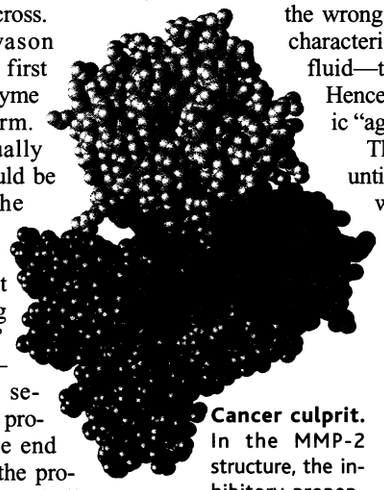
plains. The enzyme apparently helps tumor cells spread by degrading the collagen in basement membranes, a protein mesh around blood vessels and other organs that is usually the first barrier roaming tumor cells have to cross.

Now Tryggvason has produced the first picture of this enzyme in its inactive form. Because perpetually active MMPs would be dangerous to the body—"they can literally dissolve you, so you don't want them floating around freely," Tryggvason says—the enzymes are secreted as inactive proenzymes with one end of the molecule, the propeptide, serving as a built-in inhibitor that has to be cut off before the enzyme can act. Tryggvason's x-ray crystallographic structure of this molecule reveals several regions that might be targets for anticancer drugs.



Cancer culprit. In the MMP-2 structure, the inhibitory propeptide (red) blocks the catalytic core (blue).

One of these is, of course, the enzyme's active site—the part of the molecule that actually clips the substrate proteins. But previous structural studies of just the catalytic domains of several other MMPs showed that they are very similar, and this one is no exception. This similarity could make it difficult to design a specific inhibitor for MMP-2 that works by blocking the enzyme's active site.

But the proMMP-2 structure does reveal more promising targets. The inhibitory propeptide folds into several staircase-like helices, one of which completely shields the catalytic center. To activate the molecule, other proteins cleave a loop connecting the helices. This disrupts the structure of the propeptide leading to its release from the active site. The loop region in the propeptide could serve as a model for designing inhibitory drugs. "One could think of generating peptide analogs [similar to the loop region] that could block the activation step" by choking the MMP-2–activating enzyme, says William Stetler-Stevenson of the NCI's Extracellular Matrix Pathology section. Another MMP-2 region, the part that targets it to its substrate and has now been shown to have a clover leaf–like structure, might also be a drug target, especially as it has been found only in MMP-2 and another cancer villain, MMP-9.

The hunt will also be on for inhibitors of the aggrecanase enzyme, which could lead to arthritis treatments. Researchers have known for more than 20 years that the destruction of aggrecan is one of the early hallmarks of arthritis. But the original suspects, the MMPs, eventually proved innocent when researchers found that they cut aggrecan in the wrong places and failed to produce the characteristic pieces found in the synovial fluid—the lubricant—of arthritic joints. Hence, they postulated that an enigmatic "aggrecanase" was at fault.

That's pretty much how things stood until DuPont's Arner decided to take what might be called a brute-force approach, hoping that a sensitive screen applied to a large sample of cartilage would snare the molecule. Her team chopped up some 30 cow noses—"a good source for cartilage," she says—and cultured the pieces for several weeks with interleukin-1, an inflammatory protein known to bolster cartilage breakdown by inducing aggrecanase production in the cartilage cells. She and her colleagues then ran their 30-plus liters of culture fluid through several purification steps, the last of which used a metalloproteinase inhibitor as bait. Before they did that, however, they saturated the culture fluid with another inhibitor that specifically binds the MMPs, so that those enzymes could not take the bait, while any aggrecanase present could. And indeed, her team ended up with a minute 10 micrograms of a single protein that showed the arthritis-specific aggrecan cleavage signature.

Next, they determined partial amino acid sequences of the protein, translated them back into the language of DNA, and searched DNA databases. They came up with a single hit, a portion of a mouse protein of unknown function that is more than 90% identical. Using this sequence information, the researchers then fished the corresponding human gene from a heart DNA library.

Breaking down. The false-color x-ray shows erosion of the knee joint cartilage due to arthritis.

Aggrecanase-1, it turns out, is also a metalloproteinase, but it belongs to the so-called ADAMTS family that is only distantly related to the MMPs. The big question now is whether the enzyme is the main culprit in arthritis. Using a similar purification procedure, Arner and her colleagues have fished out another enzyme, aggrecanase-2, with properties very similar to those of aggrecanase-1. "Whether [aggrecanase-1] is the only player in arthritis is still out there in the open," says cell biologist Judith White of the University of Virginia, Charlottesville. The only way to tell for sure is to inactivate the aggrecanase-1 and -2 genes and see whether that prevents or retards development of arthritis in mice.

