

The cellular kinetics and anti-tumor dynamics of Kymriah

**Andrew Stein,
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Stein, Andrew M., et al. "Tisagenlecleucel Model-Based Cellular Kinetic Analysis of Chimeric Antigen Receptor–T Cells." *CPT: pharmacometrics & systems pharmacology* 8.5 (2019): 285-295.



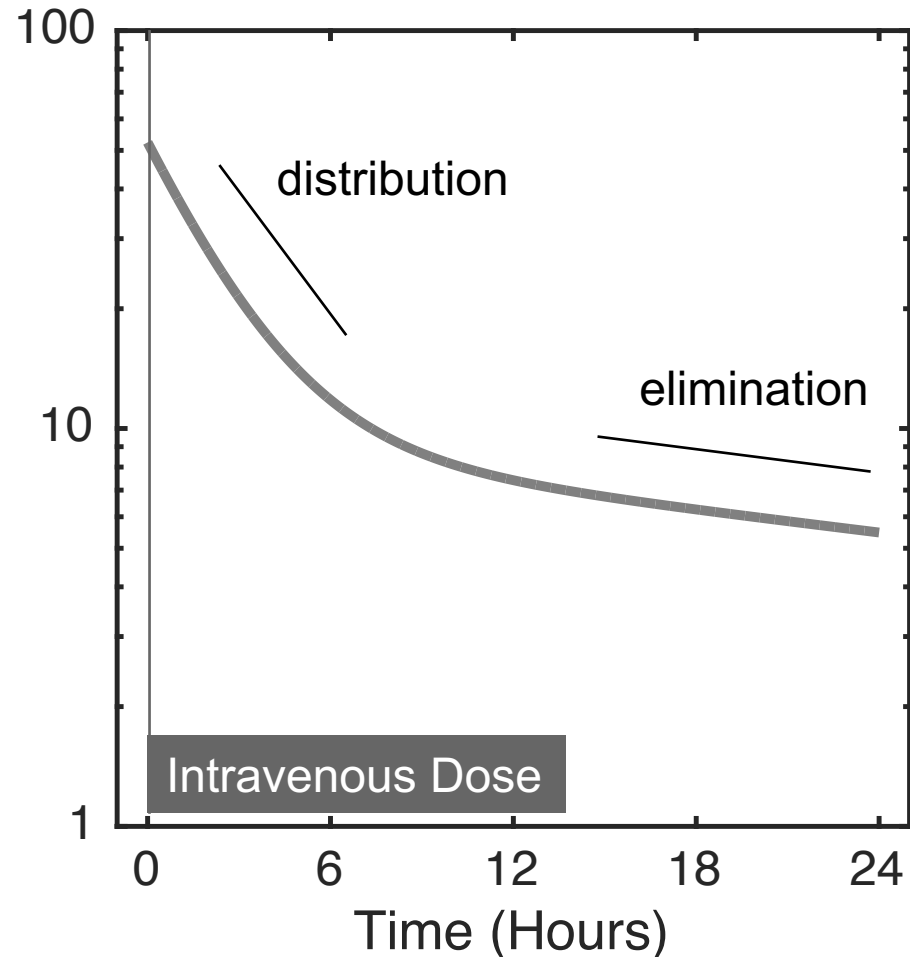
MODELING WITHOUT BORDERS ACoP 10

Executive Summary

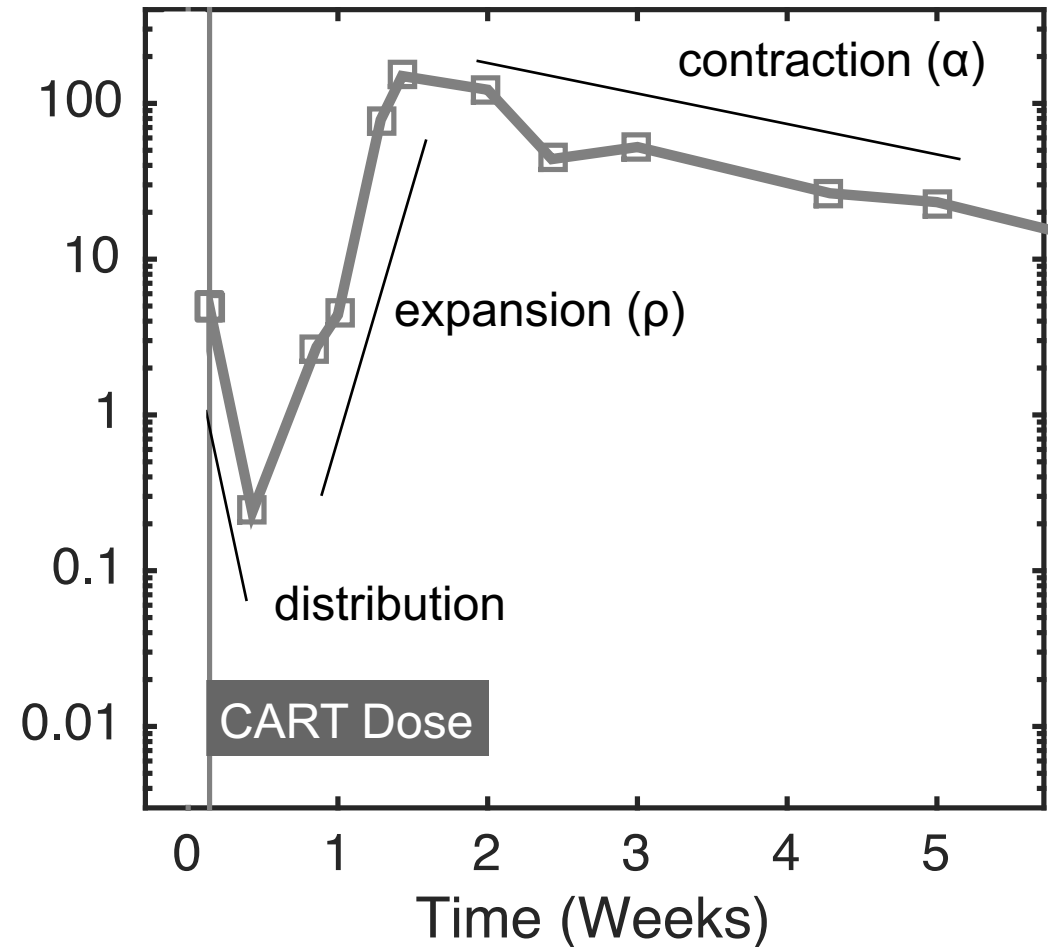
- Kymriah (CTL019) is a Chimeric Antigen Receptor T-cell (CART) therapy that is approved for pediatric ALL¹ and DLBCL².
- Because CART is a “living drug” with the ability to proliferate, traditional PKPD concepts and models are not applicable.
- Therefore, we’ve developed cellular kinetic (“CellK”) models for Kymriah
 - “Pop-CellK” model for clinical the cellular kinetics
 - “CellK-PD” model for mouse anti-tumor dynamics

