Published in final edited form as:

Clin Exp Metastasis. 2015 December ; 32(8): 847–856. doi:10.1007/s10585-015-9747-9.

Targeting IL4/IL4R for the treatment of epithelial cancer metastasis

Katherine Venmar Bankaitis and Barbara Fingleton

Dept of Cancer Biology, Vanderbilt University, Nashville, TN 37232, USA

Abstract

While progress has been made in treating primary epithelial tumors, metastatic tumors remain largely incurable and still account for 85–90% of all cancer-related deaths. Interleukin-4 (IL4), a Th2 cytokine, and the IL4/IL4 receptor (IL4R) interaction have well defined roles in the immune system. Yet, IL4 receptors are over-expressed by many epithelial cancers and could be a promising target for metastatic tumor therapy. The IL4/IL4R signaling axis is a strong promoter of pro-metastatic phenotypes in epithelial cancer cells including enhanced migration, invasion, survival, and proliferation. The promotion of breast cancer growth specifically is also supported in part by IL4-induced glutamine metabolism, and we have shown that IL4 is also capable of inducing glucose metabolism in breast cancer cells. Importantly, there are several types of FDA approved medications for use in asthma patients that inhibit the IL4/IL4R signaling axis. However, these approved medications inhibit both the type I IL4 receptor found on immune cells, and the type II IL4 receptor that is predominantly expressed by some non-hematopoietic cells including epithelial cancer cells. This article reviews existing therapies targeting IL4, IL4R, or IL4/IL4R signaling, and recent findings guiding the creation of novel therapies that specifically inhibit the type II IL4R, while taking into consideration effects on immune cells within the tumor microenvironment. Some of these therapies are currently in clinical trials for cancer patients, and may be exploitable for the treatment of metastatic disease.

Keywords

cytokine; proliferation; survival; metastasis; IL4; IL4 receptor

INTRODUCTION

Epithelial cancers of the lung, colon, breast, and prostate comprise the top four most deadly cancers, and overall 80% of all cancers are epithelial in origin. The majority of cancer-related deaths in these patients are due to the spread of metastatic disease [1]. Interestingly, the T-helper 2 (Th2) cytokine, interleukin-4 (IL4), promotes pro-metastatic phenotypes in epithelial cancer cells such as enhanced survival and proliferation [2], enhanced migration

and invasion [3,4], enhanced metabolism to support tumor growth [5], and enhanced metastatic tumor burden [4,6] through the IL4 receptor (IL4R) (Figure 1).

In the immune system, IL4 controls the development, survival, and maturation of B cells and the proliferation and differentiation of Th2 T lymphocytes. IL4 supports this enhanced proliferation and survival in part by inducing glucose uptake and metabolism [7,8] (Figure 1). IL4 can also polarize macrophages to the 'M2' or alternatively activated phenotype [9]. Immune populations that produce IL4 include activated T cells, mast cells, basophils, eosinophils [10], and myeloid-derived suppressor cells (MDSCs) [11]. In cancer, IL4 can also be produced by tumor cells themselves [12,13].

In addition to immune and pro-tumor functions, IL4/IL4R signaling is also implicated in human diseases including asthma, allergy, and atopic dermatitis [7,8]. Indeed, the contribution of IL4 to such allergic disorders has led to the production of FDA approved therapies that target the IL4/IL4R signaling axis that may be exploitable and improved upon for the treatment of metastatic cancer. The importance of epithelial IL4R expression in promoting tumor growth and metastasis is becoming less obscure, and supports research efforts focused on targeting the IL4/IL4R signaling axis as an anti-tumor therapy. Here, we describe the basics of IL4 receptor expression and IL4/IL4R signaling, review progress that has been made in attenuating IL4 and IL4R activity therapeutically, and discuss future perspectives for using such therapies to limit epithelial cancer metastasis.

IL4R Expression and Composition

In normal tissues, the primary binding chain for IL4, IL4 receptor α (IL4R α) [10,14], is expressed on T and B lymphocytes, eosinophils, macrophages, endothelial cells, lung fibroblasts, bronchial epithelial cells, MDSCs, and smooth muscle cells [11,15–20]. There are two IL4 receptor types that control the physiological functions of IL4, each consisting of two protein subunits that heterodimerize upon IL4 binding the IL4R α subunit. The type I IL4R is predominantly expressed by hematopoietic cells, and consists of the IL4R α and common gamma C (γ_c) subunits (Figure 1). The type II IL4R can be expressed by non-hematopoietic cells, and consists of the IL13R α 1 and IL4R α subunits [21,22] (Figure 1). Significantly, while the majority of normal epithelial tissues do not express IL4Rs, the type II IL4R is overexpressed on the surface of many solid tumors including, but not limited to, renal cell carcinoma, melanoma, breast cancer, ovarian cancer, colon cancer, AIDS-related kaposi's sarcoma, and head and neck squamous cell carcinoma [13,23–29]. In fact, the expression of IL4R on cancer cells is so robust that it has been used as a targeting molecule for anti-cancer toxins fused to IL4. The IL4-PE38KDEL cytotoxin is one such example that is currently in clinical trials for a variety of cancers including recurrent or metastatic breast cancer, kidney cancer, and non-small cell lung cancer [30] (Table 1).

Unlike the type I IL4R, the type II IL4R can also bind and be activated by IL13, although IL4 binds with higher affinity [22]. IL13 signaling through the type II IL4R on airway epithelial cells primarily contributes to the airway hyper-responsiveness and mucus secretion that occurs in asthma [31]. Existing data demonstrates that IL4 is responsible for inducing pro-metastatic growth phenotypes in epithelial cells [2,6], and IL4 is upregulated in the microenvironment of several epithelial tumor types including breast, colon, prostate, and

pancreatic cancer [13,32–34]. While targeting the IL4/IL4R interaction on cancer cells is the subject of this review, we acknowledge that there may still be a role for IL13 in promoting metastasis, and there are also FDA approved therapies for blocking IL13 activity in asthma [35].

IL4/IL4R Signaling

IL4Rs themselves lack intrinsic kinase ability. Upon ligand binding, IL4 receptor dimerization results in the activation of the Janus kinase (JAK) family of proteins that phosphorylate IL4R α to create docking sites for other signaling proteins. It is known that IL4R α , γ c, and IL13R α 1 activate JAK1, JAK3, and tyrosine kinase (Tyk2), respectively [10,22,36,37] (Figure 1). Because JAK3 associates with the γ c subunit, it may not have a prominent role in type II IL4R signaling in epithelial cancer cells. In accordance with this concept, IL4 induced the tyrosine phosphorylation of JAK1, JAK2, and Tyk2 but not JAK3 in human colon cancer cells where IL4R α did not associate with the γ c subunit [38] (Figure 1). The importance of epithelial IL4R expression in promoting tumor growth and metastasis is becoming less obscure, and supports research efforts focused on targeting the IL4/IL4R signaling axis as an anti-tumor therapy.

