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Editorial

CD45-targeted PET enables the visualization of inflammatory conditions

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Abstract: Inflammation is a major contributor to human mortality, accounting for over 50% of deaths worldwide. Therefore, there is an urgent need for early and accurate diagnostic methods. PET imaging targeting leukocyte common antigen CD45 presents a promising approach for detecting inflammation and monitoring therapeutic responses.

Keywords: Inflammation, CD45, nanobody, zirconium-89, positron emission tomography

Inflammation is a fundamental biological response to infection, injury, or tissue stress, serving to eliminate harmful stimuli and initiate repair. However, when dysregulated or unresolved, both acute and chronic inflammation can contribute to disease progression and adversely impact human health. Chronic inflammation, in particular, underlies a wide range of pathologies, including infections, neurodegenerative diseases, and malignancies, that collectively account for a substantial proportion of global mortality [1]. Currently, computed tomography (CT) and magnetic resonance imaging (MRI) are the most commonly used imaging diagnostic modalities for inflammation, which can detect exudation or edema based on morphological changes. However, these conventional imaging techniques lack selectivity and specificity, limiting their ability to precisely identify the location of lesions. Histopathology remains the gold standard for diagnosing inflammation, yet biopsy is invasive and not suitable for longitudinal monitoring.

Molecular functional imaging enables the non-invasive visualization of inflammation at the molecular and cellular levels [2]. Despite its utility, positron emission tomography (PET) imaging of inflammation relies heavily on [^{18}F] fluorodeoxyglucose ([^{18}F]FDG), a glucose analog that accumulates in metabolically active cells. While widely adopted in clinical practice for conditions such as vasculitis, sarcoidosis, and inflammatory bowel disease, [^{18}F] FDG suffers from limited specificity [3]. Its uptake can be influenced by normal physiological processes, including muscle activity, peristalsis, and gut microbiome metabolism, as well as non-inflammatory pathological status such as cancer or post-surgical changes. These confounding factors can lead to false positives and hinder diagnostic accuracy. Therefore, there is a growing need to develop targeted PET radiotracers that can selectively bind to molecular markers of inflammation, enabling earlier detection, improved disease characterization, and more personalized clinical management.

A growing array of radiopharmaceuticals has been developed to target specific cellular subsets, cytokines, and enzymes involved in the complex inflammatory cascade. These targets include immune cell populations such as macrophages, neutrophils, T cells, B cells, dendritic cells, and microglia as well as effector molecules like Granzyme B. Commonly used molecular biomarkers for inflammation imaging include chemokine receptor type 2 (CCR2), the very late antigen-4 (VLA-4), and folate receptor-β [4-10]. For instance, the CCR2-targeted radiotracer [^{64}Cu] Cu-DOTA-ECL1i (extracellular loop 1 inverso) has demonstrated robust performance in characterizing acute lung inflammation, atherosclerotic lesions, acute myocardial infarction, and chronic ischemic cardiomyopathy. Its uptake strongly correlates with CCR2 expression on infiltrating monocytes and macrophages, supporting its specificity for inflammatory lesions [8, 11-13]. Other radiotracers targeting innate immune activity have also shown promise. Mannes et al. introduced radiotracer [^{64}Cu]Cu-NODAGA-CG34, a chemokine-like receptor 1 (CMKLR1)-targeted probe that selectively identifies monocyte and macrophage activity, enabling the detection of lung inflammation and monitoring of therapeutic response in preclinical models [14]. Xu et al. developed [^{18}F]FBTA, a novel stimulator of interferon genes (STING)-targeted radiotracer based on a benzothiophene scaffold with high binding affinity. This probe enabled early detection of pulmonary inflammation and assessment of aspirin-mediated anti-inflammatory treatment efficacy by visualizing macrophage and neutrophil activity [15]. Despite their promise, the diagnostic utility of [^{64}Cu]Cu-NODAGA-CG34 and [^{18}F]FBTA in inflammatory conditions beyond lung inflammation and its clinical translation potential remains to be fully elucidated. The limited repertoire of clinical validated biomarkers and tracers underscores the urgent

