Reyes have evidence that the cells can become brain cells and liver cell precursors, plus all three kinds of muscle—heart, skeletal, and smooth. "They are almost like ES cells," she says, in their ability to form different cell types.

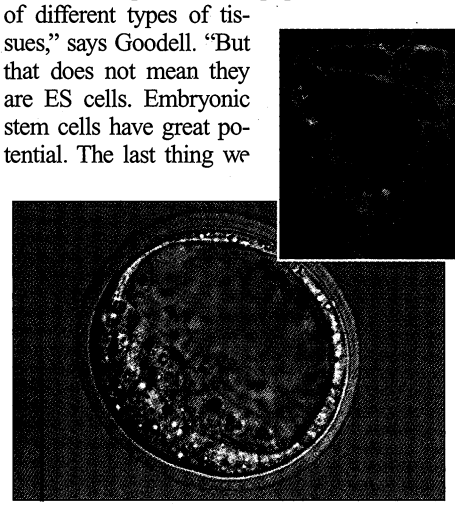
These malleable bone marrow cells are rare, Verfaillie admits. She estimates that perhaps 1 in 10 billion marrow cells has such versatility. And they are only recognizable by their abilities; the team has not yet found a molecular marker that distinguishes the unusually powerful cells from other bone marrow cells. Still, she says, her team has isolated "a handful" of such cells from 80% of the bone marrow samples they've taken. Although the versatile cells are more plentiful in children, Verfaillie's team has also found them in donors between 45 and 50 years old.

Verfaillie's work has not yet been published nor her observations replicated. Even so, many researchers are excited by the work. The cells "look extremely interesting," says hematologist and stem cell researcher Leonard Zon of Children's Hospital in Boston. Stem cell biologist Ihor Lemischka of Princeton University agrees. "I'm very intrigued," he says, although he cautions that data from one lab should not outweigh the decades of research on mouse ES cells.

Besides skirting the ethical dilemmas surrounding research on embryonic and fetal stem cells, adult cells like Verfaillie's might have another advantage: They may be easier to manage. ES cells tend to differentiate spontaneously into all kinds of tissue. When injected under the skin of immune-compromised mice, for example, they grow into teratomas—tumors consisting of numerous cell types, from gut to skin. Before applying the cells in human disease, researchers will have to learn how to get them to produce only the desired cell types. "You don't want teeth or bone in your brain. You don't want muscle in your liver," says stem cell researcher Evan Snyder of Children's Hospital in Boston. In contrast, Verfaillie says her cells are "better behaved." They do not spontaneously differentiate but can be induced to do so by applying appropriate growth factors or other external cues.

Adult stem cells have a drawback, however, in that some seem to lose their ability to divide and differentiate after a time in culture. This short life-span might make them unsuitable for some medical applications. By contrast, mouse ES cells have a long track record in the lab, says Goodell, and so far it seems that they "are truly infinite in their capacity to divide. There are [mouse] cell lines that have been around for 10 years, and there is no evidence that they have lost their 'stem cell–ness' or their potency," she says.

For these and other reasons, many researchers say, adult-derived stem cells are not going to be an exact substitute for embryonic or fetal cells. "There are adult cell types that may have the potential to repopulate a number of different types of tissues," says Goodell. "But that does not mean they are ES cells. Embryonic stem cells have great potential. The last thing we should do is restrict research." Right now, she says, stem cell specialists want to study both adult and embryonic stem cells to find out just what their capabilities might be.



Great expectations. Blastocysts, like this murine example, harbor embryonic stem (ES) cells that can become any tissue in the body. Inset shows oligodendrocytes (green) and astrocytes (red), derived from mouse ES cells.

That may be difficult. At the moment, human ES cells are unavailable to most researchers because of proprietary concerns (see next story) and the uncertain legal status of the cells. Internationally, most research on human ES cells is on hold while legislatures and funding agencies wrestle with the ethical issues. In the United States, the National Institutes of Health is the government agency that would fund the research, and currently, researchers are not allowed to use NIH funds for work with human ES cells. Many European countries, too, are still developing new policies on the use of the cells (see Viewpoint by Lenoir, p. 1425).

The final version of NIH's guidelines for use of embryonic and fetal stem cells will not appear before early summer, says Lana Skirboll, NIH associate director for science policy. The draft guidelines would allow use of NIH funds for ES cell research as long as the derivation of the cells, by private institutions, met certain ethical standards (*Science*, 10 December 1999, p. 2050). But several members of Congress are considering legislation that would overrule the guidelines and block federal funding of ES cell research. At least some of that debate is likely to focus on whether adult stem cells do in fact have the potential to do as much as their embryonic precursors.

