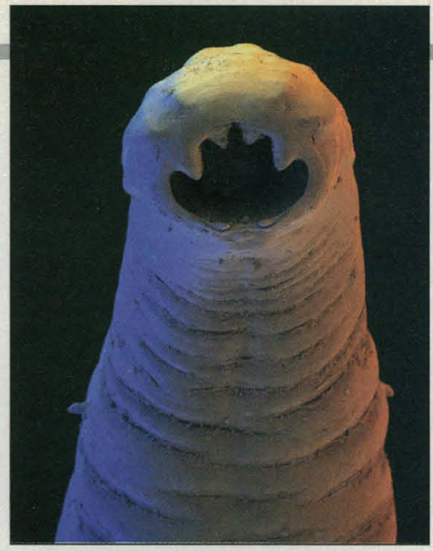
PATENT DISPUTES

New Anticoagulant Prompts Bad Blood Between Partners



DAVID SCHARF

Bloodsuckers and biotech. University and biotech workers are at odds over a protein isolated from hookworms (*above*).

When scientists from Yale University and a small San Diego–based biotechnology company joined forces in 1993, it seemed like a perfect marriage. The two were bound by a strong common interest: The Yale group wanted to develop a vaccine to protect an estimated 1 billion people infected by a blood-sucking intestinal parasite, the hookworm; and researchers at the company, Corvas International Inc., were hoping to isolate a hookworm protein that could compete in the lucrative anticoagulant drug market.

So the birth announcement this month—a report in the 5 March *Proceedings of the National Academy of Sciences* on the amino acid sequences of hookworm anticoagulant proteins—should have been a joyous occasion for the couple. It was not. The partners have separated, and one molecule may become the object of a nasty custody battle. Yale has an approved patent on it, but Corvas has recently filed its own patent application because, according to Chief Executive Officer David Kabakoff, their research has progressed "far beyond" what the Yale group did. "If they want to make an issue of it, they can try," he says.

Yale, which had hoped that a profitable anticoagulant would underwrite the costs of their vaccine development, is concerned that Corvas's patent could destroy those plans. And while both sides say they hope to reach an amicable agreement, they are haunted by the possibility of a lengthy court battle like the one that's been raging since 1988 between Corvas and—ironically—another group of Yale researchers over rights to a different protein involved in clotting (see box). These wrangles seem to be happening more often as academic scientists increasingly work with for-profit corporations, observers say. Purdue University's Teri Willey, president of the Association of University Technology Managers, calls them "special commercialization projects from hell."

This project started out with high hopes. In 1993, Yale's Peter Hotez and Michael Cappello isolated a protein from the *Ancylostoma caninum* hookworm—believed to be the world's leading cause of anemia—which prevents the host from forming blood clots, letting the worm feed without interruption. They termed the protein AcAP, for *Ancylostoma caninum* anticoagulant protein, and filed for a patent in April of that year.

As they homed in on the protein, the Yale lab began a collaboration with Corvas. Since its founding in 1987, the company had been researching natural sources of anticoagulants, such as ticks, leeches, and hookworms, and its research director, George Vlasuk, was a leading expert in the field. Yale saw a chance for additional resources, Cappello says. Corvas, although not interested in a low-profit vaccine project, did see another opportunity. As many as one fifth of all Americans die from clotting disorders such as deep-vein thrombosis and stroke, creating a demand for anticoagulants which, industry analysts estimate, will grow to at least $1.5 billion annually by the year 2000. Vlasuk, a co-author on the recent study, says that with a potent new anticoagulant his company could

Clotting Controversy

The conflict between Yale University and Corvas International Inc. over rights to hookworm proteins isn't the only item of rancor between the two institutions. An older, but unresolved, fight over the rights to a medical diagnostic tool has been simmering for years. "What was intended as a collaboration turned into something else and became quite bitter," says Yale's William Konigsberg.

