Re-Pharm

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Smart drug reprofiling

Using a unique combination of computational chemistry, pharmacology and cheminformatics methods, Re-Pharm is successfully reprofiling marketed compounds as early stage candidates ready for partnering.

Sir James Black, winner of the 1988 Nobel Prize in Physiology or Medicine, famously stated, "The most fruitful basis for the discovery of a new drug is to start with an old drug." With the cost and risks associated with developing new chemical entities at an all-time high, many companies are finding that repositioning existing pharmaceuticals for new medical uses is leading to real therapeutic and business returns.

Enter Re-Pharm, an early stage drug discovery and development company dedicated to repurposing compounds to address areas of unmet medical need. Re-Pharm combines outstanding chemistry and pharmacology expertise with the software solutions of its parent company, Cresset, to repurpose drugs currently on or near the market or that have been pulled from development for commercial reasons. Because these compounds have already undergone full or partial clinical testing and may be in active use, their safety and pharmacokinetics are generally well understood. Developers can build on existing data, significantly reducing the risks, cost and time involved in taking such drug candidates to market.

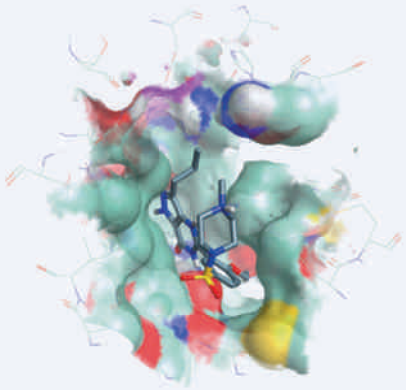
Cresset's computational chemistry tools offer unique insight into the molecular characteristics behind biological activity, taking the 3D shape and electrostatic properties of molecules into account to produce a 'protein's-eye view' of how a compound interacts with a target. "In essence we're trying to look at the skin of the molecule rather than the skeleton," explained Mark Mackey, CSO of Cresset. "If you look from that viewpoint, you find that molecules that are very similar have the same biological effect." Cresset software condenses the surfaces of the molecules to field points, making it possible to rapidly compare thousands of chemically diverse structures and fragments on the basis of biological similarity.

"Applying these computational methods to reprofiling is a way of identifying alternative targets for candidate compounds and suggesting alternative compounds for known targets," said Robert Scoffin, CEO of Re-Pharm.

A winning workflow

Successful repurposing requires a well-understood target with good commercial and pharmacological potential. Robust biological assays must also be readily available to rapidly and cost-effectively determine potential new activity for any lead.

To assess whether any existing drugs are likely to be active against a new target, Re-Pharm chemists typically build a template (essentially a complex pharmacophore) on the basis of known ligands and, where available, crystal structures, that incorporates the essential characteristics a candidate compound must possess to bind the target. The template is then screened against a database of several thousand marketed and late-stage drugs to pinpoint compounds that are biologically similar and therefore likely ligands. By comparing the possible matches, Re-Pharm can rapidly identify promising reprofiling opportunities.



Sildenafil as rendered by Cresset's Forge software. This is an example of a compound that was reprofiled from hypertension to erectile dysfunction.

Compounds of interest are then subjected to a robust triage process, which includes not only wet screening for activity but also filtering for key features that could impact future development, such as existing intellectual property, publications that reveal off-label use, side-effect problems and so on.

Intellectual property issues are a major factor in reprofiling; for potential compounds to have real commercial opportunity, it is essential that they be clear of prior art. To ensure solid patent protection, the dose, formulation and/or route of administration of the original compound may have to be altered to target the new indication.

Re-Pharm's rigorous validation process ensures that resulting candidate compounds have well-understood disease biology, robust pharmacology and a promising commercial position. "This leads to a rapid and cost-effective approach to proof of concept, and a clear and straightforward development path to clinic," confirmed Scoffin. "This gives the best chance for success."

A commercially valuable pipeline

Through its compelling strategy, Re-Pharm has built a pipeline of commercially valuable early stage assets in a variety of therapeutic areas. All have an excellent combination of decreased cost, lowered risk and faster development pathways.

The company's lead compound, RP0217, has almost completed preclinical development for a variety of inflammatory conditions with large market potential, which strongly validates Re-Pharm's approach. Currently a widely prescribed high-dose oral drug for non-inflammatory conditions, RP0217 resulted from a search for an existing drug that could be repurposed for a newly identified enzyme target. Evaluation of 50 candidates discovered through Cresset's software, followed by further testing of 12 of those compounds, identified RP0217 as an effective new agent.

"Our streamlined method made it possible to move efficiently through pharmacological assessment, computational chemistry work and initial testing in order to demonstrate novel anti-inflammatory activity for an existing drug," said Scoffin.

Time for partnering

Preclinical testing of topical and inhaled formulations of RP0217 has been completed for ophthalmic and respiratory inflammatory conditions and is under way for irritable bowel disease. Re-Pharm is looking for one or more partners to develop RP0217 into new non-steroidal treatments for these disorders. The company is also interested in operating its virtual screening and molecular-design platform on a fee-for-service basis and in acquiring early stage assets that require further validation.

"We believe that there are a wealth of unmet medical needs that can be profitably treated by using a smart approach to drug reprofiling," said Scoffin. "Our virtual platform transforms molecular design and discovery, enabling the rapid identification of reprofiling opportunities for swift and successful development."

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