

Novel Tracers and Emerging Targets for Position Emission Tomography in Alzheimer's Disease and Related Dementias

March 12–13, 2025

Acronym Definitions

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 Amnesic Neurodegenerative Syndrome

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

Executive Summary

In Session 1, the speakers discussed the critical advancements and standardization of positron emission tomography (PET) imaging across major Alzheimer's disease (AD) research initiatives, demonstrating how coordinated approaches are enhancing our understanding of neurodegenerative diseases. Through projects like the Alzheimer's Disease Neuroimaging Initiative (ADNI) and the Standardized Centralized Alzheimer's & Related Dementias Neuroimaging (SCAN) project, the Imaging Dementia—Evidence for Amyloid Scanning (IDEAS) studies, the Longitudinal multi-center head-to-head harmonization of tau PET tracers study (HEAD), the Longitudinal Early Onset Alzheimer's Disease Study (LEADS), and the Consortium for Clarity in ADRD Research through Imaging (CLARiTI), researchers have established standardized protocols and processing pipelines that enable more reliable cross-study comparisons and findings. Public sharing of these tools has extended their reach and accelerates progress. Key technological developments for harmonizing beta-amyloid and tau PET data across different tracers included the Berkeley PET Imaging Pipeline (BPIP), the Robust PET-Only Processing (rPOP) system, and the Unit Ecosystem. These approaches have revealed important influences on biomarker relationships, including sex differences in tau accumulation, *APOE4* effects, and racial/ethnic variations in amyloid positivity. The research has had direct clinical impacts, contributing to regulatory approval and coverage of amyloid PET scan, while also advancing our understanding of co-pathologies in neurodegenerative diseases. The integration of multiple imaging modalities, standardized protocols, and diverse participant populations across these platforms represents a significant step forward in improving the diagnosis, understanding, and treatment of Alzheimer's disease and related dementias (AD/ADRD).

In Session 2, the speakers discussed how to model the spread and progression of AD and related dementias with various biomarkers, imaging techniques, and genetic studies. We learned that amyloid and tau biomarkers develop predictably over decades, even before the onset of clinical symptoms, and that there are distinct subtypes of early-onset AD based on tau PET patterns, highlighting disease heterogeneity. The integration of multiple approaches—including PET imaging, neuropathological evaluation, and genetic studies—has advanced our understanding of disease mechanisms and progression. Some important discoveries include the early deposition of tau in subcortical regions before amyloid development, the complex interaction between tau and amyloid pathologies, and the identification of genetic associations through PET-based endophenotype studies. This session emphasized the value of interdisciplinary approaches and advanced imaging techniques in characterizing disease heterogeneity, understanding co-pathologies, and potentially improving patient monitoring and treatment outcomes.

In Session 3, the speakers discussed the critical role of PET imaging in understanding and diagnosing ADRDs. Cryo-EM technology has revealed diverse protein assemblies and distinct amyloid filament structures that are associated with different neurodegenerative diseases, which has implications for developing targeted PET imaging tracers. Furthermore, notable developments in this field include the identification of [^{11}C]M503 as a promising alpha-synuclein tracer, although it faces challenges with metabolite issues, and the development of tau tracers like [^{18}F]OXD-2314, which demonstrates potential in imaging various non-AD tauopathies. The speakers in this session emphasized the complexity of conditions like Dementia with Lewy Bodies (DLB) and highlighted the importance of multimodality molecular imaging for understanding pathologic and clinical heterogeneity. New approaches were discussed, including the innovative State Viewer framework using fluorodeoxyglucose (FDG)-PET scans to generate a global representation of functional state across the brain, which can improve diagnostic accuracy in AD and ADRDs and the emergence of synaptic density imaging through SV2A PET as a complementary tool to traditional amyloid and tau imaging. The speakers collectively emphasized the need for multiple tracers and the continued development of new imaging techniques.

In Panel Discussion 1, the panelists discussed several critical challenges in translating advanced PET imaging research into effective clinical practice for neurodegenerative diseases, highlighting critical needs such as: the development of more precise and nuanced biomarker interpretation frameworks; improved standards in image acquisition, reading, and clinical implementation; and the removal of barriers to clinical implementation. The panel discussed the complexities of accurately interpreting PET biomarkers and the importance of developing a more nuanced understanding of detected pathological changes. Furthermore, they addressed the importance of considering social determinants and environmental factors in interpreting PET biomarker data because they likely play a significant role in shaping an individual's long-term risk and disease trajectory. The panel also discussed that, while visual interpretation of PET scans remains crucial, sophisticated quantitative analysis methods are needed to provide additional insights into disease staging and progression. Moreover, although neuroinflammation is increasingly recognized as a crucial factor in neurodegenerative diseases, the panel noted that current PET probes targeting microglia are limited by insufficient neurobiology research and the field is still in the early stages of comprehensively understanding its mechanisms, variability, and implications for the development of interventions.

In Session 4, the speakers discussed the complex and evolving understanding of neuroinflammation in AD/ADRD. While inflammation was initially viewed as uniformly harmful, research has shown that microglial activation may play different roles at different

disease stages; it may be potentially protective early on but detrimental as disease progresses. Key scientific advances include the development of translocator protein (TSPO) PET tracers that have evolved through three generations with improving capabilities, although challenges remain with tracer specificity and interpretation. The speakers highlighted the importance of integrating multiple research approaches, including PET imaging, blood biomarkers, and brain connectivity studies, to better understand neuroinflammatory processes. Some significant findings included the discovery that astrogliosis may precede amyloid accumulation, the identification of numerous AD risk genes related to the immune system, and the observation that inflammation peaks at progression boundaries in focal neurodegeneration. Additionally, important connections revealed that the peripheral innate immune system plays a crucial role in dementia progression. Challenges in the field include the limited number of available imaging agents, the complexity of interpreting inflammatory markers, and the need for improved ligands that can accurately measure brain inflammatory processes.

In Panel Discussion 2, the panelists discussed neuroinflammation imaging biomarkers in neurodegenerative diseases. A central theme was the complex relationship between imaging tracers like TSPO and monoamine oxidase B (MAO-B) and their biological significance, with panelists acknowledging that while these tracers may not be direct therapeutic targets, they serve as valuable proxies for understanding disease pathophysiology. The panel highlighted significant challenges, including limitations of TSPO. A key scientific advancement discussed was the development of the [18F]SMBT-1 tracer; however, questions remain about its potential implementation in clinical trials. It is expected that [18F]SMBT-1 binding would provide information regarding astrocyte reactivity as it is pronominally expressed by the astrocyte's mitochondria. The panelists emphasized the need for parallel development of new, more specific tracers for microglia while continuing to utilize existing ones, particularly highlighting the importance of developing better synaptic markers and specific indicators for different microglial states. The discussion also underscored the importance of combining multiple approaches to better understand neuroinflammatory processes in AD/ADRD, while considering various environmental and physiological factors that might influence these markers.

In Session 5, the speakers discussed the critical need to expand neuroimaging techniques beyond traditional amyloid and tau approaches to better understand neurodegenerative diseases like AD/ADRD. Researchers presented promising developments in AD and ADRD PET studies, by targeting various neurochemical and molecular systems and processes, including neurotransmitter systems (serotonin, dopamine, acetylcholine, GABA, and glutamate), as well as novel targets, such as mitochondrial complex I, epigenetic markers, voltage-gated potassium channels, and cholesterol metabolism. There was discussion of

observations of early neurotransmitter system degeneration before significant amyloid accumulation, potential therapeutic interventions, and the importance of investigating complex biological processes such as oxidative damage, DNA damage, neuronal subtypes, and blood–brain barrier function. These observations have been informed by combining radiotracers for neurochemical or molecular with radiotracers or blood/CSF biomarkers for amyloid. The speakers emphasized the need for more comprehensive research that explores preclinical conditions, considering factors such as *APOE4* carrier status and sex differences, and developing next-generation tracers capable of capturing more dynamic and earlier stages of neurodegeneration. Click chemistry was also highlighted as a powerful tool for rapidly developing and optimizing molecular tracers, demonstrating commitment to precision neuroscience and facilitating a deeper understanding of neurodegenerative disease mechanisms.

In Panel Discussion 3, the participants highlighted several key considerations in choosing effective targets for PET tracer development. On the promising side, participants noted the extraordinary technical progress in tracer development, with tracers now available for a wide range of pathways implicated in neurodegenerative diseases. However, they emphasized the need to carefully prioritize which targets to pursue with PET, given patient burden of PET imaging. Challenges include the variability often seen in initial studies with new tracers, as well as the significant regulatory and logistical hurdles in getting tracers approved for clinical use. Participants discussed constraints such as high costs and the need to balance PET imaging with other biomarker modalities like blood and cerebrospinal fluid (CSF) tests. Overall, the discussion underscored the importance of strategic target selection, efficient dissemination of tracer development, and synergy between academia and industry to maximize the impact of these powerful imaging tools.

Meeting Summary

March 12, 2025

Opening Remarks: Day 1

Alessandra Rovescalli, Division of Neuroscience, National Institute on Aging

Dr. Rovescalli welcomed attendees to the workshop. This workshop, organized by the National Institute on Aging, focused on PET imaging in Alzheimer's disease and related dementias (AD/ADRD). This topic is in high demand for discussion owing to recent developments in the field, including the emergence of blood biomarkers for AD and dementia, the development of disease-modifying drugs, and an increased awareness of the impact of multiple etiologies and existing oncopathologies. This workshop provides a comprehensive overview of current PET imaging applications in AD/ADRD contexts, while facilitating discussions about the potentials of PET imaging and resources that PET imaging can provide.

