Nima Rezaei
Editor

Cancer Immunology

Cancer Immunotherapy for Organ-Specific Tumors

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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 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 learned 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 not only reflected 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!

It is a book that encompasses more than 75 chapters spanning from biological aspects of innate and adaptive immune responses to systems biology approaches to biomarker discovery to portrayals of clinical successes and discussion of regulatory processes that are about to revolutionize the development and licensing of new investigational agents.

The big 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 the understanding of the mechanistic bases of immune-mediated tumor rejection. These unarguable observations gave molecular precision to what was previously perceived as voodoo 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 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 at both the clinical and the scientific levels. Such a compendium can provide a contemporary overlook at what has happened lately, which is remarkably logarithmic from a time perspective. Yet, we wonder how elemental this edition may seem just within a few years if the field will continue 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, a three-volume book series, is intended as an up-to-date, clinically relevant review of cancer immunology and immunotherapy. *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; and finally, *Cancer Immunology*: *Cancer*

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

In *Cancer Immunology*: *Cancer Immunotherapy for Organ-Specific Tumors*, the immunopathology and immunotherapy of various cancers categorized on an organ-specific basis are discussed in detail. Notably, the principal focus is to put the basic knowledge gained on tumor immunology and immunotherapy in the other two volumes into clinical perspective with the aim to educate clinicians on the most recent approaches used in the immunotherapy of various tumors.

Twenty-four chapters are allocated to meet this purpose. At the very beginning, an overview of the beneficial effects of immunotherapy are outlined in Chap. 1; then, in Chaps. 2 and 3, various aspects of the immunotherapy of solid tumors are discussed, including vaccination against solid tumors and immunotherapy for pediatric solid tumors. Thereafter, five chapters are devoted to hematological malignancies, specifically their immune microenvironment as well as the immunotherapeutic approaches; multiple myeloma, myeloid and lymphoid leukemias, as well as Hodgkin and non-Hodgkin lymphomas are discussed in Chaps. 3, 4, 5, 6, 7, and 8.

Due to the global prevalence of gastrointestinal tumors, precise discussions are brought up in Chaps. 9, 10, 11, 12, and 13; esophageal, gastric, liver, colon, and pancreatic cancers are tackled down one by one, respectively. Skin cancers, including melanoma and squamous-cell carcinoma as well as head, neck, and oral tumors, are illustrated in Chaps. 14, 15, and 16.

A chapter is allocated to the immunopathology and immunotherapy of bone and connective tissue tumors, followed by descriptions of progress made on the immunotherapy of central nervous system and lung tumors, in Chaps. 17 and 18, respectively.

Chapters 19, 20, 21, and 22 aim to educate the reader on the immunopathology and immunotherapy of genitourinary tract tumors. Chapter 23 provides the reader with the most important detail on the application of immunotherapy in breast cancers.

To put an end to this volume and actually to the whole book series, immunology and immunotherapy of graft-versus-host disease as a common complication of organ transplantation would be highlighted.

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

Nima Rezaei, MD, PhD

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Abbreviations

5-ASA	5-Aminosalicylic acid
5-FU	5-Fluorouracil
AA	Anaplastic astrocytoma
AA	Arachidonic acid
ACT	Adoptive cell therapy
ADCC	Antibody-dependent cell-mediated cytotoxicity
ADCP	Ag-dependent cellular phagocytosis
ADCs	Antibody-drug conjugates
AFP	Alpha-fetoprotein
Ag	Antigens
AIDS	Acquired immunodeficiency syndrome
AIM	Antigen isolated from immunoselected melanoma
AJCC	The American Joint Committee on Cancer
AKAP4	A-kinase anchor protein 4
ALCL	Anaplastic large cell lymphoma
ALDH1	Aldehyde dehydrogenase-1
ALK	Anaplastic lymphoma kinase
ALL	Acute lymphatic leukaemia
Allo SCT	Allogeneic stem cell transplantation
AML	Acute myeloid leukemia
AMP	Adenosine monophosphate
AO	Anaplastic oligodendroglioma
AOA	Anaplastic oligoastrocytoma
AOM	Azoxymethane
AP-1	Activating protein-1
APC	Adenomatosis polyposis coli
APC	Antigen-presenting cells
APLs	Aspirin-triggered lipoxins
APM	Antigen-processing machinery
AS04	Adjuvant system 04
ASCT	Autologous stem cell transplantation
ATCs	Autologous tumor cells
ATF	Activating transcription factor
ATG	Anti-thymocyte globulin
ATR	Antitumor responses
ATRTs	Atypical teratoid-rhabdoid tumors

