Drug Discovery Through Drug Perturbation Pathway Modeling and Network Analysis

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Due to intrinsic complex molecular interactions, the "one disease – one target – one drug" strategy for disease treatment is no longer the best option to treat cancers. To assess drug pharmacological effects, we assume that "ideal" drugs for a patient can treat or prevent the disease by modulating gene expression profiles of this patient to the similar level with those in healthy people. A new approach for drug-protein interactions curation, drug-drug similarity network comparison, and integrative pathway model construction and evaluation was introduced to determine optimal drugs for various cancers. Drug-protein interaction curation is conducted to discover novel drug-protein relationships and is categorized as: up regulated, down regulated, indirect up or down, ambiguous and unknown. The manual curation can be utilized for drug repurposing and examining drug mechanism on a pathway level. A drug-drug similarity network model is built by examining similar targets, therapeutic mechanisms, side effects, and chemical structures. Drug similarity analysis is useful for drug repositioning because similar drugs may have compatible therapeutic or toxic effects for a disease. Drug similarity networks are constructed and examined through a molecular network visualization platform. An integrative disease-specific pathway model is also built to gain a more holistic view of disease mechanisms by including every significant disease-specific protein. Including drugs on the pathway through target information can also offer a clear mechanism for the drug's action. We also transform integrated pathways into network models and ranked drugs based on the network topological features of drug targets, drug-affecting genes/proteins, and curated disease-specific proteins. Combining our three approaches could potentially lead to advances in drug repurposing and repositioning.

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