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Overcoming barriers to the implementation of interleukin-12-based strategies in cancer immunotherapy: translational challenges, clinical integration, and public health implications

Habeeb Akorede Lawal[1,2*], Abdulrahman Olamilekan Raji[1], Aisha Eniola Olayiwola[1], Zainab Ajoke Suleiman[1], Wahab Muiz[3], Azeez Okikiola Lawal[4], Olalekan John Okesanya[5,6], Rasheed Ibrahim[1], Tolutope Adebimpe Oso[5,7]

[1]Department of Biochemistry, Kwara State University, Malete 240103, Nigeria
[2]Molecular and Infectious Diseases Laboratory, Abubakar Tafawa Balewa University Teaching Hospital, Bauchi 740101, Nigeria
[3]Department of Industrial Chemistry, Federal University, Dutsin-Ma 820001, Nigeria
[4]Department of Medical Laboratory Sciences, Kwara State University, Malete 241103, Nigeria
[5]Department of Medical Laboratory Science, Neuropsychiatric Hospital, Aro, Abeokuta 110101, Nigeria
[6]Faculty of Medicine, Department of Public Health and Maritime Transport, University of Thessaly, 38334 Volos, Greece
[7]Department of Medical Laboratory Science, McPherson University, Seiki-Sotayo 112233, Nigeria

***Correspondence:** Habeeb Akorede Lawal, Department of Biochemistry, Kwara State University, P.M.B. 1530, Ilorin, Malete 240103, Nigeria. lawalhabeeb909@gmail.com
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Abstract

Cancer immunotherapy is one of the renowned therapeutic approaches worldwide, where its intervention has scaled further than conventional therapy. This review targets oncology researchers, immunotherapy clinicians, and public health policymakers and aims to address novel strategies for overcoming the barriers that exploit the implementation of interleukin-12 (IL-12) in cancer immunotherapy. Moreover, it emphasizes the translational challenges and clinical implications for global health interventions. IL-12 cytokine therapy is a specialized type of cancer immunotherapy that involves the systemic or local administration of IL-12 to the targeted tumor microenvironment. Over the years, IL-12 therapy has shown a promising approach in its therapeutic potential in the treatment of various cancer diseases. The molecular structure of IL-12 depicts its potential for stimulating the immune system. IL-12 enhances the production of interferon-gamma (IFN-γ), a specialized cytokine used for the potential treatment of malignant melanoma and other cancer diseases. However, despite its potent antitumor effects, IL-12 therapy has been limited by considerable toxicity observed in preclinical studies, raising concerns about its safety profile. To fully harness IL-12's therapeutic potential, researchers should prioritize translational studies that mitigate toxicity and improve delivery mechanisms. This includes innovative approaches such as vector-based delivery systems (e.g., viral vectors and nanoparticle carriers), localized gene therapy platforms, and

synergistic combination regimens that reduce systemic exposure while enhancing efficacy. Policymakers should promote flexible regulatory frameworks to accommodate adaptive clinical trial designs, while funding bodies are encouraged to support high-impact translational research that accelerates the safe clinical application of IL-12 and similar immunotherapeutic agents.

Keywords

Interleukin-12 (IL-12), cancer immunotherapy, cytokine therapy, interferon-gamma (IFN-γ)

Introduction

Millions of lives were saved over the years through the invention of immunotherapy when the world knew less about vaccination. This occurred in 1796 when Edward Jenner developed a protective immunity against smallpox [1]. His invention of immunotherapeutic vaccines has significantly influenced the evolution of cancer immunotherapy. An emerging report in ancient Egypt 300 years ago from now, towards the 19th century, states a spontaneous vanishing of inflammation and tumor progression. However, the significance of immune system interventions in cancer repression was yet to be sorted [2]. Over time, the landscape of cancer immunotherapy has evolved to incorporate the intervention of cytokine therapy. In 1992 and 1998, metastatic renal cell carcinoma (RCC) and metastatic melanoma, respectively, were approved to be treated by interleukin-2 (IL-2) due to its spontaneous regressive effect upon administration [3]. Cancer immunotherapy has revolutionized oncology by harnessing the immune system's intrinsic ability to detect and eradicate malignant cells. Unlike conventional therapies such as chemotherapy and radiation, which directly target tumor cells, immunotherapy aims to stimulate or restore the immune response against cancer, leading to potentially durable and long-lasting remissions [4]. Key immunotherapeutic strategies include immune checkpoint inhibitors, which block inhibitory pathways like programmed cell death 1/programmed cell death ligand 1 (PD-1/PD-L1) and CTLA-4 to reinvigorate exhausted T cells [5]; adoptive cell therapies such as chimeric antigen receptor (CAR) T-cell therapy, which engineers patient T cells to recognize tumor antigens [6] specifically; oncolytic virotherapy that uses genetically modified viruses to selectively infect and kill cancer cells while stimulating anti-tumor immunity [7]; and cytokine-based treatments that modulate the immune milieu to enhance immune cell activation [8]. These modalities have led to unprecedented clinical successes in various malignancies, including melanoma, non-small cell lung cancer, and hematologic cancers, transforming previously lethal diagnoses into manageable conditions for some patients [9]. However, challenges remain. Immune-related adverse effects due to systemic immune activation can cause significant toxicity [10]. Efficient delivery of immunotherapeutic agents to the tumor microenvironment (TME) is often hindered by physical and immunosuppressive barriers [11]. Furthermore, tumors can evade immune detection through mechanisms such as antigen loss, immunosuppressive cell recruitment, and metabolic reprogramming, which limit the efficacy of current therapies [12]. Against this backdrop, interleukin-12 (IL-12) has emerged as a promising cytokine-based immunotherapy due to its potent ability to activate innate and adaptive immune responses.

Cytokines are proteins essential for the stimulation of both adaptive and innate immune responses. It has unveiled a significant approach to the repressive effect of cancer progression [13]. Its advancement in therapeutic efficacy has been greatly reviewed in TMEs, combination immunotherapy with checkpoint blockade, and advanced cytokine-based immunotherapy [13]. In the past 4 decades, cytokines have emerged and passed through several clinical trials, in which some were later approved by the FDA to be used for clinical cancer treatments. Interferon-alpha (IFN-α) and IL-2 are two top cytokines approved by the FDA to treat malignant melanoma and metastatic melanoma, respectively. Moreover, Proleukin (IL-2) is also approved for the treatment of metastatic RCC. However, some other cytokines underwent several clinical trials and are subject to potential cytokine therapies, such as IL-12 [14].

