Nanotechnology in Cancer

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Edited by

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She received her doctorate degree in Biomedical Engineering from Duke University, Durham, North Carolina, United States, before joining the MD Anderson Cancer Center faculty as a tenure-track Assistant Professor in 2003. She also holds two Bachelor of Science degrees with honors and one Master of Science degree from North Carolina State University, Raleigh, North Carolina, United States, and another Master of Science degree from Duke University, Durham, North Carolina, United States.

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Foreword

Application of nanotechnology in cancer is the forefront of nanomedicine that can improve quality of life of the patients suffering from disease, disability, and disfigurement. Nanotechnology can be applied to target diverse areas afflicted by cancer such as invasive and metastatic diseases, aesthetic plastic surgery, and therapeutic delivery via catheters and stent coatings.

Nanotechnology can generate various structures and shapes with programmable properties resulting in specificity of function. While research has heavily focused on carbon and gold nanoparticles, nanotubes, and other combination structures, the size of the structures defines it as nano in the range of 1−100 nm as per definition of the National Institutes of Health (https://www.nih.gov/research-training/nanotechnology-nih), Bethesda, Maryland, USA.

This edition of the book written from a major cancer center, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA, has attempted to cover the entire range of ongoing work in Nanotechnology. A major area that my group has written about in the past is Imaging Nanotechnology and that is not covered at length in this book.

Cancer is treated as compromised wound bed with issues such as heterogeneous vasculature, genetic malformations, cellular diversity, microbe infiltration, and other issues that affect its growth and preservation in the human body. Although cancer bed is a challenging environment to begin with the invasive and metastatic diseases make it impossible to treat.

The targeting of the nanotechnology-based therapeutics is multifaceted and can be customized with the specificity of the therapeutic. Further customization by surface modification techniques allows receptor−ligand specificities toward a tumor bed. Free energy of molecules in that regime is affected by entropy, disorder. The targeted therapeutic area is loaded with biological sources and synthetic molecules. Specifically, therapeutic industry such as the nutraceuticals has roots in Ayurveda medicine. Combination targeting with factors considered from ancient Ayurveda and free energy targeting by surface modifications has implications in cancer treatment.

The existence of cancer has deep roots in medicine and the complexity of the tumor and treatment may be tied together. Similar to gene therapy in the past, nanotechnology is considered a forefront of medicine targeting molecular regimes that are unexplored but challenging. Considering the factors affecting tumor treatment using nanotechnology, the science and its translation is controversial similar to gene therapy. The failure rates could be considerable if the complex molecular nature is not identified.

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Preface

I dedicate this book to my children, Roshan, Aarushi, Devan, and the one who didn't make it.

I have been working in the area of Nanotechnology applications in cancer since my appointment at The University of Texas MD Anderson Cancer Center as a tenure-track Assistant Professor in 2003. While the cancer center is rich in knowledge about cancers, I was able to collaborate with therapeutic researchers and offer my expertise as a Biomedical Engineer and build molecules such as silk fibroin−coated liposomal emodin and nanocurcumin. We have been conducting studies to assess absorption of the nanocurcumin in an in vivo rat tumor model and will continue collaborations with MD Anderson clinical and basic science collaborators. The advantages of this nanoparticle approach for clinical health applications are tremendous, such as ease of manufacturing, versatility toward any therapeutic, high efficacy against diseased cells, biodegradability, no toxic byproducts, and biodisposability.

The first edition of this book focuses on nanotechnology in cancer and has further impact in regenerative medicine with respect to complete cancer care. Combination of nanotechnology with cell and tissue engineering is the forefront in regenerative nanomedicine that can help understand disease at the nanoscale leading to novel therapy modalities and improve quality of life in cancer patients. I have cultivated multiphase strategies to address the restoration of functional tissues in cancer patients with critical size defects, by focusing my research on the development of nanoengineered regenerative biomaterials and targeted nanotherapeutics for regulated local repair. The ultimate goal of my research group is to engineer regenerative, cell-responsive, and therapeutic three-dimensional nanostructured biomaterial matrices that would recruit, guide, and renew cells at the repair site by surrendering control of the regenerative process to the cells, which regulate the process at the cell−matrix nanointerface (<100 nm). In order for investigators in this emerging field of nanomedicine and regenerative medicine to develop complete repair strategies with high efficacy, we will first have to understand the rules at the nanoscale as they pertain to tumors and regenerative stem cells. What are the nanosignatures or the quantum molecular signatures of various cells? The quantum molecular signatures of the tumor cells that are intermixed with stem cells at a repair site can help us differentiate the "target sites" on tumor cells versus the regenerating stem cells at the same location. With the assistance of microsurgery, we can reach these "targets" in order to detect, manipulate, and guide local regeneration.

