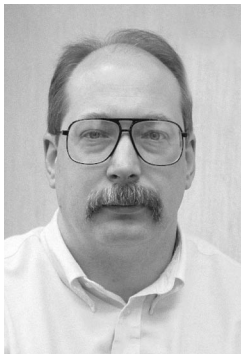
The role of natural products in a modern drug discovery program



'Natural products provide crucial, unmatched chemical diversity to modern drug discovery programs.'

Natural products (NPs) are typically secondary metabolites, produced by organisms in response to external stimuli such as nutritional changes, infection and competition. NPs produced by plants, fungi, bacteria, protozoans, insects and animals have been isolated as biologically active pharmacophores. Well-known examples of valuable NPs used widely in today's medical and animal health industries include lovastatin (anticholesterolemic agent), cyclosporin A and tacrolimus or FK506 (immunosuppressive agents), paclitaxel and doxorubicin (antitumor agents), erythromycin (antibiotic), and amphotericin B (fungicidal agent).

Approximately one-third of the top-selling drugs in the world are NPs or their derivatives. Moreover, NPs are widely recognized in the pharmaceutical industry for their broad structural diversity as well as their wide range of pharmacological activities. In light of these facts, why do NP drug discovery programs receive so little respect nowadays? This editorial will attempt to briefly discuss the perceived and real problems with NPs in modern drug discovery, as well as possible solutions to bring NP drug discovery programs back to the forefront of drug discovery.

History of the use of NPs

NPs have played an important role in the drug discovery process throughout this century and beyond. In pre-industrialized society and in agrarian societies, plant-derived NPs were used by indigenous populations as therapies for many diseases ranging from infections to emphysema. A seminal point in the use of NPs as single, pharmaceutical entities was with the well-known discovery in 1928 of penicillin, with its subsequent industrialization during World War II. By 1964, the antibacterial agents chlortetracycline, chloramphenicol, streptomycin, erythromycin, rifamycin, lincomycin, cephalosporin C, vancomycin, erythromycin and nalidixic acid (the forerunner of the fluoroquinolones), the antifungal drugs amphotericin B and nystatin, and the antitumor agent daunorubicin had been discovered. The only new chemical class of antibacterials to be brought onto the market since then are the carbapenems (such as imipenem), which are synthetic compounds based on the structure of the NP, thienamycin. The synthetic oxazolidinone, linezolid (a bacteriostatic agent in Phase III clinical trials by Pharmacia-Upjohn), should soon be a second example of a new chemical class of antibacterial agents. The incredible success of post-war NP antibacterial development triggered and supplemented NP screening programs industry-wide, and has laid a solid foundation for the advancement of the antiinfective and antitumor fields over the past half-century.

This past success of NPs, however, has led to some of the current problems, both perceived and real. To many researchers, the term 'NPs' remains synonymous with 'antibiotics', or perhaps even worse to those of us in the NP drug discovery field, to 'cytotoxic agents', although perhaps with good reason. With the noted exception(s) of the statins (lovastatin, simvastatin, pravastatin) and immunosuppressive agents (cyclosporin, tacrolimus, rapamycin), most of the other marketed NPs are antibiological agents (i.e. antibacterial, antifungal, anticancer, antiparasitic, insecticidal, etc.). In fact, before the success of the statins as antihypercholesterolemic agents in the early 1980s, NPs were not broadly included in biochemical-based assays. The evolution of NPs from their role as purely antibiological agents to their inclusion in broad-

William R. Strohl, Senior Director, Natural Products Drug Discovery – Microbiology, Merck Research Laboratories, PO Box 2000 Mail Drop RY80Y-215, Rahway, NJ 07065, USA. tel: +1 732 594 8433, fax: +1 732 594 1399, e-mail: william_strohl@merck.com

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based screening programs has not been easy, to say the least. For the past two decades, the sweeping changes in NP drug discovery programs demanded by a rapidly changing industrial environment has been inhibited by their reputation as antibiotics, the perception during the 1980s that new antibiotics were not required, and inertia.

Difficulties of NP programs versus synthetic chemicals

Four converging factors have brought pressure to bear on NP programs over the past decade:

- Most 'easy-to-find' antibacterial, antifungal and antitumor NPs had been found, and so many programs have relied heavily on dereplication programs to find new NP chemical entities for old 'cytocidal' targets.
- As the pharmaceutical industry has become more sophisticated, progressing from cell-based killing assays to more pharmacologically relevant enzyme inhibition, receptor-based assays, protein–protein interactions and other biochemically oriented assay systems, NP extracts have been broadly deemed as too 'dirty', too difficult to assay or too time-consuming to be competitive with companies' chemical collections.
- In an increasingly fast-paced drug discovery process led by the development of roboticized HTS, the time taken to progress from an NP assay hit to knowing its chemical structure (in the past, this was often measured in months) has put NPs at a significant disadvantage compared with synthetic chemicals for which the structures are already known.
- Medicinal chemists requested to derive optimized drugs from such leads often view NPs as 'ugly ducklings', possessing undesirable features such as structural complexity, multiple hydroxyl moieties, ketones and chiral centers.

