

is questionable. Secretary of Commerce Robert Mosbacher has created a special Advisory Commission on Patent Law Reform chaired by Manbeck. He and the 14 university leaders, business executives, and lawyers on the panel have a deadline of August 1992 to come up with new ideas. Their mandate is broad, as reflected in an appeal published last month by PTO. It asks for comment on software patents, the clash between U.S. and foreign standards, and the fact that "patent litigation is said to be complex, expensive, unpredictable."

One of the panel's big tasks, says assistant patent commissioner Michael Kirk, is to find out whether U.S. citizens want simplicity enough to "harmonize" with other nations. Goaded by multinational corporations, which do want a change, the patent office has been negotiating a universal patent agreement in the World Intellectual Property Organization since 1984. As part of the deal, the United States might yield on its "first-to-invent" rule, and U.S. officials have offered to move toward the "first-to-file" standard.

But a shift could hurt academia. In the United States, university scientists publish discoveries first and file for a patent later. Under most foreign systems, the inventor loses the right to a patent if he or she publishes first, and must make a first official publication through the patent office. This is why it can be so difficult for U.S. university-based scientists to get patents abroad. Although academics would like to extend their reach overseas, they don't want to reduce their freedom to publish. U.S. officials have been working on a possible compromise that would guarantee a year's "grace period" for filing an application after a discovery. Others have suggested combining the grace period with an amendment that would recognize publication in a peer-reviewed journal as a form of official notice. But so far the negotiators haven't found a solution that satisfies everyone, and they don't seem close.

Which brings us back to where we began: money. In more generous times, some of these problems would prompt temporary relief from Congress through a larger federal appropriation. This would at least help on the financial and staffing needs. But this solution isn't possible any longer. Just the opposite: The Bush Administration has made it clear that the patent office is to rely less on the Treasury. As Manbeck said recently, PTO "stands at a crossroads" this year, and it remains to be seen whether the path it has chosen—that of becoming a quasi-private agency—will streamline the system, or just make the problems more intractable.

■ ELIOT MARSHALL

Baltimore Case—In Brief

Three months after a widely leaked draft report by the Office of Scientific Integrity (OSI) within the National Institutes of Health accused Tufts immunologist Thereza Imanishi-Kari of fabricating data in a 1986 Cell paper she had co-authored with Nobel laureate David Baltimore, the controversy has become, if anything, more intense. An unusual series of published statements in Nature from the principals in the case has catalyzed a bitter debate within the biomedical community. What follows—for those weary of reading all the statements and counterstatements—are the highlights.

Imanishi-Kari's Rebuttal

Thereza Imanishi-Kari has not been silent on the OSI draft report. In her 45-page official reply to the OSI, she not only complained that OSI had denied her due process protection (thereby convincing a group of more than 100 biomedical researchers recently to agree with her in a public letter to OSI—*Science*, 21 June, p. 1607), but also denied fabricating data, calling the OSI's reliance on forensic and statistical analysis "the weakest of all possible forms of evidence."

For instance, OSI concluded that Imanishi-Kari had fabricated one set of data after a Secret Service analysis revealed a "full match" between materials (the ribbon ink, paper, and printer) ostensibly used to produce her 1985 radiation counter tapes and those from experiments done in 1981 and 1982—several years before Imanishi-Kari's laboratory had received the mice on which she was allegedly experimenting. The OSI's clear implication is that she fabricated the data by selecting old tapes and pasting them onto new pages.

Imanishi-Kari contested this finding in her reply, arguing that the comparison of tapes in the full match was "utterly lacking in scientific significance" since the two sets of tapes had been produced by different types of radiation counters with different output formats. While one immunologist friend of Imanishi-Kari's says privately that he found this reply compelling, sources familiar with the forensic work note that the two counters easily could have been connected to the same printer. (Unfortunately, those who know for certain—the OSI and the Secret Service—refuse to comment.)

