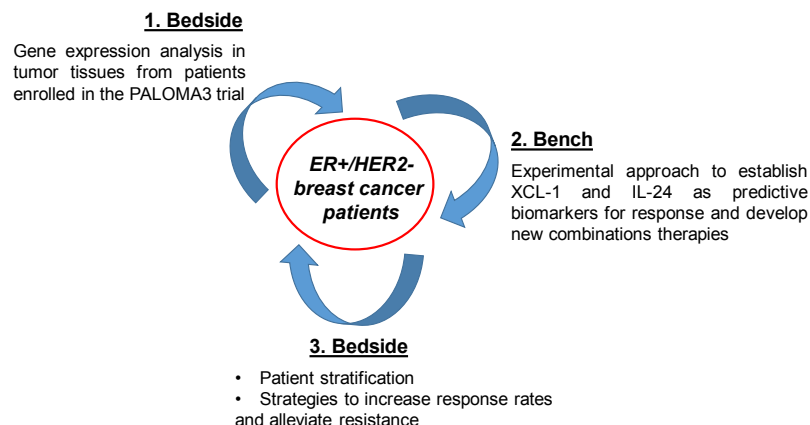


Lay abstract

Innovations in genomics have allowed oncologists to incorporate the concept of precision medicine into everyday clinical practice by determining the genetic profile of an individual's tumor. Despite the significant progress, genomic analysis has not met its full potential, and limitations prevent the selection of tailored cancer treatments. In order to formulate patient-specific treatments, development of new targeted cancer therapies should be combined with identification of genetic or molecular biomarkers to predict therapeutic efficacy against these treatment targets in metastatic breast cancer.

Endocrine therapy is the therapeutic backbone for the treatment of estrogen receptor (ER)-positive patients, but up to 50% of these patients develop recurrent or metastatic disease. Results from recent clinical trials have shown that inhibitors of the cyclin-dependent kinases 4 and 6 (CDK4/6), combined with endocrine therapy, significantly improve progression-free and overall survival, with a good tolerability profile in women with metastatic breast cancer. This positive outcome led to FDA approval of this combination treatment and has changed the treatment landscape of breast cancer patients with advanced/metastatic ER-positive/HER2-negative disease, thereby establishing a novel treatment standard. However, key challenges in the clinic remain to be overcome: 1) Which women with metastatic breast cancer will derive the largest benefit? 2) Can we integrate personalized care? 3) How can we enhance treatment response rates to CDK4/6 inhibition given that many patients do not respond to treatment? 4) How can we intervene in order to delay or reverse treatment resistance?

In our efforts to address these challenges, we have employed an unbiased approach to identify interactions between gene expression and response to CDK4/6 inhibition. For this, we have analyzed samples from patients enrolled in the PALOMA 3 trial, which is one of the clinical trials that provided compelling evidence for the clinical efficacy of CDK4/6 inhibition. Our preliminary results point to the novel role of two cytokines, X-C motif chemokine ligand 1 (XCL1) and Interleukin 24 (IL-24), in shaping the tumor microenvironment by activating specific immunomodulatory cues and eliciting cell-autonomous anti-cancer activities, respectively. Our proposed experimental work using multidisciplinary approaches, as well as pre-clinical models and clinical specimens, will provide the basis for developing these new concepts to clinical practice. Our team has a strong multidisciplinary focus including clinicians and basic scientists with backgrounds all related to this work, who are highly collaborative. Overall, our initial analysis based on clinical samples (bedside), followed by our elaborate experimental approach (bench), will significantly impact women with metastatic breast cancer currently undergoing treatment. The identified cytokines could be used as novel biomarkers to aid in patient stratification and identify individuals who are more likely to respond favorably to CDK4/6 inhibition. Given that predictive biomarkers are currently missing, our work can increase opportunities to match therapies to patient populations, and thus pave the way towards more personalized medicine. Equally important, the identified cytokine-mediated pathways/mechanisms will be exploited as novel therapies which ultimately can provide opportunities for new strategies to increase response rates and alleviate treatment resistance for women with metastatic breast cancer that receive CDK4/6 inhibitors as a standard of care treatment. Therefore, successful completion of our bedside to bench and back to bedside translational research (see graphical abstract) could result in a breakthrough towards informing clinical decisions and improving outcomes to benefit those who are living with ER+/HER2- metastatic breast cancer.



Graphical abstract. An overview of our bedside to bench and back to bedside research