ahead of the rest of the cell. Hunter agrees. The properties of the protein suggest it might work as "some sort of threshold device," he says, preventing premature functioning of certain proteins. If so, cells lacking the protein may die, because events get so out of order that they go into mitotic arrest.

Other researchers aren't convinced that the story is that straightforward, however. Cancer pharmacologists Sally Kornbluth and Tony Means of Duke University have evidence that Pin1 can bind to NIMA without the help of phosphate, and that it binds to other proteins that do not bind MPM-2. "The mechanisms that govern the effects of Pin1 in the cell ... have yet to be defined," Means says.

Indeed, Cantley cautions that no one has yet pinned down exactly what the protein does when it binds: "We have no proof that isomerization is what's required for physiological function." It is possible, he says, that simply binding to a protein is enough to slow it down. Because researchers can now identify Pin1's partners, they hope they will soon be able to sort out its role.

But even before that happens, the protein is attracting drug companies' interest. Because blocking the enzyme kills cells as they attempt to divide, drugs that inhibit the enzyme should target fast-dividing cancer cells without affecting the majority of cells in the body that divide only occasionally. "At least three or four companies are interested in looking for inhibitors," Lu says.

–Gretchen Vogel

CANCER THERAPY

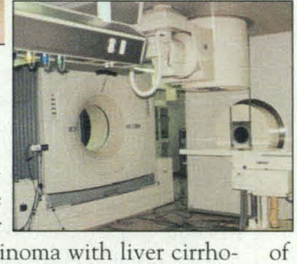
Heavy Ions Pack Powerful Punch

CHIBA, JAPAN—A high-stakes experiment in cancer therapy appears to be paying significant short-term dividends for dozens of patients. A team of researchers presented preliminary results at a recent conference here* indicating that expensive treatments with beams of carbon ions showed promise against a variety of tumors that had been considered untreatable or had resisted previous treatments. But questions remain about the long-term efficacy of the approach, as well as about its value for money.

The data were the most complete results yet from Japan's Heavy-Ion Medical Accelerator in Chiba (HIMAC), which began operating in 1995 at the National Institute of Radiological Sciences (NIRS) (*Science*, 12 May 1995, p. 797). HIMAC was built on the premise that because beams of heavy ions can be focused more precisely than x-rays, the larger mass and charge of the particles will result in greater damage to the tumor and less injury to surrounding healthy tissue. "And that's what they're seeing," says Inder Daftari, a radiation oncology physicist at the University of California, San Francisco, and a member of a team that pioneered the technique at Lawrence Berkeley National Laboratory in California until the lab's aging accelerator was shut down in 1993. "The results are very encouraging," adds John Munzenrider, a radiation oncologist at Massachusetts General Hospital and Harvard Medical School, both in Boston.

The new results come from clinical studies to evaluate both toxicity and effectiveness in patients with head and neck, lung, liver, and cervical cancers. Treatments typically consisted of periods of irradiation with carbon-12 ions, two to four times a week for 4 to 6 weeks. In all cases, alternative treatments had failed or been ruled out.

Twenty-four of 34 patients with advanced head and neck cancers had complete or substantial regression of the tumors after 6 months. And seven of nine patients treated more than 2 years ago are still alive. Just over half (23 out of 44) of the patients with non–small cell lung carcinomas showed complete or partial response 6 months after treatment, and eight of 14 patients survived the 2-year mark. For hepatocellular carcinoma with liver cirrhosis, 18 of 25 tumors showed complete or partial regression after 6 months, and three of four patients survived beyond 2 years of treatment. There were also preliminary indications of a good response for cervical cancer. "It's very impressive, especially for lung cancers," says William Chu, a radiation physicist at the Lawrence Berkeley lab.



NATIONAL INSTITUTE OF RADIOLOGICAL SCIENCE

Ion power. Chiba's accelerator *(above)* supplies carbon ions to treat cancer patients *(right)*.

Those results were achieved with dosages that started at around 2 grays and were raised to as much as three times that level in subsequent trials following an evaluation one to several months after treatment. (One gray equals 1 joule of radiation energy deposited in 1 kilogram of tissue.) But some researchers think that such high per-session dosages could cause harmful, long-term side effects. Yasuyuki Akine, director of the University of Tsukuba's Proton Medical Research Center, worries that possible damage to surrounding tissue may not surface for several years. "Before escalating [the dosage], you need to evaluate late injury 3 to 4 years after treatment," he says. Hirohiko Tsujii, head of NIRS's department of medicine, admits that the NIRS's team debated the timing but decided it would be impractical to wait 3 to 4 years before trying higher doses.

These results come, however, with a hefty price tag. HIMAC, the world's only heavy-ion accelerator dedicated to medical use, cost $326 million to build and takes $58 million a year to operate. U.S. scientists don't foresee restarting heavy-ion experiments, says Munzenrider, "because of the expense." Munzenrider and others hope, however, that many of the benefits of heavy-ion therapy can be achieved with beams of protons, which require less powerful—and much cheaper—accelerators than those needed to generate heavy-ion beams. But Daftari believes that each of the different therapies will eventually find its own niche in treating different cancers. "If effective, [heavy-ion therapy] would justify the cost," he says.

A group in Germany is waiting for government approval for a 5-year trial of up to 350 patients. It will be the first human trials for the team, which is based at GSI, the German national lab for heavy-ion research in Darmstadt. "We were very pleased to hear the [HIMAC] results," says Gerhard Kraft, a physicist who heads the group. And Japan's Hyogo Prefecture is already building a $230 million, medical-use accelerator capable of delivering both protons and heavy ions. Even so, therapy is likely to be restricted to protons until HIMAC produces recommended protocols for heavy ions. Researchers say such protocols could be ready in 4 to 5 years.

–Dennis Normile

* Proton Therapy Coordinating Group semi-annual meeting PTCOG27, 17 to 19 November in Chiba, Japan.