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Study of two new transporters of Streptococcus pneumoniae: an intriguing link between multidrug resistance and virulence

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Streptococcus pneumoniae is one of the most severe human Gram-positive pathogen with often a deadly outcome in young children, immunocompromised patients or elderly people (~ 1.6 million death/year according to the WHO), despite the availability of some vaccines which, however, tend to loose their efficacy due to serotype replacement by non vaccine pneumococcal serotypes. In addition, multidrug resistance (MDR) *S. pneumoniae* strains is spreading rapidly and causes a serious health threat. Although antibiotic resistance can have a multifaceted origin, multidrug transporters have drawn much attention lately due to their major involvement in the resistance of pathogenic microorganisms to drug treatment. Besides the harmful role of these transporters due to their capacity to expel many antibiotic, it has been reported that *Neisseria gonorrhoeae* uses a MDR transporter to counteract the action of antimicrobial peptide synthesized by the host upon infection. Thus, an emerging concept for the physiological role of MDR transporters is their implication as the first line of defence against a board range of antimicrobial compounds in ecological niches, possibly including peptides secreted by hosts to resist bacterial invasion by pathogens.

MDR transporters are found in all living organisms and can use either ions or ATP as the energy source; the latter belong to the largest family of membrane proteins, the ABC (ATP-Binding Cassette) transporters. Members of this family involved in multidrug phenotypes are found from bacteria to man and one prominent example, the P-glycoprotein, is involved in the resistance of some cancers to chemiotherapy. In the past 12 years, we and others have identified some MDR ABC bacterial members. This is, however, only the tip of the iceberg as many more 'putative' MDR ABC transporters are awaiting functional characterization. Recently, we have identified and characterized a new bacterial member from the Gram-positive bacteria archetype, *Bacillus subtilis*, which works as a heterodimer and whose expression is strongly up-regulated by several structurally unrelated antibiotics. Closely-related transporters are found in some pathogenic species including *Listeria monocytogenes* and *S. pneumoniae*. Interestingly, the *L. monocytogenes* transporter is somehow involved in the virulence of the strain because transcription of its gene was increased during infection of epithelial cells while a mutant where this gene was invalidated showed a highly reduced intracellular growth.

The goal of this project is therefore to study, both at the cellular and molecular level, two related transporters of *Streptococcus pneumoniae* in order to understand the relationship between virulence and multidrug resistance. For the molecular level, we will overexpress the two transporters and study, on membrane fractions or after purification and reconstitution into proteoliposomes, the transport abilities of both transporters including peptides secreted by human cells upon infection by *S. pneumoniae*. For the cellular level, we will inactivate either transporter and check if this affects the infection of human cells by *S. pneumoniae* mutants.