Nanostructures in Therapeutic Medicine Series

Nanostructures for Cancer Therapy

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Foreword of the Series

Material science and engineering at the nanoscale has brought revolutionary advances to the biomedical sciences, overturning many of the traditionally known approaches. Nanotechnology has driven many of the most successful innovative technologies, and the impressive record of accomplishments in the field make nanostructures promising candidates for medical therapy applications. The advantages that nanomaterials have already provided to therapeutics, such as targeted and controlled delivery, wide accessibility, high specificity, low side effects, improved efficiency, and impressive versatility are currently considered key elements in designing personalized medicine approaches for prophylaxis, diagnosis, and therapy.

Therapeutic nanostructures can be greatly diverse, and their unique properties have led to the development of highly specialized biosensors, more efficient drug delivery vehicles, and controlled release targeting systems to fight severe or incurable diseases, such as cancer, infections, and cardiovascular disease.

In view of the astounding progress made in the field of therapeutic nanotechnology and its rapidly progressing expansion, this book aims to collect in one place all the recent and most innovative aspects of nanomaterials in both current and future therapy. The series is organized into five volumes, covering the main areas that are relevant for the design and implementation of nanostructures in medical therapies.

The first volume, *Nanostructures for Novel Therapy: Synthesis, Characterization, and Applications*, describes methods to obtain and characterize nanosystems, emphasizing their biomedical applications. Special attention is paid in this volume to modern synthesis methods to reduce side effects and limit the toxicity of nanomaterials in biomedical applications. Numerous examples of nanostructures designed for therapy, as well as the most efficient synthesis and characterization routes for these materials, are clearly described and critically analyzed.

The second volume, entitled *Nanostructures for Drug Delivery*, covers one of the most widely utilized and investigated applications of nanomaterials in the biomedical field, namely, drug delivery. Designing nanostructures to specifically and safely carry therapeutic agents to their final destination is an intriguing approach to future targeted therapies. This approach could provide a treatment for previously incurable diseases, as well as reducing the side effects of current drugs. Many highly active drugs are severely limited by side effects related to their unspecific sites of action. This volume introduces the readers to the amazing field of nanomedicine by discussing the versatility and variety of nanovehicles for drug delivery and targeting. Moreover, readers will find numerous examples and will learn about the currently used or investigational drug delivery agents for therapy, prophylaxis, and diagnosis.

Volume 3, *Nanostructures for Antimicrobial Therapy*, highlights the impressive progress made by nanotechnology in the design of novel antimicrobial approaches. Since microbial resistance to antibiotics is a real and increasingly worrying issue across all countries, the development of more efficient antimicrobial agents to provide control of future infections is at a high priority. Antimicrobial nanosystems have proved to be remarkably efficient against drug-resistant microorganisms, plus they are able to fight biofilm-associated infections and can control the social behavior of microbial communities.

Nanostructures can also reduce microbial virulence factors and reduce pathogenesis mechanisms, offering a promising alternative for future therapy.

Volume 4, entitled *Nanostructures for Cancer Therapy*, covers the applications of nanomedicine in cancer diagnosis and treatment. The use of nanoparticles for cancer therapy is not in itself a new approach, but numerous recent advances have been made in this area. The aim of this volume is to cover the most interesting new approaches in the management of this deadly disease. Nanosized drugs are currently believed to represent the most efficient approach in cancer chemotherapy, and this volume provides coverage of the latest and most novel findings, while also discussing possible improvements in more established types of nanosystems that can increase the efficiency of cancer therapy.

The final volume of this series, entitled *Nanostructures for Oral Medicine*, covers the progress made in applications of nanotechnology in treating various diseases of the oral cavity, as well as progress in nanotechnology applications in dentistry. Readers can learn about the most efficient modern materials used to treat or to prevent widely encountered oral diseases, such as gingivitis, periodontitis, caries, and dental plaque. Moreover, restorative dentistry also now makes wide use of nanomaterials.

