Homotrimeric P2X7 Receptor Imaging Tracers

Subjects: Chemistry, Inorganic & Nuclear | Oncology

Contributor: Stephan Schmidt , Andreas Isaak , Anna Junker

The homotrimeric P2X7 receptor (P2X7R) is expressed by virtually all cells of the innate and adaptive immune system and plays a crucial role in various pathophysiological processes such as autoimmune and neurodegenerative diseases, inflammation, neuropathic pain and cancer. Consequently, the P2X7R is considered a promising target for therapy and diagnosis. As the development of tracers comes hand-in-hand with the development of potent and selective receptor ligands, there is a rising number of PET tracers available in preclinical and clinical studies. P2X7R antagonists can be broadly subdivided into two categories: those able to penetrate the blood-brain barrier (BBB) and enter the central nervous system, or those remaining peripherally. Commonly linked central nervous system (CNS) P2X7R applications are diseases like Alzheimer's disease (AD), Parkinson's disease (PD) or multiple sclerosis (MS), as well as the formation of different types of cancer, i.e., glioblastoma multiforme (GBM). On the other hand, peripherally bioavailable P2X7R antagonists that are not BBB-permeable are attractive candidates for the treatment/diagnosis of lung and breast cancer.

P2X7R imaging [11C]carbon [18F]fluorine purinergic signalling PET

1. Radiolabelling Strategies

The synthesis of radiolabeled homotrimeric P2X7 receptor (P2X7R) ligands comes with certain requirements. Due to the radioisotopes' short half-life time, fast and efficient labeling methods that diverge from the classical pathways in organic synthesis are necessary. Two of the most common isotopes applied in PET imaging of P2X7R expression in vivo are carbon-11 and fluor-18.

The primary source of [^{11}C]carbon is the ^{14}N(p,α)^{11}C reaction on nitrogen gas [1], doped with oxygen or hydrogen, leading to one of the two primary labeling agents, [^{11}C]carbon dioxide and [^{11}C]methan. The former in particular can be subject to carrier dilution from atmospheric carbon dioxide, while methane lacks sufficient reactivity. [^{11}C]carbon dioxide allows the introduction of carboxyl groups, but the resulting carboxylate-bearing ligands often display limited blood-brain barrier (BBB) permeability. Therefore, the primary labeling agents are commonly converted further to enable fast and efficient reactions with precursor molecules and diversify the accessible structures. One of the most widely applied secondary labeling agents is [^{11}C]methyl iodide, which can be obtained from both [^{11}C]carbon dioxide as well as from [^{11}C]methan. The former is reduced to $^{11}CH_4$ and subsequently substituted with HI or by reaction with I_2 under high pressure [2]. The 'on-line' conversion of [^{11}C]methyl iodide to [^{11}C]methyl triflate can yield another more reactive ^{11}C-methylating agent [3][4]. A practical example for the incorporation of [^{11}C]carbon into a P2X7R ligand is the *N*-methylation of [^{11}C]GSK1482160 utilizing the activated secondary labeling agent [^{11}C]CH_3OTf, which was obtained by the nucleophilic substitution of [^{11}C]CH_3I with silver

triflate and then was used to methylate the corresponding amide (Scheme 1). The tracer was obtained in high specific activity 260–360 GBq/μmol and radiochemical yield (rcy) of 30–40% [5].

For the generation of [^{18}F]fluoride, the ^{18}O(p,n)^{18}F reaction on ^{18}O-enriched water has become almost universally applied [6]. The yielded [^{18}F]fluoride ion can primarily be used in aliphatic nucleophilic substitution reactions, aromatic nucleophilic substitutions, and transition metal-catalyzed fluorination reactions. The [^{18}F]-JNJ-64413739 was synthesized via a nucleophilic substitution reaction of [^{18}F]fluoride in the presence of kryptofix, potassium oxalate ($K_2C_2O_4$) in deuterated dimethyl sulfoxide The PET tracer was prepared with a specific activity of 17–100 GBq/μmol. However, the authors did not report on the radiochemical yields (rcy) of the reaction.

