1280 MODELING OF DIRECT (EGFR- BASED) AND ADCC CYTOTOXIC EFFECT OF CETUXIMAB ON THE BASIS OF LITERATURE AVAILABLE *IN VITRO* DATA

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Background Cetuximab is a recombinant human/mouse chimeric epidermal growth factor receptor (EGFR) monoclonal antibody. Cetuximab mechanisms of action is based on disruption of EGFR signaling pathways as *dominant mechanism* and ADCC effect as a *secondary* one. The aims of this study were (1) to develop a model describing Cetuximab mechanism of action and effect on head and neck cancer cell lines observed *in vitro* with a purpose to integrate them in quantitative systems pharmacology (QSP) model of HNSCC and (2) to apply the *in vitro* model to study contributions of EGFR signaling disruption *vs* ADCC of Cetuximab for different E:T ratios.
Methods A model describing Cetuximab mechanism of action includes

- Tumor and NK cells
- Tumor cell proliferation and processes describing NK dependent and independent death
- Immunological synapse formed by Tumor and NK cell
- Binding of EGF to EGFR located at the surface of Tumor cells and disruption of the signaling complex with Cetuximab
- Formation of trimer between EGFR located on tumor cell, cetuximab and Fcg3A receptor on NK cells
- Direct effect of cetuximab on tumor cell proliferation via decrease in signaling complexes EGF-EGFR
- ADCC effect of cetuximab on Tumor cell death via stimulation of NK-mediated cytotoxicity with trimer EGFR-Cetuximab- FcgR3A

The model was calibrated against following datasets:

- EGF effect on cell culture growth: *UM-SCC-3*[1]
- Time course of cell culture growth treated with Cetuximab, NK, Cetuximab +NK for 48 hours: *SCC22b*[2]

Dependence of ADCC on Cetuximab dose treated with Cetuximab +NK for 4 hours: *Ho-1-u-1*[3]
Results Validation of the model was performed to confirm its predictive power. Datasets describing survival, cytotoxicity and ADCC as functions of E:T ratio and EGFR expression level were successfully reproduced (see example in figure 1). The model was applied to analyze contribution of signaling/direct effect of Cetuximab and ADCC for different E:T ratios. We have found that contribution of ADCC is observed starting from E:T = 1:100. Model predicts that ADCC effect contribution is comparable with that of signaling/direct effect of cetuximab in following range E:T = 1:2 – 1:1. Starting from E:T = 1:1 ADCC contribution exceeds that of signaling/direct effect.
Conclusions The developed model can adequately describe the effects of Cetuximab observed in *in vitro* experiments. The model was applied to estimate contribution of ADCC and direct effect of Cetuximab at various E:T ratios and EGFR expression levels.

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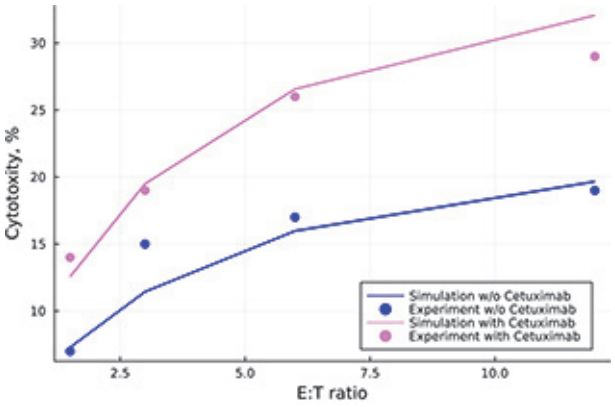

Abstract 1280 Figure 1 Correspondence between experimental data (dots) [3] and simulations (lines) describing cytotoxicity of NK cells with (magenta) and without (blue) 10 ug/ml Cetuximab. Target cells (Ho-1-u-1 cell line) were incubated with NK and Cetuximab for 4 hours and Cytotoxicity was plotted as function of effector:target ratio

http://dx.doi.org/10.1136/jitc-2023-SITC2023.1280