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COMMENTARY

Discovery of novel radioligand [^{18}F]AZD9574 for selective imaging of PARP1 in the CNS

KEY WORDS

[^{18}F]AZD9574;
PARP1 imaging;
Positron emission tomography (PET);
CNS disorders;
Oncology

Poly(ADP-ribose) polymerase-1 (PARP1) is a critical enzyme in DNA damage repair and is frequently overexpressed in various malignancies[1]. Tumors with homologous recombination deficiency often depend on PARP1-mediated DNA repair for survival, making them susceptible to synthetic lethality upon PARP inhibition[2]. Consequently, PARP1 has emerged as both a therapeutic target and a diagnostic biomarker, particularly in cancers with homologous recombination deficiencies, such as breast, ovarian, and prostate cancer[3,4]. Despite advances in PARP imaging, the development of effective PARP1-targeted agents for central nervous system (CNS) lesions has been challenging due to limited blood−brain barrier (BBB) penetration and inadequate subtype selectivity. These obstacles, combined with cross-reactivity with PARP2, have hindered the study of PARP1 functions in CNS disorders and complicated the interpretation of PET imaging results by introducing potential off-target effects[5-6].

Recently, Liang and colleagues published a study in *Acta Pharmaceutica Sinica B*, demonstrating that [^{18}F]AZD9574 represents a significant advance in selectively imaging PARP1 in the CNS. This breakthrough addresses longstanding challenges through the radiosynthesis of a radiotracer derived from the next-generation PARP1 inhibitor scaffold, AZD9574[7]. The compound exhibits exceptional selectivity for PARP1[8], with an IC_{50} of 1.2 nmol/L, an 800-fold preference over PARP2, confirmed through comprehensive enzymatic inhibition studies and competitive binding assays. The molecular design incorporates optimized physicochemical properties, collectively enabling efficient BBB penetration while maintaining favorable pharmacokinetic characteristics.

The authors initially optimized the radiosynthesis of [^{18}F]AZD9574, achieving both high radiochemical yield and excellent *in vitro* stability, supporting its potential for clinical translation. Efficient ^{18}F-labeling *via* nucleophilic aromatic substitution produced the tracer with a 25% radiochemical yield and high molar activity exceeding 37 GBq/μmol. The radioligand demonstrated robust stability, remaining over 95% intact in plasma and liver microsomes after 90 min, a critical characteristic for clinical application.

Preclinical validation studies highlight the robust utility of [^{18}F]AZD9574 across multiple model systems. *In vitro* assays using PC3 cells showed PARP1-specific tracer accumulation, while autoradiography of rodent and non-human primate brain sections revealed distribution patterns consistent with known PARP1 expression[9-10]. Dose-dependent reductions in autoradiographic signal following AZD9574 blockade, exceeding 60% in the cerebellum at higher doses, provided strong evidence of target engagement. These findings were further confirmed in PARP1 knockout mice, which exhibited negligible tracer binding, underscoring the specificity of [^{18}F]AZD9574. Notably, *in vivo* PET imaging in non-human primates revealed heterogeneous brain uptake, with the highest signals in PARP1-rich regions such as the cerebellum and hippocampus, demonstrating the tracer's efficient BBB penetration.

The development of [^{18}F]AZD9574 by Liang et al. opens new opportunities for both basic research and clinical applications. In oncology, it provides a powerful tool to study PARP1 expression dynamics across various malignancies and to monitor responses to PARP inhibitor therapy. In neurology, it represents one of the first effective probes for investigating the role of PARP1 in CNS lesions and neurodegenerative processes. Future research should focus on clinical translation, including first-in-human studies, comparative evaluations against existing PARP tracers, and expansion into additional disease models. The comprehensive

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preclinical validation of [^{18}F]AZD9574 positions it as a transformative tool, with the potential to deepen our understanding of PARP1 biology while advancing diagnostic and therapeutic strategies in precision medicine.

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