CART kinetics are very different from traditional pharmacokinetics

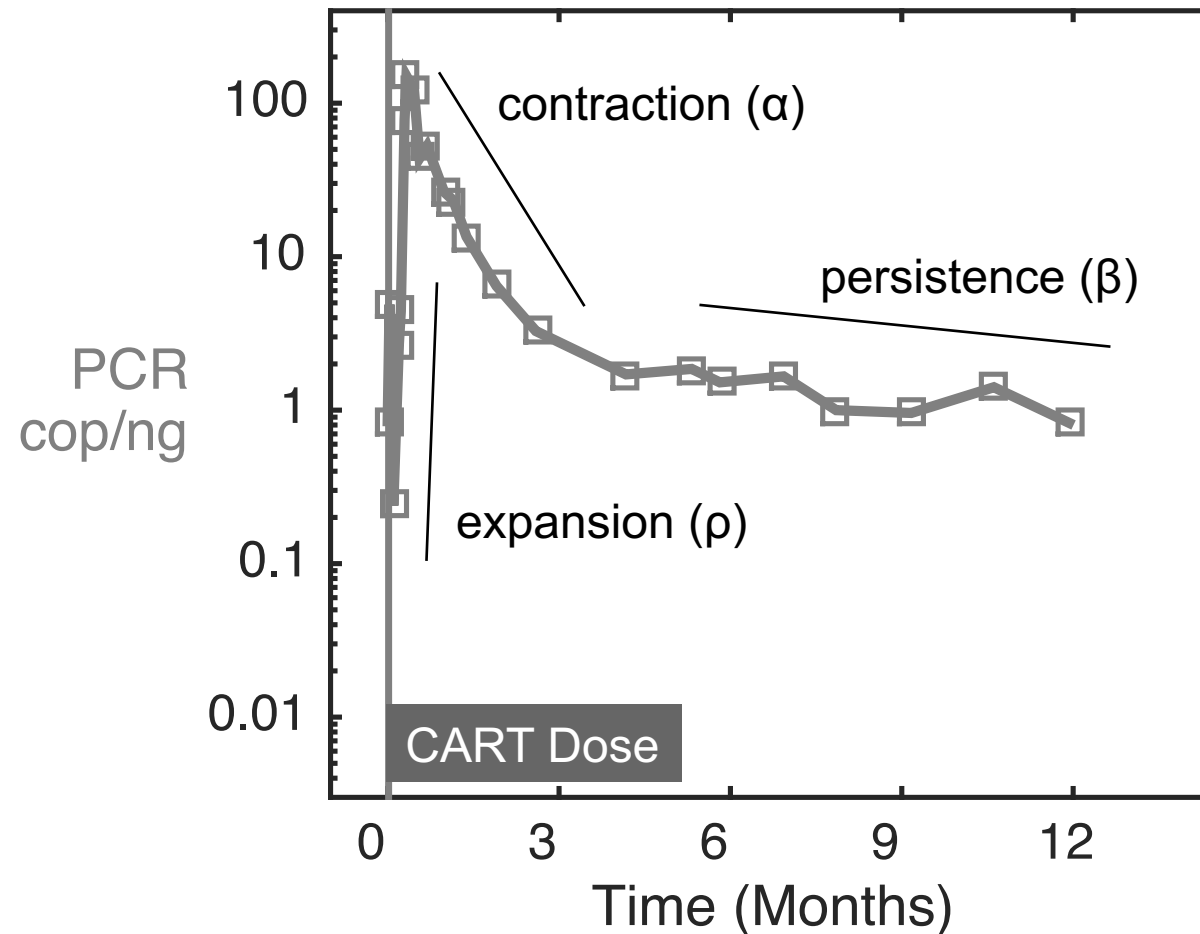
Small Molecule



Kymriah (CART)

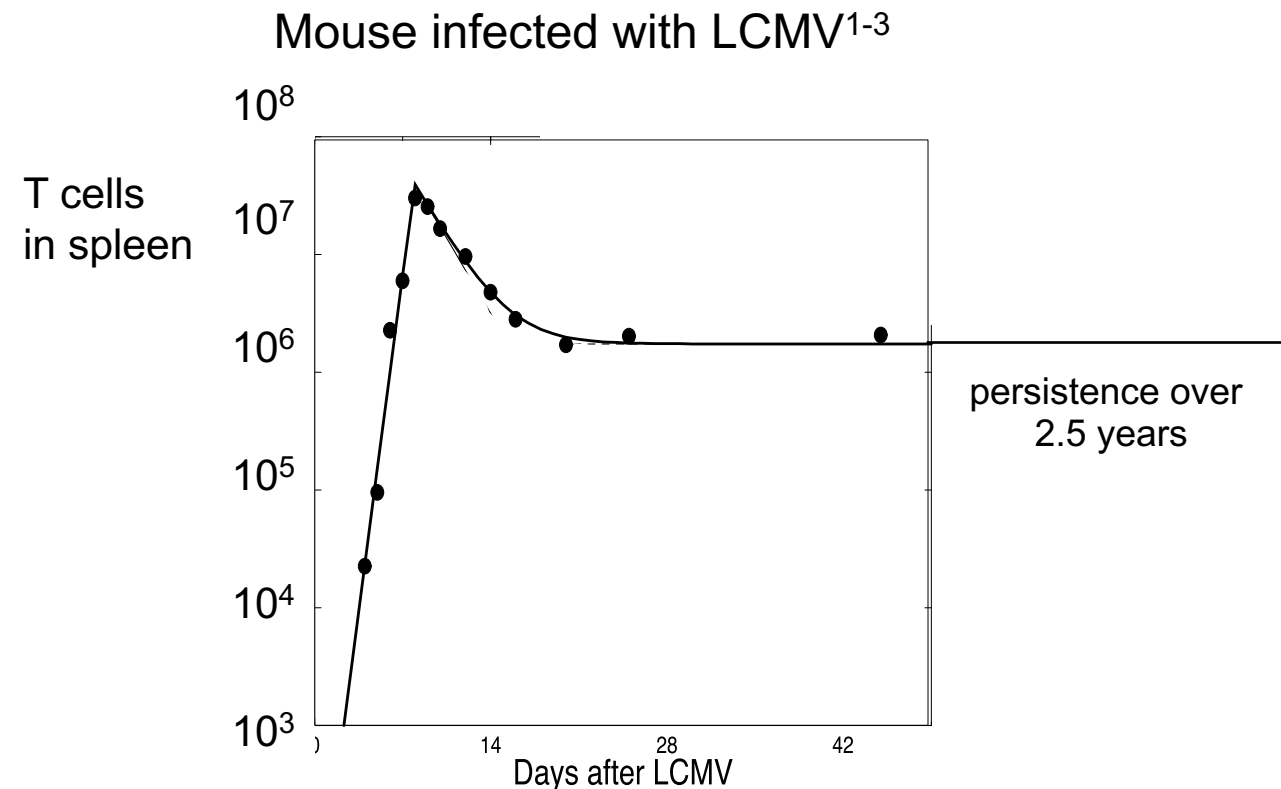
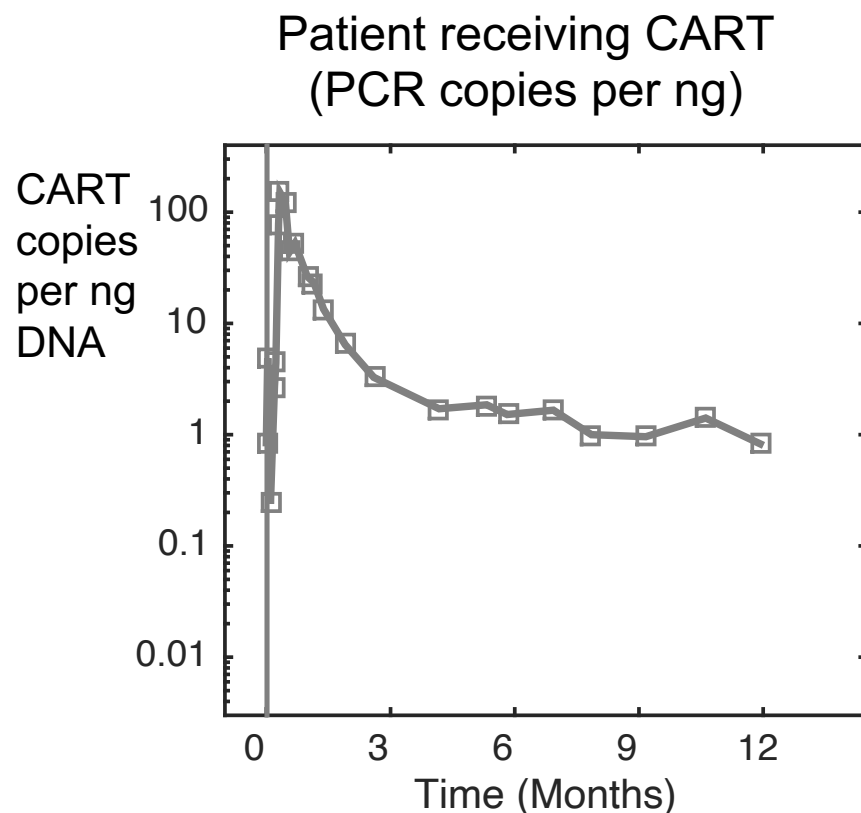


Kinetics of CART over one year



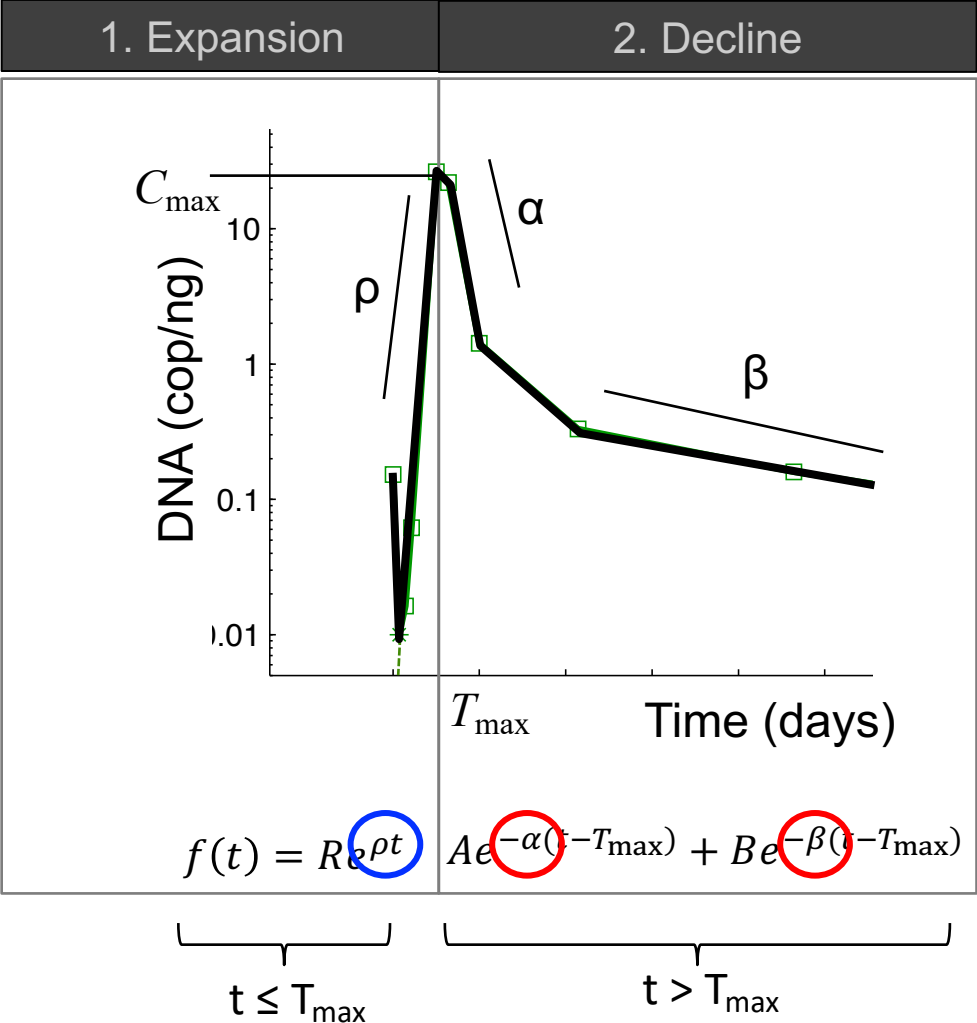
2 of 3 patients to receive CART in 2010 still have detectable cells

