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CAR T-cell therapy failure in solid tumors as a problem of temporal signal integration

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Abstract

Even though chimeric antigen receptor (CAR) T-cell therapy has revolutionized treatment for hematologic malignancies, its efficacy against solid tumors remains limited. Traditional explanations invoke antigen heterogeneity, immunosuppressive Tumor MicroEnvironments (TME), or CAR specificity. We propose that these are symptoms of a deeper, unifying issue: a temporal mismatch between transient antigen accessibility, CAR signaling integration, and metabolic constraints in the TME. Many conventional CAR designs and protocols assume static antigen presentation and unlimited signaling capacity, which rarely occurs *in vivo*. Recognizing CAR T-cell activation as a time-dependent, energy-limited process, we suggest that CAR ineffectiveness in solid tumors may result from misalignment of antigen exposure windows, the time required for CAR signaling integration, and metabolic constraints that shorten the effective T-cell activation. A central priority for future studies should hence be the development and validation of robust temporal monitoring tools for CAR T-cell antigen engagement and signaling integration in both preclinical models and clinical trials. Integrating these dynamics into a unified framework suggests new strategies, including time-synchronized CAR delivery, conditional activation systems, and metabolic support, to potentially improve CAR efficacy in solid tumors.

Keywords

CAR T-cell therapy, Solid tumors, Tumor microenvironment, Antigen availability, Antigen heterogeneity, Temporal dynamics, T-cell activation kinetics, Signal integration, Metabolic constraints, Immunotherapy

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1. Introduction

Immunotherapy has transformed cancer treatment in recent years, giving hope to patients with late-stage metastatic cancers. CAR T-cell therapy is a promising immunotherapy that uses the power of a patient's own immune system to combat cancer cells (1). It involves modifying T-cells, a type of white blood cell responsible for immune responses, to better recognize and attack cancer cells more effectively.

In CAR T-cell therapy, T-cells are collected from the patient's blood and genetically engineered to express Chimeric Antigen Aeceptors (CARs), which are designed to direct immune cells to attack specific targets (1). These modifications allow T-cells to target designated proteins found on the surface of cancer cells. Then, once the modified T-cells proliferate in large numbers in the laboratory, these 'living drugs' are infused back into the patients, circulate in the bloodstream, and attack cells expressing the target antigen.

The ability of infused T cells to circulate through the bloodstream has been a critical factor in the remarkable success of CAR T-cell therapy in the treatment of hematologic malignancies, including B-cell acute lymphoblastic leukemia, diffuse large B-cell lymphoma, and multiple myeloma. Accordingly, several CAR T-cell therapies have received approval from the U.S. Food and Drug Administration (2).

However, many conventional CAR T-cell strategies are evaluated under simplified conditions that treat antigen expression and encounters as effectively being constant during functional assays, and they rarely account explicitly for temporal variability of antigen presentation or the duration of antigen engagement required for full T-cell activation. CAR signaling requires sustained receptor engagement and metabolic support over time. Solid tumors represent dynamic, heterogeneous, and metabolically hostile microenvironments, suggesting that many therapeutic failures may stem from a temporal mismatch among antigen exposure, signal integration, and cellular energetic capacity.

2. Discussion

2.1 The implicit assumption of static antigen availability

A common implicit assumption in many CAR T-cell studies is that antigen expression on tumor cells is sufficient and static for effective T-cell recognition and cytotoxicity. Many CAR designs, whether tuned for affinity or configured with logic gates, are developed under the premise that sufficient target antigen density is sufficient to enable CAR T-cell recognition and cytotoxic function.

2.1.1 *Antigen density and spatial heterogeneity*

Solid tumors present a complex, dynamic system that challenges conventional CAR T-cell therapy design. Unlike hematologic malignancies (or blood cancers), which generally embody a lower antigen heterogeneity than solid tumors, the evolution of CAR design reflects an ongoing effort to overcome the barriers posed by the heterogeneity of Tumor-Associated Antigens (TAAs) in solid tumors (3).

