

Drug Delivery in Cancer

Part I: Technologies & Markets

By

Prof. K. K. Jain
MD, FRACS, FFPM
Jain PharmaBiotech
Basel, Switzerland

November 2021

A Jain PharmaBiotech Report

A U T H O R ' S B I O G R A P H Y

Professor K. K. Jain is a neurologist/neurosurgeon with specialist qualifications including Fellowships of the Royal Colleges of Surgeons in Australia and Canada. He has trained, practiced, and held academic positions in several countries including Switzerland, India, Iran, Germany Canada, and USA. After retirement from neurosurgery, Prof. Jain remains a consultant in neurology. He is also working in the biotechnology/biopharmaceuticals industry and is a Fellow of the Faculty of Pharmaceutical Medicine of the Royal College of Physicians of UK. Currently, he is the CEO of Jain PharmaBiotech.

Prof. Jain's 492 publications include 35 books (6 as editor+ 29 as author) and 50 special reports, which have covered important areas in biotechnology, gene therapy and biopharmaceuticals, biomarkers: proteomics, molecular diagnostics, nanobiotechnology, and personalized medicine. Contributions to MedLink, an accredited continuing education program for neurologists, include 170 articles out of a total of 1200 articles by 450 authors. These articles are updated on a yearly basis.

Prof. Jain's earlier books were the first in the areas covered: "Handbook of Laser Neurosurgery" (Charles C. Thomas, Springfield, Ill, 1983) and "Textbook of Hyperbaric Medicine" (1st ed in 1990 and 6th ed by Springer, 2017). His "Textbook of Gene Therapy" was translated into Chinese in 2000. Recent books include "Handbook of Nanomedicine" (Springer 2008, Chinese edition by Peking University Press 2011, 3rd ed 2017), "Textbook of Personalized Medicine" (Springer 2009; Japanese ed 2012; 2nd ed Springer 2015, 3rd ed 2021), "Handbook of Biomarkers" (Springer 2010; Chinese ed, Chemical Industry Press 2016, 2nd ed 2017), "Drug-induced Neurological Disorders", 4th ed (Springer 2021), "Handbook of Neuroprotection" (Springer 2011, 2nd ed 2019), "Applications of Biotechnology in Cardiovascular Therapeutics" (Springer 2011), "Applications of Biotechnology in Neurology" (Springer 2013), and "Applications of Biotechnology in Oncology" (Springer 2014). He has also edited 3 editions of "Drug Delivery System" (Springer 2008, 20012 and 2018) and "Applied Neurogenomics" (Springer 2015). Lectures on personalized medicine given at Kazakh National Medical University, Kazakhstan were translated into Russian and published as a book "Essentials of Personalized Medicine" (LITERRA Publishing House, Moscow, 2019). Currently, he is writing "The Handbook of Alzheimer Disease" to be published by Springer in 2022.

A B O U T T H I S R E P O R T

The original report on Drug Delivery in Cancer by the author was published by Decision Resources Inc in 2000 as an enlargement of the chapter on this topic in his report on Drug Delivery Technologies (1998), which was also published by Decision Resources. The second edition was published at Jain PharmaBiotech in 2003 and has been constantly updated and rewritten since then.

November 2021 (first edition published in 2000)
Copyright © 2021 by

Jain PharmaBiotech
Bläsiring 7
CH-4057 Basel
Switzerland

Tel & Fax: +4161-6924461
Email: info@pharmabiotech.ch
Web site: <http://pharmabiotech.ch/>

All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, electronic, mechanical, photocopying, or otherwise without the prior written permission of the Publisher. This report may not be lent, resold or otherwise traded in any manner without the consent of the Publisher. While all reasonable steps have been taken to ensure the accuracy of the information presented, the Publisher cannot accept responsibility for inadvertent errors or omissions.

T A B L E O F C O N T E N T S

0. Executive Summary	21
1. Introduction to cancer therapy	23
Molecular biology of cancer	
Cell cycle and cancer.....	23
<i>Apoptosis in cancer</i>	24
<i>Autophagy</i>	24
<i>Cell division and mitotic spindles.....</i>	25
<i>PD-1 Pathway.....</i>	25
<i>DNA damage, repair and cancer.....</i>	26
<i>Mechanism of DNA damage in Fanconi anemia leading to leukemia</i>	26
Cancer metabolism and energy status in relation to growth.....	26
<i>Amino acids and cancer</i>	26
<i>AMP-activated protein kinase.....</i>	27
<i>Cancer therapeutics that target metabolism.</i>	27
Cancer cell dormancy	28
<i>Dormancy and relapse in cancer</i>	28
<i>Activating dormant cancer cells for enhancing chemotherapy</i>	28
Chromosomes and cancer	29
<i>Aneuploidy.....</i>	29
<i>Chromosomal instability.....</i>	29
<i>Chromothripsis</i>	30
<i>Extrachromosomal DNA and cancer</i>	30
Telomeres and cancer	30
Genes and cancer	31
<i>Accumulation of random mutations</i>	31
<i>Oncogenes.....</i>	31
<i>Role of Bub 1 gene in cell division</i>	32
<i>Tumor Suppressor Genes</i>	32
Hallmarks of cancer.....	33
Hypoxia of cancer cells	34
Invasion and metastases	35
<i>Tumor suppressor genes and metastases.....</i>	36
Methylation and cancer.....	36
Nitric oxide and cancer	37
<i>Inflammation, NO and colon cancer.....</i>	38
<i>NO and tumor hypoxia.....</i>	38
<i>NO and p53 mutations.....</i>	39
<i>NO and matrix metalloproteinase</i>	39
<i>Role of NO in angiogenesis in cancer</i>	39
Oxidative stress and cancer.....	41
Role of platelet-derived growth factor in proliferation of cancer.....	42
RNA and cancer	42
<i>Anticancer treatments based on RNA regulation of genes</i>	42
<i>Role of microRNAs in cancer</i>	42
Stem cells and cancer.....	43
Self-sufficiency of tumor proliferation	44
Therapeutic implications of apoptosis in cancer.....	44
Tumor angiogenesis	46
<i>Pathomechanism of angiogenesis.....</i>	46
<i>Role of VEGF in angiogenesis.....</i>	48
<i>Matrix stiffness-mediated angiogenesis in tumors</i>	48
Tumor-associated macrophages in cancer	48
Cancer biomarkers.....	49
Molecular imaging of cancer	49
Cancer genomics.....	49
Gene expression profiling in cancer	49
Cancer proteomics	50
Limitations of genomics and proteomics for understanding cancer	50
Cancer microenvironment.....	51
Epidemiology of cancer.....	51
Current management of cancer.....	52
Anticancer drugs.....	52
<i>Limitations of cancer chemotherapy</i>	53
Biological therapies for cancer	53
Radiotherapy.....	53
<i>Brachytherapy</i>	53
Ideal anticancer agent	53

