

Contents

1	Frontiers in Cancer Immunotherapy	1
	Joseph F. Murphy	
1.1	Introduction	1
1.2	Innate Cells as Initiators of the Adaptive Immune Response	2
1.3	Cellular Immunotherapy	2
1.4	Active and Passive Immunotherapy	2
1.4.1	Active Immunotherapy	3
1.4.2	Nonspecific Immunotherapy	3
1.5	Stimulation of Responses In Vivo	4
1.6	Adoptive Immunotherapy	5
1.7	Cancer Vaccines	6
1.7.1	Dendritic Cells	8
1.7.2	Physical Barriers, Tumor Stroma and Vessels	10
1.8	Mechanisms of Tumor-Induced Tolerance/Escape from the Immune System	11
1.8.1	Treg Cells	12
1.8.2	Myeloid-Derived Suppressor Cells	13
1.8.3	Macrophages	13
1.9	Candidates for Immunotherapy in Oncology	14
1.10	Combination Immunotherapy	14
1.10.1	Chemotherapy and mAb	15
1.10.2	Chemotherapy and Active Specific Immunotherapy	15
1.10.3	Chemotherapy and Adoptive Lymphocyte Immunotherapy	15
1.10.4	Immunotherapy with Radiation Therapy	16
1.11	Humoral Immunotherapy	16
1.12	Concluding Remarks	17
	References	17
2	Novel Strategy of Cancer Immunotherapy: Spiraling Up	23
	Lev V. Demidov, Irina Zh. Shubina, and Mikhail V. Kiselevsky	
2.1	Introduction	23
2.2	Natural Killer Cells: The Key Effectors of Innate Immunity	24
2.3	Adoptive IL-2/LAK (or CIK) Therapy of Cancer	26
2.4	Tumor-Infiltrating Lymphocytes (TILs) in Cancer Immunotherapy	27

2.5	Autologic Vaccines on the Base of Dendritic Cells (DC Vaccines)	29
2.6	Advantages of Combined Implication of DC Vaccines and Activated Lymphocytes	30
2.7	Spiral Up	30
2.8	Concluding Remarks	31
	References	31
3	Novel Prognostic Biomarkers for Personalized Cancer Treatment	35
	Ida Contasta, Anna Maria Berghella, Roberto Lattanzio, Osvaldo Ciccarelli, Giancarlo Di Gregorio, Maurizio Vizioli, Marino Silvino, Luigi Liborio Liberatore, Luca Navarra, Giampaolo Caterino, Antonio Mongelli, Vincenzo Vittorini, Irma Campitelli, Nunzia Antonucci, Tiziana Del Beato, Enzo Secinaro, and Patrizia Pellegrini	
3.1	Introduction	36
3.2	Presentation	37
3.3	New Biomarkers for the Treatment of Tumors	37
3.4	Guidelines for the Identifications of "Suitable" Biomarkers: A Healthy Longevity Is Linked to an Healthy Function of the Immune System. The Pathology Is Generated by Alterations of This System	40
3.5	The Importance of the Evaluation of Both Genders as Independent Groups	41
3.6	Men and Women Follow Different Strategies to Regulate the Homeostasis of the Immune System	41
	3.6.1 Variations of Pro- and Anti-inflammatory Cytokine Levels Regulate the Immune Response and Could Influence the Healthy State	41
	3.6.2 "Double Prognostic Biomarkers": Appropriate Variations Between Pro- and Anti-Inflammatory Cytokines Assure the Success of the Immune Response but Following Different Gender Pathways	42
	3.6.3 The Efficiency of the Treatment Is Related to a Reestablishment of IL-6 Pathways in Women, and IFN- γ Pathways in Men	44
3.7	The Valuation of the Thioredoxin and CD30 Systems for the Prognostic, Diagnostic, and Therapeutic Stratification of Patients	44
	3.7.1 Trx1/RTx1 System	46
	3.7.2 The CD30/CD30L/sCD30 System	46
3.8	New "Double Biomarkers" That Are Prognostic for Patient Stratification and for the Personalized Therapies	47
3.9	Concluding Remarks	50
	References	50

