

Breast Cancer *Junior Clinical Research Unit*



Miguel Quintela-Fandino

Junior Clinical Research Unit Head (since March)

Miguel Quintela-Fandino was born in 1976 in La Coruña, Spain. He was awarded his MD degree from the *Universidad de Navarra* and subsequently trained in Madrid as a medical oncologist at the *Hospital Universitario 12 de Octubre*. He then received his PhD from the *Universidad Complutense de Madrid* for his research on the impact of micrometastasis in patients with locally advanced high-risk breast cancer. He also obtained a Master's Degree in biostatistics from the *Universidad Autónoma de Barcelona*.

After finishing his PhD, Miguel joined T. Mak's laboratory at the Ontario Cancer Institute, Canada, as a Postdoctoral Research Fellow for four years. His work focused on phosphoproteomic screening and the mechanisms of invasion and metastasis in breast cancer including cancer metabolism.

He complemented his clinical training through a clinical fellowship in the Drug Development Programme at Princess Margaret Hospital, Canada, working for over two years on the development of several first-in-class, first-in-human drugs. His research focused on re-designing dose-escalation strategies. Based on a pharmacodynamic approach using the RAF/VEGFR/PDGFR inhibitor sorafenib as a benchmark, he developed a methodology to perform individual drug titrations up to an optimal biological dose by measuring the effects of sorafenib on the signal transduction capacity of targeted kinases as opposed to the classic 3+3 approach.

Miguel has received several grants and honours including the ASCO Young Investigator Award and the ASCO Merit Award (twice), among others. He recently returned to Spain to lead the Breast Cancer Clinical Research Unit at the CNIO, supported by an *Asociación Española Contra el Cáncer (AECC) – Beca de Retorno* grant.

Summary

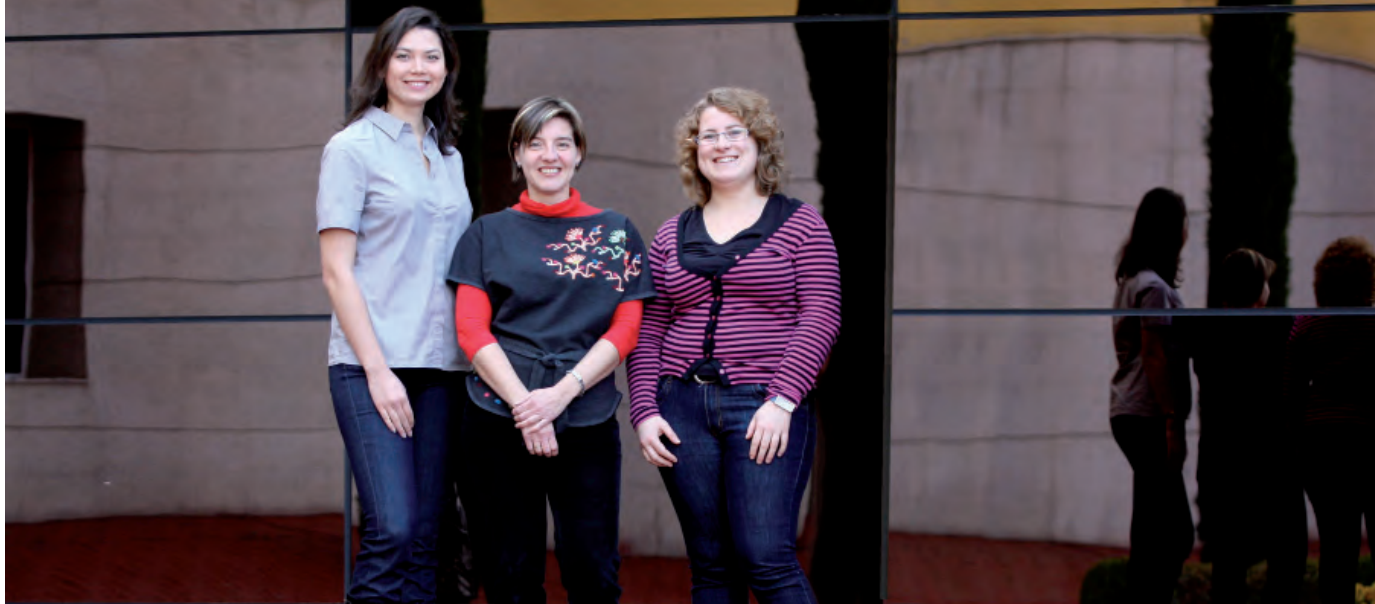
Great heterogeneity is observed among breast cancer subtypes in terms of clinical course and treatment sensitivity. Our Clinical Research Unit focuses on defining patient subgroups with a higher or lower likelihood of benefiting from different therapies.

We are developing a transversal platform aimed at defining proteome-wide phosphoproteomic signatures that will sharpen predictive power and facilitate the design of combinatorial drug regimens using available kinase inhibitors for the resistant cancer phenotypes.

A major goal of our research is to pin-point the signalling nodes that are differentially activated or shut down in breast tumours resistant to several targeted therapies. Findings will be used to screen preliminary drug combinations to reverse the drug-resistant phenotype in animal models, specially, focusing on the angiogenesis-inhibitor drug class.