Surgery	54
Basics of drug delivery in cancer	54
Role of mechanical forces in tumor growth and delivery of therapy	54
Methods of assessing drug delivery in cancer	55
Positron emission tomography (PET)	55
Historical landmarks in cancer drug delivery	55
2. Innovative treatments for cancer	58
Introduction	58
Selective estrogen receptor modulators	59
Antiangiogenic strategies for cancer	59
Development of antiangiogenic therapies	60
Classification of antiangiogenic agents	60
Examples of antiangiogenic agents	62
ACE-041	62
Angiopoietin-2 as a target	62
Chemotherapy at lower than maximum tolerated dose	62
Galectin-3 as a target for inhibiting angiogenesis	62
Inhibitors of endothelial proliferation	63
Inducers of apoptosis of endothelial cells of tumor vessels	63
Lodamin	63
Matrix metalloproteinase inhibitors	64
Monoclonal antibodies with vasculostatic properties	64
PPAR α agonists	65
Rapalogues as antiangiogenic agents	66
VEGF Trap	66
Agents that decrease the permeability of tumor blood vessels	66
Antiangiogenic agents in clinical trials	67
Antiangiogenic therapy resistance	67
Combination of antiangiogenic with cytotoxic therapy	67
Antiangiogenic therapy for hematological malignancies	68
Bacterial anticancer agents	69
Tumor-targeted bacteria	69
Bacterial protein for targeted delivery of liposomal cancer drugs	70
Bacterial carriers for targeted drug delivery to brain tumors	70
Genetically modified bacteria as anticancer agents	70
Live bacteria for delivering radioactive anticancer agents	71
Synchronized cycles of bacterial lysis with delivery of chemotherapy	71
Genetically altered strains of <i>Salmonella</i> as anticancer drug vectors	72
Inactivated but metabolically active bacteria	72
Bacterial toxins targeted to tumors	73
Immunotoxins	73
<i>Escherichia Coli</i> toxins	73
Engineered anthrax toxin	73
Recombinant fusion toxins	74
Type III secretion systems	75
Induction of apoptosis in cancer by bacterial proteins	76
Induction of immune response by bacteriolytic therapy	76
Epigenetic targets for anticancer therapy	76
Innovations in cell therapy for cancer	77
Stem cell transplantation for cancer	77
Cancer drug/gene delivery by mesenchymal stem cells	78
Personalized drug development in oncology	78
Role of molecular imaging	79
Role of molecular imaging in targeted cancer therapy	80
Screening for personalized anticancer drugs	80
Targeting pathways for personalized cancer therapy	80
Cancer immunotherapy	81
Role of biomarkers in personalized immuno-oncology	82
Role of organoids in predicting response to immuno-therapeutic drugs	83
Role of tumor-on-chips in immuno-oncology	83
Role of molecular diagnostics and sequencing in immuno-oncology	83
Genomic testing	83
Gene expression signatures	84
Personalizing immuno-oncology	84
Factors that drive the development of personalized immunotherapy for cancer	85
Computational methods for personalized immuno-oncology	85
Immune checkpoint inhibitors for cancer	85
Checkpoint inhibitors blocking PD-1 or PD-L1	86
Antibody blocking the cytotoxic T-lymphocyte-associated protein 4	86
Prediction of response to anti-PD-1/PD-L1 therapy in cancer	87

<i>Checkpoint inhibitors other than anti-PD-L1</i>	87
<i>Personalizing immune checkpoint inhibitor therapy</i>	87
Cell-based immune therapies	88
<i>Treatments for cancer by ex vivo mobilization of immune cells</i>	88
<i>Granulocytes as anticancer agents</i>	88
<i>Neutrophil granulocytes in MAb-based immunotherapy of cancer</i>	89
<i>Adoptive cell transfer</i>	89
<i>Chimeric antigen receptor T cells</i>	89
Cytokines.....	90
Cancer vaccines.....	91
<i>Adoptive cell therapy</i>	92
<i>Antigen-specific cancer vaccines</i>	94
<i>Carcinoembryonic antigen-based vaccines</i>	95
<i>Carbohydrate-based cancer vaccines</i>	95
<i>Dendritic cells for cancer vaccination</i>	95
<i>Hybrid cell vaccination</i>	97
<i>SMART vaccines</i>	98
<i>Salmonella-based oral vaccine delivery</i>	98
<i>Tumor cell vaccines</i>	98
<i>Vaccines that simultaneously target different cancer antigens</i>	99
<i>Vaccines based on multiple tumor-associated peptides</i>	99
<i>Vaccine for cancer based on antimalaria protein</i>	100
<i>Cancer Vaccine Consortium</i>	100
<i>Personalized cancer vaccines</i>	100
<i>Autologous tumor cell vaccines</i>	100
<i>DC-based cancer vaccines</i>	101
<i>Cytokines as vaccine adjuvants</i>	101
<i>Limitations of cancer vaccination</i>	102
<i>Role of neoantigens in personalizing cancer vaccines</i>	102
Delivery of cancer immunotherapy	102
<i>Nanoparticles for delivery of immunotherapy combined with photodynamic therapy</i>	102
<i>Synthetic bacteria for local tumor delivery of checkpoint blockade nanobodies</i>	103
<i>Transdermal cold atmospheric plasma mediated ICI therapy</i>	103
<i>Combination of immunotherapies for cancer</i>	103
Epigenetic modulators and cancer immunotherapies.....	104
STING activation and antitumor immunity	106
Chemoimmunotherapy	106
Concluding remarks about cancer vaccines.....	106
Targeted delivery of peptides to tumor-associated macrophages.....	107
Targeting cancer stem cells.....	107
Concluding remarks and future of personalized immuno-oncology.....	107
Monoclonal antibodies	108
<i>Murine MAbs</i>	108
<i>Humanized MAbs</i>	108
<i>Actions and uses of MAbs in cancer</i>	109
<i>Targeted antibody-based cancer therapy</i>	110
<i>Antibody-cytokine fusion proteins</i>	110
<i>Antibody ARGX-115 for targeting immunosuppressive effect of Tregs</i>	110
<i>Anti-Thomsen-Friedenreich antigen MAb</i>	111
<i>Combining MAbs with anti-CD55 antibody</i>	111
<i>MAbs targeted to alpha fetaprotein receptor</i>	111
<i>MAbs that target angiogenesis</i>	111
<i>MAbs as phagocyte checkpoint inhibitors</i>	112
<i>MAbs for immune activation</i>	112
<i>Delivery of cancer therapy with MAbs</i>	113
<i>Antibody-directed enzyme prodrug therapy</i>	114
<i>Chemically programmed antibodies</i>	114
<i>Combining diagnostics with therapeutics based on MAbs</i>	114
<i>Radiolabeled antibodies for detection and targeted therapy of cancer</i>	114
<i>Other innovations for administration of antibodies</i>	117
<i>Bispecific antibodies</i>	117
<i>Trifunctional antibodies</i>	118
<i>Tetraivalent bispecific antibodies</i>	118
<i>Immunotoxins</i>	119
<i>Immunoliposomes</i>	119
<i>Combined use of MAbs and cytokines</i>	119
<i>huHMFG1-huDnase I</i>	119
<i>MAbs that selectively target cancer</i>	120
<i>G-MAB technology</i>	120
<i>NanoMAbs for targeted anticancer drug delivery</i>	121
<i>Advantages and limitations of MAbs for cancer therapy</i>	121

