

Review Article



Harnessing the Power of IL-7 to Boost T Cell Immunity in Experimental and Clinical Immunotherapies

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ABSTRACT

The cytokine IL-7 plays critical and nonredundant roles in T cell immunity so that the abundance and availability of IL-7 act as key regulatory mechanisms in T cell immunity. Importantly, IL-7 is not produced by T cells themselves but primarily by non-lymphoid lineage stromal cells and epithelial cells that are limited in their numbers. Thus, T cells depend on cell extrinsic IL-7, and the amount of *in vivo* IL-7 is considered a major factor in maximizing and maintaining the number of T cells in peripheral tissues. Moreover, IL-7 provides metabolic cues and promotes the survival of both naïve and memory T cells. Thus, IL-7 is also essential for the functional fitness of T cells. In this regard, there has been an extensive effort trying to increase the protein abundance of IL-7 *in vivo*, with the aim to augment T cell immunity and harness T cell functions in anti-tumor responses. Such approaches started under experimental animal models, but they recently culminated into clinical studies, with striking effects in re-establishing T cell immunity in immunocompromised patients, as well as boosting anti-tumor effects. Depending on the design, glycosylation, and the structure of recombinantly engineered IL-7 proteins and their mimetics, recombinant IL-7 molecules have shown dramatic differences in their stability, efficacy, cellular effects, and overall immune functions. The current review is aimed to summarize the past and present efforts in the field that led to clinical trials, and to highlight the therapeutical significance of IL-7 biology as a master regulator of T cell immunity.

Keywords: Clinical trial; Cytokine; Immune system diseases; Inflammation; Tumor

INTRODUCTION

Adaptive immunity is the chief mechanism that ensures effective immune surveillance and provides host protection from foreign antigens and infectious diseases. Both the generation and maintenance of the adaptive immune system depend on signaling by cytokines of the common γ -chain (γ c) family, and this requirement is illustrated in the SCID of γ c-deficient humans and experimental mice (1). The γ c-deficient SCID phenotype manifests in the dramatic lack of T and NK cells in humans and the additional lack of B cells in mice, indicating that γ c cytokine receptor signaling is necessary for the development and survival of these lymphocyte subsets. The γ c family cytokines comprise 6 members, namely IL-2, IL-4, IL-

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Conflict of Interest

Choi D is employee of NeoImmuneTech, Co., Ltd. All authors declared no competing interests for this work.

Abbreviations

ADA, antidrug antibodies; ALC, absolute lymphocyte count; allo-HSCT, allogeneic hematopoietic stem cell transplantation; ATC, adoptive T cell; BM, bone marrow; BMT, bone marrow transplantation; CAR, chimeric antigen receptor; CRC, colorectal cancer; DC, dendritic cell; DLT, dose-limiting toxicity; DN, double-negative; GBM, glioblastoma; GVHD, graft versus host disease; HSC, hematopoietic stem cell; HSCT, hematopoietic stem cell transplantation; HSPC, hematopoietic stem and progenitor cell; hyFc, hybrid Fc; IAV, influenza A virus; ICL, idiopathic CD4 lymphocytopenia; ILC, innate lymphoid cell; iNKT, invariant NKT; LCMV, lymphocytic choriomeningitis virus; LIP, lymphopenia-induced proliferation; MDSC, myeloid-derived suppressor cell; MSS, microsatellite stable; MTD, maximum tolerated dose; ORR, overall response rate; PB, peripheral blood; PK, pharmacokinetics; PML, progressive multifocal leukoencephalopathy; rIL-7, recombinant IL-7; RTE, recent thymic emigrants; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SIV, simian immunodeficiency virus; SOC, standard of care; TIL, tumor infiltrating lymphocyte; TME, tumor microenvironment; γ c, common γ -chain.

Author Contributions

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7, IL-9, IL-15, and IL-21, and they share the γ c cytokine receptor for ligand binding and signaling (2,3). The γ c family cytokine receptors also share the JAK/STAT pathway for signal transduction so that all γ c cytokines signal through activation of the tyrosine kinases JAK1 and JAK3, followed by the phosphorylation, nuclear translocation, and transcriptional activation of STAT5 and other STAT molecules (2,3). Despite the common signaling pathways, however, the individual members within the γ c cytokine family are distinct in their roles and requirements, so that, for example, IL-2 is critical for Foxp3⁺ Treg cell generation (4), IL-4 is non-redundant in the generation of IFN γ -producing thymic innate CD8 T cells (5), and IL-15 plays an important role in the development of invariant NKT (iNKT) cells (6). Strikingly, IL-7 is unique among γ c cytokines as its requirement is not limited to a specific T cell subset but essential for all T cells, regardless of their lineage and functional identities. Consequently, IL-7-deficiency phenocopies the genetic deficiency of γ c (7), further documenting IL-7 as a unique and non-redundant requirement in establishing and maintaining T cell immunity. Because T cells are the main effector cells in anti-viral and anti-tumoral responses, understanding the roles and requirements for IL-7 directly translates into the ability to control T cell immune responses under steady-state and disease conditions, including viral infections and cancer. Accordingly, a large body of studies has accumulated assessing the physiological effects of altered IL-7 availability on T cell immunity. This review is aimed to summarize the recent cumulative efforts to re-engineer and manipulate IL-7 molecules and to maximize their efficacies under various immune settings, with the goal of bringing IL-7 into the clinic as a therapeutic agent.

AN IL-7 REQUIREMENT IN IMMUNE CELL DEVELOPMENT

Originally reported as a stromal cell derived factor that is critical for the generation of B cells, IL-7 was soon after also established as an essential cytokine in the generation of T cells (8). In immature pro-B cells as well as in developing $\gamma\delta$ T cells, IL-7 signaling positively regulates the accessibility of the antigen receptor gene loci to RAG recombinases, thus facilitating IgH and TCR γ chain recombination respectively (9-11). Therefore, in the early developmental stages of both B cells and $\gamma\delta$ T cells, IL-7 is necessary as it controls the gene rearrangement and expression of immunoglobulin and the TCR. In $\alpha\beta$ lineage T cells, on the other hand, IL-7 was found to be mostly important for the vigorous proliferation of immature thymocytes at the CD4, CD8 double-negative (DN) stage (8). DN thymocytes express large amounts of the IL-7 receptor, rendering them responsive to intrathymic IL-7, which is produced by thymic epithelial cells and dendritic cells (DCs) at the cortico-medullary junction (12). In this regard, genetic deficiencies in IL-7 or IL-7 receptor manifest in severely impaired thymopoiesis and dramatically decreased thymic cellularity, because the lack of IL-7 signaling in DN thymocytes impairs their proliferation and expansion (13,14). Interestingly, different levels of IL-7 receptor expression among thymic DN cells were proposed being associated with $\gamma\delta$ vs. $\alpha\beta$ T lineage differentiation, suggesting an instructive role for IL-7 in early T cell lineage decision (15). Moreover, IL-7 receptor signaling is also critical in the CD4 vs. CD8 lineage decision of positive selected thymocytes, whereby IL-7 induces the expression of the transcription factor Runx3d which promotes CD8 coreceptor expression and specifies cytotoxic T lineage fate (16,17). Importantly, IL-7-induced Runx3d is instrumental in antagonizing the CD4 lineage master regulator ThPOK, documenting a cytokine-driven circuitry of helper vs. cytotoxic lineage choice (18,19). In addition to B and T cells, IL-7 was also found to be required in the development of DCs and lymphoid tissue inducer cells, expanding the requirement of IL-7 into the innate immune system (20,21). Collectively, IL-7 is a pleiotropic cytokine that is essential for the establishment of both adaptive and innate immunity.

