

# Agent-Based Simulation of CAR-T Cell Therapy Using BioDynaMo

Progress update of Google Summer of Code Project 2025



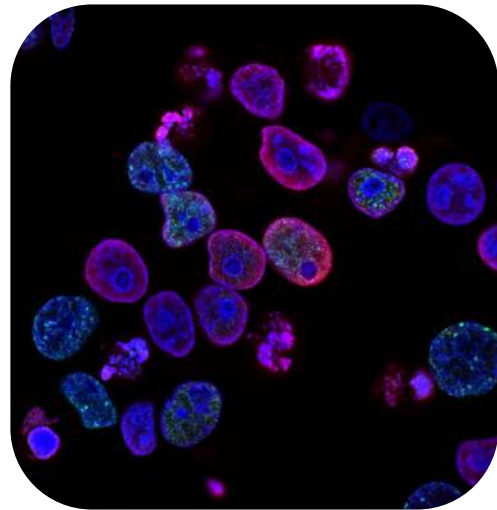
Author: Salvador de la Torre Gonzalez

Mentors: Vassil Vassilev, Lukas Breitwieser

# CAR-T Therapy & the Challenge

**CAR-T therapy:** A type of immunotherapy that engineers T-cells to recognize and kill cancer cells.

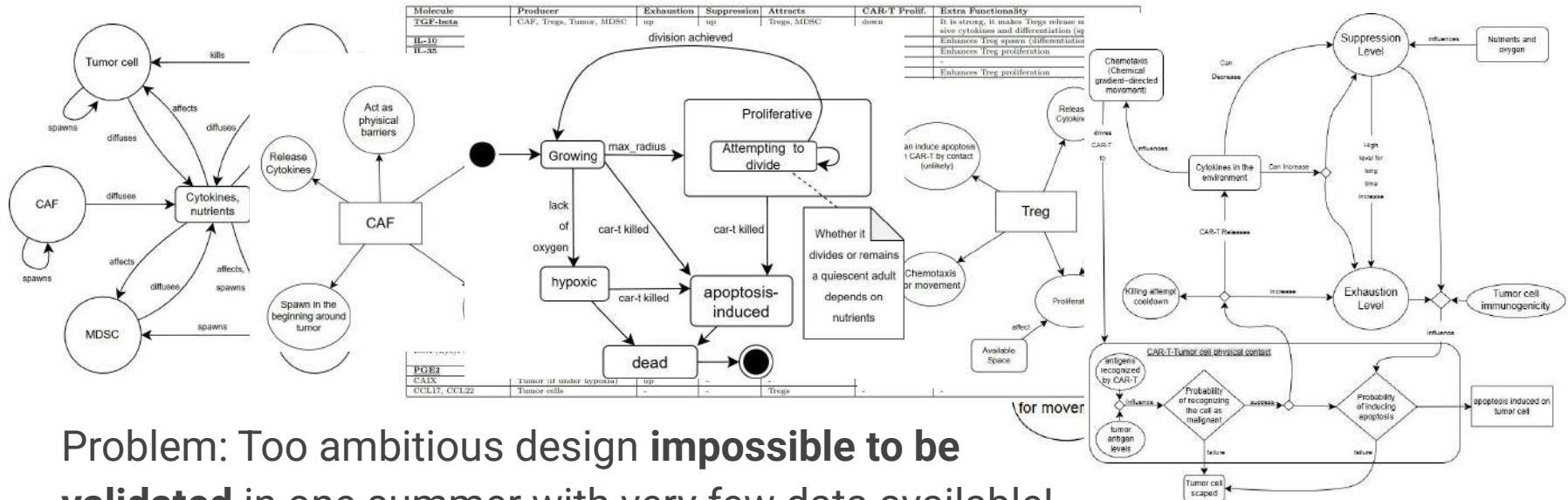
- Proven effective in **leukemia** and other **hematological** cancers.
  - In the literature, many **robust models**—typically based on differential equations—simulate CAR-T treatment in blood cancers.
- However, CAR-T still **struggles in solid tumors** due to unique tumor microenvironmental factors.
  - Researchers need models to try different treatment techniques and scenarios in order to improve CAR-T performance. However, **very few models** exist for these types of cancers, and much less data is available.



