Chemical genomics versus orthodox drug development

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The recent *Genomics on Target* conference (18–21 November, 2002, Boston, MA, USA; http://www.genomicsontarget.com) addressed major issues facing the pharmaceutical industry, from target discovery and validation to animal models. However, perhaps the most intriguing issue was chemical genomics. Although the speakers could not agree on a specific name for this new philosophy, let alone a precise definition, those present agreed that recent genomics-focused drug discovery efforts have largely been an expensive failure. Fortunately, the general consensus was that chemical genomics approaches have the potential to add real value to this current pharmaceutical orthodoxy.

Targets for drugs

Rather than finding drugs for targets (e.g. genomics-, transcriptomics- and proteomics-based hypothesis-driven strategies), chemical genomics finds targets for drugs (Box 1). Although chemical genomics has the 'omics' tag that is evidently required for all new biotechnologies, chemical biology is a better generic term for the process, as all these techniques use chemistry (e.g. small molecules with known biological activities) to probe biology (e.g. cell-based phenotypic assays). The ultimate goal of chemical biology is to discover the specific molecular targets and pathways that are modulated by a particular chemical probe. This new chemical tool, termed the 'perturbogen', is used to perturb a biological system and thus probe and understand the biochemistry underlying a chemotype (a chemically induced phenotype).

A classic chemical genomics strategy

This concept of starting with a physiological effect, identifying the drug and using it to understand mechanism of action, ultimately leading to a better drug, certainly pre-dates the genomics era. The earliest known medical treatise (the Egyptian Ebers Papyrus, *c*1550BC) describes the antirheumatic properties of the myrtle tree. Although willow and myrtle extracts were commonly used to treat pain and inflammation, the active pharmacological agent was to remain unknown for over 3300 years, until Raffaele Piria purified salicin from willow bark (*Salix alba*) in 1829. In 1897, Hoffman (at Bayer) led the first medicinal chemistry effort with the development of acetylsalicylic acid (aspirin), yet the mechanism of action for the salicylates remained a mystery until 1971, when John Vane identified prostaglandin synthesis as the target pathway for the effects of aspirin (for which he shared a Nobel Prize in 1982) (see [1]). Cyclooxygenase (COX)-1 was isolated five years later (1976) and cloned after another 12 years (1988), and COX-2 was cloned several years later (1992). Many big pharmas joined the race to identify a potentially safer COX-2 selective NSAID, with successes in 1999 for Searle (celecoxib) and Merck (rofecoxib).

A recent report characterizing a new COX activity (COX-3) highlights the crucial role of chemical genomics in pharma R&D. The existence of another COX was postulated because acetaminophen (paracetamol) has little

Box 1. Chemical genomics inverts the typical discovery process

Current pharma orthodoxy: finding drugs for targets

'Omics $\xrightarrow{1}$ Target $\xrightarrow{2}$ Compound $\xrightarrow{3}$ Effect

1 DNA, RNA, protein profiling
2 Target-focused HTS
3 Phenotype assays

Chemical genomics strategy: finding targets for drugs

Effect $\xrightarrow{1}$ Compound $\xrightarrow{2}$ Target $\xrightarrow{3}$ Better drug

1 Phenotypic HTS
2 Chemical genomics
3 Target-focused HTS, medicinal chemistry

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activity against either COX-1 or COX-2, yet is a potent analgesic. Ironically, given the vast resources (genomics, transcriptomics and proteomics) dedicated to this class of enzymes by big pharma, it took an academic group using the drug itself as a tool to find and characterize this new COX enzyme [2].

The drugable genome: unexploited territory

Gregory Petsko (Brandeis University, http://www.brandeis.edu) kicked off the conference by highlighting the harsh reality of current drug development. He described how both chemistry and biology remain largely unexplored, with ~50% of marketed drugs falling into only 32 chemical classes, and >50% of genes having no known function. How can one rationally undertake target-driven drug discovery under such circumstances, when the functions assigned to genomics-derived targets are largely speculative? Petsko also reminded us that in spite of, or perhaps because of, Lipinski's rules [3], much small-molecule space remains unexploited. For example, cisplatin, a highly successful oncology drug, contains no carbon atoms and would probably today be discarded by any pharmaceutical company.

David Brown (Cellzome, http://www.cellzome.com), who recently left big pharma after a successful record at Pfizer and Roche, proposed that the current big pharma paradigm, emphasizing target-based screening, is unsustainable. For example, less than 2% of compound screens ultimately result in a marketed NCE, at a cost of US$800 million per drug. Brown emphasized the need to exploit the 'drugable genome'; that is, to focus on targets identified using an active small-molecule probe. These, by definition, will be chemically tractable (drugable) targets and worthy of the commitment of valuable medicinal chemistry resources. Cellzome's technology, like others presented, uses a perturbogen as bait for the target(s) within a specific cell or tissue. Cellzome uses an advanced mass-spectrometry system to identify proteins pulled down by the bait molecule. Proteins that bind with high affinity are presumably those responsible for the effect of the perturbogen on phenotype. Along with many others, Brown highlighted the ability of chemical genomics to exploit known drugs with unknown mechanism of action to identify and characterize a target, thereby generating improved drugs that can circumvent intellectual property concerns.

