Dynamic in vitro PKPD assessment to improve pharmacological response profiling of T-cell bispecifics

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Introduction

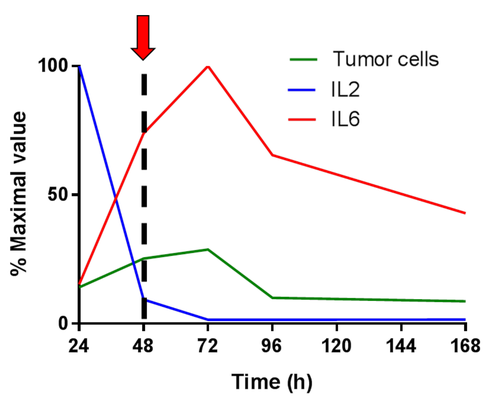
The approach for First-in-Human dose selection for cancer immunotherapy is typically based on minimally-anticipated biological effect level (MABEL) using in vitro data. Response to immuno-oncology treatment is complex and includes series of events such as tumour-cell killing, cytokine release and T-cell activation which can be related to efficacy and safety of the drug. In such a complex network these effects often occur on different time scales which may lead to a bias when two readouts are quantitatively compared based on a static assessment. This subsequently leads to uncertainty and inaccuracy in a derived MABEL dose prediction [1]. Therefore more mechanistic means are needed for a better translation from in vitro to human.

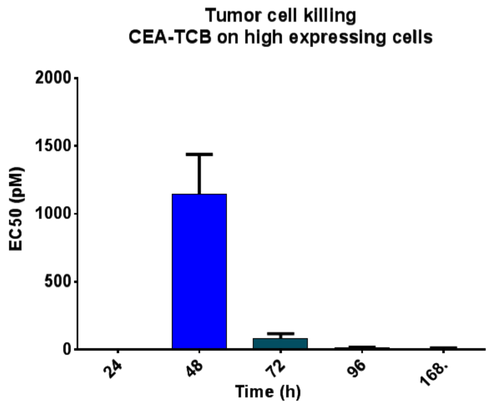
Objective

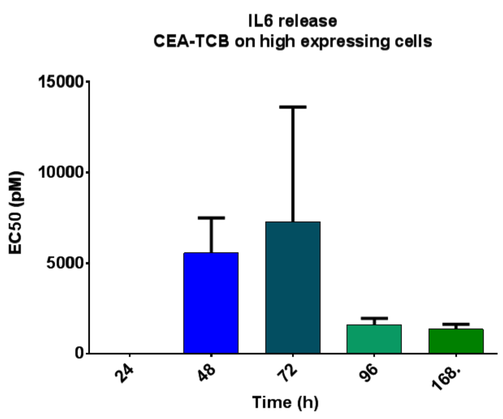
Here, we compare the performance of a static and dynamic in vitro PKPD assessment for CEA-TCB, a T-Cell-Bispecific Monoclonal Antibody targeting the carcinoembryonic antigen [2]. We outline how experiments and subsequent data analysis can be performed in order to get a more robust assessment of the drug's potency on various pharmacological readouts which are relevant for human dose selection.

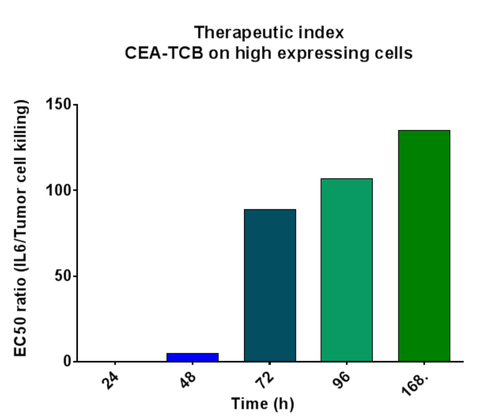
Static assessment yields inconclusive results

The immune response is highly dynamic. Estimating drug potency at one defined time point can bias the assessment as EC50 shifts with time.



