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Disclosing the CXCR4 expression status in multiple myeloma by in vivo molecular imaging

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Chemokine receptors form a large family of G-protein coupled receptors that mediate chemotaxis of cells towards a gradient of chemokines. The chemokine receptor-4 (CXCR4) exerts its biological effect by binding its ligand CXCL12 (or Stromal-cell derived factor-1, SDF-1) which activates downstream pathways, ultimately resulting in altered cell adhesion and cell homing. Physiologically, the CXCR4/CXCL12 interaction plays a pivotal role in the recruitment and homing of hematopoietic stem/ progenitor cells and immune cells. In cancer, CXCR4 expression is associated with tumor dissemination and prognosis. Using lymphomoproliferative disorders as an exemplary CXCR4-expressing cancer entity, we here first report on the preclinical evaluation of [68Ga]Pentixafor-Positron Emission Tomography (Pentixafor-PET) as a method for CXCR4 imaging. Our analyses indicate that [68Ga]Pentixafor binds with high affinity and selectivity to human CXCR4 in vitro. Furthermore, Pentixafor-PET provides images with excellent specificity and contrast when assessed in mice xenografted with human CXCR4-positive lymphoma. Next, we analyzed in vivo CXCR4 expression in a series of fifteen patients with advanced multiple myeloma (MM) who underwent Pentixafor-PET in addition to routine CT (n=1) or FDG-PET/CT (n=14). Nine of fourteen (64%) FDG-PET scans were rated visually positive, whereas eleven of fifteen (73%) Pentixafor-PET scans revealed disease manifestations. Visual comparison of FDG and Pentixafor scans resulted in comparable findings in three (21%) patients, detection of more Pentixafor-PET-positive lesions in seven (50%) patients, detection of more FDG-PET-positive lesions in two (14%) patients, and complementary information in two (14%) patients. Importantly, application of [68Ga]Pentixafor was well tolerated and assessment of blood counts and standard CD34+ flow cytometry did not reveal significant changes associated with tracer application. In summary, our data document the first methodology for clinical in vivo PET imaging of CXCR4 chemokine receptor expression in a larger series of patients with MM. This novel Pentixafor-PET based technology opens a broad field of clinical investigations on the relevance of CXCR4 expression and regulation in the cancer field and beyond.