

COMPUTATIONAL DRUG DESIGN: New Tricks for Old Drugs

By Kristin Sainani, PhD

When cheap drugs are needed fast, researchers and drug companies are increasingly turning to an interesting short-cut: repurposing existing drugs for new uses. Because drugs exert multiple actions in the body, the same drug may be able to treat disparate diseases.

“There’s a lot of evidence now that the so-called ‘magic bullet’—one-drug to specifically bind to one receptor to treat one condition—is the exception rather than the rule,” says **Philip E. Bourne, PhD**, a professor of pharmacology at the University of California, San Diego (UCSD).

Just as it speeds up the time needed to identify new drugs (see “Dock This” in <http://biomedicalcomputationreview.org/3/3/6.pdf>), computation can speed up the time it takes to find new binding partners for old drugs. Some algorithms focus on the receptors: They virtually “dock” drugs into receptors’ 3-D structures to predict how snugly they will bind. Other algorithms focus on identifying drugs that resemble one another in structure or effect, in order to determine whether they bind with the same receptors. Besides repositioning old drugs, these same *in silico* strategies can be used to predict or explain a drug’s side effects. The algorithms are already yielding some surprising and promising leads.

Virtual Docking: Focusing on Proteins

When the 3-D structure of a receptor is known, either from crystallography or modeling, researchers can virtually “dock” drugs into the receptor to determine if they fit, like a key opening a lock. Docking all drugs into all proteins is computationally costly, however, so Bourne and his team focused on proteins from *mycobacterium tuberculosis* (the bug that causes tuberculosis or TB) which, in many parts of the world, is still rapidly evolving

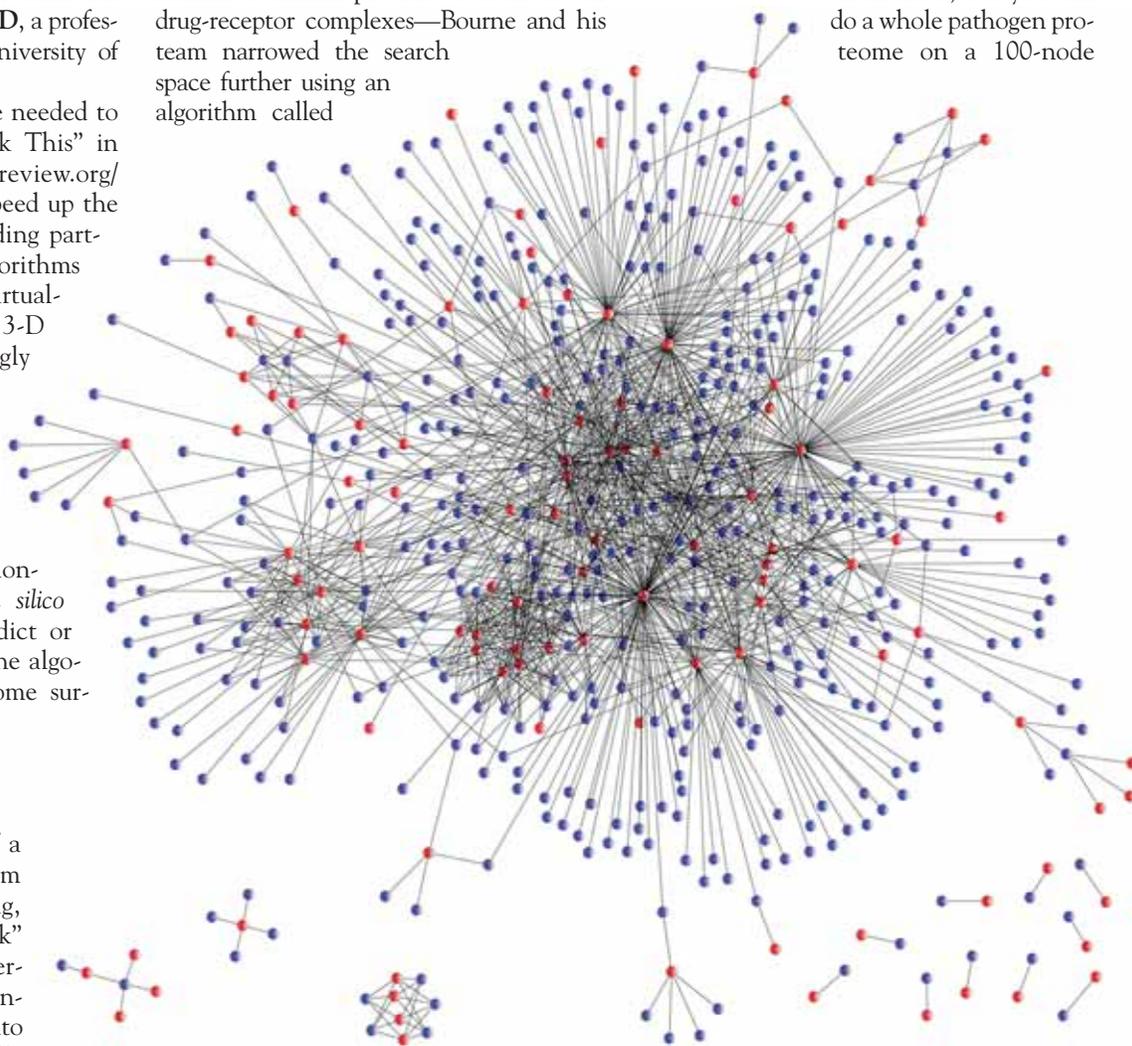
resistance to all known therapies, making urgent the need for new treatments.

