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CXCR4 and CCR7: two eligible targets in targeted cancer therapy†

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Running Title**:**

Targeted cancer therapy and chemokine receptors

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Full name	**Abbreviation**
Acute Lymphoblastic Leukemia	ALL
Acute Myeloid Leukemia	AML
Adenoid Cystic Carcinoma	ACC
Central Nervous System	CNS
extracellular signal regulated kinases 1/2	ERK1/2
Matrix metalloproteinases	MMP
Non-Hodgkin Lymphoma	NHL
Non–Small Cell Lung Cancer	NSCLC
Phosphoinositide 3-kinase	PI3K
mitogen-activated protein kinase	MAPK
stromal cell-derived factor 1	SDF-1
Severe Combined Immunodeficiency	SCID
Squamous Cell Carcinoma of Head and Neck	SCCHN
Stromal cell-derived factor-1 alpha	SDF-1α
study single-chain antibodies	scAbs

Abstract

Cancer is the most common cause of death in the world with high negative emotional, economic and social impacts. Conventional therapeutic strategies, including chemotherapy and radiotherapy have not proven satisfactory and relapse is common in most cases. Recent studies have focused on targeted therapy with more precise identification and targeted attacks to the cancer cells. For this purpose chemokine receptors are proper targets and among them, CXCR4 and CCR7, with a crucial role in cancer metastasis, are being considered as desired candidates for investigation. In this review paper, the most important experimental results are highlighted on the potential targeted therapies based on CXCR4 and CCR7 chemokine receptors.

Keywords: chemokine receptor; targeted cancer therapy, CXCR4, CCR7.

1. Introduction

The World Health Organization has announced that deaths due to cancer are high and more efforts should be exerted for prevention and treatment of this disease (World Health Organization, 2007). Metastasis is the most common challenge attributed to the high rate of mortality from cancer. So, identification of mechanisms governing this process is critical for therapeutic purposes (Christofori, 2006). Recent studies have revealed that chemokines and their receptors, which are crucial factors in cell migration, also play a key role in metastasis (Muller et al., 2001).

C-X-C chemokine receptor type 4 (CXCR-4) and C-C chemokine receptor type 7 (CCR7) are two members of the chemokine receptor superfamily with significant roles in various cellular processes such as cell migration. CXCR4 has an important role in stem cell homing and CCR7 implicates in T cell and dendritic cell migration into secondary lymphoid organs that is an important step for initiation of the acquired immune responses (Zlotnik et al 2011). Moreover, both of these receptors have functional roles in tumor progression and metastasis of many cancer cells, as described in Table 1.

Cancerous signaling pathways of CXCR4 and CCR7

CXCR4 chemokine receptor

Binding of stromal cell-derived factor 1 (SDF-1) to CXCR4 activates the downstream signaling pathways that regulate cell chemotaxis, survival, proliferation and migration in various cancer cells (Barbero et al., 2003, Fernandis et al., 2004, Kijima et al., 2002, Phillips et al., 2003). Phosphoinositide 3-kinase (PI3K) and mitogen-activated protein kinase (MAPK) pathways are important downstream pathways of CXCR4 with implication on tumor cell survival and migration (Barbero et al., 2003). It was demonstrated that SDF-1 induces matrix metalloproteinases 9 (MMP-9) expression in prostate cancer cells by activating PI3K-Akt and MEK pathways (Chinni et al., 2006) and that binding of SDF-1 to CXCR4 induces cell invasiveness by triggering the extracellular signal regulated kinases 1/2 (ERK1/2) and PI3K (Leelawat et al., 2007, Liao et al., 2015). Many proteinases are capable of degradation of extracellular matrix (ECM). Among them, however, matrix MMPs appear to be more important for this action. SDF-1 enhances the expression and also function of MMPs that are crucial elements for metastasis of cancer cells (Singh et al., 2004) (Diao et al., 2016, Heissig et al., 2002, Janowska-Wieczorek et al., 2000) (Bartolomé et al., 2004). SDF-1 is also involved in modulation of ischemic tissue and tumor vascularization by stimluation

