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Your body, your cells

Firms take a gamble on tissue engineering

John Manning Staff Reporter

Imagine watching your own aortic heart valve in action. You'd see three thin flaps growing out of the walls, with ropes of tissue running through the flaps and walls, hanging like suspension bridges. Blood flows through with each heartbeat. But as the heart's chamber refills, the direction of the blood reverses, pushing the valve shut. This cycle occurs rapid-fire, some 40 million times a year.

"It was an excellent design engineer who put this together," said Bill Mirsch, director of tissue development programs at Little Canada-based St. Jude Medical.

No matter how divine their conception, body parts such as this valve can fail. St. Jude and others have been providing mechanical substitutes for years. But now some researchers are exploring how to convince the body to help create its own replacements. The result will be replacements made of living cells instead of titanium or silicone.

"The real Holy Grail is tissue engineering," said Mirsch, using a term that can apply to a wide variety of efforts to recreate body parts and functions. Possible examples of tissue engineering include repairing bones, livers, arteries, skin and heart valves -- all using living tissue.

Tissue-engineered products could respond to problems that current synthetic materials can't solve, such as replacement of coronary arteries, said Bob Tranquillo, a University of Minnesota professor of chemical engineering and materials science. Think about a surgeon being able to order up a deep-frozen piece of tissue-engineered coronary artery -- there'd be a demand for 600,000 of those a year, he said.

And any current mechanical devices could be replaced by tissue-engineered versions. Their advantage would be a lowered chance of rejection by immune system. "I think virtually any soft and some hard tissue are on the table for the development of these tissue-engineered products," Tranquillo said.

But this potential market doesn't mean that every med-tech business in town has thrown itself into tissue engineering: Many are waiting until what seems possible becomes more probable.

"It's viewed as Star Wars by a lot of businesses, in that five years might be the soonest a real product is available," said David Clapper, director of tissue engineering at Eden Prairie-based BSI Corp. A private company, BSI makes a coating that is used by many device manufacturers and has been found to be useful in tissue engineering. Clapper said that has made it the largest local player in this new technology.

"But there are some whole companies set up around it," Clapper said, such as La Jolla, Calif.-based Advanced Tissue Sciences Inc. (ATS), which is spending about $20 million a year developing engineered tissue products. "It's kind of high-stakes poker. If it works, they're going to have something, [but] are they going to be able to do it before investors tire?"

The local scene

While Minnesota doesn't have any large all-or-nothing-players like ATS, there is some activity. Research is going on at the University of Minnesota. A small start-up is trying to get a product off

the ground. Companies such as BSI and Coon Rapids-based Cellex Biosciences Inc. are building business as suppliers. And dominant device manufacturers like St. Jude and Fridley-based Medtronic Inc. have begun to get involved.

"You can't afford not to do anything," Mirsch said. "Nothing would be worse than to have the technology leapfrogging everything we have available." After working for a couple years with ATS on some initial research, St. Jude has developed enough expertise to bring its efforts in-house. It built a new lab in early 1996 and hired researchers, though declined to disclose how many. The company's first engineered tissue product may be available within five years.

Medtronic has been increasing its research into tissue-engineered heart valves, reportedly expanding its in-house capabilities. But the company's spokesman declined to discuss those efforts.

Minnetonka-based American Medical Systems Inc. (AMS) is another device manufacturer exploring how to use tissue engineering to create new products that address urological problems. New business development senior manager Steve Mascioli said the company has a research and development alliance with another company to develop a replacement bladder that could be available within five years.

"If the project is successful, it will have a major, major impact on AMS. And if it is not, it [doesn't]," Mascioli said. "It is an area with a fair amount of risk, and to balance that risk, if the project is successful, the rewards should be substantial."

While the long-term promise may be alluring, these companies know tissue engineering isn't the path to short-term results. They will need to figure out the economics of their applications, as well as the technology.

"For us it is going to take more than `we can do it,' " Mirsch said. "The question is what balance."

With most businesses remaining cautious, the public sector is playing a key role in developing this new technology, sources said. Along with federal grants, local businesses are benefiting from the University of Minnesota's Biomedical Engineering Institute, which is where some of the necessary basic research is being done.

The university has received unofficial notice that the National Institutes of Health will fund animal studies for research involving tissue engineering and rebuilding severed nerves. Other areas university researchers are looking at include the creation of living tissue arteries, corneas and livers.

"We can take a systematic and methodical approach to developing the science that eventually these companies can benefit from," Tranquillo said.

What it's all about

BSI's Clapper had worked for years to investigate how the company's products could improve how cells bind together before he'd heard the phrase "tissue engineering." "It's interesting to be in a field and see a buzzword and realize it applies to me," he said. As a result, Clapper has changed his title, replacing "cell biology" with "tissue engineering."

Just what this new buzzword means can vary. However, many sources agreed with Dan Mooradian, a University of Minnesota professor of laboratory medicine and pathology, who said the term includes at least two main approaches, both of which rely on living, organic tissue. The first one replaces the function of the original tissue but not the tissue itself. The second approach, which Mooradian described as more difficult, replaces something of the form of the original, as well as the function.

North Oaks-based Islet Technology is a small start-up that is trying to get off the ground with an example of the first approach to tissue engineering, one that replaces the function of the organ. President and CEO Bill Drake said he's developing a technology that takes living cells and coats

them with a permeable skin that makes them invisible to the immune system but is still able to secrete a hormone into the body.

The result would be a promising treatment for diabetes, which develops when the pancreas fails. Instead of receiving insulin injections three or four times a day to make up for what the pancreas no longer does, Drake's approach would involve injecting these micro-encapsulated cells, which would be able to sense the body's glucose levels and respond by creating the correct amount of insulin.

"The beauty of this is they're self-regulating, because they respond to the body's needs," Drake said. "It is as if those cells that you've lost have been replaced."

With plans to start human clinical trials in 1998, Drake said his small company may have a large impact: "It would probably open a whole new area of medicine," he said. "I don't know if it's the equivalent of drug therapy, but it's huge."

The second approach to tissue engineering -- replacing the form and function of existing tissue -- is demonstrated by efforts to create a new kind of heart valve.

St. Jude Medical already has valves that incorporate preserved pig valves. But this tissue is both alien and dead, triggering the same fighting response from the body as a mechanical implant. "The tissue is preserved like leather, and as the surgeon who invented this said, `Even the best pair of Italian shoes wears out,' " Mirsch said.

The next step is to create an implant that uses pig tissue but preserves it in a different way so that cells from the heart's endothelial lining are encouraged to migrate onto the tissue. The benefit would be that these cells would keep the blood flowing through the area and reduce the possibility of infection, Mirsch said. This kind of valve could be available within five years.

That's relatively easy. More difficult will be creating heart valves that the body's own cells can take over completely. Ultimately, Mirsch said, a valve could be created that would be implanted in a child and develop and grow in the same way as the child's original valve.

St. Jude plans to build the new valves as extensions of its current pig valve product to win easier approval from the Food and Drug Administration (FDA).

The staged approach is likely to be common.

"As the new generation combines existing material and tissue-engineered coatings to make improved products," Clapper said, "the next generation will totally replace our current materials."

The revolution from mechanically to biologically engineered body parts is going to take a lot of effort and time. The challenge is to figure out just how to encourage the right cells to grow in the right places. "You need to leave a trail of bread crumbs to lead to the appropriate places, to entice them in," Mirsch said. And then after spurring new growth, the cells have to be told somehow when to stop.

"I'd say no one has the right mix," he said. "We've just begun to get a handle on cell biology at this level."

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