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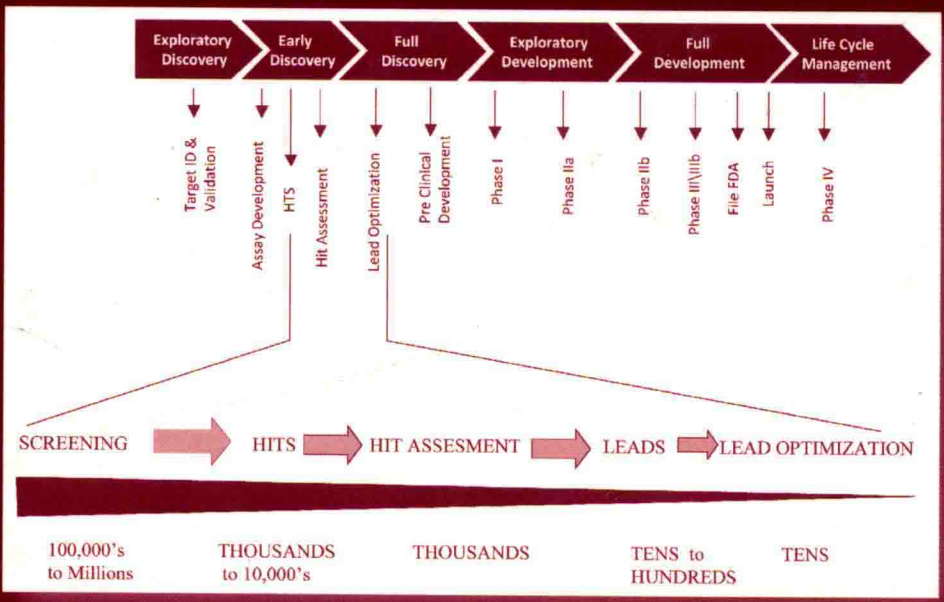
SECOND EDITION

Handbook of Drug Screening



edited by
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Preface

The success of "Handbook of Drug Screening" first edition and the profound advances in how drug screening is done today led us to the second edition of this book. Since the writing of the first edition, screening has matured and became one of the essential functions for drug discovery. Screening departments have carved out their place among the core scientific disciplines in pharmaceutical companies. The pace of drug discovery is increasing, leading to advances in target validation, compound screening, compound libraries, instrumentation, robotics, as well as data handling and mining. We hope that the second edition generates equal or more interest and satisfaction.

Some of the fundamental topics described in the first edition are retained and updated. In the last decade genomics, proteomics, assay technologies, structure-based drug design, automation, and medicinal chemistry have come together to improve the quality and efficiency of drug target validation and potential drug compound selection. New platforms for screening have been developed, with emphasis on reduction of assay cost and improvement of data quality and assay throughput. Since drug screening is a rapidly expanding science, several new chapters have been added including proteomics, microRNA, high-content screening, lead optimization, compound management, and quantitative high-throughput screening.

The completion of sequencing of the human genome has given a large amount of data for the identification of new drug discovery targets. The validation of new genes and protein function as drug targets is essential for the success of drug discovery programs. MicroRNA (miRNA) screening approach, a recent technology, has been widely used for target discovery and target validation by characterization of gene function. Homogenous systems have become the main stay of screening assays. New fluorescent probes and dyes have been used for developing assays for cellular responses and activation of signaling pathways, making it possible to screen multiple parameters in cells by high-content screening. The adaptation of nanofluidic devices and spectral and imaging technologies has led to complex systems that use multiple read-outs to examine interactions as well as multiple parameters. Miniaturization, applications of nanotechnology to screening that reduce the cost of drug discovery are described.

