May I See Your License, Please?

Disputes over the application of powerful new technologies are casting a shadow over three areas of research: AIDS virology, cancer treatments, and gene sequencing

PCR Patent Tangle Slows Quick Assay of HIV Levels

Just a week before he was scheduled to speak at a recent scientific meeting, organic chemist Paul Jung of Abbott Laboratories in Chicago was startled to learn that his talk had been dropped. "I thought it was weird," he says. Few researchers are bumped from meetings where they are scheduled to present hot new data. And Jung's message—that a new nucleic acid–analyzing machine called TaqMan holds great promise for AIDS researchers—should have been music to the ears of the meeting sponsor, PE Applied Biosystems of Foster City, California, which manufactures TaqMan. But Jung's plight is a prime example of how biomedical research is increasingly getting caught in the tangled skein of commercial licensing agreements (see stories on this page and p. 1489).

The company pulled the plug on Jung's talk because it feared getting embroiled in a fight over rights to the polymerase chain reaction (PCR), the basic analytic technique on which TaqMan is based. The problem was that Jung had used TaqMan as a diagnostic tool for measuring HIV levels—the so-called "viral load"—in the blood of patients, rather than as a research tool. Under a licensing agreement between PE Applied Biosystems' parent corporation, Perkin-Elmer, and Roche Molecular Systems Inc., which holds the patent on PCR, PE Applied Biosystems cannot promote diagnostic uses of the machine. If Perkin-Elmer had let Jung speak, it could have been accused of infringing that agreement. "Perkin-Elmer was quite appropriate in its actions," says Ellen Daniell, director of licensing for Roche Molecular Systems.

But while scientists may find the idea of a colleague being asked not to share data unpleasant, a more substantial issue lurks beneath the surface: constraints on researchers' ability to employ a powerful tool in the battle against HIV. To use TaqMan, researchers must have "probes," short stretches of nucleic acids that bind to specific targets, such as the nucleic acids of HIV and hepatitis C virus. Roche's licensing deal with Perkin-Elmer prevents PE Applied Biosystems from making any probes that might be used diagnostically to detect such pathogens and marketing them to researchers. As a result, AIDS researchers interested in using TaqMan to determine levels of HIV in a patient's blood must make their own probes, as Jung did, collaborate with Roche, or wait for Roche to perfect an HIV test of its own. "This is not a good situation," says Thomas Caskey of Merck & Co., who previously headed a board of scientific advisers to Roche.

The situation is particularly unsettling because viral-load measurements have become an integral part of AIDS treatments; they are a critical marker for both health status and the impact of drug therapy. "Quantitation of HIV is extremely important now," says Roger Pomerantz, chief of infectious diseases at Thomas Jefferson University in Philadelphia. And Pomerantz says the AIDS field would benefit greatly if TaqMan lived up to its promise of providing a faster, simpler way to measure viral loads: "It would be fantastic."

TaqMan is a next-generation, automated version of a PCR machine, which may have significant advantages over current methods. At present, Roche has the only PCR assay for quantitating HIV that has been approved by the U.S. Food and Drug Administration. That assay fishes specific pieces of HIV nucleic acids out of blood samples and then

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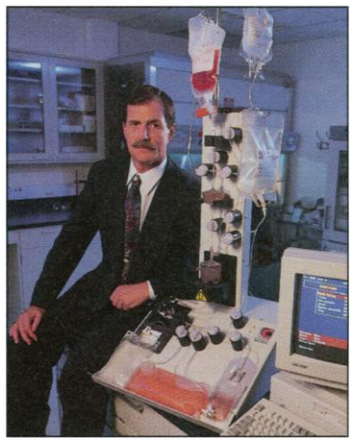
Varmus to Rule in Fight Over Cell-Sorting Technology

