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IL-15 and T cell stemness in T cell-based cancer immunotherapy

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Abstract

Preclinical models revealed that the immune system can mediate rejection of established tumors, but direct evidence in humans has been limited to largely immunogenic tumors such as melanoma. The recent success of immune checkpoint inhibitors and adoptive T cell transfer immunotherapy in clinical trials has instilled new hope for the use of T-cell immunotherapy in the treatment of cancer. Interleukin-15 (IL-15), a potent immunostimulatory cytokine, both potentiates host T and NK-cell immune responses and promotes the generation of long-lived memory T cells with superior functional capacity with potential use in adoptive T-cell transfer protocols. IL-15 has been recently tested in the clinic and showed dramatic effects at the level of responding NK and $CD8^+$ memory T cells. The recent advances in the knowledge of IL-15-dependent regulation of T-cell responses, gene expression and metabolic adaptation have important implications for the use of IL-15 in T cell-based immunotherapy of cancer.

Introduction

The immune system can prevent cancer formation and dissemination. Immune effector cells potentially infiltrate the tumor but, when the disease is established, their activity is inhibited by the presence of suppressor cells and metabolites in the tumor microenvironment, thus favoring evasion of the anti-tumor immune response. New therapeutic solutions, mainly

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based on immune checkpoint inhibitors anti-CTLA-4 and anti-PD-1/PD-L1 monoclonal antibodies, have proven efficacious in stimulating T-cell immune responses to reject established tumors, and resulted in extended survival in a subset of cancer patients (1). Recent preclinical data indicate that these strategies when combined with additional immunotherapy approaches like activating cytokines, cancer vaccines or adoptive cell transfer (ACT) of T cells redirected with tumor-specific T-cell receptors (TCRs) or chimeric antigen receptors (CARs) may result in improved efficacy. Interleukin-15 (IL-15), a potent immunostimulatory cytokine, both potentiates host T and NK-cell immune responses and promotes the generation of memory T cells with superior functional capacity with potential use in ACT protocols (2). IL-15 recently entered clinical trials in patients with metastatic melanoma and renal cell carcinoma and showed a dramatic capacity to expand effector T and NK cells (3). We discuss the potential applications of IL-15 in T cell-based cancer immunotherapy and the current strategies that are being adopted to reduce toxicity while improving efficacy *in vivo*.

Basic biology of IL-15

IL-15 is a four-α-helix-bundle cytokine playing a pivotal role in stimulation of both innate and adaptive immune cells. IL-15 induces the activation, the proliferation and the survival of T cells and contributes to generation and maintenance of high-avidity, antigen-specific $CD8^+$ memory T cells in the long-term. In addition, IL-15 is involved in the development, the persistence and the activation of NK and NKT as well as γ/δT cells (2).

The IL-15 receptor (IL-15R) is composed by 3 different molecules, better known as the α (CD215; unique to the IL-15R), the β (CD122) and the γ (CD132) chains. In particular, CD122 is also a component of the IL-2R while CD132, also known as the common γ chain (γ_c), is shared with different cytokines including IL-2, IL-4, IL-7, IL-9 and IL-21 (2). While the IL-15Rβγ complex is present on target cells, IL-15Rα can be expressed as a membrane bound complex with IL-15 on the surface of many cell types including activated monocytes, dendritic cells (DCs) and endothelial cells. Such a heterodimer is presented *in trans* to neighboring α/β, γ/δ T or NK cells (2, 4). Alternatively, it can be shed and released as a soluble factor. Recent evidence indicates that virtually all circulating IL-15 in human and mouse serum is complex with IL-15Rα (5). Triggering of the receptor activates downstream signaling pathways that include JAK1 and JAK3 as well as STAT3 and STAT5, followed by the recruitment of PI3K/AKT/mTOR and Ras/Raf/MAPK-ERK cascades. By inducing *c-fos/jun*, *c-Myc*, *NF-kB* and *Bcl2* genes expression and by decreasing the expression of Bim and PUMA, IL-15 has a stimulating effect on T cell proliferation and survival (2).

