

Review

Molecular Imaging of Chemokine Receptor CXCR4

Ido. D. Weiss¹✉ and Orit Jacobson²

1. Goldyne Savad Institute of Gene Therapy, Hadassah University Hospital, Jerusalem, 91120, Israel.
2. Cyclotron/Radiochemistry Unit/Nuclear Medicine Department, Hadassah Hebrew University Hospital, Jerusalem, 91120, Israel.

✉ Corresponding author: idowei@gmail.com.

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Abstract

CXCR4 was found to be expressed by many different types of human cancers and its expression has been correlated with tumor aggressiveness, poor prognosis and resistance to chemotherapy. CXCR4 was also shown to contribute to metastatic seeding of organs that express its ligand CXCL12 and support the survival of these cells. These findings suggest that CXCR4 is a potentially attractive therapeutic target, and several antagonists and antibodies for this receptor were developed and are under clinical evaluation. Quantifying CXCR4 expression non-invasively might aid in prognostication as a mean for personalized therapy and post treatment monitoring. Multiple attempts were done over the recent years to develop imaging agents for CXCR4 using different technologies including PET, SPECT, fluorescent and bioluminescence, and will be reviewed in this paper.

Key words: CXCR4, molecular imaging, diagnostics, cancer.

Introduction

CXCR4 is a 7-transmembrane G-coupled receptor which belongs to the chemokine receptors family, and is expressed by variety of cells during development and adult life. CXCR4 was initially cloned as an orphan chemokine receptor, and when it was identified as one of the co-receptors for T-tropic HIV, it drew much attention from both the research community as well as pharmacological companies [1-3]. The important role of CXCR4 in HIV entry to CD4 T cells initiated the development of different antagonists, both small molecules and peptide-based.

The sole universally accepted natural vertebrate ligand for CXCR4 is the chemokine CXCL12 (also known as stromal-derived factor, SDF-1) which was primarily isolated from a bone marrow stromal cell line and can also bind another chemokine receptor, CXCR7. Under normal condition, CXCR4/CXCL12 axis plays a role in leukocyte recruitment and is critical for homing and retention of hematopoietic cells, including stem cells, in the bone marrow (BM) [1, 4, 5].

Blocking of CXCR4 with antagonists such as AMD3100, BKT140 (T140) or others ligands, induces mobilization of progenitor cells from the BM into the blood, and enables collection of these cells for clinical procedures such as BM transplantation [6].

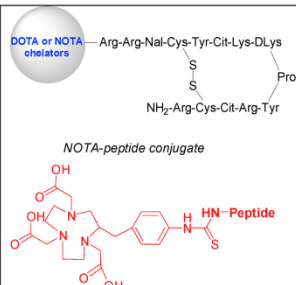
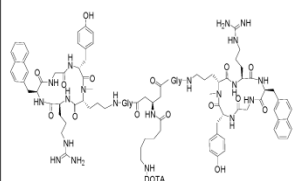
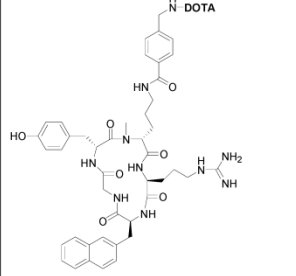
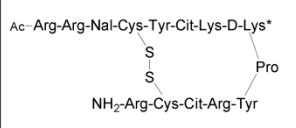
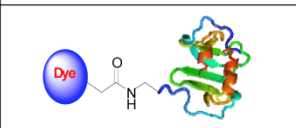
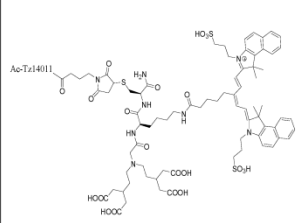
In addition to its extensive physiological roles, CXCR4 has also been found to be expressed by various human cancers including breast, prostate, lung, colon and multiple myeloma [7-14], and has been suggested to be involved in the process of cancer cell metastasis [15, 16]. The first report regarding CXCR4 role in metastasis was published by Muller et al. who showed that the metastasis of breast cancer cell line is dependent on CXCR4/CXCL12 axis [9]. Since then, multiple publications have shown that CXCR4 can provide survival and proliferation signals to cancer cells, direct these cells to specific metastatic sites and provide some resistance to chemotherapy [4, 6, 13]. CXCR4 expression, whether shown by mRNA or by immunohistochemistry, was suggested to correlate to

