### Abstract

Although antibiotics like penicillin save lives, antibiotic-resistant bacteria is a growing issue. According to Purdom (2007), over 70% of infections acquired by hospital patients post-admission, are resistant to at least one prescribed antibiotic. Penicillin, a β-lactam antibiotic, treats bacterial infections caused by bacteria producing toxins within a host. Many pathogenic bacteria need a peptidoglycan cell wall for normal functionality. Enzymes in the cell membrane help form this cell wall by cross-linking peptidoglycan units. β-lactam antibiotics bind to bacterial cell wall biosynthesis by competing with the peptide substrate for the active site in these enzymes. While not the main enzyme used to produce bacterial cell walls, R61 DD-peptidase, a cytoplasmic enzyme, is easily crystallized to show bacterial enzyme chemistry. The active site of R61 consists of amino acid residues Ser62, Lys65, Tyr159, Arg285, Thr299, and Thr301. The Messmer SMART Team chose to design a model of R61 complexed with Helen-1, a species-specific β-lactam, highlighting the functionality and chemistry of the active site amino acids and their interaction with the beta-lactam. Understanding the structure and function of the active site of penicillin binding proteins, like R61, could lead to new, species-specific antibiotics that could prevent antibiotic resistance in bacteria. 

### Bacterial Resistance

- Bacterial resistance is a serious problem because, not only are new, antibiotic-resistant strains emerging, the development of new antibiotics has slowed to a trickle. 
- β-Lactam antibiotics, primarily drugs in the penicillin and cephalosporin classes, have been our primary defense against infections since World War II. 
- β-Lactams work because the 4-membered lactam ring mimics the D-Ala-D-Ala portion of the cell wall building blocks. 
- Mimicking allows β-lactams to compete with the normal cell wall substrate for binding to active sites of cell wall building enzymes, called penicillin binding proteins or PBPs. 
- β-Lactamases, enzymes produced by certain bacteria, are accountable for the bacteria’s resistance to β-lactam antibiotics. 
- β-Lactamases most likely evolved as chemicals interfere among bacteria. 

### Current Research

Because β-lactams closely match the chemical structure of the normal cell wall substrate, researchers hypothesize that they should bind better to the enzymes, making them a more effective antibiotic than the current “general” antibiotics. Such species-specific, peptidoglycan mimetic β-lactams could also be less prone to developing antibiotic resistance and might minimize side effects by killing only the pathogen causing the infection. 

### Reactivity of Generic vs. Species-Specific Beta-lactams with R61.

<table>
<thead>
<tr>
<th>β-Lactam</th>
<th>Structure</th>
<th>k a/ M -1 s -1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzylpenicillin</td>
<td></td>
<td>1.37 x 10³</td>
</tr>
<tr>
<td>Cephalothin</td>
<td></td>
<td>1.4 x 10³</td>
</tr>
<tr>
<td>Helen-1</td>
<td></td>
<td>5.6 x 10³</td>
</tr>
<tr>
<td>Helen-2</td>
<td></td>
<td>1.5 x 10⁸</td>
</tr>
</tbody>
</table>

- This table shows the rate at which different β-lactam antibiotics react with R61. 
- The species-specific penicillin (Helen-2 in table) and cephalosporin (Helen-1, in table) are roughly 1000 times and 100 times, respectively, faster reacting, than their generic counterparts, benzylpenicillin and cephalothin. 
- The species-specific side chain allows the drugs to bind better to the enzyme. 
- A next step will be to investigate if this result extends to the larger cell wall-building enzymes in living cells. 

### Conclusion

Currently, β-lactam antibiotics are a standard measure to treat bacterial infections. However, they need to be more distinct in terms of what bacteria they are trying to annihilate. The Messmer SMART Team designed a model of R61 complexed with Helen-1 to help understand how such antibiotics interact with penicillin-binding proteins. The model demonstrates that the specific antibiotic binds better to R61 because it makes more hydrogen bonds and salt bridges with the enzyme. Utilization of this information may aid researchers in the development of the next generation of antibiotics.