Bruce Alberts is Editor-in-Chief of *Science*.

The End of "Small Science"?

I AM PROMPTED TO WRITE THIS EDITORIAL BY THE RELEASE OF 30 PAPERS THIS MONTH FROM THE ENCODE Project Consortium. This decade-long project involved an international team of 442 scientists who have compiled what is being called an "encyclopedia of DNA elements," a comprehensive list of functional elements in the human genome. The detailed overview is expected to spur further research on the fundamentals of life, health, and disease. ENCODE exemplifies a "big-science" style of research that continues to sweep the headlines, and the increased efficiency of data production by such projects is impressive. Does this mean that the highly successful "small-science" era of biological research will soon be over? Will government funding increasingly favor big-science projects? I certainly hope that the answer is no.

The striking success of the Human Genome Project, which culminated in the 2004 publication of a near-complete sequence of the more than 3 billion nucleotides of DNA in human chromosomes, has stimulated the proliferation of other large "-omics" projects in biology, including proteomics, transcriptomics, epigenomics, and metabolomics. Each of these big-science efforts drives the development of valuable new methodologies, as required to bring each type of investigation to scale. But the scale also creates a constituency that makes these projects difficult to stop, even when there are clear signs of diminishing returns. In this time of very tight resources, it becomes increasingly critical to make objective, tough decisions about what kinds of projects stand the best chance of producing the results needed for deeply understanding, rather than merely describing, biological systems.

What remains to be understood? As a coauthor of a textbook in cell biology that is updated at 5-year intervals, I am painfully aware of the huge gap that remains in our understanding of even the simplest cells. Consider, for example, the common bacterium *E. coli,* which served as a predominant model organism in the early years of molecular biology. It is very sobering to report that more than 50 years later, nearly a quarter of the more than 4000 proteins encoded by its genome have functions that remain unknown. Might some new functional classes of biological molecules, common to all cells, be discovered by a focus on such proteins?

As a second example, a typical human cell contains approximately 10,000 different proteins, organized into hundreds of different complexes that function as "protein machines," most being activated where and when needed to perform a specific function such as DNA repair or signal integration. To make sense of the biology and gain the likely health benefits from such an understanding, each of these protein complexes will need to be studied in detail by biochemists—work that typically takes place in small laboratories.

As a final point, we now know that the most interesting properties of cells are "emergent" properties, resulting from elaborate networks of interactions between many different molecules that include the protein machines. Scientists currently lack the ability to decipher this complexity, and gaining this ability will require great ingenuity and many new developments whose exact nature is unpredictable. Much of the work will need to be done through small-science research in relatively simple systems, such as the *E. coli* bacterium, with the hope that what is learned will lead to new approaches and principles that can be transferred to the more complicated cells of mammals.

Each year, the amount of factual information that scientists acquire about cells increases and, stimulated by -omics projects, the compilations of data expand at a tremendous rate. But the grand challenges that remain in attaining a deep understanding of the chemistry of life will require going beyond detailed catalogs. Ensuring a successful future for the biological sciences will require restraint in the growth of large centers and -omics–like projects, so as to provide more financial support for the critical work of innovative small laboratories striving to understand the wonderful complexity of living systems.

– Bruce Alberts

10.1126/science.1230529

CREDITS: (TOP) TOM KOCHEL; (RIGHT) SHUTTERSTOCK.COM