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Faisability pilot study to explore inflammation with [18F]-DPA-714 PET/CT versus immunochemistry in triple negative breast cancer: Design protocol

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Abstract

The Triple Negative Breast Cancer (TNBC), despite a good initial response to conventional chemotherapy, relapses frequently and has a poor prognosis after the onset of metastases. It is therefore interesting to develop new relevant targets to establish a prognosis but also potentially to propose a targeted therapy for a theranostic approach. A high density of M2-type macrophages presence in the primary TNBC tumor predicted an unfavorable prognosis. The presence of activated M2-type macrophages can be evaluated by measuring the expression of a translocating protein (TSPO) with [18F]-DPA-714 PET-CT. This proof-of-concept study with [18F]-DPA-714 PET-CT has a design to establish the correlation between immunohistochemistry tumor characterization and in vivo imaging. If a valid correlation will be established, [18F]-DPA-714 PET-CT could be a based image prognosis biomarker, apart from pathological data, which can be fragmented as biopsy or modified by previous treatments. It would allow adapting early the type/dose-intensity of treatment and considering developments of treatments targeting M2-type macrophages.

Background

Breast cancer (BC) is a heterogeneous disease grouping together several entities characterized by morphological, molecular and functional data. The accuracy of the diagnosis and the characterization of the tumor type are major issues for the choice of patient management but also for their follow-up, as well as for therapeutic evaluation. Faced with the need for classification and determination of relevant criteria to be taken into account to refine the identification of the tumor type, Perou et al. [1] established in 2000 a molecular classification which defined 6 molecular subclasses (luminal A, luminal B, claudin-low, basal like, normal like, HER2) having no simple or unequivocal link with the elements of the "phenotypic" classification: hormone receptor positive (RH), HER2 positive and triple negative (TN) BC. TNBC, with an overall unfavorable prognosis, are often of the “basal like” (BL) molecular type. However, this correspondence is not perfect and therefore there is significant heterogeneity in this subgroup. Moreover, a transcriptomic study based on 107 pathological samples from non-metastatic TNBC patients [2], identified three different clusters (C): C1 (22%) called luminal androgenic, C2 (45%) basal-like with a weak immune response and a predominance of M2 macrophages type and finally the C3 (33%) rich in mesenchymal cells with an important immune response but a low richness in M2-type macrophages. In addition, previous studies had shown in proteomic analysis that the expression of the light chain of ferritin (FLT), involved in the metabolism of iron and stored within macrophages M2-type, is a factor of poor prognosis in patients with non-metastatic breast cancer without lymph node involvement [3,4]. These various studies have highlighted the importance of the exploration of tumor micro-environment cells and in particular of tumor-associated macrophages (TAM) [5].

TAM can change their phenotypes, depending on signals from the tumor microenvironment, and can either kill tumor cells or promote their growth and metastases

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[6]. In pre-clinical studies, it has been shown that they can induce resistance to several types of treatment. In fact, it has been shown that inhibiting the recruitment of macrophages or reprogramming their phenotype improved the response to treatment in BC mouse models [7-9]. In clinical practice, as described in a meta-analysis including more than 2,000 pathological samples from BC patients of all stages, a high density of TAM infiltrating the primary tumor predicted an unfavorable prognosis [10]. The BC microenvironment is made up of fibroblasts, vessels, adipocytes and immune cells. TAM can constitute more than 50% of the number of cells in this tumor microenvironment [11,12]. They consist of monocytes which are recruited by tumors via the secretion of cytokines and which differentiate into non-polarized macrophages (M0) thanks to the factor Monocyte Colony Stimulating Factor (M-CSF) and according to environmental signals, are converted into macrophages of M1 and/or M2-type, the latter being the majority [13-16]. TAM inhibits the infiltration and function of anti-tumor CD8+ T lymphocytes, stimulates angiogenesis in tumor and promotes proliferation and metastasis [7,17]. M1-type macrophages have an anti-tumor capacity by releasing pro-inflammatory cytokines (such as TNF and interleukin (IL) -2), as well as reactive intermediates of nitrogen and oxygen [18,19]. In contrast, M2-type macrophages are stimulated by the cytokines of type 2 T-helper cells (Th2) such as IL-4, IL 10 and IL-13 and in return produce large quantities of pro-tumor cytokines to influence tumor progression [16,19-21].

