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Review Article

Theranostic applications of CXCR4-targeted imaging ligands in lymphoma: integrating diagnosis and precision therapy

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Abstract: C-X-C chemokine receptor 4 (CXCR4) is a G protein-coupled receptor implicated in immune regulation, tumor progression, and therapy resistance. In lymphoma, CXCR4 overexpression promotes malignant cell survival via microenvironmental retention and activation of pro-survival pathways, correlating with poor prognosis. Its extracellular localization makes it a strong candidate for selective molecular imaging and targeted therapy. This review summarizes recent advances in CXCR4-targeted agents for lymphoma. Peptide-based radiotracers (^{68}Ga-Pentixafor, [^{18}F]AIF-NOTA-QHY-04, [^{68}Ga]Ga-BL02) and small molecules ([^{64}Cu]AMD3100, [^{18}F]MCFB) offer high specificity and favorable pharmacokinetics for positron emission tomography (PET) and single photon emission computed tomography (SPECT) imaging. Therapeutic strategies include peptide antagonists (BL-8040, Balixafortide), radioligand therapies ([^{177}Lu]Pentixather, [^{177}Lu]Lu-BL02), small-molecule inhibitors (Plerixafor, WK1), and monoclonal antibodies (PF-06747143, Ulocuplomab, LY2624587). These approaches have demonstrated efficacy in reducing tumor burden and enhancing chemosensitivity. Key challenges include off-target uptake due to physiological CXCR4 expression and compensatory signaling via CXCR7. Future directions involve dual-receptor targeting, nanoparticle-based delivery, and integration into precision oncology for both hematologic and solid tumors.

Keywords: C-X-C chemokine receptor 4 (CXCR4), positron emission tomography (PET), single photon emission computed tomography (SPECT), molecular imaging, theranostics, lymphoma

Introduction

Personalized medicine has emerged as a strong candidate on the frontier of medical research. In which, treatment is tailored to the individual patient, moving beyond generalized treatment regimens of the past. Personalized medicine opens many new doors in oncologic research, allowing for more precise targeting of tumor-specific markers treatment. One such receptor of interest is the C-X-C chemokine receptor type 4 (CXCR4), involved in cancer and inflammatory processes.

CXCR4 is a G-protein coupled receptor (GPCR) expressed on the surface of a variety of immune cell membranes, including neutrophils, monocytes, dendritic cells, and leukocytes. The receptor's primary endogenous ligand is stromal cell-derived factor 1 (SDF-1), also known as C-X-C chemokine ligand 12 (CXCL12). The binding of CXCR4 and CXCL12 triggers a conformational change in the receptor that activates multiple intracellular signaling pathways [1]. This signaling mediates critical processes such as cell survival, proliferation, chemotaxis, and immune modulation - all processes that contribute to cancer stem cell survival. Upregulation has been known to occur due to hypoxia, stress, and injury [2].

Of note, this receptor is overexpressed on cancer stem cells in lymphoma and a variety of other cancers. Overexpression has proven to correlate with tumor aggressiveness, metastatic potential, and poor prognosis. Therefore, CXCR4 has been a highly researched target for molecular imaging and possible theranostic applications in both hematologic malignancies and solid tumors. This review describes current research efforts regarding the CXCR4 target in lymphoma theranostics, exploring different types of imaging ligands and modalities, clinical applications, and future prospects.

Biological rationale for CXCR4 targeting in lymphoma

CXCR4 signaling and lymphomagenesis

Chemokine receptors (CXCR) play important roles in immune regulation, development, and disease progression. These G-protein receptors are 7 transmembrane alpha helices with extracellular binding sites for chemokine ligands. In the case of CXCR4, its endogenous ligand is CXCL12. Binding of ligand to the receptor induces a conformational change in the protein, triggering activation of multiple intracellular pathways such as PI3K/AKT, MAPK/ERK, JAK/STAT, NF-kB. Activation of PI3K/AKT promotes cancer cell survival, growth, and drug resistance [3]. MAPK/ERK and JAK/STAT activation regulates production of transcription factors that are involved in angiogenesis, motility, and anti-apoptosis [4]. Together, their activation allows for tumor proliferation and survival as seen in **Figure 1** [2].

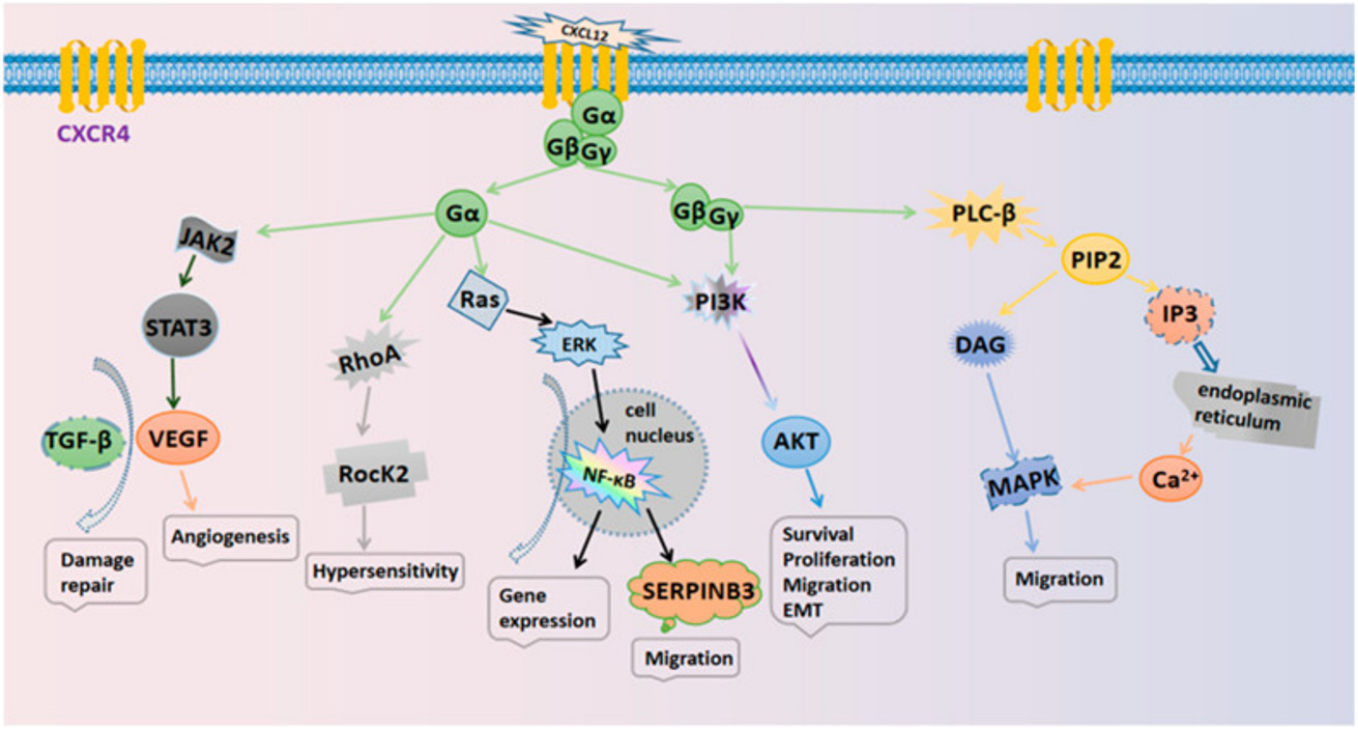


Figure 1. Intracellular signaling pathways activated via CXCL12 binding to CXCR4 transmembrane receptor. Adapted from literature [2].