–GRETCHEN VOGEL

CREDITS: DAVID SPEARS/SCIENCE PICTURES LIMITED/CORBIS; OLIVER BRÜSTLE (INSET)

NEWS

The Business of Stem Cells

Human stem cells have become one of the hottest areas in biotech as several companies have jumped in to try to exploit them commercially

When biologist James Thomson announced 15 months ago that he had grown human embryonic stem cells in a petri dish, scientists were excited about their potential uses in medicine. These cells, which are capable of developing into almost any other type of cell in the body, may one day provide an unlimited source of replacement tissues for treating human diseases. Some elected officials were less enthused, however; they were more concerned about the cells' source—human embryos. For now, at least, U.S. government rules that protect the embryo have put the cells off limits to most publicly funded researchers. But they aren't off limits for private companies. As a result, commercial enterprises now have the field almost exclusively to themselves.

One company, Geron Corp. of Menlo Park, California, has secured a commanding position. Geron not only bankrolled Thomson's work—gaining first rights to exploit the cells commercially—but it also funded the isolation of a second type of very early or "primordial" cell from human fetal tissue by John Gearhart of The Johns Hopkins University. Now, the company is gearing up an intensive research program aimed at turning both of these discoveries into therapeutic products. "We certainly have invested heavily" in the field, says Geron CEO and president Thomas Okarma, noting that exclusivity is the reward for "being smart and lucky."

While Geron has nabbed the early lead in exploiting embryonic and primordial fetal stem cells, almost a dozen other biotech firms are elbowing their way into a crowded field to develop therapies using so-called "adult" stem cells. Once thought to be less versatile than primordial stem cells because

they have already made a commitment to become particular cell types, these cells are now turning out to have greater than expected capabilities (see previous story). What's more, they pose fewer ethical problems because they can be obtained from sources other than embryos or aborted fetuses. And the companies using them argue that it may require less work to transform them into specialized cells for transplantation.

The whole field has a gold-rush aura, with biotech companies betting heavily on their own technologies and stock prices swinging on the latest announcements. Some companies are already moving into clinical trials for products that, they are quick to point out, might serve a vast pool of patients: the estimated 2 million people with severe osteoarthritis or Parkinson's disease. "The great enthusiasm for stem cells," says Ronald McKay of the National Institutes of Health (NIH), "is based on the idea that they can be manipulated and have highly reproducible properties. I think it's a very important step in biomedical research ... to be able to use them directly in therapy."

BETTING ON STEM CELLS

Company name	Location	Employees	Specialty
Aastrom Biosciences	Ann Arbor, MI	33	Hematopoietic stem cells
Geron Corp.	Menlo Park, CA	100	Embryonic, fetal stem cells
Layton BioScience	Atherton, CA	25	Fetal neural stem cells
NeuralSTEM Biopharmaceuticals	Bethesda, MD	14	Fetal neural stem cells
Neuronyx Inc.	Malvern, PA	10	Neural stem cells
Nexell Therapeutics Inc.	Irvine, CA	120	Hematopoietic stem cells
Osiris Therapeutics	Baltimore, MD	75	Mesenchymal stem cells
ReNeuron	London	17	Neural stem cells
Stem Cell Sciences	Melbourne, Australia	—	Embryonic stem cells
StemCells Inc.	Sunnyvale, CA	16	Adult neural stem cells

Embryonic potential

Much of this heady anticipation was sparked by Thomson's and Gearhart's success in growing primordial stem cells. But academic researchers have been on the outside looking in, wondering when—and under what conditions—they may get to work with the new cell lines. For Gearhart's line, the answer is entirely up to Geron and its subsidiary, Roslin Bio-Med of Midlothian, Scotland: Geron controls all uses of the cell line through an exclusive license from Hopkins.

The company has less control over Thomson's cells, however. His institution, the University of Wisconsin, Madison (UW), insisted on retaining the right to distribute the cells to academics. On 1 February, UW established a new nonprofit subsidiary—WiCell Research Institute Inc., directed by Thomson—that will provide stem cells to approved applicants. The university has already received more than 100 requests, including 12 from private companies, according to Carl Gulbrandsen, director of the Wisconsin Alumni Research Foundation (WARF), which handles UW's patents.

Gulbrandsen says that anyone who wishes to use Thomson's cells will have to promise not to share them with others, not to "mingle" them with human embryonic cells to make a human clone, and not to attempt to grow them into embryos. WiCell will review each applicant's research agenda annually, Gulbrandsen says, but WARF insists that "our intention is to make these cells widely available and at a low cost for academic researchers." Distribution hasn't begun yet, and federally funded researchers will have to wait until government rules for working with embryonic cells are finalized (*Science*, 10 December 1999, p. 2050).

