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Gastrointestinal cancers are a group of cancers that affect the digestive system and include gastric cancer, colorectal cancer, liver cancer, esophageal cancer, and pancreatic cancer. GI cancers are the leading health problem in the world and their burden is increasing in many countries. This heavy burden is due to the lack of effective early detection methods and to the emergence of chemoradioresistance. Attempts at improving the outcome of GI cancers by incorporating cytotoxic agents such as chemo drugs have been so far disappointing. These results indicate that the main challenge remains in the primary resistance of GI cancer cells to chemotherapy in the majority of patients. Therefore, improvement in the outcomes of these malignancies is dependent on the introduction of new agents that can modulate the intrinsic and acquired mechanisms of resistance.

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Recent Advancements in Biomarkers and Early Detection of Gastrointestinal Cancers

Springer

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Preface

In cancer, the novel biomarkers include substances produced by the cancer tissue or by other cells reacting to cancer in the body. They can be predominantly helpful in detecting and diagnosing, predicting responses to therapy, tracking treatment results or cancer growth, and finally determining whether a cancer has returned subsequent remission. There are three main tests: (1) Genetic tests search for abnormal changes and mutations, together with extra, missing, or erroneously placed genes. (2) Biochemical tests determine if there are too many proteins or if proteins are overactive. (3) Karyotyping identifies abnormal changes within chromosomes.

Gastrointestinal cancers (GI) signify an essential portion of global public health concern with millions of deaths annually. GI cancers are biologically and genetically heterogeneous, with a poorly understood carcinogenesis at the molecular level. Although cancer incidence is declining, the outcome of patients with GI cancers remains hugely dismal. Thus, detection at an early stage utilizing functional screening approaches, selection of an appropriate treatment plan, and effective monitoring is fundamental to reduce GI cancer mortalities. Nonetheless, there have been tremendous advancements in the multidisciplinary management of GI cancers in the past decade. The growing number of new and improved targeted agents and efficacious combination regimens yielding substantial clinical benefits at both early and late stages of the disease proved this. Moreover, breakthroughs in molecular profiling, cancer immunology, early stage detection, and novel diagnostic techniques have led to accelerated strides in GI cancer research. As the field of GI malignancies is continuously evolving, community oncologists must strive hard to keep abreast of the latest developments in novel biomarker research and resolve new issues in optimizing the management and detection of GI cancers.

In the field of cancer biology, the researchers continue to make noteworthy and exhilarating contributions to understand the fundamental biology of the GI cancers. Yet, the practical translational applications of this fascinating and enthralling area of science is little disappointing with regard to the recurrent viral outbreaks. These events underscore the need for concerted efforts to develop and implement new interventions while continuing to invest in proven public health measures.

Considering the high mortality rate, tremendous effort has been directed to address the urgent need for the discovery of effective early diagnostic tools, efficient therapeutic targets, and treatment monitoring markers for GI malignancies.

Biomarkers are one of the favorite tools with several potential applications in various aspects of clinical management of cancers. The biomarkers in GI cancer research primarily focus on the patient's unique clinical characteristics. Additionally, they facilitated the researchers and healthcare professionals to better support GI cancer patients through (1) understanding how to prevent different diseases, (2) diagnosing the sternness or stage of an illness, (3) helping to inform a patient with treatment options, and (4) determining the probability if the disease returns. However, the identification of biomarkers and continuing discovery of new ones mark the clear evolution of how clinicians and patients can effectively determine personalized treatments. Therefore, identification of novel biomarkers on the basis of clinical information (serology, metabolic and biochemical data) is mandatory, and furthermore comprehensive genome analysis could undeniably improve the diagnosis, prognosis, prediction of recurrence, and treatment response for GI cancers.

A plethora of biomarkers have been previously studied in GI cancers, of which only a handful have found their way from bench to bed. Nonetheless, there is a growing list of emerging markers with promising clinical results that need to be validated for routine clinical applications, and current data are insufficient to recommend them as part of the clinical guidelines. Biomarkers must be rigorously tested and validated in clinical studies. Biomarker research also needs to be interpreted carefully, so that the patients are not excluded from receiving potentially helpful medicines. Despite of various challenges associated with the discovery of novel biomarkers and testing for clinical studies, biomarkers are deemed to be critical components of cancer research.