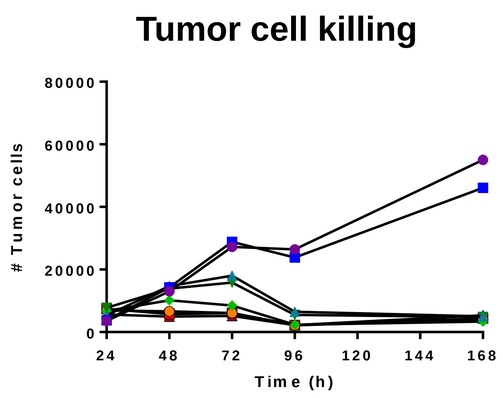


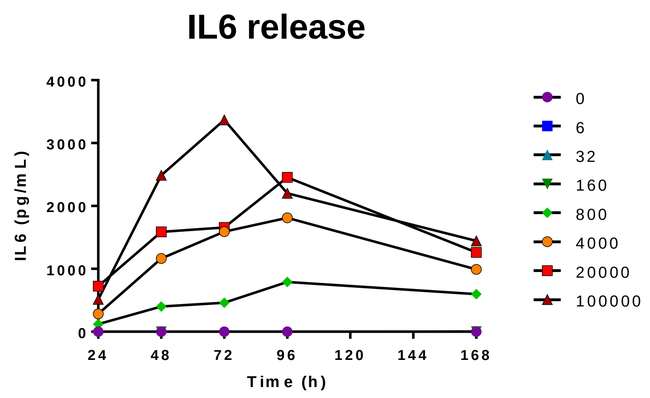


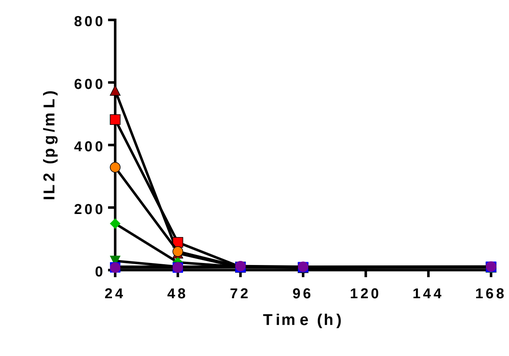


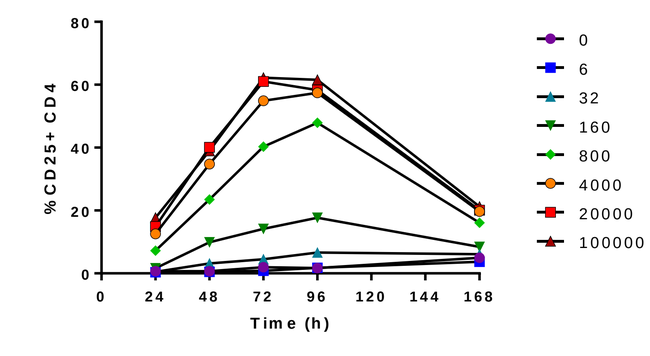
Dynamic experimental data

PD readouts for the immune response occur at different time scales. Therefore it is important assess immuno-oncology drugs while accounting for the interaction and dynamics of the various drug responses.



