BY DENISE MYSHKO

Animal Farm

XENOTRANSPLANTATION, the use of animal cells and organs for human transplantation, **has the potential to address the donor organ shortage** and provide treatments for diabetes, Parkinson's, and other chronic diseases — that is, **if researchers can ever make the process safe and effective**.

NO ONE WOULD DISPUTE THAT THERE IS A SHORTAGE OF HEARTS, KIDNEYS, OR LIVERS FOR THOSE WHO REQUIRE A NEW ONE. Last year in the United States alone, 6,000 people died while awaiting an organ transplant.

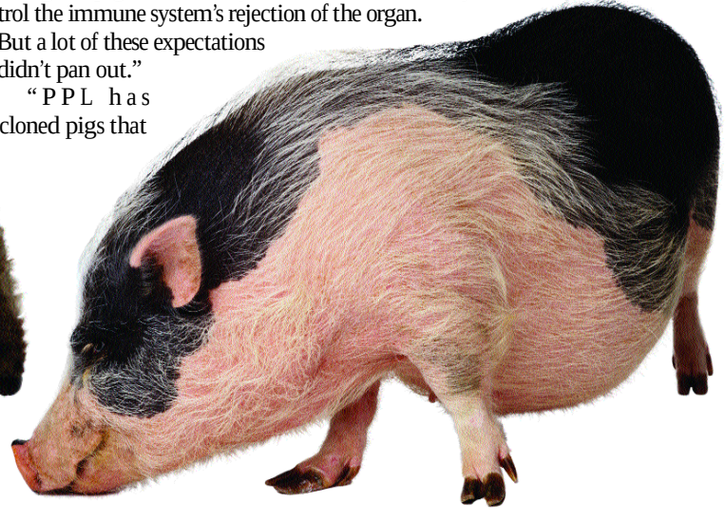
Campaigns to increase organ donation have been somewhat successful — do you have an organ donation sticker on your driver's license? But these efforts have not met the overwhelming need. In addition, an increased focus on safety, including the use of seat belts and helmets, has reduced the number of organs available as a result of fatality.

In efforts to meet demand, researchers are exploring an alternative source: animal organs. Xenotransplantation, as the process is known, is any procedure that involves the transplantation, implantation, or infusion into a human recipient of either live cells, tissues, or organs from a nonhuman source, or cells, tissues, or organs that have *ex vivo* (outside the body) contact with nonhuman cells.

But after much hype and high expectations for animal-to-human organ transplants in the past 20 years, researchers still have been unable to overcome some basic problems. Xenotransplantation is technically complicated; much still needs to be done to address the immune system's rejection of animal organs. There also are ethical concerns about "animal-part farms" and viral disease epidemics throughout the world.

Researchers say they've learned a great deal and this knowledge has led to a shift in their efforts, from a fundamental stage of discovery to efforts to develop viable treatments.

"Xenotransplantation has been an area, unfortunately, that has made some short-term promises that haven't come to fruition," says Julia Greenstein, Ph.D., president and CEO of Immerge BioTherapeutics Inc. The company is a joint venture of Novartis Pharma AG and BioTransplant Inc. formed in September 2000 to develop therapeutic applications for xenotransplantation. "There was a lot of work about five years ago to develop transgenic pigs, which everyone believed was the way to control the immune system's rejection of the organ. But a lot of these expectations didn't pan out."



"PPL has cloned pigs that

Milestones in XENOTRANSPLANTATION

1682 1905 1953 1954 1963

1682: Doctors repair the damaged skull of an injured Russian nobleman using a bit of bone taken from the skull of a dog. The surgery is said to be successful, but the Russian church threatens the nobleman with excommunication, so he has the dog bone removed.

1905: The pace of xenotransplantation picks up, and physicians begin to graft animal tissues into humans with some regularity. A French surgeon transplants slices of a rabbit kidney into a 16-year-old boy suffering from kidney failure. The patient dies two weeks later. Over the next 20 years, doctors try to transplant organs from pigs, goats, lambs, and monkeys into various patients. All the grafts fail, but no one understands why.

1953: Sir Peter Medawar of the University of London finds that animals exposed to foreign tissues while they're young — still embryos — don't reject them. Sir MacFarlane Burnet of Melbourne University postulates that the immune cells that patrol the bloodstream in search of foreign invaders somehow learn very early to accept whatever tissues are there, and only attack things that show up later. In 1960, the two scientists win a Nobel Prize for their discoveries.

