Vacant post-doc position,
focusing on mechanisms of action of glycolytic enzymes in cancer onset and progression

Term: January 1, 2019 – December 31, 2020

Project annotation: Metabolic requirements and regulatory processes in proliferating tissues such as fetal and cancer tissues differ from those in most terminally differentiated tissues. Cancer cells often have increased rates of glucose uptake but decreased rates of oxidative phosphorylation, they produce high levels of lactate, regardless the presence of oxygen and fully functioning mitochondria. This reprogramming of energy metabolism in cancer cells is considered one of the hallmarks of cancer and is known as either the Warburg or Crabtree effect. The Warburg effect denotes the long-term reprogramming of the cell, whereas the Crabtree effect denotes the short-term, reversible change in cellular metabolism in the same direction. While most tissues use the standard Embden-Meyerhof-Parnas pathway, mounting evidence suggests that the Warburg cycle is characteristic not only for cancer cells but also for multiple healthy tissues that face hypoxic conditions, particularly during embryogenesis and metamorphosis. Glucose phosphorylation is needed for all the above-described modes of glycolysis, and thus, the hexokinases have emerged as key enzymes needed for a sufficient energy supply in cancer cells. So far, principles how cancer cells alter metabolic phenotype are unknown. Many recently published studies have focused on isoforms of glycolytic enzymes and their regulations, since up-regulation of glycolytic genes was reported in cancer. Among glycolytic enzymes, hexokinases and pyruvate kinases, which catalyze the first and the last irreversible steps of glycolysis, respectively, are significantly up-regulated in cancer. These enzymes play a dual role of key cell metabolism drivers and regulators; however, the research on hexokinase and pyruvate kinase isoforms is still nascent and challenging. Particularly, comprehensive studies that would have described the uniqueness and substitutability of isoforms of hexokinase and pyruvate kinase are lacking. Concurrently, there is no experimental study, which would have focused on somatic cancer variations in glycolytic enzymes. The study on influence of these variations may help to understand how cancer cells may benefit from changes in properties of their key glycolytic enzymes. This post-doc project should thus contribute essential fragments of the mosaic of cellular metabolism in health and disease, and make it less puzzled. Recently, we formed a pipeline allowing effective and straightforward analysis of enzyme kinetics of hexokinases. We also substantially improved *in silico* predictions and suggested tailoring of state-of-the-art prediction methods, which are to be used in the proposed project. There is a synergy with institutional projects funded by the University, which aim to deliver and analyze a series of hexokinase 1 and hexokinase 2 knock-in cell lines by means of the CRISPR/Cas9 technology and allowed to develop the improvement of specificity of prediction methods and to conduct detailed analyses of diabetes and cancer-associated variations in the glucokinase. This post-doc position is aimed to build upon these projects and focus on the role of hexokinases and pyruvate kinases in cancer onset and progression, to elucidate the effects of cancer-associated variations of these molecules at the cellular level, and to find out the mechanisms that would allow to suppress their role in cancer onset and progression. Details of this post-doc project are to be set up based on the interaction with the candidate and based on candidate's prior wet lab experience as the ability to propose both ambitious but solvable project on a topic of choice belongs to key competencies used for the evaluation and scoring of the applicants.

Conditions: https://www.cuni.cz/UKEN-178.html#7

Renumeration: 30.000 EUR/year (monthly 1000 EUR from the Med School + 37.500 CZK, which is approx. 1500 EUR according to current exchange rate, from the university rectorate), minus mandatory taxes and insurance.

Mandatory attachments to the application:

- Application form: https://www.cuni.cz/UKEN-178-version1-uken_178_version1_application_form_postdoc.doc
- Letter of reference form: https://www.cuni.cz/UKEN-178-version1-uken_178_version1_postdoc_letter_of_reference.doc
- Detailed CV
- List of publications
- Copy of university diploma

Application procedure: After initial consultation with the PI, the applicant draws up a detailed project plan and submits it to the faculty by the stated deadline. His/her application must include a CV and a list of publications, a statement from his/her PhD supervisor, and a letter of recommendation from the head of the department or institute where the applicant studied for his/her doctorate ('Application for a post-doc grant at Charles University' and 'Letter of reference').

Application deadline: July 20, 2018 (first contact), **August 3, 2018** (application submission to the rectorate of the university)

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