

**PRECISION CANCER THERAPIES**

**OWEN A. O'CONNOR** SERIES EDITOR

**VOLUME**

**1**

**Targeting  
Oncogenic Drivers and  
Signaling Pathways in  
Lymphoid Malignancies**

**From Concept to Practice**

Editors

**Owen A. O'Connor • Stephen M. Ansell • John F. Seymour**

**WILEY** Blackwell

**Precision Cancer Therapies**



# Precision Cancer Therapies

Volume 1

Targeting Oncogenic Drivers and Signaling Pathways in Lymphoid Malignancies

From Concept to Practice

*Edited by*

*Owen A. O'Connor*

*Stephen M. Ansell*

*John F. Seymour*

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This edition first published 2023  
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A catalogue record for this book is available from the Library of Congress

Hardback ISBN: 9781119819929; ePub ISBN: 9781119819943; ePDF ISBN: 9781119819936; eBook ISBN: 9781119819950

Cover Image: © Jorg Greuel/Getty Images

Cover Design: Wiley

Set in 9.5/12.5pt STIXTwoText by Integra Software Services Pvt. Ltd, Pondicherry, India

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## Volume Foreword

The past two decades have seen the emergence of remarkable new insights into basic cancer biology, with the result that principles governing the approach to cancer treatment have undergone fundamental revision and reorganization. Recognizing the need to address this evolution in our understanding of how cancer treatment works, the editors and authors of *Precision Cancer Therapies* have set themselves the daunting task of providing clinicians and researchers with a basic guide to the underlying biology of cancer and, in particular, a guide to how this understanding can rationalize treatment. The first volume explores the biology of lymphoid cancer, one of the cancer types that has seen the most rapid accumulation of new agents and approaches, with particular attention to the role of small molecules and targeted agents and the nature of those agents' specific biological targets and associated pathways. Volume 2 focuses on immunotherapy, tracing how steadily accumulating insight into how the extraordinarily complex human immune system works and how, in recent years, that expanding insight has exploded with increasingly specific methods to manipulate passive and active immunity for cancer treatment. The editors' and authors' timing are impeccable. Clinicians, researchers, students, trainees, and representatives of funding and regulatory agencies will all find *Precision Cancer Therapies* the timely, in-depth resource they need to guide them through the blizzard of emerging data, trial results, drug approvals, and regulatory decisions as cancer therapy becomes ever more precise.

Throughout a century of modest steps beginning in the late 1800s, improvements in cancer treatment were slowly achieved employing surgery, radiation therapy, supportive care, diagnostic tests, and microscopic pathology. The contribution of systemic therapy to cancer treatment began during the latter half century of the 1900s with empiric interventions employing nonspecific, cytotoxic agents such as corticosteroids, alkylating agents, plant-based toxins, antimetabolites, hormonal agents, and disruptors of nucleic acid metabolism. It is only in retrospect that we have come to understand that these nonspecific interventions fundamentally rested on differential induction of apoptosis, the programmed self-destruction to which cancer cells are often more susceptible

than healthy normal cells. Although much was achieved employing these cytotoxic agents in the treatment of a short list of cancers such as Hodgkin's lymphoma, childhood leukemia, testicular cancer, and choriocarcinoma, the systemic treatment of cancer had largely stalled by the end of the century. Genuine progress required improved understanding of the fundamental biology of cancer and more precise dissection of how the immune system works. Everything that happens in every cell in the body, including normal and cancer cells, and, therefore, in every tissue of which these cells are assembled, is directed by signals that originate in the cellular genome ramified through enormously complex signaling pathways. Precision in cancer treatment thus awaited progress in genomics, which is now rapidly transforming all of medicine, especially cancer medicine. In multicellular organisms, including humans, complex signaling pathways guide pluri-potential stem cells through stepwise differentiation to finalized effector cells and then govern how these cells and the tissues which they constitute accomplish all the tasks of living including nutrition, energy metabolism, and cellular repair and replacement. These signaling pathways tell cells what to do, where to stay, how to interact with other cells, how to procreate, and when to die. When mutations, regulatory pathway disruptions, and signaling errors, lead cells to stray from their assigned tasks, move haphazardly to inappropriate locations, linger despite obsolescence, and reproduce when not needed, cancer arises. The modern era of precision medicine focuses tightly on these signaling errors, suggesting interventions that are specific to the individual signaling error and, therefore, having the potential to exert their effect solely on the broken cells and broken pathways leaving normal cells, which are not making the signaling errors, untouched. Volume 1 of *Precision Cancer Therapies* focuses on the signaling pathways prominent in lymphomas with particular attention to the drivers of lymphomagenesis, phosphoinositide 3-kinase (PI3 kinase) pathways, regulatory control of programmed cell death (apoptosis), the B-cell receptor pathways, proteasome function and regulation, and epigenetic control of these pathways, identifying promising targets within them and what has been achieved clinically by targeting them.



