Translational tidbits

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Quantitative boost for CSHL

The **Simons Foundation** has donated \$50 million to **Cold Spring Harbor Laboratory** to establish the Simons Center for Quantitative Biology. The center's goal is to develop quantitative approaches that can maximize the utility of high-content imaging and genomic data produced by the laboratory and its partners.

The center will focus on creating computational methods to mine complex genomic and imaging data related to cancer and neurological diseases including autism, schizophrenia and bipolar disorder.

Bruce Stillman, president and CEO of Cold Spring Harbor Laboratory (CSHL), told *SciBX* that high throughput studies investigating changes in neuronal connectivity need new methods of data analysis. "The sheer quantity of imaging data has made it clear that more capable algorithms and statistical methods are required to extract the full amount of buried information," he said.

In addition, he said that ongoing work at CSHL's genome center on patients with cancer, schizophrenia or bipolar disorder have generated massive genomic data sets that require an enhanced analytical tool set to reveal their information in full depth.

"These data collections are steadily growing due to the fact that conventional and single-cell genome and imaging analyses have now become major research strategies at CSHL. Multiple complex data sets need to be meaningfully integrated to identify biological and pathological principles," said Stillman.

To run the center, CSHL recruited Adam Siepel, who was previously an associate professor at **Cornell University** with a background in comparative genome biology and software development. He plans to recruit more scientists, create programs for visiting scholars and strengthen the CSHL course curriculum for quantitative biologists.

Stillman said that the new quantitative biology center will complement other regional hubs for large-scale analysis. "The center will be aligned with interests at the **Simons Center for Data Analysis** and the **New York Genome Center**, which CSHL is a founding member of," he said.

The Simons Center for Data Analysis (SCDA) was launched in New York in 2013 and is also dedicated to innovating methods to analyze large-scale data sets from genomic and neurophysiological research. Siepel's counterpart at the SCDA is Leslie Greengard, who formerly was the director of **New York University's** Courant Institute for Mathematical Sciences.

Expanded repurposing in the U.K.

The **Medical Research Council** (MRC) has added six new pharma partners to its three-year-old initiative to identify repurposing

opportunities for deprioritized and discontinued compounds. The partners hope to publish a complete list of the available compounds and solicit project proposals by year end.

Under the initial 2011 collaboration with MRC, **AstraZeneca plc** made **22 of its compounds available to academic researchers for repurposing studies**. In 2012, MRC granted a total of £7 million (\$11.8 million) to 15 academic groups to repurpose 9 of those compounds (see Table 1, "Nine starters from AstraZeneca").

Six additional companies—**Eli Lilly and Co.**, **GlaxoSmithKline plc**, **Pfizer Inc.**, **Takeda Pharmaceutical Co. Ltd.**, **UCB Group** and **Johnson & Johnson's** Janssen R&D LLC subsidiary—will now join AstraZeneca and make their discontinued and deprioritized compounds available for repurposing studies to be funded by the MRC.

MRC spokesperson Hannah Isom told *SciBX* that the seven pharmas have not yet disclosed which compounds will be available under the new partnership. "We're hoping to make the full list of compounds available to the academic community" later this year, after which researchers will be able to submit project proposals to the MRC, she said.

The MRC has no fixed budget for the new repurposing program, and proposals will be reviewed on a rolling basis by the MRC's research boards three times each year, she said.

The program is similar to the **NIH's National Center for Advancing Translational Sciences** (NCATS) Discovering New Therapeutic Uses for Existing Molecules program, which included 58 compounds from 8 pharmas.¹ Of the 13 compounds that AstraZeneca made available through the NCATS program in 2012, 7 were also made available through the 2011 MRC-AstraZeneca partnership.

