

**EMBRYONIC STEM CELLS AND THEIR POTENTIAL
IN THE TREATMENT OF BONE FRACTURES REQUIRING SURGERY**

BY

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ABSTRACT

This paper discusses the incredible potential of embryonic stem cells in medicine, their current uses, and the ethical issues surrounding such use. It will also explore the possibility of using stem cell technology to improve the treatment of bone fractures that require surgery. Currently bone fractures that require surgery are treated by using metal plates and screws to hold the bones together. This paper explores the idea of using stem cells in conjunction with adapted current medical technology to enable treatment without leaving foreign bodies in the limb after healing, and avoiding such problems as galvanic corrosion and weakening of the bones due to the metal implants.

INTRODUCTION TO EMBRYONIC STEM CELLS

Embryonic stem cells are derived from egg cells that have been fertilized in vitro. These embryos are typically four to five days old, and consist of a tiny ball of cells called a blastocyst. This blastocyst is hollow inside and this cavity is known as the blastocoel. At one end of the blastocoel is a group of around 30 cells called the inner cell mass.

The inner cell mass owes its totipotency to the fact that it expresses only the gene Oct 4, while the rest of the blastocyst expresses both this gene and also CDX 2. Oct 4 is short for Octamer 4, and is a protein involved in the self-renewal of embryonic stem cells. It helps turn genes on and off at the correct times.

Surrounding the blastocyst is a layer of cells called the trophoblast. This layer of cells will go on to form the placenta.

All stem cells are special in that they are undifferentiated. They can give rise to a number of specialized cell types, this ability to specialize becoming more restricted down the stem cell hierarchy. Some stem cells, for example those in the epidermis, can only specialize into types of skin cell.

Embryonic stem cells are so special because they can develop into any type of cell. This ability is called Totipotency, and gives them huge potential in the field of medicine.

The first embryonic stem cell line was developed by James Thomson in 1998. An embryonic stem cell line is formed from a stem cell which is removed from a living embryo and grown in vitro, where it will divide indefinitely, as long as the stem cells receive enough chemical signals instructing them to remain undifferentiated. Figure 1 shows this process.

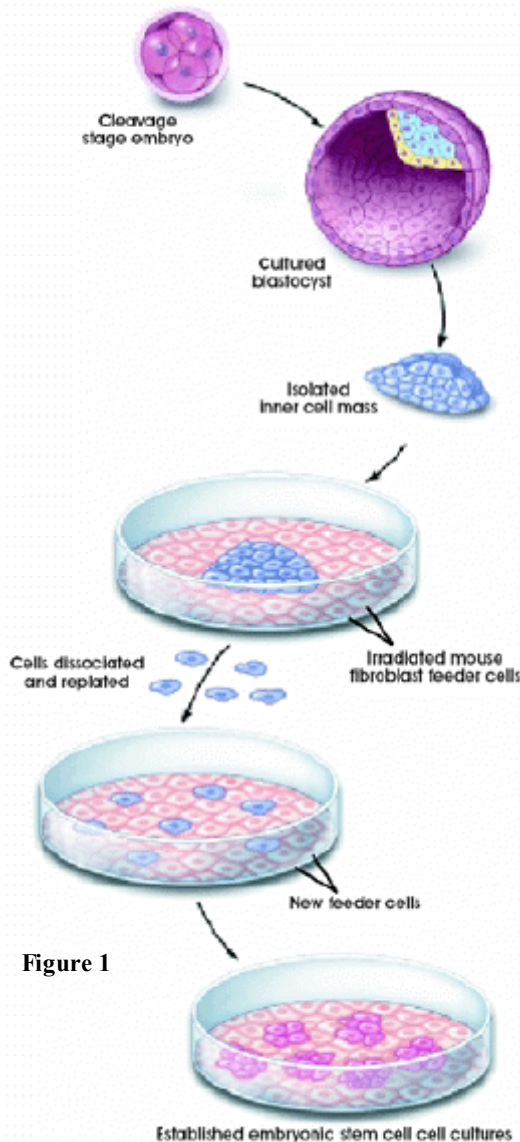


Figure 1

Because a stem cell line of this type requires a living embryo, which is killed during the process of its cells being removed, a number of ethical issues have arisen.

