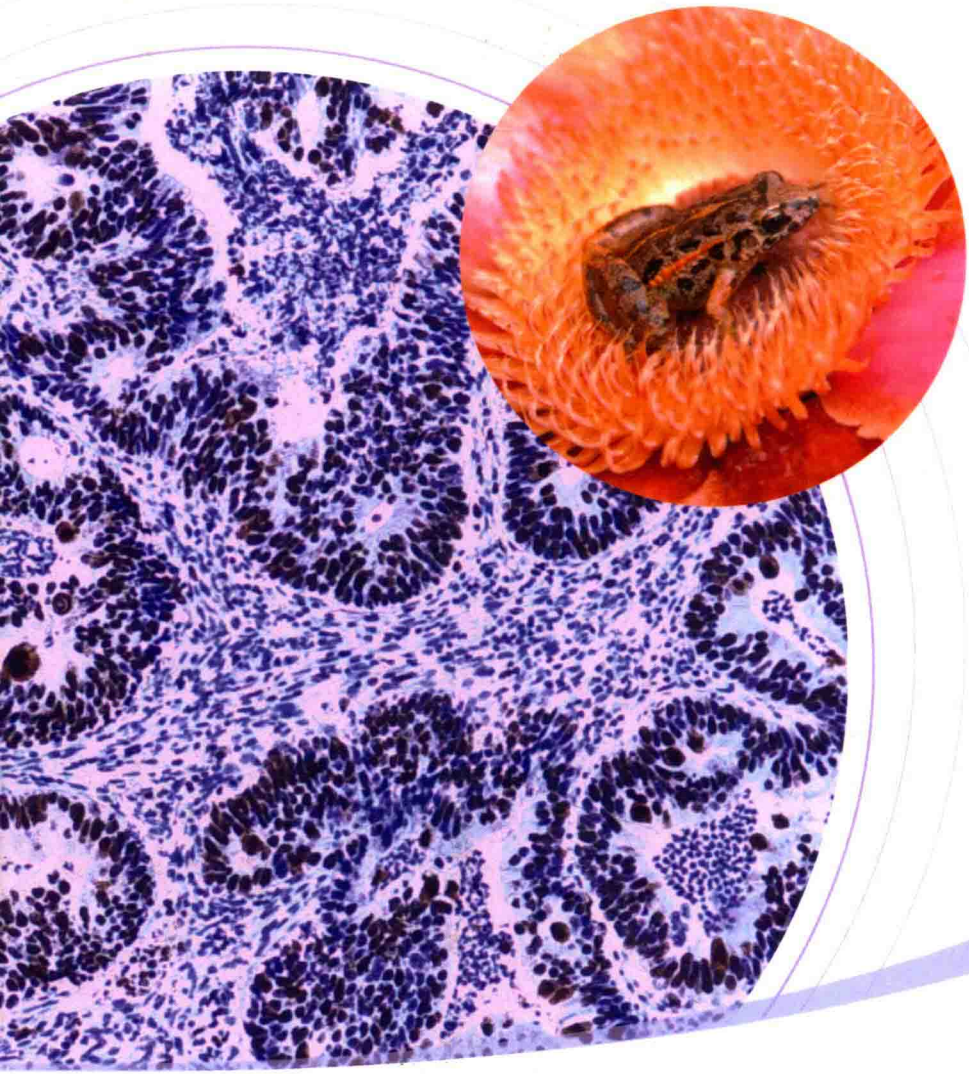
BIODIVERSITY, NATURAL PRODUCTS AND CANCER TREATMENT

Edited by

Victor Kuete · Thomas Efferth



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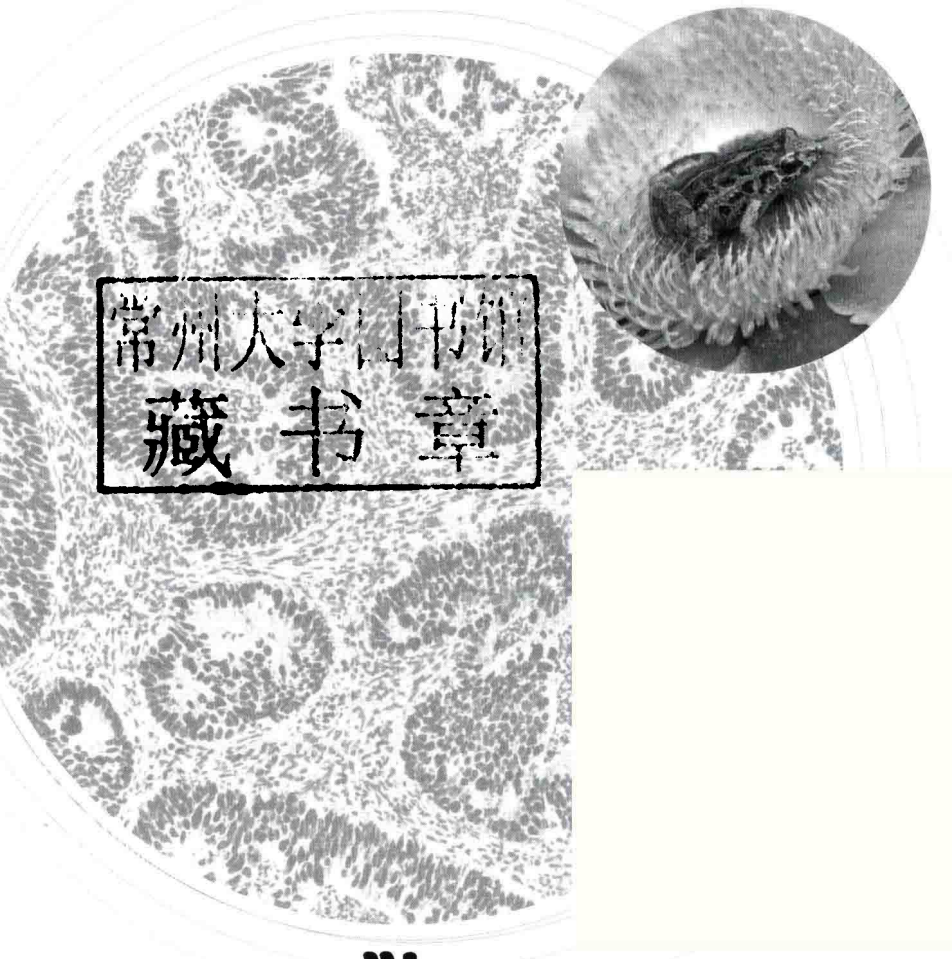

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The cover image shows a frog of the genus *Laptodactylus* sitting in a *Clusia* blossom. *Clusia* species produce antibacterial compounds, some of which are also cytotoxic towards cancer cells. The tissue in the background represents a colon carcinoma immunohistochemically stained for the proliferation marker Ki-67.

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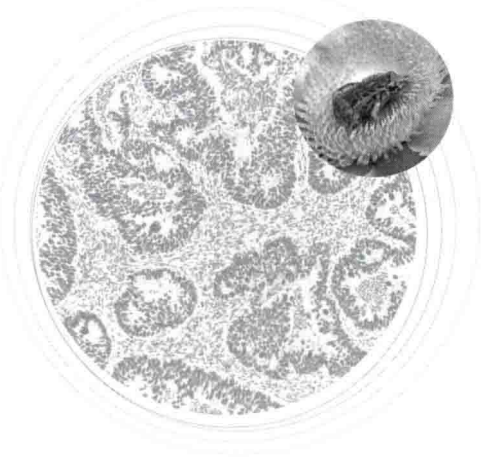

Preface

Major advances in modern medicine and pharmacology were made possible by the presence of chemical structures in nature, i.e. molecules that have developed during millennia of evolution of life in terrestrial and marine microorganisms, plants and animals. The majority of clinically established anticancer drugs are either natural products, derivatives of them, or molecules that are based on mechanistic principles taken from nature. This seemingly unexpected high number of molecules from nature in cancer therapy is not peculiar to the field of oncology. In medicine in general, a considerable proportion of all drugs across all the different therapeutic fields have their origins in natural compounds.

