Scientists find lethal vulnerability in treatment-resistant lung cancer

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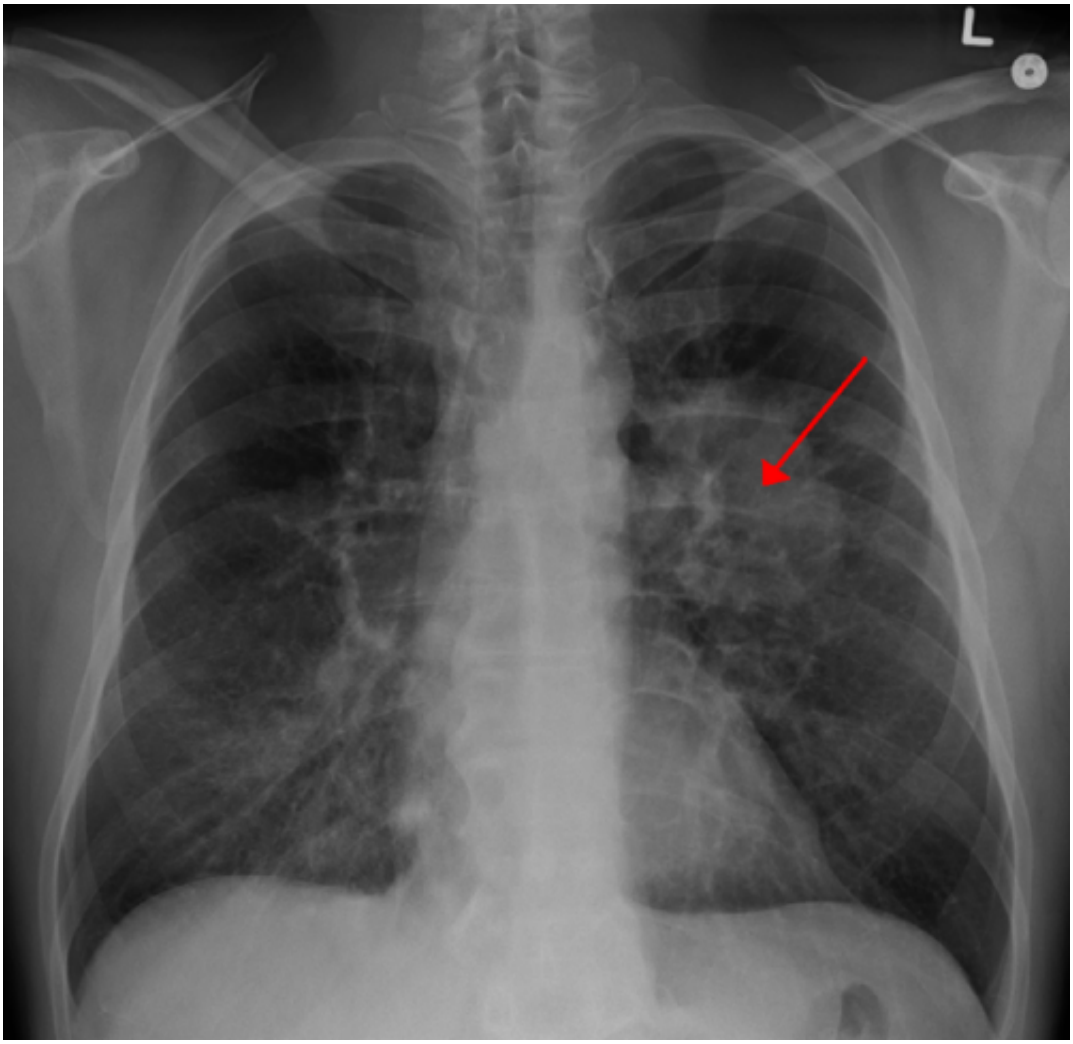

Lung CA seen on CXR. Credit: CC BY-SA 4.0 James Heilman, MD/Wikipedia

Researchers working in four labs at UT Southwestern Medical Center have found a chink in a so-called "undruggable" lung cancer's armor – and located an existing drug that might provide a treatment.

