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Review Article

CAR-NK and CAR-Macrophage cell therapies: beyond CAR-T cells

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Abstract

Chimeric antigen receptor (CAR)-T cell therapy has genuinely reshaped how we treat relapsed and refractory blood cancers, particularly B-cell malignancies. Yet its wider use is still held back by a familiar list of problems: immune-related toxicities, the sheer complexity of autologous manufacturing, high costs, antigen escape, and disappointing results against solid tumors. These roadblocks are exactly what pushed researchers toward alternative CAR-engineered immune cells — namely CAR-natural killer (CAR-NK) cells and CAR-macrophages (CAR-M). CAR-NK cells bring together the built-in killing power of NK cells with CAR-directed tumor targeting, which translates into a better safety profile, minimal risk of graft-versus-host disease, and a real shot at "off-the-shelf" allogeneic therapies. CAR-macrophages take a different route, and one that seems particularly well-suited to solid tumors: they can burrow into tumor tissue, physically engulf cancer cells, remodel the tumor microenvironment, and prime adaptive immune responses. This review walks through the biology, manufacturing strategies, and clinical progress behind CAR-NK and CAR-M therapies, and considers how they might complement CAR-T therapy and push cancer immunotherapy forward.

Keywords: Adoptive cell therapy, Cancer immunotherapy, CAR-macrophages, CAR-NK cells, Cellular immunotherapy, Chimeric antigen receptor, Natural killer cells, Next-generation cellular therapy, Solid tumors, Tumor microenvironment

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1. Introduction

Adoptive cellular immunotherapy has changed the landscape of cancer treatment by turning the patient's own immune system into a weapon against malignant cells. Of these approaches, CAR-T cell therapy stands out for its success in relapsed or refractory B-cell leukemias, lymphomas, and multiple myeloma — success substantial enough to earn regulatory approval for several CAR-T products.[1–3] These cells are engineered to carry synthetic receptors capable of recognizing tumor-associated antigens without needing MHC presentation at all. Steady refinements to CAR design — particularly optimized co-stimulatory domains like CD28 and 4-1BB — have made these cells persist longer, proliferate better, produce more cytokines, and ultimately kill tumors more effectively.[3,4] Still, real limitations remain. Cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) continue to be serious clinical concerns. Manufacturing is autologous, which means it's slow, expensive, and labor-intensive by nature and even when the product works, antigen escape, T-cell exhaustion, and an immunosuppressive tumor microenvironment tend to undercut treatment — especially in solid tumors, where CAR-T has struggled the most.

This is where alternative CAR-engineered immune cells come in. CAR-natural killer (CAR-NK) cells pair innate cytotoxicity with antigen-specific targeting, offering a safer profile, almost no risk of graft-versus-host disease, and the appeal of a ready-made, allogeneic "off-the-shelf" therapy.[5,6,7] CAR-macrophages (CAR-M) offer a different but complementary advantage, particularly for solid tumors — their natural talent for infiltrating tumor tissue, engulfing malignant cells, presenting tumor antigens, and reshaping the tumor microenvironment fills gaps that lymphocyte-based therapies can't.[8,9,10,11,12] Progress in genome editing, viral and non-viral gene delivery, induced pluripotent stem cell technology, and next-generation CAR designs — armored CARs, dual-target constructs, logic-gated

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receptors, cytokine-secreting cells, and combinations with immune checkpoint inhibitors — is expanding what these platforms can do.[13,14,15,16] This review looks at the biological groundwork, manufacturing approaches, mechanisms of action, and current preclinical and clinical standing of CAR-NK and CAR-macrophage therapies, and how they might work alongside CAR-T to improve outcomes across both hematological and solid cancers.

1.1. Biological basis of CAR-NK and CAR-Macrophage therapies

1.1.1. Natural Killer Cells as CAR Effectors

Natural killer (NK) cells belong to the innate immune system and make up roughly five to fifteen percent of peripheral blood lymphocytes. They're a first line of defense against tumor and virus-infected cells.[5] Unlike T lymphocytes, NK cells don't need MHC-restricted recognition to act — which means they can respond fast, without waiting on prior antigen coordination. What determines whether an NK cell fires is really a balance: activating receptors like NKG2D, NKp30, NKp44, NKp46, DNAM-1, and CD16 pull one way, while inhibitory receptors — killer-cell immunoglobulin-like receptors (KIRs) and NKG2A, which read self-HLA molecules — pull the other.[5,6] When activation wins out, the cell releases perforin- and granzyme-containing cytotoxic granules at the immune synapse, driving the tumor cell into apoptosis. Antibody-coated tumor cells face a second line of attack too, destroyed through ADCC via the Fc receptor CD16. Activated NK cells also secrete cytokines — IFN-γ, TNF-α, GM-CSF — along with chemokines that recruit and activate other immune cells in the tumor environment.[6,7]

