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CCR4 Antagonists Inhibit T_{reg} Trafficking into the Tumor Microenvironment

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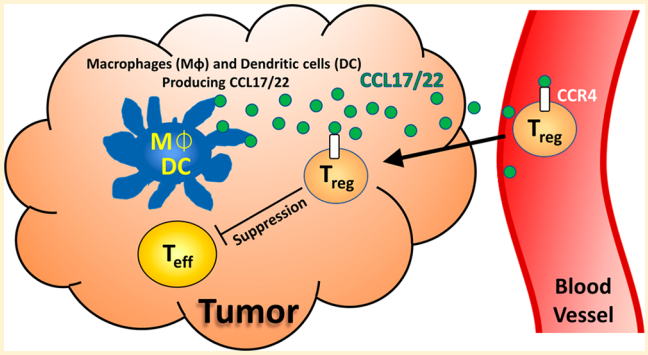
ABSTRACT: Recruitment of naturally occurring suppressive $CD4^+$, $CD25^+$, and $FOXP3^+$ regulatory T cells (T_{reg}) to the tumor microenvironment (TME) has the potential to weaken the antitumor response in patients receiving treatment with immuno-oncology (IO) agents. Human T_{reg} express CCR4 and can be recruited to the TME through the C−C chemokines CCL17 and CCL22. We have recently developed a series of potent, orally bioavailable small molecule antagonists of CCR4 that can block recruitment of T_{reg} into the TME.



KEYWORDS: *CCR4, CCR4 antagonist, T_{reg} migration*

Several pathways exist by which cancer can evade or negatively affect the immune response to the tumor. The discovery of monoclonal antibodies and small molecules that regulate the immune system's response to cancer has reshaped the way scientists design cancer therapies, leading to a plethora of research in the field of immuno-oncology.[1,2] With the FDA approval of checkpoint inhibitors such as ipilimumab or nivolumab and pembrolizumab, which target CTLA-4 or PD-1 respectively, researchers and patients have been given new hope in the battle against cancer.

CCR4 is a G protein-coupled receptor (GPCR) that is highly expressed on the most immunosuppressive $CD4^+$, $CD25^+$, and $FOXP3^+$ regulatory T cells (T_{reg}).[3] CCR4 is known to play a dominant role in the recruitment of T_{reg} into the tumor microenvironment (TME) via the chemokine ligands CCL17 and CCL22 (Figure 1).[4] While T_{reg} can prevent autoimmunity, their recruitment and eventual accumulation in the TME can also cause the functional suppression of $CD8^+$ effector T cells (T_{eff}, Figure 1), leading to a poor patient prognosis.[5] Though earlier CCR4 antagonists were developed to suppress Th2 migration for inflammatory disorders,[6] there have been few reports investigating their use to affect T_{reg} migration into the tumor microevironment.[2]

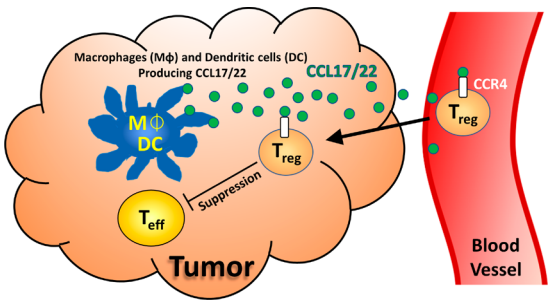


Figure 1. T_{reg}-suppressed tumor microenvironment.

Depending on their binding mode, allosteric CCR4 antagonists can be placed into two distinct classes: Class I allosteric antagonists, which are believed to bind to an extracellular portion of the receptor, and Class II, which bind to an intracellular pocket.[7] In general, Class I antagonists comprise a lipophilic arene and a side chain containing a basic amine, which are both linked to a heteroaromatic core in a 1,3-substitution pattern (Figure 2). Class II antagonists contain sulfonamides that are flanked by both a lipophilic arene and a substituted heteroaromatic ring.

