Review

Advances in in-vivo Imaging of Inflammatory Bowel Disease mediators

Nicole Dmochowska1, Hannah R. Wardill1 and Patrick A. Hughes1*

1 Centre for Nutrition and GI Diseases, Adelaide Medical School, University of Adelaide and South Australian Health and Medical Research Institute, Adelaide, Australia
* Correspondence: Patrick.hughes@adelaide.edu.au; Tel.: +61-8-81284843

Abstract:

Inflammatory Bowel Disease (IBD) is characterized by chronic remitting and relapsing inflammation of the lower gastrointestinal tract. The etiology underlying IBD remains unknown but is thought to involve a hypersensitive immune response to environmental antigen, including the microbiota. Diagnosis and monitoring of disease is heavily reliant on endoscopy, which is invasive and does not provide information regarding specific mediators. This review describes recent developments in imaging of IBD with a focus on PET and SPECT imaging of inflammatory mediators, and how this may be applied to the microbiota.

Keywords: Inflammatory Bowel Disease (IBD), colitis, PET, SPECT, microbiota, cytokine, chemokine, inflammation

1. Introduction

Inflammatory Bowel Disease (IBD) is an inflammatory disorder of the gastrointestinal (GI) tract which has a substantial impact on quality of life. The causes of inflammation in IBD remain unknown but are thought to involve a hypersensitive immune response to the intestinal microbiota. IBD is commonly associated with dysbiosis, but it remains unknown whether dysbiosis is a cause or consequence of inflammation. Diagnosis and monitoring of IBD is heavily reliant on endoscopy,
which is an invasive technique that requires bowel preparation and typically also anesthesia. Although generally well tolerated, endoscopy impacts substantially on quality of life of patients and does not provide any direct information regarding the role that specific mediators contribute toward inflammation. Therefore, new technologies are required that are sensitive enough to grade disease severity, can be optimized for detection of specific mediators and are non- or only minimally invasive. Recent developments in PET imaging, and particularly the use of antibody conjugates, have demonstrated success in cancers, but are only recently being adapted to studies of IBD. This review summarizes the evolution of these technologies in IBD studies, how they have been used to detect specific mediators of inflammation, and their potential to image microbiota.

2. Inflammatory Bowel Disease

IBD is a collection of debilitating idiopathic diseases characterized by chronic inflammation of the lower gastrointestinal tract that have a remitting and relapsing disease course. The global incidence of IBD is estimated to be 0.3% and is widely regarded as increasing [1]. The cause(s) of IBD remain unknown, however are thought to involve aberrant immune responses to environmental stimuli in people with a complex genetic predisposition. The relatively recent increase in the incidence of IBD is perplexing, but potentially highlights the importance of environmental factors in its etiology. The two major subtypes of IBD are Ulcerative Colitis (UC) and Crohn’s Disease (CD) which can typically be distinguished by pathological and histological differences. Inflammation in UC is typically restricted to the mucosal layer of the colon and progresses in a contiguous manner. CD differs in that it is characterized by transmural skip lesions that can occur anywhere in the GI tract but are typically located in the ileum with and without involvement of the colon. The initiating factors and
inflammatory aspects of UC and CD are likely to differ given the distinctions between their pathology but are only poorly understood. Much more is known about how inflammation is perpetuated in IBD, and this has led to the relatively recent development of biologic drugs targeting specific immune mechanisms. However, treatment gaps remain in IBD due to intolerance, incomplete efficacy and side effects of current therapies, and the disease course in both UC and CD is characterized by variable periods of remission and relapse. Prognostic indicators of relapse in IBD are poor, requiring patients to undergo constant surveillance. Severe persistent or relapsing symptoms may lead to surgery [2] which can be curative for UC (withstanding complications), but is not curative for CD. This high rate of surgery highlights the ongoing need for a deeper understanding of the mechanisms involved in initiating and perpetuating inflammation in IBD.

