Review

Novel PET/CT tracers for large-vessel vasculitis: molecular imaging of immune cell recruitment, myeloid activation and vascular remodelling in giant cell arteritis and Takayasu's arteritis

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ABSTRACT

Over the past decade, positron emission tomography (PET) has become an important part of the management of large-vessel vasculitis (LVV). Current clinical practice relies predominantly on [^{18}F]fluorodeoxyglucose ([^{18}F]FDG) PET combined with computed tomography (CT) for anatomical localisation. Although [^{18}F]FDG PET/CT shows high specificity and good sensitivity for primary diagnosis, persistent vascular uptake during clinical remission limits its specificity for relapse assessment and complicates longitudinal monitoring. Alongside technological advances in PET hardware, an expanding portfolio of alternative radiotracers has emerged to probe more specific inflammatory pathways and cell-associated processes.

This narrative review summarises the most informative clinical evidence currently available for novel PET tracers in giant cell arteritis (GCA) and Takayasu's arteritis (TAK). Targets related to immune cell recruitment and vascular inflammation include the vascular adhesion protein-1 (VAP-1)/sialic-acid-binding immunoglobulin-like lectin-9 (Siglec-9) axis, assessed by [^{68}Ga]Ga-DOTA-Siglec-9. Similarly, C-X-C chemokine receptor 4 (CXCR4) imaging with [^{68}Ga]PentixaFor has been explored as an approach to capture chemokine-mediated immune cell trafficking. For the assessment of myeloid activation, somatostatin receptor subtype 2 (SSTR2) imaging using [^{68}Ga]DOTATATE or [^{18}F]FET-βAG-TOCA has been explored as an approach to differentiate active from inactive disease. Imaging of the 18 kDa translocator protein (TSPO), a mitochondrial outer membrane protein associated with cellular stress and myeloid activation, seeks to provide a complementary inflammation- and stress-related readout, although its clinical applicability is influenced by ligand-specific performance and genotype-dependent binding. Finally, fibroblast activation protein (FAP)-targeted PET with fibroblast activation protein inhibitors (FAPI, e.g. [^{68}Ga]-FAPI-46) has been investigated to visualise fibroblast activation and vascular remodelling, with persistent uptake during clinical remission potentially indicating ongoing tissue repair or structural remodelling.

Introduction

Giant cell arteritis (GCA) and Takayasu's arteritis (TAK) represent the two principal forms of large-vessel vasculitis (LVV). Notably, GCA is the most common primary systemic vasculitis in Western countries, with a lifetime prevalence approaching 1%. It only affects individuals older than 50 years, with a peak incidence between 72 and 78 years, and shows a female predominance of approximately 2:1. In contrast, TAK typically affects young women between 20 and 30 years of age, with a marked female-to-male ratio of up to 9:1. The annual incidence of TAK ranges from 0.4 to 3.4 cases per million and varies geographically, with higher frequencies reported in Asian and Middle Eastern populations (1, 2).

Clinically, both GCA and TAK are characterised by inflammation of the aorta and its major branches, leading to vascular wall thickening, stenosis, occlusion, or aneurysm formation with ischemic and structural complications (2, 3). Although large-vessel involve-

ment is common to both entities, cranial artery involvement is typical for GCA and absent in TAK. Similarly, TAK less frequently presents with involvement of the axillary artery (2). Independent of phenotypic differences, early diagnosis, assessment of disease phenotype and timely initiation of therapy are critical to prevent irreversible vascular damage and long-term morbidity (4, 5).

Over the past years, positron emission tomography (PET) has become a cornerstone in the management of both LVV (6). Mechanistically, PET imaging relies on the tissue-specific accumulation of radiolabelled tracers targeting defined molecular structures. Therefore, tracer selection is central to diagnostic performance. Due to the limited spatial resolution of PET, hybrid imaging with computed tomography (CT) or magnetic resonance imaging (MRI) is regularly employed to enable precise anatomical localisation of tracer uptake (7-9).

The most widely used and clinically established tracer in both GCA and TAK is [^{18}F]fluorodeoxyglucose ([^{18}F]FDG). It visualises increased glucose metabolism in activate inflammatory cells (10). In combination with CT, [^{18}F]FDG PET/CT allows whole-body vascular assessment in a single examination (6). In GCA, it demonstrates high specificity (96%) and good sensitivity (76%) for the primary diagnosis (11). Quantitative tracer uptake typically declines with effective therapy. However, persistent vascular uptake is observed in up to 80% of GCA patients in clinical remission (12, 13), limiting specificity for relapse detection to approximately 70% (14). Conversely, prolonged glucocorticoid therapy may substantially reduce diagnostic sensitivity (15).

Independent of tracer selection, ongoing technological advances in PET imaging are expected to further enhance the diagnostic performance of PET in LVV. These include optimised acquisition protocols (16), high-sensitivity PET systems capable of visualising cranial arteries in GCA (6), and hybrid PET/MRI approaches (17, 18). Compared with PET/CT, PET/MRI offers superior soft tissue contrast and higher spatial resolution, while substantially reducing radiation exposure (18). Thus, in conventional PET/CT, the CT component accounts for the majority of radiation exposure, contributing approximately 15 mSv, compared with about 5 mSv from the PET acquisition itself (19).

Beyond hardware improvements, the development of alternative PET tracers offers an important opportunity to refine molecular imaging in GCA and TAK. Although [^{18}F]FDG sensitively captures metabolically active inflammation, it lacks cellular specificity. Thus, it may produce false-positive findings in infection, malignancy, non-vasculitic inflammatory conditions, and vascular remodelling (10). In addition, physiological glucose uptake in the brain and myocardium may hamper interpretation in adjacent vascular territories (10).

