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Commentary

Commentary on *Traditional and Modern Biomedical Prospecting: Part II—The Benefits* by Werner E.G. Müller, Heinz C. Schröder, Matthias Wiens, Sanja Perović-Ottstadt, Renato Batel and Isabel M. Müller

Anti-protozoa and antiviral activities of non-cytotoxic truncated and variant analogues of mussel defensin by P. Roch, A. Beschin and E. Bernard

Edwin L. Cooper

Marine Natural Products and their Applications

Drug Candidates and their Potential as Anti-Infective Agents

This commentary continues to focus on the two papers cited in the editorial and naturally also alludes to other papers as we continue to emphasize the value of molecules derived from terrestrial and marine species for CAM (1–8). In recent years, marine natural product bioprospecting has yielded a considerable number of drug candidates (9). Most of these molecules are still in preclinical or early clinical development but some are already in the market, such as cytarabine, and it is predicted that some, such as ET743 (Yondelis), will be approved in near future. The ecology of marine natural products reveals that many of these compounds are chemical weapons and have evolved into highly potent inhibitors of physiological processes in the prey, predators or competitors of the marine organisms that utilize them for survival. Certain natural products isolated from marine invertebrates have been shown to be, or are suspected to be, of microbial origin; this is now thought to be the case for a majority of such molecules. Marine microorganisms, whose immense genetic and biochemical diversity is only beginning to be appreciated, may become a rich source of novel chemical entities for discovering more effective drugs.

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According to Donia and Hamann (10), oceans are unique resources that provide a diverse array of natural products, primarily from invertebrates such as sponges, tunicates, bryozoans and molluscs as well as from marine bacteria and cyanobacteria. Since infectious diseases evolve and develop resistance to existing pharmaceuticals, the marine environment provides novel leads against fungal, parasitic, bacterial and viral diseases. Several marine natural products, including dolastatin 10, ecteinascidin-743, kahalalide F and aplidine, have successfully advanced to late stages of clinical trials, and a growing number of candidates have been selected as promising leads for extended preclinical assessment (11). Although many marine-product clinical trials have been conducted for cancer chemotherapy, factors such as drug resistance, emerging infectious diseases and the threat of bioterrorism, have contributed to the interest for assessing natural ocean products in treating infectious and parasitic diseases.

Enhancing Marine Natural Product Structural Diversity and Bioactivity through Semisynthesis and Biocatalysis

In recent decades, plants, animals and microbes from the marine environment have revealed only a portion of what is clearly an enormous resource for structurally diverse and bioactive secondary metabolites (12). Several of these extraordinarily sophisticated and bioactive natural products can be isolated in significant quantities without great difficulty. Thus, readily available bioactive natural products provide valuable starting materials for the rational generation of libraries of compounds against infectious diseases, cancer and neurological targets, prepared through semisynthesis and biocatalysis. Marine natural products that are utilized as starting materials consist of compounds from a variety of structural classes and include:

aureol, puupehenone, sarcophine, palinurin and manzamine alkaloids. The possibility of generating diverse bioactive products, beginning with a marine natural product scaffold, is the direct result of improvement in the technologies employed to harvest samples from the ocean, purify them and rapidly characterize complex natural products and complete chemical reactions and biotransformations in parallel. Thus, the vast resources of the ocean can now be utilized routinely to design and produce a multitude of products that can be evaluated as components of drug discovery and development programs. This is in contrast to those that require high-throughput screening (HTS) in order to become available (13).

Novel Antitumor Agents from Invertebrates and a Cartilaginous Fish—the Shark

Coral Reefs, Forests and Thermal Vents: The Worldwide Exploration of Nature for Novel Antitumor Agents

Cragg *et al*. (14) considered nature as a source of medicinal treatments for thousands of years. Plant-based systems continue to play an essential role in the primary health care of 80% of the world's population. Several of the effective anticancer agents in current use are derived from nature, including the microbially derived drugs, dactinomycin, bleomycin and doxorubicin and the plant-derived drugs vinblastine, irinotecan, topotecan, etoposide and paclitaxel. The search for novel antitumor agents from natural sources is ongoing with botanists, marine biologists and microbiologists teaming up with chemists, pharmacologists, toxicologists and clinicians in the investigation of coral reefs, rainforests and deep subsurface thermal vents for novel bioactive compounds. Cytotoxic anticancer candidates have been discovered from natural resources. According to Kim and Park (15), natural products have been regarded as important sources that could produce potential chemotherapeutic agents. Over 50% of the anticancer drugs approved by the United States Food and Drug Administration since 1960 were originally derived from natural resources, especially from terrestrial plants. Based on cytotoxicity bioassays, over 400 compounds have been isolated from plants, marine organisms and microorganisms between 1996 and 2000. Recently, research on marine organisms has slowly gained prime importance among natural product research. As a result, almost 50% of the cytotoxic compounds have been isolated from marine organisms such as sponges and corals.

