

Imaging Agents for PET of Inflammatory Bowel Disease: A Review

Farzaneh Rezazadeh, Aidan P. Kilcline, and Nerissa T. Viola

Department of Oncology, Karmanos Cancer Institute, Wayne State University, Detroit, Michigan

Inflammatory bowel disease (IBD), which encompasses ulcerative colitis and Crohn disease, is a chronic inflammatory disorder resulting from an aberrant immune response, though its exact cause is unknown. The current mainstay standard of care for the diagnosis and surveillance of IBD is endoscopy. However, this methodology is invasive and images only superficial tissue structures, revealing very little about the molecular drivers of inflammation. Accordingly, there is an unmet need for noninvasive imaging tools that provide reliable and quantitative visualization of intestinal inflammation with high spatial and molecular specificity. In recent years, several PET agents for imaging IBD have been reported. Such agents allow noninvasive visualization and quantification of dynamic molecular inflammatory processes in vivo. This review focuses on recent advancements in the development of PET tracers for imaging biomarkers of interest in IBD pathogenesis, such as cell-surface molecules that are overexpressed on immune cells and cytokines that perpetuate inflammatory signaling.

Key Words: inflammatory bowel disease; PET; noninvasive imaging; inflammation

J Nucl Med 2023; 64:1858–1864

DOI: 10.2967/jnumed.123.265935

Inflammatory bowel disease (IBD), which encompasses Crohn disease (CD) and ulcerative colitis (UC), is a chronic inflammatory disorder of the gastrointestinal tract (1). Although the exact etiology of IBD is unknown, it is closely associated with the loss of intestinal epithelial barrier functions, resulting in excessive bacterial translocation and activation of an excessive mucosal immune response (2).

Currently, diagnosis of IBD is based on endoscopy and barium-assisted radiologic examination, both of which are invasive and lack specificity (3). Accordingly, new technologies for noninvasive imaging of IBD-specific molecules that drive its pathophysiology, monitor disease activity, and evaluate treatment efficacy are required (4).

Appropriate imaging agents for PET can visualize the molecular signatures that initiate, drive, and sustain IBD with high sensitivity while also providing quantitative information (5). However, there are currently no Food and Drug Administration (FDA)-approved PET tracers specifically for IBD, and their development is currently limited to preclinical studies. This review provides an

overview of PET radiopharmaceuticals developed and evaluated specifically for the diagnosis of IBD in both preclinical and clinical settings.

PATHOGENESIS OF IBD

The pathogenesis of IBD is not completely understood because of its complexity and multitude of interrelated mechanisms. Currently, experimental data implicate abnormal gut microbiota, immune response dysregulation, environmental changes, and gene variants in its pathogenesis (2). A primary mechanism by which IBD develops lies in the disruption of homeostasis within the mucosal membrane. The mucosal barrier is susceptible to defects and modifications that increase its permeability (Supplemental Fig. 1; supplemental materials are available at <http://jnm.snmjournals.org>), leading to an imbalance of microbe communities, which is termed dysbiosis. This dysbiotic state elicits an innate immune response against intestinal pathogens, wherein activated immune cells (macrophages, neutrophils, and dendritic cells) exhibiting increased production of proinflammatory cytokines infiltrate the gastrointestinal walls (6). These innate immune cells produce reactive oxygen species, which are agents of inflammation and mucosal injury, as well as the cytokines interleukin (IL)-1 β , IL-12, tumor necrosis factor (TNF)- α , and IL-23 (7). The stimulation of IL-23 along with TNF- α triggers a proinflammatory cascade that further drives CD4⁺ T cells to proliferate into pathogenic T helper (Th) 17 cells, sustaining chronic intestinal inflammation (8).

The strong implication of IL-23 and TNF- α in the pathogenesis of IBD has led to FDA approval of therapies that block TNF- α (Remicade; Janssen) and the p40 subunit shared between IL-12 and IL-23 (Stelara; Janssen) (9,10). However, increased resistance to therapy is often observed. Accordingly, there is an unmet need for noninvasive strategies to assess disease response and inform a deeper understanding of the exact mechanisms underlying IBD relapse.

CURRENT APPROACHES FOR IMAGING IBD

There are several standard-of-care imaging techniques that are used to diagnose and monitor IBD. These include fluoroscopic imaging, ultrasound, MRI, and CT scans (11). Even though these diagnostic tools have been approved by the FDA as a standard of care, they can image only anatomic structures. Delineation of inflammation using PET probes is potentially superior for visualizing dynamic molecule-mediated events, mapping areas of inflammation, and providing quantitative information on disease severity, thus providing critical information that can guide effective patient treatments and interventions.

Received May 11, 2023; revision accepted Sep. 27, 2023.
For correspondence or reprints, contact Nerissa Viola (violan@karmanos.org).

Published online Nov. 2, 2023.

COPYRIGHT © 2023 by the Society of Nuclear Medicine and Molecular Imaging.

INFLAMMATORY BIOMARKERS FOR MOLECULAR IMAGING OF IBD

The use of molecular imaging with PET to visualize inflammatory biomarkers in IBD has been the subject of numerous preclinical and clinical studies in recent years (12–14). Attractive targets that allow the delineation of IBD include molecules that are found on cell surfaces or are required for intracellular signaling and molecules released into the extracellular milieu that are critical to the pathogenesis of IBD, such as soluble cytokines.

Glucose Metabolism

[¹⁸F]FDG PET imaging has emerged as a valuable tool for diagnosing and monitoring IBD. It capitalizes on the heightened glucose metabolism in proinflammatory immune cells, enabling the detection and assessment of disease severity (15). [¹⁸F]FDG PET provides a noninvasive means of visualizing inflammation and has shown promise in distinguishing active disease areas. It offers advantages over conventional endoscopy, particularly when combined with CT imaging, providing detailed anatomic and functional insights (16). Additionally, it has proven useful in pediatric IBD cases in which invasive procedures are less suitable (17). However, [¹⁸F]FDG PET is not specific for inflammation and may yield false-positive results due to physiologic gut activity, potentially limiting its accuracy. Furthermore, coexisting conditions such as diabetes and certain medications can interfere with the interpretation (18).

