Research Topic for the ParisTech/CSC PhD Program
(one page maximum)

Subfield: Molecular biology, molecular genetics and bacteriology)

ParisTech School:AgroParisTech / ABIES Doctoral School

Title:Metagenomic analysis of human enteric infectionsusing an insect intestinal model system.

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Short description of possible research topics for a PhD: (10-15 lines in English + optional figure)

Animals host multi-species microbial communities (microbiomes) whose inter-species interactions influence animal biology in diverse ways.One of the goals in pathogen-microbiome-host studies is to understand these microbial inter-species interactions within host-associated microbiomes and their consequences on host physiology, behavior and fitness. Our assumption is that microbial dysbiosis in the human gut can be adequately investigated using a surrogate insect model system. Here, we propose to use the larvae of the wax moth, *Galleria mellonella*, to assess the virulence and infection process of human pathogens entering by the oral route and to investigate the intestinal pathogen-microbiote-host interactions. This model system is anticipated to provide opportunities to monitor and analyze the dynamics of the resident microbiota, as well as the ensuing immune response of the host, and evaluate the real significance of these findings in the context of host responses, with a level of experimental control that is not achievable in human studies.The possibility of comparing axenic (germ-free) insects with their conventional or gnotobiotic(formerlygerm-freeorganisms in whichthecomposition of the associatedmicrobialflora is fullydefined, usuallybecause it hasbeendeliberatelyintroduced)counterparts could also be instrumental to explore the role and importance of the microbiota in resistance to colonization by opportunistic pathogens.In addition, *G. mellonella* might be a valid starting point to evaluate the efficacy and safety of candidate “probiotic” species and to deliver relevant information into potential mechanisms of their probiotic action.To set-up this model, we will use two intestinal Gram positive opportunistic enteric pathogens, the facultative aerobic *Bacillus cereus* (Bc) and the strict anaerobic *Clostridium difficile* (CD) that can be administered orally. These two pathogens produce spores that can contaminate hospital environments and infect the gut when the intestinal microbiota is altered or absent.This project will make large use of novel high throughput sequencing technologies (16S RNA, RNAseq), qRT-PCR, as well as histological approaches and live-cell imaging techniques,and will require to develop advanced integrative analyses of these large sets of data for monitoring and interpreting the dynamics of gene expression in both pathogens, microbiota and host epithelial cells, during infection,in order toestablish statistically robust and biologically meaningful functional links (crosstalks) between host-pathogen-microbiota. This will permit to address questions such as what really occurs in gene expression during interaction with the host and its natural microbiota, what mechanisms enteric pathogens use for adaptation and how the intestinal microbiota modulates infection (i.e. colonization) resistance, and eventually beneficially impact host responses, including immune regulation,resulting in subsequent inhibition of enteric pathogens..

Required background of the student: A general background in genomic sciences including classes in genetics, molecular biology, biochemistry and preferably in bioinformatics/statistics for analysis of sequence data.

A list of 5(max.) representative publications of the group:

- Kamar R, Réjasse A, Jéhanno I, Attieh Z, Courtin P., Chapot-Chartier M-P, Nielsen-Leroux C, Lereclus D, El Chamy L, KallassyAwad M, Sanchis-Borja V. (2017). DltX of *Bacillus thuringiensis* is essential for D-alanylation of teichoic acids and resistance to antimicrobial response in insects. Frontiers in Microbiology. 8:1437. doi: 10.3389/fmicb.2017.01437.

- Patino-Navarrete Rand Sanchis V. (2017) Evolutionary processes and environmental factors underlying the genetic diversity and lifestyles of *Bacillus cereus* group bacteria.Research in Microbiology. 2017 May;168(4):309-318. doi: 10.1016/j.resmic.2016.07.002. Epub 2016 Jul 16.

-Kamar R, Gohar M, Jéhanno I, Rejasse A,KallassyAwad M, Lereclus D,Sanchis V,Ramarao R. (2013). Pathogenic potential of *Bacillus cereus* strains as revealed by phenotypic analysis. J. Clin. Microbiol. 51(1): 320-323.

- Song F, Peng Q, Brillard J, Buisson C, de Been M, Abee T, Broussolle V, Huang D, Zhang J, Lereclus D, Nielsen-Leroux C. (2012). A multicomponent sugar phosphate sensor system specifically induced in *Bacillus cereus* during infection of the insect gut. FASEB J. 26(8): 3336-3350.

- Réjasse A, Gilois, N, Barbosa I, Jéhanno, I, Huillet, E, Tran, S, Ramarao N,StenforsArnesen LP, Sanchis V. (2012). Temperature-dependent production of various PlcR-controlled virulence factors in *Bacillus weihenstephanensis* strain KBAB4. Appl. Environ. Microbiol. 78(8): 2553-2561.