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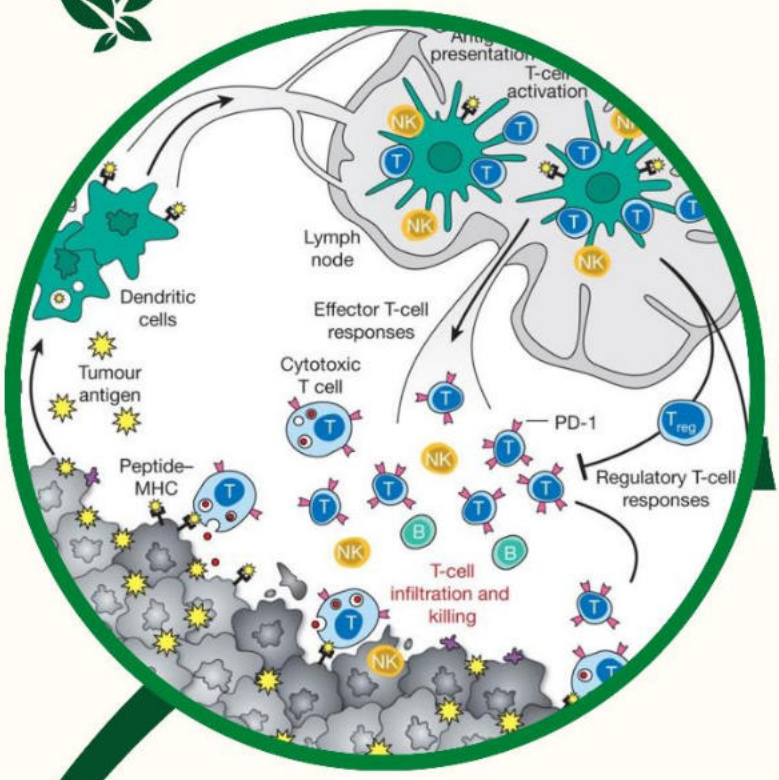
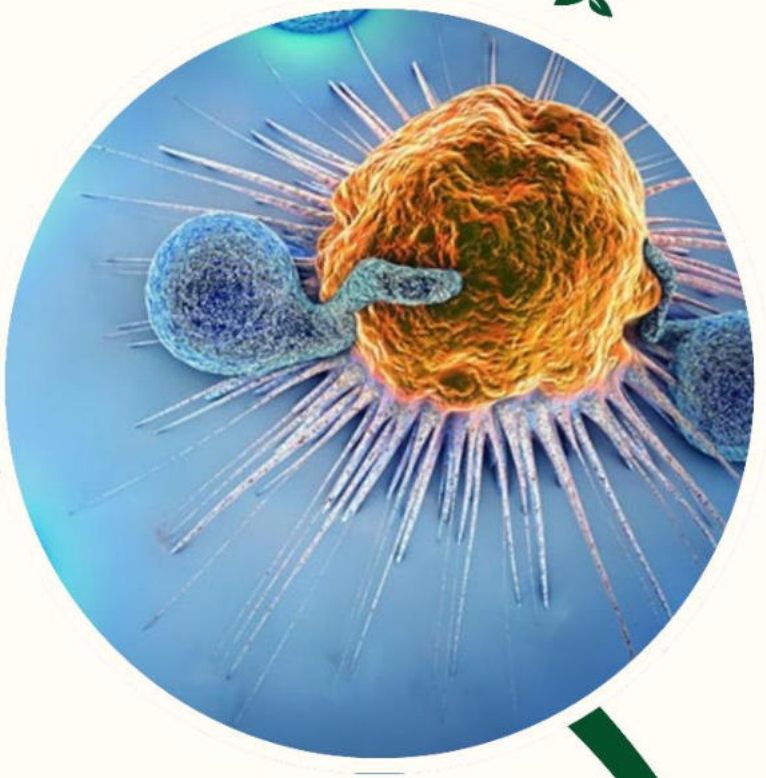
Engineering Natural Killers: A Comprehensive Review on CAR-NK Cell Therapy in Cancer Immunotherapy





