Quantitative Systems Pharmacology (QSP) enables research and translation of AMP01, a novel next generation anti PD1 bispecific that amplifies and redirects endogenous IL15 to PD1 high expressing T Cells, maximizing efficacy and therapeutic index

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ABSTRACT

Background: Safe and efficacious dosing of clinically validated cytokines is exciting but remains elusive. The primary challenge has been therapeutic index (TI), i.e., providing sufficient cytokine tumor exposure while minimizing exposure elsewhere to avoid systemic immune activation. Prior attempts to address this, including engineered IL15-fusion proteins (FP) and αPD1 x IL15 targeted FPs, have been limited by toxicity and development of anti-drug antibodies. AMP01, an AMPLIFY•R™ anti PD1 x anti IL15 bispecific biologic, is a novel solution to this challenge. It is designed to capture and redirect endogenous IL15 to PD1 high expressing T Cells, thus providing PD1 inhibition and targeted delivery of IL15 to the tumor and tumor microenvironment. By design, AMP01 promises to be a truly improved next generation PD1 program with both checkpoint inhibitory and targeted immune agonistic activity.

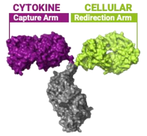
Method: We developed a QSP model by leveraging AMP01 in vitro, mouse, and non-human primate data, and previously published anti PD1, recombinant IL15, and PD1 x IL15 - fusion protein pharmacokinetic (PK) and pharmacodynamic (PD) data. The model incorporates complex biology and drug MOA, e.g., IL15 synthesis and clearance; IL15 soluble and membrane bound receptor binding; alterations in IL15 exposure upon AMP01 engagement; IL15 mediated NK and T Cell dynamics; PD1 PK and PD1 inhibition; and dynamic target mediated drug disposition or clearance (TMC) events. The model described the PK and observed cell dynamics in the plasma, and simulated effects in tumor and other peripheral tissue of comparator therapeutics and AMP01. Model development and simulations were performed using QSP Notebook (Certara).

AMP01: DESIGN OF A PD-1 DIRECTED IL-15 AMPLIFY•R™

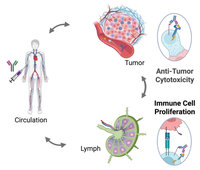
We have designed a bispecific antibody capable of co-engaging the T and NK cell stimulating cytokine, IL-15, and the immune checkpoint, PD-1.

Increase Efficacy
Selective Engagement of CD8+ T-cells
PD-1 mediated avidity for IL-15 receptor engagement can drive preferential activation of tumor primed T-cells.

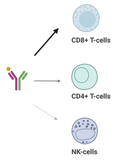
Reduce Toxicity
Avoid Systemic Immune Engagement
Modulation of IL-15 affinity for receptor chains upon Amplify•R mediated presentation biases against systemic immune activation while enhancing desired exposure.



AMP01: Modulates IL-15 Bio-Distribution & Exposure



AMP01: Redirects IL-15 Bias



QSP MODEL DIAGRAM

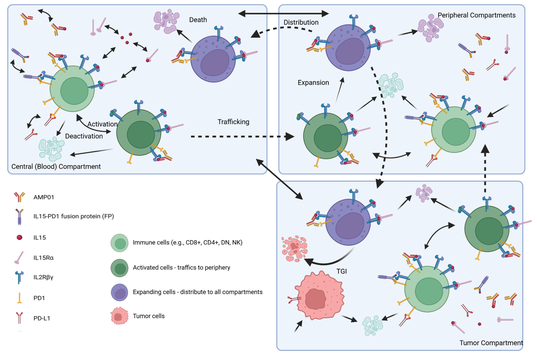
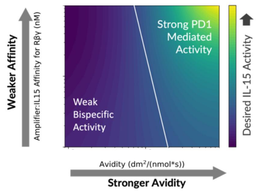


Figure 1. QSP Model Diagram: Summary of reactions and states:

- Immune cells: CD8+, CD4+, DN (Double Negative; CD8-CD4-CD3+ T Cells), and NK cells
- Immune cell states: resting, activated (for transit to the periphery (e.g., lymph)), expanding from activated immune cells in the periphery (e.g., lymph)
- Resting immune cell synthesis in the periphery (e.g., lymph) and death
- Rβγ mediated immune cell activation and trafficking
- Rβγ mediated proliferation of expanding immune cells via activated cells in the periphery (e.g., lymph)
- Transit of expanding cells into other compartments
- Deactivation of activated immune cells back to resting
- Death of activated and expanding cells
- Tumor cell death via activated immune cells
- Decreased / no tumor cell death via PD1:PD-L1
- Distribution of therapies, ligands, and cells across compartments
- Complex formation and release (e.g., IL15 + Rβγ <--> IL15:Rβγ)
- sRα, IL15, PD-L1 synthesis
- IL15, sRα, IL15:Rα, PD-L1 first order clearance
- Rβγ and PD1 synthesis and turnover on immune cells (where appropriate)
- IL15, IL15:IL15Rα, IL15:PD1 FP, AMP01 TMC via Rβγ
- PD-L1, AMP01:PD1, and IL15:PD1 FP TMC via PD1
- AMP01 and AMP01:IL15 first order clearance and TMC via Rβγ
- AMP01 and IL15:PD1 fusion protein first order clearance and TMC via Rβγ
- IV administration of AMP01, IL15:PD1 FP (e.g., IL15PD1 TaCk Xencor/Genetech or Pfizer P-07209960), or rhIL15

QSP GUIDES OPTIMIZATION OF AMP01

A: Bispecific Mediated Redirection of IL15: Tumor vs Systemic Activity



B: CD8+ Cells Have Lower Rβγ Expression vs NK Cells[1]

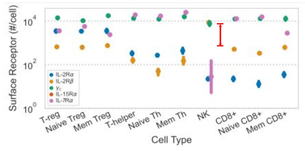
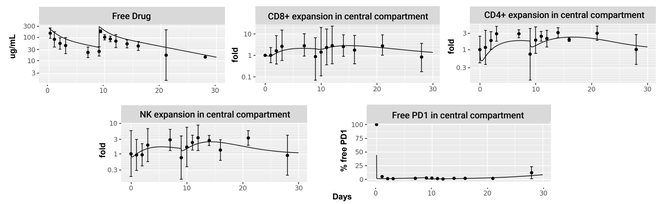


Figure 2. QSP Model Diagram: Summary of reactions and states:

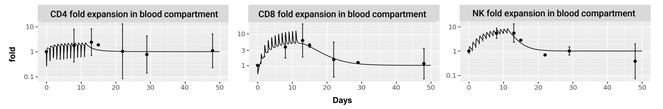
- The QSP simulations suggests weaker AMP01 binding affinity to Rβγ improves PD-1 mediated IL-15 activity.
- The QSP model analysis informed AMP01 design and candidate selection by predicting the optimal AMP01 binding characteristics to maximize TI and efficacy by selectively targeting PD1 high, Rβγ expressing immune cells while maintaining high PD1coverage in the tumor selectively

QSP MODEL BENCHMARKING IN NHP: DATA VS SIMULATIONS

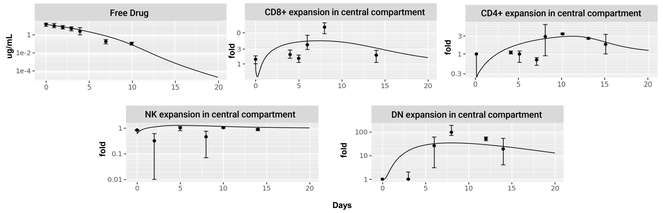
A: AMP01, (AMPLIFY•R™ IL15 and PD-1 blockade and redirection), dosed at 10 mpk on day 0 and 9 in NHP[2]



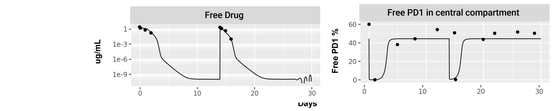
B: rhIL15 dosed at 0.05 mpk daily for 12 days in NHP[3]



C: IL15PD1 TaCk, an IL15:PD1 FP, dosed at 0.6 mpk on day 0 in NHP[4]



D: Pfizer PF-07209960, an IL15:PD1 FP, dosed at 0.1 mpk at days 0 and 14 in NHP[5]



E: Pfizer PF-07209960 dosed at 1.0 mpk at day 0 in NHP[5]

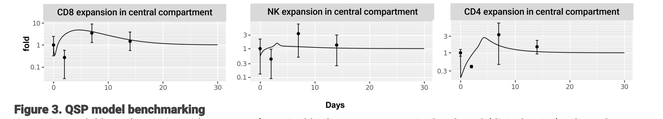
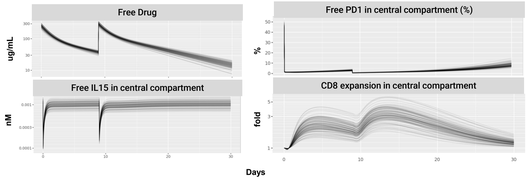