# CAR-T Simulation in BioDynaMo

**Objective:** Implement solid tumor CAR-T treatment using an agent-based simulation on **BioDynaMo**, a high-performance, open-source simulation platform ideal for capturing these microenvironmental interactions.

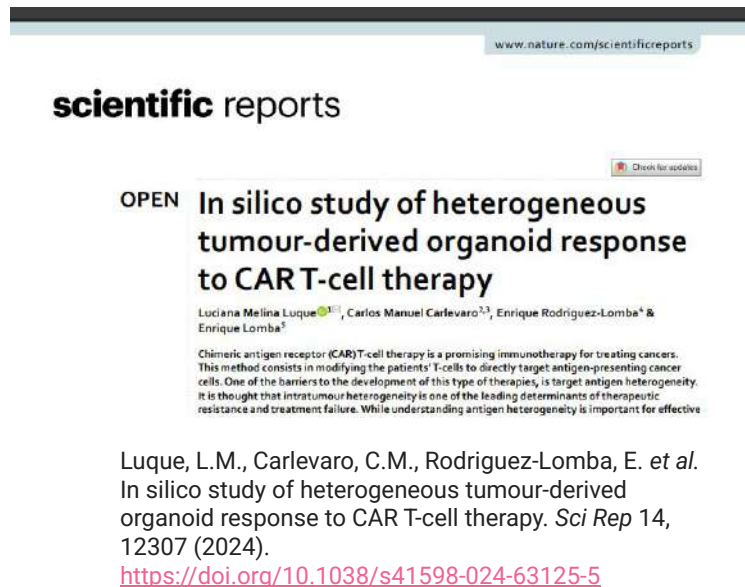
In the beginning, I designed an agent-based model on my own, by reading papers and trying to include all relevant biological dynamics. And I even implemented on BioDynaMo a third of it...



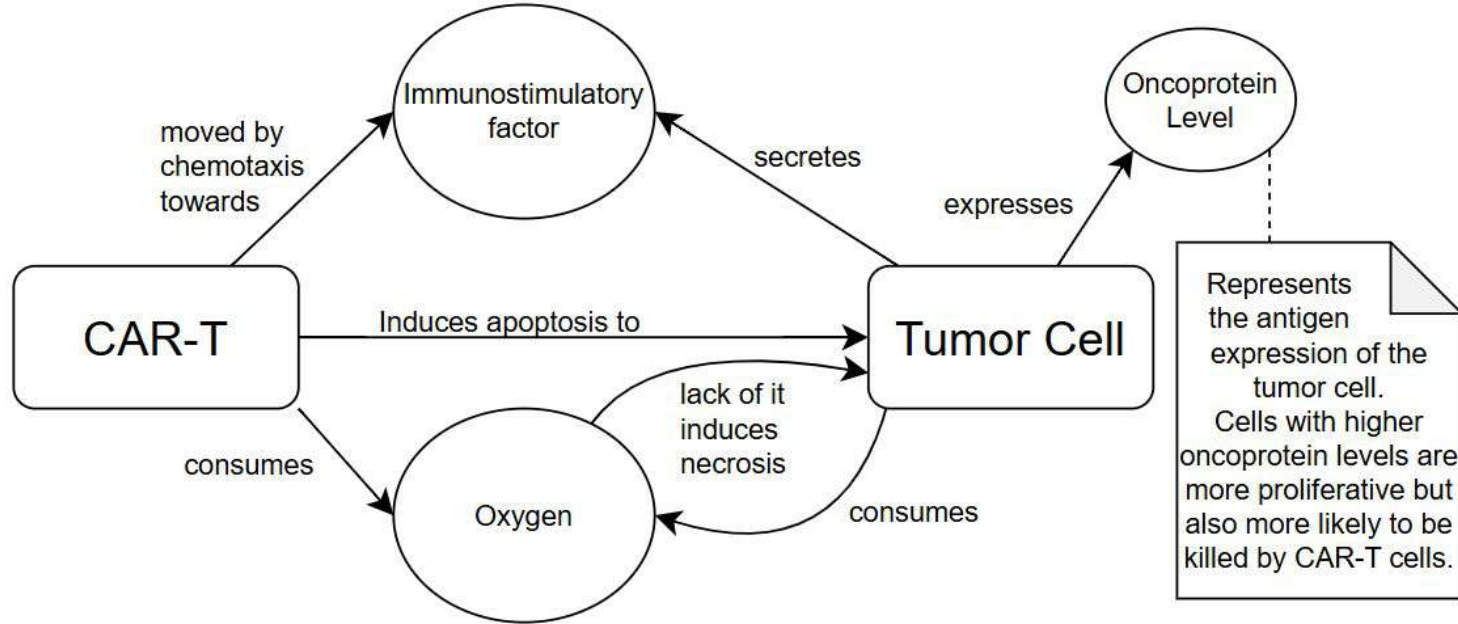
Problem: Too ambitious design **impossible to be validated** in one summer with very few data available!