When a scrappy biotech company near Seattle called CellPro Inc. lost a patent fight to Johns Hopkins University in March, it lashed out with an emotional counterattack. Aided by a high-priced publicity firm—Burson-Marsteller of New York—it began spreading a heart-tugging tale of distress. Its message: A cell-sorting device made by CellPro, which had helped save the life of the company's own CEO, Rick Murdock, and could be used to help thousands of other cancer patients, is being suppressed by its competitors, Becton Dickinson and Co. and Baxter Healthcare Corp. The two companies have licensed rights to the technology from Hopkins, which holds patents on the cell-sorting concept. To protect the public, CellPro argues, Secretary of Health and Human Services Donna Shalala should take control of the disputed patents and give CellPro a reduced-cost license to exploit them.

Shalala received CellPro's formal appeal in May amid a well-orchestrated blast of publicity and a swarm of letters from Congress favoring CellPro (see sidebar, p. 1490). She promptly handed it to Harold Varmus, director of the National Institutes of Health (NIH). It landed on Varmus's lap because NIH funded the basic science behind the device, which is used to collect stem cells from patients who are undergoing cell-killing cancer therapy. The cells are saved and returned to the patients to rebuild their blood and immune systems.



RICH FRISHMAN

Lifesaver? CellPro CEO Rick Murdock with disputed machine used in his own treatment.

CellPro is appealing to Shalala under the Bayh-Dole Act, a 1980 law designed to encourage academic scientists to patent and exploit their federally funded discoveries. The law says the government retains the right to march in and redistribute patents in rare circumstances—if the patent holder fails to develop an invention "within a reasonable time," or if the government must "alleviate health or safety needs which are not reasonably satisfied." No company has persuaded the government to do this before.

A great deal rides on Varmus's review. At this writing, a Delaware court is weighing what penalty to impose on CellPro for infringing Hopkins's patents. And CellPro claims that if it is not rescued, the court may force it to stop distributing its device to new customers, denying patients lifesaving treatment. Hopkins and its partners are trying to persuade the court to adopt an order that would, among other things, require CellPro to share about 50% of sales revenue.

Hopkins, arguing that no patients will be deprived of therapy, says

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CellPro

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the fight is really about property—whether one clever group of researchers can grab another's work. "It's scary," says Hopkins spokesperson Gary Stephenson, "to think that popular pressure might overturn our legal rights." Frank Adkinson, vice dean of research at Hopkins's medical school, says that if the government marches in to break the patent agreements, biotech companies may be scared off from investing in university projects in the future. "What's at stake here is much broader than just Hopkins's interests," says Adkinson. The CellPro appeal, he argues, puts at risk "all inventions derived from government-sponsored research."

The NIH-funded research that spawned this brawl took place in the early 1980s in the laboratory of Hopkins oncologist Curt Civin. No one disputes that Civin was the first to identify a human antibody (My-10) that binds to a surface protein on primitive cells in blood and bone marrow (now called CD34 cells). Civin's discovery, published in 1984, suggested a way to isolate large quantities of elusive stem cells, prized for their ability to generate all other types of blood cells and replenish the immune system.

After publishing his findings, Civin and Hopkins sought broad patents on the My-10 antibody and methods of using it to isolate precursor cells. They won four patents, issued from 1987 to 1992. And Hopkins licensed the commercial rights to Becton Dickinson and Co. and, in subsidiary agreements, to Baxter and two other companies.

Scientists at the Fred Hutchinson Cancer Research Center in Seattle, meanwhile, began to look for ways to exploit Civin's discovery. One group found an antibody, called 12.8, that recognizes a different element, or epitope, of the same My-10 antigen on CD34 cells. The new find proved very useful because—unlike My-10, which links only to human cells—12.8 also links to baboon CD34 cells. This makes 12.8 valuable for animal experiments, essential to pave the way to human clinical trials, which, in turn, are essential for winning marketing approval from the Food and Drug Administration (FDA) for a new medical device.

