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Buckets of money for the brain

By Michael J. Haas, Associate Editor, and Kai-Jye Lou, Senior Writer

Apart from the recent ALS ice-bucket challenge, the perception is that neurological disorders have become the poor relation of oncology and other diseases when it comes to public and private funding. But an uptick in activity on both fronts suggests the landscape of neuroscience investment may not be as bleak as presumed.

Although many researchers contend that the field is still underfunded relative to the burden of disease on society, advances in genetics, markers and disease models—as well as multidisciplinary projects focusing on the brain as a whole—are drawing investors back and prompting the creation of public-private partnerships (PPPs) that might spur yet more innovation.

Indeed, this week, the Janssen Inc. unit of **Johnson & Johnson** announced a partnership with the **University of Toronto** to fund new therapeutic approaches in mood disorders and Alzheimer's disease (AD). The deal is the 22nd neurology-based PPP this year and continues the trend of the last 3 years in which 29–57 neurology PPPs were formed annually. When that trend is compared with a range of 49–79 PPPs annually over the same period for cancer—widely considered the best-funded disease area—it suggests interest in neuroscience has not faded entirely (*see* **Figure 1.I, "Investing in the brain"**). Moreover, there were more PPPs focused on neurology than on endocrine and metabolic diseases or autoimmunity and inflammation each year between 2011 and 2013.[1]

The Janssen–University of Toronto collaboration, dubbed Neuroscience Catalyst, is designed to foster data that can attract funding and spawn new companies, said Guy Seabrook, VP of neuroscience innovation at J&J's California Innovation Center. He added that the emphasis is on asset-based opportunities such as candidate therapeutics rather than animal models, but the partners also want to fund disruptive technologies that can create value in terms of business enterprises.

"Disability created by mood disorders—depression and bipolar disorder—have a huge impact on society. Also, the standard of care only works in a subset of patients and has a long delay of onset. There is good work going on now that shows these issues are addressable."
—Guy Seabrook, Johnson & Johnson

The collaboration is structured along the no-strings-attached model of Janssen Labs because the company wants to seed ideas coming out of academia without hampering entities with respect to IP rights and other commercial issues, said Seabrook. J&J is one of the pharmas that have kept up research in neurological disease, and Seabrook said the new partnership will complement, not replace, internal programs.

Despite the retreat by some pharmas from neurological R&D, venture investment in the field lags behind oncology by only 50%. From 2011 to 2013, seed and series A investments in neurology companies ranged from $170 million to $235 million annually—with another $88 million invested through the end of August 2014 (*see* **Figure 1.II, "Investing in the brain"**).

"I think it's a great time for early stage neuroscience investing," Bruce Booth, partner at **Atlas Venture**, told *SciBX*. "Some exciting new opportunities are arising from a confluence of trends, such as genetic insights into neurological diseases or disease subsets, improved understanding of preclinical models, and better imaging and biomarker modalities."

He added, "Also, importantly, in the clinical arena the ability to dissect heterogeneous disease populations into various subpopulations should enable better trial outcomes and quicker paths to proof of concept."

Booth said these trends have tipped the balance at Atlas heavily in neuroscience's favor. "Of the 30 active portfolio companies across our last 3 funds, at least 13 of the companies—roughly 40%—are dedicated to or have pipeline programs in a variety of

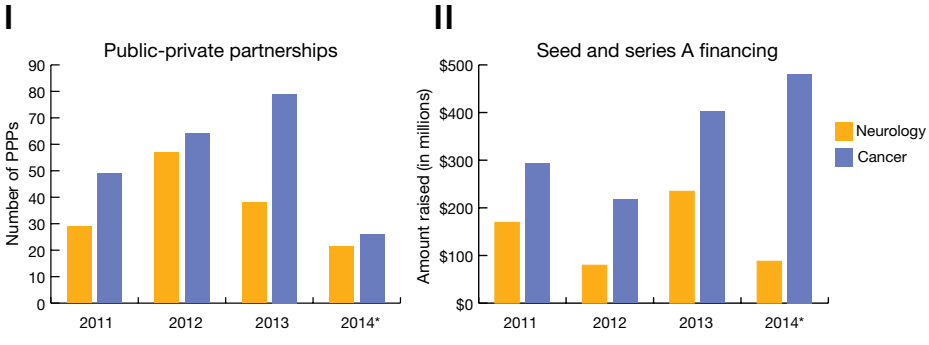

Figure 1. Investing in the brain**.** (**I**) Number of public-private partnerships (PPPs) announced for neurology or cancer indications. Data include double counting as some PPPs include multiple therapeutic areas. *2014 data are through end of August. (**II**) Seed and series A financing for companies focused on neurology or cancer. *2014 data are through end of August.

