



A dolphin's demise

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Indians wary of nuclear pact

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SCIENTIFIC PUBLISHING

A Scientist's Nightmare: Software Problem Leads to Five Retractions

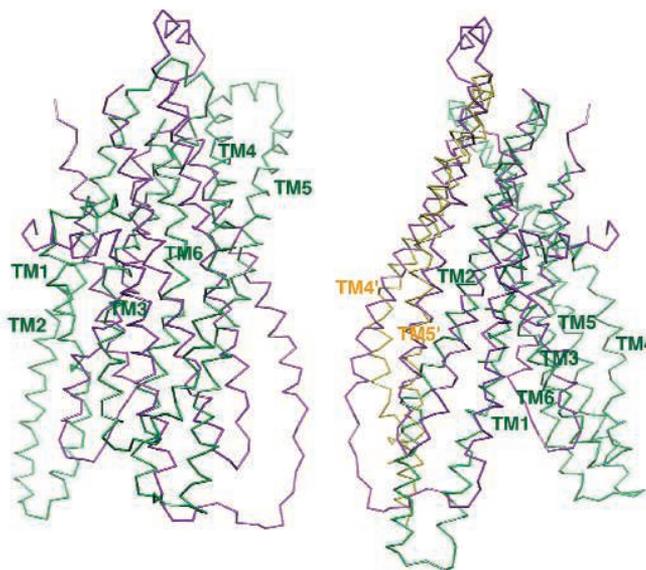
Until recently, Geoffrey Chang's career was on a trajectory most young scientists only dream about. In 1999, at the age of 28, the protein crystallographer landed a faculty position at the prestigious Scripps Research Institute in San Diego, California. The next year, in a ceremony at the White House, Chang received a Presidential Early Career Award for Scientists and Engineers, the country's highest honor for young researchers. His lab generated a stream of high-profile papers detailing the molecular structures of important proteins embedded in cell membranes.

Then the dream turned into a nightmare. In September, Swiss researchers published a paper in *Nature* that cast serious doubt on a protein structure Chang's group had described in a 2001 *Science* paper. When he investigated, Chang was horrified to discover that a homemade data-analysis program had flipped two columns of data, inverting the electron-density map from which his team had derived the final protein structure. Unfortunately, his group had used the program to analyze data for other proteins. As a result, on page 1875, Chang and his colleagues retract three *Science* papers and report that two papers in other journals also contain erroneous structures.

"I've been devastated," Chang says. "I hope people will understand that it was a mistake, and I'm very sorry for it." Other researchers don't doubt that the error was unintentional, and although some say it has cost them time and effort, many praise Chang for setting the record straight promptly and forthrightly. "I'm very pleased he's done this because there has been some confusion" about the original structures, says Christopher Higgins, a biochemist at Imperial College London. "Now the field can really move forward."

The most influential of Chang's retracted publications, other researchers say, was the

2001 *Science* paper, which described the structure of a protein called MsbA, isolated from the bacterium *Escherichia coli*. MsbA belongs to a huge and ancient family of molecules that use energy from adenosine triphosphate to transport molecules across cell membranes. These so-called ABC transporters perform many



Flipping fiasco. The structures of MsbA (purple) and Sav1866 (green) overlap little (left) until MsbA is inverted (right).

essential biological duties and are of great clinical interest because of their roles in drug resistance. Some pump antibiotics out of bacterial cells, for example; others clear chemotherapy drugs from cancer cells. Chang's MsbA structure was the first molecular portrait of an entire ABC transporter, and many researchers saw it as a major contribution toward figuring out how these crucial proteins do their jobs. That paper alone has been cited by 364 publications, according to Google Scholar.

Two subsequent papers, both now being retracted, describe the structure of MsbA from other bacteria, *Vibrio cholera* (published in *Molecular Biology* in 2003) and *Salmonella typhimurium* (published in *Science* in 2005). The other retractions, a 2004 paper in the *Proceedings of the National Academy of*

Sciences and a 2005 *Science* paper, described EmrE, a different type of transporter protein.

Crystallizing and obtaining structures of five membrane proteins in just over 5 years was an incredible feat, says Chang's former postdoc adviser Douglas Rees of the California Institute of Technology in Pasadena. Such proteins are a challenge for crystallographers because they are large, unwieldy, and notoriously difficult to coax into the crystals needed for x-ray crystallography. Rees says determination was at the root of Chang's success: "He has an incredible drive and work ethic. He really pushed the field in the sense of getting things to crystallize that no one else had been able to do." Chang's data are good, Rees says, but the faulty software threw everything off.

Ironically, another former postdoc in Rees's lab, Kaspar Locher, exposed the mistake. In the 14 September issue of *Nature*, Locher, now at the Swiss Federal Institute of Technology in Zurich, described the structure of an ABC transporter called Sav1866 from *Staphylococcus aureus*. The structure was dramatically—and unexpectedly—different from that of MsbA. After pulling up Sav1866 and Chang's MsbA from *S. typhimurium* on a computer screen, Locher says he realized in minutes that the MsbA structure was inverted. Interpreting the "hand" of a molecule is always a challenge for crystallographers,

Locher notes, and many mistakes can lead to an incorrect mirror-image structure. Getting the wrong hand is "in the category of monumental blunders," Locher says.