Bearing in mind that the very first chemical used for therapeutic purposes was morphine isolated from *Papaver somniferum* in 1804 by the German pharmacist Friedrich Wilhelm Adam Sertürmer, it should be realized that modern pharmacotherapy is not much older than two centuries. On the other hand, the various traditional medicines all around the world are probably as old as mankind. While the elaborate forms of traditional medicines such as traditional Chinese medicine, Ayurveda and others are well documented with century- or millennia-old written documents still accessible, other traditional forms of medicine are handed down from generation to generation by oral tradition, thus losing their very first roots with the passage of time. Therefore, traditional medicines are not only a valuable cultural heritage of mankind, but also a rich resource for modern drug development. Through the ages, nature has been a source and continues to be the provider of drugs for a variety of ailments.

To understand the link between chemicals from nature and human health, it is important to know the ecology of the area of the drug source.

Plants as well as many marine organisms such as sponges, corals and tunicates are sessile and live in the same environment with pathogenic bacteria, viruses and herbivores. To defend themselves, they produce phytoalexins or antibiotics, providing a possible link between chemical defense against such harmful organisms and drugs for use in humans. Marine products have long been used in traditional medicine in Taiwan, Japan, China and India and it has been known for centuries that sponges are a source of medicinally important compounds. Plants such as *Glycyrrhiza glabra*, *Commiphora* species, and *Papaver somniferum*, used today for medicinal purposes, were already used in Mesopotamia 2600 years before the Christ era. The World Health Organization (WHO) estimated in 1985 that approximately 65% of the population of the world predominately relied on plant-derived traditional medicines for their primary healthcare; meanwhile, phytochemicals or their synthesized derivatives still play an important role in drug discovery.

Examples of pharmaceuticals include the bronchodilator, chromolyn (which originated from the phytochemical, khellin, a furanochromone from *Ammi visnaga* (L) Lamk.); the antihypertensive verapamil (which originated from papaverine, an opium alkaloid antispasmodic drug from *Papaver somniferum*); the well-known antimalarial drug, quinine from Cinchona trees); and the sesquiterpene lactone artemisinin from *Artemisia annua.* Plants have also been used in the treatment of cancer and have afforded anti-proliferative drugs in clinical use, such as the *Vinca* alkaloids, vinblastine and vincristine from the Madagascar periwinkle, *Catharanthus roseus*; and etoposide and teniposide, which are semi-synthetic derivatives of the natural product, epipodophyllotoxin, from *Podophyllum peltatum.* There is also a large chemical and biological diversity of the different marine evolutionary group, making them a remarkable resource for the discovery of new drugs, including anti-neoplastic agents. Products from marine flora and fauna have in the past been used in the treatment of various human ailments. Several compounds from marine organisms such as sponges, coelenterates and microorganisms as well as echinoderms, tunicates, mollusks, and bryozoans are a source of anticancer drugs. Examples of established drug from marine organisms include the well known Ara-A and Ara-C (respectively, antiviral and anticancer from marine sponge) and the cephaolosporins antibiotics from marine fungi. Other anticancer drugs

in the clinical phase include LAF389 from sponge (phase I), Yondelis™ from sea squirt (phase II/III), Cemadotin from sea slug (phase II), and ILX651and Dolastatin-10 from sea slug (phase II).

From our point of view, it makes much sense to bring together scientists from different disciplines, e.g. medicine, pharmacology, organic chemistry, molecular biology, gene and biotechnology, botany, ethnobotany, phytochemistry, microbiology, oceanography, and other related fields to work on an interdisciplinary field such as biodiversity. This point of view is supported by the fact that biodiversity, natural products and cancer therapy have become thriving fields of research attracting numerous scientists. A comprehensive survey of published papers from 1990 to 2012 shows that such fields of research have been growing over time (Fig. 1).

