Current Radiotracers for PET Imaging of Multiple Sclerosis

Anousha Athreya, Carl Taswell

Brain Health Alliance, Ladera Ranch, CA, USA

2023 BHAVI Symposium 15 June 2023

CNS Involvement in Multiple Sclerosis

- The central nervous system acts as the interconnective bridge between the immune and nervous system.
- Adaptive immune surveillance in the meninges containing border-associated macrophages, T cells, DCs, innate lymphoid cells (ILCs), neutrophils, and B cells facilitate this communication sequence, where patrolling T cells recognize CSF-derived antigen presenting cells (Rickenbach 2022).
- Astrocytes form structurally prominent barriers that line the CNS parenchyma, non-neural cells, and meningial surfaces that aid in leukocyte traffic control.

Neuroinflammation in MS

- In multiple sclerosis, several CNS immune-mediated responses occur:
  - B cells and T cells infiltrate the brain parenchyma through the blood-brain barrier (BBB) and create new lesions, causing neuroinflammation, demyelination, and neuroaxonal loss (Kamma 2022, Richkenbach 2022).
  - Microglia and macrophages remain in a chronic state of activation, implicated in low-grade inflammation, reactivat and glutamate toxicity (Dendrou 2015).
  - CD_4^+ and CD_8^+ cells secrete IL-17 and chemokine uptake increases, causing Th17 cells to migrate into the CSF and perivascular spaces.
  - Th17 cells increase the permeability of the BBB due to the secretion of IL-17 and IL-22 and damage the CNS, creating an inflammation cascade (Hoglund 2014).

Demyelination

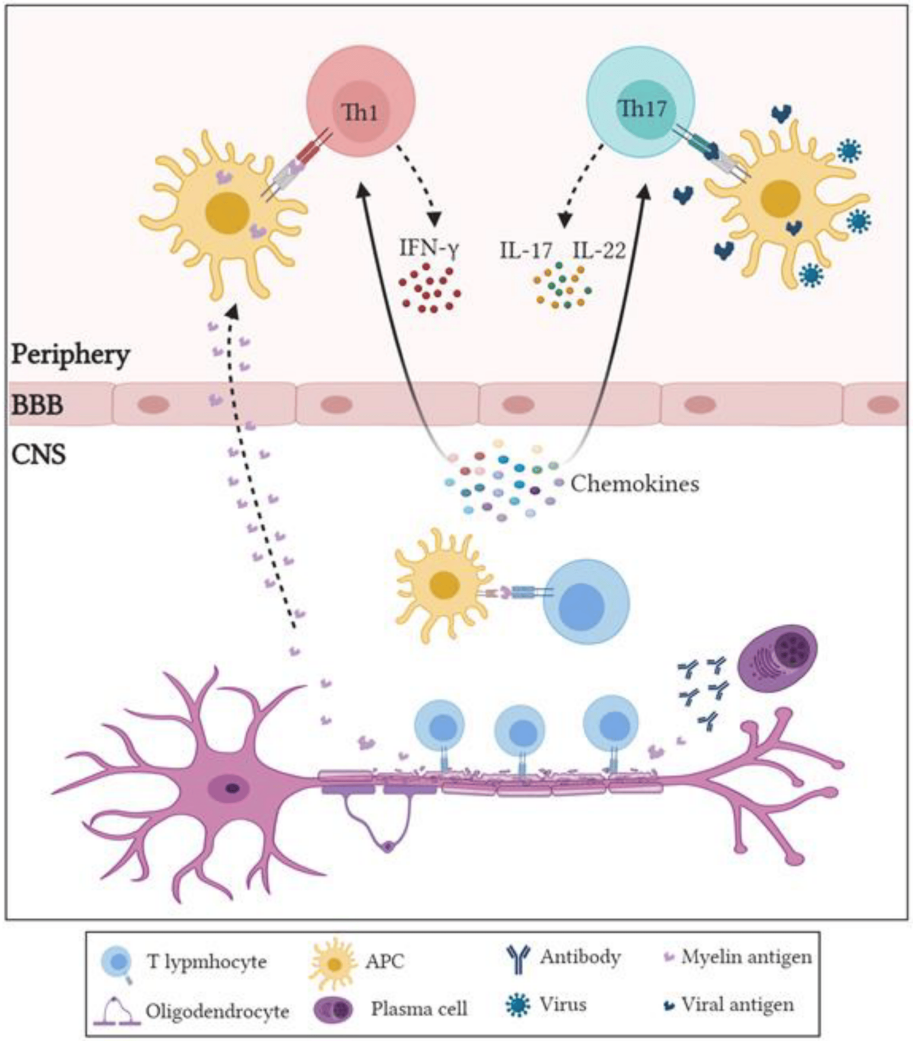

Figure: Demyelinating sequence in MS. Figure from (Dhaiban 2021)

PET imaging neuroinflammation in MS

- In the various triggers for neuroinflammation, diffuse pathology related to microglial activation and neurodegeneration can be detected via PET imaging via the 18kDa translocator protein (TSPO) (Airas 2015).
- While MR is able to highlight the areas of demyelination, molecule-specific tracers can aid in imaging overactive metabolic pathways that lead to the activation of inflammatory cells in MS lesions (Weijden 2021).
- Targeted tracers for PET imaging provide an advantage in investigating the pathophysiology of MS lesions and the different components of disease progression (Bauckneht 2019).