2. Homotrimeric P2X7 Receptor Tracers for the PET Imaging in Central Nervous System

The CNS consists of the brain and the spinal cortex and is arguably the most complex organ in our body. It has to adapt to changing environmental challenges, and to achieve this, it is isolated from the rest of the organism by the blood-brain barrier so that it can control and protect itself efficiently. The BBB enables the selective uptake of molecules as a protection mechanism. Consequently, brain-specific diseases like the aforementioned AD or PD can only be monitored and treated by compounds that cross the BBB.

The aforementioned abundance of P2X7 In the CNS and its involvement in various diseases sparked excitement in the scientific community, resulting in the advancements of tracers for imaging of neuroinflammatory responses in CNS pathologies

GSK1482160, a pyroglutamic acid amide analogue produced by GlaxoSmithKline (GSK), demonstrated high potency in in vitro assays on rat and human P2X7Rs, together with an excellent safety profile and potency in in vivo rat models [7]. These initially promising results led to the subsequent investigation of its pharmacokinetic (PK) and pharmacodynamic (PD), safety and tolerability parameters in healthy human subjects [8]. The study revealed a desirable pharmacological profile; however, it was not possible to achieve sufficient P2X7R inhibition whilst maintaining a necessary safety margin with regard to the applied dose. These findings led to a temporary halt on the further development of GSK1482160 to a therapeutic for chronic inflammatory pain [8]. Interestingly, it was discovered that GSK1482160 also showed an ability to cross the BBB and enter the CNS, making it potentially useful in a neurological context [9]. This shifted the focus to the development of a PET tracer as a potential biomarker of neuroinflammation, reviving the interest in the structure. Recent publications about GSK1482160 and derivatives exclusively contain the development of radiolabeled [^{11}C]GSK1482160. The radiolabeled compound can bind to the P2X7R and indicate the extent of expression and progression of neuroinflammation [10]. Green et al. concluded from a clinical trial (NCT00849134) in healthy subjects that even though the brain uptake was as low as 2% of the injected dose, the compound appears suitable for PET studies of the P2X7R expression for monitoring inflammatory processes [11]. In a different approach, Gao et al. tried to address the problem of low brain uptake by exchanging the aromatic chlorine for the homologous halogen substituents, forming the series [^{11}C]halo-GSK1482160 (F-, Br-, and I-); with the result that the bromo- and iodine-bearing compounds were binding with a

slightly higher affinity to P2X7R in an in vitro competitive binding assay on human P2X7R (HEK293-hP2X7R) [12]. In vivo studies still need to be conducted in order to confirm these initially promising results and show whether the addressed issues can be solved to obtain a promising candidate for clinical trials. In order to extend the available time frame for efficient synthesis and imaging studies, the GSK1482160 lead structure was modified by the introduction of the fluoroethyl substituent at the lactam portion to yield an equally P2X7R potent, 18-fluorine labeled PET tracer [^{18}F]IUR-1601. Careful optimization of the radiolabeling reaction conditions was required to suppress the competing elimination reaction leading to the formation of the vinyl side product and yielding [^{18}F]IUR-1601 in moderate molar activities and radiochemical yields [13]. The results of in vivo imaging applications using [^{18}F]IUR-1601 have yet to be reported.

Janssen et al., developed adamantane benzamide-based tracers, of which [^{11}C]-SMW139 and [^{11}C]SMW64-D16 underwent further evaluation [14]. [^{11}C]SMW64-D16 targeted inflamed areas in brain slices of two rat models but did not show sufficient brain uptake in rodent biodistribution studies via PET [15]. The trifluorinated variant of the adamantane benzamide [^{11}C]SMW139, did not show a difference in tracer binding affinity between the tissues of AD patients and healthy subjects ex vivo. However, there were promising results in an in vivo experimental autoimmune encephalomyelitis (EAE) rat model with regard to the tracer uptake at the peak of the disease in neuroinflammation imaging with the P2X7R PET tracer [^{11}C]SMW139 [16]. Most recently, with the first human studies (NCT04126772), the compound entered clinical trials, although only with a small number of subjects. It demonstrated good pharmacokinetic properties and brain uptake; moreover, higher signals were obtained from 90-min dynamic PET scans in active relapsing-remitting multiple sclerosis (RRMS) patients compared to the control group of healthy subjects [17]. As a next step, larger cohort studies, controlling for varying demographic and lifestyle factors, would undeniably be illuminating.

