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Boston Society for Cell & Gene Therapy

Making Drugs from T Cells: Model-Informed Design and Deployment of T Cell Therapies

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Mar 20, 2025

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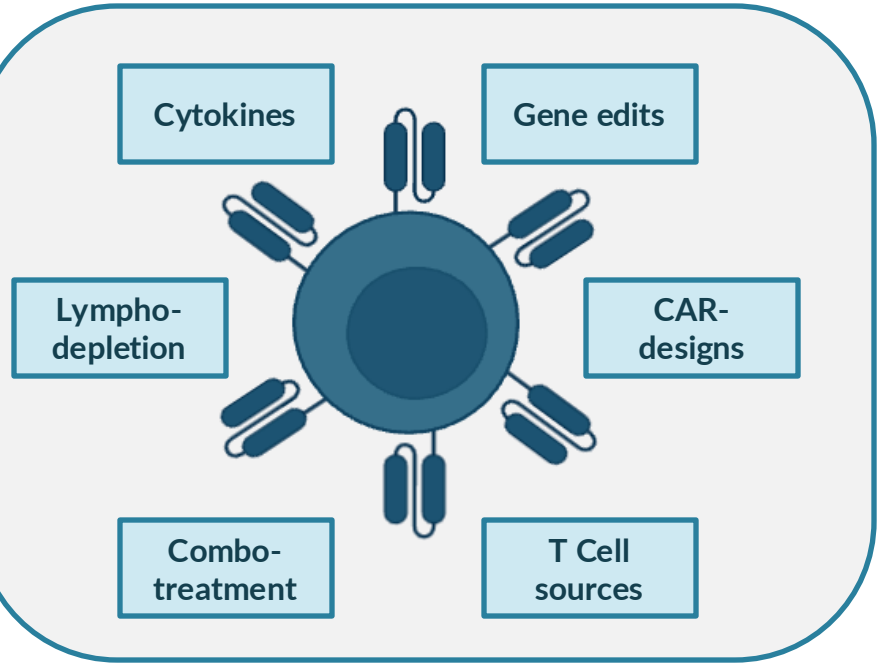
What is the value of mathematical modeling?

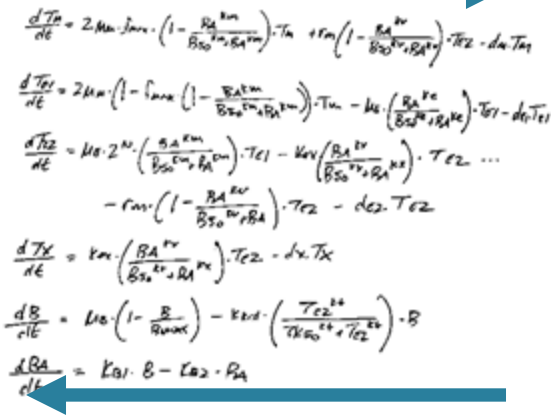
In the context of cell therapy engineering and clinical development

The number of possible experiments to conduct is infinite

Cell therapy engineering

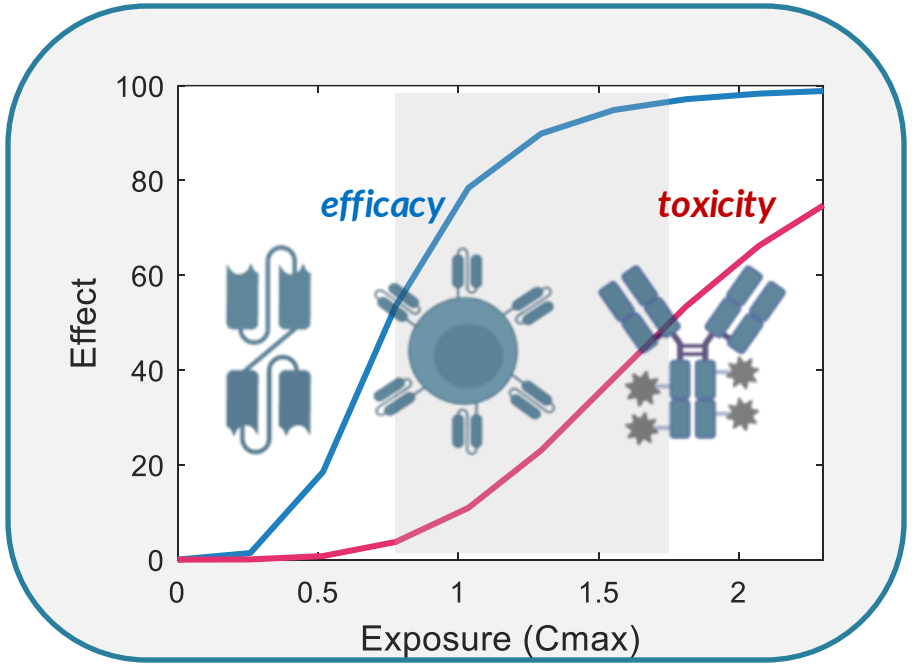


Prediction



Inference

Clinical strategy



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

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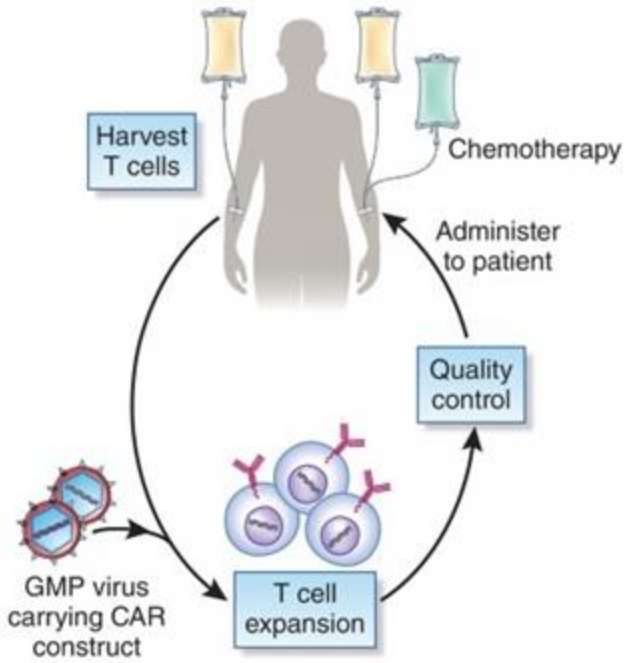
Pharmacology of Autologous T cell therapies is highly variable

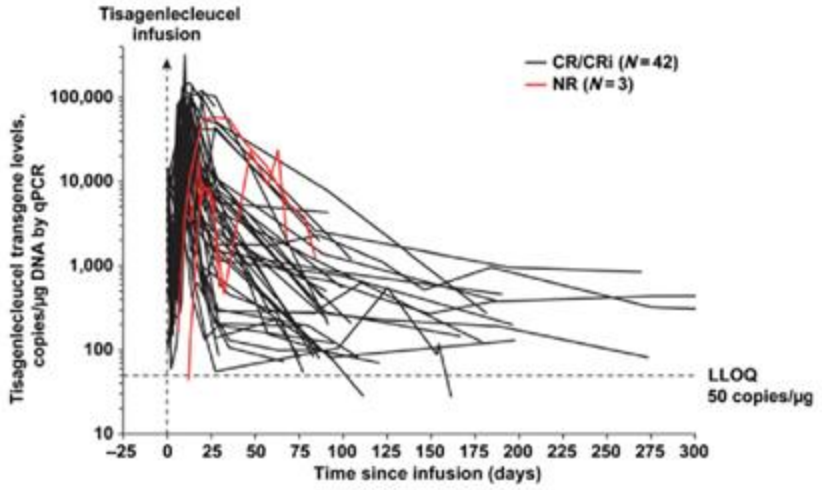
…This is problematic for drug development

Bespoke manufacturing



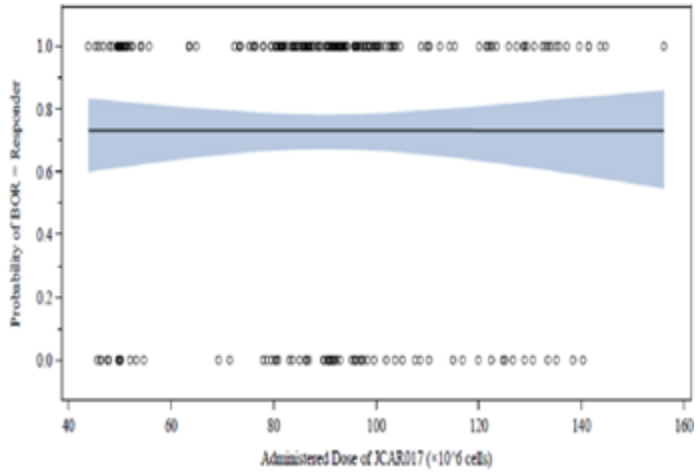
Olewus (2017) Nat Biotech **35.** 520-521

