

Radiopharmaceuticals driving the transition from metabolic to targeted precision molecular imaging in neurodegenerative diseases

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Neurodegenerative diseases (NDDs) are characterized by overlapping clinical phenotypes and heterogeneous proteinopathies, which pose substantial challenges for early and accurate diagnosis. Molecular imaging with radiopharmaceuticals has revolutionized the field by enabling the *in vivo* visualization of disease-specific biological processes. Historically, the field has progressed from glucose metabolism imaging toward the increasingly selective detection of pathological protein aggregates. Amyloid- β and tau are established biomarkers in Alzheimer's disease, and their imaging is now integrated into diagnostic and therapeutic pathways. Nevertheless, ongoing efforts continue to refine these radiopharmaceuticals, particularly in enhancing target specificity and minimizing off-target binding. In parallel, emerging targets such as α -synuclein, mutant huntingtin, transactive response DNA binding protein 43, and other pathological aggregates are expanding the molecular imaging toolbox beyond Alzheimer's disease to encompass a broader spectrum of NDDs. Neuroinflammation-targeted PET provides an additional window into disease-associated biological processes beyond protein aggregation. Nevertheless, a critical need persists for radiopharmaceuticals targeting these emerging molecular targets. Addressing these challenges and advancing multi-target PET platforms will not only enable *in vivo* detection of mixed proteinopathies and precise disease subtyping, but also provide a core infrastructure for target validation, companion diagnostics, and therapeutic monitoring across the drug development pipeline, ultimately ushering in an era of biologically defined precision medicine for NDDs.

INTRODUCTION

Neurodegenerative diseases (NDDs), including representative conditions such as Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and Huntington's disease (HD), represent a group of progressive neurological disorders characterized by irreversible neuronal dysfunction and degeneration. The clinical and pathological overlap across these disorders, coupled with diverse proteinopathies, complicates early and accurate diagnosis using conventional assessments alone. This limitation is critically underscored by recent approvals of disease-modifying anti-amyloid therapies that require biological confirmation of amyloid pathology before treatment initiation.

In this context, molecular imaging with radiopharmaceuticals has emerged as a cornerstone for the *in vivo* visualization of specific protein aggregates via positron emission tomography (PET), a nuclear medicine technique renowned for its high specificity, sensitivity, and quantifiability. While fluid biomarkers from blood or cerebrospinal fluid offer accessibility and scalability, they provide indirect, averaged measures that inherently lack the spatial resolution necessary to map protein deposition or distinguish mixed pathologies. PET, by contrast, uniquely enables topographically precise, multi-target interrogation within a single imaging session, making it an indispensable tool for the clinical evaluation and mechanistic understanding of NDDs.

Over the past two decades, this field has undergone a fundamental transformation. It has evolved from reliance on [18 F]fluorodeoxyglucose ([18 F]FDG) PET as a global marker of cerebral glucose metabolism and neuronal dysfunction toward increasingly specific molecular imaging of disease-asso-

ciated proteinopathies (Figure 1). This Perspective traces this evolution from functional metabolic imaging to molecularly targeted radiopharmaceuticals. Furthermore, expanding molecular imaging across the broader spectrum of NDDs holds the potential not only to enable more precise disease subtyping and earlier diagnosis, but also to serve as a versatile *in vivo* imaging platform across the drug development pipeline.

GLUCOSE METABOLISM IMAGING

The introduction of [18 F]FDG marked the first major advance for *in vivo* molecular imaging in NDDs. By measuring regional cerebral glucose metabolism as a marker of synaptic and neuronal integrity, [18 F]FDG PET provides a sensitive functional readout of early neurodegeneration, often preceding structural changes detectable by conventional magnetic resonance imaging (MRI) and computed tomography (CT).