Current research often addresses the challenges in isolation, yet singular approaches fail to account for the dynamic interactions between tumor cells and CAR T-cells. CAR T-cell activation depends on reaching a threshold of antigen density on target cells (3). Tumor cells with low antigen expression may evade CAR-mediated cytotoxicity, potentially contributing to incomplete tumor clearance and recurrence. However, studies often treat antigen expression as being equivalent to functional availability. Even cells with similar measured antigen levels may differ in how accessible those antigens are to CAR T-cells, influenced by extracellular matrix structures and cell surface context, such as protein folding or membrane clustering, that can impede physical access, creating spatial heterogeneity (4).

Additionally, CAR activation requires productive ligand binding with sufficient affinity to initiate downstream signaling (5). Some antigens exhibit dynamic changes in expression associated with cellular processes, suggesting that antigen presentation could vary over time; an important aspect that has not been comprehensively mapped *in vivo* (6). If CAR T-cells encounter tumor cells during periods of low antigen expression, these targets may fail to elicit sufficient CAR engagement, thereby permitting residual tumor cells to survive and subsequently repopulate the tumor.

2.1.2 *Current solutions and their limitations*

Existing strategies, such as CAR density tuning, single-chain variable fragments (scFv) binding affinity optimization, combinatorial antigen targeting, and neoantigen-based approaches, are developed under the simplifying assumption that antigen expression on the tumor cell surface reliably reflects antigen accessibility for CAR engagement (7-9).

Affinity tuning engineers CARs to recognize high antigen densities, typical of tumor cells, but ignore low levels of expression on healthy cells. CAR density modulation is designed to increase receptor abundance on T-cells (10). However, increasing affinity or CAR density alone may not overcome the absence of binding opportunities; rather, it risks amplifying off-target effects, antigen-independent signaling, and premature T-cell exhaustion when engagement does occur (3). Thus, these solutions optimize receptor sensitivity without addressing whether the receptor can actually engage its target, potentially undermining therapeutic effectiveness by increasing susceptibility to off-target effects, tonic signaling, or premature exhaustion.

Combinatorial antigen targeting, including dual CAR, tandem CAR designs, logic-gated CARs, and synNotch-based systems, aim to improve tumor specificity by requiring the co-engagement of two distinct antigens to become fully activated (8,11). The development of a special kind of logic-gated CARs, Logic-gated INtracellular networK (LINK) CAR by Tousley et al, uses proximal T-cell signaling molecules (11). These domains, which function downstream of TCR activation rather than relying on the conventional CD3ζ signaling module, have demonstrated promise in sustaining robust antitumor activity while attenuating tonic signaling, representing a meaningful step toward mitigating T-cell exhaustion. However, although these strategies

reduce off-target toxicity by enhancing specificity, they also decrease the likelihood of therapeutic efficacy by assuming concurrent accessibility of multiple antigens. Requiring simultaneous engagement of multiple epitopes renders activation vulnerable to temporal or spatial heterogeneity; if even a single requisite antigen is transiently unavailable, the entire activation logic fails. Thus, while combinatorial designs effectively safeguard normal tissues, they may inadvertently increase false-negative recognition of tumor cells.

Neoantigens appear, in principle, to circumvent many specificity concerns by focusing on tumor-exclusive targets (9). Neoantigens are peptides derived from tumor-specific somatic mutations, such as point mutations, insertions, or gene fusions, that enable CAR T-cells to selectively target cancer while protecting normal cells. However, these approaches remain constrained by the same assumptions and may not fully account for the variability in antigen persistence. Tumor heterogeneity, immune selection pressure, and temporal fluctuations in antigen presentation can reduce the functional availability of neoantigens. Furthermore, because neoantigens arise from mutations, their expression is inherently difficult to control or predict as tumors evolve. Subclonal mutations may be lost through immune-mediated elimination, where tumor cells that lack the mutation evade immune attack, allowing them to survive CAR detection and continue to proliferate (12). They may also be lost through transcriptional silencing, where epigenetic or regulatory changes shut down expression of the mutated gene.

