Scientists Crack Integrase Inhibitor Mystery

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Scientists have grown a crystal version of an integrase enzyme very similar to HIV's, which could help them better understand how integrase inhibitors such as Isentress (raltegravir) actually work and possibly help scientists design even better drugs. The research results will be published January 30 in *Nature* and were reported by ScienceDaily.

In December 1995, the very first protease inhibitor was approved for people with HIV. The potency of that class of drugs, as well as the fact that those meds were combined with two other antiretrovirals (ARVs), led to a revolutionary change in the success of HIV treatment. One of the things that helped scientists develop protease inhibitors was the fact that they had a crystal representation of HIV's protease enzyme and could design the drugs based on that.

Integrase is another key HIV enzyme. HIV uses it to integrate its genetic material into the DNA of human cells—thus causing those cells to churn out new copies of the virus. Unfortunately, because researchers have—until now—been unable to grow a crystal version of integrase, they have had to make guesses about the integrase enzyme's three-dimensional physical structure. This means that although scientists were successful in developing Isentress and other integrase inhibitors in the research pipeline, they haven't fully understood how these drugs stopped the integrase enzyme from working properly.

Now, researchers at the Imperial College of London and Harvard University in Cambridge report that they have successfully grown a crystalline version of the integrase enzyme of a little-known retrovirus called Prototype Foamy Virus (PFV). The integrase enzyme of PFV is very similar to HIV's integrase. The researchers then coated the crystal versions of the enzyme with Isentress and another experimental integrase called elvitegravir (GS-9137) to determine exactly how they attached to it.

According to ScienceDaily, the new research could ultimately be of great use. "Availability of the integrase structure means that researchers can begin to fully understand how existing drugs that inhibit integrase are working, how they might be improved."

It is also possible that studying the crystal version could help scientists develop new integrase inhibitors that are less likely to develop drug resistance.