Session 1: Integrated Platforms

1.1 Harmonization of PET data for the Analyses of Multiple Cohorts: Overview of SCAN and ADNI

Bill Jagust, University of California, Berkeley

ADNI, a longitudinal study that aims to understand and validate biomarkers in AD, has been foundational in establishing standardized protocols for PET imaging, including specific acquisition parameters, resolution standards, and consistent analysis methods. Since its inception in 2004, ADNI has accumulated over 10,000 PET scans across multiple imaging modalities, creating a robust and sharable database for Alzheimer's disease research

BPIP represents a sophisticated processing system that handles images through multiple stages: initial upload to Laboratory of Neuroimaging (LONI) at the University of Southern California, privacy-protecting defacing procedures, quality control at the University of Michigan, and final analysis at UC Berkeley. This pipeline includes both a rapid magnetic resonance imaging (MRI)-free analysis for quick visual reads and a more comprehensive MRI-based analysis that serves as the reference standard. This standardized approach has been successfully implemented across numerous major studies, including SCAN, which

has independently collected approximately 4,000 PET scans and features a more diverse participant population than ADNI.

Research has yielded several significant findings across these large datasets. Notably, there is remarkable consistency in amyloid positivity rates between ADNI and SCAN studies, and different PET tracers exhibit similar performance when standardized methods are applied. Large-scale analyses have revealed important demographic influences on biomarker relationships, including sex differences in tau accumulation (e.g., women showing higher entorhinal tau levels), *APOE4* carrier status effects, correlations with educational level, and race/ethnicity-based differences.

The standardization of methods has created a powerful platform for detecting small but potentially significant effects that require large sample sizes to identify. This work has established a valuable foundation for future Alzheimer's research and clinical trials, with data being made publicly available through various platforms. The success of these standardized protocols has led to their adoption across multiple research centers and studies, facilitating more comprehensive and comparable research outcomes in the field of AD research.

1.2 Clinical Use of PET in the “Real World”: Overview of the IDEAS/New IDEAS Studies

Gil Rabinovici, University of California, San Francisco

The IDEAS and New IDEAS studies examined the clinical utility of amyloid PET scans in real-world memory care settings. The research was conducted in partnership with Medicare and involved nearly 18,000 scans across nearly 600 clinical sites. The primary objectives were to evaluate how amyloid PET scans impact patient management and healthcare outcomes for Medicare beneficiaries with mild cognitive impairment (MCI) or dementia.

The first IDEAS study revealed significant changes in patient management, with over 60% of participants experiencing modifications in their treatment approach. Notably, the scans led to substantial diagnostic shifts, changing the diagnosis in approximately 25% of cases. In patients with a positive amyloid PET scan, AD diagnosis rates increased from 80% to over 95%, whereas negative scans dramatically reduced AD diagnosis rates from over 70% to just 10%. This study also highlighted important demographic variations, with significantly higher amyloid PET positivity rates in white individuals compared with Black, Hispanic, and Asian individuals. While this study demonstrated remarkable improvements in diagnostic confidence and AD patient management, it exhibited minimal impact on 12-month

healthcare utilization as determined by emergency room visits and overall cost. This research was crucial in informing policy, contributing to Medicare's decision to end its requirement for Coverage with Evidence Development (CED) and allowing Medicare Administrative Contractors to determine coverage for amyloid PET scans in October 2023.

The follow-up New IDEAS study expanded on the original research, achieving better demographic representation. This study also established a biorepository, banking plasma and DNA samples from approximately 1,500 individuals. Significant differences were found in demographic groups related to social determinants of health, vascular risk factor prevalence, cognitive impairment stage and diagnosis, and rates of amyloid PET positivity.

A particularly innovative aspect of this research was the development of a PET image processing pipeline (rPOP) that successfully processed 96% of archived scans for research purposes. Additional analyses revealed correlations with sex and APOE genotype, closely mirroring findings from the ADNI. This tool is publicly available via GitHub.

These real-world investigations are important for understanding amyloid PET's clinical applications, particularly as new disease-modifying therapies emerge. Furthermore, the entire dataset is available to the scientific community, providing a valuable resource for future investigations.

1.3 Longitudinal Multicenter Head-to-Head Harmonization of Tau PET Tracers: The HEAD Study

Suzanne Baker, Lawrence Berkeley National Laboratory; with Tharick Pascoal, University of Pittsburgh

The HEAD Study is a comprehensive multi-site research project aimed at comparing and standardizing multiple tau PET tracers across different research centers in the United States, Canada, and Spain. This study recruited participants across various cognitive stages, and age groups, including young individuals, cognitively unimpaired, MCI, and AD elders. This research compared multiple tau PET tracers, primarily examining Flortaucipir, MK6240, PI2620, and RO948. Detailed analyses were conducted on tracer performance, noting both similarities and differences in how these tracers detect and visualize tau pathology. A key finding was the varying dynamic ranges of tracers, with MK6240 showing the broadest range and the greatest detection sensitivity. Interestingly, Flortaucipir exhibited an early signal in the temporal cortex that was not observed with MK6240.

To address the challenges of tracer variability, the HEAD Study team developed the Unit Ecosystem, a set of user-friendly tools designed to harmonize tau PET quantification and

visualization. The Uniτ Ecosystem includes tools such as a quantitative harmonization tool that can automatically process raw PET and MRI images and a visual reading tool that guides interpretation by overlaying brain region outlines. They also created the Uni-tau scale, a novel method for converting standardized uptake value ratio (SUVR) values from different tracers to a common scale; this scale can improve comparability across studies.

These tools have both research and potential clinical applications. The visual reading method reduced disagreement between tracers by approximately half, creating a standardized approach. The tools have already gained significant traction, with over 3,000 accesses in 11 countries, primarily from academic institutions. The broader goal is to increase the usability and generalizability of tau PET research, addressing current challenges in comparing results across different tracers and research sites. By developing user-friendly tools and a standardized approach, the HEAD Study can advance our understanding of tau pathology in neurodegenerative diseases, particularly AD.

1.4 Impact of Co-pathologies and Introduction of CLARiTI

Sterling Johnson, University of Wisconsin; with Dirk Keene, University of Washington

The ADRC CLARiTI project is a multi-site research initiative that aims to facilitate accurate and comprehensive biological diagnoses across the complex landscape of dementias, based on biomarkers rather than clinical syndromes. The primary goal is to create individual etiologic profiles that capture the multiple pathologies potentially present in a single individual, recognizing that neurodegenerative conditions often involve overlapping disease processes.

This study plans to enroll 2,000 individuals through the NIA-funded Alzheimer's Disease Research Centers (ADRCs), with an anticipated participant breakdown of 60% impaired (with MCI or mild dementia) and 40% unimpaired but with risk factors. A key emphasis is on embracing clinical heterogeneity, including diverse presentations like Lewy body disease (LBD), frontotemporal dementia (FTD), atypical Alzheimer's, and cases with vascular pathology. Overlaid on the cognitive and clinical data the ADRCs already collect, the research both leverages and empowers the existing network of 35 centers across the country with 18,000 well-characterized patients and a strong brain donation culture. The study will utilize multiple imaging techniques, including amyloid PET, tau PET, FDG-PET, and MRI, with flexibility for site-specific preferences. The consortium will be ready to adopt PET tracers of other pathologies as they become available. A critical innovative component is the development of a digital pathology resource.

By collecting tissue samples from multiple brain regions and applying advanced digital pathology techniques, researchers hope to correlate pathological findings with PET imaging and biofluid biomarkers. This can help elucidate the biological correlates of biomarkers, how different pathologies contribute to disease progression, and potentially identify new targets for early intervention. This project aims to create an openly accessible digital pathology resource that will help researchers better understand the complex temporal and spatial dynamics between different neurodegenerative pathologies. Together with SCAN, over the next five years the ADRCs expect to contribute approximately 10,000 ATN (b-Amyloid-Tau-Neurodegeneration) data sets from approximately 5,000–8,000 individuals, representing an important resource for Alzheimer’s and related dementia research.

Session 2: Modeling Disease Spread and Progression

2.1 Temporal Models of Disease Progression and PET-Based “Clocks”

Tobey Betthausen, University of Wisconsin

Amyloid and tau biomarkers develop over time, starting before clinical symptoms appear, and the trajectory of these biomarkers are predictable. Researchers can now measure abnormal biomarker levels approximately 20 years before symptom onset.

There have been significant insights into biomarker progression, particularly regarding *APOE4* gene variant carriers. *APOE4* carriers were found to become amyloid positive earlier. Factors like *APOE4* carriage, older amyloid onset age, and female sex can shorten the preclinical time frame from amyloid positivity to dementia, with older amyloid onset age hastening progression more than *APOE4* carriage and sex. Notably, individuals over 70 experienced almost a four-year shorter timeframe for dementia-free survival for amyloid positivity compared with younger participants.

