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The G Protein Coupled Receptor CCR5 in Cancer.

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Abstract

The G coupled protein receptor C-C chemokine receptor type 5 (CCR5) has the unusual characteristic in humans of being a developmentally non-essential gene that participates in several pathological processes including infection with HIV (Dean et al., 1996) (Gupta et al., 2019; Samson et al., 1996), progression of stroke (Joy et al., 2019), osteoporosis (Xie, Zhan, Ge, & Tang, 2019) and the metastasis of cancer (X. Jiao et al., 2018; Velasco-Velazquez et al.) (X. Jiao et al., 2018)(Reviewed in:(X. Jiao et al., 2019)). The importance of CCR5 in HIV led to recent genetic engineering of humans to recreate a non-functional CCR5 gene. Thus, although the application of gene-editing tools, to manipulate human embryos is prohibited in the United States, and China. at the Second International Summit on Human Genome Editing in Hong Kong (<http://www.nationalacademies.org/>), it was claimed that CRISPR-Cas9 systems had been used to edit the *CCR5* gene in twin baby girls. The importance of CCR5 in stroke (X. Jiao et al., 2019) has led to clinical trials using maraviroc (NCT03172026). The key function of CCR5 in cancer metastasis and homing (X. Jiao et al., 2019; X. Jiao et al., 2018; Velasco-Velazquez et al.) (X. Jiao et al., 2019) has led to three active clinical trials for metastatic cancer using CCR5 antagonists (X. Jiao et al., 2019). Thus, it was surprising to find that the all-cause mortality rate in individuals who are homozygous for the CCR5 $\Delta 32$ allele in the UK normal population was increased >20% increase, with an almost 2 year reduction overall lifespan (Wei & Nielsen, 2019). The current review herein discusses the distinct functions of CCR5 in human disease and potential avenues for further research.

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Keywords

CCR5; metastasis; mutation; signalling

Genetics of cysteine-cysteine chemokine receptor type (CCR5).

Interestingly, a homozygous gene deletion within the CCR5 coding region occurs naturally in humans (CCR5 $\Delta 32$). These individuals remain asymptomatic throughout most of their lives. When introduced to pathogens individuals with CCR5 $\Delta 32$ have resistance to HIV (Dean et al., 1996; X. Jiao et al., 2018; Velasco-Velazquez et al.) (Samson et al., 1996)) poxvirus(X. Jiao et al., 2018; Lalani et al., 1999; Velasco-Velazquez et al.) and a *Staphylococcus Aureus* produced leukotoxin (LukED)(Alonzo et al.). In contrast CCR5 $\Delta 32$ individuals have reduced resistance to West Nile virus(Lim et al.), and tickborne encephalitis (Kindberg et al.). LukED binds to CCR5 on T cell macrophages and dendritic cells (Alonzo et al.) and may have participated in selecting for the genetic variant, which is more prevalent in individuals of European (10%) compared with individuals of Asian, Middle Eastern (2-to 5%) or African origin. Studies of mortality amongst individuals with CCR5 $\Delta 32$ showed the all-cause mortality rate in individuals who are homozygous for the CCR5 $\Delta 32$ allele was increased >20% increase, with an almost 2 year reduction overall lifespan (Wei & Nielsen, 2019). In addition to the CCR5 $\Delta 32$ polymorphism, other nonfunctional or hypofunctional CCR5 alleles are relatively frequent in human populations (Blanpain et al., 2000)and their importance in disease predisposition and overall mortality has not been determined.

CCR5 and biochemical signaling.

The signal transduction elicited by CCR5 appears to be relatively well conserved across cell types in which physiological expression (inflammatory cells) or ectopic expression (cancer cells) has been assessed. CCR5 became a focus of much interest because of its role as a co-receptor for HIV entry. In response to HIV infection, CCR5 is deployed as a co-receptor. The HIV-1 envelope glycoprotein (Env), which consists of trimeric (gp160)₃ cleaved to (gp120 and gp41)₃, interacts with the primary receptor CD4 and the coreceptor (CCR5) to fuse viral and target-cell membranes. The structure of CCR5 bound to CD4, suggests CCR5 anchors the CD4-induced conformation of Env near the cell membrane (Shaik et al., 2019).

