Development of a Preclinical Quantitative Systems Pharmacology Model for E7046, a Novel PGE_2 Receptor Type 4 Antagonist for Cancer Immunotherapy

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Introduction

Prostaglandin E2 (PGE_2) receptor 4 (EP_4) signaling has been shown to have a major role in forming an immunosuppressive tumor microevironment. More specifically, EP_4-mediated PGE_2 signaling has been shown to be important for the differentiation of monocytes into Tumor Associated Macrophages (TAM) and Myeloid-Derived Suppressor Cells (MDSC), which inhibit the anti-tumor activity of T-cells (CD8+). E7046 is an orally bioavailable and highly selective competitive inhibitor of EP_4. The inhibition of this pathway by E7046 shifts the balance towards the differentiation of monocytes into anti-tumor M1 type macrophages and antigen-presenting dendritic cells (DC), which lead to an increase in the activity of CD8+ cells, and tumor cell death (Figure 1). This mechanism is distinct but complementary to immune checkpoint blockade agents or cancer vaccines, and could be suitable for successful combination therapies. In addition, since the resulting disruption of the arachidonic acid signaling pathway downstream of where COX inhibitors act, it spares the signaling pathways mediated by the other PGE_2 receptors (Figure 2), which is believed to result in better cardiac safety profile.

Objective:

To develop a preclinical immuno-oncology Quantitative Systems Pharmacology (QSP) model for E7046 to help identify predictive biomarkers for tumor growth inhibition (TGI) in mice. Once developed and translated to humans, the model is expected to aid the selection of efficacy biomarkers in the clinical development of E7046 and test combination therapies with E7046 more likely to produce a desired anti-tumor response

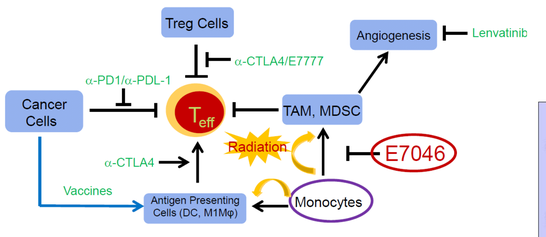


Figure 1. EP4 blockage by E7046 increases differentiation of monocytes into anti-tumor M1 type macrophages and antigen-presenting dendritic cells (DC), thus increasing in the activity of CD8+ cells, and tumor cell death. Potential combination therapy agents and mechanisms shown in green .

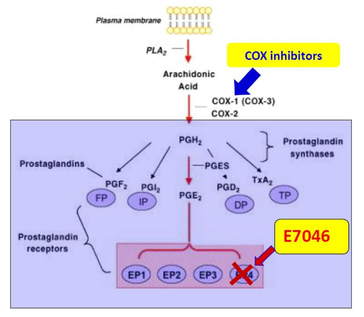


Figure 2. E7046 blocks the arachidonic acid signaling pathway downstream, and this is believed to provide better cardiac safety profile

