Theranostics 2.0: The Expanding Clinical Applications of Radioligand Therapy Beyond Oncology—A Narrative Review

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ABSTRACT

Theranostics, the convergence of molecular imaging and targeted therapy, has revolutionized cancer care and is now expanding into nononcologic domains. Increasing evidence supports its clinical potential in cardiovascular, inflammatory, and neurological diseases. This review explores emerging theranostic strategies in conditions such as atherosclerosis, rheumatoid arthritis (RA), cardiac amyloidosis, myocardial inflammation, Alzheimer's disease (AD), and multiple sclerosis. Key advancements include radioligands such as ^68Ga-DOTATATE for vascular inflammation, ^99mTc-labeled anti-TNF agents for autoimmune arthritis, and ^18F-florbetapir for cardiac amyloid imaging. Nanotechnology-based delivery systems are enhancing precision, enabling selective drug targeting, and improving imaging contrast, particularly in autoimmune and neurodegenerative conditions. The integration of artificial intelligence further refines image analysis and dosimetry, paving the way for personalized interventions. However, several challenges remain, including limited radionuclide access, regulatory complexities, and the difficulty of crossing the blood–brain barrier. Despite these hurdles, ongoing clinical trials and translational research underscore the growing viability of theranostics beyond oncology. Continued interdisciplinary collaboration, technological innovation, and standardized validation protocols will be crucial for transforming these targeted approaches into routine care for complex chronic diseases.

Keywords: Radioligand therapy, Non-oncologic theranostics, Nanotheranostics, 68GA-dotatate vascular imaging, AI-assisted dosimetry

Introduction

Theranostics is the fusion of diagnostic imaging and therapeutic intervention, representing a nuclear medicine paradigm that integrates molecular imaging with targeted therapy using the same or closely related radiolabeled compounds. This approach enables disease characterization through diagnostic imaging, typically positron emission tomography (PET) or single-photon emission computed tomography (SPECT), followed by targeted radionuclide therapy to deliver cytotoxic radiation precisely to affected cells or tissues.[1–3] Originating from its early application in thyroid cancer, theranostics supports personalized medicine by allowing real-time monitoring of both treatment efficacy and toxicity. Over the past decades, the theranostic concept has evolved considerably, from its early application in thyroid cancer to a broader clinical framework rooted in individualized medicine, where real-time assessment of treatment efficacy and toxicity becomes feasible.[3,4]

Theranostics has traditionally gained substantial clinical traction in oncology, particularly in managing neuroendocrine tumors (NETs) and prostate cancer. For instance, peptide receptor radionuclide therapy (PRRT) using radiolabeled somatostatin analogs, such as ^177Lu-DOTATATE, has demonstrated efficacy in treating NETs. On the other hand, radioligand therapies based on prostate-specific membrane antigen (PSMA) have significantly transformed the management modalities in people with advanced prostate cancer.[5,6] These advances highlight theranostics' unique capability to "see what you treat" by combining diagnosis, target confirmation, and therapy within a unified molecular strategy.[5]

Emerging studies suggest that suitable molecular targets may function dually as diagnostic markers and therapeutic entry points. The advances have brought up research on theranostics concerning various diseases such as inflammatory diseases, cardiovascular conditions, and neurological disorders. Studies indicated that good molecular targets would serve as diagnostics and therapeutic tools.[4] This is another aspect of precision medicine, as it throws interventions from molecular data into expanded clinical fields.

This narrative review aims to synthesize current knowledge and highlight emerging prospects for radioligand therapy (RLT) in nononcologic contexts. The work will analyze recent advances, clinical trials, and research within translational research settings, supporting the expanding role of theranostics beyond cancer, thus advancing the roadmap toward clinical implementation and novel innovation.

Methods

This narrative review was conducted by systematically searching PubMed, Scopus, and Web of Science for relevant peer-reviewed literature published between January 2010 and October 2023. Search terms included: "theranostics," "radioligand therapy," "nononcologic applications," "molecular imaging," combined with disease-specific expressions (e.g., "inflammation," "cardiovascular," "neurological"). Inclusion criteria included original research articles, clinical trials, preclinical studies, and translational research reports focusing on RLT in nononcologic conditions. Studies exclusively focused on oncology or non-radioligand-based therapies were excluded. The evidence was graded by study design: level I

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(randomized controlled trials), level II (observational studies), level III (preclinical studies), and level IV (case reports/expert opinion). Findings were synthesized descriptively to present current evidence and identify research gaps.

Radiotheranostics Framework Table 1: Theranostic Mechanisms: Targeting Ligands and Radionuclides

