

Contents

Preface *xiii*

Part I History of Breast Cancer 1

1 Early-Stage Diagnosis of Breast Cancer: Amelioration in Approaches 3

Nidhi Manhas, Lalita S. Kumar, and Vinayak Adimule

- 1.1 Introduction 3
- 1.2 Imaging Techniques 4
 - 1.2.1 Mammography (MG) 4
 - 1.2.2 Ultrasonography (US) 7
 - 1.2.3 Magnetic Resonance Imaging (MRI) 8
- 1.3 Microwave Breast Imaging Methods 10
 - 1.3.1 Microwave Tomography 11
 - 1.3.2 Radio-Based Microwave Imaging 12
- 1.4 Biomarkers and Biosensors for Breast Cancer Detection 14
 - 1.4.1 Biomarkers 15
 - 1.4.1.1 Nucleic Acids 15
 - 1.4.1.2 Proteins 15
 - 1.4.1.3 Tumor Cells 16
 - 1.4.2 Biosensors 16
 - 1.4.2.1 Electrochemical Biosensors 16
 - 1.4.2.2 Optical Sensors 17
- 1.5 Conclusion 19
- Acknowledgment 20
- References 20

2 DNA Replication Stress and Genome Instability in Breast Cancer 35

Kirti Sinha, Pau B. Sang, Priyanka Sharma, and Rishi K. Jaiswal

- 2.1 Introduction 35
- 2.2 Causes of Replication Stress and Genomic Instability 36
 - 2.2.1 Replication Dysfunction 36

2.2.1.1	Low and Untimely Initiation of Replication	36
2.2.1.2	Replication Fork Maintenance	37
2.2.1.3	Mitotic Defects	38
2.2.2	Transcription-Induced Stress	40
2.2.2.1	Failed Post-Replication Repair	40
2.2.3	Genomic Aberrations and Instability	40
2.2.3.1	Site-Specific Hotspots	40
2.2.3.2	Amplifier Genome	41
2.2.3.3	Replication in Inappropriate Metabolic Conditions	41
2.3	Molecular Mechanism of Genomic Instability	42
2.3.1	Problems Faced During DNA Damage Repair	43
2.3.2	Transcriptional Stress	44
2.3.3	CIN: Result of Defective Mitosis	45
2.4	Aftermath of Replication Stress on Cell and Its Fate	46
2.4.1	Conservation of Stalled Replication Forks	46
2.4.2	Chromosome Segregation Defect Check by HR Repair	47
2.4.3	Aging, Cell Death, and Senescence	47
2.5	Therapeutic Approach	48
2.6	Conclusion	50
	References	51

3 Recent Advancement of Nanotherapeutics to Treat Breast Cancer 65

Devesh U. Kapoor, Rajat Goyal, Rajiv R. Kukkar, and Rupesh K. Gautam

3.1	Introduction	65
3.2	Pathophysiology of Breast Cancer	66
3.3	Classification of Breast Cancer	66
3.4	Techniques for Breast Cancer Detection	68
3.5	Current Breast Cancer Therapies	68
3.6	Nanotherapeutics for Breast Cancer Treatment and Metastasis	69
3.6.1	Nanodiamonds (NDs)	69
3.6.2	Intrinsic Toxicity Reduction	69
3.6.3	Diminishing Chemoresistance (CR)	70
3.6.4	Delivery of Combination Therapeutics Through NDs	70
3.7	Polymer-Based Nanoparticles (PBNPs)	71
3.8	Inorganic Nanoparticles (IONPs)	72
3.9	Hydrogels (HGLs) and Microbubbles (MBs)	74
3.10	Recent Patents of Nanotherapeutics for Breast Cancer Treatment	76
3.11	Clinical Trials of Nanotherapeutics for Breast Cancer	76
3.12	Conclusion and Future Perspectives	77
	References	78

