De Novo And Acquired Resistance To Immune Checkpoint

Despite successive advances in clinical diagnosis and therapeutic intervention, cancer-associated morbidity and mortality keeps up with escalating cost to human society. Clinicians are confronted with an unprecedented challenge in curing cancers with de novo or acquired resistance. Failure to achieve effective and long-lasting treatment effects arises from the complexity of malignancies, particularly when plasticity of cancer cells is coupled with survival adaptability conferred by the pathologically co-opted stroma in the tumor microenvironment (TME). Targeting immune checkpoints, such as programmed cell death 1 (PD-1), programmed cell death ligand 1 (PD-L1) and cytotoxic T lymphocyte antigen 4 (CTLA4), provide significant benefit in multiple tumor types and produce substantial anticancer responses. Tissue resident stromal cells, although damaged together with cancer cells upon cytotoxic treatments, represent an ever-replenishing source that contributes to tumor restoration from residual cancer cells in the post-therapy stage. The TME displays a continually changing landscape, generating significant impacts on treatment outcome in clinics. Moving forward, implementing patient-specific analysis in clinical oncology with TME-oriented agents will significantly improve the specificity and efficacy of targeted therapies, thereby accelerating the translation of novel conceptions and groundbreaking discoveries in the TME biology through multiple bench-to-bed pipelines in current settings of precision cancer medicine.

Aromatase Inhibitors (AIs) treat postmenopausal estrogen receptor positive tumours, which constitute the majority of breast cancer patients. This comprehensive volume brings together the current knowledge from different relevant areas, including molecular mechanisms and translational aspects of drug resistance in AIs. Topics covered include research, experimental , and clinical data specifically focused on AI resistance in breast cancer. The volume will include three sections. The first section covers general knowledge about aromatase inhibitors, including regulation of aromatase genes, and structure and function of aromatase protein. The second section provides the detailed mechanisms of resistance to AIs, while the third section explores prediction of resistance and potential strategies to overcome resistance. Breast cancer is the most common female cancer and AIs significantly improve treatments outcomes compatibly to previously used endocrine treatments. However 10-15% of post-operative patients develop a relapse during adjuvant treatment with AIs; about 25-50% of the patients do not respond to AIs in neo-adjuvant or metastatic setting, and the majority of metastatic patients who initially respond develop resistance within 3 years. There is an important need to understand these mechanisms of resistance in order to develop methods of preventing or overcoming the resistance to AIs, which will ensure a more successful outcome in treating breast cancer.

This book represents a comprehensive description and evaluation of the most up-to-date approaches to cancer management. Each chapter, prepared by leading basic researchers and clinicians, provides an in depth description of

a specific method for cancer management. The chemotherapy section of the book is updated to include the newest drugs as well as those currently in development. Organized by drug class, this section provides the latest information on most drugs, including their mechanisms of action, interactions with other agents, toxicities, side effects, and mechanisms of resistance. The biological therapy section of the book provides expanded coverage of the currently used cytokines, vaccines, and cell based therapies of cancer. Full consideration is also given to other modern treatment approaches, such as tyrosine kinase inhibitors, inhibitors of tumor angiogenesis, and the transcatheter management of cancer. Current advances in hyperthermia in cancer treatment, hematologic and nutritional support, bone marrow transplantation, pain management and care of the terminally ill patients with cancer are also presented. In summary, this book provides a comprehensive coverage of the current knowledge on the most innovative, systematic and multidisciplinary approaches to the treatment of patients with cancer.

Diagnostics and Therapy in Veterinary Dermatology presents thorough coverage of the latest discoveries, drugs, and treatments for dermatologic conditions in animals. Chapters written by experts in each respective area of veterinary dermatology contain up-to-date information on new diagnostic tools and tests, autoimmune diseases, parasitic and fungal infections, medical management of acute and chronic conditions, alternative dermatologic therapies, and more. Offering practical solutions for both specialist and general practice veterinarians dealing with dermatology cases, this wide-ranging resource also addresses antibiotic resistance and misuse, the availability of foods for elimination diet trials, problems with generic drugs, emerging infectious diseases, and other important problems currently facing the profession. Throughout the text, veterinary practitioners are provided with real-world guidance on improving how they work up their dermatology cases and strengthening communication between the primary care veterinarian and the dermatologist. Edited by a leading board-certified dermatologist, this volume: Focuses on cats and dogs Includes numerous high-quality clinical photographs illustrating all key concepts Covers topics such as how to use your nursing staff to the fullest, the One Health movement, and how changing climate is increasing the spread of certain dermatologic diseases Discusses approaches for building a better working relationship between clients, primary care veterinarians and dermatologists Provides insights on the future of technology in the diagnosis and treatment of dermatologic diseases Covering the very latest developments in the field, Diagnostics and Therapy in Veterinary Dermatology is essential reading for veterinary dermatologists, veterinary students, and any veterinary general practitioner with a dermatology caseload.