Therefore, TAMs are potential targets of interest in BC, but how can they be identified in the tumor microenvironment? The immunohistochemical analysis (IHC) of TAM is described in the literature with the targeting of CD68 and CD163. CD68 is recognized as a pan-macrophage marker but cannot distinguish TAM subpopulations. On the other hand, CD163 has been validated as a marker for macrophages of the M2-type [5,22].

In recent years, we are witnessing the development of imaging specifically targeting the stromal compartment or the tumor filtering immune cells, such as that targeting the fibroblast activation protein (FAP) which is strongly expressed in the stroma of several tumor entities including BC [23,24]. What imaging is available for targeting TAM? The presence of activated M2-type macrophages can be evaluated in patients by measuring the expression of the translocating protein (TSPO) in positron emission tomography (PET) with the selective radiopharmaceutical of this TSPO: [18F]-DPA- 714. TSPO was originally described as the peripheral benzodiazepine receptor, selectively located outside the central nervous system, where it is only expressed during neuroinflammation, making it a selective biomarker for microglial activation. Subsequently, studies have demonstrated its expression in all organs in humans [25-27]. This protein plays a role in the transport of cholesterol through the mitochondrial membrane, a limiting step in the synthesis of steroid hormones and bile salts. It is an intracellular protein of 18kDA, which is found in the vast majority of cases on the external mitochondrial membrane but also inside and around the nuclei of breast tumor cells [28]. The TSPO protein is a ubiquitous protein whose expression varies heterogeneously within the same organism. Although it plays an essential physiological role, it seems that TSPO is also involved in various pathological phenomena, among which are tumor progression and neurodegenerative pathologies. An increase in the expression of the TSPO protein has been observed in a wide variety of human tumor cells and tissues, particularly in BC [29,30], for which the expression of TSPO even seems to be correlated with tumor progression [28,29]. Recognized as a specific and sensitive *in vivo* biomarker of peripheral inflammation of the tumor microenvironment [31], the expression of TSPO would then represent a potential biomarker for stratification and staging of the disease. Indeed, the literature suggests that for BC, the degree of inflammation is correlated with angiogenesis and the metastatic potential of the tumor and therefore with factors of poor prognosis for patients [32-34]. The expression of TSPO is measured, in most of the studies, on the protein scale by immunohistochemistry or radiolabeled ligand. But the use of genetic modulation of TSPO expression, via messenger RNA (mRNA) to detect levels of TSPO mRNA, would be of limited use in most cancers as prognostic or diagnostic biomarker, due to the very slight variations in mRNA levels observed between healthy and cancerous tissues [29,30,35-37].

In vivo TSPO PET-CT imaging by radio-labeled ligands then appears to be a non-invasive approach that is interesting to develop. Long limited to neurology and more specifically to neuroinflammation, the field of application of PET imaging of TSPO has extended to rheumatic pathology [38] but also to cancer [39]. Preclinical work on models of human mammary tumour cell transplants has validated targeting by [18F]DPA-714 of TSPO as a biomarker of the tumour microenvironment, itself involved in the progression of the disease and the therapeutic response [40]. Nevertheless, it would seem that the binding of second generation TSPO tracers (such as DPA-714) is closely linked to the TSPO genotype encoded by the rs6971 single nucleotide polymorphism (SNP). This SNP, expressed in a co-dominant manner, generates three genotypes: homozygous high affinity (HAB) binders, heterozygous mixed affinity (MAB) binders and homozygous low affinity (LAB) binders. This discovery raised questions about the relative sensitivity of second generation radioligands like DPA-714, particularly in LAB phenotypes. In the general population, it is estimated that 50% of high affinity binders (HAB), 30 to 40% of medium affinity binders (MAB) and 10 to 20% of low affinity binders (LAB) [41,42]. In Wyatt et al. pre-clinical study, TSPO in breast cancer will be a value to both the molecular imaging but also for a future treatment target of [43]. More recently, always in a pre-clinical study, Zhang et al. observed a synergistic inhibition TNBC tumour growth, with a treatment targeting cannabinoid CB2 receptor agonist but mostly phototherapy supported by TSPO [44].

