

Defense peptide found in primates may block some human HIV transmissions

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As primates evolved 7 million years ago, the more advanced species stopped making a protein that University of Central Florida researchers believe can effectively block the HIV-1 virus from entering and infecting blood cells.

HIV-1 often mutates quickly to overcome antiviral compounds designed to prevent infections. But a research team led by Associate Professor Alexander Cole of UCF's Burnett College of Biomedical Sciences has demonstrated that over 100 days the virus develops only weak resistance to retrocyclin, a defense peptide still found in monkeys and lower primates.

If additional laboratory tests demonstrate only weak resistance, Cole will study how retrocyclin could be developed into a drug designed to prevent the HIV virus from entering human cells.

Cole is also working with Henry Daniell, a UCF professor of molecular biology and microbiology, to develop a way to grow retrocyclin through genetically engineered tobacco plants. The retrocyclin gene would be incorporated into the chloroplast genome of tobacco cells before the plants grow. Daniell has developed a similar approach to growing anthrax vaccine in tobacco plants.

An inexpensive way to produce the drug with only a small amount of tobacco would help to make it accessible in areas such as Southeast Asia, Africa and the Caribbean where the disease spreads most quickly.

"If we could develop retrocyclin in plants and produce enough of the drug cheaply, we could potentially save a lot of lives," Cole said.

Cole was recently awarded about \$4 million of National Institutes of Health grants through 2011 for the HIV-1 research and similar studies. The grants were provided through the National Institute of Allergy and Infectious Diseases; National Institute of Child Health and Human Development; and the National Heart, Lung and Blood Institute.

Cole started his research into theta-defensins at the University of California, Los Angeles, before he moved to UCF in 2003. Drs. Otto Yang and Robert Lehrer, infectious disease specialists at UCLA, and researchers at the University of Pittsburgh and Emory University are collaborating with Cole.

There are three classes of defensin peptides, and most research around the world has focused on alpha and beta defensins, the two types that humans still make. Cole studies theta-defensins called retrocyclins, which are no longer made by humans or advanced primates such as chimpanzees. However, theta-defensins are more active against HIV-1 than the other two types of defensins and can be developed in laboratories, two features that suggest retrocyclins still could become an effective way to fight the virus.

HIV-1 is the most common form of the human immunodeficiency virus that causes AIDS. The disease is often transmitted sexually, and the drugs produced from Cole's research would be applied to the vagina in the form of a gel or cream. Many of the laboratory tests have shown that retrocyclin can prevent HIV-1 infection of human vaginal tissue.

Retrocyclin was still an effective inhibitor of HIV-1 even after 100 days of continuous exposure to human cells in a laboratory setting. Cole and his team are encouraged that only minimal resistance of the virus

occurred during that time. Higher resistance levels make it more difficult to develop drugs to fight the virus because doses must be increased substantially over time.

The exact reason why resistance does not develop quickly with retrocyclin is unclear, but it may be a result of retrocyclin interacting with more than one target on both the cell and virus. Viruses that have to defeat more than one antiviral mechanism often develop resistance at a much slower pace.

The next phase of Cole's research will delve more into the mutations that HIV-1 can take in an effort to minimize them as much as possible. Many series of laboratory tests would need to be completed before clinical trials could begin no earlier than 2009.

Cole's findings were published in the June 1 issue of *The Journal of Immunology*, a top journal in the fields of immunology, molecular biology and microbiology.

Source: University of Central Florida

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