SEAing change in R&D

By Kai-Jye Lou, Staff Writer

Researchers at the **University of California, San Francisco**, **SeaChange Pharmaceuticals Inc.** and the **Novartis Institutes for BioMedical Research** have developed a computational approach for large-scale, automated prediction of binding interactions between molecules and targets that have been associated with adverse drug reactions.[1] The method could help companies improve R&D productivity by pointing to safety signals and helping prioritize candidates *in silico*.

The computational approach uses a statistics-based chemoinformatics technique called the similarity ensemble approach (SEA), which the UCSF group first described in 2007.[2] SEA predicts whether a molecule will bind a target based on the similarity of the compound's chemical groups to known ligands of the target.

In March 2009, the UCSF group spun out SeaChange to develop and commercialize SEA-based computational methods that could help improve and speed up early drug R&D.[3] That year, the group also showed that a SEA-based computational method could predict new molecular targets for 878 FDA-approved small molecule drugs and another 2,787 small molecule reagents.[4]

Despite predicting a broad swath of new off-target interactions for existing drugs, the researchers still needed to manually run a laborious series of experimental assays to confirm whether an interaction actually occurred and to predict case by case whether such an interaction could lead to adverse effects.

A pivotal contribution came in 2010, when NIBR offered to test the UCSF-SeaChange predictions of drug-target interactions on a large scale, with the goal of linking them to adverse effects. The institute also brought in its own experimental and computational expertise.

NIBR is the global pharmaceutical research organization for **Novartis AG**.

"After our 2009 paper, the molecular toxicology group at NIBR got interested in our work and presented us with the opportunity to test the approach at scale," said Brian Shoichet, a professor in the Department of Pharmaceutical Chemistry at UCSF and a cofounder and scientific advisor to SeaChange.

"Novartis has access to a large number of proprietary databases that are unavailable to the public and also had the resources to test the blind predictions generated with our computational methods via a truly impressive number of high-quality experimental assays," added SeaChange cofounder and COO Michael Keiser. "With these results and databases in hand, they made it possible to calculate which predictions may be most relevant to any given drug's actual side effects in patients."

The partners used SEA to generate a list of 1,644 predicted binding interactions between 656 marketed drugs and 73 proteins that have established associations with adverse drug reactions. Next, they used information contained in the publicly accessible ChEMBL database to confirm the validity of 403 of the predicted interactions.

For 1,042 of the 1,241 interactions that could not be confirmed with ChEMBL, the group turned to the proprietary databases available to Novartis and experimental assays. Based on this, 48% of the interactions were confirmed, 46% were disproven and 6% remained ambiguous.

Keiser said these preliminary performance metrics of the SEA-based method are an order of magnitude better than those of traditional *in silico* approaches for drug discovery.

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"Unsupervised computational approaches, such as those that use the 3D structure of a protein to identify molecules with shapes that could bind to a target site, typically have hit rates in the low single-digit percentages or below" in terms of confirming the predictions, he told *SciBX*. "I was astounded by our hit rate of 48%."

In the second half of the study, the team at NIBR linked the newly confirmed drug-target interactions with patient data on adverse drug reactions for known drugs. The NIBR researchers then used these associations to create a series of networks that linked drugs to predicted targets and adverse drug reactions.

As an example, one of the networks generated from the combined datasets suggested chlorotrianisene's known side effect of upper abdominal pain could be due to a previously unrecognized inhibition of cyclooxygenase-1 (COX-1).

Chlorotrianisene is a generic synthetic estrogen that is marketed to treat symptoms of menopause, deficiencies in ovary function and prostate cancer.

Results were published in *Nature*. Shoichet is a co-corresponding author on the paper, and Keiser is the colead author. The other colead author is Eugen Lounkine, an investigator at NIBR.

"Using this and future improved versions of the method can be a game changer in how we could use *in silico* predictions for off-target effects," said Laszlo Urban, global head of preclinical safety profiling at NIBR and a co-corresponding author on the paper. "This approach can be used during early drug discovery to identify unexpected off targets associated with potentially dangerous or limiting side effects, initiate *in vitro–in vivo* testing and, if necessary, risk mitigation processes" such as modifying a molecule's structure to eliminate potentially unsafe drug-target interactions or removing such molecules from development altogether.

He added, "Another possible use is for exploiting unintended off-target/on-target pairings that might offer improved therapeutic opportunities. Thus the system also could be used to reposition marketed drugs."

Prioritizing early

Lead generation and lead optimization to get to a clinical candidate typically require around 3.5 years and $12.5 million.[5] The SEA-based computational method could improve the *in silico* candidate selection process and reduce the burden of more resource-intensive *in vitro* and *in vivo* assays.

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The algorithmic methods underlying the SEA-based computational approach are unpatented. Third parties are free to develop their own computational software packages using SEA-based methods for their own applications. SeaChange charges a fee to its clients for such services.

"The major impact is expected when the method is applied to the design of drug candidates because they can be tested prior to synthesis, and it also can pinpoint off-target effects," said Urban. "Regulatory *in vivo* pharmacology studies largely remain unaffected but could become more focused."

"Our approach could help companies increase the productivity of their medicinal chemistry programs by improving the way they prioritize molecules early in the drug R&D process and by helping them choose which safety studies to focus on first," added Keiser.

He noted that the bulk of the costs associated with use of SEA-based computational methods are in setting up a system and optimizing it for a company's chemistry and biological target space.

The costs of running *in silico* screens with a SEA-based approach after the system is set up will primarily come from maintaining and organizing high-quality discovery data for the methods to use, he added.

The partners are now trying to improve the performance of the SEA-based computational strategy and are evaluating it in additional drug R&D settings.

Urban said Novartis is trying to further improve the predictive performance of the computational approach by using larger sets of data. The pharma is using its own implementation of computational methods related to the SEA methodology.

Keiser said SeaChange is applying SEA-based computational methods to identify new potential indications for existing drugs.

He said SeaChange and UCSF also are refining the methods to improve predictive performance. Finally, he said the university and company are developing SEA-based methods for use in more specific drug R&D settings, such as augmenting standard preclinical safety panels by predicting a compound's interactions with a wide range of adverse drug reaction targets.

SeaChange's software packages using SEA-based computational methods are protected by trademark and copyright, and custom implementations of it are available for licensing discussions.

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