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Designing next-generation interleukin immunotherapy: A cytokine-guided framework for precision cancer therapy

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ABSTRACT

Interleukins (ILs) are powerful regulators of anti-tumor immunity, yet their clinical impact in cancer has remained limited despite decades of therapeutic development. Although first-generation cytokines such as IL-2 established proof-of-principle for cytokine-driven cancer immunotherapy, their broader clinical translation was constrained not by insufficient immunostimulatory potency, but by imprecise deployment, including poor receptor selectivity, systemic exposure, and inadequate alignment with tumor immune context. Despite major advances in cytokine engineering, clinical benefit has continued to lag because cytokine deployment remains insufficiently matched to receptor biology, spatial pharmacology, and immune-state architecture. In this Review, we examine how next-generation interleukins, particularly IL-15, IL-21, and IL-10, are redefining cytokine therapy through functionally specialized roles in sustaining cytotoxic persistence, preserving effector competence, and rewiring suppressive immune states. We synthesize emerging strategies in receptor-biased engineering, spatially restricted delivery, and context-matched combination design, and propose a cytokine-guided framework that integrates receptor logic, delivery geometry, immune-state matching, and biomarker-informed deployment. We further argue that the principal barriers to clinical translation are no longer primarily molecular, but translational, including biomarker insufficiency, trial misalignment, tissue-level resistance, and patient heterogeneity. Overall, next-generation interleukins are best understood not as stronger cytokines, but as more precisely deployable immunotherapeutic modules for durable and rational cancer immunotherapy.

1. Introduction

Interleukins (ILs), a subset of cytokines central to immune cell communication, have long attracted interest for their capacity to orchestrate potent anti-tumor immune responses [1]. Among them, IL-2 was the first to achieve clinical approval, establishing a foundational proof-of-concept that immune stimulation alone can induce durable remissions in select malignancies, most notably metastatic melanoma and renal cell carcinoma (RCC) [2–4]. This early success positioned cytokines as one of the earliest mechanistically rational forms of cancer immunotherapy [5]. Yet despite this landmark achievement, first-generation interleukin therapies were constrained by severe systemic toxicities, pleiotropic signaling, and poor tumor selectivity, limiting their broader clinical applicability and exposing the liabilities of empiric cytokine administration [6,7].

The rapid evolution of immuno-oncology has renewed interest in ILs, not as standalone immune stimulants, but as programmable components of rational immunotherapy [8]. Checkpoint blockade, adoptive cell

Abbreviations: ACT, Adoptive cell therapy; ALT-803, IL-15 superagonist complex also known as N-803; AM0010, pegilodecakin; CAR-T, Chimeric Antigen Receptor T-cell therapy; DC, Dendritic cell; FOXP3, forkhead box P3; IL, Interleukin; IL-2R, Interleukin-2 receptor; IL-2Rα, Interleukin-2 receptor alpha; IL-2Rβ, Interleukin-2 receptor beta; IL-7Rα, Interleukin-7 receptor alpha; IL-10R, Interleukin-10 receptor; IL-10R1, Interleukin-10 receptor 1; IL-10R2, Interleukin-10 receptor 2; IL-12R, Interleukin-12 receptor; IL-15Rα, Interleukin-15 receptor alpha; IL-21R, Interleukin-21 receptor; LNP, Lipid nanoparticle; NK cell, Natural killer cell; NKTR-214, Bempegaldesleukin; NKTR-255, Polymer-conjugated IL-15 receptor agonist; N-803, Nogapendekin alfa inbakicept formerly ALT-803; PD-1, Programmed cell death protein 1; PD-L1, Programmed death-ligand 1; PK, Pharmacokinetics; RCC, Renal cell carcinoma; SAR444245, THOR-707; ScRNA-seq, Single-cell RNA sequencing; STAT, Signal transducer and activator of transcription; TIL, Tumor-infiltrating lymphocyte; TME, Tumor microenvironment; Treg, Regulatory T cell; γc, Common gamma chain.

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therapy (ACT), and cancer vaccines have demonstrated that durable anti-tumor immunity depends not simply on immune activation, but on precise coordination of immune cell state, spatial localization, and temporal signaling [9–15]. In this context, ILs have re-emerged as attractive therapeutic tools because they directly regulate immune differentiation, effector fitness, and intercellular communication [1,16]. However, their translational trajectory has remained uneven. Although cytokine engineering has substantially improved pharmacokinetics (PK) and receptor selectivity, clinical benefit has often fallen short of mechanistic promise, underscoring a persistent disconnect between cytokine biology and therapeutic deployment [17,18].

Much of this disconnect stems from how cytokines have historically been developed. Most interleukin therapies were initially advanced under a potency-centric paradigm, in which broader immune stimulation was assumed to translate into greater anti-tumor efficacy [16,19]. Clinical experience has challenged this assumption. Cytokine activity is not defined solely by signaling strength, but by where signals are delivered, which immune subsets receive them, and in what immunologic context they are interpreted [20]. As a result, cytokines with similar immunostimulatory capacity can produce divergent or even opposing outcomes depending on receptor topology, tissue localization, and tumor immune architecture [21,22]. This has become especially evident in newer interleukin platforms, where therapeutic performance is increasingly determined less by cytokine identity alone than by the logic of cytokine deployment [19,23].

This review examines the evolving design logic of interleukin-based cancer immunotherapy, with a focus on IL-15, IL-21, and IL-10 as mechanistically distinct cytokines that exemplify next-generation strategies for tumor-selective immune modulation beyond the historical IL-2 paradigm [24]. These cytokines were selected because they represent three nonredundant therapeutic design logics that address distinct immunologic barriers to effective anti-tumor immunity. IL-15 supports cytotoxic lymphocyte persistence without preferential expansion of regulatory T cells (Tregs), making it a paradigm for durability-oriented cytokine design; IL-21 reinforces effector fitness while limiting terminal exhaustion, representing a strategy to preserve functional anti-tumor immunity; and IL-10, despite its paradoxical biology, exemplifies context-dependent immune reprogramming through its capacity to reshape suppressive myeloid environments under specific therapeutic conditions [25–27]. Rather than treating these cytokines as interchangeable immune stimulants, we evaluate them as biologically distinct immunologic platforms whose therapeutic value lies in how precisely they can be matched to immune deficits, tumor context, and treatment architecture.

We first examine the mechanistic principles that govern interleukin activity in cancer, emphasizing how receptor topology, signaling duration, and immune context shape downstream therapeutic outcomes [28,29]. We then assess why first-generation interleukin therapies underperformed clinically, focusing on the structural and pharmacologic liabilities that constrained efficacy and therapeutic index [19]. Building on this foundation, we evaluate recent advances in cytokine engineering, targeted delivery, and clinical strategy, with particular attention to how these innovations reshape ILs into more selective and programmable immunotherapeutic tools [24,30]. We then propose a cytokine-guided design framework that integrates receptor selectivity, delivery control, immune-context matching, and biomarker-informed deployment as the central organizing logic for next-generation cytokine therapy [31].

The central limitation of cytokine immunotherapy has not been insufficient immunostimulatory potency, but the failure to align cytokine biology with immune context, receptor topology, and spatial pharmacology [17,32]. We argue that the next phase of interleukin therapy will not be defined by stronger cytokines, but by rational cytokine deployment where receptor selectivity, delivery geometry, and immune-state matching determine therapeutic outcome [31].

2. Mechanisms of action of key ILs in cancer therapy

The therapeutic behavior of ILs in cancer is not determined solely by cytokine identity, but by a set of mechanistic variables that govern how cytokine signals are received, interpreted, and sustained within immune circuits [23]. While ILs are often categorized by lineage or receptor family, their translational relevance is better understood through a design-oriented framework that explains why cytokines with overlapping immunostimulatory properties can produce divergent therapeutic outcomes [33,34]. Three mechanistic principles are particularly important in this regard: receptor topology determines immune selectivity, signal duration determines immune fate, and immune context determines biological meaning [20,35]. Together, these variables define the functional logic through which ILs shape anti-tumor immunity and provide the mechanistic basis for rational cytokine design.

2.1. *Receptor topology determines immune selectivity*

A defining determinant of interleukin function is the architecture of its receptor system, which governs both cellular selectivity and downstream signaling bias [36]. Cytokines do not act on immune cells indiscriminately; rather, their effects are constrained by receptor composition, receptor affinity, and the distribution of receptor subunits across immune subsets [17]. As a result, receptor topology functions as a gatekeeper of cytokine specificity and is one of the most important variables separating therapeutic immune activation from off-target immune dysregulation [17,37].

The clearest example is the contrast between IL-2 and IL-15. These cytokines share the IL-2Rβ (CD122) and common γ chain (γc, CD132) signaling modules and activate overlapping Janus kinase (JAK) 1/3-signal transducer and activator of transcription (STAT) 5 and PI3K-AKT-mTOR pathways, yet they generate markedly different immunologic outcomes because they are presented through distinct receptor architectures [38]. IL-2 signals through a soluble trimeric receptor system composed of IL-2Rα (CD25), IL-2Rβ, and γc, enabling broad access across activated lymphocyte populations [39,40]. This architecture permits potent expansion of $CD8^+$ T cells and natural killer (NK) cells, but also strongly favors Tregs, which constitutively express high levels of CD25 and efficiently capture IL-2 at low concentrations [41,42]. Consequently, IL-2 receptor topology inherently couples immune activation to immunoregulatory feedback, creating a structural basis for both its anti-tumor efficacy and its therapeutic limitations [3,43].

By contrast, IL-15 shares downstream signaling modules with IL-2 but employs a distinct trans-presentation architecture in which IL-15 is presented in complex with IL-15Rα on dendritic cells (DCs) or monocytes to neighboring $CD8^+$ memory T cells and NK cells expressing IL-2Rβγ [44,45]. This arrangement spatially restricts signaling and functionally biases cytokine delivery toward cytotoxic lymphocytes while largely avoiding Treg expansion [31,46]. Thus, despite signaling through overlapping intracellular pathways, IL-15 and IL-2 are not functionally interchangeable. Their distinct receptor topologies impose different patterns of immune access, cellular selectivity, and therapeutic behavior [47,48].