Cell-Surface Molecules

In recent years, there has been growing interest in the potential use of cell-surface molecules as biomarkers for the advancement of molecular imaging techniques in IBD. Targeting these molecules or their interactions has been the basis for the development of various PET imaging agents and will be discussed in the following sections.

β_7 Integrin. As discussed above, the infiltration of lymphocytes is a mediator of chronic inflammation. Lymphocytes that have been stimulated at intestinal inductive regions highly express the β_7 integrin subunit (Supplemental Fig. 2A) (19). Therefore, β_7 -positive leukocyte subsets are promising targets for imaging. ⁶⁴Cu-labeled anti- β_7 -integrin antibody FIB504.64 is an immune PET agent that was evaluated for imaging inflammation using a dextran sodium sulfate (DSS)-induced acute colitis mouse model (20). In the study, mice with experimental colitis induced by 2% DSS were injected with either [⁶⁴Cu]Cu-anti- β_7 integrin or a ⁶⁴Cu-labeled antibody isotope control and then imaged by PET at 1, 24, and 48 h after injection. The volume of interest of the intestine was calculated by manually drawing a region of interest on the PET images. At 48 h, the results showed higher uptake of the [⁶⁴Cu]Cu-anti- β_7 integrin in the gut for the DSS group (5.47 ± 2.0 percentage injected dose [%ID]/g) than for the control group (4.44 ± 1.2 %ID/g) and the DSS group injected with nonspecific antibody (2.24 ± 0.14 %ID/g). However, no statistically significant differences were observed among all groups. An ex vivo biodistribution study indicated significantly higher uptake of the radiotracer in the gut of the colitis model mice than in the healthy control mice (6.49 ± 2.25 vs. 3.64 ± 1.12 %ID/g, $P = 0.038$). Nevertheless, no significant differences were observed in the uptake of the radiotracer in the colon of the DSS mice injected with ⁶⁴Cu-labeled anti- β_7 integrin and that in the DSS mice injected with ⁶⁴Cu-labeled nonspecific antibody (6.49 vs. 3.97 %ID/g, $P = 0.095$).

That work was expanded to evaluate Fab (50 kDa) and F(ab')₂ (110 kDa) fragments derived from the full-length FIB504.64 antibody with the goal of accelerating clearance from nontarget organs (21). PET imaging data indicated improved pharmacokinetic profiles for both ⁶⁴Cu-labeled fragments with faster clearance from healthy tissues. PET imaging data at 4 h after injection demonstrated that uptake of ⁶⁴Cu-labeled FIB504.64 F(ab')₂ in the colons of the DSS group was comparable to that observed for the intact antibody (7.7 vs. 5.7 %ID/g) but with lower nonspecific accumulation in nontarget tissues. The ⁶⁴Cu-labeled FIB504.64 Fab fragment showed greater gastrointestinal uptake in the DSS-treated mice at approximately 5 %ID/g than in the control group after 4 h. Conversely, the radiolabeled F(ab')₂ fragment presented high uptake values in the gut at 1 and 4 h after injection (12–14 %ID/g). The FIB504.64 Fab tracer displayed similar pharmacokinetics in both DSS-treated and control mice at 24 h after injection and was not retained well in the inflamed gut. At similar time points, greater contrast was achieved by the FIB504.64 F(ab')₂ with approximately 7 %ID/g in the inflamed gut, representing a 3- to 4-fold higher accumulation than in the alimentary tract of control mice, likely due to its divalent and relatively slow-clearing nature. The overall results of this study indicated that [⁶⁴Cu]Cu-FIB504.64 F(ab')₂ exhibits improved characteristics in terms of stronger and persistent uptake in the inflamed gut and clearance from nontarget tissues as compared with the Fab fragment.

Translocator Protein. The translocator protein (TSPO) is an 18-kDa protein that is found at high levels on the mitochondria of immune cells such as macrophages and microglia. TSPO has been found to play a role in the inflammatory response in the gut, as it modulates the function of immune cells in the intestines, including macrophages and T cells (22). The pyrazolopyrimidine ligand *N,N*-diethyl-2-(2-[4-(2-fluoroethoxy)phenyl]-5,7-dimethylpyrazolo [1,5-*a*]pyrimidin-3-yl)acetamide (DPA-714) demonstrated high specificity and binding to TSPO. Its radiofluorinated analog [¹⁸F]DPA-714 was developed for PET imaging of inflammation in many neurologic diseases and conditions (23,24). The feasibility of [¹⁸F]DPA-714 for imaging inflammation in 2 different acute IBD animal models was explored, and it was further compared with [¹⁸F]FDG (25). The first model of colitis was induced by DSS treatment in rats, wherein overexpression of TSPO in the colon was observed after 7 d of DSS treatment (26). DSS-induced IBD rats were imaged using [¹⁸F]FDG and [¹⁸F]DPA-714 at days 7 and 8, respectively. Enhanced uptake in the colon of DSS-treated animals was observed for both radiotracers in comparison with healthy animals. The uptake of [¹⁸F]FDG showed a slight increase in the colon of the rats with induced inflammation compared with the healthy group, albeit with no statistically significant distinction ($P = 0.053$). Unlike [¹⁸F]FDG, quantitative analysis of [¹⁸F]DPA-714 uptake in the colon indicated a difference between DSS-treated and nontreated rats (0.50 ± 0.17 vs. 0.35 ± 0.15 %ID/mL, $P = 0.040$). The second IBD model was developed by administering male Wistar rats with trinitrobenzenesulfonic acid in a 50% ethanol–water solution via enema. In contrast to the DSS model, inflammation induced by trinitrobenzenesulfonic acid is more localized (mainly in the upper part of the ascending colon), which was delineated by both radiotracers. Colon uptake of [¹⁸F]FDG and [¹⁸F]DPA-714 was significantly higher in the trinitrobenzenesulfonic acid-treated animals than in the untreated control mice. In both DSS and trinitrobenzenesulfonic acid IBD models, the gut uptake of [¹⁸F]DPA-714 was associated with the overexpression of TSPO in the colon tissue, as confirmed by

immunohistochemistry. The proof of concept achieved in this study may be extended to enable the detection and precise staging of IBD in patients, allowing monitoring of therapeutic efficiency or disease progression.