There are two main pathways activated in immune cells in response to IL4 after the JAK phosphorylation of IL4R α : 1) the insulin receptor substrate protein (IRS)/PI3K/AKT pathway, and 2) the JAK/signal transducer and activator of transcription factor-6 (STAT6) pathway (Figure 1). STAT6 is a transcription factor that can be further phosphorylated by JAKs, form STAT6 homodimers, and translocate to the nucleus to initiate the transcription of IL4/IL13 responsive genes. IL4 has also been shown to activate mTOR in T cells for the control of differentiation [39] (Figure 1), and ERK after IRS activation in several non-lymphoid cell types [10]. We have shown that IL4-activated AKT, ERK and mTOR can mediate enhanced colonization ability in murine mammary cancer cells in vitro, and that IL4R α expression is associated with the increased activation of STAT6, AKT, and ERK in metastatic mammary tumors in the lung [6] (Figure 1). These results highlight several targetable pathways downstream of IL4/IL4R α that can promote metastatic tumor growth.

Inhibition of IL4/IL4R α Signaling

The pharmacologic inhibition of JAK1 and/or JAK2 to attenuate the initial phase of IL4-induced signaling may be possible. Several JAK inhibitors exist for the treatment of asthma and other diseases, and more are in clinical trials for the treatment of a variety of cancers [40]. Ruxolitinib, an inhibitor of JAK1/JAK2 is already FDA approved for myelofibrosis and there are multiple trials currently recruiting patients to test its efficacy against hematopoietic and solid tumors [30] (Table 1). However, it would likely be better to target a signaling molecule that is more specifically associated with IL4/IL4R signaling, as JAKs mediate a plethora of cytokine receptor responses [41]. This is also true when considering the therapeutic inhibition of AKT, ERK, or mTOR activation in response to IL4. Therefore, STAT6 may be the most attractive therapeutic target for the selective inhibition of IL4R signaling. Although not completely specific, STAT6 activation is primarily downstream of IL4R [10], and STAT6 activation promotes pro-metastatic processes including migration

and invasion, enhanced proliferation and resistance to apoptosis in epithelial cancer cells [3,13,42] (Figure 1).

The clinical targeting of STAT6 as an anti-tumor therapy may be feasible, but two FDA approved therapies known to inhibit the phosphorylation of STAT6, leflunomide and vorinostat (suberoylanilide hydroxamic acid), each have multiple other modes of action. Leflunomide inhibits de novo pyrimidine synthesis and tyrosine kinases such as EGFR [43–45], and vorinostat inhibits histone deacetylases [46]. While there are multiple other STAT6 inhibitors currently in the preclinical discovery phase [40], there are still a few drawbacks to consider regarding the inhibition of STAT6 as an anti-metastatic therapy. It is possible that alternative pathways activated by the IL4R including AKT, ERK, or mTOR could still contribute to IL4R-induced tumor growth even in the presence of a STAT6 inhibitor [6]. Also, the inhibition of STAT6 would result in the attenuation of both IL4 and IL13 signaling in immune and non-immune cells, the implications of which are not well known.

Blocking IL4 Activity

Rather than targeting signaling pathways, an alternative approach is to block or neutralize the receptor ligand, IL4. One approach to neutralizing IL4 activity specifically has been the use of inhaled recombinant human IL4 receptor fragments that competitively inhibit IL4/IL4R binding in asthma patients. One such therapy, ‘altrakincept’ or ‘nuvance’, made it to phase II clinical trials, but development was halted due to a lack of clinical efficacy [47] (Table 1). Humanized anti-IL4 monoclonal antibodies such as pascolizumab have also been tested in asthma patients. However, the development of pascolizumab, which was given to patients intravenously, was also halted after phase II trials, again due to a lack of clinical benefit [35,47] (Table 1). While these therapies are no longer being developed, they did pass initial safety testing in humans, and anti-IL4 monoclonal antibodies in particular may still hold clinical relevance for the treatment of metastatic cancer.

The IL4/IL4R interaction is species-specific, and a neutralizing antibody against murine IL4, clone 11B11, was developed in the 1980’s [48]. 11B11 was tested in mice specifically for efficacy against metastatic tumor growth. Denardo et al. showed that treatment with 11B11 for 20 days significantly reduced metastatic tumor burden in the lungs of MMTV-PyMT mice, and also limited the number of metastatic lung tumors to a slightly lesser extent than global IL4R α knockout in the same mouse strain [4]. In that paper, the reduction in metastatic mammary tumor growth by 11B11 was attributed to the neutralization of IL4 from CD4(+) T cells, thus preventing activation of tumor-associated macrophages (TAMs) that would promote metastatic growth.

These results support other studies indicating that there are pro-tumor properties regulated by IL4 in adaptive and innate immune cells of the tumor microenvironment [49–53]. We have shown that mammary metastatic lung tumor burden is also significantly attenuated by a systemic reduction in IL4 using IL4 knockout (KO) mice injected via the tail vein with 4T1 mammary tumor cells. However, in the same study, IL4R α knockdown in the 4T1 tumor cells themselves actually limited the burden of metastatic disease in the lungs of wild-type mice to a greater extent than control 4T1 cells in IL4 KO mice [6]. This result indicates that the IL4/IL4R interaction on epithelial cancer cells may be more critical for promoting

metastatic tumor growth. Still, the implications of targeting IL4 within the immune compartment as an anti-tumor therapy is a worthwhile topic, and will be touched upon again in this review.

Inhibition of IL4R α

It was thought that continued IL13 signaling through the type II IL4R could contribute to the limited clinical efficacy of IL4-targeted treatments in asthma. Therefore, blocking the receptor subunit, IL4R α , to inhibit both IL4- and IL13-induced signaling was an enticing alternative. However, the use of monoclonal antibodies against IL4R α has yielded mixed results in patients. The humanized anti-IL4R α antibody, AMG317, showed no clinical efficacy in asthma patients, and development was abandoned after phase II clinical trials [47] (Table 1). However, a second monoclonal antibody directed against IL4R α , dupilumab, has shown efficacy in the treatment of atopic dermatitis [54], and is possibly more effective for the treatment of asthma [55] (Table 1).

