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SPECT AND PET RADIOPHARMACEUTICALS FOR THE DIAGNOSIS OF INFECTIOUS AND INFLAMMATORY FOCI

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ABSTRACT

The diagnosis of infectious and inflammatory disorders is still challenging. Molecular imaging using radiopharmaceuticals continues to play an important role in the diagnosis and monitoring of infectious and inflammatory disorders because it gives information about the site of the lesion and the molecular and functional patterns of the disorders. The aim of this review is to describe the strengths and limitations of these radiopharmaceuticals. Many radiopharmaceuticals have been developed. Even though none of them is ideal each one has its own strengths and weaknesses. Many radiopharmaceuticals have been studied but still only few of them are in clinical practice today. Therefore, it is important to accelerate the development of clinically viable radiopharmaceuticals for this area.

KEY WORDS: infection and inflammation, Radiopharmaceuticals.

INTRODUCTION

Inflammation is the body's protective reaction to harmful stimuli such as mechanical injury, chemical toxins, invasion by microorganisms, and hypersensitivity reactions. Inflammatory process involves host defense cells (platelets, granulocytes (PMNs, mast cells etc.), monocytes/macrophages, lymphocytes, and fibroblasts), blood vessels and protein. The main goal of inflammation is to bring the defense cells (immune cells) to the area of concern which is commonly mediated by chemicals like cytokines produced by damaged host cells, eliminate the initial cause of injury, remove necrotic cells and tissue as well as to initiate the process of healing (Kumar et.al. 2012).

Inflammation may be acute or chronic. Acute inflammation has an immediate reaction that lasts for a short duration (8-10 days) and the cellular infiltrate mainly contains neutrophils. It is characterized by vasodilation, vascular leakage and edema, as well as leukocyte emigration to extravascular tissue. The classical symptoms of acute inflammation include heat (calor), redness (rubor), swelling (tumor), pain (dolor) and loss of function (Rankin, 2004).

On the other hand, chronic inflammation is a sequel of acute inflammation that lasts for several weeks to years and characterized by reduction on numbers of neutrophils and increased infiltration of macrophages, lymphocytes, plasma cells, and fibroblasts (Goldsmith and Vallabhajosula, 2009).

Inflammation is normally controlled and self-limited. However, components of the inflammatory process may destroy normal tissue and inappropriate inflammatory processes (autoimmune reaction) may lead to disorder (Kumar et.al. 2012).

Infection is the invasion of a host organism's bodily tissues by disease-causing organisms (virus, fungus or bacteria), their multiplication and the reaction of host tissues to these organisms and the toxins they produce (Stolberg, 1998). From the definition we understand that, infection is just one of the possible causes of inflammation.

Infectious and inflammatory diseases are common causes of morbidity and mortality worldwide. Rational diagnosis of infection and inflammation is invaluable for better outcome and overall costs of the disease management in which radiopharmaceuticals play an important role. Several radiopharmaceuticals have been developed in the last decade for infection and inflammation imaging. Some of them have been used in clinical practice and many others are still in preclinical and clinical studies.

Fever of unknown origin (FUO) is a rise of body temperature above the normal (38.3°C or more) on and off for at least 3 weeks with no known cause. Studies show that it may be caused by infections, noninfectious inflammatory disorders, malignancies, collagen vascular disease, granulomatous diseases, pulmonary embolism, cerebrovascular accidents, drug induced fever, etc. (Roth and Basello, 2003). Radiopharmaceuticals have also played a huge role in differentiating the cause of FOU (Meller and Becker, 2001).

Currently, the diagnosis of infections and inflammatory diseases depends on patient history taking, physical examination, in vitro tests, endoscopy and imaging techniques; such as molecular imaging. Molecular imaging is a technique in which the imaging is targeted to specific molecular or cellular features. It has important advantages over the other diagnostic methods in that apart from giving information about the location of the lesions, it also provides the much needed information about the molecular and functional aspects of the disease. This is particularly useful for not only differentiating between infection and sterile inflammation, but may also point out the specific infectious organisms involved and inform treatment decisions.

Molecular imaging techniques include radionuclide imaging, optical imaging, X-Ray Computed Tomography (CT), ultrasound molecular imaging and magnetic resonance imaging (Chen, 2014). Radionuclide imaging and optical imaging are generally considered to be functional imaging techniques while magnetic resonance imaging, CT and Ultrasonography provide anatomical or structural data. Features of radionuclide imaging that give it a competitive edge above other imaging modalities are its high sensitivity, high specificity, it is also quantitative and it has a limitless tissue depth. The lack of anatomical data and poor resolution of this technique has been compensated for by using multimodality imaging in which radionuclide imaging is coupled with either magnetic resonance imaging or, more commonly, with CT.

Common radionuclide imaging techniques for clinical usage are Single Photon Emission Computed Tomography (SPECT) and Positron Emission Tomography (PET). SPECT is more popularly used than PET, partly because it is cheaper (Chen, 2014). However, the clinical application of PET imaging is gaining ground owing to its better sensitivity and spatial resolution (Rahmim, 2008). To improve their clinical utility, these imaging modalities have been fused with other imaging modalities such as MRI and CT into hybrid imaging systems such as SPECT/CT, PET/CT, PET/MRI, etc. (Cherry, 2009). Globally, the clinical application of hybrid PET-based systems is growing faster than single modality PET systems (Hricak, 2010).

The ideal radiopharmaceuticals for the imaging of infection and inflammation foci should have high sensitivity for infection/inflammation, differentiate between infection and inflammation, differentiate between acute and chronic infection, no toxicity and/or immunogenic response, minimum radiation burden to the patient and worker, high specificity, rapid clearance from circulation, no uptake in gastrointestinal tract, as well as they should be easy to prepare, have low cost and wide availability (Goldsmith and Vallabhajosula, 2009).

Unfortunately, no radiopharmaceutical used to image infection and inflammation foci has ever achieved all the ideal characteristics. The aim of this review is to describe the strengths and limitations of the currently available radiopharmaceuticals for application in this area.

SPECT Radiopharmaceuticals

SPECT radiopharmaceuticals remain the prime choice for the nuclear imaging of infections and inflammatory disorders in most clinical practice because of availability, low cost, and longer half-life of the radionuclides as well as relatively lower radiation dose to the patients compared to most PET radiopharmaceuticals.

Gallium-67 based radiopharmaceuticals for infection and inflammation imaging

Gallium is a group three element in the periodic table. It has an electronic configuration of $Ar[3d^{10}4s^{2}4p^{1}]$, hence, it mainly adopts a +3 charge in its compounds. It readily forms complexes with compounds that have nitrogen and oxygen as the donor ligands (Engesser, 2016). The three radioisotopes of gallium that have potential clinical applicability are gallium-67, gallium-68 and Gallium-66. However, the commonest are gallium-67 and gallium-68 due to their more favorable decay properties.

