# NIH Finds Fraud in *Cell* Paper

*A strongly worded draft report condemns Thereza Imanishi-Kari for fabricating data and David Baltimore for overlooking problems and making "extraordinary" statements*

THREE WEEKS AGO *SCIENCE* PREDICTED THAT the National Institutes of Health was likely to issue a harsh critique of Tufts immunologist Thereza Imanishi-Kari's role in what has become known as the "Baltimore case." Now an NIH draft report on the investigation has become public, and its verdict is stark: Imanishi-Kari committed "serious scientific misconduct" by "repeatedly present[ing] false and misleading information" to federal investigators.

Rockefeller University president David Baltimore and the four other biologists who were coauthors of the 1986 *Cell* paper* at the heart of the affair were not charged with misconduct. But the draft report, written by the Office of Scientific Integrity (OSI), sharply criticizes Baltimore for continuing to defend Imanishi-Kari "as evidence mounted that serious problems existed with the serological data," and for making what the report calls "deeply troubling" statements. For example, the report states that Baltimore told the investigators as recently as last April that "...[I]n my mind you can make up anything you want in your notebooks, but you can't call it fraud if it wasn't published."

Vindicated was whistle-blower Margot O'Toole, who was warmly praised by OSI. O'Toole first challenged the paper in 1986 as a postdoc in Imanishi-Kari's laboratory. Virtually all her charges have now been upheld. Indeed, the 219-page report ends with a remarkable paean to O'Toole, calling her actions "heroic" and praising her "dedication to the belief that truth in science matters."

The draft report is not official. It was leaked last week to major news organizations, including *Science*, after OSI circulated it to the targets of the investigation for a 30-day comment period. Thus, Imanishi-Kari may yet challenge some or all of the report's conclusions. But Baltimore, who has publicly battled every previous assault on the integrity of his colleagues and on the paper itself, released a brief statement admitting that the draft report "raises very serious questions about the veracity of the serological data in the paper." The statement added that Baltimore would ask his coauthors to retract the paper. (Baltimore declined a telephone interview through a spokesperson, and Imanishi-Kari's lawyer, Bruce Singal, did not return repeated telephone calls from *Science*.)

It took nearly 5 years of controversy to make Baltimore change his mind. The *Cell* paper has been investigated by Tufts University, the Massachusetts Institute of Technology, an earlier NIH panel of scientific experts, and a subcommittee chaired by Representative John Dingell (D–MI). Only Dingell's investigation had previously found evidence suggesting fraud. In fact, the first NIH panel concluded on 31 January 1989 that "no evidence of fraud, conscious misrepresentation, or manipulation of data was found."

The current scientific panel† was clearly impressed by U.S. Secret Service forensic analyses of Imanishi-Kari's notebook pages and tapes printed by radiation counters (*Science*, 8 March, p. 1168). Based on that evidence and a 23-month series of interviews, examination of laboratory notes and other documents, and statistical analyses of Imanishi-Kari's data, the new report concludes that two sets of data related to a key table in the paper, labeled Table 2, were "fabricated." The report also says another set of data relating to the behavior of a monoclonal antibody known as Bet-1 was "falsified" and criticizes the paper's conclusion that a gene transplanted into a line of mice indirectly altered the animals' natural repertoire of antibodies.

The centerpiece of OSI's investigation was a set of "highly significant," though unpublished, "June subcloning" data Imanishi-Kari had provided NIH in 1988 to bolster claims made in the *Cell* paper's Table 2. Until Imanishi-Kari came up with this unpublished data, the first NIH panel doubted the reliability of the data actually published in Table 2, which was considered central to the paper's main thesis. Imanishi-Kari said she generated these unpublished data in June 1985, but forensic and statisti-

*D. Weaver *et al.*, "Altered repertoire of endogenous immunoglobulin gene expression in transgenic mice containing a rearranged Mu heavy chain gene," *Cell* **45**, 247 (1986).

†The first panel included Joseph Davie, vice president of G.D. Searle Co., University of Chicago immunologist Ursula Storb, and Stanford immunologist Hugh McDevitt. University of Texas pathologist Stewart Sell and Carnegie-Mellon University biologist William McClure were added in May 1989.

