OSTP to Wade Into Gene Patent Quagmire

The fight that erupted within NIH over patenting gene fragments has now reached the White House science office

FOR THE PAST MONTH, NATIONAL INSTITUTES of Health director Bernadine Healy has said little about the furor unleashed by NIH's move to patent hundreds and perhaps thousands of unidentified gene fragments. She considered it a "tempest in a teapot," she told *The Washington Post*. Healy's public silence, however, belies the extent of the maneuvering going on behind the scenes at the highest levels of the federal science policy establishment.

Indeed, what began as a tussle between James Watson, head of the genome effort at NIH, and Reid Adler, the NIH director of technology transfer who decided to pursue the patents, has now escalated to involve Healy, her boss, assistant secretary of health James Mason, and his boss, Secretary of Health and Human Services (HHS) Louis Sullivan, who is expected to issue a statement soon. And now, asserting that this is a government-wide issue, the White House Office of Science and Technology Policy (OSTP) has joined the fracas and is setting up a working group to soothe interagency tensions and arrive at a consistent government policy.

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—Healy

At issue is whether short bits of unknown genes should be patented—especially by the barrelful, as NIH is attempting to do. Clearly, gene sequences have been patented before; what is different in this case is that NIH researcher Craig Venter, who is identifying and sequencing nearly a thousand of the gene fragments a month, has no idea what the vast majority of them are. He simply buys a "library," or collection of complementary DNA (cDNA) clones representing genes active in the human brain, then randomly fishes out the clones and sequences a few hundred bases of each, a fairly trivial task on an automated sequencing machine. When word got out that Venter and NIH had filed a patent application on the first 350 of these fragments, laying claim not just to the fragment but to the entire gene and the protein it encodes, genome project leaders in the United States and abroad hit the roof (*Science*, 11 October, p. 184).

NIH's Adler insists he is obligated to patent and license promising inventions under the 1986 Federal Technology Transfer Act. What's more, he says, providing companies with patent and license protection is the only way to ensure that they will develop any products, such as new drugs or diagnostics, that might emerge from the genes.

But Watson, David Galas, who oversees the Department of Energy (DOE) genome program, and incensed genome officials in Europe and Japan are not buying it, nor are many researchers. Just last week the American Society of Human Genetics, a group of 4500 physicians, scientists, and genetic counselors, released a position paper lambasting the NIH plan. The critics fear the scheme will have just the opposite effect of what Adler intended and will inhibit commercial development. They also charge that it will turn the genome project into a mad scramble for patents and undercut international collaboration—which may be happening already.

The very public fracas, first reported by *New Scientist* and then *Science* and *Nature*, apparently took Healy off guard. And with Watson and Adler so visibly at odds with each other, NIH looked like a divided house—presumably a view neither Healy nor her bosses at HHS savor. Shortly after the story hit the popular press, Healy interceded. She held a closed-door meeting on 29 October, attended by Adler, Venter, Elke Jordan, Watson's second in command at the genome center, DOE's Galas, D.A. Henderson, the associate director for life sciences at OSTP, and others. No one will say much about it—Venter says the group agreed to a gag rule until things calm down—and Watson, perhaps the scheme's most vehement critic, could not be reached for comment. *Science* learned, however, that at the meeting Healy put her support firmly behind Venter and Adler and the NIH patenting plan.

She reiterated that support last week at a previously scheduled meeting at NIH on technology transfer, to which Adler added an evening session on cDNA patenting. In her first public statement on the mat-ter that has so galvanized the research community, Healy noted that "NIH has a record of utilizing the patent system in a socially responsible way. When NIH does move into the patent arena, it is with the public good as a driving force and not because scientists want to get rich." Even so, she conceded NIH has landed in the middle of a heated debate. In retrospect, she told *Science*, HHS officials probably should have debated the merits of cDNA patenting in June, before the application was filed, "but I don't think anyone realized it was going to create such a tempest."

Healy would clearly like to settle the matter in-house—if not within NIH, then at least within HHS—and at the meeting she outlined her plans for doing so. By January, Sullivan will issue a Public Health Service-wide policy on patenting discoveries from cDNA research, she said. One looming question is whether Adler and Venter will go ahead and file the second patent application on about 2000 additional cDNA fragments, as planned. Healy seems to have no doubt, saying the question is not whether to file "but when and how to file the next patent or series of patents." But while she was adamant that the decision will be made within HHS, it's not clear that she will be able to keep control.

Others, like DOE's Galas, say the issue reaches far beyond NIH to involve the dozen agencies involved in biotechnology. "An agency can make a policy, but it needs to be carefully coordinated with everyone else," he maintains.

Henderson at OSTP seems to agree. The working group he is setting up, which will include representatives from HHS, DOE, the Commerce Department, the National Science Foundation, and the Agriculture Department, will "look at where we are and how we get resolution," he says. Specifically, he told *Science*, the group will look at what NIH should do about the existing patent application and whether NIH should file additional applications. Another priority, he say, is acquainting the Patent and Trademark Office with "the complexity of the issue and all its implications." The group

will push for an expedited review of the NIH patent by the Patent Office. Indeed, one of the few things on which people agree is that lingering uncertainty is bad for industry and bad for international relations. "It could be a real problem if this goes on for a long time," says Henderson.