Monoclonal antibodies for personalized management of cancer	122
Antibody-drug conjugates	122
<i>Kadcyla</i>	124
<i>Adcetris</i>	124
Antibody-drug conjugates for personalized therapy of cancer	124
Antibody-enzyme conjugates	124
Current and future trends in antibody-based cancer drugs	125
Innovative methods of radiation delivery	125
Image-guided ultrasound technology for delivery of radiation	125
Respiratory gating technology for radiation therapy	125
Positron therapy	126
Boron neutron capture therapy	126
<i>Application of drug delivery systems to BNCP</i>	127
<i>Use of nanotechnology to enhance BNCT</i>	128
Ion channels and transporters in cancer.....	128
Irreversible electroporation.....	128
Methods to overcome multidrug resistance (MDR)	129
Mechanism of MDR.....	129
<i>MDR-associated protein gene</i>	129
<i>P-glycoprotein-mediated MDR</i>	130
Strategies for overcoming MDR.....	130
<i>Blocking the action of P-glycoprotein</i>	130
<i>Combination of targeted drugs with different specificities</i>	131
<i>Enzyme Catalyzed Therapeutic Activation</i>	131
<i>Inhibition of DNA repair</i>	131
<i>Iron chelators that overcomes resistance to chemotherapeutics</i>	132
<i>Liposome formulation of anticancer drugs</i>	132
<i>Modification of the chemical structure of the anticancer drug</i>	132
<i>Managing resistance to antiapoptotic action of anticancer agents</i>	133
<i>Modulation of SPARC expression</i>	133
<i>Nanoparticles for producing reactive oxygen species in mitochondria</i>	133
<i>Nitric oxide inducers</i>	133
<i>Proton pump inhibitors</i>	134
<i>Repression of Prohibitin1 in drug-resistant cancer cells</i>	134
<i>Targeting proteins associated with cancer stem cells</i>	134
Targeted cancer therapies	135
Targeting cellular pathways.....	135
Targeting antigens in virus-associated cancer	135
Targeting the IGF-I receptor.....	136
Targeting Mcl-1 protein.....	136
Targeting mitochondrial membranes	136
Targeting tumor lymphatics.....	137
<i>LyP-1 for targeting tumor lymphatics</i>	138
Targeting tyrosine kinase receptors.....	138
<i>Inhibitors of bcr-abl tyrosine kinase</i>	138
<i>Inhibition of multiple tyrosine kinases</i>	138
<i>Inhibitors of Erbb tyrosine kinase</i>	139
Targeting the Hedgehog signaling pathway	139
Targeting caspase-8	140
Targeting metallodrugs to tumor cells.....	140
Targeting oncogenes	141
Targeting miRNA for cancer therapeutics	141
Targeting the transferrin receptor-mediated endocytosis pathway	142
Targeted anticancer therapies based on the Rad51 promoter.....	142
Targeting cancer stem cells.....	142
Targeting glycolytic pathway in cancer.....	143
Targeting glycoproteins	144
<i>Tagging cancer with modified sugars</i>	144
<i>Anticancer agents based on glycobiology</i>	145
<i>Targeting cell surface glycoproteins</i>	145
<i>Biofusion for targeted cancer therapy</i>	145
Targeting knottin peptides	146
Tarveda's Pentarin platform for targeted drug conjugates	146
Enhancing the effects of radiation and chemotherapy	146
Sensitizing and enhancing agents for chemotherapy.....	146
<i>CoFactor to enhance the efficacy of chemotherapy</i>	146
<i>Enzyme-enhanced chemotherapy</i>	147
<i>Resveratrol and quercetin for cardioprotection against chemotherapy</i>	147
<i>Tesmilifene for chemosensitization</i>	148
Sensitizing agents for radiotherapy	148
<i>IPdR</i>	148

<i>Ultrasound for enhancing response to radiation</i>	148
Manipulation of tumor oxygenation	149
<i>Hypoxia-based methods to enhance chemotherapy and radiotherapy</i>	149
<i>Hyperbaric oxygen and radiation.....</i>	150
<i>HIF-1 antagonists to enhance radiotherapy</i>	150
<i>Nonsteroidal antiinflammatory drugs enhance tumor radiosensitivity</i>	150
<i>ONCONASE as radiosensitivity enhancer</i>	150
Hyperthermia and chemotherapy/radiation therapy.....	151
<i>Techniques for hyperthermia</i>	151
<i>Trimodality therapy: radiation, chemotherapy, and hyperthermia</i>	151
Photodynamic therapy	152
<i>Photochemical internalization</i>	154
Thermal combination with focused ultrasound for drug delivery to tumors.....	154
Novel anticancer agents	155
Anti-EphA2 antibodies	155
Antioxidants	155
Brostallicin	156
Agents disrupting folate metabolism.....	156
<i>Pemetrexed.....</i>	156
Cell cycle inhibitors	156
Cytotoxic ribonucleases	157
DNA hypomethylating agents	157
Histone-based cancer therapy	158
<i>Histone deacetylase inhibitors</i>	158
<i>Modulation of p300/CBP histone acetyltransferase activity</i>	159
<i>Simulation of endogenous histone for anticancer therapy</i>	159
HSP90 inhibitors	159
Ion channel blockers	160
<i>IOT-101.....</i>	160
<i>Endovion</i>	160
LPAAT-β inhibitors.....	160
Modulation of pyruvate kinase M2	161
Modulators of protein ubiquitination	161
P13-kinase inhibitors	161
PARP inhibitors	162
<i>Targeted destruction of BRCA2 deficient tumors by PARP inhibitors</i>	162
<i>Companies developing and commercializing PARP inhibitors</i>	162
Prodrugs.....	163
<i>Enzyme-activated prodrugs.....</i>	163
<i>Ascorbic acid as a prodrug for cancer</i>	163
<i>Polarix.....</i>	164
Procaspase-3 activation	164
Protein kinase G activation.....	164
Proteasome inhibitors.....	165
Recombinant human insulin-like growth factor binding protein-3.....	165
Second generation nucleosides	166
Targeting cancer metabolism.....	166
Targeting topoisomerase IB	166
Telomerase inhibitors	167
Therapeutic strategies based on the P53 pathway	167
Therapeutic strategies based on molecular mechanisms.....	168
<i>Checkpoint activation as a strategy against cancer.....</i>	168
<i>Deletion-specific targeting for cancer therapy</i>	169
<i>In vivo models for molecularly anticancer drugs.....</i>	169
<i>Repair-blocking drugs for enhancing effect of chemotherapy</i>	169
<i>Tumor targeting fields</i>	170
<i>Targeting mTOR signaling defects</i>	170
Combining novel anticancer approaches.....	170
Personalized therapy of cancer.....	172
Promise of personalized therapy in cancer.....	172
Challenges of cancer classification.....	174
Design of future cancer therapies.....	174
3. Drug delivery systems for cancer	177
Introduction	177
Routes of drug delivery in cancer	177
Intravenous delivery systems for cancer therapy	178
<i>Intravenous versus oral ascorbate for treatment of cancer</i>	179
Subcutaneous injection of anticancer agents	179
Oral delivery of anticancer agents	179
<i>5-FU combined with eniluracil.....</i>	181

