TARGET SELECTION IN DRUG DISCOVERY

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Target selection in drug discovery — defined here as the decision to focus on finding an agent with a particular biological action that is anticipated to have therapeutic utility — is influenced by a complex balance of scientific, medical and strategic considerations. In this article, we provide an introduction to the key issues in target selection and discuss the rationale for decision making.

A GUIDE TO DRUG DISCOVERY

LIFE-STYLE MODIFYING DRUGS
For example, sildenafil for managing erectile dysfunction or anorectic drugs for obesity.

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What is meant by target selection?

The term 'target' carries several connotations in the overall context of drug discovery. Remarkable progress in molecular biology has led to the identification of numerous proteins with key roles in the function of both normal and abnormal cells, which has allowed the formation of specific hypotheses about how modulating the function of defined proteins that are linked to disease could be a route to new drugs. Such disease-linked proteins are commonly referred to as targets. The basis of the hypotheses can range from an attractive scientific theory to information obtained from genetic analysis of tissues obtained from patients with a particular disease, and the process of confirming such hypotheses (to varying degrees of confidence) is usually termed 'target validation'.

However, in this article, we consider targets in a broader sense — the target in the context of 'target selection' might comprise a therapeutic area, such as central nervous system diseases, or a specific disease itself, such as Alzheimer's disease. In addition to the question "What is the disease target?", questions such as "What is the scientific approach?" also need to be addressed. As such, there is an implicit hierarchy encompassed by the term target selection (FIG. 1), in which strategic considerations are a crucial component. In this article, we discuss the context in which target-selection decisions are made, and highlight some of the key issues involved.

The importance of context in target selection

New medicines research is carried out almost entirely by commercial organizations of varying sizes and complexity, whose assumed objective is the discovery of improved medicines for the treatment of disease. The commercial organization might range from a start-up biotechnology company, carrying out research on two or three targets, with research investments of £5–50 million, to a multinational pharmaceutical company working on 30–50 targets, whose research investment involves £100–500 million annually. In each setting, the context is the investment of private finance with the long-term purpose of providing a realistic financial return within an acceptable timeframe. Clearly, research target selection takes place in an environment that is strongly influenced by financial considerations.

Another aspect of the influence of context is the relationship of the organization of the company carrying out the drug development research to the operating environment. FIGURE 2 shows the interactive relationships between stakeholders (investors), consumers and the pharmaceutical firm, and highlights that drug discovery companies are strongly influenced in their decision making about target selection by the perceived current or future attitudes of society as revealed by social audits and as reflected by such groups as health activists, as well as governments and their health policies. A current example is the debate as to whether the development of so-called 'LIFE-STYLE MODIFYING DRUGS' are acceptable goals for new medicines research. When deciding which disease targets should be the focus of research investment and activity, such aspects form the backdrop against which decisions about research targets are debated.

Figure 1 | **Pyramid showing the hierarchy of considerations that underpin a single target selection.**

The dynamics of target selection

Decisions about target selection are made through the interaction of several groups within a company. Predictably, the interaction is more complex within a large pharmaceutical company than in a smaller biotechnology company, and the latter will be discussed separately.

In a large company, the dynamics of target selection can be described by a diagram of the type shown in FIG. 3, which has at least three levels. The first level represents the strategic level of research policy, which should be the responsibility of the chief executive officer (CEO) and the board members of the company. They approve proposals made by the research director concerning which disease areas will be the focus of the scientists within the research department. In addition, the apportionment of the research budget between the different disease targets must be agreed on. These proposals must be acceptable to the entire board, but especially to the marketing and financial directors. The approved research strategy should ensure the future viability of the company.

The second level in FIG. 3 is the creation and management of the research portfolio. This will comprise the chosen therapeutic areas approved by the company board and, more importantly, the number and scope of the projects in each therapeutic area. It is at this level that the most intense analysis and debate concerning the selection of research targets take place. The individuals who are accountable for the management of a portfolio comprise a core group of the research director and senior scientific staff (managers). A practical distinction is made between the dynamics that are required for starting new projects — that is, the inception phase or target selection, and the subsequent monitoring of the project once the work begins. In commenting on research strategy, one of its most successful practitioners, Sir David Jack, wrote:

> "The choices are made by assessing competing ideas which are invited from all the staff. The best ideas are simple, practicable with the available resources and, above all, novel enough to yield medicines that are likely to be better than probable competitors in ways that will be obvious both to doctors and their patients"[1].

