DATE: Day 01 Month 05 Year 2026

SUMMARY of
FY2025 RESEARCH RESULTS REPORT
For International Collaborative Research with IPR, The University of Osaka

Research Title		Mathematical modelling of EML4-ALK-bound adaptor proteins in condensates
Applicant	**Name**	**Josephina Sampson**
	Affiliation	**University of Leeds**
	Present Title	**Research Fellow**
Research Collaborator (Host PI)		**Prof Mariko Okada**

Summary

The EML4-ALK fusion arises through a paracentric inversion between EML4 and ALK genes on chromosome 2 and is found in 2-9% of patients with lung adenocarcinomas. 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. EML4-ALK proteins form cytoplasmic condensates that orchestrate oncogenic signalling and reveal that their assembly depends upon the conformational state of the catalytic domain and can be differentially modulated by structurally divergent ALK inhibitors. We aim to distinguish the binding competition of adaptor signalling proteins (SHC, SHP2, GRB2, SOS1) between EML4-ALK and EGFR/ERBB3(HER3) in EGF/HRG stimulated ALK+cells. Our initial results demonstrate that the mathematical modelling recapitulates the crosstalk between EML4-ALK and ERBB receptors under several conditions. The experimental data showed a prominent viability decrease in several conditions tested with ALK and ERBB inhibitors. Our initial analysis highlighted the PI3K activity as a top-ranked target to inhibit cell viability. **In the proposed study we observed downstream targets such as PI3K and AKT activities that are affected or not upon loss of EML4-ALK activity. We identified new potential targets that might be used in combination treatment with ALK inhibition for a higher sensitivity to kill those cancer cells.** We already have an extensive set of novel experimental data on the response of EML4-ALK cancer cells to ALK inhibitor, and the collaborative work proposed here will increase the impact of the study by providing a network level of understanding. 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. **Importantly, the ultimate impact of this project is to be able to identify new targets to tackle EML4-ALK signalling pathways that will be beneficial for a precise personalised treatment of patients with EML4-ALK positive NSCLC.**

***Deadline: May 11, 2026**
***Please submit it to E-mail: tanpakuken-kyoten@office.osaka-u.ac.jp.**
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