



## What Are Stem Cells and Where Do They Come From?

By Lori P. Knowles

### What Are Stem Cells?

Stem cells are very special, powerful cells found in both humans and non-human animals. They have been called the centrepieces of regenerative medicine – medicine that involves growing new cells, tissues and organs to replace or repair those damaged by injury, disease or aging. Stem cells are the precursors of all cells in the human body. What makes stem cells special is that they are regenerative and malleable. They have the ability to replicate themselves and to repair and replace other tissues in the human body. Some tissues, like skin, need constant renewal, which could not take place without skin stem cells. Other stem cells repair damage to the body's tissues, for example, rebuilding damaged or degenerating muscle tissue. New research also indicates that stem cell malfunction or damage may be responsible for certain cancers and even muscular-degeneration diseases like Muscular Dystrophy. Research on stem cell functioning is therefore a critical avenue to finding treatments for these and other diseases.

Most cells in the human body are differentiated, tissue-specific cells. These cells have a specific identity and function that cannot be changed; they might be neural cells, skin cells, blood cells, muscle cells or some other kind of cell. Unlike other cells in the human body, stem cells are undifferentiated, which means they do not yet have a fixed identity and function. Consequently, they possess an ability to be manipulated in the laboratory in ways that may change their identity and function: they can turn into a number of different types of cells or tissues. This ability to change and be manipulated makes them powerful tools for research and therapy.

### Stem Cell Sources

Stem cells differ according to their source and their malleability. Just as there are many different types of specialized or differentiated cells in the body, there are many different types of stem cells in the body. Within the human body, adult stem cells continue to replenish cells that need replacement from normal wear and tear. Adult stem cells can be found in specific tissues in the body and include neural stem cells, skin stem cells, and blood (hematopoietic) stem cells. Hematopoietic stem cells can be found in adult bone marrow and blood and umbilical cord blood. These stem cells are regularly used in standard therapies, as they make new blood cells. Adult bone marrow stem cells are used in repopulating the bone marrow and white blood cells (leukocytes) of patients suffering from leukemia. Peripheral blood stem cells can be collected from circulating blood and used to treat leukemia, other cancers and blood disorders. A particularly promising source of stem cells for treating the same type of disorder is from umbilical cord blood. After a baby is born the umbilical cord is routinely discarded. In recent years, the blood in the cord has been found to be a rich source of stem cells that are less prone to rejection from a transplant recipient's body than cells or tissues transplanted from another individual.

Additional sources of stem cells include fetal stem cells that are derived from discarded fetal tissue, and human embryonic stem cells (hES cells) that are derived from 5 day-old blastocysts – precursors to embryos. A blastocyst is a sphere of cells with an inner cell mass of about 30–34 undifferentiated cells that have the potential to form all the tissues in the human

body. hES cells are found in the inner cell mass of the blastocyst. The isolation and removal of those hES cells from the blastocyst necessarily makes it unsuitable for transfer into a woman. In other words, the removal of the hES cells from a blastocyst compromises the ability of that blastocyst to ever become an embryo, and hence its potential to develop into a baby were it implanted in a woman and born alive. It is primarily this destruction of the human blastocyst that causes hES research to be controversial.

## Are All Stem Cells the Same: Pluripotent or Totipotent?

Not only do stem cells come from different sources, but they differ according to their malleability. Stem cells at different developmental stages appear to have different capacities for self-renewal and differentiation. There is some question about whether hES cells are totipotent (able to become any type of tissue in the body) or whether they are pluripotent (able to become some, but not all of the tissue types in the body). It appears that human hES cells can become any of the 200 differentiated cell types in the body, thereby making them totipotent. Some tissue-specific, differentiated stem cells retain pluripotent capacity to generate cells of a more limited number of cell lineages, which some estimate is between six and 10 different types.

