Index

A
Activation-induced cell death (AICD), 178
Acute myeloid leukemia (AML), 5, 264
Adenosine-deaminase (ADA), 192
Adenoviral (Ad)-mediated overexpression, 65
Adoptive cell transfer (ACT), 182, 183
Adult stem cell (ASC)
    hematopoietic stem cell transplantation (HSCT)
    DC targeted vaccines, 196–197
    hematological malignancy and solid tumors, 195–196
    T cell targeted immune therapy, 197–198
    mesenchymal stem cells (MSC)
        HSCT, 200–201
        immunotherapy, 199–200
Antigen loading strategies, 161
Antigen presenting cells (APCs), 134, 174, 176, 208, 228, 292, 293
Apoptosis
    IL-18
        hepatocellular carcinoma (HCC) cells, 31
        Lewis lung carcinoma (LLC), 34
        tumor metastasis, 29
    IL-21
        B cells, 48
        chemotherapeutics, 55
        combination therapies, 50
        monotherapy, 51
        tumor necrosis factor (TNF), 53
melanoma differentiation-associated gene-7 (MDA-7)
    adenoviral (Ad)-mediated overexpression, 65
    combinational therapy, 66
    NF-kB activation, 65

B
Basic fibroblastic growth factor (bFGF), 67
B-cell leukemia (Bcl), 179
Bone marrow transplantation (BMT), 191–192

C
CD40, tumor necrosis factor receptor agonist antibodies
    in vitro and in vivo studies, 235
    toxicities, 235–236
antigen presenting cells (APC), 228
    cell death, 232
    cytokine production, 232–233
    innate and adaptive immunity
        dendritic cells (DCs), 229
        interleukin-2, 230–231
        macrophage activation, 228
    structure, 227–228
    superagonistic anti-CD28 antibody (TGN1412), 235
    tumor necrosis factor receptor (TNFR), 227
    vasculature effects
        endothelial cells, 233–234
        vascular endothelial growth factor (VEGF), 233
Chimeric receptor function
    costimulatory and stimulatory signal combination
    CD27 cells, 290–291
    CD80 and 4-1BB binding, 291
    tripartite CR (TPCR) design, 290
    signaling domains, 291
    tumor antigens, optimal recognition, 289
    tumor rejection process, 288
Complement-dependent cytotoxicity (CDC), 246
Cutaneous lymphocytic leukemia (CLL), 310
Cyclin-dependent kinase inhibitors (CKIs), 83
Cytokine sink effect, 293
Cytotoxic T lymphocyte (CTL), 86, 271
antigen-presenting cells (APCs), 138, 140–141
B7-1-modified human tumor cells, 119
IL-18, 24, 26, 34
IL-21, combination therapies, 50
IL-27 cytokine, 9, 10
IL-21 therapy, 53
PEGylated adenovirus vectors
(PEG-Ad), 101
tumor vaccines, 118–119

D
Delayed type hypersensitivity (DTH), 272
Dendritic cells (DCs), 208
antigen-specific immunotherapy, 134
clinical studies
DC-based trials, 165–167
maturity, 169
vaccines, 167–169
ex vivo modification
activation and function, 147–148
advantages and disadvantages, 136
antigen-presenting DCs, 145–147
antigen expression, processing and presentation, 147
clinical trials, 149
strategies, 137
T cell interaction, 148–149
immune tolerance
B7 costimulatory molecules, 271
CTLA-4, 271–272
delayed type hypersensitivity (DTH), 272
GCN2 kinase pathway, 274
protoleragenic cytokines, 270
T cell receptor (TCR), 271
Tyrop3-encoded DAP12 protein, 273
in vivo modification
activation and function, 141–142
advantages and disadvantages, 136
antigen-presenting DCs, 138–139
antigen expression, processing and presentation, 139–141
strategies, 137
T cell interaction, 142–144
maturation, 229–230
peptide-based vaccines, 164
properties, 135
protein-loaded and antigen-engineered DCs, 164–165
shared antigens, 162–163
significance, 134
tumor antigen
categories, 163–164
sources, 169–170
vaccines and therapies
antigen loading strategies, 161
DC maturation, 162
Th1 and Tc1 T cell responders, 160
DTH. See Delayed type hypersensitivity

