A Mechanistic PKPD Model for first-in-human dosing of a tetraspecific antibody (MDX2001) for the treatment of advanced solid tumors

Tim Lezon[2], Ben Lang[2], Marissa Renardy[2], Monette Cotreau[1], Edward Garmey[1], Dalia Buzyn[2], Anne-Laure Goenaga[1], Ronnie Wei[1], Zhi-Yong Yang, Fei Hua[2], Marc Presler[2], Kerry Culm[1]

1. ModeX Therapeutics Weston Massachusetts 2. Certara, Inc. Concord Massachusetts

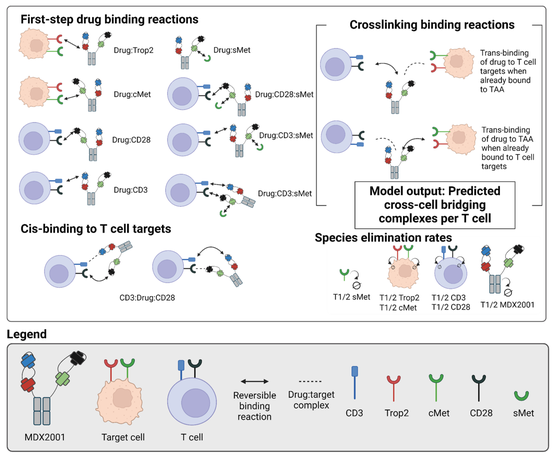
Overview

MDX2001 is a tetraspecific T cell engager that binds CD3 and CD28 on T cells and binds the tumor associated antigens (TAAs) cMet and Trop2. To inform the first-in-human dosing of MDX2001 for solid tumors, we developed a systems pharmacology model to address the complexities in translating a high valency T cell engager from the preclinical data to the clinic. The model was calibrated using data from *in vitro* binding, cytokine release and cytotoxicity assays, along with cynomolgus monkey pharmacokinetic (PK) studies and physiological target parameters in humans. Using the model, we predicted a safe clinical starting dose guided by QSP-based metrics.

Key Takeaways

- Model captures the intricate binding dynamics of a tetraspecific T cell engager that binds CD3 and CD28 on T cells and cMet and Trop2 on solid tumor cells.
- QSP model predicts cell killing and cytokine release as functions of cross-cellular molecular bridges as a model-derived biomarker for clinical translation
- A conservative starting dose was chosen to de-risk potential for on-target, off-tumor activity while informing escalation path to efficacious doses.

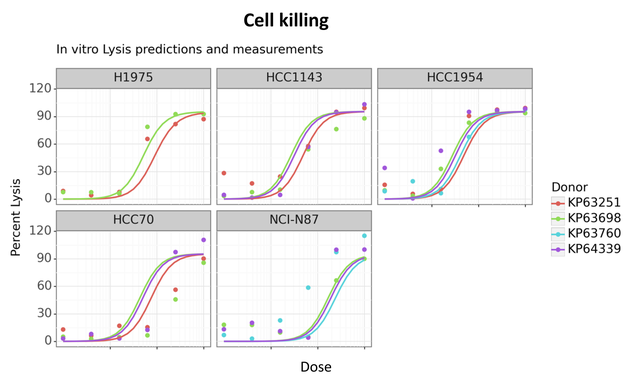
Computational Model Structure

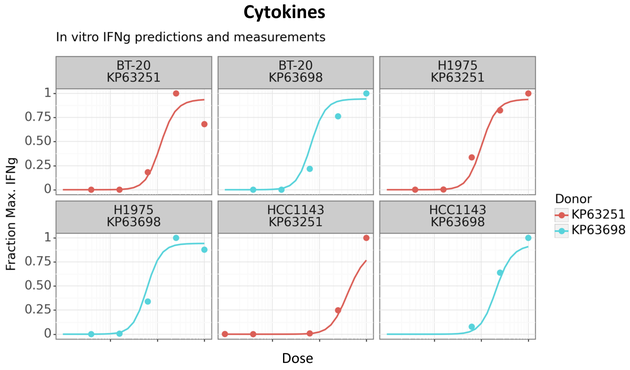


Constructed with the ModeX Therapeutics proprietary modular platform, MDX2001 consists of 2 arms, each containing 1 TAA-binding Fab and one T cell-binding Fab. Drug-mediated immunological synapse formation is a multi-step process that initiates when the molecule binds to any one of its 4 targets (below left). Subsequent binding to a second target on the complementary cell type results in an inter-cellular molecular crosslink that promotes synapse development, cytokine release and destruction of the target cell. The model additionally captured bivalent binding to CD3 and CD28 on the same T cell.