Figure 3. QSP model benchmarking
One QSP model based on MOA with one set of nominal biology parameters is developed (digital twins), where drug parameters are set per therapy. The initial conditions were set to match known conditions (e.g., number of cells, IL15 concentration, sites per cell) and unknown parameters were estimated. The model was calibrated to (A) AMP01 and (B) published rIL15 data, determining cell activation, extravagation expansion, and death rates and TMDD rates. The model was then used to estimate affinities, avidity, and half-life only for C) IL15PD1 TaCk and D) and E) P-07209960. The same model captures the complex biology and PK across different molecualr designs.

Model Diagram designed with https://BioRender.com

QSP MODEL PREDICTIONS

A: Simulated variability: AMP01 dosed at 10 mpk on day 0 and 9 in NHP



B and C: AMP01 preliminary qualitative dose response translation into patients, dosing [drug] mpk Q2W x3

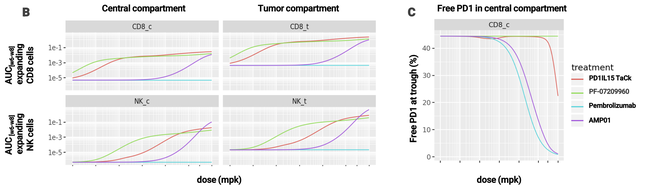


Figure 4. QSP model predictions
A) Simulated variability in NHP. Log normal distributions, centered about the nominal parameter value, with a 10% SD where generated. One hundred virtual NHP PKPD simulations were generated by randomly selecting values from the distributions, then AMP01 was dosed at 10 mpk on day 0 and 9. The simulated variability closely matches the observed variability without individual parameter estimations. Note sIL15 is captured by AMP01, and directed to PD1 high cells, and IL15 returns back to steady-state prior to second dose. Also note that PD1 >90% blocked when AMP01 is dosed at 10 mpk QW2.

B and C) A simple model translation was performed by extending the first order half-life of the therapies, volumes and mass were scaled, and PD1 was set to zero on NK cells, to match human conditions. A dose response curve was generated by simulating Q2W dosing for three doses and B) the AUC of expanding cells in the central and tumor compartments were calculated for w 6-8 and C) PD1 inhibition at week 8 was calculated. Nominal parameters were used for each dose. Note that the model predicts that P-07209960 shows a response at the lowest doses, followed by IL15PD1 TaCk, then AMP01 in the central compartment. IL15PD1 TaCk has a TI between CD8 and NK cells in the central compartment, however, it does not have high PD1 blockade at lower doses. The model predicts that AMP01 has a safer TI profile in the central compartment and can attain PD1 blockade at doses needed for robust cell expansion in the tumor compartment. These are qualitative predictions.

Results: The QSP model 1) informed AMP01 design and candidate selection by predicting optimal AMP01 binding characteristics to maximize TI and efficacy by selectively targeting PD1 high, IL15Rβγ expressing immune cells while maintaining high PD1 coverage in the tumor selectively; 2) clarified how uncertainty and variability in model parameters (e.g., soluble IL15 and IL15Rβγ concentration; membrane bound receptor expression, synthesis and clearance rates; immune cell numbers and dynamics) impacts AMP01 target engagement, mediation of cytokine activity, nonlinear PK, and dosing for simulated variability; and 3) enables *in silico* comparator differentiation to better understand safe and efficacious dosing and variability using simulated cell dynamics in the blood, tumor, and other periphery compartments. This model continues to be developed and will be used to provide first in human dose predictions to impact IND, regulatory decisions, and phase 1 trial design.

CONCLUSION

The QSP model accelerated the design and selection of AMP01, a potentially best in class novel bispecific PD1 therapy with targeted lymphoproliferative action. The model provided insights into the complexity of IL15 mediated immune cell dynamics to better understand safety and efficacy for simulated variability. Early QSP model predictions show that AMP01 has the potential to have superior TI and efficacy over competitor therapies.

References:
[1] Farhat et al., *Cell reports* (2021)
[2] Fogg, et al., *JITC, (2026)*
[3] Lugli, et. al., *Blood* (2010)
[4] Yadav, et. al., *Frontiers in Pharmacology* (2024)
[5] Ji, et. al., *PLOS ONE* (2024)

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