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*Editorial*

# Novel tracers and emerging targets for positron emission tomography in Alzheimer's disease and related dementias

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**Abstract:** This symposium provided an extensive overview of emerging positron emission tomography (PET) tracers and targets for Alzheimer's disease (AD) and related dementias (ADRD), highlighting novel approaches for imaging neuroinflammation, neurotransmitter systems, mitochondrial dysfunction, and proteinopathies. Key developments included the harmonization of PET data across cohorts, new tau and alpha-synuclein tracers, and critical advancements in understanding neurodegenerative disease heterogeneity through integrated imaging, genetic, and pathological studies.

**Keywords:** PET imaging, Alzheimer's disease, dementia, biomarkers, tau, amyloid, neuroinflammation

## Introduction

The symposium "Novel Tracers and Emerging Targets for Positron Emission Tomography in Alzheimer's Disease and Related Dementias", organized by the National Institute on Aging, brought together leading researchers and clinicians to discuss recent advances and ongoing research in PET imaging for Alzheimer's disease (AD) and related dementias (ADRD) [1, 2]. Given the complexity and heterogeneity of these neurodegenerative diseases [3], PET imaging plays a critical role in early diagnosis, disease monitoring, understanding pathological mechanisms, and assessing therapeutic efficacy. The event emphasized collaborative research efforts, integration of multimodal imaging approaches, and innovative technological advancements aimed at improving biomarker accuracy [4], exploring novel biological targets, and developing next-generation PET tracers. By facilitating dialogue among experts from various disciplines, the symposium aimed to enhance translational research and clinical outcomes for patients affected by AD and ADRD.

## Meeting summary

*Session 1: Integrated platforms*

(1) Researchers presented significant efforts such as ADNI, SCAN, IDEAS, HEAD, and CLARiTI [5], highlighting their collective impact on enhancing standardization and harmonization of PET imaging protocols. These initiatives have created comprehensive platforms that allow cross-study comparisons, fostering large-scale collaborative research efforts. The introduction of tools like BPIP (Berkeley PET Imaging Pipeline) and rPOP (Robust PET-Only Processing) has been instrumental in facilitating these processes, enabling more consistent data interpretation across diverse cohorts.

(2) Significant demographic insights were gained, revealing crucial variations in biomarkers related to factors such as sex, ethnicity, APOE genotype, and educational background. These findings have underscored the importance of including diverse populations in clinical studies to enhance the generalizability and applicability of PET imaging results in clinical practice.

*Session 2: Modeling disease spread and progression*

(1) Discussions focused on the predictive power of biomarkers such as amyloid and tau, which can be detected decades before clinical symptoms manifest, offering significant opportunities for early intervention and improved disease management. Innovative modeling techniques, including the PET-based "biomarker clocks", were highlighted for their potential in accurately tracking disease progression and informing clinical prognosis [6].

(2) Further, the LEADS study provided new insights into subtypes of early-onset Alzheimer's disease through distinct patterns of tau PET imaging. The integration of multimodal imaging, digital pathology, and genetic studies was emphasized as essential for a deeper understanding of disease heterogeneity, informing personalized diagnostic and therapeutic strategies.

*Session 3: PET imaging in ADRDs*

(1) Presentations addressed significant progress in PET imaging tracers [7], supported by structural insights from Cryo-EM techniques. Notably, the development of tracers like alpha-synuclein tracer [$^{11}$C]M503 and tau tracer [$^{18}$F]OXD-2314 were highlighted as milestones, providing



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greater specificity for disease mechanisms and enhancing diagnostic clarity in conditions such as Dementia with Lewy Bodies (DLB) and limbic-predominant age-related TDP-43 encephalopathy (LATE-NC).

(2) The session also explored the utility of synaptic density imaging (SV2A PET) as a complementary approach to traditional amyloid and tau imaging, highlighting its potential role in understanding synaptic health and cognitive decline across various ADRDs.

*Panel discussion 1*

(1) Panelists addressed practical challenges and barriers to integrating advanced PET imaging techniques into clinical practice. Critical needs identified included establishing precise biomarker interpretation frameworks, enhancing standards for image acquisition and reading, and reducing barriers to clinical implementation.

(2) The importance of considering social determinants and environmental factors in disease interpretation was highlighted, reflecting a broader need to understand how these factors influence disease risk and progression. Additionally, participants discussed the urgent necessity of developing new, more specific PET tracers to enhance clinical diagnostics and monitoring.