Radiotheranostics uses molecules that bind to diseased cells to enable the specific delivery of radionuclides for imaging or therapy. This model relies on a "see-and-treat" paradigm with diagnostic visualization coupled with targeted treatment delivery, maximizing beneficial outcomes**.** The radionuclides used in these designs participate in three major forms of emissions: beta emitters such as Lutetium-177 (^177Lu) and Yttrium-90 (^90Y), alpha emitters such as Actinium-225 (^225Ac), and Auger electron emitters.[7,8] For example, ^177Lu-DOTATATE binds to somatostatin receptors (SSTRs) and achieves considerable potency in neuroendocrine tumor PRRT. The ^225Ac-PSMA has high-level cytotoxicity for prostate cancer but little off-target damage.[9,10] In comparison, the α-emitters and Auger electrons provide high ionization density over short distances (nanometers to micrometers), thereby delivering a potent cytotoxic effect with potentially reduced off-target effects. This varied arsenal of radionuclides allows for fine-tuning of the arsenal for RLT. Careful selection of the correct radionuclide and targeting ligand has enabled a personalized treatment strategic plan within the tumor, its molecular profile, and the tumor microenvironment. This is fundamental to an optimization of therapeutic efficacy with the best possible ablation of tumor cells in conjunction with systemic toxicity, hence improving patient outcomes. Current research and development in this field keep opening up new pathways to the ever-expanding theranostic toolbox, promising even greater precision and efficacy in cancer therapeutic applications in the near future.[7–8,11] Theranostic radionuclides are shown in Table 1.

Overview of Dosimetry, Targeting Specificity, and Delivery Systems

Dosimetry can be defined as the calculation and assessment of the amount of radiation absorbed by tumors and normal tissues and is at the heart of radiotheranostics. S-values, MIRD (Medical Internal Radiation Dose) schema, and voxel-based dosimetry, all enhanced through the use of artificial intelligence (AI)-driven tools such as convolutional neural networks (CNNs), allow for very detailed segmentation of lesions and modeling of radiotracer dynamics. Individualized dosimetry helps to strike the best treatment balance between efficiently irradiating tumor tissues and avoiding injury to healthy organs, thereby enhancing both safety and therapeutic effectiveness. It is necessary to distinguish the two concepts: pretherapeutic (predictive) dosimetry, which refers to the amount of anticipated radiation dosage before treatment in planning therapy, and posttherapeutic (retrospective) dosimetry, which simply refers to the evaluation of the absorbed amount of radiation after treatment in terms of its effectiveness and toxicity. Utilizing advanced imaging modalities like SPECT/CT and PET/CT allows quantitative evaluation of biodistribution over time and individualizes dose estimate adjustments between treatment cycles. The dosimetry workflows increasingly integrate the methodologies of AI and deep learning, especially CNNs and reinforcement learning algorithms. Such platforms facilitate automatically high-precision lesion and organ segmentation, thereby addressing contouring variability, and allow dynamic analysis of radiotracer distribution for better kinetic modeling. This results in more accurate dose calculations and more reliable prognostications of therapeutic response and toxicity. Conversely, the integration of AI minimizes the variabilities in contouring thereby boosting accuracy in delivered doses and prediction of responses, but challenges concerning computational complexity and validation persist.[5,7–11]

Specific targeting will be possible through more appropriate molecular design of ligands, used to recognize disease-specific receptors or antigens to achieve selective binding and internalization into target cells. Delivery systems modified concerning pharmacokinetics and tumor retention have now been characterized by the use of novel radiopharmaceuticals showing high tumor uptake and prolonged retention while having favorable clearance profiles. These advancements must also tackle biological problems such as receptor expression differences among targeted cells in order to improve the therapeutic indices.[11,12]

General Theranostic Workflow

The theranostic workflow is characterized by the merging of diagnostics, therapeutics, and monitoring as part of a coherent precision medicine strategy. Beginning with molecular imaging, the diagnosis uses radiolabeled ligands like ^68Ga-DOTA-peptides or ^68Ga-PSMA to visualize and quantify target expression. This step allows the evaluation of target expression in the living subject and crucially affirms the presence and accessibility of the molecular target.[5,7–11] Patients with low uptake on diagnostic scans (e.g., low PSMA or SSTR expression) shall be excluded from

Table 1 | Overview of radionuclides used in radiotherapeutic applications

Radionuclide	Type of Emission	Clinical Applications
Lutetium-177 (^177Lu)	Beta	NETs (PRRT with ^177Lu-DOTATATE), prostate cancer (^177Lu-PSMA-617)
Yttrium-90 (^90Y)	Beta	General beta-emitter therapy
Actinium-225 (^225Ac)	Alpha	Prostate cancer (^225Ac-PSMA)
Auger emitters (unspecified)	Auger electrons	Under investigation for short-range cytotoxicity

therapy; this represents a critical negative selection criterion that ensures only those patients who are likely to benefit from treatment will receive it.[13] The preliminary imaging is the mainstay for patient selection since it ensures that only patients who can genuinely be expected to benefit from subsequent therapy are selected. Following this confirmation of the diagnosis, the therapeutic administration of β- or α-emitting radioligands, such as ^177Lu-DOTATATE or ^177Lu-PSMA-617, is brought into play. These agents are designed to be selective in delivering cytotoxic radiation only to tumor cells, with minimal collateral damage to healthy tissue. After treatment, imaging and dosimetry studies are performed for the assessment of drug distribution, treatment efficacy, and potential toxicity.[5,7–11] Response evaluation is carried out using RECIST, PERCIST, or some biochemical markers, providing the basis for real-time adjustments toward personalizing care.[13] This monitoring then continues in real time as a basis for subsequent care and potential dose adjustments to any future treatment cycles according to the precision medicine concept of "see what you treat," tailoring care to the biology of the individual patient and the characteristics of the tumor.[5,7–11] Radiotheranostics faces challenges such as limited isotope availability, high costs, regulatory burdens, and a shortage of trained personnel, which restrict its broader clinical applications. Biological limitations such as ineffective drug delivery, heterogeneous receptor expression in tumors, and tumor radioresistance all greatly affect therapeutic efficacy and consistent tumor control.[5,13] Theranostic workflow is shown in Figure 1.

