

**Applications of Stem Cells
in the Treatment of
Male and Female Infertility**

By

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ABSTRACT

Stem cells have the potential to revolutionise the future of medicine and give hope to people with diseases and conditions which were until recently considered to be untreatable. The possible uses of stem cells ranging from treating neurodegenerative diseases to cancers to growing new organs such as hearts and livers are now well recognised and reported. I am going to investigate and discuss the possible future uses and advantages of human embryonic and somatic stem cells in the treatment of human infertility in conjunction with or as an alternative to in-vitro fertilisation. I will also explore how stem cell research could treat related gynaecological conditions such as endometriosis which is a common cause of female subfertility and infertility.

INTRODUCTION

Embryonic Stem Cells

Embryonic stem cells (ES cells) were first reported in 1998. They are obtained from the undifferentiated inner mass cells of an early stage human embryo (sometimes called a blastocyst, which is an embryo that is between 50 to 150 cells).⁹ ES cells have the ability to develop into any type of cell due to their pluripotent nature.⁴ The ability to grow human tissue of all kinds from embryonic stem cells has paved the way to treating a range of cellular based diseases and to growing important tissues that can be used for transplantation purposes. Replacing diseased cells with healthy cells obtained from ES cell lines could offer treatments and lifelong cures to patients with diseases once thought to be incurable e.g. Parkinson's disease, diabetes.⁶ Similarly failing organs such as heart and livers could be treated by injecting healthy stem cells to replace the diseased cells. All this may sound straightforward however the real question lies in how to make the ES cells morph into the required tissue, a question which to this day continues to challenge scientists.

Somatic Stem Cells

Research on somatic stem cells started in 1960 and generated a great deal of excitement. Somatic stem cells (adult stem cells) are undifferentiated cells found in specific tissues. The role of an adult stem cell in the body is to renew and repair tissues in which they are found and are activated by disease or damage. The drawback of the use of somatic stem cells as treatments is that, unlike embryonic stem cells, they are multipotent i.e. they can only, with certain limitations, differentiate to yield all the specialised cell types of the tissue from which it originated.⁹

Now somatic stem cells have been found in many more tissues than was considered possible. Initially scientists discovered that the bone marrow contains at least two kinds of adult stem cells; hematopoietic stem cells and bone marrow stromal stem cells. Hematopoietic stem cells can form all types of blood cells in the body (red blood cells, B and T lymphocytes, natural killer cells) and stromal stem cells can generate bone, cartilage, fat and fibrous connective tissue. It was obvious from the beginning that if these cells are cultured correctly, both somatic stem cells found in the bone marrow could play a very important role in the treatment of many common diseases e.g. leukemia, Multiple Sclerosis. Only in the 1990s did scientists discover that the adult brain contains stem cells that are able to generate the brain's major cell types- astrocytes, oligodendrocytes and neurons. We now know that there are also stem cells in the blood, blood vessels, skeletal muscle, epithelial cells and the liver. It is still not fully known how many sources of somatic stem cells there are in the body.¹⁴

Research suggests that in fact some somatic stem cells are pluripotent i.e. have the ability to transdifferentiate into multiple cell types, also known as plasticity. During the past few years,

experiments have shown that hematopoietic cells may also differentiate into the three major types of brain cells, skeletal muscle cells, cardiac muscle cells and liver cells. It has also been suggested that bone marrow stromal cells can differentiate into cardiac muscle cells and skeletal muscle cells. Current scientific research is aimed at determining the mechanisms which allow somatic stem cells to be induced to transdifferentiate and so repopulate and repair diseased tissue. This also carries important implications for the treatment of many liver, heart, neurodegenerative and autoimmune diseases.

Advantages of Somatic Stem Cell Treatment

In this type of treatment the patient's own cells could be extracted and cultured, then reintroduced into the body and this would eliminate the risk of rejection. This would eradicate the use of autoimmune suppressant drugs. Ethically, it is more acceptable for scientists to experiment and promote the use of somatic stem cells as opposed to ES cells. The origins of ES cells from either aborted foetuses or the creation of human embryos solely for research purposes has created a great deal of controversy.

