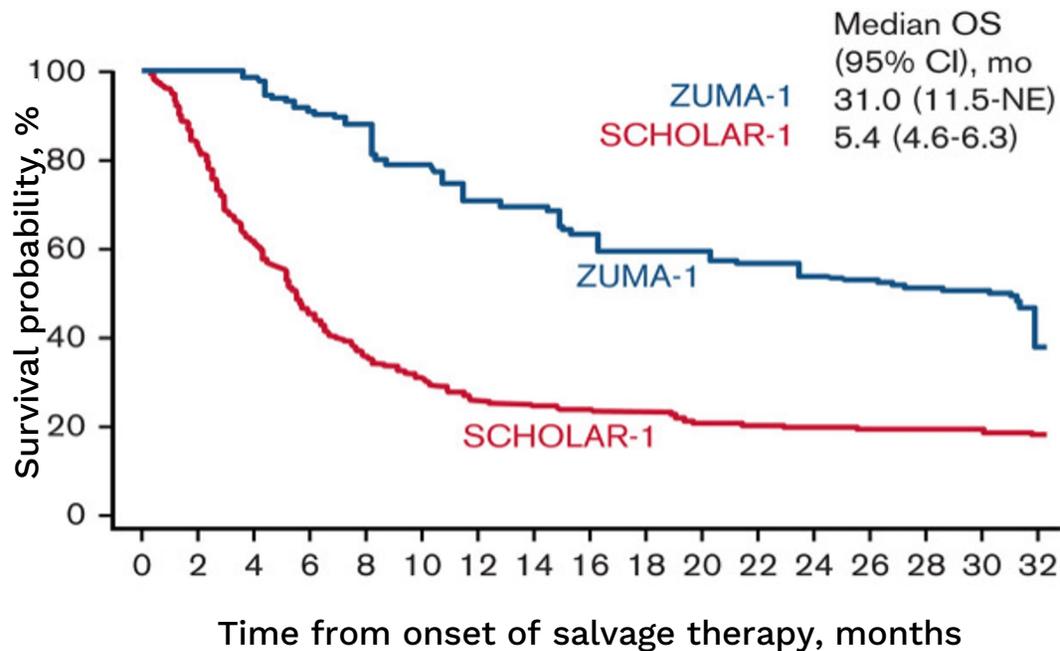


Restoring Balance: AI-assisted rapid mathematical model development for restoration ecology-guided CAR T therapy

Team Red: Allegra Love, Francois de Kermenguy, Gopinath Sadhu, Jill Gallaher, Konstantinos Mamis, Lavonte Saunders, Reshmi Patel, Shambhavi Kurup, Ari Barnett, Franco Pradelli, Sadegh Marzban, Martina Molgora, Sayeef Mirza, Jeffrey West

ZUMA-1 vs. SCHOLAR-1: CAR-T vs. chemotherapy for LBCL

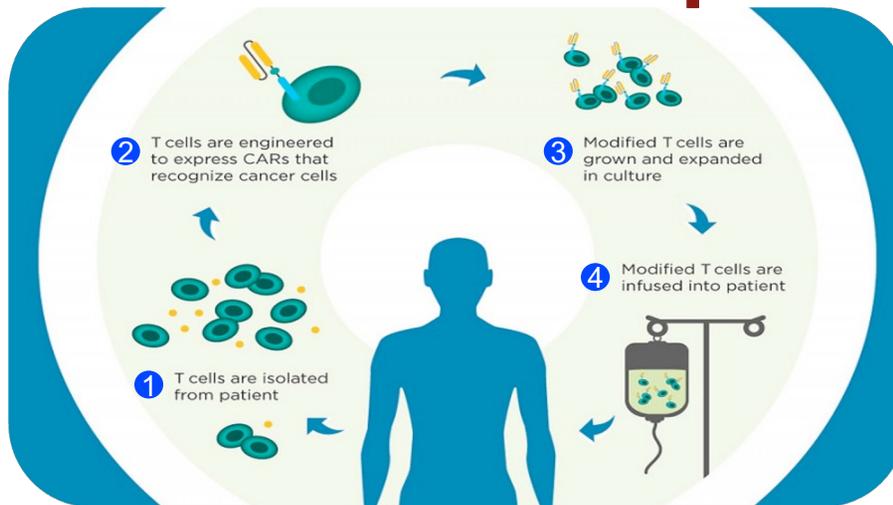
Prolonged survival with axi-cel versus (ZUMA-1; N=81) standard salvage regimens (SCHOLAR-1; N=331) in a propensity-balanced comparison



- 7.2-fold increase in odds of ORR
- 11.5-fold increase in odds of CR
- A 73% reduction in risk of death



Therapies leading up to CAR-T cell infusion

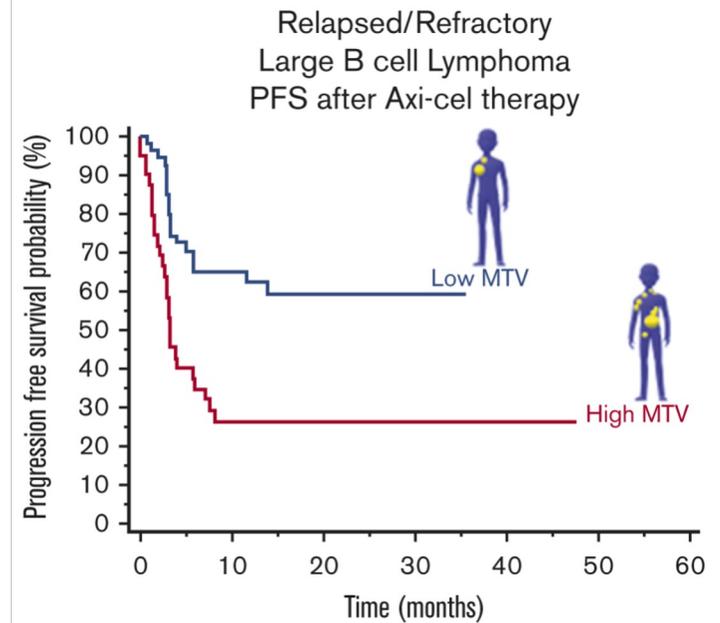
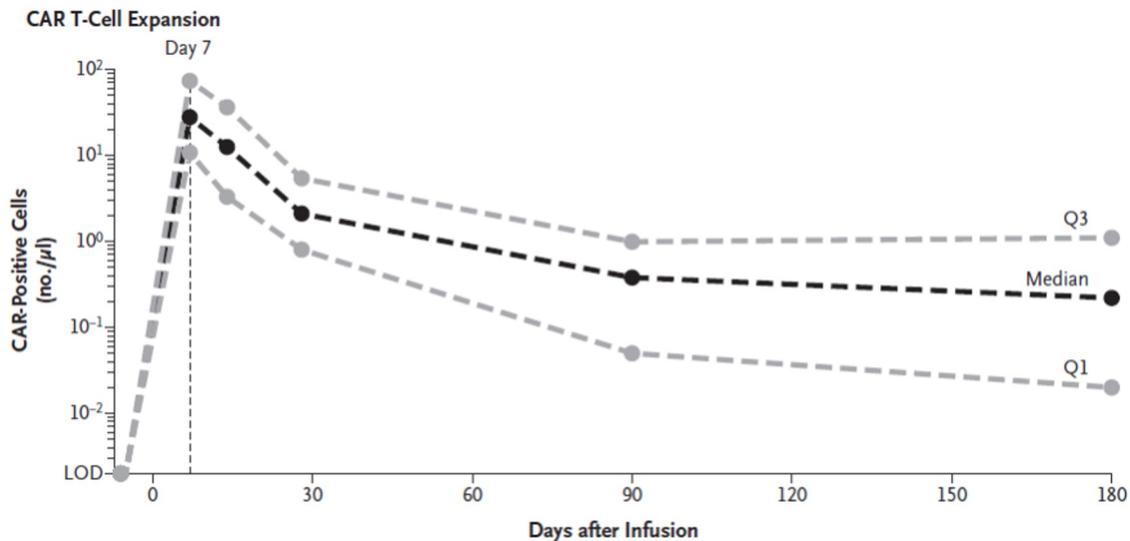


Fludarabine 30 mg/m²
OR
Cladribine 5 mg/m²
OR
Bendamustine 90 mg/m²
+
Cyclophosphamide 500 mg/m²

Bucklein et al. Hemasphere 2023

Team Red

Tumor Burden & lower CAR T Expansion lead to poor outcomes

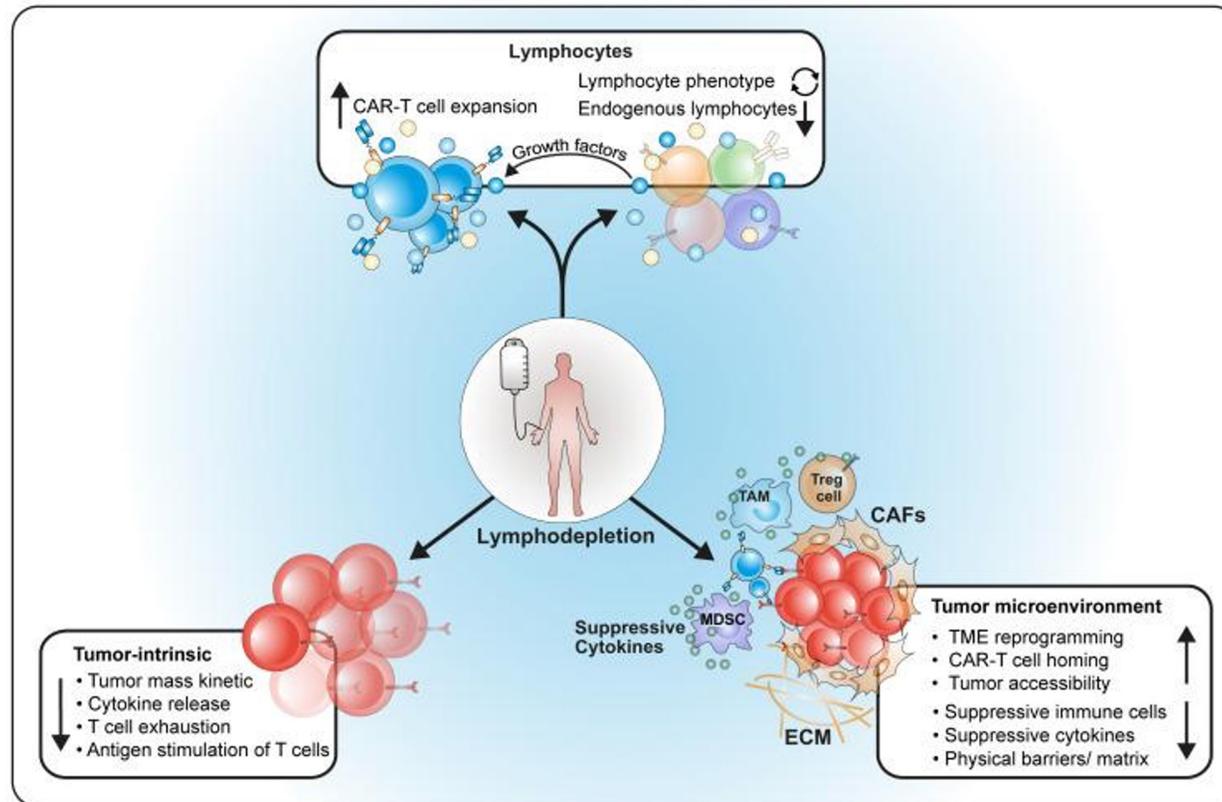


MTV = metabolic tumor volume



ZUMA-1. Neelapu, Locke et al. NEJM 2017; Dean et al. Blood Advances 2020

Possible suppressions that limit CAR-T



Lickefett et al. Frontiers in Immunology 2023



The background of the slide is white. It features several stylized red, rounded cells with small, dark brown cilia-like structures protruding from their surfaces. These cells are scattered across the top and bottom edges. In the lower right quadrant, there are two illustrations of deer running towards the right. The deer in the foreground is larger and has a brown coat with white spots and a white ruff. Behind it is a smaller, similar-looking deer.

Ecological Restoration

System Disruption



Healthy ecosystems are diverse and functional.



System Disruption



Healthy ecosystems are diverse and functional.

Disruption =



System Disruption



A disruption to the system can cause species loss, and changes to overall ecosystem function.

This motivates Ecological Restoration efforts.

