Perspective

Twenty-Five Years of Progress: The View from NIMH and NINDS

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http://dx.doi.org/10.1016/j.neuron.2013.09.041

As directors of two NIH institutes supporting neuroscience research, we explore the gap between 25 years of stunning progress in fundamental neuroscience and the persistent needs of those with brain disorders. We conclude that closing this gap will require a more detailed comprehension of brain function, a rethinking of how we approach translational science, a focus on human neurobiology, and a continuing commitment to build a diverse, innovative neuroscience workforce. In contrast to many other areas of medicine, we lack basic knowledge about our organ of interest. The next phase of progress on brain disorders will require a significantly deeper understanding of fundamental neurobiology.

In March 1988, the editors Zach Hall, A.J. Hudspeth, Eric Kandel, and Louis Reichardt launched the first issue of *Neuron*, "based on the belief that cellular and molecular neurobiology has begun a period of explosive growth, fueled by the powerful experimental tools that have recently become available" (Hall et al., 1988). What were the new tools of 1988? They cite recombinant DNA methods, new electrophysiological recording techniques (e.g., patch clamping), novel methods of introducing macromolecules into cells (e.g., viral transfection), and new approaches to cellular imaging (e.g., confocal imaging). Along with their enthusiasm for recent technical advances for molecular and cellular neurobiology, they commit the journal to the latest technology for rapid publication: "To minimize the time delays caused by distance, we shall use express mail and facsimile transmission for manuscripts from abroad."

In the 25 years since, the information revolution has obviously transformed the speed of communication and publishing: manuscripts move via email, and publications can appear a month or more before the journal is printed. But the changes in cellular and molecular neurobiology are as profound. At each level, from molecular, to cellular, to systems neuroscience, technical breakthroughs have led to conceptual progress. We are, in 2013, no less than in 1988, in a "period of explosive growth." Others in this special issue of *Neuron* have captured the many facets of this growth. Below we highlight a few of these areas, recognizing that this brief survey cannot do justice to either the technical or the conceptual advances of the past 25 years. Our charge is to relate these changes to the state of brain disorders in 2013, identifying the best bridges for translational research. We conclude that progress on brain disorders will require a significantly deeper understanding of fundamental neurobiology.

What Has Happened since 1988?
Molecular Neuroscience
The genomic revolution has not only revealed the genomic sequences of over 150 eukaryotic species but also spawned new, inexpensive technologies that have moved high-throughput sequencing from a few centers to hundreds of benchtops. One unforeseen consequence of the genomic revolution and its high-throughput methods has been the generation of a whole family of "omics," where "omics" denotes comprehensive, unbiased approaches or disciplines that begin with the word "all." We now have epigenomics identifying "all the epigenetic marks," transcriptomics identifying "all the transcripts," proteomics identifying "all the proteins," and metabolomics identifying "all the metabolites," to name just a few. While we have been concerned about the potential dominance of "big science" over the past two decades, we are now seeing that many of the tools and resources developed by large, centralized efforts like the Human Genome Project have effectively enabled innovative, investigator-initiated research. For instance, the millionfold drop in the cost of sequencing over the past decade has allowed hundreds of labs to do molecular biology on a scale once reserved for a few well-funded centers.

As a result of these new tools and comprehensive approaches, we are now in an extraordinary era of discovery science. The few hundred genes, proteins, and metabolites that appeared relevant in 1988 have been expanded with the recognition that over 80% of our approximately 20,000 genes are expressed in the human brain (Hawrylycz et al., 2012) and that many of these are expressed as unique isoforms in the brain, often in developmentally and spatially restricted patterns (Colantuoni et al., 2011; http://www.BrainSpan.org). Until recently, our focus in the genome has been on the 1.5% of the sequence that codes for protein. With the recent recognition that over 80% of the genome is transcribed, we are beginning to appreciate how the genome codes for many different species of RNA and other elements that are essential for the regulation of gene expression (Bernstein et al., 2012; Yates et al., 2013; Batista and Chang, 2013). In addition, we are discovering epigenetic processes for the regulation of gene regulation that appear to be unique to the brain (Lister et al., 2013), providing a potential mechanism for environmental influences on molecular, cellular, and systems-level processes.