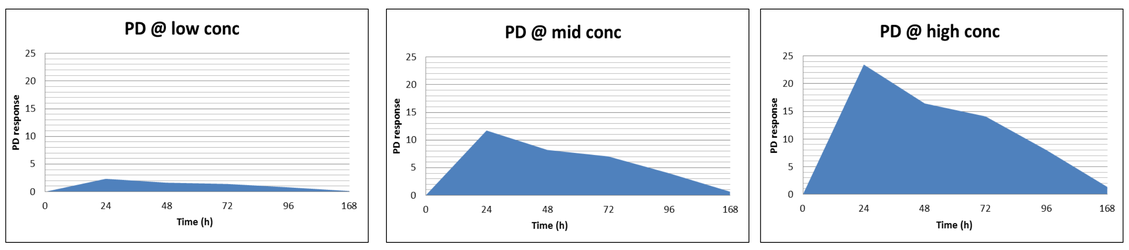




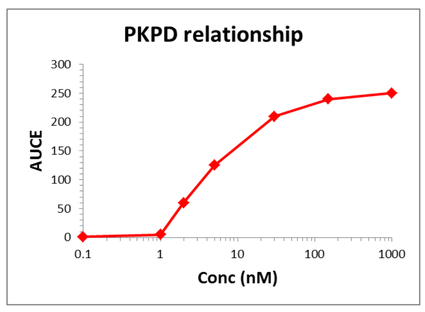


Dynamic data assessment

AUCE based PKPD analysis

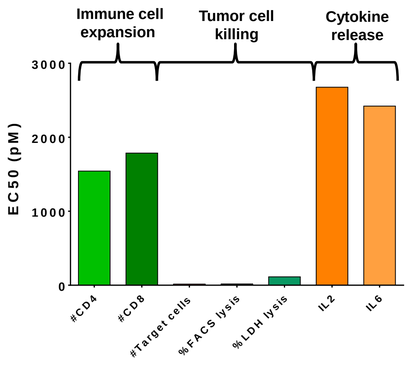


- AUCE (area under the effect curve) integrates drug effect over time
- Build PKPD relationship based on AUCE changes over concentration

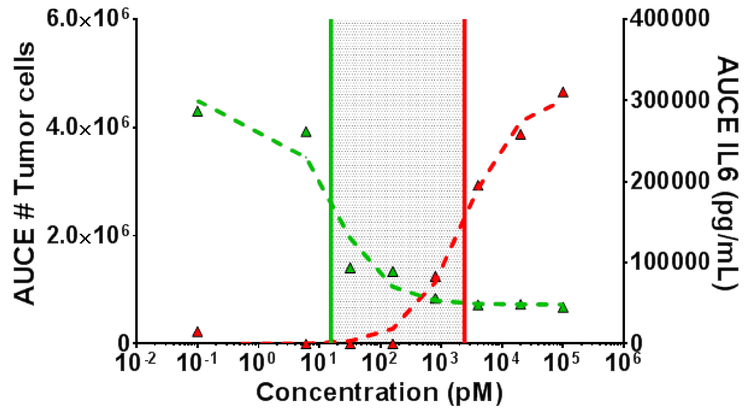


- This allows a time independent PKPD assessment
- Here, NCA and parameter estimation were done using Phoenix WinNonlin (Certara)

Therapeutic index based on dynamic assessment



- EC50s are derived for various PD readouts after TCB treatment in vitro
- Potency of CEA-TCB: Tumor cell killing > Immune expansion > cytokine release
- This indicates a potential therapeutic window
- For illustration a therapeutic index was derived as the window (grey) between EC50 for tumor cell killing (green) and IL6 release (red).



Conclusion

Our results indicate that a static comparison of the drug's effect on different PD readouts occurring at different time scales is not meaningful. This can be circumvented by considering the full time course, such as relating the integral of the time course of the effect (AUCE) versus concentration to derive the drug's potency. Such assessment enables to identify the most relevant and reliable markers for efficacy and safety and thereby improve the MABEL approach for entry in human dose prediction. Further integration of dynamic in vitro data into a systems pharmacology model will help to better understand the mechanics behind tumour lysis and immune response upon treatment with TCBs as function of target expression and drug-target interaction and to optimize compound properties in context of the selected target.

References

[1] Saber, H., et al., An FDA oncology analysis of CD3 bispecific constructs and first-in-human dose selection. Regul Toxicol Pharmacol, 2017. ***90****: p. 144-152.*
[2] 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.*