Inflammatory Diseases

Atherosclerosis and Vascular Inflammation

Atherosclerosis is a chronic inflammatory condition of blood vessels, which is one of the leading causes of cardiovascular disease. It mostly occurs due to the morphological changes in vascular smooth muscles, which lead to macrophage adhesions and activation, immune system activation, and formation of atheroma. It begins with endothelial injury, followed by lipid deposition, monocyte infiltration, and chronic immune activation leading to plaque formation.[14]

For the detection of inflammatory plaques, both invasive techniques (coronary angiography, optical coherence tomography, and infrared spectroscopy) and noninvasive techniques (MRI and PET) are available. Among noninvasive methods, PET is frequently used for inflammatory molecular imaging. Radionuclide imaging also serves as theranostics, being employed for both diagnosis and treatment of inflammatory diseases, particularly atherosclerosis. The most widely used tracer is 18-fluorodeoxyglucose (^18F-FDG), a marker of activated macrophages and an indicator of response to antiatherosclerotic therapy.[15] Other tracers primarily used for diagnostic purposes include 99m-technetium-annexin V (a marker of apoptotic macrophages and cell death).[16] ^18F-fluoromisonidazole (a marker of hypoxia in the necrotic core),[17] ^18F-sodium fluoride (a marker of microcalcification in the necrotic core),[18] and ^18F-galacto-RGD (a marker of angiogenesis).[19] Additionally, radiolabeled mannose has been used to detect M2 macrophage receptors and inflamed plaque cells. Among these agents, ^18F-FDG remains the most widely applied for detecting inflamed targets within plaques. However, despite its utility, ^18F-FDG has important limitations—most notably, it cannot be reliably used for coronary artery imaging because of high background uptake in glucose-metabolizing cells, such as myocardial muscle and normal vessel walls, leading to reduced specificity.[2]

Monocytes inside tissues become tissue macrophages that express type 2 SSTRs by pro-inflammatory M1 macrophages as a signal of their activation, detected by radiotracer gallium-68 (68Ga)–labeled DOTATATE as a neuroendocrine tumor detector. In a comparison between ^18F-FDG and ^68Ga PET-CT images, ^68Ga-DOTATATE has greater lesion specificity, and more uptake is seen on the actual inflamed sites by ^68Ga than normal vessels, as ^18F-FDG showed increased uptake by both the diseased vessel as well as by normal vessels. ^68Ga-DOTATATE PET is more novel for atherosclerotic inflammation markers and is superior for coronary imaging. It has the advantage of differentiating between high- and low-risk lesions of the coronary.[7–9]

Nanoparticles (NPs) are known for their unique potential of diagnostic and therapeutic properties, i.e., theranostics for atherosclerosis. Advancement of NPs made it possible to target the lesions in vessels. Coating

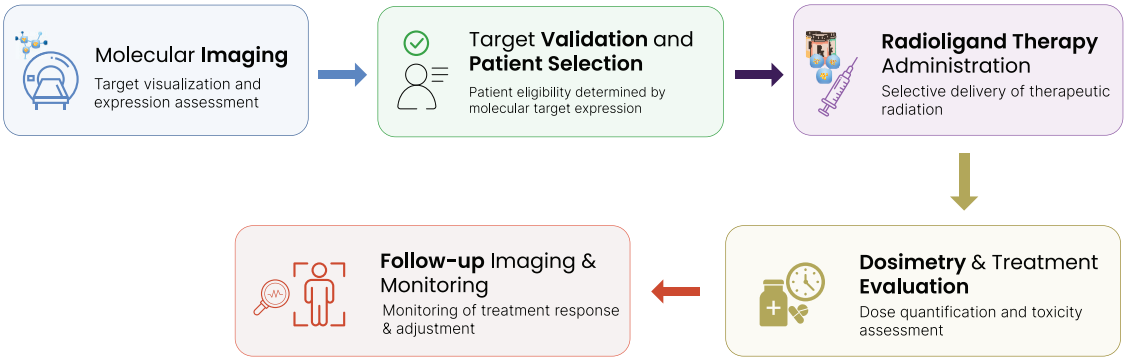

Fig 1 | The theranostic workflow: from imaging to therapy. Depicts key radionuclides and radiopharmaceutical classes

with antibodies and peptides of NPs for target ligands increases the sensitivity and specificity of NPs.[20,21]

NPs with active targeting include:

1. **Synthetic biomarker:** Vascular smooth muscle cells (VSMCs) of atheromatous plaque modify their phenotype from contractile to synthetic, which results in the formation of osteopontin (OPN), a synthetic marker that serves as a strong molecular target for imaging.[22,23] Osteopontin is a chemotactic cytokine that helps in adhesion, migration, and activation of macrophages.[13] Fibrin is also used as a sensitive synthetic detector of coagulation, and αvβ3 integrin as a biomarker of angiogenesis.[16]
2. **Theranostic agents:** Human serum albumin (HSA) engineered to form nanomedicine (NM) is used in an experiment on mice that had atherosclerotic vessels. The theranostic NM named ICG/SRT@HSA-pept NM is formed from protein-targeted OPN coated with near-infrared fluorescent dye indocyanine green (ICG) and the sirtuin 1 (SIRT1) activator SRT1720. SIRT1 is activated by NM containing SRT1720 and inhibits the phenotypic change of VSMCs, hence producing an antiatherosclerotic effect.[24]
3. **Platelet-mimetic or drug-loaded systems:** platelet-like NPs accumulated at the injured site and reduced bleeding by about 65%, working as normal platelets.[25]
4. **Imaging tracers:** Crosslinked dextran-coated iron oxide engineered for use in MRI and macrophagic ablation; protease-mediated agent for infrared imaging and elimination of macrophages; gold nanorods used in CT and macrophage ablation; silica-coated plasmonic nanorods for Intravascular and Intravascular photoacoustic imaging and plaque management; L-PLP for PET/MRI and lesion management; and doxorubicin-loaded hyaluronic acid–polypyrrole NPs for fluorescence imaging and targeting macrophage proliferation.[26] Theranostics used in MRI include high-density lipoprotein-like magnetic nanostructures (for elimination of cholesterol transport), Hybrid lipid–latex NPs (targeting macrophage proliferation), and solid-lipid NPs targeting platelet aggregation.[26] Different radiotracers for neurodegenerative diseases are shown in Table 2.

Nevertheless, there are still a number of drawbacks in such NPs with respect to stability, structure design, toxicity, targeting efficacy, and production, requiring optimization to devise nanoparticle-based therapeutic/diagnostic approaches for atherosclerosis that are clinically favorable.

NPs are used in atherosclerosis and other inflammatory diseases. However, there are still drawbacks that limit their uses, i.e., their structure design, their stability, the efficiency of their targets, their toxicity, and difficulties in their production. In the future, they might open new horizons and become capable of doing a lot more than they do today.[27]

Rheumatoid Arthritis and Autoimmune Diseases

RA is an autoimmune inflammatory disease that involves cartilage and bone destruction, causing multiple joint inflammation and deformation.[28] RA is characterized by chronic synovitis, leading to joint destruction through pannus formation, angiogenesis, and persistent inflammatory cytokine release, which disrupts bone and cartilage. In this process, there is also an increase in vascularization, i.e., angiogenesis, and increased production of proinflammatory cytokines within the joint space, including IL-1, IL-2, IL-6, IL-8, TNFα, TGFβ, GM-CSF, and TNF-alpha. Among interleukins, IL-6 is the main culprit in causing inflammation of joints and extra-articular symptoms in RA.[29] Early imaging using PET or SPECT tracers can detect subclinical inflammation before radiological joint damage plays an important role in RA management.

Theranostics in RA and other autoimmune diseases, such as ankylosing spondylitis, inflammatory bowel disease, psoriasis, sarcoidosis, anti-TNF-alpha or radioactive TNF-alpha antibodies, i.e., ^99mTc-Infliximab, ^99mTc-labeled human immunoglobulin G (HIG), and ^99mTc-Adalimumab, played a role in both diagnosis and treatment. Anti-TNF-alpha therapy plays a synergistic effect with methotrexate in the treatment of RA.[19,30]

^99mTc-Infliximab was collected in affected knees; visualized through scintigraphy scans, it showed the high levels of TNFα after 4 months of the scan; there was no uptake in inflamed knees.[31] ^99mTc-HIG uptake showed the vascularity, and it decreases only 2% of inflammation compared with 40% of infliximab, which does not help much in therapy. Similarly, radiolabeled

Table 2 | Radiotracers for neurodegenerative and neuroinflammatory disorders: clinical and theranostic applications

Radiotracer	Target	Indication	Clinical/Theranostic Role
^18F-Flortaucipir	Tau	AD	FDA-approved; visualizes tau tangles (51)
^18F-MK-6240	Tau	AD, progressive tauopathies	High-affinity second-gen tau tracer (52)
^18F-PI-2620	Tau (3R/4R)	AD, PSP, CBD	Differentiates mixed tau isoforms (53)
^18F-Florbetapir	Amyloid-β	AD	FDA-approved; detects Aβ plaques (54)
^18F-Flutemetamol	Amyloid-β	AD	FDA-approved; cortical Aβ imaging (54)
^18F-NAV4694	Amyloid-β	Research/early detection	Improved binding, research use (55)
^125I-DC8E8	Tau (aggregates)	Preclinical tauopathies	Antibody-based theranostic tracer (65)
^68Ga-PentixaFor	CXCR4	Neuroinflammation, CNS lymphoma	Images leukocyte trafficking; therapeutic analog exists (62)
^99mTc-cAbVCAM1-5	VCAM-1	Vascular inflammation (MS)	SPECT nanobody tracer (61)
^18F-DPA-714	TSPO (microglia)	MS, neuroinflammation	High-contrast TSPO imaging (58)
^11C-ER176	TSPO (microglia)	Genotype-insensitive inflammation	Third-gen TSPO tracer (59)

adalimumab reduced 25% uptake after the first injected dose of tracer, proving that it traces the TNFα in arthritic joints as well as targets it. Radiolabeled Golimumab also worked as adalimumab.[32] These radiolabeled agents can help predict patient response to biologic therapy and identify nonresponders early.

