

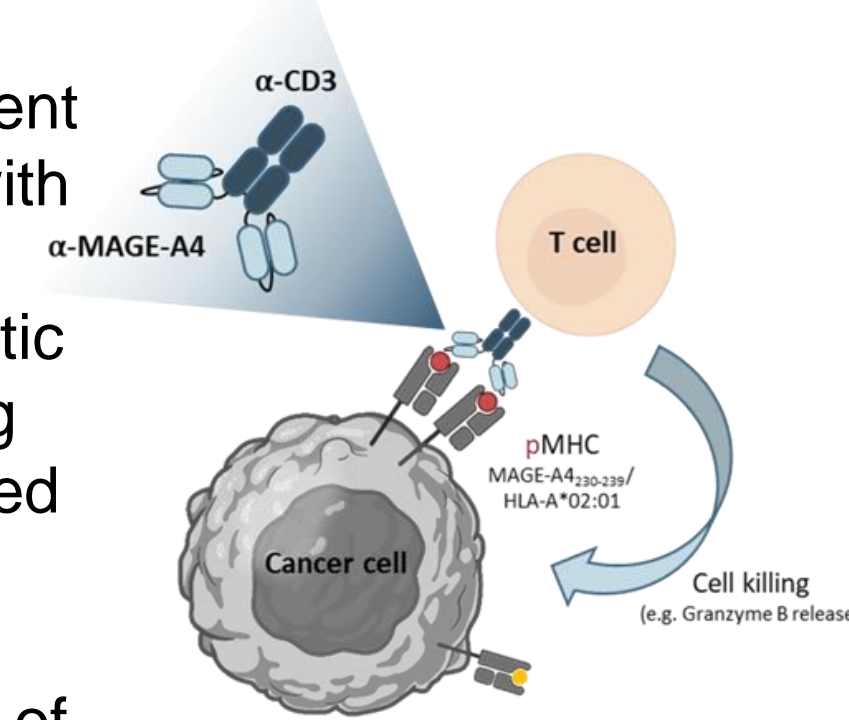
for T-cell engagers: Using Quantitative Systems Pharmacology (QSP) modeling in the development of CDR404 for solid tumors

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Introduction

- CDR404 is a highly specific and potent T-Cell engager which targets MAGE-A4/HLA-A2 on cancer cells and CD3 on T-cells.
- CDR404 is being developed for treatment of HLA-A2 patients with inoperable locally advanced or metastatic MAGE-A4 expressing tumors who have failed standard-of-care therapies.
- Through the analysis of nonclinical PK & PD data, QSP modeling can assist in developing a preliminary understanding of the risk - benefit profile of CDR404 before a phase 1 trial begins



CDR404 has a Fab-(scFv)₂ Molecular Format & T cell dependent Mechanism-of-Action (MoA)

- Here, we describe a QSP-based modeling approach for dose selection and optimization of a FiH study to enable prediction of the pharmacologically effective dose range (PEDR) in patients

Methods

The QSP model for CDR404 focused on describing the drug PK and dynamics of binding to MAGE-A4/HLA-A*02:01 and CD3 in the tumor compartment (Figure 1). Receptor dynamics (synthesis and degradation) was also included in the model. Measured binding KDs as well as MAGE-A4 peptide/HLA-A*02:01 copy numbers on cancer cells were used to inform the model development. CD3 copy numbers on T cells were derived from literature information. The association rate constant for the crosslinking step was fit to the cytotoxicity data. All models were implemented using the Applied BioMath QSP Notebook v2023.8.1.

