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Anatomy of a Stem Cell

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ANATOMY OF A STEM CELL



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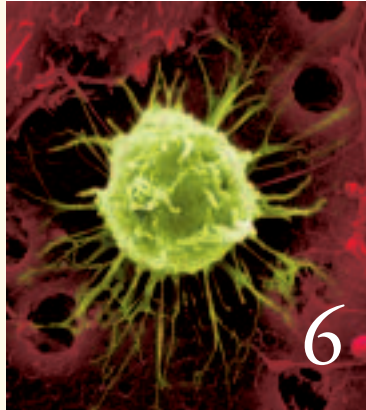
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about the cover: Color-enhanced scanning electron micrograph of a stem cell collected from human bone marrow. Most tissues contain primitive cells, called stem cells, that can divide and populate tissue to correct damage. Bone marrow retains the ability to generate stem cells throughout life. Bone marrow stem cells typically give rise to bone, blood and cartilage. Photo by Andrew Paul Leonard / Photo Researchers, Inc.



anatomy of a stem cell

Penn Veterinarians Study the Big Future for This Little Cell

BY SUSAN I. FINKELSTEIN

The process of discovery is very simple. An unwearied and systematic application of known laws to nature causes the unknown to reveal themselves.

—Henry David Thoreau

“h *ealing, Teaching and Discovery.”* Undoubtedly, the general public is most familiar with the first part of the School of Veterinary Medicine’s tri-fold mission—and with good reason. The Matthew J. Ryan Veterinary Hospital in Philadelphia sees more than 28,000 companion-animal patient visits each year, 12,000 of which

come through the Emergency Service. The George D. Widener Hospital for Large Animals at New Bolton Center accommodates more than 6,000 patient visits annually, and the Hospital’s William Boucher Field Service sees more than 19,000 animals a year. Both Hospitals are known internationally for their excellence in veterinary medical specialties, many of which originated here: cardiology, orthopaedics, oncology and medical genetics, to name only a few. Dogs, cats, birds, reptiles, horses, cows, pigs—all these, and more, can receive comprehensive treatment at Penn Veterinary Medicine, perhaps the best care anywhere in the world.

Most people are not aware, though, that the *Discovery* component of our mission undergirds the *Healing* and the *Teaching* for which the School is internationally acclaimed. Knowledge that emerges from the basic and clinical research of our scientists allows us to develop new ways to diagnose and treat disease—and to impart those findings to the next generation of veterinarians and researchers. As a partner in one of the world’s great biomedical research and training centers, Penn Vet helps both animals and people everywhere live longer, healthier lives. Truly, biomedical research is the unsung hero of our ongoing success story.

Building a Better Gene Trap

One area of research that is widely known to most people is the study of stem cells, the use of which is generating much optimism for treating human and animal diseases. For years, researchers at Penn and elsewhere have sought to understand why the body repairs and replaces some tissues, but not others. After analyzing apparently indiscriminant cell-repair mechanisms, scientists have focused on stem cells; these cells have a special capacity to renew themselves and form a variety of specialized cell types. Stem cells are capable of growing into any of the 300 different kinds of cells in the body.

