FIGHTING HIV THE Evolution Solution

BY JULIE REHMEYER

HIV seems to have learned a thing or two from Proteus. It constantly changes form, eluding the immune system much the way that mythological sea creature evaded Menelaus. Although a person typically gets infected with a single strain of the virus, after a decade of infection two HIV viruses in the body may differ by as much as 10 percent—a greater difference than that between the key regions of mouse and human DNA. So before the immune system has managed to grasp the first form of HIV, the virus has changed form enough to become unrecognizable.

For the past 20 years Bette Korber, an SFI external professor and a researcher at Los Alamos National Laboratory, has been hunting HIV, trying to develop a vaccine that could teach the immune system to grab onto the wily monster that causes AIDS. Now she and her team of researchers may have hit on something. The mosaic vaccine they have developed has entered Phase 1 clinical trials.

Every previous human vaccine attempt has either failed completely or has been only marginally useful. Their trials have taken a fairly traditional approach, exposing the immune system to proteins from a few HIV strains and hoping the body would somehow be able to generalize and recognize other strains. Though disappointing, their failure hasn't been surprising: Two HIV viruses from different people in different parts of the world can vary by as much as 30 percent. Although a single vaccine might help the immune system with strains similar to the ones it's based on, it can't do much to stop the rest.

So vaccine researchers have continued to struggle with HIV's Protean tricks. In the early 1990s, Korber came up with a novel idea: She could design an artificial protein to resemble natural proteins from all the different strains. Then, if the body could learn to recognize that single protein, it might be able to spot a great variety of natural HIV proteins.

"People kept saying this would never work," Korber says. Proteins are complicated objects, other researchers argued, that won't fold up right if they're designed willy-nilly on a computer. But Korber noted that

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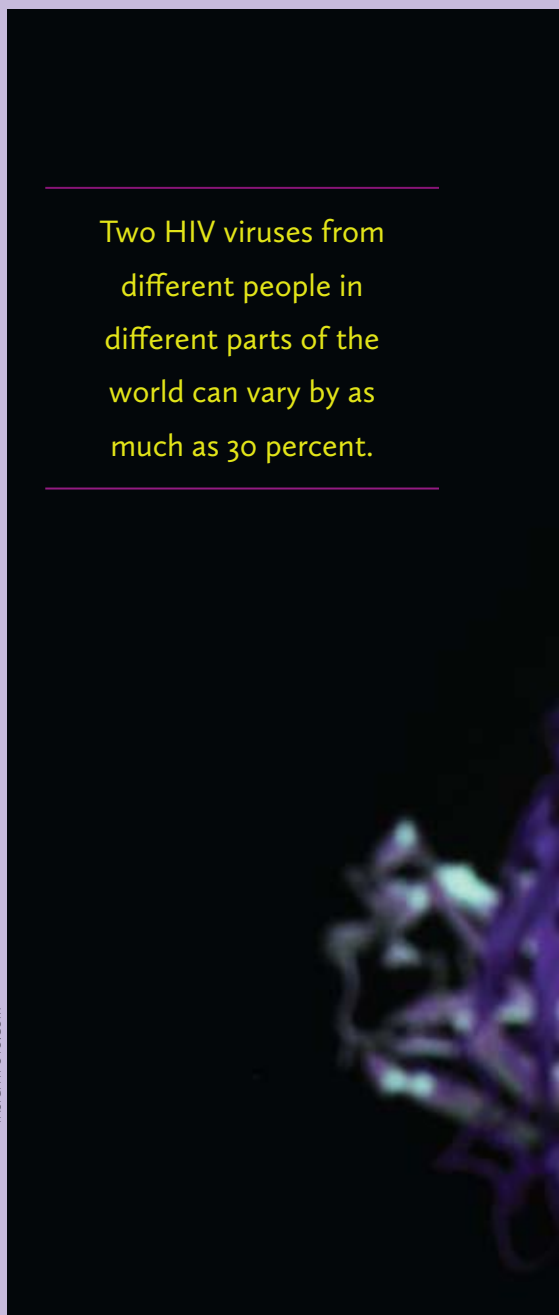

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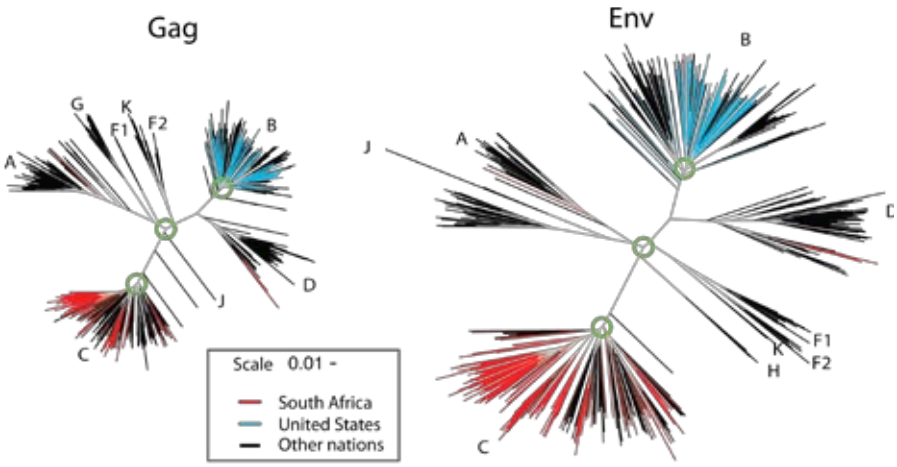
evolution itself, which produces HIV's tremendous variation, creates large, random changes in proteins, and those proteins seem to serve HIV's ends all too effectively. So she and her team stuck to her idea and produced a "consensus" protein, which is a kind of average of all of the global variants of each protein that makes up the HIV virus (one such protein, for example, forms part of the outer surface of the virus). Proteins are long strings of amino acids chained together, and in each position along the chain, their artificial protein contained the amino acid that occurs most commonly in natural HIV viruses.

