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Drugs from the deep

Is the cure for cancer lurking beneath the waves? **Emma Marris** plunges into the chemistry of marine natural products.

Walk downhill from the University of California, San Diego, towards the ocean, and you'll see bungalows draped in bougainvillea, tanned youths unloading surfboards from station wagons, and at the bottom, William Fenical's lab at the Scripps Institute of Oceanography. The chemist has white sand and palm trees both on his screensaver and outside his window. And beyond them — the sea.

Fenical and a global group of like-minded scientists believe that the sea hides a mermaid's grotto of useful chemicals. And they have been diving for corals, grinding up sponges, fermenting microbes, and poking around inside cells for decades in an effort to find them. Chemicals from these organisms — natural products — can have pharmaceutical potential. But before scientists could deliver any useful natural products, the drug industry largely lost interest in the field, slowing its growth. Fenical and others now say that the problems of the past have mostly been solved. And they may no longer need the drug industry's support.

Many of the best-known drugs are extracted from living things. A famous example is the actinomycetes, soil microbes so good at producing antibiotics that in the 1950s and beyond, pharmaceutical companies sent people tramping all over the globe to collect dirt. Most of our antibiotics still come from *Penicillium* mould or soil microbes. "Antibiotics were an astounding discovery," says Fenical from his seaside office, "without question the most important medical discovery in history."

The ocean covers two-thirds of Earth, and many branches of life — such as the group containing jellyfish and corals — are exclusively marine. Yet until relatively recently, chemists were confirmed landlubbers. "We are not marine organisms," says Fenical, "so until about 1970, no one even thought of the ocean. It was left as a deep secret." Fenical, and a few others, were the first to get their toes wet. "It seemed ridiculous to me that the ocean — with such a vast habitat — had escaped anyone's notice," he says. "But there are good reasons. People fear the ocean; it has been considered a very hostile, inhospitable place."

Thirty years later the field is having a mini renaissance[1], with strong research labs around the globe, including China. But natural-products chemists have struggled to convince pharmaceutical companies to share their enthusiasm. Most drug companies dismantled their natural-products research units in the 1990s, when combinatorial chemistry was heralded as the next wave of drug discovery. At that time, there were no drugs based on marine natural products on the shelves. Today, there is one: Prialt, a pain reliever derived from the hunting venom of the cone snail (see 'Marine medicines'). "Not to say that there aren't powerful leads in nature," says Kate Robins, a spokeswoman for Pfizer in New London, Connecticut, which closed its natural-products programme in the 1990s, "but it has been our experience that promising leads come faster and more frequently out of combinatorial chemistry and synthetic techniques."

Backwater

Fenical bemoans what he perceives as the drug companies' lack of vision. "We have done so much to prove the rich resource of the ocean. The big pharmas are apathetic and uninterested. They are risk averse." This irks him, he says, not just for professional reasons. "The fact is that no really new antibiotic has come out since the late 1980s. We are on a very dangerous collision course with a plague."

Marine natural products are attractive sources for new antibiotics because they are mostly secondary metabolites. That is, they are not essential to an organism's growth and development, but are compounds that do something else, such as deter predators — and could be re-engineered to aid our fight against infectious disease.

But infectious diseases are unfashionable with many drug companies, and the legal uncertainties around bioprospecting for natural products hasn't helped its cause. Another problem is scarcity. A compound made in tiny quantities by a sponge that lives hundreds of metres down, for example, poses challenges to traditional drug testing and development.

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SCRIPPS

So scientists are now working out how organisms make natural products. To their surprise, many compounds are generated by an associated microbe, rather than the organism itself. This means they can either grow the microbes alone in flasks, or they can identify the microbial genes responsible for making the compound, and insert them into an organism researchers find easier to work with, such as *Escherichia coli*. In addition, more and more natural products are being made from scratch as synthetic chemists get better at their art[2].