Overall, this book series provides a state-of-the-art compendium of knowledge, and a crystal ball for seeing into the future of biomedical nanotechology and nanomedicine. It has an appeal for researchers, clinicians, engineers, pharmacologists, pharmacists, oncologists, infectious disease experts, and dentists. In addition, interested general readers will discover the impact, current progress, and future applications of nanotechnology in therapeutics and diagnosis. Taken together, nanoscale approaches will improve the efficiency of personalized medicine for better management of diseases in the 21st century.

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Preface

ABOUT THE SERIES (VOLUMES I–V)

In our permanently changing world, novel therapeutics are constantly required to manage health and well-being of population. Although numerous diseases are currently considered incurable, massive progress made in biomedicine and associated fields, such as chemistry, physics, engineering, pharmacology, and materials science offers a new light to the therapeutics domain. In this context, most physicists and researchers believe that a personalized and adequate treatment may significantly improve the outcome of severe diseases and ensure a faster healing. Nanotechnology offers great perspectives for personalized medicine because nanostructured therapeutics proved their efficiency and amazing impact in improving therapy, prophylaxis, and diagnosis. The emerging field of nanosized materials has numerous applications in the biomedical field, especially in therapy. This series of five volumes came out by the need of learning about recent progress of the science of nanostructured materials to improve current therapy and lead to the next level. The books offer an interesting and updated perspective regarding applications of nanomaterials in therapy of most investigated and difficult-to-treat diseases, such as cancer and severe infections. The presentation approach of each chapter contained in those five volumes is clear and easy to understand by readers and particularly interesting for biomedical specialists, researchers, and engineers. The series is organized in an attractive manner for students and academics on the field, starting with a volume dealing with synthesis, characterization, and main applications of nanostructures, emphasizing on their impact in therapy. Next volume reveals the most recent progress made on a very investigated field, considered a key element in personalized medicine and future therapy, namely nanostructured drug delivery systems. Their impact in antimicrobial therapy is also widely discussed, and suggestive examples are given and explained. Moreover, a whole volume is dedicated to the management of the disease of the century—cancer—revealing the huge value added by the utilization of nanosystems in the therapy of this deadly disease. Important aspects related to improved diagnosis and prophylaxis are highlighted. In the last volume, the progress and novel applications of nanotechnology in oral medicine is dissected. The field of oral diseases represents an interesting and a priority field because both physicists and researchers believe that they can be prevented and treated more easily with targeting systems and nanofunctional prosthetics. All chapters are clearly illustrated to highlight important or more difficult-to-understand aspects, and suggestive examples are often enumerated in organized tables, which are explained and discussed. Overall, the series contains very recent but accessible and interesting information regarding the progress of nanostructures in therapeutics and gives a novel perspective about future therapy of severe diseases.

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ABOUT VOLUME IV

The fourth volume of the series *Therapeutic Nanostructures* is entitled *Nanostructures for Cancer Therapy*. As cancer represents the disease of the century, numerous efforts are being made to limit its consequences. Starting with the development of extremely sensitive detection kits able to sense just a

few malignant cells, and ending with specialized therapeutic agents capable of specifically targeting tumors without harming healthy tissue, nanomaterials have found numerous applications in the management of this highly life-threatening condition. The design of specialized nanosensors applied for early diagnosis of tumors is considered one of the most efficient among biomedical innovations. Early and correct diagnosis is crucial to increase the outcome of the therapy; therefore, progress made in diagnosis and prophylaxis represents another important step forward for the applicative field of biomedical nanomaterials. The design of innovative and more efficient anticancer nanostructured drugs represents the main focus of this volume. Recent progress, along with relevant challenges, proposed solutions, and current limitations of nanotechnology in the development of anticancer agents are discussed and numerous examples are given. Volume IV contains 30 chapters prepared by outstanding international researchers from the USA, Canada, Italy, Romania, Turkey, Egypt, Iran, India, Korea, Portugal, Brazil, Australia, Spain, Ukraine, Portugal, and Thailand.

