

Translational tidbits

By Kai-Jye Lou and Lev Osherovich, Senior Writers

Focusing the BRAIN

The NIH's BRAIN initiative has developed a road map for its near-term research priorities, chief among which is conducting a census of brain cells. Whether the ambitious, decades-long project will be funded at anticipated levels will depend on the outcome of Washington's stalled budget talks.

When BRAIN (Brain Research through Advancing Innovative Neurotechnologies) was announced in April, President Barack Obama and NIH director Francis Collins claimed that the project would yield technologies to image and model living human brains and techniques for manipulating brain activity in patients with neurological diseases.

Academic neuroscience researchers expressed mixed views on the initiative. Some liked the prospect for more funding, but others were concerned about the project's seemingly nebulous aims and the possible diversion of research dollars from traditionally focused research.¹

To address concerns about how to proceed with BRAIN, at the time of the project's announcement the NIH convened a working group of 15 prominent neuroscientists to define the project's overall aims and funding priorities.

The working group, which was cochaired by Cornelia Bargmann and William Newsome, published an [interim report on its recommendations](#) in September.

Bargmann is a professor and laboratory head at **The Rockefeller University** and a **Howard Hughes Medical Institute** (HHMI) investigator. Newsome is a professor of neurobiology at **Stanford University** and an HHMI investigator.

The most basic recommendation of the working group was to catalog all the different cell types found in the brain. In its interim report, the group argued that surveying the brains of animal models and human anatomical specimens to establish a census of neuronal and glial cells would help researchers develop standardized models and assays.

Variability in the cells and assays currently used by various laboratories complicates the head-to-head comparison of neuroscience data.

Next, the group recommended creating a large-scale structural map of the brain to uncover functional relationships between various circuits of interconnected neurons.

Toward that goal, the working group endorsed a slew of tool-building projects to enable better data gathering from the living brains of animals and humans, including development of instruments and techniques for recording and computational analysis of brain activity.

Likewise, the group recommended improving the resolution of existing brain imaging techniques such as functional MRI (fMRI) and PET imaging to zoom in on activity in smaller clusters of neurons than is currently possible.

Building tools to manipulate specific circuits of neurons *in vivo* is another priority for the BRAIN project. The working group suggested that a combination of optogenetic, pharmacological and electromagnetic tools should be developed to enable researchers to remotely turn individual neurons on or off.

The working group also recommended developing computational methods and models that integrate whole-brain imaging data with cellular and behavioral assays.

Finally, the working group highlighted the need to train neuroscientists in emerging techniques of brain imaging and manipulation as well as the computational and statistical methods used in the BRAIN project.

Although the scientific picture for BRAIN is becoming clearer, the project's funding prospects are clouded by Washington's budget stalemate.

For fiscal 2014, Obama proposed giving BRAIN about \$110 million from federal agencies, including about \$40 million from the NIH, \$50 million from the **Defense Advanced Research Projects Agency** and about \$20 million from the **National Science Foundation**.

Private organizations including HHMI, the **Allen Institute for Brain Science**, **The Kavli Foundation** and the **Salk Institute for Biological Sciences** planned to contribute at least \$158 million over the next 10 years.-

With the NIH and National Science Foundation closed because of the government shutdown, and the possibility of reduced federal funding across the board for fiscal 2014, it is unclear how much new federal money BRAIN will receive.

The BRAIN working group will issue its final recommendations in June 2014.

CRISPR pairings

Less than a year after the initial deluge of results demonstrated the promise of CRISPR-Cas9-based genome editing for inducing site-specific mutations, research tool suppliers have taken notice and are starting to place their bets in the space.

In mid-September, cell line and assay supplier **Horizon Discovery Ltd.** acquired a nonexclusive license to IP from **Harvard University** that will allow the company to commercialize CRISPR (clustered, regularly interspaced short palindromic repeats)-Cas9 (CRISPR-associated protein 9)-based genome-editing technologies for research use.

One week later, rodent and rabbit model supplier **Sage Labs Inc.** augmented its technology portfolio by in-licensing CRISPR-Cas9 genome-editing technologies from **Caribou Biosciences Inc.**

Financial details of the deals are undisclosed.

Horizon and Sage announced the deals about a month after separate research groups from the **Broad Institute of MIT and Harvard**, **Harvard Medical School** and the **Wyss Institute for Biologically**

Inspired Engineering at Harvard University published a pair of studies highlighting potential strategies to address the specificity concerns surrounding CRISPR-Cas9-based genome editing.²⁻⁴

The Harvard deal allows Horizon to add CRISPR to its Genesis gene-editing platform, which already includes recombinant adeno-associated virus (rAAV) and zinc finger nuclease (ZFN) technologies.

