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IL-6 Family Cytokines: Key inflammatory mediators as biomarkers and potential therapeutic targets

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Abstract

IL-6 is a critical cytokine in acute phase response and involved in the pathogenesis of several chronic inflammatory diseases including cancer. Studies have highlighted that levels of IL-6 and its family members can be useful for diagnosis, prognosis of relapse-free survival and recurrence. IL-6 family cytokines have been identified as cancer biomarkers through screening of inflammatory mediators in different fluids including saliva, serum, and bronchoalveolar lavage fluid (BALF). IL-6 can be modulated by chemopreventive drugs, small molecules, monoclonal antibodies and immune checkpoint inhibitors. Unveiling the different sources of IL-6, the interaction between IL-6 and its cellular targets, the IL-6-dependent tumor resistance mechanisms, and the identification of novel regulators of IL-6 are some of the highly complex topics included in this review and their understanding could aid cancer biomarkers and therapy development.

Graphical abstract

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Conflicts of interest statement

None.

Keywords

IL-6; IL-6 family; cytokine; cancer biomarker; immunoprevention

1. Introduction

Inflammation, one of the hallmarks of cancer, is a known contributor to cancer initiation and progression [1]. The role of IL-6 in the development and progression of inflammation-associated cancers has been widely described. Several cells in the tumor microenvironment are capable of secreting IL-6, including epithelial oncogenic cells as well as stromal cells including immune cells [2]. Besides its direct effect on tumor cell proliferation, IL-6 is also a major immunomodulatory agent, playing active roles in the regulation of acute phase reactions, activation of T helper cells, inhibition of T regulatory (Tregs) cells and differentiation of B cells by orchestrating innate and adaptive immune responses [3]. Dual roles for IL-6 have been described in some specific tumors as it is the example of lung cancer in which IL-6 has a preventive role in the tumor initiation but it is also capable of enhancing cancer progression [4] [5].

IL-6 monoclonal antibody (Siltuximab) has been tested in mouse xenografts models of lung cancer and it has tumor inhibitory effect particularly potent when cancer-associated fibroblasts were coadministered, suggesting that IL-6 secreted by the stroma might be more susceptible to the antibody effect [6]. Cancer associated fibroblasts (CAF) in hepatocellular carcinoma (HCC) also secrete high levels of IL-6 which contributes to tumor progression via recruitment of immune cells with immunosuppressive phenotype. This data suggests that IL-6 blockade in addition to immune checkpoint inhibitors may potentially overcome the immune-checkpoint inhibitor resistance in some types of cancer [7]. The gp130 f/f (IL6st) knock-in mouse model exhibits hyper activation of the STAT3 arm of IL6. When this transgenic mouse is crossed with Kras(G12D) mice to study lung tumorigenesis, an increase in atypical adenomatous hyperplasia, adenocarcinoma in situ, and invasive adenocarcinoma throughout the lung are observed, suggesting that IL-6 trans-signaling can be a target for the treatment of KRAS-driven lung adenocarcinoma [8].

2. Identification of IL-6 family cytokines as cancer biomarkers

2.1. IL-6

The IL-6-type family cytokines are IL-6, IL-11, IL-31, Cardiotrophin-1, Ciliary neurotrophic factor (CNTF), Cardiotrophin-like cytokine (CLC), Granulocyte-colony stimulating factor (G-CSF), Leptin, Leukemia inhibitory factor (LIF), Neuropoietin and Oncostatin M. The main cellular source of IL-6 is monocytes and T cells but it can also be produced by other cells including epithelial cells [9]. IL-6 promotes Th17 cells development when combined with TGF- β [10], inhibits TGF- β -induced Treg differentiation [11], plays a role in neutrophil and macrophage recruitment and is also associated with the pathogenesis of chronic inflammatory disease [12]. IL-6 activates STAT3 through two pathways: classical and trans-signaling. Classical signaling of IL-6 occurs in cells expressing IL-6R α and it induces anti-inflammatory molecules [12]. On the other hand, trans-signaling is possible in

all cells expressing gp130 and causes pro-inflammatory cytokines induction which drives chronic inflammation. IL-6 not only contributes to cancer related inflammation but also plays crucial roles in DNA damage repair, anti-oxidant defense system, proliferation, invasion, metastasis, angiogenesis and metabolic remodeling [12] (Figure 1).