In Chapter 1, entitled *Nanotechnology for Personalized Medicine: Cancer Research, Diagnosis, and Therapy*, Delia Albuleț et al. summarize the types of nanotechnologies that have made a great impact in medicine and especially in cancer research and therapy. Using drug delivery systems based on liposomes, magnetic nanoparticles, noble metal nanoparticles, polymeric nanoparticles, upconversion nanoparticles, quantum dots, or carbon nanomaterials, a new perspective in curing cancer is given.

Konstantinos Pantapasis et al., in Chapter 2, entitled *Bioengineered Nanomaterials for Chemotherapy*, presents the most investigated nanomaterials currently under consideration for anticancer approaches, along with essential information regarding their synthesis properties and most recent applications.

Chapter 3, prepared by Emine Guler et al., entitled *Biofunctionalized Nanomaterials for Targeting Cancer Cells*, gives an up-to-date overview about the most recently developed nanomaterials and the loadings of nanomaterials with various drugs to prepare nanocarrier systems, as well as the usage of the obtained nanobiomaterials in targeting cancer cells.

In Chapter 4, entitled *Improving Chemotherapy Drug Delivery by Nanoprecision Tools*, Nehal Salahuddin and Ahmed Galal discuss various aspects of nanoparticles, including polymer nanoparticles, inorganic nanoparticles, polymer/inorganic nanocomposites, formulation, characterization, and the effect of their characteristics and morphologies on their applications in delivery of chemotherapy drug molecules, including the advantages, disadvantages, and challenges facing nanomedicine in oncology.

In Chapter 5, entitled *RIPL Peptide as a Novel Cell-Penetrating and Homing Peptide: Design, Characterization, and Application to Liposomal Nanocarriers for Hepsin-Specific Intracellular Drug Delivery*, prepared by Min H. Kang et al., along with a brief introduction of cell-penetrating and homing peptides, important aspects in the design of specific peptides and targetable liposomal nanocarriers are discussed, focusing on hepsin-specific intracellular drug delivery.

Chapter 6, entitled *Progress of Nanoparticles Research in Cancer Therapy and Diagnosis*, prepared by Irina Negut et al., reviews the novel applications of magnetic nanoparticles as drug nanocarriers for the therapy of different oncological diseases, together with imaging characteristics that recommend them as efficient contrast agents in magnetic resonance imaging applications.

Suman Rana et al., in Chapter 7, entitled *Interfacial Engineering of Nanoparticles for Cancer Therapeutics*, focus on recent developments in the area of surface modification of inorganic and organic nanoparticles for selective delivery of anticancer drugs. Various examples of applications of liposomes,

micelles, vesicles, hydrogels, and protein and polymer nanoparticles, as well as the nanoparticles of metals, metal oxides, and their hybrid structure as efficient carriers of anticancer drug are briefly dissected.

Rukkumani Rajagopalan and Jatinder V. Yakhmi, in Chapter 8, entitled *Nanotechnological Approaches Toward Cancer Chemotherapy*, present an in-depth insight into the delivery and economic aspects of biodegradable and nonbiodegradable nanoparticles, and discuss the gaps that exist between lab-scale and commercial potential of therapy using them.

Tatiana Andreani et al., in Chapter 9, *Cancer Therapies: Applications, Nanomedicines and Nanotoxicology*, highlight the benefits of nanotechnology and of nanomedicines for cancer diagnosis and therapy, focusing on the relevant aspects of nanotoxicology.

Bishnu P. Bastakoti and Zongwen Liu, in Chapter 10, entitled *Multifunctional Polymeric Micelles as Therapeutic Nanostructures: Targeting, Imaging, and Triggered Release*, address the current status and possible future direction of the highly emerging area of multifunctional nanocarriers based on micelles of different block copolymers with controlled loading, targeting, imaging, and triggered release.