Radioisotopes of Gallium have important strengths in inflammation and infection imaging. As Iron (III), free gallium readily chelates with transferrin and lactoferrin which are abundant in inflammation loci. Also, it readily chelates with siderophores that are produced by bacteria in areas of bacterial infection (Tsan, 1985).

Gallium -67

Gallium-67 decays 100% through electron capture, with a half-life of 3.26 days. In the process, it emits gamma rays of various energies. The gamma rays of the energies 93 keV, 185 keV and 300 keV are clinically useful. The abundances of these rays are 39%, 21% and 17% respectively (Delacroix et al, 2002). Gallium-67 is obtained for radiopharmaceutical application, commonly through cyclotron irradiation of Zinc-68 targets with proton beams (Arzumanov, 2000).

Gallium-67 has a long enough half-life, allowing for longitudinal imaging of the infection or inflammation locus for up to one week. The long half-life is also useful for delayed imaging if it's part of slow-clearing radiopharmaceuticals. Despite that, its cyclotron production makes the radioisotope more costly than generator produced radioisotopes. Another limitation is

that its clinically useful gamma radiations are of low abundance.

Gallium citrate is the oldest radiopharmaceutical to be used in infection and inflammation imaging. Previously it had been used for the diagnosis of cancer (Lavender et al 1971). Its localization at the site of infection and inflammation is assumed to be due to Ga^{3+} dissociating from citrate and chelating to blood transferrin (Vallabhajosula et al, 1980). Then this complex extravasates to the site of inflammation due to increased capillary permeability. It also binds to lactoferrin and bacterial siderophores (Tsan, 1985) that are abundant at the sites of inflammation and infection respectively.

It has been used for the detection of vertebral osteomyelitis, chronic osteomyelitis, septic arthritis, cellulitis, and opportunistic infections in immunocompromised patients such as pulmonary infections as well as for the detection of FUO (Kalabat and Powsner, 2004).

Despite its usage, gallium citrate has its own limitations including low specificity due to its excretion through bowel, accumulation in malignant and bone remodeling areas. The high energy gamma rays lead to poor quality image and high radiation absorbed dose. Also, delayed imaging is required for optimal images to be achieved.

Because of the challenges associated with the radionuclide's nuclear characteristics there was need to explore other radionuclides with better radiation characteristics than gallium -67.

Indium-111 based radiopharmaceuticals for infection and inflammation imaging

Indium is a group thirteen element in the periodic table of elements. It has an electronic configuration of $[Kr]4d^{10}5s^{2}5p^{1}$. Its chemistry is intermediate between that of its congeners gallium and that of thallium in that apart from its usual +3 oxidation state (Wadas, 2010), some compounds in which it exists as +1 oxidation state have also been reported (Engesser, 2016).

Indium-111 decays to cadmium-111 100% through electron capture with half-life of 2.80 days. It also emits clinically useful gamma rays of energies 171 keV and 245 keV, each with an abundance that is greater than 90% (Be, 2006). Due to its chemistry, its long half-life and its high abundance of gamma rays with suitable energies, In-111 is one of the important radioisotopes for infection and inflammation imaging. One the other hand, the high abundance of both gamma rays can lower the image quality.

Several ligands can be labelled with indium-111 and used for imaging infection and inflammation foci. Ligands such as human immunoglobulins G polyclonal antibody, monoclonal antibodies, white blood cells, streptavidin-biotin, bacterial chemotactic peptides and liposomes are among the examples. The main advantage of using indium to label with ligands for clinical application is its long half-life (67 hours) allow imaging beyond 24 hr. post injection.

However, suboptimal photon energies, low resolution images, long time from injection to imaging acquisition in the case of white blood cells (Palestro et.al 2009) and the better imaging characteristics of technetium-99m for gamma camera (physical characteristics, availability, cost and lower radiation burden) challenges indium-111's application in the detection of infection and inflammation foci (de Vries et.al. 2010).

Technetium-99m based radiopharmaceuticals for infection and inflammation imaging

Technetium is an atomic number 43 transition metal with an electronic configuration of $[Kr]5s^{2}4d^{5}$, found in the group seven of the periodic table of elements. It can exist in as many as nine oxidation states; -1 to +7. Its chemistry is versatile in that it forms stable complexes with a large variety of donor and acceptor ligands, producing a wide range of inorganic functional groups (Duatti, 2011). Thus, the chemistry of technetium offers itself as an important asset for extensive radiopharmaceutical application.

Technetium-99m is still the most predominant radioisotope in radiopharmaceuticals, accounting for over 80% of all radiopharmaceuticals used worldwide (Neilly, 2015). It decays over 99.99% by isomeric transition to technetium-99. Its decay half-life is 6.0 hours and it emits gamma rays of 141 keV, with 89% abundance (Delacroix, 2002), which are highly suitable for nuclear imaging. Technetium-99m is a hugely advantageous radioisotope in infection and inflammation imaging because of the versatile technetium chemistry and its equally important nuclear properties. Since it is primarily available through a commercial GMP compliant generator, it is cheaper than many other radioisotopes used in radiopharmaceuticals such as the cyclotron produced radioisotopes. The 66-hour half-life of the parent molybdenum-99 radionuclide allows for a two week working life of the generator, thereby allowing for efficient supply logistics.

However, technetium-99m does not decay to a stable isotope. Instead, it decays to technetium-99 which is a long lived beta emitter. Technetium-99 has the same chemistry as technetium-99m, allowing it to compete with technetium-99m and reduce radiolabeling yield. Another limitation of Moly generator produced technetium-99m is its unavoidable presence of technetium-99 impurity because 12.4 % of Molybdenum-99 decays directly to tecnetium-99 (Be, 2004).

Ligands to be labeled with technetium include a wide variety of molecules such as blood cells, antibodies, peptides, antimicrobial agents, cytokines, liposomes, etc.

White blood cells (WBCs)

Chemotactic migration of WBCs to the sites of infection and inflammation is a natural immune defense mechanism. Radiolabeled WBCs have shown significant accumulation at the site of infection and inflammation foci. WBCs have been effectively labelled with Tc-hexa-methyl propylene amino oxime (HMPAO) (Peters et.al 1986).

