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strategy being tested preclinically and in clinical trials. Combining antitumorigenic chemokines with existing

therapies shows promising results in clinical research. Engineering of chimeric antigen receptor (CAR) T cells to overexpress certain chemokine ligands or receptors can improve their function and efficacy.

Immune checkpoint inhibition and chimeric antigen receptor (CAR) T cell therapy have demonstrated stunning clinical efficacy in many cancer types. However, most patients do not respond to immunotherapies or relapse after an initial response, stressing the need for improved strategies. Chemokines, as mediators of immune cell trafficking, play an important role in the composition of the tumor microenvironment and exert both pro- and antitumorigenic functions. Here, chemokines may represent valuable prognostic biomarkers of response to immunotherapy and a strategy to improve immunotherapies. In this review, the pleiotropic functions of chemokines in the tumor microenvironment (TME) and strategies of utilizing chemokines or chemokine antagonism in immunotherapy are discussed. The review highlights preclinical and clinical studies that apply or target chemokines in monotherapy or in combination therapies.

Keywords

chemokines; antibodies; inhibitors; oncolytic viruses; cancer vaccines; CAR T cells

Chemokines in homeostasis and inflammation Chemokines are small, secreted proteins forming the family of chemotactic cytokines. Based on the location of the cysteines (C) in their amino acid sequence, chemokines can be divided into four groups: C, CC, CXC, and CX3C. So far, 50 different chemokine ligands and 19 different chemokine receptors have been described in humans (Figure 1) [1]. These receptors belong to the group of conventional chemokine receptors that can induce cellular migration upon ligand binding. Additionally, there are four atypical chemokine receptors that may function as scavenging receptors [\[2](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0010)]. Following chemokine gradients, cells expressing a chemokine receptor migrate towards increasing concentrations of its respective ligand within tissues of the human body in a process called chemotaxis. Chemokines can also be classified as inflammatory or homeostatic based on their expression and function. Homeostatic chemokines are constitutively expressed and play a role in migration and homing of cells at physiological conditions, while inflammatory cytokines are rapidly secreted at sites of inflammation thereby recruiting effector cells to the inflamed tissue [\[3](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0015)]. Along these lines, chemokines and their receptors also have a central role in orchestrating the localization of cell populations both in normal bodily processes and in aberrant conditions such as infection and importantly, in cancer.

Figure 1. Redundancy of chemokine ligand–receptor binding. Chemokine receptors belonging to the CCR (green), CXCR (red), XCR (orange), or CX3CR (blue) group [1]. Chemokines are depicted in light blue boxes. Abbreviations: CCL, CC motif chemokine ligand; CCR, CC motif chemokine receptor; CXCL, CXC motif chemokine ligand; CXCR, CXC motif chemokine receptor; XCL, XC motif chemokine ligand; XCR, XC motif chemokine receptor.

Pleiotropic role of chemokines in cancer In cancer, chemokine signaling, and the chemotaxis of various cell populations play a central role in the composition of the TME. In the TME, immune cells, tumor cells, and tumor-associated cells all release a variety of chemokines that can change in a spatiotemporal manner, attracting different types of pro- and antitumorigenic immune cells [[2\]](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0010). The migration pattern of immune cells then influences the progression and metastasis of the tumor and directly shape the immune response. For instance, cytotoxic CD8⁺ T cells and natural killer (NK) cells can migrate to the tumor and drive antitumor immunity by releasing effector molecules such as granzyme B and perforin after activation. A major chemokine receptor expressed by these two cell types is CXCR3, and its ligands CXCL9 and CXCL10 have been shown to recruit these cells to tumor tissue [[4\]](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0020). Along these lines, the expression of CXCL9 correlates with increased numbers of tumor infiltrating lymphocytes in patients with breast cancer, making it a potential biomarker for immune

infiltration [[5\]](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0025). High CXCL9 levels in the tumor tissue are associated with a prolonged survival in breast cancer, adenocarcinoma, and ovarian cancer, underpinning the functional consequences of such enhanced attraction [\[5.](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0025), [6.,](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0030) [7.](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0035)]. CD103⁺ dendritic cells (DCs) have been shown as a major source of these potent antitumorigenic chemokines in the TME [[8\]](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0040).

