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EDITORIAL

# [$^{18}$F]QTFT, a nicotinate-based radiotracer targeting P2Y$_{12}$ with satisfactory blood−brain barrier (BBB) permeability

**KEY WORDS**

[$^{18}$F]QTFT;
P2Y$_{12}$ receptor;
Blood−brain barrier (BBB);
Positron emission tomography (PET);
Glioma

Recently, a novel radiotracer, [$^{18}$F]QTFT, synthesized by Li's group[1] and published in ***Acta Pharmaceutica Sinica B***, was identified as a PET tracer capable of specifically visualize the anti-inflammatory microglia target P2Y$_{12}$. Compared to other probes, it exhibited high binding affinity and superior blood−brain barrier (BBB) permeability. Moreover, the authors observed increased [$^{18}$F]QTFT uptake in lesions in neuroinflammation models, and this selective uptake could be disrupted by QTFT and P2Y$_{12}$ antagonists. Meanwhile, [$^{18}$F]QTFT targeted aberrantly expressed P2Y$_{12}$ in anti-inflammatory microglia to visualize brain lesions in models of glioma, epilepsy, and aging. Interestingly, enhanced [$^{18}$F]QTFT radioactive signals were observed in the foci of an epileptic patient during a preliminary clinical trial. These findings demonstrated that [$^{18}$F]QTFT, which targeted P2Y$_{12}$ overexpressed in anti-inflammatory microglia, may serve as a novel diagnostic tool for imaging a variety of brain diseases.

Microglia are widely distributed throughout the brain and are the main innate immune cells[2]. They are also the first responders to pathological damage and are considered to be the main defense system of the brain[3]. Additionally, in the central nervous system (CNS), microglia serve as key regulators of inflammatory responses[4]. Traditionally, microglial activation is heterogeneous and classified into two opposing phenotypes, including M1-phenotype (neurotoxic) and M2-phenotype (neuroprotective)[5,6]. It has been reported that pro-inflammatory M1-microglia are detrimental and play an important role in disease progression, while anti-inflammatory M2-microglia contribute to damage repair and remission[7]. Therefore, visualizing microglia polarization is crucial for understanding the progress of diseases.

Positron emission tomography (PET) is widely used to visualize alterations of microglia due to its ultra-high sensitivity[8]. Molecular imaging using PET helps monitor the progression of neuroinflammation[9]. Some PET tracers have been reported to visualize pro-inflammatory microglia for a variety of neuroinflammatory targets, such as purinergic receptors P2X7, mitochondrial 18 kDa translocator protein (TSPO), cyclooxygenase isoenzymes (COX), and colony-stimulating factor 1 receptor (CSF1R)[10-12]. However, these tracers have significant limitations, including low permeability of the BBB, high non-specific plasma binding, and difficulties in distinguishing phenotypes, leading to a low signal-to-noise ratio in final images[13]. Therefore, there is an urgent need for the development of PET tracers specifically designed to image anti-inflammatory microglia.

P2Y receptors (P2YR), a class of seven-transmembrane proteins coupled to G proteins, are activated by extracellular signaling molecules or nucleotides, which are secreted by damaged cells or released under ischemic, inflammatory, and hypoxic conditions[14]. Based on the structural and similarities phylogenetic, P2YR could be divided into two subgroups: the 'P2Y$_1$R-like' group (coupled to Gq) and the 'P2Y$_{12}$R-like' group (coupled to Gi)[15]. Among these, P2Y$_{12}$ subtype consists of two potential N-linked glycosylation sites and 342 amino acid residues[16]. Furthermore, P2Y$_{12}$, a metabolic purinoceptor overexpressed in anti-inflammatory microglia, has been shown to have phenotypically dependent expression [17]. Meanwhile, P2Y$_{12}$ is a promising biomarker in brain tumors, epilepsy, and Alzheimer's disease[18-20]. However, the development of PET tracers selectively target P2Y$_{12}$ in the brain has been quite limited.

