T Cells in Medicine

The Latest Science: Understanding, Engineering, and Clinical Use

---

T cells remain the single most active frontier in cellular medicine. Over the past year, research has moved on several fronts at once: manufacturing engineered T cells inside the body instead of in a lab, pushing cell therapies beyond cancer into autoimmune and even infectious disease, and unpicking the molecular biology of why T cells burn out ("exhaustion") inside tumors. This report summarizes the current state of the science and where it is headed.

1. CAR T-Cell Therapy: Maturing Beyond Cancer

Chimeric antigen receptor (CAR) T-cell therapy — in which a patient's own T cells are genetically engineered to recognize and destroy target cells — has moved from a niche blood-cancer treatment to a broader platform. Since the first approvals in 2021–2022 for hematologic malignancies, the field is now expanding into autoimmune, fibrotic, and even infectious disease, with early reported successes that include work toward HIV treatment.

Autoimmune disease: a genuine second act for CAR T

The most striking 2026 news is not in oncology but in rheumatology. At the EULAR 2026 Annual Meeting, researchers presented data showing that next-generation CAR T-cell and natural killer (NK)-cell platforms can produce drug-free clinical remission in patients with severe, treatment-refractory rheumatic disease. In the phase 1 CARLYSLE study, a CD19-directed CAR T-cell therapy called obecabtagene autoleucel ("obe-cel") — engineered with a fast-off-rate binding domain intended to reduce toxicity — was tested in adults with severe lupus who had already failed multiple prior therapies, including other B-cell-targeted drugs.

The underlying logic: CAR T cells engineered to target CD19 wipe out the B cells that drive autoimmune attacks, effectively giving the immune system a "reset." Separately, allogeneic (off-the-shelf) CAR-NK cell platforms are being explored as a faster, less individualized alternative. Researchers are also now tracking how and when relapse occurs after these living-drug treatments, since durability and retreatment strategy are becoming as important a question as initial response.

Cancer: earlier intervention and new targets

In oncology, a notable shift is CAR T-cell therapy moving earlier in the disease course. At the 2026 American Association for Cancer Research meeting, early-phase data showed that CAR T-cell therapy in high-risk smoldering multiple myeloma — a precursor condition historically just "watched" until it became symptomatic — produced rapid, sustained responses with no progression events, suggesting cell therapy may eventually be used to intercept cancer before it fully develops rather than only after relapse.

Toxicity management also continues to improve. Reported adverse events with newer CAR T constructs (such as the GPRC5D-targeted therapy BMS-986393 for myeloma) remain consistent with prior generations — manageable neutropenia and a low rate of neurotoxicity — while efficacy against previously resistant disease has improved. Researchers are also using genome-wide CRISPR screens to find genes (such as CUL5) whose removal boosts CAR T-cell persistence, opening a path to next-generation, resistance-resistant constructs.

A long-standing technical obstacle — building CAR T cells that can attack T-cell cancers themselves without the engineered cells destroying each other ("fratricide") — is being solved by knocking out or masking shared surface markers like CD3 and CD7, allowing CAR T cells to selectively target malignant T cells.

2. In Vivo CAR T Cells: Skipping the Lab Entirely

Perhaps the biggest manufacturing breakthrough under active development is **in vivo** CAR T-cell generation — engineering T cells directly inside the patient's body, rather than removing blood, genetically modifying cells in a lab for weeks, and reinfusing them.

Conventional ("ex vivo") CAR T manufacturing requires leukapheresis, viral transduction, expansion, and quality control at specialized facilities — a process that is slow, expensive, and inaccessible to most of the world. In vivo approaches instead package messenger RNA (mRNA) encoding the CAR construct inside lipid nanoparticles (LNPs) — the same delivery technology used in mRNA vaccines — and inject it directly into the patient. The LNPs are engineered to target T cells specifically (often via antibody conjugation to T-cell surface markers), delivering the CAR-encoding mRNA so the patient's own T cells transform into CAR T cells inside the bloodstream.

Why this matters

- Cost and access: removes the need for leukapheresis, viral vector production, and weeks of ex vivo culture at GMP facilities, potentially making CAR T-style therapy far cheaper and more widely available.
- Safety: because mRNA produces only transient CAR expression (versus permanent viral integration), the CAR T effect fades over time — reducing the risk of prolonged cytokine release syndrome and long-term healthy-cell depletion.
- Tunability: transient expression allows dosing to be repeated or adjusted, rather than being a single irreversible infusion.
- Reduced need for chemotherapy conditioning: engineering T cells in place may lessen the harsh lymphodepleting chemo currently required before ex vivo CAR T infusion.

