# Saving


# A Look into Stem Cell Research

## Part I—"Background"

by
**Lisa M. Rubin**
University at Buffalo
State University of New York

---

There was hardly a household in America that was not tuned in for news in the days following actor Christopher Reeve's accident at an equestrian competition in Culpeper County, Virginia, in May of 1995. Known for his professional acting career, athleticism, and advocacy work, Reeve was also a passionate rider. The accident happened on the third jump of a two-mile cross-country jumping event. His horse suddenly stopped midway over the fence. Reeve was catapulted headfirst. His fall caused multiple fractures of his first and second cervical vertebrae, shattering C1 and C2. During surgery, his head had to be literally reattached to his spinal column. The actor who was known to millions worldwide as Superman, "the man of steel," was fighting for his life.

Eight weeks after surgery, Reeve was left ventilator dependent and quadriplegic from his shoulders down because of a 20-mm gap in his spine that prevented neuron flow and movement. He endured six months of intensive physical therapy at Kessler Rehabilitation Institute in New Jersey before moving back home with his wife, Dana, and their three children—Matthew, now a recent college graduate, Alexandra, currently a college student, and Will, the youngest. Reeve's condition led to several medical complications, including pneumonia, infectious blood clots, wounds that wouldn't heal, and a condition called autonomic disreflexia that involves elevated blood pressure.

Seven years since his accident, Reeve has gradually regained sensation in his left leg, parts of his left arm, and down his spine. He has learned to breathe on his own for up to 90 minutes at a time and is currently on a treadmill routine where he walks suspended from a harness. Despite all the hardship, he has kept an optimistic outlook and is confident that one day he will walk on his own again. Founder of the Christopher Reeve Paralysis Foundation (CRPF), which is a member of the Coalition for the Advancement of Medical Research (CAMR) whose explicit goal is to raise funds for stem cell research across the globe (including the U.S., Australia, India, Sweden, and Israel), Reeve is an active advocate for federal funding and regulation of embryonic stem cell research and sincerely believes that this scientific breakthrough holds the near future therapeutic promise for repairing his damaged nervous system. In addition, he is confident that stem cell therapy will help thousands of individuals who suffer from autoimmune diseases and other illnesses, including Parkinson's disease (Michael J. Fox), diabetes, Alzheimer's disease, multiple sclerosis, paralysis, cancer, lupus, stroke, heart disease, kidney disease, rheumatoid arthritis ... the list goes on.

Cell therapy is already used in bone marrow transplants to replace the hematopoietic cells of cancer patients. Also, recent cell therapy experiments involving skin cell grafting for serious burn patients,

pancreatic cell transplants for diabetics, and dopamine-carrying cells for Parkinson's patients have shown great promise.

The Senate's indecision over approval of progressive stem cell research, recent congressional hearings, government agency meetings, increased media coverage, and advocacy by Reeve and his supporters have brought this issue into the public spotlight. It is critical that people are properly informed about the facts and concepts behind stem cell research in order to make an educated decision about the scientific, medical, and ethical issues.

**Date Posted:** 01/24/03 nas

# Saving Superman:
# A Look into Stem Cell Research

## Part I, Section A—"The Basics"

by
**Lisa M. Rubin**
University at Buffalo
State University of New York

---

What is a stem cell? Simply put, it is **a primitive, undifferentiated cell that gives rise to other types of cells**. Cells have a finite lifespan, and thus most cells in the body duplicate and replenish themselves. Through the isolation and targeted manipulation of cells in culture, scientists are finding ways to identify the various types of stem cells in order to find ways to use them to replace diseased, damaged, or dead cells in the body that cannot repair themselves. It's analogous to the concept of an organ transplant, except this time scientists are transplanting stem cells, not organs.