Chapter 11, prepared by Mara M. Mihai et al., entitled *Recent Advances in Diagnosis and Therapy of Skin Cancers Through Nanotechnological Approaches*, offers an up-to-date overview about medical nanotechnology and the ability of nanoscale materials to overcome major limitations of current therapeutic strategies in skin cancer by specifically targeting the tumor, by stabilizing chemotherapeutic compounds, and by ensuring a controlled and durable release of the drug. Moreover, due to special particularities of nanoparticles and complex nanosystems, they can be efficiently utilized for skin tumor detection in a fast and secure manner, nanoparticles being able to penetrate and be detected even in the deepest layers of the skin.

Chapter 12, prepared by Peter Tsirikis et al., entitled *Design of Nanoparticle Structures for Cancer Immunotherapy*, examines how prophylactic and therapeutic tumor immunities can be achieved using nanoparticles targeting dendritic cells in vivo. Moreover, this review elucidates the differential immunological properties of engineered nanoparticles. Surface morphology, size, shape, and surface functionalization can influence cellular uptake, toxicity, immunogenicity, and the T-helper 1 (Th1)/T-helper 2 (Th2) bias of the immune response.

Chapter 13, entitled *Recent Advances of Folate-Targeted Anticancer Therapies and Diagnostics: Current Status and Future Prospectives*, prepared by Ana M. Martínez et al., focuses on the possibilities offered by folic acid toward recent advances in cancer treatment and diagnostics, and also future perspectives on these folate-targeted therapies to fight against cancer with more efficient prophylaxis.

In Chapter 14, *Anticancer Efficiency of Curcumin-Loaded Invertible Polymer Micellar Nanoassemblies*, Ivan Hevus et al. present a new approach in polymer-based delivery of poorly water-soluble drugs. Also, the authors give an overview regarding the administration of curcumin using polymer micelle assemblies.

Chapter 15, prepared by James C. L. Chow, entitled *Dose Enhancement Effect in Radiotherapy: Adding Gold Nanoparticles to Tumor in Cancer Treatment*, offers recent insights about gold nanoparticle-enhanced radiotherapy. Also, the authors discuss the physical and radiobiological effects on the cancer cell killing in the presence of gold nanoparticles.

Oana Fufă et al., in Chapter 16, entitled *Silver-Based Nanostructures for Cancer Therapy*, give an overview regarding the latest results reported in novel silver-based nanotechnology-derived systems as promising strategies for modern cancer therapy.

Sabyasachi Maiti, in Chapter 17, *Ligand-Decorated Polysaccharide Nanocarriers for Targeting Therapeutics to Hepatocytes*, emphasizes on the synthesis of ligand-polysaccharide nanocarriers and recent trends in ligand-directed therapeutic strategies for curing liver diseases.

Chapter 18, entitled *Targeted Delivery of Anticancer Drugs: New Trends in Lipid Nanocarriers*, prepared by Mariana S. Oliveira et al., presents the recent progress about targeted delivery of anticancer drugs. Stimuli-sensitive and combination therapies and their advantages are discussed, with particular attention given to lipid-based nanocarriers. The authors focus on liposomes, lipid-based micelles, and the emerging class of particles based on lipid components other than phospholipids, including solid lipid nanoparticles and nanostructured lipid carriers.

Maria M. Cruz et al., in Chapter 19, entitled *Nanoparticles for Magnetic Hyperthermia*, present a general view of the different aspects involved in the research on nanoparticles for magnetic hyperthermia therapeutics. The recent developments to improve the nanoparticles' ability to act as nanoheaters, namely, new synthesis methods to obtain ferrite nanoparticles and core@shell nanostructures (with different magnetic phases), are discussed, together with the hyperthermia efficiency results.

Chapter 20, prepared by Denisa Ficai et al., entitled *Nanotechnology: A Challenge in Hard Tissue Engineering with Emphasis on Bone Cancer Therapy*, presents recent progress about the role of nanotechnology in developing materials for hard tissue engineering with a special attention in bone cancer therapy. Based on the recent advances in the field of materials, the most promising material for bone tissue regeneration seems to be the tissue-engineered nanocomposites, which can be designed to achieve specific functionalities.

