The Academy of Medical Sciences **FORUM**

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Medical Sciences

Drug Discovery Forum Symposium
Report by the Academy of Medical Sciences

**Report of proceedings of the Drug Discovery Symposium
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Introduction

The Academy of Medical Sciences' FORUM is an active network of scientists from industry, the healthcare sector and research funders. It currently focuses on pharmaceutical, biotechnology, medical engineering and health product sectors, with representation from relevant trade organisations. The Forum promotes interaction between industrial and academic biomedical scientists and engineers, and other groups committed to improvements in healthcare through research.

The presentation slides that accompany this lecture are available on the Academy's website **www.acmedsci.ac.uk.** Other material relevant to the points raised in this symposium is available from the Academy of Medical Sciences:

Forum Report 'Safer Medicines' on **www.acmedsci.ac.uk/p102.html**

Summary of the Forum symposium 'Experimental Medicine'
www.acmedsci.ac.uk/p50evid50.html

Summary of the 2006 Annual Forum lecture 'The human genome: realising pharmaceutical opportunities' by Tim Rolph (Pfizer) **www.acmedsci.ac.uk/p50evid49.html**

Academy statement 'Testing antibody therapies' (published in response to the TGN1412 study) **www.acmedsci.ac.uk/p99puid74.html**

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The Academy of Medical Sciences

The independent Academy of Medical Sciences promotes advances in medical science and campaigns to ensure these are translated as quickly as possible into benefits for patients. The Academy's Fellows are the United Kingdom's leading medical scientists from hospitals, academia, industry and the public service.

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Report of proceedings

In his introduction to the symposium, Barry Furr, Chair of the Academy's Industry Forum, noted that there had never been a more exciting time for drug discovery than now. The emergence of new technologies is facilitating, but also challenging, the R&D process. There is widespread interest among the UK scientific community in drug discovery but the complexities are not always appreciated. The Forum event was designed to bring together industry practitioners and academic scientists to examine issues for drug discovery and the exploitation of basic research and to clarify the risks, skills and relationships required to achieve the objective of discovering good drugs with novel profiles.

Peter Joshua (CMR International) in presenting on 'Attrition across the drug discovery value chain' drew on the data collection and benchmarking analysis of CMRI with pharmaceutical companies. There are various metrics that could be used to estimate the success of drug discovery activities and the transition to clinical development and it is also now desirable to be able to capture the impact of recent changes in drug discovery strategies whereby some companies are relying more on research from outside their own laboratories.

When CMRI combined the analysis from several of their benchmarking programmes, it became apparent that attrition rates are very high in early clinical development – this high failure rate may be attributable, in part, to decisions taken in drug discovery. The success rate for progress from first patient dose to first pivotal dose is less than 30% on average across the industry, superimposed on a success rate of 20% for the phases between a compound first entering assay development and generation of a clinical candidate.

The benchmarking databases can be used to answer some important questions on relative performance. For example, do larger companies have higher discovery success rates? Larger companies do show lower attrition rates throughout the discovery phases but it cannot be concluded from the data whether this is because they have better compounds or more money to progress compounds at a different level of scrutiny. There is some evidence (at Phase III of clinical development) to suggest that smaller companies are more successful in terms of compounds with novel mechanisms of action.

In discussion, it was observed that the failure rate may be generally higher for compounds with novel mechanisms of action – because of their intrinsically greater risk and because there may be no predictive animal model for efficacy. But it is not yet clear from the aggregated data if the attrition rates have changed over the last few years or how often compound failure can be attributed to a failure in pharmacology. Failure has experimental value if it can generate information to test the hypothesis on proof of concept, but there is a concern that some pivotal studies are not sufficiently well controlled to be relied on for target validation purposes. Explanations for compound failure include business as well as scientific reasons but discussants criticised the growing commercial influence during the discovery phase in delivering premature judgements

before the target profile is elucidated and potential clinical advantages established. Discovery scientists may sometimes need more confidence in defending compound potential, while also recognising the need to take tough decisions early in order to improve clinical success rates.

Stephen Green (AstraZeneca) considered 'What constitutes a good drug target?'. In developing their therapeutic strategies to tackle medical need, companies must decide whether to choose an unprecedented, high-risk target (compound 'first in class') or develop an improved drug for a precedented target (compound 'best in class'). Finding the right target in an era of growing costs and high failure in drug discovery involves the integration of critical steps:

- Defining the right target – by analysing disease linkage, utilising a range of methods, for example from the 'omics technologies and experimental models, and by considering issues for safety as well as efficacy (requiring evaluation of potential for target modulation in other tissues)
- Target validation in functional terms
- Biological feasibility – can the target be screened?
- Chemical feasibility – is the target druggable and how much selectivity is required?

