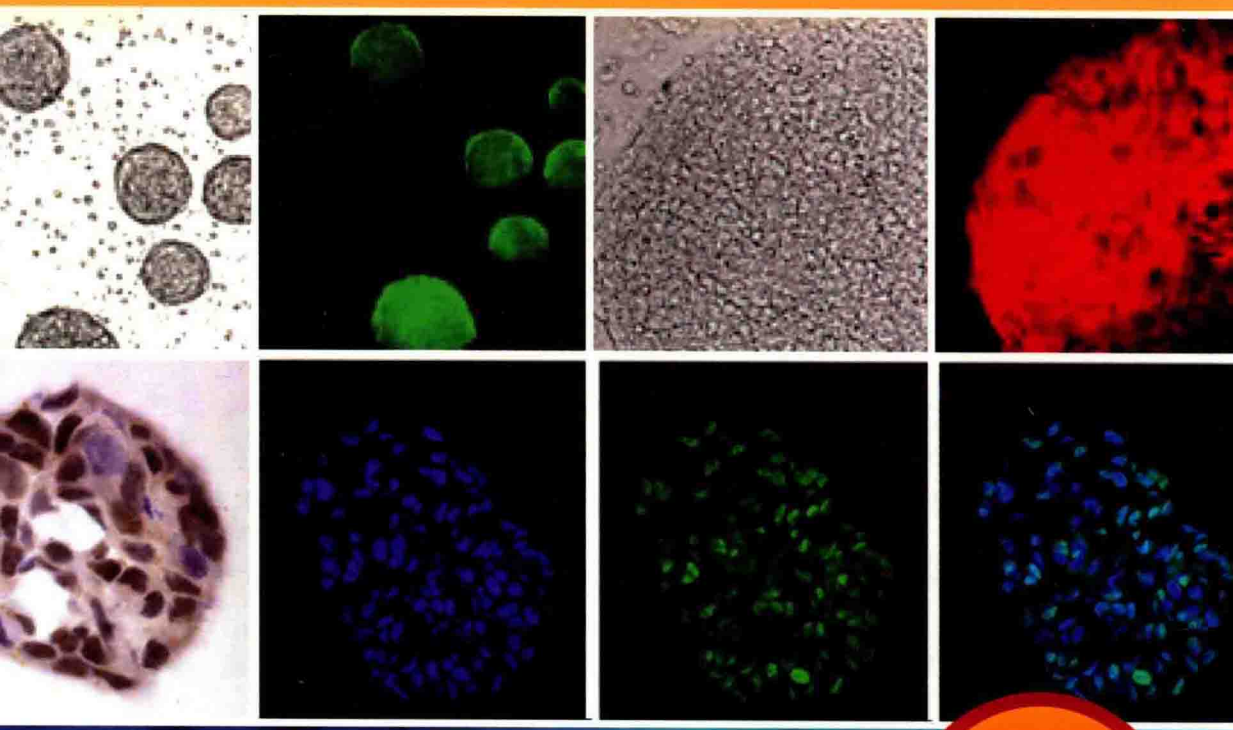

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Cancer Stem Cells

Vinagolu K. Rajasekhar

WILEY Blackwell

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Dedication

I sincerely dedicate this book to:

- All Physicians, Basic Research Scientists, Physician Scientists, Other Employees at All the Levels and Patients at Memorial Sloan-Kettering Cancer Center, New York.
- My Family: My parents, Late Mr. Vinagolu Krishnamachari and Mrs. V.K. Suseela (on her 75th Birthday), my wife, Mrs. Birgit Luise Baur, and my children Julia Ruby Vinagolu-Baur and Jessica Pallavi Vinagolu-Baur, my parents-in-law, Mr. Hugo Baur (on his 90th Birthday) and Mrs. Erika Baur, my late sister and late brother V.K. Bhanu and V.K. Suresh respectively, and other brothers, cousins (especially A.R. Thulasi Krishna and. Kumbakonam Prasaad), uncles (particularly Hari Gopal, Raghunath, A. Venkatachari, Mahi, K. Jagadeshan, and K. Chandra), aunts (particularly Jaya Aunty), nephews, nieces, and last but not least my childhood friends (R. Dharmarao, A. Ramesh Reddy, E. Lokeshwar Reddy, S. Gopi, and S. Venkateswara Prasad).
- And, many others not limited to Drs. Irv Weissman, Nahum Sonenberg, Bjørn Nicolaissen, Alan Trounson, John Dick, Max Wicha, Andreas Trumpp, David Lyden, Shahin Rafii, Laurie Glimcher, Marc Tessier-Lavigne, Elaine Fuchs, David Allison, Nancy Colburn, Knud Nierhaus, Aboulghassem Shahdadfar, Jesintha Navaratnam, Sally Temple, Craig Jordan, Inder Verma, Leonard Zon, Fred Gage, Shinya Yamanaka, Alex Meissner, Kevin Eggan, Konrad Hochedinger, Chad Cowan, Karla Kim, Douglas Melton, David Scadden, Bert Vogelstein, Tyler Jacks, Ronald DePinho, Stephen Elledge, Martin Pera, Oven Witte, Micheal Shen, George Daley, Stuart Orkin, Rudolf Jaenisch, Kornelia Polyak, Eric Holland, Harold Varmus, Robert Wittes, Stephen Nimer, Eric Lander, Craig Venter, Michael Karin, Sanjay Tyagi, Maitradas Panicker, Fay Betsou, Pasquale De Blasio, Timothy Osborne, the late William Gerald, and also to plant biology colleagues not limited to Professors Sudhir Sopory, Hans Mohr, Krishna Tewari, Michael Mulligan, Donald Fosket, Winslow Briggs, Wilbur Campbell, Brent Nielsen, Ralf Oelmuller, L. Vijayamohan Rao, M.K. Reddy, as well as The Samuel Roberts Noble Foundation, Ardmore, OK and the late: V.S. Ramadas, Sipra-Guha Mukherjee, and Christopher Lamb.

About the Editor

Dr. Vinagolu K. Rajasekhar, MSc, MPhil, PhD, is a Senior Research Scientist at Memorial Sloan-Kettering Cancer Center, New York. Dr. Rajasekhar and his research team have purified human prostate CSCs, discovered new biomarkers, and revealed a clinically relevant signaling pathway distinct from that found in bulk tumor analysis (www.Genomeweb.com). This study has also opened up a field of live biobanking of patient CSC-derived xenograft (PDX^{CSC}) tumor models amenable for individualized therapeutic testing. His publications accomplished an impressive number of citations, previews in lead journals, and exceptional post-publication reviews by Faculty of 1,000.

Dr. Rajasekhar is the senior editor of Regulatory Networks in Stem Cells, one of the top 25% most downloaded ebooks in the relevant Springer eBook Collection in 2012. His graduate work at the Jawaharlal Nehru University, New Delhi, fetched him the internationally competitive research fellowship from the Alexander von Humboldt Foundation, Germany. He has researched and/or also taught courses in other leading institutions including the University of Freiburg, Germany, Texas Tech Univeristy, Lubbock, TX, Michigan Tech University, Houghton, MI, University of California, Irvine, CA, Humboldt University, Berlin, Germany, The Samuel Roberts Noble Foundation, Ardmore, OK, MD Anderson Cancer Center, Houston, TX, and the University of Medicine and Dentistry of New Jersey, NJ. He has been a reviewer for many lead scientific journals and an invited speaker and chair/discussion leader in many national and international conferences related to Biobanking. Recently, Dr. Rajasekhar has been nominated to ISBER Biospecimen Working Group.

Dr. Rajasekhar is currently integrating the live biobanking approach to human tumor specimens from the generous pre-consented patients with the recently emerging mouse hospital concept for mechanistic studies. In principle, these approaches are aimed at combating cancers at their roots and looking forward to share the reagents worldwide for harmonization of research materials towards facilitating patient-specific translational research and also enhancing clinical cancer outcomes with fidelity.