Because sharing the β and γ components of the receptor, IL-2 and IL-15 exert similar functions on T cells. Indeed, both stimulate the proliferation of T cells, facilitate the differentiation of cytotoxic T lymphocytes (CTLs) and induce the generation and maintenance of NK cells. Nevertheless, mice deficient in IL-2 or IL-15 have different phenotypes, and administration of IL-2 and IL-15 to mice, primates or humans leads to distinct effects on cells of the immune system (2, 3, 6-8). As regards to antigen activated effector cells, while IL-2 promotes terminal differentiation and, eventually, their elimination by activation-induced cell death (AICD), IL-15 inhibits AICD and promotes the generation

of long-lived memory T cells as well as their maintenance by homeostatic proliferation (**Fig. 1A**). Notably, IL-2, but not IL-15, is involved in the prevention of autoimmunity due to the maintenance of $CD4^+CD25^+FoxP3^+$ regulatory T (Treg) cells, that also inhibit anti-tumor immunity. This observation raised concerns on the therapeutic use of IL-2 as an immunotherapeutic agent as promotion of effector T cell functions could be hampered by Treg expansion (9, 10).

IL-15 and tumor-specific T cells in ACT

Understanding the biological basis of IL-2 and IL-15 signaling on T-cell subsets has tremendous implications for expansion of tumor-specific T cells to be used in ACT immunotherapy. Historically, tumor infiltrating lymphocytes (TILs) have been isolated from tumor resections (mostly melanoma), expanded *in vitro* with polyclonal stimuli and high doses of IL-2, selected for anti-tumor activity and reinfused into the patients (11). Despite the fact that this approach led to objective clinical responses in a number of trials, exhaustion and terminal differentiation of the infused cells contributed at least in part to the limited therapeutic efficacy (11). IL-2 infusions in humans could ameliorate persistence and activity of adoptively-transferred T cells only marginally, while preclinical studies demonstrated the superior *in vivo* anti-tumor capacity of T cells either cultured in IL-15 or expressing IL-15 as a transgene (2, 12). A major breakthrough came from the observation that increased levels of IL-15 and IL-7 caused by chemotherapy-induced lymphodepletion prior to ACT effectively supports the function of transferred cells (13, 14).

Extensive research in the field of T-cell differentiation has revealed that the peripheral T-cell compartment is organized in subsets that are endowed with specialized effector capacities. The analysis of surface and intracellular markers by polychromatic flow cytometry allows the discrimination and purification of such subsets for further analysis (15, 16). Current models support the concept that memory T-cell differentiation progresses linearly in mice, nonhuman primates and humans and that T cells gradually lose some abilities while maturing, including the capacity to self-renew, expand and persist *in vivo*. In parallel, they gain others, such as effector functions and tropism to peripheral tissues (11, 15). In the context of ACT, it is worth noting that early-differentiated memory T cells, despite not showing immediacy of killing capabilities directly *ex vivo*, can differentiate to potent effectors *in vivo* following encounter with the cognate antigen (17). These cells are thought to maintain T-cell memory in a stem cell-like fashion, *i.e.*, to self-renew while simultaneously generating more differentiated progeny (15, 18). Exploiting these properties in the context of ACT proved effective in ameliorating anti-tumor T-cell responses at the preclinical level and, indirectly, in humans. ACT of TCR- or CAR-transduced T cells resulted in increased persistence compared to TILs, possibly due to the presence of early differentiated T-cell precursors in the infusion product (11, 19-21). By analyzing retroviral integration sites, Biasco et al. demonstrated that adoptively-transferred $CD8^+$ T-memory stem cells (T_{SCM}), the earliest differentiated circulating memory T-cell population possessing superior stem cell-like qualities identified thus far, preferentially survived *in vivo* compared to more differentiated central memory (T_{CM}) or effector memory T (T_{EM}) cells in patients treated with genetically-modified lymphocytes (22).