4	Tumor Antigen and Epitope Identification for Preclinical and Clinical Evaluation	55
	Shraddha S. Rane, Jaimy Mariam Sultana Javad, and Robert C. Rees	
4.1	Introduction	55
4.2	Reverse Immunology Approach to Peptide Identification. . .	57
4.2.1	Target Antigen Identification.	58
4.2.2	In Silico Peptide Predictions	59
4.2.3	Epitope Validation	61
4.3	Direct Immunology Approach.	62
4.3.1	Isolation of Peptide–MHC Complexes	62
4.3.2	Analysis and Sequencing of MHC-Associated Peptides	62
4.4	Human Immunotherapy Against Tumor-Associated Peptides	63
4.5	Strategies to Enhance the Immunogenicity of Peptide Epitopes	65
4.5.1	Potential Adjuvants for Boosting Immune Responses	66
4.5.2	TLR Agonists in Cancer Vaccine Trials	66
4.6	Future Prospects	68
4.7	Concluding Remarks	69
	References	69
5	Strategies to Target Tumor Immunosuppression	73
	Oana Draghiciu, Hans W. Nijman, and Toos Daemen	
5.1	Introduction	73
5.2	The Balance Is Tilted: Mechanisms of Tumor Immune Escape	74
5.2.1	Tolerance Mechanisms	74
5.2.2	Immunosuppression Mechanisms	75
5.3	Shifting the Balance: Strategies to Target Tumor Immunosuppression	77
5.3.1	Strategies Targeting Homing of Effector T Cells . . .	77
5.3.2	Strategies Targeting the Activity of Effector T Cells	79
5.4	Concluding Remarks	81
	References	82
6	Overcoming Cancer Tolerance with Immune Checkpoint Blockade	87
	Guy T. Clifton, Elizabeth A. Mittendorf, and George E. Peoples	
6.1	Introduction	87
6.2	Cytotoxic T-Lymphocyte-Associated Antigen-4 (CTLA-4): A Paradigm for Immune Checkpoint Blockade	89

6.2.1	CTLA-4 Function	89
6.2.2	Preclinical Development of CTLA-4 Blocking Therapy	92
6.2.3	CTLA-4 Blockade Monotherapy in Melanoma	93
6.2.4	Toxicity	97
6.2.5	Immune-Related Response Criteria	98
6.2.6	CTLA-4 Blockade in Cancers Other than Cutaneous Melanoma	98
6.2.7	CTLA-4 Blockade as Combination Therapy	100
6.3	Programmed Death 1 (PD-1) Pathway	104
6.3.1	Function	104
6.3.2	PD-1 Pathway in Cancer	105
6.3.3	PD-1 Blockade	106
6.3.4	PD-L1 Blockade	107
6.4	Combination Immunotherapy	108
6.4.1	CTLA-4 Blockade and Vaccination	108
6.4.2	CTLA-4 Blockade and Cytokine Therapy	109
6.4.3	Combination Checkpoint Blockade	110
6.5	Other Checkpoint Pathways Under Development	110
6.5.1	Lymphocyte Activation Gene-3 (LAG-3)	110
6.5.2	4-1BB	111
6.5.3	OX-40	112
6.5.4	Glucocorticoid-Induced TNFR Related Protein (GITR)	113
6.5.5	CD40	114
6.5.6	TGN1421: A Cautionary Tale	115
6.6	Concluding Remarks	116
	References	116
7	Gene Therapy and Virus-Based Cancer Vaccines	131
	Mohamed Labib Salem, Kamal Kamal Elsayed Gadalla, Burtram C. Fielding, and Steve H. Thorne	
7.1	Introduction	131
7.2	Viral Vectors Used in Cancer Gene Therapy	132
7.2.1	Retrovirus Vectors (RVVs)	132
7.2.2	Poxvirus Vectors (PVVs)	135
7.2.3	Adenoviral Vectors (AdVVs)	135
7.2.4	Adeno-Associated Virus Vector (AAVVs)	136
7.2.5	Herpes Simplex Virus Type 1 Vectors (HSVVs)	136
7.3	Non-viral Methods of Gene Delivery	137
7.3.1	Delivery of Plasmid DNA	137
7.4	Cancer Gene Therapy	138
7.4.1	Oncogene and Tumor Suppressor Gene Targeted Gene Therapy	138
7.4.2	Enhancing Pro-Drug Cytotoxicity in the Tumor Cells Through Gene Therapy	140