Coupled with the revolution of discovery science, progress over the past two decades has been accelerated by tools to manipulate the genome. In addition to describing a vast new universe of genes and molecules, we have the tools to test specific mechanisms. Over 1,200 transgenic mutant mouse lines have been produced and phenotyped. The advent of conditional knockouts and specific recombinases has made it possible to create mice to test the role of genes in specific cells and at specific developmental times. New, precise tools for manipulating genomic sequence and gene expression, such as TALENS, CRISPR, and LITE (Gaj et al., 2013; Konermann et al., 2013), are yielding even more powerful experimental techniques to link genes to function.

Cellular Neuroscience

A parallel revolution in cell biology has been equally transformative. In 1988, our picture of cellular neuroanatomy and function was much simpler than it is today. The development of various fluorophores, yielding elegant anatomical maps like Brainbow, and two-photon imaging, yielding in vivo pictures of spine formation, has given us a far more detailed understanding of the variety of cells in the brain and their complexity. CLARITY has provided a novel technique for three-dimensional neuroanatomy (Chung et al., 2013). While we still lack a comprehensive taxonomy of brain cell types (Wichterle et al., 2013), we have a better understanding of how cells develop, migrate, and communicate. Improved lineage tracking (clonal analysis) techniques have helped elucidate how neural stem cells give rise to daughter neurons, astrocytes, and oligodendrocytes, and uncovered an unexpected glia-like property of neural stem cells. Tools to report and manipulate the function of genes in specific cell types have revealed the complex interaction of guidance cues among neurons and the vital role of glia in synaptic maturation, elimination, and plasticity. We now realize that neurogenesis continues in selected populations (even in human brain) and that adult-born neurons contribute to cognitive function (Denny et al., 2012; Sahay et al., 2011).

The emergence of new cell reprogramming techniques yielding induced pluripotent stem (iPS) cells in vitro from adult fibroblasts would have been dismissed as science fiction in 1988. This technique allows human cellular and developmental processes to be modeled (Zhu and Huangfu, 2013); it has already begun to provide a new window into the role of common and rare mutations associated with neuropsychiatric disorders (Krey et al., 2013) and a new platform for screening potential therapies. Additionally, it is providing a source of patient-matched neurons that may be useful for cell therapies for neurodegenerative disorders such as Parkinson's disease.

Much of the cellular neurobiology of 1988 was focused on membrane currents, ion channels, or receptors. We now have the molecular structures of an increasing number of these membrane components, elucidating the biophysical machines responsible for neuronal activity. At the same time, emerging technologies now allow molecular analysis of single cells within a population, uncovering subtle differences that may explain phenotypic cell diversity. Such resolution will be critical in correlating molecular changes with other functional parameters among many neurons in a network.

Systems Neuroscience

Arguably the greatest progress has been in the study of brain circuits, from *C. elegans*, where the entire nervous system can be monitored, to humans, where fMRI and structural imaging have given us new insights into brain organization and function. Much of the physiology of the last 25 years has shifted from a focus on the single channel or single cell to ensembles or circuits, in search of patterns of activity that link to behavior. Recording has been expanded to ensembles of neurons, and calcium-imaging dyes or voltage-sensitive dyes are now used to monitor the activity of hundreds of neurons over time to begin to map how and where information is processed. Most recently, the capture of simultaneous, real-time activity of over 80% of the neurons in the larval zebrafish brain with lightsheet microscopy suggests patterns of large-scale activity that had not been foreseen by recording individual or even small groups of neurons (Ahrens et al., 2013).