The issue of the malleability and potency of different stem cells remains open and controversial. There is a continuing debate over the properties possessed by adult human and hES cells. Many who oppose using human blastocysts to extract hES cells maintain that adult stem cells have the same properties and capabilities for differentiation; however, many researchers maintain that hES cells are the most malleable. Research into adult stem cells continues to evaluate their ability to differentiate. Other researchers assert that we lack evidence to support or refute the claim of equivalent malleability between adult and hES cells, and until such equivalency can be proven, hES research must continue as hES cells appear to be the stronger research tool. Another difference between specialized (adult) stem cells and hES cells is their behaviour in culture. It is easier to get hES cells to replicate in culture and to keep those cells alive for a

very long time, an attribute that is very useful in creating cell lines to study diseases or cell functioning. In contrast, adult stem cells are harder to culture and keep alive. Regardless of their differences, both avenues of research will likely yield valuable and different information for development of clinical therapies.

## Creating Pluripotent Stem Cells

In addition to stem cells that are isolated from the body, scientists have found a way to create stem cells by using various reprogramming techniques in the laboratory. Two such reprogramming techniques are the creation of induced pluripotent stem cells and the use of somatic cell nuclear transfer.

In 2007 the announcement that Japanese researcher Shinya Yamanaka had created pluripotent stem cells using skin cells and not embryos caused great excitement in the stem cell community due to the possibility that they may have the same properties and benefits as ES cells. These stem cells are called “induced pluripotent stem cells” (also known as iPS and iPSC) and are created from adult (non-pluripotent) cells – often skin cells. Typically this involves the reprogramming of some of the cells through the introduction of genes commonly found in stem cells. Yamanaka introduced the reprogramming genes through viral vectors using retroviruses that transcribe the genes into the host cell DNA, which raised concerns about the effects of the retroviruses on the cell. Stem cell researchers have been able to confirm these results and view this development with great enthusiasm as iPS cells are a less controversial source of stem cells, but potentially have the same properties and benefits as hES cells.

In 2009, a Canadian-Scottish research team led by Andras Nagy was the first of several teams to announce a method to create iPS cells without the use of retroviruses.<sup>1</sup> This is an important development as it could lead to greater application of iPS cells, which are a less controversial source of stem cells. Continuing research using iPS cells is needed in order to determine whether iPS cells are as malleable as hES cells, but also because iPS cells may be an extremely powerful tool for creating stem cell lines as disease models. However, further questions about the ethical status of iPS cells have been raised that require

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1 Woltjen K, Iacovos M, et al. “*piggyBac* transposition reprograms fibroblasts to induced pluripotent stem cells” *Nature* March 1, 2009  
Epub: <http://www.nature.com/nature/journal/vaop/ncurrent/abs/nature07863.html>

consideration: it has been suggested that like hES cells, iPS cells can also generate germ cells, ova and sperm cells. If this is the case, hES cells and iPS cells may not be as ethically distinct as first suggested.

## Somatic Cell Nuclear Transfer

Another way to create stem cells is by taking a human egg (oocyte) and removing the nuclear DNA – the DNA that holds the programming for the majority of the genetic characteristics of the person. The original nuclear DNA is replaced with the nuclear DNA from a donor cell. That donor DNA comes from another human or non-human animal. The oocyte now contains the entire complement of DNA rather than just the half it originally contained. When that oocyte is stimulated in the laboratory it begins to divide and becomes a blastocyst with the same genetic make-up as the donor. Once the reprogrammed oocyte reaches blastocyst stage hES cells can be extracted from the inner cell mass and used to create a cell line in culture in a laboratory. This is a very powerful tool because the stem cells in the newly created cell line are a genetic match to the donor of the nuclear DNA that reprogrammed the oocyte. This potentially enables researchers or clinicians to create genetically identical tissue for tissue replacement. When genetically identical tissue is used in transplantation, the medical complications of rejection by the transplant recipient's immune system are eliminated and with that the need to take expensive, immune-suppressing drugs.

