

New Strategy for Small Cell Lung Cancer Treatment Emerges

Dana-Farber researchers have provided evidence needed to support a clinical trial of a new class of drugs called direct cyclin inhibitors.

August 29, 2025 By Dana-Farber Cancer Institute

New research from [Dana-Farber Cancer Institute](#) shows that a new class of drug results in cancer cell death in cancers, such as small cell lung cancer, with a disabled quality control cell cycle checkpoint known as the G1/S checkpoint. The evidence gathered in the [Oser Lab](#) at Dana-Farber supports testing of the strategy in humans. A phase 1 clinical trial is now open nationwide for patients with small cell lung cancer, triple negative breast cancer, and other cancers.

The findings were published in [Nature](#).

“This is the first clinical grade drug to directly inhibit cyclins in the cell cycle,” says [Dr. Matthew Oser](#), who is a researcher and thoracic oncologist and is senior author of the study. “Our research using cell biology and genetic screening reveals a two-step mechanism of cell death specifically in cancer cells that does not occur in normal cells.”

There is a strong need for new medicines for small cell lung cancer. Approximately 90 percent of these cancers are initiated and driven by mutations that cause the loss of two tumor suppressors, which are proteins that actively protect against cancer. Directly targeting these losses, however, is not possible with small molecule drugs.

“It’s more like losing the brakes on a car than having something that is driving growth and can be blocked,” says Oser.

The lost tumor suppressors, RB1 and TP53, are both involved in the cell cycle, in which cells progress through a series of stages of growth that leads to cell division. Specifically, RB1 helps pause the cell cycle at an early stage, known as the G1/S checkpoint, so the cell can perform quality control checks and repairs if needed. TP53 is also indirectly involved in these checks.

Research from laboratory of the Nobel Laureate William G. Kaelin Jr., MD in the late 1990’s proposed the concept of targeting cyclins in cancer cells with high activity of a factor called E2F, which is the case in cancer cells that have lost RB1 and TP53. However, it wasn’t until the late 2010’s that drug developers at Circle Pharma, a biotechnology company in San Francisco, Calif.,

discovered new chemistry that would enable the creation of drugs to precisely target cyclins allowing this to be a tractable therapeutic approach.

The Oser Lab, led by first author and post-doctoral fellow, Shilpa Singh, collaborated with Circle Pharma to determine exactly how the drugs, called direct cyclin inhibitors (more specifically cyclin A/B RxL inhibitors), affected cancer cells and normal cells. His lab's work uncovered an intricate mechanism that leads to cell death, but only in cells where the activity of E2F is already elevated.

A certain form of direct cyclin inhibitor interrupts protein-protein interactions of two different cyclins (cyclins A and B) and these interactions normally ensure quality control and proper cell cycle progression, according to the study. Blocking these interactions leads to an accumulation of errors in the cell that drives the cell to death. The first interaction is between cyclin A and E2F. Inhibition of that interaction plus elevated levels of E2F activity result in increased DNA damage. The second interaction is between cyclin B and MYT1. Inhibition of that interaction causes the cancer cell to die during the cell division phase of the cell cycle called mitosis.

Oser found that normal cells treated with the drug are not as susceptible to DNA damage and cell death because they don't have elevated levels of E2F activity.

"Normal cells are about 100 to 1000-fold less sensitive to the drug than cancer cells," says Oser. "If the drug had had the same effect in normal cells, it would not be a feasible treatment."

This finding means that there is a potential to find a dose that works against cancer without unmanageable side effects. Oser and colleagues tested the drug in patient derived xenografts and found that small cell lung cancer tumors treated with the drug stopped growing. Other preclinical experiments also suggested the drug has activity in other cancers that have disabled the G1/S cell cycle checkpoint.

Based on this evidence, a phase 1 clinical trial is now open at Dana-Farber and across the U.S. to begin testing a related compound called CID-078 in humans with small cell lung cancer, triple negative breast cancer, and other cancers.

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