7.4.3	Thymidine Kinase (TK)	140
7.4.4	Cytosine Deaminase (CD)	141
7.5	Anti-angiogenesis Gene Therapy	141
7.6	Cancer Vaccines and Vaccine Production	141
7.6.1	Virus-Based Vaccines	142
7.7	Oncolytic Viruses	142
7.7.1	Mechanism of Action	143
7.7.2	Viral Agents Used as Oncolytic Agents	144
7.8	Concluding Remarks	144
	References	144
8	Cancer Stem Cells: Biology and Potential Therapeutic Applications	151
	Monica Mangoni, Mariangela Sottili, Mauro Loi, Chiara Gerini, Icro Meattini, and Lorenzo Livi	
8.1	Introduction	151
8.2	Identification and Characterization of Cancer Stem Cells	152
8.2.1	Surface Markers	152
8.2.2	Side Population	153
8.2.3	ALDEFLUOR Assay	153
8.2.4	Sphere-Forming Assay	154
8.2.5	Signaling Pathways	154
8.3	A Dynamic Cancer Stem Cell Concept	156
8.4	The CSCs Niche	157
8.4.1	Functions	157
8.4.2	CSC Niche as Therapeutic Target	158
8.5	CSCs in Tumor Invasion and Metastasis	158
8.5.1	CSCs, EMT, and Metastasis	159
8.5.2	Signaling Pathways Involved in Metastasis	159
8.5.3	Premetastatic Niche	161
8.6	Tracking CSCs	161
8.7	CSC Resistance: Clinical Implications	163
8.7.1	Enhanced DNA Repair	163
8.7.2	Free-Radical Scavenging	164
8.7.3	Quiescence	164
8.7.4	Signaling Pathways	164
8.8	Perspectives in Radiation Oncology	165
8.9	Concluding Remarks	166
	References	166
9	Immunologic Approaches to Targeting Cancer Stem Cells	177
	Qin Pan, Qiao Li, Ning Ning, Yingxin Xu, Alfred E. Chang, and Max S. Wicha	
9.1	Introduction	178
9.2	ALDEFLUOR ⁺ /ALDH ^{high} Serves as a Specific Marker for Cancer Stem Cells in Multiple Tumor Types	178

9.3	Cancer Stem Cells Are Resistant to Conventional Tumor Therapies	179
9.4	Innate Immune Response to Cancer Stem Cells	180
9.5	Cancer Stem Cell-Primed T Cells Specifically Targeting Cancer Stem Cells	181
9.6	Development of Cancer Stem Cell-Specific Vaccine in Immunocompetent Host	182
9.7	Targeting the Tumor Microenvironment as a Strategy to Enhance Immunological Targeting of Cancer Stem Cells	184
9.8	Concluding Remarks	185
	References	185
10	Hematopoietic Stem Cell Transplantation and Lymphodepletion for the Treatment of Cancer	189
	Kristen M. Barr, Jill A. Gershan, and Bryon D. Johnson	
10.1	Introduction	189
10.2	Hematopoietic Stem Cell Transplantation (HSCT)	190
10.2.1	Sources of Hematopoietic Stem Cells (HSCs)	190
10.2.2	Autologous and Allogeneic HSCT	190
10.2.3	Graft-Versus-Host Disease and the Graft Versus Tumor Effect	191
10.2.4	Myeloablative Effects That Promote the Elimination of Hematologic Malignancies	193
10.2.5	Non-myeloablative Conditioning	194
10.3	Lymphodepletion for the Treatment of Solid Tumors	195
10.3.1	Lymphodepletion-Induced T Cell Thymopoiesis Is Important for Reconstitution of the T Cell Repertoire	196
10.3.2	Lymphodepletion-Induced Homeostatic Proliferation as Strategy to Augment Antitumor Immunity	196
10.3.3	Use of Animal Models to Address Immunological Effects of Lymphodepletion	197
10.4	Concluding Remarks	198
	References	198
11	Combination of Chemotherapy and Cytokine Therapy in Treatment of Cancers	203
	Mariana Malvicini, Manglio M. Rizzo, Laura Alaniz, and Guillermo D. Mazzolini	
11.1	Introduction	203
11.2	Immune Response in the Control of Cancer	204
11.2.1	Cancer Immunoediting Theory	204
11.2.2	Tumors Escape from the Host Immune Response	205