After its focus on signaling pathways and targets for lymphoid cancer treatment in Volume 1, Volume 2 of *Precision Cancer Therapies* shifts focus to the equally remarkable progress that has occurred mimicking and recruiting the immune system for cancer treatment. After decades of disappointment in clinicians' ability to manipulate the human immune system to attack cancers effectively, the past two decades have seen an unprecedented transformation. Passive immunotherapy employing monoclonal antibodies and, later, radioimmunoconjugates and antibody drug conjugates have now been shown to be powerful, precise ways to attack cancer cells directly while largely sparing normal cells. Immune checkpoint inhibition employing antibodies to programmed death ligand signaling molecules now allows clinicians to cancel cancer cells' ability to paralyze immune effector cells. By neutralizing the immune destruction blockers that cancer cells employ to escape detection and destruction by cytotoxic cells of the immune system, first-generation FDA-approved checkpoint inhibitors such as pembrolizumab and nivolumab, and an array of second-generation monoclonal antibodies currently in development, have demonstrated the ability of such agents to bring the highly potent but equally highly specific destructive power of the immune system into play to attack cancer cells. The success of these agents has encouraged wider exploration of the potential to recruit immune effector cells by targeting tumor-associated antigens that are intrinsic to lymphoid cancers or are expressed in lymphoid cells whose behavior has been distorted or hijacked by Epstein–Barr virus. Complementing the descriptions of passive immunologic intervention offered by monoclonal antibodies, checkpoint inhibitors, radioimmunotherapy, and antibody drug conjugates, Volume 2 of *Precision Cancer Therapies* also includes several sections devoted to active cell-based immunotherapy. Building on older experience with allogeneic hematopoietic stem cell transplantation, these sections explore the potential of chimeric antigen receptor T-cells

(CAR-T cells) to knit together the two remarkable characteristics of the effector cells of the immune system: precise specificity and extraordinary potency. This technique utilizes autologous T-cells that have been equipped in the laboratory with cell surface receptors specific for lymphoid cancer cell antigens and then clonally expanded to large numbers before being re-infused into the patient. This use of crafted “hunter-killer” cells thus brings specificity by employing antigen receptors tailored to bind to potentially unique antigens on the lymphoid cancer cells and power by employing the most potent cytotoxic cells of the immune system.

Systemic cancer treatment is currently in the midst of profound transformation. Although much was accomplished previously utilizing nonspecific interventions in which the therapeutic agents employed induce broad cell injury with the intention that the cancer cells be irreversibly damaged but normal healthy cells allowed to recover, the limits of this overall approach have become apparent. Going forward it has become clear that the key to progress in cancer treatment is precision. In *Precision Cancer Therapies*, the editors and authors provide essential guidance to how this precision is being achieved. Volume 1 addresses the way in which novel agents target key signaling pathways in lymphoid cancer cells, providing precision by focusing on unique vulnerabilities in the malignant cells. Volume 2 explores the ways in which the specificity and power of the human immune system can be employed to focus treatment precisely. Together these two volumes provide clinicians, researchers, and regulators essential insight in this exciting new era of cancer treatment.

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## Volume Preface

### What does the future hold?

Treatment for patients with lymphoid malignancies has changed dramatically in the past 20 years. Two decades ago, treatment approaches for patients with various lymphomas typically constituted the use of non-crossresistant chemotherapy drugs. These agents were used in combination and were effective in a subset of patients. However, in relapsing patients, responses to additional chemotherapy treatments were typically dramatically shorter than the benefits seen with the initial regimen, while the subset of patients who durably benefited from more chemotherapy was typically limited to those who underwent autologous stem cell transplantation. Since then, a greater understanding of the biology of lymphoid malignancies has led to the development of multiple classes of highly active new drugs. As outlined in this book, most classes of these novel agents have now been established as very effective. However, most novel therapies are not curative even though patients may benefit with extended durations of remission. As one looks to the future, rational combination approaches using these novel treatments will clearly be the next logical step.

