

Research leads to first treatment for drug-resistant HIV

August 3 2006

Doctors have their first FDA-approved tool to treat drug-resistant HIV thanks to a new molecule created by a Purdue University researcher.

"There are many treatments for AIDS on the market, but none are able to combat drug resistance," said Arun Ghosh (pronounced A-rune GO-sh), a professor with a dual appointment in the departments of chemistry and medicinal chemistry and molecular pharmacology. "This is the first treatment that is effective against the growing number of drug-resistant strains of HIV, the virus that causes AIDS. The problem is widespread."

The FDA recently approved the pill-based therapy of Ghosh's molecule, TMC-114, for medical use. The molecule, also known as Darunavir (pronounced DA-rune-a-veer), is the forerunner in a series of molecules under development by Ghosh.

Earlier research shows that almost half of patients with the human immunodeficiency virus (HIV) who initially respond to treatment develop drug-resistant strains and stop responding to treatment within eight to 10 months, he said. An additional 20 percent to 40 percent of patients have drug-resistant strains when they are first diagnosed, suggesting these strains can be transmitted from one person to the next.

This year marks the 25th anniversary of the first reported U.S. cases of AIDS, a disease that claims the lives of more than 15,000 Americans each year, according to the Centers for Disease Control and Prevention. World Health Organization figures estimate more than 40 million people

worldwide are infected with HIV.

For years the virus has frustrated drug developers through its ability to "outsmart" therapies. The virus rapidly mutates and, as parts of its structure change, it becomes resistant to treatment. Previously, patients with drug-resistant strains were out of options and had greatly reduced life expectancies.

"My only wish was that my design would help people and alleviate suffering," Ghosh said. "I'm so grateful it has turned into a drug and been approved by the FDA so quickly."

The molecule Ghosh created is expected to be available to physicians this year, he said.

"I think that this drug will have a sizeable impact on the current therapy for AIDS and HIV infection," said Hiroaki Mitsuya (pronounced HE-row-ah-key MIT-sue-ya), chief and principal investigator of the Experimental Retrovirology Section at the National Cancer Institute who collaborated with Ghosh in this research.

Molecules are made up of groups of atoms bonded together. These bonded groups form an oddly shaped structure with sections that branch off and others that form loops. Different sections are responsible for various behaviors of the molecule.

Ghosh's designed compound has selected features of naturally occurring molecules that improve its ability to fight HIV. The result is a variation of one of the most common treatments existing today, a protease inhibitor.

Protease is an enzyme necessary for HIV to reproduce properly. A protease inhibitor binds to protease, making it unusable by the virus.

Without the use of protease, HIV is incapable of infecting cells and harming the patient. By reducing the amount of active virus, patients' bodies have an increased ability to fend off opportunistic infections, the leading cause of death for those with AIDS.

Eight protease inhibitors are currently on the market and have greatly improved the quality of life for those suffering from HIV, Ghosh said. These inhibitors, however, lose their effectiveness over time, often cause severe side effects and are ineffective against drug-resistant HIV strains, he said.

Treatment using the molecule designed by Ghosh has fewer associated side effects because the dose required is significantly less than those for existing protease inhibitors. The molecule also is smaller than those that make up current protease inhibitors and is much more easily absorbed and tolerated by the body, according to research results.

"In Phase 3 clinical trials of TMC-114, the majority of patients receiving the drug did very well with relatively few side effects," Mitsuya said. "Those patients showed a significant increase in their CD4 cell counts. Many of those patients have been treated for a year or more and have shown no signs of developing a significant resistance to the drug."

Ghosh is now expanding on his design, making alterations to the original molecule aimed at making even more effective treatments.

"The most recent protease inhibitors we created are exceedingly potent," he said.

Ghosh's work has opened the door to a new path for antiretroviral therapy.

"Earlier, researchers were unsure of how to deal with drug-resistant

viruses," he said. "Problems that arose with treatments developed in the 1990s were disheartening. There was no concept on the horizon. We created a conceptually new class of protease inhibitors to combat drug resistance. That has renewed excitement in antiretroviral treatment and provided a direction for the future."

These new protease inhibitors are beneficial for reasons beyond their potency and enduring effectiveness, Ghosh said.

"Because they are synthetic, lab-created materials, they are amenable to cost-effective mass production. Keeping costs down greatly increases the accessibility of the drugs to Third World countries where the epidemic is worst."

The design, synthesis and evaluation of these new protease inhibitors will be detailed in a paper in the Aug. 24 issue of the *Journal of Medicinal Chemistry* and is currently available on the journal's Web site.

Irene Weber of Georgia State University, Eric Walters of Rosalind Franklin University of Medicine and Mitsuya co-authored the papers with Ghosh. Mitsuya characterized the molecules' effectiveness and Walters and Weber performed the crystallography that provided images of the molecules' structures.

"It is very important to have an image of the structure to see exactly how the inhibitors work," said Weber, Georgia Cancer Coalition Distinguished Cancer Scholar. "We can know a treatment is working without fully understanding its behavior. Visualizing the structure of the inhibitor as it interacts with the virus shows us how and why it works so well and greatly advances our ongoing fight against drug-resistant HIV."

Ghosh began his work at the University of Illinois and set out to design and synthesize a molecule that would interact with a part of the virus that

did not change as the rest of it mutated - the backbone of protease.

"We designed this molecule top to bottom to interact with the protease backbone and deactivate the virus," he said. "This allows it to continue to be effective as the virus mutates, when other treatments would fail."

Mitsuya said he is pleased with the effectiveness of this new class of inhibitors and sees it as a possible turning point in HIV therapy.

"This will save many lives of patients suffering from drug-resistant HIV," he said. "This is encouraging."

Ghosh said he hopes this approach could be applied to other viruses, and he is currently involved in research into the SARS virus.

Source: by Elizabeth K. Gardner, Purdue University

Citation: Research leads to first treatment for drug-resistant HIV (2006, August 3) retrieved 3 May 2024 from <https://medicalxpress.com/news/2006-08-treatment-drug-resistant-hiv.html>

| |
|--|
| <p>This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.</p> |
|--|