic journey to personhood developmentally, and the rulings that treat ensoulment and personhood as occurring over time almost synonymously, it is correct to suggest that Shi`ite and a majority of Sunni jurists will have little problem in endorsing ethically regulated research on stem cells that promises potential therapeutic value (36, 37).

As mentioned earlier, although Iran currently has no comprehensive legal framework for research on human embryos, there are guidelines, namely *the Ethical Guidelines for Gamete and Embryo Research*. Article 12 of the guidelines stresses that generating human embryos for research purposes is forbidden. Moreover, these guidelines have been provided for the use of human embryos below 14 days that were created through IVF techniques, but which are not used in assisted reproduction treatments (23). It seems that Iran sees human dignity violated by the generation of embryos exclusively for research, as the notion of human dignity implies that human life has intrinsic value independent of the approval and aims of others. However, those ethical concerns with regard to intentions and the mode of generating human embryos for research purposes do not apply to supernumerary embryos.

In 2006, Mohammad Abdur Rab, World Health Organisation representative in the Eastern Mediterranean, published a paper that called upon Islamic countries to arrive at a consensus regarding ESC research. He also pointed out that in 2005, 24 Islamic countries had supported the United Nations Declaration on Human Cloning prohibiting all forms of human cloning, while the remaining Muslim countries had abstained or voted against the declaration (38). This suggests that there are other issues beyond the influence of religion or science, that permits new knowledge to be accepted in one country and rejected in another though both may have the same religious background and scientific interests.

Although both science and religion are key factors, the full range of cultural perspectives across countries also drives legislative decisions on ESC research and human cloning. Indeed, religion and scientific progress alone cannot define the debate; other salient issues need to be considered, including cultural traditions regarding respect for human life, human dignity, and human rights; attitudes toward regulation of science; perceptions of the medical and economic values of therapeutic cloning and balance between individual and corporate identity (39).

In ancient Persian medicine, health was valued highly, and an appropriate lifestyle to maintain good health was advocated. In fact, the maintenance of health and the healing of illness were two central goals in health and medicine. Ancient Persian culture valued the accumulation of knowledge and emphasised the importance of helping others, especially the weak. After Islam, Persian culture was inspired by Islamic teaching as well (40). Iran is the only Islamic Republic whose legal system is founded solely on Shi'ite Islamic law or shari'a, which also allows democratic representation. Islamic law has historically been flexible and sensitive to public needs and socio-cultural realities. The differences in rulings of Shi`ite scholars stem from the Hadith (the Prophet's sayings) and are based mainly on the reliability of the narrators of a particular Hadith, and its conformity to the verses of the Qur'an to other similar traditions (32). Moreover, there are two principles invoked by scholars that have aided this flexibility: Istislah (consideration of the public good) and Istihsan (seeking an equitable and just solution), when the logical outcome of a ruling based on shari'a principles is harsh or impractical in application (32, 41). When faced with a health crisis on a large scale, scholars can invoke Istislah and Istihsan in their rulings on medical and health affairs, rather than considering the question in an isolated or theoretical sense as was done in the past (32) or even in the present in some countries.

Conclusion

At the global level, the number of countries that advocate therapeutic cloning and human ESC research while remaining opposed to reproductive cloning, is growing. Some countries, even in the Islamic world, are at the threshold of cutting-edge research in this area. Indeed, at the cutting-edge field of human ESC research, Iranian scientists work with broad government approval and government funding on the potent cells from early-stage embryos that researchers believe hold the promise of curing many diseases. Experts provide the inputs of scientific progress, religious traditions, individual value systems and concepts of humanity and life in order to reach a responsible decision. The flexibility of Islamic scholars in Iran has been promising for scientists in the country. However, while Iran has dealt with the debates regarding ESC research and the moral status of the embryo as regards IVF and abortion, it still needs to get to the roots of the stem cell controversy.

Acknowledgements: *This paper is the result of research performed as part of the educational programme Erasmus*

Mundus Master of Bioethics. We would like to thank Dr Pascal Borry (Leuven, Belgium), Professor Wim Dekkers, Dr Bert Gordijn (Nijmegen, The Netherlands) and Professor Corrado Viafora (Padova, Italy) for helpful suggestions and encouraging support.

