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Question: what do you call 500 scientists coming together to address the productivity gap? Answer: a start

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PharmaDiscovery 2005 brought together ~500 leading industry scientists in Washington DC (USA) to discuss issues related to the pharmaceutical industry productivity gap. The conference adopted a novel format, involving parallel sessions with defined questions, objectives and goals. The summaries of the sessions were reported back to all the delegates for information and discussion. This article intends to crystallize the findings and key learning points of the various sessions, aligned against the different phases of the drug discovery pipeline.

Setting the scene

All of us are familiar with a standard conference format, where a broad theme is approached, be it drug discovery, pharmacology, cell biology, medicinal chemistry or any number of other topics. In essence, the programme consists of highly eminent speakers who give presentations of the latest science in their field. This is a tried and trusted method of information exchange that is excellent for keeping people abreast of developments in science, as well as acting as a forum for the discussion of controversies in the field. The Elsevier event, *PharmaDiscovery*, which took place on 10–12 May 2005, attempted to present a new conference model. In this, the conference was intended as a tool to engender debate that would suggest potential solutions to the so-called productivity gap through three parallel sessions. The speakers and chairpeople were briefed to direct their presentations towards overarching questions germane to that topic. After discussion within the sessions, the chairpeople (Box 1) reported back across the sessions through 'Sum-up Sessions', which enabled all delegates to receive a summary of the key points from each session.

Here, some of the major discussion points and conclusions drawn from the various sessions are reviewed. In addition, we conducted a survey of those scientists present at the sum up sessions, by way of voting buttons, much in the style of TV quiz shows, such as 'Who wants to be a Millionaire?'. The audience was mainly composed of individuals from the pharmaceutical and biotechnology industries (59%) and academia (15%). Of those, 42% were senior management, 31% research scientists (some at senior level) and 7% were head of laboratory or lecturer. An overwhelming majority (88%) believed that the productivity gap was real, rather than perceived, although only 59% thought that the number of new chemical entities (NCEs) was a good measure of research success. Again, an overwhelming majority (89%) thought that the productivity gap had not arisen because of a reduction in productivity by scientists *per se*, but as the result of other (as yet undefined) factors. Clearly, pharmaceutical consolidation was viewed as a major factor related to productivity, with 82% of the audience feeling that it has had a negative impact on output. Perhaps of greater concern, with respect to the articles by Schmid and Smith [1] and Sams-Dodd [2] in this issue of *Drug Discovery Today*, is that 64% of the audience considered that their organization, at best, only supported innovation to a moderate extent.

Target identification and target validation

Target assessment

The goals for this session were that participants should come away knowing about the fundamentals for successful target assessment studies and how this might help elevate the number of filed NCEs. Part of what they tried to achieve was to remove layers of ambiguity with respect to definitions of systems biology (approaches and technologies) and how that might have an impact on drug discovery. One of the key conclusions was that the causal mechanisms of most of the major diseases and the status of systems biology are not understood. The overall feeling from various speakers was that the predictive capability of systems biology was surprisingly good. Modelling using a systems biology approach is aiding in a focused drug discovery effort.

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BOX 1

The summarizing chairs of the various sessions

- Steve Naylor
- Tomi Sawyer
- Jan Tornell
- Jason Altar
- Patrick Nef
- Mark Murcko
- Eric Neumann
- Ian Wilson
- Ronald Doll
- James Stevens
- Anthony Quinn
- Martyn Banks

However, if causal mechanisms of disease are not understood at a fundamental level, then how can drugs that address the root cause of disease be developed in a systematic way? It is perhaps for that reason that 64% of the audience thought that it would take at least five years for systems biology to have a meaningful impact on drug discovery.

'65% of the audience at *PharmaDiscovery* considered that sequencing of the human genome did not have even moderate effects on effective drug research'

Pharmacological models for human disease

There was a consensus that to improve the productivity of R&D it is necessary to enhance the predictive value of models used in R&D research. The knockout mouse project attempts to understand the function of all genes by using knockouts, and to put the information into the public domain. Current challenges to using mice to model human disease were identified as differences in pharmacokinetics (PK), species-specific compounds, how and what functional measurements should be made, the relative roles of homologous proteins that could have different functions and the question of differing physiologies.

Humanization of mice was seen as a possible way to address some of these issues. The introduction of human genes, such as cytochrome P450 and peroxisome proliferator-activated receptor isotypes can lead to a more human-like response with respect to drug metabolism. These methods could also produce a more predictable response in animals and help to identify fingerprints, based on proteins and metabolites, for the establishment of markers in models that are predictive for disease, safety and efficacy in humans. The importance of using multiple species to predict the outcome in humans was also stressed. Another point raised was that, although it is possible to predict efficacy data from animal models into humans, it might be more challenging to predict PK properties. It is vital to understand the opportunities, but also the limitations, of current models and perhaps, at present, this is not done in a systematic way. Understanding the limitations of models will enable the production of better models, because the technology to make such changes already exists. It is therefore essential that the model development process is iterative between clinical and preclinical research to ensure maximal predictive value.