Collectively, these approaches address what antigens are targeted, but not when, where, or for how long those antigens could be accessible. By failing to incorporate spatial and temporal dynamics of antigen exposure, current solutions present a fundamental limitation when evaluated from a systematic perspective.

2.1.3 *Proposed research pathways: integrating accessibility and dynamics*

Addressing this central assumption requires shifting from a static view of antigen expression to a dynamic, systems-level understanding of CAR-tumor interactions: understanding accessibility, temporal dynamics, and CAR signaling requirements.

First, quantifying epitope accessibility is essential to distinguish nominal antigen expression from functional antigen availability. Future studies could map the surface antigens that are physically reachable by CARs using live-cell imagining, binding kinetics assays, and structural analyses. This approach reframes antigen heterogeneity not merely as differences in expression level, but as effective exposure.

Second, mapping temporal antigen dynamics addresses the overlooked role of time in antigen availability. Numerous tumor antigens are synthesized, trafficked, or recycled in a cell-cycle-dependent manner (6). If the cancer cells are exposed to CAR during times when antigen expression is low, the interaction may not be meaningful as little to no activation would be triggered. Longitudinal profiling of antigen availability across tumor cycles would allow identification of temporal windows during which CAR engagement is most likely to

succeed, achieving synchronised CAR T-cell properties. This means that, rather than administering a cell dose on a fixed dosing schedule, CAR T-cell delivery could be aligned with periods of maximal antigen accessibility, exploring tumor-intrinsic symptoms. Such an approach could potentially improve therapeutic effectiveness, though this remains to be demonstrated experimentally.

Together, these proposed pathways reframe CAR T-cell therapy as a dynamic system in which efficacy depends on the alignment of antigen accessibility, temporal syncing, and CAR signaling thresholds, moving beyond incremental receptor engineering and addressing an important bottleneck factor limiting CAR T-cell success in solid tumors.

2.2 CAR activation as a time-integrating process

A second implicit assumption underlying some CAR T-cell strategies is that antigen recognition immediately and reliably triggers cytotoxicity. In practice, CAR activation is not instantaneous; it is a cumulative process that depends on sustained receptor engagement to integrated intracellular signals over time. Sequential phosphorylation, kinase recruitment, calcium flux, and transcriptional activation all require continuous or sufficiently repeated interactions to surpass activation thresholds (13). Intermittent or brief antigen encounters may fail to sustain the signal strength required for full activation; when occurring repeatedly in suppressive microenvironments, such suboptimal stimulation could contribute to dysfunctional T-cell states alongside other stressors such as chronic antigen exposure and metabolic constraints (14). This highlights a central conceptual point: treating CAR activation as an on–off switch may obscure a key failure mode in solid tumors, where antigen encounters may be too brief, fragmented, or interrupted to support complete signal integration.

2.2.1 *CAR signaling is sequential and kinetically constrained*

Upon antigen binding, CAR signaling proceeds through a series of ordered biochemical steps: ITAMs phosphorylation, activation of ZAP-70, activation of downstream signaling pathways, and T-cell response. Each of these steps occurs on distinct timescales and require sustained or repeated receptor engagement to accumulate sufficient signal (5).

Short-lived antigen encounters may initiate early signaling events but fail to propagate downstream. In such cases, partial phosphorylation or transient calcium flux may be insufficient to culminate in effector commitment (15). Importantly, intracellular signaling states decay over time; if engagement is interrupted before downstream thresholds are crossed, signal integration resets. Thus, CAR T-cells can be conceptualized as temporal integrators that require antigen exposure to exceed a minimum interaction time to achieve productive activation. This reframing shifts CAR failures from a question of whether binding occurs to whether – additionally - binding persists long enough for intracellular signal accumulation to downstream activation thresholds associated with effector commitment.

