Designer drugs: pipe-dreams or realities?

W. E. GUTTERIDGE

WHO/TDR/TDP, CH-1211 Geneva 27, Switzerland

SUMMARY

New chemotherapies are urgently needed for the parasitic infections of animals and for the tropical diseases of man. Rational molecular design approaches to attempt to discover such products require a massive investment of resources up-front of actual chemical synthesis. However, such investment is justified, since chemical synthesis itself is highly resource-consuming. The fact that few targets have yet been validated to justify a rational approach is an argument only to get on and validate more. Not all the components of molecular design can yet be done totally rationally, but this is not an argument against applying this approach where it is possible. Absence of a successful track record is inevitable for any newly emerging technology. It is too early to draw conclusions about the relative costs of rational design versus empirical synthesis, since the former is only now beginning to become reality and the latter is in the middle of a (combinatorial) revolution. Similarly, it is too soon to predict with certainty which of these two approaches will prevail in the long run. However, they lend themselves to parallel tracks, so both may well continue for the foreseeable future. Current concerns about who would develop successful discoveries are not reasons for stopping discovery research. Indeed, a string of putative products held at the discovery/development interface would be useful ammunition to those trying to develop partnerships such as a Tropical Diseases R&D Alliance aimed at carrying out such work and sharing costs.

Key words: parasites, targets, drugs, discovery, rational, empirical.

INTRODUCTION

The control of morbidity caused by parasites and the eradication of infection are major unfulfilled challenges for the parasitologist. Few vaccines are available for veterinary use and none for use in humans. Control strategies, therefore, focus on the vector or personal hygiene/public health measures, as appropriate, and on chemotherapy. Fortunately, many drugs are available for the chemoprophylaxis and treatment of the parasitic diseases of humans and domestic animals (Gutteridge, 1993; Croft, this volume). However, not one of these was designed totally rationally, hence the title of this review. In using it, I am not being frivolous. All too often, the negative aspects of this statement are used to assert that any attempt at rationality is a waste of time, and that what is important, if one is serious about discovering new antiparasite drugs, is to screen compounds, 10000 of them or more. The previous chapters of this book fly in the face of this approach: they indicate clearly that serious attempts are under way to take advantage of new technologies to design novel antiparasite drugs rationally, at least more so than hitherto. Therefore, what I do here is review critically the advantages, disadvantages and limitations of these more rational approaches, so as to assist a careful consideration of this question.

Initially, I need to make three points. First, most currently available antiparasite drugs are far from perfect (Gutteridge, 1993). Some have limited efficacy (e.g. nifurtimox), others show significant adverse effects (e.g. melarsaprol) and many cannot be administered by the most desirable route (e.g. suramin is not active orally). None is currently registered for use in humans against *Cryptosporidium parvum*. Many originally very effective drugs are now compromised by acquired drug resistance, especially many anticoccidials and key antimalarials such as chloroquine (Beverley, this volume; Ward, this volume; Roos, this volume). Therefore, it must be concluded that empirical chemotherapy has not provided solutions to all the problems. Secondly, it follows from this that there is an ongoing need for new chemotherapies for both treatment and prophylaxis, not only of the traditional parasitic diseases such as malaria, but also of emerging and re-emerging infections, such as *Cryptosporidium parvum* diarrhoea and toxoplasmosis. Thus, the debate on the more rational versus the empirical approach to chemotherapy is not an academic one, it is real. Thirdly, it should be noted that this debate is not one for parasitologists alone: potential strategies for anti-infective drug discovery are the same in all subdivisions of this therapeutic area. Therefore, the debate and the conclusions that emerge from it are pertinent to all scientists working on chemotherapy. The overall challenge of emerging and re-emerging infections world-wide is enormous, notably that of AIDS and its associated opportunistic infections.

CRITIQUE OF THE RATIONAL APPROACH TO ANTIPARASITE DRUG DESIGN

This discussion uses as its framework eight statements that are made time and time again when the question of more rational drug design is debated.