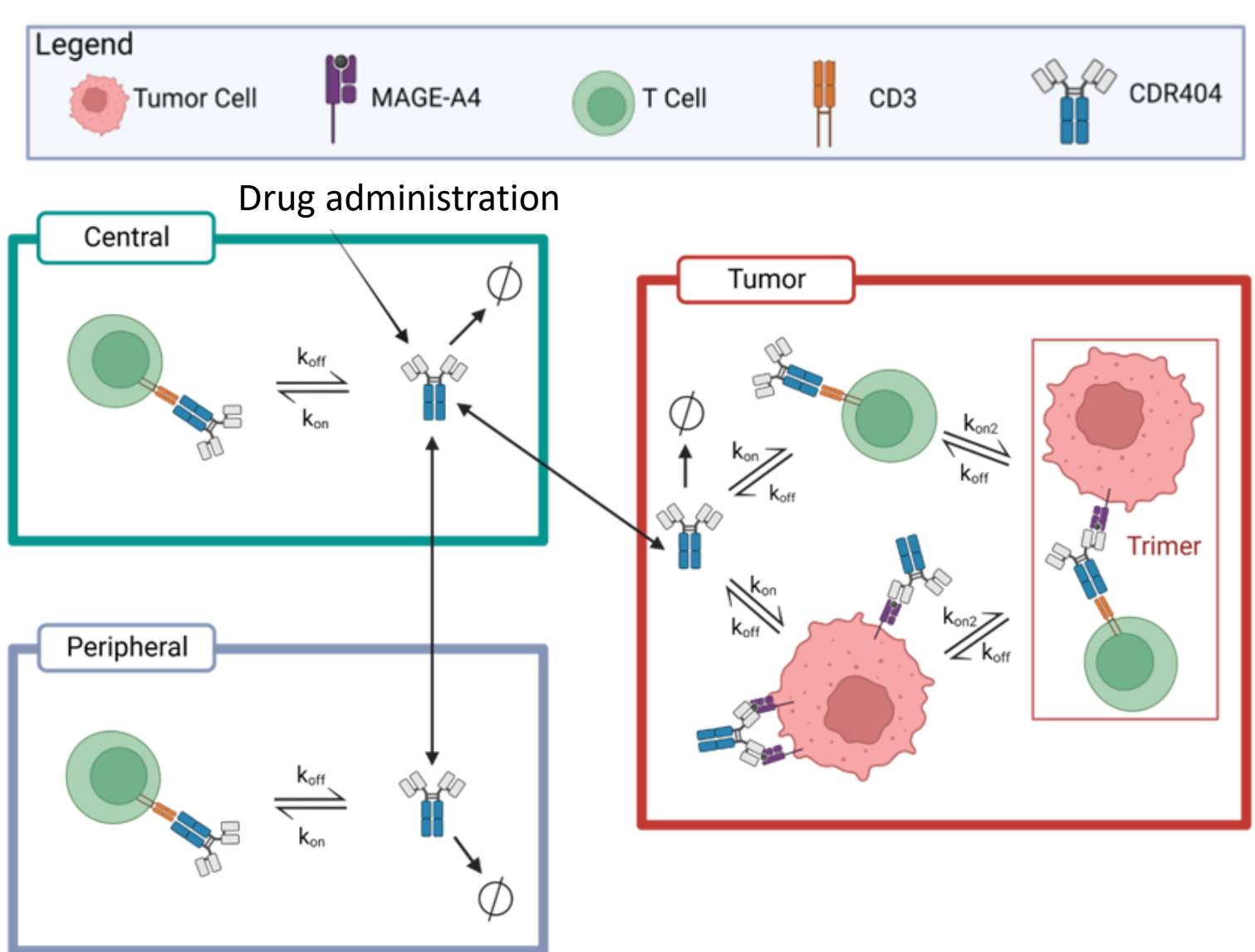


Figure 1. Human model diagram

Human model diagram. CDR404 is administered IV into the central compartment, where it can distribute to the peripheral or tumor compartments. CDR404 can be eliminated or bind to CD3 in all compartments. Crosslinking of CD3 and MAGE-A4 only occurs in the tumor. Trimer formation in the tumor compartment is linked to tumor cell death (cytotoxicity).

