CAR-T Clinical Pharmacology Considerations and Modeling in Monolix

Mitali Gaurav, Nancy Lin, Pauline Traynard

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External Presentation

SimulationsPlus

Outline

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- Approved CAR-T Cell Therapies
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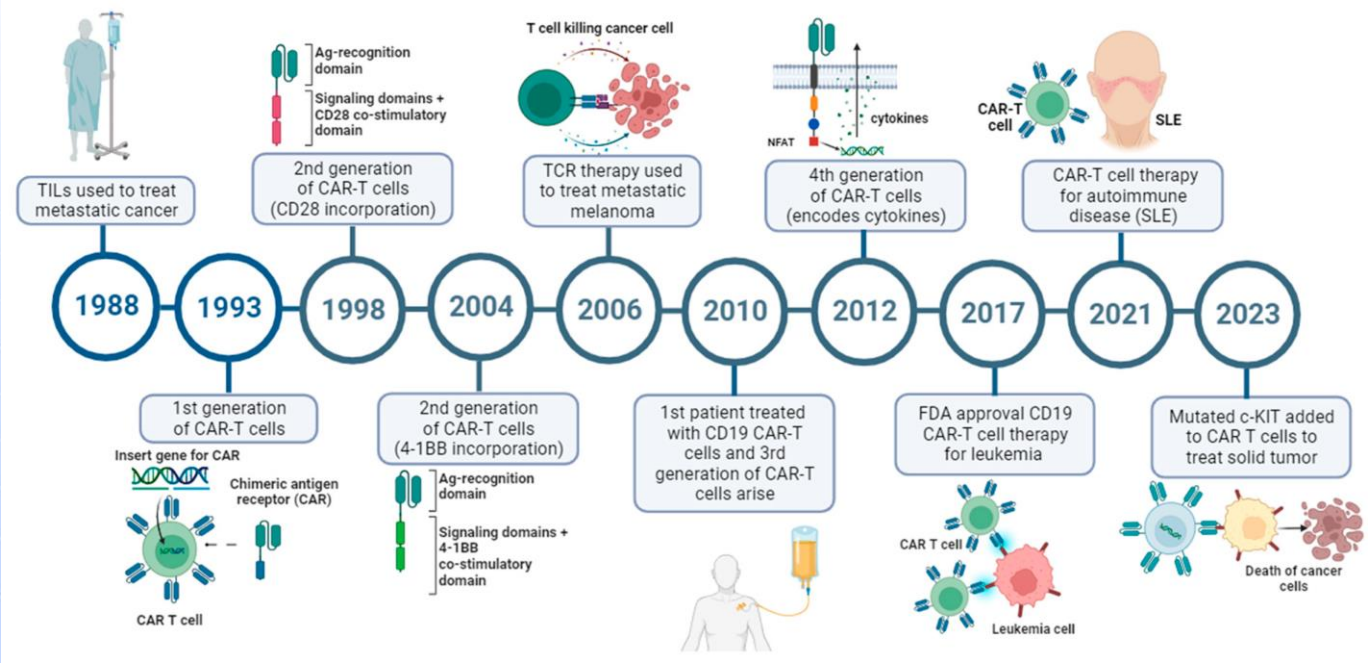
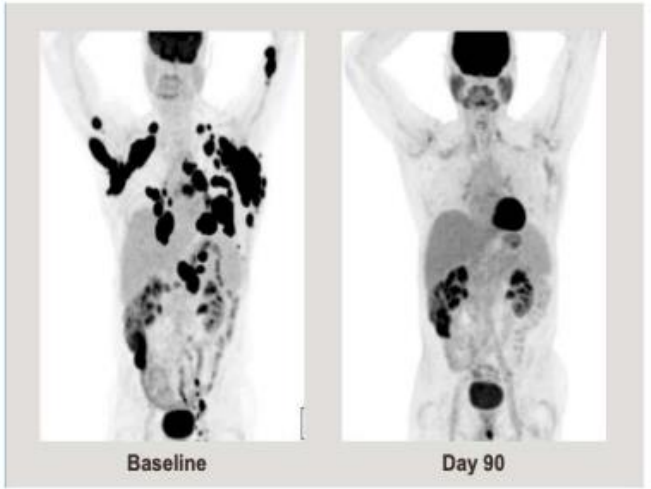
Introduction to CAR-T Cell Therapy

- CAR-T cell therapy involves genetically engineering a patient's own T cells to attack cancer cell, which are the body's primary killer of infection and other disease cell.
- FDA approved first CAR-T cell therapy in 2017 for pediatric acute lymphoblastic leukemia (ALL), since then CAR-T cell has revolutionized the treatment landscape for B-cell malignancies.



Clinical Efficacy

62 yo man with Diffuse Large B cell Lymphoma (DLBCL)
Extensive prior therapies (R-CHOP/R-GDP/R-ICE/R-Revlimid)



[3] *Int. J. Mol. Sci.* **2023**, *24*(21), 15688

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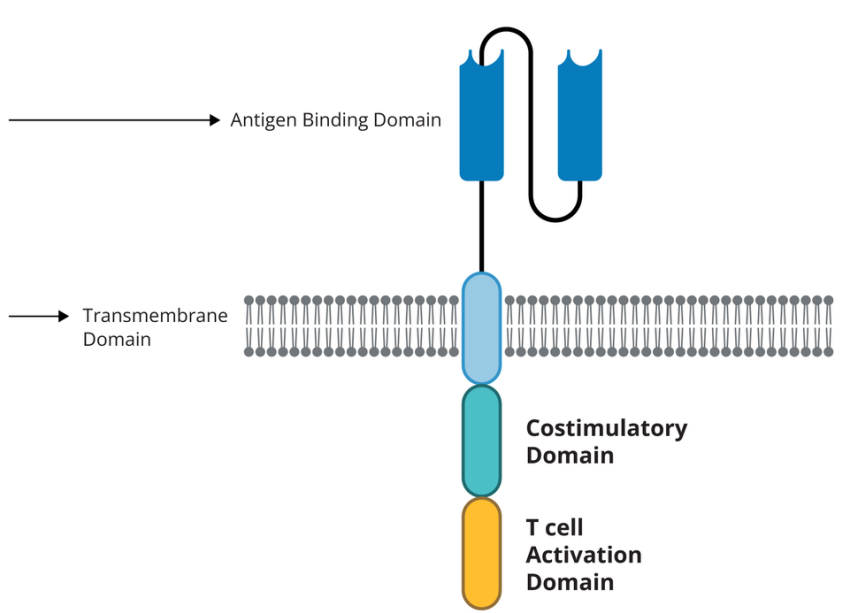
Approved CAR-T Cell Therapies

Drug	Target	Indication	Dose	Covariates Tested
Tisagenlecleucel (Kymriah)	CD-19	B-ALL (pediatric and young adult) LBCL (adult), FL (adult)	Peds: <50 kg: 0.2-5 $\times 10^6$/kg cells; >50 kg: 0.1-2.5 $\times 10^8$ cells (non-wt based) Adults: 0.6-6$\times 10^8$ cells	tocilizumab, steroids, sex, race, prior HSCT, fludarabine (U.S FDA., 2017)
Axicabtagene ciloleucel (Yescarta)	CD-19	LBCL, FL (adult)	2×10^6 cells/kg (max: 2×10^8 cells)	tocilizumab/steroids (US FDA, 2017)
Brexucabtagene autoleucel (Tecartus)[a]	CD-19	MCL (adult); B-ALL (adult)	MCL: 2×10^6 cells/kg (maximum dose: 2×10^8 cells); ALL dose: 1×10^6 cells/kg (maximum dose: 1×10^8 cells);	NA (US FDA, 2024)
Lisocabtagene maraleucel (Breyanzi)	CD-19	LBCL (adult)	50-100$\times 10^6$ cells (1:1 CD8:CD4 ratio)	age*, baseline tumor size*, tocilizumab, steroids, proposed commercial process (U.S. FDA, 2020)
Idecabtagne vicleucel (Abecma)	BCMA	MM (adult)	300-500$\times 10^6$ cells	sex, BW*, BSA*, race, ADA status, number of prior MM therapies, baseline sBCMA* , tociluzumab, steroids (only NCA&ER) (U.S. FDA, 2020)
Ciltacabtagene autoleucel (Carvykti)	BCMA	MM (adult)	0.5-1$\times 10^6$ cells/kg	age, sex, body weight, race, hepatic impairment, renal impairment, manufactured product characteristics (U.S. FDA, 2022)
Obecabtagene autoleucel (Aucatzyl)	CD-19	B-ALL (adults)	Total dose of 410 × 10^6 cells fractionated dose infusion to be administered on Day 1 and Day 10 depends on tumor burden	Tumor burden*, extramedullary disease*, tocilizumab, steroids, prior lines of therapies, response to prior therapies (U.S. FDA, 2024)

Note: [a] unique and patented XLP process that facilitates the removal of circulating CD19-expressing tumor cells after apheresis;*significant covariates;
Abbreviations: HSCT: hematopoietic stem cell transplant; ADA: anti-drug antibody; LBCL: large B-cell lymphoma; FL: follicular lymphoma; MCL: mantle cell lymphoma; B-ALL: B-cell acute lymphocytic leukemia; MM: multiple myeloma; BCMA: b-cell maturation antigen; sBCMA: soluble BCMA

