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### Title

Abstract 827: A journey to deconvolute the multifaceted functions and context-dependency of cancer driver genes

### Permalink

<https://escholarship.org/uc/item/8mt188xc>

### Journal

Cancer Research, 82(12\_Supplement)

### ISSN

0008-5472

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### Publication Date

2022-06-15

### DOI

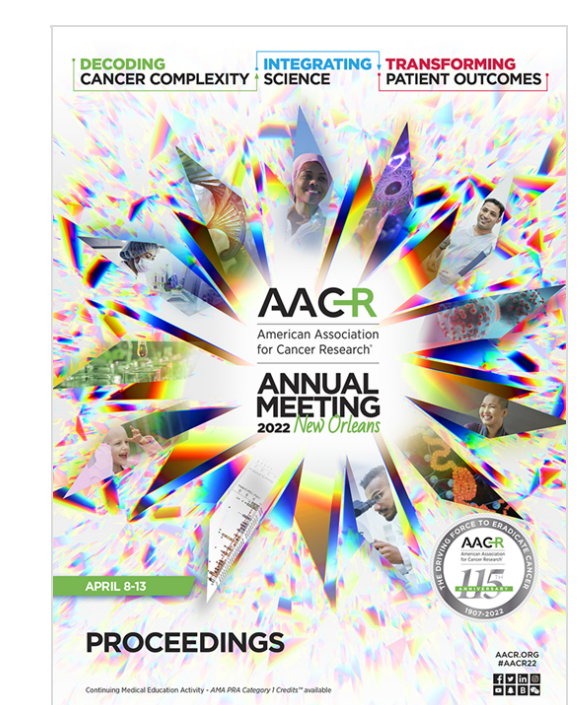
10.1158/1538-7445.am2022-827

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# CANCER RESEARCH

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**Volume 82, Issue 12\_Supplement**  
15 June 2022



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Abstract

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## Abstract 827: A journey to deconvolute the multifaceted functions and context-dependency of cancer driver genes

Hongchen Cai; Su Kit Chew; Chuan Li; Christopher W. Murray; Laura Andrejka; Jess D. Hebert; Min K. Tsai; Rui Tang; Nicholas W. Hughes; Emily G. Shuldiner; Emily L. Ashkin; Shi Ya C. Lee; Maryam Yousefi; Dmitri A. Petrov; Charles Swanton; Monte W. Winslow

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*Cancer Res* (2022) 82 (12\_Supplement): 827.  
<https://doi.org/10.1158/1538-7445.AM2022-827>

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### Abstract

Lung cancer is a lethal and genomically-complex disease. Structural genomics has largely advanced our knowledge of genomic alterations, yet the function of a majority of altered genes remains less clear. Previous in silico and in vitro functional genomics data often lead to contradictory conclusions on gene functions. Genetically-engineered mouse models are reliable approaches for in vivo functional analyses, but development of these models are lagging behind due to the throughput limit. To overcome this throughput limit, we developed tumor barcoding and ultradeep barcode sequencing (Tuba-seq) that precisely quantifies the growth metrics of hundreds of tumor genotypes, which is a huge leap forward. Through this approach, we have begun a journey to create a quantitative functional taxonomy of tumor suppression in oncogenic KRAS-driven lung cancer. For example, STAG2 and CDKN2C emerged as novel functional tumor suppressor genes in the lung, when they were often overlooked by computational analyses due to relatively low mutation prevalence. Interestingly, STK11 and PTEN, both playing an important role in tumor growth, exhibit distinct roles in tumor initiation. These findings suggest that structural genomics is not sufficient to predict cancer driver genes, and calls for closer investigation of tumor suppressor functions in specific tumorigenesis stages. Furthermore, the quantitative nature of our data has enabled systematic characterization of interactions between tumor suppressor genes. For instance, RNF43 exhibits different tumor suppression modes in the presence or absence of STK11 or TRP53, while TRP53 can play opposite roles in PTEN- and RB1-deficient tumors. In addition, Foggetti et al. (2021) reported that tumor suppressors can play opposite roles in the contexts of different oncogenes. Collectively, these findings suggest that cooccurring mutations shift the functional landscape of tumor suppressors even in the same pathological subtype of cancer. Given the genomic diversity of lung cancer patients, driver genes may change case by case. We are now investigating the molecular mechanisms underlying these tumor suppressors and their genetic interactions. Our findings underscore the necessity of determining the consequences of enormous combinations of genomic alterations in their natural environment, which is challenging but critical for understanding cancer evolution, interpreting clinical cancer genome sequencing data, and directing approaches to limit tumor initiation and progression.

**Citation Format:** Hongchen Cai, Su Kit Chew, Chuan Li, Christopher W. Murray, Laura Andrejka, Jess D. Hebert, Min K. Tsai, Rui Tang, Nicholas W. Hughes, Emily G. Shuldiner, Emily L. Ashkin, Shi Ya C. Lee, Maryam Yousefi, Dmitri A. Petrov, Charles Swanton, Monte W. Winslow. A journey to deconvolute the multifaceted functions and context-dependency of cancer driver genes [abstract]. In: Proceedings of the American Association for Cancer Research Annual Meeting 2022; 2022 Apr 8-13. Philadelphia (PA): AACR; Cancer Res 2022;82(12\_Suppl):Abstract nr 827.

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