World Journal of Gastroenterology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.3748/wjg.v22.i3.996

World J Gastroenterol 2016 January 21; 22(3): 996-1007
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

TOPIC HIGHLIGHT

2016 Inflammatory Bowel Disease: Global view

Diagnostic imaging advances in murine models of colitis

Markus Brückner, Philipp Lenz, Marcus M Mücke, Faekah Gohar, Peter Willeke, Dirk Domagk, Dominik Bettenworth

Markus Brückner, Philipp Lenz, Marcus M Mücke, Dominik Bettenworth, Department of Medicine B, University Hospital of Münster, Albert-Schweitzer-Campus 1, D-48149 Münster, Germany

Faekah Gohar, Department of Paediatric Rheumatology and Immunology, University Hospital of Münster, Albert-Schweitzer-Campus 1, D-48149 Münster, Germany

Peter Willeke, Department of Medicine D, University Hospital of Münster, Albert-Schweitzer-Campus 1, D-48149 Münster, Germany

Dirk Domagk, Department of Medicine I, Josephs-Hospital Warendorf, Academic Teaching Hospital, University of Münster, Am Krankenhaus 2, D-48231 Warendorf, Germany

Author contributions: Brückner M and Lenz P contributed equally to this work; Brückner M, Lenz P and Bettenworth D contributed to the article design, literature search, manuscript writing and final revision of the article; Mücke MM, Gohar F, Willeke P and Domagk D contributed to manuscript writing and final revision of the article; and Gohar F proofread the final revision.

Supported by The European Union Seventh Framework Programme for Research and Technological Development (FP 7) grant EUTRAIN (European Translational Training for Autoimmunity and Immune Manipulation Network, No. 289903 to Gohar F.

Conflict-of-interest statement: No author has any competing commercial, personal, political, intellectual, or religious interests in relation to the submitted work.

Correspondence to: Markus Brückner, MD, Department of Medicine B, University Hospital of Münster, Albert-Schweitzer-Campus 1, D-48149 Münster, Germany. markus.brueckner@ukmuenster.de
Telephone: +49-251-8347661
Fax: +49-251-8347570

Received: April 29, 2015
Peer-review started: May 12, 2015
First decision: August 26, 2015
Revised: September 9, 2015
Accepted: November 13, 2015
Article in press: November 13, 2015
Published online: January 21, 2016

Abstract

Inflammatory bowel diseases (IBD) such as Crohn's disease and ulcerative colitis are chronic-remittent inflammatory disorders of the gastrointestinal tract still evoking challenging clinical diagnostic and therapeutic situations. Murine models of experimental colitis are a vital component of research into human IBD concerning questions of its complex pathogenesis or the evaluation of potential new drugs. To monitor the course of colitis, to the present day, classical parameters like histological tissue alterations or analysis of mucosal cytokine/chemokine expression often require euthanasia of animals. Recent advances mean revolutionary non-invasive imaging techniques for *in vivo* murine colitis diagnostics are increasingly available. These novel and emerging imaging techniques not only allow direct visualization of intestinal inflammation, but also enable molecular imaging and targeting of specific alterations of the inflamed murine mucosa. For the first time, *in vivo* imaging techniques allow for longitudinal examinations and evaluation of intra-individual therapeutic response. This review discusses the latest developments in the different fields of ultrasound, molecularly targeted contrast agent ultrasound, fluorescence endoscopy, confocal laser endomicroscopy as well as tomographic imaging with magnetic resonance imaging, computed tomography and fluorescence-mediated tomography,

discussing their individual limitations and potential future diagnostic applications in the management of human patients with IBD.

Key words: Confocal laser endomicroscopy; Contrast enhanced ultrasound; Dextran Sodium Sulphate colitis; Experimental colitis; Fluorescence imaging; Endoscopy; Imaging; Inflammatory bowel disease; Tomography

Core tip: Murine models of experimental colitis are a vital component of research into human inflammatory bowel disease (IBD). Recent advances mean revolutionary non-invasive imaging techniques for *in vivo* murine colitis diagnostics are increasingly available. These techniques not only allow direct visualization of intestinal inflammation and enable molecular imaging of the inflamed mucosa but also allow for longitudinal evaluation of intra-individual therapeutic response. This review discusses the latest developments in the different fields of (molecularly targeted) contrast agent ultrasound, fluorescence endoscopy, confocal laser endomicroscopy as well as tomographic imaging with fluorescence-mediated tomography, discussing their potential future diagnostic applications in human IBD.

Brückner M, Lenz P, Mücke MM, Gohar F, Willeke P, Domagk D, Bettenworth D. Diagnostic imaging advances in murine models of colitis. *World J Gastroenterol* 2016; 22(3): 996-1007 Available from: URL: http://www.wjgnet.com/1007-9327/full/v22/i3/996.htm DOI: http://dx.doi.org/10.3748/wjg.v22.i3.996

INTRODUCTION

Inflammatory bowel diseases (IBD) such as Crohn's disease (CD) and ulcerative colitis (UC) are chronic-remittent inflammatory disorders of the gastrointestinal tract characterized by symptoms such as diarrhoea, abdominal pain or anaemia[1-3]. The course of IBD can be complicated and relapsing, involving challenging clinical diagnostic and therapeutic situations, which may often lead to hospitalization or surgery[4,5]. As the pathogenesis of IBD is still incompletely understood, current therapeutic regimes often are aimed at unspecific suppression of the adaptive immune system[6,7]. The therapeutic armamentarium of IBD was significantly advanced by the advent of antibodies directed towards tumor necrosis factor-α (TNF-α)[8-10]. Subsequently, various novel molecular targets have been identified and antibodies including anti-integrins and anti-interleukins have been tested for the treatment of IBD patients in clinical trials[11-13]. However, despite scientific advances in medical treatment, the success of such anti-inflammatory drugs remains hampered by potentially serious side effects including the increased risk of opportunistic infections and bone marrow suppression as well as limited long-term efficacy[14]. Furthermore, over 50% of CD patients still need surgery after 10 years of disease[15,16]. Therefore, novel therapeutic approaches are needed.

Evaluation of potential new drugs is usually performed in experimental models of colitis since sophisticated models are needed to mimic the complex pathogenesis of human IBD. Due to the abundant genetic and genomic information known and its availability in transgenic and knockout strains, the laboratory mouse *mus musculus* is the preferred animal for colitis research models[17]. These models are frequently used for evaluation of drug candidates as well as characterization of novel preclinical diagnostic or therapeutic approaches[18,19].

Daily monitoring of the murine body weight or determination of disease activity by appropriate indices[20,21] are classical *indirect* indicators for the severity of colitis and therapeutic response *in vivo*. As measurement of faecal and serum markers of inflammation[22-24] may not exactly reflect the course of the colitis, in humans or mice, histological analysis of the inflamed colon still remains the most valid approach for determining the severity of colitis[25]. Unfortunately, in mice, histological analysis of the colon commonly requires *post mortem* analyses, requiring death of the animal, and therefore do not allow for longitudinal observations at repetitive time points. Non-invasive and imaging-based methods to assess the course of experimental colitis are a promising approach to overcome this limitation.

This review summarises current crucial advances of promising imaging techniques to monitor disease activity in murine models of colitis *in vivo.* Recent developments in ultrasound- and endoscopy-based modalities as well as cross-sectional imaging are presented here. We also highlight the potential of these advances in diagnostic imaging in murine models of colitis to improve diagnosis in human IBD patients whilst also discussing their limitations.

ULTRASOUND

The quality of small animal high-frequency ultrasound and transducer techniques has dramatically improved with emerging research concerning interdependent sonographic criteria resolution, frequency and penetration[26-28]. Advanced linear transducer array technology with around 15 to over 50 MHz allowing B-mode, Doppler-mode, sophisticated contrast-agent and 3D ultrasound was broadly available since 2009[29]. As this technique facilitates imaging of small anatomical structures of about 50 μm[26], it enables the visualisation and examination of murine intestine, meeting criteria of guideline-directed human bowel ultrasound[30]. Key sonographic features of human IBD detected in

B-mode are increased bowel wall thickness and loss of bowel wall stratification[31,32]. These features are also detected with ultrasound of the colon of mice suffering from chemically induced Dextran Sodium Sulphate (DSS)-colitis and correlate strongly with established clinical parameters like weight loss[33]. Standardised examination protocols concerning comparable positioning of the animal, the transducer, anatomic landmarks and preparation of the colon with enema, help to reliably assess the course of murine colitis *in vivo* both intra-animal by longitudinal time course and inter-animal[34].

High-frequency power Doppler provides an additional *in vivo* ultrasonographic examination method, enabling examination of the murine vascular system. Moreover, high-frequency power Doppler in native small-animal ultrasound has already been used in inflammatory disorders[35] and can detect colorectal intraluminal tumours[36], quantify tumour volume and proportion of vascularisation[37,38] and may furthermore assess blood flow velocity[39].

As an advancement of classical B-mode technique, nonlinear contrast enhanced ultrasound (CEUS)[27,40] has further improved the sensitivity and specificity of small animal ultrasound, for instance in the detection and quantification of pathological vascular growth in tumour angiogenesis[41]. Ultrasound contrast agents are gas-liquid emulsions consisting of a biocompatible protein or lipidic shell and are filled with gas (perfluorocarbon, sulfur hexafluoride, or nitrogen)[42,43] which further enhance ultrasonic signal strength by displaying different acoustic properties than tissue or blood. With their micron size (usual diameter between 1-4 μm) and well-engineered technical features, microbubbles (MBs) can pass through microcapillaries like the pulmonary capillary bed and transiently persist in the blood stream[44,45]. Sophisticated ultrasound-based molecular imaging can therefore be used as a targeted modality, for example with the application of small molecules such as peptides or antibodies bound to the outer shell of MBs used as molecular contrast agents[46]. By using special software programmes, the ultrasound signals of contrast agent targeting molecular structures such as endothelial cells or intravascular blood cells of interest can be selectively enhanced in tissues or cells expressing the target molecules[42,47].

Regarding ultrasound assessment of experimental murine colitis at a molecular level, various endothelial cell adhesion molecules critically involved in leukocyte homing in intestinal inflammation have been evaluated as promising targets for contrast agents. Deshpande *et al*[48] showed *in vivo* the ultrasound signal in mice suffering from 2,4,6-trinitrobenzene sulphonic acid (TNBA)-induced colitis to be significantly higher using anti-P-selectin-targeted MBs than using control MBs, which was corroborated by measurement of mucosal P-selectin expression levels *ex vivo*. Additionally, expression of tissue- and disease-specific adhesion molecule mucosal addressin cellular adhesion molecule-1 (MAdCAM-1) used as a target molecule[49] is massively increased in the inflamed small bowel and colon of human IBD patients[50] and in murine experimental colitis[51,52]. Our group has also demonstrated earlier CEUS with anti-MAdCAM-1-labelled MBs to accurately measure the course and severity of DSS-colitis over time. Furthermore, MAdCAM-1 expression as assessed by CEUS correlated strongly with clinical parameters of colitis such as weight loss[53].

