Monkey virus may lead to anti-HIV insights

Developing new drugs to combat HIV, the virus that causes AIDS, can cost hundreds of millions of dollars and require a decade or more of research and development.

To leapfrog some of this expenditure and investment of time, many researchers are using powerful computer programs and structural information about HIV's key proteins to design highly specific anti-HIV compounds.

Now, researchers have taken another important step toward bringing this approach to bear against HIV. At a meeting of researchers this week in Washington, D.C., two teams of investigators announced that they have elucidated the structure of a key protein manufactured by the simian immunodeficiency virus (SIV), which causes an AIDS-like illness in monkeys. The protein, SIV protease, enables the virus to make copies of itself, which then infect other cells.

At the meeting, sponsored by the National Institute of General Medical Science, Robert M. Stroud of the University of California, San Francisco (UCSF), and Sherin Abdel-Meguid of SmithKline Beecham Pharmaceuticals in King of Prussia, Pa., exhibited three-dimensional, computer-generated portraits of SIV protease showing the exact locations of its constituent atoms.

Each scientist represented a large group of collaborators that independently solved the structure.

In HIV infection in humans, a nearly identical enzyme — HIV protease — enables infected cells to assemble new virus particles. Scientists unlocked the structure of HIV protease in 1987 and have since discovered scores of molecules that inhibit the enzyme's function in laboratory-grown cells.

But no one yet has demonstrated that disarming HIV protease can halt the proliferation of virus that leads inexorably to AIDS. Structural information on SIV might help resolve whether disabling the HIV replication protein is a viable therapeutic approach.

"Knowing the structure of SIV gives us a way to develop drugs faster that can then be tested in monkeys," says Charles S. Craik, a UCSF biochemist who has worked extensively with HIV protease. And because SIV and HIV are so similar, identifying a nontoxic drug that stops SIV from reproducing in monkeys could establish the feasibility of using protease-blocking drugs to combat HIV infection in humans, he adds.

By incorporating this structural information about SIV protease into computer programs, explains UCSF's Stroud, researchers can match various kinds of molecules against the shape of the active site on the SIV protease. The computer can tell which molecules are likely to bind strongly to the enzyme, gumming up viral replication. Animal studies could then prove which of the compounds prevent HIV from proliferating.

Evidence suggests that HIV-II, the virus strain that causes most cases of AIDS in Africa, evolved in primates and then made the jump to human hosts, Stroud points out.

"The disease used animals to develop this virus and give it to humans," Stroud says. "Now, we're turning it around. Using that misfortune of nature, we're going to use those same animals to help get a cure."

— D. Pendick

Mystery flu hits Southwest

A virus carried by field mice and other rodents may prove responsible for the deadly flu-like illness that has erupted mostly in Arizona and New Mexico, according to public health officials.

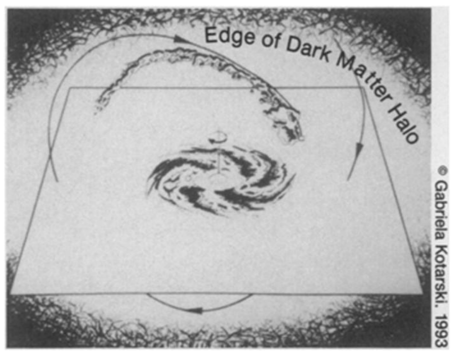
The ailment, which is known as acute respiratory distress syndrome, has killed 11 people and made nine others severely ill. The symptoms appear remarkably like those of the flu. Victims spike a fever, start coughing, and develop muscle aches and inflamed, reddened eyes. Most, although not all, of the victims lived on or near the Navajo reservation located in the Four Corners area of Arizona, New Mexico, Utah, and Colorado.

The illness primarily has hit apparently healthy people in their 20s and 30s, says epidemiologist Stuart Castle of the New Mexico State Health Department in Santa Fe. Patients have trouble breathing, and some have died of suffocation within hours of getting ill, he adds.

