DDT Vol. 7, No. 20 October 2002

Top of the form

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An unfashionable and often-overlooked part of the drug-development process is being revolutionized by a new start-up company. TransForm Pharmaceuticals (http://www.transformpharma.com/) is using high-throughput analytical tools and proprietary informatics approaches to breathe new life into what some would call an unglamorous area of R&D: drug form and formulation.

A sluggish discipline

As everyone in the industry knows, the drug discovery and development process can be tortuous, often taking more than a decade from target identification to drug approval. Somewhere in this pipeline, the form and formulation of a candidate drug must be considered. Various physical forms of the same drug are possible – for example, polymorphic crystal forms, salts, co-crystals, hydrates and solvates – and these can have widely different pharmaceutical properties. In addition, issues such as solubility, storage life and chemical and physical stability must be addressed in the formulation to ensure a drug is safe and effective. But the science of form and formulation has progressed little in comparison with other areas of R&D, and companies have been reluctant to devote resources to such studies. Typically, less than 20 form or formulation experiments are performed over a period of several months during the drug development process – hardly high-throughput! Additionally, these limited tests are normally carried out on drug leads after a good deal of R&D work has already been performed. If a suitable form and formulation cannot be found at this stage, much work will have been wasted.

Formulating changes

TransForm was spun out from Millennium Pharmaceuticals in 1999 to reinvent the

pharmaceutical industry's approach to form and formulation. According to TransForm, its tools can be applied across the entire life-cycle of a drug: from early discovery, right through to life-cycle management. In the early discovery stages, TransForm can provide its partners with rapid and comprehensive data about physical properties, which, when coupled with potency and selectivity data, enable medicinal chemists to select the best scaffolds and design the best molecules to move forward. At the preclinical stage, once a candidate has been selected, TransForm can readily discover the diverse potential solid forms of the drug, and select the best form for full-scale development. Selecting drugs with the right physicochemical properties at these stages will save much time and effort later in the process. Finally, TransForm's technology enables the reassessment of marketed products to identify untapped opportunities for performance improvements or more flexible dosing.

Although the details of TransForm's technology are confidential, a general outline has been made public. The proprietary CrystalMax™ platform is used for high-throughput crystal generation and is the key technology for rapidly identifying various forms of a compound. It is capable of running 20,000 crystallizations in parallel, using several crystallization methodologies. TransForm also has several other automated systems that it uses to test sub-milligram quantities of compounds for a broad range of parameters pertinent to formulation. The hardware is integrated by a sophisticated informatics system, which assists in the design of large, combinatorial experiments, and their robotic execution. The same software tracks and stores results as they come in, allowing data-mining and visualization at a later date. TransForm says it can use this technology to discover new, commercially useful forms of small-molecule drugs from all therapeutic categories, and superior liquid-based formulations of both small molecules and biologicals.

The company has validated its technology by discovering meaningful improvements for several marketed products and has several recent publications. In the first [1] they confirmed the existence of, and characterized, a previously theoretical third crystal form of acetaminophen. The second publication [2] demonstrated a molecular-level understanding of the mode of action of common anti-malarial drugs by identifying a quinolone-binding site on a malaria pigment crystal, potentially opening the door to novel methods of finding anti-malarial drugs.

Partners, platforms and products

In the past year, TransForm have signed multiyear deals with two major companies. The first, announced in June 2002, is with Alza Corporation (http://www.alza.com). Alza, a leader in drug delivery, recognized that it needed a way to improve the delivery of its drugs through the skin, but had no way to test the many possible formulation permutations quickly. TransForm is developing a high-throughput system to rapidly identify optimized formulations for Alza's transdermal delivery system, enabling 1536 different transdermal formulations to be tested in parallel.

 PII: S1359-6446(02)02487-X

The company also announced a second deal, this time with Eli Lilly and Co. (http://www.lilly.com). Lilly recognized that many of the more potent and selective leads emerging from discovery are also increasingly insoluble and difficult to turn into drugs. To address this problem, TransForm is performing hundreds of experiments within 2–3 week cycles on very small amounts of drug compound, to enable Lilly to select more 'developable' lead candidates. According to TransForm, both deals are ahead of schedule. Although other partnerships are being pursued, the strategy is to keep the number of deals small to ensure close collaboration.

