ISSN: 0975-766X
CODEN: IJPTFI
Available Online through
www.ijptonline.com
Research Article

INTRODUCTION TO HIGH THROUGHPUT SCREENING IN DRUG DISCOVERY

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Received on 17-01-2012 *Accepted on 31-01-2012*

Abstract

Novel technologies are emerging for high-throughput screening, driven by the needs and fine-tuning of established drug discovery activities, as well as by the emergence of novel target classes resulting from the deciphering of the human genome. Disciplines other than biology have now entered the screening scene, as bioinformatics, micro-technology and analytics provide powerful methodologies and applications that were not previously suitable for high-throughput screening. Many of these will move high-throughput screening from a numbers game to a content- and information-based approach to identify leads for novel disease targets.

Keywords: High-Throughput Screening (HTS), Automation and Robotics, Miniaturization, Z factor, Profiling, nuclear magnetic resonance

Introduction

Of late High-Throughput Screening (HTS) a high-tech approach for drug discovery is more and more gaining popularity among industrial researchers as well as students doing their post-graduate and/or doctorate research projects. It is basically a process of screening and assaying huge number of biological modulators and effectors against selected and specific targets.

The principles and methods of HTS find their application for screening of combinatorial chemistry, genomics, protein, and peptide libraries. The main purpose or goal of this technique is to hasten the drug discovery process by screening the large compound libraries with a speed which may exceed a few thousand compounds per day or per week. For any assay or screening by HTS to be successful several steps like target identification, reagent

preparation, compound management, assay development and high-throughput library screening should be carried out with utmost care and precision.[1]

Over the past decade, high-throughput screening (HTS) has become a cornerstone technology of pharmaceutical research. Investments into HTS have been, and continue to be, substantial. A current estimate is that biological screening and preclinical pharmacological testing alone account for ~14% of the total research and development (R&D) expenditures of the pharmaceutical industry. HTS is very much influenced by advances in automation and miniaturization.[2]

Purpose and method

Using robotics, data processing and control software, liquid handling devices, and sensitive detectors, High-Throughput Screening or HTS allows a researcher to quickly conduct millions of biochemical, genetic or pharmacological tests. Through this process one can rapidly identify active compounds, antibodies or genes which modulate a particular bimolecular pathway. The results of these experiments provide starting points for drug design and for understanding the interaction or role of a particular biochemical process in biology.

In essence, HTS uses automation to run a *screen* of an assay against a library of candidate compounds. An assay is a test for specific activity: usually inhibition or stimulation of a biochemical or biological mechanism. Typical HTS screening libraries or "decks" can contain from 100,000 to more than 2,000,000 compounds.

The key lab ware or testing vessel of HTS is the micro titer plate: a small container, usually disposable and made of plastic that features a grid of small, open divots called *wells*. Modern (circa 2008) micro plates for HTS generally have either 384, 1536, or 3456 wells. These are all multiples of 96, reflecting the original 96 well micro plate with 8 x 12 9mm spaced wells. Most of the wells contain experimentally useful matter, often an aqueous solution of dimethyl sulfoxide (DMSO) and some other chemical compound, the latter of which is different for each well across the plate. (The other wells may be empty, intended for use as optional experimental controls.)

To prepare for an assay, the researcher fills each well of the plate with some biological entity that he or she wishes to conduct the experiment upon, such as a protein, some cells, or an animal embryo. After some incubation time has passed to allow the biological matter to absorb, bind to, or otherwise react (or fail to react) with the compounds in the wells, measurements are taken across all the plate's wells, either manually or by a machine. Manual

measurements are often necessary when the researcher is using microscopy to (for example) seek changes or defects in embryonic development caused by the wells' compounds, looking for effects that a computer could not easily determine by itself. Otherwise, a specialized automated analysis machine can run a number of experiments on the wells (such as shining polarized light on them and measuring reflectivity, which can be an indication of protein binding). In this case, the machine outputs the result of each experiment as a grid of numeric values, with each number mapping to the value obtained from a single well. A high-capacity analysis machine can measure dozens of plates in the space of a few minutes like this, generating thousands of experimental data points very quickly.

Depending on the results of this first assay, the researcher can perform follow up assays within the same screen by "cherry picking" liquid from the source wells that gave interesting results (known as "hits") into new assay plates, and then re-running the experiment to collect further data on this narrowed set, confirming and refining observations.[4]

Nuclear magnetic resonance in high throughput screening

Among the novel technologies associated with HTS, nuclear magnetic resonance (NMR) has recently been successfully applied. NMR analysis of drug–protein interactions offers the advantage that information on the affinity of the screening compound can be obtained, as well as the binding location on the protein. NMR will thus help the medicinal chemist in the further optimization

Process of the program. The studies can be extended beyond high-throughput lead compound identification to metabolite screening and drug disposition. In particular, the coupling of NMR with other analytical methods, especially high performance liquid chromatography (HPLC), combines the structural and dynamic details available from NMR methods with the resolution and sensitivity of other analytical techniques.In contrast to the conventional screening of compound libraries, fragment-based NMR screening relies upon a significantly smaller number of compounds, and thereby demands specific efforts in the design of the library with respect to the diversity and the compilation of this collection for further drug design.

High-throughput ligand-based NMR screening with competition binding experiments also employs (19) F-labelled low affinity ligands. Fluorine is a favourable nucleus for these experiments because of the significant contribution

Of the chemical shift anisotropy to the (19) F transverse relaxation of the ligand signal when bound to a macromolecular target, resulting in a difference in the (19) F resonance line width of the reference compound. In addition, the chemical shift difference for the fluorinated ligand increases between the free and bound state.[3]

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