2.1 Imaging IBD: Current approaches

The treatment of IBD depends on clinical severity which is currently highly dependent on endoscopy, where a thin flexible tube with a camera on the end is moved through the lumen. Endoscopy directly images the gastrointestinal mucosa for assessment of disease stage and monitoring and, when forceps are attached, allows for the collection of biopsy material for analysis of pathology and mechanistic studies. Endoscopy can differentiate between UC and CD in the majority of cases [3]. However, endoscopic approaches have limitations as the quality of results is operator dependent and may not be sensitive enough for assessment of clinical severity. Furthermore, endoscopic imaging is restricted to the superficial mucosal layers of the intestine and therefore provides no information regarding inflammatory damage to the deeper layers of the intestinal wall, the degree of muscle thickness or the diameter of the lumen. Finally, a major limitation of endoscopy is the difficulty in reaching the
small intestine due to the distance needed to be covered and the complexities of intestinal anatomy with its multiple loops and folds.

A number of novel imaging technologies are emerging that complement or may even replace endoscopy as the gold standard for clinical diagnosis, as recently reviewed [4]. Chromoendoscopy involves the application of dyes onto the mucosa, improving endoscopic characterization of lesions and neoplasia and potentially correlating with histological damage, although the latter remains controversial [5]. Confocal laser endomicroscopy and endocytoscopy combine high resolution microscopic imaging with endoscopy and again are primarily used to detect colonic dysplasia and neoplasia [6]. Wireless capsule technologies may circumvent the limitations that endoscopy has in accessing difficult to reach areas of the small intestine. While these capsules provide high resolution imaging, they have similar limitations to standard endoscopy regarding assessment of inflammatory damage to the deeper layers of the colon wall, but may also require surgery for removal when stricture occurs [7]. Less invasive imaging technologies include barium X-rays, Magnetic Resonance Imaging (MRI), Computed Tomography (CT), positron emission tomography (PET) and single photon emission computed tomography (SPECT). Barium enemas provide excellent visualization of the bowel and can reveal thickening of the bowel wall but is not recommended in patients with severe inflammation due to the risk of complications such as toxic megacolon. MRI, CT, PET and SPECT are minimally invasive relative to endoscopy and offer the additional benefits of visualizing planes through the colon wall and extra-intestinal manifestations. It is important to note that while these technological advances are welcome for IBD management, none of them currently target specific mediators. This highlights the need for the development of new imaging technologies.
that are highly sensitive, quantitative and able to provide longitudinal data in real time but are also only minimally invasive. Recent advances in PET and SPECT imaging have the potential to cover all these issues.

3. Imaging inflammatory mechanisms in IBD: which targets to choose?

3.1 Immune targets

Inflammation is central to IBD however much remains to be understood regarding the causes of inflammation in human IBD. Animal models of colitis have significantly improved our understanding of how inflammation develops and perpetuates, highlighting roles for both the innate and the adaptive arms of the immune response. It is currently thought that inflammation in IBD is driven by a loss of immune tolerance to autologous proteins in the colon wall and foreign antigen in the lumen, including the microbiota. This initiates a cascade of cytokines and chemokines which cause an influx of immune cells. Immune cells are attracted to sites of inflammation by chemokines and also by upregulated expression of ‘gut-homing’ integrins on the cell surface, including $\alpha_4\beta_7$ [8].

Subsequent inflammatory lesions and damage to the epithelial wall and deeper layers of intestinal tissue result in production of damage related mediators during active disease, which progresses toward mediators related to tissue-remodeling and wound healing as disease progresses toward remission, but also toward fibrosis after repeated or extended periods of inflammation. The immunological basis for the differences in pathophysiology of UC and CD are not clear, however it is suggested that CD is driven by a T\textsubscript{h}1 / T\textsubscript{h}17 type immune response while is thought to be mediated by a T\textsubscript{h}2 type immune response (↑ IL-5, IL-13) that is atypical as IL-4 is not involved.
Recent advances in two-photon laser scanning microscopy have enabled in-vivo imaging of deep visceral tissues and immune cells in particular. This technique was elegantly used to identify goblet cell associated passage (GAPs) as the major mechanism for delivering luminal antigen to dendritic cells in the small intestine in health, but only appear in the colon after microbe sensing pathways were disrupted [9, 10]. These findings potentially highlight a role for GAPs in IBD, however they are yet to be investigated in the IBD setting. We have recently applied two-photon laser scanning microscopy to investigate immune cell migration in the tri-nitro benzene sulphonic acid (TNBS) model of colitis, demonstrating in-vivo that not only are immune cells in very close apposition to nerves within the colon wall, but also that myeloid cell infiltration is increased in TNBS colitis [11]. This technique can be easily combined with reporter mice and promises to increase the understanding of the mechanisms involved in immune cell migration from blood vessels into the lower GI tract in IBD.