These steps were illustrated by the case study of Epidermal Growth Factor Receptor (EGFR) as a target in non-small cell lung cancer – culminating in the observation of clinical activity for EGFR inhibitors.

In reviewing the diversity of drug classes currently available and the potential for new druggable genes linked to disease identified from genomic analysis, the total number of human drug targets has been estimated as

about 600, of which 100 have already been exploited. This universe of human drug targets could be expanded by targeting protein-protein interactions and by employing novel therapeutic approaches such as biologicals, gene therapy and RNAi. There are additional, anti-infective, targets obtained from microbial genomes.

The final step in target validation is clinical feedback – this furnishes proof of concept but also generates information from patients who do not respond to the compound, to help in elucidating alternative targets.

A wide range of issues was raised in discussion. The particular problem in extrapolating from animal models of cancer was highlighted and the contribution of animal research in this therapeutic area may reside more in determining pharmaco-kinetic-pharmacodynamic relationships. Discussion of the opportunities for reaching relatively inaccessible targets, in the CNS, for optimising druggability, for affecting disease progression rather than disease symptoms and for utilising compounds that do not meet the full target profiles as research tools, helped to set the scene for the later speakers.

Mike Romanos (GlaxoSmithKline) defined target validation as the ongoing process of providing confidence that a target can meet the desired product profile, allowing invest-ment to the next stage of drug discovery. Ultimate target validation can only be achieved for a given therapeutic modality in the human patient population. In addition to target selection (prior to commitment to lead generation), target validation is important at subsequent stages, including lead compound validation, on/off target ef-fects, increasing confidence of meeting the specific product profile, and translational medicine. The essential tools fall into three

types: (i) Biological systems (human patients or surrogates thereof); (ii) Target modulation tools (drugs or surrogates thereof); (iii) Analytical methods (e.g. transcriptomics).

The breadth of activity required in target validation was exemplified by case studies:

The nuclear receptor FXR as a target in cholestasis and diabetes. Compound-based functional characterisation of FXR led to the hypothesis that FXR is a master regulator of bile acid homeostasis with therapeutic application in cholestasis, which was verified *in vivo*. Although current treatments are not very effective, cholestasis is relatively uncommon and commercial attractiveness appears low. However, transcriptomic analysis serendipitously identified a role for FXR in glucose and lipid metabolism and the lead compound GW4064 is active in models of diabetes; several companies are now progressing compounds.

Vanilloid receptor in pain – validation based on the well-known properties of the ligand (capsaicin), the tissue localisation to sensory neurons, and mouse knockout models. It has proven challenging to link animal pain models predictably to clinical models, but research on human disease tissue supported the role of VR1 in multiple pain states, and the GSK antagonist is in Phase II for migraine and dental pain.

Novel inflammation targets – this area provides the paradigm for the future, since it is possible to carry out high-throughput siRNA screens for novel targets in human primary cells, followed by compound-based validation in biopsies from disease patients.

The attrition rate in the industry is very high indeed, largely reflecting the difficulty in validating targets pre-clinically.

However, reviewing the consolidated experience across the pharmaceutical sector suggests several routes to making real improvements: (i) more systematic and integrated use of multiple orthogonal target validation approaches; (ii) increasing use of cellular or pathways assays to complement the focus on single targets; (iii) consistently using all of the new tools in the toolbox (for example, RNAi); (iv) where possible, reducing reliance on animal models by using human tissue and by better linking of preclinical and clinical models (for example, using biomarkers); (v) ensuring more stringent control of clinical proof of concept studies in terms of pharmacodynamic measures of target engagement; (vi) stratification of patient populations in order to maximise the chance of detecting a signal.

Practical implications were further deliberated during discussion. The importance of securing access to diseased human tissue supplies for early experiments was emphasised; the value of pharmacogenetics in some areas is becoming clearer (for example, the cognitive response to glitazones in Alzheimer's disease according to ApoE4 status); the ability to incorporate safety assessment during target validation is being enhanced by use of bioinformatics tools (*in silico* assessment) although there are still significant challenges in predictive toxicology. Academic discussants also noted the perceived risk aversion of large pharmaceutical companies; this point was not accepted by many companies. The responsiveness of companies to new research findings from academia was also questioned and company respondents said that collaboration was welcome, a point emphasised in subsequent sessions.