A benefit of ultrasound-based molecular imaging is that MBs directed against molecular targets are delivered direct to highly localized anatomical regions using small molecules or plasmids[54]. Different methods of attaching drugs to MBs have been reviewed in detail elsewhere[55]. With the method of sonoporation for example, high-pressure ultrasound can lead to destruction of MBs with local release of encapsulated drugs into the microcirculation, however on the other hand, ultrasound itself increases cell permeability enhancing transmembrane transport of therapeutic molecules[56,57]. In this context, Tlaxca *et al*[58] report about successful specific luciferase plasmid delivery to mesenteric vasculature *via* MBs targeting MAdCAM-1 and vascular cell adhesion protein-1 in a murine model of CD.

For the future, the evaluation of optoacoustic imaging or multispectral optoacoustic imaging (MSOT) as a novel imaging tool to diagnose murine colitis is desirable. This technique is based on the absorption of ultra short light pulses that lead to the generation of acoustic waves, which in MSOT have extended the spectral identification of chromophoric molecules in tissues, and shows good results for depth resolution, accuracy and visualisation of biochemical processes[59]. Other applications reported are the detection of pancreatic lesions *via* upregulated epidermal growth factor[60] or imaging of pharmacokinetics in multiple different organs[61].

While ultrasound allows visualization and serial follow-up examinations in animals with colitis, it cannot confirm the complete absence of mucosal inflammation. However, so-called "mucosal healing" is shown to be predictive of a beneficial disease course in human IBD patients[62,63] and has emerged as a goal of treatment[64]. Therefore, endoscopy-based approaches, which may facilitate a direct assessment of the murine mucosa, represent an adjunct imaging modality.

ENDOSCOPY-BASED APPROACHES

In vivo endoscopic imaging in murine models of colitis has the potential to merge both the pathogenic understanding of human IBD by continuous monitoring of the course of disease and the specific diagnostic imaging of the mucosa. White-light colonoscopy allows repeated examination, including biopsy sampling, of one mouse following the course of disease. Becker *et al*[65,66] first described a high-resolution chromo-endoscopic system, which enables monitoring of DSS-

colitis and also colitis-associated cancerogenesis. An objective score has also been established to describe intestinal inflammation in murine models of IBD - the MEICS-Score[67]. Parameters included in this score, are: thickening of the intestinal wall, vascular pattern, presence of fibrin, granularity of the mucosal surface and also stool consistency[67].

By allowing repeated examinations and intra-individual follow up, white light endoscopy allows examination of the effect of therapeutic substances on colitis activity and may lead to further clinical studies in humans[68-71].

Additionally, white-light endoscopy in murine colitis may also be used to evaluate intestinal wound healing, administer diagnostic or therapeutic agents and obtain mucosal biopsies[72]. There has been great progress in the development of novel endoscopic techniques[73]. Video-endoscopy including magnification and high-resolution endoscopy[74], chromo-endoscopy[75], narrow-band imaging[76], auto-fluorescence imaging[77], confocal laser endomicroscopy (CLE)[78,79] and optical coherence tomography[80] are some of the recent advances that have shown promise in surveillance examinations. Regarding small animal imaging and its translation from basic science into clinical application, fluorescence imaging, fluorescence endoscopy (FE) and CLE are the most promising candidates. The latter, CLE, has been established as a new imaging technique and virtual histopathology *in vivo* has also now been realized[81-83]. In addition to morphological characterization[84,85], CLE also allows immunohistochemistry to be performed *in vivo*. Foersch *et al*[86] have demonstrated the feasibility of specifically targeting vascular endothelial growth factor expression in gastrointestinal tumors *in vivo* with labeled antibodies and CLE. Similarly, Goetz *et al*[87] were able to use fluorescently labeled epidermal growth factor receptor (EGFR) antibodies to examine EGFR expression patterns and consequently diagnose colorectal cancer and predict response to targeted therapy. Visualization of EGFR expression *in vivo* may also help to identify promising drug candidates for anti-angiogenic treatment. In experimental colitis, CLE has been successfully applied to identify intra-mucosal bacteria *in vivo*[88], to monitor the course of disease[89] and to determine the presence of intestinal cancer stem cells in colitis associated tumorigenesis[90]. Moreover, nanoparticles such as avidin-nucleic acid nano-assembly have also been used to define chronically inflamed intestinal mucosa and to characterize murine models of IBD *in vivo.* Buda *et al*[91] characterized the mucosal surface with CLE and nanoparticles demonstrating them to be only observable in the inflamed and not healthy mucosa. Confirming the significant potential of CLE for characterizing intestinal inflammation in human IBD patients, Atreya *et al*[92] recently used fluorescently-labeled antibodies to quantify membrane-bound TNF-α positive intestinal immune cells and were able to predict treatment response towards an anti-TNF-α therapy in CD patients.

FE of specific molecular targets with near-infrared light allows *in vivo* molecular imaging with simple photographic methods[93,94]. This method employs the topical application of fluorescein-labeled monoclonal antibodies. For example, by the use of antibodies directed against carcinoembryonic antigen on the mucosal surface, colorectal carcinoma detection during conventional colonoscopy was possible with a specificity of 100% in human patients[95]. Confirming it's high diagnostic potential, local sensitization with hexaminolevulinate, a selective photosensitive precursor, FE enables early detection of colonic premalignant conditions during conventional colonoscopy in patients with a reported specificity of 72%[96]. In a murine model of colon carcinogenesis, fluorescently-labeled biomarkers were used to observe the tumor microenvironment by FE over time[97]. Furthermore, a cypate-labeled cyclic peptide sequence detected flat colorectal lesions by FE in colitis-associated cancer[98]. Other groups have developed fluorescently labeled peptides to mark colitis-induced adenoma[99,100].

As a "red flag technique" FE may allow screening of the large mucosal surface for early colorectal cancer, which may be especially helpful in UC patients who are at an increased risk of colitis-associated cancer[101]. An overview of different antibodies used in FE and CLE, their mode of application and target murine model is provided in Table 1.

Nevertheless, since the diagnostic capacity of endoscopy is restricted to endoluminal findings and assessment of single molecular targets of the colonic wall, assessment of colon wall thickness or even extra-intestinal findings, cross-sectional imaging techniques including magnetic resonance imaging (MRI) and computed tomography (CT) can provide additional information.

MRI AND CT

In human patients with IBD, colonoscopy represents the gold standard to assess luminal colonic inflammation. However, MRI has been established as a non-invasive imaging technique[30]. While possessing a limited sensitivity and specificity for the detection of colonic inflammation[102,103], it can detect extramural lesions as well as IBD-related complications (*e.g.,* stenosis abscesses and fistula). In contrast to endoscopic procedures, MRI imaging does not confer a risk of endoscopy-associated complications such as infection, perforation or hemorrhage[104-106].

In experimental colitis, MRI was first described to be as useful to assess disease activity in TNBA-treated rabbits[107]. Subsequently, Larsson *et al*[108] established MRI to investigate experimental colitis in the DSS-colitis model, using colonic wall thickness, contrast media-enhanced T1-weighted (T1w)[109] as well as T2-weighted (T2w) signals to detect intestinal inflammation in accordance to the diagnostic approach

Table 1 Tracer-antibodies used in fluorescence endoscopy and confocal laser endomicroscopy

Publication	Tracer	Application	Method	Mouse model
Charanya *et al*[98], 2014	Cypate- cyclic peptide sequence, D-Cys-Gly-Arg-Asp-Ser-Pro-Cys-Lys [c(DCGRDSPC)K]	Topical	FE	AOM-CRC, mice
Gounaris *et al*[157], 2013	ProSense 680	Intravenous	FE and Fluorescence Reflectance Imaging	IL-10$^{-/-}$ mice, mice
Joshi *et al*[99], 2012	Cy5.5-AKPGYLS peptide multimer	Topical	FE	CPC; Apc mice
Miller *et al*[100], 2011	FITC-Ahx-QPIHPNNM peptide	Topical	FE	CPC; Apc mice
Urano *et al*[158], 2011	gGlu-HMRG	Topical	Laparoscopy + FE	diss. Ovarial-Ca, mice
Foersch *et al*[86], 2010	VEGF-Ab	Topical	Colonoscopy + CLE	APCmin mice, Stomach cancer
Goetz *et al*[87], 2010	EGFR-Ab	Intravenous	CLE	Balb/c nu/nu mice, CRC-cells implanted
Funovics *et al*[159], 2006	Cy5.5 nano particle u. AF750-Beacon	Intravenous	Colonoscopy + FE	APCmin mice, CT26 (CRC) in nu/nu

FE: Fluorescence endoscopy; AOM: Azoxymethane; CRC: Colorectal cancer; IL-10: Interleukin 10; Cy5.5: Cyanine 5.5; CPC: Cdx2-Cre transgene; Apc: Adenomatous polyposis coli; FITC: Fluoresceinisothiocyanat; Ahx: Aminohexanoic acid, HMRG: Hydroxymethylrhodamine green; VEGF: Vascular endothelial growth factor; CLE: Confocal laser endomicroscopy; EGFR: Epidermal growth factor receptor; Balb: Albino laboratory-bred mouse strain; AF750: Alexa fluor 750; CT26: Cancer cell line.

used in human patients with IBD[110-113]. Strong correlations between MRI measurements and clinical and histological disease activity were found. Michael *et al*[114] proposed to quantify colonic inflammation by assessment of colon wall thickness and tissue density factor. However, to achieve this, the 3D MRI with respiratory triggering required administration of spasmolytic substances to inhibit breathing and intestinal motility which was a complex and time-consuming procedure, resulting in a complete MRI examination requiring 20-30 min per animal[108]. Consequently, Melgar *et al*[115] established a 2D rapid T2$_w$ MRI protocol to provide characterization of the intestinal inflammation in under seven minutes which also avoided the need for respiratory triggering or antispasmodics. Whilst this protocol accurately detected inflammation in colonic segments below the bladder, in proximal colonic segments the MRI findings and inflammatory parameters only correlated weakly, limiting the applicability. An additional limitation of 2D acquired data sets is their prerequisite for perfect alignment of the colon along the coronal plane[115].