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Foreword

During the last decade, the conceptual themes of stem cell biology have been re-applied, with a new vigor, to the field of oncology. The idea that, similar to normal tissues, tumors can be viewed as "complex societies," where different cell types are generated as the result of multi-lineage differentiation processes, and organize themselves in hierarchical structures, has now entered the realm of solid tumor biology, and altered the way we think of cancer as a disease. Most importantly, the possibility that tumor tissues, similar to normal ones, might be sustained in their long-term growth by a subset of cancer cells endowed with stem cell properties (i.e., a mutated "cancer stem cell" population capable of both aberrant self-renewal as well as differentiation) has important implications for the future development of targeted therapies. In this beautiful book, Dr. Vinagolu K. Rajasekhar (Memorial Sloan Kettering Cancer Center, New York) thoughtfully weaved together the perspectives and contributions from several of the leading scientists in the field. This book is both an elegant review and a practical guide to the exciting, and still largely uncharted, world of "cancer stem cells," I praise the editor and the authors for this wonderful endeavor, rich of provocative ideas and challenging concepts, not only for a better understanding of basic cancer biology, but also for the future development of new, more effective, anti-tumor treatments.

– Michael F. Clarke, MD,
Stanford University, Stanford, CA, USA

"The cancer stem cell (CSC) concept posits that not all cells in tumors are equal, but that dedicated cells fuel tumor growth. A major attraction of the CSC concept rests in the explanations it provides for several poorly understood clinical phenomena. The CSCs are built to last a lifetime, to be resilient to electromagnetic and chemical insults, to be able to slumber for prolonged periods of time, and to colonize other parts of the body. Thus, the CSC hypothesis explains why a cancer patient should never be considered cured, even when the initial response to radiation or chemotherapy is encouragingly robust. The concept guides the development of more effective treatments, targeting the 'beating heart' of the tumor: the CSC. This authoritative book, written by a range of world-leading cancer researchers, provides a comprehensive overview of the cancer stem cell, its microenvironment, and how these insights will lead to novel clinical strategies."

– Hans Clevers, MD, PhD,
Hubrecht Institute, Utrecht,
The Netherlands

"The nature and clinical relevance of cancer stem cells are timely topics covered with an appropriately broad and insightful brush in this comprehensive book devoted entirely to this subject. Chapters include emerging provocative evidence that a cancer stem cell, although still necessarily defined operationally, actually refers to a molecular state that may be unstable or altered reversibly. In this respect, the cancer stem cell field has entered a new era of complexity building on discoveries of concurrent intrinsic and extrinsic regulators of the stem cell state in normal tissues. Nevertheless, in spite of this evolution, many investigations in specific types of

malignancies have proven useful and more are expected. For those wanting to stay abreast of the field from a basic as well as a clinical perspective, this book will be a welcome read and resource."

– Connie J. Eaves, PhD, FRSC,
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"Cancer stem cells have moved onto center stage for those who are interested in the behavior of solid tumors. In the context of carcinomas, these cells hold the prospect of explaining many aspects of the malignant behavior of high-grade tumor cells, including their metastatic dissemination and their responsiveness to a variety of therapies. Those who are interested in developing novel therapeutic strategies for treating solid tumors can no longer afford to ignore these important subpopulations of cancer cells, which increasingly appear to be critical determinants of the success or failure of existing treatments. This volume reports on many aspects of these cells in a variety of human tumors, justifying the notion that CSCs are likely to be important players in virtually all types of human tumors."

– Robert A. Weinberg, PhD,
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Preface

How Could Individual Cancer Treatments Be Improved Going Forward?

This provocative and challenging question provides an ideal framework for introducing this book, "Cancer Stem Cells". It broadly echoes the questions posed during many of my encounters with researchers, clinicians, and patients at Memorial Sloan-Kettering Cancer Center (MSKCC) in New York, as well as members of the general public not limited to the co-pedestrians in the streets and avenues of the Upper East Side of Manhattan to and fro MSKCC. After my first identification of a plant gene, which was previously unknown in any database and whose human homolog was subsequently characterized as the cancer related Jab 1, I first initiated studies to complement this plant gene in human system at the MD Anderson Cancer Center, Houston, Texas. Deeply touched by the patients pouring in from all over the globe and to help their strong will to survive against cancers, I began to shift my research focus from biotic and abiotic stress signaling in plants originally aimed at increasing global plant productivity towards targetable signaling in human cancers for benefitting the patients' life quality worldwide. Inspired by the tremendous progress in patient focused research performed for over 100 years, and also a new and challenging opportunity to be a part of it, I started at the MSKCC as a beginner to cancer biology and clinical translational research.

