

How the Immune System Affects Drug Response in Lung Cancer Patients

University of Colorado Cancer Center member Lynn Heasley studies potential targets to enhance response to tyrosine kinase inhibitors.

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Why do some [lung cancer](#) patients respond better to the types of drugs known as tyrosine kinase inhibitors? It may have to do with those patients' own immune systems.

That's the hypothesis being tested by [University of Colorado Cancer Center](#) member Lynn Heasley, PhD, who recently received a Merit Review Award renewal from the U.S. Department of Veterans Affairs (VA) to study the role of the immune system in patients with lung adenocarcinoma who are treated with tyrosine kinase inhibitors (TKIs).

"If you take 100 lung adenocarcinoma patients with a particular oncogene, and you treat them all with the same drug, you get a wide variation in how the patients respond," Heasley says. "Some of them show a major response that might last for many years, some of them show a more modest response, and others don't respond very well at all."

Heasley's research group and his collaborators [Raphael Nemenoff](#), PhD, [Erin Schenk](#), MD, PhD, and [Tejas Patil](#), MD, have shown over the past couple of years "that the patient's host immunity has something to say about how that response goes," Heasley says.

Signal processing

When a lung tumor is treated with a TKI, Heasley says, the medicine induces a series of signals that are released from the tumor cells and communicate with immune cells. Sometimes that communication instructs a robust response from the T cells that helps clear out the tumor, but sometimes the signal reaches immune cells that suppress the immune system to protect the tumor.

"Each of us has a variation in our immune microenvironment that allows a more robust response or a less robust response. That could be used to our advantage if we can understand how to make the immune system contribute more to attacking the tumor," he says. "If you could understand what's happening in the cancers that respond the best to tyrosine kinase inhibitors, as well as the

ones that don't respond at all, you might find biologic mechanisms that could be exploited as therapeutic targets."

With his four-year, VA-funded grant, Heasley will study animal models of lung cancer driven by oncogenes that respond to specific TKIs, with the goal of identifying a target that could be treated medically to improve the performance of TKIs in patients whose immune system makes them less responsive to the treatment.

"Adaptive immune cells, like T cells and B cells, get prompted to expand and attack foreign substances," he says. "It seems that by the time you treat them, tumor cells have already communicated with the adaptive immune system to some extent. The TKI instructs the T lymphocytes to participate strongly in eliminating the tumor, but we think there are other immune cells, like neutrophils, that are immune suppressive and dial back the response of our adaptive immune system. In cancer, we want to tell the T cells to attack the tumor, but if immune cells are suppressing that, that's something we need to try to overcome."

Proactive solution

The results of the study may be able to be used proactively, as well — if the research reveals characteristics of host immunity associated with poorer response to TKIs, a blood test might be designed such that novel immune-targeting agents might be prescribed up front to try to overcome the resistance.

"We're going to study the immune cells in the blood to see if they give us information about what may be going on in the tumor," Heasley says. "We have some pilot studies that have shown that if the number of specific immune-suppressive cells are very high, then historically, patients show a very brief response to TKIs versus ones that have low levels of those cells."

Heasley is part of a group of lung cancer researchers at the CU Cancer Center who are interested in applying artificial intelligence to tumor samples to find patterns that would let doctors know, before the patient is even treated, if the patient is going to do poorly or well on the treatment.

Longer response time

Heasley says the research will help find new ways to treat a deadly cancer that occurs in smokers and nonsmokers alike, and that tends to recur even in patients who initially respond to treatment with TKIs.

"Each time a cancer recurs following therapy, it acquires more genomic issues and becomes more difficult to treat," he says. "If you knew which patients are going to recur more quickly, it would make sense to try to find ways to intervene with a combination of medications. Can we customize your TKI treatment with additional agents that may give you a longer-lasting response? We are cautious about using the word 'cure,' but the long-term goal would be to make it so you could

manage lung cancer for 10 to 20 years. We want a more complete therapeutic regimen that allows the therapy to last much longer.”

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