The cellular kinetics and anti-tumor dynamics of Kymriah

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MODELING WITHOUT BORDERS

ACoP 10

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.

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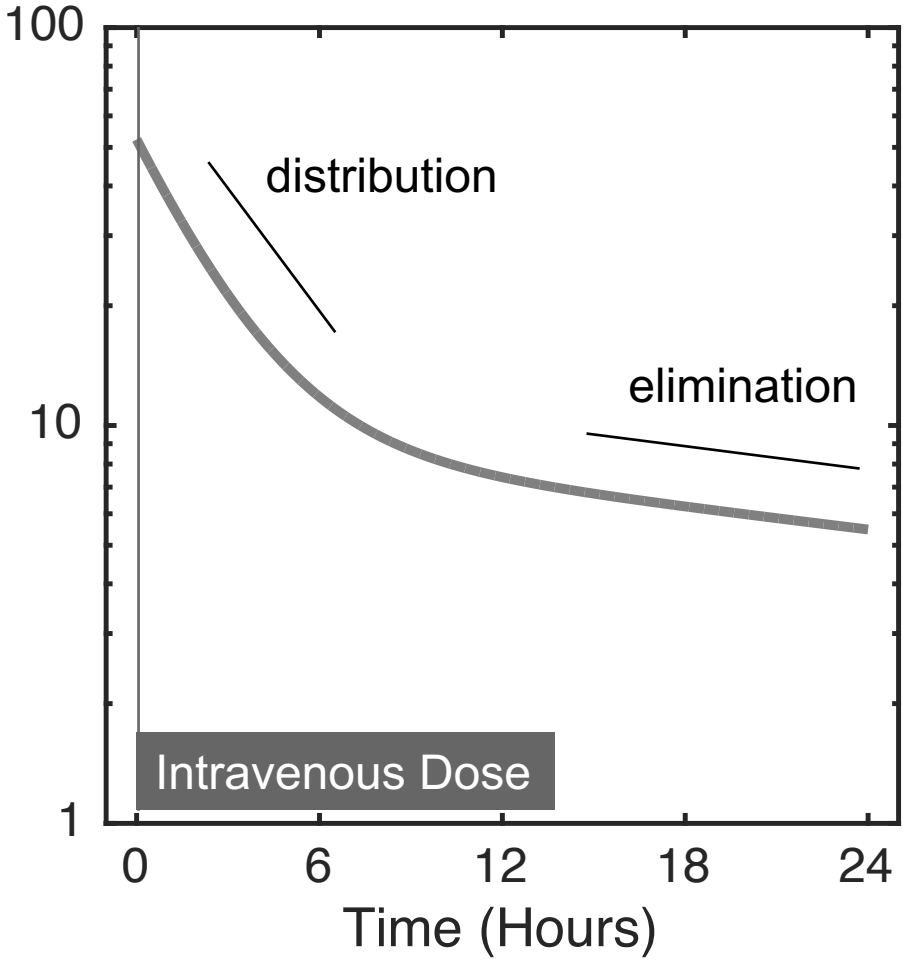
Executive Summary

- Kymriah (CTL019) is a Chimeric Antigen Receptor T-cell (CART) therapy that is approved for pediatric ALL[1] and DLBCL[2].
- 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

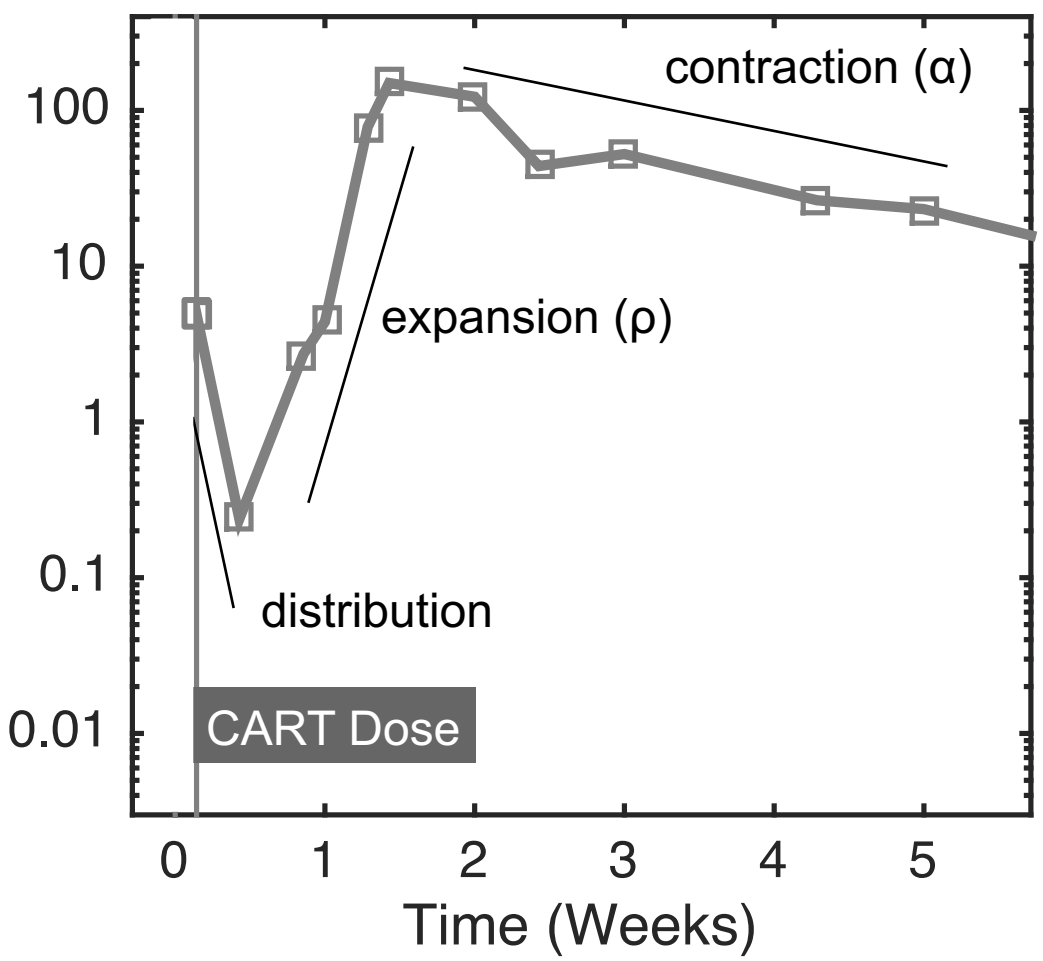
1. ALL = Acute Lymphoblastic Leukemia (relapsed/refractory)
2. DLBCL = Diffuse Large B Cell Lymphoma