The key phrase in this statement is "likely to be better than probable competitors in ways that will be obvious both to doctors and their patients". In practice, implementing such a strategy is becoming increasingly complex. To select a proposed research target, a range of issues need to be evaluated. The first, and perhaps most important, is what constitutes an improved medicine. Many descriptors of varying utility are used to describe new medicines. The current favourite is 'blockbuster drug', which is much used by stock analysts to indicate annual sales in excess of US $1 billion. We find this term unhelpful, in that, as far as we are aware, most blockbuster drugs were not forecast by the respective marketing departments of the companies subsequently benefiting from the sales at the time the decision was made to select the target (J. D. Fitzgerald, personal communication). Furthermore, if informal conversations are a reliable guide, several projects that resulted in multimillion pound sales were not strongly supported at the phase of target selection, even by the research manager (TABLE 1). Although potential sales forecasts are important in target selection, most forecasts are based on extrapolation from historical experience and assumptions of variable validity. The point here is not to criticize those who prepare sales forecasts, but to emphasize the inherently unpredictable nature of sales forecasting, particularly for truly innovative medicines.

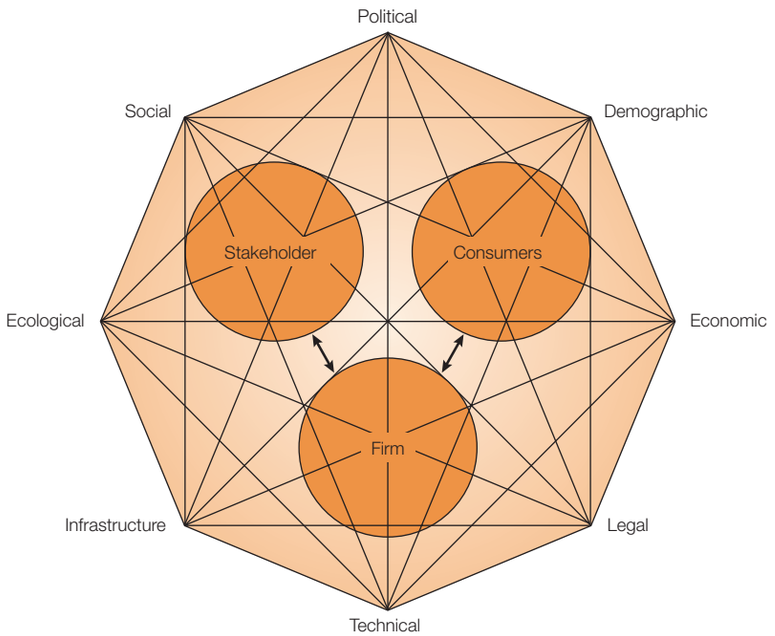

Figure 2 | **Conceptual model of the complex socioeconomic system within which industrial companies, including the research-based pharmaceutical industry, need to operate.** In relation to target selection, an appropriate balance should be struck between, for example, stakeholders (investors), consumers (patients/doctors) and other modulating factors, such as legal factors (drug regulators) and political factors (potential payers).

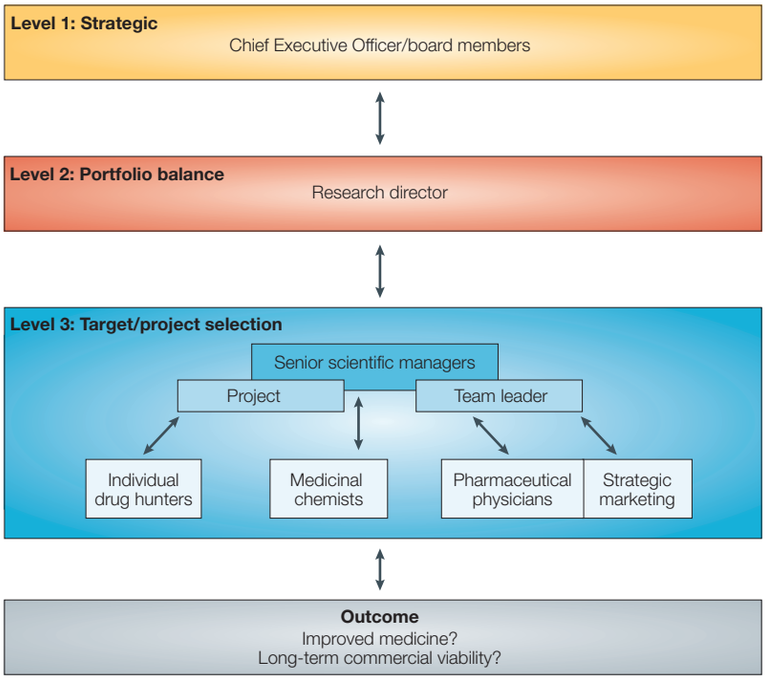

Figure 3 | **Diagram showing the interaction between different groups accountable for target selection.**

