

*For Immediate Release  
April 2, 2004*

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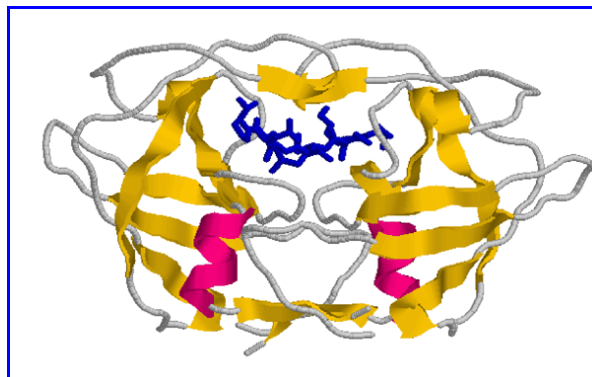
## **ENZYME INHIBITOR: RESEARCHERS TEST POTENTIAL COMPOUNDS TO STOP REPLICATION OF VIRUS THAT CAUSES ADULT T-CELL LEUKEMIA**

Researchers are analyzing several compounds that may inhibit the enzyme that is essential for the reproduction of the Human T-cell Leukemia Virus Type 1 (HTLV-I), which has infected 15 to 20 million people worldwide. The virus causes the fatal adult T-cell leukemia in up to 10 percent of those infected.

Little is known about the HTLV-I enzyme, or protease, that cuts long strings of amino acids to form functional proteins that make a mature HTLV-I virus -- a distant cousin of the HIV virus that causes AIDS. About 250 researchers worldwide are studying the HTLV-I protease, and among them are researchers at the Georgia Institute of Technology. They presented their findings April 1st at the 227<sup>th</sup> national meeting of the American Chemical Society (ACS) in Anaheim, Calif.

“There are currently no good ways to treat HTLV-I and prevent the spread of the virus,” said Suzanne B. Shuker, an assistant professor of chemistry and biochemistry at Georgia Tech. “Therapies that inhibit the life cycle of the virus have potential as treatments for HTLV-I infection. The protease from HTLV-I is therefore an attractive target for inhibitor design.”

Researchers in Shuker’s laboratory have been studying this protease for five years, building on research begun at Georgia Tech 12



*Researchers created this structural diagram of the HTLV-I protease.*

years ago by former Professor Rick Ikeda, now at the National Institutes of Health. As they test possible inhibitor compounds, Shuker and her students are also working to understand more about the enzyme’s activity and structure to help in the development effort. A Georgia Tech and Centers for Disease Control and Prevention (CDC) seed grant is funding the current work.

Research team member Bryan Herger, a fourth-year Ph.D. student in Shuker’s lab, studies how the protease functions and how it identifies the amino acids it’s supposed to cut. This information helps fourth-year Ph.D. student Kelly Dennison and other team members find compounds that mimic the HTLV-I protease’s process of cutting amino acids. The six

compounds they are investigating now contain statine, 4-amino-3-hydroxy-5-phenylpentanoic acid or hydroxyethylamine. Researchers believe these compounds are potent protease inhibitors.

They have performed kinetic assays to determine how fast each compound processes the virus proteins. The assays involve a natural substrate consisting of a segment of an amino acid chain that contains a junction where the HTLV-I protease will cut. The substrate is treated with a fluorescent agent that reveals the location of cuts in the amino acid chain. When researchers add a potential inhibitor compound to the substrate, they determine the rate at which it cuts the chain. The slower the rate, the better the inhibitor, Dennison explained.

“Later this year, we will test the most promising of these compounds on actual HTLV-I viruses in CDC labs,” Dennison added.

Meanwhile, Herger is studying the individual amino acids, or structural elements, which make the HTLV-I protease produce an infectious virus. He is determining which of these elements are involved in binding to the viral proteins and what factors are important in the assembly of viral particles. Once he identifies the approximate arrangement of amino acids, then researchers can develop inhibitors that bind in the same way to those specific amino acids.

Herger uses a lock and key analogy to explain the research. The enzyme is the lock, which has a keyhole.

“We know what the key, or the native viral protein, looks like,” he said. “And we want to know the shape of the lock to develop other keys to match it and lock it up.”

Based on the amino acids that form the keyhole for the HIV protease, which is very similar to the HTLV-1 protease, researchers can change the HTLV-I protease so it works like HIV.

“The same key works for both proteases,” he said. “So we’re doing a bit of protein engineering here. Then we can take educated guesses as to the corresponding places in HTLV-I protease and change those amino acids until they match the HIV-1 protease, a known keyhole. Based on this information, we have a better idea of the binding site, or keyhole, of the HTLV-I protease. We hope to translate this information to develop better inhibitors of the protease.”

Researchers have already identified a few amino acids they believe are critical to recognizing

the right protease inhibitors. For now, they are developing compounds that mimic peptides because they are easier to synthesize, Dennison explained. Eventually, they want to develop non-peptide, or totally synthetic, inhibitors because, as drugs to treat T-cell leukemia, they would have fewer side effects and be more effective, she added. Researchers believe this work could lead to a new pharmaceutical agent in about five years.

In a related project in Shuker’s lab, undergraduate student Katelyn Swindle is developing a rapid method for screening inhibitors for their effectiveness. It now takes a full day to study just two compounds. If Swindle’s process works, researchers could get results from 96 different compounds in just 45 minutes. This method measures the optical properties of the compounds and performs analysis without separating the chemical products in each compound.

Despite what can be tedious work, the researchers express excitement about their studies.

“It’s the unknown,” Dennison said. “There’s no rule book that comes with what to expect here. We don’t know much about this particular enzyme, so everything we find out is building our knowledge base toward understanding the effects of this virus.”

She added: “There’s also the altruistic side of it. I’ve received a number of email messages from friends who had friends with adult T-cell leukemia. This is just overwhelming to me.”

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