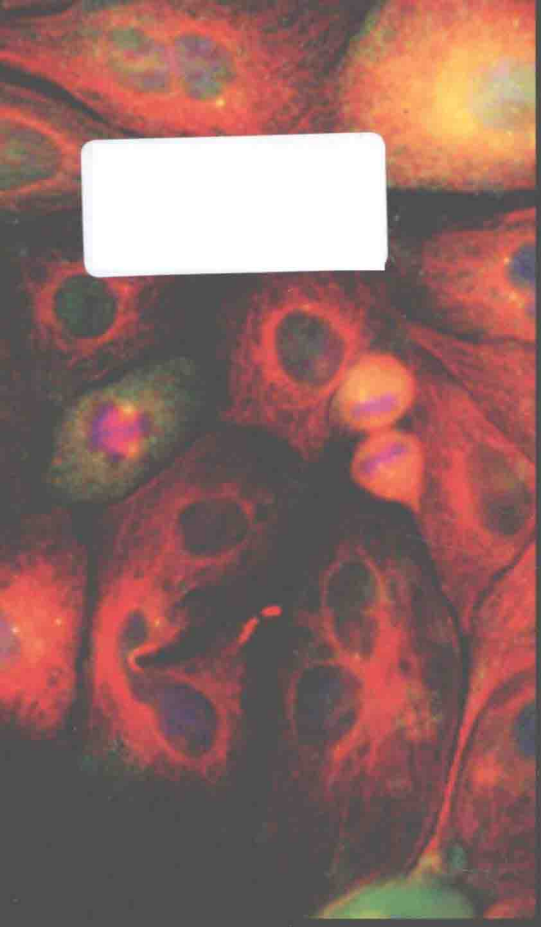

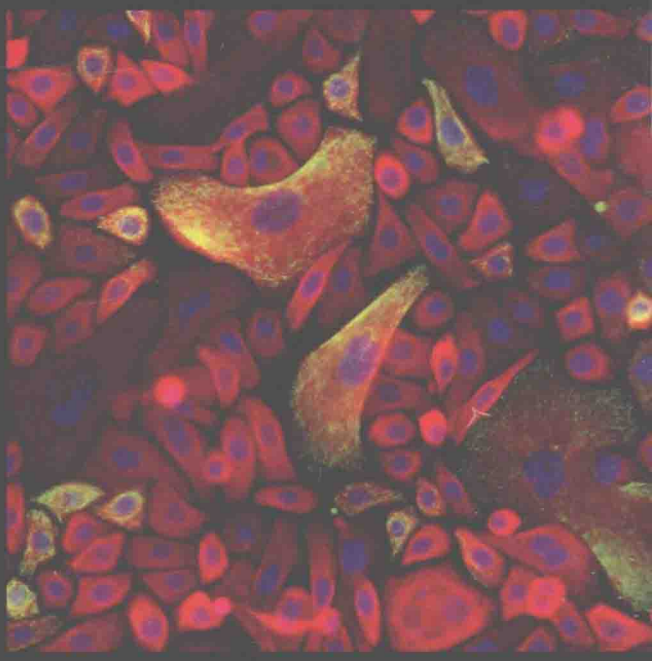

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Edited by
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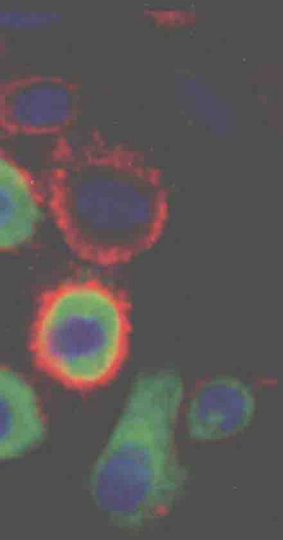

Tumor Immunology and Immunotherapy

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Tumor Immunology and Immunotherapy

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Dedication

This publication is dedicated to the work of one of the pioneers in the field of cancer immunology, Robert Baldwin. Bob's publications in the 1950s were amongst the first to provide evidence for the existence of immunity to cancer. These seminal papers set the scene for a lifelong quest to introduce immunotherapy into clinical practice, which others seek to emulate today. Bob inspired many young scientists working in the field of cancer research and he will be remembered as an innovator and founding father of the subject.

