

BUSINESS

Licensing fees slow advance of stem cells

Would-be entrants to the embryonic stem-cell business find access to the technology prohibitively expensive, **Meredith Wadman** reports.

Jeanne Loring, an embryologist at the Burnham Institute in La Jolla, California, knows all about the unrealized commercial promise of human embryonic stem-cell research. A decade ago she developed a method for deriving embryonic stem cells, and in 1999 founded Arcos BioScience to culture the cells and develop cellular therapies from them. By the end of 2000, Loring had derived nine human embryonic stem-cell lines.

But that's where the success story ended. The company, already on a shoestring budget, couldn't find the \$100,000 up-front fee that would allow it to take out a commercial research licence from the major patent holder in the field, the Wisconsin Alumni Research Foundation (WARF).

The foundation administers the intellectual property of the University of Wisconsin in Madison, where human embryonic stem cells were isolated by biologist James Thomson in 1998. It holds broad patents on a method of deriving human embryonic stem cells — and on the cells themselves.

But Loring says it has a stranglehold on the field. "The greatest roadblock to the development of human embryonic stem-cell research in the United States is WARF's fundamental patent," she says. "If it hadn't been for that patent, I would still be in biotech."

Instead, Loring's company merged with two others, and she went back to academic stem-cell research. By forcing researchers out of the commercial sector, she says, stem-cell patents

are slowing the drive to get applications into the clinic.

Seven years after WARF wrapped up its broad package of patents in the United States — it hasn't won similar patents elsewhere — complaints are mounting about the fees and conditions it imposes on commercial firms.

"The intellectual-property situation is stifling industrial research and investment in this area," complains a senior executive at one firm that aspires to enter the embryonic stem-cell business. He requested anonymity because his company is in negotiations with WARF.

WARF says it is trying to speed the development of the field while fulfilling its mandate to support research at the University of Wisconsin — and keeping the promises it made to donors who provided the embryos from which its stem-cell lines were derived. "We've tried to be a responsible citizen," says Carl Gulbrandsen, the foundation's managing director.

Paying the price

Dozens of companies around the world are working on stem cells, exploring uses that range from drug discovery to drug screening, and from toxicology to cellular therapies for Parkinson's and heart disease. But most deal with stem cells derived from adults, which are out of the reach of WARF's patents. Those that invest seriously in embryonic stem-cell work can be counted on the fingers of two hands.

About half these firms are based outside the United States, but even these will probably want to sell any products they develop in the lucrative US healthcare market. And that means facing another major obstacle: exclusive licences held by Geron, based in Menlo Park, California, which paid for much of the Wisconsin research.

Geron has secured exclusive US commercial rights to what are generally agreed to be the three most clinically promising types of cell derived from embryonic stem cells: cardiac myocytes, which could help to repair damaged hearts; neural cells, which might treat neurodegenerative diseases or spinal-cord injury; and pancreatic β -cells, which could treat diabetes.

Partly because Geron's control is so broad,

Hard cell? Carl Gulbrandsen (top right) says that licence terms for human embryonic stem-cell lines are reasonable — but Jeanne Loring argues that they are pricing companies out of business.

R. GONZALEZ/WARF

"things are moving more slowly than they otherwise would," says Rebecca Eisenberg, a law professor at the University of Michigan who specializes in intellectual-property issues in biotechnology. "The proprietary constraints are the price you pay for having to make do with private rather than public funding."

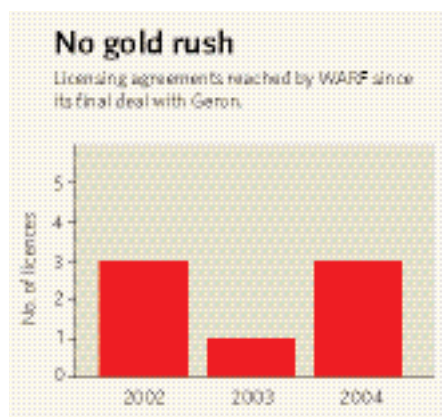
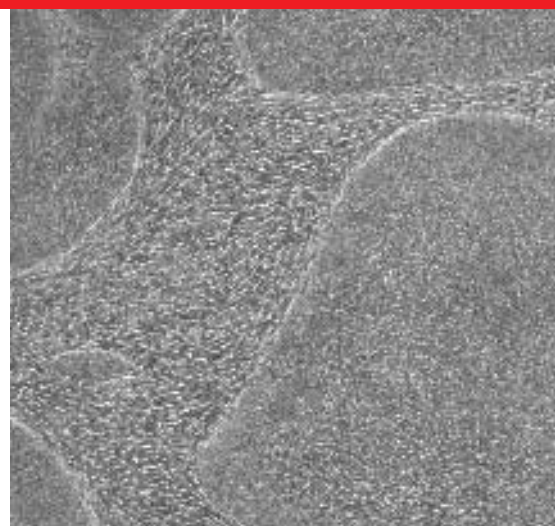
Eisenberg contrasts the situation with the handling of recombinant DNA technology in the 1980s and 1990s, when Stanford and the University of California liberally administered patents to allow free access for academics, and low-cost licensing to companies.

Academic scientists are also griping about WARF's charges for access to the five stem-cell lines that it owns. The foundation charges \$5,000 each time it supplies one of these to an academic scientist, and doesn't let them share the cells with colleagues.

"I'm a senior investigator, and I was able to get a \$5,000 grant supplement from the National Institutes of Health," says Lawrence Goldstein, a cell biologist and Howard Hughes Medical Institute investigator at the University of California, San Diego. He recently bought some cell lines from WARF, but is upset that he isn't allowed to share them with less well-funded junior colleagues: "That's not how you make science proceed, for crying out loud!"