# The Nature Paper

- Agent-based simulation modeling CAR-T cell therapy in in vitro **tumor-derived organoids**.
- Aims to allow **testing** of multiple therapeutic strategies **without the cost and time** of lab experiments.
- The research team that wrote it spent **six months solely tuning hyperparameters** with real data!
- Aim: Develop a similar simulation simulation in BioDynaMo and **replicate their results**.
  - Main advantages of BioDynaMo:
    - **Faster** simulations -> More scenarios can be tested
    - Code is much more **accessible, modular** and suitable for **future extensions**

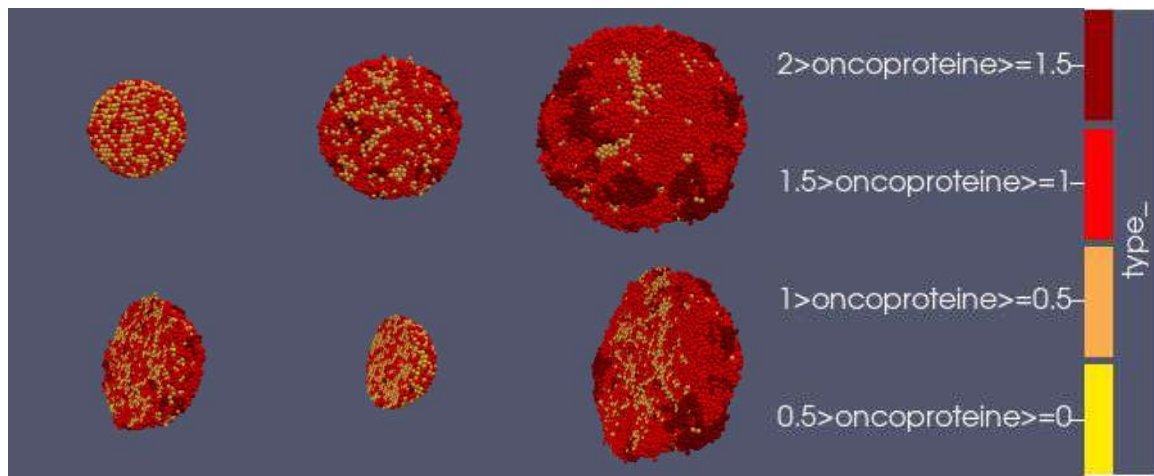


# The model



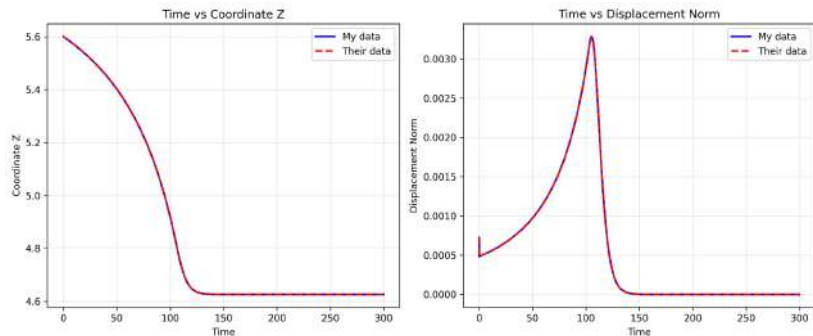
# What have I achieved so far?: Tumor Replication

- Tumor inspired by and **calibrated using liver carcinoma data**.
- Main components already implemented:
  - Chemical **diffusion module** solving the corresponding differential equations, with agents **consuming** and **secreting** substances.
  - **Forces module** computing repulsion between overlapping cells and adhesion dynamics.
  - **Tumor cell** agent with state control, **volume changes**, and **division** influenced by oxygen and oncoprotein levels, as well as **apoptosis** and **necrosis** with swelling and lysis phases.

