Proceeding Series of the Brazilian Society of Computational and Applied Mathematics, v. 11, n. 1, 2025.

Trabalho apresentado no XLIII CNMAC, Centro de Convenções do Armação Resort - Porto de Galinhas - PE, 2024

Proceeding Series of the Brazilian Society of Computational and Applied Mathematics

CAR-T Cell Therapy Resistance Modeling

Orlando W. Sudré Júnior[1]
Emanuelle A. Paixão[2]
Regina C. Almeida[3]
Laboratório Nacional de Computação Científica – LNCC, Petrópolis, RJ

Last year, Brazil's Anvisa approved immunotherapy using CAR-T cells, a groundbreaking oncological treatment. It involves extracting T lymphocytes from the patient, genetically modifying them to target the tumor's specific antigen (Ag), and expanding them in culture. Upon reintroduction into the patient, these cells effectively identify and eliminate cancer cells expressing the target antigen. It shows remarkable and promising outcomes in hematological cancers, often achieving complete remission. However, a significant number of patients encounter relapse within approximately one year post-treatment despite initial success. Relapses in CAR-T cell therapy manifest in two forms: Ag-positive and Ag-negative. Ag-positive relapse indicates persistent target Ag expression in cancer cells, suggesting CAR-T cell dysfunction or inadequate dosage. Conversely, Ag-negative relapse occurs when tumor cells significant decrease target Ag expression, evading therapy entirely. This may arise from tumor microenvironment heterogeneity, genetic mutations, or temporary antigen loss induced by therapy's immunological pressure [4]. In this work, we propose an integro-differential equation model that builds upon prior models, outlined in [2, 3, 5], aiming to investigate various mechanisms contributing to the occurrence of Ag-negative relapse.

Our model describes the interactions between tumor cells $T(x,t)$ and effector $C_T(t)$ and memory $C_M(t)$ CAR-T cells, where t and $x \in [0,1]$ represent time and the level of expression of the target Ag, respectively. A threshold at $\bar{x}$ exists below which CAR-T cells cannot identify tumor cells, leading us to categorize cells as follows: sensitive cells $T_S(t) = \int_{\bar{x}}^{1} T(x,t)\ dx$, resistant cells $T_R(t) = \int_{0}^{\bar{x}} T(x,t)\ dx$, and total tumor cells: $T_T = T_S(t) + T_R(t)$. Using the equations modeling the dynamics of $C_T(t)$ and $C_M(t)$ established in [3], our model is given by the the following system of equations:

$$\frac{\partial T(x,t)}{\partial t} = \bar{r}(1-\Theta(x))\ T(x,t) - \gamma(x)\ f(C_T(t), T_S(t))\ T(x,t) + \bar{r}\int_0^1 \Theta(y) M(y,x) T(y,t)\ dy\ , \tag{1}$$

$$\frac{dC_T(t)}{dt} = \kappa(t)\left[\frac{T_S(t)}{A+T_S(t)}\right] C_T(t) - \mu C_T(t) - \epsilon C_T(t) + \theta C_M(t) T_S(t) - \alpha C_T(t) T_T(t)\ , \tag{2}$$

$$\frac{dC_M(t)}{dt} = \epsilon C_T(t) - \theta C_M(t) T_S(t) - \mu_M C_M(t). \tag{3}$$

The main new features of our model are as follows. The density-dependent division rate of tumor cells is given by $\bar{r} = r\left(1 - \frac{T_T}{K}\right)\left(1 - \frac{P+Q}{T_T+Q}\right)$, incorporating both strong and weak Allee effects. Here, r represents the maximum growth rate, K denotes the carrying capacity, and parameters P and Q delineate the type of Allee effect [1].

