



The complexity, diversity and number of disease targets screened at high throughput screening (HTS) laboratories are increasing. **William Downey**, pharmaceutical business consultant, examines how much the targets are increasing and why directors must expand the capabilities of their HTS laboratories.

HIT THE TARGET

HighTech Business Decisions published a study of high-throughput laboratories, asking HTS directors about the number of molecular targets they screened in 2007 and expected to screen in 2008, as well as the types of targets used. In total, 46 HTS directors estimated that their laboratories will screen 867 molecular targets in 2008. In addition, the HTS directors reported that protein kinases and GPCRs were the most prevalently screened target types in 2006.

Many of the HTS directors said there was an increasing diversity in the types of targets screened. Overall, considering the number of leads produced through HTS screening operations, laboratories that screen a more diversified set of targets reported a higher than average lead generation.

Background

For this study, the respondents were divided into three segments based on throughput: high-throughput labs (HTP), medium-throughput labs (MTP), and non-commercial laboratories at academic centres or government organisations (NCL). The HTP group had an average weekly throughput that involved the reading of 100,000 wells or more per week. This group contained 37 HTS laboratories.

Laboratories in the MTP group have an average weekly throughput that involved the reading of fewer than 100,000

wells per week. There are 17 HTS laboratories in this category. In addition, 13 HTS non-commercial laboratories also took part. These respondents showed a wide range of throughputs from a low of 2,500 to a high of 100,000 wells read per week.

KEY STUDY FINDINGS

- 586 molecular targets were screened in 2006.
- The most popular targets were protein kinases at 23%.
- By 2009, the diversity of other targets screened will increase to 25%.

Number of molecular targets

The HTS directors reported 586 molecular targets screened in 2006. On average, 53 laboratories screened 13 molecular targets compared with an average of 16 molecular targets in 2004. While most of HTS laboratories expected an increased number of targets to screen, 17 expected to screen fewer targets, and in certain cases, no targets. The reasons cited for screening fewer targets included closure of HTS laboratories, consolidation of efforts and changes in strategy.

Contributor profile



William Downey is president and managing director of HighTech Business Decisions, a consulting and market research firm specialising in public and private market research in biotechnology and pharmaceuticals. Its comprehensive report *High Throughput Screening 2007: New Strategies, Success Rates, and Use of Enabling Technologies* was published in December 2007.



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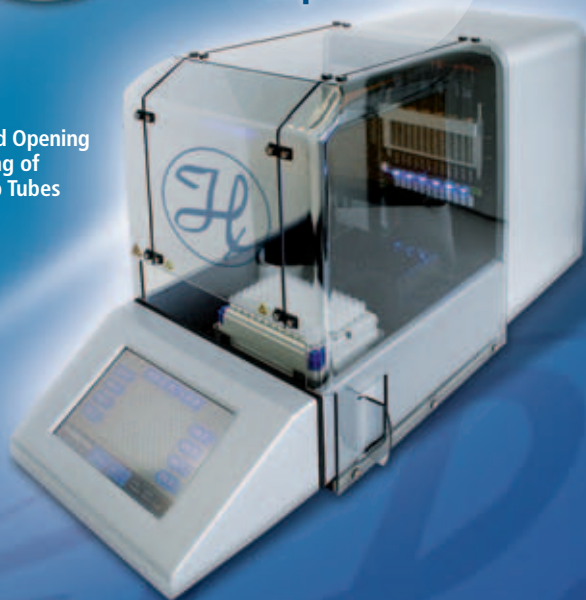
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HTS directors who reported a change in strategy pointed out that their HTS laboratories will screen fewer targets because they will focus on getting high quality leads from those targets screened. Four HTS laboratories report a decrease in the number of targets screened for 2007.

A comparison was made of the number of targets screened by throughput segment (Figure 1). While each HTS segment shows an increase in the number of targets screened per year, the non-commercial laboratories expect the highest growth.

Targets screened

HTS directors reported the types of targets they screened and provided details of their future expectations. A summary of the most popular target types in 2007 is shown in Figure 2. Protein kinases represent the largest target class screened, with an average of 23% used among 53 respondents. After protein kinases, the HTS directors reported a high average use of GPCRs, other enzymes and ion channels. In addition, several HTS directors mentioned the increasing use of cell-based assays and high content screening in the future.

The diversity of targets is increasing, as HTS directors expect that 'other targets' will make up almost one quarter of their targets, on average, by 2009. Those HTS directors that did not provide data for 2006 suggested that the target types provided by therapeutic groups vary dramatically year to year and they could not predict these shifts in target types.

To emphasise the shift in use of target types, a comparison of the use of major target types used by the HTP group in 2007 and 2009 is shown in Figure 3. In addition, a comparison of the use of major target types by the MTP group in 2007 and 2009 is shown in Figure 4. These figures show the HTP group mainly screens GPCR and kinase targets. This group and the MTP group expect to use fewer kinase targets in 2009. Both groups expect to use the same or slightly more GPCR targets. However, GPCR and kinase targets will remain the most prevalently used targets for both groups in 2009. In general, non-commercial laboratories reported using 'other' target types most often, followed by kinase assays.

During the discussion regarding the number of targets screened, some respondents explained the growth in the diversity of molecular targets.

'Ion channels will be an area of growth, driven by our increasing knowledge about them and the growing number of ways to look at them in HTS fashion,' said one pharmaceutical HTS laboratory director.