On reading the *Nature* paper, Chang quickly traced the mix-up back to the analysis program, which he says he inherited from another lab. Locher suspects that Chang would have caught the mistake if he'd taken more time to obtain a higher resolution structure. "I think he was under immense pressure to get the first structure, and that's what made him push the limits of his data," he says. Others suggest that Chang might have caught the problem if he'd paid closer attention to biochemical findings that didn't jibe well with the MsbA structure. "When the first structure came out, we and others said, 'We really ▶



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don't quite believe this is right," says Higgins. "It was inconsistent with a lot of things."

The ramifications of the software snafu extend beyond Chang's lab. Marwan Al-Shawi, a biochemist at the University of Virginia in Charlottesville, says he's now holding on to several manuscripts he was about to submit. Al-Shawi has been using Chang's MsbA structure to build computer models of an ABC transporter involved in human cancer drug resistance. David Clarke of the University of

Toronto in Canada says his team had a hard time persuading journals to accept their biochemical studies that contradicted Chang's MsbA structure. Clarke also served on grant panels on which he says Chang's work was influential. "Those applications providing preliminary results that were not in agreement with the retracted papers were given a rough time," he says.

At Scripps, colleagues are standing behind the young researcher. "He's doing some really

beautiful work, and this is just an absolute disaster that befell him," says Chang's department chair, Peter Wright. "I'm quite convinced he'll come out of it, and he'll go on to do great things." Chang meanwhile has been reanalyzing his original data and expects to submit papers on the corrected structures soon. The new structures "make a ton of sense" biologically, he says. "A lot of things we couldn't figure out before are very clear."

—GREG MILLER

U.S. OCEAN POLICY

Fisheries Bill Gives Bigger Role to Science—But No Money

New rules governing the U.S. fishing industry offer scientists much greater power to keep marine populations from collapsing. But although advocates for marine conservation are celebrating the changes in a 30-year-old law that Congress adopted earlier this month, they are disappointed that the focus remains on managing individual species rather than ecosystems. And they worry that the responsible agency—the National Oceanic and Atmospheric Administration (NOAA)—may not have enough money to implement many of the provisions in the revised law.

The bill, a reauthorization of the 1976 Magnuson-Stevens Fishery Conservation and Management Act, requires the eight regional fishery councils to follow the advice of their scientific committees, prevents continued overfishing, and calls for more research by NOAA on deep-sea corals. "We're very excited," says Steven Murawski, chief science adviser for NOAA Fisheries. The bill awaits the president's signature after legislators gave their approval in the final hours of the 109th Congress. Yet that same Congress failed to complete work on the 2007 budgets of most agencies, including NOAA's (*Science*, 15 December, p. 1666), raising doubts about how the agency will manage existing operations, let alone take on new ones. "Where is the money for all this?" wonders John Ogden, director of the Florida Institute of Oceanography in Tampa.

The new version is the first update in a decade. Environmentalists and researchers had feared that the revision might weaken the current law, because the House Resources Committee had proposed abolishing a rule requir-

ing depleted stocks to be rebuilt within 10 years. But the deadline remains in place. "I'm very gratified," says Carl Safina of Stony Brook University in New York.

The bill breaks new ground by telling councils to end overfishing within 2 years after a species is deemed overfished. The current law was vague, and some councils allowed continued overfishing on the way to a rebuilding target, a practice that has made recovery harder for some species. "It's a significant improvement," says Gerald Leape of the National Environmental Trust in Washington, D.C.



Catch phrases. New fishery legislation is intended to stop overfishing of species whose populations have crashed, such as these cod in Gloucester, Massachusetts.

In addition, councils will now be required to set catch limits and to follow scientific advice, two practices that are voluntary under the current law. But a Senate provision for penalties when fishers end up exceeding an annual limit was removed before final passage, and even setting all the catch limits is in question. The six NOAA fishery science centers that crank out most of the limits will require more resources, as well as more data from observers and NOAA survey vessels. This workload "is certainly a challenge," admits Murawski, referring to a pending 2007 spending plan that could shrink NOAA Fisheries' budget from \$667 million to \$541 million.

The same budget uncertainties imperil several other directives. A registry for recreational marine fishing and grant licenses would allow the agency to better estimate the impact of non-commercial catches (*Science*, 24 September 2004, p. 1958). But Murawski warns that "it's not going to be a cheap program." Another mandate would create a research program to map and monitor deep-sea corals.

Many scientists are deeply disappointed that the bill does not require an ecosystem-based approach to managing fisheries, as was recommended by several recent commissions. Instead, the bill continues the current species-by-species approach, while requesting a 180-day NOAA study of the state of the science of ecosystem management. It also authorizes the agency to begin funding pilot programs based on the study but doesn't set a level. "It's a major missed opportunity," says Ellen Pikitch of the University of Miami's Pew Institute for Ocean Science in Florida.

—ERIK STOKSTAD