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Editorial for the TSPO series, EJNMMI

## Imaging Translocator Protein Expression with Positron Emission Tomography

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The 18kDa translocator protein (TSPO) is constitutively expressed at low levels in healthy brain tissue predominantly in endothelial cells and is over-expressed in activated glial cells [1]. TSPO has been demonstrated as a biomarker in neurological and neurodegenerative diseases that have a component of neuroinflammation. For this reason, TSPO has been extensively used as a target for PET imaging in preclinical and clinical research protocols exploring neurological and neurodegenerative diseases over the past 30 years. The first PET tracer used to image TSPO was [<sup>11</sup>C]-(R)-PK11195. Over the last 15 years, an increased interest in neuroinflammation as contributor to a broad range of neurological conditions has led to a strong interest in TSPO imaging. A swath of research to replace [<sup>11</sup>C]-(R)-PK11195 with new tracers with lower non-specific binding hence higher signal-to-noise ratio has led to the emergence of more than 40 PET tracers with their own benefits and drawbacks. One consistent challenge for most of the new tracers developed is a sensitivity to the human genetic polymorphism rs6971 which leads to two different affinity states, with subjects having TSPO with high affinity, low affinity, or a mixture of the two. This can lead to the exclusion of research participants due to having low affinity binding, which has been shown to be about 10% of the population [2]. Despite the strong push in development of new tracers targeting TSP expression, the function and behaviour of TSPO in normal or diseased states is still not fully understood. The interpretation of the TSPO-PET signal depends on an understanding of the biological and pathological processes involved in TSPO expression and over-expression. The cellular source of TSPO is highly dependent on species [1, 3, 4], on the pathology involved as well as on the animal model. Furthermore, there are discrepancies in the field about the most appropriate PET quantification methods for different TSPO radiotracers due to the complexity of the target in healthy and pathological states.

In this series of reviews and articles we aimed to include articles that would give the state-of-the-art regarding different aspects of TSPO-PET imaging, address associated challenges, and present most recent advances in the field. Among the included articles is a review explaining the cellular source of TSPO expression in diseases by Nutma *et al.* [1] Another review by Chauveau *et al.* [5] discusses how the [<sup>11</sup>C]-(R)-PK11195 challengers developed over the past 15 years [6] have been implemented – or not – in clinical studies and whether they live up to the promise of providing an improved signal-to-noise-ratio when

compared to [ $^{11}\text{C}$ ]-(*R*)-PK11195. The challenge of quantification and kinetic modelling of TSPO PET is addressed in a review by Wimberley *et al.* [7] where the different methods and models used for quantification of TSPO PET in the literature are described. The advantages and limitations of the methods in current literature are outlined to aid researchers to choose methods that will allow them to generate the most relevant parameters and pharmacological/biological indices for their studies. A further article on the topic of quantification outlines the requirements for implementation of the supervised cluster analysis method [8] for the identification of an appropriate pseudo-reference region [9]. We have also included reviews of the use of TSPO PET imaging in several neurological diseases (apart from Alzheimer's disease, for which there are a number of reviews already [10, 11]) such as glioma [12], epilepsy [13], psychiatric conditions [14] and substance abuse [15]. One final review, by Van Camp *et al.* [16], describes the use of TSPO PET as a tool to study neuroinflammation in preclinical models where *in vivo* imaging enables longitudinal studies.

Beyond the reviews, the original articles included in the series cover a range of topics including changes in the tracer distribution in schizophrenia, leading to a different interpretation of the kinetic modelling output and therefore of the behaviour of TSPO in schizophrenia [17]. One preclinical study describes the use of TSPO PET as well as supra-paramagnetic iron oxide MRI to look at both activated microglia and infiltrating macrophages for a preclinical model of multiple sclerosis [18] where the combination of the two biomarkers brings a stronger interpretation of the neuro-immune response in the model of disease. Two articles describe preclinical characterisation of novel TSPO tracers, both with low sensitivity to the human genetic polymorphism rs6971 [19]. As mentioned before, the genetic polymorphism implies that a percentage of the population is generally excluded from research studies, and tracers that are not affected by the polymorphism are greatly needed.

Finally, we have included several articles that are non-brain TSPO studies as there has been a recent surge to use TSPO radiotracers for imaging of pathologies in organs besides the brain, which poses different problems compared to brain imaging, such as radiotracer metabolites entering the tissue. This series includes original contributions at a preclinical level, with validation of a simplified quantification method for novel TSPO tracer, [ $^{18}\text{F}$ ]-LW223, in rat heart and brain for future whole body PET studies [20] as well as clinical studies for head and neck cancer with [ $^{18}\text{F}$ ]-DPA-714 [21], and after liver transplant with [ $^{18}\text{F}$ ]-GE-180 [22].

Neuroinflammation has gathered an increasing interest as potential contributor to almost every neurological disease from acute conditions such as stroke to chronic degenerative diseases such as Alzheimer's or Parkinson's disease, and has been under-investigated in some conditions such as frontotemporal dementia (FTD) or motor neurone disease (MND). Because neuroinflammation can be driven by peripheral inflammation, the interplay between peripheral and central immune responses has also attracted a growing interest in research addressing neurological conditions. Whole body TSPO-PET might play a strong role in future work investigating the inflammatory network in all kinds of pathology from neurological disorders to immune system disorders and even cancer and heart disease. As described in a number of articles in the series, the interpretation of the PET signal is not trivial for TSPO PET and attention should be paid to the cellular source of TSPO expression, the quantification, the species and pathology under study and in humans, the genetic polymorphism leading to binding affinity sensitivity. For all these reasons, we believe that this series will be of great interest to scientists working in the field of neuroinflammation. The potential of this target as a biomarker of neuroinflammation and whole-body immune response, as well as the time and money invested in developing radiotracers, indicate that TSPO

PET imaging is set to continue to be a key component of the arsenal of useful methods for studying neuroinflammation.

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