In lymphoma, overexpression of CXCR4 in malignancies is indicative of poor prognosis, positively correlating with increased disease aggression and relapse [5]. Activation of the receptor supports survival by facilitating the homing and retention of malignant cells within protective microenvironments, such as bone marrow and lymph nodes. This mechanism allows for greater resistance to chemotherapy and promotes cell survival [6]. This makes CXCR4 a biomarker of interest both for diagnostic purposes and for targeting therapeutic treatments.

Several ongoing studies have demonstrated that pharmacologic inhibition of CXCR4 can impair tumor migration, reduce metastatic burden, and sensitize malignant cells to conventional therapies [2]. Interference with the CXCR4/CXCL12-activated processes remains a promising direction for research regarding lymphoma theranostics. These findings support the rationale for integrating CXCR4-targeted agents into lymphoma treatment regimens.

Target accessibility and clinical relevance

A desirable characteristic of CXCR4 that makes it an appealing target in oncology is its extracellular localization on the plasma membrane, allowing for efficient binding by imaging agents and therapeutic agents. This accessibility facilitates noninvasive molecular imaging, as well as selective delivery of radiotherapeutics and inhibitors, with minimized off-target effects.

CXCR4 is widely expressed on the surface of immune cells, such as T and B cells, dendritic cells, monocytes, and neutrophils, in addition to cancer stem cells [2]. Its expression is modulated in response to hypoxia, tissue injury, and inflammatory signals, which can further enhance its upregulation in the tumor microenvironment. The receptor's prevalence in hematologic and solid malignancies has made it a focus in the development of precision medicine. Advances in ligand engineering have developed agents capable of differentiating malignant from non-malignant tissues, setting the stage for targeted theranostic strategies.

Imaging ligands

Peptides

Peptide ligands have several advantages both in therapeutic and diagnostic settings when compared to other ligand bases. This is in part due to their small size, about 1-5 kDa, allowing for favorable pharmacokinetics, including rapid tissue diffusion, tumor penetration, and faster clearance [7]. This allows for improved image quality, with less background signal. Faster penetration and clearance are attractive for same-day imaging both in diagnosis of disease but also in evaluating efficacy of treatment. Peptide ligands offer modularity, allowing for selective engineering to enhance receptor specificity and affinity. This flexibility also enables radiolabeling with various positron or gamma-emitting isotopes [8]. For these reasons, peptide ligands remain a promising candidate in ongoing clinical research regarding personalized medicine.

^{68}*Ga-Pentixafor:* Currently, gallium-68 Pentixafor (^{68}Ga-Pentixafor), is the leading peptide ligand in lymphoma

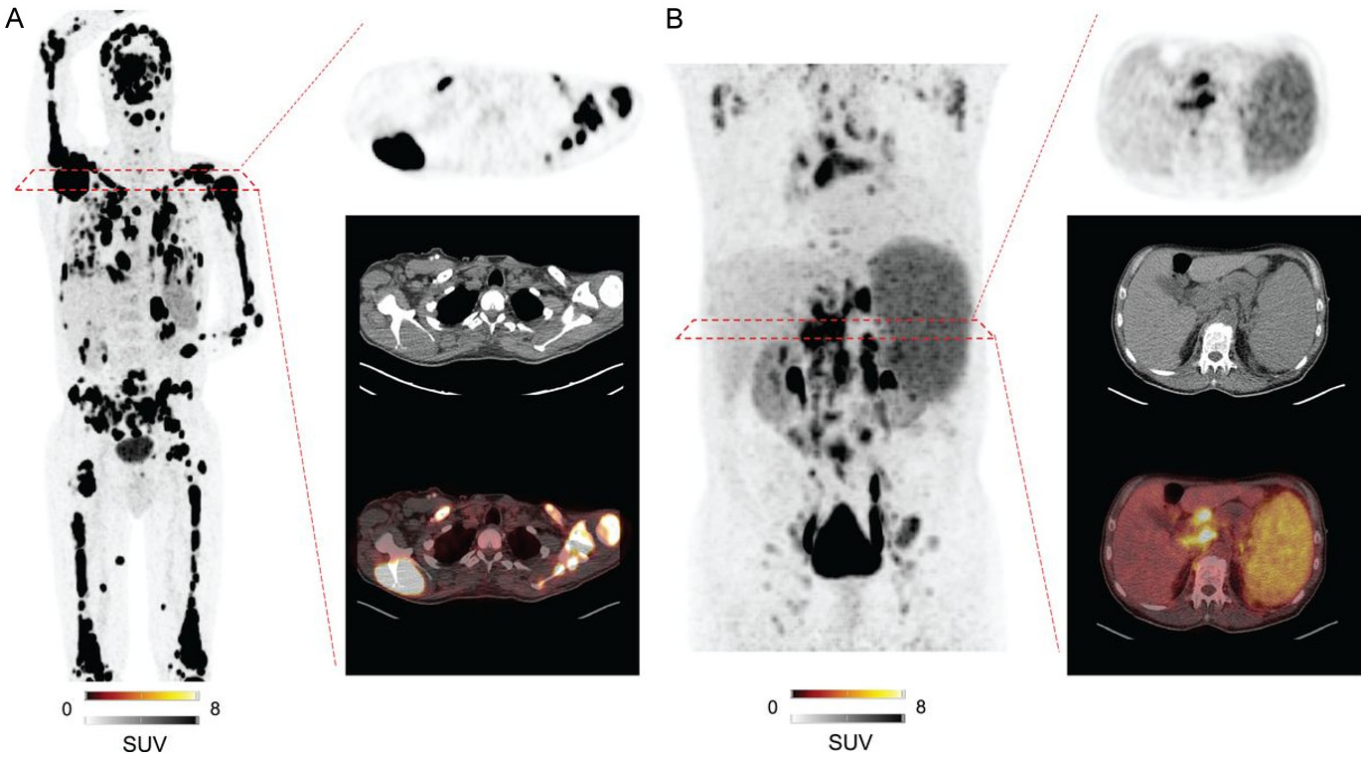


Figure 2. Maximum-intensity projections of patients with hematologic malignancies imaged with CXCR4-directed ^{68}Ga-Pentixafor imaged via PET, CT, and PET/CT. This patient has been diagnosed with multiple myeloma and mantle cell lymphoma. Substantially low background activity allowed for precise determination of disease sites. Adapted from literature [9].

imaging research. This has been under comparison to the current gold standard radiotracer in practice, 2-^{18}F-fluodeoxyglucose ([^{18}F]FDG), a small molecule. Ga-Pentixafor is studied for its potential use in single-photon emission computed tomography (SPECT) and positron emission tomography (PET) imaging of lymphoma. This cyclic pentapeptide has been designed for early assessment of treatment response and early metastasis detection. Specifically, it has been used to detect lesions in patients with multiple myeloma, marginal zone lymphoma, and some solid tumors using PET and CT imaging as seen in **Figure 2**. Pentixafor was desirable in these cases due to its high selectivity for the CXCR4 receptor as well as its renal excretion [9]. This performed superior to the [^{18}F]FDG PET radiotracer in lymphoma with a higher uptake, indicating use for both diagnosis and prognosis [10].

