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## Systems pharmacological approach for a rationally derived sequential combination therapy to enhance the delivery and efficacy of monoclonal antibodies into solid tumors

Sihem Bihorel

University of Florida, USA

HER<sub>2</sub>-positive breast cancer (BC) is fast-growing and more aggressive than other types of BC. Trastuzumab (TZM), an anti-HER<sub>2</sub> receptor humanized monoclonal antibody, is used in BC in combination with paclitaxel (PAC) in a 24 h sequence treatment during the first week followed by a simultaneous administration thereafter. There is no scientific rationale for such therapeutic regimen. Here we propose to utilize a proteomics approach to optimize the sequential combination of PAC+TZM to enhance their anti-tumoral activity, and hence patients' outcome. Six therapeutic regimens were investigated *in vitro* on BT474 cells: A human BC cell line overexpressing HER<sub>2</sub> receptor, including PAC and TZM alone at 50 and 100 nM, a tumor priming regimen (TPR) with PAC given 24 h prior to TZM, a reverse-TPR, a concurrent regimen and a vehicle as a control. Proteomics analysis was conducted in each regimen and several identified key signaling proteins in the PAC+TZM pathway were measured over time, including p21, p27, ERK1,2, JNK1,2, and cleaved-PARP. TPR showed more amplified proteins dynamic responses compared to others with: 1) Continuous activation of p21 and p27, both are hallmark biomarkers for the cell-cycle arrest response, and 2) down regulation of HER<sub>2</sub> survival pathways mediated via ERK1,2 and JNK1,2. A more efficacious ADCC and a sustained apoptotic response were also observed. TPR elicits synergistic interactions *in vitro*. The underlying mechanisms involve increased apoptosis, cell-cycle arrest, and antibody-dependent cellular cytotoxicity. The proposed research will develop and employ a systems pharmacology model to design optimal regimens for the association (PAC+TZM) in HER<sub>2</sub>-positive BC.

sihem.bihorel@cop.ufl.edu

## TRPV4 regulates cancer cell extravasation, stiffness and actin cortex

Yoon Pin Lim, Wen Hsin Lee and Lee Yee Choong

National University of Singapore, Republic of Singapore

Metastasis is a significant health issue. The standard mode of care is combination of chemotherapy and targeted therapeutics but the 5-year survival rate remains low. New/better drug targets that can improve outcomes of patients with metastatic disease are needed. Metastasis is a complex process, with each step conferred by a set of genetic aberrations. Mapping the molecular changes associated with metastasis improves our understanding of the etiology of this disease and contributes to the pipeline of targeted therapeutics. Here, phosphoproteomics of a xenograft-derived *in vitro* model comprising 4 isogenic cell lines with increasing metastatic potential implicated Transient Receptor Potential Vanilloid subtype 4 in breast cancer metastasis. TRPV4 mRNA levels in breast, gastric and ovarian cancers correlated with poor clinical outcomes, suggesting a wide role of TRPV4 in human epithelial cancers. TRPV4 was shown to be required for cancer cell invasion and transendothelial migration but not growth/proliferation. Knockdown of Trpv4 significantly reduced the number of metastatic nodules in mouse xenografts leaving the size unaffected. Overexpression of TRPV4 promoted cancer cell softness, blebbing and actin reorganization. The findings provide new insights into the role of TRPV4 in cancer extravasation putatively by reducing cell rigidity through controlling the cytoskeleton at the cell cortex.

bchlyp@nus.edu.sg