of the expression of certain angiogenic factors. It was demonstrated that pro-angiogenic factors including VEGF-A, IL-6, IL-8 and tissue inhibitor of metalloproteinase-2 are secreted in prostate cancer cells in response to SDF-1 (Wang et al., 2005a). Interestingly, SDF-1 was shown to down-regulate the glycolytic enzyme phosphoglycerate kinase 1, which is a negative regulator of VEGF and IL-8 expression (Wang et al., 2007). CXCR4 can also induce angiogenesis and progression and metastasis of the tumors by elevating the expression of VEGF through the activation of PI3K/Akt/MAPK pathway (Diao et al., 2016, Liang et al., 2007). Also, SDF-1 stimulates the production of TNF-α in ovarian cancer cells (Scotton et al., 2002) and this inflammatory cytokine is involved in the communication between the tumor and its environment (Szlosarek et al., 2003).

CCR7 chemokine receptor

Activation of CCR7 receptor by its ligands in cancer cells triggers several signaling pathways leading to cell migration and possible metastasis. CCR7 mediates survival and invasion of metastatic squamous cell carcinoma of head and neck (SCCHN) cells via activation of PI3K, that are critical in tumor progression and metastasis (Wang et al., 2005b). Also, activation of this receptor by CCL19 in SCCHN, can induce ERK1/2 and JNK phosphorylation. These could possibly serve as downstream signaling pathways of CCR7 in SCCHN (Liu et al., 2014). Moreover, CCR7 regulates cell migration and invasion through MAPKs in metastatic SCCHN (Chen et al., 2015). CCL21/CCR7 axis induces cell migration and invasion in human colon cancer (Li et al., 2011a) and B-cell chronic lymphocytic leukemia by up regulating MMP-9 expression (Redondo-Muñoz et al., 2008). This axis promotes T24 bladder cancer cell proliferation and enhances its migration and invasion via the increased expression of MMP-2 and MMP-9. On the other hand, CCL21/CCR7 has anti apoptotic effects on T24 cells via regulation of Bcl-2 and Bax proteins (Mo et al., 2015) and the axis CCL19/CCR7 up regulates the expression of heparanase via Sp1, with some degree of contribution on the invasion of human lung adenocarcinoma cells (Zhang et al., 2013). CCL21/CCR7 axis increases the expression of VEGF-D in human non-small cell lung cancer (NSCLC) cells through induced ERK1/2 and Akt phosphorylation. In addition, the expression levels of CCR7 and CCL21 were shown to correlate with VEGF-D, lymphatic vessels density (LVD), clinical stages, lymph node metastasis and patient survival in NSCLC (Sun et al., 2015). MUC1 is a transmembrane protein in cancer cells and it has a role in lymph node metastasis induced by CCL21-CCR7 in esophageal squamous cell carcinoma (ESCC). It was demonstrated that phosphorylation of the ERK1/2 and Sp1 pathways are caused by the regulation of MUC1 by CCL21-CCR7 (Shi et al., 2015).

<Table 1>

Targeted therapy is taking very high priority as an effective approach for the treatment of cancer amongst the recent strategies. It is actually the basis of several methods including the development of drugs which interfere with molecular pathways involved in the proliferation, progression, and spread of cancer cells (Sawyers, 2004). Given the pivotal roles of CXCR4 and CCR7 chemokine receptors in the metastasis of various cancers, identification of their inhibitors can be a promising strategy for abrogating metastasis. Three main strategies in targeting these receptors include application of small molecule antagonists, siRNA and monoclonal antibodies. These strategies will be discussed in this review paper from a molecular point of view in detail.

2. Therapeutic strategies based on the inhibition of chemokine receptors expression

Small molecule antagonist

In various studies listed in Table 2, the inhibitory effect of the CXCR4 antagonists have been reported as potential drugs for targeting cancer. On the other hand, some chemical antagonists like AMD3100 have been introduced for this purpose.

