bersome. The new method speeds the process by directly targeting a narrow region of the chromosome containing the defective gene.

Wilkie and Moloney already knew that Apert's syndrome is most commonly caused by one of two mutations in a copy of the gene encoding FGFR2, a membrane protein that picks up the chemical signals that prompt cell growth, division, or differentiation. To find out whether the gene came from the mother or father, Wilkie and Moloney used an established technique called the amplification refractory mutation system, or ARMS. ARMS, which is based on the polymerase chain reaction, is usually used to identify the strand of a gene containing a known mutation, but the two researchers used it instead to identify polymorphisms—harmless genetic variations—that had been inherited from each parent.

First, however, they needed to know what to look for. By screening a two-kilobase segment of the gene from each of 50 people, they found two suitable polymorphisms. Next, Wilkie and Moloney identified 30 Apert's syndrome families in which those polymorphisms would distinguish which of the child's two copies of the FGFR2 gene came from which parent. Finally, the researchers used ARMS to amplify the DNA from the children containing the two polymorphisms, and then restriction enzymes to pinpoint the strand that contained the mutated version of the *FGFR2* gene. In each of the 30 children, the mutated gene carried the father's polymorphism, showing that the defect must have been inherited from him.

That had been expected, Wilkie says, because earlier work had shown that men in their 50s have more than 20 times the risk of fathering Apert's syndrome children than men in their 20s: "The age effect had suggested that most of the mutations would be paternal in origin, but we didn't know whether to expect 80, 90, or 100%." The new results suggest, he says, that the vast majority of mutations come from the father, while the age effect suggests that the defect arises during sperm production rather than during formation of the sperm germ cells, as that happens before the father reaches puberty. So next, Wilkie says, "we are going to see whether we can find the same mutation in the sperm samples, and if so at what level it is present." If the mutation is detectable in sperm, then it might be possible to screen fathers of one Apert's syndrome child to see if they are at risk of having another.

Now that Wilkie and Moloney's technique has proven its mettle with Apert's syndrome, it may also help identify the origin of other sporadic genetic disorders—such as thanatophoric dysplasia, a lethal form of dwarfism. And just as in the case of Apert's syndrome, says Wilkie, that will allow geneticists to move on to two other questions: "The fundamental biological question of why these things arise? and, then, is there anything we can do to prevent them?"

–Rachel Nowak

AIDS RESEARCH

New Drug Shows Promise in Monkeys

When Che-Chung Tsai and his colleagues first saw the results of their monkey experiments with a potential anti-HIV drug known by the acronym PMPA, they didn't believe them. They seemed just too good to be true. "We repeated and repeated the experiment," says Tsai, a veterinarian and pathologist at the University of Washington (UW) Regional Primate Research Center. Again and again, the data were positive. "Based on antiviral effects," concludes Tsai, "PMPA is the most effective drug we've seen."

Tsai and his colleagues at UW, the National Institutes of Health, and Gilead Sciences report the results of those tests on page 1197, and they are already attracting considerable interest. "There's a great deal of guarded optimism that this is very different from all the [anti-HIV] drugs we've tested," says Nava Sarver, a molecular biologist in the Division of AIDS at the National Institute of Allergy and Infectious Diseases (NIAID). Tsai and Sarver are quick to point out, however, that there is a big leap from monkeys to humans: For starters, HIV-1, the main AIDS virus that infects humans, differs significantly from SIV, the simian relative that was used in the tests. Still, PMPA's powerful effect in monkeys is raising hopes that it may one day help prevent and treat HIV infection in people.

Like the anti-HIV drug AZT, PMPA inhibits reverse transcriptase, a key enzyme that HIV and SIV use to copy themselves. In order to replicate, these viruses must first "reverse transcribe" their genetic material from RNA into DNA, using the RNA as a template to build the DNA one nucleotide at a time. These drugs block this process by acting as decoy nucleotides, which prematurely terminate the chain. PMPA acts faster and stays in cells longer than AZT does.

PMPA, and its older sister compound PMEA, was developed by investigators at Belgium's Rega Institute for Medical Research, and both are now licensed to Gilead, a biotechnology company in Foster City, California. Tsai came into the picture after he sent out a barrage of letters to companies developing AIDS drugs and asked whether he could test their compounds in monkeys. Gilead was one of the few companies that showed any interest, and Tsai first began testing PMEA, which is currently in human trials. He then became interested in PMPA, after test tube studies showed that it was 100 times less toxic than AZT and about 10 times less toxic than PMEA.

