SONATA 17 - ABSTRACT FOR THE GENERAL PUBLIC
Applicant: Institute of Biochemistry and Biophysics PAS (IBB PAS), Warsaw, PL
Title: Immunity signalling platforms on intracellular bacteria

The niche of intracellular bacteria shields them from many canonical immune mechanisms while exposing them to a variety of cell-autonomous defences that differ greatly in nature between subcellular compartments. The intracellular immune system is a very complex machinery that relies on the synchronized action of many highly specialized signalling pathways to resist infection of microorganisms. It involves the recognition of the pathogen by the infected cell, various restriction mechanisms and the production of chemical factors that leads to the recruitment of specialised immune cells to the site of infection.

An ancient bacterial symbiont of all eukaryotic lineages, the mitochondrion, not only provides cellular metabolic power, but in metazoans this organelle is also a crucial player in co-ordinating anti-viral innate immune signalling pathways and apoptotic programs, such as RIG-I/MAVS signalling, and the NLRP3 inflammasome. Recently, the fundamental concept was unveiled that the outer membrane of present-day cytosol-invading bacteria is directly transformed by host restriction factors into a signalling platform to serve a similar purpose in anti-bacterial signalling as mitochondria in establishing the anti-viral state. Hierarchical action of interferon-induced GTP-ase family of guanylate-binding proteins (GBPs) converts the bacterial surface into a platform for activation of caspase-4 (CASP4), the non-canonical inflammasome sensor of cytosolic lipopolysaccharide. The activation of caspase-4 triggers gasdermin-D dependent cell death, pyroptosis, and secretion of the mature pro-inflammatory cytokine IL-18, thereby destroying the replicative niche for intracellular bacteria and alerting immune cells to the presence of infection. However, despite recent advances, the molecular details of how interferon-enhanced immunity protects the cytosol of human cells against bacterial incursion is not fully understood.

The aim of this project is to investigate interferon-inducible, anti-bacterial signalling platforms operating in the host cell cytosol, by a combination of cell and molecular biology methods and advanced biochemical assays. We will employ high-throughput microscopy-based method to identify new host factors required for efficient recruitment of known immunity protein to bacteria, and we will develop an in vitro system to investigate dynamics, mechanism of action, molecular organisation and downstream function of the GBP-CASP4 signalling platform. Finally, we will investigate so far unknown role in interferon-enhanced immunity of a host protein acting as a multifunctional signalling hub.

This research project will help us to understand the molecular mechanisms of innate immune initiating pro-inflammatory responses, which govern the anti-microbial defence of the host cell cytosol. In the future, this knowledge might lead to generation of therapeutics allowing to antagonize pathogens, including difficult to treat multidrug resistant strains, or reduce the excessive immune response, and hence impact on human health.