New HTS imaging technology deal

Higher-throughput and miniaturization continue to focus the thoughts of biomolecular screening professionals in the pharma/biotech industries as the trend towards ultra-high-throughput screening (ultra-HTS) continues. One technology that can facilitate these developments is the use of imaging systems to supplement traditional instrumentation such as scintillation counters and luminometers. Traditional systems tend not to cope well with high-density microtitre plate formats, whereas imaging systems can cope with thousands of wells per plate.

Advanced imaging systems

A new generation of CCD camera systems amenable to ultra-HTS are beginning to enter the market. Traditional non-imaging technologies do have the advantage of relative simple operation – they need only to control the scanning process, use a simple internal calibration and create a small array of data points to represent the plate wells. Although mechanically less complex, area imaging systems are more challenging to integrate into a screening operation, largely because of the need to prevent geometric and intensity errors. For example, use of an imaging system in a fluorescence assay would require a handling system to facilitate:

- Adequate and even illumination over an entire plate and control of a high-performance camera
- Storage capability for geometric and density corrections/calibrations
- Imaging of the plate with appropriate corrections
- Ability to locate each well, quantify light intensity and transfer the data to other programs

Due to advances in information technology, the software to enable the use of such systems is now available and should facilitate a more flexible approach to image-based screening.

One example of the utility of imaging systems is application in dynamic assays – a simple extension of traditional 'single-well' microscopic imaging. The imaging systems enable an entire plate to be viewed and to obtain repeated measurements over time. Imaging systems also have application in free-format assays as well as traditional grid-based arrays. It is clear that such imaging systems have a bright future in the world of HTS and particularly ultra-HTS.

Application to proximity assays

The advantages of advanced imaging systems have recently been harnessed by Amersham Pharmacia Biotech (APBiotech) to further strengthen their position in the HTS market. The development of the Scintillation Proximity Assay (SPA) in the 1980s and early 1990s firmly established the company as a leading HTS technology vendor. SPA offers a simple homogeneous assay in which a signal is generated only when labelled compounds are bound to a scintillant-containing bead [see Cook, N.D. *Drug Discovery Today* 1996 1, 287–294]. Traditionally, emission of photons corresponding to radioactive decay has been measured using photomultiplier tube instruments.

Imaging deal

In June 1998, APBiotech established a deal with Imaging Research Inc. (IRI) based in St Catherine's, Toronto, Canada. The companies have integrated the imaging expertise of IRI with APBiotech's next generation homogeneous assay technology to develop what they term the Leadseeker system. The new system was launched formally at the 4th Annual Meeting of the Society for Biomolecular Screening, held in Baltimore in September (1998). The Leadseeker system includes self-contained instrumentation, software and novel reagents (new homogeneous assay beads accommodating an advantageous wavelength shift), but matched to a highly sensitive digital camera and specialized lens. The company claim that the system allows a 384-well microplate to be read in 5–15 min. Further developments of the system, already in advanced development, include full automation, higher sensitivity optics and specialized assay plates.

Following an initial equity investment and R&D contract, APBiotech has acquired the option to purchase a majority shareholding in IRI, a company of 30 staff, which was founded in 1986 by Professor Peter Ramm. According to Ramm 'We knew we had the expertise and the technology to take high-throughput screening to the next level… However, we needed a partner… with Amersham Pharmacia Biotech's capabilities and long-standing relationships with the industry, they were the ideal choice'. Ramm becomes Chairman and Director of R&D at IRI.

First customer

The first deal involving the new system has been struck with Novo Nordisk. According to Mads Krogsgaard Thomsen, Vice President of Healthcare Discovery, 'When it comes to drug screening, time is of the essence. With the Leadseeker system, we now have a technology which will enable us to test a larger number of compounds at high speed – the more we screen, the greater the chance we have of discovering unique compounds for important new treatments'. The company expect the system to be integrated smoothly into their discovery operation via the well-established technology transfer system that APBiotech has already developed with many major pharmaceutical companies. Support will include assistance and training in installation, assay design, system operation, servicing and trouble-shooting. Entry into the Leadseeker programme also allows access to the more

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advanced HTS systems in development and the opportunity to influence the direction of the programme.

