

Specific detection of pathogenic myeloid cells in a mouse model of multiple sclerosis using [^{18}F]OP-801 before and after treatment with a CSF1R inhibitor

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Immune Dysfunction in Neurological Diseases



- Innate immune dysfunction plays a critical role in many neurological diseases, including Multiple Sclerosis (MS).
- Selection and monitoring of therapeutic intervention is limited by non-specific *in vivo* imaging tools.
- There is a huge unmet need to visualize and quantify innate immune activation *in vivo* in MS.

[¹⁸F]OP-801: candidate PET tracer for neuroinflammation in MS

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- This is a **PAMAM hydroxyl dendrimer** targeting reactive microglia and macrophages (>95%)
- Cy5 version tested in over 30 animal models

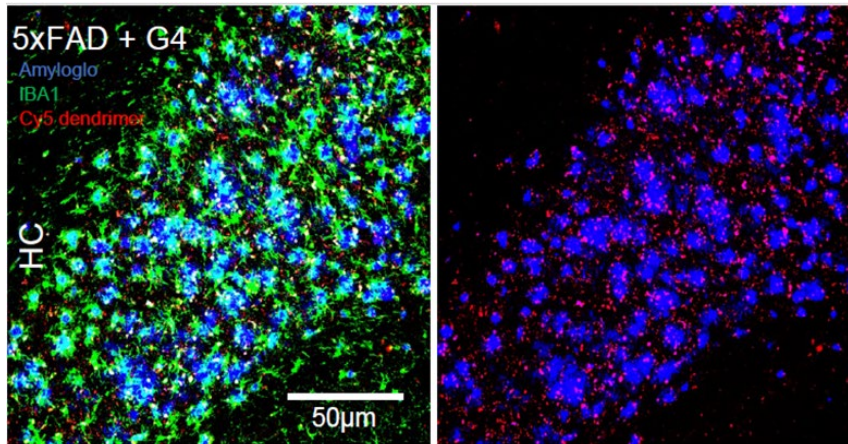
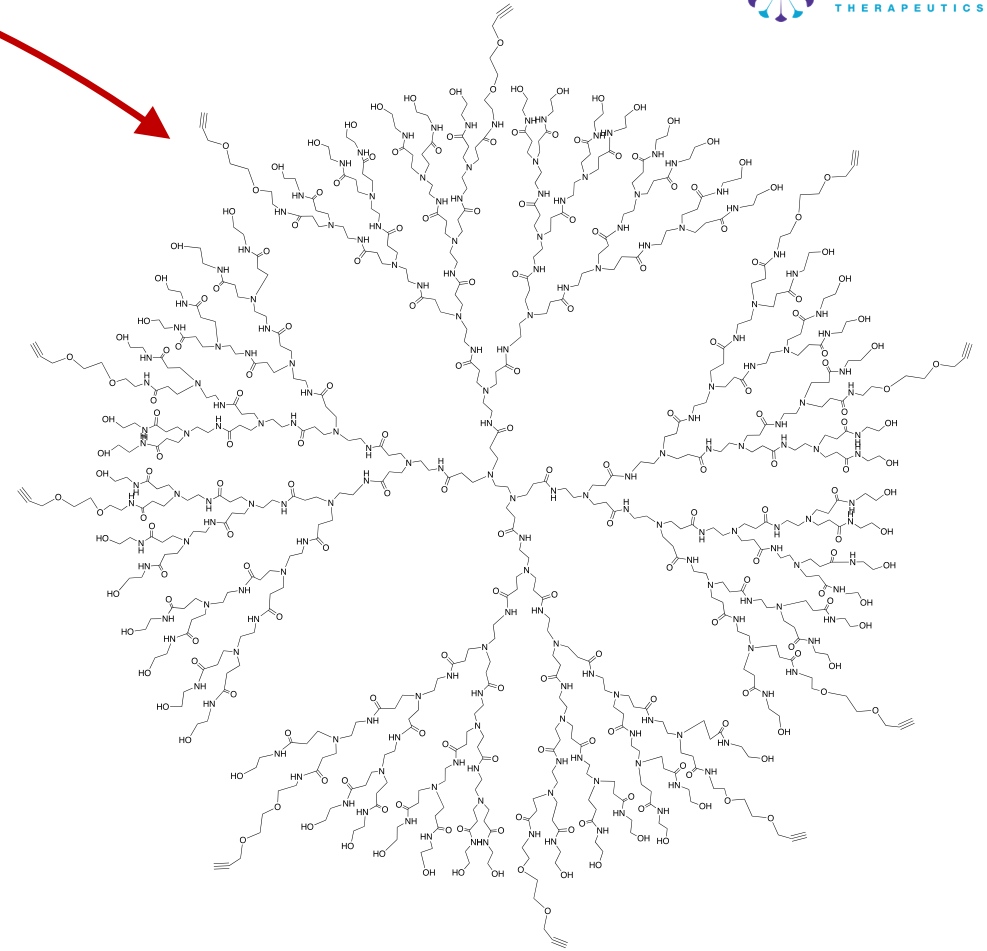