IL-7 RECEPTOR EXPRESSION AND SIGNALING IN T CELLS

The functional IL-7 receptor is composed of the γ_c and the IL-7 proprietary IL-7R α receptor. Ligand binding induces the heterodimerization of these receptors, resulting in the juxtaposition of the receptor-bound intracellular tyrosine kinases JAK1 and JAK3 which triggers their transphosphorylation and proximal downstream signaling. In contrast to the γ_c , which is constitutively expressed on all lymphoid cells, IL-7R α receptor expression is highly regulated in a developmental and activation-dependent manner (22). Consequently, the cellular abundance of IL-7R α acts as a regulatory factor that constrains IL-7 responsiveness in T cells (23). In this regard, immature CD4, CD8 double-positive thymocytes are refractive to IL-7 signaling, because they are developmentally programmed to downregulate IL-7R α expression, while mature naïve and memory T cells express high levels of IL-7R α to voraciously consume IL-7 (24,25). Importantly, IL-7 signaling was found to suppress the expression of its own receptor (17), so that T cells are hardwired to avoid excessive IL-7 signaling. In accordance, the increased exposure to IL-7 will downregulate IL-7R α expression, and IL-7 signaled cells will necessarily lose their ability to capture IL-7. In fact, prolonged and persistent IL-7 is detrimental and toxic to T cells as demonstrated in experimental mouse models where the forced expression of IL-7R α was found to induce T cell proliferation that was accompanied by large amounts of IFN γ production, leading to cytokine-induced cell death (26). Thus, IL-7 signaling is critical for the homeostatic maintenance of T cells, but IL-7 signaling also needs to be carefully timed and titrated to achieve optimal prosurvival function for T cells. Multiple redundant mechanisms are put in place to augment the negative regulatory mechanism of IL-7 receptor signaling, which include the production of soluble IL-7R α and γ_c expression by alternative splicing that results in the concomitant loss of membrane cytokine receptors (27-29), as well as in the induction of suppressors of cytokine signaling expression (30), among others.

Nonetheless, the increased protein abundance of IL-7 can substantially amplify the prosurvival and proliferative effects of IL-7 as demonstrated in several *in vivo* studies. As such, the overexpression of IL-7 reportedly caused lymphoproliferative disorders with B cell hyperplasia and ectopic B cell development in mice, but could also induce chronic colitis depending on the site of transgenic IL-7 overexpression (31-33). In this regard, a recent study circumvented these issues by generating a tamoxifen-inducible IL-7 transgene where it was found that the increased IL-7 expression led to the dramatic expansion of memory phenotype CD8 T cells that was concomitant to a decrease in Foxp3⁺ Treg cells (34). As a result, acutely induced expression of IL-7 expression significantly enhanced T cell responses as demonstrated in a graft versus host disease (GVHD) model. Moreover, exogenous administration of IL-7 significantly was found to promote the survival and proliferation of T cells, indicating that an increase in IL-7 expands the size of the T cell pool and substantially enhances T cell function. Collectively, these results led to the early realization that the *in vivo* IL-7 availability for T cells is limited, and boosting the abundance of IL-7 could serve as an important tool to augment T cell immunity.

IL-7 AVAILABILITY CONTROLS THE SIZE OF THE T CELL POOL

A major tenet in IL-7 biology posits that the production of IL-7 is constitutive but that the amount of IL-7 is developmentally set. Consequently, the availability of IL-7 is primarily

controlled by the consumption of pre-existing IL-7, instead of changing the rate of IL-7 production *in vivo*. IL-7 is consumed by most, if not all lymphocytes, including innate lymphoid cells (ILCs), which were previously identified as an IL-7 sink, whose constitutive intake of IL-7 can act as a negative regulator of IL-7 availability (35). Nevertheless, numerically, it is the T cell compartment that contains the major consumers of IL-7 because ILCs are scarce and mature B cells do not express IL-7R α and cannot internalize IL-7. Thus, T cells correspond to the largest cohort of lymphocytes that respond to, consume, and depend on IL-7. Consequently, both chronic and acute T lymphopenia create an environment where IL-7 is in excess and is highly abundant. Such increased availability of IL-7 can drive the dramatic expansion of adoptively transferred T cells, leading to a phenomenon known as lymphopenia-induced proliferation (LIP) that is strictly dependent on IL-7. LIP is an important mechanism to rapidly restore functional immunity upon lymphodepleting insults, viral infections, but also in clinical settings of bone marrow (BM) transplants (36). Because it is the increased amount of IL-7 that drives the expansion of T cells, there have been many attempts to replicate these effects by administering exogenous IL-7 to increase T cell numbers and to bolster their functional fitness.

IL-7 is optimally equipped to increase T cell numbers without aberrant immune activation because its primary function is to induce anti-apoptotic factors such as Bcl-2 and Mcl-1, as well as to promote metabolism by increasing the expression of glucose transporter 1 but not to drive effector T cell differentiation. Consequently, the infusion of exogenous IL-7 usually increases T cell numbers and expands the naïve T cell pool without eliciting autoimmunity. Because IL-7 also promotes thymopoiesis, an increase of peripheral T cells could have been either due to increased thymic output or the expansion of the preexisting T cells. In humans, it is most likely the latter case. Earlier studies have documented that the peripheral T cell pool in mice is mostly maintained by thymic output, but in humans, thymic output of newly generated T cells mostly ceases with aging (37). Thus, the effects of IL-7 administration need to be carefully interpreted depending on the experimental setting and species that were used in the study. In animal models, early experiments on IL-7 infusion started with simple injection of recombinant IL-7 (rIL-7) or administering IL-7 using osmotic pumps, and they also included complexing IL-7 with anti-IL-7 mAbs to increase their efficacy and *in vivo* half-life (38-40). In fact, the half-life of exogenous rIL-7 is considered to be short, ranging only between 6 and 10 h (41), so that the availability of re-engineered long-lasting IL-7 molecules is of particular interest. Based on these encouraging results, there has been subsequently an ongoing rush for preclinical studies and testing clinical applications of IL-7 in immunotherapies (42).