Over the past few decades, [18 F]FDG PET has become a widely adopted clinical tool and is recommended in the SNMMI/EANM Brain [18 F]FDG PET Imaging Guideline (Version 2.0) for the evaluation of NDDs.¹ It reveals disease-specific patterns of cerebral hypometabolism across both dementia syndromes and motor system disorders, thereby aiding in clinical differential diagnosis.

Although [18 F]FDG has been widely used in the evaluation of NDDs, the lack of disease specificity remains a limitation. Metabolic patterns may overlap across different disorders, particularly in early or atypical clinical presentations. This limitation has driven the transition from non-specific metabolic imaging toward molecularly targeted radiopharmaceuticals capable of directly visualizing underlying protein pathology. Nevertheless, [18 F]FDG PET indirectly reflects neuronal activity, and it continues to serve as a valuable functional surrogate when specific protein-targeted radiopharmaceuticals are unavailable, thereby maintaining a complementary role in clinical practice.

PROTEIN-TARGETED MOLECULAR IMAGING

Amyloid- β imaging

Amyloid- β (A β) deposition is a core pathological hallmark of AD and was the first proteinopathy successfully targeted in neurodegenerative imaging. A β PET enables *in vivo* visualization of cerebral A β burden and plays an essential role in supporting AD diagnosis and distinguishing it from non-AD dementias.²

[11 C]Pittsburgh compound B ([11 C]PiB) was the pioneering A β PET tracer, providing the first reliable *in vivo* visualization of amyloid pathology in AD. However, its clinical utility was severely constrained by the short half-life of 11 C. To address this limitation, 18 F-labeled A β PET tracers with longer half-lives were subsequently developed. Currently, three agents are U.S. Food and Drug Administration (FDA)-approved for clinical use in AD diagnosis: [18 F]florbetapir, [18 F]flutemetamol, and [18 F]florbetaben. These tracers share high affinity for fibrillar A β , enabling reliable detection of cerebral amyloid deposition with high sensitivity and specificity. However, current A β PET tracers primarily reflect fibrillar plaque burden and lack the sensitivity to detect soluble oligomeric A β —the species most closely linked to neurotoxicity, thereby restricting their ability to capture early-stage pathogenic aggregation.²

Beyond its diagnostic role, the recent emergence of anti-A β monoclonal antibody therapies has further elevated the importance of A β PET, making it a