CART kinetics in patients is comparable to mouse T cell dynamics



1. LCMV = Lymphocytic choriomeningitis virus
2. De Boer and Perelson, J Theor. Biol., 45, 327 (2013).
3. Splenic T cell kinetics in mice do not necessarily reflect peripheral blood kinetics in patients

Empirical model to describe CART kinetics, same model as developed for LCMV in mice¹

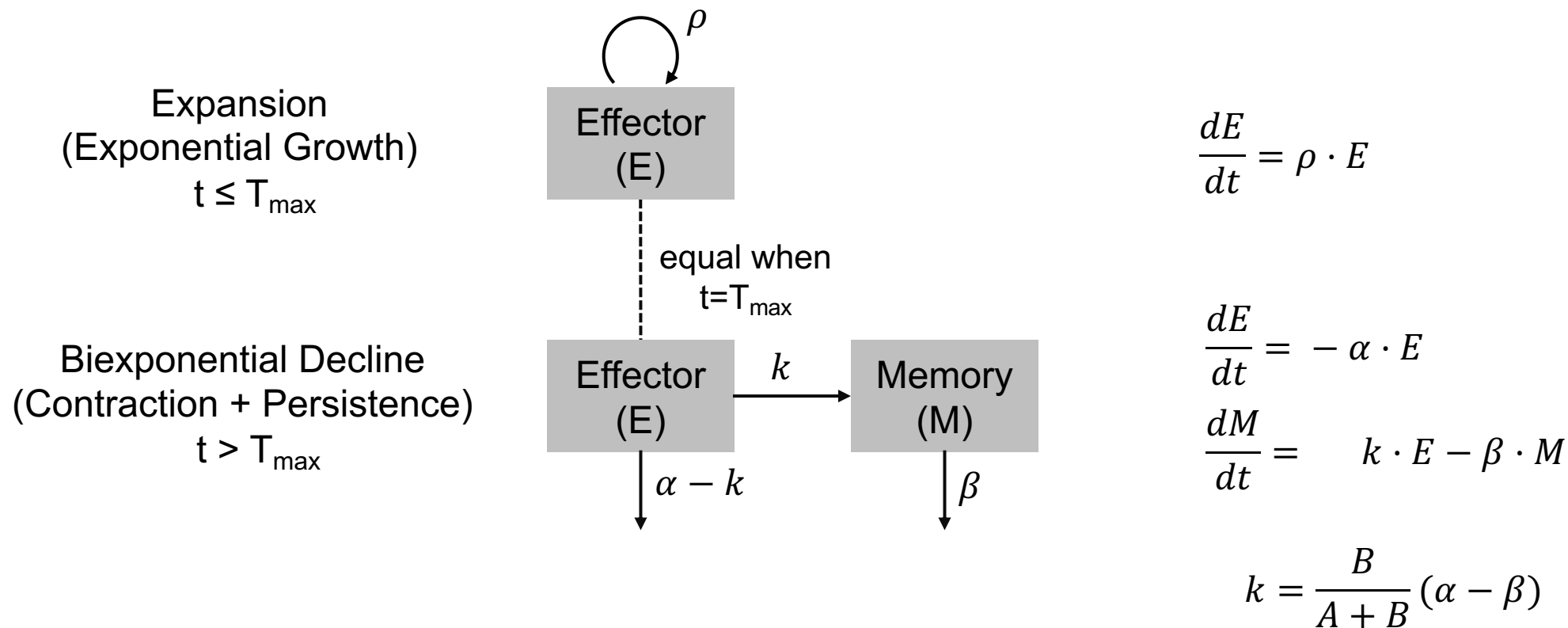


R	Initial DNA/ng (post-distribution)
ρ	Expansion rate
C_{max}	Peak expansion = $R e^{\rho \cdot T_{max}}$
T_{max}	Expansion duration
A	DNA/ng from cells that rapidly decline
α	Initial decline rate
B	DNA/ng from cells that decline slowly
β	Long-term decline rate

Traditional PK model (oral absorption):
all exponents are negative

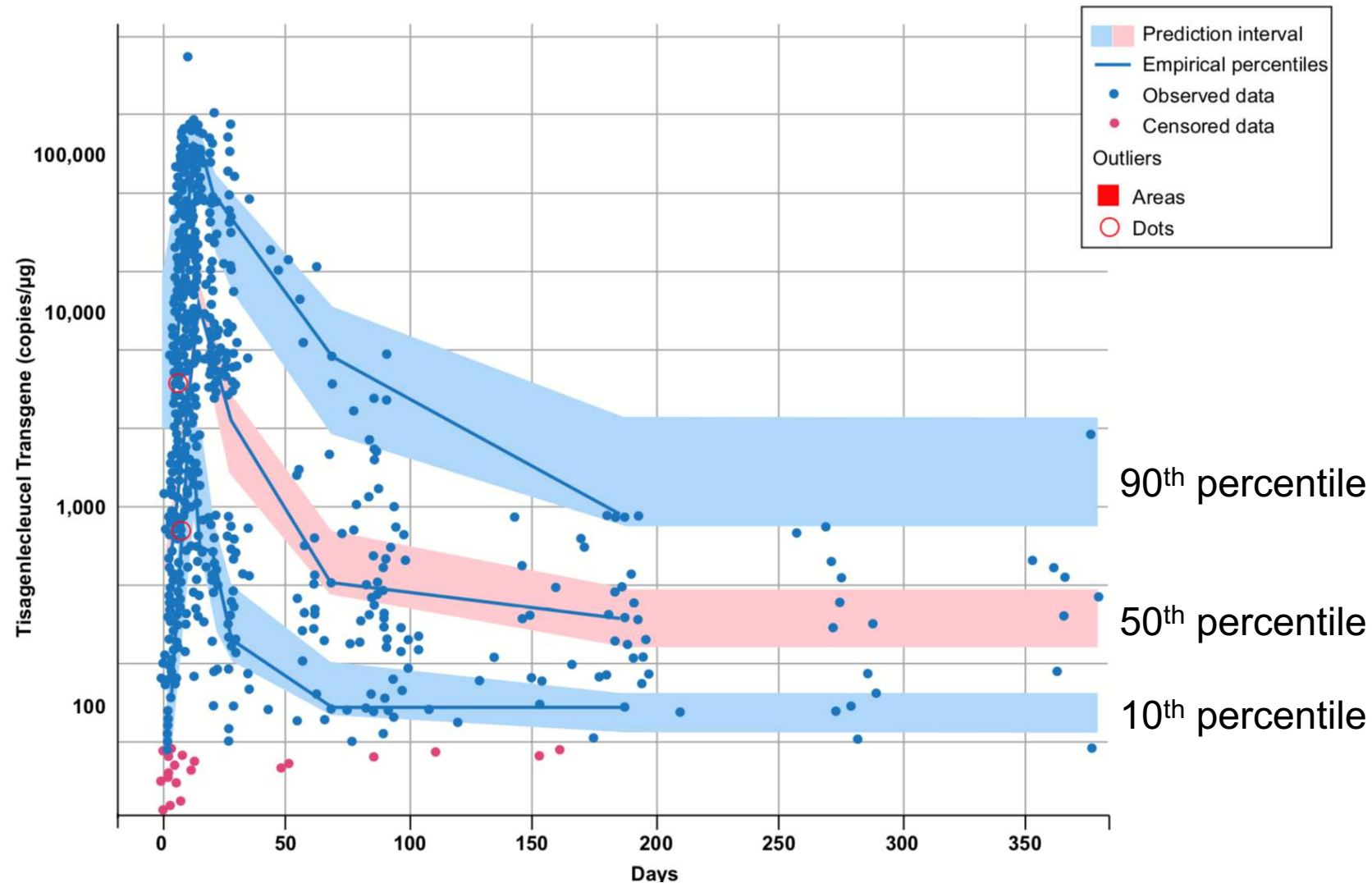
$$f(t) = -(A + B)e^{-k_a t} + A e^{-\alpha t} + B e^{-\beta t}$$