3.2 Microbiota

Recent improvements in high throughput ‘omics’ technology have also revealed the involvement of the microbiome in IBD. The general consensus indicates that active IBD is characterized by an overall loss of diversity coupled with a dysbiotic phenotype primarily depicted by elevated Proteobacteria and decreased Firmicutes, although inconsistencies between studies remain [12-14]. Functionally, the major classes of bacteria affected relate to the production of short-chain fatty acids (e.g. Faecalibacterium prausnitizii), bacteria with mucolytic activity (e.g. Ruminococcous torques) and sulfate reducing species including Desulfovibrio [15-17]. While this dysbiotic composition may contribute to disease progression through dysregulated epithelial barrier function and aberrant immune signaling,
it is currently contentious whether dysbiosis itself causes IBD or is simply an effect of the disease course [18].

Uncovering the compositional shifts in the microbiome has undoubtedly increased our understanding of its role in disease initiation, progression and relapse. However, techniques such as 16S pyrosequencing are inherently limited by the variations that exist in aspects of their methodology including inconsistent or incomplete reference libraries, the unknown impact of batched analyses, non-standardized statistical analyses, and an inability to adequately appreciate the heterogeneity in the microbiome [19]. This is further confounded by the fact that the annotation is based on putative association of the 16S rRNA gene with a taxon defined as an operational taxonomic unit (OTU) [20, 21]. Although whole genome shotgun sequencing has enhanced our ability define species taxa with more accuracy, it remains an expensive alternative to 16S and requires significantly greater data analysis [19]. As such, conclusions regarding the functional implications of compositional shifts remain difficult to draw, relying on metagenomics inference using phylogenetic investigation of communities by reconstruction of unobserved states (PICRUSt). Non-the-less changes in microbiota composition offer the intriguing potential to image microbiota as markers of disease severity in IBD.

4. PET and SPECT imaging of the gastrointestinal tract in IBD

PET studies have traditionally relied on the use of 18-fludeoxyglucose (18F-FDG), a radiolabeled glucose analogue that detects tissue glucose metabolism. This can be useful for detecting sites of inflammation but does not offer any information regarding the involvement of specific mediators. Radiolabeled leukocytes have been the gold standard for nuclear imaging of GI inflammation for
decades due to accessibility from both supply and economical ends. SPECT imaging of $^{99mTc}$-labeled leukocytes was shown nearly two decades ago to accurately assess the extent and severity of people with severe UC, correlating with endoscopic and histological findings [22]. However, limitations with radiolabeled leukocytes exist, including a relatively extensive protocol required for working up the cells, risks of cross-contamination and, importantly, the non-specific nature of the tracer. These limitations have spurred interest in developing new technologies for imaging, with antibodies in the prime place. Multiple clinical trials are currently utilizing radioisotope labelled antibodies for immunoPET in cancer to tailor personalized therapies based on specifically targeted diagnostic tests [23, 24]. However, imaging of IBD is presently limited to pre-clinical studies.

4.1. Imaging colitis in animal models

Monoclonal antibodies have exquisite selectivity for their targets which has been exploited clinically for decades. Nuclear imaging of colitis has so far relied upon two models, the TNBS model and the dextran sulfate sodium (DSS) model. TNBS is combined with ethanol to break the mucosal barrier and administered by enema, and inflammation is therefore restricted to the colon. TNBS is a hapten; it binds to autologous proteins and luminal microbiota turning them immunogenic. The colitis that develops is transmural, involves an IL-12 driven Th1/Th17 type response and is therefore considered to model CD. DSS differs as it is directly toxic to epithelial cells and, when administered by the oral route in drinking water, results in a colitis that takes longer to develop than TNBS. DSS colitis is considered to model UC as the colitis results from direct damage to the epithelial layer and is not as deep as that which occurs with the TNBS model. While animal models are useful for emphasizing the importance of specific mediators and mechanisms, it is important to note that findings from
animal models can be difficult to translate to human IBD. This is common with most chronic diseases that have a remitting and relapsing course due to the involvement of multiple and overlapping pathways that are inter-twined with disease stage as inflammation progresses and regresses, highlighting the requirement for extensive validation in human subjects.