[^{18}F]JNJ-64413739, a selective P2X7R antagonist with an affinity and potency in a low nanomolar range, was developed by Janssen Pharmaceuticals and preclinically tested in a rat lipopolysaccharide (LPS) local neuroinflammation model. For that purpose, rats were intrathecally injected either with LPS in one hemisphere to induce neuroinflammation in brain tissue or injected with phosphate-buffered saline (PBS) as a negative control. The neuroinflammation process was confirmed by the upregulation of three biomarker genes: TSPO, AIF-1, and P2X7R, evaluated by qPCR. Compared to the negative control, the expression level of P2X7R was elevated by factor two and proved this receptor once more to be a promising target for the imaging and treatment of neuroinflammation. In the preclinically performed PET imaging studies, a significant increase of the PET signal in LPS-injected rats was observed relative to both the PBS-injected control and the naïve animals. The specificity of tracer uptake in the LPS-injected hemisphere was demonstrated by blocking studies with JNJ-54175446 as an inhibitor. Compared to vehicle-control animals, the pre-treatment with JNJ-54175446 10 min before starting the PET imaging lowered the tracer uptake in the LPS-injected as well as in the non-injected hemisphere significantly., The decrease of tracer uptake was higher than at the control site supporting the hypothesis that the [^{18}F]JNJ-64413739 tracer signal is specific to the P2X7R expression mainly in the LPS-injected hemisphere [18]. Further preclinical studies from Kolb et al. investigated the level of P2X7R occupancy by the [^{18}F]JNJ-64413739 tracer in healthy rodents. Here, the expression and activity levels of the P2X7R under these physiological conditions were expected to be low. Nevertheless, the P2X7R occupancy study in healthy rats demonstrated the specificity of the

[^{18}F]JNJ-64413739 tracer by using JNJ-55308942 as an inhibitor. The one hour pre-treatment with the inhibitor prior to PET imaging resulted in a decrease in tracer uptake in the brain under physiological conditions. An additional microdosing approach with the [^{18}F]JNJ-64413739 tracer using a P2X7R knock-out (KO) mouse model suggested a certain degree of non-specific binding of the tracer in the brain tissue. The non-specific binding was also observed in a P2X7R occupancy study in healthy adult rhesus macaques (*Macaca mulatta*) as a nonhuman primate organism. Matching with previous data, the [^{18}F]JNJ-64413739 tracer accumulates in the brain tissue under physiological conditions and could be reduced in a dose-dependent manner by pre-treatment with JNJ-54175446 as an inhibitor. Furthermore, in these experiments, a certain degree of non-specific binding of the [^{18}F]JNJ-64413739 tracer could be observed to be in agreement with the previous data from the rodent experiments [19]. The high affinity, specificity, metabolic stability, and low protein-bound fraction in plasma make the [^{18}F]JNJ-64413739 tracer suitable as a clinical imaging agent. Koole et.al. evaluated the clinical biodistribution, the pharmacokinetic profile, and the P2X7R occupancy in 16 healthy subjects (NCT03088644, NCT03437590). The presented data of [^{18}F]JNJ-64413739 supports its assessment as a reliable PET tracer for quantification of P2X7R in the brain tissue to study its involvement in neuroinflammation, neurodegeneration, and mood disorders or to evaluate the occupancy level of selective BBB permeating P2X7R inhibitors [20]. Most recently, a structurally related P2X7R targeting PET tracer [^{18}F]FTTM was successfully applied in the rat model of temporal lobe epilepsy. Tracer uptake was associated with activated microglia and proved the potential of P2X7R imaging for monitoring neuroinflammation again [21].

