DATE: Day 2 Month May Year 2024

SUMMARY of
FY2023 RESEARCH RESULTS REPORT
For International Collaborative Research with IPR, Osaka University

Research Title		Computational modelling of EML4-ALK signaling pathway
Applicant	**Name**	Iosifina Sampson
	Affiliation	Faculty of Biological Sciences, School of Molecular and Cellular Biology, University of Leeds
	Present Title	Postdoctoral Researcher
Research Collaborator (Host PI)		Mariko Okada

Summary

A fusion between EML4 (echinoderm microtubule associated protein-like 4) and ALK (anaplastic lymphoma kinase), EML4-ALK, was discovered in non-small cell lung cancer (NSCLC) in 2007, and there are at least 15 different variants that differ in the breakpoint in the EML4 gene. EML4 is a member of EML protein family with functions in microtubule regulation and mitotic spindle organisation. ALK is a tyrosine kinase receptor and studies have shown that point mutations, gene amplification or gene fusions lead to oncogenic activity of ALK. The EML4-ALK fusion leads to abnormal cell signaling of PI3K/AKT, RAS/RAF, JAK/STAT and MEK/ERK and consequently increased cell proliferation and cell survival. Patients identified with EML4-ALK mutation are treated with selective ALK inhibitor such as crizotinib, ceritinib, alectinib or lorlatinib, however the type of variant influences the response of patients to ALK therapy and secondary mutations that confer resistant to these inhibitors arise in some patients within a year. The most frequently occurring variants, variant 1 and 3a/b are expressed in 33% and 29%, respectively, of positive EML4-ALK patients.

We generated a computational model that will describe resistant signalling pathways of EML4-ALK V1 and V3a/b developed by ALK inhibition, to predict drug response and new targets of each variant in response to ALK inhibition. We jointly have established a successful beginning for this project to developed a modelling platform, called BioMASS, to estimate the parameters of our model describing the biological processes of the EML4-ALK signaling. We have extended the current project and we plan to predict patient responses to ALK drugs by using a newly developed framework called Pasmopy developed by Mariko's group.

An extension to the current mathematical model, we will focus on the interactions between adaptor/signalling proteins and EML4-ALK fusion proteins. We will be able to determine the dynamic interactions between those in the presence of ALK-TKIs such as lorlatinib. We can also explore how long they reside within the EML4-ALK condensates by live cell imaging and by measuring their intensity under those conditions.

It is worth to mentioned that due to the influence of COVID-19, Iosifina Sampson was not able to visit IPR and we were not able to carry out our international collaborative research for the year 2020.

***Deadline: May 10, 2024**

***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.**