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Interplay between Intuition and Design of PET Tracers to Counteract Challenges for Imaging Alzheimer's Diseas

Alzheimer's disease (AD) is a devastating neurodegenerative disorder characterized by progressive decline in cognitive functions. For therapeutic interventions (antibodies; anti-amyloid disease modifying drugs and small organic molecules; BACE 1 Inhibitors) to be effective, drugs need to be administered at earliest stages prior to clinical manifestation of the disease. For stratification of patients likely to be benefitted from a given mode of treatment, it is imperative to diagnose AD at prodromal stages for offering significant help to effected individuals. To accomplish this objective, Florbetapir, Flutemetamol, and Florbetaben have gained FDA approval for Aβ imaging. Although promising for visualizing compact plaques in vivo, these agents also show high nonspecific white matter retention, cross reactivity with other β-sheet structures (myelin binding protein), and are unable to detect oligomers and diffuse Aβ plaques. To achieve an accurate quantification of Aβ pathophysiology non-invasively, a highly specific (at a molecular level) yet sensitive 18F-PET agent, potentially capable of binding to both fibrillar and diffuse plaques, to enable ultrasensitive detection capability (at prodromal stages of the disease) would be desired. To accomplish this objective, our lab has rationally designed a novel heterocyclic fluorescent molecule (named Fluselenamyl) belonging to an entirely new class of molecules that shows concentration dependent and saturable binding, with Kd values of 1.4±0.35nM and 2.9 ±1.35nM, to AD homogenates and preformed Aβ1-42 fibrils, respectively. The agent detects both fibrillar plaques and displays cerebral amyloid angiopathy (CAA) ex vivo in the hippocampus regions of brain sections in APPsw+/-/PS1 mice, while also exhibiting high sensitivity for detecting diffuse plaques, compact plaques, and vascular deposits (CAA) in human tissues. Further, the PET tracer 18F-Fluselenamyl demonstrates an extremely high first pass extraction in brains (8.86 ± 0.32 %ID/g %ID/g; 2 min post tail-vein injection) of FVB mice, and followed by a washout (25% faster than 18F-Avid 45) in absence of targeted plaques. Compared with FDA approved tracers undergoing facile metabolism in vivo, 18F-Fluselenamyl remains non-metabolized in human serum up to 3h. Additionally, multiphoton microscopy in live APPsw+/-/PS1 (15 months old) mice demonstrates that Fluselenamyl traverses the blood brain barrier (BBB) instantaneously to label plaques in brain parenchyma and blood vessels (CAA). Furthermore, microPET/CT imaging shows higher brain uptake of the radiotracer (30 min post-tail-vein injection), and its retention in the cortex of transgenic mice compared with their age-matched Bl6 counterparts, consistent with the binding of the tracer to Aβ plaques, which also correlates with ex vivo autoradiography and immunohistochemistry. While dosimetry studies in mice (n=40), using MIRD methodology indicate an effective dose equivalent of ^{18}F-Fluselenamyl to an allowable maximum injection of 20 mCi in humans, the radiotracer also penetrates primate brain (5%ID/g), and clears to background levels in the absence of targeted plaques. Finally and importantly, Fluselenamyl provides a highly specific molecular signature for AD (displays no cross-reactivity with biomarkers of other neurodegenerative diseases); while also detecting diffuse and compact plaques in an ^{11}C-PIB PET imaging negative, but an Aβ+ AD case. Some of these aspects would be compared with the existing state-of- the art in Neuro2017.

Speaker Biography

Following post-doctoral training with Prof. Jim Wuest in University of Montreal, Quebec, Canada, Dr. Sharma joined in August 1994 Mallinckrodt Institute of Radiology, Washington University School of Medicine, St. Louis. He is currently a tenured professor within departments of Radiology, Neurology, and Biomedical Engineering. Dr. Sharma is also a founding member of the ICCE institute, member of Siteman cancer center, and director of the radiopharmaceutical sciences in Molecular Imaging Center, AMGEN faculty mentor, and program director of MIR summer research program. He is a NIH funded principal investigator for over 20 years in biomedical research. Dr. Sharma serves on review panel of over 40 plus biomedical journals in interdisciplinary sciences, editorial boards, grant review panels for National Institutes of Aging (NIA), Mental Health (NIMH), Allergies and Infectious Diseases (NIAID), Centers for Excellence & Commercialization of Research (CECR, NSERC, Canada), and Killam Faculty Fellowship Awards (NSERC, Canada), national foundations, and AXA Research Fund, Paris, France. At School of Medicine, Dr. Sharma directs a research program focused upon design and development of PET tracers for biomedical imaging in neurodegenerative diseases, interrogating roles of adenosine binding cassette (ABC)-family of transporters in chemotherapeutic resistance including blood brain barrier, cancer biology, and cardiovascular diseases.

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