In response to ligands however GPCR undergoes a conformational change, forcing the G α i and G β γ subunits to dissociate. CCR5 is a 7 trans-membrane G-protein coupled receptor (GPCR) that binds to multiple ligands including (CCL3 (MIP1 α), CXCL13 (BCA-1), CCL4 (MP-1 β), CCL3L1, CCL8 (MCP2), CCL5 (RANTES), CCL11 (Eotaxin), CCL13 (MCP-4), and CCL16 (HCC-4) (Fig. 1) (Velasco-Velazquez, Xolalpa, & Pestell). Inflammatory or homeostatic cytokines include low molecular weight (LMW) proteins (8–14 kDa) with 47 human receptors. These are further subdivided into 4 family members, based on the location of the 2 cysteine residues located at the amino terminus (CXC, CC, XC, CX3C) (Gao & Fish).

The 19 unique GPCRs interact with 47 distinct chemokines. The cognate GPCR undergoes a conformational change when the ligand binds, dissociating the G α i and G β γ subunits and

thereby inducing signaling. Specifically, Gβγ subunits activate phospholipase Cγ, PIP2, and IP3, leading to a rapid increase in cytosolic Ca²⁺. Previous literature has shown that CCR5 activation of Ca²⁺ signaling and cellular migration is preserved in immunologic (Olson et al., 1999) and malignant cells (X. Jiao et al., 2018; Velasco-Velazquez et al.). The induction of additional pathways by CCR5, include the PI-3'K pathway and thereby PDK1 and serine/threonine kinase protein kinase B (AKT), which in turn induces cell survival, glycolysis, cell proliferation, growth and proliferation of progenitor and stem cells, immune cell differentiation and the release of eIF4E to promote cap-dependent translation (Fig. 1A).

CCR5 serves as a lynchpin in the function of T-helper cells, macrophages, eosinophils, myeloid derived suppressor cells (MDSC), microglia and dendritic cells (Fig. 1B). In addition, CCR5 can be pathologically expressed during cellular transformation. The induction of CCR5 expression leads cells to changes in genomic characteristics as well as its metastatic behavior.

CCR5 antagonists re-tasked in cancer (X. Jiao et al., 2018).

Based on the importance of CCR5 activation in the onset and progression of cancer, several CCR5 antagonists that were developed for HIV therapy, are now being retested for cancer and cancer-related diseases. The two primary CCR5 inhibitors, maraviroc and vicriviroc were used in clinical trials to treat patients with HIV. Leronlimab, a humanized monoclonal antibody inhibitor, has also demonstrated therapeutic benefit in HIV patients and has been used in more than 760 HIV⁺ patients without causing any severe therapy-related adverse events. Leronlimab and Maraviroc reached their primary efficacy endpoints in Phase 3 HIV clinical trials (Dhody, 2018; Fatkenheuer et al.; Kaplon & Reichert, 2018) (Kaplon & Reichert, 2018, 2019).

