

Timothy Wang  
James Fox  
Andy Giraud  
*Editors*

# The Biology of Gastric Cancers



Springer

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Timothy C. Wang • James G. Fox  
Andrew S. Giraud  
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# Foreword

As someone who has spent nearly half his life wondering about the relationship between *Helicobacter* and gastric cancer, I find this textbook on the subject exciting and timely. In fact, I am not aware of any other volume that has been able to distil so much new knowledge into such a comprehensive account of a poorly understood field.

Taking my own view, as a scientist placed in the middle of the spectrum between basic science and clinical medicine, I can see that the editors, Jim Fox, Andy Giraud, and Timothy Wang, provide a broad mix of expertise, which ensures that the subject is treated with the right balance. From clinicopathologic observations in humans, to epidemiology, through animal models, to molecular and cell biology, this team has hit the mark for most readers. Fox is a well-known leader in animal models with broad expertise. He pioneered the field with observations on *Helicobacter* species in animals, from the time when only one spiral gastric bacterium was known, “*Campylobacter pyloridis*.” Fox partners with Wang, whose team recently announced a dramatic advance in the field of carcinogenesis—the observation that bone marrow–derived stem cells participate in the changes that become cancer. To this nice mix has been added Andy Giraud from my own country, who brings to the table some remarkable genetic models of gastric cancer based on alterations in the gp130/stat3-signaling pathway.

Examining the structure of the book in more detail, I see that they have set the scene with chapters explaining the core knowledge that the novice must learn. The reason being: these longstanding truths will need to be accounted for in order to seek a unifying etiologic hypothesis for gastric cancer. Correa, a pathologist who is himself Colombian, starts by explaining the clinical patterns and histology noted over a lifetime dealing with gastric cancer from many of the Latin American hotspots. Then, Parsonnet summarizes 40 years of prospective data linking *Helicobacter*, by its causative role in gastritis, as the likely cause of gastric cancer also. But differing gastric cancer incidence in various countries means that *Helicobacter*, at least the main accelerant of carcinogenesis, must also interact with many dietary chemicals that directly touch the gastric mucosa. Updated knowledge of this dietary epidemiology is therefore explained.

The less common gastric tumors with immune, neuroendocrine, and genetic causes are dealt with next. MALT Lymphoma leads the list, providing the first inkling

that a lifelong immunologic insult to the gut mucosa is not without peril. These nonmucosal neoplasms must be accurately diagnosed now as their molecular triggers can be specifically treated (GIST tumors). Neuroendocrine neoplasia, always of interest in conditions in which so much therapy relates to chronic acid suppression, is carefully dealt with in two chapters as is the little-known linkage between Epstein-Barr virus and gastric tumors. Some congenital tumors even serve to demonstrate a molecular parallel with normal carcinogenesis. Appropriately, the first group of chapters is rounded off with the controversial relationships among human genetic polymorphisms, acid secretion, *Helicobacter*, and cancer; i.e., the emphasis of host factors rather than bacterial factors as determinants of cancer risk.

The second half of the book contains chapters that draw the reader into basic research and molecular aspects of gastric cancer. In the postgenomic era, as more tumor DNA libraries are collected, cancer genetics are beginning to be understood. Eventually, it is quite likely that automated DNA-based methods (e.g., gene arrays) will replace human-driven tumor diagnosis. Molecular genetics and proteomic observations already show promise as methods of sorting out premalignant and malignant conditions presently labeled rather vaguely as the “metaplasias.” As new hypotheses are developed, these need to be tested in appropriate animal models. Although many choices exist, the response of each model to *Helicobacter*, histologically and immunologically, is quite variable and not well understood. If vaccines against *Helicobacter* are ever going to be possible, better understanding of the host–bacterial interaction is necessary. Regardless of the individual deficiencies, investigators can use new animal models to rapidly dissect out disease associations such as the dietary carcinogen/*Helicobacter*/salt connection or the sexual predilection for cancer in male humans and some male mice. Throughout the book, broad chapters on animal models are bolstered by focused chapters on genetically altered mice, other rodents, and even primate models.

