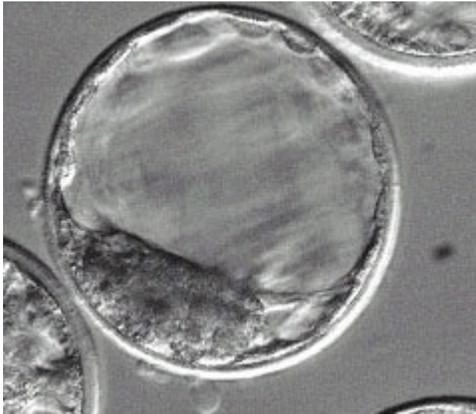


Embryonic stem cells: Hope for curing diseases?

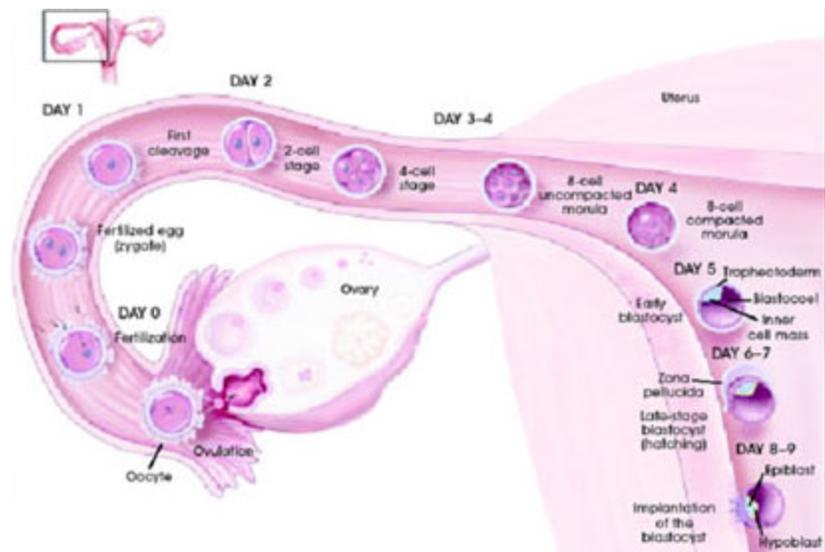


This image reveals the inner cell mass of a monkey embryo at the blastocyst stage. At this stage, the inner cell mass consists of 50 cells, some of which will become the fetus, others the placenta. Cells that will contribute to the fetus are pluripotent and are called embryonic [stem cells](#); they will give rise to each of the 200 cell types in our bodies—blood cells, skin cells, neurons, etc.—but at this stage they are a little like teenagers who don't know yet what they will do when they grow up.

Below is an illustration of very early embryo development from the time of fertilization to implantation in the uterine wall. Notice that the blastocyst with its inner cell mass develops at day 5. At an even earlier stage of embryo development, stem cells are totipotent because they give rise not just to body cells but also to the placental cells that nurture the fetus during pregnancy.

How stem cells become different specialized cells is not yet very well understood. If we could learn how stem cells differentiate, then we could encourage differentiation in one direction while discouraging it in another. We could, in other words, grow pancreatic beta cells, which produce insulin, for [diabetes](#) patients; serotonin cells, which produce a neurotransmitter that regulates mood, for patients suffering depression; dopamine neurons, which produce a neurotransmitter essential for movement, for [Parkinson's](#) disease patients.

Besides having therapeutic value—their value in curing diseases—stem cells might be turned into specific cells for the sake of drug trials. Whether the action of a drug on particular cell types is safe and effective could be tested with stem cells that have been grown into those particular cell types. This would make drug trials more precise and also reduce the number of animals necessary for testing new medications.



Learning the secrets of stem cells

How could you go about learning the secrets of stem cells?

First, you would have to have a source of embryos. From what species?

Human? Couples who go to fertility clinics for assistance in having children produce many more embryos than are implanted in the uterus during the first attempt(s) to initiate pregnancy. If they succeed in having children, frequently they will permit the extra embryos to be destroyed. Could you arrange to have such embryos, otherwise scheduled for destruction, donated to research and could you use such embryos as a source for stem cells?



Not in the United States. Currently there is a ban on the use of federal money to support research on human embryos. The only exception is for stem cell lines already in existence

before the ban went into effect in 2001, and the number of such stem cell lines is very small—about a dozen.

