The *Discussion Forum* provides a medium for airing your views on any issues related to the pharmaceutical industry and obtaining feedback and discussion on these views from others in the field. You can discuss issues that get you hot under the collar, practical problems at the bench, recently published literature, or just something bizarre or humorous that you wish to share. Publication of letters in this section is subject to editorial discretion and company-promotional letters will be rejected immediately. Furthermore, the views provided are those of the authors and are not intended to represent the views of the companies they work for. Moreover, these views do not reflect those of Elsevier, *Drug Discovery Today* or its editorial team. Please submit all letters to Rebecca Lawrence, News & Features Editor, *Drug Discovery Today*, e-mail: Rebecca.Lawrence@current-trends.com

Computational approaches in the post-genomic era – how will we cope? ▼

The post-genomic era is not in the distant future anymore. The expected number of new targets at our doorstep is in the region of 10,000. In the past, structure-based design computational techniques have proven to be successful, leading to major marketed drugs such as Losartan (Merck) or, more recently, Agenerase (Vertex). However, the majority of these new targets have a yet unknown structure. Some possible strategies to face this issue could be to use the property-based design approach by restricting the calculated 'properties' to those that are conformation-independent (topological descriptors for instance) or to extensively improve the protein folding algorithms, to enable the production of relatively accurate 3D structures for new targets.

The property-based approach is the way we are favoring in my company and appears to be a successful technique that can be used throughout the drug discovery process, from library design to the prediction of novel bioactive compounds. Although this approach does have limitations, it has the advantage of being fully developed as well as the fact that it definitely works.

To my knowledge, there is still a long way to go to make the protein folding techniques not only more reliable but orders-of-magnitude faster. It must be remembered that the size of the problem is to unravel 10,000 new structures. This means that even if all the experts in the field could compute one new reliable structure per day, it would require an estimated 5 years of work full-time.

There are certainly other alternative methods such as moving from HTS to ultra-HTS to hyper-ultra-HTS to extra-hyper-ultra HTS. However, taking into account a conservative 10^{60} possible drug-like molecules to explore and an optimistic one million molecules screened per second, this exploration would require 10^{37} times the age of the universe (assuming there is enough matter in the universe). Similarly, if 'drug space' was represented by all the grains of sand in the Sahara desert, less than one atom of one grain would yet have been explored since the dawn of humanity.

What do you think we should do? What do you think are the right current approaches?

Roger Lahana
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Computational approaches in the post-genomic era – how will we cope? – Reply ▲

Response from Dennis Church

My own, admittedly biased, vision of small-molecule discovery in the post-genomic era hinges on the concept of identifying novel, drug-like molecules as cost effectively as possible. This is done through conducting computationally driven lead discovery campaigns that use state-of-the-art screening technologies for the testing of pharmaceutically relevant, focused compound collections.

The reasons for this view stem from the experience of others, as well as from our own at Serono. The first is mathematical, and is echoed in Roger Lahana's commentary. High-throughput screening (HTS) technologies have progressed remarkably, to such an extent that some laboratories can now test hundreds of thousands of compounds in record time, and are clearly identifying interesting molecules in the process. Nevertheless, strategies that rely solely on throughput for success have a major limitation, namely that posed by the huge number of molecules that must be synthesized and tested to be consistently successful across multiple target classes, not to mention the prohibitive cost associated with such efforts. Modern HTS technologies will certainly occupy a key position in the armory of techniques used in the future, but it is questionable whether these will contribute towards alleviating the chemical space issue, even when supplemented with diversity-based screening methods.

This brings me to what I feel is the main shortcoming of strategies that rely solely on throughput for success, namely, that these strategies do not adequately exploit the laws of probability that govern the likelihood of

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finding a hit. Indeed, it can be shown that the probability P(A) of identifying at least one active compound in any screen is related to the number of compounds in the collection being tested (n), as well as to the prevalence of biologically active molecules in the same said collection (π). In fact, the relationship is given by the equation $P(A) = 1-(1-\pi)^n$ which, on inspection, indicates that increasing n or π are equally effective at increasing P(A). As such, throughput-dependent strategies rely on large values of n for their success, without recognizing that augmenting π is as equally effective. The consequence of this one-sided choice is obvious when one considers that increasing throughput 100-fold is equivalent, in terms of augmenting P(A), to increasing π by two orders of magnitude. The first approach costs millions of dollars to implement, whilst the second can be achieved by acquiring a couple of hundred biologically active compounds at a fraction of the cost.

In view of this, I believe that post-genomic discovery groups will focus on the automated, high-throughput testing of rationally designed compound sets enriched with biologically active, drug-like molecules. As already mentioned, several techniques are already available for the design of such collections. Among these, property-based methods are well suited for use with targets of unknown structure, as they enable rapid, almost real-time data analyses to be performed, thereby permitting what can be termed 'rational, high-throughput lead discovery'.

Illustrating this concept, we have recently developed our own property-based technique for the prediction of biologically active molecules. Termed discrete substructural analysis (DSA), the method enables the identification of structural determinants that are most likely to be the basis of a given pharmacological effect. By incorporating DSA directly into our HTS process, we have identified numerous novel seven-transmembrane receptor antagonists, kinase inhibitors, ion channel modulators, protease inhibitors, phosphatase inhibitors and steroid receptor ligands, and this by testing fewer than 10,000 compounds on each target. Not only is the approach extremely cost eff ective, but doubling the throughput enables the doubling of the number of targets that can be investigated at the same time. As such, our projection is that property-based, computational approaches will play a major role in drug discovery in the future.

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Whither solid-phase chemistry?

Over the past few years, we have seen a considerable consolidation of combinatorial chemistry techniques within the pharmaceutical industry. It seems that very few companies now make and screen library compounds in mixtures. Instead, the productivity now readily available from automated synthesis is being widely applied to the production of single compounds. Simultaneously, as the focus has shifted to single compounds, there appears to be a move away from solid-phase techniques towards solution-phase methods as the preferred synthetic methodology. This shift is despite the considerable academic activity in developing new solid-phase synthetic methods. Is all their work now possibly redundant?

Are these trends universal across the industry, or are there still groups that see real value in using compound mixtures in lead discovery? Likewise, does solid-phase chemistry still offer any benefits when single compounds are being prepared?

Nick Terrett
Manager
Lead Discovery Technologies
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Collaborations…

Microcide Pharmaceuticals (Mountain View, CA, USA) has signed an agreement with **Schering Plough Animal Health** (Kenilworth, NJ, USA) for joint research to discover and develop new veterinary antimicrobial drugs. The research will focus on limiting the expulsion of antibiotics from bacterial cells through the use of Microcide's technology and knowledge of bacterial efflux pumps and other resistance mechanisms. Under the terms of the agreement, Microcide will receive payments over a two-year period and milestone and royalty payments on products emerging from the collaboration while Schering Plough Animal Health will retain worldwide rights to these products. 'In addition to working with others… we are planning to develop efflux pump inhibitor/antimicrobial combinations for our own account,' said Jim Rurka, President and CEO of Microcide.

Informax (Rockville, MD, USA) and the **Whitehead Institute for Biomedical Research** (Cambridge, MD, USA) have formed a strategic bioinformatics collaboration to advance their genomic research. Under the terms of the agreement, the Whitehead Institute has licensed Genomax™ from Informax to enhance Whitehead's expertise in computational methodologies, tools and approaches to high-throughput molecular biology research. In addition, a member of the Whitehead Institute will join the scientific advisory board of Informax.