also enable us to combine the sensitivity of electrophysiology with much greater capacity.'

The future

The savings that automated screening systems could bring in terms of time and the reduced need for skilled operators could, hopes Blatz, provide new impetus to research. 'If highly skilled neurophysiologists are freed from micromanipulation and single-cell experiments, they will have much more time for innovative thinking and planning,' he says. In the long-term, Blatz and Mathes also envisage that Axon might be able to couple its genomic and proteomic developments with HTS technology. 'We cannot predict the outcome of this, as technology will need to advance to even make it possible, but this is an area that we do not want to miss out on,' concludes Blatz.

HTS in the new millennium

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Screening, in particular high-throughput screening (HTS), has taken on a broader role within discovery science as increasingly automated and robust technologies have been brought online. Consequently, the scope of the Society of Biomolecular Screening (SBS) Sixth Annual Conference and Exhibition entitled *Screening in the New Millennium* (6–9 September 2000 in Vancouver, BC, Canada) was considerably broader than previous SBS meetings, and was markedly less focused on techniques and equipment. Successful application of the principles of HTS, both for lead identification and optimization, were presented. In addition, the connection between molecular screening and compound synthesis to reduce the time taken to achieve discovery milestones was strengthened. Other presentations covered new technologies, particularly the use of microscopy in HTS, which is now more fully developed to the point of practical application in the HTS laboratory.

New leads

As the membership of the SBS has grown in number from a few hundred to a few thousand over the past six years, the operating principles of the HTS laboratory have become less idiosyncratic. This is becoming manifest in the number of new leads that are emerging as a direct consequence of the HTS laboratory. The realization of this promise was substantiated by presentations from numerous companies in several target classes. Highlights included:

- The identification of potent, selective inhibitors of the human inducible nitric oxide synthase (iNOS), discovered at Pharmacopeia and being developed by Berlex Biosciences (Kirk McMillan; Princeton, NJ, USA)
- The identification and optimization of novel non-peptide chemokine receptor 1 (CCR1) antagonists, also at Berlex Biosciences (Meina Liang; Richmond, CA, USA)
- The identification and optimization of novel melanocortin MC_1-receptor agonists at Trega Biosciences (Timothy Gahman; San Diego, CA, USA).

Stephen Rees (GlaxoWellcome, Stevenage, UK), and Matthew Sills (Novartis, Summit, NJ, USA) noted important interactions between the choice of assay technology and outcomes of screening. Sills suggested that for certain target types, the use of at least two different assay technologies per target would be justified to avoid false-negatives in screening.

Combinatorial chemistry and HTS

An increasing coordination of the efforts of combinatorial chemistry groups with those of the HTS laboratory was also noted. HTS laboratories have always needed close association with compound storage and retrieval. By more tightly linking screening with *de novo* synthesis, particularly in the context of lead generation through robotic and combinatorial chemistry, increases in efficiency are anticipated. The debate between using large combinatorial libraries (advocated by Maria Webb of Pharmacopeia, Princeton, NJ, USA) and iterative robotic synthesis (advocated by Peter Myers, DuPont Pharmaceuticals, San Diego, CA, USA) was discussed in terms of past successes, with the primary difference between sequential iterations and parallel screening being the time to achieve a lead.

Large combinatorial libraries provided optimizable leads in a variety of programs, highlighted by the successful identification and optimization of receptor antagonists specific for the human bradykinin B_1 receptor at Pharmacopeia, while iterative synthesis is being increasingly viewed as an aid to lead optimization (Raju Mohan, Berlex Biosciences, Richmond, CA, USA). Approaches towards

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integration of HTS with compounds derived from natural products were also discussed. Kollol Pal (Neogenesis, Cambridge, MA, USA) discussed a 'chemical genomics' approach for lead identification, which involves affinity selection for identification of small-molecule ligands, while Juha Hakala (Galilaeua Oy, Finland) discussed a 'combinatorial biosynthesis' approach, using molecular biology in producing organisms (e.g. *Streptomyces*) to generate novel biosynthetic pathways.

New HTS techniques

In the past 12 months, a technique for HTS that has moved from the theoretical to the practical realm is the use of microscopy in screening. Three different companies, with three distinct approaches, have come to the fore and were presented at this conference:

- The EVOscreen system offered by Evotec Biosystems (Hamburg, Germany) utilizes fluorescence correlation spectroscopy (FCS) and fluorescence intensity distribution analysis (FIDA), which are single-molecule detection techniques that stochastically sample properties of single molecules.
- Analysis of biochemical signaling as well as morphological and physiological events at the single-cell level is possible with the Arrayscan II offered by Cellomics (Pittsburgh, PA, USA). This technology is based on high-resolution fluorescence imaging of multiple targets in living cells.
- FMAT, a technology offered by Applied Biosystems (Foster City, CA, USA), enables various cell-based and cell-free biochemical interactions to be assayed without tedious washing or filtration steps, accelerating such common HTS and diagnostic applications as immunoassays and receptor binding assays.

All three methods should be useful to the HTS and compound optimization laboratories for accelerated lead discovery and optimization, and the technologies are now commercially available.

Drug development issues

Techniques and philosophies from the HTS laboratory are also being applied to issues in development, including target validation and pharmacology (ADME/tox). The specific mode for cross-fertilization has ignited a debate. At one extreme is the 'screen first, ask questions later' philosophy, which expresses little or no concern for validation (of targets) or for toxicity profiling (of chemical libraries). Meanwhile, at the other extreme is the 'conventional' approach of extensive target validation, followed by toxicity testing of promising lead compounds.

With the cost reductions attributed to HTS and related technologies, less 'up-front' work should be required in the future. Specific presentations around this subject included a talk by David Matthews (Exelixis, San Francisco, CA, USA) on the use of comparative genomics and model organisms as a method for high-throughput target validation, as well as a session on high-throughput ADME/tox assays. Assays for high-throughput determination of solubility, serum protein binding, metabolic stability (cytochrome P450 monooxygenase metabolism, in particular), and cell-based bioavailability models for cell permeability (Caco-2 model) and elimination (P-glycoprotein efflux) were also presented [Paul Johnston (Sphinx Pharmaceuticals, Research Triangle Park, NC, USA) and Ilona Kariv (DuPont Pharmaceuticals, Wilmington, DE, USA)].

The proliferation of these HTS techniques outside of conventional lead identification will undoubtedly add more credence to the broader screening (and hence understanding) of ADME/tox mechanisms across a number of chemical classes. At the same time, it seems unlikely that 'whole animal' screening (as would be needed for distribution and excretion testing) will ever be amenable to HTS methodologies.

Next year

Finally, several topics to watch in the upcoming year were presented, including unique, bead-based methods for screening. Manfred Auer (Novartis Forschungsinstitut, Vienna, Austria) presented a confocal methodology amenable to miniaturization in bead-based detection, and Matt Trau (University of Queensland, St Lucia, Australia) presented a colloidal method for fluorescently labeling beads for high-throughput synthesis and screening. Another approach, the use of microfluidic devices, was a prominent topic of earlier meetings, and a number of companies (e.g. Caliper Technologies, Cetek) were present with new devices in the field. Next year's meeting should prove the value of these technologies in practice.