IL-12 is a heterodimer molecule that promotes the differentiation of T helper cell type 1 (Th1) and plays a key role in cell-mediated type of immunity. The structure of IL-12 consists of two covalently bound

subunits, namely IL-12p35 and IL-12p40, measured in kilodaltons, which are co-dependently produced by antigen-presenting cells (APCs). IL-12, alongside its family, induces the production of interferon-gamma (IFN-γ) and enlargement and proliferation of T cells [15]. From the Protein Data Bank (PDB), the structure of p40 monomeric subunits of IL-12 is determined to a resolution of 2.5 Å. This subunit structure reveals similarities in cytokine receptors. Furthermore, upon encountering a foreign body, it is verily secreted to induce proinflammatory functions and activate natural killer (NK) cells to combat the foreign bodies. This shows the significant role it plays in pathological processes and autoimmune diseases [16]. IL-12 has been recognized for its potent immunomodulatory and anti-tumor properties, primarily due to its ability to upregulate IFN-γ production, which plays a critical role in promoting apoptosis and exerting cytotoxic effects against tumor cells [17]. Moreover, IL-12 has demonstrated non-toxic, dose-dependent inhibition of tumor metastasis in experimental models [18], further supporting its therapeutic promise. Despite these compelling biological effects, the translation of IL-12-based strategies into clinical cancer immunotherapy remains significantly hindered by several challenges. These include systemic toxicity at therapeutic doses, complexities in delivery mechanisms, immune regulation dynamics, and limited integration into current clinical protocols. Nonetheless, it continues to be praised for its multifunctional potential in cancer therapy, which includes activation of cytotoxic T lymphocytes (CTLs), anti-angiogenic activity, enhancement of chemotherapeutic efficacy, and potential utility in combination therapies and localized delivery strategies [13, 15, 16]. Given its broad immunotherapeutic profile and capacity to modulate the TME, this study is justified in seeking to explore and overcome the barriers to the implementation of IL-12-based strategies in cancer immunotherapy. Understanding the translational challenges, optimizing clinical integration, and evaluating public health implications will be essential steps in advancing IL-12 from experimental promise to clinical practice. This review aims to provide a comprehensive assessment of scientific, clinical, and public health barriers to IL-12 cancer immunotherapy and offer strategic solutions for its successful translation and integration into cancer care systems.

Method

A narrative-oriented literature search was conducted in PubMed, Scopus, and Google Scholar databases for articles published in English with no limit to publication date on barriers to the implementation of IL-12-based strategies in cancer immunotherapy, while priority was given to articles published in the last ten years for currency of data. The search strings combined Medical Subject Headings (MeSH) and free-text terms related to IL-12 and cancer immunotherapy, such as ("interleukin-12" OR "IL-12") AND ("cancer immunotherapy" OR "cytokine therapy") AND ("delivery system" OR "vector" OR "toxicity" OR "tumor microenvironment"). Articles were eligible if they reported IL-12 as a therapeutic agent (systemic or local), delivery strategies, safety/toxicity, TME interactions, and translational/public-health implications and were primary research (pre-clinical or clinical) or high-quality reviews relevant to the study's objective of exploring current challenges and potential solutions to the clinical application of IL-12-based cancer therapies that informed gaps in evidence. Relevant references within selected articles were also reviewed to ensure a comprehensive synthesis of the literature. All records were imported into the Zotero reference manager; automatic de-duplication was followed by manual verification of titles, authors, and Digital Object Identifiers. Two reviewers independently screened titles/abstracts, then full texts, resolving disagreements by consensus. After full-text appraisal, the extracted information was subjected to an inductive thematic analysis. Emerging recurrent concepts were iteratively coded and clustered into predefined, yet data-driven, thematic domains as stated below.

1. Biological basis of IL-12 in immunotherapy;
2. Therapeutic strategies involving IL-12;
3. Implementation barriers in clinical translation;
4. Public health and equity considerations;
5. Future perspectives and innovative solutions;
6. Recommendations for translational and public health advancement.

The findings were narratively integrated qualitatively under the key thematic headings identified through an iterative review of recurring concepts to highlight consensus, controversies, and knowledge gaps relevant to advancing IL-12-based cancer therapy.

Biological basis of IL-12 in immunotherapy

IL-12 is one of the groups of the class one hematopoietic family of cytokines, consisting of soluble heterodimers, α subunit (IL-12p35) and the β subunit (IL-12p40). The latter is linked to the former through disulfide bonds formed between IL-12p35 (C96) and the IL-12p40 (C199) subunit for human IL-12 [19, 20]. IL-12 signals through a heterodimeric receptor composed of IL-12 receptor β1 (IL-12Rβ1) and β2 (IL-12Rβ2) subunits, which in turn activate the Janus kinase (JAK) and signal transducer and activator of transcription (STAT) pathways [19, 21]. Although IL-12 can activate multiple STAT proteins, STAT4 is the predominant and most functionally relevant isoform in mammalian systems [22]. After binding to the receptor, the tyrosine kinase Tyk2 will be activated by IL-12Rβ1 and IL-12Rβ2 associated with JAK2, giving the addition of phosphate to the receptor's intracellular domains and recruitment of the STAT4 transcription factor. Phosphorylated STAT4 forms a dimer and moves to the nucleus to induce transcription of genes involved in Th1 differentiation and IFN-γ production [15, 21].

One of the crucial components of innate immunity is the NK cell, which is a cytotoxic cell and also known as a solid producer of immune-regulatory cytokines such as IFN-γ. IL-12 upregulates the production of NK cells' cytotoxicity by activating receptors such as NKG2D and enhancing effector molecules such as perforin and TNF-related apoptosis-inducing ligand (TRAIL), which mediate tumor cell lysis [23, 24]. To combat $HER2^+$ malignancies, IL-12 works together with the Fc portion of IgG (FcγRIII) with engagement on NK cells to amplify IFN-γ production, an important mechanism for antibody-dependent cellular cytotoxicity (ADCC) [25]. It also activates NK cells through STAT4 and extracellular signal-regulated kinases 1 and 2 (ERK1/2) phosphorylation, boosting their anti-tumor response [24, 26]. The IFN-γ production is central to IL-12's immunostimulatory effects, allowing it to further amplify through cross-talk with B cells. B cells provide IL-18 and cell-in-contact signals necessary for optimal IFN-γ secretion by NK cells in response to IL-12 [27]. This cytokine cascade polarizes immune responses toward Th1 immunity, enhancing antigen presentation and macrophage activation [24, 25]. In CTLs, the synergistic effects of IL-12 and IL-2 bring about expansion and overcome effector functions, mainly in T-cell receptor (TCR)$\alpha\beta^+$ and TCR$\gamma\delta^+$ subsets [28]. It boosts CTL-driven tumor elimination by facilitating granzyme B production and maintaining metabolic health through PI3K/Akt signaling [29]. Stimulation of NK cells with IL-12/IL-15/IL-18 creates enduring effector cell populations that can secrete substantial amounts of IFN-γ and exhibit antitumor effectiveness when transferred adoptively [30]. The combined role of IL-12 in potentiating innate and adaptive cytotoxicity, coupled with its ability to sustain IFN-γ-driven inflammation, proves its therapeutic potential in cancer immunotherapy [26, 30].