2.2.2 *Subthreshold activation and dysfunctional signaling states*

In solid tumors spatial barriers and epitope masking can result in intermittent CAR engagement (4,16). These fragmented encounters are particularly problematic because they may bias T-cells toward subthreshold activation states. Rather than remaining inactivated, CAR T-cells exposed to repeated incomplete signals may upregulate inhibitory receptors, or enter early exhaustion trajectories without eliminating tumor cells (17).

This phenomenon contributes to a recurring paradox in solid tumor CAR T-cell therapy: tumor cells that have adequate antigen density nevertheless evade killing (18). Assuming that antigen availability is not an issue, studies often interpret this failure as antigen loss or immune suppression due to physical barriers of solid tumor construction barring T-cells from reaching those tumor cells. However, within this new time-integration framework, if antigen exposure windows are consistently shorter than the required signaling integration time, activation thresholds are never crossed despite sufficient nominal expression, offering a plausible explanation for this recurring observation.

Both the physical constraints of TME between tumor cells and T-cells and the inability of T-cells to maintain the minimum time needed for full activation may contribute to tumor cell evasion, aspects that should be addressed in future studies.

2.2.3 *Proposed research pathways: integrating temporal mismatch*

Future studies should explicitly measure signaling kinetics, decay rates, and minimum integration times required for cytotoxic requirements. Live-cell imaging of CAR engagement, real-time monitoring of intracellular signaling dynamics, and computational modeling of signal accumulation and decay represent critical next steps for predicting *in vivo* performance and minimizing tumor escape when antigen availability is sufficient.

Without incorporating temporal integration into CAR design and evaluation, strategies that succeed under static conditions may continue to underperform in the dynamic, heterogeneous environment of solid tumors.

2.3 Metabolic constraints shorten effective signaling

A third, tightly coupled limitation that is often over-simplified in studies relates to metabolic environment competition within the TME. As with other signaling processes, CAR activation is energy dependent and imposes substantial metabolic demands on T cells (19). In solid tumors, these demands intersect with profound metabolic constraints, potentially limiting the duration over which CAR signaling can be sustained.

2.3.1 *CAR signaling as an energy-dependent process*

Glycolysis and mitochondrial oxidative phosphorylation must rapidly upregulate to meet these metabolic requirements. When metabolic resources such as glucose, amino acids, and oxygen are available, CAR T-cells have greater capacity to sustain effector

functions (20). In contrast, nutrient depletion and acidotic conditions typical of solid tumor microenvironments, such as amino acid scarcity and acidic pH due to tumor metabolism and competition, can undermine intracellular signaling cascades and T-cell persistence (21-23).

These conditions may not only dampen signaling strength but also limit the ability of CAR T-cells to sustain intracellular activation states over time. However, available studies have not systematically quantified how different nutrients—such as glucose, amino acids, and oxygen—are consumed or depleted over time *in vivo*. Therefore, there exists a knowledge gap in the degree to which this metabolic suppression occurs.

2.3.2 *Metabolic stress causes incomplete integration and exhaustion*

Repeated exposure to metabolically constrained activation attempts may have long-term consequences for CAR T-cell function. Under energy limitation, CAR T-cells may enter partial activation states characterized by transient signaling, altered transcriptional programs, and incomplete effector differentiation. Rather than remaining inert, such cells can upregulate inhibitory receptors and adopt exhaustion-associated metabolic profiles that further reduce future signaling capacity (20). This process may create a feedback loop: metabolic stress shortens integration time, incomplete integration promotes exhaustion, and exhaustion further limits metabolic flexibility. Over successive tumor encounters, CAR T-cells may become progressively less capable of sustaining signaling, even if antigen exposure improves.

Specifically, among the various forms of metabolic competition described above, the majority of studies have focused on competition for glucose and L-arginine (23). Although glucose competition and amino acid scarcity are frequently examined, other metabolic factors such as lactate accumulation and extracellular acidity also influence T-cell function in solid tumors and merit further attention. Focusing narrowly on selected metabolic pressures risks underestimating the cumulative stress that this competition imposes on CAR T-cells.