11.3	Immunotherapy of Cancer	206
11.3.1	Enhancing Antitumor Immunity Using Cytokines	206
11.4	Overcoming Tumor Resistance and the Use of Chemotherapeutic Agents	207
11.4.1	Chemotherapy Plus Immunotherapy	208
11.4.2	Rationale for Drug Selection	208
11.5	Combined Therapies	209
11.5.1	Preclinical Experience	209
11.5.2	What Have We Learned from the Clinical Practice?	210
11.6	Concluding Remarks	212
	References	212
12	T Cell Immunotherapy: From Synthetic Biology to Clinical Practice	217
	Ling Zhang and Rimas J. Orentas	
12.1	Introduction	217
12.2	T Cell Responses to Cancer	218
12.3	From Polyclonal to Single-Specificity Effector T Cells	218
12.4	From MHC to Antibody-Based Recognition: Therapy with T Cells Expressing CARs	220
12.4.1	History of CAR Development	220
12.4.2	Inclusion of T Cell Signaling Moieties	220
12.4.3	Vectors Used for CAR Expression	221
12.4.4	Impact of T Cell Culture and Expansion Techniques	223
12.4.5	Clinical Advances with CAR Therapy	224
12.5	Concluding Remarks	226
	References	226
13	Role of $\gamma\delta$ T Lymphocytes in Cancer Immunosurveillance and Immunotherapy	231
	Telma Lança, Daniel V. Correia, and Bruno Silva-Santos	
13.1	Introduction	231
13.2	TCR $\gamma\delta$ Repertoires and Functions	232
13.2.1	Mouse $\gamma\delta$ T-Cell Subsets	233
13.2.2	Human $\gamma\delta$ T-Cell Subsets	233
13.3	$\gamma\delta$ T-Cell Activation: TCR $\gamma\delta$ Agonists	234
13.3.1	Phosphoagonists (Phosphoantigens)	234
13.3.2	Aminobisphosphonates	236
13.3.3	Alkylamines	236
13.3.4	Protein Ligands	236
13.4	$\gamma\delta$ T-Cell Activation: Costimulatory Molecules	238
13.4.1	CD27	238
13.4.2	CD28	238
13.4.3	Fc Receptors: CD16	239

13.5	$\gamma\delta$ T-Cell Activation via Natural Killer Receptors (NKR)	240
13.5.1	NKG2D	240
13.5.2	NKG2A	243
13.5.3	Natural Cytotoxicity Receptors (NCRs)	243
13.5.4	DNAM-1	244
13.6	Tumor Cell Recognition by $\gamma\delta$ T Cells: TCRs Versus NKRs	244
13.7	$\gamma\delta$ T-Cell Responses to Tumors.	245
13.7.1	Antitumor Properties	245
13.7.2	Pro-tumor Properties	247
13.8	$\gamma\delta$ T-Cell Modulation in Cancer Clinical Trials	248
13.9	Concluding Remarks.	249
	References	252
14	Adoptive T-Cell Therapy: Optimizing Chemokine Receptor-Mediated Homing of T Cells in Cancer Immunotherapy	263
	Imran Siddiqui, Alberto Mantovani, and Paola Allavena	
14.1	Introduction	263
14.2	History of Adoptive Immunotherapy of Malignancy	265
14.3	T-Cell Infiltration Correlates with Prognosis	265
14.4	Adoptive T-Cell Therapy.	266
14.5	Challenges in Adoptive T-Cell Therapy	267
14.6	Chemokines.	268
14.7	The Role of Chemokines in Directing Tissue Trafficking in Tumors	268
14.8	Overexpression of Chemokine Receptors in Engineered Lymphocytes to Be Used for Cancer Immunotherapy	271
14.9	Concluding Remarks.	274
	References	275
15	B Cell Regulation of Antitumor Response	283
	Ahmed Al Bayati, Yu Zhang, and Joseph D. Rosenblatt	
15.1	Introduction	283
15.2	Mechanisms Underlying B Cell Modulation of Antitumor Immune Response	286
15.3	B Cells and the Role of Tregs	286
15.4	B-Regulatory Cell Infiltration into Human Tumors	288
15.5	Breg Function in Non-Hodgkin Lymphoma	288
15.6	Effects of Depletion of B Cells on Antitumor Immunity	289
15.7	Concluding Remarks.	290
	References	290