Accordingly, as also highlighted in the EULAR research agenda, there is a clear clinical need for novel PET tracers, that target defined immune cell subsets, signalling pathways, and inflammatory mechanisms in LVV (6). Depending on disease stage, vascular phenotype, treatment exposure, and the specific clinical question, different molecular targets may provide complementary biological information.

The development of novel PET tracers requires careful consideration of several key properties. An ideal radiotracer should demonstrate high affinity and specificity for its molecular target, rapid plasma clearance, favourable pharmacokinetics, low background activity, minimal toxicity, and an acceptable radiation dose (20). Numerous radiotracers have been developed or are currently under investigation for imaging vascular and immune-mediated inflammatory diseases.

Methods

This narrative review summarises the available clinical evidence on non-[^{18}F]FDG PET tracers in GCA and TAK. The review was informed by a structured, non-systematic literature search conducted in PubMed. The search included publications available from the beginning of January 2011 up to end of February 2026. Owing to the marked heterogeneity of tracers, study designs, acquisition protocols, patient populations, and reported outcome measures, a formal systematic review or meta-analysis was not considered feasible.

In a first step, a broad search strategy combined Medical Subject Headings and free-text terms related to LVV and in particular GCA and TAK, including "Large Vessel Vasculitis", "Giant Cell Arteritis", and "Takayasu Arteritis", with PET-related terminology such as "Positron Emission Tomography", "PET", "PET/CT", "molecular imaging", "radiotracer", and "targeted". In a second step, additional focused searches were performed for the specific tracer classes and molecular targets identified through the initial search, including "Siglec-9", "VAP-1", "CXCR4", "PentixaFor", "somatostatin receptor", "DOTATATE", "FET-βAG-TOCA", "TSPO", "PK11195", "PBR28", "DPA714", "fibroblast activation protein", and "FAPI". Reference lists of relevant articles were also screened to identify further eligible reports.

Eligible publications comprised original clinical reports in patients with GCA or TAK that assessed non-[^{18}F]FDG PET tracers for vascular inflammatory imaging. Prospective studies, retrospective cohort analyses, case series, and well-documented case reports were considered eligible. Preclinical studies, purely technical radiochemistry reports without clinical LVV imaging data, conference abstracts lacking sufficient methodological detail, duplicate narrative reports, and articles not directly relevant to vasculitis imaging were excluded from the main evidence synthesis, although selected translational and mechanistic studies were considered where necessary to contextualise tracer biology.

Study selection was performed iteratively. After the initial broad screening of titles and abstracts, publications were retained if they addressed clinically relevant non-[^{18}F]FDG PET imaging in LVV. Full-text review was then used to identify studies suitable for inclusion in the tracer-specific sections. No formal risk-of-bias instrument was applied. Instead, the included literature was critically appraised qualitatively through-

out the manuscript. Particular attention was paid to study design, sample size, control selection, treatment exposure, potential selection bias, standardisation of image acquisition and interpretation, availability of histopathological or translational validation, and evidence for longitudinal responsiveness to disease activity.

Molecular imaging of immune cell recruitment and vascular inflammation

Inflammation-specific radiotracers targeting molecules directly involved in pathogenic immune cell recruitment and vascular inflammation may represent a promising strategy for improving diagnostic accuracy and disease activity assessment in LVV.

Imaging of the sialic-acid-binding immunoglobulin-like lectin (Siglec)-9 and vascular adhesion protein-1 axis

One potential imaging target is vascular adhesion protein-1 (VAP-1), a type II transmembrane sialoglycoprotein encoded by the AOC3 gene. VAP-1 exists as both a membrane-bound adhesion and a soluble form (sVAP-1) with amine oxidase activity generated by matrix metalloproteinase–mediated cleavage. Functionally, VAP-1 contributes to leukocyte migration into inflamed tissue and amplifies inflammation through upregulation of adhesion molecules (ICAM-1, MadCAM-1, E-selectin, P-selectin), induction of CXCL8 secretion, activation of NF-κB, and stimulation of matrix metalloproteinases (21, 22).

Within the vasculature, VAP-1 is mainly expressed on vascular smooth muscle cells and endothelial cells. Under homeostatic conditions, it is largely confined to caveolae and intracellular vesicles. Upon inflammatory stimulation such as TNF-α, IFN-γ, or IL-1β, VAP-1 is rapidly translocated to the cell surface. This inflammation-induced and spatially restricted surface expression renders VAP-1 a biologically plausible, although still early-stage, imaging target for active vascular inflammation (21, 22).

Surface-expressed VAP-1 interacts with Sialic-acid-binding Immunoglobulin-like Lectin (Siglec)-9 on neutrophils, monocytes, and natural killer cells, as well as with Siglec-10 on lymphocytes and macrophages, mediating leukocyte rolling, tethering, and transmigration (21, 22). The radiotracer [^{68}Ga]Ga-DOTA-Siglec-9 has therefore been developed to probe VAP-1 expression and has recently been explored in immune-mediated inflammatory diseases (23-26).