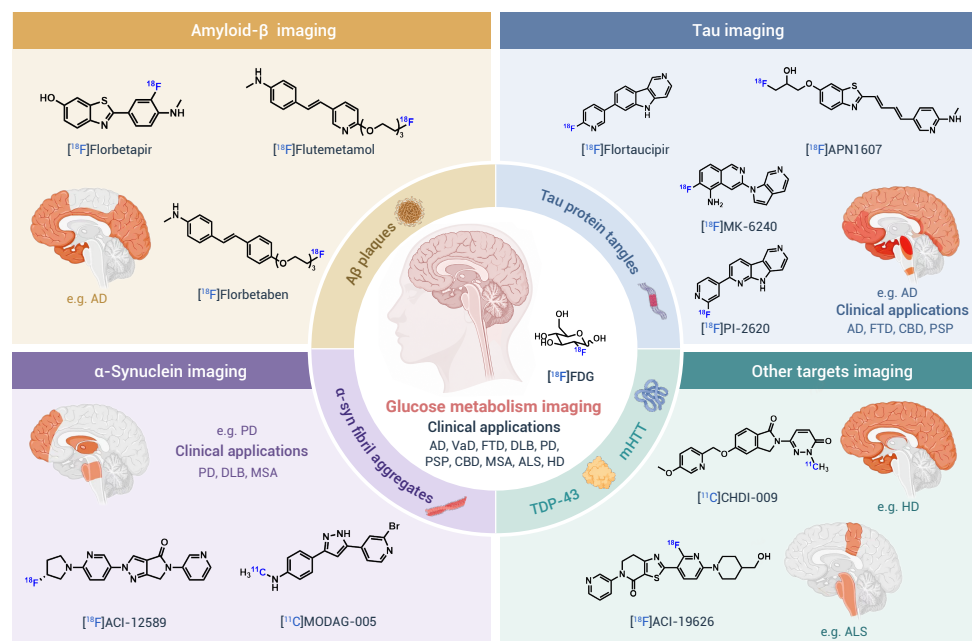


Figure 1. Molecular imaging landscape of neurodegenerative diseases from metabolic to protein-targeted PET imaging The figure illustrates the evolution from non-specific glucose metabolism imaging to protein-targeted imaging. The central part displays the molecular formula of [^{18}F]fluorodeoxyglucose ([^{18}F]FDG) along with the corresponding neurodegenerative diseases (NDDs) evaluated by glucose metabolic imaging. Surrounding the [^{18}F]FDG framework are representative protein-targeted PET imaging approaches, including amyloid- β (A β), tau, α -synuclein (α -syn), mutant huntingtin (mHTT), and transactive response DNA-binding protein 43 (TDP-43). Representative PET tracers and their chemical structures for different pathological protein targets are illustrated around the central FDG-PET framework. The corresponding NDDs and predominantly affected brain regions are indicated in the surrounding panels. AD, Alzheimer's disease; VaD, vascular dementia; FTD, frontotemporal dementia; DLB, dementia with Lewy bodies; PD, Parkinson's disease; PSP, progressive supranuclear palsy; CBD, corticobasal degeneration; MSA, multiple system atrophy; ALS, amyotrophic lateral sclerosis; and HD, Huntington's disease.

critical tool for patient selection, baseline stratification, and monitoring of therapeutic response. Moreover, the introduction of the Centiloid scale has enabled cross-tracer quantitative standardization, which is critical for using A β PET as a pharmacodynamic endpoint in multi-center clinical trials.

Tau imaging

Tau is a microtubule-associated protein that forms neurofibrillary tangles under pathological conditions. Compared with A β , tau pathology correlates more closely with neuronal loss, brain atrophy, and cognitive decline, making it a more direct indicator of disease progression and severity. Tau pathology exhibits isoform diversity, including 3R, 4R, and mixed 3R/4R aggregates, which are differentially distributed across tauopathies such as AD (mixed 3R/4R), progressive supranuclear palsy (PSP) (4R), and Pick's disease (3R). This structural diversity makes tau a more challenging target for radiotracer development than A β .

Tau PET radiopharmaceuticals have evolved from first-generation to second-generation agents. The first-generation tracer [^{18}F]flortaucipir, approved by the FDA in 2020, is the first clinically approved tau PET agent for AD and represents a major milestone in the *in vivo* visualization of neurofibrillary tangles. However, its limited sensitivity for early tau deposition, low affinity for non-Alzheimer tauopathies, and off-target retention have driven the development of second-generation tracers, including [^{18}F]MK-6240, [^{18}F]PI-2620, and [^{18}F]APN-1607.³

Among them, [^{18}F]MK-6240 shows high sensitivity and a wide dynamic range for early tau deposition in AD, and has completed pivotal Phase III studies, with its New Drug Application (NDA) approved in August 2026. [^{18}F]PI-2620 is in pivotal Phase III development and has also shown potential in 4R tauopathies, particularly PSP, although inter-subject variability limits its individual diagnostic robustness. [^{18}F]APN-1607 has completed Phase III clinical evaluation in AD in China, with additional trials are ongoing for AD-related cognitive impairment and early PSP diagnosis.

Despite these advances, tau PET tracers remain most established for mixed 3R/4R pathology in AD, whereas its ability to detect predominantly 4R or 3R tau aggregates in non-AD tauopathies is limited. To overcome this, alternative scaffolds are being explored to enable more selective imaging of 3R and 4R tau.