CNS disease models

Can neuroprotective models be predictive of what goes on in the clinic? For stroke, the models and the clinical situation are extremely different, which is reflected by the failure of molecules in the human condition. In depression, models are available, ranging from simple to the highly complex model of anhedonia. Are these predictive models? Some say aspects of these models are and some are not and only clinical studies will unravel the predictive power of these approaches.

Using imaging technologies in preclinical models could add another dimension to their predictive power, but, at present, resolution, sensitivity and cost are factors negatively affecting their impact. The final part of this section dealt with long-term potentiation in hippocampal slices. This clearly is a great departure from behavioural models of disease. However, such approaches can address the molecular and cellular bases of mechanisms essential for behaviour and brain function. These studies can provide the rationale to address a particular target and the means to discover compounds that modulate those targets. Neurochemical or neuroanatomical changes are more robust than affective or cognitive change. There is some dichotomy between the validity of neurodegenerative versus psychiatric disease models. However, we are left with the dilemma of how to advance proof-of-concept molecules that cannot, by definition, have a validated predictive model.

'79% of the audience at *PharmaDiscovery* said that productivity was hampered to a moderate or great extent by lack of access to relevant animal models'

In vivo models in drug development

This session was organized around three themes: (i) what are the major issues in drug development that new technologies are going to be useful in addressing?; (ii) a discussion about the consistencies of pathologies from model organisms (including mouse) to human conditions; and (iii) how can data from new models be integrated into conventional drug discovery paradigms, particularly when you have high content datasets?

A point made throughout the meeting was that mice do not model humans. However, what was shown here was that, at the Jackson Laboratory, there was a mouse strain that indeed models every outcome that they have studied in humans. There were some genetic traits in the mouse that could be mapped back to human disease, including a resistance factor to liver fibrosis. Strategies for polygenic trait mapping were outlined to create genetic networks that can be related to meaningful biological pathways. Next, there was a discussion on how to integrate surrogate data. Identifying the correct target is crucial but requires the ability to merge various types of data. Integration and visualization of complex datasets are important and remain a gap, which was a theme throughout the meeting. The discussion went on to outline how gene ontology mapping provides statistical correlation within biological pathways. One question that was a topic of discussion was – have new approaches really added a lot to drug discovery? The expectations for genomics ten years ago were so high that,

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no matter how successful it proved to be, it would never meet the expectations that it could solve all the problems.

Another theme was how could causalities be defined separately from correlations? When complex datasets are examined, the cause and effect relationship must be understood, as does, essentially, what is an effect due to the cause. For example, taking liver injury, most of the genes map to the response to liver injury and few map to the biochemical mechanisms dealing with the injury, then there will be a problem deconvoluting the data. Complex systems cannot be modelled without a critical understanding of the component systems (i.e. you should be aware of the strengths and weaknesses).

The question of why toxicology has apparently lagged behind the rest of the scientific community in applying genetics was raised. One of the reasons identified was that failures are rarely, if ever, studied in as much detail as successes. Clearly the level of understanding and insight derived from marketed compounds cannot be gained from those drugs with toxicological problems, even though this might greatly assist in the avoidance of those problems in the future. A topic of extensive debate was understanding phenotypic discordance (i.e. when something is toxic in humans but not toxic in a mouse, or the phenotype observed in a mouse is not the same as that seen in humans, the model might not be suitable). There was a strong opinion that phenotype can differ as long as the pathogenic mechanism is the same.

Lead identification

Chemistry driven drug discovery

A theme that ran throughout many of the talks was how various approaches existed to move away from ligands that resembled peptides to more drug-like lead series and, hence, towards a proof-of-concept. What came out of the session was an appreciation for the role of chemical diversity in early lead compound generation. There was a different emphasis on random- versus known-ligand (natural substrate) approaches and that hybridization was beneficial to bring together distinct aspects of different molecules to improve on each of them. It was pointed out that the timetable to advance a proof-of-concept lead compound is becoming much shorter.