Novo Nordisk was one of the first companies to buy into the system and they have been collaborating with APBiotech for six years. Like other companies, Novo Nordisk has found that the move towards increasingly focused libraries means that the throughput of screening programmes is often no longer the rate-limiting step. However, they are under increased pressure to develop better quality leads – the emphasis is now firmly on the identification of higher quality drug-like compounds to minimize later-phase attrition rates. They believe that such miniaturized screening technologies will enable them to do this more efficiently – both in terms of versatility, speed, overall cost and because of smaller amounts of target per well, minimization of waste and waste handling/disposal.

APBiotech claim that the new system could offer a fivefold increase in screening productivity, which could translate into an additional $40 million in sales for a major drug in terms of time gained in the screening cycle and hence reduced time to market.

Future prospects

Krogsgaard Thomsen believes that screening in the 1536 format on a regular basis is a realistic prospect within two to three years, taking into account advances in automation and integration. There is continuing debate over the requirements, changing platforms and costs associated with the trend for miniaturization of HTS (see July issue of *Drug Discovery Today*). It seems certain, however, that advanced imaging technology will provide impetus to drive screening further along this route.

Second acquisition

APBiotech appears to be in an acquisitive mood at present, as the company has recently acquired Molecular Dynamics (MD) in a deal worth $256 million. The deal will increase APBiotech's genomics capabilities and strengthen their position in this market. Having collaborated with MD on the development of its MegaBACE 1000 DNA sequencing system, launched last year, APBiotech has ~12 months to establish this technology in the marketplace before Perkin Elmer launches its PE 3700 DNA analyser, which is expected to be a strong competitor.

David Hughes

Therapeutic antibodies make a comeback

Since their discovery by Kohler and Milstein in 1975, the use of monoclonal antibodies (mAbs) in medicine has come a long way. There are now seven therapeutic mAbs approved in one or more major markets and a further 11 radiolabelled mAbs approved for *in vivo* imaging. A breakout session at the Bio '98 conference in New York, USA, on 14–18 June 1998, covered recent developments in the use of mAbs as biological response modifiers. The Chair of the session, David Glover (Cambridge Antibody Technology, Melbourn, UK) commented that the path to success for mAbs has been far from smooth and outlined some of the key difficulties that have had to be overcome in their therapeutic application. The conventional route to derive mAbs is to immunize mice. Such murine mAbs have widespread applications in research, but can trigger immune responses because of the foreign nature of the protein when introduced into humans. Several approaches have been taken in overcoming this problem, which has seen the development of chimaeric, humanized and now fully human mAbs (see Fig. 1). The speakers in the session concentrated on several antibody products that fall into the latter two categories, humanized and human mAbs, and their applications to modify biological responses.

Success of humanized antibodies

Jim Cornett of Protein Design Labs (PDL, Mountain View, CA, USA) gave a talk subtitled 'humanized antibodies succeed' focusing on PDL's product Zenapax®, the first approved humanized mAb. Before presenting details of Zenapax, Cornett indicated the importance of mAbs as biotechnological products. A recent survey suggested that over a quarter of all biotech drugs in development are mAbs. Within this group, humanized antibodies account for more than 30 products in the clinic for a wide variety of indications from autoimmune diseases to cancer.

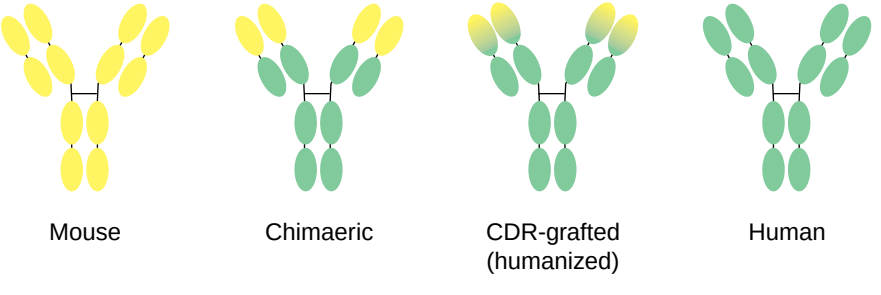

Figure 1. *Evolution of monoclonal antibodies.*

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