## Warm Praise for a Whistle-Blower

*NIH's 1989 report on the* Cell *paper conspicuously omitted praise for Margot O'Toole. The new report has this to say:*

"Dr. O'Toole suffered substantially for the simple act of raising questions about the accuracy of a scientific paper. The loss of her position in Dr. Imanishi-Kari's laboratory is only the most visible symbol of the price exacted of her after she raised the challenges to the paper. Notwithstanding the losses and costs she incurred, Dr. O'Toole maintained her commitment to scientific integrity throughout the several reviews and investigations that followed her challenges to the *Cell* paper.

"Dr. O'Toole was invaluable to the effectiveness of the OSI investigation.... [Her] actions were heroic in many respects. She deserves the approbation and gratitude of the scientific community for her courage and her dedication to the belief that truth in science matters."

Ruth Fremson/*The Washington Times*

# The Report's Principal Conclusions

*The following excerpts from the Office of Scientific Integrity's report are OSI's conclusions about the culpability of the three main authors of the* Cell *paper. Imanishi-Kari did the serology, Weaver did the molecular biology, and Baltimore was the lab chief.*

## Thereza Imanishi-Kari

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1. The forensic evidence and the extensive statistical analyses establish that the June subcloning data and the January fusion data [control data in Table 2] are fabricated. It remains unclear if these experiments actually were done...

2. Dr. Imanishi-Kari repeatedly presented false and misleading information to the NIH and OSI and to the expert scientific panels.... [Statements about] the June subcloning and January fusion experiments in particular...are false, as demonstrated in this report, and were known by her to be false, or were provided with reckless disregard for the truth.

3. It is probable that a substantial portion of the I-1 notebook, the major source of data provided to substantiate the Weaver *et al. Cell* paper, was falsified. Forensic and statistical analyses reveal the putative chronology of experiments in the notebook cannot be substantiated. Since the spring of 1989, Dr. Imanishi-Kari has claimed that the dates in her notebook are meaningless.... Resort to the argument that dates are meaningless does not answer the challenges to the paper, and, in fact, throws into question the entire fabric of the purported experimental record.

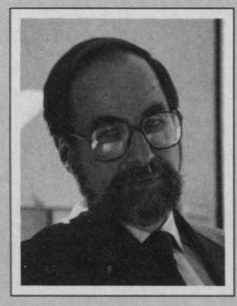
4. Dr. Imanishi-Kari...argued that data were not germane to the investigation if they were not published. But as noted throughout this report, the investigative team believed all the data are relevant and must be taken into account in determining the reliability and authenticity of the experimental record....

## David Baltimore

It may be understandable that Dr. Baltimore initially failed to credit the questions raised about the *Cell* paper, and rose to the defense of Dr. Imanishi-Kari. However, it is difficult to comprehend his maintaining this stance as the evidence mounted that serious problems existed with the serological data in the *Cell* paper....

Dr. Baltimore's most recently expressed views concerning the investigation are the most deeply troubling. These were statements Dr. Baltimore made on April 30, 1990, when he was interviewed by the OSI investigative team. Dr. Baltimore disputed the significance of the June subcloning data and he asserted that if they were fabricated, the NIH was somehow responsible for this act of scientific misconduct: "If those data were not real, then she (Dr. Imanishi-Kari) was driven by the process of investigation into an unseemly act...." (Dr. Baltimore apparently was referring to the requirement by the NIH at the conclusion of the first investigation that the coauthors publish the June subcloning data as a correction to the *Cell* paper.)

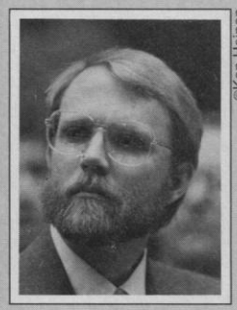
Dr. Baltimore went on to say that "...[In] my mind you can make up anything that you want in your notebooks, but you can't call it fraud if it wasn't published. Now, you managed to trick us into publishing—sort of tricked Thereza—into publishing a few numbers and now you're going to go back and see if you can produce those as fraud. But, I think you should see that was a forced situation..."



