Preface

A balance of protein synthesis and degradation is tightly regulated in our bodies in order to keep us healthy. Most intracellular proteins are degraded via the ubiquitin-proteasome pathway (UPP), and dysfunction of the UPP has been linked to the occurrence of many human diseases, including cancers. The clinical introduction of the first US Food and Drug Administration (FDA)-approved proteasome inhibitor bortezomib for the treatment of multiple myeloma (MM) and mantle cell lymphoma is an example of using the UPP as an anticancer target which has been met with success. Now, bortezomib-based therapies have become a staple for the MM treatment, contributing to a two- to threefold increase in the survival rate of the MM patients.

However, not all patients respond to bortezomib treatment and relapse occurs in many patients who initially responded. Also, bortezomib-based therapies had minimal effects in treating most of hematologic malignancies and almost all of the solid tumors. Furthermore, some neurotoxicities (such as peripheral neuropathy) were found to be associated with bortezomib treatment. Therefore, bortezomib resistance (both intrinsic and acquired) is a critical barrier to progress in bortezomib therapy for MM and other cancers.

This book, Resistance to Proteasome Inhibitors in Cancer: Molecular mechanisms and strategies to overcome resistance, focuses on the mechanisms of action and resistance of the proteasome inhibitor bortezomib in human cancers (including MM, mantle cell lymphoma, acute leukemia, and various solid tumors) and on cutting-edge strategies to overcome bortezomib clinical resistance. The second-generation 20S proteasome inhibitors carfilzomib, ixazomib, delanzomib, oprozomib, and marizomib, with different pharmacological properties and broader anticancer activities, have shown great promise in this respect; carfilzomib, the second FDA-approved proteasome inhibitor drug, induces responses in a minority of MM patients relapsed from or refractory to bortezomib. The potential reversal strategies for bortezomib resistance also include developing novel combinational therapies and identifying new targets in the UPP, such as ubiquitin E3 ligases, deubiquitinases, 26S proteasomal ATPases, histone deacetylases, oxidative stress and proteotoxic stress pathways, and pharmacogenomic signature profiling in resistant cancer cells. While
bortezomib resistance could be reversed by several aforementioned strategies in several preclinical models, the confirmation under clinical settings is needed. There are high hopes in the field that the discovery of the mechanisms of proteasome inhibitor resistance will help illuminate the future of cancer treatment.

Due to the timely nature and keen interest in the subject matter of this book, it is my wish that this book will serve as an important resource for physicians, clinician scientists, translational researchers, basic researchers, graduate and medical students, patients, consumers, and pharmaceutical companies.

I would like to thank the authors, who are among the top leaders in their areas of research, for their exceptional contributions. This volume represents one in a new book series entitled *Resistance of Targeted Anti-Cancer Therapeutics* of which Professor Benjamin Bonavida of the University of California, Los Angeles, serves as the Series Editor (published by Springer Publishing Company). I wish to thank Professor Bonavida for his encouragement. I am also indebted to Ms. Fiona Sarne, the Editor of Cancer Research for Springer Science + Business Media, for her great effort and assistance.

Detroit, MI, USA

Q. Ping Dou, Ph.D.
Resistance to Proteasome Inhibitors in Cancer
Molecular Mechanisms and Strategies to Overcome Resistance
Dou, Q.P. (Ed.)
2014, XI, 390 p. 55 illus., 51 illus. in color., Hardcover
ISBN: 978-3-319-06751-3