However, recently there is a growing body of evidence supporting the utility of MRI for the assessment of intestinal inflammation, using colon wall thickness, contrast enhancement and T2$_w$ sequences[78,116-121]. Novel parameters like dynamic contrast enhancement[117,118] are also being included and advanced criteria including target sign patterns and intramural hemorrhage detection have been introduced to characterize experimental colonic inflammation[119]. Pohlmann *et al*[78] were able to follow the course of TNBS-induced colitis in rats and the therapeutic response after anti-inflammatory treatment with sulfasalazine with repeated measurements of colonic wall thickness and T2$_w$ sequences. Colitis is characterized by inflammation-mediated edema occurring by immune cell infiltration, vasodilatation and increased capillary permeability, which eventually result in thickening of the colonic wall[20,108,122]. Therefore, MRI measurements of colon wall thickness and T2$_w$ signal intensity reflecting edema can be very sensitive for murine colon inflammation, however, these parameters are also unspecific biomarkers of inflammation. To improve the specificity, Frericks *et al*[123] administered ultra-small superparamagnetic iron oxide particles intravenously which accumulate in the reticuloendothelial system, differentiating IBD from unspecific causes of edema.

Bowel wall thickening and increased T2$_w$ signal intensity are also core features of intestinal fibrosis and partly correlate with the degree of fibrosis[124]. Therefore, MRI may also be used to detect fibrosis in murine models as well as inflammation. However, it remains challenging to accurately distinguish between persisting inflammation and fibrosis, a problem exacerbated by the fact that both are frequently simultaneously observed[125-127]. Adler *et al*[126] proposed a possible solution to this involving the application of magnetization transfer ratios in MRI not only to detect intestinal fibrosis, but also to show fibrotic progression over time. These results have been similarly reproduced in a different rat model of colitis[128], and the technique has also been used to monitor therapeutic response of anti-fibrotic therapy in rats[129]. Furthermore, Breynaert *et al*[127] found a regression in MRI T$_2$ relaxometry over the course of several DSS-cycles that might be used to differentiate early inflammation from fibrosis.

According to current guidelines, CT has high accuracy for the assessment of specific clinical questions, for example, to confirm the presence of suspected penetrating complications or abscesses in human patients with IBD[30]. Interestingly, only a few studies solely evaluate CT for the assessment of intestinal inflammation in experimental colitis. Recently, Fredin *et al*[130] demonstrated the diagnostic potential of micro-CT (μCT) to detect and monitor the course of inflammation and also therapeutic response by assessing colonic wall thickness. Moreover, based on the CT findings, the

authors were able to differentiate between responders and non-responders of anti-inflammatory treatment in early acute colitis. However, since the thickness of the colonic wall remains unchanged during the healing phase of colitis, the applicability of this read-out is restricted to the early stages of colitis. Furthermore, to obtain an image of sufficiently good quality during small animal CT-examinations, 10-fold higher dosages are required for animals compared to human CT-studies[131], which could potentially interfere with the inflammatory model being examined[132], especially when imaging is performed longitudinally for disease monitoring. Several clinical studies in human patients have confirmed CT enterography for detecting inflammation in the small bowel during CD is highly accurate[133-136]. Bodily *et al*[137] showed a strong correlation of mural enhancement and wall thickness indicating active small-bowel inflammation, which could be confirmed by histological analysis. However, to date no studies have been performed in experimental colitis[138-140].

Recently, to utilise the favourable spatial resolution of CT with a functional imaging modality to more specifically detect intestinal inflammation, μCT with positron emission tomography (PET) was introduced. Activated leukocytes accumulate ^{18}F-fluorodeoxyglucose (FDG), which can be traced by PET[141]. ^{18}F-FDG PET/CT has shown promising results for clinical assessment of IBD patients in preliminary studies[142-145]. Since acute DSS-colitis is neutrophil-mediated[146], our group have employed ^{18}F-FDG PET/CT for detecting and monitoring DSS-induced intestinal inflammation which had a strong correlation with established inflammatory parameters, endoscopic findings and histological analysis[147,148]. Furthermore, Brewer *et al*[149,150] demonstrated increased CD4+ T cell uptake of either ^{18}F-FDG or ^{18}F-1-(2'-deoxy-2'-arabinofuranosyl)cytosine (D-FAC) in chronic intestinal inflammation, a method which could be utilized for the detection of colitis. In line with those findings, another transfer colitis model was successfully used for monitoring intestinal inflammation[151]. Most recently, PET/CT was performed on a large scale in 70 mice and the findings compared to those using contrast agent-guided ultrasound for detection of intestinal inflammation[152]. One limitation of imaging colitis by PET/μCT is an obscured pelvic region because of tracer accumulation in the bladder. However, these artefacts can be minimised by emptying the bladder of the animal manually using gentle pressure[149,150] or with use of continuous bladder flushing[153]. Further studies are needed to evaluate the possible influence of radiation during the monitoring of inflammatory disease[132] and to improve limited detection rates of minor mucosal alteration[142,148].

In addition to MRI and CT, FMT can be used to characterize biological processes in experimental colitis. With the use of labelled antibodies that specifically target mucosal colitis markers or distinct cell populations on a molecular level, use of FMT to quantify protein expression and localization *in vivo* and to continuously monitor disease progression and therapeutic effects has been promising[154,155]. We could show that FMT targeting mucosal myeloid-related protein-14 expression, allows specifically detection of intestinal inflammation at early stages of DSS-colitis[156]. Tomography with fluorescent light currently yields images with a resolution of 1-2 mm. Of particular importance for potential future use in human IBD is that FMT does not require radioactive labelling. Future studies are warranted to further elucidate the full diagnostic potential of FMT.

CONCLUSION

Ultrasound diagnostics in murine colitis requires a profound and analogous preparation of the examination to reliably assess classical sonographic parameters of inflammation of the colon wall. Notably, ultrasound provides high spatial resolution, allows serial real-time examination and with the use of molecularly targeted contrast agent, tissue- and disease-specific molecular imaging can be assessed.

White light colonoscopy is an indispensable tool for direct visualization of murine mucosa in colitis models. Sophisticated advancement such as CLE and FE allow further characterization of colorectal lesion on a molecular level, may improve the understanding of the pathogenesis of colorectal disease in general and intestinal carcinogenesis in particular and may facilitate early detection of colitis-associated cancer.

Finally, MRI using T2w sequences or contrast enhancement has been successfully established for intestinal inflammation detection and monitoring of disease course and may additionally be used to evaluate intestinal fibrosis. Due to its low specificity, μCT alone remains insufficient for the diagnostic in experimental colitis; however, μCT combined with PET becomes a valuable tool for the assessment and monitoring of intestinal inflammation.

REFERENCES

1 **Lee JC**, Espéli M, Anderson CA, Linterman MA, Pocock JM, Williams NJ, Roberts R, Viatte S, Fu B, Peshu N, Hien TT, Phu NH, Wesley E, Edwards C, Ahmad T, Mansfield JC, Gearry R, Dunstan S, Williams TN, Barton A, Vinuesa CG, Parkes M, Lyons PA, Smith KG. Human SNP links differential outcomes in inflammatory and infectious disease to a FOXO3-regulated pathway. *Cell* 2013; **155**: 57-69 [PMID: 24035192 DOI: 10.1016/j.cell.2013.08.034]

2 **Neurath MF**, Schürmann G. [Immunopathogenesis of inflammatory bowel diseases]. *Chirurg* 2000; **71**: 30-40 [PMID: 10662999 DOI: 10.1007/s001040050005]

3 **Vucelic B**. Inflammatory bowel diseases: controversies in the use of diagnostic procedures. *Dig Dis* 2009; **27**: 269-277 [PMID: 19786751 DOI: 10.1159/000228560]

4 **Bettenworth D**, Rieder F. Medical therapy of stricturing Crohn's disease: what the gut can learn from other organs - a systematic review. *Fibrogenesis Tissue Repair* 2014; **7**: 5 [PMID: 24678903 DOI: 10.1186/1755-1536-7-5]

5 **Nikolaus S**, Schreiber S. Diagnostics of inflammatory bowel disease. *Gastroenterology* 2007; **133**: 1670-1689 [PMID: 17983810

