Evaluation and optimization of potential for subasumstat (TAK-981) to overcome rituximab resistance via PK/PD and QSP modeling of antibody dependent cell mediated cytotoxicity

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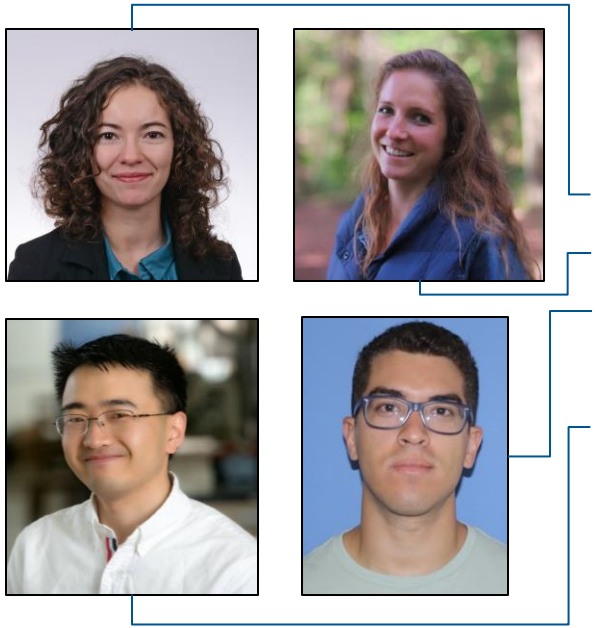
Acknowledgements



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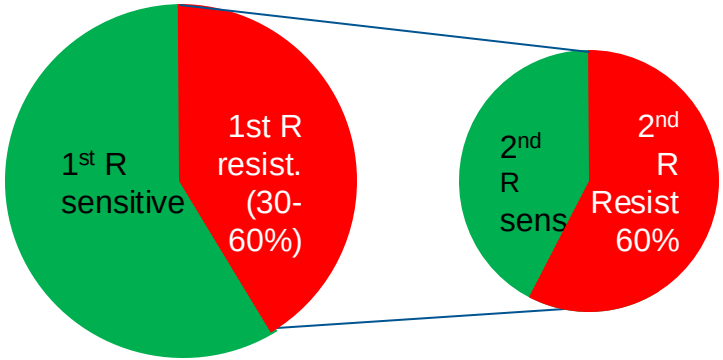
With special thanks to Hojjat Bazzazi, Takeda

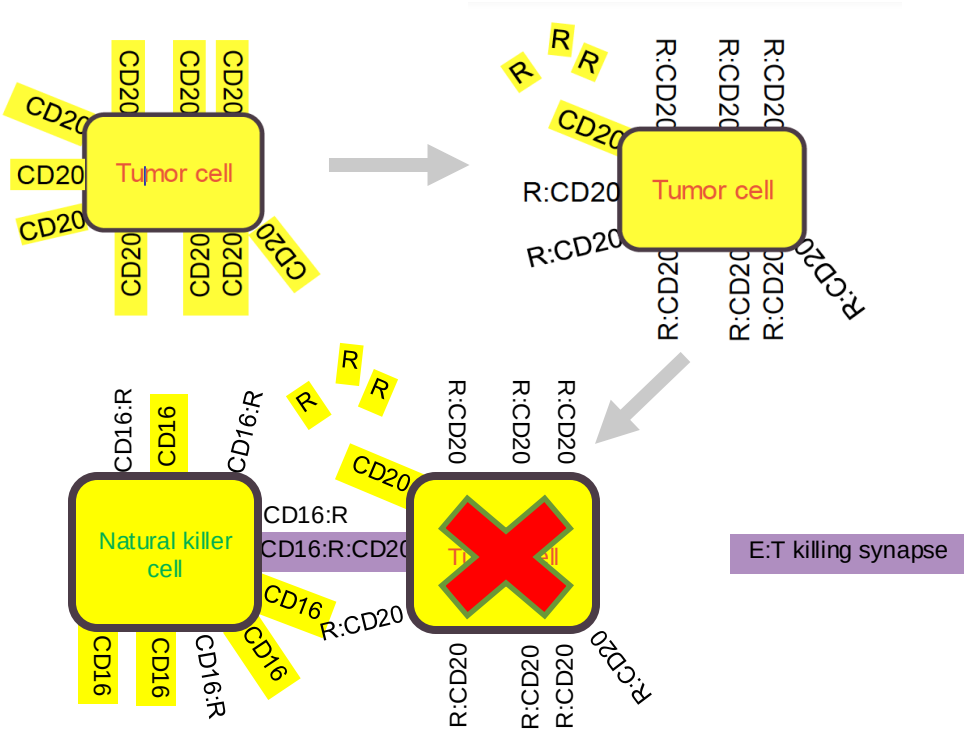
Rituximab (R) resistance remains an unmet need in Non-Hodgkin's Lymphoma (NHL)



R-CHOP 1st line therapy
If cure not achieved, options are limited

Binding of R allows interaction with effector cell via CD16, which leads to Antibody Dependent Cell-mediated Cytotoxicity (ADCC)

R resistance mechanisms include CD20 loss, CD16 loss



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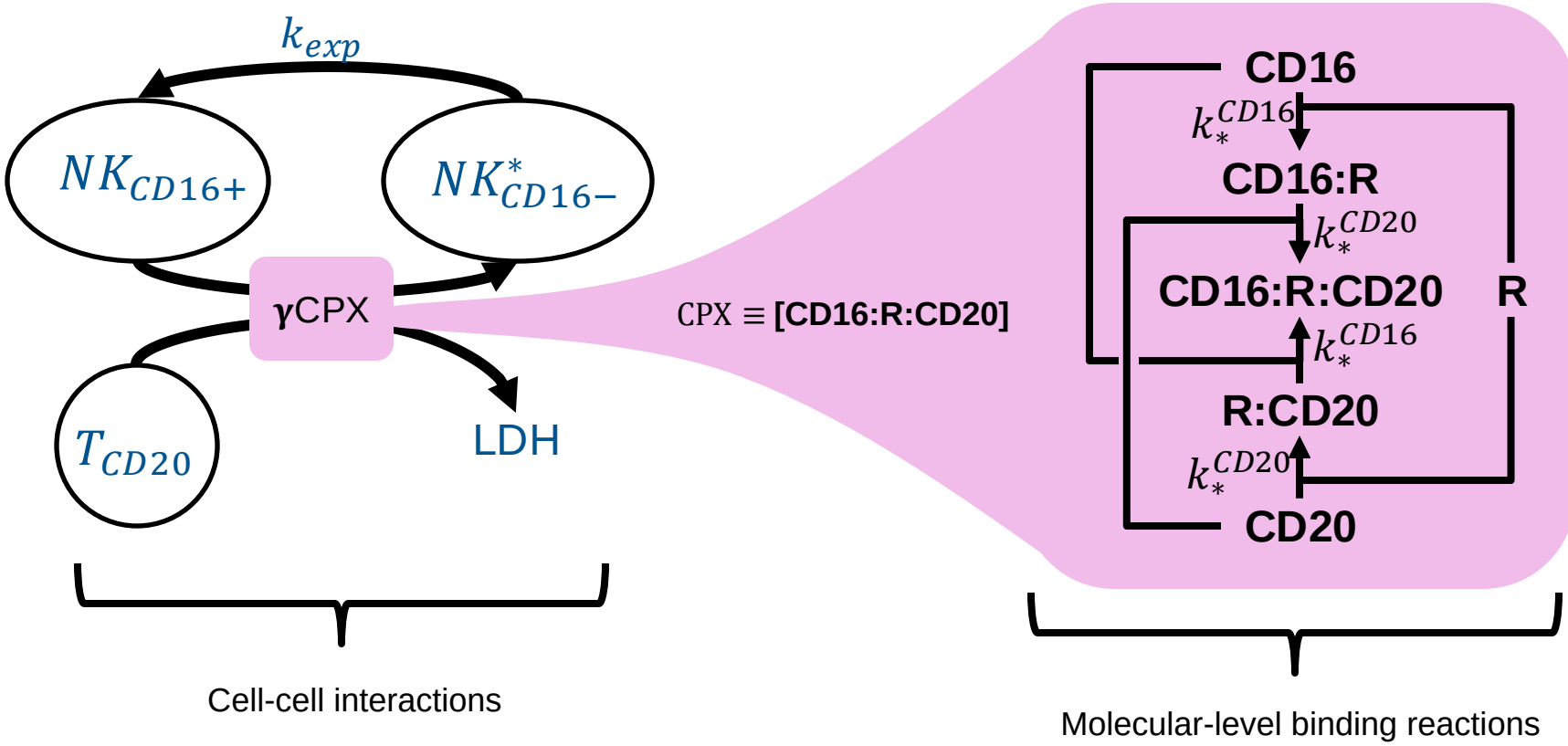
A QSP model of ADCC may be used to simulate mechanisms of RTX resistance and therapeutic mechanisms to overcome resistance