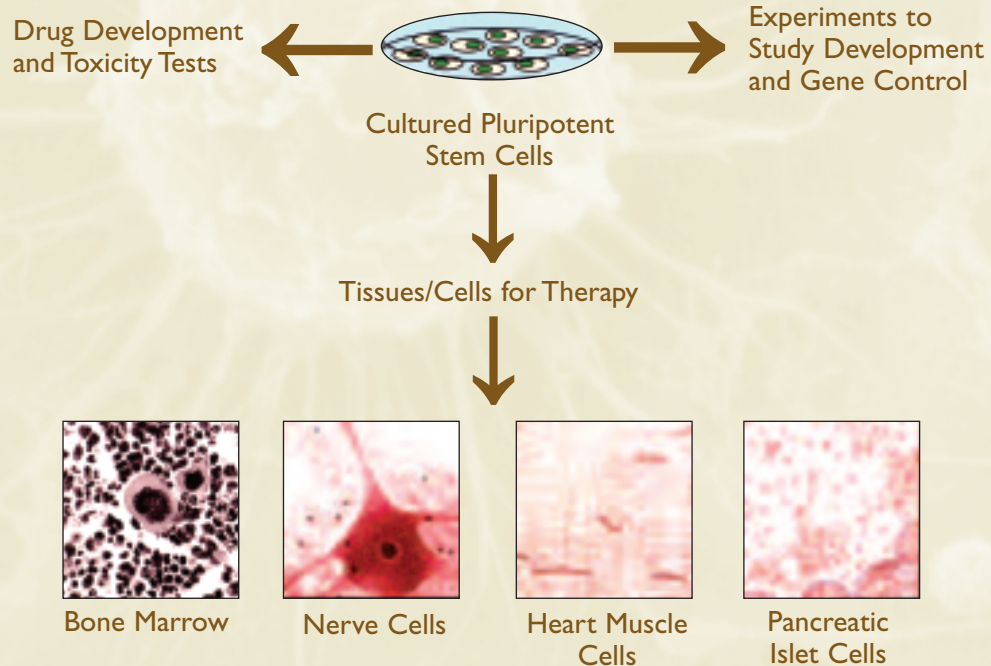
Scientists distinguish between two types of stem cells: adult and embryonic. Adult stem cells exist in developed tissues in animals or humans after birth, supplying their specific tissue with replacement cells throughout life. (For example, our blood stem cells produce five million cells per second.) Adult stem cells can be isolated from many parts of the body, including the brain, but most commonly they are drawn from the marrow in some bones. Compared to embryonic stem cells, which come from embryos and can make replacement cells for any tissue, adult stem cells are normally dedicated to making cells for one particular type. In other words, adult skin stem cells usually can only make skin, not brain or blood cells. Most experts agree, though, that the potential of stem cells to prevent, diagnose and treat disease in both animals and people is seemingly unlimited.

Dr. Ralph Brinster, V'60, GR'64, Richard King Mellon Professor of Reproductive Physiology, is a pioneer in the transplantation of certain stem cells known as “germ cells,” which are the reproductive cells of the body—eggs in females and sperm in males. “Stem cell research is an area that has a lot of promise in terms of biology and medicine,” he explained. “For example, stem cells are responsible for maintenance of many tissues and medical conditions, including cancer, so understanding stem cells will help us understand disease.”

Dr. Brinster made international news in 1994 when he transplanted the stem cells of one mouse into another. When the stem cells became germ cells, they retained the genes of the donor mouse. In an article published in the February 2006 issue of *Nature Clinical Practice*, Dr. Brinster describes a technique in which donor sperm cells from a fertile male mouse can be transplanted to the testes of an infertile male, where they can restore fertility. Eventually, this procedure can offer hope to men who have become sterile following chemotherapy or radiation treatment.

Working at New Bolton Center in Kennett Square, Pa., **Dr. Ina Dobrinski, Dr.med.vet., M.V.Sc., Ph.D.**, Marion Dilly and David George Jones Chair in Animal

The Promise of Stem Cell Research



Courtesy of the NIH

Reproduction and director of the School's Center for Animal Transgenesis and Germ Cell Research, acknowledges that much of the research in her lab has its roots in the germ cell technology that Dr. Brinster developed in the mid-1990s. Dr. Dobrinski is applying information derived from Dr. Brinster's work in the mouse to non-rodent animals, ultimately to improve the health and productivity of farm animals through transplantation of male germ cells whose genes have been manipulated. These genetically altered animals and plants are called “transgenic” and can be of enormous value in medicine and agriculture. In fact, transgenic animals were first created here at Penn, in 1981.

“Going into the male germ-line for particular stem cells was a very fascinating question because then the animal could just breed normally and transmit that fixed gene or changed gene to its offspring,” said Dr. Dobrinski. “In order to do that, to a certain degree we had to reinvent the wheel: We had to redevelop the transplantation technique [used in mice] because it doesn't work the same way in pigs or goats. We had to learn about those stem cells because we don't have the same reagents or antibodies available as we have for mouse stem cells.” One aspect of this work is the exploration of germ-line stem cell biology to develop a new approach to transgenesis in domestic animals through the alteration of the male germ-line.

In the November/December 2005 issue of the *Journal of Andrology*, Dr. Dobrinski and her colleagues relate another way in which changing the genes of certain animals can be beneficial. “. . . Transgenic pigs play a central



Photo by Sabina Louise Pierce

Cardiac cellular transplantation could have a marked effect in treating dilated cardiomyopathy, or DCM, one of the most common acquired heart diseases in large dogs. Some breeds, such as Dobermans, great Danes and boxers, are particularly prone to it. DCM causes the heart muscle to lose strength and fail to pump blood properly, and can eventually lead to heart failure. To identify genes that may play a role in the process of the disease, Dr. Oyama and his colleagues at Illinois used a commercially available gene chip, or microarray, designed for dogs—the GeneChip Canine Genome Array—a 1.5-inch square that contains more than 23,000 genes. When exposed to the genetic material from Doberman dogs that had died from heart disease, genes on the chip fluoresced, or lit up, if they were active in the sample. The researchers knew the nature and location of the genes on the chip, so they could identify the active genes in the samples and determine their level of activity by the brightness of the fluorescence. Essentially all 23,000 genes, tested at once, were narrowed down to 167 genes that could play a role in the development of DCM.

a process known as cardiac cellular transplantation. But the fundamental biological processes that govern the behavior of these cells remains a mystery, as does the long-term efficacy of the procedure.