Variable pharmacokinetics



Kymriah (Tisagenlecleucel) in B-ALL
PMID: 30190371

Little dose-response



Breyanzi (JCAR017) in NHL.
BLA: Clinical Pharmacology Review

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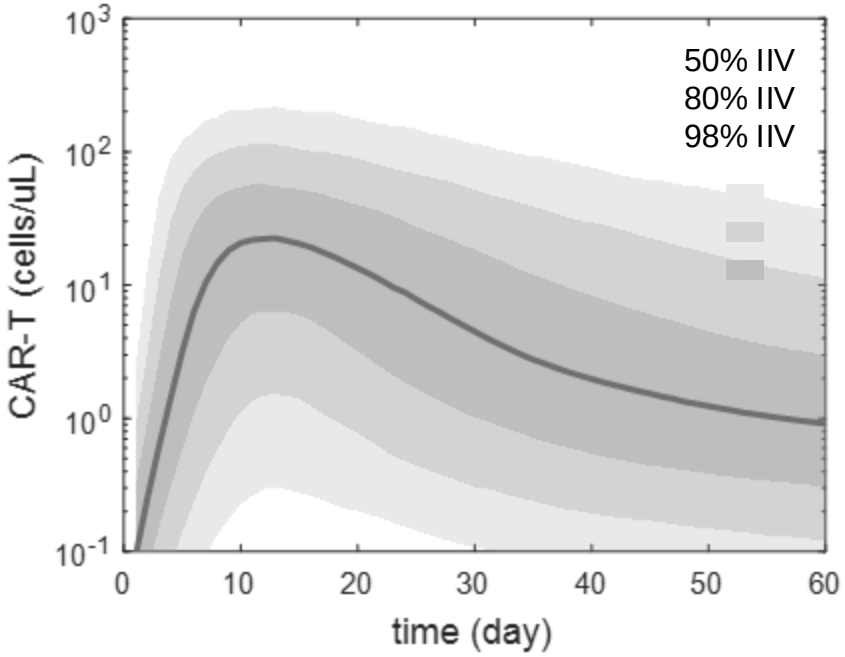
Pharmacology of Autologous T cell therapies is highly variable

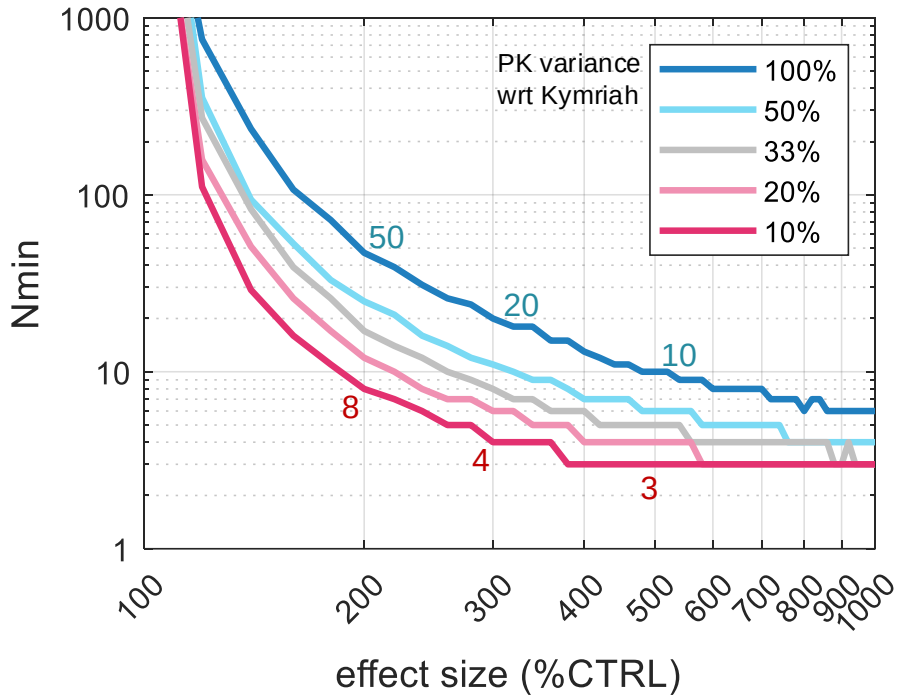
…This is problematic for drug development. E.g. Multi-arm (umbrella) trials

Kymriah popPK simulations



Population PK model of Kymriah
Stein et al (2019); PMID: 30848084

Minimum N vs. Effect-size & variance



Studying Multiple Versions of a Cellular or Gene Therapy Product in an Early-Phase Clinical Trial

Guidance for Industry **FDA, 2022**

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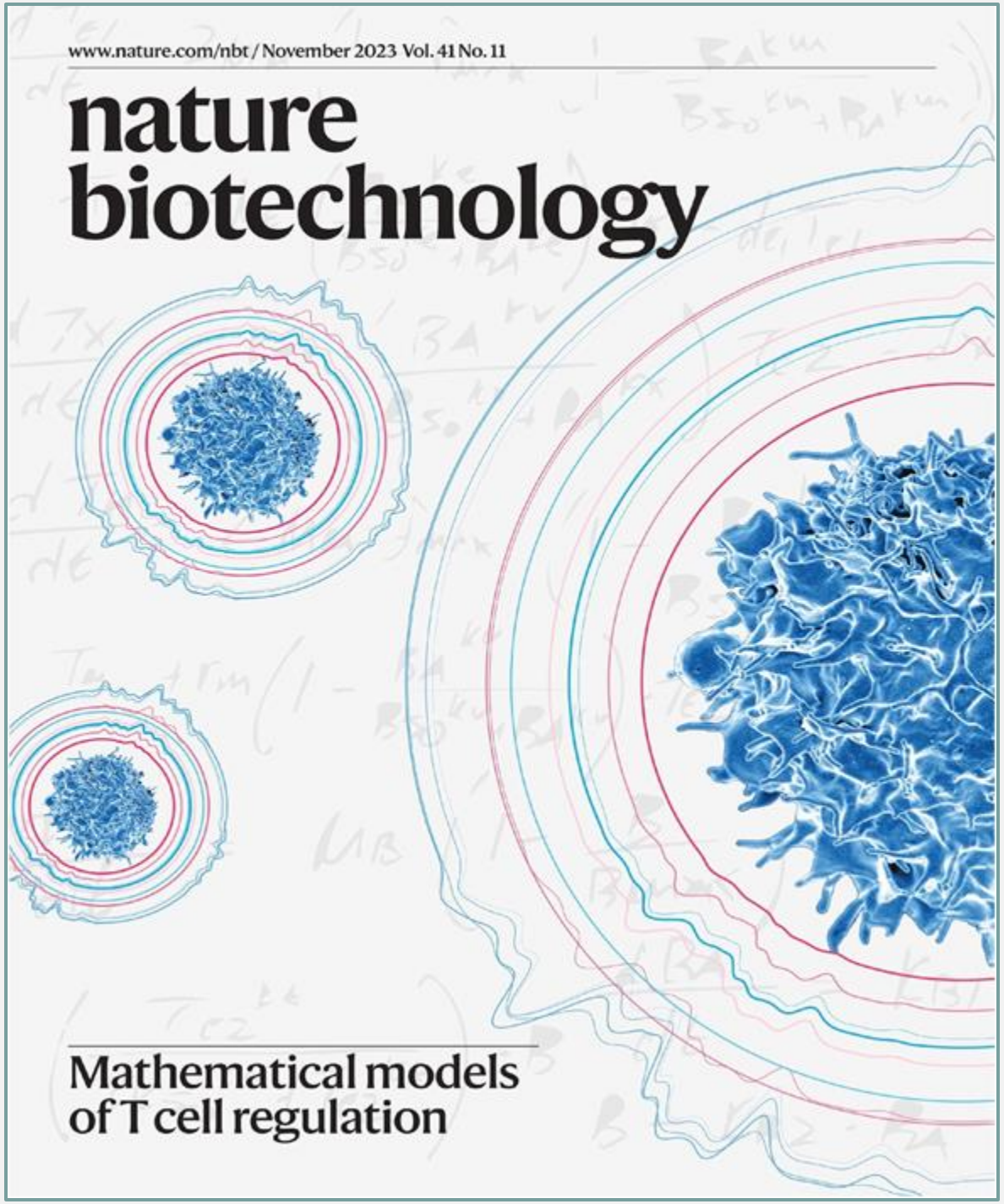


CAR-T Pharmacology

Model based inference: How do dynamic interactions between CAR-Ts, tumor and patient lymphocytes drive exposure, response, and patient variability?

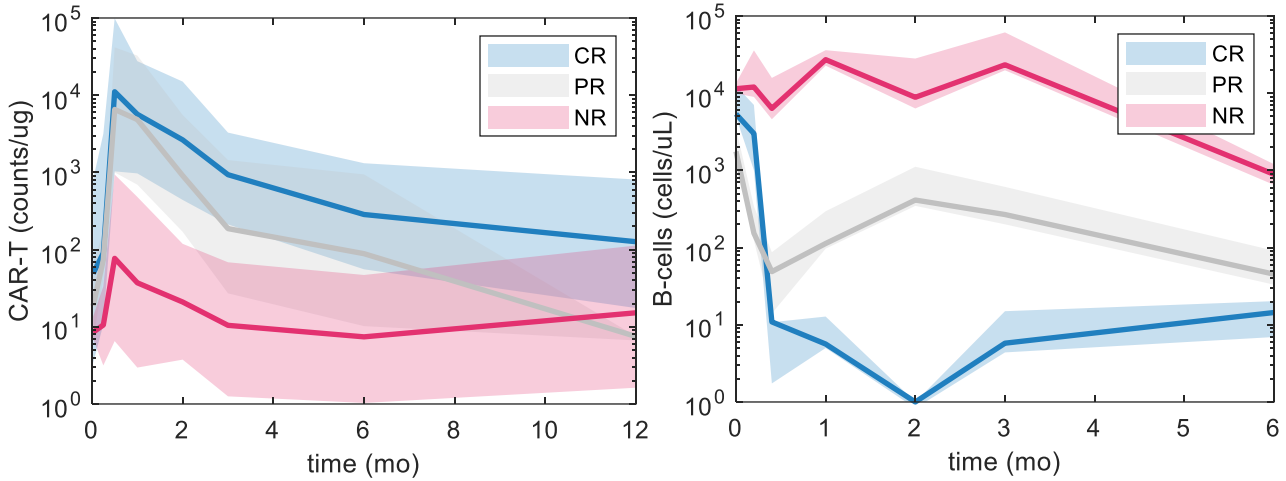
Kirouac, Zmurchok et al. (2023). Deconvolution of clinical variance in CAR-T pharmacology and response. *Nature Biotechnology* **41**:1606–1617.

