MOLECULAR SCREENING FOR THERAPEUTIC AGENTS

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1 INTRODUCTION

1.1 Historical Overview

Sequencing of the human genome in 2001 provided a conceptual infrastructure for understanding the cellular processes fundamental to life and health [1]. Following the advances in decoding the human genome at the sequence level, deciphering the function of individual proteins encoded by the genome and elucidating their respective biochemical pathways is now well on its way. As a result, cellular processes and their involvement in disease and discovery of therapeutic compounds for the various disease indications are becoming better understood. Consequently, the postgenomic era filled the drug target pipeline of the pharmaceutical industry with an unprecedented number of targets [2, 3].

In the pregenomic era, screening for therapeutic compounds of up to 10,000 compounds per diem was the scientific standard for drug discovery until the 1980s and 1990s. As more and more drug targets became available, drug discovery companies began pushing for more intelligent, productive, high-precision discovery [4]. A solution to these needs was molecular screening, the combination of molecular biology and drug screening. By means of molecular biology, it became possible to engineer assay systems that mimic a disease system and subject it to screening for therapeutic compounds [5].

Molecular screening soon became automated and enabled the use of very complex assay systems without the personnel burden normally associated with screening for bioactive compounds. [6, 7] In addition to saving labor, automation offered other compelling advantages. Experiments could be reproduced perfectly and performed on a much larger, more expansive scale. It became feasible to transfer experiments from low- to high-throughput platforms for screening of large compound sets and then transfer the experiments back again for hit validation and characterization purposes.

At the beginning of the transition to automation, most of the assays were biochemical. These assays were typically performed on single isolated proteins. Rapidly, the technology expanded to accommodate assay systems based on cells. Now, even whole organism platforms [8] are a promising new possibility, and current automation platforms are capable of handling complicated experimental protocols, opening the door to the use of molecular screening in general basic research.

These research applications of screening include functional genomics screens using small interfering ribonucleic acid (siRNAs) [9], short hairpin RNA (shRNAs) [10], and overexpression libraries [11], just to name a few. This chapter gives an introduction to the general concepts of molecular screening as they relate to discovery of therapeutic agents and highlight some research applications of molecular screening. It will give a general introduction to the concepts of molecular screening, provide an overview of the general work flow, outline different screening approaches, give an overview of the assay development and validation process, and discuss the basic readouts for assays. Then we will have a close look at compound libraries that can be

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