<i>Cyclin D-dependent CDK4 and CDK6 inhibitors</i>	181
<i>High dose administration of calcitriol</i>	181
<i>Oral fluoropyrimidines</i>	182
<i>Oral gefitinib vs intravenous docetaxel</i>	182
<i>Oral paclitaxel</i>	183
<i>Oral satraplatin</i>	183
<i>Oral UFT</i>	183
<i>Oral PXD101</i>	184
Transdermal drug delivery	184
<i>Delivery of the photosensitizer drug δ-amino levulinic acid</i>	184
<i>Nanoemulsion-based delivery of caffeine for skin cancer</i>	184
<i>Transdermal delivery of methotrexate</i>	185
<i>Transdermal nitroglycerine for prostate cancer</i>	185
<i>Transdermal delivery of peptide cancer vaccines</i>	185
<i>Intradermal delivery of cancer vaccines by adenoviral vectors</i>	185
Pulmonary delivery of anticancer agents	186
Regional intra-arterial delivery of chemotherapy	186
Gas embolotherapy of tumors.....	187
Drug delivery to lymph nodes.....	187
Intraperitoneal macrophages as drug delivery vehicle.....	188
Challenges of cancer drug delivery	188
Tumor blood vessel pore barrier to drug delivery	188
Improvement of drug transport in tumors	188
Delivery of anticancer drugs to nuclear targets	189
Innovative formulations for drug delivery in cancer	190
Cancer targeting with polymeric drugs.....	190
<i>Linking anticancer drugs to polyglutamate</i>	191
<i>Improving delivery of protein-polymer anticancer drugs</i>	191
Aldoxorubicin	192
Linker activated anticancer drug delivery	192
Macromolecules as delivery systems for taxanes.....	193
Polyamine conjugates as anticancer agents	193
Bacterial vectors as drug delivery systems for anticancer drugs	193
Microparticles as therapeutic delivery systems in cancer	194
<i>Subcutaneous injection of microspheres carrying anticancer drugs</i>	194
<i>Intravascular delivery systems using microparticles</i>	195
<i>Tumor embolization with drug-eluting beads</i>	195
<i>Tumor embolization with radioactive microparticles</i>	195
<i>Microparticles heated by magnetic field</i>	196
<i>Magnetic targeted microparticle technology</i>	196
<i>Release of drugs from biSphere by ultrasound</i>	196
<i>Release of drugs from micelles by ultrasound</i>	197
<i>Release of drugs from microcapsules by laser</i>	197
<i>Chemoembolization</i>	197
<i>Anticancer drugs bound to carbon particles</i>	198
<i>Anticancer drugs bound to protein microspheres</i>	198
<i>Nanoerythrocytes</i>	198
Nanobiotechnology-based drug delivery for cancer	198
Nanoparticle formulations for drug delivery in cancer	200
<i>Anticancer drug particles incorporated in liposomes</i>	200
<i>Doxorubicin nanocarriers</i>	201
<i>Encapsulating drugs in hydrogel nanoparticles</i>	202
<i>Exosomes</i>	203
<i>Folate-linked nanoparticles</i>	203
<i>Lipid based nanocarriers</i>	203
<i>Micelles for drug delivery in cancer</i>	204
<i>Minicells for targeted delivery of nanoscale anticancer therapeutics</i>	205
<i>Nanobombs for cancer</i>	206
<i>Nanodiamonds for local delivery of chemotherapy at site of cancer</i>	206
<i>Nanoparticle formulation for enhancing anticancer efficacy of cisplatin</i>	207
<i>Nanoparticle formulations of paclitaxel</i>	207
<i>Nanoparticles containing albumin and antisense oligonucleotides</i>	207
<i>Nanotechnology-based non-invasive refilling of drug delivery depots</i>	208
<i>Non-aggregating nanoparticles</i>	208
<i>Pegylated nanoliposomal formulation</i>	208
<i>Perfluorocarbon nanoparticles</i>	209
<i>PFTBA@Alb nanoparticles as enhancers of anti-PD-L1 immunotherapy</i>	209
<i>Polymer nanoparticles for drug delivery</i>	209
<i>Protein nanocages for penetration of airway mucous and tumors</i>	209
<i>Protosphere nanoparticle technology</i>	210
Nanoparticles-based targeted delivery of therapeutics for cancer	210

Antiangiogenic therapy using nanoparticles	211
Carbon magnetic nanoparticles for targeted drug delivery in cancer	212
Carbon nanotubes for targeted drug delivery to cancer cells	212
CRLX101 for targeted anticancer drug delivery	213
DNA aptamer-micelle for targeted drug delivery in cancer	213
Fullerenes for enhancing tumor targeting by antibodies	213
Gold nanoparticles for targeted drug delivery in cancer	214
Hepatic artery infusion of LDL-DHA nanoparticles for liver cancer	215
Iron oxide magnetic nanoparticle formulation for drug delivery	215
Laser irradiation for targeted release of drugs from nanocontainers	215
Lipoprotein nanoparticles targeted to cancer-associated receptors	216
Magnetic nanoparticles for remote-controlled drug delivery to tumors	216
Monitoring of targeted delivery by nanoparticle-peptide conjugates	217
Nanobees for targeted delivery of cytolytic peptide melittin	217
Nanocell for targeted drug delivery to tumor	217
Nanodroplets for site-specific cancer treatment	218
Nanogel-based stealth cancer vaccine targeting macrophages	218
Nanoparticle-mediated targeted delivery of peptides into tumors	219
Nanoparticle-mediated targeting of MAPK signaling pathway	219
Nanoparticles for targeted delivery of concurrent chemoradiation	220
Nanostructured hyaluronic acid for targeted drug delivery in cancer	220
Nanoparticles as antibody-drug conjugates	220
Nanoparticle-coated peptides for tumor targeting	221
Nanoparticle-mediated delivery of multiple anticancer agents	221
Nanovesicle-mediated drug delivery in cancer	221
Polymer nanoparticles for targeted drug delivery in cancer	221
Polymersomes for targeted anticancer drug delivery	222
Quinic acid-nanoparticle conjugates	222
Targeted drug delivery with nanoparticle-aptamer bioconjugates	223
Targeted nanoparticles delivery of cisplatin to mitochondrial genome	224
Time-delayed, dual-drug nanoparticle delivery system for cancer	224
Dendrimers for anticancer drug delivery	225
Application of dendrimers in boron neutron capture therapy	226
Application of dendrimers in photodynamic therapy	226
Dendrimer-based synthetic vector for targeted cancer gene therapy	227
Devices for nanotechnology-based cancer therapy	227
Convection-enhanced delivery with nanoliposomal CPT-11	227
Nanocomposite devices	227
Nanoengineered silicon for brachytherapy	228
Nanosensors for targeted drug delivery in cancer	228
Nanoparticles combined with physical agents for tumor ablation	228
Carbon nanotubes for laser-induced cancer destruction	228
Nanoparticles and thermal ablation	229
Nanoparticles combined with ultrasound radiation of tumors	231
Nanoparticles as adjuncts to photodynamic therapy of cancer	231
Nanoparticles for boron neutron capture therapy	232
RNA nanotechnology for delivery of cancer therapeutics	232
Nanocarriers for simultaneous delivery of multiple anticancer agents	233
Combination delivery systems for nanoparticle penetration into tumor tissue	233
Combination of diagnostics and therapeutics for cancer	234
Biomimetic nanoparticles targeted to tumors	234
Dendrimer nanoparticles for targeting and imaging tumors	234
Gold nanoparticle plus bombesin for imaging and therapy of cancer	234
Gold nanorods for diagnosis plus photothermal therapy of cancer	234
Magnetic nanoparticles for imaging as well as therapy of cancer	235
Nanobialys for combining MRI with delivery of anticancer agents	235
Nanorobotics for detection and targeted therapy of cancer	236
pHLIP nanotechnology for detection and targeted therapy of cancer	236
Polymer nanobubbles for targeted and controlled drug delivery	237
Radiolabeled carbon nanotubes for tumor imaging and targeting	237
Targeted therapy with magnetic nanomaterials guided by antibodies	237
Ultrasonic tumor imaging and targeted chemotherapy by nanobubbles	238
Future of nanobiotechnology and targeted cancer therapy	238
Polyethylene glycol technology.....	238
Enzon's PEG technology	239
Debiopharm's PEG biconjugate drug delivery platform	239
Nektar PEGylation	240
PEG Intron	240
Single-chain antibody-binding protein technology.....	240
Vesicular systems for drug delivery in cancer.....	241
Liposomes for anticancer drug delivery	241

