Bridging Tumor Genomics to Patient Outcomes Through an Integrated Patient-Derived Xenograft Platform

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Abstract

New approaches to optimization of cancer drug development in the laboratory and the clinic will be required to fully achieve the goal of individualized, precision cancer therapy. Improved preclinical models that more closely reflect the now recognized genomic complexity of human cancers are needed. Here we describe a collaborative research project that integrates core resources of The Jackson Laboratory Basic Science Cancer Center with genomics and clinical research facilities at the UC Davis Comprehensive Cancer Center to establish a clinically and genomically annotated patient-derived xenograft (PDX) platform designed to enhance new drug development and strategies for targeted therapies. Advanced stage non–small-cell lung cancer (NSCLC) was selected for initial studies because of emergence of a number of "druggable" molecular targets, and recent recognition of substantial inter- and intrapatient tumor heterogeneity. Additionally, clonal evolution after targeted therapy interventions make this tumor type ideal for investigation of this platform. Using the immunodeficient NOD *scid* gamma mouse, > 200 NSCLC tumor biopsies have been xenotransplanted. During the annotation process, patient tumors and subsequent PDXs are compared at multiple levels, including histomorphology, clinically applicable molecular biomarkers, global gene expression patterns, gene copy number variations, and DNA/chromosomal alterations. NSCLC PDXs are grouped into panels of interest according to oncogene subtype and/or histologic subtype. Multiregimen drug testing, paired with next-generation sequencing before and after therapy and timed tumor pharmacodynamics enables determination of efficacy, signaling pathway alterations, and mechanisms of sensitivity-resistance in individual models. This approach should facilitate derivation of new therapeutic strategies and the transition to individualized therapy.

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Introduction

Substantial advances have been made in understanding the molecular biology that drives carcinogenesis and cancer-associated proliferative and antiapoptotic signaling pathways. A wide variety of potentially "druggable" molecular targets for cancer therapy have emerged from these studies. Although a large number of molecular targeted agents have subsequently been tested, most of which showed substantial activity in available preclinical models, relatively few have been successful