poor prognosis in several cancers [17, 18], making it a potential target for anti-CXCR4 targeted therapy. However, currently there is no ability to evaluate CXCR4 expression non-invasively and in whole tumors, and tests are limited to biopsies, which are restricted to a specific site and might give false negative results.

This review will mainly focus on the research that was done to enable evaluation of CXCR4 expression in whole tumors non-invasively, by development of imaging agents using bioluminescence, fluorescent molecules or radiolabeled molecules, some of which are summarized in Table 1.

Table 1. Imaging agents targeting CXCR4.

SPECT	Structure	Radionuclide/ fluorochrome	Advantages	Limitation	Reference s
Ac-TZ14011		¹¹¹ In	- Low binding IC ₅₀ to CXCR4 of 7.6nM	- Low accumulation in CXCR4 expressing tumors (0.51 %ID/g) - Uptake in tumors reduced over time with kinetics similar to the blood	[20]
12G5		¹²⁵ I	- long half-life allows monitoring of treatment - can be labeled with Iodine-131 for radio-immuno-therapy	- High unspecific accumulation of labeled non-specific antibody in the tumors - Limited to tumors greater than 200 mm ³	[21]
MAS3-SDF-1α		^{99m} Tc	- native protein	- Binds CXCR4 and CXCR7 - Was only evaluated in myocardial infraction model in rats	[22]
PET					
AMD3100		⁶⁴ Cu	- approved drug - short radiosynthesis - high accumulation in CXCR4 positive tumor	- High accumulation in the liver (≥ 40%ID/g)	[24-26]
AMD3465		⁶⁴ Cu	- short radiosynthesis - very high accumulation in CXCR4 positive tumor (≥106 %ID/g) Very low accumulation in CXCR4 negative tumors (<4.23 %ID/g)	- High accumulation in the liver (≥ 32%ID/g)	[30]
T140		¹⁸ F	- labeling was done while keeping original peptide structure - fluorine-18 is more available than other radionuclides	- Binding to red blood cells (RBC). Overcoming this limit requires injection in low SA. - Long synthesis time - Low radiochemical yield	[31]
T140-2D		⁶⁴ Cu	- short radiosynthesis	- Binding to RBC Overcoming this limit requires injection in low SA. - Transchelation and moderate unspecific accumulation of radioactivity in the liver	[32]

