

STEM CELLS:  
THE NEXT GENERATION OF MEDICINE

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**PASS WITH DISTINCTION**

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## ABSTRACT

stem cells have the potential to revolutionise medicine through their use in regenerative medicine, tissue and organ transplants, helping scientists research the workings of disease, and indeed combating some of the fundamental mechanisms of disease itself. How stem cells are used in all of these areas will be covered later, including details of the latest research of how stem cells may hold the key to overcoming previously incurable viral infections such as HIV.

1.

## INTRODUCTION

### What are stem cells?

Stem cells are unspecialised cells with two key properties, the ability to self replicate and the unique ability to differentiate.

Differentiation is the process by which stem cells develop into more specialised types of cell e.g. skin cell, heart cell, red blood cell, (potentially any cell in the body).

This occurs when stem cells divide; they either self-replicate – forming two identical copies of the original stem cell, or as the stem cell divides one (asymmetrical division)<sup>1</sup> or both<sup>2</sup> of the new cells produced may differentiate into a different type of cell.

There are many different types of stem cell, each with varying abilities to differentiate. There is only one Totipotent stem cell, a fertilised egg known as a Zygote – from this all other types of cell eventually develop including the extra-embryonic tissues. Pleuripotent stem cells can differentiate into almost any type of cell including other types of stem cell. Multipotent stem cells have the ability to differentiate into a group of specialised cells; for example, haemopoietic stem cells can differentiate into various types of blood cell such as Red blood cell, T-cells, and platelet producing cells. There also exist stem cells which have the ability to differentiate into even fewer cell types, such as unipotent stem cells which can produce only one type of cell, and play a key role in the renewal of tissues such as skin and gut lining.

At this point it is important to mention that differentiation is a one way process, stem cells can divide to produce more specialised cells, but adult cells cannot divide to produce more stem cells.

### Where can stem cells be found?

Stem cells can be divided into two categories concerning their origin. There are Embryonic stem cells and Adult stem cells.

Embryonic stem cells are found exclusively in the Embryo, for research purposes they are extracted from the 'blastocyst' which is a stage of embryonic development roughly 5 days after fertilisation. The extracted cells are placed in nutrient rich culture dishes and stimulated to divide. Embryonic stem cells can continue to divide rapidly in a undifferentiated state for long periods of time meaning just a few embryonic stem cells can give rise to many cultures of stem cells known as a stem cell line. Embryonic stem cells are pleuripotent, easy to extract and culture, and there is already a large source of 'excess' blastocysts from IVF clinics. However, the use of embryonic stem cells has caused fierce debate within the scientific community. Although the embryonic blastocyst used is tiny, literally only 30-40 cells, the fact that it could have the potential to develop into a normal human being means that many people and particularly religious groups are violently opposed to their use in scientific research.

1) Sell, S. (2004) Stem cells. Stem Cell Handbook ed. by Sell, S. 1-18

2) <http://stemcells.nih.gov/info/scireport/chapter4.asp>

Adult stem cells are found in everyone's body, they help grow and repair the body's tissues throughout a person's life. They are found under the skin, gut, in the liver, heart, brain, blood, and many other tissues and organs. Just like embryonic stem cells, adult stem cells can be extracted and cultured. However, adult stem cells are generally found deep within organs, and in very small quantities surrounded by millions of ordinary cells making them very hard to identify and extract. Adult stem cells are also difficult to culture as it is harder to keep them in an undifferentiated state, and they are more likely to develop genetic abnormalities after many divisions. Adult stem cells are also not pluripotent; they are only multipotent - although recent research shows that adult stem cells have a degree of '*plasticity*' meaning that to an extent it may be possible to coax bone marrow stem cells into producing say liver cells.

So clearly the use of both embryonic and adult stem cells each have their own advantages and disadvantages. The main problem with embryonic stem cells are the ethical issues concerned with interfering with human life for scientific research, this slows the pace of embryonic stem cell research as for example in the US there was no federal funding for stem cell lines created after 2001 on ethical grounds (until 2009 when Barack Obama changed policies). Another problem is the fact that is impossible to genetically match any cells derived from embryonic stem cells to a recipient so there will always be a chance of rejection.