The study, published this week in *Nature,* describes how the drug Selinexor (KPT-330) killed lung cancer cells and shrank tumors in mice when used against cancers driven by the aggressive and difficult-to-treat *KRAS* cancer gene. Selinexor is already in clinical trials for treatment of other types of cancer, primarily leukemia and lymphoma but also gynecological, brain, prostate, and head and neck cancers.

Lung cancer is the No. 1 cancer killer in the U.S., responsible for more than 158,000 deaths a year, according to the National Cancer Institute (NCI), and the *KRAS* oncogene is believed to be responsible for about 25 percent of all lung cancer cases. The 5-year survival rate for lung cancer is below 18 percent.

Cancers caused by the *KRAS* mutation have been a target for researchers since the mutation was discovered in humans in 1982. But, due in part to this oncogene's almost impervious spherical shape, no one was able to find an opening for attack, said Dr. Pier Scaglioni, Associate Professor of Internal Medicine at UT Southwestern and a contributing author to the study.

Dr. Michael A. White, Adjunct Professor of Cell Biology and senior author of the study, assembled multiple research teams and used robotic machines to create and sift through trays with thousands of cancer cell/potential drug combinations to uncover the *KRAS* mutation's weakness.

The scientists found that targeting and inactivating the protein XPO1, found in the cell nucleus and used to transport gene products from the nucleus to the cytoplasm, killed most of the *KRAS* mutant cancer cells.

"We found that inhibiting the *XPO1* gene kills lung cancer cells that are dependent on *KRAS*," Dr. Scaglioni said. "The unexpected coincidence here is that there is an existing drug that will inhibit *XPO1*."

"We know that this drug hits the *XPO1* target in people," added Dr. White, also a research executive at Pfizer Inc. "But we will not know whether the drug will be effective until clinical trials are done, which should be completed in about two years."

Based on the results of this study, Selinexor, developed by Karyopharm Therapeutics, will be the focus of a multicenter lung cancer clinical trial led by UT Southwestern's Dr. David Gerber, Associate Professor of Internal Medicine. That trial is expected to open for enrollment next year.

In preclinical results from cancer cells and mouse models in the *Nature* study, 83 percent of the *KRAS* mutant lung cancers responded to Selinexor. The study found the remaining 17 percent of lung cancers could be killed by adding a second drug to inhibit *YAP1*, a gene known to be involved in the promotion of several other cancers.

Here too, there was an existing drug, Verteporfin, which appeared to be effective in blocking *YAP1*. Verteporfin is currently used to treat blood vessel disorders in the eye.

Dr. Jimi Kim, a former graduate student in Cancer Biology, was lead author of the study. Other UT Southwestern authors included: graduate student Elizabeth McMillan, research scientist Saurabh Mendiratta, and former researcher Gurbani Makkar, all in Cell Biology; Niranjan Venkateswaran, research associate in Internal Medicine; Shuguang Wei, senior research scientist in Biochemistry; Dr. Bruce Posner, Professor of Biochemistry; Dr. Michael Roth, Professor of Biochemistry and holder of the Diane and Hal Brierley Distinguished Chair in Biomedical

Research; Dr. Robin Frink, postdoctoral researcher; Dr. Boning Gao, Assistant Professor in the Hamon Center for Therapeutic Oncology Research and of Pharmacology; and Dr. John Minna, Professor in the Hamon Center and of Pharmacology and Internal Medicine, who holds the Sarah M. and Charles E. Seay Distinguished Chair in Cancer Research, and the Max L. Thomas Distinguished Chair in Molecular Pulmonary Oncology.

UT MD Anderson Cancer Center; the Severance Biomedical Science Institute in Seoul, South Korea; Karyopharm Therapeutics; and the KU Leuven Department of Microbiology and Immunology in Leuven, Belgium; also participated in the study.

More information: Jimi Kim et al. XPO1-dependent nuclear export is a druggable vulnerability in KRAS-mutant lung cancer, *Nature* (2016). DOI: 10.1038/nature19771

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