CD4. As discussed above, CD4⁺ T cells play a significant role in the pathogenesis of IBD (Supplemental Fig. 2B) (27). Recent studies have shown that CD4⁺ T cells are triggered in the periphery of DSS-induced colitis mice and infiltrate the colon during the first 3–7 d of a DSS treatment. Freise et al. used ⁸⁹Zr-labeled GK1.5 cys-diabody, an antimouse CD4 antibody fragment derived from the GK1.5 hybridoma, as a probe for targeting CD4⁺ T cells in a DSS-induced acute mouse model (12). Anti-CD4 immunohistochemistry showed enhanced numbers of CD4⁺ T cells in the colons of the colitis mice. PET imaging showed that [⁸⁹Zr]Zr-anti-CD4 visualized CD4⁺ T cells in the distal colons, ceca, and mesenteric lymph nodes of the colitis mice (Fig. 1A). Furthermore, quantitative analysis of radiotracer uptake in the distal colon region and mesenteric lymph nodes revealed a significant increase of uptake in mice with colitis. Results of in vivo imaging were confirmed by ex vivo scans showing enhanced uptake in colons, ceca, and mesenteric lymph nodes from colitis mice. Although [⁸⁹Zr]Zr-anti-CD4 enables detection of overall CD4⁺ cells in the gut, a serious drawback in targeting this immune molecule for IBD diagnosis is that it does not provide information on its activation and proliferation status or on which specific subsets (e.g., Th1, Th2, Th17, or regulatory T cells) are present.

System x_C⁻. System x_C⁻, an antiporter that imports cystine, is a major source of glutamate release during oxidative stress. It is upregulated in activated macrophages and plays a pivotal role in the control of the innate and adaptive immune systems (Supplemental Fig. 2C) (13). An ¹⁸F-labeled L-glutamate derivative, (4S)-4-(3-¹⁸F-fluoropropyl)-L-glutamate ([¹⁸F]FSPG), has been shown to detect inflammation of the lungs and sarcoidosis by targeting system x_C⁻ (28). The diagnostic utility of [¹⁸F]FSPG PET/CT was then investigated in IBD mouse models induced with either DSS or adoptive T-cell transfer (13). Both showed increased colonic uptake of [¹⁸F]FSPG compared with healthy mice, and the SUV_{max} for radiotracer uptake was found to be positively correlated with clinical disease activity and pathologic score (Fig. 1B).

The radiotracer was further examined in 20 patients clinically diagnosed with UC (*n* = 10) or CD (*n* = 10). For the UC patients, [¹⁸F]FSPG PET/CT correctly identified active inflammation in 4 of 6 patients (67%) and endoscopic remission in 2 of 4 patients (50%). The summed SUV_{max} demonstrated a significant correlation with the UC endoscopic index of severity, whereas no significant associations were observed with the partial Mayo score, C-reactive protein levels, or fecal calprotectin. All 8 CD patients with active inflammation and 2 with endoscopic remission were correctly diagnosed using [¹⁸F]FSPG-based PET/CT. The summed SUV_{max} showed robust correlations with the CD activity index, C-reactive protein levels, fecal calprotectin, and the CD endoscopic index of severity. The diagnostic validity of [¹⁸F]FSPG PET for the assessment of disease activity in subjects with IBD is currently in phase 2 clinical trials (NCT03546868).

CD11b. CD11b is a subunit of the integrin family of cell adhesion molecules and is primarily expressed on the surfaces of white blood cells, including neutrophils, monocytes, and macrophages (Supplemental Fig. 2D) (29). CD11b plays a critical role in mediating leukocyte adhesion and migration to sites of inflammation, and it has been implicated in IBD development. Immuno-PET using an antibody directed to CD11b was used for the detection of colonic inflammation in a DSS-induced IBD mouse model, and its ability

to detect inflammation in colitis was compared with standard [¹⁸F]FDG PET and MRI (5). A monoclonal α-CD11b antibody was conjugated with desferrioxamine (DFO) via an isothiocyanate linker and labeled with ⁸⁹Zr. Uptake of [⁸⁹Zr]Zr-α-CD11b in the inflamed distal colon was increased approximately 5-fold compared with that in the control mice (Fig. 1C). The sensitivity of CD11b-based immuno-PET for detecting colonic inflammation was found to be comparable to that of [¹⁸F]FDG PET and higher than that for MRI. However, unlike [¹⁸F]FDG, no correlation was observed between colitis severity as measured by percent body weight loss and the volumes of interest in the colon for [⁸⁹Zr]Zr-α-CD11b. Ex vivo tissue distribution studies revealed that uptake of the radiotracer was increased throughout the gastrointestinal tract. Uptake of the tracer in the colon and cecum of colitis mice was found to be 26- and 21-fold higher than in healthy mice. However, increased uptake of [⁸⁹Zr]Zr-α-CD11b was observed in the nongastrointestinal tissues of the colitis mice.

Inflammatory Cytokines

Cytokines play a pivotal role in mediating IBD and are critical for initiating disruption of physiologic gut homeostasis (Supplemental Fig. 1) (27). In this subsection, PET agents developed to visualize specific cytokines are discussed.