In determining the most optimal combination, a number of approaches can be considered. Firstly, one could consider a “depletion” approach where the primary focus is to suppress or eradicate the malignant clone or other cells that are facilitating the growth of the malignant cell. Clearly, if every malignant cell was eradicated, the patient would be cured of the disease and treatments that kill every malignant cell would be favored. Furthermore, the malignant cell often dictates the composition of the tumor microenvironment creating an immune niche that favors the growth and survival of the cancer cell. Lymphoma cells may also directly suppress immune cells preventing their ability to lyse the malignant clone. Additionally, cells such as monocytes and macrophages present in the tumor microenvironment, may directly support and nurture the growth of the malignant cells. Therapeutically, those populations of cells supporting the cancer clone can also be targeted and depleted, theoretically leading to an improvement in patient outcome. Clearly, this approach has met with limited success and needs to be improved. Strategies that may improve a “depletion” approach could include utilizing

targeted therapy such as antibody drug conjugates in combination with chemotherapy, or by adding immune depleting agents targeting macrophages or T regulatory cells to chemotherapy, or sequencing chemotherapy before adding immunotherapy to first suppress the malignant clone and then allow for optimal immune activation.

A second combination strategy that could be considered would be an “inhibition” approach. This approach would focus on critical intracellular pathways that support the survival of the malignant cell. A rational approach to inhibition would include potentially targeting multiple different pathways that are important to the survival of the cancer cell or alternatively targeting the same dominant pathway at multiple levels. One potential risk of this approach may be upregulation of alternative pathways when one or more critical pathways are suppressed. Furthermore, novel agents could be used to specifically upregulate particular pathways that create an additional vulnerability for the malignant cell. An example of this could be the use of HDAC inhibitors which upregulate PD-L1 expression, potentially making a cell more vulnerable to immune checkpoint therapy when given in combination. Additionally, pathway inhibitors may have off target effects that may be of significant benefit. This could include the immunological effects of BTK inhibitors, mTOR inhibitors or PI3K inhibitors, all of which have both direct effects on the malignant B-cells but also effects on immune cells including normal T-cells.

A third strategy could be an “immune optimization” approach. While not the primary focus of this book, Volume 2 of the Precision Cancer Therapies series will exclusively focus on many of the agents that mediate lymphoma cell kill through a variety of immunologic mechanisms. Specific strategies to optimize immune function could include direct activation of immune cells using small molecules, immune checkpoint targeted therapy or the use of bispecific antibodies. Additional strategies that could be used in an “immune optimization” approach could specifically suppress cells that inhibit the immune response such as regulatory T-cells or suppressive monocytes, thereby improving the antitumor response. The challenge of utilizing single agent therapy to achieve immune optimization has been the development of

immune exhaustion when cells are non-specifically stimulated. Strategies to improve this “immune optimization” approach would be to intermittently stimulate the immune system and thereby avoid exhaustion or to block inhibitory signals associated with immune exhaustion at a time when the immune system is activated. All of these strategies are being evaluated in the laboratory and in patients, though most have met with mixed results.

Possibly the optimal strategy for the future might be a “reprogramming” approach that incorporates all of the elements outlined above. This “reprogramming” strategy would potentially focus not only on directly depleting the malignant cell, but also on inhibiting specific pathways on which the cell is dependent, as well as activating the immune system. These strategies would be employed all at the same time. Just as in the past, combination non-cross-resistant chemotherapy approaches have been our most successful therapies, future approaches should utilize the varied tools we have in combination to optimize patient management. Aside from utilizing agents with different mechanisms of action in combination, future studies will also focus on whether combination treatment

should be given at the same time or sequenced in an optimal order of administration. Furthermore, it may also be necessary to determine whether some therapies may be required as longer term maintenance treatment.

All told, the future for treatment of lymphoid malignancies has many opportunities. Using new drugs and with a greater understanding of the tumor biology, we have an opportunity to impact the clinical outcome of many patients. Not only is the opportunity to increase response rates and durability of clinical benefit, but also to utilize targeted therapy and minimize toxicities. However, our challenge is to continue the research and drug development until every patient with a malignancy can be cured.

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## Series Preface

The pace of growth in scientific literature has been a subject for scientists who like to study bibliometric data, for decades. As early as 1951, Derek John de Solla Price, often regarded as one of the pioneers in studying rates of change in scientific literature, noted that the development of scientific information follows the law of exponential growth (de Solla Price 1951). In 1976, Price concluded that “at any time the rate of growth is proportional to the ... total magnitude already achieved – the bigger a thing is, the faster it grows” (de Solla Price 1976). More recently, in 2018, Fortunato et al. concluded that “early studies discovered an exponential growth in the volume of scientific literature ... a trend that continues with an average doubling period of 15 years” (Fortunato et al. 2018). Barabási and Wang suggested that if the scientific literature doubles every 15 years, “the bulk of knowledge remains always at the cutting edge” (Barabási and Wang 2021). That means, that the bulk of what a typical physician learns in undergraduate, graduate, or medical school is potentially obsolete by the time they assume responsibility for the care of patients, or that the information they rely on today was not yet in the textbooks that laid the foundation for their career.

