MipTec: breaking down the silos of information

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MipTec (http://www.miptec.com), the International Conference and Exhibition on Drug Discovery, was held on 3–6 May 2004 in Basel, Switzerland. The conference is helping to break down the 'silos of information' contained within the many sub-disciplines in the drug discovery field. It actively encourages communication between these disciplines, and has enabled important synergies and a better mutual understanding of the worlds of chemistry and biology. This year, the pre-conference session focused on innovations in anti-cancer drug discovery, in particular small molecule target-based drug discovery.

Biomolecular screening strategies

HTS technologies and processes are being used to support the optimization of leads, as well as the discovery of novel leads from existing data. An excellent example of downstream support was provided by Scott Galasinski of Amphora Discovery (http://www.amphoracorp.com), who described a high-throughput enzymology program. At the other end of the spectrum, Curtis Keith (CombinatorX; http://www.combinatorx.com) demonstrated a method of applying HTS to profile combinations of existing drugs and find new applications. This approach has already yielded multiple clinical candidates. Cellular assays clearly remain the leading technique in the hit-to-lead process, as illustrated by their use in over half the presentations.

Target identification and validation: the race is on!

Three conference sessions presented ground-breaking technologies and methods in this area. Jan Mous (IntegraGen; http://www.integragen.com) described their Genome Hybrid Identity Profiling (GenomeHIP) technology, which enables the identification of disease-related genes by highlighting shared, inherited genomic regions within affected relatives. For early onset of obesity, IntegraGen has identified short regions of the genome that contain five genes likely to be associated with this condition. Similarly, six genomic regions could be linked to the development of autism.

Many metabolic pathways are well conserved in evolution, and Cord Dohrmann of DeveloGen (http://www.develogen.com) presented an alternative approach to identifying novel targets for metabolic diseases. To identify key modifiers of metabolism, DeveloGen performed a genome-wide screen for genes causing metabolic phenotypes in *Drosophila*. This screen yielded many known regulators of metabolic pathways, as well as 200 novel candidate genes.

Gene silencing by RNA interference offers great potential in the validation of potential disease targets in cellular models. François Natt (Novartis; http://www.novartis.com) outlined the methods they used to design and acquire a whole-genome set of RNAi reagents. Novartis used this library successfully in two genome-wide screens to identify targets that modulate a specific cellular process.

Thomas Davis of PTC Therapeutics (http://www.ptcbio.com) gave a presentation on the identification of small molecules that modulate gene expression in an exceptionally selective manner. Their proprietary GEMS technology is based on an understanding of how regulatory elements within the untranslated regions (UTRs) of the mRNA of a gene determine the overall level of production. He showed how screening for modulators of VEGF expression identified potent and selective inhibitors of production.

Structure-based drug discovery and chemical genomics

Structure-based drug discovery and new computational methods are a cornerstone of MipTec. New algorithms are being developed that elucidate specific aspects of protein–protein interaction, helping scientists to better understand – for example – how protein ligands work. There is now also an increasing diversity of chemical space within data sets. Using functional genomics, companies are obtaining more and more proprietary targets, but the structure-based approach is still essential in determining the functions of proteins.

This year, the focus of the session included structural proteomics, the latest advances in small-molecule docking, examples on successful applications of SBDD technology, and attempts to understand – at a molecular level – a complex matrix of interactions of known drugs and drug candidates across a wide range of receptors.

Gerhard Klebe of the University of Marburg (http://www.uni-marburg.de) described the role in ligand binding of water molecules and local backbone

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conformational switches, while Professor Sir Tom Blundell from the University of Cambridge (http://www.cam.ac.uk) gave an overview of structural proteomics and binding studies of small ligand fragments. Flexibility of receptor pockets on binding of small molecules presents a serious computational problem for receptor-structure-based virtual ligand-screening, and Ruben Abagyan of Scripps (http://www.scripps.edu) presented new results based on improved treatment of the induced fit. This will provide better predictive power for the interaction between small molecules and protein targets.