Tracking the spatiotemporal spread of tau from the entorhinal cortex to other brain regions in late-onset sporadic AD has shown that, on average, it takes approximately seven years from amyloid positivity to entorhinal positivity, with a subsequent five-year interval for progression from entorhinal cortex to neocortical brain regions. Female participants were observed to progress slightly faster than males. At approximately 15 years after amyloid onset, about three-quarters of individuals remain dementia-free, compared with virtually no participants remaining dementia-free 15 years after meta-temporal tau onset.

Amyloid and tau trajectories are predictable once individuals become biomarker positive, and it is possible to estimate quantitative measures at other time points, including the age

at which people became amyloid or tau positive, even without direct observation. Older estimated amyloid and tau positivity onset ages are associated with faster progression to dementia, and onset ages may have some prognostic value. Consequently, biomarker-based timelines (i.e., biomarker clocks) can be used to characterize dementia risk in an intuitive time-based manner.

2.2 PET-based Subtypes of AD

Renaud La Joie University of California, San Francisco

Traditionally, researchers have categorized patients based on clinical and demographic features, but emerging research is now using advanced imaging techniques to identify more nuanced disease subtypes. LEADS (Longitudinal Early-Onset Alzheimer's Disease Study) is a study aimed at elucidating early-onset AD and includes patients under 65 years old with MCI or mild dementia.

Using a data-driven algorithm called SuStain, three distinct subtypes of early-onset AD were identified based on tau PET imaging. These subtypes showed three different patterns of tau accumulation: 1) typical, with frontal and temporal–parietal tau distribution; 2) left temporal predominant signal; and 3) posterior, with early and predominant occipital binding. These subtypes were similar across demographic factors like age and sex, but they demonstrated different clinical trajectories over time.

In LEADS, FDG-PET scans were used to better characterize cognitively impaired participants who were amyloid-negative. Although FDG is a non-specific marker (unlike amyloid and tau), the regional patterns can help inform the underlying etiology. Approximately half of these patients had normal scans and were less clinically impaired. This group showed fewer neuropsychiatric symptoms and a higher tendency for more sleep disturbances (e.g., sleep apnea). Among the amyloid-negative patients with abnormal FDG scans, patterns of potential subgroups resembled different conditions such as Lewy body disease or frontotemporal lobar degeneration (FTLD).

There are inherent limitations, such as potential inclusion biases. However, the hope is that LEADS is helpful for characterizing disease heterogeneity, elucidating the drivers of this heterogeneity, and improving patient monitoring.

2.3 Neuropathologic Evaluation of AD/ADRD PET and Fluid Biomarker Changes

Melissa Murray, Mayo Clinic Jacksonville

Early deposition of tau in subcortical regions typically occurs decades before amyloid development. The interaction between tau and amyloid is particularly destructive in AD, with the pathology being highly heterogeneous and complex. In amyloid beta pathology, it is important to understand both the presence of plaques and their molecular characteristics, including post-translational modifications and spatial biology. For example, the neuroinflammatory components surrounding these pathological markers might have clinical value.

Various imaging techniques, including PET scans, can reveal insights into brain pathology. For instance, tau antibodies can be used to understand tangle maturity, but tau accumulation is not a simple linear process. Additionally, FDG-PET can reveal glial pathology in addition to neuronal changes. Although FDG-PET may not be sensitive overall, it reflects various underlying neurodegenerative changes. Some investigations are exploring the relationship between plasma biomarkers and brain pathology. Although strong correlations were demonstrated between plasma tau measures and pathological stages, digital pathology analyses revealed that amyloid remained the stronger contributor.

FDG-PET shows promise for detecting an AD signal because it is sensitive to four-repeat (4R) tauopathies, and it could be helpful to include FDG-PET in differential diagnosis with other modalities. Additionally, such information could help elucidate instances such as non-AD cases that might be amyloid positive or non-AD cases that are amyloid negative but have more of an Alzheimer's phenotype.

Beyond simple target identification, there should be focus on the underlying biology, which can help inform our interpretation of biomarkers and be used to develop novel tracers. Additionally, going from the microscopic to the macroscopic can also help inform clinical decisions. Interdisciplinary approaches that bring together fields such as neuropathology, neuroradiology, and proteomics are important to advance our understanding of neurodegenerative diseases.

2.4 Integration of Neuropathology and Multimodal Imaging Data for Clinical Applications and Studies in ADRD

Paul Yushkevich, University of Pennsylvania

Heterogeneity in AD is a major complicating factor for understanding disease progression and co-pathologies, which complicates our understanding of how different patients might respond to treatments. Advanced imaging techniques can elucidate the heterogeneity of AD/ADRD. In particular, postmortem and antemortem imaging can be used to detect and analyze co-pathologies, which is critical for understanding disease progression and potential treatment responses. For example, this approach can be used to quantitatively characterize the distribution and spread of multiple pathologies and to infer associations between pathologies and neuroimaging signatures.

The imaging approach used involves high-resolution scanning of temporal lobe specimens. Using a multi-stage registration pipeline, serial histological images can be aligned with MRI scans, allowing three-dimensional mapping of pathological features. By scanning temporal lobe specimens, staining for tau, and using quantitative digital pathology techniques, tangle distribution and density can be described in three dimensions, which enables the distribution and spread of tau pathology to be visualized.

This imaging revealed significant insights into tau distribution, particularly in different stages of brain aging. For example, strong anterior–posterior gradient in tangle density was observed in later Braak stages. By examining both postmortem and antemortem images, techniques can be developed to predict the presence of co-pathologies using imaging and mismatch measures.

Although there are limitations to postmortem imaging, such as examining terminal disease stages and accounting for postmortem changes, there is substantial potential in using this approach. These quantitative, three-dimensional pathology mappings can be used to validate biomarkers, characterize anatomy and three-dimensional pathological distributions, and develop probabilistic measures for co-pathology presence and load. This approach can improve our understanding of how different pathologies interact and potentially impact treatment outcomes in neurodegenerative diseases.

2.5 PET as an Endophenotype for Genetic Studies of AD/ADRD

Andrew Saykin, Indiana University

Neuroimaging can serve as an endophenotype for genomic discovery by adding molecular specificity to genetic associations. Imaging genetics has evolved from early targeted approaches to more recent comprehensive genome-wide association studies (GWAS). PET plays an important role because it provides a molecular target that is related to the product of one or more genes. Consequently, PET can be used to understand the genetic underpinnings of neurological conditions.

Early studies in the Alzheimer's Neuroimaging Initiative (ADNI) began with candidate gene analyses, identifying significant associations such as a signal in the *DHCR24* gene related to cholesterol synthesis. As technology advanced, researchers moved to whole genome studies using Florbetapir PET, which revealed important genetic signals, including in *APOE* region genes, and a novel finding that variation in the butyrylcholinesterase gene is associated with amyloid deposition after covarying for age, sex, diagnosis, and *APOE* status.

Subsequent research expanded to examine longitudinal changes in amyloid deposition and discovered microglial-associated genes like interleukin-1 receptor accessory protein (*IL1RAP*). Large-scale meta-analyses emerged, with studies involving over 13,000 participants across multiple cohorts identifying significant genetic associations with amyloid deposition and exploring sex-specific genetic variations. This approach also extended to tau PET studies, with research detecting novel signals in genes related to phosphorylation and microtubule proteins and meta-analysis including over 3,000 participants across 12 cohorts, identifying a novel tau PET locus at *CYP1B1-RMDN2*.

These quantitative endophenotypes are important for understanding disease heterogeneity, can help gain better insight into the mechanistic basis of disease, and are potentially important for prognostic and longitudinal models. Looking forward, research should move beyond existing targets to explore alternative mechanisms. Some future directions of this field include the integration of gene expression studies, single-cell sequencing, advanced analytical techniques including AI/deep learning, and the mechanistic assessment of identified candidate genes with diagnostic or therapeutic potential.

Session 3: PET Imaging in ADRD

3.1 Cryo-EM Structures of Amyloid Filaments: Considerations for PET Imaging Tracers in Neurodegenerative Diseases

Benjamin Ryskeldi-Falcon, Medical Research Council Laboratory of Molecular Biology

Most neurodegenerative diseases share a common hallmark: the pathological assembly of specific proteins, such as amyloid- β , tau, transactive response DNA-binding protein 43 (TDP-43), and α -synuclein in AD and ADRD. These protein assemblies are both markers of disease and play a causal role, as demonstrated by genetic mutations that lead to inherited forms of these conditions.

There is remarkable diversity in protein inclusions, ranging from small punctate assemblies to large cytoplasmic and even extracellular deposits. Electron cryo-microscopy (cryo-EM) has enabled researchers to determine atomic-level structures of protein filaments. The cryo-EM approach allows for direct visualization of protein assemblies, providing insights into the structural mechanisms underlying neurodegenerative diseases and potentially opening new avenues for targeted diagnostic and therapeutic opportunities.

Cryo-EM has revealed novel protein assemblies and that distinct amyloid filament structures characterize different neurodegenerative diseases. For example, results from cryo-EM work showed that a single protein can form multiple different structures of amyloid filament folds, with each fold potentially characterizing different diseases. This structural diversity has implications for binder design; binders used for PET imaging might need to be specifically designed to target particular filament configurations.

Additionally, heteromeric filaments were determined to include proteins like TDP-43, annexin A11, and TAF15 in FTLD. Furthermore, TMEM106B filaments were identified; they accumulate with age and are among the most abundant amyloid filaments in the human brain, even among those with amyloid- β or tau pathology in AD.

