Nima Rezaei
Editor

Cancer Immunology

Bench to Bedside Immunotherapy of Cancers

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This book would not have been possible without the continuous encouragement by my parents and my wife, Maryam.
I wish to dedicate it to my daughters, Ariana and Arnika, with the hope that progress in the diagnosis and treatment of these diseases may result in improved survival and quality of life for the next generations and at the same time that international collaboration in research will happen without barriers.
Whatever I have learnt comes from my mentors. This book is therefore dedicated also to all of them, but most importantly to the patients and their families whose continuous support has guided me during the years.

Foreword

Several empirical observations suggested a long time ago that established human tumors could melt away in response to perturbations of the immune system such as during acute infection. Such regressions of tumors occurred most often but not exclusively when infection occurred at the tumor site and sparked the interest of investigators in identifying the mechanism leading to such occurrences based on the assumption that infection acted as an adjuvant to boost existing but insufficient immune surveillance against neoplasms. These anecdotal observations are reflected not only in the scientific literature such as the classic reports of William Cooley in the late 1800s but even discussed by classic authors such as the doctor-writer Anton Chekhov.

It took time, however, to elevate these concepts derived from empirical observations to a science of molecular precision. Skepticism dominated the scene for a long time including during the late 1980s, when the introduction of systemic IL-2 therapy for the treatment of advanced melanoma and renal cell carcinoma provided consistent and reproducible evidence that some advanced

cancers could regress and remain in long-term remission with a treatment that had for sure no direct effect on cancer cells. Retrospectively, as too often occurs in science, this skepticism was unwarranted, and the detractors of cancer immunotherapy made a disservice by slowing the progression of this budding discipline. Common criticisms were not directed against the observation that cancers could regress but rather focused on denial about the overall effectiveness of treatment, the sporadic nature of the regressions, and the relatively high toxicity. In other words, the skeptics confused the clinical effectiveness of a treatment with the value of a promising scientific observation.

I am emphasizing this because it is important to remember those difficult moments now that books as sophisticated and comprehensive are presented on a topic that was not even considered true science by most just a few decades ago. Fortunately, several investigators did not give up, but focusing on the value of an uncommon but reproducible observation carried the field forward.

Thus this book! An achievement difficult to predict only two decades ago!

A book series that encompassed 77 chapters spanning biological aspects of innate and adaptive immune responses to system biology approaches to biomarker discovery, to portrays of clinical successes and discussion of regulatory processes that are about to revolutionize the development and licensing of new investigational agents.

A significant change occurred after the identification and molecular characterization of antigens recognized by antibodies and/or T cells. Moreover, the characterization of molecular mechanisms controlling the cross talks between cancer and non-neoplastic somatic cells expanded the field and understanding of the mechanistic bases of immune-mediated tumor rejection. These unarguable observations gave molecular precision to what was previously perceived as pointless practice. However, the true revolution came with the clinical demonstration that some of the novel biological agents could significantly improve the survival of patients, receiving, therefore, acceptance and recognition as standard therapies through regulatory licensing.

Yet, challenges remain, and it is not the time to relax. Still, the benefits, though reproducible, are marginal both in terms of number of patients benefiting from the treatment and in the length of survival for those who benefit. Most importantly, the outcomes are capricious and unpredictable. Predictive and surrogate biomarkers are missing in spite of novel technologies and strategies that could help in the identification and stratification of patients. Still, most clinical trials are designed to look at outcomes rather than comprehensively learn in case of failures. Still, a gap exists between the potentials for what we could do to better understand the biology of immune responsiveness and what we actually do.

This book is written for those who want to move the field forward both at the clinical and the scientific level. Such a compendium can provide a contemporary overlook at what has happened lately, which is remarkably logarithmic on a time perspective. Yet, we wonder how elemental this edition may seem just within a few years if the field continues to evolve at the current pace. We hope that a second edition will follow soon. Perhaps the editors should have asked for a clairvoyant's chapter. Hopefully, one of the young readers of this edition may step forward and help define the new frontiers of cancer immunotherapy.

Francesco M. Marincola, MD

Preface

The rapid flow of studies in the field of cancer immunology during the last decade has increased our understanding of the interactions between the immune system and cancerous cells. In particular, it is now well known that such interactions result in the induction of epigenetic changes in cancerous cells and the selection of less immunogenic clones as well as alterations in immune responses. Understanding the cross-talk between nascent transformed cells and cells of the immune system has led to the development of combinatorial immunotherapeutic strategies to combat cancer.