[^{18}F]AIF-NOTA-QHY-04: Radiotracer [^{18}F]AIF-NOTA-QHY-04 is a novel cyclic peptide in development for use in lymphoma imaging. In vitro, this molecule proved to have high serum stability and CXCR4-receptor affinity, ideal for repeat imaging for diagnosis and monitoring of disease. [^{18}F]AIF-NOTA-QHY-04 is a promising candidate for PET imaging due to its rapid clearance from off-target tissues, such as liver, lungs and spleen, allowing for low background signal and increasing clarity of metastatic lesions as seen in **Figure 3**.

The incorporation of the radiolabel fluorine-18 enables high-yield synthesis and optimizes production and distribution due to its relatively long half-life. In regard to imaging quality, the fluorine-18 radiolabel allows for improved detection of target lesions due to lower energy positron particles when compared to other radiotracers [11]. The [^{18}F]AIF-NOTA-QHY-04 radiotracer holds strong potential as an imaging agent in lymphoma and other cancers.

[^{68}Ga]Ga-BL02: [^{68}Ga]Ga-BL02 is a gallium labeled cyclic peptide derived from LY2510924. This molecule has been designed as a targeted PET imaging agent for visualization of CXCR4-overexpressing malignancies. When compared to other gallium labeled radiotracers such as ^{68}Ga-Pentixafor in preclinical studies, [^{68}Ga]Ga-BL02 demonstrated superior tumor uptake and reduced off-target accumulation in hepatobiliary and gastrointestinal tissues [12]. It was used in combination with [^{177}Lu]Lu-BL02 as a radiotheranostic pair to diagnose, stage, and treat mantle cell lymphoma. These promising results warrant further research into clinical translation of [^{68}Ga]Ga-BL02.

Small molecules

Small molecule-based ligands represent another class of CXCR4-targeted imaging agents. Their small size facilitates rapid diffusion, tumor penetration, rapid clearance, and ease in passing biological barriers to accomplish this. This is dependent on the molecule's specific lipophi-

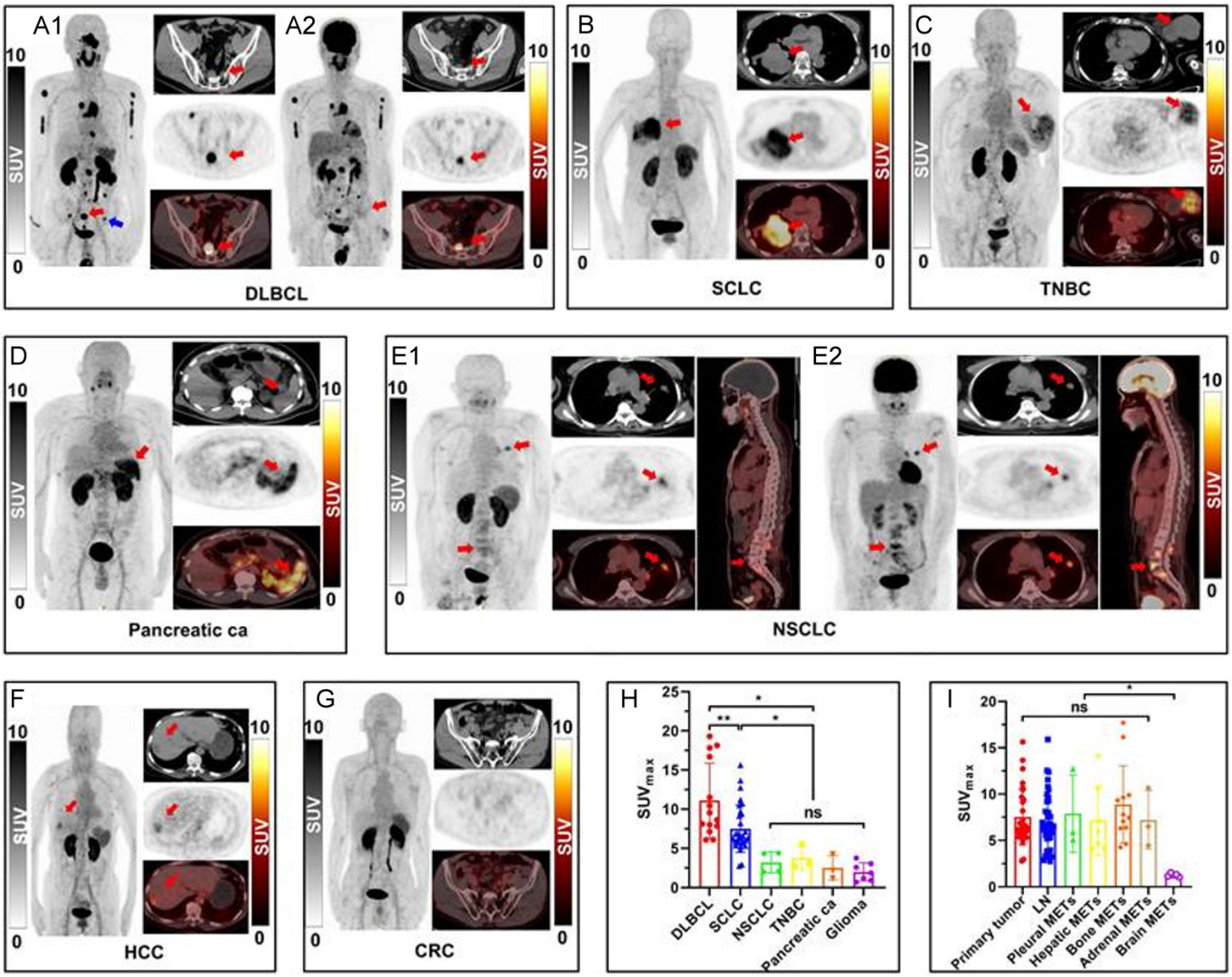
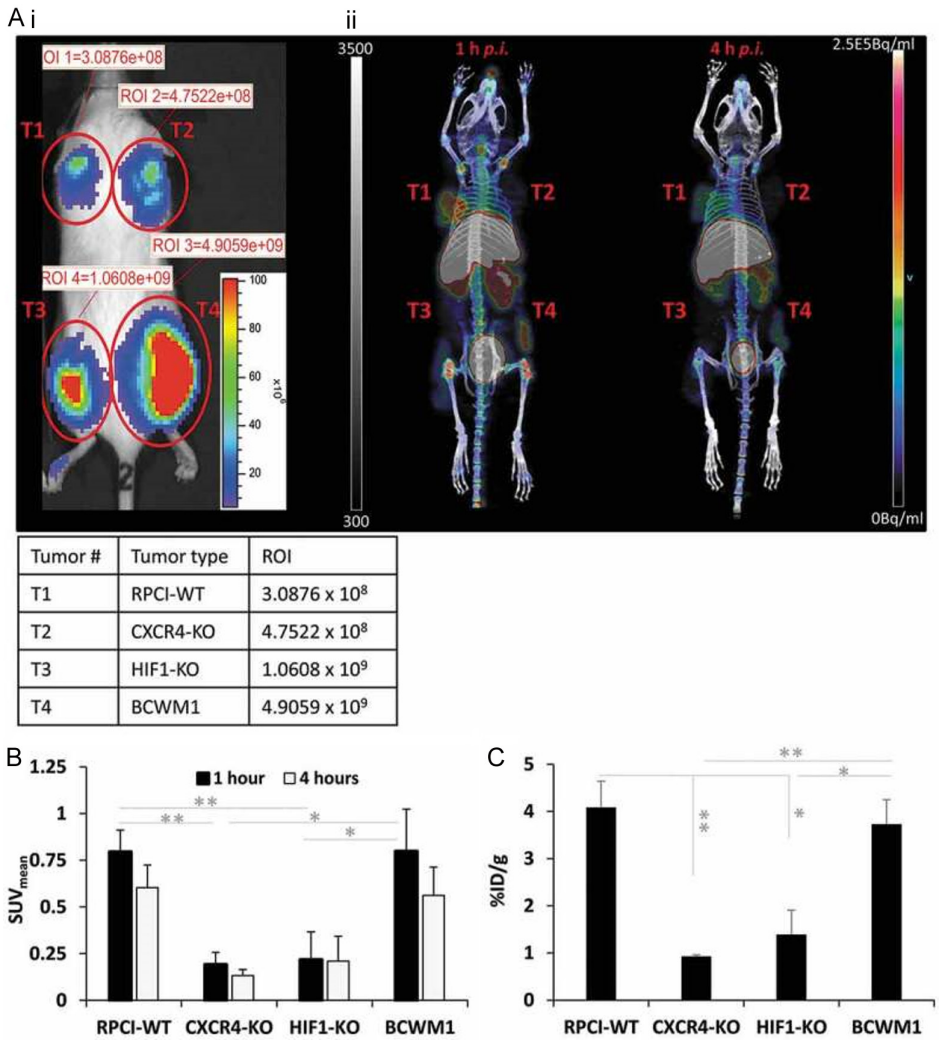


