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All systems go?

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What is systems biology? Like so many buzz-words that have floated through the drug discovery community over the years (biomarkers being an excellent example), the term has as many definitions and potential applications as there are people talking about it. Interest in systems biology has waxed and waned, and the field has experienced periods of hyperbole, caution and measured optimism. However, there is little doubt that the approach has great potential for transforming molecular knowledge into an appreciation and understanding of the complexity of pathways and networks in human physiology and disease. There is also little doubt that biomedicine and the pharmaceutical industry stand to be significant beneficiaries of the promise of systems biology, whether applied to: (i) identifying new drug targets by pinpointing key areas for intervention in disease pathways; (ii) providing insights into adverse effects of drugs; (iii) defining improved surrogate markers; or (iv) providing the means for stratifying patient populations in clinical trials. The question is, in the quest to improve poor rates of drug approval, will the pharmaceutical industry forsake the traditional high-throughput lead-finding paradigm and fully embrace the supposedly 'smarter' approaches such as systems biology? Is systems biology the answer to pharmaceutical companies' supposed woes?

These were some of the fundamental issues discussed at the Implementing Systems Biology meeting (organised by IBC Life Sciences; http://www.ibclifesciences.com), held in Boston, MA, USA, 20–22 September 2004. The conference agenda was assembled in order to facilitate dialogue and debate among attendees. Traditional short presentations, keynotes and case studies were present throughout the meeting, but the conference program was centred around eight 'scientific exchange' sessions. These sessions comprised facilitated discussions where a chairperson provided an overview of the topic of interest, defined the area to be discussed and then guided members of the audience through a debate on that topic. The idea was to use this forum to exchange ideas, respond to questions and explore key challenges in the field. In many ways this is a high-risk strategy because similar efforts at industry meetings, such as panel discussions, are often accompanied by the sound of imaginary tumbleweeds blowing through the conference venue as meaningful debate is stifled by the lack of attendee participation. Fortunately, the meeting was small (70–80 attendees), which encouraged members of the audience to get on their feet and to ask questions, to express an opinion or to simply stir things up a little with a little controversy. On the whole, these scientific exchange sessions worked very well.

Spotlight on modelling approaches

The conference opened with a 'spotlight session', where speakers gave short presentations on a variety of predictive models for systems biology research. Among these, Zoltan Szallasi (Harvard Medical School; http://hms.harvard.edu) provided a useful overview of knowledge representation and modelling approaches in biology, and Bart Hendriks from AstraZeneca (http://www.astrazeneca.com) described a collaboration with the Lauffenburger laboratory at Massachusetts Institute of Technology (http://web.mit.edu/cbe/dallab/), involving the development of a computational model of the ErbB receptor tyrosine kinase signalling network. The model has attempted to explain the complexity of the ErbB system, accounting for receptor dimerization and trafficking, and kinase cascades, for example. This model has been used to simulate various drug interventions and in an attempt to determine why many patients are not responsive to therapies that target this system. This work is particularly interesting because it has had a genuine impact on drug development at AstraZeneca, contributing to clinical trial design and target selection. Colin Hill (Gene Network Sciences, USA; http://www.gnsbiotech.com) wrapped up the session, describing the modelling technologies developed by his company, focusing on those applied to pre-clinical and clinical oncology.

Fundamental questions

The first scientific exchange session covered some of the fundamental issues concerning the implementation of integrative approaches in the drug discovery space. This session was facilitated by Steve Naylor [Computational and Systems Biology initiative (CSBi), MIT; http://csbi.mit.edu], who explained that systems biology is at an evolutionary crossroad in that there are lots of ideas and excitement, and a certain amount of infrastructure being built (e.g. the new initiatives at Harvard and MIT), but there are still questions concerning exactly how systems biology will add value to the drug discovery process and whether the

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industry will be able to justify the expense of conducting systems biology experiments. Naylor also made the perhaps provocative statement (always good for stirring up some debate in these circumstances) that if individual omic technologies have had little impact on development pipelines so far, what is the point in adopting a systems ethos and combining them to form a mess? These and other questions were thrown into the mix and it soon became apparent during this session that there are a multitude of questions and comparatively few answers at present in systems biology, particularly where drug discovery is concerned, and this disparity was noticeable throughout the meeting. Some key points emanating from this session were that pharmaceutical companies need deliverables now and that the field of systems biology is currently not in a position to oblige in any meaningful way, although there are examples of companies dipping their toes in the sea of integrative biological approaches through collaborations with academia or small systems-biology companies. However, by the time systems biology is in a more mature state, and hence in a position to contribute real value to pharmaceutical R&D, it is likely that some years would have passed – and will industry still be interested then?

The second scientific exchange session 'Are we asking the right questions in systems biology?' was chaired by Michael Liebman (Windber Research Institute, USA; http://www.wriwindber.org). Several pertinent points were raised during this session, not least by Liebman himself, who stated that it is patients who are at the top of the food chain and that these endeavours should focus on helping patients, not just improving pharmaceutical companies' bottom lines. This is something that is often overlooked as the industry frets about falling revenues and the inadequacies of current drug pipelines, and it was refreshing to hear this stated. Relating to this, the question of the kinds of datasets one needs when embracing systems approaches was raised. Genomic, proteomic and metabolomic data often tend to dominate the systems space, particularly when considering bottom-up approaches, but in order to gain new insights into the cause and progress of disease, in addition to the translation of the tools and insights of systems biology into clinical utility, the integration of clinical data such as patient studies is essential, although the 'hows' and 'whens' of this are a little more difficult to address. On a related note, from the audience, Kevin Hall (Laboratory of Biological Modeling, National Institute of Diabetes and Digestive and Kidney Disease; http://www.niddk.nih.com) raised the point that in this high-throughput omic-centric age, there are not enough people doing low-throughput physiology experiments to generate the kind of data needed to constrain and validate predictive models, something that needs to be addressed if the field is to move forward.