A Hutchinson researcher, Ronald Berenson, obtained licenses from Hutchinson to the 12.8 monoclonal antibody system, which Hutchinson had not patented, and, in 1989, joined with others to form CellPro. In 1991, CellPro received advice from its attorneys that the company did not have to honor the Hopkins patents. CellPro has subsequently argued that Civin's discovery was too obvious to deserve a patent, and that, in any case, patents based on My-10 do not cover a product based on Hutchinson's 12.8 antibody.

The Hopkins group didn't see it that way, however. After several attempts to negotiate shared rights to CD34 technology failed, Hopkins, Baxter, and Becton Dickinson sued CellPro in 1994 for infringing the Civin patents.

When CellPro's legal defenses were put to trial in Delaware's federal district court beginning in 1995, the jury ruled in favor of CellPro on every point. However, after deliberating for nearly a year, Judge Roderick McKelvie threw out the jury's verdict, saying he had made an error in instructing the jury. In 1996, McKelvie ordered a new trial, asking the jury to determine one thing: Did CellPro act willfully in infringing the patents? In March 1997, the new jury ruled that CellPro had indeed acted willfully. CellPro intends to appeal, but it isn't just waiting for the court to act.

Even before the verdict, CellPro began marshaling its political and legal forces to petition Shalala and Varmus. To present its case, CellPro hired the co-author of the Bayh-Dole Act, former Senator Birch Bayh (D–IN), and Washington, D.C., attorney and former White House counsel Lloyd Cutler. In briefs recently submitted to Shalala and NIH, they claim that Hopkins and its partners "essentially sat on the sidelines" while CellPro developed a workable CD34 cell processing de-

The Madison Avenue Treatment

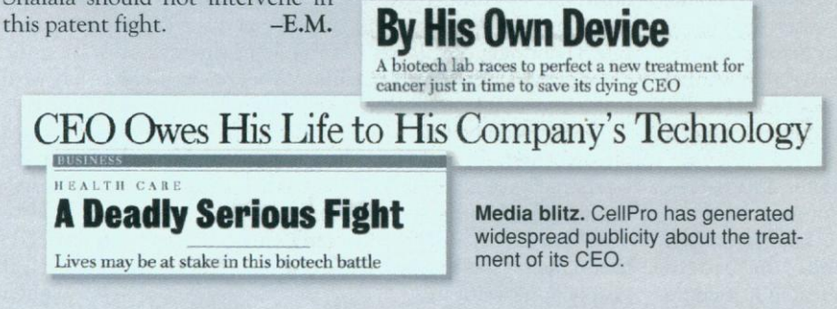
The Wall Street Journal may have been the first national publication to add a touch of human drama this spring to a fight over patents on a blood-processing technique (see main text). In a 1 May report headlined, "CEO Owes His Life to His Company's Technology," the *Journal* described how Rick Murdock, the chief executive of CellPro Inc., in Bothell, Washington, was threatened by a rare and usually fatal cancer (mantle cell lymphoma). Murdock volunteered to be a "guinea pig" in 1996 for treatment with CellPro's own machine. Physicians at the Fred Hutchinson Cancer Research Center in Seattle used the device to concentrate stem cells from Murdock's blood and rebuild his immune system after radiation and chemotherapy.

Murdock improved. But the *Journal* noted that Murdock's company might not survive because it has been sued by Johns Hopkins University for infringing the university's patents, and might be barred from selling its blood-processing machine. Shortly afterward, similar reports appeared in *Time*, *Newsweek*, and on the television show *Prime Time Live*.

Almost at the same time, members of Congress began sending appeals to their colleagues and to Donna Shalala, Secretary of the Department of Health and Human Services, urging HHS to grant CellPro a waiver from the patent laws. Representative Rick White (R–WA), whose district is home to CellPro, along with 24 other House members and 12 senators, pleaded for CellPro. The American Cancer Society also lobbied Shalala to help CellPro "on behalf of hundreds of thousands of cancer patients and their families." But two members of Congress, Senator Barbara Mikulski (D–MD) and Representative John Porter (R–IL), representing the home states of Hopkins and its business partner, Baxter Healthcare Corp., wrote to Shalala asking her not to intervene.

