The Scripps Research Institute

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Education News from The Scripps Research Institute

Chemistry Inspired by Nature, Research Driven by Passion

Few medications have greater name recognition than penicillin and morphine. Chances are good you're also familiar with acetylsalicyclic acid (aspirin) and pseudoephedrine (a decongestant widely sold under brand names like Sudafed). Names like paclitaxel (Taxol), Lipitor and Lovastatin may also ring a bell. While each of these drugs treats a different condition, all share one important trait: they were derived from or inspired by **natural products**, small molecules made by a plant, animal or other living organism found in nature.

So critical are these natural products to modern drug discovery, they constitute the primary focus for many biomedical research laboratories around the world, including several on both campuses of The Scripps Research Institute (TSRI).

Faculty members **Phil Baran** and **Ben Shen** are at the helm of two of these research groups, directing projects that aim to discover, understand, replicate and, in many cases, improve upon the chemical processes nature has evolved to build molecules of spectacular complexity with promise as treatments or cures for human disease.

"Natural products remain the best sources of drugs and drug leads," said Shen, professor and vice chair of the Department of Chemistry and director of the Natural Products Library Initiative on TSRI's Florida campus. "In particular, if you look at anti-cancer and anti-infective drugs, approximately 75% are either natural product-based, natural product-originated or natural product-inspired."

This impressive track record and potential for future discoveries is just part of why chemists like Shen and Baran chose to devote their careers to the study of natural products.

"What we both love about natural products is the biological activity and architectural beauty of the molecules," said Shen. "What I'm trying to do is learn from Mother Nature. We look first at how primitive forms of life like bacteria are making these molecules to understand how they are made so quickly and so efficiently. It's not whether or not we can make it — nature already made it, and made it using what seems like an effortless process. We try to understand the process and duplicate that process in the lab."

ROCKET SCIENCE

For Baran, a synthetic organic chemist, the challenge and excitement of constructing such complex molecules in the lab is a major source of motivation. He likens the process of natural products chemistry to NASA's missions to send astronauts into space.

"I think our mission is quite simply to go where no one has gone before and to bridge gaps in what chemistry should be doing but currently can't," said Baran, professor and Darlene Shiley Chair in the Department of Chemistry on TSRI's California campus. "We make complicated natural products for the same reason you build rockets. Building a rocket is important because of where it will take you. Making complicated natural products might look rather esoteric but in actuality it's a very application-oriented goal and one that fulfills two purposes: 1) you educate students to make them the chemical warriors, to really understand the chemistry, and 2) you can help people. The things that we invent are actually broadly useful to society at large."

By developing innovative techniques and employing advanced technologies, the Baran lab invents new ways of synthesizing (constructing) natural product-based molecules that serve as the foundation for tomorrow's medicines. The goal is to determine the optimal approach for producing large quantities of natural products as efficiently and with as few steps and materials as possible. By perfecting a laboratory-based strategy to synthesize these invaluable chemical compounds, society can benefit from the molecule without any impact on the organism that first produced it.

Research in the Shen lab also makes important contributions to this process. The lab studies how microorganisms naturally produce these chemical compounds (a process known as biosynthesis), yielding discoveries that can streamline the synthesis of these molecules in the lab or inspire new synthesis strategies altogether.

More than just studying the biosynthesis process and underlying machinery, Shen is working to engineer cells that produce these natural products in quantities large enough to research possible new drugs. It's a complex process called pathway engineering and it brings to bear a broad set of skills including chemistry, biochemistry and genetics. Creating an artificial cell that continuously produces large quantities of a natural product under mild conditions can

significantly reduce costs, simplify processes and increase sustainability.

BUILDING A BETTER LIBRARY

Efforts to discover or synthesize natural products are of little use if they're not available for study by the biologists and chemists searching for new therapeutics. To that end, Shen has been hard at work building a library.

It is fairly well known in biomedical research circles that TSRI's Florida campus is home to one of the most advanced high-throughput screening (HTS) facilities in the nation, combining robotics, state-of-the-art analytical technologies and a massive library of small molecules. (Small molecules are relatively lightweight organic compounds with the potential to regulate biological processes; most drugs on the market consist of small molecules.) The challenge is that, due to their complex structures and limited supply, natural products are woefully underrepresented in most small molecule libraries. The Natural Products Library Initiative (NPLI) aims to change this and meet the screening needs of biomedical researchers at TSRI and beyond.

By increasing the diversity of small molecules available to researchers screening against disease targets, and given the unparalleled drug discovery success rate of natural products, the prospects are bright for NPLI, opening doors to even more exciting breakthroughs in the future.

A PASSION FOR EDUCATION

Baran and Shen share more than just a passion for natural products chemistry; they're also both actively involved in supporting graduate education at TSRI. Both serve as mentors to doctoral students and teach graduate-level classes.

"From a professor's perspective, our legacy is in graduate students," said Shen. "The human aspect is more important than scientific discovery. Scientific discovery is very transient. Some people make discoveries with major impact, but in general, science is about incremental progress — our impact therefore is with people. Graduate study is wonderful and if you go to a place like Scripps you find a group of scientists that view training you as a greater researcher to be as important as advancing the discipline of science."

Baran views learning in a classroom setting as an important function (he teaches the program's Heterocyclic Chemistry course) but for him, mentoring graduate students has special significance.

"Graduate classes and undergraduate classes are about teaching the present but mentoring grad students is teaching them how to invent the things that will be in the textbooks of our future," said Baran, himself an alumnus of TSRI's Graduate Program.

Under the mentorship of K.C. Nicolaou, Baran recalls thriving in a highly focused environment. "What really attracted me to Scripps was that it's all about freedom — freedom to discover, with no red tape and no bureaucracy. I could come in and, aside from the classes that I took in the first year, focus completely on my passion and not have to worry about anything else."

Passion is a theme that resonates strongly with Shen as well. He advises students who are considering graduate school to view passion to do research as an important prerequisite.

"Science is an interesting process," explained Shen. "There are very few disciplines that deal with failed attempts as often as in science, because this is what science is all about. Imagine if you're an investment banker or a doctor — if you fail 99 percent of the time, you don't have a career. But as a scientist, if you're succeeding 99 percent of the time, you must be doing something trivial. In science, it's important to look at failure as incremental progress. If your curiosity is strong, nothing can deter you from seeking what you're interested in."

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