The Neuro Funding Rollercoaster

By Harry M. Tracy, Ph.D.

Editor’s Note: Compared to the money dedicated to cancer and cardiology, funding for neuroscience research has lagged behind for decades. But things are starting to change. From the White House’s Brain Initiative to the Ice Bucket Challenge for ALS to some recent sizeable gifts to universities, money for brain research appears to be on the rise. But, as our author explains, research and development funding from private and corporate lenders for cognitive neuroscience—an area that he has spent years tracking—is also vital to the quality of life for millions of people.
As much as we like to frame research for neurology and psychiatry as being rooted in harnessing science to improve the practice of medicine, the arguably crass but sobering reality is that while applied neuroscience may be ultimately judged by its scientific/medical achievements, the process depends upon the availability of money for the arduous research and development journey. The most extreme roller-coasters found at amusement parks have nothing on the stomach-churning oscillations of funding for research devoted to neurology and psychiatry—other than the latter is timed in months and years, rather than seconds. The past decade has seen the flow of resources for applied neuroscience sink to a stunning nadir, followed by an even more astounding resurgence.

But this recovery has been very uneven, and some areas, particularly psychiatry, have yet to rebound to anything near their former levels of fiscal well-being. Even this retrospective appraisal comes during a period of flux reflective of, and exacerbated, by geopolitical, political, and demographic dynamics currently at a peak. We recently experienced the best year for neurotherapeutics funding in over a decade, perhaps ever. But as early 2016 unfolded, the gains of 2015 receded like a favorite vacation spot shrinking in the rearview mirror; there has been a dramatic retreat from investment by both institutions and pharma partners.

As of the end of April, the annualized projection for institutional funding/investment was down more than 50 percent from last year’s total, and partnering (in terms of disclosed upfront payments) was down more than 75 percent. It remains to be seen to what degree this is a transitional hitch in the recovery process, or a return to a painfully familiar climate of angst and parsimony. We believe it is the former, but this is a hypothesis yet to be tested by time, and there is more than ample pessimism about resource-availability to be found in the venture-capitalist community.

With that caveat noted, we will examine the past decade in the funding of neuropsychopharmacology, as well as cell and gene therapeutics, in terms of the enormous perturbations that have occurred within the institutional investment climate for the neuro sector and in the pharma industry’s willingness to partner neurology/psychiatry programs in development by smaller firms. We will focus strictly upon these two fiscal domains. The third major R&D resource, governmental grant funding, took on greater salience during the recent period of fiscal
deprivation, but its role is to some degree compensatory: such funding partly (but never entirely) makes up for shortfalls in investor/pharma dedication to neurotherapeutics.

Serendipity and Stasis

Our discussion will not address the massive scale of unmet medical need to be found in populations suffering from neurological and psychiatric illness. Nor will we analyze the lack of substantive change in treatment options for these patients. Suffice it to say that, in spite of the billions of dollars spent searching for better treatments for neurological and psychiatric disorders, and the myriad advances made in basic neuroscience, when it comes to real-world therapeutic drug options, the situation has been one of near stasis. Our antidepressants do not differ significantly from those that were available 20 years ago; the same can be said of our antipsychotic options, used primarily for schizophrenia and bipolar disorder; and for the modest cognitive enhancers marketed for Alzheimer’s.

The one exception—an area where significant advances have occurred in terms of efficacy and ease-of-use—is in the treatment of Relapsing-Remitting Multiple Sclerosis (RRMS). The beta-interferons gave rise to IV natalizumab, then the oral S1P targeting compounds, and the oral fumarate-based drugs. It is the one disorder where we are now able to actually slow the progression of the disease, rather than simply masking or suppressing symptoms, and the repertoire comprises a range of choices with a spectrum of risk-reward profiles from which patients and their physicians can choose. It is also the area where the regeneration of what has been lost, in terms of neural circuits and functioning, is now being first attempted. Advances for RRMS represent the way we hope neurotherapeutics for other disorders will evolve over the next two decades.

