The discovery of the first antibiotics revolutionized public health. Contracting a bacterial infection was no longer a death sentence, and both quality and span of life were greatly improved. However, bacteria possess the ability to gain resistance to drugs used against them. Antibiotics can act as a selective agent for mutations that bestow resistance, as bacteria lacking these adaptations die when treated with the antibiotic and only the mutant bacteria reproduce. With widespread usage of antibiotics across the medical and agricultural sectors, resistant strains of bacteria have become more prevalent, such as methicillin-resistant Staphylococcus aureus(MRSA), Klebsiella pneumoniae, and vancomycin-resistant Enterococci (VRE). These resistant bacteria often warrant hospitalization, as they can cause life threatening infections.

The rise of antibiotic resistance threatens to revert modern public health to a time of untreatable infection and a precarious day-to-day existence. As we grapple with the COVID-19 pandemic, we can newly appreciate the all-encompassing implications of such a medical crisis. This other pandemic of “superbugs" looms ahead as the next public health challenge, and will likely pose a threat much deadlier than COVID-19. Despite the urgency and predictability of the situation, antibiotic discovery and production is often not prioritized in the pharmaceutical industry. The antibiotic pipeline has run dry, because these companies find the high cost of developing new antibiotics financially nonviable when bacterial resistance is inevitable and the drug is only used short-term for each patient. However, this “inevitability of resistance” can serve as further motivation to develop effective antibiotics, as well as innovative approaches to antibiotic discovery.

Thus, I seek to investigate the question: how can we rationally design small molecules and peptides (chains of amino acids) that can function against antibiotic resistant bacteria? I plan to approach this question by taking advantage of the handedness of amino acids. Nearly all proteins found in nature are composed of left-handed (L) amino acids. Therefore, cells lack the machinery to metabolize peptides made of right-handed (D) amino acids. D-amino acids grant antimicrobial peptides stability against proteases (enzymes that break down peptides), low risk of an adverse immune response,and potential for oral drug delivery. They retain the benefits of traditional peptide-based therapeutics, including specificity for their molecular target in the bacteria.The most critical advantage of using D-peptides is that bacterial resistance is slow to develop against them, so the lifespan of a D-peptide antibiotic would be significantly longer. Mirror image phage display enables identification of D-peptides with antimicrobial activity

against a bacterial target. In this technique, the enantiomer (mirror image) of a target molecule is designed, then a bacteriophage library of L-peptides is screened against itto find peptides that bind to the target (ligands). The enantiomer of the L-peptide ligands can be synthesized; this will be a D-peptide that binds to the native target. Bacteria, including resistant strains, can then be treated with these selected D-peptides to evaluate their antimicrobial activity.

In my project, I will design the target molecules and test the leads from the phage display, and explore how these leads might be optimized. The objective of my project is to identify compounds with antimicrobial activity, which would then serve as a platform for development of new antibiotics that are effective against antibiotic resistant strains of bacteria, as well as resilient against future development of bacterial resistance. The impact of my findings would be the expansion of treatments for drug resistant infections, an important step in the fight against these "superbugs." This project will span the intersection of a number of fields: synthetic organic chemistry, microbiology, cell biology, and biophysics. I anticipate learning key laboratory procedures and practices related to work within these fields, such as review and usage of primary literature, peptide synthesis, and production and analysis of quantitative data from biochemical assays. These skills will have broad applications for my future work in research. I also hope to further my ability to effectively communicate and collaborate with people in a variety of fields. As we have learned through the COVID-19 pandemic, communication of scientific knowledge is essential to public health.This is especially relevant in the case of transmittable infections, whether the infectious agent is SARS-CoV-2 or multidrug resistant bacteria. Public health is also a matter of cooperation between a variety of disciplines in order to resolve multi-faceted issues. The engaging hands-on research and leadership experiences of the Laidlaw Scholars program will help me to strengthen these skills, which are important both as a scientist and global citizen.