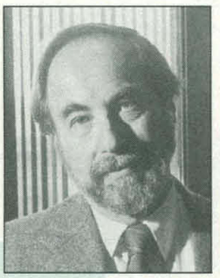
Imanishi-Kari Ruling Slams ORI

In finding that the Office of Research Integrity did not prove misconduct against a Tufts scientist, an HHS appeals panel also questioned how the government built its case

After "a decade in limbo," as Nobelist and co-author David Baltimore put it last week, immunologist Thereza Imanishi-Kari has been cleared of 19 charges that she committed scientific misconduct in connection with a 1986 paper in *Cell*. The decision, handed down on 21 June by an appeals panel of the Department of Health and Human Services (HHS), was unequivocal: The "preponderance of the evidence" did not support the government's case, the panel said. With that ruling, the panel voided a proposed 10-year funding sanction against Imanishi-Kari and laid to rest the government's best known attempt to prove scientific misconduct.

The ruling was the second significant defeat before the board for HHS's Office of Research Integrity (ORI), successor to the federal investigative team that began looking into this case for the National Institutes of Health (NIH) in 1989 and later found Imanishi-Kari guilty of misconduct. In 1993 ORI failed to convince a similar three-person panel of the guilt of AIDS researcher Mikulas Popovic (*Science*, 12 November 1993, p. 981). After that loss, ORI dropped a long-running investigation of Popovic's former boss, virologist Robert Gallo, who was then at NIH. Despite two victories, these setbacks have led some observers to suggest that HHS's system for investigating scientific misconduct is in trouble and needs fixing.

While it may be bad news for ORI, last week's decision represents a personal vindication for Imanishi-Kari and Baltimore, whose names had become linked in the headlines over the past decade. Asked repeatedly by staffers for Representative John Dingell (D–MI) and other investigative bodies to explain gaps and eccentricities in the data produced by Imanishi-Kari, Baltimore steadfastly rejected claims that his co-author had fabricated or falsified data. However, the negative publicity contributed to his decision to abandon the presidency of Rockefeller University and return to the Massachusetts Institute of Technology (MIT). "It's wonderful to be vindicated," Baltimore says. "But it is very sad that it has taken all this time, money, and energy to see what I believe was evident from the very start. Thereza has been unfairly prosecuted. ... A lot of people owe her a serious apology."



"The *Cell* paper as a whole is rife with errors of all sorts ... [including] some which, despite all these years and layers of review, have never previously been pointed out or corrected. Responsibility ... must be shared by all participants [including Baltimore]." *

"The credibility of [Imanishi-Kari's] testimony before us was bolstered ... when much of the evidence in the record, and in particular some of the document examination evidence, corroborated her statements and directly contradicted representations made by ORI."

PHOTOS BY SETH RESNICK

"It is also important to consider ... whether Dr. Imanishi-Kari had any conceivable motive for the allegedly false dating of the questioned pages. While some of the pages involved contained relevant data ... ORI offered no possible reason to fabricate other pages for which the same findings were presented."

Imanishi-Kari, who moved from MIT to Tufts University in 1986, says "It's a wonderful feeling. This was a victory for me and for my fellow scientists. It demonstrates definitely that there's something wrong with the [misconduct] process."

As might be expected, members of the investigative team that developed the evidence against Imanishi-Kari were upset with the ruling. "It's a goddamn sad day for science," says Peter Stockton, a former staff investigator for Dingell. Suzanne Hadley, another ex-Dingell investigator who had worked on the case even earlier as an NIH staffer, says the panel decision "is a stunning repudiation of the truth. ... In the long run, the truth will prevail." Margot O'Toole, who first raised questions about the paper's integrity when she was a postdoc in Imanishi-Kari's lab, was also bitter. "Given that this board tossed out the evidence," she says, "it is not surprising that they cannot believe that what I say happened, happened."