Methods

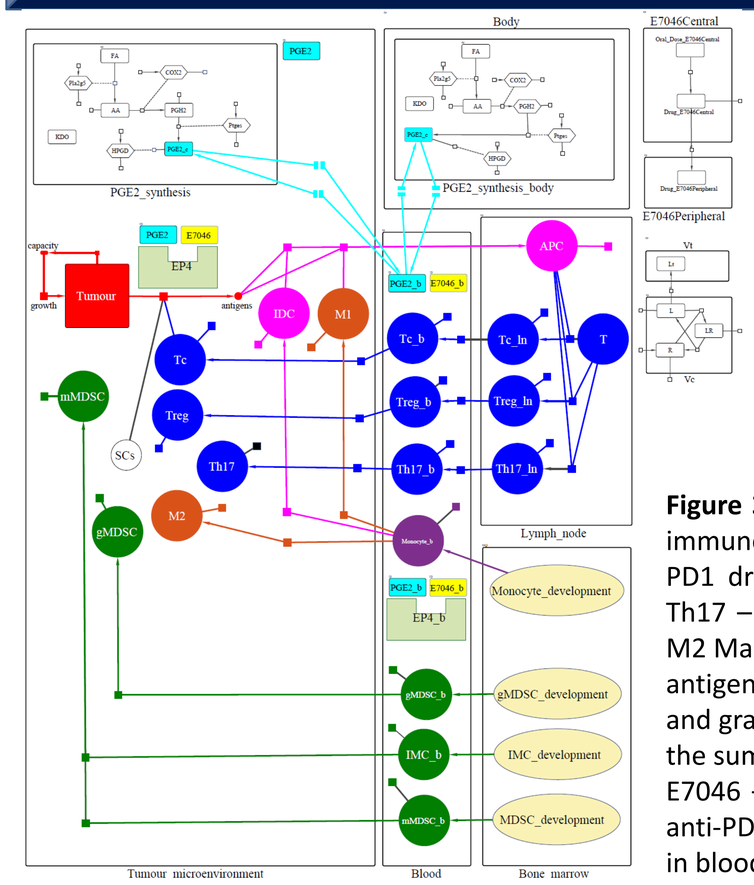
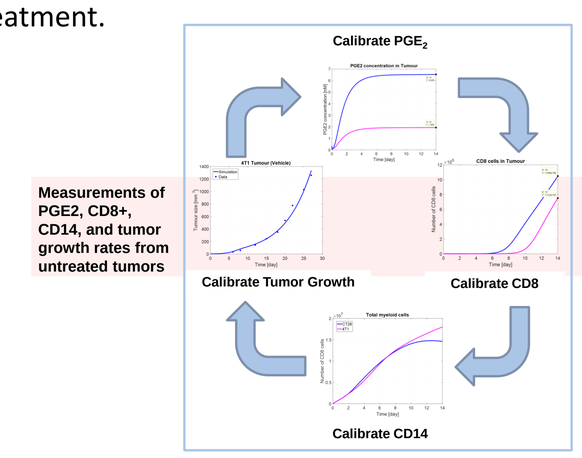


Figure 3. Biological process map. Mechanistic model of immune response to pre-clinical tumor and E7046/ anti-PD1 drug combination. Tumor – tumor size; Tc, Treg, Th17 – CD8, Treg and Th17 T-cells, M1, M2 – M1 and M2 Macrophages, IDC – immature dendritic cells, APC – antigen presenting cells, mMDSC, gMDSC - monocytic and granulocytic myeloid-derived suppressor cells, SCs – the sum of all suppressor cells, PGE2 – Prostaglandin E2, E7046 – amount of E7046, EP4 – EP4 receptor; L, R – anti-PD1 and PD1; _b, _ln, _c are tags of specie names in blood, lymph nodes and cytoplasm.

A new mechanistic and quantitative model was developed, integrating new experimental data on immune system response to pre-clinical syngeneic CT-26 tumors (a murine colon carcinoma that produces high levels of PGE_2) and enhancement of this response by E7046. The model was built from a combination of literature & data review summarizing, 161 references, 27 Eisai pre-clinical datasets on CT-26 syngeneic tumor growth inhibition (TGI) TGI, CT-26 tumor infiltration by CD8+ Tcells and monocytes, blood cell counts, intratumor and plasma PGE_2 levels. E7046 pharmacokinetics was introduced as a two compartment model, with parameters estimated from fitting inhouse mouse E7046 plasma data with Phoenix. A summarized model for a generic anti-PD1 check-point inhibitor drug was also included for initial combination therapy evaluations. Data were integrated in Simbiology with an ordinary differential equation model of 56 variables describing dynamics of molecular species and cell types in 11 compartments. The 138 parameters involved in 88 rate laws were established by literature meta-analysis and fitting to experimental data from inhouse studies. The final biological process map is presented in Figure 3. Sensitivity analysis was then used to identify drug-independent parameters that when plugged into the model (following calibration to CT-26 values - See Figure 4) would allow the prediction of TGI for additional, mouse tumors following E7046 treatment.