References

1. Thomson J. Embryonic stem cell lines derived from human blastocysts. *Science* 1998; Nov 6; 282(5391):1145-7.
2. Pedersen R. Embryonic stem cells for medicine. *Sci Am* 1999 Apr; 280(4):68-73.
3. Bavister BD, Wolf DP, Brenner CA. Challenges of primate embryonic stem cell research. *Cloning Stem Cells* 2005;7(2):82-94.
4. Heinemann T, Honnefelder L. Principles of ethical decision making regarding embryonic stem cell research in Germany. *Bioethics* 2002 Nov;16 (6):530-43.
5. Morrison DWG, Khademhosseini A. Stem Cell Science in Iran. 2006 [cited 2008 Feb 9]. Available from: http://isg-mit.org/resource/isgnews/ind.php?id=353.
6. Walters L. Human embryonic stem cell research: an intercultural perspective. *Kennedy Inst Ethics* J March 2004;14(1):3-38.
7. Larijani B, Zahedi F. Biotechnology, Bioethics and National Ethical Guidelines in Biomedical Research in Iran. *Asian Biotechnology and Development Review* 2007;9(3):43-56.
8. Larijani B, Zahedi F, Malek-Afzali H. Medical ethics in the Islamic Republic of Iran. *East Mediterr Health J* 2005 Sep-Nov;11(5-6):1061-72.
9. Baharvand H, Ashtiani SK, Valojerdi MR, Shahverdi A, Taee A, Sabour D. Establishment and in vitro differentiation of a new embryonic stem cell line from human blastocyst. *Differentiation* 2004 Jun;72(5):224-9.
10. Kinkead G. Stem cell transplants offer new hope in some cases of blindness. *New York Times* 2003 Apr 15. [cited 2008 Aug 31]. Available from: http://query.nytimes.com/gst/fullpage.html?res=9907E7DE103BF936A25757C0A9659C8B63
11. Mirzadeh H, Mohagheghi MA, Ahmadi H, Mirkhani H, Amanpour S, Salehian P. Cartilage tissue engineering for ear as in rabbit model with perforated polyurethane prosthesis: in vivo assay. *Iranian Polymer Journal* 2000;9(2):73-80.
12. Baharvand H, Ashtiani SK, Taee A, Massumi M, Valojerdi MR, Yazdi PE, Moradi SZ, Farrokhi A. Generation of new human embryonic stem cell lines with diploid and triploid karyotypes. *Dev Growth Differ* 2006 Feb;48 (2):117-28.
13. Atighetchi D. Islamic bioethics: *problems and perspectives.* AA Dordrecht, Netherlands: Springer; 2007.
14. Baharvand H, Jafary H, Massumi M, Ashtiani SK. Generation of insulin-secreting cells from human embryonic stem cells. *Develop Growth Differ* 2006;48:323-32.
15. Baharvand H, Hashemi SM, Shahsavani M. Differentiation of human embryonic stem cells into functional hepatocyte-like cells in a serum-free adherent culture condition. *Differentiation* 2008 May; 76(5): 465-77.
16. Baharvand H, Azarnia M, Parivar K, Ashtiani SK. The effect of extracellular matrix on embryonic stem cell-derived cardiomyocytes. *J Mol Cell Cardiol* 2005 Mar;38(3):495-503.
17. Ghavamzadeh A, Iravani M, Jabehdar-Maralani P, Hajrasouliha A, Tavakoli S. Allogeneic peripheral blood and bone marrow stem cell transplantation for chronic myelogenous leukemia: single center study from Iran. *Haematologica* 2003 Apr; 88 (4): ELT13.
18. Ramzi M, Nourani H, Zakernia M, Hamidian-Jahromi AR. Hematopoietic stem cell transplantation for betathalassemia major: experience in south of Iran. *Transplant Proc.* 2004 Oct; 36 (8): 2509 - 10.
19. Mohyeddin-Bonab M, Yazdanbakhsh S, Alimoghaddam K, Ghavamzadeh A, Hooshmand F, Lotfi J, et al. Mesenchymal stem cell therapy for multiple sclerosis *Int J Hematol Oncol BMT.* 2005; 2(5): 10 -4.