Recently, more attention has been directed toward the concept of modifying the IL4 cytokine into an inhibitor of IL4R α with no agonist properties. Pitrakinra, also known as IL4 double mutein or IL4-DM, is a recombinant form of human IL4 with two functional mutations at position 121 (arginine to aspartic acid) and 124 (tyrosine to aspartic acid) that acts as an IL4R α antagonist. Pitrakinra has completed phase III trials for asthma where its inhaled form was shown to be more effective than the injectable form [35] (Table 1). New IL4 variants are also being explored, and one modified at only position 121, was shown to antagonize both the type I and type II IL4 receptor [56], an improvement over pitrakinra which requires two functional mutations.

IL4-DM treatment attenuated the growth of human colon cancer xenografts in murine models [57], but it is important to note that the use of any humanized IL4 variant in murine tumor studies is limited to those in immune compromised mice due to species specificity. Also, as with STAT6 inhibitors, the function of both the type I and type II IL4R is inhibited by these antagonists, which could have negative implications for normal immune functions. Still, it is the concept of creating IL4 variants as IL4 receptor antagonists that may currently hold the greatest promise for selective anti-cancer therapies.

Selective Inhibition of the Type II IL4R

Recent advances in understanding the binding and dimerization of type I and type II IL4Rs has lead to more studies focused on improving the selectivity of IL4 receptor antagonists. The crystal structure of the ternary complex of the extracellular domains for both the type I and type II IL4 receptors was reported in 2008 [22]. These studies revealed that IL4 sits between IL4R α and the second receptor subunit, either γ c or IL13R α 1, and is in direct contact with the second subunit [22]. In 2014, fluorescence cross-correlation spectroscopy was used to observe the dimerization of the type I and II receptors in living cells after ligand binding [58]. This study confirmed previous findings demonstrating that IL4 binds with high affinity to IL4R α (K_d of ~100 pM) [59,60], and that subsequent binding with the second receptor subunit, either γ c or IL13R α 1, is a relatively low affinity interaction (0.5–4 μ M) [22,58,61]. It has been postulated that the relative expression of the second subunit may

therefore influence dimerization [62]. Collectively, these findings supported the possibility of inhibiting the contact between IL4 and either the γ c or IL13R α 1 subunits for type I or type II IL4R selectivity.

Initially, the concept of creating selectivity for one receptor over the other was examined by creating IL4 agonists that demonstrated cell-type specific effects based on the expression of the second receptor subunit. Junttila et al. increased the affinity of IL4 for the γ c subunit by modifying residues in the γ c-interacting helix (helix D), or affinity for the IL13R α 1 subunit by modifying 3 residues shown to be important for IL13 binding to IL13R α 1. These modified IL4s were termed 'superkines'. The affinity and potency of IL4 superkines in cell lines that expressed IL4R α with varying expression of the second receptor subunit, either γ c or IL13R α was then tested [62].

In A549 human lung cancer cells, the IL4 superkine designed to bind with higher affinity to IL13R α 1 induced the phosphorylation of downstream STAT6 by 3–10 fold times more than unmodified IL4 or the IL4 superkine selective for γ c. These cells were confirmed to express high levels of the type II receptor as expected for epithelial cancer cells, with little or no type I receptor expression. Ramos cells (Burkitt's lymphoma) which were used to model type I receptor signaling, but which do express a small amount of IL13R α 1, were more responsive to the superkine designed to target γ c than either unmodified IL4 or the IL13R α 1-targeted superkine [62]. These results demonstrated that the agonistic properties of IL4 could be directed to cell types including epithelial cancer cells based on their relative expression of γ c or IL13R α 1.

Medicenna Therapeutics, Inc. has taken IL4 superkines and fused them to a pro-apoptotic payload to generate 'empowered cytokines' that have the potential to induce apoptosis in 20 different cancer types overexpressing the type I or type II IL4 receptor. The original empowered cytokine, MDNA55 (Medicenna's version of the IL4-PE38KDEL cytotoxin), is not specific for one receptor type over the other, but is currently in clinical trials for central nervous system cancers known to overexpress IL4Rs [63] (Table 1). Receptor selective empowered cytokines, MDNA56 and MDNA57 are still in the discovery phase, with MDNA56 being developed for the treatment of hematopoietic cancers expressing the type I IL4R, and MDNA57 for solid tumor cells expressing the type II IL4R [63] (Table 1). These empowered cytokines are considered safe and effective [63]. Still, when targeting the expression of the type II IL4R for cancer therapy, it is important to note that myeloid cells expressing type II IL4Rs, such as macrophages and MDSCs, will also be affected. Encouragingly, there are several recent studies demonstrating that inhibition of IL4/IL4R within the immune compartment may be beneficial during anti-tumor therapy [4,12,50,53]

Targeting IL4/IL4R in the Tumor Microenvironment (TME)

Inhibiting IL4/IL4R function in pro-tumor lymphoid populations that express the type I IL4R may provide a therapeutic benefit in metastatic cancer patients. As previously mentioned, IL4 neutralization resulted in the attenuation of mammary metastatic tumor growth in the lung by reducing the pro-tumorigenic properties of both innate and adaptive immune cells of the tumor microenvironment, including CD4(+) T lymphocytes [4]. In addition, IL4 is known to impair the cytolytic activity of CD8(+) T cells by polarizing them

to type 2 cytotoxic T cells (Tc2) (Figure 2) [64–67]. A recent study actually modified IL4R to promote the activity and proliferation of cytotoxic T cells to reduce tumor growth. To do this, IL4R was fused to the IL7 receptor endodomain in transgenic T cells [50]. However, it is important to note that the systemic inhibition of either IL4 or the type I IL4R would also affect normal lymphoid processes such as B and T cell proliferation, Th2 cell differentiation, and inflammatory and immune responses.

Other immune populations in the TME that are activated in response to IL4 and express type II IL4Rs include myeloid-derived TAMs and MDSCs. Notably, MDSCs can also produce IL4 and therefore can respond in an autocrine or paracrine manner [11]. TAMs and MDSCs are both particularly important in promoting tumor growth, angiogenesis, and metastasis, and in suppressing antitumor immune responses [4,49,51,68–71] (Figure 2). Recently, an aptamer nanomolecule targeting IL4R α on TAMs and MDSCs was shown to induce apoptosis and significantly delay the progression of 4T1 tumors *in vivo* [53]. A caveat to this study is that flow cytometry was used to determine aptamer selectivity for IL4R α on TAMs and MDSCs, a method limited by markers identified by antibodies, and it is likely that IL4R α located on other cells was also targeted. A separate study using immune competent human HER2 transgenic (hmHER2Tg) mice, showed that treatment with anti-IL4 11B11 reduced the levels of myeloid chemoattractants including CCL2, CCL11, and CXCL5 within tumors, and enhanced the anti-tumor response to trastuzumab by reducing the number of tumor infiltrating myeloid cells including TAMs [12]. These studies demonstrate that inhibition of myeloid cells within the immune compartment may be beneficial for cancer patients being treated with anti-type II IL4R therapies.