Kirouac, Zmurchok & Morris (2024). Making drugs from T cells. *npg Systems Biology & Applications* **10**: 31.

Model Training Data

PKPD profiles, CAR-T product transcriptomes and immuno-phenotypes vs. response

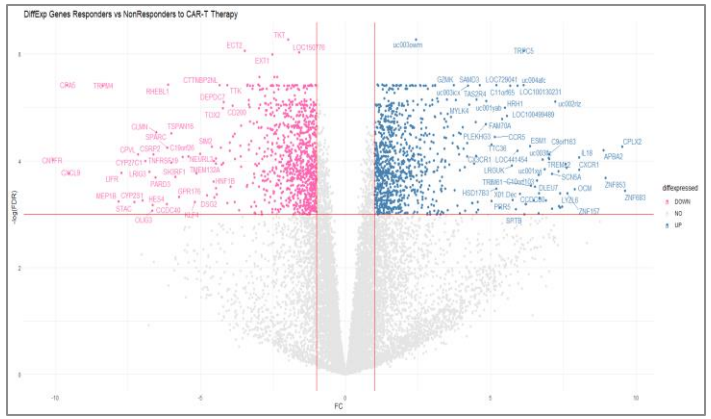
Population mean PKPD: *Kymriah* in Chronic Lymphoblastic Leukemia (CLL)



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

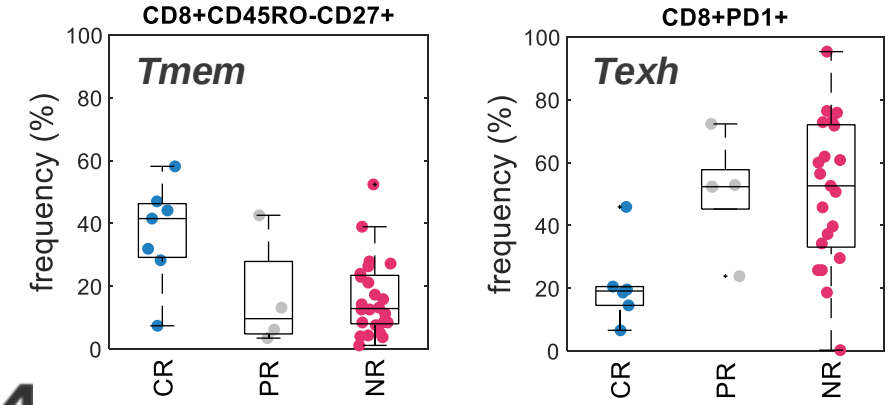
CR = Complete Response
PR = Partial Response
NR = Non-Response

Pre-infusion CAR-T transcriptomes



CR=5, PR =5, NR=21

Pre-infusion CAR-T immunophenotypes



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

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.

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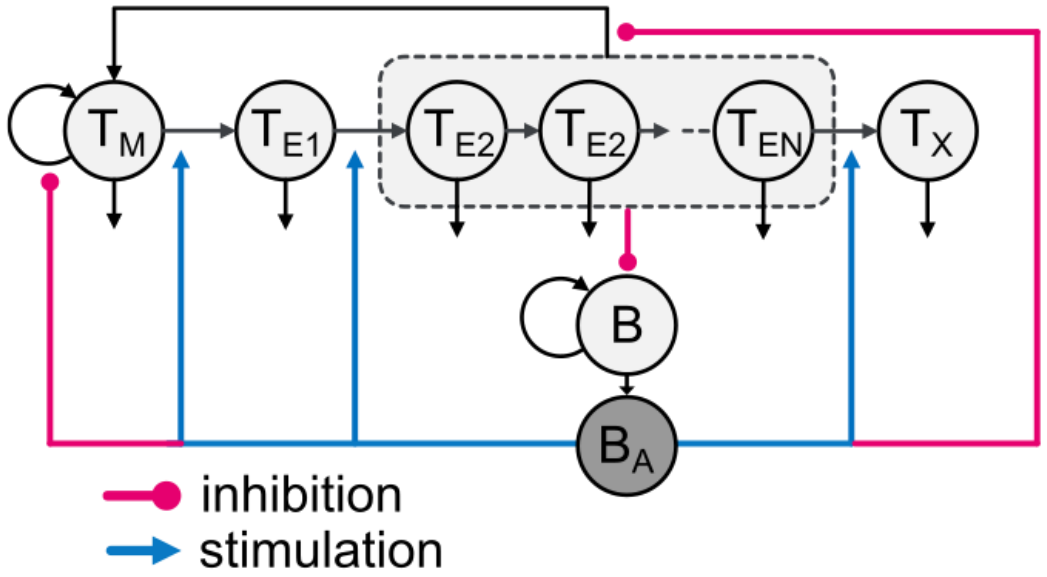
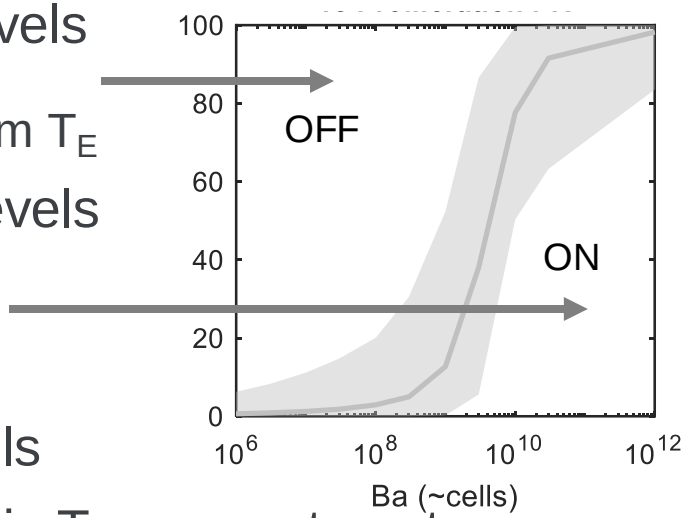
‘Toggle switch’ model structure and assumptions



- 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



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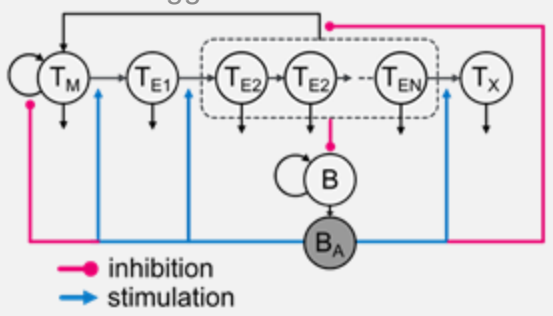
Model development and validation workflow

Conceptual model of T cell biology

Toggle switch circuit



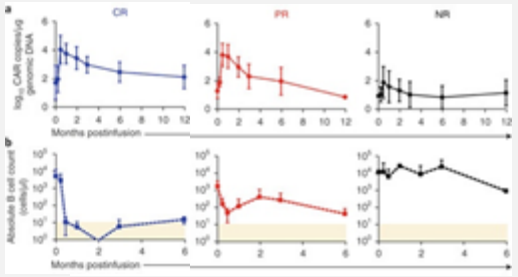
Mechanism-based dynamical model

Math

Executable code

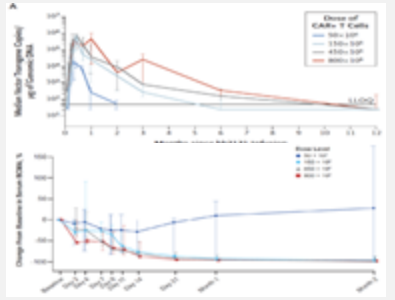
Clinical Training Data

Kymriah in CLL:
PKPD separated by response



What determines CR/PR/NR?

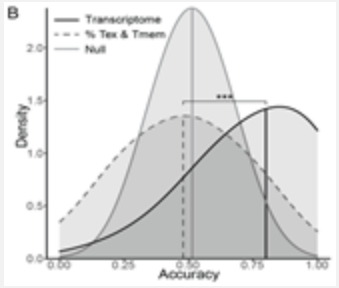
Abecma in MM:
Phase1 escalation



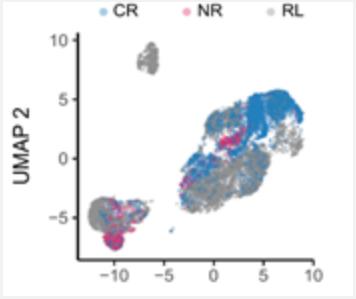
What makes an effective dose?

