Xenografts Raise Questions About Cancer Virus Transfer to Humans

When surgeons replaced the defective heart of “Baby Fae” with a baboon heart in 1984, the 15-day-old infant rejected the graft and died in less than three weeks. In spite of that, interest in cross-species transplants or xenotransplants has since grown, partly because of advances in rejection control. But the interest has also been driven by an ever-worsening shortage of human donor organs for a growing number of transplant candidates.

Pigs, rather than baboons or other non-human primates are the preferred animal donors. They have more young, mature faster, are cheaper to raise, and their organs are of the right size and physiologically similar to their human counterparts.

However, recent studies have shown that two viruses that lurk in pig organs — porcine endogenous retroviruses A and B — can jump the species barrier when hog cells are mixed with human cells in the laboratory. And although these viruses are apparently harmless to pigs, they are sufficiently similar to viruses that cause leukemia in some animals (cats, mice, and gibbons, for instance) to stir fears that swine xenografts may confer a greater than usual risk of cancer to human recipients.

Another concern is that people who come into close contact with xenograft recipients may also be at risk for infection. In October, therefore, the Food and Drug Administration put on hold all clinical trials — either already started or about to — that involve live porcine tissue.

The agency then recruited an advisory panel (soon to be renamed, but now called the Xenotransplantation Advisory Subcommittee of the FDA’s Biological Response Modifiers Advisory Committee) and asked its members to a Dec. 17 meeting to help the agency consider how to proceed. The meeting vividly illustrated the difficulties of balancing the potential benefits and potential risks of a new therapy when there is little hard data on either.

Worrisome Viruses

Underlying the concern is the knowledge that the worrisome viruses are embedded in porcine DNA and thus pass from generation to generation of swine via their eggs and sperm. As John Coffin, Ph.D., of Tufts University in Boston and the National Cancer Institute — a member of the FDA advisory panel — has explained it, “these viruses became part of the pig genome 50,000 years ago and, perhaps, even earlier. Whenever it was, they have been there ever since.

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New Assays

Still, efforts are under way to narrow the information gap. Some assays have already been developed to better detect the porcine viruses and to better characterize their structure and behavior, and still better ones can be expected as scientists at the FDA and the Centers for Disease Control and Prevention in Atlanta — among others — home in on the problem. A test for antibodies to the virus, for example, has been badly needed and was reported at the meeting to be imminent.

Similarly, Corinne Savill, Ph.D., chief operating officer and a scientist at Imutran, a London-based subsidiary of Novartis Pharma, that hopes to market pig organs for transplantation — assured the advisory panel that the company is rigorously monitoring and testing non-human primates that have had swine xenografts implanted as part of the firm’s preclinical studies. Indeed, following the report that two swine retroviruses can infect human cell lines, Imutran scientists discovered there may be a third.

Then, too, several hundred people (the exact number is unknown) have received living materials from pigs, including some diabetics who have been given porcine pancreatic islet cells. Among the other recipients are patients who have had brain implants of fetal swine neurons as potential therapy for Huntington’s Disease or Parkinson’s Disease. In January, in fact — after the FDA partially lifted its hold on the clinical trials — a middle-aged man with intractable epilepsy also had fetal swine neurons implanted.

There have, besides, been patients whose blood plasma has been run through a machine similar to a kidney dialysis machine — which relies on swine hepatocytes (liver cells) to combat acute liver failure (with the intent to allow the liver time to recover on its own or to tide the patient over until a donor liver becomes available). And there has also been at least one attempt — albeit unsuccessful — to use a pig heart to tide a patient over until a suitable human heart could be found.

Clinical Experience

“We expect that systematic follow-up of many of these patients will teach us a lot,” said Hugh Auchincloss, M.D., the FDA panel’s chair who is a transplant surgeon and an associate professor at the Harvard Medical School in Boston, Mass. “And there may be other sources of information, too: people who have had extensive burns that were temporarily covered with pig skin, for instance, and abattoir workers whose jobs expose them to hog carcasses and body fluids.”

(The porcine insulin used by diabetics does not harbor retroviruses. Nor do the swine heart valves often used to replace damaged human heart valves. In both cases, their preparation renders them free of potential pathogens.)

Encouraging as all this is, however, it will do little to resolve a list of other issues the FDA must settle if, as seems likely, it soon decides to further ease restrictions on clinical trials on xenotransplantation. At the top of this list, as discussed by the panel, are decisions about informed consent.

Should informed consent be required only of swine xenograft recipients, or also of their immediate families or other household contacts? And if so, what should these people be told? For example, recipients must agree to refrain from blood donation and continue research followup for the rest of their lives. Would people in close contact to them also have to agree to these measures?

“Again, there are no easy answers,” said Auchincloss in a later interview. “Nonetheless, some of my fellow panelists know far more than I do about retroviruses. From what they say, a cautious approach that allows a small number of pig xenotransplants to be performed with careful monitoring will be a responsible way to proceed.”

— Judith Randal

This is the first of two articles on xenotransplantation. The second will focus on a conference held at the National Institutes of Health where the public policy issues of xenotransplantation were more broadly explored.