The dispute centers on Konigsberg's claimed discovery, with Yale Nemerson of Mount Sinai Medical Center in New York, of the cDNA sequence of human tissue factor, a blood-clotting protein currently sold as a tool to measure the effectiveness of anticoagulant therapy. Before they sent their results to the *Proceedings of the National Academy of Sciences* (*PNAS*) in 1987, they say, the two researchers shared purified tissue factor samples and information with Thomas Edgington, a molecular biologist at the Scripps Research Institute in La Jolla, California.

Six weeks before the *PNAS* article appeared, Edgington announced in the journal *Cell* that his lab was "the first" to deduce the sequence. Edgington, a founder of Corvas and currently one of its directors, subsequently obtained the patent on the sequence (through his institution, Scripps) and licensed it to the company.

Not surprisingly, Konigsberg and Nemerson were not happy. In a letter published by *Cell* in March 1988, the two claimed that the Edgington group's paper was "particularly egregious" because, they believed, the Scripps scientists "had in their possession a preprint of our paper, which included the entire sequence of the 2.3-kilobase tissue factor cDNA. Thus, Edgington *et al.* knew all along that their claim of being first was insupportable."

Edgington and his Scripps colleague James Morrissey call the complaint "rather trivial." They say they had independently determined the sequence and presented it in a meeting prior to receiving the preprint. "To me, it's a pure annoyance," Edgington says. "I really don't give a damn about the whole situation." He also says his opponents are simply motivated by royalties.

Yale and Mount Sinai brought a patent interference claim against Scripps 3 years ago, and the U.S. Patent and Trademark Office may rule on it soon. Corvas's license to the technology may stand or fall with the Scripps patent.

"It's really been a knock-down, drag-out battle," says George Broze, a molecular biologist from the University of Washington in St. Louis, Missouri. And, Broze adds, "from my perspective, I'm not sure either of them should have priority." He says he was the one who first isolated the tissue factor, although he's not pressing any claim. Yet another biotech firm might, however: San Francisco's Genentech Corp. says it was first to file a patent on this cDNA sequence and may enter the legal fray.

–J.F.

capture at least 10% of this market.

Corvas assigned a team to the project, although the two groups had no intellectual property rights agreement. Both sides do agree Corvas advanced the work, allowing researchers to begin to sequence the protein and identify two others. But chinks in the relationship began to appear by 1994. Corvas had asked Yale for the license to the AcAP patent, but the university—unimpressed with the company's offer—instead sold the license to Biomedisyn, a start-up biotechnology firm near New Haven, Connecticut. Biomedisyn's founder, Frank Volvovitz (former president of vaccine-maker MicroGeneSys) was very interested in vaccines.

Corvas continued largely on its own to perform extensive tests, including full protein sequencing, cloning, and testing in animals. A company press release in December noted that at a recent conference, Corvas scientists presented "promising preclinical results on its proprietary" AcAP proteins, which it has renamed NAP, for nematode anticoagulant proteins. Kabakoff says he's confident that the company's claims—when made public at the end of the patent process—will withstand scrutiny.

Volvovitz is unconvinced. "Anytime anyone wants to ignore a patent someone has, they can come up with all kinds of reasons," he says. Volvovitz, like Yale and Corvas officials, says he holds out hope for an amicable agreement. What may make it difficult is that any profits Corvas might make from an anticoagulant could undercut Biomedisyn's attempts to use sales of a similar drug to fund vaccine work. So, says Volvovitz, "we do have some concerns over what Corvas has done so far."

This bicoastal biotech wrangling may be a harbinger of industry-academia struggles to come. The Association of University Technology Managers found in a survey last year that the number of new technology license and option agreements between industry and academia has increased 63% from 1991 to 1994, to 2484. Purdue's Willey says most of these fare much better than the Yale-Corvas deal did. Still, a survey of 210 biotechnology company executives published in the 8 February *New England Journal of Medicine* found that 34% had "disputes with their academic partners over intellectual property." Joyce Brinton, director of Harvard University's Office of Technology and Trademark Licensing, says the hookworm affair highlights the need for collaborators to make their full intentions known at the outset of the relationship. "Since the interests are different," she says, "it might be helpful if everyone talked out what everybody's objectives are."

Brinton warns, however, that caution taken to extremes could actually stifle research. "Yes, you need to make sure you've got i's dotted and t's crossed. But the last thing a scientist wants is for someone to come with 16 pages of contracts to sign."