1954: Surgeon Joseph Murray performs the world's first successful human organ transplant when he transfers a kidney from one identical twin to the other. Soon after, researchers develop the first generation of drugs that suppress the immune system and prevent organ rejection. Doctors begin using these drugs routinely to inhibit organ rejection in human-to-human kidney, liver, and heart transplants.

1963: After a lull of almost 40 years, physicians again try their hand at xenotransplantation. Dr. Keith Reemtsma, then at Tulane University, transplants more than a dozen kidneys from chimps to humans. One woman survives for nine months. Dr. Thomas Starzl, then at the University of Colorado,

lack one copy of the key gene involved in hyperacute rejection," says David Ayares, Ph.D., chief operating officer and VP of research at the U.S. division of PPL Therapeutics Plc., the company that gave the world Dolly the cloned sheep. The U.S. division of PPL is pursuing research focused on regenerative medicine, xenografts, and stem cells.

"By making pigs that lack this gene, their cells and organs are less likely to be rejected when transplanted into humans," Dr. Ayares says. "However, we can't mislead the public into thinking that this particular singular genetic strategy is the end all. Ending hyperacute rejection is just the tip of the iceberg — the first step in taking care of the very early rejection. We have to make sure people understand other issues, such as the delayed vascular rejection and virus transmission issues."

Early Attempts

Physicians and researchers have been trying to use animal parts in humans for centuries. In the past 40 years, patients have received bone marrow from baboons, kidneys from chimpanzees, baboons, and pigs, hearts from chimpanzees, and livers from baboons. In 1984, a widely publicized surgery attempted to transplant a baboon heart into an premature infant, who lived for three weeks before rejecting the organ. The first successful commercial efforts, however, will likely come in the form of transplanted cells and tissues from pigs into humans. Pigs have surpassed other animals and are now the "preferred" animal source, because they are easy to breed, and have organ sizes that are compatible with humans. Already, efforts are under way to study the transplantation of insulin-producing porcine islet cells for treating humans with diabetes. In addition, some research has begun using neuro cells from pigs in patients with Parkinson's disease.

Some small, but significant, progress has been made in these areas, but there is still much to be done. Huge problems need to be overcome, including rejection of the animal organ and tissues and disease transmission from animal to human. In fact, according to many in the field, clinical trials are not likely to advance to humans for at least three to five years.

Tracking Ethical Issues

Human clinical trials bring up the issue of informed consent, says Mark Fox, M.D., Ph.D., director of the program transplant ethics and policy at the University of Rochester Medical Center and chairman of the ethics committee at the United Network for Organ Sharing (UNOS).

"We certainly recognize the critical nature of the shortage of donor organs and there are a variety of avenues to try to increase

Milestones in XENOTRANSPLANTATION

1964

performs an additional six transplants using baboon kidneys. His patients survive from 19 to 98 days.

In one strange case, the kidneys taken from a chimp work — much too well. They produce 54 liters of urine in one day, compared with the modest two liters considered normal for humans. The patient suffers a stroke and dies of heart failure three days later. (The surgeons had transplanted both of the chimp's kidneys, which, they later say, "maybe we should not have done.")

1964: James Hardy of the University of Mississippi Medical Center attempts the first cardiac xenotransplant, using a heart from a chimp. The primate heart — too small to support the patient's circulation — functions for only two hours. Two other transplants, using pig hearts, fail due to hyperacute rejection.

Researchers studying animals are learning more about the causes of hyperacute rejection. They discover that human blood contains natural antibodies that can recognize cells from pigs, dogs, or other animals. When these antibodies encounter foreign tissue, they trigger a chain reaction that destroys the graft within hours.

1979: Christian Barnaard, the surgeon who performed the first successful human heart transplant, tries to use baboon and chimpanzee hearts as temporary backup pumps in two patients whose hearts don't function properly after cardiac surgery. The transplants do not help the patients survive.

1984: Baby Fae, an infant born prematurely with a malformed heart, receives a heart from a baboon. She lives for almost three weeks — longer than any other recipient of a heart xenotransplant — but then rejects the organ, due to a blood type incompatibility. Although it didn't save Baby Fae, cyclosporine — the granddaddy of immunosuppressive drugs — gains widespread use for human transplants. By the end of the 1980s, newer and more powerful immunosuppressive drugs, including FK506, come into vogue.

them," Dr. Fox says. "But as with any other kind of clinical-research effort, there are ethical issues and we have to be very careful about how to translate this into clinical application. We endorse continued investigation into xenotransplantation. But there are concerns particularly related to informed consent."

