of breast cancer patients. However, the proportion of patients who achieve a pathological complete response (pCR) after treatment remains low, reaching 15%-20% in the whole population. Thus, identifying predictive biomarkers of drug resistance is necessary to select the patients who are most likely to benefit from chemotherapy. Taxanes (paclitaxel, docetaxel) are potent stabilisers of the microtubule cytoskeleton, which functions are tightly regulated by a panel of MT-associated proteins and mitotic kinases. In the present study, we evaluated whether taxane resistance in breast cancer may be associated with alterations of genes encoding MT-regulatory proteins.

Material and methods Expression levels of 411 MT-related genes were analysed from Affymetrix U133 microarray of breast tumours from three independent multicentric clinical trials, namely REMAGUS-02 (115 patients), REMAGUS-04 (142 patients) and MD Anderson (133 patients). Only patients treated with neoadjuvant taxane-based chemotherapy were included in this study. Expression level of MT-related genes in tumours was compared with the ability to achieve pCR.

Results and discussions By comparing expression levels of 411 MT-related genes in three independent cohorts of breast cancer patients treated with taxane-based neo-adjuvant chemotherapy, we have identified a total of 94 MT-related genes that are differentially expressed in tumours with pCR. Among those, 18 MT-related genes are common to the three cohorts. Interestingly, all these genes appear as potential prognostic biomarkers of overall survival. Ongoing studies aim at functionally validating these candidates using siRNA screening in two different breast cancer cell lines.

Conclusion This study should lead to the identification of novel predictive biomarkers to select breast cancer patients who are likely to benefit from taxane-based chemotherapy. This should also pave the way for future targeted treatments of chemoresistant breast tumours.

One limitation of previous methods was the use of unrealistically small cell populations (10^3 - 10^6), which limits the genetic heterogeneity that is known to be pervasive in cancer. We utilised HYPERFlask technology to permit the growth of large cell populations (10^8), allowing us to explore drug treatments without the need for serial passaging that artificially reduces heterogeneity.

Results and discussions By quantitative measurements of enrichment in molecular barcodes, we identified drug-specific patterns of selection under gefitinib and trametinib that were conserved between biological replicates. These quantitative analyses were indicative of distinct, pre-existing resistance within the treatment groups, including a small multi-drug resistant subclone. Further, we used high-throughput drug screening of the pre- and post-evolution replicates to survey sensitivities to new drugs. Through mathematical modelling, we extended these quantitative results to partially determine fitness landscapes and predict sequences of inhibitors wherein each sensitises the population to the next.

Conclusion By combining evolutionary principles with mathematical modelling and quantitative measurements of evolution, we have derived a novel framework to identify collateral sensitivity. In comparison to previous approaches, this framework better captures the genetic heterogeneity that is intrinsic to many cancers, and which is known to drive drug resistance. We expect that this framework will now be used as treatment strategies for potential verification through in vivo and clinical studies.