A leading example is Capstan Therapeutics' CPTX2309, an in vivo anti-CD19 CAR-T therapy using "targeted lipid nanoparticles" (tLNPs) that entered Phase 1 trials for B-cell-mediated autoimmune disease; AbbVie acquired Capstan for $2.1 billion in mid-2025, underscoring the commercial confidence in this approach. Academic groups have also engineered LNPs with extrahepatic tropism (targeting the spleen rather than defaulting to the liver, LNPs' usual destination) and "self-activating" lipid formulations that transfect and stimulate T cells without needing an antibody targeting ligand at all

— simplifying manufacturing further. This is still largely preclinical/early-clinical work, but it represents a plausible route to making CAR T-style therapy as logistically simple as a vaccine shot.

3. T Cell Engagers: A Complementary "Off-the-Shelf" Strategy

Alongside cell therapies, T-cell engaging antibodies (bispecific or multispecific constructs that physically link a patient's existing T cells to a target cell, such as a tumor cell) have become a major clinical category in their own right. As of 2026, twelve T-cell engagers have been approved by the FDA and EMA for blood cancers and solid tumors. Unlike CAR T therapy, which is typically a single infusion, T-cell engagers are given as repeated doses (weekly or biweekly), making them logistically closer to a conventional drug. Newer generations are also being developed for autoimmune disease, not just cancer, broadening this modality's reach in parallel with CAR T's own expansion beyond oncology.

4. Understanding T Cell Exhaustion: The Core Biology Problem

A major reason T-cell therapies still struggle against solid tumors (as opposed to blood cancers) is **T-cell exhaustion** — a distinct, stable dysfunctional state that T cells enter after prolonged antigen exposure inside the hostile tumor microenvironment. First characterized in chronic viral infection research, exhaustion is now understood as a defined developmental pathway, not just generic fatigue.

Key 2025–2026 findings

- Exhaustion develops in stages: progenitor ("TCF1+") T cells — some tissue-resident and quiescent, some circulating — gradually lose the transcription factor TCF1 as they divide, passing through an intermediate exhausted state that can still be revived by checkpoint blockade (e.g., anti-PD-1 therapy), before reaching a terminally exhausted state that resists current immunotherapy.
- Key transcriptional regulators — TCF1, T-bet, and TOX — govern which path a T cell takes, making them targets for drugs designed to keep T cells in the reversible, still-treatable stage.
- Metabolic competition matters: tumor cells can out-compete CD8+ T cells for nutrients such as methionine, degrading T-cell epigenetic programming and function through the STAT5 pathway — suggesting nutrient-support or metabolic-modulation strategies could complement immunotherapy.
- Epigenetic "locking in" of exhaustion (histone and DNA methylation changes) is now viewed as a targetable, and potentially reversible, mechanism using CRISPR or RNA-based epigenetic editing.
- Combination checkpoint blockade — targeting PD-1 alongside co-expressed inhibitory receptors like TIM-3, LAG-3, and TIGIT — is showing early promise for addressing exhaustion at multiple points simultaneously, rather than relying on a single checkpoint drug.

For engineered CAR T cells specifically, researchers are now designing constructs meant to resist exhaustion from the outset — through optimized costimulatory domains, CRISPR deletion of inhibitory genes, and metabolic reprogramming — rather than only treating exhaustion after it develops.

5. What This Means, and What to Watch

- Autoimmune disease is emerging as CAR T's fastest-growing new frontier, with drug-free remission data now presented at major rheumatology conferences — a notable shift from a decade of CAR T being an oncology-only story.
- In vivo CAR T generation (via mRNA-LNPs) is the most consequential manufacturing shift in the field, with the potential to dramatically cut cost and turnaround time; watch for Phase 1/2 clinical data over the next 1–2 years as the key proof point.
- Solid tumors remain the hardest problem, gated primarily by T-cell exhaustion and the immunosuppressive tumor microenvironment rather than by target identification alone.
- Combination strategies — pairing engineered T cells or checkpoint inhibitors with metabolic or epigenetic modulators — are the direction most researchers now see as necessary to crack solid tumors.

Sources: EULAR 2026 Annual Meeting coverage (Medscape); AACR 2026 Annual Meeting coverage (Oncology News Central); AJMC, "CAR T-Cell Therapy in 2026 and Beyond" (Aug 2026); Frontiers in Immunology (2026), "Next-generation T cell engagers"; Nanoscale Horizons (2026) and PubMed/MDPI reviews on mRNA-LNP in vivo CAR-T engineering; Science (2026), "In vivo CAR T cell generation to treat cancer and autoimmune disease"; Clinical and Translational Oncology (2026) and Advanced Science (2026) on T-cell exhaustion and senescence; Signal Transduction and Targeted Therapy (2026), "Revitalizing T cells." Compiled September 2026.