Chem 124H Organic Chemistry Case Study #2: *"Overcoming Bacterial Antibiotic Resistance - the Story of Penicillin, Augmentin® and Vancomycin"*

Before 1st Class

1) Read the case. Make sure you are familiar with Ch 21.6, 26.1 and 26.11 ("Chemistry of Esters", "Amino Acid Structures" and "How do Enzymes Work?") of your assigned organic chemistry textbook (McMurry, 8th Ed.). (or Ch 17 and 23 of S&M, Ed 1).

2) Read and *familiarize* yourself with the following articles (posted on iLearn or accessible via the web):

a) Peptidoglycan (wikipedia: http://en.wikipedia.org/wiki/Peptidoglycan) (Maybe I shouldn't have used this, but it's quite a good intro that doesn't dwell on minutiae…)

b) Peptidoglycan synthesis document (a collection of figures culled from Kahne, et al Chem. Rev. **2005,** 105, 425-448; Fisher et al Chem. Rev. **2005,** 105, 395-424; Adachi et al *Biochemistry* **1992,** *31*, 430-437). The words in these articles are overrated - good pictures, though.

c) S. B. Levy, B. Marshall "Antibacterial resistance worldwide: causes, challenges and responses" *Nat. Med.* **2004**, *10*, pS122 (this is a highly biologically oriented discussion of antibiotic resistance, and is included for your interest rather than being essential for the case).

Before 2nd Class

Read and *familiarize* yourself with the following article (pdf file posted on iLearn):

"Amoxicillin", from "Molecules and Medicine", Corey, et al, Wiley 2007.

Before 3rd Class

Read and *familiarize* yourself with the following articles (pdf file posted on iLearn):

a) "Vancomycin", from "Molecules and Medicine", Corey, et al, Wiley 2007.

b) Pages S126 and S127 from S. B. Levy, B. Marshall "Antibacterial resistance worldwide: causes, challenges and responses" *Nat. Med.* **2004**, *10*, pS122.

c) "MRSA" (wikipedia, http://en.wikipedia.org/wiki/Mrsa). Again, details can only confuse you, and the wiki article on this gives a good (and terrifying) summary of the problem.

In Class

1) Class Period #1: You will be divided into collaborative groups for the pre-case discussion in which you identify the major issues of the case, and determine what types of questions need to be answered in order to resolve the case.

2) Class Periods 2 and 3: You will work in your collaborative groups and arrive at answers to the case study questions.

After Class

1) Complete the post-case study individual report. The due date for this final report is Monday, June 11th. The report can be e-mailed to Prof. Hooley (richard.hooley@ucr.edu).

The Case:

The first antibiotic was penicillin, discovered in 1928 by Alexander Fleming. Fleming used the mold penicillium notatum to kill staphylococcus aureus bacteria in the lab. The molecular structure of the active ingredient (penicillin G) as determined by Dorothy Proudfoot Hodgkin by X-Ray crystallography, leading to the production of penicillin G as an antibacterial agent. Mass production only began 14 years after the initial penicillin discovery, mainly due to the requirements in World War II. On March 14, 1942, the first patient was treated for streptococcal septicemia with U.S.-made penicillin produced by Merck & Co. Half of the total supply produced at the time was used on that one patient. Four years after the first use of penicillin, microbes were discovered that displayed resistance to it.

The biggest challenge in modern medicine is the spread of antibiotic resistant bacteria. The most notable resistant bacterium is Methicillin Resistant Staphylococcus Aureus (MRSA, "Superbug"). These bacteria are resistant to penicillin-based antibiotics, and can be resistant to other classes of antibiotics as well. Chemical methods of combating resistant bacteria are challenged by the fact that by the time the resistance is discovered, it may be too late to save the patient. Proper hygiene and sterilization are essential in hospitals to prevent the spread of MRSA and other resistant bacterial infections.

As this is a chemistry course, however, we will look at efforts to combat bacterial resistance by the pharmaceutical industry. In this case study, you will investigate the mechanism of action of penicillin-based antibiotics, as well as glycopeptide antibiotics such as Vancomycin. You will also investigate methods to combat resistance in more common bacterial infections with combination therapies such as Augmentin®.

Case Study Questions

Class Period #1) **Bacterial cell wall synthesis.**

1) What is peptidoglycan? What does it consist of? How can interrupting peptidoglycan synthesis kill bacteria?

2) There are a number of enzymes that control peptidoglycan biosynthesis. We will focus on the transpeptidase enzyme (also known as the penicillin binding protein), as this is the target of both the penicillins and vancomycin.

Compare the mechanism of action of the transpeptidase enzyme to that of the serine proteases we discussed earlier in the class. What are the similarities and differences between them?

3) What is unusual about the amino acids recognized by the transpeptidase enzyme? Why might bacteria have evolved this particular recognition mechanism? Why is this enzyme a good target for drug action?

Class Period #2) **a) Penicillin(s) as antibiotics**

1) What is the structure of penicillin? Why is it chemically reactive?

2) How does penicillin inhibit the transpeptidase enzyme? Is it a covalent or reversible inhibitor?

3) If penicillin reacts with transpeptidase in bacteria, why is it not destroyed by proteases in the human body?

b) Penicillin resistance, β-lactamases, clavulanic acid and MRSA.

What is the main method of bacterial resistance against penicillins and other β-lactams? How does this resistance work?

Clavulanic acid shows little antibacterial activity by itself, but when prescribed in combination with Amoxicillin (marketed as Augmentin) it is highly effective. What are the properties of clavulanic acid, and why is it combined with simple penicillins?

Class Period #3) **Vancomycin - the antibiotic of last resort.**

Vancomycin is a glycopeptide which acts on the transpeptidase enzyme. Describe the method of action of vancomycin. Is it a reversible or covalent inhibitor?

Describe the mechanism of bacterial resistance to vancomycin. Could co-treatment with clavulanic acid provide a method of overcoming this resistance?

These days, vancomycin is almost solely used as a treatment for MRSA, rather than a broad spectrum antibiotic. Why?

Post-Case Study Report

In a 1-2 page report, use your answers from the Case Study Questions and information from further reading of the related articles to make general conclusions about the use of antibiotics in everyday life.