

Discussion on the Future Developments in Stem Cell Research and the  
Possible Role of Synchrotron Radiation

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RESEARCH PAPER  
BASED ON  
PATHOLOGY LECTURES  
AT MEDLINK 2008

### Abstract

Currently stem cell research is moving away from embryonic stem cell research and more towards somatic and foetal cells in a bid to become more ethically correct. At the moment very few therapies exist which use stem cells as a basis, due to the fact that, for instance, cell integration techniques have not yet been perfected. Building on current scientific work several possible advancements in this field stand out as realistic future developments in stem cell research. Synchrotron radiation, already used in some areas of medicine is one such option, as is the business opportunity personalised drug manufacture presents to the pharmaceutical industry. However, whilst current advancements are promising it still remains questionable whether new types of research will replace embryonic research in the near future.

### Introduction

Embryonic stem cell research has been a controversial topic for many years, struggling to maintain the balance between the conflicting desire to quickly advance the field, and the need to abide to the social necessity of carrying out ethically viable experiments. In part this is due to the endless scope of opportunity this particular area of research offers to the world of medicine and therapeutic developments. However on top of this obvious benefit, this research allows scientists to obtain a more in depth understanding of the body on a cellular level leading to scientific advancement.

Embryonic stem cells are the most researched, yet controversial, of the three types of stem cell. Being derived from a donated egg fertilised in vitro they have the potential for life hence the hysteria that surrounds this research. Pluripotent cells are harvested at around four to five days old, from the blastocyst that has formed. These cells have the ability to self replicate as demonstrated by the work of James Thompson (1998) '*Embryonic Stem Cell Lines Derived from Human Blastocysts*'. This means, provided with the right conditions the embryonic stem cells can differentiate into any cell type in the body.

In terms of medicine, this means tissue can be grown to replace that which is damaged or diseased. Thus, the demand for whole organ transplants would be reduced, putting less strain on a system that simply does not have the supply of "spare" organs to meet demand. On top of this, the need for mechanical instruments and devices such as titanium joints would be irradiated. However, despite how wonderful this appears, creating tissue from embryonic stem cells is not without its problems. In the same way as an organ transplant, the marker proteins on the cell surface of the tissue would not be recognized by the body so there would still be a high risk of immune rejection. Immunosuppressant drugs would therefore have to be continually used by the patient to prevent the new tissue being treated in the same way as a pathogen and be destroyed. It has also been discovered that embryonic stem cells are unstable, and very difficult to control and grow in a reliable way. Unfortunately this means they often produce unexpected results or cancerous growths when they divide.

This is perhaps the reason why research has journeyed more towards the other two types of stem cell: adult (somatic) stem cells and fetal stem cells. Both of these stem cell groups bypass the main issue of the ethics debate as they do not involve embryos, yet each has their own difficulties. Adult cells, unlike embryonic cells, are multipotent meaning that whilst they are differentiated, they can form into a number of other tissues however they seem only to be able to renew themselves or differentiate to become any of the specialized cell types of their original tissue. Cord blood however, which comes under the classification of fetal stem cells, is able to differentiate into a much larger variety of cell types and is currently in use as a therapy to combat cancer and other non malignant diseases such as sickle cell anemia. Both of these types of stem cell offer a similar level of

opportunity to embryonic stem cells however using these, the battle with immune rejection could be overcome. However, unfortunately, these kinds of stem cells are fairly hard to come by.

More recently there have been several breakthroughs. It is now apparent that we can actually create stem cells, theoretically from any cell in the body however this has been tried out with a few types of cell including skin cells. These cells are known as 'Induced Pluripotent Stem Cells'. The work of Kamp, Thompson and Yu (Feb 2009) published in *Circulation Research*, a journal of the American Heart Association shows how the clock can be turned back to create a stem cell from a skin cell. It explains how a virus was used to insert four transcription factors into the genes of a skin cell to reprogram it back to an embryo like state. This means there is the potential that patients could generate their own organs and tissues from their skin cells which would prevent tissue rejection and reduce the need for organ transplants and mechanical devices once again. However, currently the new cell is retaining the virus, which could eventually cause cancer, so until the reprogramming method is perfected this kind of therapy cannot be introduced for clinical purposes. However research into this is constantly ongoing and very recently according to a study published in 'Cell' (February 5<sup>th</sup> 2009) a team of scientists lead by Hans Schöler reprogrammed neural cells back to pluripotency using only the oct4 transcription factor with successful although less efficient results.

Thompson and Yu first reported genetic reprogramming of skin cells in 2007 initially thinking it would be a powerful way to study disease. Through the use of induced pluripotent stem cells scientists can 'replay' a disease over and over to discover how it starts, what occurs in the early stages and identify and observe critical points in the development of a disease. This means new therapies can be developed to intervene at different stages of the disease and complex genetic disorders can be investigated in more detail leading to a more accurate analysis of the disease and prognosis. This is also a very valuable technology to the pharmaceutical industry as it means drugs can be tested on human cells and the responsiveness of the tissue to the drug can be assessed on a cellular level allowing any harmful side effects to be identified.

