Metastatic Disease is the Major Cause of cancer deaths. Sadly, for those with this disease, regardless of tissue origin and metastatic site, there has been little change in overall survival over the last twenty years. This contrasts with the considerable success in preventing cancer through early detection and by the treatment of early-stage cancers. Metastatic cancers thus appear to evolve resistance to existent therapies, including novel biologics. Recently, providing a glimmer of hope, there has been progress in defining mutations that might be driving metastasis, such as the BRAF mutation in metastatic melanoma. In this case, targeted therapy results in remarkable regression of metastasis in patients carrying the mutation but ultimately this success is overcome by resistance through the acquisition of other mutations that result in the reemergence of the metastases. Perhaps more positive for patients is the progress in immunotherapy, especially the use of checkpoint inhibitors that, in some cancers such as melanoma, have achieved remarkable success. However, even here, most cancers are resistant and there is a growing body of evidence of acquired resistance, even in patients whose first treatment was successful.

This Cold Spring Harbor volume, Metastasis: Mechanism to Therapy, was born through an appreciation that in order to advance therapy we need a better understanding of the biology of metastasis as well as new models and analytical methods for modeling the disease. As editors, we did not focus on a mutational analysis of cancer cells but rather the disease biology with the hope that by gaining new insights, we could inform optimal therapies. We engaged a group of leaders in the field to address particular processes in the metastatic cascade, a process whereby cells in solid cancers acquire traits to break through basement membrane, migrate into the stroma, and escape into the lymphatic or hematogenous circulation to arrive at distant sites where they extravasate, survive, and grow. We have covered the systemic influences that primary cancers exert to enhance the success of metastasizing cells and that at times define tissue site selection, the concept of the premetastatic niche.

As cancer is mostly a disease of aging, there is growing research to understand how the aging environment enhances metastasis, which is also reviewed in this volume. The book contains chapters on the ability of tumor cells to gain migratory capacity, sometimes called the epithelial-to-mesenchymal transition (EMT), and its reversal upon arrival at these distant sites. We discuss site selection for metastasis, such as the preference of breast cancers to go to bone while colorectal cancer goes to liver. We also emphasize the role for the tumor microenvironment as a major determinant of metastatic colonization and subsequent growth. Importantly, this includes the role of immune cells, particularly of the innate system, which can promote the metastatic cascade at all steps and suppress attack by cytotoxic cells such as CD8+ T and NK cells. These innate immune cells may be targets for attempts to improve immunotherapy, a subject also discussed in this volume. This is a key area where there is hope for therapeutic progress, but it will require better models and perhaps those that enable imaging, as in the zebrafish and enhanced intravital microscopy methods in mice covered by the expert contributors to this volume. Of course, the best cure is prevention and the possibility of early metastasis detection is also addressed through an update on the power of analysis in liquid biopsies.

In editing this volume, we are deeply indebted to the authors for their efforts when everyone is so busy and for their quick turnaround of chapters. From Cold Spring Harbor Laboratory Press we would like to thank Richard Sever for suggesting this volume and Barbara Acosta for her remarkable ability to get authors to write on time, for making us edit the chapters efficiently, and for bringing the project to completion. Both continue to make the Perspectives in Medicine series such a success. Jeff Pollard would like to thank his funders during the project, his Wellcome Trust senior investigator
award [101067/Z/13/Z] and the CRUK Programme grant (C17950/A26783), as well as the MRC (MR/N022556/) for supporting his Centre for Reproductive Health. He would also like to thank members of his lab, present and past, for driving his research forward on the role of the tumor microenvironment in metastatic disease. Yibin Kang would like to thank the U.S. National Cancer Institute, the Department of Defense, Susan G. Komen Foundation, the Breast Cancer Research Foundation, the American Cancer Society, the New Jersey Commission on Cancer Research, and the Brewster Foundation for funding support of his laboratory in metastasis research, and his past and present lab members for their contributions.

JEFFREY W. POLLARD
YIBIN KANG