

An exploration into the current and possible
future developments of stem cell research



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PASS WITH DISTINCTION

This paper gives a short description of the current and possible research on stem cells. It will focus on the relevance of regeneration in salamanders to medical development, the promise stem cells bring to the much-fantasised 'cure for cancer', and finally how we can use stem cells to extend life. This paper is not just focused on the development of medicine. It is a discussion where we take into account the ongoing ethics debate and how it may affect the future of stem cells. Its purpose is not to argue which side is correct and which is not. We can conclude that stem cells certainly hold a lot of promise, and the lifting of restrictions on federal funding for research on embryonic stem cells in the USA may be able to turn this early promise into reality.

Introduction

Since the discovery of stem cells in 1979¹ there has been much fascination over the topic by scientists and doctors around the world. Despite the massive development in this field since its discovery there is still a great deal that we can learn from these totipotent cells.

Stem cells are present everywhere in the body and are cells that have not yet differentiated into specialised cells. This means that they have a potential and ability to turn into any kind of cell. Stem cells can essentially be divided into two broad groups: embryonic and adult. Embryonic stem cells are more favourable to scientists because they are more successful in becoming any cell in the body, while adult stem cells have limited capabilities in comparison.

From a medical perspective, this ability gives a wide range of possible treatments varying from the swift repair of the body's tissues after surgery to the natural growth of entire body parts after amputation. Although it may seem that doctors and scientists are far from being able to do anything as complex as regenerating new limbs, a major breakthrough in recent months has been to reconstruct a bronchus by culturing stem cells around a cartilaginous scaffold. This shows the real possibilities of what stem cells can do, and will be explored in further detail later on.

There is much controversy over the harvesting of embryonic stem cells, due to the fact that embryos must be destroyed in order to remove and culture them. This argument started in the late 1970s, when IVF treatment was first developed, because most IVF clinics produce multiple embryos, and the scientists only select a few, meaning the rest are discarded. When scientists learnt how to culture human embryonic stem cells, they asked permission to use IVF embryos for this purpose to produce more. The Catholic Church in particular has opposed the production of stem cells by this method, regardless of the fact that the embryos would be discarded anyway, because they hold the belief that all human life is sacred and each embryo has the potential to bring life. The core of this debate is based around one moral equation. On one side is the potential benefit to medicine on the other is the moral cost of destroying nascent human beings. However, there are two more parts to this equation: therapeutic cloning and adult stem cells

¹ <http://www.explorestemcells.co.uk/HistoryStemCellResearch.html>

Cloning and the making of stem cells are totally irrelevant. We can clone humans without ever making embryonic stem cells and vice versa. The fusion of these two fields it is called therapeutic cloning. Therapeutic cloning differs from stem cells in one major thing. If we were for example, to repair part of the liver of a child with embryonic stem cells, the child would have a fully functional and whole liver but would require a lifelong treatment of drugs. Therapeutic cloning however takes the nucleus from the child and puts it into a donor's vacant egg. The embryo would divide into a blastocyst that would contain the stem cells in the inner cell. These stem cells that could not only differentiate into any cell but would also be a perfect immunological match. Therapeutic cloning brings the topic of cloning into 'the moral equation'. However, Therapeutic cloning also offers legitimacy to the notion of cloning.

Adult stem cells add another part to the ethical debate. The traditional view of adult stem cells has been that they only have the potential to produce their own kind of cell. However, a more modern view is that these same stem cells can be manipulated to differentiate into more than one type of cell. This idea could completely alter the course of the ethical debate, since it could mean that embryos would no longer need to be destroyed. Some people argue that since adult stem cells are pluripotent like the embryonic ones extracting the latter is not only wrong but also unnecessary. A person's own reserves of bone marrow cells provide a perfect immunological match. So there is a case that not only do adult stem cells do the same thing as embryonic ones, they are even better because using them does not lead to immunological rejection. However, there is still not enough evidence and research to suggest that bone marrow cells are going to be able to provide a person with replacement brain tissue.

Discussion

One of the most appealing capabilities of stem cells is the possibility the regeneration of human body parts. While this process is already evident in nature, it is currently much more problematic to replicate in the laboratory. Stem cells require specific conditions, such as the correct amount of nutrients and hormone levels, in order to differentiate into a certain type of cells. Studying stem cell differentiation may hold the answers to questions such as how a donor's liver can recover fully after transplantation. The salamander has been the most intriguing to scientists, because of the way it can build new limbs after an amputation.