TNF-α. TNF-α is a proinflammatory cytokine that plays a significant role in the pathogenesis of IBD. Produced by macrophages, it is an important therapeutic target of the FDA-approved biologics infliximab (Remicade) and adalimumab (Humira; Abbvie) for IBD indications (30). Although endoscopic assessment of patients treated with TNF-α therapy can determine its expression levels in biopsy samples, comprehensive measurement of TNF-α levels throughout the entire colon is still difficult to achieve. This suggests that a molecule-based tool is needed for monitoring the efficacy of anti-TNF-α therapy. In a recent study by Yan et al., infliximab was labeled with ⁸⁹Zr and investigated for imaging TNF-α levels in mice with colitis (14). Female Kunming mice were subjected to colitis development through administration of a 5% DSS solution for a duration of 7 d. Healthy and DSS-treated mice injected with [⁸⁹Zr]Zr-DFO-infliximab were imaged 2–72 h after injection. Maximum uptake of TNF-α immuno-PET in the inflamed colon was observed at 2 h after injection (Fig. 2A). At this time point, the uptake of [⁸⁹Zr]Zr-DFO-infliximab in the colon of DSS mice was around 4 times higher than in healthy mice (7.1 ± 0.3 vs. 1.7 ± 0.2 %ID/g). The colon uptake of the radiotracer in colitis mice was retained at high levels 2–10 h after injection. The in vivo specificity of the [⁸⁹Zr]Zr-DFO-infliximab was challenged by coinjection with a 5-fold excess of unlabeled infliximab. PET imaging results indicated that uptake of TNF-α immuno-PET in the colon of DSS-treated mice was notably decreased in the blocked cohort, indicating in vivo specificity of the radiotracer. Ex vivo biodistribution was studied after the last time-point imaging. The colon-to-muscle ratio in the DSS-treated group was measured to be 3.9 ± 0.5, which was significantly higher than the ratios for both the healthy control group and the blocked DSS cohort. These results agree with those obtained from PET imaging. The findings of this study will facilitate the in vivo assessment of TNF-α levels using [⁸⁹Zr]Zr-DFO-infliximab before and after therapy in patients, not only in IBD patients but also in other TNF-α-related conditions, thus offering a companion diagnostic to TNF-α-targeted therapies.

IL-1β. IL-1β is a potent proinflammatory cytokine produced by monocytes and macrophages that plays a role in the development