Horizon holds a nonexclusive license from **Sigma-Aldrich Corp.** to use Sigma's CompoZr ZFN technology. Sigma partnered with **Sangamo BioSciences Inc.** in 2007 to use ZFN technology to develop and commercialize research reagents.

Horizon said that it will use the trio of genome editing technologies in client-led projects and to expand the company's off-the-shelf cell line offerings and related products. Horizon said that it is planning for a near-term launch of a variety of rAAV, CRISPR, and hybrid rAAV and CRISPR gene-editing kits and associated reagents.

Under the Caribou deal, Sage has exclusive rights to use Caribou's CRISPR-Cas9 genome-editing technology to create and commercialize

genetically engineered rat models and nonexclusive rights to use the technology to create and commercialize mouse and rabbit models.

Sage said that CRISPR technology will expand its portfolio of animal models and decrease turnaround times for its custom model creation service, SAGESpeed.

Sigma sold its Sage Labs unit for an undisclosed sum to an undisclosed private equity firm in March as part of a reorganization.

PPP roundup

Activity in the public-private partnership space ramped up in September following a relatively quiet August (*see Table 1, "Selected public-private partnerships for September 2013"*). Notable events last month include **AstraZeneca plc's** announcement of a pair of early stage R&D collaborations covering a broad swath of disease areas, **Servier's** quartet of collaborations with research institutes in Singapore and China, and the newly formed EpimiRNA consortium.

AstraZeneca's **MedImmune LLC** unit partnered with the **University**

Table 1. Selected public-private partnerships for September 2013. After a quiet August, public-private partnership activity surged in September. Significant developments included a partnership between the Almac Discovery Ltd. unit of **Almac Group Ltd.** and **Queen's University Belfast** to discover and develop new cancer treatments, and the newly formed EpimiRNA consortium to study molecular mechanisms and diagnostics for epilepsy and develop microRNA-based therapeutics. Notably, both **AstraZeneca plc** and **Servier** spent the month farming out R&D efforts. AstraZeneca did a pair of deals covering a broad swath of disease areas with academic institutes in the U.S. and Israel, and Servier announced four collaborations with research institutes in Singapore and China.

Source: BCIQ: BioCentury Online Intelligence

Companies	Institutions	Business area	Disclosed value	Purpose
Almac Group	Invest Northern Ireland; Queen's University Belfast	Cancer	£13 million (\$20.2 million)	Three-year deal to discover and develop cancer treatments, including ALM201
Bicoll Group; Biocomputing Platforms Ltd.; DIXI Microtechniques SAS; GABO:mi GmbH; InterNA Technologies B.V.	Royal College of Surgeons in Ireland; Philipps University of Marburg; University Medical Center Utrecht; University College London; University of Verona; University of Erlangen-Nuremberg; Duke University; University of Campinas; Aarhus University; University of Southern Denmark; European Commission	Neurology	€11.5 million (\$15.4 million)	EpimiRNA consortium to investigate molecular mechanisms, diagnostics and treatments for epilepsy
Biotec Services International Ltd.; Oxford BioMedica plc (LSE:OXB)	Cell Therapy Catapult; Cranfield University; Heart of England NHS Foundation Trust	Gene and/or cell therapy	£7.7 million (\$12.1 million)	Consortium to develop a center of excellence for manufacturing gene-based therapies in the U.K. and improving supply chains
llumina Inc. (NASDAQ:ILMN); Intel Corp. (NASDAQ:INTC)	Oregon Health & Science University; Leukemia & Lymphoma Society; Stanford University; The University of Texas Southwestern Medical Center; The University of Utah	Cancer	Over \$8.2 million	Acute myeloid leukemia (AML) research initiative to create a profile of possible genetic drivers
AstraZeneca (LSE:AZN; NYSE:AZN)	University of Maryland, Baltimore	Pharmaceuticals	At least \$6 million	Five-year research collaboration focused on disease areas that include cancer and cardiovascular, metabolic, respiratory, inflammation, autoimmune and infectious diseases
Genia Technologies Inc.	Columbia University; Harvard University; NIH	Genomics	\$5.3 million	Collaboration to develop Genia's NanoTag sequencing technology
GlobeImmune Inc.	Colorado State University; NIH	Infectious disease	\$4 million	Deal to develop Tarmogen products to prevent drug-resistant tuberculosis
Roslin Cells Ltd.	Cell Therapy Catapult	Gene and/or cell therapy	£2 million (\$3.1 million)	Partnership to establish a source of clinical-grade induced pluripotent stem (iPS) cells according to GMP standards in the U.K.