This principle extends beyond IL-2 and IL-15. IL-21 signals through IL-21R and γc, preferentially activating STAT3 and STAT1 to reinforce effector differentiation, cytotoxicity, and resistance to terminal dysfunction [49,50]. IL-7 signals through IL-7Rα (CD127) and γc, favoring naïve and memory T cell maintenance with minimal Treg expansion [51,52]. IL-10 signals through IL-10Rα/β and primarily activates STAT3 in myeloid and lymphoid compartments, producing effects that are highly dependent on cellular context [53]. Across these examples, receptor topology is not merely structural biology; it is the first design variable that determines which immune compartments a cytokine can access and what therapeutic functions it can preferentially regulate [3,54].

2.2. Signal duration determines immune fate

Beyond receptor access, the duration and kinetics of cytokine signaling critically shape immune fate [55]. Cytokine signaling is not interpreted in binary fashion; immune cells respond differently to transient, sustained, or repetitive cytokine exposure, and these kinetic differences can alter proliferation, differentiation, persistence, and exhaustion. Thus, signal duration serves as a second major determinant of therapeutic outcome and helps explain why cytokines with similar immediate effects can produce divergent long-term consequences [56].

Acute cytokine exposure generally promotes activation, proliferation, and effector differentiation [57]. In contrast, sustained or repetitive signaling can induce receptor desensitization, activation-induced cell death, or terminal dysfunction [58]. This distinction is especially relevant in cancer, where chronic antigen exposure already predisposes T cells to exhaustion [59,60]. Under these conditions, prolonged cytokine stimulation may initially amplify cytotoxicity but subsequently reinforce inhibitory receptor expression, metabolic stress, and loss of functional durability [61].

IL-2 exemplifies this kinetic paradox [5]. Short-term IL-2 signaling promotes vigorous proliferation and cytotoxic activation of $CD8^+$ T cells and NK cells [62]. However, sustained IL-2 exposure can also accelerate activation-induced cell death, reinforce PD-1 and CTLA-4 expression, and promote expansion of suppressive Treg populations, ultimately constraining durable anti-tumor benefit [63,64]. In this setting, the same cytokine signal that initiates immune activation can, if prolonged, contribute to immune attrition and adaptive resistance [65].

By contrast, IL-15 is more strongly associated with persistence than acute proliferative burst [66]. In addition to supporting cytotoxic function, IL-15 sustains mitochondrial fitness, promotes oxidative metabolism, and preserves long-term survival of memory $CD8^+$ T cells and NK cells [67,68]. This kinetic profile makes IL-15 particularly compatible with ACT, where durable persistence is often more therapeutically important than rapid expansion alone [69].

IL-21 further illustrates the importance of signaling kinetics in determining immune fate [70]. Rather than driving maximal expansion, IL-21 helps preserve functional competence under chronic stimulation by sustaining effector transcriptional programs while limiting terminal exhaustion [71,72]. This property is particularly relevant in chronically antigen-exposed tumors, where durable function rather than acute expansion often determines therapeutic success [73]. Similarly, IL-7 primarily supports survival and homeostatic maintenance, making it better suited for immune reconstitution than direct effector amplification [74].

Taken together, these examples illustrate that cytokine efficacy is not simply a function of signal strength, but of signal timing. Cytokines shape immune fate not only through what they activate, but through how long they activate it [75].

2.3. Immune context determines cytokine meaning

A third and equally important determinant of cytokine function is immune context [76]. Cytokine signals do not carry fixed biological meaning independent of their environment; rather, their functional consequences are interpreted through the immune state in which they are received [77]. The same cytokine can therefore produce distinct, or even opposing, effects depending on tumor immune composition, baseline inflammation, stromal architecture, and the activation state of target cells [21,57].

IL-10 provides the clearest example of this context dependence [78]. Traditionally classified as immunosuppressive, IL-10 suppresses inflammatory cytokine production, dampens antigen presentation, and restrains myeloid activation through STAT3 signaling [34]. In inflammatory or infection-associated settings, these effects can suppress anti-tumor immunity and reinforce immune tolerance [79]. However, in chronically inflamed tumors characterized by dysfunctional myeloid activation and sustained T cell stress, IL-10 can produce markedly different outcomes [80,81]. Under these conditions, high-dose or sustained IL-10 signaling can reduce suppressive myeloid tone, preserve $CD8^+$ T cell function, and enhance intratumoral IFN-γ production. Thus, IL-10 is not intrinsically suppressive or stimulatory; its therapeutic behavior is contextually encoded [82].

This principle extends beyond IL-10. IL-21 may reinforce productive effector function in exhausted T cell states yet have limited benefit in poorly primed immune environments lacking sufficient antigen presentation [83,84]. IL-15 may effectively amplify cytotoxic lymphocytes in inflamed tumors but remain insufficient in immune-excluded tumors where trafficking and stromal access are limiting [85]. Even IL-2, despite its broad stimulatory capacity, may preferentially expand suppressive compartments in tumors enriched for Tregs and myeloid suppressor cells [86]. These examples underscore a central principle of cytokine therapy: cytokine activity is not determined solely by intrinsic ligand properties, but by the immune ecology into which the signal is introduced [87].

This context dependence helps explain why ILs with clear mechanistic activity often generate inconsistent clinical outcomes [88]. Cytokines do not fail simply because they are weak agonists, but because their biological effects are contingent on receptor accessibility, signaling kinetics, and tissue immune state [89]. Interleukin therapy is therefore best understood not as a strategy of generalized immune stimulation, but as a form of immune-state modulation in which therapeutic efficacy depends on matching cytokine function to the dominant biological constraints of the TME [90,91].

Together, receptor topology, signal duration, and immune context define the mechanistic logic that governs interleukin behavior in cancer [20,92]. These principles explain why cytokines with similar signaling capacity can produce divergent therapeutic effects and provide the conceptual foundation for the engineering strategies discussed in subsequent sections [35,93]. Rather than functioning as interchangeable immune agonists, ILs operate as context-sensitive regulators whose therapeutic value depends on how precisely their signaling logic is understood and deployed [31]. These integrated effects are summarized in Fig. 1.

3. Why first-generation ILs failed: toxicity, exposure, and therapeutic misalignment

The clinical introduction of ILs established one of the earliest proofs that immune activation alone could produce durable anti-tumor responses [63]. High-dose IL-2 demonstrated that cytokine-driven immune stimulation could induce long-term remissions in select patients with metastatic melanoma and RCC, establishing the conceptual foundation for modern cancer immunotherapy [4,94]. Yet the broader clinical failure of first-generation ILs was not due to insufficient biological potency [3]. Rather, these agents exposed a more fundamental problem: early cytokine therapies were clinically deployed without adequate control over receptor selectivity, spatial distribution, or signaling duration [31]. Their limitations were therefore not simply pharmacologic, but architectural [24]. First-generation ILs failed not because they were weak immune agonists, but because they were biologically powerful and therapeutically indiscriminate [95].

Three recurring liabilities defined this early generation of cytokine therapy: receptor promiscuity, systemic exposure, and maladaptive feedback [96]. Together, these constraints imposed a narrow therapeutic window and established the core design problems that continue to shape modern interleukin engineering [97].

3.1. Receptor promiscuity constrained immune selectivity

The first limitation of early interleukin therapy was the inability to separate productive immune activation from counter-regulatory immune signaling [98]. First-generation cytokines were deployed under the assumption that stronger immune stimulation would translate into

