Highlights of the Society for Medicines Research meeting, held March 18, 2003, at the National Heart & Lung Institute in London, United Kingdom.

Is There a Best Strategy for Drug Discovery?

By Peter Warne and Clive Page

Summary

The Society for Medicines Research held a meeting on March 18, 2003, at the National Heart & Lung Institute in London, United Kingdom, to discuss strategies for drug discovery. The meeting began with a history of the origins of drug discovery. Discussions also covered the best strategies for drug discovery, including combinatorial chemistry and high-throughput screening, and ways to meet the challenge of the so-called "innovation gap," among other topics. Speakers included a Nobel Laureate and discoverer of two of the most significant drug classes of the 20th century, and the greatest drug generator of all time. Various companies and institutions were also represented in the talks.

When a conference program starts with a Nobel Laureate and discoverer of two of the most significant drug classes of the 20th century, and ends with a presentation by the greatest drug generator of all time, it can be sure of a capacity audience. When the intervening period of the day is filled with six other papers of significant content, you may be sure that the audience went away with a feeling of a day well spent.

Sir James Black initiated proceedings with "reflections on the invention of new drugs—then, now and the future" and, in tune with his title, provided a potted history of the origins of drug discovery. From Perkins in the mid-19th century to Ehrlich with his toxic chromophores and on to the greatest drug discoverer of all time, Dr. Paul Janssen and the concept of pharmacophores. In all that time, the fundamental requirements of the discovery scientist have not changed: they are concentration, commitment and creativity.

There is probably not one single best strategy, but the principles of a good drug strategy are recognized—first and foremost, a vision of the required selectivity. Without this, the project is doomed from its inception and reduced to the level of wishful thinking. There must be a molecular template which in the past would have been generated from the structure of the physiological mediator. A bioassay is the third essential ingredient which underlies the discovery phase. Looking further, how will the drug activity be demonstrated in man and in what disease? And finally, the funds must be available—one of the great unknowns in discovery is how long it will take—and someone must be committed (even passionate) to seeing the task completed.

The last 10 years have seen remarkable changes in the pharmaceutical markets. There remains a great demand, of course, and they are international, but monopolies are being eroded by generic competition and fraud. Costs have escalated and pressure has grown to increase R&D efficiency, but with what impact upon the processes?

The new technologies are centered upon combinatorial chemistry and high-throughput screening. Systems in which the chosen candidates are predetermined and of limited structural com-

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plexity. In this system, there is no room for the iterative processes so successfully applied by Ehrlich and Janssen.

There is a view that the easy targets have all been satisfied, and what is left demands a different approach. If this is true, the new technologies do not appear to provide the answer if the increased rate of attrition in the clinic is any guide. The fault may lie particularly in the fact that modern drugs target components rather than systems. Systems often operate in such a way that the mechanisms of their modulation are obscure; many messenger substances may be involved, there is conversant control with addition and even synergistic effects. Inevitably, in such systems there is biological redundancy so that modulation of a specific link in the chain may be bypassed as the system responds to nullify the targeted effect.

Sir James provided examples in the shape of the development of tolerance to antigastrin therapy where the receptors remained blocked after 7 days' treatment, but the phenotype of the tissue had changed so that the targeted pH changes were no longer achieved. Conversely, the effect of gemcitabine upon the proliferation of pancreatic tumor cells from nude mice is minimal. Combine the treatment with an antibody to the growth factors and the effect is increased. Add in irradiation and the response is ablated. The individual targets have combined to provide therapeutic impact upon the system.

So what do the metrics of drug discovery suggest? Dr. Cyndy Lumley from the Centre for Medicines Research provided some of the answers in a broad appraisal of data which have been supplied in response to industry questionnaires.

