Quick Work Draws Scientific Praise, Colleagues' Complaints

Whenever a scientific field accelerates from zero to warp speed and researchers depend on the same resources, collisions occur. Take the back-room bickering surrounding a paper in this issue (see main text) authored by a group led by Stephen O'Brien of the National Cancer Institute (NCI).

The paper is based on an analysis of mutations in the gene for the CCR5 chemokine receptor that the O'Brien lab performed on blood samples from six cohorts of people who are HIV-infected or at high risk of becoming infected. Investigators running the cohort studies had for years sent the scarce samples to O'Brien, who transformed them into cell lines that could endlessly produce DNA. Several of these investigators say that they learned of O'Brien's CCR5 study only after a draft of the paper was written, however. Others who were conducting similar studies contend that O'Brien used his ready access to the cell lines to gain an unfair advantage.

"This whole experience has been a nightmare," says molecular biologist Philip Murphy of the National Institute of Allergy and Infectious Diseases (NIAID), who raced the O'Brien lab this summer and lost. But O'Brien says his work on the samples was permitted by agreements with the principal investigators (PIs) of the cohort studies, and his actions were "all done in good faith, and in the end everything my people and I did was aboveboard and up-front." Indeed, nobody disputes that O'Brien was within his rights to analyze the samples. But this flap is important in that it shows how poor communication in complex collaborations can lead to acrimony and bruised egos. More important still, it raises an issue that spans many areas of biomedical research: Who decides what research can be done on scarce samples?

Much of the controversy centers on a set of blood samples gathered by a 12-year-old collaboration called the Multicenter AIDS Cohort Study (MACS), funded mainly by NIAID. The MACS executive advisory committee (EAC), which manages the collaboration, had given O'Brien hundreds of samples. "We set Steve up as both a lab to look into HIV genetics and also as the person to process these cells," says the University of Pittsburgh's Charles Rinaldo, a MACS EAC member and a co-author on the O'Brien paper. O'Brien, however, says his main role was to conduct research. "They view us as a cell-transformation group," says O'Brien. "My group is a genetics group. That's all."

"We see now there was a potential for a conflict of interest," says Rinaldo. "That was our fault." That potential became clear when Murphy and Richard Koup of the Aaron Diamond AIDS Research Center in New York City requested MACS samples for CCR5 studies early this summer. According to Northwestern University's John Phair, who chairs the EAC, the committee worked out an arrangement for both to get the samples at the same time and asked O'Brien to prepare the material to send out. At about that time, EAC members learned that O'Brien was interested in doing similar analyses on the samples himself.

EAC members had thought that O'Brien would pursue CCR5 research in parallel with the other investigators. But within days, he sent them a completed manuscript with the data analyzed. One EAC member, Janis Giorgi of the University of California, Los Angeles, was so miffed that she turned down an offer for co-authorship. "I don't want to be part of something that wasn't conducted in a collegial fashion," says Giorgi. O'Brien says that he was surprised at such reactions. "They went through all this stuff about starting guns and times, and I said wait a minute, 'I have written permission to do it,' " he says. "I told them we were working on the [CCR5] gene. They didn't listen."

O'Brien's competitors say that they were surprised to learn he was a competitor. Koup and Murphy both say that their labs had spoken to O'Brien about receiving the samples and had no idea he was doing the analysis himself. "We felt somewhat blind-sided," says Koup. O'Brien says he explained his intentions and that these investigators either don't remember or "conveniently forgot." Murphy also charges that O'Brien delayed sending out samples. "We just waited and waited and waited and kept calling and calling," says Murphy, who says it took 6 weeks to get the samples. O'Brien blames the delay in part on Murphy's failure to file a required form.

O'Brien says that he was able to produce his manuscript quickly because he had already analyzed samples from the other five cohorts, and the MACS data took just a few days to process. But his work also took by surprise some PIs of those other cohorts—whom he included as co-authors on the paper. Some had even started to discuss collaborations with others on overlapping questions. "Clearly, it would have been far more civilized and politic for Steve to have mentioned this earlier on rather than to just have it show up," says NCI's James Goedert, a PI of two of the cohorts. Susan Buchbinder, PI of the San Francisco City Clinic Cohort, says "It would have been nice to get some more up-front information about the testing being done." O'Brien counters that "they didn't feel bad enough about it to pull their names off the paper," and he questions why they didn't tell him about possible collaborations when they already had one with him.

O'Brien notes that he has conducted genetic analyses on the samples for nearly a decade without raising objections—until he moved into the hot topic of the CCR5 receptor. He adds that some of his critics are upset because his quick work left them "standing there with their hats in their hands." Says O'Brien: "I'm sorry. That's the way it goes. I've been scooped hundreds of times in things like this."

Phair is philosophical about the flap. "The speed at which the chemokine receptor work moved this summer caught us all off-guard," he says. But he says MACS is now looking for a disinterested third party to make immortalized lines of its samples. **–J.C.**

data on HIV-uninfected people from the population at large, while his own team relied on well-characterized blood samples from six cohorts of people who are at a high risk of becoming infected with HIV. Because they are at high risk, he says, they provide a more stringent test of the effectiveness of heterozygosity in preventing infection—a test heterozygosity apparently failed.

O'Brien did see indications, however, that having one mutant CCR5 gene copy might slow the progression of AIDS. In the homosexual populations studied, there were more than twice as many heterozygotes among people whom the authors classified as "long-term nonprogressors"—people who show no symptoms years after being infected with HIV—compared with those classified as "rapid progressors." The hemophiliacs studied showed only a slight trend in that direction.

Many AIDS researchers are now interested in investigating whether these findings can be translated into treatments or vaccines that delay or prevent disease. Others, such as Anthony Fauci, head of the National Institute of Allergy and Infectious Diseases, caution that chemokines and their receptors are part of a vast, delicately controlled immunologic network. Fauci offers this "gentle caveat": "We better be very careful not to say we have an absolute, sure-fire target." That said, it is a target ever more researchers are beginning to fire at.

–Jon Cohen