E
Embryonic stem cells (ESC), 193
Enhanced permeability and retention (EPR), 99
Epidermal growth factor (EGF), 34, 67
Epidermal growth factor receptor (EGFR), 52
Epithelial cell adhesion molecule (Ep-CAM), 109
Epstein–Barr Virus (EBV), 5, 209

F
Fetal bovine serum (FBS), 162
Fibroblast growth factor (FGF), 27
5-Fluorouracil (5-FU), 36

G
Glucocorticoid-induced TNFR-related protein (GITR)
anti-tumor response
naive T cells, 324
non-regulatory T cells, 323
treg suppression, 326
clinical application
GITR antibody (DTA-1), 326
GITR expression, 325
structure, 323
tumor-reactive T cells, 326
Graft-versus-host-disease (GVHD), 196
Granulocyte-macrophage colony-stimulating factor (GM-CSF), 120, 161

H
Hematopoietic stem cell transplantation (HSCT)
DC targeted vaccines, 197
hematological malignancy and solid tumors, 195–196
T cell targeted immune therapy
adoptive cell transfer (ACT), 197
T cell receptor, 198
Index

Herpes simplex virus, 123
Heterodimeric cytokines
EBI3, 5
IL12p35, 4
WSX1/TCCR, 4
Hodgkin’s lymphoma (HL), 265
Human immune cell response. See also
Stem cells
humanized mice
EBV, 218–219
functional human immune responses
against HIV, 219–220
pathogenic infections, 221
immune cell engraftment
graft versus host disease (GVHD), 209
SCID-hu model, 209–210
scid mutation, 209
innate immunity, 220
pre-clinical vaccine testing, 221
stem cell engraftment, 213
β2m null mouse, 211–212
IL2Rγ–/– mouse, 212
immunodeficiency, 213
NK activity suppression, 210–211
NOD/SCID mice, 212–213
residual immunity, 210
Human papilloma virus (HPV), 122
Human T cell Leukemia virus (HTLV), 5

I
IDO. See Indoleamine 2,3-dioxygenase
IFN regulatory factor (IRF), 78
IL-24. See Melanoma differentiation-associated gene-7 (MDA-7)
IL-28A gene
B16 cells, 85–86
CD4 T cells, 87–88
CD8 T cells, 87
Colon26 cells, 86
cytokine gene therapy, 85
dendritic cells (DCs), 88
IFN-γ, 89–90
IL-12 protein, 90
MCA205 cells, 86–87
NK cells, 88
Immune T cell activation motifs
(ITAM), 291
Immunocytokines
anti-angiogenic agents, 253
antibody effector function
anti-CD20 IL-2, 245–246
GM-CSF, 246
mono-specific antibody-IL2 fusion, 246
Rituxan, 245
TNF, 247
clinical studies
DI-Leu16-IL2, 251
hu14.18-IL2, 248–250
huKS-IL2, 249–251
L19 anti-oncofetal fibronectin
protein, 251
gemcitabine, 253
IL-2, 244–245
mouse tumor models, 247–248
structures, 242–243
targeting concepts, 243–244
tumor burden, 252
vaccine antigens, 252
Indoleamine 2,3-dioxygenase (IDO)
cancer immunoediting
genetic mutations, 258
immune equilibrium stage, 259–260
immune escape stage, 260
immune stimulation vs. immune
suppression, 259
immunosurveillance, 258, 259
tumoral immune resistance
mechanism, 258
tumoral immnuny, definition, 257
tumor necrosis factor (TNF), 261–262
D-tryptophan pyrrolase, 262
GCN2 kinase pathway, 274
heme moieties, 263
immune disorders
acute myeloid leukemia (AML), 264
endothelial cells, 265
enzyme levels, 264
Hodgkin’s lymphoma (HL), 265
immunohistochemical analysis, 264
synovial fluid (SF), 265, 266
therapeutic intervention
biochemical inhibition, 277
Canvaxin, 275
L-1MT and D-1MT, 276
pharmacodynamic clinical testing, 277
tryptophan catabolizing enzyme, 262,
266–267