(Continues on p. 3)

Table 1. Selected public-private partnerships for September 2013. (continued)

Companies	Institutions	Business area	Disclosed value	Purpose
OxThera AB; Cobra Biologics AB; SymbioPharm GmbH; Ergomed Clinical Research Ltd.; Galenica Ltd.; K.A.B.S. Laboratories; Bio-Images Research Ltd.	University Hospital Bonn; Civil Hospitals of Lyon; University College London Hospitals; Institute for Microecology; TNO; European Commission	Endocrine/metabolic disease	€2.2 million (\$3 million)	Elimox consortium to develop a bacterial pharmaceutical product using <i>Oxalobacter formigenes</i> to treat primary hyperoxaluria
BioVersys AG	University of Applied Sciences and Arts Northwestern Switzerland; University of Basel; University of Bern; University of Geneva; Zurich University of Applied Sciences; Commission for Technology and Innovation	Infectious disease	CHF2.1 million (\$2.3 million)	Consortium to develop a transcription regulator inhibitory compound that targets bacterial resistance mechanisms at a genetic level to restore efficacy of conventional antibiotics
BioHealth Innovation Inc.	The Johns Hopkins University	Other	Up to \$50,000 per company	Partnership to launch DreamIt Health Baltimore project to accelerate growth of early stage health IT companies
Anida Pharma Inc.	ALS TDI	Neurology	Undisclosed	Partnership to evaluate Anida's neuroprotectin D1 in superoxide dismutase 1 (SOD1) mice as a potential treatment for amyotrophic lateral sclerosis (ALS)
AstraZeneca	Hadassah University Hospitals	Cancer; endocrine/metabolic disease; pulmonary disease	Undisclosed	Deal to discover and jointly develop compounds to treat cancer, respiratory diseases and diabetes
Bayer AG (Xetra: BAYN)	Broad Institute of MIT and Harvard	Cancer	Undisclosed	Five-year partnership to jointly discover and develop therapeutics that selectively target cancer genome alterations
C4X Discovery Ltd.	University of Southampton	Infectious disease	Undisclosed	Three-year partnership to develop HIV drug candidates derived from cyclic peptides
Evotec AG (Xetra: EVT)	Harvard University	Neurology	Undisclosed	CureMN collaboration to identify compounds that prevent or slow motor neuron loss
ImmunoGenes AG	Massachusetts General Hospital	Cancer	Undisclosed	Collaboration to identify key targets in hematological cancers and generate antibodies against them
Protea Biosciences Inc.	Virginia Commonwealth University	Cancer; Neurology	Unavailable	Partnership to develop methods to elucidate the molecular basis of diseases including cancer and Alzheimer's disease
Servier	Agency for Science, Technology and Research (A*STAR)	Cancer; autoimmune disease; transplantation	Undisclosed	Three collaborations to discover and develop compounds for indications that include cancer, autoimmune diseases and organ transplant
Servier	Chinese Academy of Sciences	Cancer	Undisclosed	Collaboration to develop cancer compound lucitanib (E-3810) in China
Teva Pharmaceutical Industries Ltd. (NYSE: TEVA); Cancer Research Technology Ltd.	Cancer Research UK	Cancer	Undisclosed	Three-year partnership to discover drugs that modulate DNA damage and repair response processes in cancer cells

of Maryland, Baltimore to pursue joint research projects relevant to the unit's core therapeutic areas, including cancer and cardiovascular, metabolic, respiratory, inflammatory, autoimmune and infectious diseases. Both parties will provide funding and scientists to work on joint projects, with MedImmune planning to contribute at least \$5 million and the university planning to contribute \$1 million over the 5-year collaboration.

MedImmune said that the deal is the first of several planned collaborations to bolster biomedical R&D activity within the state of Maryland.

AstraZeneca also announced a drug discovery alliance with **Hadassah University Hospitals** to discover and develop compounds to treat cancer, respiratory diseases and diabetes. Hadassah scientists will work with teams from AstraZeneca's Innovative Medicines & Early Development organization for an initial period of three years.

AstraZeneca declined to disclose details.

