Quantitative Pharmacological Assessment of Trastuzumab-Anthracycline Induced Cardiotoxicity

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Objectives: To quantitatively assess the nature of the interaction between Trastuzumab, a human epidermal growth factor receptor-2 (HER2) monoclonal antibody, and an anthracycline drug, Doxorubicin, at inducing cardiotoxicity, and to elucidate the underlying molecular mechanisms of this interaction using a systems pharmacology approach.

Methods: Immortalized human cardiomyocytes, AC16 cells, were exposed over 72h to a range of concentrations of Trastuzumab (0.01-50µM), Doxorubicin (0.5-500nM) as single agents, and in combination to evaluate cell viability. The concentration-response profiles from single agents were captured with an inhibitory Hill function using ADAPT5. The combination data were modeled with modified parametric competitive and non-competitive interaction models by Ariëns and Simonis [1,2] using Monolix. Three-dimensional (3D) response-surface plots were generated for the combinations based on the final parameter estimates using MATLAB. Additionally, isobologram analyses [3] were performed at different effect levels and compared to observed data to examine the nature of Trastuzumab-Doxorubicin interaction. Furthermore, in vitro time-course experiments were performed for the single agents and the combinations, and characterized using appropriate transit compartment models, to depict delay in cell death signaling.

Results: Both single agents maximally inhibited cell growth (Imax=1) over the range of concentrations tested. The estimated IC50s (mean ± SE) were 21.7±0.8 µM (Trastuzumab) and 11.6±1.5 nM (Doxorubicin). The interaction parameter Ψ was estimated at 0.85±0.03 and 0.98±0.03 with the competitive and non-competitive interaction models, indicating synergistic behavior (Ψ<1) of the combination, while the isobologram analyses predicted the interaction of the two agents to be additive and/or slightly synergistic in nature (Figure 1).

Conclusions: The Trastuzumab-Doxorubicin synergistic interaction at causing cardiotoxicity clinically was successfully assessed with proof of concept in vitro experiments and mathematical modeling. Further evaluation using a systems pharmacology approach is in progress to elucidate the intracellular protein network of this combination in human cardiomyocytes.