The scientific advances are producing potential new biomarkers for the early detection of cancer and improved disease management. Advances in genomics, proteomics, and molecular pathology have produced many candidate biomarkers with the potential to impact clinical care for GI cancers. These novel biomarkers particularly emphasizes the early detection of cancer, prediction of disease outcomes, and how the methods for such discovery are being used in personalized medicine. Understanding the basic biology of cancer and identifying new biomarkers could be critical for the growth and progression of particular GI cancers. Also finding new biomarkers for GI cancers could be of great value in the effort to determine which pathways are important to target the new investigational research.

We affirm that this book would provide enough insights into the current understanding of the prognosis and prediction of biomarkers by profiling microRNA, circulating microRNAs, serum microRNA, and plasma microRNA for diagnosing early onset of gastric cancer. This book is an attempt to compile the novel information available on recent advancements on the breakthrough technologies such as ultra-sensitive nanochip, nanosensors, nanodevices, biosensors, electrochemical biosensors, optical biosensors, and DNA biosensors for the early diagnosis of gastrointestinal cancer. The book also elucidates a comprehensive yet a representative description of a large number of challenges associated with the discoveries and the

role of molecular and biochemical biomarkers akin to volatile biomarkers, serum biomarkers, predictive and prognostic molecular markers for the early detection of gastrointestinal cancers. This book could be an essential reading for the novice and experts in the field of cancer biology, cancer immunodiagnostics, including latest developments in biomarker research. With these objectives in mind, the content of this textbook has been arranged in a logical progression from fundamental to more advanced concepts. Finally, this book also outlines the most advanced biomarker techniques used in diagnostics of GI cancers and also primarily focuses on advancements of biomarker development research and management. Development of these biomarkers in the field of cancer treatment is expected to greatly contribute to the progress of cancer, selection of appropriate therapeutic strategies, and efficient follow-up programs.

We hope that this book stimulates your creativity and wishes you success in your experiments. This book is a stunning reflection of the seriousness with which the several scientific minds are dedicated to the welfare of the scientific community. We are extremely thankful to the contributors for paying continuous attention to our request and showing faith in our capabilities. We shall always remain highly obliged to all of them forever. These words cannot justify the worthiness of their efforts. We successfully compiled our creative and thoughtful research work due to genuine concern and painstaking effort of many more well-wishers whose names are not mentioned, but they are still in our heart. So, the reward is surely worth for their efforts. We and the contributing authors hope from the bottom of our hearts that this book will be a good guidebook and compass for research studies on novel biomarkers for the early detection of gastrointestinal cancers.

Machilipatnam, Andhra Pradesh, India — Pallaval Veera Bramhachari
Visakhapatnam, Andhra Pradesh, India — Nageswara Rao Reddy Neelapu

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Our sincere thanks are extended to all the academicians and scientists who have contributed chapters and happily agreed to share their work on *Recent Advancements in Biomarkers and Early Detection of Gastrointestinal Cancers* in this volume.

This book is a stunning reflection of the seriousness with which the several scientific minds are dedicated from the scientific community. We are extremely thankful to the contributors for paying continuous attention to our request and showing faith in my competencies and capabilities. We shall always remain highly obliged to all of them forever. These words cannot justify the worthiness of their efforts. We appreciate the excellent work of the authors and co-authors who were invited to contribute chapters in this book. The credit for making this book a reality goes to them. As editors and our review team for the chapters especially appreciate sharing expertise with the contributors. Each chapter is informative and written as a stand-alone, so the reader can begin anywhere in the book depending upon his/her interests and needs.

At the same time, we also express our deepest gratitude to our family members for their kind support which has prompted us to complete the assignment on time. We are also thankful to the Department of Biotechnology, Krishna University and the Department of Biochemistry and Bioinformatics, GITAM (Deemed-to-be-University), AP, India, for the support. We are equally thankful to the Springer Nature Publishing group for their full cooperation during the peer review and production of the volume.