^{99m}Tc-HMPAO-labelled WBCs have been used for diagnosis of various infection and inflammation disorders including occult infection, inflammatory bowel disease, osteomyelitis, follow-up of patients with infections of vascular or orthopedic prosthesis, FOU, postoperative abscesses, lung infections, endocarditis, neurological infections and infected central venous catheters or other devices (de Vries et. al 2010). ^{99m}Tc-HMPAO-WBCs scintigraphy is considered as a gold standard method for detection of acute infections. Some advantages of this method are that it may selectively differentiate infection from inflammation, it is devoid of allergy reactions since patients own blood is reinjected and it achieves better anatomical localization of infection sites (Love and Palestro, 2004). Despite a wide usage of ^{99m}Tc-HMPAO-WBC, it has important drawbacks. For example, it is mainly effective in immunocompetent patient. For immunocompromised patients such as infected with HIV, patients receiving immune modulating agents and for infections that do not elicit strong immune responses such as Mycobacterium tuberculosis or Pneumocystis carinii, white blood cell labelling is not a choice to image infection and inflammation foci (Palestron and Torres, 1999). In addition, it is contraindicated in patients suffering from neutropenia because there is difficulty in obtaining sufficient amounts of WBCs to label. Sometimes, it is nonspecific. Also, false negative results in chronic infection may occur due to low granulocyte involvement in chronic infectious diseases. Preparation is time consuming, laborious, needs special facilities and carries a high risk of contamination (Petruzzi et.al.2009 & de Vries et. al 2010).

In addition, the ^{99m}Tc-HMPAO labelled WBCs have less in vivo stability than the indium-111 labeled WBCs. One example is the in vivo release of 99mTc-HMPAO from the labeled WBCs after reinjection into the patients. The free ^{99m}Tc-HMPAO is excreted via the hepatobiliary systems and the kidneys, which may hamper image interpretation. This phenomenon is not observed with ^{111}In-oxine labelled WBCs (Signore et.al 2009) and the normal distribution of indium labelled WBCs is confined to liver, spleen and bone marrow. (Palestro et.al 2009). To avoid the above limitations, other ligands have been developed. Some of the important ligands include human immunoglobulins G antibody, Antigralocyte antibodies, small peptides etc.

Antibodies

One of the methods of avoiding the limitations of radiolabeling WBCs in vitro is to radiolabel them in vivo using radiolabeled antibodies. The radiolabeled antibodies may bind to antigens on the WBCs and move to the site of infection and inflammatory foci by chemotaxis. Examples of antibody-based ligands are human immunoglobulin G, antigranulocyte antibodies and their fragments. Unlike radiolabelled WBCs, they don't require sophisticated methods of preparation.

Human immunoglobulins G antibody

It is a polyclonal antibody secreted in response to tissue damage. It can be isolated from human blood and used to enhance immunity in immunocompromised patients and other conditions which need immunity boost (Widjaksana et.al 2008).

Technetium-99m labelling of human immunoglobulin G is achieved via direct labelling and indirect methods. The direct method is where immunoglobulin's the disulfide bonds are reduced by reducing agents such as $SnCl_2$ and then the resultant sulfhydryl groups serve as binding sites for reduced technetium-99m. The indirect method of labelling requires a bifunctional chelator that attaches to both the antibody and the technetium-99m (Hnatowich et.al, 1993). Technetium-99m labelled human immunoglobulin G has been used to detect and localize musculoskeletal infections, rheumatoid arthritis and pulmonary infections; particularly in immunocompromised patients (Goldsmith and Vallabhajosula, 2009). The advantages of technetium-99m labeled human immunoglobulin G antibody include the minimized possibility of allergy reactions as human immunoglobulin G is naturally found in the human body. Other advantages are that human immunoglobulin G is already commercially available as clinically proven safe IgG formulations for intravenous injection, it is possible to formulate it as a lyophilized kit formulation for long term storage and it does not require the sophisticated preparation methods for radiolabeling WBCs (Wong et.al 1995).

However, it is nonspecific as it does not discriminate infection from sterile inflammation, it has slow clearance from the circulation and from non-target tissues and also shows slow accumulation in target lesions; to long time intervals between radiopharmaceutical administration and final diagnosis (24-48hr), (Rubin and Fischman, 1994). In addition, its high uptake in the liver, the spleen, and the kidneys makes it difficult to detect infection foci near to these tissues. Initially it was thought that the labelled human immunoglobulin G interacts with Fc-Y receptor that is expressed on infiltrating leucocyte. Nowadays, its accumulation at the site of infection and inflammation foci has been shown to occur by nonspecific extravasation due to the locally enhanced vascular permeability (Fischman et.al. 1992). Based on the same idea, monoclonal antigranulocyte antibodies were also developed with the hope that they will be

transported to the target loci by specifically bind to granulocytes.

Antigranulocyte antibodies

Anti-granulocyte antibodies are monoclonal antibodies that recognize and bind to specific antigens on granulocytes. Several anti-granulocyte antibodies have been identified of which anti-NCA-95 IgG (BW250/183), anti-NCA-90 Fab' (Immu-MN3, Sulesomab: anti-CD66), and anti-SSEA-1 IgM (LeuTech: anti-CD15) were radiolabeled with technetium-99m for detection of infection and inflammation foci and they showed significant accumulation in the target foci (Becker et. al. 1994). Their advantage over radiolabelled polyclonal immunoglobulins is that they have excellent target to background ratio.

Initially, whole antigranulocyte antibodies were radiolabeled but their slow clearance from the circulation and non-target sites and their risk of causing allergic reactions necessitated the development of radiopharmaceuticals based on antibody fragments. Consequently, more antigranulocyte antibody fragments than whole antigranulocyte antibodies have been labelled with technetium-99m. Sulesomab is an example of the antigranulocyte antibody fragments. It is an anti-CD15 antibody Fab' antibody fragment that has been labelled with technetium-99m and used to determine location and extent of infection and inflammation in bones with suspected osteomyelitis (including diabetic foot ulcers) (Delcourt et.al 2005). Also, it has shown its effectiveness in the detection of several infection and inflammation disorders including malignant external otitis and inflammatory bowel disease (Quigley et al. 2008 & Galletti et.al. 2015). However, their mechanism of localization at infection and inflammation foci appears to be different from radiolabeled WBCs. They are nonspecific in differentiating infection and sterile inflammation. Their uptake is still due to enhanced vascular permeability at the target foci (Petruzzi, 2009). Other limitations are: HAMA to the non-humanized antibodies, slow diffusion into sites of inflammation due to high molecular weight, long plasma half-lifes and high liver uptake due to their clearance by the reticulo-endothelial system (Wang et.al. 2008).

Ligands that were thought to possess less of the above limitations have been explored too. Examples include cytokines, microbial chemotactic peptides, antimicrobial peptides, etc.

Low molecular weight peptides

Cytokines

Cytokines are a group of small proteins that are secreted by immune cells for cell signaling of inflammatory cells. Their receptors are found in leucocytes. Cytokines include chemokines, interferons, interleukins, lymphokines, and tumour necrosis factors (Luster, 1998).

Interleukin 8 (IL-8) is a chemotactic cytokine that binds with a high affinity to its receptors expressed on activated neutrophils (Shahzad et.al. 2010). It is the most commonly radiolabeled interleukin for imaging infection and inflammation foci. It has been radiolabeled indirectly with ^{99m}Tc using HYNIC as a bifunctional complexing agent. ^{99m}Tc-labeled IL-8 has been studied in both humans and animals, showing promising results. It may be used for detection of pulmonary infections, osteomyelitis, and inflammatory bowel disease as well as other infectious and inflammatory disorders (Bleeker-Rovers 2007).