Forouhe Zahir et al., in Chapter 21, entitled *Combination Therapy of Macromolecules and Small Molecules: Approaches, Advantages, and Limitations*, discuss the utilization of macromolecules consisting of peptides, antibodies, and nucleic acids as novel therapeutic agents in cancer treatment. The first part summarizes several signaling pathways involved in cancer generation and progression, and approved and in-trial monoclonal antibodies related to everyone. In the second part, targeting approaches to cancer cells are discussed. Finally, different classes of nucleic acids consisting of antisense oligonucleotides, RNA ribozymes, RNAi, and aptamers are introduced.

Chapter 22, prepared by Mine S. Gunay and Yekta A. Ozer, entitled *Nanosized Drug Delivery Systems as Radiopharmaceuticals*, presents an up-to-date review about the utilization of nanosized, specifically targeted drug delivery systems for both diagnosis and therapy of several diseases as theranostics.

Chapter 23, entitled *Mesoporous Silica Nanoparticles: A Promising Multifunctional Drug Delivery System*, prepared by Priti P. Pednekar et al., addresses the synthesis, characterization, advantages, as well as applications of mesoporous silica nanoparticles in the delivery of anticancer drugs.

Chapter 24, prepared by Carla Teixeira et al., entitled *Cancer Therapies Based on Enzymatic Amino Acid Depletion*, reviews the structure, function, catalytic mechanism, and therapeutic application of some amino acid–depriving enzymes. Particular attention is given to enzymes that have potential or are currently used in the treatment of several types of cancer, namely: (1) L-asparaginase, used for the treatment of acute lymphoblastic leukaemia; (2) L-arginase and L-arginine deiminase, used in the therapy of hepatocellular carcinomas and melanomas, two diseases that account annually for approximately 1 million new cases and for which there is currently no efficacious treatment; and (3) L-methioninase, with potential to be used in the treatment of breast, colon, lung, and renal cancers.

Vivek P. Chavda and Dhaval Shah, in Chapter 25, entitled *Self-Emulsifying Delivery Systems: One Step Ahead in Improving Solubility of Poorly Soluble Drugs*, discuss the lower bioavailability of drugs and the use of a lipid formulation classification system combined with appropriate in vitro tests that

help to establish a database for in vitro–in vivo correlation studies. Certain disadvantages associated with conventional self-emulsifying drug delivery systems are now overcome by some of the recent advancements that are described in this chapter along with recent patents in such fields.

Chapter 26, entitled *Near-Infrared Light-Responsive Nanotherapeutic Agents: Application in Medical Oncology*, prepared by Viroj Wiwanitkit, details and discusses the application of new nanomolecules, namely near-infrared light-responsive agents, with applications in both diagnostic and therapeutic medical oncology.

Fabíola S.G. Praça et al., in Chapter 27, entitled *Current Aspects of Breast Cancer Therapy and Diagnosis Based on a Nanocarrier Approach*, review nanosystems containing anticancer agents that are used for metastatic breast cancer in clinical practice, clinical trials, and research orientations. Also, the authors provide an overview of biomarkers used in metastatic breast cancer allowing for improved prognosis and therapy.

Chapter 28, prepared by Kumari Varsha et al., *Natural Plant-Derived Anticancer Drugs Nanotherapeutics: A Review on Preclinical to Clinical Success*, provides an overview of the plant-originated anticancer drug nanomedicines currently undergoing preclinical or clinical trials or being used in clinics. Special emphasis is given on the elucidation of anticancer and antiangiogenic mechanisms of action of natural anticancer drugs. Moreover, attention has also been paid to passive and active targeting achieved in natural anticancer drugs by using colloidal and nanoparticulate systems–based nanomedicines.

Chapter 29, prepared by Avinash P. Ingle et al., entitled *Nanotherapy: A Next Generation Hallmark for Combating Cancer*, gives an overview about the role of nanotechnology in the form of drug delivery systems with nanoparticles (i.e., nanotherapy that shows a vast potential for cancer treatments). Nanotherapy is an actual modern mode of treatment that can be applied for cancer therapy with few or no side effects.