tumor-associated macrophages, 273
Interferon gamma (IFNγ), 230–231
Interferon-gamma-inducing factor (IGIF). See
Interleukin-18
Interleukin-2 (IL-2) family, 230–231
functions, 2
IL23
AsPC overexpression, 8
CD8 T cell production, 7
epithelial tumorigenesis, 7
Interleukin-2 (IL-2) family (cont.)
IFNγ production, 7
subunits, 7
Th17 lineage, 8
TNFα overexpression, 8
IL27
aggressive melanoma (B16F10), 9
anti-inflammatory role, 11
colon cancer 26 (CT26), 9
CTL induction, 9
EBI3 expression, 6
IL12p35 expression, 6
neuroblastoma TBJ, 9
NK cells, 11
oesophageal carcinoma Eca cells, 11
p35 induction, 6
signaling inhibition, 7
STAT1, 9
vascular endothelial cells, 10
WSX1 expression, 10
IL35
T regulatory cells (treg cells)
Foxp3, 12
induction, 14
proinflammatory environment, 13
TGFβ, 12, 13
types, 12
types
Interleukin-18
anti-tumor immune response
cytotoxic T cells, 26
IFNγ and Th1 response induction,
24–25
NK cell activation, 25–26
cancer prognostic marker, 30–32
cancer therapy
5-fluorouracil (5-FU), 36
apoptin, 34
co-stimulatory molecule, 33
DNA vaccine, 32, 35
epidermal growth factor (EGF), 34
fusion vaccines, 34
IL-18BP, 35
mucin 1 (MUC1), 35
NK cell activators, 34–35
prosthetic-specific antigen (PSA), 35
recombinant human IL-18 (rhIL-18)
administration, 32
statins, 35–36
precancerous factor
tumor angiogenesis, 27–28
tumor growth and immune evasion, 27
tumor metastasis, 28–29
production, 20
Interleukin-18 receptor (IL-18R)
regulation, IL-18 binding protein, 22
signal transduction, 21–22
structure, 20–21
Interleukin-21 (IL-21)
adoptive cell therapy (ACT), 54–55
animal tumor studies
combination therapies, 50
monotherapy, 48–49
anticancer agent, 45, 55
anti-CTLA-4, 55
chemotherapy, 54
human clinical trials
combination therapies, 51–54
monotherapy, 50–51
immune downregulation, 45
pleiotropic immune modulation,
44–45
preclinical data
B cells, 48
CD4+ T cells, 45–46
CD8+ T cells, 46–47
NK cells and NKT cells, 47
T regulatory cells (Tregs), 47
vaccines, 54–55
K
Kaplan-Meier survival analysis, 264
L
Lewis lung carcinoma (LLC), 34
M
Major histocompatability molecules
(MHC), 174
Maximum tolerated dose (MTD), 249
Melanoma differentiation-associated gene-7
(MDA-7)
angiogenesis, 67–68
apoptosis
adenoviral (Ad)-mediated
overexpression, 65
combinational therapy, 66
NF-κB activation, 65
cell growth inhibition, 65
clinical evaluation, 69–70
expression, 65
IL-22R and IL-20R complexes, 64
peripheral blood mononuclear cells, 64
pleotropic effects, 63
preclinical and clinical studies, 70
structure, 67
tumor metastases and invasion, 68–69
Mesenchymal stem cells (MSC), 111
HSCT, 200–201
immunotherapy
cytokine production, 199
tumor attraction, 199–200
Metastatic renal cell carcinoma (mRCC), 52
Moloney murine leukemia virus (Mo-MuLV), 123
Mononuclear phagocytic system (MPS), 100
Mucin 1 (MUC1), 35
Murine leukemia virus (MLV), 123
Myeloid-derived suppressor cells (MDSC), 273
Myeloid-differentiation factor 88 (MyD88), 21, 174, 183

N
Natural killer (NK) cell, 160
Newcastle disease virus (NDV), 122
Non-Hodgkin’s lymphoma (NHL), 51