As in TNBC, TAM and in particular M2-type macrophages have been defined as prognostic biomarkers, that they can be demonstrated by IHC, that molecular imaging with [18F]-DPA- 714 PET-CT could allow their expression *in vivo* and that TSPO targeting seems to be a potential promising therapeutic target, we proposed a pilot study "proof of concept" to establish the correlation between the presence of macrophage M2-type determined by IHC and in [18F]-DPA- 714 PET-CT uptake in TNBC patients immediately operable. Ultimately, both for patients operated on immediately or those receiving neo-adjuvant chemotherapy, it is hoped that *in vivo* [18F]-DPA-714 PET-CT evaluation will allow access to information on the presence or not of M2-type macrophage in tumor micro-environment and therefore to the tumor prognosis of each patient and allowing therapy to be better adapted to the aggressiveness of their tumor.

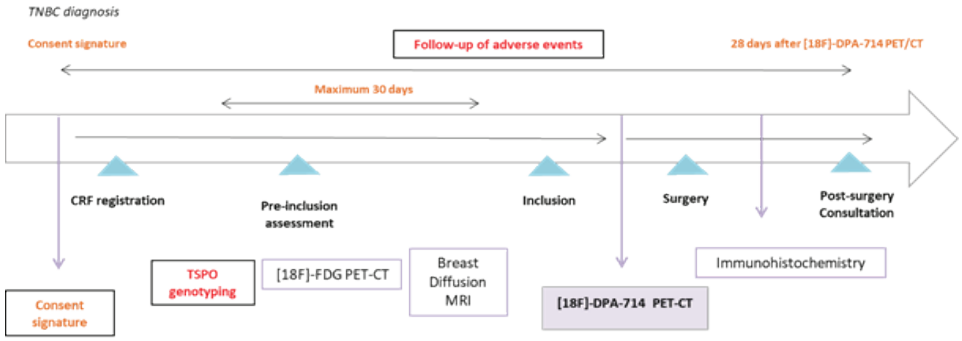

Figure 1. *Study design.*

Design and population

This study is a prospective, phase II, multicenter, non-randomized study. A total of 12 patients will be included. Recruitment is planned for 3 centers (4 sites), over a period of 12 months, with a patient follow-up period of 3 months.

The study will recruit TNBC patients (estrogen receptors <10%, and progesterone receptors <10% and HER2 unamplified or not overexpressed) with an indication of surgery. Patients with inflammatory or metastatic TNBC cannot be included. Likewise, patients who have already received anti-cancer treatment (chemotherapy, immunotherapy, hormone therapy and external radiotherapy), antibiotics and/or anti-inflammatory drugs (steroid and/or non-steroid) 30 days before inclusion, will be excluded. Finally, any diabetes should be balanced.

Patients eligible and having signed the informed consent will enter in the trial, whose the design is presented in Figure 1. First, a standard biological assessment, a blood sample for genotyping of TSPO, a FDG PET-CT and MRI with a bilateral breast and axillary areas diffusion sequence. Then, [18F]-DPA-714 PET-CT will be performed before surgery. The vital signs will be monitored before the [18F]-DPA-714 PET-CT and for 2 hours after the injection of the radiopharmaceutical. After the surgical procedure, the tumor tissue will be studied by IHC analysis and in vitro autoradiography using (3H) DPA-714. Post-surgical visit will be the study end of the study in order to research of possible late toxicity of [18F]-DPA-714 PET-CT.

Objectives

Primary objective

It will consist of the search for a correlation between the macrophage polarization M1/M2 determined in IHC in the tumor and the [18F]-DPA-714 PET-CT uptake (qualitative and texture analysis) in TNBC patients operable immediately. This macrophage polarization M1/M2 will be determined by the relationship between the expression of the macrophage marker M2 (CD163) and the pan-macrophage marker (CD68). The TAM number will be done on at least four hot spots and the average will determine the number of TAM per tumor. Based on the median results obtained on all the tumors, the polarization will be determined by distinguishing on the one hand the tumors with a high CD163/CD68 ratio which will correspond to the polarization M2 type tumors and on the other hand the tumors with a low CD163/CD68 ratio which will correspond to the polarization M1 type tumors. We will observe the difference in uptake level with Standard Uptake Value (SUV) on [18F]-DPA-714 PET-CT according to the CD163/CD68 ratio high or low obtained in IHC.