Calibration to *in vitro* Data

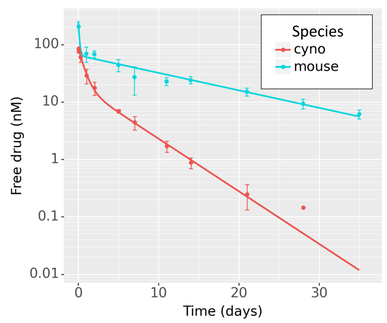
A single model was used to capture the relationship between drug binding and cytolytic and cytokine-release activity. These were modeled as monotonically increasing functions of the number of cross-linked molecular bridges per T cell. Parameter values for cell killing and cytokine release functions were determined by fitting the model to fixed-endpoint *in vitro* data using multiple tumor cell lines and T cell donors.



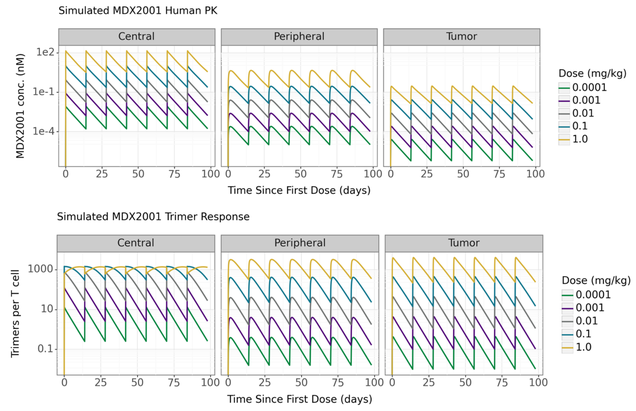


Calibration to Preclinical PK

Pharmacokinetic (PK) parameters for the clinical model were allometrically scaled from parameters that fit a 2-compartment preclinical PK model.

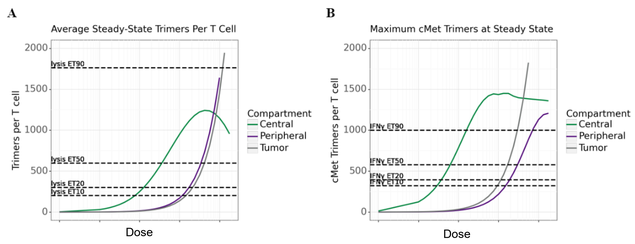


Human model



A 3-compartment human model was developed and assigned parameters from clinical literature and from preclinical fits. A range of IV doses was simulated (above) to assess efficacy and safety.

FIH dose projection



Using both “cross-cell bridging complex-based” metrics as well as exposure-based approaches for evaluating safety with regard to cytokine release. The QSP approach justified a higher EC10 of IFNγ release in the human model.

Using a similar approach to assess an efficacious dose with cytotoxicity, the EC90 of *in vitro* cell killing activity in the tumor was used to inform potential efficacious doses in the human model.

	Based on IFNγ Release		Based on Cell Lysis	
	EC_{10}		EC_{90}	
Dose metric	Max concentration in blood	Max cross-cell bridge complex per T cell in blood	Average concentration in tumor	Average cross-cell bridging complex per T cell in tumor
Target value	*41 pM*	*322*	*166 pM*	*1764*

Reference

Flowers D, et al. *A next generation mathematical model for the in vitro to clinical translation of T-cell engagers.* Journal of Pharmacokinetics and Pharmacodynamics (2023) 50:215–227. http://doi.org/10.1007/s10928-023-09846-y

QSP modeling enables harmonization of the preclinical data and physiological system parameters to predict a first-in-human dose for a tetraspecific T cell engager.

The dose projections are based on quantitative metrics to guide safety and efficacy doses provided by a single modeling framework.

Scan me

Want to learn more about model informed drug development? << Scan Here