CTM U1231 SCIENTIFIC SEMINAR

May 30, 2022
1 to 2 pm, amphi Masson, UFR des Sciences de Santé
Chairwoman: Dr Carmen Garrido

Invited speaker: Dr Julia Sanchez-Garrido
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London, UK

Bacterial effectors during infection: an intersection of pathogenic and cellular networks

Many clinically important Gram-negative pathogens, including *Salmonella enterica*, *Shigella* spp. and enteropathogenic and enterohaemorrhagic *Escherichia coli* (EPEC and EHEC), employ a molecular syringe, known as type III secretion system (T3SS), to inject bacterial proteins called effectors into the cytosol of infected eukaryotic cells. Once in the cytosol, effectors target multiple organelles and cellular processes, enabling colonisation, proliferation and evasion of immune responses. Up until now the main approach to understanding T3SS-mediated pathogenesis has been to determine the functions of one effector at a time; we have recently shown for the first time that, rather than acting individually, effectors form networks in vivo (1). As many key T3SS pathogens are human restricted (e.g., *Shigella* spp., Typhoidal *Salmonella*), we modelled the roles of T3SS effectors in vivo using the natural mouse-adapted pathogen *Citrobacter rodentium*, which encodes 31 effectors that are injected into intestinal epithelial cells (IECs) (2, 3). By analysing *C. rodentium* strains expressing different effector networks we found that rather than functioning individually or sequentially, the effectors operate as a complex but flexible interconnected ensemble that can withstand deletion of up to 60% of the effectors and still remain virulent. Surprisingly, a main function of the effectors within IECs is to inhibit secretion of cytokines from immune cells, while key immunometabolic changes were shared by the different strains, pointing towards their essentiality in establishing a successful infection. From this, we used the infection outcomes more than 100 effector mutant combinations, together with curated functional information, to build and train a machine-learning AI model that predicts the probability of colonization success of novel mutant strains. Applying AI modelling in an infection context will open new possibilities to study the function and connectivity of T3SS effectors, as well as enable the identification of key host pathways which could be targeted by new host-directed therapies (1).

1. **Sanchez-Garrido, J.**, Ruano-Gallego, D., Kozik, Z., Núñez-Berrueco, E., Cepeda-Molero, M., Mullineaux-Sanders, C., Naemi-Baghshomali Clark, J., Slater, S.L., Wagner, N., Glegola-Madejska, I., et al. (2021). Type III secretion system effectors form robust and flexible intracellular virulence networks. Science 371, eabc9531. doi: 10.1126/science.abc9531
2. **Sanchez-Garrido, J.** Ruano-Gallego, D., Choudhary, JS and Frankel, G. (2021) The type III secretion system effector network hypothesis. Trends in Microbiology. 10.1016/j.tim.2021.10.007
3. Mullineaux-Sanders C, **Sanchez-Garrido J**, Hopkins EGD, Shenoy AR, Barry R, Frankel G. Citrobacter rodentium-host-microbiota interactions: immunity, bioenergetics and metabolism. Nat Rev Microbiol. 2019 Sep 20. doi: 10.1038/s41579-019-0252-z.