The advantage of technetium-99m labeled interleukin 8(IL-8) radiopharmaceuticals is that they can be made available as lyophilized kits. They are also rapidly cleared from the circulation and non-targets tissues so that focal accumulation to sites of infection occurs as early as 4 hours after injection (Bleeker-Rovers 2007 & Gratz et.al 2001).

Inability to discriminate infection and inflammation foci and lack of clinical trial studies are the major drawbacks of interleukin based radiopharmaceuticals.

Microbial chemotactic peptides

Microbial chemotactic peptides are small molecules released from bacteria that initiate migration of inflammatory cells (chemotaxis) by binding to high-affinity receptors on the WBC's cell membranes. They stimulate biological functions such as degranulation, release of oxygen radicals, phagocytosis, and eicosanoid production. They are usually formed via the cleavage of bacterial mitochondrial proteins (Nast and LeDuc, 1988). The tripeptide, formyl-methionyl-leucyl phenylalanine (f-MLF), has been labelled with technetium-99m via its HYNIC conjugate (99mTc-fMLFK-HYNIC) and showed preferential accumulation in both infection foci and foci of sterile inflammation in rabbits within 2 hour post-injection (Edwards et.al 1999).

Chemotactic peptides can be synthesized chemically, withstand harsh condition during preparation and labelling, and they are less likely to induce immunogenic reactions. In addition, they have rapid clearance from circulation hence earlier imaging is possible (Okarvi, 2001).

The main limitation with microbial chemotactic peptides is that they cause leucopenia at low dose (Das et.al. 2002). In addition, they cannot differentiate between infection and sterile inflammation. Some peptides that were intended to localize specifically to infectious foci have been investigated.

Antimicrobial peptides

Antimicrobial peptides are biomolecules that exist in eukaryotes as a (innate immunity) defense mechanism against pathogenic microorganisms. Around 1500 antimicrobial peptides have been discovered or

synthesized up to date. They are classified based on their amino acid composition and secondary structures. They show broad spectrum of activity against bacteria, viruses and fungi (Izadpanah and Gallo, 2005).

Antimicrobial peptides selectively bind to pathogenic microorganisms due to differences in the physiological membranes of the host and the microorganisms such as membrane composition, charge, hydrophobicity, asymmetry, transmembrane potential and the existence of receptors in the pathogenic microorganism's membrane for the antimicrobial peptides (Bahar and Ren, 2013).

Antimicrobial peptides have attracted interest for specific imaging of infection foci because of their selective cytotoxicity to pathogenic microbes and their ability to selectively accumulate at the infection sites. In addition, they are cleared rapidly from the circulatory system and they rapidly accumulate at the infection foci. (Ebenhan et.al. 2014).

Among the antimicrobial peptides, ubiquicidin and its fragments are the most studied. Ubiquicidin (UBI) 29–41, is a fragment having amino acid sequence of TGRAKRRMQYNRR and a weight of 1,693 Da. It has been labelled with technetium-99m and shown promising results in clinical trials (Akhtar et.al 2005).

Techntium-99m- ubiquicidin (UBI) 29-41 may be used for detection of infections in diabetic foot, hip prostheses, or other implant related infections. Moreover, it may also detect osteomyelitis and infective endocarditis (Akhtar et.al 2012).

The drawback of this radiopharmaceutical is that antimicrobial efficacy and mechanisms are extremely sensitive to conditions such as pH, osmotic strength, solution viscosity, and temperature. Some bacteria produce proteases and degrade these peptides and lead to false negative results (enzymatic degradation). Furthermore, it does not detect infections caused by intracellular pathogens (Akhtar et.al 2012). Therefore, antimicrobial agents have been researched.

Antimicrobials agents

There has been a belief that radiolabeled broad spectrum antimicrobials that act by binding to specific microorganism's components may possess an ability to differentiate infection foci from sterile inflammation foci. Consequently, fluoroquinolones, cephalosporins, penicillins and some other antimicrobial agents were radiolabeled with technetium-99m and used for detection of infection foci. (Shahzadi et.al 2015 & Lambrecht, 2011).

Radiopharmaceuticals that have been prepared using antimicrobial agents have ease and low cost of preparation, can be availed in kit forms and they are a better choice for immunocompromised patients since they do not interact with cells involved in the inflammatory and immune processes (signh. et.al 2012).

However, in some studies it was observed that ciprofloxacin, the most commonly studied radiolabeled antibacterial, also localizes in sterile inflammation sites. Radiolabeled ciprofloxacin accumulates at the sites of infection and Inflammation foci because of increased vascular permeability (Sarda et.al. 2003). Furthermore, antimicrobial resistance may prevent the binding of the radiopharmaceutical to the bacteria, leading to false negative results. Problems relating to low radiochemical purity and poor stability have questioned its future application (Welling et. al 2001). Other nonspecific radiopharmaceuticals that base on technetium-99m include liposomes, nanocolloids, and MDP.

Liposomes

Liposomes are spherical vesicles made out of one or more lipid bilayers. Their mechanism of localization at the sites of infection and inflammation is by extravasation due to locally enhanced vascular permeability. Liposomes naturally target the mononuclear phagocytic system and radiolabeled liposomes are cleared rapidly from the circulation by the mononuclear phagocytic system. This problem can be avoided by coating the liposomes with hydrophilic polymers such as polyethylene glycol so as to avoid their rapid clearance from the circulation (Boerman, et.al.2001).

Liposomes have been radiolabeled with ^{99m}Tc, either using hexamethyl propylene amine oxime (HMPAO) as an internal label or via HYNIC as an external chelator (Akhtar, et.al. 2012). They may be useful for the detection of infection and inflammation foci (Boerman, et.al. 2000).

Technetium-99m labelled liposomes do not discriminate infection foci from sterile inflammation and they have unacceptable side effects, which limit their clinical application (Boerman, et.al.2001).

Nanocoloids

Nanocolloids are colloids of human serum albumin that measure less than 50nm in size. They have also been labelled with technetium-99m for the detection infection and inflammation foci (Flivik et.al.1993). Their localization at the sites of infection and inflammation is due to increased capillary permeability (Streule, et.al 1988).

Their application, however, is limited to musculoskeletal infections and inflammation (Das et.al 2002).

MDP (methyl diphosphonate)

^{99m}Tc-MDP is a nonspecific radiopharmaceutical that localizes at the site of infection and inflammation due to vasodilation and hyperemia. It is mainly used for imaging in bone infections such as osteomyelitis and prosthetic joint infections. Usually, it is used in

combination with radiolabeled WBCs to increase the specificity of the detection procedure. The procedure requires three phase bone imaging, usually taking 4 hours post injection (Love and Palestro, 2004).