The attempted subtle structural modifications in GSK1482160 and JNJ64413739 derived series of PET tracers are rather surprising as they have led to significant differences in the performance of the respective PET tracer, which leads to the question of the predictivity of the available in vitro models for assessing the pharmacokinetic profiles in tracer development.

The first P2X7R imaging ligand that went into in vivo testing was [^{11}C]A740003, developed by Abbott Laboratories, after showing promising results in initial in vitro assays. However, the in vivo studies showed a low brain uptake and a moderate metabolic rate in mice, disqualifying [^{11}C]A740003 for the efficient imaging of the brain [22]. In an approach to overcome the uptake issues, [^{18}F]EFB, another tracer bearing a cyanoguanidine structure, which derived from A804598, was developed. A804598 is known to be a blood-brain barrier permeable P2X7R antagonist, so the structural resemblance appeared to be promising [23]. In vitro testing in a calcium influx binding assay revealed low nM binding constants for the human P2X7R, but a 200-fold higher binding constant for the murine isoform [24]. The compound displayed a low brain uptake in rats, showing potentially limited suitability of the cyanoguanidine moiety for BBB uptake. The ligand's high potency for the human receptor and low activity at the murine/rat subtype suggests a (misleadingly) low background for potential evaluation in xenograft models of human tumor tissues implanted into mice.

There is a growing number of imaging ligands for applications in the CNS targeting the P2X7R due to its vast distribution in glial cells and, consequently, its involvement in neuroinflammatory processes (due to P2X7R's mediatory role in the release of IL-1β and the activation of the NLRP3 inflammasome). The majority of ligands discussed in this research showed good results in preclinical in vitro and in vivo evaluations, and some have

already proceeded to clinical trials, albeit with a limited number of participants. With regard to these trials, it becomes clear that the in vivo brain uptake in human patients remains a challenging task for current imaging tracers. Another difficulty for the translation of in vitro into in vivo studies involves the heterogeneity in the disease progression, e.g., the time dependence of P2X7R-expression and the expression of different P2X7R variants in the tissue. The specific imaging of acute neuroinflammatory diseases in comparison to healthy individuals displayed an additional challenging task for some of the tested tracers, as with [^{11}C]JNJ-54173717. Neither [^{11}C]A740003 nor [^{18}F]EFB showed appreciable brain uptake; nevertheless, data exist which suggest the use of those tracers outside the CNS, which shall be discussed in the following section.

3. Homotrimeric P2X7 Receptor Tracers for the Imaging Applications Outside of Central Nervous System

Of widespread interest is the role of P2X7R antagonists not only in the CNS but also in the periphery. This includes inflammatory processes, as well as different types of cancer. Tracers showing limited BBB permeation but high P2X7R binding in vivo might provide promising results in peripheral imaging applications.

In 2019, Fu et al. revealed a novel P2X7R imaging ligand, [^{18}F]PTTP, which might be useful in the screening of new drugs and in distinguishing inflammation from lung tumors [25]. [^{18}F]PTTP is based on a triazolo-tetrahydropyridine structure related to [^{18}F]JNJ-64413739 developed by Janssen Pharmaceuticals. PTTP showed promising physicochemical properties, excellent pharmacokinetic characteristics, and a strong affinity to hP2X7 and mP2X7 receptors, and was therefore selected for inflammation imaging. Compared to the aforementioned JNJ compounds, [^{18}F]PTTP showed a low brain uptake, which is, however, higher than for [^{11}C]A740003 and [^{18}F]EFB [22][26]. From their initial results, Fu et al. concluded that [^{18}F]PTTP is a better probe to localize inflammatory diseases by screening for macrophages than to identify lung tumors due to the low tumor uptake in xenograft models of human lung cancer cells in mice. However, the study addresses the great potential of [^{18}F]PTTP as a PET tracer and P2X7R antagonist for screening new drugs, quantifying the expression of P2X7R in peripheral inflammation, and distinguishing inflammation from the tumor [25]. A structurally related PET tracer [^{18}F]FTTM was not only demonstrated to provide sufficient brain uptake for the imaging of neuroinflammation in the rat model of temporal lobe epilepsy, but also to outperform [^{18}F]FDG in the imaging of the ApoE Mouse model of atherosclerotic plaques [21].