Engineering NK cells with a CAR essentially layers a new, antigen-specific targeting system on top of abilities they already have. Because CAR-NK cells still rely on their own endogenous receptors alongside the CAR, they're less vulnerable to the antigen-escape problem that plagues CAR-T cells when antigen expression is lost or uneven. They're also inherently safer — releasing far fewer of the inflammatory cytokines that drive cytokine release syndrome. Combined with their shorter lifespan and lower risk of alloreactivity, this makes CAR-NK cells a natural fit for allogeneic "off-the-shelf" manufacturing, whether sourced from peripheral blood, umbilical cord blood, iPS cells, or established NK cell lines like NK-92.[6,7,8]

1.1.2. Macrophages as emerging cellular therapeutics

Macrophages are remarkably adaptable innate immune cells, central to tissue homeostasis, pathogen clearance, inflammation, and repair. Inside the tumor microenvironment, they're often the single largest immune population present, and their behavior shifts dramatically depending on local cues—cytokines, metabolites, cell-to-cell contact.[9] The traditional way of thinking about them splits macrophages into two camps: classically activated M1 macrophages, geared toward inflammation and antitumor activity, and alternatively activated M2 macrophages, which lean toward tissue remodeling, angiogenesis, and immune suppression. That binary doesn't capture the full complexity of macrophage biology, but it's still a useful lens for understanding their role in cancer.[9,10] Tumor-associated macrophages (TAMs) typically drift toward the immunosuppressive end of that spectrum, secreting IL-10, TGF-β, VEGF, and matrix-remodeling enzymes that actively help tumors grow and spread.[10] Not surprisingly, a lot of current anticancer strategy is focused on either depleting TAMs outright or reprogramming them back toward a pro-inflammatory state.

CAR engineering offers a more targeted way to do that reprogramming. CAR-macrophages (CAR-M) are engineered to recognize tumor-associated antigens while keeping the rest of their natural biology intact. Once a CAR-M cell detects its target, it engulfs the malignant cell, processes the antigen, and presents the resulting peptides to T-lymphocytes — essentially bridging innate and adaptive immunity. On top of that, CAR-M cells release pro-inflammatory cytokines and chemokines that draw in cytotoxic lymphocytes, gradually turning an immunosuppressive microenvironment into an immune-activating one.[11,12] What really sets macrophages apart from T-lymphocytes is mobility — they can push into dense stromal tissue and hypoxic zones that T cells typically can't reach. That's precisely why CAR-M technology looks so promising for solid tumors, where poor immune-cell trafficking and a hostile microenvironment are two of the biggest obstacles CAR-T therapy runs into.[11,12,13]

1.2. Comparative biological characteristics of CAR-T, CAR-NK, and CAR-M therapies

All three CAR-based strategies rely on antigen-specific targeting through engineered receptors, but the resemblance mostly ends there — their biology and antitumor mechanisms differ substantially. CAR-T cells kill through direct, antigen-specific cytotoxicity, but that same specificity leaves them exposed to exhaustion, antigen loss, and immune-related toxicity.[3,17] CAR-NK cells work differently: they layer CAR specificity on top of the NK cell's own native signaling, which means tumor recognition can happen through CAR-dependent and CAR-independent routes alike, all without triggering cytokine release syndrome or graft-versus-host disease.[6,7] CAR-macrophages take yet another path — leaning on antigen-directed phagocytosis, cytokine secretion, antigen presentation, and remodeling of the tumor microenvironment, rather than direct cytotoxic killing.[11,12,13] Given how different these mechanisms are, it's probably more accurate to say CAR-NK and CAR-M won't simply replace CAR-T — they'll expand what adoptive cellular immunotherapy can do. That's part of why the field is increasingly gravitating toward combination approaches, pairing multiple engineered cell types with checkpoint inhibitors, monoclonal antibodies, cytokines, or standard anticancer regimens.[14,15,16]

1.3. CAR engineering strategies for next-generation cellular therapies

How well a CAR cell therapy performs depends on more than just the natural biology of the effector cell — the structure of the CAR construct itself, and how the cell is engineered, matter just as much. The basic architecture of a

