

in vitro PK/PD modeling of immunological synapse-based tumor cell killing and immune activation to predict in vitro efficacy of T-Cell Bispecifics.

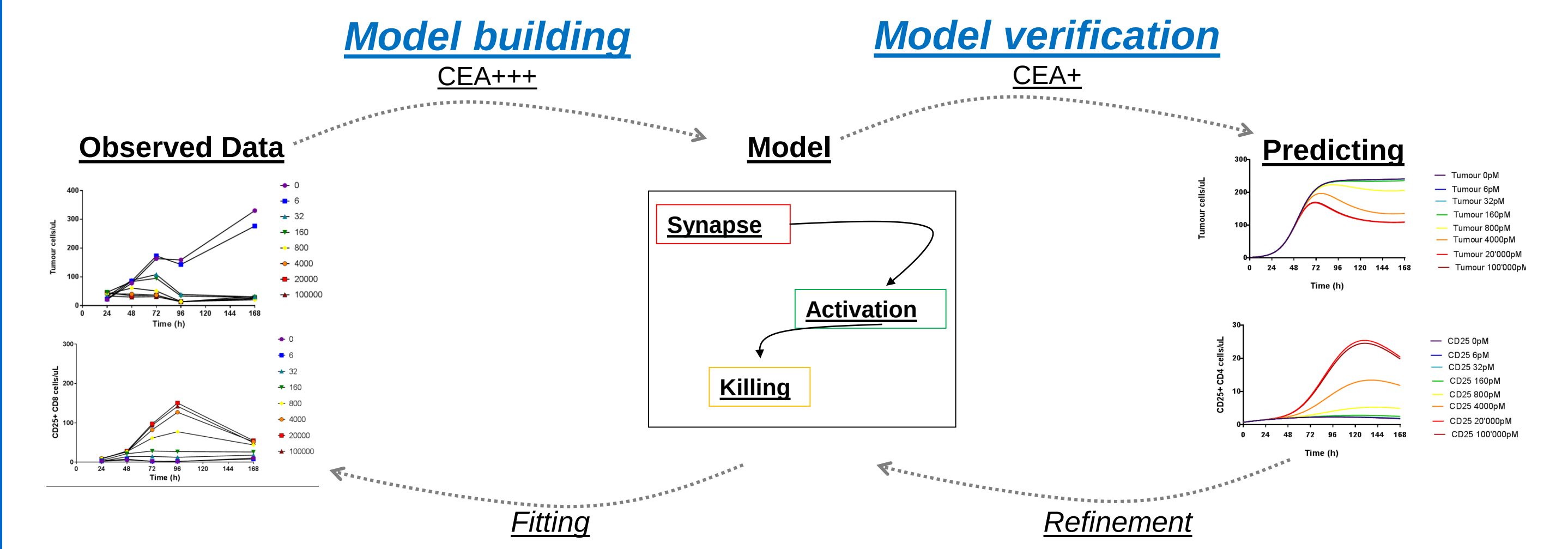


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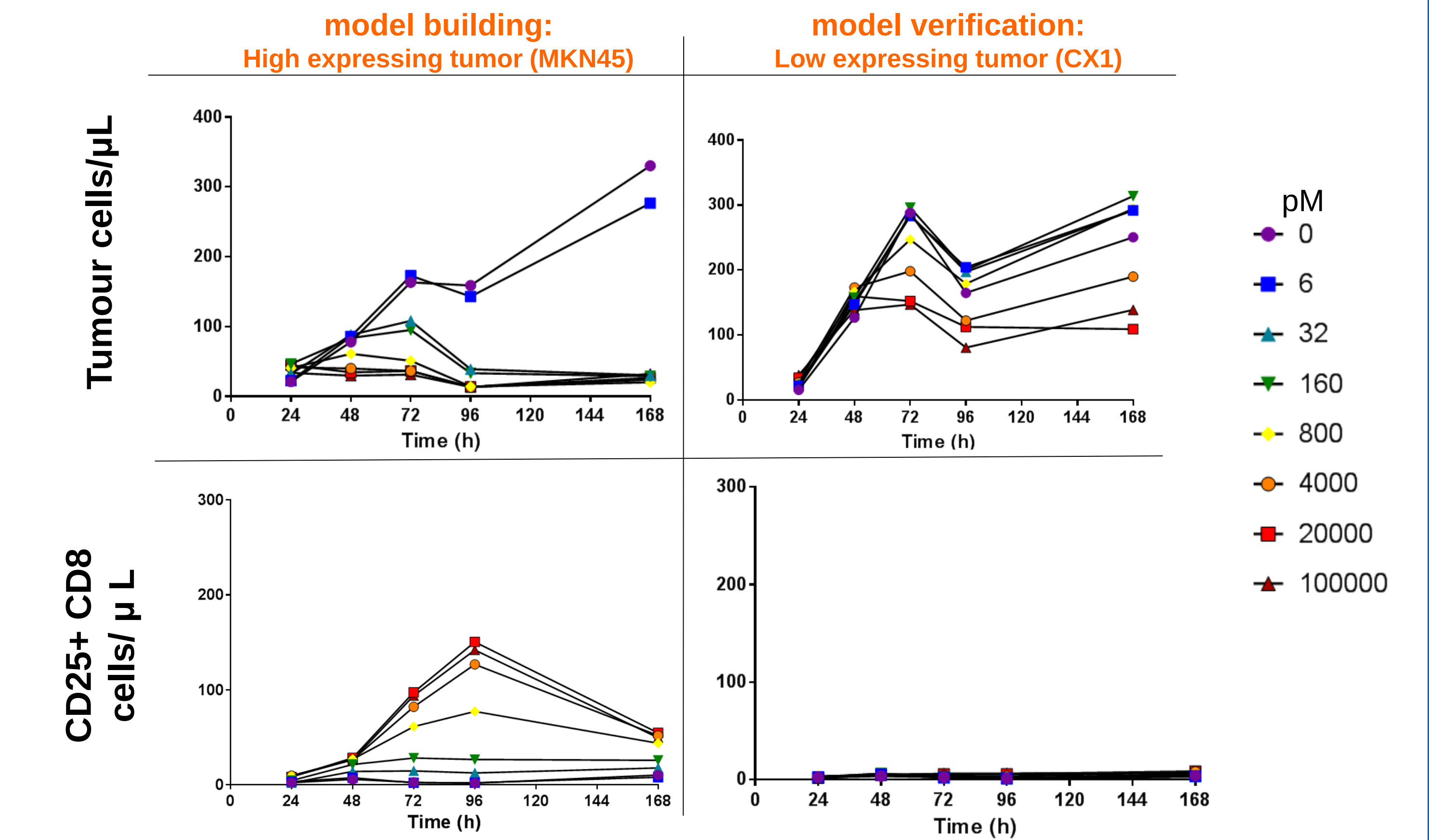
1 Project overview to support compound optimization of T cell bispecific antibodies

T-Cell Bispecifics (TCBs) are antibody constructs with binding specificities to both a tumor antigen and T cell receptor allowing for cross-linking and resulting in the formation of immunological synapses between T- and tumor cells, and subsequent T cell mediated tumor cell lysis. The goal of this work is to support compound optimization with a systems pharmacology model that predicts T cell activation, cytokine release, and tumour cell killing as a function of target affinity, antigen density, TCB concentration. Here, we developed a mechanistic model that captures relevant processes to predict tumor cell killing with Cibisatamab, a novel TCB targeting carcinoembryonic antigen (CEA). The model was developed on data from a high expressing tumour cell line and the fitted model was used to predict the killing of a low expressing tumour cell line.