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neuroscience fields such as Alzheimer's disease, Parkinson's disease, psychiatry, pain, ataxia and orphan neuroscience diseases. Since only about 14% of industry's pipeline is in neuroscience, we are significantly overweight in neuroscience and bullish given our portfolio exposure."

The PPPs formed between 2011 and July 2014 showed a similar focus on those indications. AD, amyotrophic lateral sclerosis (ALS), Parkinson's disease (PD), schizophrenia-related indications and pain have received the greatest attention. A further 50 PPPs were created for unspecified or multiple indications (*see* **Figure 2, "Neurology indications for PPPs formed since 2011"**).

Booth was not surprised that the disease-specific deals and PPPs have clustered around AD, PD and pain because of the massive disease burden and unaddressed morbidity of those three diseases. He added, "I am pleasantly surprised to see the ALS numbers as high as they are."

By contrast, anxiety and depression together represent only about 2% of the total number of partnerships. Seabrook said J&J's Neuroscience Catalyst chose mood disorders—which include depression—as a principal focus because of the very large disease burden despite the plethora of approved drugs.

"Disability created by mood disorders—depression and bipolar disorder—have a huge impact on society. Also, the standard of care only works in a subset of patients and has a long delay of onset. There is good work going on now that shows these issues are addressable," he said.

A clearer burden

Magali Haas, founder and CEO of **Orion Bionetworks Inc.**, told *SciBX* that part of the reason for increased investment is that the burden of neurological diseases on society is becoming clearer and more widely known.

Orion is a not-for-profit organization that creates alliances among its network of partners to accelerate treatments for brain disorders.

The best estimate puts the costs of neurological diseases in the U.S. at $1 trillion annually, she said. "In 2011, the **European Brain Council** looked at 19 categories of brain disorders in 27 countries and estimated that 1 in 5 people would be affected by a brain disorder at some point in their lives, with a total cost of $1 trillion annually."

Haas said these figures likely underestimate the disease burden in the U.S. and EU because most of the data come from associations and foundations focused on specific indications, so the costs of some disorders and comorbidities are not reflected in the estimates for neurological disease as a whole.

She added, "We are seeing a new focus on getting a better handle on the aggregate costs of neurological diseases through efforts by the EU, G7 countries and other international organizations."

Haas also noted that Horizon 2020—a 7-year, €80 billion ($103.5 billion) funding program in the EU—has put neuroscience at the top of its agenda "because of the huge societal impact of these disorders—which exceeds the impact of cancer, diabetes and cardiovascular disease combined."

These are among the factors that led to the Human Brain Project in the EU and the BRAIN (Brain Research through Advancing Innovative Neurotechnologies) Initiative in the U.S., Haas said.

But she argued that the investment still does not match the need. "Historically, the **NIH** invests about $5.5 billion in neuroscience, and

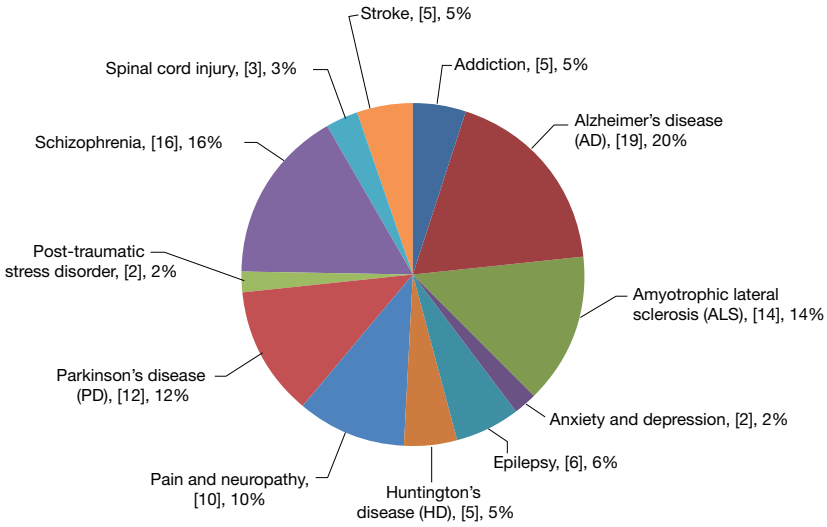

Figure 2. Neurology indications for PPPs formed since 2011. Data include double counting as some PPPs include multiple indications. Percentages are out of the total number of neurology PPPs; bracketed values are the actual number of PPPs for each indication. Schizophrenia data include psychosis, mania and cognitive function. Spinal cord injury data include nerve damage. Data are through end of August 2014. *Source: BCIQ: BioCentury Online Intelligence.*

the big pharmas also invest about $5 billion" for a total global estimate of $10–$11 billion annually, not counting venture capital investments, she said. "Is that the right amount of money to invest toward solving a $1 trillion problem? Probably not."