Secondary objectives

- Study of the correlation between the TSPO genotype (HAB, MAB and LAB) carried out at the end of the study and [18F]-DPA-714 PET-CT tumor uptake.

- Assessment of the interest of early and late imaging with [18F]-DPA-714 PET-CT by comparing the qualitative and semi-quantitative parameters at the 2 time acquisitions.

- Assessment of the characterization performance of TNCB by the three types of imaging performed in this study: [18F]-DPA-714 PET-CT, FDG PET-CT and breast diffusion MRI thanks to image texture analyzes.

- Study of the possible toxicity of [18F]-DPA-714 by measuring vital signs and monitoring the patient after the injection of the radiopharmaceutical. Any toxicity linked to [18F]-DPA-714 will be c ollected. The NCI Common Toxicity Criteria, version 5.0 reference will be used.

[18F]-DPA-714 PET-CT acquisition

All imaging sequences will be performed on an outpatient basis. The patient will be not fasting. No premedication will be carried out.

The radiopharmaceutical activity to be dispensed will be 3.5 MBq/kg ± 10%, in accordance with the data in the literature [45,46]. The syringe will be measured before and after injection to determine the activity actually injected.

A first series of dynamic PET images will be produced in List mode for 30 minutes, centered on the thorax and the axillary areas, in procubitus with the arms above the head, immediately after injection of the [18F]-DPA-714. The PET acquisition will be combined with a low dose CT scan centered on the chest.

A second PET-CT will be performed 60 minutes after the injection of the radiotracer, centered on the thorax and the axillary areas, in procubitus with the arms above the head, for 15 minutes. This second acquisition will also be combined with a "low dose scanner" centered on the chest.

Although the safety of [18F]-DPA-714 is likely based on published studies: all patients will be monitored by the investigator, by vital signs for 2 hours after intravenous injection of the tracer and during post-operative visit for long term side effects.

Statistics

As this is a "proof of concept" study, an exploratory and descriptive pilot, the number of patients included was set at 12 patients over 1 year.

Statistical analysis plan

On the [18F]-DPA-714 PET-CT acquisitions, a qualitative analysis will be carried out during each examination by at least one nuclear physician who is not aware of the results of the other imaging examinations. A centralized semi-quantitative analysis will be carried out on the lesion(s) as well as Tumor/Background reports according to the biodistribution of the radiopharmaceutical.

The "gold standard" for the evaluation of lesions will be defined by data from anatomical pathology and molecular biology.

The continuous variables will be summarized by their mean ± standard deviation and the qualitative variables by the distribution of their modalities, and this overall and by subgroups of interest (Hormonal receptors, histological type, SBR grade, mitotic index). Interest groups will be compared using the following statistical tests:

- Continuous variables: - If group variable with 2 modalities: non-parametric Wilcoxon test, - If group variable> 2 modalities: non-parametric Kruskal-Wallis test
- Qualitative variables: exact Fisher test

The correlation between continuous variables will be calculated by the Rho coefficient of the Spearman test.

Discussion

The TNBC, representing 10-20% of invasive BC, often corresponds to a cancer with large tumor size with lymph node invasion, in young women (<50 years) and with rapid evolution (so-called "interval cancer"). Despite a good initial response to conventional chemotherapy, relapse remains frequent and rapid (within 1-3 years) and has a poor prognosis after the onset of metastases [47]. It is therefore interesting to develop new relevant targets to establish a prognosis but also potentially to propose a targeted therapy performing a theranostic approach.

