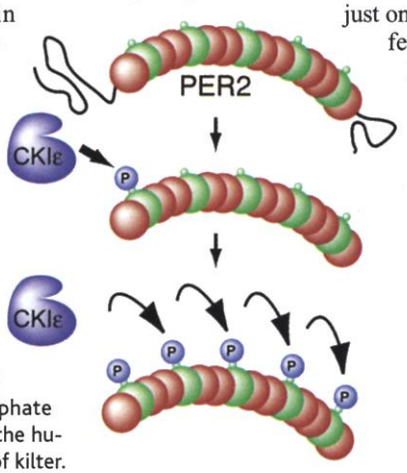
tive gene—an intriguing finding, as that's where the human equivalent of one of the animal circadian clock genes is located. The researchers soon discovered that most of the family members afflicted with FASPS, but none of those unaffected, carry a single base-pair mutation in one copy of this gene, known as h*Per2*. In addition to fingering h*Per2* as the culprit in FASPS, the finding also provided a clue as to how the mutation might be exerting its effects.

The mutation maps to a region of the h*Per2* protein, known as PER2, that looks like it might be a target for phosphate addition by an enzyme called casein kinase Iε. Last year, Takahashi's group discovered that hamsters suffering from a FASPS-like disorder carry a mutation in the gene encoding just that enzyme (*Science*, 21 April 2000, p. 483). The kinase seems to help maintain the proper 24-hour cycling of the mammalian circadian clock by phosphorylating PER proteins.



Roadblock. When human PER2 is mutated, casein kinase Iε (CKIε) can't add the first phosphate to the protein, throwing the human circadian cycle out of kilter.

Clock researchers have found that PER and other clock proteins accumulate during the 24-hour circadian cycle until they reach a concentration that acts to shut down genes, including the *per* genes themselves. The proteins' concentrations then decline until this inhibition is relieved and they start accumulating again in the next day's cycle. The correct timing of the gene down-regulation seems to depend, in part, on phosphate addition to the PER proteins by a kinase enzyme, possibly casein kinase Iε. Takahashi's team found that the mutant kinase does not phosphorylate PER proteins as well as the normal enzyme does. Combined with evidence from PER studies in fruit flies, this led the researchers to propose that, as a result, PER might build up faster than it should, shortening the circadian cycle.

The new work by the Fu and Ptáček team now provides evidence for a similar scenario in humans. They've shown that mutated fragments of PER2 are not phosphorylated as readily by casein kinase Iε as are fragments from the normal protein. So even though the human mutation differs from the hamster mutation, its similar effects on PER phosphorylation are likely to result in similar consequences: early PER2 buildup and an accelerated cycle. "This paper fits in so beautifully with [the hamster] story," says Takahashi.

But the story is far from over. Still uncertain, for example, is whether the h*Per2* mutation has other effects that might contribute to the acceleration of the body's circadian clock. In addition, the mutation is probably just one among many that can affect human clocks. Indeed, Fu and Ptáček have identified two dozen families who suffer from FASPS without carrying the h*Per2* mutation.

Ptáček now wants to search for small molecules that affect the phosphorylation state of PER2 as a first step toward developing drugs that either speed up or slow down the clock—helping not only FASPS patients but perhaps run-of-the-mill early birds or night owls, as well as jet-lagged travelers and night-shift workers. In the future, a pill may be all it takes to fulfill Franklin's sage advice.

–MARINA CHICUREL

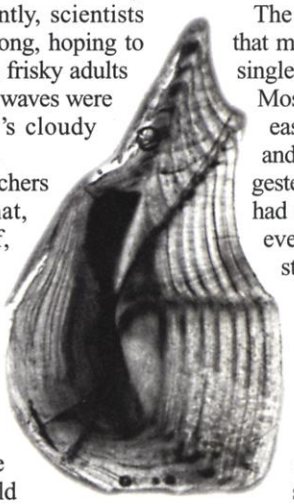
Marina Chicurel is a science journalist in Santa Cruz, California.

FISHERIES SCIENCE

Ear Bones Reveal Homing Tendencies

For centuries, anglers along the marshy Delaware Bay have eagerly awaited the annual return of the weakfish, a blue-gray finned delicacy that crowds into the estuary each spring to spawn. Recently, scientists have joined the expectant throng, hoping to test a hunch: that many of the frisky adults making whoopee beneath the waves were themselves born in the bay's cloudy waters just a few years earlier.

