Press release : 2nd of February, 2004 : COBRA starts.

COBRA, a European commission 6th framework programme, Specific Targeted Research Project funded under priority focusing on combating antibiotic resistance started on the 2nd of February 2004 .

The goal of COBRA is to better understand the various mechanisms of resistance to inhibitors of cell wall synthesis, in particular β-lactams, and to decipher recently appeared mechanisms of resistance. The research will focus on various bacteria of clinical importance among which Gram-negative bacteria including members of the family *Enterobacteriaceae* and *Pseudomonas aeruginosa*, as well as Gram-positive bacteria including *Staphylococcus aureus*, *Streptococcus pneumonia, Enterococcus faecalis,* and *Enterococcus faecium* are included. These bacteria are responsible for severe community-acquired and nosocomial infections. Most of the mechanisms of resistance explored in COBRA are either natural or have been acquired in the patient due to the selective pressure associated with the vast consumption of antibiotics.

The study of β-lactamases will include an extensive search for the discovery and characterisation of novel extended-spectrum β-lactamases and carbapenemases in Gram-negative organisms. For several of these enzymes, gene expression and the molecular basis of their dissemination will be analysed. The catalytic properties, the structure-activity relationships and the 3D structure of some of them will be determined with regard to their activities against the antibiotics. The contribution of additional factors, such as outer membrane permeability and efflux pumps, to high-level resistance to β-lactams will be investigated in detail.

This project will answer four fundamental scientific questions:

- Which structural features of different D,D-transpeptidase domains of PBPs involved in resistance to β-lactam antibiotics explain their low affinity for these antibiotics ?
- What is the role of associated critical factors and regulators involved in the expression of non β-lactamase-mediated resistance to cell wall inhibitors?
- Which are the catalytic mechanisms of the novel emerging, extended-spectrum β-lactamases of different classes with activity against β-lactams including third-generation cephalosporins and carbapenems, and how can they be understood in relation to enzyme structure?
- Which are the mechanisms involved in the regulation of the expression of different β-lactamase genes and what is the molecular basis for acquisition and mobility of new β-lactamase as well as the role of impermeability in the expression of resistance?

In response to these questions, the following achievements are expected:

- Understanding the role of those amino acid residues in PBPs that are essential for the expression of resistance and their contribution to the structure of the PBP D,D-transpeptidase domains.
- Understanding the biochemical role of the associated critical factors in the pathway of peptidoglycan synthesis, their structure, and their role in non β-lactamase-mediated

resistance; with respect to various regulators, understanding the mechanisms by which they interfere with the expression of resistance.

- Understanding the diversity of the structures of the β-lactamases observed and studied, and understanding the role of the amino acid residues essential for their catalytic properties.
- Understanding the genetic environment of the β-lactamase genes and its contribution to resistance gene dissemination as well as the associated role of porins and efflux in expression of resistance.

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