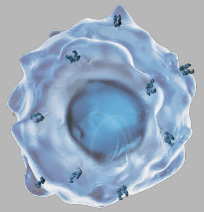
CAR T Cell Therapy in B-cell Acute Lymphoblastic Leukemia

Jasmin Jean-Louis and Kristen Mosley
Dr.Kara
Math Modeling

Background and Motivation

CAR T cell therapy is a growing form of treatment for cancer patients that uses gene-transfer technology to instruct T lymphocytes to recognize and kill cancer cells. Because it is still evolving, and clinical trials are showing positive results, there are a lot of unanswered questions.

Mathematical models can provide a mechanistic understanding of oncological treatments, and can help to find the best strategies to improve treatment outcomes.

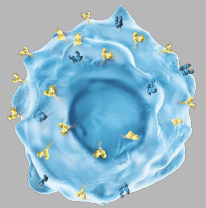


T Cell

A key fighter in the immune system

CAR

A specific receptor is added to the T cell



CAR T Cell

The T cell with the CAR added helps find and fight specific targeted cells

Summary

- For clinical application of CARs, the patient's T cells are obtained, genetically engineered ex vivo to express the synthetic receptor, expanded and infused back into the patient.
- Success in trials have led to the approval of CAR T therapies for use against CD19 for treatment of B-ALL and diffuse large B-cell lymphomas.
- Patients relapse despite the success of CAR T cell therapy.

CD19

Cell surface protein that is restricted to B cell lymphocytes (neoplastic or normal)

B-ALL

B-Cell Acute Lymphoblastic Leukaemia

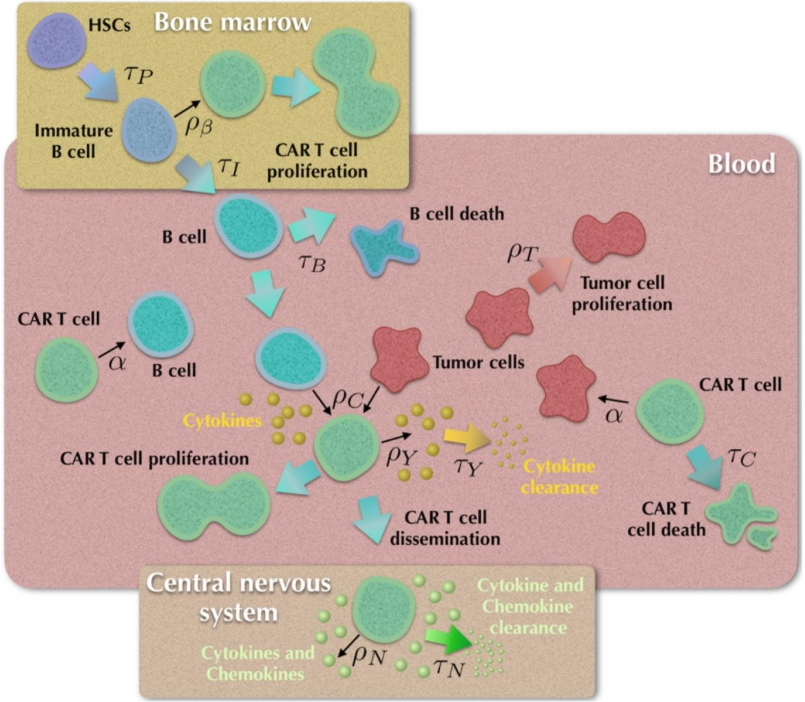
Cancer that affects B lymphocytes in a bone marrow cell

Scientific Question

How does the number of CAR T cells in a leukemia patient affect the outcome of the treatment?

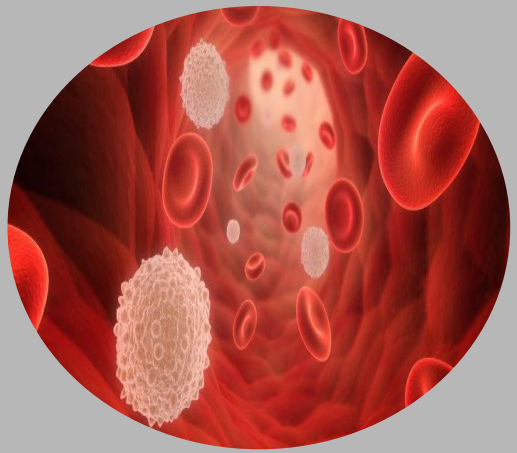
How can we control $CD19^{+}$ relapses by re-challenging the cancer early with CAR T cells?