Although atomic models from cryo-EM structures can guide the development of PET ligands for amyloid filaments, there are some important considerations when using cryo-EM. For example, because experimental models do not necessarily recapitulate disease-characteristic amyloid filament structures, we need to be cautious when using them as a tool to identify compounds.

3.2 Overview of Alpha-syn Tracers and Selective 4R, 3R Tracers

Robert Mach, University of Pennsylvania

Computational chemistry methods, specifically *in silico* screening techniques, were used to identify and develop novel molecular compounds capable of binding to alpha-synuclein and tau proteins with high specificity, and [^{11}C]M503 was identified as a PET radiotracer.

To discover the alpha-synuclein tracer [^{11}C]M503, an innovative approach was employed involving protein structure analysis and ultra-high-throughput *in silico* screening. A pseudostructure was created and millions of potential compounds screened, ultimately identifying a molecule with high affinity for alpha-synuclein and low affinity for amyloid-beta and tau. Initial non-human primate imaging studies showed promising results, with the tracer demonstrating good brain penetration and rapid washout.

In clinical trials involving healthy controls and patients with Parkinson's disease (PD), the PET imaging data showed differences between the healthy controls and the PD group, with heterogeneity in the PD group and some subjects displaying higher alpha-synuclein signals in brain regions like the brainstem, midbrain, and thalamus. Notably, unexpected uptake was observed in the cerebellum. However, a challenge with the [^{11}C]M503 tracer is a metabolite issue that lowers the signal-to-noise ratio. This necessitated using a narrow window when measuring alpha-synuclein. Regardless, this tracer showed correlations with clinical measures and demonstrated consistency with other alpha-synuclein tracers.

In parallel, a 4R tau tracer was identified using a “fingerprint search” method using fingerprints from known tau ligands and conducted an *in-silico* search. This approach identified a compound called Z-3540, from which an analog was developed ([^3H]JSS20-183A) that shows promising binding characteristics across various tauopathies. Clinical imaging studies for this tracer are currently ongoing.

These findings demonstrate the potential of computational chemistry in developing targeted molecular imaging agents and show that advanced computational techniques can overcome traditional research limitations and provide new insights into neurodegenerative disease mechanisms.

3.3 Overview of Emerging Tau Tracers

Neil Vasdev, University of Toronto

There is a critical need for more sensitive biomarkers for AD/ADRD. Some AD tau PET tracers have been repurposed for non-AD tauopathies, and tau PET tracers can be optimized for non-AD tauopathies.

Initially, research concentrated on developing tau PET tracers like T807 (later renamed Tauvid), which became the first FDA-approved radiopharmaceutical for imaging tau in 2020. The work expanded to include a second-generation tracer, [^{18}F]MK-6240, which demonstrated high sensitivity in Alzheimer's patients. However, tauopathies are complex and are characterized by aggregated tau protein across different isoforms, including those associated with conditions like Pick's Disease, Chronic Traumatic Encephalopathy (CTE), and other neurodegenerative disorders.

Development of a new tau PET tracer called [^{18}F]OXD-2314 showed promising results in imaging various tauopathies, displaying a clear autoradiography signal in AD, Pick's Progressive Supranuclear Palsy (PSP), and Corticobasal Degeneration (CBD). There are other emerging targets as well, and a project that expands the ATN criteria, ATN(S), includes synaptic density. For example, [^{18}F]SynVest-1 is a synaptic density tracer that was identified.

There is a need for multiple tracers to properly image AD/ADRD. Academic-pharmaceutical partnerships and development of new chemistry methods are important for expanding the toolbox of neuroimaging techniques, although there is a critical shortage of radiopharmaceutical scientists that are needed to fill this void.

3.4 Imaging of the Pathologic Heterogeneity Associated with Alpha-synucleinopathies with PET

Kejal Kantarci, Mayo Clinic Rochester

DLB is complex, with multiple pathologies contributing to the clinical syndrome. Amyloid positivity is common in DLB. Both amyloid and tau are associated with faster disease progression and lower survival, and they are associated with worsening in biomarkers for neurodegeneration. Imaging the regional distribution of alpha-synuclein can reveal the interactions among protein aggregates influencing neurodegeneration and enable the design of clinical trials with multi-agent approaches.

Innovative imaging techniques—particularly FDG-PET—have demonstrated promising insights into DLB progression. For example, the identification of the cingulate island sign in the mid or posterior cingulate gyrus can help distinguish DLB from AD. Additionally, FDG-PET can detect metabolic changes even in early prodromal stages, including isolated REM sleep behavior disorder, revealing both hypometabolism and unexpected hypermetabolism in certain brain regions.

Amyloid and tau imaging provided additional insights into DLB pathology. Diffuse amyloid plaques were found to significantly contribute to amyloid PET signals, and amyloid positivity increased with disease progression. Tau elevation was observed primarily in parietal, temporal, and occipital regions, with notable preservation of the medial temporal lobe. These pathological markers were found to correlate with clinical decline, atrophy rates, and white matter injury.

Multimodality molecular imaging is important for understanding individual-specific pathologic heterogeneity in DLB, and AD biomarker positivity is associated with greater rates of atrophy, faster clinical progression, and reduced survival. Limiting neurodegeneration assessment to the dopaminergic system is insufficient for DLB. Additional biomarkers are needed to comprehensively understand neurodegeneration, and how pathologic heterogeneity contributes to the disease processes.

3.5 Exploiting FDG PET in Limbic-predominant Age-related TDP43-Encephalopathy

David Jones, Mayo Clinic Rochester

Moving beyond traditional molecular descriptions, a functional approach needs to be developed to understand brain diseases. FDG-PET can be used to understand and diagnose neurodegenerative diseases, such as limbic-predominant age-related TDP-43 encephalopathy neuropathologic change (LATE-NC) and AD.

A case was described of an 83-year-old woman who had gradually progressive difficulty with short-term memory. It was suspected that she had mild dementia owing to AD, but some aspects were unusual, such as the degree of hippocampal atrophy. Given the patient's symptoms, FDG-PET showed that the degeneration was targeting the limbic system, and limbic-predominant AD was unlikely because of a lack of deposits. It was determined that the woman had a Limbic-predominant Amnesic Neurodegenerative Syndrome (LANS). Patients with a high-likelihood LANS tend to have slower disease progression, regardless of specific underlying pathologies. Functional descriptions are

important for understanding patient experiences, and these descriptions can provide complementary information to protein pathology.

A novel framework called State Viewer is a clinical decision support tool that uses FDG-PET scans to create a global functional state space. This innovative approach allows clinicians to compare a patient's brain metabolism with a comprehensive database of previously studied cases. This tool substantially improves diagnostic accuracy, reducing reading time by 50% and increasing expert-level consistency in identifying complex neurological conditions.

This approach could potentially map various neurodegenerative conditions, from AD to Lewy body disease, using a graph that visualizes brain function across different cognitive systems. Consequently, FDG-PET has potential as a tool to assess therapeutic response and inform clinical trials targeting limbic degeneration.

3.6 Synaptic PET Imaging in AD/ADRD

Barbara Bendlin, University of Wisconsin

Synaptic loss is a critical feature of neurodegeneration, closely associated with cognitive decline. While markers like amyloid and tau have been central to understanding AD, synaptic density markers are now being explored as potential complements to amyloid and tau. Synaptic vesicle glycoprotein 2A (SV2A) PET imaging is a novel technique for measuring synaptic density in neurological disorders, with a primary emphasis on AD.

The SV2A protein, located on synaptic vesicle membranes, serves as a target for PET imaging. Tracers like [^{11}C]UCB-J and an F18 version have been created for imaging synaptic density. Studies have demonstrated reduced synaptic density in individuals with AD and MCI, particularly in the medial temporal lobe, with the most significant reductions observed in individuals with diagnosed dementia. This reduction is associated with cognitive and clinical phenotypes.

The use of SV2A PET imaging has expanded beyond AD, with investigations into its potential in other neurological conditions such as Parkinson's disease and various neuropsychiatric disorders. However, synaptic density reduction likely does not represent an early preclinical marker, but rather it becomes more pronounced in later stages of neurological diseases.

Validation work, including autopsy studies, has helped show that SV2A PET is measuring actual synaptic density rather than changes in the SV2A protein itself. This technique may

show promise for clinical trials, particularly in assessing potential interventions that may protect the synapse and understanding the neural correlates of symptoms.

Panel Discussion 1

Chairs: Gil Rabinovici and Melissa Murray

Panelists: Suzanne Baker, Tobey Betthauser, David Jones, Kejal Kantarci, Renaud La Joie, Robert Mach, Pedro Rosa-Neto

This panel discussion explored critical gaps and future directions in PET research for neurodegenerative diseases. Each panelist was asked to identify the most urgent current gap in PET imaging research.

Dr. Baker's primary concern was understanding why current amyloid-lowering therapies are only partially effective and not working uniformly across patients. She argued that researchers need to investigate what triggers amyloid buildup, potentially exploring neuroinflammation or demyelination as key initiating factors.

Dr. Kantarci stressed the importance of developing tools that can more effectively track and understand synuclein pathology, particularly in Lewy body diseases. She emphasized the limitations of current α -synuclein seeding assays, which lack comprehensive quantitative and longitudinal assessment capabilities.

Dr. Betthauser advocated for more comprehensive research into social determinants and social factors, which currently have limited data. Drawing parallels to cancer research, he argued that early life experiences and social factors likely have significant long-term impacts on neurodegenerative disease development.