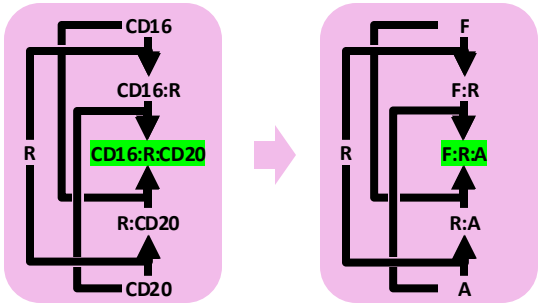


LDH=Lactate DeHydrogenase; CPX = immune synapse ComPleX

Bispecific ODE's

*New notation:

- CD16 → F ~ Fcg receptor
- Rituximab
- CD20 → A ~ Antigen



$$\frac{d}{dt}R = -\frac{1}{h}\cdot k_{FR}^{on}\cdot F\cdot R\ -\frac{1}{h}\cdot k_{RA}^{on}\cdot A\cdot R+\frac{1}{h}\cdot k_{FR}^{off}\cdot FR+\frac{1}{h}\cdot k_{RA}^{off}\cdot RA$$

$$\frac{d}{dt}A = -k_{RA}^{on}\cdot A\cdot R+k_{RA}^{off}RA-\frac{1}{h}\cdot k_{RA}^{on}\cdot A\cdot FR+k_{RA}^{off}\cdot FRA$$

$$\frac{d}{dt}F = -k_{FR}^{on}\cdot F\cdot R+k_{FR}^{off}\cdot FR-\frac{1}{h}\cdot k_{FR}^{on}\cdot F\cdot RA+k_{FR}^{off}\cdot FRA$$

$$\frac{d}{dt}RA = k_{RA}^{on}\cdot A\cdot R\ -k_{RA}^{off}\cdot RA-\frac{1}{h}\cdot k_{FR}^{on}\cdot F\cdot RA+k_{FR}^{off}\cdot FRA$$

$$\frac{d}{dt}FR = k_{FR}^{on}\cdot F\cdot R\ -\frac{1}{h}\cdot k_{RA}^{on}\cdot A\cdot FR-k_{FR}^{off}\cdot FR+k_{FR}^{off}\cdot FRA$$

$$\frac{d}{dt}FRA = \frac{1}{h}\cdot k_{FR}^{on}\cdot F\cdot RA+\frac{1}{h}\cdot k_{RA}^{on}\cdot A\cdot FR-k_{FR}^{off}\cdot FRA-k_{RA}^{off}\cdot FRA$$

Assuming R is not significantly depleted by the reactions (ie, omitting dR/dt equation) gives a closed-form steady state solution

NK ADCC model

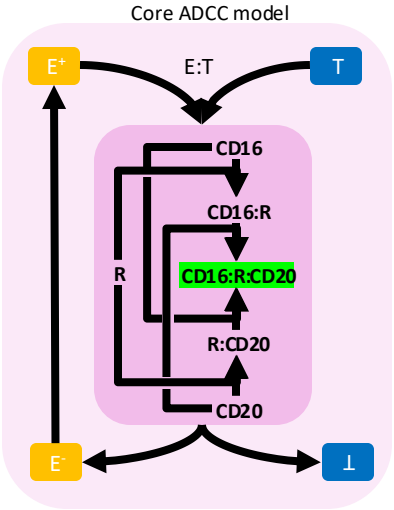
NK cells: $\frac{dN}{dt} = k_{ex}^{N}(N_0 - N) - r_N(\gamma_N f_N + \delta_N)N^{r_N}T$

Tumor: $\frac{dT}{dt} = gT - (\gamma_N f_N + \delta_N)N^{r_N}T$

$f_N = f(RTX, CD16_N, CD20_T)$, the equilibrium solution to bispecific trimer ODE's

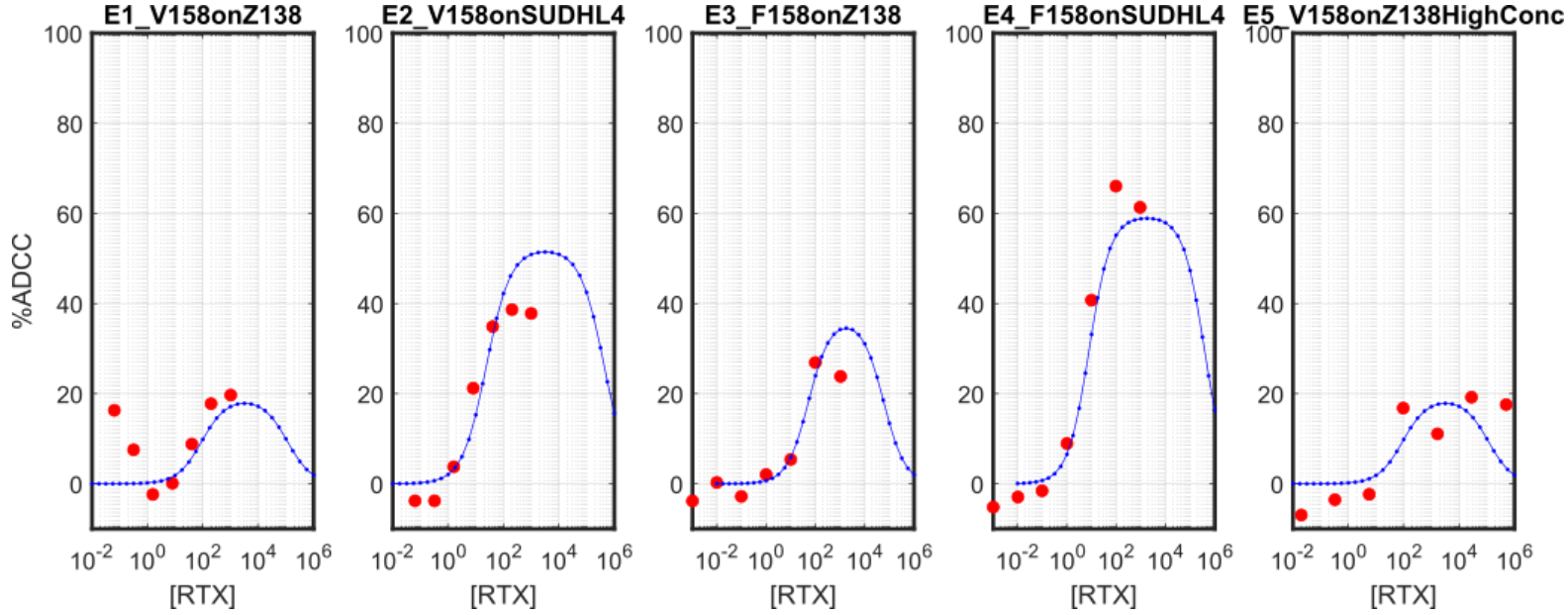
γ_N = ADCC intensity factor = $\gamma_N(CD69) = \gamma_N^0$ for unstimulated NKs

δ_N = AICC intensity factor = $\delta_N(CD69) = \gamma_N^0$ for unstimulated NKs



Model parameters can be calibrated to describe *ex vivo* data in multiple cell lines and donor CD16 SNPs

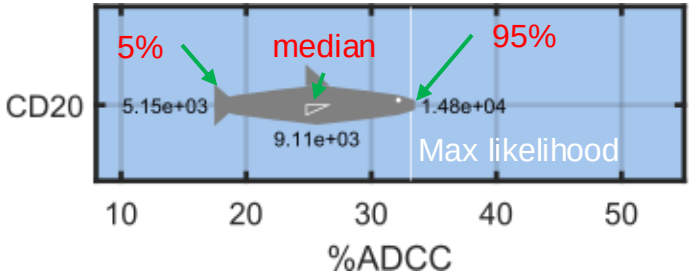
Cell line:	Z138	SUDHL4	Z138	SUDHL4	Z138
CD16 SNP:	V158	V158	F158	F158	V158