Genomic "Validation" Data

ssRNAseq:
CR vs NR classifier



ssRNAseq:
CR vs. NR in ALL

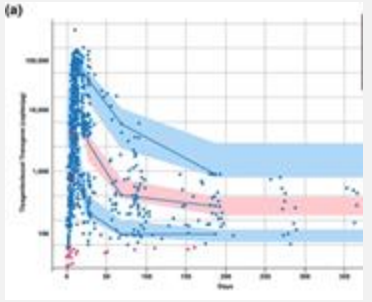


Bulk RNAseq:
CR vs. NR in CLL

How do model parameters map to cell populations and pathways?

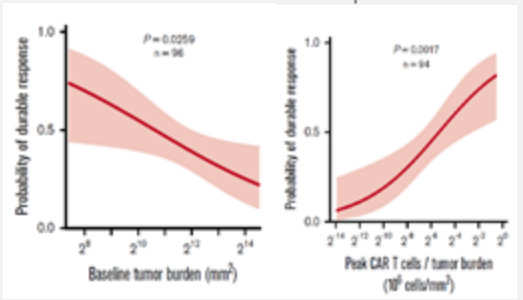
Clinical Validation Data

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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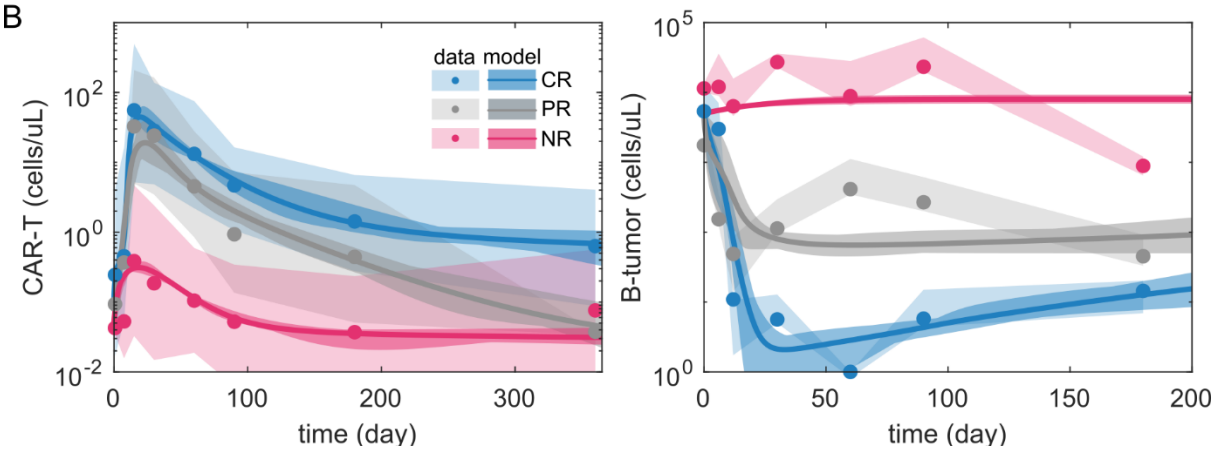
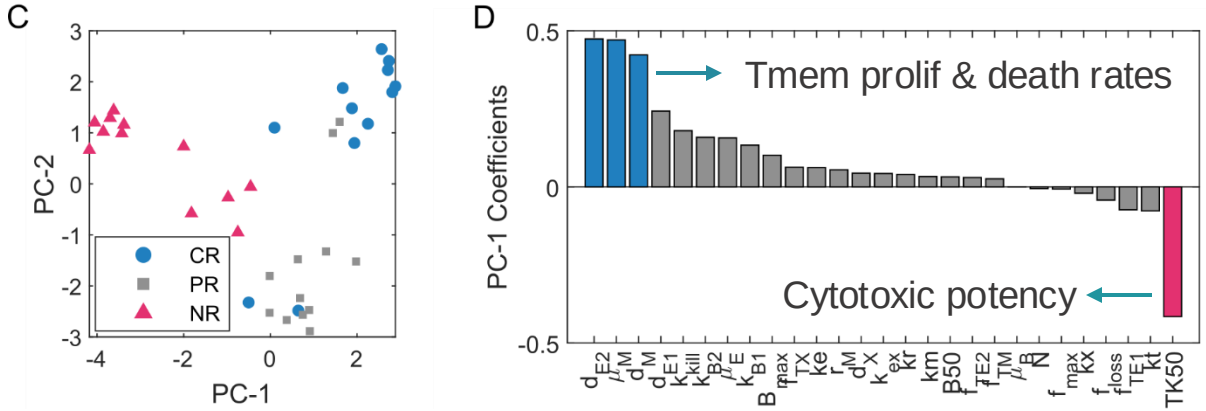
What features (parameters) separate clinical outcomes?

Model calibration



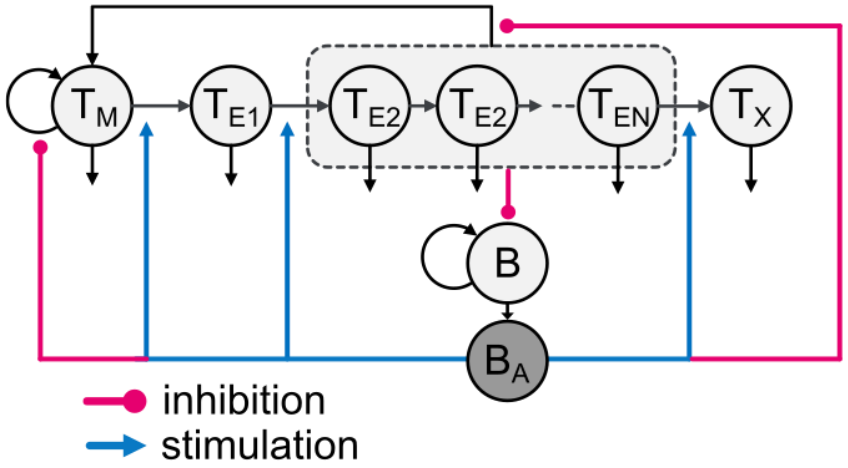
Parameter Analysis



What differentiates responders (CR) vs. non-responders (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



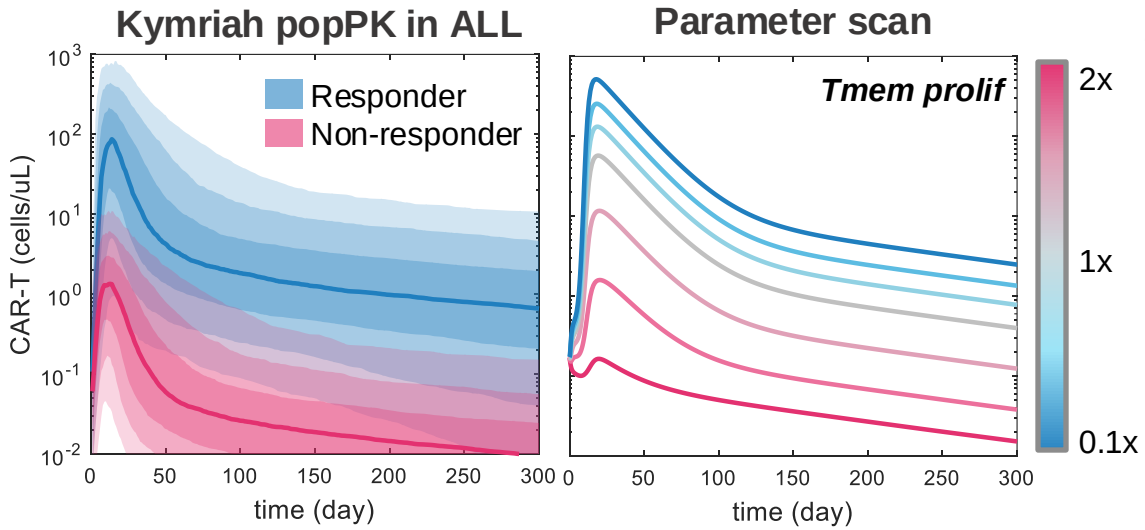
*Assume Dose = 10^8 cells, Tumor burden = 10^{10} cells (median reported); Estimate parameters using PSO: simulations represent 90% confidence intervals

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).