CAR-NK Cell Therapy: Revolutionizing Cancer Immunotherapy with Precision

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Engineering Natural Killers: A Comprehensive Review on CAR-NK Cell Therapy in Cancer Immunotherapy

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Abstract

A rapidly developing area of cancer immunotherapy is chimeric antigen receptor-engineered natural killer (CAR-NK) cell therapy, which holds great promise for overcoming the drawbacks of CAR-T cell therapies. As cytotoxic lymphocytes of the innate immune system, natural killer (NK) cells are perfect candidates for CAR engineering because they can identify and destroy cancerous cells without first sensitising them. Combining the natural cytotoxicity and safety profile of NK cells with the specificity of CAR constructs, CAR-NK cells provide benefits like a lower risk of graft-versus-host disease (GvHD) and cytokine release syndrome (CRS). Moreover, CAR-NK cells can be produced from a variety of sources, such as established NK cell lines, peripheral blood, umbilical cord blood, and induced pluripotent stem cells (iPSCs), allowing for scalable and possibly commercially available treatments.
The main facets of CAR-NK cell therapy are thoroughly examined in this review, including cellular sources, genetic engineering methods, mechanisms of action, and advantages over CAR-T therapies. It also explores the difficulties in improving cell persistence, focusing on solid tumors, and streamlining production under Good Manufacturing Practice (GMP) guidelines. Current clinical trials and commercialisation initiatives are also assessed, emphasising advancements and persistent obstacles to broad use. All things considered, CAR-NK therapy has enormous potential to transform cancer treatment by providing a more secure, expandable, and widely applicable substitute for existing immunotherapies. To fully realise its therapeutic potential in solid and haematological malignancies, more research and innovation are essential.

Keywords: Natural Killers, CAR-NK, Cytokine

1. Introduction

Oncological treatments have been transformed by cancer immunotherapy, with chimeric antigen receptor (CAR)-based strategies having a particularly significant effect on haematologic malignancies. Despite their considerable clinical efficacy, CAR-T cell therapies are frequently limited by serious side effects, including neurotoxicity, cytokine release syndrome (CRS), and the risk of graft-versus-host disease (GvHD), especially in allogeneic application [8]. Alternative cellular therapies are being investigated as a result of these safety concerns, as well as manufacturing challenges and limited persistence. Because of their inherent capacity to identify and destroy cancerous cells without prior sensitisation and with a significantly lower risk of causing GvHD, CAR-engineered Natural Killer (CAR-NK) cells present a promising approach. In addition, NK cells have a better safety margin than CAR-T cells because of their innately more regulated cytokine release profile [8] The development of universal, off-the-shelf treatments is made easier by the fact that CAR-NK cells can be obtained from peripheral blood, NK cell lines, umbilical cord blood, or induced pluripotent stem cells (iPSCs).

Improved CAR constructs and cytokine support (e.g., IL-15) are examples of recent genetic engineering advancements that have improved NK cell cytotoxicity and persistence, allowing them to target solid and haematologic tumours with greater efficacy. According to [8], these advancements have sparked a number of ongoing clinical trials that seek to make CAR-NK therapy a common cancer treatment option.

2. Natural Killer (NK) Cells- Biology

Innate lymphoid cells known as natural killer (NK) cells are essential for the body's early defence against diseased or altered cells. In contrast to T and B cells, NK cells can cause cytotoxicity without prior sensitisation or antigen presentation through major histocompatibility complex (MHC) molecules. Rather, a balance between activating and inhibitory receptors controls their activity. Under normal circumstances, inhibitory receptors, such as killer-cell immunoglobulin-like receptors (KIRs), identify self-MHC class I molecules and stop NK cell activation. However, the lack of these inhibitory signals permits NK cells to attack target cells in the setting of viral infection or cancer, where MHC expression is frequently downregulated [18].