The clustering of the majority of drug targets around few target families such as the G-protein–coupled receptors (GPCRs), ion channels, proteases, nuclear hormone receptors, protein kinases, and phosphatases prompted target family directed screening that complements the traditional screening paradigm. Target family based panel screening allowed evaluation of the compound specificity to the target without any off-target effects. In addition to optimization of the lead

molecule against the target, safety and pharmacology must be examined. Screening methods to address ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity), specific receptor panel and channels known to be the origin of some adverse effects in human are described.

The first edition gives the basic foundation of drug screening. This second edition describes advances and impacts of target validation, drug screening methods, target family based screening methods, cell-based assays, and quantitative high-throughput screening on drug discovery. The combination of these approaches improved efficiency to help the early stages of drug discovery in identifying suitable leads that fuel medicinal chemistry programs and reduced the time for preclinical development of drug candidates. Throughout this edition, the state-of-art technologies used in academic and industrial drug discovery process are discussed by experts in the field. We wish to thank all the contributors for contributing these elegant reviews.

Ramakrishna Seethala
Litao Zhang

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Contents

1 Key Factors for Successful High-Throughput Screening

John G. Houston

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INTRODUCTION

High-throughput screening (HTS) has gone through a series of significant changes over the last two decades, with many companies now describing the journey they have taken (1–4). It has evolved from an ad hoc set of lightly connected instruments and teams, producing a somewhat unpredictable end product, into a highly integrated, automated process capable of delivering a sustained, high-quality output (5). Not only has HTS managed to deliver on its core promise as a reliable platform for producing lead compounds, it has also been able to expand into academic research institutes, as scientists there seek specific compounds to probe disease models. In several companies, the technology platforms underpinning HTS have also been exported into lead optimization and drug safety teams, again showing the flexibility and maturity of the approach.

Of course, it has not all been smooth sailing, and the initial hype around HTS and its ability to transform R&D productivity has ultimately proven to be a significant hindrance in assessing where HTS can really be impactful. HTS alone was never going to be the answer to what ailed pharma companies in the late 1990s or even today. What it always had the potential to do was to provide a fast, reliable, high-capacity method for finding lead compounds and helping to profile and optimize them. Those companies that focused on delivering that type of service from their HTS platforms have probably been more successful and satisfied than those that hoped HTS would be the bedrock for generating more drugs into their late-stage pipelines. The fact that the sister technologies to HTS—genomics, proteomics, and combinatorial chemistry—also largely failed to live up to their early promise, left some observers with a somewhat jaundiced perspective on the drug discovery revolution that was expected, but seemingly failed to materialize (6).

However, the stuttering performance of most pharmaceutical companies and their R&D engines, over the last decade, cannot be placed solely at the door of discovery organizations; regulatory tightening, pricing control, access, IP, and generics have all played their part in changing the landscape for pharmaceutical companies, making it even more difficult for them to be successful. However, it cannot be denied that R&D productivity has significantly declined over a period of time when investment in R&D has been at a historical high. The answer to why that should be is no doubt complex but several scenarios that most thought would occur over the last 10 years or so have not panned out as expected.

The prediction that the human genome project would greatly improve our understanding of human disease and unleash a tsunami of targets amenable for drug intervention has not yet come to pass. Human biology and our understanding of disease mechanisms are just as complex and difficult today as they were 20 years ago (7). We may have more technologies and techniques for probing and trying to understand disease pathways of interest, but our ability to fully predict successful outcomes through drug intervention are still highly limited. In fact, the genes of interest that have come out of the genome project are so novel that one could argue that they have added to the burden of optimizing and developing drugs. More resources are needed to develop a deep understanding of the biology underpinning these targets compared to the fast follow on approaches seen with well-validated mechanisms. Although, novel gene targets offer the chance for break through medicines and the opportunity to be first in class, they come with a very high risk of failure.

We have also not significantly improved our ability to predict whether a particular drug and molecular target will be effective in the clinic. Using animal disease models as a surrogate for human disease has been an important staple of the drug discovery process over many years. The drive to show correlation between animal data and human clinical data has had some success but not enough to allow you to buy down the risk of a late-stage clinical failure. Predictive biomarkers of efficacy have fared no better outside the well-published impact of biomarkers in clinical oncology; for example, HER2/neu and Herceptin.