Meanwhile, another controversy is brewing over the United Kingdom's cDNA project—specifically, over access to their database. Tony Vickers, head of the resource center for the Medical Research Council project, insists that the UK data will be open to academic researchers, though industry will pay a subscription fee. "That is a crock," responds Norton Zinder of Rockefeller University, one of several U.S. scientists who accuse the British of planning to keep their data secret. This new dispute, as well as U.S. scheme, seem certain to be on the agenda at the first of perhaps many congressional hearings on the issue, scheduled for 20 November, 2 days after this issue of *Science* went to press. ■ LESLIE ROBERTS

FDA Committee Raises AIDS Vaccine Hurdles

A highly charged meeting of a Food and Drug Administration (FDA) advisory committee on 12 November disappointed biotech companies making AIDS vaccines and in the process triggered what some commentators called a "bloodbath" on Wall Street. The vaccines in question, though, aren't the usual suspects. When the subject of AIDS vaccines comes up, most people think of injections for those who are not infected—to prevent them from getting the disease. But one of the main types of AIDS therapies now being considered is the immunotherapeutic vaccine, a vaccine to boost the immune systems of those already infected with HIV. Several companies are now testing such vaccines in human beings and had hoped to market them soon. But the FDA advisory committee, after a sometimes heated debate, moved back the finish line that therapeutic vaccines must cross before going to market.

What stirred up all the trouble during the deliberations of the FDA Vaccines and Related Biological Products Advisory Committee (which consists of outside experts whose decisions are not official but carry weight in the FDA) was the question of what data the companies must show to prove their vaccines work. Actual clinical data showing that patients improve from a particular therapy is hard to come by, because people with HIV infection can remain disease-free for years. In the absence of clinical data, the companies had hoped to use "surrogate endpoints," such as an improvement in the number of CD4 cells, the key white blood cells that are depleted in those infected with HIV. But the committee voted unanimously that even if an experimental vaccine produced an improvement in CD4 counts, that evidence alone should not be grounds for licensing.

The committee members said they were skeptical about CD4 counts as surrogate endpoints because they do not think those numbers can be depended upon. Recent unpublished data from an ongoing clinical trial of the anti-HIV drug AZT indicates the drug can improve clinical outcome independent of CD4 levels. And, as the committee's chair, Richard Johnston Jr., a pediatrics professor at the University of Pennsylvania School of Medicine, puts it, "There is no good evidence to show that if you prop up or stabilize CD4 counts, especially by immunologic means, that it will be beneficial to patients."

Those most immediately affected by the committee's opinion are three companies that have already been given the green light by the FDA to test their vaccines in HIV-infected people. Clinical trials of AIDS vaccines from Connecticut's MicroGeneSys and San Diego's Immune Response Corp. have already shown that their products are safe and can stimulate the immune system; San Francisco's Genentech is just embarking on its first human trial.

The committee came down hardest on MicroGeneSys, which had submitted the proposal that led the FDA to call the meeting. An ongoing, double-blind, randomized trial of the company's vaccine conducted by the U.S. military in 130 patients is planned to last 3 to 5 years. MicroGeneSys had asked the FDA whether the company could file a product license application as early as 9 months into the trial if CD4 counts improved. But biostatistician Thomas Fleming from the University of Washington noted that "we should keep in mind there are substantial negative consequences when you compromise the reliability of conclusions with less rigorous scientific approaches."

Though Genentech's human trials are just beginning, the company's designs for future trials also include relying heavily on CD4 as a surrogate marker. Immune Response, on the other hand, presented a different design, one that some committee members thought could offer a way forward through the "surrogate endpoint" dilemma. Rather than using CD4 levels as a primary surrogate marker, Immune Response's clinical trial in 100 HIV-infected people is assessing its vaccine's effects on virus levels in blood cells. Some committee members suggested that combining such "viral load" data with CD4 counts could provide compelling information. This 1-year trial is planned to end in September, and the company will now likely move up a larger planned trial using clinical endpoints.

The FDA advisory committee's decision sent a strong message that CD4 count alone isn't the appropriate finish line for vaccine trials. Yet, given the urgency of the need for AIDS vaccine and therapies and the complexity of obtaining clinical data, the question of surrogate endpoints isn't about to go away. Indeed, some at the hearing argued that the use of surrogate endpoints is of real benefit to patients, and that surrogate endpoints will certainly continue to be used. Clinical pharmacologist Lewis Sheiner of the University of California, San Francisco, argued that the real question was not doing away with uncertainty, but simply "how much uncertainty we can tolerate." Said Sheiner, "It's not a question of whether we will use surrogate markers—we have and we will."

And FDA representatives at the meeting conceded that positive data based on several surrogate endpoints could lead to approval of a product, as long as the manufacturer agreed to continue gathering clinical data. If the vaccine did not reduce the amount of AIDS-related disease in immunized patients as compared to a control group, the companies would later be required to pull their products from the market.

But Wall Street wasn't mollified. Several stocks dropped, and ironically it was Immune Response, whose trial relies the least heavily on CD4 counts, that took the biggest fall, descending 15 3/4 points the day after the meeting. The financial news show CNBC, on the Financial News Network, described the drop in Immune Response's stock as a "bloodbath." Yet the bloodbath on Wall Street remains a minor affair compared to the one among AIDS patients, and there will no doubt be many further ups and downs in biotech stocks as researchers hunt for what some researchers are calling "vaccine therapy" for infected people. And that is a search in which the question of surrogate endpoints will probably take on increasing prominence. ■ JON COHEN