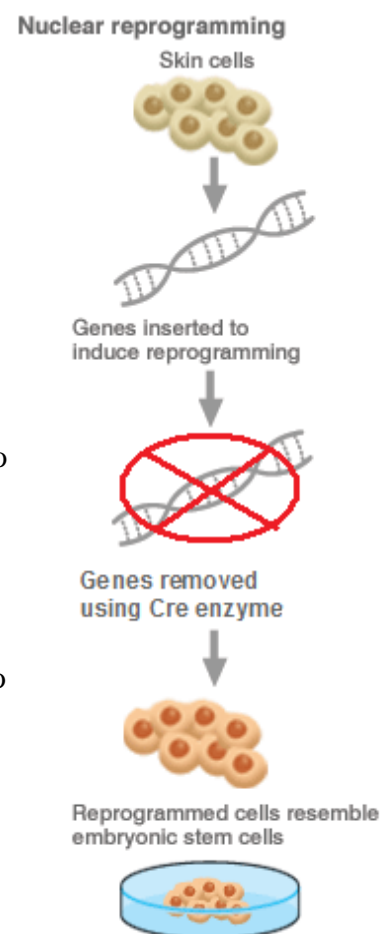
The main problem with adult stem cells is the difficulty in identifying, extracting and creating a stable stem cell line which is suitable for research or transplantation.

There is an exciting new method for creating stem cells which could potentially solve all of the disadvantages of both adult and embryonic stem cells. In 2006 scientists managed to convert adult cells into 'induced' pluripotent stem cells (iPS). This was a ground breaking discovery as previously adult stem cells had never been observed to return to a stem cell state in humans (it can happen naturally in plants). They did this through the use of viruses which enter the adult cell, then modify its DNA by transferring four genes (Oct4, Sox2, c-Myc and Klf4). However the virus inside the cell and the inserted genes (particularly Klf4) are known to cause cancer and interfere with other genes making the created cells too dangerous to use.

By early 2009 scientists have found a way to bracket the inserted genes at each end with a short DNA sequence called loxP which is recognized by the enzyme 'Cre'. This means that now once the Genes have been introduced, and hence the cell has been reprogrammed into a iPS cell state, the enzyme Cre can be introduced into the cell removing all the inserted genes without a trace.

This 'nuclear reprogramming' has already been tried in humans to create working heart muscle and dopamine producing neurons from ordinary skin cells.

Theoretically, this technique could mean that scientists have access to an unlimited source of pluripotent stem cells almost identical to embryonic stem cells, which are free of any major ethical issues, and can be genetically matched to any patient (as they would be the ones donating the adult cells to be reprogrammed).



SOURCE: Science Media Centre

Overview of steps of nuclear reprogramming  
Source: Science Media Centre  
(edited by Clay Robinson)

## DISCUSSION

3.

### Current Uses of stem cells

Having already covered what the unique properties of stem cells are, and methods of obtaining cultures of them, it is due time to introduce some of their current and future uses in medicine.

The oldest use of stem cells in medicine is bone marrow transplants. Essentially the procedure is most often used when treating cancer patients (often leukaemia) with high-dose chemotherapy, the high doses of radiation that the body is exposed to kills off much of the patients bone marrow which usually contains blood stem cells responsible for producing red and white blood cells and platelet cells. Clearly it is necessary to maintain a normal count of blood cells within the blood so the patient is given a so called 'bone marrow transplant'. This bone marrow transplant is actually a drip containing the patients own blood stem cells which have been collected prior to the chemotherapy and cultured (autogenic transplant), or a drip containing the blood stem cells of a donor (allogenic transplant). Allogenic transplants are taken from well matched donors or relatives, but even then there is a chance of the transplanted stem cells forming immune cells which fight against the patients body – Graft vs Host Disease (GvHD), or the other way round Host vs Graft Disease (HvGD).

Bone marrow transplants are also used in much the same way for conditions such as inherited severe combined immunodeficiency syndrome, and Myelodysplastic syndrome.

The first successful bone marrow transplant was completed in 1956. So knowledge of stem cells' amazing powers of regeneration has been around for quite some time, although admittedly back in 1956 they had very little knowledge of the actual workings of stem cells and it wasn't until 1968 that bone marrow transplants were used to treat a non-cancer ailment, and 1973 when the first un-related donor was used – so progress has been slow.

One of the largest use of stem cells in medicine is in tissue transplants. Bone marrow transplants are a basic type of tissue transplant, however using stem cells there is the potential to develop much more complex types of tissue transplant and even whole organ transplants.

Another example of a tissue transplant using stem cells is a skin graft. As opposed to using donor skin, or grafting skin from one area of the body to another, it is possible for patients to use their own adult skin stem cells to create perfectly matched skin grafts for surgery following burns, disfiguring accidents or even breast cancer. The use of stem cell skin grafts is particularly useful because it means that there is no chance of rejection and patients with very severe burns all over their body who would not have enough skin to cover an ordinary graft can still receive enough new skin to cover all the wounds.