In 2013, NCATS awarded grants to nine academic groups to repurpose seven of the compounds in its program, two of which were from AstraZeneca.²

Reacting with chromatin

CRO Reaction Biology Corp. has won a Phase I Small Business Innovation Research (SBIR) grant to look for interactions between FDA-approved compounds and histone methyltransferases (HMTs) in a project that could identify new HMT-targeting scaffolds and yield repurposing opportunities. Data will be placed online in a publicly accessible database and could complement probe discovery efforts by organizations such as the **Structural Genomics Consortium**.

"Although overexpression of several HMTs has been implicated in various cancers and other diseases, there is very little known about the structures of HMT inhibitors, and there are few high-quality proteins and assay reagents available," Haiching Ma, CSO of Reaction, told *SciBX*. "Most importantly, there is no database available to indicate the yet-unknown—and possibly profound—epigenetic effects of FDA-approved drugs or agents in clinical trials."

He said that the company is well positioned to perform this screen because it has developed multiple marketed drug discovery assays and protein production services for epigenetic protein families, some of which were also funded by SBIR grants.

Compounds will be sourced primarily from **Enzo Life Sciences Inc.'s** FDA-approved drug library and the NIH Clinical Collection. Additional

Table 1. Nine starters from AstraZeneca. Through a 2011 partnership with **AstraZeneca plc** (LSE:AZN; NYSE:AZN), the **Medical Research Council** (MRC) awarded a total of £7 million (\$11.8 million) to fund 15 academic projects that sought to repurpose 9 of the pharma's deprioritized compounds.

Source: BCIQ: BioCentury Online Intelligence; MRC

Academic partner(s)	Compound	Mechanism	Proposed new indication and phase of development	Original indication(s) ^A
The University of Manchester	Lesogaberan (AZD3355)	GABA _B receptor agonist	Phase II to treat chronic cough	Phase IIb for gastroesophageal reflux disease
University of Birmingham	AZD4017	Hydroxysteroid 11 β dehydrogenase 1 (HSD11B1; HSD1) inhibitor	Phase II to treat post-menopausal osteopenia Phase II to treat idiopathic intracranial hypertension	Phase II to treat raised intraocular pressure; Phase I to treat diabetes
University of Sheffield			Phase II to treat cancer-induced bone pain	
Imperial College London	Saracatinib (AZD0530)	c-Src tyrosine kinase (CSK) inhibitor	Phase II to treat schizophrenia	Phase IIb to treat ovarian, breast, prostate and renal cancers
MRC Harwell			Preclinical to treat chronic otitis media	
University College London	Zibotentan (ZD4054)	Endothelin A receptor antagonist	Phase II to treat renal disease in systemic scleroderma	Phase III to treat castration-resistant prostate cancer; Phase II to treat non-small cell lung cancer (NSCLC) and ovarian cancer; Phase I to treat solid tumors
University of Bristol			Preclinical to treat Alzheimer's disease (AD)	
The University of Edinburgh	AZD1236	Dual matrix metalloproteinase 9 (MMP9) and MMP12 inhibitor	Phase II to treat idiopathic pulmonary fibrosis	Phase IIa to treat chronic obstructive pulmonary disorder (COPD)
Royal Veterinary College			Preclinical to treat muscular dystrophy	
University College London	AZD7325	GABA _A receptor agonist	Phase I to treat peripheral neuropathy and primary dystonia	Phase IIa to treat generalized anxiety disorder
University of Glasgow	AZD8055	Mammalian target of rapamycin complex 1 (mTORC1) and mTORC2 inhibitor	Preclinical to treat chronic lymphocytic leukemia (CLL)	Phase I/II to treat advanced solid tumors
University College London	Not applicable	Purinergic receptor P2X ligand-gated ion channel 7 (P2RX7; P2X7) inhibitor	Preclinical to treat acute renal injury	Research compound to investigate P2X7 biology
University of Leeds			Preclinical to treat glioblastoma	
University of Sheffield	AZD1080	Glycogen synthase kinase 3 β (GSK3B) inhibitor	Preclinical to treat motor neuron disease	Phase I to treat AD

^ADenotes the disease indication(s) in which AstraZeneca has already tested the compound in the clinic.

tool compounds collected by Reaction will also be included. Over 1,400 compounds will be tested on about 30 HMTs. The project is expected to take a year and has received \$287,650 in funding. Ma said that the company would likely apply for a Phase II SBIR grant to expand research from *in vitro* assays into cells and to produce probes against certain targets.