IL-7 IN PRECLINICAL MODELS OF IMMUNOTHERAPIES

Because of its central role in the regulation of conventional T cell homeostasis, including proliferation, survival, and memory formation, IL-7 has been considered from early on as a key factor in immunotherapies (43,44). Nonetheless, recent findings suggest that the T cell subsets targeted by IL-7 may differ depending on the disease. Moreover, unconventional T cells, whose roles in immunotherapy have been underappreciated in the past, may also serve as important therapeutic targets for IL-7 (45). Along these lines, the remarkable advance in single-cell transcriptomics further provides the technical background for a more detailed and comprehensive analysis of the effects of IL-7 on individual cells in different tissues. In this regard, the regulation of hematopoiesis by IL-7, which has been consistently observed

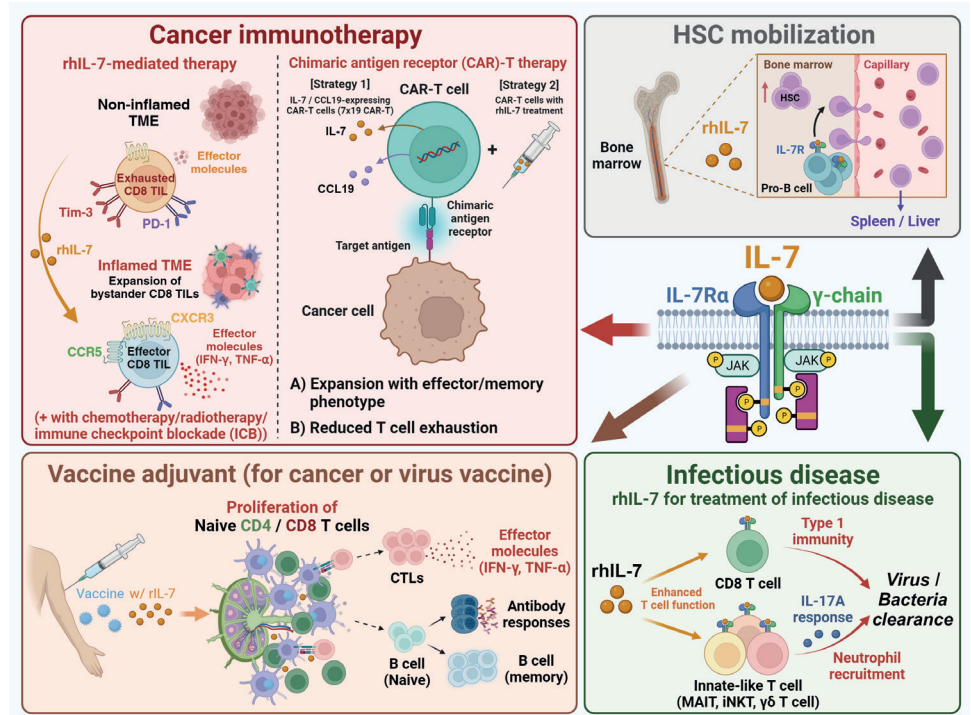


Figure 1. Summary of IL-7 immunotherapies in preclinical models.

but understudied for the past 30 years, is emerging as a new focal point. In the following, the results are reviewed in the context of preclinical studies, and mainly from data using the mice model (Fig. 1).

IL-7 in cancer immunotherapies

Early attempts to apply IL-7 in cancer immunotherapies were mostly limited to using IL-7 as an adjuvant for cancer vaccines. This topic has been broadly covered in past (46), and will be only briefly mentioned in this review. Multiple forms of IL-7 were tested as vaccine adjuvants, including IL-7 gene delivery using recombinant viruses (47), or DCs (48), and by co-injecting rIL-7 with cancer cells that express GM-CSF (49) or viral vectors that express tumor antigens (50). In these cases, IL-7 augmented the antitumor efficacy by increasing both effector and memory T cell responses to vaccine antigens (46,50).

Treating tumors with direct infusion of rIL-7 has also been attempted. However, the poor pharmacokinetics (PK) of rIL-7 necessitated the daily administration of rIL-7 for an extended period of time (51). While these early studies clearly demonstrated rIL-7-mediated anti-tumor effects, they highlighted the need for developing modified rIL-7 with improved PK as a priority. In response, multiple efforts to develop a long-acting form of rIL-7 were initiated, that include utilizing rIL-7/IL-7 mAb complexes (52) and modifying the rIL-7 with an Fc-fused form (53,54). Both methods improved the PK profiles of rIL-7 and effectively increased the *in vivo* T cell responses to a single administration.

Specifically, the Fc-fused rIL-7 was co-developed by the Pohang University of Science and Technology and the biotech company Genexine as a hybrid Fc (hyFc) format which correspond to a natural form of noncytolytic human Fc and that can serve as a long-acting carrier for recombinant proteins. HyFc is a fusion product of the IgD hinge region and the

CH2/ CH3 domains of IgG4. Its potency is illustrated in erythropoietin (EPO)-hyFc which shows improved *in vivo* bioactivity compared to conventional glycosylated EPO (55). The study of human rIL-7-hyFc was first conducted as an attempt to enhance cancer vaccine immune responses in combination of DNA vaccines (54). Specifically, intravaginal treatment of rhIL-7-hyFc was found to enhance antitumor activity against orthotopic cervical tumors by increasing the CD8 T cell responses triggered by HPV DNA vaccines. Notably and unlike previous typical cancer vaccine adjuvants, the topical treatment of IL-7-hyFc increased the expression of inflammatory chemokines and cytokines within the genital tract, which boosted the recruitment of vaccine-induced CD8 T cells (54). This protocol, which is comparable to the prime-pull strategy proposed by the Iwasaki group (56), is noteworthy in that the local treatment of IL-7-hyFc can augment the immune response of a mucosal vaccine.

The application of rhIL-7-hyFc in cancer immunotherapy as a stand-alone or combination therapy has also been studied. A single dose of rhIL-7-hyFc showed significant antitumor efficacy in murine syngeneic tumor models (57,58). Robust antitumor responses of rhIL-7-hyFc are well documented in the relatively immunogenic MC38 or CT26 colorectal cancer (CRC) models but not in the non-immunogenic B16.F10 melanoma, GL261 glioma, and 4T1 breast cancer models. These results suggest that the antitumor efficacy of rhIL-7-hyFc monotherapy varies depending on the immunogenicity and the immune-environment of the tumor. The most crucial aspect of the rhIL-7-hyFc therapy induced antitumor activity is the tumor infiltration of CD8 T cells, which were increased in their numbers in peripheral tissues, including the lymph nodes, spleen, and blood. CD8 T cells amplified by rhIL-7-hyFc displayed a central memory phenotype that was concomitant to significantly increased expression of the chemokine receptors CXCR3 and CCR5 which are considered being involved in enhanced tumor infiltration (57,59). In agreement, the antitumor effect of rhIL-7-hyFc was abolished by anti-CD8 or anti-CXCR3 mAb treatments (57,58). Another important aspect of rhIL-7-hyFc therapy is the fact the increased IL-7 availability amplifies the number of most IL-7R⁺ T cells, regardless of their TCR specificity. Thus, CD8 T cells expanded by rhIL-7-hyFc administration are polyclonal, and a significant proportion of the increased CD8 tumor infiltrating lymphocytes (TILs) in tumors are PD-1⁺ bystander T cells that are non-reactive to tumor antigens. Still, rhIL-7-hyFc treatment also increased the tumor-specific PD-1⁺ CD8 T cells in absolute numbers (57).