Subsequent exchange sessions tackled issues of organizing systems biology in pharmaceutical organizations, as well as a session chaired by Melissa Cline from Affymetrix (http://www.affymetrix.com) on the measurement technologies that are integral to systems biology and the challenges associated with precisely measuring a greater number of biological entities simultaneously.

A remedy for 'happy talk'

It was clear during this and preceding sessions that a large proportion of attendees were struggling to come to terms with the role systems biology has to play in industry. Although the field is a relatively mature one in academia, it is still at an embryonic stage in the private sector. The single target–single disease paradigm appears to be now falling short, particularly when dealing with chronic, complex diseases. There was a general consensus that systems biology has a role to play in the search for innovative targets, particularly as the datasets, and the means to generate them, are now available to move the field forward. However, there was also a fair degree of scepticism voiced by several attendees to counteract any 'happy talk' present during the discussion. Several attendees from industry explained that there are still no success stories to show management in pharmaceutical organizations, who are obviously unwilling to bank the future of a company on what is still an unproven area. It was suggested that drug discovery will probably make better progress by adopting ever higher-throughput technologies rather than systems biology – it is better to be lucky than smart, as somebody remarked. One attendee even suggested that systems biology is unlikely to deliver more than rational drug design – a buzz word of the 1980s – did, the promise of which was superseded to a certain extent by approaches such as combinatorial chemistry. Similar to rational drug design, systems biology will form part of the drug hunter's armoury, but is unlikely to be a panacea.

Teaching systems biology

A particularly interesting session on the final morning concerned the training of interdisciplinary researchers that are required to move systems biology forward. The session was chaired by Brigitta Tadmor (CSBi), who explained that systems biology requires new tools and paradigms, a new research model and a new generation of researchers, and went on to outline the MIT effort dedicated to developing interdisciplinary researchers. This graduate initiative is a multi-disciplinary effort involving the maths, physics, chemistry, neuroscience, biology, engineering health sciences

and computer science departments at MIT, and graduates are rigorously selected on the basis of their ability to interface between disciplines. Other efforts such as those at Princeton and Harvard were also outlined, although a key point that was made was whether such integrated approaches need to be taught much earlier than the undergraduate and graduate levels. Another important point raised was that these efforts are designed very much for the future of the field whereas success stories are needed now, otherwise the field will lose momentum, particularly as far as the pharmaceutical industry is concerned. Tadmor emphasized that it was important to have industry involved and that for the field to move forward it is necessary to have researchers in both academic and industrial arenas that see value in the approach, although she conceded that the pharmaceutical industry was the most conservative industry that MIT has ever collaborated with.

The final exchange session was chaired in authoritative fashion by Bernard Palsson (University of California San Diego; http://www.ucsd.edu) and served to provide a summary and overview of the meeting, identifying crucial issues in systems biology, including mathematical method development and integration of multiple high-throughput datasets.

The conference closed with a session on the leading consortium programs aiming to help speed the adoption of systems biology methodologies. These included presentations by Eric Neumann (Aventis; http://www.aventis.com) on the Semantic Web, Joanne Luciano (Harvard Medical School) on the BioPAX initiative and Randall Julian (Eli Lilly; http://www.lilly.com) discussing the HUPO Proteomic Standards Initiative.

Concluding remarks

The Implementing Systems Biology meeting was interesting and made a pleasant change to the standard conference format. This is clearly a subject that needs active dialogue within the community and this meeting, with its scientific exchange sessions, encouraged such debate. It is clear that there are many other issues within the drug discovery arena that could benefit from being discussed in a similar matter. The meeting was attended by a relatively small number of delegates and it was disappointing that there was not a greater representation from large pharmaceutical companies but, despite this, the meeting was still useful and timely. Perhaps unsurprisingly, there were little answers forthcoming to some of the issues raised but the meeting still served to provide an excellent appreciation of the current status of the field. Clearly, industry is not going to wholeheartedly embrace systems biology straightaway. However, a selective and practical introduction of systems approaches in the discovery pipeline might be the way forward. There are certain applications of integrative approaches that might pay quick dividends, such as toxicogenomics, and in this way the value of systems biology will become obvious, providing the impetus for a greater adoption of this approach within industry.

Molecular targets and cancer therapeutics

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The *16th EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics* was held 28 September to 1st October in Geneva, Switzerland. This annual meeting is the premier world conference devoted to the elucidation and validation of molecular targets in cancer and the discovery and development of cancer therapeutic strategies. The meeting is organised under the auspices of these leading cancer research societies: the European Organisation for Research and Treatment of cancer (EORTC); the US National Cancer Institute (NCI); and the American Association of Cancer Research (AACR)*.

The inclusion of parallel workshops covering contemporary topics such as 'Marketing Approval for Anticancer Agents', 'Preclinical Models', 'Mechanistic Combinations' and 'Pharmaceutical Industry, Investigators and Institutions: Partners or Tools?' was a particularly pleasing aspect of the meeting, and in the last case provoked some intense and passionate debate on the relationship between academic clinicians and 'big pharma', with notable contributions from Eric Rowinsky (Institute for Drug Development, San Antonio, Texas; http://www.ctrc.saci.org) and George Blackledge (AstraZeneca, UK; http://www.astrazeneca.co.uk).

The breadth of topics covered by the plenary presentations gives a snapshot and flavour of the most sought after

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