16	Monoclonal Antibodies for Cancer Immunotherapy	293
	Amir-Hassan Zarnani, Mahmood Bozorgmehr, Mahdi Shabani, Leila Barzegar-Yarmohammadi, Fatemeh Ghaemimanesh, and Mahmood Jeddi-Tehrani	
16.1	Introduction	294
16.2	Structural and Functional Features of Antibodies	294
16.3	Natural Antibodies in Cancer	295
16.4	Finding an Appropriate Antibody Target for Cancer Therapy	296
16.4.1	Characteristics of a Favorable Cell Surface Antigen	296
16.4.2	Classification of Cancer Antigens	296
16.4.3	Target Identification Approaches	296
16.5	Molecular Mechanisms Involved in Monoclonal Antibody-Based Therapy	299
16.5.1	Direct Tumor Cell Elimination	299
16.5.2	Harnessing the Potential Capacity of Immune System to Eliminate Tumors	299
16.5.3	Targeting Tumor Stroma and Vasculature	301
16.6	Engineered Antibodies	302
16.6.1	Murine Monoclonal Antibodies	302
16.6.2	Chimeric and Humanized Monoclonal Antibodies	303
16.6.3	Fully Human Monoclonal Antibodies	303
16.6.4	Antibody Fragments	304
16.6.5	Bispecific Antibodies (BsAbs)	306
16.6.6	Antibody Fusion Constructs	307
16.6.7	Improvement of Antibody Function	307
16.7	Evaluation of Antibody Efficacy	308
16.7.1	Preclinical Evaluations	308
16.7.2	Clinical Evaluations	308
16.8	Clinically-Approved Monoclonal Antibodies	308
16.8.1	Trastuzumab	309
16.8.2	Bevacizumab	309
16.8.3	Rituximab	310
16.8.4	Therapeutic Monoclonal Antibodies Approved by Non-FDA Organizations	310
16.9	Monoclonal Antibodies Currently Undergoing Clinical Trials	311
16.10	Combinational Monoclonal Antibody-Based Modalities	311
16.10.1	Combination with Chemotherapy	311
16.10.2	Combination with Radiotherapy	312
16.10.3	Combination with Other Immunotherapeutic Methods	313
16.10.4	Other Combinational Approaches	313

16.11	Current Limitations in Monoclonal Antibody-Based Therapies.	313
16.11.1	Tumor Escape	313
16.11.2	Relatively Low Single Agent Activity	314
16.11.3	Low Tissue Penetration.	314
16.11.4	Fc-Fc Receptor Interactions and Associated Limitations	314
16.11.5	High Production Cost	315
16.12	Concluding Remarks	315
	References	315
17	Toll-Like Receptor Pathway and Its Targeting in Treatment of Cancers	329
	Seyed Hossein Aalaei-Andabili, Shaherin Basith, Sangdun Choi, and Nima Rezaei	
17.1	Introduction.	329
17.2	TLRs Play Important Roles in Human Carcinogenesis . . .	330
17.3	TLR Regulates Tumor-Induced Immune System Response	331
17.4	TLR Targeting May Inhibit Cancer Cell Proliferation . . .	333
17.5	TLR Triggering Can Promote Antitumor Response.	333
17.6	Regulatory Effects of TLRs on PI3K/Akt Signaling Controlling Tumor Progression	334
17.7	TLR-Mediated Hypoxia-Inducible Factor 1 (HIF-1) Expression Leads to Tumor Progression	334
17.8	Role of TLRs in Tumor Cell Lysis and Apoptosis	335
17.9	TLRs are Involved in Tumor Metastasis.	335
17.10	Concluding Remarks.	336
	References	337
18	Recent Advances in the Use of NK Cells Against Cancer	341
	Amy E. Gillgrass, Tamara Krneta, and Ali A. Ashkar	
18.1	Introduction.	341
18.2	NK Cell Basics	342
18.2.1	How Do NK Cells Become Activated to Kill? . . .	342
18.2.2	Why Should NK Cells Be Targeted as Anticancer Agents?	343
18.3	Challenges Involved in Targeting NK Cells	343
18.3.1	How Many NK Cells Are in Cancer Patients and Tumors?	343
18.3.2	What Is the Functionality of NK Cells in Tumors?	344
18.4	Cancer Immunotherapies Involving NK Cells	345
18.5	Adoptive NK Cell Transfer.	346
18.5.1	How Can We Produce Large Numbers of Activated NK Cells?	346