The early response to an injury for both salamanders and humans is similar, but while human tissues soon scar, the tissues of an amputation site of a salamander revert to an embryo-like state. Bleeding is limited because blood vessels at the site of the wound contract, and a layer of skin quickly covers the site. This layer, called the wound epidermis, becomes a set of cells called the apical epithelial cap, which sends signals to commence the reconstruction of the limb. Fibroblasts, cells which hold together internal tissues, move out of the connective tissue to the site, and

they form a blastema. This is a term which refers to a ball of stem cells which are undifferentiated and have the ability to form any specialised cells.²

A blastema is the basis for the salamander's new limb, and the cells it contains are similar to those found in the limb buds of salamander embryos. Blastemas are found in mammal embryos before birth, and if for some reason a human embryo lost a limb in the womb, it would be repaired. However, this repair process evidently is not naturally present in humans after birth, and so it brings about the challenge of enabling man to do the same, resulting in huge benefits for the medical world. For example, a soldier whose leg had been destroyed by a bomb would be consoled by the possibility that he would be able to grow a new, fully functional leg. This leg would be created by his own body, eliminating the need for immunosuppressant drugs, as there would be no chance of rejection. This idea extends not only to limbs, but also to the rod and cone cells on the retina, and even nerve cells, meaning a blind man could potentially be able to see again, or a paralysed man walk. It would reduce the need for surgery, since coaxing the body to produce stem cells would not require major surgical treatment, and could be as simple as applying a dressing coated in chemicals triggering the correct genes.

The science behind the salamander's incredible discovery still requires much further research; however, the basic ideas are now well-known. One experiment conducted at the University of California which was documented in the *Scientific American* magazine in March 2008,³ explains how an incision was made into the skin of a salamander away from the normal amputation site, and although the skin repaired itself, there was no blastema. However, when skin from the other side of the limb was grafted into the wound, and a nerve was channelled to the site, a perfect limb grew out from the side, albeit in an abnormal position, but this proved the need for epidermal cells. These cells are derived from one of three primitive cells found in an embryo, known as ectoderms, which send signals to control the growth of limbs. Together these cells form the apical epidermal ridge, which from time to time produce signals such as fibroblast growth factors (FGFs) which cause many different specialist cells to be formed, allowing a complex structure such as a limb to be constructed.

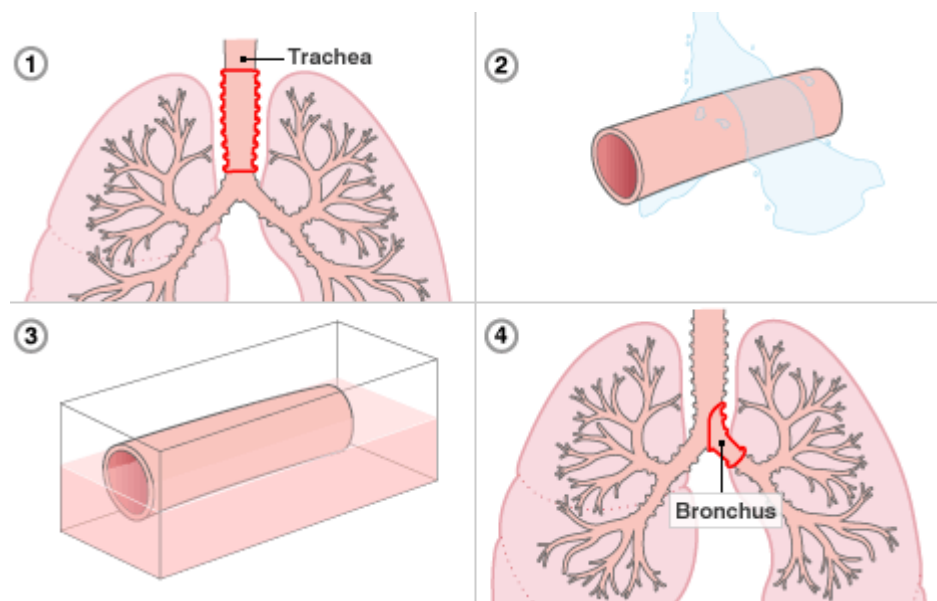
The research also showed the importance of the position of the amputation site. A set of genes known as the Hox family is involved in the positioning of limbs at the embryonic stage, and they provide instructions as to where certain cells should grow. Fibroblasts in salamander limbs have the ability to retain memory of their position in the animal. This means that in the event they are wounded, the body is able to detect what types of cell are required to repair the wound, and whether a new limb is required. However, in adulthood, most other animals normally lose the "memory" of their position in the body, and so the problem that faces scientists is not only stem-cell related, but also greatly relies on genetics, and the ability to "switch on" certain genes such as those in the Hox family.

