The discovery–development interface has become the new interfacial phenomenon

'…an *in silico* revolution is emerging that will alter the conduct of early drug development in the future.'

Today's drug development team is a collective group involving industry, academia, government agencies and health authorities, investigators, clinical trial patients and consumers of marketed products. Although everyone desires improved drugs that are developed faster and cost-effectively and that target unmet medical needs, costly failures are still being accepted as part of the normal drug development process. There are still the same statistics on drug development successes now [only 10% of drugs in investigational new drug (IND) development phases are eventually approved for use] as there were in the 1970s, 1980s and 1990s. This has triggered the re-examination of how the drug discovery–development interface is managed, that crucial area where compounds are optimized, enter (so-called) predictive preclinical models and are tested in early clinical trials.

The interface between discovery and development has been changing for the past five years, being pushed further into the discovery sector. This is happening as a by-product of an enhanced ability to both create and screen new chemical entities at rates unimaginable in the 1980s. With more hits and leads available, faster and more accurate methods are required to optimize compounds earlier in the process. As a large portion of early pipeline dropouts occur from toxicity, poor pharmacokinetic characteristics, and suboptimal absorption, distribution, metabolism and excretion (ADME) properties, increasing attention has been given to these crucial areas. Workshops and symposia are burgeoning on topics such as *Early toxicity and ADME screening* and *High-throughput ADME and toxicology* [see Sansom, C. (1999) *Drug Discovery Today* 4, 199–201]. This has truly become an interfacial phenomenon.

The interface, which used to represent a hand-over process between functional areas, must now be viewed as an area of opportunity that could develop into the next major breakthrough in the pharmaceutical industry, favorably affecting costs, resources and success rates. To many discovery scientists, the current interface represents a bottleneck that restricts the flow of promising compounds into later pre-development screens. By contrast, to many development scientists, this interface represents a filtering device 'knocking-out' compounds that are developmental 'nightmares'. However, in a more far-reaching view, an *in silico* revolution is emerging that will alter the conduct of early drug development in the future.

At the end of the 1990s, thanks in large part to this new phenomenon, the focus is finally more on predicting potential outcomes earlier in the process. New concepts of preclinical simulations of human outcomes are emerging, and it is reasonable to speculate that computational data management and simulation tools will enable work at the hit-to-lead discovery stage with information directly applicable to specific patient susceptibilities in targeted therapeutic areas.

It is now time to start a process where the team works collectively to solve the prediction dilemma. Consortia must be established where simulation models are constructed and tested against libraries of compounds with known outcomes. The rules of toxicity and ADME are being searched to streamline the process of finding better drugs. There is a unique window of opportunity starting to open and a system must be created where the rules can be elucidated but where proprietary secrets are preserved. Regardless of individual company scale, the

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diversity of models constructed and tested by multiple companies will have enormous value to all members of the team.

When this becomes a reality, the continued validity of development paradigms that become outmoded must also be challenged. Regulated non-clinical safety evaluations must incorporate new simulation tools to enhance predictability. Many of the models that have been effective in the past, but have stalled at the current success rate, must be replaced with newer approaches that incorporate technological advances.

While the new interfacial phenomenon will surely seem like an 'in-your-face' phenomenon to some, it is important to remember that 'the real voyage of discovery consists not in seeing new landscapes, but in having new eyes' – Proust.

Dale Johnston

In short…

MorphoSys AG (Munich, Germany) has developed a high-throughput technology that can generate human antibodies against expressed sequence tag (EST)-encoded protein fragments. Although large quantities of these EST gene fragments are being produced as part of the Human Genome Project, the functions of the corresponding genes are largely unknown. However, one method of determining their function is to generate antibodies against the protein fragments encoded by the ESTs whilst screening recombinant antibody libraries. This technology developed by MorphoSys uses a combination of their proprietary automated Human Combinatorial Antibody Library (HuCAL) technology with a method of producing EST-encoded protein fragments. Their Chief Scientific Officer, Thomas von Ruden, said 'We set out to develop this technology in response to the frequent demand from the pharmaceutical industry for antibodies against EST-encoded protein fragments. The success by our scientists in establishing the technology represents a significant step towards our goal of linking functional genomics and drug discovery.' The company has now filed patent applications to cover the technology.

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