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Computational shotgun drug repurposing for myriad diseases

Geetika Sethi[1], **Gaurav Chopra**[1,2], **George White**[1], **Mark Minie**[1], **Jeremy Horst**[1,2] and **Ram Samudrala**[1]
[1]University of Washington, USA
[2]University of California, USA

The goal of this study is to predict the drug behavior based on compound-proteome interaction signatures and generate high-value drug prioritizations from ranking indication-specific interaction signatures. We had previously developed a platform based on computational analysis of novel drug opportunities (CANDO) that can simultaneously predict the interactions of indication-specific drugs with a library of protein targets to generate a binary matrix of interaction signatures ("all" drugs × "all" protein structures × "all" indications), in effect inferring homology of drug behavior at a proteomic level. In the current study, a binary matrix of 180 million predicted interaction signatures (approx.) between 3,733 human ingestible compounds (FDA approved drugs and supplements) and 48278 proteins (universal proteome set) were first compared with each other and then ranked in an indication specific manner. We have developed a "hold one out" compound-centric benchmarking algorithm for 1439 disease indications (FDA and NLM), where there are at least two approved compounds so that one compound could be used as a test to fish for the other compound with the same indication. Compounds are ranked using the compound-proteome signature comparison approach and the accuracy is measured by whether related compounds are seen in the top 1% (37) of the rankings. This is contrasted to the results from best performing randomly generated matrix (out of 16) which is created by swapping the rows and columns randomly (so composition/distribution of interactions is the same). We analyzed the percentage accuracy of identifying compounds with the same indication within the top 1% (37) compounds or in other words, the likelihood that any given prediction of a compound will be effective as a drug for a particular indication. The top compounds produced by this integrated rankings method are considered to be putative repurposed drugs for their respective indications. For a total of 13746 compound-disease pairs, the average ranking for top 1% is 24.9%. Out of 1439, 654 disease indications showed a non-zero output for top 1% with an average of 33.1%. To conclude, we have developed a drug repurposing platform that considers compound-proteome interaction signatures to predict drug behavior and uncovers potential drug candidates that can be repurposed for multiple indications.

gs32@uw.edu