Results

1 Model simulation compared to cytotoxicity data as function of CDR404 concentration for two target positive cell lines

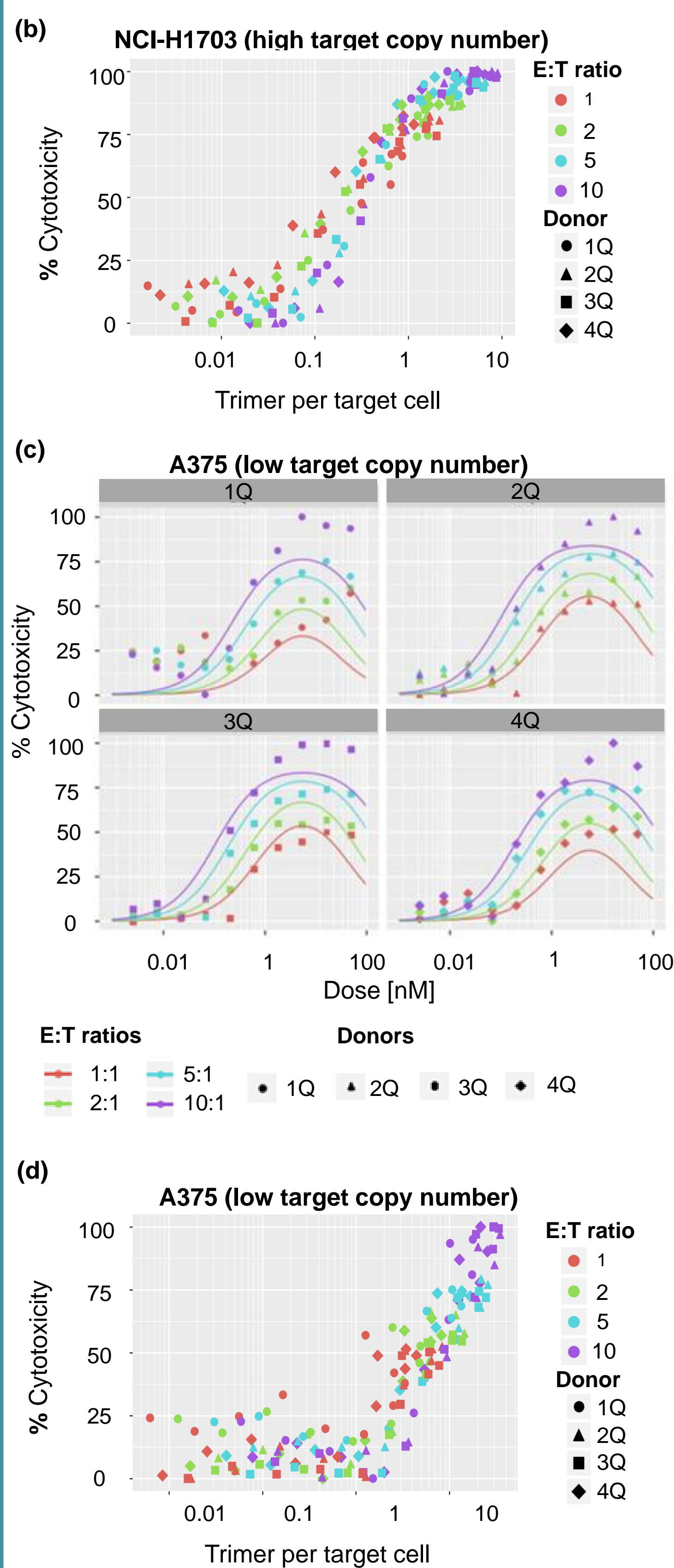
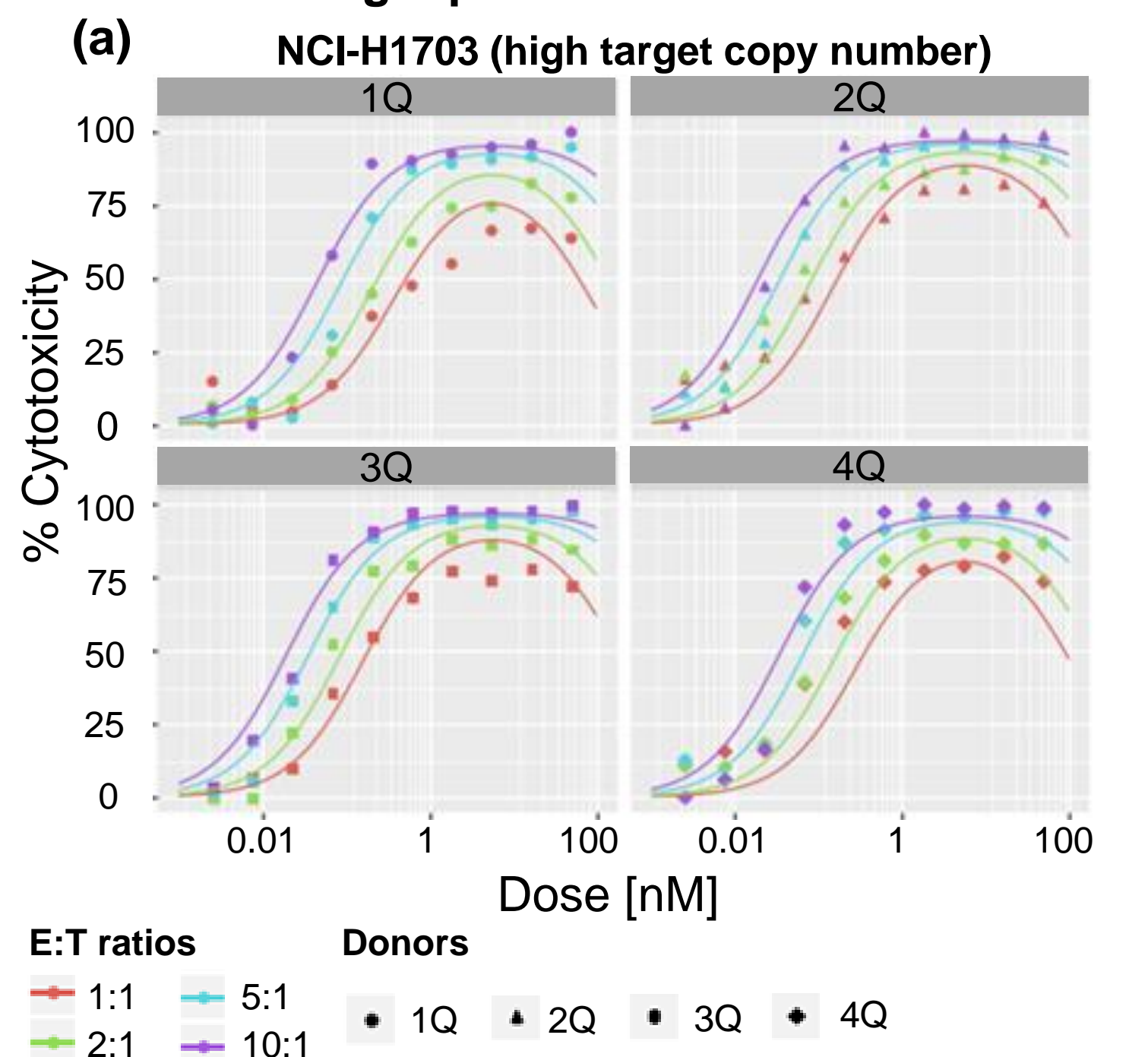