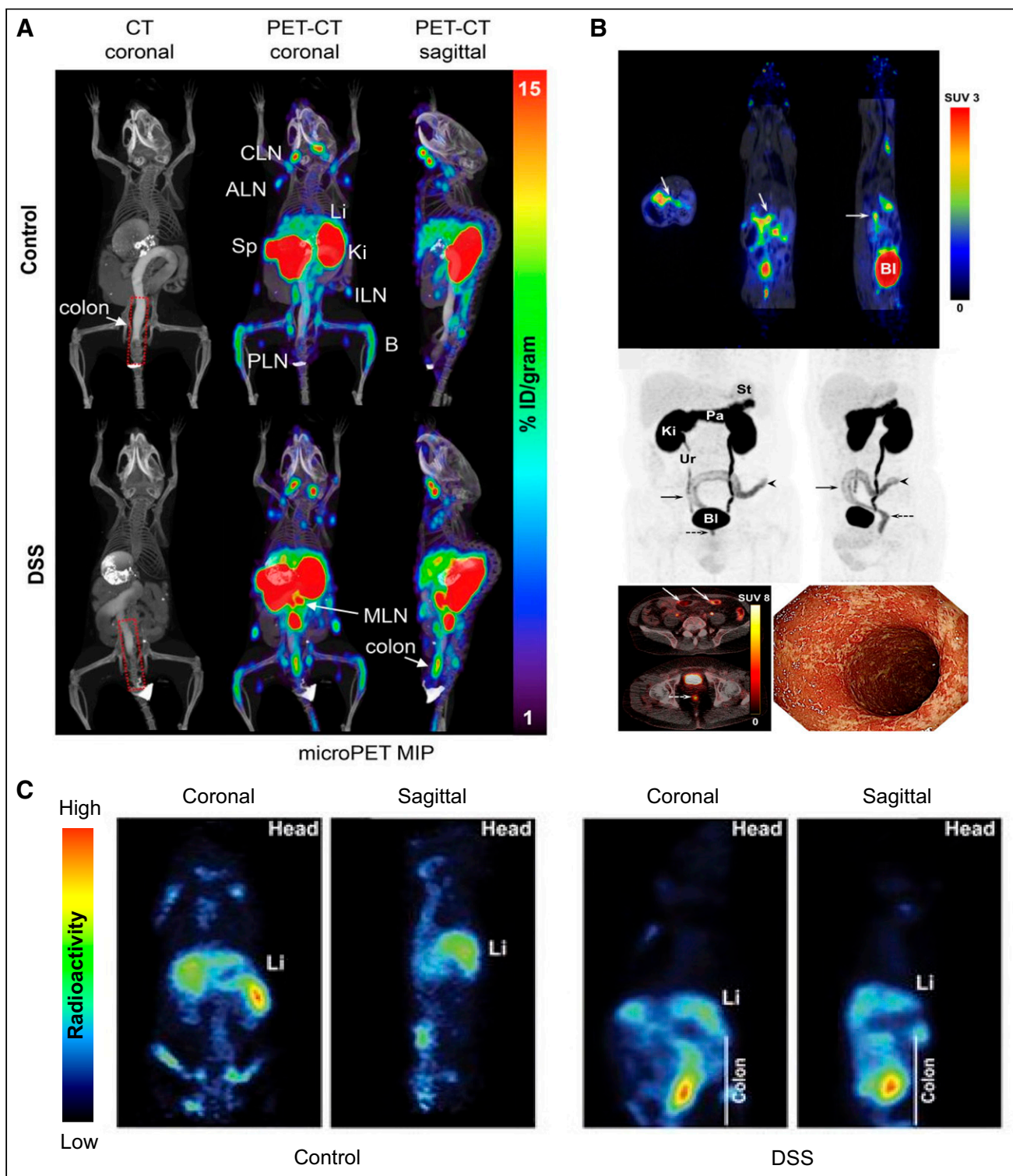


FIGURE 1. Immuno-PET imaging of cell-surface molecules. (A) Immuno-PET directed to CD4⁺ T cells for imaging colitis. Representative CT and PET/CT images of healthy and DSS-induced colitis mice were acquired 20 h after injection of [⁸⁹Zr]Zr-mal-DFO-GK1.5 cys-diabody. Colon of DSS-treated mice showed high uptake of radiotracer, whereas healthy control mice showed little to no uptake in colon. (B) PET imaging of system x_c^- in mice given DSS (top panel) using [¹⁸F]FSPG shows increased tracer uptake in colon (white arrows). Inflammation (black arrows) in the distal colon, sigmoid colon, and rectum (middle panel) was delineated by same tracer in 55-y-old male UC patient, as shown in maximum-intensity projection images. Axial PET images (bottom, left) provide semiquantitative measurement of tracer uptake, which correlates with endoscopic image of colon (bottom, right). (C) [⁸⁹Zr]Zr- α -CD11b PET imaging of colonic inflammation. Shown are representative PET images of DSS and healthy mice after injection of radiotracer. Increased uptake of [⁸⁹Zr]Zr- α -CD11b was observed in inflamed colon compared with control. ALN = axillary lymph node; B = bone; BI = bladder; CLN = cervical lymph node; ILN = inguinal lymph node; Ki = kidney; Li = liver; MIP = maximum-intensity projection; MLN = mesenteric lymph node; Pa = pancreas; PLN = popliteal lymph node; Sp = spleen; St = stomach; Ur = ureter. (Reprinted from (5,12,13).)

