Enzyme study suggests anti-AIDS strategy

Biochemists working to understand HIV infection may have found a way to slow or stop replication of the AIDS virus before it really starts.

A research team from the National Cancer Institute (NCI) in Bethesda, Md., and Temple University in Philadelphia has pinpointed the site where a key HIV enzyme latches onto RNA belonging to the infected cell. In the Nov. 12 BIOCHEMISTRY, the group also reports creating small molecules that can settle into this site. These molecules may represent a first step toward developing therapeutic compounds that can prevent the virus from co-opting a cell, says Samuel H. Wilson, who codirected the NCI work with Dolph L. Hatfield.

"[The new results] will provide us with the information necessary to design compounds that can block or interfere with the actions of the enzyme," says Wilson, who is now at the University of Texas Medical Branch at Galveston.

"It might represent a new mechanism of inhibiting the [enzyme known as] reverse transcriptase, and any novel mechanism is important," comments David K. Stammers, a biochemist with Wellcom Research in Beckenham, England. Zidovudine (AZT) also affects reverse transcriptase, but in a different way.

Indeed, according to Robert J. Suhadolnik, who led the Temple University contingent, the group has made specific binding inhibitors for reverse transcriptase. Suhadolnik and colleagues from Germany and France reported promising results from such a compound in the Feb. 26 BIOCHEMISTRY. "[Such inhibitors] could either complement AZT or lower the concentration of AZT needed, [so that one could] get away from the toxic effects," he says. "Our goal right now is to find a method by which this could be delivered into the human cell without damaging the cell."

Reverse transcriptase enables the virus to run the infected cell's genetic machinery in reverse. Usually, the coding of a cell's DNA provides instructions to RNA, which then arranges amino acids into specific proteins. HIV uses reverse transcriptase to get RNA to instead create new DNA coding that includes the virus' genetic information.

The enzyme binds to one part of a specific piece of host transfer RNA, so called because it transports amino acids for protein synthesis. To locate this binding site, the NCI-Temple group first made probes – molecules resembling transfer RNA but also containing radioactive phosphorus – and mixed them with reverse transcriptase, Wilson says. The researchers then chopped the enzyme into small pieces and scanned the pieces. They discovered that a 100-amino-acid-long section near the center of the 560-amino-acid-long enzyme had latched onto the probe.

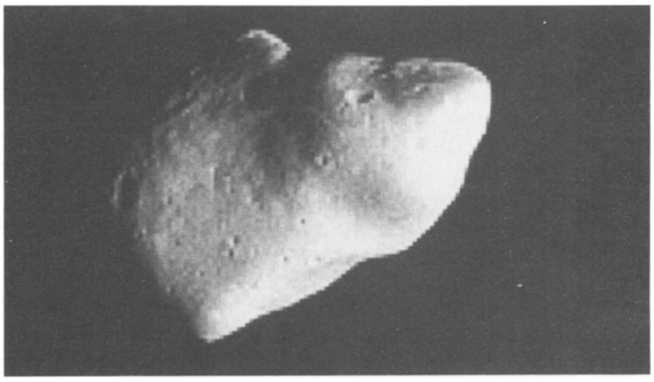
"Now we'll be able to focus on this small domain," Wilson says.

The investigators also studied the formation and stability of the RNA-enzyme complex in solutions with increasing concentrations of salt. From those studies, they concluded that the enzyme's docking site for transfer RNA consists of a groove with hydrophobic (water-repelling) protuberances as well as charged sections along the indentation. "That tells us to think in terms of developing hydrophobic compounds [to block the binding of RNA]," Wilson says.

In separate, unpublished work, molecular biologist Stuart F.J. Le Grice of Case Western Reserve University in Cleveland has identified the binding region as a smaller stretch of amino acids in the same part of the enzyme. Le Grice contends, however, that the form of the enzyme used by the NCI-Temple researchers was not the "biologically relevant" form that is active in the cell, and he expresses concern that some of the materials they used may not have been as pure as they thought.

"I doubt that the work is wrong," Le Grice says. But he thinks the story is more complicated than the new report suggests. *– E. Pennisi*

Galileo snaps first close-up of an asteroid



Galileo's view of the asteroid 951 Gaspra.