*Session 4: Neuroinflammation*

(1) Experts discussed the intricate roles of neuroinflammation in Alzheimer's and related dementias, highlighting that inflammation may initially offer protective effects but become detrimental as the disease progresses. Advanced imaging tracers such as TSPO, SMBT1 targeting MAO-B, and CSF1R were presented [8], demonstrating their utility in visualizing microglial and astroglial activation.

(2) Studies integrating imaging biomarkers with fluid biomarkers have provided new perspectives on neuroinflammation as an early and central event in the pathogenesis of AD. Researchers emphasized the critical need to refine these imaging approaches and to better understand inflammatory mechanisms to facilitate targeted therapeutic interventions.

*Panel discussion 2*

(1) This discussion centered around the complexities associated with neuroinflammation imaging tracers, particularly TSPO and MAO-B, highlighting limitations such as specificity issues and interpretation challenges. Panelists called for continued parallel development of more targeted and specific neuroinflammation tracers.

(2) There was also consensus on the need for integrating neuroinflammation imaging data with biological, environmental, and physiological data to better interpret PET findings. This comprehensive approach was emphasized as crucial for advancing the clinical relevance and accuracy of neuroinflammation imaging studies.

*Session 5: Emerging tracers and future opportunities*

(1) The symposium highlighted ongoing research efforts aimed at exploring novel imaging targets beyond traditional amyloid-beta and tau markers. Topics covered included neurotransmitter systems, mitochondrial dysfunction (particularly complex I), epigenetic alterations, cholesterol metabolism, and synaptic density. These new targets reflect a broadening understanding of the molecular complexities underlying AD and related dementias.

(2) Click chemistry emerged as a transformative technique enabling the rapid and precise development of PET tracers, exemplified by the FDA-approved tau tracer T807 (Flortaucipir) [9]. This technology promises to accelerate tracer discovery and optimization, potentially leading to more effective and earlier disease detection and monitoring.

*Panel discussion 3*

(1) The final panel discussion explored strategies for selecting effective PET tracer targets. Key points included balancing the scientific potential of novel tracers with practical considerations such as patient burden, cost, regulatory hurdles, and logistical challenges in dissemination.

(2) Participants underscored the importance of collaboration between academia and industry to optimize tracer development and validation processes. The panel concluded by emphasizing the necessity for strategic selection and efficient dissemination of new tracers to maximize their clinical impact and accelerate translational outcomes.

## Future research directions

Building on insights shared throughout the symposium, several key areas have emerged as priorities for advancing PET imaging research in Alzheimer's disease and related dementias. As summarized in **Table 1**, these include standardizing imaging protocols and promoting demographic diversity to enhance data harmonization and generalizability. There is also a strong emphasis on developing biomarker-based predictive models, characterizing disease subtypes using multimodal imaging, and integrating genetic and pathological data to capture disease heterogeneity. The refinement of tracers - particularly those targeting alpha-synuclein, tau, and synaptic density - and the development of more specific tools for neuroinflammation imaging are critical next steps. Additionally, expanding the scope of molecular targets and leveraging rapid development strategies such as click chemistry will accelerate the discovery of more precise and clinically relevant biomarkers. These directions reflect

**Table 1.** Recommendations for future research priorities and directions

| Session | Example |
|---|---|
| 1 | Enhancing standardization and harmonization across PET imaging protocols to enable reliable comparisons between different studies. |
| 2 | Develop biomarker-based predictive models; characterize disease subtypes; integrate multimodal and genetic data. |
| 3 | Refine novel tracers (alpha-synuclein, tau, synaptic density); resolve technical tracer challenges. |
| 4 | Improve specificity of neuroinflammation tracers; combine imaging and fluid biomarkers; explore central-peripheral inflammation links. |
| 5 | Explore new molecular targets; leverage click chemistry for rapid tracer development; enhance academic-industry collaboration. |

a collective effort to enhance diagnostic accuracy, monitor disease progression, and support personalized therapeutic strategies.

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## Disclosure of conflict of interest

None.

