"reservoirs"—cells that harbor the virus where antivirals cannot get at it. Now, new studies by a team at the National Institute of Allergy and Infectious Diseases (NIAID) in Bethesda, Maryland, indicate that a natural immune system regulatory molecule called interleukin-2 (IL-2), if given to patients along with combination therapy, can flush HIV from at least one reservoir out into the open. The finding raises hope that it may one day be possible to rid people of HIV entirely. "It's a courageous approach and the results are very intriguing," says immunologist Robert Siliciano at the Johns Hopkins Medical Center in Baltimore.

> **"The final proof ... will be the discontinuation of combination drug therapy and long-term follow-up."**
>
> **—Anthony Fauci**

One known HIV reservoir is in T cells—immune cells that are HIV's primary target. When infected T cells are active, any HIV they harbor is also active and begins to replicate, making it open to attack by combination therapy. But T cells also have a quiescent state, during which their latent cargo of HIV is dormant and invisible to antiviral drugs for years at a time. Because IL-2 has a potent ability to activate a number of immune cells, including T cells, NIAID director Anthony Fauci and his colleagues decided to give patients IL-2 to see if it would wake up their resting T cells and the HIV they contain and make it vulnerable to attack.

Fauci reported at the International Congress of Immunology here earlier this month that the NIAID team studied a group of 26 HIV-infected patients: 12 received a combination of at least three antiretroviral drugs for 1 to 3 years and 14 received similar combination therapy plus IL-2, given repeatedly but with a minimum of 8 weeks between treatments. After treatment, all 26 had undetectable levels of HIV in their blood. Also, Fauci's team could not detect any HIV capable of replicating in resting T cells cultured from the peripheral blood of six of the 14 subjects who had received IL-2. Even when they cultured a much larger sample of resting T cells—up to 330 million cells—from each of those six, they still could find no live virus in three of them. In contrast, the team found live HIV in the T cells from all of the 12 patients receiving combination therapy alone.

Fauci's team went on to perform a lymph node biopsy on one of the three patients who showed no sign of virus in their T cells. Again, they could find no HIV capable of replication in the lymph node tissue, Fauci says. Although the new results raise hopes that eradication of HIV may be a possibility, "we cannot yet conclude we've got eradication of the virus," Fauci says.

Joep Lange, a clinical researcher at the University of Amsterdam who is also carrying out experiments to purge HIV-infected patients of virus using a cocktail of five anti-HIV drugs plus IL-2 and an antibody against T cells, says Fauci's results are "interesting but not yet definitive." HIV may still be lurking in other known reservoirs, such as the brain, testes, gut, and within other immune cells such as macrophages. "The final proof of the feasibility of effectively controlling HIV in latently infected cells will be the discontinuation of combination drug therapy and long-term follow-up," Fauci says, adding that such trials are planned to begin early next year.

**–NIGEL WILLIAMS**

CELL BIOLOGY

## A Possible New Partner for Telomerase

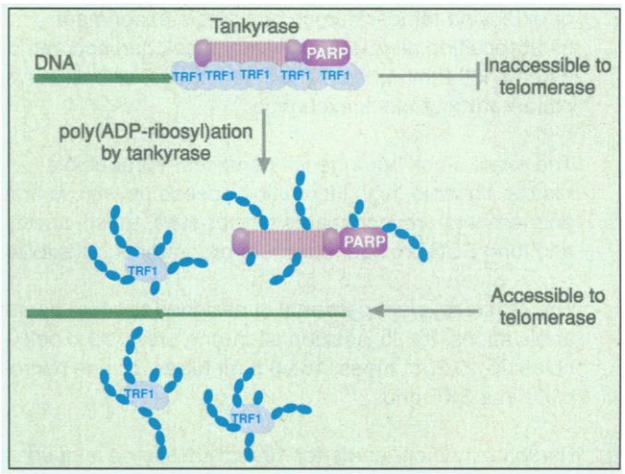
Cell biologists have discovered what may be a key switch in the control of cellular aging. In most tissues, the telomeres, repetitive DNA sequences that cap the ends of chromosomes, shorten each time the cell divides, until the chromosomes are so frayed that the cell becomes senescent. But in a few normal cells, including those that make eggs and sperm, and in cancer cells, an enzyme called telomerase rebuilds the telomeres after each division, keeping the cell immortal. Now researchers have found a second enzyme that may enable telomerase to do its work.

