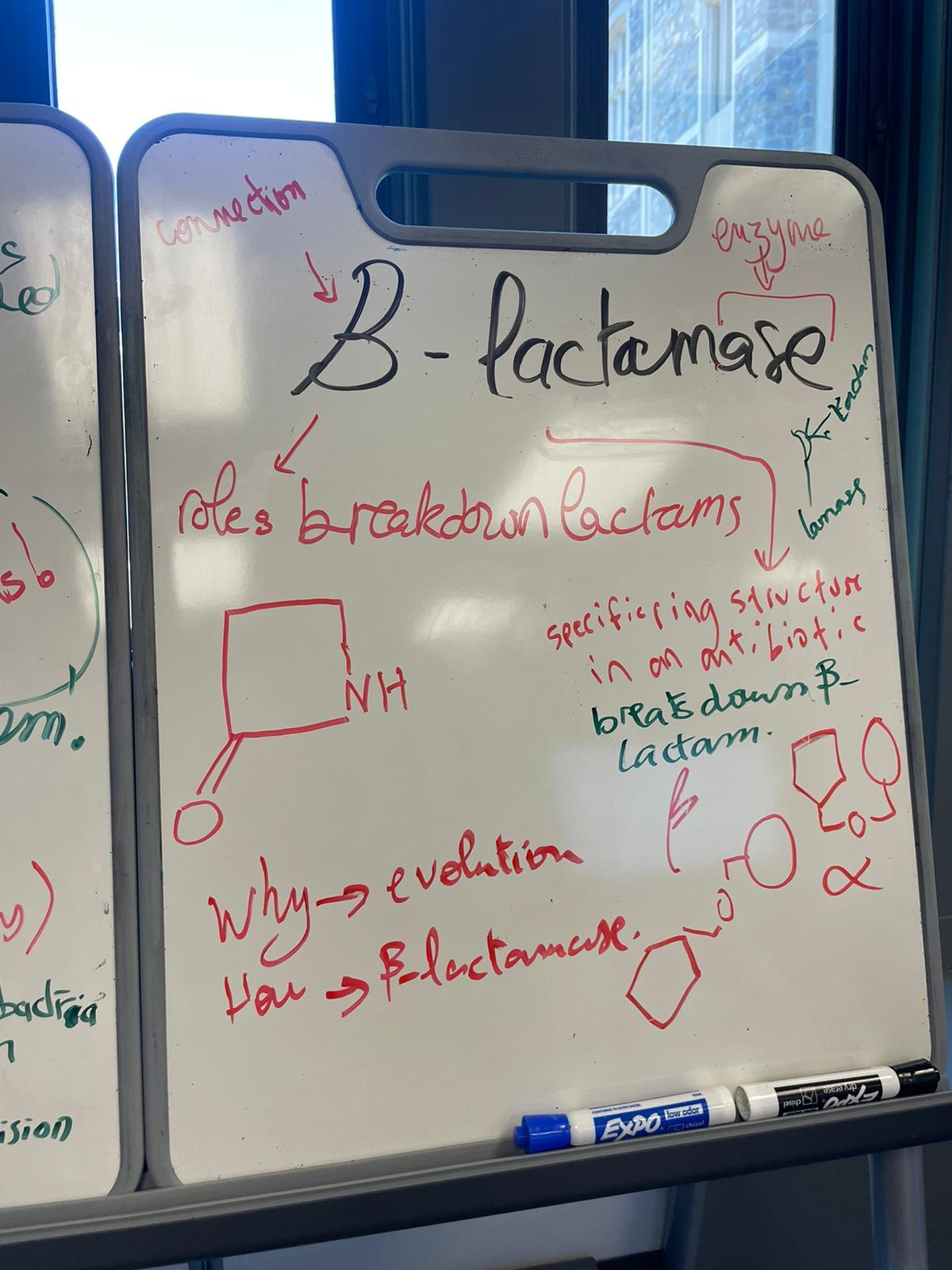
# EMMI Team MICROBES MEET #1: 15-07-2024

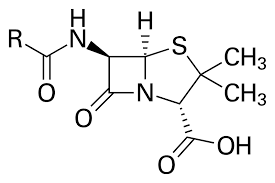
By Eya Lahiani

# Overview and Importance

Antibiotic resistance is an increasingly serious public health concern as many bacteria develop resistance to existing treatments. Among the most frequently prescribed antibiotics are β-lactams, which account for 65% of all antibiotic prescriptions.