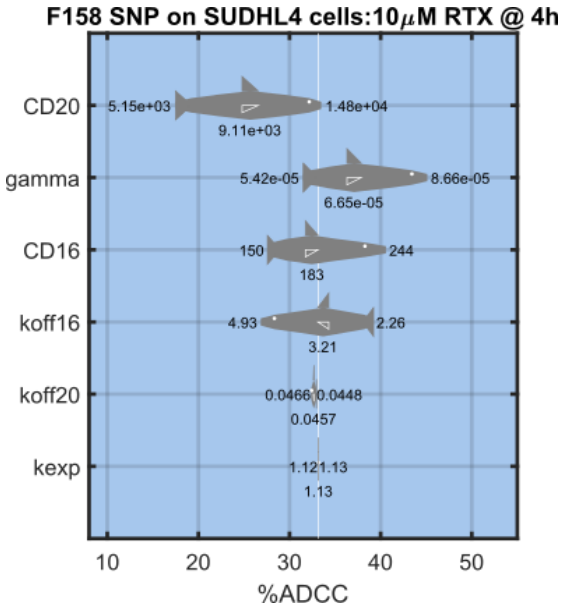


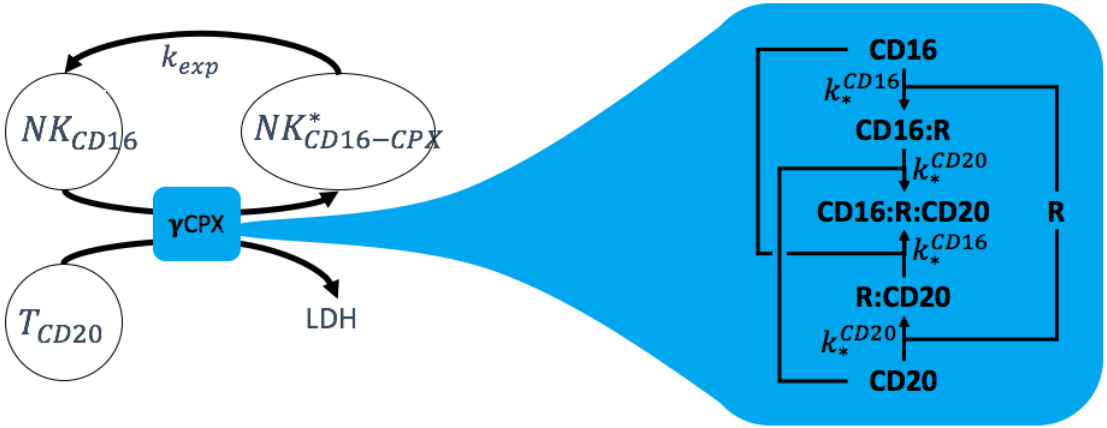
ng/mL

In vitro data: Herter et al 2013

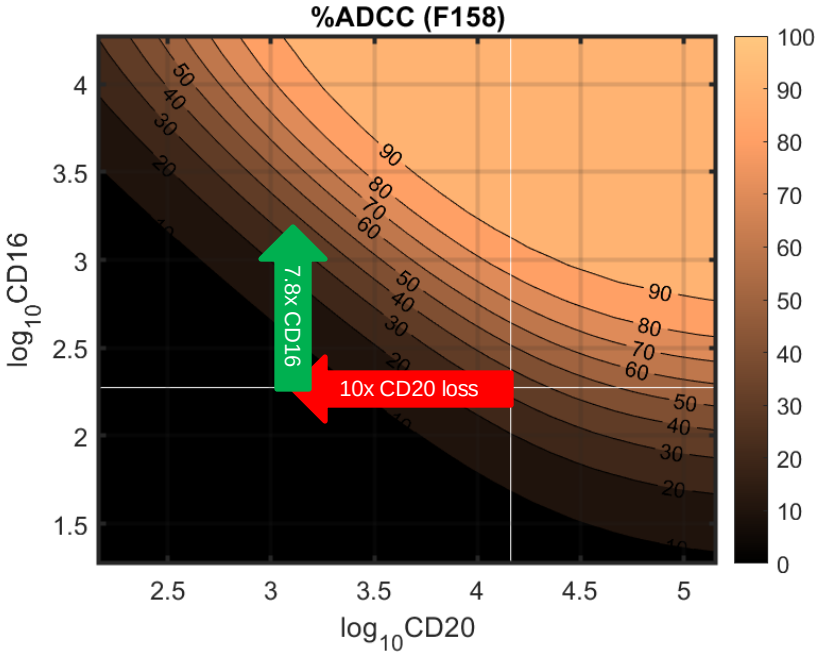
Tumor CD20 is the most sensitive (uncertainty-weighted) driver of ADCC