The macroconnectome now being developed promises to provide a reference atlas of the wiring diagram of the human brain, much as the genome project provided a reference atlas of DNA sequence (http://www.humanconnectome.org). Beyond better descriptions of connections and circuitry, tools like optogenetics (Tye and Deisseroth, 2012) and DREADDs (Nawaratne et al., 2008) have provided neuroscientists with the ability to manipulate sets of cells in circuits to test specific causal questions about circuit and network anatomy, connectivity, and function. Who could have imagined in 1988 the broad use of tools, based on advances in molecular and cellular neuroscience, for precise control over circuits in awake, behaving animals?

As a result, we can now begin to understand ongoing activity patterns that are overlaid on anatomical structure and to study how experience alters circuit function. For some invertebrate circuits, the entire network has been specified and elegantly modeled (Bargmann and Marder, 2013). These studies make clear that although form and function are related, knowing the microanatomy of connections is not sufficient to understand the function of a simple circuit. We are just beginning to understand the principles of brain organization that are essential for information encoding, storage, manipulation, and retrieval. Indeed, understanding the stages and processes of manipulation of information within neural networks will be the next major challenge for neuroscience.

What Has Not Happened since 1988?

The extraordinary progress in neuroscience over the past two decades may, in retrospect, look like the unprecedented two-decade period in physics just a century ago. New tools and new concepts have transformed the way we think about the brain and its constituent parts, a transformation that has been chronicled faithfully in *Neuron*, monthly beginning in 1988 and bimonthly beginning in 2001, as the journal, responding to the evolution of the field, expanded its scope beyond the original mandate of molecular and cellular neuroscience. What about progress in clinical research and clinical care? Has the transformation in basic neuroscience meant transformed outcomes for people with brain disorders?

Burden of Disease

The inconvenient truth in 2013 is that neuropsychiatric disorders represent the leading source of disease burden in the developed

world for people between ages 15 and 49 (Lopez et al., 2006). Over the past 25 years, success against acute infectious diseases and infant mortality has left chronic, noncommunicable diseases as the largest source of disability. In contrast to heart disease or most forms of cancer, many neuropsychiatric disorders (e.g., autism, epilepsy, schizophrenia, intellectual disability) begin early in life and contribute to lifelong disability or reduced longevity. Indeed, these disorders are now the chronic diseases of the young and globally have become the largest source of years lived with disability (Whiteford et al., 2013). At the same time, neurodegenerative disorders have increasingly become the signature disabilities of an aging population. Changing demographics ensure that brain disorders will be a greater public health challenge in the coming decades.

The public health challenge is mortality as well as morbidity. Many brain disorders are fatal. Stroke is the fourth leading cause of death in the United States and second globally. Death occurs within 5 years of a diagnosis of amyotrophic lateral sclerosis (ALS), 10 years after symptoms of Alzheimer's disease, and twenty after symptoms of Huntington's disease. The risk of sudden unexplained death in epilepsy is 24 times greater than that in the general population (Neligan et al., 2011). For serious mental illnesses, like schizophrenia and bipolar disorder, suicide is common. Indeed, most suicides involve a mental disorder, and there are now over 38,000 suicides in the United States, more than twice the number of homicides and more than the number of motor vehicle fatalities (CDC, 2013). It has been reported that, in the United States, people with serious mental illness die at least 8 years earlier than those without these illnesses (Druss and Walker, 2011). Suicide accounts for only a small fraction of this early mortality, most of which results from chronic medical conditions that are poorly treated in this population.

Perhaps it should not be surprising, given the high morbidity and mortality, that the cost of neuropsychiatric disorders trumps other chronic, noncommunicable disorders. In a World Economic Forum study of projected costs, neuropsychiatric disorders were estimated to be the most costly, accounting for more than cancer, diabetes, and chronic respiratory diseases combined (Bloom et al., 2011). For Alzheimer's disease alone, costs of care in the United States in 2010 have been estimated as between $157 billion and $225 billion (Hurd et al., 2013), with projections of costs surpassing $1 trillion in 2050.