"The media have just been pummeling us," grumbles Johns Hopkins medical school spokesperson Gary Stephenson, crediting a "phenomenal job" by CellPro's publicity agency in New York, Burson-Marsteller. Even John Osth, president of the Baxter division that licensed the Hopkins patents, marvels that his adversary's public relations has been "very, very good." When CellPro's director of corporate relations, Joann Reiter, was asked how reporters learned of Murdock's cancer, she said: "We told them. We said, 'We think this would be a great story: What do you think?' "

Baxter, meanwhile, is taking a leaf out of its competitor's notebook. It has retained the Madison Avenue firm of Manning Selvage & Lee to flog its own message—that Shalala should not intervene in this patent fight. –E.M.



Media blitz. CellPro has generated widespread publicity about the treatment of its CEO.

vice. They note that CellPro submitted a premarketing application to FDA in 1993 and won approval in December 1996. Baxter, which obtained its license in 1990, submitted its FDA application in February 1997. It cannot be certain if, or when, its machine will be approved for sale.

CellPro's lawyers pulled out all the stops in describing what may happen if the government does not intervene. "Thousands of victims of the most acute forms of metastatic breast cancer ... would be forced to undergo less optimal treatment with unnecessary suffering, and, in some cases, death," they write. And they warn that children with leukemia "will surely die" unless they are allowed to use CellPro's machine to purge aggressive T cells from imperfectly matched donor material. Hopkins dismisses these arguments, contending that Baxter's cell-concentrating device works as well as, or better than, CellPro's and has been marketed in Europe since 1995. Baxter executive John Osth claims that scores of his machines have already been approved for experimental use in U.S. clinics.

Several bone marrow transplantation experts who spoke to *Science* confirmed that both the Baxter and CellPro devices work well and are available in clinics. But Malcolm Brenner of St. Jude Children's Research Hospital in Memphis, Tennessee, says the main advantage of the CellPro machine is not its technical capabilities but the fact that the CellPro device has an FDA license. This means that any clinician can simply buy one and use it, while one must get Baxter's permission and apply for an FDA experimental-use permit to use the Baxter machine. "It certainly makes our life easier" if a machine is already approved, Brenner says.

One remarkable element in this fight is that most of the clinics that are buying the CellPro machine aren't using it for the procedure for which it was approved: autologous bone marrow transplantation. The procedure is "not done much," says Brenner, who notes that the machines are being used primarily for stem-cell collection from peripheral blood for experimental therapies—"off-label uses" not approved by the FDA. Although such uses are legal, advertising them is not. Indeed, FDA reprimanded CellPro in January 1997 for sending out a "false and misleading" Christmas card that, in FDA's view, promoted CellPro's device for use in parent-to-child peripheral blood transplants.

In serving as arbiter, NIH has set a goal of deciding within 60 days (possibly in early August) whether the evidence of a public health crisis is strong enough to warrant action. NIH may call for public hearings, providing a basis for a final decision on whether or not the government should take control of the Hopkins patents.

–Eliot Marshall

TaqMan

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quickly makes millions of copies of the original. This amplification allows researchers to detect something that otherwise would be invisible. But determining with precision how much HIV is present in an amplified sample requires diluting it repeatedly until it can be compared to a known standard. As Michael Hunkapiller, general manager of PE Applied Biosystems, explains, "PCR, by itself, is not really a good quantification test."

TaqMan's great selling feature is that it can quantitate the virus in "real time," without requiring any cumbersome additional steps after the reaction is completed. This is where the probes come in. They carry a fluorescent dye and are mixed with the sample before the PCR reaction begins. In the case of HIV, the probes bind pieces of viral nucleic acids. The dye does not fluoresce, however, until those pieces are copied. So, by monitoring the intensity of the fluorescence, TaqMan can gauge the amount of HIV present. TaqMan also processes 96 samples at a time. In all, it cuts in half the time it takes researchers to analyze their samples.