Dr. Jones noted that there are existing barriers that prevent advanced imaging technologies from becoming standard clinical tools. He advocated for improved standards in image acquisition, reading, and clinical implementation, emphasizing the need to bridge the gap between this research and practical patient care.

Dr. La Joie discussed the need for new tracers and a deeper understanding of the tracers. He noted the importance of being able to determine the minimum amount of pathology that can be detected *in vivo* and that there is need to better comprehend the qualitative differences in amyloid and tau deposits.

Dr. Mach discussed the importance of using advances in structural biology to inform tracer design. He emphasized that the field lacks a comprehensive understanding of

neuroinflammation, noting that current PET probes targeting microglia are limited as a result.

Dr. Rosa-Neto highlighted the challenge of translating animal model findings to human immune responses and noted that basic research from animals is not sufficient to tell us what we need in terms of biomarkers. However, he noted that literature from animal models can be used to conceptualize potential targets. Additionally, the development of radiopharmaceuticals is time consuming because it has to be properly validated, which raises questions about how to properly validate these technologies.

The discussion expanded to the complex relationship between amyloid and tau pathologies, the potential transformative impact of anti-amyloid therapies, and the intricate role of neuroinflammation. Participants delved into the complementary use of MRI and PET imaging, with Dr. Kantarci noting the unique insights provided by different imaging modalities.

In discussion of the amyloid–tau relationship, Dr. Jones proposed a cascading network failure model, suggesting that the spatial distribution and functional connections between brain regions play a crucial role in disease progression. Dr. Rabinovici highlighted potential molecular links and the importance of understanding individual patient variations.

The discussion underscored the field's current state of transition, with researchers pushing boundaries to develop more precise, comprehensive, and clinically applicable diagnostic tools. Ultimately, the discussion highlighted the importance of incorporating advanced imaging techniques, genetic insights, and a deeper understanding of molecular and cellular processes to advance our understanding of neurodegenerative diseases.

Welcome: Day 2

Alessandra Rovescalli, Division of Neuroscience, National Institute on Aging

Dr. Rovescalli welcomed attendees back to the workshop. Day 2 of the workshop would consist of two main sessions focusing on critical areas. The morning session would delve into neuroinflammation, examining its complex mechanisms and implications, whereas the afternoon session would explore emerging tracers and needs of the field. Each session would conclude with a panel discussion, providing participants with comprehensive insights and opportunities for in-depth dialogue about the latest developments in PET imaging research in AD/ADRD.

Session 4: Neuroinflammation

4.1 Overview of Immune Activation in Alzheimer's Disease

David Morgan, Michigan State University

There is an intricate role of inflammation and microglia in AD, which challenges the simplistic view that inflammation is uniformly harmful. The inflammation hypothesis has been in existence for at least 40 years, and there are four basic components that support the idea that inflammation is pathogenic in AD: postmortem central nervous system inflammation, risk reduction by anti-inflammatory drugs, genetic risk factors involved in cases with immune activation, and neurotoxicity of amyloid-beta-activated microglia *in vitro*. The general concept is that inflammation is in a positive feedback loop with amyloidosis.

Key research from the 1980s and 1990s first suggested inflammatory processes might be significant in disease progression. Initially, inflammation was believed to be detrimental, and individuals using anti-inflammatory drugs showed reduced AD risk; however, clinical trials of anti-inflammatory treatments proved ineffective. Dr. Morgan suggested that the observed reduced AD risk might stem from underlying physiological traits rather than the drugs themselves.

Experimental studies with mouse models revealed that vaccinations and lipopolysaccharide (LPS) injections that activated the immune system helped clear amyloid deposits in some cases. However, the same interventions had different effects on tau pathology, indicating that immune responses might differ depending on the disease stage and specific pathological process.

Large GWAS in the 2010s have provided further insight into many AD risk genes related to the immune system, identifying several genes associated with AD risk (e.g., presenilin and

amyloidosis-promoting genes) that were also associated with the innate immune system. For example, a loss-of-function variant of the *TREM2* gene increases AD risk; this could be related to the multiple functions of microglia, including phagocytosis, synaptic pruning, cytokine and chemokine release, and antigen presentation.

It is not clear why some individuals begin developing amyloidosis early and others much later. Microglial activation may play different roles at different stages of AD. Initially, it might help prevent or slow disease onset by managing early amyloid seeds. Conversely, as AD progresses, the same inflammatory response can become detrimental, potentially exacerbating tau pathology and neurodegeneration. Therefore, the microglial activation state may play different roles in preventing the onset of AD.

4.2 Imaging Glia and Neuroinflammation in Alzheimer's Disease

Pedro Rosa-Neto, University of Texas Southwestern Medical Center

From very early stages of AD, inflammation and activation of non-neuronal cells such as microglia and astrocytes have been observed to play a critical role in the disease process. Activation of these brain resident cells is part of the innate immune response to protein aggregation. Inflammatory markers appear to change in early disease stages and are even associated with aging itself. A growing body of evidence supports the notion that inflammation is not necessarily a consequence of disease, but potentially a vulnerability factor that promotes brain protein aggregation. Increased binding of inflammation imaging agents is not uniquely observed in AD but in tissue from patients with cerebrovascular, Lewy body, or TDP-43 pathologies.

Multiple imaging agents and targets are used for assessing glial activation and neuroinflammation processes. Upstream events such as availability of cannabinoid receptors type 2 (CB-2), purinergic receptors (P2X7), colony stimulating factor-1 receptor (CSF-R1), or Triggering Receptor Expressed on Myeloid cells 2 (TREM2) neuroreceptors constitute potential, yet understudied targets. Downstream glial responses following the activation of inflammation receptors constitute an attractive target to assess the status of brain innate immune cells. At the membrane level, the expression of arachidonic acid and upregulation of cyclooxygenase (COX-2) constitute potential targets amenable of PET quantification. Tracers sensitive to the increase of reactive oxidative stress are sensitive to downstream events and associated with activation of inflammation neuroreceptors. The expression of the 18 kDa translocator protein (TSPO) and monoamine oxidase B (MAO-B) occur in the mitochondria preferentially in microglia and astrocytes, respectively.

Metabolic imaging using acetate, sometimes in combination with FDG, have been suggested as a proxy of astrocyte hypermetabolism. However, this conceptual framework is hindered by various methodological limitations.

Novel imaging agents able to quantify these targets are needed for population enrichment in clinical trials, disease monitoring, disease-modifying interventions, target engagement, and measuring therapeutic interventions. However, there is also the need for large-scale studies with glial PET tracers recently developed.

Some key challenges in neuroinflammation research include the limited number of available imaging agents, cost, logistics, number of injections (dose and patient burden), and reliance on tracers for which there are limited suppliers. Additionally, the complexity of interpreting inflammatory markers is a potential issue. This can be addressed by developing comprehensive study designs that simultaneously validate inflammatory biomarkers using both imaging techniques and cerebrospinal fluid measurements. Studies that integrate imaging with fluid inflammation could help accelerate validation between imaging and fluid biomarkers.

4.3 Neuroinflammation: Focus on Astroglial Markers

Victor Villemagne, University of Pittsburgh

Astroglia activation is associated with AD. Astrocytes are the most abundant glial cells in the brain and play critical functions in maintaining brain homeostasis, including synaptic plasticity, neurotransmission regulation, and blood–brain barrier maintenance. Therefore, astroglial markers can be important for understanding neuroinflammation in the context of AD.

SMBT1, a specialized tracer for MAO-B, was used to study astrogliosis across different stages of neurodegeneration. Astrogliosis could be detected before amyloid accumulation became abnormal, suggesting it might precede amyloid accumulation. This tracer showed increased retention with age and varied in distribution across different brain regions, with notable changes in areas like the posterior cingulate and frontal regions.

Astrogliosis is highly correlated with amyloid, particularly in early deposition areas, and exhibited strong associations with plasma glial fibrillary acidic protein (GFAP). Relationships between cardiovascular risk factors, neurodegeneration, and cognitive performance were also explored, revealing that, although these factors might not directly impact amyloid or tau, they are significantly correlated with cortical thickness and neuroinflammation.

Astrogliosis appears to be a strong contributor to cognitive impairment, potentially operating through a non-amyloid pathway or a beta-independent pathway to tau deposition. The main drivers of cognitive decline were identified as cortical thickness atrophy, followed by astrogliosis and tau, rather than amyloid-beta, age, or cardiovascular-related factors.

4.4 PET Imaging of Microglia: Lessons from TSPO Imaging & CSF1-R as a Promising Imaging Target

Ansel Hillmer, University of Michigan

Recent research indicated that microglia challenge from LPS dramatically increased the number of TSPO-expressing cells, but TSPO expression per individual cell was found to remain constant, challenging the assumption that TSPO is a marker of microglial activation. This insight led to the understanding that TSPO imaging primarily captures the number of TSPO-expressing cells rather than their activation state.

CSF1R was explored as a potentially more specific imaging target for microglia. Unlike TSPO, CSF1R is primarily expressed in microglia with very low expression in other brain cells. However, current CSF1R imaging tracers face challenges, including low specific binding and reproducibility when CSF1R levels are very low.