Foreword

It is by now well established that immune responses to malignant tumors do occur and act as an immune surveillance system throughout life, although they are generally somewhat inefficient in eradicating established tumors. In fact, many types of tumors develop ways to escape from the effects of immune responses by suppressing them. In addition, certain tumors may decrease or impair their antigenic properties thus reducing their capacity to elicit untoward immune functions.

As thoroughly discussed in this volume, efforts are continuously being made to clarify the mechanisms involved in the immunological responses to tumors and to exploit the knowledge so acquired towards the development of more effective immunotherapies.

The pathways critical to antigen recognition, the process of immunoediting, tumor plasticity also as related to the function of stem cells and the capacity of certain tumors to undergo epithelial–mesenchymal transition are all illustrated in detail and are analysed for their capacity to affect negatively the development of effective immunotherapy.

The modulation of adaptive immunity by regulatory T cells or by myeloid-derived suppressor cells, the impairing functions of the microenvironment on immune responses, and the capacity of certain tumors to become 'invisible' to immunity by decreasing or eliminating their antigenic expression are each discussed as contributing to tumor escape from the immunotherapy attack.

Therapies with monoclonal antibodies are currently the most successful types of immunotherapy. It is indeed appropriate to note that the late Dr Robert Baldwin, Professor Emeritus of the University of Nottingham and a co-founder of the Journal Cancer Immunology and Immunotherapy, was a major leader in tumor immunology and a pioneer in anticipating with his work the value of antibody-based immunotherapy. In fact it is fair to say that he established an important background for today's advances in this type of immunotherapy. Antibody-based therapies are well illustrated in this volume with emphasis on both their successes and the remaining difficulties to be overcome.

The identification of tumor antigens is essential for the development of immunotherapy. In some cases tumors exhibit viral antigens that are useful handles for the stimulation of antibodies as well as the construction of vaccines. Treatments with vaccines are extensively discussed herein. Novel approaches are indicated such as the development of vaccines using tumor DNA or utilizing newly identified antigens, for instance in leukaemia. The usefulness of mucin present on tumor cells as a therapeutic target is also illustrated and represents an antigen to which many of us have preexisting immune responses. The development of vaccines based on multiple antigenic determinants is indicated as a means to improve the effectiveness of this type of treatment.

The role of natural killer cells in providing mechanisms of defence against tumors is discussed with attention to the functional interactions of these cells with the responses

of adaptive immunity. Therapeutic approaches with dendritic cells are considered with a view to utilizing their antigen presentation mechanisms for therapeutic intervention in a way that might minimize the onset of some of the tumor escape mechanisms. In this volume the complex mechanisms conditioning tumor escape from immune responses are given appropriate attention.

Adoptive transfer of T cells is now recognized as a potent type of immunotherapy and the use of TCR transgenic T cells can improve their therapeutic effectiveness. These approaches are considered in this volume within the frame of reference to other cell based treatments.

In addition, gene therapies based on the expression of chimeric antigens is considered among the therapeutic avenues to be further explored. The FDA approval of Ipilimumab as a "new generation" of checkpoint blockade therapy represents an important milestone in the development of treatments designed to mobilize the immune system against cancer.

As is indicated above, in this volume key aspects of tumor immunity and immunotherapy are critically discussed. Each chapter puts emphasis on the difficulties involved in the application of each modality of treatment as well as on the promises realistically offered in each case, and thus becomes an important reference for the topic considered. Indeed as a whole this volume should provide for a significant stimulation of new ideas which would be pivotal for the development of fruitful further investigations. There is little doubt that increasing further our knowledge of the mechanisms involved in tumor immunity and our understanding of the phenomena conditioning tumor escape are essential in order to improve the effectiveness of immunotherapy and thus to fulfil the promises offered in this important area of cancer therapeutics.