JNCI

Handbook of Therapeutic Biomarkers in Cancer

Mechanisms of Resistance in Head and Neck Cancers

A Systems Biology Approach to Identify Molecular Determinants of Resistance in Breast Cancer

Cancer Drug Resistance

Melanoma, An Issue of Hematology/Oncology Clinics of North America

Advances in Clinical Chemistry, Volume 94, the latest installment in this internationally acclaimed series, contains chapters authored by world-renowned clinical laboratory scientists, physicians and research scientists. The serial discusses the latest technologies relating to the field of clinical chemistry, with specific chapters in this new release covering Hypertensive disorders of pregnancy: Strategy to develop clinical peptide biomarkers for more accurate evaluation of the pathophysiological status of this syndrome, Clotting factors - Clinical biochemistry and their roles as plasma enzymes, Myokines: The endocrine coupling of skeletal muscle and bone, Epigenetic reprogramming and potential application of epigenetic-modifying drugs in acquired chemotherapeutic resistance, and more. Provides the most up-to-date technologies in clinical chemistry and clinical laboratory science Authored by world renowned clinical laboratory scientists, physicians and research scientists Presents the international benchmark for novel analytical approaches in the clinical laboratory

American Association for Cancer Research 2019 Proceedings: Abstracts 1-2748 - Part B

Molecular Genetics of Drug Resistance forms a vital and timely review of the genetic processes behind drug resistance. Starting with an overview of the area, each chapter focuses on a particular target with important sections on drug resistance in malaria and in cancer.

This book is a printed edition of the Special Issue "The Epithelial-to-Mesenchymal Transition (EMT) in Cancer" that was published in Cancers

Implications for PARP Inhibitor Efficacy in Pancreatic Ductal Adenocarcinoma Cells

From Biomarkers to Functional Checkpoints Enhacing ADCC Responses

Suppression of Mammary Tumorigenesis by a Gemini Vitamin D Analog and a Synthetic Truterpenoid

Prognosis, Treatment, and Prevention

ErbB2 Receptor in Breast Cancer: Implications in Cancer Cell Migration, Invasion and Resistance to Targeted Therapy

This book discusses the molecular, biological, pathological, and clinical aspects of melanoma, with special emphasis in the new concepts of melanoma genetics. A multidisciplinary group of experts in Genetics, Dermatology, Pathology, and Melanoma Medical Oncology contribute state-of-the-art knowledge in melanoma research and clinical management, not only exposing the current status of knowledge of the topics but also providing their personal experiences and ideas about the future and potential practical application of the genetic aspects of melanoma. During the last few years we have witnessed an impressive amount of discoveries in the field of melanoma genetics which have changed our approach in understanding the pathogenesis and treatment of this lethal disease. Genetics of Melanoma is a practical approach to melanoma genetic mechanisms and their application in the diagnosis and treatment of this malignancy. It is an essential source of updated information and a powerful tool for clinicians, pathologists, and basic scientists who wish to understand, apply, and investigate the multiple new aspects of melanoma genetics.

This book provides a comprehensive overview of the fast-evolving subject of clinical application of cancer therapeutic biomarkers. The second edition captures significant progress of cancer immunotherapy and emphasizes the genetic basis for selective cancer treatment. It covers an in-depth insight on biomarkers across a broad area of cancer research and oncology with a wealth of integrated genetic and molecular information about specific therapies by a multidisciplinary team of internationally recognized experts. Each chapter focuses on a class of targeted, immunologic, or chemotherapy agents and their companion biomarkers that predict response, benefit or resistance, and severe adverse event. The book will serve as a handbook for health professionals and scientists on the current applicable biomarkers in the management of cancer. The vision into the systemic classification and statistical consideration of therapeutic biomarkers summarized by the book editors and chapter authors will help advance precision medicine—a precisely tailored cancer treatment strategy for cancer patient care.