Meanwhile, Servier signed a trio of research collaborations with the Singapore Immunology Network (SIgN) research unit of the **Agency for Science, Technology and Research (A*STAR)**. Two deals focus on dendritic cell biology in cancer, organ transplantation, inflammation and autoimmune diseases. The third focuses on identifying genetic predispositions in Asian patients related to drug-induced side effects.

SIgN will be responsible for discovery research, whereas Servier will have rights to resulting compounds and will be responsible for development and commercialization. Financial details are undisclosed.

Servier also partnered with the **Chinese Academy of Sciences' Shanghai Institute of Materia Medica (SIMM)** to develop the cancer compound lucitanib (E-3810) in China. The partners will collaborate to run clinical trials, and SIMM also will conduct biomarker research. Servier said that clinical testing of lucitanib in China is scheduled to begin by mid-2014.

The current partnership includes a licensing agreement with SIMM, **Advenchen Laboratories LLC** and **SFFT Developing Co. Ltd.** that expands Servier rights to lucitanib to China.

Last October, Servier acquired exclusive rights to lucitanib outside of the U.S., Japan and China from **EOS S.p.A.** for €45 million (\$57.9 million) up front plus milestones and royalties.⁵ EOS has worldwide rights to lucitanib outside China from Advenchen.

Lucitanib, a small molecule inhibitor of fibroblast growth factor receptor 1 (FGFR1; CD331) and VEGF, is in a Phase I/IIa trial in solid tumors.

Finally, the newly formed EpimiRNA consortium received €11.5 million (\$15.4 million) in funding from the EU's Seventh

Framework Program. The consortium is co-coordinated by the **Royal College of Surgeons in Ireland** and **Philipps University of Marburg** and comprised of 6 partners from industry and 10 from academia.

The consortium's focus is on investigating molecular mechanisms and diagnostics for epilepsy and developing microRNA-based treatments that could prevent epilepsy and seizures or reverse epilepsy once it is established.

Lou, K.-J. & Oshrovich, L. *SciBX* **6**(39); doi:10.1038/scibx.2013.1084
Published online Oct. 10, 2013

REFERENCES

- Oshrovich, L. *SciBX* **6**(9); doi:10.1038/scibx.2013.206
- Mali, P. *et al. Nat. Biotechnol.* **31**, 833–838 (2013)
- Ran, F.A. *et al. Cell* **154**, 1380–1389 (2013)
- Lou, K.-J. *SciBX* **6**(35); doi:10.1038/scibx.2013.950
- McCallister, E. *BioCentury* **20**(42), A1–A6; Oct. 15, 2012

COMPANIES AND INSTITUTIONS MENTIONED

Advenchen Laboratories LLC, Moorpark, Calif.
Agency for Science, Technology and Research, Singapore
Allen Institute for Brain Science, Seattle, Wash.
AstraZeneca plc (LSE:AZN; NYSE:AZN), London, U.K.
Broad Institute of MIT and Harvard, Cambridge, Mass.
Caribou Biosciences Inc., Berkeley, Calif.
Chinese Academy of Sciences, Shanghai, China
Defense Advanced Research Projects Agency, Arlington, Va.
EOS S.p.A., Milan, Italy
Hadassah University Hospitals, Jerusalem, Israel
Harvard Medical School, Boston, Mass.
Harvard University, Cambridge, Mass.
Horizon Discovery Ltd., Cambridge, U.K.
Howard Hughes Medical Institute, Chevy Chase, Md.
The Kavli Foundation, Oxnard, Calif.
MedImmune LLC, Gaithersburg, Md.
National Institutes of Health, Bethesda, Md.
National Science Foundation, Arlington, Va.
Philipps University of Marburg, Marburg, Germany
The Rockefeller University, New York, N.Y.
Royal College of Surgeons in Ireland, Dublin, Ireland
Sage Labs Inc., St. Louis, Mo.
Salk Institute for Biological Sciences, San Diego, Calif.
Sangamo BioSciences Inc. (NASDAQ:SGMO), Richmond, Calif.
Servier, Neuilly-sur-Seine, France
SFFT Developing Co. Ltd., Hangzhou, China
Shanghai Institute of Materia Medica, Shanghai, China
Sigma-Aldrich Corp. (NASDAQ:SIAL), St. Louis, Mo.
Stanford University, Stanford, Calif.
University of Maryland, Baltimore, Md.
Wyss Institute for Biologically Inspired Engineering at Harvard University, Cambridge, Mass.