

# Researchers succeed at removing some types of pancreatic cancer in animal models

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Axial CT image with i.v. contrast. Macrocystic adenocarcinoma of the pancreatic head. Credit: public domain

Researchers from the Experimental Oncology Group, led by Mariano Barbacid at the Spanish National Cancer Research Centre (CNIO), have published in *Cancer Cell* the results of a study that shows full regression

of advanced pancreatic ductal adenocarcinoma (PDA) upon combined inhibition of the epidermal growth factor receptor (EGFR) and c-RAF kinase. This research project was funded by the Spanish Association Against Cancer (AECC) as part of its Stable Coordinated Groups system.

PDA is one of the most aggressive types of [pancreatic cancer](#). It is also highly resistant to personalised medicine or immunotherapy. For this reason, only 10 to 20 per cent of these tumours can be cured, as in most cases surgery to remove them is not possible.

Despite major advances in the field of pancreatic [cancer](#) treatment, this type of cancer still has a poor prognosis. According to the AECC Cancer Observatory, an estimated 8,000 people in Spain are diagnosed with pancreatic cancer every year. Spain shows average incidence rates of pancreatic cancer (considering the 2002 incidence in the world, which was estimated to be 6.6 per 100 thousand people in men and 3.9 in women). However, pancreatic cancer is on the rise: its incidence has been increasing since the 1950s, and today it is among the biggest causes of cancer deaths.

Pancreatic cancer is pretty rare, accounting for about 2.2 per cent of all cancers. However, it is the third leading cause of cancer deaths in Spain, only behind lung and colon cancer, and it has surpassed breast cancer in terms of mortality. Moreover, by 2030 PDA is expected to overtake colon cancer as the second cause of cancer deaths.

## **Genetically engineered mice**

Over the past five years, the research team have developed a new generation of genetically engineered mouse models. We have been using them to study the therapeutic potential of a variety of molecular targets in mice that reproduce advanced tumours, as well as the toxicity caused

by the systemic removal or inhibition of these targets.

The team initially focused on the elimination of EGFR and c-RAF separately, with no effective results. So they decided to study the therapeutic potential of inhibiting both targets simultaneously. The study showed that a significant number of high-grade tumours stopped growing and disappeared in a few weeks. Until now, no full regression had been observed in advanced pancreatic cancer in experimental models.

As to toxicity, the simultaneous deletion of EGFR and c-RAF kinase caused dermatitis that can be easily controlled. Consequently, this therapy was tested in immunodeficient mouse models with ten types of pancreatic cancer from human patients. Nine of the tumours stopped growing, which makes the deletion of these two molecules a preliminary step to translate the results to the [clinical setting](#).

More time is still needed to transfer these research results to the clinical practice, since c-RAF inhibitors for this type of tumour are currently unavailable. In any case, they would be extremely toxic drugs for humans, which means that they could not be clinically tested. However, a new approach is being implemented that uses the so-called degron chemistry, which involves a short functional element that participates in protein degradation, and could thus facilitate c-RAF degradation. When used in combination with EGFR inhibitors, it might lead to clinical trial results that are similar to those of the experiments involving genetic deletion of EGFR and c-RAF. These results—like those of the study conducted by Barbacid's team a year ago that showed the major therapeutic effects of deleting c-RAF in lung cancer—are being used in the pharmaceutical industry for the development of selective drugs that might eventually be used to treat other types of cancer.

Besides the AECC, the study has also been funded by the National

Institute of Health Carlos III, the European Research Council, the Spanish Ministry of Science, Innovation and Universities, the Ligue Contre el Cancer, the US National Institutes of Heal, the Spanish Ministry of Education and Vocational Training, La Caixa Foundation and AXA Foundation.

**More information:** María Teresa Blasco et al, Complete Regression of Advanced Pancreatic Ductal Adenocarcinomas upon Combined Inhibition of EGFR and C-RAF, *Cancer Cell* (2019). [DOI: 10.1016/j.ccell.2019.03.002](https://doi.org/10.1016/j.ccell.2019.03.002)

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