The various oncogenes and molecular switches responsible for cancer associations are examined in more detail by experts in these more narrow fields. Developmental processes required for metaplasia again raise the issue of host factors versus bacterial factors as the cause of many cancers. In the bacterial field, CagA is certainly the most studied and probably the most relevant of these, and polymorphisms within its structure might explain its variable strength as a molecular switch. The discovery of the way in which modern molecular techniques were applied to this toxin makes a fascinating story in itself.

Several chapters deal with host immunity, important because lifelong persistence of *Helicobacter* is a unique success story for the bacterium and an apparent failure for the gastrointestinal immune system. Similarly, because inflammation correlates both with increased ulcerogenesis, hyperacidity, and cancer protection in some populations with simultaneous atrophy, hyposecretion, and cancer risk in apparently similar individuals, the fine details of the immune response seem to offer a productive area of research. Again, new molecular markers, oncogenes, and even cytokines are all relevant and worthy of study.

Finally, the role of bone marrow–derived stem cells in gastric cancer is carefully addressed. Because animal models require time to develop cancer as each new

hypothesis is tested, understanding of this area serves to show where new studies are leading and how these might relate to diagnosis and prognosis as interventional human studies are planned. These would likely be bacterial eradication primarily, but the dream of most of us: that of a simple vaccine, is also addressed in a futuristic final chapter.

With such a scholarly trio of editors, this book has attracted a superlative team of contributors, each able to bring the reader up to date with the most cutting-edge advances, in chapters that will remain current for many years and continue to provide a solid foundation for study in the field for decades.

January 28, 2008

Barry Marshall

# Preface

This book represents the very first volume devoted to the subject of the basic biology of gastric cancer. Although there were major achievements 30–40 years ago in the description of the histopathology of stomach tumors and the preneoplastic conditions that preceded these lesions, it was of course the pioneering (and Nobel prize–winning) studies involving the discovery of *Helicobacter pylori* by Marshall and Warren that set the stage for the more recent insights on the role of chronic inflammation and cancer. As articulated in the chapters of this compendium, written by experts in the field, there have been many impressive advances in our understanding of the pathogenesis of gastric adenocarcinoma, gastric MALT lymphoma, gastrointestinal stromal tumors of the stomach, and gastric carcinoid tumors. The text begins with an overview of these neoplasms and their histopathology, the role of diet and *H. pylori*, and their epidemiology, before moving into the current view and understanding of molecular mechanisms. The book, of course, reflects many of the interests of the editors, with an emphasis on animal models, but also devotes considerable attention to human studies, host genetics, and the role of bacterial factors and other environmental factors influencing the pathogenesis of gastric cancer. The text pays homage to the cutting-edge concepts of cancer stem cells, tumor micro-environment, chronic inflammation, and genetic susceptibility to cancer. Although every potential mechanism contributing to gastric carcinogenesis could not be covered because of space limitations, we have attempted to highlight the important areas that would appeal to a broad readership.

The topics presented in this book should be of interest to clinicians and investigators interested in gastrointestinal cancer, as well as basic investigators in related areas of cancer research. Gastric cancer has in many respects become a paradigm for the broader association between chronic inflammation and cancer, and the association between infection and cancer. At present, it is thought that only 15%–20% of cancers can be directly attributed to infection, but the cause of many cancers is still not known, similar to the situation that existed for gastric cancer before the discovery of *H. pylori*. Thus, we believe that the insights developed from the studies described in these chapters may inform researchers working on other organ-specific neoplasms. In addition, it is our hope that this body of work will stimulate clinical and translational studies that will advance early diagnosis and treatment of gastric tumors.

We extend our appreciation not only to the authors of all the chapters in this book for the tremendous accomplishments, but also to the many reviewers who took the time to critique and edit the manuscripts. The reviewers included John Atherton, Pelayo Correa, Jean Crabtree, Stanley Falkow, JeanMarie Houghton, Peter Isaacson, Robert Jensen, Andrew Leiter, Wai K. Leung, Stephen Meltzer, Christopher A. Moskaluk, Guilleromo Perez-Perez, Arlin Rogers, Massimo Rugge, George Sachs, Linda Samuelson, and Andrea Todisco. We also thank our assistants (Mary Beth Shanahan and Lucy Wilhelm) for their work in formatting and editing the chapters. We acknowledge warmly the patience and attention put into this book by our colleagues at Springer, particularly Rachel Warren and Thomas Brazda. Finally, we especially thank the Funderberg foundation for their creation of the Robert and Sally Funderberg Gastric Cancer Awards, which stimulated interest in this field, and the National Institutes of Health for their support of basic and translational research in gastric cancer.