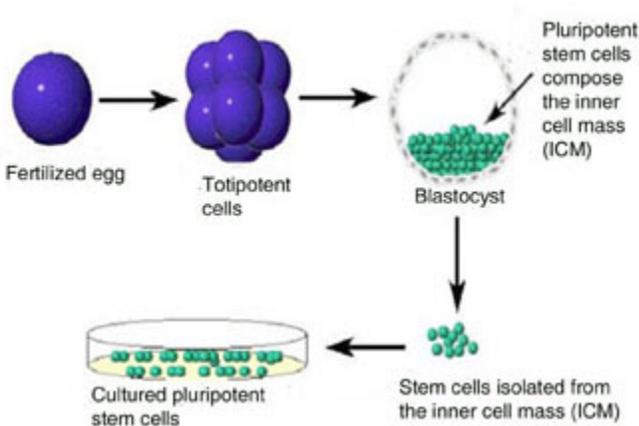
What if you were able to get access to cells from one of those cell lines? Then you could join the large number of scientists using them to discover the secrets of stem cell differentiation. But, before you get too far in your research, you might want to anticipate another problem down the line. Say that you were to get to the point at which you wanted to know if the stem cells you have made into pancreas cells or brain cells can be safely transplanted and will be effective treatments for diabetes or Parkinson's disease. Could you go ahead with experimental transplants in diabetes or Parkinson's patients? Or, would you want to try this first in animals?

Nonhuman primate? You could, of course, arrange to flush fertilized eggs from the uterus of monkeys. In fact, [James Thomson](#), the first person to isolate embryo stem cells (and a former postdoctoral fellow at the ONPRC, did exactly that.

Probably, however, you would choose to collect a clutch of eggs from the ovary of a female monkey by laparoscopic surgery and fertilize those eggs in vitro (in a glass or plastic laboratory dish). The resulting embryos, rather than being transplanted back into the females—as they are in women who go to fertility clinics for assistance in having children—would be kept in the laboratory as the source of stem cells. Such in vitro fertilization, which is frequently done at the ONPRC, involves these steps:

- 1 – Administering hormones to the monkey so that several eggs mature in the ovary in a given menstrual cycle, rather than just the one egg that is normally ovulated;
- 2 – Collecting the eggs from the ovary through laparoscopic surgery;
- 3 – Fertilizing the eggs in vitro;
- 4 – Isolating the stem cells when the embryos reach the blastocyst stage;
- 5 – Culturing the pluripotent stem cells to keep them propagating and prevent them from differentiating.

Here is a schema that illustrates in vitro (test tube) embryo development and embryonic stem cell isolation and culture:



Notice that after stem cells are isolated from the inner cell mass, they are cultured on a feeder layer of cells that produce factors that encourage their continuing proliferation but prevent them from differentiating. In other words, these stem cells, which can divide continuously and propagate more and more undifferentiated cells, can be kept from becoming the specialized cells that make up our body tissue and organs.

Cell differentiation

If we remove the stem cells from their feeder layers, they will “spontaneously” differentiate. What we want to do is to direct their differentiation. Currently, scientists are learning how to do this. They administer promoters and inhibitors of growth, using a sort of push-pull method of coaxing stem cells to become one cell type or another. ONPRC scientists have successfully directed stem cells to become [insulin-producing pancreatic cells](#) in the test tube.

They have also achieved high efficiency in coaxing stem cells to become “baby” serotonin cells —again in the test tube—that might someday be used to treat patients suffering depression. Some have also added their research to international efforts to derive brain cells that produce dopamine and that could be used to treat [Parkinson’s patients](#).

Progress is being made, but many challenges remain. One of the most critical challenges is to achieve what are called purified populations of specific cells. Say, for example, that our aim is to produce pancreatic cells. It is important that 100 percent of our cells be differentiated uniformly. If some remain as undifferentiated stem cells, then, after transplantation, those “outliers” could lead to the formation of tumors.

Stem cell transplantation

Currently, ONPRC scientists are beginning experiments to see if their stem-cells-turned-pancreatic-cells function as normal cell types in living animals, not just in test tubes. For this work, mice, in which it is easy to induce a chemical condition resembling diabetes, are valuable. Especially valuable are SCID (severely compromised immuno-deficient) mice. Having compromised or ineffective immune systems, these mice are not likely to reject transplanted cells. The scientists are able to monitor glucose levels in the SCID mice to see if the stem-cells-turned-pancreatic-cells are doing their work. Eventually, similar experiments will have to take place in monkeys, whose insulin requirements are quite different than those of mice and much more closely related to requirements in humans.

A future challenge, then, is to test whether or not stem-cells-turned-pancreatic-cells may be safely transplanted in human patients and whether or not those cells would be effective in treating the disease of diabetes. We wouldn’t want to do that without first attempting such transplantation in animals. Here, as we have already mentioned, is one value of animal models: they allow us to test safety, efficacy and feasibility before translating or applying what has been learned to humans.

For further reading:

Stem cells: <http://www.nih.gov/news/stemcell/scireport.htm> and <http://www.nwabr.org/education/articles/2003Lessons/STEMCELLS/StemCells.doc>

Juvenile diabetes: http://www.jdrf.org/index.cfm?fuseaction=home.viewPage&page_id=02DBD384-2A5E-7B6E-1AA3637745700722

Depression: <http://www.apa.org/pi/wpo/women&depression.pdf>