NK cells use both antibody-dependent cellular cytotoxicity (ADCC), which is mediated by the CD16 (FcγRIIIa) receptor, and direct cytotoxic mechanisms, such as the release of granzymes and perforin, to achieve their antitumor effects. Additionally, they generate immunoregulatory cytokines like TNF-α and IFN-γ, which help to mould the adaptive immune response.

Based on the surface expression of CD56 and CD16, human NK cells are generally divided into two major subsets: the highly cytotoxic CD56^dim CD16^+ subset and the primarily cytokine-producing CD56^bright CD16^dim/− subset. Immune surveillance and immune homeostasis maintenance depend on these functional subsets [18].

The development of engineered NK cell-based immunotherapies, like CAR-NK cells, which offer benefits in safety and allogeneic use over CAR-T therapies, has been made possible by a solid understanding of NK cell biology. They are good candidates for "off-the-shelf" therapies because of their distinct biology, which lowers manufacturing costs and time while increasing patient accessibility.

3. Chimeric Antigen Receptors (CARs) – Structure and Generations

Chimeric Antigen Receptors (CARs) are artificial receptors that, in a manner separate from the major histocompatibility complex (MHC), reroute immune cells, like T cells or NK cells, to identify and destroy tumour cells. Three main domains make up CARs: an intracellular signalling domain that mediates activation, a transmembrane domain, and an extracellular antigen-recognition domain (usually a single-chain variable fragment, or scFv, derived from a monoconal antibody) [19].

Based on the intricacy and functionality of the intracellular signalling domains, CAR evolution is divided into generations. Only the CD3ζ signalling chain was present in first-generation CARs, which was insufficient to maintain persistence and long-term activation. Co-stimulatory domains like CD28 or 4-1BB (CD137) were added by second-generation CARs, which markedly increased cytokine production and proliferation.In order to provide better expansion and cytotoxic potential, third-generation CARs additionally integrated two co-stimulatory domains (such as both CD28 and 4-1BB). Inducible cytokines, such as IL-12, are among the extra components of fourth-generation CARs, also referred to as TRUCKs (T cells Redirected for Universal Cytokine-mediated Killing), which enable improved tumour infiltration and tumour microenvironment modification [19].

CARs must be modified to fit the specific signalling machinery of NK cells. For example, to maximise activation and cytotoxic function, CAR constructs in NK cells frequently include NK-specific co-stimulatory domains like DAP10 or 2B4. Compared to CAR-T cell therapies, which can result in severe cytokine release syndrome (CRS), these designs significantly improve the cytolytic ability of CAR-NK cells while maintaining their safety profile.

Understanding the structure and evolution of CARs is critical for engineering effective CAR-NK cell therapies with improved specificity, durability, and safety in treating various cancers.

2.1. CAR Engineering NK Cell Sources

Natural killer (NK) cells from different sources are used in CAR-NK cell therapy; each has its own advantages and disadvantages in terms of biology and translation. The final CAR-NK product's scalability, safety, cytotoxic potential, and clinical applicability are all greatly impacted by the source choice.

2.2. Peripheral Blood NK Cells (PB-NK): Mature NK cells extracted straight from donor peripheral blood are known as peripheral blood NK cells (PB-NK). Despite their physiological significance and potent innate cytotoxicity, PB-NK cells frequently exhibit poor transduction efficiency and a restricted capacity for proliferation during CAR engineering. Additionally, standardisation for clinical use is complicated by donor-to-donor variability, which makes it difficult to achieve consistent therapeutic potency and phenotype across batches (Liu et al., 2020).

2.3. NK-92 Cell Line: This immortalised human NK cell line is simple to grow and modify genetically. NK-92 cells are widely used in preclinical research and early-stage clinical trials because of their homogeneity and simplicity of engineering. However, because NK-92 cells come from lymphoma, their in vivo persistence is limited because they need to be irradiated prior to infusion in order to prevent tumorigenesis (Rezvani et al., 2020).

