HIGH-THROUGHPUT SCREENING FOR SMALL-MOLECULE DRUG DISCOVERY

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1 INTRODUCTION

There is ample evidence that high-throughput screening (HTS) has become one of the main methods for generating leads for drug discovery [1]. The capacity and throughput for screening has been growing steadily for the last two decades. HTS has transformed biological testing from a process using test-tube and cuvette measurements to one using high-density, low-volume assay formats and screening systems. This transformation has been in response to rapid changes in biological target identification and validation, facilitated by advances in genomic and proteomic studies and compound synthetic methodologies. Particularly, the development and utilization of miniaturized, homogeneous assay technologies and various signal detection methodologies has made possible the screening of hundreds of thousands and even millions of compounds in a relatively short time period. Assay format standardization, instrumentation automation, assay miniaturization, and informatics tools for data analysis have greatly facilitate the screening process by increasing reliability and reducing personnel workload. Biomolecular screening has become a fast growing and critical field in early drug discovery. With the demands for ever-increasing productivity in drug discovery and development, one can only expect that the emphasis on discovering drug candidates faster and of higher quality will increase. These demands impose new challenges and also present new opportunities for the field of HTS and its related drug discovery activities.

There are many different drug discovery strategies where HTS can be applied, from the conceptually simple "screen everything we have" strategy to various strategies that call for the screening of subsets of compounds chosen to fulfill a defined hypothesis [2]. Although every strategy has its own advantages and disadvantages, they all require compounds or samples to be screened for biological activity in an efficient and reliable manner. The involvement of HTS activities in different phases of drug discovery and development are shown in Figure 1.

In a broader view, HTS should not be regarded as a specialty field, only performing assay development, method validation, and screening. HTS has become more of a collective term for a range of multidisciplinary activities, ranging from the creation of cell lines or recombinant enzymes for screening to computational and medicinal chemists designing and making screening compound libraries, and from engineers creating suitable robots and instrumentation allowing the automation of biological assays to statisticians and modelers who help analyze screening data to extract useful and predictive models of mode of interaction. Figure 2 illustrates the interconnection of scientific disciplines required for successful HTS and hit-to-lead optimization processes.

There are two major assay types in HTS, biochemical and cell-based assays, as will be illustrated in the following section. For any specific target, there are usually several assay formats available. In the past, assays involving the use of radioactive isotopes had been used

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