Squalamine and cisplatin block angiogenesis and the growth of human ovarian cancer cells with or without HER-2 gene overexpression

At UCLA's Jonsson Cancer Center, Dr. Richard J. Pietras, Professor of hematology/oncology, has been awarded funds to evaluate the efficacy of squalamine, a natural chemical (anti-angiogenic sterol) isolated from the tissues of dogfish shark, in cancer treatment. Pietras and colleagues will test the hypothesis that it may be more effective to treat breast cancer cells along with the associated blood supply system in which the tumor grows and thrives than to treat the cancer cells alone. Pietras and colleagues tested squalamine alone and in combination with other antitumor therapies. Angiogenesis is important for the growth and progression of ovarian cancers. Since HER-2 gene overexpression is associated with cisplatin resistance *in vitro* and the promotion of tumor angiogenesis *in vivo*, the response of ovarian cancer cells with or without HER-2 gene overexpression to squalamine and cisplatin has been evaluated both in tumor xenograft models and in tissue culture. Ovarian cancer cells with or without HER-2 overexpression have been grown as subcutaneous xenografts in nude mice that were treated by intraperitoneal injection with a control vehicle, cisplatin, squalamine or cisplatin combined with squalamine. At the end of the experiment, tumors were assessed for tumor growth inhibition and for changes in microvessel density and apoptosis. Profound growth inhibition was elicited by squalamine alone and by combined treatment with squalamine and cisplatin for both parental and HER-2-overexpressing ovarian tumor xenografts. An immunohistochemical evaluation of tumors revealed decreased microvessel density and increased apoptosis. Although HER-2-overexpressing tumors showed more angiogenic and less apoptotic activity than parental cancers, the growth of both tumor types was similarly suppressed by treatment with squalamine in combination with cisplatin. Using *in vitro* techniques, they found that squalamine does not directly affect the proliferation of ovarian cells; rather, it significantly blocks VEGF-induced activation of MAP kinase and cell proliferation in human vascular endothelial cells. These results suggest that squalamine is anti-angiogenic for ovarian cancer xenografts and appears to enhance cytotoxic effects of cisplatin chemotherapy independent of HER-2 tumor status.

Anti-HIV Activity of Natural Products from Marine Organisms

The oceans represent virtually untapped resources from which novel bioactive compounds can be discovered. According to Tzileleka *et al*. (16), in order to combat the human immunodeficiency virus (HIV), diverse strategies have been developed to analyze compounds that can be developed as therapeutic agents. The screening of natural products derived from numerous species has afforded metabolites with significant antiviral activity against HIV. The marine environment, representing approximately half of the global biodiversity, is an enormous resource for novel compounds. Currently, more than 150 natural products with promising level of anti-HIV activity have been isolated by following bioassay-guided protocols from aqueous or organic extracts of marine organisms. Some of the most characteristic marine metabolites that have exhibited significant anti-HIV activity using various biochemical assays designed for chemotherapeutic strategies are: Cyanovirin-N, a protein from a blue green algae; various sulfated polysaccharides extracted from seaweeds (i.e. *Nothogenia fastigiata* and *Aghardhiella tenera*); the peptides tachyplesin and polyphemusin, which are highly abundant in the hemocyte debris of

the horseshoe crabs *Tachypleus tridentatus* and *Limulus polyphemus*; sponge metabolites such as avarol, avarone, ilimaquinone and several phloroglucinols; several metabolites from marine fungi such as equisetin, phomasetin and integric acid. Antiviral drugs are as important as antibiotics, in the restricted sense of antibiotics being antibacterial. (17,18,19). The biological and chemical diversity of an ocean clearly offers a variety of unique sources of useful metabolites that can be applied to certain diseases.

Perspectives on Novel Discoveries as Contributors to Complementary and Alternative Therapies

Cragg and Newman (20) have stated that an impressive number of modern drugs have been isolated from natural sources; many have been used in traditional medicine. The use of herbal drugs is once more escalating in the form of complementary and alternative medicine (CAM). More recently, however, we have witnessed an increasing role of microorganisms in the production of antibiotics and other drugs for treating certain serious diseases. At present, with less than 1% of the microbial world been explored, the advances in procedures for microbial cultivation and extraction of nucleic acids from environmental samples obtained from soil and marine habitats and from symbiotic and endophytic microbes associated with terrestrial and marine macro-organisms will provide access to a vast untapped reservoir of genetic and metabolic diversity. By using combinatorial chemical and biosynthetic technology, novel natural product leads will be optimized based upon biological activities that could yield effective chemotherapeutic and other bioactive agents. Are there renewed prospects of chemotherapy in the 21st century?

The “Golden Era in Chemotherapy” began when penicillin was discovered in the late 1920s and continued for 20 years with several other antibiotics being discovered (21). During that period, it was realized that every infectious disease could not be eliminated with the discovery of antibiotics since the emergence of drug-resistant microbes was recognized. We are now at the crucial stage where it is essential to explore new strategies in order to combat infectious diseases. One possible strategy would be to coexist with the microbes, rather than eradicating them, as long as they do not harm the human hosts. The first step of the process by which the pathogens infect the host is the adherence of the microbes to the host cell surfaces. Therefore, the method that defines the mechanism inhibiting the adhesion of the microbes to the host cells may provide a new tool in preventing the development of infectious diseases without the elimination of microbes from the host. This is just an example of the strategy by which humans and pathogens can coexist in peace and should be taken into consideration for the development of new types of antibiotics or “anti-infective drugs” in the 21st century. Herein lies an enormous potential for complementary and alternative medicine.

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