In 2010, a study by Sorensen et al. [31] showed the exact mechanism of the anti-angiogenic effect of IL-12. The study used B16 transfected to express IL-12 (B16/IL-12), providing constant, local production of IL-12. The finding, along with others, indicated that the anti-angiogenic properties of IL-12 occur by suppressing pro-angiogenic factors like vascular endothelial growth factor (VEGF) and matrix metalloproteinase (MMP)-9 through IFN-γ-dependent mechanisms. In TME, IL-12 normalizes chaotic vasculature by downregulating VEGF receptor 3 (VEGFR3), reducing vessel leakiness, and improving immune cell infiltration. This vascular remodeling enhances chemotherapeutic delivery and immune-mediated tumor suppression [31, 32]. Studies have shown that the anti-tumor properties of IL-12 primarily operate through two key mechanisms: immune activation and direct inhibition of angiogenesis. In the immune activation pathway, IL-12 enhances cluster differentiation (CD)8^+ T cell cytotoxicity and NK cell-mediated tumor lysis by upregulating granzyme B and perforin. Additionally, IL-12-induced IFN-γ production polarizes macrophages toward antitumor phenotypes and enhances antigen presentation, further strengthening the immune response against tumor cells [32, 33]. Complementing these early observations, Savid-Frontera et al. [34] demonstrated that hydrodynamic gene transfer of as little as 1 μg of IL-12 cDNA can achieve transient systemic cytokine levels (~2.5 ng mL^{-1} at 24 h) that suppress B16 and

EL4 tumor growth, reduce platelet endothelial cell adhesion molecule (PECAM)-positive tumor vasculature, and markedly increase $CD45^+/CD8^+$ leukocyte infiltration—all without the severe toxicity seen at the higher 5 μg dose. Their work highlights hydrodynamic delivery as a practical, dose-tunable platform for exploiting IL-12's dual IFN-γ-dependent anti-angiogenic mechanisms while mitigating safety concerns, thereby offering a contemporary avenue for translating *IL-12* gene therapy into the clinic [34].

It's worthy to delve into the dual functions of IFN-γ, both its inhibitory nature and pro-tumorigenic role. In recent studies, it was reported that low-dose IFN-γ was injected into the lateral tail vein of mice, which showcases the pro-tumorigenic function of IFN-γ. Large lung metastatic nodes were observed in comparison with cancer cells treated with a neutral solvent [35]. Furthermore, IFN-γ enables the evolution of cancer stem cells to metastatic cancer stem cells due to its induction by chemokine receptors [36]. These chemokines are essentially known to attract the immune cells to the site of infections and inflammation, yet play a role in angiogenesis and cancer metastasis, most specifically C-X-C motif chemokine ligand 9 (CXCL9). A report by Ding et al. [37] showcases a broader analysis of the anti-cancer effect and pro-tumorigenic effect of CXCL9. It is well justified that CXCL9 exhibits a tumor-suppressing effect by recruiting tumor-infiltrating $CD8^+$ and NK cells, which deteriorate angiogenesis. Likewise, in breast cancer, melanoma, lung cancer, head and neck cancer, and chronic lymphocytic leukemia, CXCL9 is found to be overexpressed, whereby it serves as a detective biomarker in cancer prognosis. In conclusion, the dynamic function of CXCL9 might be due to its complex role in tumor immunity, while the contrary roles are due to its receptor's splice variants, C-X-C motif chemokine receptor 3 isoform A (CXCR3A) and CXCR3B [38].

For direct angiogenesis inhibition, IL-12 blocks pathological neovascularization in corneal and tumor models by inducing IFN-γ, which suppresses endothelial cell proliferation and destabilizes nascent vessels [39–41]. This effect persists in immunodeficient mice, indicating innate immunity-independent pathways [40, 41]. The inhibitory or stimulatory roles that preserve self-tolerance and modulate immune responses are regulated by immune checkpoint pathways [42]. The anti-tumor immunity is enhanced by the synergetic effect of IL-12 and immune checkpoint inhibitors. Combining IL-12 with PD-1/PD-L1 inhibitors like avelumab, durvalumab, nivolumab, or pembrolizumab amplifies cytotoxic T and NK cell infiltration, the production of IFN-γ, and tumor regression, even surmounting resistance [39]. The TME is further transformed toward a Th1 response by IL-12 mRNA therapies (e.g., MEDI1191). In addition, IL-12 with CTLA-4 blockade boosts effector T cells and reduces regulatory T cells, achieving complete tumor regression in preclinical models [43, 44]. The promising efficacy of these combinations demonstrates and amplifies the benefit of immunotherapy. As mentioned earlier, the integration of IL-12 and IL-2 demonstrates synergistic antitumor effects in various cancer models. This therapy triggers tumor regression through multiple mechanisms, including enhanced $CD8^+$ T cell and NK cell responses [45, 46]. The treatment results in increased tumor infiltration by $CD4^+$ and $CD8^+$ T cells, generation of tumor-specific CTLs, and establishment of protective antitumor memory [46]. The antitumor effects are critically dependent on endogenous IFN-γ production and an intact Fas/FasL pathway, which contribute to both antiangiogenic effects and direct tumor cell killing [47]. The synergistic interaction between IL-12 and IL-2 provides complementary immunoregulatory signals, making this combination a promising approach for cancer immunotherapy [48].

IL-23, a family of IL-12, and TME

IL-23 is a cytokine that belongs to the family of IL-12. It's a heterodimeric proinflammatory cytokine. They share a common subunit, p40, which covalently binds to the p35 unit with IL-12 [49]. IL-23 is mainly produced by dendritic cells and macrophages. The IL-23 receptor is composed of the IL-12 receptor (IL-12RB1) that signals through tyrosine kinase-2, as discussed initially. IL-23R induces the activity of STAT3 by signaling through JAK2 [50]. IL-23 is linked with the evasion of tumor immunity and inflammation and was first discovered to play a pro-tumorigenic role [51]. IL-23 is also evident to be involved in the enlargement of breast cancer cells and tumor metastasis. However, the blockade of the genetic makeup of IL-23 resulted in cytotoxic T-cell tumor infiltration via the TME [52]. TMEs are the ecosystem around the tumor, consisting of both malignant and non-malignant components, as well as the associated signalling

molecules they release. These components are the deciding factor of tumor growth, spread, and inhibition. Moreover, targeting specific TME cells poses a greater hurdle in the realm of cancer immunotherapy [53]. Thus, more research on the target of the TME would be essential.

Therapeutic strategies involving IL-12

Various preclinical trials have shown the therapeutic usage of IL-12, administered intravenously, intraperitoneally, subcutaneously, or intratumorally, in genetically modified mice, as it has demonstrated the ability to prevent or slow down the growth rate of tumor cells [32]. It can be administered alone or in combination with other known therapies to maximize its effectiveness against cancer cells and mitigate side effects associated with the direct delivery of IL-12.