It has been shown that a high density of TAM infiltrates and specially the M2-type macrophages presence in the primary TNBC tumor predicted an unfavorable prognosis (10). Knowing that TNBC is most often treated at diagnosis with neo-adjuvant chemotherapy, how can we appreciate the tumor microenvironment and characterize the macrophagic differentiation M1/M2 macrophages? Neo-adjuvant chemotherapy leads to the tumor microenvironment examination obsolete for breast surgery performed in a second step. The diagnostic biopsy, given the fragmentary side of the tumor fragment, also does not allow these data to be obtained. In recent years, a significant development of molecular imaging showed the advent of many PET radiopharmaceuticals more specific than FDG. In particular, the presence of activated M2-type macrophages can be evaluated in cancers by measuring the expression of the translocating protein (TSPO) with [18F]-DPA-714 PET-CT (41). This appreciation of the tumor microenvironment and macrophagic M2-type differentiation by a non-invasive in vivo imaging approach would allow, even if a primary surgery is not performed immediately, to obtain the important prognostic factors for disease management at an early stage of its development.

This proof-of-concept study of TNBC treated by surgery is the first step to the wider use of [18F]-DPA-714 PET-CT in TNBC whatever their initial care. Indeed, it is first step to establish a correlation between the tumor characterization by IHC (on the surgical tumor naive of any treatment) and PET-CT imaging.

If a valid correlation will be established, the [18F]-DPA-714 PET-CT performed at diagnosis can bring prognostic elements based on images even to patients undergoing treatment prior to surgery and perhaps very early adapt the type and dose-intensity of neo-adjuvant chemotherapy.

Subsequently, at the metastatic stage, [18F]-DPA-714 PET-CT could make it possible to visualize the M2-type macrophages infiltration in the metastatic sites usually involved in TNBC such as the lungs and the CNS and to consider developments of treatments targeting these M2-type macrophages.

In conclusion, TPSO targeting as a specific and sensitive inflammation biomarker of TNBC tumor microenvironment, could explore in vivo with [18F]-DPA-714 PET-CT, tumor progression, metastatic invasion and the therapeutic tumor response.

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Ethics approval and consent to participate

This study was approved by the Medical Ethics Review Board of "Ile de France 2" and was registered under the number 2019-001463-75.

All subjects will give written informed consent prior to study participation

Competing interests

All authors declare that they have no competing interests.

References

1. Perou CM, Sørlie T, Eisen MB, et al. Molecular portraits of human breast tumours. Nature. 2000;406:747–52.
2. Jézéquel P, Loussouarn D, Guérin-Charbonnel C, et al. Gene-expression molecular subtyping of triple-negative breast cancer tumours: importance of immune response. Breast Cancer Res. 2015;17:43.
3. Descotes F, Jézéquel P, Spyratos F, et al. Identification of potential prognostic biomarkers for node-negative breast tumours by proteomic analysis: a multicentric 2004 national PHRC study. Int J Oncol. 2012;41:92–104.
4. Ricolleau G, Charbonnel C, Lodé L, et al. Surface-enhanced laser desorption/ionization time of flight mass spectrometry protein profiling identifies ubiquitin and ferritin light chain as prognostic biomarkers in node-negative breast cancer tumours. Proteomics. 2006;6:1963–75.
5. Qiu SQ, Waaijer SJH, Zwager MC, de Vries EGE, van der Vegt B, Schröder CP. Tumour-associated macrophages in breast cancer: Innocent bystander or important player? Cancer Treat Rev. 2018 Nov;70:178-189.
6. Noy R, Pollard JW. Tumour-associated macrophages: from mechanisms to therapy. Immunity 2014;41:49–61.
7. Xu M, Liu M, Du X, et al. Intratumoural delivery of IL-21 overcomes anti-Her2/Neu resistance through shifting tumour-associated macrophages from M2 to M1 phenotype. J Immunol 2015;194:4997–5006.
8. De Nardo DG, Brennan DJ, Rexhepaj E, et al. Leukocyte

complexity predicts breast cancer survival and functionally regulates response to chemotherapy. Cancer Discov 2011;1:54–67.

