Behind the Scenes in Pharmacognosy

"Peptides in Action"

by Amy Keller

In the Drs. John W. Daly and Richard E. Moore honorary issue of the *Journal of Natural Products*, the article entitled "Functional Characterization of the Cyclomarin/Cyclomarazine Prenyltransferase CymD Directs the Biosynthesis of Unnatural Cyclic Peptides" by Andrew W. Schultz, Chad A. Lewis, Michael R. Luzung, Phil S. Baran and Bradley S. Moore appeared. The *Newsletter* interviewed ASP Member and corresponding author Dr. Moore, who generously told us more about the lab and research. This article is dedicated to Dr. Moore's father, the late Dr. Richard Moore.

How did you become interested in bioactive compounds of marine origin?

I became very interested in marine chemistry growing up in Hawai'i, where my family spent most of our free time at the beach. Hence, I grew up in and around water and became fascinated with marine life. And since I gravitated towards chemistry as a high schooler, it seemed a natural fit to explore the chemical language of marine life.

Plus, it did not hurt that my father, the late ASP member Dr. Richard E. Moore, to whom this research article is dedicated, was one of the pioneers in the field. I had the opportunity to work in his laboratory at the University of Hawai'i as an undergraduate, where I was introduced to natural product chemistry. My interests then drifted towards how these complex natural organic molecules were biosynthesized, which led me away from marine systems in my graduate and post-graduate training until I returned to explore marine questions independently as a new investigator starting in 1997.

Who in your laboratory carried out the research?

This particular study was headed by Andrew Schultz, who is a talented fifth year graduate student in my lab looking to graduate later this year.

Could you provide a brief explanation of the work and results in your own words? In what way are the data in your paper new?

Drew discovered a couple years ago that the marine bacterial cyclic peptides cyclomarazine and cyclomarin are related di- and heptapeptides exclusively derived from the same nonribosomal peptide synthetase assembly line that detects a difference in oxidation of a common enzyme-bound dipeptide intermediate that leads to these two differently sized cyclic peptides.

The priming amino acid residue in both peptides is a reverse N-prenylated tryptophan that is unique amongst bacterial natural products. Due to the novelty of this amino acid residue, Drew explored its biosynthesis which, to our surprise, led to the dis-

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Moore Research Group at the Scripps Institution of Oceanography: Bradley Moore, Peter Bernhardt, Michael Wilson, Tobias Gulder, Andrew Schultz, Andrew Kale, Tatsufumi Okino (on sabbatical from Hokkaido University), Akimasa Miyanaga, Alexandra Roberts, Anna Lechner, Kaity Ryan, Taylor Stratton, Larissa Dirr, Elisha Fielding, Amy Lane, Alessandra Eustaquio (pictured from L to R). Missing: Roland Kersten and Kari Potter.

ANDREW SCHULTZ

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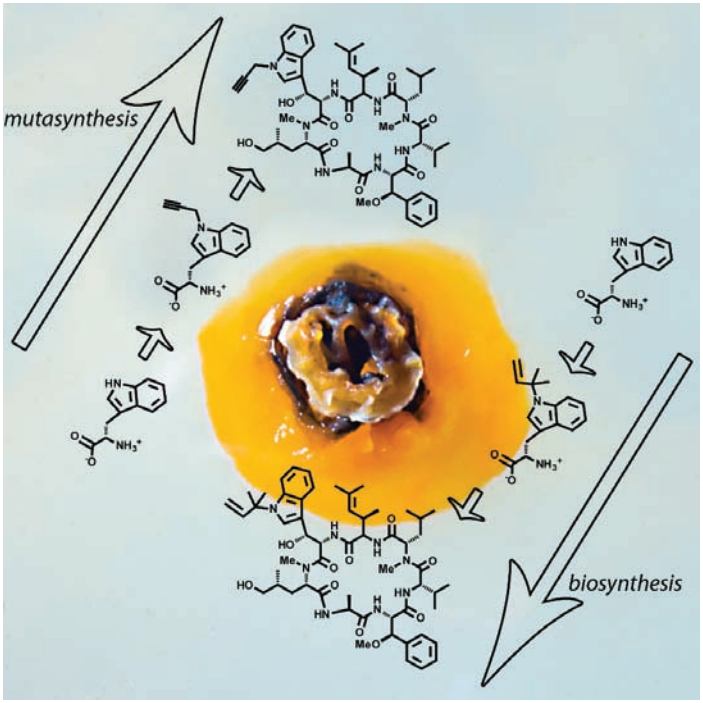

ANDREW SCHULTZ

The biosynthesis of the cyclic heptapeptide cyclomarin A in the marine actinomycete bacterium Salinispora arenicola *involves the preassembly of the nonproteinogenic amino acid residue N-(1,1-dimentyl-1-allyl)tryptophan by the action of the CymD prenyltransferase. Genetic inactivation of the cymD gene resulted in a mutant bacterium devoid of natural cyclomarin biosynthesis that facilitated the mutasynthesis of unnatural cyclomarin analogues from synthetic precursors such as N-(1-propargyl)tryptophan.*

covery of the prenylating enzyme CymD that prenylates tryptophan with dimethylallyl pyrophosphate prior to peptide assembly versus post peptide synthesis, our initial hypothesis! The early timing of prenylation was fortuitous as it allowed us a very convenient strategy to bioengineer new peptide analogues with altered N-alkyl tryptophan residues.

This is where we entered into a very fruitful collaboration with co-authors Dr. Phil Baran of neighboring The Scripps Research Institute (TSRI) and his postdocs Drs. Chad Lewis and Mike Luzung who developed a cleaver synthetic strategy to conveniently prepare tryptophan analogues. Drew genetically inactivated the CymD encoding gene that resulted in a mutant strain unable to produce the native cyclomarins and cyclomarazines. He could then rescue the wild-type phenotype by supplementing the mutatnt with the Baran lab's synthetic N-dimethylallyltryptophan as well as redirect biosynthesis to unnatural cyclic peptides by adding other N-substituted tryptophans such as the propargyl analogue that gave rise to the production of unnatural propargylated cyclic peptides. This approach combining the strengths of organic synthesis and biosynthesis nicely highlights their powerful synergy in generating focused natural product libraries that are difficult to produce by either approach alone.

What impact does this research have?
This research project extends our biosynthetic understanding of nonribosomal peptide synthetase modifying reactions and adds a new coupling enzyme to the bioengineer's toolbox for the combinatorial biosynthesis of designer molecules.

What is a favorite nonscientific activity of your lab?
Being at the Scripps Institution of Oceanography, which is located at one of the best beaches in Southern California; our favorite activities are ocean-related sports such as surfing, kayaking, and ocean swimming. Many of the students and postdocs have surfboards in their offices and can occasionally be found in the water considering their next experiment.

Each summer our lab hosts a beach party at Scripps for the UCSD marine natural product research groups. We've named the event the "Pier Swim" since we start off the gathering with a collegial swim around the Scripps Pier, where the point is to get everyone around in a safe and fun way. We then have a large barbeque feast and play lots of beach games. It's a fun way to unwind, build new friendships and even plan new joint group projects.

What is your lab's motto?
Work hard and play hard. I really have a very dedicated and talented research group who, importantly, know how to have a good time.

What is your greatest extravagance in the lab?
Our "greatest extravagance"... well, we work in a building located directly on a beautiful beach. What more can one ask for? So, whether or not you surf or swim, we all enjoy watching the daily surf action, the occasional whale sightings, and the beautiful sun sets from our laboratory and office windows. ■