Enrico Mihich

Preface

Within the past two decades, the field of cancer immunotherapy has grown, not only as an academic discipline, but also as a viable treatment option for many cancer sufferers. Pharmaceutical companies are developing cancer therapeutics that are based on vaccines which induce protective adaptive anti-tumor immunity, or antibodies which directly interact with cell surface antigens such as HER2/neu, or act to blockade molecules that have a role in inhibiting immune function. The latter approach is exemplified by current trials that are assessing the efficacy of anti-PD-1 antibody therapy. It is also recognized that antibody therapy can enhance adaptive T cell immunity to further promote tumor rejection.

This publication includes contributions from experts internationally recognized for their outstanding research in their fields and provides an up-to-date and comprehensive treatise of tumor immunity and immunotherapy. The importance of the innate (natural killer cells, macrophages) and adaptive (T cells, antibodies) immune systems for inducing robust anti-tumor activity and tumor rejection is considered in detail by several leading authorities. Several reviews also provide insight into how tumors escape host immune recognition either by downregulating major histocompatibiliy complex antigen expression and/or fostering an immunosuppressive tumor microenvironment that induces immune tolerance or anergy. Immunosuppressive mechanisms, involving regulatory T cells, myeloid suppressor cells, suppressive cytokines, or cell surface receptor–ligand interactions are discussed in depth.

Emphasis on the essential requirements for success in the clinic has been channelled through pre-clinical investigations and translated into patient care. The promotion of CD8 and CD4 T-cell immunity by vaccine-driven delivery of appropriate tumor antigens, activation of innate responses using Toll-like receptor agonists and treatments that are designed to limit pathways of immune suppression are now 'centre stage', driving advances in the clinical application of immunotherapy as a fourth treatment modality for cancer. In many instances, combining immunotherapy with conventional therapy clearly provides distinct advantages over single agents. In summary, the reviews in this publication provide scientists and clinicians with a comprehensive and in depth critique of the major areas of cancer immunology and insight into future trends in cancer immunotherapy.

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Abbreviations

5-FU	5-Fluorouracil
ACT	Adoptive T-cell therapy
ADC	Antibody-dependent cytotoxicity
ADC	Antibody–drug conjugate
ADCC	Antibody-dependent cellular cytotoxicity
AE	Adverse events
Ag	Antigen
AICD	Activation induced cell death
AIDS	Acquired immunodeficiency syndrome
AIF	Allograft inflammatory factor
AL	Ad libitum
ALL	Acute lymphoid/lymphoblastic leukaemia
AML	Acute myeloid leukaemia
ANGPT2	Angiopoietin 2
APC	Antigen-presenting cells
APM	Antigen-processing machinery
AR	Androgen receptor
ASCI	Antigen-specific cancer immunotherapeutic
ATC	Activated patient T cells
ATM	Adipose tissue macrophages
ATRA	All-trans retinoic acid
BCG	Bacillus Calmette-Guerin
BCR	B-cell receptor
BCSC	Breast cancer stem cells
bFGF	Basic fibroblastic growth factor
ß2m	ß2-Microglobulin
BiTE	Bi-specific T-cell engager
BM	Bone marrow
BMP	Bone morphogenic protein
BMT	Bone marrow transplantation
BsAb	Bi-specific antibodies
BSCS	Breast cancer stem cells
CAR	Chimeric antigen receptor
CB	Cord blood
CBT	Cord blood transplantation
CCyR	Complete cytogenetic response
CDC	Complement-dependent cytotoxicity
CDR	Complementarity determining regions
CEA	Carcinoembryonic antigen
c-FLIP	FLICE inhibitory protein
CGAP	Cancer genome anatomy project
CIBMTR	Center for International Blood and Marrow Transplant Research
CID	Cancer Immunome Database
CIN	Cervical intraepithelial neoplasia
CIP	CIMT Immunoguiding Program
CK	Cytokeratin
CLL	Chronic lymphocytic leukaemia
CLP	Common lymphoid progenitors
CML	Chronic myeloid leukaemia
CMP	Common myeloid progenitors
CMV	Cytomegalovirus
CNS	Central nervous system
COG	Cost of goods
COX2	Cyclooxygenase 2
CR	Caloric restricted
CR	Complete response
CRC	Colorectal cancer
CRP	C-reactive protein
CRPC	Castrate-resistant prostate cancer
CRS	Cytokine release syndrome
CSC	Cancer stem cell
CSF	Colony stimulating factor
CT	Cancer/testis
CTA	Cancer testis antigen
CTC	Common toxicity criteria
CTL	Cytotoxic T cell/lymphocytes
CTL	Cytotoxic T-cell lines
CTLA	Cytotoxic T lymphocyte antigen
Cy	cyclophosphamide
DAA	Disease-associated antigen
DAMP	Damage-associated molecular pattern