4.1.1. PET and SPECT imaging of immune mediators in colitis

Cell-secreted immune mediators are generally classified as chemokines or cytokines, with chemokines mediating cell attraction and cytokines mediating immune responses. Table 1 provides an overview of PET/SPECT studies of immune mediators in human IBD and animal models of colitis. The first study investigating whether radiolabeled antibodies are efficacious for imaging colitis was disappointing as $^{111}$In labelled -IgG uptake was substantially lower than $^{111}$In labelled -leukocytes, the gold standard at the time, and also the newly developed $^{111}$In labelled -liposomes in TNBS colitic rabbits [25]. While imaging of liposomes and leukocytes enabled grading of inflammation, the contrast provided from IgG labelling was not sufficient for this to occur. This result was not surprising given the large abundance of IgG in circulating blood and its relative non-selectivity for colitis. Interleukin (IL) -8, more recently renamed CXCL8, is a chemokine produced by innate immune cells but also cells in other tissues including epithelial cells and endothelial cells. IL-8 is primarily involved in attracting neutrophils to inflammatory sites, but also attracts other granulocytes including mast cells. Colonic inflammation in TNBS treated rabbits was detected more readily with $^{99m}$Tc labelled -IL-8 than $^{99m}$Tc labelled -granulocytes [26]. Furthermore, the severity of inflammation was also able to be graded with $^{99m}$Tc-IL-8, but not with $^{99m}$Tc-granulocytes. More recently, IL-8 was again labelled with $^{99m}$Tc for SPECT studies in a large clinical study of people with
IBD and was found to have higher sensitivity for detecting inflammation than endoscopy, although specificity was lower than endoscopy [27]. TNF-α is a cytokine that is secreted by a range of immune cells from both the innate and adaptive arms of the immune response. TNF-α is produced in large amounts in many autoimmune diseases, including IBD. Neutralizing TNF-α with antibodies, for example Infliximab, has proven success in treating IBD [28, 29]. In pre-clinical studies, ⁹⁹mTc labelled -Infliximab was able to discriminate between moderate and severe colonic inflammation in TNBS treated rats [30]. However, enthusiasm for Infliximab as a tracer in preclinical studies was hampered by high background uptake in healthy control rats. This study is of importance as it not only revealed TNF-α mediated inflammation, but it also demonstrated target specificity of a clinically useful drug for IBD. This is also particularly significant given the increased development of biologics, particularly antibody-based therapies, but also the relatively recent expansion of personalized medicine and theragnostic approaches toward treating disease.

4.1.2. Imaging immune cells in colitis

The DSS colitis model is the most commonly used model to image immune cells in colitis. Table 1 provides an overview of PET/SPECT studies of immune cells in human IBD and animal models of colitis. The integrins α₄ and β₇ form a heterodimer (α₄β₇) which specifically directs the migration, or homing, of immune cells to the gastrointestinal tract via interactions with its ligand the addressin MAdDCAM-1 [8]. Targeting this pathway has proved successful in IBD with the recent development of Vedolizumab, a monoclonal antibody that blocks α₄β₇ [31]. Uptake of ⁶⁴Cu labelled -β₇ antibodies was increased in DSS colitis relative to healthy controls and to ⁶⁴Cu labelled -IgG isotype negative control [32]. However, high levels of background were also observed in non-target organs including
the small intestine and stomach, prompting the development of antibody fragments. Uptake of $^{64}$Cu labelled $\beta_7$ antibody fragments was superior to both whole $^{64}$Cu labelled $\beta_7$ antibodies, but also to $^{64}$Cu labelled $\alpha_4 \beta_7$, suggesting that antibody fragments may provide enhanced signaling of inflammation in IBD than whole antibodies [33]. The concept of increased sensitivity with small antibodies has recently been validated in cancer biology and in inflammation. $^{18}$F labelled antibody fragments directed against the antigen presenting complex MHCII were much more sensitive than standard $^{18}$F-FDG in detecting xenoplanted tumors, even detecting tumors when growth was neither palpable or visible [34]. Furthermore, $^{18}$F- labelled antibody fragments directed against CD11b detected complete Freund’s adjuvant (CFA) induced inflammation in the mouse paw much earlier than standard $^{18}$F-FDG [34]. Most recently, $^{89}$Zr labelled antibody fragments against the T helper marker CD4 were observed to have higher uptake in the colon of DSS mice compared to health [35]. However, uptake was also increased in the spleen and lymph nodes, highlighting the intrinsic difficulties in imaging immune cells during inflammation as they generally migrate to the site of inflammation from distant lymph nodes.