Recently, the authors designed and synthesized four P2Y$_{12}$ radiotracers, and then found one of the tracers exhibited favorable computational binding energy with P2Y$_{12}$ protein by

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using computer-aided design (Fig. 1). Meanwhile, [$^{18}$F]QTFT showed strong stability in mice, as no significant release of free $^{18}$F or metabolites was observed within 2 h. In the membrane-binding assay, the binding affinity of [$^{18}$F]QTFT for the P2Y$_{12}$ receptor was evaluated, yielding a dissociation constant ($K_d$) of 14.43 nmol/L. Additionally, the cellular uptake of [$^{18}$F]QTFT in a P2Y$_{12}$-positive glioblastoma cell increased with incubation time and significantly decreased upon the addition of the P2Y$_{12}$ inhibitor. [$^{18}$F]QTFT demonstrated effective BBB penetration, because its endothelial transmission value reached 19.6%. In brain pharmacokinetics, the peak SUV of [$^{18}$F]QTFT was 1.77 ± 0.27 and the retention level was $SUV_{mean}$ = 0.69 ± 0.11, demonstrating high brain penetration and accumulation. With a half-life of 30.57 min, an ex vivo pharmacokinetic research showed that [$^{18}$F]QTFT exhibited rapid blood clearance. In a competitive study using a C6 glioma model that overexpresses P2Y$_{12}$, they found that clopidogrel (a P2Y$_{12}$ inhibitor) significantly inhibited the uptake of [$^{18}$F]QTFT by subcutaneous tumors. In summary, [$^{18}$F]QTFT showed high brain permeability and selective P2Y$_{12}$ binding properties, making it suitable for further imaging studies.

Compared with the LPS-induced pro-inflammatory group, the expression of P2Y$_{12}$ was higher in the IL-4-induced anti-inflammatory group, and the PET signal at the lesion site was also increased, indicating that [$^{18}$F]QTFT also exhibited good targeting specificity against P2Y$_{12}$ *in vivo*. Similarly, P2Y$_{12}$ was upregulated only in the acute phase, but not in the chronic phase, resulting in higher [$^{18}$F]QTFT PET signals in the ipsilateral hippocampus in the acute phase (T/N ratio = 1.81 ± 0.22 at 60 min p.i.), whereas the PET tracer in the latent and chronic epilepsy showed relatively lower accumulation in brain lesions (*T/N* ratio = 1.14 ± 0.05 and 1.12 ± 0.03, respectively). Aging is a significant contributor to neurodegenerative diseases. The authors also found that P2Y$_{12}$ expression was reduced in the aging brain compared to the young mice, which could be visualized using [$^{18}$F]QTFT, indicating a lower uptake. In glioma imaging experiments, it was observed that the target-to-normal (T/N) ratio of the amino acid metabolism imaging agent [$^{18}$F]FET (1.17 ± 0.02) was lower than that of [$^{18}$F]QTFT in tumors (1.47 ± 0.01). This finding further demonstrated that [$^{18}$F]QTFT could specifically image microglia expressing P2Y$_{12}$. In a pilot clinical trial involving patients with temporal lobe epilepsy, it was found that the signal intensity of dynamic [$^{18}$F]QTFT PET imaging was high ($SUV_{mean}$ of epileptic lesions was 1.29 ± 0.28). Additionally, [$^{18}$F]QTFT showed significant BBB permeability, as indicated by a peak SUV in the lesions of 2.50 ± 1.58. These findings suggested that [$^{18}$F]QTFT could be a valuable tool for localizing lesions in patients with epilepsy and indicated its potential for translational applications.

In this study, the authors designed and synthesized a series of P2Y$_{12}$-specific radiotracers, with the P2Y$_{12}$ inhibitor AZD1283 as the lead compound. They retained key binding units, such as the nicotinate group and the hydrogen bond receptor, which interacted with Tyr105 and Lys280 of the P2Y$_{12}$ receptor through hydrophobic or $\pi-\pi$ stacking interactions. Additionally, they selected QTFT for fluorine-18 radiolabeling to develop a P2Y$_{12}$-specific PET probe, which various brain disease models with P2Y$_{12}$ expression, effectively circumventing P-gp-mediated efflux and demonstrating significant BBB permeability. However, the study has certain limitations. High uptake and off-target effects of [$^{18}$F]QTFT in the liver may increase the risk of radiation exposure. Therefore, further optimization is required to enhance its targeting