Asteroids have intrigued skywatchers since astronomers first detected these rocky bodies nearly 200 years ago. From Earth, they appear only as faint streaks of light, leaving many unanswered questions about their origin, shape and chemistry. Last week, that state of knowledge changed dramatically as the Jupiter-bound Galileo craft radioed back the first close-up images ever taken of an asteroid.

On Oct. 29, Galileo's camera snapped 150 pictures as it passed within 1,600 kilometers of a tiny asteroid called 951 Gaspra. The images – only a few of which actually show the asteroid – were stored in an on-board tape recorder because researchers have been unable to open the craft's main antenna (SN: 8/3/91, p.79).

As recently as mid-October, researchers doubted they could retrieve any Gaspra images before December 1992, when the craft swings around Earth again to gain speed on its way to Jupiter. The problem: Relying on a small antenna that transmits at the painfully slow rate of 80 hours per picture, Galileo would be unable to radio more than a few images during the two weeks following the Gaspra flyby. Scientists decided the transmission effort wouldn't be worth the bother, since they wouldn't even be able to determine which stored images contained the asteroid.

As Galileo closed in on Gaspra, however, an unusually successful navigation enabled engineers to identify four likely asteroid images among a mosaic of 36 photographs. In fact, the two visible-light and two near-infrared pictures relayed to an Australian radio receiver show Gaspra at dead center, scientists reported at a briefing last week at the Jet Propulsion Laboratory in Pasadena, Calif.

These images offer graphic testimony to Gaspra's violent history, says Cornell University astronomer Joseph Veverka. The irregularly shaped asteroid, which he likens to a dented football pitted with craters, measures about 12 by 20 by 11 kilometers, he says. The craters that pepper its surface range in diameter from 2 kilometers to 160 meters – the smallest features visible in the images.

Researchers believe Gaspra is a fragment chipped from a larger object. "We suspect [Gaspra] is a survivor of a series of catastrophic collisions . . . , in which a succession of parent bodies got broken down into smaller and smaller pieces," Veverka says. On the basis of the degree of cratering discerned in the photographs and the estimated frequency of collisions that Gaspra would suffer at its current location – about 411 million kilometers from Earth, near the inner edge of the asteroid belt – astronomers calculate that the asteroid may have taken its present shape a relatively scant 300 million years ago. Before the flyby, Richard P. Binzel and Noriyuki Namiki of the Massachusetts Institute of Technology reported a similar estimate in the June GEOPHYSICAL RESEARCH LETTERS.

Gaspra's brush with violence didn't end there, Veverka notes. A series of apparent ridges or grooves on its surface suggests that a massive asteroid or some other energetic object has since slammed into Gaspra with nearly enough force to smash it into bits, he says. Astronomers have identified similar grooves on Phobos, a Martian moon roughly the same size as Gaspra.

Even Galileo's highest-resolution images and spectroscopic data, which the craft can't transmit until sometime next year, may not reveal Gaspra's interior composition, several astronomers note. The softened features of the asteroid's surface suggest that a layer of dust or soil 3 to 10 meters deep may blanket Gaspra, making it difficult to probe the interior, Veverka says.

Further analysis, he adds, may settle a debate over whether Gaspra and similar asteroids contain material that has remained basically unchanged since the solar system formed. Some scientists contend that blasts of heat may have altered the composition of these asteroids so that iron and other dense materials concentrate in the core while lower-density minerals lie closer to their surfaces.

A first look at a composite of the four Galileo images reveals subtle color differences that suggest at least some variation in Gaspra's chemical composition. And Robert W. Carlson of the Jet Propulsion Laboratory, who leads studies with Galileo's near-infrared mapping spectrometer, says the low-resolution data he received hint at compositional differences between the asteroid's northern and southern hemispheres. Finding fresh craters that expose subsurface material might offer the best hope of studying the interior, Veverka adds.

If Galileo had flown past a larger asteroid – as intended before the 1986 Challenger disaster delayed the craft's launch – it could have measured the object's gravitational tug, enabling researchers to infer its chemical makeup, Veverka says. Such studies must now await future space missions that will rendezvous with an asteroid rather than whiz past it, says William K. Hartmann of the Planetary Science Institute in Tucson, Ariz.

– R. Cowen

Kawasaki aneurysms: A lingering threat

Some children with Kawasaki disease develop a large and potentially lethal aneurysm, a ballooning of a coronary artery. A Canadian research team now reports that this weakening in the vessel wall can persist, putting the child at continued risk of a heart attack.