Mono-therapy approaches

Mono-therapy approaches in the therapeutic use of IL-12 consist of recombinant IL-12 and plasmid-based delivery, often administered through intratumoral injection. Recombinant human IL-12 (rhIL-12), an immunoregulatory protein produced via genetic engineering technology, is used due to its high purity, activity, and relatively low concentration (Table 1) [54]. It becomes the only agent that can not only improve immune response but also form and regenerate blood cells (hematopoietic function). Intratumoral administration of plasmid-encoding IL-12 has shown robust anti-tumor activity, serving as a promising strategy against cancer cells, which allows the patients' cells to produce IL-12 after treatment with plasmid-encoding IL-12, stimulating the immune cells and enhancing antitumor responses [18]. This method is used in place of the direct administration of IL-12, as it helps to overcome the toxic effects caused by the overproduction of IFN-γ and reduced delivery of IL-12 to the tumor cells. Although IL-12 monotherapy in cancer immunotherapy offers potent antitumor immune activation through NK and T cells and IFN-γ induction, it is limited by severe systemic toxicities, a narrow therapeutic window, and lack of tumor specificity that causes off-target effects and restricts clinical dosing [22, 55].

Table 1. Therapeutic strategies involving IL-12 in cancer immunotherapy

Strategy	Key features	Merits	Limitations	Key references
Monotherapy	Recombinant IL-12 or plasmid-based IL-12, often through intratumoral injection	-Potent activation of NK and T cells -Induces IFN-γ -Simple administration	-Severe systemic toxicity -Narrow therapeutic window -Lack of tumor specificity, off-target effects	[17, 39]
Combination therapy	IL-12 with chemotherapy, radiotherapy, or immune checkpoint inhibitors	-Synergistic antitumor effects -Can overcome resistance -Modulates tumor microenvironment	-Increased risk of systemic toxicity (mainly due to IFN-γ) -Complex dosing and management	[62]
Vector-based approach	Viral vectors, nanoparticles, or cell based delivery	-Localized sustained IL-12 expression -Reduced systemic toxicity -Enhanced immune activation	-Vector immunogenicity -Risk of insertional -Variable transfection efficiency	[39, 63]
Targeted delivery	Tumor-localized expression, gene therapy, oncolytic virus, immunocytokines	-Improved tumor specificity -Reduced off-target toxicity -Enhanced pharmacokinetics	-Incomplete tumor penetration -Potential immunogenicity of fusion protein -Off-tissue binding	[63]

IL-12: interleukin-12; NK: natural killer; IFN-γ: interferon-gamma

Combination therapies

Cancer was originally treated through the traditional (chemotherapy and radiotherapy) and conventional approaches, all of which may be accompanied by severe side effects [56]. Due to this limitation, IL-12 was used with these known therapies as a more efficient treatment to mitigate these side effects [57]. Chemotherapy is one of the most commonly known therapies used to inhibit the growth of cancerous cells in the body. Chemotherapeutic drugs (e.g., cisplatin) damage normal body cells as they inhibit the growth of cancer cells through cell apoptosis and the induction of cell cycle arrest, leading to side effects such as weakness, nausea, vomiting, and anemia [58]. IL-12 in combination with chemotherapy has been reported in several preclinical trials to demonstrate significant cytotoxic effects in immunogenic tumors when administered immediately after chemotherapy, highlighting the significance of early treatment [32]. Radiotherapy is another major method used to inhibit cancer cells' growth within a specific region or those that have spread to nearby lymph nodes [54]. Radiotherapy inhibits the spread of tumor cells through DNA damage, which leads to cell death, and is accompanied by side effects such as genetic mutations [59]. These side effects can be prevented through the combination of IL-12 with radiotherapy, which has been reported to cure different forms of cancer in animal models [60]. Checkpoint inhibitors, a class of immunotherapy drugs, are molecules that improve the host immune system against tumor cells by blocking the checkpoint pathway to allow the T cells to recognize and attack cancer cells [61]. IL-12 combined with chemotherapy, radiotherapy, targeted agents, or immune checkpoint inhibitors enhances antitumor efficacy by synergistically modulating the TME and overcoming resistance; however, they are often accompanied by increased systemic toxicities, mainly due to elevated IFN-γ levels and immune activation, which limits dosing and necessitates careful management [61, 62]. Using IL-12, an immunomodulator, with immunotherapy would increase the effectiveness of this approach; further clinical studies are required to determine the effectiveness of this combination.

Vector-based approaches

This comprises the use of viral vectors, nanoparticles, or cell-based IL-12 delivery approaches. Viral vectors (such as the adenovirus, herpes simplex virus, and vaccinia virus), as a means of delivering IL-12 to cancer cells in various tumor models, have demonstrated antitumor effects by inducing both innate and generalized immune responses [63]. Nanoparticles are small, ultrafine particles used as a means through which the IL-12 gene or protein is delivered to tumor cells. The use of this approach has significantly reduced systemic toxicity caused to other normal cells by the direct administration of IL-12 [64]. Cell-based IL-12 delivery has been proposed as an effective means of delivering IL-12 to tumor cells. Cells such as mesenchymal stroma cells, T cells (neoantigen-reactive T cells and engineered T cells), dendritic cells, and NK cells are used in the delivery of this therapeutic agent [63]. Vector-based IL-12 delivery enables localized, sustained cytokine expression within tumors, reducing systemic toxicity and improving immune activation, but challenges include vector immunogenicity, potential insertional mutagenesis, and variable transfection efficiency that may limit clinical efficacy [39, 62].

Targeted delivery

This refers to methods (such as tumor-localized expression, gene therapy, and oncolytic virus) used to directly target tumor cells. When IL-12 is used as a targeted delivery against tumor-localized expression, it stimulates the lymphoid cells, consisting of the T cells, NK cells, and innate lymphoid cells (Table 1). This stimulation also leads to an increase in the secretion of IFN-γ, a dual-role cytokine in the TME, which can either support tumor cells' progression or inhibit their growth [32]. Despite the controversy regarding the activity of IFN-γ, many researchers still emphasize its repressive effect. Studies have proven that the effect of IFN-γ depends on its concentration in the TME. Therefore, low-dose IFN-γ upregulates the metastatic effect, and high-dose treatment of IFN-γ represses tumor growth [65]. Upon treatment with IL-12, IFN-γ's role is shifted to its antitumor ability, inhibiting angiogenesis. On the other hand, the required concentration of IFN-γ needed to exert this inhibitory effect is yet to be known. However, more studies are required. Gene therapy approaches deliver IL-12 to the tumor cells at a relatively low concentration until

the tumor eventually disappears over time, enhancing the cytotoxic effects of this cytokine and overcoming the toxic effects caused by the administration of recombinant IL-12 in large doses [66]. Oncolytic viruses (such as the Vaccinia virus, Sendai virus, parvovirus, Newcastle disease virus, etc.) are viruses used to deliver IL-12 to cancer cells. They are either naturally occurring or genetically modified and multiply themselves in tumor cells, causing cell apoptosis without causing damage to the natural body cells. Studies have reported that the delivery of IL-12 via oncolytic agents has shown significant anti-tumor potential and also a reduction in side effects accompanied by the administration of large doses of IL-12 [67–69].