The Research Involving Embryos Bill 2002 only allows embryos to be used that are left over from IVF treatments. However, some people argue that there is a distinct and moral difference between killing an embryo (as is the case in the making of a stem cell line) and simply allowing it to die, as happens when the surplus IVF embryos would eventually expire.

It can also be argued that if society as a whole became accepting of the routine killing of embryos, it could then only be a matter of time before it became accepting of other controversial practices involving the ending of life, for example removing treatment and life support for severely disabled babies.

One of the most popular arguments is that embryos have status as human beings. As it is impossible to draw a line at a certain stage to denote when an embryo becomes a "person", it can be argued that embryos are "potential people" who should be treated with the same respect and dignity as would any other person.

Many religious people are against embryonic stem cell research as many religions hold embryos as being

“divine creations” of particular moral importance. The Holy See of the Roman Catholic Church, for example, holds that an embryo is a person. The weaknesses in this argument include that it is too strong, as it would mean stopping other destructive uses of living things, for example the use of plants for food. This also means that the destruction of embryos for stem cell therapy would only be acceptable if you argued that it is acceptable to kill some people in order to help others. Another common view is that all human beings have equal worth, regardless of talent or conditions. This would mean that no human, regardless of their age or development, should be used as an instrument or as a means to an end.

Most people would agree that embryos are harmed by their loss of life, although that harm may not be in the way that we would usually think of the idea. Philip Devine argues that loss of life is something that any living thing at any stage of development can experience, including embryos, and this loss of life is the harm being done.

However the harm being done may be something quite different. The American philosopher Joel Feinberg says that harm is the “defeating of an interest”, the interest being a living beings beliefs, desires, purposes or expectations. This means that although potential “interests” can be attributed to an embryo, the harm will only become actual as and when the interests become actual.

Another argument is that although embryos do have value and should be treated with the respect that such life commands, there are different levels of respect and value according to different stages of human life. This would mean that although it is a serious matter to kill an embryo, it would be far more serious to kill a human at a later stage of life.

It can also be argued that despite the loss of value in killing an embryo for research, this loss could be greatly outweighed by the potential for benefits that would come from that research.

There has also been research into other methods for creating totipotent stem cells without the need for embryos. By placing four genes in a skin cell, it can be changed into a cell that can produce nearly every cell type. These are called iPS cells. Because some of the inserted genes can cause cancer, these cells will not be used for any type of treatment. Recently however, researchers at the Harvard Stem Cell Institute made mouse iPS cells without inserting the cancer genes into the cell nucleus, thus reducing cancer concerns. This research, if successful, could virtually eliminate the ethical issues surrounding embryonic stem cell research.

USES OF EMBRYONIC STEM CELLS

The potential for embryonic stem cells in the field of medicine is very great indeed. However, due to the legal and ethical issues outlined above, research on them is only just beginning.

Totipotent stem cell lines would be of great use when it come to testing new drugs. Other, less potent stem cell lines are already used in this way, for example cancer stem cell lines are used to test new anti-tumour drugs. If we were to use embryonic stem cell lines we could create models of every cell type. However, we don't currently have enough knowledge about the signals controlling differentiation to do this, as we would need to make sure that we had consistently identical cells to give the same conditions for testing different drugs.

A very important potential therapy is the use of embryonic stem cells to create tissues and organs. This could lead to an alternative supply to organ donations, as well as potential treatment of such diseases as Parkinson's and Alzheimer's, as well as osteoarthritis, rheumatoid arthritis, heart disease, stroke, diabetes, spinal cord injuries and severe burns.

Recent research has been done on the use of embryonic stem cells in spinal cord injuries and stroke. Geron Corp. got FDA approval to use embryonic stem cells to treat spinal cord injuries on 23rd January 2009. Geron's president, Thomas Okarma, describes the study as “the beginning of a new chapter in medical therapeutics”. The patients will all have complete spinal cord injury between T3 and T10 spinal segments, and the treatment must be performed between 7 and 14 days after injury. Previous studies on rats at the Reeve-Irvine research centre showed that rats treated after 7 days recovered motor functions whereas rats with 10 month old injuries gained no benefits from the treatment. Patients in the study will have human embryonic stem cell-derived oligodendrocyte progenitor cells injected directly into the lesion in their spinal cord. The treatment will be assessed by a number of factors including improved muscle control and gain of sensation in the trunk and lower extremities. If the study proves successful, Geron plans to use this treatment in people with lesser spinal injuries.

