An interdisciplinary team of Santa Fe Institute scientists is working on strategies to develop an HIV vaccine to overcome the challenges of viral diversity. Bette Korber, an immunologist with the Theoretical Biology and Biophysics Group at Los Alamos National Laboratory (LANL), and Tanmoy Bhattacharya, a LANL high energy physicist, are using computational strategies to design vaccines. As Korber explained in a recent SFI joint Business Network and Board of Trustees Seminar, the failure of current vaccine production methods to produce effective protection against HIV shows a need to rethink vaccine discovery strategies.

Their approach, in addition to addressing human immunodeficiency virus (HIV), may also become the basis for developing vaccines against other lethal pathogens such as hepatitis C and Ebola. By using computational methods to design artificial proteins that are central or ancestral to current strains, Korber and Bhattacharya hope to outsmart the ever-changing virus that causes AIDS. If they succeed, not only will the world have an HIV vaccine, but theirs will also be the first computationally designed synthetic vaccine.

In her presentation, Korber gave a sobering view of the impact HIV has on public health. “With over 40 million...”
people worldwide infected with HIV," she said, “AIDS is destroying whole societies.” She cited statistics: The situation is particularly devastating in developing nations where as many as 25 to 40 percent of the adult population live with HIV. In South Africa, which has one of the fastest expanding HIV epidemics in the world, over 6.3 million people have the disease and one out of every three pregnant women is HIV positive. At the end of 2003, nearly 1.2 million people in the United States had been diagnosed with HIV.

Unlike viral pathogens that cause diseases such as polio and hepatitis B, HIV changes so rapidly that vaccines cannot protect from the ever-expanding number of antigenically distinct strains. To complicate matters further, the viruses within each patient eventually develop into a unique collection of HIV substrains or quasispecies, and divergent viruses can infect the same person and recombine to create distinctive new forms.

To give an idea how fast HIV changes, Korber compared it to the influenza virus. In a recent review published in the British Medical Bulletin, the researchers wrote, “The diversity of influenza sequences worldwide in any one flu season appears to be roughly comparable to the diversity of HIV sequences found within any single individual at one time point.”

Vaccines, by presenting the immune system with specific viral proteins, either on particle surfaces or as isolated proteins in solution, stimulate an immune system response. Because HIV surface proteins constantly change, the immune system cannot make an effective protective response against rapidly evolving new viruses. HIV infections last on average 10 years before one has AIDS signs and symptoms. This is ample time for unique mutations to develop and accumulate in each infected individual. This immune evasion and evolution within each person, and subsequent transmission of variant viruses, ultimately leads to the extraordinary diversity of HIV found at the population level.

Together, Korber and Bhattacharya, along with colleagues from Duke University Medical Center and the University of Alabama, Birmingham, have created an artificial consensus protein by computationally select-
are moving forward to begin testing this vaccine in macaques in a direct comparison with conventional natural protein vaccines," says Korber. The team hopes the results will be good enough to eventually begin small-scale human vaccine trials.

As a prelude to this work, Korber and Bhattacharya have used parallel computing tools to reveal the evolutionary origins of HIV. Many believe that HIV arose fairly recently, but their model suggests that HIV was quietly living among us for at least 50 years prior to the discovery of AIDS in 1981. There are several experimentally proven cases that support the view that HIV was with us prior to the discovery of AIDS as a disease; the earliest case comes from a frozen blood plasma sample taken from an adult male living in the Democratic Republic of the Congo (Zaire) in 1959. As people who die of AIDS die of an opportunistic infection that can manifest in many ways, it was probably difficult to detect AIDS in the human population in the early phases of the epidemic.

However, Korber and Bhattacharya’s model pushes HIV emergence back to an even earlier date. Using the global HIV sequence database developed and maintained by Korber at the Theoretical Biology and Biophysics Group (LANL), they used parallel computing methods to “clock” genetic changes back to a common viral ancestor. Their computational model correctly predicted two historical data points—the 1959 blood plasma sample and the HIV strains present at the beginning of a well-documented Thai epidemic in 1986-88. Prediction of these two “test points,” supports the validity of their assumptions, computational methods, and an emergence date that, according to Korber and Bhattacharya, could be around 1930, as early as 1915, or as late as 1940. Using the tools they developed for this study to model the emergence of HIV, they were able to create model ancestral sequences that they could ultimately use for HIV vaccine design.

For Korber, HIV is considerably more than a theoretical puzzle or an academic exercise. The origins of her passion and perseverance for HIV research goes back to her graduate school days at Caltech and a housemate who died of AIDS. In an understated, yet revealing statement, Korber says, “He taught me a lot.” To overcome her frustration and her grief, she left strictly physiological immunology and took a postdoctoral position in a laboratory doing retrovirus research as her way to “do science in service.”

In 2004, Korber received the Ernest Orlando Lawrence award for her work in delineating HIV genetics and the development of the Los Alamos HIV database. In addition to a citation signed by the Secretary of Energy and a gold medal bearing the likeness of Ernest Orlando Lawrence, the award also includes a $50,000 prize.

In keeping with her philosophy of doing science for the benefit of others, Korber used the award money, along with donations from family and friends, to build an AIDS orphanage in South Africa. “Now,” she says, “one hundred sixty five children have a place to live and people to take care of them.”

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Villagers stroll home from church Sunday morning on a street leading to the small fishing town of Gaba on the shores of Lake Victoria in Uganda.