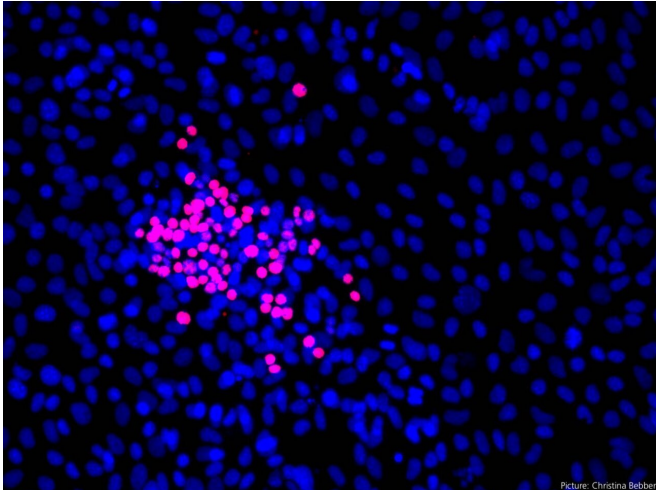


Small cell lung cancer: Scientists identify two new approaches for therapy

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Small cell lung cancer cells in culture (blue), non-endocrine cells are stained red. Credit: Christina Bebbler

Using samples of small cell lung tumors, a research team led by biologist Dr. Silvia von Karstedt has discovered two new ways to induce tumor cell death. One of two subsets of tumor cells can be targeted by activating ferroptosis: iron-dependent cell death caused by oxidative stress. In the second subtype, oxidative stress—and hence cell death—can also be induced in a different way. Both types of cell death must be triggered simultaneously by drugs to kill the majority of the tumor mass. The results of the study have been published in *Nature Communications*.

Despite many advances in treatment, a diagnosis of small cell lung cancer means a particularly poor prognosis. In Germany, up to 8000 new cases of small cell lung cancer (SCLC) are diagnosed each year. At the time of diagnosis, cancer has already found many loopholes to escape the body's immune system. "Traditional' [cell death](#) mechanisms, such as regulated cell [death](#) by apoptosis, are usually already inactivated at this

stage. That way, tumor [cells](#) can continue to divide and spread almost unperturbed.

A high cell division rate is characteristic of small cell lung cancer, which initially promises a good response to chemotherapy. "Unfortunately, in many cases the success of chemotherapy is short-lived because tumor cells rapidly develop resistance to [therapy](#). In addition, a tumor consists not only of one, but of several [cell types](#)—the so-called subtypes—each of which uses unique strategies to escape lethal therapy," said von Karstedt, research group leader at the CECAD Cluster of Excellence for Aging Research, the Department of Translational Genomics at the University of Cologne and the Center for Molecular Medicine Cologne (CMMC). This is where her research comes in. The biologist explores which cell death mechanisms are already inactivated in [cancer cells](#) and which ones can still be targeted by therapies to kill the tumor.

The research team used patient samples taken at the time of diagnosis, thus depicting the treatment-naïve tumor. To find out which pathways of cell death are still available, the scientists compared gene activity between patient cells taken inside and outside the tumor. Signaling pathways important for traditional cell death mechanisms were already switched off inside the tumor at this early stage, before therapy. In contrast, genes important for the activation of iron-dependent cell death by oxidative damage (ferroptosis) were strongly activated in the cancer cells.

Put in simple terms, small cell lung cancer cells can be divided into two subtypes: neuroendocrine cells and non-neuroendocrine cells. In the neuroendocrine cell subtype, more genes are active which are otherwise typically found in nerve cells that produce hormones. Cells belonging to the other subtype do not have this property and are therefore grouped as non-[neuroendocrine cells](#). "Several experiments showed that cells of the non-

neuroendocrine type can be killed using buthionine sulfoximine, which induces ferroptosis. In cells belonging to the neuroendocrine subtype, we found that they protect themselves from [oxidative stress](#)—and thus cell death—by producing antioxidants. However, by adding the antioxidant inhibitor Auranofin, we were able to kill these cells as well," explains doctoral researcher Christina Bebber, the lead author of the paper.

Regarding a possible application of these findings to the therapy of small cell lung cancer, the biologists made an important observation: When targeting just one of the two pathways—i.e., either activating ferroptosis or inhibiting antioxidant production—in a tumor consisting of cells of both subtypes, cancer cells were able to evade the lethal therapy. They did so by adjusting their gene expression to switch to the subtype that could resist the respective single pathway-targeting treatment.

"When we applied a combination therapy, we took away this route of escape. What is also special about the study is that we used drugs that have already been tested in extensive clinical trials or even approved for the treatment of other diseases," von Karstedt explained. Buthionine sulfoximine, which triggers ferroptosis, is already in clinical trials for cancer treatment. The gold salt Auranofin, which blocks the production of protective antioxidants in [cancer](#) cells, has been in use for decades to treat rheumatoid arthritis.

Future clinical studies using this combined therapy will clarify to what extent this targeted therapy option will improve the prognosis of [small cell lung cancer](#) patients.

More information: Bebber, C.M., Thomas, E.S., Stroh, J. et al. Ferroptosis response segregates small cell lung cancer (SCLC) neuroendocrine subtypes. *Nat Commun* 12, 2048 (2021). doi.org/10.1038/s41467-021-22336-4

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