O'Toole Fires Back

A separate firefight broke out when Margot O'Toole—the Imanishi-Kari postdoc who challenged the paper in 1986—published a 4-page statement in which she raised a number of serious allegations against

David Baltimore, Imanishi-Kari, and members of the Tufts University and MIT panels charged with investigating her challenge. Her statement was a direct response to Baltimore's earlier public apology (*Science*, 10 May, p. 768), which critics such as Harvard molecular biologist and Nobel laureate Walter Gilbert considered inadequate. Although O'Toole had made many of her charges before, most of them were news to all but the inner circle of aficionados who have been following every twist and turn in the case.

O'Toole not only charged that she had provided Baltimore and the two scientific panels with enough information in 1986 to realize something was wrong with the *Cell* paper, she claimed that in meetings with both the MIT and Tufts panels Imanishi-Kari had admitted to not performing "crucial experiments." And in spite of that evidence, she claimed, the panels had concluded no correction was warranted. O'Toole wrote that she considered it a "disgrace" that the authors had failed to retract the paper back in 1986, and complained that the senior scientists involved considered the protection of Imanishi-Kari's career more important than scientific truth.

Baltimore and the panel members haven't taken O'Toole's latest remarks calmly. In another statement in *Nature*, Baltimore charged O'Toole with creating a "misleading impression" and making numerous "overstatements and errors." Herman Eisen, who undertook the MIT inquiry, wrote that he was "puzzled" by O'Toole's "turn-around." In fact, Eisen says, O'Toole's original memo on the case "contains no suggestion that reported results were based on nonexistent or fraudulent data." As a result, he wrote, the memo hinted at little more than "a typical scientific dispute." And the Tufts panel members denied O'Toole's version of events, writing that Imanishi-Kari had never said she didn't perform important experiments.

Who really knew what when? The latest round of statements does little to answer that question. Take, for example, Eisen's response. Because he is highly thought of in biological circles, many scientists were willing to believe that O'Toole had overstepped the bounds

when she suggested he had knowingly ignored the possibility of fraud in 1986. But in testimony before Congress in 1989, Eisen stated that he was "not unaware of the possibility that [O'Toole] had in mind fraud and was unwilling to say so, and in carrying out my evaluation, this concerned me."

Scientific Community Splits

The continuing rancor is only further polarizing the biomedical community. On one side are the defenders of Baltimore and Imanishi-Kari, including a number of immunologists and Harvard microbiologist emeritus Bernard Davis. They cast aspersions on O'Toole's account and suggest that most of OSI's conclusions are "wholly dependent" on her testimony. On the other are O'Toole's champions—an array of prominent Harvard scientists, including molecular biologists Walter Gilbert, Mark Ptashne, and John Cairns—who have studied the science and history of the controversy and pronounced O'Toole correct. In the middle is what is probably the largest group: those who don't know what to think. Scripps Institute immunologist David Lo is a typical example: "Every week, *Nature* comes out with a new set of letters. Whom do you believe? Everyone sounds reasonable....It's just very uncomfortable for us all."

At issue are two distinct—and distinctly contradictory—philosophies. Davis, who describes O'Toole's statement as an "extraordinary outburst," says the rebuttals from Baltimore, Eisen, and the Tufts panel raise "very serious doubts about the reliability of much of O'Toole's testimony, however honest her intentions." The OSI, he says, relied heavily on O'Toole's statements while rejecting contradictory testimony from others. "It seems hardly credible that all these scientists at MIT and Tufts are the villains that she portrays," he says.

Cairns, on the other hand, has little patience with such views. After meeting O'Toole recently and digging into the case as a result, "I've just come to the conclusion that Margot O'Toole is absolutely right and these guys are absolutely wrong." He denounces Eisen's statement as "complete weaseling nonsense from a very highly established and respected guy [who is] blaming, as it were, the victim." And he holds a dark view of the way members of the scientific establishment have rallied around Baltimore. In a recent letter to the National Academy of Sciences, he wrote: "Nothing is likely to stop the affair from progressing to its final disastrous conclusion. I do not see how David Baltimore can escape public censure, at the very least. About the only ques-

tion remaining is whether anyone will actually go to jail."

