models for proof-of-principle studies.
- Phenotype analysis. Whole-animal cellular and molecular imaging methods can be used to assess the phenotype (structural and functional) of various tissues and organs in the selected animal models.
- Drug pharmacology. The same imaging methods can be used to investigate the pharmacology of promising leads. Pharmacokinetics, pharmacodynamic and pharmacogenomic studies can be performed at this stage.

Several imaging modalities are now available for conducting these phenotype analyses, some of which were reviewed by Contag. These include, but are not limited to, optical imaging, positron emission tomography (PET), single photon emission computed tomography (SPECT), magnetic resonance imaging (MRI) and spectroscopy (MRS), computed tomography (CT) and ultrasound imaging (US) [1–3]. These imaging technologies are finding application in several fields, including oncology, neuroscience and cardiology. For a given application, each technique has intrinsic potentials and limitations and, thus, selection of the appropriate technique is important. Overall, the use of imaging is likely to provide high quality phenotype, and in some cases genotype, information that are difficult to obtain otherwise. Of importance is the ability to use the same animal as its own control. This improves statistical quality and leads to a reduction in the number of experimental animals used in biomedical research. It is almost certain that small-animal cellular and molecular imaging will replace traditional lead optimization technologies in the future. For this to happen, acquisition and analysis interfaces need to be simplified and more efficient data storage (gigabytes), reconstruction and resolution recovery algorithms need to be developed. The challenge then, according to Contag, will be that such data generated from molecular imaging will define a 'value proposition' to the industry [1].

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High throughput in drug discovery

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Research and development costs in the pharma industry are steadily increasing, from ~US$20 billion in 1990 to ~US$50 billion in 2000; however, there is no corresponding increase in success rate. In the past two decades, the output remained constant, at 30–50 new chemical entities (NCEs) per year. To what extent can new drug discovery technologies improve this ratio? Where are the bottlenecks? How can organizations speed up and industrialize their R&D process? These questions were discussed at the recent IBC Life Sciences conference *Drug Discovery Technology Europe 2002. Where Science Meets Business*, 15–19 April 2002 in Stuttgart, Germany (www.drugdisc.com/europe).

The topics of the *Science Stream* section of the conference concentrated on better approaches for target discovery, prioritization and validation, and on dedicated methods for lead discovery and optimization. Introductory lectures presented overviews on current practices in big-pharma. Martin Mackay (Pfizer, Groton, CT, USA) discussed strategies to reduce costs, in this manner increasing productivity. Of importance are an integration of technologies, the 'industrialization' of the drug discovery process, a focus on chemistry, the investigation of target families, mining of dense arrays of data, information networks with data sharing and real time access to all data. Pfizer, as well as Novartis, heavily rely on research alliances (e.g. the Novartis–Vertex US$800 million research collaboration; ~30% of the Novartis research budget is spent in external collaborations). Target validation is a highly time-consuming process and Jutta Heim, from Novartis (Basel, Switzerland), emphasized the importance of a strict prioritization of many potential targets. In her company, the process of target validation runs parallel to the lead discovery, optimization and candidate selection process.

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Target discovery and validation

High density cDNA or oligonucleotide arrays are used for expression profiling. Onno van de Stolpe (Galapagos Genomics, Mechelen, Belgium) discussed the advantages of PhenoSelect™ arrays (adenoviral human cDNA expression libraries), to validate potential targets that induce specific, disease-related phenotypic changes in human cellular assays. Proteomics has an important role for the discovery and validation of relevant targets and for the identification of toxicity markers. Arrays of functional proteins were described by Roland Kozlowski (Sense Proteomics, Cambridge, UK). The proprietary COVET™ technology enables high-throughput parallel cloning, expression and flexible arraying of functional proteins that retain biological function in their immobilized form. The eTag™ reporter system of Aclara BioSciences (Mountain View, CA, USA), presented by Sharat Singh, enables solution-phase, multiplexed assays for the measurement of both gene and protein expression in biological samples, by concurrent measurement of intracellular, membrane and secreted proteins together with their post-transcriptional modifications.