4.2 Imaging the microbiota in colitis

As our understanding of how microbiota and host interact grows, it is necessary to move beyond current genomics technology and compositional descriptions. This remains a daunting task when imaging specific microbiota in the gut as it is limited by the diversity of materials that need to be maintained, which is of particular importance when considering the sensitivity of the mucous layer to standard fixation methods and the heterogeneity within gut microenvironments. As such, it is critical that a robust protocol including mucous-preserving sample preparation, image segmentation
and quantitative analysis tools be developed. A framework satisfying these criteria was recently
developed by Earle et al. [36], where high-resolution quantification of spatial organization of the gut
microbiome revealed that changes in the proximity of microbes to the epithelium are sufficient to
induce increased expression of key inflammatory markers despite negligible shifts in microbiota
composition. Their protocol included integrating formalin-free methacarn preservation with
fluorescent in-situ hybridization and, most importantly, high-end software analysis called BacSpace.
BacSpase enables 1) stitching of overlapping images into one continuous image, 2) landmark
definition, 3) differentiation of background autofluorescence (e.g. diet-derived plant material, shed
epithelial cells, blood and 4) measurement of cell-cell and cell-landmark distance distributions based
on a well-defined local coordinate system, revolutionizing the analysis and interpretation of
microbiome related data. Most recently, chemical imaging techniques exploiting a blinking Surface
Enhanced Raman Spectroscopy (SERS) have been used to visualize bacteria in-vitro with exquisite
resolution, and the ability to differentiate between the chemical signatures of different bacteria [37].

Several minimally invasive techniques have also been applied to investigate the activity of bacteria
in-vivo including MRI, CT, fluorescence / bioluminescence imaging and PET, however the majority
of these only provide indirect information about bacterial activity by inference from immune function
[38, 39]. Recent advances exploiting the bacterial uptake of carbohydrates have proven successful for
the selective in-vivo imaging of bacteria independently of host factors and secondary pathologies [39,
40]. Furthermore, specific bacteria have also been labelled with iron oxide nanoparticles for MRI
imaging to track bacteria longitudinally during infection [38]. These developments highlight the
potential to image specific bacteria during inflammation but are yet to be applied to IBD.
5. Limitations of radiolabeled antibodies

Radiolabeling antibodies or immune mediators offers the real potential for in vivo diagnostic imaging however several issues remain that currently limit enthusiasm for widespread use. The primary limitation is economical-based, as specialized equipment is required for the manufacture and detection of radiolabels. These costs are high, however may be mitigated by improved clinical outcomes including early detection and potential the potential development of personalized medicines to improve clinical responses and reduce side effects. Limitations related to biology also exist, particularly with relation to the relatively long half-life of antibodies and the time they require to move through the circulatory system to the site of inflammation. This relates to the increased risk of cancer due to radiation exposure, particularly as IBD patients already have a higher risk of colon cancer. However, PET is considered safe and the effective dose of whole body $^{18}$F-FDG was approximately 7 mSv, much less that the 16 mSv used for a routine abdominal-pelvic CT with contrast [41, 42]. Efforts are underway to reduce circulation time by using pre-targeted methods, as explained in more detail below. The relatively large structure of antibodies may lead to difficulties in penetration of the site of inflammation, although this may be mitigated by altering the structure of the antibody, also explained in more detail below. A limitation also relates to the single mode of PET detection; only a single mediator can be imaged. This is problematic in terms of detailed studies of immune cell subsets as they are typically identified by flow cytometry techniques requiring multiple targets. Furthermore, intracellular cytoplasmic cytokines and nuclear transcription factors are increasingly being used to characterize immune cell subsets, however this typically requires cell permeabilization which is not possible in-vivo.
6. Future directions for imaging IBD