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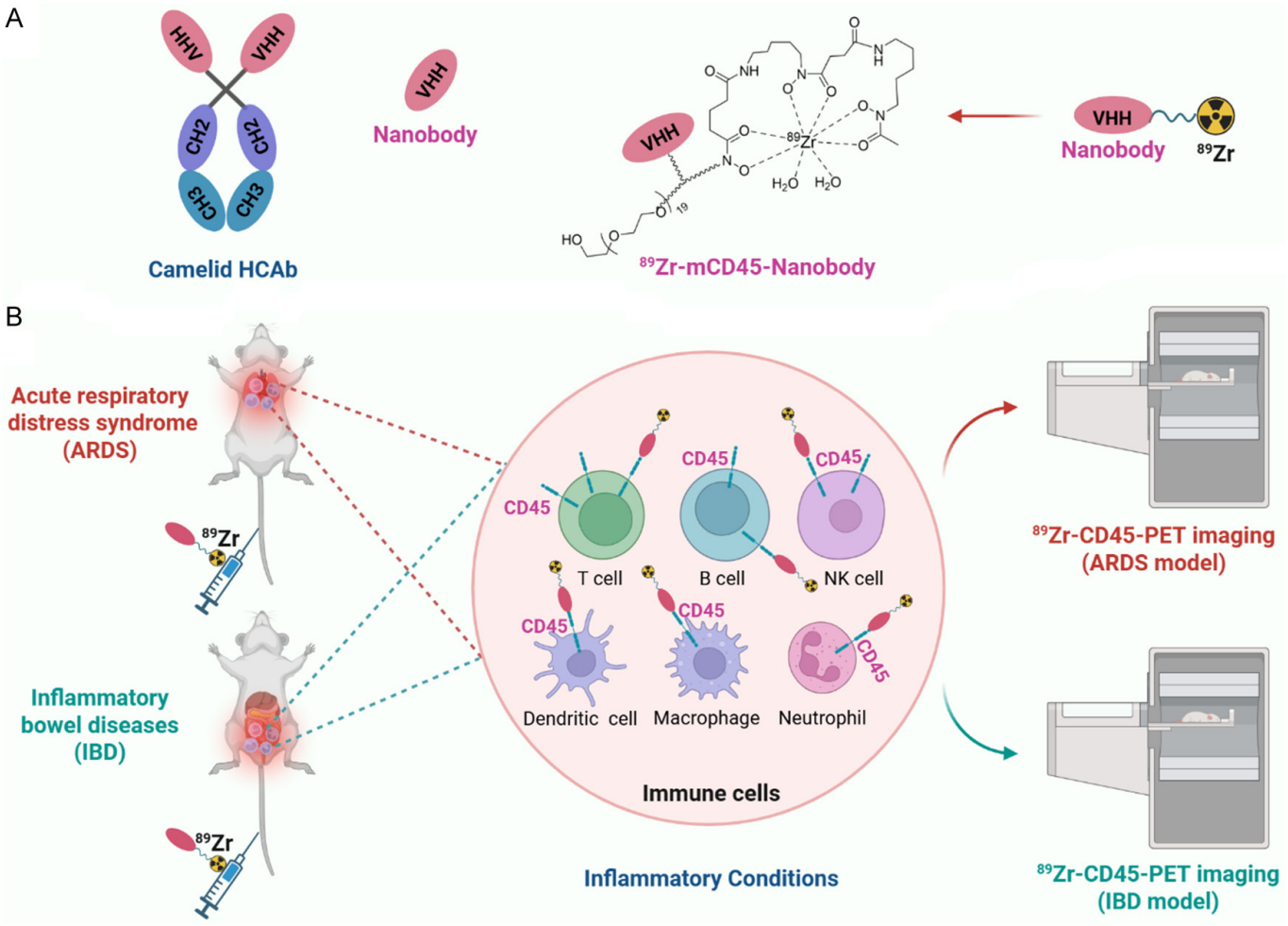

Figure 1. The structure of ^{89}Zr-mCD45 nanobody and its imaging mechanism of inflammatory conditions.

need for the continued development of novel molecular targets and imaging strategies to improve the precision and scope of inflammation imaging.

