CHEMOINFORMATICS

Where 'magic bullets' go astray

The concept of 'magic bullets' — drugs with high specificity for their target — was introduced by Paul Ehrlich almost 100 years ago. Since then, it has become clear that most drugs exhibit some degree of polypharmacology, with off-target effects that can contribute to unwanted side effects, but also to the drug's effectiveness. Reporting in *Nature*, Keiser and colleagues now present a statistics-based chemoinformatics approach that identifies the targets responsible for the polypharmacology of known drugs.

Unlike bioinformatic approaches that predict drug–target associations based on sequence or structural similarity between targets, the new 'similarity ensemble approach' (SEA) defines each target by its set of known ligands and then searches for two-dimensional structure similarities between drugs and ligands. As this compares ligand similarity rather than protein target similarity, the predicted common targets are often not related to each other.

The authors employed SEA to compare 3,665 FDA-approved and investigational drugs with over 65,000 ligands, which defined 246 drug targets. Thousands of unanticipated associations were predicted and analysed both retrospectively against known associations and prospectively for unreported drug pharmacology. Out of nearly 200 predictions without any precedent in the literature, 30 were validated experimentally in radioligand competition binding assays, and 23 interactions were confirmed. Interestingly, some of these crossed major target boundaries — for example, the HIV1 reverse transcriptase inhibitor delavirdine was found to also bind to the histamine H_4 receptor, a G protein-coupled receptor.

The new insights into off-targets of specific drugs provide fascinating clues to their mechanism of action. For delavirdine, the histamine receptor-binding activity detected by SEA could explain the painful rashes the drug can cause. Fluoxetine and paroxetine, both of which are selective serotonin reuptake inhibitors, were found to interact with β-adrenergic receptors. This could explain some of the drug's side effects, including nausea and decreased libido.

One drug that was further investigated in the study was the hallucinogen *N,N*-dimethyltryptamine (DMT), a psychoactive compound that is present in the hallucinogenic brew Ayahuasca. It had previously been identified as a regulator of the opioid σ_1-receptor. As a large number of non-hallucinogenic drugs also target this receptor, the authors tested whether the hallucinogenic properties are the consequence of an association with serotonin receptors, which was predicted by SEA. Indeed, a mouse model confirmed that 5-HT_{2A} is in fact the primary target for the hallucinogenic effects of DMT.

The authors caution that SEA does produce false positives (approximately one-third of results), as it compares drugs with ligand sets on the basis of all shared chemical patterns. It can therefore predict activity for drugs that share many features with the ligand of a target, but lack a crucial chemotype. Nevertheless, as a systematic and comprehensive method for the exploration of drug–target interactions, this is an exciting new tool in the prevention of drug safety issues and the exploration of therapeutic opportunities.

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ORIGINAL RESEARCH PAPER Keiser, M. J. *et al.* Predicting new molecular targets for known drugs. *Nature* **462**, 175–181 (2009)