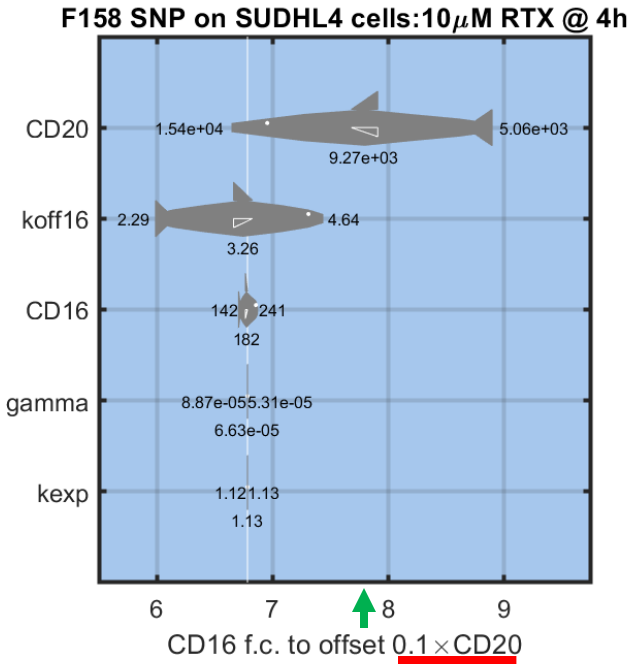




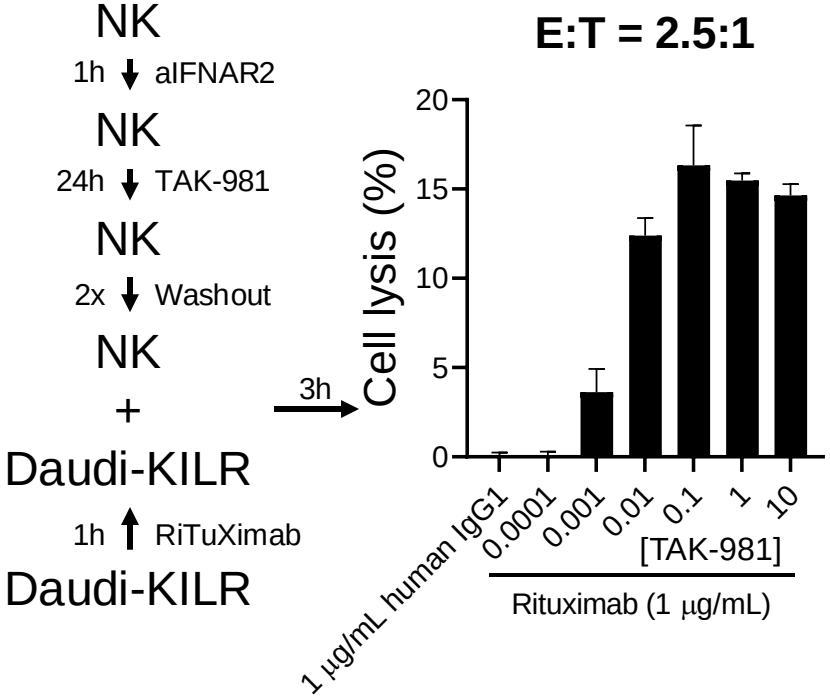


Model predicts ~8-fold increase in CD16 on NK cells can offset 10-fold CD20 loss





Questions/motivation for QSP modeling TAK-981 effects on Rituximab combo



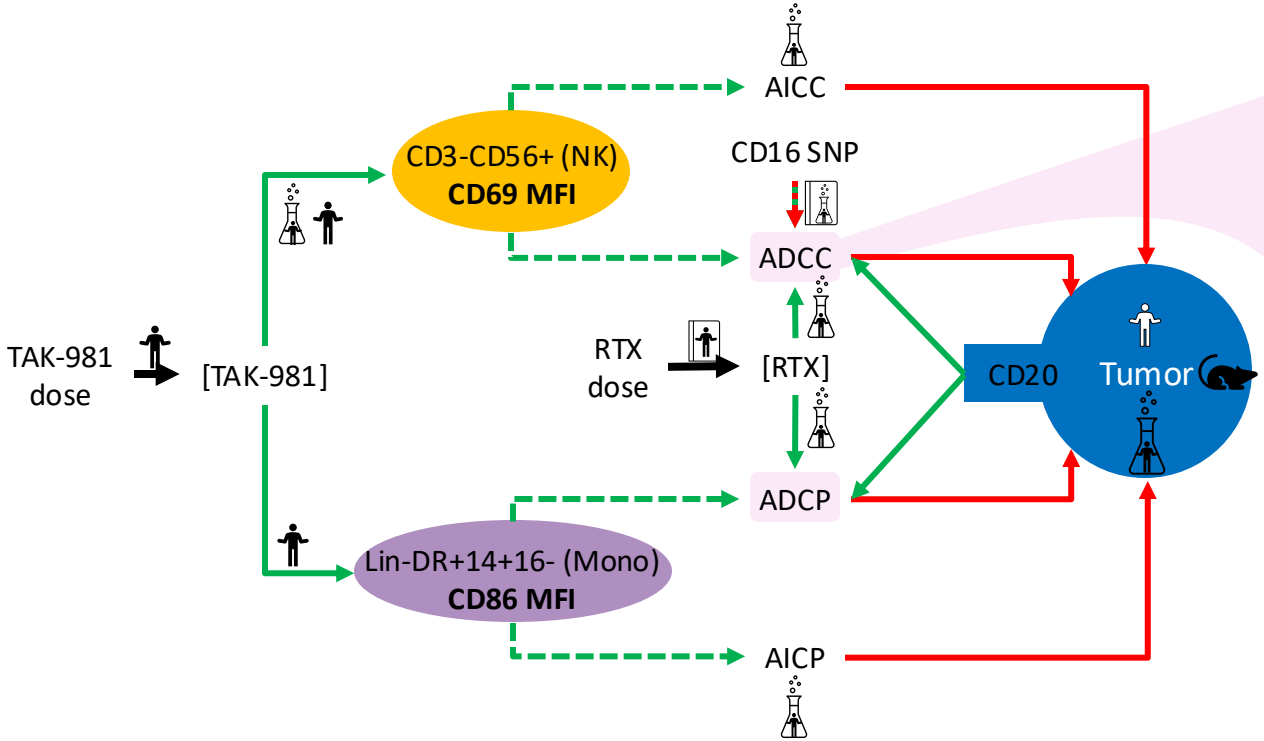
Nakamura et al, Blood 2022

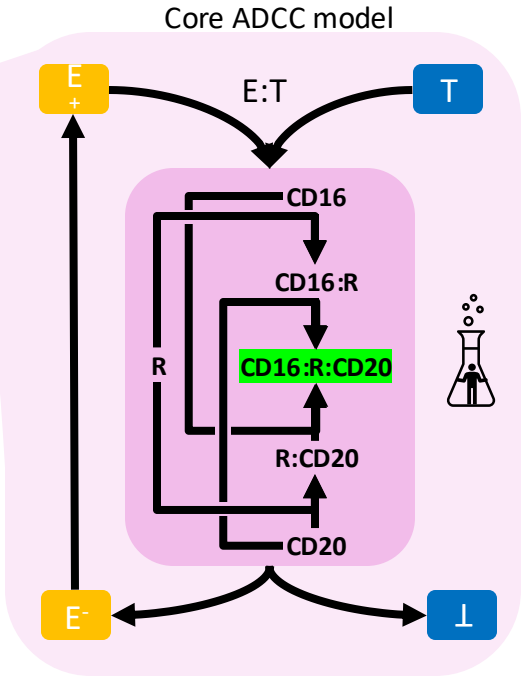
Small molecule SUMOylation inhibitor TAK-981 (subasumstat) enhances NK-mediated ADCC/AICC and Mac-mediated ADCP/AICP in presence / absence of rituximab (RTX) in human ex-vivo experiments.

1. In vitro killing → Can TAK-981+RTX deliver clinical responses in RTX R/R?
2. Optimal dose and schedule for TAK-981 + RTX?
3. Which RTX R/R patients benefit from +TAK-981?

RTX = Rituximab; NK = Natural Killer cell; Mac = Macrophage; R/R = Relapsed/Refractory