4	HER Receptor in Breast Cancer	85
	<i>Guno S. Chakraborty</i>	
4.1	Introduction	85
4.2	Role of HER Receptors in the Human Body	86
4.3	HER2 Receptor in Breast Cancer Progression	88
4.4	Conclusion	88
	References	89
5	Human Endogenous Retroviruses in Triple-Negative Breast Cancer	93
	<i>Tara P. Hurst, Timokratīs Karamitros, and Gkikas Magiorkinis</i>	
5.1	Introduction	93
5.2	HERVs in Breast Cancer and TNBC	95
5.3	TROJAN lncRNA and TNBC	96
5.4	HERVs and Breast Cancer Treatments	97
5.5	Conclusion	97
5.6	Search Strategy	97
	References	98
 Part II Novel Drug Discovery and Development 103		
6	Development in Drug Repurposing for the Treatment of Acute Leukemia Complicating Metastatic Breast Cancer	105
	<i>Nilophar M. Shaikh, Vinayak Adimule, and Santosh Nandi</i>	
6.1	Introduction	105
6.1.1	Acute Leukemia's	107
6.1.2	Mitochondrial cAMP–PKA Signaling	110
6.1.3	Nuclear Compartment	110
6.1.4	Cytosolic Compartment and Plasma Membrane	110
6.2	Conclusion	111
	References	111
7	Novel Pharmaceutical Nanomaterials to Advance the Current Breast Cancer Treatment – Current Trends and Future Perspective	117
	<i>Steven Mufamadi, Mpho Ngoepe, Aidan Battison, and Itumeleng Zosela</i>	
7.1	Introduction	117
7.2	Graphene-Based Nanomaterials for Breast Cancer	119
7.3	Light-Based Nanotechnology for Breast Cancer	120
7.3.1	Photodynamic Therapeutic Nanomaterials	120

7.3.2	Photothermal Therapeutic Nanomaterials	122
7.4	Green Synthesis of Gold Nanoparticles for Breast Cancer	122
7.5	Nanocarriers for Gene Therapy and Immunotherapy	124
7.6	Conclusion and Recommendations	125
	References	125

Part III Advanced Technologies in Breast Cancer Therapy 131

8 Artificial Intelligence-Driven Decisions in Breast Cancer Diagnosis 133

Amit Gangwal and Rupesh K. Gautam

8.1	Introduction	133
8.2	Breast Cancer	135
8.3	Diagnosis of Breast Cancer	136
8.4	Artificial Intelligence	138
8.4.1	Artificial Intelligence and Medical Imaging	140
8.5	Conclusion	142
8.6	Future Challenges	142
	References	144

9 Establishing Nanotechnology-Based Drug Development for Triple- Negative Breast Cancer Treatment 153

Ravinder Verma, Shailendra Bhatt, Rohit Dutt, Manish Kumar, Deepak Kaushik, and Rupesh K. Gautam

9.1	Introduction	153
9.2	Triple-Negative Breast Cancer	154
9.2.1	Molecular Mechanisms (Signaling Pathways) Involved in TNBC Therapeutics	156
9.2.1.1	Notch Signaling Pathway	156
9.2.1.2	Hedgehog Signaling Pathway	156
9.2.1.3	Wnt/ β -Catenin	156
9.2.1.4	Poly(ADP-Ribose) Polymerase (PARP) Inhibitors	157
9.2.1.5	EGFR	157
9.2.1.6	Mammalian Target of Rapamycin (mTOR) Inhibitors	157
9.2.1.7	TGF- β Signaling Pathway	158
9.2.1.8	CSPG4 (Chondroitin Sulfate Proteoglycan) Protein Signaling Pathway	158
9.2.2	Conventional Therapeutics	158
9.2.3	Promising Nanotechnology Innovations for TNBC Therapy	159
9.2.3.1	Nanoparticles (NPs)	160
9.2.3.2	Nanoconjugates	162
9.2.3.3	Quantum Dots (QDs)	162
9.2.3.4	Nano-Diamonds (NDs)	162
9.2.3.5	Nanocomposites	163