Tumor specific parameters for calibration:

- ***The tumor growth rate***
- ***The expression level of CD8+ cells in the tumor***
- ***The levels of PGE_2 in the tumor.***

Figure 4. Calibration scheme for generating tumor-specific input values to allow for predictions of TGI by E7046

Results

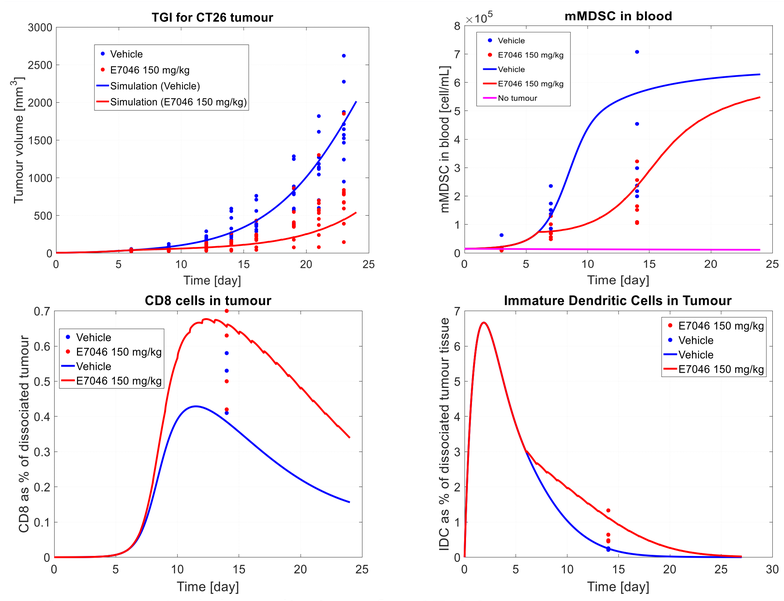


Figure 5. Model predictions for CT-26 tumors:

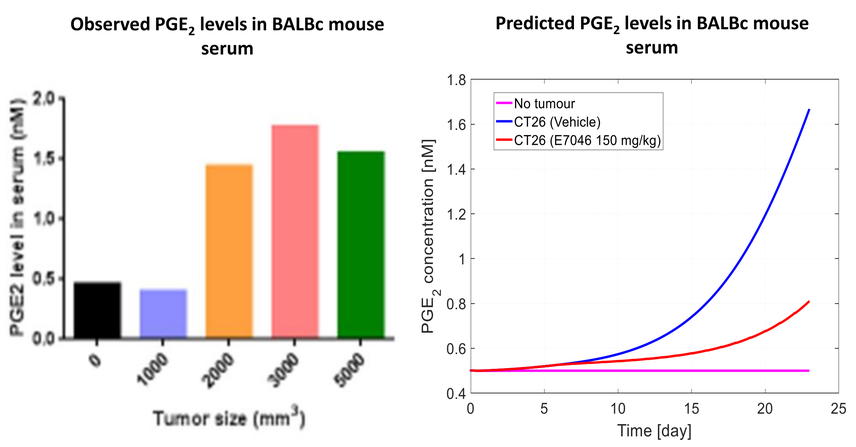


Figure 6. Baseline blood PGE_2 concentration and range of concentrations observed for CT26 tumor up to 3000 mm^3 tumor (left) and model predictions (right). Blood PGE_2 levels may be a biomarker of TGI and E7046 action in mice