Semi-mechanistic model with same analytical solution as empirical model



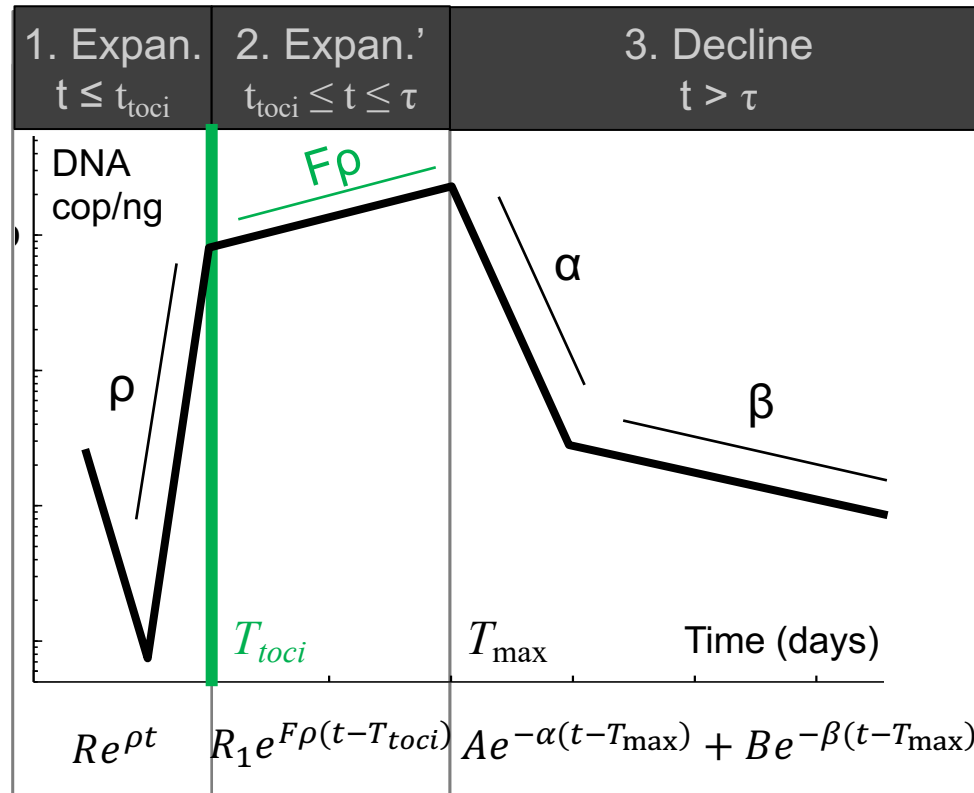
Other structural models also give exponential growth and biexponential decline

Model describes data (Visual Predictive Check)



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CART model with tocilizumab effect



R	Initial DNA/ng (post-distribution)
ρ	Expansion rate
C_{max}	Peak expansion = $Re^{\rho \cdot T_{max}}$
T_{max}	Expansion duration
T_{toci}	Time of tocilizumab dose
F	Impact of tocilizumab on expansion
A	DNA/ng from cells that rapidly decline
α	Initial decline rate
B	DNA/ng from cells that decline slowly
β	Long-term decline rate

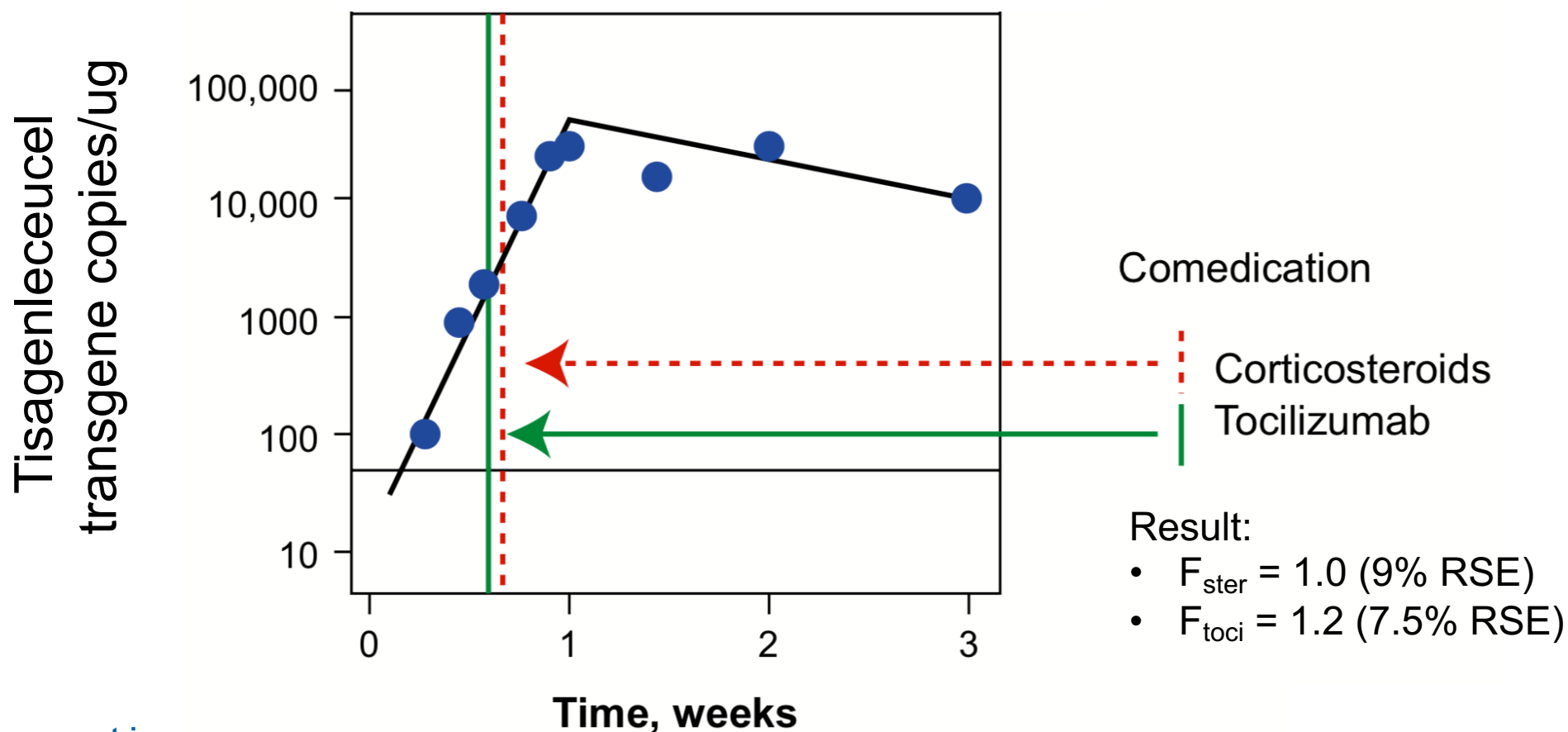
Tocilizumab effect (F).

$F = 1 \rightarrow$ no tocilizumab impact

$F < 1 \rightarrow$ tocilizumab slows expansion

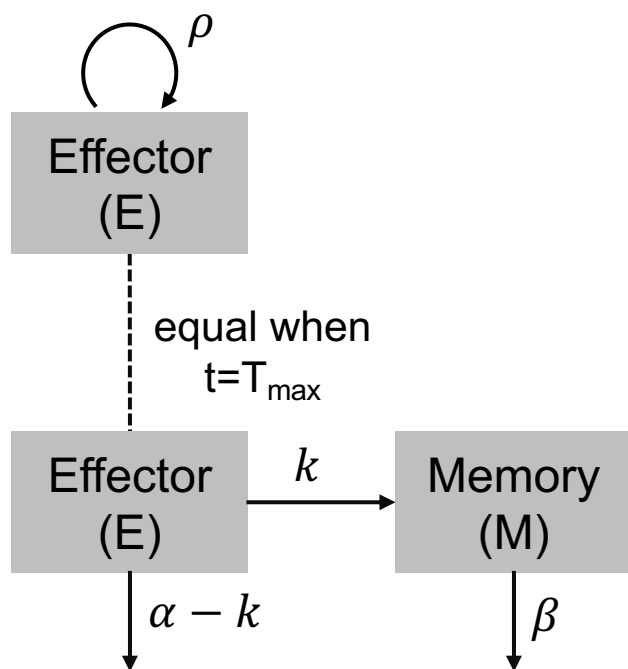
Second drug (corticosteroids) was also introduced