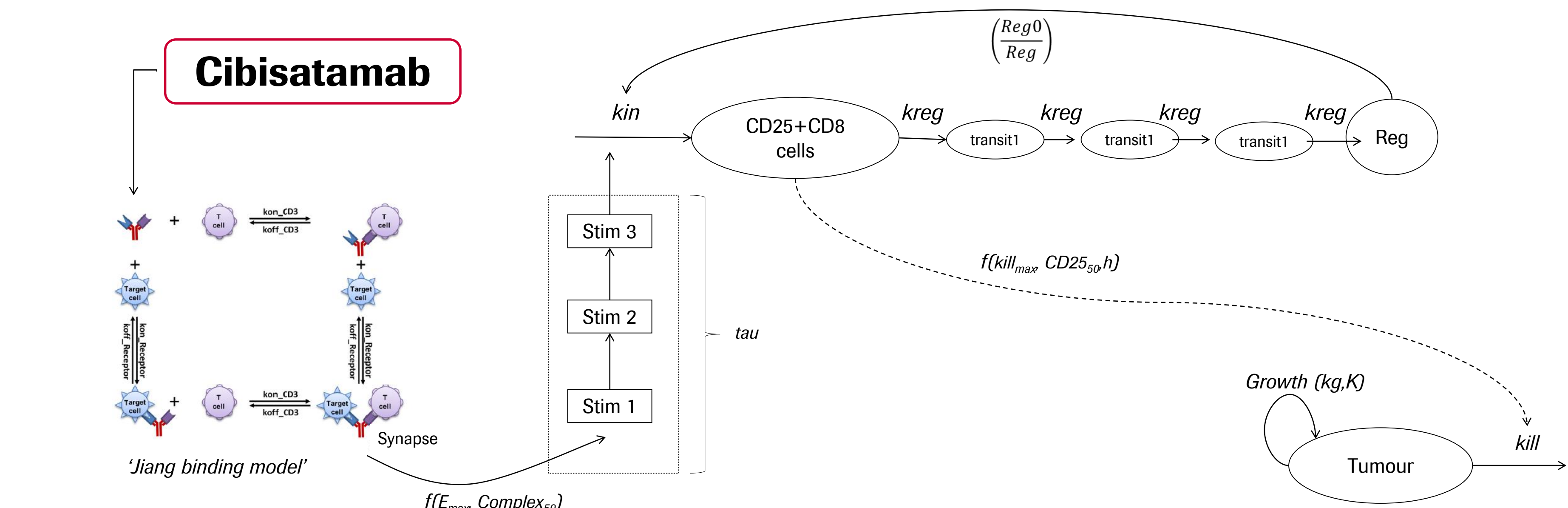
2 Dynamic experimental data from 2 scenarios

Cibisatamab was incubated at a broad range of concentrations in a co-culture with PBMCs and a high or low CEA-expressing tumour cell line. Tumour cell profiles and CD25-positive CD8-T cells over time are shown [1]. Total number of observations is 160.



3 Model structure

TCB binding to tumour (target cell) and T cells (CD3) will result in formation of immunological synapse (synapse), the extent of which is dependent on target surface expression and binding affinities [2]. The synapses will drive T cell activation (CD25+CD8) via a modified model from Friberg et al. [3], capturing time delayed (tau) T cell activation (CD25+CD8) with a negative feed-back loop for counter-regulation. Unperturbed tumor cell growth is described with a logistic growth function (kg, K) and tumor cell killing driven by activated T-cells is described by an Emax (CD25₅₀, kill_{max}, hill) function



4 Parameter Estimation

Parameter estimation was performed using nonlinear mixed effect modeling in Monolix 2018R1. Parameters for **CD25 induction** and **tumour cell killing** were estimated with the MKN45 (CEA+++) dataset and were fixed in simulation mode to verify robustness of the model by predicting the outcome from the Cx1 (CEA+) dataset. Only cell line parameters specific to Cx1 were adapted (growth rate (kg), carrying capacity (K)), CEA expression density)