IL-6 signaling, which plays a key role in RA inflammation worsening, was antagonized by a monoclonal antibody named tocilizumab. Tocilizumab was coated with gold NPs, which provided the diagnostic and therapeutic effect in a mouse model by inhibiting the vascular endothelial growth factor and IL-6R.[33]

There are emerging research tools for RA, such as fibroblast activation protein inhibitor (FAPI) and FAPI PET, which is used as a novel tool in RA imaging to detect activated fibroblasts.

For synovitis, a process called radiosynovectomy is available in which beta-emitting radioactive tracers are injected into the joint space, which resolves the inflammation of the synovium through radiation dose. This therapy is used in the resistant synovitis to oral nonsteroidal anti-inflammatory drugs and intra-articular steroidal injections.

The beta emitter used is labeled as follows:

- Yttrium-90
- Rhenium-186
- Erbium-169
- Samarium-153

Beta emitters are 51–100% effective, and most patients get pain relief within 3–4 weeks. They are used for large joints like knees, and they typically serve as a second-line therapy. Radiosynovectomy has minimal systemic side effects and is often used in pediatric or hemophilia-related arthritis.

Radiopharmaceuticals used in PET/CT detect a wide range of inflamed spots and activated macrophages, i.e., macrophages such as C-11-(R)-PK11195-folate and F-18-PEG-folate. These tracers enable combined diagnosis and therapy, making them promising theranostic tools for chronic synovitis.[34]

Cardiovascular Disorders

Cardiac Amyloidosis

Recent advancements in nuclear imaging have improved the diagnostic accuracy, subtype differentiation, and monitoring of cardiac amyloidosis. The integrated use of ^99mTc-labeled bone tracers (e.g., pyrophosphate, DPD, and hydroxymethylene diphosphonate) with serum light-chain evaluation enables noninvasive diagnosis of transthyretin (ATTR) cardiac amyloidosis with high sensitivity and specificity. There are also recent advancements in PET imaging for the diagnosis of light-chain (AL) amyloidosis. Utilization of radiotracers such as ^18F-florbetapir, ^11C-PIB, and novel immune PET agents now provides higher resolution images and functional insights to detect light-chain amyloid deposits.[35]

The current treatment of cardiac amyloidosis is subtype-specific. Chemotherapy and transthyretin (TTR) stabilizers such as tafamidis are used for AL and ATTR cardiomyopathy, respectively.[36] Although these therapies are disease-modifying, they offer limited means to monitor disease progression, which emphasizes the need for theranostic strategies. AL-targeting monoclonal antibodies, such as CAEL 101, showed myocardial delivery and exhibited a 67% cardiac response in phase 1a/b clinical trials.[37] Likewise, ^68Ga-FAPI PET/CT allows noninvasive exploration of fibroblast activation, which is directly proportional to the activity of the disease.[38] The DepleTTR CM phase 3 trial is testing the safety and efficacy of ALXN2220 for the management of ATTR-CM. ALXN2220, a TTR-depleting antibody, is also under investigation for potential radiolabeling, further enabling theranostic use.[39] Such advancing approaches underscore the possibility of theranostics that combine imaging and treatment to allow continuous assessment and individualized intervention in cardiac amyloidosis. A recent study by Clerc et al. shows that ^18F-florbetapir PET provides prognostic information in systemic AL amyloidosis. The study found that elevated left ventricular uptake correlated with a higher risk of major adverse cardiac events.[40] These advances demonstrate the potential of theranostics to provide a comprehensive approach to diagnose, treat, and monitor in a single targeted strategy for cardiac amyloidosis.

Myocardial Inflammation and Post-MI Remodeling

PET imaging has increasingly been used to evaluate fibroblast activity and immune cell infiltration following acute myocardial infarction. For instance, the gallium-paired fibroblast activator inhibitor (^68Ga-FAPI) PET/CT is specific to fibroblast activation protein and is taken up in the infarct border zone, consistent with fibrotic remodeling.[41] This can help clinicians detect patients at risk of adverse remodeling and initiate timely therapy.[42] Likewise, myocardial inflammation tracers such as ^18F-LW223, which target translocator protein (TSPO), have high specificity for macrophage influx and are not limited by genetic polymorphisms associated with binding of tracers. These tracers detect inflammation in myocarditis, sarcoidosis, post-MI remodeling, transplant rejection, and autoimmune cardiomyopathies.[43] Such tools allow for accurate characterization of tissue-level changes that can be overlooked by conventional imaging.

^64Cu-DOTATATE is another promising PET tracer that targets somatostatin receptor subtype 2 (SSTR2). Its high affinity for activated macrophages makes it a valuable tool for imaging vascular and myocardial inflammation. Compared to other tracers like ^18F-FDG, ^64Cu-DOTATATE demonstrates improved specificity for macrophage-driven inflammation and minimal background uptake in metabolically active tissues such as myocardium and skeletal muscle.[44] In a preclinical study done in rabbits that included a systematic head-to-head comparison in rabbit models, ^64Cu-DOTATATE provided significantly higher uptake in inflamed atherosclerotic plaques than ^18F-FDG and Na^18F, with no correlation between tracer signals.[45] In the first

human application (CuDOS study), ^64Cu-DOTATATE PET/CT showed comparable sensitivity but superior specificity (90% vs. 75%) relative to ^18F-FDG for detecting infective endocarditis and eliminated the need for dietary preparation.[46] This aligns with the 2023 European Society of Cardiology (ESC) guidelines, which endorse PET/CT as a major diagnostic tool for complex infective endocarditis, particularly in prosthetic valve or device-related infections.[47]

