Imanishi-Kari Case: ORI Finds Fraud

The federal government's final investigative report in this long, drawn-out saga repeats and extends earlier charges; Imanishi-Kari has appealed, and the case will now go to an appeals board

After two university inquiries, three congressional hearings, three federal probes, and one criminal investigation, the most divisive scientific misconduct case in U.S. history has finally entered the home stretch. Last week, the federal Office of Research Integrity (ORI) issued a long-delayed report concluding that Tufts University immunologist Thereza Imanishi-Kari fabricated data in a 1986 paper on immune function in mice that she co-authored with Nobel prizewinner David Baltimore and four other researchers. ORI also contended that, when the data were challenged, Imanishi-Kari tried to cover up these alleged falsifications with additional fabrications. And, in one of the harshest penalties it has ever considered, the Department of Health and Human Services (HHS) says it intends to bar Imanishi-Kari from receiving federal funds for 10 years.

This twisted saga is far from over, however. Imanishi-Kari, who earlier this week told *Science*, "I didn't falsify my results, nor [did] anybody in my laboratory," has filed an appeal, and the case will now go to a three-person panel in HHS. To prevail, ORI will have to convince the panel in open hearings that Imanishi-Kari fabricated data with intent to deceive. The defense team is expected to focus its heavy guns on the heart of the government's case: forensic evidence gathered by the U.S. Secret Service that supports ORI's charge that Imanishi-Kari did not conduct experiments when she claimed. During these hearings, Imanishi-Kari and her lawyers will get their first chance to cross-examine witnesses and rebut the evidence brought against her.

Imanishi-Kari's career hangs in the balance. And the stakes for ORI are high, too: It already suffered one humiliating defeat in November 1993 when an appeals panel dismissed misconduct charges against former National Institutes of Health (NIH) biologist Mikulas Popovic for alleged misstatements in a paper describing the identification of the AIDS virus (*Science*, 12 November 1993, p. 981). That reversal prompted ORI to drop other charges against Popovic's boss at NIH, Robert C. Gallo, in the most closely watched scientific misconduct case ORI has handled—except for this one. ORI can ill afford to lose again. Says ORI Director Lyle Bivens: "We're geared up for this one."

An 8 ½-year saga

ORI has certainly taken its time in completing its investigation of Imanishi-Kari, even though the new report essentially mirrors the findings of an earlier investigation completed in March 1991. Indeed, the case has been moving glacially for 8 ½ years—ever since Imanishi-Kari's former postdoc, Margot O'Toole, first contended that a paper in the 25 April 1986 issue of *Cell* included questionable data.

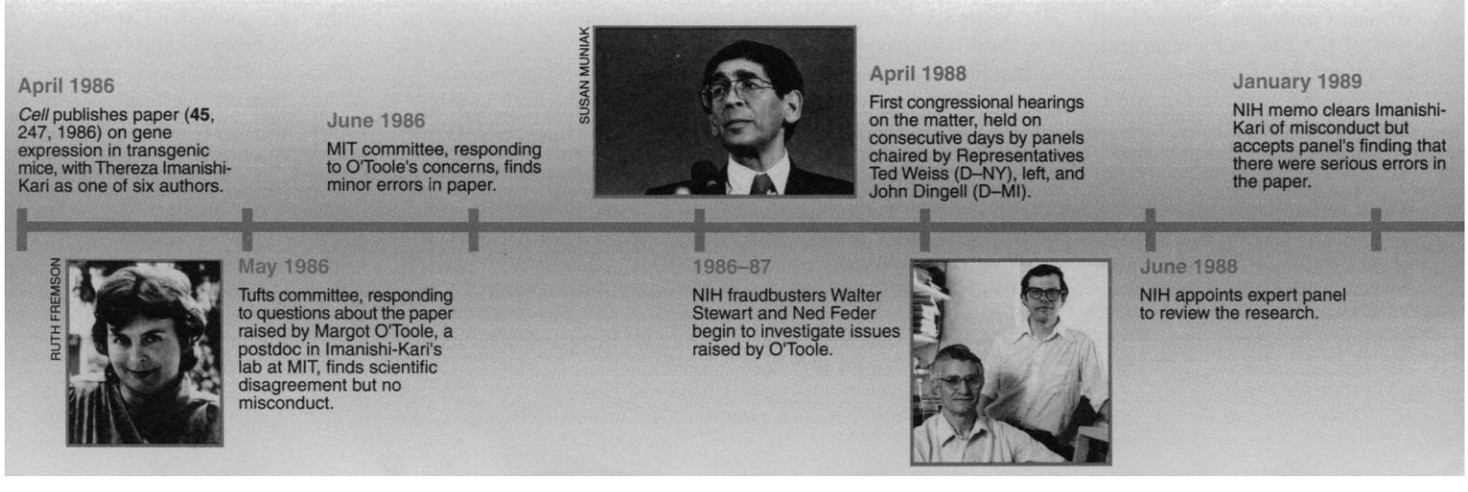
The *Cell* paper indicated that a gene transplanted from one strain of mouse to another altered the suite of antibodies produced by the host mouse's own genes. O'Toole questioned whether some of the experiments had been done as described in the paper, and her challenge resulted in separate inquiries by committees at the Massachusetts Institute of Technology (MIT), where the work was conducted, and Tufts University, which hired Imanishi-Kari in 1986 as an assistant professor. Both inquiries found errors, but no misconduct.

