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High-throughput screening technologies for drug discovery

Maosheng Wang

Shanghai Institute of Technology, 100 Haiquan Road, Fengxian District, Shanghai

953925997@qq.com

Abstract. The development of high-throughput screening technologies has revolutionized the field of drug discovery by significantly improving the efficiency of compound library screening. Traditional screening methods, such as manual screening and biochemical assays, were time-consuming and limited in their ability to identify lead compounds. However, the advent of high-throughput screening technologies has overcome these limitations and provided researchers with a more efficient and effective approach. This review begins by examining the background, characteristics, and limitations of conventional screening methods. These methods often required large amounts of time, resources, and labor, making them impractical for large-scale compound screening. In recent years, some new technologies have emerged, including virtual screening, image analysis, prediction methods, and microarray-based screening. Each of these approaches has its own strengths and limitations, but collectively they have greatly enhanced the efficiency and accuracy of compound identification. These viewpoints highlight the successful application of these technologies in identifying lead compounds for various therapeutic targets. Finally, the review envisions the future development of high-throughput screening technologies. It emphasizes the need for continuous optimization and innovation to further improve the efficiency and effectiveness of compound identification. The ultimate goal is to shorten drug development timelines and provide high-quality lead compounds for the benefit of patients. In conclusion, the emergence of high-throughput screening technologies has significantly improved the efficiency of compound library screening and provided better lead compounds for drug discovery. Ongoing advancements in these technologies hold great promise for the future of pharmaceutical research and development.

Keywords: High-throughput screening, Drug discovery, Compound libraries.

1. Introduction

However, with advancements in technology and the understanding of drug mechanisms, the 1960s saw the emergence of high-throughput screening (HTS) techniques. HTS allowed for the rapid screening of large libraries of compounds, increasing the efficiency of drug discovery. This was made possible by the development of automated systems and robotics, which could handle a large number of samples simultaneously. Additionally, the use of cell-based assays and molecular biology techniques provided more accurate and relevant data for drug screening. These advancements revolutionized the field of drug discovery and paved the way for the development of new and effective drugs [1]. These conventional screening methods either administered compounds directly to animals to observe pharmacological effects, extracted patient serum for in vitro reaction testing, or depended on simple biochemical analysis like chromatographic analysis to identify drug components. However, screening each individual

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compound required enormous amounts of time and resources using these methods. Comprehensive screening of a large compound library was barely imaginable. With the development of cell culture and tissue isolation culture technologies in the 1950s-60s, drug screening entered a new era. In this period, specific tissues or cells were isolated from human or animal bodies for in vitro culture using tissue engineering techniques. Yunru Yu [2] mentioned that isolated tissues, cells or enzymes were used for preliminary screening by detecting bio-markers like cytotoxicity, cell proliferation, enzyme activity, etc. to evaluate compound activity. This greatly improved screening efficiency. Such cell-based and biochemical screenings dramatically shortened the screening time per compound and enabled processing of more compounds. Meanwhile, the application of highly sensitive and specific immunoassay technologies like ELISA also enabled rapid detection of drug effects. Additionally, fluorescence techniques provided more intuitive means for assessing pharmacologic effects. The use of automated control equipment also allowed sample handling and detection in drug screening to be performed automatically without manual operation, further facilitating the development of high-throughput screening [3]. The combination of these technological advances laid the foundation for the emergence of high-throughput screening technologies.

2. Applications of Conventional Screening Methods

According to Adam J [4], conventional screening methods can be divided into three main categories: animal model screening, human sample screening, and biochemical screening. Animal model screening refers to directly administering compounds to animals and observing their pharmacological effects and side effects to identify safe and effective active compounds. This usually requires testing in multiple animal models like rabbits, rats, and mice to examine species-specific effects. Human sample screening involves direct in vitro reactions of extracted human serum, tissue samples, etc. to detect compound interactions and effects on human components to better evaluate pharmacological effects in humans. Biochemical screening mainly utilizes chromatographic, mass spectrometric and other techniques to detect compound interactions with target molecules by reconstituting human enzyme or receptor systems in test tubes, thereby determining the activity levels of compounds. The three conventional screening methods each have their advantages and disadvantages. Animal model screening offers greater physiological relevance, while human sample screening better predicts human effects. Biochemical screening enables high-throughput processing. Together, they laid the foundation for drug discovery and developed into screening systems that strongly supported the subsequent emergence of high-throughput screening technologies.

