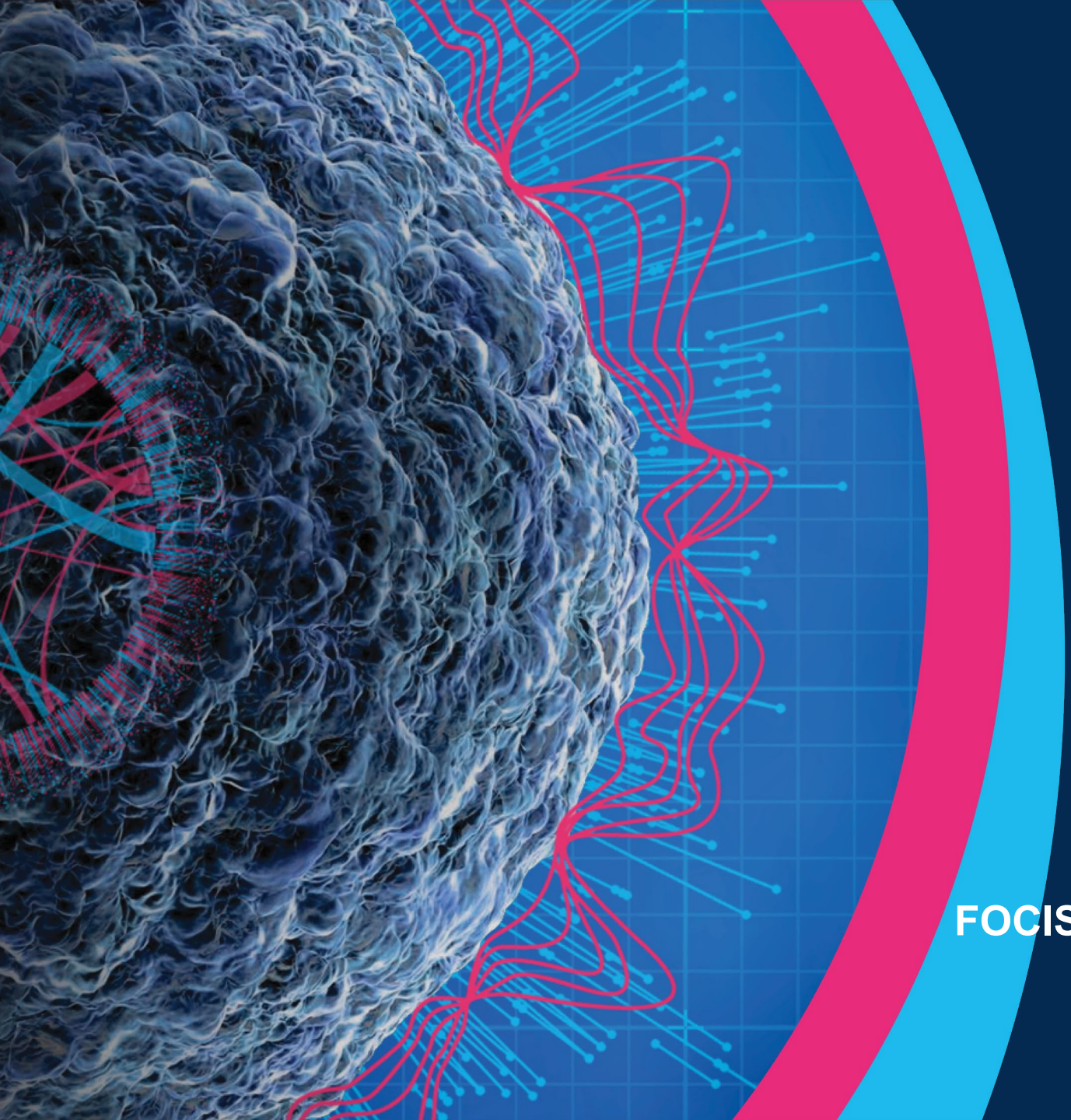


Notch THERAPEUTICS

Making drugs from T cells:
Quantitative Analysis of CAR-T Pharmacology

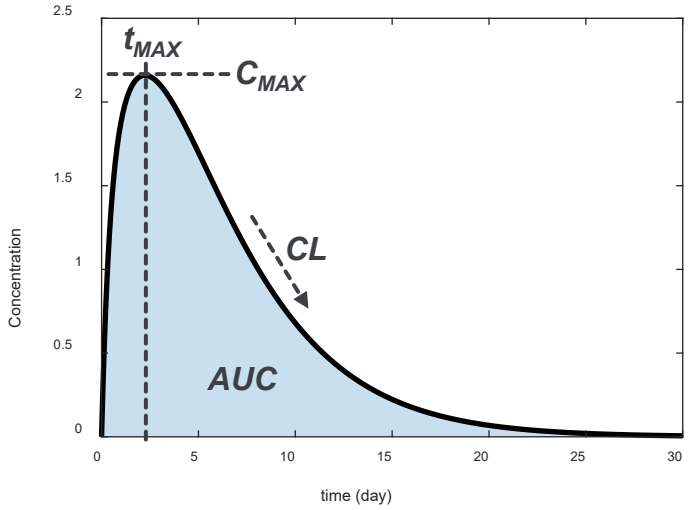
FOCIS Cancer Immunity & Immunotherapy Course

June 20, 2023

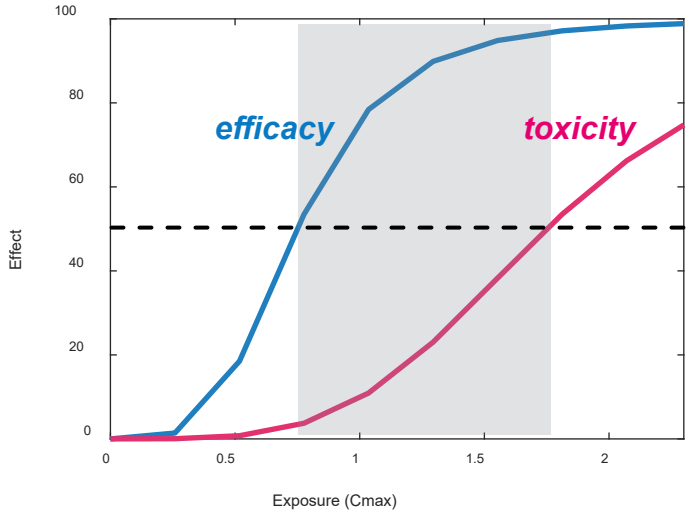
Daniel Kirouac

Pharmacometrics:
Quantitative Pharmacokinetics & Pharmacodynamics (PKPD)

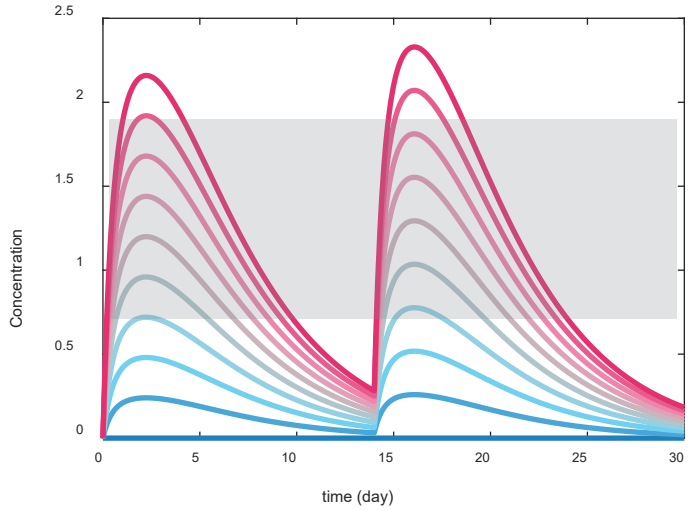
Pharmacokinetics (PK): Dose-Exposure



Pharmacodynamics (PD): Exposure-Response



PKPD: Dose regimen optimization



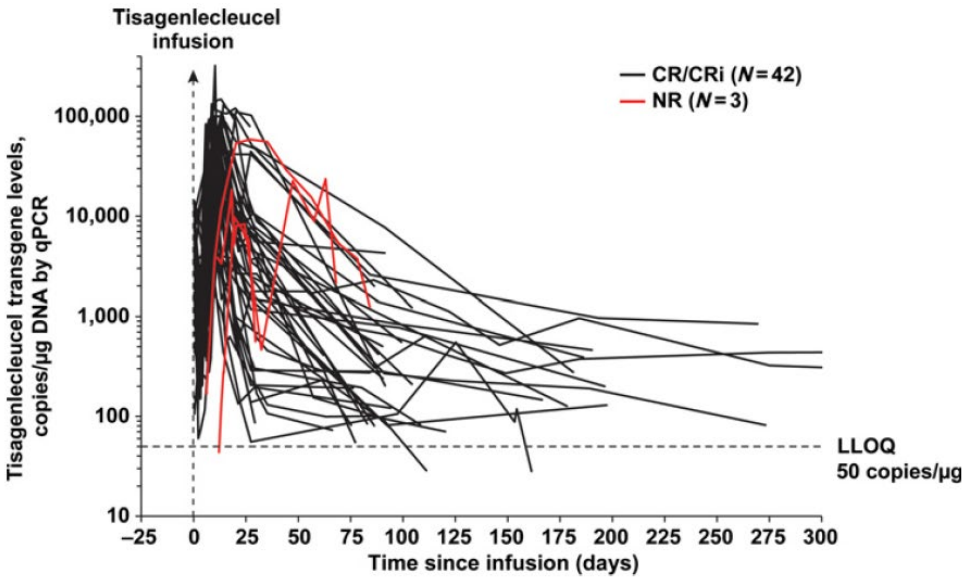
C_{max} : maximal concentration
T_{max} : time at Cmax
AUC : Area under the Curve
CL: Clearance rate (~half-life^{-1})

$$\text{Effect} = E_{max} \cdot \left(\frac{C^k}{C^k + EC50^k} \right)$$

Therapeutic index: EC50(efficacy) – EC50(tox)

How do we apply these quantitative metrics to adoptive T cell therapy?

Adoptive T cell therapy: what drives exposure/response?

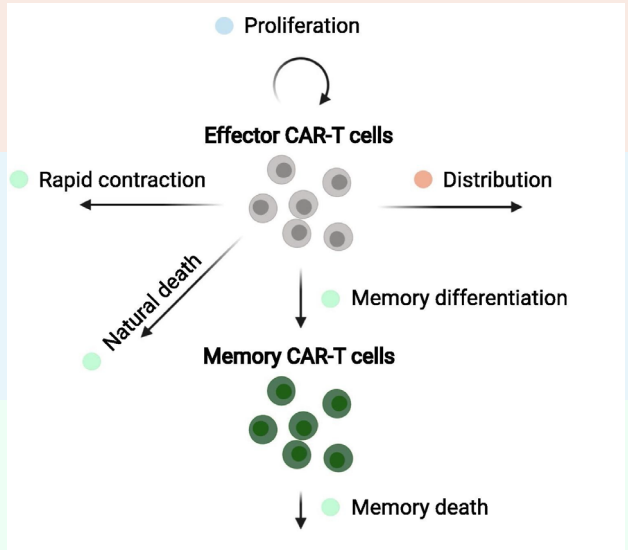


Mueller KT, Waldron ER, Grupp SA, et al (2018) Clinical Pharmacology of Tisagenlecleucel in B-Cell Acute Lymphoblastic Leukemia.
Clin Cancer Res 24(24):6175-6184

Distribution
- Where do T cells go?
- Does proliferation/expansion occur in tissues or blood?

Cell Expansion
- Memory vs. exhaustion phenotype…sometimes
- Intrinsic proliferative capacity of the cells
- CAR design & expression
- Patient cytokine levels
- Tumor burden

Contraction & Clearance/Persistence
- Memory cell generation following antigen clearance
- Competition from host T cells for ‘space’
- Allogeneic elimination (host vs. graft)



Anti-tumor efficacy & toxicity (CRS)
- Exposure (Cmax / AUC)
- Intrinsic cytotoxic potency
- CAR design & expression
- Tumor Microenvironment inflammatory/anti-inflammatory signals
- Tumor homing/penetration**

Qi T, McGrath K, Ranganathan R, et al (2022) Cellular kinetics: A clinical and computational review of CAR-T cell pharmacology. Adv Drug Deliver Rev 188:114421.

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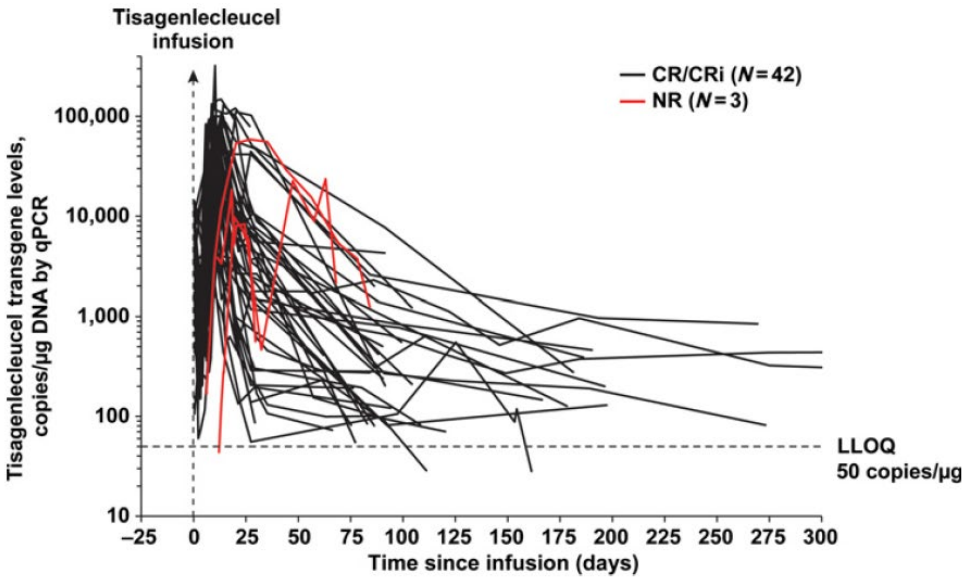
Adoptive T cell therapy: what drives exposure/response?



Mueller KT, Waldron ER, Grupp SA, et al (2018) Clinical Pharmacology of Tisagenlecleucel in B-Cell Acute Lymphoblastic Leukemia.
Clin Cancer Res 24(24):6175-6184

Outline

1. **What pharmacometrics predict patient response?**
   - *Empirical* pharmacokinetic (PK) modelling

2. **What cell-intrinsic properties of the CART product underly the wide clinical variability?**
   - *Mechanistic* PKPD modelling of Tcell:tumor interactions
   - *Machine learning* model for predicting response

3. **What patient-intrinsic factors mediate response?**
   A. T cell bio-distribution*
   B. Tumor inflammation
   C. Lympho-depletion regimen & patient response
   D. Host vs. Graft (allogeneic clearance)

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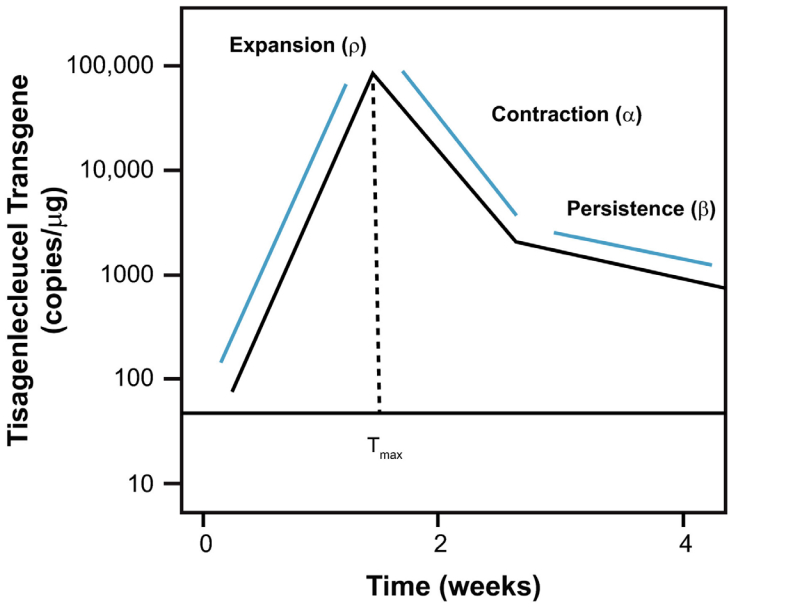
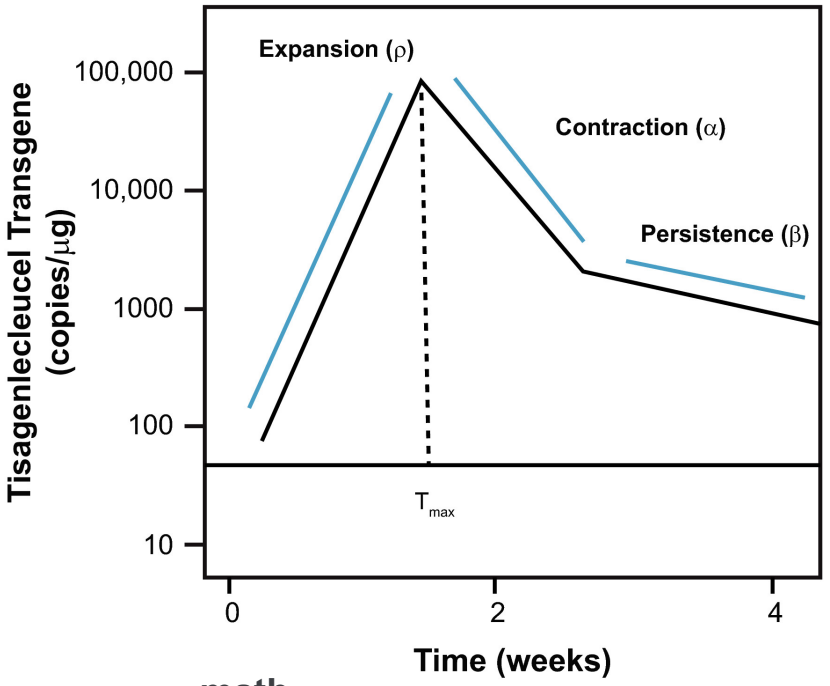
1. What CAR-T pharmacometrics predict response?