The Approach



The Approach

They use Lotka-Volterra predator-prey dynamics to predict that CD19 cancer relapses could be the result of competition between leukemia and CAR T cells.



Within the model, they account for the contribution of generations of new B-cells while simplifying the system.

After CAR T injection, they add the expansion of the cells and their effect on the leukemia and healthy B cells.

ODE Terms

The model accounts for the evolution over time of several interacting cellular populations distributed into five compartments.

C(t)	Number of CAR T cells	$\frac{dC}{dt} = \rho_C(L+B)C + \rho_\beta IC - \frac{1}{\tau_C}C$
L(t)	Number of leukemic cells	$\frac{dL}{dt} = \rho_L L - \alpha LC$
B(t)	Number of mature healthy B cells	$\frac{dB}{dt} = \frac{1}{\tau_I}I - \alpha BC - \frac{1}{\tau_B}B$
P(t)	$CD19^-$ haematopoietic stem cells (HSCs)	$\frac{dP}{dt} = \rho_P(2a_P s(t) - 1)P - \frac{1}{\tau_P}P$
I(t)	$CD19^+$ B cell progenitors	$\frac{dI}{dt} = \rho_I(2a_I s(t) - 1)I - \frac{1}{\tau_I}I + \frac{1}{\tau_P}P - \alpha\beta IC$

In the differential equations, there is no death term for C(t) because the CAR T cells do not undergo apoptosis (death)

ODE Terms

Parameter	Meaning	Value	Units
τ_B	B-lymphocyte lifetime	$30 - 60$	day
ρ_L	Leukaemic growth rates	$1/30 - 1/60$	day^{-1}
τ_C	Activated CAR T cell lifetime	$14 - 30$	day
ρ_C	Mitotic stimulation of CAR T cells by $CD19^+$ cells	$(0.05 - 2) \times \alpha$	day^{-1} $\times$ cell^{-1}
α	Killing efficiency of CAR T cells	$\sim 10^{-11}$	day^{-1} $\times$ cell^{-1}
k	ρ_C and α ratio	$0.05 - 2$	dimensionless
τ_I	Immature bone marrow B cell lifetime	$2 - 6$	day
β	Fraction of CAR T cells in the bone marrow	$0.01 - 0.5$	dimensionless

$$\frac{dC}{dt} = \rho_C(L+B)C + \rho_\beta IC - \frac{1}{\tau_C}C$$

$$\frac{dL}{dt} = \rho_L L - \alpha LC$$

$$\frac{dB}{dt} = \frac{1}{\tau_I}I - \alpha BC - \frac{1}{\tau_B}B$$

$$\frac{dP}{dt} = \rho_P(2a_P s(t) - 1)P - \frac{1}{\tau_P}P$$

$$\frac{dI}{dt} = \rho_I(2a_I s(t) - 1)I - \frac{1}{\tau_I}I + \frac{1}{\tau_P}P - \alpha\beta IC$$

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Results and Conclusions

- The number of CAR T cells initially injected does not affect the subsequent dynamics.
  - Doctors should store part of the cells generated so they can be ready for later rechallenging in case of a $CD19^{+}$ relapse
  - Periodic treatment with CAR T cells is ineffective in avoiding relapse and the model provides optimal time for re-injection
- To combat the disease, fast action after detection and an injection of a substantial number of CAR T cells is essential.
- Role of the flux of generation of $CD19^{+}$ progenitors from CD19- hematopoietic stem cells
  - Future research should consider the pharmacological stimulation of the process of stem cell asymmetric division and separation.

