From targets to targeted treatment solutions



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'The industry can no longer depend on academia for much of its preliminary knowledge of diseases and targets…'

If it is to prosper over the next decade, the pharmaceutical industry will need to define diseases with considerably greater precision and overcome its wariness of biologics [including proteins, monoclonal antibodies (mAbs), mAb fragments, peptides and antisense RNA], the two key criteria required to produce healthcare packages for patients with particular disease subtypes, or targeted treatment solutions [1]. Several companies have already adopted a disease-centric, biological approach and their example suggests how drug discovery will change.

The final nail in the coffin

The advances presaged by the application of leading-edge molecular sciences will enable the pharmaceutical industry to make totally new products for patients with specific disease subtypes, but they will also put the final nail in the coffin of the current model for making drugs.

The industry can no longer depend on academia for much of its preliminary knowledge of diseases and targets because the number and diversity of potential targets is now so great. Nor can it rely on high-throughput screening (HTS) of compound libraries to identify small molecules that can interact with increasingly challenging targets. Even the biggest libraries contain a mere two million molecules, which is neither large nor diverse enough to cater for the full repertoire of the hundreds of thousands of different proteins in the human body.

In short, the industry cannot continue to use a model that depends substantially on brute force and serendipity. Instead, it will have to learn how to manage an incredibly diverse range of potential new targets and to cut R&D cycles dramatically – changes that will dictate an increasing emphasis on biologics rather than on conventional chemistry.

A disease-centric approach

A disease-centric, biological approach to drug discovery has many advantages. It creates valuable proprietary knowledge about the disease family that is the focus of attention, and reduces the risk that a company will duplicate the efforts of competing organizations. This approach also ensures access to a sufficiently diverse set of molecules that is necessary to cope with the vast increase in the number of potential targets. For example, Cambridge Antibody Technology (CAT; http://www.cambridgeantibody.com) has created an antibody fragment library with over 100 billion different molecules. Furthermore, a disease-centric, biological approach employs the physiological dynamics of target–molecule interactions by using, for example, recombinant proteins that have been engineered for high specificity and selectivity, in a relatively predictable manner, or dynamic screening processes in which biological molecules (e.g. humanized antibody fragments) actively select specific targets. Collectively, these techniques greatly increase the likelihood of discovering a useful target–molecule interaction.

Several companies, including Amgen (http://www.amgen.com), Human Genome Sciences (HGS; http://www.hgsi.com), Celltech (http://www.celltechgroup.com) and CAT, are already using a disease-centric, biological approach to discovery, with impressive results. These companies are precisely defining different disease states at the molecular level and using genomics-based techniques to identify novel targets. Once identified, the targets are validated with biological molecules, using rapid proof-of-concept studies in humans, which reduces clinical validation cycles to about two years. One product to emerge in this way is TRAIL (tumour necrosis factor related apoptosis inducing ligand) receptor-1 agonistic human mAb for the treatment of particular forms of cancer, which was discovered by HGS and CAT and is currently in clinical trials.

These innovative approaches show how the discovery process will evolve. In future, a pharmaceutical company will begin by defining the different disease pathologies and molecular mechanisms in a particular disease family. Next,

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it will harness the power of high-throughput biology to identify suitable targets, which can subsequently be validated with clinical proof-of-concept studies that use biological molecules specifically designed to interact with the targets themselves. Simultaneously, the company would start to develop diagnostics and monitoring tests that are based on the molecular markers of disease type, progression, severity and efficacy outcome. Furthermore, the information acquired should enable the company to build a proprietary understanding of the diseases on which it is working and to discover new drugs for related diseases.

Redefining diseases with greater accuracy at the molecular level makes it considerably easier to validate a target. Furthermore, because biologics are typically less toxic than chemical entities they can be clinically tested in humans much earlier in the discovery process. This rapid validation of a target increases the chances of producing a successful drug (because a lack of target validation is one of the main reasons why drugs fail to show efficacy in the clinic) and also enables a company to begin investigating other properties of the drug at an earlier stage in the process. For example, several companies are already combining pharmacokinetic and pharmacodynamic investigations with tests to see whether or not a drug crosses the blood–brain barrier in first-in-man studies.

Patch solutions

Of course, working with biologics is not plain sailing. It is no accident that the first chimaeric and humanized mAbs did not reach the market until 1997, 22 years after César Milstein and Georges Köhler succeeded in isolating mouse mAbs. However, some of the early problems encountered have now been surmounted and although other serious drawbacks remain, including the inherent difficulty of formulating and delivering biologics compared with chemical entities, the technologies associated with the biological sciences are evolving extremely rapidly. Manufacturing costs of biologics are currently significantly greater than those of chemical entities and the impact of this on the consumer must be taken into account. However, as more of these products make their way into the realms of blockbuster sales, economies of scale and rapid advances in technology will ensure that costs are reduced to more manageable levels.