The half-life of technetium-99m is sometimes not enough to undertake certain studies. For that reason, longer lived SPECT radionuclides such as I-123 may act as useful alternatives.

Iodine-123

Iodine is a highly volatile group seven element with an electronic configuration of $(Kr)4d^{10}5s^{2}5p^{5}$. Its chemistry is dominated by both electrophilic and nucleophilic addition and substitution reactions (Koehler, 2010). It has four radionuclides that are potentially applicable for clinical gamma imaging applications; Iodine-120, Iodine-123, Iodine-124 and Iodine-131. Due to the high positron energy of Iodine-120 and the beta-minus particle emission of Iodine-131, these radioisotopes are not clinically applied for infection or inflammation imaging today.

Iodine-123 decays 97% by electron capture with a half-life of 13.2 hours to tellurium-123. In the process, gamma rays of 159 keV having an abundance of 83% is emitted (Be, 2004). The gamma energy, its abundance and the 13.2 hour half-life make iodine-123 well suited for infection and inflammation imaging, including cases where delayed or follow up imaging is necessary. One important challenge in the use of iodine-123 is its cost. This cost is contributed mainly because it is cyclotron produced. Also, the volatile nature of iodine demands more caution and dedicated equipment for the handling of radioiodine. Another challenge, like for all other iodine radioisotopes, is the risk of in vivo de-iodination and thyroid uptake of the radioiodine.

Translocator protein (TSPO)

TSPO, also called peripheral benzodiazepine receptor, is a mitochondrial membrane protein that is present in immune cells. In the CNS, it is specific for glial cells and astrocytes. Immune responses in the CNS are mediated via these cells which overexpress TSPO when they are activated during inflammation, (Chen, 2008). TSPO is therefore a useful target for the molecular imaging of neuroinflammation in vivo. According to Wu C. et al (Wu et al, 2013), radiotracers targeting this biomarker have been developed and clinically tested.

PK11195, an isoquinoline derivative, is a high affinity ligand TSPO. It has been radiolabeled with iodine-123 and clinically tested for SPECT imaging of inflammation in various tissues such as CNS (Versijpt, 2000) and myocardium (Gildersleeve, 1996) with significant accumulation at the inflammation sites.

The challenge with this ligand is that it accumulates in other organs where TSPO is abundantly expressed such as the kidneys, myocardium and also in some cancers (Batarseh A., 2010). Also, it cannot differentiate sterile inflammation from infection.

Cytokines

Interleukin-2 - IL-2

Interleukin-2 is a cytokine that is secreted by activated T cells. It has its receptors on a variety of immune cells, including macrophages, T cells, B cells and even NK cells and it is involved in both the initiation and termination of inflammation (Hoyer, 2008). By radiolabeling it with gamma emitting radioisotopes, it's possible to image inflammation loci. Iodine-123 has already been used for that and it produced useful results in humans (Signore, 2000). With these findings and others (Annovazzi, 2003), the approach of targeting IL-2 receptor bearing immune cells with radioisotopes for molecular imaging of inflammation maybe applicable for monitoring and individualizing therapy in patients with T cell and macrophage infiltrated inflammatory lesions such as in Crohn's.

Interleukin-1B IL-1B

Interleukin-1B is a pro-inflammatory cytokine, produced majorly by activated macrophages and monocytes (Lopez-Castejon, 2011). It has receptors in a variety of immune mediating cell types, including granulocytes. During inflammation, these cells upregulate their Intrleukin 1 receptors (Fasano, 1991). Since these immune cells accumulate in inflammatory loci, targeting them for nuclear molecular imaging can be an important option in detecting inflammation sites and treatment monitoring. The radiolabeling of human recombinant interleukin-1 receptor antagonist (hrIL-Ira) with Iodine-123 has already been done and it has shown preferential accumulation in the inflamed joints of rheumatoid arthritis patients with synovitis (Barrera, 2000).

Similar to all other radiolabeled cytokines, it lacks ability to distinguish infection from sterile inflammation foci.

PET radiopharmaceuticals for infection and inflammation imaging

Since SPECT technology generally has lower resolution and sensitivity than PET technology. PET radiopharmaceuticals also given significant interest in the area of infection and inflammation imaging.

Fluorine-18 based radiopharmaceuticals for infection inflammation imaging

Fluorine is a group seventeen element in the periodic table with an electronic configuration of $[He]2s^{2}2p^{5}$. Fluorine-18 is the only radioisotope of fluorine that is important for radiopharmaceutical application presently. Its radiochemistry is diverse, involving both nucleophilic and electrophilic reactions (Jacobson, 2010).

Fluorine-18 is a positron emitting radioisotope that decays into Oxygen-18 with a half-life of 1.83 hours. 97% of it decays through positron emission and the rest

is through electron capture. Its maximum and mean positron energies of 634 keV and 249 keV, respectively (Be et al, 2004). Its mean tissue positron range of about 0.6 mm (Cal-Gonzalez, 2009) yields higher PET image resolution with fluorine-18 than with other clinically available positron emitting radioisotopes. The excellent nuclear properties and fluorine's diverse chemistry (Jacobson, 2014) highlight fluorine-18's suitability for infection and inflammation imaging and for most clinical PET applications. Indeed, fluorine-18 is currently the commonest positron emitting radioisotope in clinical use. Fluorine-18 is mainly cyclotron produced through proton bombardment of Oxygen-18 gas (Jacobson, 2014). However, fluorine-18 is still more expensive to produce than generator produced radioisotopes because it requires cyclotrons.

Deoxy Glucose

2-Deoxyglucose is a derivative of glucose on which the hydroxyl group at position 2 of glucose has been replaced with hydrogen. It has similar biochemical properties with glucose. Its uptake by the cells depends on cellular metabolic rate and abundance of the glucose transporter. One of the hydrogen groups can be substituted with radioactive fluorine-18 to make radiopharmaceuticals and can be used for diagnosis of diseases in which glucose metabolism is altered in their pathophysiological processes. At inflammatory sites, upregulation of glucose transporters and increased affinity to deoxy glucose by the inflammatory cells has been observed. These properties can be targeted for the imaging of infection and inflammation with ^{18}F-Fluorodeoxyglucose (^{18}F-FDG) (Glaudemans et.al. 2015). Nowadays, this agent is the most commonly used PET radiopharmaceutical for imaging infection and inflammation.

^{18}F-FDG can be used for the diagnosis of varieties of infectious and inflammatory disorders such as sarcoidosis, peripheral bone osteomyelitis, suspected spinal infections, FOU, metastatic infections, bacteremia in high-risk patients, AIDs-related FUO, vasculitis, abdominal infections such as inflammatory bowel disease, thoracic and soft-tissue infections (Jamar et.al. 2013).

The quality of the image when compare with SPECT imaging radiopharmaceuticals is superior. High spatial resolution and rapid accumulation in infectious foci are significant advantages ^{18}F-FDG of over other radiopharmaceuticals used in conventional imaging techniques (Gotthardt et.al. 2010).