A second descriptor often applied at the target selection stage is 'innovative research' project. It should be emphasized that better medicines can be obtained in two ways: either by enhancing therapeutic efficacy or efficiency. An example of increased efficacy is provided by the statin class of anticholesterol drugs, which, as monotherapies, have achieved greater sustained reduction in plasma cholesterol in a larger number of hyperlipidaemic patients than previous therapies, such as fibrates. Statins reduce total plasma cholesterol by 20–40%, compared with the 10–15% reduction that is typically observed with fibrates. An improvement in efficiency implies that the new product, although not being intrinsically more efficacious, achieves better treatment results by using an easier route of administration, less frequent dosing or a wider patient tolerability in comparison with previous medicines used for the same disease. A contemporary example of improved efficiency is the antihypertensive agent amlodipine — a calcium antagonist — which, by having improved pharmacokinetic and receptor-binding kinetics, as well as potency, achieves greater efficiency than its predecessors, with the same mode of action.

These considerations are of practical importance in target selection and lead to the categorization of target selection strategies into two subclasses. The first can be termed a 'speculative research target' strategy, which represents cases in which the specific biological action sought has not been shown to have therapeutic utility at the inception phase of a research programme; the proof of the utility of the approach can only be established by Phase II clinical trials.

The second subclass of target selection strategy is 'innovative improvement', which is a research strategy of which the intention, at the inception phase of the research programme, is to improve on the performance of an agent with biological activity that is already known to have therapeutic utility. The aim for innovative improvement research can be to fulfill one or more of three criteria. First, greater potency, which might lead to improved efficacy and/less frequent daily dosing. This might also reduce the cost of production, particularly if the cost of large-scale synthesis is markedly reduced. Second, greater selectivity; for example, the highly β_1-adrenoceptor-selective antagonist atenolol is much less likely to induce bronchospasm in susceptible patients than its non-selective predecessor propranolol. This example also illustrates the factor of dose frequency described above — atenolol is dosed once daily, whereas propranolol requires administration three times per day and the doses are also higher. Third, a wider margin between the desired therapeutic action and unwanted effects. This type of improvement was also achieved with atenolol compared with propranolol.

Innovative improvement targets are often underestimated in their utility, both by health consumer groups and regulatory bodies. For example, the US Food and Drug Administration (FDA) classifies marketing applications for new drugs according to the perceived therapeutic improvement of the drug, and categorizes applications as Class A (high therapeutic improvement) through to Class C (little therapeutic improvement). Thirty-nine such drugs classified by the FDA as Class C were re-evaluated by Yasuda and Woosley[2] based on three criteria: therapeutic advance, improved pharmacokinetic profile and improved tolerability (that is, better adverse-event profile). Twenty eight of the thirty nine drugs evaluated were judged by these academic clinical pharmacologists to have significant clinical advantages. The reason for making this distinction between speculative and innovative improvement research targets is that the risks of the chosen target failing to show improved utility are inherently greater with the former than with the latter target.

A third descriptor used for research targets is 'me too', which is often applied by commentators on the pharmaceutical industry, but whose definition is notable by its absence. We would describe a 'me too' research target as one for which there is no hypothesis at the inception of the research, which addresses a medically defensible improvement but merely has as its aim the discovery of a patentable new chemical entity (NCE) that would provide intellectual property for the company. For example, for β_1-adrenoceptor antagonists such as bisoprolol or betaxolol, it could be argued using the above criteria for innovative improvement that these agents lack innovation from the medical standpoint. This emphasizes the need to make a distinction between innovation in relation to the need for improved medicines and innovation in relation to novel chemical structures, which, although they might be highly innovative themselves, do not necessarily offer a therapeutic advance.