There are several reasons for this era of stasis. First, the great psychiatric drug classes that emerged during the 1950s and 1960s were largely the product of serendipity; the clinical observation of therapeutic effects that led to post-hoc hypotheses explaining how these drugs might work—hypotheses that were for the most part—questionable at best, wrong at worst. They failed to provide a road map for their successors; many scientists embarked on research journeys launched by assumptions that turned out to be incorrect and guided by processes that misinformed. There was a false sense of confidence based on the commercial success of new drug classes that had
become popular due to a better side-effect profile, rather than improved efficacy, like the SSRIs and second-generation antipsychotics. The pharmaceutical industry became, for lack of a better word, “lazy” when it came to internal R&D; imitation was frequently more prized than discovery, as many companies tried to piggyback on the success of earlier drugs through tweaking rather than innovating. To the degree to which innovation was permitted and funded, there was a tendency towards premature closure, choosing new mechanisms for full development without adequately auditioning the range of alternatives. The single best example of this is Alzheimer’s, where the bulk of research funding and testing over the past 20 years has relied upon an amyloid hypothesis that, even now, has yet to prove itself to be valid.

**A Crisis of Faith**

Because the brain is often described as the most complex structure in the known universe, neuroscience is fundamentally more challenging and less advanced than other areas of medicine. One key problem has been—and continues to be—that the tools with which neuroscience R&D is carried out have been inadequate to the task, and generally less effective in their application than those available to other therapeutic endeavors. This has yielded an inevitable string of failures.

In the world of animal models, the theoretical underpinnings have mostly been dubious, and the issues numerous. The system used for classifying disorders is based on categories that date back a century or more. What’s more, the pathophysiological roots of most disorders are unknown; targets for intervention have been generally based on theories derived from animal models of ambiguous relevance, and are located behind the blood-brain-barrier, making it difficult to get drug candidates where they were needed. It has been for the most part impossible to be sure if target engagement has been achieved. And the endpoints by which clinical status and progress are measured in human testing still tend to be ambiguous and subjective, particularly in psychiatry.

From a pragmatist’s point-of-view, the question might better boil down to: Why would anyone invest in this area? The customary and admittedly true answer generally involves “unmet medical need,” but the existence of such needs, great as they may be, does not in itself form a bridge to the treatments being developed for them. To a large extent, we have been flying blind, without much in the way of instrument-assistance. The definition of success has been binary, determined by
whether the flight landed, or ended in a crash. The wreckage of many highly-touted programs litters the runways of the biopharma industry, and has come to dominate the perception of the neurotherapeutics area in the eyes of many (albeit not all) investors and pharma companies as being too risky.

Confidence in biopharma’s neuro-skillset was gradually ground down to a nub via a drawn-out series of high-profile failures, which led investors to question whether neuroscience had any idea what it was doing. The full list of failures is too long and disheartening to review in detail, but clinical landmarks that played an important role in squandering industry credibility include:

- Myotrophin and ALS (1997)
- Substance P and depression (1999)
- Free radicals and stroke (2006)
- Bapineuzumab and Alzheimer’s (2012)
- Pomaglumetad Methionil and Schizophrenia (2013)

The net effect of these failures over a period of 15 years was to flag neurology and psychiatry as 'too hard,' leading to the nearly complete departure of GlaxoSmithKline from neuroscience, and significant contractions of neuroscience programming at Sanofi, Merck, Lilly, and others.

**No Exit: The Existential Angst of the Venture Capitalist**

Even as the success rate of neuroscience R&D plummeted, the First World was approaching a macro-economic near-death experience. The fiscal crisis of 2008-2010 led to a dramatic retraction of capital investment, and investors became highly skittish when it came to investment risk. This made it extremely difficult for privately held biotech companies to go public, and threw a major obstacle into the cycle by which capital enters and exits the biopharma system.

