Supplement Article

Chimeric Antigen Receptor T Cell Therapies: A Review of Cellular Kinetic-Pharmacodynamic Modeling Approaches

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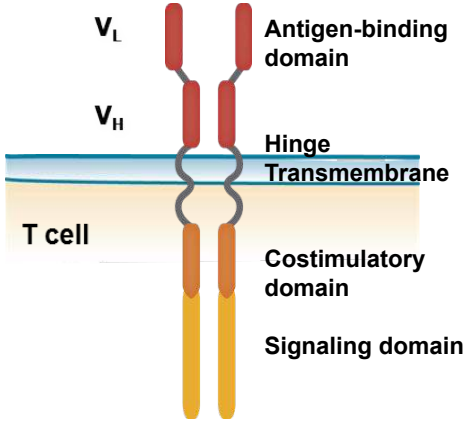
Executive Summary

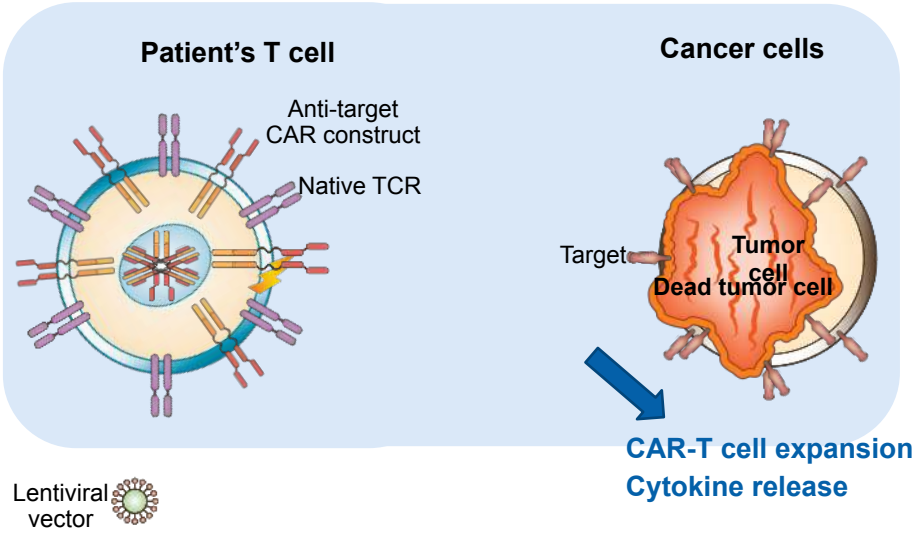
- Situation
  - How do we apply model informed drug development for CART therapy
  - Unlike traditional PopPK, there is no consensus on model structures for CART.
- Question
  - Is there a concise set of models we should explore for CART, as for PopPK?
- Answer
  - Thorough investigation of Cellular-Kinetic – Pharmacodynamic structural models
  - Survey of key scientific findings from literature that show cases where a more complex model can be utilized to answer the questions of interest.

CAR-T therapy overview

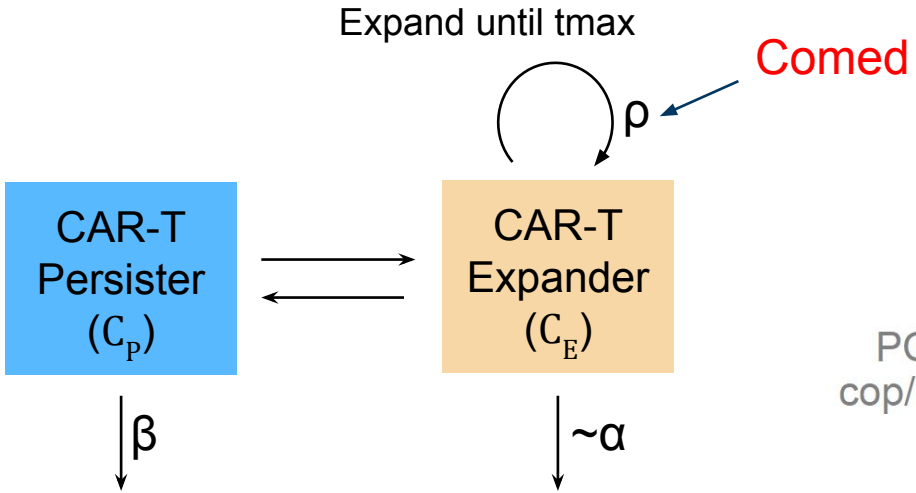
- Structure of Chimeric Antigen Receptor (CAR)

