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Drug repurposing: From big data to therapeutics

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Of 71 anti-cancer drugs for solid tumors approved by the FDA between 2002 and 2014, the median gains in progression-free and overall survival are ~2 months. These observations suggest two potential unmet clinical needs: (1) the existence of drug resistance and (2) the importance of patient stratification. In other words, it is imperative to implement a companion diagnostic biomarker along with drug discovery pipeline. To address these two questions, we have accessed several big data to identify old drugs for anti-cancer drug discovery. Firstly, resistance to chemotherapy or targeted therapy is a major problem for systemic lung cancer treatment. Such resistance may be explained by cancer stem-like cell (CSC) theory. By using the Connectivity Map dataset, we have identified phenothiazine-like antipsychotic drugs which may reverse the CSC-associated gene expression. Further, the in vitro and in vivo experiments have validated its anti-CSC effects. This study demonstrated a novel platform for screening potential anti-CSC drugs, which may overcome the drug resistance. Secondly, synthetic lethality (SL) has emerged as a novel anti-cancer strategy. SL is an interaction between two genes such that simultaneous perturbations of two genes result in cell death or a dramatic decrease of cell viability, whereas a perturbation of either gene alone is not lethal. We evaluated several old oncology drugs and mapped their corresponding SL pairs. The predicted results were further validated via in vitro biochemical assay and retrospectively sequencing of patient specimens. In conclusion, this systematic analysis strategy could rapidly place old drugs with biomarkers for clinical study.

Genetic SL partner	Event	Phenotype
WT	-	Cell viable
Mutant	-	Cell viable
WT	Drug	Cell viable
Mutant	Drug	Cell death

Biography

Chi-Ying Huang has completed his PhD from Iowa State University and Postdoctoral Studies from School of Medicine, Stanford University, USA. He is the Professor of Institute of Biopharmaceutical Sciences, National Yang Ming University, Taiwan. He has published more than 140 papers in reputed journals.

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