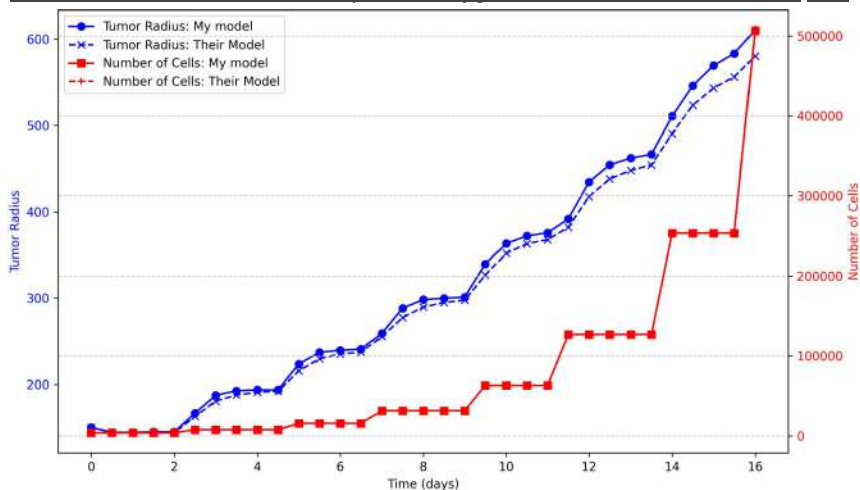


# Some plots comparing both models for testing the different modules

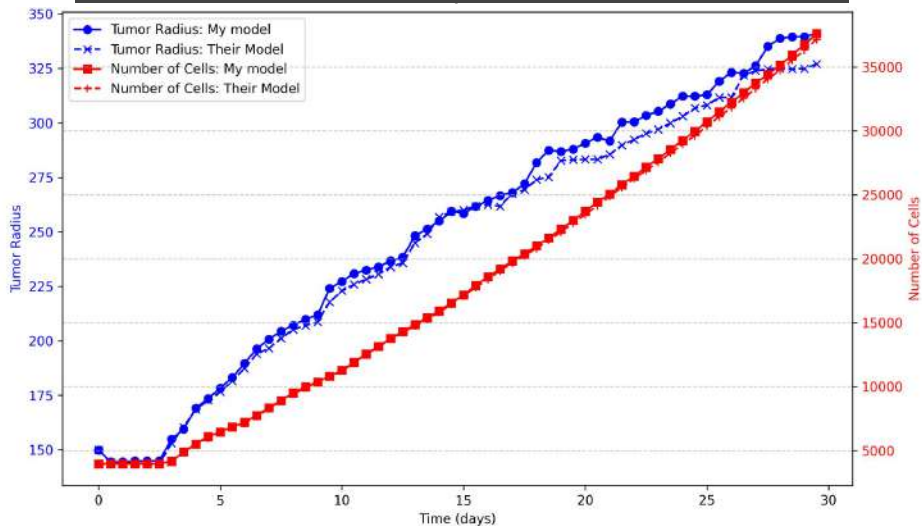
Displacement computed by the forces module between two cells