Implementation barriers in clinical translation

Biological and clinical barriers

Despite the sturdy antitumor activity of IL-12, systemic administration of IL-12 was shown to be remarkably toxic in preclinical studies. Systemic inflammation and cytokine storms are facilitated by IL-12 through inducing IFN-γ production, activating immune cells, and driving Th1 responses, linking innate and adaptive immunity, but causing damage when disrupted [16]. Systemic toxicity arises predominantly from excessive IFN-γ production and the induction of proinflammatory cytokines, including TNF-α, IL-6, and IL-8, which trigger cytokine release syndromes and severe inflammatory reactions [70]. Furthermore, IL-12 administration perturbs immunoregulatory balances within the TME, promoting immune suppression through the recruitment of regulatory T-cells and myeloid-derived suppressor cells (MDSCs) [39]. These immunoregulatory dynamics pose significant barriers to achieving sustained antitumor activity while maintaining patient safety [39]. In a phase II study by Jenks (1996), a maximal dose of 0.5 μg/kg per day led to acute side effects in 12 out of 17 patients and the death of two patients. Surprisingly, the same dose per day was found to be tolerable in patients who enrolled in the phase I study. It was observed that the difference in toxicity between phase I and II trials was due to a change in the dosage schedule. The phase I study employed a single tester dose of IL-12 a week before the multiple-dose regimen, and this blunted the toxicity induced by subsequent doses [17]. Broadly, the acute effect of discouraging tumor response in phase II trials reduced the enthusiasm for IL-12 as systemic cancer immunotherapy; hence, there is a need for a safer, targeted delivery method.

Another study by DeBonis et al. [71] investigated the IL-12 pharmacokinetics desensitization after repeated doses using a mathematical model approach. In a comparison of two mechanisms, such as increased clearance via receptor-mediated serum removal and reduced bioavailability due to IL-12 sequestration in lymphatic tissues, it was noted that the reduced bioavailability model fits accurately for a clinical trial, indicating that IL-12 retention in lymph nodes limits its entry into the bloodstream. Notably, the reduced bioavailability model fits accurately for a clinical trial, indicating that IL-12 retention in lymph nodes limits its entry into the bloodstream. The levels of IL-12 were predicted using the model, and delivery strategies were explored to reduce systemic exposure, aiding a safer therapeutic approach. An intricate system, made up of various cells, signaling molecules, and extracellular matrix, is the TME [72], which promotes the metastasis of cancer through various mechanisms, including altered cell-cell communication via TGF-β, Wnt, and Hedgehog pathways [73]; ECM remodeling by MMPs [74]; immune evasion through tumor-associated macrophages and MDSCs [75]; angiogenesis driven by VEGF [76]; and metabolic re-modulation that disrupts immune cell function [77]. These mechanisms build an oncogenic environment that promotes tumor survival, invasion, and resistance to therapies. The ability of IL-12 to induce multiple inflammatory cytokines such as GM-CSF, TNF-α, IL-8, IL-6, IL-15, and IL-18 [78] and to activate NK cells [79] to enhance the function of DCs, such as their maturation and antigen presentation [80], and to prime naïve T cells is presumed to be its result as a vaccine adjuvant [81].

Technological and regulatory barriers

Regardless of the improvement of IL-12 delivery, numerous challenges impede its application. The fusion of IL-12 with extracellular matrix or immune factors through systemic administration helps prolong half-life and reduce off-target effects, but still with toxicity risk [63]. The virus-based delivery system, though efficient, poses immune neutralization, heterogeneity, and gene integration risks [82]. Non-viral carriers

such as nanoparticles and vesicles decrease cytotoxicity, mutagenicity, and immunogenicity, but with instability, easy inactivation, and low gene expression. In addition, cell-based IL-12 delivery, even with prospects, struggles with poor cell productivity, transduction inefficiency, in vivo rejection, and patient variability [39]. These limitations outline the need for iterative enhancement to improve antitumor efficacy while improving delivery systems. The inconsistencies in dosage, delivery methods, and therapeutic outcomes for IL-12 formulation and administration across studies are a result of the absence of standardized protocols. This difference aggravates the appraisal of safety, efficacy, and reproducibility, hindering clinical translation. Moreover, differences in vector design, dosing schedules, and formulation stability [83, 84] further challenge regulatory approval and large-scale application. Establishing standardized guidelines is essential to optimize IL-12-based therapies and ensure consistent clinical results [83].

Health system and economic barriers

The widespread implementation of IL-12-based cancer immunotherapies is majorly impeded due to the health system and economic barriers, especially in the aspects of cost production, scalability, access in low- and middle-income countries (LMICs), and incorporation into standard cancer care. The production and scalability of IL-12 is one significant challenge related to IL-12. According to Liu et al. [81] and Medrano et al. [85], the production of biologically active IL-12 by using plants has shown potential as an affordable and scalable approach. Single-chain versions of murine and chicken IL-12 have been produced by using transgenic tobacco plants and root cultures. They showed accurate post-translational modifications, including glycosylation and biological activity, successfully compared to IL-12 obtained from animal cells [81, 85]. Moreover, biologically active human IL-12 has been generated and secreted by using plant cell suspension cultures [86]. HEK 293 cells in mammalian systems have been developed to isolate high yields of pure, bioactive human IL-12 without relying on affinity tags by using a simple heparin-affinity purification approach [87]. These approaches in production and purification methods may aid in addressing the high costs involved in IL-12 production.

In addition, research shows that the accessibility of IL-12-based cancer immunotherapies remains inadequate in LMICs, mainly due to financial constraints, limited infrastructure, and issues of systemic healthcare. Presently, research has prioritized localized delivery methods for IL-12, with the purpose of improving its antitumor effectiveness while reducing systemic toxicity [39]. An eminent approach includes the utilization of genetically modified T cells engineered to express IL-12 in a controllable way, which has shown significant tumor regression without any harmful impact in preclinical studies [26]. IL-12 remains insufficient in LMICs due to persistent healthcare inequity, despite its therapeutic relevance and access to immuno-oncology interventions. However, when IL-12 was delivered systemically, limited success and substantial toxicity were revealed through early clinical trials [17, 88]. Additionally, just-concluded investigations have turned in the direction of innovative delivery strategies aimed at increasing IL-12 concentration within the TME while decreasing systemic side effects. Although hurdles persist, ongoing clinical efforts are actively assessing these novel approaches to fully leverage IL-12's antitumor capabilities while addressing its associated toxicities [89].

Public health and equity considerations

Despite prior hindrances from systemic toxicity in IL-12, localized delivery strategies have shown robust antitumor effects with minimal adverse events in preclinical studies [39]. As mentioned in the earlier part of this review, IL-12 works synergistically with other cytokines and treatment modalities to influence antitumor activity and control the TME. Thus, its anti-angiogenic characteristics and ability to control tumor-associated macrophages contribute more to its treatment potential [90]. Nguyen et al. [39] highlighted that ongoing clinical trials are investigating various IL-12 delivery strategies. Besides, genetic polymorphisms in IL-12 genes may affect cancer vulnerability and could have predictive or prognostic significance in future oncogenic applications [90]. Generally, IL-12-based therapies show promise for

addressing global cancer issues through multifaceted mechanisms. However, integration in public health poses significant equity challenges.

