DATE: Day 4 Month 5 Year 2021

SUMMARY of
2020 RESEARCH RESULTS REPORT
For International Collaborative Research with IPR, Osaka University

Research Title		**Analysis of cell cycle dynamics by integration of mathematical-experimental approach**
Applicant	**Name**	**Boris Kholodenko**
	Affiliation	**Systems Biology Ireland, University College Dublin**
	Present Title	**Full Professor**
Research Collaborator (Host PI)		**Mariko Okada**

Summary

The cell cycle machinery, one of the most fundamental cell fate decision mechanisms, is the sequence of events in which a cell divides into two daughter cells. Elucidating the mechanism of the cell cycle is a basic yet uncomprehended question in cell biology. The cell cycle regulation is known to be coupled with oscillations of the core cell cycle components, cyclins and cyclin-dependent kinases. However, it remains unclear how these oscillators orchestrate to progress the cell cycle in a molecular network due to the lack of theoretical models incorporating the oscillatory dynamics. The core cell cycle components are regulated by positive- and negative- regulation. Currently, we are investigating an antagonistic relationship between positive regulation controlled by mitogenic signal cascades, such as ERK and AKT pathway, and a negative regulation involved in DNA damage which have been shown to activate p53 and leads to cell-cycle arrest because we assume escape from cell-cycle arrest is characterized by a switch in the balance between ERK/AKT pathway and p53 pathway. The main goal is to find the border surfaces between proliferation and cell cycle arrest in a 3D space of ERK, AKT and p53 activities, and we should find out which experiments could be combined with the developed model into one paper. In our study, the result of MTS assay showed that the border surfaces between proliferation and cell cycle arrest were observed by using different concentration of serum and nutlin-3, and this result could validate our previous theoretical models. In addition, these results also indicated that high levels of ERK and AKT induced by serum stimulation could overcome p53-dependent cell-cycle arrest. Fucci imaging data showed that sufficient ERK activation does not affect the entry point of cell cycle, but it affects the completion of the cell cycle. This time, the theoretical model indicated that an increase of AKT, but not ERK, can counter-act p53-induced cell cycle arrest. It is considered that the AKT activity would affect oscillations such as cyclin D1 to compete with DNA damage. To clarify this model, further analysis will be needed. The continued acceleration of our collaboration research would progress the creation of this model and advance our understanding of cell cycle dynamics as regulated by p53, AKT and ERK levels.

***Deadline: April 30, 2021**
***Please submit it to E-mail: tanpakuken-kyoten@office.osaka-u.ac.jp.**
***Please describe this summary within 1 sheet. Please DON'T add some sheets.**
***This summary will be published on the web.**