Theranostic applications are also moving at a rapid pace. Anti-inflammatory radionuclide therapy is entering the early development phase. Wang et al. employed a pretargeted nuclear imaging and therapy platform with radiolabeled antibody fragments to target Lutetium-177 (^177Lu) to inflamed myocardial tissue in a mouse model.[48] This approach had a profound effect on local inflammation, creating a possibility for targeted radiation-based immunomodulation. In the same vein, Rischpler et al. also discussed the promise of C-X-C chemokine receptor type 4 (CXCR4) targeting agents like ^68Ga-pentixafor and ^177Lu-pentixather for simultaneous imaging and treatment in cardiovascular inflammation.[49] These studies signal a future where cardiovascular inflammation is both imaged and selectively treated using theranostics. To translate these findings into clinical practice, ongoing clinical trials will be critical to determine safety, dosimetry, and response dynamics in human cardiovascular disease models.

Neurological Disorders

Alzheimer's Disease and Tauopathies

PET imaging for AD has advanced significantly with the development of successive generations of tracers to evaluate tau and beta-amyloid aggregates.[50,51] The FDA approval of the first tau PET tracer, [^18F]Flortaucipir (AV-1451), in 2020 marked a milestone by enabling in vivo visualization of neurofibrillary tangles.[50] Newer tracers such as [^18F]MK-6240, [^18F]PI-2620, [^18F]RO-948, and [^18F]GTP1 demonstrate improved tau-binding specificity and reduced off-target uptake.[51,52]

Additionally, there are FDA-approved radiotracers for amyloid imaging to assess Aβ plaques, such as [^18F]Florbetapir, [^18F]Florbetaben, and [^18F]Flutemetamol.[53] Research agents such as [^11C]PiB and [^18F]NAV4694 have further refined quantitative assessment, showing strong binding profiles and sensitivity to early pathological changes.[54]

Theranostic strategies are emerging, with radiolabeled antibodies and peptides under investigation for dual diagnostic and therapeutic roles. The ^125I-DC8E8 antitau antibody, for example, has shown high selectivity in tau-transgenic animal models.[55] Bispecific antibodies labeled with radionuclides (^18F, ^64Cu) are also being explored to enable both imaging and targeted radiation delivery to tau or Aβ deposits.[56,57] While still largely preclinical, these approaches highlight the potential for integrated diagnosis and therapy in AD.

Neuroinflammation and Multiple Sclerosis (MS)

Microglial activation is an indicator of neuroinflammation that we are usually able to visualize in MS. One of the most important molecular targets of the neuroinflammatory response is the 18-kDa TSPO. In a bid to improve imaging of MS, scientists have optimized second- and third-generation TSPO PET radionuclides. The new tracers, [^18F]DPA-714, [^18F]GE-180, and [^11C]ER176, were designed to minimize the allele variations that were prevalent in previous TSPO PET tracers, including [^11C]PK11195.[57–59] MS studies with TSPO PET have established that there is greater TSPO uptake in active lesions as well as in normal-appearing white matter and that it covaries with clinical measurements of disability and disease progression.[60]

Beyond adhesion proteins and chemokine receptors, TSPO targeting strategies have also explored molecules such as VCAM-1 and CXCR4. For example, a 99mTc-labeled anti-VCAM-1 nanobody is specific for quantifying neurovascular inflammation in preclinical models. On the other hand,[60] ^68Ga-PentixaFor, however, targets CXCR4 expression on activated leukocytes, which can be therapeutic as well as diagnostic of CNS inflammation.[61]

Concerning therapy, the modulation of the function of microglia to suppress neuroinflammation has remained the impetus. CSF-1R inhibitors BLZ945 and PLX3397 have been demonstrated to reduce neurotoxicity in MS models by depleting microglia. Despite their utility, TSPO tracers are limited by their nonspecificity to microglia alone, and their binding affinity can be affected by polymorphisms in the TSPO gene.[62] Although such strategies could minimize the deleterious effects of microglia, their complete elimination may not be ideal. Evidence suggests that rather than eliminating CNS myeloid cells, a more effective strategy is to modulate their function. Newer targets such as the colony-stimulating factor 1 receptor (CSF1R), cyclooxygenase-2 (COX-2), and P2X7 receptors are under investigation for imaging microglial activation with greater specificity.[63] Next-generation PET imaging, however, could be the cutting edge in guiding targeted therapy for microglia and the path to more targeted medicine in the treatment of MS. Future directions include using microglial PET imaging not only for disease monitoring but also for evaluating treatment response in trials of neuroinflammation-modulating agents.

Nanotheranostics

Introduction to Nanotheranostics

Nanotheranostics combines therapeutic agents with diagnostics to create "theranostic" agents; this is possible due to the NPs custom-made for high drug loading and specific targeting to tissues or cells. These NPs, which are composed of organic or colloidal makeup, can be engulfed by cells of the reticuloendothelial system, such as macrophages, dendritic cells, and neutrophils, and can also be modified on the surface to capture particular populations of lymphocytes.[64] RLT is expanding its applications beyond stabilization of diseases and improvement of quality of life in

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palliative care, as the principle of targeted therapy can be applied to nononcologic conditions.[65,66] Nanotechnology's ability to deliver and target specific cell types can address challenges posed by the broadened applications in a nononcologic framework.