Parasitology (1997), **114**, S145–S151. Printed in the United Kingdom © 1997 Cambridge University Press
https://doi.org/10.1017/S0031182097008998 Published online by Cambridge University Press

It requires massive initial investment of resources before the process can begin

One nice aspect of empirical chemotherapy is that you can begin synthesizing compounds from an existing lead structure almost instantly, using the well established methods of medicinal chemistry. All you need is an *in vitro* whole organism or small laboratory animal *in vivo* efficacy assay and you can start. Such assays already exist for most parasites. In contrast, rational design requires an enormous up-front investment of time and resources to develop *five* critical sets of information before novel synthesis can commence.

First, a potential target enzyme, receptor or pathway must be identified. Until recently, choice was constrained by the limited knowledge of parasite metabolism and physiology, and especially of the receptors and enzymes responsible for affecting it. However, genomic sequencing techniques are now being applied to many of the parasites which cause disease in humans and domestic animals. New bioinformatic approaches are providing solutions to handling the vast amount of sequence data thus generated, including likely function. Provided the latter can be uncovered, an activity which is not without its difficulties in all branches of microbiology (see Oliver, 1996), we will soon have a new problem (the converse of the old one) in that too many possible targets will have to be taken into consideration.

Secondly, an appropriate assay with the purified, functional enzyme or receptor must be available. Usually, this will be recombinant material, expressed in one of the many systems now available and purified by standard methodology. Ideally, isofunctional mammalian enzyme/receptors should also be available, so that this can be assayed in parallel to give a preliminary assessment of the selectivity and hence potential toxicity of novel compounds. The choice of assay method will be constrained by the particular enzyme/receptor concerned and the need to do kinetic studies with inhibitors, but a requirement for high through-put should not be necessary (though see below).

Thirdly, the target should have been thoroughly characterized biochemically and its three-dimensional (3-D) structure determined. Standard methodologies are available for the latter, which can readily be applied to parasite enzymes (Douglas, 1994; Hunter, this volume). The king of these as far as structure is concerned is undoubtedly X-ray crystallography, provided that usable crystals can be produced. One irony of rational drug design approaches is that crystallization strategies are still essentially empirical. This is one reason that despite there being about 60000 protein amino acid sequences known, only about 1000 3-D structures have been reported (Eisenhaber, Persson & Argos, 1995). In many instances, detailed structural information will be available for the isofunctional bacterial and/or mammalian enzymes. This allows structural modelling of a parasite target of known or predicted amino acid sequence to be carried out, based on homology, which can be used until crystals of the protein itself become available. Mammalian data are particularly important, since comparison with the parasite enzyme/receptor provides further indications as to whether or not selectivity between host and parasite might be possible. A review of progress so far with parasite proteins is provided by Hunter (this volume).

Fourthly, some chemical leads need to be established. To design a drug totally from scratch is theoretically possible (see below), but it is more complex and usually unnecessary. If data are available for bacterial or mammalian enzymes/receptors then, most likely, inhibitors will already have been described. These are unlikely to be parasite-specific, or even very potent against the parasite protein, but they can often be modelled into the target structure once this has been determined and thus provide starting points for the design of analogues. Where inhibitors are not known, they can be sought from chemical libraries, once a suitable assay has been developed. Advances in combinatorial chemistry and high through-put screening methods look set to revolutionize this part of the process (see below).

Finally, and most important of all, the target should be validated. The drug discovery and development process takes a long time and costs a considerable amount of money. It is imperative therefore that before it is begun data are obtained to confirm that inhibition of its function precipitates an event that is immediately or ultimately lethal to the parasite (for example, cell lysis, blockade of cell replication, or paralysis so critical position is lost in the blood stream or gut). Until recently, options here were limited and focused principally on the use of known specific inhibitors to demonstrate ultimate lethality. There are two problems with this approach. First, specific inhibitors usually are not known for a novel target and, secondly, even when such inhibitors are available they may not always be working by the mechanism postulated. In this latter case, correlation between the K_i against the enzyme and the IC_{50} *in vitro* against whole parasites is required before any firm conclusions can be drawn. The only alternative approach available involves target analysis of drug-resistant parasites, which is most readily done after a drug has been discovered. Thus the recent development of gene knockout technology and its application to parasitic protozoa will revolutionize target validation in parasite chemotherapy (Wang, this volume). Its value is already becoming apparent in the leishmania proteinase area (Coombs & Mottram, this volume). It is to be hoped that similar technology will soon be applicable to helminths.

https://doi.org/10.1017/S0031182097008998 Published online by Cambridge University Press

The 'bottom line' is that designer-drug strategies are not for the faint-hearted. They need careful consideration beforehand and the services of an integrated, dedicated team of biochemists, molecular biologists, physical scientists and medicinal chemists if they are to have any chance of success. Nor are antisense oligonucleotides an easy alternative option. Less work may be required before the initial sequence to be exploited can be identified and the design process can begin. However, the down-stream problems are particularly formidable (Szymkowski, 1996; Toulmé, this volume).