Surprised by results. Che-Chung Tsai.

Rather than evaluate whether PMPA could delay or prevent the onset of AIDS in SIV-infected monkeys, Tsai and his colleagues first tested it against what they believed was a lower hurdle: If given shortly before or after a monkey was exposed to SIV, could PMPA prevent the virus from establishing a permanent infection? To answer this question, the researchers injected PMPA into 15 long-tailed macaques 48 hours before they were inoculated with SIV. Five others started the drug 4 hours after inoculation, and another five began treatment after 24 hours. All the monkeys continued receiving PMPA for 4 weeks.

Eight months into the PMPA study, none of the animals has shown any sign of infection or drug toxicity. In contrast, 10 untreated animals given the same dose of SIV all became persistently infected.

These results provide no indication of PMPA's potential as a treatment for SIV infection once the virus has become established, but preliminary evidence from the California Regional Primate Research Center (CRPRC) in Davis shows promise in that regard as well. At a meeting in Monterey, California, last week, CRPRC's Koen Van Rompay, Marta Marthas, and colleagues reported that they infected eight rhesus macaques with SIV at birth and began treating four of the infants with PMPA 3 weeks later. After 6 months, these four animals remained healthy and had low levels of SIV in their blood. The four untreated newborns, by comparison, all had persistently high levels of SIV, and three died within 4 months. Veterinarian Van Rompay adds that they have yet to find any SIV in the treated animals that is resistant to the drug—a critical limiting feature of AZT and other anti-HIV drugs. Like Tsai, Van Rompay is stunned by his own results. "If I had not done the research myself, I would have doubted it," says Van Rompay.

In spite of the preliminary nature of the Tsai group's results, researchers are already speculating that PMPA might eventually find a role in preventing infection in people who have been accidentally exposed to HIV—a

serious concern for health-care and lab workers. Roberta Black, an NIAID virologist who collaborated on the study, says researchers will also be eager to see if the drug can block HIV transmission from mother to infant. And there's even talk about its potential for preventing infection in high-risk groups. "If HIV vaccine development is moving so slowly, perhaps this would give us another something to look at," says Sarver, who cautions that questions of drug toxicity would have to be solved before it could be given as a prophylactic.

Researchers warn, however, that any such uses are far down the road. Says Black: "I don't want to overinterpret the data. It's very clear-cut, and it's very compelling. But before we can find out what the potential is for human use, there's a lot more that has to be done." Adds Sarver: "People should see the red blinking light all the time."

It may not be long before that potential becomes clearer. Gilead chemist Norbert Bischofberger, a co-author of the *Science* paper, says the company, which is working on developing an oral form of PMPA, hopes to begin human trials next year.

–Jon Cohen

EARTH SCIENCE

How Vanished Oceans Drop an Anchor

The same fate awaits all ocean floor: a plunge into the planet's interior at a subduction zone. But the end doesn't always come in the same way. Off Chile, for example, the ocean floor's descent is punctuated by devastating earthquakes as it grinds under the adjacent plate. On the other side of the Pacific near the Mariana Islands, the oceanic plate glides smoothly into the mantle, generating few earthquakes. Both these extremes, and everything in between, can be found at other subduction zones around the world. Now Chris Scholz of Columbia University's Lamont-Doherty Earth Observatory thinks he can explain this puzzling spectrum of behavior.

Building on a 15-year-old proposal, he and Jaime Campos of the University of Chile in Santiago argue that what determines whether or not a slab of ocean floor slips quietly into the mantle is a "sea anchor" force, named after the canvas drogues that ships once dragged through the water to steady themselves. If the subduction zone migrates over the underlying mantle, say Scholz and Campos, the descending slab sweeps through the viscous mantle rock, generating resistance. If it acts in one direction, this force can bend the slab down into the mantle, turning off earthquakes and pulling apart the overriding crust to form a "back-arc" basin—a nascent ocean next to a subduction zone. If the force acts in the other direction, it can push the slab upward against the overriding plate and set the stage for great earthquakes.