It appears that IPS cells are probably the future for this field as in medical terms they will be more clinically relevant than embryonic stem cells due to their ability to be customized to the patient. However more research needs to be done into this area in order to develop new techniques and technology to make this a success. Although different, understanding the way in which embryonic stem cells function and by taking on board our learnings from previous experiments involving them, scientists can be helped to progress in this area and develop more ideas for the future of stem cell technologies.

## Discussion

To me it seems apparent that the main issue to be solved is how to create induced pluripotent stem cells in a way that makes it safe to use them in a clinical scenario. This means either figuring out a way to prevent the new induced cell taking up the virus used to insert the transcription factors, or finding another method by which the skin cell can be returned to a pluripotent state. Currently, there is a wealth of medical investigation focused around synchrotron radiation and it is something that could have many potential applications within medicine.

In a synchrotron, electrons are accelerated to a velocity close to that of light, their purpose being purely experimental. Synchrotron radiation sources are a source of electromagnetic radiation and provide several very intense, direct and tunable beams of photons that extend over a huge range of energies. In terms of medicine it is very useful with several beam lines already in use in x-rays,

imaging and such like however in this instance it is the protein crystallography beam line that is useful. This is because it gives a high resolution ‘determination’ of a large number of protein structures and reveals their interactions including, relevantly, viruses and nucleic acids.

One possibility is to use this technology to examine the cell surface proteins on the virus used to insert the transcription factors into the skin cell. This apparatus would allow scientists to see the shape and properties of the marker protein clearly therefore creating the possibility that an antiviral could be developed based upon the surface protein structure. Developing structural antiviruses is something scientists are experimenting with at the moment, with the protein crystallography beam line actually in use to examine viral surface proteins. However, only one or two anti-viruses have been successfully developed to date.

Theoretically this would allow the virus to be removed from the cell before it begins to replicate, without causing damage to any of the organelles of the induced pluripotent cell. This would solve the issue of the virus causing mutations in the cells or at least dramatically reduce the risk. This might mean IPS cells could begin to be put into clinical use and as said previously dramatically reduce the need for donated organs and mechanical devices. Whilst in this instance it is of little importance, as many viruses have similar surface proteins to cells found inside the body scientists would have to be careful using this idea inside of the body to ensure any structural antiviral developed didn’t harm the patient’s own cells. However, this is an issue scientists would be fully aware of.

Alternatively, instead of using a virus to reprogram the skin cell synchrotron radiation itself could do so. Research suggests that every cell contains all of your genetic material however the majority of your genes are “switched off” in any one cell, although not necessarily permanently. Scientists believe the key to the currently undiscovered “gene switch” lies in the mechanism by which a specific protein binds to a receptor protein. This is thought to change the shape of the molecule and in doing so activate a specific gene in the DNA. As synchrotron radiation allows the protein structure of DNA to be seen and examined it may be possible that the beam of electrons could be focused on a particular gene at the right intensity to switch it on or off accordingly or following the current scientific theory be used to target and signal the correct protein to induce the “gene switch mechanism”.

Although this technology is not currently available it is an extension of current research into cell signalling at labs all over the world. For example cell signalling by the epidermal growth factor receptor using synchrotron radiation source was being investigated at Daresbury in the UK and several other synchrotron sources worldwide. This would mean that cells such as skin cells could become induced pluripotent stem cells without inserting anything extra into the cell such as transcription factors. The technology may also mean conditions to create different tissue types would not be necessary as the appropriate genes could just be signalled to turn on.

If this idea worked then in theory, genetic disorders that have arisen due to a fault in a gene could be cured as the gene in question could be targeted and signalled to switch off or become inactive. However, this would have to be done whilst the cells were still in the body which could pose several safety issues. For instance several types of radiation are already used in cancer therapy to kill off cells, so it is highly likely that this technique would cause some sort of damage to surrounding cells despite its accuracy. Also if the concentration of the synchrotron radiation was too great the gene or appropriate receptor proteins at the very least may be destroyed. Whilst in many situations this could be problematic, in this case such damage may not be so much of an issue.

Another area in medicine currently under investigation looks at the difficulty in getting drugs to the area in the body in which they are needed and explores the possibility of using stem cells to administer the drugs. For instance, the work of UW-Madison neuroscientist, Clive Svendsen in 2005 on engineered human brain progenitor cells looks into this. His work is based upon the difficulty in getting drugs past the blood brain barrier in order to get medicine to treat Parkinson's and other neurodegenerative diseases to the right place. His team engineered the cells to produce a growth factor glial cell line-derived neurotrophic factor, (GDNF) and implanted the secretory cells into the brain. This was so they could migrate in critical areas of the brain and produce the growth factor. Although so far this has only been tested on animals, it was found that this method of delivery promoted the therapeutic potential of the drug. However this is still an experimental process so obstacles such as the life expectancy of the cells have not yet been overcome as the cells, to date, have been found to only live up to three months. If this were to be put into practice at this moment in time patients would be returning to hospital very frequently in order to be given replacement cells which in the long run may cause more harm than good.

