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GSK goes deep with DPAc

By Lev Osherovich, Senior Writer

GlaxoSmithKline plc's Discovery Partnerships with Academia program has struck new deals with laboratories at the **Vanderbilt University School of Medicine** and **The Hospital For Sick Children** to identify compounds for severe obesity and cystic fibrosis, respectively. The partnerships aim to re-examine previously known targets in light of new structural and functional insights.

Meanwhile, GSK has cast a broad net to draw in new academic partners through a call for proposals in which academics vie for an opportunity to conduct pilot screens of their most promising targets with GSK's compounds and at the pharma's screening facilities.

Launched in 2010, Discovery Partnerships with Academia (DPAc) is an independent unit of GSK tasked with finding discovery opportunities deemed too early stage to qualify for conventional in-licensing.

Pearl Huang, VP and global head of DPAc, said her unit complements internal discovery efforts by searching the academic space for new druggable targets or unconventional strategies to address familiar targets.

"We're disease- and geography-agnostic," said Huang. "My team is fairly senior, with people with good contacts in the academic world and favorite areas that we like to mine."

The program has partnered with nine academic laboratories in the U.K., Europe, the U.S. and Canada to identify small molecules to treat a range of rare diseases (*see* **Table 1, "GSK's Discovery Partnerships with Academia (DPAc) deals"**).

DPAc's deals are between GSK and individual academic researchers rather than through the researcher's academic institution or department. Projects typically involve two years or more of funding for discovery and preclinical work with an option to extend the collaboration through clinical development.

Huang did not disclose how much money a typical DPAc deal involves, but she said the pharma makes "significant in-kind contributions to advance these programs into the clinic."

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She said the approach results in focused, milestone-driven research with prespecified payouts for achieving research goals. Because each DPAc involves different goals and technologies, Huang's team matches academics with appropriate in-house scientists and facilities and coordinates a collaborative work plan.

"At the core is a work plan for getting these compounds all the way into humans," said Huang. The most advanced DPAc programs are now in preclinical development.

Courting melanocortin

The bulk of DPAc's nine partnerships are in the U.K. and Europe, but

Table 1. GSK's Discovery Partnerships with Academia (DPAc) deals. Since launching the DPAc program in 2010, GlaxoSmithKline plc has partnered with nine academic teams to discover therapeutics for a wide range of indications.

Institution	Lead researcher	Indication	Description
Fred Hutchinson Cancer Research Center	Stephen Tapscott	Musculoskeletal disease	Prevention of double homeobox 4 (DUX4)-mediated muscle atrophy in facioscapulohumeral muscular dystrophy (*see* Martz, L., *SciBX* **6**(1); doi:10.1038/scibx.2013.2)
The Hospital for Sick Children	Christine Bear	Pulmonary disease	Potentiators/correctors of ΔF508-mutant cystic fibrosis transmembrane conductance regulator (CFTR) to treat cystic fibrosis (CF)
University of Cambridge	David Lomas	Endocrine/metabolic disease	Treatment of α_1-antitrypsin (AAT; A_1AT; SERPINA1) deficiency using small molecule stabilizers
University College London	Mark Pepys	Endocrine/metabolic disease	Treatment of transthyretin (TTR) amyloidosis using TTR stabilizers
University of Dundee	Irwin McLean	Dermatology	Treatments for recessive dystrophic epidermolysis bullosa (*see* Haas, M.J., *SciBX* **4**(25); doi:10.1038/scibx.2011.700)
University of Dundee	Susann Schweiger	Neurology	Development of a disease-modifying approach to treat Huntington's disease (HD)
The University of Edinburgh	Damian Mole	Gastrointestinal disease	Prevention of multiple organ failure in severe acute pancreatitis
University of Paris Descartes	Alain Hovnanian	Dermatology	Topical therapy for Netherton syndrome, rosacea and atopic dermatitis
Vanderbilt University School of Medicine	Roger Cone	Endocrine/metabolic disease	Positive allosteric modulators (PAMs) of the melanocortin 4 receptor (MC4R) to treat severe obesity

the two deals signed so far this year have been with North American researchers.

These include an agreement with Roger Cone, professor of molecular physiology and biophysics at Vanderbilt, to identify positive allosteric modulators of melanocortin 4 receptor (MC4R).

MC4R is a GPCR involved in regulation of appetite. Loss-of-function mutations in even a single copy of *MC4R* cause hereditary severe obesity.

Cone said previous MC4R agonists, such as AZD2820 from **AstraZeneca plc** and **Palatin Technologies Inc.** and Palatin's bremelanotide, encountered safety problems in the clinic because of the receptor's other roles in controlling blood pressure. The compounds were discontinued in Phase I and Phase III trials, respectively.