Figure 2. Model simulation (lines) compared to cytotoxicity data (points) as a function of CDR404 concentration for NCI-H1703 (a) and A375 (c) cell lines. Model-predicted trimer per target cell vs measured percent cytotoxicity was plotted in panels (b) for NCI-H1703 and (d) for the A375 cell lines. In (a) and (c), different panels represent different PBMC donors (i.e., 1Q, 2Q, etc.). Different colors represent different E:T ratios.

The *in vitro* model only includes a single compartment, and it was used to estimate trimer numbers under assay conditions, which were then used to establish the relationship between trimer number and cytotoxicity.

2 Relationship between trimer and IFN γ release

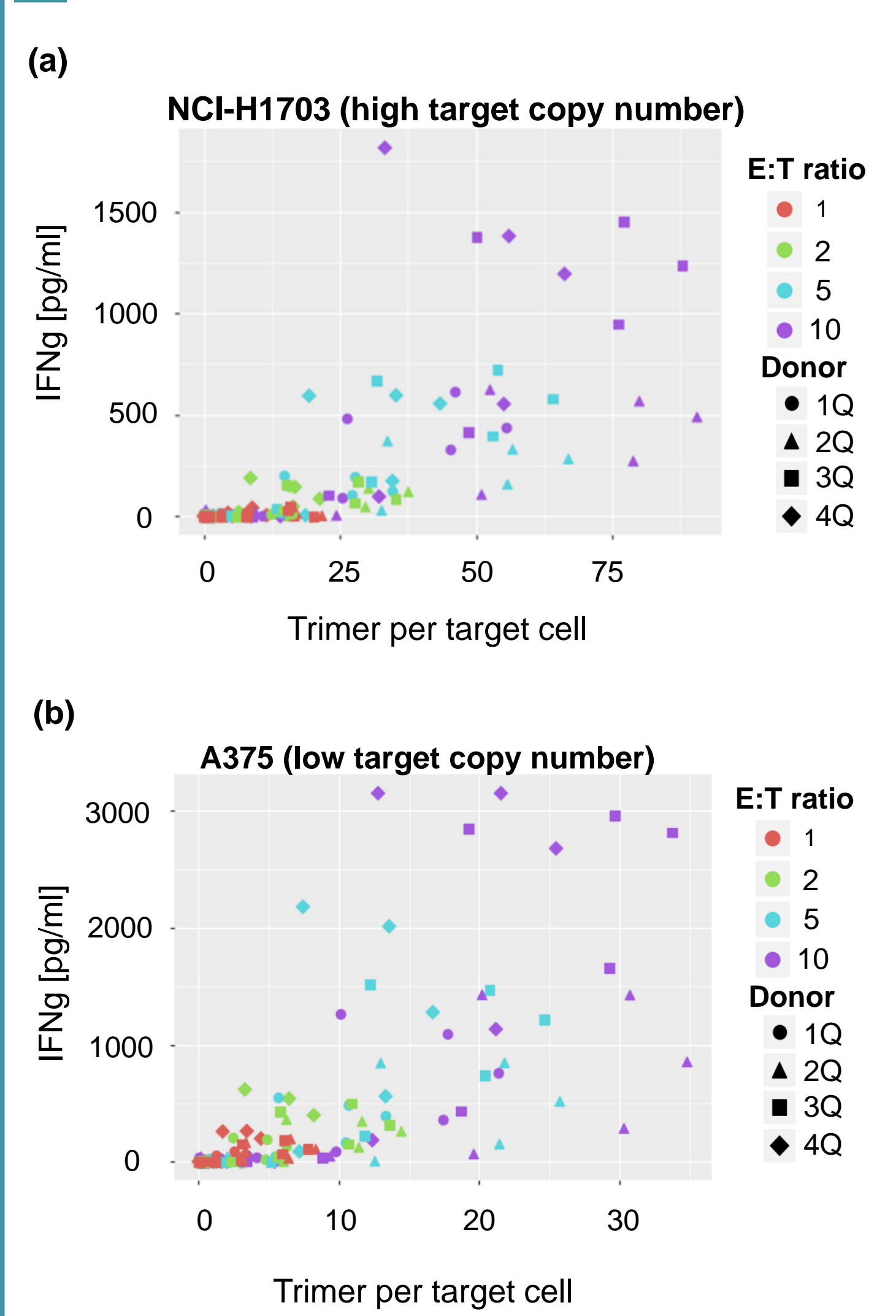


Figure 3. Relationship between model-predicted trimers per target cell and observed IFN γ release for (a) NCI-H1703 cells, and (b) A375 cells at different CDR404 concentrations with different E:T ratios from 4 donors. Colors indicate E:T ratio, symbols indicate PMBC donor.

When the trimer per target cell is greater than 10 or 25, for A375 cells and NCI-H1703 cells, significant IFN γ release started to be observed, respectively.

