

# [Stem cell college](https://assignbuster.com/stem-cell-3997-words-college/)

Few recent scientific issues have stimulated so much media attention, public debate and government involvement as that of stem cell research. Stem cells offer people hope by promising to greatly extend the number and range of patients who could benefit from transplants, and to provide novel therapies to treat debilitating diseases such as diabetes, Parkinson’s, Huntington’s, heart disease and stroke, as well as accidental damage such as spinal cord injury. So why would anyone object to research in this area? The problem is simply that a particular type of stem cell, which potentially could provide many cell types for a wide range of therapeutic uses, is obtained from the very early embryo. To make matters even more contentious, the same cloning technology that gave Dolly the sheep could in theory be used to tailor stem cells to the patient. Some people worry that we are taking research too far down paths that make them feel uncomfortable, others think it is downright immoral and against their deep-held, often religious, beliefs. But what are the scientific issues and why do many of us feel equally passionate that the research should be allowed?

What are meant by stem cells and how might they be used? There are many types of stem cell, but they share several interesting properties that set them aside from other cell types. The adult body contains hundreds of specialised or “ differentiated” cell types, each playing a particular role. Some of these are long lived and do not divide, such as nerve cells; others are short lived and need to be replaced through cell division. Usually, when cells divide, their daughter cells are identical and of the same type as the parent cell. In other words they divide symmetrically. Additionally, their fate and their properties are fixed – once a liver cell, always a liver cell.

In contrast, stem cells undergo “ asymmetric” divisions, producing both another stem cell, in a process called self-renewal, and a cell that will become differentiated. The differentiated cell may still be able to divide, but it cannot normally go back to form the original type of cell. In some circumstances stem cells can increase their numbers, giving rise only to more stem cells. However, stem cells in the adult are usually in tune with the tissue to which they belong. They divide at the appropriate rate to self renew and to give rise to just sufficient differentiated cells to replenish those that have been lost. However, with accidental trauma or disease the normal rate of regeneration is often too slow to allow for repair. This is particularly true within the nervous system, but also in other tissues where turnover is low, such as the pancreas.

How can we harness stem cells to cure diseases? We have become very used to the idea of organ transplants in medicine, to treat a wide range of problems from cataracts to kidney or heart disease. However, we are also all aware of the frequency with which they fail, often through immune rejection, and there is also a serious shortage of organ donors. Both problems could be solved if tissue could be taken from one part of the body to repair another part of the same individual. There are relatively few cases where this is done at present, e. g. using valves from leg veins to repair heart valves.

Rather than using whole donor organs or tissues, an alternative would be to use the stem cells able to form those tissues. In fact this is already done with bone marrow transplants, where the stem cells in the graft can regenerate all the different types of cell in the blood. Other types of stem cell could be used in a similar way. For example, the correct stem cell type might allow specific cell types to be replaced in the nervous system, where it is impossible to transplant whole structures. The idea is to identify and remove the stem cells from a particular tissue, multiply them outside of the body and then use them to replace damaged tissue. This is already done to some extent to repair skin in burn victims, where a small piece of skin can be grown to cover a burn many times the area of the original biopsy.

There are several problems, however, that may make it difficult to use adult stem cells. They can be hard to find and some tissues may not contain them. We often do not know the conditions that allow adult stem cells to multiply outside the body, and of course these conditions may not exist if they divide so infrequently within the body. Moreover, such stem cells are rare and in a diseased individual normal stem cells may be even rarer or they may have been lost altogether. This would necessitate finding a donor. This is done for bone marrow transplants; however, it is difficult to find a correct tissue match; the ideal source is an identical twin, which few of us have.

However, we should not despair of using adult stem cells. We may be able to find conditions where we can grow them more effectively outside of the body or even stimulate them to proliferate and do their job more efficiently in the body. There has been a lot of recent evidence to suggest that some adult stem cell types may be much more flexible than originally thought.

It now appears that in some circumstances it is possible for one type of adult stem cell to change into another, for example, for a blood stem cell to give rise to nerve cells. This might eventually allow patient-specific stem cell therapy, where stem cells from one part of the body are used to repair damage to another. For example, blood stem cells could be turned into nerve stem cells and then into the appropriate nerves for e. g. curing Parkinson’s. So, one might ask, if we can do this, why would we need even to think of using cloning techniques? This is best illustrated by looking at some of the factors that we need to consider before we can attempt to do stem cell therapy, and to compare and contrast the two methods.