Transform believes it has several advantages over other companies investigating form and formulation issues. According to Colin Gardner, TransForm's Chief Scientific Officer, the partnerships are only half the story. 'We're not just developing technology to sell it, ' he said, 'We're using it both to generate our own product opportunities as well as to make TransForm a partner of choice to pharmaceutical companies that are looking for an effective way to capture more of the intrinsic value of their proprietary pipeline.' In addition, Gardner believes that this two-pronged approach provides TransForm with more stability than start-up companies based solely on technology platforms, or whose early discovery efforts may not yield fruit for many years.

However, Ray Rowe (AstraZeneca UK), cautioned that this science is nothing new and that many companies have in-house high-throughput form and formulation systems, albeit on a smaller scale. Quoting American microscopist Walter McCrone [3], he said, '…every compound has different polymorphic forms and that, in general, the number of forms known for a given compound is proportional to the time and money spent in research on the compound.'

References

1 Peterson, M.L. *et al.* (2002) Iterative high-throughput polymorphism studies on acetaminophen and an experimentally derived structure for Form III. *J. Am. Chem. Soc.* DOI: 10.1021/ja020751w (available online at: http://pubs.acs.org/journals/jacsat)

2 Buller, R. *et al.* (2002) Quinolone binding site on malaria pigment crystal: a rational pathway for antimalarial drug design. *Cryst. Growth Des.* DOI: 10.1021/cg02550I (available online at: http://pubs.acs.org/journals/cgdefu/index.html)

3 McCrone, W.C. (1965) Polymorphism. In *Physics and Chemistry of the Organic Solid State.* (Vol. 2) (Fox, D. *et al.*, eds), pp. 726–767, Interscience

News in brief

Targets and mechanisms

Magnesium and calcium lower blood pressure independently

Scientists have revealed how magnesium can regulate blood pressure by activating ion channels in the cell membrane [1]. This new research, by scientists at Case Western Reserve University (CWRU: http://www.cwru.edu) can be used to help understand how magnesium decreases blood pressure, and also heart failure and stroke.

Jianmin Cui, lead researcher and Assistant Professor in the Department of Biomedical Engineering at CWRU, said: '…we have discovered that when magnesium is applied to calcium-activated potassium channels, these channels will open.'

Calcium-activated potassium channels are pathways in the cell membrane that relax smooth muscle in blood vessels, and also modify electrical impulses through nerve cells to the brain. This study used cloned ion channel DNA to express the channels in frog eggs. These large-conductance (BK type) channels are activated by membrane depolarization and intracellular levels of calcium and magnesium.

Various site-directed mutations were made and any functional changes were recorded; it was found that mutations that abolish the sensitivity to magnesium do not affect calcium sensitivity, and vice versa. This indicates that there are two distinct pathways for Mg^{2+}- and Ca^{2+}-dependent activation of BK-type channels.

Cui said, 'Our research is basic science, however, we hope that the results can help to explain why some treatments would work and provide rationale for development of new drugs for hypertension.'

1 Shi, J. *et al.* (2002) Mechanism of magnesium activation of calcium-activated potassium channels. *Nature* 418, 876–880

Caveolae: role in muscular dystrophy

Advances in understanding the tangled web of cell signalling might have implications for sufferers of a form of muscular dystrophy. Scientists at the University of Texas Southwestern Medical Center (http://www3.utsouthwestern.edu/) have published details of the composition of filaments found in caveolae – organelles that form a membrane system which contains cell-signalling molecules – and described how problems with formation of these filaments can lead to the muscle-wasting disease [2].

The researchers, headed by Richard G.W. Anderson, Chairman of Cell Biology at UT Southwestern, have uncovered the mechanism whereby a protein called caveolin, in conjunction with cholesterol, forms filaments on the inside surface of caveolae. Caveolae are important organelles that ensure signalling molecules are in the correct location for both intra- and inter-cell signalling. 'We believe that signal transduction is not an interaction that can take place anywhere in the cell,' said Anderson. 'Caveolae contain a whole array of signalling molecules, and their job is to spatially organize signal transduction at the cell surface.'

  PII: S1359-6446(02)02488-1