CAR-T Cell Design & Mechanism

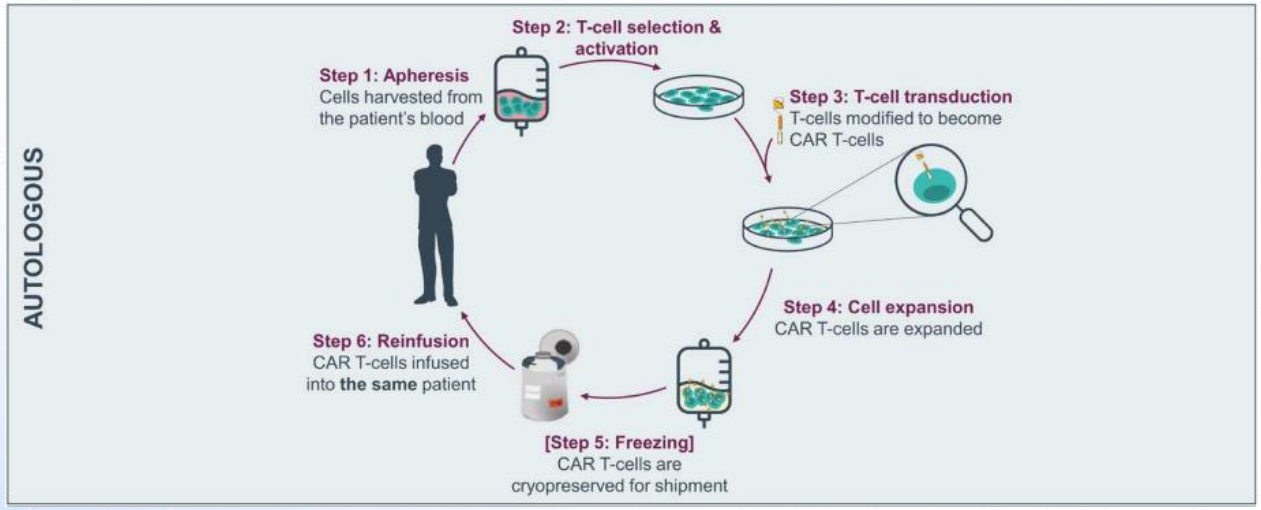
- Each chimeric antigen receptor on an individual T cell spans on the cell membrane, with part of the receptor sitting out of the cell and part within the cell.
- CARs consist of antigen recognition (external) & signaling domains (internal) .
- Common targets for external receptor domain : CD-19 (B-cell malignancies), BCMA (MM).
- After receptor binds to an antigen on a tumor cell, the internal “signaling” and “co-stimulatory” domains transmit signals inside the T cells that help expand and multiply more T cell.



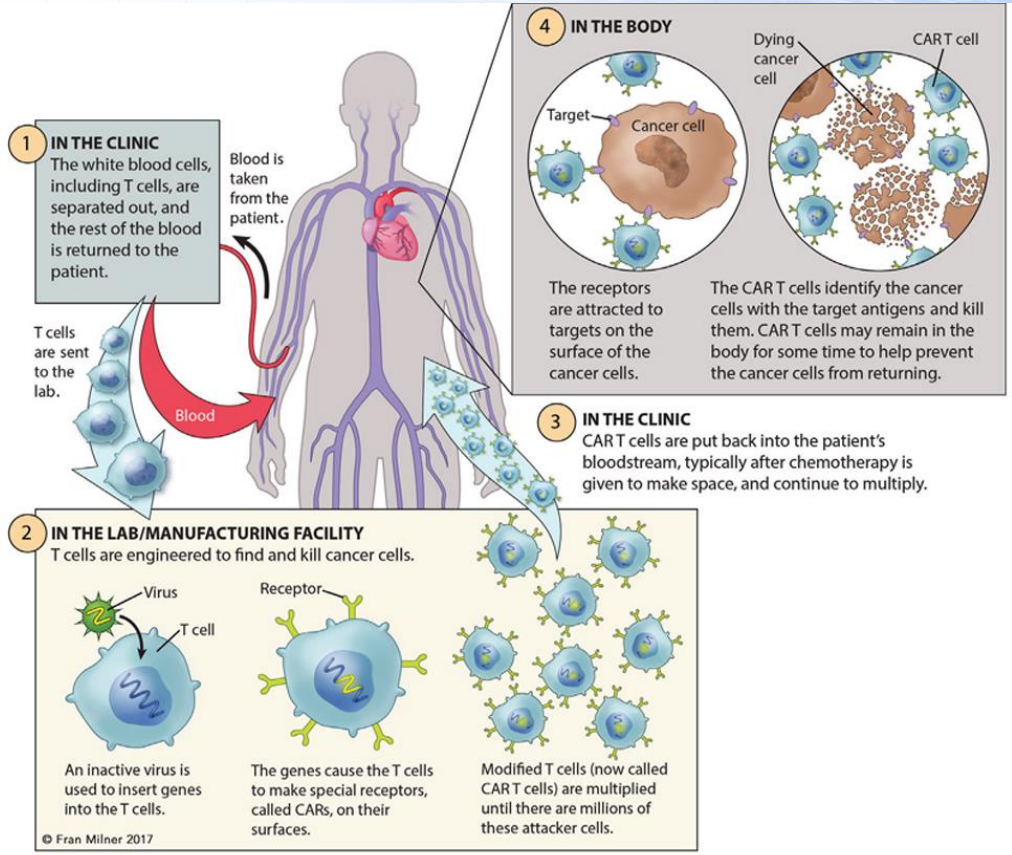
Credit: National Cancer Institute

Autologous CAR-T-Cells

Manufacturing of Autologous CAR-T-Cells



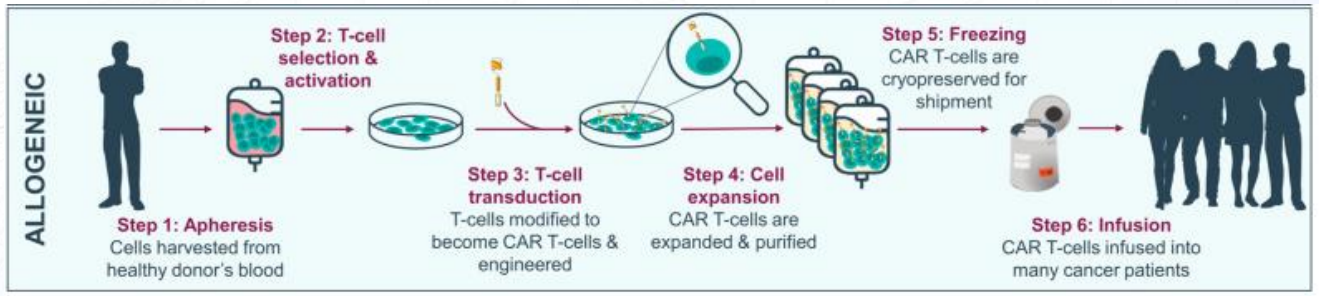
Autologous CAR-T Cell Process



- Vector: viral (e.g., lentiviral) systems used for gene transfer.
- The process can take 3-5 weeks.
- Formulation: fresh vs. cryopreserved impacts viability and logistics
- Source: autologous (patient-derived) vs. allogeneic (donor-derived).

Comparison of Autologous vs Allogenic CAR-T-Cells

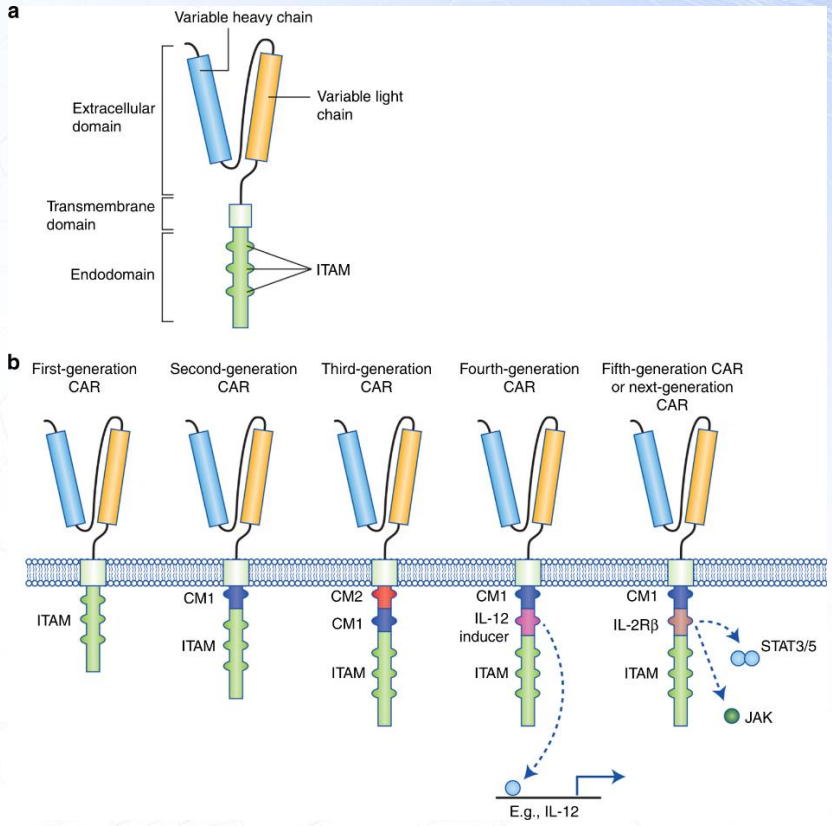
Allogenic CAR-T Cell Manufacturing Process



Allogenic	Autologous
Off-the-shelf	Patient's own cell
Easy to scale up production	Difficult to scale up, challenge to harvest for heavily pre-treated patients
Increased risk of rejection	Minimal risk of rejection
Increased risk of graft-versus-host disease (gvhd)	Little risk of gvhd
Risk of transfer pathogens from donor	Risk of cross contamination of patient's cell lines in large scale manufacturing
Manufacture from single donor cells are more homogenous	Variability in T-cell expansion between patients

Evolution of CAR-T Cell Generations

Generations	Main cytoplasmic domains	Co-stimulatory domain	Drawback
1st	a single CD3 ζ-chain	None	Failure to produce adequate IL-2, low cell proliferation, higher toxicities, and brief in vivo persistence
2nd	CD3 ζ-chain	CD28 or 4-1BB	CAR-T cell exhaustion
3rd	CD3 ζ-chain	CD28 and 4-1BB dual signaling	Adapted persistence and proliferation yet no enhanced efficacy as compared to earlier generations
4th	CD3 ζ-chain	CD28 and IL-12 inducer domain	On-target/off-tumor toxicities
5th	CD3 ζ-chain	cytoplasmic IL-2 receptor β-chain domain activating antigen-mediated JAK/STAT pathway	Preoccupied with concerns on immunogenicity and high costs
Note: All the currently approved CART are 2nd generation CAR-T			

