NEWS

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Light shed on battle against HIV

TORONTO

Why does the human body fail to defend itself from the virus that causes AIDS? The answer, researchers are finding, could be that HIV triggers a natural mechanism that impairs the main cells responsible for fighting the virus.

As a result, these cells, called killer T cells, eventually become exhausted and give up their fight. Now, research indicates that giving these tired cells a boost may be simple, and clinical trials using this strategy could start as early as next year.

"This is really a very important phenomenon, and it explains a lot of things," says Rafick-Pierre Sékaly of the University of Montreal in Quebec, senior author of one of two papers published on 20 August. "We would like to be able to push this into patients and show whether this has an effect."

Clue in mice

The story began last December, when Rafi Ahmed of Emory University in Atlanta, Georgia, reported work on mice infected with a chronic viral infection[1]. His group studied the T cells these mice made to target the long-term infection. The researchers found that the cells expressed much higher levels of a protein called PD-1 than mice infected with a short-term infection. This was intriguing, because scientists already knew that PD-1 can act as a brake on T cells that express it, forcing them to shut down their fight against infections.

Even more tantalizing was Ahmed's finding that he could release the PD-1 brake by injecting the mice with a molecule to block PD-1's interaction with another protein, called PD-1 ligand. That protein triggers the PD-1 molecule to shut off T cells. Stopping the deadly interaction between PD-1 and PD-1 ligand seems to release the restraint on T cells, Ahmed reported.

Researchers then raced to examine PD-1 in people. Teams included one led by Sékaly, now reporting results in *Nature Medicine*[2], and another led by Bruce Walker of Massachusetts General Hospital in Boston, who reports results in *Nature*[3].

Both teams found that, in human patients, the T cells that should be fighting off HIV express very high levels of PD-1. Both papers also show that levels of PD-1 expression correlate with the amount of HIV a patient has in his or her body, indicating that the protein has something to do with how well the patient controls the virus. And both papers report that interfering with the partnership between PD-1 and PD-1 ligand can rejuvenate the cells' fight against the virus.

"Exhaustion has been a proposed mechanism of T-cell failure in HIV disease for a long time," says Michael Lederman, an immunologist at Case Western Reserve University in Cleveland, Ohio, who was not involved in the work. "What seems nice about this piece is that it explains some observations that have been made for some time, and it may apply to other infections. And there's an ability to intervene."

> "This work is elegant, carefully done and solid — but we've got to be cautious."

Future trials

At least one company is already looking at ways to use the finding. Medarex, based in Princeton, New Jersey, is testing a protein that interferes with the PD-1/PD-1 ligand partnership. The company is interested in it as an anticancer agent at the moment, but is also talking to HIV researchers about potential clinical trials.

The finding could also help illuminate other chronic viral diseases, such as hepatitis C. And it could help scientists unravel another interesting story: how certain people infected with HIV can control their infections naturally, without drugs, and almost never get sick with AIDS.

On 16 August, Walker and Sékaly announced that they are beginning the first large-scale study on the genetic make-up of these people, known as 'élite controllers'. Sékaly adds that

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A vigil for past victims ends this year's international AIDS conference in Canada.

PD-1 could shed light on the subject. So far, he has studied 12 élite controllers, and all have normal levels of PD-1 expression — much lower than those found in most HIV patients.

Still, other scientists caution that the PD-1 story cannot explain everything. PD-1 is found on many cells, not just those that target HIV. So interfering with it may have unpredictable consequences, says Rick Koup, an immunologist at the US National Institute of Allergy and Infectious Diseases (NIAID).

Koup is publishing a paper on the PD-1/PD-1 ligand interaction in HIV patients on 5 September, in the *Journal of Experimental Medicine*. His findings indicate that blocking PD-1's interaction with PD-1 ligand may simply prevent T cells from dying, rather than rejuvenating them.

Anthony Fauci, director of the NIAID, agrees that further investigation is needed to follow up the PD-1 findings. "This work is elegant and very carefully done, and from a scientific standpoint it's solid," he says. "But we've got to be careful we don't make the majestic leap to say: now we've solved the issue of unresponsiveness in people infected with HIV. It may turn out to be that way, but we've got to be cautious." ■

Erika Check

1. Barber, D. L. *et al. Nature* **439**, 682–687 (2006).
2. Trautmann, L. *et al. Nature Med.* advance online publication, doi:10.1038/nm1482 (20 August 2006).
3. Day, C. L. *et al. Nature* advance online publication, doi:10.1038/nature05115 (20 August 2006).

