Stemcell 101

What are human embryonic stem cells?
The human body consists of approximately 200 cell types. Each of these cells has a special task to perform: A brain cell differs from a liver cell, a muscle cell from a heart cell, etc. Because of these differences, these cells are sometimes called "differentiated."

When human embryos begin to develop, their cells are not yet differentiated. Scientists now know that all of the body's different cell types STEM from a master cell with the remarkable potential to generate all the cell types the body needs.

During the first week of development, when the human embryo is still a hollow sphere, these master cells emerge. These cells are called "embryonic stem cells" a term coined by UCSF researcher Gail Martin. Martin co-discovered the cells in mice in 1981.

Scientists are now able to isolate human embryonic stem cells (usually from donated human embryos left over following fertility treatments) and study them in the laboratory. Their goals:

- To find the signals (the right mix of growth factors, for example) that make these master cells specialize into different cell types.
- To craft and transplant exactly the right cells that patients need to stabilize or perhaps even cure such diseases as diabetes, heart disease, Parkinson's, ALS (Lou Gehrig's disease), spinal cord injury and osteoporosis.
- To study the steps of embryonic stem cell differentiation into specialized cells, in order to identify the genetic missteps that causes diseases such as diabetes, amyotrophic lateral sclerosis (ALS) and some cancers, and that account for some cases of birth defects and infertility.

What role might human embryonic stem cells play in treating diseases?
The most publicized clinical goal of stem cell research is often called "regenerative medicine." This strategy would involve nudging stem cells in the cell culture dish to evolve, or differentiate, into the specialized cells that make up each of the body's tissues. If scientists can meet this challenge, then, theoretically:

- Beating-heart cells could be transplanted into diseased or damaged heart tissue.
- Dopamine-producing brain cells could replenish those destroyed in Parkinson's patients.

Right now, scientists can observe embryonic stem cells in the culture dish differentiate spontaneously into specialized cells. And they've learned that certain chemicals, or growth factors, can drive the cells to specialize randomly. But scientists can't yet control the direction in which the cells specialize.
They need to figure out how to control this specialization, so that they can prompt a cell to become, say, a liver cell rather than a heart cell. This requires identifying the many genetic steps that lead a cell to evolve one way or another.

UCSF's Matthias Hebrok and Michael German are working to identify the multiple steps that human embryonic stem cells take on their way to becoming pancreatic islet cells. This research involves studying the genes that turn on and off as a stem cell begins to develop. They have identified some of the key steps in the process, but they need to identify many more. If they succeed, the payoff could be great and relatively quick.

Today, scientists transplant (from cadaver donors) the full pancreas or individual insulin-producing pancreatic islet cells into patients, with some success. This is partly because UCSF scientist Jeffrey Bluestone, who oversees a major international effort to deliver more effective drugs targeting diabetes and other autoimmune diseases, has developed a drug that reduces rejection of transplanted cells.

The number of organs and cells available from donated cadavers is very limited, however. If scientists had access to a large supply of pancreatic islet cells, there is a strong likelihood that transplant therapy would eventually work in patients.

In addition to potentially treating disease, can stem cell research lead to new insights into diseases?
Yes. If scientists can identify the genes that lead to the differentiation of a healthy stem cell, they will have an opportunity to identify genetic defects that sometimes appear instead. Examples include:

- Genetic defects that lead to some cancers and neurodegenerative diseases, such as amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease.
- Genetic defects that impair the ability of pancreatic cells to produce insulin in people with diabetes.
- Genetic damage to sperm and egg cells that contributes to some cases of infertility and birth defects.

Research into the way neurons evolve and migrate to the brain's cortex is also expected to shed light on such developmental disorders as schizophrenia, epilepsy, learning disabilities and cerebral palsy.

Can stem cell research help to develop and deliver new drugs?
Yes. Scientists are exploring the possibility of using stem cells as vehicles for delivering drugs into specific tissues.

And with an eye toward drug development, scientists plan to study and test the effect of drugs on differentiated human cells derived from stem cells in a culture dish. Examples could include the specialized neurons affected by Alzheimer's or Parkinson's disease, or the liver cells involved in detoxifying and removing many drugs.

What is the difference between embryonic and adult stem cells? Embryonic stem cells emerge in the first five to seven days of the embryo's development. They have the potential to become every cell of the body.
Adult stem cells, on the other hand, emerge later in the fetus's development, when the individual tissues of the body begin to form. Adult stem cells serve as a reservoir of continuous replenishment for the tissues in which they reside.

A liver stem cell, for instance, can turn into a liver cell. It can also divide to become another liver stem cell. In this sense, it is constantly replenishing itself.

Scientists are working to determine how they can harness the capabilities of adult stem cells to treat the tissues in which they reside. Liver stem cells could treat damaged liver tissue. Neural stem cells could prove useful in treating brain diseases, and so on.

Some adult stem cells could prove to be key players in disease formation, as well. Indeed, the latest evidence suggests that neural stem cells may be the cause of the most common form of primary brain tumor - malignant gliomas.

And in a novel twist, scientists are trying to turn fat cells into bone or muscle by controlling their shared adult stem cell "parent."

**Why do some consider embryonic stem cell research controversial?**

Human embryonic stem cells emerge five to seven days into the development of the embryo, when it is a hollow sphere made up of approximately 100 to 150 cells. At this stage, the embryo is known as a blastocyst. One portion of the blastocyst contains the "inner cell mass." This is where the embryonic stem cells are.

To obtain the cells, scientists apply chemicals to the embryo, which dissolve it's coating, exposing the stem cells. This process destroys the embryo. Some people oppose the use of embryos for research because they consider them living beings.

The embryos that are studied at US universities have been donated for research by patients who have undergone fertility treatments. The embryos were created through in vitro fertilization. The embryos have been left over following the fertility treatments and, depending on the patient's request, would otherwise have been stored indefinitely or discarded.

**What major scientific obstacles still need to be overcome before patients realize the full promise of embryonic stem cell research?**

Scientists expect it will take many years, and in some cases, many decades before the full potential of stem cells to treat patients is clear.

Why so long? Consider that:

- UCSF's Gail Martin co-discovered embryonic stem cells in mice in 1981.
- It took scientists 10 years to gain the necessary insights just to control the behavior of finicky mouse embryonic stem cells in the culture dish.
- Scientists suspect it may take at least as long to learn the subtle characteristics of human embryonic stem cells, which behave quite differently from mouse cells in culture.
- Scientists still need to identify and understand the genes and growth factors that direct stem cells to form specific cell types.
- In the case of adult stem cells, scientists need to determine where these cells reside in each tissue and the roles they naturally play there. Once scientists have accomplished this, they still need to determine whether these cells behave like embryonic stem cells and can be directed to generate specific cell types needed by patients.
Whether from embryonic or adult stem cells, scientists need to determine how the body accepts and responds to stem cell-derived cells introduced into various tissues. The implications of links between stem cells and diseases such as cancer are only starting to be explored by many laboratories around the world.

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