'41% of the *PharmaDiscovery* audience thought that pharmaceutical companies should be made to develop drugs with high unmet clinical need, but low commercial value'

Chemistry driven drug discovery: breakthrough medicines

The purpose of this session was to review some successful drug candidate projects and explore whether there were any common take home messages that could be applied to new projects, so that the drug discovery process can be made more successful. Talks included the farnesyl transferase inhibitors for anticancer agents, specifically the discovery of SARASAR (Lonafarnib). These were intended to be anti-Ras, because they are farnesylated, but it became clear in the programme that these agents were working by a non-Ras mechanism. There followed discussion of raxazaban, an antithrombolytic that works through inhibition of factor Xa. The original structures were highly polar and basic and had poor oral PK profiles. Significant medicinal chemistry efforts were undertaken to improve the physicochemical properties to optimize the compounds' drug-like properties, leading to raxazaban. The development of a *src-bcr/abl* inhibitor by Bristol-Myers Squibb was then presented, suggesting that this compound was much more efficacious in animal models of leukaemia than the *bcr/abl* inhibitor, Glivec. In this project, researchers had to overcome the reservations that *src* inhibitors would not be selective and that, despite the molecule having activity against multiple kinases, it had selectivity against a panel of other kinases, and its development was a real achievement. There followed discussions on the development of ezetimibe for cholesterol absorption inhibition. Ezetimibe started out as an ancylostoma caninum anticoagulant peptide (AcAP) inhibitor project and it was noted that, although the compound reduced cholesterol, it was not an AcAP inhibitor. Instead of throwing the project out, they followed the SAR for cholesterol-lowering *in vivo*.

The take home messages from this were to focus on the goal and persevere through the hurdles; surprisingly, given that drug discovery is an experimental science, the discussions highlighted that, in many cases, people did not want to perform the experiments. It is important that, for biological targets, you have initially to validate and continue to validate not only with techniques, such as short interfering RNA, but also with compounds as they become available. The literature should always be questioned and, if it is a primary principle in your project, you had better validate it yourself. In all these projects, it is crucial that research is performed as part of a team, with biologists, medicinal chemists and drug metabolism groups, and so on. People have to convey to the team what the overall plan is, to ensure that each and every group believes in the validity of the approach.

'68% of the *PharmaDiscovery* audience considered that their organization at best only sometimes terminated non-progressing projects in a timely manner'

In silico drug discovery

In the past, many computational methods have been unable to live up to their hype and the session focused on applications of what

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the state-of-the-art is and when it is practical to use them and when it is not. The initial presentations examined whether new libraries were worth pursuing based on an intellectual property (IP) standpoint. Such IP novelty filters can be used in combination with filters for drug-likeness, for example, in a prospective manner. The session then dealt with some of the successes that you can have in developing predictive ADME computational models.

The focus then progressed to discussions of the history of *in silico* drug design, in particular docking and squaring methods, which still have yet to be totally solved. It was noted that docking can, in many cases, be used to identify novel chemical scaffolds. The clear message was that there was no single approach that could be pulled off-the-shelf and used in every case. There were some take home messages from the session. First, the field has made significant progress in the past 5–10 years in understanding how to use computational methods in a sensible way to help in the design of drugs, not just related to docking and squaring, but also to other important features of drug molecules. Second, these methods, although not perfect, are useful, but are they being used enough? How can everyone do a better job of making sure that they are integrating them into the drug discovery process? Much more work needs to be done on validating the methods and showing they are applicable to specific problems. Models have to be linked to the chemistry in a way that makes sense and is more user friendly – black box models never appeal to chemists.

Information technology infrastructure as a source of value creation

When looking at information technology (IT) infrastructure as a value creator, the end result should be controlled automation of data processing and analysis. We are moving towards more and different data types that need to be analysed. The data types are not standardized and, by definition, are diverse. The dynamic between customized systems and purchasing off-the-shelf systems has not produced consensus as to what kind of IT needs to be implemented. For example, whether you should build the whole system in-house or purchase components from various vendors. As new analysis methods are developed, actual technological limitations are revealed. That is a driver toward development of new technology.

'60% of the *PharmaDiscovery* audience thought that their work was hampered to a moderate or great extent by access to information and tools to mine it'

Data integration

It is essential to understand all the different components of drug discovery and biotechnology and to understand the data integration needs across all these. The intent was to identify useful models and approaches and what technologies exist. There were several questions posed, such as: what does data integration mean to the laboratory scientist? Is it just a matter of transferring all the data from a machine into a giant database, or is it more about the practice of how you use it to analyse and infer meaning and how you apply it to decision making? Can we find strategies to interface systems in multidisciplinary teams? This responds to the need voiced by the FDA with respect to translational medicine: how can you get the tools to work across these silos? There needs to be some consideration as to how data are viewed from a multidisciplinary approach, not just one set of users.

