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Lilly's opening moves

By Joanne Kotz, Senior Editor

When **Eli Lilly and Co.** launched its Phenotypic Drug Discovery Initiative in 2009, its goal was to apply a crowdsourcing approach to finding new small molecules from external investigators that fit the company's core disease focus areas. Based on the positive results of the program, which focuses on phenotypic assays, the pharma has added six assays against defined targets as well as a tuberculosis assay.

The renamed Open Innovation Drug Discovery platform is one of two forays the pharma is making into the open innovation space. Lilly has also joined a public-private partnership (PPP) to identify IP-free molecules against epigenetic targets. The PPP is being led by the **Structural Genomics Consortium** (SGC).

"Open Innovation is quite a broad concept and can include a variety of paths or channels for innovation to occur other than the classic 'do-it-yourself' model," according to Alpheus Bingham, founder of **InnoCentive Inc.**, a company spun out of Lilly that issues open challenges to promote R&D. InnoCentive partners with a number of companies, including Nature Publishing Group, co-publisher of *SciBX*, to help promote the challenges. Bingham was previously VP of sourcing innovation and R&D strategy at Lilly.

"We had a broader vision early on, and PD^2 [Phenotypic Drug Discovery] was the first part to be implemented," noted Alan Palkowitz, VP of discovery chemistry research and technologies at Lilly.

"The potential for PD^2 to uncover and yield interesting findings is what's driving us to expand," added Palkowitz. "In terms of ROI, the assays are investments we've already made to support internal programs—as we add external molecules, it's only a very small increase in cost."

"It is natural to extend to the target-based approaches because it complements the breadth of our small molecule discovery strategy, which focuses on both phenotypic and target-based paradigms," Palkowitz noted, adding that the expansion also features a third component that involves screening for molecules with potential efficacy against multidrug-resistant TB.

Open screens

Lilly launched PD^2 with a focus on diabetes, osteoporosis, cancer and and Alzheimer's disease (AD).

In those areas, "the biology is relatively mature, and we were hoping to tap into innovative chemicals that may exist beyond our own walls," said Palkowitz.

To identify such molecules, the company set up an online platform through which any investigator can confidentially submit chemical structures for an initial evaluation. If a submitted structure meets certain criteria, for instance if it has drug-like properties and is distinct from anything in Lilly's in-house compound library, the company requests the compound from the investigator to run in screens.

After testing the molecule in the phenotypic assays, Lilly returns the screening data to the investigator. In return, the company has first rights to negotiate a potential collaboration or licensing agreement.

Palkowitz told *SciBX* that 62,000 structures from 400 investigators spread across 255 institutions and 27 countries have been submitted to Lilly through PD^2. About 60% of these originated in academia, and the other 40% came from biotechs. About 43,000 of the submitted structures met the company's criteria for drug-like properties and structural novelty, he added.

Of the 43,000, Lilly has run 13,000 compounds through its phenotypic assays to date. "We've asked to see 126 structures," said Palkowitz, and the company has finalized deals around 3 molecules.

The two disclosed deals were with the **University of Notre Dame** for an angiogenesis inhibitor and the **University of California, Irvine** for an insulin-secretion enhancer.

In its expanded form, Lilly's Open Innovation Drug Discovery platform now includes six assays against targets in selected core therapeutic areas—endocrine disease, cardiovascular disease, neurology and cancer.

The targets include G protein–coupled receptor 119 (GPR119), which regulates glucose homeostasis in diabetes; apelin receptor (APLNR; APJ) and solute carrier family 34 sodium phosphate member 2 (SLC34A2), which are cardiovascular targets that regulate blood pressure and kidney phosphate levels, respectively; and hexokinase 2 (HK2), a glycolytic enzyme that is a cancer metabolism target.

Finally, Lilly is screening for allosteric metabotropic glutamate receptor subtype 2 (mGluR2; GRM2) antagonists for neurological or psychiatric indications and calcitonin gene-related peptide receptor (CGRP receptor) antagonists for migraine.

Molecules also will be run in a *Mycobacterium tuberculosis* growth assay at **The Lilly TB Drug Discovery Initiative**, a not-for-profit organization.

Palkowitz told *SciBX* Lilly is hoping that the expanded program will provide a greater number of opportunities for advancing molecules by expanding the diversity of the biology the company is exploring.

The precompetitive edge

Although the goal of Lilly's Open Innovation Drug Discovery platform is to cast a wide net to identify new molecules that modulate established disease targets, the pharma also is joining the SGC effort to identify molecules against unexplored epigenetic proteins and then use the molecules to understand more about the potential of these proteins as therapeutic targets, all in the precompetitive space.

Through this PPP, the members hope to jointly develop chemical probes that target members of 11 different protein families involved in the epigenetic control machinery.