–Jock Friedly

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AFFIRMATIVE ACTION

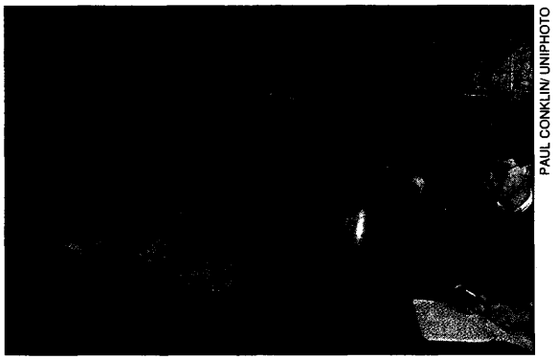
Diversity Takes a Student Body Blow

Alarms rang on campuses across the United States last week after a court ruled that the University of Texas (UT) law school's admissions policies violated the U.S. Constitution's guarantee of equal protection under the law by giving preference to blacks and Hispanics over whites. The ruling could dismantle programs to improve minority admissions rates at U.S. professional schools. And while its effects on science graduate programs are likely to be more muted and less direct, observers say they could still be profound.

The ruling in *Hopwood* v. *Texas* by the 5th U.S. Circuit Court of Appeals in New Orleans now applies only to Texas, Louisiana, and Mississippi, and UT is currently deciding whether to appeal it. If the decision is upheld by the U.S. Supreme Court, it "would render unconstitutional the admissions policies of virtually every public institution in America," says University of Virginia law professor John Jeffries.

Science graduate programs themselves are not directly in the line of judicial fire. Microbiologist John Alderete of the UT Health Science Center in San Antonio says the ruling wouldn't affect his department because there are no policies that distinguish applicants based on race or ethnicity. Chemist Billy Joe Evans of the University of Michigan, Ann Arbor, says the procedures for admission to graduate departments tend to be sufficiently informal that "we can do pretty much what we want to do." Law and medical school admissions, in contrast, rely more heavily on national standardized tests, which can be weighted to favor minority applicants. Indeed, in an analysis last year, the Association of American Medical Colleges (AAMC) found that if admissions were based solely on grades and test scores, "(with the exception of Asians) the complexion of selective higher education institutions, including medical schools, would return to that of the 1950s" (*Journal of the American Medical Association*, 21 February 1995).

Where science education would feel the impact—if the Supreme Court extends the ruling nationwide—is at the undergraduate level. "If you could not consider race at all ... [there would be] an extremely drastic decline in the enrollment of disadvantaged minorities," says Gary Orfield, professor of education and social policy at Harvard University. And that would give grad programs even fewer minority students to choose from. The effect would be "horrible," says Herbert Nickens, vice president for community and minority programs of the AAMC.



PAUL CONKLIN/ UNIPHOTO

Less diversity? The policy that admitted these students to the University of Texas can't take race into account.

Engineer Carl Pister, chancellor of the University of California (UC), Santa Cruz, says the UC system is already seeing results from the UC Regents' decision last summer outlawing race-based admissions. Even though the order doesn't go into effect until next year, he says, applications by underrepresented minorities appear to be down about 10% in anticipation. And admissions aren't the only programs touched by the ruling. Race-based scholarship programs could be in jeopardy, says the lawyer for the plaintiffs, Michael Greve of the Center for Individual Rights in Washington, D.C. And while recruitment programs would not be directly affected, says Pister, more care would have to be exercised to be sure they weren't exclusionary. That's already happening in California, he says: Outreach programs such as MESA (Mathematics, Engineering, and Science Achievement) are structured to be open to members of all racial and ethnic categories, although they are designed to attract minority candidates in particular.

Whatever the final disposition of this case, there seems to be agreement in most quarters that it is part of a larger trend (see p. 1908). Says National Science Foundation general counsel Larry Rudolph: "I think this is clearly going to be one of the more difficult and challenging issues of the next decade ... [trying to increase minority representation in education] while still being able to pass constitutional muster."

–Constance Holden