

Contents

Contributors	xi
Preface	xv

Cancer Immunosurveillance and Immunoediting: The Roles of Immunity in Suppressing Tumor Development and Shaping Tumor Immunogenicity

Mark J. Smyth, Gavin P. Dunn, and Robert D. Schreiber

1. Introduction	1
2. "Intrinsic" Versus "Extrinsic" Tumor Suppressors	2
3. The Cancer Immunosurveillance Hypothesis: Controversy to Resolution	5
4. Tumor Elimination	7
5. Immunoediting: When Tumor Cells Survive	28
6. Cancer Immunosurveillance/Immunoediting in Humans	32
7. Conclusions	35
References	36

Mechanisms of Immune Evasion by Tumors

Charles G. Drake, Elizabeth Jaffee, and Drew M. Pardoll

1. Introduction	51
2. Downmodulation of Tumor Antigen Presentation	52
3. Immunologic Barriers Within the Tumor Microenvironment	55
4. Disabled Antigen Presenting Cells	62
5. CD4 T-Cell Tolerance	63
6. Coinhibition	64
7. Regulatory T Cells	66

8. CD8 T-Cell Dysfunction.....	68
9. Summary.....	69
References	70

Development of Antibodies and Chimeric Molecules for Cancer Immunotherapy

Thomas A. Waldmann and John C. Morris

1. Introduction	84
2. Targets of Monoclonal Antibodies in the Therapy of Cancer	85
3. Monoclonal Antibodies Targeting Host Nonneoplastic Tissues.....	85
4. Monoclonal Antibodies Targeting Host Immune Cells and Proteins that Act as Inhibitory Checkpoints on the Immune System	87
5. Blockade of CTLA-4 and PD1 Inhibitory Receptors.....	88
6. Elimination of CD4 ⁺ CD25 ⁺ Foxp3 Expressing T Regs (Suppressor T Cells).....	89
7. Monoclonal Antibody Targeting of the Inhibitory Cytokine TGF- β	90
8. Mechanisms of Action of Monoclonal Antibodies	91
9. Engineering Antibodies for Greater Efficacy.....	92
10. Genetically Engineered Antibody Fragments for Cancer Immunotherapy	95
11. Unmodified Monoclonal Antibodies Approved by the FDA that Are Directed Toward Neoplastic Cells.....	96
12. Antibodies Armed with Cytokines, Chemotherapeutic Agents, Toxins, and Radionuclides Cytokine Armed Monoclonal Antibodies.....	107
13. Antibodies Armed with Chemotherapeutic Agents	107
14. Immunotoxins for the Treatment of Cancer	108
15. Systemic Radioimmunotherapy with Monoclonal Antibodies	112
16. Conclusions and Future Prospects.....	118
References	121

Induction of Tumor Immunity Following Allogeneic Stem Cell Transplantation

Catherine J. Wu and Jerome Ritz

1. Introduction	134
2. Reconstitution of Donor Hematopoiesis Following Allogeneic HSCT	134

3. Sequence of Immune Reconstitution Following Allogeneic HSCT	136
4. The Graft-Versus-Leukemia Effect	138
5. Donor Lymphocyte Infusions Induce GVL Responses After Allogeneic HSCT	141
6. The Central Role of Donor T Cells as Mediators of GVL	143
7. Target Antigens of Donor T Cells After Allogeneic HSCT	146
8. Donor Natural Killer Cells as Mediators of GVL	150
9. Donor B Cells as Mediators of GVL	154
10. Future Directions	158
References	160

Vaccination for Treatment and Prevention of Cancer in Animal Models

Federica Cavallo, Rienk Offringa, Sjoerd H. van der Burg, Guido Forni,
and Cornelis J. M. Melief

1. Introduction	176
2. Synthetic Exact MHC Class I Binding Peptide Vaccines for Induction of Protective CD8 ⁺ Cytotoxic T-Cell Responses in Mouse Models	177
3. Therapy of Established Mouse Tumors by Treatment with Synthetic Vaccines, in Particular Long Peptides	178
4. Clinical Trials with Synthetic Peptide-Based Cancer Vaccines	181
5. DC Immunotherapy	182
6. Therapeutic Interventions Counteracting Tumor-Induced Immunoregulation	183
7. Genetically Modified Mice that Develop Tumors	185
8. Mice Transgenic for Her2 Oncogene	186
9. BALB- <i>neu</i> T Mice as a Study Model for Mammary Cancer	188
10. DNA Vaccination Inhibits Her2 Mammary Carcinogenesis	191
11. The Mode of EC-TM Plasmid Delivery is Decisive for Vaccine Efficacy	193
12. The Limitations of DNA Vaccination and How They Can Be Overcome	196
13. Coordinated Low-Avidity Mechanisms	199
14. Cure Versus Control of Her2 Lesions	204
15. Conclusions	205
References	206