The latest development in stem cell tissue transplants is the transplantation of whole organs.

Currently there is a shortage of organs available for transplant, in Britain around 8000 people are on the waiting list for a transplant, 1000 of which die before they can get a transplant. Also even after a transplant is completed successfully there is the ongoing problem of rejection and although drugs are becoming more advanced, the long-term survival rates of transplanted organs is still low. After one year, transplanted heart and kidneys have a 90% survival rate however only 50% of the hearts last 5 years and 50% of the kidneys last 10 years

Currently Transplant patients have to rely on Immuno-suppressant drugs such as Cyclosporine which blocks interleukin-2, thus helping to prevent Lymphocyte proliferation and activation. However as one might guess, the non-specific suppression of such a protein as interleukin-2 results in a weakened immune system, leaving the transplant patient open to infection, on top of any other drug side effects.

Stem cells could give scientists the fantastic ability to create organs from scratch which are genetically identical to the recipient, thus solving both problems. All organs and all tissues, are ultimately derived from stem cells in the developing embryo, so theoretically any organ could be created using stem cells in the lab. The difficulty is, creating the precise conditions and stimulating the cells in the right way to make them form the correct tissues to make a working organ. This obviously means that it is very difficult to make complicated whole organs such as a heart, or lung – however scientists have had some success at creating parts of organs such as heart valves, blood vessels, and whole bladders.

In 2008 the first ever transplant of a whole organ grown from stem cells was completed successfully. The patient was a 30 year old woman whose left airway had collapsed as a result of tuberculosis, she had already had a stent implanted to reopen the airway however it had not worked so she was in need of a full transplant. In the lab, scientists stripped the donated trachea of all the original donor's cells leaving only the cartilage structure behind, then grafted the patient's own adult stem cells onto the cartilage and stimulated it with chemicals to coax the stem cells into rebuilding the trachea. Amazingly the trachea was grown successfully and when transplanted into the patient, her body accepted it without the use of inconvenient and expensive immunosuppressant drugs.

Personally I believe that through research into stem cells scientists will be able to gradually create more and more complex organs, and it will only be a matter of time until any organ can be grown in the lab and used for transplantation. Scientists can already create heart valves, muscle, and blood vessels – in a couple of decades whole heart transplants could be commonplace.

Stem Cells are being used extensively in veterinary medicine, especially in the equine field. However being an expensive and specialist treatment, only certain animals like prized racehorses or pedigree pets usually get these treatments. Currently they are being used to treat joint, ligament and bone procedures at this time, for example osteoarthritis and fractures. However promising research is being conducted to cure such diseases as myocardial infarctions, muscular dystrophy and cerebral disorders.

In the future we can expect to see more research in the fields of genetic disorders, which many pedigree dogs, like pugs, suffer from. In many ways veterinary research into stem cells is unhindered by the same restrictions as human medicine is, and thus the use of stem cells to treat cancer can proceed years ahead in animals than it can for a human counterpart. Dr. Jaime Modiano of the College of Veterinary Medicine, University of Minnesota pointed out:

*“The natural history of lymphoma, osteosarcoma, and melanoma are similar in dogs and people, and for that reason we can extrapolate information from what we learn in dogs to improve outcomes for people with these tumors and vice versa”*

This leads on to another major use of stem cells, which is to research other aspects of human biology. For example human embryonic stem cells can be used to study the earliest stages of human development. This could help us understand some still unexplained occurrences which lead to placental abnormalities, congenital birth defects, and spontaneous abortion. By studying the progress of human ES cells *in vitro*, it may be possible to identify genetic, molecular and cellular events that lead to these problems and identify methods of preventing them.

This method of *in vitro* research using stem cells can be used for almost every disease that we still do not know the workings of. For example the extremely complicated condition, Parkinson's disease, can be studied in new depth using stem cells. Using the afore mentioned method of 'nuclear reprogramming' to create stem cells, scientists have used skin cells of a Parkinson's disease patient to create dopamine-producing neurons – the very type of cell that degenerates in Parkinson's disease. These neurons will too have Parkinson's disease; this allows researchers to investigate the

progression of the disease in detail on a cellular level. This will help answer questions such as what exactly it is that kills the cells, and what might prevent this damage from occurring?