Dr. Fox says informed consent in clinical trials of animal organs and cells could be problematic. "I'm not sure that people who are sick or people who are in need of a transplant process information in quite the way that we lay it out. With xenotransplantation, part of the challenge of informed consent is that we do not have all of the information — we cannot be certain what the risks are, especially the potential infectious disease risks — so it calls for particular awareness and recognition of the need to safeguard patients' well being."

Another problem is that commercial interest in xenotransplantation is lagging. Some companies, for a variety of reasons, have even dropped out of this area of research. Dr. Ayares says this is related to two issues: controversy over genetically modified foods and the burst of the dot.com bubble.

"All the high-tech investments have taken a hit," he says. "Xenotransplantation and stem-cell research were hot buttons from a venture capital funding point of view three years ago. Now VC firms are putting money into companies with short-term product potentials, such as diagnostics or medical devices. In many cases, they are not making new investments at all and are just trying to prop up the few strong companies that are in their existing portfolios. That has affected long-term funding in technology areas such as xenotransplantation. There has to be a patient investor who is willing to wait six or seven years to reap the benefits."

In addition, the possible transmission of disease has led to ethical debates about whether the possible risk to the public is worth the effort. The Campaign for Responsible Transplantation, a coalition of doctors, scientists, and 90 public interest groups among others, believes that xenotransplantation poses a grave danger to human health because of the risk of transferring animal viruses to the human population. The coalition is committed to an outright ban on the procedure.

Liz Howard, an intellectual property partner with the law firm of Orrick, Herrington, & Sutcliffe LLP, decries the objections, "There is the knee-jerk Frankenstein reaction that xenotransplantation is not natural."

"The people most supportive of this research are those on waiting lists for human organs," Dr. Ayares says. "For some people there may be an 'ick' factor, but those who may be averse to putting pig organs into humans are healthy people, their view may be different if they were on a waiting list, dying, in hope of receiving a donor organ. All the physicians of the world actively welcome having an unlimited supply of organs. They don't want to lose patients who could be saved."

"Do we humans have the right to kill animals to use their

1992 1995 1997

1992: Xenotransplantation grabs headlines again when Dr. Starzl and his colleagues, now at the University of Pittsburgh Medical Center, perform a pair of baboon-liver transplants. One patient survives more than two months; the other, 26 days. Both die from post-operative infections that prove deadly because their immune systems are shut down by antirejection drugs. Dr. Starzl puts his xenotransplantation program on hold until the problems are better understood. Around the same time, researchers at Duke University receive permission to use a pig liver as a "bridge" to keep a critically ill woman alive as she waits for a human liver transplant. She survives only 32 hours.

Researchers at Massachusetts General Hospital discover that it's a particular sugar on the surface of pig cells that provokes the attack of the natural antibodies. If scientists can use genetic engineering to create pigs that no longer have this sugar on their cell surfaces, the animals' organs should be less irksome to the human immune system. Other researchers generate pigs that make proteins that can preemptively disable the very part of the immune system that would otherwise lay waste to the xenotransplant. Several biotechnology companies set out to make these "humanized" pigs and win approval for using pig organs in humans.

1995: Jeff Getty receives a baboon bone-marrow transplant, in hopes that the immune cells in the baboon's marrow will replace the immune cells that he has lost to the AIDS virus. The baboon cells — which are naturally resistant to HIV — only function for a brief time, but Mr. Getty remains healthy. Scientists continue to investigate how pretreating transplant recipients with marrow taken from donors might create a "chimeric" immune system that contains cells both animal and human. Such "preconditioning" might trick the body into accepting subsequent xenografts as not really foreign.

1997: Clinical studies suggest that transplants of isolated foreign cells may

organs?" asks Elliot Lebowitz Ph.D., CEO of BioTransplant Inc. "The answer that I would give is pragmatic. In the U.S. alone, 100 million pigs are slaughtered each year for food. To add another several thousand pigs that would be raised humanely and killed humanely in order to use their organs for saving human lives, I would say that society has answered that. There is a higher need to save a human life than to eat ham."

