De Novo And Acquired Resistance To Immune Checkpoint

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.

"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 with 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." --

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.

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.

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/.

?? ?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.?

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. The volume raises attention to the need of a completely new approach to breast cancer based on the knowledge collected on early breast cancer in the past two decades. The chapters are contributed by experts of all the fields participating in the clinical research and care of breast cancer. The practical importance of such a book is underlined by the increasing number of breast cancer cases, and also the increasing proportion of early stage-cases. The ultimate goal of the book is to point to the heterogeneous nature of the disease which is more striking and has more importance in care at the very early stages than at the more advanced stages. The book recommends the utilization of all the information provided by multimodality imaging and

special pathological methods, a new classification system and therapeutic guidelines since early breast cancers should not be treated based on experience obtained with palpable tumors. No similar book has been yet released to the market. The book is written for all the members of the team participating in the diagnosis and treatment of breast cancer (radiologists, pathologists, surgeons, clinical and radiation oncologists), but may be useful for medical students and residents too. The chapters are illustrated with didactic pictures, and special emphasis is given to provide a peep into the practice of the special procedures for the careful examination and individualized therapy of each case.

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

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.

Breast cancer is the second leading cause of cancer death in women in the United States. For the pathologist, almost any breast lesion may produce diagnostic difficulty, especially due to frequently small samples (core biopsy specimens) and a variety of mimics and variants seen in specific types of lesions. Additionally, the difficulty of breast lesion diagnosis has risen dramatically in recent years due to the increased emphasis on stratifying patients for appropriate therapy on an individual basis; the wider range of both local and systemic therapeutic options, and the potential for earlier diagnosis through increased mammographic breast screening leading to a higher likelihood of a favorable outcome. Difficult Diagnoses in Breast Pathology provides a highly visual presentation of the major problems and questions that a pathologist is likely to encounter in the evaluation of common and uncommon breast diseases. Coverage includes needle core biopsy interpretation, diagnosis of precursor lesions, early stage disease, and recognition of neoplastic mimics and other misleading variants. In addition, this book emphasizes particularly difficult areas including the use of newer immunohistochemical markers. Throughout, the emphasis is on an easily accessible presentation with tables and lists of key points summarizing major findings and numerous high-quality images supporting the text. Difficult Diagnoses in Breast Pathology will be a valuable

reference for every pathologist who deals with the diagnosis of breast diseases. Difficult Diagnoses in Breast Pathology Features: Each chapter authored by recognized expert in the area Hundreds of high-quality images Tables and key points in each chapter summarize the most important findings Coverage based on addressing in detail the real-world diagnostic problems the pathologist will face in daily practice

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.

The concept of cancer stem cells has great clinical implications. This is due to the fact that small subpopulations of these cells have been identified in a variety of neoplastic conditions ranging from solid tumors to liquid malignancies. Although there are some huge gaps in our current understanding of the role played by cancer stem cells in cancer biology, a growing body of

evidence provides strong support for the principal functions of these cells in tumorigenesis. This has represented the potential of cancer stem cells in the development of novel and innovative tools for the treatment of metastatic tumors. This book aims to offer a broad framework for obtaining insight into the state-of-the-art knowledge on cancer stem cell biology and highlight the therapeutic implications of these cells in the future of clinical oncology.

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

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.

The volume will serve as a primer on tyrosine kinase signaling and its importance in cancer. The volume will first introduce the common denominators of small-

molecule and antibody-derived inhibitors, as well as the general phenomenon of resistance. The volume will then detail resistance to the most commonly used classes of tyrosine kinase inhibitors, and will focus specific chapters on resistance to BCR-ABL1, FLT3, angiokinase family members, and ALK inhibitors.

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.

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

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/. HER2 overexpression accounts for approximately 15-20% of breast tumors, and mainstay therapy for these patients includes HER2-specific 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.

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 growth of cancerous cells.

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.

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.

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.

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.

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.

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 describes the challenges involved in developing mTOR inhibitors for cancer treatment, starting with an in-depth examination of their molecular mechanism of action, with emphasis on the class side-effects, efficacy and mechanisms of resistance, as well as on promising novel directions for their development, including novel compounds and rational combinations with other anti-neoplastic drugs. Over the last 10 years, inhibitors of mTOR

have emerged as a major class of anticancer drugs. Two rapamycin analogs are currently approved for the treatment of renal cell carcinoma, and it is estimated that a variety of other tumor types could benefit from mTOR inhibition, with numerous clinical trials (including pivotal registration trials) already underway. Second-generation small-molecule inhibitors of the pathway have also shown promise in terms of their superior tolerability and efficacy and are undergoing extensive clinical evaluation, with an estimated 30+ compounds currently under evaluation.