T140-NFBs	 <p>DOTA or NOTA chelators—Arg-Arg-Nal-Cys-Tyr-Cit-Lys-DLys NH₂-Arg-Cys-Cit-Arg-Tyr</p> <p>NOTA-peptide conjugate</p>	⁶⁴ Cu	<ul style="list-style-type: none"> - does not bind RBC as the original peptide - short radiosynthesis 	<ul style="list-style-type: none"> - Transchelation and some unspecific accumulation of radioactivity in the liver - Lower binding affinity to CXCR4 than parent peptide: 68nM for DOTA-NFB and 138nM for NOTA-NFB. 	[33]
FC131 dimer		⁶⁸ Ga	<ul style="list-style-type: none"> - Low binding IC₅₀ to CXCR4 (39nM). 	<ul style="list-style-type: none"> - Low accumulation in the tumor (2.08 ID/g) - High accumulation in the liver (≥44 %ID/g) 	[35]
FC131 monomer (CPCR4-2)		⁶⁸ Ga	<ul style="list-style-type: none"> - accumulation in CXCR4 positive tumors is specific - no significant accumulation in metabolic organs 	<ul style="list-style-type: none"> - Relatively low accumulation in CXCR4 positive tumors (≤6.16 %ID/g), results in low tumor-to-blood ratio of 5.81. 	[36-37]
Fluorescence					
TY14003	 <p>Ac-Arg-Arg-Nal-Cys-Tyr-Cit-Lys-D-Lys* NH₂-Arg-Cys-Cit-Arg-Tyr</p>	Carboxyfluorescein on D-Lys	<ul style="list-style-type: none"> - Allows in-vivo imaging of cancers where endoscopy is usable, such as bladder and GI. - Allows ex-vivo analysis of CXCR4 expression by cells in fluids such as urine. 	<ul style="list-style-type: none"> - Not usable for non-invasive whole body imaging 	[47]
CXCL12-IRDye®800CW		IRDye®800CW	<ul style="list-style-type: none"> - Native protein 	<ul style="list-style-type: none"> - Not usable non-invasive whole body imaging. - Binds CXCR4 and CXCR7 	[49]
Multimodal hybrid					
Ac-TZ14011-MSAP		CyAL-5.5b / ¹¹¹ In	<ul style="list-style-type: none"> - can be used as anti-cxcr4 treatment 	<ul style="list-style-type: none"> - High accumulation in the liver - Relatively low signal to background ratio 	[53]

SPECT tracers targeting CXCR4

Single photon emission computed tomography, SPECT, is a technology that utilizes radioactive isotopes which emit a photon upon decay. Detection of single photon requires physical collimators, which exhibit low geometric efficiencies, in order to reject

photons that are not within a small angular range (otherwise the angle of incidence will not be known) [19]. This method requires injection of radioactive tracer, and the distribution of the tracer is thereafter monitored using a SPECT machine. The SPECT is usually combined with a computed tomography (CT) for anatomical information.

One of the first attempts to detect CXCR4 in tumors using a radiolabeled antagonist was done by Hanaoka et al., who labeled the peptide antagonist Ac-TZ14011 with Indium-111 [20]. The researchers conjugated the antagonist to Diethylenetriamine-pentaacetic acid (DTPA) which enabled chelation of ^{111}In , to give ^{111}In -DTPA-Ac-TZ14011. The tracer was able to inhibit CXCL12 binding to CXCR4 in similar magnitude to its parent molecule, with IC_{50} of 7.6 nM. The accumulation in CXCR4 expressing tumor, however, was limited (0.51% Injected Dose (ID)/g), reduced over time with kinetics similar to the blood, and no *in-vivo* specificity was proven.

A more successful attempt to develop CXCR4 targeted tracer was done using CXCR4-specific antibody, 12G5 (Figure 1A). The antibody was labeled with Iodine-125, and injected to mice bearing glioblastoma tumors U87 and U87-transfected with CXCR4. The labeled antibody nicely accumulated in CXCR4 positive tumors, however the researchers reported on several limitations of the tracer, including relatively high unspecific accumulation of labeled non-specific antibody in the tumors, and inability to see different accumulation between the unspecific antibody and 12G5 in tumors smaller than 200 mm³ [21].

Another noteworthy research to image CXCR4 was done in rats undergoing myocardial infarction (MI), using $^{99\text{m}}\text{Tc}$ labeled CXCL12. CXCR4 was shown previously to be elevated after MI, and indeed Misra et al. were able to show significant accumulation of the tracer in the heart of rats post MI [22]. Another point that was not addressed is whether CXCR7, which is expressed in the heart valves and can bind CXCL12, had any contribution to the accumulation of labeled CXCL12 in the heart.

PET tracers targeting CXCR4

Positron emission tomography (PET) is a nuclear medicine technology that, similarly to SPECT, uses injected radiolabeled tracers for imaging their accumulation in target organs. The radionuclides which can be used for PET are different in that they emit a positron when undergoing decay. During the annihilation process between the positron and an electron in the tissue, two photons are released simultaneously in opposite direction [23]. The detection of two photons gives 2-3 orders of magnitude more sensitive than SPECT ensuing superior resolution, however production of the radioisotopes is usually more expensive and the radionuclides typically have shorter half-lives.