On page 1484, Susan Smith, Titia de Lange, and their colleagues at The Rockefeller University in New York City describe the discovery in human cells of a protein they call tankyrase. The Rockefeller team's evidence suggests that tankyrase controls whether telomerase can do its job by removing another protein that otherwise blocks telomerase's access to the chromosome ends.

If the new enzyme does play this role, the way might be open to developing compounds that would exploit tankyrase to control cell life-span. Compounds that activate it could turn on telomerase activity in cells used for gene- or cell-based therapies, extending their lives. Conversely, new anticancer agents might work by inhibiting tankyrase, thereby blocking telomerase activity and making cancer cells mortal again. "Who knows, 5 years from now, tankyrase inhibitors may be as important as telomerase inhibitors," notes Tomas Lindahl, a biochemist with the Imperial Cancer Research Fund in London. "[This discovery] could open up a whole new field."

The discovery of tankyrase by de Lange and her colleagues is an outgrowth of work in which these researchers have been looking for proteins that bind specifically to the telomeres and might therefore be important to telomere maintenance and function. They came upon the first telomere-specific DNA binding protein (TRF1) in the early 1990s. Since then, de Lange and her colleagues have shown that TRF1 somehow plays a role in regulating the overall length of the telomere, presumably by interfering with telomerase activity. To find out more about how TRF1 might contribute to the regulation of telomere length, Smith decided to look for other human proteins that link with TRF1. That screen has now turned up tankyrase.

The protein's structure provides some clues to how it may work. It has 24 so-called ankyrin repeats, which in other proteins are involved in protein-to-protein interactions. And another section of tankyrase looks like the catalytically active region of an unusual enzyme called PARP, for poly(adenosine diphosphate–ribose) polymerase. PARP plays a role in DNA repair, apparently by modifying itself and other proteins in the molecular complex that gen-




**Forever young.** By altering TRF1, tankyrase may enable telomerase to replace lost DNA on the chromosome ends.

SOURCE: SMITH *ET AL.*

erates new DNA.

PARP acts by removing ADP-ribose from a small molecule called $NAD^+$ and then adding it to the target proteins. To see whether tankyrase displays a similar catalytic behavior, Smith and de Lange did test tube studies in which they mixed the enzyme with $NAD^+$ and TRF1. They found that tankyrase adds ADP-ribose both to itself and to TRF1. Typically, TRF1 exists bound to DNA, but when tankyrase is present, "TRF1 comes off the DNA," says Smith.

De Lange cautions that they still need to demonstrate that what they see in their test tube studies occurs in living cells. But she and her colleagues suspect that TRF1 normally sits on the telomere, thereby inhibiting telomerase activity. During, or perhaps after, DNA replication, tankyrase modifies TRF1 such that it leaves the telomere, enabling telomerase to replace DNA lost during replication in blood cells, germ cells, or tumors. "It looks like [tankyrase] could be an important component in a regulatory or signaling pathway," says Tom Cech, a biochemist at the University of Colorado, Boulder.

Tankyrase is the second protein linked to DNA repair that has now been found to be associated with the telomeres; the first was a protein called Ku that binds to broken DNA. That suggests that DNA repair and telomere synthesis may have some common components. But until researchers pin down tankyrase's exact function, it's "too early to tell whether [the enzyme] is a good target for drug discovery," says telomere expert Calvin Harley of Geron Corp. in Menlo Park, California. Nevertheless, he says his company is thinking about procuring rights to pursue this possibility—Rockefeller University has filed a patent application on tankyrase—in hope of finding ways to extend the lifespan of cells. **–ELIZABETH PENNISI**

NEUROSCIENCE

## fMRI Provides New View of Monkey Brains

**LOS ANGELES**—Neuroscientists who want to map brain activity in monkeys have many options that aren't available with human subjects. But a favorite method for studying human brains, functional magnetic resonance imaging (fMRI), which delivers pictures of brain activity by measuring increases in local blood flow, has not been well suited to monkey studies until now. Aided by a specially designed magnet, Nikos Logothetis of the Max Planck Institute for Biological Cybernetics in Tübingen, Germany, has made high-resolution fMR images of the brains of both anesthetized and awake monkeys.