We are thankful to our beloved teachers and mentors, for their constant support and motivations at all stages of progress.

About the Book

This book illustrates the importance or need for the early detection or diagnosis of gastrointestinal cancer. This book *Recent Advancements in Biomarkers and Early Detection of Gastrointestinal Cancers* provides information on discovery of biomarkers by profiling microRNA, circulating microRNAs, serum microRNA, and plasma microRNA for diagnosing early onset of gastric cancer. Further, it provides breakthrough technologies such as ultra-sensitive nanochip, nanosensors, nanodevices, biosensors, electrochemical biosensors, optical biosensors, and DNA biosensors for the early diagnosis of gastrointestinal cancer. It also describes the discoveries and the role of molecular markers or biomarkers like volatile biomarkers, serum biomarkers, predictive and prognostic molecular markers for the early detection of gastrointestinal cancer. GWAS, big data analytics, computation biology, and systems biology approaches can be used to discover and develop diagnostics and therapeutics for gastrointestinal cancer. In closing, the book provides comprehensive information, inspiration, and advanced clinical applications on early diagnosis and detection of gastrointestinal cancers aiming towards personalized medicine to treat cancer.

Contents

Editors and Contributors

About the Editors

Pallaval Veera Bramhachari is currently a Senior Faculty member of the Department of Biotechnology at Krishna University, Machilipatnam, India. Earlier, I served as Postdoctoral Research Scientist at the Bacterial Pathogenesis Laboratory, Queensland Institute of Medical Research (QIMR-Berghofer Research Center), Brisbane, Australia, and DBT Postdoctoral Fellow at the Department of Microbiology and Cell Biology, Indian Institute of Science (IISc), Bangalore. I completed my Ph.D. in Microbiology from Goa University, India. My major research interests are the investigation on the applied research in microbiology and cell biology including biochemical mechanism of bacterial-biofilm formations, structure–function relationship of bacterial rhamnolipids, and basic and translational cancer research. I published more than 125 research articles including 5 international books in prestigious peer-reviewed international Scopus-indexed journals and presented 50 abstracts at various national and international conferences. I served as the Editorial Board member and as Reviewer for a number of national and international journals. I am a member of many international scientific societies and organizations, most importantly, Indian Science Congress and Society of Biological Chemists, India. I successfully completed two major research projects. I was awarded Travel Scholarship from QIMR, Australia, in 2007 for attending 4th Indo-Australian Biotechnology Conference at Brisbane, Australia, and awarded with Young Scientist

Travel Fellowship (2007) from the DST, Govt. of India, for attending XVII Lancefield International Symposium at Porto Heli, Greece (2008). Dr. Bramhachari was conferred with various prestigious awards, notably, Science Education Research Board (SERB), Government of India-Young Scientist award (2011) with a Research Project, Nominated as Associate Fellow of Andhra Pradesh Academy of Sciences (APAS) (2016), MASTER TRAINER: Andhra Pradesh, English Communications Skills Project by (British Council and APSCHE, 2017), Andhra Pradesh State Best Scientist award (APCOST, 2017), Dr. V. Ramalingaswamy Memorial award for Biomedical Sciences (2019) by Science City of Andhra Pradesh. I also obtained two Indian patents in 2017. I have more than 13 years of teaching and research experience at the university level.

Nageswara Rao Reddy Neelapu is currently an Assistant Professor in Bioinformatics Division at the Department of Biochemistry and Bioinformatics, Institute of Science, Gandhi Institute of Technology and Management (GITAM), Deemed-to-be-University, Visakhapatnam, India. He obtained his Masters in Life Science from Pondicherry Central University, Pondicherry, and Ph.D. in Evolutionary Bioinformatics from Andhra University, Visakhapatnam, India. His research interest is in Bioinformatics (with specialization in drug target discovery, HLA-based peptide vaccine design, genome analysis, phylogeny and evolution, structure–function relationship of proteins, and exploring next-generation sequencing data), Fungal Biology, and Cancer. Furthermore, he was a recipient of several fellowships like CSIR-UGC Junior Research Fellowship; and DST-DAAD Visiting Fellowship to Germany. He has published more than 50 research articles in prestigious peer-reviewed international Scopus-indexed journals and presented 18 abstracts at various national and international conferences. He has served on editorial board for a number of national and international journals, most importantly, Artificial Intelligence in Gastroenterology of **Baishideng Publishing Group Inc.** He is a member of many international scientific societies and organizations, most importantly, Indian Science Congress & Society of Biological Chemists, India. He also served