DISCUSSION

Apart from its regulatory roles in the immune system, the abnormal expression of IL4 receptor (IL4R) on epithelial cancer cells has guided the delivery of toxins fused to IL4 to reduce the growth of solid tumors for many years. Now, it is becoming clear that the IL4/IL4R signaling axis on epithelial cancer cells directly influences tumor biology, and may itself serve as a therapeutic target for limiting metastatic disease. Epithelial IL4R functions to promote several pro-metastatic phenotypes in epithelial cancer cells [2,3,5] including the colonization and outgrowth of mammary cancer metastases in the lung and liver [6]. But, is it plausible to target IL4 or the IL4R to attenuate metastatic tumor growth?

Due to its roles in promoting asthmatic and allergic responses, the IL4/IL4R signaling axis is the target of several FDA approved therapies including STAT6 inhibitors, IL4 neutralizing antibodies, and IL4R α antagonists. However, each of these current therapies inhibit the function of both the type I IL4 receptor found on hematopoietic cells and the type II IL4 receptor found on myeloid cells and other non-hematopoietic cells including epithelial cancer cells. This raises the question of whether a therapy designed to target the type II IL4R would be therapeutically effective against metastatic tumors, while limiting toxicity to normal immune populations expressing the type I receptor, particularly lymphoid populations. A type II IL4R selective therapy (MDNA57) currently in development by Medicenna Therapeutics Inc, will test this idea [63]. Notably, this therapy would target both

epithelial cancer cells and other cells within the tissue microenvironment that express the type II IL4R.

Collectively, two recent studies have demonstrated that the IL4/IL4R signaling axis in the tissue microenvironment and on epithelial cancer cells themselves promotes metastatic tumor growth. In the first study, the systemic neutralization of IL4 by a monoclonal antibody was shown to reduce metastatic lung tumor burden in a murine model of spontaneous mammary cancer [4]. In support of this data, the metastatic growth of 4T1 mammary tumors in the lung was also significantly attenuated in IL4 knockout mice [6]. The earlier study suggests that IL4 produced by CD4(+) T lymphocytes acting through tumor associated macrophages (TAMs) in the TME is critical for the reduction in metastatic tumor growth [4], while the later study demonstrated that loss of IL4R α on the tumor cells themselves lead to a more profound reduction in lung metastatic tumor growth compared with systemic loss of host IL4 [6]. These results highlight the importance of understanding the roles of IL4 in the immune system in addition to how it directly promotes the metastasis of epithelial cancer cells.

FUTURE PERSPECTIVES

The selective targeting of the type II IL4R would not only affect epithelial cancer cells, but also myeloid populations including TAMs, and MDSCs. These IL4-responsive populations promote tumor growth, angiogenesis, and metastasis, and suppress antitumor immune responses [51,68–71]. The inhibition of TAMs and MDSCs in conjunction with the inhibition of epithelial IL4R by anti-type II IL4 receptor therapies may result in the dramatic reduction of metastatic epithelial tumor growth.

In the setting of epithelial cancer and metastasis, we must acknowledge that inhibition of the type II IL4R would also likely also affect IL13 signaling, but this too may be advantageous. IL13 is upregulated in primary breast cancer tissue [72] and in the peripheral blood of patients with pancreatic, esophageal, and gastric cancer [73]. While studies focusing on the implications of IL13 signaling in epithelial cancer cells are limited, it is known to have both pro-tumorigenic and pro-metastatic roles as we have previously reviewed [2]. These results are encouraging, as therapies capable of targeting the type II IL4R highlighted in this review, would likely also impact IL13 signaling. However, more work needs to be done in order to fully understand the implications of targeting the IL4R in terms of IL13 signaling as IL13 can also signal through two other receptors [2].

Here we have reviewed the implications and benefits of inhibiting the IL4/IL4R signaling axis on epithelial cancer cells and some immune populations of the TME. We have emphasized the targeting the type II IL4R specifically to limit metastatic disease as safely as possible. However, we acknowledge the need for a deeper understanding of the complicated cellular interplay between epithelial tumor cells and the cells of the TME that express either type I or type II IL4 receptors for the effective use of anti-IL4/IL4R therapies in cancer.

Acknowledgments

This work was supported R01 CA157781 awarded to BF, and by F31 CA183539 awarded to KVB. Both awards were made by the U.S. National Institutes of Health/National Cancer Institute.

Abbreviations

FDA	Food and Drug Administration (U.S.A.)
γc	common gamma chain
IL4	interleukin 4
IL4R	interleukin 4 receptor
JAK	Janus kinase
KO	knockout
MDSC	myeloid-derived suppressor cell
STAT	signal transducer and activator of transcription factor
TAM	tumor-associated macrophage
Th2	T-helper type 2
TME	tumor microenvironment
Tc2	type 2 cytotoxic T cell
IRS	insulin receptor substrate protein
Tyk2	tyrosine kinase 2
mTOR	mammalian target of rapamycin
MAPK	mitogen-activated protein kinase
AKT	protein kinase B
PI3K	phosphoinositide-3 kinase
ERK	extracellular signal-regulated kinase
pM	picomolar
Kd	dissociation constant
IL4-DM	IL4 double mutein
NSCLC	non-small cell lung cancer
CML	chronic myeloid leukemia
AML	acute myeloid leukemia
GBM	glioblastoma multiforme

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. *CA Cancer J Clin.* 2015; 65:5–29.10.3322/caac.21254 [PubMed: 25559415]