The T_{SCM} seem therefore the ideal subset to exploit in order to induce long-lasting anti-tumor T cell responses. These cells are identified by the co-expression of multiple naïve-associated markers by flow cytometry including CD45RA, CCR7, CD27 and IL-7Rα (also known as CD127), among others, but simultaneously overexpress the memory antigens CD95, CD122 and CD58, and share properties with conventional memory cells. IL-15-dependent signals seem pivotal to generate the murine T_{SCM} (defined as $CD44^{lo}CD62L^{hi}CD122^{hi}Sca\text{-}1^{hi}$), as originally shown in the context of experimentally-induced graft-versus-host disease (23). In particular, in combination with appropriate stimulations, IL-15 has been exploited to uncouple T cell proliferation from differentiation, with the final aim to expand the tumor-specific T-cell pool while promoting and maintaining the stem cell-like state. Indeed, stimulation of human naïve T (T_N) cell precursors with anti-CD3/CD28 antibody-conjugated beads in the presence of IL-15 and IL-7 induces T cells with stem cell-like properties (**Fig. 1A**) (24). *In vivo*, T_{SCM} develop from T_N-cell precursors following transfer in lymphodepleted hosts harboring increased levels of plasma IL-15 and IL-7 (25, 26). Importantly, IL-15 also mediates self-renewal of polyclonal and antigen-specific T_{SCM} (17, 27). When redirected to recognize a specific antigen of mesothelioma through CAR transduction, these cells also displayed enhanced functionality in preclinical models of tumor xenografts (17). After adoptive transfer in immunodeficient NOD/SCID/γ $chain^{-/-}$ mice, T_{SCM} cell properties of CAR.CD19-transduced human T cells were maintained by culturing with IL-15 and IL-7 as opposed to IL-2, and correlated with improved survival and durability of the response *in vivo* (28).

It is not entirely clear how IL-2 and IL-15 signaling through the same IL-2/IL15βγ receptor complex leads to opposing differentiation programs in antigen-activated T cells. Recent results obtained on murine T cells suggest that metabolic reprogramming, downstream gene expression and, at a lesser extent, the dose of the cytokine may play a critical role in this regard. Differential gene expression could be observed when subsaturating doses of cytokines were used. However, these differences were nearly abrogated at very high doses. Interestingly, IL-2 and IL-15 bind their receptor complex in almost identical ways as revealed by X-ray crystal structures, thus leading the authors to conclude that differences in downstream signaling and mRNA transcripts could be explained by differential receptor affinities and cytokine interaction kinetics, mostly regulated at the level of the IL-2Rα and IL-15Rα chains transpresenting their related cytokines (29). Notably, $CD8^+$ memory T cells generated from antigen-activated effectors in response to IL-15 display a different metabolic response compared to effectors maintained in IL-2 (**Fig. 1A**) (30). The former mostly rely on oxidative phosphorylation (OXPHOS, taking place in the mitochondria) to support their metabolic demand for long-term survival. Conversely, the latter preferentially use glycolysis to support effector functions such as rapid IFN-γ production. Specifically, IL-15 regulates oxidative metabolism in murine $CD8^+$ memory T cells by promoting mitochondria biogenesis and expression of carnitine palmitoyltransferase 1A (CPT1A), a fatty acid transporter located in the mitochondria favoring fatty acid oxidation (FAO) (30). Given that T_{SCM} share multiple features with conventional human and murine memory T cells, it is likely, yet to be demonstrated formally, that T_{SCM} preferentially engage OXPHOS over glycolysis for their metabolic demand. Should this hypothesis be confirmed, we speculate

that modulation of T cell metabolism rather than differential cytokine stimulation could be exploited to regulate T cell fate and thus generate more potent T cells to be used in ACT.

Preclinical and clinical evaluation of IL-15 in the therapy of cancer

Although IL-2 has been approved by the FDA, IL-15 may be superior in the therapy of cancer since it has no major effect on Tregs, does not promote AICD and expands effector cells with anti-tumor potential, mostly NK and $CD8^+$ memory T cells. IL-15 showed efficacy in a plethora of murine models of cancer as a single agent alone or in combination with monoclonal antibodies or ACT (2).

In analysis of IL-15 in rhesus macaques when administered by bolus infusions, subcutaneously or by continuous intravenous infusion (CIV) the only toxicity was redistribution of neutrophils from circulation to tissues. Twelve-day bolus intravenous administrations of 20 μg/Kg/day of IL-15 to rhesus macaques was associated with 4 to 8-fold increases in the numbers of circulating NK and $CD8^+$ memory T cells (6). Administration of IL-15 by CIV at 20 μg/Kg/day for 10 days led to 10-fold increases in numbers of circulating NK cells, 15-fold increases in monocytes and 80 to 100-fold increases in circulating T_{EM} (31).