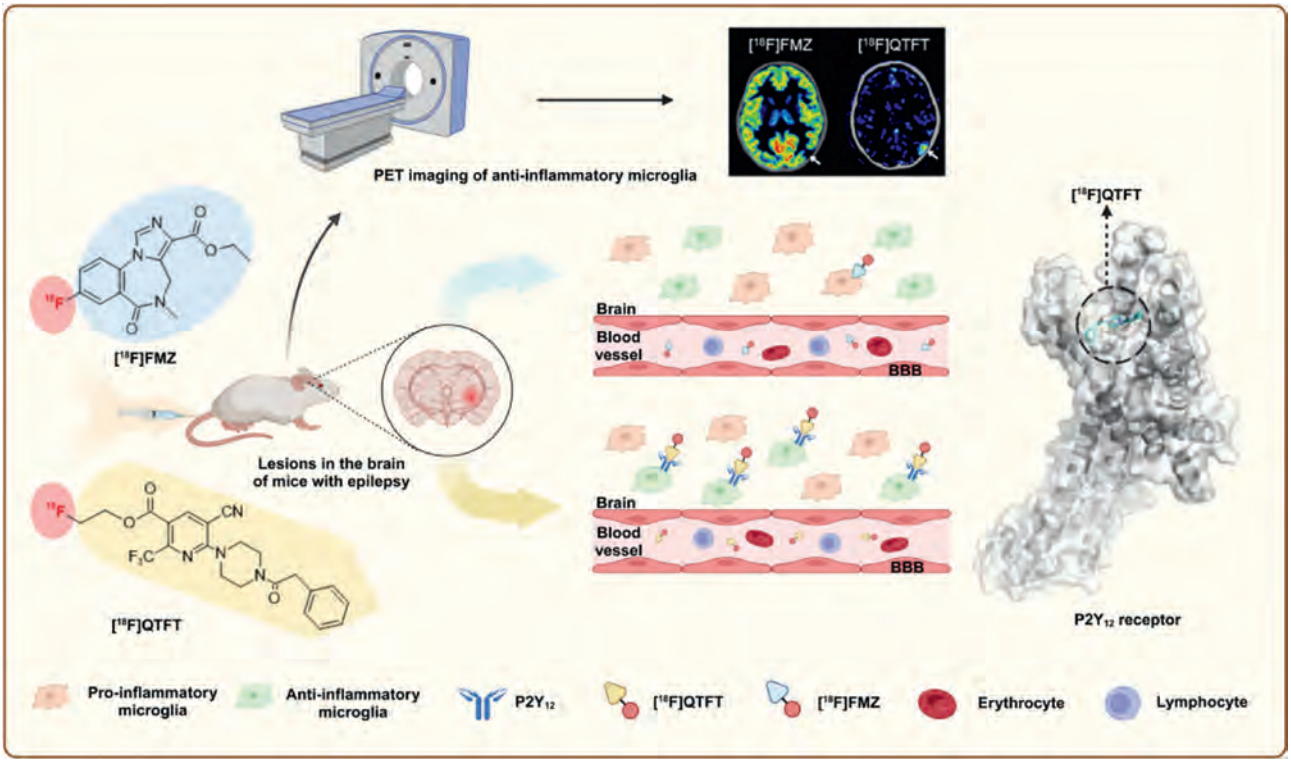


**Figure 1** Design rationale and pharmacological activities of P2Y12 receptor targeting radiotracer [$^{18}$F]QTFT. The novel PET tracer [$^{18}$F]QTFT visualizes lesions in various brain diseases by targeting the P2Y$_{12}$ receptor, which is specifically expressed in anti-inflammatory microglia.

and reduce unintended uptake. Furthermore, the study focused primarily on specific stages of epilepsy, glioma, and aging disease models. The next step should involve evaluating the imaging performance of the probe at various stages of disease progression. Consequently, this study provided a significant reference for imaging in neuroinflammation-related brain diseases, and its potential clinical application should be further explored.

