Preclinical development of the endogenous CXCR4 antagonist EPI-X4 for therapy of cancer and inflammatory diseases

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The CXCR4/CXCL12 axis plays an important role in several processes of the human body, including development, stem cell homeostasis, and immune cell function. Aberrant CXCR4/CXCL12 signaling is involved in diverse pathological conditions such as cancer and inflammatory diseases. The **E**ndogenous **P**eptide **I**nhibitor of C**X**CR**4** (**EPI-X4**) is a 16-amino acid fragment of human serum albumin, which has previously been identified in our lab. This peptide specifically binds to CXCR4, blocks CXCL12-induced signaling and migration, and acts as an inverse receptor agonist. EPI-X4 is a promising candidate for the development of improved analogues for the therapy of CXCR4-associated diseases. We optimized the antagonistic activity of EPI-X4 by combining computational approaches and rational drug design. In addition, we applied different methods to prevent enzymatic degradation and to prolong systemic circulation time *in vivo*. Compared to the wild-type peptide these newly developed EPI-X4 derivatives have a more than 1000-fold increased anti-CXCR4 activity, are stable for several hours in blood plasma, have a prolonged circulation half-life *in vivo*, and are therapeutically active in different mouse models of inflammatory diseases, e.g. topical dermatitis and eosinophilic asthma, and cancer, e.g. Waldenström's macroglobulinemia and acute myeloid leukemia. In addition, therapeutic efficacies of lead derivatives are currently being evaluated in mouse models of other CXCR4-dependent diseases like chronic lymphocytic leukemia, sepsis, and rheumatoid arthritis.