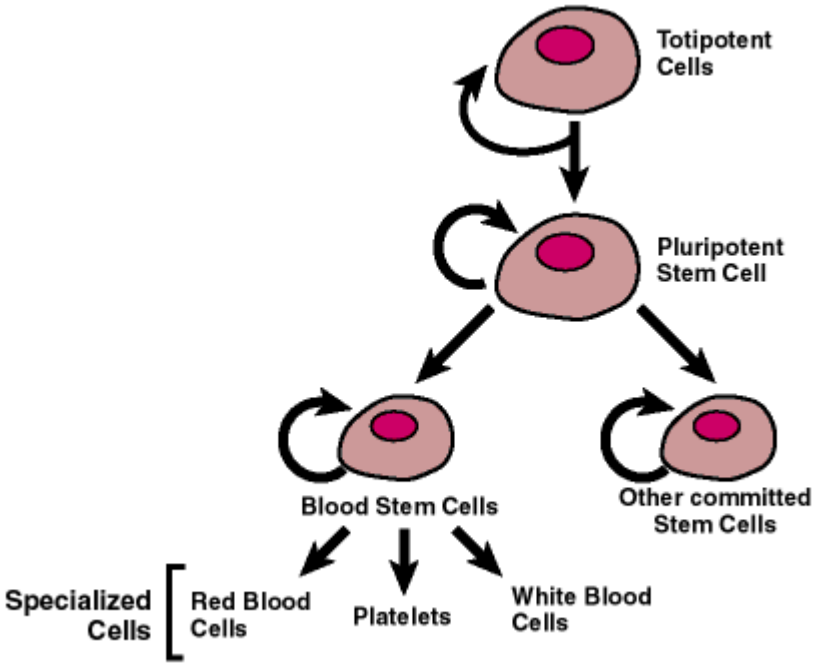
Stem cells share the three following general characteristics:

1. The ability to differentiate into specialized cells.
2. The ability to regenerate an infinite number of times.
3. The ability to relocate and differentiate where needed.

There are three main classes of stems cells: totipotent, pluripotent, and multipotent.

> ***Totipotent Cells:*** After fertilization (union of sperm and egg), the zygote created is a totipotent cell, meaning it **has the genetic potential to create every cell of the body and the nourishing placenta and extra-embryonic tissues**, and thus can form a human being. This one totipotent cell divides into multiple totipotent cells for **up to five days (three to four cellular divisions)** after fertilization.
>
> ***Pluripotent Cells (aka Embryonic Stem Cells):*** After about five days, these totipotent cells begin to differentiate, or specialize, and form a hollow ball of cells called a **blastocyst**. The blastocyst has an outer layer of cells (which becomes the placenta and fetal-supporting tissues within the uterus) and a cluster of cells inside the hollow sphere called the **inner cell mass** (which becomes every cell of the body). This inner cell mass constitutes pluripotent cells, meaning they each **have the potential to create every cell of the body but not the necessary placenta and extra-embryonic tissues**, and thus cannot form a human being. Pluripotent cells can be isolated from embryos and the germ line cells of fetuses.
>
> ***Multipotent Cells:*** Pluripotent cells soon undergo further specialization into multipotent cells (sometimes referred to as adult stem cells, multipotent adult progenitor cells, or MAPCs), which can give rise to a limited number of other particular types of cells. For example, hematopoietic cells (blood cells) in the bone marrow are multipotent and give rise to the various types of blood cells, including RBCs, WBCs, and platelets. **Multipotent cells are found in both developing fetuses and fully developed human beings. There are certain limitations to using multipotent cells, however.** Scientists have not identified

multipotent cells for every type of mature body cell; so far, private research has isolated about 60 different types. Unlike pluripotent cells, multipotent cells are often in minute quantities and their numbers can decrease with age. Multipotent cells from a specific patient may take time to mature in culture in order to produce adequate amounts for treatment. They can and often do contain DNA damage due to aging, sunlight (radiation), toxins, and random DNA mutation during replication. Spontaneous mutations are more likely to show up in older multipotent cells than younger pluripotent cells. In addition, multipotent cells may or may not offer the same level of *plasticity* as pluripotent cells, although this is presently an unresolved issue. Research on the early stages of cell specialization may not be possible with multipotent cells because they are further along the specialization pathway. Thus, study of both pluripotent and multipotent stem cells is vital to fully understand cell specialization and potentially develop new treatments or even cures for diseases.