ADME-Tox and preclinical profiling

The role of HTS in the drug discovery process is changing, and there is an increasing recognition of the importance of extending HTS into downstream ADME-Tox. The HTS community is interested in any new technology with ADME applicability, and the use of surface tension measurements is one such technology that has now been adapted from single-compound mode to 96-well plate-based screening mode. Anna Seelig of the University of Basel (http://www.unibas.ch) showed how surface tension measurements were synergistic with computational models in predicting intestinal absorption and blood–brain penetration. Similarly, Paavo Kinnunen of Kibron (http://www.kibron.com) explained how it is possible to translate a formerly slow experimental surface tension measurement to a 96-well automated format without loss of data quality.

In the ADME area, intestinal permeability remains a serious problem in terms of rescuing a flawed compound because to date there is no commercial precedent for a successful formulation. Christopher Lipinski of Pfizer (retired) discussed how pure chemistry considerations dictate when and how to calculate and screen for permeability.

New directions in proteomics

The pace of development in proteomics has accelerated through improved techniques and synergies with other disciplines, and now enables us to investigate protein biology at the molecular, cellular and organism levels. During many conference sessions, several of the speakers expressed a common interest for Alzheimer's disease.

Mass spectrometry is the fundamental technology in identifying proteins and characterizing their post-translational modifications, and its scope is expanding to include new types of preparation. Markus Stoeckli of Novartis showed how MALDI (matrix-assisted laser desorption/ionization) MS has been applied to map the spatial expression patterns on tissue sections for a large number of biomarkers. Both Stoeckli and Michael Przybylski analyzed the composition of amyloid plaques using molecular imaging and MALDI-MS respectively.

Temporal expression patterns are also important for biomarker studies, and the use of biosensors could be a promising method as they achieve excellent temporal resolution. In another innovative presentation, Hughes Bedouelle of the Pasteur Institute in Paris (http://www.pasteur.fr) showed the development of generic reagentless fluorescent immunosensors, where a fluorophore is coupled to a specific antibody. He delineated an efficient design rule that optimizes the sensitivity of the fluorescent signal while preserving the affinity and specificity of the antibody.

Assay miniaturization: small is beautiful

The field of lab chips is emerging from a long development period into an important drug discovery tool. Both off-chip and on-chip assays were covered. Aimo Kannt of Aventis (http://www.aventis.com) described their positive experience with off-chip kinase and protease assays using Caliper chips for separation and detection. The real benefit in these assays is not so much miniaturization – the assays are incubated in 4 µl volumes – but in the separation and sensitivity of measuring the ratiometric fluorescent product and reactant without antibody. Combinations of on-chip and off-chip assays for genomics and proteomics were described by Andrea Chow of Caliper (http://www.caliper.com).

An emerging field of nanostructured surfaces in biology was presented by Martha Liley of the Swiss Center for Electronics and Microtechnology (http://www.scem.ch). Cell growth, motility, gene expression and differentiation are influenced by the surface upon which the cells grow. Using different materials and techniques, self-organizing nanostructures of a great variety can be produced. This could lead to applications of more physiological environments for cell growth, arrays of material with specific binding properties, and high surface areas for miniaturized assays combining high binding capacity and high signals.

Maximizing value from compound collections: quality not quantity

The major focus in the two sessions covering compound management was compound quality. Tony Wilkinson of AstraZeneca (http://www.astrazeneca.com) presented the initiative to enhance their corporate compound collection by improving their physical, chemical and biological quality. This work has resulted in over 40% of the former Astra and Zeneca legacy compounds being removed due to insufficient quality. He also presented data demonstrating the success of target-class directed libraries where hit

rates have been enhanced by up to 100-fold.

Christopher Lipinski discussed the technical reasons for precipitation from DMSO stock solutions. He estimated that up to 20% of compounds stored as DMSO solutions might ultimately suffer from precipitation because of problems relating to crystal packing. Freeze–thaw cycles and water uptake were cited as the major contributing factor in precipitation of compounds during storage.

Best presentation and best poster awards

The Polypops Foundation award for the best presentation was given to Gail Emilsson (Yale University; http://www.yale.edu) for riboswitches as novel antimicrobial drug targets. The Best Poster Awards went to the Swiss Center for Electronics and Microtechnology for patterning of liquid droplet arrays by nanoscale dispensing; a group from the University of Rostock & Bionas for neurochip technology; and a Novartis team for analyzing the consequences of DMSO evaporation from high-density plates.