Globally, the utilization of IL-12-based therapies could have profound implications for cancer burden reduction, particularly in regions with a high incidence of immunogenic tumors [17, 91]. However, disparities in manufacturing capacity, regulatory approval pathway, and affordability contribute to unequal access. For instance, LMICs may face limitations in adopting IL-12 immunotherapy due to high costs, lack of infrastructure for localized delivery systems, and challenges in integrating these therapies into public health programs [91]. Concrete, scalable solutions include (i) technology-transfer partnerships that enable regional fill-and-finish facilities to produce GMP-grade IL-12 at reduced cost; (ii) tiered-pricing agreements similar to those negotiated for antiretrovirals; and (iii) integration of IL-12 administration into existing chemotherapy day-units and district-hospital surgical suites to leverage established supply chains and staffing [92, 93].

Considering the analysis of the National Cancer databases, there are significant disparities in access to novel cancer immunotherapies. Elements including age, sex, socioeconomic status, income levels, insurance type, and residential education impact the implementation of these treatments. Non-Hispanic Black patients encounter worse survival results, even when receiving immunotherapy, which is a result of race and ethnicity [94]. Another study revealed that bias remains before and after FDA approval of checkpoint inhibitors, notably impacting Black and Hispanic patients with no insurance or Medicaid and those with humble household incomes [95]. The result of Gupta et al. [96] confirmed that patients living in areas with lower educational attainment and economic resources are unlikely to receive immunotherapy, mainly among non-Hispanic White patients. Understanding and addressing these disparities requires a multilevel approach targeting individual and social policy levels and the healthcare system, with increased power at higher levels to overcome challenges in access to immunotherapy and clinical trials [97]. Community-engaged, decentralized clinical-trial networks, such as mobile infusion vans linked to tele-oncology hubs, can bring IL-12 studies directly to underserved neighborhoods, increase minority enrollment, and generate real-world effectiveness data relevant to resource-limited settings [98].

The discovery of dose-limiting toxicities (DLTs) of IL-12 in prior clinical experiments has allowed cancer researchers to find out how to successfully administer IL-12 to tumors, achieving treatments for different cancers while escaping the associated harmful effects. Discoveries now utilize strategies including nanoparticles, fusion proteins, and mRNA formulation to enhance local IL-12 delivery within tumors, hence reducing systemic exposure [89]. Notably, thermostable, lyophilized mRNA-lipid nanoparticles (LNPs) can be reconstituted at peripheral clinics without a continuous cold chain, while polymeric slow-release depots have enabled single-visit dosing schedules that cut patient travel costs by > 70% in LMIC pilot programs. These approaches show promise in enhancing IL-12's therapeutic index and are being tested in clinical trials [99, 100]. Simultaneously, the WHO Model List of Essential Medicines (EML) and EML for Children (EMLc) have undergone updates to ensure that recommended cancer medicines offer significant clinical benefits, including improving overall survival and enhancing the quality of life [101]. Opportunities to access essential medicines for non-communicable diseases, such as cancer, remain a significant burden as countries work towards Universal Health Coverage (UHC), and as such, it demands strengthened healthcare systems, evidence-based priority setting, and financial resources [102].

Moreover, ethical concerns in experimental therapies pose a burden that must be addressed carefully to ensure patient safety and uphold ethical standards. So far, the therapies have faced issues such as toxicity management, informed consent, clinical trial design, and balancing risk with potential benefits. To protect patients from harm, healthcare providers must focus more on rigorous dose escalation studies, as this will allow for the identification of maximum tolerated doses (MTDs). An example can be seen in a study by Minnar et al. [103], which identified the MTDs based on the number of DLTs. The results indicated that NSH-IL-12 (a fusion of IL-12 and the NSH antibody) was controlled well up to a dose of 16.8 μg/kg. Researchers must also focus on developing tumor-targeted delivery systems (e.g., membrane-anchored IL-12-T cells) to minimize off-target effects [104]. In clinical trial design, researchers must include an appropriate dosing schedule and ensure equity in the recruitment of patients [105]. Although localized IL-

12 may introduce new ethical considerations, which may be addressed accordingly, it must be given attention, as it can reduce systemic toxicity. Researchers must transparently communicate these trade-offs during trial enrollment and continually reassess protocols as new safety data emerge [103, 105]. Engaging ethicists, oncologists, and patient advocates collaboratively is crucial for addressing these challenges and promoting IL-12 as a transformative cancer treatment.

Smith-Graziani and Flowers [106] reported that issues such as socioeconomic, geographic, and systemic barriers pose equity barriers for underserved communities in immunotherapy for rare and treatment-resistant cancers. Their marginalization in clinical trials reduces safety and efficacy data and, as such, sustains disparities. Insurance coverage limitations, high costs, and transportation challenges reduce access to and treatment adherence. Distrust of medical research, language barriers, and provider biases further hinder equitable delivery. Innovations such as localized IL-12 delivery systems that reduce toxicity and treatment frequency may improve feasibility in resource-limited settings by lowering infrastructure requirements, decreasing treatment costs, and enabling administration in decentralized or community-based clinics [39]. Pilot implementation studies in sub-Saharan Africa have demonstrated that nurse-led intratumoral injections, supported by smartphone-based adverse-event reporting, are feasible in district hospitals lacking advanced radiotherapy units, providing a template for scale-up. Minority participation can increase through decentralized trials and community engagement, as demonstrated by initiatives such as the National Cancer Institute Community Oncology Research Program, which demonstrates that community-based research networks enhance access, trust, and participation among underrepresented populations [106]. Addressing the above barriers is crucial to minimizing disparities in IL-12 immunotherapy access and outcomes in the underprivileged community. Decisively, addressing the challenges faced by the public requires multidimensional approaches that will integrate equity-focused frameworks into research design, regulatory policy, and healthcare delivery. Simultaneously, achieving fair and effective results necessitates promising affordability, increasing access for underserved groups, and fostering inclusive clinical research.

Future perspectives and innovative solutions

A potential avenue for future research includes the development of two-dimensional nano-biomaterials coupled with engineered IL-12 variants. Graphene, a cutting-edge 2D nanoparticle that enhances direct penetration of the lipid makeup TME and has an exact effect on the direct nucleus of the targeted tumor cell, is another approach yet to be well elucidated [107]. Moreover, the short lifespan of cytokine-mediated therapy is due to their small molecular weight, which is subjected to poor pharmacokinetic properties upon systemic administration. The small weight enables quick renal clearance, which leads to a short half-life of the cytokines. In the end, it would require continuous administration of IL-12 to meet its dose requirement, but unfortunately, the continuity would result in low therapeutic potential due to toxicity [108]. Therefore, the abundant administration of IL-12 would result in a greater level of toxicity, which accounts for its potential to combat many healthy cells before arriving at the targeted tumor site. Thus, protein engineering has been a promising approach in elucidating the systemic and local administration of IL-12 in solid tumor therapy. In a study, an engineered cytokine (IL-12) was evaluated upon administration within a specific duration of dose contents, showcasing greater specificity to the targeted TME. However, this research has reported the lower bioavailability of IL-12 in the system in regard to low toxicity [109]. Another recent study by Horton et al. [28] shows that the absence of IL-12 receptor expression within a T-cell could lead to a primary resistance effect of systemic administration of IL-12 to the targeted tumor cell. Therein, the resistance can be reduced by the mechanistic combinations of IL-2 and an engineered variant of IL-12, which could reduce therapeutic DLT. Future studies should systematically screen and characterize novel IL-12 splice variants and fusion constructs (e.g., IL-12–IL-23 chimeras) that retain antitumor potency while minimizing pro-inflammatory signaling.

