# New Cancer Treatment Approach Targets Circadian Clock

Researchers found that the two-compound treatment restrained two functions that cancer and pre-cancerous cells need to survive by targeting parts of the clock machinery

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Targeting the body's biological clock may be a potential strategy for treating cancer, a new study shows. Two compounds that target components of the circadian clock killed several types of cancer cells in the lab and slowed the growth of brain tumors in mice without harming healthy cells, the study investigators reported.

In lab experiments and in mice, the treatment also killed a type of senescent cells—precancerous cells that have stopped growing due to a cancer-causing mutation.

The circadian clock regulates hundreds of biological functions, from sleep patterns to cell division. By targeting components of the clock machinery, the compounds restrain two functions that cancer and senescent cells need to survive, the researchers found. The NCI-funded study was published January 18 in Nature.

"This study highlights how circadian rhythms and cancer biology intersect, how important these two fields are to each other, and how we might begin to exploit that relationship to target cancers," said Joanna Watson, PhD, a program director in NCI's Division of Cancer Biology, who was not involved in the study.

The study investigators hope to develop a drug similar to the studied compounds to treat humans and believe there are many potential applications for such a therapy.

"We have found a completely new class of targets, so the options are unlimited," said the study's senior investigator Satchidananda Panda, PhD, a professor at the Salk Institute.

## The Rhythm of the Circadian Clock

The circadian clock is a complex biological circuitry that controls the daily rhythm of functions such as sleep, body temperature, and digestion. The master "clock" is an area in the brain that senses environmental cues (such as light) and communicates information to secondary clocks in other organs.

In addition, every cell in the body contains its own clock that controls the daily oscillation of multiple cellular functions. All clocks in the body are usually in sync, allowing the organism to adapt to its environment and maintain a biological balance.

The circadian clock controls the “on” and “off” cycling of many functions that are important for cancer development. Disruption of the clock may cause these functions to get stuck “on” or “off,” creating the right conditions for tumors to develop and grow, Panda explained. Studies by his group and others have shown that the first step in cancer development disrupts circadian rhythms.

REV-ERB proteins are key components of the clock machinery that repress biological functions that cancer cells depend on, such as cell division and cell metabolism. So Panda and his colleagues decided to investigate whether compounds that activate REV-ERBs (known as REV-ERB agonists) might be able to kill cancer cells by blocking functions they need to continue growing.

In lab experiments, the researchers found that two REV-ERB agonists killed different types of cancer cells (including brain, colon, and breast), even though the cells had different genetic mutations that drive cancer growth. The REV-ERB agonists did not kill healthy brain or skin cells, however.

These findings suggest that drugs that activate REV-ERBs potentially could be used to treat many different types of cancer, the researchers explained.

“That initially surprised us because it is very rare to find such versatility in a single drug,” said lead investigator Gabriele Sulli, PhD, also of the Salk Institute. But when the researchers discovered how the REV-ERB agonists kill cells, it became clearer why these compounds affect so many types of cancer cells.

## Kicking Cancer Where It Hurts

Although REV-ERB proteins control several biological functions, the researchers found that the agonists block two specific pathways. One, called autophagy, is a recycling-like process that degrades superfluous, damaged, and toxic molecules to generate nutrients. The other pathway is the synthesis of fats called lipids.

Both lipid synthesis and autophagy provide building blocks to create new cells. Healthy cells require only low levels of these pathways, but cancer cells rely on them heavily because they are constantly dividing.

“So it makes sense that the effect of the drug is independent of the type of cancer and the mechanism that’s driving continuous cell proliferation,” Panda said.

Previous research has shown that, in mice, one of the two REV-ERB agonists used in this study can cross the blood-brain barrier, a boundary that often prevents drugs from reaching the brain. In addition, when Sulli and his colleagues analyzed data from NCI’s REMBRANDT (Repository of

Molecular Brain Neoplasia Data) data portal, they found that, among people with a type of brain cancer called glioblastoma, those with higher levels of REV-ERBs lived longer than those with low levels.

In light of these findings, the researchers chose to test their approach in two mouse models of brain cancer. Treatment with the agonist reduced autophagy, killed glioblastoma cells, reduced tumor growth, and extended survival better than a control compound.

Importantly, the researchers did not observe any signs of toxic side effects in mice treated with the agonist.

## The Danger of Senescent Cells

Sulli and his colleagues also wondered if the REV-ERB agonists might kill other cells that depend on autophagy and have disrupted circadian rhythms. Senescent cells—which stop growing to prevent cancer formation—fit the bill.

Although senescent cells no longer divide, they are still active in other ways that can cause harm. For example, they can secrete factors that promote the growth of existing tumors and alter the tumor microenvironment. Recent research has also shown that senescent cells may cause or worsen side effects associated with chemotherapy and may contribute to cancer relapse. Consequently, there has been great interest in developing treatments that eliminate or neutralize senescent cells.

The researchers focused on senescent cells that form due to a cancer-causing mutation in an oncogene. In lab experiments, the agonists killed oncogene-induced senescent cells but not other nondividing cells, the researchers found. The treatment also reduced autophagy and killed senescent skin cells in benign moles on mice.

More studies are needed to determine the efficacy of REV-ERB agonists as a way to kill senescent cells, the researchers wrote.

## Inspiring More Studies of Circadian Rhythm and Cancer

Overall, said Panda, “we hope that our study is a catalyst for the scientific community to take a fresh look at the interactions between circadian rhythm and the cell biology of cancer.”

Scientists are developing drugs that activate or repress other circadian clock components, he added, and it is possible that combinations of different clock-targeting drugs or of clock-targeting drugs with other types of therapy might enhance anticancer effects. But, currently, there are more questions than there are answers.

“There are huge knowledge gaps remaining in our understanding of the relationship between the

circadian clock and cancer at all stages," said Watson.

To encourage such studies, she continued, NCI is supporting research on the consequences of circadian rhythm disruption on all stages of cancer growth and on treatment outcomes.

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