Postdoctoral position, Microbiology and Biochemistry, Alternate Pathways of Peptidoglycan Synthesis in *Mycobacterium tuberculosis* and *Enterococcus faecium*

Until recently, all β-lactam antibiotics were thought to exclusively act on the active-site serine D,D-transpeptidases (PBPs) that catalyze the final cross-linking step of peptidoglycan synthesis in the bacterial cell wall. Our team has shown that these D,D-transpeptidases can be by-passed by a novel class of enzymes, the L,D-transpeptidases (Ldt), in β-lactam-resistant *Enterococcus faecium*[1] and in *Mycobacterium tuberculosis*[2, 3]. The two modes of peptidoglycan cross-linking differ not only by the transpeptidase responsible for their formation (D,D versus L,D, respectively) but also by the structure of the stem peptide used as an acyl donor in the transpeptidation reaction (pentapeptide versus tetrapeptide, respectively). Since L,D-transpeptidases use as a donor a stem tetrapeptide ending in D-Ala^4, the pathway conveys high-level resistance to glycopeptide antibiotics, vancomycin and teicoplanin, which bind to the D-Ala^4-D-Ala^5 extremity of stem pentapeptides[4]. Since L,D-transpeptidases are not inactivated by β-lactams of the penam (penicillin) family, L,D-transpeptidation may result in resistance to these drugs. Thus, L,D-transpeptidation potentially provides cross-resistance to the two major classes of drugs used to treat infections due to Gram-positive bacteria. The general objectives of our team are to gain a better understanding of the structure[5, 6], catalytic mechanism[7, 8], and regulation of the D,D and L,D transpeptidases to identify the targets of β-lactam antibiotics in pathogenic bacteria and design inhibitors specifically acting on the two pathways[9-12]. The specific objectives of the proposed project are to identify the factors[13, 14] that determine the relative contributions of L,D- and D,D-transpeptidases to peptidoglycan cross-linking and the mechanism of inhibition of these enzymes by β-lactam of the carbapenem class, which are currently developed for the treatment of extensively drug resistant tuberculosis[15]. We seek an individual with doctoral or postdoctoral experience in one or several of the following fields: mycobacteriology, enzymology, recombinant DNA technologies, genomics, or proteomics, medicinal chemistry.

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