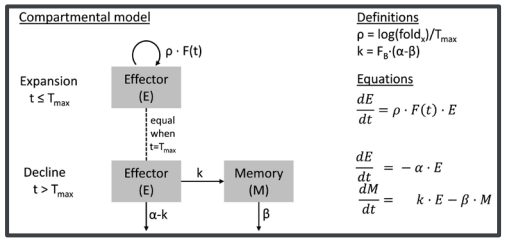


CAR-T pharmacokinetic ("cellular kinetics") model
Developed for Kymriah (TISAGENLECLEUCEL-T) BLA

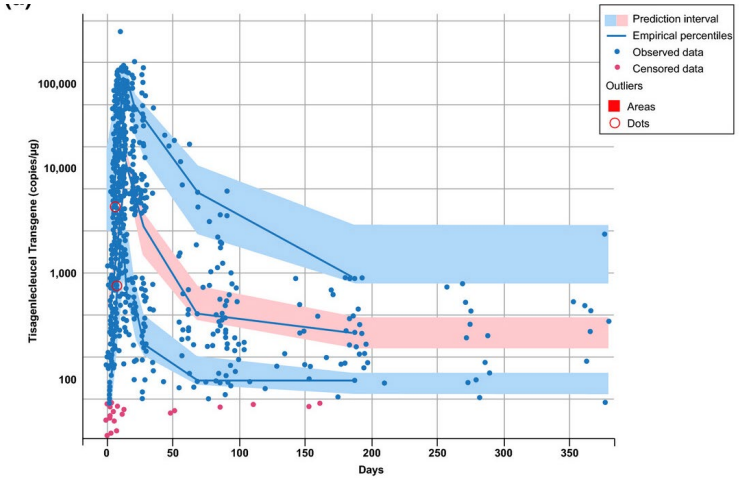
Empirical model quantifies PK curves



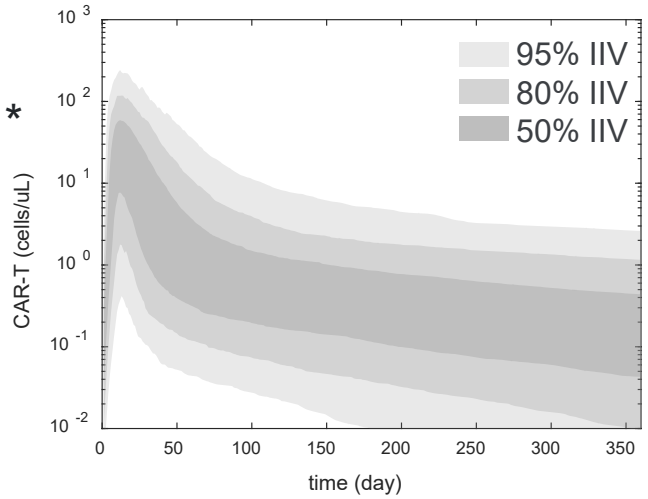
math



PK simulations vs. clinical data



Internal model simulations



*Kalos et al (2011) Sci Transl Med 3:73-95.

Model parameters

PAARAMETR	THETA (mean)	ETA (variance)
Cmax	24000 (counts/ug)	0.65
Tmax	9.3 (day)	0.38
foldX (Cmax/C_0)	3900	2.4
Fb (fraction Tm at tmax)	0.0079	0.8
Alpha (contraction)	0.16 day^{-1}	0.91
Beta (persistence)	0.0032 day^{-1}	0.86

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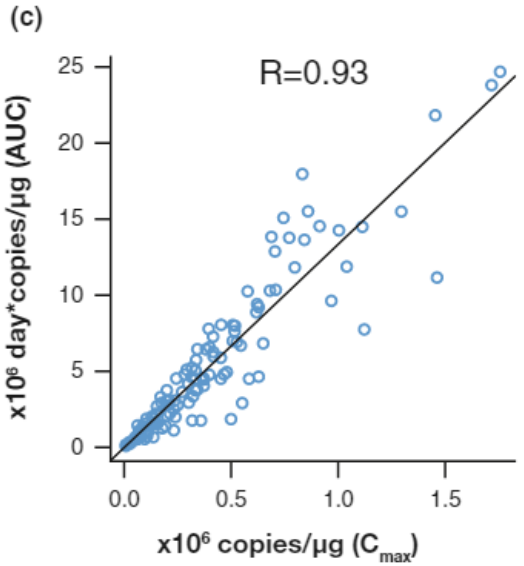
Stein AM, Grupp SA, Levine JE, et al (2019) Tisagenlecleucel Model-Based Cellular Kinetic Analysis of Chimeric Antigen Receptor–T Cells. CPT Pharmacometrics Syst Pharmacol 8:285–295.

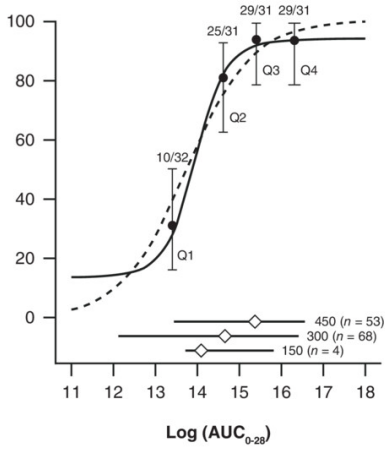
CAR-T exposure-response analyses

Abecma in Multiple Myeloma

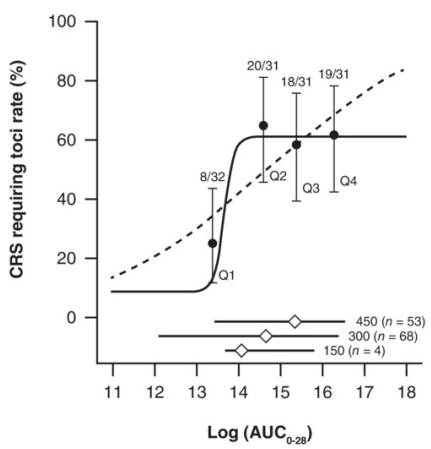
AUC ~ Cmax



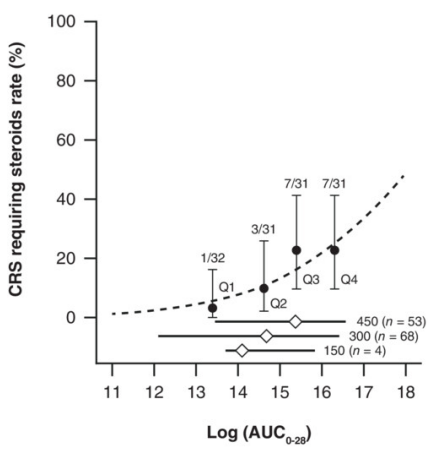
AUC (or Cmax) drives response & toxicity (CRS)



Parameter	Estimate (%RSE) on the logit scale
E_0	–2.83 (43.0)
E_{max}	2.29 (37.0)
Log (EC_{50})	2.64 (0.96)
H	3.25 (19.7)
Sex (female vs male)	1.78 (38.3)

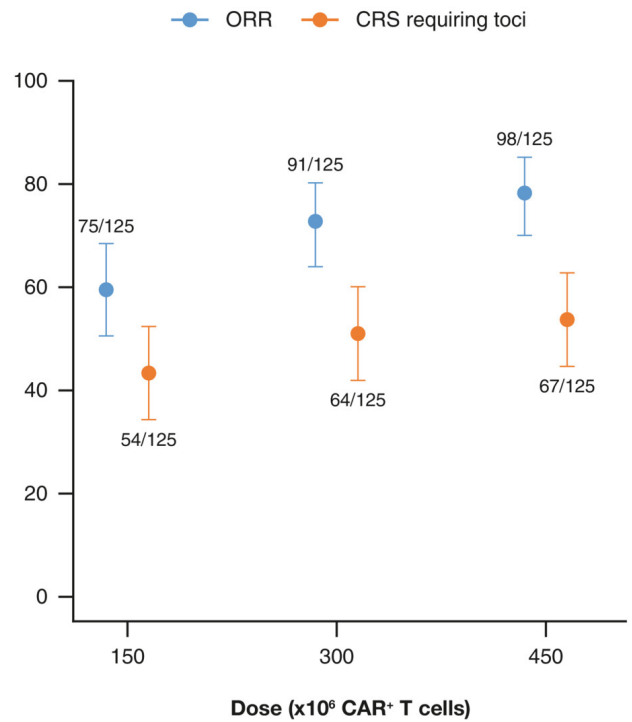


Parameter	Estimate (%RSE) on the logit scale
E_0	–2.37 (43.5)
E_{max}	0.44 (47.3)
Log (EC_{50})	2.61 (0.71)
H	4.67 (27.9)



Parameter	Estimate (%RSE) on the logit scale
Intercept	–11.1 (37.2)
Slope	0.61 (43.5)

Response vs. dose and CRS



Connarn JN, Witjes H, Geffen M van Z, et al (2023) Characterizing the exposure–response relationship of idecabtagene vicleucel in patients with relapsed/refractory multiple myeloma. Cpt Pharmacometrics Syst Pharmacol. https://doi.org/10.1002/psp4.12922

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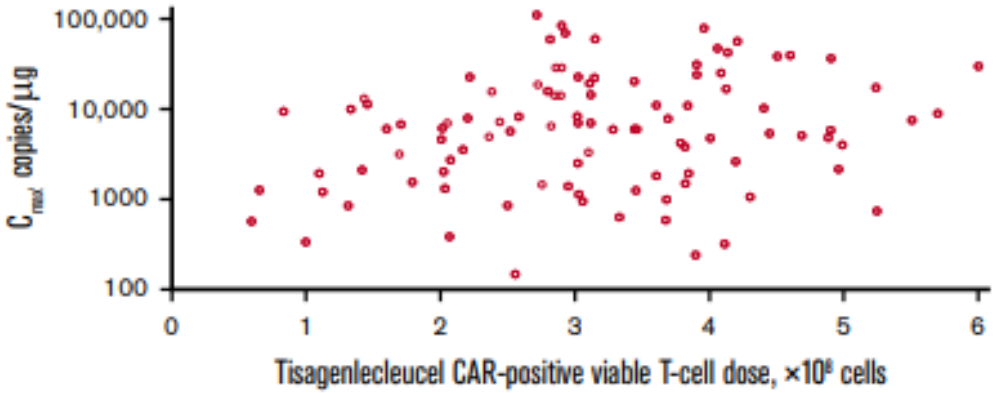
Inter-individual variability (IIV) washes out dose-responses

Kymriah in DLBCL

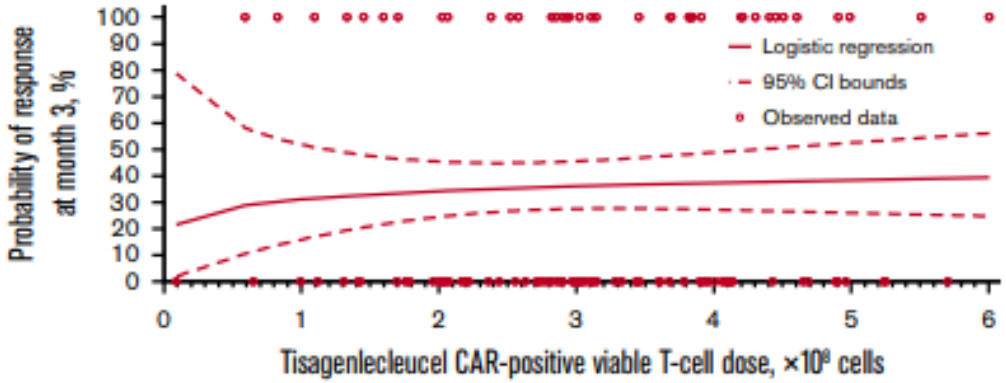
A

Cmax vs. dose

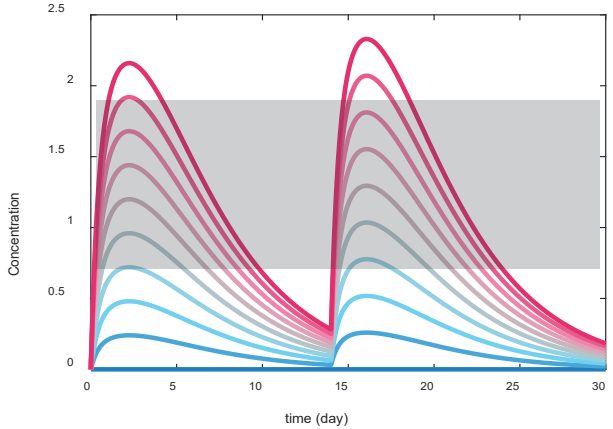


B

Response vs. Dose

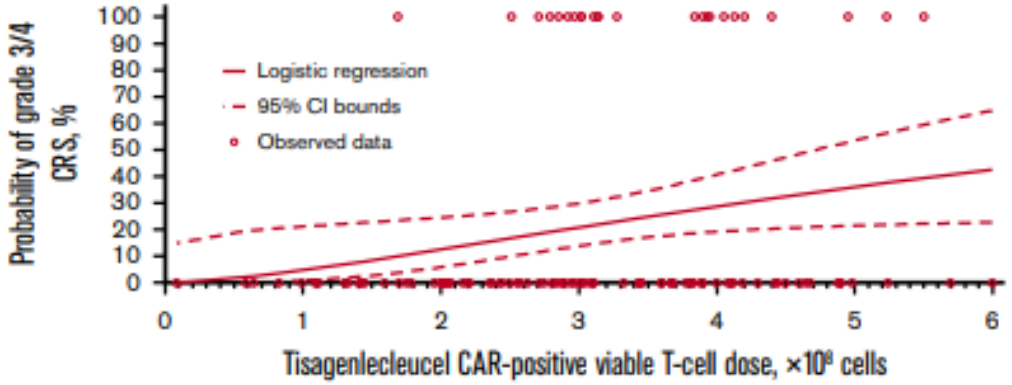


Impossible to dose-optimize (current)-CARTs



D

Toxicity vs. Dose



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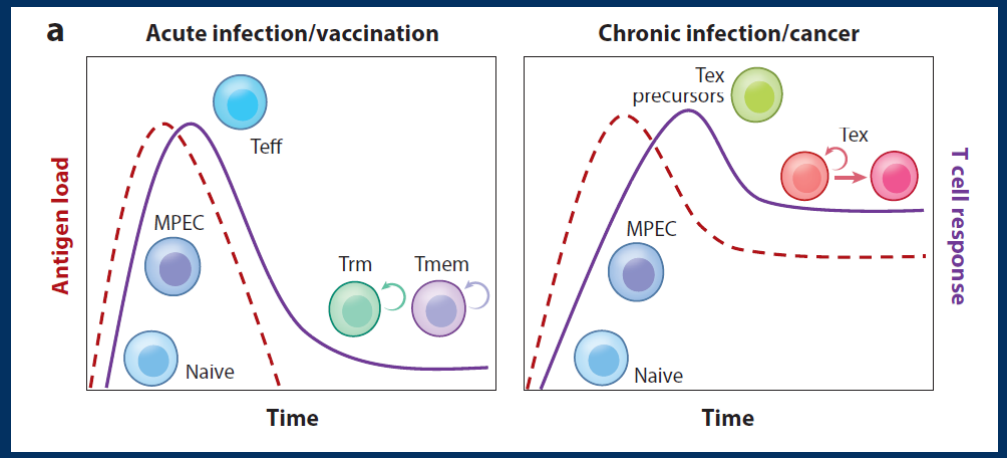
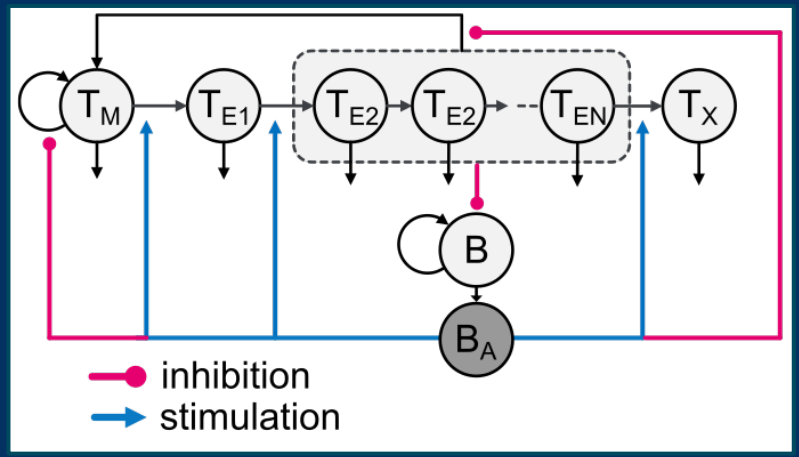
Awasthi R, Pacaud L, Waldron E, et al (2020) Tisagenlecleucel cellular kinetics, dose, and immunogenicity in relation to clinical factors in relapsed/refractory DLBCL. Blood Adv 4:560–572.