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Results

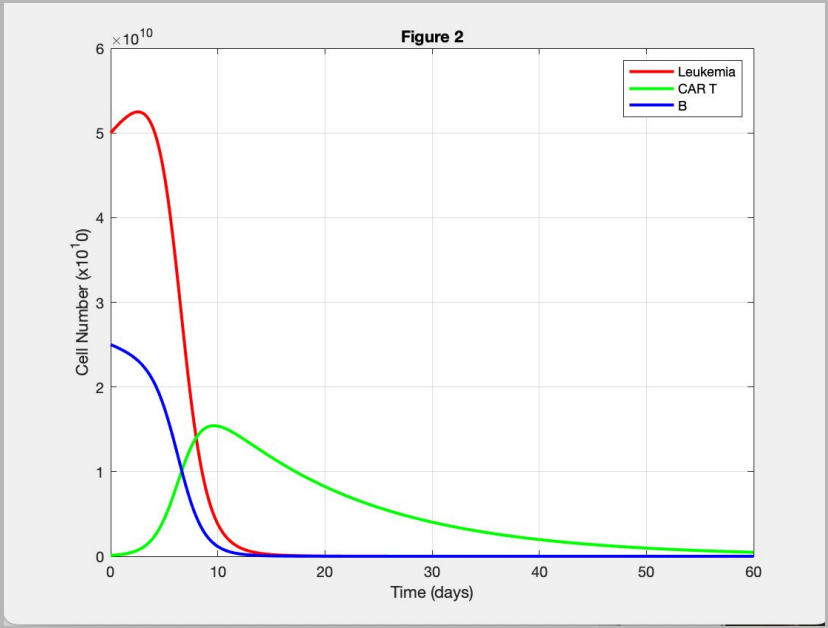
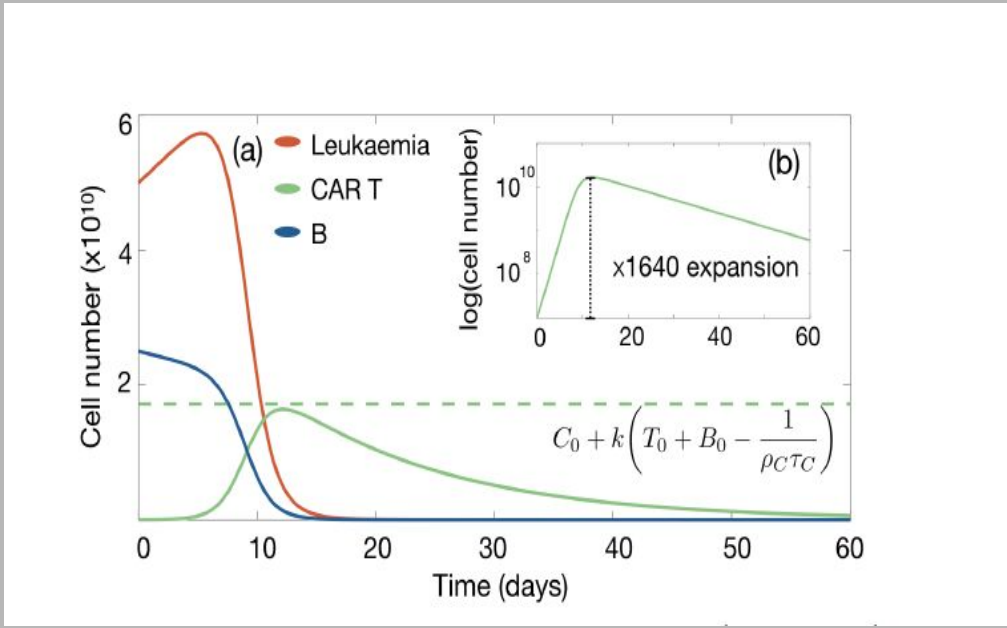


Figure 2
×10^10
Leukemia
CAR T
B
Cell Number (x10^10)
Time (days)


(a)
Leukaemia
CAR T
B
Cell number (x10¹⁰)
Time (days)
(b)
log(cell number)
x1640 expansion
$C_0 + k\left(T_0 + B_0 - \frac{1}{\rho_C \tau_C}\right)$

