

Insights into a new class of HIV retroviral drugs

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A recent study published in the journal *Nature Communications*, titled “Quenching protein dynamics interferes with HIV capsid maturation,” details a newly discovered mechanism that can interfere with the maturation of the human immunodeficiency virus, preventing its ability to be infective. The research involves preventing the maturation of the protein shell called the capsid surrounding the virus.

Currently, there are more than 25 antiretroviral medications from six major classes available for treating HIV. None, however, inhibit maturation, a mechanism in a potentially new class of drugs which could benefit patients with multidrug-resistant infections. If this new approach continues to prove fruitful, and is developed into a treatment and distributed, it would give a great deal of relief to the 36.7 million men, women and children currently living with HIV.

The study was made possible through collaboration by the University of Delaware, the University of Pittsburgh School of Medicine, the University of Illinois and Vanderbilt University Medical center. A significant part of the research was funded by DFH Pharma, a privately held specialty pharmaceutical company focused exclusively in the treatment of HIV, which began to work with the National Cancer Institute to continue development on the next generation HIV maturation inhibitor drugs and identify new drugs in this class for clinical trials.

Initial work in the early 2000s by Dr. Eric Freed, a well-known scientist in the field of HIV assembly and release, in collaboration with Panacos Pharmaceuticals, discovered and produced the first class of maturation inhibitor drugs, Bevirimat. In 2009 Myriad Genetics bought the rights to the drug for \$7 million. However, due to problems with Bevirimat’s formulation, they

halted further development in 2010.

The focus of the present study is on deducing the mechanism of this new class of anti-retroviral drugs which interfere with the development of the HIV-1 virus inside a live body. It took seven years to complete, using complex instrumentation and multi-disciplinary expertise to study the dynamic nature of the virus’s early and late life cycle.

According to a statement by Professor Tatyana Polenova of the University of Delaware’s Department of Chemistry and Biochemistry, “People used to fixate on the static structures of viruses, but they are not rock solid. Viruses like HIV and their constituent protein and nucleic acid molecules are dynamic entities that are constantly expanding and shrinking. Their motions are like breathing.”

The molecules created by the HIV virus’s RNA operate within the host in concert, but deducing these complex synchronized motions requires expertise in quantitative biophysics using supercomputers to model and simulate the moving parts of the HIV virus. The research also integrated technology to image cells and molecules directly, known as nuclear magnetic resonance (NMR), to view how the virus actual reacts to different treatments.

A major focus of this work is studying the genetic material that codes the core structural proteins of retroviruses, known as Glycosaminoglycan (abbreviated, for obvious reasons, as “GAG”).

It is one of the essential “polyproteins” of HIV, which also include the matrix, capsid and spacer peptides (chains of amino acids). Capsid is particularly important because it is the protective protein shell of the virus.

Maturation inhibitors such as Bevirimat are thought to prevent the formation of a mature shell by entering

the budding virus and binding to the cleavage site that would lead to maturation, thereby preventing this process, creating a vulnerability that the researchers are looking to exploit. The non-mature virus particle is non-infective.

Cyclophilin A, a common human protein commandeered by the virus in the assembly of the capsid protein, is essential for its life cycle and infectivity. Using NMR imaging techniques to reveal nano-second to micro-second timescales of the virus formation, the research revealed that the Cyclophilin A loop is highly flexible in the assembled capsid. Modulation of the dynamics in this loop plays a role in HIV's infectivity. In HIV, viruses that have mutations mimicking those similar to Bevirimat binding demonstrated dramatic attenuation as well as decreased infectivity suggesting this interplay as the mechanism of action for this novel class of anti-retroviral drugs.

HIV research began in 1985, four years after the first cases of an unusual type of pneumonia described among groups of men having sex with other men in the United States and two years after HIV was first identified. The first anti-retroviral drugs were introduced in 1987, followed by combination retroviral therapy in 1996 which led to decreased AIDS-defining diagnosis and mortality by 60 to 80 percent. Despite these efforts, however, HIV became and has remained a worldwide epidemic that has so far claimed 35 million lives, comparable to the number of casualties, military and civilian, in World War I.

And while 69 countries saw a decline in their population infected with HIV (or with its more advanced stage, AIDS), UNAIDS has warned that progress in preventing new infections is not occurring fast enough to meet global targets. It predicts that some regions of the world—such as Eastern Europe and Central Asia—have seen new infections rise by 60 percent since 2010. Of the world's population, 0.8 percent of adults have the virus and 30 percent of these are not aware they are infected.

Nearly 4 million new cases were reported in the past two years and 1 million have died from AIDS-related illnesses. No country is unaffected, though eastern and southern Africa suffer the majority of current cases, where 19.4 million people are infected. In countries such as Botswana, Lesotho and Swaziland HIV/AIDS infection rates among adults exceed 20 percent.



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