Disruption =



Team
Red

Ecological Restoration



Ecological Restoration

1 Establish Restoration Goals



Ecological Restoration



2 Site Selection



Ecological Restoration

3 Abiotic Intervention



Ecological Restoration



4 Biotic
Intervention

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Red

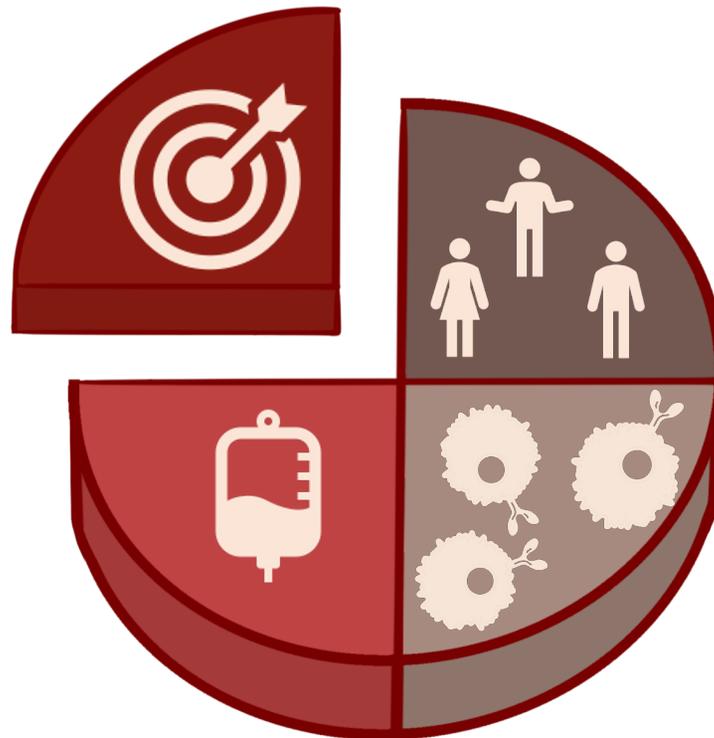
Ecological Restoration



Ecological Restoration Inspires Treatment

1 Cure via CAR-T

(Restoration Goals)



Ecological Restoration Inspires Treatment



2 Patient Stratification (Site Selection)

Team
Red

Ecological Restoration Inspires Treatment



3 Lymphodepletion (Abiotic Intervention)

Ecological Restoration Inspires Treatment



4 CAR T-cell
engineering
(Biotic Intervention)

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Bibliometric Overlap



CAR-T + B-Cell
Lymphoma

Restoration
Ecology + Math



Bibliometric Overlap



CAR-T + B-Cell
Lymphoma

Restoration
Ecology + Math



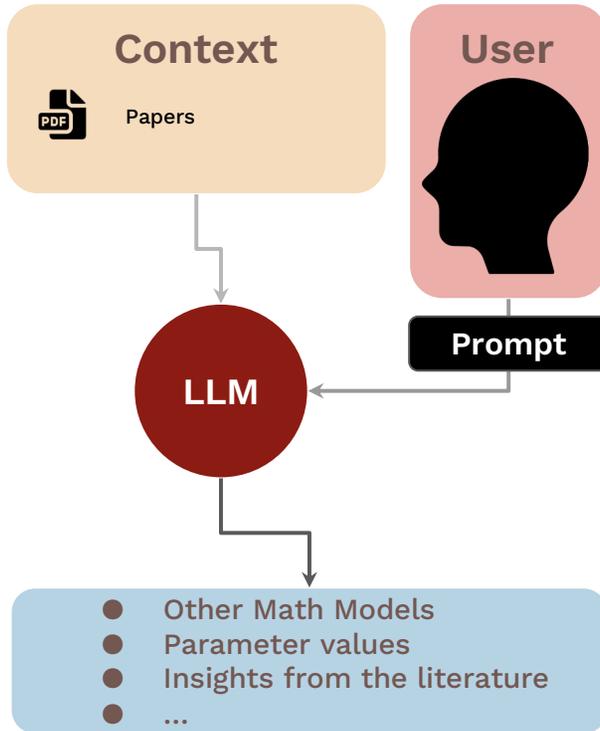
Restoration ecology is a viable path to improve CAR-T resilience



AI Research Assistant: IRIS



AI Research Assistant



IRIS
Intelligent Retrieval Information System

Upload Documents
Upload a folder containing PDF documents to begin.
Click to upload a folder
PDFs will be extracted

Source Category
Medicine

Use All Categories

CAR-T PDFs
17 PDF(s) loaded

Analysis Mode
Standard Thinking

carrying capacity) provides an accessible starting point for conceptualizing CAR T-cell/lymphoma interactions, its efficiency for comprehensive replication of the rich and varied dynamics observed in B-cell lymphoma patients is limited. More sophisticated quantitative systems pharmacology (QSP) models that incorporate cellular heterogeneity (e.g., effector, memory, exhausted CAR T-cells, healthy B-cells, and antigen-negative tumor variants), complex signaling pathways for proliferation, and aspects of the microenvironment are necessary for higher fidelity and predictive power in this complex therapeutic area.

Provide what aspects I could focus on when developing a mathematical model of CAR-T therapy

When developing a mathematical model of CAR T-cell therapy, several key aspects, spanning biological, mechanistic, and computational considerations, can be focused on, drawing insights from the provided literature:

1. Cellular Populations and Phenotypes

CAR T-cell Subpopulations: Instead of a single CAR T-cell population, differentiate them into distinct functional phenotypes based on their maturation, activity, and lifespan.

Effector/Activated CAR T-cells: Rapidly kill target cells and proliferate.

Memory CAR T-cells: Long-lived, provide long-term persistence, and can reactivate into effector cells upon re-encountering antigen.

Exhausted CAR T-cells: Cells that have lost or have impaired effector function, expansion capacity, and persistence due to prolonged or excessive antigen stimulation.

Naïve, Central Memory (TCM), Effector Memory (TEM), Terminally Differentiated Effector (TEF) CAR T-cells: A more granular differentiation that reflects T-cell lineage progression.

Ask about the document...



LLMs for Literature-informed Modeling



The provided literature contains several mathematical models of CAR-T cell therapy, most of which are variations of predator-prey systems. Based on your requirement for a two-species model (cancer B cells and total T cells, where a portion are CAR-T), a robust starting point is a model that simplifies the T cell population to a single CAR-T cell compartment (C) interacting with the B cell lymphoma population (B). This structure is common in the supplied literature (eg, Sahoo et al., 2020; Kimmel et al., 2021).

Core B-Cell Lymphoma and CAR-T Cell Model

A system of two ordinary differential equations describing the interaction between the cancer B-cell population, $B(t)$, and the CAR-T cell population, $C(t)$.

1. Cancer B-Cell Population $B(t)$:

$$dB/dt = r_B * B * (1 - B/K_B) - k_{kill} * B * C$$

- * $r_B * B * (1 - B/K_B)$: Logistic growth of cancer B-cells.
- * $- k_{kill} * B * C$: Killing of cancer B-cells by CAR-T cells (mass-action).

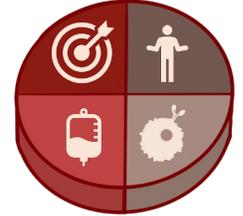
2. CAR-T Cell Population $C(t)$:

$$dC/dt = p * B * C - q_{exhaust} * B * C - m_C * C$$

- * $p * B * C$: Antigen-stimulated proliferation of CAR-T cells.
- * $- q_{exhaust} * B * C$: Exhaustion/inactivation of CAR-T cells from tumor interaction.
- * $- m_C * C$: Natural apoptosis (death) of CAR-T cells.



LLMs for Literature-informed Modeling



The provided literature contains several mathematical models of CAR-T cell therapy, most of which are variations of predator-prey systems. Based on your requirement for a two-species model (cancer B cell population, $B(t)$, and the CAR-T cell population, $C(t)$) interacting with the B cell I (eg, Sahoo et al., 2020; Kimmel et al., 2021).

Result Type 1

Core B-Cell Lymphoma and CAR-T Cell Model

A system of two ordinary differential equations describing the interaction between the cancer B-cell population, $B(t)$, and the CAR-T cell population, $C(t)$.

1. Cancer B-Cell Population $B(t)$:

$$dB/dt = r * B * B * (1 - B/K * B) - k_{kill} * B * C$$

- $r * B * B * (1 - B/K * B)$: Growth of cancer B-cells (logistic growth).
- $- k_{kill} * B * C$: Killing of cancer B-cells by CAR-T cells (mass-action).

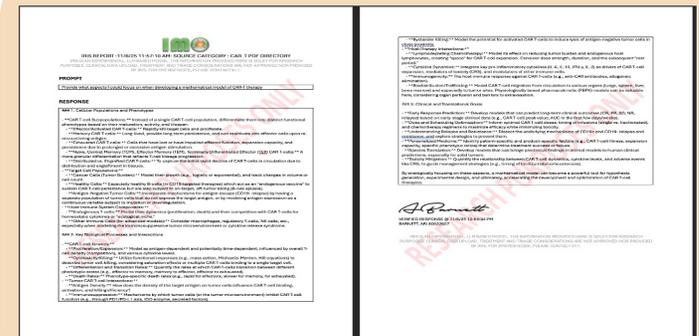
2. CAR-T Cell Population $C(t)$:

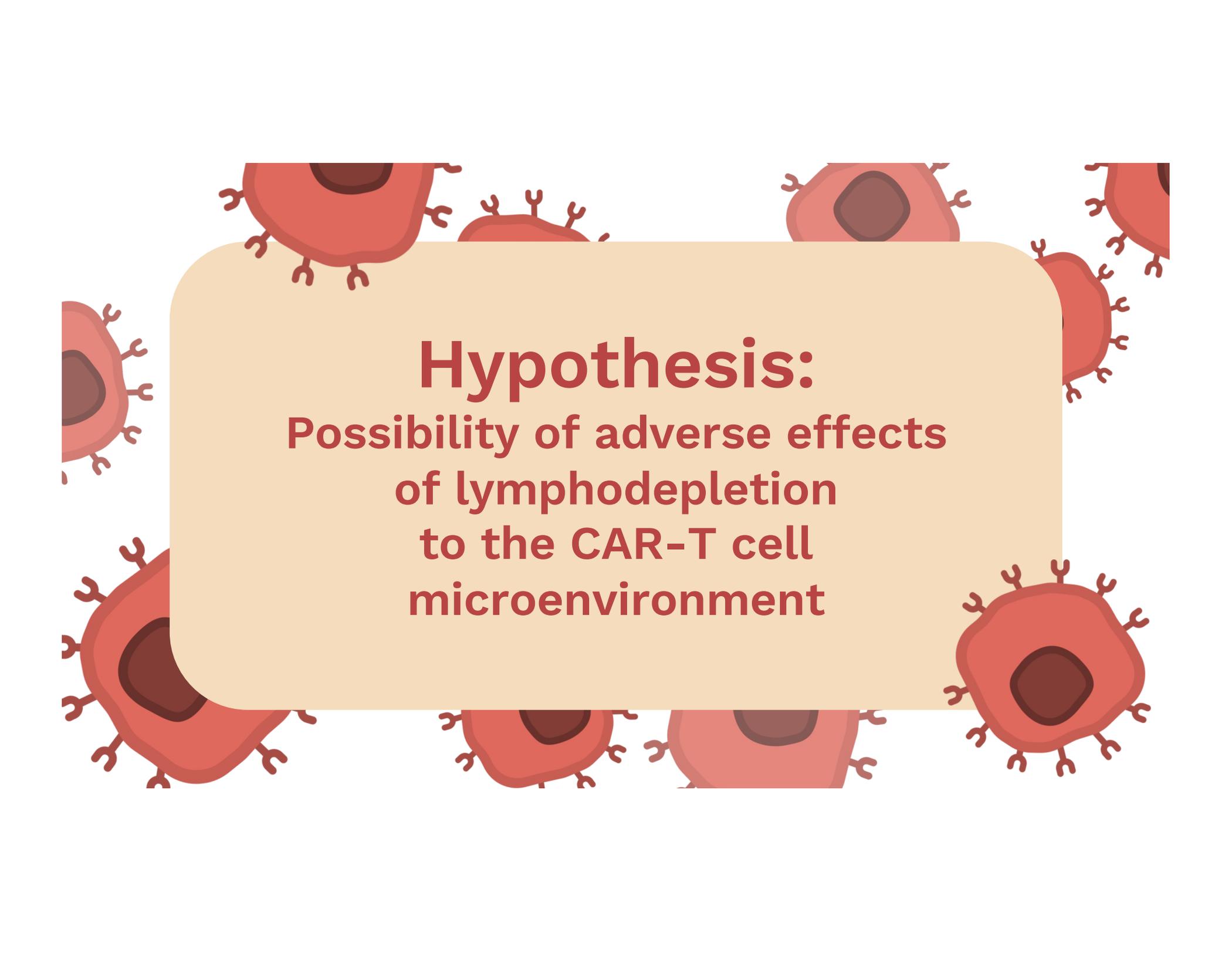
$$dC/dt = p * B * C - q_{exhaust} * B * C - m_C * C$$

- $p * B * C$: Antigen-stimulated proliferation of CAR-T cells.
- $- q_{exhaust} * B * C$: Exhaustion/inactivation of CAR-T cells from tumor interaction.
- $- m_C * C$: Natural apoptosis (death) of CAR-T cells.

Result Type 2

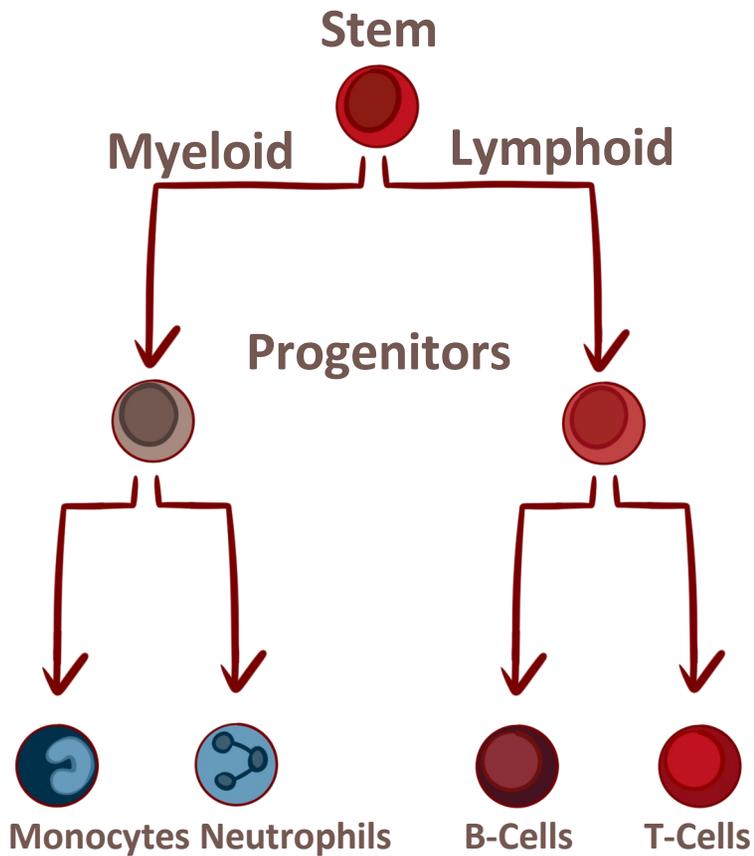
Development Assistance Report



The background of the slide features several stylized, red, irregularly shaped cells. Each cell has a dark brown nucleus and several small, dark brown cilia-like structures extending from its surface. The cells are scattered across the slide, with some partially obscured by a central text box.