2. What cell-intrinsic properties underly clinical variability and response?

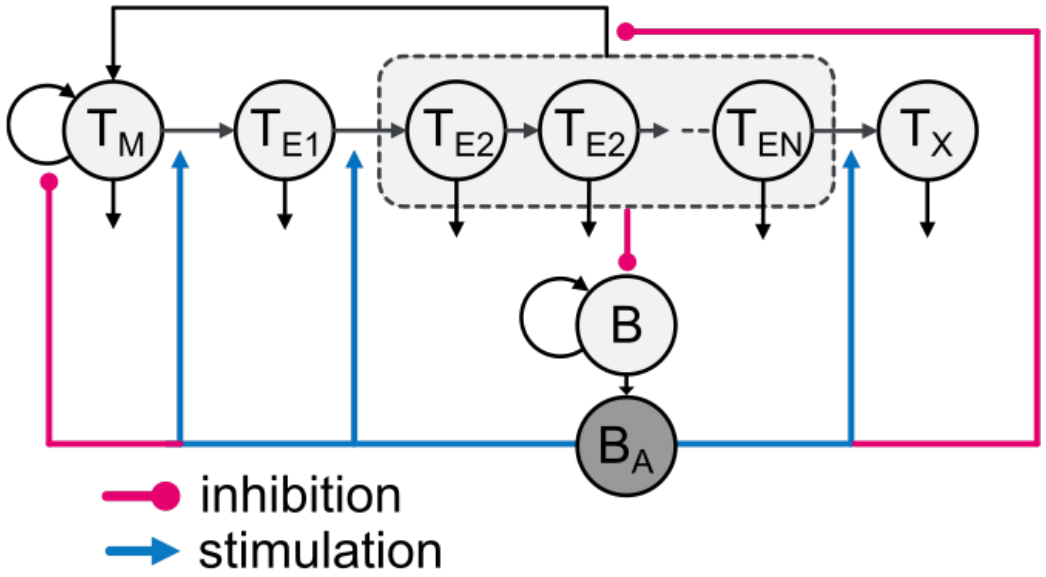




McLane LM, Abdel-Hakeem MS, Wherry EJ (2015) CD8 T Cell Exhaustion During Chronic Viral Infection and Cancer. Annu Rev Immunol 37:1–39.

DC Kirouac, C Zmurchok, A Deyati, J Sicherman, C Bond, PW Zandstra. *Deconvolution of clinical variance in CAR-T pharmacology and response.* Nat Biotech 2023

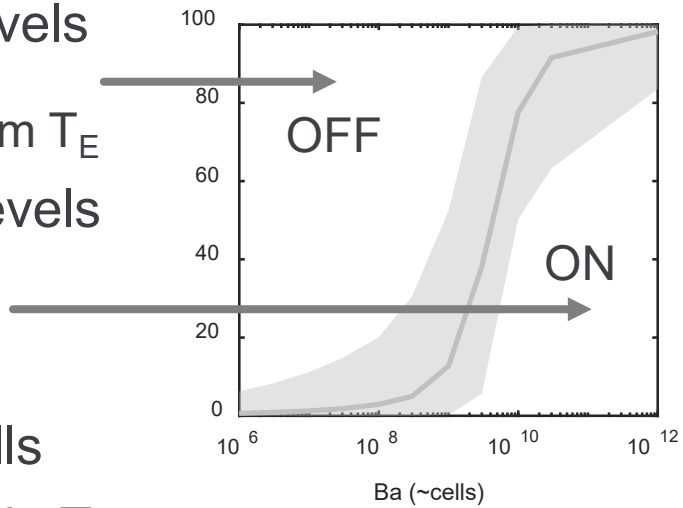
“Toggle switch” model structure and assumptions



- T_M: memory T cells
- T_E: effector T cells
- T_X: exhausted T cells
- B: B cells (tumor)
- B_A: B cell antigen

T cell differentiation *toggle switch*

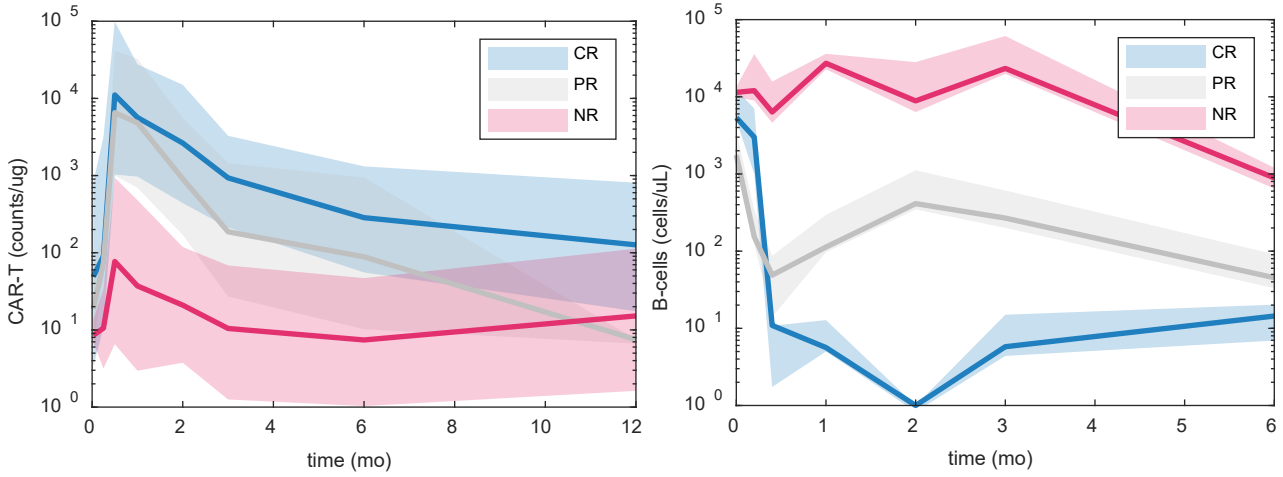
- Low antigen (B_A) levels
  - T_M self-renewal
  - T_M regeneration from T_E
- High antigen (B_A) levels
  - T_M differentiation
  - T_E proliferation
  - T_E exhaustion (T_X)
- T effectors kill B-cells
- N cell divisions within T_E compartment



DC Kirouac, C Zmurchok, A Deyati, J Sicherman, C Bond, PW Zandstra. *Deconvolution of Clinical variance in CAR-T pharmacology and response* Nat Biotech 2023

Model training data: *Kymriah* in Chronic Lymphoblastic Leukemia
PKPD profiles, CAR-T product transcriptomes and immuno-phenotypes vs. response

Population mean PKPD: *Kymriah* in Chronic Lymphoblastic Leukemia (CLL)

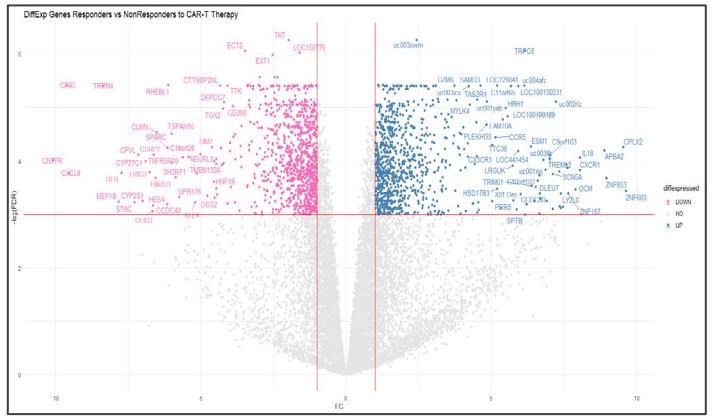


*mean ± std, digitized from publication
CR=8, PR =5, NR=25

CR = Complete Response
PR = Partial Response
NR = Non-Response

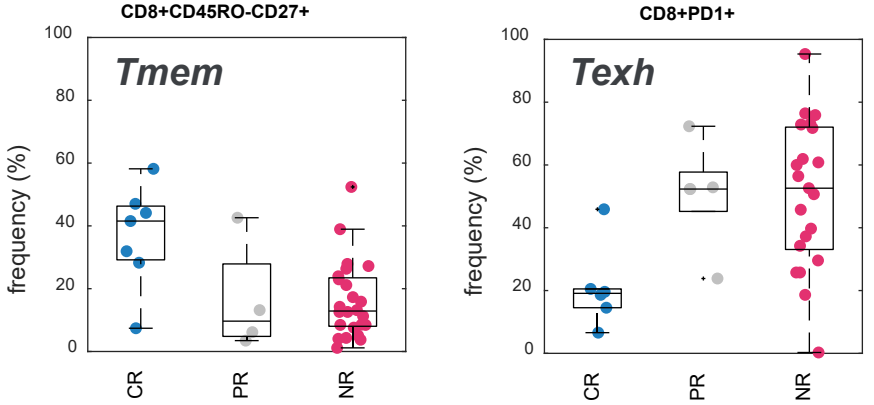
- Can we recapitulate the pharmacokinetics & tumor dynamics (PKPD) based on T cell biology?
- What kinetic parameters / molecular features distinguish robust vs. poor responding patients?

Pre-infusion CAR-T transcriptomes



CR=5, PR =5, NR=21

Pre-infusion CAR-T immunophenotype

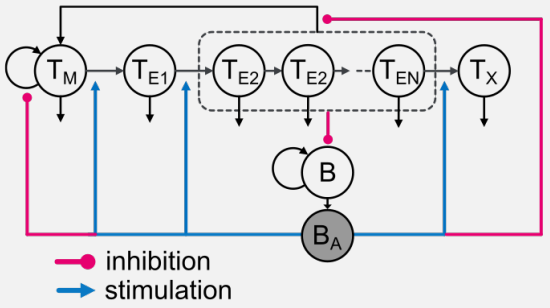


Fraietta JA, Lacey SF, Orlando EJ, et al (2018) Determinants of response and resistance to CD19 chimeric antigen receptor (CAR) T cell therapy of chronic lymphocytic leukemia. Nat Med 24:563–571.

Model development and validation workflow

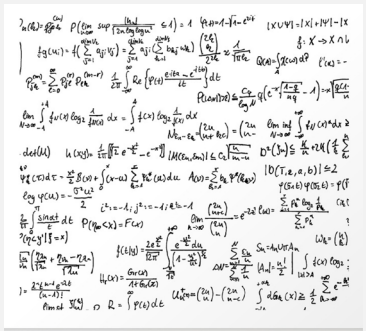
Conceptual model of T cell biology

Toggle switch circuit

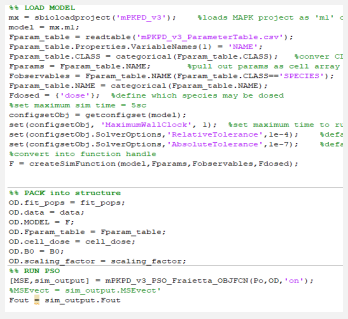


Mechanism-based dynamical model

Math

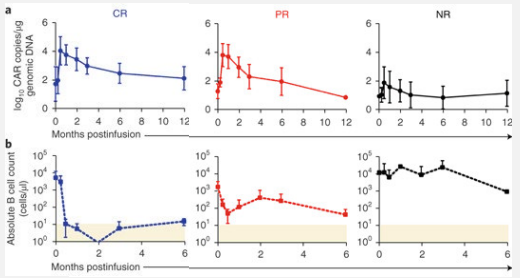


Executable code



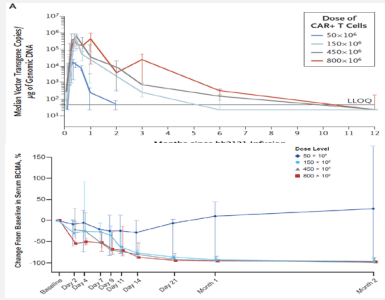
Clinical Training Data

Kymriah in CLL:
PKPD separated by response



What determines CR/PR/NR?

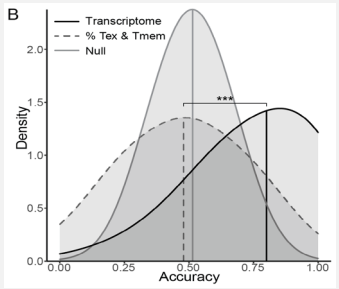
Abecma in MM:
Phase1 escalation



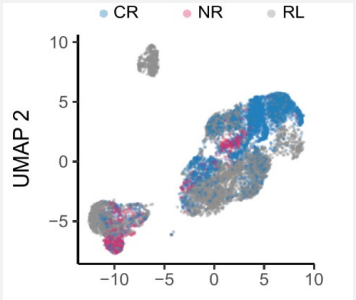
What makes an effective dose?

Genomic "Validation" Data

ssRNAseq:
CR vs NR classifier



ssRNAseq:
CR vs. NR in ALL

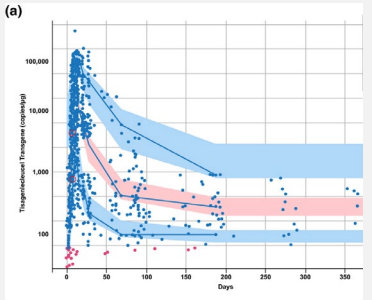


Bulk RNAseq:
CR vs. NR in CLL

How do model parameters relate to cell populations and pathways?

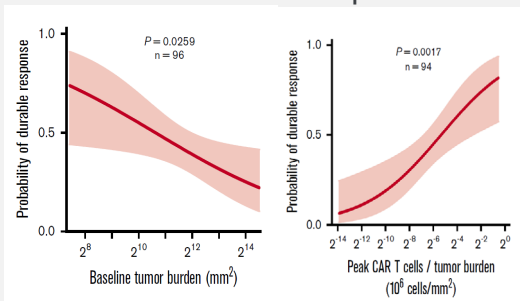
Clinical Validation Data

Kymriah in B-ALL:
Quantification of IIV



What parameters underly IIV?

Yescarta in LBCL:
Covariates of response



Do simulations predict response?

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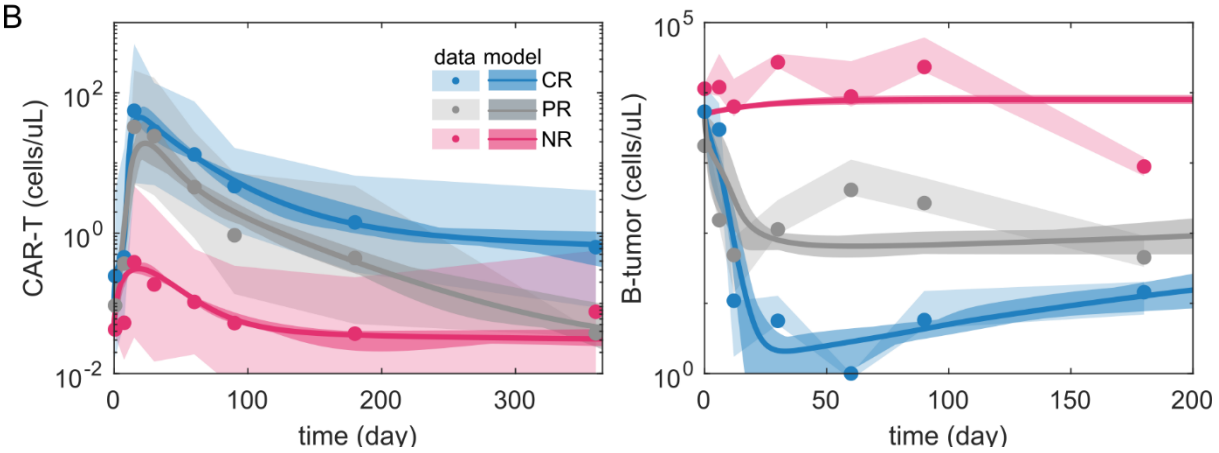
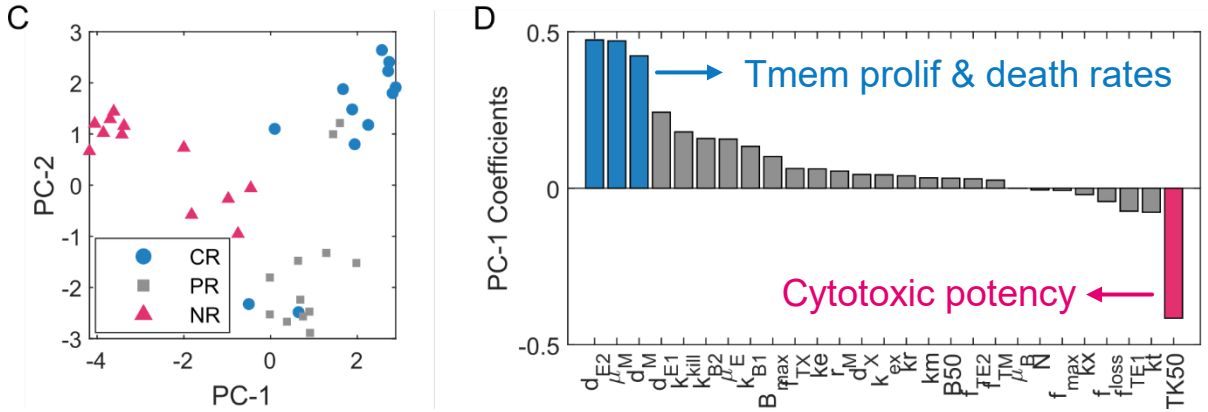
Model calibration & analysis
What features (model parameters) separate clinical outcomes?