Although ^{18}F-FDG PET imaging is very sensitive, it does not discriminate infection from sterile inflammation. Also, it lacks ability to distinguish inflammation from other conditions with high glycolytic activity such as tumors. It has difficulty to detect infection and inflammation foci near to heart and brain tissues. In addition, the high cost and limited availability of PET imaging (Basu et.al 2009) restrict its wide application in infection and inflammation imaging.

Radiolabeled WBCs have shown somewhat specificity towards infectious foci. Hence, an attempt to radiolabel WBCs with fluorine -18 has also been done.

WBCs

WBCs have been labelled with ^{18}F-FDG to take the advantage of good imaging characteristics of both ^{18}F-FDG and WBCs for visualizing infection and inflammation foci. Promising results were obtained (Pio et.al 2003).

However, the stability of ^{18}F-FDG-WBC is weak; there is a rapid release of ^{18}F-FDG from the radiolabeled WBCs. The half-life of fluorine -18 is too short for delayed imaging to be feasible, which decreases the specificity of the method. Furthermore, ^{18}F-FDG-WBC preparation is time consuming, requires highly trained personnel and special equipment which make it more expensive than both ^{18}F-FDG and ^{99m}Tc-HMPAO labeling methods (Signore et.al 2009).

Apart from the tedious process of radiolabeling WBCs with fluorine -18, ^{18}F-FDG-WBC still has the weakness of non-specificity in differentiating infection from sterile inflammation.

Thymidine kinase substrate

Thymidine kinase is an enzyme involved in the synthesis of DNA and it is found in most living cells. However, the isoforms present in human and bacteria are different. This characteristic may help to develop a substrate that is selectively metabolized by bacterial thymidine kinase and use it to formulate radiopharmaceuticals that selectively accumulate in infection foci. 3'-deoxy-3'-[^{18}F] fluorothymidine ([^{18}F]FLT) is a fluorine-18 labeled nucleoside substrate for Salmonella typhimurium thymidine kinase. It has shown significant accumulation in bacterial infection foci in mouse models (Davis et.al. 2009 and Jang et al 2012).

Other ligands for fluorine-18 for infection and inflammation imaging

In addition to deoxy glucose, other ligands have been discovered to visualize infection and inflammation foci using fluorine -18 as a PET imaging radionuclide. These ligands target different sites and receptors involved in the inflammatory process.

^{18}F-choline (^{18}FCH) targeting increased catabolism of phosphatidylcholine by inflammatory cells (macrophages and monocytes) has shown promising results in the detection of inflammation associated with atherosclerotic plaques. ^{18}F-labeled isoquinoline carboxamide (PK11195), ^{18}F-FEAC and ^{18}F-FEDAC are radioligands targeting translocator protein (TSPO) that is highly expressed in macrophages, neutrophils, lymphocytes, activated microglia and astrocytes. They have shown

high accumulation in sites of neuroinflammation and other inflammatory disorders (Wu et.al 2013).

Ligands that are targeting cannabinoid receptor 2 (CB2R) have also been labeled with fluorine-18. CB2R is mainly over expressed on activated microlgia, the resident immune cells in CNS, and promising results have been observed for the imaging of inflammatory disorders in the brain tissues (Evens et.al 2011).

^{18}F-CGS27023A and other Matrix metalloprotease (MMP) inhibitors are ligands that inhibit matrix metalloproteinases (MMPs), enzymes whose activity increases during inflammatory conditions. They can possibly be the future agents for detecting inflammatory disorders e.g. vascular inflammation (Wu et.al 2013).

Interleukin (IL)-2 is a glycoprotein synthesized and secreted by activated T lymphocytes. It binds to its specific receptor on activated lymphocytes. Radiolabeling this ligand with Flourine-18 (^{18}F-FB-IL-2) may help to visualize activated lymphocytes in inflammatory disorders (Di Gialleonardo et.al 2012).

RGD peptides are peptides that contain the three amino acid sequence Arg-Gly-Asp. They bind specifically to αvβ3, an integrin receptor that is expressed in activated inflammatory cells such as macrophages. These peptides have been labelled with fluorine-18 and they may be useful for visualizing angiogenesis in inflammation disorders (Wu et.al 2013).

Carbon-11 based radiopharmaceuticals for infection and inflammation imaging

Carbon is a group four element in the periodic table of elements with an electronic configuration of $1s^2 2s^2 2p^2$. It is a constituent of all organic molecules, hence, radioisotopes of carbon that have suitable nuclear properties are particularly useful in that they can be incorporated into any organic molecule and used to image biological processes including infections and inflammation.

Among the carbon radioisotopes, it is carbon-11 that is useful for radiopharmaceuticals today. It decays with a half-life of 20.4 minutes to Boron-11. Over 99% of Carbon-11 decays by positron emission (Be, et al, 2004). The high yield of positrons ensures the production of high abundance of annihilation photons for imaging. Also, the average positron energy of 386 keV (Be, et al, 2004) limits their average tissue range to about 1.0 mm (Cal-Gonzalez, 2009) and yield high resolution images. Of the currently used short-lived PET radioisotopes, carbon-11 is the closest to fluorine-18 in both average positron energy and tissue range. The major challenge with carbon-11 application in radiopharmaceuticals is its short half-life. Since it is usually produced as carbon dioxide gas or methane gas from the cyclotron, carbon-11 mostly requires to be converted into chemically reactive species for its incorporation into radiopharmaceuticals (Scott, 2009). The time taken during such processing may significantly lead to lower radiolabeling yields. In addition, the short half-life precludes delayed imaging of the infection or inflammation locus. High yield production of carbon-11 is done through proton bombardment of nitrogen-14 in a cyclotron (Schmor, 2011). Cyclotron production, while avoiding the challenges associated with reactor produced radioisotopes, leads to high cost of the radiopharmaceuticals produced.

Translocator protein (TSPO)

Translocator protein has also been targeted with its iodine -123 labelled high affinity ligands such as PK11195 for molecular SPECT imaging (refer to section on Iodine -123). Among the carbon-11 labeled tracers of this category, the commonest example is 11C-PK11195. In clinical trials this agent has shown preferential accumulation in inflammation sites (Wu C, 2013). Also, it may distinguish inflammation from some tumors.

Cannabinoid receptor 2

The main cannabinoid receptor that is associated with anti-inflammatory properties in the brain is CB2R (Miller, 2008). It is constitutively expressed in low amounts but its expression is upregulated in activated microglial cells, perivascular macrophages and other immune cells during inflammation (Benito, 2005). Imaging CB2R can be an important tool for diagnosing and monitoring neuroinflammation. Tracers such as 11C-A-836339, 11C-Sch 225336, [C11]NE40 and 11C-GW405833 have been developed, but mainly in the pre-clinical stages (Wu, C. 2013).

