Hypothesis Fusion to Improve the Odds of Successful Drug Repurposing

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The prediction of triangular drug-target-disease (DTD) or drug-target-side effect (DTE) relationships has been at the core of modern rational approaches to drug discovery or reprofiling. These approaches include targeted biological screening; chemical genomics profiling; and, to a smaller extent, text mining to identify well-studied drug-target and target-disease pairs to infer novel drug-disease linkages.

We advocate for an approach that fuses hypotheses generated in the aforementioned types of studies to establishing most reliable and experimentally testable DTD (or DTE) hypotheses. In a case study, we have applied this approach to the discovery of novel anti-Alzheimer indications for existing drugs1. We integrated predictions from two independent approaches: (i) QSAR models, which predicted drugs interacting with serotonin 5HT6 receptor, a known Alzheimer target, and (ii) the cmap approach2 that predicted possible anti-Alzheimer drugs based on anti-correlation of drug-induced gene expression profiles and those of the Alzheimer patients. Selective estrogen receptor modulators (SERMS) have been identified and experimentally validated as 5HT6 binders and memory and cognition enhancers. In another recent study3, we have merged concepts from pharmacovigilance, cheminformatics, and pharmacoepidemiology to identify medications likely to cause Stephens-Johnson syndrome (SJS).

The recently funded BD2K grant (1U01CA207160-01) targets the development of the integrated drug repurposing platform integrating approaches from social media mining, cheminformatics, and text mining toward the discovery of novel indications for existing drugs. We expect to identify (possibly, weak) hypotheses concerning unusual effects of medications reported in the social media. Since biological targets for many diseases are often known, we expect to use cheminformatics approaches to evaluate if direct interaction between drugs implicated in social media in connection with a disease, could bind to the known disease target. In parallel, we also plan to mine biomedical literature and, if possible, electronic medical records, to find confirmation of novel DTD relationships in clinical records.

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