Who wants to be irrational?

‘A fat cat can’t run, a lean one is fit to succeed’

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Screening the Sahara desert to get one given atom of one given grain of sand would be a small task in comparison to screening all the potential drug-like (not to mention lead-like) compounds to identify every possible drug. Indeed, the brute force approach has not delivered thus far, at least with regard to the enormous investments over the last decade in automating synthesis and screening facilities. However, in a growing number of companies, combinatorial chemistry and HTS interact with rational design techniques to make the drug discovery process less of a gamble and more of a scientific approach. The question is how to screen ‘better’ rather than ‘more’.

High-throughput technologies

High-throughput technologies (HTT) are now a commodity in the pharmaceutical industry and, thus, questioning their performance should be regarded as prudent, not sacrilegious. During a laboratory automation conference (LabAutomation 2002, Palm Springs, 27–31 January), some contemptuous comments were made by HT managers working in big pharma, when it was radically suggested that rational design could be helpful in conjunction with HT technologies. The most interesting responses were: ‘the reason why we’re screening big libraries is because we can’ and ‘we don’t care about design, we screen everything we can’.

If this is their true intention, it will keep them busy for eons. Several estimations of the total number of drug-like molecules that could possibly be envisaged have been published and proposed numbers are anywhere between 10^{20} and 10^{80}. To get a sense of the enormity of these numbers, it might be helpful to know that there are 10^{20} atoms in one grain of salt and 10^{80} atoms in the whole known universe!

Inevitably, high-throughput technologies (HTT) have improved over time, but how is this progress measured? Should it be the number of leads obtained by HTS? This number is around 1 in 100,000 today, much better than four years ago [1], but not what one could call a real breakthrough. The key measure is the impact of HTT, not on lead generation, but on new drug approvals (NDAs). One must admit that, so far, there is no visible impact on this front: while R&D expenditures have grown exponentially over the past 30 years (PhRMA Annual Survey 2002), the number of NDAs has been almost constant, actually decreasing for the 7th year in a row, with 2002 being an absolute low [only 18 NDAs by the FDA and 13 by the EMEA (http://www.fda.gov and http://www.emea.eu.int)]. Actually, the decline in small molecule NDAs is even more acute, as recombinant therapies are comprising an ever-increasing proportion of these NDAs. Several explanations for this concerning observation have been proposed: targets are more difficult to identify, regulatory administrations are more demanding and HTTs have not been used for long enough to deliver yet. These arguments are certainly valid and, like my respected HTT colleagues, I believe that the right technologies are available and that their use is continuously improving, but we should also be aware of the detrimental organizational aspects.

An organizational issue

Paul Janssen, founder of Janssen Pharmaceutical, and one of the great drug discoverers, wrote in 1980 that ‘if society really wants its essential health needs to be met quickly and fully, it should try to create a proper motivating climate in which creative drug research and development is likely to prosper’ [2]. At a recent meeting, Janssen discussed his disappointment that the situation today could still be described with those exact same words.

One source of such organizational underperformance is the compartmentalization of teams in charge of using these otherwise efficient technologies. This is illustrated by the fact that HTS personnel are commonly rewarded for productivity, rather than hit rate or hit quality. Consequently, the HTS team has the sole mission of screening at the highest possible throughput, and nothing else matters. Library design? Not concerned. Hits? That’s up to the combichem team. Hits to leads? Talk to the medchem team. New drugs? Not in this building. This ‘somebody else’s problem’ attitude can be enough, by itself, to nurture the numbers game strategy – and its failure. Another drawback is the dilution of the authorship of an

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eventual drug reaching the market – who really discovered it? Those who designed the library? Those who synthesized it? Those who screened it? Or those who built on certain hits to get the one lead with a future? No surprise if motivation is low in such organisations.

An obvious alternative is transversal project management, with multi-disciplinary teams sharing a common objective. A good illustration of this type of inter-team communication in big pharma is given by Simon McDonald [3], who outlines that, in this organizational model, hierarchy and seniority are irrelevant, only efficiency counts. To some extent, a project team can be compared to a small start-up company focused on only one project: everyone is concerned for the outcome, there is no internal competition, no finger pointing when things go wrong (if something fails, it does not mean that somebody has failed) and last, but not least, a mutual interest and trust regardless of whether the project is in its highs or its lows.

Choosing the right lead

Another central issue, besides that of the organization, is what to screen. A thorough design plan, with close interaction between chemists and biologists, can improve the hit rate and hit quality enormously, while reducing the size of libraries. Rational design enables the consideration of not only physicochemical or structural descriptors, but also practical aspects, such as, synthetic feasibility, cost of goods, process automation, and so on. Why screen tens of thousands of poorly (if at all) targeted compounds when a design plan can span an appropriate activity space with only a few hundred? Of course, this argument is more appealing to small companies than to large ones: hence, the increasing number of successes of the rational strategy coming mainly from small to medium biotech companies.

Agenerase® is one example of such a success, as is RDP58, a compound that was designed for Sangstat (http://www.sangstat.com) by Syntem (http://www.syntem.com) in 1997 and which has just successfully demonstrated its activity in Phase II on inflammatory bowel disease. From only 19 compounds previously tested by Sangstat, a virtual library of less than 300,000 virtual molecules was designed, of which just five compounds were selected, synthesized and screened, four of them being active – amongst which was RDP58. This low-throughput screening, was highly successful and inevitably, has lead to new long-term contracts for other indications. However, a five-compound library with an 80% hit rate is obviously an unusual case, with a more typical smart (i.e. designed) library usually containing no more than a few hundred compounds and resulting in a double digit hit rate.

A universal concept

So, who wants to be irrational? Small companies have no choice but to be efficient or to perish, and this is a possible reason for the increasing numbers of investigational new drugs and NDAs from biotech companies. A fat cat can't run, a lean one is fit to succeed. Interestingly, the successful big pharma are those who also have a flexible, project-oriented organization – strategies that work for small companies can also be useful to their larger counterparts. Could this be the 'cheaper-faster-better' dream come true?

References

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