Several clinical trials have been opened using IL-15 in cancer treatment (summarized in **Table 1**). In a phase I study of recombinant human IL-15 administered by bolus infusions daily for 12 days there was a constant temporal pattern of post-treatment adverse events in patients given 3 μg/Kg doses of IL-15, with fever and rigors beginning at 2 to 4 hours after infusion initiation (3). These changes were concurrent with the maximum of 50-fold elevations of serum concentrations of IL-6 and IFN-γ. The maximum tolerated dose of IL-15 was 0.3 μg/kg/day. Polychromatic flow cytometry of peripheral blood lymphocytes revealed margination or efflux of NK as well as of multiple subsets of memory T cells from circulating blood within minutes upon IL-15 administration, which protracted for a few hours (3). Notably, NK and T_{EM} tended to disappear faster than less differentiated memory T cells, likely due to the higher expression of IL-15Rβ on their surface. Early lymphopenia was followed by influx and hyperproliferation leading to 10-fold expansions of NK, γδ T cells and $CD8^+$ memory T cells that ultimately returned to baseline. Therefore, rapidity of efflux from the peripheral blood seemed to predict subsequent expansion. Previous studies in rhesus macaques showed that IL-15 targeted $CD4^+$ and $CD8^+$ T cells systemically, with the vast majority of these cells displaying markers of proliferation and activation in both lymphoid and nonlymphoid tissues (6). In the first-in-human phase I trial involving individuals with metastatic melanoma and renal cell carcinoma, 5 patients manifested decreases between 10 and 30 percent of their marker lesions and 2 patients had clearing of lung lesions (3). Daily IL-15 IV at the dose of 0.25 and 0.50 μg/Kg replaced IL-2 in a recent trial to favor the persistence and function of adoptively-transferred TILs in patients with metastatic melanoma (**Table 1**). However, the trial was stopped due to autoimmune toxicity seen in 1 patient that, according to the promoters of the study, was probably related to the IL-15 injection. These data underline the potent proinflammatory effect of IL-15 on cells of the immune system. To avoid toxicities associated with high IL-15 C_{max} levels following bolus infusions IL-15 was administered subcutaneously on days 1-5 and 8-12 or by

continuous intravenous infusion for 10 days. A dose of 2 μg/Kg/day was well tolerated (T.A. Waldmann, unpublished observation).

Although IL-15 may show efficacy in treatment of metastatic malignancy it is not optimal since there is only a low level of IL-15Rα expression on resting DCs. In addition, the biochemical instability of the soluble molecule, that undergoes rapid renal clearance, may result in reduced therapeutic potential (3). The IL-15 cytokine may be the IL-15Rα/IL-15 heterodimeric cytokine (32), that is naturally present in the serum of mice and in humans (5). IL-15 within the heterodimer has increased half-life and greater biological activity determined by the increased affinity for the IL-15Rβγ complex (29). The enhanced biological anti-tumor activity of cross-linked IL-15 protein has been tested in several metastatic preclinical models, such as B16OVA melanoma and MC38 colon cancer. Reduced metastatic foci were attributed to the increased numbers of NK and $CD8^+$ T cells within spleen, lung and liver (33). In preclinical trials IL-15 pre-associated with IL-15Rα or with IL-15Rα IgG1-Fc had improved pharmacokinetics and increased efficacy in increasing circulating numbers of NK and $CD8^+$ T cells (32). Clinical trials involving the IL-15/IL-15Rα IgG1-Fc heterodimer (ALT-803, from Altor Bioscience Corporation) have currently been initiated in the United States in patients with different types of cancer (**Table 1**).