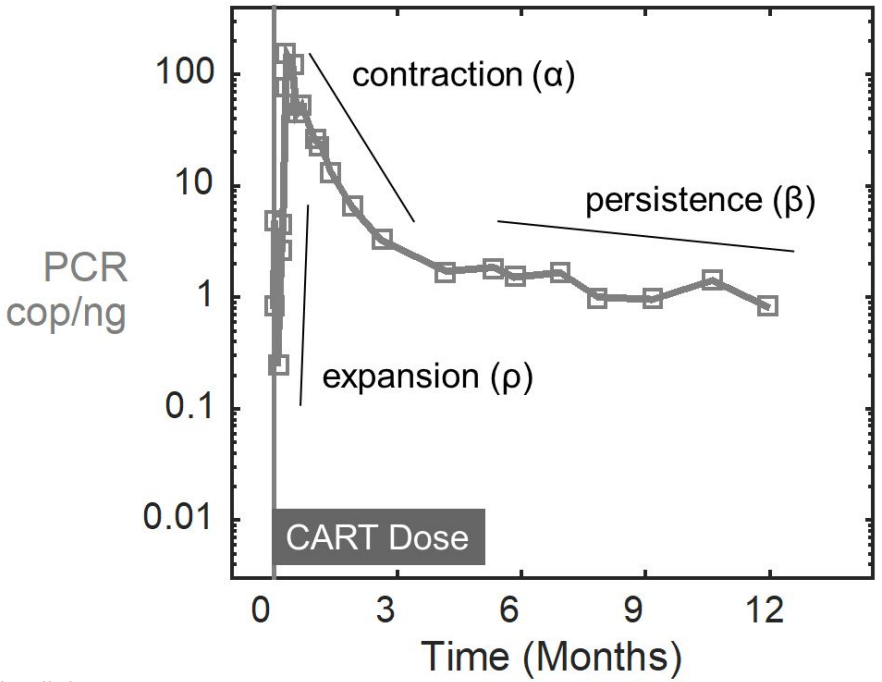


- A living drug designed to target tumor cells (Kymriah® as an example)



CART Cellular kinetic model



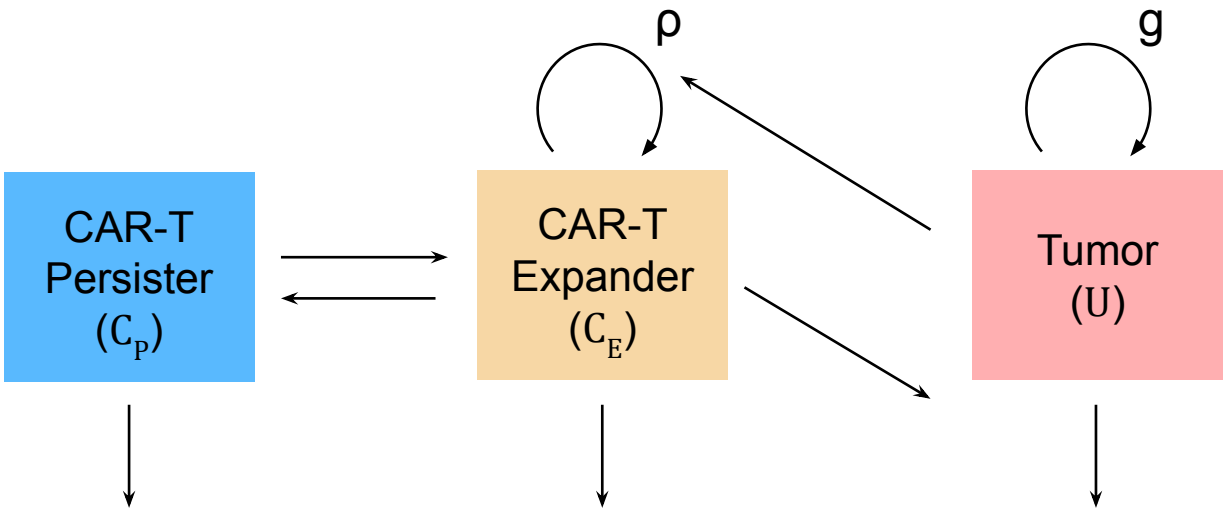


Application: Describes CART kinetics

- Demonstrated lack of impact of co-medications (tocilizumab and corticosteroids) on growth rate