The fundamental aim of a pharmaceutical company and the industry as a whole is to remain profitable. This means balancing innovation with output. In the last 10 years there have been notable increases in discovery technologies but no notable increases in the production of new molecular entities (NMEs). During the 1990s there were approximately 40 new compounds launched each year; since 2000, these numbers have declined. Pipeline numbers, too, are lower, and development time is extending owing to increased internal development hurdles and regulatory risk aversion. Conversely, sales have increased and indexed growth has risen in parallel. However, it is difficult to imagine this being sustained if there are fewer new drugs. It is equally certain that companies will react to invest in other areas of their business if the technology does not soon start to show benefit.

In 1995, Jurgen Drews foresaw what he described as the "innovation gap" and suggested some ways of meeting the challenge. Top of the list was the acquisition of compounds through licensing opportunities and particularly, from biotech companies. Biotech companies, however, find themselves in a position much like most pharmaceutical companies, and the few opportunities that are available are keenly sought. His second suggestion was to question company structures and to understand critical mass. Some companies such as GlaxoSmith-Kline have reacted to these ideas and created business units, smaller research teams created on the scale of biotech companies. The industry watches with interest to see the success of these radical organizations. Thirdly, he turned attention upon the new technologies.

The metrics of R&D investment show a marked shift from 10 years ago. While the clinical areas remain top of the poll with about 30% of total budget, discovery comes second with a 25% figure. This is a large skew upon earlier figures which is driven both by technology advances and the establishment of alliances. Nonclinical development now commands 17% of budget while phase I units take a beggarly 6% and postmarketing surveillance 5%. No surprise that pharmaceutical management is looking very closely at discovery profitability.

Measurement of discovery success poses something of a conundrum. Numbers of new compounds as a criterion has little measure of quality, and time savings in phase I or phase II measure development efficiency rather than discovery. The time taken from initiation of screen to first administration to humans is about 4.4 years, but the analyses suggest that speed (or lack of it) is not the issue. Quality, as judged by clinical success rates during the period 1994–2001, does not seem to have improved. In spite of improved selection criteria, 22% of clinical candidates fail because of insufficient efficacy, and similar numbers fail through adverse effect profiles.

The current message is that increased spending has not, so far, equated to increased productivity. Lehman Brothers have estimated that pharmaceutical investment must be at least of the order of $100 million per year to compete in the postgenomics era. New target generation from genomic technology is generating some 23% of new targets per annum with 28% of these proving novel. The trick is to identify the best targets for new drugs.

The current success of genomic-driven target generation was appraised by Dr. Steven Foord (GlaxoSmith-Kline). From a history in which new drugs have been targeted toward a few poorly understood proteins taking decades to investigate, genomic sciences certainly have the ability to identify large numbers of potential drug targets. The trick will be to reduce these numbers to manageable and useful proportions and produce clinically efficacious products. The classifications are already well in hand, clinical success will take longer to realize.

Although there are an estimated 30,000 potential drug targets in the human genome, current knowledge is limited to about 2000, and these are broadly divisible into five classes: 7 transmembrane receptors, nuclear receptors, ion channels, proteases and kinases. Of the 747 7 transmembrane

receptors, 50% can be excluded from drug discovery on the basis of phylogeny and expression analysis. Subclassification into groups A, B and C and those with and without identified ligands provides further criteria upon which to base a targeted approach. Each of these subdivisions is dependent upon genomic sciences. They also emphasize the depressingly large numbers of orphan receptors.

Genomic technology also brings the potential to clone and express human receptors for high throughput screening. Combined with high throughput functional assays, these techniques can expose unexpected pharmacological activity which, hitherto, had to await serendipitous clinical exposure. For example, the angiotensin II receptor antagonist and antihypertensive drug losartan also lowers serum uric acid levels through a mechanism not utilized by laboratory animals. Similarly, buprenorphine used in cases of narcotic addiction has a complex effect upon all opioid receptors, but in human trials has been shown to stimulate the human ORL1 receptor, which is likely to contribute to clinical efficacy. With genomic technology, screening systems can be widened appropriately to anticipate clinical responses of this type.