18.6	Autologous Transfer of NK Cells	347
18.7	Allogeneic Transfer of NK Cells	348
18.8	NK Cell Lines for Allogeneic Adoptive Transfer.	349
18.9	NK Cells, ADCC, and mAb Therapy	349
18.10	Cytokines and Promoting NK Activation/Stopping Inhibition.	351
18.11	Concluding Remarks	352
	References	353
19	Dendritic Cell Vaccines for Cancer Therapy: Fundamentals and Clinical Trials	359
	Graziela Gorete Romagnoli and Ramon Kaneno	
19.1	Introduction.	359
19.2	Strategies for Developing Clinical Grade DC Vaccines . . .	361
19.3	Routes of Administration	363
19.4	DC Vaccine for Prostatic Cancer	363
19.5	DC Vaccine for Melanoma	364
19.6	DC Vaccine for Colorectal Cancer	365
19.7	DC Vaccine for Nervous Tissue Cancer	366
19.8	Concluding Remarks.	367
	References	367
20	Tumor-Associated Macrophages and Cancer Development	375
	Ken-ichi Isobe and Hengyi Xiao	
20.1	Introduction.	375
20.2	Cancer and Inflammation	376
20.3	Development of Myeloid Lineage Cells Including Macrophages.	378
20.4	Characteristics of TAMs	379
20.5	“Reeducating” TAMs to Cytotoxic Phenotype	379
20.6	Concluding Remarks.	380
	References	380
21	Photodynamic Therapy and Antitumor Immune Response . . .	383
	Fatma Vatansever and Michael R. Hamblin	
21.1	Introduction.	383
21.2	Photodynamic Therapy	384
21.3	Closer Look Up at the PDT and Triggered Immune Response	385
21.4	Significance of PDT and Adaptive Immunity.	387
21.5	Mechanism of PDT Immunologic Effects	387
21.6	Case Studies	388
21.7	Concluding Remarks.	394
	References	395

22	Polarization of Tumor Milieu: Therapeutic Implications	401
	Stanisław Szala, Magdalena Jarosz-Biej, Tomasz Cichoń, Ryszard Smolarczyk, and Aleksander Sochanik	
22.1	Introduction	401
22.2	Recruitment of Inflammatory Cells by Cancer Cells	402
22.3	Macrophage Plasticity: M1 and M2 Phenotypes	403
22.4	TAM: Cells with M2 Phenotype	403
22.5	M1 → M2 Tumor Microenvironment Reversal: Therapeutic Approach	405
22.6	Concluding Remarks	406
	References	406
23	Immunotherapies Targeting a Tumor-Associated Antigen, 5T4 Oncofetal Glycoprotein	409
	Peter L. Stern	
23.1	Introduction	409
23.1.1	5T4 Trophoblast Glycoprotein Is an Oncofetal Antigen	409
23.2	5T4 and Epithelial Mesenchymal Transition (EMT)	411
23.3	5T4 Modulation of Chemokine and Wnt Signaling Pathways	411
23.4	Vaccines	412
23.4.1	Preclinical Studies	413
23.4.2	Early-Phase Clinical Trials of MVA-h5T4 (TroVax)	413
23.4.3	TroVax Phase III Clinical Trial in RCC	414
23.4.4	Insights from the 5T4 KO Mouse	415
23.4.5	Improving Vaccine Regimens	416
23.5	5T4 Antibody-Targeted Superantigen Therapy	416
23.5.1	Preclinical Studies	417
23.5.2	Early-Phase Clinical Studies	417
23.5.3	A Phase II/III Clinical Trial in RCC	418
23.6	Other 5T4 Antibody-Targeted Therapies	418
23.6.1	Antibody-Drug Conjugates (ADC)	418
23.6.2	Direct 5T4 Antibody Effects	419
23.6.3	5T4 Chimeric Antigen Receptors	420
23.7	Concluding Remarks	421
	References	421
24	Emerging Biomarkers During Clinical Development of Anti-CTLA4 Antibody Therapy	427
	Geoffery Y. Ku, Chrisann Kyi, and Jianda Yuan	
24.1	Introduction	427
24.2	Absolute Lymphocyte Count	428
24.3	Analyses of Different Cell Populations in Peripheral Blood	429
24.3.1	T Cell Activation Markers	429
24.3.2	Regulatory T Cells	429
24.3.3	Myeloid-Derived Suppressor Cells (MDSCs)	430

