Team discovers opportunities to overcome cancer treatment resistance

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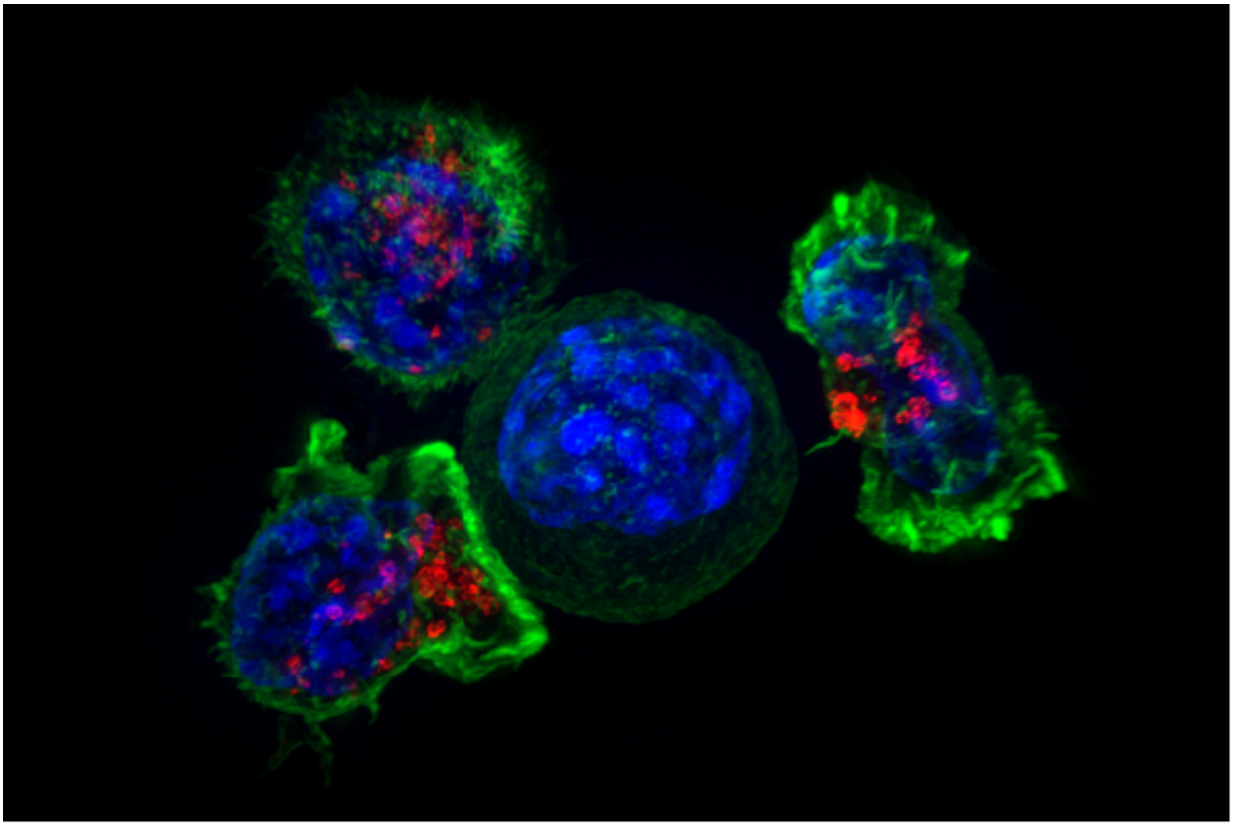

Killer T cells surround a cancer cell. Credit: NIH

A collaborative Cleveland Clinic, University of Oxford and Moffitt Cancer Center team of researchers has proven the theory that, while resistance to targeted treatment in cancer is truly a moving target, there

are opportunities to overcome the resistance that develops. Though more study is needed, researchers believe understanding and predicting tumor resistance may translate into additional treatment options in the clinical setting.

Treatment resistance that develops as cancer cells evolve is one of the major limitations of targeted cancer therapies today. During this progression, cancer cells not only change their response to the drug being used to treat the cancer, but also to many other drugs. In some cases, they become susceptible to another drug, called collateral sensitivity. In other cases, two drugs are simultaneously resisted, referred to as cross-resistance.

The research team led by Jacob Scott, M.D., a physician-scientist in the department of Translational Hematology and Oncology Research and Radiation Oncology at Cleveland Clinic, studied non-small cell lung cancer (NSCLC) cells and found that the drug resistance that developed did not apply to every drug, and were even sometimes more susceptible towards other drugs. These patterns of resistance and susceptibility changed over time. Understanding this, and how to measure these changes, the team ascertains that it may be possible to design and predict new treatment options and schedules.

"While the discovery of drugs that target molecular pathways responsible for cancer cells has been a paradigm shift in the way we treat many cancers, often the drugs inevitably fail," said Dr. Scott. "The end goal of our research is to understand, and predict, the changes tumors experience during treatment so we can better plan second-line therapy when the unavoidable drug failures occur."

In the study, researchers performed a series of evolution experiments, creating resistance to a number of drugs used to treat a specific NSCLC. They tested these evolved cells against a large family of other drugs to

better understand the changes they experienced. The impact of "drug holidays," or treatment interruptions, was also examined. This research is among the first to report on drug holidays and cross resistance together, and discovered that drug holidays impact primary drug resistance and susceptibility in a profound way.

"Researchers have known that avoiding cross-resistance is key; this investigation tells us we also need to start considering drug holidays as well," said Dr. Scott. "We hope our work informs future similar studies across a variety of cancer types, and eventually results in more tailored treatment plans for patients."

The study is published in *Scientific Reports*.

More information: *Scientific Reports*, www.nature.com/articles/s41598-017-00791-8

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