Tumor delivery of IL-15 instead of systemic administration would be optimal to decrease toxicity and increase efficacy. To this end, multiple approaches were conceived. In mouse models, the presence of IL-15 in the tumor favored tumor rejection through T-cell infiltration in a non-antigen specific manner (34) and rendered adoptively-transferred NKT cells expressing an IL-15 transgene resistant to the suppressive activity of tumor associated macrophages (35) (**Fig. 1B**). Moreover, the intratumoral injection of IL-15-expressing vectors in combination with the chemoattractant CCL21 in murine colon carcinomas (CT-26) resulted in the significant inhibition of the tumor growth and induction of cytotoxic T cells capable to produce elevated levels of IFN-γ (36). Importantly, patients bearing colorectal cancer metastasis with no deletion of the IL-15 gene had better prognosis compared to those who had gene deletion: the presence of IL-15 in the tissue was associated with increased T-cell proliferation at the tumor invasive margin (37), thereby supporting a role for IL-15-mediated T-cell immune responses in inhibition of cancer growth. However, it should be noted that injection in the tumor mass directly or incorporation of IL-15 as a transgene in adoptively-transferred cells are difficult to implement on a practical level: the presence of multiple metastatic sites or the excessive growth and potential leukemic transformation of the transduced cells, respectively, may in fact limit therapeutic relevance.

Future directions: combination therapies

Despite the increased immune functional capacity observed following monotherapy, it is probable that in the future IL-15 will be used in combination therapy (**Fig. 1B**). Recent use of immune checkpoint inhibitors anti-CTLA-4 and anti-PD-1/PD-L1 monoclonal antibodies confirmed that the immune system can reject established tumors. These two molecules target two non-overlapping inhibitory pathways and proved more effective than monotherapy when tested in combination therapy in metastatic melanoma (1). Similarly, an approach

combining the immunostimulatory cytokine GM-CSF (also known as sargramostim) in combination with the anti-CTLA-4 antibody ipilimumab improved overall survival and was associated with reduced side effects compared to ipilimumab alone in a similar cohort of patients (38). To date, combination therapies including IL-15 have been tested only in preclinical models. The simultaneous addition of antibodies to two checkpoints CTLA-4 and PD-L1 in association with IL-15 yielded additivity/synergy in three murine tumor models (39). Furthermore, co-administration of an agonistic anti-CD40 antibody with IL-15 was valuable in avoiding "helpless" $CD8^+$ T cells that were not tumor specific. In particular, the administration of the combination of IL-15 plus the agonistic anti-CD40 antibody was associated with a meaningful increase in number of TRAMP-C2 specific SPAS-1/SNC9-HA tetramer $CD8^+$ T cells which depended on the increased expression of IL-15Rα on dendritic cells, possibly promoting transpresentation of the high-affinity heterodimer. Combination therapy resulted in the protection from tumor development on rechallenge (40). Recently, a trifunctional antibody fusion protein composed by the IL-15/IL-15Rα, a tumor-specific recombinant antibody and a ligand targeting the costimulatory molecule 4-1BB (also known as CD137) was shown to be effective in reducing metastasis in a melanoma (B16-FAP) tumor mouse model (41). This fusion protein was able to increase the proliferation and specifically activation of tumor-specific $CD8^+$ memory T cells.

Concluding remarks

The predominant approaches involving IL-15 discussed above are based on the hypothesis that the host is making an immune response albeit inadequate to the tumor that can be augmented by administration of IL-15. TILs are found in the tumor site, but their activity is inhibited by multiple types of suppressor cells present in the tumor microenvironment. IL-15 seems to not influence the function of these cellular subsets directly, rather it is possible to speculate that IL-15 induces hyperactivation of tumor-resident T cells, thereby relieving them from the suppressive activity. Additionally, data from systemic administration in humans as well as in preclinical models suggest that IL-15 affects trafficking of memory T cells to tissues, and possibly localization of responding T cells to the tumor site in a nonantigen specific way (**Fig. 1B**) (3, 6, 34). In this case, infiltration of effectors derived from less differentiated memory T cells, which have not undergone extensive division, chronic inhibition or exhaustion, or are simply resistant to suppression (35, 42), may benefit tumor rejection.

It is also worth noting that suppressive cells in the tumor microenvironment along with additional components such as cancer-associated fibroblasts and the extracellular matrix physically inhibit the direct contact of T cells with the tumor itself, hence generating a site of immune privilege (43). In this context, IL-15-induced expansion of local T cells as well as the infiltration of long-lived memory T cells may be of limited value. It could thus be hypothesized, yet to be demonstrated experimentally, that IL-15 in combination with therapies capable of disrupting physical barriers may promote cancer regression. These along with other studies revealing the signaling pathways at the basis of IL-15-mediated anti-tumor activity, T-cell self-renewal and enhanced effector functions will make it possible to conceive more effective strategies of T cell-based cancer immunotherapy.