In the UK, research has just been allowed for stroke victims. On the 19th January 2009, ReNeuron, gained permission from the UK Medicines and Healthcare Products Regulatory Agency to inject neural stem cells directly into the brain of the patients, using cells from a stem cell line that was developed from the brain cell of an aborted foetus. Because of the nature of this treatment, patients will require no immunosuppressant drugs

after being injected, eliminating the risks associated with immunosuppressant drugs. After the treatment the patients will be monitored for one year, with assessments of their improvement. If this study proves successful, ReNeuron aims to carry out larger studies of this type.

Now that research of this type has begun, it is only a matter of time before we will see great advancements in the treatment of disease. However, much more intensive research is needed before these uses are realised.

DISCUSSION

A bone fracture is a medical condition in which a bone is cracked or broken. They are often referred to as “broken bones”. Many fractures are caused by high force impact or stress, but bone fracture can also occur as a result of medical conditions that cause the bones to be weaker than normal, such as osteoporosis.

Some bones are more likely to suffer from fractures than others, depending on age or activity. In childhood, it is common to break the humerus or lower leg bone due to rough play and sports. They are also more at risk of either a growth plate injury or a greenstick fracture.

A greenstick fracture occurs because the bone in a child is not as brittle as it is in an adult, and so it does not completely fracture, and instead bends without breaking completely (figure 2)

A growth plate injury is trauma that occur to the growth plates; the areas of growing tissue on the ends of the long bones. They can be caused by falls, and overuse from sports such as gymnastics and long distance running. There is also evidence that these can be caused by chemotherapy, genetic reasons and metabolic diseases. The Salter-Harris classification (figure 3) divides growth plate injuries into five types, but recently a new type has been added. This is the Peterson classification and is when a portion of the growth plate is missing.

Another possible injury in children is plastic deformation, where the bone bends permanently but does not break. These may require surgery to be fixed.

In the elderly, breaks are more common due to the bones thinning and becoming more brittle, but especially in the hip, due to falls, and the wrist through trying to break a fall by stretching out an arm.

There are several types of fracture. A comminuted or multifragmentary fracture is where the bone is shattered into several pieces. This is usually as a result of direct impact and is therefore often seen as a result of road traffic accidents. (Figure 4)

A transverse fracture is caused by a powerful force and causes a break right across the bone width. This type of break is usually stable. (figure 5)

A spiral fracture is where the bone is broken diagonally along its shaft. This type of fracture had ragged ends that may be difficult to realign. (figure 6)

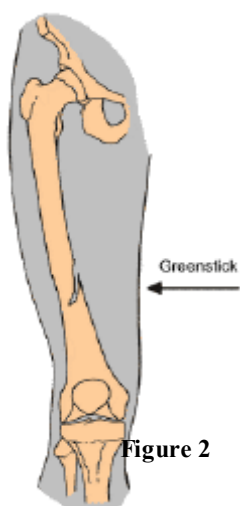


Figure 2

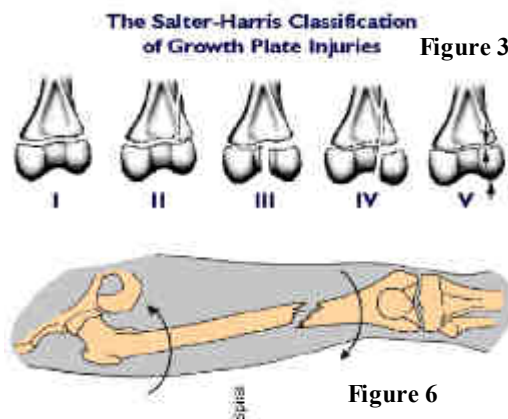


Figure 6



Figure 4

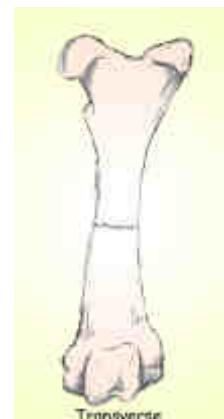


Figure 5

Certain types of bone fracture often require surgery to correct them. Most commonly these are compound and multifragmentary fractures. A compound fracture is like a multifragmentary fracture, but the bone protrudes through the skin. This makes it an open fracture.