When you add in the initial failure of combinatorial chemistry to deliver the huge increase in high-quality small molecules, one can begin to see why the R&D new world order has not yet arrived. Nevertheless, this technology did evolve by using parallel array methodologies to start to deliver very useful focused libraries.

So, does HTS deserve to be added to this list of technologies that did not deliver?

In reality, for some companies, HTS has proven to be a great success and in others it has been an abject failure (8). So, why do we see such different outcomes for a process and technology platform that is largely similar in most companies? That is the big question and no doubt the answer will not be a simple equation or solution, but I think there are a few good pointers to show the path to success.

I believe there are several major factors or observations that can determine the ultimate success or failure of any HTS operation.

KEEP CUSTOMER FOCUSED AND DON'T PROMISE WHAT YOU CAN'T DELIVER

One of the fundamental errors any HTS organization can make is to not know or understand who its customers are. This may seem obvious but there are several examples in the industry of HTS and/or technology support teams who have built enterprises that do not deliver what is actually needed by their discovery organizations. An essential step in preventing this is to ensure that HTS goals are completely aligned with the goals of the therapeutic area project teams they are supporting. This can include short-term goals such as the number of targets,

timelines, and level of support needed by the discovery projects during any particular year, as well as longer term goals such as ensuring the compound deck has a deep supply of diverse structures against targets and target classes that are of current and future interest to therapeutic area teams. It is also very important to understand, up front, the major milestones for the project being supported. Those projects that are in backup mode can have a very different set of priorities and expectations than a program just starting out. Making sure that high priority targets are screened with speed and quality almost always aligns with the goals of the therapeutic area customer.

STANDARDIZE, INTEGRATE, AND ELIMINATE WASTE

Cost-disciplined science has become a major reality for most HTS organizations over the last few years. As corporate compound collections have continued to increase along side the demand for screening, the cost burden of running a large HTS infrastructure has grown significantly. By aggressive implementation of automation, miniaturized screening formats, and waste management processes, several HTS groups have been able to increase their overall productivity while keeping their costs flat. Automation of the HTS process has also allowed the full-time employees (FTE) burden to be reduced considerably compared to 10 years ago. Modular functionality, parallel processes, and standard user interfaces along side the general standardization of work flows have greatly increased the flexibility of HTS. Once this type of flexible, standardized functionality has been put in place, the ability to offer customized services is greatly increased and can be done in a nondisruptive, cost-managed way. A fully integrated work flow from lead discovery through profiling and optimization is the best way to ensure success. Ensuring that work streams and capacity flows are matched in the lead discovery phase is a really important factor for integration and streamlined operations. Keeping HTS capacity aligned with the growth in the compound deck, or vice versa, is a basic example of this impedance matching and integration.

However, global scalability and seamless integration of a process do not naturally go hand in hand and can be incredibly difficult, if not impossible to achieve. In this type of scenario, it is critical to have strongly, aligned leadership around the accountability and role of the HTS function.

For those large global companies that have tried to centralize and standardize their HTS operations, they have hit problems of scalability and lack of integration. In these situations, trying to deliver a rapid, high-quality service that fits the needs of every therapeutic area and project team is challenging at best. This has led several large companies to look at how they operate their R&D processes and to find ways of becoming more innovative and flexible. Breaking down large organizations into smaller, more nimble, and entrepreneurial units is one strategy being employed to reduce the burden of keeping large discovery units. Another approach, employed at Bristol-Myers Squibb is to use a centralized, fully accountable base organization that is able to standardize all the lead discovery and optimization platforms and have them "exported" to the other sites in a federated fashion. This has the benefit of local therapeutic area proximity and decision making plus global standardization and elimination of duplicated efforts.