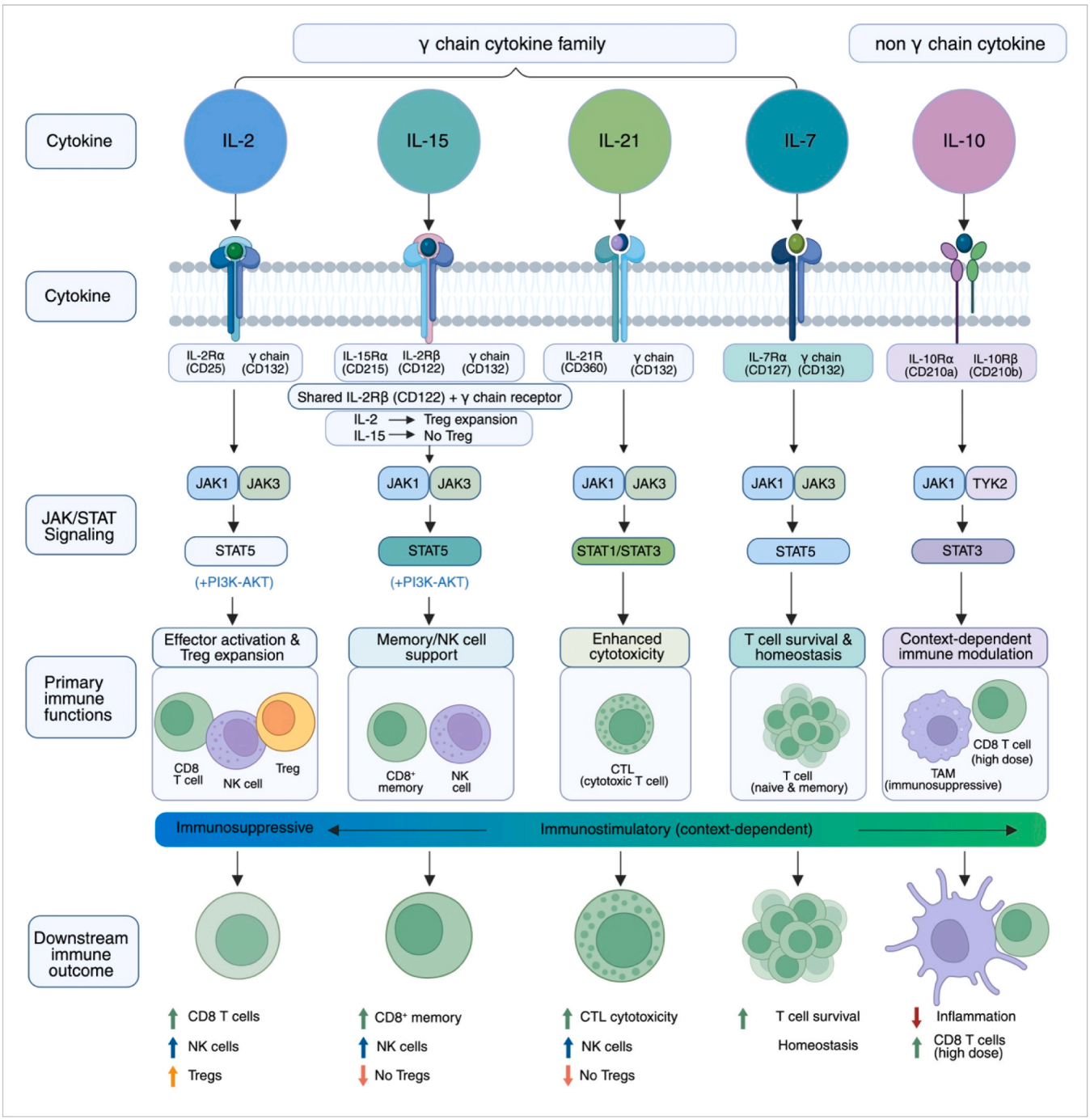


Fig. 1. Receptor engagement and downstream signaling pathways of key ILs in cancer immunotherapy. Schematic overview of cytokine-specific receptor complexes, JAK/STAT signaling cascades, and associated immune functions. IL-2 and IL-15 signal through shared IL-2Rβ (CD122) and γc (CD132), activating JAK1/JAK3-mediated STAT5 and PI3K-AKT-mTOR pathways, with IL-15 requiring trans-presentation via IL-15Rα (CD215). IL-21 binds to IL-21R and γc, activating STAT1 and STAT3 to enhance cytotoxic effector function. IL-7 signals through IL-7Rα (CD127) and γc to activate STAT5, supporting T cell survival and homeostatic maintenance. IL-10 signals through IL-10Rα and IL-10Rβ, primarily activating STAT3 to mediate context-dependent immune modulation, with effects ranging from suppression of inflammatory myeloid responses to enhancement of $CD8^{+}$ T cell function in selected therapeutic contexts. Together, these ILs illustrate the diverse immunoregulatory functions of cytokines within the tumor microenvironment (TME).

greater anti-tumor benefit [92]. Clinical experience revealed the opposite: when receptor access is broad and poorly restricted, cytokine potency amplifies both effector and suppressive circuits simultaneously [56].

IL-2 remains the clearest example of this problem [28]. Although IL-2 potently expands cytotoxic T cells and NK cells, it also strongly engages high-affinity IL-2Rα-expressing Tregs, coupling immune activation to compensatory immune suppression [42]. This duality imposed a structural limitation on IL-2 from the outset: the same receptor architecture that enabled strong cytotoxic expansion also guaranteed parallel expansion of suppressive immune compartments [3,99]. As a result, IL-2 was never simply limited by toxicity; it was limited by receptor promiscuity that prevented selective immune control [100].

This problem extended beyond IL-2. Cytokines such as IL-12 and IL-18 similarly activated potent pro-inflammatory programs, but their broad receptor accessibility and pleiotropic signaling made selective

immune engagement difficult to control [101]. In each case, early interleukin therapy lacked sufficient receptor precision to isolate desirable immune outputs from collateral inflammatory activation [102].

3.2. Systemic exposure amplified toxicity and reduced therapeutic precision

A second limitation of first-generation ILs was the absence of spatial control [103]. These cytokines were largely administered systemically, exposing multiple immune and non-immune compartments to high-intensity signaling irrespective of tumor localization [104]. This lack of spatial restriction transformed otherwise useful immune agonists into systemically toxic inflammatory stimuli [31,105].

High-dose IL-2 exemplified this trade-off. Systemic administration frequently triggered capillary leak syndrome, hypotension, pulmonary edema, and multi-organ dysfunction, reflecting widespread vascular and inflammatory activation rather than tumor-selective immune modulation [3,106]. These toxicities necessitated intensive inpatient monitoring and severely limited clinical scalability. Importantly, this toxicity was not simply a consequence of excessive dose, but of indiscriminate cytokine distribution [107].

A similar principle constrained other first-generation cytokines. Systemic IL-12 induced hepatotoxicity and cytokine storm-like inflammatory syndromes, while IL-18 was associated with immune hyperactivation and hematologic toxicity [55,108]. These toxicities reflected a shared architectural problem: cytokine activity could be intensified, but not spatially confined. Without mechanisms to localize signaling to tumors or tumor-draining immune compartments, systemic exposure consistently eroded therapeutic index [109].

3.3. Uncontrolled signaling duration reinforced immune dysfunction

A third limitation was the inability to regulate cytokine exposure over time. In addition to broad receptor access and poor spatial restriction, first-generation ILs were delivered with little control over signaling duration, creating kinetic conditions that often reinforced immune dysfunction rather than durable immune fitness [35,110].

Most native cytokines exhibit short plasma half-lives, rapid renal clearance, and unstable tissue exposure [6,7]. IL-2, for example, has a terminal half-life of only minutes, necessitating high-dose bolus or continuous infusion strategies to sustain biological activity [111]. These approaches increased peak systemic toxicity while simultaneously producing inconsistent tissue exposure and highly variable immune cell signaling. The result was not only poor pharmacokinetic control, but poor immunologic control [3,92].

Sustained or repetitive cytokine exposure further amplified maladaptive feedback [112]. Chronic stimulation could induce activation-induced cell death, receptor desensitization, and compensatory upregulation of inhibitory pathways such as PD-1 and CTLA-4 [113]. In the case of IL-2, repeated exposure often promoted T cell attrition while reinforcing Treg and myeloid suppressor expansion, thereby reducing functional durability despite initial immune activation [4,114]. These dynamics were especially limiting in poorly inflamed tumors, where chronic cytokine signaling frequently intensified dysfunction more readily than productive immunity [92,115].

Together, these limitations illustrate why first-generation ILs failed to achieve broad clinical utility despite clear mechanistic activity [7,116]. Their central limitation was not inadequate immune potency, but the inability to control where cytokine signals were delivered, which cellular compartments received them, and how long they were sustained [29,117]. Early ILs therefore revealed the core design problem of cytokine immunotherapy: therapeutic efficacy depends not simply on activating immunity, but on activating the right immune circuits with sufficient spatial, temporal, and cellular precision [118].

IL-2 exemplifies these trade-offs, with receptor promiscuity, systemic exposure, and kinetic instability defining the principal therapeutic liabilities of first-generation cytokine therapy, as illustrated in Fig. 2.

4. Engineering ILs for therapeutic precision: what improved, and what did not

The limitations of first-generation ILs made clear that cytokine efficacy could not be improved by potency escalation alone [7,31,92]. The central challenge was not how to generate stronger cytokine signals, but how to constrain those signals with greater cellular, spatial, and pharmacologic precision [119]. This realization has driven a new generation of interleukin engineering strategies aimed at improving receptor selectivity, controlling exposure, and reducing systemic toxicity [6,7]. These advances have transformed ILs from broadly acting immune agonists into increasingly programmable immunomodulators [41]. Yet recent clinical experience also makes clear that engineering alone does not guarantee therapeutic success [120]. In many cases, cytokine engineering has solved molecular promiscuity more effectively than it has solved biological uncertainty [121].

4.1. Receptor-biased engineering improved selectivity, but not necessarily efficacy

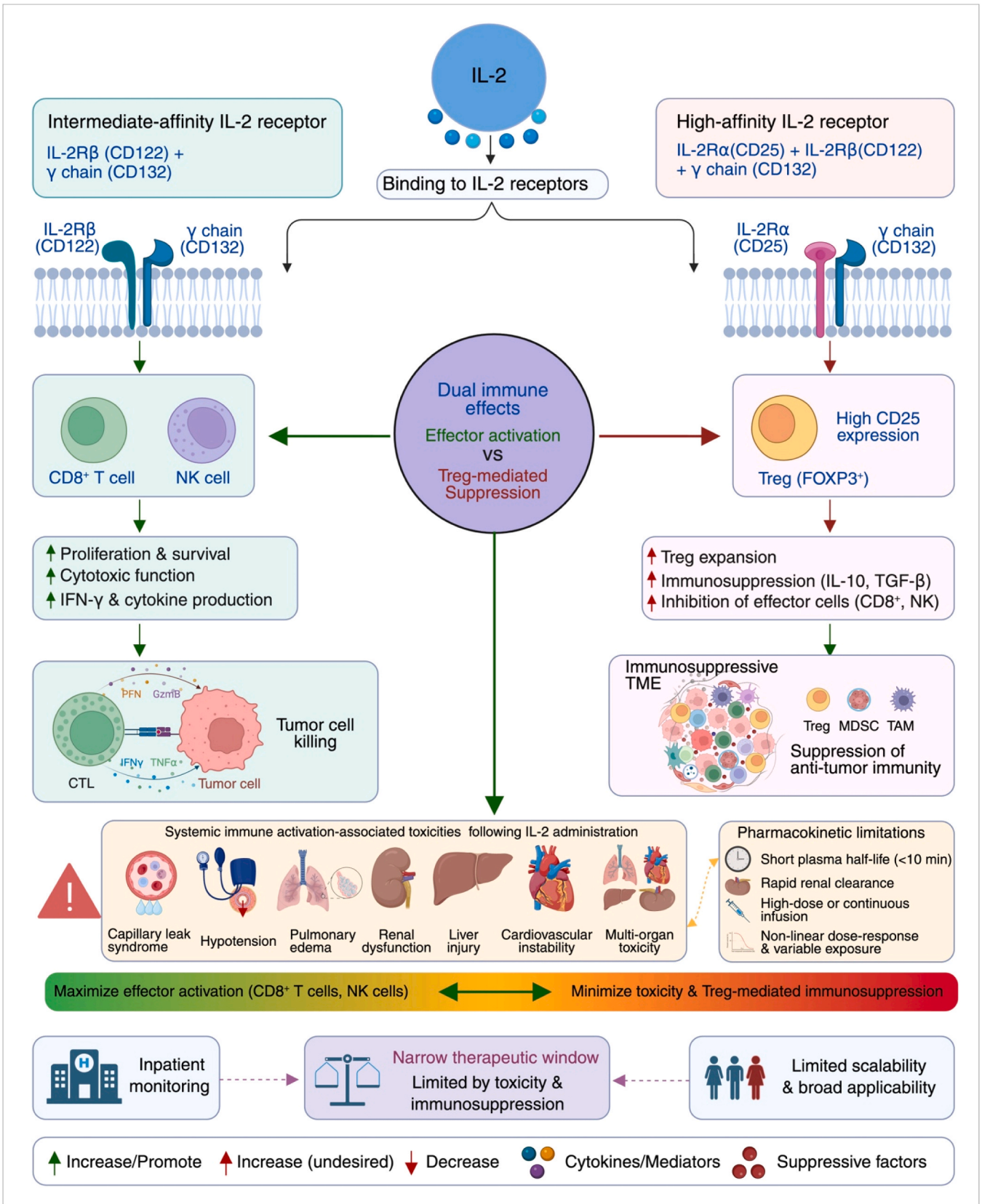
One of the earliest and most rational engineering strategies focused on reprogramming receptor engagement to improve immune selectivity [30,122]. Because the clinical limitations of IL-2 arise in part from its simultaneous activation of effector lymphocytes and CD25-high Tregs, multiple next-generation IL-2 platforms were designed to reduce IL-2Rα engagement while preserving signaling through the intermediate-affinity IL-2Rβγ complex expressed on $CD8^+$ T cells and NK cells [42,123]. These "biased agonists" were intended to uncouple cytotoxic activation from Treg expansion and thereby improve therapeutic index [124].