New York, NY, USA  
Cambridge, MA, USA  
Melbourne, Australia

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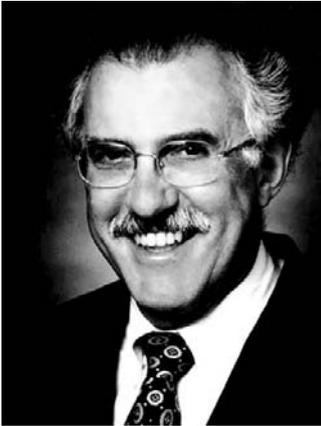
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## Timothy C. Wang, MD

Dr. Wang is the Silberberg Professor of Medicine and Chair of the Division of Digestive and Liver Diseases at Columbia University Medical Center. He is an internationally respected clinician and scientist, specializing in *H. pylori* infection and gastrointestinal cancer. He is a graduate of Columbia College of Physicians and Surgeons. He was a faculty member for ten years at Massachusetts General Hospital and Division Chief at the University of Massachusetts Medical School before returning to Columbia University in 2004 as Chief of Digestive and Liver Diseases and the Silberberg Professor of Medicine. He is a recipient of the AGA Funderberg Gastric Cancer

Award and the Victor Mutt medal in Gut Hormone Research, and is a member of American Society for Clinical Investigation (ASCI) and Association of American Physicians (AAP). He is a former and current Associate Editor of Gastroenterology, and Editor in Chief of the journal Therapeutic Advances in Gastroenterology. He is active in the American Gastroenterological Association, currently serving as chair of the Future Trends Committee, and Chair of the GCMB NIH study section. He has authored over 150 original peer-reviewed publications. Dr. Wang's research centers on the role of inflammation and stem cells in the development of gastrointestinal cancers. His main interest has been in developing transgenic mouse models of stomach cancer, and together with Dr. Fox, they have developed the first *Helicobacter*-dependent mouse models of gastric cancer. Dr. Wang's laboratory reported that gastric cancer in mice can originate in part from bone marrow-derived stem cells. As the leader of the Columbia University Tumor Microenvironment Network, he has investigated the importance of the stem cell niche in governing stem cell differentiation, and how this niche is altered in chronic inflammatory states that predispose to cancer. He is currently investigating the role of both fibroblasts and myeloid cells in carcinogenesis.



### James C. Fox, MD

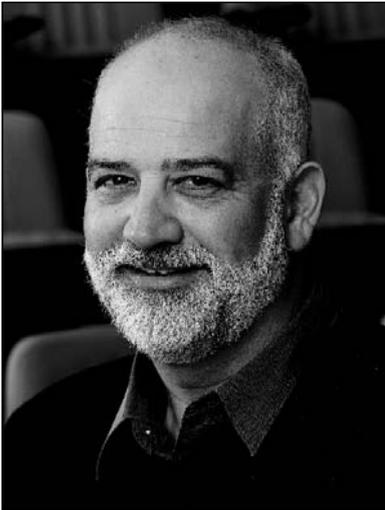
Dr. Fox is Professor and Director of the Division of Comparative Medicine and a Professor in the Department of Biological Engineering at the Massachusetts Institute of Technology. He is also an Adjunct Professor at Tufts University School of Veterinary Medicine and the University of Pennsylvania, School of Veterinary Medicine. He is a Diplomate and a past president of the American College of Laboratory Animal Medicine, past president of the Massachusetts Society of Medical Research, past chairman of AAALAC Council, past chairman of the NCCR/NIH Comparative Medicine Study Section, and a member of various