In a mouse model of pancreatic adenocarcinoma, TAK-779, a quaternary ammonium derivative, reduced T regulatory cell infiltration and tumor growth (Tan et al., 2009). Anibamine, a natural product that antagonizes CCR5, decreased the growth, adhesion, and invasion of prostate cancer. In other murine cancer models, Met-CCL5, a competitive chemokine receptor antagonist, decreased not only the tumor growth of malignant breast cancer cells, but also the infiltration of macrophages. Aplaviroc, a 2,5-diketopiperazine CCR5 entry inhibitor, has been discontinued due to its hepatotoxic side effect profile (Nichols et al., 2008). A reduction in CCR5 expression and cancer cell migration was achieved via a saponin named DT-13. The utilization of zinc finger nuclease and siRNA have also demonstrated efficacy in reducing CCR5 expression. GAG mimetics that inhibit CCL5 binding to GAG, OTR4120 and OTR4131, minimize CCL5-induced invasion and migration of hepatocellular carcinoma (HCC). Because of its failed efficacy and side effect profile, INCB9471 (Incyte Corporation) was discontinued after a phase 2 trial for HIV positive patients (Shin et al., 2011). Cinicriviroc (TBR-652) (Takeda), which is a dual CCR2-CCR5 inhibitor has completed a Phase IIb clinical trial for HIV and is now being researched for its utility in treating Nonalcoholic Steatohepatitis (NASH). Also, a soluble receptor-based fusion protein named mCCR5-Ig was found to inhibit CCR5 and is being further investigated for its therapeutic potential (X. Jiao et al., 2018; Ryu et al., 2018; Sugasawa, Ichikura, Tsujimoto, et al., 2008).

CCR5 overexpression has been demonstrated in breast (X. Jiao et al., 2018; Velasco-Velazquez et al.), prostate (Sicoli et al., 2014), and colorectal cancer (Halama et al.; Pervaiz, Ansari, Berger, & Adwan, 2015), as well as melanoma (J. Liu et al.), lymphoma (Casagrande et al.), head and neck cancer (Gonzalez-Arriagada, Lozano-Burgos, Zuniga-Moreta, Gonzalez-Diaz, & Coletta), gastric cancer (Aldinucci & Casagrande), esophageal cancer (Wu et al.), and pancreatic carcinoma (Fig. 1B). In the analysis of >2,200 breast cancer patients, >50% of patients' tumors were CCR5⁺ and >95% of triple negative breast cancer (TNBC) were CCR5⁺ (Velasco-Velazquez et al.). It was found that the higher the cytoplasmic CCR5 staining, the poorer was the prognosis (X. Jiao et al.). CCR5 is induced by oncogenic transformation (Ha-Ras, c-Myc, ErbB2, c-Src) (Velasco-Velazquez et al., 2012), DNA damage (X. Jiao et al.) and CCL5. CCR5 receptor levels correspond to poor prognosis in breast cancer and gastric adenocarcinoma (X. Jiao et al., 2018; Ryu et al., 2018; Sugasawa, Ichikura, Tsujimoto, et al., 2008).

Although CCR5 binds to many ligands in cellular proliferation, elevated levels of the ligand indicates a poor prognosis in breast (Niwa et al.; Yaal-Hahoshen et al.), cervical (Niwa et al.), prostatic (Tsukishiro, Suzumori, Nishikawa, Arakawa, & Suzumori), gastric (Sima et al.), (Sugasawa, Ichikura, Tsujimoto, et al.), colorectal (Suenaga et al.) and pancreatic cancers. (Cambien et al., 2011; Sugasawa, Ichikura, Kinoshita, et al., 2008; Vangelista & Vento, 2017).

CCR5 induces the Hallmarks of Cancer.

CCR5 expression induces cancer cell homing behavior to metastatic sites (Velasco-Velazquez et al.; Zi et al., 2017). CCR5 alters the pro-inflammatory metastatic immune phenotype (Halama et al., 2016) and enhances DNA repair, rendering cells resistant to DNA damaging agents (X. Jiao et al.).

Activating invasion and metastasis (X. Jiao et al., 2018; Velasco-Velazquez et al.).

Unique, distinct mechanisms govern the pathophysiology of tumor invasion vs. metastasis (W. Liu et al., 2014; Massague & Obenauf). Ectopic CCR5 expression within apical epithelial cells is sufficient to drive cancer cell metastasis (Velasco-Velazquez et al., 2012). Small molecular inhibitors specific to CCR5 also block the metastasis of isogenic oncogene-transformed breast cancer cells in NOD/SCID mice (Velasco-Velazquez et al., 2012) and prostate cancer metastasis in immunocompetent mice (Sicoli et al., 2014). Maraviroc inhibits SUP-B15 cells migration to CXCL12 and CXCL13, *in vitro* (Zi et al.). CCR5 induces metastasis in p53⁻ breast cancer cells *in vivo* (X. Jiao et al., 2018; Zhang et al., 2018).

