Behind The Scenes in Pharmacognosy

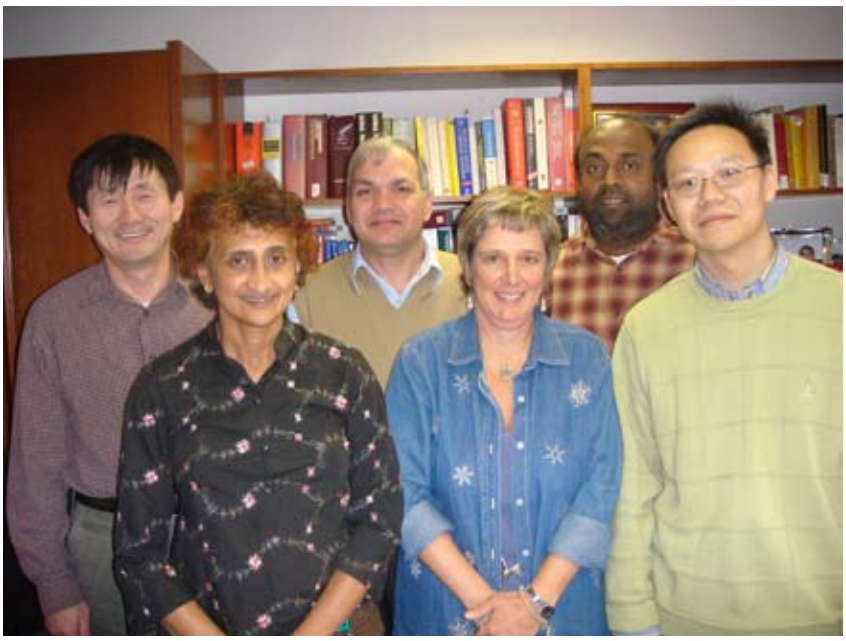
Microbes Wage a Battle of Good and Evil

by Amy Keller

In the summer of 2007, the *Angewandte Chemie International Edition* published "Isolation and Structure of Platencin: A FabH and FabF Dual Inhibitor with Potent Broad-Spectrum Antibiotic Activity", authored by Dr. Hiranthi Jayasuriya and collaborators, many of which are in the laboratory of ASP member Dr. Sheo Singh. Dr. Singh illuminates the hard work that goes into discovering novel antibacterial compounds of microbe origin at Merck & Co., Inc.

How did you become interested in antibiotic natural products and antibiotic-resistant bacteria?

Prevalence of drug resistant bacteria is increasing. Methicilli-resistant *Staphylococcus aureus* (MRSA) is certainly well known but other resistant bacteria are equally dangerous. According to the World Health Organization, the bacterial infections that contribute most to human disease are also those in which resistance is most evident such as diarrhea, respiratory tract infections, meningitis, sexually transmitted diseases, and hospital-acquired infections. The development of resistance to drugs commonly used to treat malaria is of particular concern, as is the emerging resistance to HIV drugs.



A portion of platencin discovery team:
Dr. Hiranthi Jayasuriya, Ms. Debbie Zink, Mr. Chaowei Zhang (front row from left) and Dr. Jun Wang, Dr. Sheo Singh, Mr. Kithsiri Herath (back row from left).

The structural diversity of natural products fascinated me. When working with natural products one does not know what kind of chemical structure one will discover. Natural products are a very productive source of drugs that save human lives. The structural diversity, potent biological activities, and the probability to become life saving drugs, is a very potent combination I see with natural products that continues to resonate with me. Merck has a long history of natural products and antibiotics research that include the discovery and development of imipenem in 1970s and many other antibiotics before that.

Treatment of drug resistant bacterial infection is a serious unmet medical need and Merck is committed to the discovery and development of novel antibacterials to fulfill this unmet medical need.

Who in your laboratory carried out the research?

Drug discovery is a highly complex operation performed by integrated teams. Discovery of platencin is no different. It was accomplished by a team of microbiologists, biologists, and chemists in two continents. Sample collection, microbiology and initial screening were performed in our laboratories in Madrid, Spain. Chemistry and biological evaluation were done in Rahway, New Jersey. The part of my chemistry team along with the biology champion, Dr Jun Wang is pictured in the photo.