Many NP programs have only successfully competed in pharmacological and biochemical assays when used as a last resort after failure of synthetic chemical collections to produce chemical entities possessing a high enough potency. As a result, in some cases, NP programs have remained strongly aligned with dwindling antiinfective, anticancer or agricultural programs, possibly to the detriment of both sides.

Additionally, over the past few years, combinatorial chemistry has become the 'darling' of the pharmaceutical industry, bringing with it the promise of new levels of chemical diversity. In some cases, such as at Abbott Laboratories, the promise of combinatorial chemistry has triggered the premature dissolution of NP programs. As combinatorial chemistry has matured, however, the promise of its widespread use in discovery programs has not been realized on a broad scale. Combinatorial chemistry has, however, achieved significant success in specific discovery programs (such as HIV protease inhibitors), in the generation of focused libraries and in drug development programs centered around core structures with desired activities. Moreover, combinatorial chemistry methodologies have enhanced traditional medicinal chemistry programs much in the same manner that molecular biology technology has enhanced the biochemical and physiological sciences. However, combinatorial chemistry has failed to supplant NPs as the primary source of broad chemical diversity. Both combinatorial chemistry and NPs can play vital, mostly non-overlapping, roles in a highly competitive drug discovery program.

In recent years, drug discovery has entered a more highly competitive era in which the quality of chemical collections and the time taken from assay to drug development are crucial factors in the success of a company. With even more emphasis placed on assay technology, speed and reduction in assay volumes, as well as increased pressures to move rapidly from the high-throughput assay of chemical collections to the generation of optimized lead compounds, the pressure on NP programs to compete internally with synthetic chemicals has substantially increased.

So, how can NP programs compete with synthetic chemicals in this highly competitive environment? There is no single answer to this question but, rather, a combination of strategies that can be implemented to address the key issues of speed, diversity and quality. Because the entire process has to be managed within the time-frame of modern drug discovery (i.e. months rather than years), speed from prioritizing hits to identifying the chemical structure is imperative. The much greater structural diversity inherent in NPs compared to synthetic compounds has to be efficiently and effectively accessed. NP extracts must be 'clean' enough to reduce false positive results, interference and other assay results that are difficult to interpret when run in an HTS format. Different companies will find different routes or solutions, but these are the challenges.

Advantages of an active NP program

What does an active, internally competitive NP program offer a company? Firstly, it offers a potentially infinite source of chemical diversity unmatched by any synthetic chemical collection or combinatorial chemistry approach. This can be achieved with in-house programs or by purchasing pure or semi-pure NPs from the many specialized companies that offer NP libraries to large pharmaceutical companies. Secondly, and perhaps more importantly, when an active, potent NP is found through assay-guided fractionation, these compounds can have surprising chemical structures that can lead to unexpected, alternative medicinal chemistry programs based on important biological targets. This second goal can only be achieved through the presence of a highly integrated, in-house NP discovery

program. Moreover, with the emphasis shifting towards the patenting and marketing of chiral drugs, NPs have the natural advantage of being enantiomeric, a reversal of what was a previously considered 'flaw' to a highly desirable trait.

It has been noted that in the highly competitive drug discovery environment, the pharmaceutical companies that possess the best and most diverse chemical collections will ultimately dominate the industry. In a different context, it has also been noted that NPs are an expensive endeavor. Although both these statements are true, I suggest that, 'NPs are indeed expensive, but to the pharmaceutical company desiring to possess the best and most diverse chemical collection in the industry, they are well worth the cost.'

William R. Strohl

In short…

Antisoma (London, UK) has formed a worldwide exclusive licensing agreement with **Abbott Pharmaceuticals** (Abbott Park, IL, USA) to develop, market and sell Theragyn as an adjuvant therapy for the treatment of ovarian cancer. The licence will also cover the use of Theragyn for the treatment of gastric, pancreatic, uterine and colorectal cancers. The drug is a mouse monoclonal antibody to which Yttrium-90 can be attached prior to injection, and works by using the natural targeting ability of antibodies to selectively deliver radioactivity to tumour cells. Phase II clinical trials conducted by the drug's founders, the Imperial Cancer Research Fund, have shown that the drug has a significant advantage on long-term survival of ovarian cancer patients (≈75% survival for ten years) compared with a historical control group on standard therapy (≈30%).

If approved by Antisoma's shareholders, they will receive $13 million investment from Abbott, with milestone payments for regulatory filings, product approvals and achievement of sales milestones, and royalty payments as a percentage of net sales. Glyn Edwards, Antisoma's CEO said, 'This is the most important milestone in our company's history. We are delighted that Abbott has chosen to work with us to help develop this potentially powerful cancer treatment.'

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