2. Hallett MA, Venmar KT, Fingleton B. Cytokine stimulation of epithelial cancer cells: the similar and divergent functions of IL-4 and IL-13. *Cancer Res.* 2012; 72:6338–6343.10.1158/0008-5472.CAN-12-3544 [PubMed: 23222300]
3. Li BH, Yang XZ, Li PD, Yuan Q, Liu XH, Yuan J, Zhang WJ. IL-4/Stat6 activities correlate with apoptosis and metastasis in colon cancer cells. *Biochem Biophys Res Commun.* 2008; 369:554–560.10.1016/j.bbrc.2008.02.052 [PubMed: 18294957]
4. DeNardo DG, Barreto JB, Andreu P, Vasquez L, Tawfik D, Kolhatkar N, Coussens LM. CD4(+) T cells regulate pulmonary metastasis of mammary carcinomas by enhancing protumor properties of macrophages. *Cancer Cell.* 2009; 16:91–102.10.1016/j.ccr.2009.06.018 [PubMed: 19647220]
5. Venmar KT, Kimmel DW, Cliffl DE, Fingleton B. IL4 receptor α mediates enhanced glucose and glutamine metabolism to support breast cancer growth. *Biochim Biophys Acta.* 2015; 1853:1219–1228.10.1016/j.bbamcr.2015.02.020 [PubMed: 25746764]
6. Venmar KT, Carter KJ, Hwang DG, Dozier EA, Fingleton B. IL-4 receptor ILR4 α regulates metastatic colonization by mammary tumors through multiple signaling pathways. *Cancer Res.* 2014.10.1158/0008-5472.CAN-14-0093
7. Dufort FJ, Bleiman BF, Gumina MR, Blair D, Wagner DJ, Roberts MF, Abu-Amer Y, Chiles TC. Cutting Edge: IL-4-Mediated Protection of Primary B Lymphocytes from Apoptosis via Stat6-Dependent Regulation of Glycolytic Metabolism. *J Immunol.* 2007; 179:4953–4957. [PubMed: 17911579]
8. Wang R, Green DR. Metabolic checkpoints in activated T cells. *Nat Immunol.* 2012; 13:907–915.10.1038/ni.2386 [PubMed: 22990888]
9. Martinez FO, Sica A, Mantovani A, Locati M. Macrophage activation and polarization. *Front Biosci.* 2008; 13:453–461. [PubMed: 17981560]
10. Nelms K, Keegan AD, Zamorano J, Ryan JJ, Paul WE. The IL-4 receptor: signaling mechanisms and biologic functions. *Annu Rev Immunol.* 1999; 17:701–738.10.1146/annurev.immunol.17.1.701 [PubMed: 10358772]
11. Gallina G, Dolcetti L, Serafini P, De Santo C, Marigo I, Colombo MP, Basso G, Brombacher F, Borrello I, Zanovello P, Bicchato S, Bronte V. Tumors induce a subset of inflammatory monocytes with immunosuppressive activity on CD8+ T cells. *J Clin Invest.* 2006; 116:2777–2790.10.1172/JCI28828 [PubMed: 17016559]
12. Surana R, Wang S, Xu W, Jablonski SA, Weiner LM. IL4 limits the efficacy of tumor-targeted antibody therapy in a murine model. *Cancer Immunol Res.* 2014; 2:1103–1112.10.1158/2326-6066.CIR-14-0103 [PubMed: 25204776]
13. Todaro M, Lombardo Y, Francipane MG, Alea MP, Cammareri P, Iovino F, Di Stefano AB, Di Bernardo C, Agrusa A, Condorelli G, Walczak H, Stassi G. Apoptosis resistance in epithelial tumors is mediated by tumor-cell-derived interleukin-4. *Cell Death Differ.* 2008; 15:762–772.10.1038/sj.cdd.4402305 [PubMed: 18202702]
14. Mueller TD, Zhang J-L, Sebald W, Duschl A. Structure, binding, and antagonists in the IL-4/IL-13 receptor system. *Biochim Biophys Acta.* 2002; 1592:237–250. [PubMed: 12421669]
15. Kotsimbos TC, Ghaffar O, Minshall EM, Humbert M, Durham SR, Pfister R, Menz G, Kay AB, Hamid QA. Expression of the IL-4 receptor alpha-subunit is increased in bronchial biopsy specimens from atopic and nonatopic asthmatic subjects. *J Allergy Clin Immunol.* 1998; 102:859–866. [PubMed: 9819306]
16. Andrews R, Rosa L, Daines M, Khurana Hershey G. Reconstitution of a functional human type II IL-4/IL-13 receptor in mouse B cells: demonstration of species specificity. *J Immunol.* 2001; 166:1716–1722. [PubMed: 11160216]
17. Dubois GR, Schweizer RC, Versluis C, Bruijnzeel-Koomen CA, Bruijnzeel PL. Human eosinophils constitutively express a functional interleukin-4 receptor: interleukin-4-induced priming of chemotactic responses and induction of PI-3 kinase activity. *Am J Respir Cell Mol Biol.* 1998; 19:691–699.10.1165/ajrcmb.19.4.3208 [PubMed: 9761767]
18. Doucet C, Brouty-Boyé D, Pottin-Clémenceau C, Canonica GW, Jasmin C, Azzarone B. Interleukin (IL) 4 and IL-13 act on human lung fibroblasts. Implication in asthma. *J Clin Invest.* 1998; 101:2129–2139.10.1172/JCI1741 [PubMed: 9593769]

