

Overcoming therapeutic resistance in lung cancer

August 24 2020



Dr. Chadrick Denlinger. Credit: Medical University of South Carolina

A protein highly expressed in lung cancer cells drives resistance to targeted therapies, report researchers at the Medical University of South Carolina in the *Journal of Thoracic and Cardiovascular Surgery*. In

preclinical experiments, the researchers showed that inhibiting the protein caused the death of non-small cell lung cancer cells that had become resistant to therapy.

The MUSC Team was led by Chadrick E. Denlinger, M.D., who was then surgical director of the Lung Transplant Program at MUSC Health, and MUSC Hollings Cancer Center researcher Robert Gemmill, Ph.D., who is a professor emeritus in the Department of Medicine. Denlinger is now division chief of thoracic surgery at Indiana University but continues his collaboration with Gemmill.

Lung [cancer](#) accounts for a quarter of all cancer deaths, and non-[small cell lung cancer](#) makes up 84% of all [lung](#) cancer cases. Targeted therapies can be effective for a time against selected lung cancers, but resistance to these therapy soon develops.

A cancer cell is like a small factory with many moving parts working towards one common goal: Survival and reproduction of the tumor at the expense of the patient.

A type of targeted drug, called a [tyrosine kinase inhibitor](#), or TKI, works by inhibiting a specific, vital piece of machinery within the cell factory on which it is dependent. However, the factory has many fail-safes in place and can quickly rely on another piece of cellular machinery to continue to grow and survive, even in the presence of the TKI. The ability of a cancer cell to adapt to a new strategy to survive is called "genetic resistance."

When researchers developed TKIs for the treatment of cancers such as non-small cell lung adenocarcinoma (NSCLC), they had hoped they would become the "magic bullet" to treat the disease successfully.

"One of the benefits of TKIs is that they're much less toxic and are fairly

beneficial—we see a dramatic response and the tumors shrink," said Denlinger. "But a limitation is that these effects don't last very long before the cancer [cells](#) evolve new techniques to become resistant to the drug."

Due to such resistance, the survival outcomes for patients receiving TKIs are no better than those for patients receiving conventional chemotherapy. Consequently, the need to find treatments that can overcome that resistance is urgent.

Gemmill's group, which includes Cecile Nasarre, Ph.D., Anastasios Dimou, M.D., and a summer undergraduate, Rose Pagano, recently linked drug resistance in lung cancers to the expression of a cell surface co-receptor Neuropilin 2 (NRP2). Gemmill received pilot project funds from the South Carolina Clinical & Translational Research Institute for his work with NRP2.

"One of the earliest things we discovered was that the NRP2 variant protein, NRP2b, dramatically increased in lung cancer patients who became resistant to therapy," remarked Gemmill. "This gave us the first clue that it becomes upregulated in resistant tumors."

The investigators then performed a series of experiments in which they "knocked down" NRP2b from lung cancer cell lines that were capable of developing TKI resistance.

"When we knock down NRP2b, we lose the surviving drug-tolerant cells," said Gemmill. "And by reducing that population, we believe we will reduce the ability of the tumor to develop genetic resistance."

Next, they explored how NRP2b could be contributing to drug resistance in lung cancer cells. They started with GSK3, a molecule that's involved in many different activities within the cell and has been reported

previously to interact with NRP2b during neuronal development. The investigators performed experiments to determine whether NRP2b interacts with GSK3B.

"You can think about GSK3B as a hammer," said Gemmill. "And this hammer has the job of hammering many different nails that are present in the cell. NRP2b is like the hand of the carpenter that directs that hammer to particular nails. NRP2b is using GSK3B as a hammer to drive very specific nails, and we want to stop that because those nails are driving tumor progression."

To better understand the specific nails that NRP2b and GSK3B are driving in lung cancer, the investigators performed experiments in which they measured how well lung cancer cells can migrate and survive in the presence of TKIs in the absence of these two players. With these experiments, they found that NRP2b needs GSK3B to promote cancer cell migration, an essential step in cancer progression, and drug resistance.

Now that the investigators have identified a mechanism by which cancer cells are becoming resistant to treatment, their next step will involve developing inhibitors. More specifically, they will try to develop inhibitors that interfere with the carpenter (NRP2) grabbing the hammer (GSK3B).

"Importantly, these inhibitors should not interfere with other functions of GSK3B, which will reduce potentially harmful off-target effects in a healthy cell," said Denlinger.

Currently, the team is working to test the toxicity and effectiveness of prototype drugs that could specifically disrupt the interaction between GSK3B and NRP2b. They are collaborating on this work with MUSC College of Pharmacy researchers Patrick M. Woster, Ph.D., chair of the

Department of Drug Discovery & Biomedical Sciences, and associate professor Yuri K. Peterson, Ph.D.

"Ultimately we could find a way to improve therapy for cancer patients," said Denlinger. "A therapy that could extend the influence of TKIs and potentially reduce metastatic spread and extend the lives of patients."

More information: Anastasios Dimou et al, Neuropilin-2b facilitates resistance to tyrosine kinase inhibitors in non–small cell lung cancer, *The Journal of Thoracic and Cardiovascular Surgery* (2020). [DOI: 10.1016/j.jtcvs.2020.03.166](https://doi.org/10.1016/j.jtcvs.2020.03.166)

Provided by Medical University of South Carolina

Citation: Overcoming therapeutic resistance in lung cancer (2020, August 24) retrieved 4 May 2024 from <https://medicalxpress.com/news/2020-08-therapeutic-resistance-lung-cancer.html>

<p>This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.</p>
--