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Tools & Techniques

Bigger is better

By Kai-Jye Lou
Senior Writer

X-Chem Inc. has developed a screening platform and library of DNA-encoded small molecules that enable the identification of high-quality lead candidates against difficult targets. So far, the platform has yielded a handful of discovery deals, including two that have resulted in licenses to small molecule candidates.

Most recently, on Feb. 13, X-Chem announced that **Bayer AG** licensed an undisclosed number of compounds discovered under a 2012 deal. The compounds inhibit an undisclosed epigenetic target.

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>
> **Richard Wagner, X-Chem**

The attraction of DNA-encoded platforms over traditional libraries is that they allow simultaneous screening of very large numbers of molecules against a target of interest, because each molecule is tagged with a unique DNA barcode sequence that can be used to identify that particular molecule.

In a binding assay interrogating a mixture of compounds, non-binders can be washed away and hits detected using PCR to amplify the tag. Following sequencing, the DNA code is deciphered using a series of informatics tools to determine which molecules bind to the target.

In contrast, screening of conventional small molecule libraries against a target typically involves loading each molecule into separate reaction wells on microtiter plates. Identifying individual hits from a mixture of untagged molecules quickly becomes infeasible as the number of different compounds in a mixture increases.

X-Chem has a library of over 100 billion small molecules. Co-founder, President and CEO Richard Wagner said that's at least an order of magnitude larger than DNA-encoded chemical libraries constructed with competing platforms, such as those used by **Ensemble Therapeutics Corp.**, **Nuevolution A/S** and the Philochem AG unit of **Philogen S.p.A.**

Nuevolution is focused on fragment-based drug discovery and has used its Chemetics platform to synthesize a library with over 1 billion members. The size of Philochem's library is in the millions of small molecules.

Ensemble is generating macrocycles with its Ensemblin platform and has a library also in the millions.

In 2007, **GlaxoSmithKline plc** acquired Praecis Pharmaceuticals Inc. for $54.8 million. Praecis had a discovery platform built around a DNA-encoded small molecule library that contained about 10 billion members.

Wagner, who was EVP of research at Praecis, was one of the inventors of that company's DirectSelect small molecule screening technology.

Without providing details about X-Chem's methods, he said the company's library is also more diverse than those used by its competitors. It includes small molecules, fragments and macrocycles, with the latter group alone numbering in the billions.

"The vision is that when the library is big enough, molecules that are practically drug candidates will emerge from the primary screen," Wagner told BioCentury.

"We view drug discovery as a game of chance and we think screening campaigns need to start with a larger library," he said. "Our chemical space is huge compared with that available at other companies, and conventional screening strategies can only sample a sliver of the chemical space that is out there."

Wagner said the size and diversity of the library improves the odds of getting hits, especially against difficult targets such as protein-protein interactions, ubiquitin ligases and epigenetic regulators. As the X-Chem library continues to increase in size, he said the company has seen an increase in the number of different series of drug-like molecules that interact with therapeutic targets.

X-Chem's platform can run many different screens against a particular target in parallel. Wagner said this lets the company efficiently interrogate the behavior of its molecules against a target under various conditions, which improves the odds of identifying hits that possess many drug-like properties from the start and require minimal subsequent optimization.

X-Chem's informatics tools also help it achieve a high signal-to-noise ratio when processing data from its screens.

The biotech is close to CRO **Pharmaceutical Product Development LLC,** which paid $15.5 million for a majority stake in 2010.

Focused on partnering

X-Chem started up in 2009 and in 2010 began doing a mix of external partnerships and internal drug discovery. In 2012, the company decided to focus on the former as a way to expand

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global outreach for its technology without taking a lot of dilution along the way.

CBO Diala Ezzeddine said the company already is generating sufficient revenue from partnerships to support its operations and has no plans to pursue venture financing.

Including Bayer, X-Chem has disclosed three deals granting pharmas access to its technology.

X-Chem received an upfront payment from Bayer and is also receiving research funding from the pharma. X-Chem will receive an upfront exercise fee for each program Bayer licenses and is eligible for milestones and royalties.

AstraZeneca plc also has taken licenses to compounds discovered by X-Chem. The partners signed a two-year discovery deal in May 2012.

Last September, AZ licensed three of the molecules. The molecules target an oncology protein-protein interaction, a respiratory/inflammation protein-protein interaction target and an antibacterial target.

