The AIDS virus is a quick-change artist that copies itself at lightning speed. But a team of scientists at Rutgers believes it can outsmart the killer.

HIV's crystal key

Above, Eddy Arnold works in his office at the Center for Advanced Biotechnology and Medicine at Rutgers University's Busch Campus in Piscataway. At left, Rutgers Researcher Christine Uren uses a nano loop to harvest a crystal for observation under a synchronon, a high-intensity, high-energy X-ray source. This process reveals the structure of HIV.

STORY BY KITTA MCFEGERSON • PHOTOS BY JERRY MCCREA

To change the world, Eddy Arnold has always tried to think small.

For nearly 20 years, the Rutgers University chemist has obsessively dismantled the AIDS virus to unravel its deadly submicroscopic machinery.

And it is there, in the complex world of the microscopic, he believes he finally has found a magic bullet that stops AIDS in its tracks.

Arnold and his cadre of researchers have developed what they regard as three revolutionary AIDS drugs, each part of a family they call DAPY (which rhymes with happy).

The drugs, they believe, can destroy HIV, the deadly virus that causes AIDS.

To do this, the drug does it as HIV does when it invades immune systems: They change shape. Put another way, DAPYs are master tools that can fit any strand of the virus, regardless of how it tries to disguise itself.

Arnold says: "We're on to something very special." Understanding and controlling this flexibility is crucial because HIV's biggest challenge in science and medicine has been its ability to consistently mutate, rendering any drug or vaccine custom-designed to quash it. And unlike other treatments that focus on blocking HIV from entering healthy cells or from containing contaminated ones, DAPYs do in a firecracker by interfering with any of the 20,000 or so HIV taken to copy itself at warp speed.

At the core of this discovery is reverse transcriptase — the villain in this story and a submicroscopic protein not normally found in healthy human cells. The team believes RT is the ideal protein to disable it. [Continued on Page 11]

IN OTHER NEWS

Bush tackles Social Security
Setting out to overhaul Social Security, the president will face critics, Republicans want a heavy hand, Democrats are opposed, and there are the fighting mail senior citizens. Page 4

Candidate poisoned in Ukraine
Presidential contender Viktor Yushchenko was given dioxins, his doctors said, adding that the high toxic chemical could have been put in the candidate's food. Page 11

As Kerik apologizes for 'mistake,' N.J. frets over

BY MARK MUKLEBER

Bernard Kerik, who abruptly withdrew from consideration to lead the Homeland Security Department over the lax and immigration status of a nanny he employed, apologized yesterday for making a "stupid mistake" that he said had caused embarrassment to the Bush administration.

Kerik, a Pearson native who gained prominence as New York City's police commissioner, told reporters outside his Franklin Lakes home that he had little choice but to withdraw as President Bush's nominee after discovering he had not paid all required taxes as associated with the woman's employment and that she may have been in the country illegally.

According to Kerik, the discovery followed Kerik's, re- ported as a woman who was his personal assistant, had been living here for him for the nomination he did not have a "strong problem," which has ended three high-level Cabinet appointees. Kerik said: "We are working on a solution."

"This is my responsibility," Kerik said. "I am a mistake. I want to move on with my life as a white House."

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In the process, Kerik's, re- report on the spending of public officials to private citizens been a running theme in this world. Page 8

He has separated from his second wife, Matos, and fled the elegant of Drumthwacket to a two-bedroom apartment in Morristown. Political states don't seem his life, and all his friends stop by to visit.

"Sometimes, like any young, single man who has been to war," Kerik said. "I don't know where I am going to be tomorrow."

The decision to run a Democrat as president John Lynch at the University of Illinois.

Kerik met with his former political tensions and gruffly dismissed him, according to three people who were there, saying he was more the Kerik's friend in a talk, at a separate table with his two bosses, Ray Le, and Paul Wolf.

Lentil, like most of the former governor's 85

Phone does not ring for form

BY DEBORAH HOWELST

former Gov. James E. McGreevey staffed his

for the politically connected Barrow law firm. Former Laccone, who is a Democratic former governor, is being considered for the post. Page 4

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Life cycle: How HIV infects cells and reproduces

The four classes of drugs that target HIV's actions:

1. The virus floats in the bloodstream along with thousands of other cells and microscopic organisms.

2. Receptors on the outside of the virus seek and attach to receptors on healthy cells, typically human immune cells.

3. The virus then fuses into the cell, sending its genetic material toward the cell's nerve center, the nucleus.

Reverse transcriptase inhibitors

One of the first treatments developed, they seek to block the machinery that creates DNA. Without DNA, the virus cannot take over the host cell. Mutations have enabled the virus to overcome many of these drugs. The drug being developed by Eddy Arnold's team is this type; see below.

