Math Wizards Develop New HIV Drug Candidates

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Using a blend of high-level math and chemical engineering, a team of researchers at Princeton University has discovered several new drugs that their colleagues at Johns Hopkins University in Baltimore say are potent against HIV. Their process for finding new drugs against diseases, outlined in a paper published online November 17 in *Biophysical Journal*, could significantly speed up the laborious task of searching for and testing promising chemical compounds.

Discovering a new drug is time-consuming and expensive. Typically, companies physically test their libraries of millions of chemical compounds against a biological target to look for activity. This process, if researchers are lucky, yields perhaps a half- dozen candidates. Yet it is only the first step in the process, as these candidates must not only be active against the virus or bacteria in question, but also be judged safe for humans to take—and be easily made into a pill or injectible solution. This can mean spending years and millions of dollars and ending up with no viable treatment options.

Now a doctoral student at Princeton, Meghan Bellows-Peterson, and the head of her lab, Christodoulos Floudas, PhD, are publicizing their work with noted Johns Hopkins AIDS researcher Robert Siliciano, MD, PhD, to discover and test new compounds that are similar to the HIV drug Fuzeon (enfuvirtide), but possibly more potent, cheaper to make and easier to take.

Using a combination of two forms of math and engineering—optimization theory and computational biology—Bellows-Peterson and her team calculated which of the long strings of amino acids (called peptides) in Fuzeon were most likely responsible for keeping the virus from fusing with, and entering, CD4 cells.

“The actual mechanism for [HIV] entering cells is still uncertain, but there is a lot of evidence that points to [a specific] structure on the virus,” Bellows-Peterson said. “We used the available data on the proteins that form the structure to help us predict what kind of drug might be effective against the virus.”

Reasoning that a string of peptides shorter than the 36 that make up Fuzeon would be cheaper to make and much less fragile in the body (perhaps leading to better dosing options than the twice-daily injections required for Fuzeon), Bellows-Peterson and her colleagues calculated the likelihood of millions of other peptide configurations to stop HIV entry. They found five promising candidates,

each of which has strings of peptides that are two thirds shorter than Fuzeon.

The team next worked with Siliciano and his colleagues to make and test the new peptides against actual virus in the lab and found one that is particularly potent against HIV, even against HIV that has become resistant to Fuzeon.

Floudas's lab is interested in seeking drugs based on even shorter strings of peptides, which could possibly be taken as oral drugs. While this approach could take years to produce a viable new treatment option for HIV, the success in proving its potential could open up a quicker and cheaper way to bring new drugs to the market.

"One could never test all the possible peptides to see if they are effective against HIV," Floudas said. "But this model was able to sort through millions of possibilities and identify just a few that show promise."