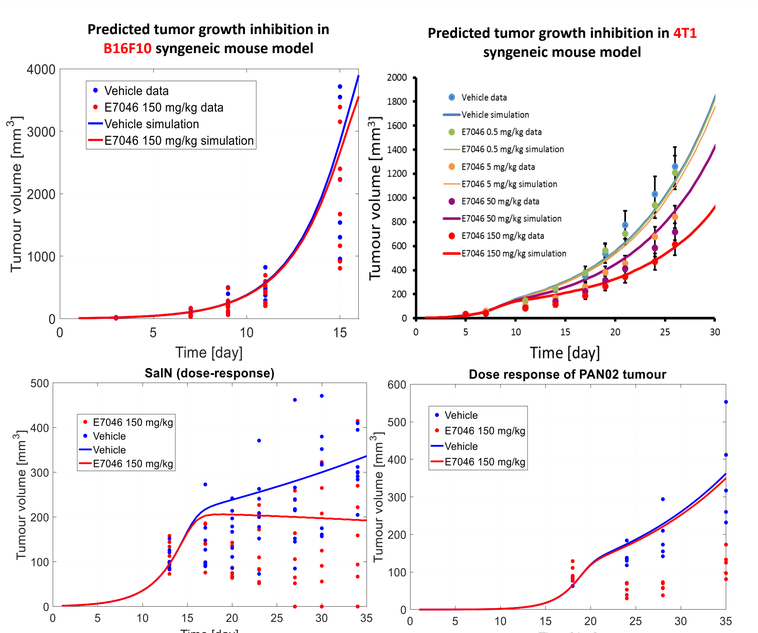


Figure 7. Predicted TGI for 4 different syngeneic tumor models based on calibrated inputs

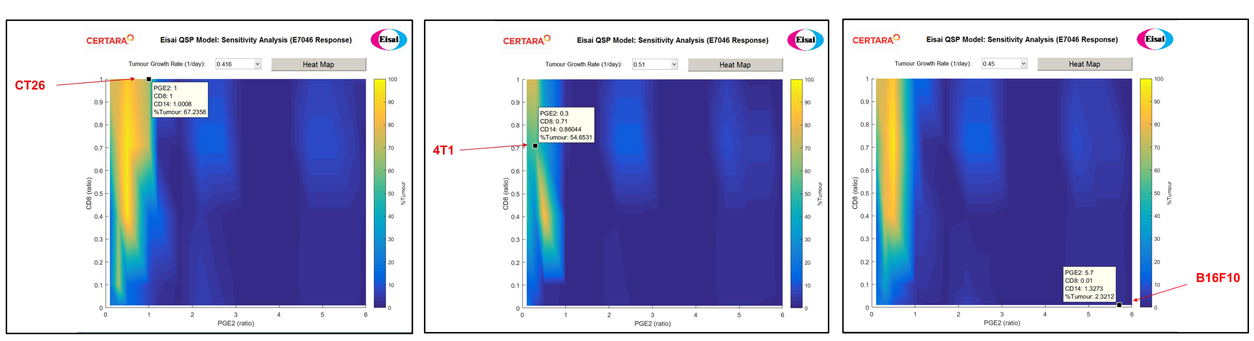


Figure 8. Quick Assessment Visual tool developed for TGI prediction for E7046 at specific tumor growth rates for various tumor types. The x- and y-axis represent the tumor-specific calibrated values of CD8+ and PGE_2.

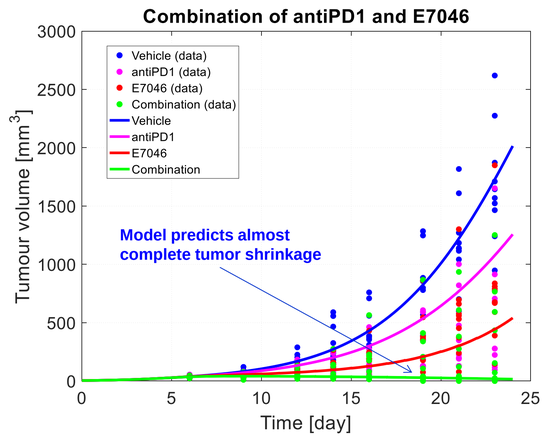


Figure 8. Predicted TGI for E7046 and anti-PD1 combination. Model currently over-predicts the TGI of the combination

Summary and Conclusions

- A successful immuno-oncology QSP model for E7046 was developed. It predicted the TGI of CT26 by E7046 in mice, as well as tumor and blood profiles of PGE_2 and various cell populations (Figure 5). It also reproduced baseline blood PGE_2 concentration observed for CT26 tumor (Figure 6) suggesting that blood PGE_2 may be a biomarker of TGI and E7046 action in mice.
- Three system parameters were identified as predictors of E7046 induced TGI, which were used to successfully predict the TGI for 3 out of the 4 mouse tumors tested (Figure 7).
- The model was used to make predictions of TGI resulting from different doses of E7046 and its combination with a mouse PD-1 checkpoint inhibitor. Results currently show over-prediction, indicating further work is needed (Figure 9).