BREAST CANCER JUNIOR CLINICAL RESEARCH UNIT

Miguel Quintela-Fandino
Junior Clinical Research Unit Head

Staff Scientists
María José Bueno, Silvana Andrea Mouron

Clinical Research Fellow
Jorge Silva (since July)

Post-Doctoral Fellow
Rebeca Gema Jimeno

OVERVIEW

The Breast Cancer Clinical Research Unit (BCCRU) focuses on the translational interface of therapeutic development. Breast cancer is a heterogeneous disease, and thus, there are large inter-patient variations in terms of disease course, prognosis, relapse and resistance to conventional or targeted therapeutics.

Our activities are directed towards personalised treatment and range from preclinical models to correlative studies and clinical trials. Specifically, our research areas cover the:

- → Study of the mechanisms of resistance against CDK inhibitors.
- → Characterisation of aberrant signalling axes in triple-negative breast cancer.
- → Role of FGFR1 in cancer progression and therapeutic resistance in hormone-positive cancer.
- → Study of the implications of hypoxia in response to immunotherapy.

"We have provided clinical proof-of-concept of the synergy between antiangiogenics and mitochondrial inhibitors in breast cancer, which we previously described in animal models."

Graduate Students
Sara Fernández, José Luis Ruiz

Technicians
Verónica Jiménez, Manuel Muñoz

Titulado Superior (Advanced Degree)

Student in Practice
Katarina Mick (January-May) (*University of Zagreb*, Croatia)

Visiting Scientists
Ramón Colomer (*Hospital Universitario de la Princesa*, Madrid, Spain), Liany Luna (*Universidade Federal de São Carlos*, Brazil), Ana López (*Hospital Universitario de Fuenlabrada*, Spain), Lucas Moreno (*Hospital Vall d'Hebron*, Barcelona, Spain), Berta Nassarre (*Apices Soluciones S.L*, Madrid, Spain), Ana Roncero (*Hospital Universitario 12 de Octubre*, Madrid, Spain)

RESEARCH HIGHLIGHTS

The following highlights some of the achievements of the Breast Cancer Clinical Research Unit during 2020:

- → We demonstrated that PD-L1 inhibitors in combination with antiangiogenics in advanced breast cancer restrict their activity to those cases in which antiangiogenics normalise tumour hypoxia and vasculature.
- → We confirmed our preclinical findings regarding acquired resistance against antiangiogenics: in those cases where antiangiogenics normalise tumour hypoxia and vasculature, a targetable mitochondrial switch takes place. Consequently, mito-inhibitors were found to synergise with antiangiogenics. We confirmed the findings in a clinical trial in early breast cancer.
- → In parallel, in the preclinical setting, we are solving the mechanism of escape against antiangiogenics that increases vascular abnormality and tumour hypoxia. Preliminary data suggested that hypoxic areas are excluded from the antitumor immune response. Diverse therapeutic avenues are being explored to induce immune re-infiltration in hypoxic areas.
- → We characterised FGFR1 as a driver of acquired resistance to combined treatment with hormonal and CDK inhibitors. We found that in FGFR1-amplified or overexpressed tumour models, the triple combination of FGFR1, CDK4/6 and ER blockade is the only one able to completely suppress RB phosphorylation.
- → Completion of the first phosphoproteomic screening in a randomised clinical trial in early breast cancer treated with paclitaxel monotherapy revealed that elevated P70S6K and CDK4 are highly reliable biomarkers of sensitivity to this drug. ■

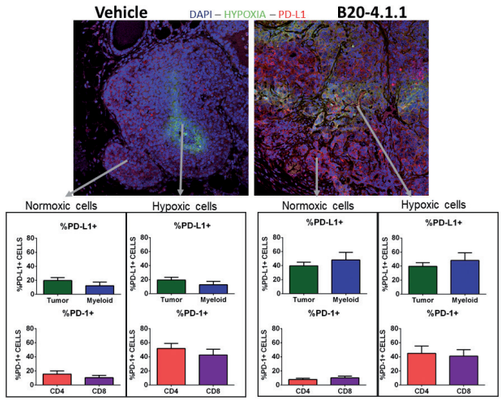

FIGURE Tumours treated with antiangiogenic (B20-4.1.1) become hypoxic (green), and express high PD-L1 (red). The immune infiltrate is excluded from hypoxic areas (upper charts); a detailed analysis shows that PD-L1 is mostly expressed by tumour cells in hypoxic areas (lower charts).

PUBLICATIONS

- Moreno-Lama L, Galindo-Campos MA, Martínez C, Comerma L, Vazquez I, Vernet-Tomas M, Ampurdanés C, Lutfi N, Martin-Caballero J, Dantzer F, Quintela-Fandino M, Ali SO, Jimeno J, Yélamos J (2020). Coordinated signals from PARP-1 and PARP-2 are required to establish a proper T cell immune response to breast tumors in mice. *Oncogene* 39, 2835-2843.
- Quintela-Fandino M, Holgado E, Manso L, Morales S, Bermejo B, Colomer R, Apala JV, Blanco R, Muñoz M, Caleiras E, Iranzo V, Martinez M, Dominguez O, Hornedo J, Gonzalez-Cortijo L, Cortes J, Gasol Cudos A, Malon D, Lopez-Alonso A, Moreno-Ortíz MC, Mouron S, Mañes S (2020). Immuno-priming durvalumab with bevacizumab in HER2-negative advanced breast cancer: a pilot clinical trial. *Breast Cancer Res* 22, 124.
- Bueno MJ, Quintela-Fandino M (2020). Emerging role of fatty acid synthase in tumor initiation: implications for cancer prevention. *Mol Cell Oncol* 7, 1709389.
- Colomer R, Mondejar R, Romero-Laorden N, Alfranca A, Sanchez-Madrid F, Quintela-Fandino M (2020). When should we order a next generation sequencing test in a patient with cancer? *EClinicalMedicine* 25, 100487.

AWARDS AND RECOGNITION

- Scientific Advisor, the Kærtor Foundation Cancer Innova Program, Spain.