U.S. Department of Health and Human Services Secretary Donna E. Shalala has sent federal investigators to help state and local epidemiologists nab the culprit in this deadly cluster of cases. Preliminary evidence suggests that the illness is caused by airborne spread of dried urine or fecal matter from rodents infected with some type of virus, possibly a *Hantavirus*. Health officials have urged people living on or near the reservation to avoid rodent nests.

The disease does not appear to be transmitted by contact with infected people, Castle adds. No health workers have become infected. Furthermore, the investigators turned up only one instance in which several members of the same family got sick. □

Nearby galaxy sheds light on dark matter



Large Magellanic Cloud, trailed by a gas stream, orbits the Milky Way's poles.

Astronomers have measured for the first time the movement across the sky of a galaxy other than our own. Using the new data, which characterize the orbit of the Milky Way's nearest galactic neighbor, California researchers have made what they consider the most accurate estimate to date of the amount and shape of dark matter in our galaxy. Dark matter — hypothetical material thought to make up 90 to 95 percent of the mass in the universe — doesn't emit light, yet it exerts a gravitational tug.

According to the new calculations, the mass of the Milky Way contains five to 10 times as much dark matter as visible stars. Moreover, the team infers that this unseen material lies in a giant halo at least six times larger than the visible disk of the galaxy. A halo this big would not only dwarf the visible Milky Way, it would extend far beyond the Milky Way's nearest neighbor and satellite galaxy, the Large Magellanic Cloud (LMC).

While astronomers had already derived similar estimates for the size and mass of dark matter in the Milky Way, "this measurement is much more reliable than all previous measurements," says Douglas N.C. Lin of the University of California, Santa Cruz. He and his Santa Cruz colleagues, Burton F. Jones and Arnold R. Klemola, reported the work this week at a meeting of the American Astronomical Society in Berkeley, Calif.

Since dark matter can't be seen, astronomers use its gravitational influence on visible objects as an indirect means of detecting it. To search for dark matter in the Milky Way, therefore, Lin and his coworkers decided to study the motion of the LMC, bound to our galaxy in an orbit that takes it above and below the Milky Way's disk. Many astronomers had previously measured the LMC's radial velocity, or motion along the line of sight to the Milky Way. But Lin's team sought its transverse velocity — its motion across the sky — which no one had ever measured for any galaxy but our own.

Such motion is extremely difficult to

detect because at a great distance from Earth, even a speedy galaxy appears to cross the sky at a snail's pace. In their study, the astronomers compared photographs, taken 15 years apart at the Cerro Tololo Inter-American Observatory in La Serena, Chile, of a star-packed region at the LMC's northeastern edge.

Using an electronic scanner, they could discern the slight shifts in position, relative to a fixed background of distant galaxies, of 250 LMC stars during those 15 years. Based on this analysis, the researchers report that the satellite galaxy moves across the sky at a brisk 220 kilometers per second. To keep the LMC gravitationally bound to the Milky Way despite this transverse velocity, the team calculates, our galaxy must contain at least as much mass as 600 billion suns – about five times as much mass as the visible galaxy.

Deriving the shape of the proposed halo of dark matter surrounding the Milky Way requires further knowledge of the LMC's orbit. Lin's team reconstructed the galaxy's likely path by examining a huge comet-like stream of hydrogen gas that astronomers believe was torn from the LMC by the Milky Way's gravity. Lin suggests that the stream trails the LMC and marks the galaxy's path at the time of its previous revolution around the Milky Way, about 2.5 billion years ago. "The stream provides a tracer, just as a jet [contrail] shows where a jet used to be," he notes.

Lin notes that segments of the hydrogen stream have a large radial velocity. Since this velocity had to have originated from the stream's parent galaxy, the LMC, this indicates that the galaxy takes a highly elliptical, rather than circular, path around the Milky Way.

A distribution of dark matter that extends far beyond the LMC best explains the galaxy's elliptical path. The LMC lies about 170,000 light-years from the center of the Milky Way. In comparison, the Milky Way's halo of dark matter may have a minimum radius of 300,000 light-years, Lin says, and could extend as far as 800,000 light-years.