Model calibration



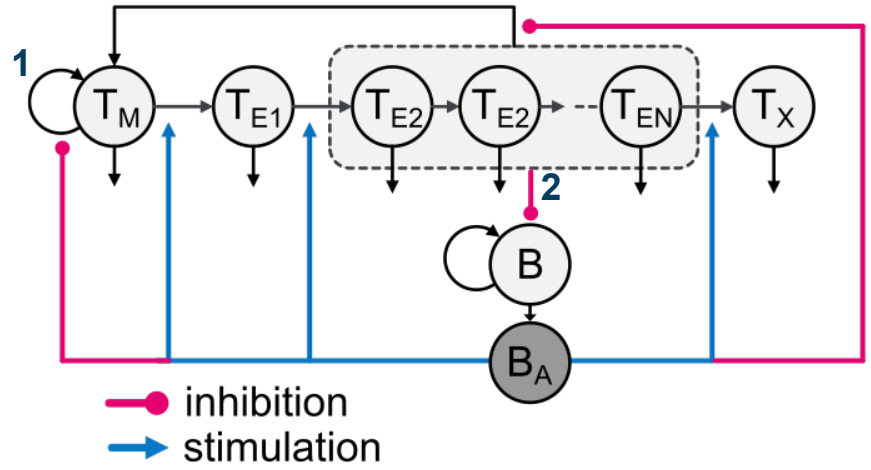
Parameter Analysis



What differentiates CR vs. NR ?

CAR-T products in CR vs. NR show:

1. Heightened memory cell turnover (μ_M, d_M)
2. Heightened cytotoxic potency (*TK50*)
3. Little difference in Tmem/Texh frequency



*Assume Dose = 10^8 cells, Tumor burden = 10^{10} cells (median reported); Estimate parameters using PSO: simulations represent 90% confidence intervals

Scale counts/ug to cell/uL using data from: Kalos, M. et al. T Cells with Chimeric Antigen Receptors Have Potent Antitumor Effects and Can Establish Memory in Patients with Advanced Leukemia. Sci Transl Med 3, 95ra73-95ra73 (2011).

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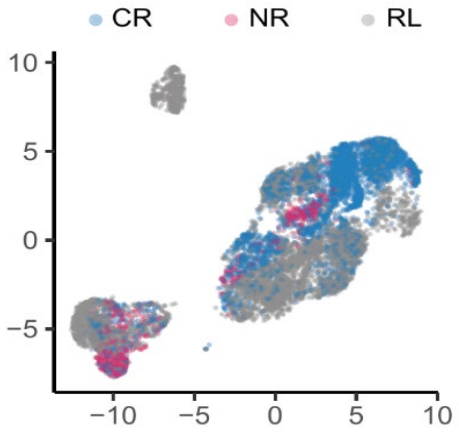
‘Validation’ of model inferences via single-cell transcriptomes

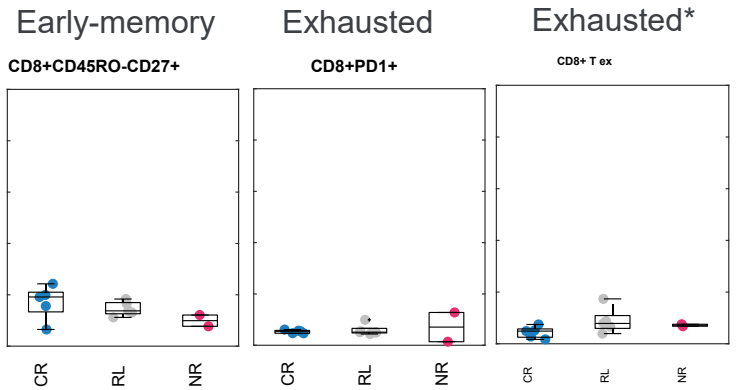
Mathematical inferences assessed in an additional blood cancer: Acute Lymphoblastic Lymphoma

T cell composition (memory vs. exhausted cells) does not substantially vary by response category

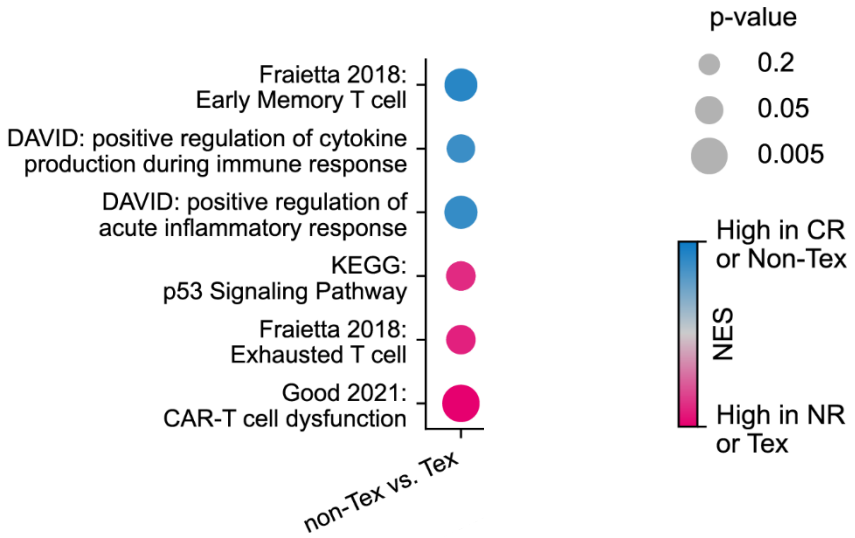
scRNAseq: Kyrmiah in ALL annotated by Response



T cell population frequencies by response category



Cell-intrinsic differences



***ProjecTILS annotation**: Andreatta M, Corria-Osorio J, Müller S, et al (2021) Interpretation of T cell states from single-cell transcriptomics data using reference atlases. Nat Commun 12:2965.

CART Dysfunction: Good CR, Aznar MA, Kuramitsu S, et al (2021) An NK-like CAR T cell transition in CAR T cell dysfunction. Cell.

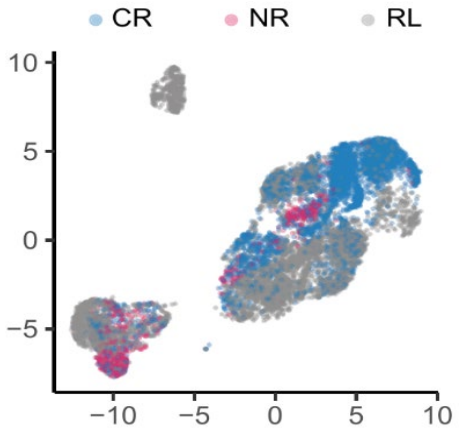
Data Source: Bai Z, Woodhouse S, Zhao Z, et al (2022) Single-cell antigen-specific landscape of CAR T infusion product identifies determinants of CD19-positive relapse in patients with ALL. Sci Adv 8:.

‘Validation’ of model inferences via single-cell transcriptomes

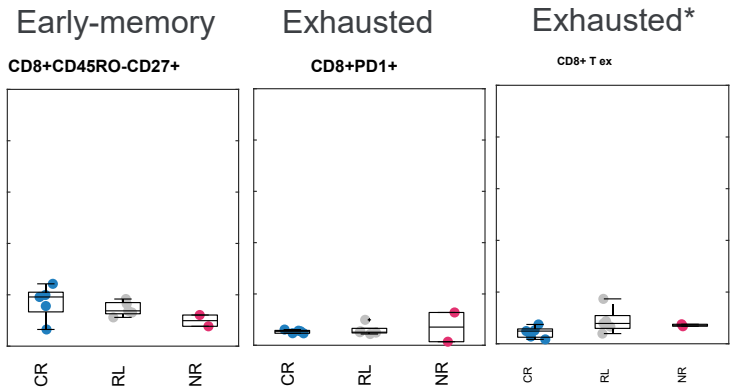
Mathematical inferences assessed in an additional blood cancer: Acute Lymphoblastic Lymphoma

T memory cells from NR patients display intrinsic functional deficits analogous to T cell exhaustion

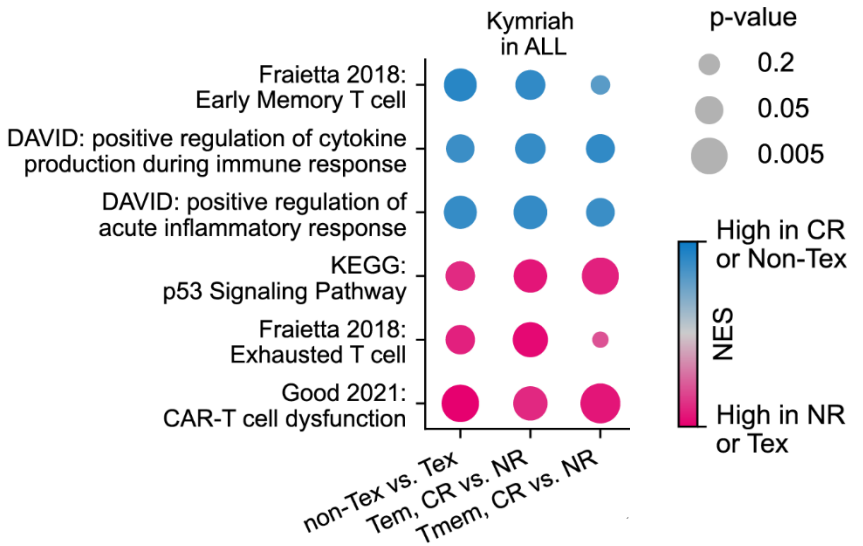
scRNAseq: Kyrmiah in ALL annotated by Response



T cell population frequencies by response category



Cell-intrinsic differences



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CART Dysfunction: Good CR, Aznar MA, Kuramitsu S, et al (2021) An NK-like CAR T cell transition in CAR T cell dysfunction. Cell.

Tem, Tmem cells from NR samples appear functionally exhausted
***Tem: defined via ProjecTILs algorithm**
***Tmem: defined via CD8+CD45RO-CD27+ CITEseq tags**

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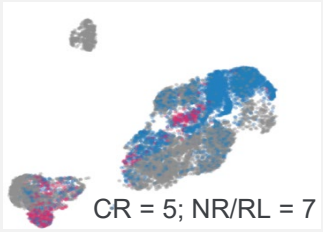
Data Source: Bai Z, Woodhouse S, Zhao Z, et al (2022) Single-cell antigen-specific landscape of CAR T infusion product identifies determinants of CD19-positive relapse in patients with ALL. Sci Adv 8:.

CAR-T clinical response prediction

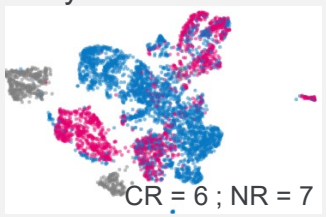
Are pre-infusion CAR-T transcriptomes predictive of clinical response (CR vs. NR)?

scRNAseq pre-infusion CAR-Ts
CR/NR/PR classes

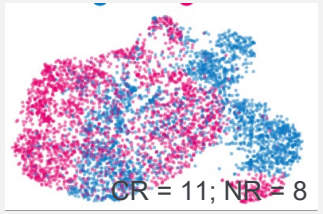
Kymriah in ALL



Kymriah in LBCL



Yescarta in LBCBL



CR PR NR

Machine learning workflow

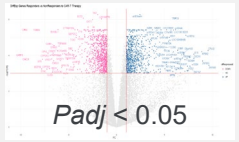
"Feature Engineering"

Feature Compression

ssGSEA: Pathway databases

20K genes →

Feature selection 1



7500 signatures →

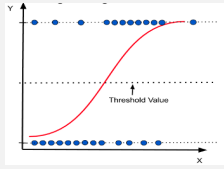
Model training & validation:
Repeat 2,500X: 40:60 test:train splits

Feature selection 2

Genetic Algorithm (GA)

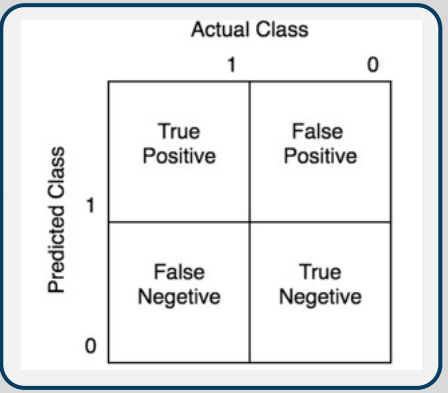
28 pathways →

Classifier model training



2-7 pathways →

CR vs. NR calssification



$$Accuracy = \frac{TP + TN}{TP + TN + FP + FN}$$

Lage P, small N problem: the central challenge in biomedical genomics

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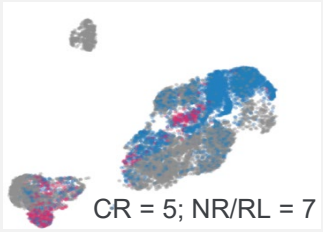
CAR-T clinical response prediction

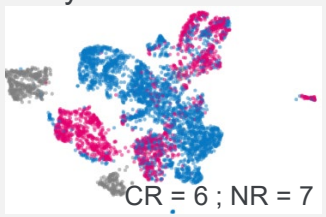
Are pre-infusion CAR-T transcriptomes predictive of clinical response (CR vs. NR)?

scRNAseq pre-infusion CAR-Ts CR/NR/PR classes

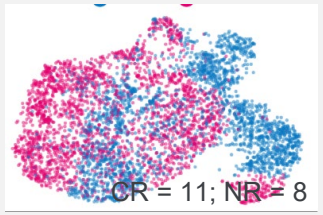
Kymriah in ALL



Kymriah in LBCL



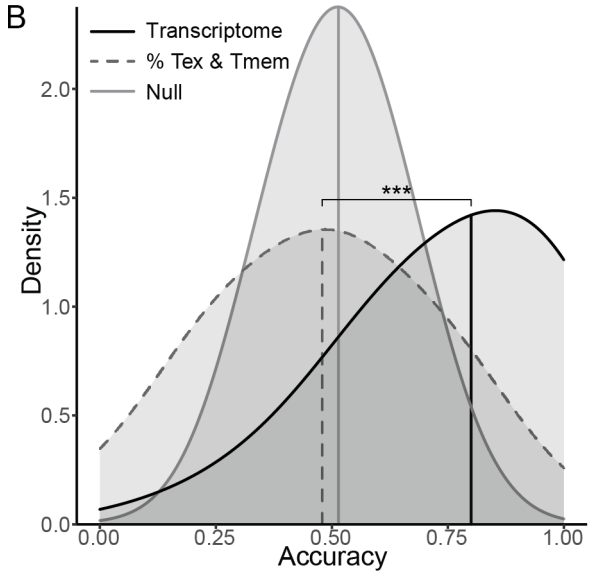
Yescarta in LBCBL



CR PR NR

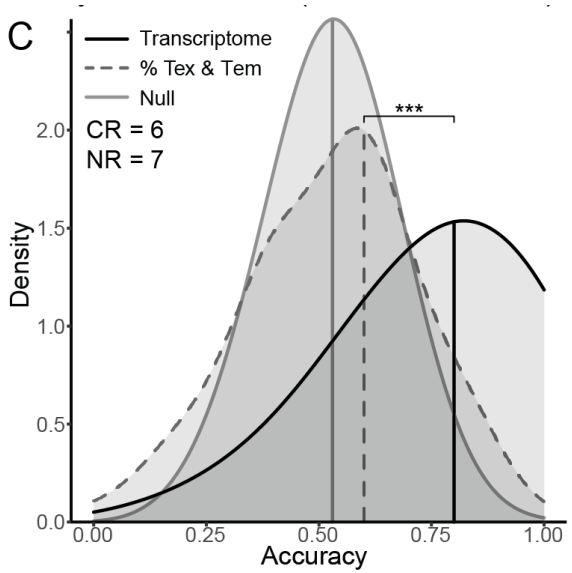
Predictive accuracy of response classification using 60:40 train:test splits

Kymriah in ALL (Bai 2022)



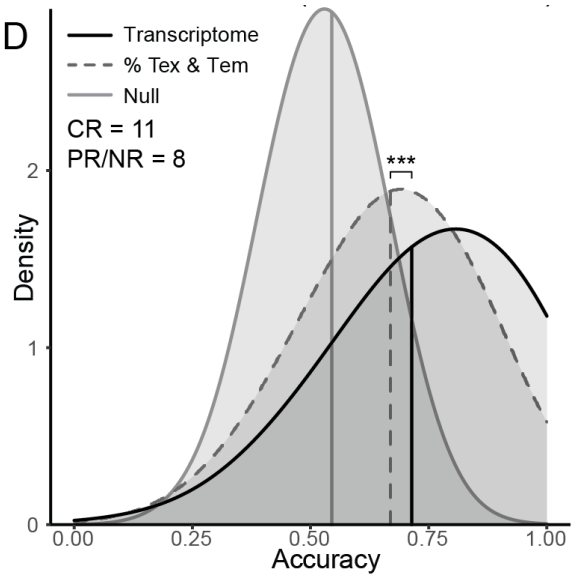
Accuracy = 80%
Tmem, Tex: CITESeq data
CR = 5; NR/RL = 7