2.4.NK cells derived from induced pluripotent stem cells (iPSCs): iPSCs provide a genetically flexible and renewable source of NK cells. "Off-the-shelf" CAR-NK treatments are made possible by the large-scale production of iPSC-derived NK (iPSC-NK) cells under Good Manufacturing Practice (GMP) guidelines. Because of their improved engineering potential and consistent phenotype, these cells have demonstrated promise in both haematologic and solid tumour models (Liu et al., 2020).

2.5. Haematopoietic Stem Cells (HSCs): HSCs have the capacity to differentiate into NK cells outside of the body, which may lead to the production of CAR-NK cells that are more persistent and have a longer lifespan. HSC-derived CAR-NK therapies are still being studied, but they have the potential to facilitate allogeneic applications and sustain longer-lasting antitumor responses [20].

3. NK Cell Sources for CAR Engineering

The source of NK cells used for genetic modification has a major impact on the effectiveness and scalability of CAR-NK therapies. There are several sources being studied at the moment, each with unique benefits. Although peripheral blood-derived NK (PB-NK) cells are readily available and mature, their inconsistent transduction efficiencies and restricted ex vivo expansion make large-scale production difficult. Despite being less mature, umbilical cord blood (CB-NK) cells exhibit superior proliferative capacity and are more amenable to genetic engineering, which makes them suitable for off-the-shelf use with a low risk of graft-versus-host disease (GvHD) [2].
A genetically flexible and renewable source of natural killer cells, induced pluripotent stem cells (iPSCs) provide homogeneous populations and allow for precise gene editing in GMP-compliant settings [2]. Although they are not as frequently used, haematopoietic stem cells (HSCs) can be engineered to improve durability and function by

differentiating into NK cells ex vivo. Achieving a balance between clinical applicability, manufacturing scalability, safety, and efficacy requires careful source selection [1][2].

4. Methods of Genetic Modification

The effectiveness and accuracy of genetic modification methods used to create NK cells with chimeric antigen receptors (CARs) are critical to the success of CAR-NK cell therapy. A major obstacle in genetic modification is that NK cells are intrinsically more resistant to viral transduction than T cells. Retroviral and lentiviral transduction are two of the most popular methods because they provide stable integration of CAR constructs. However, risks associated with viral vectors include manufacturing complexity and insertional mutagenesis [2]. Non-viral techniques like mRNA electroporation and transposon systems (like Sleeping Beauty or PiggyBac) have been used to allay these worries (Figure 1). Because of its transient expression and low genomic integration, mRNA electroporation is beneficial for short-term therapeutic approaches with a lower risk of genotoxicity [5]. Conversely, transposon systems offer a balance between safety and stability, and PiggyBac's higher cargo capacity and reduced toxicity make it particularly useful in NK cell engineering [6]. Additionally, CRISPR/Cas9 genome editing is becoming a game-changing technique for precisely inserting CAR constructs, improving precision, and enabling multiplex editing to eliminate inhibitory receptors or increase persistence [7]. These developments are increasing CAR-NK cell platforms' therapeutic potential.