Hypothesis:
Possibility of adverse effects
of lymphodepletion
to the CAR-T cell
microenvironment

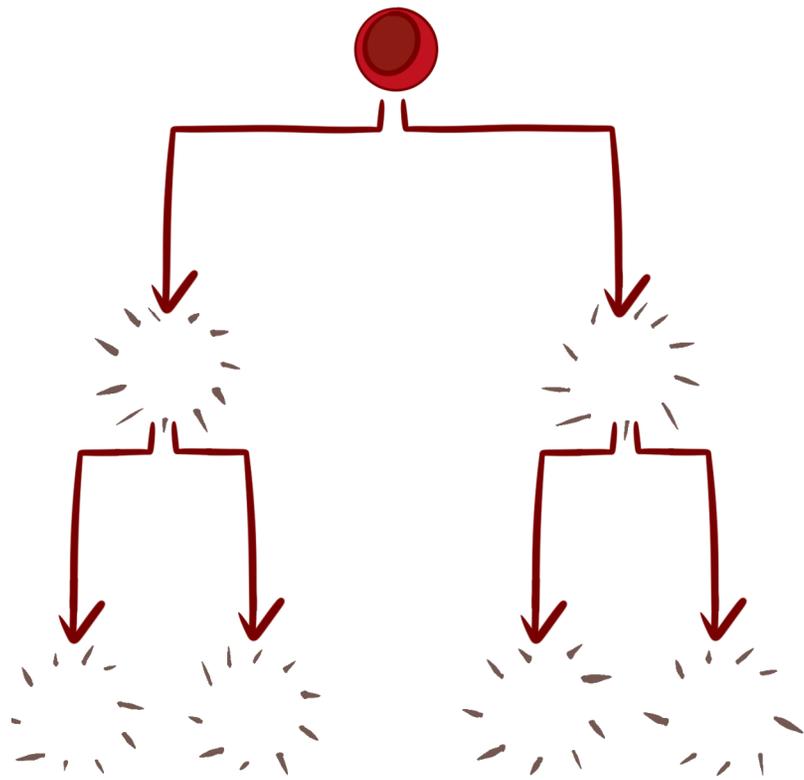
Hematopoietic Hierarchy in Homeostasis



Healthy hematopoiesis maintains a normal balance of myeloid and lymphoid cells



Lymphodepletion Before CAR T Therapy



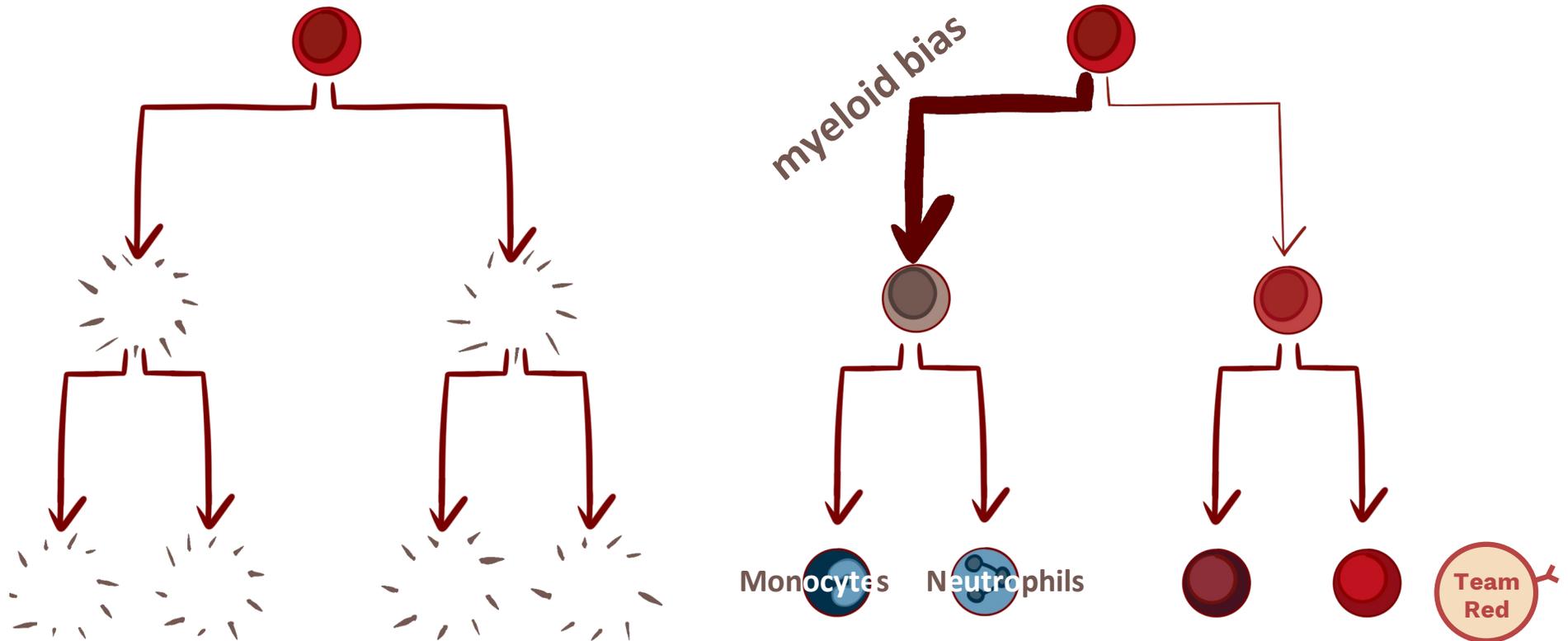
Lymphodepletion (LD) reduces white blood cell count to create space for CAR T-cells



Emergency myelopoiesis



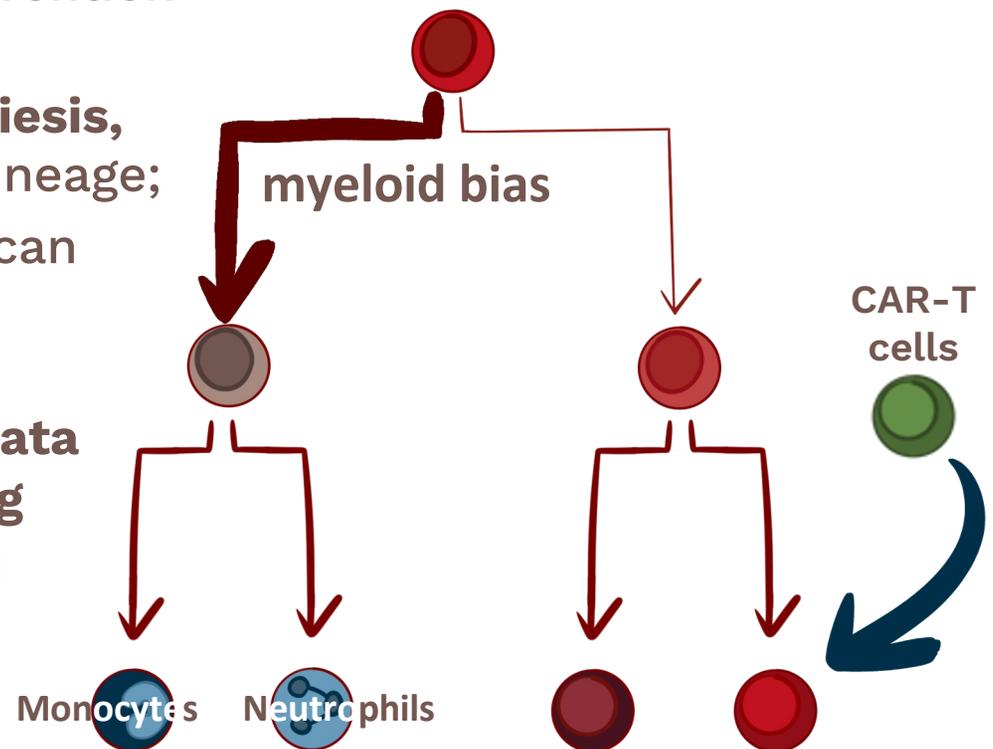
LD triggers **emergency myelopoiesis** that boosts myeloid cell production



Hypothesis



- **LD** is a necessary abiotic intervention before CAR-T therapy;
- its result, **emergency myelopoiesis**, increases cells from myeloid lineage;
- such cells, like **macrophages**, can suppress (or promote) CAR-T cell activity.
- Use of **clinical/experimental data** and **AI-assisted math modeling**
- to categorize, understand, and **manipulate the CAR-T microenvironment**.



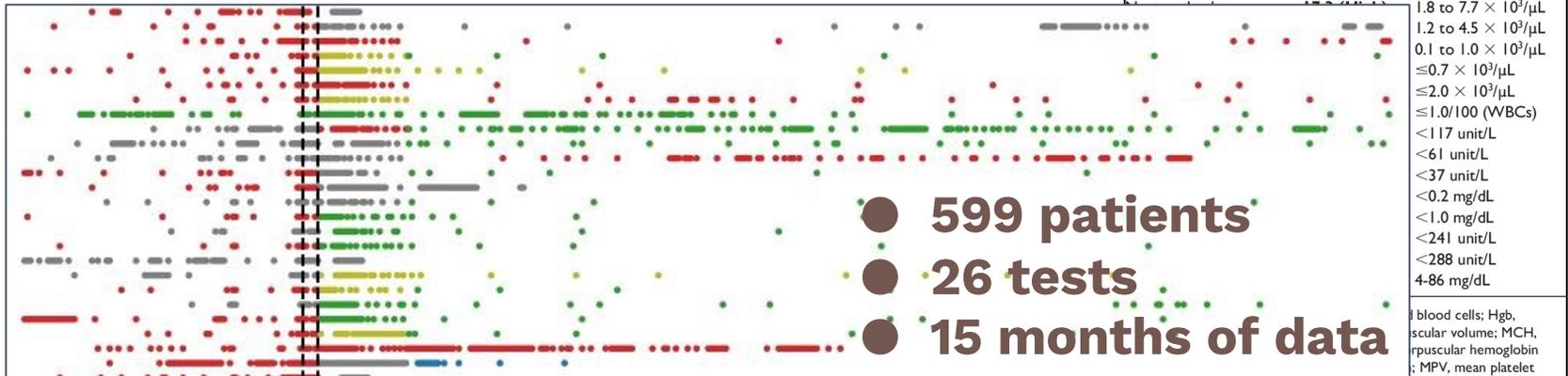
Clinical blood test dataset

Subject: Your large urgent data request

Hi Dr Mirza,

We have finished your data – or at least wh

	Values	Reference ranges
WBC	18.6 (High)	4.5 to 11 × 10 ³ /μL
RBC	5.31	4.26 to 5.80 × 10 ⁶ /μL
Hgb	14.7	13.2 to 17.4 g/dL
Hct	44.3	38.9% to 51.0%
MCV	83.4	80.0 to 98.0 fL
MCH	27.6	27.1 to 34.0 pg
MCHC	33.1	32.4 to 35.9 g/dL
RDW	13.3	11.4% to 14.1%
Platelets	243	150 to 450 × 10 ³ /μL
MPV	8.7	6.5 to 10.5 fL
Neutrophils auto%	93.2 (High)	50.0% to 75.0%
Lymphocytes auto%	3.8 (Low)	20.0% to 45.0%
Monocytes auto%	2.4	2.0% to 12.0%
Eosinophils auto%	0.1	≤6.0%
Basophils auto%	0.5	≤2.0%



- 599 patients
- 26 tests
- 15 months of data

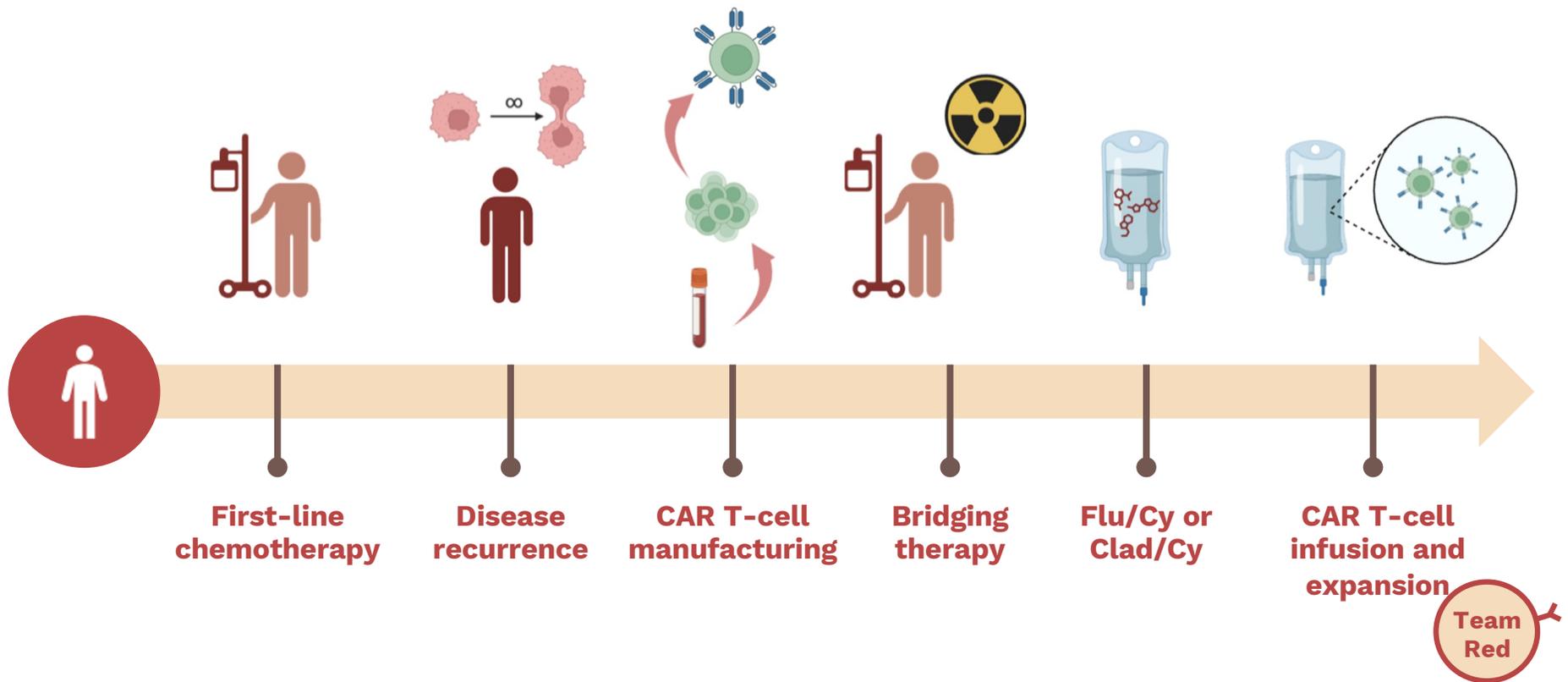
1.8 to 7.7 × 10³/μL
 1.2 to 4.5 × 10³/μL
 0.1 to 1.0 × 10³/μL
 ≤0.7 × 10³/μL
 ≤2.0 × 10³/μL
 ≤1.0/100 (WBCs)
 <117 unit/L
 <61 unit/L
 <37 unit/L
 <0.2 mg/dL
 <1.0 mg/dL
 <241 unit/L
 <288 unit/L
 4-86 mg/dL

volume; NRBC, nucleated red blood cells; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; IgG, immunoglobulin G.

