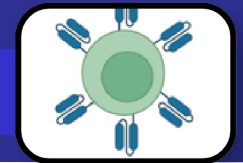


260051: RECENT ADVANCEMENTS AND PERSISTING CHALLENGES IN THE EVOLUTION OF NEXT GENERATION CAR T CELL THERAPY FOR SOLID MALIGNANCIES.

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INTRODUCTION

- Cellular Immunotherapy has evolved as a highly successful cancer treatment approach in recent years. The technique requires genetically altering T cells, the immune system's defense cells, such that they can identify and target tumor.

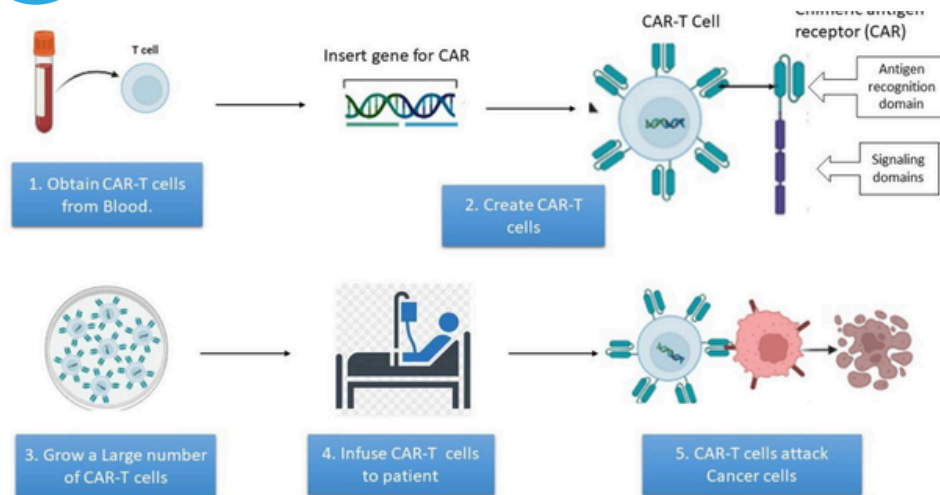
AIM OF STUDY

- THIS STUDY AIMS TO PRESENT A COMPREHENSIVE OVERVIEW OF THE MOST RECENT ADVANCEMENTS FROM 2021 TO 2025, CONCENTRATING ON TECHNOLOGICAL BREAKTHROUGHS, NEW ANTIGEN TARGETS, AND COMBINATION APPROACHES

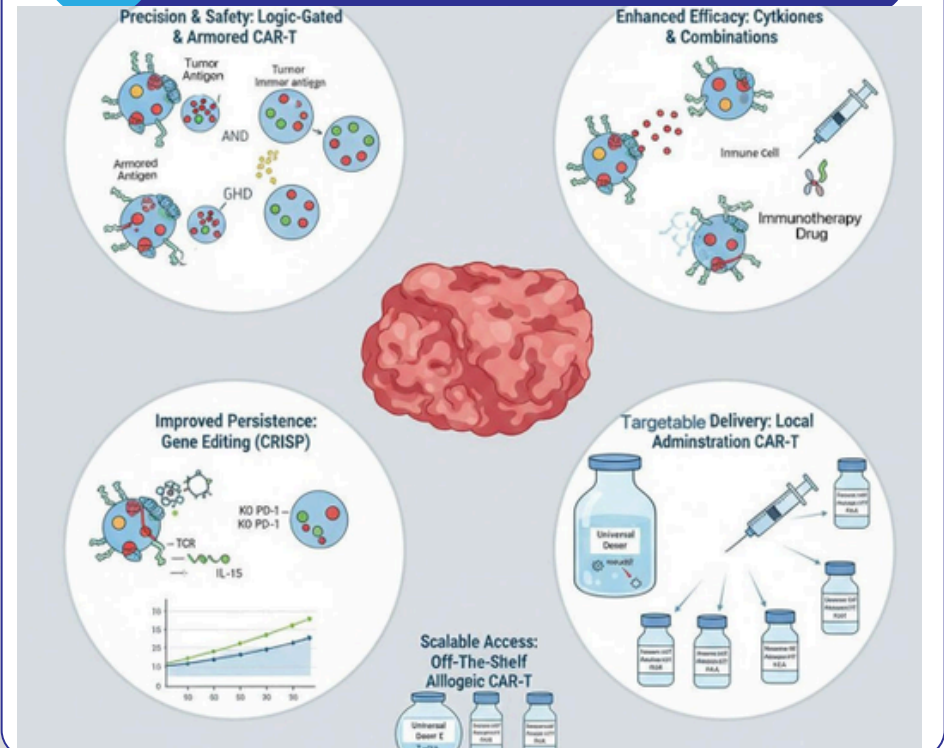
METHODOLOGY

- An extensive literature search was carried out in the following electronic databases: PubMed, ScienceDirect and Google Scholar. The search involved articles that were published since January 2020 up to November 2025, combining a set of keywords and Medical Subject Headings (MeSH) terms.

