# ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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## Developing Anticancer Agents From Natural Sources

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**H&O** What is the rationale for pursuing the discovery and development of natural anticancer compounds?

**GS** In cancer therapeutics, and in the treatment of many other types of diseases, there are two main sources for new candidate compounds: naturally occurring compounds and those synthesized in the laboratory and directed against a specific target identified as being potentially relevant to a particular disease.

In nature, the balance among living species gives rise to a very rich biochemistry, usually serving as a defense mechanism against natural aggressors. This could be a poison to paralyze and kill a predator, or a toxic product to cause repulse or avoidance. These defense mechanisms are most likely the result of evolutionary trial and error, conserving by selection the most efficient biochemical solutions to keep predators under control.

In the history of medicine, there are many examples of agents isolated from natural products that interfere very efficiently with biochemical pathways related to proliferation, such as DNA, RNA, and the mitotic apparatus, or other targets in the cell. Nearly half the compounds used today in the treatment of cancer come from a lead compound derived from natural sources.

**H&O** What are some examples of anticancer drugs that are derived from natural products?

**GS** The vinca alkaloids—vincristine, vinblastine, vinorelbine—come from the *Vinca rosea*, originally discovered in Madagascar through a program aimed at finding new drugs for the treatment of diabetes. The researchers who were investigating this plant hypothesized that it might contain antiproliferative compounds because its effects, such as asthenia, myelosuppression, hair loss, and mucositis, were very similar to those of known cytotoxic agents. The agents that were created from this natural source are very important in the routine management of patients with cancer. Vincristine is a component of treatment regimens that can be curative for leukemia and lymphoma, as well as for other adult and pediatric solid tumors. Vinblastine is used for the treatment of germ-cell tumors, certain types of lymphoma, and various solid tumors. Finally, vinorelbine is employed in the treatment of non–small cell lung cancer (NSCLC) and breast cancer.

The anthracyclines originally came from fermentation products of microorganisms isolated in soil. These agents, which include doxorubicin and daunorubicin, as well as later derivatives such as epirubicin and idarubicin, are used in the treatment of leukemia and lymphoma, breast cancer, lung cancer, sarcomas, childhood tumors, and others.

Importantly, the vinca alkaloids and the anthracyclines have completely different mechanisms of action. The vinca alkaloids interact with tubulin, a protein used to build the apparatus for mitosis and for the cytoskeleton of the cell, thereby interfering with cell division. The anthracyclines interact with topoisomerase II and intercalate DNA, blocking cell proliferation at the level of DNA.

Another group of agents originally found in nature are the photophilotoxin derivatives. These plant products were used in the medicinal practices of Native Americans and other cultures. Etoposide and teniposide are semisynthetic derivatives. Etoposide is an important agent in cancer therapy, used in the treatment of germ-cell tumors, lung carcinomas, and various other tumor types. In recent years, the camptothecin derivatives have become an important class of anticancer agents. This class of drugs was isolated from *Camptotheca acuminata*, originally found in China and used as an antiproliferative agent in folkloric medicine. Laboratory investigations of this plant eventually led to the development of two semisynthetic derivatives, irinotecan and topotecan, the former used in the treatment of colorectal cancer, lung cancer, and various pediatric malignancies, and the latter used for the treatment of ovarian cancer and pediatric malignancies.

There are also many interesting stories emerging from the search for anticancer drugs among marine compounds. Cytosine arabinoside, derived from Caribbean sponges, acts as a fraudulent base for the synthesis of purine nucleotides, interfering with DNA synthesis. In fact, cytosine arabinoside also served as a model for the development of many C-nucleoside derivatives, which led to the development of antiretroviral agents. Cytosine arabinoside is important in the treatment of leukemia and lymphoma. More recently, gemcitabine, a synthetic derivative with a more favorable tissue accumulation in solid tumor models, was shown to be an important agent for the treatment of pancreatic, lung, breast, bladder, and other types of cancer.

### **H&O** Could you describe the process for conducting natural product research?

**GS** In general, promising compounds are identified from folkloric information, random collection, or the evaluation of preselected species related to those that have demonstrated anticancer activity. These materials are collected, fractionated, and tested in tumor cell lines. The observation of significant in vitro antiproliferative effects as well as the pattern of activity are critical in the decision whether to continue evaluation. Potential candidates are then fractionated and tested again in the same and other tumor cell lines, to confirm the presence of antiproliferative effects and to isolate the active compounds. Compounds exhibiting a novel chemical structure and/or a unique mechanism of action are usually given priority for further development and moved forward to in vivo testing in animal models.

Until recently, natural product–derived anticancer drug development was focused on terrestrial sources—fermentation products, plant products, etc. Over the past few years, the interest in marine compounds has grown as the technology for deep-sea collection has become available. The development of aquaculture and marine culture techniques enables investigators to maintain and grow marine compounds. Considering the tremendous biodiversity present in the water, it is very exciting that we now have the capability to study such compounds. In Europe, the company Pharmamar has a leading role in the study of marine compounds. ET-743, a tunicate derivative that shows unique effects in DNA, is currently undergoing clinical trials in solid tumors, especially sarcomas.

In our program, we collect plant species from all over Brazil for in vitro testing. That is done on the basis of ethnopharmacologic information as well as chemosystematic tools. The working team includes top biologists, biochemists, and botanists from the main universities in the country. Under the framework of a scientific collaboration, we have acquired human cell lines from the National Cancer Institute in vitro tumor cell panel and are using them to screen a large number of compounds. Thus far, we have several hundred extracts that have shown activity in vitro and some are being studied in animal models.