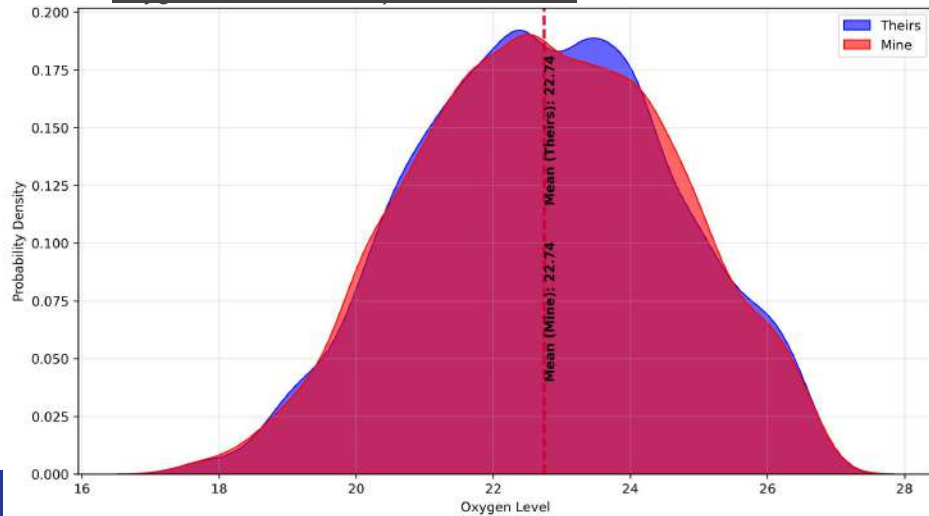
Tumor evolution with fixed oncoprotein, oxygen level and constant random rate



Tumor evolution with fixed oncoprotein and constant random rate



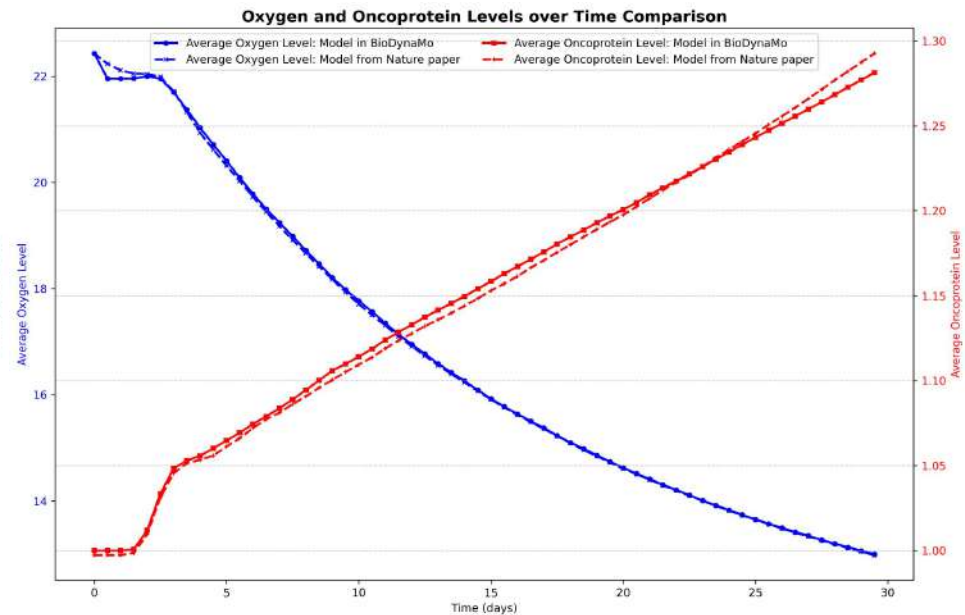
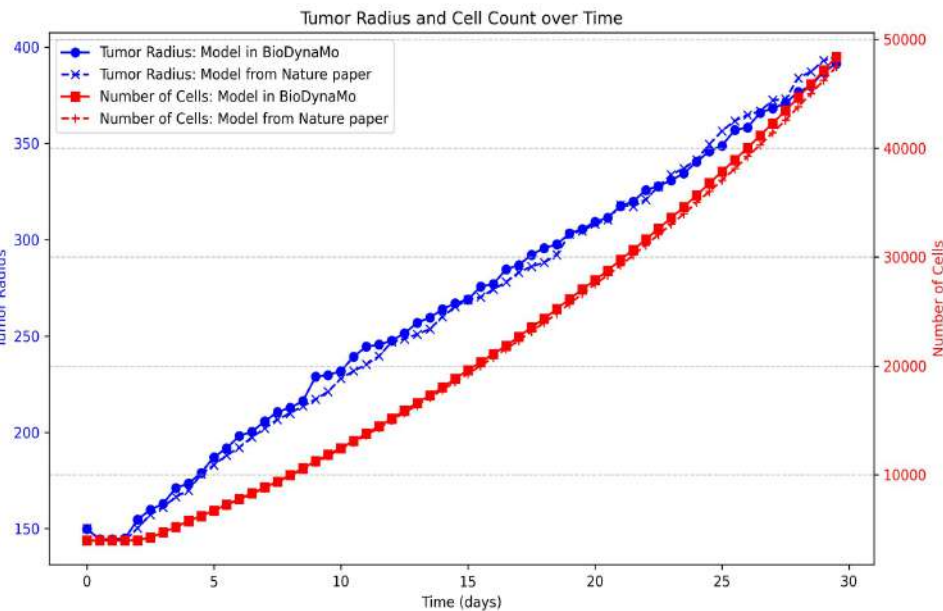
Oxygen levels in a 150  $\mu\text{m}$  radius tumor





