BDR SEMINAR in Osaka

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14:00-15:30, 3F Large Conference Room, QB Building A

Getting Insights into Cell Biology by Network Reconstruction and Modelling

Summary

Omics technologies have generated large inventories of genes, transcripts, proteins, and metabolites. The challenge is to find out how they work together to regulate cellular responses to external and internal cues. Computational models provide insight into the intricate relationships between stimuli and cellular responses. I first overview a suite of physics-based methods, known as Modular Response Analysis, which infer both direct causative connections and their strengths in cellular signaling and gene networks from perturbation data (https://www.ncbi.nlm.nih.gov/pubmed/12242336). Further, I show that drug resistance resulting from dimerization of kinases (such as, BRAF/CRAF, JAK2, etc.) can be explained by allosteric inhibitor effects and the emergence of different drug affinities between free kinase monomers versus dimers (https://www.ncbi.nlm.nih.gov/pubmed/26344764). Finally, I overview an exciting and counterintuitive discovery made using a new type of mathematical modelling, which combines aspects of protein structure, posttranslational modifications, thermodynamics, and dynamic reaction mechanisms (https://www.ncbi.nlm.nih.gov/pubmed/30007540). We used model predictions to block oncogenic RAS signaling in metastatic melanoma cells. RAS is mutated in 30% of all human cancers, and RAS mutated cancers are clinically considered to be undruggable and resistant to current treatments. Our approach identified non-intuitive drug combinations that synergize to block critical RAS effector pathways.

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