

BREAST CANCER CLINICAL RESEARCH UNIT

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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.

Our current research areas aim to:

- Study the implications of hypoxia for immunotherapies.
- Understand the individual factors regulating the response to immunotherapy in breast cancer, taking advantage of an advanced, personalised “tumouroid” platform.
- Tackle the mechanisms of resistance against novel therapies in advanced breast cancer.
- Incorporate our findings into concept-driven clinical trials.

“At the Breast Cancer Clinical Research Unit, we are focused on individualising therapy for advanced breast cancer.”

RESEARCH HIGHLIGHTS

We have established a collection of 35 patient-derived *tumoroids* from breast cancer patients. We call a *tumoroid* a mix of a patient-derived organoid (a well-established model for cancer research, which perpetuates the tumour material from a given patient, preserving its mutations and general features, and is highly reliable for drug screening and predictive purposes) and the patient’s cells derived from the immune system. This sophisticated model allows us not only to screen conventional drugs, but also to understand their impact on the ability of the immune system to reject the tumour, a feature that is absent in common patient-derived mouse models of cancer. Tumoroids enable us to improve our understanding of immunotherapy and to better understand the impact of other drugs on the immune system, allowing for personalised synergistic treatment combinations. This collection is expanding, and we plan this to be the core of our research in the coming years.

A critical problem in hormone-positive breast cancer is the development of clonal heterogeneity. Tumours, after progression on aromatase plus CDK4/6 inhibitors, develop many different mutations to circumvent drug exposure, impacting the duration of response to subsequent treatment lines. Our preliminary data suggest that different tumour sub-compartments harbour different sets of mutations, and even selecting a “right” therapeutic choice is insufficient for eradicating a whole tumour. We are now undertaking an approach based on mutational signatures that are pervasive across different clones and that may allow for selecting therapies that kill broader tumour compartments than therapies selected according to traditional point mutations. This is being tested in patient tumoroids.

We finalised our work regarding predictive factors of sensitivity to paclitaxel in early breast cancer from the perspective of phosphorproteomics. A CDK4-Filamin A axis that converges in the regulatory machinery of tubulin acetylation is responsible for turning cancer cells sensitive to this drug. This pair of markers is highly accurate in predicting sensitivity in the clinical setting. ■

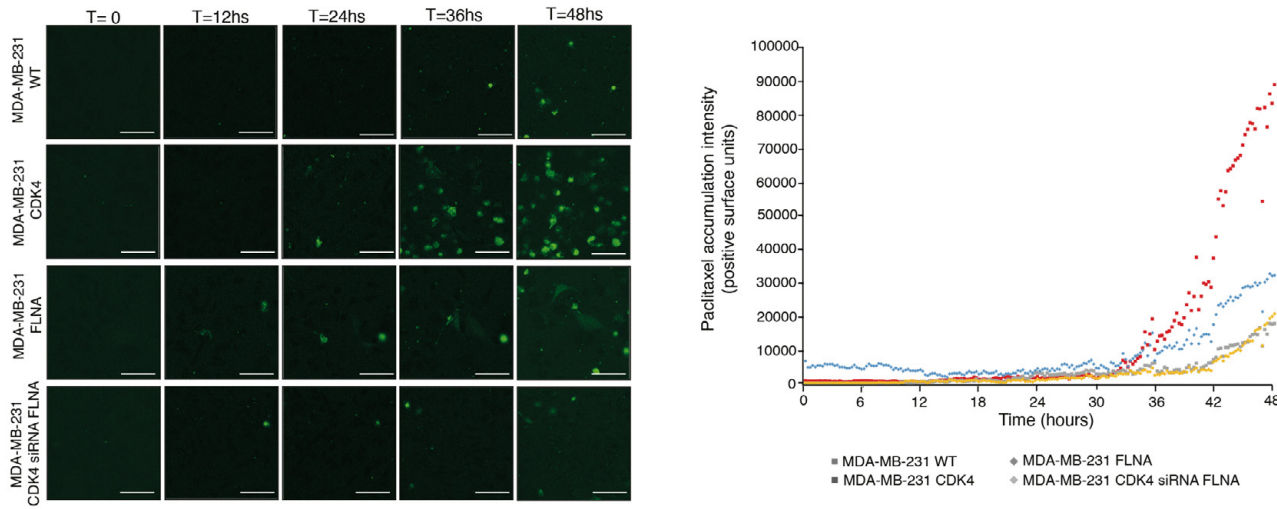


FIGURE 1 Fluorescently labelled paclitaxel was added to live cultures of MDA-MB-231 WT, CDK4 or FLNA cells. MDA-MB-231 CDK4 cells with filamin A knockdown were added to the experiment as well. The greater the green signal, the higher the amount of paclitaxel bound to microtubules. One can appreciate how both CDK4- and filamin A-overexpressing cell lines display both earlier and higher paclitaxel binding. Scale bar: 75 micrometres. The chart on the right-hand side depicts the signal (in fluorescent surface units) tracing paclitaxel accumulation over a 48-hour time interval, displaying a clear increase in