T140

T22 ([$Tyr^{5,12}$, Lys^{7}]-polyphemusin II) is a synthetic analog peptide of polyphemusin II with three substituted amino acids with strong anti-HIV activity, exerted by CXCR4 neutralization (Masuda et al., 1992). On the basis of T22 structure, Tamamura et al. designed a small-sized effective CXCR4 inhibitor with low molecular weight and 14-residue peptide, i.e. T140 ([L-3-(2-naphthyl)-$alanine^{3}$]-T134) (Tamamura et al., 1998). This inhibitor had higher affinity with CXCR4 and hence more anti-HIV activity than the original T22 and AMD3100, reported up until that time (Tamamura et al., 2001). The suppressive effects of T140 analogs on the migration and pulmonary metastasis of MDA-MB-231 breast cancer cells and human leukemia T cells in SCID mice have also been studied (Tamamura et al., 2003a).

TN14003

The protein structure of T140 is not stable in serum because of the cleavage of Arg14 under such conditions. So, the C-terminal amidation of T140 was proposed to protect the protein from degradation. Consequently, citrulline (Cit)-substitution for a reduction of total cationic charges in T140 molecule was thought to be useful for the development of a novel effective CXCR4 inhibitor and anti-HIV agent with low cytotoxicity, TN14003 ([Cit6]-T140 with the C-terminal amide), with stability in serum (Tamamura et al., 2001). Treatment of pancreatic cancer cells with TN14003 was demonstrated to reduce the actin polymerization and block the cell migration and invasion by preventing the SDF-1-induced phosphorylation of the MAP kinases (Mori et al., 2004). In another study in small cell lung cancer cells, TN14003 disrupted the CXCR4/CXCL12 interactions and inhibited the cell adhesion and chemoresistance (Hartmann et al. , 2005). TN14003 also has the same inhibitory role on breast cancer metastasis (Liang et al., 2004) and prevents the growth and of primary tumors of squamous cell carcinoma of head and neck (SCCHN) cells and their metastasis toward lung in orthotopic mouse model (Yoon et al., 2007).

BKT140

BKT140 (4F-benzoyl-TN14003) is a novel analog of T140 with 14-residue bio-stable synthetic peptide which was shown to have an inhibitory effect on HIV infection in cells (Beider et al., 2011, Tamamura, 2003a, Tamamura et al., 2003b). BKT140 is more potent than AMD3100 in the mobilization of hematopoietic stem cells (Abraham et al., 2007). Also, it is a stimulator for recovery of bone marrow after transplantation (Abraham et al., 2009). It carries CXCR4 antagonistic properties with greater affinity than AMD3100 (Peled et al., 2014). Targeting the CXCR4 by BKT140 was reported to stimulate cell apoptosis in multiple myeloma (MM) and lymphoma cells in xenograft model and tumors treated with BKT140 were significantly smaller in size and weight (Beider et al., 2011). In a similar study, BKT140

decreased tumor development and increased the effects of chemotherapy and radiotherapy on patients with NSCLC (Fahham et al., 2012). Furthermore, BKT140 had an inhibitory effect on tumor progression and metastasis in Non-Hodgkin Lymphoma (NHL) cells that represent a novel CXCR4-targeted therapy for NHL patients (Beider et al., 2013). BKT140 is currently in clinical evaluation as stem cell mobilizer, for MM, leukemias and lymphomas. The safety and efficacy of this CXCR4 antagonist for mobilization of human CD34+ cells in patients with MM has been reported (Peled et al., 2014).

RCP168

RCP168 is an analogue of the viral macrophage inflammatory protein II in which the first 10 amino acids in the N terminal of the protein structure are exchanged with D stereoisomers. RCP168 is a prototype molecule of a novel family of synthetically and modularly chemokines that are highly selective and potent CXCR4 inhibitors, compared with natural chemokines. It has been reported that RCP168 and SDF-1α bind onto the overlapping distinct sites on the CXCR4 receptor. RCP168, however, disrupts HIV infection much more than SDF-1α /CXCR4 axis (Zeng et al., 2006). SDF-1α/CXCR4 axis has a crucial role in the resistance of leukemia cells to chemotherapy-induced apoptosis, while the CXCR4 inhibitor of RCP168 disrupts this interaction by suppression of the SDF-1α–induced AKT and extracellular signal-regulated kinase phosphorylation. This would lead to an increase in the efficacy of the related chemotherapy (Zeng et al., 2006). The inhibitory effects of RCP168 are sufficient to inhibit the SDF-1α/CXCR4 interactions in comparison with other peptidic inhibitors of CXCR4 such as T140 (Burger et al., 2005, Zeng et al., 2006).

