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SPECIAL FEATURE

Medicines from nature: are natural products still relevant to drug discovery?*

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Historically, most drugs have been derived from natural products, but there has been a shift away from their use with the increasing predominance of molecular approaches to drug discovery. Nevertheless, their structural diversity makes them a valuable source of novel lead compounds against newly discovered therapeutic targets. Technical advances in analytical techniques mean that the use of natural products is easier than before. However, there is a widening gap between natural-product researchers in countries rich in biodiversity and drug discovery scientists immersed in proteomics and high-throughput screening.

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The costs of drug discovery and drug development increase all the time, but there is a decrease in the number of new medicines introduced to the world market[1–4]. Efforts are being made to improve the efficiency of the drug discovery process by using high-throughput chemistry and high-throughput screening. This raises questions about whether the previously most successful source of drugs (i.e. natural products) has any place in modern drug discovery.

Against this background, it is worth considering how new medicines have been discovered (see Box 1). Broadly speaking, three different approaches have been, and continue to be used. These are: traditional, empirical and molecular. The traditional approach makes use of material that has been found by trial and error over many years in different cultures and systems of medicine. Examples include drugs such as morphine, quinine and ephedrine that have been in widespread use for a long time, and more recently adopted compounds such as the antimalarial artemisinin. The empirical approach builds on an understanding of a relevant physiological process and often develops a therapeutic agent from a naturally occurring lead molecule. Examples include tubocurarine and other muscle relaxants, propranolol and other β-adrenoceptor antagonists, and cimetidine and the histamine H_2 receptor antagonists. The molecular approach is based on the availability or understanding of a molecular target for the medicinal agent. With the development of molecular biological techniques and the advances in genomics, the majority of drug discovery is currently based on the molecular approach.

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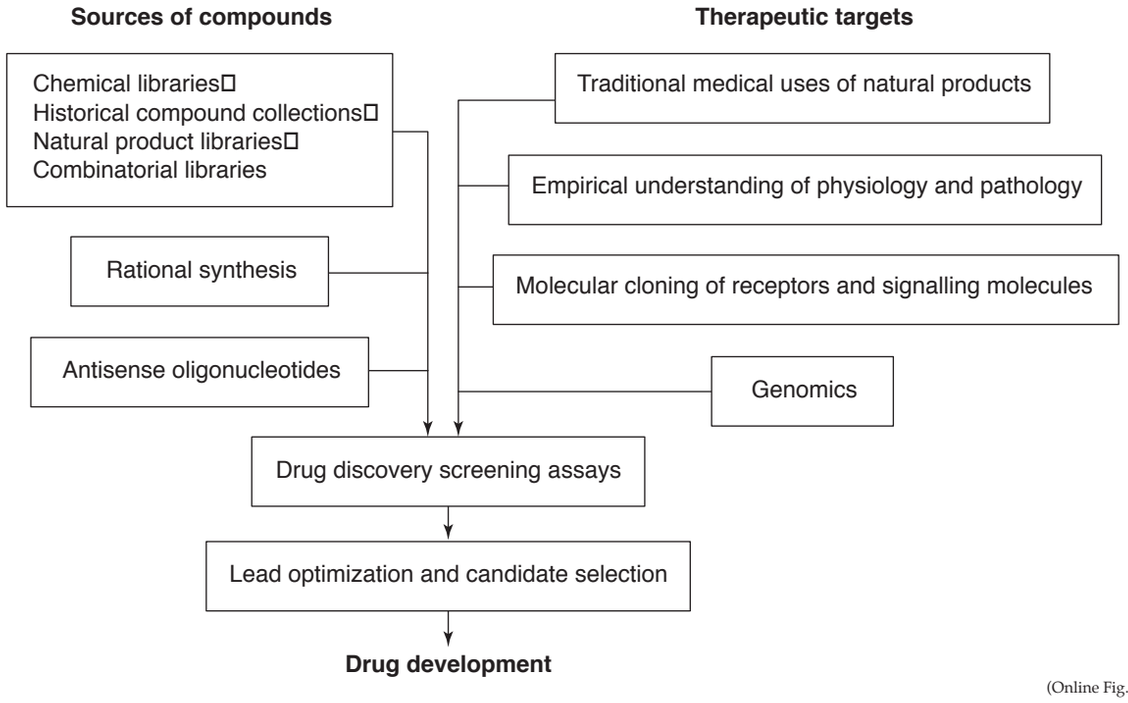
Box 1. Drug discovery sources in context

Different types of chemical compounds (top left-hand side of diagram) are tested against bioassays that are relevant to therapeutic targets, which are derived from several possible sources of information (right-hand side). The initial lead compounds discovered by the screening process are optimized by analogue synthesis and tested for appropriate pharmacokinetic properties. The candidate compounds then enter the development process, involving regulatory toxicology studies and clinical trials.



(Online Fig. I)

Molecular approaches to drug discovery

The molecular approach to drug discovery can be further subdivided into three general categories. The first is rational drug design using computer-aided techniques. A second area is the antisense approach, which is based on manipulation of genetic targets. The third technique, which currently dominates drug discovery activity, is the pragmatic approach of random screening[5].

With recent technological developments in molecular biology, instrumentation and information technology, screening of compounds can be conducted at throughputs that could not have been imagined, even a few years ago[6]. The availability of molecular targets, the ability to engineer such targets into simple reporter systems such as yeasts[7], and the use of robotics to handle the samples and conduct the assays make random screening of chemical diversity a very attractive approach to the discovery of novel activity.