BAFF	B-cell-activating factor
BBB	Blood-brain barrier
BCC	Basal cell carcinoma
BCG	Bacillus Calmette-Guérin
BCMA	B-cell maturation antigen
bFGF	Basic fibroblast growth factor
BID	Bowel inflammatory disease
BM	Bone marrow
BMI	Body mass index
BMSCs	BM stromal cells
BMT	Bone marrow transplantation
B-NHLs	B-cell non-Hodgkin's lymphomas
BTLA	B- and T-lymphocyte attenuator
C	Chemotherapy
CAC	Colitis-associated cancer
CAFs	Cancer-associated fibroblasts
CAK	Cytokine activated cells
CAR	Chimeric antigen receptor
CD	Cytosine deaminase
CDC	Complement-dependent cytotoxicity
CDR	Complementary-determining region
CEA	Carcinoembryogenic antigen
cHL	Classical HL
CHP	Cholesterol-bearing hydrophobized pullulan
CI	Confidence interval
CIK	Cytokine-induced killer
cILCs	Colonic innate lymphoid cells
CIN	Cervical intraepithelial neoplasia
CIS	Carcinoma in situ
CLL	Chronic lymphocytic leukemia
CLP	Common lymphoid progenitor
CMC	Complement-mediated cytotoxicity
CML	Chronic myeloid leukaemia
CMP	Common myeloid progenitor cells
CMV	Cytomegalovirus
CNS	Central nervous system
COG	Children's Oncology Group
COX	Cyclooxygenase
COX-2	Cyclooxygenase-2
CPG ODN	CpG oligodeoxynucleotides
CR	Complete remission
CR	Complete response
CRC	Colorectal cancer
CRI	Cancer-related inflammation
CRP	C-reactive protein
CRPC	Castration-resistant prostatic carcinoma
CSCs	Cancer stem cells
CSF-1	Colony-stimulating factor

CTAs	Cancer/testis antigens
CTL	Cytotoxic T lymphocyte
CTL4	Cytotoxic T lymphocyte antigen-4
CTLA	Cytotoxic T-lymphocyte-associated
CTLA-4	Cytotoxic T lymphocyte-associated antigen 4
CTLs	Cytotoxic T lymphocytes
CTTNB1	Beta-catenin gene
DALY	Disability-adjusted life year
DAMPs	Damage-associated molecular patterns
DAPK	Death-associated protein kinase
DC	Dendritic cell
DFI	Disease-free interval
DFS	Disease-free survival
DHA	Docosahexaenoic acid
DHFR	Dihydrofolate reductase
DKK1	Dickkopf-related protein 1
DLBCL	Diffuse large B-cell lymphoma
DLI	Donor lymphocyte infusion
DMFI	Distant-metastasis-free interval
DMH	Dimethylhydrazine
DR5	Death receptor 5
DSS	Dextran sulfate sodium
DTH	Delayed-type hypersensitivity
EAU	European Association of Urology
EBV	Epstein-Barr virus
ECAD	E-cadherin
ECM	Extracellular matrix
ECP	Extracorporeal photochemotherapy
EFS	Event-free survival
EGCs	Esophageal and gastric cancers
EGF	Epidermal growth factor
EGFR	Epidermal growth factor receptor
EMEA	European Medicines Agency
EMT	Epithelial-mesenchymal transition
EOC	Epithelial ovarian cancer
EORTC	European Organisation for Research and Treatment of Cancer
EP1	Prostaglandin E receptor-1
EPA	Eicosapentaenoic acid
Eph	Ephrin
ER	Estrogen receptor
ERK1/2	Extracellular signal-regulated kinase 1/2
ESCC	Esophageal squamous cell carcinoma
ESHAP	Etoposide, doxorubicin, methylprednisolone, cytarabine, and cisplatin
ET-1	Endothelin-1
ET_AR	Endothelin A receptor
EWSR1	Ewing's sarcoma breakpoint region 1
FAP	Familial adenomatous polyposis