The OSI found Dr. Baltimore's statements to be extraordinary. They are all the more startling when one considers that Dr. Baltimore, by virtue of his seniority and standing, might have been instrumental in effecting a resolution of the concerns about the *Cell* paper early on, possibly before Dr. Imanishi-Kari fabricated some of the data later found to be fraudulent...

## David Weaver

...It appears Dr. Weaver was not alert to, nor concerned about, the significance of double expressors [cell lines that were expressing two types of antibodies, the existence of which was explicitly denied in the *Cell* paper] as long as it did not affect his molecular assays and as long as there did not appear to be so many double expressors that the overall assessment of the hybridoma population was affected. This narrow focus was inappropriate for the first author of an important paper, and it seems to have been shared by Dr. Baltimore. Since the experimental record from Dr. Imanishi-Kari concerning these issues is so questionable, it is not clear what information was available to Dr. Weaver at the time the research for the *Cell* paper was being done (although Dr. Weaver stated he believed he had access to all of Dr. Imanishi-Kari's records). Taking all these considerations into account, the OSI concluded there was not a sufficient basis for further inquiry into the conduct of Dr. Weaver.



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cal analysis of her notebooks contradicted her claims.

For instance, the radiation counter tapes attached to Imanishi-Kari's notebooks were of a distinctive greenish hue. When the Secret Service examined more than 60 notebooks from other scientists in the same laboratory, they found no similar tapes dated later than January 1984. A more detailed analysis involving tape color, type font, and ink type produced what the Secret Service called a "full match" between Imanishi-Kari's tapes and tapes produced by Charles Maplethorpe, then a graduate student in her laboratory, between 26 November 1981 and 20 April 1982. This suggests they were not generated as part of the research for the *Cell* paper at all. Furthermore, OSI statistical analyses found that several columns of data Imanishi-Kari says she copied from a counter tape to a notebook page did not fit an expected distribution with a probability greater than 0.01%.

The report makes a similar finding regarding control data actually published in Table 2. These data were based in part on a greenish counter tape similar to those presented by Imanishi-Kari as part of the June subcloning data, and they exhibited unusual statistical properties not found in unchallenged data, the report stated.

Although three of the panel members agreed with all the report's findings, two

others—Hugh McDevitt of Stanford University and Ursula Storb of the University of Chicago—filed a minority opinion in which they disputed the statistical analysis of Imanishi-Kari's data, describing it as "new and untried...in establishing proof of fraud." They also objected to several findings of fraud they felt could plausibly be explained by "alternative interpretations." And the two dissented from the report's severe criticism of the way Baltimore defended the paper, arguing that scientific collaborations are built on trust. "Once you [begin a collaboration], you...tend to believe that person," McDevitt told *Science*. "David didn't have any choice but to support her." McDevitt and Storb did, however, agree that both sets of Table 2-related data had been fabricated.

This draft report is far from the last word on this affair. OSI will incorporate comments from those under investigation into a final document, and recommend whatever penalties it finds appropriate. Those recommendations will also be provided to the accused for comment. The final report must then be reviewed and approved by two additional offices within the Public Health Service before it is officially made public.

OSI deputy director Suzanne Hadley points out that an official finding of "failure to provide truthful information" could lead OSI to refer the matter to the Justice Department for criminal investigation. (Some of the Secret Service evidence has already been impounded by the U.S. Attorney's office in Baltimore.) And the apparent inability or unwillingness of Imanishi-Kari's coauthors—and of Tufts and MIT—to investigate O'Toole's charges thoroughly is already part of yet another NIH inquiry.

John Dingell is not done with the case, either. An aide revealed that Dingell's subcommittee will release its own report on the MIT, Tufts, and NIH investigations within a month. Dingell also plans another subcommittee hearing to which MIT and Tufts officials are likely to be called, probably sometime in May.

