Peptidomimetic Antibiotics: a New Class of Drugs to Combat Resistant Bacteria?

By Daniel Haldar

A typical visit to the doctor's office often culminates in the prescription of an antibiotic drug for the patient; although these drugs are beneficial in the treatment of infections, the increased prevalence of antibiotic use has led to the emergence of a problematic trend in medicine. Over the last few decades, treatment of bacterial infections has become increasingly difficult due to bacteria gaining resistance to the antibiotic agents traditionally used against infectious disease. Antibiotic resistance is becoming a critical public health issue as infections caused by resistant bacteria result in extended infection times, severe complications, and increased mortality. In order to combat these challenges presented by resistant bacteria, scientists are currently attempting to develop innovative solutions that simultaneously maximize the efficacy of antibiotic drugs while minimizing the harmful consequences of antimicrobial resistance. Most recently, scientists at the University of Zurich, in conjunction with the biotechnology company Polyphor Ltd., Inc., have discovered a molecule, POL7080, that could lead to a new class of drugs capable of targeting strains of resistant pathogens (1).

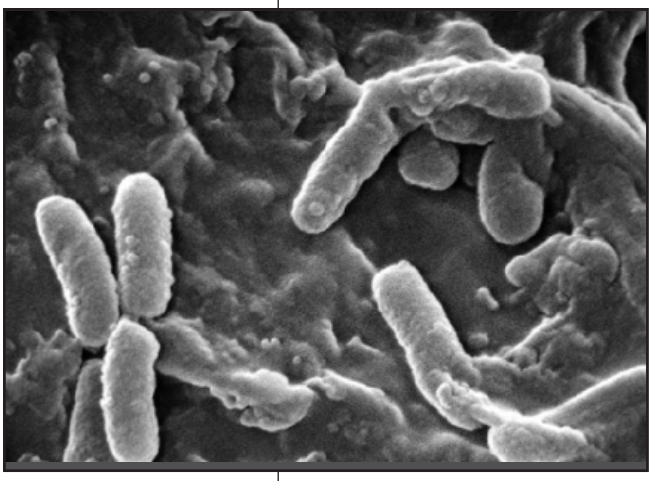

Figure 1. Scanning Electron Micrograph image of Gram-negative *Pseudomonas aerugosina* bacteria.

credit: http://commons.wikimedia.org/wiki/File:Pseudomonas_aeruginosa_SEM.jpg

Antibiotics normally work by binding and inhibiting a protein associated with the bacterium's ability to replicate DNA, produce essential proteins, or form the bacterial cell wall (2). However, bacteria can evade these therapies by developing resistance through two main mechanisms: mutation and horizontal gene transfer. If the bacteria contain a genetic mutation that alters the DNA that encodes such proteins, antibiotics are no longer able to bind to and kill the mutant bacteria. Due to the principles of natural selection, the mutated pathogens are more likely to survive, which leads to a continuous process of building evolutionary resistance (2). Moreover, bacteria can gain resistance to antibiotics through a mechanism known as horizontal gene transfer, a process by which organisms can swap genetic material between different species without a parent-offspring relation. When certain bacteria develop immunity to a particular antibiotic, they can spread the specific genes involved in resistance to other bacteria using conjugation (exchange of plasmids through direct cell-cell contact) or transformation (the uptake of naked DNA from the surrounding environment) (2).

In order to differentiate between various bacterial strains, scientists employ the technique of Gram staining to separate bacteria into two broad categories, Gram-positive and Gram-negative, based on the biochemical properties of their cell walls. A Gram-positive bacterium contains a plasma membrane surrounded by a small periplasmic space that is enclosed within a thick cell wall composed of peptidoglycans (sugar-amino acid polymer) (3). Gram-negative bacteria are surrounded by outer shells that differ in the composition and sequence of their layers; most notably, Gram-negative bacteria possess exterior membranes which protect the peptidoglycan cell wall (3). Since many traditional antibiotics target the cell wall, it has been observed that Gram-negative bacteria are more likely to develop resistance because this outer membrane serves as a protective barrier against the binding of antibiotics (4).

In response to the growing threat of multidrug resistant Gram-negative infections, a research team led by Professor John Robinson

at the University of Zurich in collaboration with Polyphor Ltd., Inc., has employed a peptidomimetic approach to developing drugs that target resistant pathogens. Peptidomimetic drug design recognizes the value of using 3D structures of biologically active peptides as starting points for the synthesis of new drugs that mimic and inhibit targets associated with bacterial mechanisms of action and replication (1). Although peptidomimetic compounds mimic the structure of important peptides, they often possess specific structural differences that promote the stability and efficacy of the compounds as potential drugs. In this study, the scientists employed Protein Epitope Mimetics (PEM) technology to create a family of new antibiotic agents derived from the peptide Protegrin I (1). Protegrins are small peptides that display observable antibacterial activity in many prokaryotes and fungi. Because protegrins can disrupt bacterial cell membranes, they are useful as starting points for the development of antibiotics using peptidomimetic drug design.

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Of the number of peptidiomimetic compounds synthesized in this study, the most promising candidate for drug development is an antibiotic agent called POL7080. Robinson and his team discovered that POL7080 is effective in selectively killing *Pseudomonas aeruginosa*, a certain strain of Gram-negative bacteria that often causes severe pulmonary infections in hospital settings (4). In particular, the study revealed that POL7080 kills Pseudomonas bacteria by targeting a protein involved in the formation of the outermost membrane that is characteristic of Gram-negative pathogens (1). This protein, called LptD, is a novel antibiotic target. Although POL7080 is derived from Protegrin I, its molecular structure is slightly altered so that it targets LptD instead of the lipids normally targeted by Protegrin I. Since the LptD protein is only observed in Pseudomonas, the POL7080 has enhanced selectivity and reduced toxicity in comparison to Protegrin I because POL7080 cannot target other strains of bacteria or molecules in the cells of the host. In addition, POL7080 has higher stability in the bloodstream than natural peptides because the body's enzymes are unable to break down the synthetic peptidomimetic compound (1). In order to test the potency of POL7080, Robinson's team used a mouse model of *Pseudomonas septicemia*. This model revealed that POL7080 was significantly more effective at curing septicemia in comparison with a standard antibiotic used as a control. The study further concluded that inhibiting the LptD protein increased the permeability of the peptidoglycan cell wall of Pseudomonas, which could potentially create greater access for other antibiotics used concomitantly with POL7080 (1).

Due to its tremendous promise as a drug candidate, POL7080 is currently in primary clinical trials conducted by Polyphor. If the clinical trials are successful, Polyphor intends to release a drug derived from POL7080 in the near future that can treat resistant infections caused by Pseudomonas. This study is just one example of many similar success stories to come – peptidomimetic drug design has the potential to produce antibiotics that can combat the most challenging infectious diseases of our time. H

— Daniel Haldar '13 is a Chemistry concentrator in Kirkland House.

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