² <http://medical-dictionary.thefreedictionary.com/blastema>

³ <http://www.sciam.com/article.cfm?id=regrowing-human-limbs>

While the focus on salamanders and the completely natural growth of a new limb in humans is ideal to scientists, other more potent techniques are being used, such as the culturing of a patient's cells around a donated scaffold of the required organ, proved successful in the construction of a patient's trachea in Spain in November 2008⁴. The patient, a 30-year-old lady named Claudia Castillo, had bronchomalacia, a weak left bronchus which had effectively sealed up after she suffered from tuberculosis. This resulted in her not being able to breathe through her left lung, and she found it hard to "walk, play or have a long conversation".⁵

The diagram below, taken from the BBC website, outlines the process which took place in the construction of the new bronchus.⁶ The donor trachea (1) was stripped of all its cells and MHC antigens (2), which help the body to determine whether a material is self or non-self. The patient's cells, a combination of epithelial cells and adult stem cells taken from her hip, were then cultured on the collagen scaffold (3). The trachea was then cut to shape and surgery took place to replace her damaged bronchus with the new one (4). The incredible success of the surgery, and the improvement of the patient's quality of life, show some of the capabilities of stem cells – there was no reaction to the graft by her body, and an immediate improvement could be noticed.



There is much hope for stem cells and their role in regeneration in the future. Robert Edwards, 82, who was the first scientist to produce a test-tube baby, said last year that humans would be able to regenerate in the future, based on the fact that blastemas are found in human fetuses but disappear after birth, meaning that there is much scope for switching the genes back on.⁷

⁴ [http://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(08\)61598-6/abstract](http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(08)61598-6/abstract)

⁵ <http://news.bbc.co.uk/1/hi/health/7735298.stm>

⁶ <http://news.bbc.co.uk/1/hi/health/7735696.stm#graphic>

⁷ <http://www.timesonline.co.uk/tol/news/uk/science/article3867838.ece>

One of the most concerning medical issues that face the human race is cancer. As average life expectancy increases, the population becomes more prone to this particular disease because the immune system weakens and the chance of a mistake during cell replication rises. Also the increased level of carcinogens in our natural environment, such as asbestos, means that the disease is on a steep rise. For example it is estimated that there were 400,000 more cancer cases in 2006 than in 2004 (2.9 million cases) and 1.7 million deaths from the disease in the whole of Europe⁸. The search for a cure for cancer has become a holy grail for many pharmaceutical companies. However different types of cancer act completely differently and they are hard to control. Thus it may be impossible to find a single and effective treatment for the disease.

This is where the stem cell research may come in: stem cells may be the key to fighting cancer. T-cells, also known as 'killer cells', are naturally present in our body and are formed from stem cells in the bone marrow then finally mature in the thymus gland. Each type of T-cell is specific to a certain antigen, and in the event of the body detecting foreign cells, a specific T-cell is produced. T-cells attack an organism's own cells that contain abnormal or non-self material because these cells present antigens on their cell-surface membranes. This allows for T-cells to home in on the target cells. Luckily, cancer is one of these antigen-presenting cells. Therefore when the cell cycle does not regulate itself properly and a healthy cells turn into cancerous cells, the cytotoxic T-cells detect and kill cancerous cells by producing a protein that makes a hole in the membrane.

T-cells can be artificially cultured from adult stem cells. The production of T-cells happens in our body all the time in order to fight any antigens that invade or develop in the body. Boosting a cancer patient's T-cell count may mean that the chances of fighting cancer are higher because there will be more of the correct T-cells to destroy them. Moreover, cancers sometimes develop when the immune system does not function properly. Hence boosting the T-cell count will help in fighting against each cancer.