To date, too few potential targets in parasites have been properly validated for the approach to be justified

The necessary experimentation to develop these five sets of information is extensive, and thus time-consuming and expensive. Not surprisingly, therefore, few parasite targets have been studied in depth in this way. The accompanying reviews (Coombs & Mottram, this volume; Schmatz, this volume; Urbina, this volume; Martin *et al*., this volume) provide more detail on the more studied putative targets.

No registered antiparasite drug has been designed totally rationally

The statement cannot be denied. Equally, most of today's antiparasite drugs have been on the market for many years and were discovered long before it became possible even to consider seriously the possibility of alternative approaches. Furthermore, an increasing degree of rational thought can be applied (Hudson, 1994) and indeed this has been the case with some of the antiparasite drugs discovered recently. For example, Glaxo Wellcome's atovaquone, at present with the UK regulatory authorities as an antimalarial fixed combination with proguanil as Malarone, certainly comes into this category (Hudson *et al*. 1991; Canfield, Pudney & Gutteridge, 1995). Accompanying reviews recount progress so far in attempts to exploit parasite proteinases (Coombs & Mottram, this volume), enzymes of mannitol metabolism (Schmatz, this volume) and sterol and lipid metabolism (Urbina, this volume), and a range of helminth receptors (Martin *et al*., this volume) as targets in rational antiparasite drug design. Moreover, techniques for computer-aided molecular design *de novo* have improved remarkably in recent years (Li, 1996). Information on the binding site of a target receptor can be used to define the likely characteristics of the ligands in terms of hydrogen bonding patterns, hydrophobic binding regions and charge centres. Such calculations are based on molecular recognition rules derived from analysing X-ray crystallographic databases. Chemical databases of 3-D structures of molecules and molecular fragments can then be searched in order to find potential ligands that can satisfy these binding characteristics. Finally, the chemical structures thus generated can be evaluated using a scoring function which takes account of factors such as interaction energy, conformational flexibility and chiral centres. Such progress is being made that it can be argued that tomorrow's potential antiparasite development candidates will have been discovered much more rationally than yesterday's.

Appropriate characteristics of absorption, distribution, metabolism and excretion (ADME) cannot be designed totally rationally

The rational designer of drugs is primarily concerned with hitting the target: making sure the molecules made by the medicinal chemist will have a high affinity and selectivity for an appropriate region of the parasite enzyme or receptor. However, in the real world, this is only the final part of a multi-stage process. Since few drugs are administered intravenously, drug has first to be distributed from the site of administration, be it the skin, muscle or gut, into the body fluids of the host. Once there, provided it does not bind irreversibly to plasma proteins, it has to find its way to the site of the parasite, penetrate into host cells if the parasite is intracellular, and then, usually, into the parasite itself. There, its affinity and selectivity for the target must be such that it does not divert and bind significantly to an alternative parasite enzyme or receptor. While in the body fluids the drug will pass through the liver, where it must not be metabolized too rapidly to an inactive form and/or be excreted too readily in the bile. Similarly, it will pass through the kidney where ideally it will be reabsorbed. The drug should exert its effects on the parasite before the metabolism and elimination that does occur reduces blood levels below effective concentrations. General guidelines on what will facilitate or prevent such absorption, distribution and metabolism are known, but so far only in a most general way such as the influence of molecular weight, aqueous solubility and $\log P$ on oral bioavailability (see, for example, Navia & Chaturvedi, 1996). However, computer analysis of databases containing the 2- and predicted 3-D structures and important biochemical properties of known drugs is already underway (see, for example, Bemis & Murcko, 1996). Such studies will surely shed more light on this situation in due course. In the meantime, detail for any particular chemical series can only be determined empirically.

