

NEUROSCIENCE

Hot Pepper Receptor Could Help Manage Pain

Bite into a hot pepper, and the pain that engulfs your tongue and palate really does feel like a burn. Several years ago, scientists uncovered the apparent reason: a cell-surface protein that in cultured cells responds both to heat and to capsaicin, the active ingredient in chili peppers. But cultured cells don't experience pain, and researchers weren't sure of the molecule's importance in animals. Now, genetically altered mice that possess an amazing tolerance for hot sauce



Hot stuff. Mice lacking the VR1 receptor are impervious to the burn of hot peppers and are less sensitive to high temperatures.

have demonstrated that the protein plays a key role in several kinds of pain. The finding may eventually aid in the development of new pain-killing drugs.

In work described on page 306, neuroscientists Michael Caterina, David Julius, and Allan Basbaum of the University of California, San Francisco, Martin Koltzenburg of the University of Würzburg, Germany, and their colleagues genetically altered mice to remove the receptor that responds to heat as well as to capsaicin and other so-called vanilloid compounds. The mice behaved normally in most respects, but showed less sensitivity to high temperatures and drank capsaicin-laced water freely. Their neurons also failed to respond to normally noxious stimuli.

Those traits, Julius says, show that the receptor is not only "an essential part of vanilloid sensitivity" but also plays an important role in several other kinds of pain. Indeed, neurosurgeon James Campbell of The Johns Hopkins University School of Medicine in Baltimore says that the receptor is a promising drug target. "If we go after these receptors, we may be able to control [certain kinds of] pain," he says.

Researchers knew that neurons containing the capsaicin receptor, dubbed VR1 (for vanilloid receptor 1), respond to capsaicin and other painful stimuli in culture. But it was only after Julius and Caterina decided

ScienceScope

Looking East Germany's Max Planck Society, which recently completed an expansion into the former East Germany, is now stretching even farther eastward. Society officials announced last week that they will set up a joint "junior research group" with Poland's Academy of Sciences.

The collaboration between Germany's premier basic-research organization and Warsaw's year-old International Institute of Molecular and Cell Biology is seen as a possible model for joint efforts in other fields and with other central European countries. The new research group will be led by a scientist under age 35—chosen after a global search—and will include several Polish postdocs and young researchers. Max Planck, which will pay for salaries and equipment costs, has set up similar groups in France, Israel, and China.

"We want to show that outstanding biology can be done in Poland," says Polish biochemist Maciej J. Nalecz, the director of the Polish academy's Institute of Experimental Biology. "We also want to keep outstanding biologists in Poland." In a reciprocal move, Poland hopes to set up its own satellite research group at the Max Planck Institute of Molecular Cell Biology and Genetics in nearby Dresden.

Vaccine Trial Convinced that vaccines caused his grandson's autism, Representative Dan Burton (R-IN, below) said last week he will ask the National Institutes of Health and other health agencies to investigate his theory.

Burton, who chairs the House Committee on Government Reform, held a 7-hour hearing on autism and vaccines on 6 April. It included testimony from parents, a touter of vitamin cures, and a practitioner who said that stretching the heads of autistic children relieves symptoms. Also on hand was Andrew Wakefield of the Royal Free and University College Medical School in London. In 1998, Wakefield and colleagues published a paper—since refuted by larger studies—that linked one kind of autism to measles, mumps, and rubella vaccination. But when an infectious disease specialist testified that the link was highly unlikely, Burton accused him of conflict of interest because his research was funded by a vaccine maker.

Such badgering drew attention. "I'm troubled by this hearing," said Henry Waxman (CA), the committee's ranking Democrat. "This was structured to satisfy the chair's point of view."



ficient" way to determine which BACs to sequence, and in what order.

The result, announced in simultaneous press briefings last week in Beijing and Tokyo, is a map that covers some 80% of the rice genome at least four times over—a good enough draft to enable gene prediction programs to find many of the estimated 30,000 genes, Mahairas says. Neither the UW team nor Monsanto would reveal how long the project took or how much it cost. Mahairas would only say that "the whole approach worked very, very rapidly."