9. Shiao SL, Ruffell B, DeNardo DG, Faddegon BA, Park CC, Coussens LM. TH2-polarized CD4(+) T cells and macrophages limit efficacy of radiotherapy. Cancer Immunol Res 2015;3:518–25.
10. Zhang Q, Liu L, Gong C, et al. Prognostic significance of tumour-associated macrophages in solid tumour: a meta-analysis of the literature. PLoS One 2012;7:e50946.
11. Mantovani A, Marchesi F, Malesci A, Laghi L, Allavena P. Tumour-associated macrophages as treatment targets in oncology. Nat Rev Clin Oncol 2017;14:399–416.
12. Pollard JW. Macrophages define the invasive microenvironment in breast cancer. J Leukoc Biol 2008;84:623–30.
13. Franklin RA, Liao W, Sarkar A, et al. The cellular and molecular origin of tumour-associated macrophages. Science 2014;344:921–5.
14. Martinez FO, Gordon S, Locati M, Mantovani A. Transcriptional profiling of the human monocyte-to-macrophage differentiation and polarization: new molecules and patterns of gene expression. J Immunol 2006;177:7303–11.
15. Mosser DM, Edwards JP. Exploring the full spectrum of macrophage activation. Nat Rev Immunol 2008;8:958–69.
16. Mantovani A, Sozzani S, Locati M, Allavena P, Sica A. Macrophage polarization: Tumour-associated macrophages as a paradigm for polarized M2 mononuclear phagocytes. Trends Immunol 2002;23:549–55.
17. Ruffell B, Coussens LM. Macrophages and therapeutic resistance in cancer. Cancer Cell 2015;27:462–72.
18. Biswas SK, Mantovani A. Macrophage plasticity and interaction with lymphocyte subsets: cancer as a paradigm. Nat Immunol 2010;11:889–96.
19. Martinez FO, Gordon S. The M1 and M2 paradigm of macrophage activation: time for reassessment. F1000Prime Rep 2014;6:13.
20. Aras S, Raza Zaidi M. TAMeless traitors: macrophages in cancer progression and metastasis. Br J Cancer 2017;117:1583–91.
21. Sousa S, Brion R, Lintunen M, et al. Human breast cancer cells educate macrophages toward the M2 activation status. Breast Cancer Res 2015;17:101.
22. Ni C, Yang L, Xu Q, et al. CD68- and CD163-positive tumour infiltrating macrophages in non-metastatic breast cancer: a retrospective study and meta-analysis. J Cancer 2019; 10(19):4463-4472.
23. Blykers A, Schoonooghe S, Xavier C, et al. PET imaging of macrophage mannose receptor-expressing macrophages in tumour stroma using 18F-radiolabeled camelid single-domain antibody fragments. J Nucl Med. 2015;56(8):1265-71.
24. Giesel FL, Kratochwil C, Lindner T, et al. 68Ga-FAPI PET/CT: Biodistribution and Preliminary Dosimetry Estimate of 2 DOTA-Containing FAP-Targeting Agents in Patients with Various Cancers. J Nucl Med. 2019;60(3):386-392.
25. Benavides J, Dubois A, Dennis T, Hamel E, Scatton B. Omega 3 (peripheral type benzodiazepine binding) site distribution in the rat immune system: an autoradiographic study with the photoaffinity ligand [3H]PK 14105. J Pharmacol Exp Ther. 1989;249(1):333-339.
26. Anholt RR, Pedersen PL, De Souza EB, Snyder SH. The peripheral-type benzodiazepine receptor. Localization to the mitochondrial outer membrane. J Biol Chem. 1986;261(2):576-583.
27. Antkiewicz-Michaluk L, Guidotti A, Krueger KE. Molecular characterization and mitochondrial density of a recognition site for peripheral-type benzodiazepine ligands. Mol Pharmacol. 1988;34(3):272-278.
28. Hardwick M, Fertikh D, Culty M, Li H, Vidic B, Papadopoulos V. Peripheral-type benzodiazepine receptor (PBR) in human breast cancer: correlation of breast cancer cell aggressive phenotype with PBR expression, nuclear localization, and PBR-mediated cell proliferation and nuclear transport of cholesterol. Cancer Res. 1999;59(4):831-842.