When Korber's colleagues for the experiment tested her vaccine, it caused vaccinated monkeys' immune systems to recognize many more variants of HIV than vaccines based on natural proteins had. Now that Korber's approach has shown success, she's received the ultimate compliment from other researchers: Not only are other groups embracing her approach and pursuing similar ideas themselves, the success of the method is now seen by many as obvious.

The consensus vaccine is one of the approaches about to be tried in humans. Still, Korber and her team worried that it might not be good enough. Current HIV viruses could be so diverse that the body might not recognize their proteins as being related to the average, consensus protein.

Bette Korber



A phylogenetic tree depicts the relatedness of different organisms and can be used to reconstruct lineages. In these trees, each branch tip represents an HIV sequence isolated from a different person. The different "clades" or branches are groups of genetically related sets of HIV sequences, designated by letters A, B, C…

So Korber and her team developed another way of designing an artificial protein, one that could be even more powerful. Because defending the body from outside attack is such a complex job, the human immune system takes a belt-and-suspenders approach, with independent, overlapping defenses. Traditional vaccines teach the body to quickly produce antibodies that can recognize proteins on the outer shell of a virus and mark the virus for destruction. Korber's team's new approach focuses on a different part of the immune system, the T cell. Rather than trying to detect free-floating viruses, T cells sniff out cells that have been taken over by viruses and then destroy them. A T-cell vaccine wouldn't stop infection entirely, but it would allow the immune system to fight back faster and keep the infection under control.

Healthy cells protect themselves from these killer T cells much the way the Torah says the Israelites marked their homes' doorposts with lamb's blood to persuade God's angel of death not to harm them. Cells persuade the killer T cells to leave them unharmed by placing a little cup on the outside of their cell membrane and filling it with tiny, chopped-up bits of the proteins they're making. If the protein bits in the cup are from normal human proteins, the killer T cells will pass over the cell and leave it alone. But if the killer T cell recognizes a bit of viral protein in the cup, it mercilessly attacks.

Korber and her team hatched a plan to create a vaccine that could teach the T-cell assassins to recognize the wide variety of protein bits produced by variants of HIV. They did this by exposing the body to a set of proteins that were a kind of mosaic, pieced together from fragments of all the different HIV proteins.

Carrying this out was tricky, though. They couldn't simply smash together a bunch of protein bits at random, because the resulting protein might be unlike a natural HIV protein. If the cell chopped the protein up incorrectly, the killer T cells wouldn't learn to recognize infected cells. Even worse, the cells could end up producing other harmless protein bits that would busy the immune system with useless reactions and distract it from its real work.

The problem was a stumper, one that had hung up previous groups that had tried a similar approach. So instead of relying on their own ingenuity to design the answer to the problem, Korber and her team set evolution—the very tool HIV uses in its shape-shifting stratagem—against the virus.

"We evolved the virus in the same way it evolves itself in people," Korber says. Rather than doing so inside the body, though, they did it inside a computer. The method is an application of the "genetic algorithm" concept developed in part by SFIers John Holland, Melanie Mitchell, and Stephanie Forrest. Korber and her team started with a database of every variant of a given protein produced by HIV and declared this their first "generation" of proteins. They then "mated" them to create a new generation.

Then the computer passed judgment on each of the proteins, deciding on its fitness. To do so, it chopped each protein into nine amino-acid-long bits, ranked those bits according to how commonly each occurs in natural HIV proteins, and added up those rankings. In creating the subsequent generation of proteins, the computer "bred" the high-scoring proteins more often than the low-scoring ones. After many generations, the highest-scoring set of proteins was chosen.

The result of this process was a set of proteins that contained a wide variety of the common protein bits from HIV viruses and very few uncommon ones.

ABOVE AND RIGHT: WWW.NCBI.NLM.NIH.GOV/PUBMED AND LOS ALAMOS NATIONAL LABORATORY

Furthermore, within each small stretch of amino acids, their artificial proteins would look just like natural HIV proteins, making the body more likely to treat their protein as if it were real.

The team coded up the idea and ran it. The results, says Tanmoy Bhattacharya, an SFI professor and a member of Korber's team, were remarkable: "It beat all of our ideas hands down."