CSF1R imaging has potential to advance understanding of microglia dynamics in AD/DRD onset and progression. However, there are several critical considerations for future microglial imaging, including the need for complementary markers to understand immune responses, careful evaluation of specific binding, consideration of the dynamic nature of immune signaling, and understanding how recent immune events might impact imaging results.

4.5 TSPO PET Tracers-Utility in Early-Onset Dementia and Insights from Clinical Trials

Belen Pascual, Houston Methodist Hospital

TSPO tracers have progressed through three generations, with each iteration addressing previous limitations, although challenges persist. A major consideration across all generations is the rs6971 polymorphism, which affects binding affinity and requires genotype stratification in study design. The first-generation tracer, ^{11}C -(R)PK11195, had low specific binding, poor metabolite profiles, and unstable binding potential (BP), making it

less suitable for clinical applications. Second-generation tracers, including ^{11}C -PBR28, improved signal quality but required careful genotype consideration. While ^{11}C -DPA-713 exhibited the highest signal-to-noise ratio among second-generation tracers, it had an unfavorable metabolic profile, whereas ^{18}F -DPA-713 demonstrated a better metabolite profile but with lower binding. Third-generation tracers aimed to overcome these challenges, but ^{18}F -GE180 showed poor blood–brain barrier penetration, low signal-to-noise ratio, and unfavorable metabolite characteristics. ^{11}C -ER176 emerged as the most promising third-generation tracer, offering a favorable metabolite profile, stable values across different binding affinities, and higher specificity with lower inter-subject variability, making it more suitable for statistically robust clinical studies.

TSPO tracers have been instrumental in mapping inflammation patterns across various neurodegenerative conditions, including frontotemporal dementia (FTD), primary progressive aphasia, and early-onset Alzheimer's disease (AD). These tracers have demonstrated remarkable specificity, revealing distinct inflammatory profiles that align with the brain regions affected in each disease, providing critical insights into the spatial dynamics of neuroinflammation. Imaging studies with ^{11}C -PBR28 and ^{11}C -ER176 have shown that inflammation peaks at the progression boundary in focal neurodegeneration and co-localizes with tau deposition in mild cognitive impairment (MCI) due to early-onset AD. The strong correlation between inflammation and tau pathology highlights the potential of TSPO tracers to monitor disease progression and identify therapeutic targets.

A preliminary clinical trial using low-dose IL-2 and ^{11}C -ER176 PET showed regulatory T cell expansion and potential inflammation reduction, but no change in TSPO signal. This lack of change likely reflects the limited treatment duration, as longer periods beyond six months may be needed to detect measurable effects, given that brain inflammatory cells, including microglia, are unlikely to change significantly within a short timeframe. Despite these limitations, TSPO tracers remain valuable biomarkers for assessing neuroinflammatory processes across various neurodegenerative conditions.

4.6 Immunological Profiles in AD/ADRD and Their Correlation to PET Measures of AD/ADRD

Maura Malpetti, University of Cambridge

There is a critical role of multidisciplinary approaches in understanding neuroinflammation because of the complex inflammatory framework in neurodegenerative diseases. TSPO PET imaging can help identify inflammation patterns across different neurological conditions such as AD, FTD, and PSP.

Using advanced imaging techniques, distinct inflammation profiles were revealed for various neurodegenerative diseases. By scanning patients and following their clinical progression over 3–5 years, high levels of inflammation in specific brain regions were found to be correlated with worse cognitive decline and clinical progression over time. Notably, TSPO PET identified inflammatory changes even before brain atrophy occurred in presymptomatic genetic FTD carriers.

Understanding the cellular specificity of TSPO PET signals provides crucial insights into the cellular mechanisms of neuroinflammation. For example, through postmortem studies of PSP, TSPO was found to be more strongly co-localized with macroglia, especially in white matter regions, much more than with astrocytes. Although there was an increase in astrocyte co-localization with TSPO, it was not significantly higher than in controls. This indicates that TSPO PET reflects microglial activation and density.

In AD, peripheral inflammation was examined by analyzing blood-based biomarkers, such as CSF, and analyzing the cells and cytokines. By phenotyping peripheral blood mononuclear cells (PBMCs) and measuring cytokine levels, distinct inflammatory profiles were identified across different neurodegenerative diseases. Low levels of TREM2-positive cells and high levels of monocytes were strongly associated with shorter patient survival and correlated with brain inflammation signals. This suggests a role of the peripheral innate immune system in dementia, and that the crosstalk of central and peripheral inflammation may play a core role in disease progression.

Integrating multiple research approaches—including PET imaging, postmortem analysis, and blood biomarkers—can help improve our understanding of neuroinflammation. This work is being expanded through a large study called ON-FiRE, which aims to recruit 1,000 participants with FTD to further investigate inflammation profiles and link them with imaging and other more sophisticated markers.

4.7 Integration of MRI Brain Connectivity with PET Tau/Inflammation to Inform Disease Pathophysiology

Julie Ottoy, Sunnybrook Research Institute, University of Toronto

The brain is a complex network, similar to a highway system, where neural connections allow information flow between different regions. Using advanced neuroimaging techniques like diffusion-weighted MRI and functional MRI, structural and functional connectivity can be mapped. Because neuronal activity and hyperactivity can facilitate tau spread between neurons via synaptic connections, brain networks can serve as

therapeutic targets, potentially allowing interventions that reduce hyperactivity or block tau progression between brain regions.

The brain's network is organized as a hierarchical organization, exhibiting various connectome gradients. Connectome gradients can be used to inform disease pathophysiology. An innovative approach using connectivity gradients revealed smooth transitions in brain organization, moving from unimodal (i.e., sensorimotor) to transmodal (i.e., higher-order cognitive) regions. By analyzing these gradients, regions with similar connectivity patterns were discovered to be more likely to show comparable pathology loads. Notably, there were correlations of tau and TSPO PET with functional/structural connectivity gradients, suggesting that the spread of pathology aligns with the brain's intrinsic organization. Differences have also been observed in brain network organization between healthy and cognitively impaired individuals, with a network de-differentiation in which distinct functional brain networks become less specialized.

The intrinsic local vulnerability or regional susceptibility also influences tau seeding and spreading. Correlating connectome gradient differences with underlying spatial transcriptomics revealed that the profile was enriched in synaptic function and synaptic signaling. Therefore, transcriptomics can be integrated with *in vivo* imaging to characterize the gene pathways of interest that relate to changes in the organization of functional network connectivity in AD.

Ultimately, multimodal, longitudinal studies that incorporate molecular, functional, and structural measures and multi-omics are needed to better understand and potentially develop targeted interventions for neurodegenerative diseases. The development of therapeutic strategies for AD could benefit from the consideration of both molecular targets and the individual's brain network physiology and architecture, thereby providing unique opportunities for precision medicine.

Panel Discussion 2: Inflammation

Chairs: Tharick Pascoal and Maura Malpetti

Panelists: Pedro Rosa-Neto, Victor Villemagne, David Morgan, Ansel Hillmer, Robert Mach, Belen Pascual

The panel discussion centered around neuroimaging tracers, particularly TSPO and MAO-B, and their role in understanding neuroinflammation and neurodegenerative diseases. The conversation began with a question about the utility of tracers that may not be direct

therapeutic targets. Dr. Pascual noted that some tracers, such as SMB21 and MAO-B, will not be targets for clinical trials.

Dr. Villemagne emphasized that while tracers like MAO-B may not be direct therapeutic targets, they are valuable for understanding disease pathophysiology. Dr. Morgan provided insights about TSPO's limitations, noting that experimental literature rarely uses TSPO, and questioned its specificity in identifying microglial states. Dr. Rosa-Neto discussed TSPO's role as a marker of cellular response and when interpreting images, we should not expect pathophysiological phenomena to have a one-to-one relationship with the images.

Dr. Malpetti raised questions about whether to continue TSPO-PET research alongside developing new tracers, with the panel agreeing that parallel approaches are needed. Dr. Pascoal and Dr. Rosa-Neto discussed addressing limitations associated with reference regions and associated ligands. Dr. Rosa-Neto brought issues related to endogenous competition on the interpretation of P2X7 and CSF-R1 neuroreceptor images. Dr. Saykin noted that implementation depends on having a viable reference strategy. There was a consensus that while current tracers like TSPO have limitations, they still provide valuable information about disease processes, and continued development of more specific markers is crucial. Dr. Villemagne discussed the prospects of using SMBT1 as a tracer.

The panelists also discussed whether anti-inflammatory diets may lead to reduction or increase of neuroinflammation. Dr. Morgan noted that caloric restriction reduced amyloidosis but did not affect tauopathy, and ketogenic diets did not have an impact.

Dr. Mach emphasized that caution should be taken when proceeding with biomarkers tested in murine models, citing differences between rodent and human models. Dr. Morgan contributed insights about astrocytes' critical role, sharing unpublished research from the 1980s showing that selective destruction of astrocytes led to neuronal death.

The discussion addressed future directions. Dr. Villemagne emphasized the need for better synaptic markers, Dr. Rosa-Neto advocated for developing ligands for oxidative reactive species and excitatory amino acid transporters (EAATs). Dr. Malpetti noted the importance of trying to understand more about how the central and peripheral systems interact and identifying specific targets, and Dr. Morgan suggested the need for specific markers for homeostatic, DAM, and antigen presentation markers to better define what's going on with respect to microglial activation under various conditions.