These sobering statistics about brain disorders stand in stark contrast to the progress in neurobiology. Why the gap? Why has 25 years of "explosive growth" in neurobiology failed to reduce the morbidity or mortality of virtually all brain disorders? One explanation is that our basic science is misguided, not relevant to clinical problems. Another explanation, which we favor, is that we do not know enough yet to translate basic neurobiology into the new diagnostics and therapeutics that will transform public health outcomes. Let's look at both of these possibilities.

Relevance of Basic Science to Clinical Care
Although clinical progress is usually measured in breakthrough therapies, progress in improving diagnostics, elucidating disease pathogenesis, and generating biomarkers can be as important and may be a prerequisite for better treatments. Since 1988, there has been considerable scientific progress on brain disorders.

In the past 25 years, genetic mutations underlying a myriad of inherited neurologic disorders have been identified. These discoveries now enable rapid and accurate diagnosis, reducing or even eliminating the diagnostic odyssey, and in some cases even allow for presymptomatic diagnosis. Whole-exome sequencing of families with affected individuals promises to uncover genetic causes of scores of diseases and already has identified de novo mutations for a number of the childhood epilepsies (Allen et al., 2013). For neurodegenerative disorders, rare disease-causing mutations in common conditions such as Alzheimer's disease (*APP*, *presenilin*) and Parkinson's disease (*synuclein*, *Parkin*, *Pink1*, *LRRK2*) and rare diseases like ALS (*superoxide dismutase*, *C9orf72*) are shedding light on causative molecular pathways (Bertram and Tanzi, 2005). These pathways in turn may lead to "druggable targets" for potential disease-modifying therapy. In the near term, projects like the Alzheimer's Disease Neuroimaging Initiative are yielding biomarkers to track disease progression in patients. For Alzheimer's disease, it is possible to image sentinel molecules, like tau- and β-amyloid, and to measure them in cerebrospinal fluid, as well as track hippocampal atrophy (Toledo et al., 2013). Similar efforts are underway in Parkinson's disease. The impact of these kinds of biomarkers can be seen in multiple sclerosis, where the prevention of gadolinium-enhancing MRI lesions has accelerated the development of treatments (Bermel et al., 2013).

While we still lack biomarkers for mental disorders, the tools of basic science are now beginning to change how we approach diagnosis. The discovery of shared genetics, often implicating genes critical for brain development, has supported a new formulation of mental disorders as neurodevelopmental disorders (Smoller et al., 2013). With functional MR and PET imaging, specific circuits have been implicated in depression, obsessive-compulsive disorder, and posttraumatic stress disorder (Insel, 2010). A new approach to classification of psychiatric disorders, called the Research Domain Criteria (RDoC) project, is based on cognitive domains and circuitry (Cuthbert and Insel, 2013). RDoC attempts to transform diagnosis by building on the findings of neuroscience and cognitive science, rather than relying solely on presenting symptoms, as done for the past century. This approach presumes that what we now call "depression" or "schizophrenia" are, in fact, many different disorders with distinct underlying biological causes that require different treatments. While this approach is not ready for clinical use, it demonstrates the extent to which mental disorders are now addressed as brain disorders, or, more specifically, as brain circuit disorders.

Across brain disorders, whether primarily neurologic or psychiatric, there is an increasing recognition that behavioral symptoms are late manifestations of disease. This insight for Alzheimer's, Parkinson's, schizophrenia, and autism represents a fundamental shift in emphasis, similar to the shift in the treatment of atherosclerosis and hypertension before they cause ischemic heart disease or stroke. This preemptive approach focuses on early detection of brain changes and the development of early interventions that can prevent or forestall neurodegenerative or neurodevelopmental disorders.