CART kinetics are very different from traditional pharmacokinetics

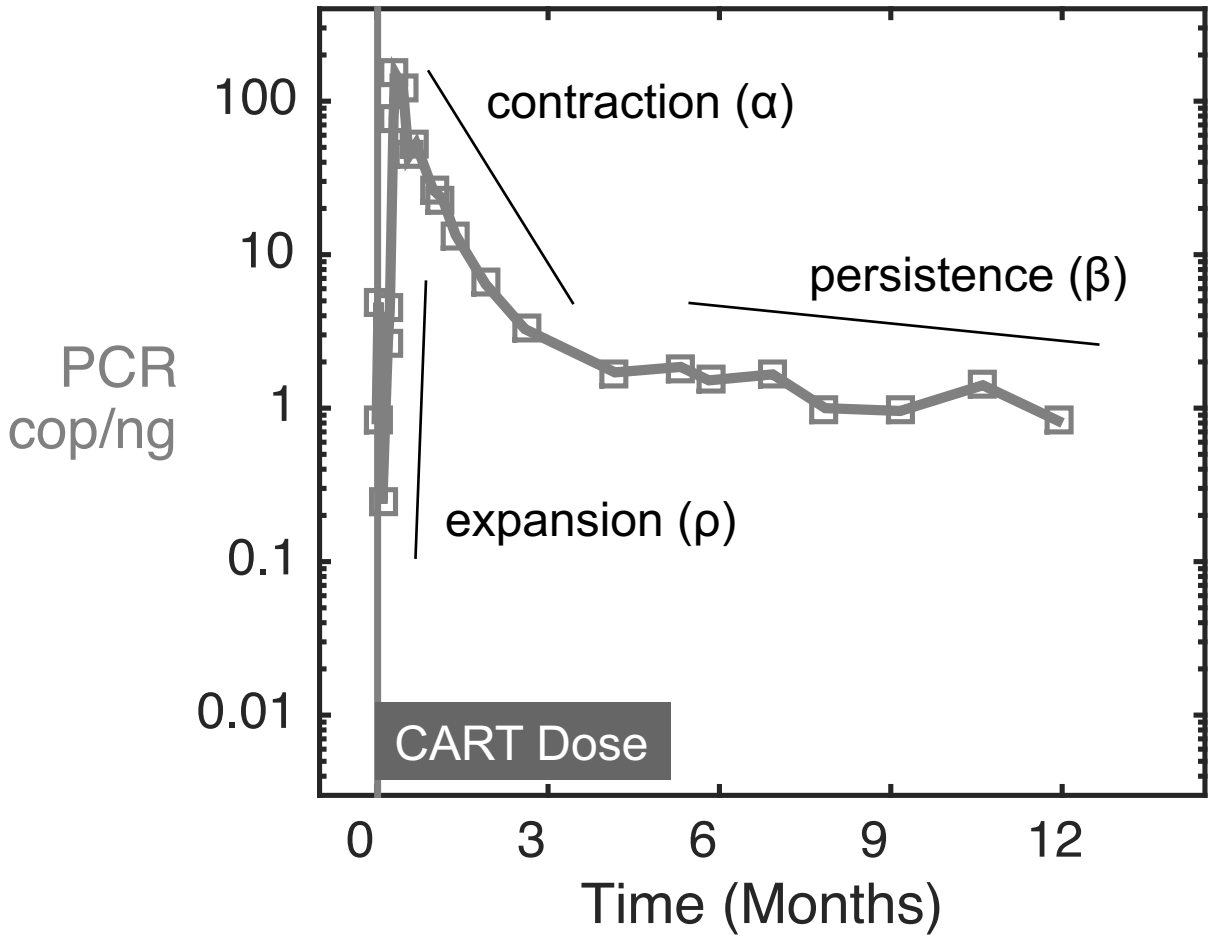
Small Molecule



Kymriah (CART)



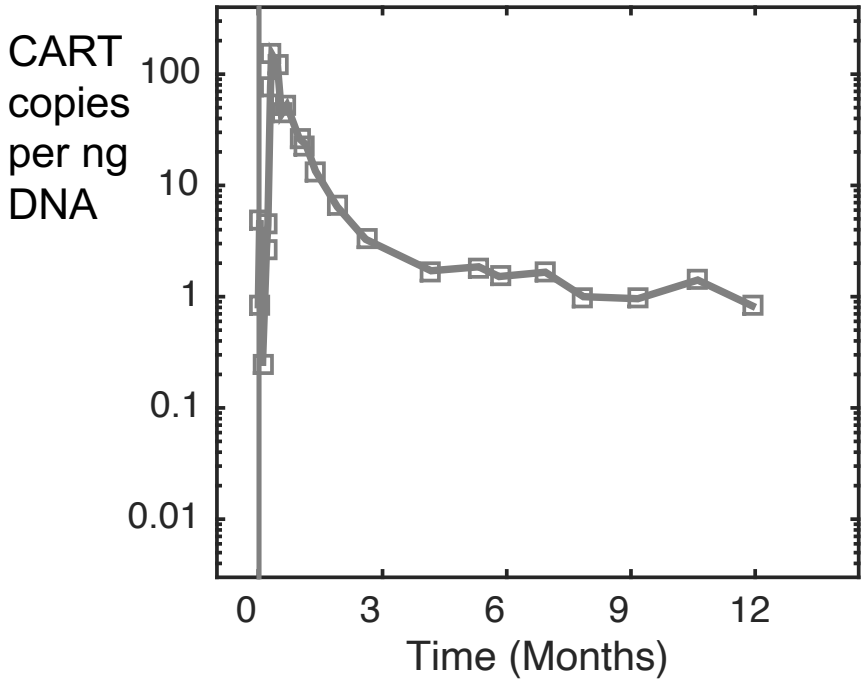
Kinetics of CART over one year



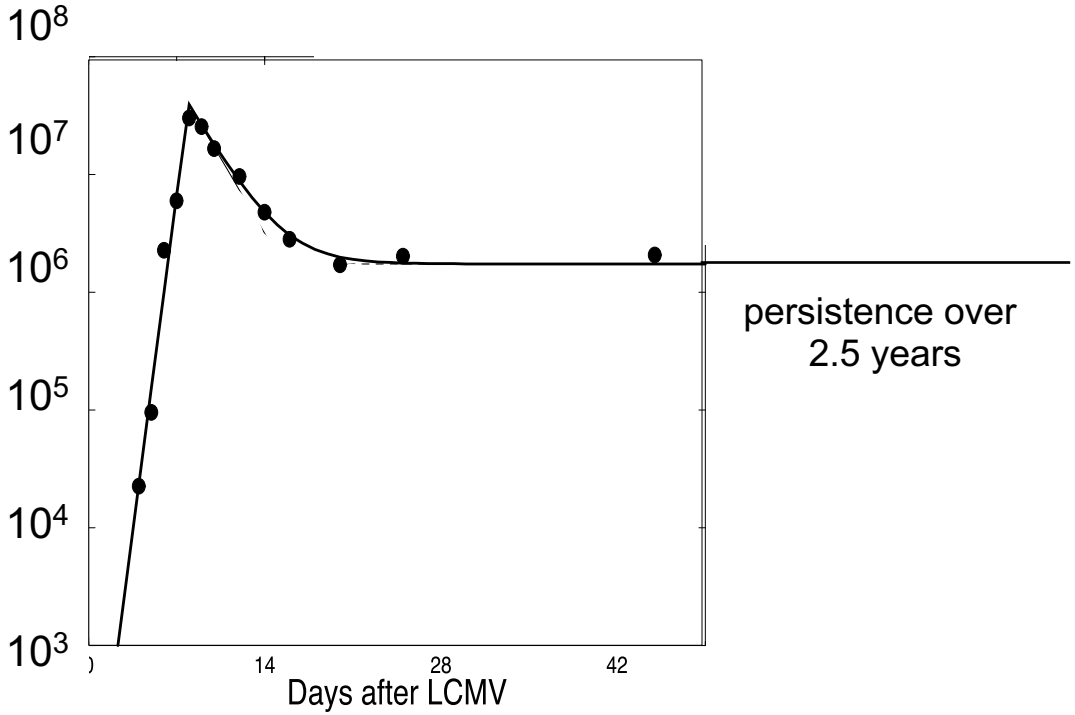
2 of 3 patients to receive CART in 2010 still have detectable cells

CART kinetics in patients is comparable to mouse T cell dynamics

Patient receiving CART
(PCR copies per ng)