CAR is largely conserved across cell types, but researchers have made substantial modifications to boost signaling, persistence, trafficking, and killing capacity specifically in CAR-NK and CAR-M cells.[3,4]

1.3.1. Evolution of CAR design

A typical CAR is built from four core pieces: an extracellular antigen-recognition domain, a hinge or spacer, a transmembrane domain, and intracellular signaling domains. The extracellular piece is usually a single-chain variable fragment (scFv) derived from a monoclonal antibody, which lets the receptor bind tumor antigens directly, with no need for MHC presentation. The hinge and transmembrane regions give the receptor structural flexibility and stability, while the intracellular domains actually trigger the immune cell once antigen is recognized.[3,4] Each successive CAR generation has built on the last. First-generation CARs relied solely on the CD3ζ signaling domain and, unsurprisingly, struggled with poor persistence and proliferation. By the third generation, a dual co-stimulatory design was added to strengthen activation signals, and fourth-generation CARs — often nicknamed "armored CARs" or TRUCKs — went further still, incorporating immune-modulating cytokines like IL-12, IL-15, or IL-18 to extend persistence and reshape the tumor microenvironment. The newest addition, fifth-generation CARs, carries a signaling motif that activates the JAK/STAT pathway, driving proliferation and boosting the activity of engineered T cells.[4,14,15] These principles were developed for CAR-T therapy first, but with the right adjustments, they translate reasonably well to NK cells and macrophages too.

1.3.2. Engineering strategies for CAR-NK Cells

Designing a CAR-NK cell means working with intracellular signaling that actually fits how NK cells operate naturally. The classic CD3ζ-based CAR still gets the job done, but newer designs incorporate NK-specific adaptors — DAP10, DAP12, 2B4 (CD244), and Fc receptor γ (FcRγ) — components already involved in how NK cells activate on their own. The idea is to boost antitumor potency while leaving the cell's native character intact. One thing that really sets CAR-NK therapy apart is the sheer range of possible cell sources. Peripheral blood NK cells are straightforward to obtain but typically need extensive ex vivo expansion. Umbilical cord blood offers an immediately available, low-immunogenicity alternative. iPSC-derived NK cells bring standardized manufacturing with minimal donor-to-donor variability, and the NK-92 cell line can be manufactured at scale for research and clinical use (after irradiation to stop it from proliferating indefinitely). Getting genetic material into NK cells has never been easy — these cells are notoriously resistant to manipulation. Viral vectors, particularly retroviruses and lentiviruses, remain popular because they achieve high transduction efficiency and stable expression. But concerns around insertional mutagenesis, along with the cost and complexity of viral manufacturing, have pushed the field toward non-viral alternatives: mRNA electroporation, transposon systems like Sleeping Beauty and piggyBac, and CRISPR/Cas-based editing.[13,14,15]

1.3.3. Engineering strategies for CAR-Macrophages

Macrophages present their own set of headaches. Mature macrophages come equipped with strong intrinsic antiviral defenses, which tend to blunt standard viral transduction methods. That said, recent work has shown that adenoviral vectors — Ad5f35 in particular — can deliver CAR constructs into macrophages effectively, without hurting their viability or function.[11,12] Researchers are also exploring lentiviral vectors, mRNA electroporation, lipid nanoparticles, and CRISPR editing as ways to make manufacturing more efficient and scalable.[13] Unlike CAR-T or CAR-NK cells, CAR-macrophages aren't built for direct cytolysis — their job is to ramp up antigen-dependent phagocytosis instead. So the CAR constructs used here typically carry intracellular signaling domains from Fc receptor γ, MEGF10, or another phagocytic receptor, which activates the macrophage once it recognizes tumor antigen. That signaling drives efficient phagocytosis while still allowing the macrophage to process tumor antigens, activate dendritic cells and T lymphocytes, and secrete pro-inflammatory cytokines that push back against local immunosuppression.[11,12,13]

A second engineering goal is keeping these macrophages pro-inflammatory once they're infused — no small feat, since the immunosuppressive tumor microenvironment tends to polarize macrophages toward tumor-promoting states and strip away their cytotoxic edge. To counter this, CAR-M platforms are being built with sustained inflammatory cytokine expression, greater resistance to TGF-β, and better metabolic fitness for surviving hypoxic tumor conditions — all aimed at boosting antitumor activity while also opening the door for the body's own immune cells to infiltrate the tumor.[10,12,15]