In contrast, immunosuppressive, protumorigenic immune cells can also be attracted to the tumor, chief among them regulatory T cells (Tregs), tumor-associated macrophages (TAMs), and myeloid-derived suppressor cells (MDSCs). The main axis attracting TAMs to the tumor is the CC motif chemokine ligand (CCL)2– CC motif chemokine receptor (CCR)2 axis [[9\]](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0045), with high levels of CCL2 correlating with increased macrophage infiltration in gastric carcinomas [[10\]](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0050), and associated with decreased survival in patients with breast cancer [[11\]](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0055). Furthermore, CCL22 released by DCs and binding to CCR4 on Tregs has been identified as a necessary chemokine for Treg migration and DC–Treg contact in the lymph nodes; a prerequisite for the immunosuppressive function of Tregs in the periphery [[12\]](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0060).

In addition to their function in chemotaxis, chemokines play an important role in the activation, differentiation, proliferation, and apoptosis of immune cells. For instance, CXC motif chemokine ligand (CXCL)12 promotes CD4⁺ T cell survival via binding to CXC motif chemokine receptor (CXCR)4 and subsequent activation of the PI3K and MAPK signaling pathways [[13\]](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0065). Another key axis for T cell survival is CCL19 and CCL21 binding to CCR7. CCR7 expression correlates with higher antiapoptotic Bcl-2 but lower proapoptotic Bax and Fas expression levels in CD8⁺ T cells in healthy controls and patients suffering from squamous cell carcinoma [[14\]](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0070). Similar results can be observed when CD8⁺ T cells are directly stimulated with CCL19 or CCL21, suggesting an antiapoptotic effect for T cells through CCR7 [\[14](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0070)]. Also, chemokines can directly promote proliferation and survival of tumor cells. The most prominent chemokines fostering tumor cell survival and proliferation are CCL2 in breast cancer models [\[15](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0075)] and CXCL12 in models of ovarian cancer [\[16](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0080)]. Similarly, lower expression of CXCL12 is correlated with prolonged survival and better overall prognosis in pancreatic ductal adenocarcinoma [[17\]](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0085), and esophagogastric and lung cancer [\[18](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0090)]. In breast cancer however, high expression of CXCL12 is associated with a prolonged disease-free and overall survival [[19\]](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0095), probably due to reduced metastasis of breast cancer cells, as shown in preclinical models [[20\]](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0100). The opposite prognostic values of CXCL12 in different cancer types and its diverging effects on immune and cancer cells reflect the pleiotropic function of chemokines and the complexity of the chemokine–chemokine receptor system in the context of cancer. Given the various avenues in which chemokines can orchestrate the TME and determine disease outcomes, chemokine manipulation represents a promising pathway for the improvement of immunotherapy (see Glossary) and is summarized in the present review.

Strategies for utilizing or antagonizing chemokines in immunotherapy

Generally, there are two approaches for utilizing chemokines in immunotherapy: first, targeting protumorigenic chemokines, and second, increasing the concentration of antitumorigenic chemokines; both as standalone therapies or in combination with other therapeutic strategies. These approaches mainly target chemokine ligands. A third approach that arose recently with the advent of adoptive cell therapy (ACT) involves overexpression of chemokine receptors binding to specific chemokine ligands to improve their infiltration into tumor areas (Figure 2).

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Figure 2. Strategies of utilizing pro- (A, B) and antitumorigenic chemokines (C–H) in immunotherapy.

Neutralizing protumorigenic chemokines with antibodies (A) [[22](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0110)[,27](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0135),[35\]](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0175) or inhibitors (B) [\[43](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0215)[,47](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0235)]. (C) Genetic engineering of oncolytic viruses to encode antitumorigenic CXCL9 and CXCL11 [\[53](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0265),[54\]](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0270). Cytokines are expressed after infection of tumor cells. (D) CXCL10–antibody fusion constructs targeting tumor antigens and recruiting CXCR3⁺ effector cells to the tumor microenvironment [\[56](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0280),[57\]](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0285). (E) DNA or tumor cell lysate-based cancer vaccines with CCL21 as adjuvant are injected intradermally in order to recruit dendritic cells and T lymphocytes, enhancing the tumor antigen-specific immune response [\[63](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0315),[66\]](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0330). Genetically engineered dendritic cells expressing CCL21 (F) [\[70](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0350)] or CCL19-IL7 CAR T cells (G) [[71,](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0355)[72\]](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0360) release chemokines into the tumor microenvironment to enhance recruitment of endogenous effector cells. (H) CXCR6- or CCR8-engineered CAR T cells migrate to CXCL16- or CCL1-expressing tumors [\[79](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0395)[,80](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0400)]. Depicted chemokine ligands and receptors are only examples and do not represent an exhaustive list. Abbreviations: CCL, CC motif chemokine ligand; CCR, CC motif chemokine receptor; CXCL, CXC motif chemokine ligand; CXCR, CXC motif chemokine receptor.