Cancer Immunology Series, a three-volume book series, is intended as an up-to-date, clinically relevant review of cancer immunology and immunotherapy. The book *Cancer Immunology*: *A Translational Medicine Context*, is focused on the immunopathology of cancers. *Cancer Immunology*: *Bench to Bedside Immunotherapy of Cancers*, is a translation text explaining novel approaches in the immunotherapy of cancers. Finally, the book entitled *Cancer Immunology*: *Cancer*

Immunotherapy for Organ-Specific Tumors, thoroughly addresses the immunopathology and immunotherapy of organ-specific cancers.

In the book: *Cancer Immunology*: *Bench to Bedside Immunotherapy of Cancers*, clinical applications of cancer immunotherapy are fully described. Notably, the principal focus is very much on putting the basic knowledge gained on tumor immunology in volume I into a clinical perspective, with the aim to educate clinicians on the most recent approaches used in tumor immunotherapy.

Twenty-seven chapters are allocated in this regard. At the very beginning, an overview on frontiers in cancer immunotherapy is given in Chap. 1; then, novel strategies in cancer immunotherapy are discussed in Chap. 2. Thereafter, immunologic biomarkers possessing prognostic importance as well as tumor antigens valuable in the treatment and clinical evaluation of tumors are outlined in Chaps. 3 and 4, respectively.

Due to the importance of overcoming tumor immunosuppression and cancer tolerance when treating tumors, Chaps. 5 and 6 aim to tackle these crucial and challenging issues. From this point, more precise focus is given to introducing novel immunotherapeutic approaches by allocating Chaps. 7, 8, 9, and 10 to gene therapy, virus-based vaccines, cancer stem cells, hematopoietic stem cell transplantation, and lymphodepletion. Chapter 11 provides the readers with the most important details on the combination of chemotherapy and cytokine therapy in tumor management. Various aspects of the role of T lymphocytes in cancer immunotherapy are explained in Chaps. 12, 13, and 14, with special attention to their synthetic biology, clinical application, and roles in immunosurveillance and immunotherapy as well as in optimizing chemokine receptor–mediated homing of T cells in cancer immunotherapy.

Regulating B cells in order to provoke antitumor response and a general discussion on the multitude of monoclonal antibodies used in the clinical and preclinical setting are brought up in Chaps. 15 and 16, respectively. Chapter 17 aims to familiarize readers with the roles of pattern recognition receptors and Toll-like receptor pathway, while Chap. 18 discusses the role of NK cells in cancer immunotherapy. Novel vaccines produced by dendritic cells for cancer therapy are elucidated in Chap. 19. Thereafter, Chap. 20 explicates the role of tumor-associated macrophages in tumor development.

The implication of photodynamic therapy and polarization of the tumor milieu are brought up in the following two chapters, Chaps. 21 and 22, followed by Chap. 23 which discusses targeting 5T4 oncofetal glycoprotein as an immunotherapeutic approach. Novel biomarkers discovered during anti-CTLA4 antibody therapy are described in Chap. 24. Chapters 25 and 26 discuss radioimmunotherapy and psychoneuroendocrinoimmunotherapy, respectively. Finally, the book concludes by pointing to the ethical considerations crucial during cancer immunotherapy.

The Cancer Immunology series is the result of valuable contributions of more than 250 scientists from more than 100 well-known universities/institutes worldwide. I would like to hereby acknowledge the expertise of all contributors for generously devoting their time and considerable effort in preparing their respective chapters. I would also like to express my gratitude to Springer for providing me the opportunity to publish the book.

In the end, I hope that this translational book will be comprehensible, cogent, and of special value to researchers and clinicians who wish to extend their knowledge on cancer immunology.

Nima Rezaei, MD, PhD

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Abbreviations

3′-UTR	3′-untranslated region
3D	Three-dimensional
3-MA	3-Methyladenine
4-OHT	4-Hydroxytamoxifen
5AC	5-Azacytidine
Ab	Antibody
ABC	Adenosine triphosphate-binding cassette
Abs	Antibodies
AC	Adenocarcinoma
ACC	Acinar cell carcinoma
ACC	Adenoid cystic carcinoma
Ad5	Adenovirus serotype 5
ADCC	Antibody-dependent cellular cytotoxicity
ADCP	Antibody-dependent cellular phagocytosis
ADP	Anti-adipophilin
Ag	Antigen
AHR	Aryl hydrocarbon receptor
AIA	Ag-induced arthritis
AICD	Activation-induced cell death
AIDS	Acquired immune deficiency syndrome
AIF	Aapoptosis-inducing factor
AILT	Angioimmunoblastic T-cell lymphoma
AIRC	Italian Association for Cancer Research
AIRE	Autoimmune regulator
ALK	Anaplastic large cell lymphoma kinase
ALL	Acute lymphoblastic leukemia
ALP	Alkaline phosphatase
alphaGalCer	Alpha-galactosylceramide
ALPS	Autoimmune lymphoproliferative syndrome
AML	Acute myeloid leukemia
ANCs	Absolute neutrophil counts
ANN	Artificial neural network
ANT	Adenine nucleotide translocase
APC	Antigen-presenting cells
APCP	Adenosine 5′-(α, β-methylene) diphosphate
APCs	Antigen-presenting cells

