Screening Novel Inhibitors of *Helicobacter pylori*
Tessa Epstein '19

The infection of the pathogenic bacteria *Helicobacter pylori* is a worldwide health crisis. *H. pylori* is a gram-negative bacterium that infects over 50% of the world population (1, 2). *H. pylori* infection often leads to the development of duodenal and gastric ulcers and cancers along the gastric tract (1). Current treatment methods of *H. pylori* consist of a triple therapy of potent antibiotics, which have toxic physiological effects, most notably on the healthy gut microbiome (1, 3). Additionally, there is an increasing presence of antibiotic resistant strains of *H. pylori*, meaning that these toxic treatments are unable to successfully eradicate *H. pylori* infection for a growing population of patients (1, 3). As antibiotic resistance continues to grow, the discovery of alternative treatment methods is of urgent necessity.

Auranofin, a gold containing sugar-based molecule, is a potential alternative therapeutic for the treatment of *H. pylori* infection. Auranofin received FDA approval for the treatment of rheumatoid arthritis in 1985 but has recently been discovered to have inhibitory properties against a range of human diseases such as cancer, Alzheimer's and bacterial infection (4). Auranofin initiates cellular death through the inhibition of thioredoxin reductase (TrxR), which disrupts cellular thiol redox balance (5, 6). While auranofin is a promising drug candidate, it causes a range of harmful physiological side effects (4). A compound that resembles auranofin in its interaction with pathogens but that has a decreased toxicity against mammalian would be an ideal alternative therapeutic.

My research this summer examined a novel series of auranofin derivative compounds, synthesized by Mingdi Yan at the University of Massachusetts, Lowell, in the hope of developing new small molecule drug inhibitors of *H. pylori*. These compounds all resemble auranofin through their gold side chain and sugar-base but vary by the side chain attached to the second carbon on the glucose ring (Figure 1). Dr. Yan's lab has established that one of the derivative compounds is five times less toxic against mammalian cells than auranofin, making the derivative compounds promising candidates for treatment against *H. pylori*.

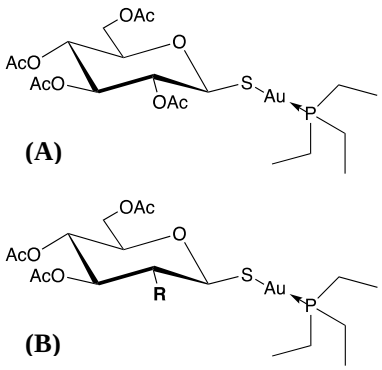

Figure 1. *(A)* chemical structure of auranofin. *(B)* The auranofin derivatives vary in structure at the second carbon of the glucose ring.

First, I established the minimum inhibitory concentration (MIC) against *H. pylori* of each compound. While all compounds successfully eradicated *H. pylori* growth, two of the compounds, including the compound determined to have decreased toxicity against mammalian cells, inhibited *H. pylori* growth at a concentration lower than auranofin.

Next, I was able to determine that the novel compounds obstruct *H. pylori* growth in the same manner as auranofin, through the inhibition of TrxR. I determined the half maximal inhibitory concentration (IC_{50}) for each compound against TrxR to discover that the same two compounds that decreased MIC values from auranofin also had decreased IC_{50} values.

I plan to continue this research as an honors project during the upcoming academic year. My future research will focus on understanding why the chemical variations between the compounds yield differences in inhibitory properties. Gaining insight into why changes in chemical structures yield more promising therapeutics will provide us with greater rationale for the design of future analog compounds. These compounds truly have the potential to revolutionize treatment methods of *H. pylori* infected individuals.

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