PhD stipend offer in the research project OPUS

Impact of oncogenic mutations on information transmission in the MAPK signaling pathway

(*Wpływ onkogennych mutacji na przepływ informacji w szlaku sygnałowym MAPK)*

financed by the National Science Foundation (Poland).

Information about the project and stipend

Principal Investigator: prof. Tomasz Lipniacki
Project duration: 48 months
Institution: Institute of Fundamental Technological Research, Polish Academy of Sciences

We offer 5000 PLN/month stipend for 48 months, starting from September 1, 2020.

PROJECT ABSTRACT

Signaling pathways transmit and process cytokine signals to effector kinases such as ERK or AKT, that regulate key physiological cellular processes. We conjecture that pulsatile cytokine stimulation is physiologically most ubiquitous due to local secretion and subsequent endocytosis of receptor-bound cytokines, and that this stimulation mode enables information transmission at the highest rate (of several bits per hour per cell). We also hypothesize that oncogenic mutations of the ERK and AKT pathway components diminish the capacity of these pathways to properly transmit cytokine signals, which leads to improper regulation of proliferation, apoptosis and motility. Throughout the project we will thus focus on pulsatile stimulation and use information theory to analyze the impact of oncogenic mutations on signal transmission.

OBJECTIVES: The main aim of the project is to determine the influence of oncogenic mutations, G12V in KRAS and H1047R in PI3K, on the information transmission rate and regulation of proliferation, apoptosis and motility. Our main objectives are as follows:

1) Quantification of the upper limit for information transmission rate for WT and KRAS- or PI3K-mutated cells. We aim to verify our conjecture that mutations decrease the bit rate by causing spontaneous ERK activation events and by broadening temporal ERK activity profile.
2) Analysis of the mechanism of spontaneous onset of ERK and AKT activity in cells with oncogenic mutations. We will investigate whether these onsets of activity are spatially organized across cell monolayer.
3) Analysis of local RAS activation and subsequent signal transmission to RAF/MEK/ERK in response to light activation of opto-FGFR in a small fraction of the cell membrane. We hypothesize that local RAS activation has a switch-like character, but when averaged over the whole cell membrane it is gradual. Consequently, AKT activation is also gradual, proportional to the fraction of the membrane harboring active RAS, while the ultra-sensitivity resulting from bisphosphorylation of MEK and ERK causes switch-like activation of ERK.
4) Development of a mathematical model of the ERK/AKT pathways crosstalk, that captures spatial effects of RAS activation. Development of an agent-based model (with cells as agents executing a regulatory program) of ERK activity propagation in the epithelium in response to single-cell apoptosis or wounding.

METHODS: We will use WT and PI3K- or KRAS-mutated MCF-10A cell lines harboring light-activated FGFR (fibroblast growth factor receptors) as well as ERK and AKT activity markers. These lines, developed recently by our project partner, Prof. Olivier Pertz (Institute of Cell Biology, Bern, Switzerland), will allow us to stimulate cells with precisely defined pulsatile protocols and use live confocal imaging to obtain time profiles of ERK and AKT activity. RAS and PI3K activity reporters, introduced using transient transfections, will be used to record local activation of these proteins in TIRF live imaging. On the mathematical side, to construct and analyze computational models we will use partial differential equations, stochastic agent-based modelling, as well as information theory to estimate the bit rate from the gathered data.

IMPACT/SIGNIFICANCE: For the first time, based on single-cell time-lapse data, we will estimate information transmission rate in the signaling cascade. We will determine whether and to what extent this rate is decreased by the oncogenic mutations in the ERK pathway (G12V in KRAS) and in the cross-talking AKT pathway (H1047R in PI3K). Oncogenic mutations, in addition to causing an overall increase in ERK and AKT activity, may render cancer less controllable by external signals. This can be a limitation for cancer therapies that aim only at reducing activation of the ERK and AKT pathways.

Requirements for candidate
The recruitment will follows the rules of the National Science Foundation (Poland) given in

https://ncn.gov.pl/sites/default/files/pliki/uchwaly-rady/2019/uchwala25_2019-zal1.pdf

For our challenging project we seek outstanding master degree candidate who ideally should combine some wetlab experience with good mathematical/physical background. The candidate is expected to:

conduct single cell experiment,
analyze fluorescent microscopy data,
build mathematical models using ODE/PDE as well Markov processes formalism,
use information theory to characterize behavior of molecular regulatory pathways.

Required documents
1. Copy of MSc diploma. Bachelor diplomas may be also included for evaluation.

2. CV containing information about:
Publications,
Conference presentations,
Prizes and stipends,
As well as other information that can help to evaluate, experience, achievements, and scientific standing of the candidate.

Please include in your CV the following clause: "I agree to the processing of personal data contained in my job offer for the needs necessary to carry out the recruitment process conducted by IPPT PAN with headquarters in Warsaw, ul. A. Pawińskiego 5B, according to art. 13 para. 1 and 2 of Regulation (EU) 2016/679 of the Parliament and of the Council of 27 April 2016 on the protection of individuals with regard to the processing of personal data and the free movement of such data and the repeal of Directive 95/46 / EC (RODO).

The documents should be sent till July 24, 2020 to the Project PI, prof. Tomasz Lipniacki tlipnia@ippt.pan.pl with a copy to Department Secretary Ms. Agnieszka Ponarska aponar@ippt.pan.pl. If needed the candidates will be contacted and invited for the interview.