Results

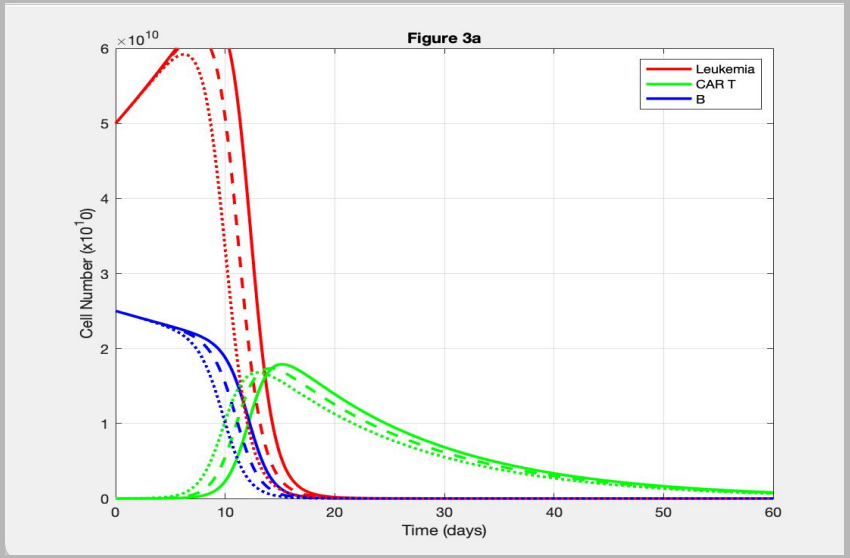
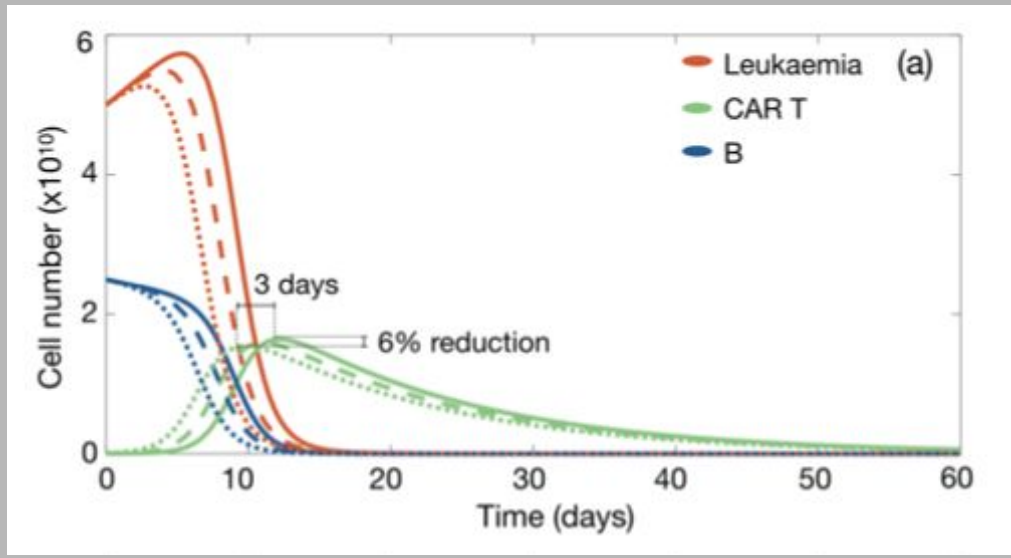


Figure 3a
×10^10
Leukemia
CAR T
B
Cell Number (x10^10)
Time (days)
0
1
2
3
4
5
6
0
10
20
30
40
50
60


Leukaemia
(a)
CAR T
B
3 days
6% reduction
Cell number (x10^10)
Time (days)
0
2
4
6
0
10
20
30
40
50
60