Animal model selection is being influenced by reciprocal blast technology, phylogenetic analysis and synteny. According to criteria generated by these systems, more than 95% of human drug targets have murine equivalents. Of course, the mere existence of a target does not necessarily mean a similar function, but in practice murine knockouts usually reflect human physiology. This is if one is able to ask the right question; H2 and 5HT1D receptor knockouts, for example, would not have suggested a route to the treatment of gastric ulcers and migraine. Conversely, H1 knockouts show signs of drowsiness, and those without the gene for cysLT1 have improved lung responses. Elsewhere, there are successes and failures with genomic technologies; almost all 7 transmembrane receptors can be detected in Taqman analysis, but the relevance of mRNA expression to protein synthesis is variable. Equally, array analyses are frequently limited by current knowledge.

Knowledge limitations ensure that 7 transmembrane receptors can be difficult to identify within biological systems. It is becoming increasingly difficult to fill in the gaps within systems and to pair ligands with receptors. It is true that for some classes, such as chemokines, clusters of ligands can be recognized and new drugs can be expected in the near future, but many remain outside simple classification. As an aid to target hunting, there have been attempts to look back through the evolutionary tree and look for functionality based upon the premise that if there is no receptor there will be no ligand. This technology is as applicable to the kinome as much as 7 transmembrane receptor targets.

Inheritance, like the biological systems for which it codes, is not passed on through individual genes but as ill-defined blocks of information. This makes the association of individual genotypes with disease difficult to predict but this is increasingly the objective of genomic research in the areas of pharmacogenetics and disease susceptibility.

Pharmacogenetics is the study of abnormal responses to drugs and was reviewed by Professor Rob Kerwin from Kings College, London. He differentiated his subject from pharmacogenomics which concerns the identification and characterization of drug targets.

In the U.S. alone, 2 million patients per year present with serious adverse effects to their therapy, and these symptoms result in 100 deaths. The U.K. suffers a similar *pro rata* experience. Approximately 10% of schizophrenic patients commit suicide, which is itself a mark of treatment failure, but when other markers are factored in, treatment failure rates in complex disease are between 20% and 30%. In psychotic patients, generally one in five can be said to have responded, in 30% there is no response and the rest experience adverse events.

While it is true that drugs are expensive, these costs pale when set against the costs of rehabilitation or patient containment. Pharmacogenetic profiling makes sound economic sense as a treatment goal.

Pharmacogenetics can affect drug activity in several ways. Kinetic variation of a number of products is known to be influenced by P450 enzyme variants which accelerate or slow their elimination, giving rise to suboptimal therapy or toxic side effects, respectively. In asthma, single nucleotide polymorphism (SNP) variants of the β receptor result in structural changes and altered susceptibility to bronchodilators. In cancer and Alzheimer's disease, several genes have been associated with disease development and a similar story is starting to emerge with psychotic patients.

In schizophrenia, remission rates are 0%, and there is a high treatment failure rate. There are high costs to be borne through the social impact of the disease, and so drug price increases to fund pharmacogenetic profiling are economically sound. Equally, there are ethical points to consider; most notably, do we deny a patient their treatment on the basis that their profile suggests that, for them, the drug won't work? This and other issues are complicating the subject which for many is predicting over-optimistic gains.

Pharmacogenetic profiling in schizophrenia is currently targeting a profile of the most beneficial treatment. This will, in turn, provide information for target validation and target hunting. The approach is to apply association methodology to clinical samples in a multi-gene testing paradigm.

Although there is opportunity for toxicogenetics and Cyp profiling, this has not proved useful in psychotic disease. Instead, the approach has been to

investigate SNP variation of those genes which "light up" during therapy. For example, the dopamine receptor has been a strong candidate for an association with the disease for many years. SNPs have been identified in all subtypes from D1 to D5, but it is the D3 and D4 subtypes which present opportunities for novelty. The D3 gene has a positive association with the disease, and the correlation of nonresponders to clozapine therapy with SNPs validates D3 as a novel target. Similarly, serotonin has been a candidate mediator of schizophrenia for many years, and SNP analysis of the 5HT2A gene is proving useful in the prediction of responders.

