Charles Wira, Ph.D.: Viral warrior

By Amos Esty

Charles Wira's most recent scientific breakthrough came about as a result of thinking like a virus.

A professor of physiology at DMS, Chuck Wira studies how human immunodeficiency virus (HIV) infects cells in the female reproductive tract—a problem that has only recently started to attract significant attention. About 33 million people worldwide are currently infected with HIV, and 85 percent of new cases are the result of sexual transmission from men to women.

That means it's essential to know how the initial infection occurs, says Wira (whose name is pronounced WEER-uh). "If you don't understand the events taking place at the main portal of entry," he points out, "then you're not going to make very much progress in terms of coming up with protective mechanisms."

Grew up: Edison, N.J.

Education: Delaware Valley College '62 (B.S. in animal husbandry), Michigan State University '66 (M.S. in physiology), Dartmouth Medical School '70 (Ph.D. in physiology)

Training: Postdoctoral research fellowship from 1970 to 1972 at the University of Paris in France

Hobbies: Horseback riding and playing polo

Number of countries represented by the staff in his lab: Five (China, India, Kenya, Zimbabwe, and the United States)

Alumni service: President, DMS Alumni Council, 2002-2004

Number of children: Three (Charles, DMS '00; William; and Christopher)

Major upcoming project: Serving as cohost of the 2013 World Congress of Reproductive Immunology

Wira traces what he calls his "watershed moment" to a regular weekly lab meeting early in 2008.

Earlier this year, Wira began developing a new answer to the question of how HIV evades the immune system and establishes itself in the female reproductive tract. His central insight is that sex hormones temporarily suppress several components of immunity just after ovulation. This process results in what Wira calls a "window of vulnerability," a seven- to ten-day phase in the middle of the menstrual cycle during which women might be more likely than at other times to contract HIV and other diseases.

Wira's findings, published this past fall in the journal *AIDS*, were the culmination of years of research and could lead to new lines of attack in the battle against HIV. Recent setbacks in HIV treatment—including the cancellation of a vaccine trial in 2007 and the failure of a microbicide trial that same year—make his recent finding all the more important.

Given his current interest in human disease, it's a bit surprising that as an undergraduate, Wira studied animal husbandry. "I thought I wanted to be a cattle rancher," he explains. But the problem with ranching, he says, was that "you had to be a millionaire [and] buy into it, or marry into it, and neither of those was a good possibility." Instead, "after a series of bumpy transitions," he earned a master's degree in physiology from Michigan State University. Wira then moved east to enter the fledgling Ph.D. program in physiology at Dartmouth Medical School, where he became the first graduate student in the lab of physiology professor Allan Munck, Ph.D.

Munck was studying glucocorticoids, a type of hormone involved in metabolism, when Wira arrived. Wira was a "very dedicated" student, Munck recalls, but it was clear his primary interests lay in reproductive biology. Munck says that the time Wira spent in his lab was his "training ground, so to speak, so that he could go off on what he really wanted."

Wira had a chance to do just that in 1970, after earning his Ph.D., when he accepted a postdoctoral position at the University of Paris. There, he studied the effects of estrogen on the reproductive tract of female rats. Two years later he returned to DMS, this time as an assistant professor of physiology.

Over the next two decades, Wira continued to use rats as a model to learn more about the relationship between sex hormones and innate immunity. Among other findings, Wira discovered that the hormone estradiol—a form of estrogen involved in regulating ovulation—controls the presence of antibodies in the uterus. As the amount of estradiol increases, so, too, does the number of antibodies. As estradiol wanes, antibody levels decline.

Armed with the knowledge he'd gained from years of studying rats, Wira shifted his focus in the 1990s from rodents to humans. Beginning in 1993, a five-year Program Project grant from the National Institutes of Health allowed Wira to pull together a number of collaborators with expertise in different aspects of the immune system. For the rest of the decade, Wira continued to study immunity in the female reproductive tract. He also "became intrigued," he says, with the idea that his research might have implications for HIV infection. To help him pursue this line of research, Wira contacted DMS microbiologist Alexandra Howell, Ph.D., who by that time had been studying HIV for several years.