Kymriah in LBCL (Haradhvala 2022)



Accuracy = 80%
Tmem, Tex: ProjecTILS*
CR = 6 ; NR = 7

Yescarta in LBCL (Haradhvala 2022)



Accuracy = 71%
Tmem, Tex:ProjecTILS
CR = 11; NR/PR = 8

****P* < 10^{-8} (rank-sum test)

Functional attributes predictive of clinical outcomes are CART-cell-intrinsic & indication-agnostic
Transcriptome > 'gold standard' immunophenotyping

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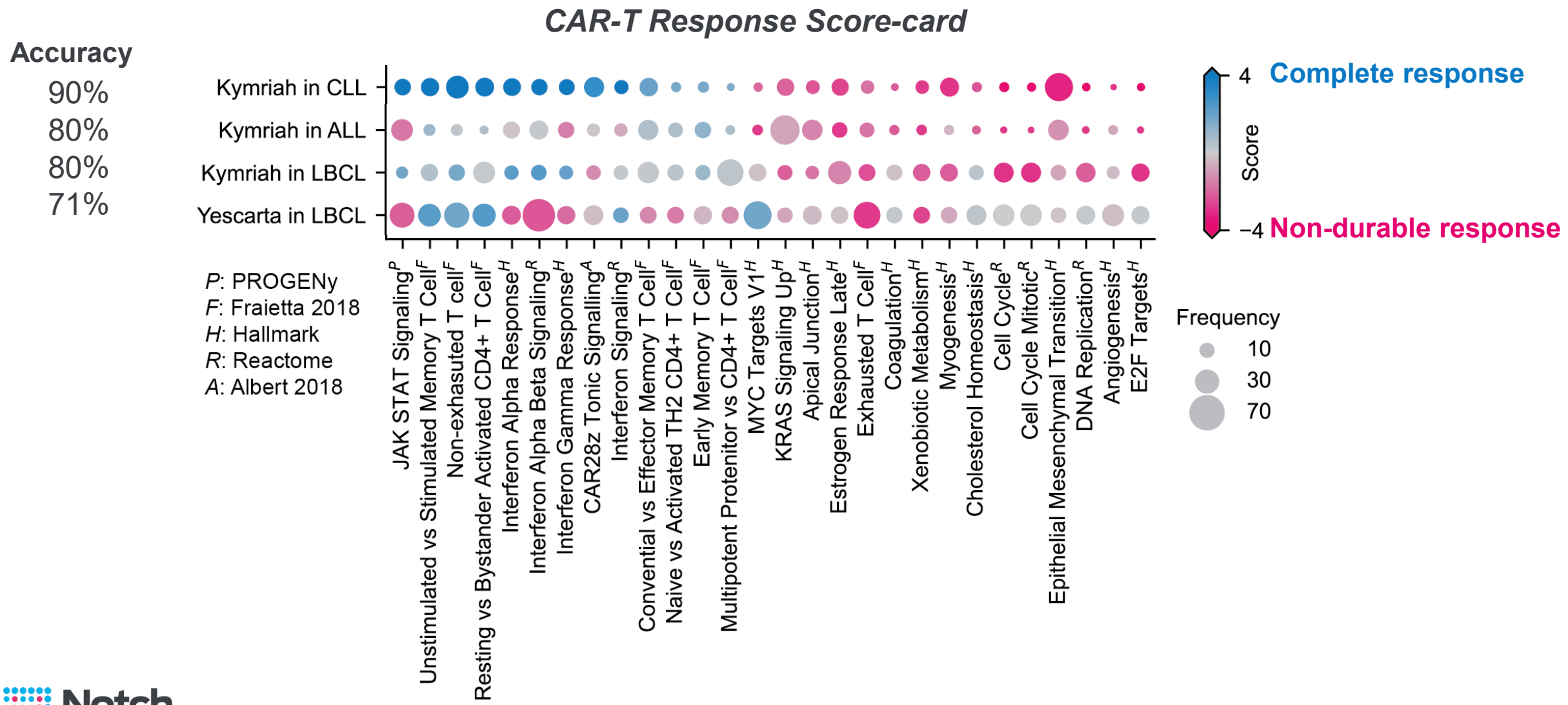
CAR-T clinical response prediction

What transcriptional signatures are predictive of CAR-T response?



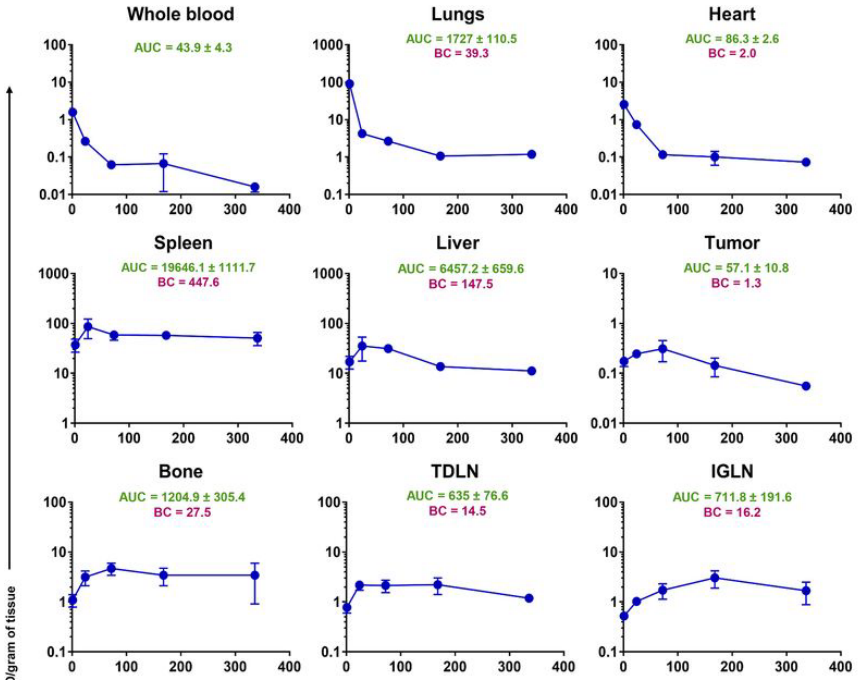
3. Patient-intrinsic factors mediating response

A. T cell biodistribution
B. Tumor Inflammation
C. Response to Lympho-depletion & host-T cell competition
D. Host vs. Graft response (allogeneic elimination)

3A. Adoptive T cell Biodistribution

Where do CAR-Ts go once administered? What happens in tissues vs. Blood?

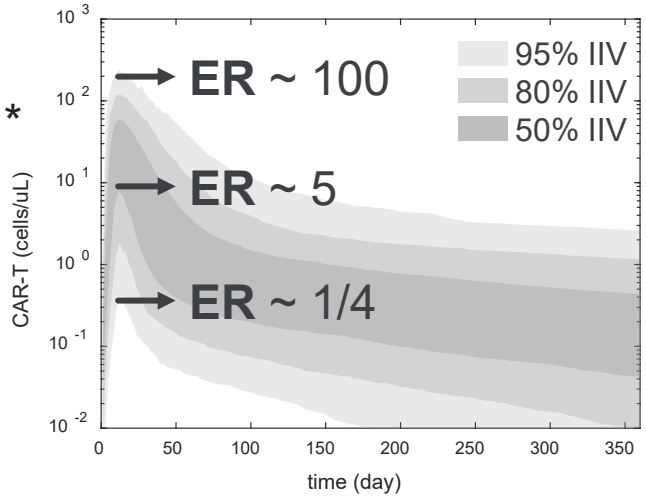
Pharmacokinetics & biodistribution of radio-labelled T cells in mice



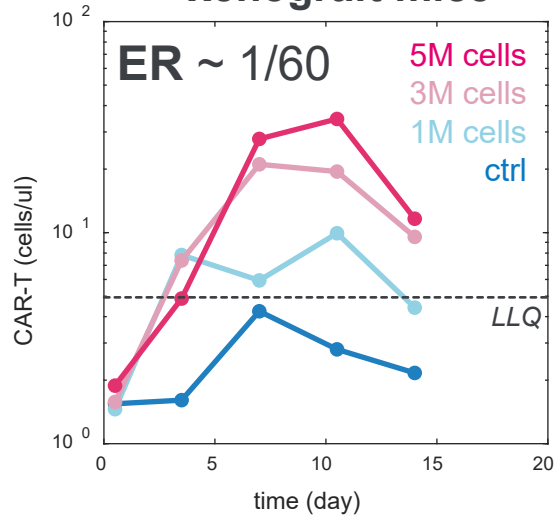
*BC = Biodistribution Coefficient.
= AUC of T cells in tissue vs. blood

Pharmacology 'accounting' in man vs. mouse

Kymriah in B-ALL



Kymriah in NALM6 xenograft mice



*ER = Expansion Ratio. How many cells do you detect at Cmax per infused?
= Cmax*Vblood / Dose

Majority of administered T cells distribute to lungs, spleen, liver, kidney & lymph nodes.

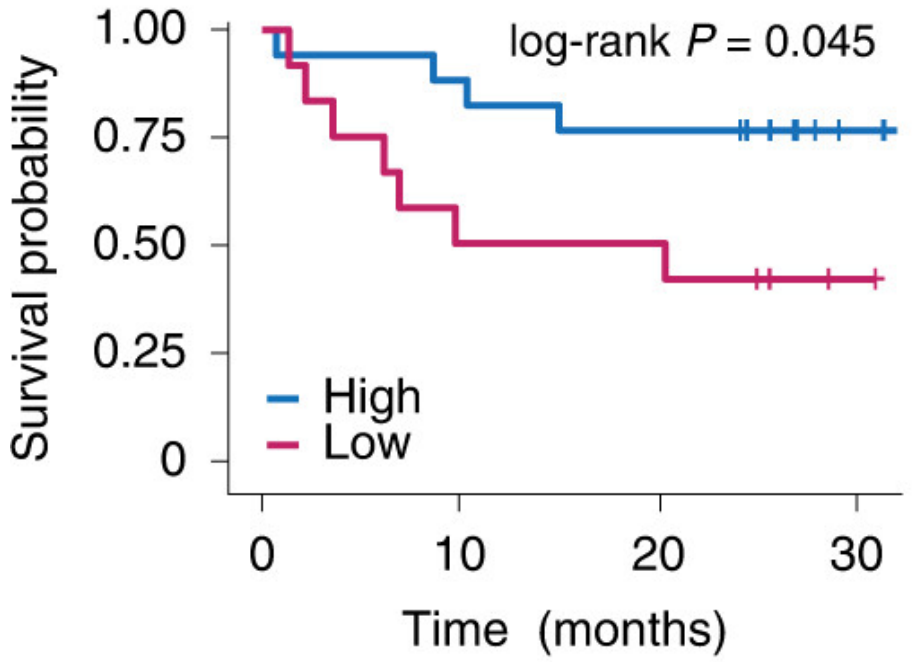
Q: Where do the majority of CARTs distribute
Q: Where does the 'action' happen (tissue vs. blood)?

Khot A, Satoko M, Thomas VA, et al (2019) Measurement and Quantitative Characterization of Whole-Body Pharmacokinetics of Exogenously Administered T Cells in Mice. J Pharmacol Exp Ther 368:jpet.118.252858.

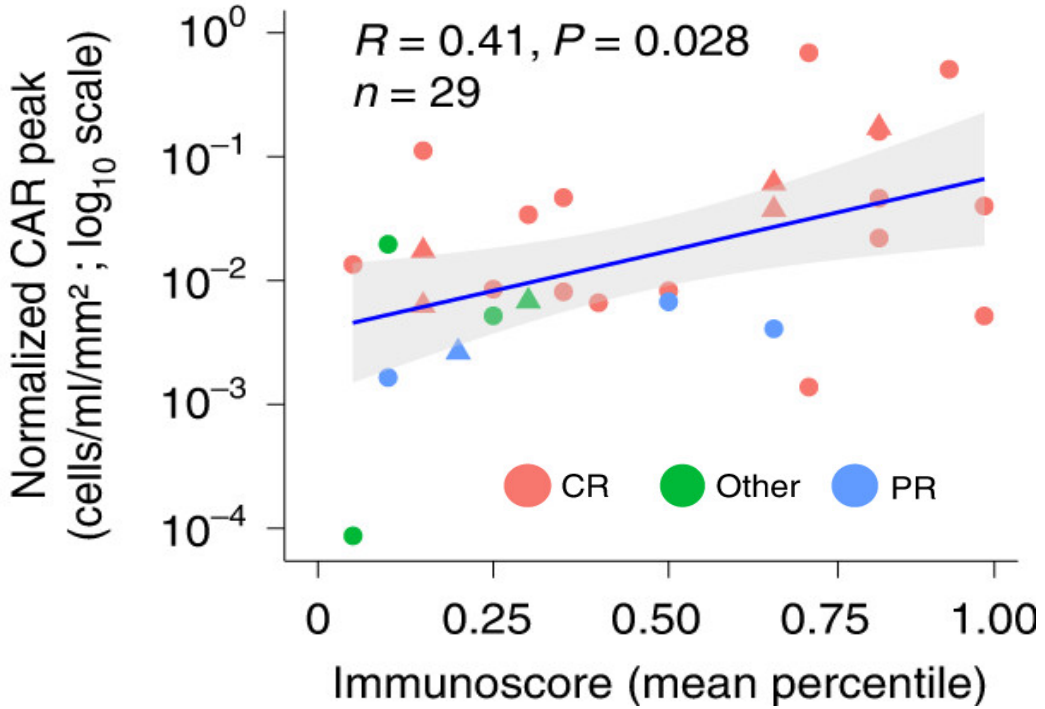
3B. Tumor inflammation and CAR-T response

Yescarta (CD19-CART) in DLBCL: ZUMA-1 trial

‘Immunoscore’ (Tumor inflammation) is the most significant patient-intrinsic predictor of CART response



Immunoscore (Tumor inflammation) also drives Cmax



Q: How would pre-existing TILs influence CAR-T expansion?

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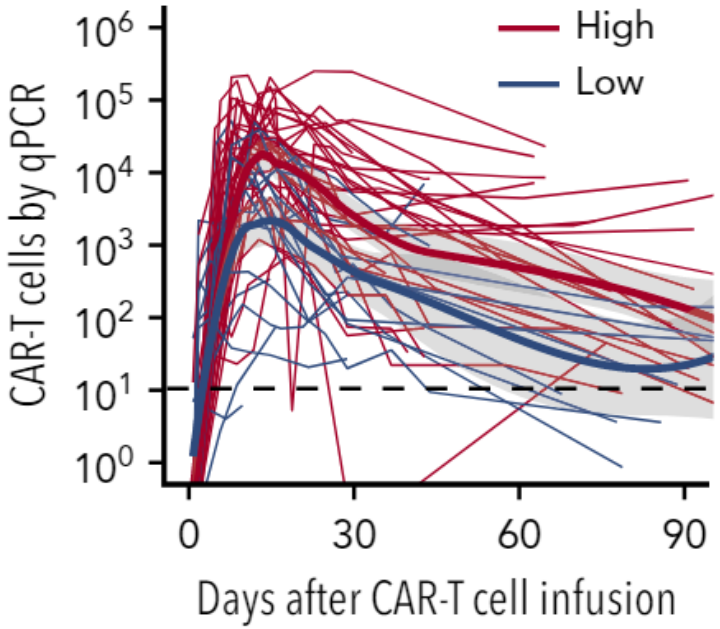
Scholler N, Perbost R, Locke FL, et al (2022) Tumor immune contexture is a determinant of anti-CD19 CAR T cell efficacy in large B cell lymphoma. Nat Med 1–11.

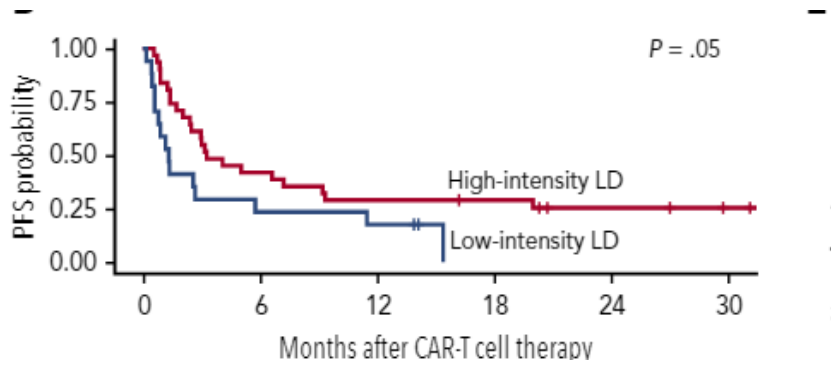
3C. Lympho-depletion intensity & response
via IL7 availability?