In the context of the innovative solution in overcoming the barriers to the administration of IL-12 in cancer immunotherapy, understanding of vast aspects of oncology and its smart drug administration would be crucial. Despite all the advancements in cancer research and high resistance effect of cancer therapy,

conventional therapy is still the most commonly used therapy. Elucidating nanoparticle smart drug administration would be crucial to bringing IL-12 cytokine-mediated therapy to life. The polymer nanoparticle has been a great watch-out in the studies of immunotherapy due to its essential properties of biocompatibility, smaller size, biodegradability, and very high stimulation of the immune system [110]. Studies have proven nanoparticles to be significant contributors to the success of cancer immunotherapy. It has shown the effect of activation of APC; likewise, it is an immunosuppressive agent of TME. It also allows the uptake of immunostimulatory cytokines for the induction of B-cell and T-cell responses. Whereas, they act as an adjuvant [111]. This nanoparticle systemic-delivery effect engulfs the cytokines to be delivered to the targeted TME for easy transmission and proactiveness of the IL-12 without losing its pharmacokinetic properties. With this mechanism, the lifespan of the cytokines is elongated for it to exert the intended effect at the site of action [112]. Emerging research has also highlighted the role of tumor cell metabolism and post-translational modifications in shaping immune responses to cytokine therapies. Modulation of post-translational modifications such as lysine vitcylation and succinylation has emerged as a novel strategy to enhance STAT1-mediated immune responses, offering potential synergy with IL-12-based cancer immunotherapies. These approaches may unlock new avenues to improve efficacy while mitigating systemic toxicity [113]. Combining IL-12 with checkpoint inhibitors, oncolytic viruses, or adoptive cell therapies warrants dedicated preclinical pipelines to identify synergistic schedules (e.g., IL-12 priming followed by anti-PD-1) and to define biomarkers that predict additive toxicity.

Despite the advancement in cancer immunotherapy, the emerging resistive effect experienced by some individuals has posed a greater threat to the future of cancer immunotherapy and its relevance. This issue called for many oncologists to depict another preclinical intervention, which leads to the identification of some predictive and prognostic biomarkers in elucidating and understanding the mechanism of action of cytokine therapy with immune checkpoint blockade (ICB) [114]. The mechanistic ICB has shown a durable antitumor effect on metastatic melanoma and other types of tumor cells [115]. Verily, the interactions of PD-1/PD-L1 within the system could counter the defeat of cancer cells with the use of the immune system. Studies have now shown that the anti-tumor properties of IL-12 primarily operate through two key mechanisms: immune activation and direct inhibition of angiogenesis. In the immune activation pathway, IL-12 enhances $CD8^+$ T cell cytotoxicity and NK cell-mediated tumor lysis by upregulating granzyme B and perforin as discussed earlier. Additionally, IL-12-induced IFN-γ production polarizes macrophages toward antitumor phenotypes and enhances antigen presentation, further strengthening the immune response against tumor cells [116]. These approaches of personalized immunotherapy guided with biomarkers and genomes are another promising future perspective and innovation in enabling a precise administration of IL-12 to the targeted TME. Refining IL-12 dosing schedules, such as ultra-low continuous infusion versus high-intensity pulses, should be prioritized in phase I trials, with adaptive designs to balance efficacy and cytokine-release syndrome risk [117].

The recent advancement in technology of utilizing mRNA-based delivery of IL-12 and CRISPR-assisted gene editing to make a precise and localized IL-12 expression, with reduced off-target effect, has been greatly appreciated. In the local administration of IL-12 encapsulated within LNPs, research shows a potent inhibitory effect of IL-12 against cancer cells, with a statistical preference of 91.26% outperforming IFN-γ and IL-7 in both a syngeneic mouse model and a humanized model [75]. Without prevailing systemic toxicity, intravenous administration of IL-12 LNP encapsulation shows a 0.5 in 1 reduction of liver tumor burden in the MYC hepatocellular carcinoma model through $CD8^+$ T cell activation [118]. One of the profound delivery-targeted strategies lies in the administration of a low dose of IL-12 mRNA. In reference, the administration of 0.5 μg of IL-12 mRNA achieves tumor regression in melanoma and colorectal tumor models when combined with anti-PD-L1 [119]. As it's understood that mRNA-mediated IL-12 enables dose-controlled administration [75], CRISPR enables the induction of a specific tumor and prevents constitutive expression risk [119]. In recent research, where a novel CAR-T product is being engineered from the CRISPR system called RB-312, upon encountering a specific antigen, the product is being activated to extinguish the antigen. Once the antigen vanishes, the antigenic stimulus vanishes as well, which is because of reducing systemic toxicity [119]. IL-12, serving as an adjuvant, enhances the effectiveness in immune

activation of dendritic cell maturation and production of IFN-γ when combined in a cancer vaccine [91, 120]. Within CAR-T strategies of administering IL-12, research shows that ovarian and breast cancer models were administered with an engineered membrane-bound IL-12, resulting in a prompt elimination of antigen-negative tumors, outperforming the usual CAR-T cell therapy [121]. The road ahead must also confront manufacturing scalability, regulatory hurdles for gene-edited products, and the risk of immune escape driven by chronic IL-12 exposure, challenges that future investigations should model in clinically relevant settings. The aforementioned future perspectives are renowned and a novel approach that tends to reduce systemic toxicity in the administration of IL-12. Provided are innovative solutions that call the attention of researchers to achieving global cancer freedom.

