change the pig—not the patient," says Cambridge's White, co-founder of the Sandoz-sponsored xenotransplant company Imutran. White and his co-workers have genetically engineered pigs so that their cells carry human DAF on their surfaces and found that the transgenic pig's heart continues beating for up to 4 hours while being perfused with human blood—a dramatic improvement over the unmodified pig heart, which dies within minutes.

Platt's team, working with researchers at Nextran, a Princeton, New Jersey, biotechnology company, whose major stockholder is Baxter Healthcare Corp., has also created several families of transgenic pigs that express various combinations of DAF, MCP, and CD59. One of the earlier pig lines expressed the proteins only at low levels. Nonetheless, when researchers transplanted hearts from these pigs into three baboons (whose complement response is similar to that of humans), the hearts continued beating for between 4 and 30 hours.

Subsequently Nextran and the Platt team have honed their transgenic approach, says Nextran's vice president of research, John Logan, and next year they will test a new strain of pig that permanently expresses complement inhibitors in the hopes that transplanted hearts from these animals will survive much longer in primates. Despite the hope they offer, genetically engineered pigs alone are "not going to make xenotransplantation suddenly possible," says Logan. "This is going to be just one in a series of steps."

And, most researchers agree, 1995 will be the pivotal year for deciding how rapidly the next steps can taken. They hope that by using the transgenic pigs they will be able to see what can be achieved by blocking the hyperacute rejection. Among the questions to be answered are: Will pig organs function in a human body? Will genetically engineered pig organs be subject to an acute vascular and cellular rejection that will prove more difficult to handle than those triggered by human organs? And will they be subject to the little-understood chronic rejection that, even in the face of apparently adequate immunosuppression, strikes human organs years after transplantation?

Even if those key scientific questions can be answered, there's one more potential barrier to success. "The fear is," says Platt, that some transplant surgeons "will be cavalier in their approach ... and cast a shadow over the whole field"—just as the Baby Fae episode did. That's where the IOM report could help, as its new committee plans to highlight the ethical issues associated with xenotransplantation. IOM's Valerie Setlow argues that these issues should be considered now, because, she says, when it comes to xenografts, the main question is "not if, but when."

**–Rachel Nowak**

INDUSTRY COLLABORATIONS

# Networking Gene Therapy

If you think about the most successful technology-based companies of the 1970s and '80s, the name Microsoft inevitably comes to mind. By meshing the disparate technologies of personal computing, Bill Gates made that company a runaway success. Now the U.S.–French pharmaceutical company Rhône-Poulenc Rorer (RPR) says it will try to emulate this approach for one of the key emerging technologies of the 1990s: cellular and genetic therapies. This week RPR announced that it has set up a network of 14 partnerships with labs and companies in these fields; the company will spend at least $100 million per year over the next several years supporting their research.

RPR's announcement follows similar initiatives by other major pharmaceutical companies—including SmithKline Beecham, Glaxo, Roche, and Eli Lilly—to join forces with academia and start-up biotechnology companies in tackling gene-based research. But the new network is unique in bringing together so many groups with a focus on gene therapy, which remains an unknown quantity commercially.

Various groups around the world are attempting trials of gene therapies for cystic fibrosis, but RPR is the first company to launch such an aggressive attack on more common diseases—its targets are cancer, atherosclerosis, and central nervous system disorders such as Alzheimer's disease. "All of [RPR's] incremental research and development [spending] has gone on gene therapy [and related biotechnologies]," says pharmaceuticals analyst Ian Smith of Lehman Brothers stockbrokerage in London. "They've basically taken a bet with themselves that this is the way ... to carve out a leading-edge position in gene therapy. It takes courage to do what they're doing."

RPR has risked a big stake on that bet: By the end of the year the company will have plowed $300 million into setting up the network, which will be focused around a new division of the company, RPR Gencell, with headquarters in Collegeville, Pennsylvania, and a staff of 150. The range of problems to be tackled is unprecedented: Partners in the network are studying the roots of diseases, characterizing the gene or genes involved, and going back to treat the diseases with gene-based therapies.

The company has also opted to form a loose federation of partnerships, rather than taking over companies or labs. So far, all the partners are based in France or the United States, homes of RPR's two headquarters. The researchers receive an injection of cash and placement of RPR staff or funds for staff and technicians, followed by later milestone payments depending on performance; in return they sign over to RPR equity, rights on specific projects, and first right of refusal or negotiation over products arising from the joint effort. "We want to split the responsibility, let academic researchers do what they do best—get proof of the principles—then make the connections [with industrial expertise]," says Jean-Bernard Le Pecq of RPR Gencell.

Such a flexible arrangement is more attractive than a series of mergers, argues David Nance, president of Introgen Therapeutics, a network partner, because "sometimes a big company can take over a small biotech company and all the things that were exciting and desirable about the small company seem to dissolve." The 14 partnerships agreed to so far will not be the whole story, says Le Pecq, because RPR will seek new collaborations "any time some team in the world find a new principle."

Scientists involved are enthusiastic about the network. The work is "collaborative ... it's not limited to funding, but it's an exchange of information," says virologist Jean-Michel Heard of the Pasteur Institute in Paris. RPR funds two scientists from Heard's team of 12 working on ways to replace the protein that is missing in lysosomal storage disease. This condition is the result of a defect in one gene, so reinserting the functional gene would result in re-expression of the protein. But it would be impossible to deliver the DNA to the relevant cells in all the affected tissues—liver, spleen, bone, and joints. Instead, Heard's team aims to insert the gene into other cell types, such as fibroblasts or muscle cells, so that they express the missing enzyme and secrete it into the serum, from where diseased cells can absorb it. RPR is interested in how this technology could be used to deliver proteins that alter the metabolism of cholesterol into the serum constantly, helping to clear lipoproteins from the blood.

It isn't only those involved in the network who tout its benefits. Outsiders agree that loose federations may be the way to go in large collaborations involving academic labs and companies. Dinko Valerio, the head of IntroGene, a small biotech company in Rijswijk, the Netherlands, working on gene transfer in precursor blood cells, believes "the organization of such a large network could be difficult ... [but considering] all the different technologies and know-how that have to be combined in order to get gene therapy to work ... it sounds like it's the right thing to do."

**–Claire O'Brien**

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