The functional changes of tumor-specific CD8 TILs in rhIL-7-hyFc treated tumor models can be characterized as follows. The expression of proinflammatory cytokines, such as IFN- γ and TNF- α , increases in T cells, whereas the expression of immune checkpoint molecules, including PD-1 and Tim-3, conversely decreases. Therefore, rhIL-7-hyFc is likely to inhibit T cell exhaustion during CD8 T cell differentiation in tumors (57,58,60). Indeed, scRNA-seq of tumor-specific CD8 TILs from rhIL-7-hyFc treated tumors showed decreased expression of immune checkpoint molecules and transcription factors that are associated with T cell exhaustion as well as an impairment in their glycolysis pathway (SW Lee, unpublished results). These data suggest that rhIL-7-hyFc treatment suppresses T cell dysfunction by modulating immune inhibitory signaling and metabolism in tumor-specific CD8 TILs.

Given IL-7's ability to regulate T cell homeostasis, IL-7-mediated immunotherapy may be more effective in lymphopenic conditions where T cell numbers are significantly reduced. In agreement, in lymphopenic models, such as thymectomized mice, rhIL-7-hyFc showed effective antitumor response by increasing T cell numbers. Additionally, in a mouse model of glioblastoma (GBM), a representative immune-cold cancer, Campian et al. (58) observed

that a combination of radiotherapy and chemotherapy could induce lymphopenia similar to the clinical situation. Under this lymphopenic setting, the administration of rhIL-7-hyFc conferred a significant survival benefit against GBM. Curiously, however, the increase in CD8 TILs as observed by rhIL-7-hyFc monotherapy did not happen when rhIL-7-hyFc was administered in combination with radio and chemotherapy. Thus, rather than an increase in CD8 TIL number, it is presumably the increased effector function of CD8 T cells, such as IFN- γ secretion, that contributed to the antitumor efficacy. Given that many cancer patients may experience lymphopenia for various reasons (61), conducting further in-depth studies on the antitumor immune responses induced by rhIL-7-hyFc in lymphopenic mouse models will be valuable.

The administration of rhIL-7-hyFc also increased CD4 T cell numbers in peripheral tissues and tumor of most syngeneic graft tumor models (57,58), but without much impacting Foxp3⁺ Treg cells. Although the antitumor activity of rhIL-7-hyFc was reduced by CD4 T cell depletion in some tumor models (55), the role of CD4 T cells in rhIL-7-hyFc-mediated antitumor response is thought to be limited, compared to its apparent effect on CD8 T cells. rhIL-7-hyFc monotherapy induces a significant increase in the CD8/Treg cell ratio in most tumors, which is considered an inflammatory marker of the tumor microenvironment (TME) (57,58). Interestingly, rhIL-7-hyFc also affected hematopoiesis in the BM, promoting lymphopoiesis but inhibiting myelopoiesis. Since myeloid-derived suppressor cells (MDSCs), the central immunosuppressive cells in tumors, also differentiate from the BM and enter the tumor, rhIL-7-hyFc therapy significantly reduced the number of MDSCs in the tumor (57). Collectively, the ability of rhIL-7-hyFc to form an inflamed TME by regulating the number and function of various immune cells in the tumor suggests that rhIL-7-hyFc may act synergistically with various antitumor therapies. In fact, rhIL-7-hyFc showed improved antitumor efficacy when combined with standard cancer therapies, comprising chemotherapy, radiotherapy, and immune checkpoint blockade, such as anti-PD-1/PD-L1/CTLA-4 mAb, when compared to monotherapy (57,58).

The role of IL-7 in T cell proliferation and survival also suggests that rhIL-7 may be compatible with adoptive T cell (ATC) therapy. Indeed, in polyfunctional CD4 T cell therapy following lympho-depletion, rhIL-7-hyFc treatment increased antitumor activity by enhancing the number and function of effector T cells (62). In CD8 ATC therapy, rhIL-7-hyFc treatment after lympho-depletion also increased the antitumor effect in the melanoma model through an increase in transferred CD8 T cell numbers (63). Interestingly, the increased antitumor activity of rhIL-7-hyFc was not observed in lymphocyte-replete normal mice. The authors speculated that an increase in adoptively transferred CD8 T cells is limited in normal lympho-replete mice because of the amplification of endogenous T cells in response to rhIL-7 (63).

Administration of rhIL-7 has also been applied to chimeric antigen receptor (CAR)-T cell therapy (64). In a pioneering study, Adachi et al. (65) reported significantly enhanced antitumor effects and immune memory responses in various tumor models when CAR-T cells were engineered to co-express IL-7 and CCL19 (7 \times 19 CAR-T) compared to conventional CAR-T cells. Interestingly, CAR-T cells expressing only IL-7 or CCL19 did not show enhanced antitumor activities, suggesting that IL-7 and CCL19 expressed by stromal cells in the T cell zone of lymph nodes act synergistically in CAR-T cell therapy. The 7 \times 19 CAR-T cells expressed low levels of PD-1, LAG-3, and TIGIT in the tumor, similar to what was observed in tumor-specific CD8 TILs in response to rhIL-7-hyFc therapy, suggesting that IL-7 may inhibit T cell exhaustion in CAR-T cells as well (65). While other CAR-T cell studies have shown improved

antitumor activity with IL-7 expression alone (66), dual expression of CCL19 and IL-7 in CAR-T cells appears to induce the most potent antitumor response across a wide range of mouse tumor models. In another attempt to utilize the effect of IL-7 infusion, CAR-T cell delivery was followed by rhIL-7-hyFc treatment to promote their *in vivo* expansion and persistence (60). In this protocol, both human and mouse CAR-T cells showed dramatic improvements in T cell expansion and antitumor activities. Moreover, rhIL-7-hyFc also increased IFN- γ /TNF- α expression, cytotoxic activity, and diminished the T cell exhaustion profile in CAR-T cells, similar to its effects on endogenous CD8 T cells.

Finally, while the systemic administration of rhIL-7 has a relatively good safety profile compared to IL-2 and IL-12 administration (46,67), there could be still risks associated with systemic infusions of high-dose long-acting rhIL-7. Consequently, oncolytic viruses such as adenoviruses or vaccinia viruses carrying the IL-7 gene have been used to induce the secretion of IL-7 proteins in tumors (68,69). While such approaches can have a significant impact on TILs and CAR-T cells by the targeted overexpression of IL-7 exclusively in the tumor (70), it also comes with the caveat that it is significantly less effective at systemic T cell amplification.