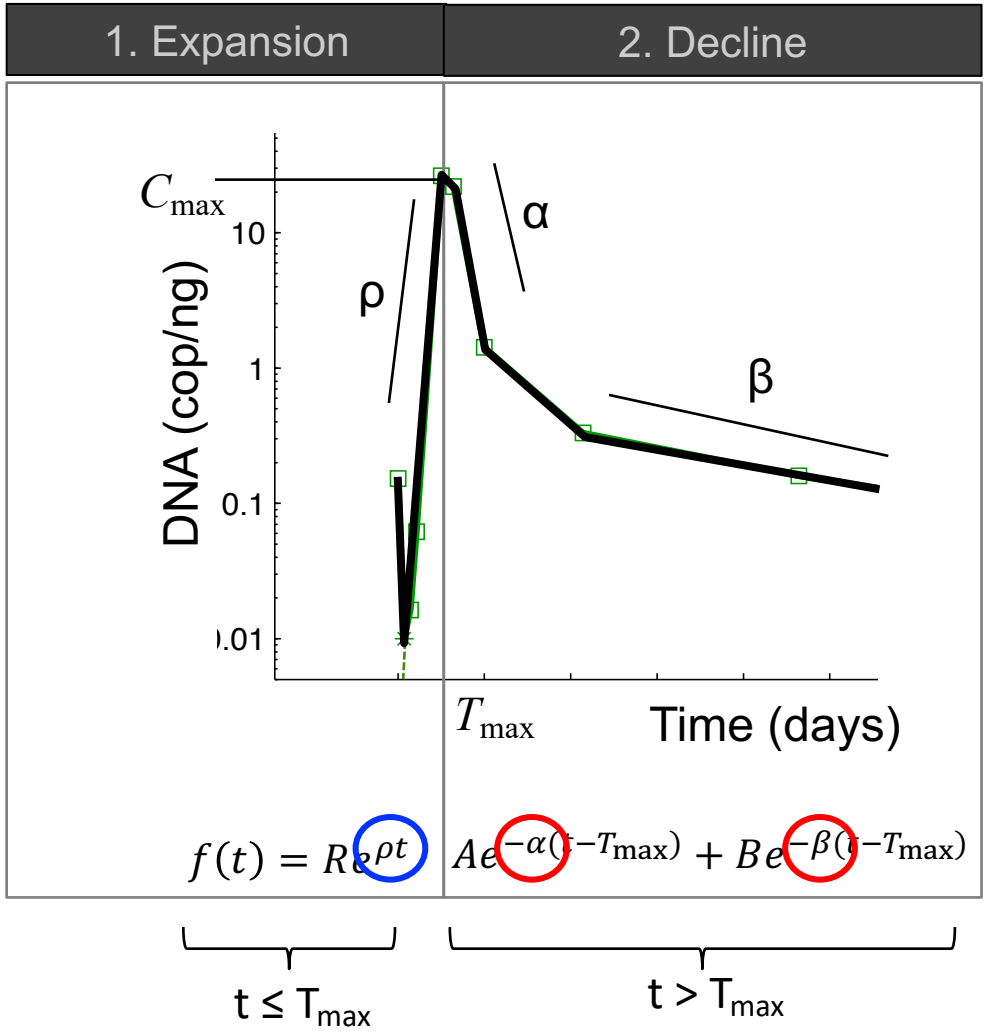


Mouse infected with LCMV[1-3]



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 mice[1]



R	Initial DNA/ng (post-distribution)
ρ	Expansion rate
C_{max}	Peak expansion = $Re^{\rho \cdot T\max}$
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

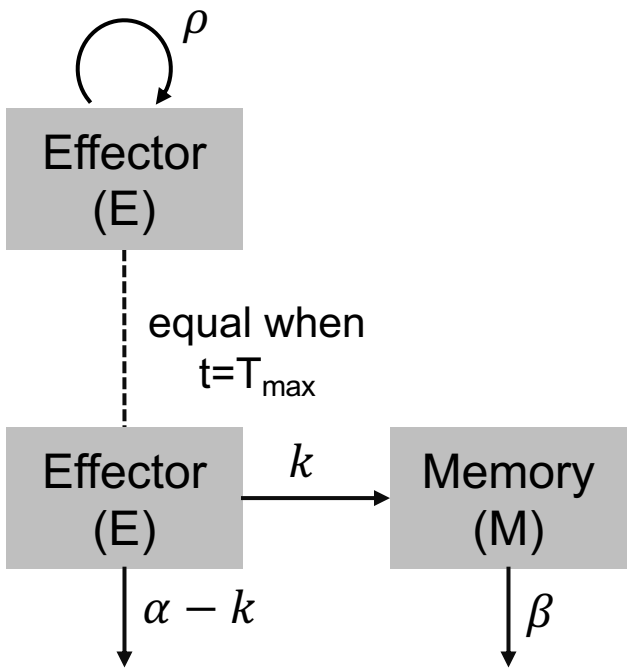
$$f(t) = -(A+B)e^{-k_a t} + Ae^{-\alpha t} + Be^{-\beta t}$$

1. De Boer et al., J Immunol, 171, 3928 (2003)

Semi-mechanistic model with same analytical solution as empirical model

Expansion
(Exponential Growth)
$t \leq T_{max}$

Biexponential Decline
(Contraction + Persistence)
$t > T_{max}$



$$\frac{dE}{dt} = \rho \cdot E$$

$$\frac{dE}{dt} = -\alpha \cdot E$$

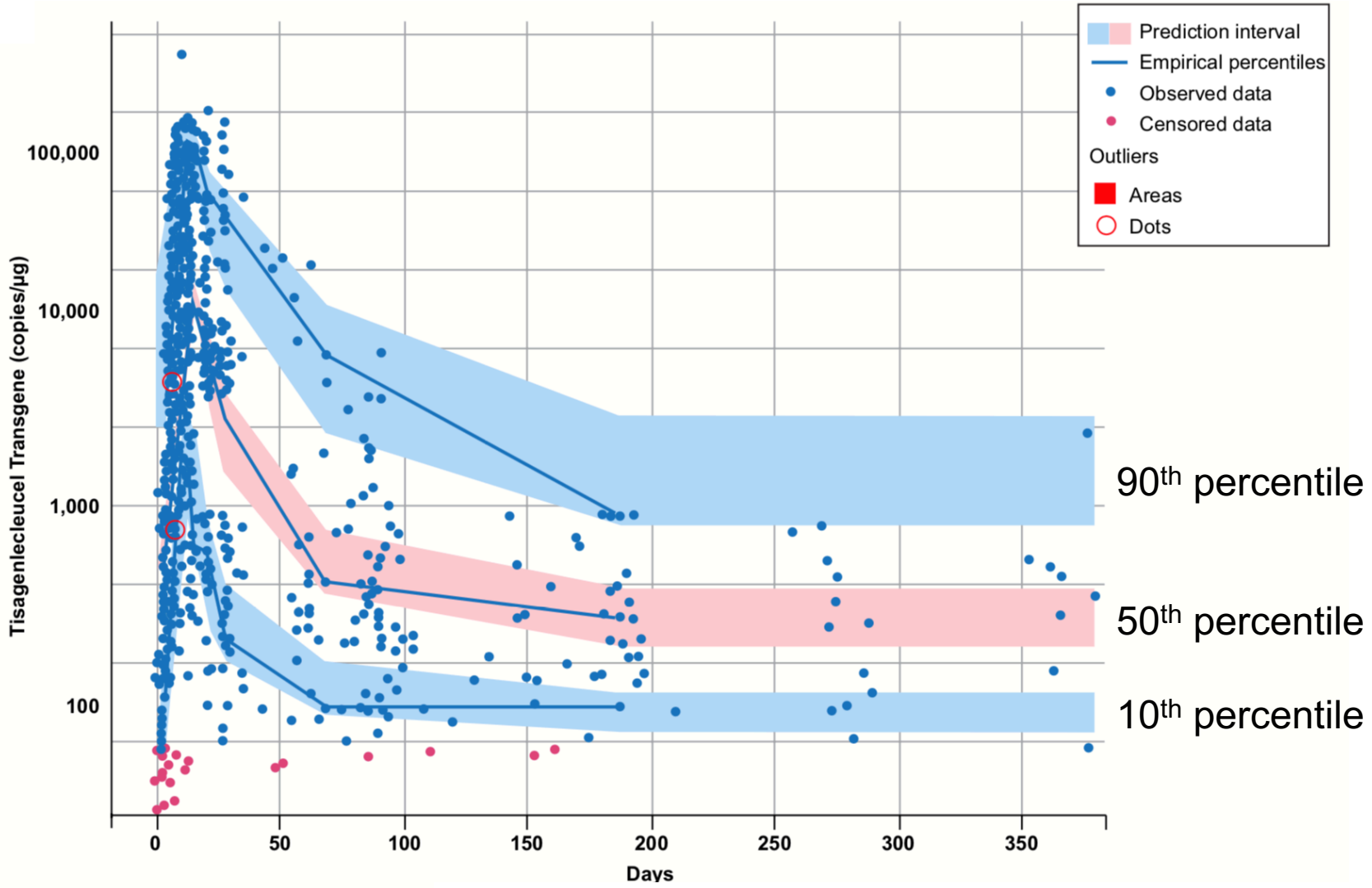
$$\frac{dM}{dt} = k \cdot E - \beta \cdot M$$