Fluorine-18 and carbon-11 are produced from cyclotron, making them expensive. Gallium- 68 is produced from generators and it can serve as a cheaper alternative for PET.

Galium-68

Gallium-68 decays 89% by positron emission and 11% by electron capture, with a half-life of 1.13 hours to zinc-68. 88% of the times, it emits positrons having mean energy of 844 keV (Delacroix, 2002) and a simulated mean tissue range of 2.21mm (Cal-Gonzalez 2009). It is available for clinical application mainly through the germanium-68/gallium-68 generator (Velikyan, 2015).

Its commercial availability from the inexpensive germanium-68/gallium-68 generator makes the radioisotope less costly than cyclotron produced radioisotopes. Also, its high positron yield means that it achieves high abundance of its 511 keV annihilation gamma rays. The 270-day half-life of the parent (germanium-68) allows for a very long working life of the generator (one year). Some of its limitations are that its positrons have a higher mean energy and a longer tissue range, hence poorer image resolution than seen with other positron emitting radioisotopes such as carbon-11, fluorine-18 and copper-64 (Cal-Gonzalez

2009). Its half-life of 68 minutes is also unsuitable for labeling slow plasma clearing molecules.

Successful usage of gallium-67 citrate with SPECT lead to the application of positron emitting gallium-68 for infection and inflammation imaging. ^{68}Ga-Citrate and ^{68}Ga-transferrin have been used as PET alternatives to gallium-67 citrate imaging. They have been used for the detection of bone infections such as osteomyelitis (Kumar and Boddeti, 2013). However, the short half-life of ^{68}Ga is a challenge since these agents require delayed imaging, just as with ^{67}Ga-citrate.

Small peptides have fast kinetics and they are rapidly cleared from plasma and other non-target tissues, making them interesting ligands for the short half-life positron emitting gallium-68. Peptide-based radiopharmaceuticals that are radiolabeled with gallium-68 have been developed to detect infection and inflammation foci. A pre-clinical study on the antimicrobial peptide TBIA101 labeled with gallium-68 (68Ga-DOTA-TBIA101) targeting bacterial lipopolysaccharides has shown localization in E. coli infected tissues (Mokaleng et al, 2010).

Recently, it has been shown that a peptide the Siglec-9 targets vascular adhesion protein 1 (VAP-1). VAP-1 is a human endothelial protein whose cell surface expression is induced under inflammatory conditions. It controls the extravasation of leukocytes. ^{68}Ga-DOTA-Siglec-9 was developed and tested in clinical studies where it has demonstrated significant accumulation in S. epidermidis or S. aureus infected rat tissues (Ahtinen, H et.al 2014).
The hemoglobin scavenger receptor CD163 is overexpressed in a large range of inflammatory diseases. ^{68}Ga labeled anti-CD163-antibody for arthritis imaging in rodent PET showed promising results (Christensen et.al 2015).

Over-expression of somastatin receptors (SSTR) on activated lymphocytes and macrophages has been observed. Peptide ligands such as TATE (Tyr octreotate) and TOC (Tyr octreotide) octreotide analogue that binds to somastatin receptor 2(SSTR2) have been labeled with ^{68}Ga through DOTA-derived bifunctional chelators. They have been used to visualize inflammation foci in atherosclerosis, pulmonary fibrosis as well other conditions. These radiopharmaceuticals are especially important in imaging of coronary artery plaques since there have low uptake in the myocardium (Pettinato et.al 2008 & Banerjee and Pomper, 2013).

Long lived PET radionuclide.
Since the above PET radionuclides have a short half-lives, longer lived PET radionuclides would offer the advantage of studying the uptake of the tracers for longer periods of time.

I-124

Targeting enzymes

Enzymes that are specific for, or more abundant in, inflammatory cells or pathogens are potential targets for molecular imaging of inflammation and infection using radiolabeled enzyme substrates. The important factor about this approach is that the enzyme must be substrate-specific and its products must be selectively retained within the target cells or tissues so as to minimize the background uptake of the radiotracer. Enzymes that have already been targeted include Matrix Metalloproteinases (MMP), Caspases and Thymidine kinase.

Matrix metalloproteinases - MMP

Matrix metalloproteinases are a class of proteolytic enzymes that are produced constitutively in physiological amounts in almost all tissues, where they have multiple physiological roles (Loffeck, 2011). Also, they have been implicated in pathologies such as inflammatory diseases, etc. where they are significantly overexpressed in the affected loci (Muller-Quernheim, 2011). By radiolabeling specific inhibitors of these enzymes, in vivo imaging of inflammation loci has been successful in animal models. For instance, Hartung et al. showed that 124I-HO-MIP (CGS 27023A) preferentially accumulated in loci of carotid inflammation in mice (Hartung et al, 2007).

Thymidine Kinase

Thymidine kinase is a phosphotransferase that catalyzes the conversion of thymidine to thymidine monophosphate, an important process in nucleic acid synthesis. Even though the enzyme is ubiquitously expressed in both prokaryotes and eukaryotes, there are significant differences in the isoforms and also substrate specificity (Wellin, 2004). This difference has been exploited using ^{124}I-FIAU for the molecular imaging of bacterial infections. ^{124}I-FIAU is a specific substrate of the bacterial isoforms of the enzyme (Diaz, 2007). One advantage of this approach is the possibility of differentiating infection from sterile inflammation. However, some clinical studies have posted poor outcomes. (Zhang et.al. 2016).

Monoclonal antibodies

Targeting CD20

CD20 is a B-cell specific surface antigen that is important for B cell activation and function (Kuijpers, 2010). In some inflammatory conditions such as rheumatoid arthritis, B cell infiltration and accumulation into inflamed joints occurs in some patients (Bugatti, 2014). In such patients, rituximab, an anti-CD20 monoclonal antibody, is still applied for their therapy. Therefore, molecular imaging to determine B cell infiltration in rheumatoid arthritis patients can be very valuable for patient classification, individualizing therapy and patient monitoring. For PET imaging of B cell infiltration of inflamed joints, ^{124}I-rituximab demonstrated clinical usefulness in clinical studies (Tran, 2011).

Copper-64 based radiopharmaceuticals for infection and inflammation imaging

Copper is a transition metal with an electronic configuration of $[Ar]3d^{10}4s^{1}$. Its radiopharmaceutical chemistry is dominated by its +2 oxidation state (Cai, 2014). In this state, copper is able to form stable complexes with nitrogen-containing bifunctional chelating agents that can subsequently be chemically attached to bioactive molecules for imaging biological processes. Radioisotopes of copper that have potential usefulness in imaging include copper-60, copper-61, copper-62 and copper-64. However, copper-64 is the commonest applied for clinical positron emission tomography because of its appealing nuclear properties.