Estimated parameters

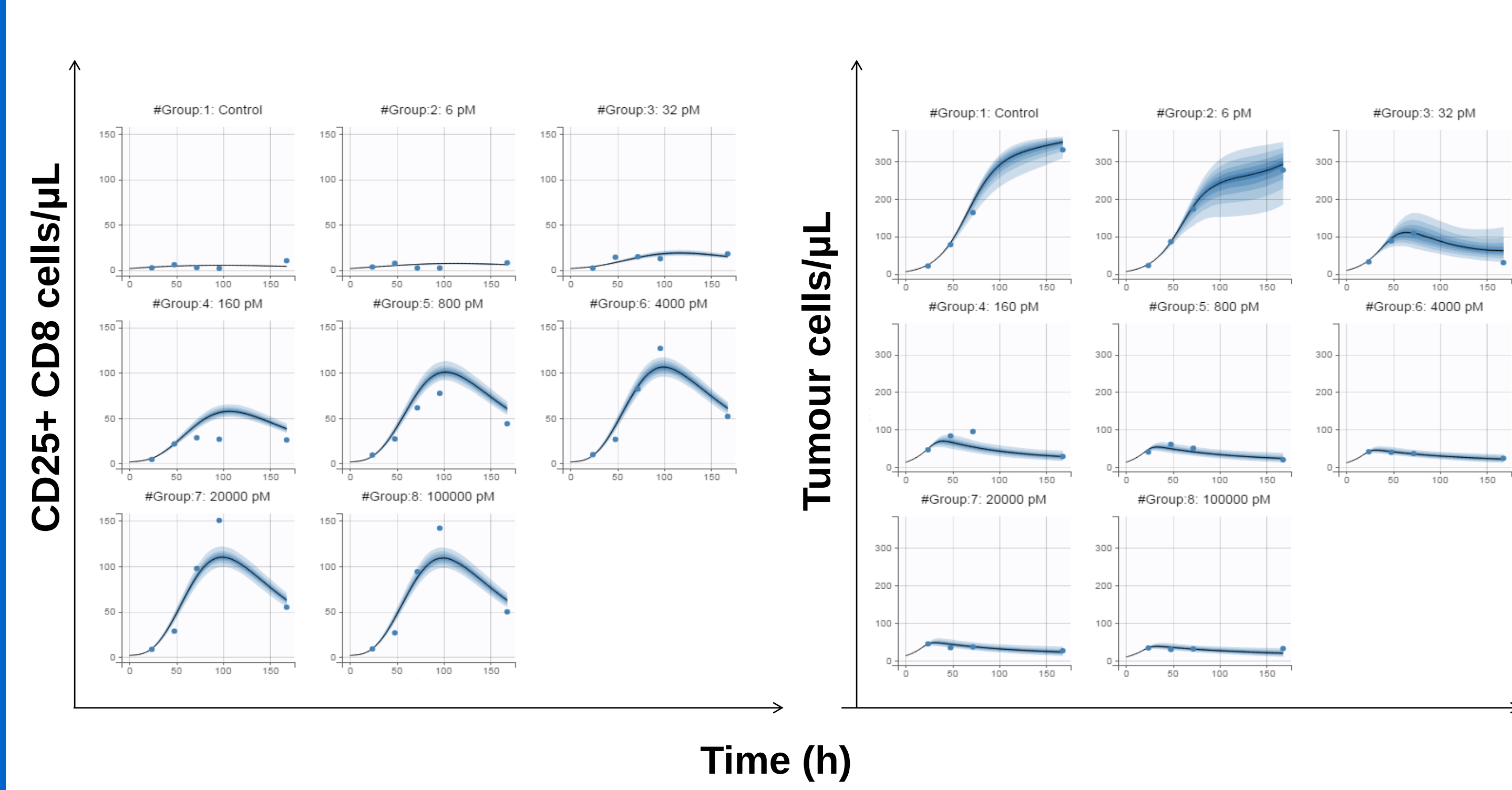
Parameter	Mean	SE	RSE%
K_{in} [1/h]	0.11	0.02	19.2
$Complex_{50}$ [nM]	0.058	0.016	28
Emax	43.7	9.8	22.4
CD25 ₅₀ [cells/μL]	9.97	0.98	12.3
Kill _{max} [1/h]	0.06	0.0017	2.8
Hill	2.92	0.66	22.5
CD25base [cells]	1.7	0.34	20.2