  
One of our board drawings; we were trying to understand what β-lactams and β-lactamase stand for.

This class includes a variety of compounds, such as penicillin, the first widely used antibiotic.

  
Penicillin core structure, where "R" is the variable group, Wikipedia.

β-lactams work by preventing cell wall formation during cell division, effectively killing the bacteria. However, due to their widespread use, many bacterial strains have already developed strong resistance to these drugs.

# Mechanisms of Resistance

Bacteria can develop resistance to antibiotics through the production of specific proteins. Some bacteria produce proteins capable of breaking down the antibiotics, rendering them ineffective. Typically, bacteria produce these proteins in small amounts, which can be countered by higher concentrations of antibiotics. However, when bacteria are exposed to low antibiotic concentrations or over prolonged periods, they may mutate to produce more of these proteins or to enhance their effectiveness. This results in the need for increasingly higher concentrations of antibiotics to achieve the same bactericidal effect.

Bacterial strains develop strong resistance to β-lactam antibiotics through several mechanisms:

1. **Production of β-lactamase Enzymes**:
   * **β-lactamase Production**: Bacteria can produce enzymes called β-lactamases that break down β-lactam antibiotics, rendering them ineffective. These enzymes cleave the β-lactam ring, a crucial structure in these antibiotics, thus neutralizing their antibacterial activity.
   * **Gene Acquisition**: Bacteria can acquire genes encoding β-lactamase enzymes through horizontal gene transfer. This transfer can occur via plasmids, transposons, or bacteriophages, allowing rapid spread of resistance among bacterial populations.
2. **Modification of Target Sites**:
   * **Altered Penicillin-Binding Proteins (PBPs)**: β-lactam antibiotics target penicillin-binding proteins (PBPs) involved in cell wall synthesis. Mutations in the genes encoding these PBPs can alter their structure, reducing the binding affinity of β-lactam antibiotics. This means the antibiotics can no longer effectively inhibit cell wall synthesis.
3. **Efflux Pumps**:
   * **Active Efflux**: Some bacteria possess efflux pumps that actively expel antibiotics from the cell. This reduces the intracellular concentration of the antibiotic, allowing the bacteria to survive and multiply despite the presence of the drug.
4. **Reduced Permeability**:
   * **Porin Modification**: Gram-negative bacteria have an outer membrane that contains porins, which are channels allowing the passage of molecules, including antibiotics. Mutations or changes in the expression of porins can decrease the permeability of the outer membrane to β-lactam antibiotics, limiting their access to the target PBPs.
5. **Biofilm Formation**:
   * **Protective Biofilms**: Bacteria can form biofilms, which are structured communities of bacteria encased in a self-produced extracellular matrix. Biofilms can protect bacteria from antibiotic penetration and the host immune response. Within biofilms, bacteria can exchange resistance genes more readily, enhancing the spread of resistance.

**=> Evolutionary Pressure and Mutation:** When bacteria are exposed to β-lactam antibiotics, especially at sub-lethal doses or for extended periods, selective pressure favors the survival of resistant mutants. These resistant bacteria reproduce, passing on their resistance traits to subsequent generations. Over time, the proportion of resistant bacteria in the population increases, leading to the widespread prevalence of resistant strains.

# β-lactamase

β-lactamase is an enzyme produced by bacteria to degrade β-lactam antibiotics. Bacteria producing high levels of β-lactamase become resistant to β-lactams, and new mutations can make β-lactamase more efficient at breaking down these antibiotics. Inhibiting β-lactamase can prevent the degradation of β-lactams, allowing the antibiotics to remain effective in combating bacterial growth. Thus, targeting β-lactamase is a promising strategy for developing novel inhibitors to counteract antibiotic resistance.

# Associated Diseases and Current Strategies

Many bacteria now produce excessive amounts of β-lactamase, rendering β-lactams ineffective on their own. Consequently, most β-lactam prescriptions today involve a combination of **antibiotics** and **β-lactamase inhibitors**. A common combination is amoxicillin and clavulanate. Clavulanate, a β-lactamase inhibitor, binds more strongly to β-lactamase than amoxicillin, thereby protecting the antibiotic. This allows amoxicillin to inhibit cell wall formation and stop bacterial cell division effectively.

However, recent mutations in β-lactamase have made the enzyme more selective, resulting in weaker binding of known inhibitors while enhancing the binding affinity for β-lactam antibiotics. This ongoing evolution necessitates the continuous search for new β-lactamase inhibitors to keep pace with emerging resistant bacterial strains.

# Meeting Gallery:

