Advances in neuroscience and surging markets may spur deal activity

After a period of setbacks and the exodus of high-profile companies from neuroscience R&D, industry leaders predict a rebound in neuroscience investment and deal activity in areas such as pain.

BY CHRIS MORRISON

A resurgence in venture financing and merger and acquisition (M&A) activity alongside advances in clinical trial design, imaging and biomarkers have added up to renewed interest in drugs to treat central nervous system (CNS) disorders. That interest coincides with the emergence of a variety of innovative mechanisms of action and technologies such as gene therapy that are driving early-stage dealmaking and investment.

Over the past decade, several large companies have partially or altogether exited neuroscience research. Some have spun off assets that have matured within venture-backed biotech environments. Others remain interested in the space but are reluctant to make a deal before a drug has reached human proof-of-concept. Risk in neuroscience drug development meant that active players tended to focus on life-cycle management of existing products through reformulation or new delivery methods.

This retrenchment is at odds with increasingly dire demographics. CNS disorders are among the most prevalent causes of death and disability; for example, the World Health Organization estimates that worldwide more than 350 million people suffer from depression, and the devastating physical, social and economic consequences of dementia continue to vex health systems globally (see "Approaches to age-related disorders evolve", page B14).

According to a June 2015 report from the Biotechnology Innovation Organization (BIO), a biotech-industry lobbying group, venture funding of companies with lead programs in neurology and psychiatry was about $5 billion in 2005–2014 (13% of all biotech venture dollars, behind only oncology). The space was dominated by venture funding of pain R&D, which accounted for 42% of that funding over the ten-year period. This dwarfed all other neuroscience disease areas, none of which breached the $500 million mark (multiple sclerosis, Alzheimer's disease and Parkinson's disease were the most significant also-rans in the category). But over that span, nearly half of pain's venture capitalist (VC) investment haul was not devoted to novel drug R&D but instead pegged for reformulations of old therapies and various new routes of administration. VCs who invest in the CNS and pain areas say that it can be difficult to syndicate deals because fewer large pharma companies are interested in the space, and the odds of striking large deals that can offset a company's burn rate are lower than those in hot areas such as oncology and immunology.

Neurology and psychiatry also combined to rank second in R&D-stage licensing-deal dollars over the ten-year period, with 16% of the total (about $5.6 billion). The area fared poorly in terms of racking up M&A dollars, however, accounting for only about 5% of R&D-stage acquisitions and 5% of acquisitions of companies with products on the market, according to the BIO data.

But in the past two years there has been a shift toward investing in novel drug R&D and away from reformulations, as biotechs advance molecules through the clinic that aim to modulate new drug targets. New modalities, such as gene therapy, are also being brought to bear; Sanofi recently committed $100 million up front in an alliance with CNS gene therapy specialist Voyager Therapeutics, for example. In addition, several large acquisitions, such as Biogen's January 2015 takeover of the VC-backed pain-focused Convergence Pharmaceuticals ($200 million up front with up to $475 million in earn-outs), Novartis' June 2015 acquisition of the Australian pain company Spinifex ($200 million up front plus earn-outs) and Teva Pharmaceuticals' acquisition of Auspex Pharmaceuticals for $3.2 billion in March 2015 to access that biotech's lead program in Huntington's chorea, have sparked investor enthusiasm. Perhaps the best example of buy-side interest in neurological disease came in July 2015, when Celgene paid $7.2 billion for Receptos, whose lead sphingosine 1-phosphate 1 (S1P) receptor modulator ozanimod is in phase 3 trials for multiple sclerosis and ulcerative colitis (**Table 1**).

"It's a fascinating time right now," said Bruce Booth, a partner at Atlas Venture, based in Cambridge, MA. "In some ways the evolution of neuroscience R&D is like the previous evolution in oncology R&D, in that it's becoming precision-medicine oriented." Industry research is being augmented by large public efforts, such as the EU Human Brain Project and the US National Institutes of Health's Brain Research through Advancing Innovative Neurotechnologies (BRAIN) initiative. As neurological conditions give up their genetic secrets, previously heterogeneous disease populations can be subtyped, said Booth, leading in some cases to an 'orphanization' of neuroscience. "We are starting to pick apart different diseases" in areas such as neurodegeneration, pain, epilepsy and even psychiatry, said Booth. "We previously thought about these diseases as large and amorphous, but the biology is providing interesting proof points for drug discovery campaigns, especially for small companies" who could not afford to invest resources in broader disease settings. The Atlas Venture portfolio, Booth said, comprises about two dozen companies that are beyond seed stage, and those companies are engaged in a total of 75 R&D projects. Of those projects, 40% are in neuroscience.

Table 1. Selected major M&A deals in the neuroscience area (July 2014–July 2015).

Companies	Headline	Date	M&A value (US$ million)
Celgene; Receptos	Celgene acquires Receptos and phase 3 multiple sclerosis candidate	July 2015	7,200
Teva; Auspex	Teva acquires neurology-focused Auspex in $3.5 billion deal	March 2015	3,500
Otsuka Pharmaceutical; Avanir Pharmaceuticals	Otsuka acquires CNS-focused Avanir for $3.5 billion	December 2014	3,500
Biogen; Convergence Pharmaceuticals	Biogen acquires pain specialist Convergence	January 2015	675
Allergan; Naurex	Allergan spends $560 million to buy antidepressant maker Naurex	July 2015	560
Acorda; Civitas	Acorda acquires neurological drug-maker Civitas for $525 million	September 2014	525
Roche; Trophos	Roche buys Trophos to expand portfolio in neuromuscular disease	January 2015	515
Novartis; Spinifex	Novartis buys pain drug developer Spinifex	June 2015	200 (Upfront payment)

Data sourced from BioCentury BCIQ.

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Emerging mechanisms in pain

Various manifestations of pain—postoperative pain, chronic pain, migraine and many others—remain largely unchecked. Moreover, most are treated with drug classes discovered decades ago, such as nonsteroidal anti-inflammatories (NSAIDs) and opioids (and recently approved abuse-deterrent versions), although α2δ calcium channel modulators (for example, Pfizer's Neurontin (gabapentin) and Lyrica (pregabalin)) have been introduced for some indications more recently.

"In pain there's such a huge unmet need, and such a huge problem with opioid abuse and addiction," said Stan Abel, president and CEO of pain-focused SiteOne Therapeutics. The Convergence and Spinifex deals "are a reflection of how big these opportunities can be for novel non-opioid pain therapies," he said. What's more, "there's been an unbelievable explosion and advancement in basic neuroscience over the past few years," said Richard Brudnick, VP and co-head of business development at Biogen. "That plus a robust financial market that has reawakened venture investment and the successes of Biogen and others in neurology has stimulated a lot of entrepreneurial activity," he said.

Advances in ion channel technologies have allowed researchers to greatly increase the throughput of screening technologies, and advances in stem cell technologies have allowed for much better models of disease, said David Reynolds, VP and site head of Neusentis, Pfizer's specialized unit for pain and ion channel R&D. "These are tools that had been missing from our toolbox," he said. Over time, this increased bandwidth and unprecedented access to models of the human nervous system "should increase our success rate for drugs going into early clinical trials," he said. New research is unraveling the origins of pain and the fundamental mechanisms that carry those signals to the brain, as well as how pain becomes permanent, said Husseini Manji, global therapeutic head for neuroscience at Johnson & Johnson's Janssen Pharmaceuticals unit. "Until now we've tried to make you not feel pain instead of working on the fundamental mechanisms that cause it, but now we're in a position to intervene at the root of what is going on."

Biogen's acquisition of Convergence—a 2010 spin-out from GlaxoSmithKline (GSK), which owned a minority stake in the company—landed the big biotech company a suite of assets for the treatment of chronic pain that target voltage-gated sodium channels. Inhibitors of the Nav1.7 channel are something of a poster child for genetically informed drug development; naturally occurring but rare mutations that lead to loss of function of the channel have been identified in people who are unable to perceive pain, and rare gain-of-function mutations in *SCN9A* have been identified in families with the congenital pain disorder primary erythermalgia, which causes burning pain in the extremities. Biogen is preparing its lead program, CNV1014802, for phase 3 after positive mid-stage results in trigeminal neuralgia, a severe form of facial pain. "In ideal circumstances, you have a genetically validated target and a biomarker to measure whether you're engaging with and modulating the target," said Brudnick. "That allows you to test in a smaller patient population and increases your chance of success, and those are big steps forward" in neuroscience drug development in the past decade, he said.

Other players in the Nav1.7 space include Xenon, who licensed its lead Nav1.7 inhibitor to Teva for $41 million up front in December 2012 (the small biotech company also has a pain-focused deal with Roche's Genentech, signed in January 2012 and worth up to $646 million in total potential payments), and newcomer SiteOne Therapeutics, which in July 2015 finalized its first round of financing. "What's interesting about this particular target is that there's partnering interest at all stages of development," pointed out Abel, whose previous companies Corthera, Cerexa and Peninsula were sold to Novartis, Forest and Johnson & Johnson, respectively. "I've sold three biotechs, and all have been after phase 2 data, but this is a target where a deal much earlier than that might be possible." Abel notes SiteOne is open to a variety of partnership structures.

Other new targets, as well as new approaches to existing targets, are attracting similar attention. Afferent Pharmaceuticals, a 2009 spin-out from Roche that is focused on developing drugs for pain and related sensory pathologies, is developing its lead asset AF-219 as a treatment for chronic, pathologic cough that results when nerves fail to return to a quiescent state after an acute event such as a respiratory infection. Afferent's target is an ATP-gated ion channel receptor called P2X3 that is often upregulated after nerve injury or inflammation and thus may be modulated to treat a variety of pain and related conditions. "Once we saw there were P2X3 receptors selectively expressed by sensory fibers which aren't involved in fundamental processes but signs and symptoms in pathology, pain was an obvious way to go," said Anthony Ford, CSO. The company published proof-of-concept data for its lead cough program in *The Lancet* in November 2014, and it landed $55 million from a syndicate of crossover investors (investors who invest in both privately held and publicly traded companies) in July 2015, potentially signaling an impending IPO. "We've validated this target across indications from a clinical perspective, and that's caused a lot of pharmaceutical companies to take note," said Afferent CEO Kathy Glaub.

Older targets can be modulated in new ways to avoid some deleterious effects of older therapies. G protein-coupled receptors (GPCRs) represent an enormously popular class of drug targets and the largest family of transmembrane receptors. For years researchers treated the receptors like switches that could be turned on or off using agonists or antagonists, said Trevena scientific co-founder Jonathan Violin, who runs the company's investor relations. But a pair of discoveries upended that notion. First, GPCRs were found to couple to more than one signaling pathway: alongside G protein-mediated signaling is a distinct pathway mediated by β-arrestin. Second, researchers learned that those distinct

pathways can lead to different pharmacological outcomes. “With the right kind of molecule, you can activate one pathway or the other,” said Violin, and in the case of Trevena’s lead pain program, it could be possible to avoid on-target effects associated with μ-opioid receptor agonists, such as respiratory depression.

Activating only the G protein-mediated pathway would mean “you could get an opioid with a much better side-effect profile,” explained Neusentis’ Reynolds, who said Pfizer is among a group of companies trailing Trevena’s TRV130, an intravenously administered small molecule that has completed a phase 2 study for use in acute postoperative pain. A second phase 2 study, for management of postoperative pain after abdominoplasty, should read out in the third quarter of 2015, said Violin. He also said that Trevena aims to license ex-US rights for the molecule’s intravenous formulation, and possibly rights for other formulations and indications, such as transmucosal delivery for breakthrough cancer pain or transdermal delivery for chronic pain.

Ramping up CNS R&D via partnerships

When it comes time for Afferent, Trevena, SiteOne and others to partner, a larger audience may await them than would have been the case in years past. There will be stalwarts such as Biogen and Johnson & Johnson, of course, but also deal-hungry specialty pharma companies such as Shire, Teva and Allergan, the last of which expanded its CNS efforts recently by bringing Merck & Co.’s oral calcitonin gene-related peptide (CGRP) migraine drugs into its pipeline via a $250 million up-front deal in July 2015. CGRP is a hot migraine target, but most of the competition is among antibody drugs from Amgen, Teva, Lilly and Alder Pharmaceuticals. Teva’s TEV-48125 came from its 2014 acquisition of Labrys Biologics ($200 million up front). Similarly, Lilly acquired its compound from Arteaus Therapeutics in January 2014 (Atlas Venture-backed Arteaus had originally licensed the drug from Lilly, in 2011, taking on the risk and eventual reward of the drug’s success in a clinical proof-of-concept trial).