In LVV, the current clinical evidence remains limited. An initial exploratory case report described focal vascular uptake of [^{68}Ga]Ga-DOTA-Siglec-9 PET/CT in a patient with relapsing GCA. Tracer accumulation showed abrupt spatial transitions along the descending aorta without corresponding calibre changes on CT, suggesting a signal related more to endothelial activation than to fixed structural remodelling (27). This observation was followed by a small pilot case series of eight patients with clinically confirmed GCA relapse. In the study, localised and patient-specific increases in vascular SUVmax were observed, particularly in the thoracic and abdominal aorta, correlated with intima-media thickness on vascular ultrasound. Extra-vascular uptake in the shoulder region of patients with concomitant polymyalgia rheumatica further suggested that this tracer may capture inflammatory processes beyond the vessel wall itself (28).

Additional mechanistic support was provided by complementary immunologic analyses. Increased Siglec-9 expression was observed on intermediate monocytes, plasmablasts, naïve B cells, and natural killer cells in relapsing GCA. Elevated CRP and MMP-9 levels, together with a positive association between sVAP-1 and CRP, were also consistent with activation of the VAP-1/Siglec-9 axis in the systemic inflammation (28).

Taken together, these early findings suggest that Siglec-9-targeted PET/CT may provide a biologically distinct readout of endothelial activation and leucocyte dynamics and may therefore complement metabolism-based imaging with [^{18}F]FDG. At present, however, its clinical role remains undefined. The available data are restricted to very small exploratory studies, predominantly in relapse settings, and do not yet establish incremental value for primary diagnosis, routine relapse assessment, or longitudinal treatment monitoring. Likewise, it remains unclear whether VAP-1-directed imaging can reliably distinguish active vasculitis from chronic remodeling, low-grade endothelial activation, or other inflammatory signals. Larger controlled studies with longitudinal follow-up, direct comparison with [^{18}F]FDG PET, and validation against clinical and tissue-based reference standards will be required before its place in diagnostic or monitoring workflows can be defined more clearly (Fig. 1).

Imaging of the C-X-C motif chemokine receptor 4

Both GCA and TAK are driven by complex interaction between innate and adaptive immune responses at both systemic and tissue levels. Chemokine-mediated leukocyte recruitment to the arterial wall represents a central pathogenic mechanism. Members of the C-X-C motif chemokine receptor (CXCR) family are G protein-coupled receptors expressed on multiple immune cell subsets and contribute to endothelial adhesion, and transendothelial migration in response to locally upregulated chemokine gradients within inflamed vascular tissue (29).

The CXCR4 is broadly expressed on lymphoid and myeloid cells and binds with high affinity to its ligand C-X-C motif chemokine 12 (CXCL12) (30). The CXCR4-CXCL12 axis is a well-characterised pathway involved in leukocyte recruitment, and the promotion of granulomatous inflammation including GCA (31, 32). Based on this pathophysiological role, the CXCR4-targeted PET tracer [^{68}Ga]PentixaFor has been explored in cardiovascular diseases and immune-mediated inflammatory conditions (33).

In LVV, the available clinical evidence remains preliminary. Initial support for a possible role of CXCR4 imaging was provided by a case report in TAK, in which [^{68}Ga]PentixaFor PET/CT demonstrated tracer uptake in the aortic

