Stem Cell Science in Iran

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ABSTRACT

Human embryonic stem (hES) cells may potentially revolutionize biomedicine through their use as a renewable source of cells for regenerative medicine. However, despite much promise the use and derivation of these cells in many countries is ethically challenging. Interestingly, stem cell research in Iran's Royan Institute is thriving despite many challenges and has led to the generation of novel hES cell lines. Unfortunately, Iranian scientists still have many difficulties to overcome such as inconsistent funding opportunities, sanctions which prevent the import of materials and supplies. We propose that the implementation of a governmental agency to promote the development of science as well as improved international relations could potentially eradicate these hurdles and aid in the development of stem cell science in Iran.

INTRODUCTION

Stem cell research has emerged as one of the most promising research areas in modern biomedicine. As evident by the intense media coverage and interest in the science and the policy of stem cells, the recent scientific outburst regarding stem cell research has occurred on a worldwide scale. Unfortunately for scientists, their work regarding stem cell development has been faced with great controversy in many regions of the world. Moral and ethical debates surrounding human embryonic stem cell research arise from conflicting opinions regarding the fabrication and use of human embryos for purely scientific research purposes. The debate focuses on contrasting views regarding when life begins and when individual rights should be granted to a fetus. Many of these differing opinions originate from religious views and writings, which widely vary from country to country, and religion to religion.

Stem cells are classified as multi-potential, undifferentiated cells that are capable of continuously dividing and generating renewable cell sources. Although the existence of stem cells was demonstrated in the early 1960"s, the first human embryonic stem (hES) cell lines were initially established in 1998. In simultaneous publications scientists from University of Wisconsin and Johns Hopkins University published the derivation of embryonic stem cells from human embryos from fertility clinics. Since then the science has progressed such that currently there are multiple sources for hES cells: 1) human fetal tissues following abortions, 2) human embryos (at a multi-cellular stage called the blastocyst) created through *in vitro* fertilization, 3) cloned human embryos and 4) early stage fertilized eggs during the 8 cell stage. Historically, in many regions of the world these methods have been the root of the many ethical, moral and political objections that have ultimately slowed the progress of embryonic stem cell research. Thus it appears that countries with the luxury of avoiding these objections have a significant advantage in the development of hES cell research.

Iran has a long history of scientific achievement. In ancient time, Iran"s geographical location between Greece and India frequently placed them in the crossroads of medical developments in the eastern and western worlds. Prior to Islam, Iran was a leader in mathematics and astronomy, however, much like the rest of the Middle East, the scientific power of Iran declined as Europe entered "The Renaissance period" in the early 1300"s. Over the next several hundred years Iran was slowly developed, but was unable to reach its full potential scientifically.

Science in Iran was strengthened in the early 1970"s under support from the Shah, however, political unrest surrounding the nation around the time of the revolution of 1979 caused Iran to suffer a significant "brain drain". After decades of neglecting science, Iran is now starting to invest heavily into it. Specifically, there have been some major improvements in areas regarding stem cell research. Unfortunately, continuing political unrest between Iran and the western world is a source of difficulty and hinders Iran from making significant progress in the world of science. Political and economic sanctions are restricting the access Iranian scientists have to international conferences and minimize the availability of supplies and equipment that must come from the United States. The lack of a federally operated and funded organization, like the United States National Science Foundation (NSF) or the National Institute of Health (NIH), is also impeding the progress of Iranian scientists. All of these factors combine to negatively influence native Iranians and international scholars when they make decisions regarding locations to complete graduate educations and to begin their research careers.

The goal of this paper is to analyze the factors affecting stem cell research in the Islamic Republic of Iran. The paper will begin by outlining the moral and ethical views regarding stem

cell research from an Islamic perspective and outline the Iranian government"s policy towards this work. The historical background and future prospects of the country"s major stem cell institute, the Royan Institute, will be also be presented along with some of the accomplishments of the country"s finest scientists. The paper will conclude by identifying some of the challenges that Iranian stem cell researchers currently face and suggest some mechanisms to help develop Iranian science to become a major contributor to stem cell science and technology.