29. Beinlich A, Strohmeier R, Kaufmann M, Kuhl H. Relation of cell proliferation to expression of peripheral benzodiazepine receptors in human breast cancer cell lines. Biochem Pharmacol. 2000;60(3):397-402.
30. Galiègue S, Casellas P, Kramar A, Tinel N, Simony-Lafontaine J. Immunohistochemical assessment of the peripheral benzodiazepine receptor in breast cancer and its relationship with survival. Clin Cancer Res. 2004;10(6):2058-2064.
31. Campanella M. Editorial: The physiology and pharmacology of the mitochondrial 18 kDa translocator protein (TSPO): an emerging molecular target for diagnosis and therapy. Curr Mol Med. 2012;12:355.
32. DeNardo DG, Barreto JB, Andreu P, et al. CD4(+) T cells regulate pulmonary metastasis of mammary carcinomas by enhancing protumour properties of macrophages. Cancer Cell. 2009;16:91–102.
33. Lin EY, Li J-F, Gnatovskiy L, et al. Macrophages regulate the angiogenic switch in a mouse model of breast cancer. Cancer Res. 2006;66:11238–46.
34. Pierce BL, Ballard-Barbash R, Bernstein L, et al. Elevated biomarkers of inflammation are associated with reduced survival among breast cancer patients. J Clin Oncol. 2009;27:3437–44.
35. Wu, X.; Gallo, K.A. The 18-kDa translocator protein (TSPO) disrupts mammary epithelial morphogenesis and promotes breast cancer cell migration. PLoS ONE 2013, 8, e71258.
36. Hardwick M, Cavalli LR, Barlow KD, Haddad BR, Papadopoulos V. Peripheral-type benzodiazepine receptor (PBR) gene amplification in MDA-MB-231 aggressive breast cancer cells. Cancer Genet Cytogenet. 2002;139(1):48-51.
37. Bhoola NH, Mbita Z, Hull R, Dlamini Z. Translocator protein (TSPO) as a potential biomarker in human cancers. Int J Mol Sci. 2018;19(8):2176.
38. Bruijnen STG, Verweij NJF, Gent YYJ, et al. Imaging disease activity of rheumatoid arthritis by macrophage targeting using second generation translocator protein positron emission tomography tracers. PLoS One. 2019;14(9):e0222844.
39. Austin CJD, Kahlert J, Kassiou M, Rendina LM. The translocator protein (TSPO): a novel target for cancer chemotherapy. Int J Biochem Cell Biol. 2013;45:1212–6.
40. Zheng J, Boisgard R, Siquier-Pernet K, Decaudin D, Dollé F, Tavitian B. Differential expression of the 18 kDa translocator protein (TSPO) by neoplastic and inflammatory cells in mouse tumours of breast cancer. Mol Pharm. 2011;8:823–32.
41. Yoder KK, Nho K, Risacher SL, Kim S, Shen L, Saykin AJ. Influence of TSPO genotype on 11C-PBR28 standardized uptake values. J Nucl Med. 2013;54:1320–2.
42. Owen DR, Yeo AJ, Gunn RN, et al. An 18-kDa translocator protein (TSPO) polymorphism explains differences in binding affinity of the PET radioligand PBR28. J Cereb Blood Flow Metab. 2012;32:1–5.
43. Wyatt SK, Manning HC, Bai M, et al. Molecular imaging of the translocator protein (TSPO) in a pre-clinical model of breast cancer. Mol Imaging Biol. 2010;12(3):349-58.
44. Zhang J, Zhang S, Liu Y, et al. Combined CB2 receptor agonist and photodynamic therapy synergistically inhibit tumour growth in triple negative breast cancer. Photodiagnosis Photodyn Ther. 2018;24:185-191.

45. Arlicot N, Vercouillie J, Ribeiro M-J, et al. Initial evaluation in healthy humans of (18F)DPA-714, a potential PET biomarker for neuroinflammation. Nucl Med Biol. 2012;39:570–8.

46. Wimberley C, Lavisse S, Brulon V, et al. Impact of endothelial 18-kDa translocator protein on the quantification of 18F-DPA-714. J Nucl Med. 2018;59:307–14.

47. Kumar P, Aggarwal R. An overview of triple-negative breast cancer. Arch Gynecol Obstet. 2016;293:247-69.