Inez Jabalpurwala, president and CEO of **Brain Canada**, agreed. "There is definitely a disconnect between what we can and need to understand about the brain and its functions and the level to which those efforts are funded." She added, "It is not just a question of how many dollars you can get together—it's also a question of what you do with the money once you have it," she said. "For instance, the ALS ice-bucket challenge has raised over $100 million—but what do you do with that? And is it a disproportionate amount for one disease?"

In July and August, the act of dumping a bucket of ice-cold water on a person's head to promote awareness of ALS went viral on social media, resulting in $111.1 million in donations to **The ALS Association** as of Sept. 9.

Haas said, "The question about investing in neuroscience is often asked in the wrong direction: What can I do with the money I have or I can get? The better question is: What do we need to do to address the problem of neurological diseases? From there, design the study you want to do, see what it will cost and decide whether the return on investment makes it worth that cost."

"We had the feeling that most of the work that was published on the mechanisms underlying resistance to BRAF and MEK inhibitors somehow overlooked what lies downstream."

—Stéphan Vagner, Institut National de la Santé et de la Recherche Médicale

For example, she said, neuroscientists frequently decry the lack of data for the healthy, ageing population that is needed to differentiate normal ageing processes from the pathological processes of AD and dementia.

"A study to acquire that data could be done for about $100 million, but no agency gives this much to one project," she said. "So even though this is exactly what we need to do, no one will make that huge one-time investment to do it. Instead, the funds get divided into small quanta and spent on a range of smaller projects."

But government agencies could, and have, put up as much as $10–$20 million for a single project, she said. "If that were matched by funding from PPPs, these big studies could be done and everyone could benefit from the results—and from the establishment of best practices, the synergy of multidisciplinary interactions and the elimination of redundancies that come from working in isolation on a problem. The whole would be more than the sum of its parts."

Whole-brain thinking

Haas and Jabalpurwala both emphasized that the field is moving from thinking about specific indications to viewing neurological disorders in the context of the whole brain. That echoed the position taken by a recent panel of neurology experts convened by *SciBX*, who described a trend toward looking at functions of different brain regions in an integrated manner, rather than focusing on individual molecules, for diseases such as schizophrenia, depression and autism.[2]

"While we had the 'war on cancer' and the 'war on cardiovascular disease', we still look at neurological diseases by specific indications instead of by common biological mechanisms and pathways as a whole or shared by many disorders," Haas said. "But Parkinson's disease, Lewy body disease and dementia are all related. Cognitive impairment is found across many disorders. We should be investing in them together."

"A broader approach can shift how we understand brain functions and brain diseases," Jabalpurwala said. "For instance, Alzheimer's disease has both psychological and neurological components, while other neurological indications might actually be a collection of several different diseases. Investments are better made with this broad view in mind and looking for the bigger pieces of the puzzle."

Indeed, she said, "the whole-brain view that we take at Brain Canada doesn't involve just biological neuroscientists. It is a multidisciplinary approach that involves chemists, computational scientists and researchers in other areas. We do this because breakthroughs in one area often come from areas outside one disease, where someone realizes that what they've found could apply to another area."

She noted that Brain Canada's whole-brain approach does not discourage research on one disease but instead encourages researchers to think about how one disease might connect to others. "Questions about a specific disease are asked in a broader context."

According to Jabalpurwala, the hands-off approach of the Canadian government enables Brain Canada to take the kind of risks that are going to be needed to advance the field. "Everything we fund with our dollars is matched by government dollars and has to be linked to an outcome," she said. "The Canadian government provides leadership by funding basic research, then partners with Brain Canada and other organizations to bring in the outcomes-oriented piece."

"Our donors and partners have interest in certain disease areas. But exactly where the funding goes is determined by the project proposals we receive. We take risks on solid ideas from solid research teams," she said.

Through the Canada Brain Research Fund, Brain Canada has committed to raising C$100 million ($91.7 million) from private and nongovernmental sources that will be matched on a 1:1 basis by the Canadian government. The 5-year fund was announced in the federal budget in 2011 and launched in 2012.

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2. Fishburn, C.S. & Osherovich, L. *SciBX* **7**(31); doi:10.1038/scibx.2014.913

COMPANIES AND INSTITUTIONS MENTIONED

The ALS Association, Washington, D.C.
Atlas Venture, Cambridge, Mass.
Brain Canada, Montreal, Quebec, Canada
European Brain Council, Brussels, Belgium
Johnson & Johnson (NYSE:JNJ), New Brunswick, N.J.
National Institutes of Health, Bethesda, Md.
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University of Toronto, Toronto, Ontario, Canada