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Editorial

Beyond the CAR T Cells: TIL Therapy for Solid Tumors

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Abbreviations
CAR, chimeric Ag receptor; FDA, Food and Drug Administration; NCI, National Cancer Institute; TIL, tumor-infiltrating lymphocyte.

T cells, key players in the body's immune system, are instrumental in cancer immunotherapy, a revolutionary approach to cancer treatment. These specialized cells possess the remarkable ability to recognize and destroy malignant cells, offering a potent defense against the disease.

One remarkable advancement in cancer treatment field is the development of chimeric Ag receptor (CAR) T-cell therapy, which has shown tremendous promise in cancer immunotherapy (1). CAR T cells are genetically engineered immune cells that are designed to recognize certain proteins, called antigens, present on the surface of cancer cells. The concept of CAR T cells originated from the idea of enhancing T cell specificity and efficacy by genetically modifying them to express synthetic receptors that can bind to tumor antigens with high affinity. This approach allows CAR T cells to bypass the complex process of antigen recognition and activation, enabling them to directly target cancer cells for destruction. CAR T cell therapy has demonstrated remarkable clinical responses in treating certain types of blood cancers, such as B cell leukemia and lymphoma, with many patients achieving long-lasting remissions even after conventional treatments have failed. This groundbreaking therapy represents a paradigm shift in cancer treatment, offering new hope to patients and paving the way for the development of personalized and precision medicine approaches in oncology.

However, the efficacy of CAR T cells against solid tumors, such as melanoma, has been limited by the formidable barriers presented by the tumor microenvironment. Unlike blood cancers, where malignant cells circulate freely, solid tumors construct a fortress that hampers the infiltration and function of CAR T cells, thereby diminishing their capacity to seek out and destroy cancer cells effectively.

This is where tumor-infiltrating lymphocyte (TIL) therapy steps in, with a rich history dating back to the pioneering work of Dr. Steven Rosenberg and his team at the National Cancer Institute (NCI), USA. Developed in the 1980s, this groundbreaking research laid the foundation by demonstrating that T cells extracted from within tumor tissues, amplified *ex vivo*, and reintroduced into tumor-bearing hosts could wield significant suppressive effects on tumor growth (2,3). However, the road from laboratory bench to bedside treatment proved to be challenging, primarily due to the heterogeneous nature of TILs.

The brilliance of TILs lies in their ability to replenish the body with cancer-fighting T cells which naturally possess the remarkable capacity to recognize distinctive markers on the

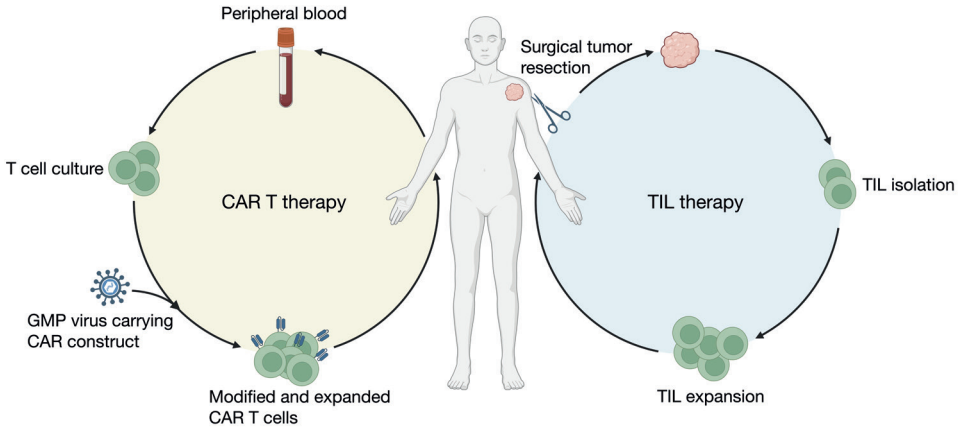

Figure 1. CAR T versus TIL therapy. CAR T cell therapy involves isolating patient T cells, engineering them to express a CAR targeting specific cancer markers, and expanding them in bioreactors. Upon reinfusion, CAR T cells target and eliminate cancer cells expressing the designated marker, such as CD19 or BCMA. TIL cell therapy, on the other hand, uses T lymphocytes extracted from solid tumor tissue and expanded outside of the body. These TILs are directed to target neoantigens presented by the MHC on cancer cells. Figure created with BioRender.com.
BCMA, B-cell maturation antigen; GMP, Good Manufacturing Practice.

surface of cancer cells and mount a potent attack. Unlike CAR T cells, which are engineered to target specific antigens present on cancer cells (**Fig. 1**), TILs constitute a diverse arsenal of T cells that recognize a spectrum of antigens. This inherent variability has presented a hurdle in achieving consistent therapeutic outcomes in clinical trials over the past few decades. The journey of TIL therapy has been marked by peaks of optimism followed by troughs of setbacks, reflecting the intricate complexities involved in harnessing the full potential of the immune system against cancer.

Nevertheless, recent advances, spearheaded by biotechnology companies like Iovance, have propelled TIL therapy to the forefront of melanoma treatment. By adeptly navigating the nuances of TIL therapy and leveraging early technologies licensed from Dr. Rosenberg and the NCI, USA, Iovance has achieved the monumental feat of securing Food and Drug Administration (FDA) approval through an accelerated approval pathway for their TIL therapy lifileucel, or Amtagvi in February 2024 (4). This drug is the first personalized TIL therapy to reach the market. In a clinical study leading to the FDA approval, lifileucel showed remarkable efficacy against melanoma. In this study, 31.5% of patients experienced a reduction in tumor size, and 43.5% remained in remission for more than a year (4). This milestone marks a significant leap forward in the battle against melanoma, offering renewed hope to patients grappling with this formidable disease.

The FDA approval of TIL therapy for melanoma heralds the dawn of a new era in cancer treatment. It represents a beacon of hope for patients confronted with the daunting challenges of solid tumors. As researchers continue to refine and expand upon this groundbreaking approach, the horizon gleams with the promise of more effective treatments for other solid tumors like non-small cell lung cancer. The transformative potential of immunotherapy in oncology stands illuminated, underscoring the relentless pursuit of innovation in the fight against cancer.

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