No impact of tocilizumab on CART expansion rate has been observed

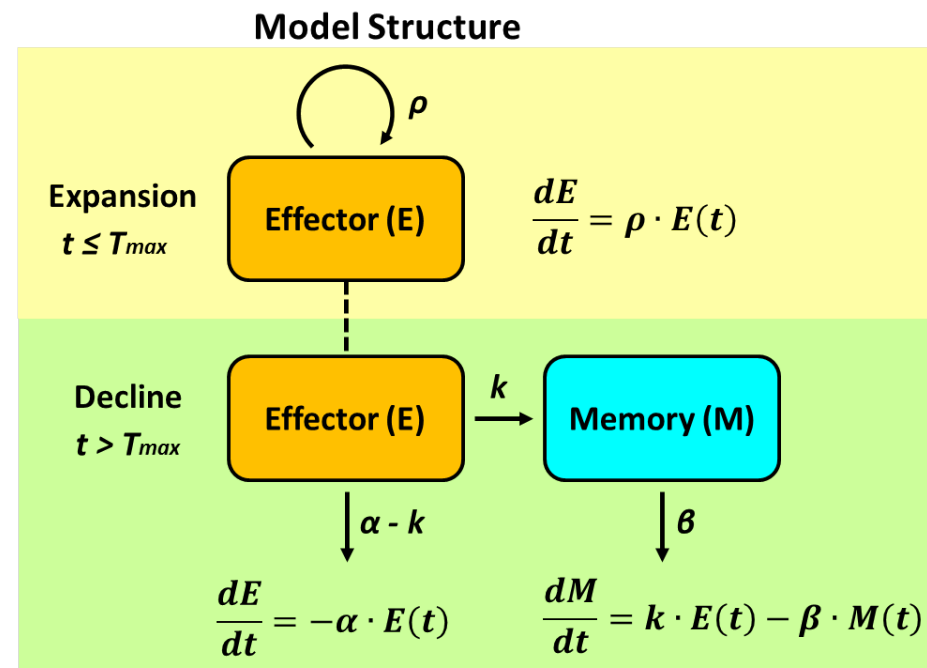


FDA used the same model in their analysis of both Kymriah + Yescarta

Novartis Publication



FDA Presentation at ACoP Conference



Key parameters ρ : proliferation rate β : slow declining rate (M)
 α : rapid declining rate (E) k : memory cell forming rate

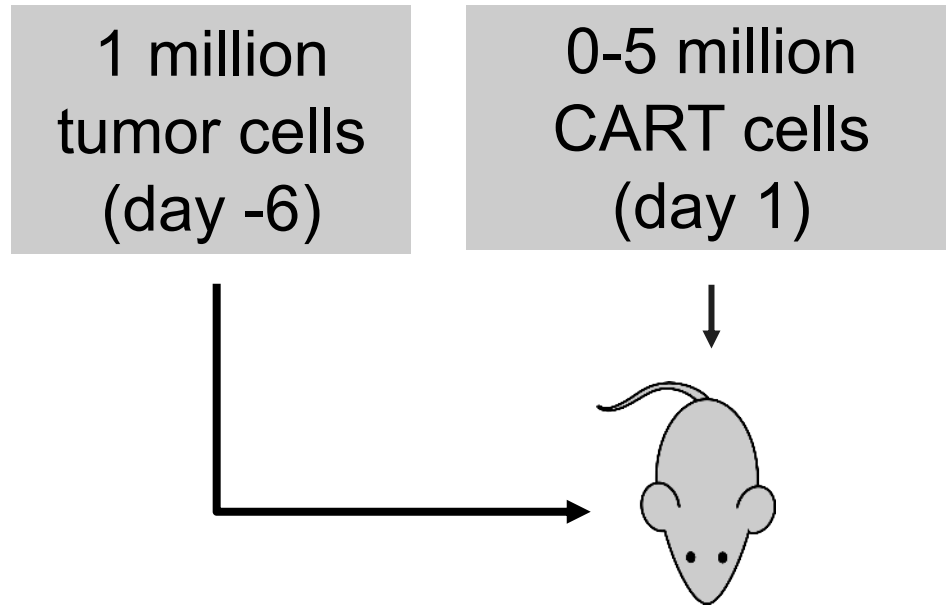
We have a cellular kinetic model

We are now developing models for the PD

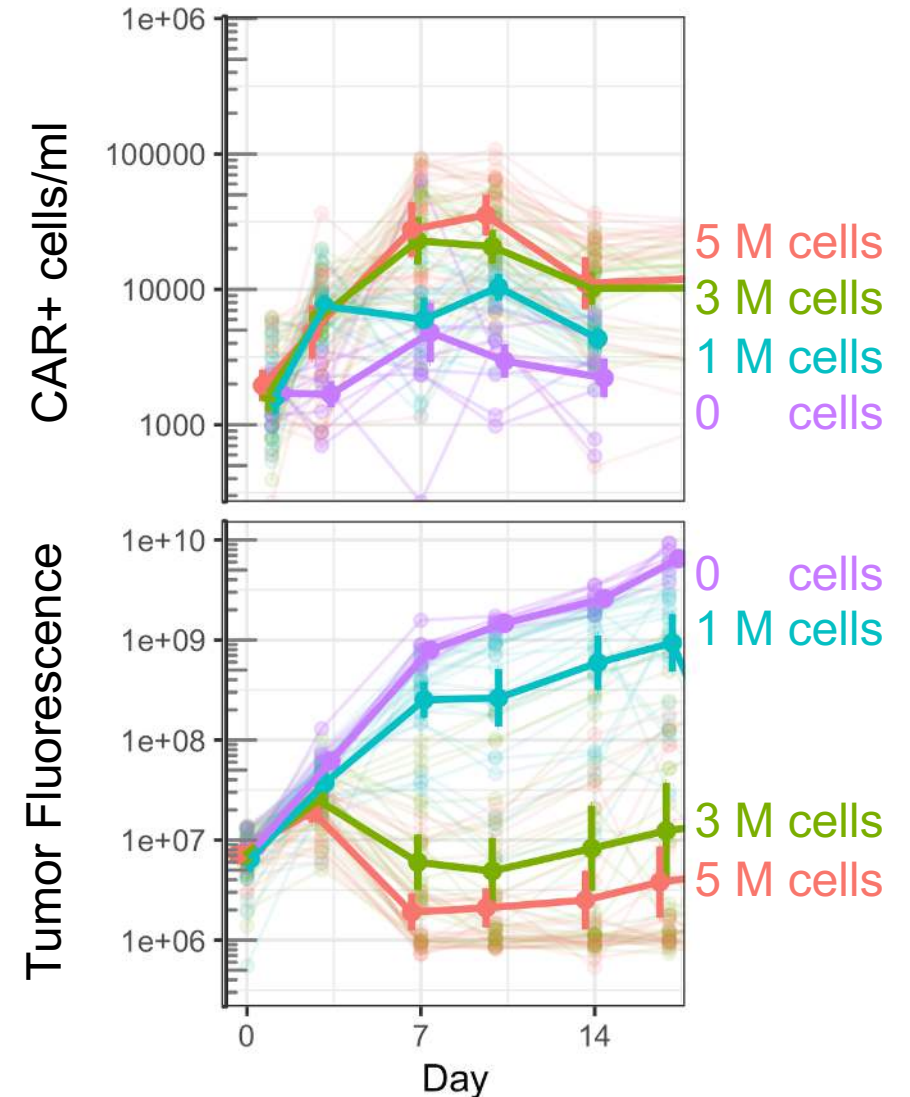
- Challenges in modeling safety: cytokine release syndrome (CRS)
 - **Cytokine data** is rich and could be modeled¹, but how to link the cytokines to efficacy metrics?
 - **Temperature and blood pressure** may be the best biomarkers to model, but we don't currently have rich enough sampling in our clinical database to model this data.
- Challenges in modeling efficacy in pediatric ALL – limited tumor burden data
 - Most patients achieve complete response at first assessment; measurable tumor data is limited.
- Therefore, we focus here on mouse data.

1. Hardiansyah, Deni, and Chee Meng Ng. "Quantitative Systems Pharmacology Model of Chimeric Antigen Receptor T-Cell Therapy." Clinical and translational science (2019).

Clear dose-exposure-response relationship is observed in Nalm6 mouse model

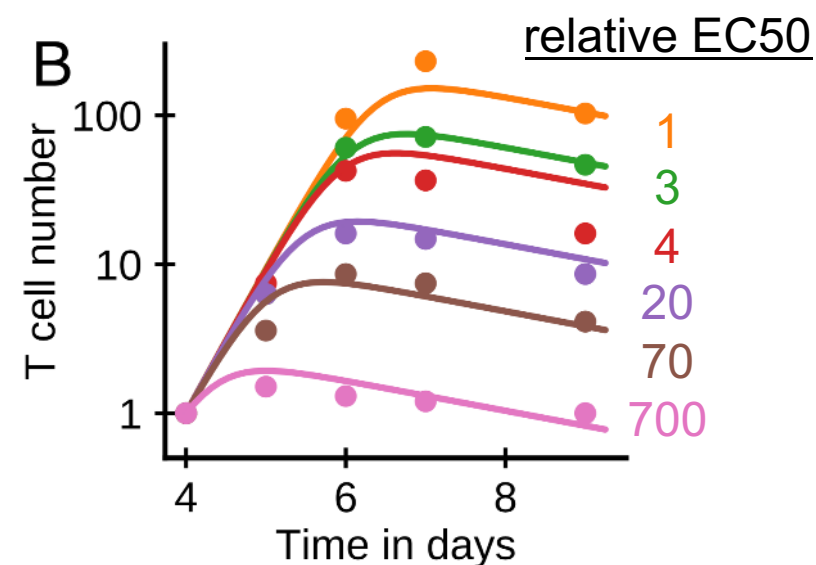
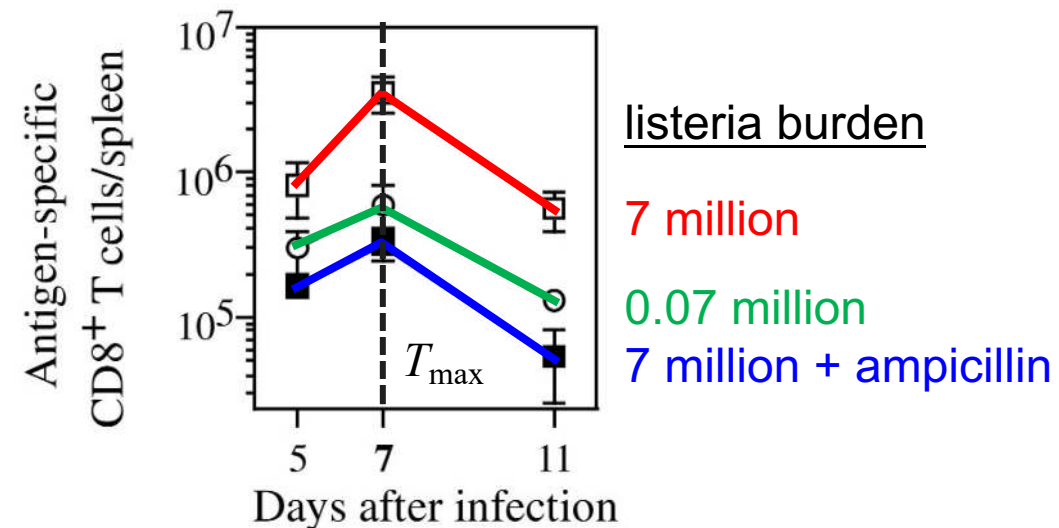