IL-7 in immunotherapies against infectious diseases

The requirement for IL-7 in T cell homeostasis has led to attempts utilizing rIL-7 as a therapeutic for HIV and simian immunodeficiency virus (SIV) infections. In SIV-infected nonhuman primates, rIL-7 administration increased the numbers of CD4 and CD8 T cells (71,72), and these encouraging results led to the trial with HIV patients of rhIL-7 therapy in combination with antiretroviral therapy. These findings will be covered in further detail in the clinical study section of the current review.

The role of IL-7 therapy against persistent viruses has been primarily studied in the lymphocytic choriomeningitis virus (LCMV) clone 13 infection model in mice. rhIL-7 treatment increased the number and function of effector T cells in LCMV clone13 infection, which could contribute to viral clearance. Similar to cancer immunotherapy, rhIL-7 treatment in LCMV clone 13 infection increases polyfunctional CD8 T cell numbers with a non-exhausted phenotype (73,74). These results suggest that rhIL-7 may utilize a common pathway of maintaining T cell numbers and function when exposed to chronic antigens, which would be the case for both cancer and chronic viral infections.

The effects of rhIL-7 therapy in acute infections have been assessed primarily in respiratory virus and bacterial infection models. Intranasal pretreatment with rhIL-7-mFc, which is rhIL-7 fused to murine nonlytic Fc, prevented the lethal infections of various influenza A virus (IAV) strains (75). In this case, the systemic delivery of rhIL-7-mFc via intramuscular or intravenous routes had no prophylactic efficacy; however, intranasal administration of rhIL-7-mFc resulted in a remarkable increase in antiviral function that was dependent on T cells and the neonatal Fc receptor in the lung epithelium. Furthermore, antiviral functions were observed even when FTY 720 treatment significantly reduced the migration of peripheral T cells into the lungs, indicating that IL-7-mFc treatment controls IAV infection by affecting lung tissue-resident cells (76). Interestingly, while the antitumor activity of rhIL-7-hyFc is dependent on CD8 T cells, the antiviral efficacy of rhIL-7-mFc in this model is more dependent on CD4 T cells and plasmacytoid DCs (75,76).

Recently, the same group reported that intramuscular delivery of rhIL-7-hyFc showed antiviral activities against major human respiratory viruses, including influenza viruses (IAV and IBV),

severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the respiratory syncytial virus (77). These broad-spectrum antiviral effects of rhIL-7-hyFc were more dependent on lung-resident unconventional innate-like T cells such as mucosal-associated invariant T, α NKT, and gd T cells rather than conventional T cells. Of note, rhIL-7-hyFc increased type 17 innate-like T cells, and neutralization of IL-17A abrogated the antiviral efficacy of rhIL-7-hyFc against IAV and SARS-CoV-2. The antiviral efficacy against IAV exhibited by rhIL-7-mFc vs. rhIL-7-hyFc is different regarding the mode of action, which should be further explored in subsequent studies. Similarly, studies of long-acting IL-7 in respiratory bacterial infections cement the notion that IL-7 also regulates innate-like T cells. Accordingly, in a *Streptococcus pneumoniae* respiratory infection model, rhIL-7/anti-IL-7 mAb complex treatment induced an increase in IL-17A-producing innate-like T cells in the lungs (78). Importantly, the rhIL-7/anti-IL-7 mAb complex was sufficient to reduce the bacterial burden, it did not lead to an increased survival benefit. However, combining the IL-7 complex with a suboptimal dose of α -galactosylceramide increased the survival rate with an enhanced IL-17A response. Collectively, long-acting IL-7 proteins can exert a broad range of protective effects in respiratory viral and bacterial infections, which appear to be dependent on respiratory tract resident type 17 innate-like T cells rather than on conventional T cells. Given that simultaneous or sequential viral and bacterial infections in acute respiratory infections cause severe pathology in patients, together with the emergence of new respiratory pandemic viruses, the possibility of anti-infectious immunotherapy with rhIL-7-hyFc deserves further consideration.

rIL-7 has also been studied as vaccine adjuvants for various infectious agents. Increased Ab responses were observed when rhIL-7-mFc and rhIL-7-hyFc for mice and macaques, respectively, were intramuscularly injected with a trivalent influenza virus vaccine (79). Mechanistically, rhIL-7-mFc increased the germinal center response in mice by promoting follicular helper T cell development in an IL-6/IL-21-independent manner. Recently, local delivery of recombinant glycosylated simian IL-7 (rs-IL-7gly) to the site of infection, *i.e.*, the vaginal mucosa, was attempted in SIV-infected macaques (80). Administration of rs-IL-7gly induced strong chemokine expression in the vaginal mucosa, increasing both innate and adaptive immune cells. In particular, when the antigen was coadministered with rs-IL-7gly, the generation of tertiary lymphoid structures and the production of IgA⁺ plasma cells in the vaginal mucosa were observed. These results suggest that rIL-7 can be used with various vaccines as an effective mucosal adjuvant.

IL-7 in modulating hematopoiesis

The modulation of hematopoiesis through rIL-7 was first aimed to induce peripheral T cell expansion or to increase thymic output in acute lymphopenia, such as sepsis or upon bone marrow transplantation (BMT) (8). As expected, rhIL-7 administration after allogeneic BMT in mice promoted the reconstitution of various immune cells, including T cells, in the central and peripheral organs. Excessive amplification of donor-derived T cells can lead to an acceleration of GVHD, but rhIL-7 administration did not worsen GVHD, while it maintained graft-versus-leukemia activity (81). On another note, in autologous CD34⁺ BM cell transplantation in nonhuman primates, rhIL-7 treatment enhanced CD4 T cell reconstitution, although some GVHD reactions were observed (82).

