Optimizing first-in-human dose for HPN536, a T-Cell Engager Targeting Mesothelin: comparison of MABEL PK-driven approach and mechanistic translational PK/RO/PA modeling

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Introduction

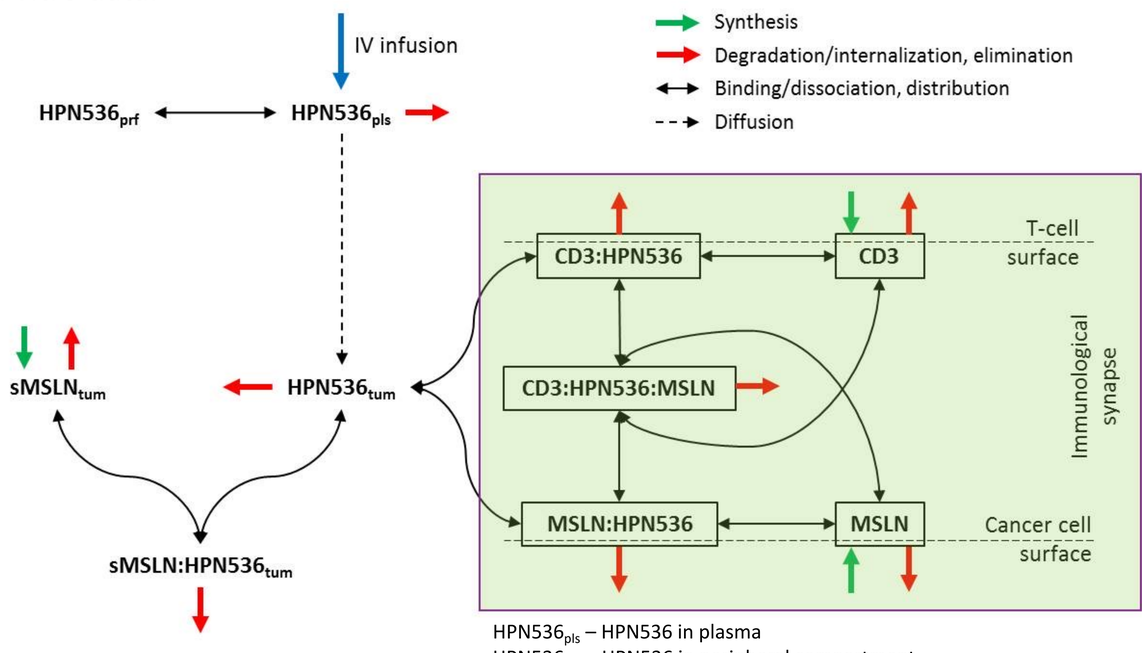
HPN536 is a 53-kDa, trispecific, T-cell-activating protein-based construct, which binds to MSLN-expressing tumor cells, CD3 on T cells, and to serum albumin. The minimal anticipated biological effect level (MABEL) approach is recommended for determining the safe clinical starting dose for T-cell engagers (TCE). However, this method can sometimes yield a low minimal recommended starting dose (MRSD) resulting in treatment of patients with sub-therapeutic doses and multiple dose escalations [Saber et al 2017]. Objectives:

1. To predict the MRSD for HPN536 utilizing a comprehensive approach that integrates mechanistic translational pharmacokinetic (PK), receptor occupancy (RO), and pharmacological activity (PA) modeling.
2. To compare this predicted MRSD with that calculated using the MABEL PK-driven approach.

