Determining Success or Failure in Cholesterol-Controlling Drugs

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Researchers at the University of California, San Diego have discovered that a complex network of interactions between drugs and the proteins with which they bind can explain adverse drug effects. Their findings suggest that adverse drug effects might be minimized by using single or multiple drug therapies in order to fine-tune multiple off-target interactions.

Philip Bourne, PhD

"The traditional way of thinking of one drug binding to only one receptor to treat a single disease is outmoded," said Philip Bourne, professor of pharmacology with UC San Diego's Skaggs School of Pharmacy and Pharmaceutical Sciences. "We found that a drug may have a cumulative effect through acting on multiple receptors at the same time, rather than acting on a single receptor."

The term polypharmacology has been coined to describe this phenomenon, which may explain the failure of an anti-cholesterol drug called Torcetrapib which – after 15 years of research and $850 million in development costs – was withdrawn from stage III clinical trials as a result of instances of cardiovascular disease which resulted in death.

"Torcetrapib actually acted on a dozen different receptors, resulting in an unanticipated side effect," said Bourne. "This multi-inhibitor binding pattern may not be at all unusual."

In studying protein-drug interaction networks of a class of drugs known as cholesteryl ester transfer protein (CETP) inhibitors, and aided by computational modeling done at the San Diego Supercomputer Center (SDSC) at UC San Diego, the research team found evidence that CETP inhibitors bind to a variety of receptors. Their work, published in the May 15 issue of *PLoS Computational Biology*, uses a novel computational strategy to identify protein-ligand binding

profiles on a genome-wide scale. In this case, the strategy was applied to explain the molecular mechanisms associated with adverse drug effects.

"At this time we do not have a complete structural proteome to analyze, one that maps all the protein structures in the genome – either experimental or model – to which drugs could bind," said Bourne, director of structural bioinformatics and an SDSC Distinguished Scientist. "So though we still may not have a complete understanding of off-target binding, this strategy is already useful."

Studying the panel of off-targets for Torcetrapib and other CETP inhibitors from the human structural genome, the researchers mapped those targets to biological pathways using the existing literature. "The predicted protein-ligand network is consistent with experimental results from multiple sources and reveals that the side-effects of CETP inhibitors are modulated through the combinatorial control of multiple, interconnected biochemical pathways," said Li Xie, lead author on the study.

In other words, Xie explained, a combination of many different pathways, impacted when a molecule or ligand binds to several receptors, possibly inhibiting a number of different proteins – all lead to the overall physiological effect of that drug.

Besides the CETP inhibitor, Torcetrapib, two related drugs, Anacetrapib and JTT-705, were also analyzed. The final panel of off-targets for these drugs is associated with many physiological processes including cell proliferation, inflammation and hypertension.

"Ironically, Torcetrapib is more specific than JTT705, yet it is less effective in controlling cholesterol levels with minimal side effects," said Lei Xie, a senior scientist in the Bourne group and the major developer of the computational methodology. "This is contrary to conventional wisdom, which implies that the more specific the binding, the fewer the side-effects."

For example, JTT-705 has a binding profile that impacts numerous biological pathways, but none of them result in hypertension – a side effect that is observed in the Torcetrapib, which binds more specifically.

Among a number of cumulative effects, the scientists predicted different binding profiles of CETP inhibitors to several nuclear receptors. They discovered that JTT-705, unlike Torcetrapib, is involved in the activation of nuclear receptors that contribute to both positive and negative control of aldosterone, a hormone responsible for increased blood pressure. This differs from Torcetrapib, which only increases aldosterone production and therefore has a purely positive, or increased, effect on blood pressure.

Mapping the off-targets to biochemical pathways that are currently known provides new insights with the potential to improve the design of effective and safe pharmaceuticals.

"This work extends the scope of chemogenomics – the study of genomic responses to chemical compounds – and exemplifies the role that systems biology has in the future of drug discovery," Bourne said.

An additional contributor includes Jerry Li, from Torrey Pines High School in San Diego. This work was supported by a grant from the National Institutes of Health.

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