The first CXCR4 antagonist to be labeled with PET radionuclide was AMD3100, which was labeled

with copper-64. AMD3100 is a bicyclam, that can chelate metal ions and therefore the synthesis of ^{64}Cu -AMD3100 is quick and relatively simple resulting in high radiochemical yield. ^{64}Cu -AMD3100 was first evaluated by us in normal mice [24], and showed rapid clearance from the blood and accumulation in CXCR4 expressing organs such as the BM and spleen. The tracer was later reported by us and others to specifically accumulate in CXCR4 expressing tumors (Figure 1B) [25, 26]. The main drawback of the tracer was high accumulation (>40% ID/g) in the liver, which was specific to the parent molecule, and masked some of the adjacent organs. This phenomenon is not CXCR4-specific binding in the liver because (a) high CXCR4 expressing organs such as the spleen do not display such high uptake of the tracer; (b) only limited liver cells express CXCR4 [27-29]; and (c) other tracers such as labeled T140 discussed below do not show high accumulation in the liver. Another similar small molecule, AMD3465, which structure contains one cyclam that can chelate copper-64, was also evaluated as a PET tracer for imaging CXCR4 and showed very high accumulation in CXCR4 expressing tumor (~100% ID/g), and lower but significant (40% ID/g) accumulation in the liver (Figure 1D) [30].

A peptide based CXCR4 antagonist, similar to Ac-TZ14011 previously labeled with ^{111}In , but had a fluoro-benzyl group at the N-terminus, was also labeled by us using the nuclide fluorine-18 [31]. The peptide, named T140, was labeled without changing its chemical structure to give ^{18}F -T140, and evaluated *in-vivo*. Surprisingly, we found that the molecule had CXCR4-independent binding to red blood cells, which we were able to overcome by injecting the tracer in low specific activity (Figure 1C). Another drawback of this labeled tracer was its long synthesis time and relatively low radiochemical yield. To shorten the synthesis, we have introduced the chelator 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA), on the lysine groups of the peptide and labeled it with copper-64 to give ^{64}Cu -T140-2D. This peptide tracer showed similar binding to red blood cells as the fluorine-18 labeled T140 [32] [33], and in low specific activity form could be used for imaging CXCR4 positive tumors. Similar method was used by us and others to label T140 with gallium-68 without significant differences [32, 34]. It is important to note that the accumulation of radioactivity in the liver was significantly higher when T140 was labeled with chelated radiometals than when it was labeled with ^{18}F . This suggests that some of the radioactivity in the liver is due to transchelation of the radiometal and the chelating moiety should be improved to prevent this phenomenon.

