

Preface

Since the dawn of human medicine, compounds derived from animals, plants, and microbes have been used to treat disease. The treatment of cancer in particular has been profoundly impacted. No other disease area, with the exception of anti-infectives, has seen a greater proportion of its small molecule drugs sourced directly from natural products. The list of natural product cancer therapeutics is impressive—*Vinca* alkaloids, anthracycline antitumor antibiotics, camptothecins, epothilones, podophyllotoxins, rapamycin mTOR inhibitors, taxanes, to name a few. Indeed, entire drug families, chemical and mechanistic classes of anticancer agents, have their origins in the secondary metabolites produced by microbes, plants, and now recently even marine organisms. Many of these agents were discovered on the basis of their striking antitumor activity in phenotypic assays, or in vivo efficacy screens. These successes drove an emphasis on natural products discovery beginning in the 1950s extending into the 1980s, which saw virtually every major pharma company utilize natural products as a major platform for drug lead generation.

But then came a change. Beginning in the 1980s the pharmaceutical industry gradually turned away from efficacy-driven drug discovery and instead adopted a process-based target-driven strategy, relying on high-throughput biochemical screening (HTS) of large collections of synthetic compounds or natural products extracts against defined targets, followed by rapid hit-to-lead and lead optimization phases to ultimately provide clinical candidates. This move was driven by a number of factors, including the desire for earlier understanding of drug mechanism, and a steady decline in the number of truly novel natural products being isolated in traditional pharma programs. Overall, natural products-based drug discovery is challenged to meet the rapid cycle times that are characteristic of the HTS approach, and has not thrived in the HTS arena. As a result, major Pharma has de-emphasized natural products discovery as a core platform for discovering new cancer drugs. We are now in a landscape where the programs that drive natural products discovery are not concentrated within large pharmaceutical companies, but instead are distributed amongst various pharma, biotech, and academic groups. Remarkably, even with the greatly reduced pharma presence, we continue to see each year the approval of one or more natural product-derived anticancer drugs—a testimony to the privileged

nature of these molecules. Ironically, new discoveries in the fundamental sciences relating to natural products discovery coupled with dramatic advancements in enabling technologies have placed natural product researchers into a position to redefine the impact on cancer drug discovery in a major way. These include (1) advances in synthetic chemistry that make it possible to produce complex natural product molecules at a scale that is sufficient for clinical advancement, (2) new appreciation of targets that are uniquely druggable by complex natural product structures, (3) advances in genomics, molecular biology, and cultivation of natural product producing organisms which provide a means of accessing new chemotypes, optimizing natural product lead structures, and enabling large-scale production of drug candidates, (4) new methods of delivering natural product cytotoxins to tumors, and (5) advances in chemical biology which enable natural products to be effective tools for identification of new drug targets. The challenge will be to leverage these advances in the new landscape of cancer drug discovery.

The purpose of this book is to provide some perspective on key areas where natural products will impact cancer drug discovery, both today and in the future. The volume is comprised of chapters written by leading researchers in drug discovery, natural products chemistry, cancer biology, and chemical biology. The volume begins with a chapter by Ganesan, who concisely describes the unique structural and physicochemical features of natural products which impart biological activity and chemical space complementarity to synthetic drugs. Four chapters then follow which relate to specific cancer targets and therapies. Hooper, Loganzo, May, and Gerber discuss in detail the identification and development of natural product drugs which interfere with tumor growth by targeting tumor vasculature. They describe current preclinical and clinical natural product drug candidates and provide an analysis of the challenges and opportunities which lie ahead in this class. Longley then presents a highly illustrative case study on the vascular targeting agent, discodermolide, describing the myriad challenges which must be met in order to successfully advance an anticancer marine natural product from initial discovery to the clinic. Salvador and Luesch then review the discovery of natural product drugs in a newly emerging class of anticancer agents—histone deacetylase inhibitors. They enumerate the challenges in the development of these agents and provide insights in the continuing role of natural products in the discovery of HDAC inhibitors and other epigenetic modulators. In the final therapeutically related chapter, Koehn describes the attributes of natural product cytotoxins which make them uniquely suited as payloads for anticancer antibody drug conjugates.

The second section of the book details advances in the science underlying natural products drug discovery. Mang and Hausteadt provide an in-depth review into sources, structural features, and structure–activity relationships of a selection of natural product chemical scaffolds frequently used in cancer therapy. Their detailed case studies show that the total synthesis of highly complex natural products is now an approach that can deliver clinical candidates. For microbial natural products, genetic engineering of the producing organism is becoming an increasingly important means of enabling the discovery of novel anticancer agents. Unsin, Rajski, and Shen highlight in their chapter recent genetic engineering advances, such as meta-

bolic engineering and combinatorial biosynthesis, that have been successfully applied to the development of microbial natural product anticancer agents. This is followed by a chapter by Leone and Roberts who examine the growing capabilities of plant combinatorial biosynthesis and cell culture in the production of plant metabolites, and highlight the cases of paclitaxel and cyclopamine—developments which have fueled new optimism for future plant anticancer agents. In the concluding chapter, Beutler examines a special attribute of natural products, namely the identification of new anticancer targets.

Most researchers will agree that the fields of cancer drug discovery and natural products are in the midst of significant change. While we might agree on these points, there is less clarity around precisely what the path toward the future will look like. The goal of this volume is to assess the current landscape and to help point the way to the future of natural products in cancer drug discovery. The journey should prove exciting.

Groton, CT, USA

Frank E. Koehn



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