Critical Need

As is to be expected, research into animal-to-human transplantation is being driven by necessity. Although organ donations in the U.S. increased 7% in 2001 from 2000, according to a report issued by the Department of Health and Human Services in April 2002, this increase is not enough to address the needs of people waiting to receive organs. More than 79,000 people currently are awaiting an organ, according UNOS. Yet in 2000, less than 23,000 transplants were performed in the U.S., and everyday more than 15 people die while awaiting an organ.

Many experts say those waiting for an organ are just a small percentage in terms of potential demand. Estimates are that there are just as many people who need an organ transplant but don't make it onto the waiting lists because they are ineligible.

Additionally, researchers say there are many times more patients who have disorders that are caused by the functional loss of highly specialized cells, and who could benefit from the transplantation of animal cells and tissues. This includes about 17 million people in the U.S. who have diabetes; between 180,000 and 230,000 patients suffering from spinal cord injuries; 1 million to 1.5 million people with Parkinson's disease; 4.8 million people with congestive heart failure; and 25 million Americans with liver, bile duct, or gallbladder disease. The use of animal cells could be used to treat previously untreated or undertreated patients in these areas.

"The increase over the past year in the number of donors mostly has been realized from living kidney and liver donors," Dr. Fox says. "But living donation raises other concerns. A liver donor in New York died recently. That gives us pause. Are we being overly aggressive? There certainly are people in the transplant community that say this isn't without its cost and let's be careful."

However, there always will be a finite number of cadaveric organs available, he adds. An increased focus on safety in society, as well as an aging population where older people may die with other diseases, means not all available organs can be used.

"Xenotransplantation is an elegant idea to address the supply shortage of organs and tissues for transplantation," says Matt Kaplan, a biotechnology analyst, with Punk Ziegel & Co., an

Milestones in XENOTRANSPLANTATION

1997

fare better than whole organs. In 1997, researchers report on the first clinical trial using nerve cells from fetal pigs to treat a dozen patients with Parkinson's disease. The patients show marked clinical improvement.

Other researchers try wrapping animal cells in a capsule that prevents immune cells from getting at them.

1997: PPL Therapeutics Plc. and Ian Wilmut of the Roslin Institute for the first time successfully clone a sheep, named Dolly, using genetic material from a 6-year-old ewe. In 1999, researchers discover that cells in Dolly's body appear to be aging at the same rate as the 6-year-old ewe. In 2002, Dolly is discovered to be suffering from arthritis. This discovery renews debates about whether cloning resulted in premature aging. Nonetheless, Dolly opens the way for further advancements in xenotransplantation by enabling experiments with cloning pigs that don't have the gene responsible for rejection.

2001

2001: PPL and Immerge BioTherapeutics, successfully "knock out" one of the specific genes in the pig that produce an enzyme responsible for making a sugar molecule, called alpha-1,3-galactosyltransferase, which leads to hyperacute rejection. The hyperacute rejection response occurs when human antibodies attach to sugar molecules on the surface of the transplanted pig organ's cells. Once they attach, human antibodies kill the cells, destroying the organ within minutes.

2002

2002: Immerge identifies a miniature swine that failed to produce porcine endogenous retrovirus (PERV), which has been shown to infect human cells in laboratory tests. Researchers are uncertain of what, if any, illnesses the porcine virus could lead to if it infects human cells. So they are working to identify pigs that have a nontransmitting form of PERV.

Source: Office of Science Education, National Institutes of Health, Bethesda, Md.

investment banking company. "But there is more work that needs to be done. It's a very risky area. In addition, there is a huge potential market for other serious unmet medical needs."

In fact, some estimates indicate that the market for solid organs alone could be valued at more than $5 billion, and $6 billion for cellular therapies for diabetes, Parkinson's disease, and Alzheimer's disease.

"There is a general thought that it would be easier to control the immunological response in a cell than in an organ," Dr. Greenstein says. "We may see more clinical trials in this area for Parkinson's disease, diabetes, stroke, and spinal cord using pig-cell transplants."

Xenotransplantation research, she says, is a positive for the pharmaceutical and biotechnology industries.

"The future of transplantation biology requires better and more specific ways to inhibit the immune response," Dr. Greenstein says. "Pharmaceutical companies that are dedicated to immunosuppressive drug development have looked at xenotransplantation as a possible source of revenue because patients may need to use immunosuppressive drugs. A few of the large pharma companies have become dedicated to the xenotransplantation marketplace."

JULIA GREENSTEIN, PH.D.