3. Applications of High-throughput Screening Technologies

Currently, high-throughput screening technologies have been applied in multiple fields. Natarajan Arul Murugan [5] pointed out that High-throughput screening (HTS) technologies have become indispensable tools in various fields. In drug screening, HTS allows for the rapid testing of large compound libraries to identify potential drug candidates. Gene screening using HTS techniques enables the identification of genes associated with specific diseases or biological processes. Antibody screening helps in the discovery of novel therapeutic antibodies for various diseases. Material screening using HTS methods aids in the development of new materials with desired properties. Cell screening allows for the identification of compounds that affect cellular processes or have therapeutic potential. HTS is also used in pharmacologic and toxicity screening to assess the effects of compounds on biological systems. Lastly, HTS plays a crucial role in target identification, helping researchers identify potential targets for drug development. Overall, high-throughput screening technologies have revolutionized multiple fields, accelerating research and discovery processes.

Specifically, in drug screening, high-throughput cell screening can rapidly identify potential lead compounds that inhibit or stimulate disease-relevant cell lines among large compound libraries containing tens of thousands of compounds within a short period of time. Meanwhile, high-throughput enzyme activity screening can rapidly evaluate in vitro the effects of massive amounts of compounds on enzymatic targets related to key diseases.

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In gene screening, high-throughput gene knockout technologies such as those by Hunter Sturm, Jonas Teufel [6], can scan the whole genome for deletions within days and establish genotype-phenotype relationships through high-content imaging detection of phenotypes, providing foundations for understanding biological processes.

For antibody screening, large-scale antibody libraries can be cloned or synthesized and combined with cell surface display technologies to rapidly obtain highly specific antibodies for new drug development or clinical disease detection [7].

In material screening, combining chip technologies and combinatorial chemical synthesis can produce tens of thousands of materials simultaneously to rapidly screen for those with desired electrical, magnetic and other properties [8]. Additionally, in cell screening, high-throughput imaging can quickly distinguish morphological and functional changes between cells in different states during in vitro culture. In summary, high-throughput screening technologies can be widely applied across multiple fields by virtue of their high-speed and high-throughput characteristics, promoting scientific research and development.

4. Challenges and Limitations of High-throughput Screening

High-throughput screening has significantly enhanced screening efficiency, but it faces both challenges and limitations that need to be addressed for more effective drug discovery. Bhaskarjyoti Gogoi [9] has identified several challenges:

1) Variability in Compound Libraries: Existing compound libraries often suffer from structural redundancy and incomplete coverage of chemical space, limiting the diversity of compounds that can be screened.

2) False Positives: Simplified high-throughput screening conditions can result in false positives due to non-specific binding, necessitating time-consuming validation processes.

3) Simplified Models: Many screens rely on simplified models that do not fully replicate in vivo environments, such as exclusive use of cell-based screening without organismal models.

4) Data Processing: The massive volume of data generated during screening requires expertise for analysis, and improper data mining can lead to the loss of valuable information.

5) Complex Process: The screening process involves multiple steps, from compound preparation to data processing, which require careful coordination and optimization to improve efficiency.

Addressing these challenges is essential to accelerate drug development. Additionally, current high-throughput screening methods have their limitations, including the use of tumor cell lines instead of patient primary cells, reliance on isolated systems in small molecule screens, and difficulties in constructing disease models for certain conditions like neurological disorders. Overcoming these limitations is crucial to enhance the accuracy and efficiency of high-throughput screening technologies.

5. New Technologies to Overcome Current Screening System Limitations

To address the limitations of current screening systems, researchers have developed some new technologies. Guihua Zou [10] proposed using cell and tissue engineering technologies to construct more realistic screening systems, such as 3D cell culture and organ chips. Navjot Kaur Gill [11] utilized multi-omics integration to predict in vivo information. Additionally, Biswajit Naik [12] employed artificial intelligence and big data technologies to uncover new compound-target relationships. These emerging technologies offer possibilities for obtaining more accurate screening outcomes.

Advances in Compound Identification Using High-throughput Screening Technologies

In recent years, various high-throughput screening technologies have made important advances in compound identification.

5.1. Virtual Screening Technology

Guihua Zou [13] utilized high-throughput virtual screening technology to discover 3 potential multi-target anti-COVID-19 compounds from natural compound databases, providing a strategy for rapid drug

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design. Teal demonstrated that high-throughput virtual screening can still effectively identify new compounds without high-resolution structural information.