My alternative perspective steered me away from conventional cancer research studies towards the poorly understood origins of cancer and the undiscovered layers of molecular control in oncogenesis. This book will introduce cancer stem cells (CSCs) to scientists unfamiliar with this area of cancer research and to clinicians interested in developing careers as physician-scientists. To provide this audience with an appropriate context for the discussions in this book, I will present my own casual appraisal of CSCs from the conclusions of prior literature, which is too extensive to list here with my sincere apologies, that laid the foundation for our current work on this topic. The goal is to synthesize a coherent set of queries so that inquisitive readers will be provoked to go online, investigate further, conceive more research themes, and even amend my thoughts here and those of the authors of the book chapters. Often, after analyzing the complexity of the questions raised by my own translationally oriented basic research and contemplating the general topic of CSCs, I find myself returning to the same fundamental issue: to improve cancer treatments we must unearth the roots of cancer and understand the soil nourishing them as much as we prune and fight against the more easily accessible, wild bushy branches of the disease. These roots include the ability to initiate, sustain and metastasize tumor growth. These are the properties of CSCs that drive tumor initiation and possibly thrive minimal residual disease in cancers, which are the focus of the chapters to follow.

Why have many human cancers remained largely incurable?

I will begin by discussing the above recurring theme: While we continue to make progress

on extending the list of curable cancers, many cancer types are still associated with extremely high mortality rates and short survival. Over the last century, we have significantly advanced our understanding of cancer, beginning with the earliest microscopic observations of transformed cancer cells and progressing to current in vitro techniques of functional interrogation and manipulation of established cancer cell lines. Through these efforts, we have learned a great deal about the cellular properties of cancer, knowledge which has undoubtedly influenced developments in clinical treatment. Extensive progress has also been made in the modeling of human cancers in animals, as in the many genetically engineered mouse (GEM) models that provide the tumors for testing drug toxicity and treatment strategies. However, studies in these animal models can only inform us to a certain degree, and the substantial gap that separates these model tumors from those of cancer patients means many of the treatment strategies fail to make the jump to real-world efficacy.

Undoubtedly, there has been significant progress in improving our understanding of oncogenesis. But until recently, most researchers in the field generally interpreted their data within a broader paradigm in which any elevated or inhibited signaling pathway intermediates were correlated to a presumed linear functional representation of the relevant genes in the bulk tumors. Oncogenes (tumor-causing) and tumor suppressor (tumor-inhibiting) genes that are represented by mutations etc., in otherwise normal developmental genes have been extensively pursued as the true targets of cancer treatment, employing several related GEM models irrespective of the fact that those models are unlikely to reflect the clinical heterogeneity of actual patient or the behavior and interaction of these tumor cells within the body. The overwhelming confidence in this paradigm continues, even though we are now realizing, based on the ongoing human cancer genome sequencing initiatives, that mutated oncogenes may be present in the mature cells of a healthy person's body, in which malignant disease does not develop for exceptionally long times, or perhaps ever.

I will not even dare to delve extensively into the subject of chromothripsis, a chromosome catastrophe characterized by several gene copy numbers and cataclysmic genome disruptions, even within a single chromosome, that occurs within at least 2–3% of cancer genomes and 25% of all bone cancers, or any of the other unknown mechanisms that are challenging the thus far believed conventional model of sequential accumulation of mutations in the biogenesis of cancers. Moreover, such new observations would raise even more questions if the often overlooked layers of regulatory control and additional feedback mechanisms may impinge into other unexplored signaling cascades within cancer cells. Some of such over looked layers of control could include: (i) distinct signals in CSCs versus bulk tumor cells, (ii) an aberrant control in the early steps of polyribosome recruitment of oncogenic transcripts, (iii) altered metabolism in the cytoplasm of the CSCs involving the intracellular organelles like mitochondria, (iv) epigenetic modifiers in the functional genomic loci, etc. Nevertheless, most studies still continue to concentrate largely on tumor shrinkage rather than the biology of the disease and the impact of therapeutics on the functional cells that actually initiate tumors. It is important to note that, clinically, there is now an increasing understanding that decreasing the tumor burden is not necessarily a functional criterion for cancer cure; because of this, we must relentlessly identify and track the mechanisms of metastasis and treat the true tumor-initiating CSCs.

From Simple Concepts to Complex Signaling Networks

Unfortunately, concomitant with the persistently high proportion of incurable cancers, the list of new oncogenes and tumor suppressors continues to grow with the increasing