$$k = \frac{B}{A+B}(\alpha - \beta)$$

Other structural models also give exponential growth and biexponential decline

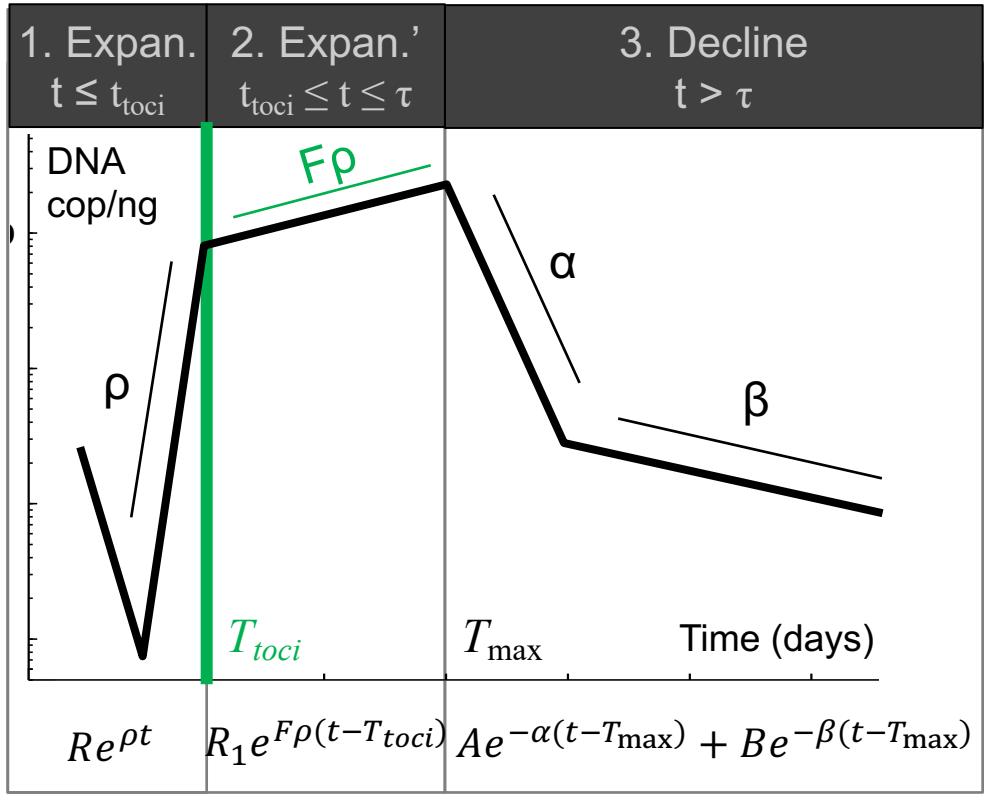
Stein, Andrew M., et al. "Tisagenlecleucel Model-Based Cellular Kinetic Analysis of Chimeric Antigen Receptor–T Cells." *CPT: pharmacometrics & systems pharmacology* 8.5 (2019): 285-295.

Model describes data (Visual Predictive Check)



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.

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 → no tocilizumab impact

F < 1 → tocilizumab slows expansion

Second drug (corticosteroids) was also introduced

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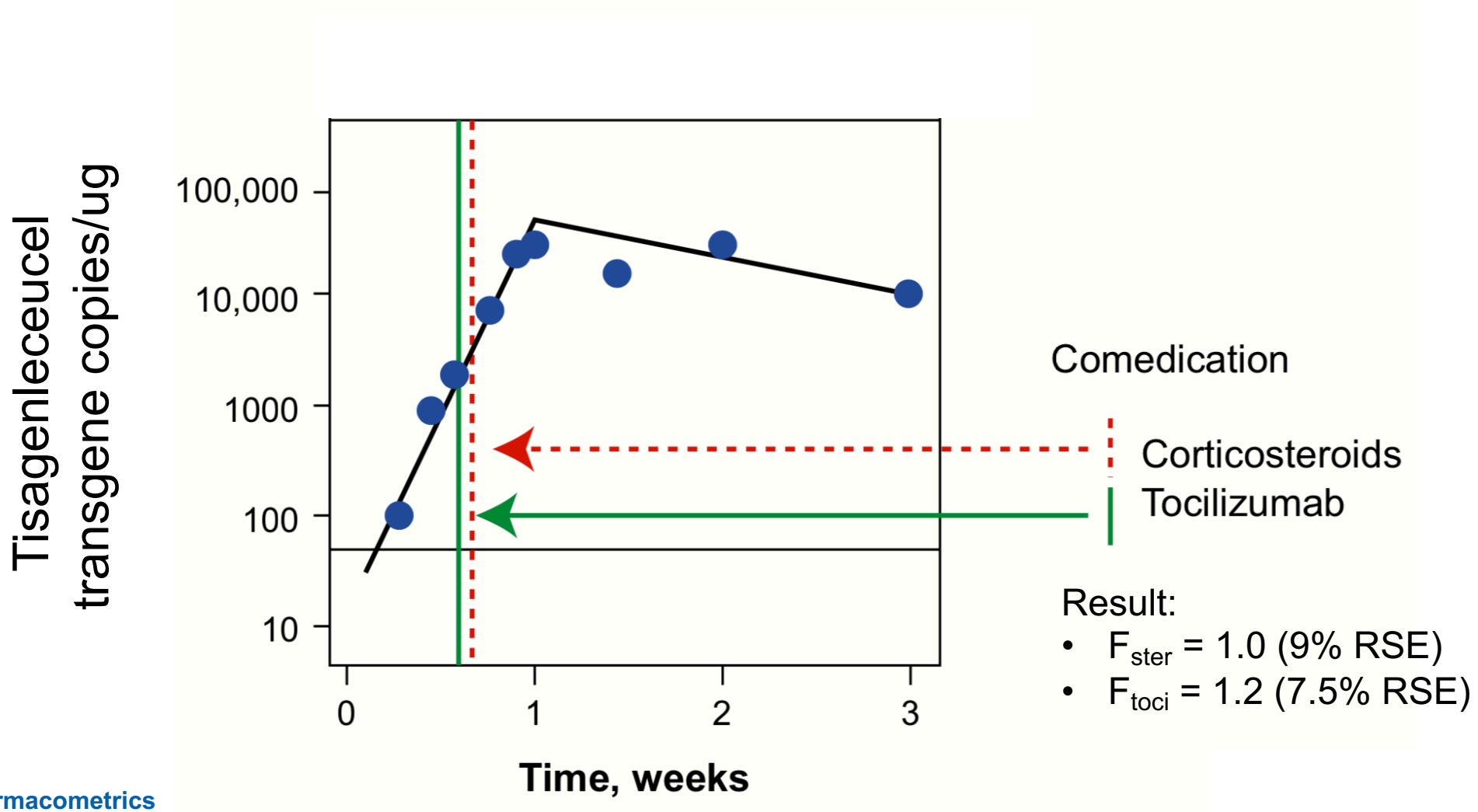
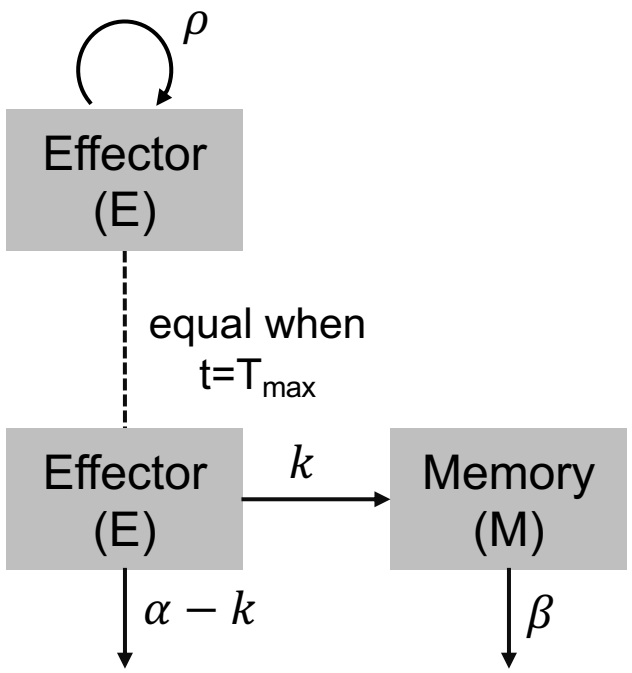
No impact of tocilizumab on CART expansion rate has been observed

