Discovery of Novel PET Tracers to Image Aggregated Tau in Alzheimer's Disease

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Objectives: Aggregates of tau and beta amyloid (Ab) plaques constitute the histopathological hallmarks of Alzheimer's disease (AD) and are prominent targets for novel therapeutics and biomarkers for diagnostic in vivo imaging. In recent years much attention has been devoted to the discovery and development of new PET tracers to image tau aggregates in the living human brain [1,2]. The objective of this study was to identify such a novel radiotracer, in order to support the clinical development of novel therapies targeting aggregated forms of tau.

Methods: A medicinal chemistry PET tracer discovery program identified several candidate structures. Among these, the three novel tau ligands RO6924963, RO6931643 and RO6958948 were selected for radiolabelling alternatively with tritium and a PET nuclide. Tritiation of RO6924963 and RO6958948 was achieved by direct ^{1}H to ^{3}H exchange reaction with Crabtree's catalyst. [^{3}H]RO6931643 was prepared in one step by methylation of an anilinic precursor with [^{3}H]MeONs. [^{11}C]RO6924963 and [^{11}C]RO6931643 were obtained by methylation of the corresponding precursors with [^{11}C]MeI. The ^{18}F-fluorination of RO6958948 was accomplished by nucleophilic aromatic substitution of a nitro precursor. The tritiated ligands where evaluated by in vitro autoradiography on AD and healthy control brain sections. Additional co-localization experiments with selective antibodies for tau or Ab were performed. The ^{11}C- and ^{18}F-labelled tracers were evaluated in PET in tau-naïve baboons after *i.v.* administration.

Results: The tritiated ligands were obtained with SA > 900 GBq/mmol and radiochemical purities > 94%. ^{11}C-Labelled tracers were isolated with high SA > 200 GBq/mmol. [^{18}F]RO6958948 was obtained with SA > 660 GBq/mmol. In vitro autoradiography revealed a heterogeneous distribution pattern co-localized with the binding pattern of the tau antibody. Very low non-specific binding in healthy brain tissue excluded significant radioligand binding to any other CNS target. The time-activity curves for brain regions in baboons indicated good brain uptake and rapid washout for all three tracers.

Conclusions: [^{11}C]RO6924963, [^{11}C]RO6931643 and [^{18}F]RO6958948 are promising PET tracers for the visualization of tau aggregates in AD. On account of these results, these tracer candidates have been progressed into a clinical validation study in healthy controls and patients with AD (ClinicalTrials.gov Identifier: NCT02187627).

[1] M. Ariza *et al.*, *J. Med. Chem.* **2015**, *58*, 4365-4382.
[2] A. Walji *et al.*, *J. Med. Chem.* **2016**, *59*, 4778-4789.