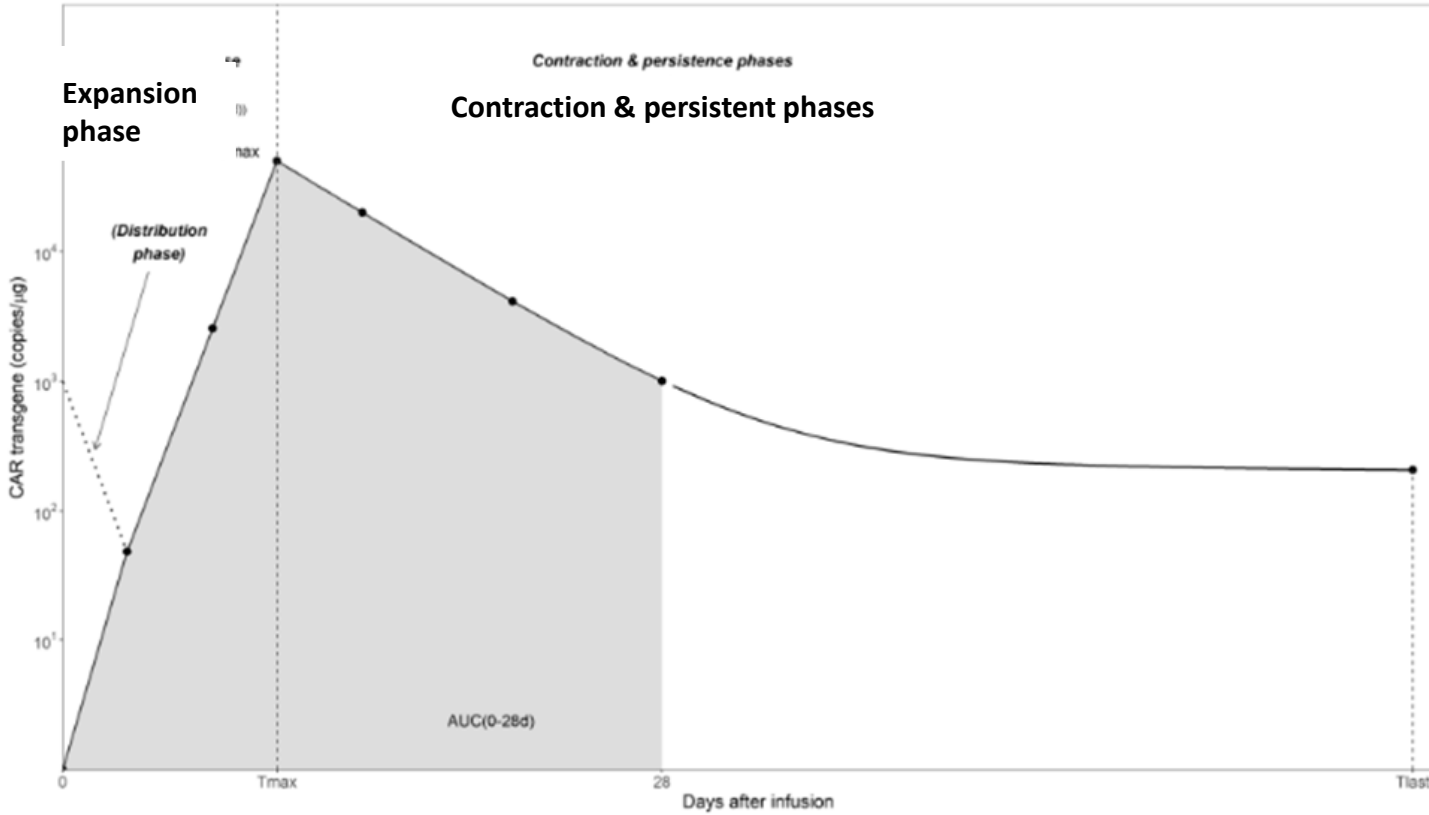


Multiphasic Cellular Kinetics of CAR-T-Cells

Distribution → Expansion → Contraction → Persistence

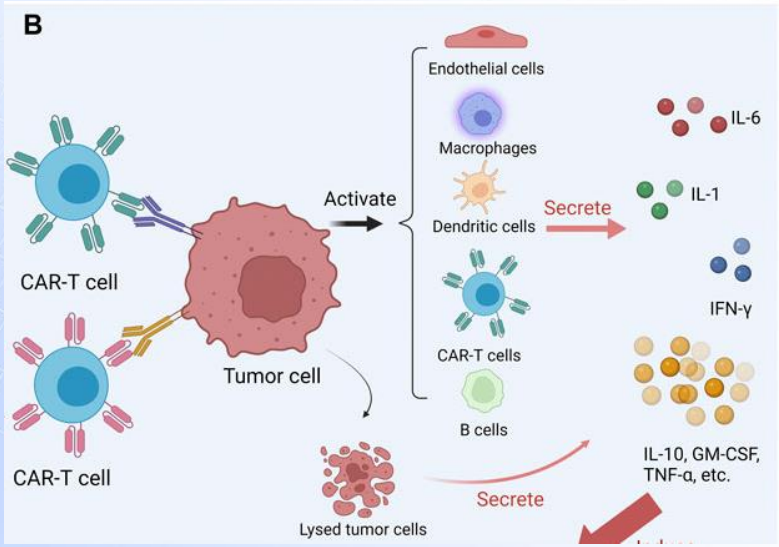
- Distribution: from central to peripheral
- Expansion: Cmax, Tmax, $AUC_{0\text{-}28d}$ indicate proliferation.
- Contraction: $t_{1/2}$ reflect decline phase.
- Persistence: long-term presence linked to durability (tlast).

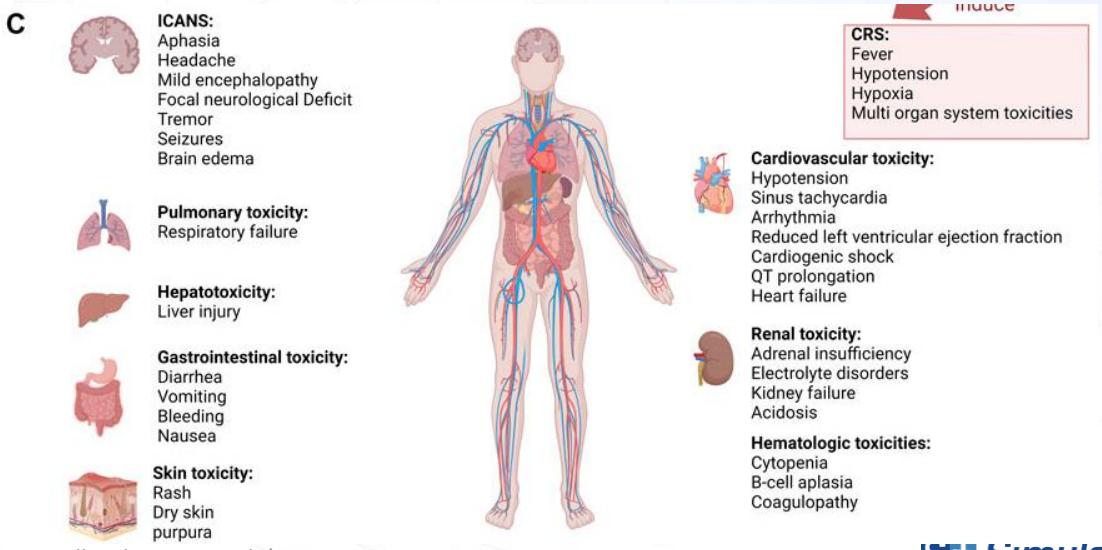
- Classical ADME parameters such as clearance and volume of distribution are irrelevant.



CAR-T cell Toxicities

- Cytokine release syndrome (CRS):
  - Release of cytokines from bystander immune and non-immune cells
  - Onset: variable; peaks 2-7 days after infusion and delays up to 3 weeks
  - Symptoms: fever, tachycardia, hypoxia, nausea, headache, rash, shortness of breath, hypotension
  - Management: IL-6 antagonists **tocilizumab** in lower-grade CRS and corticosteroids in refractory high grade CRS. Alternatives include **siltuximab** and **clazakizumab**.





CAR-T cell Toxicities (Continued)

- Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)
  - A pathologic process involving CNS following any immune effector therapy that results in the activation or engagement of endogenous or infused T cell or other immune effector cells.
  - Symptoms: aphasia, altered mental status, impaired cognitive skills, motor weakness, seizures and cerebral edema.
  - Onset: 4 days after infusion, last 5-17 days
  - Management: supportive care and corticosteroids

ASCO guidelines: Management of Immune-Related Adverse Events in Patients Treated With CAR-T cell Therapy: ASCO Guideline (Santomasso, 2021)

CAR-T cell Toxicities (Continued)

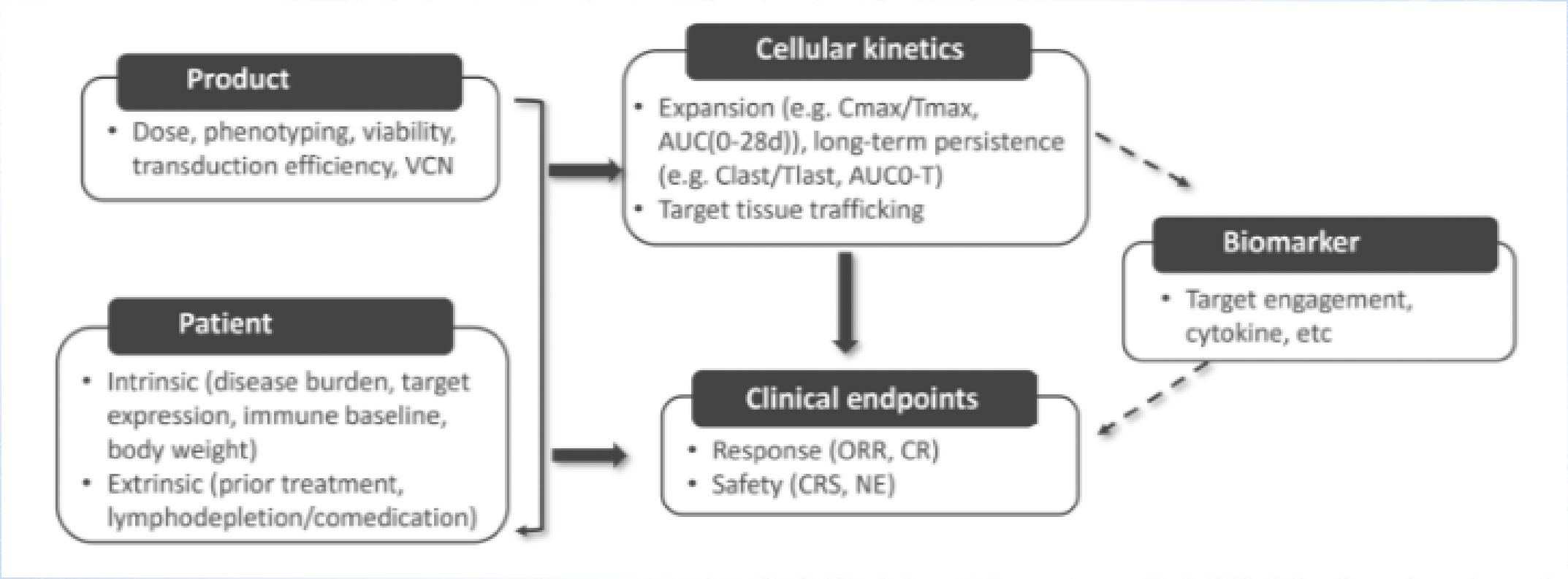
- Hemophagocytic lymphohistiocytosis (HLH):
  - Histiocytes and lymphocyte build up in organs include skin, spleen and liver and destroy other blood cells.
  - Rare: 3.5% incidents
- Other: B-cell aplasia, cytopenia, disseminated intravascular coagulation, infection
- ‘On-target, off-tumor’ effects (OTOT):
  - Significant concern for solid tumors
  - Expression of targe on healthy tissue
- Exposure safety
  - Generally higher expansion is associated with grade 3 neurotoxicity and CRS