MSX-122

MSX-122 (N,N`-(1,4-phenylenebis(methylene))dipyrimidin-2-amine) is a small molecule known as a partial CXCR4 antagonist or biased antagonist. It shows anti-metastatic activity by blocking the homing of the cells through CXCR4 disruption (Liang et al., 2012). Chemotherapy combined with the application of MSX-122 in lung cancer of orthotopic mouse model was proved to be more effective (Zhang et al., 2008). In a similar study, MSX-122 blocked lung metastasis of breast cancer and SCCHN, and also liver metastasis of uveal melanoma(Liang et al., 2012). Also, it inhibits the development of fibrotic process in mice after radiation-induced lung injury with no mortality (Shu et al., 2013).

CTCE-9908

CTCE-9908 is a small peptide antagonist of CXCR4 that comprises of 17 amino acids with dimerized sequence of the disordered NH2-terminal of CXCL12 (Faber et al., 2007, Wong et al., 2006). It exhibits an inhibitory roles on the progression and metastasis in several cancer cells. In one study, CTCE-9908 reduced tumor metastasis in a murine orthotopic model of human prostate cancer and a phase I study showed its safety in healthy adults (Wong et al., 2006). Also, in a similar study, CTCE-9908 abolished cellular proliferation and decreased the size of prostate tumors that is associated with the knockdown of VEGF, suppression of angiogenesis and lymphangiogenesis and induction of apoptosis in the xenograft model (Porvasnik et al., 2009). In another study, blockage of CXCR4 activity by CTCE-9908 suppressed the proliferation of tumor cells and induced cell apoptosis in Hepatocellular carcinoma (HCC) cells. It significantly decreased the number of cancer cells and tumor nodules in the lung of orthotopic HCC model (Kok et al., 2007). Phase II clinical trials of this CXCR4 antagonist, in patients with HCC, have been under evaluation (Wong and Korz., 2008). The preventive effects of CTCE-9908 on the migratory

behavior of melanoma and Lewis Lung carcinoma (LLC) cells were demonstrated. It reduced the metastasis of melanoma cells and LLC cells to the lung (Abramovich et al., 2007). In a similar study, CTCE-9908 decreased the migration, invasion and pulmonary metastasis of osteosarcoma and melanoma cells (Kim et al., 2008). Additionally, it had the same inhibitory effects on the primary tumor growth and metastasis of breast cancer. After treatment of breast cancer model with CTCE-9908, the size of metastasis in lung and bone was decreased (Richert et al., 2009). Also, in combination with docetaxel or an anti-angiogenic substance, the anti-tumor effects of CTCE-9908 were significantly enhanced (Hassan et al., 2011, Huang et al., 2009). CTCE-9908 induced cell death in ovarian cancer cells by mitotic catastrophe. This is a unique cytotoxicity action by CTCE-9908 because other CXCR4 antagonists, including AMD3100, CXCR4 inhibitory antibody and CXCR4 siRNA, did not induce any mitotic catastrophe in ovarian cancer cells (Kwong et al., 2009). CTCE-9908 is the only CXCR4 antagonist approved by the FDA for solid tumors, especially for treatment of osteogenic sarcoma (Burger et al., 2009).