Chapter 30, entitled *Nanostructures for Cancer Therapy: From Targeting to Selective Toxicology*, by George M. Vlasceanu et al., presents an up-to-date overview about one of the most controversial cancer treatments: targeted cancer therapy. Even though nanostructures may offer a great advantage in cancer therapy, numerous toxicity-related aspects should still be considered to implement the use of anticancer nanosystems in current cancer treatment.

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CHAPTER

1 NANOTECHNOLOGY FOR PERSONALIZED MEDICINE: CANCER RESEARCH, DIAGNOSIS, AND THERAPY

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CHAPTER OUTLINE

1 INTRODUCTION

Cancer represents an important health problem at a global level being the second cause of death in the United States. The American Cancer Society provides each year relevant data about the number of deaths caused by cancer, and it is believed that cancer-related deaths could surpass the number of deaths caused by heart diseases in the next years (Siegel et al., 2015). Cancer is a multistep process and appears as a consequence to the loss of control of cell division, leading to uncontrolled cellular proliferation (Bashyam, 2002), and also appears as the ability of the abnormal cells to overwhelm other tissues (Aly, 2012).

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The EUROCOURSE project developed a special program known as the European Cancer Observatory (ECO) to collect all the information available on cancer incidence, survival, prevalence, and mortality in Europe from 40 European countries, estimated for 2012. Based on this data, more than 3.3 million new cancer cases have been estimated, apart from nonmelanoma skin cancer. The widespread cancers were those of lung, prostate, large bowel, and breast, representing 1.7 million cases. The cancer with the greatest number of deaths is lung cancer, while the cancer with the greatest number of prevalent and incident cases is breast cancer (Steliarova-Foucher et al., 2015).

Normal cells become tumor cells through changes taking place in their DNA, under the pressure of the environmental factors that cause the initial mutation. Normally, when DNA sequences are injured, the cells activate their repair mechanism or, if the damages are too extensive, the cells die. The development of tumors derives from single modified cells that begin to proliferate abnormally because of the unrepaired DNA mutations. Tumor progression is viewed as a multistep process involving mutation and selection of cells with progressively increasing capacity for proliferation, survival, and invasion. One of the hallmarks of cancer is represented by the rapid growth of tumors, which leads to low oxygen rates (hypoxic conditions) (Blazejczyk et al., 2015).

Nowadays, the genomic alterations that lead to cancer are better understood and the connections between genes and the conditions of the human body have been studied to prevent cancer initiation.

The genes that cause tumor development under the mutation process are usually grouped in two main categories:

1. *Cancer-promoting oncogenes*, also known as protooncogenes, which are frequently activated in cancer cells, giving new properties, such as hyperactive division and growth, ability to become recognized in new tissues, or protection against apoptosis (programmed cell death).
2. *Tumor suppressor genes* (antioncogenes or TSG), which are inactivated in cancer cells (Aly, 2012; Harrington, 2011).

To develop a malign neoplasm, mutations in both types of genes are expected. Substances that can cause the DNA mutations (also known as carcinogens) are linked to specific types of cancer. For example, smoking is connected to lung cancer, and solar ultraviolet radiation may cause skin cancer.

The ability of abnormal cells to grow or spread to other vital organs is called metastasis and it is the most common cause of death for patients with malign neoplasm. The metastasis process takes place when the abnormal cells access the body's blood vessels to move to other parts of the human body where they can proliferate and develop new tumors (Le Dévédec et al., 2010). Certainly, about 90% of malign neoplasm deaths come from metastasis (Ganapathy et al., 2015). At the beginning of the metastasis process, abnormal cells activate the epithelial-to-mesenchymal transition, also known as EMT, which refers to the activation of the latent embryonic program by the cancer cells (Pietilä et al., 2016).