Overexpression of ErbB2 is found in several types of human carcinomas. In breast tumors, ErbB2 overexpression is detected in up to 20% of patients. Breast cancers in with amplification of ErbB2 are characterized by rapid tumor growth, lower survival rate and increased disease progression. The molecular mechanisms underlying the oncogenic action of ErbB2 involve a complex signaling network that tightly regulates malignant cell migration and invasion and hence metastatic potential. Recent efforts have been made to identify gene expression signatures of ErbB2-positive invasive breast cancers that may represent important mediators of ErbB2-induced tumorigenesis and metastatic progression. In this chapter, we will discuss the canonical ErbB2 signaling pathways responsible for tumor growth and dissemination along with newly identified mediators such as adaptor protein p130Cas and miRNAs. From a therapeutic point of view, the treatment with anti-ErbB2 monoclonal antibody trastuzumab has greatly improved the outcomes of patients with ErbB2 aggressive cancer. Nevertheless, de novo and acquired resistance to trastuzumab therapy still represent a major clinical problem. In the second part of the chapter, we will provide an overview of the mechanisms so far implicated in the onset of resistance to targeted therapy and of the new strategies to overcome resistance.

De novo and acquired resistance to anti-estrogen therapy and aromatase inhibitors remains a challenge in the treatment of estrogen-receptor positive breast cancer. We employed a systems biology approach to identify survival determinants of estrogen independent breast cancer cells with varying sensitivities to hormonal therapeutics. An estrogen receptor-centered network was

developed using bioinformatics databases to probe, with a network-targeted 631-element siRNA library, for essential genes involved in the proliferation and survival of estrogen independent breast cancer cells. We identified a unique subset of 25 genes that are essential for the proliferation of estrogen independent breast cancer cells, 15 of which also promote apoptosis.

Journal of the National Cancer Institute

Lung Cancer and Personalized Medicine: Novel Therapies and Clinical Management

DARPP-32 Expression in Acquired Resistance of Breast Cancer Cells to Trastuzumab

Design, Manufacturing, Behavior and Performance

Cultured Cells—Advances in Research and Application: 2012 Edition

HuR Regulates Poly ADP Ribose Glycohydrolase

Cultured Cells—Advances in Research and Application: 2012 Edition is a ScholarlyBrief™ that delivers timely, authoritative, comprehensive, and specialized information about Cultured Cells in a concise format. The editors have built Cultured Cells—Advances in Research and Application: 2012 Edition on the vast information databases of ScholarlyNews.™ You can expect the information about Cultured Cells in this eBook to be deeper than what you can access anywhere else, as well as consistently reliable, authoritative, informed, and relevant. The content of Cultured Cells—Advances in Research and Application: 2012 Edition has been produced by the world's leading scientists, engineers, analysts, research institutions, and companies. All of the content is from peer-reviewed sources, and all of it is written, assembled, and edited by the editors at ScholarlyEditions™ and available exclusively from us. You now have a source you can cite with authority, confidence, and credibility. More information is available at http://www.ScholarlyEditions.com/.

Stephen P. Ethier and a panel of leading investigators comprehensively analyze the cellular, molecular, and endocrine factors in the development of cancers of the breast, prostate, endometrium, and ovary. Concentrating on defining the most important unresolved issues in the field, the authors review how steroid hormones function to regulate normal mammary gland homeostasis in humans, with particular emphasis on the roles of estrogen, progesterone, and growth factors. Comprehensive and up-to-date, Endocrine Oncology offers both basic and clinical researchers not only the latest molecular and cellular findings on endocrine cancers, but also a powerful critical analysis that will prove invaluable to all endocrinologists and oncologists working in the area today.

Cancer is the leading cause of death in most countries and its consequences result in huge economic, social and psychological burden. Breast cancer is the most frequently diagnosed cancer type and the leading cause of cancer death among females. In this book, we discussed various therapeutic modalities from signaling pathways through various anti-tumor compounds as well as herbal medicine for this deadly

cancer. We hope that this book will contribute to the development of novel diagnostic as well as therapeutic approaches.

Steroid Receptors—Advances in Research and Application: 2012 Edition is a ScholarlyEditions™ eBook that delivers timely, authoritative, and comprehensive information about Steroid Receptors. The editors have built Steroid Receptors—Advances in Research and Application: 2012 Edition on the vast information databases of ScholarlyNews.™ You can expect the information about Steroid Receptors in this eBook to be deeper than what you can access anywhere else, as well as consistently reliable, authoritative, informed, and relevant. The content of Steroid Receptors—Advances in Research and Application: 2012 Edition has been produced by the world's leading scientists, engineers, analysts, research institutions, and companies. All of the content is from peer-reviewed sources, and all of it is written, assembled, and edited by the editors at ScholarlyEditions™ and available exclusively from us. You now have a source you can cite with authority, confidence, and credibility. More information is available at http://www.ScholarlyEditions.com/.

