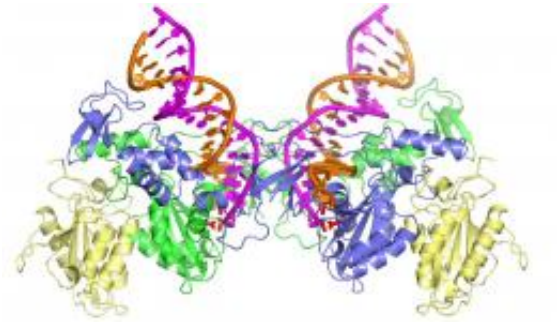
HIV researchers solve key puzzle after 20 years of trying (w/ Video)

31 January 2010



The structure of integrase bound to viral DNA. Credit: Imperial College London

Researchers have made a breakthrough in HIV research that had eluded scientists for over 20 years, potentially leading to better treatments for HIV, in a study published today in the journal *Nature*.

The researchers, from Imperial College London and Harvard University, have grown a crystal that reveals the structure of an enzyme called integrase, which is found in retroviruses like HIV. When HIV infects someone, it uses integrase to paste a copy of its genetic information into their DNA.

Prior to the new study, which was funded by the Medical Research Council and the US National Institutes of Health, many researchers had tried and failed to work out the three-dimensional structure of integrase bound to viral DNA. New antiretroviral drugs for HIV work by blocking integrase, but scientists did not understand exactly how these drugs were working or how to improve them.

Researchers can only determine the structure of this kind of molecular machinery by obtaining high quality crystals. For the new study, researchers grew a crystal using a version of integrase borrowed from a little-known retrovirus called Prototype Foamy Virus (PFV). Based on their knowledge of PFV integrase and its function, they were confident that it was very similar to its HIV counterpart.

Over the course of four years, the researchers carried out over 40,000 trials, out of which they were able to grow just seven kinds of crystals. Only one of these was of sufficient quality to allow determination of the three-dimensional structure.

Dr Peter Cherepanov, the lead author of the study from the Department of Medicine at Imperial College London, said: "It is a truly amazing story. When we started out, we knew that the project was very difficult, and that many tricks had already been tried and given up by others long ago. Therefore, we went back to square one and started by looking for a better model of HIV integrase, which could be more amenable for crystallization. Despite initially painstakingly slow progress and very many failed attempts, we did not give up and our effort was finally rewarded."

After growing the crystals in the lab, the researchers used the giant synchrotron machine at the Diamond Light Source in South Oxfordshire to collect X-ray diffraction data from these crystals, which enabled them to determine the long-sought structure. The researchers then soaked the crystals in solutions of the integrase inhibiting drugs Raltegravir (also known as Isentress) and Elvitegravir and observed for the first time how these antiretroviral drugs bind to and inactivate integrase.

The new study shows that retroviral integrase has quite a different structure to that which had been predicted based on earlier research. 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, and how to stop HIV developing

resistance to them.

More information: “Retroviral intasome assembly and inhibition of DNA strand transfer” *Nature*, Sunday 31 January 2010

Provided by Imperial College London