Currently, logistic/linear regression analysis of multiple genes provides an indication of likely responders to clozapine, but the reverse is not always true. The combination of 5HT and H1 analysis, for example, seems to identify responders but is less predictive for nonresponders. Conversely, SNP analysis of olanzapine sensitivity seems to be more predictive for nonresponders. Always the complexity of these relationships demands more data before greater reliance can be placed upon the apparent conclusions.

So far, the studies have been retrospective, and from the data the prediction of clozapine responders appears to be about 80%. There are no data, as yet, from prospective studies, but these are in hand, as are the development of comparable tests for olanzapine, risperidone and haloperidol. These may not only be able to identify responders but also mark out those most susceptible to side effects such as agranulocytosis, tardive dyskinesia, weight gain and so on.

In parallel with inadequate clinical efficacy, preclinical toxicology combined with clinical safety are the other single-largest reason for stopping projects in development. According to the Centre for Medicines Research metrics, the attrition due to toxicity is 23% so that any measures that can be taken to filter out these candidates from the selection process is welcomed. Dr. Mark Cronin from Liverpool (John Moores) University provided a summary of the potential and status of *in silico* systems for achieving just that.

E-screens for toxicity testing are attracting the attention of both the pharmaceutical industry and the regulators. For the industry, these systems are cheap and may provide direction for medicinal chemistry strategies. They can also cast a light upon mechanisms of action. Equally, there is increasing evaluation of these systems by the FDA who, in the future, are expected to prioritize, classify and assess risk by consideration of data currently being generated in toxicity databases.

In silico screens are generated according to similarity and here lies both their strength and their weakness. The strength is directly proportional to the stringency of the rule base, the weakness is knowing upon what to base similarity. Quantitative structure activity relationships (QSARs) have been used to classify narcosis and formalized to generate expert systems. One of the better known systems, DEREK, is knowledge based, and databases are also being generated by both the FDA and OECD. To date, the focus of activity has been upon mutagenicity, carcinogenicity and skin sensitivity, but following several years of research and data manipulation, no system has emerged as reliable.

Understanding the poor performance of the current crop of systems is also proving problematic. It is probable that current knowledge is inadequate, a situation fueled by the pharmaceutical industry's reluctance to release sensitive safety data. Equally, e-screens seek to analyze complex phenomena by as-yet simplistic comparator techniques.

The most obvious short-term advances are likely to be made by increasing the knowledge base. First and foremost, the area needs an influx of quality *in vivo* data, and this is most likely to be sought from the pharmaceutical industry. Similarly, the collation of human tolerance data will prove a valuable resource if made available. However, the knowledge base could also advance through the generation (or acquisition) of *in vitro* data or that to be accessed through toxicogenomics and microarray technology.

Toxicogenomics, the study of differential gene expression following a toxic insult, provides, in principle, the message by which to fingerprint toxic compounds. In turn, this can generate information upon mechanisms of toxicity and ultimately may facilitate prediction of toxicity. These ideas are at present only goals. They are unlikely to be realized without the provision of more data, and it is likely to depend upon the larger pharmaceutical companies to seize the initiative.

The chemical structures of drugs are also providing a basis for the mapping of the genome and the identification of the most suitable targets for their drug-like (drugability) properties. This is the thesis of Dr. Andrew Hopkins (Pfizer) and his publishing colleague, Dr. Colin Groom, now with Celltech.

According to current estimates, the genome contains approximately 30,000 targets (considerably fewer than first thought), but without further division, the industry is unlikely to make beneficial use of this information. It must recognize which of these targets will make a suitable drug target.