Government officials responsible for the handling of the investigation were silent. Lyle Bivens, the recently retired director of ORI, declined comment, and ORI lawyer Marcus Christ said he'd been instructed by HHS not to comment. HHS Secretary Donna Shalala, whose department includes both the office that brought the charges against Imanishi-Kari and the board that dismissed them, made no attempt to clarify the discrepancy. Through a spokesperson, Shalala simply said that the decision "speaks for itself." Dingell also declined to comment, saying he had not read the report.

The long road

The appeals panel reached its conclusion after sitting through 6 weeks of hearings last summer, reading thousands of pages of statements, and studying the records of earlier investigations. The hearing also offered Imanishi-Kari her first opportunity to confront and cross-examine her accusers. The proceedings focused chiefly on data that she provided as support for the 1986 *Cell* paper, which claimed to show that inserting a foreign mouse gene into a certain strain of mice caused changes in the host mouse's repertoire of antibodies.

It was the fifth time the data had been scrutinized by an investigatory body. O'Toole's original doubts had led to investigations by committees at MIT and Tufts, where Imanishi-Kari had become an assistant professor. The academic committees found errors, but no misconduct.

The judgments of these university-based panels were soon overshadowed, however, by a series of congressional hearings chaired by Dingell. His committee had asked the Secret Service to undertake forensic studies of material from Imanishi-Kari's lab—notebook pages, counter tapes from assays of radiolabeled reagents, and inks. In May 1989, Dingell

* This and other highlighted quotes are taken from the appeals panel's decision.

released his findings: Some of the notebook entries, his staff concluded, appeared to have been wrongly dated and were possibly fabricated. The hubbub led the NIH, which in 1988 had appointed a panel that found serious errors in the paper but no misconduct, to reopen its investigation.

Two years later, NIH's draft report on the case found Imanishi-Kari guilty of "serious scientific misconduct" for "repeatedly present-[ing] false and misleading information." The report also handed O'Toole a bouquet for her "courage" and dedication to the truth, while admonishing Baltimore for not taking the accusations more seriously. In a final report released in November 1994, ORI charged Imanishi-Kari with 19 counts of scientific misconduct and recommended that she be banned for 10 years from receiving federal funding.

Imanishi-Kari appealed, and her case was heard by two HHS lawyers, Cecilia Sparks Ford and Judith Ballard, and immunologist Julius Younger, an emeritus professor at the University of Pittsburgh School of Medicine.

Unconvincing evidence

As in 1994, ORI focused its case before the appeals board on the forensic and statistical analyses of Imanishi-Kari's notebooks. But the appeals panel was not impressed. A good example is its treatment of the "June subcloning data," a set of unpublished results that Imanishi-Kari produced for an early inquiry to buttress conclusions in table 2 of the *Cell* paper.

Imanishi-Kari said that she had done the experiments in June 1985, but ORI claimed, based on the Secret Service forensics, that Imanishi-Kari had used green radiation counter tapes left over from an old experiment to fabricate the results. ORI noted that the tapes didn't match those in other contemporaneous notebooks but did match the color, font, and ink of tapes from another researcher's notebook used in 1981 and 1982.

The panel brushed aside this coincidence as "meaningless." The panel found that innocent explanations for matches and mismatches of tapes and printer fonts were as plausible as guilty ones, suggesting that someone might have changed a printer ribbon, switched printers, or used a leftover roll of paper in a way that the Secret Service had not anticipated. In addition, in reviewing scrambled dates on pages of Imanishi-Kari's notebooks, the panel suggested that ORI didn't examine enough notebooks from other researchers to establish a "norm" from which Imanishi-Kari may have deviated.

ORI also argued that a statistical analysis of numbers copied by hand into one of Imanishi-Kari's notebooks indicated that the last digits in a series of columns were not random and that the data had been fabricated. But the appeals board expressed doubt that ORI's methods were "commonly accepted" and found that other analytical techniques could lead to different conclusions.