Bempegaldesleukin (NKTR-214) exemplified this strategy [125]. As a pegylated IL-2 prodrug designed to favor CD122-biased signaling, NKTR-214 showed encouraging early evidence of immune activation, including increased tumor-infiltrating lymphocytes (TILs) and improved pharmacokinetic exposure [126]. However, its subsequent failure in Phase III trials demonstrated a central translational lesson: pharmacodynamic expansion does not necessarily translate into clinical benefit. Enhanced immune activation, even when measurable in blood or tumor tissue, is not equivalent to productive anti-tumor immunity [23,127]. Similarly, THOR-707 (SAR444245) and related CD25-sparing IL-2 variants represent a more refined approach to receptor bias, but whether improved receptor selectivity alone can generate durable clinical benefit remains unresolved [128,129]. These experiences suggest that receptor bias improves cytokine precision but does not by itself resolve the broader biologic constraints that limit efficacy in complex tumor ecosystems [23,31,130].

4.2. IL-15 engineering improved persistence and pharmacology

IL-15 engineering addressed a different limitation: how to preserve cytotoxic persistence without inducing the regulatory liabilities associated with IL-2 [69,131]. Because native IL-15 depends on IL-15Rα-mediated trans-presentation, early development was limited by poor pharmacologic stability and inefficient delivery [132]. Engineering efforts therefore focused less on receptor bias and more on stabilizing physiologic signaling architecture [133].

ALT-803 (N-803) exemplifies this approach. By coupling IL-15 to an IL-15Rα fusion scaffold, N-803 mimics native trans-presentation while improving stability, bioactivity, and signaling durability [134,135]. This design promotes sustained activation of memory $CD8^+$ T cells and NK cells while largely avoiding Treg expansion, making IL-15 a more persistence-oriented cytokine platform [9,45]. Polymer-conjugated agonists such as polymer-conjugated IL-15 receptor agonist (NKTR-255)



(caption on next page)

Fig. 2. Why IL-2 established both the promise and the failure mode of first-generation cytokine therapy. IL-2 illustrates the central design liabilities that constrained first-generation cytokine immunotherapy. Through engagement of distinct IL-2 receptor configurations, IL-2 simultaneously activates cytotoxic and suppressive immune programs. Signaling through the intermediate-affinity IL-2Rβγ complex promotes CD8⁺ T-cell and NK-cell proliferation, survival, and cytotoxic function, supporting anti-tumor immunity. In parallel, high-affinity engagement of the trimeric IL-2Rαβγ complex on CD25-high Tregs drives Treg expansion, suppressive cytokine production, and inhibition of effector lymphocytes, coupling immune activation to compensatory immune suppression. Systemic IL-2 administration further amplifies this duality by exposing vascular and peripheral tissues to high-intensity cytokine signaling, resulting in capillary leak syndrome, hypotension, pulmonary edema, cardiovascular instability, and multi-organ toxicity. These liabilities are compounded by rapid plasma clearance, short half-life, and non-linear exposure kinetics, which necessitate high-dose or continuous administration and further increase systemic toxicity while reducing pharmacologic control. Overall, IL-2 exemplifies the three core liabilities of first-generation cytokine therapy: receptor promiscuity, systemic exposure, and kinetic instability, explaining why early interleukin therapy established both the therapeutic promise and the translational limitations of cytokine immunotherapy.

extend this logic further by prolonging exposure and supporting durable NK- and CD8⁺ T-cell fitness, particularly in combination with adoptive cell therapies or checkpoint blockade [136,137].

These platforms illustrate a distinct engineering principle: cytokine efficacy can be improved not only by changing who receives the signal, but by changing how long useful immune programs are sustained [138]. However, although IL-15 engineering has improved pharmacology and cellular persistence, its broader clinical advantage remains context-dependent and still appears constrained by tumor accessibility, immune architecture, and treatment context [34,139].

4.3. Spatial targeting improved localization and therapeutic index

A second major engineering axis has focused on restricting cytokine activity in space rather than simply refining receptor engagement [140]. Because systemic cytokine exposure was a central liability of first-generation ILs, multiple next-generation strategies have aimed to localize signaling within tumors or tumor-draining immune compartments [5,141].

Immunocytokines exemplify this approach. By coupling cytokines to tumor-targeting antibodies or extracellular matrix-binding domains, these constructs aim to enrich cytokine activity within the TME while limiting peripheral exposure [142]. Examples such as NHS-IL-12 and L19-based cytokine fusions illustrate how antibody-guided targeting can improve local immune activation and reduce systemic toxicity, particularly in immune-excluded tumors where localized immune remodeling may be more valuable than systemic immune amplification [143,144].

This principle has been extended further through protease-activatable or "masked" cytokines, which remain functionally inert until cleaved within protease-rich tumor environments [145]. These designs introduce a more stringent level of spatial gating and represent one of the most conceptually attractive strategies for improving therapeutic index. Their importance lies not simply in reducing toxicity, but in redefining cytokines as locally activated immune regulators rather than systemically distributed inflammatory ligands [146].

4.4. Delivery engineering improved exposure control, but remains translationally immature

In parallel with ligand engineering, delivery systems have emerged as a complementary strategy for controlling cytokine exposure in space and time [147]. Nanoparticles, hydrogel depots, biodegradable microparticles, and lymph node-targeted delivery systems offer the possibility of sustained and localized cytokine release while minimizing systemic spillover [10,15,148]. These platforms are particularly attractive because they address a limitation that receptor engineering alone cannot: pharmacologic geometry.

Preclinical studies consistently show that localized or depot-based delivery of IL-2 or IL-15 can improve anti-tumor activity while reducing systemic toxicity [131,149]. These systems also offer opportunities for immune compartment targeting, allowing cytokines to be preferentially delivered to tumors, draining lymph nodes, or selected immune subsets [150,151]. In principle, such approaches move cytokine therapy closer to controlled immune programming than systemic immune stimulation [152].

However, despite strong conceptual appeal, most delivery platforms remain preclinical or early translational [153]. Their principal limitation is no longer biologic rationale, but manufacturability, reproducibility, and regulatory scalability. Delivery engineering has improved pharmacologic control in theory and in preclinical models, but its clinical maturation remains substantially behind its mechanistic promise [154].

4.5. Combination strategies revealed the limits of engineering alone

Clinical strategy has evolved in parallel with molecular and delivery engineering. Engineered ILs are now increasingly deployed in combination with checkpoint inhibitors, adoptive cell therapies, and cancer vaccines rather than as cytokine monotherapies [41,131]. This shift reflects a more sophisticated understanding of cytokines as immunologic amplifiers whose therapeutic value depends less on intrinsic potency than on the biologic state of the immune system into which they are introduced [155].

Yet combination trials have also revealed the limits of engineering alone. The failure of NKTR-214 plus nivolumab was particularly instructive: even when cytokine engineering improves receptor bias, PK, and measurable immune activation, clinical benefit may still fail if the underlying immune context is poorly matched [125]. Increased TILs, peripheral expansion, or receptor engagement are not sufficient biomarkers of therapeutic success if these changes do not produce durable immune state transition within the TME [156].

This has become one of the clearest lessons of next-generation cytokine development: engineering can improve cytokine behavior, but it cannot by itself resolve poor patient selection, suboptimal biologic dosing, or immune contexts that remain structurally resistant to productive immune remodeling [7,23]. Cytokine design therefore cannot end at molecular optimization. It must extend into clinical architecture, where biomarker selection, treatment sequencing, and immune-state matching become equally important determinants of therapeutic success [157].

Viewed as a whole, these advances have substantially improved the precision, controllability, and therapeutic logic of interleukin-based therapy. Receptor engineering has improved selectivity, IL-15 scaffolding has improved persistence, spatial targeting has improved localization, and delivery systems have improved exposure control [158]. Yet these advances have also clarified a central limitation: engineering can improve cytokine pharmacology more readily than it can resolve tumor ecological resistance [7,92]. The next challenge is therefore no longer simply to engineer better cytokines, but to integrate engineered cytokines into biologically coherent treatment frameworks defined by immune context, spatial logic, and mechanistic biomarkers [7,159]. These integrated design strategies are summarized in Fig. 3.