Almost 30 years ago, 3 studies reported the intriguing finding that rhIL-7 treatment promoted the migration of long-term hematopoietic stem cells (HSCs) or myeloid progenitors from the BM into peripheral blood (PB). Concomitantly to a decrease in hematopoietic stem and progenitor cells (HSPCs) in the BM, there was an increase in HSPCs in the spleen and liver

of rhIL-7-treated mice (83,84). However, the mechanisms behind this puzzling observation remained unclear because it was technically difficult at that time to separate HSPCs and assess their activities. Nonetheless, changes in HSPCs in the BM have been consistently observed in mice receiving rhIL-7-hyFc immunotherapy, raising fundamental questions about the role of rIL-7 in regulating hematopoiesis (57,58). A recently published study by Kim et al. (85) answered many of these questions. As expected, rhIL-7-hyFc administration reduced myelopoiesis while increasing lymphopoiesis in the BM. Consistent with the results from 3 decades ago, rhIL-7-hyFc effectively trafficked HSCs into the PB of both mice and humans. Since HSCs do not express IL-7R α , this was clearly not a direct effect of rhIL-7-hyFc on HSCs. Instead, rhIL-7-hyFc induced a huge increase in IL-7R $^+$ pro-B cells in the BM, and when IL-7R was deleted specifically from B-lineage cells, the rhIL-7-hyFc-induced HSC mobilization was no longer observed. Thus, the HSC mobilization by rhIL-7 therapy was induced by increased B cell progenitors in the BM, and not by peripheral T cell expansion (85). Notably, rhIL-7-hyFc promoted the peripheral migration of HSCs in synergy with clinically used agents such as rhGM-CSF and AMD3100, opening new possibilities for developing rhIL-7-hyFc as an HSC mobilizer. Not surprisingly, any significant alteration in hematopoiesis profoundly affects the composition and number of immune cells in the peripheral organs (86). These results, therefore, highlight the need for careful consideration of changes in hematopoiesis when attempting rhIL-7-mediated immunotherapy in cancer, infections, and vaccines.

IL-7 IN HUMAN CLINICAL TRIALS

To date, the clinical trials for IL-7 in humans have encompassed various modalities, including recombinant proteins, cell therapies, and gene therapies. The recombinant protein category comprises unglycosylated IL-7 variants, such as CYT99007, a glycosylated form of IL-7 (CYT107), and IL-7-hyFc (NT-I7/GX-I7/TJ107; efineptakin alfa), as well as a bioactive IL-7 peptide fused to IgG2 Fc (MDK703). Cell therapy approaches, on the other hand, comprise CAR-T cells that encode IL-7, such as TAK102, TAK103, NIB101, CT048, and CT0181, which are currently in phase 1 studies. As for gene therapies in phase 1 trials, IL-7 has been tested in mRNA (BNT152) and oncolytic virus (ASP9801) approaches. Notably, ASP9801 has been halted in its phase 1 study as of February 2023 (Table 1). A comprehensive overview of clinical trials involving IL-7 is outlined in **Supplementary Table 1**, and the key highlights are listed below.

Table 1. IL-7 utilization strategies in clinical trials

Modality	Drug name	Drug description	Platform
Protein	CYT99007	Unglycosylated IL-7 produced in <i>Escherichia coli</i>	
	CYT107	Glycosylated recombinant human IL-7	
	NT-I7; GX-I7; TJ107 (IL-7-hyFc) (INN*:efineptakin alfa)	Homodimeric genetically modified IL-7 molecule fused to a stable hyFc platform	hyFc
	MDK703	Biologic IL-7 mimetic consisting of an IL-7 PEPTIKINE fused to an immunoglobulin Fc-domain	PEPTIKINE™
CAR-T	TAK102	Autologous T cells are transduced with a GPC3-targeting CAR and genes that encode IL-7 and CCL19	PRIME T
	TAK103	Autologous T cells are transduced with a mesothelin-targeting CAR and genes that encode IL-7 and CCL19	PRIME T
	NIB101	Autologous T cells are transduced with a GM2-targeting CAR and genes that encode IL-7 and CCL19	PRIME T
	CT048	Autologous T cells are transduced with a CLDN18.2-targeting CAR gene and genes that encode IL-7 and CCL21	CycloCAR®
	CT0181	Autologous T cells are transduced with a GPC3-targeting TCR and the gene encoding IL-7	
mRNA	BNT152	Modified mRNA for IL-7 contained within a lipid nanoparticle, leading to expression of IL-7	Ribocytokine
Oncolytic virus	ASP9801	Tumor-selective oncolytic vaccinia virus encoding IL-7 and IL-12	

INN, international nonproprietary names.

Recombinant human unglycosylated IL-7: CYT99007

The inaugural human clinical trial for IL-7 was initiated in 2003 with cancer patients (NCT00062049) and using unglycosylated IL-7 (CYT99007) that was produced in *Escherichia coli*. CYT99007 was developed by Cytheris, which later changed its name to RevImmune. In this trial, CYT99007 was subcutaneously administered every 2 or 3 days, with a total of 8 doses. While PB CD4 and CD8 T cell counts steadily increased, the proportion of Foxp3⁺ Treg cells conversely decreased. Additionally, there was a preferential expansion of the TCR repertoire in recent thymic emigrants (RTE) and naïve T cells (41,87). As a key pharmacodynamic characteristic, blood T cell levels peaked between day 21 and 28 after CYT99007 administration, while Ki-67 levels in T cells reached its maximum at day 7. Moreover, IL-7 receptor down-regulation continued until day 7, followed by a recovery to basal levels by day 21 and/or day 28 (87). The calculated half-life of unglycosylated IL-7 was between 6 and 10 h (41,88). Despite the observed increase in T cell numbers, particularly non-Treg cells, it is crucial to highlight that no patients demonstrated an objective clinical cancer response in these phase 1 studies (NCT00091338, NCT00099671). In particular, there are reports indicating that IL-7 leads to an increase in CD4 and CD8 T cell numbers. These expanded T cells reacted to HIV antigens, producing IFN- γ and IL-2 in HIV-infected patients. However, it is noteworthy that the expanded CD4 T cells harbored genome integrated HIV DNA (89,90).

As the rIL-7 was produced in *E. coli* and lacked the typical glycosylation found in eukaryotic IL-7, there was a concern about the potential immunogenicity of the unglycosylated IL-7. In concordance, all the patients who received doses ranging from 10 to 60 $\mu\text{g}/\text{kg}$ of IL-7 developed low-titers anti-IL-7 Abs by day 28, 7 days after the final injection of IL-7. On the other hand, it is important to consider that none of them reached the defined positive threshold outlined in the protocol (88). Nonetheless, it appears that Cytheris later developed a glycosylated form of IL-7 precisely to avoid such undesired effects. In a study involving HIV patients (NCT00099671), 2 individuals in separate cases encountered dose-limiting toxicities (DLTs) at the 60 $\mu\text{g}/\text{kg}$ dose, determining the maximum tolerated dose (MTD) to be 30 $\mu\text{g}/\text{kg}$ (90). The most predominantly observed side effect of unglycosylated IL-7 was mild to moderate, and with transient injection site reactions (89).

Recombinant human glycosylated IL-7: CYT107

The reported half-life of glycosylated IL-7 (CYT107) administered via the subcutaneous route is between 9 and 35 h (91), indicating a longer duration compared to that of unglycosylated IL-7 (6–10 h). Consequently, the dosing schedule has been adjusted from every 2 or 3 days for a total of 8 doses to a weekly regimen consisting of 3 or 4 doses. The dosage for CYT107 was maintained at less than 20 $\mu\text{g}/\text{kg}$ due to the well-tolerated nature of rhIL-7 at 10 or 20 $\mu\text{g}/\text{kg}$. However, at 30 $\mu\text{g}/\text{kg}$, DLT was noted in 2 subjects. One experienced a transient grade 3 increase in alanine aminotransferase, while the other exhibited a grade 2 rash (92). Notably, the MTD of glycosylated IL-7, *i.e.*, CYT107 (20 $\mu\text{g}/\text{kg}$), was lower than that of unglycosylated IL-7, CYT99007 (30 $\mu\text{g}/\text{kg}$).