Therapeutics
What about new treatments? Basic science has yielded several new molecular targets that have become the basis of new

therapies. For neurological disorders, the past two decades have brought breakthroughs in the treatment of migraine (triptans; Lipton, 2011), multiple sclerosis (beta interferon, copolymer, fingolimide, and difumarate; Stankiewicz et al., 2013), acute stroke (tissue plasminogen activator), and a number of new agents for epilepsy, including rapamycin for epilepsy in tuberous sclerosis (Krueger et al., 2013). For mental disorders, we have seen the development of second-generation antipsychotics and antidepressants, with different side effect profiles but little improvement in efficacy over the medications of 1988. There have been few novel targets in this space, in part because of the limited understanding of the pathophysiology of neurodevelopmental disorders, relative to the progress on neurodegenerative diseases (Hyman, 2012). One hopeful discovery is the relatively recent insight that antidepressant effects can be achieved within hours rather than weeks (Martinowich et al., 2013). The observation that ketamine resolves even treatment-refractory depression in less than 24 hr has changed our expectations for the development of new antidepressants.

Basic science has also yielded insights about circuitry that have been translated into new, effective therapies. Modulation of circuits through deep brain stimulation (DBS) has proven to be effective for movement disorders including Parkinson's disease, essential tremor, and dystonia (Miocinovic et al., 2013). Development of DBS surgery for Parkinson's disease resulted from decades of basic science studies of basal ganglia circuitry in nonhuman primates (DeLong and Wichmann, 2007). More recently, DBS in the subcallosal cingulate region, identified as metabolically hyperactive in patients with severe drug-resistant depression, showed dramatic antidepressant effects (Holtzheimer et al., 2012). Epilepsy, a classic neural circuit disorder, is treated continuously with levels of drugs that have a wide range of unwanted CNS side effects. Yet the epileptic discharges are paroxysmal, and seizures occur intermittently in most patients. An accurate detection of preseizure neural activity might lead to more beneficial delivery of drug therapy or even direct brain stimulation to abort seizures with greater efficacy and less adverse side effects (Stacey and Litt, 2008).

In 1988, treatments in psychiatry were largely divided between psychotherapy and pharmacotherapy. While it would be naive to suggest that this division no longer exists, cognitive neuroscience in the past decade has begun to put psychotherapy into the context of neural plasticity, with studies of how the brain changes during psychotherapy and the development of cognitive therapies based specifically on feedback from fMRI signals (Linden et al., 2012).

In sum, our basic science has not been misdirected—it is unfinished. In 2013, basic science insights have begun to inform diagnostics and therapeutics, but we are still at the very beginning of an unpredictable journey. We simply do not know enough yet to solve the very complex problems of brain disorders. In contrast to cardiology, nephrology, and pulmonary medicine, we know comparatively little about the organ involved in neuropsychiatric disease. To ensure that the next 25 years closes this gap between basic science and clinical need, we must overcome four critical barriers. In the remainder of this essay we explain each of these.

What Do We Need in 2013?
Basic Science
Our biggest barrier is simply that we need a deeper understanding of how the brain works if we are to understand brain disorders. We still do not have the fundamentals. How do different cell types develop? What roles do glial and immune cells play in development, homeostasis, and neurodegeneration? How do cells form circuits? How do circuits encode information? How does the brain support mental life? For some disorders (e.g., ALS and epilepsy), single-cell biology may bring the critical insights. For others (e.g., schizophrenia and autism), understanding the development of circuits will likely be essential. Neurodevelopmental disorders may pose even greater challenges than neurodegenerative disorders, especially when the critical changes are prenatal. While we are acutely aware of the urgency of translation, we believe that the translational bridge must be built on a solid footing in fundamental neuroscience.

This deeper understanding requires better tools. The theoretical physicist Freeman Dyson famously noted that "new directions in science are launched by new tools much more often than by new concepts" (Dyson, 1997). We agree. The BRAIN Initiative is a new commitment to create the tools for understanding the "language of the brain." We are just at the beginning of this initiative, but if recent progress in molecular and cellular technology is a prologue, we can expect rapid progress. Specifically, we will need tools for more precise monitoring and manipulation of brain function over time in awake, behaving animals.

