BREAST CANCER JUNIOR CLINICAL RESEARCH UNIT

Miguel Quintela-Fandino
Clinical Research Unit Head

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

→ Discovery of new targets for breast cancer prevention: role of fatty acid synthase (FASN).
→ 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.
→ Conduct investigator- initiated clinical trials.

"In 2016, the Breast Cancer Group has tackled the mechanisms of resistance against antiangiogenics, implementing these findings into clinical trials."

Clinical Research Fellow
Laura M. Medina (until July)

Post-Doctoral Fellow
Franciso J. Blanco (until June)

Graduate Students
Sara Fernández, Gonzalo Pérez, Ivana Zagorac

Technicians
Verónica Jiménez, José Francisco López (TS)*, Esperanza Martín

**Titulado Superior* (Advanced Degree)

RESEARCH HIGHLIGHTS

In the field of functional taxonomy, we have completed our study in triple-negative breast cancer. We have interrogated the disease from the bimodal relapse pattern point of view, and performed a phosphoproteomic screening that would reduce the countless patterns of genomic, epigenomic and transcriptomic aberrations into a discrete number of patterns of hardwired signalling pathways. We found 6 kinases whose hyperactivity accounted for 94% of the relapsed cases. These kinases were grouped into a maximum number of 34 patterns, the largest of which (25%) was virtually associated with cure. This taxonomy was also useful because all the kinases in the final 'relapse signature' were also targetable nodes.

Regarding the study of targeted therapies, we have observed that the generally assumed hypothesis of vascular normalisation upon exposure to antiangiogenics is not always true. In fact, resistance against antiangiogenics can originate after a vascular normalising or 'abnormalising' response. Whether a tumour experiences the former or the latter depends on the tumour type and the type of agent. What is quite important from the clinical point of view is that we can track, individually, whether a tumour experiences a normalising or an abnormalising response after less than 2 weeks of exposure to the agent, using a non-invasive imaging test with 18F-fluoromisonidazole. This has been demonstrated in animals and in patients. The applicability of this finding lies in the fact is that we have also unravelled the mechanisms of resistance depending on whether the tumour reacts with normalisation or abnormalisation against antiangiogenics: in the first case, the tumour switches from glycolytic to mitochondrial metabolism,

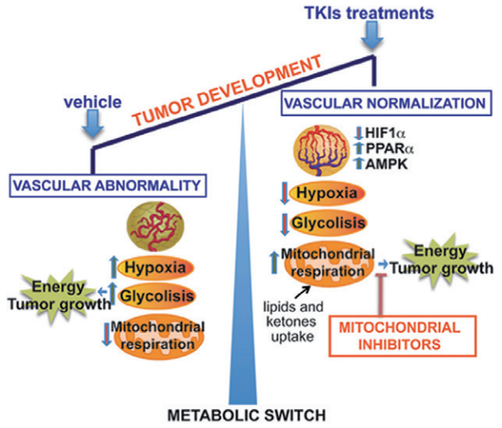

Figure Depiction of the metabolic adaptation of tumours when experiencing vascular normalisation upon exposure to antiangiogenics. An alternative response, increased vascular abnormality, occurs in roughly 30% of the cases. This response is coupled with immune reprogramming.

which is reversible by mitochondrial inhibitors. In the latter, the tumour experiences an immune-switch. Since both mechanisms are targetable, we can now individually track which pathway a tumour is undergoing upon exposure to antiangiogenics and tailor which synergistic agent that patient would need. ■

PUBLICATIONS

- Quintela-Fandino M, Lluch A, Manso LM, Calvo I, Cortes J, Garcia Saenz JA, Gil JM, Martinez-Jez N, Gonzalez Martin A, Adrover E, De Andres R, Viñas G, Llombart-Cussac A, Alba E, Guerra K, Bermejo B, Zamora E, Moreno-Anton F, Pernas Simón S, Carrato A, Lopez A, Escudero MJ, Campo R, Carrasco EM, Palacios J, Mulero F, Colomer R (2016). 18F-fluoromisonidazole PET and activity of neoadjuvant nintedanib in early HER2-negative breast cancer: a window-of-opportunity randomized trial. *Clin Cancer Res*. PMID: 27587436.
- Mateo F *et al.* (incl. Quintela-Fandino M) (2016). Stem cell-like transcriptional reprogramming mediates metastatic resistance to mTOR inhibition. *Oncogene*. PMID: 27991928.
- Navarro P, Bueno MJ, Zagorac I, Mondejar T, Sanchez J, Mouron S, Muñoz J, Gomez-Lopez G, Jimenez-Renard V, Mulero F, Chandel NS, Quintela-Fandino M (2016). Targeting tumor mitochondrial metabolism overcomes resistance to antiangiogenics. *Cell Rep* 15, 2705-2718.
- Manso L, Mouron S, Tress M, Gomez-Lopez G, Morente M, Ciruelos E, Rubio-Camarillo M, Rodriguez-Peralto JL, Pujana MA, Pisano DG, Quintela-Fandino M (2016). Analysis of paired primary-metastatic hormone-receptor positive breast tumors (HRPBC) uncovers potential novel drivers of hormonal resistance. *PLoS One* 11, e0155840.
- Bueno M, Sanchez J, Colomer R, Quintela-Fandino M (2016). Antiangiogenics and hypoxic response: role of fatty acid synthase inhibitors. *Curr Drug Targets* 17, 1735-1746.
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- Lord S, Funes JM, Harris AL, Quintela-Fandino M (2016). Antiangiogenic resistance and cancer metabolism: opportunities for synthetic lethality. *Curr Drug Targets* 17, 1714-1727.

PATENT

- Gold D.P., Quintela-Fandiño M.A. (2016). Combination Therapies. *WO/2016/126618*.

AWARDS AND RECOGNITION

- 2016 AstraZeneca Award for Young Investigators, Spain.