QSP model combines the ADCC 'core' model with clinical PK/PD models





Core ADCP model is identical but with CD64 instead of CD16

Human ex vivo

Human in vivo

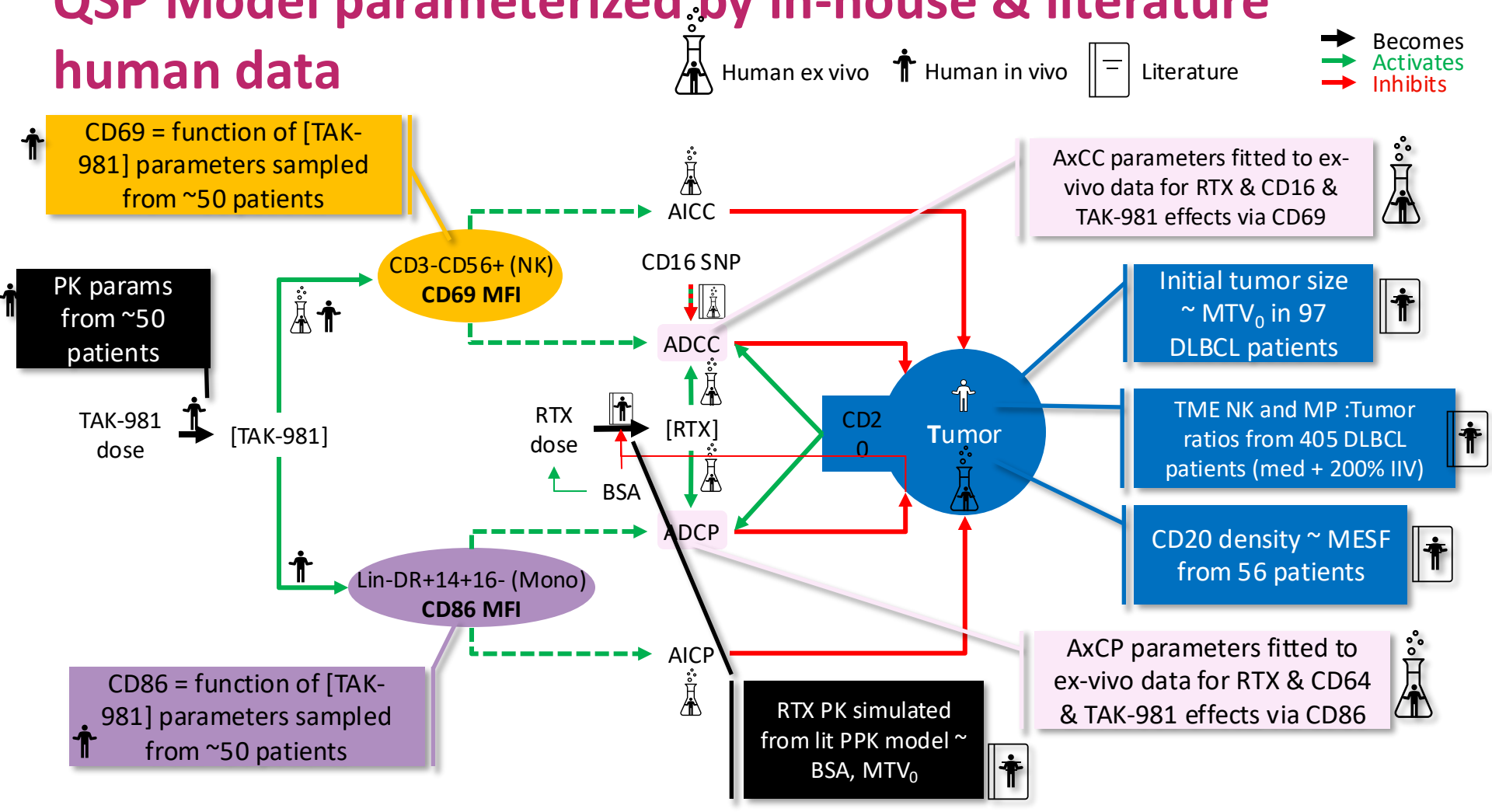
Literature

Becomes

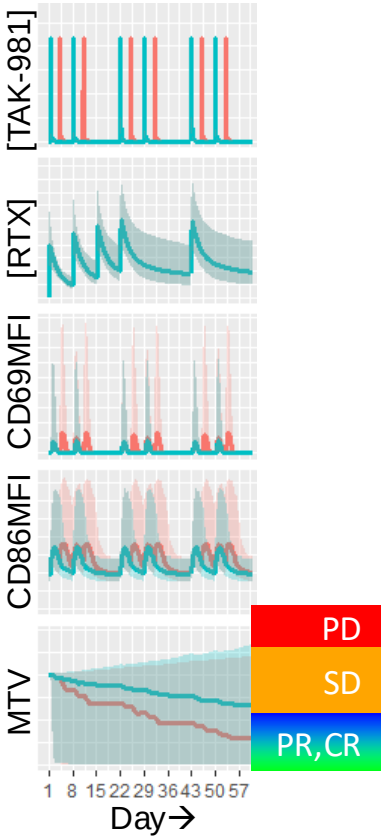
Activates

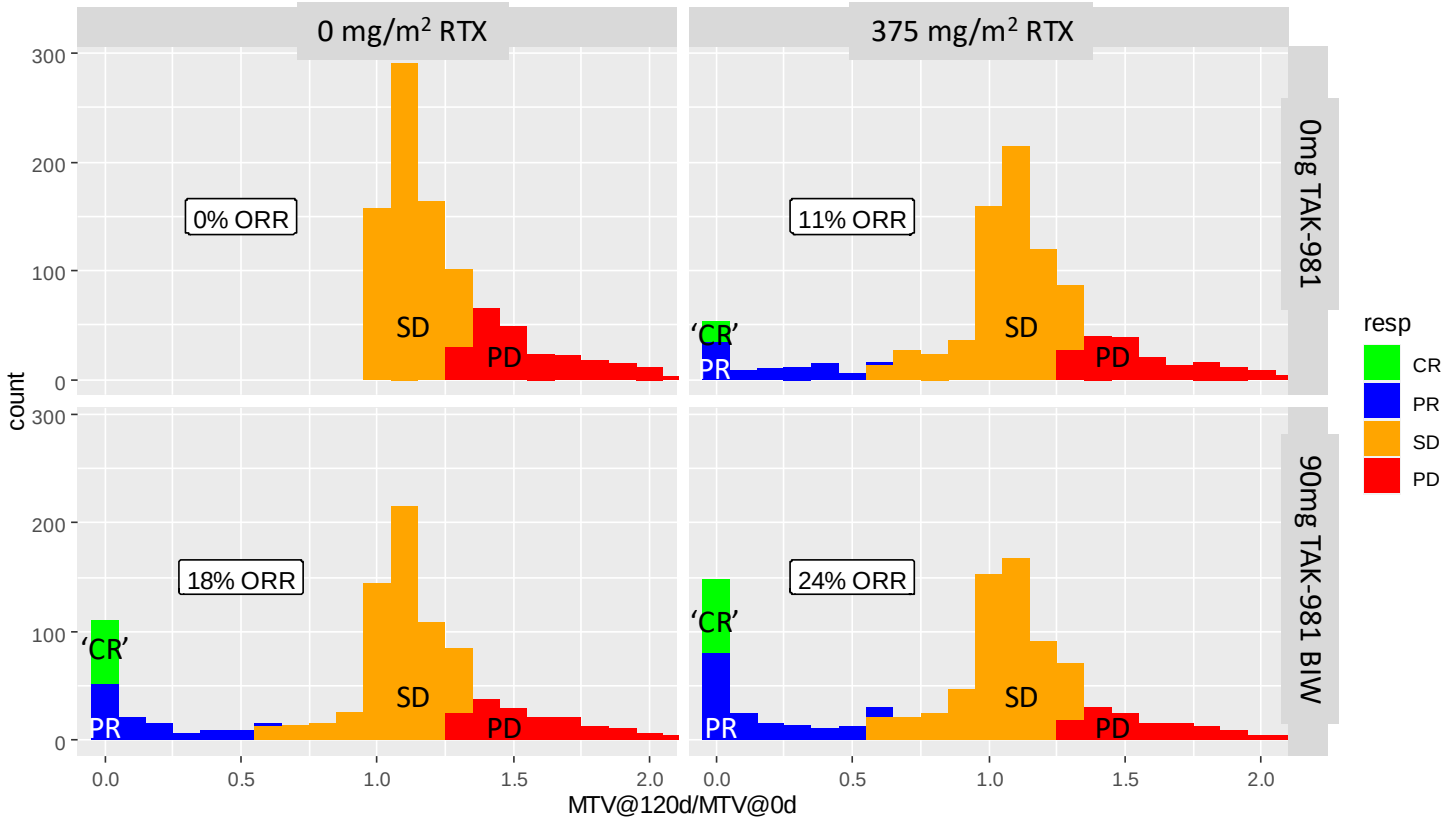
Inhibits

QSP Model parameterized by in-house & literature human data



Without additional parameter calibration, QSP model predicts 0% spontaneous Overall Response Rate (ORR), 11% ORR with Rituximab single agent

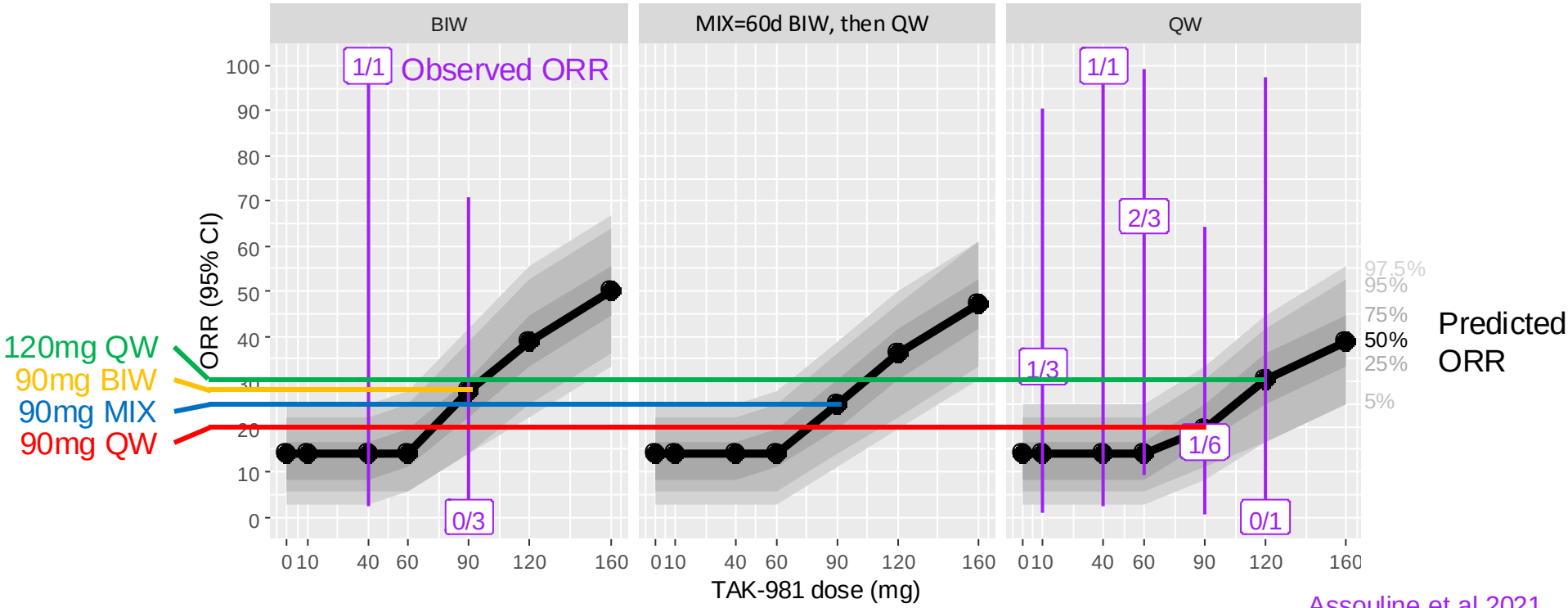




MTV = Metabolic Tumor Volume; PD=Progressive Disease; SD=Stable Disease; PR/CR = Partial/Complete Response; ORR = Objective Response Rate

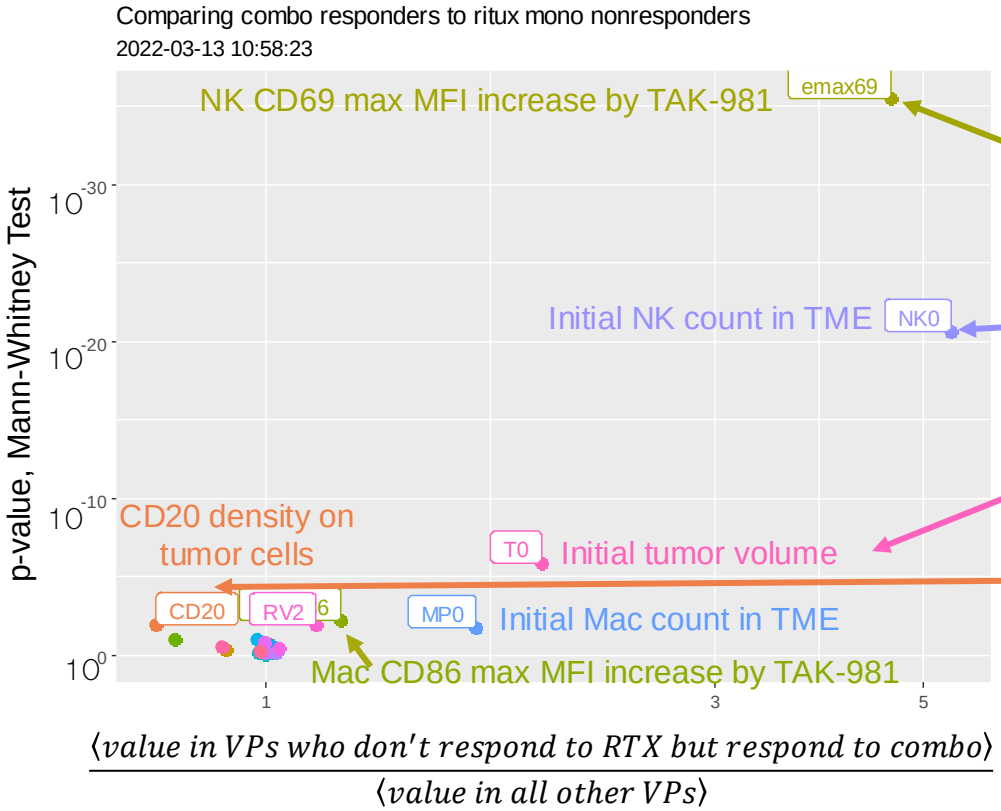
Model predicts ORR for 120mg QW > 90mg BIW~90mgMIX > 90mg QW

