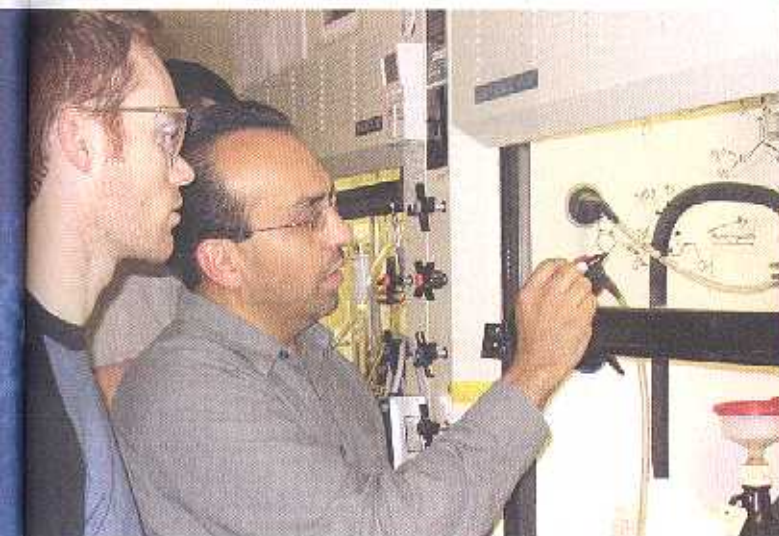


Drug Discovery Center studies marine organisms for new medicines and biological insights.

COMBINING NATURE for Cures

From neurotoxins to state-of-the-art cancer drugs, nature produces a stunning diversity of organic molecules. Many of these natural products have useful biological effects, and their unique architectures continue to inspire many of the newest drugs on pharmacy shelves.

A new team of four scientists, including Dr. Daniel Romo and Dr. Coran Watanabe from Texas A&M's Department of Chemistry, aims to put newly discovered natural products to work, both as leads for new medicines and as tools for studying the fundamental operations of cells. The four scientists constitute the Natural Products-Based Drug Discovery Center at Texas A&M, established in July 2004. The center is starting out at a time when major pharmaceutical companies, disappointed by lackluster results in the field of combinatorial chemistry, have shown resurgent interest in natural products, says Romo.



Dr. Daniel Romo discusses latest synthesis results of post-doctoral co-worker, Dr. Paul Dransfield, who is developing a synthetic strategy to the antimicrobial, marine natural product, axinellamine D.2.



Dr. Coran Watanabe helps graduate student Scott Angell, examine marine natural product extracts for anti-cancer activity.

The field of natural products-based drug discovery crosses many disciplinary boundaries, but Watanabe says it is hard for one scientist to be good at everything. The research center combines the talents of different scientists, she says, and establishes a magnet for funding and other resources. Joining Texas A&M's Romo and Watanabe in the cross-country collaboration are Dr. Jun O. Liu of Johns Hopkins University and Dr. Jeffrey Smith of the Burnham Institute in California.

However, the road from sponge to marketable drug is uphill. Just isolating a natural product and determining its chemical structure is a challenge. In the case of PatA, a kilogram of sponge yields about 17 milligrams of natural product, equivalent to a few grains of sand. Working with limited quantities from nature, researchers scrutinize the natural product for potentially useful biological activity and determine its chemical structure. Then, synthetic chemists

“It’s amazing that these complex molecules are produced by sponges or symbiotic bacteria and also show potential for treating human ailments.”

The center's beginnings can be traced to a species of sponge in the chilly waters off New Zealand's coast. The sponges produce small quantities of the natural product pateamine A (PatA). PatA is an immunosuppressant, so it could block the body's immune system from mounting an assault on foreign organs like a transplanted liver or heart. PatA has also proven to be 2,000 times more toxic to tumor cells than to healthy cells.

Romo was initially attracted by PatA's unique structure and its immunosuppressive activity. “It's amazing that these complex molecules are produced by sponges or symbiotic bacteria and also show potential for treating human ailments,” he says. “These organisms, endowed with complex biosynthetic machinery, are extremely clever at synthesizing potent protein inhibitors...arguably the world's best synthetic chemists!”

like Romo build the natural product piece by piece in a laboratory.

Romo's 24-step recipe for PatA took three years of trial-and-error experiments to develop. His research group has also synthesized 16 derivatives of PatA. One of these derivatives can be synthesized in 10 fewer steps than PatA, and it exhibits similar immunosuppressive and anticancer potency properties as well as improved stability. That derivative has been forwarded to a pharmaceutical company in the Boston area for clinical trials, though it could be 10 years before it could appear on drugstore shelves. Even if the derivative doesn't pass muster in clinical trials, Romo, Watanabe, and their collaborators will be able to use PatA and its derivatives to study which proteins in the body are involved in the human immune response and also uncover new signaling pathways involved in cancer. 