Most seismologists who know of the proposal, which appears in the November issue of the *Journal of Geophysical Research*, are reserving judgment until they can study it in detail. But the prospect of a full explanation of why subduction zones behave so differently is enticing, says Larry Ruff of the University of Michigan, because so far "we've not been able to complete the loop in terms of a comprehensive physical theory." For example, he and other earth scientists have noticed that great earthquakes often strike where the plates are converging fast and the ocean floor is warm and buoyant because it was recently created by volcanic activity. But while these correlations "have stood the test of time," Ruff says, "their physical significance isn't clear."

Scholz himself says he realized the limits of the existing understanding in 1993, when a magnitude 7.8 earthquake struck a subduction zone near Guam. "That was a big shocker," he recalls. Most of the subduction zone—the same one that extends north past the Marianas and on toward Japan—doesn't generate big earthquakes. Now seismologists "had to explain why one part is coupled, generating earthquakes, and the other part is decoupled," says Scholz. What's more, he adds, the situation doesn't fit the traditional picture: "The subducting plate is the same age everywhere, and the velocity isn't that different."

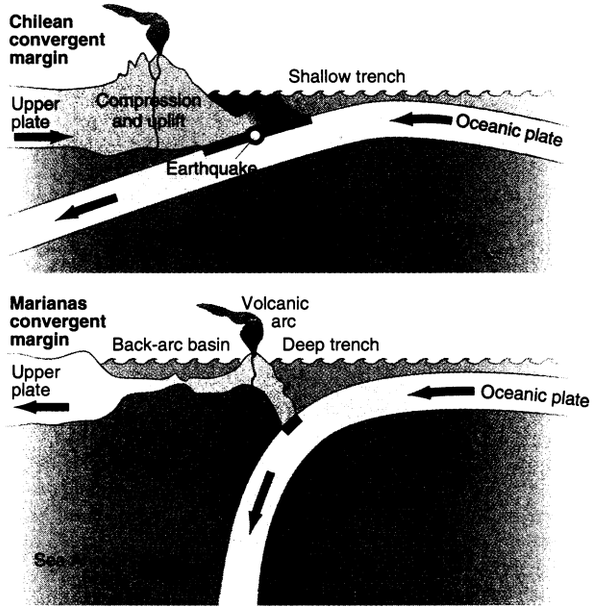
So he and Campos built on an idea originally proposed in the late 1970s by seismologists Seiya Uyeda of Tokai University in Japan, Hiroo Kanamori of Caltech, and others. They had argued that a descending plate is fixed laterally in the mantle by the viscosity of the surrounding rock, rather like a spoon in a honey pot. The anchoring, recalls Kanamori, implied that "the absolute velocity of the upper plate can be a big factor." If the upper plate is moving toward the anchored lower plate, the subduction zone binds and produces earthquakes; if the upper plate is backing away, the zone is quiet.

Uyeda and Kanamori didn't elaborate on that simple picture. But Scholz and Campos have now turned it into a dynamic model of the forces on a subduction zone by assuming that instead of being fixed, the slab sweeps ponderously through the mantle as the upper plate moves—in effect turning the slab into a sea anchor. Unlike earlier ideas, says Scholz, this model can explain that puzzling subduction zone running north from Guam.

Along much of the subduction zone, the upper plate is retreating and the slab is moving along with it, generating a sea anchor force that pushes the slab down into the mantle. To the north, Scholz and Campos's calculations show, the force should be high enough to prevent the slab and plate from sticking and generating earthquakes. At the center of the zone, near the Mariana Islands, a change in slab orientation adds to the force pushing the slab down into the mantle and puts crust near the subduction zone under enough tension to fracture, opening a back-arc basin. But at the southern end of the subduction zone, where the slab shortens and the subduction zone changes direction again, the sea anchor force should drop off. "If you think of the slab as a sail, it's sort of spilling its wind," says Scholz. The result, in the model and in the real world: earthquakes.

The model doesn't contradict earlier correlations between great earthquakes and fast convergence or young crust: Convergence rate depends partly on upper plate motion, and the buoyancy of young crust does enter into the model. But it's more general, says Scholz. When he and Campos applied the model to some 30 subduction zones around the world to see how well it predicted the presence or absence of great earthquakes and back-arc spreading, "it worked for about 80% of the cases," says Scholz. "We think it's a fantastic success. In geophysical models, a global correlation that good is hard to come by."

–Tim Appenzeller



SOURCE: LAMONT-DOHERTY

Major drag. A sea anchor force can press descending ocean floor up against the overriding plate or drag it down, turning earthquakes on or off.