RELIGIOUS CONSIDERATIONS

Among Islamic countries, Iran has recently emerged as a leader in hES cell research. Iranians scientists are able to investigate the properties and characteristics of hES cells with a much greater freedom than researchers from many other countries. In a large fraction of Western countries, including the United States, many hES cell researchers face ethical and governmental regulations as well as the public"s religious and moral standpoints, which suggest that individuality begins immediately after conception. Furthermore, some feel that unborn fetuses deserve the same rights and freedoms as individuals. This belief is not shared by all religions of the world, and as such, countries such as Iran are not as restricted as several of their international counterparts in terms of stem cell research and development. This is in sharp contrast to countries such as the United States. In the United States the derivation of new stem cell lines and research on hES cells that are not „approved" by the government cannot be supported by federal funds. Many researchers believe that the hES cell lines that have been approved by the United States government are too few and since they have all been contaminated with animal serum, that is used to maintain their properties in culture, they are virtually useless for clinical applications. In addition, the approved cell lines do not represent the genetic diversity of human populations thus they will be rejected upon implantation into patients. The government restrictions on hES cell research, has resulted in the formation of „private" or state funding

sources for supporting hES cell research. However, despite significant resources directed towards stem cell research, little of the promised support has actually reached the stem cell researchers. For example, California's highly publicized stem cell institute has not received any of its promised 3 billion dollars.

In Iran and other Islamic countries, embryonic research policies are influenced by the religious belief that full human life with its attendant rights begins only after the 'ensoulment' of the fetus. The Quran states that there is a distinction between the different stages of human development and Muslim jurists have stated, based on the opinions of the Sunni and Shi'a Muslim scholars, this distinction occurs four months (120 days) after conception (Figure 1).

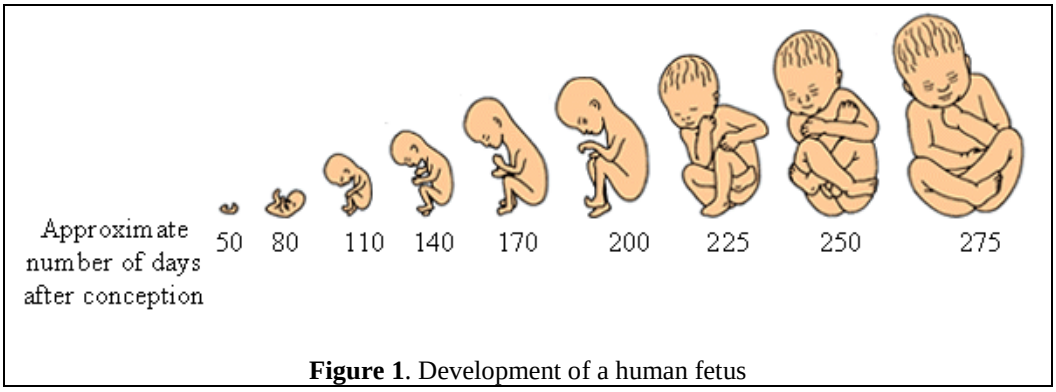

Figure 1. Development of a human fetus

This fact, in conjunction with the importance of preventing illness and suffering as expressed in the Quran, means that stem cell research in Iran involving unborn embryos is relatively uncontroversial. Correspondingly, abortion before the ensoulment of the fetus is viewed as permissible by the Islamic faith when there is a physical or emotional threat to mother. These examples show how Islamic views do not stand in the way of hES cell research and illustrate the tremendous advantage Iranian scientist have over scientists in many other countries.