Furthermore, combining this treatment with conventional cancer therapies may enhance the prognosis. In particular, using this treatment with biological therapies may be the future of the cancer treatment. Biological therapies involve using Biological Response Modifiers, also known as BRMs, such as monoclonal antibodies, cytokines and interferon⁹. They are able to enhance the body's immune system and sometimes have a direct anti-tumour effect. The advantage of using this therapy with T-cells produced from stem cells is that there will be less adverse effects compared to current cancer therapies such as radiotherapy, which destroys healthy cells as well as cancerous cells. This new therapy will be selective and less harmful for patients. What is more is that there are currently therapies available which

⁸ <http://www.bio-medicine.org/medicine-news/Marked-Increase-of-Cancer-Cases-Among-Aging-Population-18061-1/>

⁹ <http://www.cancer.gov/cancertopics/factsheet/Therapy/biological>

restore the damaged immune system after cancer treatments such as chemotherapy¹⁰. This improves the general health of the patient after the treatment and allows them to recover more quickly.

If this treatment becomes available, there would be limitations, as myeloid-derived suppressor cells (MDSCs), which normally maintain the immune system so that healthy tissues are not attacked, can restrain the anti-tumour response of the immune system to cancer¹¹. This means that the cancer cells could become invisible to the immune system with the result that the T-cells could not attack them anymore. However, using this kind of therapy in the first stages of the disease would be very beneficial because the T-cells could get to everywhere in the body. This is an advantage because current therapies cannot completely eradicate cancer cells in the body which brings the problem of recurrence. Plus it will not have any adverse effects because its body's own cell and hence it will not attack healthy tissues.

Furthermore, studying more about stem cells may revolutionise our understanding of cancer. Current research shows that when stem cells in the body replicate incorrectly, they may differentiate into cancers¹². This explains how cancer cells are able to come back after being almost destroyed by cancer therapies. It may be that the mutation occurs to the stem cells themselves. Who knows? Studying these mechanisms through stem cell research may result in developing more effective drugs against cancer.

They might not only be helpful in the search for a cure for cancer, but stem cells could also be a possibility in the care of HIV patients, whose immune system is compromised by the deadly virus. When the T-cell count gets critically low, the body is much more susceptible to infections. There are anti-retroviral drugs available that lower the number of viruses in the body which are not inside cells. This allows the body to recover and rebuild its immunity. However the effect of the drug decreases with time and eventually the disease will be terminal. Combining this treatment with T-cell boosters from stem cells could prolong a patient's life and decrease their dependency on the drugs.

One of the more far-fetched developments that could happen in the future of stem cells is the possibility of a 'cure for time'. A few years ago this idea would have been dismissed as impossible and labelled as 'Star Trek' science. However, recent research has shown this as a misconception. Although there is currently insufficient data to reinforce the theory that stem cells have the capability to slow down ageing in humans, it is widely accepted that the body's maintenance and repair systems in humans deteriorate with age. As the body gets older cells are lost and therefore need to be replaced. This source of cells comes from stem cells. However, as the body ages, mistakes are made in the DNA or the DNA becomes damaged and breaks off. Cells are not replicated perfectly and so lose their effectiveness. This is

¹⁰ <http://www.cancercenter.com/stem-cells.htm>

¹¹ http://www.hopkinsmedicine.org/Press_releases/2007/07_16_07.html

¹² <http://www.nytimes.com/2006/02/21/health/21canc.html>

particularly evident in the immune system of an elderly person. As a person ages their immune system deteriorates, and this is because their 'old' stem cells differentiate into imperfect white blood cells that are not as capable to fight off disease as someone who is younger. The stem cells can no longer cope with the degree of cell division needed to keep the organs, tissue and cells young.

The effects of haematopoietic stem cells (HSC) have been researched by scientists around the globe. Hematopoietic stem cells are stem cells that have the ability to differentiate into blood cell types such as lymphocytes, macrophages, megakaryocytes and other cellular components of the blood. Research has shown that when old and young HSCs were added to mice whose bone marrow cells were destroyed the old HSCs would begin to produce less bone marrow cells after about 8 weeks to 16 weeks of transplantation¹³. The drop in old HSCs' contributions suggests that aging HSCs lose their repopulating capacity.