CD45, a receptor-type protein tyrosine phosphatase, is a well-characterized pan-leukocyte marker expressed on all nucleated hematopoietic cells, excluding mature erythrocytes and platelets [16]. To enable selective imaging of CD45$^+$ immune cells, researchers have increasingly turned to nanobodies-single domain antibody fragments derived from the variable domain of heavy-chain-only antibodies (VHH) found in camelids. These nanobodies represent the smallest functional antibody fragment and offer several advantages over conventional monoclonal antibodies, including high target affinity, improved tissue penetration, rapid systemic clearance, and ease of engineering. Their favorable pharmacokinetics also support same-day imaging, making them particularly attractive for clinical translation [17, 18]. In a recent study published in *Nature*, Rashidian and coworkers introduced a novel CD45-targeted imaging probe based on nanobody technology (^{89}Zr-mCD45 nanobody) and investigated its efficiency for detecting acute lung injury (ALI) and inflammatory bowel disease (IBD), and further explored the feasibility of clinical translation of CD45-PET using ^{89}Zr-hCD45 minibody in humanized mice models (**Figure 1**) [19]. Their findings demonstrated ^{89}Zr-mCD45 nanobody's specificity for inflammation and its potential for monitoring treatment responses, highlighting CD45-targeted PET imaging as a promising strategy for non-invasive inflammation diagnostics.

In this study, Rashidian and colleagues developed a murine CD45-targeted probe (^{89}Zr-mCD45 nanobody) by site-specific labeling using Gly3-deferoxamine (DFO)-azide and polyethylene glycol (PEG), with high affinity binding (EC_{50} = 0.35 nM) and high stability. Compared with no PEG and PEG10 (10 kDa) groups, DFO-labeled nanobodies with PEG20 (20 kDa) exhibited the highest uptake in immune-cell rich organs, mainly including lymph nodes, bone marrow, and spleen, while demonstrating minimal accumulation in the kidneys, liver, lungs, heart, colon and muscle in healthy C57BL/6 mice. Blocking studies further validated the probe's specificity, as PET imaging demonstrated a substantial reduction in tracer uptake in the spleen, bone marrow, lymph nodes, and liver following competitive blockade, while renal uptake remained unchanged, indicating renal excretion as the

primary clearance route. Moreover, to confirm the specificity of ^{89}Zr-mCD45 nanobody, the researchers also developed a structurally similar human leukocyte antigen (HLA)-targeted probe (^{89}Zr-hCD45 nanobody [VHH4]) for comparison. Notably, PET imaging revealed that while both probes exhibited comparable renal, cardiac, large bowel, and muscle uptake, ^{89}Zr-hCD45 nanobody displayed negligible accumulation in lymph nodes, spleen, bone marrow, liver and lung, further supporting the specificity of ^{89}Zr-mCD45 nanobody.

ALI, caused by diffuse alveolar damage, is characterized by non-cardiogenic pulmonary edema and acute hypoxic respiratory failure. It represents a common and serious cause of mortality in critically ill patients [20]. To assess the potential of CD45-targeted PET imaging for detecting ALI, an acute respiratory distress syndrome (ARDS) mouse model was established using intranasal administration of lipopolysaccharide (LPS) at high and low doses (3 vs. 1 μg/g), respectively. This approach elicited a robust pulmonary inflammatory response predominantly driven by neutrophil and macrophage infiltration. *In vivo* ^{89}Zr-mCD45 nanobody PET imaging revealed significantly increased tracer uptake in LPS-exposed mice in a dose-dependent manner, with SUV_{mean} of 2.32 ± 0.16, 1.18 ± 0.15, 0.83 ± 0.12 for the high dose, low dose, and control groups, respectively. Lung tissue immunohistochemistry staining confirmed CD45 overexpression in LPS-induced mouse models, and a strong correlation was observed between CD45-PET uptake and CD45 expression (r = 0.91, P = 0.0006). Phosphor screen autoradiography further validated that the regions with CD45$^+$ immune infiltrates corresponded to positive CD45-PET signals. Haematoxylin and eosin (H&E) staining demonstrated significant neutrophilic alveolitis, atelectasis and necrosis in high-dose mouse model, while mice with low dose LPS exposure exhibited interstitial neutrophilic infiltrates with focal areas. *In vivo* CD45-PET uptake in the lung, both *ex vivo* PET and biodistribution studies demonstrated a correlation between CD45-PET signal and weight loss, a clinical indicator of disease severity in model mice. Furthermore, to confirm the specificity of CD45-PET imaging, non-targeting ^{89}Zr-hCD45 nanobody imaging was employed, ruling out the possibility that accumulated lung signal was due to increased vascular permeability in LPS-induced ARDS mice. Similar to the findings of Rodrigues et al. [21], [^{18}F]FDG PET imaging could detect LPS-induced ALI at an early stage due to enhanced glucose metabolism of activated neutrophils. However, [^{18}F]FDG uptake was not correlated with CD45$^+$ staining, weight loss, or lung injury scores (P > 0.05 for all). CD11b, a surface marker expressed on various inflammatory (granulocytes, monocytes and macrophages) and myeloid cells, serves as an important target for molecular imaging of inflammation. Cao et al. developed a CD11b-targeted tracer, [^{64}Cu] αCD11b, which successfully detected and differentiated acute and chronic inflammation in murine models of lung or ear lesions at local and systemic levels [22]. In this study, Rashidian and coworkers introduced a CD11b-targeted nanobody probe (CD11b-PET) to identify ALI for comparison. While CD11b-PET demonstrated high uptake in LPS-treated mice and showed significant correlation with body weight loss and pulmonary injury score (r = 0.66 and 0.72, all P < 0.02), it failed to distinguish the mice in high or low LPS exposure group. These results highlighted the superior specificity of CD45-PET in detecting and stratifying ALI severity.

