# PhD Position in Cancer Research - Plasticity and Heterogeneity of Cancer

## JOB DESCRIPTION

The PhD programme will provide opportunities for research and teaching experience at the Institute of Biophysics of the Czech Academy of Science, Masaryk University, International Clinical Research Center and nearby research institutions in Brno, Czech Republic. PhD positions are available immediately to study various aspects of tumor heterogeneity and plasticity. Two PhD positions are available to outstanding young scientists with biological background and clearly demonstrated potential for future independent and highly successful scientific career.

## CANDIDATE PROFILE

Complete MA / Mgr. / MSc. Degree with experience in biochemistry, molecular biology or cell biology. Well-organised and motivated.

## WE OFFER

International multidisciplinary team engagement in highly ambitious projects of medical biology research. Work in an inspiring and highly collaborative environment. Various opportunities for further education, training and professional growth.

## APPLICATIONS

The candidates are invited to send their CV (including contact details, nationality and current address, education, degrees and dates) and the statement of their research interest (e.g., a cover letter explaining why you apply for this project and why you are the perfect candidate). Please, send the applications directly to Karel Soucek, Ph.D.(ksoucek@ibp.cz).

Deadline: By 30 March 2018 (with official interview at MU in the 2nd half of June)

Start date: August/September 2018

## Project Description

Institute of Biophysics of the Czech Academy of Sciences

International Clinical Research Center

Department of Experimental Biology – Faculty of Science, Masaryk University, Brno

The intratumoral heterogeneity (ITH) and heterogeneity in microenvironmental constituents significantly account for patient prognosis and response and resistance to therapies. ITH, characterized by the presence of multiple distinct clones of cancer cells within a single tumor, is one of the main obstacles in effective cancer treatment. Since the cancer is in general considered to arise from a single cell, mechanisms that induce cancer cell plasticity and clonal evolution must take place during the tumor growth. The resulting ITH, thus, can be driven and maintained by multiple pathways, including events associated with the acquisition of novel genetic mutations, epigenetic changes and stimuli from other key players of the tumor microenvironment, such as fibroblasts, stromal cells, and immune cells. One of the widely accepted mechanisms, contributing to ITH and driving the cancer cell plasticity is an epithelial-to-mesenchymal transition (EMT), an evolutionarily conserved, developmental program often misused by cancer cells. A typical hallmark of EMT is the loss of epithelial features, giving rise to mesenchymal cancer cells with decreased cell-to-cell adhesion and increased motility. As some of these mesenchymal clones may possess a stem-like phenotype, these cells are prone to therapy resistance and immune evasion. Such highly motile and invasive cancer cells easily intravasate tumor vasculature, survive in circulation and colonize distant tissues. Quiescent, disseminated cancer cells also contributes to late recurrences and latent metastasis. We hypothesize that the activity of a stem-like and mesenchymal transcriptional program is manifested also on the surface of these rare cells.

To shed a new light on ITH, we introduced a high-throughput, flow cytometric screening platform for simultaneous analysis of hundreds of cell surface antigens in multiple cell lines in a single run. Such analysis of surface fingerprint of multiple epithelial cell lines and their mesenchymal counterparts revealed distinct surface changes, accompanying EMT in these models. To prove the clinical relevance of our findings, we further validated heterogeneity in expression of ten most robustly changed antigens, denoted as ‘ten molecule surface signature’, in dissociated patient samples at single cell resolution.

The analysis of clinical specimen surfaceome revealed an unexpected degree of ITH and epithelial-mesenchymal plasticity. For this reason, we adjusted the previously introduced multicolor panel for sorting of a limited number of viable cells from selected subpopulations and optimized the pipeline for their subsequent RNA-seq analysis. To describe the role of these rare cancer cell subtypes in tumor microenvironment and dissemination to secondary sites, we plan to analyze their transcriptional programs and introduce subpopulation-specific molecular signatures. Identification of novel key drivers, modulators and markers of mesenchymal phenotype and description of their function may, with future research, help to develop cancer-specific targeted therapies.

**SELECTED PUBLICATIONS:**

•Remšík, J. et al. Plasticity and intratumoral heterogeneity of cell surface antigen expression in breast cancer*.* ***Br J Cancer***, in the press, (2018).

•Samadder, P. *et al.* Synthesis and Profiling of a Novel Potent Selective Inhibitor of CHK1 Kinase Possessing Unusual N-trifluoromethylpyrazole Pharmacophore Resistant to Metabolic N-dealkylation. ***Mol Cancer Ther*** **16**, 1831-1842, (2017).

•Slabakova, E. *et al.* Opposite regulation of MDM2 and MDMX expression in acquisition of mesenchymal phenotype in benign and cancer cells. ***Oncotarget*** **6**, 36156-36171, (2015).