Having carried out the first stages of target selection and validation, the next task in

drug discovery is to generate lead compounds, a process that has recently been transformed in ways exemplified by the next two speakers in the symposium.

John Steele (AstraZeneca) examined lead generation by 'High throughput, tailored library and subset screening', drawing on the experience of very large increases in the quantity and quality of screened compounds during the last decade. Issues for quality lead generation were discussed in terms of the access to the right compounds (with appropriate, drug-like, physico-chemical properties, for example by using *in silico* property prediction to identify problems prior to compound synthesis) and the right targets (recognising that there is considerable value in revisiting previously-failed targets with better compounds). One major research objective has been to find new ligands for G-Protein Coupled Receptors (GPCRs); although this is a relatively well-mined area, there are good opportunities to create new leads by distinguishing between categories of GPCRs and informing chemical library design by analysis and clustering of GPCRs based on properties of the ligand binding site (a ligand road-map).

In developing the overall strategy for reducing compound design to practice, there is a core role for the selective acquisition of compounds to enrich internal collections; moreover there is an increasing tendency to outsource the synthesis of internally-designed libraries. What metrics might be used to measure success? 'Hit rate' is deemed a poor indicator, because it will still encompass too many unattractive compounds; a better performance guide is project progression. Achievements in high throughput screening and lead generation were exemplified by case studies on targets:

CXCR2 (GPCR chemokine receptor) – a relatively straightforward leadgeneration campaign with informative Structure-Activity Relationships, high potency and bioavailability delivered in one chemical series.

JNK, c-jun N-Terminal Kinase – lead generation required a radical change in compound structure to improve potency, greatly assisted by early access to the target protein crystal structure.

CCR4 (GPCR chemokine receptor) – an unsuccessful case-history illustrating the danger of over-reliance on efficacy SAR rather than addressing clear pharmacokinetic issues. Ultimately, a consistent lack of bioavailability necessitated termination of the lead series.

Critical success factors in lead generation programmes received further attention during discussion: the importance of evaluating pharmacokinetic data early; the ability to learn how to overcome bioavailability obstacles (for example, attention to transporter binding); the appropriate staffing of lead optimisation activities. The size of the library collection was scrutinised – is it necessary to screen so many compounds if the collection is well designed and diverse? In practice, lead generation usually proceeds by intelligent selection (according to target characteristics) of subsets from the library but the existence of a large parent collection from which to select is a powerful resource.

The crucial role of structural biology in drug discovery was substantiated in the presentation by **Harren Jhoti** (Astex Therapeutics) on 'Fragment screening approaches'. Conventionally, structural biology had been confined to lead optimisation but advances in technology to underpin high throughput screening have enabled the use of X-ray crystallography in lead generation.

The fragment-based approach starts from the premise that conventional lead generation methods select compounds that are too large and complex, resulting in a high propensity for metabolism and clinical failure. Starting with a smaller fragment, by sampling chemical space, can increase the likelihood of subsequent optimisation as a drug candidate conforming to the required physicochemical properties. In terms of the quality of hits, the essential problem for smaller compounds is their low affinity binding. Nonetheless, the fragment may have high ligand efficiency so that by a fragment evolution strategy of chemically linking fragments binding to adjacent sites on the target protein, high affinity binding can be conferred. Because this iterative, directed medicinal chemistry is informed by the data from crystallography platform automated analysis of protein-ligand structures, progress from lead compound to optimised drug candidate requires relatively few intermediate steps (typically a series of about 50 compounds).

The growing drug discovery opportunities afforded by the fragment-based approach were exemplified by case studies demonstrating the relative economy and speed by comparison with traditional high throughput screens:

Beta secretase, key in Alzheimer's disease, was targeted and identified dihydroisocyto-sines as inhibitors.

Fragment screening of *HSP90*, a target in cancer, resulted in a development candidate AT13387

Cyclin dependent kinases CDK 1 and 2, also cancer targets, were targeted and resulted in AT7519, which is now in Phase I-II.

The potential applicability of the fragment-based approach can be judged by the numerous collaborations formed between Astex and larger pharmaceutical companies, although the emerging technology has some current limitations as noted in the discussion. The approach is dependent on a solved or solvable protein structure so that membrane proteins and multi-protein complexes are currently usually beyond reach of the technology. Proteins undergoing a large conformational change on ligand binding are also technically challenging. Some discussants were concerned at the potential for fragment binding to protein sites other than the active site. Although non-specific binding is rarely observed in practice, it would be instructive to determine if allosteric binding could be evaluated.