For practicing oncologists, there in lies the problem. How does one stay abreast of these incomprehensible changes in scientific knowledge, much less understand it in a manner that can be used to help their patients. Cancer medicine has become a field where the need to appreciate basic science, and I emphasize “appreciate” not “comprehensively understand,” has become indispensable. Cancer medicine has become the place where fundamental cellular biology, pharmacology, and clinical medicine all collide, as physicians struggle to understand how they should integrate and evaluate diverse streams of information in order to arrive at the best solution for the patient sitting before them. It has become a field where translating the details of science has taken on larger and larger roles as physicians consider how to cure a disease, palliate pain, or improve the status quo, using only the information they have at their disposal.

Precision Cancer Therapies is designed to try and meet that very need. The volumes that will be produced in the series, the first two of which are devoted to the lymphoid malignancies,

are developed around categories of diseases that share common themes in their pathogenesis, and, potentially, the strategies one might consider in targeting their dysregulated biology. Sections are organized around select mechanistic themes in disease biology established as being potentially important in disease pathogenesis, followed by a chapter on the pharmacology of drugs identified as effective in nullifying that abnormal biology. Subsequent chapters in each section are focused on the translational aspects: how does one use the drugs at hand to alter the pathology in a therapeutically meaningful manner. Succeeding chapters highlight actual clinical data with specific drugs as both monotherapies and in “rational” combination. The sections within a volume are designed to share information using the same kind of logic a clinician might invoke in thinking about their patient. Here are some pertinent questions:

- i) What is the disease biology causing the problem?
- ii) What are the drugs at my disposal?
- iii) What is the data for the use of these drugs?
- iv) Are there ways to improve on these drugs’ efficacy by considering combination effects?

The sections take a decidedly translational approach to the problem.

With the advent of so much web-based learning and now the passion around how artificial intelligence (AI) might transform our approach, some might suggest, why another book, let alone a series of books. The answer lies in the simple fact that there is no substitute or singular surrogate that can replace your very own fund of knowledge. Perhaps the most widely recognized and touted AI approach ever to come to our attention did so in 2011, when we watched, with complete astonishment I might add, IBMs Watson beat the famed Ken Jennings and Brad Rutter in Jeopardy. Jennings and Rutter were the greatest Jeopardy champions of all time: more wins and more money than any other contestants in the history of the show. But, despite their intellectual prowess, they were no match for a computer that had intensely trained for years and “learned” how to beat Jennings and Rutter by playing simulated games against 100 of the best Jeopardy contestants ever. Yes, Watson too had to learn, and read, and assimilate

years of information to compete with the human brain. While Jeopardy may be the most widely recognized and successful adventures for a room-sized computer, other forays of AI – and Watson in particular – in the field of oncology have, thus far at least, fallen short. IBM’s Watson for Oncology has been in development since 2012. It is being developed to provide state-of-the-art personalized treatment recommendations for patients with very specific kinds of malignant disease. Watson has undergone extensive “learning” at some of the most prestigious cancer centers in the world, being nurtured on the nuances of cancer medicine. Comprehensive details around the interpretation of blood tests, pathology, genetics, imaging data, and patient-oriented detail get fed into the computer. Then, the computational prowess of Watson combs through the vast medical literature we discussed above, to generate an evidence-based treatment recommendation for that specific patient. Why did Watson outperform on Jeopardy and underperform in oncology? One reason may be obvious. The state of cancer research and its impact on the practice of cancer medicine is extremely dynamic and in constant flux, at times it relies on instinct and experience, apparently making an appearance on Jeopardy look easy. Encyclopedic facts about the real world change slowly, if at all. Acknowledging that this type of AI technology is in its infancy (though most of us completed medical school, residency, and fellowship in the time Watson has been in development), the decade-long experience of Watson in cancer medicine has to date been less than flattering. The lay press has taken a decidedly negative impression of Watson’s first steps (watson-ibm-c), suggesting that while AI may have enormous appeal to the average observer, it is likely to never replace the intellectual prowess – and instinct – of that physician sitting in front of a patient. It re-enforces a centuries-old and fundamental truth, “knowledge itself is power,” at least as Sir Francis Bacon understood it.

And so, with some data in hand, and curiosity in endless supply, Precision Cancer Therapies intends to help keep physicians, scientists, health care providers, and the motivated reader stay up to date on the dynamic and every growing state of information in our fascinating profession. Sure, Watson and PubMed and Society Guidelines can aid us in our decision-making. However, there is nothing that can replace a good old-fashioned education nor the instinct of an informed practitioner of this most rewarding of crafts.

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