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INFORMATICS

New targets for old drugs

Unexpected drug side effects may often be attributed to actions on additional targets (off-targets) to those for which they were designed for. Now, writing in *Science*, Campillos and colleagues exploit side-effect profiles to determine the likelihood that drugs act on the same target molecule and identify novel potential therapeutic applications for marketed drugs.

Off-target effects are typically unwanted and may be harmful, but in some cases they have proved beneficial, resulting in new and unexpected indications for drugs. Furthermore, similar side effects evoked by unrelated drugs have, in some cases, been shown to be due to their common off-target interactions.

With these observations in mind, Campillos and colleagues proposed that a shared side-effect profile between drugs may be used to predict previously unknown targets. To test this theory, Campillos and colleagues first devised a computational measure for side-effect similarity. Side effects were classified according to the Unified Medical Language System ontology for medical symptoms using information from drug package inserts. As not all side effects are independent of one another and some occur more frequently than others, side effects were weighted accordingly.

Using these weighting schemes and incorporating assessments of statistical significance, a measure for side-effect similarity was established. The predictive power of this measure was then assessed using a reference set of 502 drugs with known human targets. Within this set, a clear correlation between side-effect similarity and the likelihood that two drugs share a protein target was identified.

To further investigate the potential of their predictive technique, the authors analysed a larger set of 746 human marketed drugs for which side-effect information was available, 244 of which were without annotated human targets. Based on similarities in side effects, they predicted 1,018 pairs of drugs to share a target, with a probability of at least 25%. A network was constructed from the corresponding 424 drugs, in which 261 pairs represented chemically dissimilar drugs from distinct therapeutic indications. Twenty of these drug pairs were selected for further analysis in *in vitro* cell assays. Binding activity to at least one of the predicted targets was verified for 13 out of the 20 drug pairs, 11 of which exhibited binding affinities strong enough to cause side effects. Among these confirmed predictions was the identification of two previously unknown nervous system off-targets for the proton-pump inhibitor rabeprozole: the dopamine receptor (DRD3) and the serotonin receptor (HTR1D). Rabeprozole, currently used as an anti-ulcer drug, may therefore have potential applications in additional therapeutic categories.

The application of this technique to marketed drugs or as a preclinical screen has the potential to expedite drug development and may also provide novel insight into the molecular basis of drug side effects.

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ORIGINAL RESEARCH PAPER Campillos, M. *et al.* Drug target identification using side-effect similarity. *Science* **321**, 263–266 (2008)