Student Profile

Tackling Multidrug-Resistant Bacteria Through Novel Approaches

While some students quickly learn that research might not quite be the path for them, many others get a solid conviction that they are on the right track.

After completing his honours research project, fourth-year U of M Chemistry student Liam Berry has decided research is the career path for him.

Berry's work with Prof. Frank Schweizer, faculty member in the Departments of Chemistry and Medical Microbiology & Infectious Diseases, focused on the development and evaluation of novel antimicrobials against multidrug-resistant bacteria. The Schweizer group specializes in organic and medicinal chemistry.

"Last year in America, a woman died from a bacterial infection that was resistant to every class of antibiotic," said Berry, referring to the widely-covered 2017 case of a Nevada woman who died from a multidrug-resistant bacterial infection after treatment with 26 different antibiotics.

The first case of antibiotic resistance was reported in 1940 when an *E. coli* strain was observed to deactivate penicillin by producing an enzyme called penicillinase. This happened a little over a decade after penicillin was discovered in 1928. The discovery of penicillin revolutionized medicine and benefited humanity in immeasurable ways, and diverse antimicrobials have been discovered since. However, microbes have been shown to continuously adapt resistance mechanisms to hinder the action of these antimicrobials.

The development of new antimicrobials is currently unable to keep pace in the evolutionary arms race between humans and disease-causing microbes.

Antimicrobial resistance (AMR) is a growing public health concern across the globe. AMR-related deaths worldwide were estimated at 700,000 per year as of 2014, and will reach an estimated 10 million by the year 2050 if necessary actions are not taken. The increased frequency of AMR infection cases suggests we are approaching a "post-antibiotic era" where common microbial infections that were once easily treated may now cause mortality. "Superbugs" may become more than just a buzzword.

Different antibiotics have different methods of penetrating the protective membranes of bacteria. Berry's project focused on two modes of cell entry. One type of antibiotic — pore invaders — combats gram negative bacteria by inhibiting DNA synthesis, which requires it to enter the bacterial cell. It enters the cell through tiny pores that can be found in the protective membrane of the bacteria. Fluoroquinolones are a family of antibiotics that use this mode of action. Cationic antimicrobial peptides — membrane destabilizers — are another family of antibiotics, which combat bacteria by destabilizing the chemical structure of the protective outer membrane. Once the structure is destabilized, these antibiotics are then able to penetrate the membrane.

Levofloxacin is a clinically used pore invader, and Colistin is a type of membrane destabilizer. Liam's research goal was to determine whether these two modes of cell entry could be combined in a single antibiotic, while retaining the original modes of action.

The Schweizer lab has successfully made twelve different derivatives of the pore invading antibiotic and tweaked each by adding various parts of the membrane destabilizing molecule. They expected that the resulting hybrid antibiotic may have "dual action" because it will be able to enter the bacteria through pores, as well as by destabilizing the bacterial protective membrane, increasing the amount of antibiotic able to enter the cell.

They tested these twelve hybrids against five different bacterial species, but none of them were effective antibiotics on their own.

One of the primary ways that bacteria develop resistance is by expelling antibiotics as they enter the cell. Colistin is not susceptible to expulsion (efflux), so further research at the Schweizer lab will explore whether the hybrid antibiotics can avoid a similar fate or prevent other currently used antibiotics from being expelled. The results of this next phase will determine whether the antibiotic hybrids they developed can overcome bacterial resistance, and whether they can be used in combination with other antibiotics.

"This whole process taught me how to be productive," said Berry who took a full course load with his research.

"It probably would scare some people, but I think people should do things that scare them sometimes. It is a good learning experience," he added, acknowledging the personal transformation that he has experienced through the discipline and dedication that his research project demanded.

Berry gave his final project presentation on April 7, 2018. He was runner-up in the biochemistry oral presentations of the Western Canadian Undergraduate Chemistry Conference (WCUCC) held at the University of Winnipeg from April 30 to May 3, 2018. He also won third place at the inaugural Manitoba Chemistry Symposium in May 2018 at the University of Winnipeg, where he represented the Schweizer group in the undergraduate oral presentation. Berry has decided to put off medical school to pursue a master's program once he completes his undergraduate degree.

— David Zirangey

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