other organizations including AAAS, AALAS, AVMA, AAVMC, IDSA and ASM. He also is an elected fellow of the Infectious Disease Society of America, a past member of the Board of Directors of Public Responsibility in Medicine and Research (PRIM&R), ACLAM, AAALAC, MSMR, AAVMC and is currently Chairman of the AVMA and AAVMC Animal Welfare Committee. Professor Fox is the author of over 460 articles, 75 chapters, 4 patents and has edited and authored 12 texts, in the field of in vivo model development and comparative medicine. He has given over 250 invited lectures, consults nationally and internationally with government, academia and industry, has served on the editorial board of several journals, is a past member of the NIH/NCRR Scientific Advisory Council, and a current member of ILAR Council of the National Academy of Sciences.

Recently Professor Fox was elected to the Institute of Medicine of the National Academy of Sciences. He has received numerous scientific awards including the AVMA's Charles River Prize in Comparative Medicine, the AALAS Nathan Brewer Scientific Achievement Award, and the AVMA/ASLAP Excellence in Research Award. In 2006, Dr. Fox received the Distinguished Alumni Award from Colorado State University and in 2007 was selected as the inaugural recipient of the American College of Laboratory Animal Medicine Comparative Medicine Scientist Award. He has been studying infectious diseases of the gastrointestinal tract for the past 30 years and has focused on the pathogenesis of *Campylobacter* spp. and *Helicobacter* spp. infection in humans and animals. His laboratory developed the ferret as a model for both campylobacter and helicobacter associated disease as well as the first rodent model to study helicobacter associated gastric disease, including gastric cancer. Dr. Fox is considered an international authority on the epidemiology and pathogenesis of enterohepatic helicobacters in humans and animals. He is largely responsible for identifying, naming, and describing many of the diseases attributed to various *Helicobacter* species; most notably their association with hepatitis, liver tumors, inflammatory bowel disease and colon cancer. His laboratory most recently has described the pivotal role that *Helicobacter* spp. play in the development of cholesterol gallstones in mice fed a lithogenic diet; thus linking this finding to his

earlier description of *Helicobacter* spp. associated chronic cholecystitis and gallstones in Chilean women, a population at high risk of developing gallbladder cancer. He also has had a long-standing interest in zoonotic diseases as well as biosafety issues associated with *in vivo* models.

His past and current research has been funded by NIH and NCI, as well as by private industrial sources, for the past 30 years. Dr. Fox ranks in the top 5% of all NIH awardees during the past 25 years. He has been the principal investigator of an NIH postdoctoral training grant for veterinarians for the past 20 years and has trained 45 veterinarians for careers in biomedical research. He also has a NIH training grant to introduce veterinary students to careers in biomedical research. He recently chaired a committee for the National Academy of Sciences which published a report entitled "National Need and Priorities for Veterinarians in Biomedical Research" which highlights the urgent need for increased numbers of veterinarians involved in the biomedical research arena. He currently is a member of NAS "Committee to Assess the Current and Future Workforce Needs in Veterinary Medicine."



### **Andrew S. Giraud**

Dr. Giraud is currently Professor and Research Theme Director, Infection, Immunity and Environment at Murdoch Childrens Research Institute in Melbourne, Australia. His research interests are: (1) establishing mouse genetic models of gastric cancer in order to better understand how initiating factors promote inflammation, metaplasia and neoplasia. (2) translation of outcomes from mouse models in order to better understand, detect and treat human gastric adenocarcinoma. For instance we have found that in the mouse and in human gastric cancer the transcription factor STAT3 is continuously activated and promotes tumor growth. We are currently testing new

small molecule STAT3 inhibitors as anticancer agents. (3) investigating the biology and mechanisms of activation of the gastrophilic and trefoil peptide families, members of which are stomach-specific tumor suppressor genes.

Dr. Giraud is a member of the American Gastroenterology Association and the Gastroenterological Society of Australia. He has published widely in gastroenterological science including in a number of papers in *Gastroenterology* and *Nature Medicine* in the last six years.

*(continued)*

Currently Professor and Research Theme Director, Infection, Immunity and Environment at Murdoch Childrens Research Institute in Melbourne, Australia.

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