1.3.4. Emerging engineering innovations

Synthetic biology has pushed CAR design toward increasingly precise, lower-toxicity platforms. Dual-target and tandem CARs, for instance, can bind two tumor antigens simultaneously, cutting the odds of antigen escape. Logic-gated CAR systems go a step further, using Boolean "AND," "OR," or "NOT" circuits so that activation only happens when specific antigen combinations are present — improving specificity and cutting down on off-target effects.[14,15,16] Genome editing, especially CRISPR/Cas9, now allows precise knockout of inhibitory checkpoints, removal of receptors linked to exhaustion, and insertion of the CAR construct at defined genomic sites for more consistent expression. Multiplex editing takes this even further, allowing simultaneous edits across pathways controlling persistence, metabolism, and immune evasion — producing highly optimized cell products that are well suited to allogeneic manufacturing.[13,14,15,16]

Taken together, these engineering advances are turning CAR-NK and CAR-M therapies into genuinely flexible, scalable platforms — ones that might sidestep many of the constraints conventional CAR-T therapy still runs.

As receptor design, gene delivery, and manufacturing continue to mature, clinical translation is likely to speed up, further widening what next-generation cellular immunotherapy can achieve.

1.4. Preclinical and clinical evidence

The past decade has brought a real acceleration in moving CAR-engineered NK cells (CAR-NK) and CAR-macrophages (CAR-M) from lab concept to clinic. CAR-T therapy still leads the field in terms of clinical maturity, but a growing body of preclinical data and early-phase trials suggests that both CAR-NK and CAR-M bring distinct biological strengths — strengths that may, in certain settings, complement or even outperform conventional CAR-T.[6,11,14]

1.4.1. CAR-NK therapy

Preclinical Advances and Clinical Translation: Preclinical work has repeatedly shown potent antitumor activity from CAR-NK cells, both in hematologic malignancies and solid tumors. Genetic engineering sharpens NK-cell cytotoxicity without erasing the cell's own receptor-mediated recognition, so tumor killing can happen through CAR-dependent and CAR-independent channels at once. That dual mechanism reduces vulnerability to immune escape driven by uneven or diminished antigen expression — a resistance pathway that shows up often after CAR-T therapy.[6,7,8] Experimental models have shown encouraging activity in CD19-positive acute lymphoblastic leukemia, chronic lymphocytic leukemia, non-Hodgkin lymphoma, acute myeloid leukemia, and multiple myeloma. CAR-NK cells engineered against HER2, EGFR, mesothelin, PSMA, and GPC3 have also shown solid preclinical efficacy in breast, ovarian, pancreatic, prostate, hepatocellular, and glioblastoma models.[7,14] Beyond direct killing, CAR-NK cells release a range of immune-modulating cytokines and chemokines capable of recruiting and activating other immune cells, amplifying the antitumor response within the tumor microenvironment itself.

The first clinical trial to report success with CAR-NK therapy generated considerable excitement in the field. It used cord blood–derived, anti-CD19 CAR-NK cells engineered to express IL-15 to treat patients with relapsed/refractory CD19+ malignancies. Most patients showed objective clinical responses, and notably, there was no severe cytokine release syndrome, no ICANS, and no graft-versus-host disease. The CAR-NK cells also persisted and expanded in vivo — likely thanks to IL-15 signaling — despite being allogeneic, which hints at real potential for an "off-the-shelf" cellular product.[18] Since then, a number of early-phase trials have tested CAR-NK therapy against CD19, CD22, CD33, BCMA, NKG2D ligands, and HER2 in both hematological and solid tumors. Results so far show good safety, along with some evidence of efficacy, but CAR-NK cells consistently persist less well than CAR-T cells post-infusion. That's driving a lot of current research toward strengthening IL-15 signaling, adjusting infusion schedules, and refining CAR design to extend persistence.[7,14,18]

1.4.2. CAR-Macrophage therapy

Emerging Preclinical and Early Clinical Evidence: CAR-macrophages still have several developmental hurdles to clear before becoming a routine clinical option, and they're earlier in clinical translation than CAR-NK cells. Still, the preclinical picture has been genuinely encouraging. One of the biggest advantages macrophages bring is their built-in ability to push through dense stromal tissue and immunosuppressive microenvironments — territory that often keeps lymphocytes out entirely. Once CAR-mediated antigen recognition kicks in, these engineered macrophages engulf tumor cells, process and present tumor antigens to T cells, and release pro-inflammatory cytokines capable of turning immunologically "cold" tumors "hot".[11,12] Experimental studies have consistently shown tumor cell phagocytosis and meaningful antitumor activity across a range of solid tumor models — ovarian, pancreatic, colorectal, breast, glioblastoma, and HER2-positive cancers. Beyond direct tumor clearance, CAR-M therapy also boosts dendritic-cell activation, encourages $CD8^+$ T-cell infiltration, and promotes epitope spreading — broadening and prolonging adaptive immune responses well past the original target antigen.[11,12,13]