ASCO guidelines: Management of Immune-Related Adverse Events in Patients Treated With CAR-T cell Therapy: ASCO Guideline (Santomasso, 2021)

Concern for PK Variability from Immunogenicity

- Data from current approved CAR-T therapies does not seem to have apparent immunogenicity impact on CK, safety, and efficacy
  - Cellular immune response (T cell recognize CAR-T-Cells)
    - Onset: ~3-6 months
    - Does not impact the expansion and target engagement
    - Impact long term persistence, but no data suggest impact on clinical response
    - No need to perform cell mediated immunogenicity assessment due to lack of cytotoxic T cell (CTL) mediated killing in current treatment scheme not compromising persistent
  - ADA-mediated immune response (Antibody recognize CAR-T-Cells)
    - Low likelihood in B-cell targeting therapies
    - Murine or humanized scFv regions
    - Testing neutralizing antibody is not needed when efficacy was not compromised

Concern for PK Variability from Products, Patients and Biomarkers



Preclinical-to-Clinical Translation Considerations

- **Interspecies**
  - difference between preclinical model and human creates translational challenges
  - immune system, mimicking expression, intrinsic properties of tumor antigen, tumor microenvironment
  - CK profile and clinical responses are dependent on various patient-specific factors and product-specific characteristics
- **Complex CAR-T design**
  - binding region, co-stimulatory, and activating domain; different phenotypic composition
- ***In vitro* studies**
  - assess CAR binding, antigen-dependent CAR-T proliferation, killing potency, and cytokine induction -> CAR-T sensitivity to tumor antigen expression
- ***In vivo* studies**
  - demonstrate proof of concept
  - evaluates multi-dose cellular kinetic profile: antigen dependent-expansion, contraction & tumor kill dynamic.
  - Persistence phase is not assessed due to GvHD
- **Limitations:**
  - lack of interplay among complex human immune component
  - limits direct translation to guide FIH
  - lack animal models to assess CRS and neurotoxicity, thus irrelevant for safety margin dose derivation

Empirical Starting Dose Selection for FIH

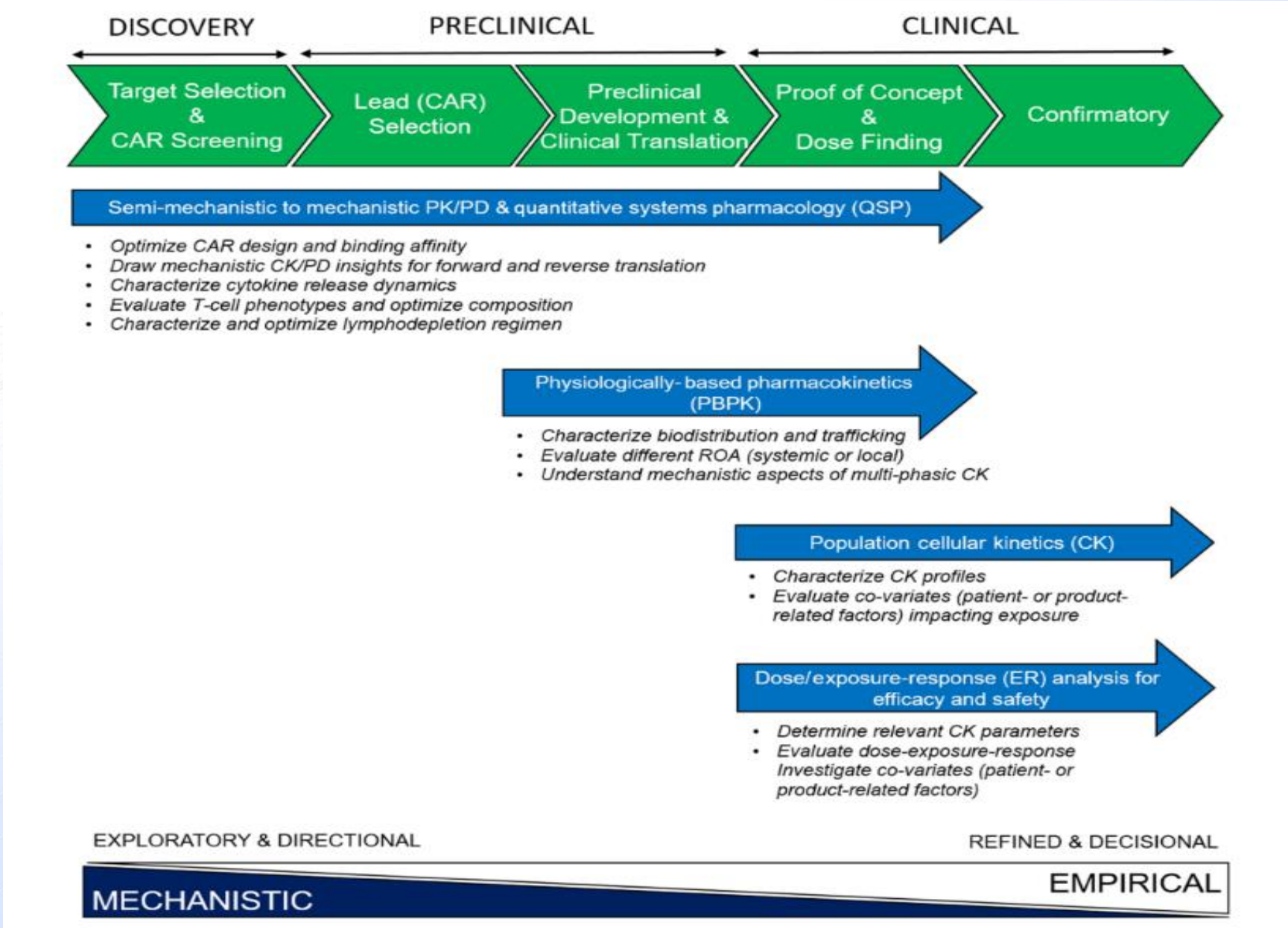
- **Relevant CAR-T products:**
  - Learn from prior clinical experience from previous CAR-T products
  - Typical starting dose: million CAR + T cells/kg
- **Disease factor:**
  - Disease type impacts dosing: type of malignancy, immune condition, antigen expression, and site of action
  - Population: adults vs pediatrics, tumor burden
- **Product factor:**
  - CAR design and cell composition, co-stimulatory domain, phenotype, manufacturing condition
- **Preclinical to FIH:**
  - Preclinical data is used guide feasibility and anti-tumor activity, but not to directly scale dose
  - Define the empirical activity factor; limitations- benchmark CAR-T should bind to same or similar functional target

Study Design Considerations

- **Body weight-based vs fixed dose**
  - mg/kg dosing is more common in peds
  - Both strategies has been used in adults
  - Body weight /BSA are not found to impact cellular kinetics or exposure and efficacy
  - Recommendation: fixed dose to initiate FIH
- **Dose fractionation (over 2-3 days) or tumor-burden based dose**
  - Dose Fractionation: Mitigate toxicity for patients with high tumor burden (KYMRIAH)
  - Tumor-burden based dose: lower dose for high tumor burden patients to mitigate CRS and neurotoxicity; may lead to suboptimal efficacy
- **Single vs repeat dosing**
  - May benefit in relapsed/refractory patients after first dose; not feasible for autologous transplant
- **Dose escalation strategy**
  - Should consider safety, efficacy, variability due to patient and product
  - Could use : Toxicity and Efficacy Probability Interval (TEPI) and Bayesian Optimal Interval (BOIN)-guided escalation strategy
- **Selection of lymphodepletion agent**
  - Improve CAR-T cellular kinetics, and efficacy, and long term survival
  - fludarabine+cyclophosphamide is the most common conditioning regimen

PK/PD Analysis of CAR-T-Cells

- Conventional model-based approaches translating ADME to the mammalian models such as 1- 2- or 3- compartment models are not applicable for CAR-T.
- Statistical population PK models were developed to:
  - capture the cellular kinetics,
  - identify covariates and
  - predict dose-exposure response
- Due to high variability related to patient-product specific characteristics, safety, and efficacy- various M&S approaches can be applied
- Mechanistic models such as PBPK and QSP are also utilized to capture the impact of physiology, product or disease related factor from a bottom up approach.