Resistance and the DAPY compounds

How resistance happens

Simply put, the virus, in its endless rounds of replication, constantly makes copies of itself that contain tiny mistakes in genetic code, producing offspring that are slightly different. If the differences change the part of the virus a drug was targeting, the drug may no longer be effective and the virus is said to have a "resistant" strain.

As viral varieties targeted by drugs die off, mutant strains thrive, ultimately predominating.

How DAPY compounds avoid resistance

Early RT inhibitors were rigid. They formed a "pocket" that was part of the machinery of RT. But new virus strains had a differently shaped pocket, and the inhibitors were rendered obsolete. The DAPY compound is flexible and essentially "wiggles and jiggles" to jam the pocket on each strain of the virus. It is a master key, seemingly made of Silly Putty, so far overcoming resistance that cooled earlier RT inhibitors.

"This was a high-risk project, and he (Arnold) was competing with the super-duper labs of the world..."
Seeing the unseeable: X-ray crystallography

The reverse transcriptase protein, part of the machinery involved in the replication of HIV, is too small to be seen under powerful microscopes. To design drugs that latch onto the protein and block its operation, scientists must use an elaborate process that allows them to discern the protein's structure.

This technique, called X-ray crystallography, allows scientists to study a substance that is virtually invisible.

Making the crystal
First, scientists take samples of RT and the RT inhibitor and combine them. Each protein is a complex of thousands of inhibitor-bound RT molecules arranged in an orderly pattern and is an excellent subject for atomic analysis of the protein molecule. To make a crystal, scientists take samples of the protein in solution and place small droplets of the six-phase solution on a glass plate called a cover slip. Each droplet is misted with a precipitating solution containing salt or an organic solvent like alcohol. Finally, they seal the droplet with a glass well containing a higher concentration of precipitation solution. As the droplets dry, they solidify, and the protein molecules gradually assemble to form a crystal in the hanging droplet that is smaller than a teardrop. "The crystals are grown in a cryostat and frozen in liquid nitrogen."

X-ray vision
To get at the structure of the molecules, scientists blast the frozen crystal with highly energetic X-ray beams. The beam scatters off particles in the crystal. The scattered X-rays are recorded on a CCD or charge-coupled-device detector, which registers images and can be viewed. Each image contains thousands of dots. The resulting pattern reveals the atomic content and molecular structure of the crystal.

The 3D picture
Through extensive computation based on data gathered by X-ray analysis, scientists can eventually construct a three-dimensional image of the protein and its structural units. In the diagram above, the double helix structure of DNA can be seen in purple in the middle. The RT is captured in the process of creating DNA.

Ribbon diagram
The analysis produces what is known as a ribbon diagram of the molecule. A simplified version of the protein and the drug showing the key structural units. In the diagram above, the double helix structure of DNA can be seen in purple in the middle. The RT is captured in the process of creating DNA.

The Stalagliss
SOURCE: Center for Advanced Bioimaging, Medizins, Rutgers University and University of Wisconsin-Madison

It will take an extraordinary remedy to beat AIDS for good. After being held in check for 17 years — first by workhorse medications such as AZT, introduced in 1987, and then by drug cocktails, available since 1996 — the disease is now becoming resistant to long-held treatments.

Worldwide, acquired immune deficiency syndrome has killed 25 million people since it was first identified in the United States in 1981. And 40 million now live with the dis
case, according to United Nations statistics.

In New York, more than 32,000 people suffer from AIDS, the highest rate in the country. In the developing world, where many cannot afford even generic versions of AIDS medications, the virus kills people during their most productive years and decimates regions.

It also has been an expensive fight. Government funding for research, prevention and assistance was more than $4.7 billion in 2002.

Arnold thinks he can solve some of these problems.

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4. Another enzyme, called integrase, takes this viral DNA and inserts it into the host cell's DNA. Once complete, this cell is permanently infected and begins creating more virus.

5. The host cell can remain dormant for months or years. Once activated, it becomes an HIV factory.

6. An enzyme called protease triggers the final assembly of the virus. Once assembled, the virus breaks away, ready to infect another host.

Integrase inhibitors
Theoretically, this class of drugs would disrupt the process of combining the HIV DNA and host DNA. So far, this treatment has been difficult to develop.

Protease inhibitors
These drugs disable the protease enzyme so the new virus does not mature and is noninfectious. Side effects and resistance have made these drugs increasingly unpopular.
THE BREAKTHROUGH

A crystallographer with just the right mix of curiosity, luck and intelligence can believe he has a shot at understanding any life-form's structure.

Even if a molecule is too tiny to see with a microscope, a crystallographer can figure out its shape and composition — what scientists call its structure.

About 2 weeks before one spring night in 2004, Rutgers University professor-turned-crystallographer Darby MacDowell was sitting before a computer monitor in the basement of his Edison townhouse.