Screening of cytokines can serve to identify immunological response-related soluble factors which may be increased in cancer even at early stages. A study that included 224 hepatocellular carcinoma (HCC) cases and 644 controls revealed that higher serum levels of IL-6 are predictive of increased HCC risk, independently of hepatitis virus infection, radiation exposure and lifestyle-associated factors [13]. IL-6 can also be involved in stemness and metastasis via its downstream target, Osteopontin, in HCC. Plasma levels of IL-6 and Osteopontin were found to be independent prognostic factors for HCC patients [14].

Serum levels of IL-6 have been associated with tumor progression. In bladder cancer, IL-6 serum levels were found to be remarkably higher in patients with recurrence compared to non-recurrent patients [15]. In pancreatic ductal adenocarcinoma (PDAC), serum levels of IL-6 can be useful as diagnostic biomarker and this cytokine has also been implicated in the progression of this type of tumor [16]. It has also been reported as a useful classifier for the identification of high-risk stage I lung adenocarcinoma patients [17]. In addition to serum based studies of inflammatory mediators, tissue microarray and immunohistochemistry analysis of IL-6 in human cervical cancer tissues suggest its usefulness as prognostic biomarker as well as potential therapeutic targets for treatment of cervical cancer [18]. Advanced or metastatic colorectal cancer patients with high serum IL-6 levels had poorer overall survival (OS), progression-free survival (PFS) and anti-VEGF resistance [19] than patients with lower levels. In addition to solid tumors, elevated serum levels of IL-6 can serve as a biomarker in hematological malignancies like Hodgkin's lymphoma [20]. IL-6 and the JAK-STAT3 signaling pathway have also been found upregulated in myeloproliferative neoplasms (MPN). Interestingly, the recent JAK1/2 inhibitor trials in MPNs demonstrated that lessening inflammation can be even more helpful than targeting mutations [21].

Besides serum levels, IL-6 detection in saliva has been proposed as a useful diagnostic biomarker of cancers like oral squamous cell carcinoma (OSCC) [22]. In OSCC, IL-6 modulates resistance to radiation by inhibiting oxidative stress through the Nrf2-antioxidant pathway [23].

2.2. IL-6 as a critical inflammatory marker in murine models

IL-6 is the most highly elevated cytokine in COPD-like inflammatory mouse model and is required for lung cancer promoted by COPD-like inflammation [24]. IL-6 differently modulates both tumor initiation and progression via activating STAT3 in a mouse model of lung cancer induced by the Kras oncogene. It suppresses lung cancer initiation via sustaining lung homeostasis, modulating lung macrophages and activating cytotoxic CD8⁺ T cells under Kras oncogenic stress, and on the other hand it promotes lung cancer cell growth by promoting the cell proliferation regulator Cyclin D1 [4]. In a different lung cancer mouse model, Ccsp^{Cre/+} Kras^{LSL-G12D/+} (CC-LR), IL-6 and IL-6 class cytokine LIF were highly

detected in BALF from mice with tumors. Chemopreventive treatment of mice with *myo-inositol* diminished IL-6 and phospho-STAT3 signaling, a process likely mediated by tumor associated macrophages [25].

In the pancreas, Kras^{G12D} activation induces premalignant lesions called pancreatic intraepithelial neoplasias (PanINs). IL-6 trans-signaling-dependent activation of Stat3/Socs3 is required to promote murine PanIN progression to PDAC [26]. In a similar fashion, IL-6 has been described as a critical tumor booster during early colitis-associated cancer (CAC). Its production by myeloid cells in the lamina propria has a protective role on normal and premalignant intestinal epithelial cells (IECs) against apoptosis [27].