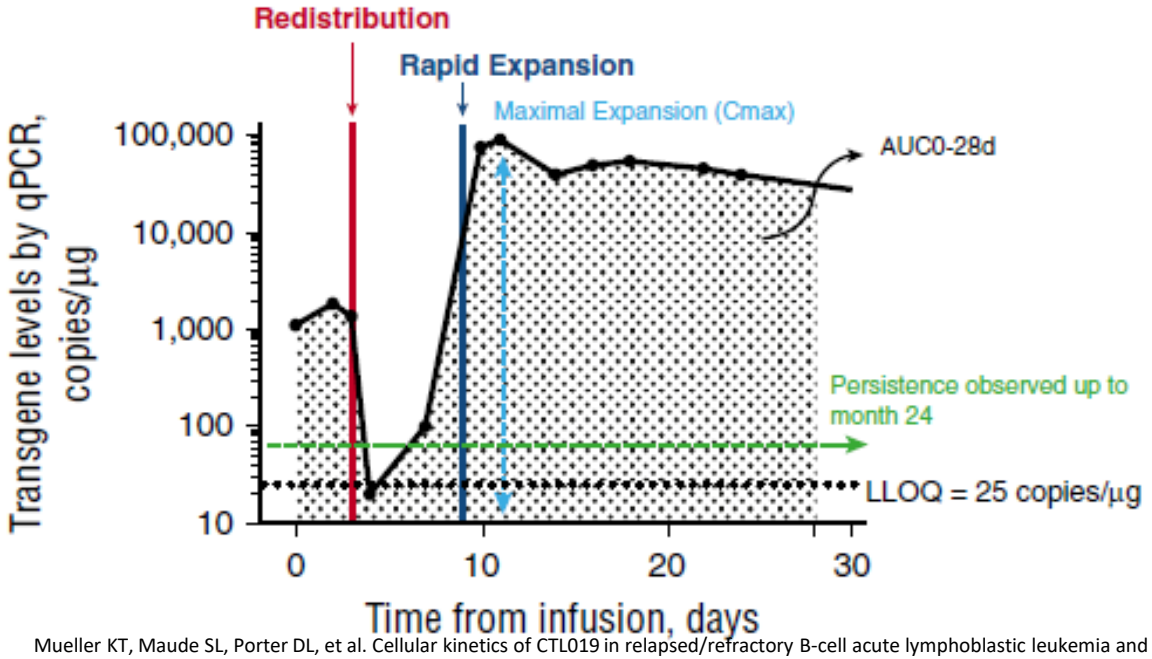
Mody H, Ogasawara K, Zhu X, et al. Best Practices and Considerations for Clinical Pharmacology and Pharmacometric Aspects for Optimal Development of CAR-T and TCR-T Cell Therapies: An Industry Perspective. Clin Pharmacol Ther. 2023;114(3):530-557. doi:10.1002/cpt.2986

Non Compartmental Analysis

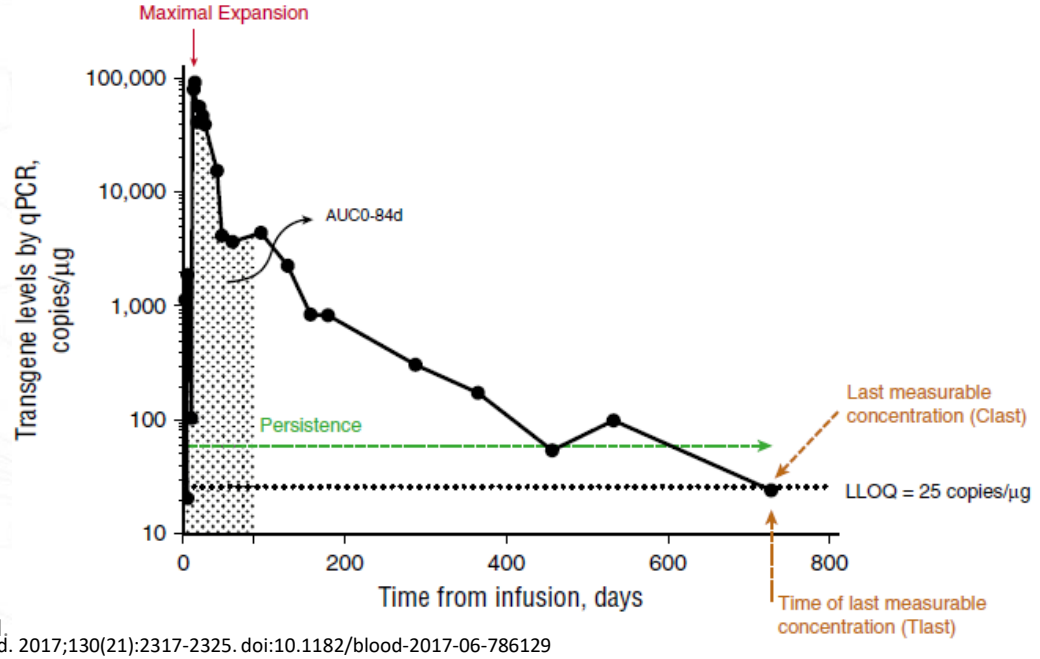
- Characterize the expansion and persistence phase
  - C_{max}, T_{max} : describe expansion
  - $AUC_{0\text{-}28d}$: sufficient to capture cell expansion, relevant for both expansion and persistence, and can serve as an indicator for responders (high exposure) versus non-responders (low exposure)
  - T_{last} , C_{last} , and terminal $t_{1/2}$: describe persistence phase and used for long term safety monitoring

A Selected CTL019 CK Profile from infusion to:

a) Day 28



b) Day 84



Mueller KT, Maude SL, Porter DL, et al. Cellular kinetics of CTL019 in relapsed/refractory B-cell acute lymphoblastic leukemia and chronic lymphocytic leukemia. Blood. 2017;130(21):2317-2325. doi:10.1182/blood-2017-06-786129

Non Compartmental Analysis (Continued)

Core findings from Muller et al. 2017 publication on Cellular Kinetics of CTL019:

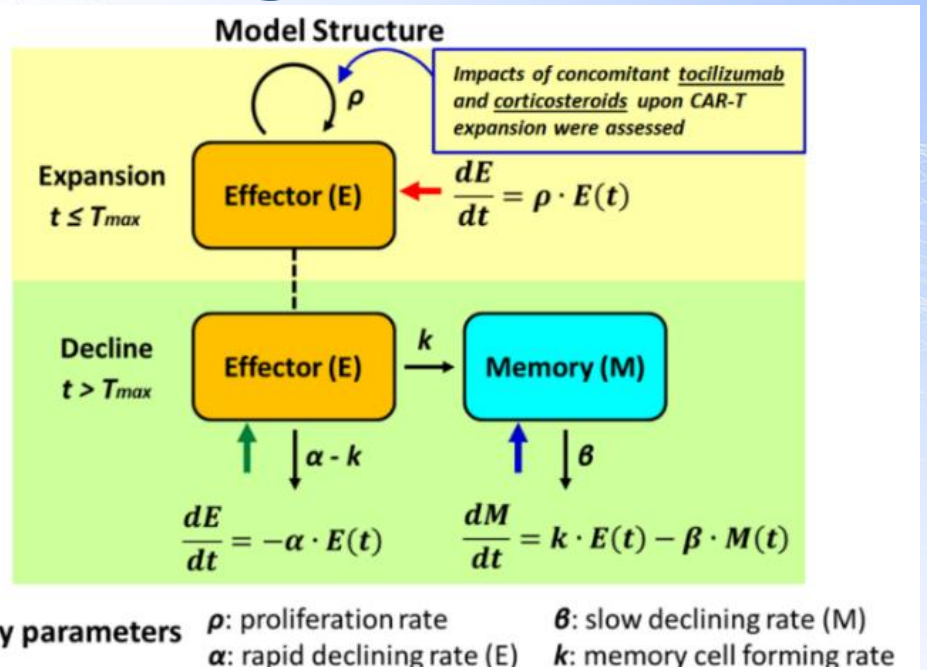
1. Tmax ~10-14 days for peak CAR-T
2. Persistence phase: CAR-T detectable up to ~780 days in blood, bone marrow and CSF
3. CAR-T expansion and persistence (Cmax and AUC) were correlated with clinical efficacy
   - Patients who responded to therapy had greater CAR-T expansion
   - Suggests early expansion and high overall exposure are predictors of efficacy
4. Higher tumor burden prior to CAR-T was associated with greater expansion (i.e higher Cmax, AUC)
5. Patients who developed severe CRS had ~2X higher Cmax reflecting relationship between expansion and toxicity

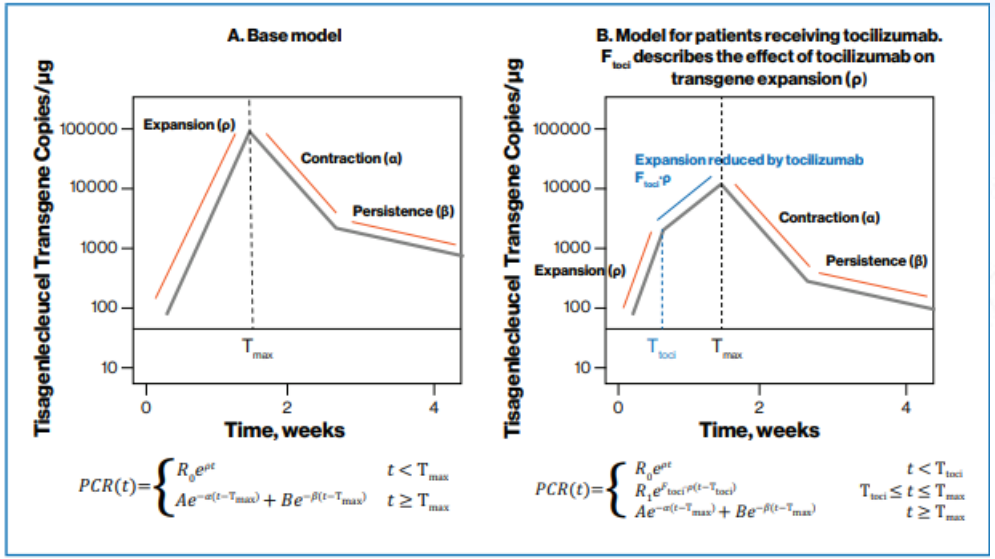
Mueller KT, Maude SL, Porter DL, et al. Cellular kinetics of CTL019 in relapsed/refractory B-cell acute lymphoblastic leukemia and chronic lymphocytic leukemia. Blood. 2017;130(21):2317-2325. doi:10.1182/blood-2017-06-786129