Nef and Nef-M1

Nef protein is a N-terminus myristylated protein with 205 amino acids that is expressed by mRNAs of HIV-1, HIV-2 and SIV, early after the establishment of the provirus in host cells (Herbein et al., 1998). It was demonstrated that Nef protein targets CD4+ T Cells and induces apoptosis in these cells by interacting with CXCR4 receptor (James et al., 2004). Two apoptotic motifs were identified in Nef, which appear to be necessary for the induction of apoptosis in the CD4+ lymphocytes through CXCR4 (Huang et al., 2004). A significant inhibitory effect of Nef on the growth of primary human colorectal cancer was demonstrated (Bumpers et al., 2005). The apoptotic motif in the HIV-1 Nef protein (Nef-M1) is cytotoxic to various human cancer cell lines, including breast cancer. Nef-M1 (Nef protein amino acids 50 - 60) is an antagonist for CXCR4 that enhances apoptosis, impaired breast cancer tumor formation and metastasis *in vitro* and *in vivo*. This antagonist peptide seems to be an efficient activator of caspase-3, a key molecule of the apoptotic process and inhibitor of primary tumor development and metastasis of breast cancer (Bumpers et al., 2013). Nef-M1 also demonstrated a dramatic reduction of primary colorectal tumor growth in the spleen and secondary invasion of the liver and induced apoptosis through physical interaction with CXCR4 (Willie Harrington III et al., 2009).

LY2510924

LY2510924 (Cyclo[Phe-Tyr-Lys(iPr)-D-Arg-2-Nal-Gly-D-Glu]-Lys(iPr)-NH2) is a small cyclic peptide antagonist of CXCR4 consisting of non-natural amino acids with high stability in humans (Galsky et al., 2014). LY2510924 inhibits the binding of SDF1 to CXCR4 and was demonstrated to suppress the SDF1 signaling and its antitumor effects were demonstrated in various types of human cancer including non-Hodgkin lymphoma (NHL), colon cancer, non–small cell lung cancer, renal cell carcinoma and breast cancer (Galsky et al., 2014). It has been demonstrated that LY2510924 abrogated growth in solid tumors and breast cancer cell migration *in vivo* (Peng et al., 2015b). Based on these findings, the Phase I Trial of LY2510924 in patients with advanced cancer was carried out (Galsky et al., 2014).

AMD3100

Bicyclams are the first class of CXCR4 inhibitors with chemical structure including two monocyclam (1, 4, 8, 11-tetraazacyclotetradecane), connected by an aliphatic or aromatic linker (Bridger et al., 1995).

AMD3100 (mozobil or Plerixafor) is the octahydrochloride dihydrate of 1,1`-[1,4-phenylenebis(methylene)]-bis-1,4,8,11-tetra-azacyclotetradecane} that is the first of this class which has highly potent CXCR4 antagonist and selectively inhibits X4 HIV strains (Donzella et al., 1998, Schols et al., 1997). It is a bicyclam reversible antagonist, the most studied among CXCR4 inhibitors. It blocks the CXCL12-mediated calcium mobilization, chemotaxis, and GTP-binding (De Clercq, 2003). The efficacy of this chemical CXCR4 antagonist in hematopoietic stem cell mobilization was tested in two successful phase III clinical trials on HIV-1 patients (DiPersio et al., 2009) and it was approved by the FDA in 2008 for the mobilization of hematopoietic stem cells in multiple myeloma and non–Hodgkin lymphoma patients (DiPersio et al., 2009, Stone et al., 2007). Systemic administration of AMD 3100 inhibits the growth of intracranial glioblastoma and medulloblastoma xenografts by increasing apoptosis and decreasing the proliferation of tumor cells. AMD3100 is able to reduce the activation of extracellular signal-regulated kinases 1 and 2 and Akt, which are downstream pathways of CXCR4 (Rubin et al., 2003). Association of AMD3100 with bis-chloronitrosourea, showed antitumor efficacy in orthotopic models of glioblastoma, demonstrating the synergism between CXCR4 inhibition and conventional cytotoxic therapies (Redjal et al., 2006). The same role of AMD3100 for blocking CXCR4 was also demonstrated in ovarian cancer (Righi et al., 2011). Also, AMD3100 has the anti-angiogenic efficacy that is associated with a reduction of tumor growth and invasiveness in orthotopic glioblastoma xenotransplanted rats (Ali et al., 2013). In another study, the clinical relevance of CXCR4 neutralization with siRNA or AMD3100 in chondrosarcoma (Sun et al., 2013) and adenoid cystic carcinoma (ACC) were investigated and the results indicated a decreased tumor growth and metastasis dissemination (Jeong et al., 2014). AMD3100 is used as a cell mobilizing drug in stem cell therapy and also has an anti-HIV potential for AIDS patients (De Clercq, 2015).

