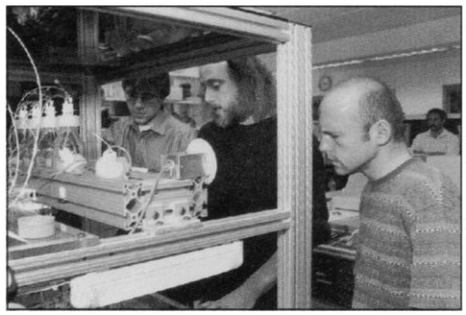
Exclusive License Rankles Genome Researchers

Imagine building a better mousetrap, and nobody beats a path to your door. That's essentially what happened 2 years ago to Ronald Davis, head of a genome center at Stanford University. Tom Brennan and others in his lab had just built a powerful new machine that made oligonucleotides—short stretches of nucleotides, which are the building blocks of DNA—for a fraction of what it then cost to buy the so-called "oligos" from commercial firms. Because oligos are a critical tool for researchers involved in the Human Genome Project, the international effort to spell out the entire genetic code of a human, the machine held the promise of speeding that mammoth enterprise.

Davis says that at the time, however, he "was quite discouraged" because no one showed interest in the oligomaking machine. But that's no longer the case. And what has happened since has raised troubling questions about technology transfer, intellectual property, and moving science forward as quickly as possible. Stanford licensed exclusive rights to the machine to a company that sells oligos to researchers but won't allow others to buy the machine itself, while an upstart university group has developed its own machine and is making it available to other groups with no licensing fee.



UT SOUTHWESTERN MEDICAL CENTER

Machine politics. UT Southwestern built its own oligosynthesizer (shown here), although Stanford had previously built one.

Some genome researchers claim that Stanford's decision to issue an exclusive license is counterproductive to the goal of completing the Human Genome Project as quickly as possible. "What really frosts me is they gave an exclusive to a company that refuses to sell the machine to anybody," says Bruce Roe, head of the genome center at the University of Oklahoma, whose lab was the first to purchase a machine from Stanford's new competitor, the University of Texas Southwestern Medical Center at Dallas (UT Southwestern). Roe notes that federal government money paid for the development of a machine that is now unavailable to other scientists working on a federally supported project, a situation he calls "immoral."

Roe says that cheap, abundant oligos open up new strategies for deciphering the vast stretches of DNA that genome scientists have yet to decode. Jeff Schloss of the National Human Genome Research Institute says cheaper oligos also could "dramatically" affect genome researchers' thinking: "People's concepts of what's possible, what strategies they'll adopt, really depend on the tools. It seems counterproductive to me to have these limited because of issues about intellectual property."

When Stanford first developed its machine, however, few researchers were interested in these tools. Reports on the "Parallel Array Synthesis" machine were relegated to poster sessions at scientific meetings, a paper Davis submitted to *Science* was rejected, and Stanford had little luck finding companies that wanted to develop the machine. "The community was not ready for this machine," says Davis. "The whole genome field could have had it [back then] if they wanted it."

Ultimately, the university found just one taker, Protogene, a Palo Alto, California, start-up company co-founded by Brennan from Davis's lab. But Protogene, which is backed by Life Technologies Inc., of Gaithersburg, Maryland—the current holder of the Stanford license—was only interested if it could have an exclusive deal. As a result, no one else can buy the Stanford machine.

Casey Eitner, a vice president of Life Technologies Inc., says the arrangement has greatly benefited researchers by driving down the price of oligos dramatically; a 30 May press release from Life Technologies says the price has dropped "200-300 percent since 1994 for an estimated savings of $20 million by researchers in the United States." Eitner adds that Stanford did not simply hand over a ready-to-go product: "The technology required a substantial investment from us to complete its development and commercialization."

Not everyone is swayed by his arguments, however. Harold "Skip" Garner, associate director of the genome center at UT Southwestern, believes Life Technologies still charges too much for oligos. Garner was one of the few researchers to recognize quickly the potential value of the Stanford machine to help unravel DNA sequences.

He told Davis in the summer of 1995 that he was interested in building a replica of the Stanford oligosynthesizer. "We had no objection to that, so much so that we gave them a parts list," says Davis. That August, Garner and a postdoc flew to Stanford to inspect the machine. But a few days into their visit, Garner and his postdoc were asked to leave when Stanford's Office of Technology Licensing got wind of the visit.

Garner was not dissuaded, however. He decided to go ahead and build his own machine anyway. Life Technologies at one point offered UT Southwestern a chance to lease the Stanford machine, but Garner says the terms were "prohibitive." On 23 May, UT Southwestern announced that any university or other nonprofit laboratory involved in the Human Genome Project could buy the machine Garner developed, called MerMade, and use it without paying a licensing fee. With UT's machine, researchers can make their own oligos for about $2, compared to the $12 or more that Protogene and other companies would charge for the same thing. But while Garner says "I have the perfect right to go off and invent my own," Eitner isn't so sure. "We very much are awaiting knowledge of the machine to determine whether there are any infractions [on the patent] to the machine we have," says Eitner.

Both Davis and Eitner also caution genome centers that making their own oligos may not be as much of a bargain as it seems, because they have to consider their overhead costs and issues such as quality control and the maintenance of the machine. "If you sit down and go through the math, ... you'll find it's not as attractive a proposition as it seems," says Eitner. He adds, however, that Life Technologies still has not ruled out the idea of leasing the Parallel Array Synthesis machine: "I've made it clear that we'd make it available under the right circumstances."

That would be fine with Davis, who still wishes the Stanford oligosynthesizers could have been made widely available. "What we should have done, in retrospect, is to have said 'no' to exclusive licensing and to have been more aggressive on marketing," he says. "But [the synthesizers] weren't viewed as critical then." The lesson, he says, is that you can't transfer technology effectively if people don't want it.

–Jon Cohen