DISCUSSION

I have decided to discuss possible future developments of ES and somatic stem cells in the treatment of both female and male infertility which could ensure a higher success rate than the current IVF treatments available. The use of stem cells could also eliminate the need for the use of donor gametes. I am also going to discuss the use of stem cell therapy on the treatment of endometriosis, a common cause of infertility amongst women.

Formation of Gametes from Stem Cells

Scientists at Sheffield University (2005)^{10, 13} have shown that it is possible to create Primordial Germ Cells, which are the precursors of egg and sperm cells, from human ES cells and subsequently produce sperm or egg cells. Therapeutic cloning (nuclear transplantation of a patient's own cells) could be used so that the gametes carry the same genes as the parents. Previous research in the United States and Japan has shown that this is possible in adult mice and have managed to produce a mouse embryo from a sperm produced in this way.¹³ Scientists predict that the easiest way for these PGCs to develop into gametes is if they are transplanted directly into the testes or the ovary where the environmental and hormonal conditions are optimal. Producing functional gametes in the laboratory would be much more difficult as it would be essential to recreate the environment of either the developing follicle or the tissue in the testes.⁵

This development could offer a solution for infertile couples and stop the need for the use of donor gametes, however this infertility treatment gives rise to even more controversy due to the fact that, using this technique, it would be possible for homosexual couples to have children that carry the genes of both parents. Another controversial application of this development could enable a single man or woman to provide both the sperm and egg cell and in essence creating a clone of themselves. Although this needs to be considered, it is unlikely to ever be permitted for ethical reasons and also because a reduced gene pool could lead to genetic defects in the offspring.

Sperm Stem Cell Transplants

A research project by Rachel Nowak (2003) has shown that infertile mice were able to father offspring after being given a frozen sperm stem cell transplant. However, the results are not particularly encouraging as only one out of nine of the adult mice with an abnormality that prevents them making

sperm, fathered young naturally, after having a testicular stem cell transplant. She also reported that one out of twelve adult mice, given chemotherapy drugs, which would also destroy sperm stem cells, could father young after a transplant. However in this case it was necessary for the sperm to be injected directly into an egg.¹¹

If this procedure could be improved and modified to work in humans, it could be a major advance in the treatment of male infertility. Sperm stem cells could be collected from a cancer patient before treatment, frozen and then transplanted back into the testes after treatment. Similarly it could also be possible to freeze ovarian stem cells for use in the same way.

Bone Marrow Stem Cells to Replenish Ovaries with Eggs⁷

Jonathan Tilly and colleagues from Harvard Medical School and Massachusetts General Hospital in Boston (2005) claim that somatic stem cells found in the bone marrow and the blood could help a woman with depleted ovaries to replenish her supply of eggs within a few weeks creating a possible cure for female infertility. Researchers sterilised adult female mice using a chemotherapy drug that destroyed the eggs in their ovaries. Surprisingly when the mice were tested 12 to 24 hours later, the researchers found signs that the eggs were rapidly regenerating and within two months of being given the chemotherapy drug the ovaries of the mice were producing eggs normally.

This evidence contradicts the generally accepted view that female mice have a finite supply of eggs which decline as the mouse gets older. This finding suggested the existence of female germline stem cells in bone marrow. According to the researchers mice that had been rendered infertile started to produce eggs after being given a bone marrow or blood transplant. Although this study focuses only on mice, the researchers also cite cases where women, thought to be infertile, became pregnant after having a bone marrow transplant due to the donor bone marrow containing stem cells with stimulate the production of oocytes.

Not only could this technique be used to cure female infertility, it could extend fertility by delaying menopause. This could be of benefit to women who wish to concentrate on their careers before having children. However it could also be argued that older women physically could not cope as well with pregnancy as younger women and that subjecting the body unnaturally to the high levels of oestrogen in their forties and fifties could also lead to a rise in cancers particularly oestrogen receptor-positive cancers.

Researchers led by Antonin Bukovsky of the University of Tennessee claim that, contrary to common belief that women are born with a fixed supply of eggs, it was relatively simple to harvest stem cells scraped from the surface of women's ovaries (epithelial tissue) using keyhole surgery. Professor Bukovsky reported in May 2005 that his team had managed to obtain ovarian stem cells from five women aged between 39 and 52 and within 5 days were able to develop the ovarian stem cell into human oocytes suitable for fertilisation.³ However, Martin Pera, a researcher at Monash University and the Australian Stem Cell Centre claimed that this research, although interesting, was preliminary and that it is not fully known if the oocytes produced from the ovarian stem cells can actually be fertilised.