Companion and Complementary Diagnostics

Breast Cancer

Diagnostics and Therapy in Veterinary Dermatology

The Epithelial-to-Mesenchymal Transition (EMT) in Cancer

Melanoma, An Issue of Hematology/Oncology Clinics,

Beyond the Antiestrogen

"Amplification of the receptor tyrosine kinase ErbB-2 has been linked to the proliferation of breast cancer cells.1,2 Trastuzumab targets the extracellular domain of ErbB-2, leading to growth inhibition of approximately 15% of the breast cancers with genomic amplification of the ERBB2 gene.3 Clinical studies have demonstrated its efficacy in both early4 and metastatic breast cancers. 5,6 However, many tumors wit ERBB2 amplification are not responsive to treatment.7 Moreover, the ones that initially respond, eventually progress and acquire drug resistance.8 An in vitro model for this acquired resistance was established by Chan & al.9 The breast cancer cell line, BT474, containing amplified ERBB2, was grown in the presence of trastuzumab for several months until subclones outgrew. Gene expression profiling was performed on these clones to determine differentially expressed genes between the parental and resistant cells. DARPP-32 (Dopamine and cAMP regulated phosphoprotein of 32kDa) was, by far, the most overexpressed transcript. DARPP-32 is coamplified with ERBB2 on the same amplicon of chromosome 17.10 This protein has been mostly described in neurobiology, but DARPP-32 overexpression was recently reported in gastrointestinal, esophageal, prostate and breast cancer.11 Therefore, we suggest that overexpression of DARPP-32 can cause acquired resistance of breast cancer cells to trastuzumab. The in vitro knockout of DARPP-32, using stable shRNA transfection, abolishes the resistance to trastuzumab in the clones, while overexpression of DARPP-32 in the parental cells results in de novo resistance. Overall, our results suggest that DARPP-32 may be a potential therapeutic target in breast cancer patients who develop acquired trastuzumab

resistance." --

This issue of Hematology/Oncology Clinics, guest edited by Dr. F. Stephen Hodi, is devoted to Melanoma. Articles in this issue include: The current state of Melanoma; Understanding the Biology of Melanoma Development and Therapeutic Implications; Surgical Management of Melanoma; Targeted Therapies for Cutaneous Melanoma; Treatments for Non-cutaneous Melanoma; Resistant Mechanisms and Therapeutic Implications; The Role of the Immune System in Melanoma Development and Treatment; Vaccines and Melanoma; IL-2, Interferon, and Cytokines; Immune Checkpoint Blockade; Adjuvant Treatments, Chance for Cure in Melanoma; and Combinatorial Approach to Treatment of Melanoma.

Reviews the origins of molecular oncology, including technologies for cancer analysis, key pathways in human malignancies, and available pharmacologic therapies.

HER2 overexpression accounts for approximately 15-20% of breast tumors, and mainstay therapy for these patients includes HER2-specifi antibodies in combination with chemotherapy. Although the efficacy of anti-HER2 antibodies has significantly improved disease control, some patients show de novo or acquired resistance to treatment, evidencing the need for biomarkers and therapeutic strategies improving patients treatment. Natural killer cells (NK) are cytotoxic innate lymphocytes specialized in the defense against virus infected and transformed cells. Several observations support the contribution of NK cells to the efficacy of anti-HER2 therapeutic antibodies in breast cancer and NK cell dysfunction, owing to immunosuppressive factors present in the tumor, has been related to tumor progression in metastatic patients. In this context, strengthening NK cell responses is envisaged as a relevant option for enhancing the therapeutic benefit of anti-HER2 mAbs. In this work we provide novel insights on the role of NK cells in the efficacy of anti-HER2 antibodies in breast cancer by describing NK cell aging as a factor potentially limiting the efficacy of anti-HER2 antibodies, and disclose the potential of CD137 costimulation for enhancing NK cell effector function despite immunosuppression.