Results

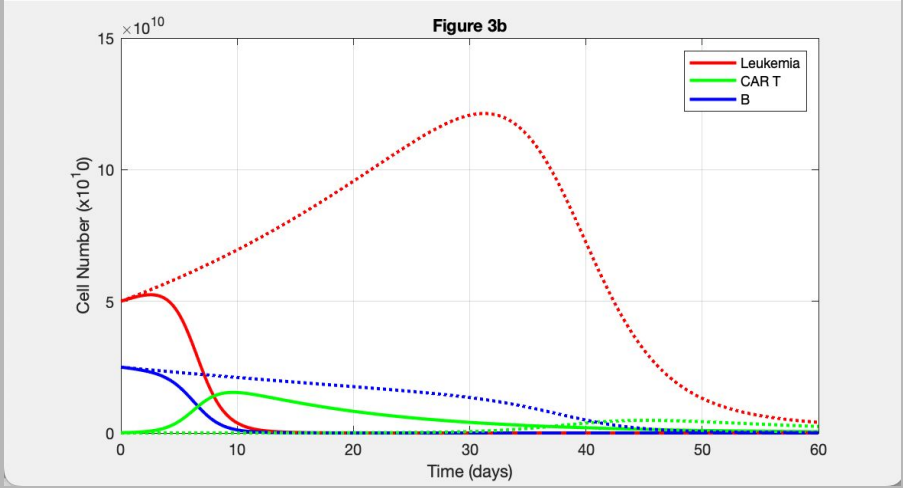
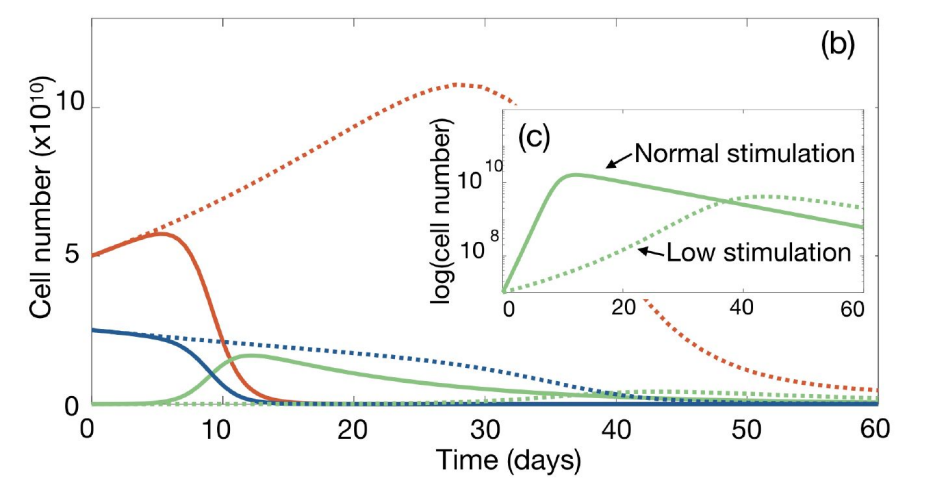


Figure 3b
×10^10
15
10
5
0
Cell Number (x10^10)
0
10
20
30
40
50
60
Time (days)
Leukemia
CAR T
B


(b)
Cell number (x10^10)
10
5
0
0
10
20
30
40
50
60
Time (days)
(c)
log(cell number)
10^10
10^8
Normal stimulation
Low stimulation
0
20
40
60

