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LGG-29. BEYOND MAPK SIGNALING - GENOME-SCALE CRISPR/CA9 SCREENS REVEAL NEW TARGETS FOR TREATMENT OF KIAA1549::BRAF-DRIVEN PEDIATRIC LOW-GRADE GLIOMA
Anna Bożeniewicz1,2, Sean Misek3,4, Alexander Zhang5,6, Ruth Fekade1,7, Timothy Rapaport1,2, Aaron Fulstein2,3, Kevin Zhou1,2, Daniel Bondeson2, Dana Novikov1,2, Sher Bahadur1,2, Seung (Riley) H Choi1,2, Amy Goodale1,8, Alexandra L. Condurat1,2, Carolina Ortiz Cordero9, Nicole Persky2,10, Laura Kessler11, David Rost12, Michael Eck13, Jesse Boehm11, David Jones14, Ramesh Beroahkim15, Pratim (Mimi) Bandopadhyay16,17
1Department of Pediatric Oncology, Dana-Farber Cancer Institute, Boston, MA, USA, 2Broad Institute of MIT and Harvard, Cambridge, MA, USA, 3Departments of Cancer Biology and Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA, 4Massachusetts Institute of Technology, Cambridge, MA, USA, 5Department of Biological Chemistry and Molecular Pharmacology, Harvard Medical School, Boston, MA, USA, 6Department of Cancer Biology, Dana-Farber Cancer Institute, Boston, MA, USA, 7Hopp Children’s Cancer Center at the NCT Heidelberg, Heidelberg, Germany, 8Division of Pediatric Neurooncology, German Cancer Consortium, German Cancer Research Center (DKFZ), Heidelberg, Germany, 9Dana-Farber/Boston Children’s Cancer and Blood Disorders Center, Boston, MA, USA

Since the KIAA1549::BRAF fusion was discovered as the most common driver of pediatric low-grade glioma (pLGG), it has been hypothesized that the fusion induces oncogenicity through BRAF activation as a result of KIAA1549 replacing the BRAF negative regulatory N-terminus. This led to the rapid translation of MAPK pathway inhibitors into the clinical setting. Despite most tumors exhibiting promising initial responses, some tumors are not sensitive and about half of responsive tumors grow back after treatment cessation. Therefore, strategies that result in sustained tumor responses are desperately needed. We have recently performed genome-scale CRISPR/Cas9 screens across isogenic neural stem cell models transduced to express pLGG-associated oncogenes (KIAA1549::BRAF, BRAFV600E, and multiple FGFR1 and MYB family alterations) to generate a dependency map of genetic vulnerabilities associated with expression of these oncogenes. We also included normal neural stem cells to allow identification of genetic dependencies specifically induced by the expression of each oncogene. Surprisingly, through these efforts, we have discovered KIAA1549::BRAF expressing cells to harbor striking and specific dependency on multiple members of an enzymatic complex that exerts its activity outside of the MAPK signaling axis. Importantly, this enzymatic complex has been described to modify only a few substrates, including KIAA1549, suggesting specificity. We have now validated this dependency across other isogenic models of KIAA1549::BRAF expressing cells. Finally, our KIAA1549::BRAF-expressing models exhibit preferential sensitivity to a tool compound that targets our novel enzyme, suggesting novel therapeutic potential for KIAA1549::BRAF. These findings highlight a MAPK pathway-independent avenue for therapeutically targeting the most frequent genomic alterations in pediatric brain tumors. Consequently, we also propose that the fusion partner KIAA1549 is instrumental for the aberrant BRAF signaling driving pLGs. (1 we are currently in the process of working with our IP offices to ensure that we can disclose the names of the genes and proteins at the ISPNO meeting)