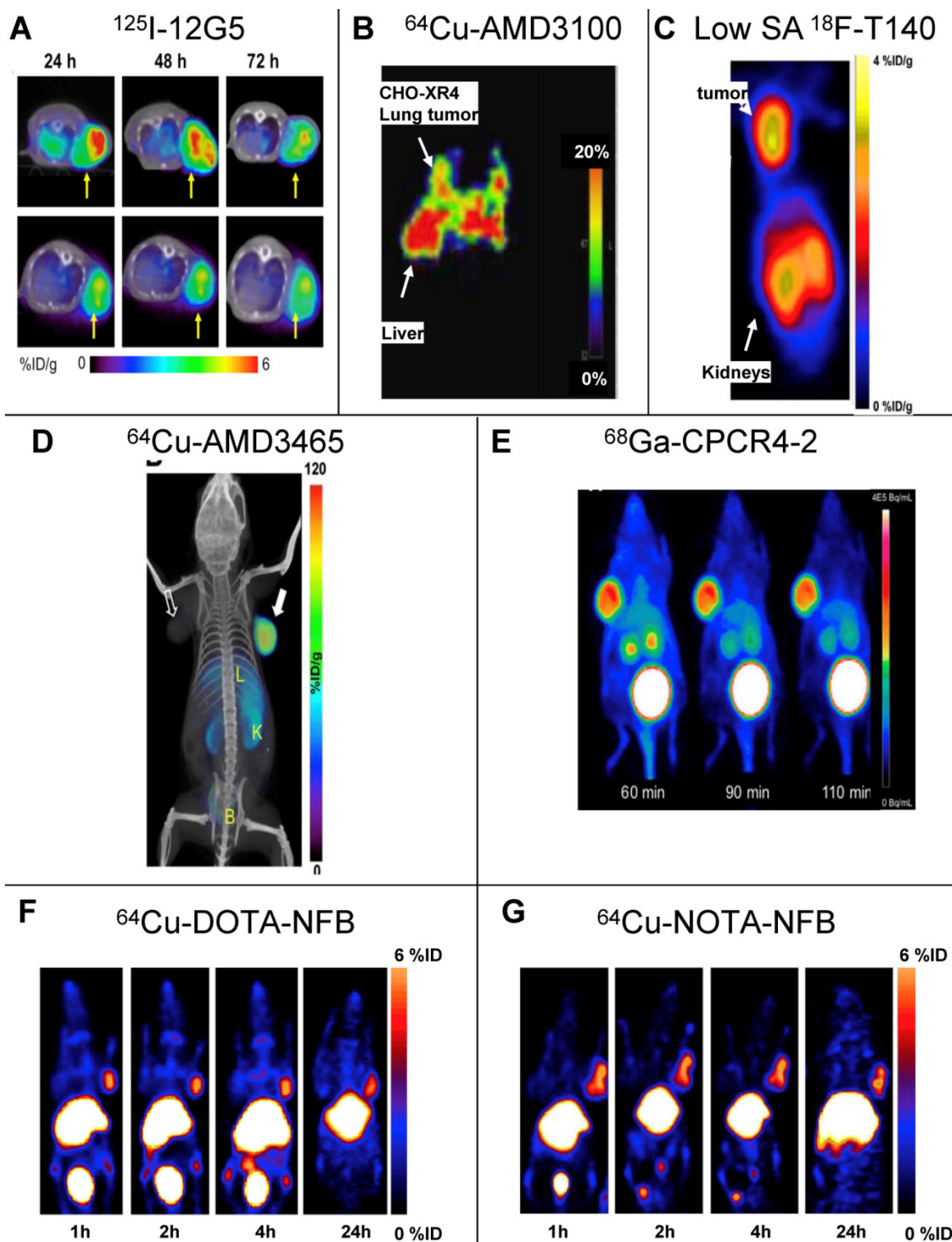


Figure 1. SPECT and PET imaging of subcutaneous tumors using CXCR4 specific tracers. (A) SPECT imaging of tumors of U87 cells transfected with human CXCR4 using the anti-CXCR4 antibody 12G5 (upper) or isotype antibody (lower) labeled with Iodine-125, 24, 48 and 73h post injection [21]. (B) PET imaging of lung metastasis of CHO cells transfected with CXCR4 using CXCR4 antagonist AMD3100 labeled with copper-64, 1h post injection [25]. (C) PET imaging of subcutaneous tumors of CHO cells transfected with CXCR4 using CXCR4 peptide antagonist T140 labeled with fluorine-18. The tracer was injected in low specific activity (SA) after adding 10 μ g of unlabeled peptide, images were taken 2h post injection [31]. (D) PET imaging of subcutaneous tumors U87 cells transfected with CXCR4 using CXCR4 antagonist AMD3465 labeled with copper-64, 90min post injection [30]. (E) PET imaging of subcutaneous tumors of OH1 cells using cyclic CXCR4-binding pentapeptide CPCR4-2 labeled with Gallium-68, at 60, 90 and 110min post injection [37]. (F,G) PET imaging of subcutaneous tumors of CHO cells transfected with CXCR4 using CXCR4 peptide antagonist T140 after substitution of the 4F-benzyl group at the N-terminus of the peptide with DOTA (F) or NOTA (G) labeled with copper-64, up to 24h post injection. The substitution with either chelators allowed using high SA peptide unlike the original peptide shown in (C) [55]. Reprinted by permission of the Society of Nuclear Medicine.