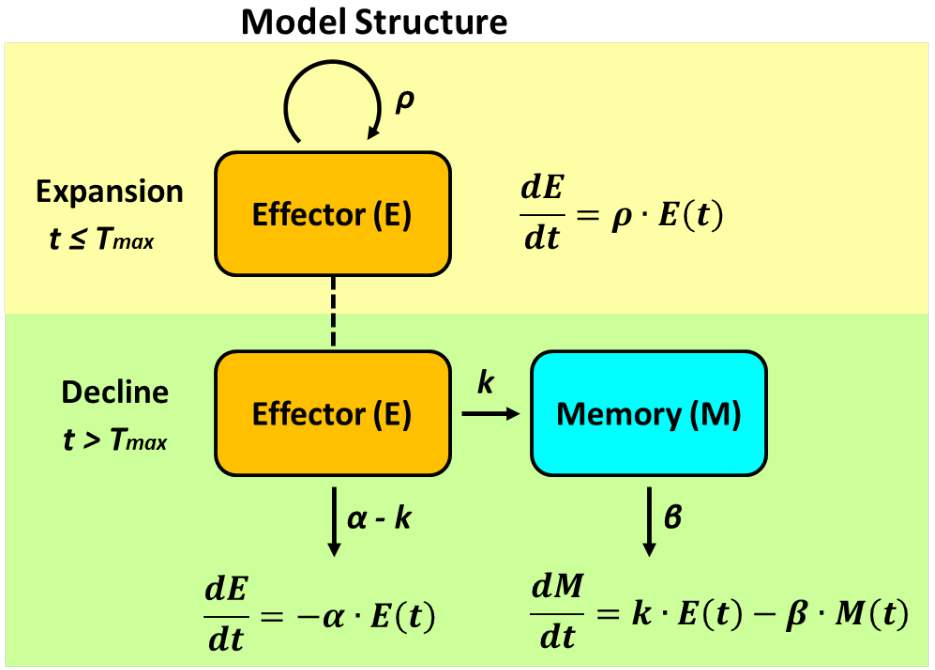


FDA used the same model in their analysis of both Kymriah + Yescarta

Novartis Publication



FDA Presentation at ACoP Conference



Key parameters

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

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We have a cellular kinetic model
We are now developing models for the PD

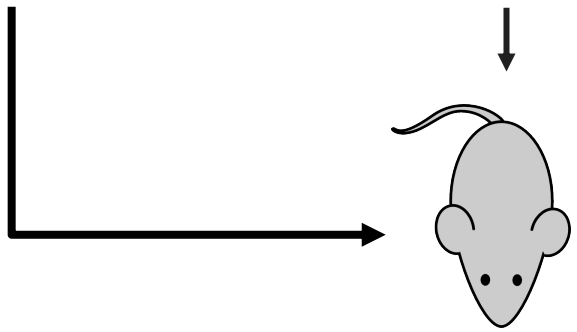
- Challenges in modeling safety: cytokine release syndrome (CRS)
  - **Cytokine data** is rich and could be modeled[1], but how to link the cytokines to efficacy metrics?
  - **Temperature and blood pressure** may be the best biomarkers to model, but we don't currently have rich enough sampling in our 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).

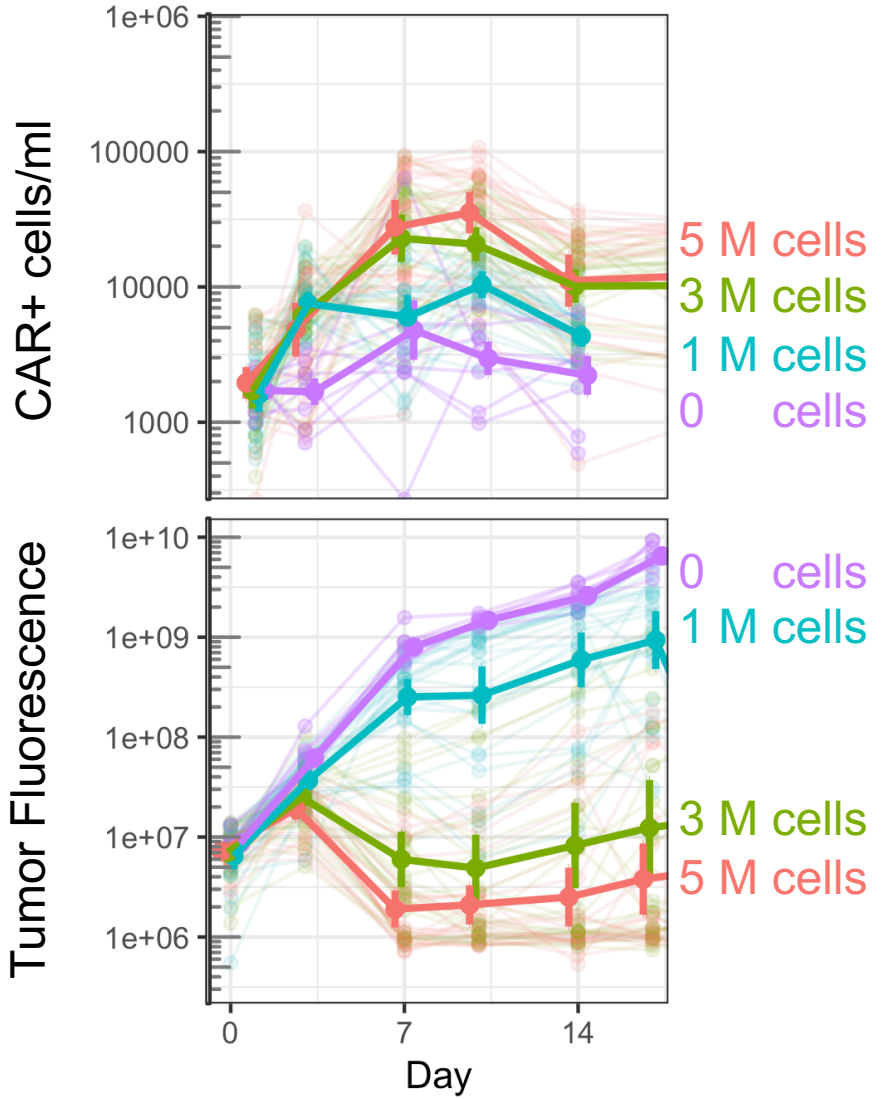
Clear dose-exposure-response relationship is observed in Nalm6 mouse model

1 million tumor cells (day -6)

0-5 million CART cells (day 1)



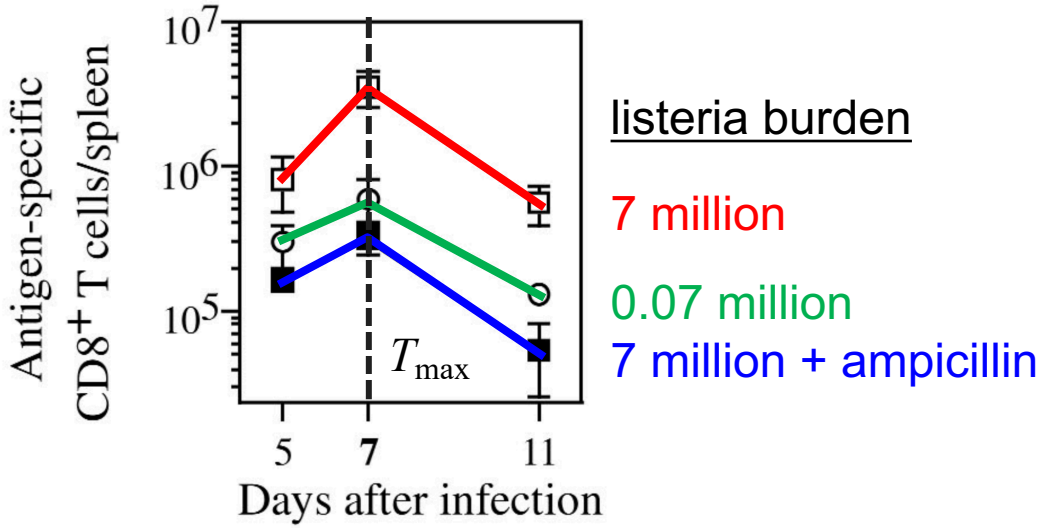
What explains the limited anti-tumor effect at a 1 million cell dose?

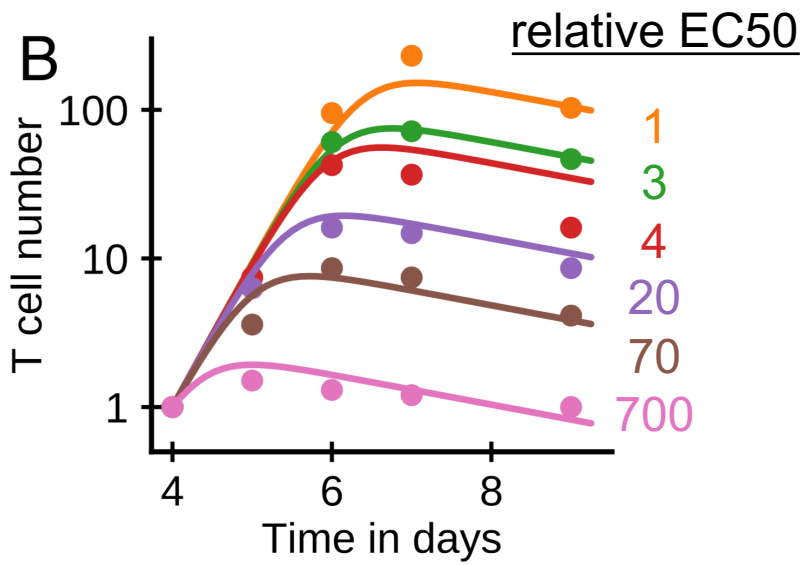


Similar to experiment from: Milone et al., *Mol Ther,* 17, 1453 (2009)

What are the determining factors of Tmax?