Table 1: Current summary of PET radiotracers for MS (Bauckheht et al. 2019, NIH CNS Radiotracer Table)

Target molecule	Radiotracers	Clinical/Experimental
TSPO	^{11}C−PK11195	Clinical
	^{11}CPRB28	Experimental
	^{11}CPBR06	Experimental
	^{18}F Flutriciclamide	Experimental
	^{18}F DAA1106	Experimental
	^{18}F DPA713	Experimental
Demyelination, Amyloid	^{18}F-florbetapir	Clinical
	^{18}F3F4AP	Experimental
	^{11}CPiB	Clinical
	^{18}F-florbetaben	Experimental
Adenosine Receptor	^{11}C-DPCPX	Experimental
	^{18}FCPFPX	Experimental
	^{11}CMPDX	Clinical
	^{11}CKF15372	Experimental
Inflammation	^{18}FDG	Clinical
GABA-A	^{11}C flumazenil	Experimental
AChE	^{11}CMP4A	Clinical
CB2	^{11}CNE40	Experimental
Astrocyte activation	^{11}C-acetate	Clinical
MER Tyrosine Kinase	^{18}F-MIPS15692	Experimental

Disease-Modifying Therapies

- Disease-modifying therapies are treatments that slow down the development of relapsing-remitting MS or primary progressive MS and suppress inflammatory activity.
- DMTs such as Ocrelizumab and Copaxone may work to reduce inflammation as a whole, or affect particular cells involved in the inflammatory and demyelinating process (Bross 2020).
- A study conducted by researchers at the University of London found that factors, such as the quality of life, cognitive ability, any disability, alcohol consumption, education, how informed they were on their condition, and age affected the adherence of patients to their DMT regimen (Washington 2022).

References

- Bauckneht, M., Capitanio, S., Raffa, S., Roccatagliata, L., Pardini, M., Lapucci, C., ... & Morbelli, S. (2019). Molecular imaging of multiple sclerosis: from the clinical demand to novel radiotracers. EJNMMI radiopharmacy and chemistry, 4(1), 1-25.
- Høglund, R. A., & Maghazachi, A. A. (2014). Multiple sclerosis and the role of immune cells. World journal of experimental medicine, 4(3), 27.
- Kamma, E., Lasisi, W., Libner, C., Ng, H. S., & Plemel, J. R. (2022). Central nervous system macrophages in progressive multiple sclerosis: relationship to neurodegeneration and therapeutics. Journal of Neuroinflammation, 19(1), 45.

- Dhaiban, S., Al-Ani, M., Elemam, N. M., Al-Aawad, M. H., Al-Rawi, Z., & Maghazachi, A. A. (2021). Role of peripheral immune cells in multiple sclerosis and experimental autoimmune encephalomyelitis. Sci, 3(1), 12.
- Poutiainen, P., Jaronen, M., Quintana, F. J., & Brownell, A. L. (2016). Precision medicine in multiple sclerosis: future of PET imaging of inflammation and reactive astrocytes. Frontiers in molecular neuroscience, 9, 85.
- Rickenbach, C., & Gericke, C. (2022). Specificity of adaptive immune responses in central nervous system health, aging and diseases. Frontiers in Neuroscience, 15, 1913.
- Dendrou, C. A., Fugger, L., & Friese, M. A. (2015). Immunopathology of multiple sclerosis. Nature Reviews Immunology, 15(9), 545-558.
- Sofroniew, M. V. (2015). Astrocyte barriers to neurotoxic inflammation. Nature Reviews Neuroscience, 16(5), 249-263.

- Bross, M., Hackett, M., & Bernitsas, E. (2020). Approved and emerging disease modifying therapies on neurodegeneration in multiple sclerosis. International journal of molecular sciences, 21(12), 4312.
- Washington, F., & Langdon, D. (2022). Factors affecting adherence to disease-modifying therapies in multiple sclerosis: systematic review. Journal of neurology, 269(4), 1861-1872.
- van der Weijden, C. W., Meilof, J. F., & de Vries, E. F. (2021). PET imaging in multiple sclerosis. PET and SPECT in Neurology, 893-916.