Following this research, it appears that the next logical step would be to develop a technique by which stem cells can be used as 'drug delivery vehicles'. Induced pluripotent stem cells could be genetically engineered to produce a certain chemical, drug or growth factor and implanted so as to positively impact the desired place within the body. For example, for people with diabetes pancreatic cells could be genetically engineered to produce insulin and implanted to prevent the necessity of injecting insulin. There is even the possibility that these cells might integrate into the normal tissue so replacement cells may not be needed on a regular basis. Integration however, is an area which needs to be cleared up as scientists have not yet discovered a way to ensure the integration of new cells.

Taking this yet another stage further, this idea could be developed to include the genetic modification of stem cells to produce chemicals not usually found within the body. Working on the same theory these chemicals could be delivered via stem cells. If by continuing research into this area, scientists could find a way to genetically engineer a cell to produce any kind of drug not just those found naturally in the body it would mean that treatment for a variety of diseases and disorders could be treated internally through integration of the engineered cells into the appropriate tissue.

However, this could have several issues such as dosage control, so further research and experimentation would have to be done in order to discover a way to signal these cells to turn on and off or discover a way to control how much of the drug was secreted during the engineering process. Once again, synchrotron radiation offers a potential resolution for this as the cell signalling research currently being undertaken could be tailored to signal these genetically engineered cells possibly through the proteins on the cell membrane.

Currently one of the most important applications of induced pluripotent stem cells is the ability they have to be manipulated to play out the cycle of a disease in a Petri dish. This is especially useful in pharmacology and to the pharmaceutical industry as it means that they can see what effect the drugs they produce have on a cellular level. This technology poses an opportunity for individual people to have their disease/condition analyzed in such a way so that drug companies could tailor their original drugs for that specific disorder to meet the individual's exact needs. Dosage could be prescribed exactly and alterations to the drug could be made depending upon the exact symptoms and the receptiveness of the tissue. Overall this would theoretically mean that the drug would be more effective.

Such a service may be quite costly to do for every individual however the possibility of people paying extra is not unquestionable. For a service that gives the opportunity of better medicine and

more effective treatments few would object to an extra fee as many medicines cost money for people to take anyway. Some may disagree with this option naturally, but because of current pressures upon the NHS it is very unlikely that this organization would be able to fund such a scheme. Unfortunately, and predictably, this means of course that personalized drug based therapy would most likely be more available to those with more money however it could not really be helped as it would be something the pharmaceutical companies would introduce to increase profits. This in itself raises an entirely new ethical issue similar to that of the NHS versus private health care, surrounding how social class and enterprise within the pharmaceutical industry has an effect upon the opportunity people have to have healthcare of an equal quality.

## Conclusion

There is so much research being undertaken in all areas of medicine and stem cell research with scientific breakthroughs occurring all the time so that undoubtedly in time methods to advance stem cell research will become clear. Similarly technological advancements and research into possible medical applications is advancing at the same rate so some sort of development into using induced pluripotent cells either clinically or in the pharmaceutical industry is almost unquestionable.

Technology of some variety is needed to advance this due to the pure nature of the task at hand and I believe a synchrotron radiation source may hold the key to several problems in the current development of induced pluripotent stem cells. The fact that it enables scientists to examine the protein structure of virus' and nucleic acids means that even if the radiation beam lines themselves cannot be employed to better the method of inserting transcription factors to cells or signalling proteins and genes to alter in some way, it can help scientists discover the exact mechanisms behind DNA transcription for example.

So many areas of medicine will be impacted by even the smallest of advancements in this field from a clinical perspective in relation to stem cell therapies and tissue transplants to industry and scientific testing. Who knows induced pluripotent stem cells may one day be used as a substitute for animal drugs testing as clearly the tissue will give a better indication of the effects it will have on a human. It has the possibility to end some of the most ethically, politically and morally sensitive battles in science so all possible technologies need to be exploited.

Whilst further research into adult, fetal and embryonic stem cells may not seem like advancement in the shadow of the newly developed induced pluripotent stem cells it is not the case. Despite controversies surrounding embryonic research and the limitations posed by the other two naturally occurring stem cells it is important to consider that cord blood is currently very important due to its use as a therapy for many diseases including cancer so stopping research in this area would be both unrealistic and irresponsible. Additionally, further research can lead to advancements in other area of science and medicine not necessarily just stem cell research for example advancements in embryonic stem cell research may lead to improvements for the technique on in vitro fertilization a common procedure.

In conclusion, until induced pluripotent stem cells are perfected, tested and available for widespread use whether it is due to synchrotron radiation or any other kind of technology no current research or possibilities should be overlooked regardless of ethical implications. As James Thompson notes 'more study of the newly made cells is required to ensure that cells do not differ from embryonic stem cells in a clinically significant or unexpected way, so it is hardly time to discontinue embryonic stem cell research'.

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