PROJECT TITLE: Interaction of natural killer cells with infected cancer cell population: microfluidics-based experiments and single-cell-level mathematical modeling

OBJECTIVES. The aim of the project is to analyze interactions of natural killer (NK) cells with an infected epithelial cell population at the single-cell resolution. We will investigate two respiratory epithelial cell lines: cancerous and non-cancerous, and two respiratory viruses: respiratory syncytial virus (RSV) and influenza A virus (IAV). Our main objectives are as follows:

a) Elucidation of the impact of the NK cell-induced cell death on the dynamics of propagation and eradication of RSV and IAV infections.

b) Determination of the potential of NK cells to induce immunogenic cell death in infected cells, that can potentially activate adaptive immune response.

c) Development of a droplet-based microfluidic system to perform experiments on co-cultures of epithelial and NK cells (living in droplets), that will enable data acquisition at the single-cell resolution.

d) Development of a mathematical model capturing interactions of NK cells with an infected cell population at the single-cell resolution.

METHODOLOGY. We will combine a microfluidic-based experimental techniques with methods of single-cell imaging and mathematical modeling. We will analyze interactions of NK cells with the population of infected epithelial cells, focusing on the physiologically relevant scenarios in which initial fraction of infected cells is small. As observed in our current studies, in such a case cell population responses are highly heterogeneous and the observed heterogeneities are important for development of innate immune response. We will overcome challenges arising in the study of such a heterogeneous cell population by integrating the following techniques:

a) Microscopy imaging of living cells using fluorescent markers that allow visualization of time-varying level of viral proteins, activation of key cellular proteins, and induction of cell death.

b) Microscopy imaging of fixed (non-living) cells that allow to measure levels of more components of the innate immune system, but in selected time points only.

c) Droplet-based microfluidic systems to culture epithelial and NK cells, and allow to apply measurement techniques from points a) and b).

d) Mathematical modeling accounting for stochastic effects in heterogeneous population responses. Mathematical models are indispensable to verify causative consistency of arising theories.

IMPACT. Outcomes of the project will increase our understanding of

a) The role of NK cells in elimination or suppression of virus propagation,
b) The role of NK cells in cancer immunotherapies,

and will advance microfluidics technologies in application in biomedical research.

The project will be conducted within cooperation between IPPT PAN (principal investigator institute) and SINTEF MiNaLab (partner institute).