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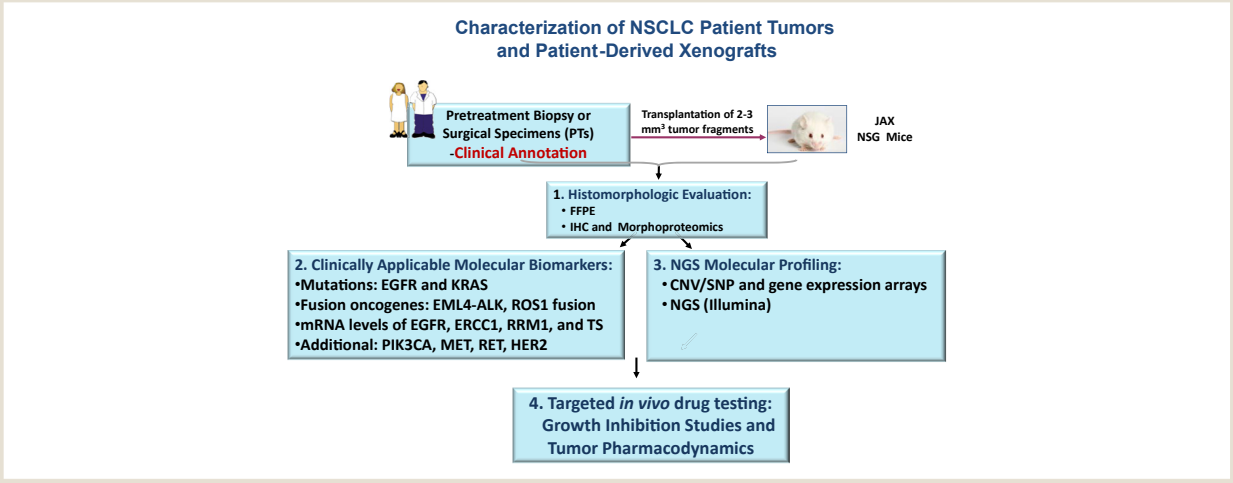
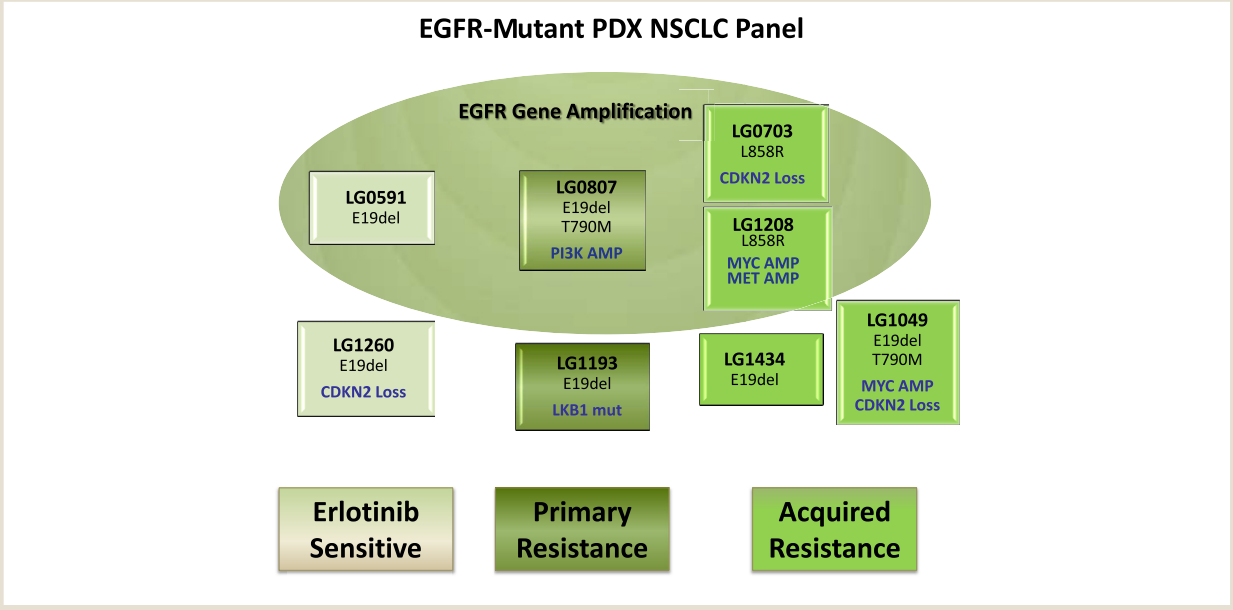
Figure 1 Algorithm of Patient-Derived Xenograft (PDX) Creation. Candidate Patients (PTs) Were Identified and Provided Consent for Tumor Collection. After Biopsy, Pleural Effusion Fluid Collection, or Surgical Resection, Viable Portions of the Fresh Specimens Were Rapidly Transported to the Jackson Laboratories-West Facilities for Implantation Into the NSG Mouse Model. Concurrently, Remaining Portions of the PT Specimen Were Fixed and Subsequently Characterized and Molecularly Profiled. A PDX Model Was Considered "Established" After Demonstrating Growth in Passage 1, After Successful Implantation, Development and Transplantation From Passage 0. Histomorphologic Evaluation and Molecular Profiling of the PDX Model Was Conducted and Results Compared With the Contributing Human Specimen. When PDX Models Reach Passage 2, Cohorts Can Be Prepared for Growth Inhibition and Tumor Pharmacodynamic Studies



Abbreviations: CNV = copy number variation; FFPE = Formalin-fixed, paraffin-embedded; IHC = immunohistochemistry; NGS = next-generation sequencing; NSCLC = non–small-cell lung cancer; SNP = single-nucleotide polymorphism.

Figure 2 Panel of Non–Small-Cell Lung Cancer (NSCLC) Patient-Derived Xenograft (PDX) Models That Harbor Epidermal Growth Factor Receptor (EGFR)-Activating Mutations. Models Are Organized According to Patient Clinical Status at the Time of the Originating Biopsy. "Erlotinib Sensitive-Naive" Models Were Acquired Before Treatment With Any EGFR Inhibitor; "Primary Resistance" Models Were Derived From Tumors That Showed No Clinical Benefit From Erlotinib; "Acquired Resistance" Models Were Derived From Tumors That Initially Responded to Erlotinib But Had Progressed at the Time of Biopsy. Models Were Also Subdivided According To Those With EGFR Gene Amplification (Upper Circle). Additional Information Is Provided in Each Box, Indicating Oncogenic Abnormalities of Interest



Abbreviations: AMP = amplification; mut = mutation.