An important aspect can be highlighted in the context of utilizing chemokines as a therapy – a huge degree of redundancy in chemokine ligand to receptor binding – with different chemokines able to bind to one receptor and vice versa (Figure 1) [[3\]](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0015). For instance, this has been shown for CCL5 that binds to CCR1 and 5 in glioblastoma [\[21](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0105)]. Only the simultaneous inhibition of both receptors blocked the CCL5-induced migration of microglia suggesting their redundant function in glioblastoma [\[21](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0105)].

Due to the redundancy in chemokine ligand–receptor binding, the additive manipulation of chemokine ligands or receptors allows for intervention in the signaling of multiple chemokine pathways, while conversely, disruptive manipulation is weakened by the redundancy of the system. The present review therefore discusses both strategies, while focusing on additive concepts.

Neutralizing protumorigenic chemokines in immunotherapy

Antibody-mediated blockade of protumorigenic chemokines Carlumab (CNTO 888) is a high-affinity monoclonal antibody targeting specifically CCL2 [\[22](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0110)]. Carlumab treatment inhibits CCL2 mediated TAM migration to the tumor; a population highly expressing CCR2 and correlating strongly with potent immunosuppression [[23](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0115)[,24](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0120)]. In preclinical models of human prostate and breast cancer, carlumab treatment resulted in a decreased tumor growth at primary and metastatic sites, inhibition of angiogenesis, and a prolonged survival of treated mice [\[24](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0120)[,25](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0125)]. However, the first clinical trial in solid tumors failed to stably reduce the serum level of CCL2 (NCT00537368; Table 1). A second trial 1 year later in patients with solid tumors resulted in an initially reduced serum CCL2 level but reversed shortly afterwards to exceed pretreatment levels (NCT01204996). Carlumab treatment failed to influence response rates and was therefore discontinued, despite

having shown potent therapeutic efficacy in preclinical mouse models [[26\]](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0130).

Table 1. Utilizing chemokines in clinical trials

Abbreviations: ALL, acute lymphoblastic leukemia; R/R, relapsed/refractory.

Another antibody approach uses HuMax-IL8 (BMS-986253) to target CXCL8 [\[27](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0135)]. CXCL8, also named interleukin (IL)-8, binds to CXCR1 and CXCR2 on neutrophils, monocytes, and endothelial and cancer

cells [\[28](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0140)[,29](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0145)]. It is normally induced at sites of inflammation, thereby recruiting neutrophils and granulocytes [[30\]](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0150). In cancer, CXCL8 promotes tumor progression, epithelial–mesenchymal transition (EMT), and recruitment of MDSCs [\[31.](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0155), [32.,](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0160) [33.](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0165)], with high serum levels correlating with poor prognosis in breast cancer patients [\[34](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0170)]. Preclinical studies have shown that CXCL8 blockade with HuMax-IL8 reduces EMT and recruitment of MDSCs to the tumor site [\[27](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0135)]. The first clinical study started in 2015, treating patients with metastatic or unresectable solid tumors (NCT02536469). There, serum CXCL8 levels could be decreased, although no objective tumor responses were detected. The following Phase II clinical trials are still ongoing and combine HuMAX-IL8 and immune checkpoint inhibitors (ICIs) in various solid tumors (NCT03689699, NCT04050462, NCT03400332, NCT04123379, NCT04848116, and NCT02451982).

Antibody-mediated depletion of CXCL13 has been tested in preclinical mouse models [\[35](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0175)[,36](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0180)] but has not progressed to clinical trials. CXCL13 has been identified as a regulator of T cell subsets and B cell homing [[37\]](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0185) and plays a key role in inflammatory diseases [\[38](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0190)]. In breast cancer, CXCL13–CXCR5 coexpression drives disease progression and metastasis [\[39](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0195)[,40](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0200)]. The depletion of CXCL13 led to a decreased tumor volume and growth in a murine breast cancer model [\[36](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0180)], although the exact mechanism was not elucidated. Together, these application examples highlight the potential and feasibility of chemokine neutralization through antibodies for therapy, although their clinical potential remains to be demonstrated.

