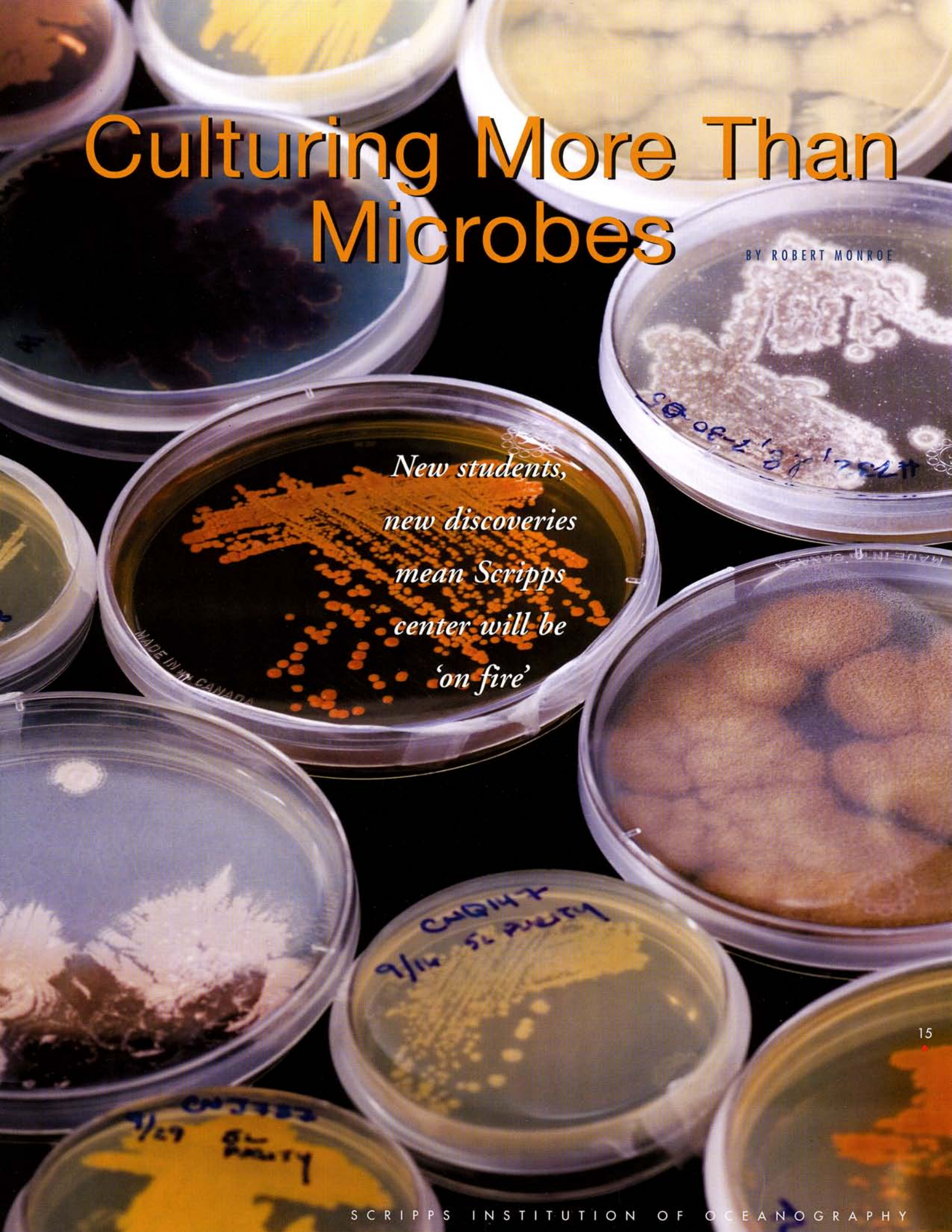
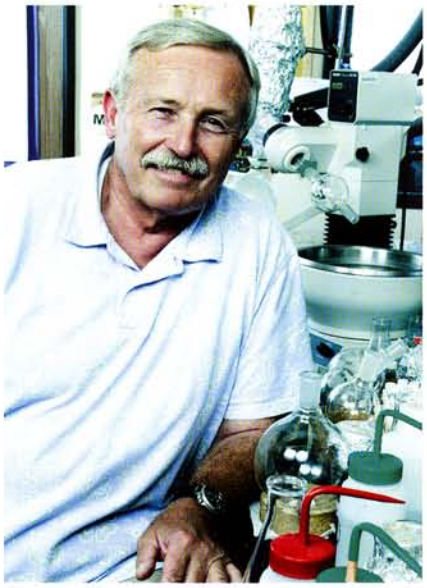
Culturing More Than Microbes

BY ROBERT MONROE

New students, new discoveries mean Scripps center will be 'on fire'





WILLIAM FENICAL EXTENDS THE GAP between his thumb and forefinger to the thickness of the San Diego phone book.