Unraveling the Complex Relationship Between Cancer Immunity and Autoimmunity: Lessons from Melanoma and Vitiligo

Hiroshi Uchi, Rodica Stan, Mary Jo Turk, Manuel E. Engelhorn, Gabrielle A. Rizzuto, Stacie M. Goldberg, Jedd D. Wolchok, and Alan N. Houghton

1. Introduction	216
2. Immune Ignorance and Tolerance	217
3. Melanoma and Vitiligo	219
4. Active Immunization with Differentiation Antigens as Altered Self	222
5. Passive Immunization with Antibodies Against Differentiation Antigens	226
6. Adoptive Transfer of CD8 ⁺ T Cells Specific for Differentiation Antigens in Adoptive Immunotherapy	228
7. Blockade of CTLA-4	228
8. Overcoming Effects of Suppressor Populations of T Cells	229
9. Dendritic Cells as Adjuvants	230
10. Mouse Model of Spontaneous Melanoma-Associated Vitiligo	230
11. Clinical Trials in Melanoma	231
12. Conclusions	233
References	234

Immunity to Melanoma Antigens: From Self-Tolerance to Immunotherapy

Craig L. Slingluff, Jr., Kimberly A. Chianese-Bullock, Timothy N. J. Bullock, William W. Grosh, David W. Mullins, Lisa Nichols, Walter Olson, Gina Petroni, Mark Smolkin, and Victor H. Engelhard

1. Introduction	244
2. Molecular Definition of Tumor Antigens Recognized by CD8 T Cells	245
3. Why Study Peptide Vaccines?	246
4. Clinical Studies with Peptide Vaccines	248
5. Vaccination with Single Melanoma Peptide and Nonspecific Helper Peptide in Adjuvant	248
6. Evaluation of Immune Responses in the Sentinel Immunized Node	250

7. Vaccination with Peptides in Adjuvant Is More Immunogenic than a Dendritic Cell Vaccine Using Monocyte Derived Immature DC Pulsed with Peptides	250
8. Low-Dose IL-2 Administered Early with Multipeptide Vaccine Does Not Augment Immunogenicity	251
9. Expanding the Repertoire of Melanoma Reactivity Using Multipeptide Vaccines	252
10. <i>Ex Vivo</i> Analyses of T-Cell Responses to Class I MHC Restricted Peptides.....	259
11. Modulation of Responses by Combination of CD4 and CD8 T-Cell Vaccination, and Modulation of Regulatory Function	260
12. Cancer Vaccine Development Requires Elucidation of Biology of the Host-Tumor Relationship in Human and Murine Systems, <i>In Vivo</i> and <i>In Vitro</i>	265
13. A Murine Model to Evaluate Immunity to the MDP-Derived Peptide Ag from Tyrosinase	266
14. Nature of Self-Tolerance to <i>m</i> TyR ₃₆₉ and Its Effect on Tumor Control	267
15. MDP-Specific Immune Responses in Tolerant Mice Enable Control of Tumor Outgrowth	273
16. Peptide-Pulsed Exogenous DC as a Vehicle to Influence the Quality of the Tumor-Specific Immune Response	275
17. Summary of Preclinical and Clinical Studies and Future Directions.....	282
References	284

Checkpoint Blockade in Cancer Immunotherapy

Alan J. Korman, Karl S. Peggs, and James P. Allison

1. Introduction	297
2. The Extended CD28:B7 Immunoglobulin Superfamily	300
3. Preclinical Models of Checkpoint Blockade as Tumor Immunotherapy	310
4. Clinical Trials of CTLA-4 Blockade: Overview	317
5. Other Potential Coinhibitory Targets for Checkpoint Blockade ...	323
6. Conclusions.....	328
References	329

Combinatorial Cancer Immunotherapy

F. Stephen Hodi and Glenn Dranoff

1. Introduction	341
2. Endogenous Host Responses	342
3. Enhancing Tumor Antigen Presentation	343
4. GM-CSF Secreting Tumor Cell Vaccines	344
5. Targets of Vaccine-Induced Tumor Destruction	347
6. Cytotoxic T Lymphocyte Antigen-4 Antibody Blockade	352
7. Combination Immunotherapy: The Next Paradigm?	358
References	358
Index	369
Contents of Recent Volumes	379