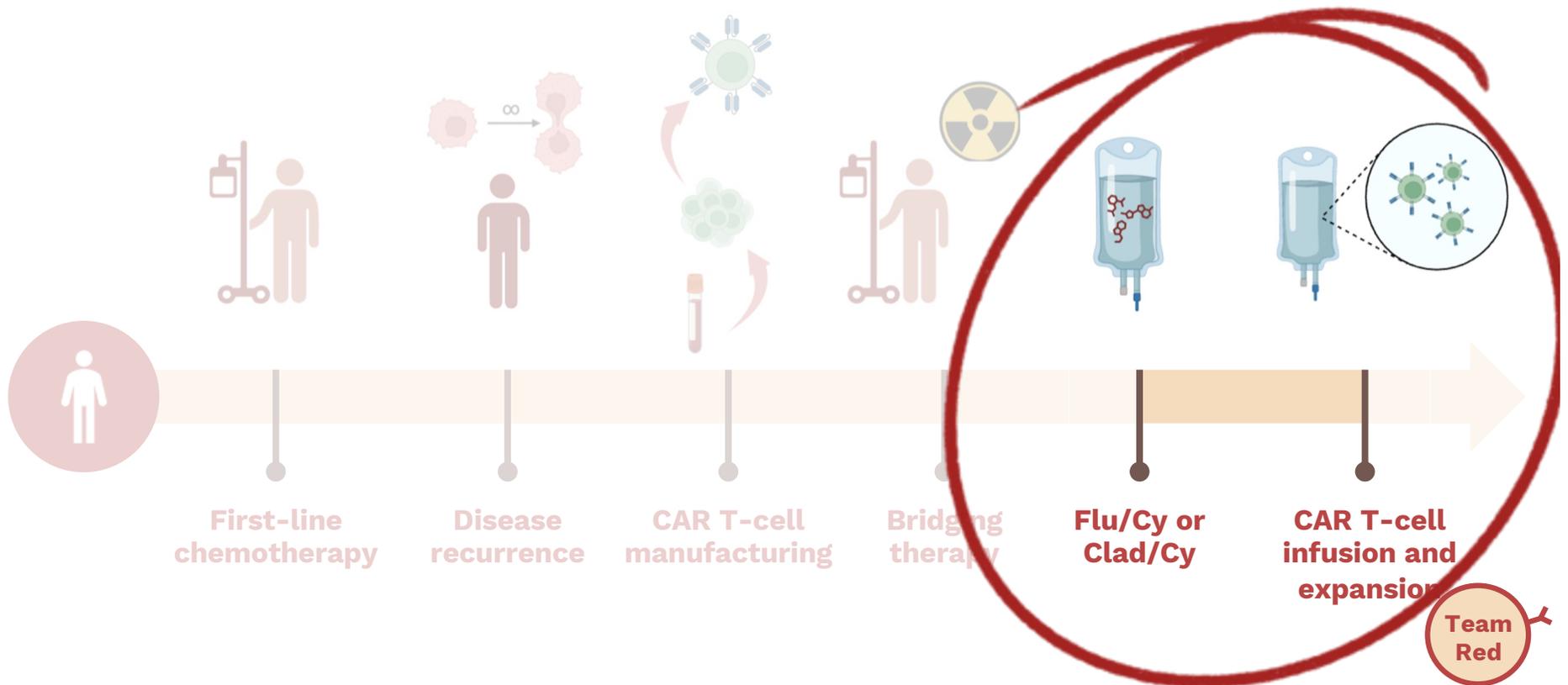
LD CAR-T



CAR T-cell Therapy Timeline



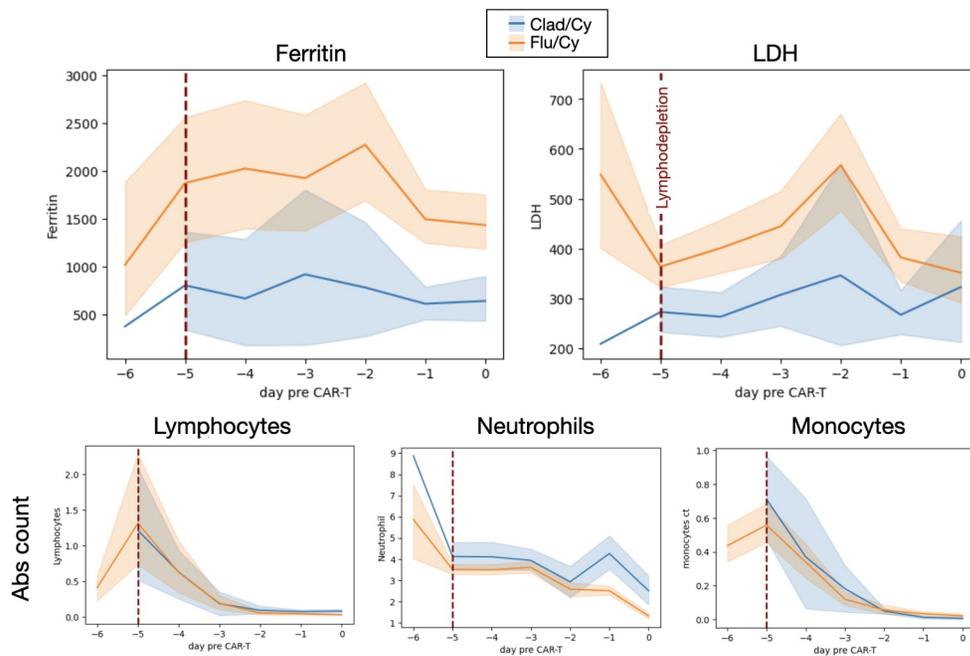
Clinical Blood Test Dataset



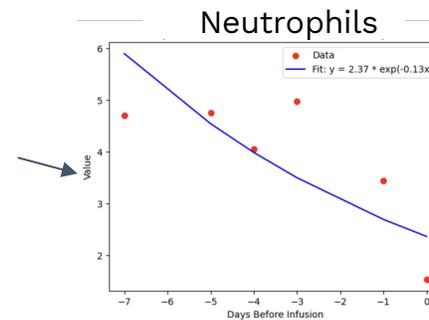
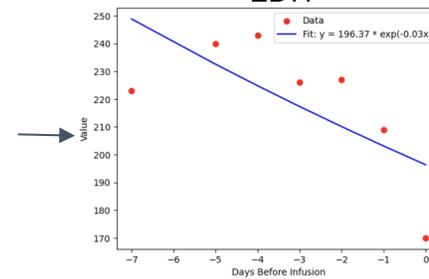
Lymphodepletion Dynamics



Does Flu/Cy or Clad/Cy lymphodepletion promote a more favorable immune microenvironment?



$$y = re^{\alpha x}$$



Quantifying patient-specific cell kinetics



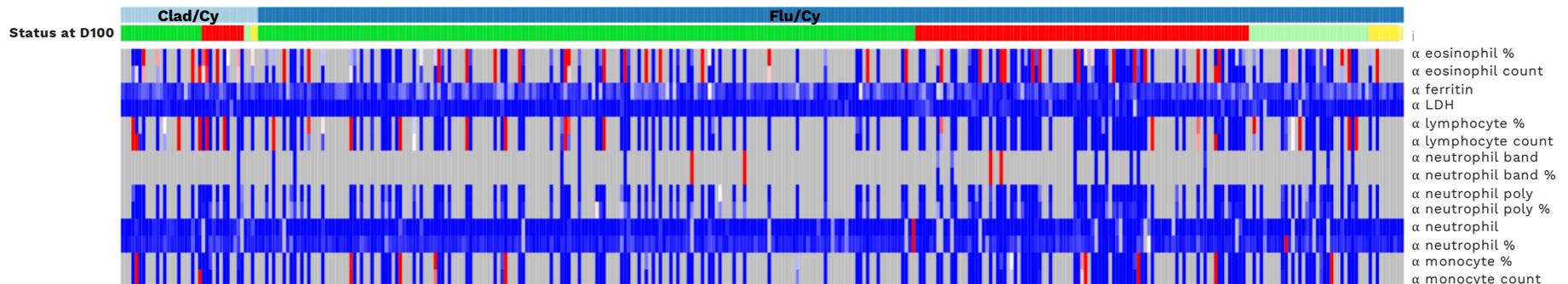
- Each column is a patient
- Each row measures the rate of immune cell kinetics for each subpopulation

LD Agent

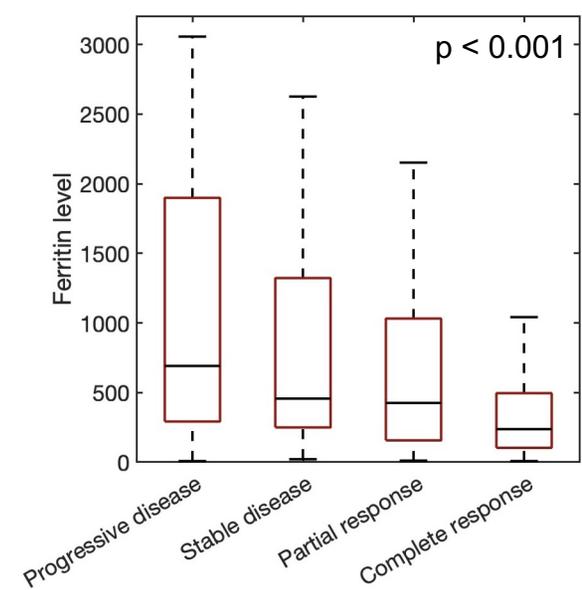
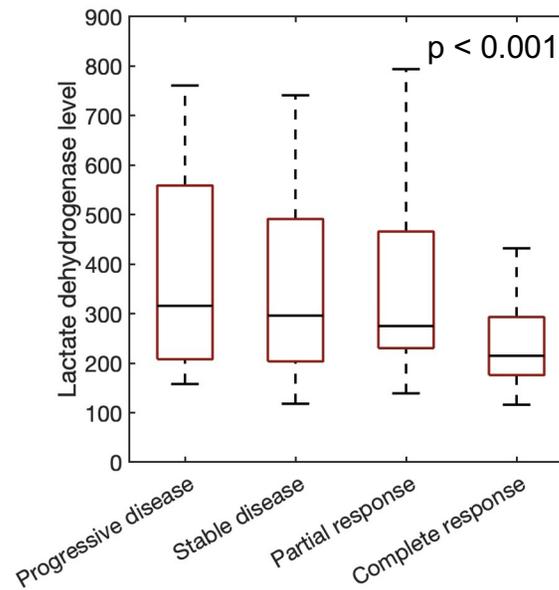
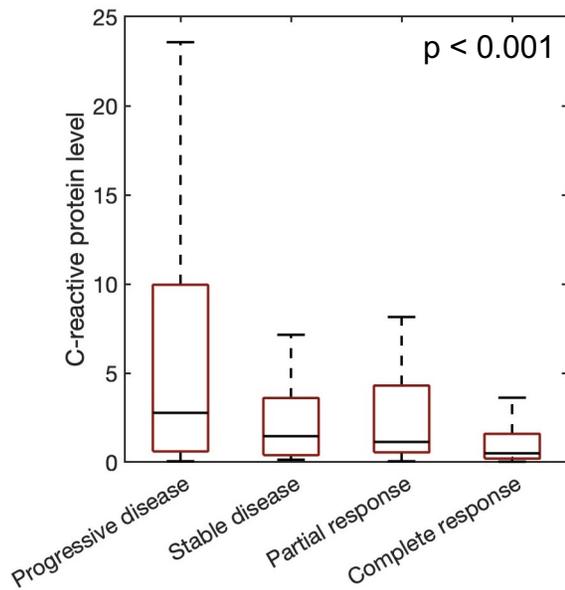
- Clad/Cy
- Flu/Cy
- Unknown