In 1997, Wira, Howell, and several other investigators made an important discovery. In a paper published in the *Journal of Virology*, they showed that HIV can infect cells throughout the reproductive

Amos Esty is senior writer for Dartmouth Medicine *magazine.*

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HIV exploits a "window of vulnerability" in the female reproductive tract, says Wira.

tract—not just in the vagina and cervix, as had been previously thought. Since then, Wira has continued to work on defining the roles of the different components of immunity and on applying that understanding to HIV infection. And that brought him to his recent breakthrough.

Wira traces what he calls his "watershed moment" to a regular weekly lab meeting early in 2008. Munck, who is now an emeritus professor of physiology, challenged Wira to change his approach to solving the problem of HIV infection. "It just went through my mind," Munck recalls, "that it was really time to break out of the old style and think of something new and fascinating to go for. And that's when Chuck came up with a very bright idea. He gives me credit for having stimulated him to do that, which I am very proud of. But," Munck emphasizes, "it was his idea."

Wira remembers the meeting well, and he says that Munck's comments helped change his perspective. "For all the years that I've been looking at this interface of endocrinology and immunology, I'd always been seeing it from the standpoint of the beneficial effects . . . in terms of enhancing protection," he says. After that meeting, Wira began to take a different tack. "If I was a virus," he asked himself, "what would be the most opportune time for infection to succeed?"

Over the next few months, Wira reexamined years of research and elicited input from other members of his lab. John Fahey, Ph.D., a researcher in Wira's lab and a coauthor on the 2008 *AIDS* paper, says that the major obstacle to understanding HIV infection was that they had previously focused on how the individual parts of the immune system provided protection in the female reproductive tract. But they now began to consider more closely how the immune system might be failing women.

Eventually, the researchers identified the "window of vulnerability," where the immune system is temporarily suppressed. The explanation for this phenomenon, in evolutionary terms, is that it prevents the immune system from attacking sperm or a fertilized egg. But the cost of facilitating reproduction is an increased likelihood of infection in the week or so following ovulation.

A second observation made by Wira and Fahey paints an even darker picture. HIV often gets a foothold by infecting immune cells that express certain molecules on their surface. These molecules act as receptors for HIV, allowing the virus to enter a cell, embed itself in the host's DNA, and produce copies of itself that will eventually spread to other parts of the body. During a woman's window of vulnerability, the fluctuation in sex hormones seems to draw these immune cells to the reproductive tract, giving HIV more opportunities for infection.

Wira hopes that a better understanding of how HIV spreads will lead to progress in efforts to stop the disease. "I'm very excited about this *AIDS* paper, because it's an opportunity to really pull things together and to see things in a completely different perspective," he says. "I don't know what the consequences of it are going to be, but I find it very exciting to think about ways in which this information can be brought to bear to affect people's lives."

Wira is quick to credit his colleagues for making the findings possible, and he says he has benefited from the collaborative environment at DMS. But, as Fahey points out, Wira has himself played a role in fostering that kind of environment. When Fahey joined Wira's lab about 12 years ago, Wira encouraged him to pursue his own research interests, and, says Fahey, Wira does the same for his graduate students. "What I've always liked about Chuck [is] he always listens," Fahey says. "I think he always has looked out for the people in his lab."

Over the past few years, as Wira has taken on more administrative duties and increased his involvement in international AIDS-prevention activities, he has had less opportunity to work at the lab bench—something he regrets. At the same time, he's excited about the turns his career has taken. He recently got back from his third trip to Africa, where he has taught one-day courses on the immunology of HIV and helped develop international collaborations.

But even if Wira no longer spends as much time as he'd like peering through a microscope, his lab continues to produce important findings—and to impress his mentor. "His work keeps blossoming," says Allan Munck. "It really is quite remarkable." ■