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Breakthrough in battling HIV

Crystal reveals structure of enzyme called integrase that is found in retroviruses

By Brian Bell

LONDON: Chemists have made a remarkable advance in the battle against HIV, finding an outcome that has eluded scientists for more than 20 years and potentially leading to better treatments.

According to a study recently published in the journal *Nature*, researchers from Imperial College London and Harvard University have grown a crystal that reveals the structure of an enzyme called integrase that is found in retroviruses such as the human immunodeficiency virus (HIV).

When HIV infects humans, it uses integrase to paste a copy of its genetic

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information into their DNA (deoxyribonucleic acid).

Prior to the new study - funded by the UK's 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.

The latest anti-retroviral 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, scientists 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.

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

Dr Peter Cherepanov, the leading 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 crystallisation.

"Despite initially painstakingly slow progress - and very many failed attempts - we did not give up and our effort was finally rewarded," he added.

After growing the crystals in the laboratory, the researchers used the massive synchrotron machine at the Diamond Light Source in Oxfordshire to collect x-ray diffraction data from these crystals and this 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 anti-retroviral drugs bind to and inactivate integrase.

The study shows that retroviral integrase has quite a different structure to the one that had been predicted based on earlier research.

Availability of the integrase structure means that researchers can begin to understand fully how existing drugs that inhibit integrase are working, how they might be improved, and how to stop HIV developing resistance to them. — LPS

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— Dr Peter Cherepanov, researcher

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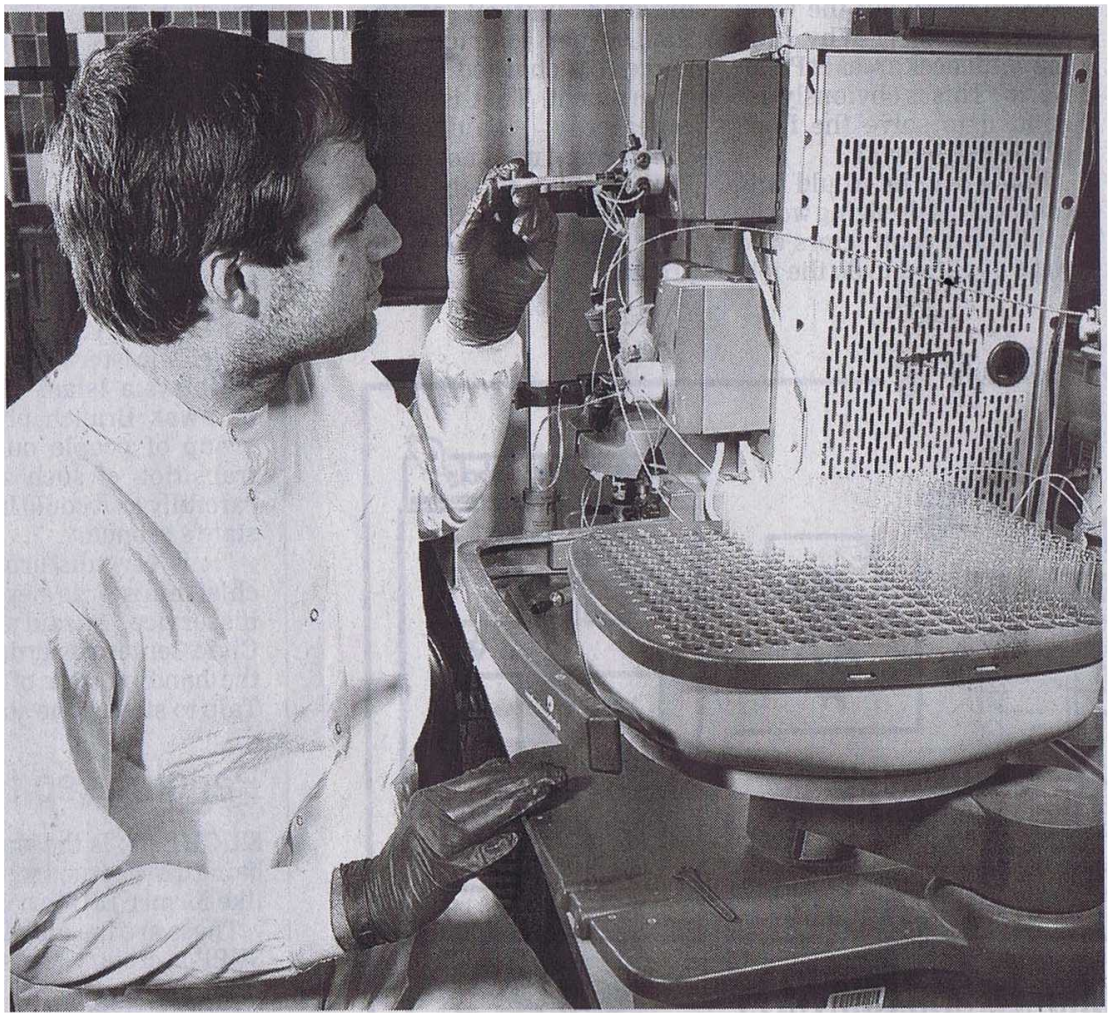

VIRUS FIGHTER ... UK and US doctors have made one of the most important discoveries in HIV research for more than 20 years. Dr Stephen Hare (pictured in London) prepares isolation of viral proteins for crystallisation using chromatography. – LPs photo