He stared at an image of a DAPY drug — TMC-110 — that had been shown in his studies by scientists at Monash University. There was a hitch, though: The people who made the compound did not yet understand exactly how it worked.

How is it, Darby wondered, that the compound could hit so neatly into the cleft of so many versions of the viral protein, effectively blocking its copying action? To do this, the molecule he was staring at had to change shape.

Just then, he thought back to his childhood, to the wording caves near a Hindu temple his family attended in India. He remembered how he had to twist and turn to make it back toward the light.

Darby then reasoned that the atoms at the extreme end of the compound inhabited a "conformational flexibility" like the movement of a gate swinging on hinges attached to a post. The molecule, he ventured, also had to juggle, or rock lightly. In short, the compound seemed to be flexible.

Darby was excited.

A drug that could wiggle and juggle — acting like a master key — would be groundbreaking.

The Rutgers group had kicked around the idea of molecular nimbleness for a couple of years and several earlier compounds had shown some degree of bending. But nothing had acted like this. Now it would be the team's job to see crystallography figure out exactly how the DAPYs worked.

The battleground would be a tiny room at the Cornell High Energy Synchrotron Source in Ithaca, N.Y., a favorite destination for the Rutgers crystallographers more than a decade.

CHESS is one of the world's leading centers for X-ray research in biology and materials science, a 23-year-old facility in Wilson Laboratory under a football field-size dome.

The facility's workhorse is the synchrotron, a massive, ring-shaped machine that essentially is the size of the field under which it sits. It accelerates subatomic particles to the speed of light, producing synchrotron radiation — a form of light researchers shine on molecules, crystals and other forms of new materials to understand their structure and behavior.

The radiation gives researchers unparalleled power and precision to probe the fundamentals of matter. The light is as million times brighter than sunlight and a billion times greater than the radiation from a typical lab X-ray.

The emerging teams are just a few nanoseconds, a millisecond across and are emitted in a catenary short pulse, typically 10 to 100 picoseconds (billionths of a second) in length. The beams barely scrape the precious crystals.

Collaborators often told Darby he had a wild card up his sleeve. When others brought dozens of crystals and left without relevant data, Darby brought one or two and always got results. That is, until he ran into DAPY.

For months, Darby blasted through hundreds of crystals at CHESS and other synchrotrons. Still, he could not obtain useful data.

"We had the crystals and they didn't diffract," said Darby, measuring samples failed to yield patterns revealing chemical structure. "That was surprising and frustrating. I know I was doing everything right.

In October 2006, the Rutgers lab crystal maker Art Clark gave Darby one crystal for a trip to CHESS. The sample, carrying a spark of life with the TMC-110 inhibitor, was as clear and glossy as a diamond in images that had been eluding the team for so long.

ONE MORE HURDLE

In fall 2001, after a year of testing, testing and testing, editors at both Science and Nature rejected Darby's paper on the work, saying it was focused on drug development and not of sufficient general interest. The team took it hard, especially since, as Arnall put it, the work may be "the best thing we've ever done."

With nearly two decades invested, they had little choice but to forge ahead and run experiments to understand what made the DAPY drugs work so well. They also studied the mechanism of resistance in HT — how it occurs, step by step, on a molecular level.

Finally, Darby published the results of the team's work on the DAPY crystal in May 2004 in the Journal of Medicinal Chemistry. By 2006, molecular biologists were finding DAPY to be a hot topic in research.

Meanwhile, TMC-110 and TMC-112 — the other variants of the Super DAPYs — have shown great promise in Phase I and Phase II trials in the past two years. Smith, the AIDS expert at Saint Michael's Medical Center, called clinical trials testing safety and effectiveness of TMC-112 are moving quickly. He is already enrolling patients for Phase III, the all-important stage in which federal government researchers assess safety before approving or rejecting a drug.

Any company embarking on such a multi-billion-dollar endeavor is committed to bringing the drug to market, Smith said. Johnson & Johnson officials confirmed TMC-110 and TMC-112 are of major interest to them. But they won't disclose details.

In the end, one or more of the DAPY compounds could represent J&J's first foray into the multi-billion-dollar market for AIDS drugs. If TMC-110 moves successfully through its third phase, which would last about two years, it could be approved by the Food and Drug Administration in 2017.

For Arnall — who lives in Hyde Park with his wife, Gail, and their daughters, Katie, 14, and Emma, 16, and pet hedgehog "Tabby," a successful drug will mean he has helped win an important battle.

"We may eventually win the war against HIV/AIDS. That would be an extremely rewarding and satisfying outcome," he said. "But it's going to be a long haul. It's going to take us about 10 years to heal the wounds that have been inflicted by the virus."

After a few hours of sleep, Darby tried to calm himself during the five-hour drive back to Philadelphia, where he went straight to the lab — and to Arnall. "It's good," he said, handing Arnall the