Molecule designed to treat lung cancer shows promising results in mice

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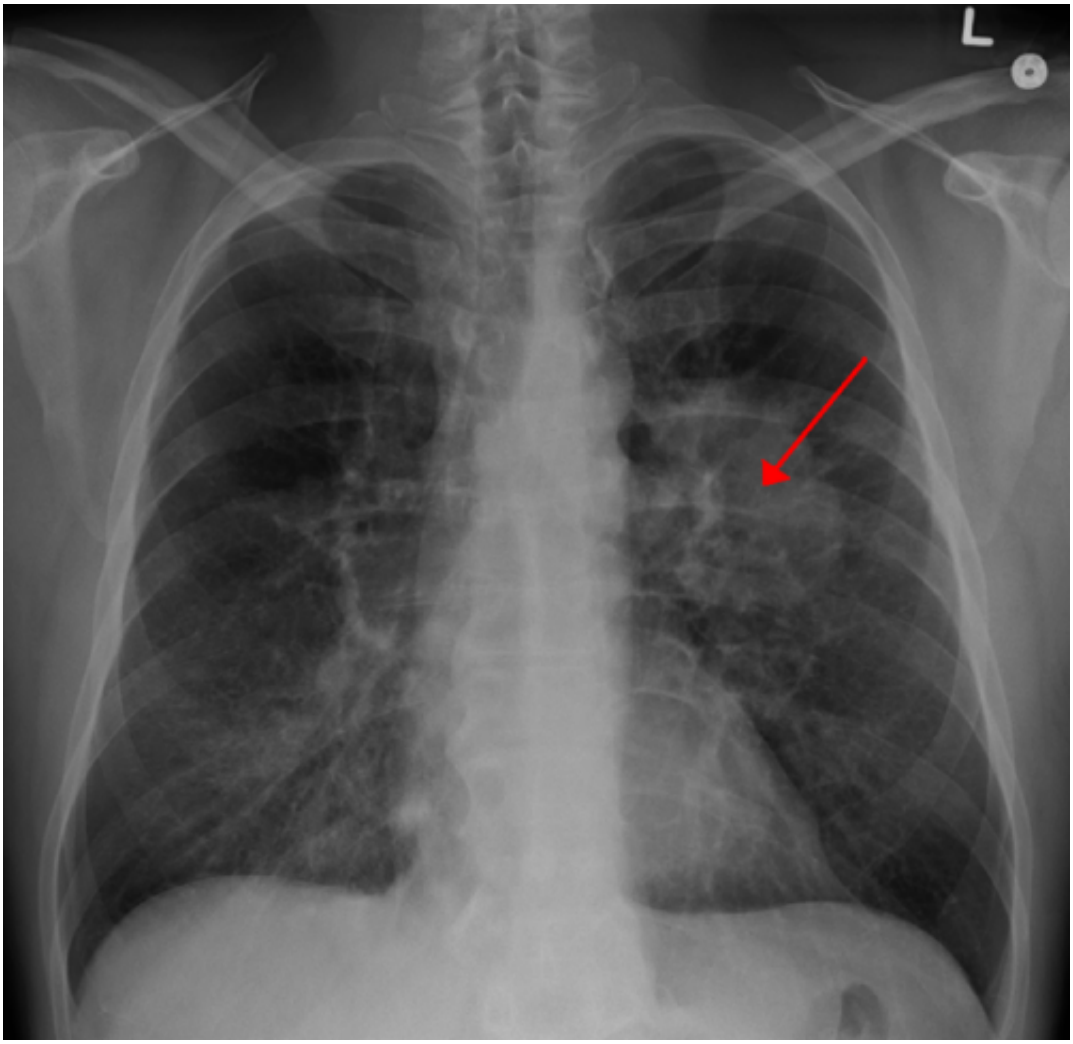

Lung CA seen on CXR. Credit: CC BY-SA 4.0 James Heilman, MD/Wikipedia

A multidisciplinary team led by Johns Hopkins researcher Venu Raman, Ph.D., with notable contributions from Guus Bol, Farhad Vesuna and Phuoc Tran of Johns Hopkins, has identified a new therapy for lung cancer, the most common cancer worldwide. The therapy has been in development for six years and involves a first-in-class molecule designed by the team. The molecule, RK-33, interrupts the cell cycle of lung cancer cells without harming normal cells, and it is effective both on its own and in combination with radiation therapy.

The team designed the molecule to bind to DDX3, an enzyme that normally helps in RNA unwinding and translating RNA into proteins. In addition, the team identified that DDX3 is involved in DNA repair. Normal cells have many such enzymes, but some cancers, including over 90 percent of the lung cancer samples studied by the team, overexpress DDX3. Binding DDX3 with RK-33 reduces the amount of DDX3 available, thus causing the cancer cells to die and making radiation therapy—which damages DNA—more effective.

"We can lower the dose of radiation significantly but actually get more bang for your buck" by pretreating lung cancer with RK-33, says Raman, an associate professor of radiology and radiological science, of oncology and a member of the Johns Hopkins Kimmel Cancer Center.

Published in the May issue of *EMBO Molecular Medicine*, the team's study primarily focuses on lung cancer, yet further studies with RK-33 are ongoing in multiple cancer types, including breast cancer, prostate, sarcoma and colorectal cancer.

"DDX3 is an extremely novel target associated with many cancer types," says Raman, "and perturbing its function with a small molecule will enhance efficacy for cancer treatment."

The team identified DDX3 while studying the effects of cigarette smoke

on normal breast cells by looking for changes in gene expression. Given his training in developmental biology, Raman focused the team to seek a novel drug target on genes important to the development of model organisms—fruit flies (Drosophila) and yeast (Saccharomyces cerevisiae)—rather than on oncogenes that transform a normal cell into a cancer cell.

Unlike most biomarkers for cancer, DDX3 mRNA expression only increased slightly in the exposed breast cells, but the corresponding proteins levels were significantly higher. "We were pleasantly surprised by this finding," Raman says, "because it's not just finding a biomarker that matters. The key part is finding a biomarker that is druggable."

To test DDX3's druggability, the team chose to design its own small molecule rather than screen libraries of molecules already created. "If you find something that appears to work, you have the ability to modify the parent compound to generate more potent molecules," says Raman.

It took many attempts before the team hit upon RK-33. "It is a lot of intelligent planning and hard work, but we have to get lucky too," says Raman, "because the risk of it not working—using rational drug design—is reasonably high."

"It is hard to find a magic bullet for cancer treatment," says Raman, "but because RK-33 is nontoxic and is a phenomenal radiosensitizer, there are so many opportunities." Patents in the U.S. and in several international markets already have been awarded both for the composition of RK-33 and for the use of RK-33 as a radiosensitizer. Raman says the next big steps are in overcoming the technical challenges of delivering the drug, and completing the experiments essential to file for an Investigational New Drug Application with the Food and Drug Administration to start clinical trials.