Model-predicted ORR by schedule and dose (50/90/95%PI in a 36-patient cohort)
Observed ORR by schedule and dose (with 90% Clopper Pearson CIs)



Assouline et al 2021

How do virtual patients (VPs) who benefit from TAK-981 added to rituximab differ from the rest? *Synthetic Volcano Plot (preliminary results)*



Virtual Patients benefitting from RTX + TAK-981 vs RTX:

- *5x greater NK CD69 increase by 981*
- *5x greater initial NK count in TME*
- *2x larger tumors at baseline*
- *25% lower CD20 density on tumor cells*

Questions/predictions for QSP modeling TAK-981 effects on RTX combo

1. Based on in vitro activity, could we expect TAK-981/RTX combo to deliver clinical responses in RTX R/R NHL patients?
   - **The model predicts TAK-981 at 90mg BIW increases ORR from ~11% to 24%**
2. What is optimal dose and schedule for TAK-981 in combo with RTX?
   - **120mg MIX (BIW for 60d, then QW)**
3. Which RTX R/R patients are most likely to benefit from TAK-981 in this context?

   Patients with:
   - **High maximum levels of CD69 MFI increase due to TAK-981**
   - **Higher levels of NK cells in tumor microenvironment at baseline**
   - **Larger tumors at baseline**
   - ***Lower* CD20 on tumor cells**

Conclusions

- The 2019 Fields Institute Industry Problem Solving Workshop team
  - Derived steady-state solution for bispecific binding of rituximab to CD20 and CD16
  - Derived an NK-Tumor interaction model & fit to published ADCC data
  - Predicted degree of increase in ADCC factors required to offset loss of rituximab sensitivity

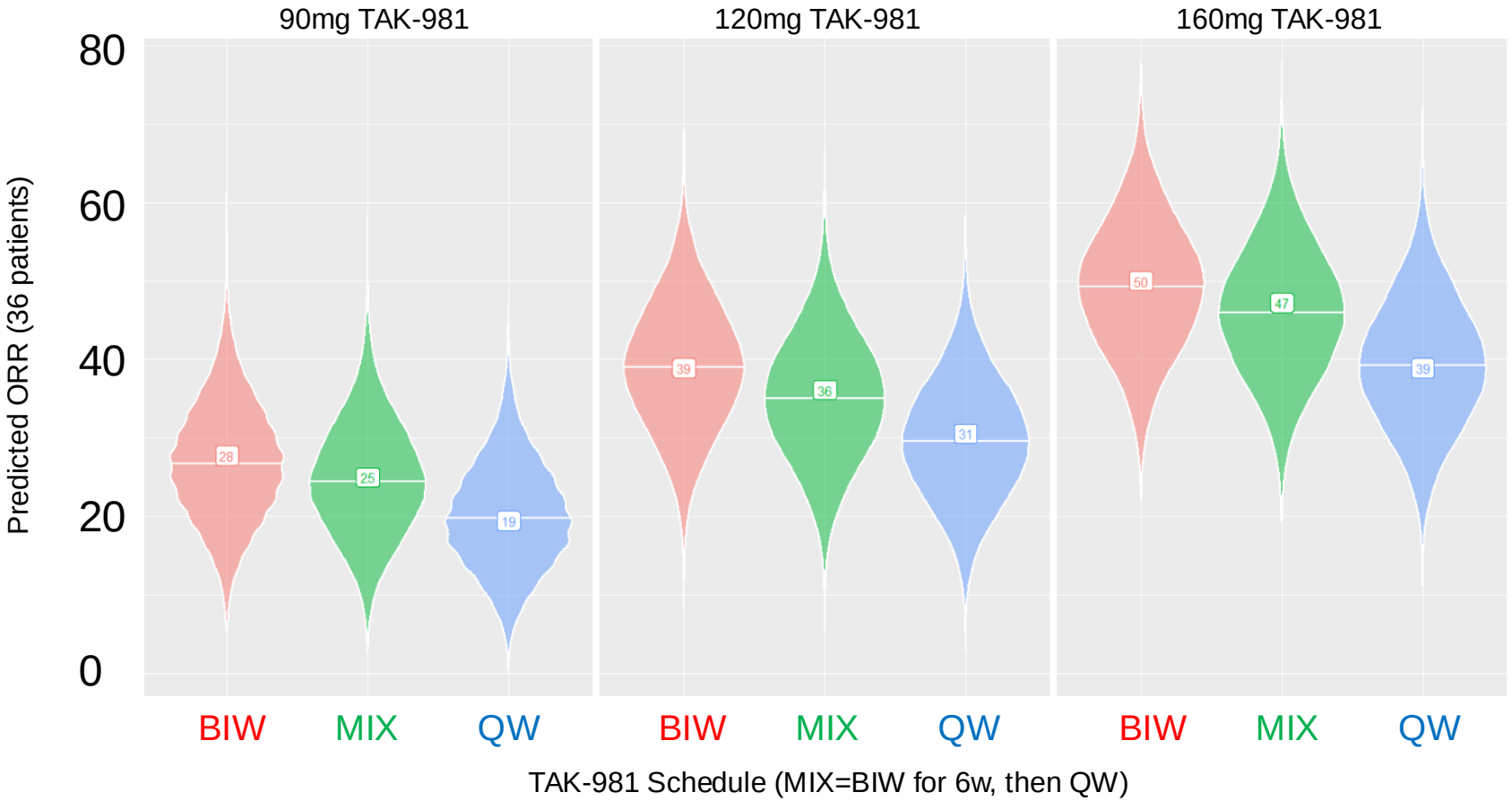
- The academic/industry ‘open source’ model was then incorporated into a proprietary TAK-981 model to address key program questions:
  - Feasibility
  - Optimal dose and schedule
  - Factors predicting benefit

Thank you!

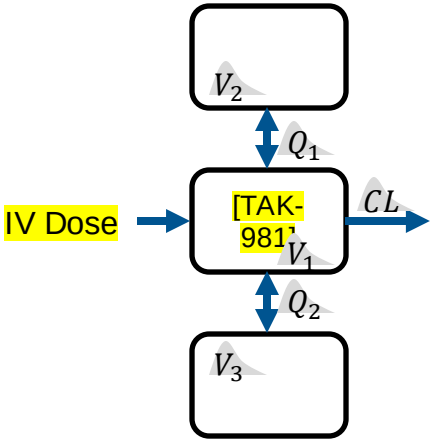
The model can be used to quantify the magnitudes of therapeutic mechanisms required to offset a given mechanism of RTX resistance

Mechanism of RTX resistance (MoRR)	ADCC fold change due to MoR (90% CI)
10x loss of CD20 on tumor	0.16 (0.13,0.20)
10x loss of RTX exposure	0.17 (0.14,0.21)
10x decrease in CD16 affinity	0.16 (0.13,0.20)

We can use the QSP model to stimulate overall response rates (ORRs) at various doses and schedules