In an attempt to limit undesired binding of labeled T140 to red blood cells, we synthesized the peptide with DOTA or 1,4,7-triazacyclononane-N,N',N''-triacetic acid (NOTA) chelators at the N-terminus, replacing the fluoro-benzoyl group and thereafter labeled the tracers with copper-64. Replacing the fluoro-benzoyl group with either DOTA or NOTA diminished the binding of labeled T140 to red blood cells, while only slightly reducing the binding to CXCR4 (Figure 1F and 1G, respectively) [33]. These two optimized tracers, used in high specific activity, showed high accumulation in CXCR4 positive tumors but not in CXCR4-negative tumors, and high tumor-to-background ratio, while having short radio-synthesis time, high radiochemical yield and no non-specific binding to red blood cells.

Another Tracer that was developed for PET imaging of CXCR4 was based on a dimer of cyclic penta-peptide FC131, which was conjugated with DOTA, and thereafter labeled with Gallium-68. The dimer tracer gave a limited accumulation in the tumor, while displaying very high accumulation in the liver (~44%ID/g) [35]. The researchers suggested that the dimer has suboptimal biodistribution due to its high lipophilicity, and evaluated the FC131 cyclic penta-peptide as a monomeric form (CPCR4-2) [36] [37]. Although the monomeric tracer hypothetically have lower polyvalency, it showed better biodistribution *in vivo*, with significantly lower accumulation in the liver, higher accumulation in the tumor and tumor to muscle ratio of about 18 (Figure 1E) [36] [37].

An interesting small molecule that was described by Liang Z et al. called MSX-122 and displayed CXCR4 antagonist properties, was labeled with fluorine-18, to give ¹⁸F-MSX-122F [38]. The labeled derivative showed binding to CXCR4 *in vitro* however the authors did not report *in vivo* experiments thus far.

Bioluminescence tracers targeting CXCR4

Bioluminescence is based on detection of light produced by the catalytic activity of luciferase using small substrate molecules, luciferins. The absence of noise in the reporter system when used in animals gives extremely high sensitive due to the extraordinary signal-to-noise ratios [39]. The major limit of this method is that the luciferase gene is not of mammalian origin and has to be introduced into the cells, making unusable for human patients, can only be used for research..

The usage of bioluminescence as a reporter gene for evaluating the role of CXCR4 in different settings such as tumor development was reported by various laboratories, and had a significant impact on understanding the role of CXCR4 in various biological systems [40-42]. However, those indirect methods where

luciferase was used only as a mean to evaluate differences between CXCR4 positive and negative cells and was not used to image CXCR4 itself will not be discussed herein.

A very interesting method for direct imaging of CXCR4 and its interaction with its ligand CXCL12 using bioluminescence was recently developed by Luker et al. [43]. These researchers made CXCL12 fused to *Gaussia* luciferase, and were able to detect binding of the fused chemokine to its receptors CXCR4 and CXCR7 *in vitro*. The fusion protein was transduced into human mammary fibroblasts that were co-injected with breast cancer cells into mice, and this bioluminescence system was elegantly used to show that CXCR7-positive breast cancer cells enhanced proliferation of CXCR4-positive breast cancer cells in orthotopic tumors and spontaneous metastases[44]. The same researchers also published an improved method for imaging CXCL12/CXCR4 and CXCL12/CXCR7 interaction *in vivo*. In order to achieve this, Luker et al. used a method of *Gaussia* luciferase (GLuc) complementation, where CXCL12 is fused to the C-terminus fragment of GLuc and either CXCR4 or CXCR7 are fused to the N-terminus fragment [45]. This is a fully reversible system that allowed the researchers to compare in a semi-quantitative manner the interaction of CXCL12 with either CXCR4 or CXCR7, which was reported to favor towards CXCR7 in MDA-MB-231 breast cancer cells. This system also allowed the researchers to evaluate CXCL12/CXCR4 inhibition *in vivo* by using CXCR4 antagonist AMD3100. On the other hand, inhibition of CXCL12/CXCR7 interactions, was not inhibited using CXCR7 inhibitor CCX771, which, as the authors suggest, might be due to short exposure to the chemical and the low amounts that were used [45].

