

## Researchers come together to study natural HIV resistance

Not everyone who is exposed to HIV becomes infected. In fact, some individuals fail to contract the infection even after repeated exposure to the virus. Researchers all over the world have been working separately for decades to determine what makes these people apparently resistant to HIV. In mid-November, they'll come together in Winnipeg, the capital city of the Canadian province Manitoba to compare notes and coordinate their efforts.

"It's really timely," says Galit Alter, an immunologist at the newly formed Ragon Institute, located at the Massachusetts General Hospital in Boston, who is on the symposium's scientific steering committee. Interest in natural resistance is growing, she says. "We need to make a concerted effort as a community to come together and to try and look at these people in an organized way." The mechanisms that control natural resistance could be used to develop a new vaccine or new therapies. "Without having this kind of initiative," she says, "we go nowhere."

The three-day symposium, expected to draw about 150 researchers from around the globe, is the brainchild of Francis Plummer, a professor of medicine and microbiology at the University of Manitoba and scientific director general of the Public Health Agency of Canada's National Microbiology Laboratory. Plummer has been studying the spread of HIV among Kenyan prostitutes for more than two decades. In the late 1980s, he noticed that some of the women seemed to be naturally resistant to the virus, remaining free of HIV despite years of unprotected sex work.

"Everything that we find points to these individuals being immune to HIV," Plummer says. "It's not dumb luck," he adds. "We can show that statistically." Compared with so-called 'elite controllers' (people who are HIV infected but do not progress to AIDS), those who are deemed 'resistant' to HIV do not have the virus in their system despite repeated exposure to it.



Protection vehicle: A truck distributes condoms in Kenya to those who need them

To date, researchers have managed to uncover only one clear-cut mechanism to explain natural resistance in a small subset of individuals. HIV relies on one of two co-receptors to enter a cell: CXCR4 and CCR5. Some people carry a mutated form of the CCR5 gene that renders the receptor useless. Individuals who carry two copies of this mutation, about 1% of people of European descent, have almost no chance of contracting HIV. But the mutation, called delta 32, doesn't explain resistance in Plummer's cohort.

The delta 32 mutation also doesn't entirely explain natural resistance among a group of hemophiliacs in the US who were repeatedly exposed to high amounts of HIV in tainted blood products during the late 1970s and early 1980s. Sixteen percent of those that remained uninfected carry two copies of the delta 32 mutation. "We haven't a clue as to what protected the other 84%," says Michael Lederman, co-director of Case Western Reserve University's Center for AIDS Research in Cleveland, Ohio.

Luck probably plays a part, but it's not the whole story, says David Goldstein, director of Duke University's Institute for Genome Sciences and Policy in Durham, North Carolina. Goldstein is in the process of sequencing the entire genomes of 50 of the highly exposed uninfected hemophiliacs. He and his colleagues are looking for rare genetic variants. Variants that show up more frequently in this group than they do in the general population may confer protection against HIV, Goldstein says. He and his colleagues have already finished sequencing ten individuals' genomes and plan

to have the remaining 40 completed in the next five months.

Plummer hopes the symposium will lead to a research consortium that will allow the scientists to pool data, share samples and standardize their methodologies. "One of the problems with the field has been that no one group has got a large enough group of individuals to make broad sweeping statements," Plummer says.

Understanding the mechanisms that provide natural resistance may give the researchers a leg up when it comes to designing a protective vaccine or antiretroviral drugs. The discovery of the CCR5 mutation's role in natural resistance, for example, led to a class of drugs that block the CCR5 receptor. One CCR5 blocker—maraviroc (Selzentry)—has received US Food and Drug Administration approval, and many more are in development.

"Let's propose that we can identify an innate defense that is protective," Lederman says. "If we could learn how to amplify the magnitude of that defense, maybe we can protect people from infection." The type of therapy—vaccine, drug, microbicide or something else—will depend on the mechanisms that are uncovered.

What's clear, says Daniel Douek, an immunologist at the US National Institute of Allergy and Infectious Diseases' Vaccine Research Center in Bethesda, Maryland, is that these uninfected individuals are telling us something.

"I think it would be remiss of us not to investigate this," he says. "It's a gold mine of information."

Cassandra Willyard, New York



Vive la résistance: Francis Plummer