A meaningful milestone came with the launch of first-in-human trials testing HER2-directed CAR-macrophages in patients with advanced, HER2-overexpressing solid tumors. Early results suggest the treatment is generally well tolerated, with macrophages successfully infiltrating tumors, showing signs of activation, and favorably remodeling the tumor immune microenvironment. Long-term efficacy is still an open question, but these early trials at least confirm the approach is feasible — and they've spurred development of next-generation CAR-M platforms.[12,19] There's also growing interest in combining CAR-M therapy with checkpoint inhibitors, chemotherapy, radiotherapy, or oncolytic viruses to strengthen macrophage function and push back against the persistent immunosuppression found in solid tumors — an approach that may be especially valuable for tumors marked by heavy stromal barriers and strong immune exclusion.[11,14]

1.4.3. Comparative therapeutic performance **(Table 1)**

Lined up side by side, CAR-T, CAR-NK, and CAR-M therapies each bring something different to the table (Table 1). CAR-T still has the strongest clinical track record and remains the go-to option for many hematological malignancies, largely thanks to its robust in vivo expansion and durable persistence. But that success comes with real costs — significant treatment-related toxicity, patient-specific manufacturing, and comparatively weak performance against solid tumors.[17,20,21,22] CAR-NK therapy, by contrast, offers a different set of practical and safety advantages: lower rates of cytokine release syndrome and neurotoxicity, minimal graft-versus-host risk, faster manufacturing, and the possibility of allogeneic "off-the-shelf" products. The tradeoff is that post-infusion persistence and resistance to tumor microenvironment suppression remain open problems.[6,7,14]

CAR-macrophages are a fundamentally different animal, given how much of their value comes from innate,

tissue-level function rather than lymphocyte-style killing. Their capacity to penetrate dense stroma, phagocytose tumor cells continuously, remodel the extracellular matrix, present antigens, and recruit additional immune effectors makes them a particularly strong fit for solid tumors. That said, controlling macrophage polarization, manufacturing complexity, and limited clinical experience are all still unresolved.[11,12,13] Table 1 lays out the major biological and translational differences among CAR-T, CAR-NK, and CAR-M therapies, covering mechanism of action, safety, manufacturing, and clinical applications. Rather than thinking of these as competing technologies, it's probably more useful to view them as complementary — each exploiting a different facet of immune function. As the field matures, it seems likely that future treatment strategies will combine or sequence CAR-T, CAR-NK, and CAR-M therapies alongside other immunotherapies to maximize antitumor effect while keeping toxicity in check.[14,15,16]

Table 1: Comparative characteristics of CAR-T, CAR-NK, and CAR-Macrophage therapies

Characteristic	CAR-T cells	CAR-NK cells	CAR-Macrophages (CAR-M)
Primary effector cell	Cytotoxic T lymphocyte	Natural killer cell	Macrophage
Immune system	Adaptive immunity	Innate immunity	Innate immunity
Mechanism of tumor killing	Perforin/granzyme-mediated cytotoxicity, Fas/FasL signaling	Perforin/granzyme release, TRAIL/FasL-mediated apoptosis, antibody-dependent cellular cytotoxicity (ADCC), endogenous NK receptor-mediated killing	Antigen-specific phagocytosis, antigen presentation, cytokine secretion, remodeling of tumor microenvironment
MHC dependence	MHC-independent after CAR engineering	Naturally MHC-independent	MHC-independent for CAR-mediated recognition
Recognition of antigen-loss variants	Limited	Preserved through endogenous activating receptors	Moderate; influenced by phagocytic activity and antigen presentation
Primary clinical success	Hematological malignancies	Hematological malignancies; expanding into solid tumors	Predominantly preclinical and early-phase clinical studies in solid tumors
Efficacy in solid tumors	Limited	Promising	Highly promising
Tumor infiltration	Frequently limited by stromal barriers	Moderate	Excellent due to natural macrophage trafficking into tumors
Activity within immunosuppressive tumor microenvironment	Frequently impaired	Moderately resistant	Can actively remodel the tumor microenvironment toward an inflammatory phenotype
Antigen presentation	Absent	Minimal	Strong; promotes activation of adaptive immune responses
Cytokine release syndrome (CRS)	Relatively common	Rare	Rare in current studies
Immune effector cell-associated neurotoxicity syndrome (ICANS)	Well recognized	Uncommon	Not reported to date in clinical studies
Risk of graft-versus-host disease (GVHD)	Significant with allogeneic products	Minimal	Minimal
Persistence after infusion	Long-term persistence common	Moderate; generally shorter than CAR-T	Under investigation
Manufacturing	Mostly autologous, individualized	Allogeneic "off-the-shelf" products feasible	Manufacturing protocols still evolving
Available cellular sources	Peripheral blood T cells	Peripheral blood, umbilical cord blood, induced pluripotent stem cells (iPSCs), NK-92 cell line	Peripheral blood monocytes, macrophages differentiated ex vivo, induced pluripotent stem cell-derived macrophages