20. Mohamadnejad M, Namiri M, Bagheri M, Hashemi SM, Ghanaati H, Zare Mehrjardi N, Kazemi Ashtiani S, Malekzadeh R, Baharvand H. Phase 1 human trial of autologous bone marrow-hematopoietic stem cell transplantation in patients with decompensated cirrhosis. *World J Gastroenterol.* 2007 Jun 28;13(24):3359-63.
21. Mohyeddin-Bonab M, Mohamad-Hassani MR, Alimoghaddam K, et al. Autologous in vitro expanded mesenchymal stem cell therapy for human old myocardial infarction. *Arch Iran Med.* 2007 Oct; 10 (4): 467 - 73.
22. Ghavamzadeh A, Bahar B, Iravani M, Jahani M, Gholibeikian S, Eghbal L. Peripheral Blood Stem Cell Transplantation in Patients with Beta-Thalassemia Major. *IJHOBMT* 2004;1(2):8-10.
23. Medical Ethics and History of Medicine Research Center (MEHR). Guidelines for research on gamete and embryo [Farsi]. 2005 [cited 2008 Jan 20]. Available from: http://mehr.tums.ac.ir/code.asp.
24. Aramesh K, Dabbagh S. An Islamic view to stem cell research and cloning: Iran's experience. *Am J Bioeth* 2007 Feb;7(2):62-3.
25. Hug K. Therapeutic perspectives of human embryonic stem cell research versus the moral status of a human embryo--does one have to be compromised for the other? *Medicina (Kaunas)* 2006;42(2):107-14.
26. Denker HW. Potentiality of embryonic stem cells: an ethical problem even with alternative stem cell sources. *J Med Ethics* 2006; 32 (11):665-71.
27. Rao MS. Mired in the quagmire of uncertainty: The "catch-22" of embryonic stem cell research. *Stem Cells Dev* 2006 Aug; 15(4):492-6.
28. Cregan K. Biotechnology across the Borders of Life. *International Journal of the Humanities.* 2003; 1:1057-64.
29. Nippert I. The pros and cons of human therapeutic cloning in the public debate. *J Biotechnol* 2002; Sept 11 98(1):53-60.
30. Sandel MJ. Embryo ethics - the moral logic of stem-cell research. *New Eng J Med* 2004 Jul 15; 351 (3): 207-9.
31. Caulfield T, Bubela T. Why a criminal ban? Analyzing the arguments against somatic cell nuclear transfer in the Canadian parliamentary debate. *Am J Bioeth.* 2007 Feb;7(2):51-61.
32. Hedayat KM, Shooshtarizadeh P, Reza M. Therapeutic abortion in Islam: contemporary views of Muslim Shiite scholars and effect of recent Iranian legislation. *J Med Ethics* 2006 Nov ;32 (11): 652-7.
33. Larijani B, Zahedi F. Islamic perspective on human cloning and stem cell research. *Transplant Proc* 2004; 36(10):3188-9.
34. Daar AS, al Khitamy AB. Bioethics for clinicians: 21. Islamic bioethics. *CMAJ* 2001 Jan 9;164(1): 60-3.
35. Hathout M. Cloning: Who will set the limits? *The Minaret* 1997 Mar; 19(3):8.
36. Al-Aqeel AI. Ethical guidelines in genetics and genomics. An Islamic perspective. *Saudi Med J* 2005 Dec;26(12):1862-70.
37. Sachedina A. Islamic perspectives on cloning. 2006 [cited 2008 Feb 12]. Available from: http://www.agora.forwomeninscience.com/bioethics/2006/09/islamic perspectives on clonin.php.
38. Abdur Rab M, Khayat MH. Human cloning: Eastern Mediterranean Region perspective. *East Mediterr Health J.* 2006; 12 (Suppl 2):s29-37.
39. Prentice DA. Cloning and culture: legislation at home and abroad. *Georgetown Journal of International Affairs.* 2004 Summer/Fall; 5(2): 65-72 .
40. Yar-Shater E. The History of Medicine in Iran. Encyclopaedia Iranica Foundation 2004.
41. Aksoy S. Making regulations and drawing up legislation in Islamic countries under conditions of uncertainty, with special reference to embryonic stem cell research. *J Med Ethics* 2005; 31(7):399-403.