2.3.3 *Metabolism as a determinant of temporal alignment*

Metabolic capacity is a key factor influencing whether antigen exposure, CAR signaling kinetics, and integration time can align. Even when antigen accessibility windows are sufficiently long, inadequate metabolic support may prevent signaling from persisting long enough to reach activation thresholds associated with effector commitment. Conversely, enhancing metabolic resilience may effectively extend the duration over which CAR T-cells can integrate signals, increasing the likelihood that transient antigen encounters become productive.

This perspective reframes metabolic suppression as not only an inhibitory influence but also as a temporal coordination challenge. The relevant question then becomes whether sufficient energy is available to sustain signaling for the required duration, not merely whether signaling durations are suppressed.

2.3.4 *Proposed research pathways: integrating metabolism*

Recognizing metabolic constraint as a limiter of signaling time shifts priorities in CAR T-cell engineering and evaluation. Rather than focusing exclusively on receptor potency or specificity, strategies could aim to extend metabolically supported signaling duration.

To address the lactate accumulation, one conceptual approach is to regulate the pH in the TME to counteract the accumulation of lactate from glycolysis in cancer cells. By neutralizing extracellular acidity through buffering strategies or by inhibiting lactate transporters such as MCT4, CAR T-cells may function more effectively within a more favorable microenvironment. To counteract the metabolic suppression, we can either measure and understand the full scope of the suppression, and adapt the CAR T-cells' dosing accordingly; or, preserve essential metabolites in the TME by using metabolic adjuvants. Other potential approaches include engineering CAR T-cells with enhanced metabolic flexibility, or temporally aligning CAR activation with periods of reduced metabolic stress, such as strategies designed to enhance metabolic support during periods of CAR engagement.

Critically, metabolic state should be measured alongside antigen exposure dynamics and signaling kinetics in preclinical models. Without integrating these variables, CAR designs optimized under static or metabolically permissive conditions may continue to underperform in the dynamic, energy-limited environment of solid tumors.

2.4 Design implications: synchronizing CARs in time

The insights from temporal, signaling, and metabolic limitations converge on a central design principle: CAR efficacy in solid tumors is not solely determined by which antigens are targeted, but also by antigen accessibility, the timing of antigen encounter, and the duration over which CAR signaling can be sustained. Explicitly incorporating temporal and metabolic dynamics into CAR T-cell therapy may open new strategies to address limitations observed in solid tumors. Several approaches are discussed below.

2.4.1 *Time-synchronized CAR delivery*

This conceptual strategy is to explore whether aligning CAR T-cell dosing with periods of enhanced antigen expression in tumors could improve engagement. Rather than relying on continuous or arbitrary infusion schedules, temporally optimized delivery may ensure that CARs encounter their targets during windows when signaling integration is achievable, potentially maximizing cytotoxic potential while reducing wasted cellular effort. Identifying such windows and demonstrating clinical benefit, however, remains untested.

2.4.2 *Conditional activation systems with sustained antigen engagement*

synNotch or logic-gated CARs aim to improve specificity by requiring defined combinations of signals before full activation; future designs could incorporate features that additionally favor sustained rather than transient antigen engagement.

2.4.3 *Metabolic enhancement and support*

With the two changes above, we must also consider the metabolic state of CAR T-cells.

Engineering T-cells with enhanced energy flexibility or preconditioning the TME to buffer acidity, preserve nutrients, or neutralize lactate accumulation could extend the duration over which CAR signaling can be maintained. Such metabolic priming may help ensure that T-cells have the energetic capacity to integrate signals fully during periods of antigen availability, potentially reducing early signaling collapse and exhaustion.

This temporal perspective integrates antigen dynamics, intracellular signal accumulation, and metabolic constraints, reframing CAR T-cell therapy as a coordinated, time-dependent system. By designing CARs with explicit temporal synchronization in mind, future therapies may achieve more robust and predictable efficacy in the complex environment of solid tumors.

