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HIGH-THROUGHPUT SCREENING IN DRUG DISCOVERY

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Abstract:

High-throughput screening (HTS) is one of the newest techniques used in drug design and may be applied in biological and chemical sciences. This method, due to use of robots, detectors and software that regulate the whole process, enables a sequence of analyses of chemical compounds to be conducted in a short time and the resemblance of biological structures which is often related to toxicity to be defined. The HTS method is more frequently utilized in conjunction with analytical techniques such as NMR or coupled methods e.g., LC-MS/MS. Series of studies enable the establishment of the rate of affinity for targets or the level of toxicity. Moreover, researches are conducted concerning conjugation of nano-particles with drugs and the determination of the toxicity of such structures. For these purposes there are frequently used cell lines. Determination of cytotoxicity in this way leads to a significant decrease in the costs and to a reduction in the duration of the study.

***Keywords**: High-throughput screening (HTS), drug development, drug discovery*

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INTRODUCTION:

High-Throughput Screening (HTS) is an approach to drug discovery that has gained prevalent popularity over the last two decades and has become a standard method for drug discovery in the pharmaceutical industry. It is principally a process of screening and assaying a large number of biological modulators and effectors against selected and specific targets.[1] It is used not only among industrial scientists but also among academic researchers. HTS assays are used for screening of different types of libraries, including combinatorial chemistry, genomics, protein, and peptide libraries.[2] The main aim of the HTS technique is to speed up drug discovery by screening large compound libraries at a rate. It is very important; because parallel and combinatorial chemical synthesis generates an enormous number of novel compounds.[3] High-throughput screening methods are also used to characterize metabolic, pharmacokinetic and toxicological data about new drugs. HTS technology can reduce the costs of drug development.[4]

HTS consist of several steps such as target identification, reagent preparation, compound management, assay development and high-throughput library screening. The effective nature of HTS for identification of target specific compounds is attributed to its precise focus on single mechanism. The development of this technology is closely connected to the changes in strategy of chemical synthesis. The huge number of compounds produced by combinatorial chemistry and the possibility of testing many compounds in a short period of time by HTS has attracted the attention of many scientists. Various techniques like fluorescence resonance energy transfer (FRET) and homogeneous time resolved fluorescence (HTRF) are available for identification of compounds.[2]

At present, high-density arrays of micro-reaction wells are gaining popularity in pharmaceutical analysis and drug discovery. Initially there were used 96-well plates but now this format of microplates is currently being replaced by higher density microplates with up to 1586-wells per plate. The typical working volume for these microplates is in the range of about 2.5 to 10 µL total volume, a standard volume is 5 µL per well.[5] However; there are still ongoing trends towards miniaturization of plates. Several examples of biological assays in 3456-well microplates have been reported where the total assay volume was 1–2 µL. However, the use of these ultra-high density plates seems to have some technical hurdles.[6]

It is possible to screen up to 10,000 compounds per day by means of typical HTS. Ultra High-Throughput Screening (UHTS) can conduct even 100,000 assays per day. At first compounds are tested in primary screens which are less quantitative than biological assays. If an examined compound gives a positive result or "HIT" in such test a more precise secondary screening is conducted and calculations of IC_{50} values are performed. Secondary screening is performed by means of adopted biological and biochemical tests. Assays are mainly of two types either heterogeneous or homogeneous which is simpler and cheaper than heterogeneous. However, heterogeneous assays appear to be more sensitive.

HTS are frequently performed by means of miniaturized cell-based assays. Cell-based assays enable chemical libraries to be screened for molecules that present different biological activities. Cellular microarrays are used in the pharmaceutical industry and utilize 96- or 384-well micro-titer plates with 2D cell monolayer cultures.[7] Cellular microarrays comprise a solid support wherein small volumes of different bio-molecules and cells can be displayed, allowing the multiplexed interrogation of living cells and, afterwards, the analysis of cellular responses.[8]