But even if it does, drug developers will have to deal with a specificity problem similar to that with MMP-2. Not only are there at least 11 ADAMTS gene sequences reported thus far, but to make matters worse, aggrecanase-1 is not exclusive to joint cartilage. Arner's team found it in the heart, lungs, and brain as well. What it does there is not yet known, but the finding suggests that inhibiting the enzyme might cause unwanted side effects.

Still, as Amanda Fosang of the University of Melbourne, Australia, points out, "This is only the beginning. There's a lot more to come." Arner is quick to agree. "I think I'm going to be pretty busy in the next few years."

—MICHAEL HAGMANN

UNIVERSITY FUNDING

Japan Wants Results To Influence Budgets

TOKYO—Japan's Education Ministry is weighing a plan to make an institution's track record a criterion in future spending on new research buildings and large equipment. The approach would break with the current practice of allocating infrastructure funds to universities and the ministry's institutes through a formula based primarily on size and tradition. Most scientists applaud the idea of a more rigorous evaluation of research programs, although some are concerned about what measures would be used and how the process might affect the research enterprise. "Outside evaluations are necessary," says Kozi Nakai, a physicist at the private Science University of Tokyo. But he warns that, if the evaluations are not done right, "they could be dangerous."

The recommendations were contained in an interim report released last week by the Science and Technology Council, which advises the Ministry of Education, Science, Sports, and Culture (Monbusho) on research matters. The report echoes a similar call last November by the University Council, which reviews ministry policy on higher education, to carry out evaluations of all educational programs. Evaluations of research efforts are likely to be based on both objective data, such as the numbers of recent papers and citations by faculty, and onsite program reviews by expert committees. Details will be worked out over the next year and made part of the mandate of a new evaluation body under Monbusho.

CREDITS: (TOP TO BOTTOM) KARL TRYGGVASON, KAROLINSKA INSTITUTE, STOCKHOLM, SWEDEN; MIKE DEVLIN/PHOTO RESEARCHERS

The new policy, if adopted, would mark a significant step in an ongoing campaign to increase the level of accountability at Japan's universities and research institutes. Until fairly recently, universities and professors operated free of almost any type of oversight. Faculty members arrived on campus with jobs for life and received guaranteed, although modest, funding for research even if they never published a paper or submitted a patent application. Infrastructure funds for the 98 national universities were split depending on enrollment and tradition and rarely varied.

That system has started to crumble in the past decade as the amount of research money made available to scientists through competitive, peer-reviewed grant schemes has nearly tripled, to $1.9 billion, while the base funding has grown more slowly, to $1.3 billion. "Individual researchers are now largely subjected to peer review of their work," says Masayuki Shibata, director of Monbusho's Office of Science Policy.

Progress has been less dramatic on the institutional level, however. Although some departments invite blue-ribbon panels from around the world to review their research and education programs, most universities have opted for committees drawn from within. "These self-assessments just don't go far enough in an era when science and technology have become borderless," says Hiroyuki Abe, president of Tohoku University in Sendai and chair of the science council's working group on research evaluation. The council's report recommends "third party," or external, evaluations to remedy that problem.

Although the use of outside evaluations to shape government funding decisions for institutions has broad support, some scientists are worried about the details. Nakai, who also served on the evaluation working group, fears a centralized evaluation would tend to apply the same evaluation criteria across disciplines and between fields. The criteria for groups working in accelerator physics should be different from other areas of physics, not to mention engineering, he says, noting the variations between large and small science and the differing attitudes among disciplines toward the importance of publication. He also worries that a centralized system will seek a common denominator and penalize universities that cater to local needs. "Everyone recognizes that Japanese primary and secondary education is overly focused on the single objective of doing well on university entrance exams," he says. "There is a possibility of making the same sort of mistake on this."

Abe, who also serves on a new committee that will advise Monbusho on the envisioned evaluation body, says that policymakers and advisers share these concerns. The report, which is intended to "advance the nation's scientific research," also recommends that Monbusho create a mechanism that allows universities to collect overhead on government-sponsored research and improve ties between universities and the private sector. The report also asks Monbusho to revise rules that restrict the hiring of research assistants and technicians.