Given that Pfizer has been one of the leading exponents of what a molecule needs to make it a drug, they have been in a good position to assess drugability, an assessment of the tractability of a given drug target. Armed with this experience, the authors have sought sites suitable for the discovery of small-molecule, orally available compounds and based their early classification upon the assumptions made by their colleague Lipinski when he described his "Rule of 5." However, they have gone further and superim-

posed consideration of ligand interaction parameters and the observation that most successful drugs are mimics of the endogenous mediator. Uncompetitive drugs binding at allosteric sites being rare. Applying these criteria to gene sequences and extrapolating the information to gene families (assuming that common sequences are indicative of a similar active site architecture), the number of drugable targets is not 30,000 but about 3,000. Although some 50% of proteins have yet to be discovered, it appears that all large protein families are accounted, and it is unlikely that the number of targets will increase much above the current estimates.

Even so, the number of proteins against which one might want to target a drug is likely to be lower than 3,000, because only those linked with disease can be appropriate. By capturing proteins bound by a wide range of experimental drugs and eliminating those not modulated by compounds compliant with the "Rule of 5," most of the chemical compounds, according to the above assumptions, do look like their endogenous ligand. The sequence data of the targets identified are representative of only 130 protein families, and nearly half of the targets derive from a mere six: G-protein–coupled receptors, two classes of kinases, metalloproteases, nuclear hormone receptors and phosphodiesterases.

Genomic sequence analyses of the types described have identified a relatively limited number of protein classes which satisfy the industry predilection for orally administered medication. The predictive power of the techniques remains to be demonstrated, but as of today they represent a plausible method of directing medicinal chemistry towards tractable targets. This may not only provide a practical means of exploiting the enormous potential of the human genome but may also improve the quality of NMEs and reduce attrition, which is not, to date, demonstrably better than it was 10 years ago.

The opening sequence of slides from Dr. David Brown (previously Head of Discovery at Roche and currently CEO of Cellzome) described project attrition data derived from studies at Roche which he believes to be representative of the industry as a whole. According to these data, one in 57 novel compounds is progressed to the market. The figure is slightly better for "MeToos" where the chances are 1 in 25.

In discovery, 37% are lost through a failure to validate the target and 62% because either a lead cannot be found or optimized. In development, attrition is due to poor portfolio decisions, preclinical toxicity and poor efficacy in phase II trials.

Conversely, the chances of success are enhanced by selection of an appropriate target type and early clinical input. For all the years of pharmaceutical research, four target classes have proved most susceptible to modulation by chemicals: G-protein–coupled receptors, enzymes, ion channels and nuclear receptors. Selection of targets in these classes is still expected to pay dividends. Equally, the existence of surrogate clinical markers and/or clear disease endpoints greatly improve the chances of success. Where there are no surrogates or clear disease endpoints, the prospects for success are very low.

Timing is also of the essence. Like all growth curves, the introduction of new technology follows a sigmoid curve with lag, exponential and maximal phases. How early to invest may be a key decision, striking a balance between maintaining a competitive position while curbing expenditure. There may be advantage to a late intervention with the opportunity to leapfrog others and buy state-of-the-art equipment at the outset. Alternatively, late investment may be a deterrent to potential investors.

So what really helps? Knowing what the competition is doing is important both with respect to technology platforms and processes. Target identification technologies, including both bio- and chemoinformatics, may prove positive as will (and always has) chemical tractability. The technology to support rapid chemical assessment and multidimensional optimization, according to the metrics has yet to prove its worth. The figures superficially suggest that high throughput ADME (absorption, distribution, metabolism and excretion) technologies have reduced attrition attributed to inappropriate pharmacokinetics. However, it appears that the early data were skewed by large numbers of poorly absorbed antibiotics, so that even this apparent success may require further investigation. Toxicity databases are making little progress because the industry is reluctant to share its data.

So what hope for the future? This was a subject addressed by one of the scientists most fitted to do so—the one person responsible for more novel drugs than any other (by a long way). Dr. Paul Janssen chose to address the issue by reading from a presentation he had made some 25 years ago, and it was a stark message to all that not very much had changed.