Representative engineered interleukin platforms, their design logic, and corresponding clinical experience are summarized in Table 1.

5. Functional classes of next-generation ILs: persistence, exhaustion control, and immune-context rewiring

If IL-2 defined the first generation of cytokine immunotherapy, IL-15, IL-21, and IL-10 define a more functionally specialized second

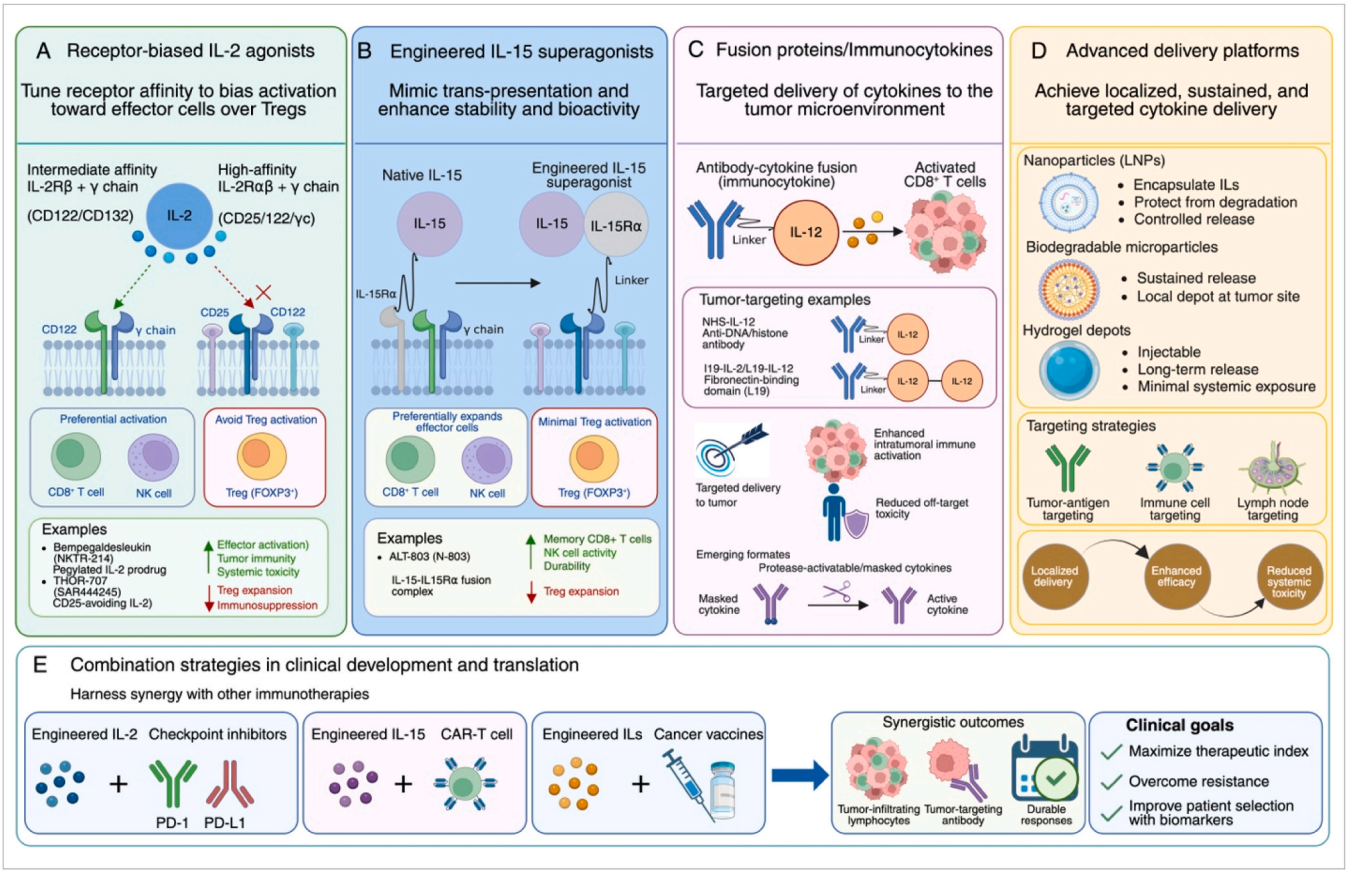


Fig. 3. Strategies in interleukin engineering for cancer therapy. Schematic overview of major engineering and clinical strategies designed to enhance the efficacy, specificity, and safety of interleukin-based immunotherapies. (A) Receptor-biased IL-2 agonists tune receptor affinity, particularly by reducing IL-2Rα engagement, to preferentially activate CD8⁺ T cells and NK cells while limiting Treg expansion. (B) Engineered IL-15 superagonists, such as IL-15-IL-15Rα fusion complexes (e.g., ALT-803/N-803), mimic trans-presentation to enhance stability, bioactivity, and sustained activation of memory CD8⁺ T cells and NK cells. (C) Fusion proteins and immunocytokines deliver cytokines selectively to the TME through antibody-mediated targeting (e.g., NHS-IL-12, L19-IL-2/L19-IL-12), thereby enhancing intratumoral immune activation and reducing off-target toxicity; emerging formats include protease-activatable (masked) cytokines. (D) Advanced delivery platforms, including lipid nanoparticles (LNPs), biodegradable microparticles, and hydrogel depots, enable localized, sustained, and targeted cytokine release with reduced systemic exposure. (E) Combination strategies integrate engineered ILs with checkpoint inhibitors, adoptive cell therapies (e.g., CAR-T), or cancer vaccines to achieve synergistic anti-tumor responses, increase TILs, and improve durability of response. Together, these approaches aim to expand the therapeutic window, enhance immune coordination, and overcome resistance mechanisms within the TME.

generation [63,69,160]. These cytokines are not simply safer or more selective alternatives to IL-2; they represent mechanistically distinct immunologic tools that solve different therapeutic problems [16]. Their value lies less in generalized immune stimulation than in their ability to reinforce specific immune functions that are frequently limiting in cancer: durable cytotoxic persistence, resistance to terminal exhaustion, and reversal of suppressive immune context [161]. Viewed in this way, IL-15, IL-21, and IL-10 are best understood not as interchangeable cytokine substitutes, but as functionally distinct therapeutic classes [162].

5.1. IL-15 as a persistence cytokine

IL-15 is best understood as a cytokine optimized for immune persistence rather than acute immune amplification [69]. Unlike IL-2, which drives rapid proliferative expansion at the cost of regulatory feedback and eventual attrition, IL-15 preferentially sustains NK cells and memory CD8⁺ T cells without substantial Treg expansion [163]. Its biologic advantage lies in its ability to preserve cytotoxic lymphocyte survival, metabolic fitness, and long-term functional durability under conditions where durable immune maintenance is more therapeutically valuable than rapid expansion [164].

This persistence-oriented biology has made IL-15 particularly attractive in settings where longevity of immune function is a primary therapeutic constraint, including ACT, post-lymphodepletion recovery, and tumors characterized by weak but recoverable cytotoxic immunity [160,165]. By supporting mitochondrial fitness, memory maintenance, and sustained effector competence, IL-15 functions less as an acute immune accelerator than as a cytokine scaffold for durable cytotoxic support [72]. This distinguishes IL-15 from IL-2 not simply by reduced toxicity, but by a fundamentally different therapeutic role.

5.2. IL-21 as an anti-exhaustion cytokine

Where IL-15 reinforces persistence, IL-21 is better understood as a cytokine that preserves functional competence under chronic immune stress [162]. Its principal therapeutic value lies not in maximal expansion, but in sustaining effector quality under conditions of prolonged antigen exposure, where T-cell dysfunction and terminal exhaustion often become dominant barriers to anti-tumor immunity [26,84].

Through STAT3- and STAT1-dominant signaling, IL-21 supports cytotoxic differentiation, sustains IFN-γ and granzyme production, and preserves transcriptional programs associated with effector competence [49,166]. This profile is especially relevant in chronically stimulated immune environments, where IL-21 appears to preserve function more effectively than it drives expansion [167]. In this context, IL-21 is best

Table 1
Representative engineered cytokine platforms in cancer immunotherapy: design logic, clinical status, and translational lessons.

Cytokine	Agent	Mechanisms	Clinical status	Combination strategies	Key translational lesson
IL-2	Bempegaldesleukin (NKTR-214)	CD122-biased pegylated IL-2 prodrug designed to reduce CD25 engagement and limit Treg expansion	Phase III discontinued, failed to improve outcomes in combination with nivolumab	Anti-PD-1 (nivolumab)	Pharmacodynamic expansion did not translate into clinical benefit
IL-2	THOR-707 (SAR444245)	CD25-sparing IL-2 variant engineered to preserve IL-2Rβγ signaling while limiting Treg activation	Early clinical evaluation; translational potential remains under assessment	Checkpoint inhibitors	Improved receptor bias alone may not overcome context-dependent resistance
IL-15	ALT-803 (N-803)	IL-15 superagonist complex engineered to mimic physiologic trans-presentation and improve persistence	FDA-approved (2024, with BCG) for BCG-unresponsive NMIBC; favorable efficacy and tolerability	CAR-NK, checkpoint blockade, intravesical BCG	Enhanced persistence improved efficacy, but clinical efficacy remained context-dependent
IL-15	NKTR-255	Polymer-conjugated IL-15 receptor agonist designed to prolong IL-15Rβγ signaling and sustain NK/CD8⁺ T-cell fitness	Early clinical development; favorable immune persistence profile	CAR-T/NK cell therapy, anti-PD-1/PD-L1	Prolonged cytotoxic support may improve durability, but requires immune-state alignment
IL-21	Recombinant IL-21	Effector-support cytokine designed to enhance cytotoxic differentiation and preserve functional competence	Phase II; limited monotherapy activity, greater promise in rational combinations	CAR-T, cancer vaccines, checkpoint blockade	Effector support alone is insufficient without coordinated immune priming
IL-10	Pegilodecakin (AM0010)	Pegylated IL-10 agonist designed to amplify intratumoral CD8⁺ T-cell activity and IFN-γ production	Late-stage clinical evaluation failed to demonstrate sufficient efficacy despite biologic activity	Anti-PD-1	Context-dependent cytokine polarity limited generalizability
IL-12	NHS-IL-12	Tumor-targeted immunocytokine designed to localize IL-12 activity and reduce systemic toxicity	Early clinical evaluation; demonstrated localized immune activation with manageable safety	Combination immunotherapy	Spatial restriction improved tolerability, but not necessarily sufficiency

viewed as an anti-exhaustion cytokine: one that helps maintain productive effector states, improves compatibility with checkpoint blockade, and supports sustained immune function in tumors where chronic antigen exposure would otherwise favor terminal exhaustion [26,168].