Model Description

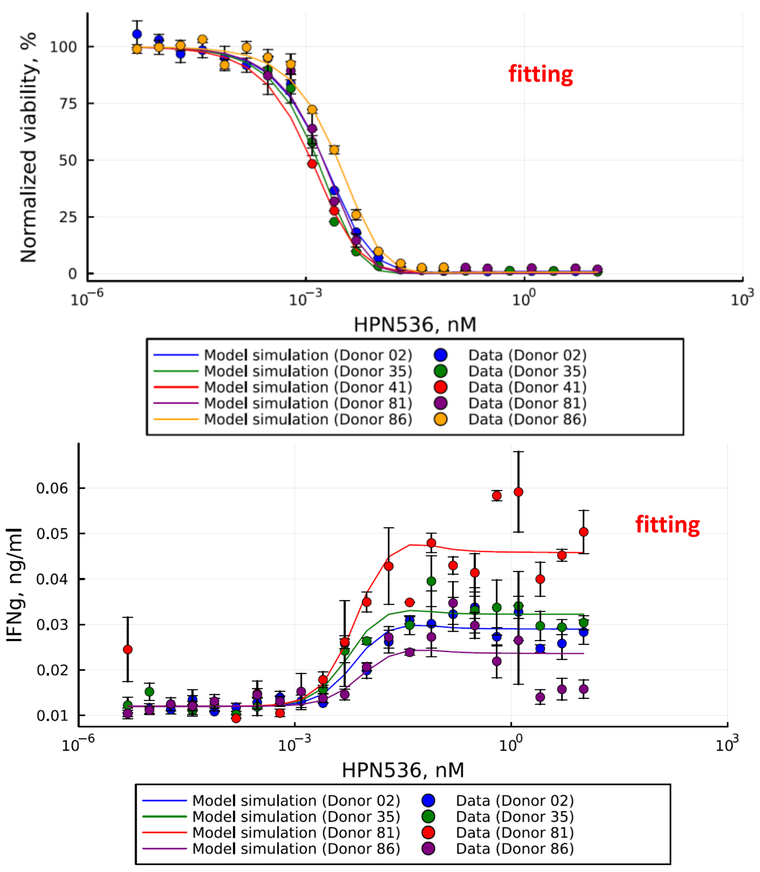
PK/RO model includes:

- 2-compartmental PK model.
- Mechanistic modeling of HPN536 transport into the tumor.
- Formation of trimer complex in immunological synapse via binding of HPN536 with MSLN expressed on cancer cells and CD3 expressed by T-cells.
- Binding of HPN536 with soluble MSLN (sMSLN) in the tumor.
- PA is described as a function of trimers (CD3:HPN536:MSLN) and EC50 fitted against in vitro data.



$HPN536_{pls}$ – HPN536 in plasma
$HPN536_{prf}$ – HPN536 in peripheral compartment
$HPN536_{tum}$ – HPN536 in tumor

- **In vitro model** describes binding of HPN536 with MSLN and CD3, formation of trimers (CD3:HPN536:MSLN) in immunological synapse, synthesis and degradation/internalization of free and bound receptors as in PK/RO model.
- PA is described as a function of trimers (CD3:HPN536:MSLN) using Hill equation. EC50 (expressed as trimers number) values were fitted for each in vitro assay: T-cell dependent cytotoxicity (TDCC), IFNg, TNFa, and CD25. Hill coefficients for cytokines were 2.

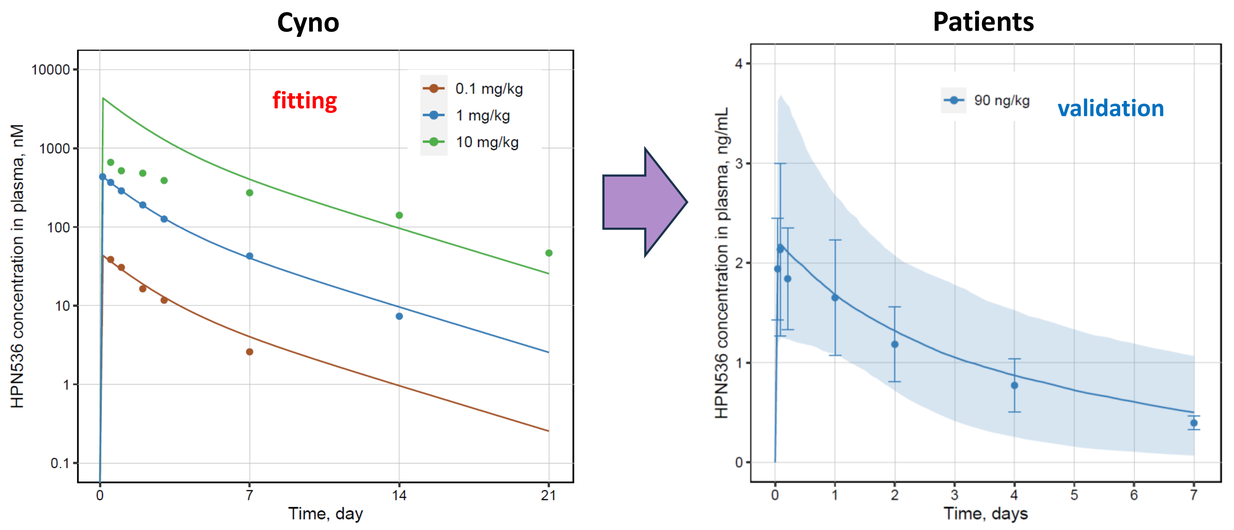


In vitro model fitting examples: specific lysis of MSLN-expressing ovarian cancer cells by T-cells in the presence of HPN536 and IFNg secretion by T-cells in the presence of MSLN-expressing ovarian cancer cells and HPN536.

