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## Identificación del proyecto

Uncovering resistance to monoclonal antibodies in colorectal and breast cancer (EXPTE. PIE15/00008)

## Descripción del proyecto

The proposed project builds on the expertise of various participating clinical PIs in the study of resistance mechanisms to monoclonal antibodies (cetuximab, panitumumab, trastuzumab and newer ones) in colorectal and breast cancer. The best example was the discovery of EGFR ectodomain mutations as a mechanism of acquired resistance to cetuximab in colorectal cancer, which is now investigated in many clinical settings. However, tumor heterogeneity, cancer cell reprogramming and immune response variability to cancer therapeutics calls for multidisciplinary collaborative efforts. Therefore, we propose here to integrate groups of clinical research, basic research, immunology, integrative bioinformatics and computational genomics to approach more comprehensively the problem of resistance and in order to have a greater potential to discover additional clinically meaningful resistance mechanisms. Briefly, the specific aims include;

- (1) To study molecular mechanisms of resistance in models of both primary and acquired resistance to monoclonal antibodies in vitro and in vivo.
- (2) To validate in prospective patient serial tumor biopsies and blood samples specific biological mechanisms preclinically identified associated to resistance.
- (3) To develop and study xenograft models and ex vivo tissue cultures from colon and breast cancer patients sensitive versus resistant to monoclonal antibodies.
- (4) To study the role of immune response in the activity of therapeutic antibodies and in the development of tumor recurrence after surgery with curative intent.
- (5) To interrogate tumor biopsies, blood samples (plasma cfDNA) and publically available databases from patients with colorectal or breast cancer sensitive and resistant to monoclonal antibodies.
- (6) To develop bioinformatics approaches to support the previous objectives, including the identification of new diagnostic biomarkers and therapeutic targets and strategies.

In terms of healthcare impact, we expect to discover novel mechanisms of resistance to traditional and novel therapeutic antibodies in colon and breast cancer patients that may improve patient selection and the development of combination strategies to prevent or circumvent resistance.

## Financiación

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