BREAST CANCER JUNIOR CLINICAL RESEARCH UNIT

Miguel Quintela-Fandino
Junior Clinical Research Unit Head

Staff Scientists
María José Bueno, Silvana A. Mouron

Clinical Research Fellow
Juan V. Apala

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 the sponsoring of multicentric clinical trials. Specifically, our research areas are:

- → Discovery of new targets for breast cancer prevention.
- → Breast cancer functional taxonomy: by using a systems biology approach, we are clustering the disease into subtypes defined by biologic features that constitute therapeutic targets.
- → Study of the mechanisms of resistance against targeted therapies.

"In 2018, the BCCRU completed the first study elaborating a kinase-based taxonomy of triple-negative breast cancer. This will enable therapeutic and biomarker-based precision-medicine initiatives."

Graduate Students
Elena Arconada (until November), Sara Fernández, José Luis Ruiz (since November)

Technicians
Verónica Jiménez, Manuel Muñoz

Titulado Superior (Advanced Degree)

RESEARCH HIGHLIGHTS

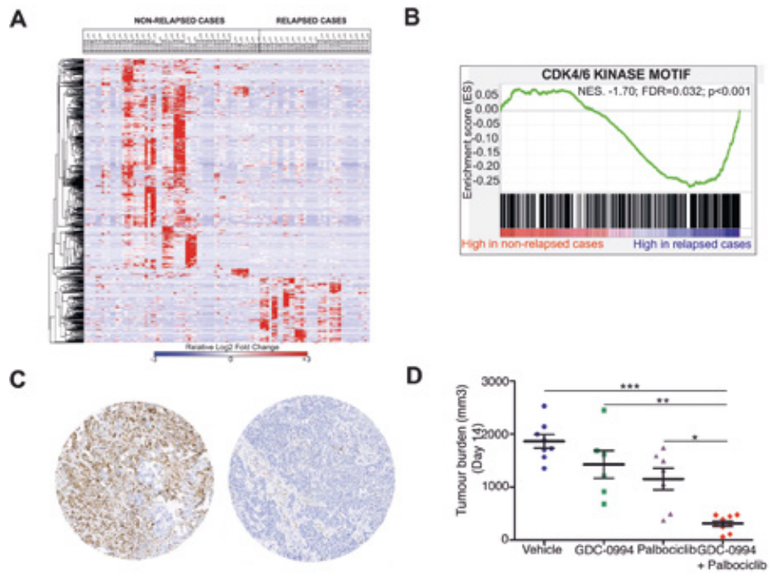

Figure (**A**) Phosphorylation profiles of whole tumours from TNBC with and without relapse were obtained by mass spectrometry. (**B**) Kinases with increased function accounting for such profiles were solved through an in-house algorithm ("Kinase-set enrichment analysis" or KSEAS"). (**C**) This information was then translated to immunohistochemistry; the left sample shows a patient with hyperactivated ERK, compared to a hypoactive one. (**D**) Combined treatment with agents targeting the 2 top-hits (CDK4/6 plus ERK inhibitors) in TNBC xenografts achieved a synergistic effect.

This year, we completed the first phosphoproteomic taxonomy of triple-negative breast cancer (TNBC), the most deadly subtype of this disease. Next-generation sequencing studies have failed in the task of finding simple biomarkers for complex phenotypic traits, such as response or resistance to therapeutic agents or disease course outside the context of penetrant oncogenic-addiction drivers. Rather, the TNBC phenotype traits are the result of multiple contributing low-penetrance mutations. We have found that different clusters of mutations collapse into discrete patterns of activation of the proteome in the form of protein phosphorylation, and that such patterns are driven by a small number of hyperactive/hypoactive kinases. Specifically, we found 6 kinases that, when all of them are "switched off", patients are long-term disease-free after >10 years. However, when 1 or more of those kinases are "on", the risk of relapse increases 10-fold. More importantly, all 6 kinases are actionable and we have found profound synergy in all 2-by-2 combinations in preclinical models.

On the clinical side of our activities, during 2018, we completed 2 clinical trials that were launched based on our research. Specifically, one of the trials explored the reversal of immune-tolerance induced by chronic hypoxia observed after prolonged exposure to antiangiogenics. A second trial explored the reversal of the metabolic switch of tumours experiencing vascular normalisation in response to antiangiogenics. Both trials implement targeted agents (a PD-L1 inhibitor or a mitochondrial inhibitor, respectively) directed against the 2 main regulatory nodes in each of the 2 major patterns of angiogenesis inhibitor escape identified during the period 2015-2017. ■

PUBLICATIONS

- Zagorac I, Fernandez-Gaitero S, Penning R, Post H, Bueno MJ, Mouron S, Manso L, Morente MM, Alonso S, Serrra V, Muñoz J, Gomez-Lopez G, Lopez-Acosta JF, Jimenez-Renard V, Gris-Oliver A, Al-Shahrour F, Piñeiro-Yañez E, Montoya Suarez JL, Apala JV, Moreno-Torres A, Colomer R, Dopazo A, Heck AJR, Altelaar M, Quintela-Fandino M (2018). In vivo phosphoproteomics reveals kinase activity profiles that predict treatment outcome in triple-negative breast cancer. *Nat Commun* 9, 3501-15.
- Alvarez-Fernandez M, Sanz-Flores M, Sanz-Castillo B, Salazar-Roa M, Partida D, Zapatero-Solana E, Ali HR, Manchado E, Lowe S, VanArsdale T, Shields D, Caldas C, Quintela-Fandino M, Malumbres M (2018). Therapeutic relevance of the PP2A-B55 inhibitory kinase MASTL/Greatwall in breast cancer. *Cell Death Differ* 25, 828-40.