IL-6 has also been found increased during the development and malignant progression of astrocytomas [28]. Although suppression of IL-6 does not influence preneoplastic astrogliosis, it prevents tumor formation in a spontaneous GFAP-v-src^{+/-} mouse astrocytoma model. In a murine model of osteosarcoma, tumor progression and recurrence are modulated by IL-6 via promoting tumor self-seeding by CTCs [29].

In murine models of hematological malignancies such as CML, increased IL-6 levels were detected in BCR/ABL transgenic mice. IL-6 produced by myeloid CML cells inhibits lymphoid differentiation from multipotent progenitor cells [30] and shapes the CML pathogenesis.

Apart from tumor cells derived IL-6 secretion, mesenchymal stem cells (OvMSC) can secrete IL-6 which contributes to tumor progression in models like ovarian cancer. Coinjection of OvMSC with ovarian cancer cells enhances ovarian tumor development in NOD-SCID mice [31]. In a murine model of hepatocellular carcinoma (HCC), IL-6 is predominantly expressed by CAFs creating an immunosuppressive environment via up-regulation of inhibitory immune checkpoints [7] (Figure 2).

A study of gastric tumorigenesis in mice challenged with N-methyl-N-nitrosourea demonstrated the importance of IL-6 in driving tumor development through STAT3 stimulation by using IL-6 knockout mice [32]. Inoculation of another chemical carcinogen, diethylnitrosamine (DEN), remarkably increased serum interleukin-6 (IL-6) concentration in males compared to females. Estrogen-mediated suppression of IL-6 production by Kupffer cells diminished liver cancer risk in females in the DEN-induced hepatocellular carcinoma mouse model [33], suggesting that suppression of IL-6 abrogates the gender differences in hepatic carcinogenesis.

2.3. IL-11

IL-11 was identified as a 19 kDa soluble factor belonging to the IL-6 cytokine family in the supernatant of bone-marrow derived stromal cell. The main cellular source of IL-11 are bone, connective tissue, and malignant cells [34]. Through transmembrane protein glycoprotein-130 beta subunit, IL-11 shows pro-tumorigenic activities such as proliferation, self-renewal, invasion and angiogenesis [34]. In a prospective cohort of 60 smokers including patients with lung cancer, COPD and both, IL-11 was found to be a specific biomarker for the diagnosis of lung adenocarcinoma in BALF specimens [35].

Although there is a limitation with cohort size and short follow-up time, IL-11 has been found to be a useful biomarker for diagnosis and prognosis in patients with pancreatic cancer [36]. Assessment of IL-11 expression by immunohistochemistry in clear-cell RCC (ccRCC) has demonstrated its association with increased risk of recurrence and poor survival for ccRCC patients with early-stage disease. As a result of immunohistochemical evaluation of tissue microarrays including paired tumor/peritumoral liver tissue from 290 patients who had undergone hepatectomy for histologically proven HCC, intra-tumoral IL-11 is significantly concordant with higher tumor node metastasis (TNM) stage and has been found to be an independent prognostic factor for progression-free survival (PFS) [37], [38].

2.4. Oncostatin M

Oncostatin M (OSM) is produced by monocytes, macrophages, T cells, neutrophils and dendritic cells. Oncostatin M plays fundamental roles in heart remodeling, inflammation, hematopoiesis, liver regeneration and cancer [39]. OSM levels are associated with inflammatory response-genes, epidermal growth factor (EGF) signaling and epithelial-to-mesenchymal transition (EMT) in human estrogen receptor (ER)-negative/human epidermal growth factor receptor 2 (HER2)-negative breast cancer [40]. High expression of OSM and OSM receptor (OSMR) mRNA have been associated with reduced ER and progesterone receptor (PR) protein levels in a cohort of 70 invasive breast cancers [41]. OSM stimulates the expression of *ZEB1*, Snail (*SNAIL*), and *OSMR* as well as the CSC phenotypes in pancreatic cancer, suggesting that therapeutic targeting of the OSM/OSMR axis could be useful for patients with PDAC [42]. Analysis of serum diagnostic biomarkers in PDAC showed that OSM was overexpressed in PDAC patients versus controls (AUC=0.744). OSM could also be a predictive biomarker for treatment of PDAC response to drugs like gemcitabine and erlotinib [43].