Last October, the partners extended the discovery deal into 2017.

Wagner said the terms demonstrate the potential value that could be realized from a single pharma deal.

X-Chem will conduct drug discovery on at least 10 therapeutic targets per year and will receive undisclosed R&D funding for each project. It is eligible for $26 million in development and sales milestones for each project AstraZeneca licenses.

"The X-Chem platform has become an integral part of our small molecule discovery strategy and complements internal activities including high throughput screening and structure-guided drug design," said Steve Rees, VP of screening sciences and sample management at AstraZeneca.

He said the pharma was attracted to X-Chem's platform because it provides access to very large libraries of novel compounds and because the biotech has been able to identify hits for less tractable drug targets.

X-Chem also has a 2010 discovery deal for undisclosed targets with **Roche**. The biotech received undisclosed upfront and research payments as well as technology access fees and is eligible for milestones and royalties.

X-Chem declined to update the status of the deal.

Roche signed a diagnostics development deal with Ensemble in 2007 and the pharma's **Genentech Inc.** unit partnered with Ensemble in 2012 to discover macrocyclic drug candidates.

AstraZeneca's Cambridge Antibody Technology Group plc subsidiary partnered with Philogen in 2007 to discover small molecule therapeutics.

Bayer has not disclosed any other deals with companies for access to DNA-encoded chemical libraries.

X-Chem also has a preferred service model agreement under which it contracts out standard chemistry to PPD's BioDuro LLC subsidiary.

Spinouts and start-ups

X-Chem hasn't abandoned internal discovery. It sources targets from academic collaborations and selects them for screening based on their interest to industry and their perceived lack of druggability.

X-Chem externalizes the promising leads it identifies from its in-house screens.

The company spun out **X-Rx Inc.** in January 2013 with $8.5 million in the first round of a planned $12 million of seed financing from PPD and X-Chem's founders.

"We realized that there were assets identified that could be valuable with extra financing, but this was outside of the X-Chem model," said Wagner, who is also X-Rx's president and COO. "Thus, it was in X-Chem's and PPD's interest to spin the asset out. Both X-Chem founders and PPD invested in X-Rx, with PPD taking a majority interest."

X-Rx has two disclosed small molecule programs. X-022 is a selective irreversible antagonist of Bruton's tyrosine kinase (Btk) in development for cancer. X-165 is an inhibitor of autotaxin (ENPP2; ATX) in development for fibrosis.

Last month, X-Chem announced a partnership with psychiatric medicines start-up **PsyBrain Inc.** to discover compounds to treat psychiatric illnesses.

PsyBrain was founded by academics from **Massachusetts General Hospital** and **Harvard Medical School** who collaborated with X-Chem under a 2012 deal.

X-Chem will receive R&D funding for each project under the collaboration. The biotech is eligible for preclinical, clinical and sales milestones on programs that PsyBrain chooses to license.

"With PsyBrain, we worked with a group of academics to come up with ideas of novel targets to screen our library against and gave them access to our discovery capabilities," said Ezzeddine.

X-Chem would not say whether it has an equity stake in PsyBrain, nor is it saying whether it will have equity stakes in future start-ups formed through its partnership model.

COMPANIES AND INSTITUTIONS MENTIONED

AstraZeneca plc (LSE:AZN; NYSE:AZN), London, U.K.
Bayer AG (Xetra:BAYN), Leverkusen, Germany
Ensemble Therapeutics Corp., Cambridge, Mass.
Genentech Inc., South San Francisco, Calif.
GlaxoSmithKline plc (LSE:GSK; NYSE:GSK), London, U.K.
Harvard Medical School, Boston, Mass.
Massachusetts General Hospital, Boston, Mass.
Nuevolution A/S, Copenhagen, Denmark
Philogen S.p.A., Siena, Italy
Pharmaceutical Product Development LLC, Wilmington, N.C.
PsyBrain Inc., Chestnut Hill, Mass.
Roche (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland
X-Chem Inc., Waltham, Mass.
X-Rx Inc., Waltham, Mass.

BioCentury®
The Bernstein Report on BioBusiness

PO Box 1246
San Carlos CA 94070-1246
Voice: 650-595-5333
Fax: 650-595-5589
www.biocentury.com

DAVID FLORES
President & CEO

KAREN BERNSTEIN, Ph.D.
Chairman & Editor-in-Chief