First-in-human dosing model for MDX2004, a novel trispecific CD3xCD28/4-1BB antibody-fusion protein for advanced malignancies

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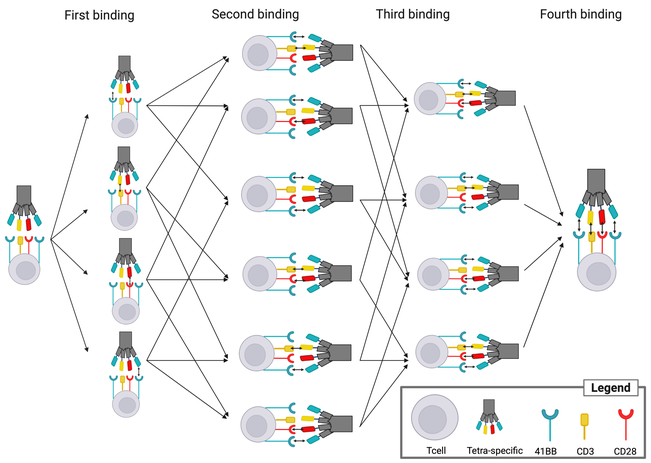
Overview

MDX2004 is a trifunctional antibody-fusion protein that binds to CD3, CD28 and 4-1BB on human T cells. To inform the first-in-human dosing of MDX2004 for solid tumors, we developed a systems pharmacology model to address the complexities in translating a high valency T cell stimulant 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 trispecific T cell activator that binds CD3, CD28 and 4-1BB on T cells.
- QSP model predicts bound receptors per T cells as a model-derived biomarker for clinical translation and identifies CD3 binding as the key dosing metric.
- A conservative starting dose was chosen to de-risk potential for on-target toxicity while informing escalation path to efficacious doses.

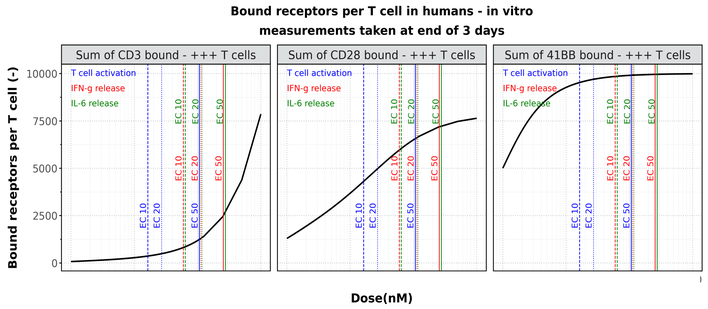
Computational model structure



Constructed with the ModeX Therapeutics proprietary MSTAR platform, MDX2004 recognizes CD3, CD28, and 4-1BB on human T cells. Anti-CD3 provides the primary signal for T cell activation while anti-CD28 delivers the secondary signal for enhanced T cell activation, survival, and proliferation, supporting robust and healthy T cell availability for effective anti-tumor activities. MDX2004 also contains 2 trimeric 4-1BB ligands (4-1BBLs) to confer additional signaling via 4-1BB on T cells for more durable T cell responses through the expansion of memory T cells and stem-like T cells. The developed model captured the cis-binding to targets on the same T cell.

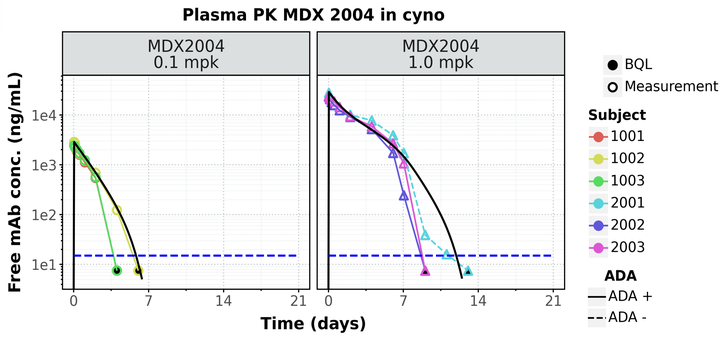
Binding dynamics

The *in vitro* model was used to simulate number of bound receptors per T cells (#BRPTC) at different ECs (10, 20 and 50) of: a) T cell activation, b) IFN-γ release and c) IL-6 release *in vitro* assays. In addition to the human *in vitro* model, an *in vivo* mouse model was used to simulate # BRPTC at doses where tumor growth inhibition was observed. These # BRPTC were used as a metric in the human *in vivo* dose response simulations to project starting and efficacious dose.

