now trying to find subtle genetic changes that may have caused the mutants to lose their taste for alcohol.

As for the other discrepancies, the researchers can only conclude, Crabbe says, that they are the result of very subtle differences in lab conditions, like the chemical composition of the water, or the way the researchers handled the animals, or even the way the scientists and technicians looked or smelled. In Edmonton, a research assistant was highly allergic to mice and wore a respirator. "That looks weird to us; it may look strange to a mouse, too," says Crabbe.

Crabbe doesn't have a clear solution yet to the problems that the study lays bare, but he is now planning experiments to find out if a combination of three or more different tests, designed to measure the same behavioral trait in different ways, would produce more reproducible results than a single test.

Meanwhile, he says, the field of behavioral genetics should at least standardize its tests and perform them just as attentively as, say, a DNA extraction. But because even that won't eliminate outcome differences, every result should be replicated with a new batch of mice within the same lab, and perhaps even elsewhere, before it's published.

–MARTIN ENSERINK

EXPERT TESTIMONY

Project Offers Judges Neutral Science Advice

Federal judges looking for impartial scientists to help sift through complex technical evidence will soon have an easy way to find them. Last week the American Association for the Advancement of Science (AAAS, publisher of *Science*) launched a 5-year pilot project to supply judges with lists of experts who can provide advice in complicated cases, such as claims of software patent infringement or illness from exposure to a toxic substance. The project is intended to cut through the legal confusion generated when expert witnesses hired by each side dispute the significance of such evidence. Pamela Ann Rymer, a judge with the U.S. Court of Appeals for the Ninth Circuit in Pasadena, California, and chair of the project's advisory committee, welcomes the arrival, "for the first time, [of] a single, independent, and neutral source for identifying potential experts."

Courting science. Judge Pamela Rymer lauds project to provide impartial experts.

The $500,000 project, with support from the Leland Fikes Foundation of Dallas and financier George Soros's Open Society Institute, grows out of a 9-year-old idea from a joint panel of AAAS and the American Bar Association. Its stock rose after a 1993 Supreme Court decision urged judges to act as "gatekeepers" for scientific evidence, disallowing expert testimony that doesn't meet accepted scientific standards. The court expanded the ruling earlier this year to include evidence involving the expertise of engineers and those in other technical fields (*Science*, 2 April, p. 21).

The Court Appointed Scientific Experts (CASE) project will rely on a panel of scientists, professional societies, and even the Internet "to help identify people respected in their field" in response to a request from a judge, says project manager Deborah Runkle. It will also develop guidelines for measuring potential conflicts of interest. A 1993 survey by the Federal Judicial Center (FJC) suggests that district judges would welcome input from an impartial expert, who might be involved in everything from tutoring judges and juries in computer codes to explaining the methodology underlying scientific testimony.

Why would a scientist want to get involved in a court case? "It's a service," says Runkle, just like testifying before Congress or serving on a blue-ribbon panel. Adds CASE advisory panel member Sheila Widnall, an aeronautics professor at the Massachusetts Institute of Technology, "It's extremely important for our society, as issues get more and more complicated, that there is a voice" from scientists. The FJC will evaluate the project's impact after 5 years.

Opening for business this fall, the project has already drawn criticism from trial lawyers, who fear that it could tip the balance in the current adversarial system. Ned Miltenberg of the Association of Trial Lawyers of America in Washington, D.C., says that scientists are deeply divided on such legal hot buttons as whether animal tests should be admitted as evidence of causation in toxic tort cases. Putting a stamp of approval on a witness, says Miltenberg, could easily lead "overawed" judges and juries to defer to the court-appointed expert's opinion.

But Runkle says "any good scientist" will acknowledge legitimate opposing views. Besides, she adds, conflicts "are going to exist whether we are here or not."

–JOCELYN KAISER

CELL BIOLOGY

New Leads to Cancer, Arthritis Therapies

Some enzymes get the glamorous jobs: repairing damaged DNA, for example, or shuttling other substances into and out of cells. Others pursue seemingly boring occupations. The enzymes known as metalloproteinases, for instance, simply chew up proteins. They are every bit as essential, however. By breaking down collagen and the other proteins that make up connective tissue, they remodel the entire body during embryonic development and help migrating cells, such as immune cells or the cells necessary for wound healing, move to where they are needed. And like their glamorous cousins, the protein-degrading molecules can cause serious problems when they become overactive, allowing cancers to spread or eroding joints in arthritis. Now, two new findings about the metalloproteinases could open the way to controlling the enzymes.

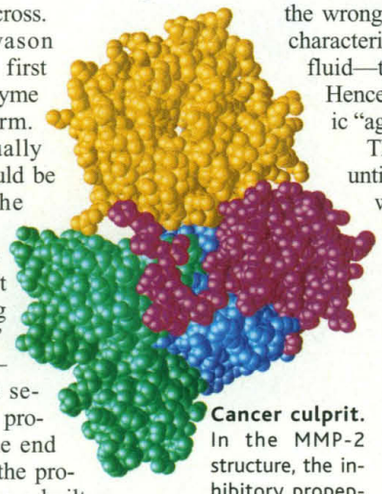
On page 1667, Karl Tryggvason and his colleagues at the Karolinska Institute in Stockholm, Sweden, describe for the first time the complete three-dimensional structure of a metalloproteinase. This enzyme, known as MMP-2 (for matrix metalloproteinase 2), is usually found only in the developing embryo and healing wounds. But it can also help cancer cells spread in the body and allow growing tumors to build new blood supply lines, and so researchers have been looking for drugs that inhibit its action—a quest that the new structure may aid.

And on page 1664, a team led by Elizabeth Arner at DuPont Pharmaceuticals Co. in Wilmington, Delaware, reports the cloning of a new metalloproteinase that seems to play a key role in the development of arthritis by breaking down a cartilage protein called aggrecan; it may thus be a target for antiarthritis drugs. "Everyone looking for arthritis targets is very excited, [because] understanding cartilage destruction had been on hold until the 'aggrecanase' activity was found. This will set the stage for a lot of activity," predicts arthritis expert John Sandy of the Shriners Hospital for Children in Tampa, Florida.

The MMPs, so named for the zinc ion in their catalytic centers, first appeared in the late 1960s when MMP-1, a collagen-degrading enzyme, was discovered. After a long gap, in 1980, Lance Liotta of the National Cancer Institute (NCI), working with Tryggvason, found that various tumor cell lines produce huge amounts of a related enzyme, MMP-2, and linked the enzyme to metastasis. "MMP-2 is not active in benign tumors; it only becomes activated once the tumors become invasive," Tryggvason ex-

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).

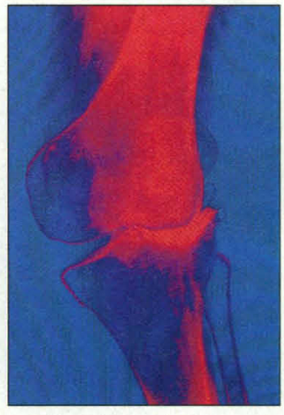
One of these is, of course, the enzyme's active site—the part of the molecule that actually clips the substrate proteins. But previous structural studies of just the catalytic domains of several other MMPs showed that they are very similar, and this one is no exception. This similarity could make it 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