It does not allow exploitation of all potential mechanisms of selective toxicity

Studies of existing antiparasite drugs indicate that five basic mechanisms underlie the selective toxicity

https://doi.org/10.1017/S0031182097008998 Published online by Cambridge University Press

of drugs whereby they kill parasites but leave hosts relatively unharmed:

- They interact with a target unique to the parasite (e.g. dihydropteroate synthase/anticoccidial and antimalarial sulphonamides).
- They discriminate between isofunctional parasite and host targets (e.g. tubulin/anthelmintic benzimidazoles).
- They affect both parasite and host molecules, but effects on the mammalian system are not significant because of alternative pathways (e.g. maybe, pyruvate kinase/antitrypanosomal arsenicals) or high mammalian enzyme turnover (e.g. ornithine decarboxylase/antitrypanosomal eflornithine).
- Active drug is formed by metabolism only in the parasite, not in the host (e.g. anaerobic protozoa/5-nitroimidazoles).
- Drug only penetrates into the parasite, not into the host cells (e.g. antitrypanosomal diamidines).

Drugs can be designed rationally to exploit the first three of these mechanisms, though the third is not an attractive one because many such products, e.g. the arsenicals, have narrow therapeutic windows. However, it has proved difficult to design drugs rationally to exploit the final two mechanisms and those that work in this way have been discovered by chance.

It may require only limited chemical synthesis and biological testing, but cost savings here are offset by high expenditure on physical sciences

A need for only limited chemical synthesis is the converse of the extensive biological studies required before the design process can begin. An average chemical series developed by a classical medicinal chemist to explore structure/activity relationships will usually be in the range of 300 compounds. In contrast, programmes of rational design, even though they will involve iterative cycles of design, synthesis, assay and remodelling, will not reach treble figures and may well not exceed 30 key compounds. Bearing in mind that each new synthesis costs several thousand pounds, savings at this stage begin to produce a significant return on the enormous up-front biological investment detailed above. However, the savings on medicinal chemistry and biological evaluation are offset significantly by the continuing investment in the biophysical sciences resource that is required to continue the design process.

It will be overtaken by the combinatorial chemistry revolution

There have been many detailed reviews of combinatorial chemistry and the challenge/opportunity it poses to drug discovery (see Felder, 1994; Terrett *et al*. 1995; Gordon, Gallop & Patel, 1996; Patel & Gordon, 1996; Service, 1996). Conventional medicinal chemistry involves the synthesis of target molecules one at a time. A series of chemical reactions is usually required for this, involving one or more substrate molecule in solution in one reaction vessel, and producing a single intermediate or final product. In contrast, combinatorial chemistry takes a range of related molecules and reacts these with another range to make combination products in all permutations. For example, if in conventional medicinal chemistry joining monomer X with monomer Y yields the product X–Y, then in combinatorial chemistry, mixing $X_1, X_2, X_3, \ldots, X_n$ with $Y_1, Y_2, Y_3, \ldots, Y_n$ in one reaction vessel allows the synthesis of $X_{1-n} - Y_{1-n}$. The combinatorial library of compounds thus created can either be stored and screened as a mixture or the individual products can be separated and then screened. Since such separation is most readily achieved if the synthesis has been carried out on, for example, a resin bead, initially most libraries were constructed using solid phase chemistry. A bonus of this approach is that by-product formation tends to be minimized. However, the range of chemical reactions that could be carried out under these conditions was somewhat limited until recently; for example, peptide synthesis. This was not ideal as peptides generally do not make good drugs (ADME issues are difficult to resolve satisfactorily). More recently, techniques have been developed to allow combinatorial libraries to be synthesized using solution chemistry. This has increased the opportunities immensely.

The great advantage of combinatorial chemistry is that it allows the synthesis of large numbers of related molecules more quickly, more efficiently and more cheaply than orthodox medicinal chemistry. Large numbers initially meant hundreds, but very rapidly this has become thousands and soon no doubt will be millions. Not surprisingly, therefore, the pharmaceutical industry has moved rapidly to adopt this new technology: all the major pharmaceutical companies have either developed an in-house combinatorial chemistry department or they have bought one ready-made. They see combinatorial chemistry, when coupled with automated and robotized screening at the target enzyme/receptor level (the so-called HTS, high through-put screening) and modern data handling technology, as the way forward to revolutionize their lead discovery and lead optimization programmes.