Functional proteomics can be approached by chromophore-assisted laser inactivation (CALI) of proteins, as illustrated by Gerald Beste (Xerion Pharmaceuticals AG, Munich,Germany). This technology and its industrial scale extension XCALIbur™ enable temporary and locally restricted protein knockouts. Unknown targets can be simultaneously identified and functionally validated. Whereas some companies, for example, WITA Proteomics AG (Teltow/Berlin, Germany), have brought proteomics to ultra-high resolution (10,000 spots in one gel), Celera Genomics (Rockville, MD, USA) follows a different strategy, as described by Terence E. Ryan. An industrialization of the proteomics laboratory has been achieved by digesting all proteins, separating the peptides by HPLC and characterizing them by sophisticated MS methods (another 'shotgun' approach, now in proteomics!), instead of investigating 2D gels.

Lead discovery and optimization

An aequorin-based screening technology for GPCR ligands was reported by Paolo Meoni from Euroscreen (Brussels, Belgium). Many GPCRs are already coupled to calcium ions and others can be coupled, regardless of their physiological transduction pathways. This enables the detection and characterization of ligands by a homogeneous fluorescence test. A general model for ligand screening was presented by Sanj Kumar, DiscoveRx (Fremont, CA, USA). A deletion mutant of β-galactosidase is only functionally active in the presence of a peptide that contains the deleted sequence. Coupling of this peptide with the ligand of a test protein prevents association and abolishes β-gal activity because of the affinity of the ligand to its protein; if competing ligands are present, the ligand–peptide conjugate can re-establish β-galactosidase, which is monitored by its enzymatic activity.

The concept of chemogenomics was illustrated by Paul R. Caron, Vertex Pharmaceuticals (Cambridge, MA, USA). It is impossible to investigate the chemical universe against the target universe, however, the focus on certain chemotypes and target families offers certain advantages. The investigation of kinases has produced >300 biologically active scaffolds that cover 80% of the kinase space. Several presentations discussed the importance of 'beautiful compounds' (drug-like, orally available, non-toxic, pure and exclusive) and 'beautiful binding sites' (druggable targets are often characterized by buried binding pockets that have hydrophobic character but also the potential of hydrogen bond interactions). In addition to therapeutic relevance, druggability of a target is a major issue.

High-throughput ligand discovery

Special emphasis is put on high-throughput crystallography in drug discovery. Mike Tennant (Syrrx, San Diego, CA, USA) described their 'gene to drug' platform, including HT crystallography, computer-aided ligand discovery, the use of small molecular probes, docking and scoring. Advances in the expression of different constructs, automated protein crystallization and the speed-up in X-ray data collection and analysis were the focus of the presentation by Tom Blundell, University of Cambridge and Astex Technology (Cambridge, UK). Recent highlights were the crystallization of several human CYP isoforms and the first 3D structure elucidation of one of the CYPs that is relevant in human drug metabolism (type not disclosed).

Virtual screening technologies were discussed in detail by David Bailey, De Novo Pharmaceuticals (Cambridge, UK), Rob Brown, Accelrys (San Diego, CA, USA) and Hugo Kubinyi (University of Heidelberg and BASF AG, Ludwigshafen, Germany). Although there is further progress in pharmacophore recognition, for example, Quasi2™ (De Novo Pharmaceuticals), and docking methods, reliable scoring functions are still a major issue. New developments are design strategies for combinatorial libraries, for example, the program CombiGen (Thierry Langer, University of Innsbruck, Austria) and combinatorial docking of ligands (FlexX-C, BioSolveIT, Sankt Augustin,Germany).