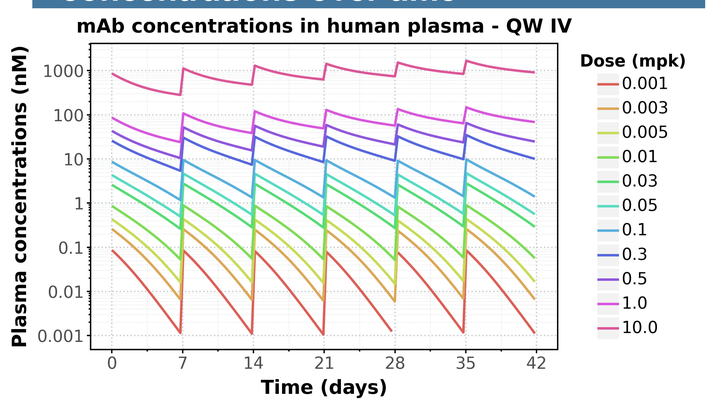


Calibration to NHP pharmacokinetics

Pharmacokinetic (PK) parameters for the human model were allometrically scaled from parameters that fit cynomolgus monkey preclinical PK model.

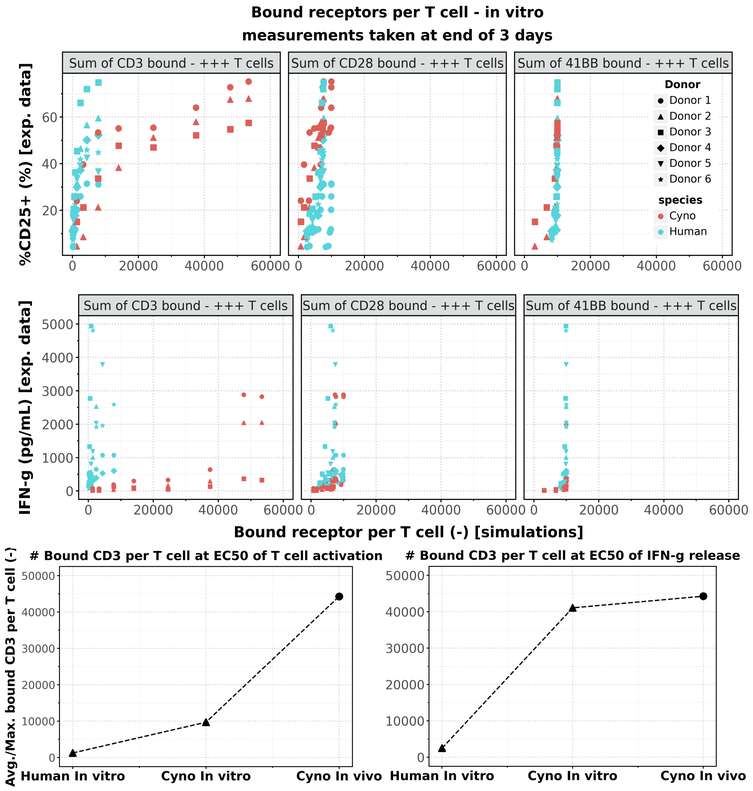


Simulations of human plasma concentrations over time



Differential CD3 binding between NHP and humans

Binding to different receptors in these two species show that the slope of predicted CD3 binding vs. observed % of CD25+ T cells as well as IFN-γ are different between humans and cynomolgus monkeys. In addition, fewer bound CD3 receptors have higher effect of T cell activation and IFN-γ release in human than in cynomolgus monkeys.



Analysis showed that human cells *in vitro* were more sensitive to cytokine release in comparison to NHP *in vitro* and *in vivo*. Accordingly, the human cell based binding metrics (bound receptors per T cells) were used, driving a lower dose than the animal models suggested. Binding metrics obtained by simulating the *in vitro* QSP model in humans, and the *in vivo* QSP model in mice were used to predict the starting and efficacious dose in humans, respectively. Based upon effective concentrations for T cell activation, the model predicted a MABEL of 18.5mg/kg.

Summary of model predicted bound receptors per cell by key assay thresholds

Assay / Study	Binding metric	Bound receptors per T cell
EC_{10} of T cell activation in human in vitro PBMCs	Maximum of sum of CD3 bound	363 bound CD3
Tumor growth inhibition observed at 250 ug/kg in in vivo mouse studies	Average of sum of 4-1BB bound	9,847 bound 4-1BB

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 novel trispecific T cell activator.

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

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