19. Van der Velden VH, Naber BA, Wierenga-Wolf AF, Debets R, Savelkoul HF, Overbeek SE, Hoogsteden HC, Versnel MA. Interleukin 4 receptors on human bronchial epithelial cells. An in vivo and in vitro analysis of expression and function. *Cytokine*. 1998; 10:803–813.10.1006/cyto.1998.0365 [PubMed: 9811535]
20. Siddiqui S, Mistry V, Doe C, Stinson S, Foster M, Brightling C. Airway wall expression of OX40/OX40L and interleukin-4 in asthma. *Chest*. 2010; 137:797–804.10.1378/chest.09-1839 [PubMed: 20139223]
21. Ito T, Suzuki S, Kanaji S, Shiraishi H, Ohta S, Arima K, Tanaka G, Tamada T, Honjo E, Garcia KC, Kuroki R, Izuhara K. Distinct structural requirements for interleukin-4 (IL-4) and IL-13 binding to the shared IL-13 receptor facilitate cellular tuning of cytokine responsiveness. *J Biol Chem*. 2009; 284:24289–24296.10.1074/jbc.M109.007286 [PubMed: 19586918]
22. LaPorte SL, Juo ZS, Vaclavikova J, Colf LA, Qi X, Heller NM, Keegan AD, Garcia KC. Molecular and structural basis of cytokine receptor pleiotropy in the interleukin-4/13 system. *Cell*. 2008; 132:259–272.10.1016/j.cell.2007.12.030 [PubMed: 18243101]
23. Obiri NI, Hillman GG, Haas GP, Sud S, Puri RK. Expression of high affinity interleukin-4 receptors on human renal cell carcinoma cells and inhibition of tumor cell growth in vitro by interleukin-4. *J Clin Invest*. 1993; 91:88–93.10.1172/JCI116205 [PubMed: 8423237]
24. Obiri NI, Siegel JP, Varricchio F, Puri RK. Expression of high-affinity IL-4 receptors on human melanoma, ovarian and breast carcinoma cells. *Clin Exp Immunol*. 1994; 95:148–155. [PubMed: 8287600]
25. Leland P, Taguchi J, Husain SR, Kreitman RJ, Pastan I, Puri RK. Human breast carcinoma cells express type II IL-4 receptors and are sensitive to antitumor activity of a chimeric IL-4-Pseudomonas exotoxin fusion protein in vitro and in vivo. *Mol Med*. 2000; 6:165–178. [PubMed: 10965493]
26. Kioi M, Takahashi S, Kawakami M, Kawakami K, Kreitman RJ, Puri RK. Expression and targeting of interleukin-4 receptor for primary and advanced ovarian cancer therapy. *Cancer Res*. 2005; 65:8388–8396.10.1158/0008-5472.CAN-05-1043 [PubMed: 16166317]
27. Puri RK, Leland P, Kreitman RJ, Pastan I. Human neurological cancer cells express interleukin-4 (IL-4) receptors which are targets for the toxic effects of IL4-Pseudomonas exotoxin chimeric protein. *Int J Cancer*. 1994; 58:574–581. [PubMed: 8056454]
28. Husain SR, Gill P, Kreitman RJ, Pastan I, Puri RK. Interleukin-4 receptor expression on AIDS-associated Kaposi's sarcoma cells and their targeting by a chimeric protein comprised of circularly permuted interleukin-4 and Pseudomonas exotoxin. *Mol Med*. 1997; 3:327–338. [PubMed: 9205948]
29. Kawakami K, Leland P, Puri RK. Structure, function, and targeting of interleukin 4 receptors on human head and neck cancer cells. *Cancer Res*. 2000; 60:2981–2987. [PubMed: 10850446]
30. Clinicaltrials.gov. [Accessed June 5,2015] <https://clinicaltrials.gov>
31. Kasaian MT, Miller DK. IL-13 as a therapeutic target for respiratory disease. *Biochem Pharmacol*. 2008; 76:147–55.10.1016/j.bcp.2008.04.002 [PubMed: 18502398]
32. Conticello C, Pedini F, Zeuner A, Patti M, Zerilli M, Stassi G, Messina A, Peschle C, De Maria R. IL-4 protects tumor cells from anti-CD95 and chemotherapeutic agents via up-regulation of antiapoptotic proteins. *J Immunol*. 2004; 172:5467–5477. [PubMed: 15100288]
33. Roca H, Craig MJ, Ying C, Varsos ZS, Czarnieski P, Alva AS, Hernandez J, Fuller D, Daignault S, Healy PN, Pienta KJ. IL-4 induces proliferation in prostate cancer PC3 cells under nutrient-depletion stress through the activation of the JNK-pathway and survivin upregulation. *J Cell Biochem*. 2011; 113:1569–1580.10.1002/jcb.24025 [PubMed: 22174091]
34. Prokopchuk O, Liu Y, Henne-Bruns D, Kornmann M. Interleukin-4 enhances proliferation of human pancreatic cancer cells: evidence for autocrine and paracrine actions. *Br J Cancer*. 2005; 92:921–928.10.1038/sj.bjc.6602416 [PubMed: 15714203]
35. Maes T, Joos GF, Brusselle GG. Targeting interleukin-4 in asthma: lost in translation? *Am J Respir Cell Mol Biol*. 2012; 47:261–270.10.1165/rcmb.2012-0080TR [PubMed: 22538865]
36. Kuperman DA, Schleimer RP. Interleukin-4, interleukin-13, signal transducer and activator of transcription factor 6, and allergic asthma. *Curr Mol Med*. 2008; 8:384–392. [PubMed: 18691065]

37. Oh CK, Geba GP, Molino N. Investigational therapeutics targeting the IL-4/IL-13/STAT-6 pathway for the treatment of asthma. *Eur Respir Rev.* 2010; 19:46–54.10.1183/09059180.00007609 [PubMed: 20956165]
38. Murata T, Noguchi PD, Puri RK. Receptors for Interleukin (IL)-4 Do Not Associate with the Common Chain, and IL-4 Induces the Phosphorylation of JAK2 Tyrosine Kinase in Human Colon Carcinoma Cells. *J Biol Chem.* 1995; 270:30829–30836.10.1074/jbc.270.51.30829 [PubMed: 8530527]
39. Delgoffe GM, Kole TP, Zheng Y, Zarek PE, Matthews KL, Xiao B, Worley PF, Kozma SC, Powell JD. The mTOR Kinase Differentially Regulates Effector and Regulatory T Cell Lineage Commitment. *Immunity.* 2009; 30:832–844.10.1016/j.immuni.2009.04.014 [PubMed: 19538929]
40. Miklossy G, Hilliard TS, Turkson J. Therapeutic modulators of STAT signalling for human diseases. *Nat Rev Drug Discov.* 2013; 12:611–629.10.1038/nrd4088 [PubMed: 23903221]
41. Aaronson DS, Horvath CM. A road map for those who don't know JAK-STAT. *Science.* 2002; 296:1653–1655.10.1126/science.1071545 [PubMed: 12040185]
42. Li BH, Yang XZ, Li PD, Yuan Q, Liu XH, Yuan J, Zhang WJ. IL-4/Stat6 activities correlate with apoptosis and metastasis in colon cancer cells. *Biochem Biophys Res Commun.* 2008; 369:554–560.10.1016/j.bbrc.2008.02.052 [PubMed: 18294957]
43. Siemasko KF, Chong AS, Williams JW, Bremer EG, Finnegan A. Regulation of B cell function by the immunosuppressive agent leflunomide. *Transplantation.* 1996; 61:635–642. [PubMed: 8610393]
44. Cherwinski HM, Byars N, Ballaron SJ, Nakano GM, Young JM, Ransom JT. Leflunomide interferes with pyrimidine nucleotide biosynthesis. *Inflamm Res.* 1995; 44:317–322. [PubMed: 8581517]
45. Mattar T, Kochhar K, Bartlett R, Bremer EG, Finnegan A. Inhibition of the epidermal growth factor receptor tyrosine kinase activity by leflunomide. *FEBS Lett.* 1993; 334:161–164. [PubMed: 8224241]
46. Friedman Ohana R, Kirkland TA, Woodroffe CC, Levin S, Uyeda HT, Otto P, Hurst R, Robers MB, Zimmerman K, Encell LP, Wood KV. Deciphering the Cellular Targets of Bioactive Compounds Using a Chloroalkane Capture Tag. *ACS Chem Biol.* 201510.1021/acscchembio.5b00351
47. Gibeon D, Menzies-Gow AN. Targeting interleukins to treat severe asthma. *Expert Rev Respir Med.* 2012; 6:423–439.10.1586/ers.12.38 [PubMed: 22971067]
48. Ohara J, Paul WE. Production of a monoclonal antibody to and molecular characterization of B-cell stimulatory factor-1. *Nature.* 315:333–336. [PubMed: 2582266]
49. Umansky V, Sevko A. Tumor microenvironment and myeloid-derived suppressor cells. *Cancer Microenviron.* 2013; 6:169–177.10.1007/s12307-012-0126-7 [PubMed: 23242672]
50. Leen AM, Sukumaran S, Watanabe N, Mohammed S, Keirnan J, Yanagisawa R, Anurathapan U, Rendon D, Heslop HE, Rooney CM, Brenner MK, Vera JF. Reversal of tumor immune inhibition using a chimeric cytokine receptor. *Mol Ther.* 2014; 22:1211–1220.10.1038/mt.2014.47 [PubMed: 24732709]
51. Wang H-W, Joyce JA. Alternative activation of tumor-associated macrophages by IL-4: priming for protumoral functions. *Cell Cycle.* 2010; 9:4824–4835. [PubMed: 21150330]
52. Qian B-Z, Pollard JW. Macrophage diversity enhances tumor progression and metastasis. *Cell.* 2010; 141:39–51.10.1016/j.cell.2010.03.014 [PubMed: 20371344]
53. Roth F, De La Fuente AC, Vella JL, Zoso A, Inverardi L, Serafini P. Aptamer-mediated blockade of IL4Rα triggers apoptosis of MDSCs and limits tumor progression. *Cancer Res.* 2012; 72:1373–1383.10.1158/0008-5472.CAN-11-2772 [PubMed: 22282665]
54. Beck LA, Thaçi D, Hamilton JD, Graham NM, Bieber T, Rocklin R, Ming JE, Ren H, Kao R, Simpson E, Ardeleanu M, Weinstein SP, Pirozzi G, Guttman-Yassky E, Suárez-Fariñas M, Hager MD, Stahl N, Yancopoulos GD, Radin AR. Dupilumab treatment in adults with moderate-to-severe atopic dermatitis. *N Engl J Med.* 2014; 371:130–139.10.1056/NEJMoa1314768 [PubMed: 25006719]
55. Wenzel S, Ford L, Pearlman D, Spector S, Sher L, Skobieranda F, Wang L, Kirkesseli S, Rocklin R, Bock B, Hamilton J, Ming JE, Radin A, Stahl N, Yancopoulos GD, Graham N, Pirozzi G.

