Assembling the pieces

Balancing big science projects with smaller-scale mechanistic studies provides a collaborative approach for integrating scientific knowledge and addressing major scientific challenges.

Traditional 'small science' is performed by individual scientists and research groups and is generally focused on specific scientific areas. In contrast, 'big science' initiatives take a different approach: they equip large research teams with substantial resources and charge them with the task of finding solutions to pressing scientific or technological challenges. Recent big science initiatives such as the Human Genome Project have transformed the culture of chemical biology research (*Nat. Chem. Biol.* **6**, 847–854, 2010). Big science has shifted our perspective on scientific questions and has also changed how we fund research, define disciplines and view collaboration. Yet small science investigations still offer a proven method for generating scientific knowledge and training scientists. A collection of commentaries in this issue highlights the fact that, as chemical biologists embrace both large-scale and small-scale approaches, they need to consider the best ways to integrate tools and ideas from across scales and disciplines while they seek to understand biological systems at the molecular level.

Big science has attracted attention from scientists, funding agencies and the general public, because the projects typically have specific quantifiable goals that, if achieved, have potentially great scientific and societal impacts. For example, big science initiatives in systems biology, which seek a global perspective of biomolecules and the networks through which they interact, are beginning to provide a more integrated view of biology and medicine. High-throughput 'omics' technologies have generated new hypotheses and accelerated data acquisition; these new tools and large-scale data sets have enabled scientists to ask increasingly sophisticated questions about complex biological systems. More generally, large-scale approaches have further blurred the boundaries between traditional disciplines and have fostered a wider culture of collaboration within science. It is hard to imagine how recent discoveries in chemical biology could have been achieved in the absence of focused, well-funded and standardized large-scale biology efforts, such as the International HapMap project (http://hapmap.ncbi.nlm.nih.gov/) or the Molecular Libraries and Imaging program of the US National Institutes of Health (http://mli.nih.gov/mli/).

Although big science efforts may improve the scope and efficiency of experiments, they have also been criticized for their limited ability to provide a truly integrated view of a system down to its molecular details. Thus, even in the big science era, the mechanistic viewpoint of small science investigations remains critical for obtaining a complete picture of biological systems. For instance, The Cancer Genome Atlas (http://cancergenome.nih.gov/) is providing a comprehensive profile of the genomic changes that occur within specific tumors, but more traditional studies will still be necessary to distinguish the mutations that drive tumorigenesis from those that are passengers. From a training perspective, many scientists continue to feel that smaller-scale research groups or academic departments provide an optimal environment for scientific education, even in interdisciplinary fields such as chemical biology.

In balancing large-scale and small-scale science, it is worth considering when big science projects are needed and how they arise. The Human Genome Project, widely viewed as a milestone for biology, naturally called for a top down approach. More frequently, large-scale science projects take shape in response to needs of a particular community. Tom Laue and Borries Demeler (page 331) present the open analytical ultracentrifuge (AUC) project as one successful example of a large-scale community effort for providing a more integrated view of protein function in cells. Chemical biologists should consider whether there are similar major questions or unmet technological needs at the interface of chemistry and biology that require coordinated efforts.

Early-stage drug discovery may be one area of chemical biology research in which greater collaboration and better integration of scientific approaches will enhance our ability to meet scientific and practical challenges. As highlighted by Mark Bunnage (page 335), the pharmaceutical industry is facing an "alarming" dip in productivity. He argues that identifying high-quality disease-relevant targets is the primary challenge facing the drug development pipeline and that overcoming this will require fundamental changes in discovery research. In particular, collaboration in the form of cross-industry and academic-industrial partnerships and an emphasis on data sharing and precompetitive agreements will become increasingly common. These larger scale initiatives will also need to be balanced with investigator-driven chemical biology, including the identification of high-quality chemical probes and the development of robust chemical tools with drug discovery applications. From another perspective, Robert Murphy (page 327) looks at how the large-scale approaches of machine learning offer emerging tools for early-stage drug discovery. In addition to supporting analysis of data sets coming from large-scale screens, active-learning methods will be essential for constructing better models from large data sets by guiding experimental choices. Finally, Hiroaki Kitano, Samik Ghosh and Yukiko Matsuoka (page 323) make a compelling case that big science principles, including knowledge integration and open collaboration, should be applied to change the landscape of drug development for neglected diseases. This 'virtual' process will provide a mechanism to better integrate big science and small science projects on a global scale in a way that could have a major impact on human health.

Kitano, Ghosh and Matsuoka (page 323) also note that today's big science has a 'social engineering' aspect that capitalizes on community enthusiasm for an effort based on its potential scientific and societal impacts. Yet shared enthusiasm can carry a project only so far. Though successful large-scale science requires effective leadership supported by clear goals, community standards and financial and infrastructural resources, it also depends heavily on the contributions of individual scientists, most of whom are also working on smaller-scale projects. As these authors note, leaders of large-scale initiatives need to understand the strengths and motivations of participating scientists and ensure that they are rewarded and properly acknowledged for their contributions. As chemical biologists lead and participate in big science projects, they need to ensure that we make full use of the complementary benefits of big and small science to best advance our shared goals of enhancing our understanding of biological systems and supporting chemical biology as a discipline.