Lymphodepletion intensity drives CART expansion

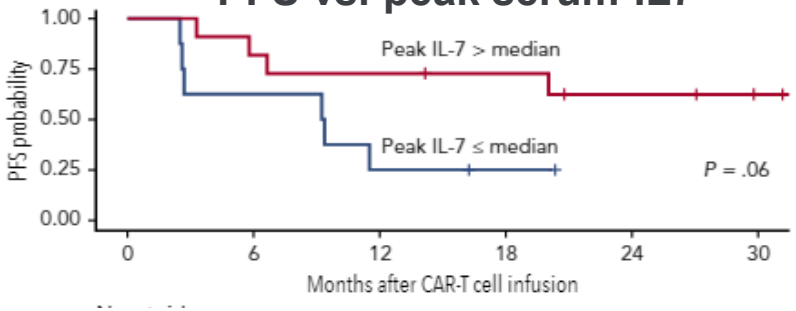


*60 vs. 30 mg/kg cyclophosphamide, CD19 CART therapy in NHL

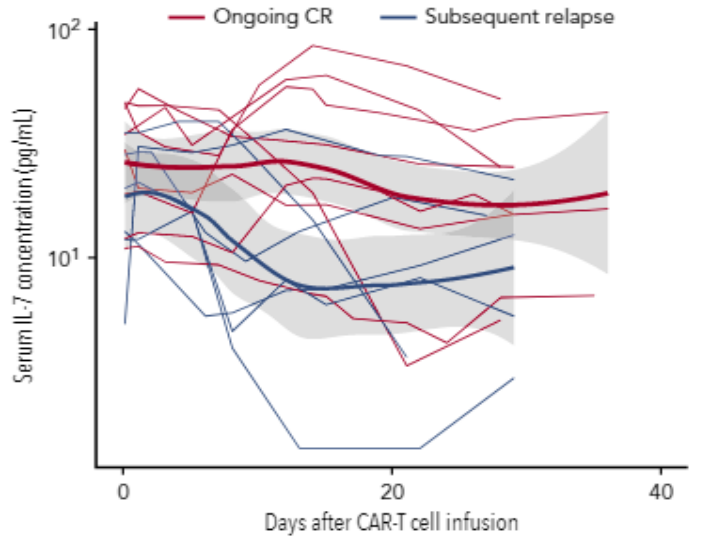
PFS vs. lymphodepletion



PFS vs. peak serum-IL7



Lymphodepletion intensity drives IL7 expression

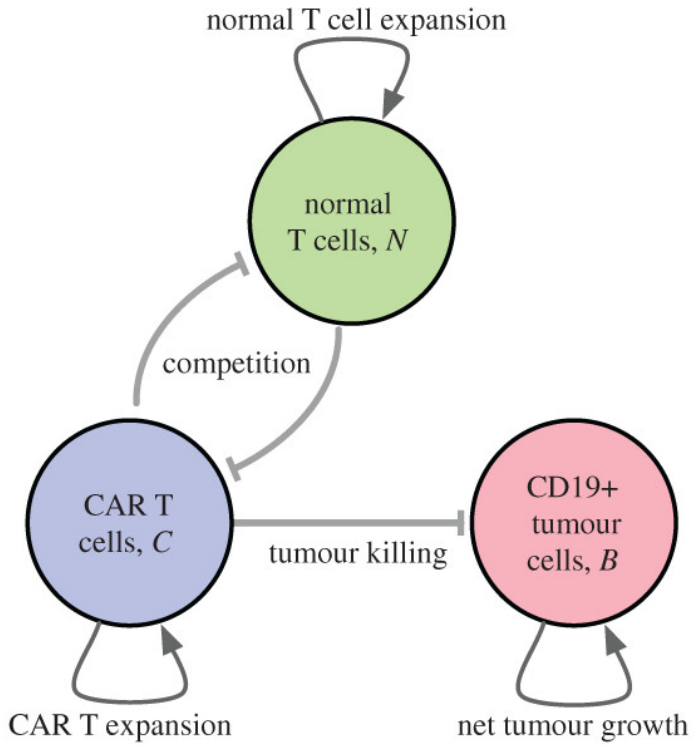


Q: How does Lympho-depletion intensity affect CAR-T expansion and peak IL7 concentration?
Q: Can we *mimic* intense-LDT via cytokine support?

Hirayama AV, Gauthier J, Hay KA, et al (2019) The response to lymphodepletion impacts PFS in patients with aggressive non-Hodgkin lymphoma treated with CD19 CAR T cells. Blood 133:1876–1887.

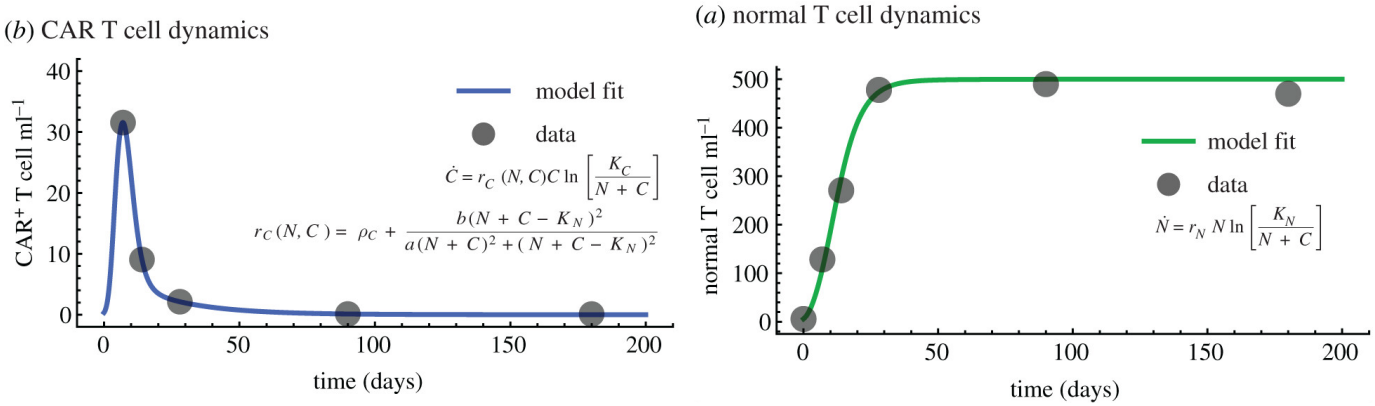
Competition between Adoptive vs. Patient T cells

Model structure

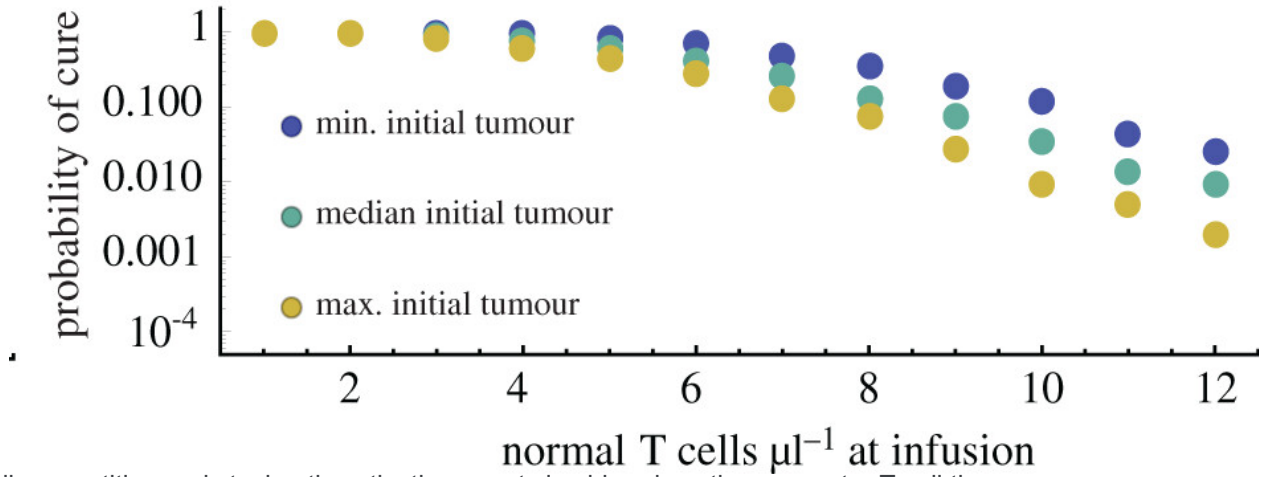


Q: What is the mechanism underlying T cell competition for limited ‘space’?

Model fitting: Yescarta in LBCL (ZUMA-1)
CAR-T and Host-T cell kinetics



Model simulations: Response vs. Tumor burden & LDT depth



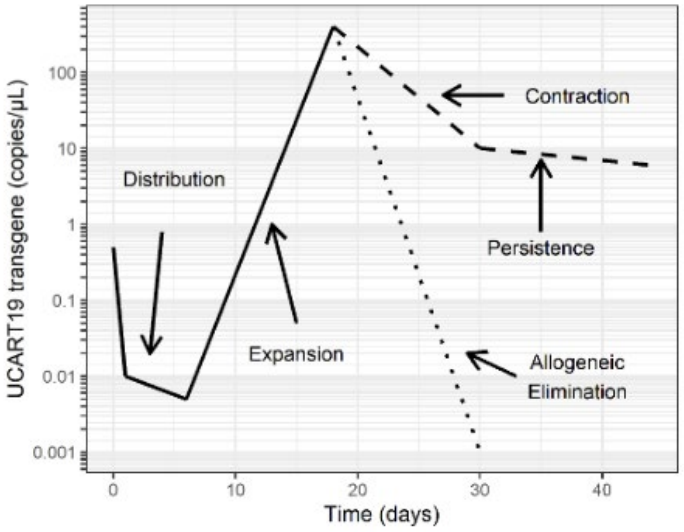
Kimmel GJ, Locke FL, **Altrock PM** (2021) The roles of T cell competition and stochastic extinction events in chimeric antigen receptor T cell therapy. Proc Royal Soc B 288:20210229.

3D. Host vs. Graft response (allogeneic elimination)

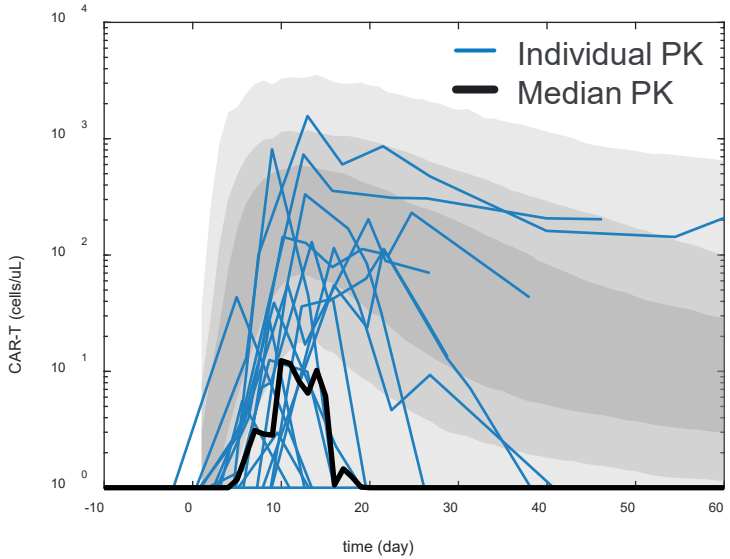
Host T cells actively clear (allogenic) T cell grafts

UCART19 in B-ALL: The first reported allogeneic CAR-T clinical data
CD19-CART, allogeneic (healthy donor-derived) T cells, *TRAC*$^{-/-}$

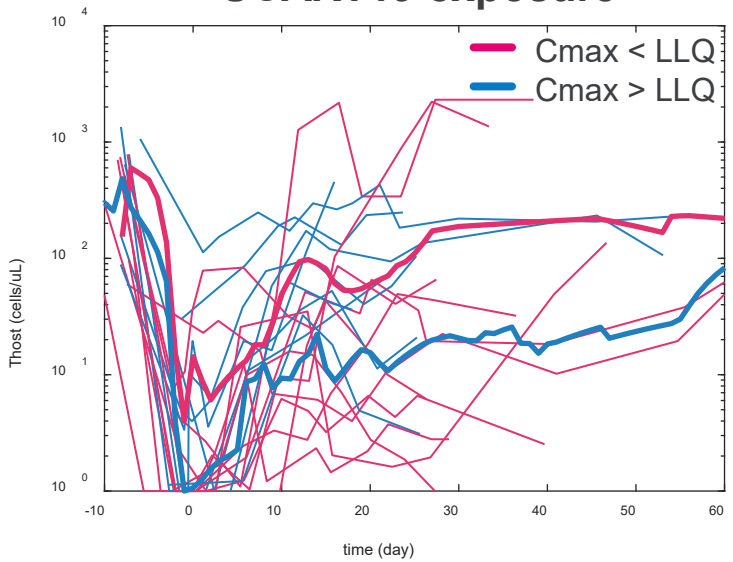
Allogeneic Elimination



UCART19 vs. Kymriah CART Pharmacokinetics



Host T cell reconstitution ~ UCART19 exposure



- Deeper LDT & slower T cell reconstitution ~ greater allogenic CART exposure

Q: How would additional gene edits (i.e. MHC-knock out) affect allo-clearance rates

Data digitized from: Derippe T, Fouliard S, Marchiq I, et al (2022) Mechanistic modeling of the interplay between host immune system, interleukin 7 and UCART19 allogeneic CAR-T cells in adult B-cell acute lymphoblastic leukemia. Cancer Res Commun 2:1532–1544.

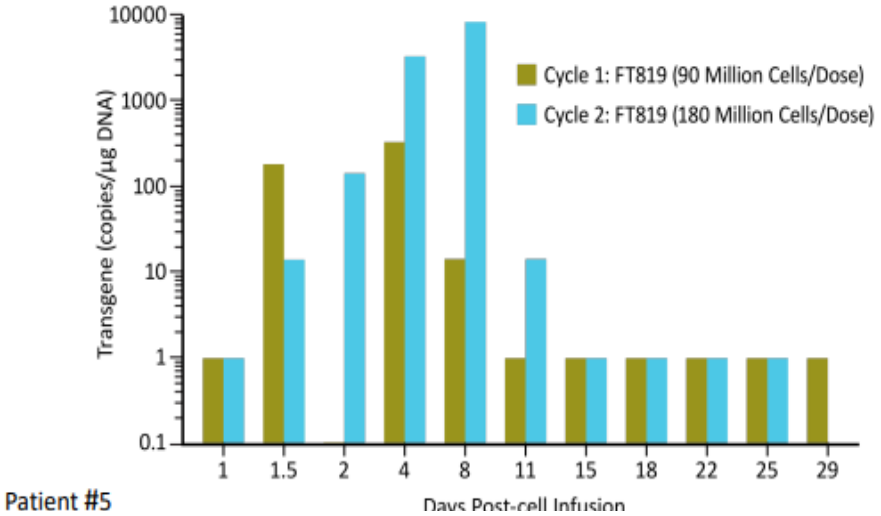
Kymirah PK simulations: Stein AM, Grupp SA, Levine JE, et al (2019) Tisagenlecleucel Model-Based Cellular Kinetic Analysis of Chimeric Antigen Receptor–T Cells. Cpt Pharmacometrics Syst Pharmacol 8:285–295.

Notch THERAPEUTICS

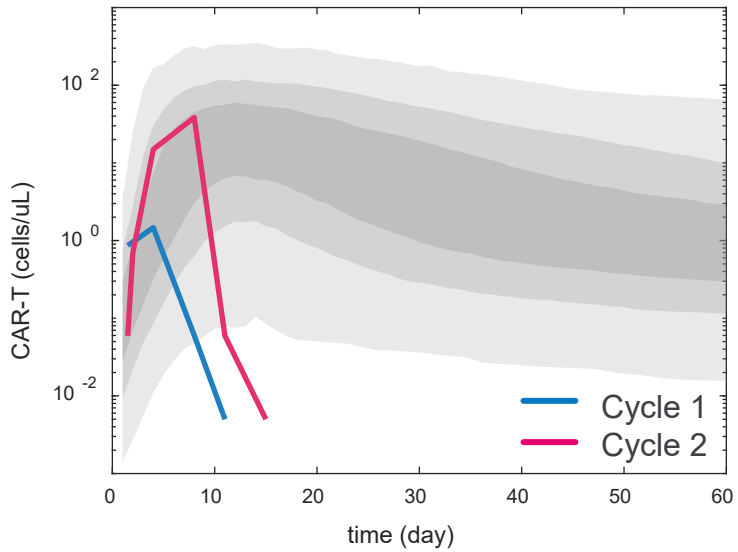
The next frontier: iPSC-derived CAR-Ts

FT819: The first reported clinically tested iPSC-derived CART
CD19-CART, allogeneic (iPSC-differenentiated) T cells, *TRAC*$^{-/-}$

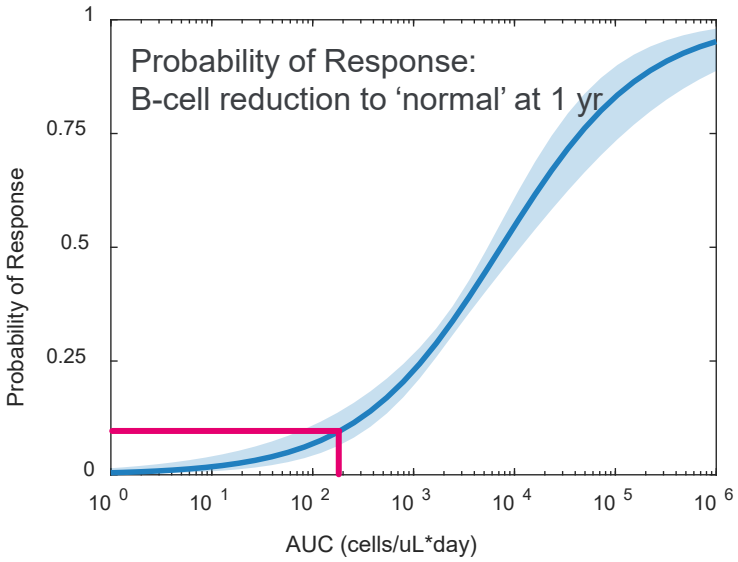
PK data digitized from ASH poster
***n=1 patient**



FT819 vs. Kymriah
CART Pharmacokinetics



AUC vs. Durable Response



- Both robust cell expansion + persistence (AUC) is required for clinical activity

Q: Why are (FT819) iPSC-CARTs incapable of persistence - *Cell intrinsic* deficit vs. *allogeneic*-clearance?

