High-throughput screening brings in the crops

Screening is the acknowledgement of ignorance. Such a provocative statement might not amuse our community and, in fact, an incredible quantity of knowledge does go into each screen. However, from a structural point of view, screening is where serendipity meets prediction.

▼ Most of the screens performed in industry involve an encounter between a known target molecule and a series of chemical compounds in order to identify a hit, which is nothing more than a structural match. In a screen, the plethora of molecular interactions is tested simultaneously, but only the net result is usually observed by the scientist. Dynamic events, separation into ionic and non-ionic interactions and indirect effects of the respective molecular environment remain camouflaged under a sole signal identified by the reader. Hence, in the past, the predictive power of screens has been limited.

However, improvements are on the way: the protein structure database is growing exponentially*; the resolution of chemical space is improving; a variety of devices detecting the different nature of molecular interactions is appearing, and the number of success stories is increasing. Often, Mother Nature has been the best guide: most of the screening – evolution – had already been done before the design of new insulins, the development of peptidic antagonists stemming from the natural ligand, or the exploitation of RGD motifs in drug discovery. Iterative crystallization of target/compound pairs, meanwhile, has also achieved several 'home-runs' (e.g. HIV protease, interleukin-1-β-converting enzyme, carboanhydrase), thereby increasing the level of independence from physiological interactions. Series of focussed chemical libraries used in high-throughput screening (HTS) already balance the 'millions-of-compounds' approach when it comes to a structurally well known target class or hit optimization. Molecular interactions are now increasingly observed on a molecular level and on- and off-rates are becoming part of primary screens. The concurrent recording of several detection modes at the same time, from the same well, increases the resolution of information obtained and verifies it by immediately cross-checking the results[1].

To utilize the predictive power of such information, the appropriate interpretation has to be in place. This comprises a successful combination of statistics, visualization, databases and models – all of which are heavily developed in academia and industry. Again, the driving force here is efficiency because, despite the ever-increasing throughput numbers, the most time- and cost-effective way to create a drug is immediate and successful prediction based on solid information.

So, will that determine the fate of screening? Just the opposite. We have not even completely arrived at the most simplistic level of predicting the molecular interactions between a structurally known protein and a compound, although good progress has been made in ensuring short turn-around times in compound synthesis and screening. Already, however, the next level of complexity – a structurally unknown target – leaves us with little option but screening to generate knowledge. Not to speak of cellular target screens, reporter assays, biological specificity issues or absorption, distribution, metabolism and excretion (ADME) tests like the blood–brain-barrier passage. It is the assay design, in combination with the respective screening platform, where information is accumulated through a thoughtful combination of molecular biology, protein chemistry, library design and interpretation of the obtained data.

HTS is not challenged by rational drug design – the former is feeding the latter, whereas the latter is reshaping and continuously rejuvenating the former. Good *et al.* describe a good example of this approach in this supplement. The harvest is on, and HTS is reaping the crops.

* See the latest version of the PDB database, Stony Brooks.

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Reference

1 Haupts, U. *et al.* (2000) Macroscopic versus microscopic fluorescence techniques in (ultra)-high-throughput screening. *Drug Discov. Today* 5 (Suppl. *High-throughput Screening*), 3–9

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