The matter might have rested there, except that two NIH researchers with budding reputations for investigating alleged scientific misconduct, Ned Feder and Walter Stewart, began an unofficial investigation. Their probe eventually led to an official inquiry by NIH. Representative John Dingell (D–MI) then stepped in with two high-profile hearings in April 1988 and May 1989, the second featuring a Secret Service analysis, commissioned by Dingell's staff, of notebooks and radiation counter tapes that appeared to indicate that data supporting the *Cell* paper had been fabricated. Prompted by this new forensic evidence and Dingell's keen interest, NIH launched a full-scale investigation through its Office of Scientific Integrity (OSI).

OSI's work, overseen by a panel of five scientists,* culminated in a damaging draft report that was promptly leaked to the media in early 1991 (*Science*, 8 March 1991, p. 1168 and 29 March 1991, p. 1552). The OSI panel concluded that Imanishi-Kari committed "serious scientific misconduct" by "repeatedly present[ing] false and misleading information" to federal investigators. The panel did not accuse the other co-authors of misconduct, but it did criticize Baltimore for failing to take accusations against Imanishi-Kari seriously as evidence of problems mounted. The panel had nothing but praise for O'Toole, however, saying she deserved "the approbation and gratitude of the scientific community for her courage and her dedication to the belief that truth in science matters."

Soon after the draft report was made public, the U.S. Attorney in Baltimore launched his own investigation. In July 1992, how-

*Joseph Davie, G. D. Searle and Co.; Ursula Storb, University of Chicago; Hugh McDevitt, Stanford University; Stewart Sell, University of Texas; and William McClure, Carnegie Mellon University.



ever, he decided not to prosecute, citing the complexity of the science and the difficulty of proving Imanishi-Kari intended to deceive (*Science*, 17 July 1992, p. 318). By that time, NIH's scientific misconduct squad had been moved to a new position within HHS and given a new name—the Office of Research Integrity (ORI). ORI put a team of three staff scientists on the inquiry: geneticist Barbara Williams, statistician James Mosimann, and immunologist John Dahlberg.

It took the ORI staffers 2 years to prepare a report, released on 25 November, that reaches similar conclusions to those in OSI's 1991 draft—although it lacks either praise for O'Toole or criticism of Baltimore. It concludes that "not only did [Imanishi-Kari] fabricate and falsify critical areas of the reported results, but in denying the original misconduct, she further compounded these violations by fabricating data that she claimed supported her initial findings."

Central to ORI's conclusions are analyses performed by the Secret Service on Imanishi-Kari's lab notebooks and printouts from radiation counters. The Secret Service team concluded that the color, type font, and ink type of these tapes indicated that some of them were generated long before the experiments reported in the *Cell* paper had even begun, and so "could not have been related to the results reported." ORI contended that Imanishi-Kari used these old tapes to fabricate results.

In addition, ORI conducted a statistical analysis of the frequency of digits that appear in some radiation counts hand-copied by Imanishi-Kari into a lab notebook. The analysis found that the distribution of digits was nonrandom, from which ORI concluded that the data "were fabricated." (The OSI draft report included a similar statistical analysis, but two of OSI's scientific advisers criticized the approach in a minority report, calling it untested.)

ORI Director Bivens says his office also "did a substantial amount of additional work" to probe allegations that Imanishi-Kari falsified data to obtain an NIH grant in 1985 that, in part, funded the research reported in *Cell*. The ORI report charges that Imanishi-Kari's application "suggested that she had obtained meaningful data from cloned cell lines of transgenic mice when, in fact, she had not even begun the cloning experiments."