It seems there is no general panacea to solve the whole problem, but the session began by focusing on integrating information around compound assays, not just on the data and how you pack it, but presenting sufficient meaning with each of the data elements. The approaches enabled the capture of context from these data points by layering semantics on top of federated information. The discussion moved on to *in silico* chemistry workflow models to assimilate and build chemical knowledge around early predictions of ADMET, with solubility and the human ether-à-go-go-related gene (HERG) being the initial focus of this session. Being able to annotate and save additional information is important, because important nuggets of knowledge might otherwise be lost.

Lead optimization

Preclinical safety and drug development

This is a rapidly developing area, having a major effect on drug development. Also, it is one that 44% of the *PharmaDiscovery* audience considered would have a moderate to great effect on productivity. This area is becoming important because it gives the ability to identify adverse event targets and develop methods for monitoring and measuring the perturbation of that target – a key step in the risk management of drug-induced adverse effects. One of the main issues when starting a new drug development programme is how quickly you can determine what the issues associated with the target will be and how they can be avoided or managed. Getting all the new biology (the '-omics') together and integrated to develop a kind of systems approach to this is desirable, if somewhat challenging at the moment. One of the themes that came out was that of translational medicine. If you are going to do a good job in drug development, the preclinical and clinical teams must communicate well. This relates to hypothesis generation, data information sharing and mutual understanding.

Efficacy biomarkers in early clinical development

Clearly, this is an area of great interest to the audience, in that 80% considered that biomarkers will have a moderate or significant impact on clinical success rates and development times in the next ten years. The theme for this session was to understand the issues hindering introduction of biomarkers into the early development process. Why are efficacy biomarkers often viewed in isolation and not as part of an integrated programme? What are the current limitations on the discovery of new biomarkers and how might they be used? The discussion highlighted that there does appear to be increasing integration in companies between preclinical and clinical areas. This is helping to introduce biomarkers into the early development programmes.

The area where the approach seems to have greatest utility at present is in patient selection, which is largely focused on the use of pharmacogenetics. The other area is searching for pharmacodynamic effects. By contrast, the area that is currently least well-developed is the use of information

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generated in preclinical studies to drive new safety markers. One of the major issues in early development is an uncertainty with respect to the predictive power of new biomarkers. There has to be some acceptance that not everything that is introduced, at least for the first phase, is going to be a stop or go decision maker. However, it will produce some supportive information. It is clear that this is an issue for several companies and could hamper introduction of biomarkers into several of their projects.

Evaluating success in drug discovery

The first area examined in this session was the effect of enabling technologies on R&D productivity. The issue with the next generation of targets is that there is more uncertainty than with the targets today, and it is still necessary to adhere to the timelines and economics of drug discovery. Technology benefits greatly if it is used in the right way, and when used in an integrated and holistic way. Another topic covered during this session was how understanding mechanistic events underpinning toxic events can enable the rescue of drugs that had previously failed in clinical trials. This is an interesting way to improve productivity, through understanding and dealing with the events that produce failures. What lessons have been learned from failed drug discovery projects? What are the technological solutions that will drive success and are we blind to fundamental approaches that have not been taken advantage of? There was little response from the audience to the last question. The common themes were that rescuing drugs is a potential way to fill the productivity gap – but how do companies other than Pfizer view that?

The biomarker challenge to increase drug development and efficiency in oncology had one strong take home message, that it is likely that the cost to the user of modern pharmaceuticals is going to be at such a level that, in the future, it will be mandatory to have biomarker validation that a particular therapy is going to be efficacious in an individual. Productivity is a function of uncertainty and inefficiency and where this technology should be used is to reduce uncertainty and increase efficiency. The concept of using robust, validated technology to free up scientist's time to think about the data, make libraries and deliberate about hypotheses will be of great importance.

Conclusions

Did the conference work as a new model? Feedback from attendees certainly suggested that they were impressed with the level of scientific address and debate. Whether the conference succeeded in generating solutions to various aspects of the productivity gap can only be assessed by the individual scientists. If, as a result of attendance, they return to their organizations to implement something that they have gleaned from this conference, then hopefully it will have been worthwhile. If those changes have an impact on the productivity gap, then clearly the conference will have been a success. I would value any comments from readers, because this will help us to improve future conferences. If you have any ideas for future themes that significantly impact the drug discovery industry, as always, I would be glad to read them. I hope that you enjoyed the *PharmaDiscovery* conference and, if you were unable to attend on this occasion, I hope that, on behalf of the Reed Elsevier team, we will be able to welcome you to *PharmaDiscovery 2006*.

References

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2 Sams-Dodd, F. (2005) Optimizing the discovery organization for innovation. *Drug Discov. Today* 10, 1049–1056

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