Dave Allen (GlaxoSmithKline) reviewed the next step in the drug discovery process 'Lead optimisation', the activities involved in progressing from tractable hit to candidate selection and guided by the objectives for product profile, clinical proposition and medical/market needs. The lead optimisa-tion screening cascade requires early assays to have the capacity rapidly to inform medicinal chemistry strategies. As discussed by previous speakers, compound selection also involves early assessment of 'off-target' activity and pharmacokinetics and, if possible, using disease-relevant target cells to optimise efficacy in conjunction with *in vivo* models as appropriate (committing to the ongoing goals of 'Replace, Reduce, Refine' animal studies). Attention to pharmacokinetics has transformed the attrition pattern in R&D. Pharmacokinetics was the main cause of failure in the early 1990s but is now an uncommon reason.

A key feature of lead optimisation activities is the coordination to involve to involve a range of other R&D functions, including

and pharmaceutical development groups, safety assessment, drug metabolism and discovery medicine, such that a fully integrated team is regarded as a critical success factor.

Discussion returned to some of the pervasive themes in the symposium. What is the place of animal models? Experience shows that mechanistic animal models can be valuable but disease-based models are often poor in predicting clinical response. How best to apply technology advances (for example, gene expression profiling) in predictive toxicology? The interpretation of multiple gene changes can be difficult.

The challenges to integrate evaluation of toxicity alongside efficacy – to reduce the current high degree of attrition attributable to toxicity – were described by **Christopher Powell** (GlaxoSmithKline) in 'Early drug safety'. The different safety evaluation routes into clinical research can be sum-marised as:

(i)   Conventional (14/28 days toxicology studies) – this route is taken by 90% of orally-administered compounds;
(ii)   Screening Investigational New Drug (IND) – used in the USA, but infrequently;
(iii)   Exploratory IND – a new route, introduced by the FDA in 2006;
(iv)   Microdose clinical study – FDA and EU CPMP guidance is now available for very low doses (without anticipated pharmacological effect).

Options (ii) – (iv) may economise on initial compound requirements and provide a quicker route to clinical entry allowing a go/no go decision, but subsequent progress will probably be slower. A range of options is also available for front-loading safety studies

with the objective to obtain critical results early and, so, reduce the risk of later failure. These tools for early safety prediction – illustrated from a broad selection of experimental studies – include *in silico* evaluation (as discussed previously), measurement of genotoxic potential, assessment of toxic and metabolic liability, cardiac safety pharmacology, phototoxicity and other organ-specific focused screening.

Two broad strategic issues emerged in discussion. First, how can the ambition to accelerate pharmaceutical R&D (for example, the FDA Critical Path Initiative) be reconciled with the increasing concerns expressed about drug safety occasioned by several recent high-profile incidents? It can be assumed that the Regulatory Authorities will be increasingly vigilant on drug safety. Secondly, what is the rationale for reclinical assessment of biological drug safety requiring only one animal species whereas chemical compound assessment requires two species? The logical basis for assay of biologicals is to evaluate in a species known to be responsive in pharmco-dynamic terms; this is a logic that could be (but isn't) extended to lower molecular weight compounds.

Harsukh Parmar (AstraZeneca) provided a complementary, clinical perspective on safety and efficacy considerations at the interface of drug discovery and development in 'Early clinical trial considerations'. The generation of preclinical data to inform (in particular, to provide signals for) the early clinical development decisions has been described by preceding speakers but clinical research involves additional levels of uncertainty related, for example, to individual variations in response and the impact of intercurrent disease. Discovery and development should not be viewed as a simple linear process; as described

previously there is significant feedback from the clinic to discovery laboratories to clarify disease mechanisms and target evaluation.

Critical issues in early clinical development are well illustrated by the case study on TGN1412 super-agonist interaction with CD28 receptors. It has now become apparent that there are qualitative and quantitative differences between man and the cynomologus monkey, used as experimental model, in cytokine response, and the excessive activation of both innate and adaptive immune responses induced multiple organ failure in the volunteers. Calculation of receptor occupancy by TGN1412 indicated 90% occupation after the single administration despite following the regulatory guidelines. In consequence, recommendations have been made for a new approach relating the selection of the starting dose level in man to the biological no adverse effect level in experimental animals.

The clinical strategies used for establishing proof of mechanism and proof of principle were illustrated by case studies on AZD6140 (an anti-platelet agent now in Phase III) and SD3651 and Singulair (in asthma). Work on P2Y2 in psoriasis showed that proofs of mechanisms, principle and concept might be demonstrable in a single experiment. Considerable effort in early clinical development is also now aimed at elucidating the promise of pharmacogenomics for personalised therapy, illustrated by characterisation of the response to Taxol in non-small cell lung cancer, according to beta-tubulin gene mutation.