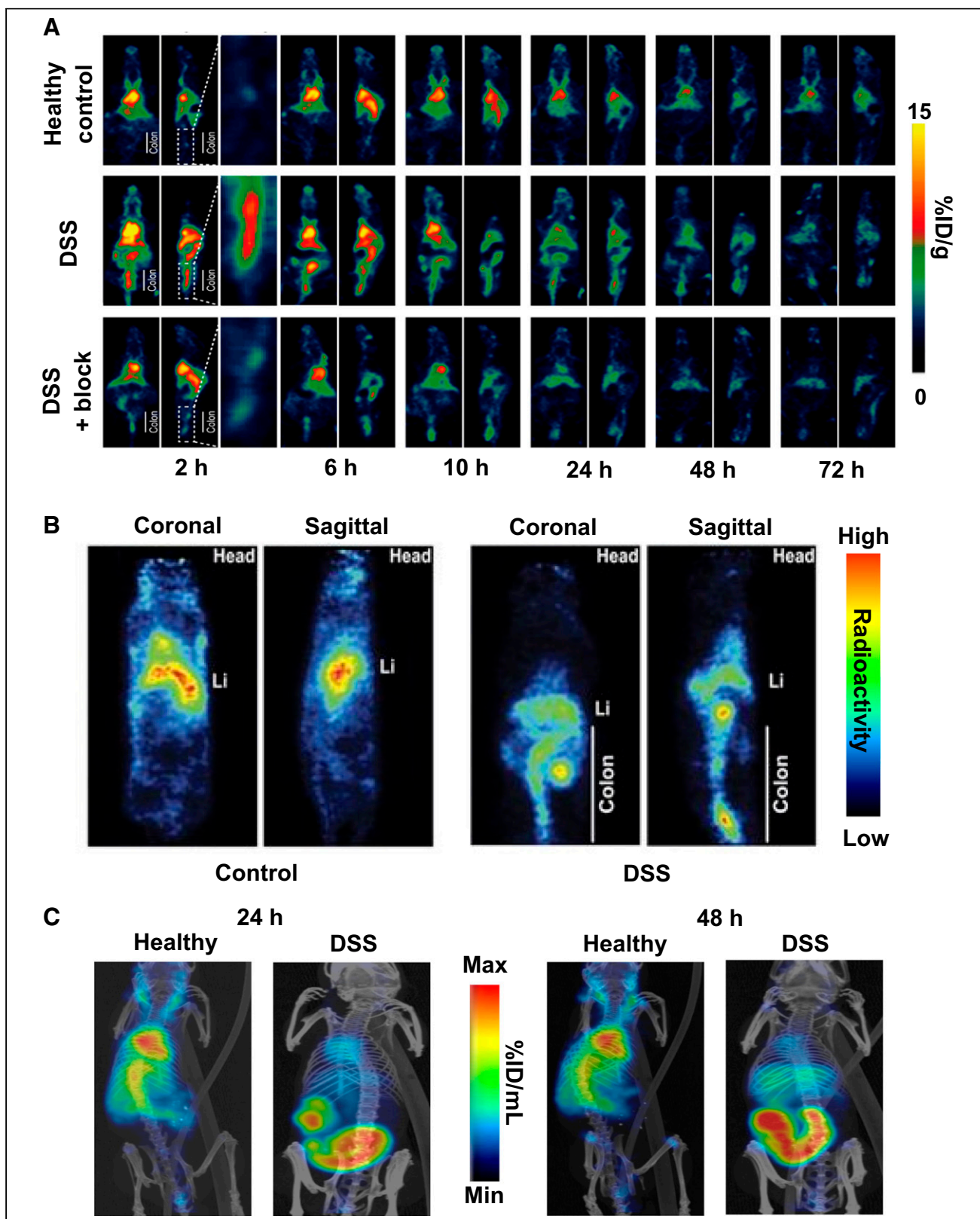


FIGURE 2. Immuno-PET imaging of inflammatory cytokines in IBD. (A) Immuno-PET imaging of TNF- α in colitis mice. Shown are representative PET images of control, DSS-treated, and blocked DSS-treated mice at different time points after injection of [^{89}Zr]Zr-DFO-infliximab. Tracer clearly delineated inflamed colon as early as 2 h after injection. (Reprinted with permission of (14).) (B) [^{89}Zr]Zr-a-IL-1 β PET imaging of colonic inflammation. Shown are representative PET images of DSS and healthy mice acquired 24 h after injection of tracer. (Reprinted from (5).) (C) Immuno-PET/CT imaging of IL-12/23p40 in healthy and DSS-treated mice. Shown are representative PET/CT (maximum-intensity projection) images of healthy and colitis mice acquired at 24 and 48 h after injection of [^{89}Zr]Zr-DFO-anti-IL-12/23p40. Tracer clearly delineated intestinal inflammation. (Reprinted from (34).) Li = liver.

and prolongation of intestinal inflammation in IBD (31). The utility of immuno-PET directed to IL-1 β as a marker of innate immunity was investigated for imaging inflammation in DSS-induced colitis mice and compared with standard [^{18}F]FDG and MRI approaches (5). PET imaging and ex vivo distribution analysis indicated that distal colonic uptake of [^{89}Zr]Zr- α -IL-1 β was increased about 3-fold ($P < 0.05$) relative to that in the control mice. The detection rate was found to be similar to that for [^{18}F]FDG, and it was more sensitive than MRI (Fig. 2B). Furthermore, a strong correlation between colonic uptake of [^{89}Zr]Zr- α -IL-1 β and colitis severity was observed. Although the findings of this study support the potential utility of IL-1 β as an imaging biomarker for IBD, the clinical relevance of IL-1 β in IBD remains unclear as its blockade in patients did not result in positive responses (32).

IL-12 and IL-23. Recent studies have identified a pivotal role of cytokine IL-23 in the pathogenesis of IBD. IL-23, a member of the IL-12 family of cytokines, exerts a proinflammatory effect by promoting the activity of Th17. Increased production of the p40 subunit of IL-12 and IL-23 has been observed in colitis mouse models and in patients with IBD (33). The ability of an immuno-PET for targeting IL-12/23p40 was investigated for imaging inflammation in a DSS-induced colitis mouse model. In a study by Rezazadeh et al. (34), an anti-IL-12/23p40 immuno-PET agent was developed by radiolabeling an antimouse IL-12/23p40 antibody with the PET radionuclide ^{89}Zr using DFO as the chelator. The tracer clearly delineated intestinal inflammation in the colon, cecum, and small intestine of DSS mice at 24 and 48 h after injection (Fig. 2C). The colonic uptake of [^{89}Zr]Zr-DFO anti-IL-12/23p40 in DSS and healthy mice indicated higher uptake of IL-12/23p40 immuno-PET in inflamed colons compared with that in the healthy control. The in vivo specificity of the radiotracer was evaluated by imaging a separate cohort of DSS mice injected with ^{89}Zr -radiolabeled isotype control antibody, which did not show specific accumulation in the colon. Ex vivo PET imaging of the large intestine showed focal uptake in the cecum and mid colon. The tracer uptake correlated with increased IL-12/23p40 levels in the serum. This novel imaging technology can aid in the detection and precise staging of IBD in patients by creating a comprehensive in vivo map of IL-12/23p40-driven inflammation throughout the entire gastrointestinal tract. It can further serve as a companion diagnostic to ustekinumab.

DISCUSSION

Detecting and tracking chronic inflammation in the gastrointestinal tract are critical to improving outcomes among patients with IBD. None of the available standard-of-care diagnostic tools, whether used alone or in combination, completely meets the needs for safe, accessible, reliable, and quantitative visualization of gastrointestinal inflammation with high spatial and molecular specificity (35). Thus, there is an unmet clinical need for diagnostic alternatives.

Applications of PET imaging in IBD have only recently started gaining traction and have not received widespread attention. Most prominently, [^{18}F]FDG, considered the gold standard for staging cancer, has been investigated in IBD settings (36). However, because [^{18}F]FDG is a marker of metabolism, [^{18}F]FDG-based PET provides indirect information as it marks the energy consumption of the mucosal layer infiltrating immune cells within the inflamed tissue (18). As an alternative to [^{18}F]FDG PET,

several biomarkers that are clinically relevant to IBD can be targeted and imaged via PET. Most of the tracers are still in preclinical studies, with only 2 agents progressing to clinical trials. PET/CT imaging using [^{18}F]FSPG for assessing disease activity in patients with UC and CD is in phase 2 clinical trials (NCT03546868). Another PET tracer in clinical trials for diagnosis of IBD is [^{68}Ga]Ga-fibroblast activation protein inhibitor, a radiotracer that targets the fibroblast activation protein, which is often overexpressed in various cancers and inflammatory conditions (37). A prospective study in early phase 1 is currently under way to investigate whether [^{68}Ga]Ga-fibroblast activation protein inhibitor PET/CT may be superior to [^{18}F]FDG PET/CT for diagnosis, therapy response assessment, and follow-up for IBD (NCT04507932).

There is a clear and compelling need to direct research efforts toward imaging this autoimmune condition on the molecular level, not only to interrogate IBD pathobiology for clinical treatment guidance but also to alleviate patient burden arising from extensive preparations and procedures necessitated by endocolonoscopies. However, there are several surmountable challenges to move these agents from the bench to the clinic. At the forefront of these challenges is a lack of understanding of the mediators of IBD that can be targeted via PET. By understanding the underlying molecular targets or pathways, it becomes possible to develop PET tracers that specifically bind to these biomarkers, enabling accurate visualization and characterization of IBD-related inflammation. Preclinical studies should focus on optimizing tracer design, targeting mechanisms, and imaging properties. It is crucial that the tracer's specificity, sensitivity, pharmacokinetics, and toxicity are assessed using suitable animal models that mimic IBD.

