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Researchers identify potential targets for novel treatments for lung cancer

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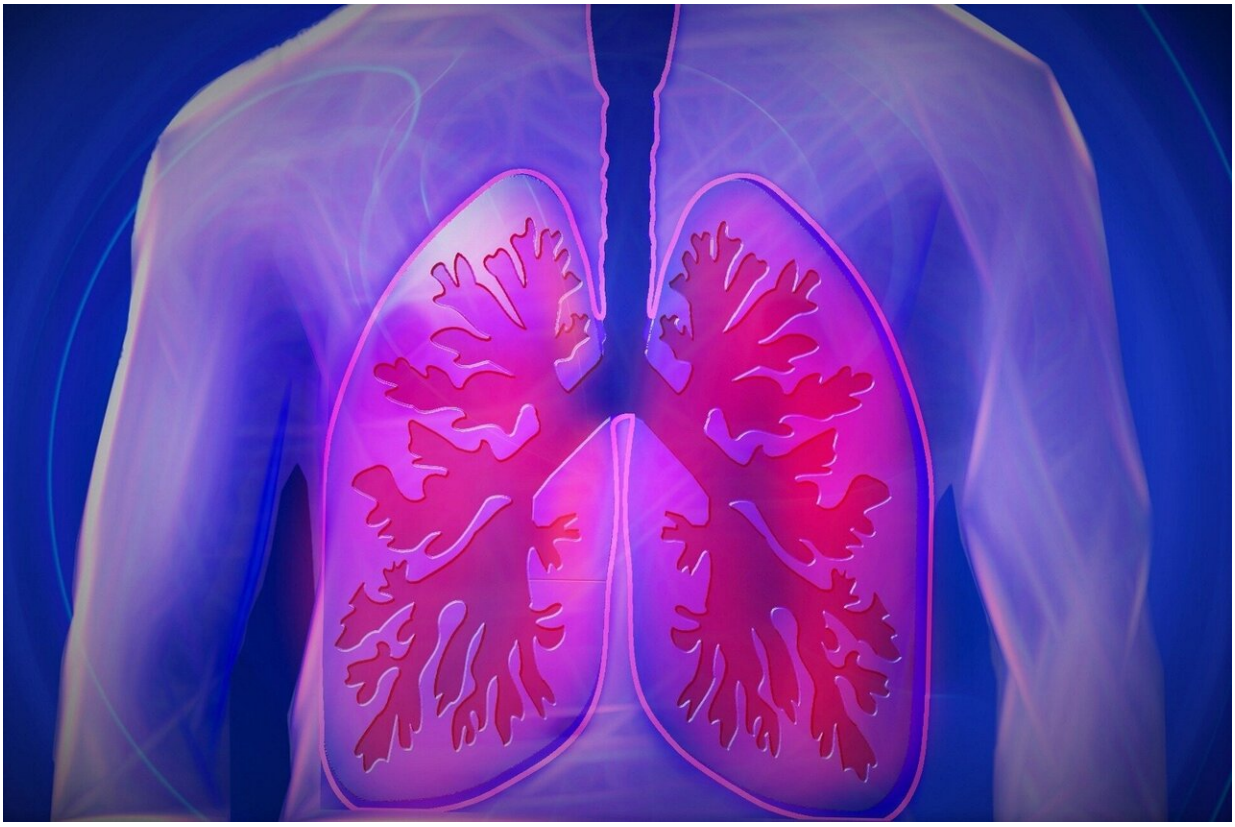

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Lung cancer is the most common cause of cancer deaths, accounting for about a third of all tumor-related deaths. Adenocarcinomas, a non-small cell lung cancer (NSCLC), account for about 40 percent of cancer

diagnoses, but few treatments are available for the disease.

A team of investigators led by Elena Levantini, Ph.D., a research associate in Hematology-Oncology in the laboratory of Daniel Tenen MD, at Beth Israel Deaconess Medical Center (BIDMC), evaluated a novel agent, PTC596, capable of decreasing tumor growth in preclinical studies performed on a mouse model of mutant K-RAS lung cancer. The research—performed in collaboration with the Cancer Science Institute of Singapore at the National University of Singapore (CSI NUS) – were published today in the journal *Communications Biology*. The findings, which represent a comprehensive snapshot of the tumor's components, will facilitate the development of novel therapies to overcome relapse and tumor progression in patients with NSCLC.

Using single cell RNA sequencing methodology, Levantini and colleagues sampled the whole transcriptome—the full set of RNA molecules expressed by a cell—of individual tumor cells from the team's murine model and from clinical pulmonary specimens. In addition to highlighting a high degree of similarity between the species, the scientists also identified a specific population of tumor cells in both mice and humans present only in tumors positive for the mutated oncogene K-RAS, and not in healthy lung cells. Next, the team used the murine model to evaluate a novel therapy currently in Phase 1b clinical trials. The drug, PTC596, aims to eliminate cancer cells by inhibiting the activity of the BMI1 oncogene.

"Identifying these molecular networks underlying cancer is an important step toward producing new targeted drugs—so-called molecular or personalized therapy," said Levantini, who is also an Instructor of Medicine at Harvard Medical School (HMS). "Currently, most patients receive generalized chemotherapy treatments which do not target the specific molecules involved in the tumor process, which can also cause damage to healthy cells. Until we are able to decipher the complexity of

the tumor cell subpopulations, we will not be able to design targeted therapeutic options to decrease the number of patients who experience tumor recurrence."

Levantini and colleagues previously identified the key role BMI1 plays in tumor growth. With the work published today, the researchers have paved the way for future clinical applications for using the new therapeutic option in a relevant subset of lung cancer patients with K-RAS mutated. Levantini stresses, however, that further careful validation is required before proceeding to treat patients with the new therapeutic option. The team's findings could have important implications for other cancers as well, given that the activity of the oncogene BMI1 is also significantly increased in other subtypes of lung cancers, as well as in other solid tumors (skin cancer, breast, colon and intestinal, and in glioblastoma) as well as in leukemias and lymphomas.

More information: Giorgia Maroni et al. Identification of a targetable KRAS-mutant epithelial population in non-small cell lung cancer, *Communications Biology* (2021). DOI: 10.1038/s42003-021-01897-6

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