Avoiding immune destruction-the anti-tumor immune response (Blattner et al., 2018; Hawila et al.).

Tumorigenesis induces ligands for CCR5 promoting pro-metastatic and inflammatory pathways via distinct mechanisms. Recent evidence supports a hypothesis that CCR5 inhibitors may have a potential synergy with the canonical immune checkpoint inhibitors. In current clinical trials by Pfizer and Merck, CCR5 inhibitors (Maraviroc, Vicriviroc) are being used in combination with a checkpoint inhibitor (Pembrolizumab). The recruitment and migration of innate lymphoid cells (ILCs) tumor-infiltrating lymphocytes (TILs), Tregs

(Schlecker et al.) mesenchymal stem cells (MSCs) and immature dendritic cells (DCs), participate in tumor-induction and anti-tumor immunosuppression (Sleeman). The mechanism by which tumors evade destruction involves an active process of inducing immune tolerance via recruitment of CD4⁺CD25⁺Foxp3⁺ regulatory T cells (Treg).

Cellular expression of CCR5 occurs in many other cell types including stem cells (Fig. 1). For instance, MSC produce CCL3, CCL4 and CCL5. Maraviroc reduces the MDSC-induction of colon cancer metastasis (Nishikawa et al., 2019). Furthermore, CD4⁺ Foxp3⁺ Treg, preferentially express CCR5 compared with CD4⁺ Foxp3⁻ effector T cells; which participate in the migration and growth of pancreatic adenocarcinoma (Tan et al., 2009).

Conversely, an absence of CCR5 ligand expression has a strong correlation to a diminished infiltration of antigen specific T cells and metastasis (Harlin et al., 2009). It is also been hypothesized that through TGFβ (Chang, Lin, Mahalingam, et al., 2012), tumor-derived CCL5 impedes the anti-tumor T cell response to thereby enhance proliferation of murine mammary carcinoma (Adler, Lemken, Katchen, & Kurt, 2003). CCR5 is part of a CCL3-CCR5/CCR1-mediated DC cell migration to lymph nodes and the tumor microenvironment (TME). CD4⁺ T cells interact with DC, CCL3, and CCL4 which are released into tissues for the activation of CCR5⁺ naïve CD8⁺Tcells (Castellino et al., 2006). CCR5 and its ligands promote the proliferation of CCR5⁺ PMN-MDSCs into the bone marrow and, later, trigger immunosuppressive activities at the site of tumor burden via arginase-1.

CCR5 guides CD11b⁺Gr1⁺Ly6C^{low} polymorphonuclear myeloid cells from the bone marrow to promote tumor development (Hawila et al., 2017). The subtypes CD11b⁺Ly6G⁻Ly6C^{hi} monocytic MDSCs and CD11b⁺Ly6G⁺Ly6C^{low} polymorphonuclear (PMN) both contribute to tumor growth and immunosuppression (Hawila et al., 2017). In mice, CCR5 blockade with anti-CCR5 antibody decreases growth of B16 melanoma and reduces MDSC accumulation. Also, the endogenous ligand CCL8, is produced by F4/80⁺ macrophages in the lungs of mice with metastatic primary tumors (Halvorsen et al., 2016). Reduction in the migration of Tregs towards CCL8 *ex vivo* in the presence of the CCR5 inhibitor Maraviroc has been demonstrated. Finally, mice that were treated with Maraviroc showed reduction in the level of CCR5⁺ Tregs and metastatic tumor burden in the lungs (Halvorsen et al., 2016).