The clinical trials for CYT107 encompassed indications such as cancer and viral infections (HIV, HBV, HCV, progressive multifocal leukoencephalopathy [PML], coronavirus disease [COVID]), idiopathic CD4 lymphocytopenia (ICL), sepsis, and hematopoietic stem cell transplantation (HSCT). Importantly, AIDS was a primary target indicator for CYT107 (NCT00477321, NCT01190111, NCT01241643, NCT01019551), because of the CD4 T cell cytopenia associated with AIDS, which propelled the testing into phase 2 trials.

As demonstrated earlier with CYT99007, the administration of CYT107 and dual ART intensification induced an amplification of the HIV reservoir, despite a mild HIV reactivation. This outcome was the unintended consequence of a central-memory CD4 T cell expansion, which constrained the effectiveness of this IL-7-based strategy (93). Nevertheless, IL-7 therapy also led to a noticeable enhancement in gut barrier integrity 12 wk post-administration. Plasma levels of sCD14 and D-dimer, markers of systemic inflammation, decreased following IL-7 therapy in HIV patients (94,95).

CYT107 was administered to cancer patients alongside therapeutic cancer vaccines (NCT00923351, NCT01339000, NCT01881867). Reportedly, adjuvant immunotherapy in conjunction with tumor lysate/keyhole limpet hemocyanin-pulsed DC vaccinations and CYT107 may enhance survival in patients with metastatic pediatric sarcoma (96). Additionally, the use of CYT107 after Sipuleucel-T treatment, the first Food and Drug Administration-approved DC-based vaccine, in patients with metastatic castration-resistant prostate cancer, resulted in improved antigen-specific humoral and T cell proliferative responses, along with increased expression of activation markers and beneficial cytokines (97). However, it appears that there are no ongoing or planned clinical trials for the combination with a dendritic cancer vaccine.

And in a study (NCT01339000), there is also an investigation into the effects of IL-7 on immune system function in the elderly (NCT01339000). These individuals received vaccines before and after CYT107 administration, whereby the vaccines included diphtheria and tetanus, polio, pneumococcus (with 2 booster shots), hepatitis B (with 2 booster shots), and hepatitis A (with one booster shot). Although the study was completed in 2016, unfortunately, the results are not publicly available. Nonetheless, the co-administration of vaccines and CYT107 demonstrates the potential of this regimen in augmenting the number and proliferation of tumor-specific T cells. However, further clinical studies are necessary to accumulate conclusive data.

In a study (NCT01368107), where CYT107 was administered during chemotherapy in lymphopenic metastatic breast cancer patients, notably, there were no changes in the functional competence of immune cells was observed (67), suggesting that T cells proliferated by exogenous IL-7 administration are functionally normal. Moreover, T cells expanded by CYT107 in patients with ICL could produce cytokines following mitogenic stimulation (98). Throughout this study, no significant difference was observed in progression-free survival or overall survival among the 12 cases. Additionally, a phase 2 study combining CYT107 and Atezolimumab was initiated in 2019 for Metastatic Urothelial Carcinoma, but the results are still pending (NCT03513952). Based on these clinical evidence, CYT107 was administered to patients undergoing allogeneic hematopoietic stem cell transplantation (allo-HSCT) and cord blood stem cell transplants (NCT00684008, NCT03941769). Here, CYT107 enhanced immune recovery after T cell-depleted allo-HSCT without causing significant GVHD or other serious toxicity (91).

ICL and PML are rare diseases characterized by low CD4 T cell numbers. A recent case report highlighted the efficacy of CYT107 in treating ICL and PML (98). In ICL patients, CYT107 resulted in increased numbers of circulating CD4 and CD8 T cells, as well as tissue-resident T cells in the gut mucosa and BM (98). Intriguingly, clinical improvements were observed, including stabilized lesions on magnetic resonance imaging, neurological examination improvement, and a reduction in JC viral load, attributed to CYT107 and the ensuing JC virus-specific immune response (99-101).

CYT107 also demonstrated clinical promise in sepsis and coronavirus disease 2019 (COVID-19), where the low number of T cells is a hallmark of disease progression and likely a key mechanism contributing to morbidity and mortality. In sepsis and COVID-19, CYT107 reversed the significant loss of CD4 and CD8 immune effector T cells without evidence of inducing a cytokine storm (102,103). This is noteworthy, emphasizing that IL-7 is a relatively safe cytokine. The initial dosing route for CYT107 was subcutaneous, followed by evaluations of intramuscular and intravenous routes in clinical trials. The half-life of CYT107 in the intramuscular route was found to be 7–23 h (99), comparable to the subcutaneous half-life of 9–35 h (91). The intravenous route was assessed in sepsis patients, but this study was prematurely halted due to fever and respiratory distress approximately 5–8 h after intravenous administration that developed in 3 out of fifteen patients (104). Given equivalent positive laboratory and clinical responses, more favorable PK, and better patient tolerability, intramuscular administration of CYT107 is deemed preferable compared to intravenous administration (104).

Because of the induction of antidrug antibodies (ADA) by CYT99007, CYT107 also leads to ADA induction. In these studies (NCT01190111, NCT01241643), one cycle is defined as 3 doses weekly. Following a repeat cycle, at the end of the first cycle, ADA to CYT107 had developed in 6 out of 23 patients in NCT01190111 (26%) and 14 out of 86 (16%) in NCT01241643. For these patients, anti-drug Abs persisted for a median (interquartile range) of 6 (3–9) months, except for 3 patients in whom they persisted until the end of the study. After the second cycle, these proportions increased to 82% and 77% in the 14 and 44 exposed patients, respectively. Neutralizing Abs developed in none of the 23 patients in NCT01190111 and in 1 out of 86 in NCT01241643 after the first cycle, and in 6 (38%) and 21 (37%) patients after the second cycle in NCT01190111 and NCT01241643, respectively. However, there was no clear impact of the presence of Abs on CD4 T cell dynamics (95).