Xenotransplantation has been an area, unfortunately, that has made some short-term promises that haven't come to fruition.

Learning From History

Over the past century, doctors have tried to use organs from pigs, goats, lambs, monkeys, and even rabbits in human transplants. All the grafts failed, but no one really understood why. In the 1950s, researchers Sir Peter Medawar of the University of London and Sir MacFarlane Burnet of Melbourne University theorized that the immune cells patrol the bloodstream in search of foreign invaders. In their research, they discovered that animals exposed to foreign tissues while young don't reject those tissues.

But it wasn't until 1992 when researchers at the Massachusetts General Hospital discovered that it is a particular sugar on the surface of pig cells and other animals that provokes the immune system's attack on the organ.

It would be five more years, however, before attempts to genetically engineer pigs became technically possible. In 1997, PPL Therapeutics and Ian Wilmut of the Edinburgh-based Roslin Institute successfully cloned a sheep from adult mammal cells. The sheep, named Dolly, was created using genetic material from a 6-year-old ewe. This opened the way for further advancements in xenotransplantation by enabling researchers to experiment with cloning pigs that don't have the sugar gene that triggers rejection by the recipient's immune system. There also are efforts to "humanize" pigs to make proteins that can preemptively disable the recipient's immune system to destroy the organ.

Pigs are now the preferred species for xenotransplantation, although early research studied the use of organs from baboons and chimpanzees.

"The pig is picked for its size," says Robert Mendez, M.D., chairman and co-founder of the National Institute of Transplantation at St. Vincent Medical Center in Los Angeles. "The pig can be grown for whatever size the human organ is. Size, especially of the heart, lung, and liver, is very important. Baboons and chimpanzees have smaller organs."

Dr. Mendez, a kidney transplant surgeon, is a member of the National Institutes of Health's advisory committee on xenotransplantation. The committee advises the secretary of the U.S. Department of Health and Human Services on issues related to xenotransplantation.

The pig, Dr. Mendez says, has a much shorter gestational period of life and also grows to adulthood much more rapidly than primates.

"And from a biogenetic standpoint, though the pig is much more disparate than primates, this may be good in terms of our general natural immunity to the viruses that the pig may have," he says. "Primates may have organisms that could be easily transferable to humans, like the AIDS virus was."

Researchers are working to address safety concerns about using animal cells and organs. Immerge has identified a miniature swine that failed to produce porcine endogenous retrovirus (PERV) that can infect human cells in laboratory tests.

"Every species has viruses that are specific to itself that don't cause disease — we have them, pigs have them, monkeys have them," Dr. Greenstein says. "In general, there has been no disease associated with endogenous retroviruses. They became part of the genome millions of years ago, and they are brought along in the DNA."

Researchers, however, are uncertain what, if any, illnesses the porcine virus could cause if it infects human cells. So they are erring on the side of caution and working to identify pigs that have a nontransmitting form of PERV.

"We need to understand if there is any risk of the porcine endogenous virus getting activated post transplant and infecting the human recipient," Dr. Greenstein says. "Then we need to determine whether there is a possibility that the recipient could pass a virus onto somebody else."

The pig also is a better choice from an ethical, and socially acceptable standpoint, Dr. Mendez says. "We slaughter thousands of pigs daily for consumption purposes. So there really isn't an ethical problem about using them for organs for humans. It would be very unethical to use primates that may be an endangered species for our own purposes."

Unlimited Patent Protection, Potentially

In addition to providing a theoretically unlimited supply of organs and tissues for transplantation, xenotransplantation methods would offer broad patent protection to the innovator companies.


BILL ANTHONY

There are probably a dozen or more ways to patent xeno-transplantation.

"There are probably a dozen or more ways to patent xenotransplantation," says Bill Anthony, an intellectual property partner with the law firm of Orrick, Herrington, & Sutcliffe LLP. "That web of patents gives strength to the patent portfolio. So xenotransplantation will be a formidable weapon and is stronger than what is seen in other fields."

Liz Howard, also an intellectual property partner at Orrick, Herrington & Sutcliffe, contends that a genetically engineered life form or the method to create that life form can be patented.

"A genetically altered mouse was patented in the late 1980s," Ms. Howard says. "This was the first example of a higher organism to be patented. Genetically altered yeast was patented decades ago. And methods for generating these organisms also can be patented. But it is important to remember that what is patented is the 'thing' itself, and it's not specific to an individual. For example, the gene erythropoietin is patented. But that doesn't mean that my personal erythropoietin is patented."