Chemokine inhibitors

Besides depleting chemokines with antibodies, small molecule inhibitors have been tested with some degree of success. DSTAT, also known as CX-01, is a low molecular weight heparin derivative that, among other functions, binds CXCL12. CXCL12 normally binds to CXCR4 and CXCR7 on stromal cells, fibroblasts, and epithelial cells [\[41](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0205)]. In the case of ovarian cancer, it furthers tumor development and metastasis by activation of Akt/protein kinase B and p44/42 mitogen-activated protein kinase pathways [\[42](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0210)]. Targeting CXCL12 in combination with chemotherapy aims at sensitizing tumor cells to chemotherapy by inhibiting CXCR4 dependent migration of quiescent leukemic stem cells to protective bone marrow niches [[43\]](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0215). This could be shown for the blockade of CXCR4 with AMD3465 [\[44](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0220)]. In a first Phase I clinical trial, patients suffering from acute myeloid leukemia (AML) were treated with DSTAT in combination with the chemotherapeutic agents cytarabine and idarubicin (NCT02056782). The observed response rate was higher compared to the response rate of patients treated with the chemotherapeutic agents in a previous clinical trial [\[45](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0225)]. The results of a subsequent Phase II trial were comparable to the first (NCT02873338). In another Phase I trial, patients with AML or myelodysplastic syndrome were treated with DSTAT and the chemotherapeutic agent azacitidine (NCT02995655). Albeit in small patient numbers, higher response rates and favorable overall survival were observed compared to historical controls [[46\]](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0230). In 2021, DSTAT progressed to a Phase III study assessing its effectiveness in combination with standard chemotherapy in AML patients and results are eagerly awaited (NCT04571645).

Further targeting CXCL12, NOX-A12, a pegylated L-enantiomeric oligoribonucleotide (a so-called Spiegelmer) that binds the chemokine, was developed. Like DSTAT, NOX-A12 treatment aims at reducing CXCL12-induced chronic lymphocytic leukemia cell chemotaxis and resistance to chemotherapy [[47\]](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0235). In a first clinical Phase I study in healthy volunteers, NOX-A12 was well tolerated (NCT00976378). Administration of NOX-A12 in cynomolgus monkeys and in healthy volunteers (NCT01194934) led to effective CXCL12 neutralization, thereby inhibiting the activation of CXCR4 and CXCR7 and successfully mobilizing white blood cells and hematopoietic stem cells [\[48](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0240)]. In the following Phase II clinical study, NOX-A12 was tested in combination with rituximab and chemotherapy in patients with chronic lymphocytic leukemia (NCT01486797) and multiple myeloma (NCT01521533) with results pending.

Based on the findings in a murine pancreatic adenocarcinoma model that the CXCL12–CXCR4 axis conferred resistance to ICIs by inhibiting T cell infiltration into the tumor [[49\]](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0245), NOX-A12 was tested also in combination with programmed death (PD)-1 blockade in a murine model of colorectal cancer [[50\]](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0250). NOX-A12 increased the number of tumor-infiltrating lymphocytes (TILs) and synergistically inhibited tumor growth in combination with IC blockade [\[50](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0250)]. This approach proceeded to Phase II clinical trials treating patients with colorectal and pancreatic cancer (NCT04901741, NCT03168139). The combination therapy was able to stabilize disease in heavily pretreated patients for prolonged periods [[51\]](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0255). Besides targeting of CXCL12, CXCR4 inhibitors in combination with IC blockade have shown promising results [[52\]](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0260), providing evidence for the clinical benefit of targeting the CXCL12–CXCR4 axis in cancer.

Increasing the concentration of antitumorigenic chemokines

Chemokines in combination with oncolytic viruses Chemokines can be combined with oncolytic virus (OV) therapy to increase the concentration of inflammatory chemokines in the tumor, recruiting endogenous effector cells and strengthening the effect of concurrent antitumor therapy.

Oncolytic poxvirus encoding for CXCL11 could promote recruitment of T and NK cells to the tumor, resulting in reduced tumor growth and prolonged survival in murine colon adenocarcinoma models [\[53](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0265)]. In a similar approach, an oncolytic vesicular stomatitis virus (VSV) was engineered to encode CXCL9 and tested in a murine model of multiple myeloma and a human model of squamous cell carcinoma [\[54](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0270)]. These experiments showed that administration of the OV encoding CXCL9 did not mediate an enhanced recruitment of activated T cells compared to the basic OV, despite a clear increase in CXCL9 levels in the tumor [[54\]](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0270). They hypothesized that the administration of the basic oncolytic VSV already enhanced the CXCL9 concentration and further boosting of CXCL9 expression only had incremental effects on immune cell infiltration [[54\]](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0270).