Finally, there are numerous ligands that were proven to modulate the P2X7R activity in the search for new therapeutic strategies, such as AZ10606120 [27][28], A-438079 [29], AZD9056 (NCT00908934, NCT00920608, NCT00700986, NCT00736606, NCT00520572), CE-224535 (NCT00628095), and GSK1482160 (NCT00849134). Subtle structural modifications to introduce radioactive isotopes are rather unlikely to impact the affinity of the ligand to the receptor significantly; consequently, already known ligands with high affinity and selectivity for the P2X7R bear the potential to function as a starting point for the development of novel radiotracers.

References

1. Wolf, A.P.; Redvanly, C.S. Carbon-11 and radiopharmaceuticals. Int. J. Appl. Radiat. Isot. 1977, 28, 29–48.
2. Schubiger, P.A.; Lehmann, L.; Friebe, M.; Yang, D.J. PET Chemistry: The Driving Force in Molecular Imaging. J. Nucl. Med. 2007, 48, 1750.
3. Någren, K.; Müller, L.; Halldin, C.; Swahn, C.G.; Lehikoinen, P. Improved synthesis of some commonly used PET radioligands by the use of methyl triflate. Nucl. Med. Biol. 1995, 22, 235–239.
4. Lundkvist, C.; Sandell, J.; Någren, K.; Pike, V.W.; Halldin, C. Improved syntheses of the PET radioligands, FLB 457, MDL 100907 and β-CIT-FE, by the use of methyl triflate. J. Label. Compd. Radiopharm. 1998, 41, 545–556.
5. Han, J.; Liu, H.; Liu, C.; Jin, H.; Perlmutter, J.S.; Egan, T.M.; Tu, Z. Pharmacologic characterizations of a P2X7 receptor-specific radioligand, GSK1482160 for neuroinflammatory response. Nucl. Med. Commun. 2017, 38, 372–382.
6. Guillaume, M.; Luxen, A.; Nebeling, B.; Argentini, M.; Clark, J.C.; Pike, V.W. Recommendations for fluorine-18 production. Int. J. Radiat. Appl. Instrum. Part A Appl. Radiat. Isot. 1991, 42, 749–762.
7. Abdi, M.H.; Beswick, P.J.; Billinton, A.; Chambers, L.J.; Charlton, A.; Collins, S.D.; Collis, K.L.; Dean, D.K.; Fonfria, E.; Gleave, R.J.; et al. Discovery and structure–activity relationships of a series of pyroglutamic acid amide antagonists of the P2X7 receptor. Bioorg. Med. Chem. Lett. 2010, 20, 5080–5084.
8. Ali, Z.; Laurijssens, B.; Ostenfeld, T.; McHugh, S.; Stylianou, A.; Scott-Stevens, P.; Hosking, L.; Dewit, O.; Richardson, J.C.; Chen, C. Pharmacokinetic and pharmacodynamic profiling of a P2X7 receptor allosteric modulator GSK1482160 in healthy human subjects. Br. J. Clin. Pharmacol. 2013, 75, 197–207.
9. Burnstock, G.; Knight, G.E. The potential of P2X7 receptors as a therapeutic target, including inflammation and tumour progression. Purinergic Signal. 2018, 14, 1–18.
10. Territo, P.R.; Meyer, J.A.; Peters, J.S.; Riley, A.A.; McCarthy, B.P.; Gao, M.; Min, W.; Green, M.A.; Zheng, Q.H.; Hutchins, G.D. Characterization of 11C-GSK1482160 for Targeting the P2X7 receptor as a biomarker for neuroinflammation. J. Nucl. Med. 2017, 58, 458–465.
11. Green, M.; Hutchins, G.; Fletcher, J.; Territo, W.; Polson, H.; Trussell, H.; Wissmann, C.; Zheng, Q.-H.; Gao, M.; WANG, M.I.N.; et al. Distribution of the P2X7-receptor-targeted GSK1482160 radiopharmaceutical in normal human subjects. J. Nucl. Med. 2018, 59, 1009.