This technique is called nuclear transfer since the nucleus of one cell is transferred to another. It is also known as somatic cell nuclear transfer (SCNT) since a cell from the body tissues (a somatic cell) is used in the nuclear transfer. Somatic cell nuclear transfer is a type of reprogramming technique that is also used in “cloning” technology. For this reason the creation of embryos by SCNT in hES research has been variously referred to as “research cloning” and “therapeutic cloning.” Until such time as there are clinically available applications of this technique, the most appropriate description would be “research cloning.” Many authors have opined that the use of the term “cloning” has created a tempest about the use of SCNT. While SCNT may be a cloning technique it does not result in a baby or living clone. The use of cloning techniques to create genetically identical embryos

that are then implanted in a woman who gives birth to a genetically identical child (a kind of intergenerational identical twin to the DNA donor), is called “reproductive cloning.” It has been widely prohibited around the world, and is prohibited under Canada's *Assisted Human Reproduction Act*.

SCNT is used to create hES cell lines necessary for autologous transplantation and for the creation of disease-specific cell lines. Due to the fact that it is a cloning technique and that people are fearful about reproductive cloning, there has been significant controversy about this method of creating hES cell lines. There are ethical arguments against using SCNT to create embryos for research. These include arguments against creating embryos for an instrumental purpose and against the endorsement of a technique requiring a large source of human eggs since this may lead to the exploitation of women. These arguments are discussed in Knowles L., [“The Use of Human Embryos in Stem Cell Research”](#) Stem Cell Network, and Knowles L., [“Commercialization and Stem Cell Research”](#) Stem Cell Network.

Other arguments against using SCNT to create embryos reflect a fear that using such a technique could lead to reproductive cloning. This is not primarily an ethical objection but evidence either of confusion between the two uses of cloning technology – one for research and eventually therapy, and one for reproduction – or a lack of trust in stem cell scientists. The lack of trust indicates that people are fearful that scientists may move from research cloning to reproductive cloning, as in sliding down a slippery slope. To date this has not happened, but rigorous professional standards among stem cell scientists and infertility clinicians are a crucial part to maintaining the integrity of the research and people's trust. SCNT remains today a powerful technique to harness the potential of stem cell research through creating cell lines with a specific genetic makeup.

## Somatic Cell Nuclear Transfer and the United Nations

The acceptability of SCNT and research cloning is at the heart of deep disagreements that thwarted attempts to pass a treaty condemning and prohibiting human reproductive cloning at the United Nations (UN). At issue

was the scope of any such treaty. Although there was consensus among member states regarding a call for a ban on reproductive cloning, there was no consensus on the appropriate response to research cloning.

In 2001 Germany and France lead a campaign to create a binding treaty banning reproductive cloning. While a majority of countries supported the proposal to begin negotiating a treaty to ban reproductive cloning, a minority of countries led by Spain and the United States lobbied to ban both types of cloning in the initial treaty. A decision about the scope of the treaty was delayed until September 2003. In September, the Interacademy Panel on International Issues, composed of more than 60 scientific academies from every continent in the world called on the UN to adopt a ban on reproductive cloning, but to permit an exemption for research cloning. A proposal to ban both types of cloning led by Costa Rica and the United States

was defeated by one vote and in November, 2003 further work on the convention was delayed for one year despite attempts by Costa Rica and the United States to force another vote on the resolution in December. In March 2005, after four years of disagreement and behind the scenes negotiation, the UN's General Assembly adopted resolution 59/280, containing in its annex the text of the *United Nations Declaration on Human Cloning*. The *Declaration* is not legally binding, but has persuasive authority. It calls upon member states to "prohibit all forms of human cloning inasmuch as they are incompatible with human dignity and the protection of human life." Member states such as the United Kingdom, which legally permits SCNT, were quick to criticize the resolution, but the political difficulties getting the resolution adopted mirror the continuing lack of consensus about using cloning technology in hES research.

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