TISSUE CULTURE

STORM BUILDS OVER FETAL CELL TRANSPLANTS

NEW YORK—Stepping boldly into an arena where few dare to tread, Hana Biologics (Alameda, CA) is developing methods to propagate human fetal tissue for transplanting into patients suffering from intractable diseases such as type I diabetes and Parkinson's. The company, whose main business of making tissue culture media has kept it invisible to the public eye, now sits firmly in the middle of one of today's most controversial issues—whether it is right, moral, or ethical to use human fetal tissue for *any* purpose.

Fetal tissue transplants have, in fact, been occurring for a number of years. Denise Gilbert, an analyst at Montgomery Securities (San Francisco, CA), estimates that, since 1985, about 60 transplants of unmodified fetal pancreatic tissue have occurred in the United States, with another 40 in China. Why fetal tissue, when it seems that adult donor pancreases would suffice? For one thing, adult tissue is subject to immunorejection, a major problem. Of the 150 pancreas transplants performed in 1984, for example, only 30 percent were successful—and then only because the recipients were taking immunosuppressive drugs. Moreover, adult pancreases are in short supply: in 1984, only 3,000 were available. That same year, 10,000 new cases of type I diabetes were reported.

Fetal tissue is not that abundant, either, and the pancreatic islet progenitor cells make up only a small percentage of the total. According to H. Fred Voss, Hana's vice president of R&D, of the eight million cells in the fetal pancreas, about half are fibroblasts. Of the remainder, 10–15 percent are recoverable when the pancreas is processed by standard procedures. Voss says it is unclear how many of these "conventional" donor organs are necessary for one transplant. The Chinese have used 10–20 per patient; others get good results with 2–4. He claims that, with Hana's technology—which expands progenitor islet cells in tissue culture—40 times as many patients can be treated than by "conventional" fetal tissue transplants.

Hana's scientists, according to Voss, have developed a combination of methods to isolate a population of islet precursor cells. Under the correct culture conditions, the cells proliferate, a situation that is monitored by counting nuclei. Peter Brown, now at Chiron (Emeryville, CA), warns that the means by which cellular proliferation is measured are critical. Brown's experiences with growing human fetal islets stem from his days at Bio-Response (Hayward, CA); he found that expanding such cultures was no easy task.

What was apparent, according to Brown, was that beta cells—the subpopulation that actually synthesizes insulin—are not enough: cell-cell contact seems to play a critical role. Hana scientists must agree: they mix the proliferated, harvested cells with specific proteins, including those of the extracellular matrix, which maintains islet architecture. The mixture contracts, says Voss, reconfiguring the cells into a three-dimensional structure that approaches tissue density. The cells are not encapsulated: they are "totally exposed," he explains, "to become part of the recipient's tissue." The precursor cells do not differentiate until after transplantation—islets form in 90–120 days in nude mice; in humans, it takes from 6–12 months, Voss says.

Hana entered clinical trials in August 1987. The Phase I studies involved 23 immunosuppressed diabetics. Surgeons transplanted the fetal cells either during kidney transplant or 6–9 months later. The safety trials are complete; Voss predicts that Phase II efficacy studies should commence by fall.

Hana's Parkinson's disease research program is much less advanced. Nonetheless, Voss claims that researchers have already been able to reverse Parkinson's symptoms in rats, using fetal pig or rat neural tissue; the next step is to test human neural cells in rats and monkeys. There is some precedent here, as well: Gilbert says that other research groups have reversed chemically induced Parkinson's in monkeys by using fetal tissue.

Hana's intent is to propagate developing neural tissue from the substantia nigra lineage. These brain cells produce dopamine, the chemical that is lacking in Parkinson's disease. So far, says Voss, some of the neural cultures—which are a complex mix of cell types—have expanded 100–fold.

"The challenge [in culturing neural tissue] is to know what cells are actually growing," according to Barbara Cordell, vice president of research in California Biotechnology's (Mountain View, CA) neurobiology program. Neuronal cells are an especially difficult target, she adds, because the population is complex and no specific tools exist to fish out the subpopulation of interest. "And," she concludes, "if one is to make a business out of this, the process must be reproducible."

Making a business out of this is exactly the point that has turned the issue into an ethical battlefield. Right-to-Lifers are not the only group to argue that using fetal tissue not only condones abortions, it actually encourages them. Arthur Caplan, director of the Center for Biomedical Ethics at the University of Minnesota (Minneapolis), believes that the only way around this problem is to place fetal tissue under the aegis of the Organ Transplant Act, thereby preventing any incentive for compensation and maintaining the anonymity of the tissue's source and destination.

Jeremy Rifkin (Foundation on Economic Trends, Washington, D.C.) couldn't agree more. Rifkin, always in the thick of things, has petitioned Health and Human Services to include fetal tissue under the Act. In fact, he has requested a specific provision that "any biotechnology process conducted on these fetal parts does not alter their noncommercial status."

—Jennifer Van Brunt

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Top: **Pre-islet cells, isolated from donor tissue.** ***Bottom:*** **Pre-islet cells were grown in tissue culture and then transplanted into a diabetic mouse. The transplanted cells secreted insulin (stained areas) and the mouse returned to a normal glycemic level.**