Adult stem cells are often very rare and inaccessible. Blood stem cells are present in very low numbers in blood, about one in ten million. They are more frequent in bone marrow, but still rare, and bone marrow biopsy is an operation with some risk and discomfort. Umbilical cord blood obtained at birth is another source of blood stem cells and could be banked and stored in anticipation of any future disease. Although this is already being done in some centres, it obviously cannot be done retrospectively. Furthermore, there is at present no indication that cord blood cells can give rise to any cells other than those of the blood system. The stem cells of the pancreas, which can give islet cells, are thought to be in the pancreatic ducts, but methods of isolating them so that they can be expanded in the laboratory have not been found. With respect to the nervous system, stem cells do exist in the brain and spinal cord, but these are rare and tend to be in regions that are difficult to access safely. There is also concern about grafting cells from the nervous system from one individual to another, not only because of the possibility of rejection, but also because of hidden diseases such as Creutzfeldt-Jakob Disease.

For many adult cell types it is not known where the stem cells are or if they even exist. No one has identified stem cells that would replace the cells that line the lung, needed in cases of Cystic Fibrosis, emphysema or after inhalation burns.

Stem cells are also present in the embryo or fetus. These divide frequently, are easier to grow outside the body and many have the potential to give rise to a wide range of more specialised cell types. They are therefore considered as multipotent. However, while these “ fetal stem cells” undergo asymmetric divisions with respect to the fate of their daughter cells, this does not necessarily involve exact self-renewal. The daughter stem cells progressively become restricted in the variety of cell types they can produce.

The stem cells with the greatest potential, however, are called, Embryonic Stem cells. These are derived from a very early embryo called a blastocyst, a ball of cells found after five days of development in humans or three days in mice. At this stage there are up to one hundred cells, comprising just two cell types. The outer cells of the ball will form part of the placenta, the inner cells will form the embryo itself. In fact, even though cells in the inside may each have the potential to contribute to the embryo, the majority of them will give rise to components of the embryo’s support system, which is discarded at birth. In fact, it is not possible to point to a single cell at the blastocyst stage and say that this will contribute to the newborn animal or person. Both cell types in the blastocyst depend on each other for their proper development and survival. The inner cells will not develop into an embryo if they are removed from the outer cells. However, they can be grown in the laboratory where they readily give rise to Embryonic Stem cells.

Embryonic Stem cells have a number of remarkable properties. They can essentially be grown indefinitely, and in very large numbers. However, unlike other permanent cell lines which have mutations in genes that allow permanent growth, or carry a transforming gene from a virus or tumour that has the same effect, Embryonic Stem cells are normal cells by all criteria. They also have the ability, under the right conditions, to give rise to all cell types of the body. The test of this, using laboratory mice, is to inject them into a blastocyst, when they reintegrate and can eventually contribute to all tissues in the resulting animal. Such chimaeric mice can live a normal life, with no greater incidence of tumours or other diseases than normal mice.

Embryonic Stem cells can also form a wide range of cell types in culture and it is already known how to direct them to form certain types of cell purely in culture, for example, nerve cells, muscle cells, cells that form blood vessels and pancreatic islet cells. Cells made like this can then be grafted back into animals, where they have been shown at least partially to correct a range of diseases similar to Parkinson’s Disease, multiple sclerosis and diabetes.

So, could human Embryonic Stem cell lines be used to treat any of a wide range of diseases, by cell-based therapies? It would seem likely, except for the big problem of immune rejection. The few lines of cells that have been established so far would not overcome this problem. One possibility is to have many lines available, perhaps a bank of a hundred or even a thousand, which would be tissue-typed, so that a close enough match would be available for most patients and for most types of therapy. This would still require the use of drugs to prevent rejection of grafted cells, which can have a number of severe consequences for the patient, including increased likelihood of infections or possibly tumours. These consequences would have to be weighed against the likely benefit of the therapy. Some types of graft are known to require closer tissue matches than others. Bone marrow grafts are the most extreme case partly because there is the possibility that the graft can reject the host, as well as the usual problem of the host rejecting the graft. However, other potential cell-based therapies may also require very close tissue matching. For example, many cases of diabetes occur when the beta-cells in the islets of the pancreas, which are the cells that make insulin, have been destroyed by the patient’s own immune system.

To make human Embryonic Stem cells, the use of spare embryos from In Vitro Fertilisation programmes may need to be considered. Clearly the number of spare embryos is limiting. However, many more are currently discarded than would be needed to establish say a thousand Embryonic Stem cell lines over a period of a few years. Even from the few studies done so far, it seems that the frequency of deriving human Embryonic Stem cells from normal blastocysts is very high. With more experience it may be possible to improve the efficiency of this step even more.