FasL	Fas ligand
FcR	Fc receptor
FDA	Federal Drug Administration
FFS	Failure-free survival
FGF	Fibroblast growth factor
FGF2	Fibroblast growth factor 2
FGFR 4	Fibroblastic growth factor receptor 4
FIGO	International Federation of Gynecology and Obstetrics
FL	Follicular lymphoma
FLI1	Friend leukemia virus integration 1
FOLFIRI	5-Fluorouracil, leucovorin, irinotecan
FOLFOX	5-Fluorouracil, leucovorin, oxaliplatin
FOXp3	Forkhead box P3
FRα	Folate receptor α
GAA	Glioblastoma-associated antigen
GBM	Glioblastoma multiforme
GC	Gemcitabine and carboplatin
G-CSF	Granulocyte-CSF
GCT	Germ cell tumors
GI	Gastrointestinal
GISTs	Gastrointestinal stromal tumors
GITR	Glucocorticoid-induced tumor necrosis factor receptor
GLSG	German low-grade lymphoma study group
Gly	Glycine
GM-CSF	Granulocyte-macrophage colony-stimulating factor
GMP	Good manufacturing practice
GPC3	Glypican-3
GPI	Glycosylphosphatidylinositol
GPR9	G protein-coupled receptor 9
GSC	Glioma stem cells
GSTP1	Glutathione S-transferase P1
GSTP1	Glutathione S-transferase p1 gene
GVH	Graft-versus-host
GVHD	Graft versus host disease
GVL	Graft-versus-leukaemia
GVT	Graft-versus-tumor
HAART	Highly active antiretroviral treatment
HAMA	Human anti-mouse antibody
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HDI	Human development index
HDL	High-density lipoprotein
HER2	Human epidermal growth factor receptor 2
HETE	Hydroperoxyeicosatetraenoic acid
HGG	High-grade glioma
HHV8	Human herpesvirus 8
HIF	Hypoxia-inducible factor
HIV	Human immunodeficiency virus

HL	Hodgkin's lymphoma
HLA	Human leukocyte antigen
HLA-G	Human leukocyte antigen G
HMG	High-mobility group
HMGB1	High-mobility group box 1
HNSCC	Squamous cell carcinoma of the head and neck
HOX	Homeobox
HPCs	Hematopoietic progenitor cells
HPV	Human papillomavirus
HRS	Hodgkin and Reed-Sternberg
HRT	Hormone replacement therapy
HSC	Hematopoietic stem cells
HSCT	Hematopoietic stem cell transplantation
HSP	Heat shock protein
HSPPCs	Heat shock protein peptide complexes
HSPs	Heat shock proteins
HTLV-I	Human T-lymphotropic virus-I
HVG	Host-versus-graft
IAP	Inhibitor of apoptosis protein
IBD	Inflammatory bowel disease
ICE	Ifosfamide, carboplatin, and etoposide
IDH	Isocitrate dehydrogenase
IDO	Indoleamine 2,3-dioxygenase
IEDB	Immune Epitope Database and Analysis Resources
IFN	Interferon
IFN-α	Interferon-α
IFNγ	Interferon gamma
IGF-1	Insulin-like growth factor-1
IGF-1R	Insulin-like growth factor 1 receptor
IGF-BPs	Insulin-like growth factors binding proteins
IGFs	Insulin-like growth factors
IGKC	Immunoglobulin κ C
IHC	Immunohistochemistry
IL	Interleukin
IL-10	Interleukin-10
IL-18	Interleukin-18
IL-18R	IL-18 receptor
IL-2	Interleukin-2
IL-4	Interleukin-4
IL-6	Interleukin-6
IL-8	Interleukin-8
IMSCs	Immature myeloid suppressor cells
IMTs	Inflammatory myofibroblastic tumors
INF-γ	Gamma interferon
INGR	International Neuroblastoma Risk Group
iNOS	Inducible nitric oxide synthase
INSS	International Neuroblastoma Staging System
Ipb	Ipilimumab