Validation of model inferences via Clinical PKPD Data

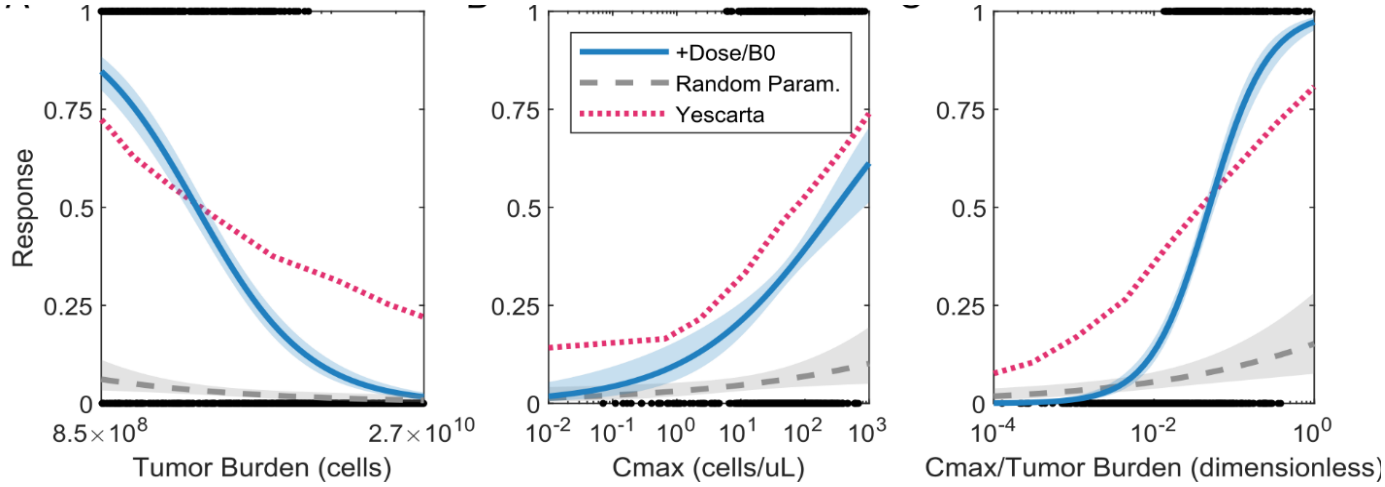
Prediction: Tmem from CR-CART products have heightened intrinsic proliferative capacity

Tmem* proliferation is explanatory of PK/response: R vs. NR, Kymriah in ALL



*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. 109(3):716-727

Predicted covariates of response (Cmax & tumor burden): *Virtual Population* vs. Yescarta in LCBCL (ZUMA-1)*



*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.

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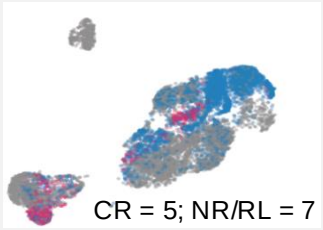
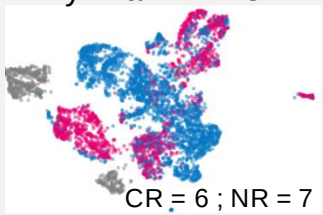
Can we predict response based on pre-infusion transcriptomes?

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

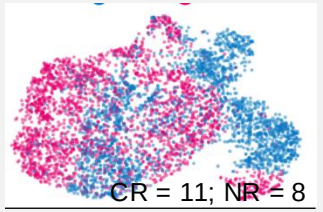
Kymriah in ALL



Kymriah in LBCL



Yescarta in LBCL



CR PR NR

Machine learning workflow

"Feature Engineering"

Feature Compression

ssGSEA: Pathway databases

Feature selection 1

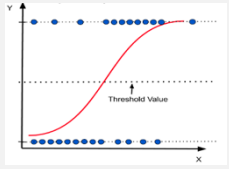
20K genes → **7500 signatures** →

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

Feature selection 2

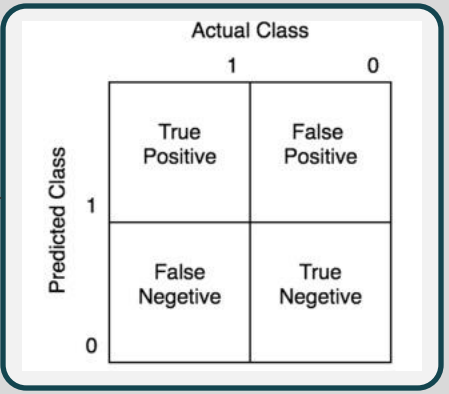
Genetic Algorithm (GA)

Classifier model training



28 Δpathways → **2-7 pathways** →

CR vs. NR calssification



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

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

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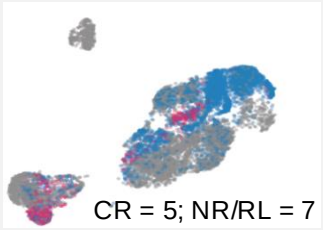
Can we predict response based on pre-infusion transcriptomes?

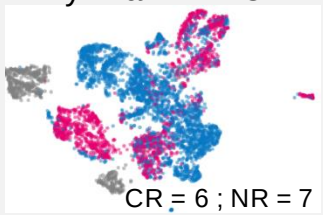
Much better than expected by change, and better than immunophenotyping

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

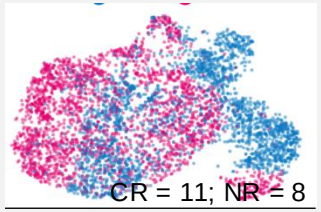
Kymriah in ALL



Kymriah in LBCL



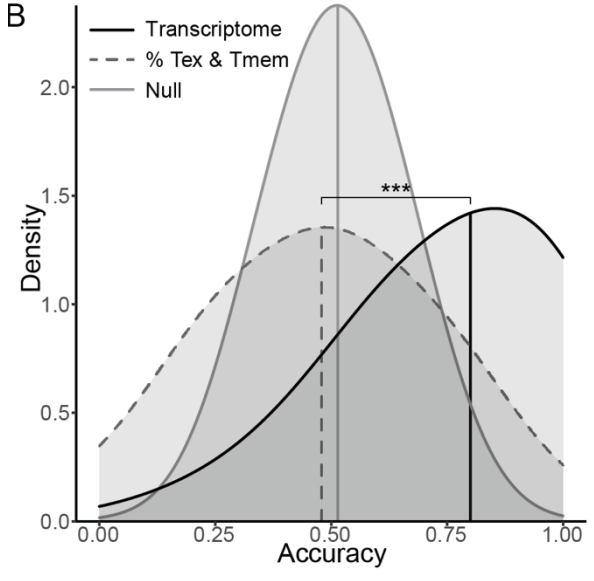
Yescarta in LBCL



CR PR NR

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

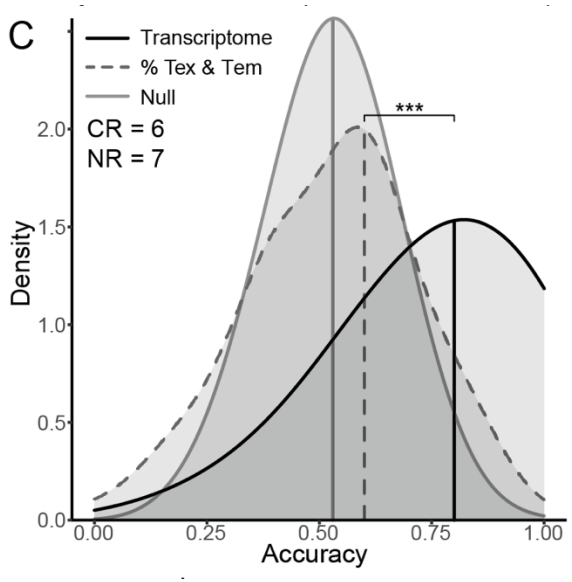
Kymriah in ALL (Bai 2022)



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

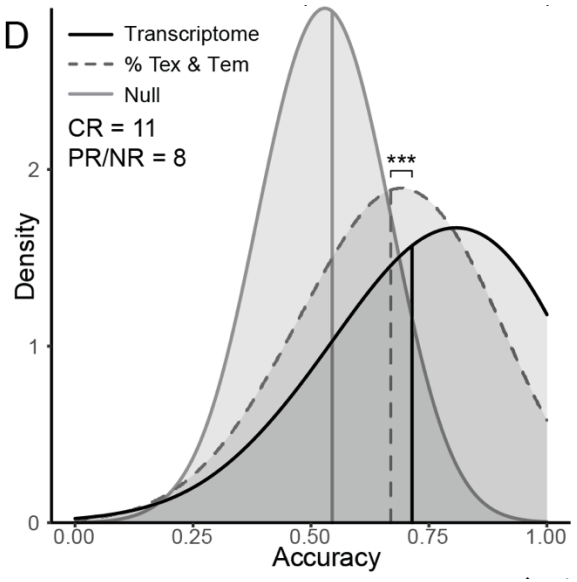
***$P < 10^{-8}$ (rank-sum test)

Kymriah in LBCL (Haradhvala 2022)



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

Yescarta in LBCL (Haradhvala 2022)