This type of research is particularly useful for diseases such as Parkinson's which are currently very difficult to study as the brain is clearly a fairly inaccessible area. This method could be used to give scientists a whole new take on many diseases including, multiple sclerosis, ALS, Alzheimer's, types of cancer, diabetes, and many more.

Embryonic stem cells are used in drug development, screening, and testing. For example, stem cells can be cultured then stimulated to differentiate into say liver cells, one batch will be infected with a liver disease and another batch left to remain healthy – then a new drug will be tested on both cultures and the effects observed. This can be used in combination with the usual drug testing, meaning that the drug has been tested on both animals and human tissue derived from stem cells before entering real human trials.

A recent revolutionary application of stem cells is its experimental use in the treatment of HIV, which could lead on to similar treatments for a wide range of diseases and conditions.

It was announced in mid-February 2009 that a man in Germany had been reported free of HIV following a bone marrow transplant. The donor was known to have copies of a gene that stops HIV from invading white blood cells. This is the first example of the virus being stopped completely, as opposed to its progress being slowed by antiretroviral therapies.

Antiretroviral Therapy is the main treatment of HIV, consisting of three or four Antiretroviral Drugs, also known as Highly Active Anti-Retroviral Treatment (HAART). They are designed to stop the virus at varying stages of its cell cycle, some prevent complete synthesis of the viruses DNA preventing it from multiplying, others help stop the virus from binding to new cells. These drugs have clear drawbacks, they are expensive, unreliable, interfere with the patients immune system, have extreme side effects (e.g. insomnia, nausea, lipodystrophy), and disrupt the patients ordinary lifestyle.

The patient was a 42 year old American, who had come to Germany to undergo an operation to cure his leukemia and also take part in an experimental treatment of his recently contracted HIV using gene therapy.

The gene mutation, known as CCR5 delta32, is found in just 1-3 percent of white populations of European descent. This mutation removes the CCR5 receptor, which is the “door-handle” into the cell for HIV. Without this point of entry, the virus is unable to enter the cell and is subsequently destroyed by the host's unimpeded immune system. This is why some people are naturally immune to HIV. However the gene is recessive and requires both parents to have a copy.

The treatment is a more elaborate form of the bone marrow transplant which any leukaemia patient would typically undergo. The donated bone marrow was taken from an individual who had the rare gene mutation CCR5 delta32. The idea was that when the leukaemia patients immune system was destroyed by the High Dose Chemotherapy, it would be rebuilt by the donated bone marrow which contained stem cells genetically immune to HIV.

However in the future there may be another way to use CCR5 delta32 mutation to combat HIV. The theory is; genetically engineer our own extracted stem cells to become immune to HIV in the lab, then transplant your own stem cells, now containing the mutated gene, back into your body.

This research is being pioneered by David Baltimore of the California Institute of Technology and Irving L. Weissmann, Stanford University. The idea is thus, stem cells are extracted from a patient,

and treated with RNA to remove the CCR5 antigen producing gene. These protected cells are then re-injected into the patient, where they would be strong enough to fight the infection and create daughter cells.

*“Potentially, we could reengineer the body’s immune system so it’s protected for life”* Irvin Chen, UCLA  
Getting the strand of relevant RNA into the cells has always been the main challenge, however it is theorised that you can actually use HIV itself as a delivery system. By stripping away the disease causing genes, you can create the perfect transport protein, who’s only instruction is to deliver the RNA to the cell. 6.

However this gene therapy has come up against a lot of opposition. It raises many ethical issues as to whether we should “mess about” with genes, and whether we really know enough. For example, in a study of gene therapy in France, lead to children developing cancer, so the US Food and Drug Administration halted research in this area.

This method probably holds the greatest chance of success in combating HIV, and as it directly involves the genes, it is a permanent treatment. A lot of effort is being put into this research; however this type of gene therapy has many other applications in the world of pathology.

This kind of gene therapy 'custom designed' specifically to treat different diseases. It would be most effective for combating diseases which effect organ systems which can easily be replaced by donor stem cells. Most notably are diseases of the blood, like HIV and anaemia. Possibly in the case of anaemia, a gene may be injected which contains instructions for more haemoglobin for each blood cells.

Of course the main ailments that this technique would work on would be genetic and viral diseases. Many of the treatments that may be undertaken rely heavily on research into the Genome Project. By isolating defective gene, and recognising alleles that could lead to better health, we could replace the genes. It would be a slow process and as you would be replacing the defective cells by introducing new, modified stem cells. It would require long procedures with multiple transplants by specially trained surgeons, especially if treating diseases of the brain or other sensitive organs.

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