12. Gao, M.; Wang, M.; Meyer, J.A.; Territo, P.R.; Hutchins, G.D.; Zarrinmayeh, H.; Zheng, Q.-H. Synthesis and in vitro biological evaluation of new P2X7R radioligands halo-GSK1482160 analogs. Bioorg. Med. Chem. Lett. 2019, 29, 1476–1480.
13. Gao, M.; Wang, M.; Glick-Wilson, B.E.; Meyer, J.A.; Peters, J.S.; Territo, P.R.; Green, M.A.; Hutchins, G.D.; Zarrinmayeh, H.; Zheng, Q.-H. Synthesis and preliminary biological evaluation of a novel P2X7R radioligand IUR-1601. Bioorg. Med. Chem. Lett. 2018, 28, 1603–1609.
14. Janssen, B.; Vugts, D.J.; Wilkinson, S.M.; Ory, D.; Chalon, S.; Hoozemans, J.J.M.; Schuit, R.C.; Beaino, W.; Kooijman, E.J.M.; Van Den Hoek, J. Identification of the allosteric P2X7 receptor antagonist SMW139 as a PET tracer of microglial activation. Sci. Rep. 2018, 8, 6580.
15. Janssen, B.; Ory, D.; Wilkinson, S.M.; Vugts, D.J.; Kooijman, E.J.; Verbeek, J.; Funke, U.; Molenaar, G.T.; Kruijer, P.S.; Lammertsma, A.A. Initial evaluation of P2X(7)R antagonists A-740003 and SMW64-D16 as PET tracers of microglial activation in neuroinflammation. J. Label. Comp. Radiopharm. 2015, 58, S277.
16. Beaino, W.; Janssen, B.; Kooijman, E.; Vos, R.; Schuit, R.; Kassiou, M.; Vugts, D.; de Vries, H.; Windhorst, A. Neuroinflammation imaging with the P2X(7)R PET tracer SMW139 in the experimental autoimmune encephalomyelitis (EAE) model. J. Label. Compd. Radiopharm. 2019, 62, S73–S74.
17. Hagens, M.H.J.; Golla, S.S.V.; Janssen, B.; Vugts, D.J.; Beaino, W.; Windhorst, A.D.; O'Brien-Brown, J.; Kassiou, M.; Schuit, R.C.; Schwarte, L.A. The P2X7 receptor tracer SMW139 as an in vivo marker of neuroinflammation in multiple sclerosis: A first-in man study. Eur. J. Nucl. Med. Mol. Imaging 2020, 47, 379–389.
18. Berdyyeva, T.; Xia, C.; Taylor, N.; He, Y.; Chen, G.; Huang, C.; Zhang, W.; Kolb, H.; Letavic, M.; Bhattacharya, A.; et al. PET Imaging of the P2X7 Ion Channel with a Novel Tracer JNJ-64413739 in a Rat Model of Neuroinflammation. Mol. Imaging Biol. 2019, 21, 871–878.
19. Kolb, H.C.; Barret, O.; Bhattacharya, A.; Chen, G.; Constantinescu, C.; Huang, C.; Letavic, M.; Tamagnan, G.; Xia, C.A.; Zhang, W.; et al. Preclinical Evaluation and Nonhuman Primate Receptor Occupancy Study of 18F-JNJ-64413739, a PET Radioligand for P2X7 Receptors. J. Nucl. Med. 2019, 60, 1154–1159.
20. Koole, M.; Schmidt, M.E.; Hijzen, A.; Ravenstijn, P.; Vandermeulen, C.; Van Weehaeghe, D.; Serdons, K.; Celen, S.; Bormans, G.; Ceusters, M.; et al. 18F-JNJ-64413739, a Novel PET Ligand for the P2X7 Ion Channel: Radiation Dosimetry, Kinetic Modeling, Test-Retest Variability, and Occupancy of the P2X7 Antagonist JNJ-54175446. J. Nucl. Med. 2019, 60, 683–690.
21. Fu, Z.; Lin, Q.; Xu, Z.; Zhao, Y.; Cheng, Y.; Shi, D.; Fu, W.; Yang, T.; Shi, H.; Cheng, D. P2X7 receptor-specific radioligand 18F-FTTM for atherosclerotic plaque PET imaging. Eur. J. Nucl. Med. Mol. Imaging 2022, 49, 2595–2604.