What explains the limited anti-tumor effect at a 1 million cell dose?



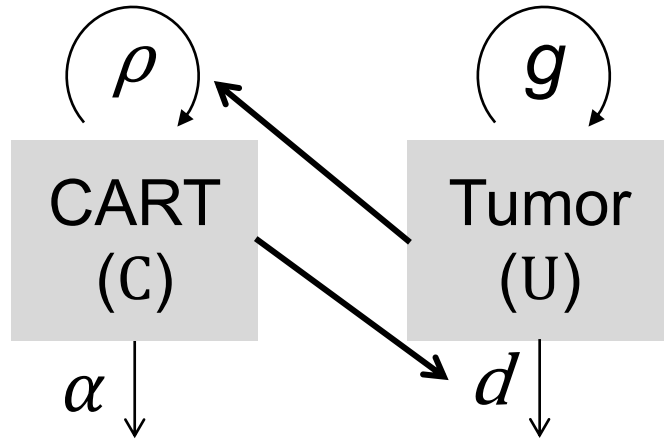
What are the determining factors of T_{max} ?

- In mice infected with listeria, T_{max} is independent of antigen level, suggesting the duration of proliferation is pre-programmed¹⁻²
- T_{max} may depend on binding affinity of TCR to antigen³
- T cell exhaustion (PD-1 expression) is also relevant⁴.



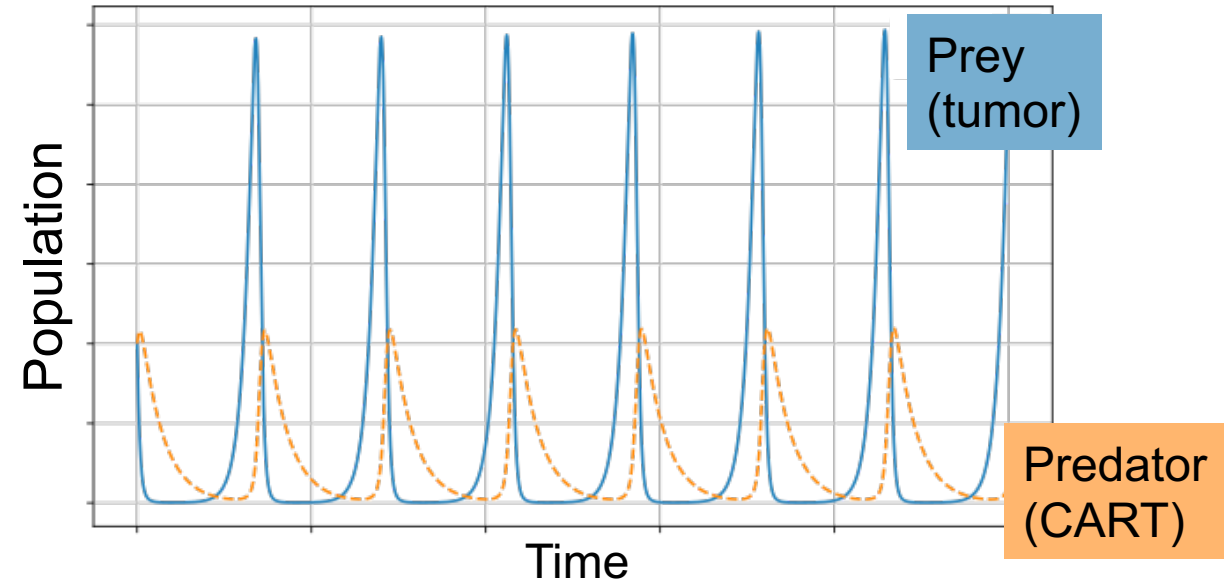
1. Badovinac, V et al "Nature immunology 3.7 (2002): 619.
2. De Boer and Perelson, J Theor. Biol., 45, 327 (2013).
3. Mayer, A, et al. PNAS, 116.13 (2019): 5914-5919.
4. Fraietta, J, Nature medicine 24.5 (2018): 563.

The Lotka-Volterra Predator-Prey Model¹⁻² is frequently used for immune-tumor dynamics



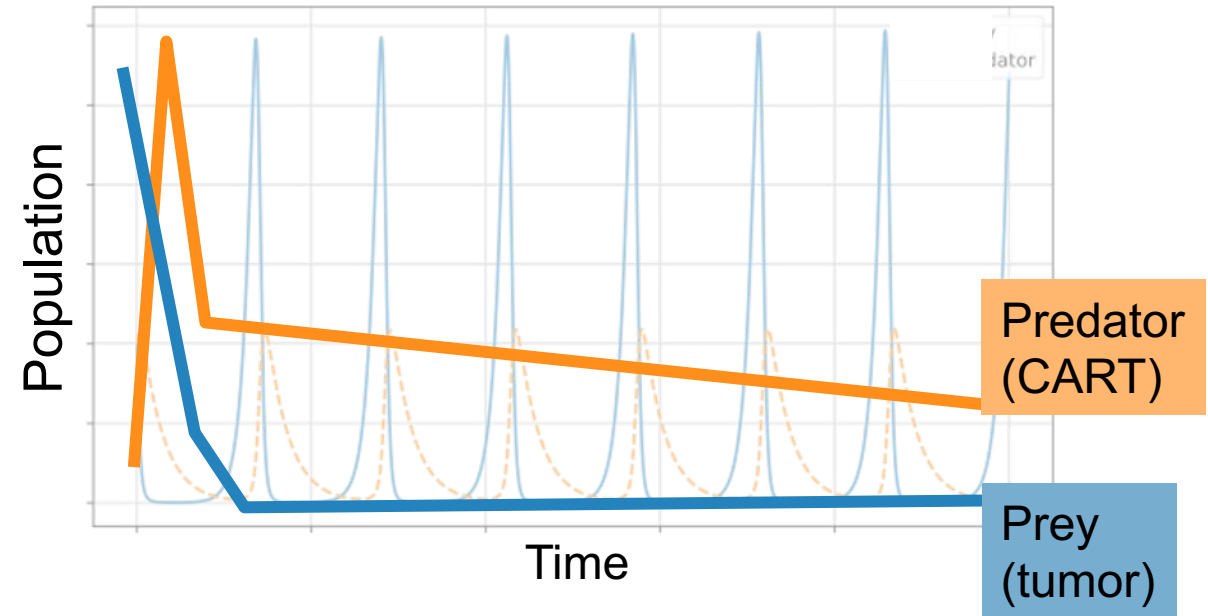
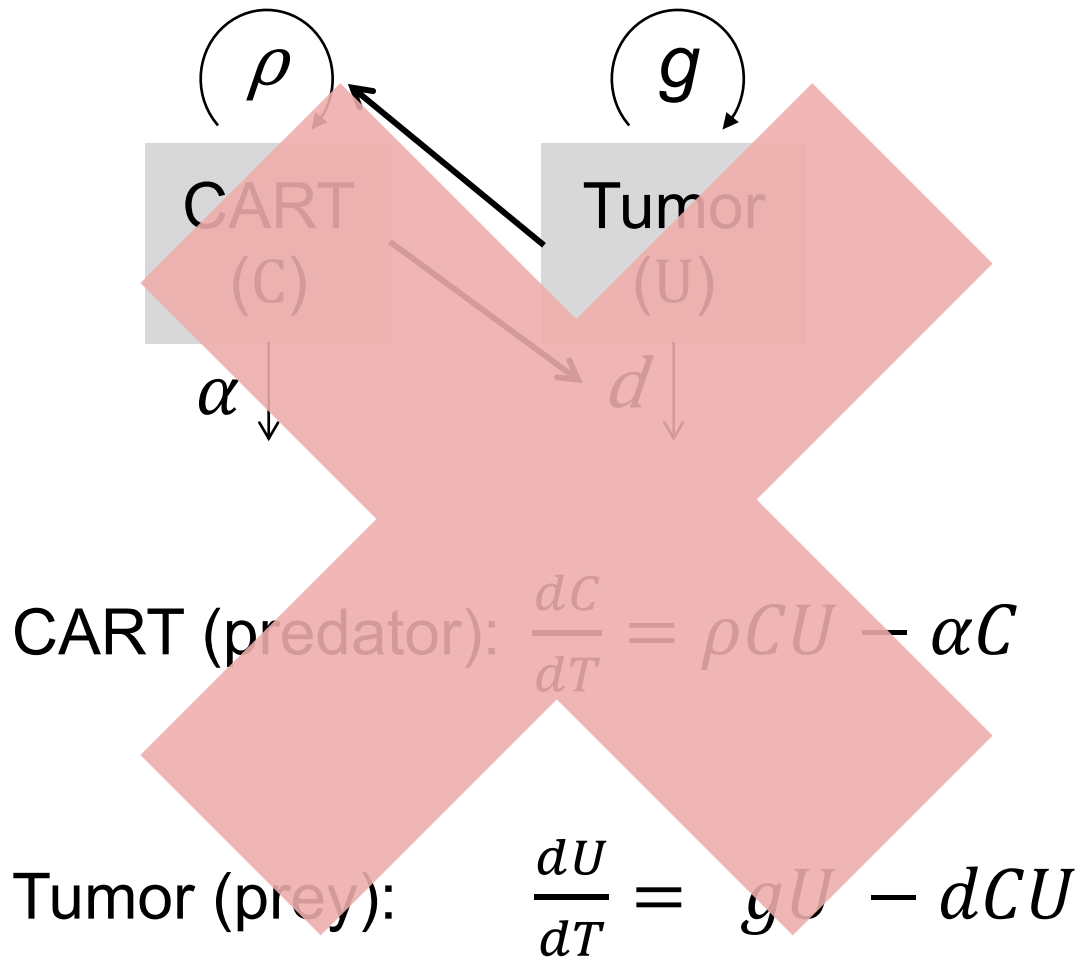
CART (predator): $\frac{dC}{dT} = \rho CU - \alpha C$

