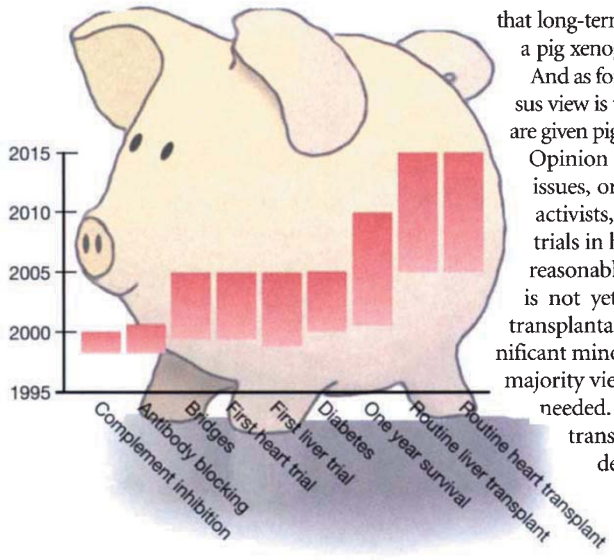
whelming choice of donor animal. There is less optimism that porcine grafts will actually work in humans. A small but significant minority believes that organs from the baboon or some other nonhuman primate will be used in xenotransplantation.

Genetic engineering is seen, almost universally, as vital to clinical xenotransplantation. Most attention has focused on transgenic pigs expressing human complement inhibitors, such as decay-accelerating factor (DAF) or membrane cofactor protein, and ultimately, animals carrying multiple transgenes may be necessary. A greater understanding of the immunological and inflammatory mechanisms underlying xenograft rejection is also seen as important. Chronic rejection is also thought likely to be a significant problem.

Preclinical developments that would counter the problems are relatively close at hand, say the study's respondents: Agents that block complement effectively are likely to be developed by the end of 1999, while those that remove or block graft-directed antibodies are expected the following year.

That paves the way for clinical development. But, according to the survey, trials of pig-liver xenografts and heart transplants are unlikely to begin until 2002. At roughly the same time, xenografts are likely to be in clinical use as "bridges"—keeping patients alive until a human organ becomes available. The study predicts that pig tissue (pancreatic islet cells) will begin to be used to treat human insulin-dependent diabetes toward the end of 2003. But it is not until 2005 that long-term survival (more than a year) of a pig xenograft is expected to be realizable.



Xenographs. The likely timing of preclinical and clinical milestones for animal to human transplants. Bars represent the upper and lower quartiles of the range of dates for each advance, as predicted by those in the field.

And as for routine clinical use, the consensus view is that it will be 2010 before people are given pig organs on a regular basis.

Opinion is divided over whether ethical issues, or a backlash from animal rights activists, will delay the start of clinical trials in humans. Interestingly, there is a reasonably clear consensus that the time is not yet right to begin clinical xenotransplantation programs, although a significant minority is keen to push ahead: The majority view is that more basic research is needed. Whether the costs of xenotransplantation programs will hinder their introduction is unclear, although the weight of opinion is slightly against the idea.

Generally, commercial organizations are seen in a positive light. Biotechnology and pharmaceutical companies are considered likely to be important in the move from laboratory to clinic. There is, however, a belief that competitive pressures and the desire to patent findings may be a negative factor.

Ian Jones

Ian Jones is a freelance writer in London specializing in xenotransplantation.

*The 1995 Xenotransplantation Foresight Study is available from *Xeno* (Editor-in-Chief, Fritz H. Bach), PO Box 2491, Bishop's Stortford, Herts, CM23 3AE, UK.

Heliosynthese takes on Martek infant formula market

Before the end of 1996, a French algal biotechnology company, armed with a curious patent, will challenge a more-established US counterpart in the infant-formula supplements market. The company, Heliosynthese, based in Aix en Provence, plans to use its intellectual property position to persuade major European formula companies to switch from their existing sources of docosahexaenoic acid (DHA) and arachidonic acid (ARA)—fish oil, frequently—to the company's own algal-based supply. Its rival, Martek (Columbia, MD) has already shown that a market for algal products exists. During 1994 and 1995, the US company licensed Formulaid (a combination of DHA and ARA) to several major companies, including Nutricia (Zoetermeer, the Netherlands), the Bristol-Myers Squibb subsidiary, Mead Johnson (Evansville, IN), American Home Products (New York) Sandoz Nutrition (Basel, Switzerland), and Maabarot Products (Israel). Martek's chairman and CEO, Henry Lisert, estimates that Martek's licensees provide access to 42–43% of the $250 million world formula market.

DHA and ARA, both polyunsaturated fatty acids, appear to be important for neurological development in fetuses and newborn infants. Nutricia was the first of Martek's licensees to market, launching its infant formula in Belgium in December 1994; it received approval to sell the product in the Netherlands in April 1995.

Ironically, it is these European markets of Martek's that the Heliosynthese patent threatens. "Martek is clearing the route for us," said Heliosynthese chairman and CEO, Patrick Rousseau. "They have made algal technology credible." The intellectual property in question, however, does not concern the production method. It started life as a French patent (#255361), granted to a company called Bio Extraction, and described a process for extracting polyunsaturated fatty acids (PUFAs) from human placentas. Importantly, the patent also claimed the use of the PUFAs as nutritional supplements in milk formulas for newborn babies and infants. The patent was extended to apply in Belgium, Great Britain, Germany, Italy, the Netherlands, and Sweden, too, before it was acquired by Imedex (Lyon, France), part of Pasteur Mérieux Sérums et Vaccins. Finally, at the beginning of 1996, by virtue of an asset swap, the PUFA patent passed to Heliosynthese, while Imedex became an shareholder in Heliosynthese.

Rousseau plans to begin negotiations with major companies in the nutrition markets—Nestlé (Geneva, Switzerland), Hoffmann-La Roche (Basel, Switzerland), and Nutricia. "The patents have been checked by several patent attorneys and by some potential commercial users," says Rousseau. "We now believe that this patent covers this use [as a nutritional supplement], whatever the source of the fatty acids."

At this stage, though, Lisert is not concerned about Heliosynthese. He believes that Martek's production system will, in any case, provide economic advantages that the formula companies will not be able to ignore. "The algae we work with is a primary producer of DHA. Efficiency-wise, [it is] by far the best producer."

Both companies use heterotrophic algal production systems for their PUFA products: The microscopic plants do not photosynthesize but, instead, gain energy and carbon from substrates in the nutrient media. Heliosynthese's weakness may be that its production system is less well tried. But its patent may compensate for that.

John Hodgson