Session 5: Emerging Tracers and Future Opportunities

5.1 Neurotransmitter System PET Tracers: Applications in AD/ADRD

Gwenn Smith, Johns Hopkins University

Neurotransmitters are major targets of drug discovery, with over one-third of current clinical trials targeting neurotransmitter receptors for neuropsychiatric symptoms and cognition. In addition to being potential therapeutic targets, neurotransmitters may represent early indicators of AD progression. For example, the earliest detected AD neuropathology is the tau protein in the locus coeruleus and dorsal raphe nuclei and the basal forebrain cholinergic nuclei.

There has been increasing appreciation of the link between serotonin and AD pathology from animal models and neuroimaging data, and the serotonin system has been the primary area of molecular imaging investigation. Animal models demonstrated that cortical serotonergic and noradrenergic projections begin to degenerate prior to significant amyloid accumulation. Notably, early serotonergic interventions (primarily selective serotonin reuptake inhibitors such as paroxetine) have demonstrated potential in reducing tau and amyloid pathology and memory deficits in animal models.

The serotonin transporter has shown widespread decreases in cortical and limbic regions that are correlated with memory and semantic fluency deficits. Modelling the association of cognition (memory and semantic fluency) with gray matter volumes and amyloid, model fit is improved by adding serotonin transporter binding both cross sectionally and longitudinally. Other neurotransmitter systems such as dopamine, acetylcholine, and glutamate each showed distinct patterns of change in AD. Unexpected cholinergic and serotonergic hyperfunction was observed in *APOE4* carriers. The dopamine system exhibited decreased transporter binding in ventral striatum and reduced D1/D2 receptors, and the cholinergic system has demonstrated widespread decreases in vesicular cholinergic transporter and acetylcholinesterase. Glutamate receptor research has focused on targets including mGluR5, which is correlated with cognitive deficits and has demonstrated decreases in the hippocampus, parahippocampal gyrus, and entorhinal cortex.

There are some gaps in current research, including limited data on preclinical conditions (*APOE4* carriers), sex differences, and domain-specific cognitive correlations.

Neurotransmitter research is complex but has potential for future discoveries in understanding and potentially treating AD. Multiple radiotracer studies should be expanded to understand the relationship between neurotransmitters and AD neuropathological mechanisms, and novel targets should be investigated, such as the serotonin 5-HT1B

receptor, muscarinic receptors, the glutamate system (EAAT2), reactive oxygen species, and insulin.

5.2 Potential Utility of Mitochondrial Complex 1 PET Imaging in Neurodegenerative Diseases

Sarah Berman, University of Pittsburgh

Mitochondrial dysfunction—especially in the electron transport chain—plays a significant role in neurodegenerative diseases, particularly DLB and Parkinson’s disease (PD). Specifically, mitochondrial complex I (Mito C1) has been identified as a critical area of interest, with evidence showing that its dysfunction by using a Mito C1 inhibitor can occur before the formation of Lewy bodies, thereby indicating its utility as a potential therapeutic target. PET neuroimaging has the potential to provide insights into how the respiratory pathway is associated with neurodegenerative diseases.

A pilot study investigated if 18F-BCPP-EF—a PET tracer that binds to Mito C1—could detect mitochondrial dysfunction in PD and DLB and deficits related to cognitive dysfunction. Initially, correlations were not detected between Mito C1 binding and the United Parkinson’s Disease Rating Scale (UPDRS) motor score. However, analyzing disease duration revealed significant declines in Mito C1 binding over time in several brain regions. Early in the disease process, there were instances of high binding, potentially indicating a mechanism in which the body attempts to upregulate mitochondrial function, which then started to decline. Cognitive impairment correlations were also explored, with notable observations in the occipital cortex and midbrain. In the hippocampus, there may be differences in binding patterns between DLB and AD.

However, Mito C1 in isolation only provides limited insight. A more comprehensive study is being conducted called BioEnergetic Hallmarks of Lewy Body Dementia (BEHOLD). This expanded research incorporates multiple imaging techniques, such as PET scans (e.g., Mito C1, FDG-PET, and Pittsburgh Compound-B [PiB] scans for amyloid pathology), phosphorus magnetic resonance (MR) spectroscopy, and anatomical/vascular imaging.

5.3 Emerging Targets in AD/ADRD: An Overview of New Tracers Under Evaluation in Humans

Steven Liang, Emory University

There is interest in expanding PET imaging targets beyond traditional amyloid-beta and tau approaches. PET tracer development is a collaborative effort, with the ultimate goal of gaining deeper insights into the biological mechanisms of AD and related disorders. A few examples of possible imaging targets were discussed.

Martinostat targets histone deacetylase (HDAC) enzymes, particularly Class I subtypes highly expressed in the brain. This tracer shows promising results in examining epigenetic dysregulation, with preliminary findings indicating that HDAC1 levels are reduced in patients with AD compared with MCI and healthy controls.

Some other emerging tracers include i) [^{18}F]3F4AP, which targets voltage-gated potassium channels responsible for maintaining cellular membrane potential and can potentially image demyelination; ii) an excitatory amino acid transporter (EAAT2) tracer designed to explore glutamate clearance mechanisms to prevent glutamate excitotoxicity, which is a major driver of the cause for neuronal death in neurodegenerative disease such as AD; iii) a microtubule-specific tracer ([^{11}C]MPC-6827) that showed statistically significant uptake by the brain in AD mice compared with wild-type mice; and iv) a fibrin-targeting tracer (fibrin binding probe 8, FBP8) to detect pathological fibrin deposits, which are linked to AD and neuroinflammation.

Although amyloid-beta tracers are commonly used, there are limitations. For example, existing imaging agents primarily bind to insoluble plaque formations and miss critical soluble oligomer stages. Therefore, there is a need for next-generation tracers that can capture earlier, more dynamic stages of amyloid-beta aggregation.

Another tracer ([^{18}F]CHL-2205) has shown promise in preclinical studies. This tracer targets cholesterol metabolism in the brain, specifically the cholesterol 24-hydroxylase enzyme (CYP46A1), which is a key enzyme in brain cholesterol homeostasis. Preclinical validation demonstrated a characteristic heterogeneous distribution pattern, with varying uptake across different brain regions.

5.4 Other Biological Processes We Should Monitor in AD. What Are We Missing? Blood Brain Barrier and Lymphatic Function

David Morgan, Michigan State University

There is need to understand complex, interconnected biological processes in AD. There are critical biological processes that should be monitored in AD with multiple potential markers and mechanisms of neurodegeneration beyond traditional amyloid, tau, and inflammation research. Consequently, it is important to understand various cellular and molecular changes that occur during disease progression.

There are several significant areas of neurological investigation, including oxidative damage, DNA damage, neuronal subtypes, dysmyelination, and atrophy and synapse loss. For example, oxidative damage markers such as lipid oxidation, protein oxidation, and DNA oxidation are potential indicators of neurodegeneration. DNA damage assessment through markers like gamma-H2AX phosphohistone, which binds to double strand breaks, provides insights into cellular breakdown mechanisms. Measuring the loss of specific neuron subtypes could have merit because there are several inhibitory interneurons that are found to be lost early in disease, particularly in areas like the hippocampus. A particular neuron of interest is the RELN neuron, which can be protective against presenilin mutations and may confer vulnerability to tau in early-stage disease. Additionally, some think that the first step of AD is myelin fragmentation, not demyelination, and this dysmyelination might precede amyloidosis and tauopathy. Atrophy and synapse loss is also an important area of interest because ligands bind to receptors.

Other areas that should receive more attention include proteostasis, which may underlie at some level virtually all of the neurodegenerative disorders; assessing blood–brain barrier measurements; and investigating peripheral immune cell infiltration into the brain. Monocytes may represent a potential gene therapy vector, and different immune cells like T cells might contribute to neurotoxicity. Additionally, brain shuttle/Trojan horse technology enhances blood–brain barrier penetration by antibodies, and antibody-based ligands can be made to measure specific antibodies.

There are many targets that can monitor the sequence of events leading to AD. These targets may help us understand the sequence of events, and the potential roles of some responses, such as inflammation. Additionally, some markers may be predictive of long-term clinical benefit (e.g., markers that are predictive of better clinical outcomes).

5.5 From Click Chemistry to Precision Neuroscience

Hartmuth Kolb, Enigma Biomedical Group

Click chemistry was developed to simplify chemical processes and rapidly explore chemical spaces; it can make compounds based on transformations that are modular, wide in scope, give very high yields, and generate only inoffensive byproducts that can be removed by nonchromatographic methods. This methodology facilitates rapid compound generation, precise targeting, and optimization based on pathological protein. The key innovation was the copper-catalyzed alkyne cycloaddition reaction, which allows for quick and reliable molecular connections, likened to a LEGO-like approach to chemistry.

Using click chemistry, tracers have been developed for various neurological conditions. For tau tracer development, pathological tau protein was detected from Alzheimer's patient brain slices and brain extracts. This approach led to the development of T807 (Flortaucipir), which was readily labeled, tested, and selected as a clinical candidate; this is now an FDA-approved tau tracer that can effectively distinguish tau pathology in brain imaging. This tracer demonstrated a linear correlation with tau levels and minimal binding to amyloid-beta, providing crucial insights into AD progression.