The definition of RLT has been removed to avoid redundancy

Advantages of Nanotechnology in Nononcologic RLT

RLT can be greatly improved by using nanotechnology due to several key advantages.

Nanoscale tailoring of NPs increases precision targeting, which allows radiopharmaceuticals to accurately interact with certain cells or tissues without interfering with normal biological processes.[64] Such accuracy is also associated with improved pharmacokinetics and biodistribution, resulting in optimal delivery and accumulation within cells by overcoming biological barriers through NPs that facilitate controlled and enhanced targeted delivery.[67,68] Moreover, theranostics holds the potential to advance biomedical research toward personalized medicine by offering a holistic disease management solution that integrates diagnostic and therapeutic modalities into a single platform, strategically embedding molecular or material tools to enable simultaneous treatment and imaging for assessing disease staging, treatment planning, and therapeutic efficacy as seen in enhanced drug delivery and real-time tracking in diabetes treatment by combining therapy and imaging in a single probe, allowing for pancreas-specific drug and insulin delivery.[69,70]

Nononcologic Applications

The nononcologic applications of nanotheranostics and RLT are still expanding. For some infectious diseases, such as COVID-19, NPs provide the ability to specifically direct drugs to infected cells, eliminating obstacles like low solubility and rapid clearance. These NPs enable real-time monitoring of therapeutic response through radiolabeled and carbon nanotube-based systems, due to their selective targeting capabilities and minimized toxicity to healthy tissues.[69] Applications in inflammatory and autoimmune disease therapies target specific areas with NPs, greatly reducing adverse effects as compared to the classical treatments while enhancing drug availability.[67] As an example, albumin–nanoceria targets inflamed RA joints, with improved therapeutic efficacy while enabling theranostic monitoring.[71] Immune cells can also be directly targeted by NPs to precisely modulate immune responses.[67] In neurodegenerative pathologies, nanoparticle-conjugated antioxidants demonstrate enhanced stability and bioavailability, allowing them to cross the blood–brain barrier (BBB) more effectively. These systems protect the antioxidant payload from premature degradation and facilitate the neutralization of neurotoxic enzymes, thereby mitigating neuronal damage.[69]

Future Challenges and Directions

Despite rapid advances, several hurdles must be addressed before nanotheranostics achieve broad clinical translation. AI-driven design platforms are beginning to optimize nanoparticle parameters such as size, charge, and ligand chemistry, accelerating the creation of safer and more effective agents.[72] However, scalability and reproducibility remain major concerns, as manufacturing complex nanocarriers at clinical-grade standards requires ensuring batch-to-batch consistency in biodistribution and clearance.[73] Secondly, Biological barriers also persist, particularly in achieving efficient BBB penetration, minimizing rapid renal or hepatic clearance, and avoiding off-target immune activation.[74,75] These challenges highlight that while nanotheranostics represent a transformative frontier at the intersection of molecular imaging, therapy, and AI-assisted design, their successful clinical integration will depend as much on addressing translational and regulatory barriers as on advancing technological innovation.

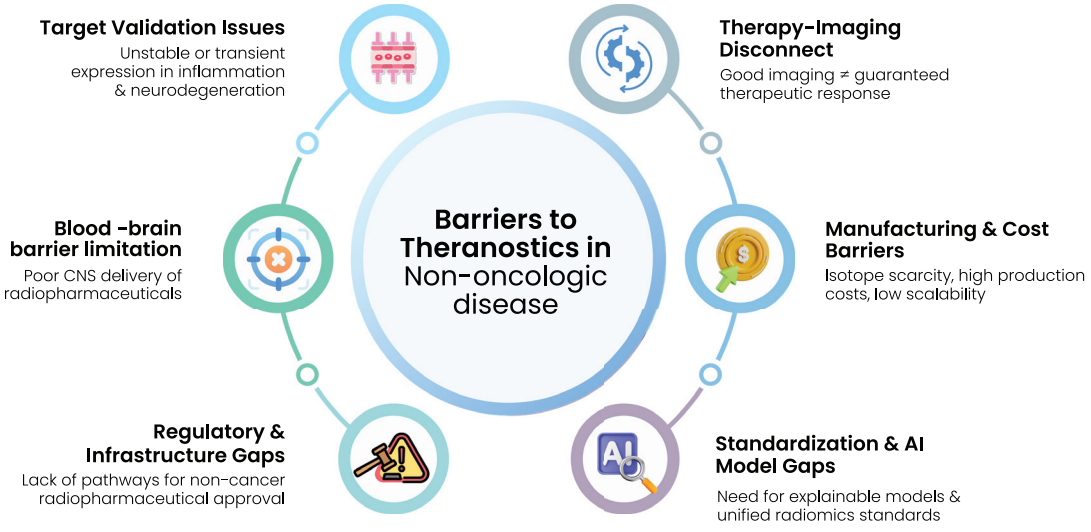

Fig 2 | Challenges to theranostics in nononcologic disease

Challenges and Considerations

Theranostic expansion to nononcologic diseases, as shown in Figure 2, presents several challenges that must be tackled strategically.