APECED	Autoimmune polyendocrinopathy with candidiasis and ectodermal dystrophy
APL	Acute promyelocytic leukemia
APM	Antigen presentation machinery
APS-1	Autoimmune polyendocrine syndrome type I
ARB	Average relative binding
ARDS	Acute respiratory distress syndrome
ASCs	Adult stem cells
ASM	Acid sphingomyelinase
ASPS	Alveolar soft part sarcoma
ATCL	Anaplastic large cell lymphoma
ATLL	Adult T-cell lymphoma/leukemia
ATM	Ataxia telangiectasia mutated
ATO	Arsenic trioxide
ATP	Adenosine triphosphate
ATR	Ataxia telangiectasia/Rad3-related kinase
ATRA	All-trans retinoic acid
B SLL/CLL	B-cell small lymphocytic lymphoma/chronic lymphocytic lymphoma
BAFF	B-cell activating factor
BALs	Bronchoalveolar lavage
BCA	Basal cell adenocarcinoma
BCC	Basal cell carcinoma
BCG	Bacillus Calmette-Guérin
BCR	B-cell antigen receptor
BER	Base excision repair
bFGF	Basic fibroblast growth factor
BLI	Bioluminescence imaging
Bregs	Regulatory B cells
BSO	Buthionine sulfoximine
BTK	Bruton's tyrosine kinase
BTLA	B- and T-lymphocyte attenuator
C/EBPb	CCAT/enhancer-binding protein b
CAFs	Cancer-associated fibroblasts
CaP	Prostate cancer
CARD	Caspase-recruitment domain
CBA	Cytometric bead array
CBR	Clinical benefit response
CC	Choriocarcinoma
CC	Chromophobe carcinoma
CCS	Clear cell sarcoma
CD	Clusters of differentiation
CD40-B	CD40-activated B
CD40L	CD40 ligand
CDC	Complement-dependent cytotoxicity
c-FLIP	Cellular FLICE-inhibitory protein
CFSE	Carboxyfluorescein diacetate succinimidyl ester
CGN	Chromogranin

CHL	Classic Hodgkin lymphoma
CHS	Contact hypersensitivity
CIA	Collagen-induced arthritis
CIC/CRI	Cancer Immunotherapy Consortium of the Cancer Research Institute in the USA
CIHR	Canadian Institutes of Health Research
CIMT	Cancer Immunotherapy
CIP	CIMT Immunoguiding Program
CK	Cytokeratin
CLA	Cutaneous lymphocyte-associated antigen
CLEC9A	C-type lectin domain family 9A
CLL	Chronic lymphocytic leukemia
CLRs	C-type lectin and lectin-like receptors
CLRs	C-type lectin receptors
CMA	Chaperone-mediated autophagy
CMC	Chronic mucocutaneous candidiasis
CML	Chronic myeloid leukemia
CNS	Central nervous system
Con	Concanavalin
CP	Core particle
CpG-A ODN	CpG-A oligodeoxynucleotide
CpG-ODN	CpG oligodeoxynucleotide
CPS	Cancer Prevention Study
CQ	Chloroquine
CR	Complete remission
CRC	Colorectal cancer
CRCC	Clear RCC
CRDs	Cysteine-rich domains
CrmA	Cytokine response modifier A
CRP	C-reactive protein
CRT	Calreticulin
CS	Classic seminoma
CS&T	Cytometer setup and tracking
CSC	Cancer stem cell
CSF-1	Colony-stimulating factor
CSF-1R	CSF-1 receptor
CSF3R	Colony-stimulating factor 3 receptor
CSR	Class switch recombination
c-state	Cytosolic state
CTC	Circulating tumor cells
CTL	Cytotoxic T lymphocyte
CTS	Cathepsins
CTVT	Canine transmissible venereal tumor
CVID	Common variable immunodeficiency
Cyt	Cytochrome
DAMP	Damage-associated molecular pattern
DC	Dendritic cells
DCC	Deleted in colorectal cancer