Table 1 | **'Blockbusters' whose success was not anticipated at the time of target selection**

Agent	Position in class	Indication	Initial sales forecast
Tamoxifen (Novaldex)	First	Breast cancer	£100,000
Captopril (Capoten)	First	Hypertension, heart failure	US $20 million
Cimetidine (Tagamet)	First	Peptic ulcer	£700,000
Fluoxetine (Prozac)	Second	Depression	?*
Atorvostatin (Lipitor)	Fifth	Hyperlipidaemia	?‡

*Not supported initially by research management. ‡Licence offer rejected by several companies. Current sales US $6 billion.

A consideration of the proposed properties of the NCE is important in target selection and debate as to what constitutes an improvement on a currently available medical therapy can be protracted and contentious. This is because the evaluation depends on the background and value systems of those accountable for the appraisal. There are at least eight constituencies, which are shown in FIG. 4. For example, the drug regulator might well take a different view as to the degree of improvement that a new drug shows in comparison with the opinion of the drug hunter who discovered it. Similarly, the physician and the consumer are likely to have different views from those of the marketeer. The heterogeneity of cultural attitudes and value systems of these different constituencies inevitably leads to conflicting views as to what constitutes an improved medicine. A recent example of differing value systems was provided by Morgan[3] in an article on the proposed merger between Glaxo Wellcome and SmithKline Beecham. Morgan wrote:

> "Pharmaceuticals is a long-term game and much of the far-off stuff can only be understood by people with a strong scientific background. The City, on the other hand, thinks after lunch is a long time away".

Clearly, the external constituencies, such as regulators or stock analysts, will not be directly involved at the stage of target selection but, as emphasized earlier, their probable views in the future need to be considered, even at the time of target selection.

Target selection criteria

Two pivotal questions face a research director in deciding whether to accept or reject a new research target. First, what is the probable risk and the likely financial return of the target? It is sobering to reflect on a retrospective analysis of the risk/return of a large number of NCEs that were marketed between 1975 and 1984 (FIG. 5). This analysis revealed that 55% of the medicines marketed at that time had a low risk of failure, but also had a low financial return. Although risk/return assessment is imperfect at the inception phase of target selection, the challenge is to avoid high-risk targets with a potentially low financial return. Second, the judgment that the research director has to make is "Will the project provide the company with the right drug, for the right market niche, at the right time and at the right price?". The issue of drug pricing is often contentious. There is an excellent overview describing the approach used by research-based companies in identifying the right price for a new product and this should help to correct some of the public misconceptions in this area[4].

To address these issues, companies use generic criteria, with the aim of devising an approach that is likely to lead to an improved medicine in one or more of the fields in which most drug research companies are working; namely, central nervous system, cardiovascular system, infection, cancer, inflammatory and allergic conditions, respiratory, gastrointestinal and metabolic diseases. Three sets of criteria are commonly used.

First, what is the probability of achieving the action(s) sought? Answering such a question involves determining whether therapeutic utility has already been established for the biological action being sought; if not, then the quality of the scientific hypothesis, the calibre of the scientific team tackling the problem and the estimated feasibility of making chemical molecules relevant to the target needs to be addressed. A further factor to consider is the probability of the project being 'blind-sided' by an important, but unanticipated, technical advance in the field.

Second, what is the probability of maintaining a competitive advantage with the proposed project? To assess this, the research director needs information on the current scientific understanding of the disease target, a critical profiling of current therapy, a critical analysis of unmet medical needs and the preferred future needs (data for which are ideally generated from structured interviews with the relevant disease specialists in different countries). These considerations are particularly important when the research director is assessing proposed targets aimed at improving drug efficiency (see above).

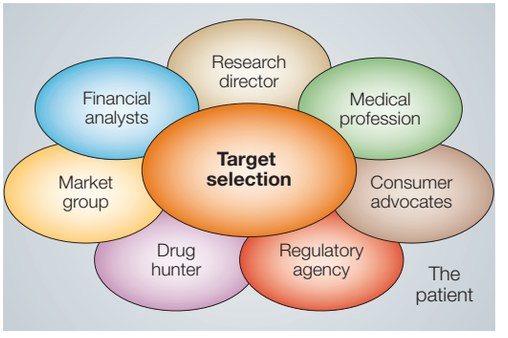

Figure 4 | **The differing constituencies with a current or future stake in target selection, and their overlap.**

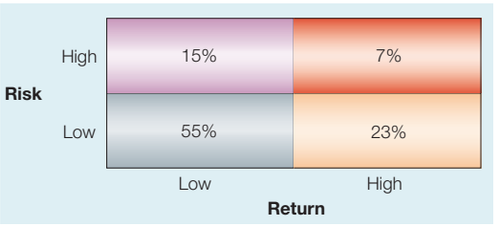

Figure 5 | **Risk/return analysis of new chemical entities marketed between 1975 and 1984.** This analysis revealed that 55% of the medicines marketed at that time had a low risk of failure, but also had a low financial return. Data from Touche Roche Management Consultancy quoted in REF. 18.