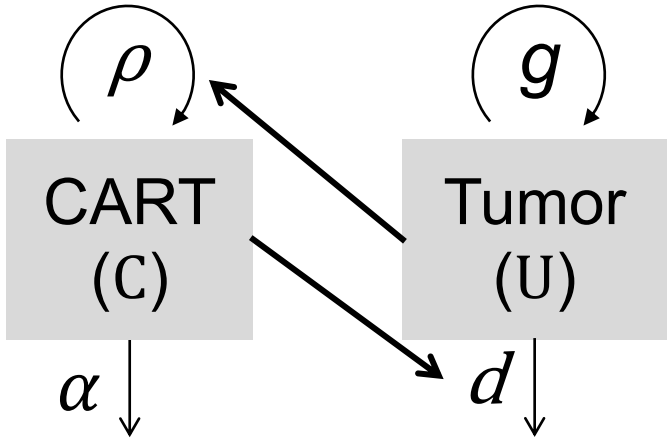
- In mice infected with listeria, T_{max} is independent of antigen level, suggesting the duration of proliferation is pre-programmed[1-2]
- T_{max} may depend on binding affinity of TCR to antigen[3]
- T cell exhaustion (PD-1 expression) is also relevant[4].

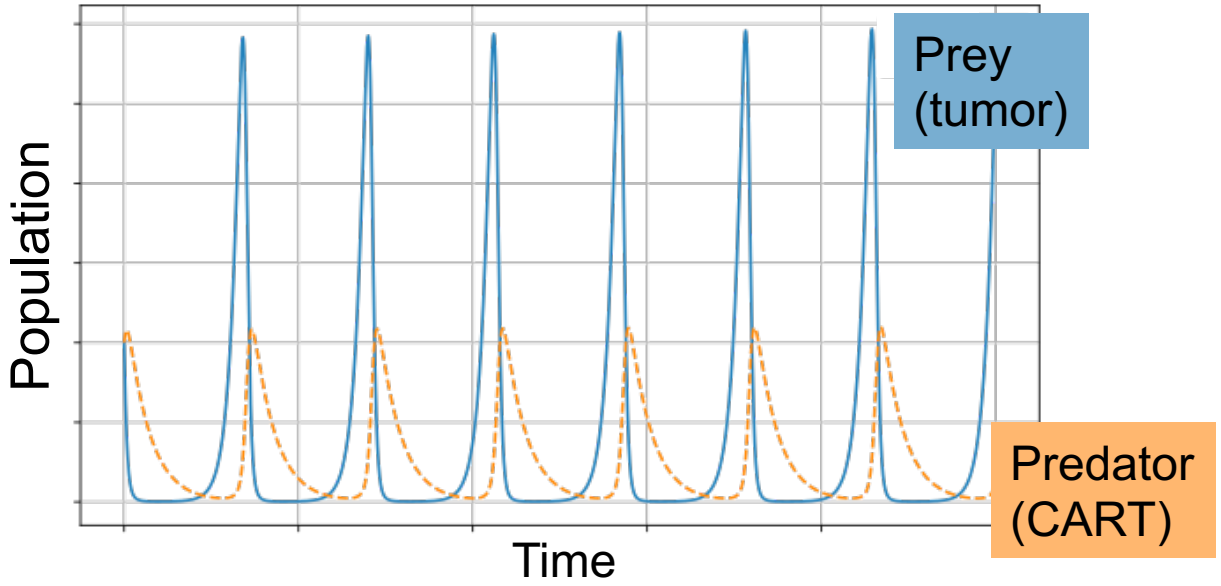




1. Badovinac, V et al "Nature immunology 3.7 (2002): 619.
2. De Boer and Perelson, J Theor. Biol., 45, 327 (2013).
3. Mayer, A, et al. PNAS, 116.13 (2019): 5914-5919.
4. Fraietta, J, Nature medicine 24.5 (2018): 563.

The Lotka-Volterra Predator-Prey Model[1-2] 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.

1. https://en.wikipedia.org/wiki/Lotka%E2%80%93Volterra_equations
2. Wodarz, Dominik. J PKPD 41.5 (2014): 415-429.

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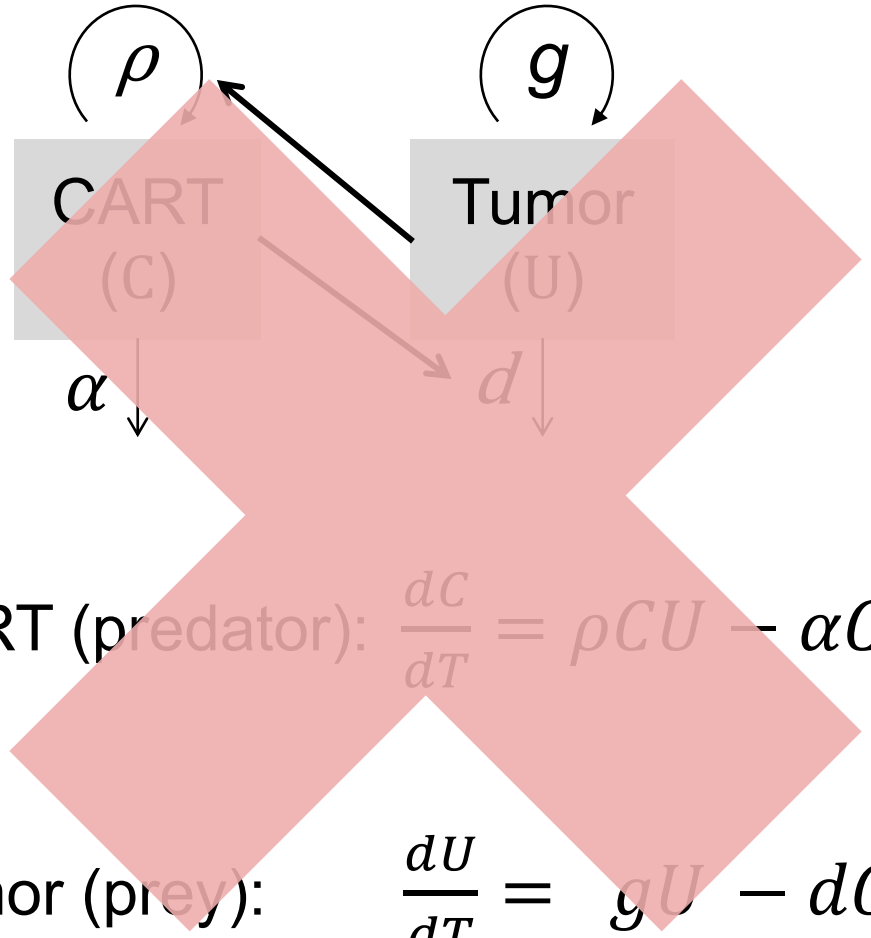
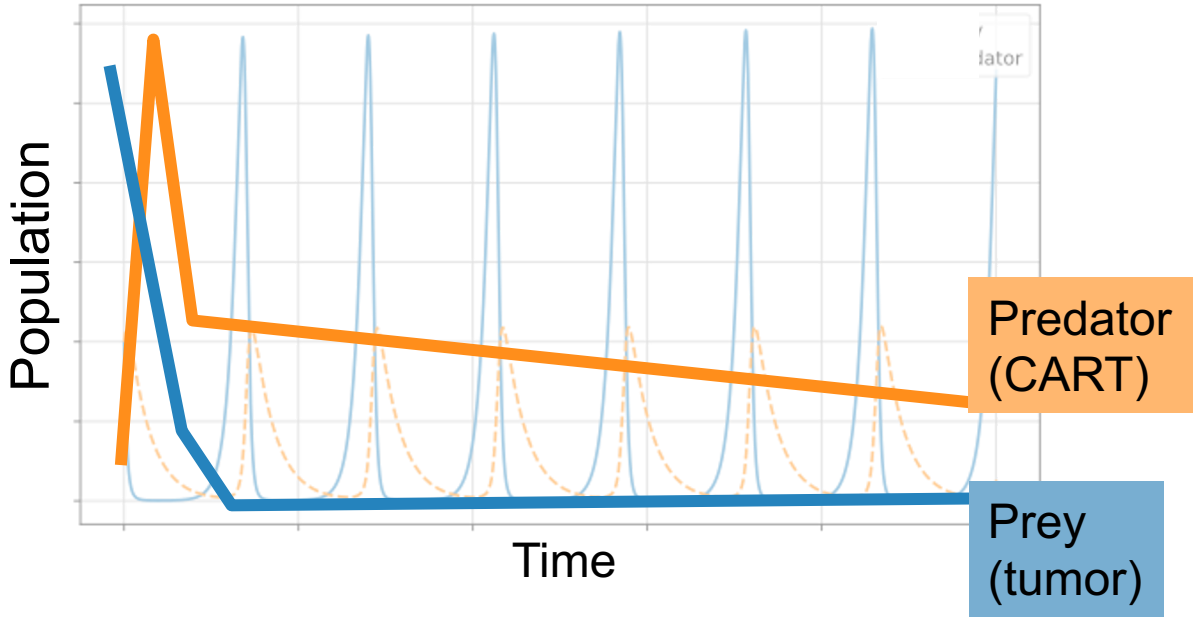
The Lotka-Volterra Predator-Prey cyclic behavior does not match clinical observations.