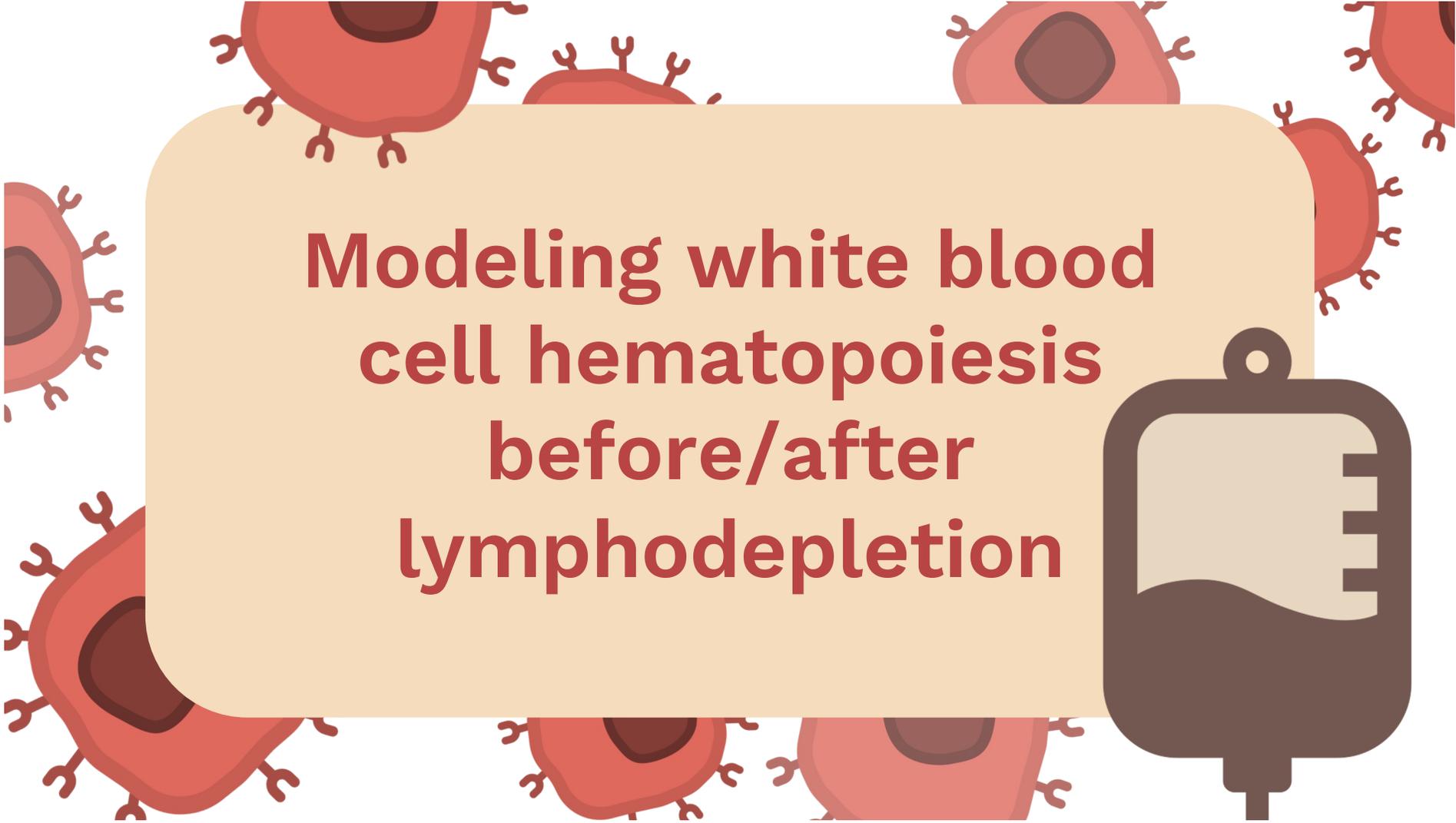
Status at day 100

- Complete Remission
- Unknown
- Progressive Disease
- Partial Remission
- Stable Disease

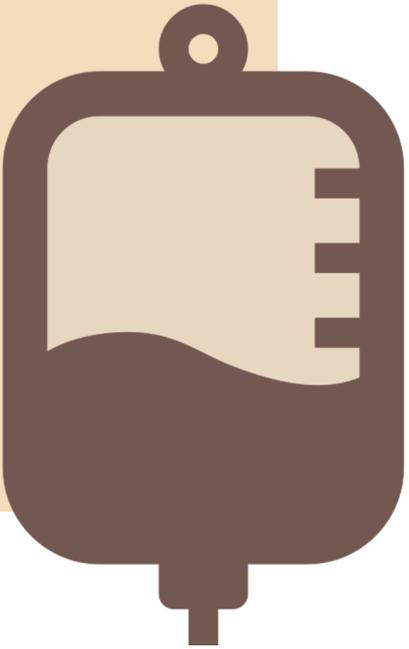


Blood biomarkers of response

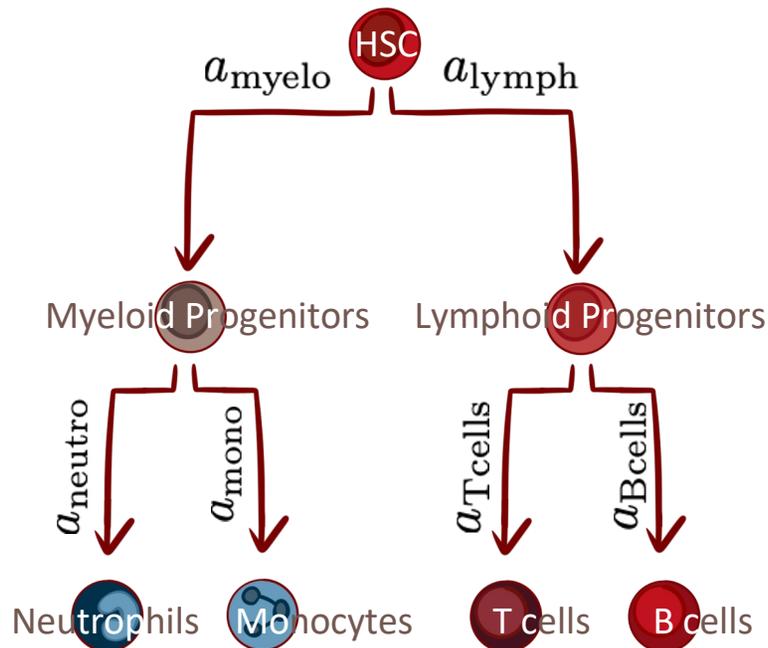




**Modeling white blood
cell hematopoiesis
before/after
lymphodepletion**



Hierarchical model for hematopoiesis



System of ODEs

$$\dot{N}_{\text{mono}} = a_{\text{mono}} r_{\text{mono}} P_{\text{MP}} - b_{\text{mono}} N_{\text{mono}}$$

$$\dot{N}_{\text{neutro}} = a_{\text{neutro}} r_{\text{neutro}} P_{\text{MP}} - b_{\text{neutro}} N_{\text{neutro}}$$

$$\dot{N}_{\text{Tcells}} = a_{\text{Tcells}} r_{\text{Tcells}} P_{\text{LP}} - b_{\text{Tcells}} N_{\text{Tcells}}$$

$$\dot{N}_{\text{Bcells}} = a_{\text{Bcells}} r_{\text{Bcells}} P_{\text{LP}} - b_{\text{Bcells}} N_{\text{Bcells}}$$

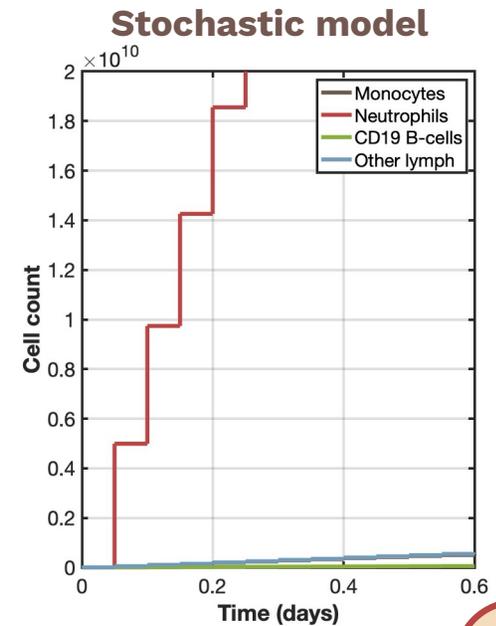
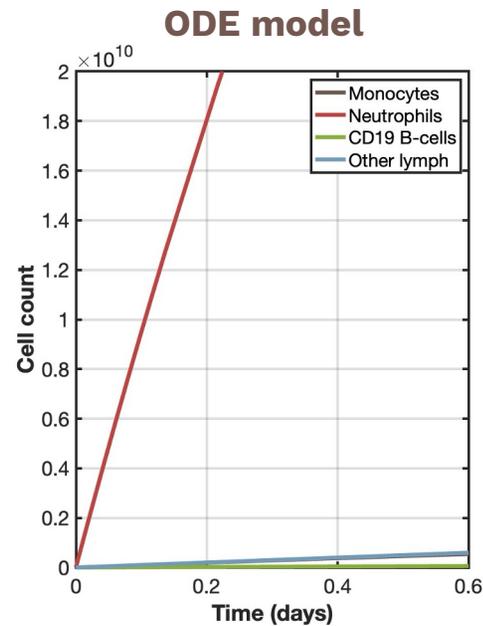
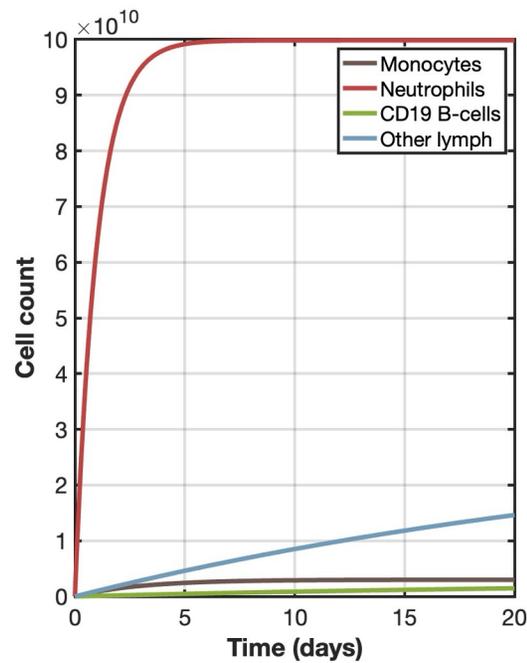
A hierarchical model captures the stepwise nature of hematopoiesis: each layer feeds the next, from stem cells to specialized blood cells.



ODE vs. Stochastic Model for Hematopoiesis



Cells divisions, differentiations and deaths occur at random: stochastic model



when populations are small, random events have a large impact on dynamics



Lymphodepletion & Emergency Myelopoiesis



Experimental data from mice (Molgora lab)

Cell Type	Before LD (10^6 cells)	After LD (10^6 cells)
Monocytes	0.089	0.117
Neutrophils	0.640	1.900
CD19 B-cells	4.100	3.500
Other lymphoid cells	1.800	1.600

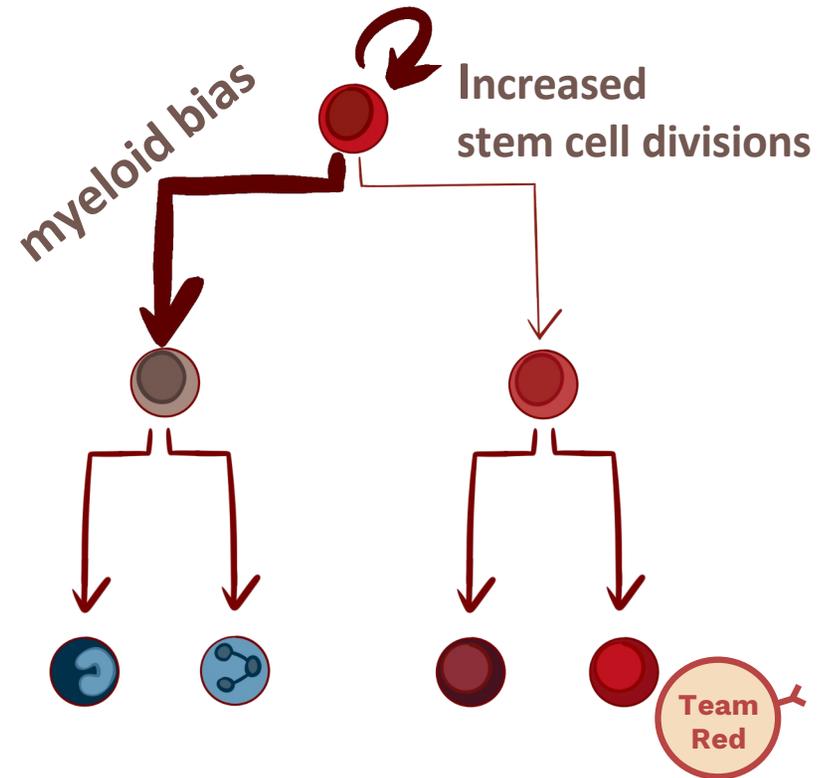
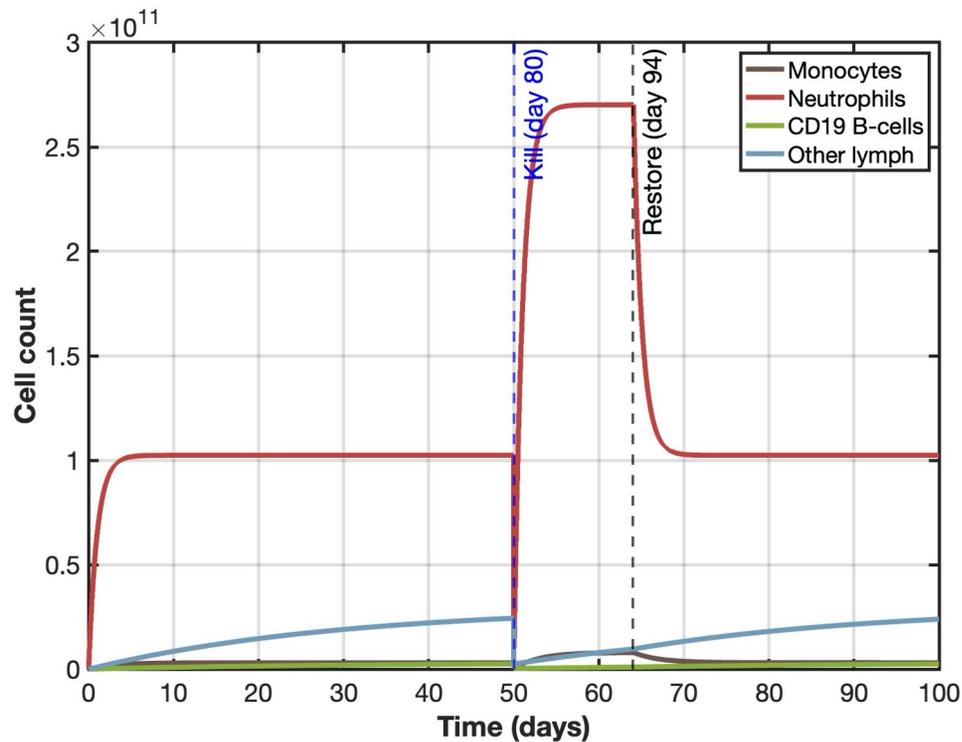
Quantify the changes in hematopoiesis during emergency myelopoiesis