5.3. IL-10 as a context-switch cytokine

IL-10 occupies a distinct functional category because its therapeutic role is defined less by direct immune amplification than by context-dependent immune rewiring [169]. Unlike IL-15 or IL-21, which primarily reinforce cytotoxic lymphocyte function, IL-10 exerts much of its therapeutic influence by altering how immune signals are interpreted within suppressive tissue environments [82,170].

Traditionally classified as immunosuppressive, IL-10 suppresses inflammatory cytokine production and restrains myeloid activation through STAT3-dependent signaling [169,170]. Yet in tumors characterized by chronic inflammation, dysfunctional myeloid activation, and persistent immune suppression, these same properties can become therapeutically advantageous [171]. Under these conditions, IL-10 may dampen maladaptive inflammatory signaling, recondition myeloid signaling, and indirectly preserve productive CD8⁺ T-cell activity [172]. At higher doses or in appropriately conditioned settings, IL-10 may further support intratumoral CD8⁺ T-cell expansion and IFN-γ production, revealing a context-dependent immunostimulatory role that diverges sharply from its conventional classification [170].

Despite this therapeutic rationale, IL-10 biology remains inherently paradoxical and requires cautious translational interpretation [27,173]. In many tumor settings, constitutive or dysregulated IL-10 signaling has been associated with immune escape through suppression of antigen presentation, attenuation of pro-inflammatory cytokine production, impaired dendritic cell activation, and reinforcement of suppressive myeloid programs [169]. Elevated IL-10 expression has also been associated with adverse clinical outcomes in several malignancies, underscoring that IL-10 cannot be universally interpreted as immunorestorative [27,82]. These contradictory observations likely reflect the profound context dependence of IL-10 biology, in which dose, timing, cellular target engagement, immune composition, and co-administered therapies determine whether IL-10 constrains productive immunity or facilitates immune reprogramming [174,175]. This mechanistic ambiguity remains a major translational limitation, as robust biomarkers capable of distinguishing therapeutically permissive from suppressive IL-10 states remain poorly defined [176].

IL-10 is therefore best understood not as a purely suppressive cytokine, but as a context-switch cytokine whose therapeutic function depends on the immune state into which it is introduced [169,177]. Its value lies in its capacity to re-encode suppressive immune environments into more permissive states for productive anti-tumor immunity [41,178].

Together, IL-15, IL-21, and IL-10 illustrate a more functionally organized view of next-generation cytokine therapy [131,162,179]. Rather than serving as broad-spectrum immune stimulants, these ILs operate as specialized immunologic regulators: IL-15 sustains persistence, IL-21 preserves effector competence, and IL-10 rewires suppressive context [180,181]. This functional classification helps clarify why newer ILs should not be viewed as incremental substitutes for IL-2, but as distinct cytokine classes with separable therapeutic roles in precision immunotherapy [7,17]. Their complementary but nonredundant functions are summarized in Fig. 4.

The functional distinctions among these ILs, including their dominant immune targets, signaling programs, and therapeutic constraints, are summarized in Table 2.

6. Cytokine-guided design logic for next-generation immunotherapy

The central lesson of modern cytokine immunotherapy is that therapeutic performance is determined less by cytokine potency than by cytokine deployment [182]. As mechanistic understanding has improved, ILs have increasingly shifted from broadly acting immune stimulants to programmable immunologic components whose efficacy depends on how precisely they are matched to immune architecture, spatial constraints, and therapeutic context [183]. This shift requires a design logic that moves beyond cytokine identity alone and instead integrates receptor biology, delivery geometry, immune-state matching, combinatorial coherence, and biomarker-guided deployment [184]. In this framework, the next generation of cytokine therapy is defined not by stronger cytokines, but by more rational cytokine use.

6.1. Receptor logic determines cellular selectivity

The first principle of cytokine-guided design is selective control of

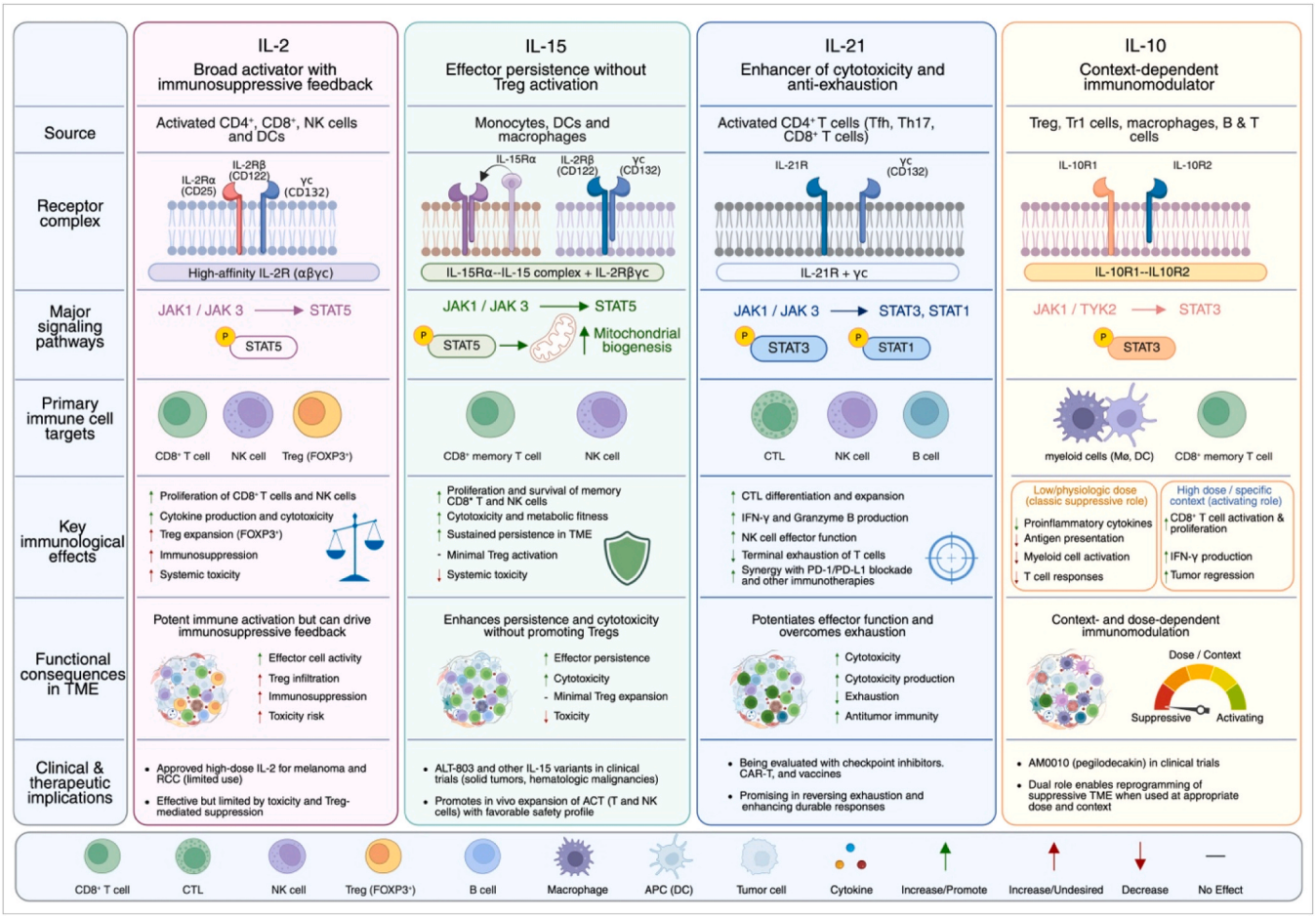


Fig. 4. Functional classes of next-generation ILs in cancer immunotherapy. Comparative overview of the distinct functional roles of major ILs in cancer immunotherapy. IL-2 functions as a broad immune amplifier, promoting cytotoxic lymphocyte expansion but also driving regulatory feedback, systemic toxicity, and immune counter-regulation. In contrast, IL-15 functions primarily as a persistence cytokine, sustaining NK-cell and memory CD8⁺ T-cell survival, metabolic fitness, and long-term cytotoxic competence with limited Treg expansion. IL-21 functions as an anti-exhaustion cytokine, preserving effector differentiation, sustaining cytokine production, and maintaining functional competence under chronic antigen exposure. IL-10 functions as a context-switch cytokine, reshaping suppressive myeloid and inflammatory signaling and, in defined settings, restoring conditions permissive for productive CD8⁺ T-cell immunity. Together, these ILs represent functionally distinct cytokine classes whose therapeutic value lies in selectively reinforcing persistence, preserving effector quality, or rewiring suppressive immune context.

Table 2
Functional classes of key ILs in cancer immunotherapy.