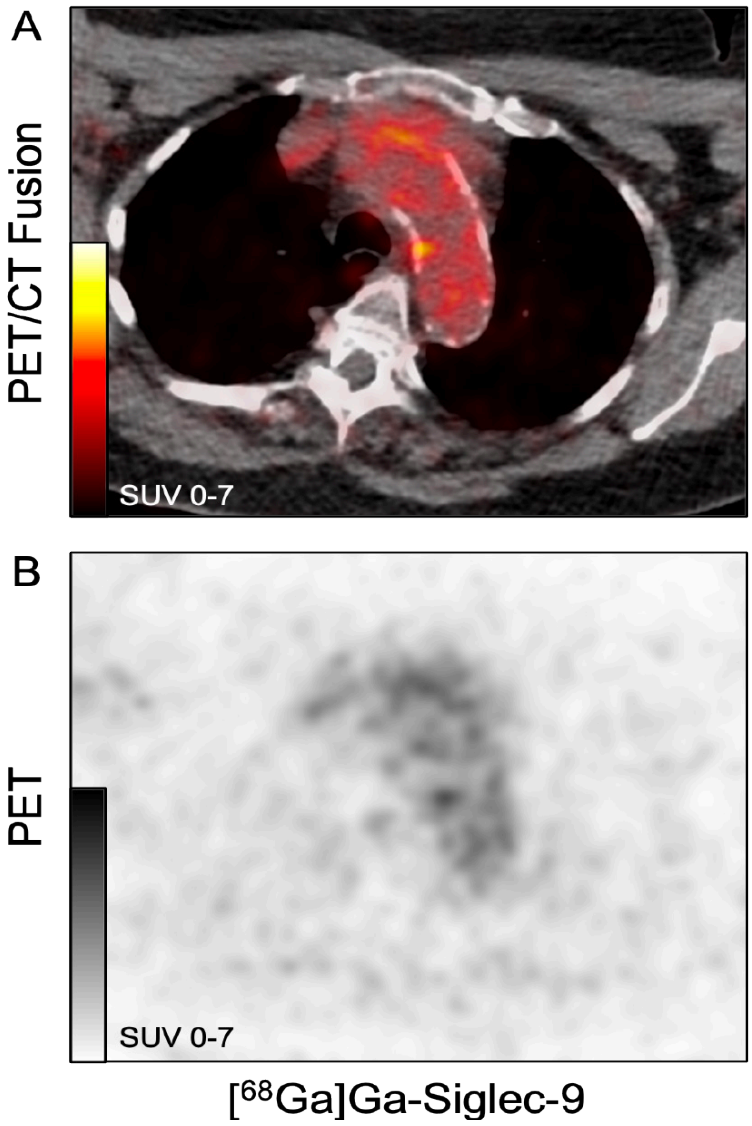

Fig. 1. VAP-1-Targeted imaging with [^{68}Ga]Ga-DOTA-Siglec-9 PET/CT in GCA.
Axial image of VAP-1-targeted PET/CT of the thoracic aorta in active GCA. The upper panel shows a fused PET/CT image demonstrating visually increased tracer uptake along the aortic wall, consistent with active large-vessel inflammation. The lower panel displays the corresponding PET image (same SUV scale 0–7) illustrating the distribution pattern of vascular tracer accumulation without anatomical overlay. Image material provided by Dr. F. Gärtner.
CT: computed tomography; FAPI: fibroblast activation protein inhibitor; Ga: gallium; PET: positron emission tomography; SUV: standardised uptake value.

wall, with vascular inflammation also confirmed by [^{18}F]FDG PET/CT (34). More recently, Fröhlich *et al*. prospectively evaluated [^{68}Ga]PentixaFor PET/CT in ten treatment-naïve patients with large-vessel GCA and mandatory [^{18}F]FDG positivity. Both scans were performed within a median interval of two days without intervening therapy. Thirteen predefined large-vessel segments per patient were systematically analysed. In that study, target-to-background ratios (TBR) were significantly higher in GCA patients compared with non-vasculitis controls on [^{68}Ga]PentixaFor PET/CT. Importantly, there was no evidence of substantial blood-pool contamination, supporting vessel wall-specific signal interpretation. Although [^{18}F]FDG uptake was numerically higher in selected vascular territories, CXCR4-directed uptake largely paralleled FDG-defined inflammation in untreated disease, with moderate-to-high correlations of TBR values across most arterial regions (35).
Complementary flow cytometric analyses further demonstrated broad CXCR4 expression across circulating leukocyte subsets in GCA, with highest levels detected on naïve CD4$^+$ T-helper cells and monocytes (35). This supports the biological plausibility of CXCR4 as an imaging target and suggests that [^{68}Ga]PentixaFor PET may capture a dimension of vascular inflammation related to immune cell trafficking and compartmentalisation (35).
From a clinical perspective, however, its role remains uncertain. Current data do not yet establish whether CXCR4-directed PET provides pronounced diagnostic value over [^{18}F]FDG PET. Practical limitations also remain relevant, including restricted tracer availability, limited clinical accessibility, and the absence of standardised acquisition and interpretation frameworks in LVV.

Molecular imaging of myeloid activation

Macrophages are key effector cells in both GCA and TAK. Within the arterial wall, they sustain granulomatous inflammation through cytokine release, reactive oxygen species generation, extracellular matrix degradation, and crosstalk with T cells and vascular stromal cells. Beyond mediating tissue injury, macrophages contribute to intimal hyperplasia and vascular remodelling, thereby linking immune activation to structural damage. Against this background, receptor-specific tracers directed at macrophage-associated pathways may offer an attractive molecular imaging target, providing a cell-oriented assessment of vascular inflammation (32).

Imaging of the somatostatin receptor

Somatostatin receptors (SSTR1-5) are G protein-coupled receptors involved in neuroendocrine regulation but also implicated in chronic inflammatory and immune-mediated diseases (36). Among the receptor subtypes, SSTR2 is of particular interest in LVV because it is upregulated in activated immune and stromal cells, including classically activated (M1) macrophages, CD4$^+$ T cells, dendritic cells, and subsets of fibroblasts under pro-inflammatory conditions (37). In contrast, SSTR5 expression has likewise been described in inflammatory settings, albeit to a lesser

extent and more prominently in tissue-resident stromal compartments associated with chronic remodelling (38). Induction is mediated by cytokines such as TNF-α, IFN-γ, and IL-1β via NF-κB- and STAT1-dependent signalling pathway (39, 40).

Among the receptor subtypes, SSTR2 is the main target of clinically available radiolabelled somatostatin analogues. Following ligand binding, receptor-mediated internalisation results in sustained intracellular tracer retention, theoretically enhancing lesion-to-background contrast (37, 38).

Several SSTR2-targeting radiotracers are available, including [^{68}Ga]DOTATATE, and the 18F-labelled analogue [^{18}F]FET-βAG-TOCA. Preclinical and translational studies have confirmed SSTR2 expression in CD68^{+} macrophage-rich vascular lesions, providing mechanistic support for its use in vasculitis imaging (37).

The most informative clinical data currently come from a proof-of-concept study by Ćorović *et al*. It investigated SSTR2-targeted PET/MRI in 27 patients with LVV and 34 controls. Both [^{68}Ga]DOTATATE and [^{18}F]FET-βAG-TOCA were applied and subsequently pooled due to comparable imaging performance. Quantitative vascular uptake was higher in clinically active or 'grumbling' LVV than in inactive disease and non-vasculitic controls, whereas healthy subjects showed no relevant arterial signal (32).

In a subset with contemporaneous [^{18}F]FDG PET/CT, tracer concordance was generally high. Notably, SSTR2 imaging exhibited lower physiological background uptake in the brain and myocardium, facilitating assessment of cranial and pericardial vessels. In selected cases with clinically active disease but negative FDG findings, SSTR2 PET detected uptake in vertebral and intracranial arteries, suggesting improved sensitivity in anatomically challenging regions.