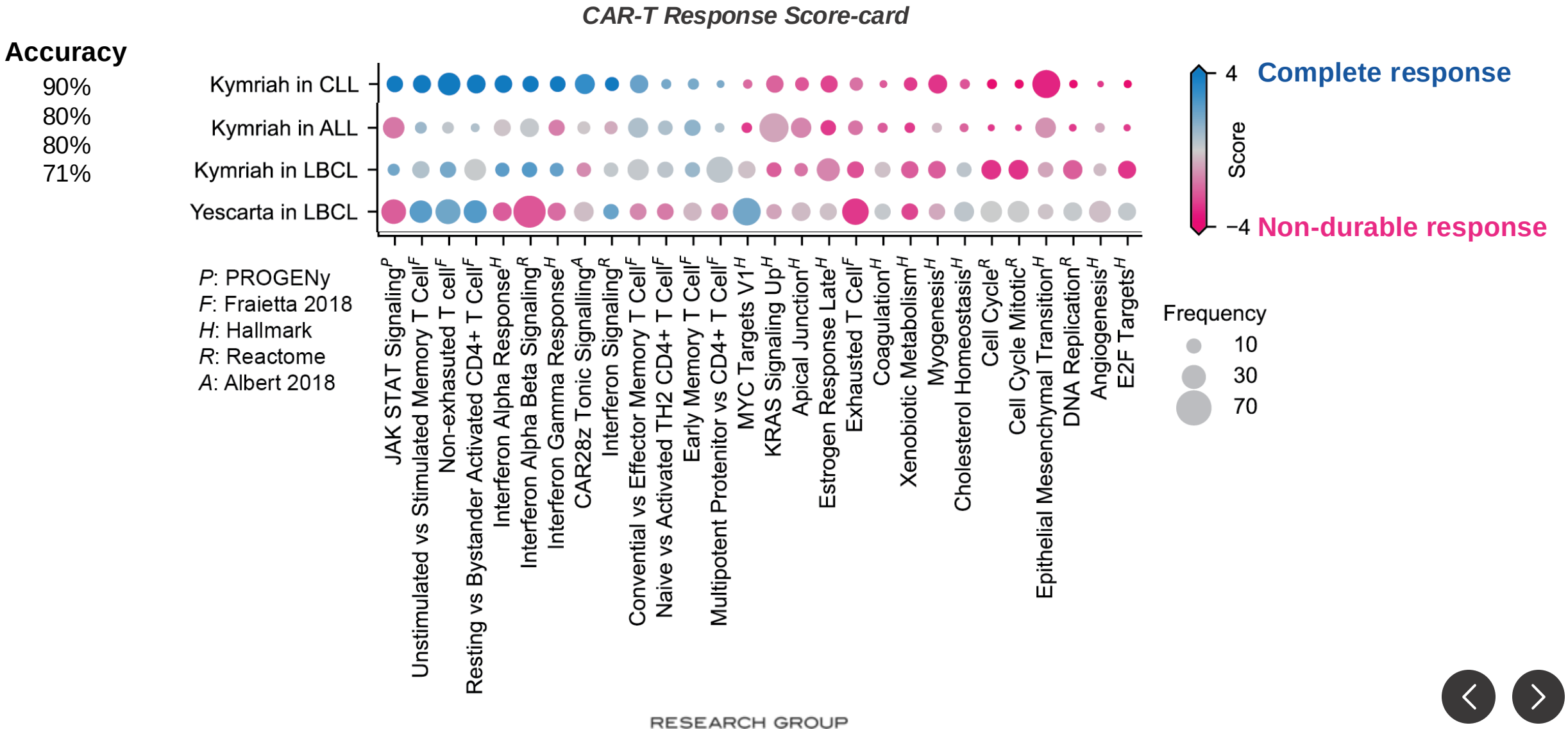


Accuracy = 71%
Tmem, Tex:ProjecTILS
CR = 11; NR/PR = 8

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

What transcriptional features predict response?

Multivariate predictive biomarkers



Method-agnostic modelling

Dynamical systems modelling, bioinformatics and machine learning

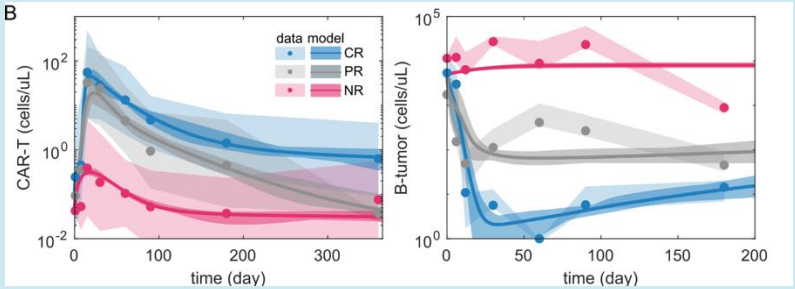
Motivation

If we can identify functional attributes of CAR-Ts which result in robust exposure & clinical response,
Then we can design these attributes into products

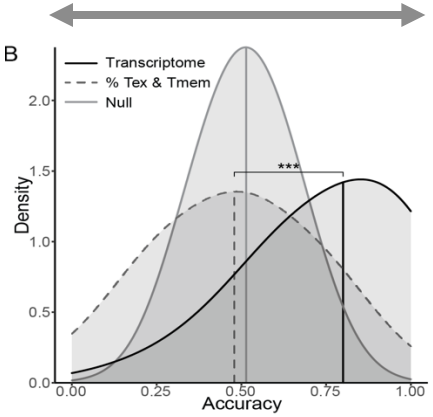
Approach

Dynamical Modelling

Hypothesis-based
Math = Differential equations
Dept: Translational & Clinical Pharmacology

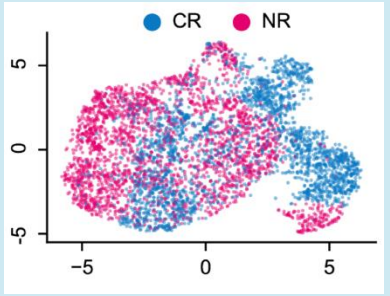


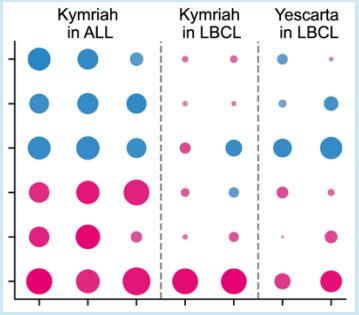
Machine Learning



Bioinformatics

Hypothesis-free
Math = statistics
Dept: Discovery bioinformatics / Clinical biostats





Key finding

Not all memory cells are created equal: Tmem associated with non-durable response display functional defects characteristic of exhaustion – reduced proliferative and functional capacity

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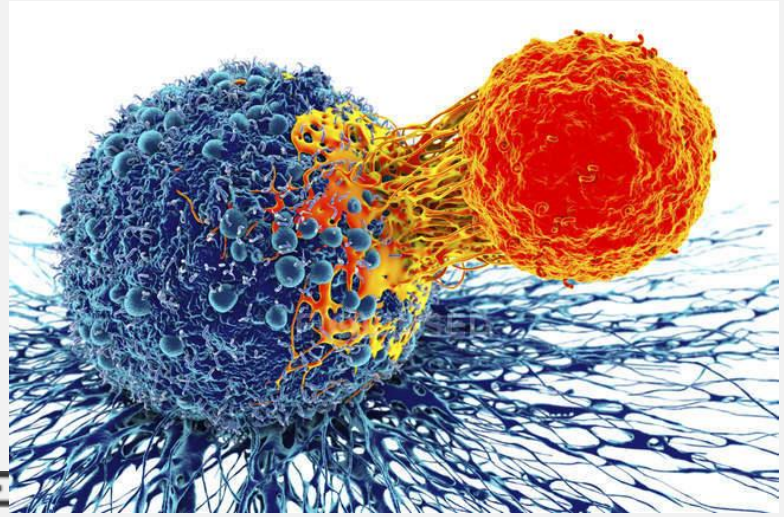
Translational (T cell) pharmacology

Quantifying & predicting T cell potency



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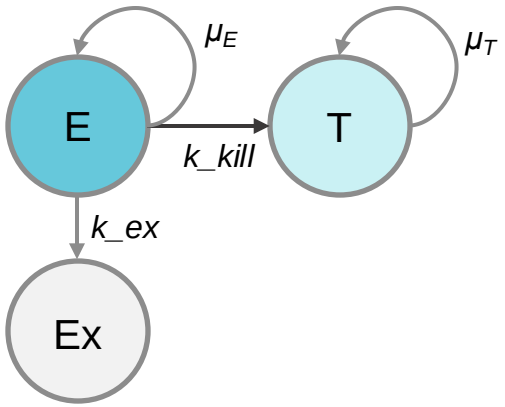
Quantifying T cell potency from co-culture assays