Okarma also says his company won't try to go it alone in developing embryonic stem cells. Geron intends to recruit outsiders to work with its scientific staff to "drive" the stem cells into specific applications. In December, Geron held a meeting with 45 researchers at the Asilomar conference center in Monterey, California, to begin building a collaborative network. The conference brought together experts in cell regulation, gene insertion, and nuclear transfer (cloning), Okarma says. But the agenda and guest list are confidential.

Geron is also still very much involved in basic research. In the past year, Okarma says, company scientists have produced cardiac muscle cells and three types of nerve cells from the stem cells. They have also had "some success" in introducing new genes into stem cells to control their differentiation into specialized cells. Indeed, Okarma predicts, the first commercial payoff will come from identifying genes that either initiate, or help maintain, the development of specific cell types. The information will be useful, he hopes, in designing new therapies and screening candidate drugs.

New cells, familiar sources

Primordial cells like Thomson's and Gearhart's have captured most of the attention, but adult stem cells have so far attracted far more investment. Many companies have focused on the hematopoietic stem cells of bone marrow, which give rise to all types of blood cells. Typical of this group are Nexell Therapeutics Inc. of Irvine, California, and Aastrom Biosciences of Ann Arbor, Michigan, both of which are developing systems to isolate such cells and grow them in large quantities, chiefly to aid in restoring cancer patients' immune systems after intense radiation or chemotherapy.

Osiris Therapeutics Inc. of Baltimore, Maryland, has identified a different type of cell in the supportive tissue that surrounds bone marrow, or stroma, called mesenchymal stem cells. It has patented systems for isolating and producing these cells and launched two clinical trials. Initially, Osiris is using the cells to help restore bone marrow in cancer patients, as the other companies are doing.

Meanwhile, because mesenchymal cells can differentiate into cartilage, muscle cells, and possibly even some neuronlike cells, according to Osiris, the company is investigating whether they can be used to replace cartilage in arthritis patients, fix damaged tendons, and repair brain tissue. To help in these endeavors, Osiris's chief scientific officer, Daniel Marshak, says, "we are making the cells available" to all nonprofit labs through a private distributor, "so that everybody in the research community can move the field forward."

Neural stem cells came on the scene later than the hematopoietic and mesenchymal cells, but in the past year they have become hot items because of their potential for treating patients whose brains have been damaged by disease or trauma. Indeed, investors are so keen on this idea that each new neural stem cell discovery seems to attract immediate investment. And the field is highly competitive.

Layton BioScience, a small private company in Atherton, California, has already begun clinical trials. It developed a line of cells derived from a germ line tumor that behave like neural stem cells, according to CEO Gary Snable. In 1998, University of Pittsburgh neurosurgeon Douglas Kondziolka transplanted the cells into the brains of 12 stroke patients and later reported that brain scans revealed increased glucose uptake in the affected area in several patients, an indication that the cells were alive and metabolically active.

In late 1999, Layton licensed a different cell line derived from human fetal tissue and patented by neuroscientist Evan Snyder of Children's Hospital and Harvard Medical School in Boston. Snyder's team has shown

that the cells will engraft in the brains of experimental animals and is now testing them in models that mimic human diseases and spinal cord injury in preparation for a potential clinical trial next year. Snyder worries, however, that the field is becoming so hot that its credibility could be damaged by hype, and he says he aims to help deflate exaggerated claims.

Another small private company, NeuralSTEM Biopharmaceuticals of Bethesda, Maryland, plans to exploit human neural stem cells derived from embryos. Karl Johe, a former researcher in McKay's lab at NIH and now at NeuralSTEM, discovered a method of isolating and growing these cells in animals. NIH released the patent on the cells to NeuralSTEM, which was founded by McKay, attorney Richard Garr, and another investor. Garr, the CEO, says the company's first goals are to produce cells that can be transplanted into Parkinson's disease patients and develop vectors that can deliver therapeutic proteins to the brain.

A similar project is taking shape on the West Coast, under the direction of Nobuko Uchida, who previously worked in immunologist Irving Weissman's lab at Stanford University. Uchida is now chief of neurology research at StemCells Inc., which Weissman helped found. StemCells is a subsidiary of a public company known as CytoTherapeutics Inc., in Sunnyvale, California, which announced last year that it was shedding all other investments to focus entirely on stem cells. It aims to commercialize Uchida's pending patent on a method that uses surface markers to isolate adult neural stem cells from brain tissue. Once the cells are in hand, the goal is to use them to treat patients with neurodegenerative diseases.