Figure 3. [^{18}F]AlF-NOTA-QHY-04 PET/CT scanning of patients with hematologic malignancies or different solid tumors. A-G. For each case, maximum-intensity projections (MIP) are presented on the left, with corresponding transaxial CT (top), PET (middle), and fused PET/CT (down) images shown on the right. A2 and E2 are [^{18}F]FDG PET/CT images, the others are [^{18}F]AlF-NOTA-QHY-04 PET/CT images. Red arrows indicate CXCR4-positive tumor lesions; the blue arrow indicates the inguinal lymph node. H. SUV max of [^{18}F]AlF-NOTA-QHY-04 in 6 types of tumor patients. I. Comparison of SUV max values in primary tumors and metastases of 30 SCLC patients. ns, not statistically significant. *P < 0.05, **P < 0.01. Adapted from literature [11].

licity and charge. Both characteristics can be tailored to specific targets, an attractive feature of this ligand [13]. Small molecules could bind at multiple sites on protein receptors, allowing for enhanced accumulation and detection sensitivity [14]. Additionally, small molecules have a low immunogenicity, making it preferable for a multi-use imaging agent to ensure patient safety.

[^{64}Cu]AMD3100 (Plerixafor): [^{64}Cu]AMD3100, also known as Plerixafor, is a well-characterized small molecule radiotracer developed for imaging CXCR4-expressing tumors as seen in **Figure 4** [15]. It is a bicyclam derivative that exhibits high binding affinity for CXCR4 and has been validated in several preclinical lymphoma models. Notably, [^{64}Cu]AMD3100 has shown significant accumulation in immune-related organs such as the spleen, lymph nodes, and bone marrow-reflecting both its on-target activity and challenges in differentiating malignant from physiological CXCR4 expression [16]. The function of this therapy as an adjuvant interferes with adhesive cellular interactions and allows mobilization of hematopoietic stem cell. This has been FDA approved and used for autologous transplant [17].

[^{18}F]MCFB: The cyclam-based peptide radiotracer, [^{18}F]MCFB, is under development as a CXCR4-targeted imaging agent in hematologic malignancies, including lymphoma. This radiotracer leverages ADM3465 as reference due to established high affinity and selectivity. In vitro assays demonstrated CXCR4-dependent cellular uptake of the radiotracer with knockdown of the receptor decreasing uptake and increased radioligand uptake in the setting of hypoxia, consistent with CXCR4 expression. The incorporation of a fluorine-18 radiolabel was selected



Tumor #	Tumor type	ROI
T1	RPCI-WT	3.0876×10^8
T2	CXCR4-KO	4.7522×10^8
T3	HIF1-KO	1.0608×10^9
T4	BCWM1	4.9059×10^9

Figure 4. PET imaging with ^{64}Cu-AMD3100 detects localized WM tumor cells with high CXCR4 expression *in vivo*. Adapted from literature [15].

over copper due to reduced off-target hepatic uptake. This translated to in vivo PET imaging, as [^{18}F]MCFB demonstrated high tumor-to-background localization allowing for tumor detection, as seen in **Figure 5** [18]. This CXCR4-targeting tracer has diagnostic potential in hematologic malignancies.

Therapeutic agents

Beyond diagnostic imaging applications, CXCR-4-targeted ligands are increasingly being developed for therapeutic use. Examples of these consist of radioligand therapies, chemokine receptor antagonists, and monoclonal antibodies. These agents exploit the overexpression of CXCR4 on malignant cells to selectively deliver therapy or inhibit critical signaling pathways that promote tumor survival and drug-resistance.

Peptide-based therapeutics

Peptide ligands can be used not only in imaging agents, but also as therapeutic tools given their structural similarity to endogenous ligands and favorable biocompatibility. Their ability to mimic natural ligands allows for high affinity and specificity to the receptor of interest. The similarity to endogenous molecules means the peptide ligands often have lower off-target effects and lower immune response, both goals in therapeutic treatments [19]. High specificity and affinity support site-specific delivery of the molecule to the target tissue. Versatility of design allows peptides to play a variety of potential roles including agonists, antagonists, or inhibitors dependent upon composition [20]. This translates to peptide ligands with different uses such as imaging agents, as previously discussed, or as therapeutic agents.

BL-8040 (Motixafortide): BL-8040, also known as Motixafortide or BKT140, is a cyclic peptide currently under clinical evaluation. It functions as an antagonist at the CXCR4 receptor. By blocking downstream signaling pathways, BL-8040 effectively mobilizes hematopoietic stem cells (HSCs) for autologous transplantation. In addition, BL-8040 has shown antineoplastic activity in vitro and in vivo models of hematologic malignancies, including multiple myeloma, lymphoma, and leukemia, with significant apoptosis [21].

BL-8040 has also been researched in combination with other current chemotherapeutic agents. It showed a synergistic effect when used in combination with rituximab with enhanced apoptosis in lymphoma cells both in local tumors and bone marrow [22]. This dual mechanism-mobilization of immune and tumor cells and inhibition of pro-survival signaling-makes BL-8040 a promising candidate for combination therapy.

Balixafortide (POL6326) and SPX5551 (POL5551): Derived from the horseshoe polyphemus peptide, Balixafortide, also known as POL6326 (Polyphor Ltd.), is another synthetic cyclic peptide undergoing research to determine its efficacy in lymphoma treatment. Balixafortide has proven to bind to CXCR4 with high affinity and selectivity [23]. Upon binding, Balixafortide acts as an antagonist, inhibiting beta arrestin recruitment and calcium influx. This blocks activation of the pERK/pAKT pathways and, therefore, SDF1-dependent chemotaxis [24].