2.5. IL-31

IL-31 is mainly expressed by circulating Th2 lymphocytes and skin-homing CLA⁺ CD45RO⁺ T cells. IL-31 binds its heterodimeric receptor formed from IL-31RA and the OSMR chains and this leads to phosphorylation of Jak1/2, which in turn, triggers phosphorylation of STAT1/3/5 or PI3K/AKT. These pathways promote skin inflammation, development of T cell type-2 inflammation in asthma and allergic rhinitis as well as gut inflammation. Elevated serum levels of IL-31 contribute to the pathogenesis of different tumor types including endometrial, lung cancer, cutaneous T cell lymphoma, follicular B cell lymphoma [44] [45]. Expression of IL-31 was found to be increased in patients with mastocytosis compared with those seen in healthy control subjects ($P < .0473$) [46].

3. Identification of IL-6 family cytokines as potential cancer treatment target

3.1. IL-6

Activation of IL-6/STAT3 pathway has been reported in various cancer types. Blockade of IL-6/STAT3 has been targeted by potent chemopreventive drugs. As an example, disulfiram, targets cancer stem cells [47] and STAT3 signaling in triple-negative breast cancer [48]. Targeting STAT3 could cause elimination of cancer stem-like cells and contribute to

blockade of recurrence in breast cancer. Recently published papers have also focused on small molecules such as Tanshinone IIA (Tan-IIA) possessing anti-cancer and anti-inflammatory activities or proteins like repebody which binds IL-6 ligand with high affinity attenuating STAT3 signaling and inhibiting human breast cancer stem cells growth and NSCLC, respectively [49] [50]. In prostate cancer, elevation of IL-6 and loss of ESE3/EHF, required for differentiation of human prostate epithelial cells, were associated with STAT3 activation. IL-6 upregulates cancer stem-like and metastatic spread-related gene expressions, indicating that identification of the novel regulator sites in IL-6 promoter could be beneficial for prostate cancer with loss of ESE3/EHF. Besides transcriptional modifiers, a long non-coding RNA identified as antisense IL6 stimulates IL-6 expression, which induces IL-6/STAT3 activation and increases invasive ability of glioblastoma cells [51].

Interleukin-6 (IL-6) is a growth factor for estrogen receptor- α (ER α)-positive breast cancer. Preclinical models have shown that breast cancer patients-derived xenografts respond to IL-6 blocking antibody [52]. Siltuximab has been well tolerated in patients with solid tumors including ovarian and KRAS-mutant cancers [53]. Siltuximab inhibits the growth of human renal cell carcinoma (RCC) in nude mice and remarkably stabilizes disease in patients with progressive metastatic RCC [54]. Since IL-6 has been involved in resistance to anti-angiogenic treatment, combinational therapy targeting angiogenic factors could be useful to prevent or minimize side effects of the monoclonal antibody.

3.2. IL-11

IL-11 is the dominant IL-6 family cytokine identified as an inducer of oncogenic STAT3 activity in the gastrointestinal (GI) epithelium during tumorigenesis, which can be targeted pharmacologically. mIL-11 Mutein treatment remarkably diminished overall tumor burden, gastric epithelial hyperplasia and reduced expression of the inflammatory mediators in the gastrointestinal tumorigenesis model [55]. IL-11/IL-11R α axis modulates human osteosarcoma through STAT3 [56–58]. Bone metastasis-targeting peptidomimetic (BMTP-11) directed against IL-11R α retards primary tumor growth and lung metastasis in preclinical models of human osteosarcoma. BMTP-11 in combination with gemcitabine shows better outcomes than BMTP-11 alone [59]. Similarly, targeting IL-11R α in combination with doxorubicin therapeutically improves the effect of chemotherapy in high grade Type I endometrioid cancer [60].