Platencin was isolated from the fermentation broth of the microbial cultures by Dr. Hiranthi Jayasuriya supported by Mr. Kithsiri Herath. The structure was elucidated by Dr. Jayasuriya, Mr. Chaowei Zhang, and Ms. Debbie Zink with help from other members of the team.

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?

Platencin is produced by a strain of *Streptomyces platensis* and was discovered from soil samples collected in Spain. The soil sample was identified as a part of Merck's discovery efforts in which we collect the soil and environmental samples throughout the world following the Convention of Biological Diversity treaty. The selection process is based on

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geography and climate, but otherwise is random.

At the time of collection, we do not know whether the soil sample will provide anything worthwhile. It is after long and hard work that we discover a compound like platencin, with lots of failure in the way. We discovered platencin by screening approximately 250,000 extracts originating from nearly 83,000 microbial cultures.

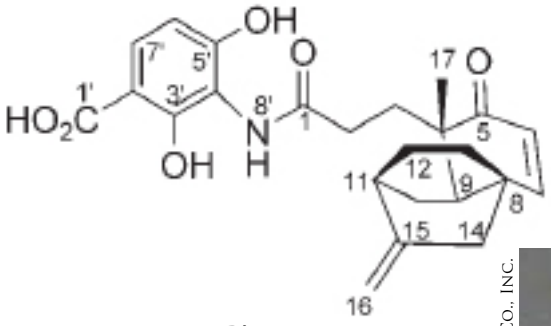
The biggest asset that enabled us to differentiate the extract containing platencin from others containing known antibiotics was the biological screening assay that we used for this discovery. The assay that was used for this discovery was a target-based whole cell differential sensitivity assay using antisense technology for target sensitization. This process allowed us to make the assay more sensitive to identify what we would have missed in the past and also allowed us to discover natural products with predicted mechanisms.

For natural products-based discovery one needs to have highly sensitive robust biological assays, diverse sources that will produce diverse chemical structures, and the capability and know-how to combine these to translate into fast isolation and characterization of structures of compounds and their biology. It has to be a highly integrated team approach that comprise of natural products chemists, microbiologists, biochemists, and other biological expertise. This was all in place for the efficient discovery of platencin.

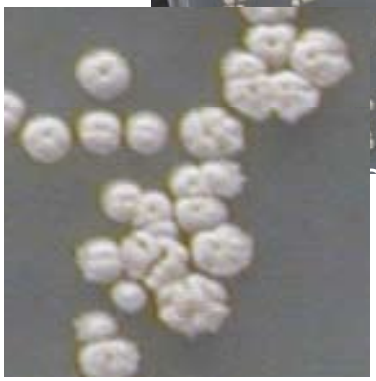
Platencin is a novel natural product with unprecedented structural features and is a highly effective Gram-positive antibacterial agent. It inhibited growth of key pathogenic Gram–positive bacteria including MRSA- and other drug-resistant Gram-positive bacteria. It has a unique mode of action. It inhibited both FabF and FabH enzymes of bacterial fatty acid synthesis pathway. More specifically, platencin inhibits the acyl-enyzyme intermediate, the second (condensation) step of the enzyme reaction. It showed in vivo activity against *Staphylococcus aureus*-infected mouse model.

What impact does this research have? How does this affect the world of natural products and the future treatment of bacterial infections?

The antibiotics we use today fall into one of only a few families, including erythromycins, tetracyclines and cephalosporins, to name a few. When bacteria develop resistance to one product, they usually develop quick resistance to other members in an antibiotic family. What is different about platencin is that it targets a process in the bacterial cell that no other currently available antibiotic targets. It inhibits the fatty acid synthesis which is essential for bacterial survival. The discovery of platencin and earlier report of discovery of platensimycin suggests that an untapped source for chemical diversity with huge therapeutic potential still remains in nature. Continued discovery of new molecules with new mode of action is the key to combat the bacterial resistance.



Platencin



Streptomyces platensis