ments. And many of the details of the latest package, including amounts for science-related projects, are yet to be worked out. The Science and Technology Agency (STA) has requested $2.3 billion.

One new project high on the list is a $2.9 billion International University Village, a joint effort of STA and the ministries of Education (Monbusho) and International Trade and Industry to encourage more international exchange students and scholars to spend time in Japan. The collection of midrise buildings on a Tokyo site will include housing, a library, and other amenities for international exchange students and visiting researchers. It will also feature laboratories for venture businesses and for such research schemes as STA's ERATO program, under which research teams are assembled for 5 years. The three agencies are hoping for as much as half the total construction cost of the project, to be completed in early 2001.

Both Monbusho and STA have also requested significant amounts from the stimulus package to upgrade lab equipment and refurbish laboratories, as well as to accelerate big science projects already under way. The Institute of Physical and Chemical Research (RIKEN), an STA affiliate just outside Tokyo, could get as much as $52.5 million for its Radioactive Isotope Beam Factory, a $200 million facility with a superconducting synchrotron that would produce the world's most intense beams of unstable nuclei.

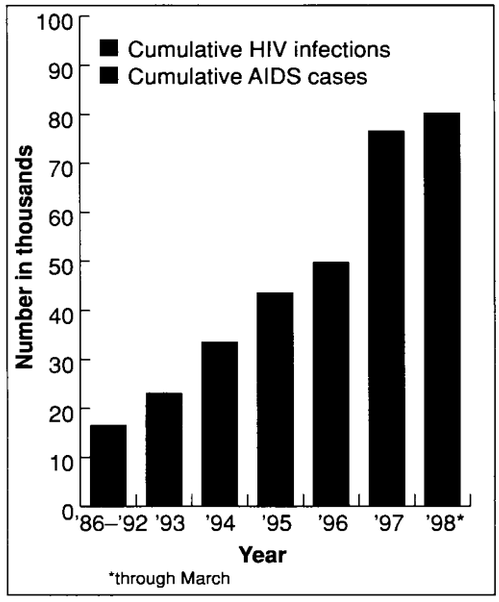
Yasushige Yano, the RIKEN physicist heading the project, says that the extra funding would restore the project's completion date of 2003 after cuts in this year's regular budget pushed that timetable back by 2 years. "It means we can meet our original completion plans," Yano says. Ocean research is another big winner. STA's wish list includes a proposed $113 million for the deployment of instrumented buoys and the addition of various instruments to Japan's fleet of research vessels to facilitate studies of global climate change and to monitor seafloor seismic activity.

But the largess doesn't stretch to big projects still in the planning stages. For example, the Japan Hadron Project at the High-Energy Accelerator Research Organization (KEK), the former National Laboratory for High-Energy Physics, is not in line for any of the stimulus spending because it requires further development and testing before it can move into the construction phase. "It's extremely disappointing," says KEK Director-General Hirotaka Sugawara. But KEK officials aren't standing still: They are looking for help in the regular 1999 budget, which will be finalized in the next 6 weeks.

–DENNIS NORMILE

India Prepares to Join U.S., World Teams

NEW DELHI—India is drawing up plans to participate in global efforts to develop and test vaccines against AIDS. The decision, made at the end of a meeting here earlier this month of AIDS scientists and government officials from India and the United States, represents a major step for a country traditionally very sensitive about its status in international medical research projects. But Indian officials say it will likely take a few years to decide how to marshal the country's R&D resources and link them with ongoing activities around the world.



Crisis ahead. Number of Indian cases of HIV infection and AIDS is rising rapidly.

"A good collaboration will really cut [development] time," says Seth Berkley, president of the New York–based International Aids Vaccine Initiative. India, he says, is one of only a handful of countries in the developing world that has both the scientific base and the technological capability to produce vaccines commercially. In addition, Berkley says, India is facing "a real emergency" based on a rising number of reported cases of HIV and AIDS (see graph).

A low-cost vaccine is seen as the only realistic way to combat AIDS in countries that cannot afford the expensive multidrug treatments now available in the industrial world. "Vaccines are absolutely essential to interrupt this epidemic in developing countries," says Anthony Fauci, the head of the U.S. delegation and director of the National Institute of Allergy and Infectious Diseases. "India should definitely take a leadership role in this area," he adds, estimating that it might be 3 to 5 years until a vaccine suitable for India is ready to be tested.

Toward that goal, Fauci and other National Institutes of Health (NIH) officials invited Indian scientists to participate in two upcoming grants competitions for vaccine clinical trials, as well as to take advantage of existing U.S.–Indian agreements for collaborative research. Indian officials pledged their "deep commitment" to such joint efforts, adding that they hope NIH will provide much of the funding once they draw up a detailed plan. "We can take advantage by learning from the failures of others," says J. V. R. Prasad Rao, project director for the National AIDS Control Organization (NACO) of India.

The most advanced trials of a candidate vaccine, performed by Vaxgen of San Francisco, began at 15 U.S. sites this summer. Two other candidate vaccines also produced in the developed world are being tested for safety in Thailand and Uganda. Indian officials say their participation in future vaccine development is predicated upon getting in on the ground floor. "Unless India is made a full and equal partner in the development of a vaccine, and unless the candidate vaccine has been developed collaboratively, India will never allow the testing of a vaccine," says Manju Sharma, secretary of India's department of biotechnology. Officials also want to ensure that the vaccine protects against strains of the virus common in India rather than in Europe or North America.

U.S. and Indian scientists are already collaborating on a $750,000 project involving India's National AIDS Research Institute in Pune and Johns Hopkins University in Baltimore. Researchers are collecting baseline data that could be used as part of a larger vaccine trial at Pune and other sites in India. "We are willing and enthusiastic about accepting Indian collaborations in vaccine development [in the hope that] it might lead to a quicker solution," says Fauci. Its absence, he adds, "will surely slow down" the global effort to control AIDS.

–PALLAVA BAGLA

Pallava Bagla is a correspondent in New Delhi.

Can IL-2 Smoke Out HIV Reservoirs?

NEW DELHI—Potent cocktails of anti-HIV drugs have been enormously successful in keeping AIDS at bay in HIV-infected people. But although these combination therapies can knock the virus back to undetectable levels in patients' blood, HIV continues to lurk in

CREDIT: NACO, INDIA

"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

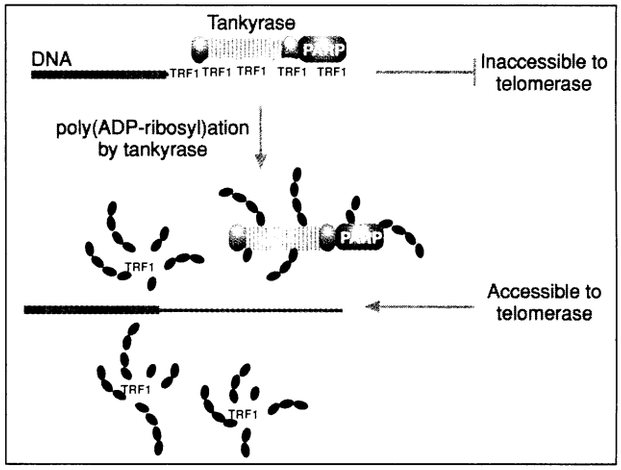
Cell biologists have discovered what may be a key switch in the control of cellular aging. In most tissues, the telomeres, repetitive DNA sequences that cap the ends of chromosomes, shorten each time the cell divides, until the chromosomes are so frayed that the cell becomes senescent. But in a few normal 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.*