Then the long process of bringing their idea to reality began. Their colleagues in the experiment turned the virtual proteins into real ones and tested them in monkeys. The vaccine produced both an immune response to many more strains of HIV than a conventional vaccine and to many more strains than their own consensus vaccine.

Both vaccines have entered Phase 1 clinical trials. These test how safe the vaccines are and also determine which vaccine—one based on a natural HIV strain, a consensus strain, or a mosaic combination—elicits the best immune response in humans. Though animal tests suggest that the mosaic vaccine is more powerful, results in humans might vary. Furthermore, the consensus vaccine is the least expensive to produce, making it advantageous if sufficiently effective. If successful, trials for efficacy will follow.

While Korber is hopeful that this new research will work, she's even more optimistic that the ideas behind the consensus and mosaic vaccines will at least contribute to an eventual vaccine. And a vaccine, she believes, is what we need. "People have made beautiful progress on treatments for HIV, but it is very expensive and difficult to deliver," she says. "You want to be able to protect people without having to give them drugs for life. A vaccine, if we could create one, would be the simplest and best solution." ◀

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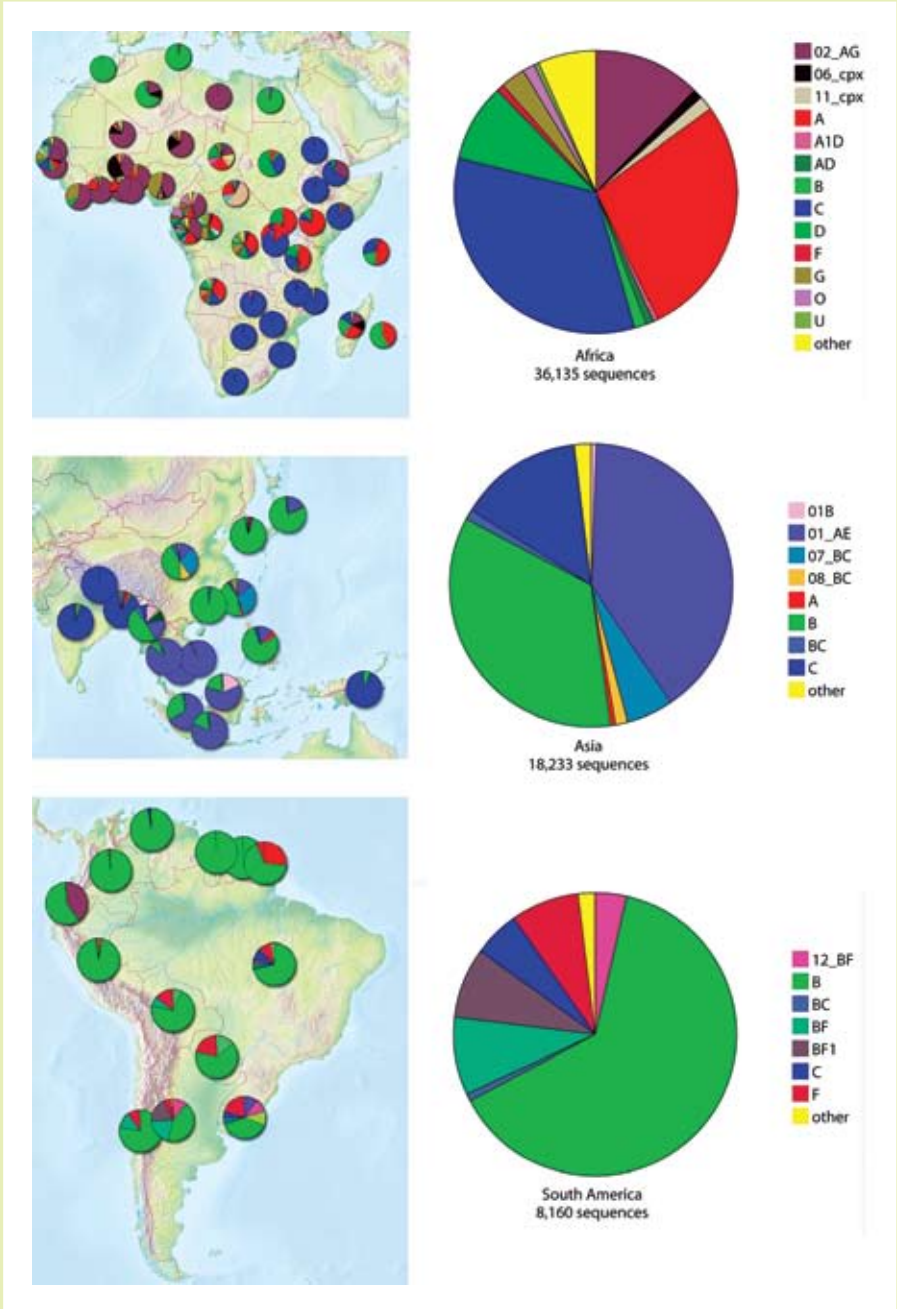

Right: These maps reflect what researchers know about global distribution of HIV subtypes. The sequences are often single genes and fragments, so inter-subtype recombination is underestimated. They are not sampled randomly but are the product of all HIV studies with sequences submitted to GenBank.