Molecular Mechanisms of Tumor Cell Resistance to Chemotherapy

Cancer Management in Man: Chemotherapy, Biological Therapy, Hyperthermia and Supporting Measures

Steroid Receptors—Advances in Research and Application: 2012 Edition

Ridaforolimus (MK-8669) Synergizes with Dalotuzumab (MK-0646) in Hormone- Sensitive Breast Cancer

Elucidating the Role of EZH2 in Drug Resistance and Mouse Mammary Gland Tumorigenesis

Colorectal Cancer

Overcoming drug resistance requires identification of redundant survival signals. Even in the best case scenario of personalized medicine wherein cancer- specific genomic alterations are treated with molecular targeted therapeutics, increasing resistance predicates concurrent identification of compensatory mechanisms. For a lethal malignancy with limited treatment options such as pancreatic ductal adenocarcinoma (PDA), the development and clinical implementation of a novel targeted strategy i.e. PARP inhibitors was a major breakthrough. However, PARPi have not progressed as a frontline therapy for PDA patients despite being in the

clinical trials pipeline for over a decade now. Identifying and combating de novo and acquired PARPi resistance mechanisms is a critical medical goal in oncology, and the focus of this study. Attempts to target the most frequent mutations in PDA patient samples, including KRAS (86%), TP53 (68%), CDKN2A (21%), SMAD4 (21%) and EGFR (7%) identified through multiple next-generation sequencing studies haven't yielded any considerable success. However, over 10% of PDA patients are associated with germline or sporadic loss of DNA repair and genome maintenance genes, specifically BRCA1 and BRCA2, which compromises repair of damaged DNA resulting in increased chromosomal instability (CIN). Paradoxically, while CIN promotes tumorigenesis, these genetic mutations become the tumor cells' "Achilles heel". These DDR- defective cells rely heavily on an alternative DNA repair pathway dictated by PARP1, and thus are particularly susceptible to PARP inhibitors and intra-strand crosslinkers such as mitomycin C, cisplatin, etc. Therefore, DNA damage repair (DDR), one of twelve core signaling pathways dysregulated in PDA, has provided a promising approach for treating selective patients with DNA repair-deficient tumors. Unfortunately, there is an unmet demand to understand how initially responsive patients develop resistance to PARPi. While genomic and proteomic alterations, such as BRCA reversion mutation or upregulation of a PARPi efflux pump respectively, have been widely explored as PARPi resistance mechanisms, rapid reprogramming of the RNA expression signature in response to PARPi exposure has been largely ignored. This is the first study to demonstrate that post-transcriptional gene regulation (PTGR) by an RNA- binding protein HuR upregulates expression of a novel resistance gene Poly-ADP Ribose Glycohydrolase (PARG) which supports DNA damage response and facilitates PARPi resistance. We have previously shown that HuR-mediated transcriptomic rewiring causes PDA cells to reprogram core cellular processes and enhance expression of several pro-survival factors such as DCK, WEE1 and PIM1 which, in turn, support acute chemoresistance and survival of PDA cells in a harsh tumor microenvironment. The ultimate clinical goal of this study relates to 1) optimizing and extending a proven synthetic lethal therapeutic strategy to all pancreatic cancer patients, regardless of their DNA-repair status, 2) recognizing PARG as a more suitable target over PARP1 due to its ability to be acutely induced in response to drug exposure and 3) inhibiting PARG and/or HuR as an effective therapeutic strategy to improve efficacy of not only PARP inhibitor therapy but other chemotherapy regimens in pancreatic cancer.

Mammalian target of rapamycin (mTOR) represents a key downstream intermediate for a myriad of oncogenic receptor tyrosine kinases. In the case of the insulin-like growth factor (IGF) pathway, the mTOR complex (mTORC1) mediates IGF-1 receptor (IGF-1R)-induced estrogen receptor alpha (ERalpha) phosphorylation/activation and leads to increased proliferation and growth in breast cancer cells. As a result, the prevalence of mTOR inhibitors combined with hormonal therapy has increased in recent years. Conversely,

activated mTORC1 provides negative feedback regulation of IGF signaling via insulin receptor substrate (IRS)-1/2 serine phosphorylation and subsequent proteasomal degradation. Thus, the IGF pathway may provide escape (e.g. de novo or acquired resistance) from mTORC1 inhibitors. It is therefore plausible that combined inhibition of mTORC1 and IGF-1R for select subsets of ER-positive breast cancer patients presents as a viable therapeutic option. Proceeds from the sale of this book go to support an elderly disabled person.