3 Human model predictions of free CDR404 PK in the tumor at various IV QW dose levels.

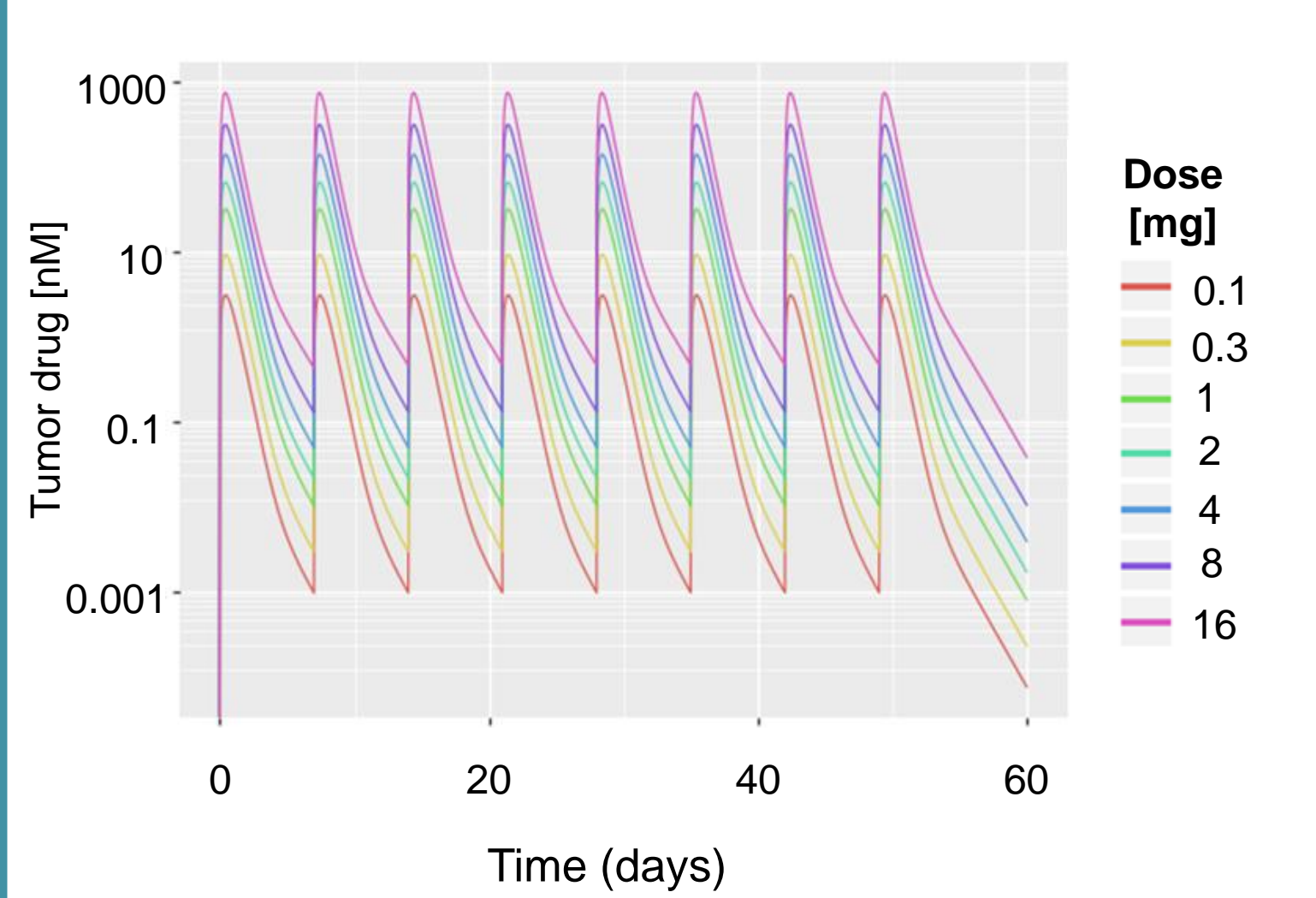


Figure 4. Human model predictions of free CDR404 PK in the tumor

4 Human model predictions of CDR404-mediated trimer formation in tumor and tumor cell cytotoxicity at various IV QW dose levels