In seeking to resolve the problems of high attrition rate during R&D, there are additional challenges to be faced in the significant late failure rate for compounds during Phase III and in post-approval drug

withdrawal. From the clinical perspective (and reiterating the advice from previous speakers), what is needed to address the problems of attrition is a better understanding of the relationships between targets and disease process, increased availability of novel biomarkers and better predictive systems to forecast clinical efficacy, toxicity and drug interactions.

Panel discussion **'Support for Drug Discovery in Academia'**

Public sector research-funding agencies acknowledge the importance of translating basic research into products to address unmet medical needs (including poverty-associated diseases), encouraging excellence in innovative biology and multi-disciplinarity. Perceiving an increasingly risk averse culture in industry and venture capital sectors,some feel it is now harder to create partnership activities even though, in principle, it is becoming easier to accomplish standardised medicinal chemistry and screening activities within academia. What more could be done to increase partnership opportunities?

Richard Seabrook described how the Wellcome Trust is in the second year of Seeding Drug Discovery, an initiative for applicants to undertake drug-like compound discovery and/or lead optimisation involving the disciplines of disease biology, medicinal chemistry and pharmacology. The goal is for funded projects to progress to a stage whereby there is sufficient evidence to make the project results and intellectual property attractive to follow-on developers/investors who may be from the commercial or not-for-profit sectors. Applicants are encouraged to use commercial sources to access the full range of disciplines and to deploy industry experienced project management.

Roberto Solari discussed a different approach adopted by the MRC to reach the same goals: funding an internal drug discovery group, encompassing medicinal chemistry and screening plus the specialised skills from the MRC experience on monoclonal antibodies. An external advisory board is populated mainly from industry. The MRC aims to progress up to the lead molecule stage to attract subsequent collaboration with companies.

Keith Blundy reviewed the Cancer Research UK commitment to turning its biology into new drugs – by coordinated funding of academic groups and by an internal drug discovery group progressing to proof of concept, and anticipated to double in size in the next two years.

Mike Collis from the Academy's Forum Advisory Board welcomed these initiatives, which will be attractive to industry, if generating novel ideas and leads, on validated mechanisms, with a reasonable level of confidence attained on safety and tractability of chemistry.

General discussion identified some additional points for building success in collaborative endeavours:

• The opportunity for these initiatives to fund spin out companies as well as academic laboratories
• The need to attract funding for developing country diseases – potentially from other endowed foundations, but the areas will also become more attractive for commercial entities to invest if some of the early risk in discovery has been removed
• The importance of capitalising on the advantage of the public sector funders in their access to clinician scientist skills – but in order for them to utilise these skills in the clinical development phases, it is first necessary to overcome the rate-limiting factor of lack of medicinal chemistry skills for lead optimisation
• There is a general UK weakness in training the next generation of medicinal chemists, that must be reversed
• The quality of the chemical library is one key to success and there may be opportunities for the UK funders collectively to emulate the US NIH efforts to generate an open access library of compounds for screening.

Appendix I Symposium timetable

09.20 **Introduction to the meeting**
Professor Barry Furr OBE FMedSci, Chair of the Forum

09.30 **Attrition across the drug discovery value chain**
Dr Peter Joshua, CMR International

10.10 **What constitutes a good drug target?**
Dr Stephen Green, AstraZeneca

10.50 **Tea**

11.00 **Target validation**
Dr Mike Romanos, GlaxoSmithKline

11.40 **Lead Generation**
(a) High throughput, tailored library and sub-set screening
Dr John Steele, AstraZeneca

12.20 **(b) Fragment screening approaches**
Dr Harren Jhoti, Astex Therapeutics

13.00 **Lunch**

13.40 **Lead optimisation**
Mr Dave Allen, GlaxoSmithKline

14.20 **Early drug safety**
Dr Christopher Powell, GlaxoSmithKline

15.00 **Early clinical trials considerations**
Dr Harsukh Parmar, AstraZeneca

15.40 **Tea**

15.55 **Support for Drug Discovery in Academia (panel discussion)**
Dr Roberto Solari, Chief Executive, MRC Technology

Dr Richard Seabrook, Head of Business Development, Technology Transfer,
The Wellcome Trust

Dr Keith Blundy, Chief Operating Officer, Cancer Research Technology

Dr Mike Collis, Forum Advisory Board