Another remaining challenge related to using PET tracers in clinical practice is distinguishing between inflammation and infection. Both inflammation and infection can trigger increased metabolic activity and recruitment of immune cells, leading to similar PET signal uptake. This similarity can make it difficult to accurately diagnose and distinguish one over the other. Combining PET imaging with other diagnostic modalities, including blood-based molecular assays, may provide complementary information to improve diagnostic specificity.

Once successful preclinical validation of these PET imaging agents is achieved, translation of these PET imaging agents from the bench to IBD patients can be initiated. PET/CT imaging of the abdominal region provides a critical advantage over endoscopies, as the former can provide full-abdominal images whereas the latter can only scope through specific areas of the alimentary tract. Moreover, endoscopies cannot be performed frequently because of their extensive preparatory procedures and risk of bowel perforation.

There are practical considerations to take into account if we are to move PET/CT toward translation. These radiotracers must be produced in accordance with good manufacturing practices. A clinical team consisting of a gastroenterologist and a nuclear medicine physician would ensure continuous IBD patient referral to clinical trial recruitment. Another main consideration for effective translation centers on establishing imaging protocols. It is important to identify whether an intravenous CT contrast is necessary for accurate full abdominal mapping (38). Metrics for analysis of acquired images need to be established to ensure a harmonized protocol for readers. For example, with [^{18}F]FDG-based PET/CT, semiquantitative SUV readings of the tracer uptake in the bowel are compared against hepatic SUVs (e.g.,

grades 0–1, normal; grade 2, bowel SUV > liver SUV but not more than 3-fold; grade 3, bowel SUV > 3 × liver SUV) (15,39). Others have used a global PET/CT scoring system that sums the SUV_{max} for all bowel segments (15). As mentioned above, radiation exposure can be a limiting factor for frequent PET/CT scans of IBD patients. Dose calculations have shown that approximately 45% of radiation exposures are from CT scans in patients administered 3.7 MBq/kg (4.6 mSv for the CT, 5.7 mSv for [¹⁸F]FDG PET) (15). The dose absorbed in the bowel is 0.5 mSv with a 185-MBq (5 mCi) [¹⁸F]FDG dose (17). An alternative to CT is to use PET with MRI. Other ways to further minimize exposure is to lower the doses of the PET agents needed to be evaluated for optimization and to consider longer acquisition times. Moreover, detector sensitivity has improved since the development of PET/CT scanners in the early 2000s, with more sophisticated scanners having higher sensitivity. Although this list is not exhaustive, these factors are critical to effectively transition current and new PET tracers from bench to bedside, with the future outlook being to launch and establish these agents as the mainstream standard of care.

CONCLUSION

There exists a need to address the current limitations of standard-of-care diagnosis in IBD. Although the application of PET imaging in IBD diagnosis and detection is still in its infancy, there is a clear opportunity for nuclear medicine to move in this direction and to develop new tools for surveillance and more accurate diagnosis.

DISCLOSURE

This work is supported by NIH/NCI R37 CA220482 (to Nerissa Viola). Nerissa Viola is an inventor of an IL-12 immuno-PET agent (PCT/US2020/047016). No other potential conflict of interest relevant to this article was reported.