The director of the Center for Marine Biotechnology and Biomedicine (CMBB) at Scripps Institution of Oceanography does this while describing the application he and colleagues filled out last year to win one of the National Institutes of Health's (NIH) most coveted and selective grants. The prize at the end of the process made the writer's cramp worth it. The $616,000 training grant to be distributed over five years will fund the education of four students in one of biotechnology's most rapidly emerging areas of study.

"The NIH wants to see us train the next generation of marine biomedical researchers," Fenical said.

But like the students yet to set foot on campus, things not readily seen are marking the progress of CMBB and the field of marine biomedicine itself. In the laboratory of microbiologist Paul Jensen grow batches of "*Marinispora*" isolates. This genus of bacterium found in seafloor mud is the latest CMBB find to exhibit potential as a source of antibiotic and anticancer compounds. Along with that of *Salinispora* (*"Salinispora" on page 7*), its development could not happen fast enough.

The two genera are members of the bacterial group actinomycete, the source of 70 percent of the world's antibiotics. Until the 1980s, pharmaceutical companies had been able to depend on finding new actinomycete strains on land to counter the emergence of drug-resistant forms of infectious bacteria. In 1987, the year the last genus of terrestrial actinomycete was found, the game of leapfrog stopped—with pathogens in the lead.

At that time, marine natural products chemistry was a field in its infancy. Fenical and the late John Faulkner, another Scripps researcher, had spent the previous decade collecting organisms like corals and sponges—creatures that depend on chemistry for survival—to understand and possibly exploit the compounds they produce.

Even before CMBB was founded in 1997, the researchers had already scored one success. Fenical discovered that the common Caribbean sea whip contains pseudopterosin, which is now the basis of a skin cream effective against conditions such as contact dermatitis. A decade after reaching the market, the cream remains CMBB's sole royalty-producing find.

KEY TERM

GENOME: An organism's entire set of hereditary information, mostly packaged in the form of genes within cells. Scientists estimate that the human genome has 20,000–30,000 genes.

KEY TERM

PHYLOGENOMICS: Field of study that uses genetic information to taxonomically classify organisms.

Fenical predicts, however, that this will change in a new era of genomic discovery in which bioengineered proprietary bacterial compounds will be used in fields ranging from medicine to cleanup of toxic wastes.

"It's more than finding a bug out there," he said. "We can find whole new genomes that can be used in industrial activities. We're going to be on fire around here with respect to new intellectual properties and discoveries."

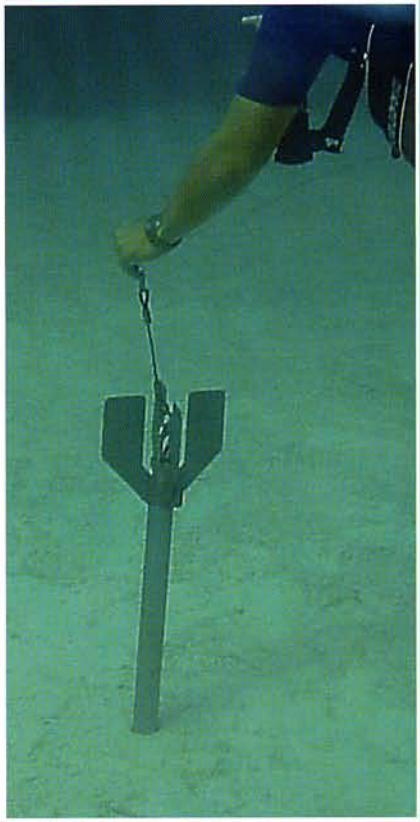
The discovery of ocean-dwelling actinomycetes could put medicine one large step ahead of infectious agents as well as cancers. Fenical's group has already found 15 actinomycete genera in marine sediments, with as many as 1,000 species in each, and an untold number of potentially therapeutic compounds.

The first step is to identify the microbes. A companion to the discovery of interesting compounds is the use of genomics to accurately identify and classify organisms taxonomically, a field known as phylogenomics. It is one of several specialties that students in the new training program will have available to them.

Is there even more out there? Fenical and fellow CMBB researchers

CMBB researchers William Fenical (right) and Paul Jensen see medicinal promise in the seafloor bacteria "Marinispora," isolates of which are grown in Scripps laboratories (above left).

On an expedition to the Bahamas to collect marine actinomycetes with possible antibiotic properties, Jensen gathers seaweed samples (top). Researchers plunge a sediment corer into seafloor sands to retrieve samples (middle right). Others, like staff research associate Chris Kauffman (bottom right), collect mud samples by hand.