Notably, vascular tracer uptake correlated with periaortic wall thickening on MRI. Longitudinal follow-up demonstrated a significant reduction in SSTR2 signal under effective immunosuppressive therapy. Extra-vascular uptake in shoulder joints was observed in patients with concomitant shoulder girdle pain (32).

Importantly, the *in vivo* imaging findings were supported by tissue level. *Ex vivo* analyses of affected vascular tissue demonstrated SSTR2 expression in inflammatory macrophages, as well as in pericytes and perivascular adipocytes within the arterial wall. Complementary bulk and single-cell RNA sequencing of temporal artery biopsies confirmed increased SSTR2 transcription in GCA, predominantly localised to macrophage clusters and independent of short-term glucocorticoid exposure, supporting interpretation of SSTR2 uptake as a receptor-specific marker of vascular inflammation rather than non-specific tracer accumulation (41).

In summary, SSTR2-targeted PET appears promising, particularly for assessing active or persistent disease in territories with high physiological [^{18}F]FDG background. Its current role, however, remains investigational. Broader clinical integration will require validation in larger controlled studies, direct comparison with [^{18}F]FDG PET across defined clinical scenarios such as diagnosis, relapse evaluation, and treatment monitoring, as well as greater standardisation, regulatory accessibility, and practical availability.

Imaging of mitochondrial 18 kDa translocator protein

The 18 kDa translocator protein (TSPO) is located on the outer mitochondrial membrane and is involved in the regulation of mitochondrial membrane potential, bioenergetics, oxidative stress, and apoptosis (42). Expression of TSPO increases under conditions of cellular activation and stress (42). Because TSPO is expressed by multiple cell types, including macrophages, other myeloid cells, endothelial cells and cardiomyocytes, tracer uptake may reflect a composite signal integrating inflammatory activation, mitochondrial dysfunction, and vascular remodelling rather than macrophage-specific inflammation alone (43-45).

Originally developed for neuroinflammatory imaging, TSPO-targeted radiotracers have subsequently been explored in cardiovascular disease, atherosclerosis, and vasculitis (44, 46). Early proof-of-concept studies in LVV using first-generation ligands such as [^{11}C]PK11195 demonstrated increased arterial wall uptake in clinically active disease compared with inflammatory controls (47, 48). However, these first-generation TSPO tracers are limited by high nonspecific binding and suboptimal signal-to-noise characteristics in the vasculature. Interpretation is further complicated by the common rs6971 polymorphism, which substantially affects ligand binding affinity and necessitates genotyping (44, 46).

Although second-generation tracers were developed to improve binding characteristics, results have not been consistent across ligands. In one study, [^{11}C]PBR28 failed to demonstrate relevant vascular uptake in patients with GCA and TAK, highlighting variability across ligands (45). This heterogeneity currently limits straightforward clinical interpretation.

More recently, TSPO imaging was re-evaluated using the second-generation tracer [^{18}F]DPA714 in a head-to-head comparison with [^{18}F]FDG. In that study, eleven treatment-naive patients with active LVV (five TAK and six GCA) underwent both scans. [^{18}F]DPA714 uptake was significantly increased across most arterial territories compared with controls, and kinetic modelling supported enhanced vessel wall binding. Although absolute SUVs were lower than with FDG, vessel wall-to-lumen contrast was modestly but significantly higher with [^{18}F]DPA714. This difference was most pronounced in patients with relatively low systemic inflammation. When stratified by median CRP, [^{18}F]DPA714 detected a greater inflammatory burden than FDG in the lower-CRP subgroup, whereas no meaningful inter-tracer difference was observed in patients with high CRP. These findings raise the possibility that TSPO-targeted imaging may be sensitive to low-grade or smouldering vascular inflammation in situations where [^{18}F]FDG performs less well (44).

Additional mechanistic support was provided by peripheral blood flow cytometry, which demonstrated TSPO