DOI: 10.1053/j.gastro.2007.09.001]
6 **Dignass A**, Lindsay JO, Sturm A, Windsor A, Colombel JF, Allez M, D'Haens G, D'Hoore A, Mantzaris G, Novacek G, Oresland T, Reinisch W, Sans M, Stange E, Vermeire S, Travis S, Van Assche G. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 2: current management. *J Crohns Colitis* 2012; **6**: 991-1030 [PMID: 23040451 DOI: 10.1016/j.crohns.2012.09.002]
7 **Dignass A**, Van Assche G, Lindsay JO, Lémann M, Söderholm J, Colombel JF, Danese S, D'Hoore A, Gassull M, Gomollón F, Hommes DW, Michetti P, O'Morain C, Oresland T, Windsor A, Stange EF, Travis SP. The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: Current management. *J Crohns Colitis* 2010; **4**: 28-62 [PMID: 21122489 DOI: 10.1016/j.crohns.2009.12.002]
8 **Hanauer SB**, Feagan BG, Lichtenstein GR, Mayer LF, Schreiber S, Colombel JF, Rachmilewitz D, Wolf DC, Olson A, Bao W, Rutgeerts P. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet* 2002; **359**: 1541-1549 [PMID: 12047962 DOI: 10.1016/S0140-6736(02)08512-4]
9 **Sandborn WJ**, Hanauer SB, Rutgeerts P, Fedorak RN, Lukas M, MacIntosh DG, Panaccione R, Wolf D, Kent JD, Bittle B, Li J, Pollack PF. Adalimumab for maintenance treatment of Crohn's disease: results of the CLASSIC II trial. *Gut* 2007; **56**: 1232-1239 [PMID: 17299059 DOI: 10.1136/gut.2006.106781]
10 **Colombel JF**, Sandborn WJ, Rutgeerts P, Enns R, Hanauer SB, Panaccione R, Schreiber S, Byczkowski D, Li J, Kent JD, Pollack PF. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. *Gastroenterology* 2007; **132**: 52-65 [PMID: 17241859 DOI: 10.1053/j.gastro.2006.11.041]
11 **Feagan BG**, Greenberg GR, Wild G, Fedorak RN, Paré P, McDonald JW, Dubé R, Cohen A, Steinhart AH, Landau S, Aguzzi RA, Fox IH, Vandervoort MK. Treatment of ulcerative colitis with a humanized antibody to the alpha4beta7 integrin. *N Engl J Med* 2005; **352**: 2499-2507 [PMID: 15958805 DOI: 10.1056/NEJMoa042982]
12 **Feagan BG**, Greenberg GR, Wild G, Fedorak RN, Paré P, McDonald JW, Cohen A, Bitton A, Baker J, Dubé R, Landau SB, Vandervoort MK, Parikh A. Treatment of active Crohn's disease with MLN0002, a humanized antibody to the alpha4beta7 integrin. *Clin Gastroenterol Hepatol* 2008; **6**: 1370-1377 [PMID: 18829392 DOI: 10.1016/j.cgh.2008.06.007]
13 **Sandborn WJ**, Feagan BG, Fedorak RN, Scherl E, Fleisher MR, Katz S, Johanns J, Blank M, Rutgeerts P. A randomized trial of Ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with moderate-to-severe Crohn's disease. *Gastroenterology* 2008; **135**: 1130-1141 [PMID: 18706417 DOI: 10.1053/j.gastro.2008.07.014]
14 **Ardizzone S**, Bianchi Porro G. Biologic therapy for inflammatory bowel disease. *Drugs* 2005; **65**: 2253-2286 [PMID: 16266194 DOI: 10.2165/00003495-200565160-00002]
15 **Bernell O**, Lapidus A, Hellers G. Risk factors for surgery and recurrence in 907 patients with primary ileocaecal Crohn's disease. *Br J Surg* 2000; **87**: 1697-1701 [PMID: 11122187 DOI: 10.1046/j.1365-2168.2000.01589.x]
16 **Solberg IC**, Vatn MH, Høie O, Stray N, Sauar J, Jahnsen J, Moum B, Lygren I. Clinical course in Crohn's disease: results of a Norwegian population-based ten-year follow-up study. *Clin Gastroenterol Hepatol* 2007; **5**: 1430-1438 [PMID: 18054751 DOI: 10.1016/j.cgh.2007.09.002]
17 **Neurath MF**. Animal models of inflammatory bowel diseases: illuminating the pathogenesis of colitis, ileitis and cancer. *Dig Dis* 2012; **30** Suppl 1: 91-94 [PMID: 23075875 DOI: 10.1159/000341131]
18 **Wirtz S**, Neufert C, Weigmann B, Neurath MF. Chemically induced mouse models of intestinal inflammation. *Nat Protoc* 2007; **2**: 541-546 [PMID: 17406617 DOI: 10.1038/nprot.2007.41]
19 **Valatas V**, Vakas M, Kolios G. The value of experimental models of colitis in predicting efficacy of biological therapies for inflammatory bowel diseases. *Am J Physiol Gastrointest Liver Physiol* 2013; **305**: G763-G785 [PMID: 23989010 DOI: 10.1152/ajpgi.00004.2013]
20 **Melgar S**, Karlsson A, Michaëlsson E. Acute colitis induced by dextran sulfate sodium progresses to chronicity in C57BL/6 but not in BALB/c mice: correlation between symptoms and inflammation. *Am J Physiol Gastrointest Liver Physiol* 2005; **288**: G1328-G1338 [PMID: 15637179 DOI: 10.1152/ajpgi.00467.2004]
21 **Melgar S**, Karlsson L, Rehnström E, Karlsson A, Utkovic H, Jansson L, Michaëlsson E. Validation of murine dextran sulfate sodium-induced colitis using four therapeutic agents for human inflammatory bowel disease. *Int Immunopharmacol* 2008; **8**: 836-844 [PMID: 18442787 DOI: 10.1016/j.intimp.2008.01.036]
22 **Serada S**, Fujimoto M, Terabe F, Iijima H, Shinzaki S, Matsuzaki S, Ohkawara T, Nezu R, Nakajima S, Kobayashi T, Plevy SE, Takehara T, Naka T. Serum leucine-rich alpha-2 glycoprotein is a disease activity biomarker in ulcerative colitis. *Inflamm Bowel Dis* 2012; **18**: 2169-2179 [PMID: 22374925 DOI: 10.1002/ibd.22936]
23 **Turovskaya O**, Foell D, Sinha P, Vogl T, Newlin R, Nayak J, Nguyen M, Olsson A, Nawroth PP, Bierhaus A, Varki N, Kronenberg M, Freeze HH, Srikrishna G. RAGE, carboxylated glycans and S100A8/A9 play essential roles in colitis-associated carcinogenesis. *Carcinogenesis* 2008; **29**: 2035-2043 [PMID: 18689872 DOI: 10.1093/carcin/bgn188]
24 **Sprong RC**, Schonewille AJ, van der Meer R. Dietary cheese whey protein protects rats against mild dextran sulfate sodium-induced colitis: role of mucin and microbiota. *J Dairy Sci* 2010; **93**: 1364-1371 [PMID: 20338413 DOI: 10.3168/jds.2009-2397]
25 **Dieleman LA**, Palmen MJ, Akol H, Bloemena E, Peña AS, Meuwissen SG, Van Rees EP. Chronic experimental colitis induced by dextran sulphate sodium (DSS) is characterized by Th1 and Th2 cytokines. *Clin Exp Immunol* 1998; **114**: 385-391 [PMID: 9844047]
26 **Foster FS**, Pavlin CJ, Harasiewicz KA, Christopher DA, Turnbull DH. Advances in ultrasound biomicroscopy. *Ultrasound Med Biol* 2000; **26**: 1-27 [PMID: 10687788]
27 **Goertz DE**, Needles A, Burns PN, Foster FS. High-frequency, nonlinear flow imaging of microbubble contrast agents. *IEEE Trans Ultrason Ferroelectr Freq Control* 2005; **52**: 495-502 [PMID: 15857059]
28 **Needles A**, Couture O, Foster FS. A method for differentiating targeted microbubbles in real time using subharmonic micro-ultrasound and interframe filtering. *Ultrasound Med Biol* 2009; **35**: 1564-1573 [PMID: 19632763 DOI: 10.1016/j.ultrasmedbio.2009.04.006]
29 **Foster FS**, Mehi J, Lukacs M, Hirson D, White C, Chaggares C, Needles A. A new 15-50 MHz array-based micro-ultrasound scanner for preclinical imaging. *Ultrasound Med Biol* 2009; **35**: 1700-1708 [PMID: 19647922 DOI: 10.1016/j.ultrasmedbio.2009.04.012]
30 **Panes J**, Bouhnik Y, Reinisch W, Stoker J, Taylor SA, Baumgart DC, Danese S, Halligan S, Marincek B, Matos C, Peyrin-Biroulet L, Rimola J, Rogler G, van Assche G, Ardizzone S, Ba-Ssalamah A, Bali MA, Bellini D, Biancone L, Castiglione F, Ehehalt R, Grassi R, Kucharzik T, Maccioni F, Maconi G, Magro F, Martín-Comín J, Morana G, Pendsé D, Sebastian S, Signore A, Tolan D, Tielbeek JA, Weishaupt D, Wiarda B, Laghi A. Imaging techniques for assessment of inflammatory bowel disease: joint ECCO and ESGAR evidence-based consensus guidelines. *J Crohns Colitis* 2013; **7**: 556-585 [PMID: 23583097 DOI: 10.1016/j.crohns.2013.02.020]
31 **Di Mizio R**, Maconi G, Romano S, D'Amario F, Bianchi Porro G, Grassi R. Small bowel Crohn disease: sonographic features. *Abdom Imaging* 2004; **29**: 23-35 [PMID: 15160749]
32 **Panés J**, Bouzas R, Chaparro M, García-Sánchez V, Gisbert JP, Martínez de Guereñu B, Mendoza JL, Paredes JM, Quiroga S, Ripollés T, Rimola J. Systematic review: the use of ultrasonography, computed tomography and magnetic resonance imaging for the diagnosis, assessment of activity and abdominal complications of Crohn's disease. *Aliment Pharmacol Ther* 2011; **34**: 125-145 [PMID: 21615440 DOI: 10.1111/j.1365-2036.2011.04710.x]

33 **Brückner M**, Stypmann J, Bettenworth D, Heidemann J. Ultrasonographic Characterization of Murine DSS-Colitis - 40 Mhz In Vivo Hydrosonography Monitors Features of Colonic Inflammation in Mice. *Gastroenterology* 2011; **140**: S-697 [DOI: 10.1016/S0016-5085(11)62894-1]

34 **Hyvelin JM**, Tardy I, Arbogast C, Costa M, Emmel P, Helbert A, Theraulaz M, Nunn AD, Tranquart F. Use of ultrasound contrast agent microbubbles in preclinical research: recommendations for small animal imaging. *Invest Radiol* 2013; **48**: 570-583 [PMID: 23511194 DOI: 10.1097/RLI.0b013e318289f854]

35 **Barry CT**, Hah Z, Partin A, Mooney RA, Chuang KH, Augustine A, Almudevar A, Cao W, Rubens DJ, Parker KJ. Mouse liver dispersion for the diagnosis of early-stage Fatty liver disease: a 70-sample study. *Ultrasound Med Biol* 2014; **40**: 704-713 [PMID: 24412179 DOI: 10.1016/j.ultrasmedbio.2013.10.016]

36 **Barbieri A**, Barretta ML, Rea D, Picone C, Fabozzi O, Palma G, Antonio L, Federico A, Bimonte S, Setola F, De Lutio Di Castelguidone E, Castellano M, D'Errico AG, Caraglia M, Arra C. Intraluminal gel ultrasound and eco-color doppler: new tools for the study of colorectal cancer in mice. *In Vivo* 2013; **27**: 443-450 [PMID: 23812213]

37 **Linkous A**, Geng L, Lyshchik A, Hallahan DE, Yazlovitskaya EM. Cytosolic phospholipase A2: targeting cancer through the tumor vasculature. *Clin Cancer Res* 2009; **15**: 1635-1644 [PMID: 19240173 DOI: 10.1158/1078-0432.CCR-08-1905]

38 **Zhang W**, Matrisian LM, Holmbeck K, Vick CC, Rosenthal EL. Fibroblast-derived MT1-MMP promotes tumor progression in vitro and in vivo. *BMC Cancer* 2006; **6**: 52 [PMID: 16515711 DOI: 10.1186/1471-2407-6-52]

39 **Di Lascio N**, Stea F, Kusmic C, Sicari R, Faita F. Non-invasive assessment of pulse wave velocity in mice by means of ultrasound images. *Atherosclerosis* 2014; **237**: 31-37 [PMID: 25194332 DOI: 10.1016/j.atherosclerosis.2014.08.033]

40 **Goertz DE**, Cherin E, Needles A, Karshafian R, Brown AS, Burns PN, Foster FS. High frequency nonlinear B-scan imaging of microbubble contrast agents. *IEEE Trans Ultrason Ferroelectr Freq Control* 2005; **52**: 65-79 [PMID: 15742563]

41 **Horie S**, Chen R, Li L, Mori S, Kodama T. Contrast-enhanced high-frequency ultrasound imaging of early stage liver metastasis in a preclinical mouse model. *Cancer Lett* 2013; **339**: 208-213 [PMID: 23791880 DOI: 10.1016/j.canlet.2013.06.006]

42 **Klibanov AL**. Ligand-carrying gas-filled microbubbles: ultrasound contrast agents for targeted molecular imaging. *Bioconjug Chem* 2005; **16**: 9-17 [PMID: 15656569 DOI: 10.1021/bc049898y]

43 **Klibanov AL**. Preparation of targeted microbubbles: ultrasound contrast agents for molecular imaging. *Med Biol Eng Comput* 2009; **47**: 875-882 [PMID: 19517153 DOI: 10.1007/s11517-009-0498-0]