IBD, encompassing Crohn's disease and ulcerative colitis, is a chronic, idiopathic inflammatory disorder of the gastrointestinal tract [23]. Noninvasive assessment of intestinal lesion activity and monitoring treatment response are crucial for improving the management of IBD patients [24]. Recently, inflammation imaging agents beyond [^{18}F]FDG have gained attention for detecting IBD in clinical settings. For example, Ismail et al. demonstrated that prostate-specific membrane antigen (PSMA)-targeted [^{18}F]DCFPyL PET/CT effectively localized active inflamed lesions, and assessed disease activity and severity in a pilot study including three IBD patients [25]. Chen et al. successfully visualized intestinal lesions and mesenteric lymphadenitis using CXCR4-targeted [^{68}Ga]Ga-Pentixafor PET/CT in five IBD patients, and demonstrated [^{68}Ga]Ga-Pentixafor PET is a promising tool for evaluating both active inflammatory intestinal lesions and related lymphadenitis [26]. Moreover, [^{18}F]DCFPyL and [^{68}Ga]Ga-Pentixafor PET do not require patients to fast or empty their bowels, and are not affected by medications such as metformin, indicating its logistical advantages than [^{18}F]FDG. While they show some promise for clinical application, they are non-specific imaging agents for the detection of inflammation and their clinical value still needs to be further verified due to the limited sample size.

At present, a growing body of inflammation-specific radiotracers has been developed for detecting inflammatory activity in IBD [27]. For example, Granzyme B, a serine protease involved in the activation of cytotoxic T cells and natural killer cells, has emerged as an early biomarker of active inflammatory lesions in Crohn's disease [28]. Heidari et al. developed a Granzyme B-targeted radiotracer, [^{68}Ga]Ga-NOTA-GZP, based on a murine binding peptide, and their study demonstrated its potential to visualize active inflammation and predict therapeutic response in preclinical colitis models [7]. Furthermore, Granzyme B expression was confirmed to be significantly increased in patients with active IBD through tissue immunofluorescence staining and bioinformatic analysis, indicating the clinical transformation potential of Granzyme B-targeted imaging probes [7]. In addition, glucagon-like peptide 1 receptor (GLP-1R)-targeted [^{68}Ga]Ga-NOTA-MAL-Cys^{39}-exendin-4 PET could detect the dynamic changes of GLP-1R expression in IBD rat models, which offers another promising tool for improving the diagnosis and management of IBD [29]. Given the low background accumulation in the gastrointestinal tract, CD45-targeted PET imaging holds promise for detecting intestinal inflammation. CD45-PET

imaging using ^{89}Zr-mCD45 nanobody revealed significantly higher and heterogeneous tracer uptake in the large bowel of 4% dextran sodium sulfate (DSS)-treated C57BL/6 mice compared to controls [19]. The rectum exhibited higher SUV_{mean} but less heterogeneity compared to the large bowel. High-signal mice demonstrated substantial tracer uptake not only in the large bowel but also in mesenteric lymph nodes and the appendix. Morphological assessments in these mice revealed wall edema, hemorrhage, and bowel shortening. Moreover, *ex vivo* SUV_{mean} of bowel segments correlated with the severity of immune infiltration. *In vivo* PET signals in the colon and rectum were associated with body weight of mice (r = 0.89 and 0.61; all P < 0.02), but only the uptake in the large bowel was related to inflammation activity score (r = 0.79, P < 0.001). A systematic comparative study between CD45-PET and [^{18}F]FDG revealed diffusely increased [^{18}F]FDG uptake in the large bowel of DSS-induced mice, whereas CD45-PET showed focal accumulation. However, only CD45-PET uptake in the colon associated with body weight (r = 0.78, P = 0.02), while [^{18}F]FDG uptake did not (r = 0.21, P = 0.62). In terms of assessment of treatment response, both dexamethasone-treated and water-only control groups showed decreased PET signal intensity in the colon and rectum, with the degree of uptake reduction correlating with mouse weight gain. These findings highlighted the potential of CD45-PET for the detection of IBD-related inflammatory conditions and monitoring treatment efficacy in preclinical models.