Data quantification & compression

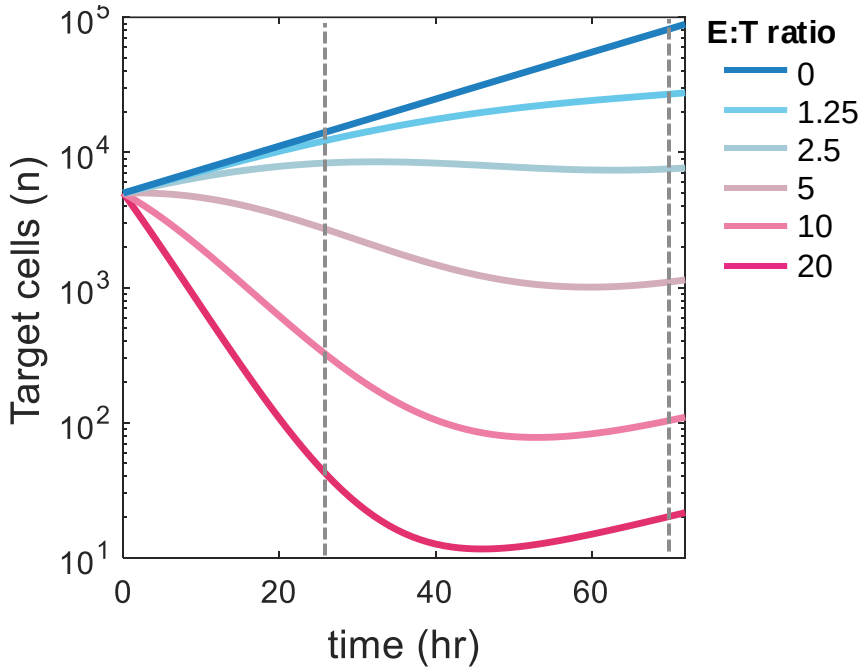
Model structure



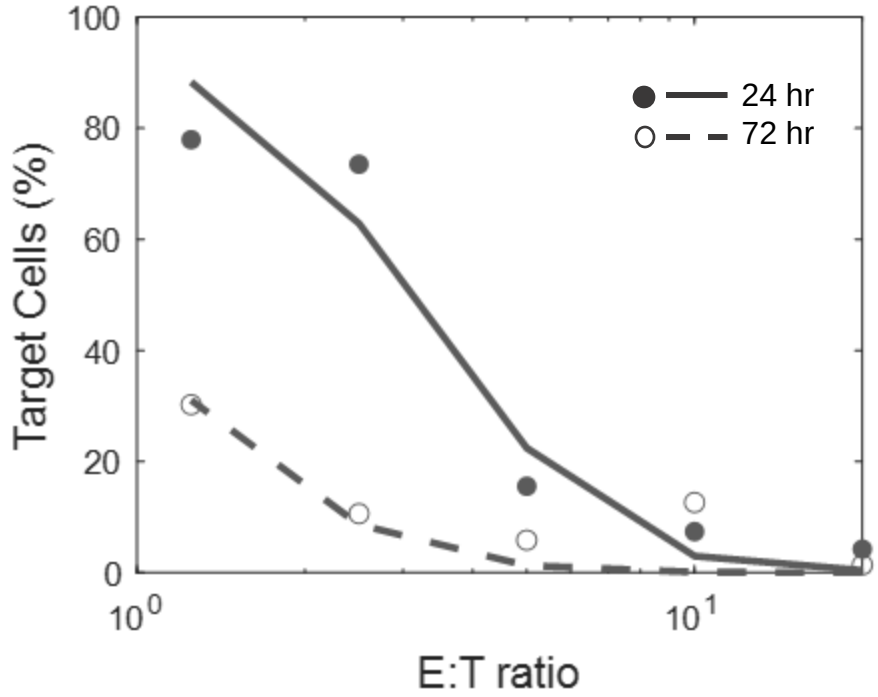
Species	Description
T	Target cells (n)
E	Effector cells (n)
Ex	Exhausted effector cells (n)

Parameter	Description
u_E	effector proliferation rate (hr^{-1})
T50	EC50 limiting cell proliferation (cells)
u_T	target cell proliferation rate (hr^{-1})
k_kill	killing rate (hr^{-1})
E50	EC50 effector cell killing (cells)
Ke	Hill coefficient of cell killing
k_ex	Exhaustion rate (hr^{-1})

Model Simulations: Target (cancer) cell dynamics



Model Fitting: Target (cancer) cell viability



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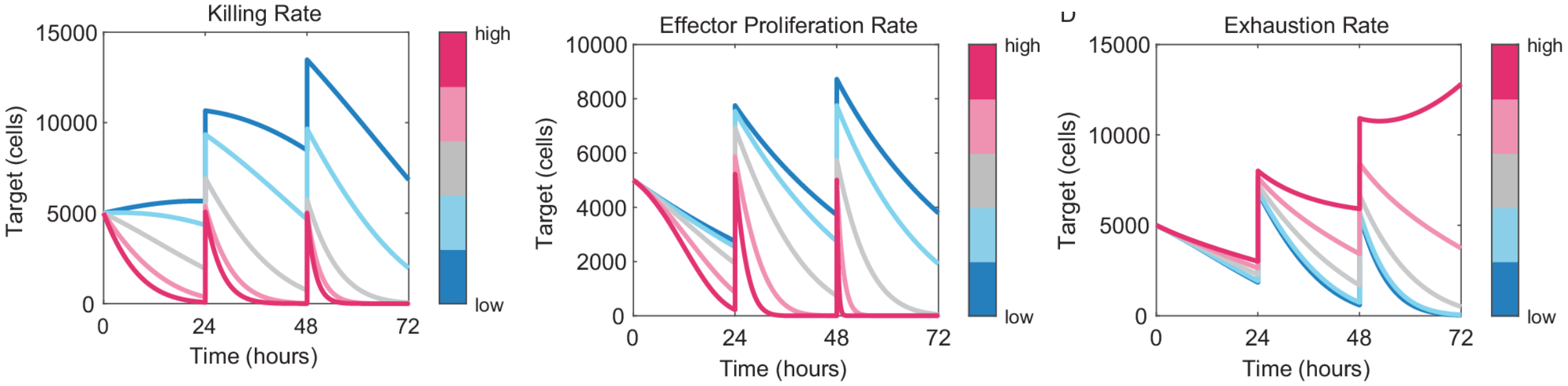
Model-based inference from serial-killing assay data

Cytotioxc potency, Proliferation & exhaustion can be inferred using ‘simple’ models



Utility: We can map the effect of molecular perturbations to functional kinetic parameters

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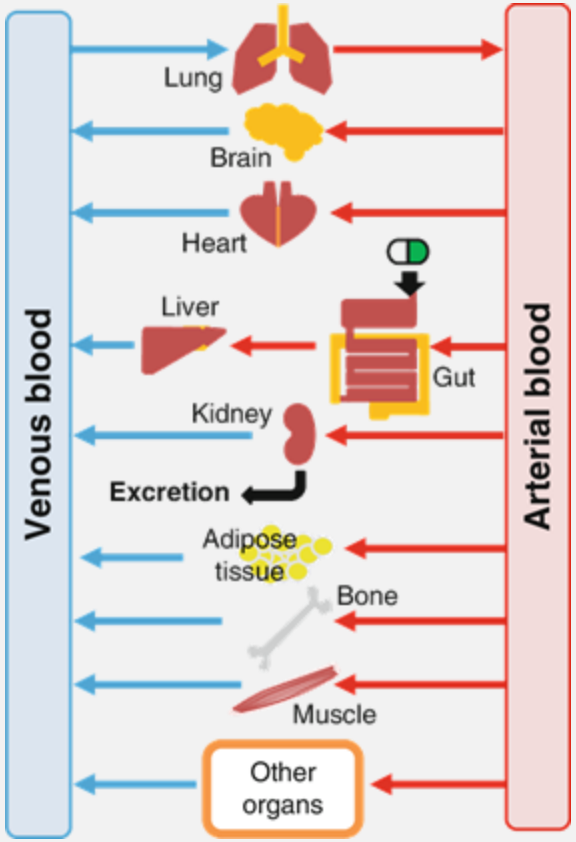

T Cell Biodistribution:

the elephant in the (CART pharmacology) room

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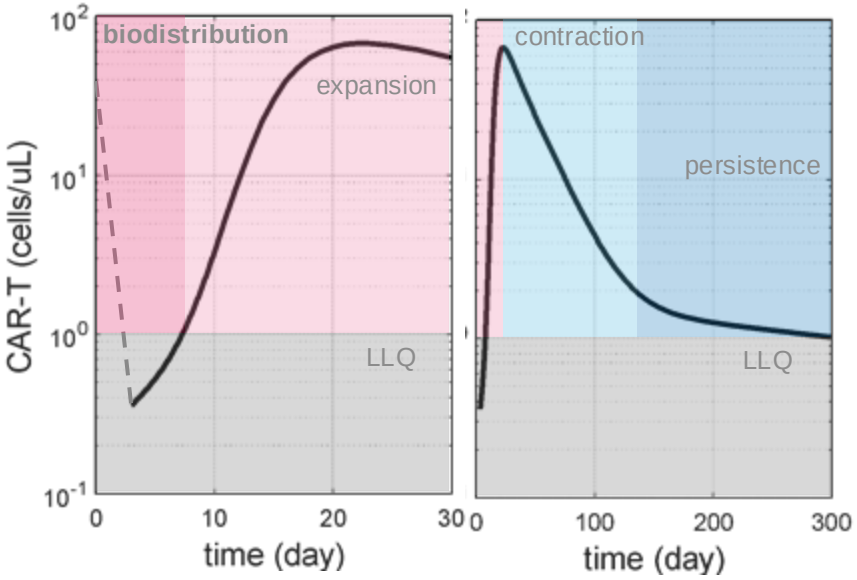
We can *model* tissue distribution

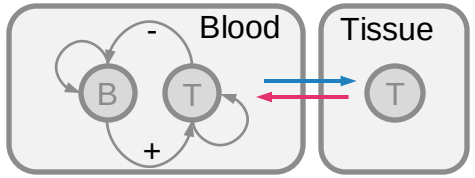
...but we don't have the data to constrain the models or make predictions