Population PK Modeling

- Non-Linear Mixed Effect Modeling approach
- Describes cellular kinetics, evaluate the effect of covariates, using compartmental modeling
- Stein Model:
  - Notable publication in CAR-T domain
  - Describes CAR-T expansion, rapid contraction, and long-term persistence characterize different phases of CK
  - and their relationship to clinical outcomes in hematological malignancies
  - Model integrated patient specific factors such as tumor burden and immune system environment to predict CAR-T behavior
  - Limitation: Needs rich data and parameter assumption

❖ CAR-T-case-study-Monolix





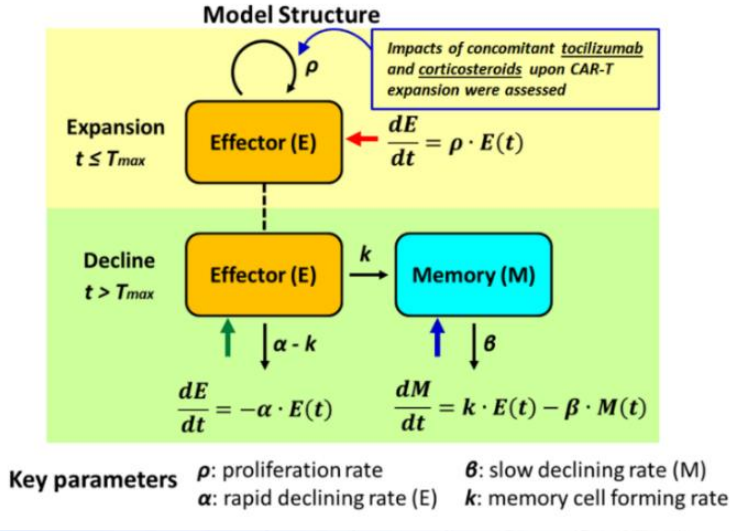
Ftoci, tocilizumab-specific factor; PCR, polymerase chain reaction; Tmax, peak concentration time ; Ttoci, time of tocilizumab administration.

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. doi:10.1002/psp4.12388

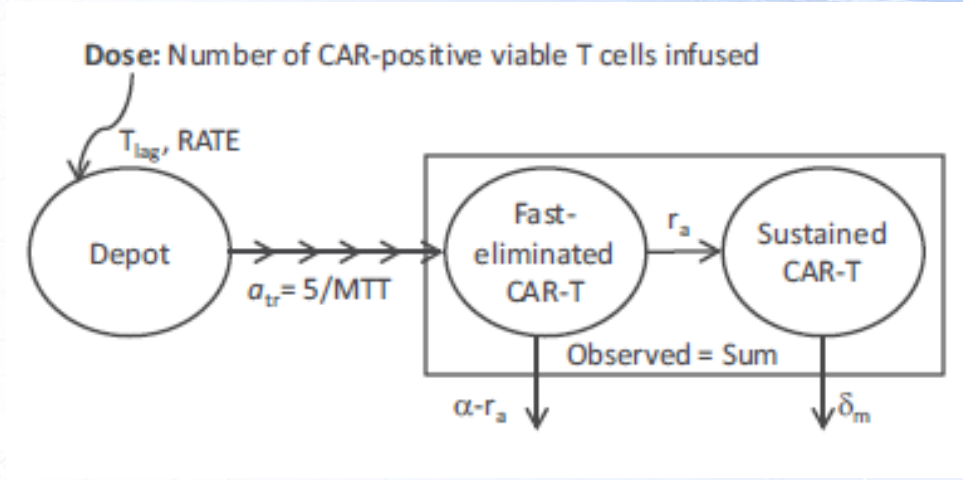
Population PK Modeling

-Variation of Stein model were used in the pharmacometrics submissions for tisa-cel, axi-cel, liso-cel, ide-cel, and cilta-cel

Stein et al, Yescarta



Wu et al



Ogasawara et al

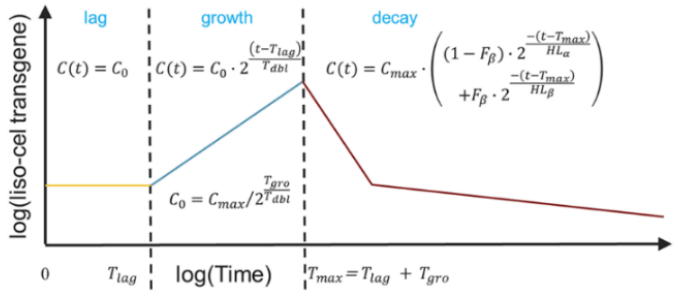
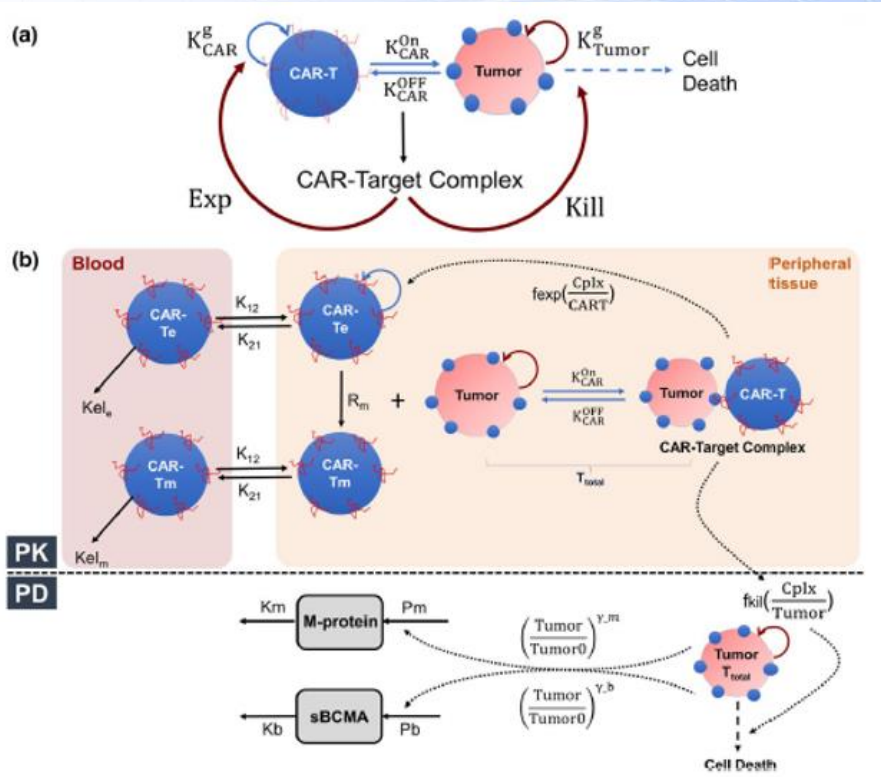


Fig. 1 Cellular kinetic model of liso-cel. C_0 initial transgene levels, C_{max} maximum transgene levels, F_β fraction of C_{max} that appears in the β or terminal phase, HL_α initial (α phase) decline half-life, HL_β terminal (β phase) half-life, T_{dbl} doubling time during growth phase, T_{gro} growth phase duration, T_{lag} lag phase duration, T_{max} time to maximum transgene levels

Semi-mechanistic PK/PD Modeling

- Translational PK/PD , characterize BCMA targeting CAR-Ts and tumor/biomarker dynamics
  - Cell level PD model in an *in vitro* culture
  - PK/PD Model: PK in blood and tissues (site of action)
  - Biomarkers M-protein, and sBCMA are described with a turnover model using zero-order production and first-order elimination
- Limitation:
  - Requires rich phenotyping, distribution data.
  - Model is not validated by other data and reproducibility is questionable.

Model structure



Singh AP, Chen W, Zheng X, et al. Bench-to-bedside translation of chimeric antigen receptor (CAR) T cells using a multiscale systems pharmacokinetic-pharmacodynamic model: A case study with anti-BCMA CAR-T. *CPT Pharmacometrics Syst Pharmacol*. 2021;10(4):362-376. doi:10.1002/psp4.12598

Longitudinal Exposure

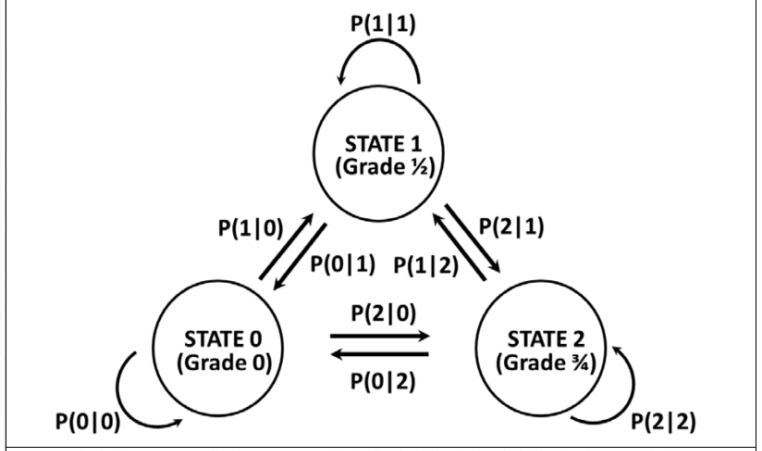
Adverse Event:

- First-order Markov model is used to condition the probability of transition between different severity of the adverse effects between one time point and another.
- Used to quantify the longitudinal relationship between CAR-T and toxicity endpoints (CRS and Neurotoxicity)
- CRS:
  - a higher expansion rate was associated with higher probability of CRS onset and exacerbation for Yescarta and Kymriah
  - greater decline rate of CK was associated with more likelihood of CRS remission for Yescarta and Kymriah
- Neurotoxicity
  - CAR-T concentration was associated with neurotoxicity onset and exacerbation for Yescarta

Time-to-Event:

- Cox proportional hazard model is used to evaluate the relationship between CAR-T exposure and multiple time-to-event endpoints (PFS, OS, DOR)

Figure 7: Model structure for CAR-T kinetics vs. longitudinal adverse events



Note: each circle represents distinct states: no CRS, Grade ½ CRS, Grade ¾ CRS. The arrow is the transition from the current state to the next state. P(X|Y) is the transition probability to state X given the current state is Y.
Source: FDA reviewer's analysis

