AIDS RESEARCH

Novel Protein Delivers HIV to Target Cells

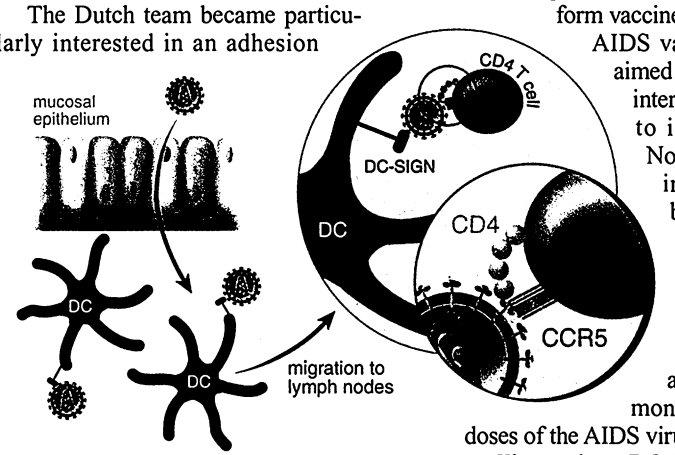
HIV may well be the most studied virus of all time, yet the steps between its introduction into the body by sexual intercourse and an established infection still remain mysterious. Now, tumor immunologists have joined with AIDS researchers to uncover intriguing evidence that a little-understood protein may play a key role in HIV infection, enabling the virus to sneak behind the body's defenses. In addition to elucidating the mechanism of sexual transmission of AIDS, these findings may open new possibilities for AIDS vaccines.

The work, described in two papers in the 3 March issue of *Cell*, focuses on a protein dubbed DC-SIGN that juts from the surface of dendritic cells, sentries that alert immune system central when invaders breach the body's borders. The papers reveal that DC-SIGN behaves like fingers on the arms of dendritic cells, helping them carry HIV from the mucosal lining of the cervix or rectum to remote lymph nodes. There, DC-SIGN hands HIV over to $CD4^+$ T lymphocytes, the immune system cells that the virus readily infects and destroys, eventually leading to AIDS.

The researchers also show that when HIV is bound to DC-SIGN, the virus remains viable for several days longer than it would on its own, thus increasing the odds that a tiny dose of the virus will reach its target. "It's very elegant work," says Douglas Richman, an AIDS researcher at the University of California, San Diego, who has studied the interaction of HIV and dendritic cells. "It proposes another ingenious way in which HIV exploits the immune system to create mischief."

The discovery that DC-SIGN appears to play a critical role in HIV infection began in the lab of Yvette van Kooyk, a tumor immunologist at the University Medical Center St. Radboud in Nijmegen, the Netherlands. Van Kooyk, Carl Figdor, Teunis Geijtenbeek, and their co-workers were not studying AIDS but were investigating how dendritic cells and T lymphocytes interact. Work by Ralph Steinman of The Rockefeller University in New York City and others had established that dendritic cells initiate an immune response by "presenting" foreign antigens such as viruses to the T lymphocytes. The T lymphocytes then send other immune troops into battle. But details about this antigen presentation have remained sketchy, including how dendritic cells and T cells attach to each other using so-called adhesion molecules on the cell surfaces.

The Dutch team became particularly interested in an adhesion molecule called ICAM-3 that is abundant on T cells. In one of the two *Cell* papers, the Dutch researchers describe how they isolated a new dendritic cell protein that binds ICAM-3 much more strongly than anything previously studied. (They called it DC-SIGN because it is a dendritic cell–specific, ICAM-3–grabbing nonintegrin.)



Protein power. DC-SIGN delivers HIV to $CD4^+$ lymphocytes.

Only later did the connection to AIDS turn up, as described in the second *Cell* paper. To the Dutch researchers' surprise, a database search revealed that in 1992 scientists at Bristol-Myers had found an identical protein in placental cells. The Bristol-Myers team did not link the protein to dendritic cells but did describe how it strongly binds gp120, HIV's surface protein that allows it to grab onto the cells it infects.