Another company that aims to attack the same medical problems is Neuronyx Inc., which just set up shop this month in Malvern, Pennsylvania, with backing from Hubert Schoemaker, the former CEO of Centocor. Johnson & Johnson recently bought Centocor for $4.9 billion, and Schoemaker is using some of the proceeds to create his new company, which hopes to exploit embryonic stem cells for an agenda to be developed by research chief Tony Ho, a neuroscientist recently hired from Johns Hopkins.

Although most of this new business activity is taking place in the United States, several companies have sprung up elsewhere. ReNeuron, a small British company with a staff of about 17, is trying to commercialize stem cell work by three faculty members at the Institute of Psychiatry in London. With backing from the large biotech fund called Merlin Ventures, ReNeuron has established a line of neuroepithelial stem cells derived from fetal tissue. According to CEO Martin Edwards, the company hopes to begin transplanting these cells into stroke patients in a clinical trial "around the end of 2000." Stem Cell Sciences, based in Melbourne, Australia, which has ties to embryologist Austin Smith of the University of Edinburgh in Scotland, is raising money for unspecified therapies using stem cells.

It is of course far too early to judge the likelihood of success for any of these investments. But one thing is certain: We will be hearing a lot more about the promise of stem cells in the next few years.

–ELIOT MARSHALL

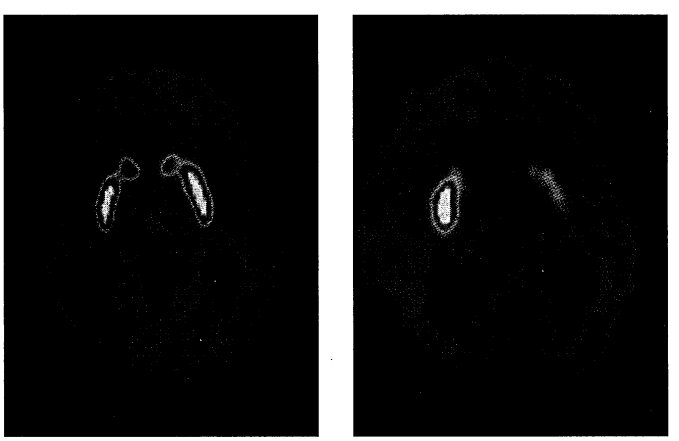
NEWS

Fetal Neuron Grafts Pave the Way for Stem Cell Therapies

A decade of experimental treatments using fetal neurons to replace brain cells that die in Parkinson's disease can provide lessons for planning stem cell therapies

Swedish neuroscientist Anders Björklund and his colleagues may have caught a glimpse of what the future holds for the treatment of failing organs. For more than 10 years, Björklund has been part of a team at Lund University in Sweden that has been grafting neurons from aborted fetuses into the brains of patients with Parkinson's disease. In many cases, the transplanted cells have dramatically relieved the patients' symptoms, which include slowness of movement and rigidity. That is just the kind of therapy that stem cell researchers hope to make routine for treating all sorts of degenerative diseases, if they can coax the cells to develop into limitless supplies of specific cell types that can be used to repair or replace damaged organs.

Although the current Parkinson's treatment uses fetal cells that have already developed into a particular type of neuron, the promising results represent a "proof of principle that cell replacement actually works," says Björklund. The results have given researchers increased confidence that, if they can manipulate stem cells to develop into the kind of neuron the Lund group and others are using—a big challenge—the new cells would take over the work of damaged cells in the brains of Parkinson's patients. If so, Parkinson's treatment could be among the first applications of stem cell therapy.



CREDIT: P. PICCINI *ET AL.*, *NATURE NEUROSCIENCE* 2, 1137 (1999)

Persistence. As shown by the red and white colored area, a fetal graft implanted in the brain of a Parkinson's patient 10 years ago *(right)* still produces normal levels of dopamine. A normal brain scan is at left.

The successes have also increased the urgency of developing stem cell treatments, because despite their promise, there are many reasons that fetal cells will never be widely used to treat Parkinson's disease. The reasons range from ethical concerns, such as the protests by antiabortionists that led the governor of Nebraska to urge that research involving fetal tissue be shut down at the University of Nebraska (*Science*, 14 January, p. 202), to the fact that there will never be enough fetal tissue to treat all the people who need it. Parkinson's disease afflicts 1 million people in the United States alone.

Researchers are now looking closely at the results from fetal cell transplants for lessons that will help guide future work with stem cells. There are still many hurdles to overcome, but this first round of cell replacement in the brain sets a "gold standard" that stem cells must meet if they are to become the basis for new Parkinson's treatments, says neuroscientist and stem cell researcher Evan Snyder of Harvard Medical School in Boston.

Parkinson's disease is a logical candidate for cell replacement therapy, in part because conventional treatments have had limited success. The disease is caused by the death, for unknown reasons, of a particular group of brain