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

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



1. https://en.wikipedia.org/wiki/Lotka%E2%80%93Volterra_equations
2. Wodarz, Dominik. J PKPD 41.5 (2014): 415-429.

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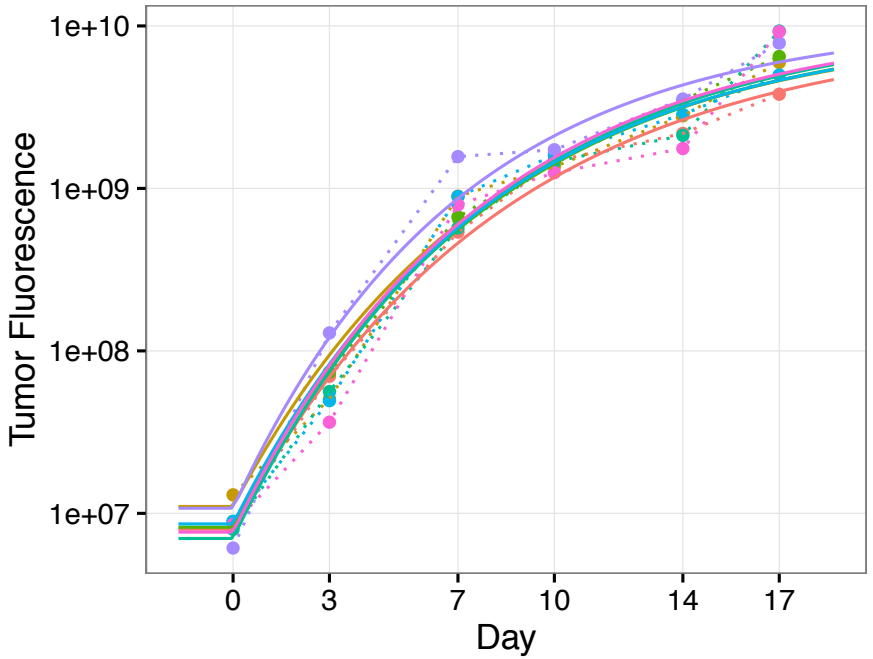
Saturable tumor growth (Gompertz)

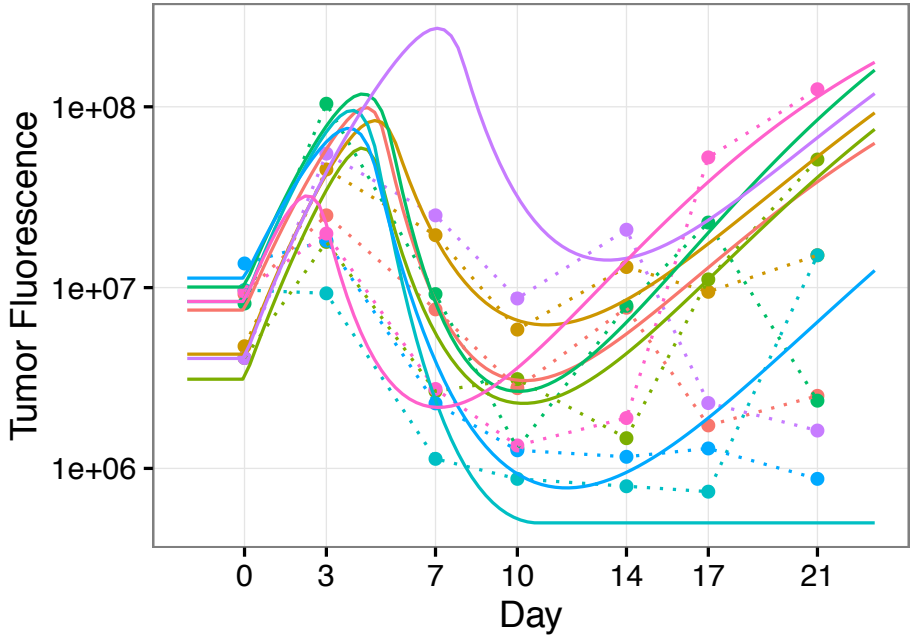
$$\frac{dU}{dt} = g \cdot U \cdot [\log(\text{Umax}) - \log(\text{U})]$$



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)

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



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

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.

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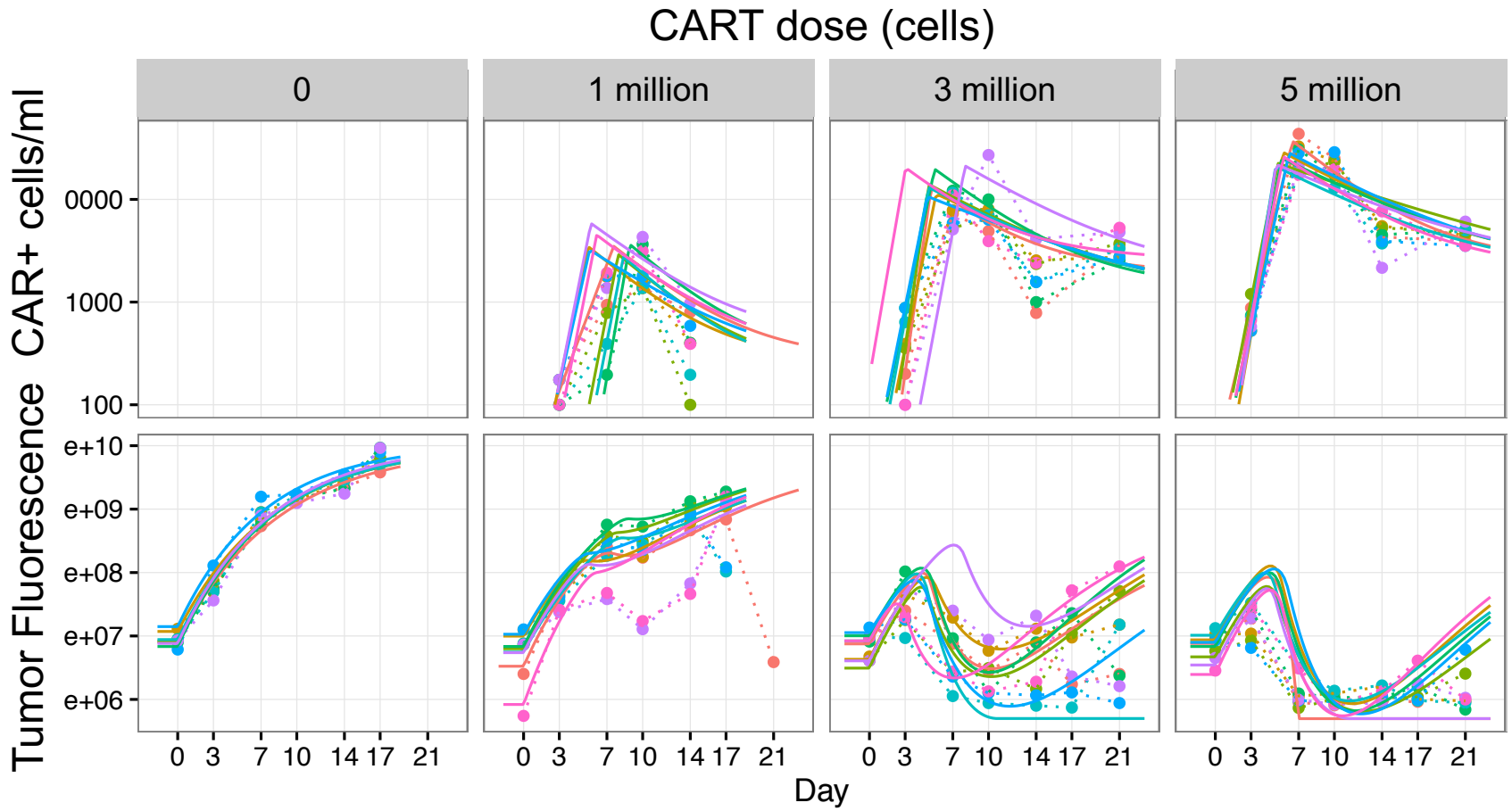
Simple model with “pre-programmed” cell expansion until Tmax describes the data



