

## Setting Sights on New Antibiotics

Bacterial infections once thought to be on the verge of eradication have been making a comeback, like *Mycobacterium tuberculosis*, the bug that causes tuberculosis. The rate of antibiotic resistance is on the rise as bacteria become resistant faster than we can come up with new drugs—often because patients fail to complete their prescribed course of antibiotics. The problem is compounded by the fact that new antibiotics are usually developed by modifying existing ones. Thus, bacteria that become resistant to an antibiotic often also become resistant to other drugs in the same class.

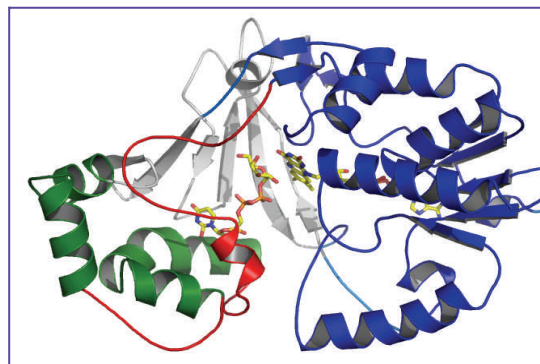
University of Saskatchewan researcher David Sanders is trying to buck this trend. Using the Canadian Light Source, Sanders and his team are undertaking work that may lead to the development of an entirely new class of antibiotics to which no bacteria have resistance by targeting the building blocks of the bacteria's cell wall. Using a technique called protein crystallography, Sanders' team are studying the molecular structure of an enzyme known as UGM.

"Protein crystallography is a powerful technique for looking at the details of how proteins function," says Sanders. "It's an area of research that allows me to look at many different biological questions."

Sanders and his team have used the intense X-rays of the CMCF beamline to generate a highly resolved crystal structure of UGM. The enzyme is crucial for making a sugar that is an ingredient for lipopolysaccharide, one the building blocks of bacterial cell walls. Lipopolysaccharide protects a bacterium from a host's immune system. It is known as a "super-antigen" for its ability to send the immune system into overdrive, causing inflammation at the site of infection and fever.

Until now, researchers have had difficulty determining the structure of the UGM enzyme from common bacteria, such as *E. coli*. By crystallizing the UGM enzyme from a less-common bacterium, the Sanders lab was able to develop a three dimensional model of the enzyme in action, binding to the sugars – known as a substrate - that form lipopolysaccharide. By seeing how and where the enzyme interacts with the substrate, Sanders hopes to identify drug molecules that can act as inhibitors, blocking how the enzyme works with the substrate and halting the chemical pathway that leads to the formation of lipopolysaccharide and, ultimately, a bacterium's cell wall.

"The structure of UGM with its substrate was the first step in using protein structure to help develop new inhibitors," says Sanders. "Our system has already enabled us to begin looking at UGM bound to inhibitors" – the next step towards development of a new class of antibiotics.



Structural diagram of the UGM enzyme, derived from data collected at the CLS. This structural information is key to developing inhibitor compounds for new types of antibiotics. Image courtesy of David Sanders, University of Saskatchewan.

### Fast facts:

- Antibiotic resistance in bacteria is a growing concern that has been hard to fight, since most antibiotic drugs in use today are modifications of existing drugs—meaning that bacteria that are resistant to one drug are often also resistant to all the other antibiotics in the same class.
- Using the CLS, researchers are hoping to develop entirely new antibiotics by targeting one of the key building blocks of a bacterium's cell wall.
- By studying the molecular structure of an enzyme called UGM, scientists hope to short-circuit the production of lipopolysaccharide, a key ingredient for building cell walls that is also responsible for causing severe inflammation and fever in infected people.

**Reference:** S.K. Partha, K.E. van Straaten, D.A.R. Sanders, 2009. Structural Basis of Substrate Binding to UDP-galactopyranose Mutase: Crystal Structures in the Reduced and Oxidized State Complexed with UDP-galactopyranose and UDP. *Journal of Molecular Biology*, 394(5), pp. 864-77. DOI:10.1016/j.jmb.2009.10.013