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Abbreviations

IL-15	Interleukin-15
ACT	adoptive cell transfer
TCR	T cell receptor
CAR	chimeric antigen receptor
T_{SCM}	T stem cell memory
T_{CM}	central memory T cells
T_{EM}	effector memory T cells
AICD	activation-induced cell death
Treg	$CD4^+$ regulatory T cells
TILs	tumor infiltrating lymphocytes
CIV	continuous intravenous infusion

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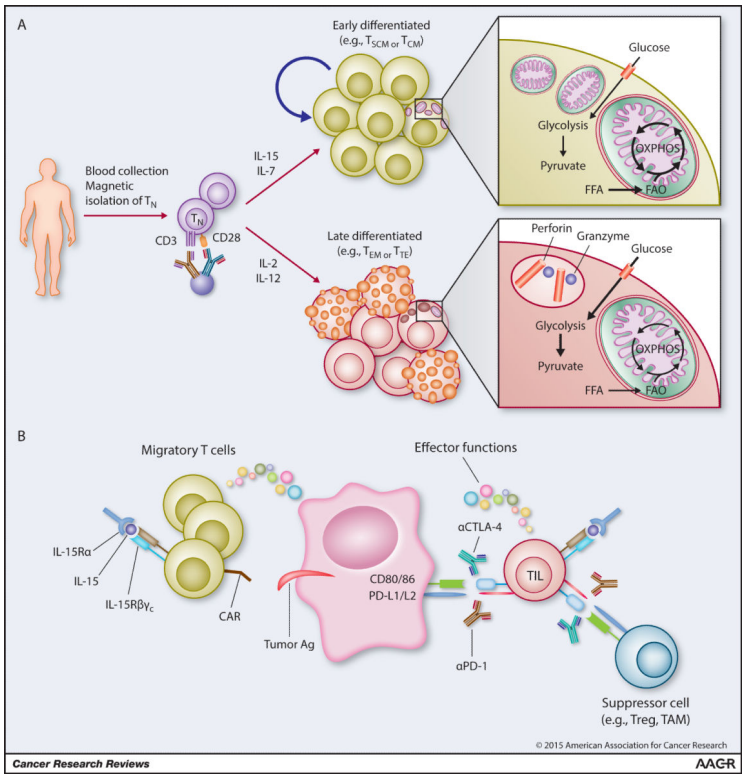

Figure 1. T cell immunotherapeutic applications of IL-15 for the treatment of cancer

A) Early-differentiated T_{SCM} or T_{CM} capable of self-renewal (circular blue arrow) are generated from circulating naïve T (T_N) cells following activation with anti-CD3/CD28 antibody-conjugated beads in the presence of IL-15 and/or IL-7. In contrast, IL-2 and/or IL-12 induce terminal differentiation and apoptosis. The generated cells display differential metabolic reprogramming, mitochondrial content and immediacy of effector functions. **B)** IL-15 or IL-15/IL-15Rα stimulations induce localization of redirected T cells to the tumor site and hyperactivation of resident TILs. Simultaneous blockade of CTLA-4 and PD-1/PD-L1 immune checkpoints enhances T cell effector functions and tumor rejection. See text for details. FFA, free fatty acid; TN, naïve T cells; T_{TE}, terminal effector T cells; Ag, antigen.