Reagents in HTS assays such as enzymes (e.g., tyrosine kinase) cannot be contaminated and have to be optimized. For this purpose Aptamers (nucleic acids) are used due to the speed of their identification, their high affinity for protein targets, and their compatibility with various detection strategies.[1] Currently seeing a trend towards automation and miniaturization of HTS techniques. Miniaturization of bio-analytical processes has become an important area in research with particular focus on laboratory-on-a-chip technology.[9] Advantages of these analytical systems include a reduction in manufacturing costs, ease of transport, and minimal space requirements in the laboratory. Furthermore, miniaturization enables the desired screening rates to be obtained, but on the other hand, it may contribute to long design and implementation time, non-stable robotic operation, and limited error recovery abilities. In the process of automation there are involved multiple layered computers, various operating systems, a single central robot and complex scheduling software. A central robot is equipped with a gripper that can pick and place microplates around a platform. The duration of a single run depends on the type of assay, and during it there are processed from 400 to 1000 microplates. At the beginning of the experiment the screener loads the robotic platform with microplates and reagents and

afterwards the assay is processed. Microplates are then passed down a line in serial fashion to consecutive processing modules. Each module, equipped with its own simple pick and place robotic arm and microplate processing device, provides one step of the assay.[1]

HTS IN DRUG DISCOVERY:

The importance of high-throughput screening systems based on multiplex detection for clinical and genetic analysis has attracted much attention in various diagnostic fields, especially in chip-based or particle-based assay.[10]Over the past two decades scientific efforts have been made to develop innovative methods for screening compounds against a large number of potential therapeutic agents. Advances in molecular biology, bioinformatics, and systems biology have led to the application of new methods in the field of drug discovery. In silico methods are one of the few techniques that have the potential to significantly improve drug discovery and development. Furthermore, these methods enable the prediction of toxicity from chemical structure.[11]They contribute to the early identification of serious toxicological issues before significant investment of time and financial resources are spent in clinical trials. The advantages of these methods are low costs, standardization, minimal equipment needs, and short time of execution.[12]

Another method is HTS which enables the estimation of the potential for toxicity and the understanding of mechanisms of action of a large number of chemicals. HTS techniques are used in the pharmaceutical industry for screening of enormous numbers of compounds in the drug development process. Chemicals are chosen to cover large areas of chemical diversity and to broadly probe biological function without earlier assumptions.[13] Detection systems in HTS are frequently fluorescence, scintillation proximity assays (SPA) and luminescence. These methods facilitate simple and convenient assay procedures and provide high levels of sensitivity. The whole process relies on automation and robotics, thus there is a possibility to test from thousands to a million samples per day. This is possible due to the use of a wide variety of HTS bioassay screens which measure biochemical activity and different cell functions.[14] Generally, HTS assays can measure direct binding to key targets, changes of specific biomarkers, or cellular alteration such as cell shape changes or cell death.

These assays enable structure-activity information to be obtained. The next step of analysis is matching these chemical-activity profiles with proper reference toxicological data. Establishment of a chemical structure and biological activity interface results in a comprehensive insight into activity mechanisms similar to an integrated animal response. One of the most crucial advantages of HTS screening tests is a substantial reduction in costs and animal use. Furthermore, they allow the examination of chemicals at relevant exposure levels.[15]

CONCLUSION:

Drug discovery, placed in the field of medicine, pharmacology and biotechnology, is associated with research on drug targets and mechanisms. In the past most drugs have been discovered by identifying the active ingredient from traditional resources (plants, minerals, etc.) or by discovery. Drug-discovery is a highly complex, multidisciplinary and time-consuming program, which typically starts with the identification of suitable drug targets (e.g., biomolecules such as receptors, enzymes and ion channels). The next step is target validation in which it is established whether the target is of relevance to the disease under study. Afterwards modulators of the target have to be identified.

Such modulators are agonists or antagonists of receptors, activators or inhibitors of enzymes, and openers or blockers of ion channels. Suitable assays are then developed to monitor the target under study. An example is HTS which exposes the target to a large number of chemical compounds. In this phase "lead" compounds are obtained which are characterized by a certain degree of selectivity for the target. These 'lead' compounds are then optimized in terms of their potency, selectivity, physicochemical properties, and pharmacokinetic and toxicity properties. The last phases of the drug discovery processes are human trials. Due to vast computational possibilities concerning the number of chemical compounds of whose parameters can be established in a short time, HTS assays are utilized not only in research and development centers but also in pharmaceutical companies.

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