LIZ HOWARD

The first example of a higher organism to be patented was a genetically altered mouse in the late 1980s.

Mr. Anthony says this broad protection is a positive for the industry. "Patents do not diminish the expenditures or the efforts to do research and development. Even though a patent may close a particular product or method, this becomes an inducement for other companies to design around the innovator method. If other companies want to enter the marketplace, they're going to have to do it differently. Designing around patents is good, because it creates competition and innovation. Sometimes, in the effort to design around a patented process, a better product or a cheaper product is created."

A Knock-Out Discovery

Controlling the human immune response to transplanted animal organs is one of the biggest challenges for researchers. The aggressive (hyperacute) rejection response occurs when human antibodies attach to sugar molecules on the surface of the transplanted pig organ's cells. Once these antibodies attach, human antibodies kill the cells, destroying the organ sometimes within minutes.

At least two companies, PPL and Immerge, are attempting to "knock out" the specific gene in the pig that produces the enzyme responsible for making this sugar molecule, called alpha-1,3-galactosyltransferase (GGTA1). Further complicating research is that the gene is present in two copies. Both companies have made progress in knocking out one of the genes that express the GGTA1 sugar.

PPL and Immerge made separate announcements in January 2002 that they had successfully cloned pigs that did not have one copy of the sugar gene. Immerge's research, done in conjunction with the University of Missouri-Columbia, produced miniature swine pigs born in September and October 2001. PPL's piglets were born on Christmas day 2001 at the company's U.S. subsidiary in Blacksburg, Va.

This work only really became possible after cloning technology became practical in 1997, Dr. Greenstein says.

"What everyone involved in xenotransplantation research has tried to do is to block the activity of that antibody," she says. "One way is to remove the antibody from the circulation, making transgenic pigs that perhaps could inhibit the effector function. What happened was that over time when the transplanted organ was put into an experimental model antibody, reactivity always caused the rejection of the organ."

Immerge is continuing its research to knock out the second copy of the GGTA1 sugar gene. Dr. Greenstein says the company is considering two avenues: either breeding the newly cloned pigs or doing subsequent genetic modification.

"One is easier and takes longer; one is more risky but would be faster," Dr. Greenstein says. "Until we knock out both genes, there is no change in the expression of the sugar."

Dr. Greenstein anticipates human clinical trials of organs from the cloned pigs within three to five years. She says the company's researchers will have a pig with both genes knocked out within a year and a half. Subsequent preclinical research could last two years. The company's primary models are in using kidneys and hearts for transplantation, and Dr. Greenstein says the company is beginning a program to transplant porcine islet cells for use in treating diabetes.

Piggy Banks

Officials from PPL say they have 100 large white pigs — 40 female and 60 male — that have one copy of the sugar gene knocked out. Their plan is to breed these pigs to have litters where both copies of the gene are knocked out, which would be the target animal for preclinical work.

"As far as cloned knockout pigs go, the females have one normal copy and one mutated copy," Dr. Ayares says. "The males are the same. So genetics tells us that by breeding those two together, 25% of the animals that are born will have both of the alpha gal gene

deleted. We anticipate having the first of the animals in the first quarter of 2003."

He says subsequent plans involve using cells and organs from these pigs for transplantation into primates to show that cells and organs can be tolerated long term without rejection.

"The primate trials will take at least a year and we hope to be able to go to the FDA around the end of 2004 to see what the conditions are for human trials," Dr. Ayares says. "Most likely the first product will be insulin-producing cells from the pancreas of these pigs."

PPL also is continuing work to add genes to its pigs to "humanize" these organs. PPL already has a number of these genes isolated.

"These are human genes that will be added to cloned pigs," Dr. Ayares says. "We have proof of concept in small animals and we are just now introducing them into the pig. We need to have additional genetic manipulation to address issues beyond this hyperacute rejection. We have long-term strategies to deal with vascular rejection and T cell mediated chronic rejection as well." Results are expected within one to two years, he adds.

"Because we are activating the rejection response, there is an inflammatory response that's caused by up-regulation or by the turning on of adhesion molecules," he continues. "We have strategies for down modulating the expression of those pig adhesion molecules. In addition, in the xenografts, when they are put into humans or put into a xenospecies, there is a loss of anticoagulants from the surface, so we're going also to be adding human anticoagulant genes. Now we'll have human anticoagulant genes that are expressed on the surface. This will prevent the organ from being choked off by the coagulation cascade."