*Source: National Institutes of Health,* http://www4.od.nih.gov/stemcell/fig2.gif

## Concept Check:

1. In vivo, the embryonic stage (both pre-implantation and post-implantation) lasts from the second cellular division until 8-12 weeks after conception. Then, the fetal stage begins. Is it possible to extract totipotent cells at any period of the embryonic stage of development? What about pluripotent cells?
2. If a scientist were to implant only a pluripotent cell into the uterus of Lois Lane, could she carry a baby to term? Why or why not?
3. Besides hematopoietic cells, can you think of other multipotent cells in the body?
4. Why might there be ethical issues surrounding the manipulation of pluripotent stem cells?
5. What are a few limitations to using multipotent stem cells? Can you think of other possible limitations not mentioned?
6. What is one advantage of multipotent cells over pluripotent cells? (HINT: it involves immunosuppression).

# Saving Superman:
# A Look into Stem Cell Research

## Part I, Section B—"Pluripotent Stem Cell Isolation"

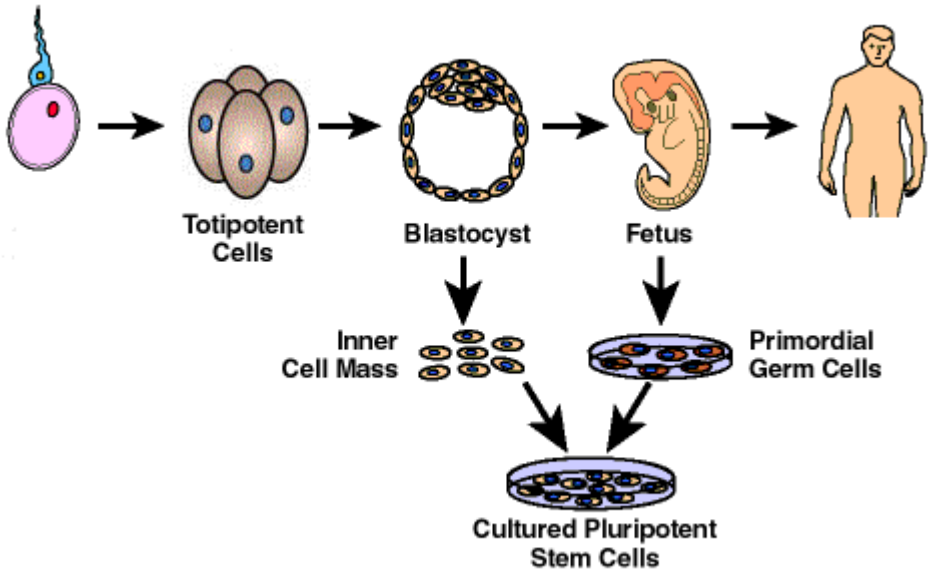
by
**Lisa M. Rubin**
University at Buffalo
State University of New York

---

There are three ways thus far in which scientists can isolate human pluripotent cell lines. Other methods currently under research, including parthogenesis, have not been successful with human cells.

***Inner Cell Mass Isolation from Embryonic Tissue:*** The inner cell mass of the blastocyst of an embryo constitutes pluripotent cells. With permission from patients, researchers obtain excess embryos from in-vitro fertility clinics to isolate these cells, which are called embryonic stem cells (ES).

***Primordial Germ Line Isolation from Fetal Tissue:*** Pluripotent stem cells can be derived from the primitive germ line stem cells that exist from the blastocyst stage until their migration to and conversion within the developing gonads into either sperm or egg stem cells. Researchers obtain these stem cells from terminated pregnancies, where parents independently decide to end the pregnancy and give consent. These cells are called embryonic germ line stem cells (EG) and have very similar properties to ES.




