IA20
Pan-Cancer Convergence to a Small-Cell Neuroendocrine Phenotype that Shares Susceptibilities with Hematologic Malignancies

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Small-cell neuroendocrine (SCN) cancers are an aggressive cancer subtype. Transdifferentiation toward an SCN phenotype has been reported as a resistance route in response to targeted therapies. This has important consequences in that SCN cancers, once considered rare in many tissue types, may become increasingly common with the emergence of resistance cases. Here, we identified a molecular convergence to an SCN state that is more widespread across various epithelial cancers than previously realized, with these additional cases associated with poor prognosis. More broadly, non-SCN metastases have higher expression of SCN-associated transcription factors than non-SCN primary tumors. Drug sensitivity and gene dependency screens demonstrate that these convergent SCN cancers have shared vulnerabilities. These common vulnerabilities are found across unannotated SCN-like epithelial cases, pediatric small round blue cell tumors, and unexpectedly in hematologic malignancies. The SCN convergent phenotype and common sensitivity profiles with hematologic cancers can guide treatment options beyond the limitations of tissue-specific targeted therapies.

IA21
ASCL1 Represses a Latent Osteogenic Program in Small-Cell Lung Cancer Arising from Multiple Cells of Origin

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Small-cell lung cancer (SCLC) has been treated in the clinic as a single disease, but our previous work demonstrated that MYC drives a unique molecular and therapeutically relevant subset of SCLC (Mollaoglu et al., Cancer Cell 2017; Chalishazar et al., Clin Can Res 2019). Four major molecular subsets of SCLC have now been identified, and they are associated with high expression of four key developmental transcription factors: ASCL1, NEUROD1, POU2F3, and YAP1 (Rudin et al., Nat Rev Can 2019). ASCL1 is a lineage-specific oncogenic driver of SCLC, highly expressed in a significant fraction of tumors, that is required for the development of SCLC in specific mouse models. However, ~20% of human SCLC are ASCL1-low and associated with a non-neuroendocrine fate and high MYC expression. The role of ASCL1 in the MYC-driven subset of SCLC is unknown. Using genetically engineered mouse models (GEMMs), we show that alterations in Rb1/Trp53/Myc can drive SCLC in multiple cell types of origin and that these tumors initially express ASCL1. Genetic depletion of ASCL1 in MYC-driven SCLC dramatically inhibits tumor initiation but, surprisingly, converts tumors to an RUNX2+ osteogenic cell fate. Thus, ASCL1 normally represses the osteogenic fate in MYC-driven SCLC arising from multiple cells of origin. MYC-driven SCLC harbors gene signatures that resemble neural crest and mesenchymal stem cells, which have the cell fate options of becoming neuroendocrine or bone. These data suggest that ASCL1 is critical for neuroendocrine tumor cell fate even when initiated in non-neuroendocrine cells. Together, specific genetic alterations can promote remarkable plasticity or deprogramming of adult lung cells, with ASCL1 repressing the emergence of nonendodermal tumor fates.

IA22
Identifying Chemically Tractable Vulnerabilities in Small-Cell Lung Cancer

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Small-cell lung cancer is a clinically aggressive neuroendocrine cancer. Genome sequencing studies have failed to reveal frequent somatic mutations in genes encoding proteins that are targetable with currently available therapeutics. We have developed a series of tumor cell lines derived from genetically engineered mouse models of cancer (GEMMs) and performed a phenotypic small-molecule screen to identify SCLC/neuroendocrine-selective anticancer toxins. We will present preliminary results from this screening campaign, and recently developed methods used for identification of the molecular targets of small molecules identified from this and other HTS studies.

IA23
Developing New Therapies in Small-Cell Lung Cancer Using Parallel Clinical and Laboratory-Based Studies

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Small-cell lung cancer (SCLC) is an aggressive high-grade neuroendocrine malignancy with high metastatic potential and poor clinical outcomes. My translational research program utilizes both preclinical studies and clinical trial strategies to develop improved treatments for patients with SCLC. Preclinical and clinical studies have demonstrated activity of poly (ADP-ribose) polymerase (PARP) inhibitors in SCLC, though overall the activity of PARP inhibitor monotherapy has been quite modest. Combinations with other DNA-damaging agents have shown greater potential in trials. We conducted a phase I/II trial of combination olaparib tablets and temozolomide in previously treated SCLC. We established a recommended phase 2 dose (RP2D) of olaparib 200 mg PO BID with temozolomide 75 mg/m2 daily, both on days 1-7 of a 21-day cycle, and expanded to a total of 50 patients. The confirmed overall response rate (ORR) was 41.7% (20/48 evaluable), median progression-free survival (mPFS) was 4.2 months (95% CI 2.8-5.7), and median overall survival (mOS) was 8.5 months (95% CI 5.1-11.3) after a median follow-up of 7.1 months (Farago et al., Cancer Discovery 2019, PMID 31416802). Overall, these results indicate promising activity of combination olaparib and temozolomide in SCLC. In parallel, we have generated a panel of patient-derived xenograft (PDX) models of SCLC, using both tissue biopsies and circulating tumor cells (Drapkin et al., Cancer Discovery 2018, PMID 29483136). This panel includes 6 PDX models derived from patients enrolled to the olaparib/temozolomide trial. The responses of these in vivo tumor models to olaparib/temozolomide recapitulated the clinical responses of the corresponding patients. This enabled a coclinical trial in 32 PDX models, which we then utilized to identify putative biomarkers of response and resistance to olaparib/temozolomide. Using paired-end transcriptome sequencing, we identified a correlation between low basal expression of inflammatory response genes and cross-resistance to both olaparib/temozolomide and standard first-line chemotherapy, etoposide/platinum. We are now exploring mechanisms of acquired resistance to olaparib/temozolomide using serially derived PDX models from patients before and after treatment with this regimen. Updated data will be presented at the meeting.