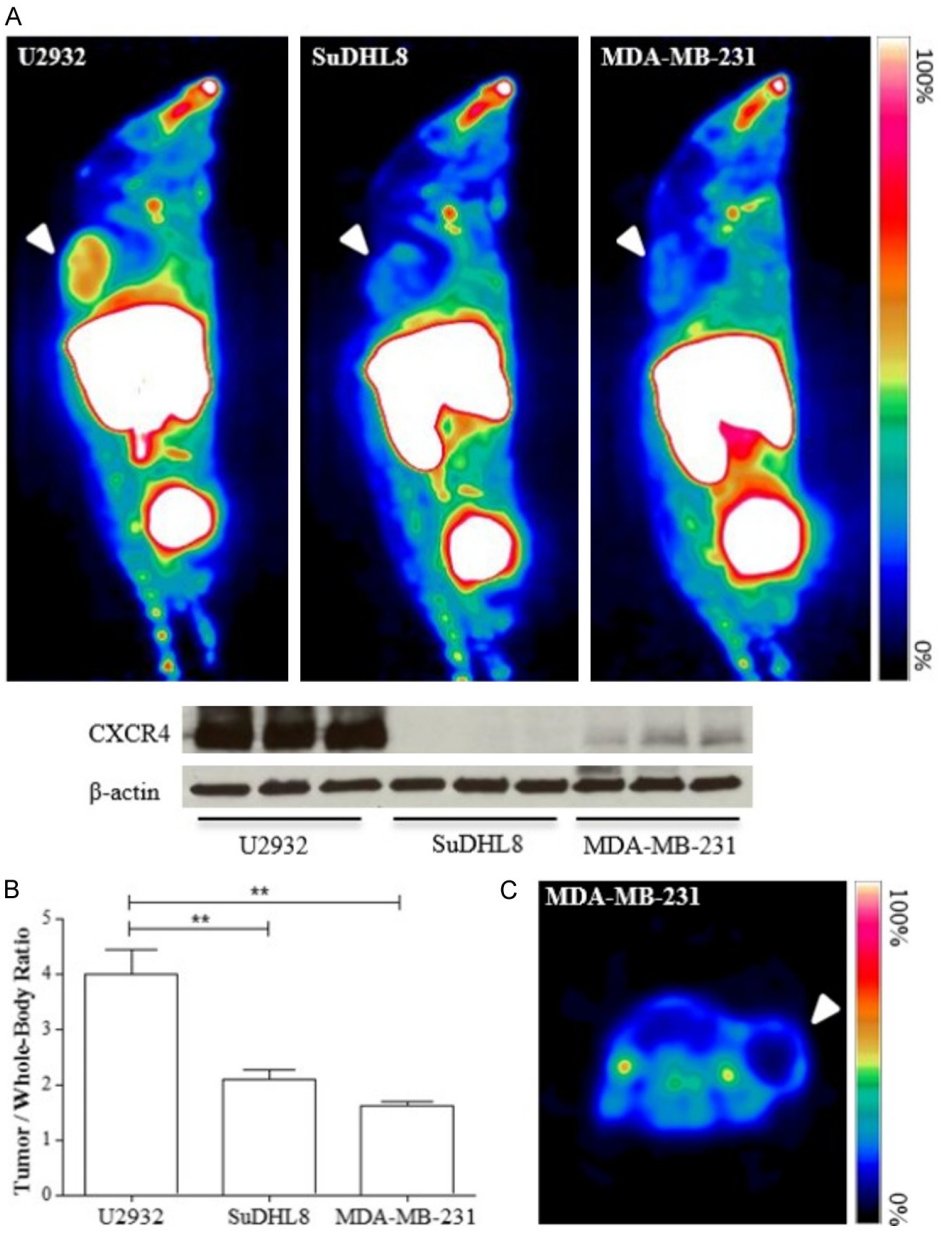


Figure 5. [^{18}F]MCFB discriminates differential CXCR4 expression *in vivo*. Adapted from literature [18].

SPX5551 (POL5551), a peptidomimetic macrocycle and potent CXCR4 inhibitor developed as a structural analogue of Balixafortide (POL6326). Like Balixafortide, SPX-5551 acts as a selective antagonist of the CXCR4 receptor, disrupting the CXCR4/CXCL12 axis which is implicated in chemotherapy resistance and tumor microenvironment protection. Preclinical evidence suggests such CXCR4 inhibitors can synergize with various chemotherapeutic agents, and it has also been researched in combination therapies with existing chemotherapy drugs. Both SPX5551 and Balixafortide belong to the peptidomimetic macrocycle chemical class and act as antagonists at the CXCR4 receptor. SPX5551 was found to the effects or potency of current lymphoma treatments including ibrutinib, copanlisib, rituximab, and R-CHOP. In mantle cell lymphoma, this peptide inhibited AKT and NF-kB signaling leading to increased apoptosis induction [25].

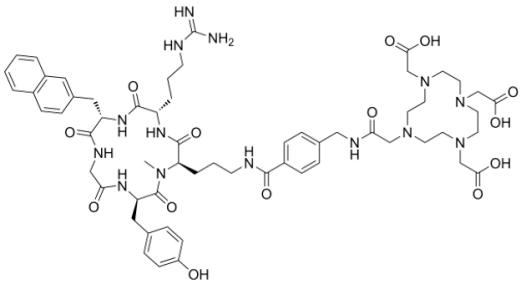
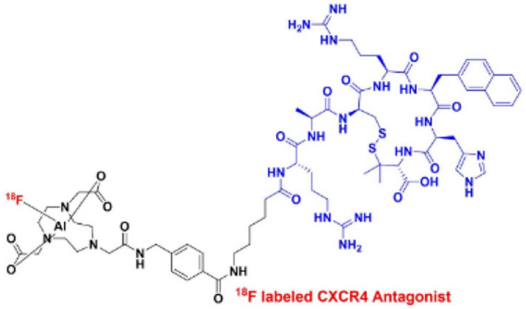
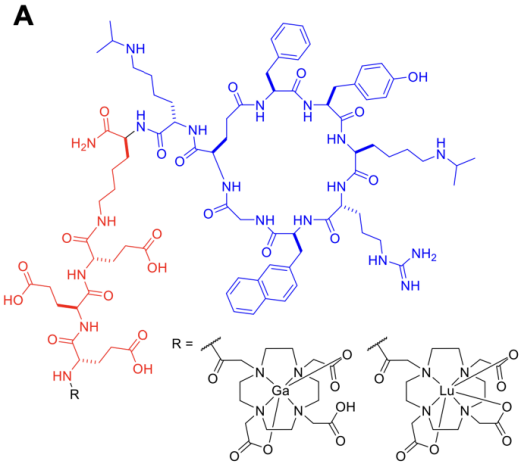
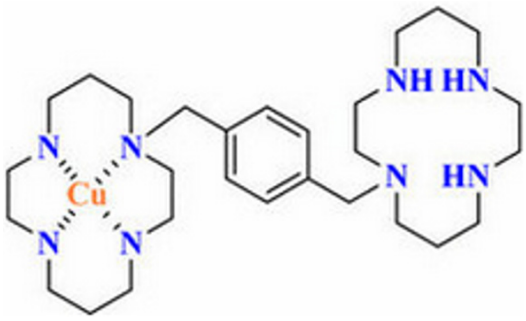
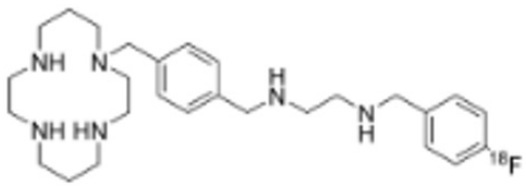
[^{177}Lu]Pentixather: [^{177}Lu]Pentixather is a structural analog of the imaging molecule ^{68}Ga-Pentixafor, designed for targeted radionuclide therapy. Compared to its diagnostic counterpart, Pentixather proved to have higher CXCR4 affinity and prolonged tumor retention. This is partially attributed to its increased lipophilicity relative to Pentixafor, leading to delayed clearance from circulation and background tissues [26]. In both preclinical and early-phase clinical studies, [^{177}Lu]Pentixather exhibited effective tumor localization and minimal off-target toxicity. This molecule has the ability to destroy malignant cells in addition to freeing them from bone marrow to peripheral blood [27]. This feature allows sensitization of cancer stem cells (CSCs) to other therapies, proving potential use of [^{177}Lu]Pentixather in combination with current treatments [28].