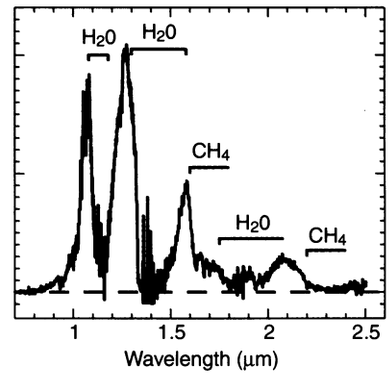
–DENNIS NORMILE

ASTRONOMY

The Coolest Brown Dwarfs Proliferate

CHICAGO—By collecting and cataloging hundreds of millions of celestial objects, the Sloan Digital Sky Survey may turn a rare oddball into a common denizen of the heavens. The $80 million project is designed to create a three-dimensional map of galaxies extending to hundreds of millions of light-years. But the Sloan, which is still in a shakedown phase, has demonstrated that its census-taking power extends to our cosmic neighborhood as well. At an American Astronomical Society meeting here on Monday, survey members announced that it has turned up two of the coolest, dimmest stars called brown dwarfs ever seen, lurking by themselves in the equatorial sky.

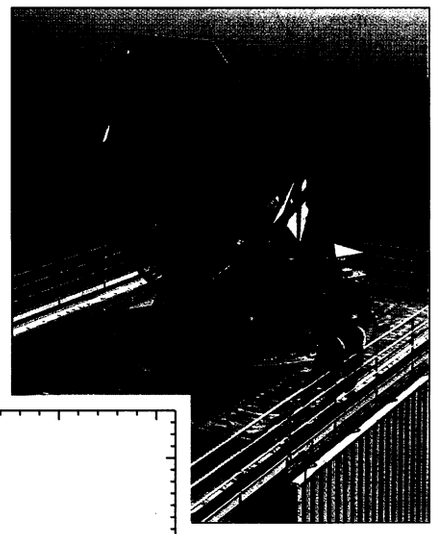
Probably located within 30 or 40 light-years of Earth, the brown dwarfs are so small that their surface temperature is no more than 1000 Kelvin, cool enough for methane and water—compounds normally associated with planets—to survive. Until now these molecules had been seen in only one other brown dwarf (*Science*, 1 December 1995, p. 1435), which was tethered to a brighter and more massive companion. "They're the first methane brown dwarfs found floating out there in isolation," says David Golimowski of Johns Hopkins University and the Sloan team—and a hint that, as theorists have predicted, large numbers of such stars are waiting to be found. "Given that the sky survey was built for other purposes, that's a really handsome payoff," says Alan Boss, an astrophysicist at the Carnegie Institution of Washington.



The Sloan's special wide-field telescope on Apache Peak, New Mexico, is combing wide swaths of sky to compile a "field guide" of hundreds of millions of objects, from which the million brightest galaxies can be selected for detailed mapping. Like a trawl of the heavens, the effort also nets objects ranging from nearby stars to the most distant quasars—brilliant beacons in the early universe (*Science*, 11 December 1998, p. 1969).

Sloan astronomers stumbled across the brown dwarfs while searching for new quasars in data from a test period. Because quasars are so distant that their light is shifted toward the red end of the spectrum, they glimmer in the Sloan's long-wavelength, infrared channels but vanish in optical bands. So do brown dwarfs, as Michael Strauss and Xiaohui Fan of Princeton University and Zlatan Tsvetanov and Wei Zheng of Johns Hopkins found when detailed studies of the objects' spectra revealed that they were cool, dim, and close by.

Defined as stars with less than about 8% of the mass of the sun (or 80 Jupiter masses), brown dwarfs never ignite much fusion burning in their cores and gradually dim after they form. Dozens of garden-variety brown dwarfs, called L dwarfs, slightly too massive and warm to host water and methane, have turned up over the last couple of years, many of them in the infrared 2-Micron All-Sky Survey at the University of Massachusetts, Amherst. But theorists expected that the smaller methane dwarfs would be common as well, because a cloud of gas as small as 10 Jupiter masses can, in principle, collapse into a star. "It's nice to see some confirmation of that theoretical prejudice" from the Sloan results, says Boss.



Faint tracks. The Sloan telescope in New Mexico captured evidence of water and methane in a brown dwarf.

As the Sloan expands its view to cover much of the northern sky, the smallest dwarfs could become a tribe. "They're oddballs at the moment," says Golimowski, "but I'm confident they'll be pretty boring objects within a few months."

–JAMES GLANZ

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