24.4	Antigen-Specific Immunological Monitoring	430
24.4.1	Antigen-Specific Antibody Response	431
24.4.2	Antigen-Specific T Cell Response	431
24.5	Analyses of Specific T Cell Populations in the Tumor Microenvironment	432
24.6	Future Perspectives	433
24.7	Concluding Remarks	434
	References	435
25	New Advances in Radioimmunotherapy for the Treatment of Cancers	441
	Françoise Kraeber-Bodéré, Caroline Bodet-Milin, Caroline Rousseau, Thomas Carlier, Ludovic Ferrer, Nicolas Chouin, Férid Haddad, François Davodeau, Jean-François Chatal, Alain Faivre-Chauvet, Jean-François Gestin, Michel Chérel, and Jacques Barbet	
25.1	Introduction	442
25.2	Principles of Radioimmunotherapy	442
25.3	Radionuclides and Radiolabeling Techniques for Therapy	443
25.3.1	Radionuclides	443
25.3.2	Labeling Techniques	444
25.4	The Treatment of B Cell Lymphoma with Anti-CD20 Antibodies	446
25.5	Promising Results in Hemopathies Using Other Antibodies	447
25.5.1	Targeting of Lymphoma with Anti-CD22 Antibodies	447
25.5.2	Targeting of Multiple Myeloma Using Anti-CD138 Antibodies	448
25.6	RIT of Metastatic Prostate Cancer	449
25.7	RIT with Alpha-Emitting Radionuclides	450
25.7.1	Therapeutic Indication	450
25.7.2	Limited Availability	451
25.7.3	Issues and Current Developments	451
25.8	High Efficacy of Pretargeting Approaches in Metastatic Thyroid Carcinoma	451
25.9	Immuno-PET: The Future for Dosimetry Assessment and Patient Selection	452
25.9.1	Immuno-PET and Development of New Drugs	453
25.9.2	Patient Selection for Therapy	453
25.9.3	Determination of the Cumulated Activity Concentration for RIT	453
25.9.4	Therapy Response	454
25.10	Concluding Remarks	454
	References	454

26	Psychoneuroendocrinoimmunotherapy of Cancer	461
	Paolo Lissoni, Giusy Messina, and Franco Rovelli	
26.1	Introduction.	461
26.2	The Physiopathology of Anticancer Immunity.	462
26.3	The Fundamental Phases of Tumor Onset and Dissemination.	463
26.4	Main Cancer-Related Immunoneuroendocrine Alterations.	464
26.5	Preliminary Clinically Applied PNEI Strategies	464
26.6	Future Perspectives	465
26.7	Concluding Remarks	466
	References	466
27	Ethical Considerations in Cancer Immunotherapy	469
	Maurie Markman	
27.1	Introduction.	442
27.2	Ethical Issues in Immunotherapy of Cancer.	470
27.3	Unique Toxicities	470
27.4	Evaluation of Efficacy in the Clinical Trial and Non-research Settings.	470
27.5	Ethical Justification for Initiation of Treatment in Individual Patients.	471
27.6	Concluding Remarks.	472
	References	472
	Index	473