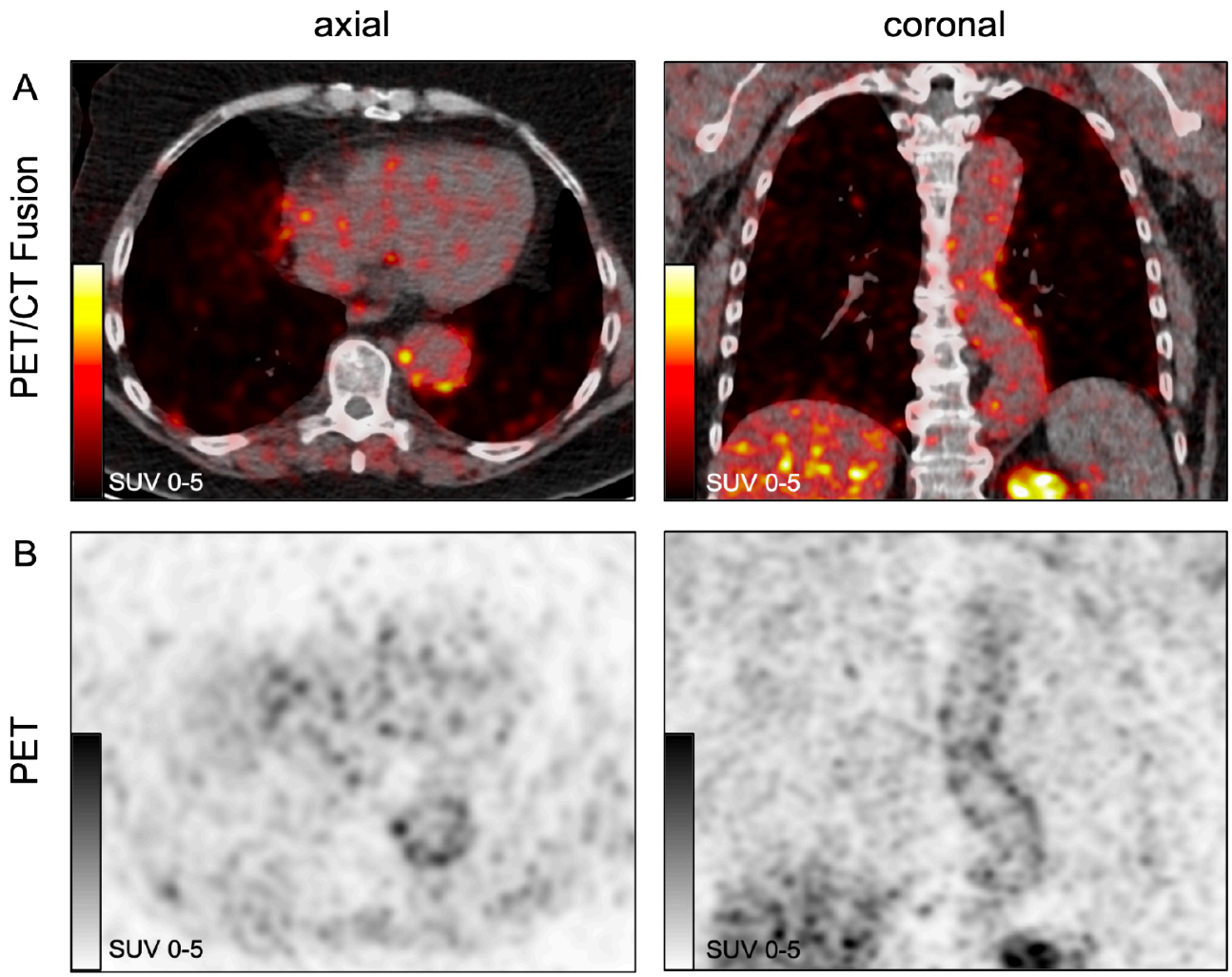

Fig. 2. Visualisation of fibroblast activation by [^{68}Ga]FAPI-68 PET/CT in GCA.
Multiplanar [^{68}Ga]FAPI-68 PET/CT of the thoracic aorta in clinically active GCA. Axial (left) and coronal reconstructions (right) are shown. Hybrid PET/CT (upper row) depict tracer enrichment along the aortic wall. Stand-alone PET images (lower row) emphasise the vascular signal pattern independent of structural CT information. Image material provided by Dr. F. Gärtner.
CT: computed tomography; FAPI: fibroblast activation protein inhibitor; GA: gallium; PET: positron emission tomography; SUV: standardised uptake value.

expression predominantly in monocytes and neutrophils. This observation is consistent with the concept that TSPO uptake in both GCA and TAK may reflect activation of myeloid cells and endothelial stress responses rather than a single cell-specific inflammatory pathway (44).

From a clinical perspective, TSPO-targeted PET remains an investigational approach. Its potential strengths may lie in the evaluation of persistent or low-grade vascular inflammation and comparison with [^{18}F]FDG in patients with low systemic inflammatory activity. However, broader implementation is currently mainly limited by ligand-dependent variability, the need for genotyping, lack of standardisation, and restricted tracer availability. Larger controlled studies with longitudinal follow-up will be necessary before a clearer role in diagnosis, relapse assessment, or treatment monitoring can be established.

Molecular imaging of fibroblast activation and vascular remodelling

Fibroblast activation protein-targeted PET

Both GCA and TAK are characterised not only by immune cell–driven arterial wall inflammation but also by sustained tissue responses involving extracellular matrix remodelling, wall thickening, and progressive structural alteration in chronic disease stages (49, 50). This makes fibroblast activation an attractive, mechanistically distinct target for molecular imaging beyond inflammation-focused tracers.

Fibroblast activation protein (FAP) is a type II transmembrane serine protease of the dipeptidyl peptidase family that is selectively expressed on activated fibroblasts, whereas quiescent fibroblasts show little or no expression (50). Proinflammatory cytokines such as TNF-α, IL-1β, IL-6, and oncostatin M, as well as profibrotic mediators including TGF-β, induce FAP expression (51). Functionally, FAP contributes to extracellular matrix degradation and tissue remodelling (49). In vasculitis, activated fibroblasts are thought to not only in structural remodelling but also in cytokine production and local cel-

lular crosstalk within the arterial wall (52). Until recently, fibroblast-driven remodelling could only be inferred indirectly from morphological imaging findings (53).

The development of radiolabelled fibroblast activation protein inhibitors (FAPI) has enabled direct PET-based visualisation and quantification of activated fibroblasts (54). Initially introduced in oncology, FAPI tracers have subsequently been applied in inflammatory and fibrotic diseases (49, 55, 56). In LVV, however, the clinical evidence remains limited and should be interpreted cautiously.