rhIL-7-hyFc: NT-17/GX-17/TJ107, efineptakin alfa

rhIL-7-hyFc (efineptakin-alfa) is a recombinant human IL-7 fused to the hyFc domain of IgD/IgG4 immunoglobulin. It is identified by 3 code names: NT-17, GX-17, and TJ107. The original developer, Genexine, licensed out their rights to NeoImmunotech in the USA and in Europe, and to I-MAB in China. Despite the different code names, it is the same moiety. Due to its fusion with the hyFc, the intramuscular half-life is approximately 63 h (105), which is significantly longer than the half-life of CYT107. Therefore, the dosing regimen for NT-17 is a single dose in a cycle, while CYT107 is administered in 3 doses weekly. The pharmacodynamic feature of NT-17 is akin to that of CYT99007 and CYT107. NT-17 leads to an increase in absolute lymphocyte counts (ALCs), predominantly in T-cells, peaking 3 wk after administration and persisting for several additional weeks. This results in a sustained elevation in the CD4 and CD8 T cell numbers, while Tregs remain unaffected in healthy volunteers (105). In this particular study, the subcutaneous administration was compared with intramuscular administration of NT-17. NT-17 substantially increased ALC, demonstrating both dose-dependent effects and greater prominence when administered intramuscularly compared to subcutaneously. This enhanced effect via the intramuscular route is likely to be attributed to nearly 2-fold greater systemic exposure to NT-17 after intramuscular administration than after subcutaneous administration at the same dose of 60 µg/kg. While NT-17, composed of 2 IL-7 and the hyFc, exhibit about 5-fold difference in molecular weight compared to CYT107, which correspond to one IL-7 molecule, the MTD is notably higher for NT-17 (1,200 µg/kg) compared to CYT107 (20 µg/kg). The cause of this substantial MTD difference remains unclear. On another note, CYT107 selectively expands RTE, naïve, and central memory T cells,

whereas NT-I7 promotes the expansion of various T cell subsets, that comprise naïve, central/effector memory, effector, TEMRA, with a remarkable approximately 50-fold increase in Tscm observed in the blood from baseline. When combined with pembrolizumab, NT-I7 augments TILs, leading to the infiltration of CD8 T cells into the TME in over 80% (22/27) of the analyzed samples (NCT04332653). Additionally, there is an expectation that NT-I7 alone may also induce TIL infiltration, as observed in a mouse tumor model (57).

In the phase Ib/II study of NT-I7 plus pembrolizumab in patients with R/R mTNBC (NCT03752723/KEYNOTE-899), NT-I7 at 1,200 µg/kg every 9 wk was identified as the recommended phase 2 dose. The overall response rates (ORRs) ORR in PD-L1 positive (combined positive score ≥10%) and negative patients were 60% (6/10) and 0.0% (0/15), respectively.

Microsatellite stable (MSS) CRC or pancreatic cancer, which are immunologically cold tumors, are challenging to treat with the standard of care (SOC) being chemotherapy. For those with relapsed/refractory MSS disease, it is an even greater challenge, as checkpoint inhibitors have limited activity. The combination of NT-I7 and pembrolizumab is being explored in checkpoint inhibitor-naïve, relapsed/refractory MSS CRC and pancreatic cancer from the phase 1/2 study (NCT04332653).

In addition, GX-188E (a DNA cancer vaccine), and NT-I7 were administered to patients with human papillomavirus-16- and/or 18-positive head and neck squamous cell carcinoma, resulting in a promising clinical outcome with manageable safety profiles. NT-I7 has expanded its target indications to include GBM in combination with SOC, anti-VEGF therapy, or pembrolizumab (NCT03687957, NCT05191784, NCT05465954). Additionally, it is being explored as a treatment for large B-cell lymphoma in combination with CAR-T and NT-I7 (NCT05075603), with preclinical efficacy demonstrated (60). Similar to CYT107, NT-I7 is also being investigated for ICL and PML as target indications.

Other modalities include MDK703, CAR-T cells encoding IL-7, mRNA encoding IL-7, and oncolytic viruses encoding IL-7

Medikine's primary candidate, MDK-703, is an Fc-fusion protein incorporating an IL-7 PEPTIKINE™. This compound mimics the therapeutic attributes of IL-7, a cytokine crucial in the differentiation, maintenance, and survival of T cells. A noteworthy characteristic is its ability to circumvent the generation of neutralizing Abs to native IL-7. The pipeline is currently in phase I/II (NCT05716295). A total of 5 CAR-T pipelines encoding IL-7 are presently in phase I (refer to **Table 1**, NCT04405778/NCT05164666/NCT05192174/NCT05393986/NCT04973098). Thus, CAR-T studies with IL-7 currently employ 2 distinct strategies: 1) combining CAR-T with exogenous IL-7 treatment (NT-I7) and, 2) CAR-T encoding IL-7. As these investigations are in their early stages, the results will be disclosed in the future. The combination of 2 mRNA pipelines encoding IL-7 and IL-2 (BNT152 and BNT153) commenced a phase 1 clinical study in June 2021 (NCT04710043). Additionally, a clinical study involving an oncolytic virus encoding IL-7 was initiated but discontinued its development for cancer in phase I in February 2023 (NCT03954067).

PERSPECTIVES

The era of cancer immunotherapy has arrived with the advent of immune checkpoint inhibitors. Through the successes and failures of cancer immunotherapy, T cells have

emerged and highlighted as key players, leading to an emphasis on enhancing the activity and increasing the numbers of T cells. In recent years, significant advancements have been made in research focused on boosting the T cell immunity. While cytokines like IL-2, IL-7, and IL-15 can increase T cell numbers, IL-7 stands out as the sole cytokine capable of generating long-lived T cells. For successful cancer immunotherapy, it is crucial not only to increase tumor-specific T cells but also to sustain them over an extended period. However, unfortunately, using IL-7 as a standalone therapy is limited in its effectiveness for anti-cancer treatment because it increases overall T cell numbers (*i.e.*, The T cell increased by IL-7 primarily involves non-tumor-specific T cells, with minimal impact on tumor-specific T cells). Therefore, a combination strategy utilizing therapies that directly administrate tumor-specific T cells such as CAR-T and TIL therapy into cancer patients or therapies that generate and rejuvenate tumor-specific T cells such as cancer vaccines and immune checkpoint inhibitors respectively may be a promising approach for effectively applying IL-7 in cancer immunotherapy.

There are several cell types expressing IL-7 receptors including not only T cells but also ILC, $\gamma\delta$ T cells, M1/M2 monocytes, DCs, eosinophils, and neutrophils. When IL-7 is administered through subcutaneous or intramuscular route, various skin-related side effects can occur due to the response of skin-resident ILC or $\gamma\delta$ T cells to IL-7. Changing the administration route to intravenous injection can help address these issues. Alternatively, developing an immunocytokine with targeting moiety to T cell such as anti-CD3, -CD4, or -CD8 that selectively activates IL-7 in T cells through 'cis-acting' could be another viable option, reducing the activation in non-target cells. The longevity of IL-7-amplified T cells varies among species: 2–3 wk in mice, 10–12 wk in monkeys, and over 12 wk in humans. Therefore, considering these species-specific differences of long-term survival rate of T cells is necessary when translating the observed anti-cancer effects of IL-7 in mice to those in humans.

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SUPPLEMENTARY MATERIAL

Supplementary Table 1

Clinical trials for IL-7-based modalities

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