Results

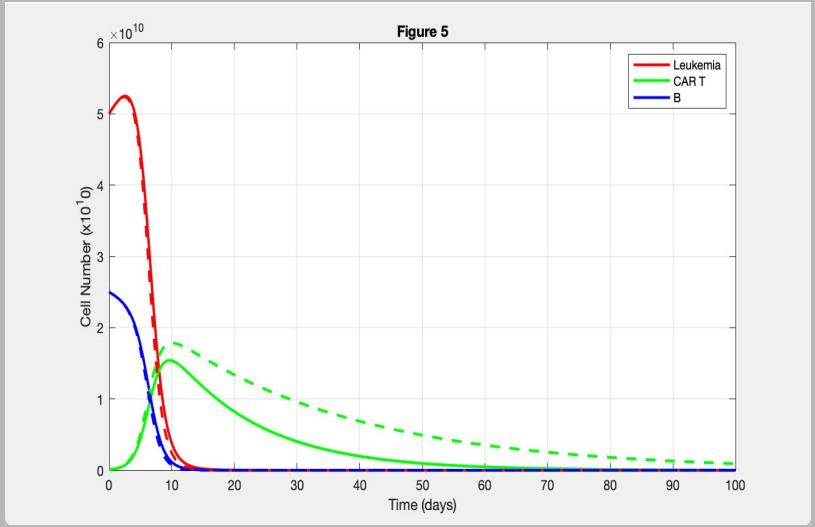
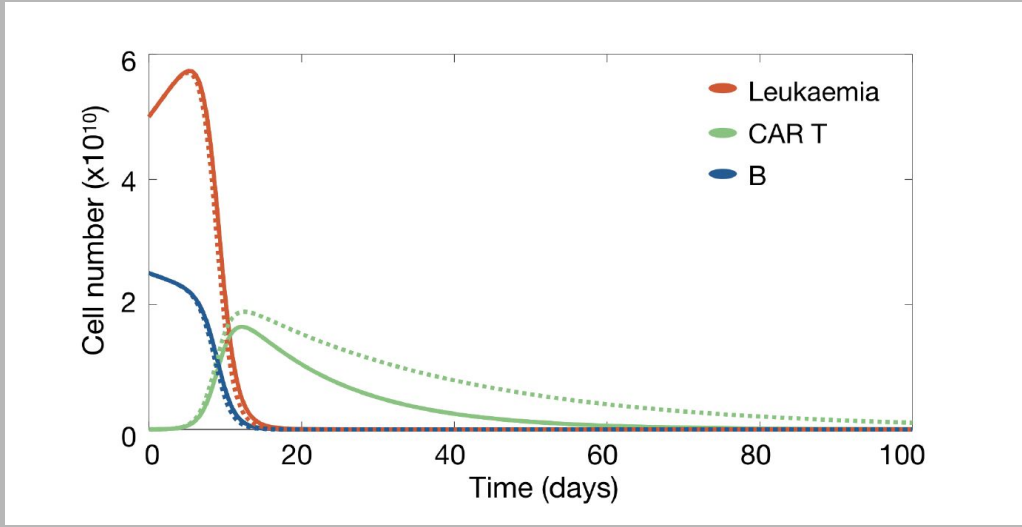


Figure 5
×10^10
Leukemia
CAR T
B
Cell Number (x10^10)
Time (days)


Leukaemia
CAR T
B
Cell number (x10^10)
Time (days)

Results

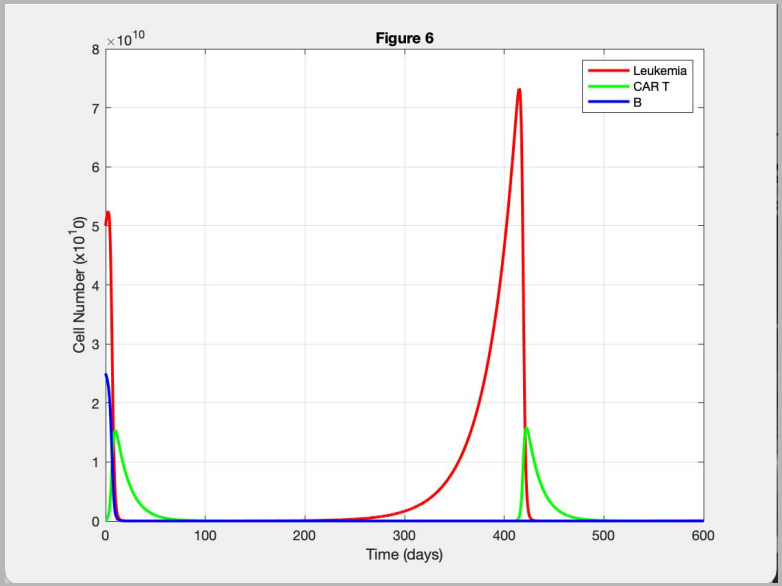
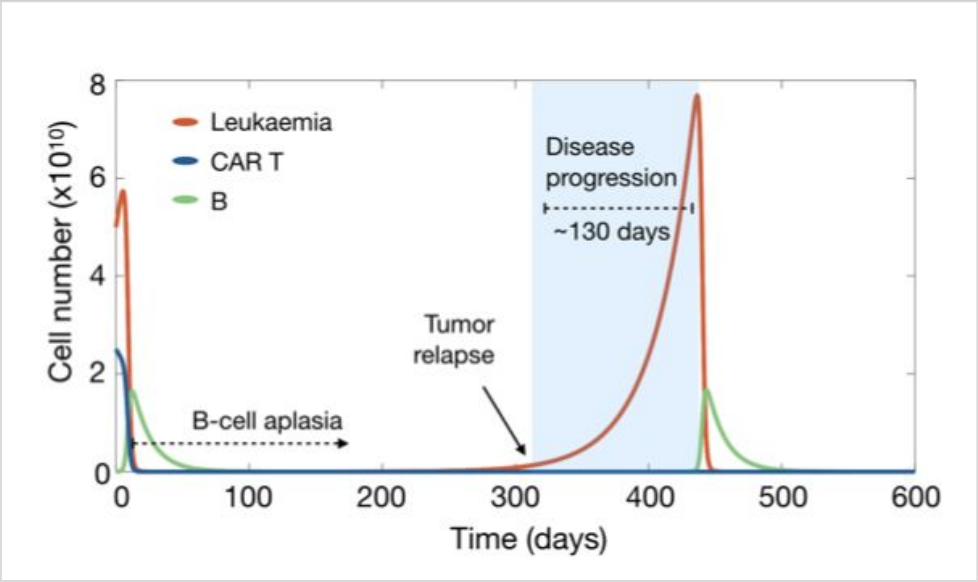


