Whither high-throughput screening?

'...today's HTS will become the fulcrum that fully leverages genomics in drug discovery'

▼ In this supplement to *Drug Discovery Today*, HTS takes center-stage in the process of discovering new drugs. This appearance in the spotlight is neither uncommon nor surprising, because drug discovery today is under enormous pressure to improve efficiencies, while remaining largely an empirical science. Today, HTS provides the efficient empiricism required to alleviate at least some of the pressure.

But, as skeptics have been known to ask, where has screening been a proven success? As many breakthrough drugs have been discovered serendipitously, it is difficult to correlate improvements in efficiency with agreed-on and quantitative outcomes, such as the number of new drugs appearing on the market. Let us rephrase the skeptic's question in a more measurable way by asking, 'Had today's screening technologies been available in the mid-1980s when today's breakthroughs were first discovered, would the timeline of discovery have been shorter?' If we look closely at the nine breakthrough pharmaceuticals introduced in 1999 (Ref. 1), the origins of at least six of these (66%) can be unequivocally traced back to the use of screening techniques. So, even the skeptic must conclude that HTS is a proven, effective technique for drug discovery.

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HTS in the future

Today, HTS is a valuable technology, but what does the future hold for it? Several trends in screening are evident, through from miniaturization (uHTS) to functional assays (primarily cell-based assays) to increasing the quantity of data generated from each well (increasing the content of the assay database by taking more measurements on every sample). A common requirement, which is addressed in this issue by Bryn Roberts (AstraZeneca, Macclesfield, UK), is informatics, applied to transform the extensive quantity of data that these new techniques are generating into useful information[2]. In pharmaceutical drug discovery, informatics is a science in its infancy, but it must mature rapidly. Today, the data-intensive pursuit of genomics and pharmacogenomics is leading to an information-driven consolidation of technology for target identification and validation, just upstream of HTS. To accommodate this growing number of targets, scientists engaged in HTS must ascend the learning curve rapidly. This HTS supplement will highlight to many readers the particular aspects of this evolution. However, the broad picture that emerges from this metamorphosis is even more compelling. These 'islands' of knowledge are becoming integrated into an increasingly efficient system that converts validated targets suggested by genomic data into lead compounds that can be used to further validate the target in a functional setting.

In foretelling this next technological trend, many companies have begun to recite the mantra 'gene to lead'. The successful acceleration of this process is essential, not only to the companies that claim to enable such acceleration, but also for the entire pharmaceutical discovery industry. In identifying this need, it is important to appreciate that effective communication between scientists (increasingly, through Web-based systems) must drive this fusion. The sources of data and technology (sequence databases, instrument manufacturers and service providers) and the users of technology (the scientists at biotechnology and pharmaceutical companies that are involved in bringing new lead molecules onto the market) must communicate more effectively. Simply collecting and controlling the data is not sufficient: improved communication, both through and with external providers, will come with some perceived loss of privacy, but a more vital and productive industry will emerge.

Another often-recited phrase is 'fail early', which recognizes that there is a certain inevitable failure rate in drug discovery and, to control rising costs, failures must occur earlier in the process. Even describing the termination of a discovery project as a 'failure' is unfortunate, as identifying problematic leads (with, for example, ADME/tox issues) earlier in their life cycle represents a crucial success in conserving valuable time and money that might otherwise be wasted on an ultimately unmarketable drug. Such early identification requires starting with more and higher-quality lead compounds, as well as improved informatics.

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Notably, these aspects are essential for HTS (or for what HTS is becoming). Many advances, such as improved pharmacological modeling, or more effectively designed or selected libraries for screening, will play important roles in moving the decision points to earlier in the process.

The changing role of HTS

As HTS or, more generally, the synergy of chemistry, biology, engineering and informatics for lead discovery, progresses into the 21st century, a consolidation of technologies that requires not only effective innovation, but also implementation, is both anticipated and possible. To maintain the phenomenal growth rate that the pharmaceutical industry has enjoyed over the past two decades, it has been estimated that the number of new chemical entities (NCEs) introduced per year must triple[3].

Taken together, both the opportunity and the motive will compel the future of drug discovery. In the coming years, even more than the current 66% of breakthroughs will be seen to come from screening, as better lead compounds will be identified earlier, enabling the more timely validation of both targets and their associated leads in a clinical setting. In this way, today's HTS will become the fulcrum that fully leverages genomics in drug discovery.

References

1 PhRMA Report (2000) *New Drug Approvals in 1999*, http://www.phrma.org/pdf/charts/nda99.pdf

2 Roberts, B.R. (2000) Screening informatics: adding value with meta-data structures and visualization tools. *Drug Discovery Today: HTS suppl.* 1, 10–14

3 Drews, J. (1996) *Innovation Deficit in the Pharmaceutical Industry*, Drug Information Association