Model organisms: uncovering potential targets

Another theme of the meeting was the power of model organisms in both target discovery and screening. Guri Nina Giaever (Stanford University, http://www.stanford.edu) presented a fascinating approach using yeast as a model system for chemical genetics. Giaever's group exploits the simple premise that a haploid yeast, defective in one allele of a given gene, is more sensitive to the effects of perturbogens that specifically affect that target protein [4]. They have taken the brute-force approach of generating ~6000 haploid strains covering essentially all yeast genes, treating this pool with a drug, and then analyzing growth effects on the mixed population. Strains haploid for the target of the drug will grow more slowly and thus be under-represented in the final population. A major benefit of a yeast model system vs the typical proteomics approach is that ~1000 perturbogens with unknown mechanism of action can be screened per year. Successful examples of this approach included cisplatin, methotrexate and amphotericin B.

Moving further along the evolutionary scale, Kevin Fitzgerald (Bristol-Myers Squibb, http://www.bms.com) described how *Caenorhabditis elegans* could be used to uncover potential targets for human diseases as complicated as Alzheimer's and spastic bladder incontinence. He reminded us of the many marketed drugs with unknown mechanism of action (including thalidomide, metformin and lithium), and also echoed a common theme of the meeting – that every big pharma drops good compounds from development because of a lack of understanding of their mechanism of action. These compounds, elegantly named 'fallen angels', can now be resurrected through a chemical genomics approach. Fitzgerald also highlighted the powerful synergy of chemical genomics with tools that modulate gene expression. For example, if RNA interference (RNAi) ablation of a putative target mRNA accentuates a chemotype caused by a perturbogen, this certainly strengthens the case for the role of that target in the effect of the drug.

High-throughput target discovery

Other companies reported on uHTS cell-based approaches. For example, Kalypsys (http://www.kalypsys.com) uses phenotypic and target-based screens to plough through a massive 2.2 million-compound library at 1.5 million datapoints per day in a 1536-well format. Given the volume of hits generated by such approaches, timely presentations from several medicinal chemists reminded the automation-obsessed biologists that the real bottleneck of chemical biology is the chemical aspect. Lutz Weber (Morphochem, http://www.morphochem.com), Gerhard Müller (Organon, http://www.organon.com), and Herbert Waldmann (Max Planck Institute of Molecular Physiology, http://www.mpi-dortmund.mpg.de), emphasized that when targets are well-defined, chemists are much more likely

to generate compounds with appropriate drug-like properties. Müller noted that a relatively small number of similar pharmacophores have been successfully exploited against many different targets (e.g. in developing inhibitors of COX-1 and -2, the DAT dopamine transporter, p38 kinase and the CB1 cannabinoid receptor). He therefore suggested that a 'master key' approach can generate privileged backbone structures designed for specific target classes, and that these backbones can be readily fine-tuned for particular targets.

In contrast to the ultra-HTS (uHTS) screening strategy, David Szymkowski (Xencor, http://www.xencor.com) presented a new approach to chemical genomics. Xencor uses small molecules as target bait; however, rather than purifying and identifying proteins directly (described as the Lady MacBeth approach to proteomics – 'out, damn spot... hell is murky'), Xencor's ProCode™ technology tags each protein with the unique expression vector containing its relevant cDNA. Once the drug bait pulls down the protein–DNA complex through affinity panning, the protein is discarded and the remaining DNA tag is isolated, cloned, amplified and sequenced. Thus, selection is based on protein binding, but all later steps take advantage of the DNA tag, which ultimately identifies the original target of the perturbogen.

Do better targets make better drugs?

The meeting also emphasized how chemical genomics can help balance a portfolio of intrinsically high-risk novel genomics targets by identifying lower-risk drugable targets. An excellent session on the business aspects of chemical genomics suggested that the goal of biotech and pharma should neither be to develop 'me too' versions of drugs on the market, nor to focus solely on novel genomics targets. Rather, as explained by Steven Holtzman (Infinity Pharmaceuticals, http://www.ipi.com), the greatest value might be generated by developing drugs for new targets in validated ('precedented') pathways (e.g. the clinically proven TNF signaling pathway). Philip Ma, a consultant with McKinsey (http://www.mckinsey.com), presented a realistic but gloomy picture of drug R&D: productivity is down while costs are up in both pharma and biotech. According to Ma, even if chemical genomics generates more INDs, the only way this early-stage technology could have an impact on the bottom-line is if it significantly reduces late-stage development failures. Thus, the true value of the chemical genomics approach cannot be assessed for 5–10 years.

Future implications

In spite of the depressed biotech market, the mood was upbeat for this very young field. Participants and speakers felt they were a part of a truly new approach to develop biologically relevant and drugable targets. Whether we called our strategies chemical genomics, chemogenomics, chemical genetics or chemical biology, the consensus was that great value lies in understanding how drugs work. Whether derived from pharmacologically active natural products or cell-based phenotypic screening, too many marketed drugs or 'fallen angels' have an unclear mechanism of action or unexplained side-effects. Chemical genomics can now help to identify the molecular targets of these drugs; therefore, rather than following the current pharmaceutical orthodoxy of starting with the target to find the drug, the approach should generate targets that are inevitably drugable. This early marriage of biology and chemistry promises to reduce the enormous risk associated with target selection, screening, and drug development. Although this second annual Cambridge Healthtech chemical genomics conference was short on concrete examples of 'finding targets for drugs', it is still early days. Certainly, the list of orphan compounds in the Physician's Desk Reference alone will provide enough material for the creative energy of chemical biologists for the foreseeable future.

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