3.3. Oncostatin M

The role of Oncostatin M on tumor progression is controversial. A lung cancer study has shown that Oncostatin M inhibits metastasis of lung adenocarcinoma by suppressing SLUG expression via STAT1/STAT3 dependent signaling [61].

Oncostatin M (OSM) was described as a robust inducer of mesenchymal/CSC. Eradication of OSM or suppression of STAT3 or SMAD3 causes a significant reversion to a non-invasive, epithelial phenotype [62]. OSMR has been described as an inducer of mesenchymal properties in glioblastoma. Analysis of TCGA data has showed that OSMR but not IL-6R or LIFR is upregulated in GBM [63]. In contrast to osteosarcomas and chondrosarcomas, OSM induces proliferation of Ewing carcinoma cells which are rare bone

malignant cells, suggesting its potential utility for therapeutic intervention [64]. In sum, OSM/OSMR could be potential cancer therapeutic targets besides their usefulness as diagnostic biomarkers [63].

4. Promising Trials targeting IL-6/ IL-6R and IL-11/IL-11R α in cancer

Inhibition of IL-6 and IL-6R using specific monoclonal antibodies is being tested therapeutically for many different types of cancer [65]. Phase I and II studies assessed siltuximab in various solid tumors including ovarian, pancreatic, colorectal, head & neck and lung neoplasms [66]. In addition to solid tumors, siltuximab has also been evaluated for patients with multiple myeloma who are relapsed or refractory [67]. Phase I trials related to siltuximab are also undergoing in hematological tumors including non-Hodgkin's lymphomas (NHL) and B cell Chronic Lymphocytic Leukemia [68]. In pancreatic cancer, a current phase II trial will evaluate the safety and efficacy of gemcitabine and nab-paclitaxel with or without tocilizumab (monoclonal antibody against IL-6 receptor) (Clinical trial identification: NCT02767557). IL-6R has been described as an independent prognostic factor and potential therapeutic target for ovarian cancer. Tocilizumab has been found to be well tolerated in clinical trials [69]. The on-going phase I trial will evaluate tolerability and safety of tocilizumab given with trastuzumab and pertuzumab in subject with metastatic HER2⁺ breast cancer (Clinical trial identification: NCT03135171).

Recombinant IL-11 (Neumega) is also under clinical development for acceleration of platelet recovery and inhibition of inflammation in cancer patients to prevent chemotherapy-induced thrombocytopenia [70]. BMTP-1 for IL-11R α has been shown as a promising drug candidate in metastatic prostate cancer [71]. A comprehensive list with the completed and ongoing clinical trials targeting IL-6 family cytokines as well as their receptors can be found in Table 1.

5. IL-6/STAT3 pathway can be targeted for cancer prevention

Chemoprevention targets many steps including tumor initiation, promotion and progression. Dietary derived products play a role in all steps of the carcinogenic process [72]. Administration of α -Tocopherol (vitamin E) in an inducible mouse model of non-Hodgkin's T-cell lymphoma diminishes IL-6 gene and protein expression [73]. In a similar manner, plant derived glycoprotein (UDN glycoprotein) inhibits the levels of IL-6 in *1,2-dimethylhydrazine*-treated mice, suggesting that UDN glycoprotein may be an effective agent for colon cancer prevention [74]. Intragastric treatment with Isoliquiritigenin, originated from licorice root, downregulates IL-6 signaling in a chemically induced mouse model of colon carcinogenesis and it suppresses macrophage polarization into M2-like phenotype partially through IL-6/STAT3 pathway [75]. IL-6/STAT3 pathway can be also regulated by balsalazide (a 5-ASA prodrug) and probiotic agent VSL#3 in colorectal cancer chemoprevention [76]. The diet-derived polyphenols Apigenin and luteolin have an inhibitory effect on angiogenesis mediated by IL-6/STAT3 pathway in human endothelial cells [77]. Another example of IL-6 suppression is the mechanism of Quercetin, a compound found in many plant-based foods, which has been proposed for chemoprevention and treatment of glioblastoma [78]. Finally, the estrogen receptor modulator Evista (Raloxifene