Although direct real-time monitoring of CAR T-cell signal integration in patients remains a technological frontier, a convergence of *in vitro* real-time assays, biosensor imaging, non-invasive *in vivo* tracking, and quantitative modeling provides a robust toolkit for probing temporal dynamics. These emerging capabilities make the temporal mismatch framework conceptualized in this paper not merely theoretical, but experimentally testable and clinically relevant. A central priority for future studies should be the development and validation of robust temporal monitoring tools for CAR T-cell antigen engagement and signaling integration, both in preclinical models and clinical trials.

3. Conclusion

CAR T-cell failures in solid tumors are not solely due to suboptimal antigen choice, immune suppression, or toxicity—common problems that research frequently revisits. Reframing CAR activation as a time-dependent, energy-limited signal integration process provides a unifying explanation for diverse failure modes. This perspective is actionable: it prioritizes experimental measurements of temporal antigen accessibility, CAR activation kinetics, and T-cell metabolic status.

By focusing on temporal dynamics and metabolic capacity, CAR research can shift from incremental optimization to mechanistically informed strategies, guiding engineered T-cells to act when and where they are needed most and providing a pathway toward durable solid tumor therapy.

4. References

1. Mohanty, R., Chowdhury, C. R., Arega, S., Sen, P., Ganguly, P., Ganguly, N. (2019). CAR T cell therapy: A new era for cancer treatment. *Oncology Reports,* 42(6), 2183–2195. https://doi.org/10.3892/or.2019.7335

2. Brudno, J. N., Maus, M. V., Hinrichs, C. S. (2024). CAR T cells and T-cell therapies for cancer: A translational science review. *JAMA,* 332(22), 1924–1935. https://doi.org/10.1001/jama.2024.19462

3. Chen, N., Li, X., Chintala, N. K., Tano, Z. E., Adusumilli, P. S. (2018). Driving CARs on the uneven road of antigen heterogeneity in solid tumors. *Current Opinion in Immunology,* 51, 103–110. https://doi.org/10.1016/j.coi.2018.03.002

4. Warda, W., Da Rocha, M. N., Trad, R., Haderbache, R., Salma, Y., Bouquet, L., *et al.* (2021). Overcoming target epitope masking resistance that can occur on low-antigen-expresser AML blasts after IL-1RAP chimeric antigen receptor T cell therapy using the inducible caspase 9 suicide gene safety switch. *Cancer Gene Therapy,* 28(12), 1365–1375. https://doi.org/10.1038/s41417-020-00284-3

5. Wu, L., Wei, Q., Brzostek, J., Gascoigne, N. R. J. (2020). Signaling from T cell receptors (TCRs) and chimeric antigen receptors (CARs) on T cells. *Cellular & Molecular Immunology,* 17(6), 600–612. https://doi.org/10.1038/s41423-020-0470-3

6. Ullah, M., Aoudjeghout, W., Pimpie, C., Pocard, M., Mirshahi, M. (2020). Mitosis in cancer cell increases immune resistance via high expression of HLA-G and PD-L1. *Cancers,* 12(9), 2661. https://doi.org/10.3390/cancers12092661

7. Ahmad, Z. A., Yeap, S. K., Ali, A. M., Ho, W. Y., Alitheen, N. B., Hamid, M. (2012). scFv antibody: Principles and clinical application. *Clinical and Developmental Immunology,* 2012, 980250. https://doi.org/10.1155/2012/980250

8. Takahashi, Y., Demachi-Okamura, A., Oya, Y., Nakada, T., Sakakura, N., Kuroda, H., Matsushita, H. (2020). Research advance in tumor specific antigens. *AME Medical Journal,* 6, 3. https://amj.amegroups.org/article/view/6102

9. Xie, N., Shen, G., Gao, W., Huang, Z., Huang, C., Fu, L. (2023). Neoantigens: Promising targets for cancer therapy. *Signal Transduction and Targeted Therapy,* 8(1), 9. https://doi.org/10.1038/s41392-022-01270-x