CAR-T pharmacokinetics: 4 phases

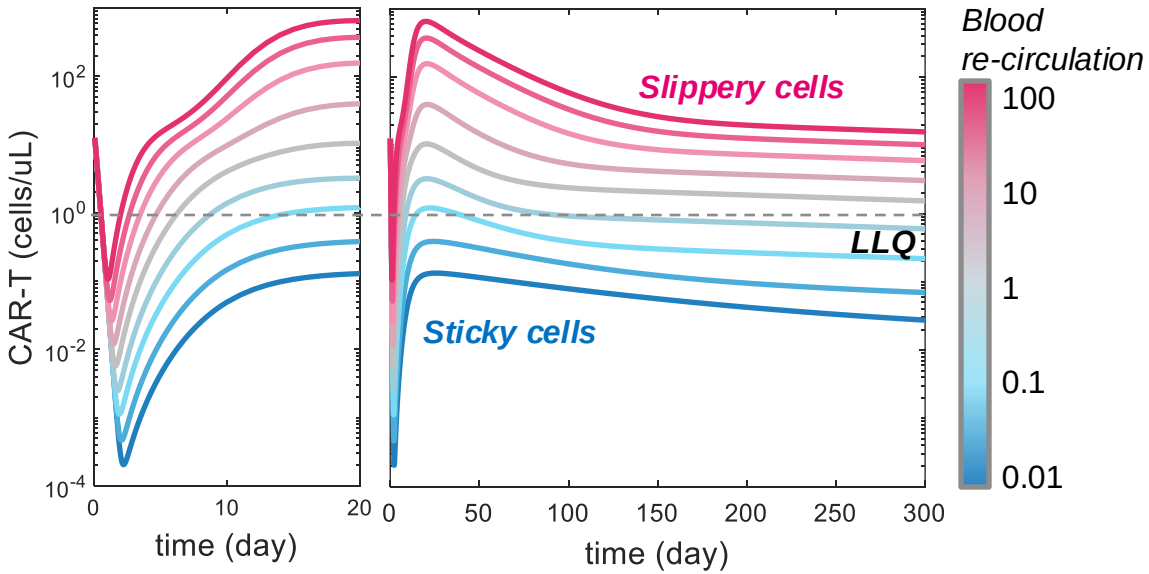


**biodistribution* phase is poorly characterized

Tissue distribution can dominate T cell pharmacokinetics



Blood re-circulation rate:
K_blood / K_tissue



PKPD model of Kymriah-Responders with tissue-distribution incorporated

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Model *remixing* for the next phase of CAR-T clinical development

How to position cell therapies for autoimmunity & beyond?

Model of TCE PKPD in Lymphoma

npj | Systems Biology and Applications

www.nature.com/npjsba

ARTICLE OPEN

Check for updates

Mitigating the risk of cytokine release syndrome in a Phase I trial of CD20/CD3 bispecific antibody mosunetuzumab in NHL: impact of translational system modeling

Iraj Hosseini[1], Kapil Gadkar[1], Eric Stefanich[1], Chi-Chung Li[1], Liping L. Sun[1], Yu-Waye Chu[1] and Saroja Ramanujan[1]✉

Model of Lupus disease progression

ARTICLE

Disease trajectory of SLE clinical endpoints and covariates affecting disease severity and probability of response: Analysis of pooled patient-level placebo (Standard-of-Care) data to enable model-informed drug development

Kosalaram Goteti[1] | Jonathan French[2] | Ramon Garcia[2] | Ying Li[1] | Florence Casset-Semanaz[1] | Aida Aydemir[1] | Robert Townsend[1] | Cristina Vazquez Mateo[1] | Matthew Studham[1] | Oliver Guenther[3] | Amy Kao[1] | Marc Gastonguay[2] | Pascal Girard[4] | Lisa Benincosa[1] | Karthik Venkatakrishnan[1]

Model of CAR-T PKPD in Lupus

Clinical and Translational Science

ARTICLE OPEN ACCESS

Mechanistic Evaluation of Anti-CD19 CAR-T Cell Therapy Repurposed in Systemic Lupus Erythematosus Using a Quantitative Systems Pharmacology Model

Hyunseo Park[1,2] | Ganesh M. Mugundu[1] | Aman P. Singh[1]

Model of CAR-T PKPD in lymphoma

nature biotechnology

Article

https://doi.org/10.1038/s41587-023-01687-x

Deconvolution of clinical variance in CAR-T cell pharmacology and response

Received: 14 March 2022

Accepted: 20 January 2023

Daniel C. Kirouac[1]✉, Cole Zmurchok[1,3], Avisek Deyati[1,3], Jordan Sicherman[1], Chris Bond[1] & Peter W. Zandstra[1,2]

In Silico clinical trials for head-to-head comparisons

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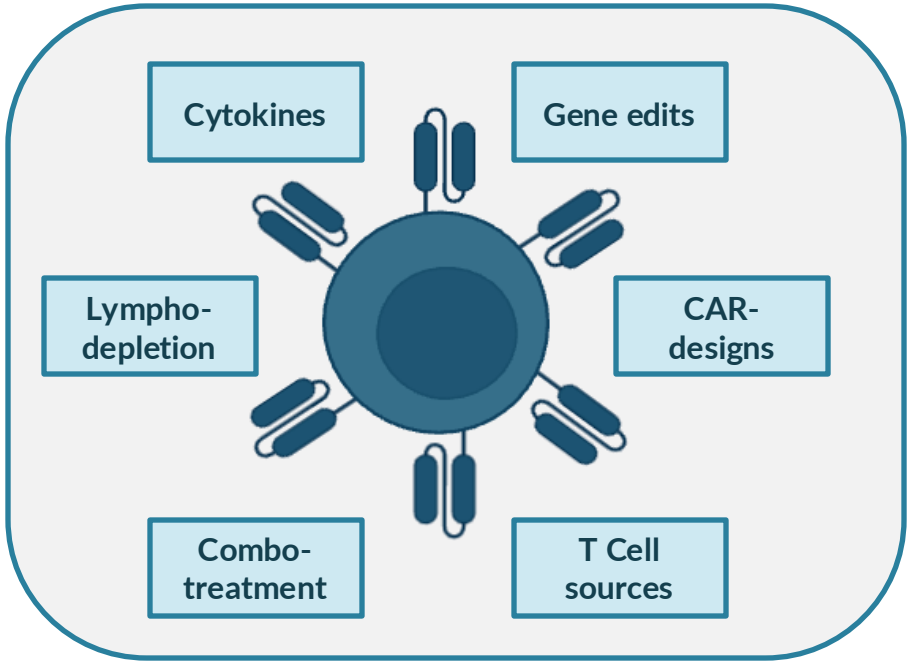
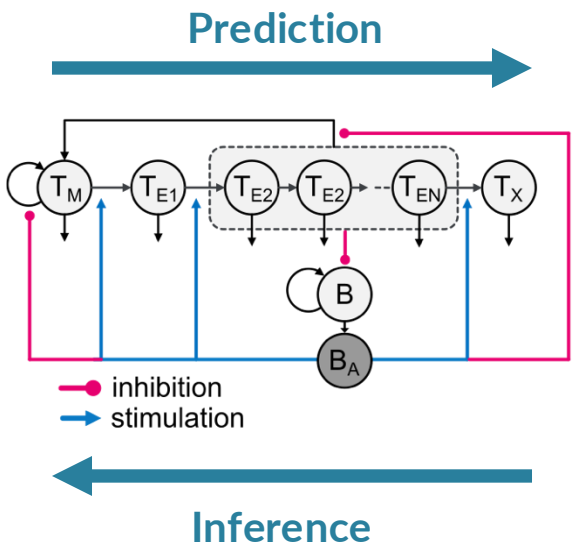
What is the value of mathematical modeling?

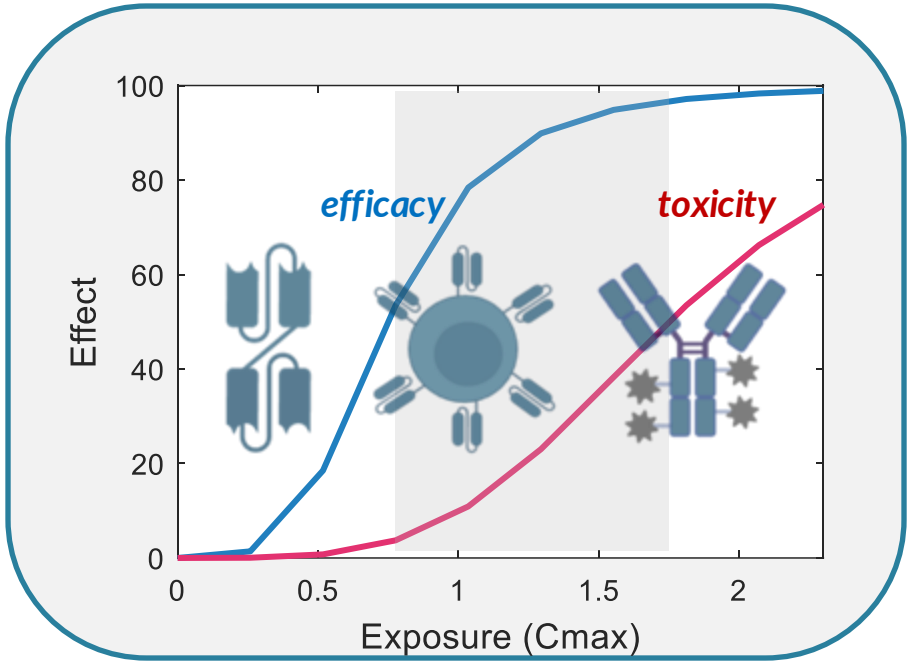
In the context of cell therapy engineering and clinical development

Cell therapy engineering





Clinical strategy



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