Antibody-targeted liposomes for cancer therapy	242
ALZA's Stealth liposomes	242
Boron-containing liposomes	242
DepoFoam technology	243
Hyperthermia and liposomal drug delivery	243
Liposomal doxorubicin formulation with N-octanoyl-glucosylceramide	243
Liposome-nucleic acid complexes for anticancer drug delivery	244
Non-pegilated liposomal doxorubicin	244
Tumor-selective targeted drug delivery via folate-PEG liposomes	244
Ultrasound-mediated anticancer drug release from liposomes	244
Companies developing liposome-based anticancer drugs.....	245
Pharmacosomes for controlled anticancer drug delivery	246
Emulsion formulations of anticancer drugs.....	246
Albumin-based drug carriers	247
Anticancer drugs that bind to tumors	247
Monoclonal T cell receptor technology	247
Radioactive materials for diagnosis and targeted radiotherapy	248
Intraperitoneal vs intravenous radioimmunotherapy	248
Peptide receptor radionuclide therapy	249
Pretargeted radioimmunotherapy of cancer	249
Radiolabeled somatostatin receptor antagonists.....	249
Theophylline enhances radioiodide uptake by cancer	250
Strategies for drug delivery in cancer	250
Direct introduction of anticancer drugs into the tumor	251
<i>Injection into the tumor.....</i>	251
<i>Antineoplastic drug implants into tumors</i>	252
<i>Tumor necrosis therapy</i>	252
<i>Injection into the arterial blood supply of cancer.....</i>	253
<i>Electrochemotherapy.....</i>	254
<i>Pressure-induced filtration of drugs across vessels to the tumor</i>	255
Improving drug transport to tumors	255
<i>Carbohydrate-enhanced chemotherapy.....</i>	255
<i>Dextrans as macromolecular anticancer drug carriers</i>	255
<i>In situ production of anticancer agents in tumors.....</i>	256
<i>Iotophoresis for localized delivery of cancer chemotherapy</i>	256
Strategies for increasing drug penetration into solid cancers	256
Selective destruction of cancer cells	257
<i>Hyperbaric oxygen</i>	257
<i>Sphingolipids.....</i>	257
<i>Targeting response to transformation-induced oxidative stress</i>	258
<i>Targeting enzymes to prevent proliferation of cancer cells.....</i>	258
Targeted drug delivery in cancer	258
<i>Affibody molecules for targeted anticancer therapy</i>	260
<i>Fatty acids as targeting vectors</i>	260
<i>Genetic targeting of the kinase activity in cancer cells</i>	261
<i>Heat-activated targeted drug delivery.....</i>	261
<i>Novel transporters to target photosensitizers to cancer cell nuclei</i>	262
<i>Photodynamic therapy of cancer</i>	262
<i>Radionuclides delivered with receptor targeting technology</i>	263
<i>Targeting ligands specific for cancer cells</i>	263
<i>Targeting abnormal DNA in cancer cells</i>	263
<i>Targeted delivery by tumor-activated prodrug therapy</i>	263
<i>Targeting glutathione S-transferase</i>	265
<i>Targeting tumors by exploiting leaky blood vessels</i>	266
<i>Targeted drug delivery of anticancer agents with controlled activation</i>	266
<i>Targeted delivery of anticancer agents with ReCODE™ technology</i>	266
<i>Transmembrane Carrier Systems</i>	267
<i>Transferrin-oligomers as targeting carriers in anticancer drug delivery.....</i>	267
<i>Tumor targeting with peptides.....</i>	267
<i>Tumor-targeted delivery of immune checkpoint inhibitors</i>	268
<i>Ultrasound and microbubbles for targeted anticancer drug delivery</i>	268
<i>Ultrasound for targeted delivery of chemotherapeutics</i>	269
<i>Vitamin B12 and folate for targeting cancer chemotherapy.....</i>	269
Cell-based drug delivery in cancer.....	270
<i>Red blood cells as vehicles for drug delivery</i>	271
<i>Cells as vehicles for gene delivery.....</i>	271
Drug delivery in relation to circadian rhythms.....	271
Implants for systemic delivery of anticancer drugs	272
<i>Drug-eluting polymer implants</i>	273
Angiogenesis and drug delivery to tumors	273
Antiangiogenesis strategies	274

<i>Targeting tumor endothelial cells</i>	274
<i>Methods for overcoming limitations of antiangiogenesis approaches</i>	275
<i>Vascular targeting agents</i>	275
<i>Alpha-emitting antibodies for vascular targeting</i>	276
<i>Angiolytic therapy</i>	276
<i>Anti-phosphatidylserine antibodies as VTA</i>	276
<i>Vadimezan</i>	277
<i>Cadherin inhibitors</i>	277
<i>Fosbretabulin tromethamine</i>	277
<i>Drugs to induce clotting in tumor vessels</i>	278
<i>Selective permeation of the anticancer agent into the tumor</i>	278
<i>Targeted delivery of tissue factor</i>	279
<i>Vascular targeting agents versus antiangiogenesis agents</i>	279
<i>ZD6126</i>	280
<i>Delivery of proteins and peptides for cancer therapy</i>	280
<i>CELLECTRA™ electroporation device</i>	281
<i>Emisphere's Eligen™ system</i>	281
<i>Diatos Peptide Vector intra-cellular/intra-nuclear delivery technology</i>	281
<i>Lytic peptides and cancer</i>	282
<i>Modification of proteins and peptides with polymers</i>	282
<i>Peptide-based targeting of cancer biomarkers for drug delivery</i>	283
<i>Peptide-cytokine complexes as vascular targeting agents</i>	283
<i>Peptide-polymer conjugates with radionuclides</i>	283
<i>Transduction of proteins in vivo</i>	284
<i>Tumor targeting by stable toxin (ST) peptides</i>	284
<i>Image-guided personalized drug delivery in cancer</i>	284
<i>A computational approach to integration of drug delivery methods for cancer</i>	284
4. Delivery of Biological Therapies for Cancer.....	287
Introduction	287
Antisense therapy	287
<i>Basics of antisense approaches</i>	287
<i>Antisense cancer therapy</i>	287
<i>Mechanisms of anticancer effect of antisense oligonucleotides</i>	288
<i>Selected antisense drugs in development for cancer</i>	288
<i>Antisense targeted to ribonuclease reductase</i>	288
<i>Immune modulatory oligonucleotide</i>	289
<i>Ribozyme therapy</i>	289
<i>Spiegelmers</i>	290
<i>Antisense drug delivery issues</i>	290
<i>Strategies to overcome delivery problems of antisense oligonucleotides</i>	291
<i>Antisense delivery in microspheres</i>	291
<i>Delivery of antisense using nanoparticles</i>	291
<i>Delivery across the blood-brain barrier</i>	292
<i>Delivery of ribozymes</i>	292
<i>Iontophoretic delivery of oligonucleotides</i>	292
<i>Liposomes-mediated oligonucleotide delivery</i>	293
<i>Neugene™ antisense drugs</i>	293
<i>Oral delivery of oligonucleotides</i>	293
<i>Peptide nucleic acid delivery</i>	294
<i>Receptor-mediated endocytosis</i>	294
<i>Delivery of ribozymes</i>	294
<i>Combination of antisense and electrochemotherapy</i>	295
<i>Aptamers for combined diagnosis and therapeutics of cancer</i>	295
<i>Antisense compounds in clinical trials</i>	296
RNA interference	296
<i>Basics of RNAi</i>	296
<i>Comparison of antisense and RNAi</i>	296
<i>RNAi applications in oncology</i>	297
<i>siRNA-based cancer immunotherapy</i>	298
<i>Delivery of siRNA in cancer</i>	299
<i>Delivery of siRNA by nanoparticles</i>	299
<i>Delivery of siRNA by nanosize liposomes</i>	299
<i>Lipid nanoparticles for delivery of anticancer siRNAs</i>	300
<i>Polymer nanoparticles for targeted delivery of anticancer siRNA</i>	301
<i>Lipophilic siRNA for targeted delivery to solid tumors</i>	302
<i>Companies developing cancer therapies based on antisense and RNAi</i>	302
DNA interference	303
Cancer gene therapy	303
<i>Basics of gene therapy</i>	303
<i>Strategies for cancer gene therapy</i>	304

