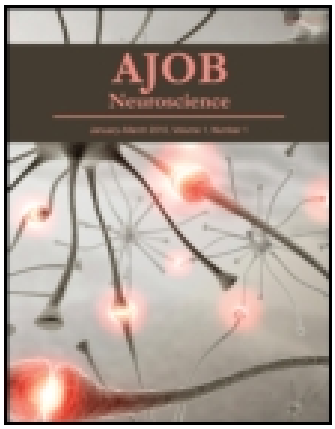

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Ethical Challenges of Stem-Cell Transplantation in Parkinson's Disease: Islamic Viewpoint

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Ethical Challenges of Stem-Cell Transplantation in Parkinson's Disease: Islamic Viewpoint

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We read with great interest the article entitled "Ethical Criteria for Human Trials of Stem-Cell-Derived Dopaminergic Neurons in Parkinson's Disease" by Hurst and colleagues (2015). Hurst and colleagues discussed three challenges with relation to such trials: participant selection, informed consent, and sham surgery.

Over the past two decades, the clinical application of stem cells has dramatically shifted from the treatment of blood disorders and malignancies to several different areas of medicine, including neurological disease such as Parkinson's disease (PD) (Barker and de Beaufort 2013). Stem-cell transplantation appears to be a promising choice for the treatment of neurological diseases. However, extra work that improves our understanding of stem cell biology will help us move a step forward and identify the best cell type to use (Batista et al. 2014). Previously, nerve cells from suprarenal medulla were transplanted to treat Parkinson's disease. The international boxer Mohammed Ali Clay had such an operation and it had no effect on his condition.

The question is raised: Should patients with Parkinson's disease participate in research involving stem-cell treatments? And are induced pluripotent stem cells the ethical solution to the moral issues pertaining to embryonic stem cells?

A stem cell is defined as a cell that has the ability to continuously divide and differentiate into various kinds of cells/tissues, thus generating large numbers of cells from a limited source. Stem cells are derived from the embryo (e.g., embryonic stem cells [ESCs]) or fetus, or the umbilical cord at time of birth, or from the adult (e.g., bone-marrow mesenchymal stem cells) (Barker and de Beaufort 2013).

During the first wave of cell trials of neural transplantation in the 1980s and 1990s, the most extensively debated ethical issue related to the use of human fetal tissues was derived from elective abortion for research and clinical development into neuronal therapies. Intentional destruction of the embryo at the blastocyst stage to create the ES cell line has attracted major and sustained resistance from religious and political "pro-life" groups, in particular in the United States and some Catholic European countries, resulting in political pressures to ban all such research (Dunnett and Rosser 2014).

The key ethical issue with the human embryonic stem cells (hES) is how they are derived and what it means for the embryo from which they are generated, since the generation of an hES involves destruction of the embryo. Also, at what point does humanness or personhood start in the developing human embryo or fetus (Barker and de Beaufort 2013)?

So, what are the Islamic views in this matter? Islamic bioethics derives from a combination of principles, duties, rights and virtues. It is intimately linked to the broad ethical teachings of the Qur'an and the tradition, legal ways of the Prophet Muhammad (Sunna), and thus to the interpretation of Islamic law (Shari'a). The essential core of Islamic teachings is the perfection of ethical conduct of a human being. It is amazing to find a saying of the Prophet Muhammad Peace Be Upon Him (PBUH), as narrated by Sahih Muslim, ordering Muslims to: (i) Do and promote good. (ii) Remove evil or harm. (iii) Prevent evil or harm and enjoin doing good and preventing harm, and the least thing one can do is not to inflict harm.

Medical research is Islamically encouraged and acceptable under the following conditions: (1) The purpose of the study is to secure an absolute benefit, that is, enhancing human health, or to prevent an instance of absolute harm that impairs health, or to give priority to securing an outweighing benefit over preventing a less substantial instance of harm. (2) The benefit does not violate a legal stipulation or contradict any absolute ruling of Islamic jurisprudence. (3) The research itself should be legitimate—that is, both the means and end must be legally permissible. (4) The design of study should be scientifically sound so that it should be more likely to achieve the purpose it is expected to accomplish. This is based on the rule that "every action that ceases to pursue its objective is unacceptable" (Fadel 2010, 62). (5) That the research team is qualified and competent to conduct the research as consistent with the Prophetic saying: "Allah loves the person who is performing a job to do it in the best possible way."

The principles and components of "informed consent" that are generally acceptable in Western countries are also applicable to Muslim community. However, Muslims, in general, will often want to consult with family members

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and religious scholars, particularly in aspects of religious and social relevance (Chamsi-Pasha and Albar 2013).

With such trials in patients with PD, patients must receive all available, critical information that is neither trivial nor irrelevant. Information must be comprehensive, even excessive, because the overinformed person may be inconvenienced; the underinformed person would have his or her autonomy violated. A recent study from Turkey (where 95% of the population are Muslims) showed that 54.8% of patients did not read the informed consent and that the majority of patients did not understand the importance of the informed consent (Ozhan et al. 2014). In a study published by Krupp and colleagues (2000) in patients who did not have a neurological disease, it was determined that 65% of the patients could not remember more than 2 of the 6 major complications in the information given verbally about surgery and that the rate of generally recalled information was 18%.

The competence of adult subjects to decide about their own bodies is generally the default assumption. However, special considerations may be required in neurodegenerative diseases, particularly where cognitive impairment is a known component of the syndrome. Therefore, careful consideration is needed by the ethical committees for obtaining a consent while the patient is fully competent earlier in the course of disease and/or a requirement for additional consent(s) by family members (Dunnett and Rosser 2014).

