Teaching old drugs new tricks

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Researchers from the European Molecular Biology Laboratory discovered a new way to make use of drugs' unwanted side effects. They developed a computational method that compares how similar the side effects of different drugs are and predicts how likely the drugs act on the same target molecule. The study, published in *Science* this week, hints at new uses of marketed drugs.

Similar drugs often share target proteins, modes of action and unpleasant side effects. In reverse this means that drugs that evoke similar side effects likely act on the same molecular targets. A team of EMBL researchers now developed a computational tool that compares side effects to test if they can predict common targets of drugs.

"Such a correlation not only reveals the molecular basis of many side effects, but also bears a powerful therapeutic potential. It hints at new uses of marketed drugs in the treatment of diseases they were not specifically developed for," says Peer Bork, Joint Coordinator of EMBL's Structural and Computational Biology Unit.

The approach would prove particularly useful for chemically dissimilar drugs used in different therapeutic areas that nevertheless have an overlapping, so far unknown protein target profile. Similar strategies have proven successful in the past. For example, the drug marketed as Viagra was initially developed to treat angina, but its side effects of prolonged penile erection led to a change in its therapeutic area.

Applying the new method to 746 marketed drugs, the scientists found

261 dissimilar drugs that in addition to their known action also likely bind to other unexpected molecular targets. 20 of these drugs were then tested experimentally and 13 showed binding to the targets that were predicted by side effect similarity. Testing 9 of these drugs further in cellular assays they all showed activity and thus a desired effect on the cell through their interaction with the newly discovered target proteins.

The results reveal that side effects can help find new, relevant drug-target interactions that might form the basis of new therapies. The brain enhancer Donepezil, for example, proved to share a target with the anti-depressant Venlafaxine, supporting that Donepezil could be also used to treat depression.

The big advantage of marketed drugs is that they have already been tested and approved for safe use in patients. This means they can move a lot faster from bench to bedside than newly discovered drugs that often take up to 15 years before they can be applied in patients.

"With some more tests and refinement our method could in future be applied on a bigger scale. New drugs could routinely be checked in the computer for additional hidden targets and potential use in different therapeutic areas. This will save a lot of money and would speed up drug development tremendously," concludes Bork.

Source: European Molecular Biology Laboratory