While travelers tend to ignore the safety feature demonstrations provided by a flight attendant before each take-off, assuming that exits available for emergencies will not be needed, such is not the case for venture capital and institutional investors, for whom the location and timing of an exit are core components of their investment model. In biopharma, such exits take the form of IPOs, wherein public money comes into a company, replacing much of the private investment that
sustained the company to that point, and provides continued liquidity via stock sales. The simultaneous withdrawal of Big Pharma as a potential acquirer, along with this closing of the IPO “window,” meant one thing above all for anyone contemplating investment in the neurotherapeutics area: Once invested in a small company, there was no near-term exit at hand.

Even worse, with no promise of new investors, the initial investors were increasingly confronted by the choice of either doubling down on a high-risk venture, or letting it wither and die. Venture capitalists, who operate in pre-defined life-cycles, typically less than ten years, could not credibly assure investors that they would be able to retrieve their investment, hopefully with profits attached, in that promised timeframe. This, in turn, reduced the inflow of resources to these venture capitalists, impairing their ability to sustain old investments, let alone make new ones, and thus produced a vicious cycle of the first order.

To illustrate, consider the casualty rate amongst 81 private cognitive neuroscience companies that NI Research tracked, beginning in 2003: Of those companies, only 19.7 percent provided an exit for their investors (12.3 percent via acquisition, 7.4 percent via IPO), and 61 percent went out of business entirely, representing a complete loss for their investors. The remaining 19 percent have continued in private operation, many of them barely alive, a herd of neurotech zombies. They are far more likely to end up in the failure than the success column.
This chart illustrates the correlation between the availability of IPO exits and the availability of investment for new and young CNS companies, which represents the 'entrance' of money into the small company CNS arena. Over the ten years from 2004 through 2013, there were a total of just 21 IPOs by private CNS companies. In fact, there were none at all in 2008-2009. But in 2014-15, there were 23 CNS companies that completed IPOs. As the number and total raised by these IPOs began to accelerate, there was an even more dramatic flow of investment into the CNS sector, far exceeding the amount that exited. Reinforcing this transformation was the less dramatic, but still vitally important return of some large and midsize pharma companies to neuroscience, while partnering external research. Indeed, many large companies have essentially outsourced much of their neuroscience research to smaller companies.

**Resourcing Neurotherapeutics 2004-15**

This chart shows the past decade’s transformation of resources overall for the small CNS company world, from both investors and pharma partners. The spectacular escalation of resource availability, particularly from investors, began towards the end of 2013, and accelerated over the next two years. What accounted for this turnaround? To some degree it was due to the economic recovery overall, particularly in the US, yielding capital that was looking “for a home.” In spite of the legacy of failure and frustration, there were factors that began to make the neurotherapeutics area palatable, even desirable, to investors.
There is the belief, perhaps more akin to faith, that the genomics advances that allowed the development of precision medicines in oncology may yet prove useful in neuroscience, the greatest untapped market of all. Beyond these nascent genomics advances were the maturation of neuroimaging (e.g. amyloid plaque, tau), CSF biomarkers, changes in nomenclature (the National Institute of Mental Health research domain criteria [RDoC] initiative), and technologies allowing the tracking of trial and treatment compliance. In aggregate, these constitute the harbinger of an era in neuroscience wherein guesswork is being replaced with something more substantive.

We are better equipped to track target engagement—at least for some targets—and RRMS is now seen as the leading edge, rather than the sole outlier. Induced pluripotent stem cell (iPSc) models, modified via gene editing, offer a more face-valid screen for early drug development than the animal models upon which the sector has too long relied. Remote biosensors and big data analytics offer the prospect of being able to sift huge datasets for meaningful relationships, defining pathways where new and more impactful targets may exist, and the concept of brain and brain pathology as based on networks of circuits can be reified and tested via techniques like optogenetics. Parsing this list, in a highly oversimplified fashion, it can be argued that there were three events or dynamics that set the stage for this transformation: Personalized oncology, Hepatitis C treatment, and neuroimaging.