Remarkable progress has been achieved in recent years toward the understanding of IBD and its underpinning disease mechanisms. This has resulted in a wide array of specific biologics for treatment, but they are yet to be applied to diagnosis or surveillance. The complex immunological mechanisms of IBD indicate that there are multiple markers that could potentially be used for diagnostic imaging on the one hand, and drug bio-availability at the inflammatory site on the other. Imaging specific sites of inflammation should be achievable relatively easily, however determining markers that differentiate between IBD and other gastrointestinal disease, such as cancer, is more problematic and requires extensive pre-clinical validation.

Intact antibodies are increasingly used as therapeutics, however their utility as imaging agents is reduced by their extended half-life as the duration of time required to reach a sufficient signal to noise ratio is long. Furthermore, extended half-lives may also lead to other unwanted biological activity and side effects, which may alter the biological function being imaged. Recent developments in antibody engineering include a shift from whole IgG antibodies to fragments which enhances their physical properties, leading to enhanced efficacy as extensively reviewed in [43]. Enzymatic cleavage or restructuring of the antibody attenuates the problems associated with half-life by decreasing clearance times. Furthermore, the decreased amount of time required to reach a suitable signal also allows for the use of short-lived isotopes decreasing radiation exposure.

Pre-targeting strategies have also emerged as a means of improving efficacy whilst reducing radiation dose. Cook et al (2017) describe a novel approach for pre-targeted PET based on a
biorthogonal inverse electron demand Diels-Alder reaction between a $^{64}$Cu-labelled radioligand and a site specific immunoconjugate. This occurs in four steps: injection of the modified antibody, accumulation of the antibody at its target site and clearance from the blood, 24 hours later the injection of the radioligand and the *in vivo* click ligation between the immunoconjugate and radioligand and subsequent excretion of excess radioligand. Target tumor tissue was able to be delineated four hours post injection of the radioligand, with image contrast improving with time with an ideal sound to noise ratio at 24 hours. This pre-targeting approach and similar approaches may expedite clinical translation of future immunoconjugates for imaging.

A tantalizing approach is the potential to image different bacterial species, however is currently again limited by the lack of knowledge of functional roles for specific microbiota in IBD on the one hand, and the limited ability of PET to simultaneously label multiple targets. Furthermore, imaging of microbiota in general currently requires models where the bacteria can be isolated, labelled and re-administered. Future developments including the ability to use multiple labels, but also advances in the identification of bacterial species of interest and anaerobic culture of microbiota would be a welcome addition for preclinical models of IBD in the first instance before clinical studies are warranted. Furthermore, the potential to exploit factors that are selectively produced by bacteria and differentiate between active and quiescent states provides an intriguing insight. Bacterial toxins may be the ideal sensor, as they are typically only secreted during disease, readily identifiable by antibodies and relatively easily attached to various detection technologies. However, biosensing technology remains limited in its ability to provide insight into the spatial organization of the
microbiome, and as such the ideal microbial analysis tool remains elusive and current investigations must combine genomic, visual and activity-based measures.

7. Summary:

Imaging has a critical role in the diagnosis and management of IBD patients. Endoscopic studies are currently the gold standard. However, the clear need for new technologies that are less invasive than endoscopy. Animal studies indicate that PET and SPECT imaging of immune cells and/or mediators may be useful for the management and diagnosis of IBD. However, translation of these technologies into human studies is currently lacking, despite progress in this area in other diseases including cancer. Numerous immune cells and mediators are potential targets for PET/SPECT imaging of active IBD, however options for imaging of microbiota are limited by the lack of understanding of the role specific microbiota contribute toward IBD.
Author Contributions: ND, HRW and PAH conceptualized, wrote and edited the review.