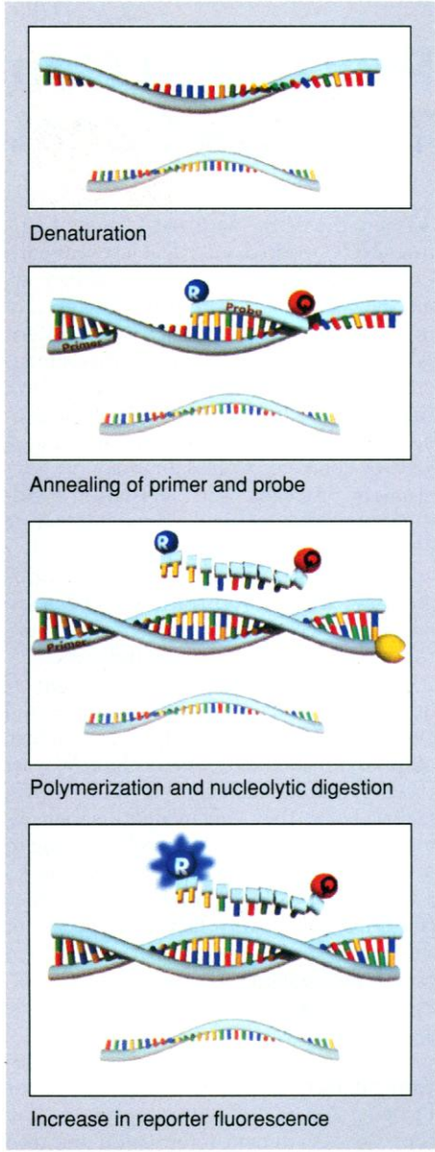
Roche well realizes that TaqMan may prove to be a faster way to analyze HIV levels than is currently possible. "We, too, are very excited about TaqMan," says Roche's John Sninsky, senior director of research. Indeed, says Sninsky, Roche encouraged PE Applied Biosystems to make the machine under license in the first place. But he says there are several scientific obstacles that still have to be worked out—which a Roche team is aggressively addressing—before TaqMan can reliably assess HIV levels. One critical problem is that it is easy to get a false negative if the PCR amplification begins before the probe binds to its target. "Until we have been able to solve the problems and validate the technology, we're hesitant to encourage people to use it," says Sninsky.

Pomerantz counters, however, that the companies could speed development of the assay by making the probes widely available. "What you'd like to have is cross-fertilization between academia and industry," says Pomerantz. Asked whether providing HIV probes to academics might help work out the kinks in the system, Sninsky says "That's an interesting point," and adds that they have offered to make the probes for some collaborators. Having people make their own probes instead is a "terrible" idea, Pomerantz adds: "You need [the probes] to be standardized or else you won't know how [an HIV] level from Thomas Jefferson compares with one from the University of Michigan."

Sninsky, who notes that Roche scientists have presented their research with HIV and TaqMan at several public conferences, wants academics to help them push the technology forward—but by analyzing things other than HIV. "We hope people will gain experience on the less squirrelly targets," says Sninsky. At the top of the list is using TaqMan to quantify gene expression in different cells, a critical question for the sea of researchers now decoding the human genome.

Then, again, if Roche and PE Applied Biosystems don't move quickly on TaqMan, they may find that their competitors have figured out a way to beat them at their own game. Abbott Labs, for one, has researchers who know a thing or two about HIV and TaqMan—or at least they know enough to be disinvited from a talk at a PE Applied Biosystems meeting.

–Jon Cohen



Probing questions. Researchers want to know why TaqMan probes, like the one depicted here, aren't universally available for HIV.