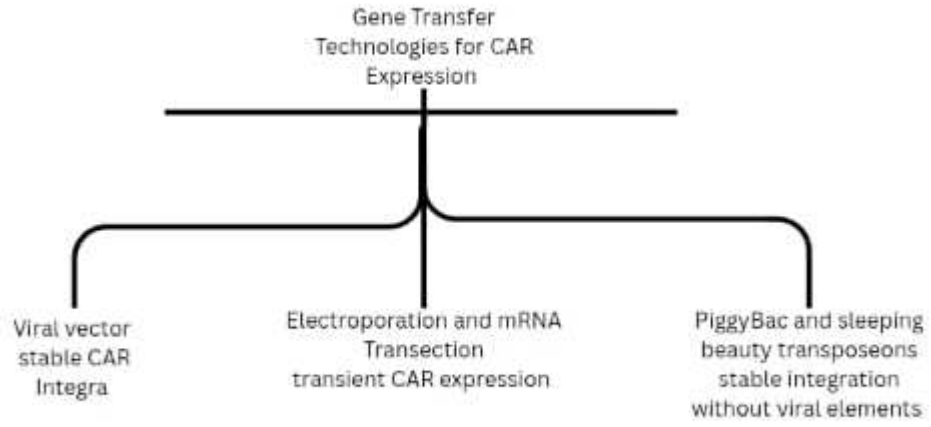


Figure 1: Types of Gene Transfer

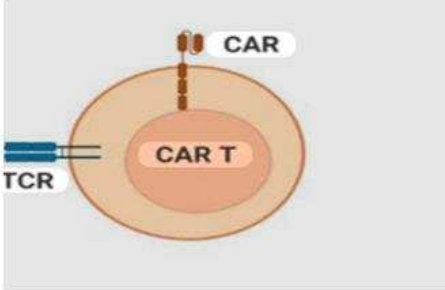
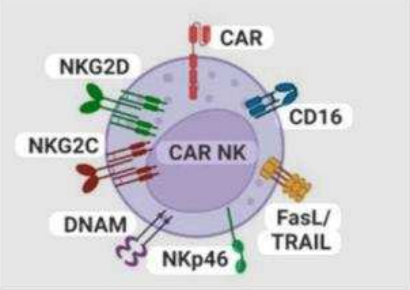
5. CAR-NK Therapy's Benefits Over CAR-T Therapy

In the context of cancer immunotherapy, chimeric antigen receptor-engineered natural killer (CAR-NK) cells have a number of clear advantages over CAR-T cells. Safety is one of the main advantages. CAR-NK cells are less likely to result in neurotoxicity and cytokine release syndrome (CRS), two frequent and potentially fatal side effects of CAR-T therapy [1]. This is mostly because, when activated, NK cells naturally control immune responses and release fewer inflammatory cytokines.

The potential to use allogeneic (donor-derived) CAR-NK cells without causing graft-versus-host disease (GvHD) is another significant benefit. CAR-NK cells can be derived from a variety of sources (such as cord blood, iPSCs, and NK cell lines), in contrast to CAR-T cells, which frequently need autologous (patient-derived) sources to prevent immune rejection. This allows for "off-the-shelf" therapeutic products, which save money and time during manufacturing [8].

Furthermore, through mechanisms unrelated to CAR signalling, NK cells exhibit innate cytotoxicity against tumour cells. This dual-mode killing lowers relapse rates and improves the chance of eradicating antigen-heterogeneous tumours [9]. When combined, these qualities make CAR-NK therapy a more secure, adaptable, and widely used substitute for CAR-T cell therapy (Table 1).

Table 1: Differences between CAR-NK and CAR-T Cells

	CAR- NK Cells	CAR-T Cells
Origin	Allogenoic	Autologous
Cytokine profile	Low levels IL-6 and IFN	High level
GvHD Risk	No	Risk
CRS Risk	Lower	Higher risk
Scalability	Off-the-shelf	Scalability
Cost	Less expensive	More expensive
		

6. Robust Tumour Obstacles and Techniques

Although CAR-NK cell therapies have shown encouraging results in haematological malignancies, there are a number of important obstacles to overcome before they can be used in solid tumours. The immunosuppressive tumour microenvironment (TME) is one of the main barriers, impeding the infiltration, persistence, and cytotoxic activity of NK cells. TME elements that can suppress NK cell activity and encourage tumour immune evasion include TGF-β, indoleamine 2,3-dioxygenase (IDO), and regulatory T cells [10].

Poor tumour homing and infiltration present another difficulty. Solid tumours, as opposed to blood cancers, are encircled by thick stroma and aberrant vasculature, which makes it challenging for CAR-NK cells to efficiently reach and enter tumour sites. [11]. Furthermore, because tumour cells may downregulate or lose the targeted antigen, antigen heterogeneity in solid tumours may result in immune escape.