Stein AM, Grupp SA, Levine JE, et al. Tisagenlecleucel model based cellular kinetic analysis of chimeric antigen receptor–T Cells. CPT Pharmacometrics Syst Pharmacol. 2019;8(5):285-295.

CART Cellular Kinetic – Pharmacodynamic model



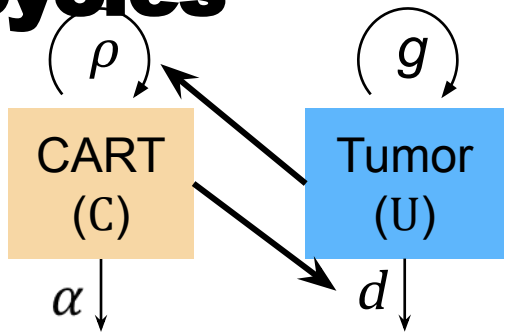
Application

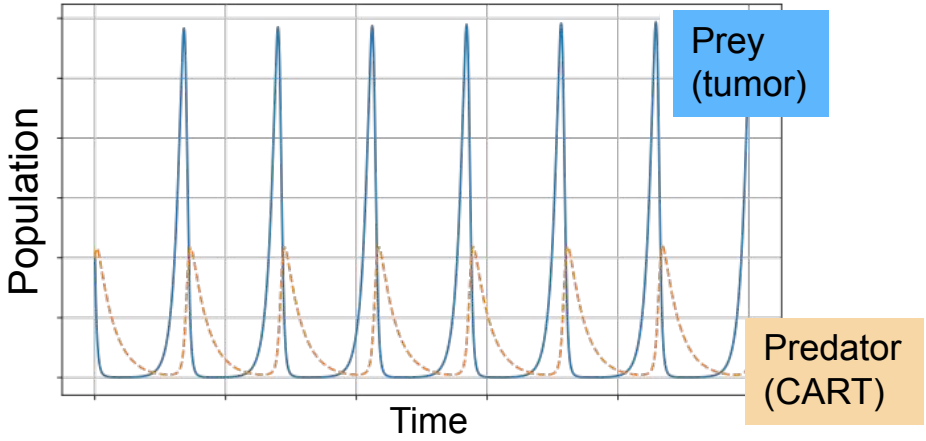
- Assess impact of tumor burden on CART kinetics.
- Characterize relationship between dose, cellular kinetics and tumor killing.

Question/Challenge

- Choosing correct functional forms for growth and killing

Example: Lotka-Volterra Predator-Prey Model [1-2] is frequently used, but has cycles





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

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

Cyclic behavior is not observed in the clinic.

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

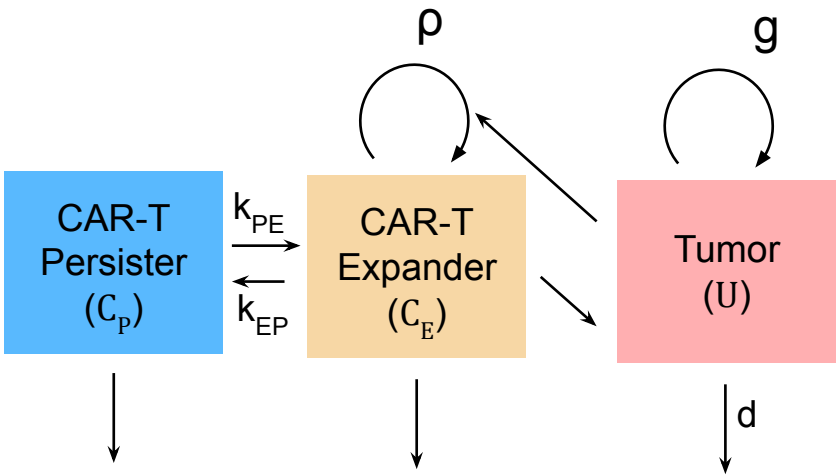
List of criteria a CellK-PD model should have