Scientific and Logistic Hurdles

Target validation remains a challenge, especially in inflammatory and neurological disorders where expression of the target may be transient, heterogeneous, or stage/comorbid-dependent. The dynamic nature of immune modulation and inflammation makes it difficult to identify stable, disease-specific molecular targets for RLT.[76,77]

One of the major obstacles in neurology is the BBB. Many therapeutic radiopharmaceuticals have poor CNS bioavailability. Novel technologies such as nanoparticle carriers and receptor-mediated transcytosis hold high potential for better central delivery, but translation to human models is immature. Such underdevelopment is influenced by interspecies pharmacokinetic differences, high development costs, and variability of the immune system.[78,79]

Economic and Isotope Production Challenges

The economic viability of nononcologic theranostics remains a major challenge. Producing novel radionuclides is both costly and limited in availability—for example, a single cycle of ^177Lu-DOTATATE therapy in the United States can cost nearly $50,000.[5] Beyond treatment itself, routine clinical use is hindered by complex and inconsistent reimbursement systems. In some countries reimbursement depends on government funding, while in others it is insurance-based. Cost calculations also differ, and in many regions theranostic agents are not readily accessible. As a result, reimbursement often fails to cover the true expense of care.[5] These financial barriers, coupled with the high capital investment required for imaging infrastructure such as PET/CT scanners, risk limiting access to specialized centers and widening health disparities between high-income countries and low- and middle-income countries. For instance, a tertiary center in India reported that the annual cost of running a PET/CT unit was about $1,020,495, with 76% attributed to capital costs and 24% to operating expenses.[80]

Regulatory and Dosimetric Hurdles

The regulatory pathway for nononcologic radiopharmaceuticals is less defined than oncology, potentially delaying their clinical adoption. In addition, ensuring the best therapeutic effect while minimizing radiation exposure requires advanced dosimetry. Transitioning from tumor-focused dosimetry to calculating absorbed doses in dynamic, nonmalignant tissues introduces a unique challenge, one that current models are not yet fully equipped to address.[81] Second, the interface of therapeutic use and imaging diagnosis continues to be a bottleneck. The majority of molecular targets have good imaging potential, but response to therapy is no guarantee. As an example, amyloid-binding tracers in AD have had excellent imaging use but did not become therapeutic interventions.[82] Imaging biomarkers must exactly predict response to therapy, and translational shortfalls in this space need to be better addressed by well-designed clinical trials and biomarker qualification strategies.

Limitations of this Review

As a narrative review, this analysis comes with its own set of limitations. The nonsystematic methodology may introduce selection bias, potentially overlooking relevant studies or negative findings. Furthermore, the rapid evolution of the field means that the scope of clinical trials and technological breakthroughs is constantly changing, and this review reflects the current state of progress.

Future Directions

Advancements in nononcologic theranostics in the future will be contingent, in part, on creating longer clinical trials and more precise molecular targets. Clinical trials for cardiovascular inflammation (e.g., using somatostatin or FAP ligands), RA (TNF-α tracers), and AD (tau-targeting constructs) are ongoing, with initial-phase studies demonstrating promising safety and pharmacokinetics.[83,84] The fusion of nanotechnology and biologics is extremely promising. Nanotheranostics, including liposomes, dendrimers, and albumin-based drug delivery systems, are being engineered to deliver selectively with reduced systemic toxicity, especially for autoimmunity and chronic infectious diseases.[85,86] These formats allow for multimodal functions—diagnosis, treatment, and follow-up in a single agent, which in the context of complex systemic diseases is especially valuable. AI is also poised to become a theranostic agent of revolution. Machine learning models trained on radiomic and molecular imaging data can identify targets more accurately, tailor treatment planning, and predict response directions more effectively than traditional methods. Pilot studies have already shown that AI-driven FDG PET radiomic models can predict neuroinflammatory responses accurately.[87,88] Challenges remain, however, such as the need for standardized input data, explainable models, and transparent regulatory paths.[87] Interdisciplinary team science—combining nuclear medicine, molecular biology, neurology, cardiology, and regulatory science—is required to leapfrog beyond existing boundaries and bring these technologies to the clinical front burner. Future directions are shown in Figure 2.

Conclusion

Once largely confined to oncology, theranostics is now rapidly expanding into inflammatory, cardiovascular, and neurological diseases, driven by advances in molecular targeting and radioligand design. While formidable challenges related to target validation, BBB penetration, isotope availability, cost, and regulatory pathways remain, emerging technologies, particularly nanotechnology and AI, offer compelling solutions. Importantly, RLT for nononcologic conditions is no longer theoretical; clinical trials and translational research are already

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underway. This shift signals a new era in precision medicine, where diagnosis, treatment, and monitoring are integrated into a single, patient-centered framework. To fully realize this potential, the field must prioritize rigorous clinical validation and equitable access, particularly across low- and middle-income settings. With sustained multidisciplinary collaboration, theranostics could transform the way we approach disease management. This not only improves outcomes but also redefines what precision medicine can achieve. The journey from diagnostic imaging to a curative treatment for non-cancerous diseases has begun, marking a new frontier in molecular medicine.

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