Preface

High-throughput screening (HTS) has seen over a decade of deployment in the pharmaceutical industry as an early discovery platform to feed lead compounds into pipelines culminating in the development of therapeutic agents. In recent years, interest in HTS within the academic community has increased dramatically, as an engine of discovery for potential drug candidates, for novel probes to understand fundamental biological processes, and for developing cheminformatic rules governing the interaction between chemistry and biology. A number of academic screening centers have existed for several years, including those members of the NIH-sponsored Molecular Library Probe Production Centers Network and the NCI-sponsored Initiative for Chemical Genetics, with many more facilities in the planning and start-up stages. As HTS develops into a legitimate academic pursuit, the need for reference materials regarding the philosophy and practice of screening becomes ever more pressing. Although a large proportion of screening experiments reported in the literature has been based on biochemical interactions between small molecules and purified proteins, a rich body of literature has developed around cell-based assays. We have built upon this foundation to create an easily accessible reference volume for cell-based phenotypic screening.

We encourage the reader to view this reference in a modular way. Although each chapter presents an individual protocol peculiar to the assays being discussed, in groups they represent the four governing principles of this text: (1) model biological systems, (2) screening modalities and assay systems, (3) detection technologies, and (4) approaches to data analysis. Each chapter begins with an overview of the relevant component of HTS, providing examples of its use as well as appropriate considerations and caveats. Each chapter then presents state-of-the-art methods in terms of actionable protocols; we anticipate that the reader will be interested in direct application of the methods presented.

Taken together, the methods presented in this reference can further be used in a modular fashion, culling one chapter per section to design new screens on the basis of published methods. For example, a researcher considering a fluorescent dye-based assay in mammalian cell culture might consult both Chap. 3 (Mayer et al.) on screening with mammalian cells, and Chap. 7 (An) on fluorescent dyes. Similarly, one interested in high-content imaging of zebrafish might benefit most from chapters 4 (Hong) on zebrafish screening, and 14 (Carpenter) on extracting rich information from images. We feel that this reading technique will allow researchers to take a modular approach to the design of their assays. Rather than mimic a particular screen of interest exactly, researchers might apply theory and design principles from several sections of this reference to the development of novel and creative ways of addressing biological questions using HTS.

In summary, we expect that this reference will serve three purposes. First, each chapter will present an overview of relevant approaches taken in this relatively young field. Second, each chapter will provide sufficient methodological detail to enable direct application of existing methods to new discoveries. Third, the book itself will inspire researchers to approach their screening projects in a conceptually modular fashion, enhancing the power for discovery through new combinations of existing approaches.

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