Sasaki, who has seen the data, says the quality of the sequence varies from BAC to BAC, but "it's still very valuable." Rod Wing, a molecular biologist at Clemson University in South Carolina who has been scrambling to determine the optimal set of rice BACs for the sequencing consortium, is more circumspect: "We're going to have to look at the data very closely" to determine how best to use both the public and Monsanto sets. Some partners may take up where Mahairas left off, using the Monsanto BACs directly in their sequencing efforts; Wing, on the other hand, is considering using the company's data to make the sequencing of his own BACs more efficient.

Although some researchers wonder whether Monsanto will be as forthcoming with the data as promised, Hood insists it will. He describes the project as a "win-win situation": Monsanto gets a jump start on finding the genes with commercial value, and the consortium saves several years and perhaps as much as \$100 million.

Rockefeller's Toennissen holds out Monsanto's data-release policy as a model for other public-private collaborations. Some details are unclear, but as early as next month, the consortium will have access to much of Monsanto's data. Once a piece of Monsanto sequence goes into the consortium's public database, anyone—even competitors—can use it, no strings attached, says Sasaki. Until then, however, other academic researchers who want to use Monsanto's sequence must agree to give the company an option to negotiate nonexclusive rights to license any patents derived from its use. "It would be nice if other companies followed suit and made their fundamental genomics information available under similar circumstances," says Toennissen.

DuPont, for example, has a private rice database, as does Novartis. Neither has released these data, but Novartis did help to launch the public rice effort by supporting Wing's research. Says Michael Bevan, a plant molecular geneticist at the John Innes Centre in Norwich, U.K., Monsanto's actions "certainly put other companies on the spot."

—ELIZABETH PENNISI

With reporting by Dennis Normile in Tokyo, Pallava Bagla in India, and Li Hui in China.

SPACE RESEARCH

Mir Gets New Lease on Its Scientific Life

After more than 7 months in mothballs, the Mir space station is once again open for business. A Netherlands-based company called Mir Corp. is helping to fix up the aging and trouble-plagued facility to make it ready for researchers—and eventually rich tourists. But it could be a short-lived venture: The Russian government, which owns the 14-year-old facility, has not decided how long to keep it in orbit, and U.S. space officials say privately they would love to see it shut down once and for all.

Mir Corp. has pledged to spend at least \$20 million on the venture. It is backed by several wealthy American investors, including Washington, D.C.-based telecommunications millionaire Walter Anderson, and the majority shareholder is the Russian space company Energia, which operates Mir for the Russian government. As a start, Mir and Energia bankrolled the launch on 4 April of a Soyuz spacecraft carrying two cosmonauts to Mir. They will check out life-support systems on Mir's collection of pressurized modules, fix a small leak, and conduct some 50 Russian science and technology experiments. Mir Corp. officials hope that a successful mission will help convince Western governments and companies to reactivate experiments they already have on board and attract new paying customers.

Jeffrey Manber, Mir Corp. president and a former Washington representative of Energia, argues that Mir offers opportunities "ranging from industrial production and scientific experimentation to space tourism and in-orbit advertising." With completion of the international space station expected to slip from its scheduled 2004 date, Manber says Mir can serve as a temporary substitute for companies and governments that have set aside money for experiments: "There is already equipment on Mir which can be used very cost effectively."

Manber admits that doing science aboard Mir won't be a big moneymaker, and the company ultimately hopes to lure wealthy and adventurous tourists to visit the station. That idea received an unexpected boost last week from U.S. Transportation Secretary

Rodney Slater, who applauded the company's efforts to create a space tourism business during a speech to aerospace industry officials in Colorado Springs, Colorado.