- **Personalized Oncology:** The human genome was sequenced in 2000, but it has taken a long time for the genomics revolution to make a tangible difference in the practice of medicine. We would argue that it is in the area of personalized medicine in the treatment of cancer that the highest profile gain from genomics has been realized: Rather than relying upon trial-and-error (and tradition) in offering patients various cocktails of chemotherapeutics, oncology began to parse cancer into subcategories based on genetic factors. This altered the climate of frustration and delay that had grown around genomics, and raised the question: where else might this work? When it comes to large-scale, heterogeneous populations of uncertain etiology, nothing exceeds the scale offered by the worlds of neurology and psychiatry, and the belief system within the investment world has begun to shift towards the anticipation that genomics will render these disorders more comprehensible and tractable.
• Hepatitis C: A disease that formerly could only be treated palliatively turned into a disease for which “magic bullets” can provide a cure. The fact that these treatments can be premium-priced and yet make pharmacoeconomic sense has also hit home for the investment community. In an era where treatment pricing had turned into a war of attrition between payors, generic manufacturers, and pharma companies, and like personalized treatments for cancer, this portended a time where a successful new product could be once again expected to produce outsized profits. No area had been hit harder by the advent of generics than neuroscience as a whole, psychiatry in particular, and this provided a road map for returning some pricing control to the neuropharm world.

• Neuroimaging: As was mentioned earlier, it was the success of disease-modifiers in the treatment of Relapsing-Remitting Multiple Sclerosis that for a very long time was the only example of substantive, rather than incremental, progress in the treatments of CNS disorders. What made RRMS different? One critical element was the availability of imaging technology that could provide an objective, empirical measurement of therapeutic impact on the rate at which the disease progressed. As gadolinium-enhanced imaging was for MS, the advent of florbetapir as a means of empirically quantifying amyloid plaque in Alzheimer’s has served as a beacon of hope that biomarkers would begin to take neurotherapeutics out of its familiar morass of “squishy,” subjective endpoints. The fact that amyloid plaque’s utility as a biomarker has yet to be fully established has been less important than its role as the poster child for a new era of objective measures in neuroscience. Other imaging markers (e.g., tau) and a plethora of blood and CSF biomarkers have emerged, albeit yet-to-be-proven in their ability to focus and accelerate CNS drug development.

Other Factors Carrying Weight
While the process of testing candidate drugs in clinical trials remains a high-risk, high-anxiety endeavor for neuroscience, new tools offer greater assurance that participants in drug trials are real patients, not ‘professional patients,’ and are actually taking the medications as they are supposed to. Patients, who are not ill, or who do not take the medication being evaluated, simply
are not a valid template for testing the efficacy of such a drug. We will never know how many clinical trials have been ruined by noncompliant patients; one must wonder how many potentially useful drugs had the signal of their therapeutic impact obscured by a flawed clinical testing process. Clinical trial professionals have come to realize, sometimes at odds with the companies sponsoring the trials, that in this context, “speed kills.” Companies have started to cooperate in flagging 'fake' patients; and are beginning to explore technologies (like a chip on a pill) that allow accurate monitoring of what a patient takes, and when.

And in an environment where generic drugs have become king, the pharma industry and its investors have finally come to recognize that redundancy no longer is remunerative, and that they will have to grapple with the risk, along with the potential reward of novel mechanisms for intervention. As confidence in the tools has grown, so too has the willingness of both pharma partners and investors to bet on higher-innovation, higher-risk programs, because making significant inroads on the huge, unmet needs of neurology and psychiatry will require new and 'disruptive' technologies.