Instead of activating MC4R outright, Cone wants to find compounds that enhance the receptor's activity only in places where it encounters its natural ligand, the hormone α-melanocyte stimulating hormone (α-MSH).

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>
> *—Roger Cone, Vanderbilt University School of Medicine*

"Our approach is different in that we're going after allosteric modulators that would only work in the presence of the endogenous agonists," said Cone. "We started this as an NIH-funded project to treat MC4R haploinsufficiency–associated morbid obesity, which causes 5% of syndromic obesity in children. These individuals have one good copy of the receptor. We wanted to bump up the activity twofold."

Cone said GSK's initial interest is in treating syndromic obesity caused by MCR4 mutations, but the bigger prize is to modulate the activity of wild-type MC4R in a broader population of patients with obesity.

"GSK thought that this target might be relevant to more common forms of obesity," he noted.

Before GSK entered the picture, Cone's team already had identified lead compounds at the Vanderbilt Center for Neuroscience Drug Discovery.

"GSK will work with us on our hits, providing the medicinal chemistry to make these more drug-like," said Cone. "We will be doing the pharmacology and the animal testing."

Structure correction

DPAc's cystic fibrosis (CF) partnership is with Christine Bear, senior scientist in molecular structure and function at The Hospital for Sick Children and professor of physiology at the **University of Toronto**.

CF results from loss-of-function mutations in cystic fibrosis transmembrane conductance regulator (CFTR), an ion channel that transports chloride to epithelial cell surfaces. The most common form of CF is caused by the ΔF508 mutation, which leads to a structurally defective protein that becomes trapped in the endoplasmic reticulum in a misfolded state and is unable to reach the cell surface.

Bear thinks the best way to treat ΔF508-variant CF is to correct the normal structure of the protein with small molecules that directly bind the misfolded protein.

"We've been working on reconstituting full-length and mutant CFTR *in vitro* to understand the consequences of the CF-associated mutations and to understand what the molecules being developed for CF are doing to the protein's activity," said Bear. "I believe that small molecules for CF need to target the protein itself."

Bear has developed an assay of CFTR structure and function with purified recombinant CFTR inserted into reconstituted phospholipid micelles, which are membranous bubbles that mimic the cell surface.

Bear showed GSK preliminary assay results that suggested compounds that correct the structure of CFTR can also improve the protein's *in vitro* activity.

"I presented results using proof-of-concept small molecules available to the academic community that could bind directly and correct the fold and function of CFTR," said Bear. "GSK has the capability to develop a screening platform for millions of compounds, something I don't otherwise have access to. They were interested in identification of leads and lead optimization."

Bear's *in vitro* screening approach contrasts with the cell-based phenotypic screening used by **Vertex Pharmaceuticals Inc.** Bear said Vertex's approach is likely to hit other targets involved in CFTR folding and function besides CFTR itself.

Earlier this month, Vertex's lumacaftor (VX-809) entered Phase III testing for ΔF508 CF in combination with Kalydeco ivacaftor, a potentiator that enhances CFTR's ion transport activity.

Under the DPAc deal, Bear said GSK will fund postdocs and technicians based in her academic lab who will help pharma counterparts to run the *in vitro* assay at GSK's facility in Mississauga, Ontario.

Come one, come all

Huang's next step in growing DPAc is a call for proposals for academics who want to access the pharma's screening resources for their therapeutically relevant targets.

The contest, termed Discovery Fast Track, will start accepting entries in May. Huang said it will initially be open to U.S. and Canadian researchers.

"The first step is to send us a one-page, nonconfidential description of the proposed research," said Huang. "We will pick some finalists and ask them to submit a more detailed proposal with some confidentiality. If the investigator is bringing reagents to the table, we will arrange a material transfer agreement, and then we will run a pilot screen in house."

Huang hopes to select up to 10 such mini-projects a year for rapid preliminary screening and said some of these will go on to become full-fledged DPAc deals. She said DPAc has funds to sustain up to 13 concurrent full-scale collaborations.

Although all current DPAc projects involve small molecules, Huang said DPAc is open to targets that are better approached with biologics.

"What interests us is the strength of the hypothesis," she said.

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COMPANIES AND INSTITUTIONS MENTIONED

AstraZeneca plc (LSE:AZN; NYSE:AZN), London, U.K.
GlaxoSmithKline plc (LSE:GSK; NYSE:GSK), London, U.K.
The Hospital for Sick Children, Toronto, Ontario, Canada
Palatin Technologies Inc. (NYSE-M:PTN), Cranbury, N.J.
University of Toronto, Toronto, Ontario, Canada
Vanderbilt University School of Medicine, Nashville, Tenn.
Vertex Pharmaceuticals Inc. (NASDAQ:VRTX), Cambridge, Mass.