'GPCRs, ion channels, kinases and metabolic enzymes will all remain strong,' said another HTS director. 'In addition, we also look at proteases, TNF and transporters. Transporters are of interests for derisking early clearance of molecules and understanding the bioavailability and distribution of endogenous or exogenous molecules.'

Figure 1. Average number of molecular targets screened per laboratory by throughput group.

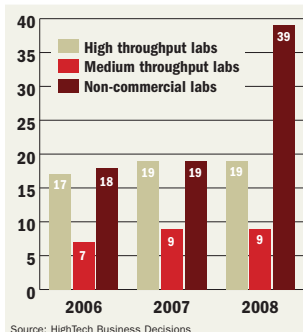
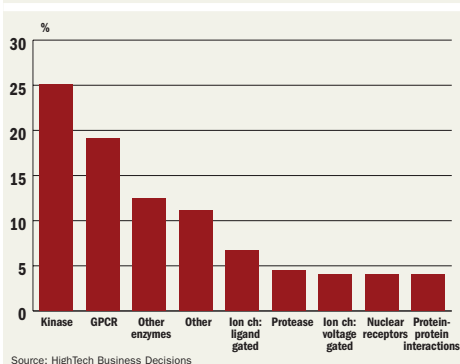


Figure 2. Summary of percentage use of popular target types in 2007: all respondents.



operations, and the age of their operation. In this study, the HTS directors provided the percentage of total wells screened by target type. The HTS labs are grouped into three categories based on the mix of target types used to screen wells: high diversity, medium diversity or low diversity.

HTS laboratories in the high diversity group use their most prevalent molecular target class for less than one third of the total wells read for the year. The HTS laboratories in the medium diversity group use their most prevalent molecular target class between one third and two thirds of the total wells read for the year. While laboratories in the low diversity

group use their most prevalent molecular target class for more than two thirds of the total wells read for the year.

The average number of leads generated from the HTS laboratories was 20 in 2006. High diversity or medium diversity HTS laboratories on average generated more leads than those HTS laboratories that ran a lower set of targets. Even considering the age of the HTS laboratory, those HTS laboratories that screen a diverse set of target classes report on average more leads.

Road to complexity

Summarising the diversity of targets, one HTS director said that the main growth area would involve expanding to targets less traditionally thought of as drugable by small molecules.

‘The big thing in cancer therapy is kinase inhibitors, but in a few years, some company will have screened all the therapeutically relevant kinases,’ he stated. ‘Kinases were the easy fruits – that is you could run 50 kinase screens in two years, but there are other interesting classes of targets, for example, other enzyme classes, chaperonins and protein-protein interactions. The feasibility of targeting protein-protein interactions will increase through advances in technology and in understanding the interactions.’

The increasing complexity and diversity of disease targets

‘There are many ion channels and GPCRs that will be validated as time goes on,’ added a third HTS director. ‘Even though much effort has gone into targeting kinases, there is still a lot that can be done. Protein-protein interactions, especially those with lipid-dependent interactions, are where we are going to put some effort, even though it’s difficult to develop a primary assay for some of them.’

Diversity of targets versus leads generated

Following the analysis of major target types used by the HTS laboratories, the directors provided the number of leads generated from their laboratory in 2006. While the definition of a lead varies widely, for this study it was defined as, ‘a hit confirmed by more than one assay in vitro, and if possible in vivo, in a manner that shows biologically relevant activity that correlates to the target. To be a lead, the compound must show evidence of a structure-activity relationship between the compound and the target.’

The average number of leads generated in 2006 by the HTS laboratories is 20. As expected, larger laboratories generate more leads than smaller laboratories. The HTP group discovered an average of 26 leads in 2006. In contrast, the MTP group discovered an average of 11 leads in 2006.

The HTS laboratories were categorised by the diversity in the number of different types of targets screened in their

Figure 3. Use of major target types for 2007 and 2009: HTP screening group.

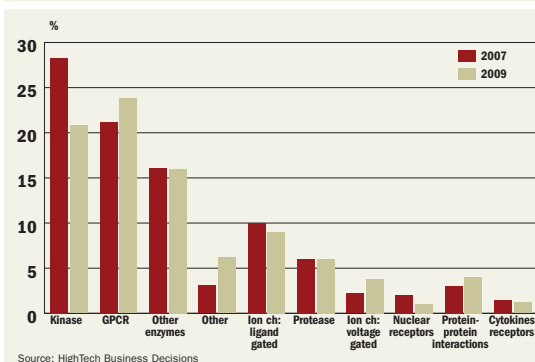
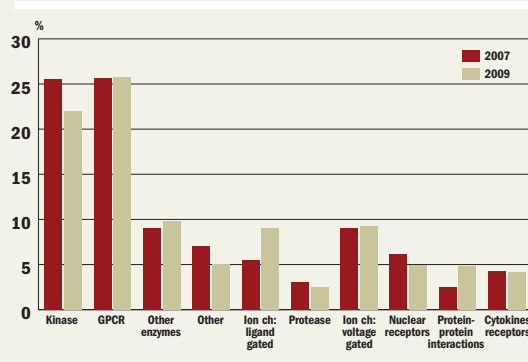


Figure 4. Use of major target types for 2007 and 2009: MTP screening group.



screened at HTS laboratories worldwide require that HTS laboratories not only have state-of-the-art equipment and a strong skill base, but also a high degree of flexibility. HTS laboratories are migrating to more complex and diverse targets for lead discovery. **WPF**