Characteristic	CAR-T cells	CAR-NK cells	CAR-Macrophages (CAR-M)
Production time	Usually several weeks	Potentially shorter	Currently intermediate; under optimization
Cost	High	Potentially lower because of scalable allogeneic manufacturing	Currently uncertain; expected to decrease with manufacturing advances
Major limitations	CRS, ICANS, antigen escape, T-cell exhaustion, poor efficacy in solid tumors, complex manufacturing	Limited persistence, lower expansion in vivo, transduction challenges	Macrophage polarization, manufacturing complexity, limited clinical experience
Current stage of clinical development	Multiple regulatory approvals worldwide	Numerous Phase I/II clinical trials	Early clinical evaluation with encouraging preliminary results
Future prospects	Improved CAR design, dual-target CARs, armored CARs, combination immunotherapy	Universal allogeneic products, cytokine-enhanced CARs, genome editing, combination therapy	Tumor microenvironment remodeling, combination with checkpoint inhibitors, next-generation synthetic biology platforms

2. Future challenges and emerging directions

Adoptive cellular immunotherapy has come a long way, but CAR-natural killer (CAR-NK) cells and CAR-macrophages (CAR-M) still face real biological, manufacturing, and translational obstacles that keep them from wider clinical use. Both platforms have shown genuine promise — solid efficacy and reassuring safety in preclinical work and early trials — but there's still a gap between where they are now and the clinical maturity CAR-T therapy has already reached. Continued progress in genetic engineering, synthetic biology, and precision medicine should help close that gap.[13,14,15,16]

2.1. Manufacturing, standardization, and scalability

One of the real selling points of CAR-NK cells is that they can be produced as a standardized "off-the-shelf" product — sourced from healthy donors, umbilical cord blood, iPSCs, or established NK-cell lines — which cuts down manufacturing time and makes treatment more accessible. That said, donor-to-donor variability, quality control, GMP compliance, and keeping cells functional after cryopreservation are all still unresolved issues. CAR-macrophages are, frankly, harder to manufacture still. Mature macrophages don't proliferate much, transduce poorly compared to other cell types, and are biologically plastic enough that stable, large-scale production remains genuinely difficult.[6,7,11,12,13,14,15]

2.2. Limited persistence and functional durability

Getting the therapeutic effect to last is one of the bigger hurdles here. CAR-NK cells simply don't persist in vivo the way CAR-T cells do, which has pushed researchers toward strategies like incorporating IL-15, engineering cytokine receptors, using CRISPR/Cas9 editing, and fine-tuning dosing schedules to compensate. CAR-M therapy faces a somewhat different version of the same problem — it's less about how long the cells survive and more about whether they stay pro-inflammatory once they've infiltrated the tumor, since tumor-derived signals have a tendency to reprogram macrophages right back into an immunosuppressive state.[6,7,10,11,12,13,14,15,16]

2.3. Overcoming the immunosuppressive tumor microenvironment

The tumor microenvironment remains a stubborn barrier to immune-cell activity, regardless of which platform is used. Current strategies include building armored CAR-NK cells that resist inhibitory signaling, and engineering CAR-macrophages that hold onto their inflammatory character despite hostile local conditions. Pairing these approaches with checkpoint inhibitors, chemotherapy, radiotherapy, or anti-fibrotic agents may push antitumor responses further still.[20,21,22,11,14,15,16]