David Newman, director of the natural-products division at the US National Cancer Institute in Bethesda, Maryland, sums it up: "In the 1980s, the field was hyped, but we had not solved the supply problem. By the end of the 1990s, what came together was molecular biology, which allowed you to go looking for the producing genes, the ability to grow microbes, and synthetic chemists who could either do total synthesis or work from a structure."

Fenical's research followed a similar pattern. He previously studied invertebrates on coral reefs, where low nutrient levels create competition for food and may favour the evolution of toxins. Resilience, a skin cream made by Estée Lauder (selling for $50 an ounce), contains an

PHARMAMAR

Treasure hunters: divers from biotech company PharmaMar collect marine life in the search for drugs.

Marine medicines

PHARMAMAR

Ecteinascidia turbinata, a Caribbean and Mediterranean sea squirt, makes a compound that PharmaMar has brand-named Yondelis. The firm is awaiting marketing approval from the European Medicines Agency for this antitumour compound for soft-tissue sarcomas. Trials are also under way for ovarian cancer.

PHARMAMAR

Aplidium albicans. Another anticancer drug has been isolated from this sea squirt. PharmaMar calls it Aplidin and is testing its efficacy.

V. STEGER/SPL

Conus magus. This cone snail paralyses its prey using a poison-tipped barb (right). The poison is a painkiller many times more potent than morphine, and is now on the market as Prialt.

anti-inflammatory that Fenical found in soft corals during those years. But he eventually left the invertebrate field: "It was almost impossible to develop a drug, because we could not provide lots and lots of it."

Instead, he turned to microorganisms. With patience and luck, marine microbes are fermentable — they can be grown in large flasks, if the right mix of nutrients is provided.

The lab made its first big discovery in deep-ocean sediment. There the team found lots of actinomycete species, despite the received wisdom that there were none in the sea. The team named the first genus of these *Salinospora*[3]. And from one of them, in 2003, came salinosporamide A, a compound that binds extremely selectively to the proteasome in tumour cells[4]. It is now in clinical trials for multiple myeloma, a cancer of the blood.

Recently, the lab has discovered another new genus, *Marinispora*, which produces compounds with promising antibiotic and anticancer properties[5]. Fenical says the limiting factor now is time and the logistics of getting samples from deep-sea mud.

Working with Scripps technicians, Fenical has devised probes that fall to the sea floor, drive a corer into the mud, release weights and rise to the surface. The samplers take 45 minutes to fall 6,000–7,000 metres to the ocean floor and return — if they come back at all.

Technical advances are changing the field in other ways. Studies using nuclear magnetic resonance imaging need only tiny quantities of compounds, making the work easier and more ecologically sound, says John Blunt, a chemist at the University of Canterbury in Christchurch, New Zealand. "The other area that is developing is assays," says Blunt. "We used to use simple cytotoxic and antibiotic assays. Now specific enzymes are being used." So instead of finding out whether a compound has any biological activity, researchers can find out whether it binds to a particular target.

Find a niche

Whether big drug firms renew their interest in marine products may not matter — small institutional labs or companies can take them on. "Many of our big-pharma competitors who have moved out of this effort are getting back in through collaborations with smaller companies," says Guy Carter, vice-president of research at drug firm Wyeth in Pearl River, New York, which, unlike most drug companies, retains a natural-products unit employing 50 people.

For 20 years, the Madrid-based biotech company PharmaMar has sought cancer drugs in marine natural products. It investigates compounds found by academics, and has its own explorers. It now has a library of more than 40,000 compounds, six of which are in clinical trials. Fenical helped found a spin-off, called Nereus, after the Greek god of the Mediterranean. The eight-year-old company has two compounds in preclinical trials for cancer.

Despite the scarcity of new drugs on the market, marine drug discovery still attracts newcomers. Robert Jacobs, a marine natural-products biologist at the University of California, Santa Barbara, has a tip for new recruits. "When we started out in the early 1970s, just about anything you picked up, you'd find something new. These days we recommend that people think ecologically." That is — find a niche where secondary metabolites are likely to be abundant and focus on it. In the vastness of the oceans, there's still much to explore. ■

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