9.2.3.6	Nano-Matryoshkas	163
9.2.3.7	Polymeric Micelles (PM): A Miracle Ball in Cancer Therapy	163
9.2.3.8	Dendrimers	163
9.2.3.9	Folded Graphene: Carbon nanotubes (CNTs)	164
9.2.3.10	Virus-Like Particles (VLPs) as Novel Nanovesicles	164
9.2.3.11	Liposomes	164
9.2.4	Vaccines Under the Clinical Trial (CT) for TNBC Treatment	165
9.2.4.1	Peptide-Based Vaccines	166
9.2.4.2	Viral Vector-Based Vaccines	166
9.2.4.3	Gene-Based Vaccines	166
9.2.5	USFDA-Approved Clinical Trials	166
9.2.6	Current Status of TNBC Treatment	167
9.2.7	Recent Patents Based on Nanoformulations for TNBC Treatment	167
9.3	Challenges	168
9.4	Future Perspectives on TNBC Metastasis Therapy	168
9.4.1	NEO Adjuvant Modeling	169
9.4.2	Execution of <i>In Vivo</i> Genetic Screening	169
9.4.3	Identification of Effective Drugs for TNBC	169
9.4.4	Synergistic Effect of Drugs that Almost Eliminate Tumor	169
9.5	Conclusion	169
	References	170

10 Etiology and Therapy of Hormone Receptor-Positive Breast Cancer 181

Nalini Kurup and Darshana Warekar

10.1	Introduction	181
10.2	Etiology	182
10.2.1	Role of Estrogen Hormone	182
10.2.2	Role of Progesterone Hormone	182
10.2.3	Estrogen Receptor (ER)	183
10.2.4	Progesterone Receptor (PR)	184
10.3	Human Epidermal Growth Factor-2 (HER-2)	184
10.4	Various Types of Breast Cancer Detected Under Hormone Receptor Breast Cancer	185
10.4.1	Estrogen Receptor (ER) Positive	185
10.4.2	Progesterone Receptor (PR) Positive	185
10.4.3	Hormone Receptor (HR) Negative	185
10.5	Detection	186
10.6	Therapy	187
10.6.1	Selective Estrogen-Receptor Response Modulators (SERMs)	188
10.6.2	Aromatase Inhibitors	188
10.6.3	Estrogen-Receptor Down Regulators (ERDs)	188
10.6.4	Luteinizing Hormone-Releasing Hormone Agents (LHRH)	189
10.7	Limitations of Hormone Therapy	190
10.7.1	Tamoxifen	190

10.7.2	Raloxifene	190
10.7.3	Aromatase Inhibitors	190
10.7.4	Fulvestrant	191
10.8	Triple-Negative Breast Cancer	191
10.8.1	Clinical History of Triple-Negative Breast Cancer	191
10.8.2	Imaging Characteristics/Features of Triple-Negative Breast Cancer	191
10.8.3	Subtypes of TNBC	192
10.8.3.1	Basal-Like Subtype: (i) BL1 (ii) BL 2	192
10.8.3.2	Claudine Low Subtype	192
10.8.3.3	Immunomodulatory Subtype (IM)	192
10.8.3.4	Mesenchymal Subtype (M)	192
10.8.3.5	Mesenchymal Stem-Like Subtype (MSL)	192
10.8.3.6	Luminal Androgen Receptor Subtype (LAR)	193
10.8.4	Treatment of Triple-Negative Breast Cancer	193
10.8.5	Advance TNBC	193
10.8.6	Pharmacogenomics	194
10.9	Conclusion	195
	References	196
11	Donor–Acceptor-Based Heterocyclic Compounds as Chemotherapy and Photothermal Agents in Treatment of Breast Cancer Cell	201
	<i>Vinayak M. Adimule, Sheetal R. Batakurki, Maya M. Pai, and Santosh Nandi</i>	
11.1	Introduction	201
11.2	Causes for Breast Cancer	202
11.3	Imaging and Screening of Breast Cancer	202
11.4	Photothermal Therapy (PTT)	203
11.5	Acceptor–Donor-Based Heterocyclic Compounds	208
11.6	Examples of Organic-Based Donor–Acceptor	210
11.6.1	Indocyanine	210
11.7	Polymers-Based Agents	211
11.7.1	Phthalocyanine	211
11.8	Conclusion	212
	References	213

Part IV Regulatory, Clinical Aspects and Case Studies 221

12	An Insight into Drug Regulatory Affairs and the Procedures	223
	<i>Shaik A. Begum and Joshna Rani S</i>	
12.1	Endpoints of Clinical Trials for the Approval of Cancer Drugs and Biologics	223
12.2	Statutory and Regulatory Requirements for Effectiveness	223
12.2.1	Endpoints Supporting Previous Oncology Approvals	224
12.2.2	Endpoints Based on Tumor Assessments	225