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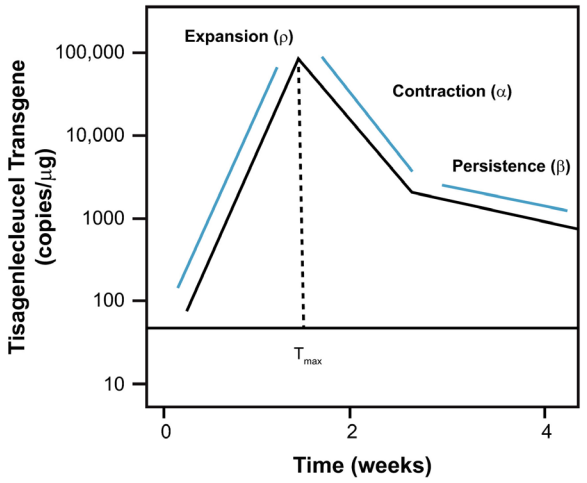
Mehta et al. Interim Phase 1 clinical data of FT-819-101, a study of the first ever, off-the-shelf, iPSC-derived TCR-less CD19 CART therapy for patients with relapsed/refractory B cell malignancies. ASH 2022.

Summary

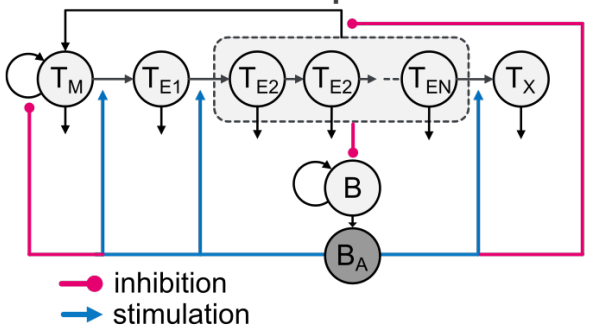
1. Empirical PKPD models

- Cmax predicts response
- High variability makes dose-optimization infeasible



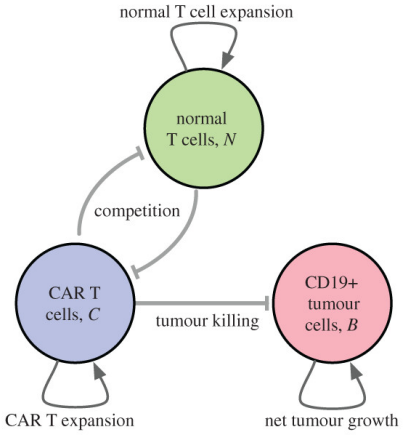
2. Mechanistic modelling & machine learning

- Product intrinsic-proliferation of memory cells is important for clinical response
- Predictive features are buried in CART transcriptomes



3. Patient-intrinsic effects

- Biodistribution, inflammatory state, lympho-depletion response, and Host vs Graft affect PK and response



Mathematical models can enable CAR-T design, optimization and data interpretation
Quantitative data is required to translate measurements to kinetic parameters

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Thank You!

Vancouver, BC

- ✓ Developmental immunology
- ✓ Systems Biology and T cell pharmacology

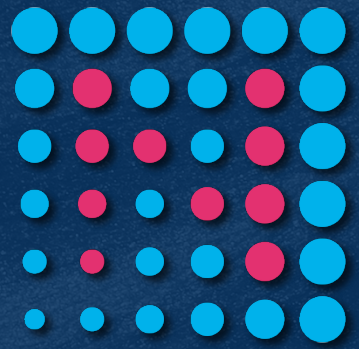
Toronto, ON

- ✓ GMP iPSCs and gene editing
- ✓ T cell manufacturing
- ✓ QA/QC

Seattle, WA

- ✓ Protein and genome engineering
- ✓ Translational sciences
- ✓ Cancer biology

Avisek Deyati,
Jordan Sicherman
Cole Zmurchok
Peter Zandstra,
Chris Bond,
Gregory Block
Irja Elliott Donaghue



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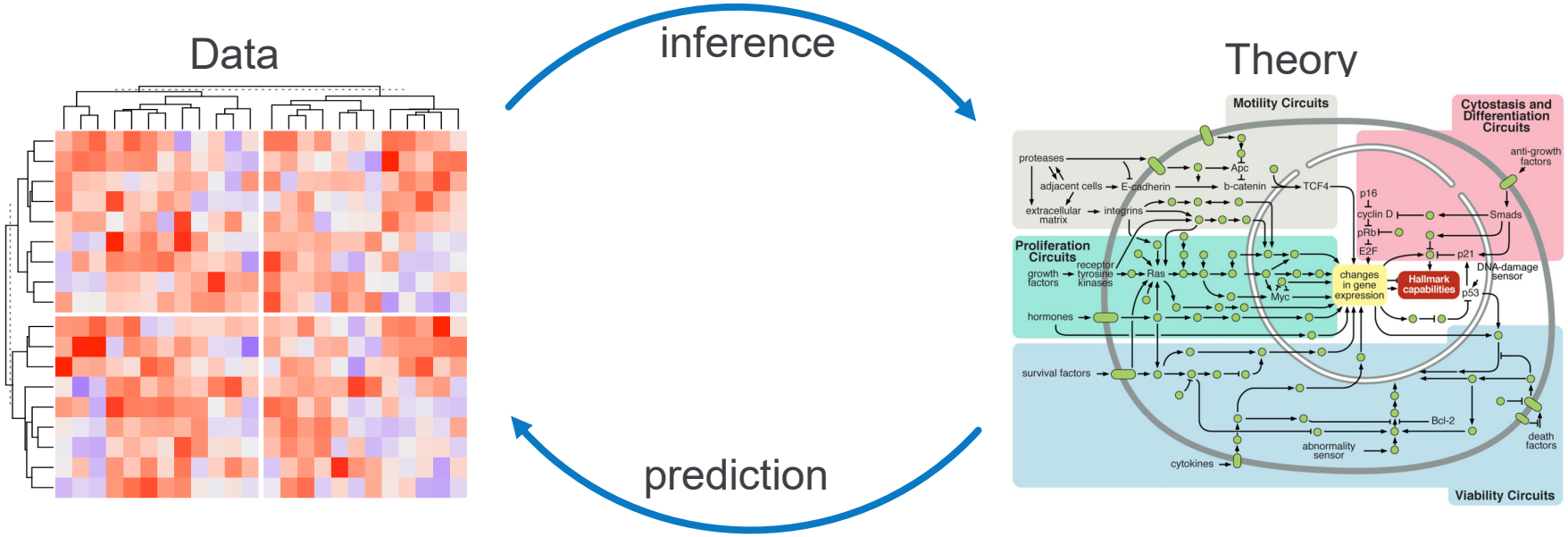
What value does modelling bring to drug development?

The biological mechanisms underlying experimental data are often complex and non-intuitive



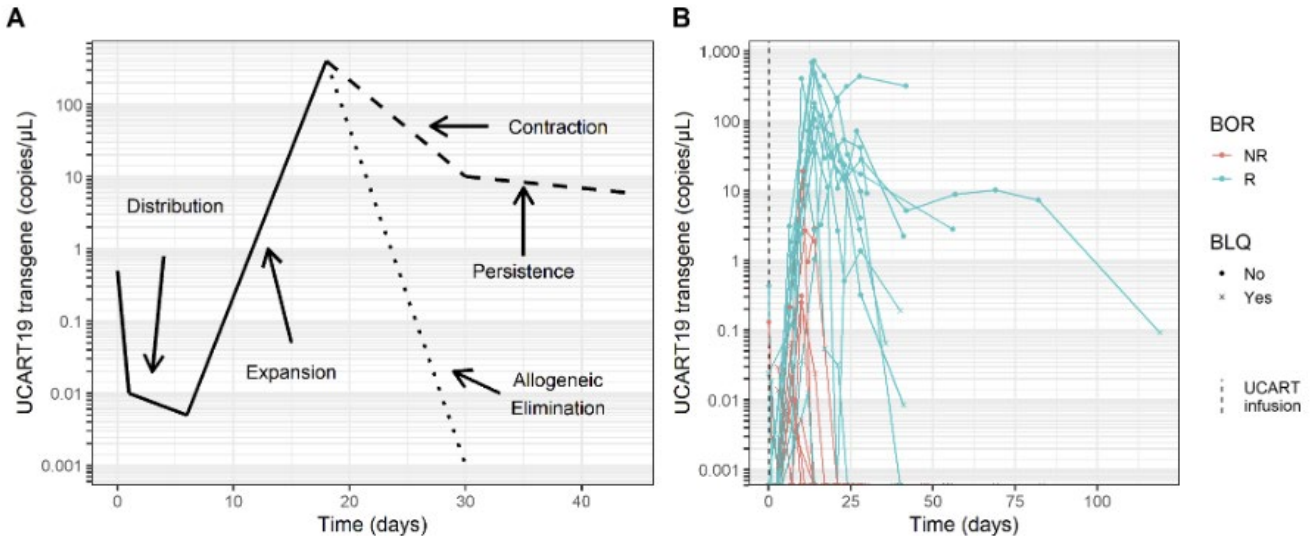
The number of possible experiments to conduct is infinite

3D. Host vs. Graft response (allogeneic elimination)

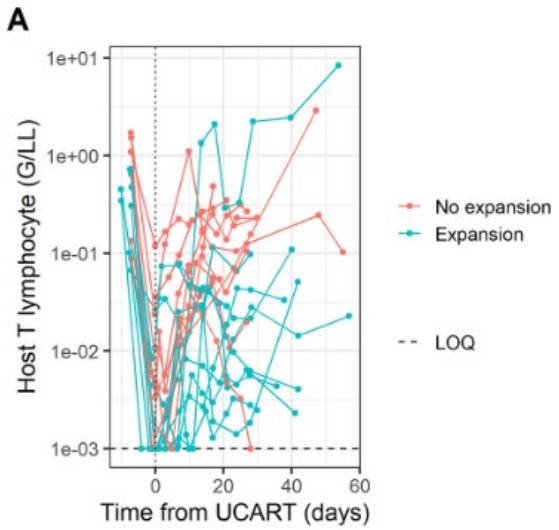
Host T cells actively clear (allogenic) T cell grafts

UCART19 in B-ALL: The first reported allogeneic CAR-T clinical data
CD19-CART, allogeneic (healthy donor-derived) T cells, *TRAC*$^{-/-}$

Cmax predicts response

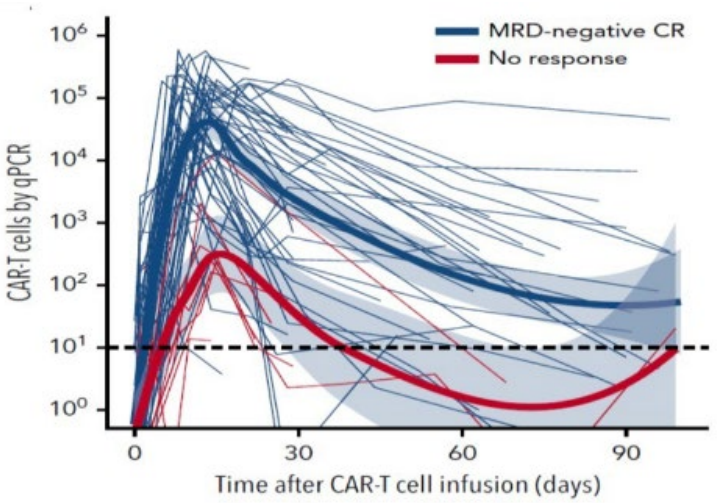


Host T cell reconstitution limits CAR-T expansion



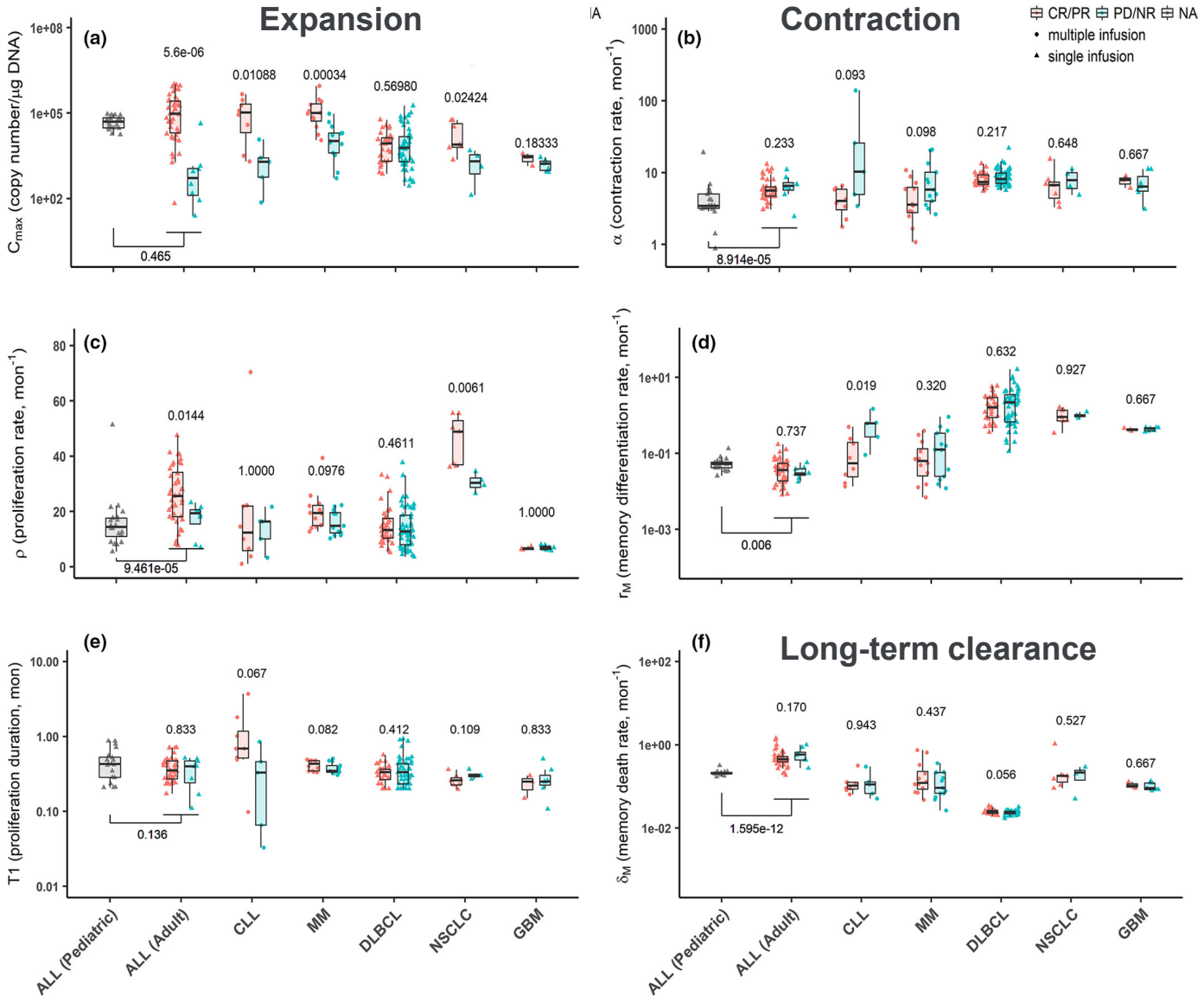
Dupouy S, Marchiq I, Derippe T, et al (2022) Clinical Pharmacology and Determinants of Response to UCART19, an Allogeneic Anti-CD19 CAR-T Cell Product, in Adult B-cell Acute Lymphoblastic Leukemia. Cancer Res Commun 2:1520–1531.

Initial expansion (Cmax) predicts response for multiple CAR-Ts
Clearance does not (for autologous products)



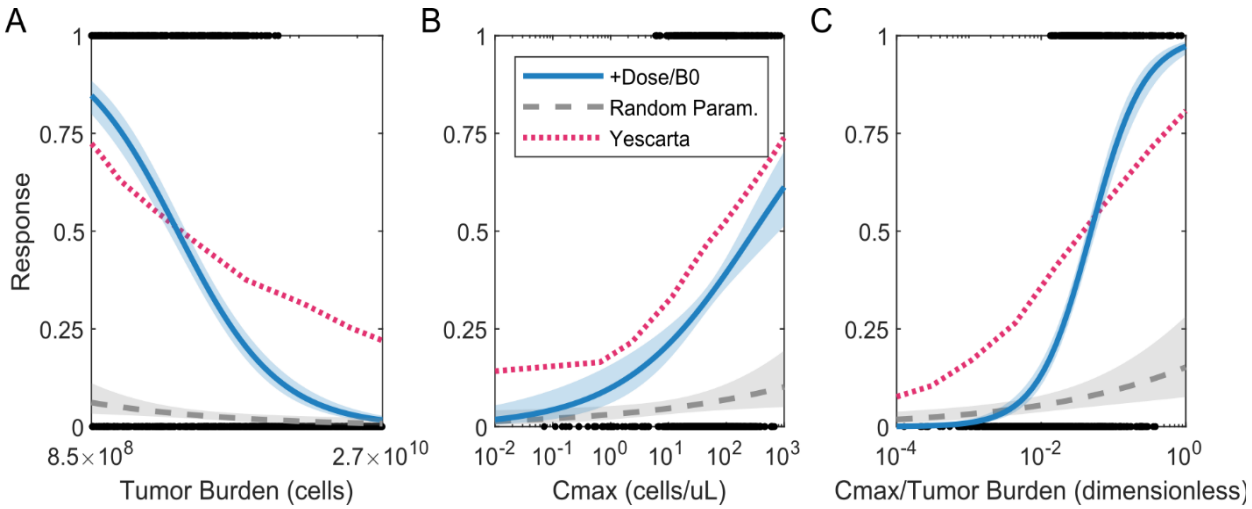
Liu C, Ayyar VS, Zheng X, et al (2020) Model-based Cellular Kinetic Analysis of Chimeric Antigen Receptor-T Cells in Humans. Clin Pharmacol Ther.