TAMs express CCR5; they are comprised of macrophages (M1 to M2 spectrum) and express variable levels of arginase and interleukins (IL4, IL10, and IL13). F4/80⁺ macrophages are strongly implicated in human cancer progression and are well known participants in the onset and progression of mammary tumors in murine models (Qian & Pollard, 2010). Recruitment of TAMs towards the tumor burden are facilitated by ligands including RANTES (Azenshtein et al., 2002). Through binding to CCR5 and CCR1, CCL3 promotes tumorigenesis through recruitment of pro-tumorigenic macrophages into the TME (Kitamura et al., 2015). Interestingly, gene deletion of *CCL3* in murine macrophages reduced the number of lung metastasis and an adoptive transfer of wild type inflammatory monocytes increased the number of lung metastasis in *Ccl3* deficient mice (Kitamura et al., 2015).

Other ligands including EGF, CSF1, HGF, CCL2, CXCR4/CXCL12 and Tie2 collectively contribute to the diversity of inflammatory subtypes seen within the tumor

microenvironment necessary for tumor progression (Arwert et al., 2018). Moreover, single cell sequencing to assess the expansion of immune cell phenotypes and diversity of cell states within the tumor microenvironment demonstrated that there exists evidence for *CCR5* as a gene that is highly correlated with the activation of tumor heterogeneity found in the breast cancer tumor microenvironment (Azizi et al., 2018).

Moreover, several lines of evidence suggest that CCR5 and its ligands appear to participate in the canonical immune check point response. The Programmed Cell Death Protein 1 (CD279 and PD-1) and its ligand PD-1 Ligand (PD-L1) signaling pathway are critical players in immune checkpoints. PD-1 signaling plays an important role in tumor evasion from the innate immune system. In addition, tumor-infiltrating lymphocytes (TILs) serve as a biomarker for predicting responses to PD-L1 blockade therapy. Recent evidence supports that tumors responsive to immunotherapy tend to infiltrate with T cells in response to CTLA-4 and PD-1 antagonism; this process is referred to as a “T cell-inflamed” tumor microenvironment (Gajewski, 2015; Ji et al., 2012; Tumeh et al., 2014). CCL5 upregulation was demonstrated in PD-L1-positive melanoma tumors along with IFN γ and several IFN γ -related genes (Ayers et al., 2017; Taube et al., 2015). Tumor burden and a T cell-inflammatory gene expression were independently predictive of the response to the PD-1 antibody pembrolizumab (Cristescu et al., 2018).

It is also important to analyze the role of MDSC. CCR5^{high} MDSC have higher immunosuppressive activity than CCR5^{low} MDSC (Chang, Lin, Kang, et al., 2012), and when disrupted, MDSC trafficking enhances anti-PD1 therapy (Highfill et al., 2014). As described above, CCL5 promotes not only the influx of CD8⁺ T-cells (Harlin et al., 2009), but also the expression of PD-L1 when associated with increased TILs. Relatedly, the Keynote-028 study demonstrated that the tumors with high PD-L1 and T cell inflammatory gene expression, were associated with a positive outcome from monoclonal antibody therapy (pembrolizumab) (Seto, Sam, & Pan, 2019). Collectively, these studies suggest that overlap exists between the CCR5 non-canonical and canonical immune checkpoint pathways.

Induction of Proliferative signaling, angiogenesis (Ben-Baruch, 2012; Soria & Ben-Baruch) and resistance to cell death (X. Jiao et al.).

Support for the requirement of CCR5 in oncogene-induced cellular proliferation was provided by transgenic studies in which MMTV-PyMT-induced mammary tumors were reduced in *CCR5*^{-/-} mice (Gao, Cazares, & Fish, 2017). CCL5 promotes cellular spreading and tumor migration. Malignant cells produce VEGF upon CCL5 stimulation and by secreting CCL5 recruit CCR5-expressing TAMs (Frankenberger et al., 2015; Robinson et al., 2003). There is also evidence that CCR5 inhibitors can reduce angiogenesis in triple negative breast cancer (TNBC) cell line xenografts (Kang et al., 2009; Wang et al., 2016).

Deregulated cellular energetics and Cancer stem cells.