44 **Bouakaz A**, de Jong N, Cachard C, Jouini K. On the effect of lung filtering and cardiac pressure on the standard properties of ultrasound contrast agent. *Ultrasonics* 1998; **36**: 703-708 [PMID: 9651600 DOI: 10.1016/S0041-624X(97)00137-6]

45 **Wen Q**, Wan S, Liu Z, Xu S, Wang H, Yang B. Ultrasound contrast agents and ultrasound molecular imaging. *J Nanosci Nanotechnol* 2014; **14**: 190-209 [PMID: 24730259 DOI: 10.1166/jnn.2014.9114]

46 **Gessner R**, Dayton PA. Advances in molecular imaging with ultrasound. *Mol Imaging* 2010; **9**: 117-127 [PMID: 20487678 DOI: 10.2310/7290.2010.00022]

47 **Schumann PA**, Christiansen JP, Quigley RM, McCreery TP, Sweitzer RH, Unger EC, Lindner JR, Matsunaga TO. Targeted-microbubble binding selectively to GPIIb IIIa receptors of platelet thrombi. *Invest Radiol* 2002; **37**: 587-593 [PMID: 12393970 DOI: 10.1097/01.RLI.0000031077.17751.B2]

48 **Deshpande N**, Lutz AM, Ren Y, Foygel K, Tian L, Schneider M, Pai R, Pasricha PJ, Willmann JK. Quantification and monitoring of inflammation in murine inflammatory bowel disease with targeted contrast-enhanced US. *Radiology* 2012; **262**: 172-180 [PMID: 22056689 DOI: 10.1148/radiol.11110323]

49 **Bachmann C**, Klibanov AL, Olson TS, Sonnenschein JR, Rivera-Nieves J, Cominelli F, Ley KF, Lindner JR, Pizarro TT. Targeting mucosal addressin cellular adhesion molecule (MAdCAM)-1 to noninvasively image experimental Crohn's disease. *Gastroenterology* 2006; **130**: 8-16 [PMID: 16401463 DOI: 10.1053/j.gastro.2005.11.009]

50 **Briskin M**, Winsor-Hines D, Shyjan A, Cochran N, Bloom S, Wilson J, McEvoy LM, Butcher EC, Kassam N, Mackay CR, Newman W, Ringler DJ. Human mucosal addressin cell adhesion molecule-1 is preferentially expressed in intestinal tract and associated lymphoid tissue. *Am J Pathol* 1997; **151**: 97-110 [PMID: 9212736]

51 **Kato S**, Hokari R, Matsuzaki K, Iwai A, Kawaguchi A, Nagao S, Miyahara T, Itoh K, Ishii H, Miura S. Amelioration of murine experimental colitis by inhibition of mucosal addressin cell adhesion molecule-1. *J Pharmacol Exp Ther* 2000; **295**: 183-189 [PMID: 10991977]

52 **Gorfu G**, Rivera-Nieves J, Ley K. Role of beta7 integrins in intestinal lymphocyte homing and retention. *Curr Mol Med* 2009; **9**: 836-850 [PMID: 19860663 DOI: 10.2174/156652409789105525]

53 **Brückner M**, Stypmann J, Bettenworth D, Heidemann J. Mo1799 Targeting Endovascular Adhesion Molecules With Ultrasound Contrast Agent In Vivo to Characterize Murine DSS-Colitis in Mice. *Gastroenterology* 2012; **142**: S-688 [DOI: 10.1016/S0016-5085(12)62652-3]

54 **Unger EC**, Matsunaga TO, McCreery T, Schumann P, Sweitzer R, Quigley R. Therapeutic applications of microbubbles. *Eur J Radiol* 2002; **42**: 160-168 [PMID: 11976013 DOI: 10.1016/S0720-048X(01)00455-7]

55 **Dijkmans PA**, Juffermans LJ, Musters RJ, van Wamel A, ten Cate FJ, van Gilst W, Visser CA, de Jong N, Kamp O. Microbubbles and ultrasound: from diagnosis to therapy. *Eur J Echocardiogr* 2004; **5**: 245-256 [PMID: 15219539 DOI: 10.1016/j.euje.2004.02.001]

56 **Lawrie A**, Brisken AF, Francis SE, Tayler DI, Chamberlain J, Crossman DC, Cumberland DC, Newman CM. Ultrasound enhances reporter gene expression after transfection of vascular cells in vitro. *Circulation* 1999; **99**: 2617-2620 [PMID: 10338452 DOI: 10.1161/01.CIR.99.20.2617]

57 **Ferrara KW**. Driving delivery vehicles with ultrasound. *Adv Drug Deliv Rev* 2008; **60**: 1097-1102 [PMID: 18479775 DOI: 10.1016/j.addr.2008.03.002]

58 **Tlaxca JL**, Rychak JJ, Ernst PB, Konkalmatt PR, Shevchenko TI, Pizarro TT, Rivera-Nieves J, Klibanov AL, Lawrence MB. Ultrasound-based molecular imaging and specific gene delivery to mesenteric vasculature by endothelial adhesion molecule targeted microbubbles in a mouse model of Crohn's disease. *J Control Release* 2013; **165**: 216-225 [PMID: 23142578 DOI: 10.1016/j.jconrel.2012.10.021]

59 **Ntziachristos V**, Razansky D. Molecular imaging by means of multispectral optoacoustic tomography (MSOT). *Chem Rev* 2010; **110**: 2783-2794 [PMID: 20387910 DOI: 10.1021/cr9002566]

60 **Hudson SV**, Huang JS, Yin W, Albeituni S, Rush J, Khanal A, Yan J, Ceresa BP, Frieboes HB, McNally LR. Targeted noninvasive imaging of EGFR-expressing orthotopic pancreatic cancer using multispectral optoacoustic tomography. *Cancer Res* 2014; **74**: 6271-6279 [PMID: 25217521 DOI: 10.1158/0008-5472.CAN-14-1656]

61 **Taruttis A**, Morscher S, Burton NC, Razansky D, Ntziachristos V. Fast multispectral optoacoustic tomography (MSOT) for dynamic imaging of pharmacokinetics and biodistribution in multiple organs. *PLoS One* 2012; **7**: e30491 [PMID: 22295087 DOI: 10.1371/journal.pone.0030491]

62 **Frøslie KF**, Jahnsen J, Moum BA, Vatn MH. Mucosal healing in inflammatory bowel disease: results from a Norwegian population-based cohort. *Gastroenterology* 2007; **133**: 412-422 [PMID: 17681162 DOI: 10.1053/j.gastro.2007.05.051]

63 **Baert F**, Moortgat L, Van Assche G, Caenepeel P, Vergauwe P, De Vos M, Stokkers P, Hommes D, Rutgeerts P, Vermeire S, D'Haens G. Mucosal healing predicts sustained clinical remission in patients with early-stage Crohn's disease. *Gastroenterology* 2010; **138**: 463-468; quiz e10-e11 [PMID: 19818785 DOI: 10.1053/j.gastro.2009.09.056]