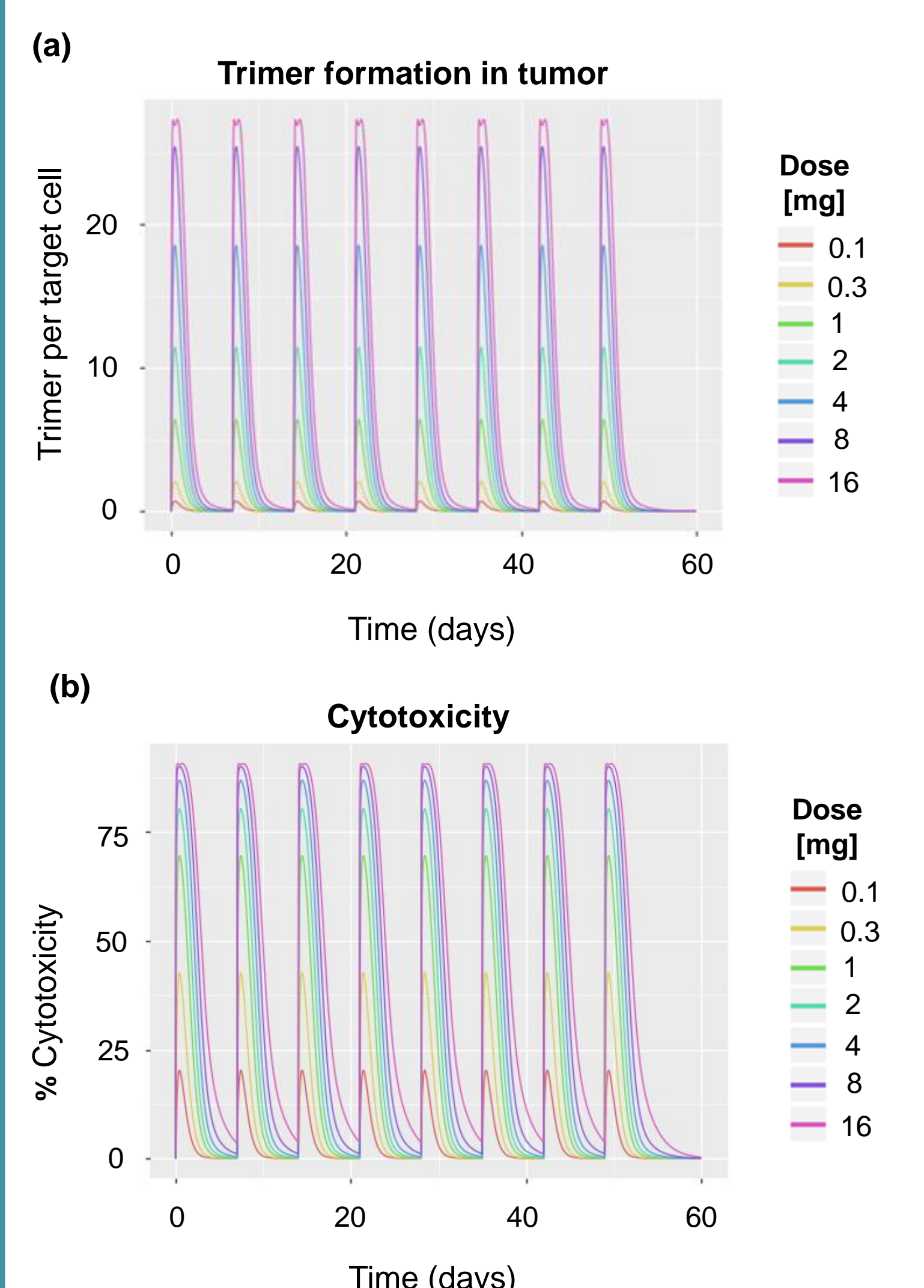


Figure 5. Human model predictions of CDR404-mediated trimer formation in tumor (a) and tumor cell cytotoxicity (b)

5 Sensitivity analysis of how MAGE-A4 receptors per cell (RPC) and T cell density affect cytotoxicity at 100 μ g (left) and 7 mg dose (right)