O
Optimal biological dose (OBD), 249
OX40, tumor necrosis factor receptor
anti-tumor response, 322–323
clinical application, 330–332
expression pattern, 321–322
structure, 320

P
Pancreatic ductal adenocarcinoma (PDA), 264
Pathogen-associated molecular patterns (PAMPs), 302
Peptide-based vaccines, 164
Peripheral blood mononuclear cells (PBMCs), 64, 309
Platelet derived growth factor (PDGF), 27
Prosthetic-specific antigen (PSA), 35
*Pseudomonas aeruginosa*, 23

R
Renal cell carcinoma (RCC), 98
Renal cell carcinoma (RENCA), 127
Response evaluation criteria in solid tumors (RECIST), 168
Reticulo-endothelial system (RES), 100
S
Signal transducer and activator of transcription (STAT), 76, 81–82
Single nucleotide polymorphisms (SNPs), 263, 305
Stem cells. See also Adult stem cell (ASC); Mesenchymal stem cells (MSC)
differentiation, NOD/SCID/γcnull mice
DC subsets, 217
de novo human T cell, 215
histological analysis, 216
influenza virus, 217
naïve T cells, 215
engineering (see also Adult stem cell (ASC))
adult tissue-resident stem cells, 194
embryonic stem cells (ESC), 193
gene therapy, 202
hematopoietic stem cells (HSC), 193
immunotherapy protocols, 202
lentiviral vector system, 201–202
umbilical cord blood stem cells (UCB-SC), 194
sources
injection of human stem cells, 214–215
NOD/SCID/γcnull mice, 214
Suppressor of cytokine signaling (SOCS), 81–82, 142
Suppressor of tumorigenicity-16 (ST-16). See Melanoma differentiation-associated gene-7 (MDA-7)
Synovial fluid (SF), 265, 266