This, the second of two volumes on personalized medicine in lung cancer, touches upon the recent progress in targeted drug development based on genomics; emerging biomarkers and therapeutic targets such as EMT, cancer stem cells, and the tumor microenvironment; current personalized clinical management and radiation therapy for lung cancers; and the promise of epigenetics and next-generation sequencing for the advancements towards personalized therapy of lung cancer patients. With chapters on state-of-the-art therapies and technologies written by leading experts working to develop novel companion diagnosis tools for the personalized treatment of lung cancer patients, this volume brings readers up-to-date by presenting the current knowledge on the efforts to make personalized management of lung cancer patients a reality.

This reference examines the biological factors and genetic and molecular pathways potentially responsible for the development and progression of breast cancer-analyzing the latest therapeutic strategies as well as breakthroughs in endocrine treatments, angiogenesis, and non-hormonal approaches to predict, control, and inhibit the formation and grow

From Biomarker Discovery to Clinical Implementation

Apoptosis in cancer

Health Issues

Estrogens, Progestins, and Their Antagonists

Particles and Nanoparticles in Pharmaceutical Products

Tamoxifen

Breast cancer is a heterogeneous disease categorized into multiple subtypes, including luminal, HER2-positive and basal-like subtypes, which exhibit distinct gene signatures and clinical outcomes. Basal-like breast cancer has the worst prognosis among these subtypes and has no clinically approved targeted therapy. While HER2-targeting therapy with a humanized HER2 monoclonal antibody markedly improved the prognosis of HER2-positive breast cancer, the de novo and acquired resistance against the antibody has emerged as a new challenge for patients with HER2-positive breast cancer. MCF10 cell lines, a human breast cancer progression model representing the basal-like breast cancer subtype, were employed to identify key proteins involved in

different stages of mammary tumorigenesis. Increased levels of IGF-IR, cyclin D1 and c-Myc were associated with HRAS-driven transformation. Higher levels of pErk, pAkt, STAT3 and Pak4 contribute to tumorigenicity in vivo, whereas CD44, HER2, COX-2 and Smad4 may be involved in the breast cancer progression. The MCF10DCIS.com cells, one of the MCF10 cell lines, highly express a breast cancer stem cell marker, CD44. A Gemini vitamin D analog BXL0124 markedly repressed the CD44 protein level and the growth of MCF10DCIS.com xenograft tumors. CD44 overexpression was correlated with invasive phenotype in MCF10DCIS.com cells, and the repression of CD44 by BXL0124 contributed to the inhibition of cell invasion. STAT3, which interacts directly with CD44, was identified as a key downstream signaling molecule affected by BXL0124 in MCF10DCIS.com cells. The CD44 knockdown study supported the critical role of CD44-STAT3 signaling in the invasive potential of MCF10DCIS.com cells in vitro and in vivo. The anti-cancer effects of BXL0124 and a synthetic triterpenoid CDDO-Im on HER2-positive breast cancer were tested in MMTV-HER2/neu transgenic mice. BXL0124, CDDO-Im and their combination delayed the development of mammary tumors and markedly inhibited the activation of HER2 and EGFR as well as their downstream molecules, such as Erk, Src and c-Myc in MMTV-HER2/neu mammary tumors. In conclusion, we demonstrated therapeutic potential of Gemini vitamin D analog BXL0124 targeting CD44-STAT3 signaling in basal-like breast cancer. In addition, we found anti-cancer activities of BXL0124 and CDDO-Im in HER2-positive breast cancer and potentially additive effects of their combination.
Companion and Complementary Diagnostics: From Biomarker Discovery to Clinical Implementation provides readers with in-depth insights into the individual steps in the development of companion diagnostic assays, from the early biomarker discovery phase straight through to final regulatory approval. Further, the clinical implementation of companion diagnostic testing in the clinic is also discussed. As the development of predictive or selective biomarker assays linked to specific drugs is substantially increasing, this book offers comprehensive information on this quickly-evolving area of biomedicine. It is an essential resource for those in academic institutions, hospitals and pharma, and biotech and diagnostic commercial companies. Covers all aspects, from biomarker discovery, to development and regulatory approval Explains the "how to" aspects of companion diagnostics Incorporates information on the entire process, allowing for easier and deeper understanding of the topic
With international experts sharing their experience and knowledge on these different aspects in the management of colorectal cancer, this book has this opportunity to offer all physicians treating colorectal cancer, as well as researchers, updated information concerning the biology, diagnosis, screening, and treatment

of colorectal carcinoma. This book provides a detailed evaluation of diagnostic modalities, in-depth analysis of screening for colorectal cancer, recent advances in treatment, and principles and trends in the management of colorectal cancer. This updated knowledge will be an interesting and informative read for any clinician involved in the management of patients with colorectal cancer. In addition, readers such as related physicians, researchers, and colorectal cancer patients are potential beneficiaries of this book.