Application of Modeling Approaches in CAR-T Therapy

Modeling Approach	Application	Strength	Limitation
Non-Compartmental Analysis (NCA)	Characterize cellular kinetics, in particular expansion and persistence	Simple, fast, no model assumptions	No mechanistic interpretation, limited predictive value, need rich data
Population PK Modeling (PopPK)	Describes cellular kinetics and IIV in CAR-T; covariate analysis and exposure-response	Estimates population parameters, explores covariate relationships, can handle sparse data	Assumes pre-defined structure
Physiologically Based PK (PBPK)	Characterize biodistribution and trafficking	Mechanistic tissue distribution, scalable across species	Complex to implement for “living drug”, limited data on tissue-specific kinetics
Mechanistic Modeling	Translational, characterize CRS, optimize binding affinity, T cell phenotype, and lymphodepletion therapy	Biologically interpretable	Complex as more parameters to estimate, requires rich data

Challenges for CAR-T Cell Therapy

Despite the promise of CAR-T cell therapy, several challenges persist:

- **Safety Concerns:** Risks include cytokine release syndrome (CRS), neurotoxicity, and ‘on-target, off-tumor’ effects.
- **Efficacy:** solid tumors still an obstacle. Results can be highly patient-specific, leading to variable outcomes.
- **Accessibility:** High costs and complex manufacturing processes limit the widespread availability of this treatment.
- **Variability**: Product, patient and biomarker contribute to PK/PD variability
- **Prior CAR-T History**: Not common to re-administer another dose of CAR-T due to T cell exhaustion or resistance, lack of benefit, toxicity concerns and manufacturing logistics

Challenges for CAR-T Cell Therapy

- Lack of preclinical model to translate to FIH study
- **Dose-Exposure**
  - No apparent dose-exposure relationship; as initial dose is not determining the final exposure.
  - Exposure is measured by Cmax and AUC and not by dose infused
- **Exposure-Response**
  - Exposure correlates better than dose with response and toxicity
  - Response linked to higher expansion metrics (Cmax, AUC)
  - Higher expansion is also linked to higher risk of CRS
  - Tmax generally similar in responders/non-responders. However, early expansion is associated with durable response
  - Longer persistence may indicate durable response, buy may be confounded by longer follow-ups
  - Systemic exposure may not reflect exposure at site of action (lymphoma, solid tumors)

Summary: Key Takeaways

- CAR-T cell therapy shows promise in hematologic malignancies.
- Unique T-cell pharmacology require tailored modeling approaches, PK/PD evaluation must consider cellular kinetics, not classical ADME.
- Modeling tools such as NCA, and PopPK are vital to understand the cellular kinetics but are dependent on the scope, scientific question, available data, and the stage of the program
- Early PK/PD modeling can help forecast CRS risk and efficacy outcomes, as safety (CRS/ICANS) and efficacy (expansion/persistence) are exposure-related.
- Modeling supports dose selection, risk mitigation, and response prediction.

Modeling of Tisagenlecleucel CAR-T cells

A Monolix Case Study

Introduction

Tisagenlecleucel:

- Chimeric antigen receptor–T cell therapy that facilitates the killing of CD19+ B cells
- Produces durable responses in pediatric and young adult patients with relapsed or refractory B cell acute lymphoblastic leukemia (r/r B- ALL)

Dataset (simulated):

- Published and modeled in:

  Stein, A. M., Grupp, S. A., Levine, J. E., Laetsch, T. W., Pulsipher, M. A., & Boyer, M. W. (2019). *Tisagenlecleucel Model- Based Cellular Kinetic Analysis of Chimeric Antigen Receptor – T Cells*. *2019*, 285–295. https://doi.org/10.1002/psp4.12388

- Pooled from two phase II studies in pediatric (61 patients) and young adult (29 patients) relapsed/refractory B cell acute lymphoblastic leukemia
- 35 patients received therapies for treating cytokine release syndrome : tocilizumab and corticosteroids
  - treatment with tocilizumab and/or corticosteroids may slow the rate of expansion of tisagenlecleucel
  - the requirement of treatment for CRS may be predictive of C_{max} because patients with higher exposure are more likely to have CRS and receive tocilizumab

Goal: model the kinetics of tisagenlecleucel and the impact of therapies for treating cytokine release syndrome (tocilizumab and corticosteroids) on CAR-T expansion phase

Introduction

log-transformed tisagenlecleucel levels reported as transgene copies/µg of genomic DNA

time of first comedication of tocilizumab

1 = received comedication of tocilizumab

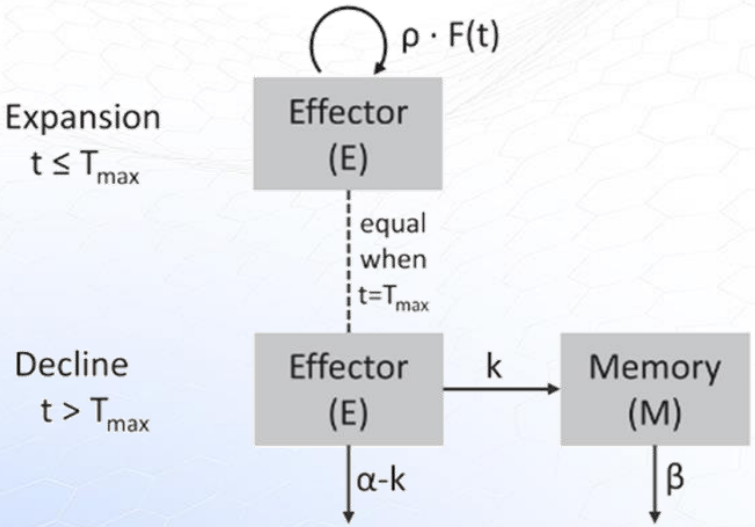
time of first comedication of corticosteroids

1 = received comedication of corticosteroids

ID	TIME	OBSERVATION	CENSORING	REGRESSOR	CONTINUOUS COVARIATE	CATEGORICAL COVARIATE	REGRESSOR	CONTINUOUS COVARIATE	CATEGORICAL COVARIATE
id	time	LNDV	CENS	TOCI1T_reg	TOCI1T	TOCI1_comed	STERSTT_reg	STERSTT	STERST_comed
1					**10.485**	**1**		**9.587**	**1**
1	8.028	9.39192	notCensored	10.485	10.485	1	9.587	9.587	1
1	9.022	12.4602	notCensored	10.485	10.485	1	9.587	9.587	1
1	10.022	13.6336	notCensored	10.485	10.485	1	9.587	9.587	1
1	10.446	13.4327	notCensored	10.485	10.485	1	9.587	9.587	1
1	10.586	13.7698	notCensored	10.485	10.485	1	9.587	9.587	1
2					**1.82**	**1**		**0.108**	**1**
2	3.775	9.08494	notCensored	1.82	1.82	1	0.108	0.108	1
2	4.702	9.65751	notCensored	1.82	1.82	1	0.108	0.108	1
2	6.761	9.51166	notCensored	1.82	1.82	1	0.108	0.108	1
2	8.008	10.6915	notCensored	1.82	1.82	1	0.108	0.108	1
2	8.531	9.75844	notCensored	1.82	1.82	1	0.108	0.108	1

Base structural model

Compartmental model



Parameters:
T_{max}, C_{max}, $fold_x$, α, β, F_B

ODE system

Equations

$$\frac{dE}{dt} = \rho \cdot F(t) \cdot E$$

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

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

Initial Conditions

at t = 0: $E(0) = C_{max}/fold_x$

at $t = T_{max}$: $E(T_{max}) = C_{max}$
$M(T_{max}) = 0$

Definitions

$\rho = \log(fold_x)/T_{max}$
$k = F_B \cdot (\alpha - \beta)$

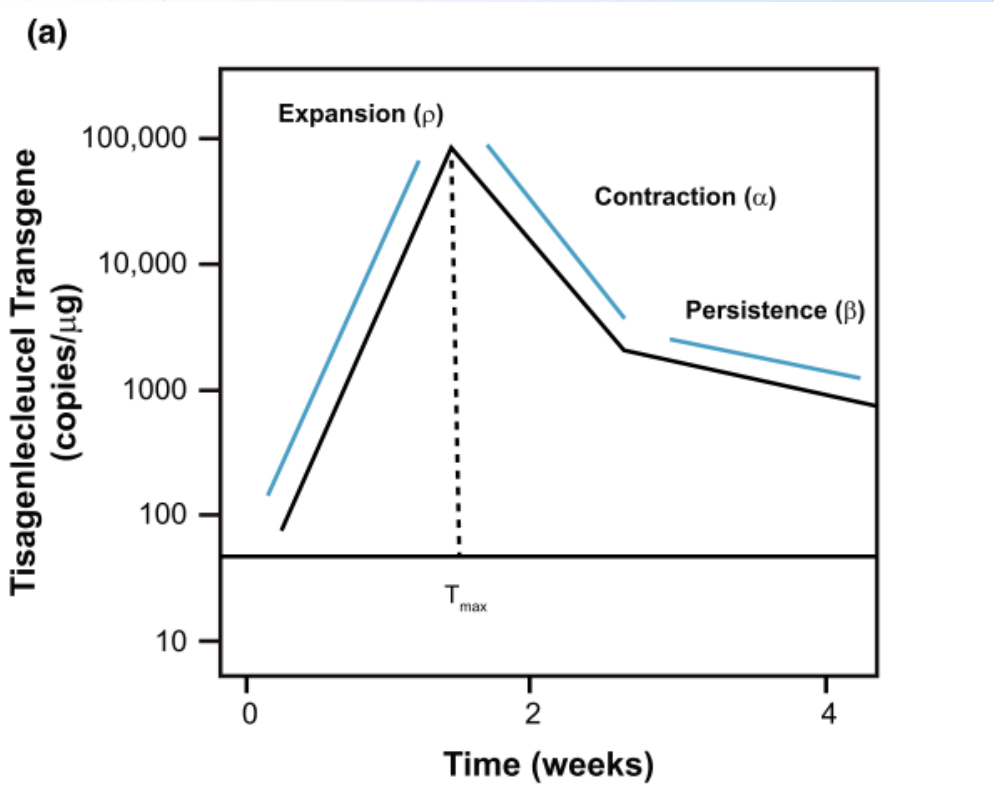
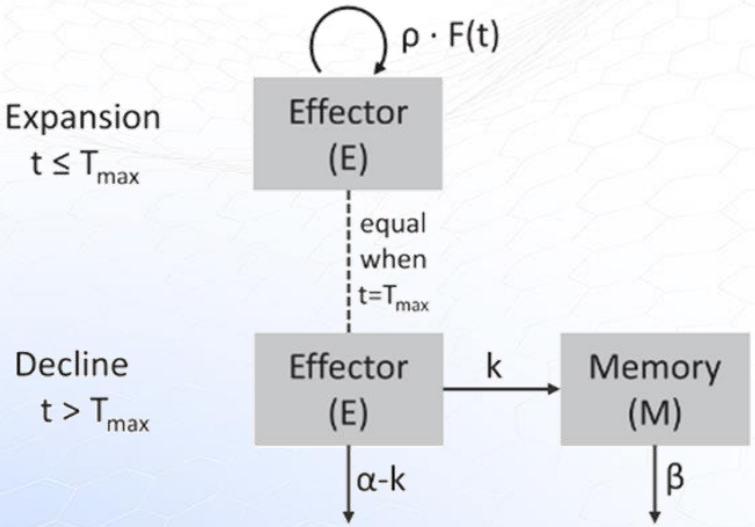