Figure 6
×10^10
Leukemia
CAR T
B
Cell Number (x10^10)
Time (days)


Leukaemia
CAR T
B
Disease progression
~130 days
Tumor relapse
B-cell aplasia
Cell number (x10^10)
Time (days)

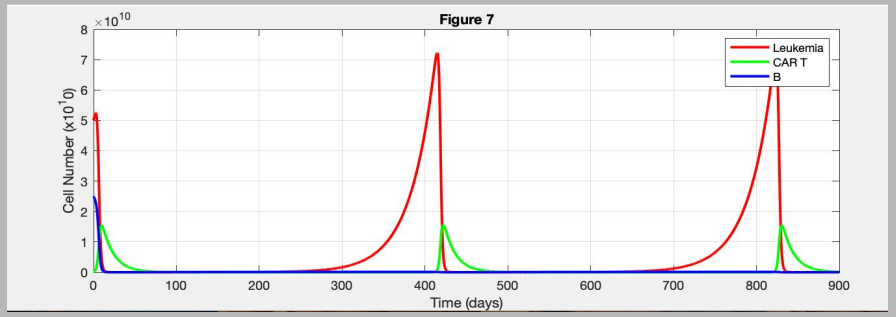


Figure 7
×10^10
Cell Number (x10^10)
Time (days)
Leukemia
CAR T
B

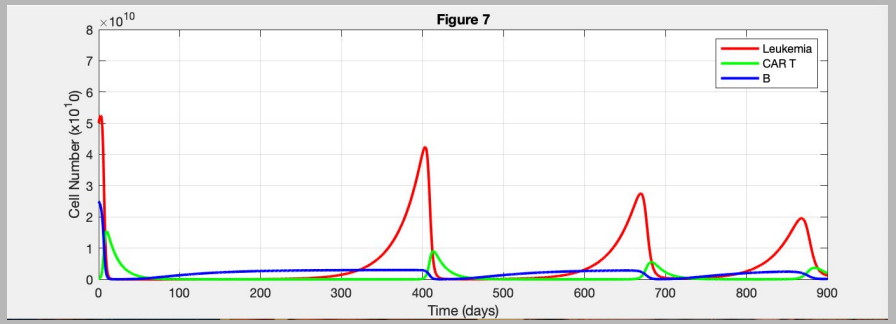


Figure 7
×10^10