This issue of Hematology/Oncology Clinics, Guest Edited by F. Stephen Hodi, is devoted to Melanoma. This issue is one of six selected each year by our series Consulting Editors, George P. Canellos and Edward J. Benz. Topics discussed in this important issue include: State of Melanoma, Biology of Melanoma, Epidemiology of Melanoma, Surgical Management of Melanoma, Melanoma Adjuvant Therapy, Targeted Therapies for Melanoma, Non-cutaneous Melanomas, Immune Checkpoint Therapies for Melanoma, Resistance Mechanisms to Current Therapies, Cellular Therapy and Cytokine Treatments for Melanoma, Combinatorial Approaches to the Treatment of Melanoma, and Melanoma Future Directions.

Resistance to Aromatase Inhibitors in Breast Cancer

Molecular Genetics of Drug Resistance

AACR 2019 Proceedings: Abstracts 2749-5314

Genetics of Melanoma

Targeted Therapies to Reverse Resistance

Diagnosis, Screening and Management

This edited volume brings together the expertise of numerous specialists on the topic of particles – their physical, chemical, pharmacological and toxicological characteristics – when they are a component of pharmaceutical products and formulations. The book discusses in detail properties such as the composition, size, shape, surface properties and porosity of particles with respect to how they impact the formulations and products in which they are used and the effective delivery of pharmaceutical active ingredients. It considers all dosage forms of pharmaceuticals involving particles, from powders to tablets, creams to ointments, and solutions to dry-powder inhalers, also including the latest nanomedicine products. Further, it discusses examples of particle toxicity, as well as the important subject of pharmaceutical industry regulations, guidelines and legislation. The book is of interest to researchers and practitioners who work on testing and developing pharmaceutical dosage and delivery systems.

"HER2-positive breast cancers represent 15-20% of all breast cancer cases and are associated with high risk of metastasis and poor prognosis. While a number of HER2-targeted therapies have been developed in the past 20 years, intrinsic or acquired resistance to these therapies are a common occurrence. Yet, resistance to the dual EGFR/HER2 tyrosine kinase inhibitor lapatinib has not been well characterized. Using human and mouse-derived lapatinib-resistant cell lines, we have highlighted the implication of de novo serine biosynthesis pathway in lapatinib resistance. Expression of PHGDH and flux through the serine biosynthesis

pathway as well as the methionine cycle were found to be increased in lapatinib-resistant cells compared to lapatinib-sensitive cells. Interestingly, we have also linked this metabolic reprogramming to the epigenetic repressor EZH2. EZH2 expression was higher in lapatinib-resistant cells and inhibiting PHGDH induced a reduction in EZH2 levels. Our results suggested that increase in de novo serine biosynthesis provides carbon units that fuel the one-carbon metabolism network and ultimately lead to the production of SAM, the substrate of EZH2. Lapatinib-resistant cells were sensitive to both PHGDH and EZH2 inhibition, which provides interesting therapeutic perspectives. In addition, we further examined the role of EZH2 in breast tumorigenesis using mouse models of gain-of-function EZH2. However, our data did not reveal any role for EZH2 in cancer initiation and development. Together, the work presented here uncovers a new mechanism involved in lapatinib-resistance that revolves around the metabolic control of EZH2." --

The third edition of this critically acclaimed book has updated and expanded the survey of clinical, biological and pathological management of localized and advanced renal cell carcinoma. Internationally renowned editors and contributors explore the latest developments in molecular genetics, focusing on the novel targets that have been discovered in epithelial renal tumors. Comprehensive and authoritative, Renal Cell Carcinoma: Molecular Targets and Clinical Applications, Third Edition is the definitive text on the rapidly evolving landscape of experimental therapeutics, written and edited by leaders of the field.

Leading experts summarize and synthesize the latest discoveries concerning the changes that occur in tumor cells as they develop resistance to anticancer drugs, and suggest new approaches to preventing and overcoming it. The authors review physiological resistance based upon tumor architecture, cellular resistance based on drug transport, epigenetic changes that neutralize or bypass drug cytotoxicity, and genetic changes that alter drug target molecules by decreasing or eliminating drug binding and efficacy. Highlights include new insights into resistance to antiangiogenic therapies, oncogenes and tumor suppressor genes in therapeutic resistance, cancer stem cells, and the development of more effective therapies. There are also new findings on tumor immune escape mechanisms, gene amplification in drug resistance, the molecular determinants of multidrug resistance, and resistance to taxanes and Herceptin.