The advent of molecular biology has revolutionized almost all fields in the life sciences. This is a very illustrative example that inter- and cross-disciplinary approaches do not only cross-fertilize the various disciplines, but also can lead to scientific revolutions and major breakthroughs with gain of new knowledge. At our universities, we are frequently faced with tightly packed curricula, resulting in a lack of room for topics outside the

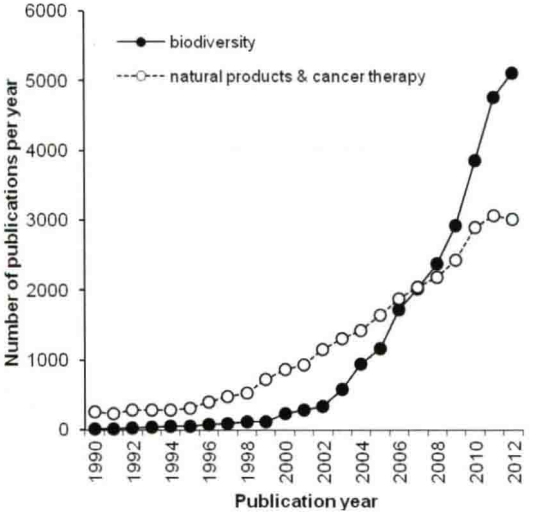

Figure 1 Survey of the literature documented in the PubMed database from 1990 to 2012 with the keywords "biodiversity" and "natural products and cancer therapy."

classical teaching content. Inter- and cross-disciplinary topics are mostly not sufficiently represented in academic teaching. Therefore, we felt that it is necessary to further strengthen inter- and cross-disciplinary research and teaching and try to span a bow from biodiversity to cancer therapy with several of its major topics.

The highlight of this book is an exhaustive compilation of scientific data on Biodiversity of medicinal plants (Chapter 1), Biodiversity and metagenomics (Chapter 2), Chemical ecology of medicinal plants (Chapter 3), Chemical ecology of marine organisms (Chapter 4), Natural products from terrestrial microbial organisms with activity towards cancer cells (Chapter 5), Marine organisms (Chapter 6), Ethnopharmacology and phytotherapy (Chapter 7), Contribution of African flora in the worldwide fight against cancer (Chapter 8), Natural products derived from terrestrial plants with activity towards cancer cells (Chapter 9), and Established anticancer drugs from natural origin (Chapter 10).

These topics have been chosen for seminars in the Pharmacy and Molecular Biotechnology programs at the Universities of Mainz and Heidelberg, Germany during the past few years. Students have chosen topics of their interests, prepared papers based on up-to-date knowledge taken from literature and presented them to the plenum. Hence, the existing curricula have been used to establish possibilities for inter- and cross-disciplinary topics, which are of high relevance not only for research and education in pharmacy and biotechnology, but also in related fields such as molecular medicine, pharmacology, drug development, medicinal chemistry, molecular biology etc.

In doing so, students acquired not only knowledge but also a sense how fertile inter- and cross-disciplinary research can be. This might be helpful in their later professional life.

The book discusses the state-of-the-art of each documented topic to serve as a reference resource tool for scientists and scholars in pharmaceutical sciences, pharmacology, organic chemistry and biochemistry, pharmacognosy, phytochemistry, ethnomedicine and ethnopharmacology, complementary and alternative medicine, medical and public health sciences and others.

In 2007, one of the editors (TE) met Dr. Ben ter Welle (Georgetown, Guyana) during an expedition in the rainforests of Guyana. Dr ter Welle's

excellent knowledge of the plants and ecology of the rainforest was impressive and gave the motivation for a book which brings together biodiversity, chemical ecology, phytochemistry and cancer therapy. Without his inspiring love of nature, the idea to write a book like this would not have been born. Thank you, Ben!

We are also grateful to the Scientific Editor, Sook-Cheng Lim and her team from World Scientific Publishing. The realization of this book would not have been possible without their support and patience. Furthermore, we thank Karen Duffy (Cornell University, Ithaca, NY, USA) for reading and correcting the manuscripts as a native speaker. A special thanks also to Ilona Zirbs for her secretarial support in preparing the manuscripts.

Victor Kuete and Thomas Efferth
Mainz, October 2013

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