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References; 3 Structure, Function and Inhibition of Aromatase ; Abstract ; Abbreviations; Introduction; Crystal Structure of Human Placental Aromatase; Architecture of the Active Site; Structural Perspective on the Mechanism of Action; Membrane Integration
Oligomerization of AromataseRoles of Critical Residues; Motion and Flexibility of the Aromatase Molecule; Aromatase Inhibitors: Recent Developments; Phosphorylation of Aromatase and Estrogen Signaling: The New Frontier; Concluding Remarks; References; 4 In Vivo Models of AI Resistance ; Abstract ; Abbreviations; Introduction; Carcinogen Induced Syngeneic Tumor Model; Xenograft Model Using the Nude Mouse; Intra-tumoral Aromatase Xenograft Model; Aromatase Inhibitors as First Line Agents; AI Resistance Models; Estrogen Deprivation Based Models; LTED Model; UMB-1Ca Model
Letrozole Resistance ModelTransplanted Tumors; Activation of Growth Factor Pathways; Other Models; Variations Between the Models of AI Resistance; Discrepancies Between Animal Models and Clinical Data; Conclusion; References; 5 Ineffective Inhibition of Aromatase: A Cause for AI Resistance? ; Abstract ; Abbreviations; Introduction; The Aromatase Enzyme and Estrogen Disposition in Postmenopausal Women; Plasma Estrogen Measurements in Relation to Treatment with Aromatase Inhibitors; Tracer Studies; Tissue Estrogen Levels; Conclusions; References
6 Understanding the New Biology of Estrogen-Induced Apoptosis and Its Application in Patient Care Abstract ; Abbreviations; Introduction; Selective Estrogen Receptor Modulators (SERMs); Contribution of SERM Resistance in Understanding Estrogen-Induced Apoptosis; Long-Term Estrogen Deprivation; Molecular Mechanisms of Estrogen-Induced Apoptosis; Estrogen-Induced Apoptosis: Clinical Translation Opportunities; Perspectives and Conclusions; References; 7 Ligand-Independent Signalling Through Estrogen Receptor Pathways in Breast Cancer ; Abstract ; Abbreviations; Introduction
Background: Classical Ligand-Dependent Estrogen Receptor Signalling

Sommario/riassunto

The book brings together current knowledge about molecular and clinical aspects of resistance to aromatase inhibitors (AIs). The topics and features include: The history of development and clinical role of aromatase inhibitors in breast cancer. The structure and function of aromatase gene and protein, including tissue-specific splicing and regulation of the gene, crystal structure of the enzyme, functioning of its active site and structural basis for development of new aromatase inhibitors. Experimental and pre-clinical models of resistance to aromatase inhibitors (including cell lines and xenografts) as well as methods and results of measuring oestrogen concentrations in blood and tumour tissue of breast cancer patients. Diversity of molecular mechanisms of AI resistance, including (i) ligand-independent signalling through oestrogen receptor pathway, (ii) hypersensitivity to low concentrations of oestrogens, (iii) crosstalk with non-endocrine signalling (including PI3K/mTOR, IGF, GDNF and Myc pathways), (iv) involvement of oestrogen-induced apoptosis and tissue microenvironment (including inflammatory immune cells and adipocytes) as well as (v) the role of epigenetic mechanisms and pioneering factors in ER signalling and AI resistance. Molecular markers and multi-gene signatures to predict response to AIs, clinical trials aimed at preventing or overcoming resistance by combining AIs with novel targeted agents (including AI combinations with HER2, EGFR, mTOR, PI3K, Akt, CDK4/6, FGFR, HDAC, IGF-1, Src, proteosome- and angiogenic- targeting agents). A review of the effects and clinical indications of aromatase inhibitors beyond breast cancer. Many of the chapters provide extensive historical overviews to connect current

knowledge with the history and inner logic of the field. The authors' team includes world-leading experts, making the book an essential resource for scientists developing new treatments for breast cancer and for medics treating breast cancer patients with aromatase inhibitors.