Gene transfer techniques as applied to cancer gene therapy.....	305
<i>Viral vectors</i>	305
<i>Nonviral vectors</i>	306
<i>A polymer approach to gene therapy for cancer</i>	306
Direct gene delivery to the tumor	307
<i>Injection into tumor</i>	307
<i>Reversible electroporation</i>	308
Hematopoietic gene transfer	309
<i>Genetic modification of human hematopoietic stem cells</i>	309
Gene-based strategies for immunotherapy of cancer (immunogene therapy).....	310
<i>Cytokine gene therapy</i>	311
Monoclonal antibody gene transfer.....	314
Transfer and expression of intracellular adhesion-1 molecules	314
Other gene therapy techniques for immunotherapy of cancer	314
<i>Chemokines</i>	314
<i>Engineered viruses as anticancer immunotherapy vectors</i>	315
<i>Fas (Apo-1)</i>	315
<i>IGF (Insulin-Like Growth Factor)</i>	315
<i>Major Histocompatibility Complex (MHC) Class I</i>	315
Inhibition of immunosuppressive function	316
microRNA gene therapy	316
Delivery of toxic genes to tumor cells for eradication (molecular chemotherapy)	316
<i>Gene-directed enzyme prodrug therapy</i>	316
Combination of gene therapy with radiotherapy	317
Multipronged therapy of cancer with microencapsulated cells	318
Correction of genetic defects in cancer cells (mutation compensation)	318
Targeted gene therapy for cancer	319
<i>Transcriptional targeting for cancer gene therapy</i>	319
<i>Targeted epidermal growth factor-mediated DNA delivery</i>	319
<i>Gene-based targeted drug delivery to tumors</i>	320
<i>Targeting gene expression to hypoxic tumor cells</i>	320
<i>Targeting gene expression by progression-elevated gene-3 promoter</i>	321
<i>Targeted delivery of retroviral particles hitchhiking on T cells</i>	321
<i>Targeting tumors with genetically modified T cells</i>	321
<i>Targeting tumors by genetically engineered stem cells</i>	322
<i>Tumor-targeted gene therapy by receptor-mediated endocytosis</i>	322
<i>Targeted site-specific delivery of anticancer genes by nanoparticles</i>	322
<i>Immunolipoplex for delivery of p53 gene</i>	323
<i>Combination of electrogene and electrochemotherapy</i>	323
Virus-mediated oncolysis	323
<i>Targeted cancer treatments based on oncolytic viruses</i>	324
<i>Oncolytic gene therapy</i>	324
<i>Cancer terminator virus</i>	325
<i>Cytokine-induced killer cells for delivery of an oncolytic virus</i>	325
<i>Facilitating oncolysis by targeting innate antiviral response by HDIs</i>	326
<i>Oncolytic HSV</i>	326
<i>Oncolytic adenoviruses</i>	327
<i>Oncolytic Coxsackie virus A21</i>	328
<i>Oncolytic vesicular stomatitis virus</i>	329
<i>Oncolytic measles virus</i>	329
<i>Oncolytic paramyxovirus</i>	329
<i>Oncolytic reovirus</i>	330
<i>Oncolytic vaccinia virus</i>	330
<i>Synthetic oncolytic virus</i>	330
<i>Monitoring of viral-mediated oncolysis by PET</i>	331
<i>Companies developing oncolytic viruses</i>	331
Antiangiogenic therapy for cancer	332
Apoptotic approach to improve cancer gene therapy.....	333
Bacteria as novel anticancer gene vectors	333
Concluding remarks on cancer gene therapy	333
Cancer gene therapy companies	334
Cell therapy for cancer.....	336
Cellular immunotherapy for cancer.....	337
Treatments for cancer by ex vivo mobilization of immune cells	338
Granulocytes as anticancer agents	338
Neutrophil granulocytes in antibody-based immunotherapy of cancer	338
Use of hematopoietic stem cells for targeted cancer therapy	339
Cancer vaccines	339
Cell-based cancer vaccines.....	340
<i>Autologous tumor cell vaccines</i>	340
<i>Vaccines that simultaneously target different cancer antigens</i>	341

<i>Delivery systems for cell-based cancer vaccines</i>	341
<i>Intra-lymph node injections of cancer vaccine antigens</i>	341
Nucleic acid-based cancer vaccines	342
<i>Antiangiogenic DNA cancer vaccine</i>	342
<i>DNA cancer vaccines</i>	342
<i>Methods of delivery of DNA vaccines</i>	343
<i>RNA vaccines</i>	344
Viral vector-based cancer vaccines	344
Companies involved in nucleic acid-based vaccines	344
Genetically modified cancer cells vaccines	345
<i>GVAX cancer vaccines</i>	346
<i>Genetically modified dendritic cells</i>	346
Multipeptide-based cancer vaccines.....	346
5. Delivery strategies according to cancer type and location	349
Introduction	349
Bladder cancer.....	349
Intravesical drug delivery.....	349
Intravesical agents combined with systemic chemotherapy	349
Targeted anticancer therapy for bladder cancer	350
Prodrug EQuin for bladder cancer	350
Antisense treatment of bladder cancer.....	351
Gene therapy for bladder cancer	351
Brain tumors.....	351
Methods for evaluation of anticancer drug penetration into brain tumor	352
Innovative methods of drug delivery for glioblastoma	352
Delivery of anticancer drugs across the blood-brain barrier	353
<i>Anticancer agents with increased penetration of BBB</i>	353
<i>BBB disruption</i>	354
<i>Nanoparticle-based targeted delivery of chemotherapy across the BBB</i>	355
<i>Tyrosine kinase inhibitor increases topotecan penetration into CNS</i>	356
Bypassing the BBB by alternative methods of drug delivery.....	356
<i>Intranasal perillyl alcohol</i>	356
<i>Intraarterial chemotherapy</i>	356
Enhancing tumor permeability to chemotherapy	357
Local delivery of chemotherapeutic agents into the tumor	358
<i>Carmustine biodegradable polymer implants</i>	358
<i>Fibrin glue implants containing anticancer drugs</i>	358
<i>Biodegradable microspheres containing 5-FU</i>	359
<i>Magnetically controlled microspheres</i>	359
Convection-enhanced delivery	359
<i>CED for receptor-directed cytotoxin therapy</i>	359
<i>CED of topotecan</i>	360
<i>CED of a modified diphtheria toxin conjugated to transferrin</i>	360
<i>CED of nanoliposomal CPT-11</i>	360
<i>CED for delivery ¹³¹I-chTNT-1/B MAb</i>	361
Anticancer drug formulations for targeted delivery to brain tumors	361
<i>Intravenous delivery of anticancer agents bearing transferrin</i>	361
<i>Liposomes for drug delivery to brain tumors</i>	361
<i>MAbs targeted to brain tumors</i>	362
<i>Multiple targeted drugs for brain tumors</i>	362
<i>Nanoparticles for targeted drug delivery in glioblastoma</i>	363
<i>Aurora kinase B siRNA & lactoferrin nanoparticles with temozolomide</i>	364
<i>Targeted antiangiogenic/apoptotic/cytotoxic therapies</i>	364
<i>Targeted drug delivery to gliomas using cholera toxin subunit B</i>	365
Introduction of the chemotherapeutic agent into the CSF pathways.....	365
<i>Intraventricular chemotherapy for meningeal cancer</i>	365
<i>Intrathecal chemotherapy</i>	366
Interstitial delivery of dexamethasone for reduction of peritumor edema	366
Combination of chemotherapy with radiotherapy	367
Photodynamic therapy for chemosensitization of brain tumors	367
<i>Nanoparticles for photodynamic therapy of brain tumors</i>	367
Innovative delivery of radiotherapy to brain tumors	368
<i>GliaSite Radiation Therapy System</i>	368
<i>Boron neutron capture therapy for brain tumors</i>	368
Cell therapy for glioblastoma	369
<i>Chimeric antigen receptor T cells</i>	369
<i>Mesenchymal stem cells to deliver treatment for gliomas</i>	369
<i>Stem cell-based therapy targeting EGFR in glioblastoma</i>	369
Gene therapy for glioblastoma.....	369
<i>Antiangiogenic gene therapy</i>	371