Luker et al. have established another method using similar technique - *firefly* luciferase complementation - to test CXCR4 activation both *in vivo* and *in vitro*, by fusing CXCR4 to the N-terminus of luciferase and fusing the C-terminus to β -arrestin [46]. The researchers were able to show inhibition of CXCR4 activation *in vitro* using both CXCR4 antagonists AMD3100 and TF14013, and inhibition of CXCR4 activation *in vivo* using AMD3100.

Both luciferase complementation methods established by Luker et al. [45, 46] are very elegant and allow assessment of CXCL12/CXCR4 signaling *in vitro* and *in vivo*, however as mentioned above they can only be used in animal models. Each of the technique also have its own downside when compared to the other - CXCR4/ β -arrestin complementation offer usage of one transfected cell line, however baseline bioluminescence seems to be relatively high. CXCL12/CXCR4 complementation, on the other

hand, requires the use of two transfected cell lines but has low background and can also allow testing the inhibition of CXCL12/CXCR7.

Fluorescent tracers targeting CXCR4

Fluorescent labeling and staining, when combined with an appropriate imaging instrument, is a sensitive and quantitative method. Fluorescence results from a process that occurs when certain molecules (generally polyaromatic hydrocarbons or heterocycles) called fluorophores, fluorochromes, or fluorescent dyes absorb light. The absorption of light by a population of these molecules raises their energy level to a brief excited state. As they decay from this excited state, they emit fluorescent light. The major downside of fluorescence imaging is the limited depth that the fluorescent light can penetrate before it is absorbed by the tissue; hence the imaging is limited to superficial organs or tumors [47].

Nishizawa et al. avoided the depth limitation by aiming at imaging of bladder cancer and of urothelial cells found in the urine of bladder cancer patients [48]. The researchers used a derivative of the T140 CXCR4 antagonist, TY14003, which was labeled with carboxyfluorescein on the D-Lysine group [49]. Fluorescent TY14003 was shown to specifically bind to urothelial cancer cells in the urine sample but also to white blood cells; however the cell types were clearly distinct from one another by shape and size. The fluorescent tracer showed great potential under the microscope but was less convincing when the authors tried to image bladder cancer in mice using fluorescent endoscopic observation. Nishizawa et al. did not evaluate fluorescent TY14003 in low-grade bladder cancers due to low CXCR4 expression by these tumors and suggested that the tracer might prove to be very helpful tool in cytology of urine samples. It might also be interesting to test the tracer as a reagent for flow cytometry analysis of urine samples, and compare it to commercially available fluorescent labeled anti CXCR4 antibodies.

A different method to overcome the depth limitation of fluorescent imaging was done by using near-infrared (NIR) probe, which theoretically allows detection of tracers up to few cm into the tissue. Meincke et al. conjugated CXCL12 to NIR dye, and evaluated whether this setting allows imaging of tumors expressing CXCR4 and CXCR7 [50]. Although the NIR dye allows deeper imaging, the researchers were limited by tissue penetration, and used subcutaneous tumor models. CXCL12 conjugated to the NIR dye was shown to be very sensitive, and allowed visualization of the tumor for up to 4 days, while some of the background and unspecific accumulation of the tracer reduced after 2 days. This method for

imaging CXCR4 or CXCR7 positive tumors is not usable for whole body imaging, however it might be useful for live detection of tumor cells and metastasis to tumor draining lymph nodes under surgery, and allow the surgeon to remove all CXCR4 positive malignant cells.