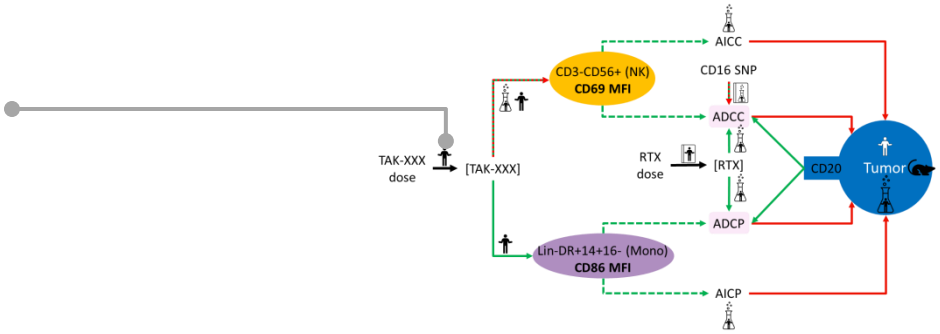


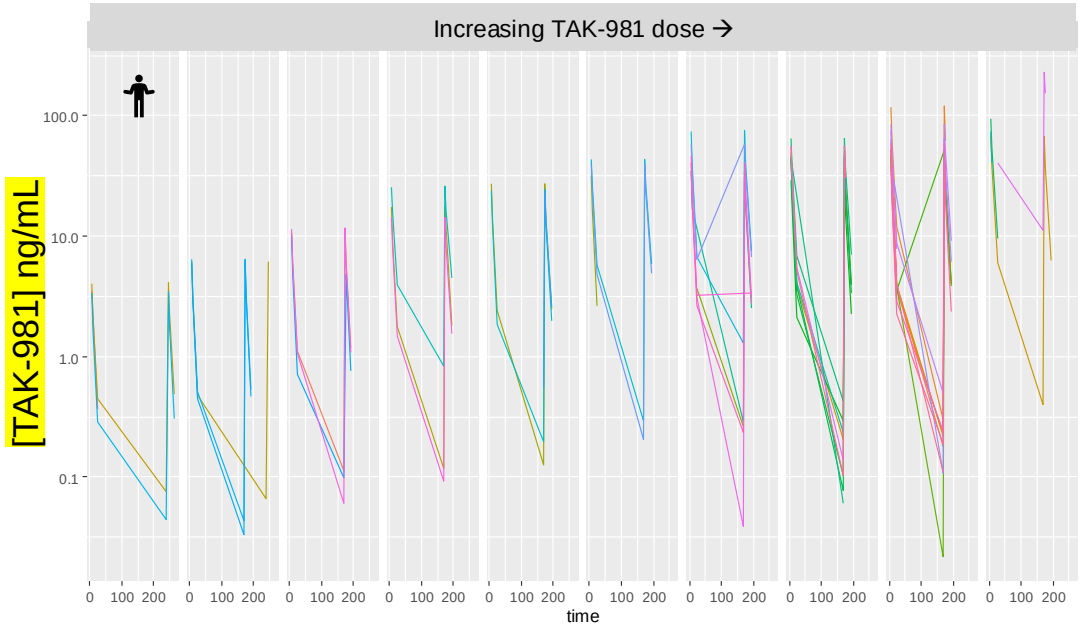
TAK-981 popPK model based on FIH PK data



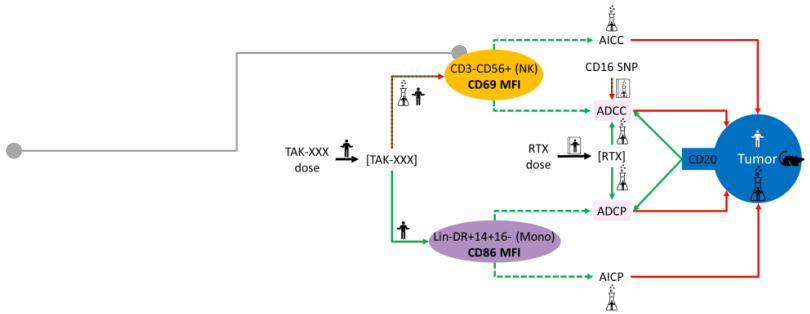
Inter-individual variability

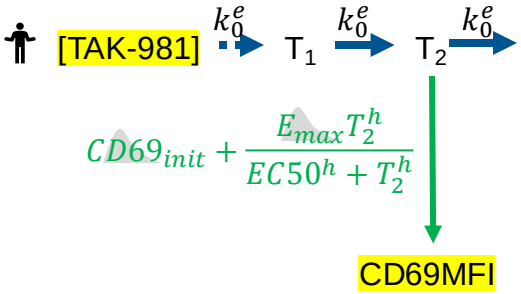
Observation





TAK-981 NK activation (CD69 MFI) module based on patient-level PK/PD data





Inter-individual variability

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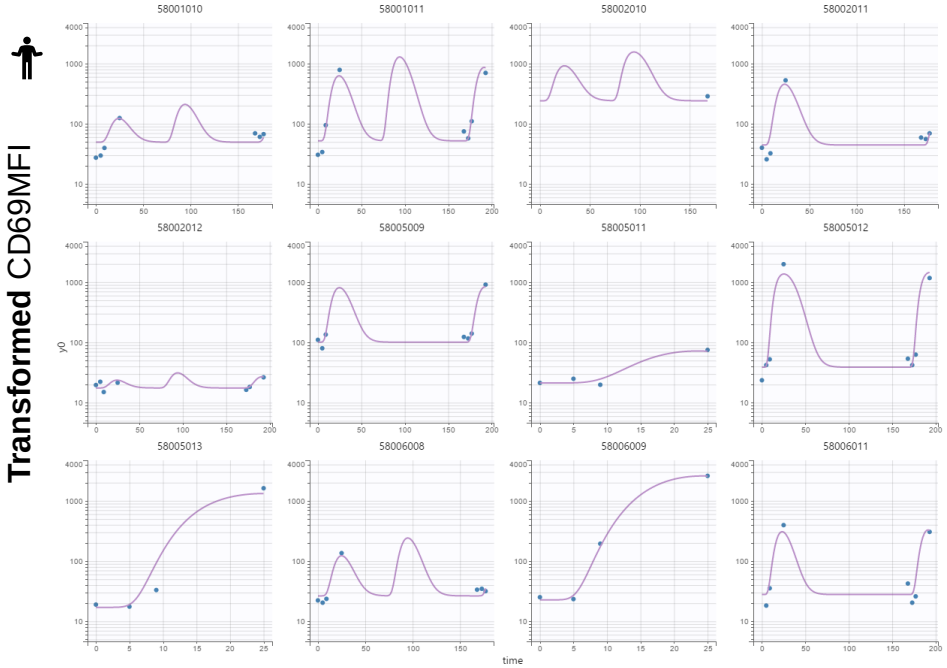
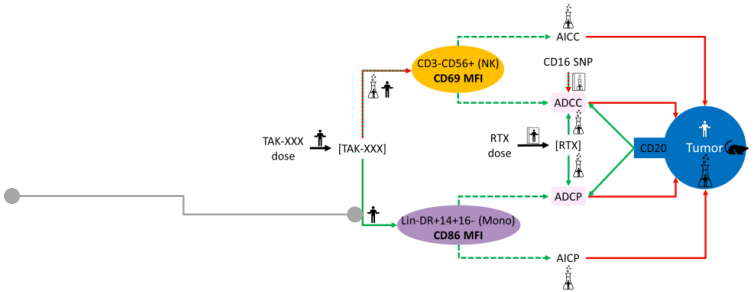
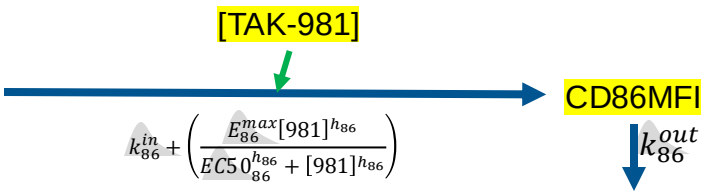


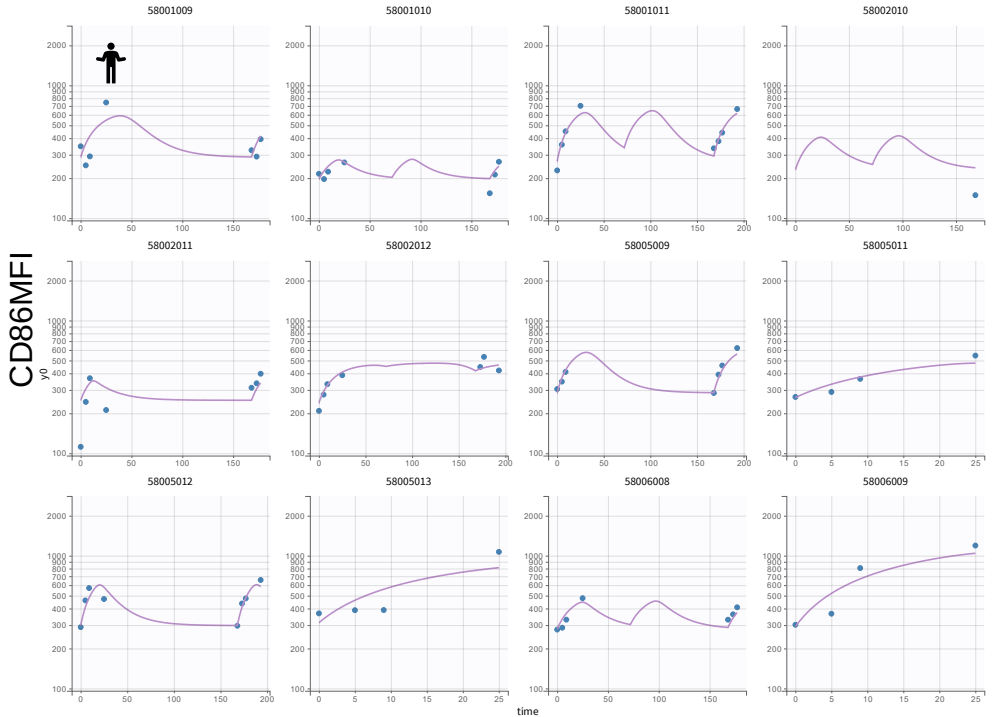
TAK-981 Mac/monocyte activation (CD86 MFI) based on FIH patient-level PK/PD data