Kawasaki disease causes fever, sore throat, and inflammation of various tissues. Scientists don't know what triggers this generally rare childhood illness, which disproportionately strikes youngsters of Asian ancestry. The acute symptoms usually subside after two or three weeks, but cardiac complications can linger.

Last week, at the American Heart Association's 64th scientific sessions in Anaheim, Calif., cardiologist Teiji Akagi of the Hospital for Sick Children in Toronto presented data on 537 youngsters with Kawasaki disease, the largest series of North American Kawasaki patients ever reviewed.

Seventy of these children had developed coronary artery aneurysms, which were identified by a variety of imaging methods. In reviewing the patients' medical records, Akagi and his colleagues discovered nine small aneurysms, 40 moderate ones and 21 large ones, measuring about one-third of an inch wide.

For most of these children, the coronary aneurysm eventually vanished. Two years after diagnosis, all nine of the small aneurysms had disappeared; five years after diagnosis, 80 percent of the moderate aneurysms had regressed. But the five-year picture for the large aneurysms remained disappointing: All 21 persisted, and nine children with this condition suffered a heart attack. Five of the nine had a heart attack within one year of their Kawasaki diagnosis, Akagi says.

The turbulent blood flow in a large aneurysm may lead to a blood clot, which can block the coronary artery, causing a heart attack, he explains.

Some of the children received anti-inflammatory medication during the early stage of the illness. Akagi's group found that aneurysms were most likely to subside in children treated with gamma globulin, a protein produced by the body to fight inflammation. Two years after diagnosis, 80 percent of the 16 gamma globulin patients showed no sign of aneurysm. Five years after diagnosis, only half of the 46 kids treated with aspirin, another anti-inflammatory drug, showed aneurysm regression.

The cardiac risk faced by children with large aneurysms suggests a need for more aggressive treatment, he adds. These youngsters may benefit from bypass surgery, in which surgeons replace the weakened coronary artery with a healthy vessel, Akagi says.

Even patients who show no sign of persistent aneurysm must be monitored closely for coronary artery damage, warns Hirohisa Kato, who studies Kawasaki disease at Kurume (Japan) University. When the aneurysm heals, the body adds scar tissue to the artery wall – a process some researchers fear may heighten the risk of heart attack, Kato says.

– K.A. Fackelmann

Illuminating tiniest microlaser on a chip

The notion of a laser beam shooting out of a disk small enough to fit easily inside a red blood cell seems more the stuff of science fiction than the laboratory. But advances in technology have put just such a device well within reach.

Investigators at AT&T Bell Laboratories in Murray Hill, N.J., have now fabricated and successfully operated disk-shaped semiconductor lasers measuring 2 to 10 microns in diameter. Commercial semiconductor lasers, such as those used in compact-disk players, typically measure 250 microns across.


Scanning electron micrograph of disk-shaped semiconductor microlaser.

AT&T Bell Labs

In terms of volume, the new devices are the smallest semiconductor lasers yet produced, says Sam McCall, who designed the disk lasers. McCall and his collaborators described these devices earlier this month at a meeting of the Optical Society of America, held in San Jose, Calif. Further details will appear in APPLIED PHYSICS LETTERS in January.

Resembling a miniature thumbtack, the novel microlaser consists of a layered disk only 400 or so atoms thick mounted on a slender pedestal. The disk – a thin layer of indium gallium arsenide sandwiched between layers of indium gallium arsenide phosphide – absorbs light from a helium-neon laser to generate coherent infrared radiation at wavelengths ranging from 1.3 to 1.5 microns.

"We've been working at low temperatures where we cool the substrate with liquid nitrogen," McCall says. "But we've also warmed them up, and they've worked at a few degrees above freezing."

These microdisk lasers operate in what researchers call a "whispering gallery" mode, named for the way words whispered at one location near the interior wall of a circular, domed chamber can be readily overheard anywhere else along the wall. Like these echoing whispers, photons travel along a disk's edge for long periods with little loss.

"In the perfect geometry, the beam would come out along the edge and would sort of spray out in the plane of the disk," McCall says. "We can change the ideal geometry a little bit to get the beam to go where we want it to. For example, by putting grooves at just the right places on the top surface, we can get the beam to come out vertically."

– I. Peterson