Another OV, NG-641, which encodes a bispecific T cell activator that targets cancer associated fibroblasts (FAP-Tac) was successfully tested in preclinical experiments [[55\]](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0275). The OV was then further genetically engineered to express CXCL9, CXCL10, and interferon-α to enhance the recruitment of endogenous effector cells to the tumor. In a Phase I clinical trial, the engineered OV, NG-641, was tested in patients suffering from metastatic or advanced epithelial tumors with results pending (NCT04053283). Additionally, NG-641 in combination with ICI will be evaluated in two clinical Phase I trials in metastatic or advanced epithelial tumors (NCT05043714) and in squamous cell carcinoma of the head and neck (NCT04830592).

Administration of fusion proteins

Several fusion protein concepts combining chemokines and other proteins in an effort of directed delivery, have been developed to target cancer. One approach, so-called chemokine–antibody fusion proteins, enhances intratumoral effector cell recruitment by targeting the chemokine to tumor cells directly. A CXCL10– EGFRvIII single chain variable fragment (scFv) fusion protein targeting glioma was designed and tested in combination with tumor antigen-specific CD8⁺ T cells [[56\]](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0280). Administration of the fusion protein led to prolonged survival, inhibited tumor angiogenesis and increased numbers of brain-infiltrating lymphocytes in preclinical models [\[56](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0280)]. In a similar approach, an anti-human endoglin scFv was fused to CXCL10 [\[57](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0285)]. The intravenous injection of NKT cells was combined with the

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8. S. Spranger, *et al.* Tumor-residing Batf3 dendritic cells are required for effector T cell trafficking and adoptive T cell therapy Cancer Cell, 31 (2017), pp. 711-723 e4 [Article](https://www.sciencedirect.com/science/article/pii/S1535610817301587) **D** [Download PDF](https://www.sciencedirect.com/science/article/pii/S1535610817301587/pdfft?md5=2222707af37dc0294e633570a5f9b8ed&pid=1-s2.0-S1535610817301587-main.pdf) [View Record in Scopus](https://www.scopus.com/inward/record.url?eid=2-s2.0-85019144614&partnerID=10&rel=R3.0.0)

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intravenous injection of NKT cells was combined with the

intratumoral injection of the scFv fusion protein enhancing the antitumor activity of NKT cells in nude mice bearing human hepatocellular carcinoma [\[57](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0285)]. Similarly, a CCL4-collagen binding domain fusion protein to target the tumor stroma has been probed [\[58](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0290)]. CCL4 effectively enhanced the recruitment of CD103⁺ DCs to the tumor in murine models of breast cancer and melanoma, mediating an improved antitumor effect in combination with ICI [\[58](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0290)].

In another approach, CCL20 fused to patient specific scFv were generated to target CCR6 on antigen-presenting cells. Thereby, CCL20 mediated specific internalization of the fusion protein and enhanced the subsequent immune response against the scFv [\[59](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0295)]. In a Phase I clinical trial, DNA vaccines encoding patient-specific single chain variable fragments fused to CCL20 were injected intradermally into asymptomatic phase lymphoplasmacytic lymphoma patients (NCT01209871). The treatments were well tolerated and the efficacy of the vaccine will likely be evaluated in a future Phase II clinical trial [[59\]](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0295).

Chemokines as adjuvants in vaccine therapy

Chemokines can be applied as adjuvants for various cancer vaccines to mediate more robust recruitment of various desired effector cell types [[60\]](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0300). Due to its ability to attract DCs and T lymphocytes thereby initiating T cell immune responses, CCL21 has been extensively used in such cancer vaccines [\[61](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0305)]. CCL21 also plays a role in the proliferation, differentiation, and activation of T cells via binding to its receptor CCR7 [[62\]](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0310). A DNA vaccination study utilizing CCL21 revealed that CCL21 administration at the same vaccination site 24 h before DNA vaccine injection enhanced antigen-specific immunity in murine melanoma and breast cancer models [[63](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0315)[,64](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0320)]. Additionally, the combination of a DNA vaccine, PD-1 blockade, and CCL21 as adjuvant enhanced cytotoxic T lymphocyte proliferation and achieved tumor control in a murine cervical cancer model [[65\]](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0325).

