Behind The Scenes

by Dr. Amy Keller

This summer, the Journal of Natural Products *published an article from ASP member Dr. Jurgen Rohr and his colleagues entitled, "Saquayamycins G–K, cytotoxic angucyclines from* Streptomyces *sp. including two analogues bearing the aminosugar rednose." When interviewed Dr. Rohr related, "Thanks for featuring my group in the* ASP Newsletter. *I consider that a great honor." Please read the full article in the* Journal of Natural Products, *2012, 75(7), 1383-1392.*

1. How did you become interested in working with *Streptomyces*, and how did you come to focus on cytotoxic compounds?

MS. CATINA ROSSOL

Khaled Shaaban, Nidhi Tibrewal, Tyler Huber, Jürgen Rohr, Madan Kharel, Jhong-Min Chen (back), Guojun Wang (front), Theresa Downey

My PhD training as organic natural product chemist was with Dr. Axel Zeeck in Gottingen, Germany. In his lab, I worked on isolation/structure elucidation of *Streptomyces* products. The material we used were crude products from *Streptomyces* fermentation, obtained from Dr. Hans Zahner's lab. The work triggered me to also get a microbiology minor degree. For that, I was partly trained in the lab of the late Dr. Zahner, who worked on *Streptomyces* his entire life. Dr. Zahner was a fascinating and ingenious researcher, really inspiring, and also a very humorous anti-bureaucrat. Finally, I worked as post-doc with Dr. Heinz Floss, who was probably the most influential scientist for my career; he brought me to the fascinating field of biosynthetic natural product biochemistry, which I am predominantly pursuing since I became independent. Dr. Floss also taught me how to lead a scientific group, and I basically followed his philosophy (see below). I ran into interesting cytotoxic compounds partly coincidentally, but the fact that my father Paul Rohr died from colon cancer also played a significant role.

2. Who in your laboratory carried out the research?

For the success of the recent *Journal of Natural Products* paper, I would name two main players: Dr. Madan Kharel, who collected the soil sample and isolated the Streptomyces strain, and Dr. Khaled Shaaban, who isolated the compounds and did all the structure elucidation work. Both are great scientists and work currently in the Kentucky Center of Pharmaceutical Research Innovation, Lexington, Kentucky, which is directed by my colleague, Dr. Jon Thorson.

3. 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?

The *Journal of Natural Products* paper describes the isolation and structures of new angucycline anticancer antibiotics. Most fascinating was the occurrence of the rare aminosugar rednose, which had been found only once before, in the 'bohemian' anthracycline rudolphomycin, hence the name. The paper followed up on my idea that the micro-fauna of the Southern Appalachian Mountains was never really explored, although that region is known for unprecedented life diversity, mostly known for plants, salamanders, and mushrooms. That paper is one of the few non-biosynthetic

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manuscripts we submitted in the past 15 years, and proves that terrestrial resources are by far not exploited. However, most of our work centers on biosynthetic studies. The newest direction is combinatorial biosynthetic enzymology, which uses enzyme mixtures (we used up to 15 enzymes in such cocktails) to elucidate biosynthetic sequences of event. The advantage is that these enzymes mixtures are free from artifacts caused by whole cell systems. The results are clearer and unambiguous, and we published several papers this year on that topic.

4. What impact does this research have on natural product science and health research in general?

Understanding complex biosynthetic machinery opens up new directions of drug discovery, namely the chemoenzymatic generation of new active compounds. Since we focus mainly on post-PKS (polyketide synthase) enzymes, the methods will lead to new, significantly improved drugs, like the recently published new mithramycin analogues, which have a great potential to be developed as clinical drugs.

5. What is a favorite nonscientific activity of your lab?

That is different from co-worker to co-worker. As a group, we like to hike or canoe. I like skiing a lot, and we tried a skiing outing once, but that was a disaster (most of my people didn't manage to go down a 4-inch steep hill)!

6. What is your lab's motto?

We do not have a motto. My general leadership style to leave talented co-workers a lot of free hand to explore their own ideas and to integrate these into their theses or postdoctoral work (this is a philosophy adopted from Dr. Floss). That not only motivates people, it also opens up great new directions and synergistic ideas; for example the above mentioned 'combinatorial biosynthetic enzymology' was initiated by Dr. Kharel on deoxysugar pathways. Later we used this to explore entire post-PKS cascades, with remarkable success.

7. What are your current highlights in the lab?

That is hard to answer, and always changes. Right now it is the work on fascinating post-PKS enzymes. We discovered that many of these have at least dual functionality, e.g., we recently published a glycosyltransferase that uses two significantly different acceptor and two significantly different donor substrates. Nothing like that had ever been discovered before. We also discovered PKS release enzymes that in addition catalyze decarboxylation and dehydration reactions, but look from a BLAST search like oxygenases. Most recently, we also published two reductase/methyltransferase dual action enzymes, which each closely cooperate with another enzyme of the pathway, in one case that is the above mentioned glycosyltrasferase, in the other case that is a cooperation to regenerate the co-factor FADH2. ■

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