This is still an exciting advance for women undergoing in-vitro fertilisation as this approach might be able to produce more eggs than the present way of collecting ripe eggs from the ovary and according to Bukovsky the technique is less complex. The production of oocytes from stem cells would eliminate the need for fertility drugs used to stimulate egg production which can have severe side effects e.g.

ovarian hyperstimulation syndrome. It is also thought that any treatment which uses drugs to stimulate the ovaries may lead to an increased chance of developing ovarian cancer.

Stem Cells to Offer a Cure for Endometriosis

Endometriosis, a cause of female subfertility and infertility, is a painful reproductive and immunological condition in which the endometrial tissue grows outside the uterus and attaches to other organs such as the fallopian tubes, ovaries, intestine, bowel, bladder and other areas of the pelvic cavity.¹ During a week shadowing a consultant gynaecologist at St James's University Hospital, Leeds I observed a laparotomy in which a young childless woman of 22 years had to undergo the removal of both ovaries due to Endometriosis. I am particularly interested in researching how stem cells could be used to treat women with Endometriosis and therefore treat a common cause of infertility.

Endometriosis, an autoimmune disease, bears many similarities to cancer i.e. an abnormal proliferation of cells.¹⁷ Natural killer (NK) cells, a type of lymphocyte which acts without recognising a specific antigen, have been found to play a primary role in preventing and destroying certain tumour cells. Endometriosis causes increased oestrogen levels which depress the levels of NK cells which have been proven to be sensitive to B-oestradiol and this effectively weakens the natural immunosurveillance system of the body allowing endometrial implants to develop in the pelvis.²

Research at the University of Minnesota (2005) has shown that it is possible to create human embryonic stem cell-derived natural killer cells which are able to treat and fight some cancers (leukaemia and lymphoma).^{8, 12} It is therefore feasible to assume that any possible treatment of cancers using stem cells to produce NK cells can also be used to treat endometriosis. This treatment could eradicate the need for invasive surgery and other hormone treatments which create negative side effects e.g. weight increase, depression and could give hope to women who having been diagnosed with endometriosis are having difficulty conceiving.

CONCLUSION

A serious problem with treatments using ES cells is that they all carry a risk of rejection as the cells do not come from the patient's own body and therefore they would not be a precise genetic match. However, scientists in Germany have recently isolated a new kind of pluripotent stem cell found in testes of adult mice. It is highly probable that this could also be true of humans and could effectively eliminate the use of ES cells, removing the need for therapeutic cloning and overcoming the problem of rejection. This suggests that pluripotent stem cells may be present in all tissues of the body. The study will be published at the end of March 2006 in *Nature*.¹⁵ This could be of particular benefit to women who have had to undergo an ooverectomy or had cancer treatment. It is possible that in the future eggs could be developed from pluripotent cells found in their other tissues. However the future potential of this discovery depends upon scientists discovering the mechanisms which allow pluripotent stem cells to transdifferentiate and therefore discover how to control this process.

The controversy surrounding ES cell has slowed down the advances in stem cell research due to many countries prohibiting the use of embryos for research purposes. The significant breakthrough that pluripotent somatic stem cells have been found will enable scientists to make more rapid progress in the development of treatments.

The treatment of endometriosis using NK cells will be dependant upon scientists discovering the immunological mechanisms by which NK cells attack specific tissues. It is vital that scientists develop

NK cells that target and destroy the endometrial tissue in the pelvic cavity only. A solution to this could be to genetically modify NK cells to carry artificial receptors on their surface that make them effective killers that attack only endometrial implants. This technique has been used to generate NK cells specifically designed to kill leukemik cells.

Current research into the use of stems cells certainly offers hope for the future for infertile couples. Potentially the stem cell treatments discussed could be much more successful than IVF which only offers a current success rate of up to 38.8%. The treatments could also require less medical intervention than IVF by enabling more couples to conceive naturally.