Cell Kinetic model to data from 7 CART trials (Jansen)



Model-based insights into clinical response:
cell dose & tumor burden

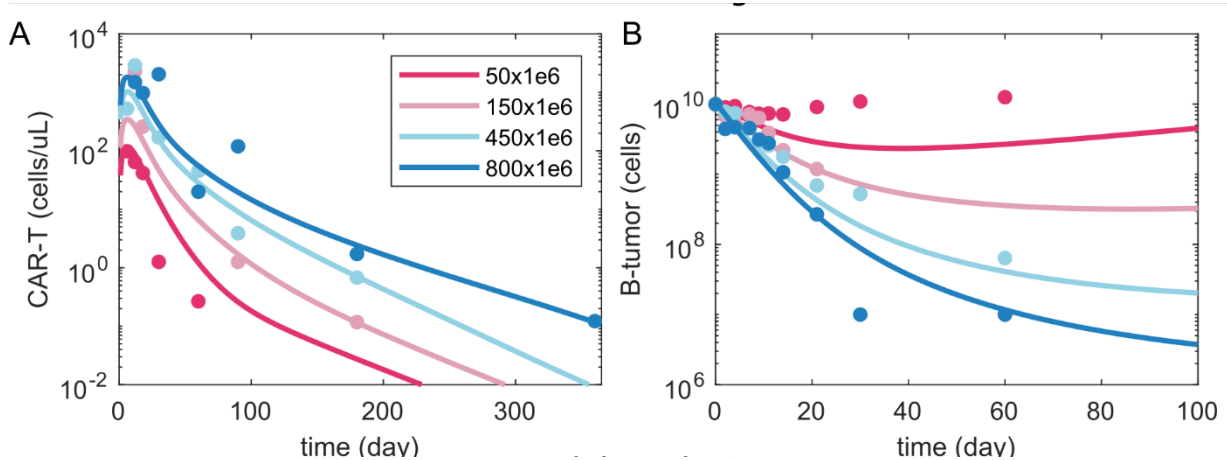
Predicted covariates of response: Cmax vs. Tumor Burden
Virtual Populations vs. Yescarta in LCBCL (ZUMA-1)



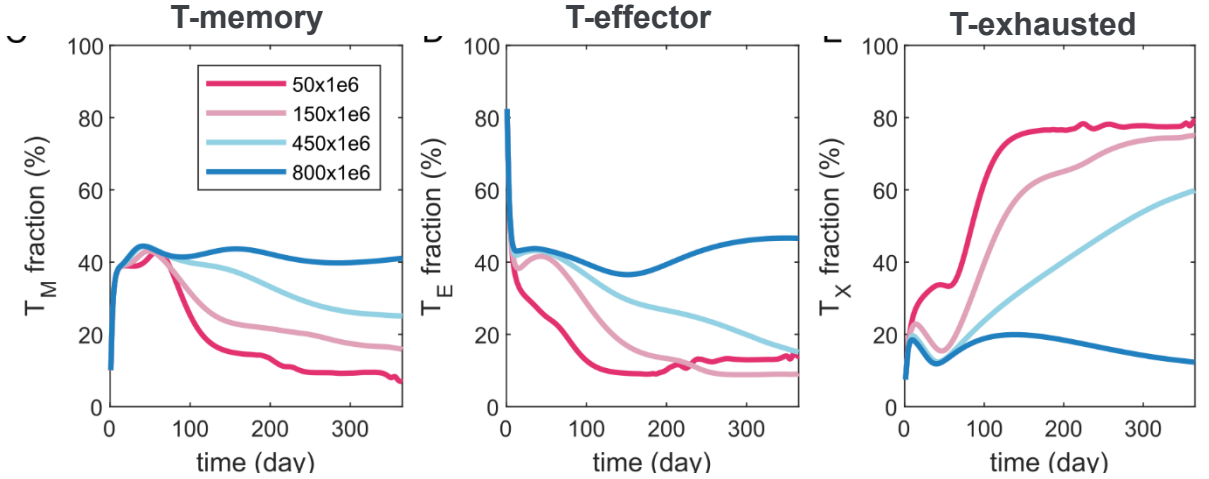
Data source: Locke FL, Rossi JM, Neelapu SS, et al (2020) Tumor burden, inflammation, and product attributes determine outcomes of axicabtagene ciloleucel in large B-cell lymphoma. Blood Adv 4:4898–4911.

Mechanism-based models can *predict* biological processes underlying clinical observations

Model training: Ph1 Abecma dose escalation (BCMA, Multiple Myeloma)



Predicted sub-population dynamics: Ph1 dose escalation



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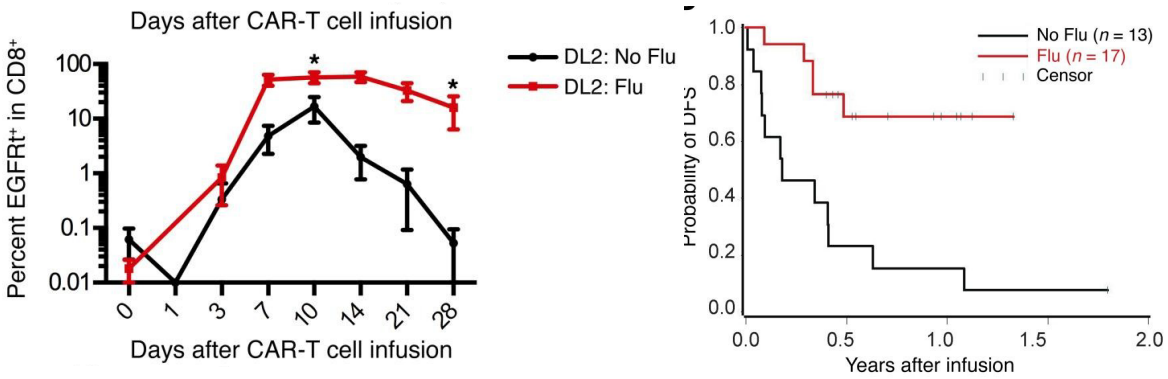
Lympho-depletion intensity & response
via IL7 availability?

Cycolophosphamide (Cy) vs. Cy + Fludarabine (Flu):
CD19-CART therapy in B-ALL

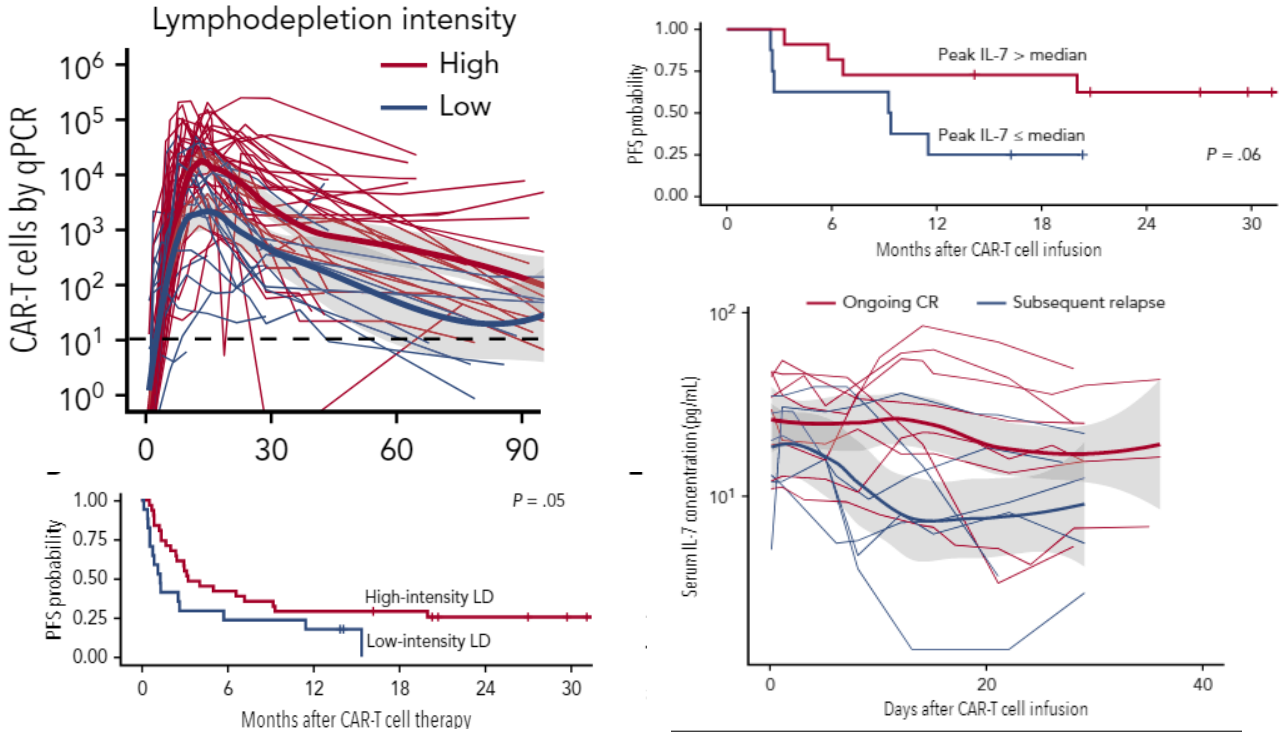


Turtle CJ, Hanafi L-A, Berger C, et al (2016) CD19 CAR–T cells of defined CD4+:CD8+ composition in adult B cell ALL patients. J Clin Invest 126:2123–2138.

Q: How does Lympho-depletion intensity affect CAR-T expansion and peak IL7 concentration?

Q: Can we *mimic* intense-LDT via cytokine support?

High vs. Low-intensity Cy+Flu:
CD19-CART therapy in NHL



*60 vs. 30 mg/kg cyclophosphamide

Hirayama AV, Gauthier J, Hay KA, et al (2019) The response to lymphodepletion impacts PFS in patients with aggressive non-Hodgkin lymphoma treated with CD19 CAR T cells. Blood 133:1876–1887.

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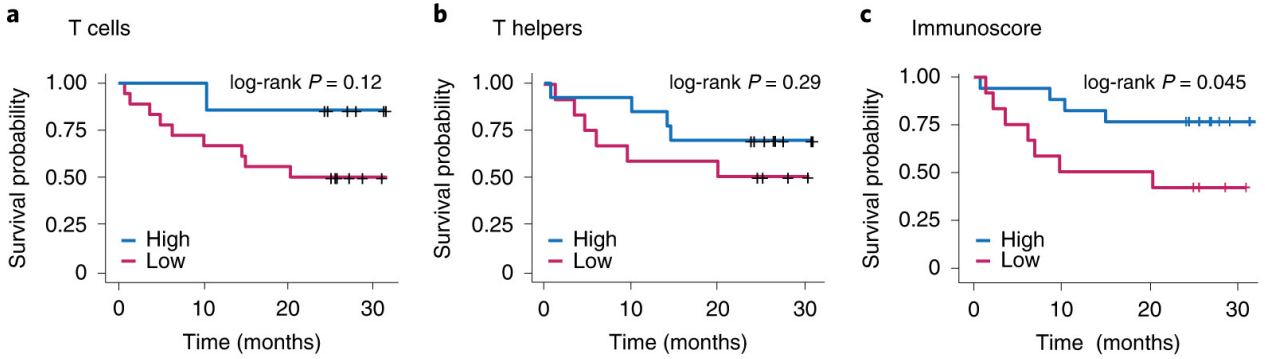
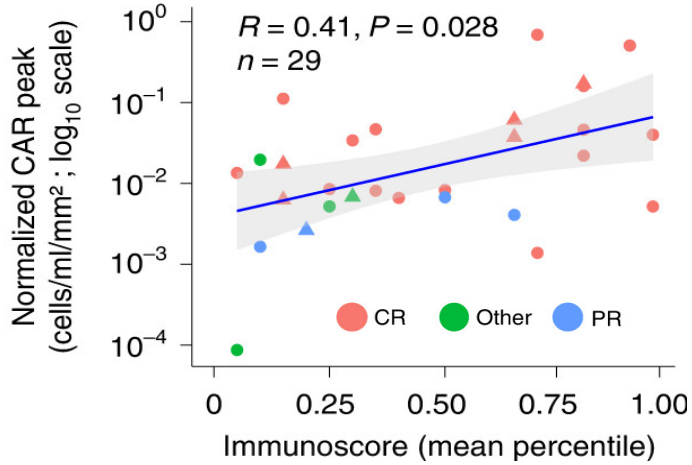
3B. Tumor inflammation and CAR-T response

Yescarta in DLBCL: ZUMA-1

T cell inflamed tumors ~ improved survival

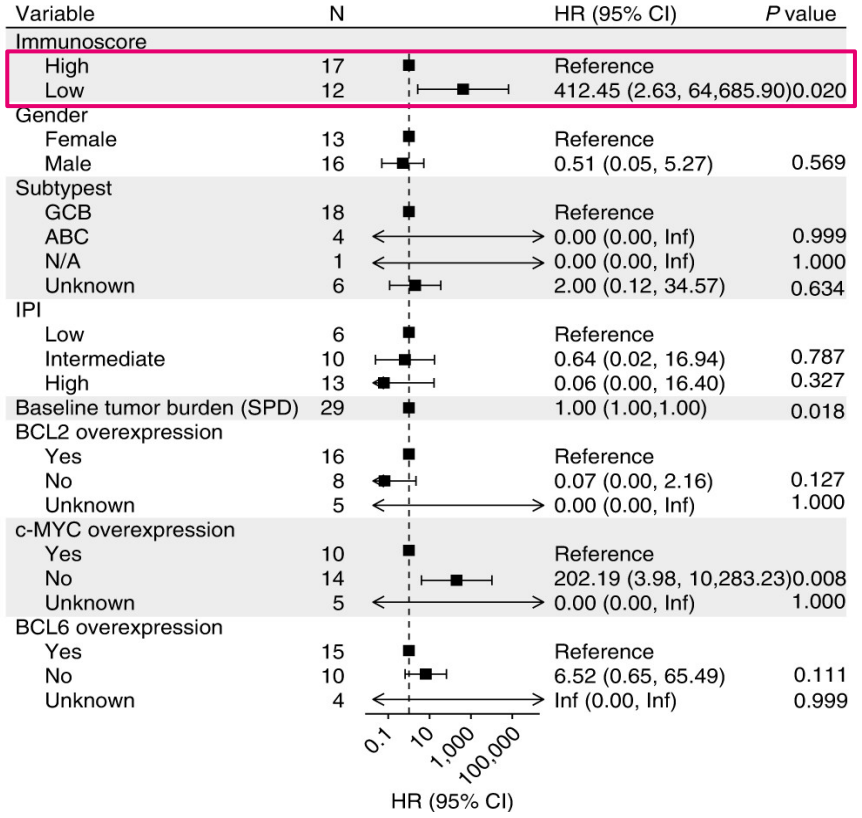


Tumor inflammation ~ Cmax (CART expansion)



Immunoscore is the most significant "co-variate"

Cox-regression (statistical) model



Variable	N	HR (95% CI)	P value
Immunoscore			
High	17	Reference	
Low	12	412.45 (2.63, 64,685.90)	0.020
Gender			
Female	13	Reference	
Male	16	0.51 (0.05, 5.27)	0.569
Subtypest			
GCB	18	Reference	
ABC	4	0.00 (0.00, Inf)	0.999
N/A	1	0.00 (0.00, Inf)	1.000
Unknown	6	2.00 (0.12, 34.57)	0.634
IPI			
Low	6	Reference	
Intermediate	10	0.64 (0.02, 16.94)	0.787
High	13	0.06 (0.00, 16.40)	0.327
Baseline tumor burden (SPD)	29	1.00 (1.00,1.00)	0.018
BCL2 overexpression			
Yes	16	Reference	
No	8	0.07 (0.00, 2.16)	0.127
Unknown	5	0.00 (0.00, Inf)	1.000
c-MYC overexpression			
Yes	10	Reference	
No	14	202.19 (3.98, 10,283.23)	0.008
Unknown	5	0.00 (0.00, Inf)	1.000
BCL6 overexpression			
Yes	15	Reference	
No	10	6.52 (0.65, 65.49)	0.111
Unknown	4	Inf (0.00, Inf)	0.999

Q: How would pre-existing TILs influence CAR-T expansion?

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Scholler N, Perbost R, Locke FL, et al (2022) Tumor immune contexture is a determinant of anti-CD19 CAR T cell efficacy in large B cell lymphoma. Nat Med 1–11.