## References


1. Yao B, Kong Y, Li J, Xu F, Deng Y, Chen Y, et al. Synthesis, preclinical evaluation and pilot clinical study of a $P2Y_{12}$ receptor targeting radiotracer [$^{18}$F]QTFT for imaging brain disorders by visualizing anti-inflammatory microglia. *Acta Pharm Sin B* 2025;**15**: 1056−69.
2. Kwon HS, Koh SH. Neuroinflammation in neurodegenerative disorders: the roles of microglia and astrocytes. *Translational neurodegeneration* 2020;**9**:42.
3. Nayak D, Roth TL, McGavern DB. Microglia development and function. *Annu Rev Immunol* 2014;**32**:367−402.
4. Colonna M, Butovsky O. Microglia function in the central nervous system during health and neurodegeneration. *Annu Rev Immunol* 2017; **35**:441−68.
5. Subhramanyam CS, Wang C, Hu Q, Dheen ST. Microglia-mediated neuroinflammation in neurodegenerative diseases. *Semin Cell Dev Biol* 2019;**94**:112−20.
6. Yu H, Chang Q, Sun T, He X, Wen L, An J, et al. Metabolic reprogramming and polarization of microglia in Parkinson's disease: role of inflammasome and iron. *Ageing Res Rev* 2023;**90**:102032.
7. Tang Y, Le W. Differential roles of M1 and M2 microglia in neurodegenerative diseases. *Mol Neurobiol* 2016;**53**:1181−94.
8. Beaino W, Janssen B, Vugts DJ, de Vries HE, Windhorst AD. Towards PET imaging of the dynamic phenotypes of microglia. *Clin Exp Immunol* 2021;**206**:282−300.
9. Shojaei M, Schaefer R, Schlepckow K, Kunze LH, Struebing FL, Brunner B, et al. PET imaging of microglia in Alzheimer's disease using copper-64 labeled TREM2 antibodies. *Theranostics* 2024;**14**: 6319−36.
10. Meyer JH, Cervenka S, Kim MJ, Kreisl WC, Henter ID, Innis RB. Neuroinflammation in psychiatric disorders: PET imaging and promising new targets. *The lancet Psychiatry* 2020;**7**:1064−74.
11. Fu Z, Lin Q, Xu Z, Zhao Y, Cheng Y, Shi D, et al. P2X7 receptor-specific radioligand (18)F-FTTM for atherosclerotic plaque PET imaging. *Eur J Nucl Med Mol Imag* 2022;**49**:2595−604.
12. Placzek MS, Wilton DK, Weïwer M, Manter MA, Reid SE, Meyer CJ, et al. A fast-binding, functionally reversible, COX-2 radiotracer for CNS PET imaging. *ACS Cent Sci* 2024;**10**:1105−14.
13. Tronel C, Largeau B, Santiago Ribeiro MJ, Guilloteau D, Dupont AC, Arlicot N. Molecular targets for PET imaging of activated microglia: the current situation and future expectations. *Int J Mol Sci* 2017;**18**:802.
14. Ma C, Li B, Silverman D, Ding X, Li A, Xiao C, et al. Microglia regulate sleep through calcium-dependent modulation of norepinephrine transmission. *Nat Neurosci* 2024;**27**:249−58.
15. Cattaneo M. P2Y12 receptors: structure and function. *J Thromb Haemost : JTH* 2015;**13**(Suppl 1):S10−6.
16. von Kügelgen I. Molecular pharmacology of P2Y receptor subtypes. *Biochem Pharmacol* 2021;**187**:114361.
17. Li F, Xu D, Hou K, Gou X, Li Y. The role of P2Y12 receptor inhibition in ischemic stroke on microglia, platelets and vascular smooth muscle cells. *J Thromb Thrombolysis* 2020;**50**: 874−85.
18. Zhou R, Ji B, Kong Y, Qin L, Ren W, Guan Y, et al. PET imaging of neuroinflammation in Alzheimer's disease. *Front Immunol* 2021;**12**: 739130.
19. Morrone FB, Vargas P, Rockenbach L, Scheffel TB. P2Y(12) purinergic receptor and brain tumors: implications on glioma microenvironment. *Molecules* 2021;**26**:6146.
20. Wang Q, Shi NR, Lv P, Liu J, Zhang JZ, Deng BL, et al. P2Y12 receptor gene polymorphisms are associated with epilepsy. *Purinergic Signal* 2023;**19**:155−62.



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