1. Exponential expansion
2. Fast initial decline
3. Slow long term slow decline
4. No cyclic behavior
5. Antigen drives expansion
6. CART expansion is not infinite, despite large antigen burden

EC50 expansion + EC50 killing model had all desired properties

Criteria	Mayer et al. + Gompertz	Sahoo et al.	Kuznetsov et al.	Lotka-Volterra	Newly proposed model structure
1. Exponential Expansion	yes	yes	yes	yes	yes
2. Fast initial decline	yes	yes	yes	yes	yes
3. Slow long term slow decline	no	no	no	no	yes
4. Antigen drives expansion	yes	no	yes	yes	yes
5. CART expansion not infinite	no	no	no	no	yes
6. No cyclic behavior	possibly	possibly	possibly	no	yes

Newly proposed CART CellK-PD model structure that meets all criteria



$$\frac{dC_E}{dt} = \begin{cases} \rho \cdot \frac{C_E \cdot U}{EC_{50,\rho} + C_E + U}; & t \le T_{\max} \\ -(k_{EP} + k_E)C_E; & t > T_{\max} \end{cases}$$

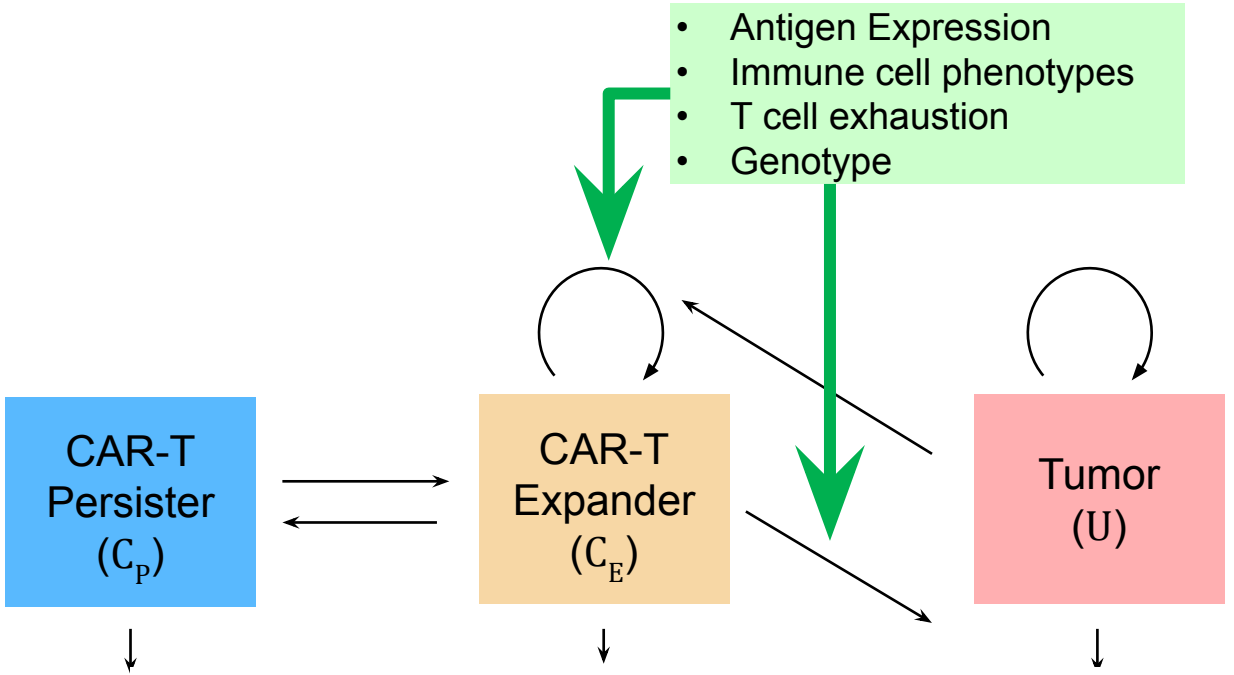
$$\frac{dC_P}{dt} = \begin{cases} 0; & t \le T_{\max} \\ k_{EP}C_E - \beta C_P; & t > T_{\max} \end{cases}$$

$$\frac{dU}{dt} = gU\frac{\log(U_{\max}) - \log(U)}{\log(U_{\max})} - d \cdot \frac{C_E \cdot U}{EC_{50,d} + C_E + U}$$

EC50 formula is derived from a traditional binding model.