12.2.3	Clinical Practice Guideline for the Diagnosis, Staging, and Treatment of Patients with Metastatic Breast Cancer	225
12.2.4	Cancer Drug and Diagnostic Regulation by the FDA	226
12.2.5	Considerations for Clinical Trial Design and Analysis	227
12.2.6	Single-Arm Studies	227
12.2.7	Randomized Studies Designed to Demonstrate Noninferiority	227
12.3	Clinical Trial Design Considerations	228
12.4	Clinical Trial Analysis Issues	228
12.5	Use of Pathological Complete Response as an Endpoint to Support Accelerated Approval in Neoadjuvant Treatment of High-Risk Early-Stage Breast Cancer	228
12.6	Developing Treatments for Premenopausal Women with Breast Cancer	229
12.7	Recommendations by FDA	230
12.7.1	Access to Experimental Cancer Drugs	230
12.7.2	How to Get a Hold of an Experimental Drug	230
12.7.3	Access to More Information (Compassionate Use)	231
12.8	What is Right to Try?	231
12.9	Examples of Drugs Approved for Breast Cancer	232
	References	233
13	A Comprehensive Review of Some Heat-Shock Proteins in the Development and Progression of Human Breast Cancer	237
	<i>Xolani H. Makhoba and Ofentse J. Poore</i>	
13.1	Introduction	237
13.1.1	Cancer and Its Economic Burden on Human	238
13.2	Structure-Functional Features of HSPs	239
13.2.1	Heat-Shock Protein 40	239
13.2.2	Heat-Shock Protein 60	239
13.2.3	Heat-Shock Protein 70	240
13.2.4	Heat-Shock Protein 90	241
13.3	Conclusion and Future Perspectives	242
	Acknowledgments	244
	References	244
14	Nanoparticle-Based Therapeutics for Triple Negative Breast Cancer	249
	<i>Isidore A. Egebe and Kamalinder K. Singh</i>	
14.1	Breast Cancer: State of Research and Practice	249
14.2	Triple Negative Breast Cancer (TNBC) and Treatment Approaches	252
14.3	Nanoparticle Therapeutics for TNBC	253
14.3.1	Metallic Nanoparticles	255
14.3.1.1	Gold Nanoparticles (AuNPs)	255
14.3.1.2	Silver Nanoparticles (AgNPs)	255
14.3.2	Dendrimers	255

14.3.3	Lipid-Based Nanoparticles (LNPs)	256
14.3.3.1	Liposomes	256
14.3.3.2	Nanoemulsions (NEs)	258
14.3.3.3	Solid Lipid Nanoparticles (SLNs)	259
14.3.3.4	Nanostructured Lipid Carriers (NLCs)	259
14.3.3.5	Lipid Polymer Hybrid Nanoparticles (LPH-NPs)	260
14.3.4	CRISPR Nanoparticles	261
14.3.5	Exosomes (Exo)	261
14.3.6	Nucleic Acid (NAs)-Based Therapeutics	262
14.4	Ligands Used to Enhance Nanoparticle Therapeutics in TNBC	262
14.4.1	Antibodies	262
14.4.2	Peptides	262
14.4.3	Aptamers	263
14.4.4	Small Molecules	263
14.5	Conclusion	263
	References	264

15 Current Updates in Breast Cancer Drugs 273

Nitu L. Wankhede, Mayur B. Kale, Pranali A. Chandurkar, Manish M. Aglawe, Ashwini K. Bawankule, Brijesh G. Taksande, Milind J. Umekar, Rupesh K. Gautam, and Aman B. Upaganlawar

15.1	Introduction	273
15.2	Therapeutic Approaches	274
15.2.1	Hormonotherapy	275
15.2.2	Chemotherapy	276
15.3	Targeted Therapy	276
15.3.1	Drug Repurposing	276
15.3.2	HER2 Inhibitors	278
15.3.3	PARP Inhibitors	280
15.3.4	Immunotherapy	280
15.3.5	Others Novel Targets	281
15.3.5.1	Histone Deacetylase (HDAC) Inhibitors	281
15.3.5.2	Angiogenesis Inhibitors	281
15.4	Conclusion	284
	Acknowledgment	284
	References	285

Index 295