Another fresh issue in the new ORI report is that Moema Reis, a co-author of the *Cell* paper who was working at the time as a postdoc in Imanishi-Kari's lab, may have been implicated in some data fabrication. ORI contends that six data points in figure 1 of the *Cell* paper were fabricated. According to ORI, Imanishi-Kari and Reis both told investigators that Reis had performed the experiments to get these data one day after the rest of the data in the figure were generated. Reis did not record the experiment in any lab notebook, however.

ORI contends that "scientific and forensic evidence demonstrated that it was neither feasible nor credible to have conducted the experiment ... on the day following the experiment that produced the other points. Therefore, the points in question were fabricated." ORI stated that there was insufficient evidence to attribute this alleged fabrication to Imanishi-Kari and that it is now investigating Reis's actions. Imanishi-Kari says Reis took sick leave from MIT shortly after the paper was published and never returned. "Our understanding is that she is in Brazil," says Bivens.

Focus on forensics

Imanishi-Kari was sent a copy of the ORI report in August and was given 90 days to respond. Her lawyer at the time, Bruce Singal, replied with a blistering letter accusing ORI of "excessive delay" in preparing its report and demanding additional time to rebut the charges. When ORI went ahead with its planned release of the report, Imanishi-Kari filed her appeal, and last month she hired Joseph Onek, the lawyer who successfully represented Gallo.

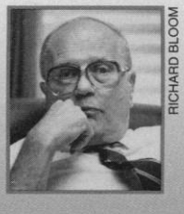
The appeal is expected to focus on an analysis of the Secret Service data conducted for Singal by Albert H. Lyter III, a forensics expert and consultant. Lyter reviewed the forensic evidence in 1992, when the U.S. attorney was considering prosecution, and in an affidavit, he accused the Secret Service of sloppy analyses and failing to conduct sufficient tests to buttress its conclusions. The Secret Service responded early last year, however, with a critique calling Lyter's accusations unfounded.

Imanishi-Kari, for her part, told *Science* that she is looking forward to the appeals board hearing. "For the first time in all these years I can really see all the so-called evidence," she says. Imanishi-Kari maintains that she did not fabricate any of the data in the *Cell* paper and derides the thrust of ORI's report: "I, by myself in a vacuum, made up the results. ... [This] is absolutely inconceivable."

As lawyers and public officials dig deeper into this celebrated case, a strange thing has happened to the science: It has quietly faded into the woodwork. Imanishi-Kari has continued publishing data that support the conclusions she reached in her original *Cell* paper (*Science*, 21 May 1993, p. 1073). But few researchers have shown an interest in following her lead, and no one has replicated her study. "There are fashions in science," just as in clothes, explains biologist Herman Eisen of MIT, and "fashions change." He suggests that using transgenic mice to search for evidence of host expression of antibodies that mimic those from the transplanted gene just isn't a hot topic any more.

That may be. But some people seem to consider it almost too hot. For example, immunologist Alfred Nisonoff of Brandeis University fended off questions this week about the credibility of Imanishi-Kari's data by saying "I wouldn't touch that subject with a 100-foot pole." Yet some of Nisonoff's colleagues say he wrote an extensive rebuttal of her most recent paper, mailed it to her for comment, and—receiving no response—circulated it among a handful of interested scientists. Nisonoff declined to discuss his critique for the record, saying he didn't want to inflame the debate further. But he agrees with some other noted immunologists, including Alan Stall of Columbia University, that while he disputes Imanishi-Kari's interpretation of the data, there are "alternative ways" to explain her results than to believe she engaged in fraud. That will now be up to the HHS appeals board to determine.

–Richard Stone and Eliot Marshall


RICHARD BLOOM


KEN HEINEN

May 1989
Dingell holds second hearing, featuring Secret Service analysis of lab notebooks; NIH reopens its investigation.

May 1990
Dingell holds third hearing.

June 1990
NIH suspends grants to Imanishi-Kari pending completion of its investigation.

March 1991
Leaked draft report of NIH panel accuses Imanishi-Kari of fabricating data and praises O'Toole for speaking up.

July 1992
Federal prosecutors decide not to prosecute Imanishi-Kari.

April 1993
Imanishi-Kari publishes papers in *Journal of Immunology* that build on results in *Cell* paper.

November 1994
Office of Research Integrity publishes final report charging Imanishi-Kari with 19 counts of misconduct. Imanishi-Kari files appeal.