For cells to undergo uncontrolled division, they require an environment that provides them increased amounts of glucose uptake (Gao & Fish; Gao, Rahbar, & Fish; Martinez-Outschoorn, Peiris-Pages, Pestell, Sotgia, & Lisanti). Analysis of MDA-MB-231 breast cancer cell line demonstrated that CCR5 governs a dramatic (>1,000-fold) increase in

activation of RNA governing ribosomal biogenesis and cell survival signaling pathways (X. Jiao et al., 2018). Furthermore, CCR5⁺ breast cancer epithelial cells revealed features of oncogenic stem cells; forming mammospheres and initiating tumorigenesis with a >60-fold efficiency in mice (X. Jiao et al.).

Preclinical analysis of CCR5 inhibition in metastatic cancer.

CCR5 antagonists (maraviroc and vicriviroc) blocked metastasis of human breast cancer xenografts (MDA-MB-231 cells) in immuno-deficient mice. This process was mediated by the inhibition of the tumor cell homing as well as the enhanced killing of these cells via DNA damaging agents (X. Jiao et al., 2018; X. Jiao, Wang M, Pestell RG, 2019; Velasco-Velazquez et al., 2012). The combination of maraviroc along with nanotechnology targeting CCL5 in the bone marrow augmented anti-tumor immunity (Ban et al.). Both maraviroc and vicriviroc reduced prostate cancer cell metastasis to bone and brain in immune-competent mice (Sicoli et al., 2014). Partly by limiting fibroblast accumulation, maraviroc reduced the growth and spread of colon cancer in orthotopically injected mice (Tanabe, Sasaki, Mukaida, & Baba, 2016). In addition, anti-CCR5 antibody inhibited melanoma (B16) cellular proliferation and MDSC accumulation in tumor tissues (Tang, Jiang, & Liu, 2015). TAK-779 reduced pancreatic cancer cell growth and metastasis with a noticeable reduction in the migration of Tregs into the tumors (Tan et al., 2009).

Evidence has also suggested that chemokines participate in the development of nonalcoholic steatohepatitis (NASH) and thereby progression to hepatocellular cancer (Kutlu, Kaleli, & Ozer, 2018). In this context, maraviroc reduced lipogenesis and β -oxidation in NASH, thereby decreasing insulin resistance and steatosis. Maraviroc therapy decreased the development of NASH and hepatocellular carcinoma in a murine model of NASH (Perez-Martinez et al., 2018) (Ochoa-Callejero et al., 2013).

Clinical studies.

Patients with advanced-stage metastatic colorectal cancer (CRC), who were refractory to standard chemotherapy (Halama et al., 2016), were treated with maraviroc. (The objective response rates in metastatic CRC patients on, or after, the third line of chemotherapy, is typically around 5%–10% to other agents). In this phase 1 pilot (MARACON) study, a reduced proliferation rate was seen in all tumor samples examined. An inverse correlation was also found between “immune CCR5” levels and the maturation status of tumor-infiltrating neutrophils as well as 5-year-survival rates (Ban et al.). From the 11 patients of the core cohort, an additional five patients were given further chemotherapy. Three of these five patients had objective partial responses. These findings compared favorably with historical response rates in this patient population.

Three additional studies which combine a drug and a biologic for CCR5⁺ metastatic cancer have been approved by the FDA. The phase 1 study of pembrolizumab with maraviroc in patients with refractory microsatellite stable (MSS) CRC is supported by Pfizer (Table 1). The second, a phase 2 study is assessing safety and efficacy of vicriviroc in combination with pembrolizumab (MK-3475) in patients with advanced metastatic MSS-CRC. The third is a phase 1b/2 study using carboplatin and leronlimab for CCR5⁺ metastatic triple negative

breast cancer (Table 1). The impact on progression-free survival (PFS) will be assessed. Interestingly, the secondary objectives will assess both the overall response rate (ORR), the number of circulating tumor cells (CTC), and will measure time to new metastasis. As CTC express CCR5 and the number of CTC reflect metastatic tumor burden, the outcome of CCR5 inhibitors on CCR5⁺ CTC may provide a useful surrogate measurement in the future for metastatic cancer studies.