Bourne and his colleagues screened 274 drugs approved for human use against 1730 TB proteins with known structures (about 40 percent of the proteome). They reported their results in the November 4 issue of *PLoS Computational Biology*.

Starting with 274 approved drugs that had been co-crystallized with at least one human or animal protein—a total of 962 drug-receptor complexes—Bourne and his team narrowed the search space further using an algorithm called

SOIPPA (Sequence Order Independent Profile-Profile Alignment Algorithm), which was developed by Bourne and **Lei Xie, PhD**, research scientist at UCSD. For each drug-receptor complex, SOIPPA searched for TB proteins with structurally similar binding sites. Then Bourne’s team virtually docked the drug into these TB proteins to look for matches.

“There’s a computer cost associated with our method, but you can do a whole pathogen proteome on a 100-node



*In this network representation of the TB-drugome, red nodes are FDA approved drugs and blue nodes are binding sites on TB protein receptors. An edge is drawn between drug and receptor if the drug is believed to interact with the protein. Bourne’s group hypothesizes that the highly connected drugs present the most opportunity for disrupting the normal functioning of TB. Courtesy of Philip Bourne. Reprinted from Kinnings, SL, et al., 2010, *The Mycobacterium tuberculosis Drugome and Its Polypharmacological Implications*, *PLoS Computational Biology* 6(11): e1000976. doi:10.1371/journal.pcbi.1000976.*

cluster in a couple of weeks,” Bourne says.

They connected 123 drugs to 447 TB proteins, and validated some of the most interesting associations experimentally. “Many of these drugs have never been looked at in the TB medicinal chemistry world. No one’s ever thought of trying them,” Bourne says. For example, two drugs for Parkinson’s disease were unexpectedly found to bind to an important TB enzyme.

Some drugs bound as many as 18 different TB proteins, which is a potential boon for preventing drug resistance. If a drug only disrupts one protein, TB can easily develop a mutation that escapes the drug, Bourne says. “So what you really want is something that’s going to bind several sites and disrupt multiple pathways.”

The findings also greatly expand the drug-target space for TB—previously only nine TB proteins had been investigated as potential therapeutic targets, Bourne says.

And the algorithm can be used to discover potential drugs for other diseases as well as to predict drug side effects. For example, in an earlier study, the researchers identified secondary binding sites for the breast cancer drug tamoxifen that help explain why it can cause cardiac abnormalities and blood clots.

Guilt by Association: Focusing on Ligands

Protein-centric methods are limited by the need for 3-D protein structures, says **Michael J. Keiser, PhD**. Keiser is President & COO of SeaChange Pharmaceuticals, Inc, a company that is using drug repurposing to search for new treatment options for orphan diseases (among other goals). His team builds structure-free profiles of the receptors. “We forget everything we know about the targets except one single thing: what its known ligands are,” Keiser says. Using an algorithm called Similarity Ensemble Approach, or SEA, these ligands are combined into a composite based on the similarities of their chemical structures.

In a 2009 paper in *Nature*, his team screened 3665 drugs (FDA-approved or investigational) against a panel of 1400 human protein targets looking for novel matches. They compared each drug with the ligand composite developed for each protein target. “The new idea that we brought in was to compare a drug to an entire set [of ligands] rather than on a one-by-one basis,” Keiser says. They identified 6928 drug-target pairs that were statistically likely to bind. When they tested 30 pre-

viously unknown associations experimentally, 23 bound with high affinity.

“There are quite a few examples that we’re very excited about,” Keiser says. For example, Doralese—an antihypertensive drug—was predicted to bind to an off-target receptor, dopamine D4. In experiments, it bound to this receptor 10 times more strongly than to its primary target (alpha-1 adrenergic receptor).