10. Hamieh, M., Mansilla-Soto, J., Rivière, I., Sadelain, M. (2023). Programming CAR T cell tumor recognition: Tuned antigen sensing and logic gating. *Cancer Discovery,* 13(4), 829–843. https://doi.org/10.1158/2159-8290.CD-23-0101

11. Tousley, A. M., Rotiroti, M. C., Labanieh, L., Rysavy, L. W., Kim, W. J., Lareau, C., *et al.* (2023). Co-opting signalling molecules enables logic-gated control of CAR T cells. *Nature,* 615(7952), 507–516. https://doi.org/10.1038/s41586-023-05778-2

12. Tufail, M., Jiang, C. H., Li, N. (2025). Immune evasion in cancer: Mechanisms and cutting-edge therapeutic approaches. *Signal Transduction and Targeted Therapy,* 10(1), 227. https://doi.org/10.1038/s41392-025-02280-1

13. Lindner, S. E., Johnson, S. M., Brown, C. E., Wang, L. D. (2020). Chimeric antigen receptor signaling: Functional consequences and design implications. *Science Advances,* 6(21), eaaz3223. https://doi.org/10.1126/sciadv.aaz3223

14. Kouro, T., Himuro, H., Sasada, T. (2022). Exhaustion of CAR T cells: Potential causes and solutions. *Journal of Translational Medicine,* 20(1), 239. https://doi.org/10.1186/s12967-022-03442-3

15. Harris, M. J., Fuyal, M., James, J. R. (2021). Quantifying persistence in the T-cell signaling network using an optically controllable antigen receptor. *Molecular Systems Biology,* 17(5), e10091. https://doi.org/10.15252/msb.202010091

16. Kankeu Fonkoua, L. A., Sirpilla, O., Sakemura, R., Siegler, E. L., Kenderian, S. S. (2022). CAR T cell therapy and the tumor microenvironment: Current challenges and opportunities. *Molecular Therapy – Oncolytics,* 25, 69–77. https://doi.org/10.1016/j.omto.2022.03.009

17. Gumber, D., Wang, L. D. (2022). Improving CAR-T immunotherapy: Overcoming the challenges of T cell exhaustion. *EBioMedicine,* 77, 103941. https://doi.org/10.1016/j.ebiom.2022.103941

18. Martinez, M., Moon, E. K. (2019). CAR T cells for solid tumors: New strategies for finding, infiltrating, and surviving in the tumor microenvironment. *Frontiers in Immunology,* 10, 128. https://doi.org/10.3389/fimmu.2019.00128

19. Xu, X., Gnanaprakasam, J. N. R., Sherman, J., Wang, R. (2019). A metabolism toolbox for CAR T therapy. *Frontiers in Oncology,* 9, 322. https://doi.org/10.3389/fonc.2019.00322

20. Frlic, T., Pavlin, M. (2025). Metabolic reprogramming of CAR T cells: A new frontier in cancer immunotherapy. *Frontiers in Immunology,* 16, 1688995. https://doi.org/10.3389/fimmu.2025.1688995

21. Liberti, M. V., Locasale, J. W. (2016). The Warburg effect: How does it benefit cancer cells? *Trends in Biochemical Sciences,* 41(3), 211–218. https://doi.org/10.1016/j.tibs.2015.12.001

22. Navarro, F., Casares, N., Martín-Otal, C., Lasarte-Cía, A., Gorraiz, M., Sarrión, P., *et al.* (2022). Overcoming T cell dysfunction in acidic pH to enhance adoptive T cell transfer immunotherapy. *OncoImmunology,* 11(1), 2070337. https://doi.org/10.1080/2162402X.2022.2070337

23. Hope, H. C., Salmond, R. J. (2021). The role of non-essential amino acids in T cell function and anti-tumour immunity. *Archivum Immunologiae et Therapiae Experimentalis,* 69(1), 29. https://doi.org/10.1007/s00005-021-00633-6