ScholarlyBrief

Advances in Clinical Chemistry

Targeted Cancer Therapy

Updated Landscape of the Tumor Microenvironment and Targeting Strategies in an Era of Precision Medicine

Apoptosis in Carcinogenesis and Chemotherapy

Endocrine Oncology

Tamoxifen has persisted as a widely accepted and administered drug for almost 25 years. Following the many scientific papers and books on the subject, it has remained a very intriguing substance. This, perhaps, is the reason for another monograph on Tamoxifen. It is regrettably true that overviews, even when up to date after exhaustive research - the shibboleth of our cultures -, rapidly lose relevance with the passage of time. Scientists can sometimes be pictured as deep sea divers, who plunge into the unknown in search of a hitherto unknown world. Their descent is exciting, but eventually they must come up for air and integrate their experiences with others who also had to resurface. This book intends to collect and, where possible, to collate recent, but

sometimes seemingly unrelated information. To quote Stephane Mallarme: "Everything in the world exists to end up in a book". Even if this is a tad cynical, it might not be far from the truth. If a little knowledge is a dangerous commodity, one can also add - tongue in cheek - that a vast amount of knowledge can be truly hazardous. It is likely that what might seem as entangled data is confusing, especially for those satisfied with the comfortable interpretation of Tamoxifen as an antiestrogen which has long been found insufficient. The complexity of its mechanisms and effects defies simple explanations and may even seem capricious, but only because of our ignorance.

Emerging technologies in target identification, drug discovery, molecular markers, and imaging are rapidly changing the face of cancer. This book provides a foundation of knowledge in targeted cancer therapeutics. The treatment of cancer is increasingly being individualized, based on an understanding of underlying biologic mechanisms. Poised to change the landscape in oncology, this volume provides a state-of-the-art overview. It will be valuable to practicing and academic physicians, fellows, residents and students, as well as basic scientists, interested in the cancer field.

?????This volume gives the latest developments in on the mechanisms of cancer cell resistance to apoptotic stimuli, which eventually result in cancer progression and metastasis. One of the main challenges in cancer research is to develop new therapies to combat resistant tumors. The development of new effective therapies will be dependent on delineating the biochemical, molecular, and genetic mechanisms that regulate tumor cell resistance to cytotoxic drug-induced apoptosis. These mechanisms should reveal gene products that directly regulate resistance in order to develop new drugs that target these resistance factors and such new drugs may either be selective or common to various cancers. If successful, new drugs may not be toxic and may be used effectively in combination with subtoxic conventional drugs to achieve synergy and to reverse tumor cell resistance. The research developments presented in this book can be translated to produce better clinical responses to resistant tumors.

De Novo Acquisition of BCR-ABL Mutations for CML Acquired ResistanceCancer Drug ResistanceSpringer Science & Business Media

Renal Cell Carcinoma

Molecular Oncology

Molecular Targets and Clinical Applications

Current and Alternative Therapeutic Modalities

De Novo Acquisition of BCR-ABL Mutations for CML Acquired Resistance

Role of NK Cells in the Efficacy of Anti-HER2 Therapeutic Antibodies in Breast Cancer

Although research on carcinogenesis has focused more on cellular proliferation than on cell death, yet understanding the mechanism of apoptosis may have important implications for cancer therapy. This book brings together experts from around the world who will discuss the common cancers encountered in clinical practice in the laboratory setting. During the induction of these common cancers, the role of apoptosis in cellular and molecular changes is emphasized, critically highlighting possible anti-cancer strategies. For those who are interested in carcinogenesis and for those who are seeking new approaches to anti-cancer therapy, this book is an important reference. It serves not only as a reference of the current understanding of apoptosis in common cancers but also an important bridge between the laboratory and clinical

practice. The editors and contributors are to be congratulated in bringing together an important pool of up-to-date knowledge to light and further our interest in this exciting and expanding ?eld. Arthur K. C. Li Emeritus Professor of Surgery The Chinese University of Hong Kong v Preface The role of apoptosis in cancer development and emerging treatment strategies has rapidly expanded over the past few years. The novel discovery in the apoptotic pa- ways and their relevant molecules provides us not only the knowledge how tumors develop but also the opportunity to design new therapeutic tools to prevent or inhibit the growth of tumors with minimal side-effects. Undoubtedly, understanding the events involved at a molecular level can permit the manipulation of apoptosis for therapeutic purposes.