The application of combinatorial chemistry to parasite chemotherapy is still in its infancy, though at least one paper has already been published (Marsh, Smith & Bradley, 1996). Needless to say, however, this chemical revolution is already raising questions about whether or not attempts to design drugs more

https://doi.org/10.1017/S0031182097008998 Published online by Cambridge University Press

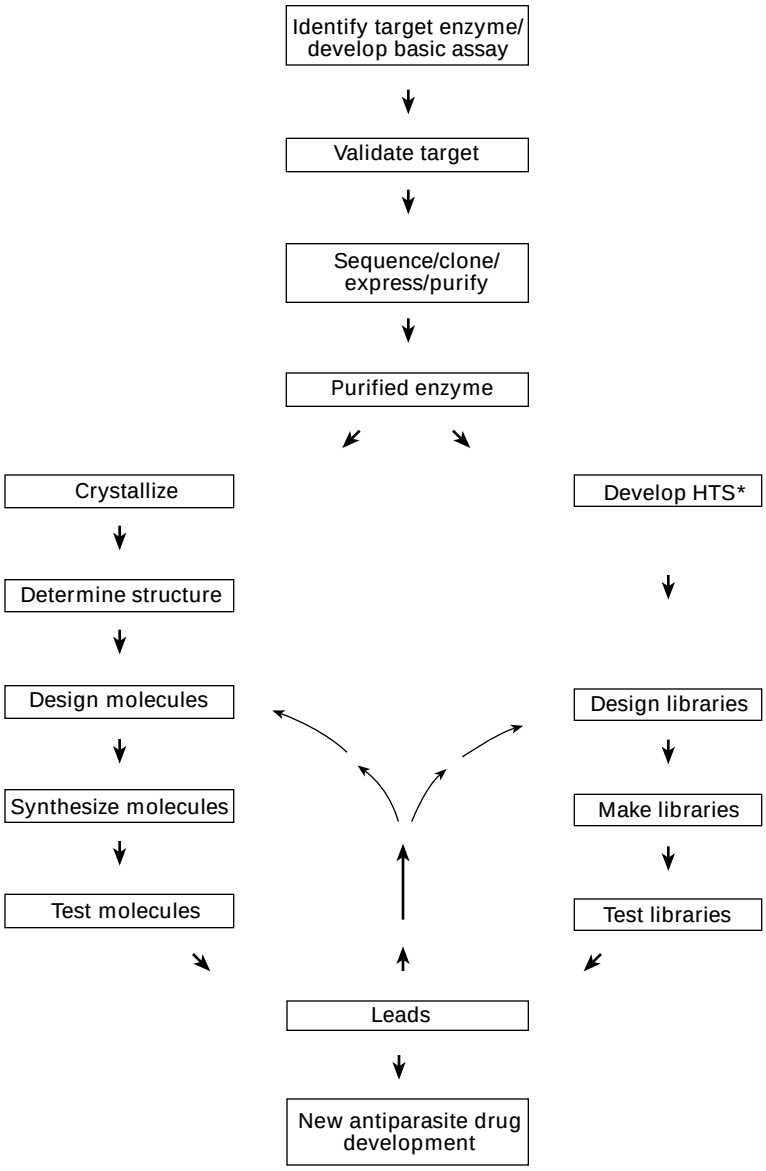


Fig. 1. Potential interplay between rational and combinatorial chemical approaches to drug discovery.

rationally should be continued. Combinatorial chemistry is held by some as allowing the ultimate in empirical chemotherapy – the discovery of a lead molecule and the synthesis of all possible analogues in a time and for a cost less than that required to design rationally and synthesize a small number from scratch. Molecules discovered with the help of combinatorial techniques are already in clinical trials, but it is still far too early to decide whether or not this investment will prove in the long term to be justified in terms of a superior yield of new products. In the mean time, my impression is that industry is sitting on the fence, maintaining its drug design teams and developing its combinatorial chemistry departments. This makes a lot of sense, for two main reasons. First, it is far too soon to decide what impact combinatorial chemistry will make on drug discovery. Secondly, combinatorial chemistry may be cost-effective in synthesizing compounds, but by the time the robots are installed to do the synthesis and screening and computers are installed to handle the data thus generated it still involves a large capital investment and high operational costs. Therefore, combinatorial chemistry libraries are only likely to be made and tested against well validated target enzymes and receptors. The work required to do this is essentially the same as that required before a rational design exercise can begin (see Fig. 1). Combinatorial chemistry is a potentially valuable mechanism to develop rapidly the structure/activity relationship of an active lead designed *de novo*. Conversely, if the coordinates of the biological target of a series of projected combinatorial libraries are known, then these can be used for the basis of a database search prior to synthesis to select the most promising groups of compounds (reviewed in Finn,

https://doi.org/10.1017/S0031182097008998 Published online by Cambridge University Press

1996). Thus, the two approaches run nicely in parallel, allowing potentially valuable interplay between the two discovery teams involved (Li, 1996; Fig. 1).