The Scientific Results

Still under OSI and congressional investigation is the question of how, exactly, the MIT and Tufts investigations went awry—and who is to blame. O'Toole has long argued that when she based her initial challenge on data she unearthed in 17 pages of laboratory notes—data that was actually published in the *Cell* paper's Table 2—it should have led everyone to second thoughts. The OSI struck a similar stance in its draft report, noting that these pages provide "prima facie" evidence contradicting the paper's central claim. Eisen, however, has written that one reason he disagreed with O'Toole's arguments was that he found them implausible. Now, however, Eisen admits that he might have misunderstood a key element in O'Toole's scientific reasoning—one that might have led him to conduct a more thorough inquiry. Although couched in the specialized language of immunology, this point could become highly significant in the ongoing investigations.

The *Cell* paper's main thesis held that a "transgene," a gene inserted into a line of mice, could indirectly influence its natural array of antibodies by somehow forcing native genes to produce antibodies that "mimicked" a feature of transgenic antibodies known as their "idiotype." As a result, one key issue for the experimenters involved determining whether a given idiotype-positive antibody had been produced by native genes or the transgene. Fortunately, antibodies have another distinctive feature, known as isotype, that is useful in this regard. Because the transgene produced only antibodies with an isotype known as μ^a , the researchers could safely assume that antibodies with different isotypes, such as μ^b or γ , were produced by native genes.

In her challenge, O'Toole concluded that monoclonal cell cultures testing positive for idiotype did so because they were producing antibodies with the μ^a isotype—an indication of transgene activity that would undermine the paper's main conclusion. Eisen, however, wrote that he found this argument unpersuasive at the time, since he assumed O'Toole was postulating the existence of "hybrid" antibodies with more than one isotype. He viewed such hybrids as unlikely in this case, since the paper had reported that a majority

of the cell cultures under study produced antibodies with a γ isotype—one that rarely, if ever, combined with μ isotypes. This claim was later withdrawn.

Earlier this month, however, Eisen met with four Harvard scientists—Gilbert, Ptashne, biochemists Paul Doty and John Edsall—at Harvard, where they discussed the science and concluded that O'Toole hadn't been postulating a μ - γ hybrid after all, but a more plausible μ^a - μ^b hybrid. Eisen and Ptashne, in fact, are considering co-authoring a letter on this matter. Eisen, however, doesn't believe that his misunderstanding changed the course of his inquiry, saying that



Counterpunching. Margot O'Toole (left) and Thereza Imanishi-Kari traded statements in *Nature*.

"you can't be sure [such an effect] is real unless you perform further tests."

OSI Flip-Flops on Storb

Two weeks ago, the OSI asked University of Chicago immunologist Ursula Storb to resign from the scientific panel in the Baltimore case, citing a letter of recommendation she had once written for Imanishi-Kari (*Science*, 21 June, p. 1607). Last week, the office reversed itself, according to Storb, and withdrew its request. "It was a total turnabout," she says. "I guess finally the OSI decided there was no conflict of interest." Storb, who claims she had forgotten about the letter when invited to join the panel, says the Tufts pathology department had "solicited" the recommendation letter from her because of her experience. "The issue wasn't conflict of interest, it was an appearance of conflict," says OSI Director Jules Hallum. "In retrospect, I think we did the right thing."

While Storb is apparently off the hook, one NIH overseer—Representative John Dingell (D-MI)—is not pleased. "Obviously, he doesn't think much of [the OSI reversal]," says an aide. "He likes to say that even in the defense industry, they recognize a conflict. Apparently scientists don't even do that."

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