Companies that have pulled back in the past are eyeing the field for opportunities. GSK, alongside a handful of other large companies, has committed $25 million in capital to the Dementia Discovery Fund, a $100 million public–private UK-based partnership that will invest in dementia-related opportunities. GSK expects to expand its business development activities in neuroscience as it embraces advances in the field’s foundational biology. But at the same time, said Min Li, SVP and head of GSK’s neuroscience therapeutic area unit, “each subspecialty in neuroscience is an area of deep biology, and it’s certainly unrealistic for us to develop an in-house effort with sufficient bandwidth to accommodate these significant new discoveries; thus externalization through partnering is key to expanding our coverage.”

Even big companies with long-standing neuroscience R&D commitments are increasingly looking elsewhere for innovation. “Because of the magnitude of the problem, the degree of complexity, it’s necessary to bring together different groups of people with complementary skills, talents and approaches to tackle problems in neurological disease,” said Janssen’s Manji.

Manji has high hopes for a renaissance in neuroscience R&D. “It’s unfortunate that some companies have pulled back in neuroscience. But 15 or 20 years ago, people had similar concerns about oncology,” said Manji. A handful of “big breakthroughs” later, he said, “every company is back in oncology; that’s exactly what could happen in neuroscience.” Among the positive signs Manji sees are the application of ‘big data’ approaches to neuroscience problems, and technologies embedded in smartphones and wearable devices that will allow researchers to gather signals and data from people in the real world to better track the natural progression of neurological disorders. “We’re also seeing a lot of device companies moving into the neuroscience space,” he said, “because there’s a recognition that the brain is an electrical organ, and there are opportunities for devices to engage specific circuits.” These approaches could be complementary to pharmacological approaches, he said.

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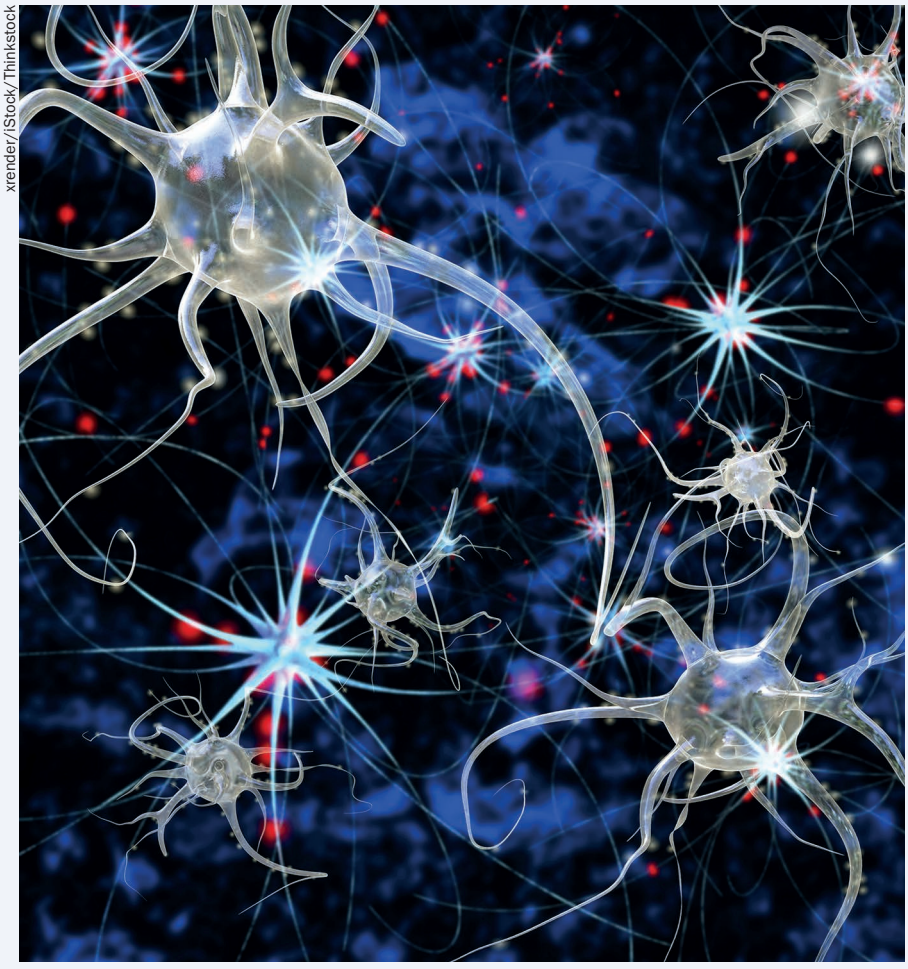

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