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Abbreviations

5,6-dihydroxy-5,6-dihydrothymidine	Thymidine glycol
ACRG	Asian Cancer Research Group
ACS	American Cancer Society
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase
AMPK	5′-AMP-activated protein kinase
APC	Adenomatous polyposis coli
ASR	Analyte-specific reagent
AST	Serum Aspartate Transaminase
BCFA	Branched chain fatty acids
BCOC	Be Clear on Cancer
BUN	Blood Urea Nitrogen
CAG	Chronic atrophic gastritis
CC	Creatinine Clearance
CCC	Cytoplasmic cell-adhesion complex
CDSS	Clinical Decision Support System
CDX-2	Caudal type homeobox-2
CE	Chromoendoscopy
CEA	Carcinoembryonic antigen
CE-MS	Capillary electrophoresis-mass spectroscopy
cfDNA	Circulating cell-free DNA
CIP	Cancer Imaging Program
CTCs	Circulaing Blood Cells
CIS	Chromosomal instability
CK	Creatine Kinase
CKs	Cytokeratins
CLE	Confocal laser endomicroscopy
CLIA	Clinical Laboratory Improvement Amendments

CMS	Centers for Medicare and Medicaid Services
CNT	Carbon Nanotubes
CNV	Copy number variation
CPCA	Consensus PCA
CRC	Colorectal cancer
CRP	C-reactive protein
CSB	Cancer systems biology
CSG	Chronic superficial gastritis
CT	Cytoplasmic tail
CT scan	Computerized tomography scan
CTCs	Circulating tumor cells
ctDNA	Circulating tumor DNA
cTn	Cardiac Troponin
CYP2D6	Cytochrome P450-2D6
ddPCR	Droplet digital PCR
DGC	De novo diffuse-type Gastric Cancer
DNMT1	DNA methyltransferases
DNMT3A	DNA methyltransferase-3A
DSS	Decision support system
DYS	Gastric dysplasia
EGC	Early gastric cancer
EGTM	European Group on Tumor Markers
EMT	Epithelial–mesenchymal transition
EpCAM	Epithelial cell adhesion molecule
ESCC	Esophageal squamous cell carcinoma
EZH2	Enhancer of zeste homolog 2
FDG-PET	Fluorodeoxyglucose Positron Emission Tomography
FICE	Flexible spectral imaging color enhancement
FISH	Fluorescent in situ hybridization
FMo3	Monooxygenase-3 or CYP1A2
FMo3	Flavin-Containing Monooxygenase-3 or CYP1A2
FOBT	Fecal occult blood testing
FOXO4	Forkhead box protein O4
FRET	Forster Resonance Energy Transfer Biosensors
FTICR	Fourier transform ion cyclotron resonance
FT-IR	Fourier Transform Infrared
FXR	Farnesoid X receptor
GCA	Graded clustering analysis
GC-MS	Gas chromatography-mass spectroscopy