64 **Levesque BG**, Sandborn WJ, Ruel J, Feagan BG, Sands BE,

Colombel JF. Converging goals of treatment of inflammatory bowel disease from clinical trials and practice. *Gastroenterology* 2015; **148**: 37-51.e1 [PMID: 25127678 DOI: 10.1053/j.gastro.2014.08.003]
65 **Becker C**, Fantini MC, Neurath MF. High resolution colonoscopy in live mice. *Nat Protoc* 2006; **1**: 2900-2904 [PMID: 17406549 DOI: 10.1038/nprot.2006.446]
66 **Becker C**, Fantini MC, Wirtz S, Nikolaev A, Kiesslich R, Lehr HA, Galle PR, Neurath MF. In vivo imaging of colitis and colon cancer development in mice using high resolution chromoendoscopy. *Gut* 2005; **54**: 950-954 [PMID: 15951540 DOI: 10.1136/gut.2004.061283]
67 **Pickert G**, Neufert C, Leppkes M, Zheng Y, Wittkopf N, Warntjen M, Lehr HA, Hirth S, Weigmann B, Wirtz S, Ouyang W, Neurath MF, Becker C. STAT3 links IL-22 signaling in intestinal epithelial cells to mucosal wound healing. *J Exp Med* 2009; **206**: 1465-1472 [PMID: 19564350 DOI: 10.1084/jem.20082683]
68 **Ali H**, Weigmann B, Neurath MF, Collnot EM, Windbergs M, Lehr CM. Budesonide loaded nanoparticles with pH-sensitive coating for improved mucosal targeting in mouse models of inflammatory bowel diseases. *J Control Release* 2014; **183**: 167-177 [PMID: 24685705 DOI: 10.1016/j.jconrel.2014.03.039]
69 **Chua AC**, Klopcic BR, Ho DS, Fu SK, Forrest CH, Croft KD, Olynyk JK, Lawrance IC, Trinder D. Dietary iron enhances colonic inflammation and IL-6/IL-11-Stat3 signaling promoting colonic tumor development in mice. *PLoS One* 2013; **8**: e78850 [PMID: 24223168 DOI: 10.1371/journal.pone.0078850]
70 **Sina C**, Lipinski S, Gavrilova O, Aden K, Rehman A, Till A, Rittger A, Podschun R, Meyer-Hoffert U, Haesler R, Midtling E, Pütsep K, McGuckin MA, Schreiber S, Saftig P, Rosenstiel P. Extracellular cathepsin K exerts antimicrobial activity and is protective against chronic intestinal inflammation in mice. *Gut* 2013; **62**: 520-530 [PMID: 22442160 DOI: 10.1136/gutjnl-2011-300076]
71 **Ueno Y**, Tanaka S, Sumii M, Miyake S, Tazuma S, Taniguchi M, Yamamura T, Chayama K. Single dose of OCH improves mucosal T helper type 1/T helper type 2 cytokine balance and prevents experimental colitis in the presence of valpha14 natural killer T cells in mice. *Inflamm Bowel Dis* 2005; **11**: 35-41 [PMID: 15674111 DOI: 10.1097/00054725-200501000-00005]
72 **Brückner M**, Lenz P, Nowacki TM, Pott F, Foell D, Bettenworth D. Murine endoscopy for in vivo multimodal imaging of carcinogenesis and assessment of intestinal wound healing and inflammation. *J Vis Exp* 2014; (**90**): e51875 [PMID: 25226434 DOI: 10.3791/51875]
73 **Kiesslich R**, Goetz M, Hoffman A, Galle PR. New imaging techniques and opportunities in endoscopy. *Nat Rev Gastroenterol Hepatol* 2011; **8**: 547-553 [PMID: 21894196 DOI: 10.1038/nrgastro.2011.152]
74 **Kara MA**, Peters FP, Rosmolen WD, Krishnadath KK, ten Kate FJ, Fockens P, Bergman JJ. High-resolution endoscopy plus chromoendoscopy or narrow-band imaging in Barrett's esophagus: a prospective randomized crossover study. *Endoscopy* 2005; **37**: 929-936 [PMID: 16189764 DOI: 10.1055/s-2005-870433]
75 **Jung M**, Kiesslich R. Chromoendoscopy and intravital staining techniques. *Baillieres Best Pract Res Clin Gastroenterol* 1999; **13**: 11-19 [PMID: 11030630 DOI: 10.1053/bega.1999.0004]
76 **Hamamoto Y**, Endo T, Nosho K, Arimura Y, Sato M, Imai K. Usefulness of narrow-band imaging endoscopy for diagnosis of Barrett's esophagus. *J Gastroenterol* 2004; **39**: 14-20 [PMID: 14767729 DOI: 10.1007/s00535-003-1239-z]
77 **Haringsma J**, Tytgat GN, Yano H, Iishi H, Tatsuta M, Ogihara T, Watanabe H, Sato N, Marcon N, Wilson BC, Cline RW. Autofluorescence endoscopy: feasibility of detection of GI neoplasms unapparent to white light endoscopy with an evolving technology. *Gastrointest Endosc* 2001; **53**: 642-650 [PMID: 11323596 DOI: 10.1067/mge.2001.114419]
78 **Pohlmann A**, Tilling LC, Robinson A, Woolmer O, McCleary S, Kruidenier L, Warnock LC, Lewis HD, Hobson AR, James MF. Progression and variability of TNBS colitis-associated inflammation in rats assessed by contrast-enhanced and T2-weighted MRI. *Inflamm Bowel Dis* 2009; **15**: 534-545 [PMID: 19058230 DOI: 10.1002/ibd.20800]
79 **Kiesslich R**, Goetz M, Vieth M, Galle PR, Neurath MF. Confocal laser endomicroscopy. *Gastrointest Endosc Clin N Am* 2005; **15**: 715-731 [PMID: 16278135 DOI: 10.1016/j.giec.2005.08.010]
80 **Testoni PA**, Mangiavillano B. Optical coherence tomography in detection of dysplasia and cancer of the gastrointestinal tract and bilio-pancreatic ductal system. *World J Gastroenterol* 2008; **14**: 6444-6452 [PMID: 19030194 DOI: 10.3748/wjg.14.6444]
81 **Inoue H**, Igari T, Nishikage T, Ami K, Yoshida T, Iwai T. A novel method of virtual histopathology using laser-scanning confocal microscopy in-vitro with untreated fresh specimens from the gastrointestinal mucosa. *Endoscopy* 2000; **32**: 439-443 [PMID: 10863908 DOI: 10.1055/s-2000-654]
82 **Sakashita M**, Inoue H, Kashida H, Tanaka J, Cho JY, Satodate H, Hidaka E, Yoshida T, Fukami N, Tamegai Y, Shiokawa A, Kudo S. Virtual histology of colorectal lesions using laser-scanning confocal microscopy. *Endoscopy* 2003; **35**: 1033-1038 [PMID: 14648417 DOI: 10.1055/s-2003-44595]
83 **Kiesslich R**, Burg J, Vieth M, Gnaendiger J, Enders M, Delaney P, Polglase A, McLaren W, Janell D, Thomas S, Nafe B, Galle PR, Neurath MF. Confocal laser endoscopy for diagnosing intraepithelial neoplasias and colorectal cancer in vivo. *Gastroenterology* 2004; **127**: 706-713 [PMID: 15362025 DOI: 10.1053/j.gastro.2004.06.050]
84 **Goetz M**, Memadathil B, Biesterfeld S, Schneider C, Gregor S, Galle PR, Neurath MF, Kiesslich R. In vivo subsurface morphological and functional cellular and subcellular imaging of the gastrointestinal tract with confocal mini-microscopy. *World J Gastroenterol* 2007; **13**: 2160-2165 [PMID: 17465494 DOI: 10.3748/wjg.v13.i15.2160]
85 **Goetz M**, Toermer T, Vieth M, Dunbar K, Hoffman A, Galle PR, Neurath MF, Delaney P, Kiesslich R. Simultaneous confocal laser endomicroscopy and chromoendoscopy with topical cresyl violet. *Gastrointest Endosc* 2009; **70**: 959-968 [PMID: 19595315 DOI: 10.1016/j.gie.2009.04.016]
86 **Foersch S**, Kiesslich R, Waldner MJ, Delaney P, Galle PR, Neurath MF, Goetz M. Molecular imaging of VEGF in gastrointestinal cancer in vivo using confocal laser endomicroscopy. *Gut* 2010; **59**: 1046-1055 [PMID: 20639250 DOI: 10.1136/gut.2009.202986]
87 **Goetz M**, Ziebart A, Foersch S, Vieth M, Waldner MJ, Delaney P, Galle PR, Neurath MF, Kiesslich R. In vivo molecular imaging of colorectal cancer with confocal endomicroscopy by targeting epidermal growth factor receptor. *Gastroenterology* 2010; **138**: 435-446 [PMID: 19852961 DOI: 10.1053/j.gastro.2009.10.032]
88 **Moussata D**, Goetz M, Gloeckner A, Kerner M, Campbell B, Hoffman A, Biesterfeld S, Flourie B, Saurin JC, Galle PR, Neurath MF, Watson AJ, Kiesslich R. Confocal laser endomicroscopy is a new imaging modality for recognition of intramucosal bacteria in inflammatory bowel disease in vivo. *Gut* 2011; **60**: 26-33 [PMID: 20980342 DOI: 10.1136/gut.2010.213264]
89 **Waldner MJ**, Wirtz S, Neufert C, Becker C, Neurath MF. Confocal laser endomicroscopy and narrow-band imaging-aided endoscopy for in vivo imaging of colitis and colon cancer in mice. *Nat Protoc* 2011; **6**: 1471-1481 [PMID: 21886109 DOI: 10.1038/nprot.2011.377]
90 **Choi JW**, Kim JK, Choi M, Kim YR, Yun SH. In vivo imaging of Lgr5-positive cell populations using confocal laser endomicroscopy during early colon tumorigenesis. *Endoscopy* 2014; **46**: 1110-1116 [PMID: 25216325 DOI: 10.1055/s-0034-1377631]
91 **Buda A**, Facchin S, Dassie E, Casarin E, Jepson MA, Neumann H, Hatem G, Realdon S, D'Incà R, Sturniolo GC, Morpurgo M. Detection of a fluorescent-labeled avidin-nucleic acid nanoassembly by confocal laser endomicroscopy in the microvasculature of chronically inflamed intestinal mucosa. *Int J Nanomedicine* 2015; **10**: 399-408 [PMID: 25609952 DOI: 10.2147/IJN.S70153]
92 **Atreya R**, Neumann H, Neufert C, Waldner MJ, Billmeier U, Zopf Y, Willma M, App C, Münster T, Kessler H, Maas S, Gebhardt B, Heimke-Brinck R, Reuter E, Dörje F, Rau TT, Uter W, Wang TD, Kiesslich R, Vieth M, Hannappel E, Neurath MF. In vivo imaging using fluorescent antibodies to tumor necrosis factor predicts therapeutic response in Crohn's disease. *Nat Med* 2014; **20**:

313-318 [PMID: 24562382 DOI: 10.1038/nm.3462]
93 **Bremer C**, Ntziachristos V, Weissleder R. Optical-based molecular imaging: contrast agents and potential medical applications. *Eur Radiol* 2003; **13**: 231-243 [PMID: 12598985 DOI: 10.1007/s00330-002-1610-0]
94 **Ntziachristos V**, Bremer C, Weissleder R. Fluorescence imaging with near-infrared light: new technological advances that enable in vivo molecular imaging. *Eur Radiol* 2003; **13**: 195-208 [PMID: 12541130 DOI: 10.1007/s00330-002-1524-x]
95 **Keller R**, Winde G, Terpe HJ, Foerster EC, Domschke W. Fluorescence endoscopy using a fluorescein-labeled monoclonal antibody against carcinoembryonic antigen in patients with colorectal carcinoma and adenoma. *Endoscopy* 2002; **34**: 801-807 [PMID: 12244502 DOI: 10.1055/s-2002-34254]
96 **Mayinger B**, Neumann F, Kastner C, Degitz K, Hahn EG, Schwab D. Early detection of premalignant conditions in the colon by fluorescence endoscopy using local sensitization with hexaminolevulinate. *Endoscopy* 2008; **40**: 106-109 [PMID: 18197583 DOI: 10.1055/s-2007-967019]
97 **Leung SJ**, Rice PS, Barton JK. In vivo molecular mapping of the tumor microenvironment in an azoxymethane-treated mouse model of colon carcinogenesis. *Lasers Surg Med* 2015; **47**: 40-49 [PMID: 25487746 DOI: 10.1002/lsm.22309]
98 **Charanya T**, York T, Bloch S, Sudlow G, Liang K, Garcia M, Akers WJ, Rubin D, Gruev V, Achilefu S. Trimodal color-fluorescence-polarization endoscopy aided by a tumor selective molecular probe accurately detects flat lesions in colitis-associated cancer. *J Biomed Opt* 2014; **19**: 126002 [PMID: 25473883 DOI: 10.1117/1.JBO.19.12.126002]
99 **Joshi BP**, Liu Z, Elahi SF, Appelman HD, Wang TD. Near-infrared-labeled peptide multimer functions as phage mimic for high affinity, specific targeting of colonic adenomas in vivo (with videos). *Gastrointest Endosc* 2012; **76**: 1197-1206.e1-e5 [PMID: 23022051 DOI: 10.1016/j.gie.2012.07.017]
100 **Miller SJ**, Joshi BP, Feng Y, Gaustad A, Fearon ER, Wang TD. In vivo fluorescence-based endoscopic detection of colon dysplasia in the mouse using a novel peptide probe. *PLoS One* 2011; **6**: e17384 [PMID: 21408169 DOI: 10.1371/journal.pone.0017384]
101 **Nowacki TM**, Brückner M, Eveslage M, Tepasse P, Pott F, Thoennissen NH, Hengst K, Ross M, Bettenworth D. The risk of colorectal cancer in patients with ulcerative colitis. *Dig Dis Sci* 2015; **60**: 492-501 [PMID: 25280558 DOI: 10.1007/s10620-014-3373-2]
102 **Schreyer AG**, Rath HC, Kikinis R, Völk M, Schölmerich J, Feuerbach S, Rogler G, Seitz J, Herfarth H. Comparison of magnetic resonance imaging colonography with conventional colonoscopy for the assessment of intestinal inflammation in patients with inflammatory bowel disease: a feasibility study. *Gut* 2005; **54**: 250-256 [PMID: 15647190 DOI: 10.1136/gut.2003.037390]
103 **Ajaj WM**, Lauenstein TC, Pelster G, Gerken G, Ruehm SG, Debatin JF, Goehde SC. Magnetic resonance colonography for the detection of inflammatory diseases of the large bowel: quantifying the inflammatory activity. *Gut* 2005; **54**: 257-263 [PMID: 15647191 DOI: 10.1136/gut.2003.037085]
104 **Jiménez-Perez FJ**, Echarri A, Jiménez E, Borda F. Colonic hemorrhage after standard biopsy. *Am J Gastroenterol* 1994; **89**: 1123-1124 [PMID: 8017387]
105 **Hall C**, Dorricott NJ, Donovan IA, Neoptolemos JP. Colon perforation during colonoscopy: surgical versus conservative management. *Br J Surg* 1991; **78**: 542-544 [PMID: 2059801 DOI: 10.1002/bjs.1800780509]
106 **Ferreira J**, Akbari M, Gashin L, Cullen G, Moss A, Leffler DA, Aronson M, Cheifetz AS. Prevalence and lifetime risk of endoscopy-related complications among patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2013; **11**: 1288-1293 [PMID: 23669305 DOI: 10.1016/j.cgh.2013.04.047]
107 **Knollmann FD**, Dietrich T, Bleckmann T, Böck J, Mäurer J, Radtke C, Felix R. Magnetic resonance imaging of inflammatory bowel disease: evaluation in a rabbit model. *J Magn Reson Imaging* 2002; **15**: 165-173 [PMID: 11836772 DOI: 10.1002/jmri.10054]
108 **Larsson AE**, Melgar S, Rehnström E, Michaëlsson E, Svensson L, Hockings P, Olsson LE. Magnetic resonance imaging of experimental mouse colitis and association with inflammatory activity. *Inflamm Bowel Dis* 2006; **12**: 478-485 [PMID: 16775491 DOI: 10.1097/00054725-200606000-00006]
109 **Kominsky DJ**, Campbell EL, Ehrentraut SF, Wilson KE, Kelly CJ, Glover LE, Collins CB, Bayless AJ, Saeedi B, Dobrinskikh E, Bowers BE, MacManus CF, Müller W, Colgan SP, Bruder D. IFN-γ-mediated induction of an apical IL-10 receptor on polarized intestinal epithelia. *J Immunol* 2014; **192**: 1267-1276 [PMID: 24367025 DOI: 10.4049/jimmunol.1301757]
110 **Maccioni F**, Colaiacomo MC, Parlanti S. Ulcerative colitis: value of MR imaging. *Abdom Imaging* 2005; **30**: 584-592 [PMID: 15886952 DOI: 10.1007/s00261-004-0284-2]
111 **Low RN**, Sebrechts CP, Politoske DA, Bennett MT, Flores S, Snyder RJ, Pressman JH. Crohn disease with endoscopic correlation: single-shot fast spin-echo and gadolinium-enhanced fat-suppressed spoiled gradient-echo MR imaging. *Radiology* 2002; **222**: 652-660 [PMID: 11867781 DOI: 10.1148/radiol.2223010811]
112 **Koh DM**, Miao Y, Chinn RJ, Amin Z, Zeegen R, Westaby D, Healy JC. MR imaging evaluation of the activity of Crohn's disease. *AJR Am J Roentgenol* 2001; **177**: 1325-1332 [PMID: 11717076 DOI: 10.2214/ajr.177.6.1771325]
113 **Maccioni F**, Viscido A, Broglia L, Marrollo M, Masciangelo R, Caprilli R, Rossi P. Evaluation of Crohn disease activity with magnetic resonance imaging. *Abdom Imaging* 2000; **25**: 219-228 [PMID: 10823437 DOI: 10.1007/s002610000004]
114 **Michael S**, Keubler LM, Smoczek A, Meier M, Gunzer F, Pöhlmann C, Krause-Buchholz U, Hedrich HJ, Bleich A. Quantitative phenotyping of inflammatory bowel disease in the IL-10-deficient mouse by use of noninvasive magnetic resonance imaging. *Inflamm Bowel Dis* 2013; **19**: 185-193 [PMID: 22570250 DOI: 10.1002/ibd.23006]
115 **Melgar S**, Gillberg PG, Hockings PD, Olsson LE. High-throughput magnetic resonance imaging in murine colonic inflammation. *Biochem Biophys Res Commun* 2007; **355**: 1102-1107 [PMID: 17336266 DOI: 10.1016/j.bbrc.2007.02.090]
116 **Young MR**, Ileva LV, Bernardo M, Riffle LA, Jones YL, Kim YS, Colburn NH, Choyke PL. Monitoring of tumor promotion and progression in a mouse model of inflammation-induced colon cancer with magnetic resonance colonography. *Neoplasia* 2009; **11**: 237-246, 1p following 246 [PMID: 19242605 DOI: 10.1593/neo.81326]
117 **Mustafi D**, Fan X, Dougherty U, Bissonnette M, Karczmar GS, Oto A, Hart J, Markiewicz E, Zamora M. High-resolution magnetic resonance colonography and dynamic contrast-enhanced magnetic resonance imaging in a murine model of colitis. *Magn Reson Med* 2010; **63**: 922-929 [PMID: 20373393 DOI: 10.1002/mrm.22229]
118 **Aychek T**, Vandoorne K, Brenner O, Jung S, Neeman M. Quantitative analysis of intravenously administered contrast media reveals changes in vascular barrier functions in a murine colitis model. *Magn Reson Med* 2011; **66**: 235-243 [PMID: 21254214 DOI: 10.1002/mrm.22798]
119 **Charpentier C**, Marion-Letellier R, Savoye G, Nicol L, Mulder P, Aziz M, Vera P, Déchelotte P, Savoye-Collet C. Magnetic resonance colonography in rats with TNBS-induced colitis: a feasibility and validation study. *Inflamm Bowel Dis* 2012; **18**: 1940-1949 [PMID: 22262626 DOI: 10.1002/ibd.22897]
120 **Köhnke T**, Gomolka B, Bilal S, Zhou X, Sun Y, Rothe M, Baumgart DC, Weylandt KH. Acetylsalicylic Acid reduces the severity of dextran sodium sulfate-induced colitis and increases the formation of anti-inflammatory lipid mediators. *Biomed Res Int* 2013; **2013**: 748160 [PMID: 24083240 DOI: 10.1155/2013/748160]
121 **Guseva D**, Holst K, Kaune B, Meier M, Keubler L, Glage S, Buettner M, Bleich A, Pabst O, Bachmann O, Ponimaskin EG. Serotonin 5-HT7 receptor is critically involved in acute and chronic inflammation of the gastrointestinal tract. *Inflamm Bowel Dis* 2014; **20**: 1516-1529 [PMID: 25072499 DOI: 10.1097/MIB.0000000000000150]
122 **Mori M**, Stokes KY, Vowinkel T, Watanabe N, Elrod JW, Harris

NR, Lefer DJ, Hibi T, Granger DN. Colonic blood flow responses in experimental colitis: time course and underlying mechanisms. *Am J Physiol Gastrointest Liver Physiol* 2005; **289**: G1024-G1029 [PMID: 16081759 DOI: 10.1152/ajpgi.00247.2005]

123 **Frericks BB**, Wacker F, Loddenkemper C, Valdeig S, Hotz B, Wolf KJ, Misselwitz B, Kühl A, Hoffmann JC. Magnetic resonance imaging of experimental inflammatory bowel disease: quantitative and qualitative analyses with histopathologic correlation in a rat model using the ultrasmall iron oxide SHU 555 C. *Invest Radiol* 2009; **44**: 23-30 [PMID: 18836385 DOI: 10.1097/RLI.0b013e3181899025]

124 **Melchior C**, Loeuillard E, Marion-Letellier R, Nicol L, Mulder P, Guerin C, Bôle-Feysot C, Aziz M, Déchelotte P, Vera P, Savoye G, Savoye-Collet C. Magnetic resonance colonography for fibrosis assessment in rats with chronic colitis. *PLoS One* 2014; **9**: e100921 [PMID: 25000184 DOI: 10.1371/journal.pone.0100921]

125 **Stidham RW**, Xu J, Johnson LA, Kim K, Moons DS, McKenna BJ, Rubin JM, Higgins PD. Ultrasound elasticity imaging for detecting intestinal fibrosis and inflammation in rats and humans with Crohn's disease. *Gastroenterology* 2011; **141**: 819-826.e1 [PMID: 21784048 DOI: 10.1053/j.gastro.2011.07.027]

126 **Adler J**, Swanson SD, Schmiedlin-Ren P, Higgins PD, Golembeski CP, Polydorides AD, McKenna BJ, Hussain HK, Verrot TM, Zimmermann EM. Magnetization transfer helps detect intestinal fibrosis in an animal model of Crohn disease. *Radiology* 2011; **259**: 127-135 [PMID: 21324841 DOI: 10.1148/radiol.10091648]

127 **Breynaert C**, Dresselaers T, Perrier C, Arijs I, Cremer J, Van Lommel L, Van Steen K, Ferrante M, Schuit F, Vermeire S, Rutgeerts P, Himmelreich U, Ceuppens JL, Geboes K, Van Assche G. Unique gene expression and MR T2 relaxometry patterns define chronic murine dextran sodium sulphate colitis as a model for connective tissue changes in human Crohn's disease. *PLoS One* 2013; **8**: e68876 [PMID: 23894361 DOI: 10.1371/journal.pone.0068876]

128 **Dillman JR**, Swanson SD, Johnson LA, Moons DS, Adler J, Stidham RW, Higgins PD. Comparison of noncontrast MRI magnetization transfer and T2 -Weighted signal intensity ratios for detection of bowel wall fibrosis in a Crohn's disease animal model. *J Magn Reson Imaging* 2015; **42**: 801-810 [PMID: 25504823 DOI: 10.1002/jmri.24815]

129 **Adler J**, Rahal K, Swanson SD, Schmiedlin-Ren P, Rittershaus AC, Reingold LJ, Brudi JS, Shealy D, Cai A, McKenna BJ, Zimmermann EM. Anti-tumor necrosis factor α prevents bowel fibrosis assessed by messenger RNA, histology, and magnetization transfer MRI in rats with Crohn's disease. *Inflamm Bowel Dis* 2013; **19**: 683-690 [PMID: 23429466 DOI: 10.1097/MIB.0b013e3182802c32]

130 **Fredin MF**, Hultin L, Hyberg G, Rehnström E, Hultgren Hörnquist E, Melgar S, Jansson L. Predicting and monitoring colitis development in mice by micro-computed tomography. *Inflamm Bowel Dis* 2008; **14**: 491-499 [PMID: 18161841 DOI: 10.1002/ibd.20343]

131 **Boone JM**, Velazquez O, Cherry SR. Small-animal X-ray dose from micro-CT. *Mol Imaging* 2004; **3**: 149-158 [PMID: 15530250 DOI: 10.1162/1535350042380326]

132 **Rödel F**, Keilholz L, Herrmann M, Sauer R, Hildebrandt G. Radiobiological mechanisms in inflammatory diseases of low-dose radiation therapy. *Int J Radiat Biol* 2007; **83**: 357-366 [PMID: 17487675 DOI: 10.1080/09553000701317358]