DART	Dual-affinity re-targeting
DASL	DNA-mediated annealing, selection, and ligation
DC	Dendritic cell
DCT	Dopachrome tautomerase
DD	Differential display
DFI	Disease-free interval
DFS	Disease-free survival
DISC	Death-inducing signalling complex
DLI	Donor lymphocyte infusion
DNMTi	DNA methyltransferase inhibitors
DOX	doxorubicin
DR	Death receptors
DTH	Delayed-type hypersensitivity
EBV	Epstein-Barr virus
ECD	Extracellular domain
ECM	Extra cellular matrix
EGF	Epidermal growth factor
EGFR	Epidermal growth factor receptor
ELISA	Enzyme-linked immunosorbent assay
ELISpots	Enzyme-linked immunosorbent spots
ELN	European LeukemiaNet
EM	Effector memory
EMAPII	Endothelial monocyte-activating polypeptide-II
EMT	Epithelial–mesenchymal transition
EP	Electroporation
ER	Endoplasmic reticulum
EROTC	European Organization for Research and Treatment of Cancer
ES	Embryonic stem
EST	Expressed sequence tags
FADD	Fas-associated death domain
FDA	Food and Drug Administration
FFA	Free fatty acid
FL	Follicular lymphoma
FR4	Folate receptor 4
GAVI	Global Alliance for Vaccines and Immunisation
GBM	Glioblastoma multiform
GM-CSF	Granulocyte-macrophage colony-stimulating factor
GMP	Good manufacturing practice
GPA	Granulomatosis with polyangiitis
GS	Gene signature
GvHD	Graft-versus-host disease
GvL	Graft-versus-leukaemia
GvL	Graft-versus-leukaemia
GvT	Graft-versus-tumor
HBC	Hepatitis C virus
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCGP	Human cancer genome project
HCV	Hepatitis C virus
HDACi	Histone deacetylase inhibitors
HGF	hepatocyte growth factor
HHV-8	Human herpesvirus type 8
HIF	Hypoxia-inducible factor
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HMGB1	High-mobility group box 1
HNV	Hematopoietic necrosis virus
HPV	Human papillomavirus
HRE	Hypoxia responsive elements
HSC	Haematopoietic stem cells
HSCT	Haematopoietic stem cell transplantation
HSP	Heat shock protein
HSV	Herpes simplex virus
HTLV	Human T-lymphotropic virus
IAP	Inhibitors of apoptosis proteins
IC	Immune complexes
ICD	Immunogenic cell death
ICS	Intracellular cytokine staining
IDO	Indoleamine 2,3 dioxygenase
IFN	Interferon
IL	Interleukin
iNKT	Invariant natural killer T cell
iNOS	Inducible nitric oxide synthase
IPF	Idiopathic pulmonary fibrosis
IRF-I	Interferon regulatory factor 1
IRP	Immune risk profile
irRC	Immune-related response criteria
ITAM	Immunoreceptor tyrosine-based activation motif
KIR	Killer-cell immunoglobulin-like receptors

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