Infertility is a condition which is likely to become more prevalent in the close future due to increased transmission of sexually transmitted diseases such as Chlamydia and pollutants in the environment e.g. increased levels of oestrogenic chemicals in the water supplies affecting the fertility of both males and females.¹⁸ Stem cell treatments will undoubtedly be an invaluable tool in the treatment of infertility.

REFERENCES

1 Understanding Endometriosis; Past, Present and Future? By Endometriosis Research Centre
<http://www.endocenter.org/EndoPPF.htm>

2 Immune Response to Endometriosis by Georgia Reproductive Specialists
<http://www.ivf.com/endoimm.html>

3 IVF hope from stem-cell breakthrough by Deborah Smith Science Editor
<http://www.smh.com.au/news/Science/IVF-hope-from-stemcell-breakthrough/2005/05/06/1115092631678.html>

4 Pluripotential hemopoietic stem cell from Wikipedia
http://en.wikipedia.org/wiki/Pluripotential_hemopoietic_stem_cell

5 Development of Gametes from Embryonic Stem Cells
http://www.obgyn.net/displayarticle.asp?page=/news/ASRM_pr102005_gametedevlopment

6 What are stem cells and what are they used for?
<http://www.howstuffworks.com/question621.htm>

7 Stem Cells Restore Egg Production in Mouse Ovaries
http://www.kaisernetwork.org/daily_reports/rep_index.cfm?DR_ID=31707

8 Cancer killing cells
<http://www.freerepublic.com/focus/f-news/1501060/posts>

9 What are Stem Cells? By The International Stem Cell Forum
http://www.stemcellforum.org/about_stem_cell_research/what_are_stem_cells.cfm

10 Stem Cell Finding Offers IVF Hope by BBC news
<http://news.bbc.co.uk/1/hi/health/4104680.stm>

11 Stem Cells allow infertile males to be fathers by Rachel Nowak

<http://www.newscientist.com/article/mg18024251.900.html>

12 Researchers Use Human Embryonic Stem Cells to Kill Cancer Cells by Science Daily
<http://www.sciencedaily.com/releases/2005/10/051012084443.htm>

13 Stem-Cell Sperm could Conquer Infertility by Mark Henderson
<http://www.timesonline.co.uk/article/0,,2-1661243,00.html>

14 Stem Cell Information by The National Institute of Health
<http://stemcells.nih.gov/info/basics/basics4.asp>

15 Testicles may provide a better kind of stem cells by Mark Henderson
<http://www.timesonline.co.uk/article/0,,13509-2102393,00.html>

16 Vernon, M & Shepperson Mills, D. (2002).Endometriosis: A Key to Healing Through Nutrition, HarperCollins

17 Ballweg, M L.(1995)The Endometriosis Sourcebook: The Definitive Guide to Current Treatment Options, the Latest Research, Common Myths About the Disease and Coping Strategies - Both Physical and Emotional, Contemporary Books Inc

18 Nutritional and Environmental Approaches to Infertility by Jaqueline Johnson

<http://www.positivehealth.com/permit/Articles/Environment/john58.htm>

Spermatogonial stem cells maintain spermatogenesis throughout the reproductive life of mammals. They are undifferentiated cells defined by their ability to both self-renew and differentiate into mature spermatozoa. Germ cell transplantation is not yet ready for the human fertility clinic, but it may be reasonable for young cancer patients, with no other options to preserve their fertility. Whereas this technique has become an important research tool in rodents, a clinical application must still be regarded as experimental, and many aspects of the procedure need to be optimized prior to a clinical application in men. In future, a range of options for the preservation of male fertility will get a new significance. Download full-text PDF. Source. Stem Cells. Can they treat male infertility? You are here: Home. Fertility News. Could Stem Cells Treat Male Infertility? New developments in stem cell research may mean a breakthrough in the treatment of future male infertility. Using mice embryonic stem cells (ESC), researchers in China have been able to recreate working sperm cells. Despite not being fully mature, these cells were still advanced enough to father fertile offspring after successful IVF treatment in female mice. Human clinical applications are currently considered remote. Germ cells of humans and mice develop differently. Nevertheless, the concept is still encouraging. New studies are already planned and underway to further explore the findings of Zhao and colleagues.