IPI	International prognostic index
IRC	Immune-related criteria
irPFS	Immune-related progression-free survival
irRC	Immune-related response criteria
IRS	Intergroup Rhabdomyosarcoma Study
I-TAC	Interferon-inducible T-cell α-chemoattractant
ITK	Inducible T cell kinase
IV	Intravenous
IVIG	Intravenous immunoglobulin
kg	Kilogram
KHL	Keyhole limpet hemocyanin
KIF	Kinesin superfamily protein
KIR	Killer-cell immunoglobulin-like receptor
KLH	Keyhole limpet hemocyanin
KO	Knockout
KRAS	Kristin rat sarcoma
KS	Kaposi's sarcoma
KSHV	Kaposi's sarcoma herpesvirus
LAA	Leukemia-associated antigen
LAK	Lymphokine-activated killer
LCMC	Lung Cancer Mutation Consortium
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
LMP1	Latent membrane protein 1
LOH	Loss of heterozygosity
LOX	Lipoxygenase
LPA	Lysophosphatidic acid
LPS	Lipopolysaccharide
LSA	Leukemia-specific antigen
LSC	Leukemic stem cell
LT	Lymphotoxins
LTs	Leukotrienes
M	Months
mAb	Monoclonal antibody
MALP-2	Macrophage-activating lipopeptide
MAPKs	Mitogen-activated protein kinases
MCA	Methylcholanthrene
MCL	Mantle cell lymphoma
MCP-1	Monocyte chemotactic protein 1
MCP-3	Monocyte chemoattractant protein-3
MCPs	Macrophage chemotactic proteins
M-CSF	Monocyte colony-stimulating factor
MDS	Myelodysplasia
MDSCs	Myeloid-derived suppressor cells
MFH	Malignant fibrous histiocytoma
mg	Milligram
MGMT	Methylguanine-DNA-methyltransferase
MGMT	O(6-methylguanine-DNA methyltransferase

MGUS	Monoclonal gammopathy of undetermined significance
MHC	Major histocompatibility complex
MHC I	Major histocompatibility complex I
MHC II	Major histocompatibility complex II
MIATA	Minimal information about T cell assays
MIF	Migration inhibitory factor
MiHA	Minor histocompatibility antigens
MIP-3α	Macrophage inflammatory protein-3
MLL	Mixed lineage leukemia
MM	Multiple myeloma
MMAE	Monomethyl auristatin E
MMP	Matrix metalloproteinases
MP	Myeloid progenitors
MPIF-1	Myeloid progenitor inhibitory factor-1
MPL	Monophosphoryl lipid A
MR	Minor response
MRD	Minimal residual disease
MSC	Mesenchymal stem cells
MSI-H	High-level microsatellite-unstable
MTD	Maximum tolerated dose
mTOR	Mammalian target of rapamycin
MTP-PE	Muramyl tripeptide phosphatidylethanolamine
MTX	Methotrexate
MUC	Mucin
MVD	Microvessel density
N	Nodes
NA	Not available
NCI	The National Cancer Institute
NF	Nuclear factor
NF-κB	Nuclear factor-κB
NHL	Non-Hodgkin's lymphoma
NK	Natural killer
NKT	Natural killer T
NKTCs	Natural killer T cells
NLPHL	Nodular lymphocyte predominant HL
NMIBC	Nonmuscle, invasive bladder cancer
NMSCs	Non-melanocytic skin cancers
NO	Nitric oxide
NRAS	Neuroblastoma RAS oncogene
NRSTS	Non-rhabdomyosarcoma soft tissue sarcomas
NSAIDs	Nonsteroid anti-inflammatory drugs
NSCLC	Non-small cell lung carcinoma
NTS	Nuclear targeting sequence
OFA	Ofatumumab
ORR	Overall response rate
OS	Osteosarcoma
OS	Overall survival
OT	18α-Olean-12-ene-3β-23,28-triol