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Role of Tumor Microenvironment in Tumor Progression and Treatment Response: A 30 Years' Journey

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This special issue of *The Cancer Journal* celebrates the 30th anniversary of the continuing medical education course entitled, “Critical Issues in Tumor Microenvironment: Angiogenesis, Metastasis, and Immunology.” This annual course was first offered in 1986 by one of us, Rakesh K. Jain, PhD, then a professor of chemical engineering at Carnegie Mellon University in Pittsburgh, and by Pietro M. Gullino, MD.¹ At that time, Dr Gullino had just moved to the University of Turin in Italy after serving as chief of the Laboratory of Tumor Pathophysiology at the National Cancer Institute (NCI) from 1973 to 1985. The goal of this course was to examine solid tumors as complex organs and to discuss how the host-tumor interactions contributed to tumor progression, metastasis, and treatment resistance, areas not very popular or taught anywhere at that time.

The course had 2 unique features: each lecture was allotted 90 minutes to allow ample time for discussion, and the 5-day course included a 1-day laboratory tutorial of various in vivo techniques that could be used to investigate tumor pathophysiology. From 1986 through 1991, Gullino and Jain gave 8 lectures each, except in 1990 when Thomas Maciag, PhD,² gave a lecture on endothelial cell biology. Gullino provided the biological and clinical perspective, whereas Jain provided the engineering/physical science perspective on the host-tumor interactions. Each lecture summarized what we knew and what were the critical outstanding questions in the field. In the first offering of this course, only 7 students signed up. The number went up to 24 in the second offering, and for the past 25 years it has ranged from 60 to 100 participants from academia, industry, and government. The participants include beginning researchers to senior scientists to clinicians to the heads of laboratories/divisions and have come from more than 20 countries.

The topics of lectures evolved each year based on the course participants' input as well as emerging findings in oncology. Notable examples of these changes include tumor metabolism and tumor immunology. Both topics were extensively discussed in the late 1980s and early 1990s, then the interest shifted to angiogenesis in the late 1990s, and now they are back again. Because there were no text books or comprehensive reviews on tumor microenvironment, the students were provided copies of all lecture slides and key references, so that they could pay attention to the topic rather than frantically taking notes.

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In fact, these class notes formed that basis of comprehensive reviews on the determinants of tumor blood flow and transvascular and interstitial transport in tumors,^{3–5} as well as physiological resistance to cancer treatment,⁶ also made available to the course participants in subsequent years.

With Jain's move to Boston in 1991, the course has been offered through Massachusetts General Hospital and Harvard Medical School CME Division beginning 1992. Thirty-two new faculty members from Harvard, Massachusetts Institute of Technology, and elsewhere joined the course faculty since then. These include leaders in the area of tumor angiogenesis (Judah Folkman, MD,⁷ Napoleone Ferrara, MD, Peter Carmeliet, MD, PhD), stroma generation (Harold Dvorak, MD), metabolism (Lewis Cantley, PhD), metastasis (Isaiah J. Fidler, PhD, Richard Hynes, PhD, Robert Weinberg, PhD, Bruce Zetter, PhD, Joan Massague, PhD), leukocyte-endothelial interactions (Michael Gimbrone, MD), immunology (Jim Allison, PhD, Drew Pardoll, MD, PhD, Glenn Dranoff, MD, Thomas Tedder, PhD, Thomas Stossel, MD, Stephen Hodi, MD, Lisa Coussens, PhD, Zena Werb, PhD, Jeffrey Pollard, MD), tumor models (Robert Kerbel, PhD), biomarkers (Marsha Moses, PhD, Raju Kucherlapati, MD), clinical translation (Herbert Horowitz, MD, George Sledge, MD, Jose Baselga, MD, Jeffrey Engelman, MD, PhD, Daniel Von Hoff, MD), drug delivery (Robert Langer, DSc, Ian Tannock, MD, Erkki Ruoslahti, PhD), and imaging (Gregory Sorensen, MD) (Table 1). We are very pleased that nearly half of these course faculty members have contributed to this special issue. Another one of us (D.G.D.) served as scientific coordinator of the course for the last decade. Finally, Suresh Mohla, PhD, who was a course participant in (1995), and his NCI colleagues have offered their perspective and strong support on challenges and opportunities in the area of tumor microenvironment.

