Doctoral School of Information and Biomedical Technologies
Polish Academy of Sciences (TIB PAN)

SUBJECT: Understanding of multi-scale innate immune responses against bacterial pathogens

SUPERVISOR: dr. hab. inż. Paweł Paszek, Profesor of IPPT

DESCRIPTION: Infection triggers complex signalling events in cells, which aim to kill the pathogen directly or induce a protective cytokine response to activate bystander cells. Paradoxically, the immune cell activation exhibits extreme variability, for example protective cytokines are produced by a small subset of genetically identical macrophages. Consequently, the interactions between host and pathogen are inherently heterogenous and result in different and "seemingly" probabilistic outcomes at the single cell level. How a robust immune response emerges from the heterogenous single cell behaviour remains one of the fundamental questions in immunology and infection biology. The main aim of the project is to quantitatively understand mechanisms involved in the muti-scale coordination of innate immune responses against bacterial pathogens at the single cell level. We will focus on events occurring at low physiological multiplicities of infection and physiological febrile temperature range, which give rise to heterogenous and stochastic effects in the infected population. We will study direct interactions between innate immune macrophages and the important food-borne bacteria *Listeria monocytogenes* that causes significant levels of human morbidity and mortality. Using live-cell microscopy approaches and mathematical modelling to elucidate how pathogen threats are encoded in dynamical responses of NF-κB/STAT/IRF systems upon *L. monocytogenes* infection and how they relate to different (and seemingly probabilistic) outcomes of single-cell host-pathogen interactions. The goal of this proposal is to identify key regulatory mechanisms and understand how to change the course of infection in single cells and cellular populations.

BIBLIOGRAPHY:

1. Moran, J., Feltham, L., Bagnall, J., Goldrick, M.C., Lord, E.A., Nettleton, C., Spiller, D.G., Roberts, I., and Paszek, P. (2023). Single-cell imaging reveals non-cooperative and cooperative infection strategies of Listeria monocytogenes in macrophages. (2023) Frontiers immunology, in press. 10.3389/fimmu.2023.1235675
2. Alachkar N, Norton D, Wolkensdorfer Z, Muldoon M, Paszek P. Variability of the innate immune response is globally constrained by transcriptional bursting. (2023) *Frontiers in Molecular Biosciences*. 2023;10. doi: 10.3389/fmolb.2023.1176107.
3. Kalliara E, Kardyńska M, Bagnall J, Spiller DG, Muller W, Ruckerl D, Biswas SK, Śmieja J, Paszek P, Post- transcriptional regulatory feedback encodes JAK-STAT signal memory of interferon stimulation, (2022) *Frontiers in Immunology*:13, 10.3389/fimmu.2022.947213
4. Bagnall J., Rowe W, Alachkar N, Roberts R, England H, Clark C, Platt M, Jackson D, Muldoon M, Paszek P, Gene-specific linear trends constrain transcriptional variability of the toll-like receptor signalling, 2020, *Cell Systems*, 11, 1-15
5. Bagnall, J., Boddington, C., England, H., Brignall, R., Downton, P., Alsoufi, Z., Boyd, J., Rowe, W., Bennett, A., Walker, C., Adamson, A., Patel, N., O'Cualain, R., Spiller, D., Jackson, D., Muller, W., Muldoon, M., White, M. & Paszek, P. "A quantitative analysis of competitive cytokine signaling predicts tissue thresholds for the propagation of macrophage activation", *Science Signalling* 11(540),eaaf3998
6. Adamson A, Boddington C, Rowe W, Bagnall JS, Downton P, Lam C, Schmidt L, Harper CV, Spiller DG, Rand DA, Jackson DJ, White MRH and Paszek P. "Signal transduction controls heterogeneous NF-κB dynamics and target gene expression through cytokine-specific refractory states", *Nature Communications* 2016 *7:12057*