Recommendations for translational and public health advancement

Despite the significant anti-tumor activity of IL-12, it has encountered an enormous setback since the late 1990s in its use due to the systemic toxicity associated with the administration of IL-12 to tumor cells [39]. However, several approaches have been developed to offer solutions to each delivery strategy's limitations, reducing the toxicity level associated with the systemic administration of IL-12, the most commonly reported being neutropenia and thrombocytopenia [104]. With this improvement, IL-12 can finally fulfill its antitumor potential in cancer immunotherapy. Translational research consortia play a significant role in bridging the gap between laboratory testing and the pharmacological use of IL-12 in tumor cells and providing possible solutions to the limitations of its systemic administration. In a study reported by Dong et al. [63], the fusion of IL-12 to extracellular matrix proteins, collagens, and immune factors significantly increased its antitumor potential, thereby inhibiting cancer cells more effectively and with no systemic toxicity. They also stated that the use of viral vectors (such as the oncolytic viruses, poxvirus, adenovirus, and vaccinia virus) as a delivery system for IL-12 has significantly reduced the toxicity associated with the systemic administration of IL-12 and enhanced antitumor effects by inducing both innate and adaptive immune responses. An extracellular matrix fusion protein that consists of the human monoclonal IgG1 antibody NHS76 fused at each CH3 C-terminus to human IL-12, NHS-IL12, is a fusion protein that is structured to target single- and double-stranded DNA in regions consisting of dead cells due to insufficient oxygen supply within solid tumors [103]. NHS-IL12 has demonstrated significant Th1 immune activation and the ability to slow down or inhibit tumor cells by activating NK cells and $CD8^+$ T lymphocytes. With this great approach, IL-12 administration to cancer cells would have barely any systemic toxicity.

Global health partnerships (GHPs) are collaborative networks guided by equity, which involve complex relationships between individuals and organizations from low-income, middle-income, or high-income countries around the world based on past collaborative work [122], for instance, the therapeutic use of IL-12 in cancer immunotherapy. The GHP's main goal is to provide everyone with equal access to essential health services and products, irrespective of their economic income, to improve global health. Also, senior health workers have taken bold steps towards overcoming the barrier of accessing adequate health facilities across the world by forming a body called the Future of Health (FOH) [123]. These bodies came together and identified actions that can be taken to overcome this major health challenge, which include leadership prioritization and accountability, designing and implementing comprehensive measures to overcome inequity, defining, monitoring, and measuring progress on equity access, and fostering partnerships with other bodies that enhance the future of equitable access of individuals to quality health services and products.

The importance of strengthening health systems to improve immunotherapy readiness and access is highlighted by current research. The disparities in patients' access to cancer care and outcomes are a result of novel, improved cancer diagnosis and treatment [97]. However, as disparities in access to immunotherapy persist, interventions at the policy level, healthcare systems, and multilevel approaches targeting individuals are necessary to ensure equitable access to clinical trials and regular care. Technologies like e-health can improve patient adherence and communication for immunotherapy, possibly reducing costs and improving outcomes [124]. Data-driven health systems strengthening interventions at the district level have shown promise in improving facility readiness, including infrastructure, clinical

services, and medical equipment to provide quality care [125]. The National Cancer Institute Minority-Underserved Community Oncology Research Program and the Affordable Care Act, which are sponsored by the government and have expanded clinical trials and high-quality cancer care, have shown promising efficacy [97]. Therefore, it is essential to reinforce health systems' preparedness to improve overall healthcare delivery and outcomes.

Despite the development of improved therapies for IL-12, financial constraints pose a significant limitation on its use, particularly in LMICs. This limits the accessibility of individuals to the use of this therapeutic agent in cancer immunotherapy, leading to poor global health [126]. To overcome this price constraint and ensure the sustainability of healthcare systems funded by the public, various strategies have been developed. One of these strategies is the value-based pricing (VBP) for innovative drugs such as immune-oncology (I-O) drugs, which determines the benefits a particular patient gains from an antitumor innovative drug to estimate its best price [127], although the implementation of VBP is still undecided in the United States. To rationalize global clinical trials and approval processes, regulatory bodies should collaborate on IL-12 immunotherapy standards. Clinical trials can also be accelerated by the International Council for Harmonization (ICH) through the development of harmonized guidelines specific to immunomodulatory agents like IL-12, ensuring consistent evaluation criteria across regions. Implementing adaptive trial designs, seamless phase II/III trials, and master protocols can also improve efficiency by enabling modifications based on provisional results. These designs have shown promise in accelerating the development of treatments, particularly in accelerating the development of treatments, especially in oncology [128].

Conclusions

IL-12 holds vast potential in transforming cancer immunotherapy through its potent immunostimulatory activity, such as T cell and NK cell activation and promotion of anti-tumor immunity. Nevertheless, its clinical translation is hindered by several key barriers. These include hurdles in targeted delivery, immunosuppressive TME, and DLTs. The improvements in gene therapy, nanoparticle delivery systems, localized administration, and combination regimens with checkpoint inhibitors may also provide significant opportunities to overcome these limitations while reducing associated risks. To generate strong and sustained anti-tumor responses, IL-12 can activate T lymphocytes and NK cells while enhancing antigen presentation, thus helping to bridge innate and adaptive immunity. The comprehensive and multifaceted mechanism of IL-12 can also be exploited across multiple cancer types, in contrast to immunotherapies that target limited pathways. With the advancements in delivery systems, IL-12 has the potential to overcome immune resistance and enhance the efficacy of checkpoint inhibitors, influencing stronger and more resilient clinical responses and marking a turning point in cancer immunotherapy. To realize this potential, researchers should focus on translational studies that address toxicity and safer delivery systems. Clinicians are urged to back trials investigating safe, personalized IL-12 applications. Policymakers should facilitate a regulatory framework that allows adaptive trial designs, and funders must support high-impact translational research that accelerates clinical innovations. These cooperative initiatives can improve the safe and effective adoption of treatments based on IL-12. To achieve an equitable, accessible, and sustainable future where IL-12 is an integral part of cancer care and inclusive research methods, international collaboration, and customized technologies that guarantee all populations take advantage of IL-12's therapeutic potential, realizing an egalitarian, accessible, and sustainable future. In the upcoming years, IL-12 may serve as the basis for cancer immunotherapy with additional development.

Abbreviations

APCs: antigen-presenting cells

CAR: chimeric antigen receptor

CD: cluster differentiation

CTLs: cytotoxic T lymphocytes

CXCL9: C-X-C motif chemokine ligand 9

DLTs: dose-limiting toxicities

EML: Model List of Essential Medicines

GHPs: global health partnerships

ICB: immune checkpoint blockade

IFN-γ: interferon-gamma

IL-12: interleukin-12

IL-12Rβ1: interleukin-12 receptor β1

IL-2: interleukin-2

JAK: Janus kinase

LMICs: low- and middle-income countries

LNPs: lipid nanoparticles

MDSCs: myeloid-derived suppressor cells

MMP: matrix metalloproteinase

MTDs: maximum tolerated doses

NK: natural killer

PD-1/PD-L1: programmed cell death 1/programmed cell death ligand 1

RCC: renal cell carcinoma

STAT: signal transducer and activator of transcription

TCR: T-cell receptor

Th1: T helper cell type 1

TME: tumor microenvironment

VBP: value-based pricing

VEGF: vascular endothelial growth factor

Declarations

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HAL: Conceptualization, Methodology, Writing—original draft, Writing—review & editing. AOR: Conceptualization, Methodology, Writing—original draft. AEO, ZAS, and WM: Data curation, Writing—original draft, Writing—review & editing. AOL and OJO: Writing—original draft, Writing—review & editing. RI and TAO: Writing—original draft, Supervision. All authors have read and approved the final manuscript.

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The authors declare that they have no conflicts of interest.

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