

He and others pointed out that it is difficult for viral particles in blood to penetrate the nuclei of sperm, although they may more easily enter seminal fluid. And he noted that risks can be reduced easily by requiring subjects to use barrier contraception methods until all traces of the vector have disappeared. Other officials commented privately after the meeting that the Food and Drug Administration (FDA), which ordered the experiment to be put on hold, seems ready now to let it resume. But FDA almost certainly will ask the investigators to run more tests of germ line effects.

Kay interpreted the review as "reasonably favorable." So did Grossbard. But Grossbard noted a potentially big logistical problem. The first volunteer was given a low dose of the vector, and future volunteers who receive higher doses may take longer to clear the vector. If so, and if the FDA continues to insist that each patient be free of vector DNA for 3 months before the next is treated, Grossbard estimated that the time to complete a basic safety trial "may approach or exceed 5 years." He suggested that this was a heavy price to pay for "a very small theoretical risk."

Presenting FDA's concerns, agency scientist Stephanie Simek agreed that the risk was low but insisted that it is real. She also pointed out that the risk had not been flagged by preclinical animal studies and warned that there's a possibility that "all treated subjects" may test positive, at least initially. She then asked a provocative question: "Does the potential benefit of a [gene therapy] product outweigh the potential risk of developing a transgenic human?"

The most likely compromise, according to one observer who did not want to speak for attribution, may be to have the hemophilia B trial go forward as planned, but with a requirement that investigators collect additional sperm samples and analyze them "in a more timely fashion" than in the past.

—ELIOT MARSHALL

## CARCINOGENIC BACTERIA

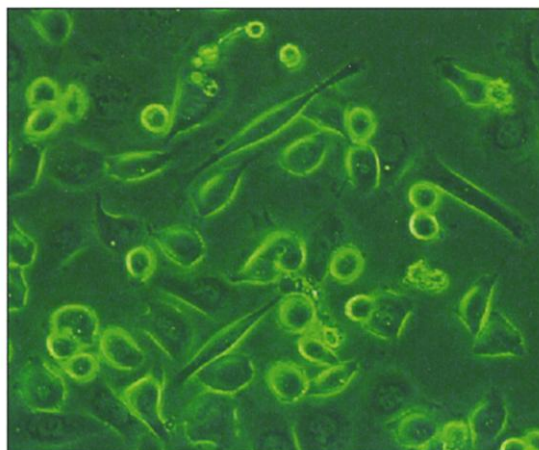
### Cracking Gut Bugs' Cell-Skewing Strategy

Most of the bacteria that cause disease were tracked down long ago, but for decades one microbe got away with murder. Discovered in 1982, *Helicobacter pylori* infects two-thirds of the world's population; it causes ulcers and cancer that kill 7 million people each year (*Science*, 21 May 1999, p. 1328). Researchers have learned a lot about how the microbe digs into the wall of the stomach to cause ulcers, but they knew little about how the bug makes cells malignant—until now.

In a study published online by *Science* this week ([www.sciencexpress.org](http://www.sciencexpress.org)), molecu-

lar oncologist Masanori Hatakeyama of Hokkaido University in Sapporo, Japan, and his colleagues have shown exactly how one of the bacterium's proteins hijacks a signaling pathway in stomach cells, pushing them to change shape and allowing them to move—an early step toward turning cells cancerous. "It's a major step forward," says cellular microbiologist Brett Finlay of the University of British Columbia in Vancouver.

*H. pylori* infections are about half as carcinogenic as smoking cigarettes: People infected with the bacterium are two to six times as likely as uninfected people to develop either gastric cancer, which is derived



**Haywire.** By commandeering a signaling pathway, *H. pylori* causes cells to malform.

from cells in the lining of the stomach, or mucosal-associated lymphoid tissue (MALT) lymphoma, which is derived from immune cells that move to the stomach to battle the *H. pylori* infection. Researchers knew that when virulent strains of *H. pylori* infect the stomach lining, they cause stomach cells to elongate until they resemble hummingbird beaks. And virulent, but not benign, strains of the microbe inject a protein called CagA into the stomach cells, which then tag CagA with phosphate groups. Because tumor-causing viruses trigger cancer in part by spurring cells to add or remove phosphates from proteins, "I was wondering if such things also happen in bacterial infection," Hatakeyama says.

To find out, the researchers first made an educated guess about which human protein CagA interacts with once inside stomach cells. Others had shown that human cells treated with hepatocyte growth factor (HGF) also resemble a hummingbird beak and that HGF-treated cells tag a receptor protein with phosphates, much as occurs with CagA. The HGF receptor alters a signaling protein called SHP-2. Suspecting that this might be one more similarity between HGF and CagA, "we decided to examine if SHP-2 was involved with

*Helicobacter*-induced morphological change," Hatakeyama says.

It was. Antibodies to CagA fished out SHP-2 and vice versa, suggesting that the two proteins team up inside the cell. What's more, cells infected with a mutated version of CagA that didn't bind SHP-2 no longer elongated into their characteristic shape.

Next, Hatakeyama's team asked whether CagA boosts SHP-2's ability to pass on signals. Ordinarily, cells send messages using a molecular bucket brigade. In HGF-induced signaling, SHP-2 is one of the recruits; it joins the HGF receptor and clips phosphates off other proteins. SHP-2 and CagA appear to form a similar complex: They team up only when CagA is phosphorylated, and SHP-2 clips phosphates from other proteins only when joined to CagA. That means CagA plugs into the normal cellular signaling system, Hatakeyama says, leading the cell astray and making it vulnerable to becoming cancerous.

Bacteriologist Stanley Falkow of Stanford University says the work "speaks to what must be an important event that predisposes [cells] to malignancy." But cell biologist Michael Naumann of the Max Planck Institute for Infection Biology in Berlin cautions that other signaling molecules probably help pass along the signal to elongate. Indeed, in work in press in *Molecular Microbiology*, microbiologists Rino Rappuoli, Antonello Covacci, and their colleagues at Chiron Corp. in Siena, Italy, identified two enzymes, c-Src and Lyn, that tag CagA with phosphates inside stomach cells. Many of the molecular links between *H. pylori* and cancer still remain to be discovered, Falkow emphasizes—but *H. pylori* investigators are closing in on their quarry.

—DAN FERBER

## INDIA

### New Report Tackles Wealth of Problems

**NEW DELHI**—The Indian government last week produced a harsh assessment of the state of science as part of a new draft statement on what's needed to help the country compete in a global economy.

"There is an urgent need to revitalize the scientific enterprise," declares the government's long-awaited draft of the Millennium Science and Technology Policy,\* the first document of its kind since the country's independence in 1947. But its analysis should

\* [www.insa-india.org/newsdesk/sc-tc-pl.htm](http://www.insa-india.org/newsdesk/sc-tc-pl.htm)