COMMENTARY

New drug research—A medicinal chemist's perceptions

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The signing of the Dunkel draft, our imminent acceptance of Trade Related Intellectual Property Rights (TRIPS) and the eventual drastic modifications of our patent law relating to pharmaceuticals to give product protection for 20 years have created understandable anxiety and concern among people connected with the Indian Drug Industry. A news item 'New focus for drug research' in the January Issue of *The Hindu* (p. 17), brought together the views of eminent people, some of them in the drug industry but suffered from a serious lacuna. Views had been elicited from the barons of drug industry, from scientists who have worked on process development and molecular biology researchers with an awareness of what was happening in the world but with no hands-on experience in drug development. The reporter had not elicited the views of people (alas! far too few in this country) who have been engaged in the development of new drugs which the article purports to deal with! As a medicinal chemist who has spent the best part of the professional career in *new drug development*, I seek to share my views with your readers through this article.

The country has a record of at least four decades of basic research for discovery of new drugs, the Central Drug Research Institute being the oldest of them. Over the years, it has developed, registered and introduced a few drugs through Indian companies, like Centbutindole, Centpropazine etc; the latest one with antifertility activity, Centchroman can be considered a significant contribution. The Sarabhai Research Centre in Baroda was active in the sixties, but had no useful discovery till its closure. Ciba Research Centre in Bombay inaugurated in 1963 had made sizeable contributions to drug development apart from having outstanding publications, till its demise towards end of 1988. The Centre had obtained marketing permissions for Sintamil, an antidepressant, Nonaperone, an antipsychotic, Tinazoline, a nasal decongestant, Ancletol, an anthelmintic and Satranidazole, an antiamoebic among which the first one has been marketed. The Boots Research Centre in Bombay had a reasonable record during its short life, including development of a new antidiabetic, now in phase II clinical trials in UK, till its closure in 1992. The SKF Research Centre, Bangalore was another institute with a short innings and was involved in antibiotics research. The Hoechst Research Centre is the only R&D Centre left in the private sector which is very well equipped for basic research for new molecules and has a sizeable budget. Although it has not introduced any new drug yet from its research efforts, it can claim credit for having given a valuable pharmacological tool to the biochemists of the world in the form of forskolin (alias coleonol of CDRI), besides having important molecules in various phases of development.

Scientific activities in the field of drug development are as much governed by the state of the art of the times as in any other field. The approaches of the Indian medicinal chemists were in a sense 'traditional' in earlier years depending upon lead-based or biochemistry-based approaches or random screening with lead optimisation dictated by available knowledge or intuition. These were supplemented or replaced as time went on by quantitative structure activity relations-based (QSAR) techniques.

Computer-assisted rational drug design is no doubt the latest approach, but not the only approach to drug development and cannot still boast of many successes. The much-maligned earlier approach of random screening, has now metamorphosised and wears a more respectable cloak and is called 'The search for molecular diversity'. This essentially means subjecting as wide a variety of new molecules from diverse sources—synthesis, plants, fermentation, etc. to as many different tests as possible. The construction of recombinant and synthetic randomised peptide libraries coupled to receptor binding studies is another manifestation of random screening as also the synthesis of 'sense' and 'antisense' oligo nucleotides. Rapid *in vitro* screening is now possible by binding studies with receptors which are available readily and in large number by cloning techniques. This however will not obviate the lengthier *in vivo* characterization which will inevitably follow. The discovery of useful therapeutic properties for plant derived drugs [recent examples–camptothecin (cancer), taxol (cancer) and artemesinin (malaria)] has ushered in a resurgence of interest in plant chemistry in the West as witnessed by the recent commitment of funds by Pfizer in this field. India can ignore this development of bioactivity-based phytochemistry only at its peril.

Before talking of rational drug design, the country should have laboratories and interdisciplinary teams equipped to carry out new drug development. Apart from CDRI and Hoechst, there are no major research centres in this country at this moment devoted to this work.

It is heartening to note that some larger Indian pharmaceutical houses are willing to invest significant sums for this purpose. History may show that multinational firms who did not invest for this in India or withdrew from it were shortsighted. On the other hand, let us not underestimate the demands that new drug development will make in terms of men, money and materials. It is easy to delude ourselves into thinking that given a powerful enough computer and fancy software, we shall be able to churn out drugs by the dozen. If this were so, the world would have seen the introduction of not 37 new molecules in 1990 but hundreds.

Equally important is to note that the 'design' and synthesis of a drug is but the remote beginnings of its development. The path is long and tortuous; the pitfalls are many. It requires the cohesive strength of a multidisciplinary team to strike success. Finally the financial viability of such a new drug is assured only if a world market is targeted and global patent protection is available. Hence the ultimate cost of development of the drug may not be a few crore rupees as some of our exuberant countrymen would want us to believe, although it may not be as high as the $280 million cited by international statistics. In this context, I am not sure how well a consortium approach consisting of the government, CSIR and two or three companies will work. The obvious problems are procedural bottlenecks of

the first two and competition and rivalry among the companies.