The techniques of molecular cloning provide the possibility of deriving an understanding of physiological processes at the molecular level. Currently, over 250 gene products relating to major neurotransmitters are known, and hundreds of different subtypes of ion channels have also been characterized genetically. There has been a similar increase in the understanding of intracellular signalling pathways, opening up the possibility of many new target sites for drugs.

The molecular approach should also enable a molecular dissection of any disease process. However, in practice this is unlikely to be simple: the reductionist approach loses the systems integration that is a key feature of many physiological and pathophysiological processes. Molecular biology provides more potential therapeutic targets than can be experimentally validated, and target validation becomes a potential bottleneck for high-throughput screening.

Another challenge for successful application of random screening is to find sufficient numbers of compounds for testing. The compounds also have to be structurally diverse in order to increase the chance of finding activity at the molecular target. Natural products could have a key role, if they could be made more user-friendly, that is reliably and consistently supplied, limited to compounds with drug-like properties[8], and accessed without worries about political concerns over rights to biodiversity[9].

Compounds for high-throughput screening

Over the past ten years, many biochemical assays have been adapted for use on 96-well microplates, and more dense formats are becoming common. This has enabled enormous increases in throughput to be achieved, but this in itself creates new problems[10]. For example, the increase in the number of assays from 10 000 per year to, potentially, 100 000 per day implies an enormous increase

in the cost of consumables and creates a vast requirement for data handling. In addition, there is the problem of finding sufficient chemical diversity to feed the screens. Apart from re-using in-house collections of compounds, many companies are hoping that combinatorial chemistry will provide the necessary chemical diversity.

Combinatorial chemistry is the general term for the approach to synthesizing compounds in parallel rather than sequentially[11–14]. Various techniques have been developed, and some of them are capable of generating vast numbers of different compounds very rapidly. These methods tend to be based on peptides or oligonucleotides so that, although biological activity could be discovered on high-throughput screening, the active compound is unlikely to have physiochemical properties suitable for use as a drug. Most recent developments in combinatorial chemistry have concentrated on use of small organic building blocks, such as benzodiazepine or other heterocyclic nuclei, in order to create libraries with more drug-like qualities[14]. However, it is not yet clear how much three-dimensional diversity can be obtained from such libraries.

The other major source of chemical diversity for screening purposes is natural products. Historically, of course, these have been the basis for many clinically successful drugs and there are also more recent examples of natural products introduced into the market, for example the antimalarial artemisinin, and the anti-cancer agent taxol. In a recent survey, Cragg *et al*.[15] estimated that 39% of all 520 new approved drugs in 1983–1994 were natural products or derived from natural products, and 60–80% of antibacterial and anticancer drugs were derived from natural products. Other examples of biodiversity in current drug discovery are discussed by Harvey and Waterman[16]. They include compounds active on tumour cells[17], as anxiolytics[18] and HIV reverse transcriptase[19].

The major advantage of natural products for random screening is the structural diversity provided by natural products, which is greater than provided by most available combinatorial approaches based on heterocyclic compounds. In addition, many natural products are relatively small (>1000 Da), and they have 'drug-like' properties (i.e. they can be absorbed and they are metabolized). Bioactive natural products often occur as part of a family of related molecules so that it is possible to isolate a number of homologues and obtain structure-activity information. Of course, lead compounds found from screening of natural products can be optimized by traditional medicinal chemistry or by application of combinatorial approaches. Overall, when faced with molecular targets in screening assays for which there is no information about low molecular weight leads, use of a natural products library seems more likely to provide the chemical diversity to yield a hit than a library of similar numbers of compounds made by combinatorial synthesis.

Since only a small fraction of the world's biodiversity has been tested for biological activity, it can be assumed that natural products will continue to offer novel leads for novel therapeutic agents, if the natural products are available for screening. However, natural products are unattractive to many drug discovery companies because of perceived difficulties relating to the complexities of natural product chemistry and to the access and supply of natural products. The technical difficulties relating to isolation and structural elucidation of bioactive natural products are being solved by contributions from many different natural product researchers. For example, extracts can be processed before use in bioassays to remove many of the reactive compounds that are likely to cause false-positive results in assays. Fractionation of extracts that are active in a screen can be performed rapidly using high-performance liquid chromatography (HPLC), and fractions can be passed directly for analysis by LCMS or even nuclear magnetic resonance (NMR) spectroscopy. By comparing MS data with those from a library of known compounds, novel molecules in the extract can be distinguished from previously identified compounds. With automated sample injection and fraction collection, HPLC systems can readily and rapidly be used to isolate tens of milligrams of pure compound, whose structure is usually resolvable by use of NMR spectroscopy. The entire procedure of going from an active extract to a defined molecule can be a matter of days rather than the several months which was routine a few years ago.

With regard to accessing biodiversity from developing countries, much of the political discussion appears to focus on exploitation of traditional ethnobotanical knowledge, without considering the interest in natural products for random screening[9]. It might be helpful if the two issues, indigenous rights and random screening, could be debated separately. However, many of the groups working on natural products are based in universities and research institutes throughout the world, and they are not very familiar with or well adapted to the molecular trends in drug discovery. Ways to improve communication between the practitioners of molecular drug discovery and natural products researchers would be helpful so that the chemical diversity that exists in nature is not lost to drug discovery.

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