The ideal option would be to isolate Embryonic Stem cells from the patients themselves, but of course the right cell type to do this only exists within the very early embryo. What if the normal direction of differentiation could be reversed and suitable stem cells obtained from an adult cell? The techniques that gave rise to Dolly the cloned sheep and subsequently to cloned mice, cows, goats and pigs, showed that it is indeed possible to reprogramme the nucleus of an adult cell. The rationale behind these experiments was that the most likely source of factors that could reprogramme an adult cell to become an embryo cell, would be from an early embryo itself or from the cells that normally have the potential to give rise to an embryo. These are the germ cells, which are present as unfertilised eggs in the female and as sperm in the male.

The unfertilised egg, or oocyte, in addition to carrying one set of chromosomes containing the female parental genetic information in DNA, contains a large amount of jelly-like material known as cytoplasm. This contains the factors that normally reprogramme the incoming sperm nucleus to become involved in the formation of the embryo. It also turns out that the cytoplasm can reprogramme an adult cell nucleus into the nucleus of a one-cell embryo. So, by removing the oocyte’s own nucleus and replacing it with one from an adult donor cell, it is possible to obtain an embryo. This is the nuclear transfer technology that allows cloning. Many experiments have shown that quite early in development embryo cells lose the ability to reprogramme a transferred nucleus, suggesting that the required factors are no longer present once embryonic development has begun.

Can this technology be used to derive human Embryonic Stem cells that can be used for therapeutic purposes? And could it work well enough to be done with the patient’s cells, to overcome problems of immune-rejection? The simple answer is we do not know and this is one of the reasons why research in this area is necessary. While it has worked in a handful of very different species, there are others for which it has so far been unsuccessful such as rats and monkeys. The situation for humans is unknown. A company in the USA recently claimed to have cloned early human embryos. This has been controversial but their evidence has failed to convince many experts in the field.

What would be the procedure? Adult cells would be taken from a patient by biopsy and by nuclear transfer into oocytes, an adult cell nucleus reprogrammed to form an early embryo. This would be cultured outside the body to the blastocyst stage and then the inner cells isolated and used to derive Embryonic Stem cells. These would have the same genetic make-up as the patient. Indeed, they can be considered an extension of the patient. Techniques could then be applied, many of which have been learned from studying mouse Embryonic Stem cells, to form the relevant cell type to treat the patient with Parkinson’s, heart disease or spinal cord injury. Recent work has already suggested that it is possible to direct human Embryonic Stem cells to differentiate along specific pathways. If there is a genetic cause to the disease, such as cystic fibrosis or muscular dystrophy, it may be possible to correct the genetic defect in the stem cells, prior to grafting the cells back into the patient. Techniques for doing this are well established with mouse Embryonic Stem cells. Clearly, once Embryonic Stem cells have been made for an individual, they would be available for treating any other problem present in that person.

The best source of cells for the original biopsy in humans is not yet known. Several cell types have worked in other species, including the tip of the tail in mice, which is essentially a skin biopsy. This is another area where research is needed. It is possible for example that some easily accessible human cell types will make particularly good nuclear donor cells.

For some people, who believe that life begins at fertilisation, the use of spare embryos left over from In Vitro Fertilisation programmes to derive Embryonic Stem cell lines may be unacceptable. However, the cell nuclear replacement technique uses unfertilised eggs. These do not present the same ethical consideration and especially as their genetic material is removed and replaced with an adult cell nucleus, they could be considered as simply an extension of the adult donor: a universal organ available specifically for donation! If made on a patient-specific basis, this would also overcome some religious objections to transplants between individuals.

But of course some people object to the whole idea of cloning, even if it is just for these potentially beneficial therapeutic purposes. They are often worried that this will lead to reproductive cloning, which is certainly not safe at the moment (many cloned animals die around birth or develop problems postnatally). However, just because it is possible to use a technique for one purpose does not mean that it will also be used to bad effect. The best approach is to make laws that will ban what you do not want to happen, and reproductive cloning is now illegal in the UK.