IRANIAN GOVERNMENT POLICY

Historically, the interactions of the Iranian government with science has been unstable and dynamic. After the country's revolution in 1979 there was a long period of scientific stagnation

as many universities were closed for over three years. Science was rejected as a product of the West and the country focused on an "Islamic science" that revolved around development. This period of scientific languish started to dissipate in 1988 after the end of the Iraq/Iran war. In 1989 the country appointed Mostafa Moin minister of culture and higher education. His stated goal was to "breath life into the largely moribound universities". In the time after his appointment enrollment at Iranian universities has increased 10 fold. Correspondingly, government spending on science has increased from 0.2% of the country"s gross domestic product (GDP) in 1990 to 0.65% in 2005. Although this is still much smaller than the percentage of GDP that is invested in science and technology in developed countries such as the US, its growth is a clear sign of the increased value of science in Iran.

The current government supports stem cell research in Iran. In 2002, Iran"s supreme leader, Ayatollah Ali Khamenei, publicly supported human embryo research, suggesting Iran"s goal should be to become the "leader of science" in the Middle East in the next 20 years. Iran's clerics and political leaders have also actively promoted science and technology in an attempt to enhance the country"s global status. The scientific progress of Iranian science has been demonstrated by the recent publication of paper in the prestigious journal Nature as well as the stream of articles in Science and Nature about the progress in Iran"s science.

Unfortunately, Iran is still hampered by political and economical sanctions that prevent the transport of necessary materials from other areas of the world, namely the US. Many Iranian scientists depend on the „black market" to obtain simple reagents that are required for common scientific practices. This is particularly disruptive in biological research due to the specialized reagents and antibodies, many of which are produced exclusively by companies located in the

United States. Due to the inability of the Iranian biomedical scientists to purchase directly from the manufacturers, the cost of purchasing supplies in Iran is typically much more expensive than prices in the US. In addition, the quality of these products is often compromised, to a degree that some scientists perform their experiments on multiple independently obtained batches of reagents to ensure that the products are authentic. Additionally, Iranian researchers commonly are not granted visas to other country"s and are therefore unable to attend valuable conferences and have meaningful collaborations.

THE ROYAN INSTITUTE

The Royan Institute is Iran"s leading stem cell research center and one of its best infertility clinics. Named after the Persian word for "embryo", the Royan Institute is located in the northern part of Iran in the capital city of Tehran (**Figure 2**) and was originally established in 1991 as an infertility clinic. In 1998 the Ministry of Health approved the Royan Institute as a cell-based research center. It currently houses both basic and applied research and departments in the following six fields of study: stem cells, embryology, gynecology, genetics, andrology and epidemiology. Additionally, the institute plays host to Iran"s largest annual scientific event, the Royan International Congress. This conference is well publicized and aims to promote stem cell science in Iran. In addition, Royan Institute hosts an annual international paper competition which draws papers in stem cells from many countries in Europe and Asia.

The Royan Institute's Department of Stem Cells originated in 2002 with the goal of establishing embryonic stem cell lines and developing techniques to differentiate these lines into various mature cell types, including cardiomyocytes, cells and neural cells. The head of department, Dr. Hossein Baharvand (**Figure 3**), states that the department's "... vision is to efficiently put stem cell research findings into operation in disease treatment to increase the level of health". Shortly after its inception, the Department of Stem Cells disbanded into nine main research groups spanning embryonic/adult stem cell biology, mesenchymal stem cells, neural cells, cells and germ cells as well as groups focused on stem cell research regarding the heart, eye, liver and physicochemical growth factors. These combined efforts have all contributed to the institute's recent progress.