"Epigenetics is a new area of biology, and the rate at which pharma, biotech and academia can explore its therapeutic potential can be accelerated by collaboration," said Kevin Lee, VP and head of **GlaxoSmithKline plc**'s EpiNova DPU in the Immuno-Inflammation Therapy Area Unit.

Stephen Burley, distinguished research scholar at Lilly, agreed, adding that "by combining our resources and expertise, we will be more able to address important scientific questions at the precompetitive level and, from there, use the data within individual companies—including our own—to conduct research, develop commercial products and generate IP to protect those products."

"This was the idea right from the beginning. Our aims were to show the relevance of the target in disease and that it could be modulated by small molecules; with this knowledge, pharma and biotech can now do what they do best—discover novel molecules and develop drugs."

—Aled Edwards, Structural Genomics Consortium

The PPP launched at the end of 2008 with SGC and GSK as founding members. The group has since grown to include **Pfizer Inc.**, **Novartis AG** and a large network of academic collaborators.

Lilly joined the consortium in September 2011.

Two probes have been released to date, with "5 to 10 more expected within the next year, including several from our pharma partners" said Aled Edwards, director and CEO of the SGC.

The two released probes are JQ1, an inhibitor of BET bromodomains (bromodomain containing 2 (BRD2), BRD3 and BRD4) and UNC0638, an inhibitor of euchromatic histone-lysine N-methyltransferase 1 (EHMT1; GLP) and EHMT2 (G9A).

JQ1 has made a particularly rapid impact, according to Edwards. "GSK advised us in 2009 that bromodomains could be targeted by small molecules and pointed us to a chemical starting point. After that, everything has happened fast. Within a year, JQ1 was developed and now it has been given away to over 100 labs. There are dozens of papers in the pipeline in all sorts of areas of biology and disease."

"The consortium has made good progress, and the benefits can be witnessed by the current levels of interest seen in BET bromodomain inhibitors," agreed Lee. "GSK and the industry at large have benefitted from this through the rapid production of novel information in an area of biology that hadn't been well characterized."

Edwards is not surprised by the commercial activity around the unpatented JQ1 probe. "This was the idea right from the beginning. Our aims were to show the relevance of the target in disease and that it could be modulated by small molecules; with this knowledge, pharma and biotech can now do what they do best—discover novel molecules and develop drugs."

Lee told *SciBX* that "GSK has a number of BET bromodomain inhibitors, which it is investigating across a broad range of therapeutic indications."

Earlier this month, the company reported in *Nature* preclinical results showing efficacy of an internally discovered BET bromodomain inhibitor in leukemias characterized by myeloid-lymphoid or mixed-lineage leukemia (MLL; HRX) fusions.[1]

Constellation Pharmaceuticals Inc. has made use of JQ1 to report the effects of inhibiting BET bromodomains in mouse models of acute myeloid leukemia (AML) and Burkitt's lymphoma.[2] The company has a preclinical program targeting BET bromodomains in cancer and inflammation.

In addition, James Bradner, a co-discoverer of JQ1 and an attending physician in hematology and oncology at the **Dana-Farber Cancer Institute**, recently founded **Tensha Therapeutics Inc.**, which is developing JQ1 derivatives for cancer and other indications.[3]

Edwards believes the decision not to patent JQ1 was critical. "We'd still be talking to lawyers if we had to figure out who owned the IP. It is fair to say that the commercial activity around bromodomains happened much faster because of the speed with which the chemical probe was made available," he said.

"In these cases the very stats are the measure of success, that is, it's 13,000 structures that would not have been screened by Lilly, and it's 2 chemical probes of novel targets that might otherwise have waited years or decades before being put in a 'toolbox'," said Bingham.

He added that "these efforts share the common virtue that they show deliberate transparency and openness—and the future of pharma is written in such concepts. I have no doubt that many of the open innovation modes and business models of the present will be seen as 'initial baby steps' at some future point—but that's the pattern expected of evolving new and original ideas."

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COMPANIES AND INSTITUTIONS MENTIONED

Constellation Pharmaceuticals Inc., Cambridge, Mass.
Dana-Farber Cancer Institute, Boston, Mass.
Eli Lilly and Co. (NYSE:LLY), Indianapolis, Ind.
GlaxoSmithKline plc (LSE:GSK; NYSE:GSK), London, U.K.
InnoCentive Inc., Waltham, Mass.
The Lilly TB Drug Discovery Initiative, Seattle, Wash.
Novartis AG (NYSE:NVS; SIX:NOVN), Basel, Switzerland
Pfizer Inc. (NYSE:PFE), New York, N.Y.
Structural Genomics Consortium, Toronto, Ontario, Canada
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