Development of patient-derived xenograft models for small cell lung cancer as a preclinical platform for drug development

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Small cell lung cancer comprises 15-20% of all lung cancer cases, and is more invasive and has a higher rate of proliferation than non-small cell lung cancer, leading to a higher mortality rate. Most cases are responsive to chemotherapy, however there is a high rate of recurrence and those in advanced stage of the disease often have a refractory response. As such, the need for new treatment modalities is critical.

In this work, we have reported using the Molecular Response tumor bank, comprising >144,000 viable tumor specimens, to establish more than 350 PDX models of various cancer types. In this work, we describe the development of 8 new SCLC PDX models established from a collection of >300 small cell lung cancer specimens, many of which come from prior-treated and metastatic patients. We report a comprehensive characterization of these models, including: histopathology, immunohistochemistry, and mutation analysis. Additionally, we have evaluated functional response of these models with in vivo pharmacology studies. Current studies are underway to derive correlations between in vivo drug response and mutational status of these models. Our data strongly suggests the potential to use these unique PDX models to aid in efforts in drug development efforts in oncology.

Living Tumor Bank & Patient Derived Xenograft Models

PDX Model Development

- Improved preclinical models are required to advance our understanding of the molecular alterations that underpin cancer
- Patient-derived primary tumor cell models grown in mice have proven critical for developing and deploying targeted therapies to improve patients’ lives.

Patient Information

- SCL Patients Information: A summary of relevant patient data for the SCL models developed. Prior treatment history, metastatic vs. primary information available.

Mouse Model Builds

- Establishment of PDX Models: Mice were inoculated with human tumor samples (PD) and monitored for engraftment. Cells from the tumors were reinoculated into animals to confirm the growth as a PDX model (xP1) and banked down for future use.

Histology

H&E Slides: (A) Original Patient Slide (B) P0 PDX Tumor (C) P1 PDX Tumor (D) P2 PDX Tumor. Each patient features unique SCL histologies which are maintained throughout PDX model development from patient through P2.

AmpliSeq Results:

All SCL samples were run on a panel targeting 50 oncoproteins and tumor suppressor genes. LU65 showed the presence of the KIT gene and was used for further pharmacological testing.

Conclusions

- Our novel small cell lung cancer models retained their unique histology over passage.
- Patient information concerning prior drug treatment as well as sequencing information looking at presence of oncogenes and tumor suppressor genes provide valuable tools towards choosing the right model for drug development.
- Our SCL models show significant drug response in vitro and in vivo.