Rethinking Translation
The recent history of progress in other areas of medicine reminds us that transformative clinical applications can arise from basic science that is not targeting a specific disease or clinical need. This will be equally true in neuroscience, as demonstrated by studies of synaptic plasticity that have unexpectedly led to a new therapeutic approach to fragile X syndrome (Michalon et al., 2012). Indeed, given the fundamental role of nervous system plasticity across domains of function and the lifespan, it is clearly a key focus for unraveling the causes of neuropsychiatric disorders and developing targeted and effective pre-emptive interventions, well beyond the example of fragile X. We have made great strides in understanding how plasticity is regulated by biophysical and epigenetic mechanisms within cell compartments, across cell types, and across circuits, but there are significant gaps that prevent the application of basic neuroscience insights to clinical application.

As NIH institute directors, we have a growing concern about the tendency for every basic science grant application to mention a disease or to defend its translational impact. These "translational blurbs," which seem increasingly to be essential for some reviewers to assign a fundable score, are rarely substantive, may be misleading, and fail to recognize the large gap that remains between the state of our basic understanding and what is required for clinical application.

Simply put, this gap requires more fundamental neurobiology. This gap will not be bridged by superficial associations between basic science and human disease or by assuming that transgenic mice are phenocopies of human disease. It has become abundantly clear that so-called "disease models" fall short when it comes to developing treatments and cures for human

disorders. But the problems with "animal models" do not invalidate the use of "model animals" (Insel, 2007). The value of using model systems is that we can learn about fundamental principles of brain organization. While most scientists think of translation as moving from bench to bedside or mouse to man, the future may belong more to reverse translation, moving from an observation in humans to experiments in a nonhuman species that can provide insights into fundamental mechanisms that are similar to or informatively different from humans. Studying the nervous system in model animals not only gives us insight into basic mechanisms but also helps us understand what makes us uniquely human.

Human Neurobiology

In considering what we need in 2013, one area that deserves special mention is human neurobiology. Human neurophysiology has begun to inform neuroprosthetics (Chadwick et al., 2011) and new interventions for epilepsy (Smart et al., 2012). Invasive techniques such as DBS and noninvasive techniques, such as regional transcranial magnetic stimulation (rTMS), are being used to explore brain activity as well as for treating brain disorders (Demirtas-Tatlidede et al., 2013). Tools for imaging hemodynamic or metabolic signals in the human brain during tasks or at rest have given us a rich literature, extending from anatomy to economics. But we need to be mindful of the limitations of these tools. The fastest hemodynamic signals occur over seconds, at least two orders of magnitude slower than the speed of information processing in the brain. Imaging with the highest spatial resolution, currently a voxel of about 1 cubic mm isotropic, has been estimated to contain 80,000 neurons and 4.5 million synapses. Moreover, these techniques are cross-sectional, yielding a picture of blood flow or metabolism at a point in time. Relative to the tools we have for experimental animals, including not only longitudinal in vivo cellular resolution imaging but also manipulations such as optogenetics, our toolkit for human neurobiology remains primitive. This is especially unfortunate because so many of the important questions linking brain and mind involve functions that may be unique to humans.

Human Capital

One of the most important needs is not a tool or a technique but a workforce. As directors of two of the major neuroscience institutes at NIH, we think a lot about the workforce. Although our budgets have increased more than 3-fold since 1988, funding has been cyclical and, recently, mostly flat or decreasing. Indeed, over the past decade we have watched our purchasing power decline by over 20% (Wadman, 2012). The tightening of the NIH budget, sometimes called the "undoubling," has led to falling paylines and intense competition for research support. It has also raised important questions about training. How can we balance the workforce pipeline and the research payline? Who should be in the pipeline? What skills will future neuroscientists need? We have two general answers to these questions.

