receptor modulators (SERMs) as promising hormone replacement therapy drugs [10]. Thus, phenomena of unique signaling profiles dictated by particular ligands at a given receptor are not limited to the GPCR family. Such phenomena seem to be imperative for drug development and we believe that depiction of ligand-selective signaling profiles should become a key part of preclinical drug development. Seemingly, compounds exhibiting selective signaling profiles would be more likely to exhibit reduced desensitization and fewer side-effects, making them superior candidates for further drug development.

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The language of screening evolves

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The value of HTS to the drug discovery arena was debated widely at the *Society for Biomolecular Screening (SBS) 9th Annual Conference and Exhibition*, in Portland, OR, USA, (21–25 September 2003). The solution could lie, in part, in the diversity of SBS sessions beyond traditional HTS single-point assay technology.

As Jeff Pasley from Wyeth (http://www.wyeth.com) discussed in a session titled *Point/Counterpoint: Is HTS Worth the Cost?*, HTS is moving beyond activity assays into the ADME arena for determination of compound characteristics *in vitro*. However, as counter proponent Mel Reichman (drughunter@aol.com) added, HTS is more a commodity in the rapidly evolving oligopoly pharmaceutical discovery market. With the low barrier to entry, many academic institutions are now implementing HTS to protect their target intellectual property (see http://iccb.med.harvard.edu/screening/index.htm).

Furthering HTS

Within small molecule discovery at many pharmaceutical companies, HTS is now being supplemented and iteratively used with a variety of new methodologies, including computational modelling of compound activity, data quality, systems biology and mechanisms of action at the cellular and organism level. HTS is evolving beyond a search for a needle in a haystack to become a generic, efficient method for testing a hypothesis. Screening assay data is being quantified, both in range and quality, so all results, both negative and positive, can be used to better understand the target, compound selectivity and the systems biology underlying the *in vivo* therapeutic interaction.

The SBS sessions investigated two major avenues:

- A better understanding of systems biology in order to more accurately select and screen the drugable therapeutically relevant targets
- A more efficient selection of compounds that will be potent against the target as well as readily bioavailable as an oral therapeutic.

Meeting highlights

- Systems biology for increased understanding of physiology and target identification

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- High Content Screening (HCS) for a more mechanistic approach to activity screening
- Ion channel targets and screening methodologies
- Focused compound libraries and scaffolds for selective screening, 'lead-likeness' and QSAR for predictive properties
- Data mining/effective data QC/quantifying false negatives and false positives for better selectivity screening.

Each of the SBS keynote speakers, Roger Perlmutter of Amgen (http://www.amgen.com), Christopher Lipinski, formerly of Pfizer (http://www.pfizer.com), and Leroy Hood of the Institute for Systems Biology (http://www.systemsbiology.org), spoke of the need for a deeper understanding of human systems biology, both to identify drugable therapeutic targets as well as to deliver effective therapeutics systematically. Despite the influx of gene data, determining the role each gene might play in systems biology and in a targeted disease is an unmet challenge.

Targeting obesity

As Perlmutter described in his keynote address, Amgen's development of Leptin (see http://whyfiles.org/051fat_fixes/leptin.html) as a therapeutic, initially based on the study of target in an animal obesity model, has resulted in treatment for only a small group of the targeted human population suffering from obesity. Often, as illustrated by the cox-2 receptor, a target first identified in one area of therapeutic research (inflammation and pain), could have therapeutic indications in a completely unrelated medical area (cancer) [1].

Arthur Sands of Lexicon Pharmaceuticals (http://www.lexgen.com/pharma/) discussed this as part of Lexicon's strategy to use its gene knockout technology to map true physiological response: very few of the physiological predictive models based upon gene family and sequence are accurate [2]. It is more effective for Lexicon to observe physiology via the phenotype of its knockout animals and then release the target to the appropriate therapeutic research for further investigation than to rely on current predictive physiological models based on gene family and sequence. Leroy Hood is essentially taking the same approach at the Institute of Systems Biology, modelling physiology as a feedback-regulated system from gene to protein to cellular and organism function.