2.4. Advances in synthetic biology and genome engineering

A wave of newer technologies is reshaping what's possible here — logic-gated and dual-target CARs, CRISPR/Cas9 genome editing, inducible CAR systems, synthetic receptors, and programmable activation circuits are all improving specificity, durability, and safety, while also opening the door to universal donor cell products.[13,14,15,16]

2.5. Future clinical perspectives **(Figure 1)**

Looking ahead, it seems likely that CAR-T, CAR-NK, and CAR-M therapies won't be used in isolation so much as combined — alongside other immunotherapies, targeted agents, and radiotherapy — to take advantage of their complementary mechanisms. Artificial intelligence, multi-omics approaches, standardized manufacturing, validated biomarkers, and closer collaboration across disciplines are all likely to speed up progress toward truly personalized cellular immunotherapy. Taken as a whole, CAR-NK and CAR-M therapies look set to become valuable partners to CAR-T rather than replacements for it — and as the underlying technology keeps advancing, their role in treating both hematological and solid cancers should only grow.[13,14,15,16]

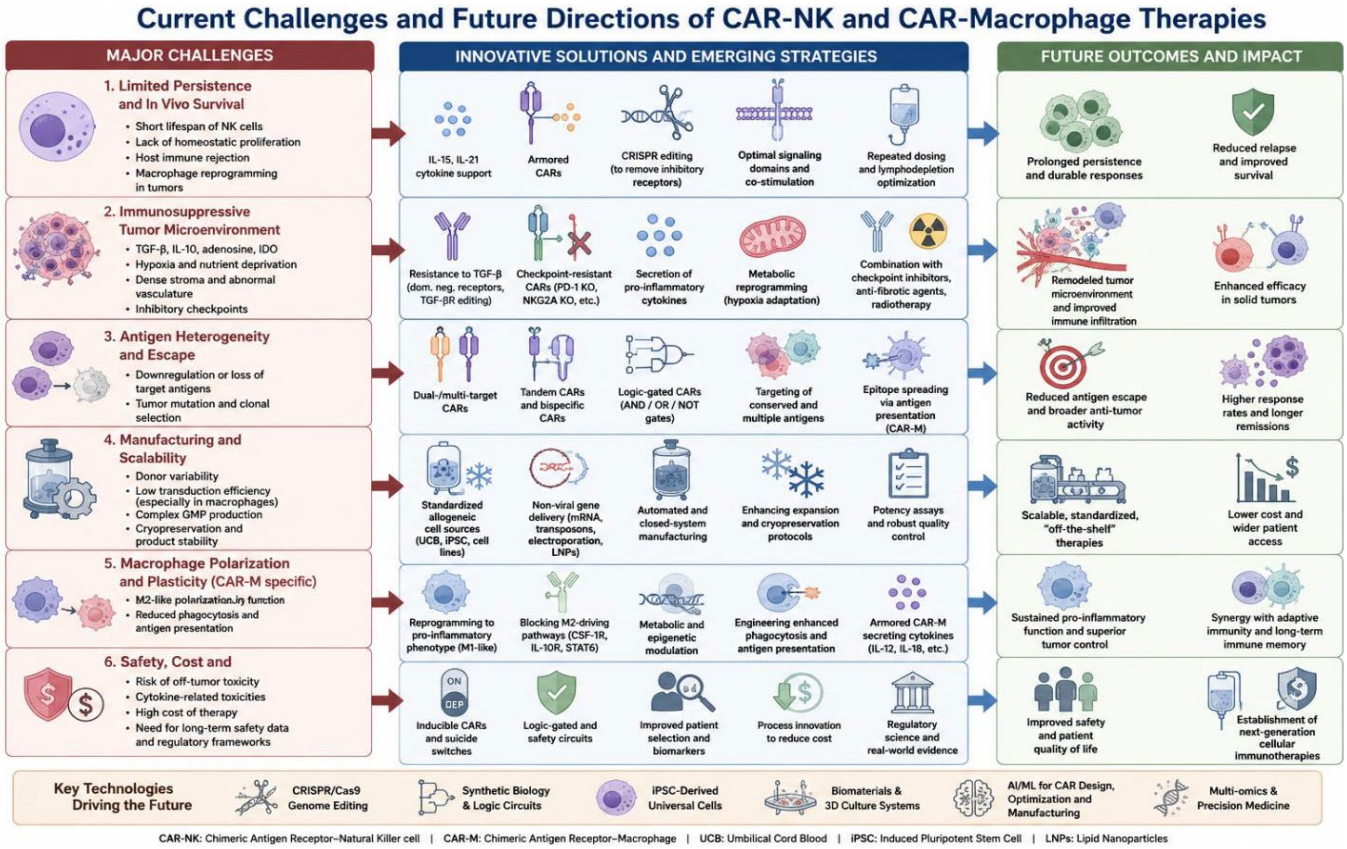

Figure 1: Current challenges and future directions of CAR-NK and CAR-macrophage therapies