These vaccination approaches combined with chemokines have progressed to clinical trials. In a Phase I/II clinical trial, intradermal vaccination with the tumor cell vaccine GM.CD40L in combination with CCL21 was compared to GM.CD40L alone (NCT01433172). This setup involves using two types of cells, the lymphoma line K562 as a bystander cell expressing granulocyte–macrophage colonystimulating factor and CD40L to boost the immune response, and a lung adenocarcinoma cell line H2122 as a tumor antigen source expressing CCL21, with the chemokine acting to recruit and mobilize T cells [[66,](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0330)[67\]](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0335). Median overall survival of patients with advanced lung adenocarcinoma was similar in both groups, but one patient treated with the vaccine and CCL21 combination displayed enhanced TILs, warranting further studies on GM.CD40L combination treatments in more refined groups of patients [\[66](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0330)].

Overexpression of chemokines in DCs

Chemokines also feature prominently in DC vaccination schemes, where CCL21 is utilized in the engineering of DCs against multiple tumor indications. CCL21 is engineered into DCs via adenoviral transduction; a process that both leads to CCL21 expression and protects DCs from apoptosis [[68\]](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0340). CCL21 overexpression in these engineered DCs results in increased infiltration of endogenous DCs and T cells into the tumor as well as potent antiangiogenic effects leading to enhanced tumor clearance [\[69](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0345)]. CCL21-transduced DC vaccination has led to Phase I clinical trials as monotherapy in nonsmall cell lung cancer (NSCLC) patients (NCT01574222), melanoma patients (NCT00798629), and in combination with pembrolizumab, in NSCLC patients (NCT03546361). Results released so far include data for the monotherapy trial in NSCLC patients, which achieved modest results with median survival increasing by 3.9 months, with roughly half of the patients showing increased immune infiltration into the tumor [[70\]](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0350).

Overexpression of chemokines in T cell therapies

Chemokines have further been used to enhance the effect of a burgeoning class of treatments – cellular therapies – through both the engineered direct expression of the chemokines or as an indirect effect of immunomodulators combined with cellular therapies. In the case of the former, the cells are engineered to coexpress the chemokine ligands either by themselves or in addition to a main effector construct. These chemokines then are secreted, affecting chemotactic gradients within the tumor with the aim of increasing the effectiveness of cellular therapy.

An approach that is the subject of several recently completed or ongoing clinical trials involves the overexpression of the chemokine CCL19 in combination with IL-7 to increase the performance of CARs against both hematological and solid tumors. As CAR T cells migrate and anchor themselves in tumor areas, CCL19 expressed in these cells serves to attract migration of endogenous T cells and DCs into the tumor via CCR7 ligation. This has been shown to lead to a synergistic antitumor activity between adoptively transferred and endogenous cells and to increase overall therapeutic efficacy in solid and liquid tumor models [[71,](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0355)[72\]](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0360). This approach has been applied in various clinical trials utilizing anti-CD19 CAR T cells against B cell lymphomas (NCT03258047). Although no results have been reported yet, a Phase II clinical trial was initiated (NCT03929107). In addition, CCL19-IL7 engineering is featured in Phase I clinical trials utilizing anti-GPC3 CAR T cells against hepatocellular carcinoma (NCT03198546); anti-integrin β7, anti-BCMA, anti-CS1, anti-CD38, and anti-CD138 single or dual targeting CAR T cells against relapsed-refractory multiple myeloma (NCT03778346); anti-Nectin-4 CAR T cells against Nectin-4-positive advanced-stage solid tumors (NCT03932565); and anti-CD19 CAR T cells in combination with anti-PD-1 checkpoint blockade against B cell lymphomas (NCT04381741). These trials have shown good safety profiles and promising efficacy. Along the same lines, CAR T cells have also been engineered to overexpress IL-7 with CCL21, another ligand of CCR7. Though only at the preclinical stage so far, these cells elicit similar migration of endogenous immune populations into tumor areas but with superior efficacy compared to CCL19-IL7 CAR T cells in *in vivo* models [[73\]](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0365).