Mayer, Andreas, et al. "Regulation of T cell expansion by antigen presentation dynamics." *Proceedings of the National Academy of Sciences* 116.13 (2019): 5914-5919.

Confounding factors that make E-R analyses challenging [1-3]



Challenge

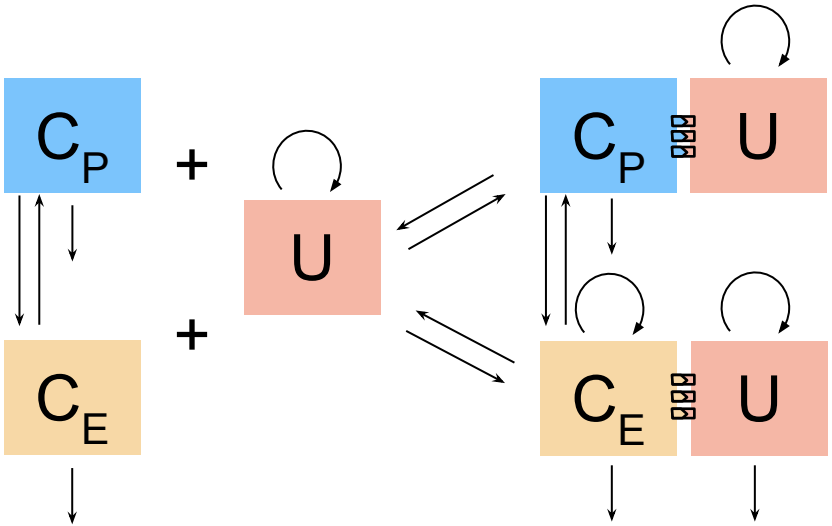
- Factors that can affect both exposure and response mean that E-R relationship may not be causal

Path Forward

- Measure as many confounders as possible
- Build more mechanistic models

1. https://en.wikipedia.org/wiki/Simpson%27s_paradox
2. https://sites.google.com/site/andrewsteinphd/causality
3. Yang, Jun, et al. "The combination of exposure-response and case-control analyses in regulatory decision making." The Journal of Clinical Pharmacology 53.2 (2013): 160-166.

Introduction of binding kinetics to account for antigen burden



Application

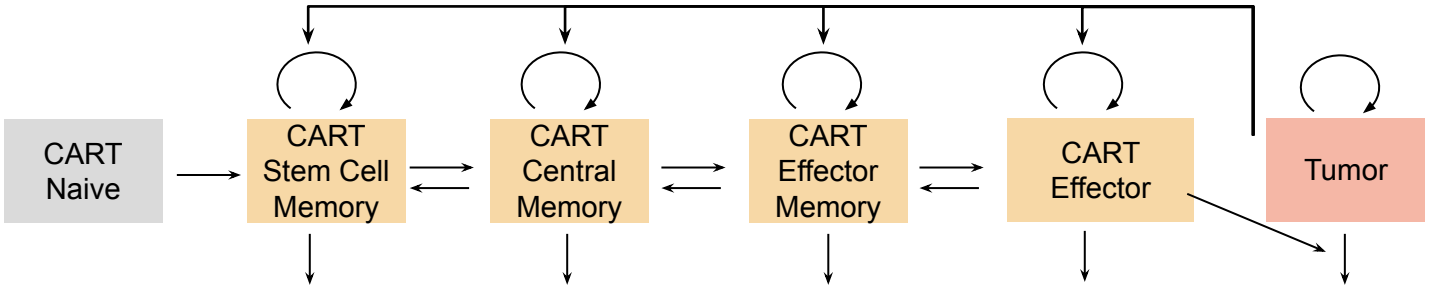
- Assess optimal binding affinity
- Assess impact on cellular antigen density on CART kinetics

Challenge: potential umbrella shaped affinity-response curve [1]

1. Exhaustion (excessive signaling),
2. Restrict T cell killing to only one tumor cell due to lasting synapse
3. Restrict the T cell's ability to generate persistent memory cells.
4. T cell loss via activation-induced cell death

1. Watanabe K, Kuramitsu S, Posey AD, June CH. Expanding the therapeutic window for CAR-T cell therapy in solid tumors: The knowns and unknowns of CAR-T cell biology. Front Immunol. 2018;9(OCT):1-12.