Another surprise: they discovered that the antidepressants Prozac and Paxil (which act on neurons) also act as weak beta blockers; they bind to the beta-1 adrenergic receptor, located in heart muscle and blood vessels. The finding may explain why some people who stop taking these drugs experience changes in heart rate and blood pressure (“SSRI discontinuation syndrome”).

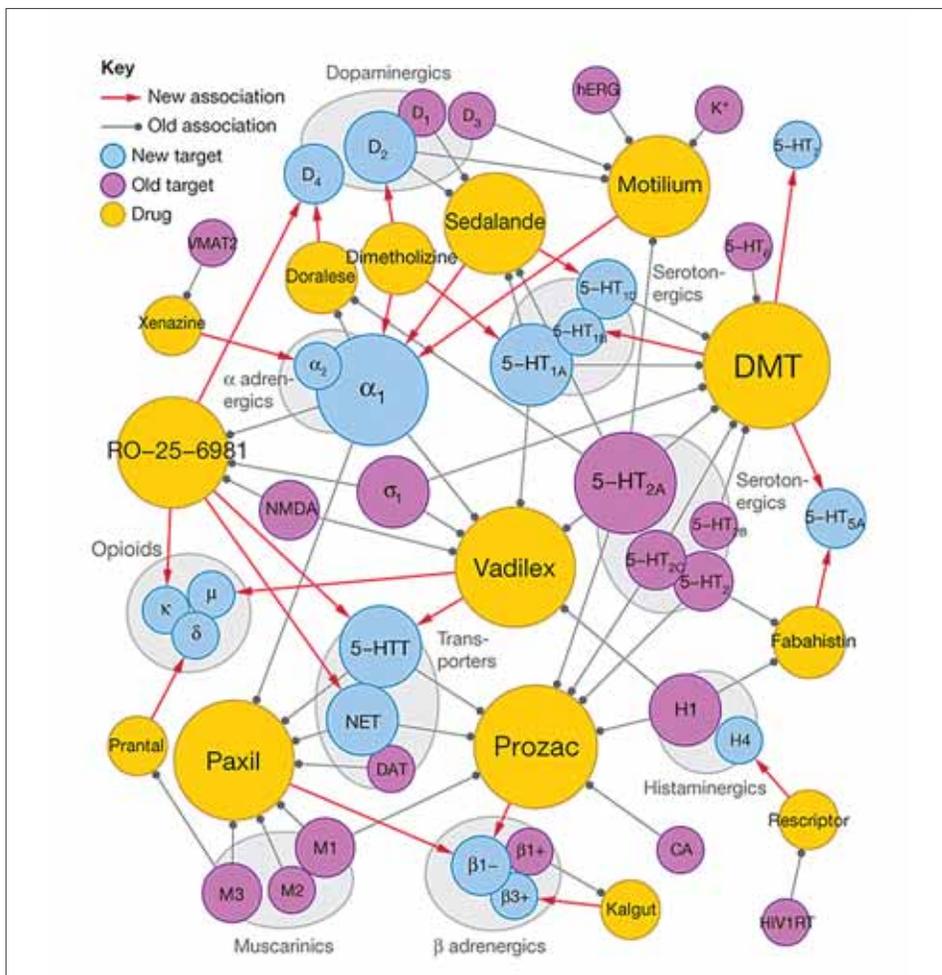
Other ligand-centric approaches connect drugs based on their phenotypic similarities, for example gene expression or side effect profiles. In a 2008 paper in *Science*, researchers used text-mining to compare 746 marketed drugs solely based on the side effects listed on their inserts. They found more than 1000 pairs of side-effect related drugs, including a couple hundred pairs that were otherwise unlike. In tests of 20 of these, they verified 13 novel drug-target interactions. For example, rabeprazole, a proton pump inhibitor used to treat ulcers, was found to bind neurologic targets, including dopamine and serotonin receptors.

Going Forward: Complementary Approaches

Each of these approaches complements the other, Keiser says. Though ligand-based approaches don’t require 3-D structures, they are limited to protein targets that are already known to bind to drugs.

Finding drugs and proteins that bind is only the first step in drug repurposing. Researchers then have to show that a given drug actually has a therapeutic effect at a reasonable dose.

Drug researchers now have thousands of new drug-target pairs to explore. If even just a few prove effective, these could provide life-saving alternatives for devastating diseases such as drug-resistant TB. □



Ignoring structures and focusing only on ligand binding, Keiser and his colleagues identified new targets (blue) to existing drugs (gold) The drugs' known targets (violet) connected to the drugs by gray lines. Node sizes increase with number of incident edges. Reprinted with permission from MacMillan Publishers Ltd, Keiser, M, et al., Predicting new molecular targets for known drugs, Nature (2009).