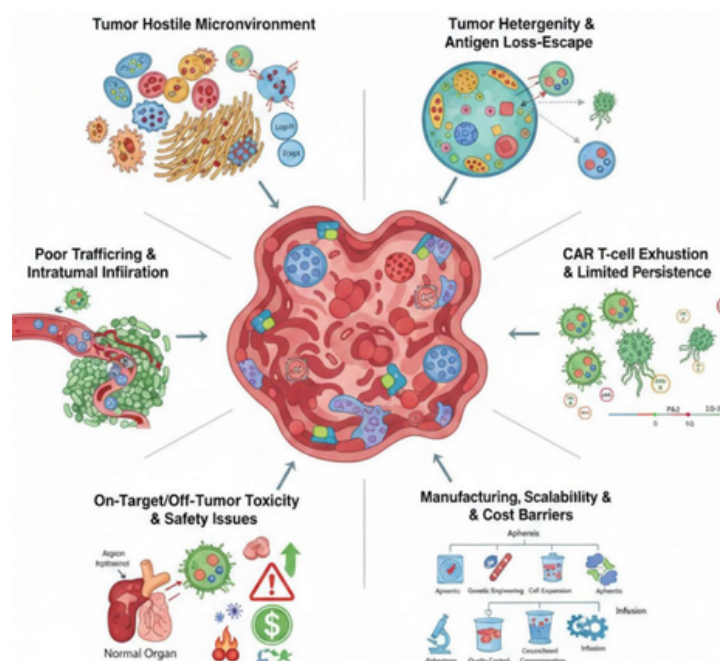
MECHANISM OF CAR-T CELL TREATMENT



ADVANCED CAR-T CELL INNOVATIONS



CHALLENGES OF CAR-T CELL THERAPY FOR SOLID TUMORS



MAJOR CLINICAL TRIALS: SOLID TUMOR DIRECTED CAR-T THERAPY

Study	Phase	Design	Response Rate	Median OS	Median PFS	CR	Notes
CT041 (CLDN18.2)	[127]	Phase II RCT; NCT04581473	22% vs. 4%	3.25 vs. 1.77 mo	63% vs. 25%	NR	Median OS: 7.92 vs. 5.49 mo
GD2-CAR T; high-risk neuroblastoma	[128]	Phase I/II; NCT03373097	66%	NR	NR	NR	CR 37-40%; 5-year OS 42.7%
PD-L1 CAR T	[129]	Preclinical	N/A	N/A	N/A	N/A	Tumor eradication demonstrated in intracranial GB models
GD2-CAR T; H3K27M-DMG	[61]	Phase I; NCT04196413	NR	NR	NR	NR	Neurologic improvement 9/11 patients
EGFR/IL13Ra2 CAR T	[130]	Phase I; NCT05168423	8%	1.9 mo	62%	NR	Intrathecal delivery produced rapid tumor regress
CD133-CAR T	[131]	Phase I/II	4.8%	6.8 mo	71.5%	NR	Median OS: 12 mo
BNT211 (CLDN6+CARVac)	[132]	Phase I/II; NCT04503278	45%	NR*	74%	NR	6-month PFS: 42%*
MSLN-CAR T+PD-1	[133]	Phase I; NCT02414269	NR	NR	NR	NR	Median OS: 23.9 mo
P-PSMA-101	[134]	Phase I; NCT04283071	NR†	NR	NR	NR	PSA reduction observed i

FUTURE PERSPECTIVES ON EMERGING ALTERNATE THERAPIES

- EMERGING CELLULAR TREATMENTS SUCH AS CAR-NK CELLS, CARMACROPHAGES, AND TCR-ENGINEERED T CELLS OFFER ALTERNATE OPTIONS TO CIRCUMVENT THE LIMITATIONS OF CAR T-CELLS IN SOLID TUMORS.

CONCLUSION

- NEXT-GENERATION CAR DESIGNS, AI-DRIVEN DESIGN ALGORITHMS, AND THE CREATION OF ALTERNATIVE CELLULAR THERAPIES ALL POINT TO A BRIGHT FUTURE. WHEN THESE MULTIDISCIPLINARY ADVANCEMENTS COME TOGETHER, THE FULL THERAPEUTIC POTENTIAL OF CAR T-CELLS WILL BE UNLOCKED, BRINGING SOLID TUMOR IMMUNOTHERAPY CLOSER TO CONSISTENT CLINICAL SUCCESS.

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