High-throughput virtual screening utilizes computer to conduct large-scale virtual screening of compound libraries, and rapidly predicts potentially active compounds based on the theoretical binding affinity of each compound in the library with the drug target [14]. Compared with high-throughput experimental screening, virtual screening has the advantages of faster speed and lower cost. Currently, high-throughput virtual screening technology is widely used in new drug research and development.

Firstly, high-throughput virtual screening can rapidly screen large compound libraries, quickly narrowing down hundreds of thousands or even millions of compounds to hundreds of potential active compounds, providing candidate compounds for subsequent drug optimization and experimental validation. Secondly, virtual screening can evaluate the binding forces of known compounds in public databases with newly discovered drug targets, accelerating the discovery of hit compounds. Thirdly, even without the 3D structure information of the target molecule, some virtual screening methods designed for specific chemical categories can still achieve the identification of active compounds. Finally, this technology can screen out multi-target active compounds, which is helpful for discovering drugs with new mechanisms.

5.2. Microscopic Image Analysis

Ali Raza [15] used pre-trained deep learning models to extract features from high-content microscopic images for rapid evaluation and classification of cell phenotypes, effectively assisting experts in compound screening.

Deep learning models pre-trained on large datasets can extract high-level features from images that are useful for downstream tasks. By using these pre-trained models, Raza et al. were able to extract meaningful features from high-content microscopic images of cells without the need to train a model from scratch. These features enabled the rapid evaluation and classification of cell morphological phenotypes induced by compound treatments. This allows the deep learning model to act as an automatic screening system that can process images rapidly and identify treatments that induce interessant phenotypic changes. The model outputs serve as a tool to assist experts in focusing their efforts on the most promising compound treatments identified in the high-throughput screens. Overall, this demonstrates the power of transfer learning in Deep learning models for extracting useful features from images to enable rapid analysis for drug discovery.

5.3. Molecular Aggregation Prediction Technology

Hunter Sturm [16] used interpretable graph neural networks to predict molecular aggregation phenomena, guide compound prioritization, reduce false positives, and accelerate hit identification.

They developed graph neural networks that operate on molecular graphs to predict aggregation risks. The interpretability of the models allowed them to identify structural features driving aggregation, like charge interactions, which helped prioritize compounds with lower aggregation risks as screening candidates. By filtering out likely aggregators early, they could focus screening on compounds less likely to be false positives. This improved hit identification efficiency by avoiding time spent on aggregators that would ultimately fail experimental validation.

5.4. Directed Evolution Screening Technology

Natarajan Arul Murugan [17] developed a method to directly screen enzyme reaction products from cells without needing purification or modification, greatly shortening screening times and yielding improved enzymatic catalysts.

They engineered E. coli to export target products extracellularly, enabling direct analysis and screening of compounds produced by active enzymes without extract purification. By screening enzyme libraries expressed in these cells, they rapidly identified mutant enzymes with enhanced catalytic activity and stereoselectivity. Skipping extract purification and derivatization steps enabled ultra-high-throughput screening and accelerated the engineering of superior biocatalysts.

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5.5. Fluorescence Technology Applications

Philip T [18] utilized high-throughput fluorescence microscopy imaging to develop a non-invasive cellular ATP estimation model for continuous monitoring of compound effects on cell viability. Current Challenges and Future Outlook for High-throughput Screening Technologies

Currently, high-throughput screening technologies still face some challenges that require continuous optimization. Niklas M [19] proposed using non-precise quantum computation methods to obtain molecular structures, followed by data augmentation to improve predictivity, providing possibilities for practical applications. Additionally, the cell deformation-based screening chip developed by Ali Raza [20] offered a new approach for rapid discrimination of cell states. With technological advances, high-throughput screening platforms are progressing towards more accurate and information-rich directions. Application of these emerging screening technologies will accelerate target discovery and validation for diseases and aid in discovering more high-quality lead compounds, providing strong support for drug development.

6. Conclusion

The development of high-throughput screening technologies has revolutionized compound identification and drug discovery. These advancements have made it easier and faster to identify potential drug candidates. Additionally, emerging technologies such as virtual screening, image analysis, and prediction methods have further enhanced the support for pharmaceutical research and development. With ongoing optimization and innovation in high-throughput screening, it is anticipated that more high-quality lead compounds will be discovered, ultimately leading to shorter drug development timelines and improved patient outcomes.

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