The board essentially rejected all the statistical and forensic analyses because it found "no independent or convincing evidence" of fabrication in them. Instead, the members tried to recreate the conditions under which the science was performed and weighed the credibility of each side's arguments. Here, Imanishi-Kari came out on top even though the board found the paper was "rife with errors of all sorts" and that Imanishi-Kari had a "cavalier attitude toward dates."

The board noted, for example, that none of the scientists involved in the MIT, Tufts, and NIH panel investigations had found evidence of misconduct. It said that ORI's charges, to be credible, "would require a conspiracy of authors and an intentional cover-up" by the MIT and Tufts review committees. The board also noted that most of the challenged data wasn't included in the *Cell* paper or was "trivial or peripheral" and that some of the allegedly fabricated data was "bizarre" or worked against the thesis of the paper.

"After hearing Dr. O'Toole and the other witnesses testify and examining all of her statements over the years, we question the accuracy of Dr. O'Toole's memory and her increasing commitment to a partisan stand."

"We are concerned about the implications of involving a whistleblower too heavily in an investigation. Such involvement can compromise both the ability of the investigators to maintain objectivity and the ability of the whistleblower to avoid becoming too vested in the outcome. We think that happened here."

At the same time, the panel aggressively criticized important elements of the government's case. ORI "misstated" what the Secret Service tests were capable of proving, it said, by claiming they demonstrated that certain pages were created at the same time when the tests showed only that they "could have" been. The panel also questioned "the accuracy of Dr. O'Toole's memory" and her objectivity, and it suggested that the Secret Service's objectivity was "under ... threat" from the Dingell committee, noting that the examiners, for instance, "gladly accept-[ed]" the committee's advice about which of Imanishi-Kari's notebooks to examine.

How did the appeals panel and ORI reach such different conclusions based on the same evidence? Explanations vary widely.

Joseph Onek, the attorney at the Washington, D.C., firm of Crowell & Moring who handled Imanishi-Kari's appeal, believes ORI failed to recognize flaws in its own case that undermined its credibility. "When you set up an office with nothing to do" but look for scientific misconduct, Onek asked, "aren't you going to get sort of exaggerated zealotry?" Barbara Mishkin, an expert in misconduct regulations at the Hogan & Hartson law firm in Washington, D.C., said she thought ORI's staff in the past lacked adequate training to prepare such a difficult case.

Hugh McDevitt, a Stanford University biologist who sat on the early NIH panel that found no misconduct, said that he believed ORI ran into trouble after its evidence was challenged in the June 1995 public hearings. He says he pointed out early on that much of the circumstantial evidence ORI was developing might have an innocent explanation. "Ten coincidences—even if you add them together—don't prove guilt," says McDevitt.

While the ruling marks the end of an ordeal for Imanishi-Kari, it may accelerate efforts by HHS to rebuild its system for investigating scientific misconduct for the second time since 1989. "The current system is broken; it turns it into a lawyer's game," says C. K. Gunsalus, associate provost at the University of Illinois, Urbana-Champaign. Cases are heard by "too many levels, by too many people, and by the wrong people at the wrong levels." Baltimore believes that ORI needs to be "reconstituted" to give the accused a "fair set of rights," and Onek notes that "you shouldn't wait 9 years for an opportunity for cross-examination."

One change already in the works is a set of recommendations for "streamlining the process and making it go faster," says HHS science adviser William Raub. Raub was chair of an intramural working group that forwarded its advice to Shalala last week (*Science*, 21 June, p. 1735). Its message—that HHS should give institutions more responsibility to carry out investigations—is likely to get a sympathetic reaction from Shalala, who "hopes to make a decision soon," according to her spokesperson. But if the appeals board ruling is any guide, the government must do more than speed up the process to establish faith in its ability to investigate and prosecute misconduct in research.

–Jocelyn Kaiser and Eliot Marshall