The surgery is done by using surgical plates and screws to hold the bones in place. This can lead to a much higher risk of infection. Infection is especially dangerous in bones, because they have a limited blood flow. Bone tissue is mostly an extracellular matrix, as opposed to living cells, so there are fewer blood vessels able

to bring in antibodies to fight infection. Therefore, open fractures and osteotomies need very careful antiseptic procedures and antibiotics.

Other issues with using this type of surgery include corrosion, damage to the bone tissue, and stress shielding. Stress shielding is a problem that occurs when the metal implants take too much of the bones load, and this causes atrophy. This problem can be reduced, but not eliminated by using low-modulus materials such as titanium or titanium alloys. However, if different metals are used in the implants, galvanic corrosion will occur. The metal ions produced will damage local tissue. Another issue is the heat created through the installing of the implants which will damage and weaken bone tissue.

I am aiming to find a way of treating fractures requiring surgery, and reducing their healing time and risk of infection. Healing for this type of fracture can take several months and the area of the break will never regain the same strength of an unbroken bone.

My idea was inspired by the treatment of Claudia Castillo's damaged bronchus. She was the first person to have an organ tailor-made for her from her own stem cells. A donor Bronchus was used and stripped of the cells that could cause an immune reaction, until the cartilage was left. This was then imbued with stem cells from Claudia's hip, lungs and nose to grow a new bronchus around the cartilage.

If we were to use a similar technique to treat severe bone fractures, we would need to use something that dissolved after the bone had grown. My idea is to use a tube of synthetic polymer fibres, which are used to create dissolvable stitches.

Dissolvable stitches are made of materials which break down in tissue after a certain amount of time. This can be from 10 days to 8 weeks. I would be using the latter sort, as bone fractures are usually mostly healed by 2-3 months. Dissolvable stitches are used internally as there is no need to reopen a wound to remove them. Originally sutures were made from animal guts, but nowadays they are made from synthetic polymer fibres. These are very rarely rejected by the body.

The problem with multifragmentary fractures is the large number of bone fragments needing to knit together. This can mean an increased risk of non-union between the bone fragments. My theory is that if you remove the fragments of bone altogether you can use the type of dissolvable glue commonly used to close small wounds in hospital to glue a sheet of the synthetic polymer fibres round the two broken ends. Embryonic stem cells that have been specialized to create osteoblasts can be injected into the lesion site. Because a lot of bone has been removed the ES-derived osteoblasts will speed up healing. After the bone has healed, the tube and glue will dissolve, leaving no foreign bodies inside the fracture site.

This method would speed up healing processes and would avoid the risks of galvanic corrosion and weakening of the bone through the insertion of implants. The growth of bone between the broken ends would be significantly speeded up and the risk of non-union reduced.

One of the problems with this method is that no weight could be put on the limb whilst the bone was healing. However, the patient could have a normal cast placed around their limb which would support the injured area. Another problem is rejection of the dissolvable tube of polymer fibres but these, when used in stitches, are very rarely rejected. If they were rejected it would cause swelling, but the bone should still heal normally.

CONCLUSION

Embryonic stem cells hold great potential in the future of medicine and the improved treatment of many diseases and injuries that we see today. There are a huge number of possible uses for them but also a great many ethical issues surrounding their use.

I have also discussed the possibility of their use in treating bone fractures which at present require surgery to be fixed. This method cannot be used currently as we do not yet fully understand what causes cells to become differentiated, but it is possible in years to come that bone fractures can be treated in a more efficient way due to stem cell research.

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Figure 1

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Figure 2

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Figure 3

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Figure 4

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Figure 5

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Figure 6

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