Those who saw his presentation here last week at the 28th annual meeting of the Society for Neuroscience say the work is a marked advance over the only other published fMR images of monkey brains, reported last summer by two teams (*Science*, 10 July, p. 149). Some researchers worried that the several-millimeter resolution of those images was not good enough to see some of the structures in monkey brains, which are much smaller than those of humans. And because those experiments, like all other fMRI studies done on monkeys until now, used a horizontal magnet designed for supine human patients, the animals had to crouch in an awkward position that promised to make it hard to perform the choice-based tasks on which many brain activation experiments are based. Also the monkeys were awake because previous work had failed to obtain fMR images on the anesthetized monkeys used for many other types of neurophysiological studies.

**Seeing is believing.** A monkey's visual cortex responds to a moving image.

CREDIT: N. LOGOTHETIS

Logothetis, however, produced images from anesthetized animals with a resolution of less than a millimeter, close to the theoretical limits of the technique, which detects magnetic signals from oxygenated blood, says fMRI expert Robert Turner of University College London. Indeed, he calls the work "a technical tour de force." In the specialized setup, Logothetis also got crisp images from awake monkeys sitting in the position to which they were accustomed and performing choice tasks. The results will convince many researchers of the usefulness of monkey fMRI, says neuroscientist Leslie Ungerleider of the National Institute of Mental Health. "I thought it would be 10 years before imaging in the monkey reached this level of sophistication," she adds.

Such images have been eagerly awaited because neuroscientists want to compare fMR images of monkey brain activity to data gathered by sticking electrodes directly into monkey's brains and use that information to infer more about the neuronal activity that underlies human fMR brain images. They also would like to use fMRI to identify new areas of activity in monkey's brains that they can then study with electrodes. And being able to study anesthetized animals is a plus, because sensory stimulation of unconscious animals is a widely used method for mapping areas of brain activity.

To develop his system, Logothetis turned to Bruker Medical Instruments in Ettlingen, Germany, to design a vertical, monkey-sized magnet with a field three times stronger than those of the magnets commonly used on humans, a change that improves spatial resolution. He also refused to accept reports that fMRI wouldn't work on anesthetized animals. Researchers had blamed earlier failures on effects the anesthesia might be having on blood flow response to brain activity, but Logothetis felt that shouldn't be the case if the monkey were monitored as carefully as a human patient.

Consequently, he hired a professional anesthesiologist who anesthetized the animals while keeping parameters such as pulse, blood gases, blood pressure, and blood volume "absolutely within the normal range." He then tested his method by recording fMR images of the anesthetized monkeys viewing visual images, such as moving patterns, and got high-resolution images of activation in the monkeys' visual cortex.

Logothetis notes that his team's results remain just a demonstration that the technique works and have not yet answered any research questions about brain function. In that respect, monkey fMRI has some catching up to do. Japanese researchers have for several years been studying brain activation in monkeys with positron emission tomography (PET), which uses radioactive tracers to detect blood flow changes. For example, using a dedicated monkey PET scanner at Hamamatsu Photonics in Hamakita, Japan, Hirotaka Onoe's team at the Tokyo Metropolitan Institute for Neuroscience last year discovered a new site of color processing in the monkey visual system. PET in monkeys has better resolution than it does in humans, says Ichiro Fujita of Osaka University, who has been doing monkey PET studies at Hamamatsu. That's because monkeys can be scanned repeatedly, while the risks of the radioactive exposure limit human subjects to a few scans. This forces researchers to average the data from several different subjects, reducing the image quality.

But even monkey PET cannot match the temporal and spatial resolution of fMRI, says Akichika Mikami of Kyoto University, who also does PET studies on monkeys. He predicts PET will be eclipsed by fMRI, except in specialized niches such as using radioactive neurochemicals to visualize their receptors in the brain, which is not possible with fMRI. Turner agrees and expects a rapid research boom in monkey fMRI: "I've been taking bets on how many presentations there will be at next year's meeting," he says. "I'm going to put money on there being more than fifty."

**–MARCIA BARINAGA**