It is clear that a single-point HTS activity assay does not model an *in vivo* response or the logic of the cellular event within its natural system. However, as Laszlo Urban of Novartis (http://www.novartis.com) illustrated, use of HTS methodology to develop an early preclinical profile of the compound via *in vitro* screens for absorption, metabolism and toxicology can reduce expensive clinical development time and risk. This process helps to benchmark not only a compound's targeted activity but also its drugability *in vivo* before it is ever tested in the clinic. Part of the HTS-based approach to compound profiling is an effort to understand variability within screening data, so that both positive and negative data are truly selective. As Leo Bleicher of Merck (http://www.merck.com) and others illustrated, the data can then be mined for promiscuous scaffolds and cross-reactive species.

Investigating target response

Another theme prevalent at SBS was renewed interest in HCS and other multi-parameter measurement methods for investigation of target response in the context of the cellular system. HCS is increasingly useful for target validation and mechanism of action studies, ensuring that a hit candidate is selected based not only on an order of magnitude over background, but also highly selective, target-specific activity. Perhaps to the chagrin of the early leaders in HCS technology, the price for these systems has become competitive but is now both more affordable for and applicable to broader areas of therapeutic research. Managing the data produced by these systems is still a challenge as many of the vendors try to go it alone, rather than integrate with data management systems already in place and in use among their customers.

Ion channels have become a significant target therapeutic area in the few years since their discovery. SBS included a session on 'Advances in Ion Channel Technology' just weeks before the 2003 Chemistry Nobel Prize was awarded to biochemists Peter Agre of Johns Hopkins University (http://www.jhu.edu) and Roderick MacKinnon of Rockefeller University (http://www.rockefeller.edu) 'for discoveries concerning channels in cell membranes'. The primary challenge for drug discovery is how to mimic the complex physiological environment of ion channels in an HTS format. Ion channels might not yet fit well into a homogenous plate-based assay format but they represent 5% of all molecular targets. There are several systems for directly measuring ion-flux, and these will only get better and more cost-effective.

The reality of virtual screening

A corollary to the systems biology emphasis at SBS was a focus on developing effective therapeutics that work within systems effectively because of good ADME characteristics, target specificity, minimal drug–drug interactions and minimal side effects.

For therapeutically relevant enzymes such as kinases and phosphatases, high throughput crystallography and NMR have become extremely powerful tools

for modelling structure, binding domains and protein–ligand interactions.

Virtual screening has developed beyond a buzzword to a constructive reality in drug discovery, as illustrated by Steve Muchmore of Abbott Laboratories (http://www.abbott.com). These techniques might have limited success for targets such as GPCRs and other membrane-bound receptors, because of the lipid bilayer that they span. However, using the concept of privileged scaffolds [3], Aventis, BMS and Vertex have been able to focus their compound screens around target-selective compound scaffolds. Gilbert Rishton of Amgen has identified 'lead-likeness' [4] physicochemical properties to preselect compounds for active screening. The outcome is that the compounds identified for HTS activity screening have been directed, or enriched, for the target or for both 'lead-like' and 'drug-like' physicochemical properties.

The final and perhaps most important discussion concentrated on how to leverage more value from screening data. By understanding the noise within an assay, one can more readily compare activity across different screens, regardless of format, or whether biochemical or biological. One can then recognise cross-reactive or promiscuous compounds and scaffolds that would be problematic for further development, and focus only on the compounds that are truly active and selective for the target of interest [5].

To conclude, the data is the most important factor and the basis from which all our future drug discoveries will be made. What SBS concluded is that we need more information, an increased understanding of systems biology and improved methods of delivering an effective therapeutic to that biological system. In order to do this, our efforts and data must be integrated and, as Christopher Lipinski formerly of Pfizer concluded, the language and culture of chemistry and biology made increasingly more common.

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