<i>Anticancer drug delivery by genetically engineered MSCs.....</i>	371
<i>Gene transfer to brain tumor across the BBB by nanobiotechnology</i>	371
<i>Intracerebroventricular delivery of gene therapy for gliomas by NSCs.....</i>	371
<i>Intravenous gene delivery with nanoparticles into brain tumors</i>	372
<i>Ligand-directed delivery of dsRNA molecules targeted to EGFR</i>	372
<i>MSC-based gene delivery to glioblastoma</i>	373
<i>Neural stem cells for drug/gene delivery to brain tumors</i>	373
<i>Peptides targeted to glial tumor cells.....</i>	374
<i>RNAi gene therapy of brain cancer</i>	374
<i>Single-chain antibody-targeted adenoviral vectors</i>	375
<i>Targeting normal brain cells with an AAV vector encoding interferon-β.....</i>	375
<i>Treatment of medulloblastoma by suppressing genes in Shh pathway</i>	375
Virus-mediated oncolytic therapy of glioblastoma.....	376
<i>Clinical trials of viral oncolysis of glioblastoma</i>	377
<i>Oncolytic viral delivery by stem cells for brain metastases</i>	378
<i>Future of viral-mediated oncolysis.....</i>	379
Vaccination for glioblastoma.....	379
<i>Cell-based vaccines for glioblastoma</i>	379
<i>Peptide vaccines for glioblastoma.....</i>	379
<i>Poliovirus-based vaccine for glioblastoma.....</i>	380
Breast Cancer	381
Therapies for breast cancer involving innovative methods of drug delivery	382
Injectable biodegradable polymer delivery system for local chemotherapy	382
MammoSite brachytherapy.....	382
Monoclonal antibodies targeted to HER2 receptor.....	383
Breast cancer vaccines	383
<i>HER-2 DNA AutoVac™ vaccine</i>	384
<i>Recombinant adenoviral ErbB-2/neu vaccine</i>	384
<i>Gene vaccine for breast cancer</i>	385
<i>NeuVax.....</i>	385
Gene therapy for breast cancer.....	386
Antisense therapy for breast cancer	386
Inhibitors of growth factors FGF2 and VEGF for breast cancer.....	387
Targeted multi-drug delivery approach to breast cancer.....	387
Cancer of the cervix and the uterus	387
Gene therapy for cervical cancer.....	387
Delivery of chemoradiation therapy	387
Cervical cancer vaccines	388
Cancer of the liver	388
Hepatocellular carcinoma	388
Treatment of liver metastases	389
Gastrointestinal cancer	390
Colorectal cancer	390
<i>Oxaliplatin long-circuting liposomes</i>	390
<i>Perifosine.....</i>	390
<i>Targeted delivery of triple anticancer therapy by local patch.....</i>	391
Gastrointestinal stromal tumor	391
Vaccines for gastrointestinal cancer.....	391
Hematological malignancies	391
Leukemia.....	391
<i>Clofarabine</i>	392
<i>Ibrutinib</i>	393
<i>Idelalisib for CLL.....</i>	393
Multiple myeloma.....	393
<i>Monoclonal antibody therapy in multiple myeloma</i>	393
Non-Hodgkin's lymphoma	394
<i>Idelalisib for NHL</i>	394
<i>Pixantrone</i>	394
<i>Rituximab after autologous stem-cell transplantation.....</i>	394
Malignant melanoma	395
Targeted therapies for melanoma	395
Immunotherapy for malignant melanoma	396
Gene therapy for malignant melanoma	396
Nasopharyngeal carcinoma.....	398
Synergistic effect of gene therapy with 5-FU	398
Neuroblastoma	399
Genetically modified NSCs for treatment of neuroblastoma	399
Non-small cell lung cancer.....	399
Aerosol delivery of anticancer agents for lung cancer.....	400
Aerosol gene delivery for lung cancer	401
Complex nanoscale pulmonary delivery of drugs for resistant lung cancer	401

Intratumoral administration of anticancer drugs through a bronchoscope.....	402
Ovarian cancer.....	402
Dendritic cell vaccination for ovarian cancer	402
Gene Therapy for ovarian cancer	402
Innovative drug delivery for ovarian cancer.....	403
Intravenous ascorbate for ovarian cancer.....	404
Intrapерitoneal delivery	404
Intrapерitoneal hyperthermic chemotherapy in ovarian cancer.....	405
Modulation of protein ubiquitination	405
Targeting Notch pathway to overcome resistance to chemotherapy.....	405
Pancreatic cancer	406
Delivery of chemotherapy for pancreatic cancer	406
<i>Local drug delivery</i>	406
<i>Localized drug delivery by iontophoresis</i>	406
<i>Nanoparticle-based delivery of tumor-penetrating peptides</i>	407
<i>Targeted chemotherapy for pancreatic cancer</i>	407
<i>Transport properties of pancreatic cancer and gemcitabine delivery</i>	407
Vaccine for pancreatic cancer	408
Gene therapy for pancreatic cancer	408
<i>Correction of altered genes</i>	408
<i>Targeted gene therapy</i>	409
<i>Targeting in pancreatic adenocarcinoma with cell surface antigens</i>	409
<i>Targeted Expression of BikDD gene</i>	409
<i>Viral oncolysis in pancreatic cancer</i>	409
Prostate cancer.....	410
Alpha emitter radium-223 for targeting bone metastases in cancer	411
Brachytherapy for cancer of prostate.....	411
<i>Brachytherapy via paravertebral approach lymph node metastases</i>	411
Capridine-beta.....	411
LHRH for prostate cancer	412
<i>LHRH analogs</i>	412
<i>Histrelin implant</i>	412
Immunomodulatory drugs.....	412
MAbs for prostate cancer	412
PACLIMER Microspheres.....	413
PRX302	413
Targeted therapies for prostate cancer	414
<i>Delivery of cisplatin to prostate cancer by nanoparticles</i>	414
<i>Delivery of siRNAs to prostate cancer with aptamer-siRNA chimeras</i>	414
<i>Delivery of siRNA for prostate cancer with metastases</i>	414
<i>Gold nanoparticles targeted to laminin receptor in prostate cancer</i>	414
<i>PSA-activated protoxin that kills prostate cancer</i>	415
<i>Targeted delivery of a nanoparticulate platinum prodrug</i>	415
<i>Targeting oncogene MDM2 in prostate cancer</i>	415
<i>Vascular targeting of prostate cancer</i>	416
Gene therapy for cancer of prostate	416
<i>Experimental studies</i>	416
<i>Nanoparticle-based gene therapy for prostate cancer</i>	416
<i>Tumor suppressor gene therapy in prostate cancer</i>	417
<i>Vaccines for prostate cancer</i>	417
<i>Clinical trials of gene therapy for prostate cancer</i>	418
Viral oncolysis for prostate cancer	419
Combined approaches	419
<i>Combined autovaccination and hyperthermia</i>	419
Thyroid cancer	420
6. Cancer drug delivery markets	421
Introduction	421
Global markets for drug delivery	421
Estimation of cancer drug delivery markets	421
<i>Methods used for market estimation</i>	421
<i>Cancer epidemiology</i>	422
<i>Cost of patient care in cancer</i>	423
Market forecasts 2019-2029	424
Cancer drug market	424
<i>Market for leukemia</i>	425
<i>Market for lymphoma</i>	425
<i>Markets for brain tumors</i>	425
<i>Market for breast cancer</i>	426
<i>Market for ovarian cancer</i>	426
Geographical distribution of cancer markets	426