“I think people get excited about it because of the huge potential that it has,” Dr. Oyama said. “Even in people, it’s an area about which very little is known. When they’re doing stem cell transplants in people, yes, it appears to improve the heart function, but when you ask the scientists ‘How is it doing that?’ nobody knows. They don’t have any idea. Cells go in there, and somehow

role as a potential source of tissues and organs for [transplantation] to humans and are of increasing interest as models for biomedical research. Similarly, transgenic dairy goats are of significant economic value for the production of biopharmaceutical proteins in their milk. . . .”

Another article co-authored by Dr. Dobrinski in the same issue of the *Journal of Andrology* (published online ahead of print) explains how stem cell transplantation can help conserve species of animals that are endangered due to loss of genetic diversity. “We are attempting to develop . . . stem cell transplantation [of undifferentiated sperm cells] in the cat as a tool to preserve and propagate male germplasm [DNA] from genetically valuable animals, be they threatened wild species or lines of cats used as models for inherited diseases.”

Mending a Broken Heart

Some 35 miles away from the Center for Animal Transgenesis and Germ Cell Research, **Dr. Mark Oyama**, associate professor of cardiology at the Ryan Veterinary Hospital, has studied how stem cell research might be used to treat dogs with heart disease. Even with the development of new technology and medications, even with an ever-broadening knowledge base about the causes and courses of heart disease, illness and death in dogs with heart problems remains high. According to the American Veterinary Medical Association, approximately 3.2 million dogs in the United States that have annual veterinary examinations suffer from some form of “acquired” heart disease and may be in heart failure.

Dr. Oyama came to Penn last year from the University of Illinois College of Veterinary Medicine, where he investigated how damaged heart cells in dogs could be repaired by transplanting the animals’ own stem cells into their hearts—

they’re making the heart function better.”

Cardiac cellular transplantation already has been performed in people who have suffered from heart attacks. The early results suggest that a variety of adult stem cells implanted in the heart are able to survive and grow into cardiac-like muscle tissue, “rebuilding the heart one cell at a time,” as Dr. Oyama wrote in *Veterinary Medicine* (February 1, 2005).

Because a particular type of heart disease in dogs involves much more of the heart than in people with a similar disease, local injections of cells during surgery—which is often used for people—would be inefficient for dogs. “If the whole heart is diseased, that’s a lot harder. So now you have to put in maybe 20 or 30 of these little injections everywhere and hope that the cells spread out. Every time you poke the heart, it’s conceivable that the heart will have abnormal heart rhythms, it can bruise the heart muscle and create lots of other problems,” Dr. Oyama said.

One Medicine

One of the reasons that Dr. Oyama chose to come to Penn was its unique position as part of a vast network of biomedical research facilities—and he has already begun to take full advantage of the extraordinary opportunities this offers. A certain kind of heart-valve disease in dogs resembles that which occurs in some people who have taken the diet drug “phen-fen” (a combination of phentermine and fenfluramine). Dr. Oyama has begun work with Robert J. Levy, M.D., William J. Rashkind Endowed Chair in Pediatric Cardiology at the Children’s Hospital of Philadelphia, in looking at valve tissue in humans and trying to better understand how a certain pathway involving serotonin and transforming growth factor beta contributes

to the disease. (*Serotonin* is a neurotransmitter believed to play an important role in the regulation of mood, sleep, vomiting, sexuality and appetite. *Transforming growth factor beta* is one of many characterized growth factors that are involved in tissue development, cell differentiation, embryonic development and many other signaling pathways.)

“We are doing some combined experiments to compare mitral disease in dogs with mitral disease in humans,” Dr. Oyama explained. “If similarities exist, we can look at the dog as a model of disease for people, as well as apply what we know about the human disease to figure out why older, small-breed dogs are so predisposed to the disease. This comparative study hopes to merge Dr. Levy’s expertise in serotonin valve disease with our expertise in the canine disease.”