Figure and equations from Stein, et al. (2019)

Base structural model

Compartmental model



Parameters:
T_{max}, C_{max}, $fold_x$, α, β, F_B

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at t = 0: $E(0) = C_{max}/fold_x$

at t = T_{max}: $E(T_{max}) = C_{max}$
$M(T_{max}) = 0$

Definitions

$\rho = \log(fold_x)/T_{max}$
$k = F_B \cdot (\alpha - \beta)$

Equivalent equations

$$f(t) = \begin{cases} R_0 e^{\rho t}, & t < T_{max} \\ Ae^{-\alpha(t-T_{max})} + Be^{-\beta(t-T_{max})}, & t \geq T_{max} \end{cases}$$

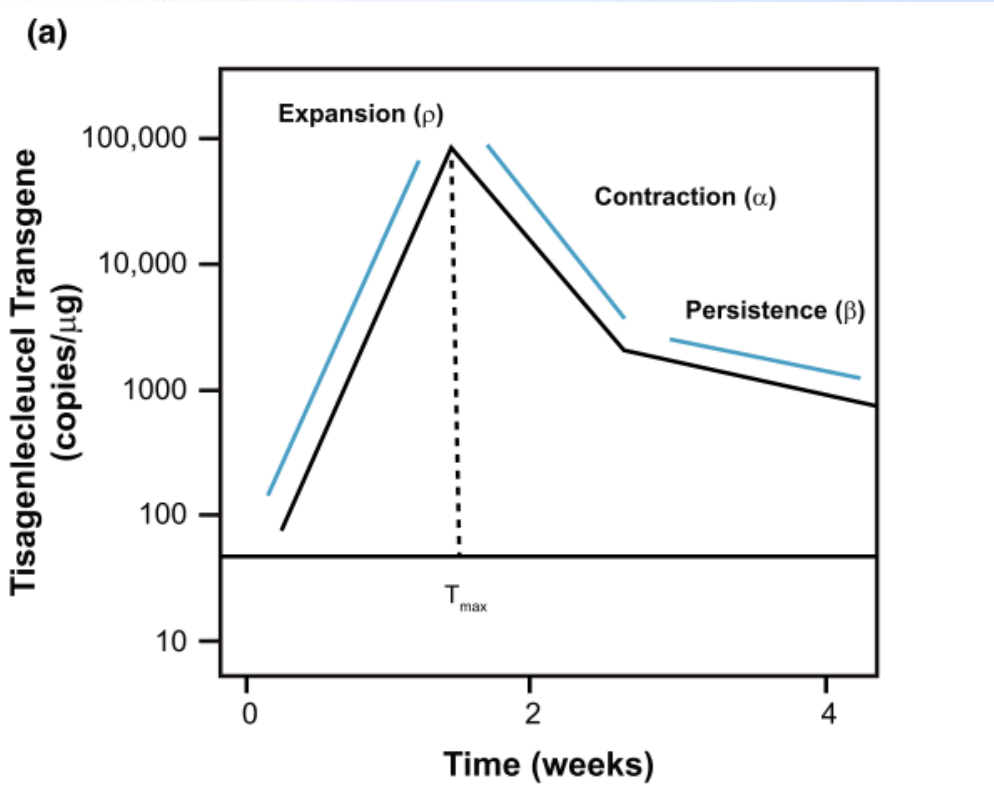
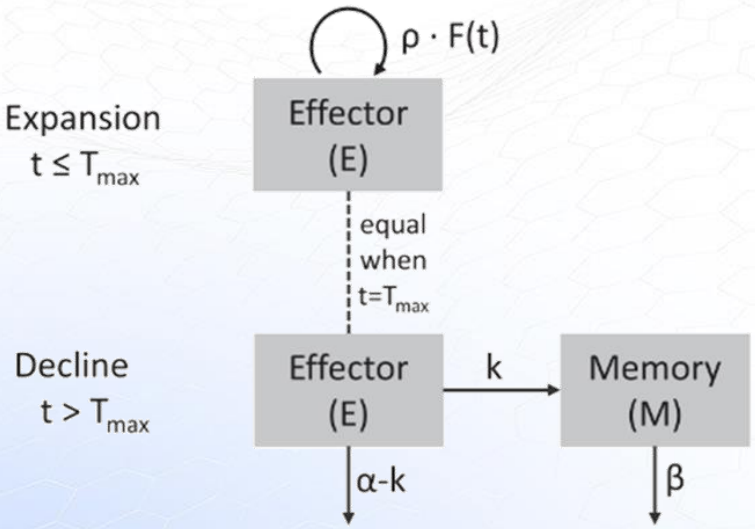


Figure and equations from Stein, et al. (2019)

Extended structural model with comedication effect on expansion

Compartmental model



Comedication Effect: F(t)

$$F(t) = f_{toci}(t) \cdot f_{ster}(t)$$

$$f_{toci}(t) = \begin{cases} 1 & t \le T_{toci} \\ F_{toci} & t > T_{toci} \end{cases}$$

$$f_{ster}(t) = \begin{cases} 1 & t \le T_{ster} \\ F_{ster} & t > T_{ster} \end{cases}$$

ODE system

Equations

$$\frac{dE}{dt} = \rho \cdot F(t) \cdot E$$

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

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

Initial Conditions

at t = 0: $E(0) = C_{max}/fold_x$

at $t = T_{max}$: $E(T_{max}) = C_{max}$, $M(T_{max}) = 0$

Definitions

$\rho = \log(fold_x)/T_{max}$

$k = F_B \cdot (\alpha - \beta)$

Equivalent equations

$$f(t) = \begin{cases} R_0 e^{\rho t}, & t < T_1 \\ R_1 e^{F_1 \cdot \rho (t - T_1)}, & T_1 \le t < T_2 \\ R_2 e^{F_1 F_2 \cdot \rho (t - T_2)}, & T_2 \le t < T_{max} \\ A e^{-\alpha (t - T_{max})} + B e^{-\beta (t - T_{max})}, & t \ge T_{max} \end{cases}$$

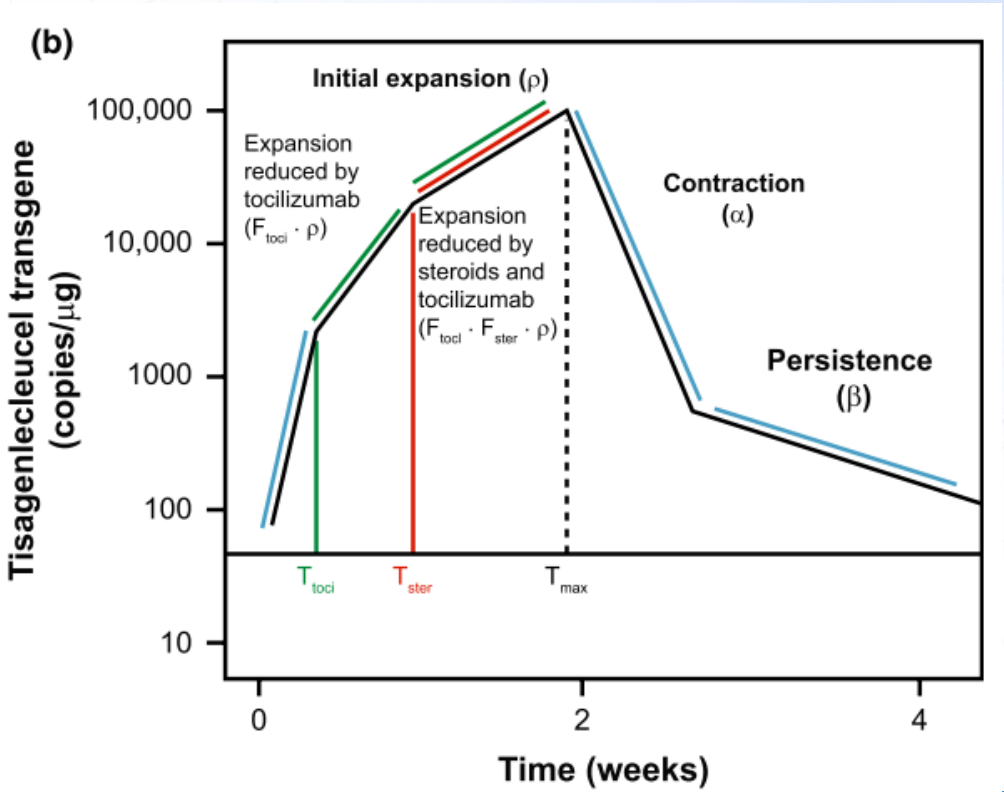


Figure and equations from Stein, et al. (2019)

Conclusion

The **mixed-effect cellular kinetic model** used in this case study:

- **characterized well the expansion and persistence** of tisagenlecleucel,
- shows **no significant impact of the comedication** on the expansion,
- may be used to **describe other types of genetically modified cells** across multiple disease indications,
- demonstrates the **value of population PK models** in predicting the behavior of CAR T-cells in vivo.

Case study available at: **https://monolixsuite.slp-software.com/tutorials/2024R1/car-t-case-study**

Resources and Key References

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