[^{177}Lu]Lu-BL02: [^{177}Lu]Lu-BL02 is the second radiotracer in the CXCR4-targeting radiotheranostic pair, developed along with [^{68}Ga]Ga-BL02 to identify and treat lymphomas. Currently under evaluation in clinical trials for treatment of mantel cell lymphoma, [^{177}Lu]Lu-BL02 demonstrated high tumor precision relative to off-target tissues. [^{177}Lu]Lu-BL02 showed high heterogeneous binding to the mantle cell lymphoma (MCL) graft. Increased specificity is necessary for high therapeutic index and minimal unwanted adverse effects that are seen with standard chemotherapies. Clinical trials have indicated that additional doses of the radiotracer could enhance effectiveness and duration of treatment. The combination therapy with [^{177}Lu]Lu-BL02 and [^{68}Ga]Ga-BL02 offers a dual diagnostic and therapeutic tool for hematologic malignancies [12].

Small molecule-based ligands

Small molecules were the entry into targeted therapeutics and personalized medicine. These are low molecular weight compounds with stable structures allowing for interaction with specific targets and biological barrier

Table 1. The representative CXCR4-targeted ligands

Ligand	Structure
Peptide imaging ligands	
^{68}Ga-Pentixafor	
[^{18}F]AlF-NOTA-QHY-04	
[^{68}Ga]Ga-BL02	
Small molecule imaging ligands	
[^{64}Cu]AMD3100 (Plerixafor)	
[^{18}F]MCFB	

penetration. Small molecules have a higher oral bioavailability allowing for self-administration. Their small size allows for gastrointestinal (GI) tract absorption and avoiding adverse immune responses [29]. Small molecule production also has advantages in cost of production as they can be easier to synthesize and scale when compared to ligands such as monoclonal antibodies [30]. In CXCR4-targeted therapy, several small molecule antagonists have shown utility in both stem cell mobilization and direct antitumor activity.

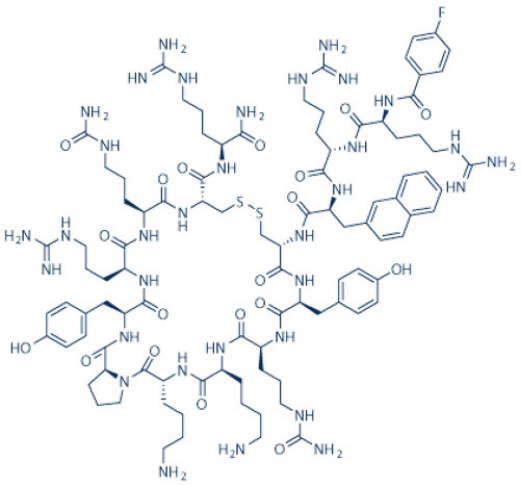
Plerixafor (AMD3100): Plerixafor is a small molecule CXCR4 inhibitor approved by the FDA (U.S. Food and Drug Administration) in 2008 for stem cell mobilization in combination with granulocyte colony-stimulating factor (G-CSF) for patients with non-Hodgkin lymphoma and multiple myeloma. Disruption of the CXCR4/CXCL12 interaction frees CD34+ HSCs from bone marrow, allowing mobilization to peripheral blood. Plerixafor is used for autologous transplant in non-Hodgkin's lymphoma and multiple myeloma [31].

In lymphoma, this small molecule has also been studied in combination with rituximab, a current therapy. Plerixafor worked synergistically to reduce diffuse B-cell lymphoma proliferation, proven by decreased CXCR4 fluorescence intensity post-combination treatment. Plerixafor also proved to reduce drug resistance when used in combination with the R-CHOP regimen used to treat B-cell lymphomas [30]. Plerixafor currently remains under research to determine its full potential as a small molecule inhibitor in therapeutic treatment.

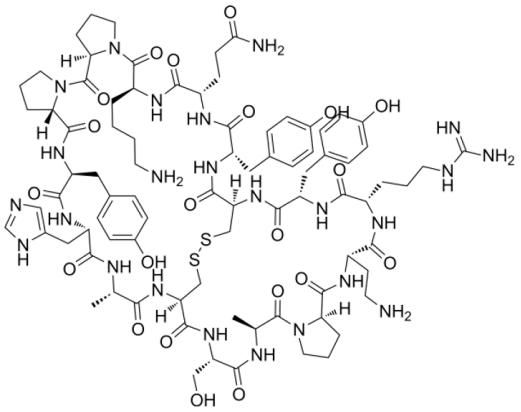
WK1: WK1 is a small molecule CXCR4 antagonist designed to treat lymphoma. Blocking cell signaling pathways resulted in reduced expression of JNK-, ERK1/2-, and NFκB/BCR-target genes. Inhibition of JNK signaling decreases cell proliferation and differentiation. The ERK pathway functions to promote cell survival via resistance to apoptosis, inhibition allows for pro-apoptotic effects. Activation of the NFκB/BCR pathway upregulate anti-apoptotic genes and drives cellular proliferation via induction of cell cycle regulators

zPeptide therapeutic agents

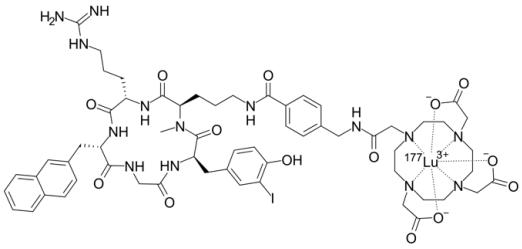
BL-8040 (Motixafortide)



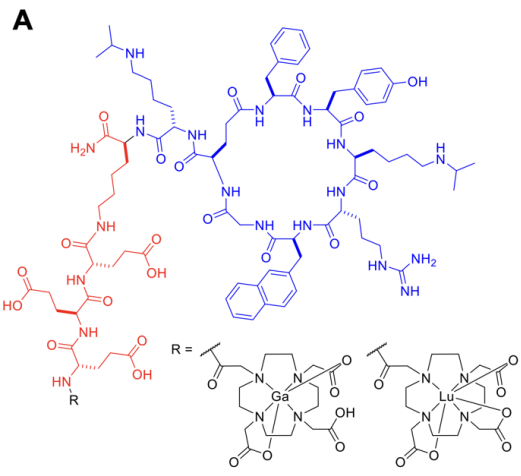
Balixafortide (POL6326)



[^{177}Lu]Pentixather



[^{177}Lu]Lu-BL02



[32]. This small molecule exerted pro-apoptotic effects in vitro on CXCR4 expressing lymphoma cells, making it a promising candidate for in vivo research.

Monoclonal antibodies (mAbs)

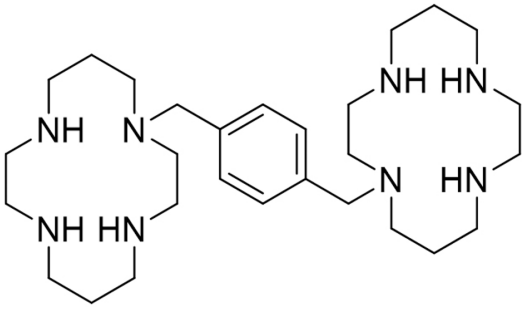
At the forefront of targeted therapy research is monoclonal antibodies. Antibodies can be designed to recognize specific antigens on tumor cells allowing for precision targeting and delivery of the attached drug or therapy [33]. CXCR4-targeted antibodies can block receptor-ligand interactions, induce antibody-dependent cellular cytotoxicity, or be used as a therapeutic delivery tool. In addition, increased precision limits off-target effects commonly seen with use of traditional chemotherapy treatments that have a more systemic effect [34]. To minimize potential unwanted immune activation, monoclonal antibodies are completely humanized or chimeric proteins [35].