Immunophenotype modeling framework



Application

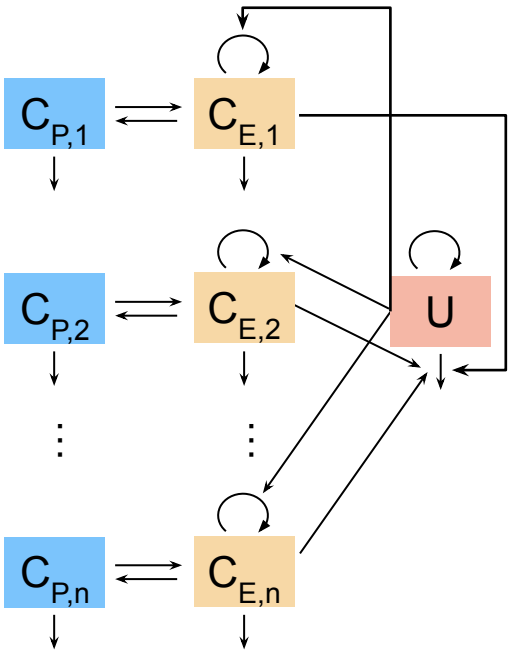
- Understanding how immunophenotype properties of the product impact tumor kinetics

Challenge

- Choosing which cell surface markers to use.
- Identifying the right structural model to characterize both expanding cells and persistent cells. Published preclinical models currently focus on the expansion phase [1]
- Collecting sufficient clinical data to inform model (more subsets mean more BLOQ data)

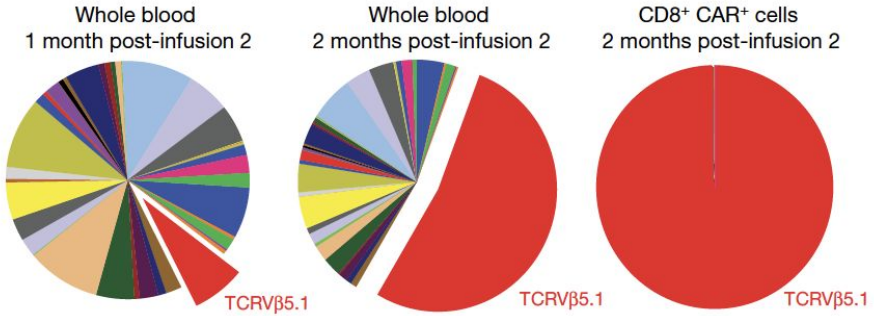
1. Buchholz VR, Flossdorf M, Hensel I, et al. Disparate individual fates compose robust CD8+ T cell immunity. Science. 2013;340(6132):630-635.

Importance of genotype heterogeneity



Challenge

- Insertion of CAR gene can disrupt another gene (e.g. TET2 or CBL-B) [1, 2], which can lead to a single clone that contributes to response.



Path Forward

- Collection of clonal heterogeneity data is crucial to understanding response.

1. Fraietta JA, Nobles CL, Sammons MA, et al. Disruption of TET2 promotes the therapeutic efficacy of CD19-targeted T cells. Nature. 2018;558(7709):307-312.
2. Shah NN, Qin H, Yates B, et al. Clonal expansion of CAR-T cells harboring lentivector integration in the CBL gene following anti-CD22 CAR-T cells therapy. Blood Adv. 2019;3(15):2317-2322.

Summary

- We propose a framework for cellular kinetic pharmacodynamic (CellK-PD) model structure to try out for future preclinical and clinical studies.
- Many model extensions were proposed, but each have challenges associated with them.

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