Scientists accelerate progress in preventing drug resistance in lung and pancreas cancers

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In healthy bodies, NTRK1 has critical functions in the development of nerve cells, particularly those that send signals to the brain about pain, temperature, and touch. In some cancers, these powerful genes malfunction to send signals to cells, instructing them to grow constantly.

The study, published in the journal *Cell Reports*, was led by Martin McMahon, Ph.D., senior director of preclinical translation at HCI and professor of dermatology at the U of U, and Aria Vaishnavi, Ph.D., a postdoctoral fellow in McMahon's lab. McMahon's team focuses on cell-cell communication, like the signaling promoted in some cancers by NTRK1.

One way to examine this experimentally is to devise a way to model human cancers in mice. This process produces a new tool, a "mouse model," which allows scientists to analyze in a laboratory setting how a cancer develops, how it behaves over time, and to test potential new drugs and treatment targets. The researchers hope the new NTRK1 mouse models reported today will accelerate progress toward finding more effective treatments for patients with NTRK1-driven lung and pancreas cancers.

A conversation with Ignacio Garrido-Laguna, MD, Ph.D., a physician-scientist at HCI, associate professor of internal medicine at the U of U,

and director of the HCI Phase I Clinical Research Program, inspired the idea for this study. Garrido-Laguna was caring for a pancreatic cancer patient who was participating in a clinical trial at HCI (NCT02568267). The patient's tumor had a mutation in NTRK1 and then had a remarkable response to the NTRK1 inhibitor drug being evaluated. Hence, it made sense to Garrido-Laguna and McMahon that the response might be related to inhibition of the mutated NTRK1.

McMahon posited that if NTRK1 signaling was responsible, disruption of that signaling might be beneficial. "Pancreatic cancers have proven to be a particularly recalcitrant to treatments, so we wanted to thoroughly evaluate such a dramatic response as we work to identify new potential treatments for this disease," said McMahon. Moreover, since the responses to the NTRK1 inhibitors are often short-lived, McMahon and colleagues wanted to design new combination therapies that prevented the onset of lethal drug resistance.

As a graduate student in the lab of Robert Doebele, MD, Ph.D., at the University of Colorado, Denver, Vaishnavi was the lead author on the discovery of the involvement of NTRK1 fusions in lung cancer. That work led to the rapid testing and approval of drugs called TRKA inhibitors in the clinic. These drugs were the first ever "agnostic" agents approved by the US Food and Drug Administration, meaning the drugs were approved for any patient with a type of cancer that carried the NTRK1 abnormality. Vaishnavi's background studying these molecules in lung cancer was essential to the current pancreas cancer project.

To better understand cancers that carry this abnormality, McMahon, Vaishnavi, and Conan Kinsey, MD, Ph.D., a physician-scientist at HCI and assistant professor of internal medicine at the U of U with expertise in pancreatic cancer biology, developed mouse models for both pancreas cancer and lung cancer driven by the NTRK1 abnormality. "The lung and pancreas are two clearly distinct organs with unique features that

shape the development of solid tumors," says Vaishnavi. "It is important to study how cancers begin and operate in the correct tissue context and microenvironment."

In this study, McMahon and his colleagues evaluated rational drug combinations that greatly enhanced the durability of tumor response and prevented the onset of lethal drug resistance in the mouse models. Their hope now is for this laboratory research to progress toward clinical trials in patients, and, ultimately, to improve treatment options for patients affected by these aggressive cancers.

Provided by Huntsman Cancer Institute