AMD3465

AMD3465 is a monocyclam {N-[1,4,8,11- tetraazacyclotetradecanyl-1,4-phenylenebis(methylene)]-2-(aminomethyl)-pyridine} with decreased molecular charge. It carries more potency in anti-HIV activity and CXCR4 antagonism as compared to AMD3100 (Hatse et al., 2005). AMD3465 effectively blocks the binding of anti-CXCR4 mAb 12G5 and CXCL12, and potently inhibits the CXCL12-induced intracellular calcium mobilization, MAP kinase phosphorylation, receptor internalization and chemotaxis (Hatse et al., 2005). AMD3465 antagonizes the SDF-1–induced and stroma-induced chemotaxis and inhibits the activation of the survival signaling pathways in leukemic cells. *In vivo* studies demonstrated that AMD3465 alone or in combination with granulocyte colony-stimulating factor (GCSF), induces the mobilization of acute myeloid leukemia (AML) cells into circulation and enhances the anti-leukemic effects of chemotherapy and sorafenib, resulting in markedly reduced leukemia burden and increased survival of animals (Zeng et al., 2009). The effect of AMD3465 in breast cancer model indicated that the oncogenic signaling in breast cancer cells and also metastasis towards lung and liver were reduced, mediated by a reduction in STAT3, JAK2, AKT, and CXCR4 phosphorylation and the reduced expression of GSK3 and cMYC (Ling et al., 2013).

<Table 2>

These findings, in general, show the therapeutic potential of the CXCR4 antagonists in the targeted cancer therapy. However, further studies are required for their establishment in clinic and the role of CCR7 antagonists in the targeted cancer therapy has yet remained to be elucidated.

Targeted siRNA delivery

RNA interference technology is a proper tool in gene silencing and a powerful method for investigation of gene function or even designing drugs for cancer therapy (Dorsett et al., 2004).

Down regulation of the *CXCR4* gene in model animals by siRNA was shown to result in the disruption of invasiveness of breast cancer cells and their metastasis towards the lung (Liang et al., 2005). It is known that low levels of E-cad and high levels of IGFBP-5, FN and MMP-2 increase metastasis. Based on this, treatment of the TD47 breast cancer cells with CXCR4 siRNA was also shown to increase the expression levels of E-cad, while the IGFBP-5 expression was down regulated (Zhang et al., 2007). The therapeutic application of CCR7 siRNA is also extremely promising. The inhibitory effects of CCR7 siRNA on the metastasis of colon carcinoma have been reported by suggestion of the CCR7 siRNA technology as a useful candidate for colon cancer therapy (Shuyi et al., 2008). In another study, it was demonstrated that miRNA let-7a binds to the 3'UTR of CCR7 mRNA and causes down regulation of the CCR7 expression in breast cancer cells. It was followed by a reduction in breast cancer metastasis which represents the therapeutic properties of let-7a in breast cancer (Kim et al., 2012). Furthermore, it was suggested that treatment of the esophageal carcinoma cells by CXCR4 siRNA, would decrease the levels of CXCR4 expression and cell proliferation, invasiveness and metastasis. These results provide a basis for the treatment of ESCC by down regulation of the *CXCR4* gene, using RNAi technology (Wang et al., 2013). CXCR4-siRNA was designed in another study and transmitted into the HER2+ breast cancer cells by arginine nonamer peptide fusion protein (e23sFv-9R) as a siRNA carrier. This CXCR4-siRNA was shown to reduce the expression of CXCR4 in the breast cancer cells followed by impaired proliferation and metastasis and induced apoptosis in the HER2+ breast cancer BT-474 cell line. Additionally, the systemic delivery of CXCR4-siRNA by e23sFv-9R inhibited tumor growth and metastasis without any systemic toxicity in mice model (Jiang et al., 2015).