To advance the clinical translation of CD45-PET imaging, a human CD45-targeted specific probe (^{89}Zr-hCD45 minibody PET) was developed using a smaller antibody fragment derived from a clinical full-length monoclonal antibody (cloneBC8), known as a minibody (80 kDa) [19]. This probe demonstrated high binding affinity (EC_{50} = 5 nM), excellent specificity, and high stability. To evaluate its efficacy, NOD.Cg-*Prkdc*^{scid} *IL2*^{rgtm1wjl}/SzJ (NSG) deficient mice were humanized by receiving 10 million human peripheral blood mononuclear cells (PBMCs). ^{89}Zr-hCD45 minibody PET successfully visualized the spleen of humanized mice where human PBMCs are located, showing significantly higher signal intensity (SUV_{mean}, 29.38 ± 6.96) compared to non-humanized controls (SUV_{mean}, 4.47 ± 1.62). Notably, the clearance rate of the probe in humanized mice was five times faster than in control group, indicating that human immune cells acted as an antigen sink and facilitating faster probe clearance. Increased vascular permeability caused by inflammation did not result in increased non-specific tracer accumulation in the lungs. These findings suggest the effectiveness and specificity of ^{89}Zr-hCD45 minibody PET in detecting inflammation. To further validate its utility, the authors conducted serial ^{89}Zr-hCD45 minibody PET imaging to monitor the inflammatory process in humanized mice with graft-versus-host disease (GVHD), with a significant reduction in spleen uptake from day 21 to day 112 in mice with GVHD symptoms. While most other organs displayed increased tracer uptake with unique feature in each mouse at day 112, no statistically significant differences were observed in the bone marrow and liver, likely due to variability in GVHD progression among the mice.

Over the past two decades, the development of numerous radiolabeled targeted probes has significantly advanced the field of molecular imaging for inflammatory disease [10-12, 15, 30, 31]. The advent of next-generation PET/CT scanners, such as total-body PET/CT systems, offer markedly enhanced sensitivity and spatial resolution. These technological advancements enable faster imaging protocols, reduced radiotracer doses, and lower overall radiation exposure for patients [32, 33]. The integration of PET/MR holds considerable promise in the imaging of inflammatory conditions. By replacing CT with MR, radiation exposure is further minimized, while the combination of PET's molecular sensitivity and MRI's superior soft tissue contrast establishes PET/MR as a powerful modality for detecting and characterizing inflammatory disorders [34-37]. Despite these technological strides, the clinical translation of many inflammation-targeted PET tracers remains limited. Common barriers include high background uptake in non-target tissues, suboptimal pharmacokinetics, and extended imaging windows that are impractical for routine clinical use. Future efforts must prioritize the optimization of probe specificity, pharmacokinetics, and imaging protocols to facilitate boarder clinical adoption and ultimately improve patient outcomes.

In summary, Salehi Farid et al. present a novel, non-invasive PET imaging strategy that enables sensitive, quantitative, and whole-body detection of inflammation across multiple disease models. By leveraging the abundant and exclusive expressing of CD45 on all immune cell subtypes, CD45-PET achieves high specificity, detectability, and diagnostic versatility across diverse inflammatory contexts. While the approach does not differentiate among immune cell subtypes and may be less suited for lymphoid-rich organs, its robust performance in non-lymphoid tissues makes it well-suited for evaluating systemic inflammation. CD45-PET holds considerable promise as a first-line diagnostic tool for inflammatory conditions, enabling disease stratification and evaluation of treatment responses. Its ability to provide comprehensive, whole-body imaging of inflammation positions it as a valuable asset in both preclinical research and future clinical practice.

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Disclosure of conflict of interest

None.

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