3. Discussion

The rise of CAR-natural killer (CAR-NK) cells and CAR-macrophages (CAR-M) has opened up the field of adoptive cellular immunotherapy considerably, offering real ways to work around some of the core limitations that still dog conventional CAR-T therapy. CAR-T cells have undeniably transformed treatment for several hematological malignancies, but their clinical reach is still constrained by severe immune-related toxicities, complex patient-specific manufacturing, steep costs, antigen escape, and underwhelming results in solid tumors.[1,2,3,4,17,20,21,22] These shortcomings are exactly what's driving interest in alternative CAR-engineered immune cells with different, complementary biology. CAR-NK cells in particular have become an attractive option because they merge innate immune surveillance with CAR-directed tumor targeting. Lower risk of cytokine release syndrome, neurotoxicity, and graft-versus-host disease — plus the prospect of ready-made allogeneic "off-the-shelf" products — gives them a clear practical edge over autologous CAR-T therapy.[6,7,18] That said, limited persistence after infusion is still a real sticking point. A lot of current work is aimed at extending their longevity through cytokine support, refined signaling domains, and genome editing, though matching the long-term persistence CAR-T cells achieve remains elusive.[13,14,15,16]

CAR-macrophages take a fundamentally different approach, one that fits solid tumors particularly well. Their natural knack for migrating into dense tumor tissue, engulfing malignant cells, remodeling the extracellular matrix, and triggering adaptive immune responses lets them tackle aspects of tumor biology that lymphocyte-based therapies simply aren't built.[11,12,13] Early results are encouraging, but there's still a real need for further clinical work to nail down long-term efficacy, phenotypic stability, and the best manufacturing protocols. It's worth stressing that CAR-NK and CAR-M aren't meant to replace CAR-T cells — they're better understood as complementary platforms. CAR-T therapy still holds the edge for many blood cancers, CAR-NK cells bring better safety and manufacturing flexibility to the table, and CAR-macrophages look especially well-suited to breaking through the immunosuppressive microenvironment that defines solid tumors. Given all that, future treatment is likely to become more disease-specific — matching the engineered immune cell to the tumor biology at hand. Combining these therapies with checkpoint inhibitors, chemotherapy, radiotherapy, monoclonal antibodies, or oncolytic viruses could push efficacy further while helping curb resistance.[14,15,16,23]

There's still real work to do before any of this becomes routine clinical practice. Standardized manufacturing, dependable predictive biomarkers, thorough long-term safety data, and regulatory harmonization all remain priorities.[13,14,15,16] At the same time, the field is moving fast — synthetic biology, genome editing, artificial intelligence, and multi-omics technologies are reshaping what's achievable, enabling cellular therapies that are both more precise and

more durable. As these tools mature, CAR-NK and CAR-macrophage therapies seem poised to become core parts of next-generation cancer immunotherapy — not competing with CAR-T so much as rounding it out, and widening the treatment options available for patients with both blood cancers and solid tumors.[24]

3. Conclusion

CAR-based immunotherapy has genuinely reshaped how hematological malignancies are treated, but CAR-T cells alone still fall short in important ways — treatment-related toxicity, manufacturing complexity, high cost, antigen escape, and weak performance against solid tumors all continue to limit what's possible. That's precisely what's fueling growing interest in CAR-NK cells and CAR-macrophages, each of which brings something CAR-T doesn't.[25] CAR-NK cells pair strong innate cytotoxicity with a safer profile and lend themselves naturally to allogeneic, ready-to-use production. CAR-macrophages, meanwhile, seem particularly well-matched to solid tumors, given their ability to infiltrate tumor tissue, clear malignant cells through phagocytosis, and reshape the surrounding microenvironment. Early studies point to encouraging safety and antitumor activity for both platforms, though persistence, manufacturing, and immune suppression remain open problems. As cell engineering and combination immunotherapy continue to advance, both platforms look set to strengthen their clinical footing — pushing precision cancer immunotherapy further into the future.

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None.

5. Conflict of Interest

None.

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