PF-06747143 (Pfizer): PF-06747143 is a fully humanized IgG1 monoclonal antibody developed by Pfizer. It functions as an antagonist to block CXCL12 binding to CXCR4 and inhibit signaling pathway activation to prevent promotion of cell survival. This antibody demonstrated preclinical efficacy in hematopoietic stem cell (HSC) mobilization and inducing cytotoxicity via antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) in non-Hodgkin lymphoma and multiple myeloma models [36].

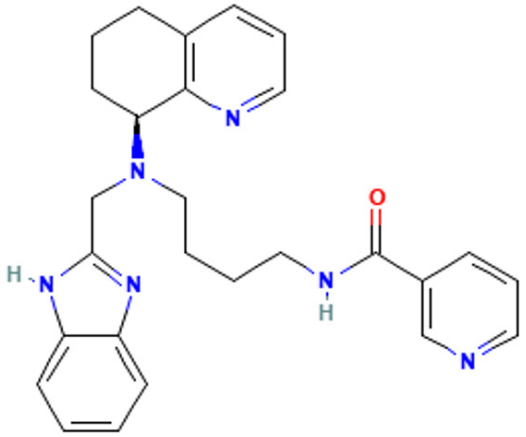
Ulocuplomab (MDX1338): Often compared to PF-06747143, Ulocuplomab, also known as MDX1338, is another widely studied humanized monoclonal antibody. This monoclonal antibody functions by inhibiting CXCL12 from interacting with CXCR4, diminishing downstream cell signaling involved in cell survival [37]. Ulocuplomab exhibited induced apoptosis in multiple tumor models, including non-Hodgkin's lymphoma and multiple myeloma, via reactive oxygen species (ROS)-dependent mechanisms, independent of caspase or complement activation [38]. Ulocuplumab and Ibrutinib, a Bruton's tyrosine kinase inhibitor, are being stud-

Small molecule therapeutic agents

Plerixafor (AMD3100)



WK1



ied in combination to treat B-cell malignancies. The monoclonal antibody has been proven to sensitize cells to the Ibrutinib therapy, shortening response time to treatment [39].

LY2624587 (Eli Lilly): LY2624587 is a monoclonal antibody developed by Eli Lilly. This molecule acts as a CXCR4 antagonist, blocking CXCL12 binding to CXCR4, inhibiting signals involved in cell migration and activation of the MAPK (mitogen-activated protein kinase) and AKT (protein kinase B) pathways. In vitro and in vivo, this monoclonal antibody downregulated CXCR4 density on the cell surface and exhibited dose-dependent apoptosis and tumor growth inhibition in human hematologic cancer cells [40]. Clinical trials are still being conducted on LY2624587 to determine the mechanism it induces apoptosis by.

The representative CXCR4-targeted ligands are listed in **Table 1** and compared in **Table 2**.

Challenges and future directions

CXCR4 remains a strong target of interest in lymphoma research with a multitude of imaging and therapeutic agents in development. The availability and specificity of this receptor and the flexibility of ligands makes it the ideal candidate for targeted therapeutic research. Despite its promising potential, there are some limitations when considering use of CXCR4 imaging ligands. First, CXCR4 is not specific to cancer sites as the receptor is heavily expressed in a variety of immune cells in healthy tissues. This can create problems during imaging due to increased accumulation at off-target sites, such as immune organs like the liver, kidneys, and spleen [41]. A higher background signal can mask tumor detection and limit the therapeutic window for radioligands. It is also important when considering therapeutic treatment with these tracers, as off target toxicity is possible and has been noted in previously reviewed compounds. Peptide based ligands have a higher physiological uptake in the liver, spleen, and kidneys interfering with detection of liver metastases. Small molecules have an even higher uptake in the liver, as well as in red marrow, reducing the possible therapeutic index. Off-target interactions in small molecules are more concerning because of their higher accumulation in non-target organs due to an increased lipophilicity. To attempt to avoid these off-target interactions, researchers in the field have taken several different approaches. Introducing albumin binders allows for prolonged circulation time allowing for more background clearance. Another method involves engineering for a more rapid renal clearance to reduce hepatic exposure.

In addition to engineering the molecules themselves, mitigation strategies regarding dosage and timing can also be optimized. Pre-dosing with an unlabeled ligand before the imaging agent allows for blockage of physiological CXCR4 sites, reducing background uptake. Adjusting dosage based on imaging results can help eliminate background signal or ensure a higher saturation of CXCR4. When considering the timing of collecting images, delayed imaging allows clearance of the tracer from non-target tissue to reduce background signal.

Another limitation of CXCR4 is due to its ligand, SDF-1 or CXCL12, which can bind to both CXCR4 and CXCR7. This could allow for potential roundabout activation of cellular pathways as this second site acts as a scavenger, bypassing the CXCR4 receptor altogether. CXCR7 signals via β-arrestin mediated pathways leading to enhanced cell survival and drug resistance. This receptor mediates the adhesion of lymphoma cells to stromal cells in protective niches (e.g., bone marrow, lymph nodes), physically shielding them from therapeutic agents. CXCR7 expression has also been found to be upregulated following CXCR4-targeted therapy.

A further area of interest that has not been widely explored is on ligands targeting both the CXCR7 receptor and CXCR4 or the use of potential CXCR7 targeted molecules in combination with current CXCR4 targeted molecules.

