OMICS International
conferenceseries.com
6th International Conference & Expo on
Proteomics
March 29-31, 2016 Atlanta, USA

Sihem Bihorel, J Proteomics Bioinform 2016, 9:3 (Suppl)
http://dx.doi.org/10.4172/0974-276X.C1.082

Proteomics approach for *in vitro* proof of mechanism of action of trastuzumabin a time sequence association with paclitaxel in HER2-positive breast cancer

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HER2-positive breast cancer (BC) is fast-growing and more aggressive than other types of BC. Trastuzumab (TZM), an anti-HER2 receptor humanized monoclonal antibody which 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 over expressing HER2 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 signalling 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 continuous activation of p21 and p27, both are hallmark biomarkers for the cell-cycle arrest response and down regulation of HER_2 survival pathways mediated via $ERK_{1,2}$ and $JNK_{1,2}$. A more efficacious ADCC and sustained apoptotic responses 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_2-positive BC.

Biography

Sihem Bihorel has joined the Department of Pharmaceutics at the University of Florida as an Assistant Professor. Her laboratory is located at the Center for Pharmacometrics and Systems Pharmacology in Lake Nona, Orlando. Her research interests are in the areas of preclinical and clinical pharmacokinetic and pharmacodynamics (PK/PD) analysis, Omics, PK/PD modeling and simulation, systems pharmacology and population modeling, large molecule therapeutics (proteins, monoclonal antibodies), liposomes, targeted therapeutics and anti-angiogenic therapeutics. She utilizes quantitative systems pharmacology approaches to guide the development of new therapies and the identification of promising combination therapies as well as of novel biomarkers in oncology. She integrates quantitative systems pharmacology with PK/PD modeling and simulation to advance drug discovery and development and leverage the understanding of drugs action which holds great promise to facilitate translational research. Her research is also focused on investigating how priming solid tumors with a pro-apoptotic agent then combining a subsequent large therapeutic with anti-angiogenic agent can defeat drug resistance in cancer and further enhance the efficacy of targeted anticancer agents and translating these findings toward clinical settings.

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