The Dutch tumor specialists decided to join forces with Dan Littman's team, which studies HIV entry mechanisms at New York University's Skirball Institute of Biomolecular Medicine. In a series of test tube experiments, the researchers demonstrate that, contrary to their initial hunches, HIV does not use DC-SIGN to slip into dendritic cells. Rather, DC-SIGN enhances HIV's ability to infect CD4 cells, in part by binding tightly to the virus and stabilizing it during the journey from mucosa to lymph nodes. This stabilization makes a huge difference: Another experiment showed that HIV bound to DC-SIGN could still infect CD4 cells after 4 days, while HIV alone lost its infectivity in less than a day. "This certainly gives the dendritic cell a lot more capability of stealth," says Steinman.

On a practical front, the findings may inform vaccine design. To date, many AIDS vaccine designers have aimed to elicit antibodies that interrupt the fusion of HIV to its CD4 cell targets. Now, they might seek to induce antibodies that block the binding of DC-SIGN to gp120, derailing the infection prior to HIV-CD4 fusion. Studies can also now ask whether such antibodies can protect monkeys given infectious doses of the AIDS virus.

The work on DC-SIGN also underscores the benefits that can accrue when "newcomers" from other disciplines turn fresh eyes on long-standing questions, in this case, about HIV infection. Says van Kooyk, "You never know how science will work out."

–JON COHEN

CREDITS: (TOP) MODIFIED FROM GEIJTENBEEK *ET AL.*, *CELL* (IN PRESS); (BOTTOM) AP PHOTO/UWE LEIN

STEM CELLS

Protest Leads Europeans To Confess Patent Error

Prodded by environmental activists, politicians, and the media, the European Patent Office (EPO) has said that it made a mistake last December in granting too broad a patent on a method to isolate genetically engineered stem cells. Last week EPO offi-

Solid front. Activists use bricks to block entry to the European Patent Office in Munich, urging "no patents on life."

cials declared that the patent, awarded to the University of Edinburgh, U.K., should have been restricted to "nonhuman" animals to prevent the possible cloning of humans. The German government has announced its intention to file a formal complaint, and the company licensed to use the technology says it is eager to work with EPO officials "to rectify the problem."

The patent covers a genetic selection method for purifying the highly treasured stem cells, a possible fountain of youth for all kinds of deteriorating organs. The last of its 48 claims refers to "a method of preparing a transgenic animal" using the stem cells. The patent uses the term "animal" in its scientific sense, to include humans. But that definition flies in the face of European patent guidelines that explicitly prohibit the patenting of processes that tinker with the genetic makeup of humans.

The apparent breaching of those guidelines sent activists into the streets in Munich, where they bricked up the main EPO entrance during a 22 February rally. "Issuing a patent that can be applied to create genetically engineered human embryos poses both ethical and legal problems," says Christoph Then, a gene technology expert at Greenpeace, the organizer of the event. The day before, Greenpeace had published a report on the patent that coincided with an article in *Financial Times Germany*.

Later that day, EPO issued a statement that admitted its "error" and said the EPO "regrets that it has occurred." But EPO can't erase that mistake by itself, says spokesperson Rainer Osterwalder. Critics have 9 months to respond to any patent issued, he explains, after which EPO will review the comments and take action. Any change in the patent could take several years, he notes. A day later, the German ministers of Health, of Education and Research, and of Justice decided to challenge EPO's decision.

But the controversy may not drag on that long. Co-inventor Peter Mountford, chief scientific officer of Stem Cell Sciences (SCS) in Melbourne, Australia, which has an exclusive license on the technology, says the company's goal is to coax the isolated stem cells to turn into several different cell types, such as nerve cells or liver cells, and then use them in drug-screening assays. "That would allow us to save lots of laboratory animals," says Mountford. SCS is "already talking to the EPO and exploring possibilities for clearing up the mistake," says George Schlich, the company's patent attorney.