22. Janssen, B.; Vugts, D.J.; Funke, U.; Spaans, A.; Schuit, R.C.; Kooijman, E.; Rongen, M.; Perk, L.R.; Lammertsma, A.A.; Windhorst, A.D. Synthesis and initial preclinical evaluation of the P2X7 receptor antagonist A-740003 as a novel tracer of neuroinflammation. J. Label. Compd. Radiopharm. 2014, 57, 509–516.
23. Donnelly-Roberts, D.L.; Namovic, M.T.; Surber, B.; Vaidyanathan, S.X.; Perez-Medrano, A.; Wang, Y.; Carroll, W.A.; Jarvis, M.F. A-804598 (2-cyano-1--3-quinolin-5-ylguanidine) is a novel, potent, and selective antagonist radioligand for P2X7 receptors. Neuropharmacology 2009, 56, 223–229.
24. Fantoni, E.R.; Dal Ben, D.; Falzoni, S.; Di Virgilio, F.; Lovestone, S.; Gee, A. Design, synthesis and evaluation in an LPS rodent model of neuroinflammation of a novel 18F-labelled PET tracer targeting P2X7. EJNMMI Res. 2017, 7, 31.
25. Fu, Z.; Lin, Q.; Hu, B.; Zhang, Y.; Chen, W.; Zhu, J.; Zhao, Y.; Choi, H.S.; Shi, H.; Cheng, D. P2X7 PET Radioligand 18F-PTTP for Differentiation of Lung Tumor from Inflammation. J. Nucl. Med. 2019, 60, 930–936.
26. Ory, D.; Celen, S.; Gijsbers, R.; Van Den Haute, C.; Postnov, A.; Koole, M.; Vandeputte, C.; Andrés, J.I.; Alcazar, J.; De Angelis, M.; et al. Preclinical evaluation of a P2X7 receptor-selective radiotracer: PET studies in a rat model with local overexpression of the human p2x7 receptor and in nonhuman primates. J. Nucl. Med. 2016, 57, 1436–1441.
27. Adinolfi, E.; Capece, M.; Franceschini, A.; Falzoni, S.; Giuliani, A.L.; Rotondo, A.; Sarti, A.C.; Bonora, M.; Syberg, S.; Corigliano, D. Accelerated tumor progression in mice lacking the ATP receptor P2X7. Cancer Res. 2015, 75, 635–644.
28. Adinolfi, E.; Raffaghello, L.; Giuliani, A.L.; Cavazzini, L.; Capece, M.; Chiozzi, P.; Bianchi, G.; Kroemer, G.; Pistoia, V.; Di Virgilio, F. Expression of P2X7 receptor increases in vivo tumor growth. Cancer Res. 2012, 72, 2957–2969.
29. Jelassi, B.; Chantome, A.; Alcaraz-Perez, F.; Baroja-Mazo, A.; Cayuela, M.L.; Pelegrin, P.; Surprenant, A.; Roger, S. P2X7 receptor activation enhances SK3 channels-and cystein cathepsin-dependent cancer cells invasiveness. Oncogene 2011, 30, 2108–2122.

Retrieved from https://www.encyclopedia.pub/entry/history/show/90798