HCl), found to also inhibit IL-6/GP130 protein interaction, represents a promising chemopreventive agent for breast, colon, multiple myeloma and liver cancer [79] [80].

6. Conclusion & Perspectives

IL-6 is a multi-functional cytokine and its abnormal expression levels are associated with cancer diagnosis, prognosis and disease progression. Recently, the new area of immunoprevention has gained major attention. Direct targeting of the IL-6 family members with some of the monoclonal antibodies currently described in clinical trials for treatment of various cancers could potentially be used for cancer prevention [81] [82].

Development of monoclonal antibodies and small molecules in addition to defining *de novo* transcriptional regulators targeting trans-signaling of IL-6 would improve cancer therapeutic strategies. Defining the origin of IL-6 and IL-6 family cytokines in the tumor microenvironment and molecular stratification of cancer subtypes based on these key inflammatory mediators would open up novel insights for chemoresistance and immunotherapy in cancer therapy. Using *in vivo* models, application of combinational therapies including IL-6 blockade and conventional chemotherapeutic or immunotherapy drugs will provide basis for clinical research.

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Abbreviations

BALF	Bronchoalveolar lavage fluid
CAC	Colitis-associated cancer
CAF	Cancer associated fibroblast
ccRCC	Clear cell renal cell carcinoma
CLC	Cardiotrophin-like cytokine
CML	Chronic myeloid leukemia
CNTF	Ciliary neurotrophic factor
COPD	Chronic obstructive pulmonary disease
CTC	Circulating tumor cells
EGF	Epidermal Growth Factor
EMT	Epithelial–mesenchymal transition
GCSF	Granulocyte-colony stimulating factor

Gp130	Glycoprotein 130
HCC	Hepatocellular carcinoma
IEC	Intestinal epithelial cells
IL-11	Interleukin 11
IL-31	Interleukin 31
IL-6	Interleukin 6
IL-6R	Interleukin 6 receptor
Jak1/2	Januse kinase 1/2
LIF	Leukemia inhibitory factor
LIFR	Leukemia inhibitory factor receptor
MAPK	Mitogen-activated protein kinase
MPN	Myeloproliferative neoplasms
Nrf-2	Nuclear factor (erythroid-derived 2)-like 2
NHL	Non-Hodgkin's lymphomas
NSCLC	Non-small cell lung cancer
OSCC	Oral squamous cell carcinoma
PanIN	Pancreatic intraepithelial neoplasia
PDAC	Pancreatic ductal adenocarcinoma
PFS	Progression-free survival
PI3K/AKT	The phosphatidylinositol-3-kinase/Protein kinase B
RCC	Renal cell carcinoma
STAT1	Signal transducer and activator of transcription 1
STAT3	Signal transducer and activator of transcription 3
TNM	Tumor node metastasis
Treg	Regulatory T cell

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Biographies

Nese Unver received her PhD in Tumor Biology and Immunology from Hacettepe University in 2012. Dr. Unver is a Postdoctoral Research Fellow in the Department of Clinical Cancer Prevention. Her research focuses on understanding of crosstalk between cancer cells and cancer-associated immune cells, especially macrophages, cytokine/chemokine mediated modulation of tumor microenvironment, uncovering the potential effects of chemopreventive drugs on lung tumor progression using *in-vivo* models and discovery of novel cancer biomarkers in solid tumors through utilization of translational medicine approaches.