China set to make fusion history

The world's first fully superconducting tokamak is soon to produce a discharge of ionized gas or plasma.

If all goes as planned, China's Experimental Advanced Superconducting Tokamak (EAST) project will make its first plasma in the next few weeks.

EAST uses superconducting coils to create a magnetic field that confines plasma inside a doughnut-shaped vessel known as a tokamak. The behaviour of the plasma should shed light on the potential of nuclear fusion as an energy source.

Conventional experimental fusion machines use copper coils, or a combination of copper and superconducting coils, to trap the hot plasma. But copper coils heat up and need to be cooled down regularly, thus limiting operating time. EAST has only superconducting coils so it can be operated continuously.

The US$25-million machine sets the stage for the multibillion-dollar ITER fusion experiment that is to be built in France; ITER, due to start operations in 2016, is similarly designed to be all-superconducting.

"We'll need new energy resources for a long-term period, and fusion will be one of them," says Peide Weng, deputy manager and chief engineer of the EAST project at the Institute of Plasma Physics of the Chinese Academy of Sciences. "For commercial use, it should be superconducting because it will need continuous operation."

China approved the machine in 1998, as part of a push towards new energy sources. Construction then began in 2000 in Hefei, in southern China. The 150-member EAST team imported some material and components, but designed and fabricated the bulk of the equipment on its own.

EAST is only one-tenth the volume of Japan's JT-60 tokamak, and one-hundredth the expected volume of ITER. It won't produce fusion power, and is designed to study advanced tokamak physics. The first plasma, created from heated hydrogen gas, will probably last for only a few seconds. Still, "it will be a very important step forward," says Toshihide Tsunematsu, director-general of the Naka Fusion Institute of the Japan Atomic Energy Agency, who visited EAST a few weeks ago. The agency owns the JT-60 tokamak.

Eventually, the EAST team aims to hold a plasma for study for as long as 1,000 seconds. In other tokamaks plasmas last for only a few tens of seconds.

South Korea is currently developing a tokamak similar to EAST, called the Korean Superconducting Tokamak Reactor (KSTAR), whose construction is expected to be completed at the end of 2007. Japan also plans to upgrade its JT-60 machine to make it fully superconducting in a few years.

International physicists praise what China has accomplished so far. In 2003, 25 physicists visited EAST as part of its international advisory committee.

"Everybody came away very impressed," says Dale Meade, a physicist with the Princeton Plasma Physics Laboratory in Princeton, New Jersey, and a member of the group. The committee plans to hold another meeting in October, when China hosts a conference of the International Atomic Energy Agency.

In the meantime, the EAST researchers have plenty to work on, says Tsunematsu. They will have to improve key technologies, such as a device to heat the plasma, and be able to effectively control high-temperature plasma for a long period of time. "China will face a real challenge," he says. ■

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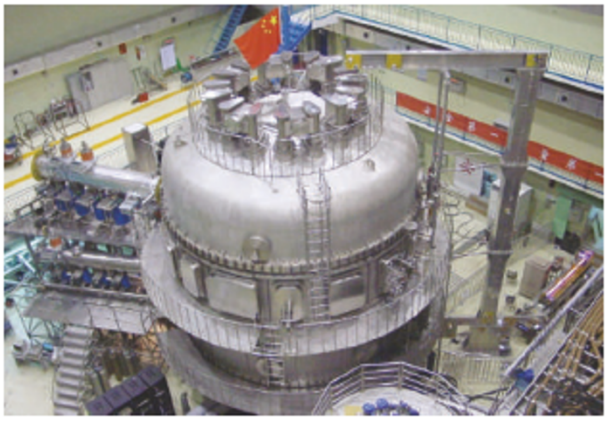
With additional reporting by Geoff Brumfiel



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In the lead: if China's EAST project is a success, it will pave the way for other major fusion experiments around the world.