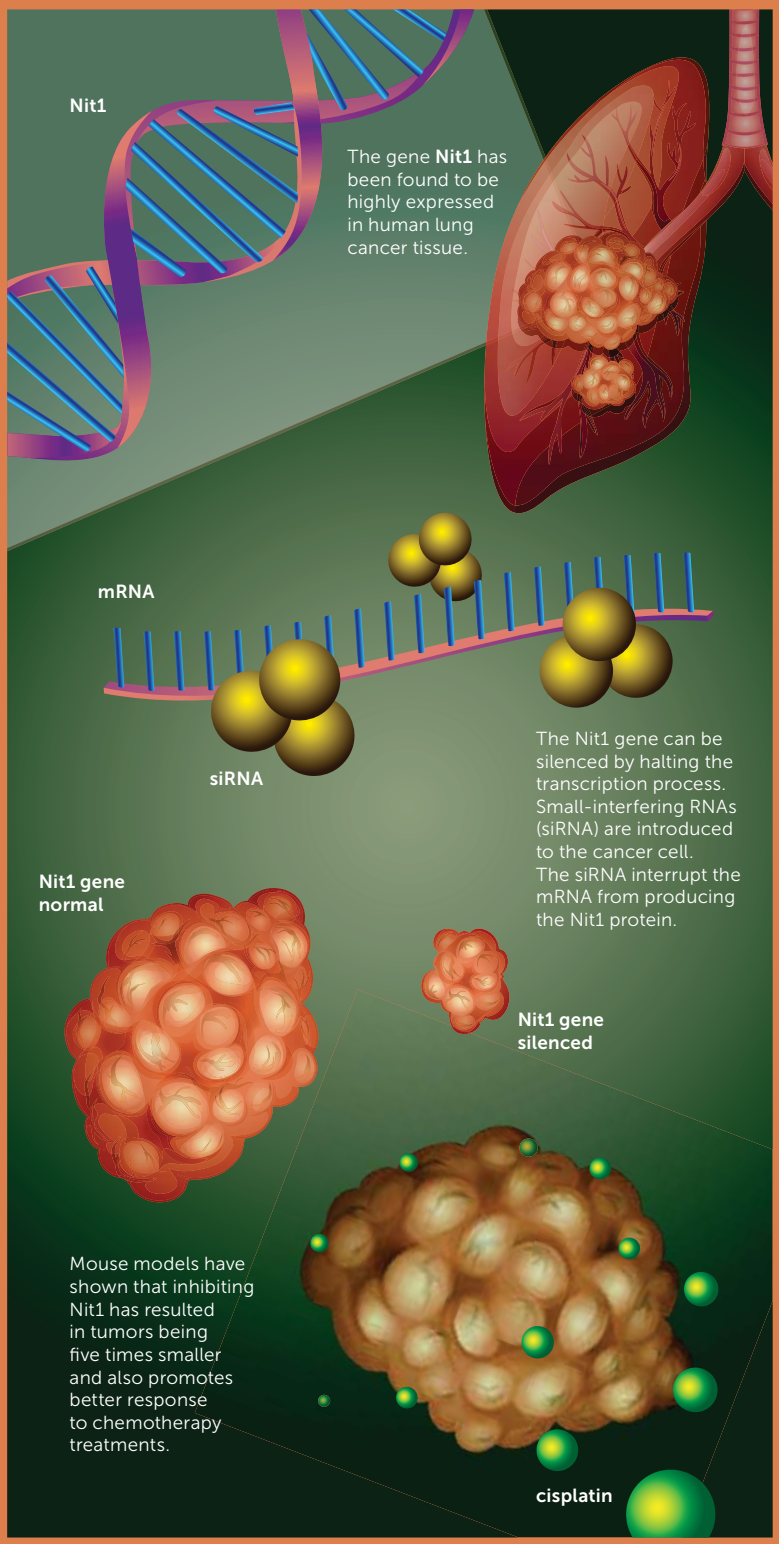
Researchers Find Highly Active Gene in Aggressive Human Lung Cancer



Scientists believe that "conserved" genes—those found in life forms that range from bacteria to plants, insects and humans—perform vital biological functions across species. And limited research on one of those genes, Nitrilase 1 (Nit1), suggested it acts to inhibit cancer development.

But researchers at the Sidney Kimmel Cancer Center at Jefferson have found Nit1 is significantly overproduced in common lung cancer compared to normal cells—and that when Nit1 is silenced, growth of lung tumors is suppressed.

Their study, published in the journal *Oncotarget*, is the first to characterize the contribution of Nit1 to growth and progression of non-small cell lung cancer. The findings strongly suggest that Nit1 may represent a much-needed new target for drug therapy, says the study's senior researcher, Bo Lu, MD, PhD, radiation oncologist at SKMC.

"Lung cancer in most patients is becoming increasingly resistant to the therapies that exist today, making lung cancer the leading cause of cancer death worldwide," Lu says. "There is a critical need for new agents, and an inhibitor of Nit1 may represent a new drug strategy."

The study is a "nice example of how research designed to understand basic mechanisms in lung cancer can lead to identification of possible new drug targets," says Adam Dicker, MD, PhD, chair and professor of radiation oncology.

Lu and his colleagues created mouse models that develop lung cancer due to a mutation in the KRAS gene in the presence or absence of Nit1 in the mouse genome (human lung cancers with KRAS mutations—about 20–30 percent of all lung cancers—are much more aggressive and difficult to treat).

Using a mouse model lacking Nit1, which was created by Jefferson researcher Jianke Zhang, PhD, the scientists then crossbred these mice and found that lack of Nit1 resulted in tumors that were five times smaller than those that developed in mice with an active Nit1 gene.

They also found that Nit1 is highly expressed in human lung cancer tissues and cell lines, and that silencing Nit1 in these cancer cells decreased survival of cancer cells.

Investigators then tested whether inhibiting Nit1 could increase the benefit of cisplatin, a commonly used lung cancer chemotherapy, in mice with lung tumors. "The cancer was significantly more sensitive to cisplatin when Nit1 was silenced," Lu says. "This is a story of discoveries—a tale of a false assumption that has led to a possible new drug strategy."

Lu and his colleagues are continuing to study the mechanisms behind Nit1 expression and inhibition and their potential impact on immune surveillance over lung cancer development.