Conflict at the RAC

Researchers protest delay in approving gene therapy protocols; panel members shoot back with criticisms of the science

TEMPERS FLARED and emotions ran high at an unusual meeting of the NIH's Recombinant DNA Advisory Committee (RAC) meeting on 30 March as what was supposed to be a discussion about human gene therapy boiled over into a debate about the RAC's role in clinical research.

The RAC and its human gene therapy subcommittee were accused of hindering vital medical research. Oncologist Steven A. Rosenberg vented frustration over procedural hurdles that will delay approval of a plan to give dying cancer patients the gene for tumor necrosis factor—a killer cell. The RAC will not even look at the proposal until its October meeting. Rosenberg called the delay "unconscionable."

RAC members took offense at the implication that they are twiddling their bureaucratic thumbs while cancer victims die.

Because some RAC members are themselves conducting research on gene therapy, and are thus competitors of Rosenberg and others whose proposals they are considering, suggestions of conflict of interest were in the air. And the very ability of NIH's intramural scientists to exercise sound judgment in clinical research was called into question.

The meeting agenda was straightforward enough. First was a request from Rosenberg who asked permission to expand his ongoing study in which terminally ill melanoma patients receive potentially therapeutic tumor infiltrating lymphocytes (TIL) labeled with a neutral marker gene that is used to track the path of TIL in the body.

Second on the agenda was an entirely new protocol from R. Michael Blaese of the cancer institute and W. French Anderson of the heart institute who want approval to give children with a rare and lethal immune disorder the gene for adenosine deaminase (ADA)—a missing enzyme (*Science*, 16 March, p. 1287).

Rosenberg's request seemed uncontroversial. Several months ago he got RAC's approval to try the TIL/gene marker combination in ten patients. Having studied six with what he believes is some success (*Science*, 22 September 1989, p. 22), he sought permission to include up to 40 patients more.

Rosenberg presented data on the six patients he has treated to date and suggested that TIL work by directly invading a tumor. Scott McIvor of the University of Minnesota wasn't convinced. "I don't see evidence that you're really getting homing to tumor," said McIvor, who is a member of both the RAC and the gene subcommittee.

William N. Kelley, founder of the new human gene therapy program at the University of Michigan and now dean of the medical school at the University of Pennsylvania, is also a member of both committees. He asked for data on the half-life of the TIL, and suggested there should be more animal data to support Rosenberg's hypotheses about how TIL may be working.

Richard Mulligan of the Whitehead Institute at the Massachusetts Institute of Technology, who also works in the human gene therapy arena and holds a seat on RAC and its subcommittee, suggested a new forum for data review: a subcommittee of the subcommittee to evaluate the raw data on behalf of the full subcommittee.

Henry Miller of the Food and Drug Administration, which, he said, exercises continuous oversight of the Rosenberg experiment, appeared ready to explode. The "safety data are impressive," he said. The request was for a simple expansion of an on-going experiment. "We should vote to approve," said Miller, "and move on."

Rosenberg took the opening to say that "the delay built in to the review process is out of keeping with all other reviews of clinical research."

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—William Kelley

In the end, both the gene subcommittee and the RAC voted unanimously to allow Rosenberg to expand his TIL study. But by then tensions were high, and by the time the Blaese-Anderson proposal for the ADA gene study reached the floor, it was apparent that it was in for a rough time. It did not pass scientific muster and was sent back to the drawing board, notwithstanding the fact that it had been approved by internal NIH review bodies.

NIH, it was said, would need to draw on experts nationwide to conduct tough in-house reviews. Someone mentioned that Mulligan himself had been an outside reviewer on the NCI panel that approved the Rosenberg experiment. But there was no equivalent review of the ADA proposal.

One had the feeling of watching an existential play.

Was the RAC imposing bureaucratic delay or exercising good scientific judgment? "If we were dealing with impeccable science, there wouldn't be any delays," Kelley said pointedly. He made a startling suggestion: the scientific underpinnings of a new protocol should be debated by the committee in secret, without the press and, even more important, without the investigators whose protocol is being judged.

Mulligan concurred. He usually had "a hundred questions," he said—questions whose significance is not always apparent to those who are not gene insiders. "I'm often considered a nitpicker here," Mulligan admitted. Mulligan and Kelley are among the committee members whose scientific questions and requests for more data are most likely to be interpreted as a source of delay. Each is seen as a direct scientific competitor to the NIH team. Is there an unacknowledged conflict of interest here?

In an interview with *Science*, Kelley took the question head on. "I have no connection whatsoever to any private biotech company," he stated. (Through an NIH cooperative agreement, Anderson and Blaese have ties to Genetic Therapy Inc.) "And since I've become a dean I am out of this business. It's my job to see we get the very best science here and I'm going to do it."

Mulligan notes that any thorough scientific review by peers in a small field is bound to include people who are competing professionally—people who can ask not "nitpicking" but challenging questions.

Although Kelley's idea for closed scientific review met with resounding rejection, his unhappiness with the format for scientific review turned out to be shared by several people around the table.

Solutions were put forward. All the data should be sent to the committee in writing a couple of weeks before the meeting. No data at the last minute—a practice that Mulligan says makes the protocol a "scientific moving target." There should be primary and secondary reviewers, chosen from the ranks of committee members with the greatest pertinent scientific expertise. Their reviews should be in writing. And so it went.

Everyone favored reform; a new system for scientific review will be worked out before the next meeting. Perhaps the tension served a useful purpose. The drama continues on 1 June.

■ BARBARA J. CULLITON