First, we will continue to need outstanding new and established investigators who want to explore the vast areas of molecular, cellular, and systems neuroscience that, despite having been revealed by the "omics," remain largely frontier territory. Even in tight funding times, indeed especially in tight funding times, we are committed to supporting curious, rigorous investigators who are not following the crowd. Scientists with backgrounds in engineering, computation, nanotechnology, and a range of other disciplines may be especially suited to colonizing the many frontiers of neuroscience in this next decade.

A second workforce issue for both NINDS and NIMH is the clinical or translational workforce. We have long marveled how neurology and psychiatry are two disciplines separated by a common organ. Recent discoveries from genomics and imaging as well as the apparent "comorbidities" across brain disorders (e.g., depression in Parkinson's and epilepsy in autism) remind us that the separation of neurology and psychiatry is based more on history than biology. Once a single discipline before psychoanalysis split neurology and psychiatry, the modern view of both neurological and mental disorders as brain disorders dictates a remarriage, rebranded as "clinical neuroscience" (Insel and Quirion, 2005). Joint training would be a good place to begin, with all clinical neuroscientists exposed to modern neuroscience as the core of their training.

Final Thoughts

The past 25 years have seen spectacular progress, but much of this has yet to change the lives of millions struggling with CNS disorders, from autism to Alzheimer's disease. The urgency of this need dictates we do better. Many have argued that "better" means "faster" translation—the need to move more quickly from the bench to the bedside. We agree that time matters and the needs are urgent. Unfortunately, for most clinical problems, we still do not have the fundamental knowledge to translate. Moving from genomics to biology, from cells to circuits, from mice to people, has proven more far more challenging than expected. We need a deeper understanding of the basic biology of how the brain works in both health and disease. This understanding will require better tools, more basic science, more human neurobiology, and a continued commitment to a diverse workforce funded for innovation.

As with many areas of science, neuroscience in the United States in 2013 faces a precarious future. Today, while the opportunities for progress have never been more obvious, the certainty of funding to support rapid progress is not. The President's BRAIN Initiative, scheduled for 2014, includes a commitment for new funding for neuroscience, especially for new tool development. If this funding is appropriated by Congress, we are hopeful that what the President has called "the next great American project" will launch a new investment in neuroscience. But it is important to put this in context. Biomedical research in the United States has traditionally been supported heavily by industry. Indeed, the research and development investment from pharmaceutical and biotech companies of roughly $50 billion easily surpasses the NIH budget of roughly $30 billion. In 2013, neuroscience in the United States faces double jeopardy: in addition to the sequester-driven cuts to NIH funding, many pharmaceutical companies have reduced their commitments to research on brain disorders. Thankfully, several foundations have arisen that are committed to supporting neuroscience research directly. The Simons Foundation Autism Research Initiative, the Michael J. Fox Foundation for Parkinson's Research, and the CHDI Foundation are just a few of the organizations that are making a difference by funding relevant basic science as well as clinical research. At the Janelia Farm

Research Campus, the Howard Hughes Medical Institute has established a program to map the structure and function of neural circuits, including optimization of tools like GCaMP. Perhaps there is no more remarkable example of how the support of science has changed since 1988 than the Allen Institute for Brain Science. Who would have imagined a neuroscience research institute funded with over $500 million of private money (roughly the NIMH or NINDS budget of 1988) would provide the field with public atlases of the mouse, monkey, and human brains, as well as map the mouse visual system?

For the generation just entering our field, this must seem like scientifically the best of times and financially the worst of times. Those of us who have been in neuroscience for decades have seen tough times before. But we have never seen a period of such promise for innovation and discovery. We are committed to ensuring that the best science continues to be supported, especially the fundamental science that will ultimately lead to the breakthrough diagnostics and therapeutics so urgently needed.

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