Third, what is the probable financial return? The answer to this question depends on the provisional marketing and product evaluation. For this evaluation, research directors are crucially dependent on the skills of their strategic marketing colleagues. There are inherent difficulties in obtaining consistent market forecasts for reasons that are described elsewhere[5].

Target selection in biotechnology companies

The above description of target selection is based on processes that are commonly used in established pharmaceutical companies. In the setting of a new biotechnology company, the principles described still apply, but the staff involved and the evaluation process differ. Most of these start-up companies are involved in biotechnology with the purpose of exploiting advances in genomics and proteomics with potential utility in cancer, inflammatory diseases and cardiovascular diseases. These companies usually comprise a core group of scientists who believe that they have made exploitable observations in basic science. Typically, an initial group of less than 20 staff comes together to seek funding from various sources, particularly venture capitalists. In the early 1990s, such funding was relatively easy to access, especially in the United States. To attract investors, a detailed business plan has to be drawn up and a key element of this plan is a description and justification of the target selection. The arguments used to support the technical element of the plan are identical to those described for a large pharmaceutical company, but are addressed to a different audience. Once the plan is submitted to a venture capitalist group, it is subject to a due diligence evaluation by an external consultant whose role is analogous to that of the research director of a large company, without, however, being accountable for the long-term validity of any opinion expressed. Another difference between a small biotechnology company and a large pharmaceutical company is that nearly all of the proposed research projects are based on speculative research ideas and are, consequently, high risk. However, if these companies were to be successful in the fields of cancer, inflammation or cardiovascular disease, then the potential for a high financial return is considerable.

The recent adjustment in the world stock market has markedly changed the attitudes of investors to biotechnology risks. At a recent UK BioIndustry Association meeting, the general consensus was that more product approvals and merger and acquisition activity, with at least one company success story, would be the catalyst required to pull the sector out of the doldrums[6]. Such a view emphasizes the inherent risks in a portfolio comprising solely speculative research targets with no counterbalance of innovative improvement projects.

Techniques to support target selection

The description provided here of the dynamics of target selection indicates that the basic task is that of making judgements about the future with its attendant uncertainties. Judgements have to be made about the science, the clinical status of treatment and the probable commercial return. A range of modelling techniques, many of which are based on models used in predicting future performance in financial markets, have been applied to target selection in pharmaceutical companies. There are many differing techniques[13–16] (BOX 1), each of which has its proponents. Possibly the main value of these techniques is in providing a framework for ensuring that the criteria for target selection are consistently applied and that there is transparency in articulating the assumptions underlying decisions about target selection.

Current and future issues in target selection

The sequencing and initial characterization of the human genome heralds the beginning of a new era in biomedical research, with important practical implications for the diagnosis, prevention and treatment of disease. The discipline of genomics is the elucidation of the function of all genes and their products and the effects of their interaction with the environment. It is now estimated that the human genome contains 30,000–35,000 genes, <50% of which can be assigned a putative biological function on the basis of sequence data[7]. These genes have the theoretical potential to synthesize more than 100,000 proteins[7]. The challenge for the understanding of disease mechanisms, the modulation of which by synthetic chemicals might lead to improved medicines, is to determine which proteins might be a viable research target, with estimates of the number of such targets ranging from 600–1,500 (REF. 8) to 5,000–10,000 (REF. 9).

Substantial progress has been made in identifying genetic mutations associated with common diseases. In the field of cancer, for example, mutations of the *BRCA1* and *BRCA2* genes are associated with a marked increased risk of breast or ovarian cancer. The detection of *BRCA1*-positive patients is now used to select anticancer therapy with the monoclonal antibody trastuzumab (Herceptin; Genentech)[10]. However, the precise relationship between disease state, genomic abnormality and protein target is often difficult to determine. We are dealing with complex biological systems, and the current drug discovery paradigm of gene→protein→ target→hit is probably oversimplified. The view is now emerging that creating an inventory of genes, proteins and metabolites is

Box 1 | **Selected techniques for predicting future commercial outcomes**

In general, two analytical processes — decision analysis and valuation of alternative outcomes — are used to facilitate decision making.