Cytokine	Functional class	Dominant immune targets	Key signaling pathways	Principal anti-tumor role	Major limitations
IL-2	Broad immune amplifier	CD8⁺ T cells, NK cells, Tregs	JAK1/3-STAT5	Rapid immune expansion and cytotoxic activation	Treg expansion, systemic toxicity, narrow therapeutic window
IL-15	Persistence cytokine	Memory CD8⁺ T cells, NK cells	JAK1/3-STAT5, PI3K-AKT-mTOR	Sustains cytotoxic persistence, metabolic fitness, and long-term effector competence	Requires trans-presentation, context-dependent efficacy
IL-21	Anti-exhaustion cytokine	CD8⁺ T cells, NK cells	STAT1, STAT3	Preserves effector competence, supports cytotoxic differentiation, limits terminal exhaustion	Limited monotherapy activity, context-dependent efficacy
IL-10	Context-switch cytokine	CD8⁺ T cells, myeloid cells	STAT3	Reprograms suppressive immune context and restores permissive anti-tumor immunity	Functional polarity is highly context-dependent
IL-7	Homeostatic support cytokine	Naïve and memory T cells	JAK-STAT, PI3K-AKT	Supports T-cell survival, immune reconstitution, and post-lymphodepletion recovery	Limited direct cytotoxic or tumor-remodeling activity

receptor engagement [185]. Because cytokine signaling is constrained by receptor topology and receptor distribution, therapeutic efficacy depends in part on directing cytokine activity toward the immune compartments most capable of productive anti-tumor function while limiting access to suppressive or non-productive populations [186].

This principle underlies receptor-biased IL-2 engineering, in which signaling is redirected toward IL-2Rβγ-expressing CD8⁺ T cells and NK cells while reducing access to CD25-high Tregs [100,187]. A related logic applies to IL-15 superagonists, which preserve physiologic trans-presentation while preferentially reinforcing cytotoxic persistence without substantial Treg expansion [131]. In both cases, receptor engineering transforms cytokines from broad immune agonists into more selectively deployed signaling modules [92]. The key design principle is not simply stronger receptor binding, but more selective receptor access.

6.2. Delivery geometry determines where and how cytokines act

A second principle is control of cytokine exposure in space and time [188]. Cytokines are not interpreted identically across tissues, and therapeutic outcome depends heavily on where signals are delivered, how broadly they diffuse, and how long they persist [189]. Delivery therefore functions not merely as a pharmacologic variable, but as a determinant of how cytokine signals are biologically interpreted [190].

This principle motivates strategies such as depot-based release, nanoparticle encapsulation, lymph node targeting, and local intratumoral administration, all of which aim to impose spatial and temporal structure on cytokine signaling [15,191]. Protease-activatable cytokines extend this logic further by restricting activity to proteolytically permissive tumor environments [192]. These approaches reposition delivery from a passive formulation consideration to an active element in cytokine therapy.

Beyond these approaches, cytokine engineering is increasingly shifting toward conditionally activated and structurally programmable platforms designed to further improve spatial precision and therapeutic index [16,138]. Emerging strategies include masked cytokines that remain functionally inactive until tumor-specific activation, cytokine prodrugs with conditional unmasking, immunocytokines that direct cytokine payloads toward tumor-associated targets, and engineered cytokine mimetics or multicyclic peptide scaffolds designed to selectively recapitulate receptor signaling while minimizing systemic toxicity [159,193]. These innovations reflect a broader shift from simply attenuating cytokine toxicity toward actively programming context-restricted cytokine function. Although many remain early in clinical development, they substantially expand the engineering design space for next-generation cytokine therapeutics.

6.3. Immune context determines cytokine utility

Cytokine function must also be matched to the immune architecture of the tumor in which it is deployed [31]. Because tumors differ substantially in baseline immune infiltration, stromal restriction, myeloid suppression, and antigen presentation, the same cytokine may be productive in one setting and ineffective or counterproductive in another [194]. Cytokines are therefore most effective when selected not for intrinsic potency alone, but for their ability to correct the dominant immune deficit of a given tumor state [186].

This principle reframes cytokines as context-matched immune tools. Immune-inflamed tumors may benefit most from cytokines that reinforce cytotoxic persistence or preserve effector function, such as IL-15 or IL-21 [162]. By contrast, immune-excluded or myeloid-dominant tumors may require cytokines that reprogram suppressive immune architecture, improve antigen presentation, or alter stromal exclusion, as seen with IL-10, IL-12, or related context-rewiring cytokines [31,195]. In this framework, cytokines are not general immune enhancers, but selective instruments for correcting specific immune-state defects.

6.4. Combination logic determines mechanistic coherence

Cytokines rarely function optimally as monotherapies and are increasingly best understood as components of broader immunologic regimens [196]. Their therapeutic value often depends on how effectively they reinforce, sequence with, or stabilize the activity of other immune interventions [197]. Cytokine-guided design therefore requires not only molecular optimization, but mechanistic coherence across combination strategy [5].

In this context, IL-15 and IL-21 are particularly well suited to reinforce checkpoint blockade by supporting cytotoxic persistence and limiting terminal exhaustion, whereas IL-7 may be more useful in immune reconstitution after lymphodepletion [72,198]. Conversely, cytokines such as IL-10 or IL-12 may be highly sequence-dependent, with therapeutic benefit determined by whether they are introduced before, during, or after antigen priming and myeloid remodeling [199]. The key principle is that cytokine combinations should be mechanistically coordinated, not empirically layered [17].

6.5. Biomarker logic determines who should receive which cytokine

Finally, cytokine-guided design requires biologic stratification [200]. Cytokine responsiveness is shaped by baseline immune composition, receptor abundance, prior treatment, stromal architecture, and host-specific variation in cytokine signaling [201]. As a result, the same cytokine is unlikely to produce uniform benefit across biologically heterogeneous patients [31].

This makes biomarker integration essential rather than optional. Cytokine receptor expression, T-cell clonality, inflammatory state, and spatial immune architecture are likely to be critical variables for patient selection, biologic dosing, and treatment sequencing [202,203]. In this setting, biomarkers are not simply correlates of response; they are part of the therapeutic logic that determines which cytokine should be used, in whom, and in what context [204].

Taken together, cytokine-guided design reflects a shift from empirical cytokine administration to rational immune programming [118]. Rather than functioning as generalized immune stimulants, next-generation ILs are increasingly being developed as modular immunotherapeutic components whose value depends on receptor selectivity, delivery geometry, immune-state matching, mechanistic combination logic, and biomarker-informed deployment [205]. These integrated principles define the operational logic of precision cytokine therapy and provide the conceptual framework for translating engineered ILs into more durable and biologically coherent cancer immunotherapy [206]. Fig. 5 summarizes this cytokine-guided design framework.

7. Translational bottlenecks now define the field

The principal barriers to broader clinical translation of cytokine therapy are no longer primarily molecular. Over the past decade, interleukin engineering has substantially improved receptor selectivity, pharmacologic control, and mechanistic sophistication [17,18]. Yet clinical benefit has advanced far more slowly than molecular design. The dominant limitations are now translational: how to identify the right patients, define biologically meaningful dosing, overcome tissue-level resistance, and deliver cytokines in clinically scalable ways [6,7]. In this sense, the field's central bottlenecks are no longer molecular, but translational, ecological, and trial-architectural.

7.1. Biomarker insufficiency limits patient selection

The absence of validated predictive biomarkers remains one of the most persistent barriers to clinical translation [207]. Unlike checkpoint blockade, where imperfect but actionable biomarkers such as PD-L1 expression and TMB can at least partially guide treatment selection, interleukin-based therapies still lack clinically deployable biomarkers that reliably identify biologically responsive patients [208].

This limitation is especially consequential because cytokine responsiveness is highly state-dependent [209]. Receptor abundance, immune cell composition, stromal restriction, prior treatment, and baseline inflammatory tone all shape whether a given cytokine will reinforce productive immunity, induce compensatory suppression, or produce little meaningful effect [55]. Yet most cytokine trials continue to enroll biologically heterogeneous and largely unstratified populations [19]. Although candidate biomarkers including cytokine receptor expression, circulating inflammatory mediators, and spatial immune architecture have shown promise, they remain largely exploratory and have rarely been prospectively integrated into trial design or treatment assignment [210].

