

Drug Discovery Technologies from Invitrogen

a report by

Invitrogen Ltd

Compensating for the high attrition rates of new compounds and targets in pre-clinical drug discovery projects is key to maintaining a steady flow of lead compounds in the drug discovery pipeline. Over the past year, through key acquisitions and research and development (R&D), Invitrogen Ltd has developed a uniquely broad portfolio of products, technology platforms and services to better serve the needs of customers in the pharmaceutical and biotechnology industries. Invitrogen can now offer customers a competitive advantage in achieving reliable and accurate data quicker and more effectively, while being sensitive to costs and technological demands of such work. Our aim is to offer our pharmaceutical and biotech customers access to these technologies through focused contact at all levels and by building strategic partnerships for your drug discovery projects.

The three main areas of focus we have identified for addressing drug discovery projects are as follows:

- target identification and validation;
- high-throughput drug screening; and
- absorption, distribution, metabolism, elimination, toxicity (ADME/Tox).

Target Identification and Validation

Advances in existing molecular biology technologies have made this a very exciting area of research, characterised by the search for new druggable targets through gene identification followed by assessing their suitability through a variety of functional studies. Below are just some of the key technologies we can now offer:

- The recent acquisition of Sequitur by Invitrogen reflects the growing use of ribonucleic acid interference (RNAi) in such projects, and we are pleased to offer Sequitur's extensive experience in optimising protocols for introducing small interfering RNAs (siRNAs) into mammalian cells as a custom service.
- The widest choice of siRNA delivery options are available, from the unbeatable performance of Lipofectamine™ 2000 together with Stealth™

siRNA oligos in gene silencing, to vector-based silencing mechanisms such as the Lentiviral BLOCK-iT™ RNAi system for generating stable cell lines in virtually any mammalian cell type.

- Cell culture-based assays such as the CyQUANT® cell proliferation assays from Molecular Probes are now available for rapid and reliable validation of potential mitotic or antimetabolic effects of compounds and targets.
- The GeneBLAzer™ system in CellSensor™ cell lines for use as reporters of gene induction offers a powerful tool for designing high-content screens. Using beta-lactamase and a Fluorescence Resonance Energy Transfer (FRET)-based cleavable substrate allows ratiometric and accurate read-out, with the added value of enabling live cell sorting for downstream work. We offer a fully collaborative or commercial service to help you to develop this technology into whatever cell-based assay you need, with more open licensing policies to allow access to this technology.
- For customers wishing to save time on cloning target genes or wishing to rapidly obtain multiple members of gene families, we offer a full range of Ultimate™ ORFs, Gateway®-adapted full-length cDNAs ready for efficient and convenient downstream shuttling into expression vectors for further study.
- Added to this for functional analysis of expressed genes we can offer gene-discovery and custom antibody production services through EvoQuest™ Custom Services. See <http://www.invitrogen.com/Evoquest> for further details.

High-throughput Drug Screening

Industry requires evermore miniaturisable assays to allow the use of higher-throughput plate formats such as 1,536- and 3,456-well in large screens. This cannot be done at the expense of robustness and reliability, whether using biochemical assays or using living cells in assays. Through the acquisition of PanVera in mid 2003, Invitrogen now offers a comprehensive range



of screening technologies against the major target classes commonly studied as druggable targets. Products offered include the following:

- Classic fluorescence-based biochemical assays for screening nuclear receptors and protein kinases based on fluorescence polarisation available in red and green detection formats to get around any background interference arising from compound autofluorescence.
- The Z LYTE™ technology platform includes peptide panels for selectivity profiling of protein kinases, as well as detection kits based on a selected peptide for studying kinase activity. These offer more versatility than traditional assays, which are often limited by the availability of phosphopeptide-specific antibodies.
- The Lanthascreen™ terbium chelate reagents further offer reductions in background fluorescence using time-resolved FRET for detection. This can potentially increase data accuracy when carrying out nuclear receptor or kinase screens.
- Sensitive detection and accurate measurement of Ca²⁺ signalling using dyes such as fluo-4 and fura-2 from molecular probes are now available for use in low- and high-throughput screening formats.
- Voltage Sensor Probes are cell-based assays for screening compounds affecting membrane polarisation. They are increasingly being used for study of ion channels and compounds affecting them, offering far more high-throughput format than existing technologies such as patch-clamp methods.
- The knowledge and extensive application expertise in R&D associated with the range of PanVera drug discovery technologies is freely available to collaborators and research partners alike. Full screening services are available using existing technologies, however, we also offer custom assay design and testing as a service.

ADME/Tox

The final stage before any compound(s) can move to clinical trials involves safety testing. This often

presents a significant bottleneck in the flow from lead compound to full commercialisation of a drug, and so technologies are required to eliminate potentially toxic compounds in a timely and reliable manner.

- Vivid® substrates and reconstituted reagent systems for individual CYP450 isozymes are designed for accurate biochemical measurement of drug interaction based on fluorescence intensity measurements. Substrates and enzymes cover all the major isozymes currently studied.
- From molecular probes we can now offer the LIVE/DEAD® viability/cytotoxicity assays and the Vybrant® cytotoxicity assays to test compounds for toxic effects on living cells.
- We aim to meet the increasing demand for cell-based systems allowing detection of CYP450 induction and drug interaction by designing, testing and bringing to market novel assays throughout 2004, using the GeneBLAzer™ technology.
- Concurrent with your needs and time constraints, we aim to provide a full screening service in 2004 to save you time and to provide you with reliable ADME/Tox data on your chosen compounds.

Invitrogen aims to become your valued partner in drug discovery offering innovative technologies and capabilities to suit your needs; we deliver them to you with a strong commitment to fair pricing, high quality and full customer service. We are also pleased to offer you access to a team of Executive Technology Specialists with wide-ranging capabilities in connecting you with all resources at Invitrogen's disposal, in Europe and globally, to keep your Drug Discovery pipelines flowing. ■

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