Now, on page 297, researchers offer intriguing evidence that, contrary to common belief, weakfish do indeed have a strong homing instinct. The finding, based on a study of chemical isotopes bound up in the fishes' tiny ear bones, suggests that many marine fish populations may be more complex than once envisioned. The research could also prompt fisheries managers to rethink how they regulate catches and help conservationists design more effective marine reserves.



Lend me your ears. Weakfish otoliths, or ear bones, provide geochemical clues to the fish's birthplace.

Biologists have long known from tagging and genetic studies that salmon and some other anadromous fish have a remarkable ability to navigate back to their birth rivers after years at sea. But documenting similar "natal homing" in fish that spend their entire lives in salt water has proved difficult. One problem is that these fish generally don't display telltale genetic differences; they also produce young that are too small, too numerous, or too dispersed for easy tagging or recapture.

To get around these difficulties, Simon Thorrold, currently of the Woods Hole Oceanographic Institution in Massachusetts, and his team looked to chemical clues contained in otoliths, tiny concretions that form in the ears of many fish. As the otolith grows, each new layer of calcium carbonate captures the chemical signature of the surrounding water. As a result, the bony pebble "acts like a flight recorder, encoding time-specific information about the waters through which the fish passes, from birth to death," says Robert Warner, a fish biologist at the University of California, Santa Barbara.

To begin their study, in 1996 Thorrold's team analyzed otoliths from hundreds of juvenile weakfish caught in Delaware Bay and four other major estuaries along the East Coast of the United States. Each estuary, they discovered, has a unique geochemical signature created by different ratios of chemical isotopes, including carbon-13, oxygen-18, and various forms of magnesium, barium, and strontium. The team returned to the same areas in 1998 and captured 2-year-old weakfish fresh from their wintering grounds off Cape Hatteras, North Carolina. The researchers then analyzed the central cores of the adult fishes' otoliths, formed when the half-meter-long spawners were mere minnows, to see where they originated.

The results were "surprising," given that most biologists view weakfish as a single coastwide stock, says Thorrold. Most of the 2-year-old fish could be easily matched to their home waters, and subsequent statistical work suggested that up to 81% of the spawners had found their way back home. And even the 19% to 40% of fish that strayed to new spawning grounds didn't miss by much, typically ending up in adjacent estuaries.

That mixing probably explains why weakfish up and down the coast are genetically similar, Thorrold says. But it may be a mistake, he adds, for state and federal fisheries managers to ignore the geographically distinct spawning populations even if they are not genetically different. "You can't assume that vagrants from one estuary can

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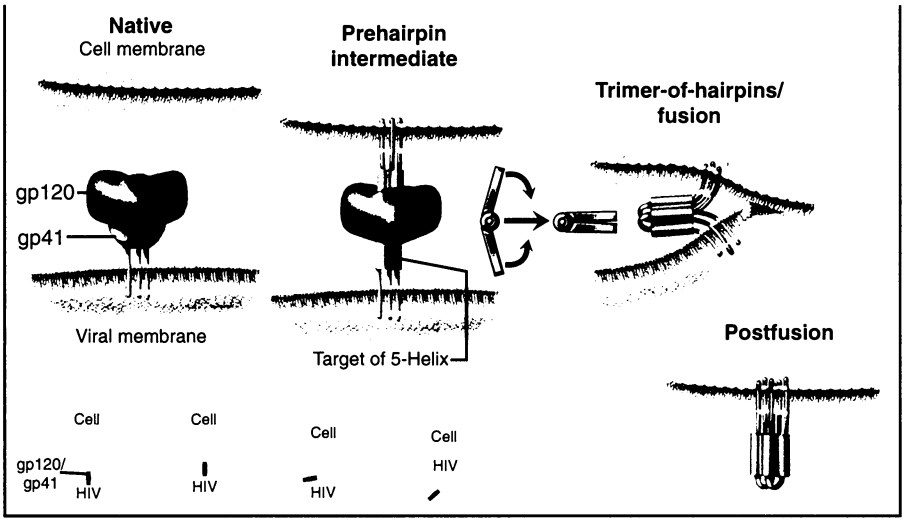
quickly replenish another estuary's stock that has been overfished," he says. Similarly, designers of protected reserves—often touted as nurseries that will supply fish to areas where fishing is allowed—may have to reshape plans. "Putting a reserve in one estuary may not do a lot of good" for another area's stocks, Thorrold says.

Although the study's policy impacts may not be felt for years, researchers say it is another sign of the otolith's growing value to scientists. European researchers, for instance, have recently launched a multimillion-dollar effort to use otolith signatures to track cod and other economically important fish. Steven Campana, a biologist at the Bedford Institute of Oceanography in Dartmouth, Nova Scotia, says otoliths "give you some very precise information not available from other kinds of studies." –DAVID MALAKOFF



Interference. A new compound, 5-Helix, stops HIV from fusing its membrane with a host cell's.