Numerous tactics have been put forth to address these issues. These include modifying CAR-NK cells to secrete

cytokines like IL-15 to promote in vivo proliferation and persistence or to express chemokine receptors (such as CXCR4, CCR5) to improve trafficking to tumours. To increase specificity and resistance to immune suppression, bispecific CAR constructs that target multiple antigens and the co-expression of dominant-negative TGF-β receptors are also being investigated [12].

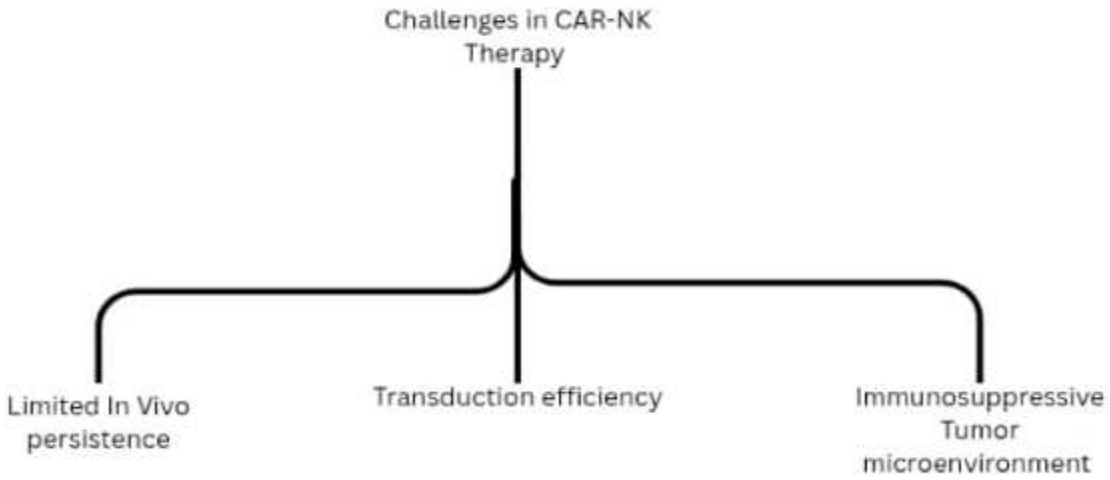


Figure 2: Challenges in CAR-NK Therapy

7. Clinical Trials and Commercialisation

With several early-phase trials assessing its safety and effectiveness in treating solid and haematological tumours, the clinical development of CAR-NK cell therapy is progressing quickly. The first-in-human trial employing cord blood-derived CAR-NK cells that target CD19 in patients with relapsed or refractory CD19-positive cancers was documented in a seminal study by Liu et al. (2020). With no significant toxicities, such as neurotoxicity or cytokine release syndrome, which are frequent in CAR-T treatments, the treatment demonstrated a 73% response rate [1]. CAR-NK therapies that target antigens like CD19, CD33, HER2, and MUC1 are currently being evaluated in more than a dozen clinical trials (clinicaltrials.gov). In an effort to reduce costs and streamline production, a number of platforms are utilising commercially available allogeneic NK cells derived from umbilical cord blood, NK cell lines (such as NK-92), and induced pluripotent stem cells (iPSCs) [13]. CAR-NK therapies provide a more scalable and economical model than autologous CAR-T therapies from the standpoint of commercialisation. With the promise of standardised production and enhanced clinical accessibility, businesses such as Takeda and Fate Therapeutics are investing in iPSC-derived NK platforms [14]. These treatments could become a common immunotherapeutic choice with a broad range of clinical uses as they move through clinical pipelines.

8. Improving Function and Persistence

Ensuring long-term persistence and sustained cytotoxic activity after infusion is one of the main challenges in CAR-NK cell therapy. NK cells may not be able to proliferate in vivo and have a shorter lifespan by nature than T cells. Several tactics have been used to improve CAR-NK cell function and persistence in order to get around this restriction. Cytokine support systems, like IL-15 expression within the CAR construct, have been introduced by genetic engineering techniques, which greatly increase NK cell survival and antitumor function without the need for exogenous cytokine administration [15].Preclinical and clinical research has shown that IL-15-expressing CAR-NK

cells exhibit enhanced cytotoxicity, in vivo expansion, and proliferation.