T
T-body approach
chimeric receptor function
costimulatory and stimulatory signal combination, 289–291
signaling domains, 291
tumor antigens, optimal recognition, 289
tumor rejection process, 288
genetic engineering, 296
human T cells transduction
differentiation state, 294–295
preparation, clinical application, 295
monoclonal antibodies, 286
safety, optimization, 294
single chain Fv (scFv)-based chimeric receptor, 287
survival and efficacy
homeostatic cytokines, 293
immunosuppressive cells elimination, 292
tumor infiltrating lymphocytes (TIL), 286
TNF receptor-associated factor-6 (TRAF-6), 21
Toll-IL-1 receptor (TIR), 20
Toll-like receptors (TLRs), 141
antitumor immunity, 185–186
CD4+ T cell function, 181–182
clonal expansion, 178–179
CTL effector function, 179–180
in vivo technique, 182–183
memory T cell development, persistence, and migration, 180–181
microbial-derived molecules, 174, 175
regulation, 176–178
synergistic effects, 184–185
TCR signaling cascades, 184
TLR-3
dendritic cell (DC), 306
injections of poly, 307
NK cells, stimulation of, 306
synthetic double stranded RNA, 305
TLR4
high-mobility-group-box 1 (HMG1), 303
lipopolysaccharides (LPS), 302
TLR4 ligands, 303
TLR-5
flagellin, 307
peritumoral injections, 308
TLR-7
imiquimod, 310
new chemical entities, 309
polyribonucleotides, 309
TLR-9, CpG-ODN
BALB-neuT mice, 312
combination therapy, 313
CpG motifs, 311
PF-3512676, 312
rituximab, 313
syngeneic and transgenic tumor models, 311
T regulatory cells (Tregs), 312
Transcription factors (TF), 179–180
Transforming growth factor-β (TGF-β), 269
T regulatory cells (treg cells), 144, 292
Foxp3, 12
induction, 14
pro-inflammatory environment, 13
types, 12
Tryptophan catabolism
cellular pathways, signaling
Akt inhibitors, 270
cyclooxygenase 2 (COX-2)
activation, 269
immunoregulatory cytokines, 267
implications, 270
interferon-γ (IFN-γ), 268, 269
LIP and kynurenine, 267
IDO2, 266–267
Tumor-associated antigen (TAA), 163–164
Tumor-associated macrophages (TAMs), 273, 274
Tumor cell vaccine therapy
immunogenicity
allogeneic tumor cell vaccine, 121
antigens, 118–119
costimulatory molecules transduction, 119–120
GM-CSF transduction, 120–121
viral vectors, 122–124
immunological response
CD8+ T cells, 124–125
coinhibitory signal blockade, 125–126
tumor-reactive memory T cells, 127–128
Tumor homing cytokine therapies
antibodies, active targeting
L19 immunocytokine, 107
in vivo biopanning, 111
murine hybridoma technology, 107
gene therapy, 99
immunomodulatory treatments, 99
intracellular signaling proteins, 98
peptides, ligand targeting
cyclic NGR peptides, 104
doxorubicin, 105
melphalan, 103
NGR-TNFα, 104
RGD-integrin interactions, 104
RGD peptides, 102
virus vectors, 106
poly-ethylene glycol, passive targeting
enhanced permeability and retention (EPR), 99
PEGylated adenovirus vectors (PEG-Ad), 101
PEGylation, 100
poly(methoxypolyethylene glycol-cyanoacrylate-co-n-hexadecyl cyanoacrylate), 101
tumor microenvironment, 99
Tumor infiltrating lymphocytes (TIL), 286
Tumor necrosis factor (TNF), 62, 98, 261–262
Tumor necrosis factor receptor (TNFR), 227
anti-cancer agent, 319
anti-tumor responses
CD27, 324–325
CD134, 326–329
CD137, 329–330
Forkhead-Box Protein 3 (FoxP3), 323
Tissue factor (TF), 179–180
glucocorticoid-induced TNFR-related protein (GITR), 325–326
pre-clinical studies, 323
regulatory T cells (Tregs), 322
CD40
agonist antibodies, 235–236
antigen presenting cells (APC), 228
cell death, 232
cytokine production, 232–233
innate and adaptive immunity, 228–231
structure, 227–228
superagonistic anti-CD28 antibody (TGN1412), 235
tumor necrosis factor receptor (TNFR), 227
vasculature effects, 233–234
clinical application
anti-CD134 drug, 331
CD134 agonist, 331
CD134 specific fusion protein, 331
CD137-specific monoclonal antibodies, 331
GITR agonists, 332
TNFR aptamers, 332
expression
endogenous TNFR signaling, 322
T cell activation/differentiation, 321
structural and signaling features, 320
Tumor necrotic therapy (TNT), 243
Tumor-specific T cells
activation and differentiation, 176, 177
immunotherapy, 174, 176
toll-like receptor
antitumor immunity, 185–186
CD4 + T cell function, 181–182
clonal expansion, 178–179
CTL effector function, 179–180
in vivo technique, 182–183
memory T cell development, persistence, and migration, 180–181
microbial-derived molecules, 174, 175
regulation, 176–178
synergistic effects, 184–185
TCR signaling cascades, 184
tumor regression, 173
Type III interferons
antigen-specific immunity, 91
antiviral cytokines, 78
encoding genes, 77
growth-inhibitory effect, 84
IL-28A gene
B16 cells, 85–86
CD4 T cells, 87–88
CD8 T cells, 87
Colon26 cells, 86
cytokine gene therapy, 85
dendritic cells (DCs), 88
IFN-γ, 89–90
IL-12 protein, 90
MCA205 cells, 86–87
NK cells, 88
IL-28R receptor, 79–81
mRNA, 83–84
p21Waf1/Cip1, 84
polymorphonuclear neutrophils, 88–89
signal transduction, 81–82
sources and regulation, 77–79
type I IFNs
apoptosis induction, 84
clinical oncology, 82
cyclin-dependent kinase inhibitors (CKIs), 83
host immune cells, 76
IFN-α/β, 75
protein kinase R and ribonuclease L, 83
tumor-induced angiogenesis, 84–85
vascular endothelial cells, 85
Tyrosine kinase inhibitors (TKIs), 52
Tyrosine kinase Mer (MerTK), 148

U
Umbilical cord blood stem cells (UCB-SC), 194

V
Vascular endothelial growth factor (VEGF), 27, 52, 67, 304