Inter-individual variability

Observation



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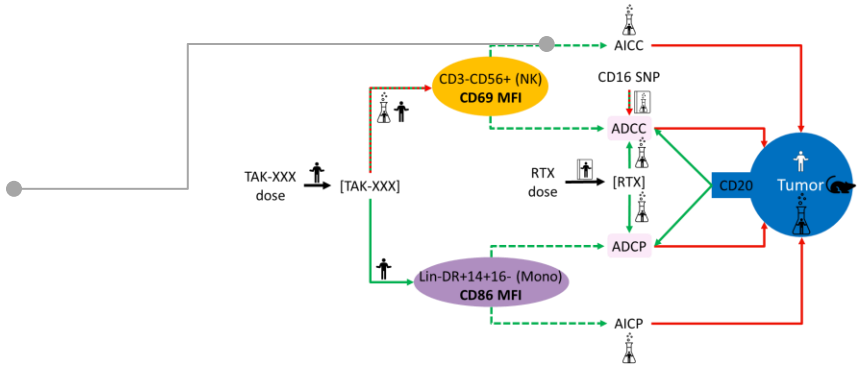
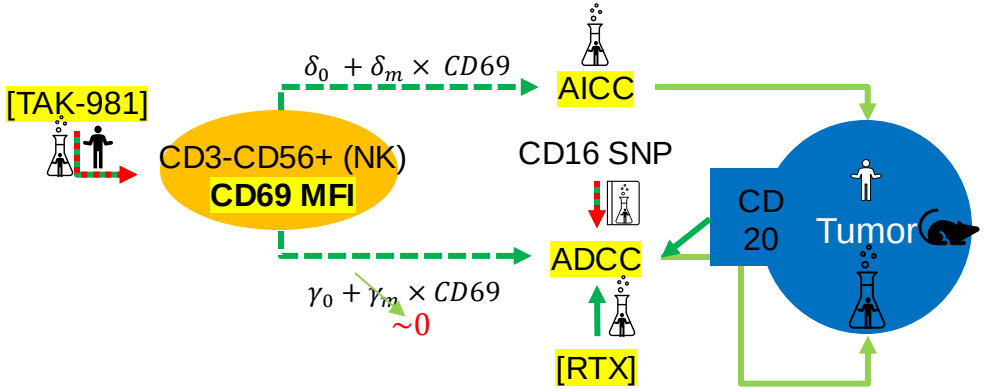
Model of CD69MFI effects on ADCC/AICC calibrated to ex-vivo CD69 & cytotox data





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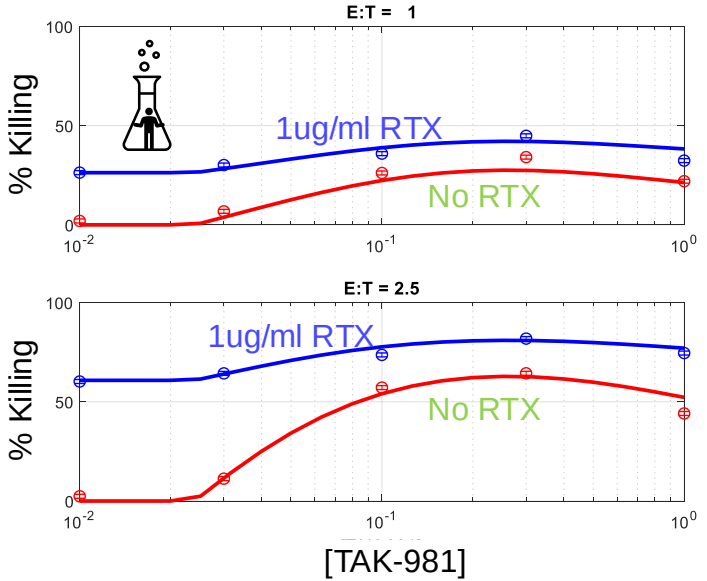
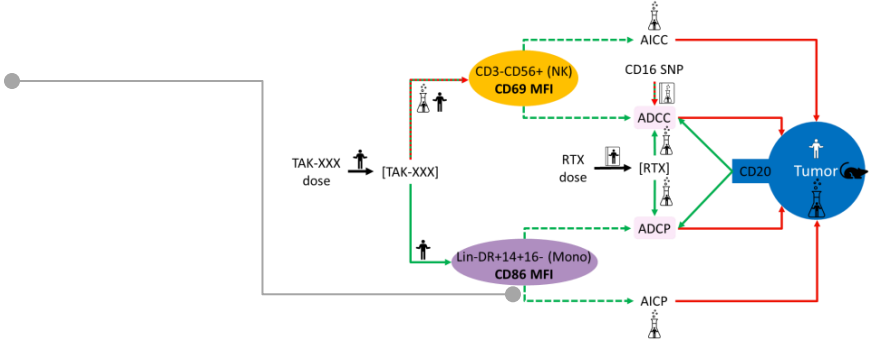
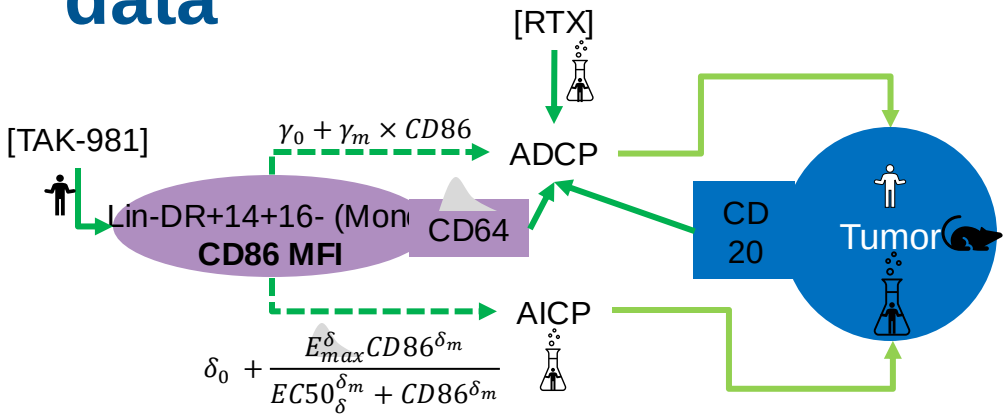
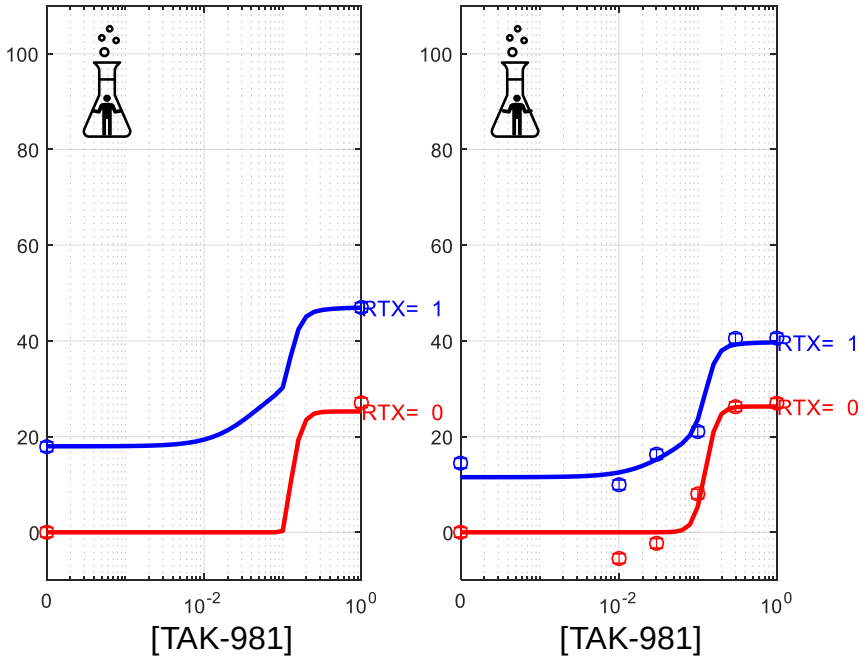


Model of CD86MFI effects on ADCP/AICP calibrated to ex-vivo phagocytosis data







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