Expanding beyond tau, tracers for neuroinflammation and other neurodegenerative markers have been explored. For example, ligands were developed for P2X7 and CSF1R, targeting microglia (and oligodendrocytes for P2X7), with the goal of creating more specific neuroinflammation imaging agents. Click chemistry is also now being used to develop tracers for alpha-synuclein and TDP-43, which are associated with neurodegenerative diseases such as AD and other neurodegenerative diseases.

Panel Discussion 3: How do we choose a good target for PET tracer development, what are the promises, challenges and constraints?

Chairs: Julie Price, Mass General Research Institute; Elizabeth Mormino, Stanford University

Panelists: Hartmuth Kolb, Steven Liang, Andy Saykin, Sarah Berman, Neil Vasdev, Robert Mach, Gwenn Smith, David Jones

The conversation began with Dr. Mach highlighting alpha-synuclein as a critical target, drawing parallels to the early days of tau imaging. He predicted that, like tau imaging, initial alpha-synuclein studies would yield varying results that would become clearer as

structural biology advanced, and that it would be important to integrate PET tracer development with advances in structural biology and computational chemistry to develop probes that are highly specific for these protein targets.

Dr. Kolb built on these points by emphasizing the prevalence of co-pathologies in dementia patients, noting that brain bank studies frequently found alpha-synuclein and TDP-43 alongside amyloid and tau in AD brains. This led to a discussion about the importance of proper patient diagnosis for effective treatment. Dr. Hsiao then raised concerns about tracer dissemination. Dr. Vasdev noted how Canadian trials often offer a faster and more cost-effective pathway for first-in-human studies, while highlighting the challenges posed by U.S. requirements.

Dr. Liang emphasized the importance of publishing results in the public domain to attract industry interest, distinguishing between academic and pharmaceutical approaches to PET imaging. He noted that a significant number of tracers are developed during drug discovery for use as tools to determine target engagement, but they are never disseminated to the scientific community for research use. Dr. Saykin then broadened the discussion by noting the extensive progress in tracer development across 20–25 major pathways implicated in AD, raising important questions about which biomarkers should be measured through PET versus other modalities.

The conversation shifted when Dr. Smith discussed her work integrating blood biomarkers for AD pathology with PET neurotransmitter studies. Developing and validating neurotransmitter biomarkers with PET would address the challenges in patient selection and study execution. Dr. Mormino and Dr. Berman emphasized the unique value of PET imaging in understanding biological mechanisms in the living human brain, with Dr. Berman particularly highlighting the importance of studying mechanisms beyond end-product pathologies.

The discussion concluded with practical considerations about FDA approval processes, exemplified by a discussion of FDG-PET's status, and the broader challenges of bringing new tracers to clinical use. Throughout the conversation, participants emphasized the need for better dissemination of tracer development, the importance of understanding multiple pathologies, and the crucial role of commercial partners in bringing these tools to clinical practice.

Day 2 Wrap-Up and Closing Remarks

Dr. Rovescalli concluded the event by expressing satisfaction with the conversations and perspectives shared. She thanked the speakers, panelists, steering committee, and several staff members who helped with event logistics.

Appendix A: Agenda

DAY 1: March 12TH, 2025

9:15 AM Opening remarks

TOPIC 1: INTEGRATED PLATFORMS

9:30 AM Bill Jagust, University of California Berkeley: Harmonization of PET Data for the analyses of multiple cohorts: Overview of SCAN and ADNI

10:00 AM Gil Rabinovici, University of California San Francisco: Clinical Use of PET in the “real world: Overview of the IDEAS/new IDEAS studies

10:30 AM Tharick Pascoal, University of Pittsburgh with Suzanne Baker, University of California Berkeley: Longitudinal multicenter head-to-head harmonization of tau PET tracers: The HEAD Study

11:00 AM Sterling Johnson, University of Wisconsin with Dirk Keene, University of Washington: Impact of co-pathologies and introduction of CLARITI

11:25 AM BREAK

TOPIC 2: MODELING DISEASE SPREAD AND PROGRESSION

11:30 AM Tobey Betthausen, University of Wisconsin: Temporal models of disease progression and PET-based “clocks”

11:50 AM Renaud Lajoie, University of California San Francisco: PET- based subtypes of AD.

12:10 PM Melissa Murray, Mayo Clinic Jacksonville: Neuropathologic evaluation of AD/ADRD PET and fluid biomarker changes

12:30 PM Paul Yushkevich, University of Pennsylvania: Integration of neuropathology and multimodal imaging data for clinical applications and studies in AD and ADRDs

12:50 PM Andy Saykin, Indiana University: PET as an Endophenotype for Genetic Studies of AD/ADRD

1:10 PM Lunch Break

TOPIC 3: PET IMAGING IN ADRDs

- 1:40 PM Benjamin Ryskeldi-Falcon, Medical Research Council Laboratory of Molecular Biology:** Cryo-EM structures of amyloid filaments: Considerations for PET imaging tracers in neurodegenerative diseases
- 2:10 PM Robert Mach, University of Pennsylvania:** Overview of alpha-syn tracers and selective 4R, 3R tracers
- 2:40PM Neil Vasdev, University of Toronto:** Overview of emerging tau tracers
- 3:10 PM Kejal Kantarci, Mayo Clinic Rochester:** Imaging of the pathologic heterogeneity associated with alpha-synucleinopathies with PET
- 3:30 PM David Jones, Mayo Clinic Rochester:** Exploiting FDG PET in Limbic-predominant age-related TDP43-encephalopathy
- 3:50 PM Barbara Bendlin, University of Wisconsin:** Synaptic PET imaging in AD/ADRD
- 4:10 PM Day 1 Panel Discussion**
Chairs: Gil Rabinovici and Melissa Murray
- 4:40 PM Day 1 Closing Remarks and Adjournment**

DAY 2: March 13TH, 2025

TOPIC 4: NEUROINFLAMMATION

- 9:30 AM David Morgan, Michigan State University:** Overview of Immune Activation in Alzheimer's disease
- 10:00 AM Pedro Rosa-Neto, University Texas Southwestern:** Imaging glia and neuroinflammation in Alzheimer's disease
- 10:20 AM Victor Villemagne, University of Pittsburgh:** Neuroinflammation: Focus on astroglial markers
- 10:40 AM Ansel Hillmer, University of Michigan:** CSF-1R as a promising PET imaging target

- 11:00 AM** **Belen Pascual, Houston Methodist:** TSPO PET Tracers-Utility in Early-Onset Dementia and Insights from Clinical Trials
- 11:20 AM** **Maura Malpetti, University of Cambridge:** Immunological profiles in AD/ADRD and their correlation to PET measures of AD/ADRD
- 11:50 AM** **Julie Ottoy, Sunnybrook Research Institute:** Integration of MRI brain connectivity with PET Tau/inflammation to inform disease pathophysiology
- 12:10 AM** **Panel Discussion on Inflammation**
Chairs: Tharick Pascoal and Maura Malpetti
- 12:40 PM** **Lunch Break**

TOPIC 5: EMERGING TRACERS AND FUTURE OPPORTUNITIES

- 1:10 PM** **Gwenn Smith, Johns Hopkins University:** Neurotransmitter system PET tracers: applications in AD/ADRD
- 1:30 PM** **Sarah Berman, University of Pittsburgh:** Potential Utility of Mitochondrial Complex 1 PET Imaging in neurodegenerative diseases
- 1:50 PM** **Steven Liang, Emory University:** Emerging targets in AD/ADRD: an overview of new tracers under evaluation in humans
- 2:20 PM** **David Morgan, Michigan State University:** Other Biological Processes we should Monitor in AD. What are we missing? Blood brain barrier and lymphatic function
- 2:50 PM** **Hartmuth Kolb, Enigma Biomedical:** From click chemistry to precision
- 3:20 PM** **Panel Discussion:** How do we choose a good target for PET tracer development, what are the promises, challenges and constraints?

Chairs: Julie Price, Mass General Research Institute and Elizabeth Mormino, Stanford University
- 3:50 PM** **Day 2 Wrap-Up and Closing Remarks**

Appendix B: List of Participants

Suzanne Baker
University of California Berkeley

Barbara Bendlin
University of Wisconsin

Sarah Berman
University of Pittsburgh

Tobey Betthausen
University of Wisconsin

Ansel Hillmer
University of Michigan

Sterling Johnson
University of Wisconsin

Bill Jagust
University of California, Berkeley

David Jones
Mayo Clinic Rochester

Kejal Kantarci
Mayo Clinic Rochester

Dirk Keene
University of Washington

Hartmuth Kolb
Enigma Biomedical Group

Renaud Lajoie
University of California San Francisco

Steven Liang
Emory University

Robert Mach
University of Pennsylvania

Maura Malpetti
University of Cambridge

David Morgan
Michigan State University

Elizabeth Mormino
Stanford University

Melissa Murray
Mayo Clinic Jacksonville

Julie Ottoy
Sunnybrook Research Institute

Tharick Pascoal
University of Pittsburgh

Belen Pascual
Houston Methodist

Julie Price
Mass General Research Institute

Gil Rabinovici
University of California San Francisco

Pedro Rosa-Neto
University Texas Southwestern

Alessandra Rovescalli
National Institute on Aging

Benjamin Ryskeldi-Falcon
*Medical Research Council Laboratory of
Molecular Biology*

Andrew Saykin
Indiana University

Gwenn Smith
Johns Hopkins University

Neil Vasdev
University of Toronto

Victor Villemagne
University of Pittsburgh

Paul Yushkevich
University of Pennsylvania