*Source: National Institutes of Health*, http://www4.od.nih.gov/stemcell/fig3b.gif

***Somatic Cell Nuclear Transfer (aka "Therapeutic Cloning"):*** This process involves the use of an unfertilized egg cell. First, the nucleus of the egg is removed. Then, the nucleus of a somatic cell (body cell) is transplanted into the enucleated egg. The egg contains special factors to "reprogram" the genes of the body cell nucleus so that the result is a totipotent cell. The cell is kept in culture in a nutrient bath for a few days until cellular division creates a cluster of 120 pluripotent cells, which researchers then isolate. There are a few critical points to keep in mind. Unlike the traditional method where a sperm and egg unite to form a totipotent zygote, nuclear transplantation involves the use of an **unfertilized egg** to form a totipotent cell. Also, this cell is ***not*** implanted into a uterus and thus cannot develop into a human being on its own, a point that Reeve stresses in his advocacy for nuclear transplantation. This is ***not*** reproductive cloning, but a way to produce stem cells that are compatible with a person's own body.

## Concept Check:

1. What is one issue you think has arisen concerning the process of primordial germ line isolation? How do you feel about it?
2. What are some possible ways in which the processes outlined above could be abused?
3. Using the diagram above, show how nuclear transplantation fits into the picture.
4. In what ways is nuclear transplantation so advantageous?
5. One important issue with stem cell research concerns the public vs. private sectors. President Bush has agreed to federal funding only for the approximate 60 stem cell lines that have already been isolated. He does not support further study of embryos. With what you know so far, do you agree or disagree with this? Why?
6. What consequences could arise by leaving future research unregulated in the private sector or by completely banning it? What do you think are some advantages or disadvantages to having federally regulated research?

# Saving Superman:
# A Look into Stem Cell Research

## Part I, Section C—"Stem Cell Applications"

by
**Lisa M. Rubin**
University at Buffalo
State University of New York

---

While scientists continue to try and isolate other adult stem cells (multipotent cells) in the body, the greatest potential seems to lie in embryonic (pluripotent) stem cells. This research will allow for the following:

- Pluripotent stem cell research will allow scientists to study factors involved in cell specialization, which is needed if stem cells can be used therapeutically. Scientists will need to know how to direct a stem cell to function specifically as a heart cell, liver cell, neuronal cell, etc. This regenerative therapy could solve the transplant supply shortage problem in hospitals.

- By studying normal cell specialization, scientists will gain insight into the specific causes of diseases, which are most often the result of abnormal cell division and/or cell specialization. Although animal testing is helpful, it cannot always reveal the exact pathology and etiology of human disease.

- Human pluripotent stem cell research could change pharmaceutical drug testing. All drugs go through extensive trials before being tested on humans or getting FDA approval. Pharmacologists could use human stem cell lines to test drugs, which could decrease animal testing and prove safer for human trials. This would reduce costs and streamline the approval process.

- Stem cells could be directed to function as heart cells to replace those damaged in a heart attack.

A recently raised issue facing researchers is whether adult stem cells (multipotent) can in fact be directed to specialize into various different cell lines like pluripotent cells can. If so, this could sidestep several ethical issues and perhaps make Reeve's dream of walking again a reality. Also, since the multipotent cells would come from Reeve's own body, they would not be rejected during transplantation.

Several studies thus far have led researchers to believe adult stem cells can indeed be manipulated like embryonic stem cells. NIH researchers injected adult bone marrow stem cells into areas of the heart damaged by heart attack in mice. Newly formed heart tissue occupied 68% of the damaged ventricles nine days after transplantation, suggesting that the bone marrow cells specialized into heart muscle cells. Researchers at Duke University Medical Center have shown that adult liver stem cells responded to the tissue microenvironment of the heart in mice to repair damaged heart muscle. University of Minnesota Stem Cell Institute researchers, headed by Dr. Catherine Verfaillie, transplanted adult bone marrow stem cells from rats and humans into mice and found that the cells differentiated according to their environment. For example, if they were injected into the liver, lung, or stomach, they specialized into those cell types. Also, the stem cells did not divide uncontrollably. Verfaillie and her colleagues

believe that selected adult bone marrow stem cells can act as multipotent adult progenitor cells (MAPCs), meaning they are as versatile as embryonic (pluripotent) stem cells and can be manipulated to the same extent.