He highlighted assay development for the nuclear SET domain-containing protein subfamily of HMTs as a particular goal of this effort. Nuclear SET domain-containing protein 2 (WHSC1; MMSET; NSD2) has proven a tough drug target to tackle in part because of difficulties working with the protein *in vitro*. Last year, two independent teams showed that gain-of-function mutations in NSD2 can drive pediatric acute lymphoblastic leukemia (ALL) in subsets of patients.³

The company has experience with producing publicly available databases and in 2011 published work in *Nature Biotechnology*

describing interactions between 170 compounds and the kinome, in collaboration with the **Fox Chase Cancer Center**.⁴ At least one other CRO, **Eurofins Scientific S.A.**, screened FDA-approved compounds against some epigenetic targets, but the results are only available for purchase.

Public-private funds for neurology

Two large, U.K.-based public-private partnerships focused on Alzheimer's disease (AD) topped the list of disclosed deals in June with a combined value of at least £116 million (\$197 million; see **Table 2**, "Selected public-private partnerships for June 2014").

Alzheimer's Research UK launched its 5-year, £100 million (\$169.8 million) Defeat Dementia campaign to support research on the diagnosis, prevention and treatment of AD and other dementias. Separately, the MRC launched the UK Dementias Research Platform

Table 2. Selected public-private partnerships for June 2014. In June, the U.K. made strong commitments to Alzheimer's disease (AD) and other forms of dementia via new public-private partnerships. **Alzheimer's Research UK** launched its £100 million (\$169.8 million) Defeat Dementia campaign, while the **Medical Research Council (MRC)** initiated the UK Dementias Research Platform with £16 million (\$27.2 million) in funding. **Pfizer Inc.** (NYSE:PFE) also announced the first ex-U.S. partnership under its Global Centers for Therapeutic Innovation initiative last month. The pharma and Australia's **Monash University** will focus on projects related to large-molecule therapeutics.

Source: *BioCentury Archives*

Companies	Institutions	Business area	Disclosed value	Purpose
None	Alzheimer's Research UK	Neurology	£100 million (\$169.8 million)	Defeat Dementia campaign to fund research on the diagnosis, prevention and treatment of AD and other dementias
Araclon Biotech S.L.; Ixico plc (LSE:IXI); SomaLogic Inc. ; AstraZeneca plc (LSE:AZN; NYSE:AZN); GlaxoSmithKline plc (LSE:GSK; NYSE:GSK); Johnson & Johnson (NYSE:JNJ)	MRC	Neurology	£16 million (\$27.2 million)	MRC-led UK Dementias Research Platform, a public-private consortium for dementia research
Pfizer	Monash University	Pharmaceuticals	A\$12–A\$14 million (\$11.3–\$13.2 million) per project	Partnership under the pharma's Global Centers for Therapeutic Innovation initiative to pursue projects related to the development of large-molecule therapeutics
Johnson & Johnson	Dana-Farber Cancer Institute	Cancer	\$10 million	Partnership to develop immunotherapies for lung cancer
Zealand Pharma A/S (CSE:ZEAL)	University of Copenhagen	Cardiovascular disease	kr.1 million (\$182,400)	Partnership to elucidate the cell-protective properties and therapeutic potential of danegaptide
Alexion Pharmaceuticals Inc. (NASDAQ:ALXN)	Cincinnati Children's Hospital Medical Center	Pharmaceuticals	Undisclosed	Partnership to fund selected research programs for rare diseases
Amarantus BioScience Holdings Inc. (OTCQB:AMBS)	Washington University in St. Louis	Endocrine/metabolic disease	Undisclosed	Partnership to evaluate the efficacy of mesencephalic astrocyte-derived neurotrophic factor (MANF; ARP; ARMET) in animal studies to treat Wolfram syndrome
AmorChem L.P.	Hospital Maisonneuve-Rosemont	Ophthalmic disease	Undisclosed	Partnership to discover inhibitors of semaphorin 3A (SEMA3A) to treat diabetic macular edema
Fluxion Biosciences Inc.	Stanford University	Cancer; pharmacogenetics	Undisclosed	Partnership to develop tests to subtype different forms of disease and develop more effective, individualized treatments for patients with prostate or kidney cancer
Kineta Inc.	Seattle Children's Research Institute	Autoimmune disease	Undisclosed	Alliance for Children's Therapeutics to develop drugs for children and teenagers with autoimmune diseases
PaxVax Inc.	University of California, San Diego	Infectious disease	Undisclosed	Partnership to develop a combination vaccine to prevent genital herpes simplex virus infection
RuiYi Inc.	ShanghaiTech University	Antibodies	Undisclosed	Partnership to apply RuiYi's intermembranous conformation antigen-presenting system to create mAbs with specific binding to GPCRs
Seres Health Inc.	Mayo Clinic	Infectious disease	Undisclosed	Partnership to identify indications for which a microbiome-based therapy might change the course of disease
Trovagene Inc. (NASDAQ:TROV)	Northwestern University	Diagnostics; cancer	Unavailable	Partnership to evaluate Trovagene's urine-based, cell-free oncogene mutation monitoring technology in clinical practice