During division, tumor cells may undergo mutations, with the corresponding fraction of cells expressing antigen level x denoted by $\Theta(x) \in [0,1]$. Thus, the fraction of cells undergoing faithful division is represented by $(1-\Theta(x))$. The mutation kernel is represented by the probability density function $M(y,x) = \frac{1}{\varepsilon\sqrt{2\pi}} \exp\left(-\frac{(y-x)^2}{2\varepsilon^2}\right)$ that expresses how mutation occurs from cells with

[1]owarlem@posgrad.lncc.br, [2] earantes@lncc.br, [3] rcca@lncc.br

antigen expression levels y to those with level x, where $y > x$. This condition specifically accounts for antigen-loss mutation-driven mechanisms. For a given y, $M(y, x) \approx 0$ outside the range between x and $x + \varepsilon$, where $0 < \varepsilon \ll 1$. Thus we can slow down or accelerate the loss of antigen expression by tuning ε. Through the mutation kernel, we allow the tumor cell population to not only acquire resistance but to present heterogeneity on antigen expression levels.

Effector CAR-T cells kill sensitive tumor cells depending on the level of antigen expression and the antigen burden. To capture this mechanism, we define the cytotoxic rate as the increasing function $\gamma(x)$ and the Hill function $f(C_T, T_S) = \dfrac{C_T/T_S}{d + (C_T/T_S)}$. When $x < \bar{x}$, $\gamma(x)$ is very small, representing the killing rate attributed to bystander effects from endogeneous antitumor T lymphocytes and other pro-inflammatory molecules. The saturation function $f(C_T, T_S)$ expresses the accessibility of effector CAR-T cells to each sensitive tumor cell. For details regarding the equations governing $C_T(t)$ and $C_M(t)$, please refer to [3]. These equations encompass mechanisms involving Ag-modulated patient-specific expansion at a rate $\kappa(t)\left[\frac{T_S(t)}{A+T_S(t)}\right]$, the transition between effector and memory CAR-T cells depending on coefficients ϵ and θ, immunosupression by tumor cells scaled by α, and natural mortality given by rates μ and μ_M.

This research is a work in progress. We are currently in the process of implementing the model using the Generalized Collocation method for discretizing the tumor cell population equation (1). After partitioning the antigen expression "space" domain $[0, 1]$ into N collocation points, the dependent variable $T(x, t)$ is interpolated as a linear combination of Sinc basis functions defined in each collocation point [2]. In this way, the initial-boundary value problem is transformed into a system of N ordinary differential equations. This system of equations together with equations (2)-(3) are then solved using the fourth-order Runge-Kutta method.

Our core hypothesis is that both the Allee and bystander effects will have a direct impact on the type of therapy relapse, specifically on those that are Ag-negative. We anticipate that the findings from this study will enhance our comprehension of therapy failures and provide valuable insights into preventive strategies, thereby enhancing the efficacy of CAR-T cell immunotherapy.

Acknowledgements: O.W.S.J. acknowledges support from CAPES. E.A.P. and R.C.A. acknowledge CNPq grants 301546/2024-0 and 306588/2022-6.

References

[1] F. Courchamp, L. Berec, and J. Gascoigne. **Allee Effects in Ecology and Conservation**. Oxford University Press, 2008.

[2] J. Greene. "Mathematical models of tumor heterogeneity and drug resistance". PhD thesis. University of Maryland, 2015.

[3] E. A. Paixão, L. R. C. Barros, A. C. Fassoni, and R. C. Almeida. "Modeling patient-specific CAR-T cell dynamics: Multiphasic kinetics via phenotypic differentiation". In: **Cancers** 14.22 (2022), p. 5576. DOI: 10.3390/cancers14225576.

[4] M. Ruella, F. Korell, P. Porazzi, and M. V. Maus. "Mechanisms of resistance to chimeric antigen receptor-T cells in haematological Malignancies". In: **Nature Reviews Drug Discovery** 22.12 (2023), pp. 976–995. DOI: 10.1038/s41573-023-00807-1.

[5] D. S. Santurio, E. A. Paixão, L. R. C. Barros, R. C. Almeida, and A. C. Fassoni. "Mechanisms of resistance to CAR-T cell immunotherapy: Insights from a mathematical model". In: **Applied Mathematical Modelling** 125 (2024), pp. 1–15. DOI: 10.1016/j.apm.2023.08.029.