Table 2. Comparative analysis of key CXCR4-targeting agents

Agent	Affinity	Pharmacokinetics	Advantages	Disadvantages
^{68}Ga-Pentixafor	Nanomolar binding affinity (~5-10 nM), minimal off-target binding to CCRs	Rapid blood clearance, predominant renal excretion, and low nonspecific background uptake	Strong tumor-to-background, rapid imaging workflow, theranostic pairing with Pentixather	Variable uptake across histology, potential inflammation-related signal, not universally approved/standardized
[^{18}F]AlF-NOTA-QHY-04	Nanomolar range binding affinity, high specificity for CXCR4	Rapid blood clearance, predominant renal excretion, and high tumor-to-background contrast	Longer half-life of 110 minutes, high tumor to background contrast, lower hepatic uptake	Kidney/bladder dose higher, marrow uptake complicates analysis, Risk of false positives in inflammation, marrow-rich tissues
[^{68}Ga]Ga-BL02	Nanomolar range binding affinity	Rapid blood clearance, renal excretion, and high tumor-to-background contrast	Reduced kidney uptake improves lesion detectability in abdominal regions Generator-based ^{68}Ga labeling allows same-day synthesis and imaging	Shorter half-life of 68 minutes, Physiological uptake in hematopoietic organs can complicate interpretation in patients with marrow involvement
[^{64}Cu]AMD3100 (Plerixafor)	Nanomolar range binding affinity	Rapid uptake, hepatic and renal excretion	Longer half-life of 12.7 hours allows for delayed imaging, FDA approved for stem cell mobilization	High liver uptake, higher radiation exposure due to longer half-life, cyclotron dependence
[^{18}F]MCFB	Low nanomolar range binding affinity	Rapid blood clearance, renal excretion, and high tumortobackground contrast	Longer half-life of 110 min, low nonspecific uptake in brain and muscle, stable monocyclam scaffold	Physiological uptake in hematopoietic organs can complicate interpretation in patients with marrow involvement, requires cyclotron for production, higher radiation dose to kidneys/bladder
BL-8040 (Motixafortide)	Sub-nanomolar range binding affinity	Rapid absorption, prolonged half-life, and sustained CXCR4 blockade, half-life of 10-12 hours	Very high binding affinity, long half-life allows for less frequent dosing, effective stem cell mobilization, antitumor and immunomodulatory effects	Injected subcutaneously, requires clinical supervision for dosing, reported adverse events include injection-site reactions, transient leukocytosis, and mild gastrointestinal symptoms, high cost
Balixafortide (POL6326)	Nanomolar binding affinity for CXCR4 (< 10 nM), negligible activity against CXCR7	Given intravenously, rapid distribution, cleared via renal and hepatic pathways, half-life of 30-50 hours	High affinity and selectivity, long half-life supports sustained receptor blockade and less frequent dosing, strong mobilization of hematopoietic stem cells, well tolerated in clinical studies	IV administration limits outpatient/self-administration, reported adverse events include infusion-related reactions, transient leukocytosis, and mild gastrointestinal symptoms
[^{177}Lu]Pentixather	Low nanomolar range binding affinity (~5-10 nM)	Rapid blood clearance, strong uptake in CXCR4-expressing tissues, and predominant hepatobiliary excretion, 6.7-day half-life	High affinity, theranostic pairing with [^{68}Ga]Pentixafor, prolonged radiation to tumor sites, rapid blood clearance, strong tumor uptake	Organ toxicity risk, production requires specialized radiopharmacy infrastructure, limited therapeutic window
[^{177}Lu]Lu-BL02	Low nanomolar range binding affinity (~5-10 nM)	Intravenous injection, rapid systemic distribution, mixed hepatobiliary and renal clearance, 6.7 day half life	High CXCR4 affinity, sustained radiation delivery, rapid blood clearance, novel option for relapsed/refractory MCL AML, MM	Organ toxicity risk limits therapeutic window, requires specialized radiopharmacy infrastructure for production, limited clinical data from mantel cell lymphoma xenograft models, narrow therapeutic window
Plerixafor (AMD3100)	Micromolar binding affinity (~0.65-1.2 μM)	Subcutaneous injection, rapidly absorbed, not metabolized, renally cleared, half-life of 3-5 hours	FDA approved for stem cell mobilization, rapid response, works synergistically with G-CSF, mild side effects, ease of administration, cost effective	Lower binding affinity, short half-life requires repeated dosing for continued effect, only approved in non-Hodgkin's lymphoma and multiple myeloma, renal clearance dependent
WK1	Nanomolar binding affinity (~2-5 nM)	Rapid distribution, rapid receptor engagement, minimal metabolism, renal clearance	High binding affinity, increased potency over first gen, longer receptor occupancy	In preclinical research, unknown pharmacokinetics in humans
PF-06747143 (Pfizer)	Low nanomolar binding affinity (~2-5 nM)	Intravenous infusion, low distribution volume, catabolized via proteolytic degradation, eliminated via reticuloendothelial system, half- life of ~10-20 days predicted	High binding affinity, dual mechanism of action, preclinical efficacy in AML/CLL, weekly dosing	Development discontinued, risk of immunogenicity, complex administration
Ulocuplomab (MDX1338)	Nanomolar binding affinity (~2-6 nM)	Intravenous infusion, low volume of distribution, metabolized via proteolytic degradation, eliminated via reticuloendothelial catabolism, half-life of ~14-21 days	High binding affinity and specificity, unique MOA via ROS-dependent cell death, mobilization of malignant cells, infrequent dosing	Early development stage, complex administration, unclear therapeutic window
LY2624587 (Eli Lilly)	Low nanomolar binding affinity (~2-5 nM)	Intravenous administration, low volume of distribution, catabolized via proteolytic degradation, cleared via reticuloendothelial system, half-life ~14-21 days	High binding affinity and specificity, direct apoptosis induction, mobilization of leukocytes and stem cells, preclinical efficacy in AML, CLL and NHL models, infrequent dosing	Development discontinued, complex administration

Table 3. Current combination therapies in clinical trials

Agent	Combination	Mechanistic Rationale
^{68}Ga-Pentixafor	[^{90}Y]Pentixather	To visualize, treat, and monitor treatment
SPX5551 (POL5551)	Ibrutinib	Synergistic apoptosis via NF-kB/PI3K inhibition
	Rituximab	Enhance chemotherapy efficacy
Plerixafor	R-CHOP	Mobilizes tumor cells and sensitizes to chemotherapy
	Etoposide	Mobilizes tumor cells
Ulocuplumab	R-ICE	Mobilizes tumor cells and sensitizes to chemotherapy
	Bortezomib	Mobilizes tumor cells and sensitizes to chemotherapy
	Rituximab	CXCR4 blockade + chemoimmunotherapy
	Ibrutinib	CXCR4 blockade + BTKi
[^{68}Ga]Ga-BL02	[^{177}Lu]Lu-BL02	Identifying suitable patients for treatment
BKT140	Rituximab	Enhancement of chemotherapy effects

One design concept describes engineering current CXCR4 peptides to be bispecific with two distinct pharmacophores linked via spacer, allowing the molecule to engage both receptors on the same cell [42]. Current CXCR4 small molecules are in development to add a CXCR7 head that would have β-arrestin engagement via a PEGylated spacer. Combination regimens are currently under investigation, aiming to simultaneously disrupt both axes and prevent compensatory signaling that can occur when only one receptor is targeted.

CXCR4-targeted radiotherapeutics remain therapies of interest in a wide variety of cancers, but specifically in lymphoma. Many of the therapies described in this paper are still currently involved in clinical and preclinical trials to determine dosimetry, long term effects, and possible combination therapies. Some combination therapies consist of CXCR4 inhibitors and targeted therapies, exploring increased sensitivity to the therapy. Others are focused on engineering nanoparticles with the ability to target multiple cancer stem cell markers, allowing for wider coverage of treatment enhancing treatment effectiveness and potentially preventing treatment evasion. The current combination therapies in clinical trials are summarized in **Table 3**. There is a wide variety of directions to take regarding the future potential of CXCR4-targeted radiotracers in both the diagnosis and treatment of lymphoma. Applications of such research will be applicable to numerous cancers and inflammatory processes, benefitting the diagnosis, treatment, and management of multiple illnesses.

Concluding remarks

CXCR4 has emerged as a pivotal biomarker and therapeutic target in lymphoma, bridging the gap between molecular imaging and precision therapy. Its extracellular accessibility, high prevalence in malignant cells, and role in promoting tumor survival position it at the forefront of theranostic innovation. The expanding repertoire of peptide- and small molecule-based ligands, radiolabeled therapeutics, and monoclonal antibodies underscores the translational momentum in this field. Overcoming current limitations such as off-target uptake in healthy immune tissues and compensatory CXCR7 signaling will require next-generation approaches, including dual-receptor targeting, nanocarrier delivery systems, and synergistic combination regimens. As these strategies advance from preclinical validation to clinical integration, CXCR4-directed theranostics have the potential not only to transform lymphoma management but also to redefine targeted oncology paradigms across hematologic and solid malignancies.

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Disclosure of conflict of interest

None.

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