In studies of hepatocellular cancer prevention targeting NASH, liver fibrosis improved after 1 year of therapy with cenicriviroc, leading to the implementation of a phase 3 trial (AURORA) (Tacke). Tropifexor (LJN452) and cenicriviroc are being assessed for safety, tolerability, and efficacy in patients with NASH and liver fibrosis (TANDEM) ([NCT03517540](#)).

Relevant progress has been made in the treatment of bone marrow transplant-related graft vs. host disease (GVHD) with CCR5 inhibitors. A trial has shown maraviroc decreased the incidence of GVHD without incurring a likelihood of disease relapse (Moy et al., 2017). Maraviroc is therefore being assessed for GVHD prophylaxis in pediatric and adult patients who require stem cell transplants ([NCT02167451](#)). Based on the reduction of GVHD in a murine model (Burger, Parker, Guinta, & Lindner, 2018) an open-label, single-arm, Phase II study of the safety and efficacy of leronlimab (Pro-140) is being conducted for prophylaxis of GVHD in patients undergoing reduced intensity conditioning (RIC) allogeneic stem-cell transplantation ([NCT02737306](#)).

The GPCR CCR5 has become an important new target for cancer therapies because of the clear role in metastasis and the anti-tumor immune response of several cancers. The current clinical trials have been open to accrual for less than a year at the time of writing this review. Chemotherapy and radiation induced side effects remain substantial. Given the increased selective cancer cell killing that occurs when CCR5 inhibitors are added to either chemotherapy or radiation (X. Jiao et al., 2018) the potential for reducing the dose and thereby side effects of current cancer therapies through deploying CCR5 inhibitors represents a substantial opportunity to improve patients' quality of life.

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Figure 1.

CCR5 signaling in immune and cancer cells. (A) Schematic representation of a T cell expressing CCR5 with the intracellular signaling cascade activated by ligand. The diverse ligands for CCR5 are shown in green. The pathological response induced by CCR5 on cancer cells is shown in the yellow box. (B) The diverse type of cells expressing CCR5 are shown. (C) CCR5 expression derived from TCGA with square indicating effect of upregulation in cancer vs normal tissue shown as a calorimetric display of fold increase in expression as a hazards ratio. (RNA-seq TCGA data (v2 RSEM values) was downloaded using Fire-browser and FPKM values were log2-scaled and quantile normalized (Mean differences between cancer and normal tissues were calculated). (D) Representative PET-MRI images from a patient receiving chemotherapy (CHT) after participation in the phase 1 pilot MARACON study, in which patients with advanced-stage metastatic colorectal cancer who were refractory to standard chemotherapy (Halama et al., 2016), were treated with maraviroc. White arrow indicates liver with metastatic lesions. Red spots indicate high glucose uptake typical for metastases, and green indicates low background glucose uptake.

Table 1:

Active Clinical Trials using CCR5 Inhibitors

CCR5 Antagonist	Mechanism	Administration	Reference
Maraviroc UK-427857 (Pfizer) Approved for HIV 2007		Maraviroc (days 1–21 of each cycle) + Pembrolizumab (day 1, day 22)	1. Phase 1 study of Pembrolizumab with Maraviroc in patients with refractory microsatellite stable colorectal cancer. NCT03274804 . 2. GVHD, Phase 1 NCT00948753 . Phase 2 NCT02167451 .
Vicriviroc CH 417690 (Merck)	Pyrimidine CCR5 inhibitor	Vicriviroc + Pembrolizumab	1. Phase 2, Vicriviroc in combination with Pembrolizumab (MK-3475) in patients with advanced metastatic microsatellite stable colorectal cancer. NCT03631407 .
Leronlimab (Pro-140) (Cytodyn)	Humanized monoclonal antibody	Weekly self-injection	1. Phase 2 study for CCR5 ⁺ triple negative breast cancer using Carboplatin and Leronlimab NCT03838367 . 2. Phase 2 GVHD NCT02737306 .