In the long run, SCS also plans to develop cell replacement therapies for certain human disorders, such as neurodegenerative diseases or diabetes. "But the company never intended to produce genetically engineered humans," Mountford insists. Then says he never thought so, but he wonders if human stem cells "will be taken out of the patent entirely" given some of the company's therapeutic goals.

In the meantime, the patent remains in effect, and work, mainly with rodent stem cells, continues in Australia and in the United Kingdom, under co-inventor Austin Smith. Even so, a patent does not sanction work that violates national laws, notes Osterwalder, and neither country allows human cloning. –MICHAEL HAGMANN

CHEMISTRY

Novel Catalyst Runs Quick and Clean

Score at least a partial victory for green chemistry, the campaign to make industrial processes more environmentally benign. On page 1636 of this issue, three researchers at Delft University of Technology in the Netherlands report a way to clean up a commonplace family of chemical reactions—turning alcohols into aldehydes, ketones, and carboxylic acids, starting materials for everything from pharmaceuticals to fragrances. The Dutch work replaces reactions that rely on the toxic heavy metal chromium and dangerous organic solvents with alternatives that work with everyday oxygen and water. If adopted by industry, the new process has the potential to displace thousands of tons of hazardous waste every year.

"It's very interesting chemistry," says Terry Collins, a chemist at Carnegie Mellon University in Pittsburgh, Pennsylvania. "Getting rid of chromium is a great thing to be doing." Collins and others caution that the new method of converting alcohols to other compounds may not be quite ready for prime time. But in the lab, at least, it far outshines the standard approach.

Alcohols are short hydrocarbons that harbor an extra oxygen and hydrogen atom. To transform them, chemists must oxidize them in a controlled manner by stripping off two or three hydrogen atoms. The widely used oxidant chromium oxide is a master at such reactions, so thirsty for electrons that it readily swipes a pair of electrons from an alcohol's hydrogen atoms and pulls the protons along with them for good measure.

The problem is that once satiated, the chromium oxide is unable to give up the hydrogens again. To transform another alcohol molecule, more chromium is needed, so waste is generated as fast as the desired product is. To get rid of chromium, the Delft researchers—organic chemists Roger Sheldon and Isabel Arends and graduate student Gerd-Jan ten Brink—sought a catalyst that could perform the same reaction over and

ScienceScope

Second Helping Thrilled by the response to a 1997 program to refit university laboratories, the Canadian government surprised academe on Monday by announcing that it would pump an additional $615 million into the Canada Foundation for Innovation (CFI) for ongoing rejuvenation of academic research infrastructure.

The money is part of the government's 2000–01 budget, which starts on 1 April. With the CFI awash in applications and its existing $680 million endowment scheduled to run dry next year, a cash injection is needed to maintain "one of the cornerstones of our plan to support the new economy," says Finance Minister Paul Martin. Martin also announced that Ottawa will spend $109 million to establish five centers for genome mapping and proteomics. The new investments, combined with existing plans to spend $245 million over 3 years to create 2000 new research chairs (*Science*, 22 October 1999, p. 651), represent a "significant" reaffirmation of the value of academic research, says Robert Giroux, president of the Association of Universities and Colleges of Canada.

Brain Trust In one of the largest gifts ever to a U.S. university, a high-tech couple is giving $350 million over the next 20 years to the Massachusetts Institute of Technology (MIT) for a brain research center. The new McGovern Institute for Brain Research, based at MIT in Cambridge, Massachusetts, will be directed by MIT molecular biologist Phillip Sharp.

The McGoverns (right, with MIT president Charles Vest) have deep connections to MIT. Patrick McGovern studied neuroscience as an undergraduate and later founded the International Data Group, a $2.6 billion computer publishing company in Framingham, Massachusetts. Lore Harp McGovern, a computer entrepreneur, has chaired the board of MIT's Whitehead Institute for Biomedical Research for the past 3 years. The McGoverns said their gift will enable neuroscientists to "address the daunting complexity of the mammalian brain and to begin to understand the biological basis for human thought, language, and behavior." Sharp, a Nobel laureate, says he plans to assemble a team of 16 investigators, including 10 with faculty appointments, in biology, computer science, and linguistics.

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