Preface

LUNG CANCER REMAINS THE MOST SIGNIFICANT cause of cancer-related deaths for both men and women in the United States and in many parts of the world. In the United States, more women die of lung cancer than breast cancer. However, there is tremendous hope on the horizon. With the turn of the 21st century, there have been amazing advances in our understanding of the fundamental mechanisms underlying the molecular pathogenesis of lung cancer, in early detection of lung cancer in high-risk patients, and in the development of multiple new treatment modalities for lung cancer patients. These discoveries that occurred both in the clinic and laboratory have led to changes in patient diagnosis and treatment regimens with clinically significant benefit in terms of survival, symptom relief, and quality of life. A key aspect of this period has been the realization of the importance of "clinical translational" research, that is, bringing key observations from the clinic to the laboratory for analysis and then bringing discoveries made in the laboratory back to the clinic through the implementation of rational clinical trials with rigorous correlative studies.

This period of discovery and clinical translation was ushered in by dramatic changes in cigarette-smoking cessation efforts enacted in the time between 1980 and 2000. However, these efforts, which were of significant public health importance, also led to the realization that even people who stopped smoking could develop lung cancer decades later because of the changes induced by cigarette carcinogens and cancer promoters. It is estimated that more than 50% of people diagnosed with lung cancer in the past 20 years stopped smoking many years before diagnosis. Thus, it is important to understand that the burden from tobacco smoking and the increased risk of developing lung cancer is going to be with us well into the 2050s. Also, the frequency (∼15% of all new cases of lung cancer) and importance of lung cancer arising in "lifetime never smokers" (people who smoked less than 100 cigarettes in their lifetime) to the overall cancer burden in the United States became clear and approximated the number of people developing pancreatic cancer.

The turn of the century has also ushered in the era of "big data." For example, The Cancer Genome Atlas (TCGA) program from the National Cancer Institute (NCI, U.S.) provides detailed molecular annotation (complete mutational and expression analyses of individual lung cancers) of large numbers of lung cancers along with clinical/demographic information. More recently, components of the epigenome and proteome, together with detailed molecular analyses of thousands of tumor and stromal cells at the single-cell level, have been characterized. Coupled with this has been the beginnings of large databases of genetic and chemical (drug) functional dependencies, such as the Broad Institute's Dependency Map (DepMap) and Cancer Cell Line Encyclopedia (CCLE), which have identified specific gene dependencies in individual lung cancers that can form the basis for future therapy development. Equally important has been the development of large numbers of preclinical models to study the disease including patient-derived tumor cell lines and xenografts (PDXs) and genetically engineered mouse models (GEMMs) of lung cancer. Importantly, all of these information resources are made available in easily accessible databases and there has been worldwide distribution of hundreds of preclinical models for study throughout the lung cancer research community, which have "democratized" the study of lung cancer.

In the clinic, other key advances include the discovery of mutated driver oncogenes to which individual lung cancers are "addicted," resulting in the development of oral medications blocking mutated oncogene function; the development of advances in computerized tomography screening combined with large randomized trials showing survival benefit for lung cancer screening that is equivalent to the survival benefit seen for breast cancer screening; advances in stereotactic radiation

therapy that include not only control of local disease, but the possibility of using radiation to treat oligometastatic disease; the use and benefits of immune checkpoint blockade, which has led to likely very long-term survival in patients with distant metastatic disease; early indications that chemotherapy or immunotherapy given early in the disease as "neoadjuvant" therapy before surgery is of potential benefit; information on the tumor microenvironment (TME) indicating the ability of some lung cancers to generate an immune suppressive TME; and the beginning of an appreciation of mechanisms of resistance to chemotherapy, targeted therapy, and immune checkpoint blockade.

Perhaps more than anything, the general accessibility of data and annotated materials to study has increased the speed of lung cancer translational research by an order of magnitude. A key aspect of these common data sets and common use of preclinical models is that any new finding of importance is immediately validated (or discarded) by multiple independent laboratories around the world. These resources have also been avidly embraced by pharmaceutical and biotech companies so they have also stimulated the development of therapies by the commercial sector, leading to clinical trials and ultimately approval for routine clinical use. As part of this there have been advances in clinical trial methodology, including important interweaving of molecular characteristics of individual patient tumors with treatment approaches, to begin to develop true "precision medicine." We have learned from these studies that once lung cancer is diagnosed, we now have a greatly improved ability to stage the disease in individual patients and understand what it has done to the patient. We also have CLIA-based laboratory tests to molecularly characterize each patient's tumor and have seen important advances in thoracic surgery and radiation therapy to treat localized disease even in frail patients. Despite all of these advances, and while tumor responses, symptomatic benefit, and survival increases have significantly increased, the large majority of patients ultimately succumb to this disease, usually with widespread metastases, and develop resistance to our best chemotherapy, targeted therapy, and immunotherapy. In fact, the more successes we have in developing new treatments for lung cancer (such as mutated oncogene-targeted therapy or immune checkpoint blockade), the more we see examples of lung cancers that become resistant to these therapies indicating the "lineage plasticity" ability of lung cancers to avoid systemic therapy efforts.

There is still a lot of work to be done for lung cancer in terms of understanding how to identify and attack acquired vulnerabilities and to develop new approaches for prevention, early detection, and treatment. The broad spectrum of these advances and current research activities are discussed by the different chapters in this volume: Early Diagnosis and Screening for Lung Cancer; Molecular Pathology of Lung Cancer; Tumor Immunology and Immunotherapy of Non-Small-Cell Lung Cancer; Radiation Therapy in Non-Small-Cell Lung Cancer; Preclinical Models for the Study of Lung Cancer Pathogenesis and Therapy Development; Lung Cancer Stem Cells and Their Clinical Implications; Application of Radiomics and Artificial Intelligence for Lung Cancer Precision Medicine; Metabolic Phenotypes, Dependencies, and Adaptation in Lung Cancer; Targeting Epigenetics in Lung Cancer; Advances in Small-Cell Lung Cancer (SCLC) Translational Research; and Lung Cancer Computational Biology and Resources. We first want to thank the authors for the tremendous effort and thought that went into each chapter throughout the preparation of this book. In addition, we have been encouraged and helped by the amazing Cold Spring Harbor Laboratory (CSHL) Press staff, including Barbara Acosta and Richard Sever. We owe the authors and CSHL our deepest gratitude. Finally, we want to thank the entire lung cancer community—most of all the patients—for their unwavering dedication and incredible support toward making outcomes better for everyone who is battling lung cancer. We are stronger together.

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