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Repairing BRCA1 science

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As a leading authority on DNA repair contests findings that he falsified data about a key breast cancer gene, other researchers in the field are preparing a salvage operation to make sure good science is not lost in the melee.

Steven A. (Tony) Leadon resigned as director of radiobiology at the University of North Carolina at Chapel Hill(UNC) in March, after a five-member panel at the school alleged that he had tampered with data related to the antibody assay he developed to test how *BRCA1* encodes a protein to repair DNA damage. His case is now under review by the US Department of Health and Human Services Office of Research Integrity(ORI).

"We have an interest in cleaning up the literature," said Christopher Pascal, director of ORI, of the review process. "There's a presumption of innocence until proven guilty here. ORI can't jump the gun."

"For the scientific community, first and foremost, we need to find what are the pieces of the science that are correct, regardless of whether the particular experiments were correct or not," said Philip C. Hanawalt, the Stanford University researcher in whose laboratory transcription-coupled DNA repair was discovered. "If the experiments were not correct, that does not mean the conclusions were wrong. In a number of cases we know in fact that the conclusions are correct."

Leadon insists the description of the DNA repair pathway involving BRCA1 stands, even if some data were incorrect.

"The pathway that we initially characterized is still a valid pathway," Leadon told us. "I think that some of the data that we had which pointed to the pathway was flawed, but fundamentally the results still stand." Leadon takes responsibility for incorrect data that came from his lab, but denies UNC allegations that he fabricated it, he added.

Leadon's lawyer says that his client was set up and that the case was concocted with the aid of a graduate student and pushed through a kangaroo court.

"The record viewed in an unbiased manner indicates honest differences of opinion about laboratory procedure that he has been trying to improve for 15 years," said Alan McSurely of Chapel Hill, Leadon's attorney. "Respondent [Leadon] more than anyone was aware that the DNA assay was difficult to work with and a more robust assay had to be developed."

According to McSurely, a student in Leadon's laboratory switched test tubes in a series of sting operations - experiments of her own meant to prove the researcher was falsifying data. Hers was the critical testimony that swayed a university panel involved in a process "polluted" with secret meetings and second-hand evidence, Leadon's attorney said.

UNC is withholding comment. Interim General Counsel B. Glenn George and Assistant General Counsel David M. Parker cited North Carolina state law in refusing to answer questions about the case, including questions about letters the school sent to as many as ten scientific journals alerting them that Leadon's work should now be considered suspect.

Hanawalt, who received one of the letters from UNC, has embarked on a review of the extensive literature touched by Leadon, who was once a postdoc in Hanawalt's laboratory.

Hanawalt is contacting coauthors on Leadon's papers and plans to publish an analysis in DNA Repair, a journal he once edited. "I will simply focus on the conclusions that are valid from the results in a number of laboratories and those that should be reevaluated because the studies are suspect," Hanawalt said. "We do not yet know how many papers are suspect."

Errol C. Friedberg, current editor of *DNA Repair*, was the first to publish Leadon's retraction of a publication in March of this year (*DNA Repair*, 2:361, March 1, 2003). Friedberg, who chairs the department of pathology at the University of Texas Southwestern Medical System, plans to publish an amendment to the retraction, one that states that coauthor Anna V. Avrutskaya was not implicated in the misconduct findings.

He is working with Hanawalt to clear up the record on the science. "He and I are anxious to restore the conclusions that have been independently validated," Friedberg said. "This is part of what's so messy. It's not just a question of being able to say, ignore certain papers."

Keeping collateral damage to a minimum will be important to many in the small community of scientists who study the cellular processes of DNA repair.

"There are those who, since some of his work has been called into question, would want to throw it all out," said Isabel Mellon, associate professor in the department of pathology and laboratory medicine at the University of Kentucky Medical Center. "We're talking about 15 years of work, and I'm not sure we want to do that."

Mellon also studied under Hanawalt in a postdoc that overlapped by 1 year with Leadon. She published with Leadon as recently as last year. "It's important for people to continue to look at the original data and for all of the collaborators to have time to digest what has happened," she said.

Rumored for months among scientists in the field, many of whom saw the March retraction in *DNA Repair*, the Leadon case went very public last week when Science magazine ran a retraction of his groundbreaking article describing the necessity of BRCA1 for transcription-coupled repair of oxidative DNA damage (*Science,*281:1009, 1998).

The June 13 *Science* retraction noted that Leadon disputes the findings of UNC's ad hoc investigatory committee and that the other authors, Lori C. Gowen of New York, Anne M. Latour and Beverly H. Koller of UNC's department of medicine, and Avrutskaya, also of Chapel Hill, were not implicated. None of them could be reached for comment.

Leadon wrote to *Science* in May 2002 indicating there were problems with the data, according to *Science*executive editor Monica M. Bradford, who said UNC's concerns seem to focus on data drawn from an antibody assay Leadon originated.

"It seems the piece they are most concerned about is any data based on transcription-coupled DNA repair assays, the assay [Leadon] developed for transcription-coupled DNA repair," Bradford said. "I think the other authors stand very strongly behind the paper," she added.

ORI is now reviewing the record of UNC's investigation, including laboratory notes that Leadon's attorney says were taken from his client and never returned, an alleged violation of a deal with the university that the defense argues is one of many critical flaws in the probe.

McSurely, a civil liberties lawyer, said that he was reduced to the role of a "potted plant" at the proceedings, not allowed to cross-examine witnesses, and that his client was left to fend for himself in an emotionally charged atmosphere whose outcome had already been decided behind closed doors.

Leadon says he has heard from some colleagues, who privately express support. "This is their worst nightmare type of situation. They have all thought about it happening to them," he said.

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