Factors affecting future cancer markets	426
Market share according to cancer drug delivery technologies.....	427
Antiangiogenesis therapies.....	427
Antibody drug conjugates	428
Antineoplastic drug implants for systemic administration	428
Antisense therapy and RNAi	428
Cancer vaccines.....	428
Cell/gene therapy	429
Liposomes for anticancer drugs	429
Monoclonal antibodies	429
Modulators of protein ubiquitination	430
Strategic aspects of cancer drug delivery	430
Unmet needs in cancer drug delivery.....	430
Future of cancer drug delivery.....	431
Cancer drug delivery and pharmacogenomics	431
Cancer immunotherapy markets	432
Drug delivery for cancer in the postgenomic era	432
Role of nanobiotechnology in development of cancer drug delivery markets	432
Expansion of cancer drug delivery markets in developing countries	432
Drivers for the development of drug delivery technologies in cancer.....	432
7. References.....	435

Tables

Table 1-1: Estimated new cases of cancer in the US at most involved organs – 2017	52
Table 1-2: Historical landmarks in drug delivery for cancer	55
Table 2-1: Innovative strategies against cancer.....	58
Table 2-2: A classification of antiangiogenic therapies	61
Table 2-3: Selected antiangiogenic agents in development for cancer.....	67
Table 2-4: Approaches to cancer therapy based on bacteria	69
Table 2-5: Cell therapy technologies used for cancer	77
Table 2-6: Classification of various therapeutic approaches to cancer immunotherapy	81
Table 2-7: Non-nucleic acid cancer vaccines without genetic modification	91
Table 2-8: Monoclonal antibodies for cancer approved by the FDA	109
Table 2-9: Anticancer agents linked to monoclonal antibodies	113
Table 2-10: Monoclonal antibodies in clinical trials for cancer	116
Table 2-11: Antibody drug conjugates in clinical trials for cancer	123
Table 2-12: Third generation boron delivery agents currently under investigation	127
Table 2-13: Cellular pathways as targets for anticancer therapies	135
Table 2-14: Examples of anticancer agents that target mitochondrial membranes.....	136
Table 2-15: Drugs targeting oncogenes	141
Table 2-16: PARP inhibitors for cancer therapy	162
Table 2-17: Cancer therapies based on the P53	168
Table 2-18: Promise of personalized therapy in cancer	172
Table 2-19: Companies developing personalized therapy for cancer	172
Table 3-1: Routes of drug delivery in cancer	178
Table 3-2: Systemic intravenous drug delivery systems for chemotherapy of cancer	178
Table 3-3: Approved oral chemotherapy drugs	180
Table 3-4: Microparticles as therapeutic delivery systems in cancer	194
Table 3-5: Classification of nanobiotechnology approaches to drug delivery in cancer.....	198
Table 3-6: Approved anticancer drugs using nanocarriers	199
Table 3-7: Clinical trials of anticancer drugs using nanocarriers	199
Table 3-8: Marketed preparations for liposome-based anticancer drugs	245
Table 3-9: Clinical trials of liposome-based anticancer drugs	245
Table 3-10: Strategies for drug delivery in cancer	250
Table 3-11: Implant systems for delivery of anticancer drugs into tumors.....	252
Table 3-12: Targeted delivery of anticancer therapeutics	259
Table 3-13: Methods of delivery of antiangiogenesis therapies.....	274
Table 3-14: Companies developing vascular targeting agents	275
Table 4-1: Mechanisms of anticancer effect of antisense oligonucleotides	288
Table 4-2: Methods of delivery of oligonucleotides for cancer therapy	290
Table 4-3: Antisense oligonucleotides in clinical trials for cancer	296
Table 4-4: Companies developing antisense and RNAi therapies for cancer	302
Table 4-5: Strategies for cancer gene therapy	304
Table 4-6: Enzyme/prodrug combinations employed in suicide gene therapy	317
Table 4-7: Mutation compensation strategies used clinically	318
Table 4-8: Companies developing oncolytic viruses	331
Table 4-9: Companies involved in cancer gene therapy	334
Table 4-10: Cell therapy technologies used for cancer	337

Table 4-11: Companies developing nucleic acids/genetically modified cells-based cancer vaccines	344
Table 5-1: Innovative methods of drug delivery for glioblastoma	352
Table 5-2: Strategies for gene therapy of malignant brain tumors.....	370
Table 5-3: Clinical trials of virotherapies for glioblastoma	378
Table 5-4: Therapies for breast cancer involving innovative methods of drug delivery	382
Table 5-5: Drug delivery for hepatocellular carcinoma	388
Table 5-6: Gene therapy for malignant melanoma	397
Table 5-7: Targeted treatment of non-small cell lung cancer	400
Table 5-8: Clinical trials of gene therapy in ovarian cancer.....	403
Table 5-9: Methods of drug delivery in pancreatic cancer.....	406
Table 5-10: Pharmacological strategies under investigation for cancer of the prostate	410
Table 5-11: Clinical trials of gene therapy for prostate cancer	418
Table 6-1: Worldwide drug delivery market growth 2020 to 2030	421
Table 6-2: Worldwide prevalence of cancer according to type of cancer 2020-2030.....	422
Table 6-3: Estimated number of cancer patients in major markets 2020-2030	423
Table 6-4: Worldwide anticancer drug sales for from 2020 to 2030	425
Table 6-5: Geographical distribution of cancer markets 2020-2030	426
Table 6-6: Market values of cancer drug delivery technologies from 2020-2030.....	427

Figures

Figure 1-1: Structure of PD-1 pathway	25
Figure 1-2: Signaling pathway changes during adaptation of cancer cell to hypoxia.....	34
Figure 1-3: Nitric oxide: tumor enhancement or inhibition	37
Figure 1-4: Role of nitric oxide in angiogenesis.....	41
Figure 1-5: An overview of some key steps in tumor angiogenesis.....	47
Figure 2-1: Targeting tumors with light-emitting engineered bacteria.....	71
Figure 2-2: Enhancing tumor-cell visibility to the immune system by viral mimicry	105
Figure 2-3: Schematic role of T helper cells in immune response to cancer	94
Figure 2-4: G-MAB™ technology	120
Figure 2-5: Antimetabolic anticancer effect of SR9243 by inhibiting Warburg effect.....	166
Figure 3-1: Cyclacel's Penetratin Transport System for delivery of drugs to targets.....	190
Figure 3-2: Linker Activated Drug Release	192
Figure 3-3: Micelle for drug delivery in cancer	204
Figure 3-4: Targeted drug delivery with QA-NPs via peritumoral blood vessels	223
Figure 3-5: Mechanism of action of Targaceutical drugs.....	260
Figure 3-6: VIADUR leuproreotide acetate using DUROS implant technology	273
Figure 4-1: Mechanism of action of oncolytic viruses	324
Figure 5-1: A concept of targeted drug delivery to GBM across the BBB	355
Figure 5-2: Mechanism of antitumor effects of poliovirus-based vaccine for glioblastoma.....	381
Figure 6-1: Unmet needs in cancer drug delivery	431