Cell line specific parameters

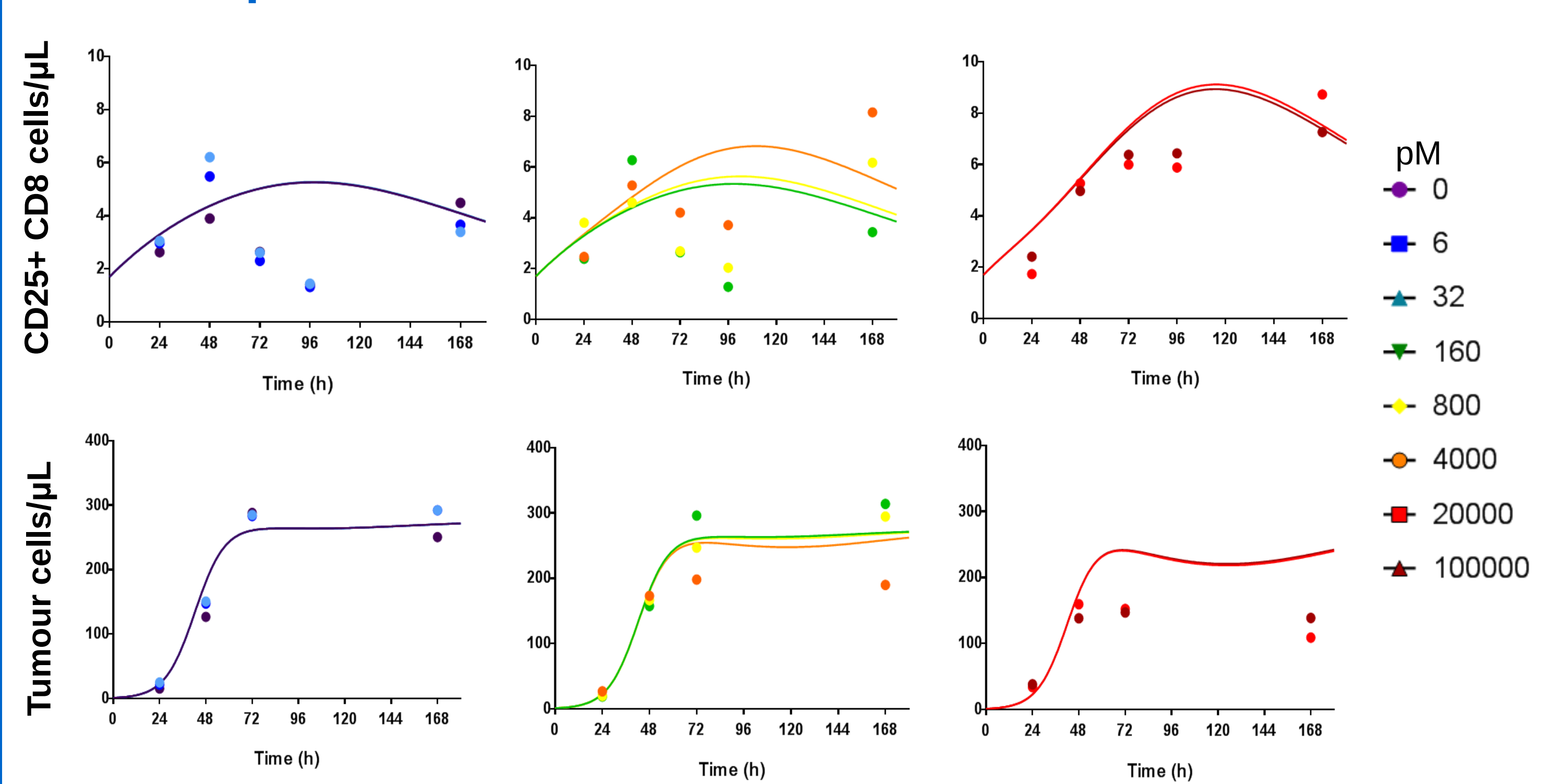
Parameter	MKN45 model building (RSE%)	Cx1 model verification (RSE%)	Source
Kg [1/h]	0.057 (3.6)	0.13 (4.2)	Estimated from control group
K [cells/μL]	331.3 (0.2)	274 (7.3)	
Initial tumour [cells/μL]	5.8 (7.2)	1.1 (11.2)	
CEA density	230000	2000	Internal data

5 Model building: Fitting of CEA-MKN45

Prediction Distribution profiles



6 Model verification: overlay of observed and predicted mean tumour and CD25 profiles for CEA-Cx1



Conclusion and outlook

In the present study, we have build a mechanistic systems pharmacology model to guide compound optimization. The proposed model predicts T-cell activation and T-cell mediated tumor killing as a function of drug concentration, target expression on tumor cells and drug target affinity to tumor target. For model verification, we showed that model correctly predicts the extent of T cell activation and tumour cell killing dependent on the expression level of the tumour antigens. These results suggest that the model can be applied in early drug discovery and development to guide target selection and compound optimization. As next steps, we plan to link T cell activation to cytokine signaling in the model and to verify the robustness of the model in describing data from different TCBs.

[1] Bacac, M., et al., A Novel Carcinoembryonic Antigen T-Cell Bispecific Antibody (CEA TCB) for the Treatment of Solid Tumors. Clin Cancer Res, 2016. 22(13): p. 3286-97.
[2] Jiang, X., et al., Development of a Target cell-Biologics-Effector cell (TBE) complex-based cell killing model to characterize target cell depletion by T cell redirecting bispecific agents. MAbs, 2018. 10(6): p. 876-889.
[3] Friberg, L.E., et al., Model of chemotherapy-induced myelosuppression with parameter consistency across drugs. J Clin Oncol, 2002. 20(24): p. 4713-21.