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.

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.

Medicinal Chemistry of Anticancer Drugs, Second Edition, provides an updated treatment from the point of view of medicinal chemistry and drug design, focusing on the mechanism of action of antitumor drugs from the molecular level, and on the relationship between chemical structure and chemical and biochemical reactivity of antitumor agents. Antitumor chemotherapy is a very active field of research, and a huge amount of information on the topic is generated every year. Cytotoxic chemotherapy is gradually being supplemented by a new generation of drugs that recognize specific targets on the surface or inside cancer cells, and resistance to antitumor drugs continues to be investigated. While these therapies are in their infancy, they hold promise of more effective

therapies with fewer side effects. Although many books are available that deal with clinical aspects of cancer chemotherapy, this book provides a sorely needed update from the point of view of medicinal chemistry and drug design. Presents information in a clear and concise way using a large number of figures Historical background provides insights on how the process of drug discovery in the anticancer field has evolved Extensive references to primary literature

Revealing essential roles of the tumor microenvironment in cancer progression, this book provides a comprehensive overview of the latest research on how different signaling pathways are important in the tumor microenvironment. Multiple signaling pathways are covered, including Src, Neuregulin, Adenosine, TGF?, Androgen, Wnt, and more. Taken alongside its companion volumes, these books update us on what we know about various aspects of the tumor microenvironment as well as future directions. Tumor Microenvironment: Signaling Pathways – Part B is essential reading for advanced cell biology and cancer biology students as well as researchers seeking an update on research in the tumor microenvironment.

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.

Practical Surgical Pathology of the Breast is a comprehensive and accessible guide for the practicing pathologist and trainee. It provides anatomic pathologists with the essential knowledge and tools to navigate breast cases and classification systems that are commonly and uncommonly found in everyday practice. Particularly challenging topics such as understanding the molecular mechanisms linked to breast cancer and the interpretation of molecular tests, are covered in clear prose, along

with useful discussions on diagnostic challenges written by world experts. The use of immunohistochemistry in breast pathology is discussed in detail and how to apply it to resolve diagnostic problems. As a result, the book simplifies difficult-to-master issues such as recognizing therapy-induced changes to breast specimens and identifying borderline breast lesions and many more. Each chapter features high-quality images and stains, tables that emphasize differential diagnoses, text that highlight common diagnostic pitfalls with corresponding tips, as well as helpful key points and how to reach an accurate diagnosis using appropriate procedures and tests. With Practical Surgical Pathology of the Breast as a guide, practitioners and residents can hone their diagnostic skills, resolve difficult cases and improve their approach to breast cases in their daily practice. Key Features: Written by world-renowned breast pathology experts Emphasizes the differential diagnosis problem-solving process found in everyday practice Contains over 700 high-quality images including numerous immunohistochemical stains which are essential when comparing breast entities Includes detailed coverage of core biopsy interpretation, precursors of mammary carcinoma and their mimics, papillary lesions, flat epithelial atypia, adenosis, microinvasive carcinoma, carcinomas with good prognosis, mesenchymal

lesions, triple negative carcinomas, lymphomas of the breast, and interpretation of therapy-related changes Highlights diagnostic pitfalls and common problems that a pathologist will encounter and includes practical tips throughout to guide the proper interpretation of breast lesions and the proper application of tests to reach accurate diagnoses 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.

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. This Special Issue of Cancers (Basel) is mainly dedicated to selecting papers from the talks given during the first Joint Meeting on Lung Cancer (JMLC) between the MD Anderson Cancer Center

(Houston, Texas USA) and the Hospital University Federation (HUF) OncoAge (University Côte d'Azur, Nice, France) (Nice, September 2018). The central theme of JMLC is to discuss new advances and exchange ideas regarding lung cancer. Notably, the talks covered different topics on new therapeutic strategies (targeted therapy and immuno-oncology), molecular and cellular biology, biomarkers, and the epidemiology of lung cancer. Special attention was also given to lung cancer in elderly patients. The articles published in this Special Issue covered subjects such as the assessment of new biomarkers and new approaches for the early detection of lung cancer, epidemiological data, and emphasized a place for the newly characterized cellular pathways in lung cancer, which opens room for therapeutic perspectives for lung cancer patients.