The debate is academic, as there are no pharmaceutical companies left in the antiparasite drug development business

The costs of product discovery and development in the pharmaceutical industry have escalated dramatically during the past 25 years. In consequence, pharmaceutical companies have necessarily focused their research and development activities on areas where potential market returns are commensurate with such costs. A recent effect of this economic rationalization within the industry has been a major reduction in the R&D spend on antiparasitics intended for veterinary use and the complete withdrawal by the major companies of activities directed towards the discovery of products aimed at tropical diseases.

Many international and national agencies have long supported research that provides basic information essential to the discovery of new drugs, vaccines and diagnostics for tropical diseases, and more recently have also funded projects that actually discover putative products in this area. Only WRAIR and WHO/TDR have in place infrastructures capable of developing such products and thus ensuring that the results of at least some of their research are not wasted. Unfortunately in terms of antiparasite chemotherapy, the WRAIR is being scaled down as military budgets are reduced. The product development activities of WHO/TDR have always been limited by lack of resources; currently such constraints are particularly severe, with a declining TDR budget. It is clear therefore that unless new initiatives in this area are developed soon, the supply of new products for tropical diseases will dry up completely.

However, this is not an insoluble problem and I wish to propose a possible solution. A way forward would be the formation of a partnership between the public sector (international and national agencies, non-governmental organizations including charities) and the private sector (especially the pharmaceutical industry). The prime objective of a Tropical Diseases R&D Alliance (TDRA) would be the development and registration of products for tropical diseases. Secondary objectives would include limited and focused research support, making arrangements for manufacture in certain circumstances, and liaising with field-based agencies to develop understanding of what new products are needed and how best they could be marketed and used. No large up-front capital expenditure is envisaged for buildings and/or equipment. Instead, a TDRA would operate as a 'virtual' company. Development would be contracted out as discrete components through a combination of resource donations and competitive tenders, mostly for the preclinical work packages, and longer-term funding of centres, principally for the clinical trials. Day to day management and administration would be in the hands of a management team of professionals recruited from and financed initially by the pharmaceutical industry through a programme of sponsorships and/or secondments. Payroll-associated costs would be less than \$3M *per annum*, depending on geographic location. Other administrative costs, including office rentals, would be no more than \$2M *per annum*. Financial support for operations of about \$20M *per annum* would be sought initially as cash or 'gifts in kind', about half from the public sector and the other half from the private sector. Depending on what is finally agreed to be its appropriate financial status, TDRA could set up its own technology transfer company and thus move towards becoming self-financing in the longer term. Donors would automatically become members of the alliance and be represented on its council. With such an alliance, a professional management team, and a total annual budget of about \$25M (including administrative costs of no more than 20%), it should be possible to run an internationally credible operation for the development of new products for tropical diseases. Because not all of its activities would involve full development of new chemical entities, with its focus in the anti-infective area and an absence of overheads, such an operation should have the ability to get products to market with time lines, costs and success rates better than those of the industry average.

CONCLUSIONS

- New chemotherapies are needed for parasitic infections of humans and animals.
- Rational molecular design approaches aimed at solving this problem may require a massive investment of resources in advance of chemical syntheses.
- The fact that few targets have yet been validated is an argument only to get on and validate more.
- Not all the components of molecular design can yet be done totally rationally, but this is not an argument against applying this approach where it is possible.
- Absence of a successful track record is inevitable for any newly emerging technology.
- It is too early to draw conclusions about the relative costs of rational design versus empirical synthesis, since the former is only now beginning to become reality and the latter is in the middle of the combinatorial chemistry revolution.
- It is too soon to predict with certainty which of these two approaches will prevail in the long run.

https://doi.org/10.1017/S0031182097008998 Published online by Cambridge University Press

They lend themselves to parallel tracks, so both may well continue for the foreseeable future.