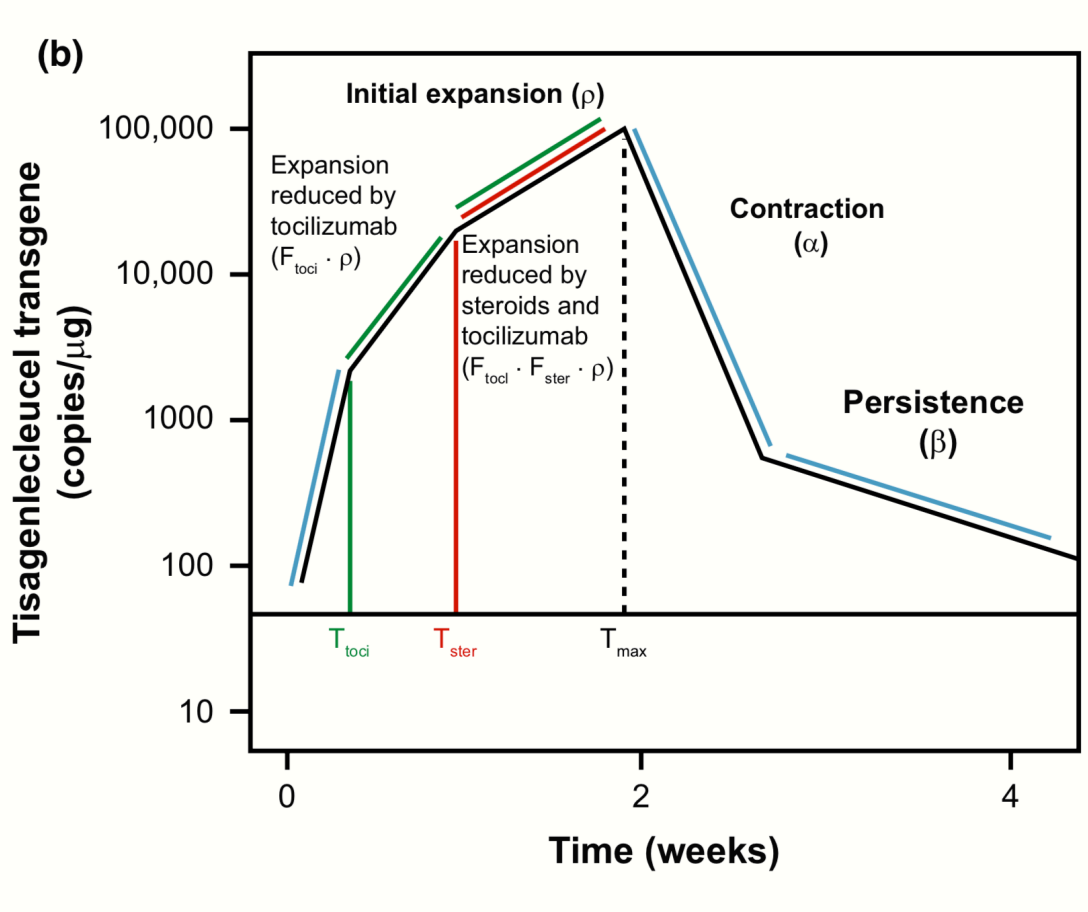
A more complex explanation isn’t needed to for why 1 million cells is not enough to eliminate the tumor

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

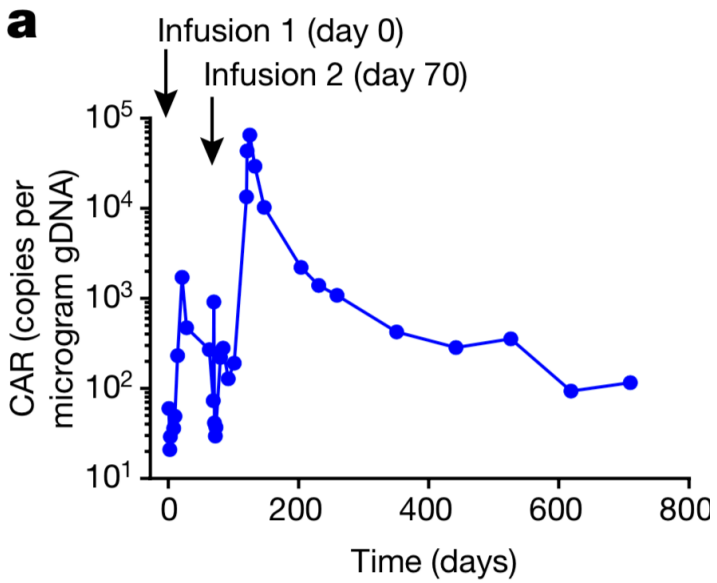


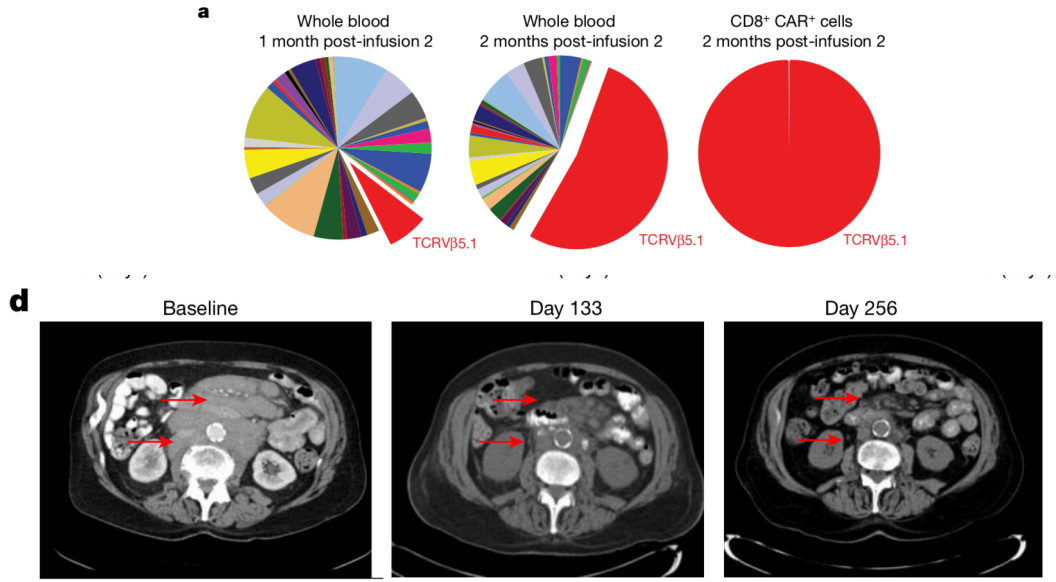
$$f(t)=\begin{cases} R_0 e^{\rho t}, & t<T_1 \\ R_1 e^{F_1\cdot\rho(t-T_1)}, & T_1\le t<T_2 \\ R_2 e^{F_1F_2\cdot\rho(t-T_2)}, & T_2\le t<T_{\max} \\ Ae^{-\alpha(t-T_{\max})}+Be^{-\beta(t-T_{\max})}, & t\ge T_{\max} \end{cases}$$

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

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

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

Fraietta, Joseph A., et al. Nature 558.7709 (2018): 307.