Bred in the Bone

Cardiac tissue is not the only subject of stem cell research at the School. In the Section of Surgery of the Department of Clinical Studies—Philadelphia, **Dr. Susan Volk, V’95, GR’99**, lecturer, has joined the faculty at Penn’s Medical and Dental schools in studying how stem cells derived from bone marrow can eventually become bone cells.

Most injured tissues heal by forming a scar, but injured bone heals by actually forming new bone. Even in its uninjured state, bone undergoes constant remodeling to maintain its ability to move and support the body and to sustain constant calcium levels. Both these processes—healing and remodeling—are dependent on undifferentiated bone cells, as well as stem cells that can be induced to form bone. If the recruitment, differentiation and/or induction steps of new bone formation do not occur, the body can develop orthopaedic disorders such as osteoporosis and slow- or non-healing fractures. Because people in industrialized countries are living longer, orthopaedic disease is having a greater economic impact on health-care resources. This factor, as well as the significant decrease in quality of life associated with these conditions, has made studies involving orthopaedic disease a high priority within the field of biomedical research.

Delayed bone healing in dogs requires extended medical care, with prolonged patient illness and increased client expense. Bone grafts using tissue from the patient’s own body are frequently used to help bone union after surgery. Several concerns, however, are associated with graft harvesting: problems or infection at the collection site, increased anesthetic time and limited volume and donor cell number. Bone-marrow stem cells (MSCs) are an accepted source of bone-forming cells recruited during normal bone growth, remodeling and fracture repair. Therefore, they are logical agents for use in cell-based therapies where induced bone growth is required. Pure populations of culture-expanded, inducible MSCs can be a potent alternative to bone grafting with fewer complications.

Although MSCs enhance the repair of canine fractures and bone gaps, the specific inducers necessary to cause canine MSCs to become bone-forming cells have yet to be identified. Although MSCs from all species studied can be induced to eventually form bone cells, the potency of

inducers varies markedly from one species to the next. The work of Dr. Volk and her colleagues, published in the October 2005 issue of the *American Journal of Veterinary Research*, suggests that differences exist in the most efficient inducers of bone growth among species. “Defining which growth factors are most efficient to induce [bone formation] in these cells has important clinical implications for their use in cell-based therapies. In addition, we are defining differences that exist in the differentiation capacity of these cells based on their source (i.e., site of bone-marrow harvest and age of donor), which has important implications for the development of MSC-based therapies in our small-animal surgical patients, as well as in humans,” Dr. Volk explained.

In addition to Dr. Volk’s interest in MSCs for orthopaedic applications, she is also investigating their use for soft-tissue surgical applications. In collaboration with Drs. Kenneth Liechty and Alan Flake at the Children’s Institute for Surgical Science, Children’s Hospital of Philadelphia, she has focused on establishing their effect in the treatment of oxygen-deprived (ischemic) wounds and dissecting mechanisms of their therapeutic effects. Complicated wound healing imposes a formidable clinical challenge in both human and veterinary medicine, with prolonged hospitalization and substantial health-care expenditure. To date, effective therapies for ischemic ulcers and other chronic non-healing wounds are lacking. Dr. Volk’s research suggests that MSCs directly participate in wound healing and indirectly influence surrounding cells to improve healing of ischemic wounds. Studies are underway to characterize how topical application of MSCs can improve the phases of healing in ischemic wounds. Knowledge about tissue engineering gained from this research can provide substantial insight into molecular mechanisms critical for healing chronic wounds and other ischemic tissues.

Full Steam Ahead

Research is the cornerstone on which Penn—and any other research university, for that matter—must build its future, on which medical science itself is perpetually balanced. Stem cell technology has already revolutionized modern biology and promises to provide unique opportunities in understanding mechanisms behind basic biological processes and in the treatment of disease. Among its countless applications in human and veterinary science, researchers hope to eventually use stem cells to repair spinal cords; cure Crohn’s, Alzheimer’s and Parkinson’s diseases; re-grow arteries and limbs; replace damaged kidneys and hearts; cure diabetes by substituting nonfunctioning pancreatic cells; restore vision and hearing; and treat leukemia, lymphoma and brain cancer. In fact, most of these treatments have already been studied, and with promising results. Granted, years of additional research are still necessary to realize this technology’s full therapeutic potential, but work at Penn Vet in the laboratories of researchers like Drs. Brinster, Dobrinski, Oyama and Volk—and in labs across campus and around the world—is proceeding full steam ahead. 🍷