Florencia McAllister received medical degree from National University of Rosario in 2000 and completed postdoctoral training at the University of Pittsburgh and Johns Hopkins University in Basic and Tumor Immunology, Oncology and Clinical Pharmacology. Dr. McAllister Lab at MD Anderson Cancer Center is focused on developing novel cancer immunopreventive and immunotherapy approaches for cancer.

Highlights

- IL-6 and its family members can be useful for diagnosis, prognosis of relapse-free survival and recurrence.
- The identification of novel regulators of IL-6 family cytokines could help cancer treatment.
- Defining the origin of IL-6 family cytokines in the tumor microenvironment would open up novel insights for chemoresistance and immunotherapy.
- Development of monoclonal antibodies targeting IL-6 family cytokines would improve cancer therapeutic strategies.

Figure 1.
IL-6 classic- and trans-signaling pathways and their downstream targets.

Figure 2.
Graphical scheme showing the complex role of IL-6 in multiple cancer types *in vivo*.

Table 1
Clinical trials registered at ClinicalTrials.gov targeting IL-6 family members or its receptors.

Drug type	Drug target	Single agent or combination	Cancer type	Study Status (completed/ongoing)	Clinical Trial Identification
Siltuximab	IL-6	Single agent	Ovarian, pancreatic, colorectal, head and neck, lung neoplasms	Phase I and Phase II, completed	NCT00841191
			Multicentric Castleman's Disease	Phase II, ongoing	NCT01400503
			High-risk Smoldering Multiple Myeloma	Phase II, ongoing	NCT01484275
			Relapsed or Refractory Multiple Myeloma	Phase II, completed	NCT00402181
			Prostate cancer	Phase II, completed	NCT00433446
Tocilizumab	IL-6R	in combination with Bortezomib	Multiple myeloma	Phase II, ongoing	NCT00401843
			Multiple myeloma	Phase II	NCT00911859
		in combination with Velcade-Melphalan-Prednisone (VMP)	Recurrent ovarian cancer	Phase I, completed	NCT01637532
		in combination with standard chemotherapy Carboplatin or Doxorubicin	Metastatic HER2 positive breast cancer	Phase I, ongoing	NCT03135171
		in combination with Trastuzumab and Pertuzumab	Unresectable pancreatic carcinoma	Phase II, ongoing	NCT02767557
		in combination with Gemcitabine/Nab-paclitaxel	Leukemia, Myeloid, Acute	Phase I, ongoing	NCT02057770
		Allogeneic or Haploidentical Stem Cell Transplant Followed By High-Dose Cyclophosphamide in Patients With Relapsed or Refractory Acute Myeloid Leukemia	B-Cell Chronic Lymphocytic Leukemia	Phase I, ongoing	NCT02336048
Neumega	IL-11	in combination with oral chlorambucil to participants with previously untreated BCLL who have comorbidities	Non-Hodgkin's Lymphoma	Phase I, ongoing	NCT03075696
		in combination with RO7082859 and Obinutuzumab	Breast cancer, gestational trophoblastic tumor, kidney cancer, lymphoma, neuroblastoma, ovarian cancer, sarcoma, testicular germ cell tumor	Phase II, completed	NCT00004157
rhIL-11	IL-11	in combination with G-CSF to Mobilize Autologous Peripheral Blood Stem Cells	Thrombocytopenia associate with imatinib or other tyrosine kinase inhibitor therapy in patients with CML	Phase II, completed	NCT00403181
		Single agent	Chemotherapy-induced Thrombocytopenia	Phase III, completion not been verified	NCT01663441
		Single agent	Patients With Castrate-Resistant Prostate Cancer With High-Volume Osseous Metastases and no Standard Treatment Options	Phase I, completed	NCT00872157