Moreover, co-stimulatory domains like DAP10 and 2B4 (CD244) are being added to CAR constructs to encourage IFN-γ production, activation, and degranulation. Furthermore, checkpoint inhibition (e.g., targeting NKG2A, PD-1/PD-L1 axis) and metabolic reprogramming have demonstrated promise in maintaining CAR-NK activity in the immunosuppressive tumour microenvironment [16].
New developments in gene editing technologies, such as CRISPR-Cas9, also make it possible to precisely alter signalling pathways to improve functionality. These developments are bringing CAR-NK therapy one step closer to producing the strong, enduring effects required for clinical success.

9. GMP Compliance, Manufacturing, and Cryopreservation

To guarantee consistency, safety, and effectiveness in the production of CAR-NK cells—especially for clinical and commercial applications—careful standardisation is necessary. Large-scale production is more feasible because CAR-NK therapies, in contrast to autologous CAR-T cells, are frequently made as allogeneic, commercially available products. Nevertheless, this calls for rigorous adherence to Good Manufacturing Practice (GMP) guidelines throughout the formulation, genetic modification, and ex vivo expansion procedures.
Cryopreservation is an essential step in the process that allows for worldwide distribution and long-term storage. To preserve viability, functionality, and cytotoxic potential after thawing, optimal freezing procedures utilising cryoprotectants such as DMSO are crucial. According to studies, cryopreserved CAR-NK cells can still have antitumor activity, but results are greatly impacted by variables like cell density and freeze-thaw cycles [8].
GMP-compliant production has been made easier with the development of scalable platforms like bioreactors and closed-system culture technologies. To satisfy regulatory requirements, strict quality control is also required, including cytotoxic assays, vector integration evaluation, and sterility testing [4].
The translation of CAR-NK cell therapies from bench to bedside is generally being driven by improvements in manufacturing technology and cryopreservation protocols; multiple products are presently making their way through clinical pipelines under GMP-compliant conditions.

10. Emerging Innovations and Future Outlook

With a number of cutting-edge strategies ready to get past present obstacles and increase clinical applications, the field of CAR-NK cell therapy is developing quickly. Enhancing NK cell persistence, specificity, and resistance to the immunosuppressive tumour microenvironment through the use of gene editing technologies like CRISPR/Cas9 is one promising avenue. By introducing cytokine genes or disrupting inhibitory receptors, this precision editing enhances CAR-NK function [1].
Using induced pluripotent stem cells (iPSCs) as a renewable source to produce standardised CAR-NK cells is another innovative advancement. Scalability, decreased variability, and the possibility of "off-the-shelf" availability are features of iPSC-derived NK cells that could significantly reduce costs and increase accessibility [2].

11. Conclusion

With major benefits over traditional CAR-T therapies, including decreased toxicity, improved safety profiles, and the possibility of "off-the-shelf" allogeneic use, CAR-NK cell therapy is a revolutionary development in cancer immunotherapy. NK cells' distinct biology, which includes their natural ability to target tumours and their ability to circumvent tumour escape mechanisms, makes them a promising treatment option for solid tumours as well as haematological malignancies. Ongoing advancements in genetic engineering, cell sourcing, and combination treatment approaches continue to improve CAR-NK efficacy in spite of obstacles relating to persistence, tumour microenvironment suppression, and manufacturing complexity.
Up until now, clinical trials have shown promising safety and initial efficacy outcomes, indicating the possibility of

wider use and eventual commercialisation. However, more research is required to fully realise the promise of CAR-NK therapy. Numerous present constraints should be addressed by integrating cutting-edge technologies like CRISPR and iPSC-derived NK cells.

To sum up, CAR-NK therapy is a promising next-generation immunotherapeutic strategy. The conversion of these developments into efficient, generally available cancer treatments will depend heavily on ongoing interdisciplinary research, clinical development, and regulatory alignment efforts.