Section I of this issue is dedicated to tumor vasculature as a target for therapy and begins with a review by Harold Dvorak on tumor stroma and antiangiogenesis approaches. It continues with an overview of angiogenesis with emphasis on the emerging concepts on the role of endothelial cell metabolism in angiogenesis by Peter Carmeliet. Section II is dedicated to reviews on tumor microenvironment and its role in cancer progression and treatment resistance. The first one discusses the role of stroma in tumor development by Zena Werb, the second one by Ian Tannock addresses the causes and consequences of limited distribution of anticancer drugs in tumors, and the last one by Suresh Mohla offers NCI's perspective on the importance of studying tumor microenvironment. Section III is dedicated to the biology and treatment of cancer metastasis. Bruce Zetter reviews the contribution of angiogenesis to metastasis, Robert Kerbel discusses the importance of preclinical modeling for drug development in metastatic diseases, and Isaiah J. Fidler provides an overview of the biology and challenges for therapy in brain metastatic disease. Section IV includes review on novel therapeutic strategies for cancer. It begins with a perspective from George Sledge on targeted therapies in the genomic era, continues with a summary by Daniel Von Hoff of advances in personalized cancer therapy, and ends with reviews by Rakesh Jain on targeting the tumor microenvironment in pediatric brain cancer treatment and by Robert Langer on using nanomedicine to target tumor microenvironment. Section V is on the role of biomarkers in cancer therapies. Herbert Hurwitz discusses the identification of blood-based protein biomarkers for antiangiogenic therapy; Marsha Moses summarizes the efforts on mining the human proteome for urine-based biomarker discovery,

and Gregory Sorensen sums up the use of vascular magnetic resonance imaging as imaging biomarker for antiangiogenic therapy of brain tumors. Last section is dedicated to reviews on the role of the immune microenvironment in cancer therapy. Lisa Coussens discusses the role of myeloid cells as targets for therapy in solid tumors, and Thomas Tedder focuses on the role of tumor microenvironment in immunotherapy for lymphoma.

We are grateful to the course faculty and participants who have contributed to this course over the past 30 years, to the continuing education staff of Carnegie Mellon University and Harvard Medical School, and to various pharmaceutical and biotechnology companies that have provided educational grants for the course. We would like to dedicate this issue to the late Drs Gullino, Folkman, and Maciag for their seminal contributions to these areas of investigation. We sincerely hope that the readers of this special volume will see the excitement and potential for successful clinical translation of research in tumor microenvironment.

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TABLE 1

Tumor Microenvironment Course Faculty 1986–2015

Rakesh K. Jain, PhD	1986 to present
Pietro M. Gullino, * MD	1986–1994
Thomas Maciag, † PhD	1990
Judah Folkman, ‡ MD	1992–2007
Harold F. Dvorak, MD	1992–2015
Michael A. Gimbrone, Jr, MD	1992–1994
Bruce R. Zetter, PhD	1992–2001
Richard O. Hynes, PhD	1995–1996; 2003–2004; 2012
Ian F. Tannock, MD, PhD	1995–2000
Thomas F. Tedder, PhD	1995–1997
Thomas P. Stossel, MD	1997
Robert S. Kerbel, PhD	1998–2015
Erkki Ruoslahti, MD	1998–2002
Peter Carmeliet, MD, PhD	2001–2013; 2015
Isaiah J. Fidler, MD	2002–2011; 2014
Marsha A. Moses, PhD	2005–2015
Herbert I. Hurwitz, MD	2007
George W. Sledge, MD	2008–2015
A Gregory Sorensen, MD	2008–2011
Robert A. Weinberg, PhD	2008–2011; 2015
Robert S. Langer, ScD	2008–2011; 2014
Daniel D. Von Hoff, MD	2008–2009; 2012–2013, 2015
Raju Kucherlapati, PhD	2009–2015
Lisa M. Coussens, PhD	2010–2013, 2015
José Baselga, MD, PhD	2011
Jeffrey W. Pollard, PhD	2011–2015
Joan Massagué, PhD	2012–2013
Lewis C. Cantley, PhD	2012–2014
Napoleon Ferrara, MD, PhD	2013; 2015
Jeffrey Engelman, MD, PhD	2014
Glenn Dranoff, MD	2014
Drew Pardoll, MD, PhD	2014–2015
Zena Werb, PhD	2014
James P. Allison, PhD	2015
F. Stephen Hodi, Jr, MD	2015

* Deceased 2001; <http://cancerres.aacrjournals.org/content/61/24/8930.full>.

† Deceased 2004; <http://www.ascb.org/files/0405obit.pdf>.

‡ Deceased 2008; <http://www.jci.org/articles/view/35291>.