Yet another approach, developed by Costerton, zaps existing biofilms with low-dose electric current. Patented in 1994, the method disrupts the electrical charge of the polysaccharide coating, rendering the underlying bacteria more susceptible to antibiotics. Costerton and his colleagues have treated lab-grown biofilms with electric charges and antibiotics simultaneously. When they zapped the biofilms first, they could kill them with just 0.1% of the antibiotic required to wipe out an untreated biofilm. Costerton plans to use the technology, which is now licensed to a Montana firm, to sterilize repeat-use sigmoidoscopes (instruments used to explore the colon for tumors), to prevent spreading of biofilms. In the long term, infected implants may someday be treated in vivo with electric currents.

While the new work in biofilms should lead to better ways to control them, the same research is also helping find ways to use beneficial biofilms. "Biofilms have a good and bad side," says Bryers. For instance, biofilms have been used for 50 years to degrade common contaminants in waste water. In the last few years, they have also become a hot item for in situ bioremediation of toxic contaminants like jet fuel and carbon tetrachloride. Researchers simply gather bacteria found at toxic sites, then select for species with an appetite for the targeted contaminant and cultivate them to thrive as biofilms, explains Bryers.

Beneficial biofilms also serve as biobarriers in the oil industry. To pump oil out, water is pumped in. Once the oil is removed, water tends to flow into the empty space, which reduces the water pressure available for pumping more oil. Oil-industry engineers once used hazardous chemicals to fill the holes and redirect the water. Now they pump in biofilms in a starving state, and the bacteria grow rapidly on local nutrients. They "explode like popcorn and fill the holes and make the area impenetrable," says Bryers. Such beneficial applications are continually being improved, as researchers mix biofilms of various species to maximize various bacterial activities, whether it be filling underground holes or degrading specific contaminants.

Despite all the recent activity in biofilm research, plenty of unanswered questions remain, such as why some bacteria are better than others at forming biofilms, and exactly how biofilms manage to resist antibiotics. "Biofilms cause enormous problems and still aren't recognized by many who are affected by them," says White. "I don't think it's possible to go too fast in this area."

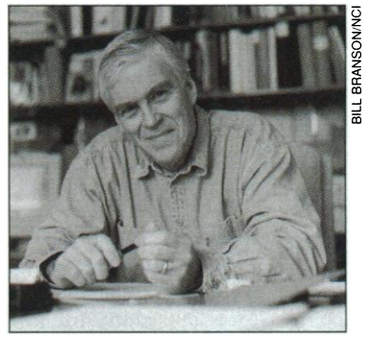
–Carol Potera

Carol Potera is a science writer in Great Falls, Montana.

AIDS RESEARCH

Receptor Mutations Help Slow Disease Progression

In a mere 9 months, a group of natural chemicals called chemokines has rocketed from obscurity to celebrity in the AIDS research community. First, researchers found that a trio of chemokines appears to potently suppress HIV's ability to infect cells and, more recently, that the cellular receptors through which these chemicals exert their effects are critical "coreceptors" to which HIV must bind in order to enter cells (*Science*, 21 June, p. 1740).



BILL BRANSON/NCI

Powerful study. Stephen O'Brien led largest study yet of CCR5 mutations.

The latest chapter in this fast-moving saga appears on page 1856. Population geneticist Stephen O'Brien of the National Cancer Institute, his NCI colleagues Michael Dean and Mary Carrington, and their collaborators provide strong confirmatory evidence that people who have two mutant copies of the gene for CCR5 (also known as CKR5), the chemokine receptor that HIV uses when it initially infects white cells, are highly resistant to HIV infection. Another, entirely new, finding is that people who do get infected with HIV, but have one mutant copy of the CCR5 gene, progress to AIDS more slowly than do people without the mutation.

"It's the most impressive data I've seen so far in this area," says Robert Gallo, head of the University of Maryland's Institute of Human Virology. Oncologist James Hoxie of the University of Pennsylvania, who has long studied how HIV enters cells, has high praise, too. "The implications are really remarkable about what it might be telling us about the risk of infection and how the natural history of disease might be affected," says Hoxie.

In addition to possibly clarifying questions of HIV pathogenesis, these discoveries have raised high hopes of developing new AIDS therapies or vaccines. It might be possible, for example, to prevent HIV from infecting cells by mimicking the way chemokines suppress HIV infectivity: blocking the receptor that they and HIV share. As molecular biologist Marc Parmentier of the Université Libre de Bruxelles in Belgium, whose lab first cloned CCR5, explains, this new work "demonstrates quite clearly that CCR5 is the most important coreceptor for strains of HIV [that establish the initial infection]." (After the initial infection, HIV mutates and different strains take over—and use different chemokine receptors.)

The first evidence that mutations in the CCR5 gene might protect people from HIV came from a team led by Ned Landau and Richard Koup at the Aaron Diamond AIDS Research Center in New York City (*Science*, 19 July, p. 302). Landau, Koup, and co-workers found two individuals who had been repeatedly exposed to HIV without becoming infected, in whom both copies of the gene were mutated. The finding suggested that these "homozygotes," who were unable to produce the receptor, were resistant to HIV because the virus could no longer enter their cells. (The results were published in the 9 August issue of *Cell*.)

Further evidence for that came from Parmentier's group, which had independently identified the same CCR5 mutation. As these researchers described in the 22 August issue of *Nature*, they found that none of 723 HIV-infected Caucasians they studied were homozygous for the mutation. The Parmentier group further reasoned that because this infected population had fewer people with one mutant gene copy (so-called heterozygotes) than did the uninfected group (10.8% versus 16.2%), even heterozygosity may offer some degree of protection from infection.

O'Brien's team at NCI has now looked for CCR5 mutations in some 1955 people, making it the largest study of its kind to date. In keeping with the Parmentier study, the O'Brien team found no homozygous, infected people. And O'Brien also saw the mutant allele much more frequently in Caucasians than in people of African descent, although the difference was less dramatic. Parmentier found the mutation in 17% of 704 Caucasians, compared to none in 124 central and western Africans, while O'Brien found the allele in 11% of Caucasians and 1.7% of African Americans analyzed.

But there were also some notable differences between the two studies. O'Brien found no indications that heterozygotes were protected against HIV infection: There were roughly the same number of heterozygotes in both infected (15%) and uninfected (14%) populations. O'Brien attributes this to the fact that Parmentier derived the bulk of his

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