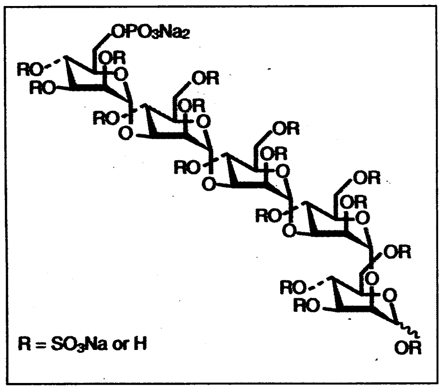

Drug prospect. The heparanase inhibitor PI-88 may be tested in cancer patients.

ing tips penetrate new tissue.

Researcher first made the connection between metastasis and heparanase in the mid-1980s. Three groups—Garth Nicolson's at M. D. Anderson Cancer Center in Houston as well as Parish's and Vlodavsky's—were following up on the finding that the natural anticoagulant, heparin, inhibits the spread of cancer in animals. The prevailing belief was that heparin worked because it prevented platelets from clotting around cancer cells, an event likely to help the cells lodge into, and ultimately penetrate, the vessel wall. But "heparin" is a family of molecules, only some of which inhibit clot formation. And the three groups independently showed that it still inhibits metastasis, even when depleted of its anticlotting activity.

The researchers then traced that effect to molecules that inhibit heparanase, an enzyme then known only on the basis of its ability to break down heparan sulfate. Both Parish and Vlodavsky had already shown that heparanase helps immune cells traverse blood vessel walls on their way to infection sites. The evidence that it might be doing something similar for cancer cells, says Parish, "immediately made people think about getting better [heparanase] inhibitors."

But getting the pure enzyme that researchers wanted for their studies proved to be difficult. Not only is heparanase unstable, but the only assay then available was slow and cumbersome, which often meant the enzyme died before it could be recovered. Indeed, along the way, different laboratories appeared to be chasing different enzymes ranging in size from 8 to 137 kilodaltons.

Nevertheless, the Israeli group finally managed to purify heparanase from a human liver cancer cell line and also from human placenta, while the JCSMR group purified it from human platelets. After determining partial amino acid sequences of the purified proteins, the researchers then screened databases looking for gene sequences that could encode those amino acid sequences. And contrary to expectations that there might be more than one heparanase, both groups found themselves with the same gene—the only one like it in the databases.

Experiments by the two groups confirm that the gene they have cloned aids the spread of cancer cells. When Vlodavsky and his colleagues introduced a copy into nonmetastatic mouse melanoma and lymphoma cancer cells, they turned into rampantly malignant cells that colonized the lung and liver when injected into mice. And Parish, looking at several different types of rat cancer cells, found that their invasiveness correlates with the activity of their heparanase gene.

Conversely, inhibiting the enzyme inhibits cancer metastasis. In work in press in *Cancer Research*, Parish reports that a previously identified inhibitor of heparanase called PI-88 decreased by 90% the number of lung tumors formed by breast cancer cells injected into rats. It also cut the blood supply of the primary tumors by some 30% and—perhaps as a result—slowed their growth by half. The encouraging animal results have already led Progen to test the safety of the inhibitor in healthy volunteers. "The drug was well tolerated over the few days" it was tested, says Parish.

A trial in cancer patients should begin soon in Australia, and it is unlikely to be the last. InSight has its own active program to look for heparanase inhibitors, and other companies may well follow suit. "Now that the sequence is published, the competition [to find heparanase inhibitors] will be tough," Vlodavsky says.

–ELIZABETH FINKEL

Elizabeth Finkel writes from Melbourne, Australia.

ELECTRONIC PUBLISHING

Java Applet Lets Readers Bite Into Research

Luis Mendoza first began writing scientific demonstrations in the computer language called Java for an introductory astronomy course at the University of Washington (UW), Seattle. The language had several advantages for teaching students about such hard-to-visualize concepts like redshift and parallax: It is interactive, it works the same way on every type of computer, and its "applets," or programs, run easily on browsers linked to the World Wide Web. Now Mendoza, a UW graduate student, has gone far beyond Astronomy 101 with what may be the first electronically published astrophysics paper to use an interactive Java applet.

Although the project was modest, allowing users to run a calculation of element-forming processes during the big bang, it bears watching in a field that has been a scientific bellwether in the use of electronic media and the Web. " 'Pioneer' sounds a little grand," says Craig Hogan, the UW astrophysicist who recruited Mendoza for the project, "but it does make the precise predictions of the theory more accessible." Subir Sarkar, a physicist at the University of Oxford in the United Kingdom, sees it as "a handy tool to enable observers to interpret their data."

Java, developed and copyrighted by Sun Microsystems of Palo Alto, California, is already in wide use for business and consumer applications, especially on the Web, where recent versions of most browsers can run Java applets. Java has also made inroads into teaching. Mendoza, for example, had developed an Astronomy 101 site containing applets such as a three-dimensional simulation of parallax, showing a star field and Earth moving in its orbit, seen from an angle chosen by the viewer.

"There are all these young people in Seattle who do all this groovy stuff," says Hogan. Taking advantage of that milieu, Hogan asked Mendoza to write an applet incorporating recent calculations by Sarkar and others on the generation of the light isotopes deuterium, helium-3, helium-4, and lithium-7 in the big bang. The amounts created depend on the overall mass density of the universe. The applet lets the user specify the value for one of the isotopes and then shows—within error bars reflecting imperfectly known nuclear reaction rates—the predicted values for the others and for the overall mass density.

The applet can be found on the Los Alamos preprint server (http://xxx.lanl.gov/abs/astro-ph/9904334) and at www.astro.washington.edu/research/bbn. Researchers like Sarkar are already asking for upgrades, and at least one other astrophysicist—Paul Steinhardt of Princeton University—wants to take things a step further. He's planning to incorporate Java into a more comprehensive set of cosmology calculations recently published in *Science* (28 May, p. 1481) and nicknamed "the cosmic triangle." Whether for research or for Astronomy 101, says Mendoza, the goal is the same: "It's just trying to communicate or teach what you have found."

–JAMES GLANZ

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