A few words on 'me-too' drugs, which are condescending if not denigratory terms for 'look-alikes'. The international research director of a MNC probably put it in proper perspective when he termed them as products of 'molecular evolution' (earlier, manipulation) as against breakthrough drugs which are from 'molecular revolution'. The latter represent quantum jumps while the former afford incremental improvements. We must understand that the patenting of a 'me-too' drug has to satisfy the criterion of novelty; since this is not possible in terms of chemical structure, it must do so in its biological profile. Further the 'me-too' ness of the 'look-alike' does not shorten the process of its development, which goes through detailed biology, toxicology, metabolism, pharmacokinetics and clinical trials.

The contribution of Indian chemists to the synthesis of bulk (known) drugs is very significant, having made these available at low prices, in some cases because of improvements to available processes. While we should be justly proud of this achievement made possible for brand new drugs by the existing patent regimen, we must not lose sight of realities—much of the cost of drugs abroad arises from the ever-soaring cost of developing a new drug. A second factor is undoubtedly cheaper Indian labour. A last but not least important factor is the heavier expenses incurred abroad for pollution containment in bulk drug production processes. Increasing emphasis on the last parameter in the coming years is bound to push up our prices as well.

Apart from process development of synthetic drugs, it must be noted that some of our capable scientists have ventured successfully into the synthesis of biologically active molecules in the areas of cancer, AIDS and bacterial infections. It was common knowledge that these would never become cost-effective processes; but it was however felt that the approaches could produce newer and cheaper analogues. It was evident at that time, and it has been confirmed in retrospect, that this was wishful thinking since neither the desire nor the mechanisms to have the new molecules screened properly have been in place.

In conclusion, the development of a new drug is a complex conglomeration of many activities. While this has been a desirable national objective so far, it has become imperative in the light of the expected changes to our patent laws. Fully realizing the enormity of the task, the country can undertake it optimistically and we should congratulate the larger Indian drug companies venturing into this area. Chemistry, which is but one of the many disciplines involved, has demonstrated its ability in the synthesis of drugs. Expertise in other disciplines like different areas of biology, drug metabolism, toxicology, etc. are both scarce and currently, not focused to the task in this country. Success in new drug development will smile on those institutions where these disciplines are knit into a cohesive team by an understanding management with defined targets and adequate resources.

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SCIENTIFIC CORRESPONDENCE

Graphical representation of long DNA sequences

Apropos the article on a new graphical representation and analysis of DNA sequences[1], it has been brought to my attention recently that a similar technique was presented by M. A. Gates[2] some time ago.

Gates had proposed to plot the DNA sequence in a simple metric space to enable visualization by choosing a C–G, A–T axes system based on the redundancy of the genetic code; it generates sequence maps that *a priori* resemble the maps we had independently proposed in our paper. However, when analysing genome length DNAs, it is not codon degeneracy but macro aspects like, e.g. purine-pyrimidine abundances, distribution of bases, etc. that are important. The non-trivial choice of a symmetric purine-pyrimidine axes system plotting A–G, C–T along the two axes introduces subtle differences in the new sequence representation which give more significant information of current biological interest

For instance:

– In the light of recent interest in long range correlation effects in long DNA sequences as observed by Peng *et al.*[3] by an analysis of purine-pyrimidine abundances, we have shown[4] that the maps of the myosin heavy chain genes in our representation can be taken as pointers to a possible source of the long-range correlation effects;

– At a more direct level, our graphical representation serves to explicitly demarcate purine and pyrimidine abundances as in the case of the gamma globins where the alternating A, G runs are seen to be clearly superposed on a strong pyrimidine backbone (Figure 2 in Ref. 1);

– In this particular choice of axes, transition types of evolutionary changes are suppressed leading to easier identification of significant evolutionary developments in the gene sequences;

– As we show also[4], detailed analysis of the maps in our representation can lead to indications of regions of gene duplication and repetition.

Thus, while the graphing technique is similar in Gates and our case, our choice of particular axes system based on macroscopic aspects provides an effectively new representation and approach to analysis of DNA sequence composition and distribution that is potentially of significant biological interest.

1. Nandy, A., *Curr Sci.*, 1994, **66**, 309–314.
2. Gates, M. A., *J. Theor Biol.*, 1986, **119**, 319–328.
3. Peng, C–K, *et al.*, *Nature*, 1992, **356**, 168–170.
4. Nandy, A. and Nandy, P., 1994, communicated.

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