Angiogenesis process involves the endothelial cells, which break free from the blood vessels and develop tubes during the proliferation process (Tsimberidou et al., 2015). The cancer cells located in tumors are an abundant resource of proangiogenic molecules that guide the activity of endothelial cells, promoting their migration and determination. The endothelial cells manage the activity of platelets and they have an antiinflammatory, anticoagulant, and antiadhesive phenotype. The structure of tumor vessels is correlated with the malignancy of the tumors because of the cancer cells that grow along the existing vessels (Blazejczyk et al., 2015).

The platelets are well known for their main function: to stop hemorrhage after tissue damage and vascular injury, because they have the ability to release bioactive factors when they become

activated (when matrix is exposed or if inflammation appears and disturbs the endothelium) (Yan and Jurasz, 2015). Besides their function in hemostasis, activated platelets also contribute to tumor cell metastasis with an intense impact on circulating tumor cell survival, growth, and invasiveness. Their influence on abnormal cells is based on mechanisms such as the release of GFs (growth factors), proteins, and so on. The cancer cells have the ability to control the platelets function so as to improve their extravagation and development (Tesfamariam, 2016).

Disorder prevention is built around the idea that several risk factors may be controlled, for example, decreasing exposure to notorious causes of cancer, such as sunlight exposure, cigarettes, alcoholic drinks, unhealthy meals, and so on, or promoting activities that are correlated with reduced cancer risks (Bashyam, 2002; White et al., 2013).

In the past few years, the main role of numerous intracellular or extracellular biochemical signals in malign neoplasm cell proliferation, metastasis, and invasion has been revealed. The mechanical properties of the ECM (extracellular matrix) showed an important influence in the metastasis process. In vivo and in vitro tests showed that enhanced tissue rigidity has a functional role in controlling the malign character of a tumor and tumor invasion (Wei and Yang, 2015).

Solid tumors are living units made of various complex cell types that may even surpass the healthy tissues. According to Jiang et al. (2015), a new theory about the malignant progression of cancer was developed indicating the idea that this evolution not only depends on abnormal cells genetic aberrations, but also on the bidirectional dynamic and complex connections between stroma and cancer cells within the tumor microenvironment.

Breast, lung, and prostate cancer are among the most frequent forms of solid tumors. Cancerous cells found in solid tumors enroll inflammatory cells, producing inflammatory stroma. The invasiveness and the resistance of the metastatic breast cells are the result of the oncogenic epithelial to mesenchymal transition. In this case, cells undergoing EMT hit the nearby stroma causing the extravasations of cells in the blood, individually or as a mass (Subramanian et al., 2015).

The epithelium is a well-established structure with a uniform layer formed by the epithelial cells. In the case of the breast, these types of cells develop the lining of canals, which are responsible for milk transport in the lactation process. The most common type of carcinoma in breast cancer is the ductal carcinoma appearing both in men and women, but its prevalence in men is uncommon (Videira et al., 2014).

An important role in encouraging the proliferation process of both the neoplastic and the normal breast epithelium is given by estrogens (Russo and Russo, 2006). There are many types of physiological estrogens, such as estrogen, progesterone, cortisol, and aldosterone, but the main physiological estrogen in mammals is estradiol (E2) (Baker, 2013). Estradiol is the most biologically active hormone located in the breast tissue and it stimulates the breast evolution at puberty and during sexual maturity. In vivo and in vitro tests revealed the idea that E2 has the ability to induce full neoplastic transformation of epithelial cells (Russo and Russo, 2006).

A significant regulator in breast cancer is the extracellular matrix. It produces several modifications in organization and structure, in comparison to the mammary gland under homeostasis. A number of ECM elements play an important role in metastasis and progression of breast cancer, such as collagens, specific laminins, fibronectin, glycosaminoglycan, proteoglycans, and ECM remodeling enzymes.

Other common cell types that take part in tumor development are CAFs (cancer-associated fibroblasts, neuroendocrine cells, adipocytes) and MSCs (human mesenchymal cells or blood stem cells). These cells are located in the tumor microenvironment (TME). Additionally to cellular components,