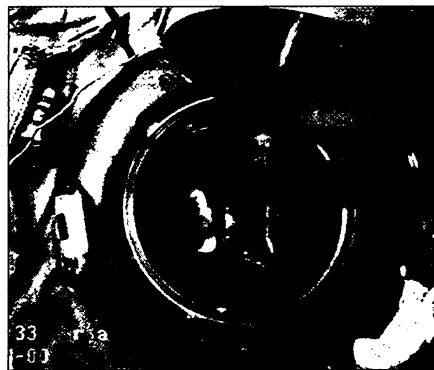
But many U.S. aerospace industry officials, NASA managers, and others familiar with Mir are skeptical about the company's prospects. Mir has suffered computer and power shutdowns, a fire, and a collision with a resupply vehicle that damaged one of its modules. And Russia's financial troubles

prevented significant upgrades during the 1990s. Moreover, the U.S. government in recent years has encouraged the Russians to deorbit Mir and concentrate the country's limited resources on building and launching its portion of the international station.

"There's a tough road ahead," says Manber, acknowledging the uncertain status of the facility. He is hopeful,

however, that the current mission will be followed this fall by a crew conducting experiments on behalf of Western scientists. But for now, Mir is proving that space stations can have many lives.

—ANDREW LAWLER



Back in business. Cosmonaut Alexander Kaleri waved as he entered Mir last week.

GENOME SEQUENCING

Claim and Counterclaim On the Human Genome

J. Craig Venter stole the show last week. The day before Venter appeared at a hearing of a House science subcommittee on 6 April to review research on the human genome, his company, Celera Genomics Corp. of Rockville, Maryland, issued a press release announcing that it had "completed the sequencing phase of one person's genome." The notice, which had a ring of finality about it, indicated that Celera's computers are poised to assemble the human data into a complete genome—a formidable task that Venter predicted at the hearing would take "3 to 6 weeks." Sometime later this year, he says, he will make the data available on Celera's Web site. Celera's stock, which had fallen abruptly in mid-March, soared.

It was an effective bit of propaganda: Celera released no new scientific data, but left the impression that it has bagged the human genome—just as it bagged the genome of the fruit fly in collaboration with the Berkeley *Drosophila* Genome Project earlier this year. But members of the nonprofit consortium that aims to complete

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to inactivate or "knock out" the *VR1* gene that they found that the resulting mice are impervious to capsaicin-induced pain.

For example, capsaicin injected into the hind paw of a normal mouse causes the animal to lick and shake the tender paw. However, the mutant mice barely reacted to the injection, and their paws did not swell or become inflamed as much as they do in normal mice. When researchers laced the drinking water of normal mice with capsaicin, the normal mice took one sip, rubbed their snouts, and stayed clear of the water bottle. The mutant mice, however, drank happily, says Caterina, who is now at Johns Hopkins University.

The mutant animals also tolerated high heat better, including having their tails immersed in a hot water bath and their paws put in contact with a hot plate. The animals did eventually react in both tests, showing that sensitivity was lessened, not eliminated, Caterina notes. This suggests that other heat-sensing channels play a role as well, he says.

Another type of test suggests that *VR1* plays a role in the extra sensitivity to heat usually displayed by inflamed tissues. Mustard oil painted onto the paws of normal mice causes them to become inflamed and very sensitive to heat—just as sunburned skin is seared by warm water or sunshine. But in the mice lacking *VR1*, the mustard-oil treatment did not enhance the response to heat, although the animals still displayed the hypersensitivity to touch that develops in inflamed tissues. Because touch-sensitive pain must be triggered by other neuronal responses, says Julius, the finding suggests that blocking *VR1* would not relieve a common, painful condition—extreme sensitivity to touch, such as that accompanying shingles.

The mouse work suggests, however, that such inhibitors may help combat another type of especially troubling pain, the chronic internal pain that can accompany tissue damage. Julius and his colleagues suspect that *VR1* receptors might contribute to such pain. They found, for example, that neurons carrying the receptors can be excited by the acidic environment produced by inflammation. But neurons from *VR1*-deficient mice bathed in an acidic solution did not react as vigorously as neurons from normal mice did. Thus, the researchers hope that blocking the *VR1* receptor might help relieve chronic internal pain.

The fact that the *VR1* knockout mice seem otherwise normal is encouraging for drug development, Campbell says. "It would appear that the [*VR1* receptor] molecules are specific to pain-sensing neurons," he says. That could lead to drugs with few side effects—perhaps only an inability to taste Tabasco sauce.

—GRETCHEN VOGEL