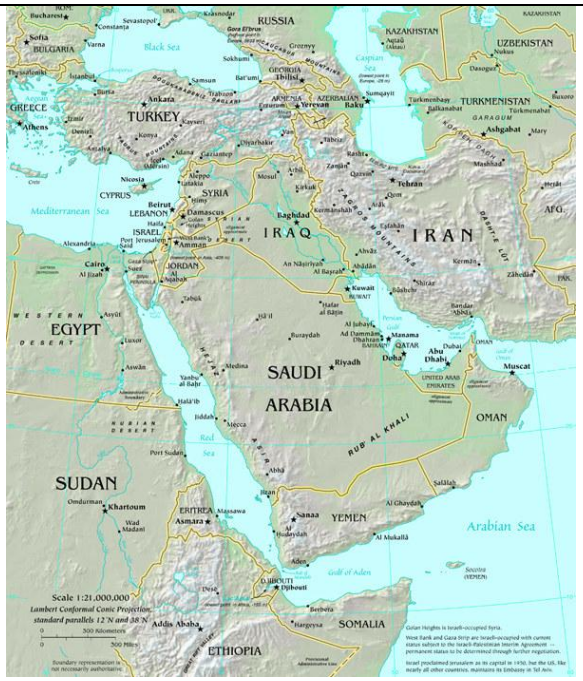

Figure 2. Map of the Iran and the Middle East (taken from http://www.world-maps.co.uk/maps/600-middle_east.jpg)

Royan Institute is one of the few places in the world that can derive human embryonic stem cells. Iranian scientists have established 6 human embryonic stem cell lines since 2004. This achievement, although not a breakthrough on its own, has enabled Iranian scientists to pursue many avenues of research into methods of generating therapeutic cells from these cells. For example, recently work has been performed in differentiating hES cells into pancreatic, heart and liver cells.

In addition, research recently conducted at the Royan Institute has focused on developing proteomic signatures for multiple hES cell lines. Scientists used two-dimensional gel electrophoresis to identify 685 proteins, 60 of which were classified as the most abundant. They were successful at identifying chaperones, heat shock proteins, ubiquitin/proteosome and oxidative stress response proteins. They also found that proteins involved in cell proliferation and differentiation were largely expressed. This example was the first hES proteomics study and the knowledge presented by the authors will be used worldwide to better understand hES and their biological properties. Interestingly, due to the lack of required technology in Iran, the scientists had to send their samples outside of Iran for analysis.

Figure 3. Hossein Baharvand, Head of Stem Cell Department Royan Institute, Tehran, Iran

IRANIAN SCIENTIFIC ACCOMPLISHMENTS

Although the country was not a major contributor to science in the late 20th century, Iran is beginning to show promising signs that suggest it may become a scientific force in the Middle East, along with Israel. These accomplishments include a tremendous increase in journal publication rate, development of multiple hES lines and recent success in cloning a sheep.

As of the mid-1980's, Iranian scientists are publishing research in academic journals at an increasing rapid pace. For example, from 1985 to 2003 the number of scientific papers published by Iranian scientists in international journals increased 30 fold . Of these papers, scientists working at the Royan Institute have increased their output of publications from two (in 1996) to 67 (in 2005) (**Figure 4**). Additionally, Royan Institute scientists have also published 24 papers in international journals, compared to zero in 1996.