### **H&O** What is the South American Office for Anticancer Drug Development?

**GS** This organization was created in the early 1990s, when I returned to Brazil after many years of working on drug development in Europe and the United States. The office was established for the purpose of, first, trying to identify new and interesting compounds for investigation and drug development, and second, to create a program for early clinical trials that would engage South American countries in early cancer drug development. Today, this office has an in vitro program for natural products, an in vitro program for molecular biology, biochemistry, and preclinical pharmacology, and a clinical program that conducts phase I, early phase II, and phase III trials and is engaged in international cooperative clinical trials.

### **H&O** What is your general outlook on drug discovery and development?

**GS** I think it is crucial to keep a broad view of anticancer drug discovery. Looking critically at our current armamentarium of anticancer agents, interesting observations can be made both from rational drug development and from nature. The key to drug development is to take these observations and see if an effective compound can be isolated and the mechanism of action identified, with the ultimate goal of developing an agent with a therapeutic index that will lead to improvements in the treatment of patients.

The majority of anticancer drugs being used today stem from classic, nontargeted strategies. However, regardless of the approach—rational or natural—the key is to employ a scientific process. The essence of developing a successful new anticancer agent is to focus on the "proof of principle," which means identifying a relevant molecular target and directing efforts to find agents that are able to interact with that target (in the case of rationally developed molecular-targeted agents). Another important avenue of research is to identify the mechanism(s) of action of a classic cytotoxic agent in an effort to improve the lead compound toward a more specific antitumor agent with the best possible therapeutic index.

When the earliest anticancer drugs were developed, their mechanisms of action were not clearly understood. For example, it took several years of research to fully elucidate the mechanism of action of active anticancer drugs such as methotrexate and doxorubicin. The evidence for activity existed in preclinical models and was confirmed

in clinical trials; over the years, as our knowledge of these drugs improved, we refined the way in which we use them in the clinic. Currently, these agents are part of various curative regimens against human cancers.

Both rational development of targeted agents and the development of drugs from natural products are important and should be actively pursued, and there is solid scientific evidence to support both therapeutic approaches. Cancer morbidity and mortality are too important for us to neglect the potential contribution of new agents coming from both approaches.

Molecularly targeted agents such as imatinib are very exciting, and show promise in chronic myelogenous leukemia and gastrointestinal stromal tumors. More recently, agents such as epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors gefitinib and erlotinib, as well as the anti-vascular endothelial growth factor (VEGF) antibody bevacizumab, have shown their potential as anticancer agents. However, at least for the EGFR tyrosine kinase inhibitors, they require that patients express the specific target for activity. Bevacizumab plus chemotherapy leads to improved survival among lung and colorectal cancer patients, and it is likely that patients who express VEGF will receive treatment with both the novel agent and classic cytotoxic drugs.

However, it is important to keep an open mind in drug development because the current agents are not curing patients; most are still dying of their disease. Common cancers, such as lung, breast, and colorectal have a very complex molecular biology and are probably a consequence of the accumulation of several mutations, which could be difficult to target with individual, very selective agents. Tumors with such a complex molecular biology may require that several targets be addressed at the same time and at an early stage, probably together with cytotoxic therapy.

NSCLC provides a very interesting example of the importance of both approaches. Pemetrexed is a classic cytotoxic drug that is the result of very interesting biochemical research that began in the 1940s. At that time, it was observed that children with leukemia seemed to do worse when given folic acid supplements. Researchers began to investigate ways to block folates, which led to the synthesis of the first antifolate agents. The mechanism of action of methotrexate—the inhibition of the enzyme dihydrofolate reductase—was discovered in the 1950s. Methotrexate produced prolonged remissions in children with acute leukemia and was tested in other tumor types. Four decades of research into this class of agents has led to the development of other interesting antifolates, such as raltitrexed and, more recently, pemetrexed, a multitargeted antifolate that is associated with a response rate of 15–20% in patients with advanced NSCLC. Looking critically at the development of methotrexate, raltitrexed, and pemetrexed, it is evident that a lot of good science was necessary to refine our understanding of these agents in order to best exploit them therapeutically for the benefit of patients.

**H&O** What are some of the natural compounds that you are currently investigating in your laboratory?

**GS** We currently have several plant products of interest that are showing antiproliferative activity. Some interact with DNA or tubulin and others are G1 or G2 cell cycle blockers. Right now about 25 plant extracts are completing in vitro evaluation and are undergoing in vivo studies in animal models. It should be noted that most of the active candidates so far are derived from plants related to species that have led to successful anticancer agents in the past.

Efforts to interact with native cultures in order to understand their medicinal practices have been disappointing, probably due to their close contact with urban areas and the lack of a pure and well-preserved folklore medicine. It should also be considered that information on cancer therapies from native cultures is usually inconsistent.

One interesting aspect of this program is that compounds with antiproliferative effects are also submitted for other screening tests, such as antibacterial, antifungal, and antimalarial activity, and others. Notably, we have identified a very potent antimalarial compound in vitro and in murine models, that was originally included in our antitumor screening program. In drug development, it is very important to explore all research opportunities that are based on a sound scientific rationale. It would be very rewarding if we could also identify candidates for the treatment of other diseases, such as malaria, that kill millions of people throughout the world.

## Suggested Reading


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