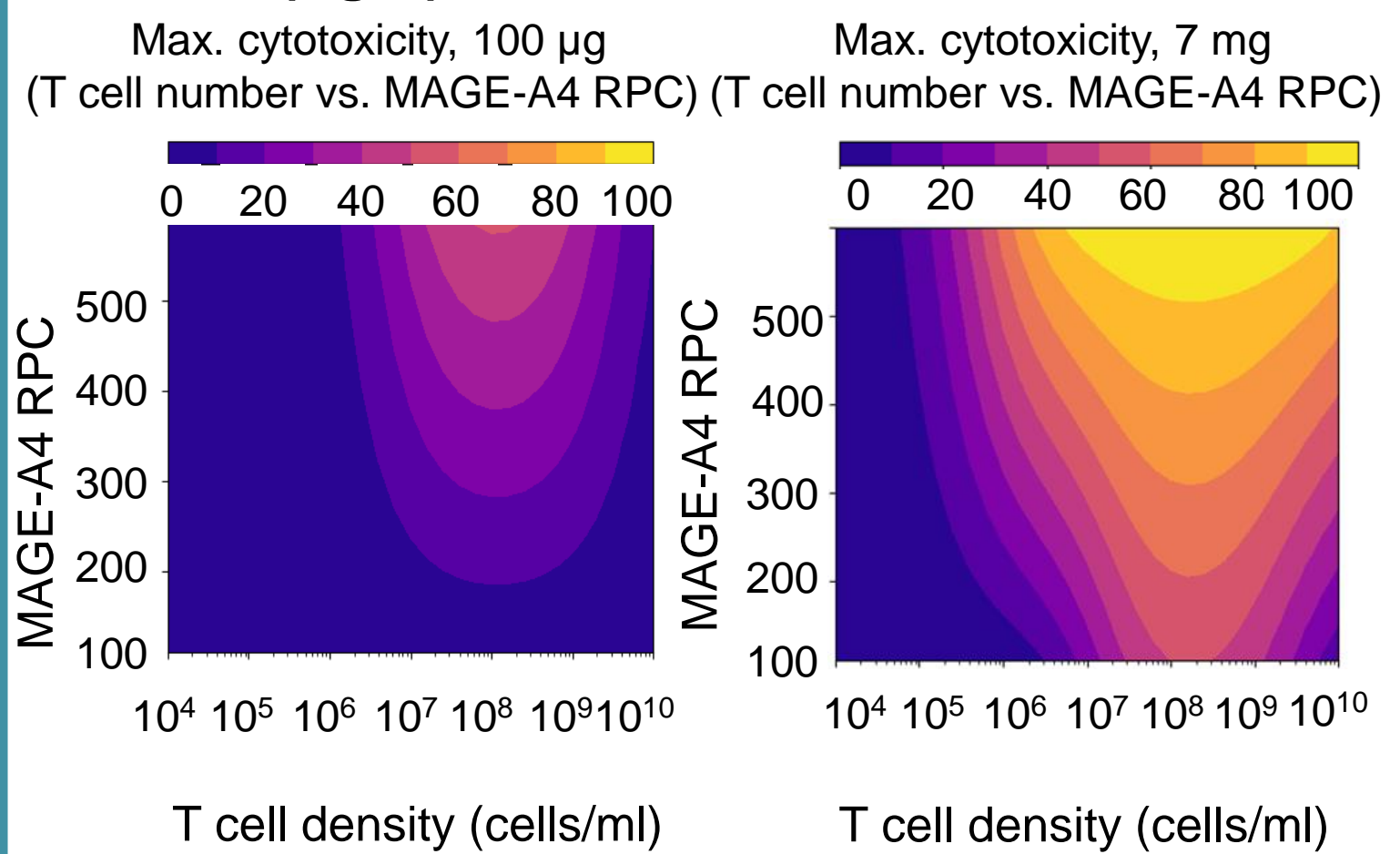


Figure 6. Sensitivity analysis with varying MAGE-A4 receptor number and T cell density

Conclusions

- A multi-tumor phase 1 trial of CDR404 is expected to begin in 2024 with prospective patient selection for both HLA-A*02:01 and tumor MAGE-A4.
- A QSP model developed by integrating preclinical PK, *in vitro* data and literature information predicts linear PK for CDR404 and that it is active in the single mg dose range.
- The model provides a dose-response relationship prediction to guide the starting dose selection and efficacious dose prediction.
- The model is sensitive to the MAGE-A4 expression level as well as T cell density in tumor, which provides guidance on patient selection.
- The model can be updated with patient PKPD data during the Phase 1 trial to identify CDR404 doses with the most favorable risk-benefit profile.