aim to use LCS3 as a tool compound to characterize a cancer dependency that can be exploited for the benefit of LC patients with advanced tumors, for whom treatment is urgently needed.

B15
COP1 E3 Ligase Modulates Response to Oncogenic MAPK Pathway Inhibition

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Oncogenic activation of the RAS-MAPK pathway drives several cancers, including a majority of non-small cell lung adenocarcinomas (LAD). RAS-MAPK pathway is activated in lung adenocarcinomas via diverse genetic alterations in upstream receptor tyrosine kinases such as EGFR and ALK as well as in RAS, BRAF, MEK, and the RAS GTPase activating protein (GAP) and tumor suppressor, NF1. Therapeutically targeting components of the RAS-MAPK pathway can lead to initial tumor responses in many patients. However, very few patients show complete responses despite harboring the targeted RAS-MAPK pathway activating genetic lesion in the tumor. Responses and hence patient survival can be improved by better characterizing the molecular basis of response and resistance to therapies targeting the RAS-MAPK pathway in lung adenocarcinomas. To identify modulators of response to MAPK pathway inhibition in lung adenocarcinomas, we conducted genetic screens in BRAF-driven human lung adenocarcinoma cells. This identified the E3 ubiquitin ligase COP1/RFWD2 as a previously unknown genetic modifier in lung adenocarcinomas. We found that depletion of COP1 and members of its protein complex, as well as proteasomal subunits, confers resistance to RAS-MAPK pathway inhibition in patient-derived lung adenocarcinoma cells with oncogenic RAS-MAPK signaling. Intriguingly, oncogenic targets of COP1 include critical MAPK pathway effectors such as ETV1. Hence, we tested if depletion of COP1 protects those MAPK pathway effectors from the impact of RAS-MAPK pathway inhibitors. COP1 depletion had a substantial impact on the levels of these effectors in the presence of RAS-MAPK small-molecule inhibitors. Upon analyzing the transcriptomic and signaling changes, we found that low levels of COP1 facilitate survival of lung adenocarcinoma cells upon inhibition of the RAS-MAPK pathway by buffering the cells from the impact of the MAPK pathway inhibitor and thereby sustaining prosurvival pathways. Additionally, depletion of COP1 in in vitro derived models of resistance also re sensitized them to MAPK pathway inhibition. This study has furthered our understanding of the molecular basis of tumor cell resilience during initial treatment as well as of secondary treatment resistance. We are examining if COP1 also modulates response to MAPK pathway inhibition in vivo and if levels of COP1 could be a biomarker for predicting response to RAS-MAPK pathway inhibitor therapy in patients.

B16
The ROS1 Cancer Model Project: A Unique Patient-Driven Partnership to Accelerate Research

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Background: ROS1 rearrangements (ROS1+) are found in a wide variety of cancer types but are relatively uncommon, occurring in 1-3% of lung, gastric, and ovarian cancers, as well as melanoma, cholangiocarcinoma, glioblastoma, and other tumor types. ROS1 has been studied primarily in lung cancer, where there are now several FDA-approved drugs to treat advanced ROS1+ lung cancer. The rarity of ROS1 fusions makes studying them more challenging, as patients are too geographically dispersed to support a traditional clinical research study. To address this challenge, the ROS1ders joined forces with a leading lung cancer advocacy organization, an international research consortium, industry, and leading academic investigators to focus efforts on this rare molecular subset of tumor. Method: The ROS1 Cancer Model Project currently consists of two studies supported by the Addario Lung Cancer Medical Institute’s research infrastructure and remote study capabilities. Patients are empowered to contact the study team directly and do not have to be seen at a specific site to participate in the studies and donate samples for research. Due to the sparsity of research tools available to study ROS1+ cancer, the first study focuses on creation of patient-derived xenograft (PDX) models while the second study supports creation of cell lines. The ROS1ders and G2 Foundation for Lung Cancer have effectively utilized social media to connect with ROS1+ patients across the globe to educate them about the opportunity to participate in these ongoing research efforts. Both studies are currently open to ROS1+ patients located in North America. Results: The ROS1 Cancer Model Project has successfully demonstrated the feasibility and power of patient-driven research and cross-sector collaboration to implement an innovative study motivated by patient need. Since its launch, the project has effectively mobilized the international ROS1+ patient population to create new cancer models for this rare molecular subset. To date, over 30 patients have been screened, with five patients referred to the PDX study and eight patients referred to the cell line study. Together, these studies have led to the successful development of new murine and cell-line research tools and have resulted in a doubling of the preclinical models now available for ROS1 research. Conclusion: Through unique partnerships, the ROS1ders have accelerated the creation of new cancer models that will further researchers’ understanding of this rare molecular subset. The success of this collaboration highlights the power of patients in driving research and has laid the foundation for similar efforts by other patient groups. This effort is part of the larger Global ROS1 Initiative, which is working to address the ongoing needs of the international ROS1+ patient community.

B18
Structural Insight into Sensitivity and Resistance of RET Mutants to Selpercatinib (LOXO-292)

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Selpercatinib (LOXO-292) is a RET-selective protein tyrosine kinase inhibitor (TKI) designated as breakthrough therapy by the United States Food and Drug Administration. However, structural detail of its binding to RET was elusive. Protein tyrosine kinase targeted therapies often encounter resistance due to on-target mutations. Knowledge of TKI binding and resistant mutants is important for continuous TKI pipeline development and disease management. We have identified a panel of selpercatinib-resistant RET mutants in a preclinical model and determined the co-crystal structure of RET-selpercatinib complex to 2.06-Å resolution. Unlike vandetanib or nintedanib that insert into the gate, selpercatinib anchors one end in the front cleft and wrap around the 2.06-Å resolution. Unlike vandetanib or nintedanib that insert into the gate, selpercatinib anchors one end in the front cleft and wrap around the gate wall to access the back cleft without penetrating the gate. The selpercatinib anchors one end in the front cleft and wrap around the gate wall to access the back cleft without penetrating the gate. The selpercatinib interacts with hinge and solvent-front residues. Our study details how selpercatinib uses an