Tumor (prey): $\frac{dU}{dT} = gU - dCU$



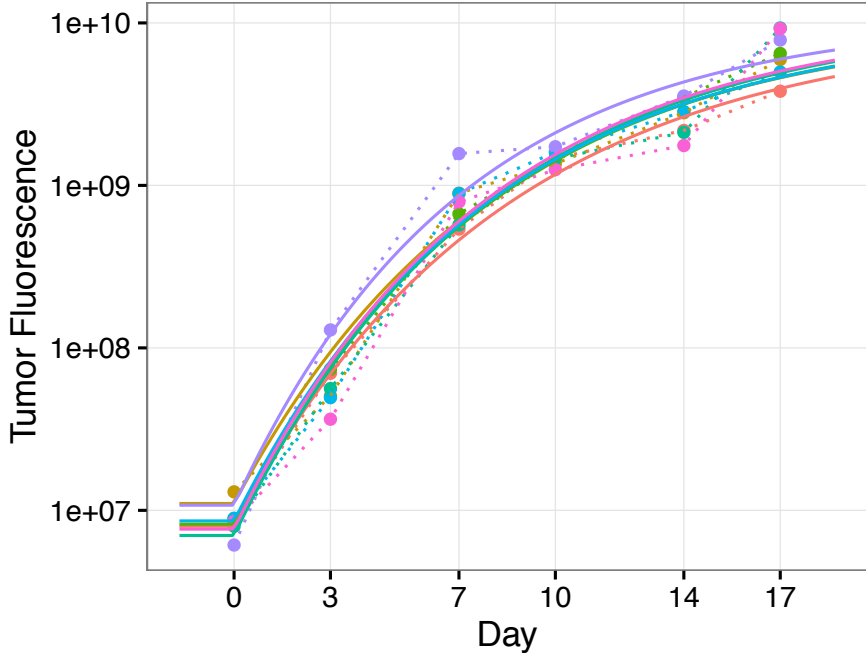
The Lotka Volterra is a classical, simple, and elegant model.

The Lotka-Volterra Predator-Prey cyclic behavior does not match clinical observations.



Saturable tumor growth (Gompertz)

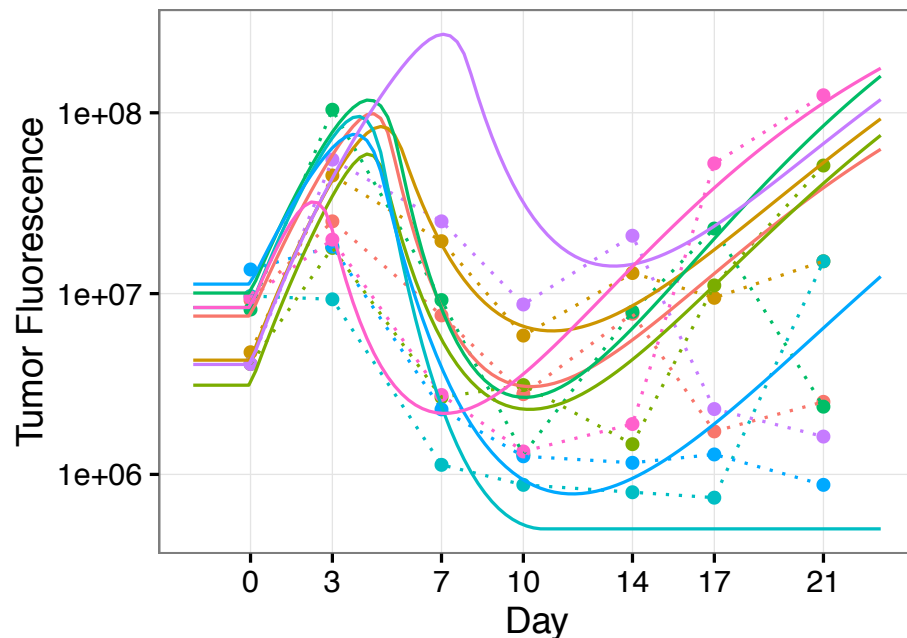
$$\frac{dU}{dt} = g \cdot U \cdot [\log(U_{\max}) - \log(U)]$$



U	Tumor cells
U0	Initial tumor burden
g	Initial exponential growth rate
Umax	Maximum tumor burden

CAR T-cells kill the tumor cells (mass action)

$$\frac{dU}{dt} = g \cdot U \cdot [\log(U_{\max}) - \log(U)] - d \cdot C(t) \cdot U$$



U	Tumor cells
U0	Initial tumor burden
g	Initial exponential growth rate
U _{max}	Maximum tumor burden
d	Tumor kill rate
C(t)	$CART = \begin{cases} Dose \cdot Re^{\rho t} & \text{if } t \leq T_{\max} \\ Ae^{-\alpha t} & \text{if } t > T_{\max} \end{cases}$

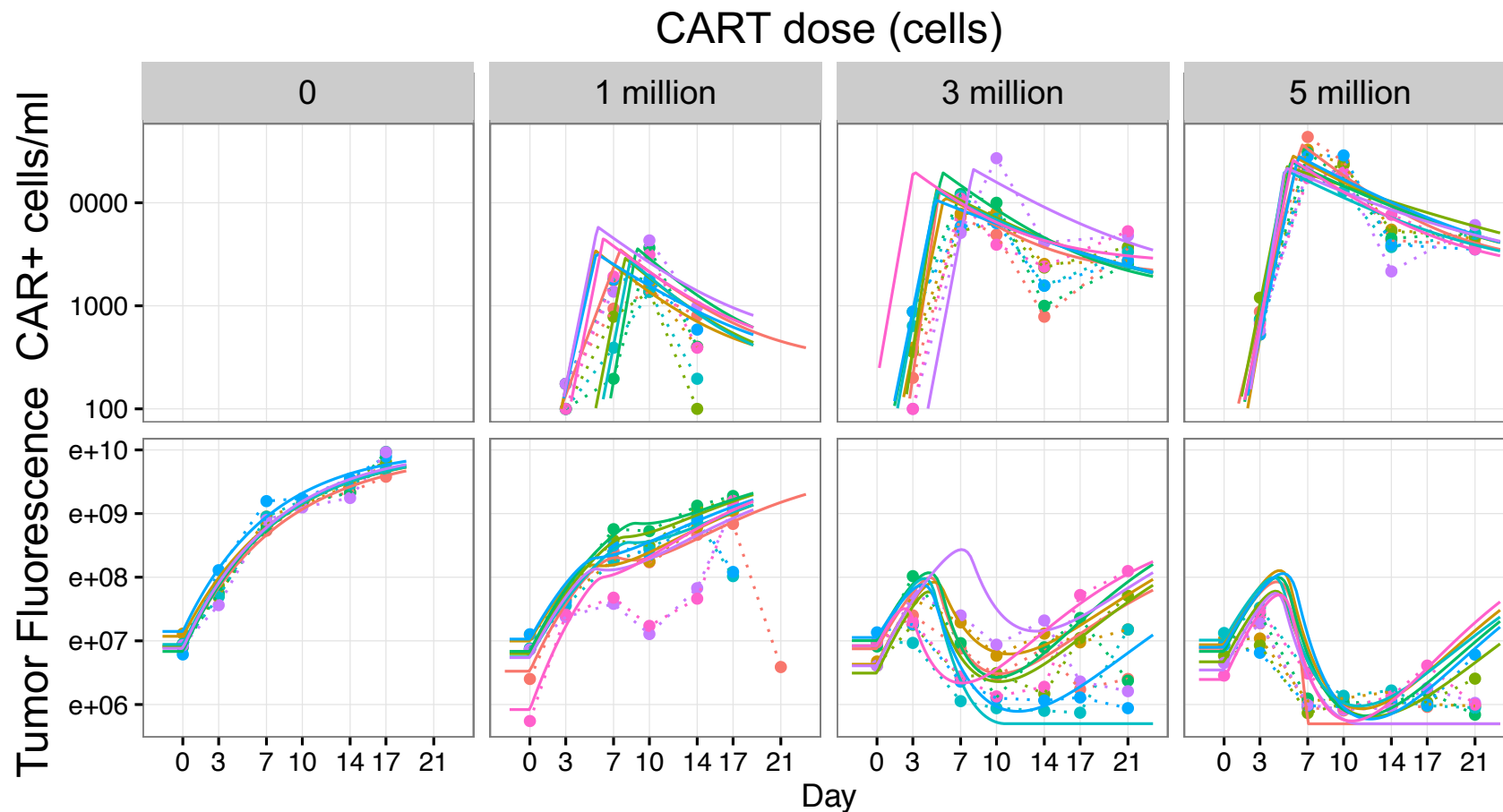
Model assumptions:

