DATE: Day 22 Month April Year 2024

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

Research Title		Does the KSR scaffold control dose-responses to RAF and MEK inhibitors and their combinations in RAS mutant cells?
Applicant	**Name**	Boris Kholodenko
	Affiliation	Systems Biology Ireland, University College Dublin
	Present Title	Full Professor of Systems Biology, Director of Computational Modelling
Research Collaborator (Host PI)		Mariko Okada (Mariko Okada)

Summary

The perfect fit of a drug to a target does not always imply high biological efficacy. Paradoxical RAF activation, i.e., RAF inhibitors (RAFi) activating the ERK pathway rather than inhibiting it, shows our limited knowledge of drug effects at the cell level. Increasing evidence suggests that allosteric interactions of RAFi and MEKi with a variety of protein complexes of the ERK cascade, intertwined with multiple feedback regulations, dramatically change the responses of ERK signaling to clinically used drugs. Complex interactions between multiple RAS/KSR/RAF/MEK isoforms and clinically used kinase inhibitors result in our poor ability to predict the efficacies of these drugs. Pseudokinases, KSR1 and KSR2, related to the RAF family kinases have been described as scaffolds, which assemble KSR-MEK-RAF-ERK complexes. Recent structural work has led to new insights into KSR function. KSR does not merely work as a scaffold channeling the successive phosphorylations from RAF to MEK to ERK via the assembled three kinase complex. To a certain extent, KSR resembles a catalyst: MEK binding to the kinase domain of KSR allosterically drives the BRAF–KSR1 heterodimerization through a conserved side-to-side interface, resulting in BRAF activation. Active BRAF bound to KSR1 phosphorylates and activates free MEK molecules in the bulk phase. Therefore, the KSR1 abundance influences the efficacy of clinically used MAPK pathway inhibtors.

Combining modeling and experiments being conducted in Prof. Okada's lab, we systematically delineated how the KSR1 abundance and conformational specificity of RAF and MEK inhibitors control drug responses of the RAS/RAF/KSR/MEK/ERK pathway in RAS-mutant cancer cells.
We showed that the KSR1 abundance critically affects the potency and efficacy of conformation-selective drugs and predict and experimentally validate best inhibitor combinations. Our findings demonstrate that for the same RAS-mutant cancer types, responders and non-responders can merely differ by the abundance of KSR1.

***Deadline: May 10, 2024**
***Please submit it to E-mail: tanpakuken-kyoten@office.osaka-u.ac.jp.**
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