- My own view is that rational molecular design will not be eclipsed by the combinatorial chemistry revolution, but will be complementary to it.
- Current concerns about who would develop successful discoveries are not reasons for stopping discovery research. Indeed, a string of putative products held at the discovery/development interface would be useful ammunition to those trying to develop partnerships such as TDRA aimed at carrying out such work and sharing such costs.
- The bottom line has to be 'travel hopefully', exploiting all the tools currently being developed in the pharmaceutical industry.

ACKNOWLEDGEMENT

I thank my colleague, Dr Colin Ginger, for much help, constructive criticism and debate during the preparation of this article.

REFERENCES

BEMIS, G. W. & MURCKO, M. A. (1996). The properties of known drugs. 1. Molecular frameworks. *Journal of Medicinal Chemistry* **39**, 2887–2893.

CANFIELD, C. J., PUDNEY, M. & GUTTERIDGE, W. E. (1995). Interactions of atovaquone with other antimalarial drugs against *Plasmodium falciparum in vitro*. *Experimental Parasitology* **80**, 373–381.

DOUGLAS, K. T. (1994). Rational drug design in parasitology. *Parasitology Today* **10**, 389–392.

EISENHABER, F., PERSSON, B. & ARGOS, P. (1995). Protein structure prediction: recognition of primary, secondary and tertiary structural features from amino acid sequence. *Critical Reviews in Biochemistry and Molecular Biology* **30**, 1–94.

FELDER, E. L. (1994). The challenge of preparing and testing combinatorial compound libraries in the fast lane, at the front end of drug development. *Chimia* **48**, 531–541.

FINN, P. W. (1996). Computer-based screening of compound databases for the identification of novel leads. *Drug Discovery Today* **1**, 363–370.

GORDON, E. M., GALLOP, M. A. & PATEL, D. V. (1996). Strategy and tactics in combinatorial organic synthesis. Applications to drug discovery. *Accounts of Chemical Research* **29**, 144–154.

GUTTERIDGE, W. E. (1993). Chemotherapy. In *Modern Parasitology*, 2nd edn (ed. Cox, F. E. G.), pp. 219–242. Oxford, Blackwell.

HUDSON, A. T. (1994). The contribution of empiricism to antiparasite drug discovery. *Parasitology Today* **10**, 387–389.

HUDSON, A. T., DICKINS, M., GINGER, C. D., GUTTERIDGE, W. E., HOLDICH, T., HUTCHINSON, D. B. A., PUDNEY, M., RANDALL, A. W. & LATTER, V. S. (1991). 566C80: a potent broad spectrum anti-infective agent with activity against malaria and opportunistic infections in AIDS patients. *Drugs in Experimental Clinical Research* **XVII**, 427–435.

LI, J. (1996). CAMD in modern drug discovery. *Drug Discovery Today* **1**, 311–312.

MARSH, I. R., SMITH, H. & BRADLEY, M. (1996). Solid phase polyamine linkers – their utility in synthesis and the preparation of directed libraries against trypanothione reductase. *Chemical Communications* **1996**, 941–942.

NAVIA, M. A. & CHATURVEDI, P. R. (1996). Design principles for orally bioavailable drugs. *Drug Discovery Today* **1**, 179–189.

OLIVER, S. G. (1996). From DNA sequence to biological function. *Nature* **379**, 597–600.

PATEL, D. V. & GORDON, E. (1996). Applications of small-molecule combinatorial chemistry to drug discovery. *Drug Discovery Today* **1**, 134–144.

SERVICE, R. F. (1996). Combinatorial chemistry hits the drug market. *Science* **272**, 1266–1268.

SZYMKOWSKI, D. E. (1996). Developing antisense oligonucleotides from the laboratory to clinical trials. *Drug Discovery Today* **1**, 415–428.

TERRETT, H. K., GARDNER, M., GORDON, D. W., KOBYLECKI, R. J. & STEELE, J. (1995). Combinatorial synthesis – the design of compound libraries and their application to drug discovery. *Tetrahedron* **51**, 8135–8173.

https://doi.org/10.1017/S0031182097008998 Published online by Cambridge University Press