Table I

Completed and ongoing clinical trials involving IL-15 therapy

Clinical ID	Phase	Aim	Status	Study period	Tumor type	Nº of patients	Age of patients (min-max)	Treatment	IL-15/ALT-803 (dose, μg/Kg)	Principal Investigator	Responsible Party
NCT01021059	I	Safety	Completed	2009-2014	Metastatic Melanoma, Metastatic Renal Cell Carcinoma	18	18 - 85	rhIL-15 (IV)	0.3 - 25	Thomas A. Waldmann	National Cancer Institute, MD, US
NCT01369888	I/II	Safety/Efficacy	Terminated	2011-2014	Metastatic Melanoma	3	18 - 66	Cyclophosphamide + Fludarabine + TILs + rhIL-15 (IV)	0.25 - 0.50	Steven A. Rosenberg	National Institute of Health, MD, US
NCT01385423	I	Safety/Efficacy	Recruiting	2011-2015	AML	Estimated 34	≥ 18	Fludarabine + Cyclophosphamide + Haploidentical NK cell + rhIL-15 (IV)	0.25 - 3	Jeffrey S. Miller	Masonic Cancer Center, MN, US
NCT01572493	I	Safety	Recruiting	2012-2017	Lymphoma, Carcinoma	19	≥ 18	rhIL-15 (IV)	0.1 - 8	Kevin C. Conlon	National Institute of Health, MD, US
NCT01727076	I	Safety	Recruiting	2013-2016	Advanced Melanoma, Renal Cell Cancer, Non-Small Cell Lung Cancer, Head and Neck Squamous Cell Cancer	Estimated 30	≥ 19	rhIL-15 (SC)	NA	Jeffrey S. Miller	National Institute of Health, MD, US
NCT01885897	I/II	Safety/Efficacy	Recruiting	2013-2015	AML, ALL, MDS, Lymphoma, Myeloma, CLL, CML	Estimated 61	≥ 18	ALT-803 (IV)	1-30	Jeffrey S. Miller	Masonic Cancer Center, MN, US
NCT01875601	I	Safety	Recruiting	2013-2022	Solid Tumors, Brain Tumors, Sarcoma, Pediatric Cancers, Neuroblastoma	Estimated 51	2 - 25	autologous NK cell infusion + rhIL-15 (IV)	0.25 - 0.75	Melinda S. Merchant	National Cancer Institute, MD, US
NCT01946789	I	Safety/Efficacy	Recruiting	2014-2016	Melanoma, Renal Cell, Non-Small Cell Lung Cancer, Squamous Cell Head and Neck Cancer	Estimated 20	≥ 18	ALT-803 (IV)	NA	Kim Margolin	Altor Bioscience Corporation
NCT02138734	I/II	Safety/Efficacy	Recruiting	2014-2018	Non-muscle Invasive Bladder Cancer	Estimated 18	≥ 18	intravesical BCG+ALT-803	NA	Hing C. Wong	Altor Bioscience Corporation
NCT02099539	I/II	Safety/Efficacy	Recruiting	2014-2020	Relapsed or Refractory Multiple Myeloma	Estimated 50	≥ 18	ALT-803 (IV)	NA	Hing C. Wong	Altor Bioscience Corporation
NCT02395822	II	Efficacy	Active, not recruiting	2015-2019	AML	Estimated 24	18 - 70	Fludarabine + Cyclophosphamide + Haploidentical NK cells activated ON with 10ng/ml of IL-15 + rhIL-15 (SC)	2	Jeffrey S. Miller	Masonic Cancer Center, MN, US
NCT02452268	I	Safety	Recruiting	2015-2016	Skin Melanoma, Renal Cell Cancer, Non-Small Cell Lung	Estimated 42	≥ 18	hetIL-15 (IL15/sIL-15Ra)	NA	Kevin C. Conlon	National Institute of Health, MD, US

Clinical ID	Phase	Aim	Status	Study period	Tumor type	Nº of patients	Age of patients (min-max)	Treatment	IL-15/ALT-803 (dose, μg/Kg)	Principal Investigator	Responsible Party
					Cancer, Head and Neck Squamous Cell Carcinoma						
NCT02384954	I/II	Safety/Efficacy	Recruiting	2015-2023	B Cell Non-Hodgkin Lymphoma	Estimated 75	≥ 18	Rituximab + ALT-803 (IV)	NA	Hing C. Wong	Altor Bioscience Corporation

Abbreviations: ALL, Acute Lymphoblastic Leukemia; ALT-803, Interleukin-15 (IL-15) super agonist complex; AML, Acute Myelogenous Leukemia; BCG, *Bacillus Calmette-Guerin*; CLL, Chronic Lymphocytic Leukemia; CML, Chronic Myelogenous Leukemia; IL-15, Interleukin-15; IV, Intravenous; MDS, Myelodysplastic Syndromes; NA, Not Available; rh, recombinant human; SC, Subcutaneous; TIL, Tumor Infiltrating Lymphocytes.