GRAL PhD PROJECT 2020-2023

Title of the PhD project: Exploring Two Partner Secretion in virulence of Gram-negative pathogens

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Summary of the project: Many Gram-negative bacteria, pathogens for humans, use toxins for host cell manipulation. Two Partner Secretion systems (TPS) allows the export of high molecular weight secreted proteins (160 kDa - 400 kDa) across the outer membrane by a cognate outer membrane protein. TPSs are responsible for diverse functions from pore formation into the host-cell membrane to adhesion of the bacteria. This project will built on our previous studies on *Pseudomonas aeruginosa* TPS toxin Exolysin. Exolysin-like proteins with divergent C-terminal sequences, which carry the activity functions, were found in different *Pseudomonas* species. We will explore their structure – function relationship by using approaches ranging from biochemistry to cellular and virulence tests *in vivo* on different models, such as *Drosophila* and *Galleria*. We will also investigate non-exolysin TPSs in *P. aeruginosa.* Indeed, in addition to Exolysin, *P. aeruginosa* clinical strains encode five more TPSs, including a filamentous hemagglutinin (FHA)-like adhesin, PdtA, whose exact role in virulence is still obscure. We propose to study the function and structure of PdtA, in particularly, and to explore its immunogenic properties. Indeed, FHA proteins are highly immunogenic and may be used in active immunization, as demonstrated in *Bordetella pertussis*.

Keywords: bacterial toxins, host-pathogen interactions, secretion, anti-virulence

Applicant profile: microbiology, genetics with notions of biochemistry

Three recent publications of the PhD supervisor

Reboud, E., Bouillot, S., Patot, S., Beganton, B., Attree, I. and Huber, P. (2017) Pseudomonas aeruginosa ExlA and Serratia marcescens ShlA trigger cadherin cleavage by promoting calcium influx and ADAM10 activation. *PLoS Pathogens*, 13, e1006579.

Elsen, S., Huber, P., Bouillot, S., Coute, Y., Fournier, P., Dubois, Y., Timsit, J.F., Maurin, M. and Attree, I. (2014) A type III secretion negative clinical strain of Pseudomonas aeruginosa employs a two-partner secreted exolysin to induce hemorrhagic pneumonia. *Cell Host & Microbe*, 15, 164-176.

Basso, P., Ragno, M., Elsen, S., Reboud, E., Golovkine, G., Bouillot, S., Huber, P., Lory, S., Faudry, E. and Attree, I. (2017) Pseudomonas aeruginosa Pore-Forming Exolysin and Type IV Pili Cooperate To Induce Host Cell Lysis. *mBio*, 8.