Fitted EC50 values were in the range 500-900 trimers.

Cyno-to-Human PK translation

- Cynomolgus monkey (cyno) PK data were fitted with standard 2-compartmental PK model.
- PK was translated from cyno to human using allometric scaling approach.
- PK data in cancer patients were used to validate the translation. See example below:



Dots – experimental data (mean +/- SD)
Solid lines – model simulations (median with 95% CI)

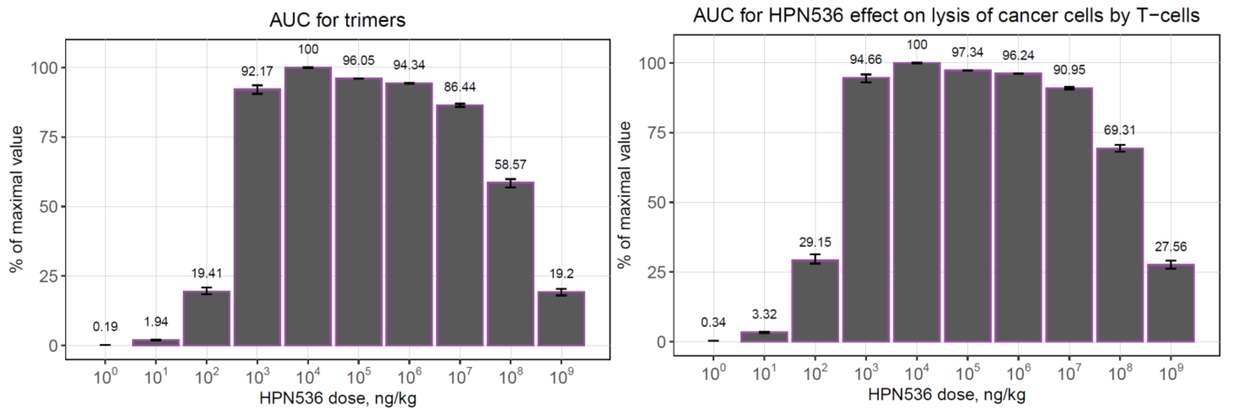
Data were taken from [Molloy et al 2021] & [Harpoon Therapeutics Investor Presentation June 2020]

Results

- Predicted MRSD range was based on doses resulted in 20%-50% PA.
- **MRSD range predicted by MABEL PK-driven approach was significantly lower than those predicted by the model**: 1 - 23 ng/kg vs 35 - 228 ng/kg.
- **Available first-in-human trial information** [Harpoon Therapeutics Investor presentations]. Starting dose of HPN536 was 6 ng/kg. CRS grade 3 occurred in one patient at dose 54 ng/kg without premedication with dexamethasone. Premedication is applied to all doses starting from 68 ng/kg. Maximal tolerated dose (MTD) was not reached even at dose 3600 ng/kg. No responders were reported.
- Predicted MRSD range was lower (18 – 114 ng/kg) when binding of HPN536 with soluble MSLN was turned off in the model.
- Concentration of soluble MSLN in the tumor and % of MSLN-positive cancer cells are very important parameters affecting dose predictions. However, the data are very limited.

Assay	Dose by MABELPK-driven approach {ng/kg}	Dose by mechanistic modeling {ng/kg}	Dose by mechanistic modeling {ng/kg} (w/o sMSLN)
TDCC	0.93 – 3.71	45 – 179	24 – 92
TNFa	7.35 – 11.6	86 – 172	45 – 88
IFNg	14.22 – 22.58	113 – 228	59 – 114
CD25	2.29 – 3.64	35 – 138	18 – 71

- AUC values were calculated for the simulated curves to evaluate dose dependence of trimers number and PA (effect of HPN536 on specific lysis) in cancer patients.
- 10 - 100 ug/kg resulted in maximal number of trimers and PA in the model.
- Auto-inhibition phase of bell-shaped dose-response relationship was predicted to start at dose 10 mg/kg (=10^7 ng/kg) or higher.



Conclusions

1. Mechanistic translational model predicted higher MRSD range than conventional MABEL PK-driven approach (based on PA 20% - 50%): 35 – 228 vs 1 – 23 {ng/kg}.
2. Advantage of the modeling approach is mechanistic description of antibody distribution to the tumor, antibody binding with its target(s) including trimer formation, etc.
3. Maximal number of trimers and PA were predicted at doses 10 – 100 ug/kg (~ 0.7 – 7 mg), whereas auto-inhibition phase of bell-shaped dose-response relationship was started at dose 10 mg/kg or higher.