Decision analysis is a systematic approach for analysing all the elements to be considered in the decision process: the elementary decisions to make, the uncertain events and the alternative outcomes. For example, the decision-tree technique, also known as the decision diagram or decision-flow network, shows the time sequence of the activities involved in a project, capturing all the possible outcomes of each activity and all the elementary decisions to make along the project progression. All the possible outcome scenarios are represented by branches of the decision tree, keeping in mind that only one of the scenarios will become reality. The decision-tree technique allows a quantitative probability analysis of each possible outcome (risk assessment).

Valuation of alternative outcomes aims to quantify the possible commercial or financial return of a project. It is based on business simulation models — mathematical algorithms to simulate a business market, combined with financial measures. Business simulations have to recognize both commercial risks and uncertainties. This is the purpose of probabilistic methods, such as the Monte-Carlo simulation, which provide both the value of a possible outcome and its likelihood, using randomly selected 'what if?' trials. The most commonly used measures to express the value of a project come from the financial community: discounted cash flow and net present value. The cash flow represents the time sequence (generally on a yearly basis) of 'inflows' (products sales and other project-specific revenues) and 'outflows' (all project-specific costs). As the value of money decreases over time (one dollar today is worth less than one dollar tomorrow), cash flows are discounted over time, using an appropriate discount rate that captures both the cost of capital and the investment risk. The discounted cash flow technique allows the level of possible revenues to be balanced with their timing. The net present value provides an easy, single value with which to characterize a project, by summing up the discounted cash flows from today (first year) until the end of the product life or the end of patent protection.

Combining these techniques, such as in the multi-attribute decision analysis approach pioneered by Phillips[16] at the London School of Economics, is attracting increasing attention, perhaps owing to its use of risk-adjusted total benefit in relation to cost. Its main use is for use in balancing risk-adjusted benefits across a research portfolio using the commercially available Equity program.

necessary, but not sufficient, to understand the integrated roles of the genome, transciptome, proteome and metabolome[11]. Much of the current emphasis in target identification is based on finding associations between sequence data (for example, DNA microarrays, expressed sequence tag (EST) databases and so on) and disease. However, caution is required, as a simple association between gene expression and disease does not necessarily validate it as a therapeutic target. Genetically modified animals (for example, knockout or knock-in mice) provide a much clearer link between gene and phenotype. Advances in chemical genomics and proteomics using cell-based assays and covalent binding compounds is helping to solve these problems, which cannot be solved by genetic manipulation and genomics[17].

In general, the validity of targets identified through genomics, proteomics and the screening of libraries of small molecules against particular proteins with activities that could potentially be modulated therapeutically — that is, 'targets' in the narrower context described in the introduction — is the subject of considerable debate at present. The potential to exploit the identification of novel, endogenous ligands, such as urotensin, trace amines in the central nervous system or the hormone leptin from adipose tissue, which have generated great interest as novel targets, has also been widely discussed. In each case, much remains to be understood about their role in disease states, and initial enthusiasm is often dampened by subsequent research findings. In this context, the views of the Nobel-prize-winner Sir James Black, one of the most successful drug hunters, are of relevance. In a recent paper that addressed future perspectives in pharmaceutical research, Black wrote:

> "During the last forty years I have seen the tremendous success that the pharmaceutical industry has achieved by basing its drug strategy around the naturally occurring molecules, hormone and substrates, etc. These native molecules were the leads. Close analogues and derivatives were then designed around these leads. Classical bioassays and biochemistry were able to select-in those compounds that competed with the native molecule for the same active site. Compounds with a high degree of selectivity were regularly produced. The new strategy (ie, combinatorial chemistry and HTS) may not be so lucky. Proteins are inherently 'sticky' molecules. There may well be a danger that the binding reactions used in the high-throughput screening that is used in conjunction with combinatorial chemistry will select-in nonspecific molecules. Non-selectivity may not become visible until the development stage involving intact animals is reached. Too much combinatorial chemistry might well come to be seen as a risk factor to the corporate health"[12].

Many will disagree with these warning words, but they do contribute to the ongoing debate about the optimal approach to target selection. Whatever strategy is adopted, a key determinant of future success is the quality of the intellectual activities and skills associated with target selection.

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Acknowledgements

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DATABASES

The following terms in this article are linked online to:

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