## Concept Check:

1. Some of the current drawbacks of drug testing include: (a) expense, (b) the issue of animal testing, (c) risk in human trials, and (d) delayed FDA approval. How could stem cell use potentially improve this process?
2. Why is it critical that scientists effectively control stem cell division?
3. Why is the finding by Dr. Verfaillie and her colleagues significant?
4. Potentiality is a complex issue. Do you think stem cell research serves as a potential for human healing or a way to perhaps create a real Superman? Is there a way to find a common ground and protect public health while respecting all opposing views?

# Saving


# A Look into Stem Cell Research

## Part II—"Role Play/Jigsaw"

by
**Lisa M. Rubin**
University at Buffalo
State University of New York

---

Each student will be assigned to one of the following six groups representing a specific viewpoint on the issue of stem cell research and therapeutic use. Each group has a particular set of biases that are listed below. Also listed are some questions for each group to consider.

1. *Stem Cell Researchers*
    a. Research will allow for new understanding in human genetics, development, and cell specialization:
        i. What causes stem cells to stay in an undifferentiated state?
        ii. What cues them to start or stop dividing?
        iii. What genetic/environmental cues signal differentiation?
    b. ES cells could provide an environment for study of diseases that can't be cultured effectively in animal models. They could also serve as a transferring medium in gene therapy.
    c. Bone marrow transplants already exist as a form of stem cell therapy for cancer patients.
    d. The potential to cure disease signifies a means of protecting public health and human life; thus the government should expand federal funding.
    e. With federal funding, researchers can focus more on the science rather than on raising private funds.

2. *Pharmacologists*
    a. The economic and psychological effects of autoimmune diseases and other illnesses are enormous. It costs the government billions of dollars each year in treatment.
    b. Animal testing is a controversial issue in itself.
    c. Stem cell testing could make animal and human trials significantly safer. Could it negate the need for animal and/or human testing?
    d. Drug costs would most likely decrease.

3. *Senators*
    a. Federal funding encourages public review and regulation, broader scientific participation, sound social policy, increased public understanding, and prioritizes public safety and benefit over economic benefit.
    b. To deny federally funded ES research could jeopardize the pre-eminent position of the U.S. as a world leader in health research.

c. The aim of public policy is to protect widely varying individual conceptions of the public good while promoting public health and safety.
d. Current federal regulation (Public Health Service Act Section 498A) clearly separates a woman's decision to have an abortion from her decision to donate tissue.
e. Just as organ donation has a specific protocol, ES and EG donation should require a specific protocol.

4. *Ethicists from National Bioethics Advisory Commission (NBAC)*
   a. The federal government should consider ways to achieve equitable access to the potential benefits derived from stem cell research.
   b. Exclusive private funding raises a potential for research to be guided by market profitability rather than public interest.
   c. Families should not be compensated for embryo or fetal tissue donations.
   d. Women should not be allowed to undergo extra ovulation cycles.
   e. There are two general opposing views concerning human embryos and fetuses: some consider them to be human beings with a moral status and thus consider it wrong to use them for research while others believe that life may be taken for the sake of saving other lives.
   f. There is debate whether ES cells are "embryos" or just "specialized bodily tissues." Since they possess the human genome and the potential to produce a human being, do they possess a moral status?
   g. Excess embryos can be donated to research, destroyed, or donated to infertile couples.

5. *Right-to-Life Committee Members*
   a. The human embryo possesses moral status and potential for life. Any use other than to produce life is wrong.
   b. Women may be persuaded to terminate pregnancies (abortion) or produce extra embryos for monetary compensation.
   c. Some members support consent if the abortion is spontaneous (yet this tissue often contains genetic abnormalities).
   d. Most members support adult stem cell (multipotent) research.