Another company, Nextran, a subsidiary of Baxter Healthcare Corp., also has conducted preliminary research in the area of xenotransplantation in collaboration with the Mayo Clinic. Last year, Nextran concluded a Phase I clinical trial that used transgenic pig livers as an *ex vivo* support system for patients with acute liver failure. The pig liver was used to bridge the gap between organ failure and obtaining an appropriate human liver for transplantation in these patients.

A Baxter spokeswoman, however, says the company does not plan to pursue Phase II trials and has no plans to license the technology. The company's objective is focused on solid organ transplantation. Preclinical work continues in this area, but the company would not comment on the specific projects.

Another company pursuing xenotransplants is Alexion Pharmaceuticals Inc., which is pursuing preclinical research in nonhuman cell, tissue, and organ transplants into humans, with an initial focus on spinal-cord injuries and Parkinson's disease. Alexion has developed transgenic pigs with cells and tissues that display substantially reduced levels of reactive-sugar-like markers,

while also featuring a protective human complement-inhibiting protein, which causes inflammation. The two modifications on the surface of the animal cells could help to reduce hyperacute rejection.

The company's program for spinal-cord injuries, UniGraft-SCI, is a product candidate that consists of transgenically engineered pig cells. Preliminary results from preclinical work indicate that process cells, immunoprotected with the UniGraft technology, transplanted into a primate model of spinal-cord injury resulted in successful engraftment and restored a normal myelin covering of the damaged nerve fibers. Additional preclinical work continues.

Alexion also is pursuing UniGraft-PD, a product candidate that consists of transgenically engineered pig cells that, after transplant into an animal with Parkinson's lesions, have been demonstrated to restore brain function. Preliminary preclinical studies indicate that transplantation of porcine neurons, immunoprotected with the UniGraft technology, into a primate model of Parkinson's disease resulted in successful engraftment and restored dopamine production locally and selectively in the affected part of the primate's brain.

Parkinson's disease is a challenging indication to pursue. Objective clinical endpoints in central nervous system programs are difficult to measure. Research partners Genzyme General and partner Diacrin Inc. announced in 2001 that a Phase II clinical trial of NeuroCell-PD, which is derived from porcine fetal neural cells, for the treatment of patients with Parkinson's disease failed to reach primary endpoint. A Genzyme spokesman says this research is not being pursued further.

Diacrin is continuing with other research with porcine cells. The company has initiated a six-patient, Phase I clinical trial using porcine liver cells for the treatment of acute liver failure. The company believes liver-cell transplantation could become a viable alternative to whole-liver transplantation for the treatment of acute liver disease. Porcine liver cells will be infused into the spleen or liver of these critically ill patients by minimally invasive procedures, thus avoiding a surgical procedure. In addition to the high level of quality control that can be maintained over the production of porcine liver cells, these cells also have the advantage of being resistant to infection by human hepatitis B and C viruses. Since a majority of the patients enrolled in this study are likely to carry these viruses, the resistance of the porcine liver cells to infection may provide an advantage over human liver transplantation in which hepatitis B and C reinfect donor livers. As of March 15, 2002, one patient had been treated. Diacrin is recruiting patients for this clinical trial.

Diacrin also is working with the FDA to obtain clearance to continue recruiting patients in Boston for a Phase I clinical trial using porcine fetal neural cells in stroke patients. In April 2000, the trial, which was being conducted with Beth Israel Deaconess Medical Center and Brigham and Women's Hospital, was suspended by the FDA to allow investigation of the cause of two serious adverse events. At the time the trial was suspended the company had treated five patients. Both patients who suffered adverse events have recovered. After a review, it appears these events were most likely associated with the surgical procedure used to implant the cells.

In an animal model of stroke, the company has shown that transplanted porcine fetal neural cells survive at high frequency. These cells not only survived in the brain cavity, but formed solid grafts that integrated appropriately with the normal brain tissue surrounding the cavity. Diacrin researchers have observed extensive neural outgrowth from the graft to the surrounding brain and behavioral improvements in a rat model of stroke after transplantation of porcine fetal neural cells. The transplanted cells have the capacity to form billions of new synaptic connections as well as to release other chemicals that promote neural cell growth. ✦

PharmaVoice welcomes comments about this article. E-mail us at feedback@pharmalinx.com.

Experts on this topic

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