Based on the concept that human life in Islam does not start until ensoulment, which is stated by the Prophet Muhammad to be on the 120th day after conception (fertilization), the great majority of Muslim scholars agree that research on the pre-embryo, i.e., the preimplantation embryo, is permissible, provided that these pre-embryos were legitimately developed. The word *Janin* in Arabic (embryo) denotes that it is hidden in the womb. If it is not in the womb, then it is not a *Janin* (embryo). The permissibility is also conditioned such that these embryos are not produced specifically for research. Supernumerary embryos produced in infertility clinics are considered legitimate (Fadel 2012). A fully informed consent of the parents should be obtained in every case.

The Sixth International Conference of Islamic Jurists, held in Jeddah in 1990, sanctioned the transplantation of nerve tissues to treat ailments such as Parkinsonism, if this method of treatment proved superior to other well-established methods of treatment. The source of the nerve tissues could be the suprarenal medulla of the patient himself (autograft), the nerve tissues from an animal embryo (xenograft), or cultured human nerve cells obtained from spontaneous abortion or medically indicated abortions (Albar 2012).

The Islamic Fiqh Council of the Islamic World League, Makkah (2003) issued a Decree on Stem Cell Therapy:

> It is permissible to obtain stem cells, to be grown and used for therapy or for permissible scientific research, if its source is legitimate, as for example: 1. Adults if they give permission, without inflicting harm on them. .2. Children provided that their guardians allow it, for a legal benefit and without inflicting harm on the children. .3. The placenta or the umbilical cord, with the parents' permission. 4. A fetus if spontaneously aborted or when aborted for a therapeutic reason permitted by Sharia, with the parents' permission. 5. Left-over zygotes remaining from in vitro fertilization, if donated by the parents, when it is ascertained that they will not be used in an illegal pregnancy.

A similar attitude was also maintained in 2001 by the Fiqh Council of North America, which consists of health care professionals living in the United States, and Muslim jurists and scientists. They plead against using implanted embryos for the purpose of research. However, this council supports stem-cell research on spare embryos from in vitro fertilization. The Islamic Medical Association of North America (IMANA) Ethics Committee also approved stem-cell research. In addition, the Islamic Institute of Turkey and the Malaysian National Fatwa Council also supported hESC research (Fadel 2012; IMANA Ethics Committee 2007). Shite clergy encourage stem-cell research including hESC research. In 2002, Grand Ayatollah Ali Khamenei issued a stem-cell fatwa that declared experimentation with human embryonic stem cells consistent with Shiite Islam, hence legitimizing stem-cell research in Iran (Ilkilic and Ertin 2010).

With regard to the sequel involved with these trials, the Islamic jurisprudence states, "Avoiding harm takes precedence over bringing good." This simply means if a certain action ends in both good and harm, then it is preferable first to thwart off the harm. However, if the benefit far outweighs the harm, then that action could be applied. Al Izz ibn Abdul Salam (d. 1262), a renowned Islamic jurist, in his book "Basics of Rulings" said "The aim of medicine is to preserve health, restore it when it is lost; remove ailment or reduce its effect. To reach that goal it may be essential to accept the lesser harm, in order to ward off a greater harm, or lose a certain benefit to procure a greater one" (Chamsi-Pasha and Albar 2013, 11).

Finally, it seems that the future of stem-cells therapy for neurodegenerative disease is bright, complex, and stepwise in finding solutions for multiple specific issues.

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Risk of Tumorigenesis and Patient Hope

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At the Center for iPS Cell Research and Application, Kyoto University, with which we are affiliated, clinical research into the autologous transplantation of dopaminergic (DA) neurons produced from the human induced pluripotent stem cells (iPSCs) of patients with Parkinson's disease (PD) is planned for 2016 at the earliest. Additionally, clinical trials for allogeneic transplantation of DA neurons produced from the iPSCs of healthy volunteers, starting in 2018, are being considered. The recent article by Hurst and colleagues (2015), which analyzes challenges in first-in-human PD research using stem cells, is therefore both highly interesting and particularly timely. The three topics that they identified, participant selection, informed consent, and sham surgery, should all be considered during the implementation of research, and our viewpoint is generally in agreement. However, in this commentary we identify two important points not addressed by Hurst and colleagues (2015).

Our first argument relates to the tumorigenicity of transplanted cells. For the transplantation of stem-cell derived DA neurons, feasible sources of the stem cells include aborted human fetuses, human embryonic stem cells (hESCs), and human iPSCs (hiPSCs) (Abbott 2014). Of these, research using fetuses has been carried out since 1987 (Barker et al. 2013), and these studies can no longer be considered first-in-human research. Accordingly, the ethical issues related to first-in-human trials raised by the article by Hurst and colleagues apply only to hESC and hiPSC research. The unique property shared by hESC and hiPSC research, but not by research using fetal cells, is the risk of tumor formation.

In fact, the report by Barker and colleagues (2013), which reviewed studies of fetal-cell implantation into patients with PD over the last 20 years, identified side effects such as graft-induced dyskinesias, but did not reference tumorigenicity. It has been long thought that undifferentiated cells may contribute to tumorigenesis when hESC- and hiPSC-derived cells are transplanted. Thus, the appropriate management of tumorigenesis is one of the biggest challenges in the clinical use of hESCs and hiPSCs. Although Hurst and colleagues (2015) only included a minimal discussion of the tumorigenicity, a more detailed discussion was warranted. What is the permissible risk for tumorigenesis? As long as the PD condition improves, are asymptomatic and nongrowing benign tumors permissible? For how long after a Phase I/II intervention is patient follow-up necessary? What is the shortest observation time needed to

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