Funding: This research was funded by a University of Australian Postgraduate Award and a William T Southcott Nuclear Medicine Scholarship to ND, a NHMRC C.J. Wright Biomedical Fellowship to HRW and a NHMRC R.D. Wright Biomedical Research Fellowship to PAH.

Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

\(^{18}\text{F}\) 18Fluorine
\(^{89}\text{Zr}\) 89Zirconium
\(^{99m}\text{Tc}\) 99mTechnetium
\(^{111}\text{In}\) 111Indium
CD Crohn’s Disease
CD4 Cluster of differentiation 4
CFA Complete Freund’s Adjuvant
CT Computed Tomography
CXCL8 C-X-C motif chemokine ligand 8; interleukin 8
DSS Dextran sodium sulfate
GI Gastrointestinal
GIT Gastrointestinal tract
Fab Fragment antigen-binding
HMPAO Hexamethylpropyleneamine oxime
HYNIC Hydrazinonicotinic acid
IBD Inflammatory bowel disease
IgG Immunoglobulin G
IL Interleukin
MAdCAM-1 Mucosal vascular addressin cell adhesion molecule 1
MHCII Major histocompatibility complex II
MRI Magnetic resonance imaging
mSv Milisieverts
OTU Operational taxonomic unit
PET Positron emission tomography
rRNA Ribosomal ribonucleic acid
SERS Surface enhanced Raman spectroscopy
SPECT Single photon emission computed tomography
TNBS Tri-nitro benzene sulfonic acid
TNF\(\alpha\) Tumor necrosis factor alpha
VHH Variable domain of heavy chain antibodies
WBC White blood cell

References


Table 1: Summary of PET / SPECT imaging of human IBD and animal models of colitis.

<table>
<thead>
<tr>
<th>Target</th>
<th>Tracers</th>
<th>Species</th>
<th>Model</th>
<th>Outcome</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukocytes</td>
<td>99mTc-HMPAO-leukocytes</td>
<td>Humans</td>
<td>UC</td>
<td>+</td>
<td>[22]</td>
</tr>
<tr>
<td>CXCL8</td>
<td>99mTc-CXCL8</td>
<td>Humans</td>
<td>CD and UC</td>
<td>+</td>
<td>[27]</td>
</tr>
<tr>
<td>β7</td>
<td>64Cu-FIB504.64-Fab</td>
<td>Mice</td>
<td>DSS</td>
<td>+</td>
<td>[32]</td>
</tr>
<tr>
<td>α4β7</td>
<td>64Cu-DATK32</td>
<td>Mice</td>
<td>DSS</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>β7</td>
<td>64Cu-FIB504.64-Fab</td>
<td>Mice</td>
<td>DSS</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>β7</td>
<td>64Cu-FIB504.64-F(ab'2)</td>
<td>Mice</td>
<td>DSS</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>CD4</td>
<td>89Zr-GK1.5 cys-diabody</td>
<td>Mice</td>
<td>DSS</td>
<td>++</td>
<td>[35]</td>
</tr>
<tr>
<td>TNFα</td>
<td>99mTc-Infliximab</td>
<td>Rats</td>
<td>TNBS</td>
<td>+</td>
<td>[30]</td>
</tr>
<tr>
<td>IgG Leukocytes</td>
<td>111In-liposomes</td>
<td>Rabbits</td>
<td>TNBS</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td>Liposomes</td>
<td>111In-IgG</td>
<td>Rabbits</td>
<td>TNBS</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>IL-8 Granulocytes</td>
<td>99mTc-HYNIC-IL-8</td>
<td>Rabbits</td>
<td>TNBS</td>
<td>++</td>
<td>[26]</td>
</tr>
<tr>
<td></td>
<td>99mTc-HMPAO-Granulocytes</td>
<td></td>
<td></td>
<td>+</td>
<td></td>
</tr>
</tbody>
</table>

- Suitable for colitis imaging, + satisfactory image quality, ++ excellent image quality.