How can we target the CXCL12-CXCR4 axis in oncology patients?

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The CXC–chemokine receptor-4 (CXCR4) pathway plays a role in cancer cell homing and metastasis, and thus represents a potential target for cancer therapy. Although there has been great enthusiasm, to date the promise has yet to be fulfilled. A new class of CXCR4-antagonist cyclic peptides was recently developed by us (PCT/IB2011/000120; EP 2 528 936 B1; US2013/0079292A1). Based on a rational design a small domain was identified as structural overlapping motif common to CXCL12 , the CXCR4-CXCR7 activating ligand, and to vMIP-II, an inhibitory chemokine herpes virus 8 secreted (HHV8). Based on this motif, secured by a cysteine bond , a small library of nineteen peptides was designed and evaluated for the in vitro capability to inhibit the CXCR4 receptor. From the in vitro screening three peptides emerged as powerful antagonists. These peptides were further evaluated in *in vivo* models of B16-hCXCR4 metastasis in immunocompetent mice and in human renal cancer xenograft models. The compound named Peptide R was identified as the most active. With the intent to improve efficacy and biodistribution, stealth liposomes decorated with Peptide R were developed (PL-Peptide R). *In vitro* PL-Peptide R efficiently inhibited CXCR4- dependent migration and *in vivo* significantly reduced lung metastases and increased overall survival in B16-CXCR4 injected C57BL/6 mice. CXCR4 is expressed on immune cells including monocytes, B cells and naive T cells in peripheral blood and CXCL12 acts as a chemoattractant for immature and mature hematopoietic cells; it thus plays an important role in inflammation and immune surveillance of tissues. Effective immune cell access to tumor is controlled by CXCL12. CXCL12 repels tumor-specific effector T cells and recruits suppressive cell populations at tumor sites thus impairing effective immune response. Peptide R, inhibits CXCR4 receptor in cancer cells and reverts the Tregs immunosuppressive function. Targeting the CXCR4–CXCL12 axis thus offers the possibility of affecting CXCR4-expressing primary tumor cells, modulating the immune response, or synergizing with other targeted anticancer therapies.