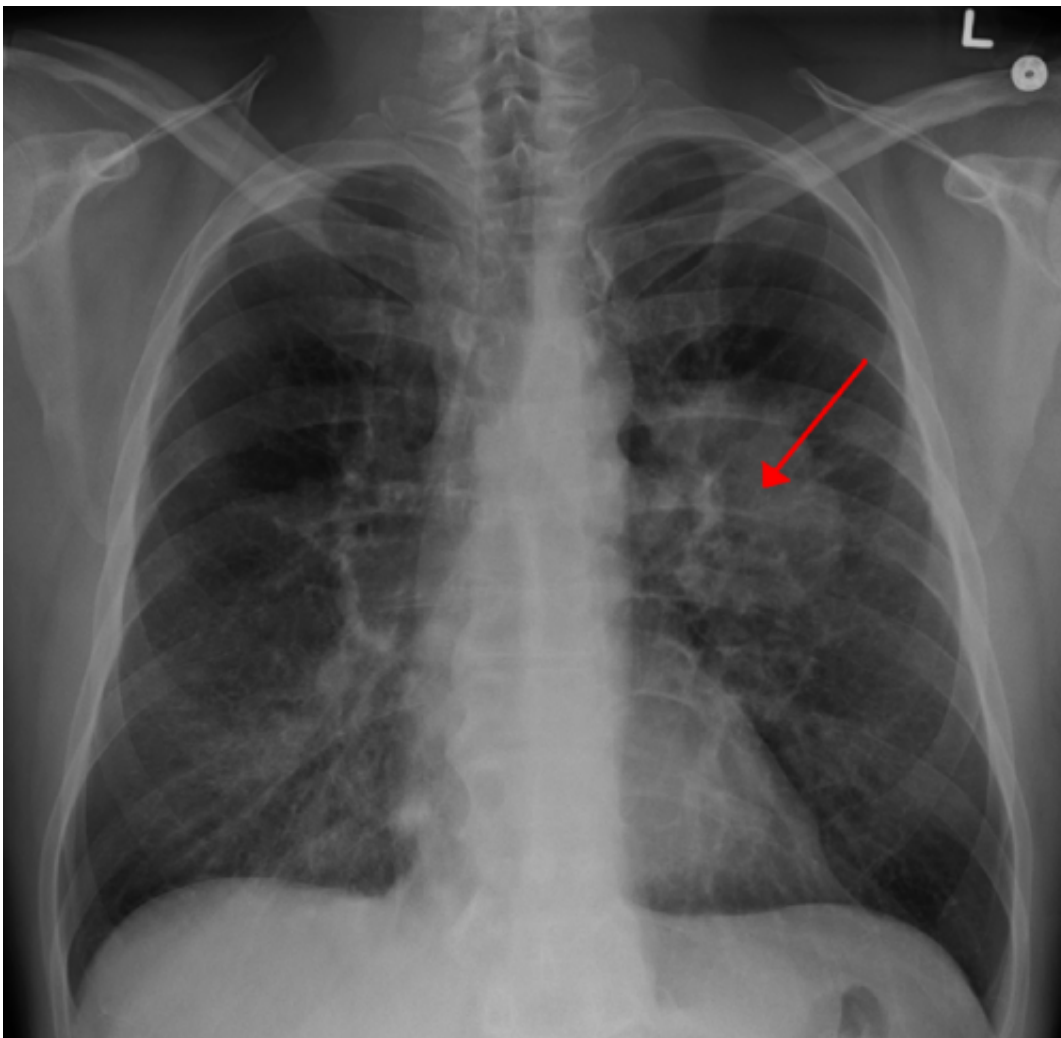


# Epigenetic regulator explains why some lung cancer patients become resistant to common therapeutics

April 12 2022, by Brittany Steff

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Lung CA seen on CXR. Credit: [CC BY-SA 4.0](https://creativecommons.org/licenses/by-sa/4.0/) James Heilman, MD/Wikipedia

Doctors typically treat people with non-small cell lung cancer, a prevalent and typically incurable type of cancer that makes up 80%-85% of lung cancers, with tyrosine kinase inhibitors, specifically epidermal growth factor receptor inhibitors. About 15%-20% of these patients will become resistant to these standard treatments, resulting in their eventual death. Researchers understand part of the reason for this: The cells develop a mutation that leads to resistance. But about half of those resistant patients remain unexplained.

Andrea Kasinski, a Purdue University cellular biologist, and her lab have discovered that some of the explanation is epigenetic. When cells lose the histone methyltransferase (KMT5C), genes that KMT5C were repressing instead become expressed, leading to resistance to epidermal growth factor receptor inhibitors. This understanding lays the groundwork for future therapeutics and gives researchers and doctors a deeper insight into the biology and progression of cancers, especially the role that epigenetic-modifying proteins play in drug resistance, a phenomenon that is not well understood.

"For the majority of genes that contribute to cancer, we're not sure how they work yet," Kasinski said. "And for many, we don't have a way to therapeutically target them. Research like this, that helps us understand how those genes work to determine cancer outcomes, adds to our understanding of the network. This knowledge will ultimately lead us to better therapeutics."

Kasinski is an expert in how epigenetic factors, especially non-coding RNAs, affect cancer outcomes, including resistance to therapeutics. She is the William and Patty Miller Associate Professor in the Department of Biological Sciences in Purdue's College of Science, as well as a researcher studying cell identity and signaling with the Purdue Center for Cancer Research. She is an expert in target discovery and characterization, delivery and formulations and in vivo disease models

with the Purdue Institute for Drug Discovery.

Kasinski and her team identified the KMT5C gene using a global CRISPR-Cas9 screen after challenging the cells with an epidermal growth factor receptor inhibitor. They selected cells that grew out and then identified the [mutations](#), finding that KMT5C was the most significantly mutated gene in the screen. They validated the results in other cell lines using genetic knockdown and chemical inhibition of KMT5C, leading them to discover that the gene MET, a prominent cancer gene, was upregulated. They used chromatin immunoprecipitation with an antibody for the methylation mark made by KMT5C to determine that an RNA that enhances MET expression is normally methylated and, thus, not expressed. When cells lose KMT5C, the RNA is expressed, leading to MET expression and the subsequent resistance to therapeutics.

Their paper is published in *Cancer Research*.

**More information:** Arpita S. Pal et al, Loss of KMT5C Promotes EGFR Inhibitor Resistance in NSCLC via LINC01510-Mediated Upregulation of MET, *Cancer Research* (2022). [DOI: 10.1158/0008-5472.CAN-20-0821](#)

Provided by Purdue University

Citation: Epigenetic regulator explains why some lung cancer patients become resistant to common therapeutics (2022, April 12) retrieved 25 April 2024 from <https://medicalxpress.com/news/2022-04-epigenetic-lung-cancer-patients-resistant.html>

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