- Dupilumab in persistent asthma with elevated eosinophil levels. *N Engl J Med*. 2013; 368:2455–2466.10.1056/NEJMoa1304048 [PubMed: 23688323]
56. Duppatla V, Gjorgjevikj M, Schmitz W, Hermanns HM, Schäfer CM, Kottmair M, Müller T, Sebald W. IL-4 analogues with site-specific chemical modification at position 121 inhibit IL-4 and IL-13 biological activities. *Bioconjug Chem*. 2014; 25:52–62.10.1021/bc400307k [PubMed: 24341642]
 57. Todaro M, Alea MP, Di Stefano AB, Cammareri P, Vermeulen L, Iovino F, Tripodo C, Russo A, Gulotta G, Medema JP, Stassi G. Colon Cancer Stem Cells Dictate Tumor Growth and Resist Cell Death by Production of Interleukin-4. *Cell Stem Cell*. 2007; 1:389–402.10.1016/j.stem.2007.08.001 [PubMed: 18371377]
 58. Gandhi H, Worch R, Kurgonaite K, Hintersteiner M, Schwille P, Bökel C, Weidemann T. Dynamics and interaction of interleukin-4 receptor subunits in living cells. *Biophys J*. 2014; 107:2515–2527.10.1016/j.bpj.2014.07.077 [PubMed: 25468331]
 59. Kruse N, Tony HP, Sebald W. Conversion of human interleukin-4 into a high affinity antagonist by a single amino acid replacement. *EMBO J*. 1992; 11:3237–3244. [PubMed: 1387082]
 60. Kruse N, Tony HP, Sebald W. Conversion of human interleukin-4 into a high affinity antagonist by a single amino acid replacement. *EMBO J*. 1992; 11:3237–3244. [PubMed: 1387082]
 61. Zhang J-L, Buehner M, Sebald W. Functional epitope of common gamma chain for interleukin-4 binding. *Eur J Biochem*. 2002; 269:1490–1499. [PubMed: 11874464]
 62. Junttila IS, Creusot RJ, Moraga I, Bates DL, Wong MT, Alonso MN, Suhoski MM, Lupardus P, Meier-Schellersheim M, Engleman EG, Utz PJ, Fathman CG, Paul WE, Garcia KC. Redirecting cell-type specific cytokine responses with engineered interleukin-4 superkines. *Nat Chem Biol*. 2012; 8:990–998.10.1038/nchembio.1096 [PubMed: 23103943]
 63. Medicenna Therapeutics Inc. [Accessed June 5,2015] <https://medicenna.com>
 64. Kienzle N, Olver S, Buttigieg K, Groves P, Janas ML, Baz A, Kelso A. Progressive differentiation and commitment of CD8+ T cells to a poorly cytolytic CD8low phenotype in the presence of IL-4. *J Immunol*. 2005; 174:2021–2029. [PubMed: 15699131]
 65. Kienzle N, Buttigieg K, Groves P, Kawula T, Kelso A. A clonal culture system demonstrates that IL-4 induces a subpopulation of noncytolytic T cells with low CD8, perforin, and granzyme expression. *J Immunol*. 2002; 168:1672–1681. [PubMed: 11823496]
 66. Helmich BK, Dutton RW. The role of adoptively transferred CD8 T cells and host cells in the control of the growth of the EG7 thymoma: factors that determine the relative effectiveness and homing properties of Tc1 and Tc2 effectors. *J Immunol*. 2001; 166:6500–6508. [PubMed: 11359800]
 67. Kemp RA, Ronchese F. Tumor-specific Tc1, but not Tc2, cells deliver protective antitumor immunity. *J Immunol*. 2001; 167:6497–6502. [PubMed: 11714817]
 68. Yang L, DeBusk LM, Fukuda K, Fingleton B, Green-Jarvis B, Shyr Y, Matrisian LM, Carbone DP, Lin PC. Expansion of myeloid immune suppressor Gr+CD11b+ cells in tumor-bearing host directly promotes tumor angiogenesis. *Cancer Cell*. 2004; 6:409–421.10.1016/j.ccr.2004.08.031 [PubMed: 15488763]
 69. Van Kempen LCL, Coussens LM. MMP9 potentiates pulmonary metastasis formation. *Cancer Cell*. 2002; 2:251–252. [PubMed: 12398887]
 70. Gabrilovich DI, Nagaraj S. Myeloid-derived suppressor cells as regulators of the immune system. *Nat Rev Immunol*. 2009; 9:162–174.10.1038/nri2506 [PubMed: 19197294]
 71. Pollard JW. Tumour-educated macrophages promote tumour progression and metastasis. *Nat Rev Cancer*. 2004; 4:71–78.10.1038/nrc1256 [PubMed: 14708027]
 72. Srabovici N, Mujagic Z, Mujanovic-Mustedanagic J, Muminovic Z, Softic A, Begic L. Interleukin 13 expression in the primary breast cancer tumour tissue. *Biochem medica*. 2011; 21:131–138.
 73. Gabitass RF, Annels NE, Stocken DD, Pandha HA, Middleton GW. Elevated myeloid-derived suppressor cells in pancreatic, esophageal and gastric cancer are an independent prognostic factor and are associated with significant elevation of the Th2 cytokine interleukin-13. *Cancer Immunol Immunother*. 2011; 60:1419–1430.10.1007/s00262-011-1028-0 [PubMed: 21644036]