Scott D. Tremaine of the University of Toronto says the study is important but that its implications for measuring dark matter are far from clear-cut. "Most people will probably be a little cautious in applying this; it's easy to underestimate [errors] in determining dark matter. It's not like [measuring] the orbit of a planet, which we can study as it goes around many times. Here you have just one snapshot."

Lin says the study indicates that the LMC and perhaps other satellite galaxies of the Milky Way are about 1 to 2 billion years younger than the oldest stars in our galaxy. Bit by bit, the Milky Way's gravity is tearing apart the LMC and will gobble it up entirely in about 20 billion years, he adds. *– R. Cowen*

Lipoprotein link to heart disease revealed

High concentrations of the cholesterol carrier lipoprotein(a) in the blood are a known risk factor for heart disease. Indeed, cardiologists estimate that Lp(a) – a close cousin of low-density lipoprotein, itself a heart threat – may be responsible for up to 25 percent of heart attacks that strike relatively early in life. The trouble is, scientists don't understand the mechanism underlying this molecule's role in the drama of heart disease.

Now, an international scientific team suggests that elevated concentrations of Lp(a) in the bloodstream may cause smooth muscle cells within the artery wall to proliferate. As a cholesterol carrier, Lp(a) also deposits cholesterol and other fatty debris on the vessel's inner wall. The thickening of the blood vessel that results is a hallmark of atherosclerosis.

Biochemist David J. Grainger of the University of Cambridge in England and molecular biologist Richard M. Lawn at the Stanford University School of Medicine grew smooth muscle cells taken from healthy human arteries in laboratory dishes. When the team exposed those cultured cells to Lp(a), the cells began to divide more rapidly than usual. The researchers report their findings in the June 11 SCIENCE.

The new study suggests that Lp(a) interferes with a natural growth-restraining system that operates in human arteries. The group showed that Lp(a) inhibited the activation of an antiproliferative substance called transforming growth factor-β. Without enough of this activated factor, smooth muscle cells continue their division unchecked, an insidious process that could lead to clogged arteries, Lawn says.

People with high concentrations of Lp(a) in their blood may suffer the double whammy of too much arterial muscle cell proliferation plus large deposits of cholesterol inside their artery walls. Such a mechanism may explain the elevated risk of heart attack for such people, Lawn adds.

However, both Lawn and Grainger warn that their study only looked at this cholesterol carrier's impact on smooth muscle cells grown in laboratory dishes. The team has yet to determine whether such proliferation takes place in humans.

If it does, cardiologists may one day be able to stave off atherosclerosis in people who produce too much Lp(a), says Grainger. One approach would be to use drugs that block the excess proliferation of smooth arterial muscle cells, he speculates. *– K.A. Fackelmann*

Rippling the surface of an electron sea

Eigler/IBM Research

If it weren't for the unnaturally luminous colors, you might think you were looking at ripples centered around a pair of barely submerged rocks in a pool of water. But this is a new kind of waterscape – one that originates in the realm of atoms, electrons, and quantum physics.

Metal atoms readily lose one or more electrons, and these electrons roam freely within the metal crystal to form a pervasive "electron sea." At the surface of a metal crystal, however, the loose electrons usually are confined to a thin layer. Free to move only in two dimensions, these particles also behave like waves.

Donald M. Eigler and his co-workers at the IBM Almaden Research Center in San Jose, Calif., used a scanning tunneling microscope at 4 kelvins to detect tiny variations in the concentration of electrons across the surface of a copper crystal. They observed distinctive patterns of electron density corresponding to standing waves, in which the locations of the peaks and troughs of the electron waves remain fixed.

In the image shown, a pair of imperfections on the surface of a copper crystal deflects electrons in such a way that the incoming and scattered electron waves overlap to create concentric ripples at each defect. The electron layer responsible for generating this standing-wave pattern is just 0.02 angstrom deep.

Eigler and his colleagues describe their technique for imaging electron waves in the June 10 NATURE. Researchers at the IBM Thomas J. Watson Research Center in Yorktown Heights, N.Y., have recently obtained similar images of standing electron waves on a gold surface at room temperature.