Neurotherapeutics is, of course, not a unitary construct, and it is informative to consider where resources are flowing more specifically. The breakdown over the past decade, parsing the area into four categories (Neurodegenerative disease-modifiers, Neurology-symptomatics, Psychiatry, Pain) yields the following in terms of funding therapeutic subareas from 2009 to 2015:
Playing Favorites: Where the Therapeutic Areas Rank

After several years where no neuroscience area was favored in terms of funding, there was a dramatic surge in 2014, with the most spectacular rise in funding for symptomatic treatments for neurological disorders, including levodopa-induced dyskinesia, and cognition or psychosis associated with neurodegeneration. This is a relatively lower risk area compared to programs aimed at slowing or stopping the course of a neurodegenerative disease, which received the least funding of the four in 2014. But in 2015, while there was continued, slowly growing interest in symptomatic treatments, investors finally became willing to fund disease-modifiers, reflecting the belief that improvements in neuroscience tools would mean that these high-risk programs stood a better chance of success.

It should be noted that the willingness to put venture capital into higher-risk programs has been anything but across-the-board, but there are some VCs who have the long-term perspective and neuroscience background that allows them to be more risk-tolerant. Thus, in 2014-15, the roster of VCs leading investment rounds in highly innovative research included Fidelity Biosciences (Denali Therapeutics, Yumanity Therapeutics, Forum Pharmaceuticals); Third Rock (Voyager Therapeutics); Atlas Ventures (Lysosomal Therapeutics and Rodin Therapeutics) and Clarus Ventures (Annexon). The fact that the Denali Series A round of $217 million was by far the largest such round ever completed by a CNS company provided a signal to more reticent VCs that 'smart money' is starting to find its way into neurodegeneration research—and that they should consider participating, even if not leading. Another important development has been heightened activity from pharma companies investing through venture arms, giving them the benefit of the investment itself and insight into ongoing research activities, without having to buy in completely.

In the other therapeutic subdomains, Pain enjoyed steadily increasing investment, partly due to the growing visibility of opioid abuse, enhancing the potential prospects for novel analgesia alternatives. Finally, Psychiatry, long out of favor, rebounded somewhat in 2014, the most apparent trigger being the rising profile of the rapid-acting-antidepressant class, epitomized by ketamine, which for the first time in 20 years seemed to offer the potential of a genuinely differentiated new antidepressant option. But the investment in Psychiatry plateaued in 2015, its flat growth leaving it well behind the other three areas in garnering investment dollars.
No Place for Vertigo: The Oscillations Continue

Overall, the past decade or two have constituted a humbling process to which the neurotherapeutics sector has had to submit, where scientists have had to accept the limitations of their knowledge base and research tools, finally going back to the drawing board. This has led to the growing salience of genomics, biomarker analyses, brain imaging, and sophisticated behavioral assessment technologies, providing an entirely revised approach to drug target delineation and validation. To be clear, the confluence of these technologies has yet to come to fruition. Outside of MS, no new drugs have been identified, refined, and proven via the new generation of techniques.

But there is a renewed emphasis upon empirical, scientific inquiry and validation, which has given the investment community hope that the brain will not continue to be a black box whose workings—and our impact upon them—can only be guessed at. Beyond imaging and biomarkers, there is an array of new tools that portend an era of greater productivity for neurotherapeutics, which inspired—at least through the end of 2015—a resurgence of optimism and an influx of resources. Whether that will continue will depend on macro-economic forces completely beyond the control and influence of the biopharma industry, and the degree to which clinical successes begin to provide tangible proof that this is in fact a new era for neuroscience.

Bio

**Harry M. Tracy**, Ph.D., is the founder and president of NI Research in Cardiff, CA. NIR’s bimonthly publication, *NeuroPerspective*, is utilized by pharmaceutical companies and venture capital professionals. NIR has also published *NeuroLicensing* and the *Private CNS Company Review*. NIR provides consulting services to pharmaceutical companies and to venture capital/private equity groups. Tracy also practiced for thirty years as a clinician and consultant in a variety of psychiatric and neurological settings. He received his Ph.D. from the University of Miami, and completed his clinical training at Massachusetts General Hospital/Harvard Medical School. He has been a research associate in the Department of Neurology at the University of California, Davis.