The future of nanotechnology at MD Anderson Cancer Center lies in continuing to develop collaborative efforts across the institution in order to study the regulation of cells at a molecular scale to achieve repair, reconstruction, and regeneration in cancer patients via molecularly engineered materials. I plan to lead initiatives at the national level to build this area of research and develop a

translational device platform in the area of regenerative materials and quantum-targeted nanotherapeutics.

I would like to thank my Sr. Administrative Assistant, Ms. Micquelyn Titus, and the Department of Plastic Surgery for their administrative support. The Elsevier team and the publisher have provided publishing infrastructure for me to be able to edit this book. I would also like to acknowledge my family.

This book brings together my work since 2003 at UT MD Anderson Cancer Center and I hope that the community can grasp how the two independent areas of Nanotechnology and Cancer come together.

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Introduction to Bio-Nanotechnology

The properties of cells and tissues, whether they are diseased like cancer or healthy, are a function of their interactions with each other and have to be treated as an integrated closed system. The key is to recognize that the macrotissue properties are driven by its microenvironment, which is affected at the nanoscale by an integrated cellular assembly and its mechanical interactions with the other cells and matrix components. From an engineer's perspective, the divide in knowledge between cancer and health is due to the divide between engineers/biophysicists and cancer cell biologists working independently in their own research microculture. For example, engineering methods of study in these cancer systems could get trapped in in vitro 2D monolayer experiments and new systems designed by engineers/biophysicists who probe cells at nanoscale and below with instrumentations such as surface force apparatus and atomic force microscopy or model such effects using finite element modeling at the microscale may not translate into the cancer world. The fanciest experiments are in 3D in situ live animal imaging with multiphoton second harmonic generation confocal imaging, which gives structural information and cell−cell interactions at a global tissue level. Cancer cell biologist can break the cellular pathways down to their microRNA but compromise the cohesiveness of the integrated cellular unit. The next generation of instrumentations have to be developed in collaboration between cancer cell biologist, who have the molecular knowledge of which molecules are being expressed by the cells, and engineers/biophysicists, who know how to combine the latest technologies that will allow probing of cells at the nanoscales and below in their native 3D microenvironments, such that differences between cancer and normal tissues properties can be built into a library that has quantitative information about an integrated cell−matrix assembly. For example, tumor type (breast, liver, pancreas, etc.), cell type (epithelial cell, hepatocyte, endothelial cell, etc.), Ligand X interacts with Receptor X on the cell with an adhesion strength of Y and drives actin microfilament cytoskeletal assembly to form stress fibers that may increase the stiffness Z of the cell globally, as the signal travels down to the cell−integrin interactions that leads to integrin clustering, which feeds back into the cytoskeletal stress fiber assembly and perhaps increases/decreases/balances the expression of Receptor X. If we have all of this information about integrated closed tumor systems, we can develop targeted nanotherapeutics with minimal toxicity and advance our knowledge for treatment of other diseases also.

Engineers have developed imaging technologies such as quantum dots (QDs) to overcome issues with cancer microenvironment. Although QDs have unique optical properties, such as size tunable absorption and emission at various wavelengths, improved photostability, and narrow emission peak to enable multiplexing, the toxicity associated with QDs in biological systems is a major

shortcoming that can be overcome using biological coatings. For example, the synthesis, characterization, and application of silk fibroin (SF)-coated semiconductor nanocrystals, a.k.a. QDs, in cellular systems was reported. The coating of QDs with SF provides a biological and biocompatible alternative to traditional fluorescent markers for in vitro and in vivo cellular imaging applications. The biocompatible interface provided by the SF coatings would be expected to assist in the clearance of SF-coated QDs. These features increase the potential for administration of SF-coated QDs for in vivo imaging administration for versatile disease-specific imaging needs. From a nanoparticle size perspective, it is interesting to note that SF has the molecular composition and structural features to allow it to coat particles <10 and >100 nm.

Biological nanocoatings have also been used to overcome numerous barriers to drug delivery into the tumor site. Careful considerations are required when designing a new "capsule" formulation of a drug for high efficacy at the tumor site. The success of a therapeutic/drug is dependent upon its mode of delivery and its potency at the site of tumors. At the site of a solid tumor, key issues that make the drug delivery to tumors a challenging affair are heterogeneous vascular architecture and permeability, high interstitial pressures in the necrotic core, large interstitial distance between the tissue mass and vessels, low convective transport, acidic pH, hypoxia, and lack of lymphatic drainage. In addition, due to lack of specificity of the delivery device for tumor cells, administration of high dosage of the drug causes drug resistance and toxicity to normal tissues. Thus biological nanocoatings have been developed that enhance targeting to a tumor cells, increase retention of the drug, release drug in a controlled manner, and enhance the efficacy of a drug/therapeutic. The integration of therapeutic that may have targeted specificity for a tumor type with a delivery device that does not compromise its specificity for the tumor is a critical parameter to consider.

Treatment modality to revolutionize the way cancer is treated currently is to stay with a comprehensive approach yet maximize targeting and specificity. The entire approach and its individual components are innovative in their own respect.