Until late 2017, the most advanced CCR4 antagonist to be involved in clinical trials was a Class II antagonist from GlaxoSmithKline, GSK2239633.[8] Between 2010 and 2011, GSK2239633 entered healthy volunteer studies with asthma as a possible therapeutic indication. Although no dose limiting toxicity was identified, clinical trials for this compound were discontinued based on its low exposure and target engagement in the blood. Additionally, AstraZeneca has recently disclosed two Class II antagonists as preclinical candidates, AZD-1678 and AZD-2098.[9] In 2013, AZD-2098 was licensed to Cancer Research UK for the treatment of kidney cancer; however, no further development has been reported to date.[2]

In addition to small molecule antagonists, a cell depleting monoclonal antibody recognizing CCR4, mogamulizumab (KY-0761, Kyowa Hakko Kirin Co., Ltd.), has been in several clinical trials.[10] In 2014, mogamulizumab received approval for the treatment of hematological malignancies and Cutaneous T-cell Lymphoma (CTCL) in Japan. Data from their recent

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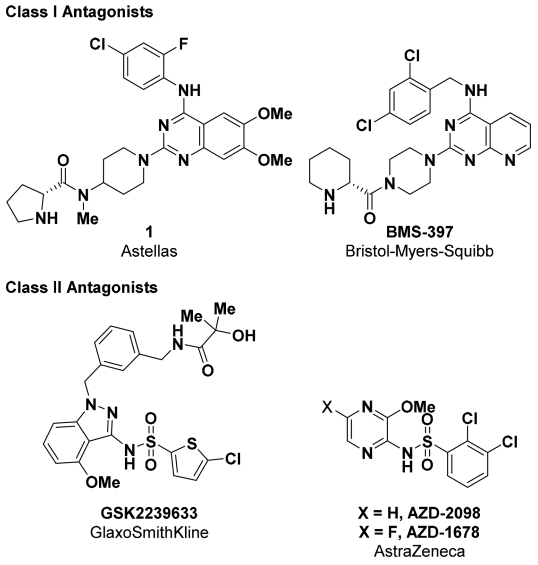

Figure 2. Representative CCR4 antagonists.

phase III multicenter study known as MAVORIC showed a statistically significant increase in progression-free survival and overall response rate for CTCL patients when compared to vorinostat, an FDA approved treatment for CTCL. Based on their results, the FDA has approved the use of mogamulizumab for the treatment of adult patients who have received at least one prior systemic therapy for two subtypes of CTCL, mycosis fungoides (MF) or Sézary syndrome (SS). Significantly, mogamulizumab is the first drug approved by the FDA to specifically treat SS and the first approved biologic to target CCR4.

A depleting antibody that causes ADCC (antibody-dependent cell-mediated cytotoxicity) has a vastly different mechanism of action when compared to a small molecule antagonist and may not be ideal for IO. One possible advantage of targeting CCR4 with a small molecule antagonist when compared to a depleting antibody is its ability to block T_{reg} migration into the tumor without depletion of cells from normal tissues or depletion of beneficial immune cells.

Our efforts to design an orally bioavailable small molecule IO therapy have led us to the discovery of FLX475, a potent and selective CCR4 antagonist that blocks T_{reg} migration to the TME in several tumor models.[11] Phase I trials for FLX475 are currently in progress. Harnessing data from The Cancer Genome Atlas (TCGA), we have found that several human tumor types present high levels of CCL17 and CCL22 gene expression and show an increased infiltration of T_{reg}.[12] These data support the potential for a targeted approach in selecting patient populations.

The field of immuno-oncology has presented the scientific community with new strategies for developing cancer therapies. With several known pathways to target and many more yet to be discovered, our clinical studies could prove pivotal in determining if using small molecule antagonists to inhibit CCR4 will increase patient survival.

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Notes

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ABBREVIATIONS

CCR4, CC chemokine receptor 4; CCL17/22, CC chemokine ligand 17/22; FOXP3, Forkhead box protein 3; CD4/25, Cluster of differentiation 4/25

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