REFERENCES

- Chang JT. Pathophysiology of inflammatory bowel diseases. *N Engl J Med*. 2020; 383:2652–2664.
- Lee SH, Kwon JE, Cho, M-L. Immunological pathogenesis of inflammatory bowel disease. *Intest Res*. 2018;16:26–42.
- Negreanu L, Voiosu T, State M, Voiosu A, Bengus A, Mateescu BR. Endoscopy in inflammatory bowel disease: from guidelines to real life. *Therap Adv Gastroenterol*. 2019;12:1756284819865153.
- Dmochowska N, Wardill HR, Hughes PA. Advances in imaging specific mediators of inflammatory bowel disease. *Int J Mol Sci*. 2018;19:2471.
- Dmochowska N, Tieu W, Keller MD, et al. Immuno-PET of innate immune markers CD11b and IL-1β detects inflammation in murine colitis. *J Nucl Med*. 2019; 60:858–863.
- Guan Q. A comprehensive review and update on the pathogenesis of inflammatory bowel disease. *J Immunol Res*. 2019;2019:7247238.
- Brown SJ, Mayer L. The immune response in inflammatory bowel disease. *Am J Gastroenterol*. 2007;102:2058–2069.
- Gálvez J. Role of Th17 cells in the pathogenesis of human IBD. *ISRN Inflamm*. 2014;2014:928461.
- Sands BE, Sandborn WJ, Panaccione R, et al. Ustekinumab as induction and maintenance therapy for ulcerative colitis. *N Engl J Med*. 2019;381:1201–1214.
- Genaro LM, Gomes LEM, de Freitas Franceschini APM, et al. Anti-TNF therapy and immunogenicity in inflammatory bowel diseases: a translational approach. *Am J Transl Res*. 2021;13:13916.
- Kilcoyne A, Kaplan JL, Gee MS. Inflammatory bowel disease imaging: current practice and future directions. *World J Gastroenterol*. 2016;22:917.
- Freise AC, Zettlitz KA, Salazar FB, et al. Immuno-PET in inflammatory bowel disease: imaging CD4-positive T cells in a murine model of colitis. *J Nucl Med*. 2018; 59:980–985.
- Seo M, Kim Y, Ye BD, et al. PET imaging of system x_c⁻ in immune cells for assessment of disease activity in mice and patients with inflammatory bowel disease. *J Nucl Med*. 2022;63:1586–1591.
- Yan G, Wang X, Fan Y, et al. Immuno-PET imaging of TNF-α in colitis using ⁸⁹Zr-DFO-infliximab. *Mol Pharm*. 2022;19:3632–3639.
- Louis E, Ancion G, Colard A, Spote V, Balaiche J, Hustinx R. Noninvasive assessment of Crohn's disease intestinal lesions with ¹⁸F-FDG PET/CT. *J Nucl Med*. 2007;48:1053–1059.
- Das CJ, Makharia G, Kumar R, et al. PET-CT enteroclysis: a new technique for evaluation of inflammatory diseases of the intestine. *Eur J Nucl Med Mol Imaging*. 2007;34:2106–2114.
- Lemberg DA, Issenman RM, Cawdron R, et al. Positron emission tomography in the investigation of pediatric inflammatory bowel disease. *Inflamm Bowel Dis*. 2005;11:733–738.
- Glaudemans AW, de Vries EF, Galli F, Dierckx RA, Slart RH, Signore A. The use of F-FDG-PET/CT for diagnosis and treatment monitoring of inflammatory and infectious diseases. *Clin Dev Immunol*. 2013;2013:623036.
- Gorfu G, Rivera-Nieves J, Ley K. Role of β₇ integrins in intestinal lymphocyte homing and retention. *Curr Mol Med*. 2009;9:836–850.
- Dearling JL, Park EJ, Dunning P, et al. Detection of intestinal inflammation by microPET imaging using a ⁶⁴Cu-labeled anti-β₇ integrin antibody. *Inflamm Bowel Dis*. 2010;16:1458–1466.
- Dearling JL, Daka A, Veiga N, Peer D, Packard AB. Colitis immunoPET: defining target cell populations and optimizing pharmacokinetics. *Inflamm Bowel Dis*. 2016;22:529–538.
- Adhikari A, Singh P, Mahar KS, et al. Mapping of translocator protein (18 kDa) in peripheral sterile inflammatory disease and cancer through PET imaging. *Mol Pharm*. 2021;18:1507–1529.
- Hamelin L, Lagarde J, Dorothée G, et al. Early and protective microglial activation in Alzheimer's disease: a prospective study using ¹⁸F-DPA-714 PET imaging. *Brain*. 2016;139:1252–1264.
- Lavis S, Goutal S, Wimberley C, et al. Increased microglial activation in patients with Parkinson disease using [¹⁸F]-DPA714 TSPO PET imaging. *Parkinsonism Relat Disord*. 2021;82:29–36.
- Bernards N, Pottier G, Thézé B, Dollé F, Boisgard R. In vivo evaluation of inflammatory bowel disease with the aid of μPET and the translocator protein 18 kDa radioligand [¹⁸F]DPA-714. *Mol Imaging Biol*. 2015;17:67–75.
- Ostuni MA, Issop L, Pérani G, et al. Overexpression of translocator protein in inflammatory bowel disease: potential diagnostic and treatment value. *Inflamm Bowel Dis*. 2010;16:1476–1487.
- Leppkes M, Neurath M. Cytokines in inflammatory bowel diseases: update 2020. *Pharmacol Res*. 2020;158:104835.
- Chae SY, Choi C-M, Shim TS, et al. Exploratory clinical investigation of (4S)-4-(3-¹⁸F-fluoropropyl)-L-glutamate PET of inflammatory and infectious lesions. *J Nucl Med*. 2016;57:67–69.
- Schittenhelm L, Hilkens CM, Morrison VL. β₂ integrins as regulators of dendritic cell, monocyte, and macrophage function. *Front Immunol*. 2017;8:01866.
- Cui G, Fan Q, Li Z, Goll R, Florholmen J. Evaluation of anti-TNF therapeutic response in patients with inflammatory bowel disease: current and novel biomarkers. *EBioMedicine*. 2021;66:103329.
- Dosh RH, Jordan-Mahy N, Sammon C, Le Maitre C. Interleukin 1 is a key driver of inflammatory bowel disease-demonstration in a murine IL-1Ra knockout model. *Oncotarget*. 2019;10:3559.
- Mao L, Kitani A, Strober W, Fuss IJ. The role of NLRP3 and IL-1β in the pathogenesis of inflammatory bowel disease. *Front Immunol*. 2018;9:2566.
- Marafini I, Angelucci E, Pallone F, Monteleone G. The IL-12/23/STAT axis as a therapeutic target in inflammatory bowel disease: mechanisms and evidence in man. *Dig Dis*. 2015;33:113–119.
- Rezaazadeh F, Ramos N, Saliganan A-D, et al. Detection of IL12/23p40 via PET visualizes inflammatory bowel disease. *J Nucl Med*. 2023;64:1806–1814.
- Vashist NM, Samaan M, Mosli MH, et al. Endoscopic scoring indices for evaluation of disease activity in ulcerative colitis. *Cochrane Database Syst Rev*. 2018;1:CD011450.
- Spier BJ, Perlman SB, Jaskowiak CJ, Reichelderfer M. PET/CT in the evaluation of inflammatory bowel disease: studies in patients before and after treatment. *Mol Imaging Biol*. 2010;12:85–88.
- Kratochwil C, Flechsig P, Lindner T, et al. ⁶⁸Ga-FAPI PET/CT: tracer uptake in 28 different kinds of cancer. *J Nucl Med*. 2019;60:801–805.
- Bhattar A, Borja A, Zhang V, et al. FDG-PET/CT as the superior imaging modality for inflammatory bowel disease [abstract]. *J Nucl Med*. 2020;61(suppl 1):1159.
- Perlman SB, Hall BS, Reichelderfer M. PET/CT imaging of inflammatory bowel disease. *Semin Nucl Med*. 2013;43:420–426.