74. Ostojic A, Vrhovac R, Verstovsek S. Ruxolitinib: a new JAK1/2 inhibitor that offers promising options for treatment of myelofibrosis. *Future Oncol.* 2011; 7:1035–1043.10.2217/fon.11.81 [PubMed: 21919691]
75. Borish LC, Nelson HS, Lanz MJ, Claussen L, Whitmore JB, Agosti JM, Garrison L. Interleukin-4 receptor in moderate atopic asthma. A phase I/II randomized, placebo-controlled trial. *Am J Respir Crit Care Med.* 1999; 160:1816–1823.10.1164/ajrccm.160.6.9808146 [PubMed: 10588591]
76. Hart TK, Blackburn MN, Brigham-Burke M, Dede K, Al-Mahdi N, Zia-Amirhosseini P, Cook RM. Preclinical efficacy and safety of pascolizumab (SB 240683): a humanized anti-interleukin-4 antibody with therapeutic potential in asthma. *Clin Exp Immunol.* 2002; 130:93–100. [PubMed: 12296858]

Figure 1. IL4/IL4 receptor signaling in epithelial cancer cells and hematopoietic cells of the tumor microenvironment (TME)

IL4 induces heterodimerization of the IL4R α and γ C subunits to form the type I IL4 receptor in hematopoietic cells including lymphocytes (depicted). This results in the activation of JAK proteins. The two main pathways activated after the phosphorylation of JAKs in response to IL4 in immune cells are the IRS/PI3K/AKT pathway and the JAK/STAT6 pathway. Activation of these pathways in lymphocytes results in the transcription of IL4 responsive genes and the promotion of pro-growth phenotypes. IL4 has also been shown to activate mTOR in T lymphocytes for the regulation of differentiation. Some non-hematopoietic cells including epithelial cancer cells can express the type II IL4R, consisting of the IL4R α and IL13R α 1 subunits. IL4 directly promotes pro-growth and pro-metastatic phenotypes downstream of the type II IL4R in epithelial cancer cells through several signaling pathways including PI3K/AKT, MAPK/ERK, JAK/STAT6, and mTOR.

Figure 2. IL4 binds and activates the type I IL4 receptor on hematopoietic cells, and the type II IL4R on myeloid cells of the tumor microenvironment (TME) to promote metastatic tumor growth

Th2 T lymphocytes, including CD4(+) lymphocytes, are one of the main producers of IL4 in the tumor microenvironment (TME) that have been shown to promote metastasis. In the TME, IL4 promotes tumor growth and metastasis by polarizing macrophages to M2 tumor associated macrophages (TAMs), impairing the cytolytic ability of CD8(+) T lymphocytes by polarizing them to type 2 cytotoxic T cells (Tc2), and activating myeloid-derived suppressor cells (MDSCs). These activated MDSCs no longer differentiate into mature macrophages, dendritic cells, or granulocytes, and instead adopt a pathological tumor-promoting phenotype. These pro-tumor MDSCs suppress the anti-tumor immune functions of T cells and promote tumor growth and metastasis in epithelial cancer cells. MDSCs can also produce IL4, which can act in an autocrine fashion, and TAMs can stimulate the production of IL4 from CD(4)+ lymphocytes.

Table 1

Summary of clinical approaches for inhibiting IL4/IL4R activity in humans.

Product	Effect	Clinical Trials	Dose-limiting toxicities	Ref.
IL4-PE38KDEL Cytotoxin or MDNA55	IL4 fused to a truncated <i>Pseudomonas</i> endotoxin induces death in cells bearing IL4Rs	Phase I trials completed for kidney cancer, NSCLC, and breast cancer. Phase I/II trials completed for GBM. Ready to enter a phase I trial for pediatric glioma, and a phase II trial for brain metastases.	None noted	[30,63]
Ruxolitinib	Inhibitor of JAK1/2 results in inhibition of STAT6 phosphorylation	FDA approved for myelofibrosis. Patients being recruited for phase I/II trials for CML, AML, colorectal cancer, NSCLC, lung adenocarcinoma, and breast cancer.	Thrombocytopenia	[30,74]
Altrakinept/Nuvance	Recombinant human IL4R fragment competitively inhibits IL4 binding	Phase I/II trials completed in asthma then development halted due to lack of efficacy.	None observed	[35,47,75]
Pascolizumab	Humanized anti-IL4 (IgG1) antibody	Phase I/II trials completed in asthma then development in asthma halted due to lack of efficacy. Phase II trial currently recruiting tuberculosis patients.	None observed	[30,47,76]
AMG317	Humanized anti-IL-4Ra mAb	Phase I/II trials completed in asthma then development halted due to lack of efficacy.	None noted	[35]
Dupilumab	Humanized anti-IL-4Ra mAb	Completed phase II trials for asthma, atopic dermatitis, and nasal polyposis with sinusitis. Phase III trials for asthma and atopic dermatitis are ongoing.	None observed	[30,54]
Pitrakinra	Recombinant form of IL4 acts as IL-4Ra antagonist	Completed phase I/II/III trials in asthma where it was effective in eosinophilic asthma. Phase II trial in eczema also completed.	None noted	[30,35,47]
MDNA56	Modified IL4 fused to a pro-apoptotic payload, specific for type I IL4R	Still in discovery phase	Not applicable	[63]
MDNA57	Modified IL4 fused to a pro-apoptotic payload, specific for type II IL4R	Still in discovery phase	Not applicable	[63]

Abbreviations: NSCLC, non-small cell lung cancer; CML, chronic myeloid leukemia; AML, acute myeloid leukemia, GBM, glioblastoma multiforme. 'None noted' indicates that no listed toxicities could be found. 'None observed' indicates there was a study examining toxicity, and none were observed.