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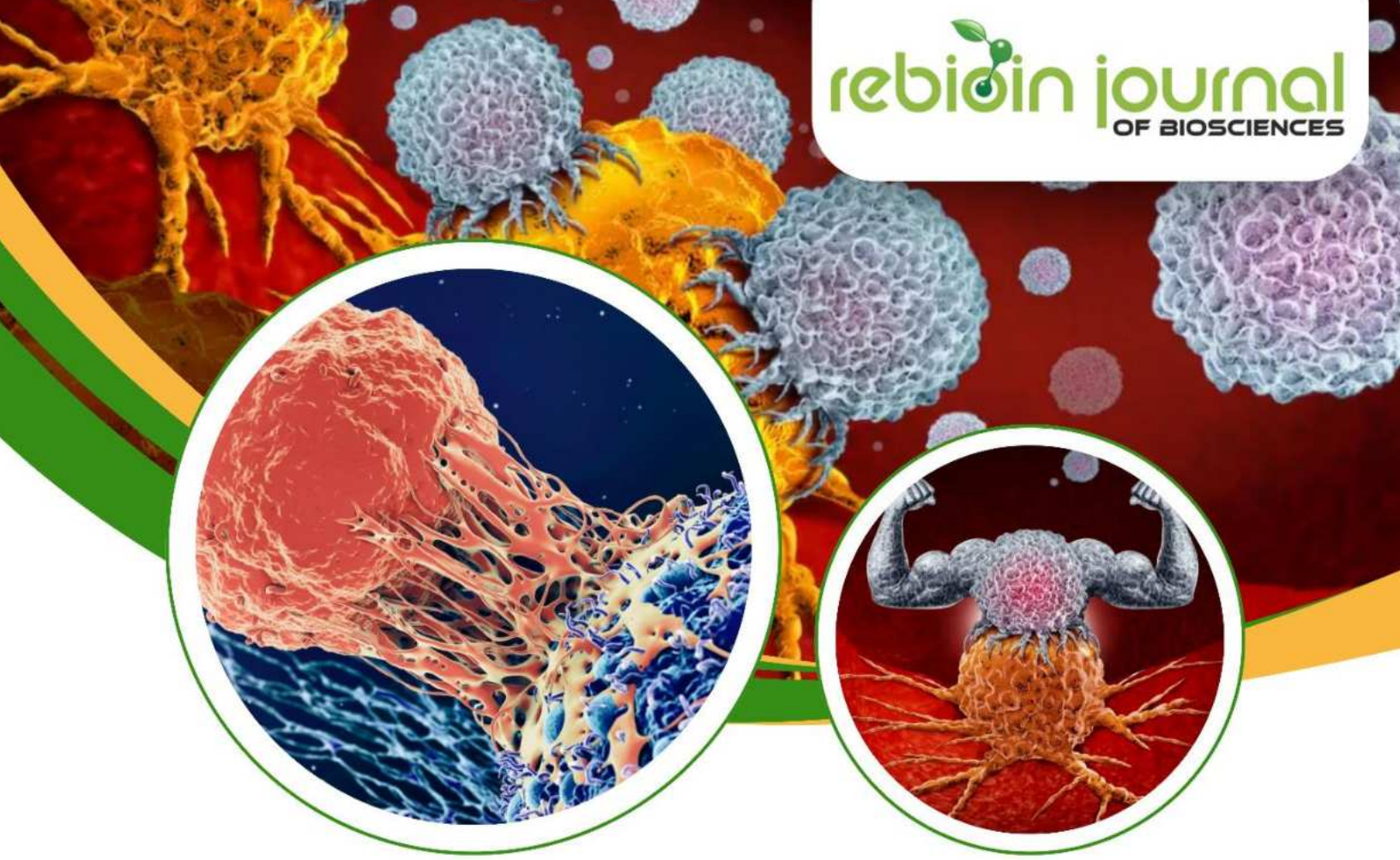

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