New computational technique can predict drug side effects

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Early identification of adverse effects of drugs before they are tested in humans is crucial in developing new therapeutics, as unexpected effects account for a third of all drug failures during the development process.

Now researchers at the University of California, San Diego (UCSD) have developed a novel technique using computer modeling to identify potential side effects of pharmaceuticals, and have used the technique to study a class of drugs that includes tamoxifen, the most prescribed drug in the treatment of breast cancer. Their study is currently available on line at *PLoS Computational Biology*.

Conventional test methods screen compounds in animal studies in advance of human trials in the hope of identifying the side effects of promising therapeutics. The UCSD team – led by Philip Bourne, Ph.D., professor of pharmacology at UCSD's Skaggs School of Pharmacy and Pharmaceutical Sciences and Lei Xie, Ph.D., of the San Diego Supercomputer Center at UCSD – instead uses the power of computational modeling to screen specific drug molecules using a worldwide repository, the Protein Data Bank (PDB), containing tens of thousands of three-dimensional protein structures.

Drug molecules are designed to bind to targeted proteins in order to achieve a therapeutic affect, but if the small drug molecule that functions as a "key" attaches to an off-target protein that has a similar binding site, or "lock," side effects can result.

To identify which proteins might be unintended targets, the UCSD researchers take a single drug molecule and look for how it might bind to as many of the proteins encoded by the human proteome as possible. In this published case study, they looked at Select Estrogen Receptor Modulators (SERMs), a class of drug that includes tamoxifen, to illustrate the novel approach.

“The computer procedure we developed starts with an existing three-dimensional model of a pharmaceutical, showing the structure of a drug molecule bound to its target protein; in this case, the SERM bound to the estrogen receptor,” said Bourne, who is co-director of the PDB. The scientists then use computer analysis to search for other binding sites that match that drug binding site – like looking for other locks that can be opened by the same key.

In this study, the team found a previously unidentified protein target for SERMs. The identification of this secondary binding site explains known adverse effects, and opens the door to modifying the drug in a way that maintains binding to the intended target, but reduces binding to the second site.

“If a drug has adverse side effects, it is likely that drug is also binding to an unintended, secondary molecule; in other words, the key that allows it to attach to its target fits more than one lock,” said Bourne. He explained that using this computational technique to find another “lock” could result in one of three things: the new lock might show no effect; the lock could explain an adverse side effect of the drug; or the research could potentially discover a new therapeutic effect for an existing drug – drug repositioning.

The UCSD researchers are continuing their studies, which Bourne says can be applied to any drug on the market for which a structure of the drug bound to the receptor exists in the PDB. Bourne emphasized that

results from this approach still needed to be tested experimentally.

Source: University of California - San Diego