CART expansion is preprogrammed to stop after time $T_{\max}$.

Initial CART population is proportional to dose.

CART decline is only monophasic (α) because of limited follow-up time.

Simple model with “pre-programmed” cell expansion until T_{max} describes the data



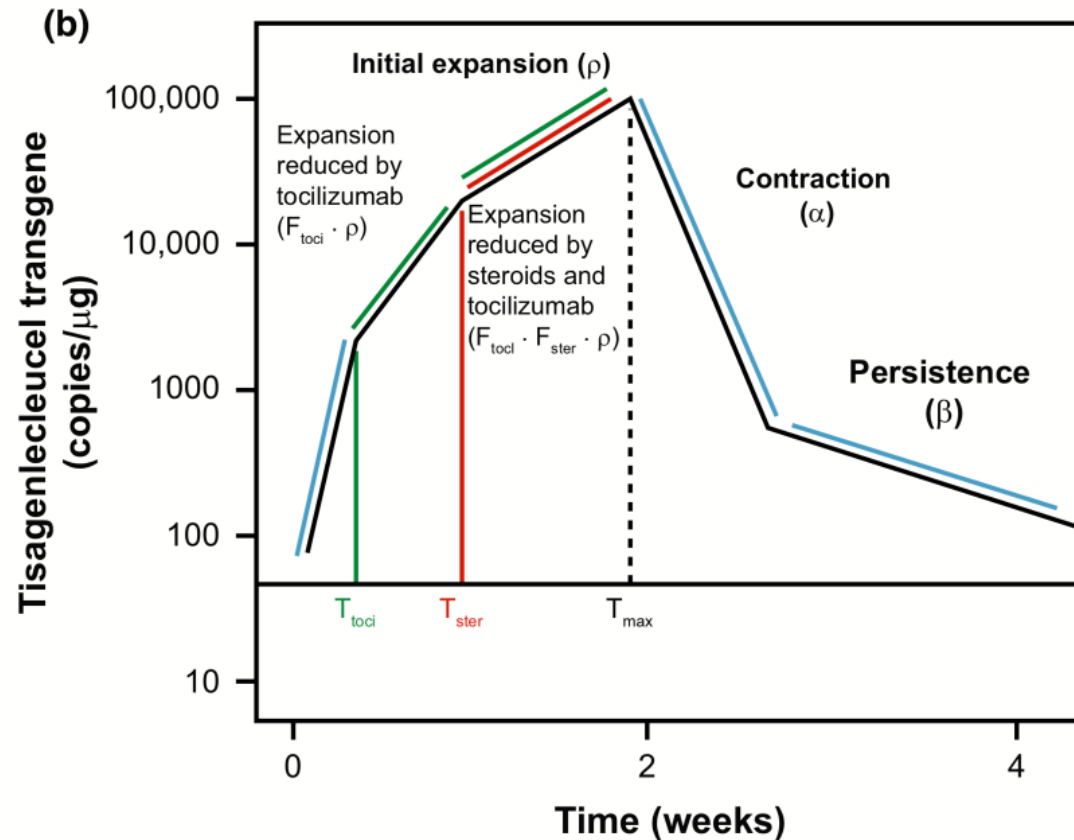
A more complex explanation isn't needed to for why 1 million cells is not enough to eliminate the tumor

Summary

- Population cellular kinetic (Pop-CellK) for Kymriah
 - Fundamentally different from a traditional PopPK model.
 - No impact of corticosteroids or tocilizumab on expansion rate was observed.
- Cellular kinetic, tumor dynamic (Pop-CellK-PD) for Kymriah
 - We're continuing to learn which factors impact CART expansion, contraction and tumor killing.
 - The classical Lotka-Volterra Predator-Prey model is inconsistent with preclinical and clinical observations.
 - A precompetitive consortium pooling preclinical data may help in developing a structural CellK-PD model.

Backups

Effect of two drugs on Kymriah

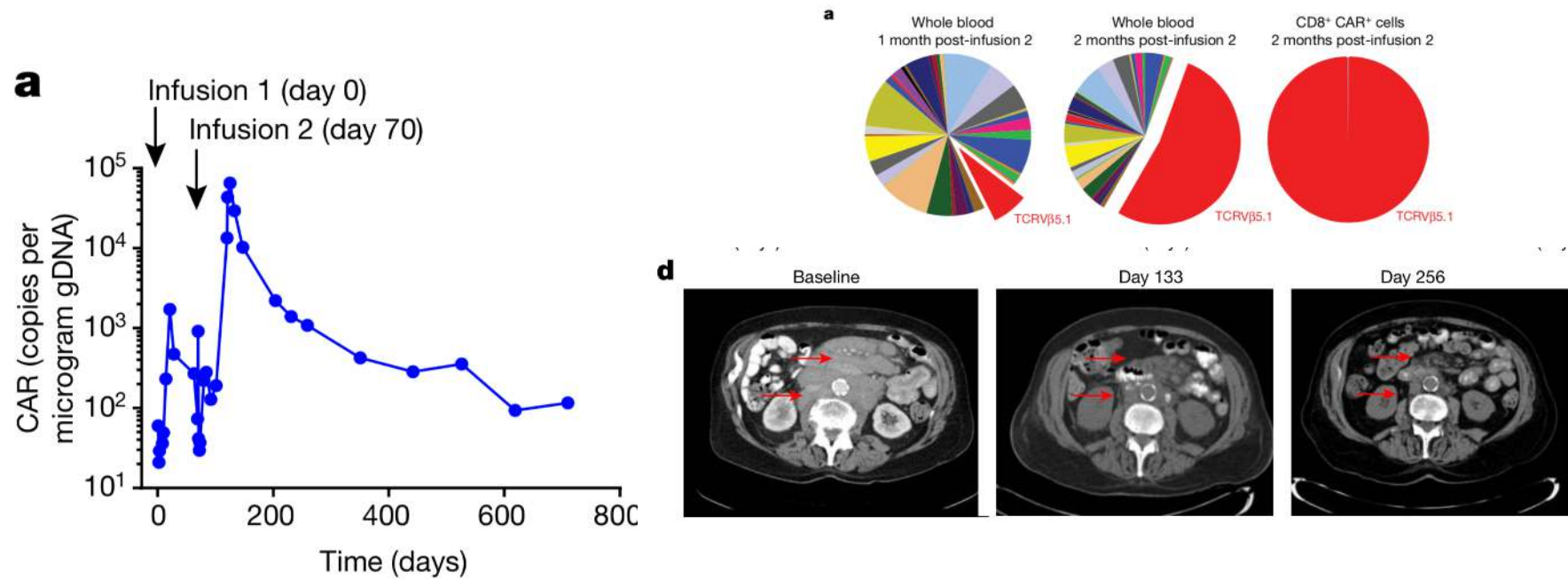


$$f(t) = \begin{cases} R_0 e^{\rho t}, & t < T_1 \\ R_1 e^{F_1 \cdot \rho(t-T_1)}, & T_1 \leq t < T_2 \\ R_2 e^{F_1 F_2 \cdot \rho(t-T_2)}, & T_2 \leq t < T_{\text{max}} \\ Ae^{-\alpha(t-T_{\text{max}})} + Be^{-\beta(t-T_{\text{max}})}, & t \geq T_{\text{max}} \end{cases}$$

$$R_1 = R_0 \cdot e^{\rho T_1}$$

$$R_2 = R_1 \cdot e^{\rho F_1 (T_2 - T_1)}$$

Clinical observation related to TET2 locus



- Two months after second infusion, CART peaked
- Almost all CART cells were TCRVβ5.1 and thus originated from a single cell [this clonal dominance is not generally observed]
- CAR was integrated into TET2 – a tumor suppressor gene and master regulator of blood cell formation