α -Synuclein imaging

α -Synuclein (α -syn) is a central pathological protein in PD, dementia with Lewy bodies (DLB), and multiple system atrophy (MSA), collectively referred to as synucleinopathies. Its pathological aggregation is considered a key driver of neurodegeneration, making it an attractive therapeutic target and a major unmet need in molecular imaging. Currently, synucleinopathies are still

diagnosed primarily through clinical phenotype and indirect functional imaging biomarkers

rather than direct visualization of α -syn pathology.

Developing α -syn PET tracers is particularly challenging. The low absolute concentration of α -syn deposits demands sub-nanomolar affinity, while the β -sheet structural elements resemble those of A β and tau, leading to off-target cross-reactivity and co-pathology confounds. Additionally, α -syn fibrils exhibit conformational polymorphism without a stable binding pocket, and the intracellular location of aggregates requires tracers to cross both the blood-brain barrier and cell membranes, a difficulty further compounded by the complex lipophilic structure of Lewy bodies. Moreover, recombinant fibrils do not fully recapitulate α -syn aggregates in human brain tissue. High affinity *in vitro* may not necessarily predict selective binding to native pathology.⁴

Promising direct tracers are now emerging. [^{18}F]ACI-12589 demonstrates good affinity and selectivity for pathological α -synuclein, and shows pronounced retention in the cerebellar white matter and middle cerebellar peduncles in MSA, distinguishing MSA from PD, DLB, and healthy controls in first-in-human PET studies.⁵ [^{11}C]MODAG-005, structurally derived from earlier tracer versions and an α -syn oligomer modulator, exhibits high binding affinity and specificity for recombinant α -syn fibrils and inclusions in human brain tissue. First-in-human studies have demonstrated specific uptake in target brain regions, including the putamen and cerebellum in MSA and PD patients.⁶ [^{18}F]FD4 is a novel α -syn PET tracer with preclinical and early first-in-human studies demonstrating favorable blood-brain barrier penetration, rapid brain clearance, and low background signal, and preliminary clinical data have shown differential regional uptake in PD and MSA patients (ChiCTR2400093084). All these tracers have now entered Phase I clinical evaluation.

Despite this progress, α -syn PET tracers remain at an early stage of clinical translation. The major challenge is not simply to identify α -syn-binding ligands, but to develop radiopharmaceuticals that retain molecular selectivity and favorable pharmacokinetics in the complex human disease environment, while ensuring sufficient sensitivity and specificity across heterogeneous synucleinopathies.

Other pathological protein targets imaging

Beyond A β , tau, and α -syn, increasing efforts have focused on extending molecular imaging to additional pathological proteins involved in NDDs.

In HD, pathological aggregation of mutant huntingtin (mHTT) is a key driver of disease progression and represents a critical pharmacodynamic biomarker for monitoring therapeutic efficacy. The first-generation tracer [^{11}C]CHDI-180R has completed Phase I clinical evaluation, providing early evidence for the feasibility of imaging mHTT pathology *in vivo*, although its clinical performance remains limited by non-specific binding and suboptimal selectivity. Subsequent second-generation isindolinone-based tracers, including

[¹¹C]CHDI-009 and ¹⁸F-labeled derivatives, have demonstrated improved binding affinity and pharmacokinetic profiles in preclinical studies but remain at the preclinical stage.⁷ mHTT PET shows significant potential for therapeutic monitoring, providing a direct readout of target engagement and treatment response.

Transactive response DNA binding protein 43 (TDP-43) is a cross-disease pathological protein implicated in ALS, frontotemporal dementia (FTD), and limbic-predominant age-related TDP-43 encephalopathy (LATE). TDP-43 PET would therefore be critical for differentiating LATE, a condition frequently misdiagnosed as AD. TDP-43 co-pathology frequently coexists with Aβ and tau in elderly AD patients and is an important explanatory factor when cognitive decline exceeds what would be expected from Aβ or tau burden alone. A TDP-43 targeted PET tracer, [¹⁸F]ACI-19626, has entered Phase I clinical evaluation, marking an important step toward direct *in vivo* imaging of TDP-43 pathology.⁸ In parallel, misfolded superoxide dismutase 1 (SOD1), a key driver of familial ALS, is being targeted using antibody-based PET imaging strategies. [⁸⁹Zr]Zr-DFO-AP-101 has entered Phase I clinical evaluation, demonstrating the feasibility of immuno-PET approaches in ALS.⁹ By contrast, imaging of fused in sarcoma (FUS) protein aggregation remains entirely at the preclinical stage, and no PET tracers targeting FUS pathology have yet progressed into human studies. Accordingly, clinical evaluation of FUS-related ALS continues to rely on indirect metabolic imaging approaches such as [¹⁸F]FDG PET.