A lot of hope can be garnered from this experiment. From this experiment we can gather that young HSCs are much more active in their differentiation than their elder forms. The ability to transplant HSCs into humans, who are unable to effectively replenish their reserve of white blood cells, would be a breakthrough against the fight against current and future pathogens. In this case the white blood cells would have little or no functional defects that would make them susceptible to diseases. The irony of the situation is that the body's own immune system could reject this new influx of HSCs. This is a major stumbling block that is preventing the advancement of this research. We cannot take stem cells from a foetus or a child and put them into 60-70 year old person. The immune system would immediately reject this new flood of foreign cells. Currently, it is implausible to suggest that immunosuppressant drugs will be able to repress the immune system. The HSCs would differentiate into blood cells that would be present all over the body making it very difficult for current drugs to suppress them all. The success rate would be extremely low because of the huge number of blood cells, it would be incredibly costly and the amount of drugs that would be needed would significantly weaken the immune system increasing the chance of infection. We cannot yet find a way of taking the nucleus of a young HSC and using therapeutic cloning, harvest more young HSCs.

A practical example of this in the medical world is the issue of brain diseases such as Alzheimer's, which is a big problem as an aging population is becoming more prevalent. Although sufferers' conditions can be alleviated with drugs, such as L-Dopa for Parkinson's, these degenerative diseases are incurable. This drug increases dopamine levels in the brain cells to allow the body to move normally, but does not replace any cells. Growing brain cells from adult stem cells would have several benefits. Firstly, the stem cells would be extracted from the patient, meaning that they would contain the patient's DNA and would contain the same marker proteins. This would rule out the need for any drugs to prevent rejection, meaning that there

¹³ PLoS Biology (2007, July 30), *Effects of Aging in Stem Cells*, ScienceDaily. Retrieved March 15, 2009, from <http://www.sciencedaily.com>

would be no side effects. Also, if the technique for manipulating the stem cells into brain cells such as astrocytes and oligodendrocytes is refined, then almost all cells cultured by this method will be without any defects. This would reduce the risk of faulty cells causing further damage in the brain and worsening the condition.

We are a far cry from reaching the stage where we can develop a 'cure for time'. It will certainly take decades before we can devise a way to prevent the immunological rejection of stem cells. However, if we were to find a way to circumvent this outcome, most likely through therapeutic cloning, then the reality of the situation could arrive much faster than expected.

Conclusion

There are many potential problems in the theories presented above. However, there are also many ways of overcoming these obstacles. The involvement of the USA in the research of stem cells means the world will have access to its vast amount of resources. The collaboration of scientists means that it will become much easier to 'fix' these problems. We do not necessarily have to 'solve' the problem but instead bypass it. For example, as mentioned above, the transplantation of HSCs from one person to another is held back by the problem of immunological rejection. However, we could bypass this problem via genetics. Researchers from the University of Pennsylvania have shown that if the gene ATR was deleted then there were signs of premature ageing. The study showed that mouse cells without ATR had an overwhelming amount of DNA damage and could not contribute to tissue renewal. There is a possibility that if we prevented this gene from being deleted then we would be able to minimise DNA damage and therefore reconstitute healthy tissue. This is only an example of the possible coinciding research between two fields; genetics and stem cells.

It is important that we keep all channels of research open. Cutting one would not only completely end a branch of research but have a huge detrimental effect on other fields of research. Of course, we cannot dismiss the important ethical issues that are intertwined within all matters of research; human morals and values are at stake. However, science has always been a double-edged sword. The physics that gave us mobile phones and MRI scans also brought us nuclear weapons. The chemistry that gave antibiotics and cars also brought about the destruction of the ozone layer. The argument 'will the end justify the means?' is an unceasing circle. Research is unpredictable; we can guess where we would like science to go, we cannot predict the outcome of it.

"Each tributary we block will cut down the flow of knowledge and the benefits, predictable and unpredictable, that will trickle down to society."¹⁴

¹⁴ Finkel, E. (2005) Stem Cells – Controversy at the frontiers of science, Sydney, ABC books ISBN 07333 1248 9

*Cover image taken from <http://healthcare.zdnet.com/images/stem-cell-harvest.jpg>

