How many leads from HTS?

'How many leads have we got from combinatorial chemistry and high-throughput screening so far? – none!'

At the recent Cambridge Healthtech Institute meeting on *High-throughput technologies* held in Washington (DC, USA) on 3–5 May 1999, the audience was asked an apparently simple question during a concluding panel discussion: for those of you who work in large pharmaceutical companies, how many leads have you got from combinatorial chemistry (CC) and high-throughput screening (HTS) so far? Surprisingly, all the represented companies gave the same answer, none. They all agreed that it was possible to obtain hits, but that there was little chance of obtaining any leads, as all successful optimizations so far have been obtained through classical medicinal chemistry.

It might therefore be asked whether the tremendous investment worldwide in CC/HTS has been justified by the results. So far, the answer appears to be no, although, with some CC design strategies, this might not be so surprising. After all, it can be surmised that when trying to find a needle in a haystack, the best strategy might not be to increase the size of the haystack. I have heard that if the 'drug universe' included all the possible drug-like molecules, its size would be 10^{62} molecules (other authors have proposed 10^{200}). Even if half of the currently known chemicals were drugs (a very optimistic assumption), this would produce 10^{7} molecules. Therefore, at most, only 10^{-53}% of the possible drug-like molecules are known. Possibly naively, I believe that by relying on a relatively biased random procedure to discover new blockbusters in such a universe, there should be little surprise if it does not work. Furthermore, HTS strategies are geared to increasing the number of compounds per plate to increase the number of screens per day, and the same common sense tells me that this exponential race is leading nowhere.

This is why, of course, there is so much effort being put into discovering a more rational design for chemical libraries in terms of, for example, diversity analysis, drug-like behaviour and reagent selection. The size of the problem makes it obvious to me that efficient drug discovery today will rely mainly on computational methods. However, it still could be asked why so few computational drug discovery companies are considered by the large pharmaceutical companies as serious alternatives to essentially brute force techniques, and why there is so little logical design in such a large number of commercially available libraries. One point of view is that many so-called drug discovery technologies are overstated in their effectiveness. I actually think that there are perhaps less than ten effective drug discovery companies worldwide and, incidentally, most of them were in the same room at that meeting in Washington. This is not to say that combinatorial processes are leading companies in the wrong direction, but rather that they could be much more useful if they were used in a truly rational way through appropriate computational drug discovery techniques, hence adding biological knowledge to simple hits.

To our company, this means three things. Firstly, at the design level, the only information required is the molecules sharing a given activity and their most similar analogues that do not exhibit this activity, which can be provided by combinatorial chemistry hits or by known drugs. As all the information resides in these molecules, there is no need to know the receptor or the mechanism of action. After all, if the receptor can discriminate between active and inactive molecules, a computational process should be able to do it, and such a process could be thought of as 'virtual receptor' screening.

Secondly, knowledge of how this information can be extracted is also required. Provided that the molecules are described in a 'proper' way, this is a data-mining problem. To me, 'proper' means not being driven by artificial conventions such as 'this part of the molecule is the scaffold, that one is a substituent', or 'these three substituents should make a pharmacophore'. Such conventions have their origin in the history of chemistry and are there to make chemical representation simpler to humans. One should not presume that certain atoms in molecules have less weight than others for hypothetical (if not aesthetical) reasons. Why not leave this weighting to an objective calculation?

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Finally, once the model has been obtained, combinatorial libraries are useful to provide real molecules, but they should be screened in their virtual form before synthesizing anything. If the model is good (i.e. robust, validated, predictive as objectively defined by 'good statistical practices'), then the screening process involves calculating descriptors for all available drug-like libraries, applying the model to these numbers and retaining only those virtual molecules that match the model. Only then should the best virtual molecules be synthesized and tested.

As Alan Walton said, the objective of biotechnology is to help the pharmaceutical industry to make better drugs faster and cheaper. He added that, to him, the old drug discovery company comprised 150 employees, had a $20 million-per-year burn-rate and a null return on investment (ROI) after four years. By contrast, the new (computational) drug discovery company comprises 30 employees and ten computers, has a $3 million-per-year burn-rate with a 60% ROI. This is just another way to define the right strategy and to get plenty of leads from what could be termed 'knowledge-based combinatorial chemistry'.

Roger Lahana

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