Copper-64 decays with a half-life of 12.7 hours by beta-minus emission to zinc-64 (39%), positron emission (18%) and electron capture to Nickel-64 (Be, 2004). Its maximum positron energy of 653 keV (Be, 2004) and mean positron range are similar to those of fluorine-18 (Belov, 2011). Hence, the image resolution is expected to be similar to that obtained from fluorine-18 scans. Its half-life is also long enough for the performance of delayed and longitudinal imaging.

Some challenges with copper chemistry include the low in vivo stability of many of its complexes (Zhengxin, 2014), causing high radiocopper uptake by non-target tissues. Its high abundance beta-minus emission is another challenge because it may contribute to high unwanted radiation dose to the patient. Also, the cost of copper-64 is high since it's produced through the cyclotron.

Currently, there are a few ligands that have been labelled with copper-64 for the detection of infection and inflammation foci.

WBCs

WBCs have also been labeled with copper-64 for infection and inflammation imaging. ^{64}Cu-WBCs labeling efficiency and viability were comparable or superior to ^{111}In-WBCs, and significantly higher than ^{18}F-FDG-WBCs in human volunteers (Bhargava et.al. 2009).

Formyl peptide receptor (FPR) ligands

FPR is a type of G-protein coupled receptor expressed on neutrophils. It is involved in chemotaxis (Le et.al. 2001). The peptide cinnamoyl-F-(D)L-F-(D)L-F (cFLFLF) is an antagonist to the FPR. It has been labelled with Cu-64(cFLFLFK-PEG-(64) Cu) and showed significant accumulation in lungs of a Klebsiella infected mouse model (Locke et.al. 2009).

RGD peptides

RGD peptides are ligands that bind to Integrin αvβ3, a cell adhesion molecule. αvβ3 is overexpressed in some inflammatory cells, such as macrophages. The radioligand ^{64}Cu-DOTA-E[c (RGDyK)] 2}2 that binds to integrin αvβ3 has shown promising results in imaging the chronic inflammation process (Cao et.al. 2007).

Natriuretic peptide

^{64}Cu-labeled atrial natriuretic peptide (^{64}Cu-DOTA-C-ANF) has been applied for the detection of atherosclerotic plaques on rabbit (Liu et.al 2010)

Anti-b7 integrin antibody

Integrins are cell surface glycoprotein receptors that are involved in leucocyte adhesion, signaling, proliferation and migration by binding as heterodimers to specific ligands. The β7 integrin forms heterodimers with ligands expressed on lymphocytes, and other cells to mediate leucocyte infiltration into the gastrointestinal tract (Stefanich et.al. 2011). ^{64}Cu-labeled anti-b7 integrin antibody has shown significant uptake in dextran sulfate sodium (DSS) induced colitis in mice (Dearling and Packard, 2012)

Nanoparticle

^{64}Cu-labelled chitosan-coated magnetic nanoparticles are taken up by granulocytes through phagocytosis. They have shown suitability for use as infection and inflammation radiopharmaceuticals. (Pala et.al. 2012)

Zirconium-89 based radiopharmaceuticals

Zirconium is a group four transition metal with an electronic configuration of $[Kr]4d^{2}5s^{2}$. Zirconium, in its +4 oxidation state, forms stable complexes with nitrogen and oxygen containing electron donor ligands. The commonest ligands studied are bifunctional chelators based on desferrioxamine for radiolabeling of biomolecules (W Severin, 2011). Ziconium-89 is the commonest studied zirconium isotope for radiopharmaceutical application. It decays by positron emission (23%) and electron capture with a half-life of 78.43 hours (3.27 days) to Yttrium-89 (Kocher, 1981). Apart from the advantages of its long half-life, its average positron energy of 397 keV (Kocher, 1981) may achieve an image resolution similar to that of carbon-11 imaging since it has similar mean positron energy. However, its emission of high abundance (99%) high energy photons (909 keV) (Kocher, 1981) and its high cost of production from cyclotron constitute some of its important limitations.

Currently, there are a few ligands that have been labelled with zirconium-89 and used for the detection of infection and inflammation foci. WBCs were labelled with zirconium-89-loaded chitosan nanoparticles (CN) and copper-64-loaded CN. ^{89}Zr-loaded-CN showed fast kinetics of leukocyte association, high labelling efficiency and a relatively good intracellular retention of the radioactivity than copper-64-loaded CN (Fairclough et.al. 2016).

In another study ^{89}Zr-oxalate was compared with [^{18}F] FDG and sodium [^{18}F] fluoride. ^{89}Zr-oxalate showed higher selectivity index to inflammation at a delayed

time point after injection (24 h) than [^{18}F]FDG and sodium [^{18}F]fluoride. Significant uptake in inflammatory lesions of a mouse model of rheumatoid arthritis (RA) was also revealed (park et.al. 2016).

Other promising radionuclides

Manganese radioisotopes

Manganese is a group seven transition metal. A number of radioisotopes of manganese are potentially useful for radioimaging of biological processes such as infection and inflammation. They include Manganese-52 and Manganese-52m. Manganese-52 decays by positron emission (29%) and electron capture to Chromium-52 in a half-life of 5.6 days while Manganese-52m decays to Manganese-52 (96%) in a half-life of 21.2 minutes (Delacroix, 2002). Manganese-52, because of its long half-life of 5.6 days is more useful for imaging slow biological processes and radiolabeling large biomolecules of slower in vivo kinetics than Manganese-52m. With maximum and average positron energies of 575 keV and 241 keV respectively, Manganese-52 may yield images of better resolution than Manganese-52m which emits high abundance (96.6%) positrons with an average energy of 1172 keV (Kocher, 1981).

Terbium radioisotopes

Terbium is a lanthanide of atomic number 65 and an electronic configuration of [Xe]4f^{9}6s^{2}. It has two radioisotopes that are potentially useful for clinical imaging applications; Tb-152 for PET and Terbium-155 for SPECT. Terbium-152 decays by positron emission (17%) and electron capture to gadolinium-152 in a half-life of 17.5 hours (Muller, 2012). It's one main weakness is its high average positron energy of 1080 keV. Terbium-155, on the other hand, decays 100% by electron capture in a half-life of 5.32 days to gadolinium-155 with the emission of a spectrum of gamma rays. The high abundance gamma rays of 86.6 keV (32%) and 105.3 keV (25%) are useful for clinical imaging (Muller, 2012). Its half-life is also long enough for imaging of radiopharmaceuticals that possess slow in vivo kinetics.

CONCLUSION

Radiopharmaceutical are providing very important advantages over other diagnostic modalities for the diagnosis and monitoring of infectious and inflammatory disorders. Hence, interest in this area has increased in the last decade. However, the currently used radiopharmaceuticals are still far from ideal; for instance, they lack capability to differentiate infections from sterile inflammation. Many radiopharmaceuticals have been studied, so far, but still only few of them are in practice today. Therefore, it is important to accelerate the development of clinically viable radiopharmaceuticals for this area.

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