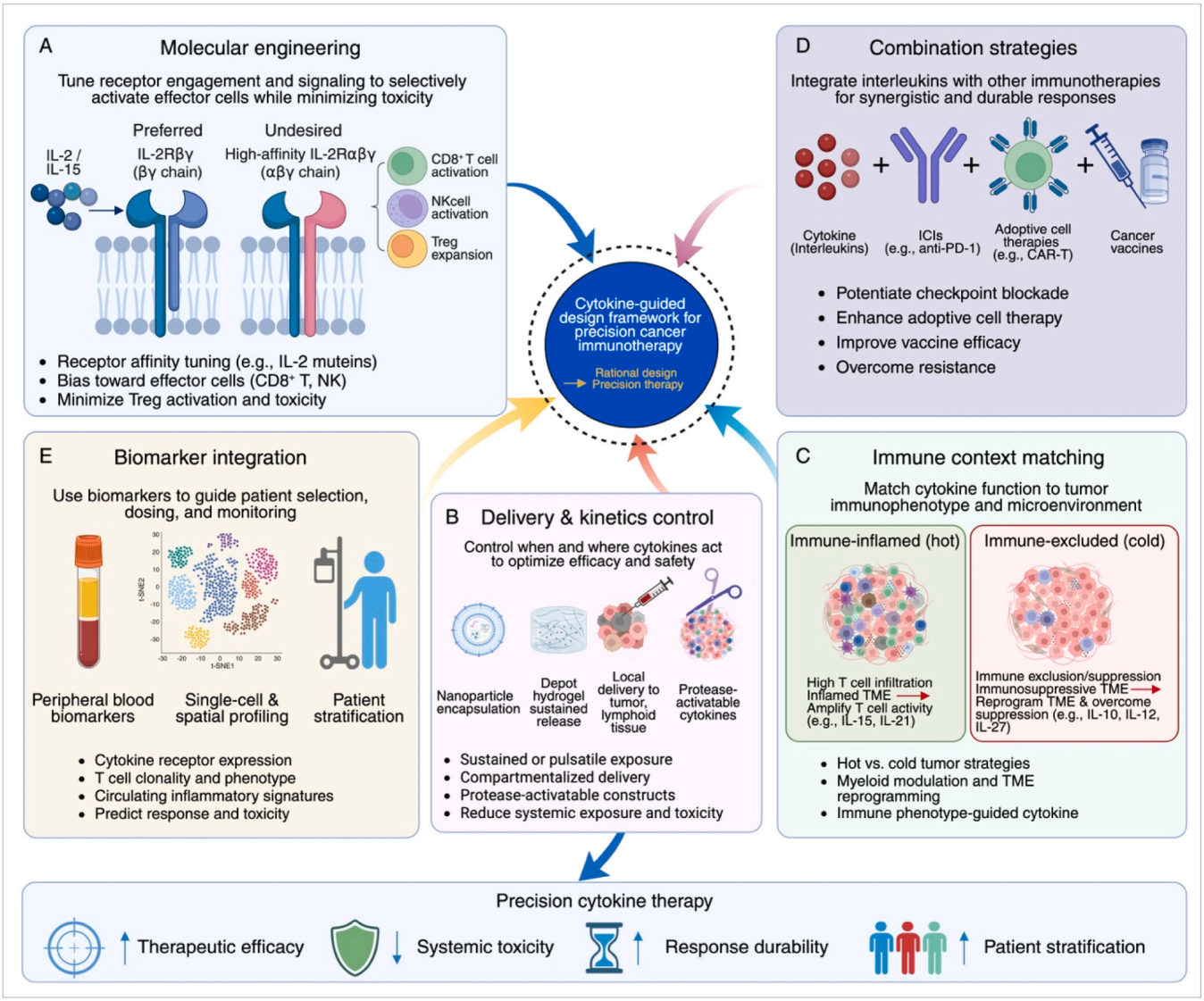


Fig. 5. A cytokine-guided design logic for precision cancer immunotherapy. Conceptual framework outlining five operational principles that govern next-generation cytokine therapy. (A) Receptor logic: receptor topology and signaling bias are engineered to direct cytokine activity toward productive immune compartments while limiting suppressive signaling. (B) Delivery geometry: cytokine exposure is spatially and temporally constrained through local delivery, sustained-release systems, or conditional activation to improve therapeutic precision. (C) Immune-context matching: cytokines are selected according to the dominant immune deficits and structural constraints of a given tumor state. (D) Combination logic: cytokines are mechanistically coordinated with checkpoint blockade, ACT, or immune priming to reinforce coherent immune state transitions. (E) Biomarker logic: molecular and cellular biomarkers guide patient selection, dosing, and treatment sequencing. Together, these principles define a cytokine-guided framework for rational and precision-oriented interleukin immunotherapy.

7.2. Trial architecture remains poorly aligned with cytokine biology

Clinical trial design remains another major constraint. Many cytokine studies continue to rely on empiric combinations, static dosing schedules, and toxicity-driven escalation models that are poorly suited to immunomodulatory agents whose therapeutic value depends on immune state transition rather than maximal tolerated dose [211,212].

This mismatch is especially problematic in cytokine therapy, where maximal tolerated dose often does not reflect maximal biologically effective dose [213]. Yet many studies still prioritize conventional escalation paradigms while underutilizing pharmacodynamic endpoints such as immune cell reprogramming, transcriptional state change, receptor occupancy, or dynamic remodeling of the TME [195]. Without these mechanistic readouts, dose selection remains empiric and biologic interpretation remains shallow. More adaptive trial architectures that incorporate biologically informed dosing, on-treatment immune monitoring, and real-time stratification remain urgently needed but are still uncommon [214,215].

7.3. Tumor ecology still constrains cytokine efficacy

Even when cytokines are molecularly optimized, many tumors remain structurally resistant to productive immune remodeling [216]. Solid tumors often retain entrenched ecological barriers including stromal exclusion, vascular dysfunction, hypoxia, metabolic suppression, and myeloid dominance that continue to restrict cytokine

trafficking, immune cell access, and downstream responsiveness [13,217].

These ecological barriers manifest differently across tumor contexts and therefore impose distinct therapeutic constraints. Immune-inflamed tumors such as subsets of melanoma and non-small cell lung cancer may retain substantial T-cell infiltration yet exhibit progressive checkpoint-mediated dysfunction and terminal exhaustion, creating conditions in which cytokines that preserve effector competence or cytotoxic persistence, such as IL-21 or IL-15, may be mechanistically advantageous [218,219]. By contrast, immune-excluded tumors such as pancreatic ductal adenocarcinoma or immune-excluded stromal-rich colorectal cancer are dominated by stromal restriction and impaired lymphocyte trafficking, conditions that may substantially limit the effectiveness of systemically deployed cytokines unless paired with strategies that overcome spatial exclusion [220,221]. In tumors characterized by suppressive myeloid dominance, including selected hepatocellular carcinoma, ovarian cancer, and colorectal cancer contexts, cytokine responsiveness may be further constrained by immunoregulatory macrophage and myeloid signaling networks that actively suppress productive immune remodeling [222,223]. These distinctions underscore that cytokine deployment must be matched not only to cytokine biology, but to the dominant ecological constraints of specific tumor ecosystems.

These constraints help explain why improved cytokine pharmacology does not consistently translate into durable clinical benefit [31]. Engineering can improve receptor selectivity, signaling bias, or local retention, but it does not by itself resolve the ecological constraints that determine whether cytokine-responsive immune cells can access, persist within, or function productively inside tumor tissue [7,23,224]. In many solid tumors, cytokine potency remains limited less by ligand design than by tissue-level resistance that cytokine signaling alone cannot overcome [225].

7.4. *Delivery remains mechanistically promising but clinically immature*

Delivery remains another major translational bottleneck. Although cytokine delivery platforms have become increasingly sophisticated, most remain substantially more mature in concept than in clinical execution [226]. Nanoparticles, depot systems, and local delivery platforms offer clear theoretical advantages in spatial control and exposure restriction, but most have yet to demonstrate robust clinical scalability, reproducibility, and regulatory tractability [227–229].

This gap is no longer primarily conceptual. The biologic rationale for improved delivery is strong; the challenge is translational execution [230]. Manufacturing complexity, formulation variability, uncertain pharmacokinetics, and regulatory burden continue to limit clinical adoption of otherwise promising delivery systems. As a result, many cytokines with increasingly sophisticated engineering still remain constrained by relatively conventional delivery infrastructure [147,231].

7.5. *Patient heterogeneity remains the hardest unresolved variable*

Perhaps the most difficult unresolved challenge is biologic heterogeneity. Cytokine responsiveness is shaped not only by tumor type, but by baseline immune tone, prior therapy, host genetics, comorbid inflammation, and tissue-specific immune architecture [14,232,233]. These variables introduce substantial interpatient variability that remains poorly captured in both preclinical models and current clinical enrollment strategies [234].

This heterogeneity likely explains much of the inconsistency observed across cytokine trials. A cytokine that reinforces productive immunity in one immune state may be ineffective or counterproductive in another [235]. Uniform cytokine deployment is therefore unlikely to succeed broadly. Future progress will require defining clinically meaningful response endotypes and prospectively aligning cytokine strategies with these immune states [236].

Overall, the major barriers to cytokine therapy are no longer best understood as problems of molecular insufficiency [237]. The field has already demonstrated that cytokines can be engineered with greater precision, selectivity, and pharmacologic control [31]. The more difficult challenge now is translational execution: identifying biologically responsive patients, designing trials around immune-state change, overcoming tissue-level resistance, and translating delivery innovation into clinically scalable platforms [238]. Future progress will depend less on generating more complex cytokines and more on resolving these translational bottlenecks through biomarker-guided patient selection, immune-informed trial design, scalable delivery systems, and endotype-based therapeutic deployment [184].

8. Concluding perspectives

Interleukin-based cancer immunotherapy is undergoing a conceptual transition from empiric cytokine administration to rational immune programming. What began with IL-2 as proof-of-principle for cytokine-driven tumor control has evolved into a broader recognition that therapeutic efficacy depends less on indiscriminate immune amplification than on deploying cytokine signals with greater cellular, spatial, and temporal precision. In this emerging framework, ILs are no longer best understood as broadly acting immune stimulants, but as programmable immunologic components whose therapeutic value lies in how precisely they reshape immune state, tissue context, and treatment response.

This shift has redefined the role of next-generation ILs. Cytokines such as IL-15, IL-21, and IL-10 are not simply improved successors to IL-2, but functionally specialized immunologic tools that sustain cytotoxic persistence, preserve effector competence, and recondition suppressive immune environments [69,91]. Their value lies not only in improved tolerability or receptor selectivity, but in the ability to resolve distinct immunologic constraints that limit anti-tumor immunity. The future of cytokine therapy will therefore depend less on discovering stronger cytokines than on defining more precise cytokine functions.

At the same time, the principal barriers to clinical success are no longer primarily molecular. Engineering has improved receptor bias, pharmacologic control, and delivery precision, but these advances alone have not resolved the translational constraints that continue to limit durable benefit. Biomarker insufficiency, biologic heterogeneity, tissue-level resistance, and poorly aligned clinical trial architecture now represent the dominant barriers to effective cytokine translation [31,157]. Future progress will depend less on expanding cytokine complexity than on integrating cytokines into biologically coherent treatment frameworks guided by immune state, spatial logic, and mechanistic biomarkers.

The next phase of cytokine immunotherapy will likely be defined not by cytokines as standalone drugs, but by cytokines as modular components of larger therapeutic systems. Their most durable roles may be to reinforce checkpoint blockade, stabilize adoptive cell therapies, reprogram suppressive myeloid states, and coordinate transitions between innate and adaptive immunity. In this setting, cytokine function will be determined not only by molecular design, but by how effectively cytokines are integrated into mechanistically coherent therapeutic architectures.

Ultimately, the next success in cytokine immunotherapy will likely not come from a more potent cytokine, but from a more intelligently deployed one.

CRediT authorship contribution statement

SH and WM jointly conceived and designed this review. CW, XW, YX, SH, and WM contributed to drafting and revising the manuscript. SH and WM supervised the study. WM designed and finalized the figures using BioRender. All authors contributed to the manuscript revision and approved the final version.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

Not applicable

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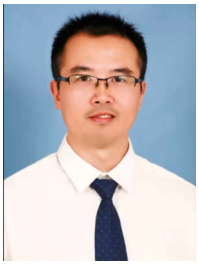
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