With respect to the use of nuclear transfer to reprogramme an adult cell both the source of unfertilised eggs and suitable donor cells will need careful consideration. Some have raised the problem that there would be a shortage of unfertilised eggs to contemplate anything on a large enough scale to have patient-specific stem cell therapy. This is probably true if it is necessary to use only those eggs leftover from In Vitro Fertilisation programmes. However, it is possible that only a small fraction of egg cytoplasm is required to reprogramme some adult cells and, ultimately, it may be possible to define and isolate the factors from the egg cytoplasm that are responsible. If research shows that this is indeed the case, the need to use any eggs could eventually be removed.

There are other sources of unfertilised eggs than those available from In Vitro Fertilisation programmes. Techniques are being developed in the mouse and in farm animals to remove from the ovary so called primordial follicles, which contain an oocyte that has not yet begun to grow. These are found at all stages from the foetus to the adult and can be maintained in culture in conditions that promote growth. Ethical issues notwithstanding, this raises the possibility of using oocytes obtained from the ovaries of aborted foetuses. It is also possible that in the future women may become more willing to donate unfertilised eggs, if they knew that their loved ones could benefit from stem cell therapy.

With respect to adult donor cell types, if a skin biopsy can be used then this would pose no problems in terms of either source or rarity. If other cell types are found to be even better there is the additional advantage that very few cells are actually needed for the nuclear transfer step. We know that skin stem cells are one of the few adult stem cell types able to divide extensively, so perhaps these would be ideal nucleus donors. Blood stem cells may be even better, if simple and effective methods for their isolation are developed.

Embryonic Stem cells can be purified very easily, they grow very well in culture and they are essentially immortal. There is good evidence that the reprogramming by the cell-nuclear replacement (“ cloning”) technique also rejuvenates the adult cell nucleus. We know that Embryonic Stem cells can give rise to any cell type within the body, so potentially they can be used to treat any disease. In addition, we already know how to select particular cell types from differentiating mouse Embryonic Stem cells and to do this in a relatively controlled manner. In several studies these have been tested in animal models of the corresponding human disease or injury. Three recent studies are particularly noteworthy. Firstly, the derivation of a stem cell type able to give rise to all the cell types that makes up blood vessels. These would have obvious potential to treat a range of chronic problems, including coronary heart disease. Secondly, through the discovery of a new factor, a Japanese team have been able to obtain relatively pure populations of the type of neurons that are defective or missing in Parkinson’s disease. Finally, a team in the USA were able to derive insulin-producing cells from Embryonic Stem cells in culture, something not achieved from any adult stem cells to date.

How soon then will methods for patient specific stem cell therapy be established, and why is it necessary to do research on human embryos? In mice, recent work has shown that it is possible to begin with a biopsy, use the nuclei from one of its cells to replace the nucleus of an unfertilised egg, grow the embryos formed to blastocyst stages in culture and then use these to derive Embryonic Stem cell lines. At least some of these cells were shown to have properties expected of Embryonic Stem cells since they could differentiate into a wide range of cell types.

It is possible at high efficiency to derive Embryonic Stem cells from cultured human blastocysts from spare embryos obtained in In Vitro Fertilisation programmes, but it is not yet known if the nuclear transfer technology can be used to reprogramme adult cells taken from a patient and to obtain suitable blastocyst stage embryos. Recent studies with human Embryonic Stem cells look very promising, as it is certainly possible to obtain many different cell types from them in the laboratory. However, there are some differences between mouse and human Embryonic Stem cells that need further research.

There is therefore a need to explore the usefulness of human Embryonic Stem cells in treating diseases, but how to do this will be a major challenge. Some animal studies can be undertaken, but eventually human trials have to be performed. As part of this methods of quality control, to know that any cells used will be safe and reliable, will be needed. All the evidence obtained with mouse Embryonic Stem cells suggests that they probably will be, but it is important to show this for human Embryonic Stem cells.

That Embryonic Stem cells are able to give rise to any cell type within the body is a normal process, not one that involves a rare cell changing its potential. They would therefore seem to be an ideal source of cells for cell-based therapies. However, if they were to be made on a patient-specific basis using current techniques, this would require the use of many unfertilised eggs, as discussed above. However the reprogramming mechanism elicited by egg cytoplasm after nuclear transfer is still the only way known to reprogram an adult cell in a controlled manner. Once the mechanisms are understood, perhaps adult cells could be treated in an appropriate way to turn them into the equivalent of Embryonic Stem cells, eventually without having to use any human eggs.

Clearly work on adult stem cells is also a priority. Adult stem cells will probably turn out to be entirely suitable to treat some diseases, whereas Embryonic Stem cells will be necessary for others. There is no logic in stopping research on one to concentrate on the other, especially when we know so little about either.