the 2 overexpressing transfectants (CDK4 and FLNA) compared to the parental cell line, and a reversion of the phenotype by filamin A knockdown in MDA-MB-231 CDK4 cells. General methodology for patient-derived organoid generation.

► PUBLICATIONS

► S. Mouron, M. J. Bueno, A. Lluch, L. Manso, I. Calvo, J. Cortes, J. A. Garcia-Saenz, M. Gil-Gil, N. Martinez-Janez, J. V. Apala, E. Caleiras, Pilar Ximénez-Embún, J. Muñoz, L. Gonzalez-Cortijo, R. Murillo, R. Sánchez-Bayona, J. M. Cejalvo, G. Gómez-López, C. Fustero-Torre, S. Sabroso-Lasa, N. Malats, M. Martinez, A. Moreno, D. Megias, M. Malumbres, R. Colomer, M. Quintela-Fandino (2022). Phosphoproteomic analysis of neoadjuvant breast cancer suggests that increased sensitivity to paclitaxel is driven by CDK4 and filamin A. *Nat Commun* 13, 7529.

► Choudhury AD, Higano CS, de Bono JS, Cook N, Rathkopf DE, Wisinski KB, Martin-Liberal J, Lynch M, Heath EI, Baird RD, García-Carbacho J, Quintela-Fandino M, Barry ST, de Bruin EC, Colebrook S,

Hawkins G, Klinowska T, Maroj B, Moorthy G, Mortimer PG, Moschetta M, Nikolaou M, Sainsbury L, Shapiro GI, Siu LL, Hansen AR (2022). A Phase I study investigating AZD8186, a potent and selective inhibitor of PI3Kβ/δ, in patients with advanced solid tumors. *Clin Cancer Res* 28, 2257-69.

► Zhu L, Retana D, García-Gómez P, Álvaro-Espinosa L, Priego N, Masmudi-Martín M, Yebra N, Miarka L, Hernández-Encinas E, Blanco-Aparicio C, Martínez S, Sobrino C, Ajenjo N, Artiga MJ, Ortega-Paino E, Torres-Ruiz R, Rodríguez-Perales S; RENACER, Soffietti R, Bertero L, Cassoni P, Weiss T, Muñoz J, Sepúlveda JM, González-León P, Jiménez-Roldán L, Moreno LM, Esteban O, Pérez-Núñez A, Hernández-Lain A, Toldos O, Ruano Y, Alcázar L, Blasco G, Fernández-Alén J, Caleiras E, Lafarga M, Megías D, Graña-Castro O, Nör C, Taylor MD, Young LS, Varešlija D, Cos-

grove N, Couch FJ, Cussó L, Desco M, Mouron S, Quintela-Fandino M, Weller M, Pastor J, Valiente M (2022). A clinically compatible drug-screening platform based on organotypic cultures identifies vulnerabilities to prevent and treat brain metastases. *EMBO Mol Med* 14, e14552.

► Hühn D, Martí-Rodrigo P, Mouron S, Hansel C, Tschapalda K, Porebski B, Häggblad M, Lidemalm L, Quintela-Fandino M, Carreras-Puigvert J, Fernandez-Capetillo O (2022). Prolonged estrogen deprivation triggers a broad immunosuppressive phenotype in breast cancer cells. *Mol Oncol* 16, 148-165.

► **PATENT**

► Quintela Fandiño MA. P27 single-nucleotide polymorphism as a predictor of benefit of hormonal therapy alone or in

combination with CDK inhibitors in breast cancer. PCT application (2022). *PCT/EP2022/051700*. *WO2022161984A1*.

► **INTELLECTUAL PROPERTY REGISTRATION**

► Luis Manso Sanchez, Miguel Quintela-Fandino (2022). LUMICA V.1.0. Algorithm – a proprietary algorithm for precision nutrition allocation for cancer patients. Registered with Safe Creative with registration code 2210252495358.

► **AWARDS AND RECOGNITION**

► Panel Member, *Proyectos de Investigación en Salud, Instituto de Salud Carlos III (ISCIII)*, Spain.