with £16 million (\$27.2 million) in funding from the council and 6 companies to create and analyze a cohort of about 2 million dementia patients and controls.⁵

Whereas the U.K. programs are focused on dementia, psychiatric research got its own boost in July with a \$650 million funding commitment from philanthropist Ted Stanley to the **Broad Institute of MIT and Harvard**. The gift will support research aimed at

understanding the biology of various psychiatric disorders, such as autism, bipolar disorder and schizophrenia.

The Broad Institute said that the funding commitment is the largest ever for psychiatric research and will help it achieve at least four major goals. These include creating a comprehensive list of genes with roles in severe psychiatric disorders, identifying the biological pathways in which they act, developing new cellular and animal models, and

identifying and developing molecules that modulate biochemical pathways and serve as drug leads.

Stanley committed \$100 million to the Broad Institute in 2007 to establish the Stanley Center for Psychiatric Research. With the current funding commitment, Stanley's philanthropic support to the Broad Institute now totals over \$825 million.

Boettner, B. *et al. SciBX* 7(29); doi:10.1038/scibx.2014.849
Published online July 31, 2014

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COMPANIES AND INSTITUTIONS MENTIONED

Alzheimer's Research UK, Great Abington, U.K.
AstraZeneca plc (LSE:AZN; NYSE:AZN), London, U.K.

Broad Institute of MIT and Harvard, Cambridge, Mass.
Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y.
Cornell University, Ithaca, N.Y.
Eli Lilly and Co. (NYSE:LLY), Indianapolis, Ind.
Enzo Life Sciences Inc., Farmingdale, N.Y.
Eurofins Scientific S.A. (Euronext:ERF), Kraainem, Belgium
Fox Chase Cancer Center, Philadelphia, Pa.
GlaxoSmithKline plc (LSE:GSK; NYSE:GSK), London, U.K.
Johnson & Johnson (NYSE:JNJ), New Brunswick, N.J.
Medical Research Council, London, U.K.
National Center for Advancing Translational Sciences, Bethesda, Md.
National Institutes of Health, Bethesda, Md.
New York Genome Center, New York, N.Y.
New York University, New York, N.Y.
Pfizer Inc. (NYSE:PFE), New York, N.Y.
Reaction Biology Corp., Malvern, Pa.
Simons Center for Data Analysis, New York, N.Y.
Simons Foundation, New York, N.Y.
Structural Genomics Consortium, Oxford, U.K.
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