Exploring the *Pseudomonas aeruginosa* cell envelope as a source of novel protein drug targets

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ABSTRACT

We are now facing a challenging era in which antibiotic resistance complicates the treatment of nearly all common bacterial infections, representing a clinical, economic and social problem that is here to stay. Developing of new antibiotics with novel mechanisms of action and/or cellular targets represents an essential strategy against antibiotic resistance, as resistance inevitably builds over time.

The Gram-negative bacterium *Pseudomonas aeruginosa* is currently regarded as one of the most dreaded pathogens in the hospital setting, and represents a prototype of multi-drug resistant "superbugs" for which effective therapeutic options are very limited.

In order to identify new promising candidates as potential drug targets, we combined large-scale transposon mutagenesis data analysis and bioinformatics predictions, to retrieve a number of novel putative essential genes of *P. aeruginosa* that are predicted to encode for cell-envelope proteins. The rationale for focusing on cell-envelope-located proteins is that they are expected to be more accessible to drugs, and that drugs binding to cell-envelope targets likely escape efflux pump-mediated resistance.

The main goal of the present project is to experimentally verify the essentiality of the selected genes, as well as the specific subcellular localization of their protein products. The newly identified essential cell-envelope proteins will be further investigated in order to (i) determine their three-dimensional structure and (ii) assess their functional role in a number of phenotypes which are crucial for *P. aeruginosa* pathogenicity, such as cell-envelope integrity, biofilm stability, growth and persistence during infection.

The expected outcome of this project is the functional and structural characterization of novel essential cell-envelope proteins of *P. aeruginosa*. Our results could, on one hand, shed light on still-unexplored biochemical, molecular and physiological aspects of the cell wall of Gram-negative bacteria and, on the other hand, pave the way for the structure-based rational design of new antimicrobial agents active against *P. aeruginosa*.

Internal collaborators

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