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Limits to growth: why neuroscience needs large-scale science

Almost 20 years ago, Bruce Alberts published a commentary in *Cell* entitled, "Limits to growth: In biology, small science is good science"[1]. Noting that doing good science is different from baking bread, Alberts decried the emergence of large, science manager–driven laboratories, which he viewed as less efficient and less interesting than those comprising a single investigator with his or her post-doc and graduate student. Today, this judgment remains compelling. Although many small labs feel threatened by what they perceive as the increasingly industrialized culture of science, in neuroscience as in other areas of biology, we need innovative investigators working in small, focused labs to develop and test hypotheses about neural development, neurodegeneration and neural plasticity. But large-scale, industrial-strength science is not bad science. Our field is currently in a discovery phase, where large-scale science is critical for progress.

In what areas do we need large-scale neuroscience? As directors of neuroscience institutes at the National Institutes of Health, we have been asking this question in the context of developing a blueprint for research for the next 5 years. Clearly, there are several areas where having the neuroscience equivalent of the Human Genome Project will result in rapid progress in understanding the brain and its disorders. As with the Human Genome Project, we need the databases, infrastructure and technology that will enable a more rapid and comprehensive pursuit of the brain's physiology and pathophysiology. Here we suggest three areas of need, without any presumption that this represents a complete or final list.

First, we need to understand how, when and where genes and the proteins they encode are expressed in the mammalian brain. Of the roughly 30,000 genes in the mammalian genome, at least half are expressed in the brain[2]. Until very recently, one could safely estimate that 99% of the literature in neuroscience was restricted to less than 1% of the genome. With the advent of transcriptional profiling, BAC transgenics and *in situ* hybridization mapping of new genes and expressed sequence tags (ESTs), we are exploring more of the previously uncharted 99% of the genome[3]. But there is still much to learn about function. Developmental and neuroanatomical patterns of gene expression should provide important clues to function. Although nearly 10% of the mouse genome has been targeted by transgenesis, most of these mice are not available to the academic neuroscience community. We believe that a public repository of transgenic mice or ES cells with null mutations of each of the genes expressed in the brain could transform research on genes that are important for neural function. Ultimately, however, we want to know how gene expression is regulated in different brain regions and how environmental factors influence these patterns. Large-scale brain genomics, what Boguski and Jones call neurogenomics[4], should also inform the molecular pathophysiology of brain disorders, describing how allelic variation alters protein expression and how changes in protein expression lead to changes in cells and circuits that disrupt perception, cognition and behavior.

Second, we need to find better ways to manage information. Imaging technology is generating ever-increasing databases of information, but we have yet to organize, synthesize or harmonize these databases to maximize their utility. Ideally, we need tools that will allow consensus mapping of cellular phenotypes, physiological networks and functional maps throughout the brain in an electronic hierarchical format that can be easily accessed and modified to incorporate new information. Maps need to be inter-operative so that data from fMRI or other *in vivo* imaging experiments can be mapped onto atlases generated by cellular techniques in both humans and experimental animals. Although phenotyping continues to be one of the greatest challenges, whether one is interested in transgenic mice or human diagnosis, we have yet to design the kind of ambitious approach to the "phenome" that has proven so useful for understanding the genome[5]. This is clearly the kind of 'large-science' initiative that will require collaboration, coordination and computation from a broad neuroscience community, including clinical neuroscientists.

A third large-scale need derives from our clinical research effort. Currently clinical research on brain disorders is divided among neurological, psychiatric and addictive disorders as well as various disorders of visual or auditory function. In the past decade, clinical scientists in each domain have developed large-scale networks with thousands of patients for epidemiologic, genetic and therapeutic studies. Although these studies have addressed the challenge of large datasets, they have not yet overcome the somewhat arbitrary divisions between these domains. It is remarkable, for instance, that independent networks have been developed for patients with substance abuse and depression, even though these disorders may be co-morbid in more than 50% of patients. Similarly, the mood disorders of patients with Parkinson disorder have been overlooked as a result of our separation of psychiatry from neurology, although both are effectively disciplines within clinical neuroscience. The opportunity to study neurodegeneration in the retina along with neurodegeneration in the brain has not been fully realized. In the future, an important opportunity for large-scale research will involve the integration of these clinical programs so that brain and sensory disorders can be studied across what are now considered separate disciplines. The NIH Roadmap initiative, "Re-engineer-

ing the Clinical Research Enterprise," will develop strategies to coordinate these efforts, including databases to facilitate sharing among research groups (http://nihroadmap.nih.gov/grants/rm-04-23.htm).

What are the impediments to these large-scale efforts in genomics, imaging and clinical neuroscience? These projects are costly. They require a broad and systematic effort that is not entirely hypothesis-driven. And they require the coordinated efforts of several laboratories. With NIH budgets predicted to grow at roughly 3% each year in the near future, an investment in a large-scale project means less funding for single-laboratory, hypothesis-driven, R01-type projects. Although we have been searching for the correct balance between large-scale and small-scale science, we recognize that these ambitious projects have the capacity to help both. If the Human Genome Project is an indication, we can expect that some of the large-scale efforts described above will be especially enabling for small laboratories. For instance, a laboratory using a single knock-out strain could begin to access scores of relevant strains from a public repository of transgenic mice. A modest-sized neuroanatomy laboratory could use a comprehensive transcriptional map of the mammalian brain to investigate a broad range of colocalized mRNAs or to map diverse proteins. Of course, the key to using large repositories and databases is public access. Large-scale science is only worth the investment if it enables progress from a broad community of scientists.

Alberts was right, small science is good science. It is equally true, however, that at this point in the history of neuroscience, large-scale research promises to deliver the enabling tools for both small and large laboratories to address some of the most challenging questions in brain structure and function. Indeed, with proper coordination and integration of resources, 'small science' is not incompatible with large-scale research; in fact, small laboratories could be an integral part of large-scale efforts. This special focus issue of *Nature Neuroscience* provides a good introduction to this promise. We look forward to the full delivery of high-throughput neuroscience over the next few years.

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