N. Nagarsheth, *et al.* Chemokines in the cancer microenvironment and their relevance in cancer immunotherapy Nat. Rev. Immunol., 17 (2017), pp. 559-572 **7 [View PDF](javascript:;)** [CrossRef](https://doi.org/10.1038/nri.2017.49) [View Record in Scopus](https://www.scopus.com/inward/record.url?eid=2-s2.0-85028431759&partnerID=10&rel=R3.0.0)

Another avenue of engineering T cells with chemokines shown thus far only in preclinical models is the editing of SynNotch T cells with CXCL10. CXCL10 is a potent chemokine involved in the arrest of angiogenesis, induction of tumor apoptosis, and chemotaxis of immune cell populations [\[74](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0370)]. These cells were designed to bind mesothelin in an antigen-specific manner, and once bound to express CXCL10, which eventually led to inhibited tumor growth in *in vivo* models, but the added clinical value remains to be seen [\[75](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0375)].

2. [Google Scholar](https://scholar.google.com/scholar_lookup?title=Chemokines%20in%20the%20cancer%20microenvironment%20and%20their%20relevance%20in%20cancer%20immunotherapy&publication_year=2017&author=N.%20Nagarsheth) V. Mollica Poeta, *et al.*

3. [Google Scholar](https://scholar.google.com/scholar_lookup?title=Chemokines%20and%20chemokine%20receptors%3A%20new%20targets%20for%20cancer%20immunotherapy&publication_year=2019&author=V.%20Mollica%20Poeta) X. Blanchet, *et al.* Touch of chemokines

6. Y. Zhang, *et al.*

7. [Google Scholar](https://scholar.google.com/scholar_lookup?title=CXCL9%20as%20a%20prognostic%20inflammatory%20marker%20in%20early-stage%20lung%20adenocarcinoma%20patients&publication_year=2020&author=Y.%20Zhang) H. Bronger, *et al.*

Overexpression of chemokine receptors in CAR T cells In addition to chemokine ligand overexpression, CAR T cell therapy can also be improved by the addition of chemokine receptors for directed homing. The choice of the chemokine receptor mainly relies on the chemokine ligand expression of both tumor-associated cells in the TME or the tumor cells themselves compared to healthy tissue. Overexpression of the respective chemokine receptor in CAR T cells can then mediate increased migration of the adoptively transferred T cells and thereby tackle one of the major limitations in treating solid tumors with ACT: insufficient T cell infiltration [\[76](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0380)]. For example, a study demonstrated the critical role of CXCL16, the

ligand of CXCR6, in regulating the survival of T cells in the TME and their role in immunosurveillance [\[77](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0385)]. CXCL16 attracted T cells to DCs providing proliferative and antiapoptotic signals [[77\]](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0385). In addition to relevant CXCL16 expression by the TME, a substantial expression of CXCL16 was found in cancer cells of, among others, pancreatic cancer [\[78](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0390)]. The addition of CXCR6 to anti-EpCAM and anti-mesothelin CAR T cells enhanced tumor-directed migration, antitumoral activity, and prolonged survival in syngeneic, xenograft, and in patient-derived models [[79\]](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0395). Leveraging CCL1, a key chemokine aberrantly recruiting suppressive immune cells such as Tregs, it was tested whether coexpression of its receptor on therapeutic T cells would enhance their therapeutic efficacy. Using anti-EpCAM or anti-mesothelin CAR T cells coexpressing CCR8 in combination with a dominant negative transforming growth factor (TGF)-β receptor to additionally shield cells from immunosuppression, improved tumor infiltration, and therapeutic efficacy in mice bearing human or murine pancreatic tumors [[80\]](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0400). These strategies are planned to be probed in a clinical trial. Various other chemokine receptors have been shown to improve ACT by also homing the cells to tumor areas. CCR4 engineering improved anti-CD30 CAR T cells in preclinical lymphoma models [[81\]](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0405) and subsequently progressed to a Phase I clinical trial with patients suffering from Hodgkin's or T cell lymphoma (NCT03602157). Two Phase I clinical trials testing anti-BCMA and anti-CD19 CAR T cells edited to overexpress CXCR4 have been launched in patients with multiple myeloma (NCT04727008) or relapsed/refractory B cell malignancies (NCT04684472). A Phase I/II trial involving CXCR2 engineered TILs is being conducted in patients with advanced melanoma (NCT01740557), and two Phase I clinical trials testing CXCR5-modified epidermal growth factor receptor (EGFR) targeting CAR T cells have been initiated in patients suffering from advanced adult NSCLC (NCT04153799 and NCT05060796). Furthermore, cellular therapies utilizing CXCR1 [[82\]](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0410), CCR2 [[83.,](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0415) [84.](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0420), [85.\]](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0425), and CX3CR1 [\[86](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0430)] are in various stages of preclinical testing. These are promising strategies that can foster the development of new cancer therapies, especially in the context of personalized medicine.

