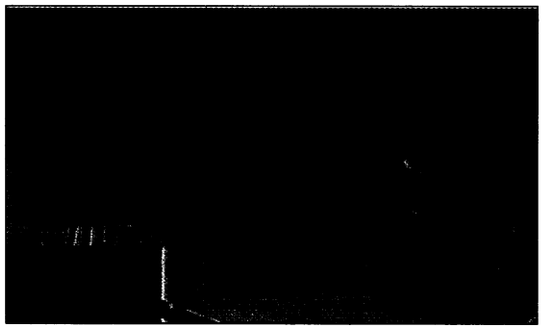
says there is no way of knowing the size of Neandertal turbinates or whether their nostrils were downward-directed. Gannon also says that no matter what the shape of the nose, the airflow is normally laminar when humans inhale, and he thinks it unlikely that Neandertal breathing would be any different. Franciscus, too, says Churchill makes too many assumptions about the size of Neandertal noses. "They're no different from cold-adapted early modern humans," he says. Churchill responds that turbinate remains on two Neandertal specimens indicate they were large, and the large base of the Neandertal septum indicates a downward turning nose.

As the nose exchanges continue, the research is also spilling over into other areas of the Neandertal head. For example, Franciscus says his measurements do confirm one "completely unique" Neandertal feature: the shallow depth of the throat. The vertical distance between the back of the roof of the mouth (the hard palate, which is also the floor of the nose) and the hole where the spinal cord exits the skull is much shorter in Neandertals than in either living or early modern humans, a characteristic first noted by Laitman more than 20 years ago.

At the time, Laitman thought this trait might have limited Neandertal speech, but scientists are now trying to focus on less speculative issues. Franciscus says he sees the short throat as a by-product of other Neandertal traits. He notes that they, like modern humans, had big brains. But they were more like the earlier *Homo erectus* in their patterns of facial growth. To fit this big brain on top of their primitive face, they had to alter their braincase—and ended up with an unusually short throat, he theorizes.



Nose in action. Acrylic model of human nose submerged in water. Dye shows how air would flow.

Laitman's group thinks that Neandertal uniqueness also extends to respiratory tracts, inner ears, eustachian tubes, and sinuses. "I say when you take the upper respiratory tract together with [these other features] we may be looking at a very distinctive *bauplan*," he says. The bottom line, he contends, is that all these features support the notion that Neandertals relied more heavily on nose breathing than do modern humans. Franciscus, who thinks Neandertal noses were nothing special, isn't persuaded, insisting that "from everything we can measure about their internal nasal morphology, they breathed the same as we do."

With plenty of disagreement left, it's probably going to be a long time before scientists reach consensus on how Neandertals breathed—let alone what that might say about their relation to ourselves. But paleontologist Fred Spoor of University College London believes the field is taking a promising direction. There's less "storytelling" going on, as research shifts from the species question to how Neandertal physiology worked. "There's a bit of a new school of people saying ... let's try to make a testable hypothesis," he says, and that's "ultimately a more scientific approach."

–CONSTANCE HOLDEN

CANCER RESEARCH

Potential Target Found for Antimetastasis Drugs

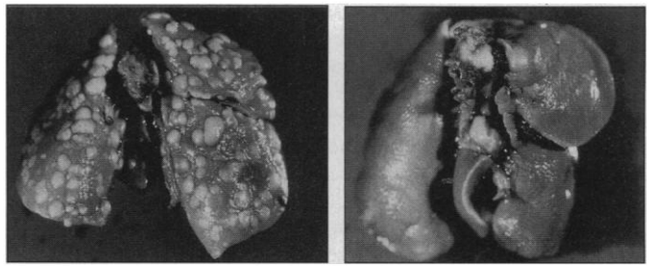
Researchers have finally cloned the gene for the enzyme heparanase, which helps cancer cells escape to new sites in the body

Cancer cells are dangerous not so much because they've lost the brakes on their growth. Rather, it's their ability to metastasize—escape from the original tumors and spread through the circulation to new sites in the body—that makes cancer so tenacious and deadly. Now, researchers have gotten their hands on a key enzyme that helps cancer cells roam the body and may thus be a good target for anticancer drugs.

Like the patrolling cells of the immune system, spreading cancer cells have to be able to breach such barriers as the extracellular matrix (ECM), the glue that holds cells together in tissues, and the basement membranes that surround the blood vessels. These consist of proteins embedded in a fiber meshwork consisting mostly of a complex carbohydrate called heparan sulfate. In previous work, researchers had cloned several genes for the enzymes, called proteases, that cancer cells use to break down the protein portion of the ECM and basement membranes.

But even though researchers suspected for nearly 15 years that the cells also produce an enzyme that snips the heparan sulfate meshwork, that enzyme had eluded them—until now. Two groups, one led by Christopher Parish of the John Curtin School of Medical Research (JCSMR) in Canberra, Australia, in partnership with Progen Industries in Brisbane, and the other by Israel Vlodavsky at Hadassah-Hebrew University in Jerusalem and Iris Pecker of the biotech firm InSight Ltd. in Rehovot, Israel, report in the July issue of *Nature Medicine* that they've finally cloned the long-sought heparanase gene.

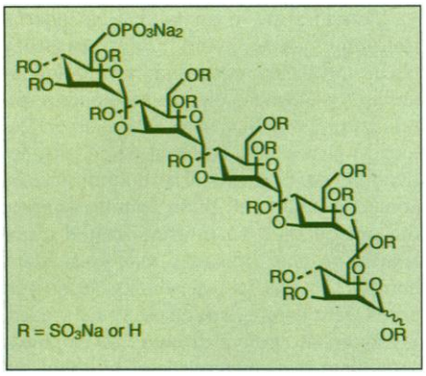
The wait was apparently worth it. Although metastasizing cancer cells may produce as many as 15 different matrix-digesting proteases, the new work suggests that there is only one heparanase. Thus, if its activity can be inhibited—and indications are that it can be—other heparanases shouldn't be around to cover for it. "This is very exciting and surprising," says Lance Liotta, a metastasis expert at the National Cancer Institute in Bethesda, Maryland, whose own work has focused on the proteases.



Metastasis blocker. The lungs of rats injected with breast cancer cells and treated with a heparanase inhibitor *(right)* have far fewer metastases than controls *(left)*.

What's more, a blow to heparanase apparently packs a double punch. Besides inhibiting cancer cells' ability to roam, blocking heparanase also hinders the formation of the new blood vessels that feed tumors, perhaps because the enzyme helps the vessels' grow-

CREDITS: (TOP TO BOTTOM) S. CHURCHILL; K. EDWARDS/CANBERRA



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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