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Philip T. Cagle · Timothy Craig Allen
Mary Beth Beasley · Lucian R. Chirieac
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# Molecular Pathology of Lung Cancer

Springer

## Molecular Pathology Library Series

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# Series Preface

The past 2 decades have seen an ever-accelerating growth in knowledge about molecular pathology of human diseases which received a large boost with the sequencing of the human genome in 2003. Molecular diagnostics, molecular-targeted therapy, and genetic therapy are now routine in many medical centers. The molecular field now impacts every field in medicine, whether clinical research or routine patient care. There is a great need for basic researchers to understand the potential clinical implications of their research whereas private practice clinicians of all types (general internal medicine and internal medicine specialists, medical oncologists, radiation oncologists, surgeons, pediatricians, family practitioners), clinical investigators, pathologists and medical laboratory directors, and radiologists require a basic understanding of the fundamentals of molecular pathogenesis, diagnosis, and treatment for their patients.

Traditional textbooks in molecular biology deal with basic science and are not readily applicable to the medical setting. Most medical textbooks that include a mention of molecular pathology in the clinical setting are limited in scope and assume that the reader already has a working knowledge of the basic science of molecular biology. Other texts emphasize technology and testing procedures without integrating the clinical perspective. There is an urgent need for a text that fills the gap between basic science books and clinical practice.

In the Molecular Pathology Library series, the basic science and the technology is integrated with the medical perspective and clinical application. Each book in the series is divided according to neoplastic and nonneoplastic diseases for each of the organ systems traditionally associated with medical subspecialties.

Each book in the series is organized to provide specific application of molecular pathology to the pathogenesis, diagnosis, and treatment of neoplastic and nonneoplastic diseases specific to each organ system. These broad section topics are broken down into succinct chapters to cover a very specific disease entity. The chapters are written by established authorities on the specific topic from academic centers around the world. In one book, diverse subjects are included that the reader would have to pursue from multiple sources in order to have a clear understanding of the molecular pathogenesis, diagnosis, and treatment of specific diseases. Attempting to hunt for the full information from basic concept to specific applications for a disease from varied sources is time-consuming and frustrating. By providing this quick

and user-friendly reference, understanding and application of this rapidly growing field is made more accessible to both expert and generalist alike.

As books that bridge the gap between basic science and clinical understanding and practice, the Molecular Pathology Library series serves the basic scientist, the clinical researcher, the practicing physician, and other health care providers who require more understanding of the application of basic research to patient care, from "bench to bedside." This series is unique and an invaluable resource to those who need to know about molecular pathology from a clinical, disease-oriented perspective. These books are indispensable to physicians and health care providers in multiple disciplines as noted above, to residents and fellows in these multiple disciplines as well as their teaching institutions, and to researchers who increasingly must justify the clinical implications of their research.

Houston, TX, USA Philip T. Cagle, MD

# Preface

The past few years have seen a revolution in the molecular pathology of lung cancer, including exciting advances in predictive biomarker testing and molecular targeted therapy. Clinical trials in 2009 demonstrated the superiority of tyrosine kinase inhibitor therapy to conventional chemotherapy in patients with advanced lung cancers with activating epidermal growth factor receptor (EGFR) mutations. Response to anaplastic lymphoma kinase (ALK) inhibitor was demonstrated in patients whose lung cancers contained ALK fusion genes in 2010. These and other advances have led to a proposed new classification of adenocarcinoma of the lung by the International Association for the Study of Lung Cancer in February 2011 and Lung Cancer Predictive Biomarker Guidelines to be published by the College of American Pathologists, the International Association for the Study of Lung Cancer and the Association for Molecular Pathology in 2012. This breathtaking chain of events is the impetus for the publication of this book, *Molecular Pathology of Lung Cancer*, in the Molecular Pathology Library series. The editors have been involved in both original research on these topics and in the expert panel for biomarker guidelines referred to above. Our objective is to provide the reader with a basis for understanding current concepts in the molecular pathology of lung cancer in keeping with the aspirations of this book series.

Houston, TX, USA — Philip T. Cagle, MD

# Contents

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# Part I

# Molecular Pathology of Lung Cancer: General Principles

# Approach to Personalized Care of the Lung Cancer Patient

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Philip T. Cagle

As part of the personalized health care of lung cancer patients, identification of predictive biomarkers for targets of molecular therapy is the most reliable basis for selecting patients for targeted therapies. Currently "established" predictive biomarker tests for lung cancer are EGFR mutation analysis and FISH for ALK fusion gene that are the primary subject of the new College of American Pathologists (CAP)/International Association for the Study of Lung Cancer (IASLC)/Association for Molecular Pathology (AMP) Lung Cancer Biomarker Guidelines. Multiple other predictive biomarkers, particularly K-Ras, are mentioned in the guidelines as forthcoming [1].

There is an association between the cell type of a lung cancer, and even cell subtype, and the presence of specific predictive biomarkers [1–9]. For example, EGFR mutations and ALK fusion genes that are likely to respond to currently available tyrosine kinase inhibitors are both strongly associated with adenocarcinoma cell type. Both also have associations with subtypes of adenocarcinoma (lepidic, papillary, and micropapillary patterns are associated with EGFR mutations and solid and acinar patterns are associated with ALK fusion genes) [1–9]. Since exclusion based on clinical criteria, such as gender, ethnicity, and smoking status are likely to omit patients who might benefit from targeted therapy, current evidence indicates that tumor histology is the most reliable criteria for selecting patients for biomarker testing [1]. Therefore, the pathologist has a crucial role in the selection of which lung cancers receive testing for a particular predictive biomarker. This is a major development after decades in which the primary role of the pathologist in patient therapy was to diagnose small cell carcinoma versus non-small cell carcinoma [3, 4].

Either the pathologist or oncologist may order the biomarker test on an individual case basis in some institutions, but automatic reflex testing of all lung cancers meeting selection criteria may be required in other institutions. Pathologists who supervise molecular diagnostic laboratories may be directly involved in the performance of predictive biomarker tests for molecular targeted therapies, but currently a greater number of pathologists are involved in diagnosing, processing, and selecting tissues for these tests. In the pre-analytic phase of testing, a pathologist must review a representative tissue section to determine the cellularity and purity of the tumor sample being submitted for biomarker testing. The pathologist must differentiate cancer from noncancer, viable tissue from nonviable tissue, adequate sample size from inadequate sample size, etc., when selecting tissue samples to send for biomarker testing. Although histology does not trump molecular analysis in predicting which lung cancers are likely to respond to a targeted therapy,

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pathologists have a crucial new role in suggesting which molecular tests are most likely to yield positive results for a given cancer based on the association of specific mutations with specific histologic types and subtypes [1, 3–5].

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