133 **Choi D**, Jin Lee S, Ah Cho Y, Lim HK, Hoon Kim S, Jae Lee W, Hoon Lim J, Park H, Rae Lee Y. Bowel wall thickening in patients with Crohn's disease: CT patterns and correlation with inflammatory activity. *Clin Radiol* 2003; **58**: 68-74 [PMID: 12565208 DOI: 10.1053/crad.2002.1068]

134 **Maglinte DD**, Gourtsoyiannis N, Rex D, Howard TJ, Kelvin FM. Classification of small bowel Crohn's subtypes based on multimodality imaging. *Radiol Clin North Am* 2003; **41**: 285-303 [PMID: 12659339 DOI: 10.1016/S0033-8389(02)00117-3]

135 **Chiorean MV**, Sandrasegaran K, Saxena R, Maglinte DD, Nakeeb A, Johnson CS. Correlation of CT enteroclysis with surgical pathology in Crohn's disease. *Am J Gastroenterol* 2007; **102**: 2541-2550 [PMID: 17900329 DOI: 10.1111/j.1572-0241.2007.01537.x]

136 **Solem CA**, Loftus EV, Fletcher JG, Baron TH, Gostout CJ, Petersen BT, Tremaine WJ, Egan LJ, Faubion WA, Schroeder KW, Pardi DS, Hanson KA, Jewell DA, Barlow JM, Fidler JL, Huprich JE, Johnson CD, Harmsen WS, Zinsmeister AR, Sandborn WJ. Small-bowel imaging in Crohn's disease: a prospective, blinded, 4-way comparison trial. *Gastrointest Endosc* 2008; **68**: 255-266 [PMID: 18513722 DOI: 10.1016/j.gie.2008.02.017]

137 **Bodily KD**, Fletcher JG, Solem CA, Johnson CD, Fidler JL, Barlow JM, Bruesewitz MR, McCollough CH, Sandborn WJ, Loftus EV, Harmsen WS, Crownhart BS. Crohn Disease: mural attenuation and thickness at contrast-enhanced CT Enterography--correlation with endoscopic and histologic findings of inflammation. *Radiology* 2006; **238**: 505-516 [PMID: 16436815 DOI: 10.1148/radiol.2382041159]

138 **Hamdani G**, Gabet Y, Rachmilewitz D, Karmeli F, Bab I, Dresner-Pollak R. Dextran sodium sulfate-induced colitis causes rapid bone loss in mice. *Bone* 2008; **43**: 945-950 [PMID: 18675386 DOI: 10.1016/j.bone.2008.06.018]

139 **Radhakrishnan VM**, Ramalingam R, Larmonier CB, Thurston RD, Laubitz D, Midura-Kiela MT, McFadden RM, Kuro-O M, Kiela PR, Ghishan FK. Post-translational loss of renal TRPV5 calcium channel expression, Ca(2+) wasting, and bone loss in experimental colitis. *Gastroenterology* 2013; **145**: 613-624 [PMID: 23747339 DOI: 10.1053/j.gastro.2013.06.002]

140 **Holgersen K**, Dobie R, Farquharson C, van't Hof R, Ahmed SF, Hansen AK, Holm TL. Piroxicam treatment augments bone abnormalities in interleukin-10 knockout mice. *Inflamm Bowel Dis* 2015; **21**: 257-266 [PMID: 25569742 DOI: 10.1097/MIB.0000000000000269]

141 **Pellegrino D**, Bonab AA, Dragotakes SC, Pitman JT, Mariani G, Carter EA. Inflammation and infection: imaging properties of 18F-FDG-labeled white blood cells versus 18F-FDG. *J Nucl Med* 2005; **46**: 1522-1530 [PMID: 16157536]

142 **Louis E**, Ancion G, Colard A, Spote V, Belaiche J, Hustinx R. Noninvasive assessment of Crohn's disease intestinal lesions with (18)F-FDG PET/CT. *J Nucl Med* 2007; **48**: 1053-1059 [PMID: 17574978 DOI: 10.2967/jnumed.107.040436]

143 **Meisner RS**, Spier BJ, Einarsson S, Roberson EN, Perlman SB, Bianco JA, Taylor AJ, Einstein M, Jaskowiak CJ, Massoth KM, Reichelderfer M. Pilot study using PET/CT as a novel, noninvasive assessment of disease activity in inflammatory bowel disease. *Inflamm Bowel Dis* 2007; **13**: 993-1000 [PMID: 17394243 DOI: 10.1002/ibd.20134]

144 **Spier BJ**, Perlman SB, Reichelderfer M. FDG-PET in inflammatory bowel disease. *Q J Nucl Med Mol Imaging* 2009; **53**: 64-71 [PMID: 19182729]

145 **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 [PMID: 19430844 DOI: 10.1007/s11307-009-0232-1]

146 **Okayasu I**, Hatakeyama S, Yamada M, Ohkusa T, Inagaki Y, Nakaya R. A novel method in the induction of reliable experimental acute and chronic ulcerative colitis in mice. *Gastroenterology* 1990; **98**: 694-702 [PMID: 1688816]

147 **Hindryckx P**, Staelens S, Devisscher L, Deleye S, De Vos F, Delrue L, Peeters H, Laukens D, De Vos M. Longitudinal quantification of inflammation in the murine dextran sodium sulfate-induced colitis model using μPET/CT. *Inflamm Bowel Dis* 2011; **17**: 2058-2064 [PMID: 21910167 DOI: 10.1002/ibd.21578]

148 **Bettenworth D**, Reuter S, Hermann S, Weckesser M, Kerstiens L, Stratis A, Nowacki TM, Ross M, Lenze F, Edemir B, Maaser C, Pap T, Koschmieder S, Heidemann J, Schäfers M, Lügering A. Translational 18F-FDG PET/CT imaging to monitor lesion activity in intestinal inflammation. *J Nucl Med* 2013; **54**: 748-755 [PMID: 23516311 DOI: 10.2967/jnumed.112.112623]

149 **Brewer S**, McPherson M, Fujiwara D, Turovskaya O, Ziring D, Chen L, Takedatsu H, Targan SR, Wei B, Braun J. Molecular imaging of murine intestinal inflammation with 2-deoxy-2-[18F]fluoro-D-glucose and positron emission tomography.

Gastroenterology 2008; **135**: 744-755 [PMID: 18639553 DOI: 10.1053/j.gastro.2008.06.040]

150 **Brewer S**, Nair-Gill E, Wei B, Chen L, Li X, Riedinger M, Campbell DO, Wiltzius S, Satyamurthy N, Phelps ME, Radu C, Witte ON, Braun J. Epithelial uptake of [18F]1-(2'-deoxy-2' -arabinofuranosyl) cytosine indicates intestinal inflammation in mice. *Gastroenterology* 2010; **138**: 1266-1275 [PMID: 20080095 DOI: 10.1053/j.gastro.2010.01.003]

151 **Heylen M**, Deleye S, De Man JG, Ruyssers NE, Vermeulen W, Stroobants S, Pelckmans PA, Moreels TG, Staelens S, De Winter BY. Colonoscopy and μPET/CT are valid techniques to monitor inflammation in the adoptive transfer colitis model in mice. *Inflamm Bowel Dis* 2013; **19**: 967-976 [PMID: 23407045 DOI: 10.1097/MIB.0b013e3182802c7c]

152 **Wang H**, Machtaler S, Bettinger T, Lutz AM, Luong R, Bussat P, Gambhir SS, Tranquart F, Tian L, Willmann JK. Molecular imaging of inflammation in inflammatory bowel disease with a clinically translatable dual-selectin-targeted US contrast agent: comparison with FDG PET/CT in a mouse model. *Radiology* 2013; **267**: 818-829 [PMID: 23371306 DOI: 10.1148/radiol.13122509]

153 **Deleye S**, Heylen M, Deiteren A, De Man J, Stroobants S, De Winter B, Staelens S. Continuous flushing of the bladder in rodents reduces artifacts and improves quantification in molecular imaging. *Mol Imaging* 2014; 13 [PMID: 24825484 DOI: 10.2310/7290.2014.00013]

154 **Al Rawashdeh W**, Arns S, Gremse F, Ehling J, Knüchel-Clarke R, Kray S, Spöler F, Kiessling F, Lederle W. Optical tomography of MMP activity allows a sensitive noninvasive characterization of the invasiveness and angiogenesis of SCC xenografts. *Neoplasia* 2014; **16**: 235-246, 246.e1 [PMID: 24784000 DOI: 10.1016/j.neo.2014.03.005]

155 **Li R**, Zheng K, Hu P, Chen Z, Zhou S, Chen J, Yuan C, Chen S, Zheng W, Ma E, Zhang F, Xue J, Chen X, Huang M. A novel tumor targeting drug carrier for optical imaging and therapy. *Theranostics* 2014; **4**: 642-659 [PMID: 24723985 DOI: 10.7150/thno.8527]

156 **Bettenworth D**, Hasenberg F, Eisenblaetter M, Tiemann K, Heidemann J, Domschke WW, Luegering A. S1642 New Tools for In Vivo Imaging of Murine DSS-Colitis - Mrp14-Directed Fluorescence-Mediated Molecular Tomography (FMT) and High-Resolution Ultrasound Imaging. *Gastroenterology* 2009; **136**: A-240-A-241 [DOI: 10.1016/S0016-5085(09)61088-X]

157 **Gounaris E**, Martin J, Ishihara Y, Khan MW, Lee G, Sinh P, Chen EZ, Angarone M, Weissleder R, Khazaie K, Barrett TA. Fluorescence endoscopy of cathepsin activity discriminates dysplasia from colitis. *Inflamm Bowel Dis* 2013; **19**: 1339-1345 [PMID: 23591598 DOI: 10.1097/MIB.0b013e318281f3f8]

158 **Urano Y**, Sakabe M, Kosaka N, Ogawa M, Mitsunaga M, Asanuma D, Kamiya M, Young MR, Nagano T, Choyke PL, Kobayashi H. Rapid cancer detection by topically spraying a γ-glutamyl-transpeptidase-activated fluorescent probe. *Sci Transl Med* 2011; **3**: 110ra119 [PMID: 22116934 DOI: 10.1126/scitranslmed.3002823]

159 **Funovics MA**, Alencar H, Montet X, Weissleder R, Mahmood U. Simultaneous fluorescence imaging of protease expression and vascularity during murine colonoscopy for colonic lesion characterization. *Gastrointest Endosc* 2006; **64**: 589-597 [PMID: 16996355 DOI: 10.1016/j.gie.2006.02.048]

P- Reviewer: Fichna J, Yoshida H **S- Editor**: Gong ZM
L- Editor: A **E- Editor**: Ma S

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com

ISSN 1007-9327