Initial support for a possible role of FAPI imaging came from a first case report in TAK demonstrating vascular tracer uptake in clinically active disease (57). Subsequent data from a small cohort of eight LVV patients showed vascular [^{68}Ga]-FAPI-46 PET uptake in both active and, to a lesser extent, clinically inactive aortitis, whereas matched controls exhibited no relevant arterial signal. Importantly, tracer uptake frequently persisted during prolonged clinical remission, including in patients with low inflammatory activity on MRI. This pattern suggests that FAPI PET may detect fibroblast-driven processes that extend beyond acute inflammation alone. At the same time, the study did not allow clear discrimination between predominantly inflammatory lesions and fibrotic or scar-associated remodelling, indicating that FAPI uptake likely reflects a continuum of inflammation, repair, and structural remodelling rather than a single pathological state (58).

Additional evidence for the utility of FAPI targeted imaging in LVV was provided in a dual-tracer study comparing [^{18}F]FDG and [^{18}F]FAPI-42 in 17 GCA and TAK patients. While overall detection rates were high for both tracers, FAPI identified more extensive vascular involvement and demonstrated higher TBR despite similar SUVmax values. Notably, temporal artery involvement was detectable with FAPI imaging, exceeding FDG in some cases. On follow-up imaging, FAPI signal intensity decreased in parallel with clinical remission and reductions in ESR and CRP, suggesting some responsiveness to treatment. Nevertheless, residual uptake frequently persisted despite clinical quiescence and low MRI activity scores (59).

The persistent uptake during remission raises an important interpretive challenge. Ongoing FAPI signal may reflect subclinical vasculitis, sustained fibroblast-mediated remodelling, reparative processes contributing to vascular stability, or established fibrosis (60). In this context, vascular remodelling should not be considered a passive end-stage phenomenon but rather a metabolically active process driven by activated fibroblasts with proinflammatory and profibrotic properties (58, 61, 62). It is also conceivable that active fibroblasts may contribute to residual FDG uptake in otherwise remitted disease (63).

Potentially, FAP-targeted PET may be most informative in scenarios where persistent vascular abnormalities remain difficult to interpret with inflammation-oriented imaging alone. This may include patients in clinical remission with ongoing PET or MRI abnormalities, as well as situations in which differentiation between active inflammation and remodelling-associated tissue responses is clinically relevant. However, the current evidence does not yet establish whether FAPI PET improves primary diagnosis, reliably distinguishes relapse from repair, or provides actionable information for routine treatment monitoring beyond [^{18}F]FDG PET.

Several practical barriers also limit immediate integration into routine care. FAPI tracers are not yet broadly available in vasculitis imaging, access remains largely restricted to specialised centres, and standardised acquisition, interpretation and reporting frameworks are still lacking. Regulatory approval and reimbursement pathways also remain limited in many settings.

Its main contribution at this stage lies in highlighting a biologically distinct dimension of disease. Whether this signal reflects residual inflammatory risk, maladaptive remodelling, or stable vascular repair remains unresolved. Larger controlled studies with tissue-level validation, longitudinal follow-up, and direct comparison with [^{18}F]FDG PET will be needed to define the clinical relevance of FAPI imaging more clearly (Fig. 2).

Future perspectives in PET imaging of large-vessel vasculitis

Rapid advances in the understanding of LVV immunopathology, together with the development of increasingly target-specific radiotracers, are shifting PET imaging from purely metabolic assessment toward biologically informed, cell- and pathway-directed characterisation of vascular inflammation. This transition may ultimately enable a more differentiated evaluation of disease activity, tissue remodelling, and treatment response. At present, however, most emerging tracers remain at an early stage of clinical development.

Beyond the targets discussed in this review, additional molecular pathways may further expand the PET imaging repertoire in LVV. One example is folate receptor beta (FRβ), which is highly expressed on activated macrophages in inflammatory disease. In GCA, FRβ-positive macrophage infiltration within the intima has been linked to intimal hyperplasia, a key correlate of luminal narrowing and ischemic risk (64). FRβ-targeted PET ([^{18}F]fluoro-PEG-folate and [^{18}F]AzaFol) may therefore provide complementary information on macrophage burden and remodelling-associated tissue responses (53). Their relevance in LVV, however, remains to be established in dedicated clinical studies.

Other biologically plausible targets include the C-C chemokine receptor type (CCR) 2, which interacts with C-C Motif Chemokine Ligand (CCL) 2 and contributes to granulomatous inflammation in GCA (29). CCR2-directed imaging could therefore be of interest for visualising inflammatory cell tracking within affected vessel walls (53). Similarly, T-cell-directed tracers targeting IL-2 receptors, CD4, or CD8 molecules could enable direct assessment of adaptive immune cell infiltration, thereby adding another mechanistic layer to LVV imaging (65). Additional exploratory signals may also arise from