What do we mean by a better drug? A substance that treats a disease better than another and when two drugs are equiefficacious, the adverse event profile may provide the differentiation. Only patients can decide, and they may base their decision upon wholly parochial parameters such as the ease of compliance and even the color of the tablet.

How to find them? Surely no accident that Dr. Janssen returned to a message earlier given by Sir James Black: drug hunting requires persistence. But here there was a humanitarian slant that persistence will only be found in a creative, free-thinking world. It cannot operate in a selfish world loaded with bureaucracy, regulations, old prejudices and habits of mind.

The air is filled with skepticism that the pharmaceutical industry is seen as a professional exploitation of disease. The birth rate of new drugs is low and declining and was highlighted by the failure to develop antiprotozoal drugs.

All this was 25 years ago. He left us to discuss among ourselves just how much had changed. If there was a single message, it may have been that the golden age of drug discovery—an age in the late 1980s and early 1990s that could benefit from a vast knowledge base—was over; at least until the knowledge base takes another leap forward. The day's presentations had provided considerable grounds for optimism that the new generation of knowledge development is under way.

Prous Science has collaborated with the Society to make the symposium available, free of charge, in a Webcast format (http://www.prous.com/drugdiscovery). Visitors to the Webcast can hear each speaker's voice synchronized with the complete set of slides, graphics and photographs.

Dr. Peter Warne and Prof. Clive Page are Conference Organizers and Members of the Society for Medicines Research. The SMR Committee organizes conferences on behalf of the Society for Medicines Research four times a year. These one-day conferences are of a multidisciplinary nature, therapeutically focused and normally staged in or around London. Details about forthcoming meetings can be obtained from: SMR Secretariat, 20/22 Queensberry Place, London SW72DZ, U.K. Tel: +44 171 581-8333; Fax: +44 171 823-9409; E-mail: smr@iob.org; URL: http://www.socmr.org.

KEY PRODUCT AND CORPORATE HIGHLIGHTS AT HUMAN GENOME SCIENCES

On April 24, 2003, Human Genome Sciences, Inc. updated the status of several of its drugs after progress in the first quarter of 2003.

Phase I results were reported for *LymphoStat-B*™ (**belimumab**), a human monoclonal antibody to B-lymphocyte stimulator (*BlyS*™), showing that *LymphoStat-B* is well tolerated and biologically active in patients with systemic lupus erythematosus (SLE). Based on these results, it is shortly due to be advanced into phase II trials. *LymphoStat-B* has been awarded fast-track designation for the treatment of SLE. Phase II trials in rheumatoid arthritis are also planned.

Phase II results for **repifermin** (keratinocyte growth factor-2, KGF-2) were reported shortly after the close of the first quarter, demonstrating that repifermin is well tolerated and has efficacy in treating cancer therapy-induced mucositis. Development plans will be discussed with the FDA, clinical investigators and Human Genome Sciences' partner GlaxoSmithKline.

Human Genome Sciences also announced the discovery and development of *Abthrax*™, a human monoclonal antibody drug that is effective in protecting against the lethal effects of anthrax in multiple experimental models in animals. A single dose of *Abthrax* significantly increased survival in rabbit and nonhuman primate models of inhalational anthrax. *Abthrax* will be developed as a prophylactic and therapeutic drug to prevent and treat anthrax infections. An IND filing is expected in the near future to allow clinical testing in healthy volunteers.

During the quarter, Human Genome Sciences' partner GlaxoSmithKline commenced clinical trials of **659032** (**SB-659032**), a second small-molecule inhibitor of lipoprotein-associated phospholipase A_2 (Lp-PLA_2), an enzyme associated with the formation of atherosclerotic plaques. 659032 is the third genomics-derived small-molecule drug coming from a collaboration between the two companies to enter clinical development. Human Genome Sciences received a clinical milestone payment from GlaxoSmithKline in the first quarter, triggered by initiation of clinical trials of 659032. The company has an option to co-promote an approved drug in North America and Europe.

Human Genome Sciences established a new subsidiary in Europe with responsibility for European clinical trials.