6. *Patients with Autoimmune Diseases/Other Illnesses*
   a. Stem cell therapy may offer better treatments and/or cures for diseases.
   b. Stem cell therapy could potentially solve organ shortages and the need for immunosuppressive therapy.
   c. With nuclear transplantation, pluripotent cells can be made without the use of a fertilized egg; the procedure is done in vitro, not in a uterus. The risk of tissue rejection is eliminated as well.
   d. Some research findings suggest that certain adult stem cells can act as pluripotent cells. With continued research, clarity of this matter may solve the ethical issues behind ES isolation and research and provide hope for patients.

## Your Assignment

Using what you've learned from this case study (as well as additional sources if desired), each group (except for the "senators") must come prepared two class periods from today with a one- to two-page statement of its position on stem cell research. Be sure to cover topics such as adult stem cell versus embryonic stem cell research, possible uses and abuses, pros and cons, public versus private funding, ethical issues, etc.

Each group will be given time in class to review its position and strategy. Each group will also have to choose two questions to submit to the "senators" to ask the other groups during the public meeting. It is important that the "senators" understand the key concepts, for its members will be responsible for making and justifying the final decision.

Once each group has represented its position and questions have been addressed, the groups will jigsaw—that is, new groups will be formed. The new groups will consist of one member from each group plus a "senator" acting as a leader/facilitator. The "senator(s)" in each new group will be responsible for leading their group towards a final position: to support or deny expanded stem cell research (public and/or private). The "senator(s)" will be responsible for writing up the group's policy on the issue (one to two pages), which will be due next class period. The following website provides a list of United States senators who presently support or oppose stem cell research: http://nchla.org/campaign/cosponsors.pdf.

In addition, each student must read the following paper: Blau et al., "The Evolving Concept of a Stem Cell: Entity or Function?" *Cell* 105: 829-841, June 29, 2001. Further assignments will be given at a later date.

## References:


- Advances in Alternatives to Embryonic Stem Cell Research. *Stem Cell Report*, May/June, 2001. http://www.stemcellresearch.org/stemcellreport/scr-may2001.htm
- A Paradigm Shift in Stem Cell Research. *The Scientist* 14 [5]: 1, Mar. 6, 2000. http://www.the-scientist.com/yr2000/mar/lewis_p1_000306.html (Requires free registration before viewing.)
- Christopher Reeve Homepage/Biography. Steven Younis, June 24, 2002. http://www.fortunecity.com/lavender/greatsleep/1023/biography.html
- Defining Stem Cells. Joshua Tusin, *Journal of Young Investigators*, 2001. http://www.jyi.org/issues/issue5/features/tusin.html
- Definitions. International Society for Stem Cell Research, 2002. http://tnt.tchlab.org/stemcells/definitions.htm
- Frequently Asked Questions: Human Cloning and Nuclear Transplantation to Produce Stem Cells. Heather Rieff, Ph.D. Federation of American Societies for Experimental Biology. http://www.faseb.org/opa/ppp/q_and_a.html
- Hearts and Livers and Brains OH MY! Robert Moss. *The Ranger*. Sept. 28, 2001, vol. 72, issue 3. http://www.actx.edu/~ranger/sept28/issues
- Stem Cells: A Primer. National Institutes of Health, May, 2000. http://www.nih.gov/news/stemcell/primer.htm
- *Stem Cell Research and Applications—Monitoring the Frontiers of Biomedical Research*. American Association for the Advancement of Science, November, 1999. http://www.aaas.org/spp/sfrl/projects/stem/report.pdf
- Frequently Asked Questions. Stem Cell Research Foundation, 2002. http://www.stemcellresearchfoundation.org/About/FAQ.htm
- Fact Sheet: Embryonic Stem Cell Research. The White House, August 9, 2001. http://www.whitehouse.gov/news/releases/2001/08/20010809-1.html
- Two New Studies Bolster Promise of Stem Cells. Peter Gorner. *Chicago Tribune Online*, June 21, 2002. http://www.chicagotribune.com/news/local/showcase/chi-0206210219jun21.story