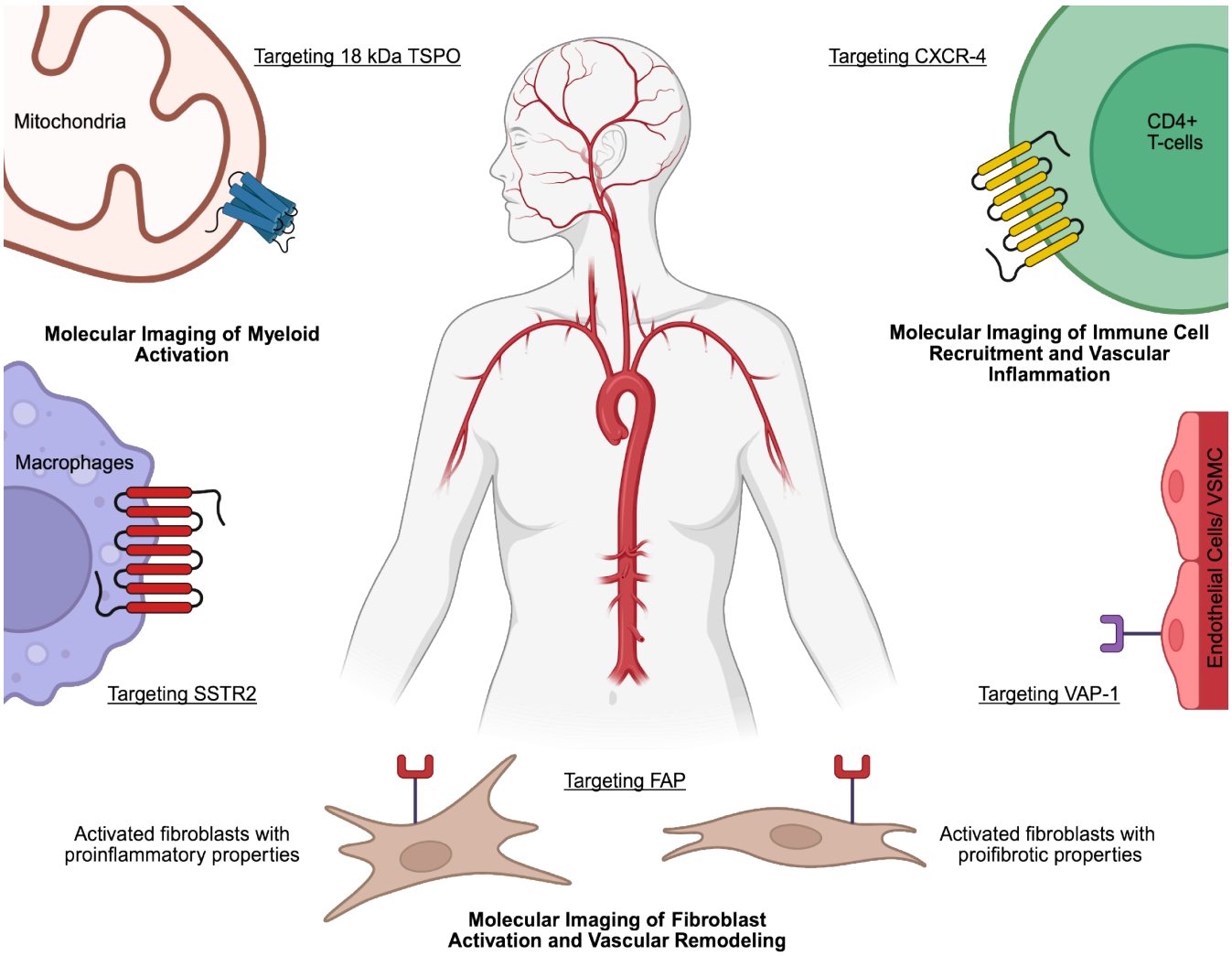

Fig. 3. Molecular targets of novel PET tracers in LVV.
Schematic overview of key cellular and molecular structures being targeted with PET tracers. Highlighted membrane-bound receptors and surface molecules illustrate potential targets for pathway-specific PET tracers, enabling *in vivo* visualisation of immune cell recruitment, endothelial activation, and fibroblast-driven vascular remodelling.
CD4: cluster of differentiation 4; CXCR4: C-X-C motif chemokine receptor 4; FAP: fibroblast activation protein; PET: positron emission tomography; SSTR: somatostatin receptor; VAP-1: vascular adhesion protein 1; VSMC: vascular smooth muscle cells. Image created with Biorender.

tracers not specifically developed for vasculitis imaging. In this context, vascular uptake on [^{68}Ga]PSMA PET/CT has been reported in an isolated case of GCA, although its biological significance and clinical relevance in LVV remain unclear (66). Overall, however, evidence for all these approaches in vasculitis is currently absent or limited to early translational and conceptual observations.

Looking ahead, single-tracer approaches may prove insufficient to capture the multidimensional biology of LVV. Dual-tracer or multimodal imaging approaches protocols may provide complementary insights into immune cell composition, myeloid activation, endothelial activation, and fibroblast-driven remodelling. Although such concepts are scientifically attractive, their feasibility, added clinical value, and cost-effectiveness remain to be demonstrated.

Despite encouraging early data of the tracers of this review, several challenges must be addressed before broader clinical implementation can be considered. Histopathologic validation of PET-positive vascular segments remains essential to define cellular correlates of tracer uptake. Standardisation of acquisition protocols, image interpretation and quantitative thresholds will be required to improve reproducibility across centres. Longitudinal studies are needed to determine responsiveness to therapies and to clarify whether tracer uptake predicts relapse, vascular progression, or ischaemic complications. Most importantly, the incremental value of pathway-specific tracers over [^{18}F]FDG has not yet been established in adequately powered comparative studies across clinically relevant scenarios such as diagnosis, relapse assessment, and treatment monitoring.

Practical considerations also remain substantial. Compared with [^{18}F]FDG, many novel tracers are less accessible because of production complexity, limited radiochemistry infrastructure, regulatory constraints, and uncertain reimbursement pathways. As a result, their

current use is likely to remain confined to specialised academic centres and research settings.

To conclude, molecular PET imaging in both GCA and TAK is moving toward a more precise biological characterisation of disease. The ability to visualise distinct immune pathways and remodelling processes may eventually improve disease phenotyping, refine treatment monitoring, and support more mechanism-based clinical decision-making (Fig. 3). For now, however, most applications remain investigational, and robust validation will be required before these tracers can be meaningfully incorporated into routine clinical care.

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