Modeling Lymphodepletion Dynamics



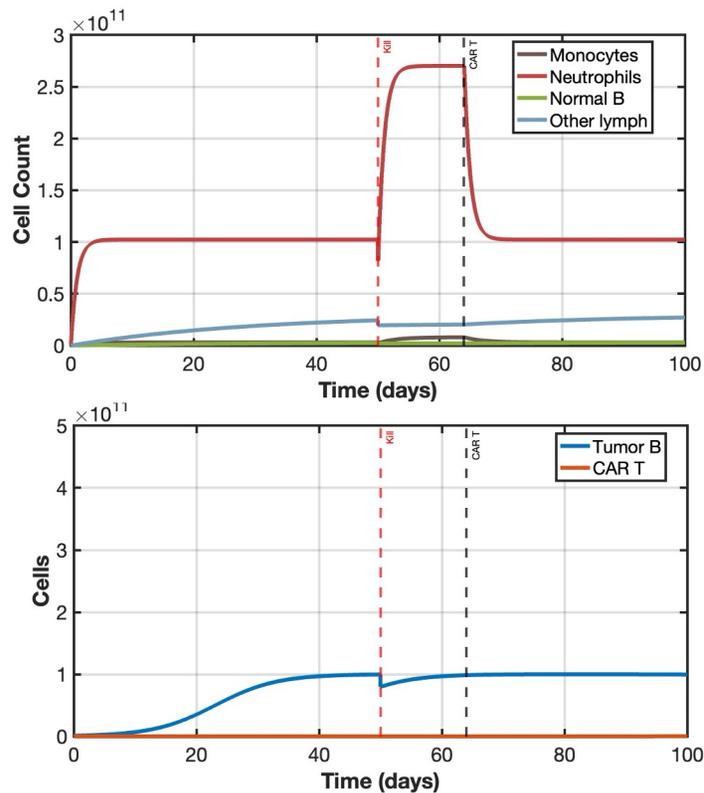
Monocytes increase after LD, potentially suppressing CAR-T expansion



Effect of microenvironment on CAR-T



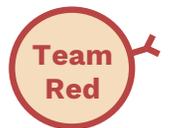
Model for B cells containing cancer cells, and T cells containing CAR-T cells



Case 1: Biotic Intervention + Weak Abiotic Intervention

$$\frac{dB}{dt} = r_B B \left(1 - \frac{B}{K_B} \right) - k_{\text{kill}} C B$$

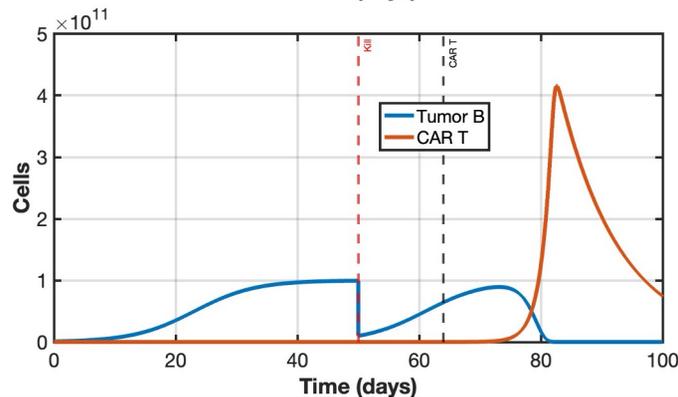
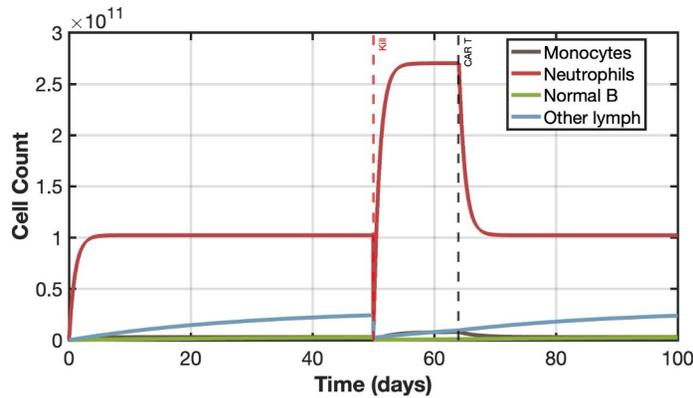
$$\frac{dC}{dt} = r_C C \frac{N_{\text{Bcells}}(t)}{h_{\text{Ag}} + N_{\text{Bcells}}(t)} - d_C C$$



Effect of microenvironment on CAR-T



Model for B cells containing cancer cells, and T cells containing CAR-T cells

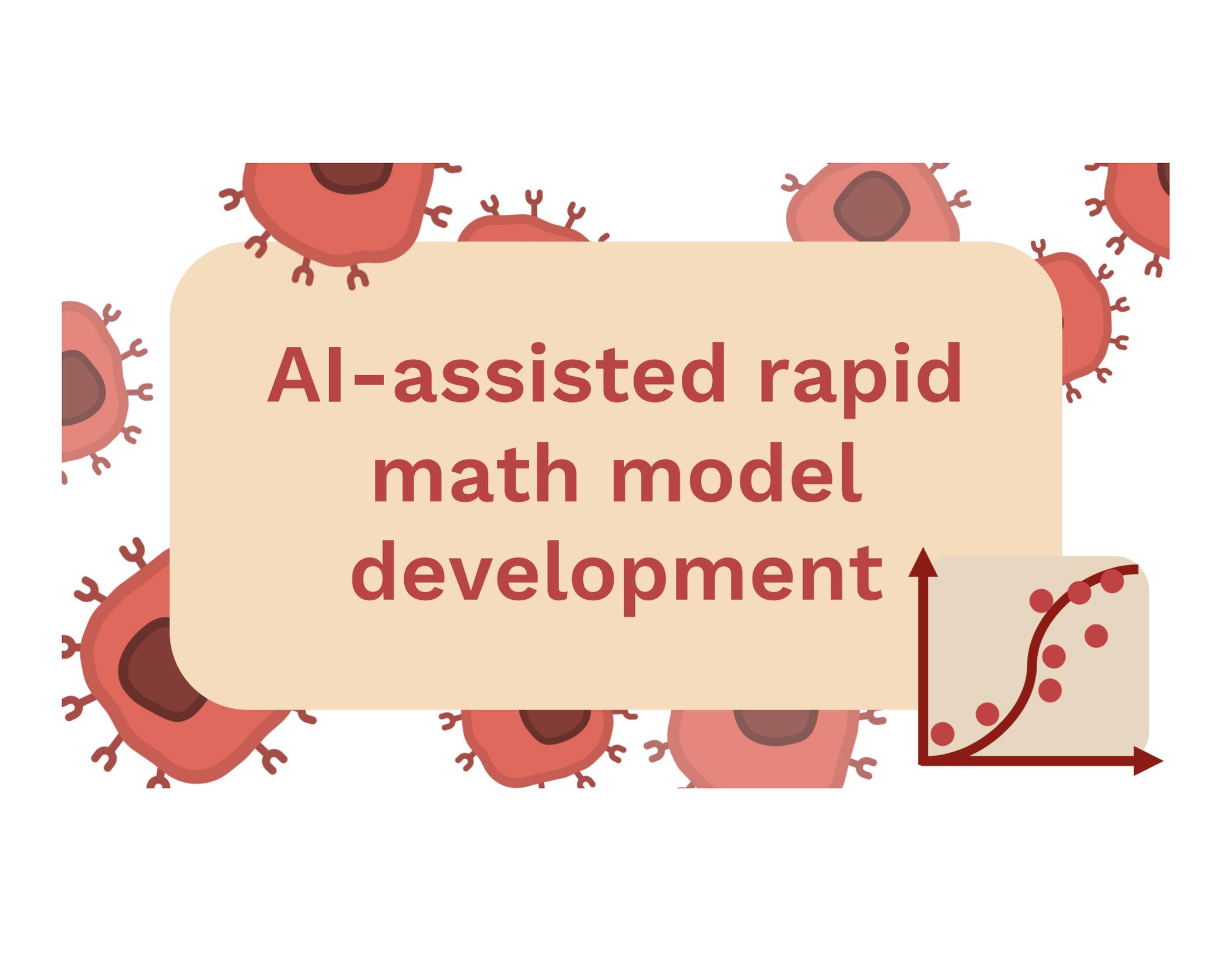


Case 2: Biotic Intervention + Strong Abiotic Intervention

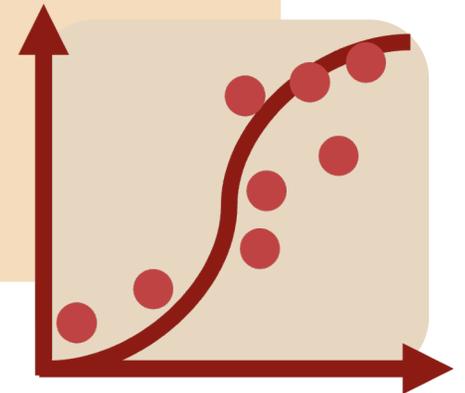
$$\frac{dB}{dt} = r_B B \left(1 - \frac{B}{K_B} \right) - k_{\text{kill}} C B$$

$$\frac{dC}{dt} = r_C C \frac{N_{\text{Bcells}}(t)}{h_{\text{Ag}} + N_{\text{Bcells}}(t)} - d_C C$$

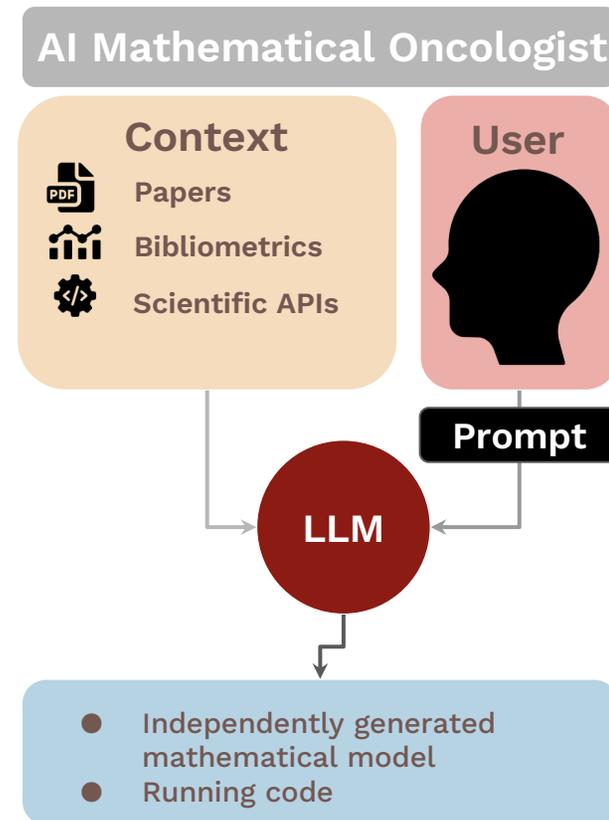
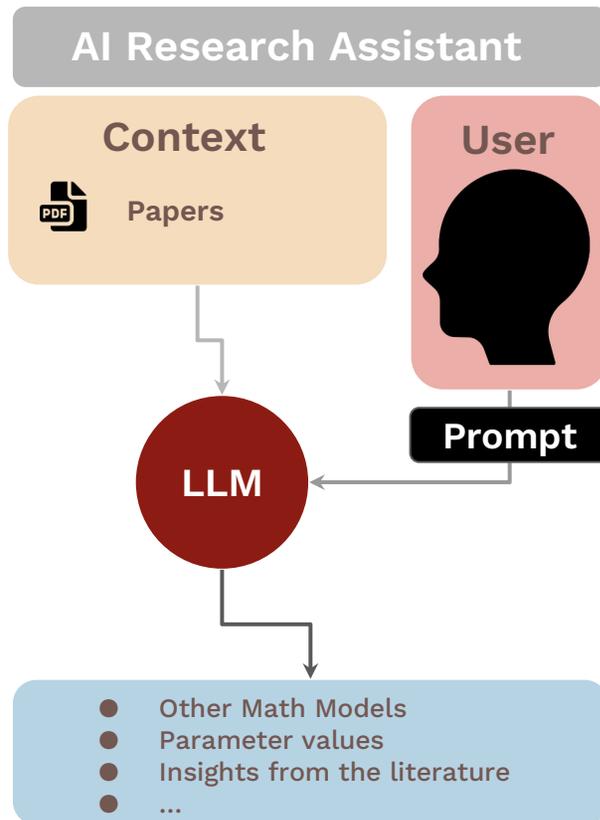




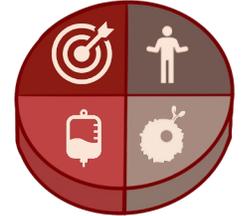
**AI-assisted rapid
math model
development**



Expanding the AI-assistant suite



Expanding the AI-assistant suite



No sensitive data was
uploaded to LLMs
during our
investigation



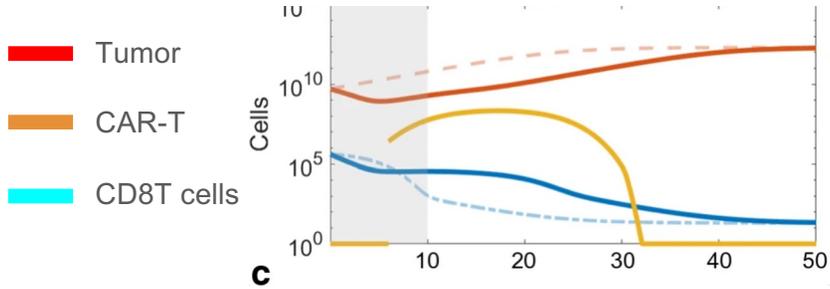
AI-Mathematical Oncologist



Modeling CAR T-Cell Therapy with Patient Preconditioning

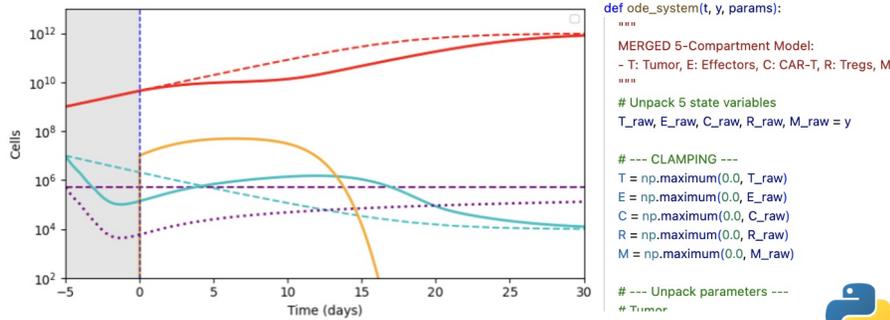
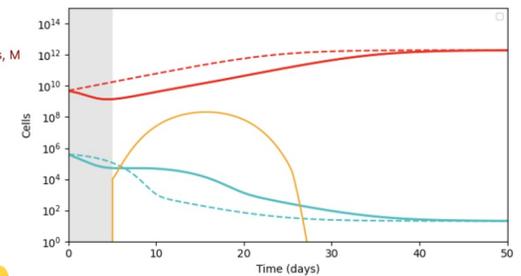