AIDS RESEARCH

HIV Inhibitor Blocks Virus From Cell

HIV, the virus that seemed invincible in the early days of the AIDS epidemic, has yielded ground to drugs that block its replication. But some strains of the wily virus have developed resistance to current drugs, and not all patients respond well to today's cocktail treatment. Searching for alternatives, researchers in the past several years have focused on another of the virus's vulnerable spots: the mechanism that snaps the virus into place against a host cell, allowing it to enter. Now, a team of researchers reports a new way to gum up that mechanism and prevent HIV's envelope from melding with a host cell membrane. They've designed a molecule that, in cell culture at least, prevents HIV from infecting cells.

"One wants to continue to identify new targets to attack HIV and add to the combination regime," says structural biologist Peter Kim of the Whitehead Institute for Biomedical Research at the Massachusetts Institute of Technology in Cambridge, whose team designed the molecule.

In the early 1990s Kim, recently tapped to head research and development at Merck Research Laboratories worldwide, and other research teams figured out how influenza infiltrates host cells. Many other viruses, including HIV, use a similar trick. The attack begins when HIV encounters a CD4 receptor on a T cell. This triggers a protein called gp41 that's anchored to the surface of the virus. The gp41 protein shoots out a harpoonlike projection that pierces the T cell's membrane. Then the two ends of the stretched-out gp41 protein snap together, pulling the virus's envelope and the cell membrane together. They fuse and allow the virus to penetrate the T cell.

Once this harpoonlike mechanism was understood, researchers began looking for wrenches to throw in the works. They've found two, and this week, in a paper published online today by *Science* (www.scienceexpress.org), Kim's group reports designing a third.

Before gp41 snaps the two membranes together, it's elongated in an intermediate formation. The two arms of the protein, called the C-terminal (anchored to the virus) and the N-terminal (hooked into the T cell) regions, are exposed. Drugs that bind to either end prevent the extended protein's two arms from clicking together into the final structure. Compounds that grab hold of the N-terminal region are currently in clinical trials, where they've been shown to reduce the viral load in people infected with HIV. Now Kim's team has designed a compound that binds to the C-terminal region.

The new molecule, dubbed 5-Helix, is the product of a "very clever, rational drug design," says HIV researcher John Moore of Cornell's Weill Medical College in New York City. The compound closely mimics the final structure that gp41 assumes when it fuses the viral and cellular membranes. That conformation contains six interconnected coils that fold together to look like a cluster of three hairpins. 5-Helix has five of the six coils, and it desperately wants another coil to fill in the gap. It does so by binding to the C-terminal end of the stretched-out gp41 much more effectively than the N-terminal end of the protein, thus preventing gp41 from folding together.

"The issue now," says Moore, "is not, 'Does [such a compound] work in vitro?,' but 'Can you translate it to in vivo?' " If 5-Helix or a related compound does work in humans, it probably won't dominate the market, he says. The protein would be digested if taken orally and so would have to be injected, limiting its appeal. But such a compound could help people who don't respond to other drugs.

Although he admits it's a long shot, Kim thinks 5-Helix might also serve as the basis for a new AIDS vaccine—ultimately, the only hope for curtailing the worldwide epidemic. The linear sequence of amino acids that make up gp41 varies a lot among different HIV strains, so antibodies against the unfolded protein wouldn't protect very efficiently. But the surfaces of the coiled protein that are exposed just before gp41 snaps into place are highly conserved—that part of the protein looks similar in all HIV clades. And that, says Kim, suggests that antibodies to 5-Helix, which displays some of the same coiled fragments of protein as gp41, might also attack the virus.

Robert Lamb, a virologist at Northwestern University in Evanston, Illinois, says that using 5-Helix as the basis for an AIDS vaccine is an "exciting possibility" and worth trying. Conceptually, he says, the same sort of strategy would also apply to other viruses, including Ebola, that use a similar harpoon-protein mechanism to fuse their membranes with a host's.

–LAURA HELMUTH

PALEONTOLOGY

Mammoth Hunters Put Hopes on Ice

CAMBRIDGE, U.K.—In an anticlimactic ending to last year's TV special, a block of permanently frozen ground hewn from the Siberian tundra appears to contain only scattered remains of a woolly mammoth. But researchers say that the team's brute-force method of hauling remains to a lab for study while they are still frozen holds promise for more-intact

ILLUSTRATION: CAMERON SLAYDEN