Strategic Goals

- Set up a platform for the analysis of proteome-wide phosphorylation patterns in tumour tissue
- Generate a functional breast cancer taxonomy of therapeutic value (sensitive/resistant tumours)
- Implement our findings into concept-driven prospective clinical trials for breast cancer



Staff scientist: Paloma Navarro (since April). **Graduate student:** Natalia Sherina (since October). **Technician:** Tamara Mondejar (since May).

Highlights

Using an endogenous-growth tumour model we have begun to study the effects of anti-angiogenic drugs in primary and acquired drug resistant breast cancer. We have subsequently overcome the difficulties of xenograft-based work – preserving the immune system and maintaining an isogenic stroma. These two concepts, key in angiogenic regulation, are absent in studies that involve the grafting of human material into immunocompromised animals. In addition, the growth kinetics (and thus, the vascularisation kinetics) of grafted clumps of cells, is not analogous to that of a mass arising from one single transformed cell.

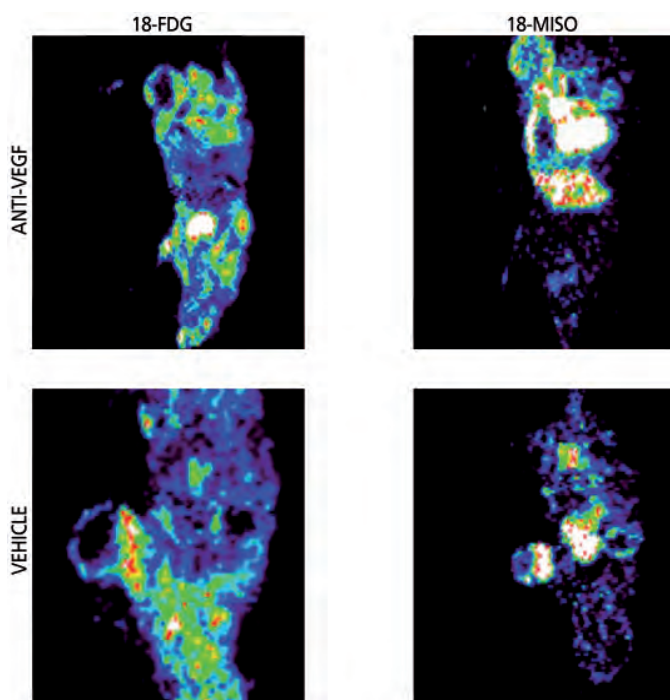


Figure: Progression of a breast tumour treated (top panels) and untreated (lower panels) with anti-VEGF therapy. Tumour metabolism (left panels), as measured by ^{18}F -fluorodeoxyglucose PET, is higher in the untreated mice. However, the ^{18}F -fluoromisonidazole probe (which accumulates on the hypoxic areas) reveals that tumour oxygenation (and thus perfusion, and subsequently glucose delivery) is higher in treated mice.

We are working on two hypotheses to explain the resistance to blocking blood vessel growth: the presence of redundant systems and a relative unresponsiveness to decreased blood flow. Interestingly, in the Tg.MMTV-PyMT (FVB) model we have found that after blockade of VEGF, tumour hypoxia actually decreases (Figure). This event was however accompanied by a decrease in tumour metabolism rather than an increase in metabolic rate (expressed by glucose uptake). Ongoing research in our laboratory aims to explain this apparent paradox.

Lastly, in collaboration with the two most important breast cancer groups in Spain (GEICAM and SOLTI), our Unit is sponsoring an ongoing phase-0 clinical trial for early-stage breast cancer patients. Chemo-naïve patients with single-lesion localised breast cancer are treated with a single agent course of VEGFR/PDGFR/FGFR inhibitor for four weeks. Fresh tumour biopsies are obtained pre- and post-treatment. Findings from preclinical experiments will be validated and corroborated in this patient cohort.

Publications

Quintela-Fandino M, González-Martín A, Colomer R (2010). Targeting cytoskeleton reorganisation as antimetastatic treatment. *Clin Transl Oncol* 12, 662-669.

Published at other institutions

Quintela-Fandino M, Arpaia E, Brenner D, Goh T, Yeung FA, Blaser H, Alexandrova R, Lind EF, Tusche MW, Wakeham A, Ohashi PS, Mak TW (2010). HUNK suppresses metastasis of basal type breast cancers by disrupting the interaction between PP2A and cofilin-1. *Proc Natl Acad Sci USA* 107, 2622-2627.

Quintela-Fandino M, Le Tourneau C, Duran I, Chen EX, Wang L, Tsao M, Bandarchi-Chamkhaleh B, Pham NA, Do T, MacLean M, Nayyar R, Tusche MW, Metser U, Wright JJ, Mak TW, Siu LL (2010). Phase I combination of sorafenib and erlotinib therapy in solid tumors: safety, pharmacokinetic, and pharmacodynamic evaluation from an expansion cohort. *Mol Cancer Ther* 9, 751-760.