The development of new forms of female contraceptive has already proved that it is possible to deliver large molecules via transdermal patches and slow-release implants. Significant advances have also been made in the formulation and delivery of insulin. GlaxoSmithKline (http://www.gsk.com/index.htm) is experimenting with an oral insulin pill and Altea (http://www.alteatherapeutics.com) is developing a patch that uses electrical stimulation to increase the permeability of skin cells, which subsequently releases a small dose of insulin directly into the body. In addition, several companies are exploring the potential for oral insulin sprays and 3M (http://www.3m.com) is investigating the application of such principles to the delivery of a broad range of proteins and peptides.

Although it remains unclear whether biologics can penetrate the brain, carrier vector technologies have shown that antibody fragments can cross the blood–brain barrier. Some of the other problems associated with biologics, for example, their limited distribution and rapid turnover rate in the body, can be resolved with more conventional techniques. It is possible to adjust the pharmacokinetic properties and dosing regimen of biologics using long-established chemistry approaches. In other words, many of the traditional arguments against the use of biologics no longer apply, or apply with diminished force. The main obstacle that large pharmaceutical companies now face is a lack of experience in working with large molecules, an obstacle that can only be overcome with practice – as illustrated by the resolution of the solubility and bioavailability problems associated with small molecules in the late 1970s and early 1980s.

A gradual transition

The transition from the old to the new model of drug discovery will possibly not take place overnight. For the larger pharmaceutical companies, the drug discovery process will probably incorporate an intermediate stage in which biologically based molecules are used to conduct faster proof-of-concept studies in humans. Once a target has been validated, pharmaceutical companies will be able to feed that target into the traditional drug discovery process, safe in the knowledge that the probability of attrition because of a lack of efficacy will be significantly lower.

The ultimate step is to adopt a totally new approach to drug discovery, which has several implications. First, when the starting point of the drug discovery process is the precise molecular definition of disease mechanisms, rather than 'druggable' classes of well-characterized targets, it is the clear and proprietary understanding of a specific disease that places a company in an advantageous position, not the possession of a large compound library. Therefore, the most successful pharmaceutical companies of the future will be those that can build a franchise of particular disease families as soon as possible. Second, the pharmaceutical industry will need to abandon its preconceptions of the type of drugs that become blockbusters. It is often said that discovery scientists lack commercial acumen, but too narrow an application of the conventional therapeutic profile has sometimes stifled the development of products

that could actually be profitable. Getting the right balance is essential, which means creating an organization in which scientific knowledge is integrated with commercial awareness. Third, the industry will need to communicate with the regulators and ensure compliance with good manufacturing practice at a much earlier stage in the R&D process. At present, the first formal contact with the regulators occurs when a company files an investigational new drug application before starting Phase I trials. However, with the use of proof-of-concept studies in humans at earlier stages for target and molecule validation, it will be necessary to consult the regulators and manufacture trial supplies long before this point. Fourth, the pharmaceutical industry will have to manage multiple product types for many years to come. Clearly, no business can simply purge its drug development programs and start afresh. Therefore, most companies will have to continue supporting drugs that conform to the conventional therapeutic profile alongside new, second-line treatments for clinically defined populations. Ultimately, companies will have to manage conventional and novel product types and simultaneously develop targeted treatment solutions. In essence, they will have to work on multiple disease families and multiple product types (including diagnostics, biomarkers of clinical efficacy, delivery devices and patient services) that use different R&D, manufacturing, marketing and sales techniques – a challenge as great as trying to land a man on the moon.

The shift to a new discovery model has further consequences. For example, it will blur the boundaries between chemistry and biology and discovery and development, accelerate the decision-making process and increase the volume and complexity of the data the industry generates. Furthermore, as a result of the increasing role of modelling and simulation in the drug discovery process, new forms of data will be produced that will ultimately enhance the understanding of biology as a complex system that interacts in multiple ways.

Big winnings

The transition to a new drug discovery model will require a huge effort; however, the potential benefits are enormous. The Tufts Center for the Study of Drug Development (http://csdd.tufts.edu) recently concluded that using the most modern preclinical screens to boost success rates would save about US$242 million. Cutting development and regulatory review times by 25% would save another US$129 million, reducing costs per drug to US$431 million, which is almost half the current average. The new model of discovery outlined in this editorial could do more. It does not presage the end of the small molecule, which will continue to play a key role in pharmaceutical R&D. However, as experience in the most ground-breaking companies illustrates, the biological approach often works where the chemical approach cannot. In addition, the biological approach can significantly reduce lead times, attrition rates and costs. In other words, it has the potential to alter the entire economic basis on which the industry operates.

Reference

1 Arlington, S.A. *et al.* (2002) *Pharma 2010: The Threshold of Innovation*, IBM Business Consulting Services

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