Cell Number (x10^10)
Time (days)
Leukemia
CAR T
B

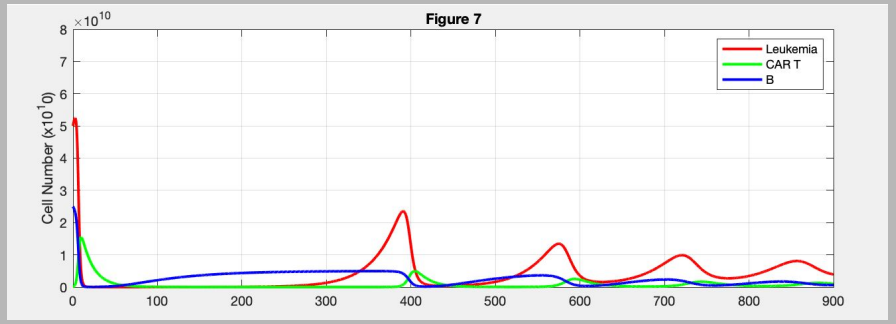
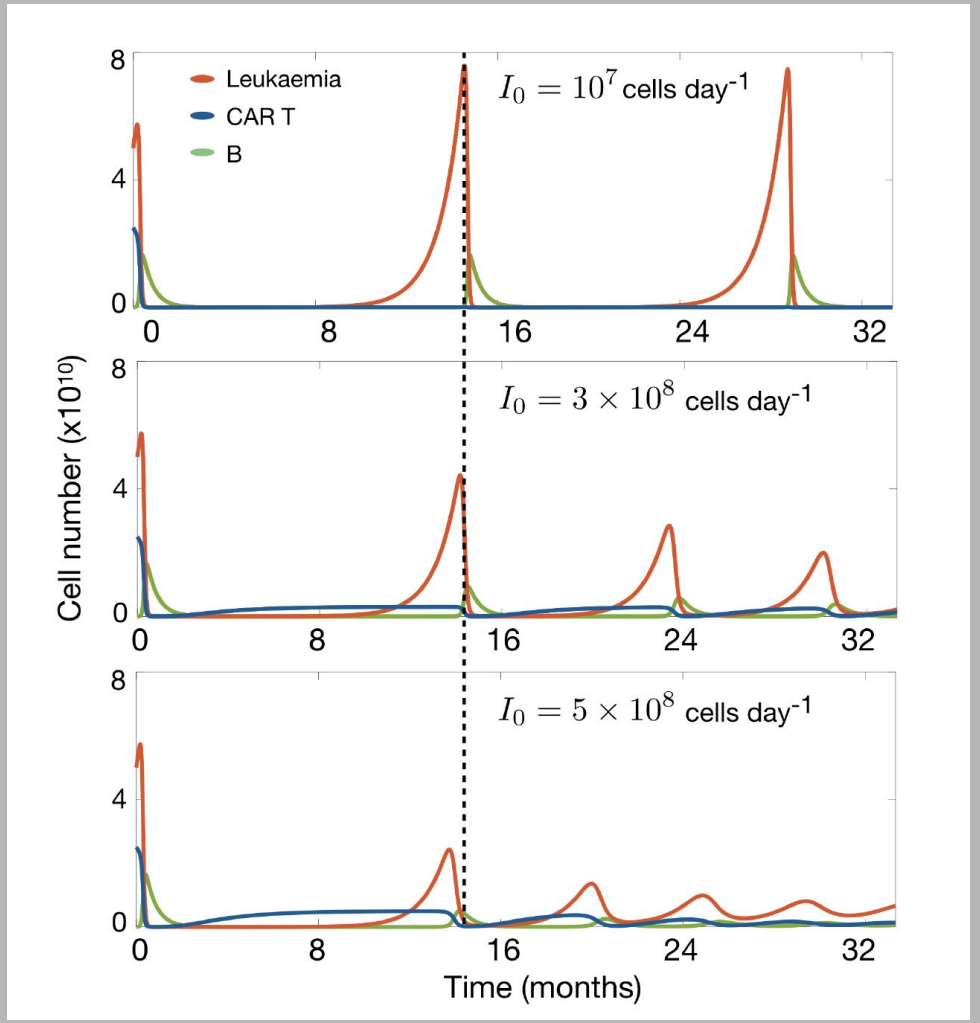


Figure 7
×10^10
Cell Number (x10^10)
Leukemia
CAR T
B


Leukaemia
CAR T
B
$I_0 = 10^7$ cells day^{-1}
$I_0 = 3 \times 10^8$ cells day^{-1}
$I_0 = 5 \times 10^8$ cells day^{-1}
Cell number (x10^{10})
Time (months)