Lead discovery is accelerated by compound file enrichment, ultraHTS and hit optimization with structure-enabled drug design, as exemplified by Jeremy R. Everett (Pfizer, Sandwich, UK). Novel parallel synthesis technologies in conjunction with novel design principles achieve high productivity and high quality in hit-to-lead projects. Roger Crossley, BioFocus (Sittingbourne, Kent, UK), illustrated the design of biased libraries for GPCRs, whereas Gert Bolwig from Combio A/S (Copenhagen, Denmark) discussed the screening of on-bead

libraries for specific metalloprotease inhibitors. Stephen L. Gallion, ArQule (Medford, MA, USA), presented biased ligand arrays for voltage-gated ion channels; chemical libraries are characterized by 10,000–20,000 analogues of multiple chemotypes.

MIDAS™, a synthetically driven platform for rational identification of peptide ligands and their potential conversion to non-peptidic analogues, was described by Shubh Sharma, Palatin Technologies (Princeton, NJ, USA). Cys-containing peptides form chemically stable complexes, in which an X–Y–Cys sequence is conformationally restricted by complexation with an oxo-Re metal ion.

Nucleic acid inhibitors, especially aptamers, were discussed as tools for the validation of drug targets and for the development of small-molecule leads by Michael Famulok, University of Bonn (Germany), and Michael Blind (NascaCell GmbH, Tutzing, Germany). From libraries containing up to 10^{15} different sequences, functional oligomers are selected for their ability to bind to a certain protein. The process of selection and optimization of the nucleic acids has recently been automated.

The outcome

Although some contributions raised more questions than answers, the conference provided an excellent overview on current drug discovery technologies and especially on the enormous progress that has been made in recent years in target validation, as well as lead discovery, optimization and development. An exhibition with ~70 participating companies gave an overview on the available commercial solutions.

Bioinformatics – From Genomes to Drugs

Edited by Thomas Lengauer, Wiley-VCH, 2001, Price £170.00, 680 pp, ISBN 3-5272-9988-2

Bioinformatics is big business today for simple reasons of supply and demand. Consider the 'supply' to be the burgeoning corpus of data requiring our urgent attention, culminating in the sequencing of the human genome, but extending also to all manner of scaled-up platform technologies. The 'demand' then arises from the ultimate economic basis for the lion's share of this activity: human health, in particular the need to apply genomic knowledge to the discovery of new drugs. *Bioinformatics – From Genomes to Drugs* promises by its title to be the first book to comprehensively close the loop between genome-based bioinformatics and actual drug discovery. Such an expectation is reinforced by the fact that this publication represents Volume 14 in the Wiley-VCH series *Methods and Principles in Medicinal Chemistry*. So, how does it go about attempting this connection, and how well does it succeed?

The book is a compendium of review articles by 14 different sets of authors, and as in many such collections, the entries on each topic range from comprehensive reviews of the literature, to rather more didactic presentations of the subject matter, to even more detailed methodological disquisitions skewed towards the author's own work. In this book, the articles tend to be of a high quality; most make a useful reference for their individual topics. As well as the utility of the discrete articles within such an anthology, their selection and organization, and how this framework contributes to the overall theme, is also of interest. In structuring the collection the editor posits a basic distinction between 'intrinsic' approaches, centered on the fundamental problems in the field and the technologies adopted to address them, and 'extrinsic' approaches involving actual applications. The book is presented in two volumes to reflect this, with the first part, *Basic Technologies*, being approximately twice the length of the second, *Applications*.

Although bridging the gap between basic technologies and applications is a well-worn path in science, it proves to be dissimilar to connecting the undoubted riches of the genome to the promise of new drugs. The comparatively slim tome addressing extrinsic applications does not convincingly close this gap, and in fact the overall content leaves one with the impression that there is a more significant and persistent division in the field than that between the intrinsic and the extrinsic. Rather, the truly notable hiatus evident in this book is that between the bioinformatics of genes and genomes, and the computational structural biology and chemistry that actually deals with targets and drugs. Divided along these lines, the content is actually split more nearly down the middle.

The half of the book that deals with informatics of genes and genomes covers such topics as sequence analysis, gene identification, regulatory region analysis, support of sequencing projects, database technologies, and so on. These

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