NEUROINFLAMMATION IMAGING

Neuroinflammation is a key pathological process in NDDs, contributing to neuronal injury, disease progression, and cognitive decline. The 18-kDa translocator protein (TSPO), an outer mitochondrial membrane protein upregulated during glial activation, remains the most extensively investigated molecular target for neuroinflammation PET imaging.¹⁰

The first-generation TSPO radiotracer [¹¹C]PK11195 was the first widely used PET tracer for imaging neuroinflammation. However, its clinical application was limited by a low signal-to-noise ratio resulting from high nonspecific binding and limited brain penetration. Second-generation TSPO tracers exhibited higher affinity and improved imaging performance but remained susceptible to the TSPO rs6971 single-nucleotide polymorphism, which causes substantial interindividual variability and compromises quantitative accuracy. These limitations have driven the development of newer-generation TSPO radiotracers with reduced sensitivity to genetic polymorphisms and improved pharmacokinetic properties. Among these, [¹⁸F]GE-180 has been extensively investigated in AD and multiple sclerosis, whereas emerging tracers such as [¹⁸F]LW223 are undergoing early human evaluation to further optimize quantitative performance and clinical applicability.¹⁰

Despite continuous optimization of TSPO radiopharmaceuticals, TSPO lacks sufficient cellular and inflammatory-state specificity. Consequently, increasing efforts have focused on alternative neuroinflammatory targets that may provide more specific biological information, including monoamine oxidase B, purinergic receptor P2X7, colony-stimulating factor 1 receptor, and sphingosine-1-phosphate receptor 1. These emerging radiopharmaceuticals may complement TSPO imaging by enabling more precise characterization of distinct cellular and molecular components of neuroinflammation across different stages of NDDs.

CONCLUSION

The evolution of molecular imaging in NDDs over the past two decades has been nothing short of transformative, evolving from a diagnostic tool to a platform spanning the entire drug development pipeline, including target validation, patient selection, and therapeutic monitoring. While Aβ and tau imaging have achieved a high degree of clinical maturity, reliable radiopharmaceuticals for α-syn, TDP-43, mHTT, and other pathological proteins remain a major unmet need. Neuroinflammation-targeted PET represents another

emerging direction. Designing superior radiopharmaceuticals for these challenging molecular targets represents both a significant challenge and a compelling opportunity for medicinal chemists and pharmacists today.

Looking forward, the ultimate goal is a comprehensive molecular imaging framework that enables simultaneous or sequential interrogation of multiple pathological processes, including proteinopathies and neuroinflammation, within individual patients, thereby allowing precise disease subtyping and detection of mixed pathology. Achieving this vision would resolve the diagnostic uncertainty that has long challenged the field, moving NDDs from a clinical puzzle to a biologically definable and therapeutically targetable spectrum of disorders.

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Y.Z. and H.F. contributed equally to this paper. Y.Z. and H.F. wrote and revised the manuscript. X.L. supervised the manuscript. J.R. proposed the concept and supervised the manuscript. All authors contributed to the manuscript and approved the final version.

DECLARATION OF INTERESTS

The authors declare no competing interests.

ETHICAL STATEMENT AND PATIENT CONSENT

Not applicable.

DATA AND CODE AVAILABILITY

Not applicable.