Concluding remarks and future perspectives

Chemokines have pleiotropic functions capable of affecting both antitumor immune response and tumor progression. Taking this into account, versatile strategies that utilize or target chemokines have been established in the past decade leading to novel drug candidates tested in clinical trials.

Therapeutics targeting protumorigenic chemokines such as HuMax-IL8, DSTAT, and NOX-A12, have shown promising results. A potential application might lie with combination treatments, where chemokine neutralization to reset protumoral properties is utilized as a building block of treatment (see Outstanding questions). Difficulties with these approaches of antagonizing a single chemokine cannot be overstated, mostly because of the redundancy of the chemokine ligand–receptor system. In fact, alternative ligands can bypass the blockade by binding to the same receptors, undermining the initial effect. Alternatively, utilizing antitumorigenic chemokines in combination with cancer vaccines, OVs, and CAR T cell therapies have been recently established and this strategy is now being explored in Phase I and II clinical trials. These approaches share the goal of enhancing the recruitment and activation of endogenous effector cells by increasing antitumorigenic chemokine concentrations mediating a potent antitumor immune response. The strategy of applying antitumor therapeutics while simultaneously maximizing their potential to mobilize endogenous immune cells with chemokines and interleukins presents a powerful strategy for the future.

Outstanding questions

Can antagonizing individual chemokine ligands effectively improve therapeutic outcome of cancer patients?

Does equipping OVs with chemokine ligands enhance therapeutic efficacy in patients?

How can a personalized CAR T cell treatment utilizing chemokine ligand or chemokine receptor expression be established?

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Declaration of interests

S.K. has received honoraria from TCR2 Inc., Novartis, BMS and GSK. S.K. and S.E. are inventors of several patents in the field of immunooncology. S.K. and S.E. received license fees from TCR2 Inc. and Carina Biotech. S.K. and S.E. received research support from TCR2 Inc. and Arcus Bioscience for work unrelated to the manuscript.

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Current status and perspective of CAR-T and CAR-NK cell therapy trials in Germany

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Glossary

Adoptive cell therapy

for adoptive cell transfer, immune cells can be reactivated, engineered, and expanded before reinfusing them back into patients to enhance anticancer immune response. So far, only chimeric antigen receptor engineered T cells were approved. Engineered T cell receptor (TCR) therapy that removes T cells from the body, genetically engineers the TCR to better target tumor antigens, and then reinfuses them back into the patient, is clinically tested [\[87](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0435)]. In addition, NK cells and macrophages are equipped with CAR constructs and tested in clinical trials [[88\]](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0440).

Cancer vaccines

can either be applied to protect against cancer development or for cancer treatment to enhance the body's own antitumor immune response. They can be generated from ribonucleic acids, peptides, proteins, genes, or whole cancer cells. Besides stimulating antigen presenting cells in the patient's body, autologous DCs that have been stimulated *in vitro* can be administered as a vaccine.

Immune checkpoint inhibitors

target immune checkpoints, main regulators of the immune system that can dampen the immune response. Monoclonal antibodies blocking those receptors enhance the antitumoral immune response. So far, antibodies targeting CTLA-4, PD-1, and PD-L1 have been approved [[89\]](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0445).

Immunomodulators

Immunomodulators, like interleukins, interferons, chemokines, or immunomodulatory imide drugs, boost the activity of the patient's own immune system in general.

Immunotherapy

immunotherapy aims at fostering the body's own immune system to fight cancer by enhancing tumor cell recognition and lysis. There are different types of immunotherapy treatments.

Oncolytic viruses

viruses are modified to preferentially target and lyse cancer cells, thereby releasing chemokines, interleukins, and pathogen-associated molecular patterns to stimulate the endogenous antitumor immune response [[90\]](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0450). In 2015, talimogene laherparepvec, the first OV therapy, was approved for the treatment of advanced melanoma [[91\]](https://www.sciencedirect.com/science/article/pii/S2405803322000875?dgcid=coauthor#bb0455).

[View Abstract](https://www.sciencedirect.com/science/article/abs/pii/S2405803322000875)

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