Therapeutic monoclonal antibodies

Specific anti-CXCR4 and CCR7 antibodies have been used for cancer diagnosis or treatment purposes in several studies.

Bertolini et al. showed that CXCR4 neutralization with specific antibody leads to abolishing of NHL cell migration. This also decreases the cell proliferation and increases apoptosis in these cells in SCID mice (Bertolini et al., 2002). In a similar study it was demonstrated that CXCR4 antibody treatment in human osteosarcoma xenografts prevented lung metastasis of the cells (Brennecke et al., 2014). Single-chain antibodies (scAbs) were designed and shown to block the CCR7 signaling activation. This was followed by the inhibition of T-cell acute lymphoblastic leukemia (T-ALL) cell migration to the CNS. This study suggested a new approach by means of CCR7 antibody to inhibit brain metastasis in T-ALL patients (Cunningham et al., 2014).

Cancer diagnosis is another benefit of targeting chemokine receptors. Klinguer-Hamour et al. have provided a novel anti-CXCR4 antibody that is used in the detection and diagnosis of cancer (Klinguer-Hamour et al., 2013). These experiments have revealed the considerable potential of anti-CXCR4 and CCR7 in cancer diagnosis and cancer therapy.

3. Conclusions

Conventional therapeutic approaches have proved to be inefficient when it comes to cancer where relapse always exists. Accordingly, targeted cancer therapy has attracted increasing attention and experimental support. It is believed that CXCR4 and CCR7 are crucial factors in progression of cancer and also metastasis. Therefore, they could be suggested as proper targets for targeted cancer therapy. Establishment of strategies like using small molecule antagonists and monoclonal antibodies and also targeted siRNA delivery against CXCR4 and CCR7 is a step forward for successful targeted cancer therapy. These candidate approaches can reduce or inhibit progress of metastasis providing great opportunities for ongoing efforts to combat this terrible disease.

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Table 1. CXCR4 and CCR7 in progress of various cancers.

Cancer type	CXCR4	CCR7	References
Acute Lymphoblastic Leukemia (ALL)	+		(Wu et al., 2006)
Acute Myeloid Leukemia (AML)	+		(Spoo et al., 2007)
Adamanti-nomatous Craniopharyngioma	+		(Gong et al., 2014)
Adrenocortical Carcinoma		+	(Heinze et al., 2015)
Atypical Ductal Hyperplasia	+		(Schmid et al., 2004)
Basal Cell Carcinoma	+		(Chen et al., 2006)
Bladder	+	+	(Eisenhardt et al., 2005; Mo et al., 2015)
Breast	+	+	(Muller et al., 2001)
Cervical	+	+	(Kodama et al., 2007)
Cholangiocarcinoma	+		(Leelawat et al., 2007)
Chronic lymphocytic leukemia	+	+	(Alfonso-Pérez et al., 2006; Burger et al., 1999; O'Hayre et al., 2010; Till et al., 2002)
Chronic Myelogenous Leukemia	+		(Salgia et al., 1999)
Colon Cancer	+	+	(Li et al., 2011a; Zeelenberg et al., 2003)
Colorectal	+	+	(Günther et al., 2005; Schimanski et al., 2005)
Ductal Carcinoma In Situ	+		(Schmid et al., 2004)
Endometrial Cancer	+	+	(Gelmini et al., 2009; Kodama et al., 2006)
Esophageal	+	+	(Ding et al., 2003; Kaifi et al., 2005)
Ewing Sarcoma	+		(Jin et al., 2012)
Gallbladder Cancer	+		(Yao et al., 2011)
Gastric	+	+	(Mashino et al., 2002; Yasumoto et al., 2006)
Gastrointestinal	+		(Schimanski et al., 2008)
Glioma	+		(Ehtesham et al., 2006)
Head and neck	+	+	(Muller et al., 2006)
Hepatocellular carcinoma	+	+	(Schimanski et al., 2006a; Schimanski et al., 2006b)
Langerhans Cell Histiocytosis		+	(Fleming et al., 2003)
Laryngeal and hypopharyngeal squamous-cell cancer	+	+	(Chen et al., 2013; Tan et al., 2008)
Melanoma	+	+	(Scala et al., 2006; Wiley et al., 2001)
Merkel Cell Carcinoma	+		(Knapp et al., 2012)
Mesothelioma	+		(Li et al., 2011b)