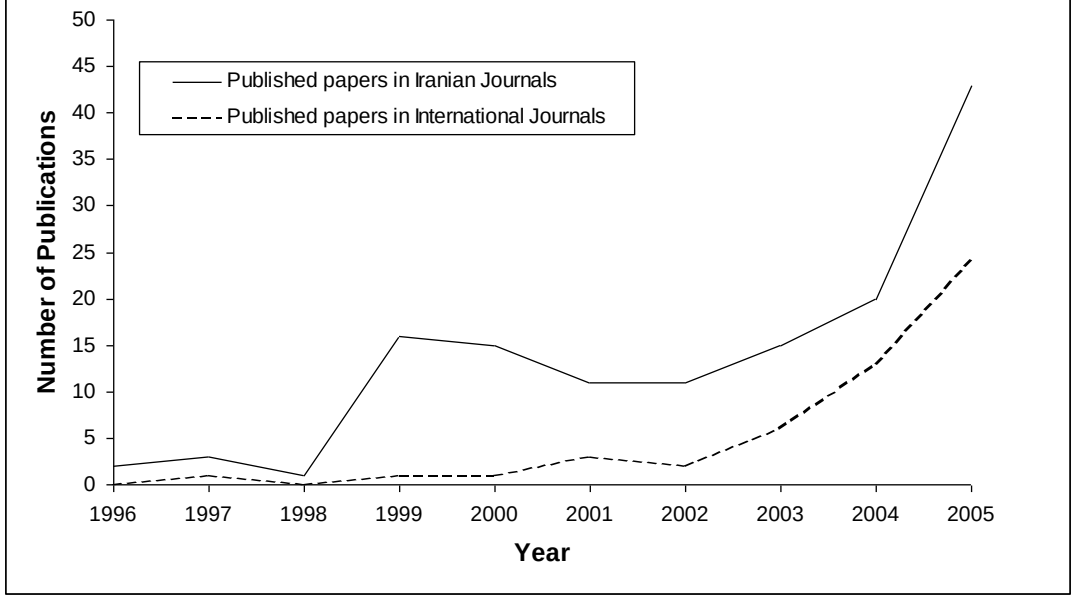

Figure 4. Iranian published papers in international and Iranian journals from 1996-2005

Iran was the 10th country in the world to produce, culture and freeze hES cells(http://www.payvand.com/news/03/sep/1010.html). The nine previous countries were Sweden, Japan, the United States, Australia, Britain, India, South Korea, and Singapore. Stem cell research is on the cutting edge of scientific discovery and Iran"s inclusion in such an exclusive group of countries stands as another tremendous example to the quality of research that is being achieved in the country. At this moment, the Stem cell department of the Royan Institute has established two mouse embryonic stem (mES) cell lines in collaboration with Australia, three mES cell lines supported by the Molecular Medicine Network (located at the Iran Pasteur Institute), and six hES cell lines. One of these lines is registered in the International Society for Stem Cell Research (ISSCR), while the other two lines will be published in the near future.

In addition, on August 2nd, 2006 researchers at the Royan Institute were witness to the birth of the first cloned sheep born in Iran. After many unsuccessful attempts, researchers were able to

artificially fertilize the female sheep, which gave birth approximately one week early. Although the newborn lamb died minutes after birth as a result of respiratory problems, nonetheless, this is a tremendous example of the progress of Iranian science.

CHALLENGES OF CONDUCTING STEM CELL RESEARCH IN IRAN

Despite the recent advances and accomplishments of researchers in Iran, there are still many obstacles and challenges that scientists must overcome in conducting research. These include, but are not limited to:

- Lack of a government agency to provide consistent funding and review for researchers.
- Lack of sufficient resources to establish a „large" stem cell community in Iran.
- Difficulties related to importing necessary materials and reagents.
- Loss of many top students to internationally renowned schools.
- Difficulties in publishing manuscripts in international journals from Iran.
- Lack of private sources of funding for supplementing stem cell research.

FUTURE OF STEM CELL RESEARCH IN IRAN

The lack of a federally funded organization to distribute funds and conduct reviews is a major hindrance to Iranian researchers. In the United States, the National Science Foundation (NSF) is an independent federal agency with the task of promoting the progress of science and keeping the United States on the leading edge of discovery. By implementing this type of agency and solidifying the research and development funding structure of the country, the Iranian government could help scientists obtain adequate funding to conduct their work as well as improve their scientific global image. In turn, this could potentially lead to attracting international scientists and improving the sanctions currently restricting Iranians from attending valuable conferences and maintaining collaborations with international academic faculties.

Furthermore, the development of an agency to review the work of researchers within the country could continue to improve the quality of work produced and lead Iran to become a scientific leader of the Middle East. This peer review process could be similar to the peer review system of the NIH in which scientists gather in panels and rigorously review funding proposals. Such merit-based funding mechanism may be of great benefit in increasing the competitiveness of scientists in Iran.

With the substantial amount of evidence presented above, there is plenty to suggest that continuing to increase the governmental support for scientific discovery would result in improving the quality and quantity of scientific achievements attained by Iranian scientists. Correspondingly, this could also improve the global image of Iran. Local students would be more apt to remain in the country if Stem cell research is rapidly developing into powerful technologies, and if the Iranian government can acknowledge that the lack of moral and ethical objections from its Muslim population is a significant advantage over other nations, then there is great potential for Iranian scientists to lead the country back to international notoriety and regain the respect of other independent nations.

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