Katherine Owens¹ · Ivana Bozic¹



Reproduced results

```
def ode_system(t, y, params):  
    """  
    MERGED 5-Compartment Model:  
    - T: Tumor, E: Effectors, C: CAR-T, R: Tregs, M  
    """  
    # Unpack 5 state variables  
    T_raw, E_raw, C_raw, R_raw, M_raw = y  
  
    # --- CLAMPING ---  
    T = np.maximum(0.0, T_raw)  
    E = np.maximum(0.0, E_raw)  
    C = np.maximum(0.0, C_raw)  
    R = np.maximum(0.0, R_raw)  
    M = np.maximum(0.0, M_raw)  
  
    # --- Unpack parameters ---  
    # Tumor
```



```
def ode_system(t, y, params):  
    """  
    MERGED 5-Compartment Model:  
    - T: Tumor, E: Effectors, C: CAR-T, R: Tregs, M  
    """  
    # Unpack 5 state variables  
    T_raw, E_raw, C_raw, R_raw, M_raw = y  
  
    # --- CLAMPING ---  
    T = np.maximum(0.0, T_raw)  
    E = np.maximum(0.0, E_raw)  
    C = np.maximum(0.0, C_raw)  
    R = np.maximum(0.0, R_raw)  
    M = np.maximum(0.0, M_raw)  
  
    # --- Unpack parameters ---  
    # Tumor
```



chatgpt.com/c/690cba28-0138-8332-9ed4-b71b6084f608

Adapt this model to my problem

We should add a suppressive immune compartment



The background features several stylized red cells with dark brown nuclei and small protrusions on their surfaces. In the bottom right corner, there is a stylized red mouse with a white belly and a long tail. A large, light beige rounded rectangle is centered on the page, containing the text.

Experimental Integration

Experimental design



Aim:

Determine the effect of lymphodepletion on the generation of an immunosuppressive non-favorable environment prior to CAR-T cell infusion.

Hypothesis

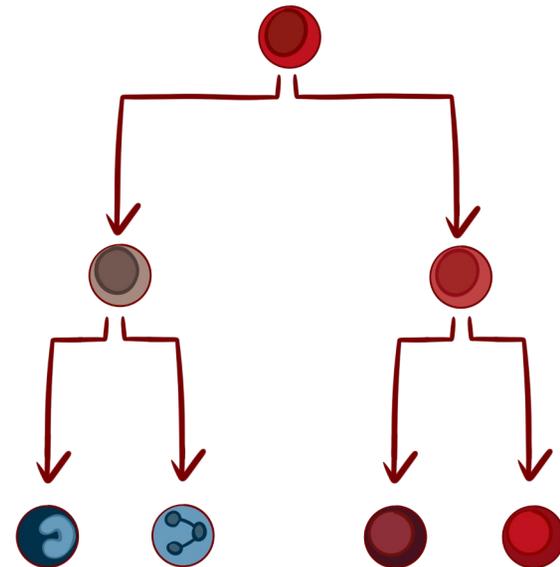
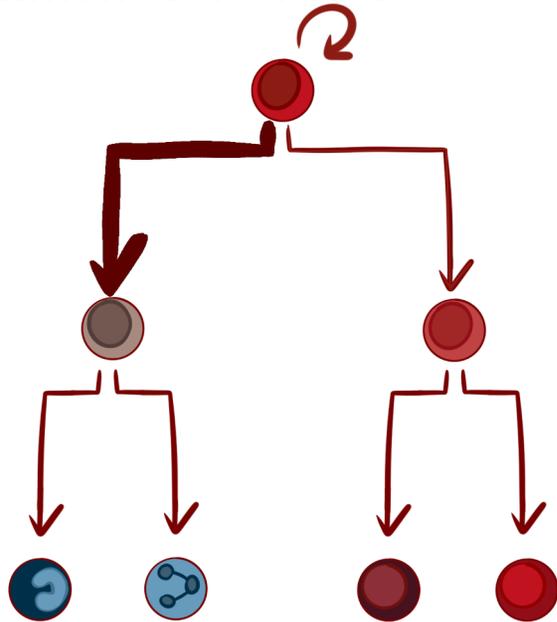
We hypothesize that targeting myeloid suppression and myelopoiesis represents a promising avenue for prophylactic intervention to improve CAR-T therapy.



Dampening myelopoiesis to restore a favorable environment



- How do lymphodepletion regimens affect myelopoiesis and immune cell repopulation?
- Can we inhibit stress-induced myelopoiesis to restore a favorable environment for CAR-T cells?



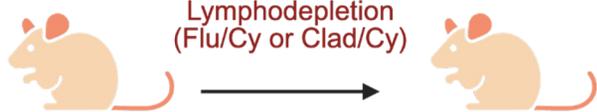
Dampening myelopoiesis to restore a favorable environment



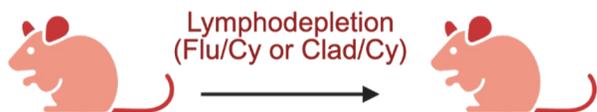
Abiotic intervention:

- How do lymphodepletion regimens affect myelopoiesis and immune cell repopulation?
- Can we inhibit stress-induced myelopoiesis to restore a favorable environment for CAR-T cells?

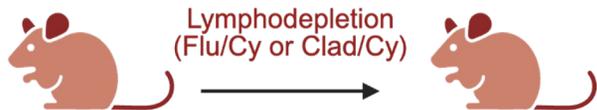
CTRL



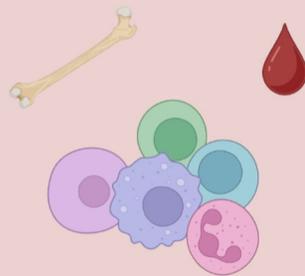
Anakinra



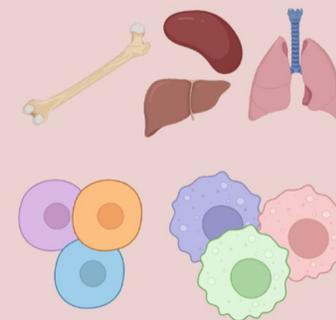
IL1R1KO



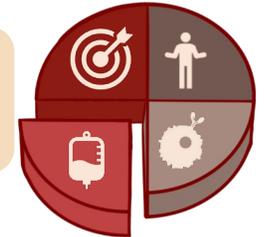
Blood and bone marrow analysis at different time points to characterize cell repopulation



Emergency myelopoiesis and tissue macrophages analysis

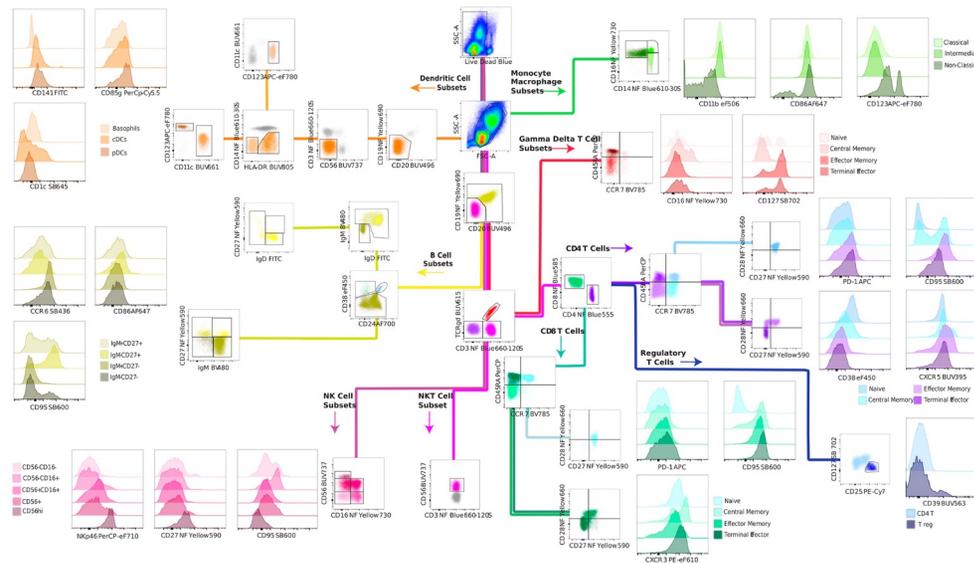


Immunophenotype of peripheral blood immune cells



- Can we identify immune cell targets in pre/post- CAR-T infusion samples associated with CAR-T response?

35 parameter-flow panel



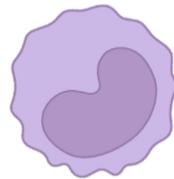
Modeling macrophage states



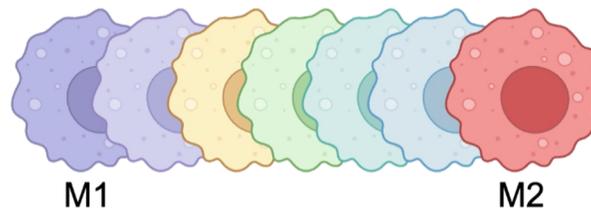
- How are differentiated macrophages affected by lymphodepletion, and how do they affect CAR-T therapy?

Mathematical and experimental model to mimic macrophage functional states

Monocyte



Macrophages



Budget: \$50,000



Supplies:

Mice: \$2,000

Flow antibodies: \$3,000

Chemicals: \$5,000

Enzymes: \$500

Cytokines: \$500

Cell isolation kits: \$1,000

Reagents: \$500

Plastics: \$500

Personnel:

Postdoc (Immunology): \$10,000

Postdoc (IMO): \$10,000

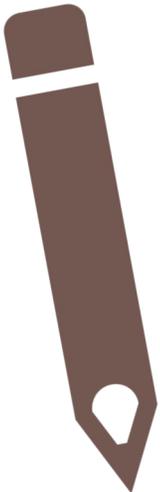
Other expenses:

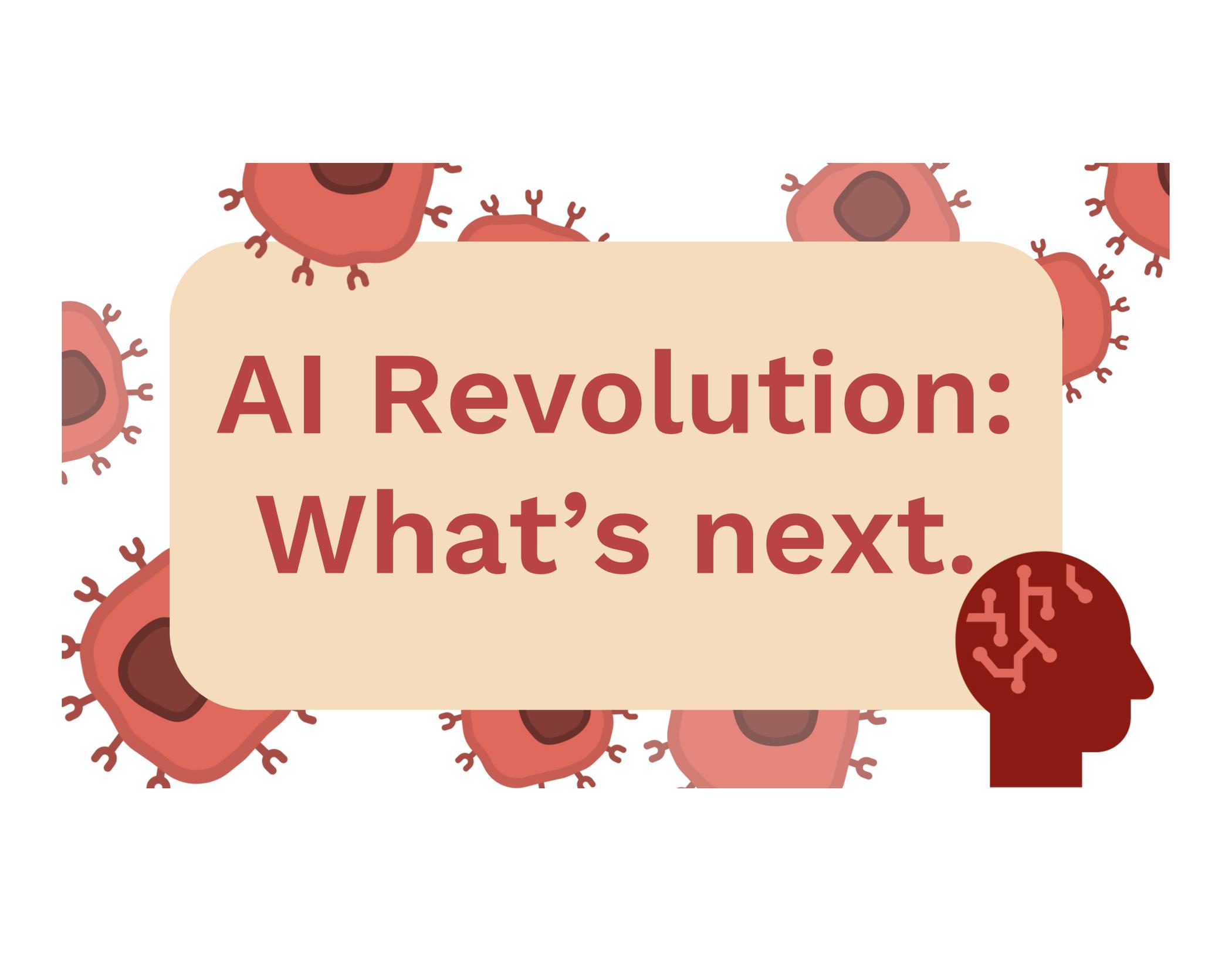
Mouse facility: \$6,000

Flow core: \$1,000

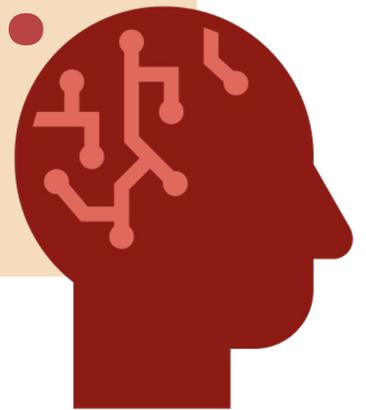
Tissue Core: \$9,994.67

AI team (OpenAI): \$5.33

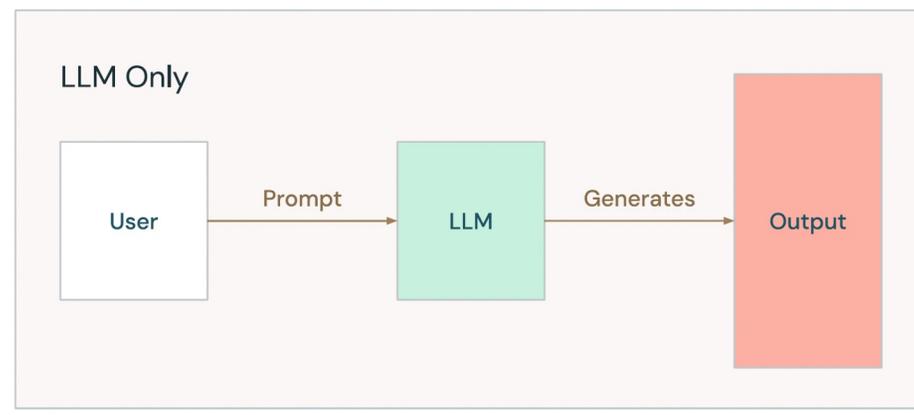




AI Revolution: What's next.



Interaction with LLMs



Pros

Easy

Effective (especially with recent iteration)

Cons

Can hallucinate

Not grounded on domain specific knowledge

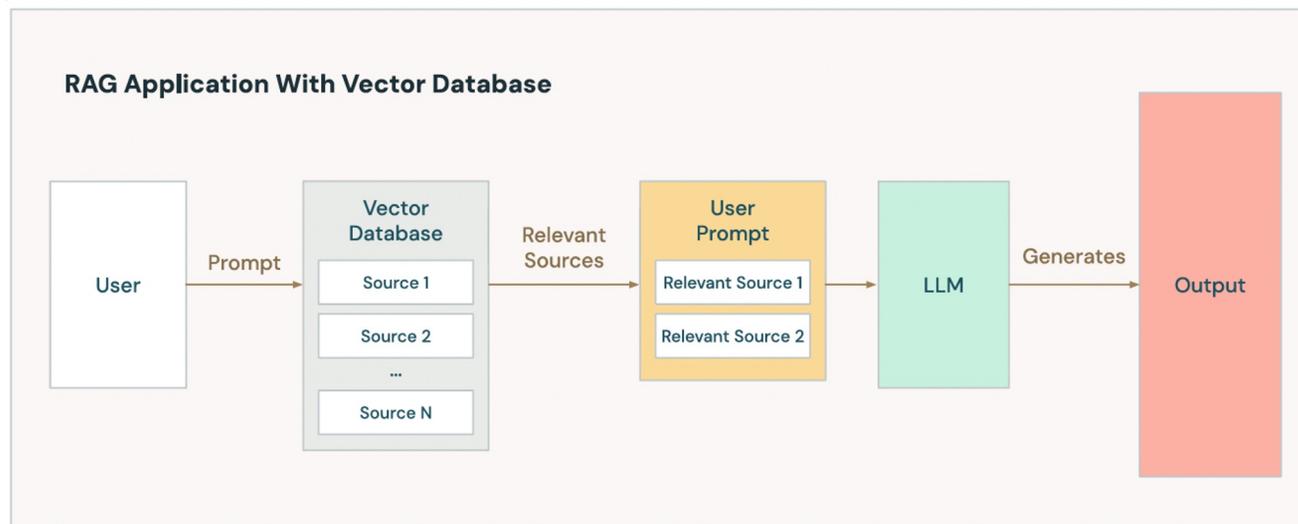


Interaction with LLMs: RAGs

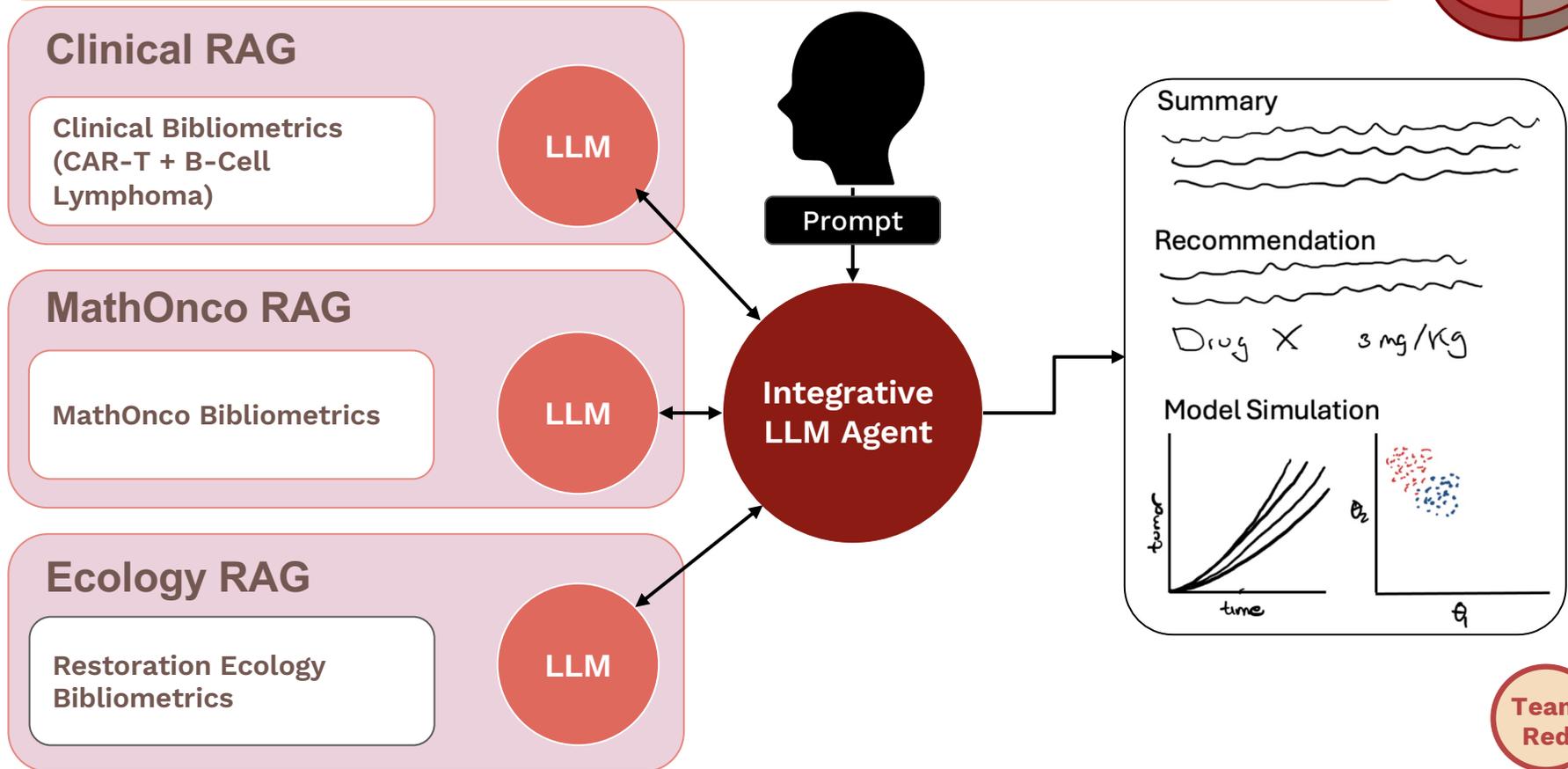


Retrieval-Augmented Generation is a technique to ground LLMs on a database of knowledge

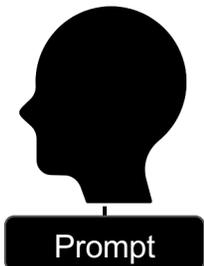
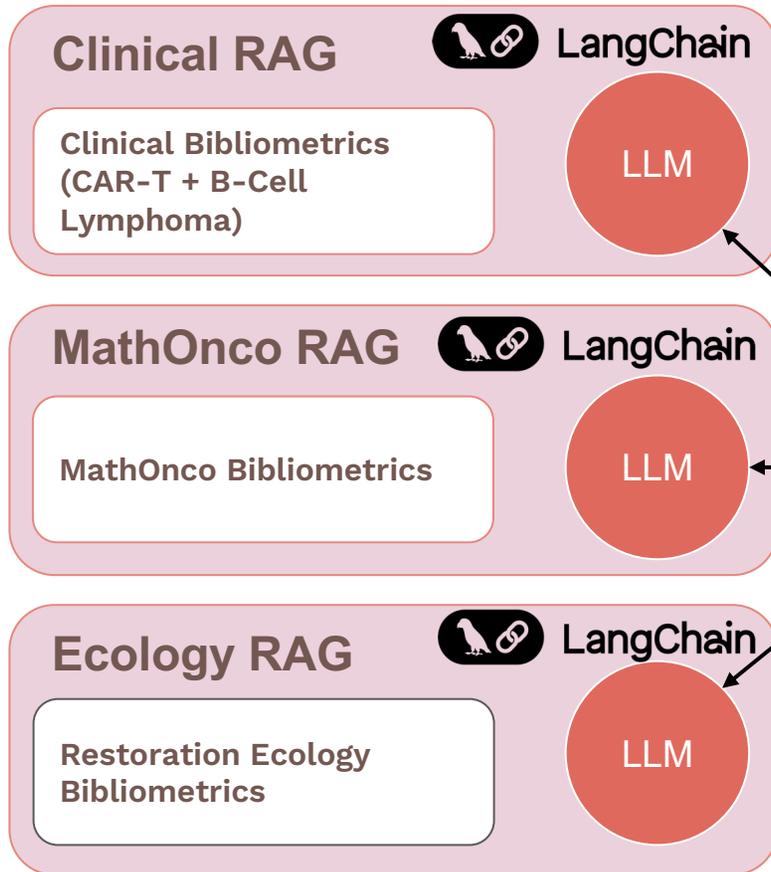
Efficient search using embeddings
Grounded on knowledge
Ensures privacy



Interaction with LLMs: RAGs



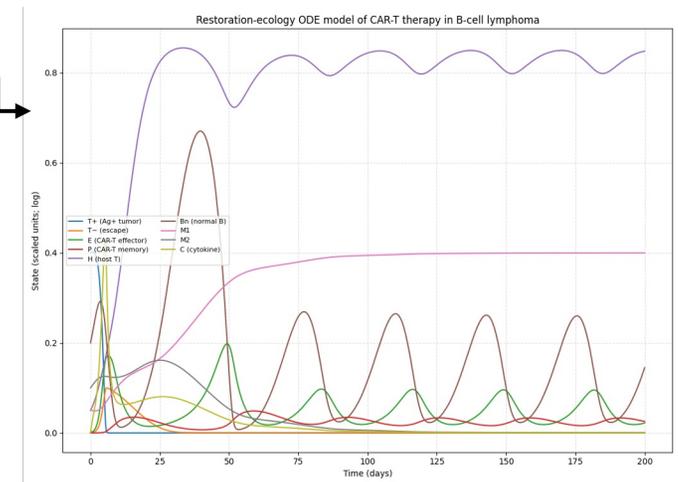
Interaction with LLMs: RAGs



A restoration-ecology ODE model of CAR-T therapy for B-cell lymphomas

Abstract (≤300 words)

We propose an original ordinary differential equations (ODE) model of CAR-T therapy for B-cell lymphomas that explicitly blends restoration ecology and tumor immunobiology. The lymphoma is framed as an invasive species displacing a native community (normal B cells and healthy immunity). CAR-T cells are an introduced predator to restore ecosystem balance. The model tracks nine interacting “functional groups”: antigen-positive tumor (T+), antigen-negative escape (T-), CAR-T effectors (E), CAR-T memory/persistent cells (P), host T cells (H), normal B cells (Bn), macrophages (M1/M2), and an aggregate inflammatory cytokine (C, e.g., IL-6). Interactions include saturating CAR-T predation and antigen-driven expansion, macrophage polarization (M1↔M2) that modulates efficacy, niche competition among lymphoid lineages, and trogocytosis-driven antigen loss.



Conclusion



In this work, we explored CAR-T therapy in B-Cell Lymphomas from a revolutionary angle (restoration ecology) using a revolutionary methodology (AI-assisted research), for a revolutionary clinical impact (prophylactic myelopoiesis inhibition).

- Generated math modeling to improve CAR-T through holistic, ecological approach, inspired by clinical and preclinical data
- Developed experimental plan to measure myeloid suppression and emergency myelopoiesis
- Demonstrated the possibility of rapid math model prototyping using AI leveraging the context to generate novel fully implemented ideas



The background of the slide is decorated with several stylized red blood cells. Each cell is depicted as a red, roughly circular shape with a darker red nucleus in the center and several small, Y-shaped cilia extending from its surface. The cells are scattered around a central, light beige rounded rectangle.

Thank You!

Team RED

Allegra Love, Francois de Kermenguy, Gopinath Sadhu, Jill Gallaher, Konstantinos Mamis, Lavonte Saunders, Reshmi Patel, Shambhavi Kurup, Ari Barnett, Franco Pradelli, Sadegh Marzban, Martina Molgora, Sayeef Mirza, Jeffrey West