WARF has sent cell lines to 231 research groups worldwide and signed material-transfer agreements with more than 200 US academic institutions, Gulbrandsen points out. He adds that it has lost \$1.3 million by distributing the cell lines through the WiCell Research Institute, a subsidiary that WARF established in 1999.

Gulbrandsen says he is weary of getting a bum rap from all concerned. Strict rules preventing sharing of those lines between university researchers are needed, he explains, so WARF can honour promises made to the donors from whose leftover embryos the cells were generated. Each scientist or company that





receives a cell line signs an agreement not to do experiments to implant the line in an embryo, generate an embryo, or implant an embryo in a uterus. If WARF allowed free sharing, it couldn't police this, Gulbrandsen notes.

He doesn't deny that WARF is seeking six-figure sums — a \$25,000 annual maintenance fee plus \$100,000 up-front fee — from companies taking out commercial licences. "But we've tried to be accommodating where a smaller company thinks that the price is too high," he says — in one case, WARF accepted equity in a firm instead of cash.

WARF has issued seven commercial licences to companies (see chart, left) since its first broad patent in 1998, but declines to identify them. Becton, Dickinson & Company, a New Jersey-based drugmaker, says it has a licence. Advanced Cell Technology (ACT) of Worcester, Massachusetts, told *Nature* that it, too, has signed a deal with WARF. *The Wall Street Journal* reported last month that General Electric and Novartis are about to launch US projects with embryonic stem cells — General Electric will develop drug-testing products for sale to pharmaceutical companies, and Novartis aims to turn stem cells into heart cells. And Johnson & Johnson, the New Jersey-based maker of medical products, has bought an equity stake in Novocell of Carlsbad, California, which seeks to generate insulin-secreting pancreas cells from stem cells.

The disgruntled blame the small number of licences on WARF's prices and restrictions. "It granted only seven commercial licences in seven years, on a technology that is hot — why?" demands the anonymous executive. He adds that US-based firms feel hamstrung by one requirement in particular: "If we sign an agreement with WARF in the United States, it wants to place restrictions on us globally, even though the patents do not apply worldwide."

But Robert Lanza, vice-president of medical and scientific development at ACT, says that the price his company paid the foundation for a commercial research licence was "very fair". In WARF's position, many companies might overcharge licensees, he says. "And WARF isn't. My hat's off to them." ■

IN BRIEF

DISEASE TEST APPROVED The US Food and Drug Administration has approved the first genetic blood test for cystic fibrosis. The Tag-It test, made by TM Bioscience of Toronto, Canada, can now be used to identify children and adults who carry the disease. Cystic fibrosis is the most common inherited fatal disorder, afflicting about 1 in 3,000 babies in the United States. The test identifies only some of the 1,300 genetic variations associated with the disease, and the terms of the approval require that it be used with other approaches to diagnose cystic fibrosis.

VACCINE MAKERS FLOUNDER The number of US companies manufacturing vaccines has fallen from 26 in 1967 and 17 in 1980 to just 5 last year, and shows no sign of reviving. Writing in this month's *Health Affairs*, Paul Offit, head of infectious-disease research at the Children's Hospital of Philadelphia, says that high development costs, low revenues and the threat of legal liability are forcing manufacturers out of the vaccine business. Offit says the US government should provide more financial incentives for vaccine development and amend a 1986 law designed to limit manufacturers' exposure to legal liability for ill-effects caused by vaccines.

UP IN SMOKE European car makers are falling short of voluntary targets agreed with the European Commission to increase fuel efficiency and decrease carbon dioxide emissions from their vehicles. Average new-vehicle emissions fell by 1.8% last year, the *Financial Times* reports, against a 3.3% average reduction needed to meet the emissions target of 140 g per km by 2008. European manufacturers have launched smaller models, such as the BMW 1 Series, with a view to improving the figures. The industry fears that the European Union will set compulsory limits if the voluntary one isn't met.

MARKET WATCH



Nanotechnology stocks have lost ground rapidly over the past two months, according to one of the first stock-market indices devoted to tracking them. But analysts still expect the field to attract \$400 million in venture capital this year — the most it has managed since 2002.

The downturn reflects the general doldrums in technology shares this year, says Peter Hebert, chief executive and co-founder of Lux Research, the consultancy in New York that developed the index.

"Most of it has to do with the overall market for technology stocks," he says, adding that "the Lux' has taken an even harder hit this year than the Nasdaq — the main US index for technology stocks — because the former is weighted towards smaller firms, whose shares tend to suffer most when investors are feeling cautious.

But 2005 is shaping up to be a bumper year for venture-capital investment in nanotechnology. Lux reports that

\$66 million was raised in March alone for three US companies — Nanomix, Nantero and Nano-Tex — and estimates that the flow of venture capital into US nanotechnology firms will double this year from the \$200 million raised during 2004.

Tracking the financial performance of something as loosely defined as nanotech isn't easy, Hebert concedes. Lux has had a stab by pulling together companies that supply nanotech products, build nanotech tools such as atomic-force microscopes, or use nanotech in their businesses. Its index allocates equal weighting to all of the firms — effectively giving more clout to the smaller, more specialized ones.

"We've been one of the first to stress that nanotechnology isn't an industrial sector per se," says Hebert. "It's an enabling technology. Investors have been perplexed about how to approach nanotech — but we're seeing progress now." ■

▶ www.luxresearchinc.com