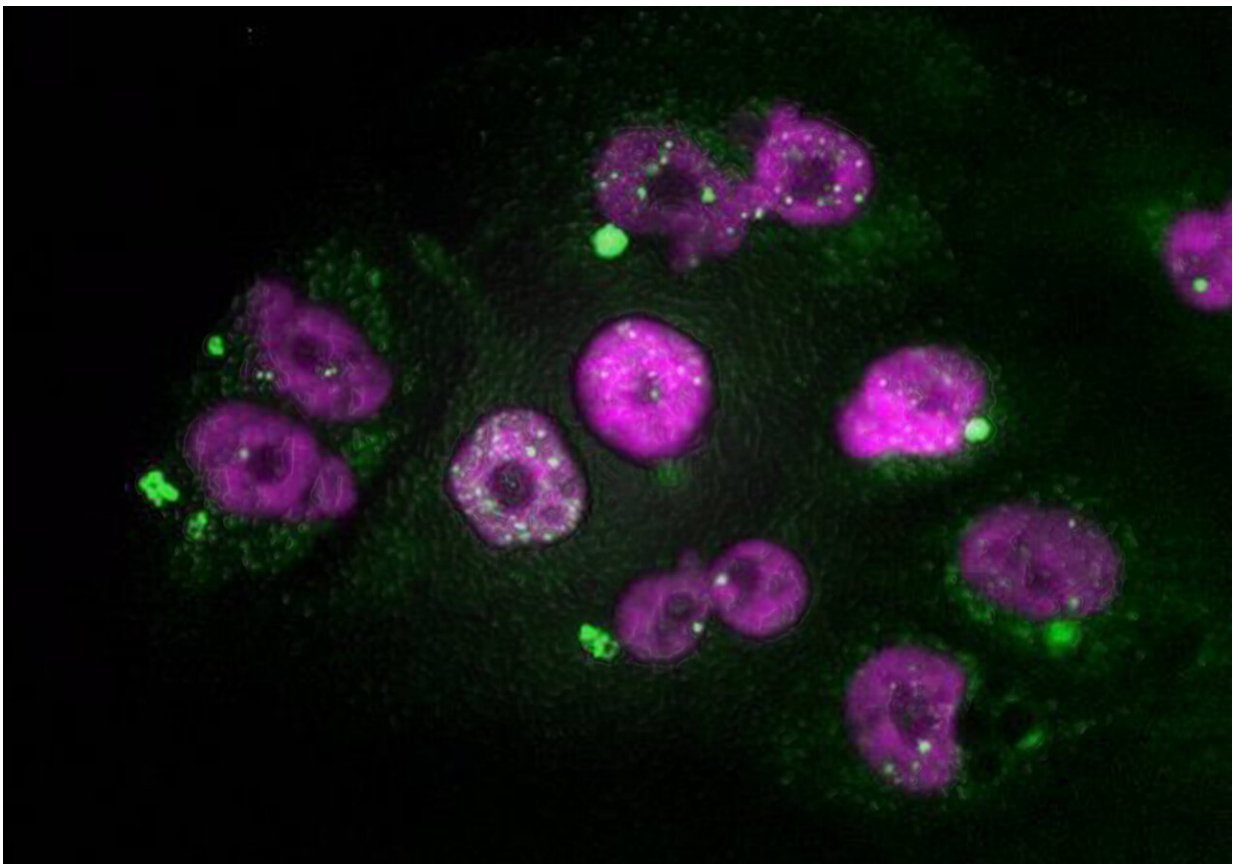


A new strategy to prevent the most aggressive tumors from generating resistance to chemotherapy

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Pancreatic adenocarcinoma tumor cells showing signs of damage in the DNA of the nucleus (white dots) and micronuclei (in green), after treatment with taxol followed by CDK4/6 inhibitors. Credit: CNIO

One of the most frequent problems when treating cancer is that the tumors develop resistance to therapies; at that point, treatments cease to be effective at stopping tumor growth. This is especially relevant in patients with aggressive diseases such as pancreatic cancer or patients with metastases, who must often undergo frequent changes in treatment. Now, a study led by the Spanish National Cancer Research Centre (CNIO) in collaboration with researchers from the Weill Cornell Medicine Center and Pfizer Inc. (U.S.), proposes a novel combined approach to avoiding pancreatic cancer resistance to chemotherapy, and thus treat these tumor cells effectively. The work is forthcoming in the journal *Cancer Cell*.

Effective therapies in breast cancer

One of the characteristics of cancer is the alteration of the cell cycle, that is, the alteration of normal activity related to cell growth, maturation and death. Concerning this, there are molecules called CDK4 and CDK6 that are involved in uncontrolled [cell growth](#), which ends up generating a tumor mass.

In recent years, drugs have been developed that inhibit the action of CDK4 and CDK6 and are very effective in stopping the growth of advanced [breast cancer](#). Their [clinical use](#), in combination with hormone therapy, has been approved in the United States since 2015 and in Europe since 2017 for patients with this type of cancer. The success of this combination has made it the standard treatment for these patients. However, until now it was not clear if these benefits could be extended to other types of cancer.

"A problem with CDK4/6 inhibitors is a consequence of their mechanism of action that prevents tumor cells from multiplying," explains Marcos Malumbres, head of the CNIO Cell Division and Cancer Group and principal investigator of the project. "Most of the

current chemotherapies involving, for example, platinum or taxol derivatives, act only on tumor cells that are dividing. Therefore, if we inhibit CDK4/6 and thus prevent these cells from dividing, we prevent chemotherapies from working properly. For this reason, until now, it was believed that we could not combine CDK4/6 inhibitors with classical chemotherapy."

Not at the same time, but after

During her predoctoral work at the CNIO, researcher Beatriz Salvador sought to design a new strategy in which CDK4/6 inhibitors would be used not at the same time as chemotherapy, but after chemotherapy to prevent the recovery of tumor cells. The results of the study show that administering CDK4/6 inhibitors after the drugs commonly used against various metastatic tumors prevents tumor cells from resisting these treatments and growing again after chemotherapy.

The study was carried out in both genetically modified mouse models and in mice with grafts from patients with pancreatic adenocarcinoma, one of the most aggressive tumors with the worst prognosis. While tumor cells treated with taxol or other agents repair the damage caused by these therapeutic agents in a few days, subsequent treatment with CDK4/6 inhibitors prevented this repair of the tumor cells and caused them to continue accumulating damage, thus preventing their renewed growth. "All animals treated with this combination showed a stable tumor, while mice that were not treated this way died rapidly," continues Malumbres.

Classical chemotherapy is still the most common treatment for patients with metastatic cancer, not only for breast and [pancreatic cancer](#) but for most tumor types. "Being able to use CDK4/6 inhibitors to prevent tumor cells from recovering from these treatments can open new avenues for improving the effectiveness of these therapies in various types of cancer that are currently treated with classical radiotherapy or

chemotherapy," Malumbres says. This finding could have a positive impact on thousands of patients who are currently being treated with these therapies.

"However, this strategy must be validated in the clinic," says Malumbres. "We are currently in contact with [pharmaceutical companies](#) to address this proposal in clinical trials, probably in breast and lung [cancer](#)."

More information: CDK4/6 inhibitors impair recovery from cytotoxic chemotherapy in pancreatic adenocarcinoma. Beatriz Salvador-Barbero et al (*Cancer Cell*, 2020). [DOI: 10.1016/j.ccell.2020.01.007](https://doi.org/10.1016/j.ccell.2020.01.007)

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