Several other reagents were developed by different groups, including T140 derivative TZ14011 coupled to iridium complex [51], anti-CXCR4 antibody labeled with fluorescent metal nanoshell [52], and a quantum dot conjugated to proteinA-anti CXCR4 antibody [53]. These reports, although very interesting, did not show *in vivo* imaging and limited the experimental design to cell binding and cell imaging hence will not be reviewed in this paper.

CXCR4 multimodal hybrid imaging

The development of multimodal probes is attaining a significant interest in the field of molecular imaging. Such probes can be used in more than one imaging modality. Each modality has its own strengths and weaknesses, and therefore, a combination of modalities can be used in the clinic for optimal detection. Kuil et al. developed a multimodality probe based on T140 derivative, Ac-Tz14011, by conjugating the D-lys of the peptide to multifunctional single attachment point reagent that contains a DTPA chelate and a CyAL-5.5_b fluorochrome [54]. The researchers chelated Iridium-111 into the DTPA and performed SPECT/CT and fluorescent imaging of tumor bearing mice. The reagent showed a tumor-to-muscle ratio of 4.55 ± 0.68 in mice bearing CXCR4-positive tumors and 1.2 ± 0.12 ratio in mice bearing CXCR4-negative tumors, a difference that was significant, however seem to be less impressive than similar ratios reported for molecules described above. Another setback was the relatively high accumulation in the liver, of about 20%ID/g. Due to the bimodality of the tracer, the researchers were able to show the accumulation of the tracer in the tumor by fluorescent imaging after surgically revealing the tumor [54]. To try and improve the multimodal tracer, the same researchers tried to combine the multifunctional single attachment point reagent with dimer and tetramer of Ac-Tz14011, with the rationale that multimerization will enhance binding to CXCR4 while reducing the influence of the labeling dye on tracer biodistribution and non-specific binding [54]. Unfortunately, the multimerization of Ac-Tz14011 showed inconclusive results *in vivo*, with lower %ID/g in the tumor compared to the monomer and slightly higher tumor-to-muscle ratio for the dimer.

Conclusions

Multiple attempts to develop imaging agents

targeting CXCR4 were done in the recent years. A limit that is evident for all the tracers is the normal expression of CXCR4 in several tissues such as the BM, spleen and lymph nodes. Some of the agents are not usable for whole body human imaging because of the technology being use, such as bioluminescent and fluorescence; In the future, fluorescent probes can prove useful in clinical procedures employing endoscopic examination of GI and bladder and might also be applied as guidance for tumor and metastatic cells resection. Currently, only PET and SPECT nuclear medicine imaging agents can be utilized clinically. Of the different nuclear medicine tracer reviewed above, the PET tracers are more promising agents for CXCR4 non-invasive imaging in the clinic. Imaging CXCR4 in patients might give guidance to physicians as to the nature of the tumor in regard to aggressiveness and potential to metastasis and help in the decision of suitable treatment. In addition, anti-CXCR4 therapy is currently being evaluated in clinical trials, and application of CXCR4 imaging tracers described herein might benefit these trials as well as future treatment of patients with CXCR4-positive tumors, and avoiding unnecessary treatment of patients with CXCR4-negative tumors. It is our hope that the use of molecular imaging modalities with specific tracers in the diagnosis and management of patients with cancer may lead to more effective interventions tailored to an individual's needs.

Acknowledgment

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Nimmagadda S, Pullambhatla M, and Pomper MG. Immunoimaging of CXCR4 Expression in Brain Tumor Xenografts Using SPECT/CT. *J Nucl Med.* 2009; 50(7): 1124-1130. Figure 3

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Competing Interests

The authors have declared that no competing interest exists.

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