Multiple Myeloma	+		(Alsayed et al., 2007)
Mycosis Fungoides		+	(Hu et al., 2014)
Nasopharyngeal	+		(Wang et al., 2005)
Nasopharyngeal carcinoma	+		(Hu et al., 2005)
Neuroblastoma	+		(Russell et al., 2004)
Non-Hodgkin's lymphoma	+	+	(Beider et al., 2013; Yang et al., 2011)
Non-Small Cell Lung	+	+	(Phillips et al., 2003; Takanami, 2003)
Oral squamous-cell cancer	+	+	(Shang et al., 2009; Uchida et al., 2003)
Osteosarcoma	+		(Oda et al., 2006)
Ovarian	+	+	(Cheng et al., 2014; Jiang et al., 2006)
Pancreatic	+	+	(Marchesi et al., 2004; Nakata et al., 2008)
Primary CNS Lymphoma	+	+	(Jahnke et al., 2005)
Prostate	+	+	(Darash-Yahana et al., 2004; Peng et al., 2015a)
Renal cell carcinoma	+		(Wang et al., 2009)
Rhabdomyosarcoma	+		(Libura et al., 2002)
Salivary Gland Cancer	+		(Uchida et al., 2013)
Small Cell Lung	+		(Hartmann et al., 2005)
Soft Tissue Sarcoma	+		(Kim et al., 2010)
squamous cell carcinoma of the tongue	+	+	(Delilbasi et al., 2004; Xia et al., 2015)
T cell leukemia		+	(Buonamici et al., 2009)
Testicular tumors	+		(Gilbert et al., 2009)
Thymoma	+		(Wang et al., 2015)
Thyroid	+		(Avilla, 2009; Sancho et al., 2006)

Table 2. Small molecule antagonists used for modulation of CXCR4 in various cancers.

Peptide antagonist	Cancer type treatment	References
T140	Breast cancer Leukemia	(Tamamura et al., 2003a)
TN14003	Pancreatic cancer Small cell lung cancer Breast cancer Squamous cell carcinoma of head and neck	(Hartmann et al., 2005; Liang et al., 2004; Mori et al., 2004; Yoon et al., 2007)
BKT140	Multiple myeloma Lymphoma Non–small cell lung cancer Non-Hodgkin Lymphoma	(Beider et al., 2011; Beider et al., 2013; Fahham et al., 2012)
RCP168	Chronic and acute Leukemias	(Zeng et al., 2006)
MSX-122	Lung cancer Breast cancer Uveal melanoma	(Liang et al., 2012; Zhang et al., 2008)
CTCE-9908	Prostate cancer Hepatocellular carcinoma Melanoma Lung carcinoma Osteosarcoma Melanoma Breast cancer Ovarian cancer	(Abramovich et al., 2007; Huang et al., 2009; Kok et al., 2007; Kwong et al., 2009; Kim et al., 2008; Richert et al., 2009; Wong et al., 2006)
Nef-M1	Colorectal cancer Breast cancer	(Bumpers et al., 2005; Bumpers et al., 2013)
LY2510924	Non-Hodgkin lymphoma Colon cancer Non–small cell lung cancer Renal cell carcinoma	(Galsky et al., 2014; Peng et al., 2015b)

AMD3100	Breast cancer Glioblastoma Medulloblastoma Ovarian Chondrosarcoma Adenoid cystic carcinoma	(Jeong et al., 2014; Rubin et al., 2003; Righi et al., 2011; Sun et al., 2013)
AMD3465	Breast cancer Leukemic	(Ling et al., 2013; Zeng et al., 2009)