# Evolution of a 150 $\mu\text{m}$ radius tumor with no CAR-T treatment: models comparison

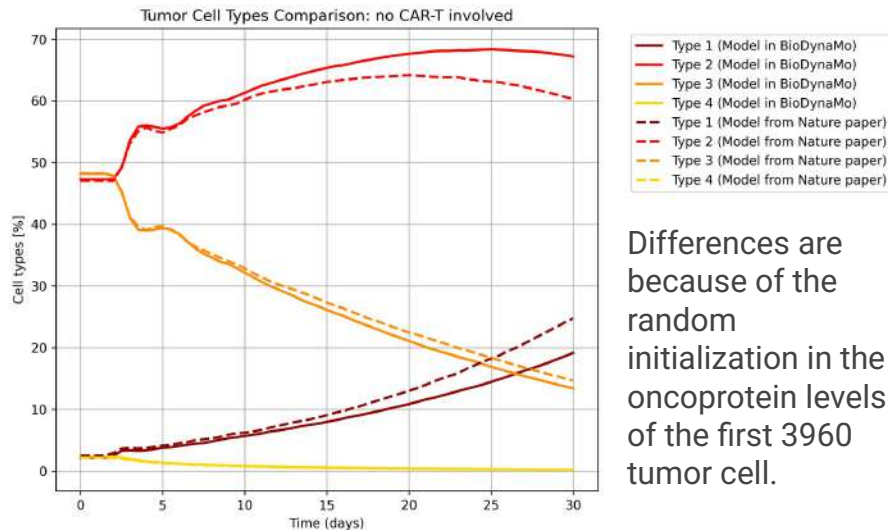
- As the tumor grows:
  - The oxygen levels lessen: more cells means more oxygen consumption.
  - The average oncoprotein level increases: cells with higher levels are more proliferative and since the oncoprotein is inherited in division the average value goes up in time.





**Oncoprotein levels** are continuous, but cells are grouped into four **types (1–4, high → low)**.

- Type 1 cells: they are the **most proliferative** so their proportion in the tumor **increases**.
- Type 3–4 cells: **divide less frequently** and lose oxygen in a **resource-competitive** environment. Therefore become **less and less common**.



Differences are because of the random initialization in the oncoprotein levels of the first 3960 tumor cell.

## Performance Comparison:

Preliminary execution time comparison for a 30 days simulation (AMD Ryzen 5 3600, 6 cores / 12 threads, 16 GB RAM):

- Mine:  $\approx 8,982$  hours
- Theirs:  $\approx 18,848$  hours
  - My (yet unoptimized) model in BioDynaMo is more than **twice as fast**.

# What's the next goal?

- Add **CAR-T** (already in progress)
- Add **parameter files** to allow modification without recompiling
- Clean and **polish the code**
- Write a **scientific-style document** describing the model, and **results** replicating the Nature paper findings.
- In the long term: Extend the simulation to include immunosuppressive chemicals and secreting agents (**T-regs**). Compare different **patient and treatment scenarios** for example:
  - Reduce oxygen levels to study hypoxia and necrosis (already implemented).
  - Study higher proliferation rates, as occurs in pediatric tumors.
  - Some people present with more rigid tissues, which result in higher cell forces that can affect CAR-T tumor infiltration.