KEY TERM

RIBONUCLEIC ACID (RNA): A molecule responsible for conducting protein synthesis in cells and other key functions. Different types include messenger RNA (mRNA) and ribosomal RNA (rRNA).

Paul Jensen and William Gerwick have research cruises scheduled to find out. Though "*Marinispora*" was found in waters only 50 meters (164 feet) deep, nearly visible from Fenical's office, he plans to search for microbes in the South Pacific at depths up to 3,000 meters (9,843 feet). Gerwick is sifting through marine sands in places such as Papua New Guinea and Panama in search of cyanobacteria, a group of algalike microbes that could bear a number of therapeutic compounds.

Fenical may be one of the few program leaders who will not have to put funding at the top of his needs list in an era of intense competition for federal grants. In fact, the only hindrance to this explosion of discovery may be time. Though global warming may take centuries to reach the depths he is plumbing to find interesting microbes, pollution in the ocean is likely changing its chemistry now. Even slight changes are enough to alter microorganisms, causing them to disappear, go dormant, or evolve into chemically different creatures. The additional marine biomedicine specialists CMBB hopes to mint in coming years will not want for work.

"We've got a whole lot of needs for the next century," Fenical said. "It's going to take 50 years of work to exploit sediments, but the question is, are we going to have 50 years or is something catastrophic going to happen first?"

"SAL-A" IS ON ITS WAY

AN ANTICANCER COMPOUND derived from a marine microbe first identified at Scripps could be ready for human trials by 2006.

But as Scripps partner Nereus Pharmaceuticals wraps up preclinical studies on Salinosporamide-A, scientists at the Center for Marine Biotechnology and Biomedicine (CMBB) are ramping up their own search for the next big compound to come from *Salinispora*, an ocean-dwelling bacterium that they discovered and named.

Through the use of genomics, the researchers are supplanting a needle-in-the-haystack search through the world's ocean for potentially beneficial compounds like the compound they refer to as "Sal-A."

"This discovery has the potential to change the way natural products are found," said Paul Jensen, the CMBB microbiologist who first cultured members of the genus *Salinispora* from sediments collected from the seafloor.

Traditionally, enthusiasm among researchers about marine natural products discovery has been tempered by the knowledge that each potential antibiotic or cancer therapy would need years or even decades of development before becoming useful.

But having an organism's genome as a reference could accelerate the process by allowing researchers to better estimate the likelihood that the creature makes compounds of potential medical value known as secondary metabolites.

"It gives us a road map," said Brad Moore, who recently joined CMBB after collaborating with Jensen and CMBB Director William Fenical as a University of Arizona researcher. "Now we can ask questions like 'What else can *Salinispora* do?'"

Jensen and Moore succeeded this summer in adding the genomes of two *Salinispora* species, S. *tropica* and S. *arenicola*, to the list of those being sequenced by the U.S. Department of Energy's Joint Genome Institute. The sequences, which will be completed in 2006, will help them find the biosynthetic pathway by which the microbes manufacture Sal-A. Such knowledge could help refine the drug by allowing researchers to distinguish the important coding material in the bacteria's genome from its "junk" DNA.

KEY TERM

NUCLEOTIDE: A unit of DNA or RNA consisting of a base, molecule of sugar, and a molecule of phosphate.

Even in its current state, the drug known as Nereus compound NPI-0052 has impressed its developers. Kobi Sethna, president and chief executive officer of Nereus Pharmaceuticals, reported that in preclinical trials NPI-0052 is active against multiple myeloma, a particularly recalcitrant form of cancer that is resistant to other chemotherapeutic agents and certain tumors. Sethna stressed, however, that such results are not predictive of results in humans.

If Sal-A makes it to the marketplace, it would only be the second proteozome inhibitor available to cancer patients. The compound works by inhibiting the machinery that degrades proteins within the cell and thus helps restore the cellular activities that run amok in cancer, Jensen said.

Salinispora belongs to a biomedically important group of bacteria, the actinomycetes, and has come a long way since the early 1990s when Jensen first collected these bacteria (see "Microbial Warriors," *Explorations*, Summer 2002). Land-dwelling actinomycetes are the source of the majority of the world's antibiotics, and most researchers had thought that these bacteria could not survive in the ocean environment. CMBB researchers have shown that not only does *Salinispora* require seawater for growth, but these actinomycetes are unique to the ocean and therefore represent an entirely new resource for drug discovery.

In the laboratory, *Salinispora* microbes have demonstrated potent antibiotic and antifungal properties as well. Fenical said that CMBB is currently exploring these bacteria as a source of antibiotics to treat emerging drug-resistant bacterial infections, and he hopes that these bacteria can lead to new cures for infectious diseases as well as cancer.