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Trust me – I'm a doctor! ▼

A pertinent article by Tim Peakman *et al.* [1] suggests the transfer of manufacturing techniques into discovery to improve the use of HTS capacity, enhance overall discovery capabilities and, thereby, cure the ailing pharmaceutical patient. The authors' promise of a panacea via planning and scheduling techniques sounds attractive – but can it really transform the world of drug discovery?

Risking the wrath of the technology fans, let me nevertheless present some alternative views. After all, Western manufacturing continued to ail for years, despite a plethora of techniques ranging from Japanese-style 'just-in-time' management to Western solutions, such as material requirement planning [2]. Such 'production line' improvements required significant cultural and structural changes, together with sustained investment and top management support, to become effective. Although Peakman *et al.* argue that their approach aims to leverage, rather than remove innovation, if pushed to the extreme, such methods could well cause scientists to vote with their feet. What is more, at least to my knowledge, no production line in the world, no matter how efficient it was, has ever invented anything. That is the domain of R&D, where processes are intrinsically more individualistic, innovative and unpredictable, even in manufacturing R&D departments.

So, should discovery swallow such a bitter (and expensive) pill to improve its health in the long-term, despite potential undesirable side effects? In fact, it is difficult to choose which pill, because the unfortunate patient has by now been provided with a bewildering range of cures. Some are based on bigger haystacks, assuming the science of drug discovery follows the principle of random motions and that by screening many targets against many compounds more drugs will emerge at the other end.

These, of course, would play to Peakman *et al.*'s proposal. The caveat is that, so far, random screening has led to many shiny gadgets in laboratories, which impress unsuspecting visitors, but has done little to increase the ability of R&D to produce drugs. Yes, it has yielded more lead compounds for discovery but many turned out to have even less chance of surviving R&D than more traditional approaches. Yet, it is largely the failure rates that make R&D so costly. Not taking advantage of the capacity of HTS, no matter what the cause, pales into insignificance compared to the costs of late-stage development failure. Thus, the patient's fever will not break, unless we increase compound survival rates.

The authors suggest that large-scale *in vitro* profiling *à la* HTS, before entering development, could help. Of course, this approach can be useful in discarding the worst compounds. But how much does such a random approach, no matter how integrated into the rest of the discovery processes, help us weigh the die towards success? I would submit that it can only take us some of the way. To go beyond, we need brains – not brawn – and we also need to design better molecules against better targets. But how do we know what is better?

It is a real pity that few opinion makers take the trouble of making a trip back into history to analyze what made the pharmaceutical patient so healthy in the past. Yes, the future might be different from the past but it is a fact that most of the major drug classes [3] were brought to market before 1995. That is well before HTS started to become the medicine for all pharmaceutical woes. In this deprived, HTS-less era, drug discoverers had to improve existing imperfect drugs and natural compounds by rational design, or exploit chance events such as iproniazid's unexpected mood elevating effects in tuberculosis patients, which gave rise to tricyclic antidepressants. Both routes yielded many successful drugs.

Such trips into the past, and our HTS experience so far, could provide opportunities to improve drug discovery and reduce failure rates. For instance, the concept of 'druggable' targets was derived mostly from HTS failures; lead properties became an issue as medicinal chemists struggled to convert lipophilic brick-dust into drugs – and failed. The rule-of-five [4] was derived subsequently from the properties of marketed drugs. So, in essence, we are still learning how to do HTS effectively, never mind efficiently. Few drugs on the market or in late development today are HTS-derived. Even Gleevec, a recently approved

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kinase inhibitor for cancer [5], has come out of subset screening rather than full HTS, making the use of HTS capacity a moot point. Unfortunately, we can not go back to the world of pure rational design because we need more leads than the old paradigm alone can provide. So, like addicts, we can no longer live without HTS, but we can not afford to live with it in its current form.

The question is, to be more successful does HTS need to be scheduled and more integrated into discovery processes? I suggest the effort is better spent in applying historically successful concepts of rational drug design to HTS, and worry about capacity and integration issues at a later stage. So, the idea is to do the right projects correctly, to concentrate on the science, and the ailing big pharma patient will soon be back in glowing health. That is, if you trust the doctor!

References

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Esther F. Schmid
Research Strategic Planning
Sandwich Laboratories
Pfizer Global Research and Development
Sandwich, Kent, UK CT13 9NJ

Targeting structured nucleic acids with antisense agents

During the past 20 years, the development of novel gene-targeting antisense agents have almost exclusively been evaluated on the basis of thermal denaturation measurements for T_m determination of hybrids (duplexes) with short RNA or, more often, DNA targets. This is despite the fact that many biological targets might adopt secondary and tertiary structures and a simple T_m determination does not necessarily reflect the thermodynamic (and kinetic) situation at a physiologically relevant temperature (37°C). Undoubtedly, this situation reflects the ease by which T_m values could be obtained and the much more elaborate studies that are required for a thermodynamic/kinetic description of the system.

The importance of investing the effort in thermodynamic/kinetic evaluations is convincingly demonstrated by recent work on peptide nucleic acids (PNAs), as reviewed by Armitage in a recent issue of *Drug Discovery Today* [1].

The most illustrative example is probably the efficient hybridization of a PNA oligomer to a DNA hairpin despite the fact that the thermal stability (T_m) of the hairpin is dramatically higher (>50°C) than the T_m of the resulting PNA–DNA duplex. Obviously, this is only possible because of the vastly different temperature dependence of ΔG (e.g. via different ΔS terms) stressing the need for actually determining these parameters.

Why not just avoid structured targets in biological targeting? Because structured targets, such as quadruplexes in DNA and hairpins and pseudoknots in RNA, are often biological recognition elements or switches, and the disruption of these structures could indeed elicit warranted biological and/or therapeutic effects. The Tat-binding Tar-element in HIV RNA is a notable example of a medicinally relevant RNA hairpin that has been successfully targeted by a variety of oligonucleotide derivatives. However, in this case, a thorough thermodynamic/kinetic analysis that could help to understand the results and thus to design better agents is lacking.

It is, therefore, most welcome and highly overdue that much more focus is put on detailed studies and understanding of the interactions of gene targeting 'oligonucleotide' agents with well-defined, structured DNA and RNA targets and the biological consequences of such targeting. The studies reviewed by Armitage are the first small steps along this road, and many more are encouraged.

Reference

1 Armitage, B.A. (2003) The impact of nucleic acid secondary structure on PNA hybridization. *Drug Discov. Today* 8, 222–228

Peter Nielsen
University of Copenhagen
Copenhagen
Denmark

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