The Baltimore report is just the latest in a series of investigations—all inspired by Dingell in one fashion or another—that has many elements of the scientific establishment reeling. Only 2 weeks ago, Stanford University underwent a public hazing for misallocating its indirect costs. According to insiders, it is only a matter of weeks until a long-awaited draft OSI report on the early AIDS research of Robert Gallo is completed. One top official at the National Academy of Sciences privately told *Science* he despairs over the image that U.S. science may be developing in the public mind and on Capitol Hill. And the Baltimore case isn't even over. ■ DAVID P. HAMILTON

# Who Found AZT Works for AIDS?

For years, researchers at the National Cancer Institute (NCI), including its present director, Samuel Broder, have argued that they deserve the scientific credit for determining that AZT is an effective treatment for HIV infection and AIDS. But as far as the U.S. Patent Office is concerned, that credit goes exclusively to scientists from Burroughs Wellcome Co., the drug's manufacturer. Last week, however, a coalition of AIDS patients took up the NCI scientists' cause, filing a lawsuit in federal court challenging Burroughs Wellcome's patent. Their aim: to bring down the price of the drug.

Burroughs Wellcome's patent gives the company exclusive rights to market AZT, and critics charged that the company has used its monopoly position to reap big profits. It now costs between $2000 and $3000 for a year's supply of AZT, and sales of the drug amounted to $287 million worldwide last year. If the patent is declared invalid, generic drug companies would be free, with the government's permission, to make AZT. According to a spokesman for Apotex, a company in Canada already making the drug for export to countries that do not recognize patent protection for pharmaceuticals, the price could drop by more than half.

Burroughs Wellcome argues that its researchers were responsible for bringing AZT to the market as an anti-AIDS drug. In the early 1980s, the company argues, its chemists had developed a method for synthesizing the drug and were studying it as an antibacterial agent. In June 1984, the company says it began searching for chemical compounds that have activity against HIV, and in November of that year its scientists identified AZT as potentially useful against AIDS. According to the company, in the spring of 1985, at its request, labs at Duke University, the Food and Drug Administration, and the NCI confirmed AZT's in vitro activity against HIV (it blocks the transcription of viral RNA into DNA). In the summer of that year, the FDA gave Burroughs Wellcome permission to begin trials in humans. A Phase I trial began in July, and by December it appeared from initial patient responses that the drug was helping to restore patients' immune responses.

But throughout that period, NCI scientists, particularly Samuel Broder and Robert Yarchoan and Hiroaki Mitsuya, were also characterizing and developing AZT. For example, in October 1985 Mitsuya, from Broder's NCI laboratory, was first author on a paper in *Proceedings of the National Academy of Sciences* that described AZT's in vitro activity against HIV, and in January 1986 Broder presented evidence of AZT's effectiveness at a scientific meeting (*Science*, 31 January 1986, p. 450).

Michael Davis, a faculty member at the Cleveland-Marshall College of Law, expects Burroughs Wellcome to argue that NCI was merely screening one of its compounds, in which case the company would retain the exclusive patent. NIH scientists, including Broder, will not comment on that question. But the lawsuit, filed by the Public Citizen Litigation Group on behalf of the People With AIDS Health Group, claims that NCI contacted Burroughs Wellcome in September 1984—2 months before the company says it identified AZT as a potential anti-AIDS drug—asking the company to supply potential antiretroviral agents, including nucleoside analogs, to an NCI program aimed at developing AIDS treatments. (AZT is a nucleoside analog.)

Burroughs Wellcome may try to get the suit dismissed on procedural grounds, arguing that Public Citizen's clients have no legal right to bring suit because they are not capable of infringing the patent, an ability required to sue a patent holder. Davis, who is working with Public Citizen on the suit, argues, however, that the people most entitled to challenge the patent are those who use the drug.

Even if the Public Citizen suit fails, Burroughs Wellcome will not be off the hook. Apotex and Novopharm, another Canadian drug manufacturer, have challenged Burroughs Wellcome's Canadian patent. Apotex spokesperson Elie Betito says its U.S. affiliate, Barr Laboratories, plans similar action in the United States. And NIH may get directly into the legal fray. "NIH has been meeting with Burroughs Wellcome over the past several months to discuss the inventorship of the patents relating to AZT," said NIH acting director William F. Raub in a statement last week. "We believe that NCI researchers should have been named as coinventors on these patents." Burroughs Wellcome disagrees and remains confident that it can uphold its patent claims. It may take a court battle to decide who is right. ■ JOSEPH PALCA