# Combination of conventional and new drugs enhances tumor cell death

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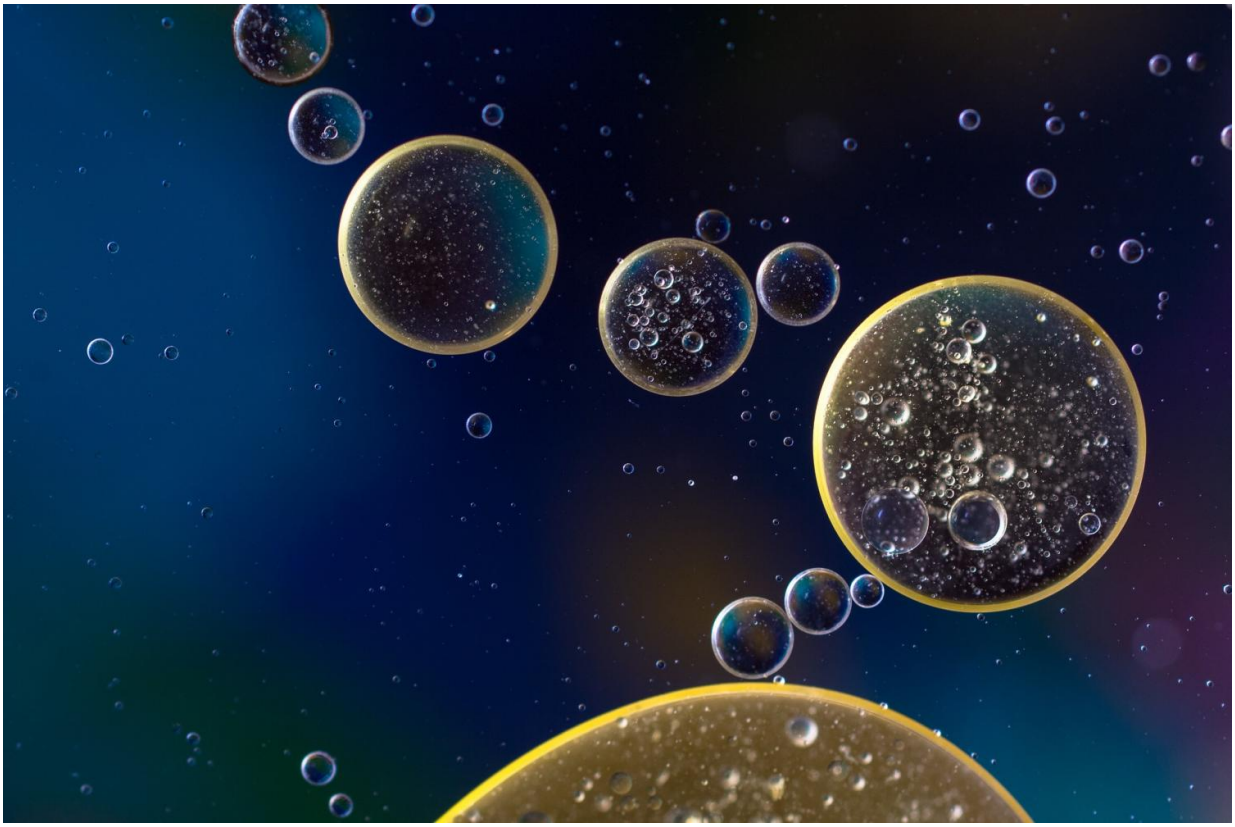

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Cancer is one of the major causes of death worldwide affecting 8.2 million of people per year, and in the US, the number of new cases will achieve 1.6 million in 2017. The global impact of this disease costs a

trillion of dollars, which makes critical the development of new drugs and treatment against it.

In a recent study published in the scientific journal *Translational Oncology*, researchers from the Federal University of Rio de Janeiro (UFRJ), State University of West Zone, (UEZO) and D'Or Institute for Research and Education (IDOR) tested the therapeutic effect of a combination of conventional - common anti-cancer agents - and new drugs - under clinical trials. "The results were very exciting because the successful outcome depended on the chemotherapy regimens. On the other hand, "wrong" combination of drugs could elicit harmful effects", states Helena Borges, professor at Institute of Biomedical Sciences of UFRJ, and study leader.

## The disease

Cancer is characterized by abnormal cell growth that invades other parts of the body. It is known that this abnormal pattern of cell growth depends on several signaling mechanisms inside the cells involving the protein pRB. pRB plays multiple roles, including controlling cell division, which prevents abnormal growth. In cancer cells, both cell division and apoptosis (programmed cell death) are impaired because tumor suppressor agents, such as pRB, are not fully available. As a result, cell number increases drastically since cell death and division do not occur appropriately.

Many anti-cancer drugs widely used were developed more than 50 year ago, when the cancer-related cellular mechanisms were poorly understood. Among them, cisplatin and 5-FU act inducing DNA damage or preventing DNA production, leading to a reduction of cancel cells. Recent findings about the central role of pRB on cancer revealed it is a potential target for treatments with fewer side effects. Indeed, new drugs were developed to act on the pRB pathway, fostering its functioning and

allowing the appropriate control of cell growth. Some of these drugs are under clinical trials and may be incorporate as alternative anti-cancer treatment soon.

## The study

Researchers from Rio de Janeiro investigated whether cisplatin and 5-FU would be able to interfere with pRB. Also, they evaluated the impact of the drugs on tumor cell death induction and on the standard treatment against cancer.

First, they described that the signaling pathway in which the pRB plays a key role is impaired in esophageal cancer, the sixth most common cause of cancer-related death worldwide. Human esophageal biopsies coming from non-tumoral tissue, esophageal pre-cancer and advanced stages of disease were assessed for pRB expression. As a result, a positive correlation between pRB expression and cancer progression was observed: the more advanced the stage of the esophageal tumor, the greater pRB inactivation was found.

"This result reinforces the notion that impaired pRB signaling contributes for the esophageal cancer progression", points Prof. Borges.

Then, researchers focused on a family of proteins responsible for pRB inactivation, named CDKs. Blocking CDKs' activity is the mechanism of action of new anti-cancer drugs under clinical trials.

The group aimed to clarify whether blocking CDKs combined with conventional drugs, such as cisplatin and 5-FU, would increase cell death, making the treatment more effective.

The analyses revealed that blocking CDKs, associated with cisplatin, increased mortality of tumor cells. On the other hand, opposite effects

were observed when treating cells with 5-FU: esophageal cancer cells became resistant to the drugs, showing decreased death rates.

Stevens Rehen, researcher from IDOR and professor at the Institute of Biomedical Sciences/UFRJ, co-author of the study, highlights the importance of gathering knowledge of cell biology in order to strategically identify and test anti-cancer drugs.

"The results bring attention to studies that investigate the combination of CDKs' inhibitors and conventional anti-cancer drugs. CDKs' inhibitors seem to enhance the treatment, but depending on the situation, combining them with 5-FU can be disastrous" says Prof. Borges. New studies have been conducted to investigate the effects of specific CDKs' inhibitors on new combinations of several types of cancer.

**More information:** Rossana C. Soletti et al, Inhibition of pRB Pathway Differentially Modulates Apoptosis in Esophageal Cancer Cells, *Translational Oncology* (2017). DOI: 10.1016/j.tranon.2017.06.008

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