GFR	Glomerular Filtration Rate
GGT	Gamma-Glutamyl Transferase
GI	Gastrointestinal cancer
GNCA	Gastric cardio adenocarcinoma
GO	Graphene Oxide
GOBIOM	GVK Bio Online Biomarker Database
GSK-3β	Glycogen synthase kinase 3β
GWAS	Genome-wide association studies
HbA1c	Glycosylated hemoglobin
HER2	Human epidermal growth factor receptor 2
HGF	Hepatic growth factor
HNF4A	Hepatocyte nuclear factor 4 alpha
HO$*$	Hydroxyl radicals
HPLC-MS	High performance mass spectroscopy
HR	Novel high-resolution virtual chromoendoscopy
IGC	Intestinal-type Gastric Cancer
IGCLC	The International Gastric Cancer Linkage Consortium
IHC	Immunohistochemistry
IL1B-31T	Interleukin-1 beta
IM	Intestinal metaplasia
IVD	In vitro diagnostic
IVUS	Intravascular Ultrasonography
JAK2	Janus kinase 2
KIM-1	Kidney Injury Molecule-1
LC-MS	Liquid Chromatography-Mass Spectrometry
LDH	Lactate Dehydrogenase
lncRNAs	Long noncoding RNAs
LOD	Limit of detection
LOH	Loss of heterozygosity
LPA	Lysophosphatidic acid
LysoPC	4-Lysophosphatidylcholines
MA-CD	Magnetic cyclodextrin polymer
MALT	Mucosa-associated lymphoid tissue
MFCs	Microbial fuel cells biosensor
MIAMOD	Mortality and Incidence Analysis Model
MP	Microparticles
MRI	Magnetic resonance imaging
MRS	Magnetic resonance spectroscopy
MS	Mass spectrometry
MSI	Microsatellite instability
MSP	Methylation-specific PCR

MudPIT	Multidimensional Protein Identification Technology
MVDA	Multivariate data analysis
NAG	*N*-acetyl-β-D-glucosaminidase
NBI	Narrow-band imaging
NBIA	National Biomedical Imaging Archive
NGAL	Neutrophil Gelatinase-Associated Lipocalin
NM	Nuclear medicine
OPLS-DA	Orthogonal partial least squares discriminant analysis
OSC	Orthogonal signal correction
PCA	Principal component analysis
PD-L	Programmed death ligand
PET	Positron emission tomography
PFAA	Plasma-free amino acid
PIAMOD	Prevalence and Incidence Analysis Model
PK	Pharmacokinetic measurements
PLS-DA	Partial least squares discriminant analysis
POMA	Pipeline of outliner MicroRNA analysis
PPIs	Protein–protein interactions
prGO	Partially reduced Graphene Oxide
pTNM	Pathologic tumor-node-metastasis
PTPRC or CD45	Protein tyrosine phosphatase
PTPRCAP	Protein tyrosine phosphatase receptor type C-associated protein
PTR-MS	Proton transfer reaction mass spectrometry
QCA	Quantitative Coronary Angiography
qPCR	Quantitative polymerase chain reaction
qRT-PCR	Quantitative reverse transcriptase polymerase chain reaction
QTLs	Quantitative trait loci
q-TOF	Quadrupole time-of-flight
RFA	Recurrent focal amplifications
rGO	Reduced graphene oxide
RH	Rheumatoid arthritis
RhoA	Ras homolog family member A
ROC	Receiver operating characteristics
ROCK1	Rho-associated coiled-coil containing protein kinase 1
RTKs	Receptor tyrosine kinases
SAGE	Serial analysis of gene expression
SC	Serum creatinine
SELDI	Surface-enhanced laser desorption/ionization

SELDI-TOF	Surface-enhanced laser desorption/ionization Time-of-flight
SFKs	Src family kinases
SIFT-MS	Selected ion flow tube mass spectrometry
SNPs	Single nucleotide polymorphisms
SOPs	Standard operating procedures
SPECT	Single Photon Emission Computed Tomography
SPME	Solid-phase microextraction
SQUID	Superconducting quantum interference device
SVM	Support vector machine
TCA	Tricarboxylic acid
TCGA	The Cancer Genome Atlas
TCIA	The Cancer Imaging Archive
TFF1	Trefoil factor 1
TIMP1	Metallopeptidase inhibitor 1
TOF	Time-of-flight mass spectrometry
TSH	Thyroid-stimulating hormone
TTR	Time to results
UPLC-MS	Ultra performance mass spectroscopy
US	Ultrasound
USPSTF	United States Preventive Services Task Force
VEGF	Vascular endothelial growth factor
VOCs	Volatile organic compounds
XRCC1	X-ray repair cross-complementing group 1
ZIKV	Zika virus antigens