## Abbreviations

4R, four repeat; AD, Alzheimer's Disease; ADNI, Alzheimer's Disease Neuroimaging Initiative; ADRC, Alzheimer's Disease Research Center; ADRD, Alzheimer's disease-related dementia; APOE, apolipoprotein E ATN β-Amyloid/Tau/Neurodegeneration; BEHOLD, BioEnergetic Hallmarks of Lewy Body Dementia; BP, binding potential; BPIP, Berkeley PET Imaging Pipeline; CB-2, cannabinoid receptors type 2; CBD, Corticobasal Degeneration; CED, Coverage with Evidence Development; CLARiTI, Consortium for Clarity in ADRD Research through Imaging; COX-2, cyclooxygenase-2; Cryo-EM, cryo-electron microscopy; CSF, cerebrospinal fluid; CSF-R1, colony stimulating factor-1 receptor; CTE, Chronic Traumatic Encephalopathy; CYP46A1, cytochrome P450 family 46 subfamily A member 1/cholesterol 24-hydroxylase; DLB, Dementia with Lewy Bodies; EAAT, excitatory amino acid transporter; FBP8, fibrin binding probe 8; FDG, fluorodeoxyglucose; FTD, frontotemporal dementia; FTLD, frontotemporal lobar degeneration; GFAP, glial fibrillary acidic protein; GWAS, genome-wide association studies; HDAC, histone deacetylase; HEAD, Longitudinal multi-center head-to-head harmonization of tau PET tracers study; IDEAS, Imaging Dementia-Evidence for Amyloid Scanning; IL1RAP, interleukin-1 receptor accessory protein; LANS, Limbic-predominant Amnestic Neurodegenerative Syndrome 3; LATE-NC, Limbic-predominant age-related; TDP-43, encephalopathy neuropathologic change; LBD, Lewy body disease; LEADS, Longitudinal Early Onset Alzheimer's Disease Study; LPS, lipopolysaccharide; LONI, Laboratory of Neuroimaging; MAO-B, monoamine oxidase B; MCI, mild cognitive impairment; Mito C1, mitochondrial complex I; MR, magnetic resonance; MRI, magnetic resonance imaging; PBMC, peripheral blood mononuclear cell; P2X7, purinergic receptor P2X 7; PD, Parkinson's Disease; PiB, Pittsburgh Compound-B; PET, positron emission tomography; PSP, Progressive Supranuclear Palsy; Rpop, Robust PET-Only Processing; SCAN, Standardized Centralized Alzheimer's & Related Dementias Neuroimaging; SUVR, standardized uptake value ratio; SV2A, synaptic vesicle glycoprotein 2A; TDP-43, transactive response DNA-binding protein 43; TREM2, Triggering Receptor Expressed on Myeloid cells 2; TSPO, translocator protein; UPDRS, United Parkinson's Disease Rating Scale.

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## References

[1] Rong J, Haider A, Jeppesen TE, Josephson L and Liang SH. Radiochemistry for positron emission tomography. Nat Comm 2023; 14: 3257.

[2] Deng X, Rong J, Wang L, Vasdev N, Zhang L, Josephson L and Liang SH. Chemistry for positron emission tomography: recent advances in $^{11}$C-, $^{18}$F-, $^{13}$N-, and $^{15}$O-Labeling reactions. Angew Chem Int Ed Engl 2019; 58: 2580-2605.

[3] Scheltens P, Blennow K, Breteler MM, de Strooper B, Frisoni GB, Salloway S and Van der Flier WM. Alzheimer's disease. Lancet 2016; 388: 505-17.

[4] Hansson O, Blennow K, Zetterberg H and Dage J. Blood biomarkers for Alzheimer's disease in clinical practice and trials. Nat Aging 2023; 3: 506-519.

[5] Mormino EC, Biber SA, Rahman-Filipiak A, Arfanakis K, Clark L, Dage JL, Detre JA, Dickerson BC, Donohue MC, Kecskemeti S, Hohman TJ, Jagust WJ, Keene DC, Kukull W, Levendovszky SR, Rosen H, Thompson PM, Villemagne VL, Wolk DA, Okonkwo OC, Rabinvovici GD, Rivera-Mindt M, Foroud T and Johnson SC. The consortium for clarity in ADRD Research Through Imaging (CLARiTI). Alzheimers Dement 2025; 21: e14383.

[6] Dukart J, Kherif F, Mueller K, Adaszewski S, Schroeter ML, Frackowiak RS and Draganski B; Alzheimer's Disease Neuroimaging Initiative. Generative FDG-PET and MRI model

of aging and disease progression in Alzheimer's disease. PLoS Comput Biol 2013; 9: e1002987.
[7] Valotassiou V, Malamitsi J, Papatriantafyllou J, Dardiotis E, Tsougos I, Psimadas D, Alexiou S, Hadjigeorgiou G and Georgoulias P. SPECT and PET imaging in Alzheimer's disease. Ann Nucl Med 2018; 32: 583-593.
[8] Zhou R, Ji B, Kong Y, Qin L, Ren W, Guan Y and Ni R. PET imaging of neuroinflammation in Alzheimer's disease. Front Immunol 2021; 12: 739130.
[9] Okamura N, Harada R, Ishiki A, Kikuchi A, Nakamura T and Kudo Y. The development and validation of tau PET tracers: current status and future directions. Clin Transl Imaging 2018; 6: 305-316.