

Researchers Find New Way to “Sweeten” Key Drugs

UW professors at forefront of cancer-treating agents

by Terry Devitt. Reprinted with permission from *Wisconsin Week*, September 6, 2006.

Probing a class of enzymes routinely used to synthesizing some of nature’s most potent drugs, a team of Wisconsin scientists has found a new way to expand on nature’s chemical creativity to make critical anticancer agents and antibiotics.

Writing in the journal *Science* (Sept. 1), a team led by Jon S. Thorson, a professor of pharmaceutical sciences at the University of Wisconsin-Madison, describes the discovery of a simple process that may yield a raft of promising new agents to treat cancer and the most stubborn antibiotic-resistant infections.

“The work opens the door to a variety of new opportunities in the natural product drug arena,” says Thorson. “There are a number of antibiotics and anticancer agents this can be applied to.”

In nature, plants and other organisms such as bacteria make many chemicals that can be used to treat human disease. Such natural agents are primary sources of drugs employed to fight cancer and thwart infection.

Key chemical features of such drugs are natural sugars, molecules that frequently dictate a chemical compound’s biological effects. For years, medicinal chemists have modified those natural agents to develop variants that have new or more potent disease-fighting properties. But for the most part, scientists have found it difficult to easily and routinely modify the sugar molecules that make such agents medicinally useful.

Now, Thorson and colleagues Changsheng Zhang and Byron Griffith have discovered a new and simple method to manipulate the family of enzymes nature uses

to position the sugar molecules of a drug and confer a specified biological effect. The technique, according to the *Science* paper, has already yielded more than 70 variants of calicheamicin, an anti-tumor drug, and novel analogs of vancomycin, an antibiotic used to fight drug-resistant bacterial infections.

Prior to the new Wisconsin work, there were hints that a key class of enzymes known as glycosyltransferases - the biological catalysts responsible for decorating many natural compounds with unique sugar molecules - could be more expansive in their capacity to deploy molecules from a large library of potential sugar donors.



Jon S. Thorson, PhD

In earlier studies, Thorson and his colleagues capitalized on this flexibility by synthesizing and presenting large sets of the unique sugar “building blocks” to the flexible glycosyltransferases in a method known as natural product “glycorandomization.” That process paid great dividends toward optimizing certain anticancer drugs and antibiotics, Thorson explains, but there

were limitations to making the exotic sugar donor building blocks.

In the new study, the Wisconsin team found that the enzymes are capable of modifying natural products in a much more flexible way than previously thought. The key new finding, he says, is the catalytic activity of the enzymes can be reversed to swipe a sugar molecule from one natural product and confer it on another in a single reaction.

“In essence we’re pirating nature’s sugars,” Thorson says. “This discovery provides a one-pot reaction that eliminates the need to synthesize exotic sugar donors.”

EVA VIVIAN, PHARM.D

Dr. Eva Vivian has been appointed as clinical associate professor at the UW School of Pharmacy. She previously taught at the Philadelphia College of Pharmacy and the Western University of Health Sciences. She earned her doctor of pharmacy degree from



the University of Illinois College of Pharmacy. She completed a pharmacy practice residency at the VAMC San Francisco as well as a primary care

specialty residency at the VAMC San Diego. She is a board certified pharmacist and a certified diabetes educator. She currently maintains a clinical practice at the University of Wisconsin Hospital and Wingra Family Medical Center.

Vivian’s research interest focuses on identifying disparities in the treatment of hypertension, diabetes, and other chronic diseases among ethnic minorities, particularly African American and Latino patients and developing and implementing strategies to reduce and eliminate them.

Vivian has authored several articles, instructional materials, abstracts, and book chapters. She is a peer reviewer for the *Annals of Pharmacotherapy*, *Clinical Therapeutics*, *Ethnicity and Disease*, *Current Medical Research and Opinion*, and *Diabetes Educator*. She has lectured at medical meetings, conferences, and symposia across the United States.

Vivian has held numerous leadership positions within professional pharmacy associations. She currently serves on the board of directors of the Association of Black Health System Pharmacists and is chair-elect of the Specialty Pharmacy Group of the American Association of Diabetes Educators. She is also a member of the American Society of Health-System Pharmacists, American College of Clinical Pharmacy, and American Diabetes Association. ●

The enzymes' flexibilities "appear to be much more universal than previously thought," Thorson says. "The utility of that wasn't clear before."

The Wisconsin team's discovery, Thorson adds, may have implications beyond the ability to soup up natural drugs because similar sugar-transferring enzymes play many other roles in biology.

More immediately, the new finding means that it may now be possible to alter the beneficial properties of many of nature's most useful compounds to create thousands of variants that can be screened for their therapeutic value, Thorson argues. "It is going to be very useful in the context of these kinds of molecules."

What's more, according to Thorson, the technology required to create the new compounds is simple and scalable, which may make it more attractive to the pharmaceutical industry.

"The process is very efficient," Thorson explains. In one vessel, the enzyme can be used to do all of the chemical heavy lifting, synthesizing the new compounds according to how the enzyme is manipulated.

The need for such new drugs, says Thor-

son, is acute. The human pharmacopoeia, for example, is in desperate need of new antibiotics to combat bacteria that have become resistant to existing drugs. The new vancomycin variants, for example, may become important in the battle against drug-resistant staph infections. A study published last month in the *New England Journal of Medicine* found that an alarming 59 percent of skin and soft tissue infections in emergency rooms nationwide were resistant to antibiotics now in use.

The new technique, according to Thorson, will play a prominent role in the new UW-Madison National Cooperative Drug Discovery Group, a consortium of UW-Madison scientists seeking to develop new anti-cancer drugs from natural products. The group was recently formed with the help of a \$5.6 million grant from the National Cancer Institute.

The studies that underpin the new Science report were funded by the National Institutes of Health. In addition to Thorson, Zhang and Griffith, authors of the new Science paper include Qiang Fu, Christoph Albermann, Xun Fu, In-Kyung Lee and Lingjun Li. ●

MAUREEN ROLLMAN, PHARM.D

Dr. Maureen Rollman is a 2004 graduate of the UW School of Pharmacy and has accepted a position as clinical instructor in the pharmacotherapy labs.

After graduation, she completed the William S. Middleton VA Primary



Care residency in Madison. Rollman then joined the UW Hospital and Clinics as a clinical ambulatory pharmacist. In addition to working at different

ambulatory pharmacies, she works in the UW Anticoagulation Clinic and works closely with diabetes patients. Her main area of interest is primary care, including diabetes, hyperlipidemia, hypertension and anticoagulation management.

In her free time, Rollman enjoys spending time with her husband, traveling, reading and knitting. ●