Image courtesy of Ashvattha Therapeutics, Henningfield 2020.



- ¹⁸F version developed in our lab
 - Tested in 3 murine models

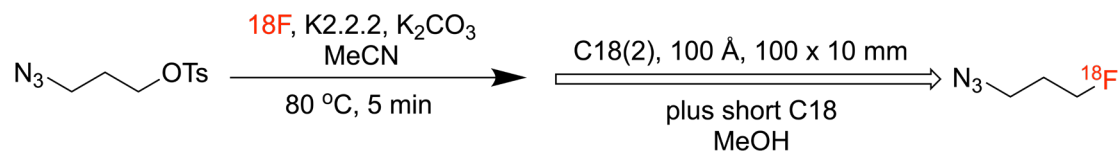
Our approach to investigating immune dysfunction in MS

Using the experimental autoimmune encephalomyelitis (EAE) mouse model, we:

1. Evaluated [^{18}F]OP-801 **sensitivity** at pre-symptomatic and symptomatic timepoints using PET imaging
 - Validated PET imaging results with biodistribution, autoradiography, and immunohistochemistry
2. Evaluated [^{18}F]OP-801 **specificity** at symptomatic timepoints using a novel hydroxyl-dendrimer-based **CSF1R inhibitor treatment (HD-CSF1R-i)**
 - Evaluated treatment efficacy in reducing neuroinflammation and symptom severity

[¹⁸F]OP-801 Optimized Radiosynthesis

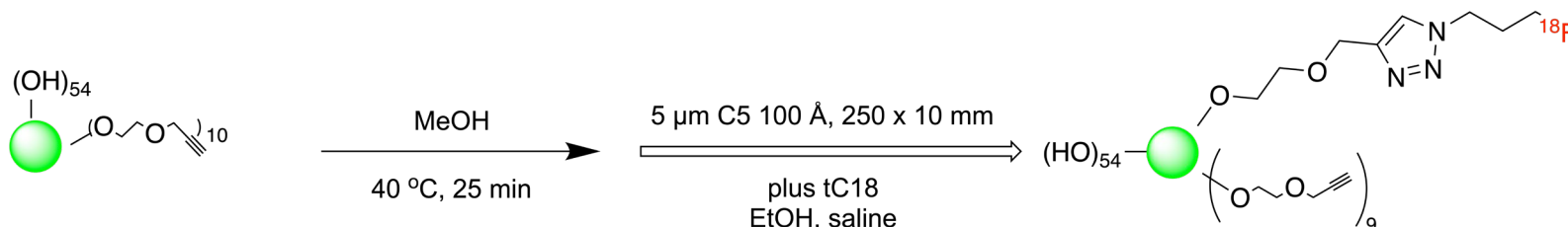
1. [¹⁸F] 3-fluoroPropylazide step:



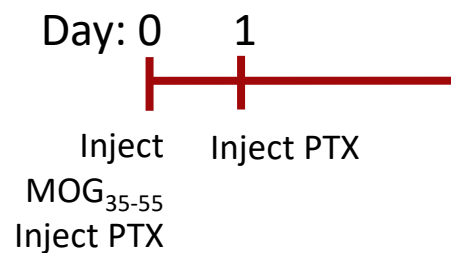
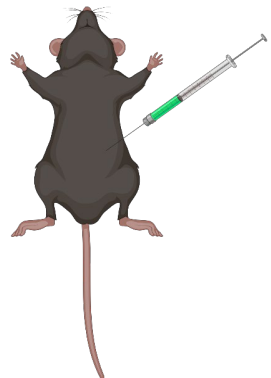
Recorded talk:
Isaac Jackson

*Streamlined Production of
[¹⁸F]OP-801 and Radiation
Dosimetry to Enable Clinical
Translation for Imaging
Neuroinflammation*

2. CuAAC of alkyne precursor:

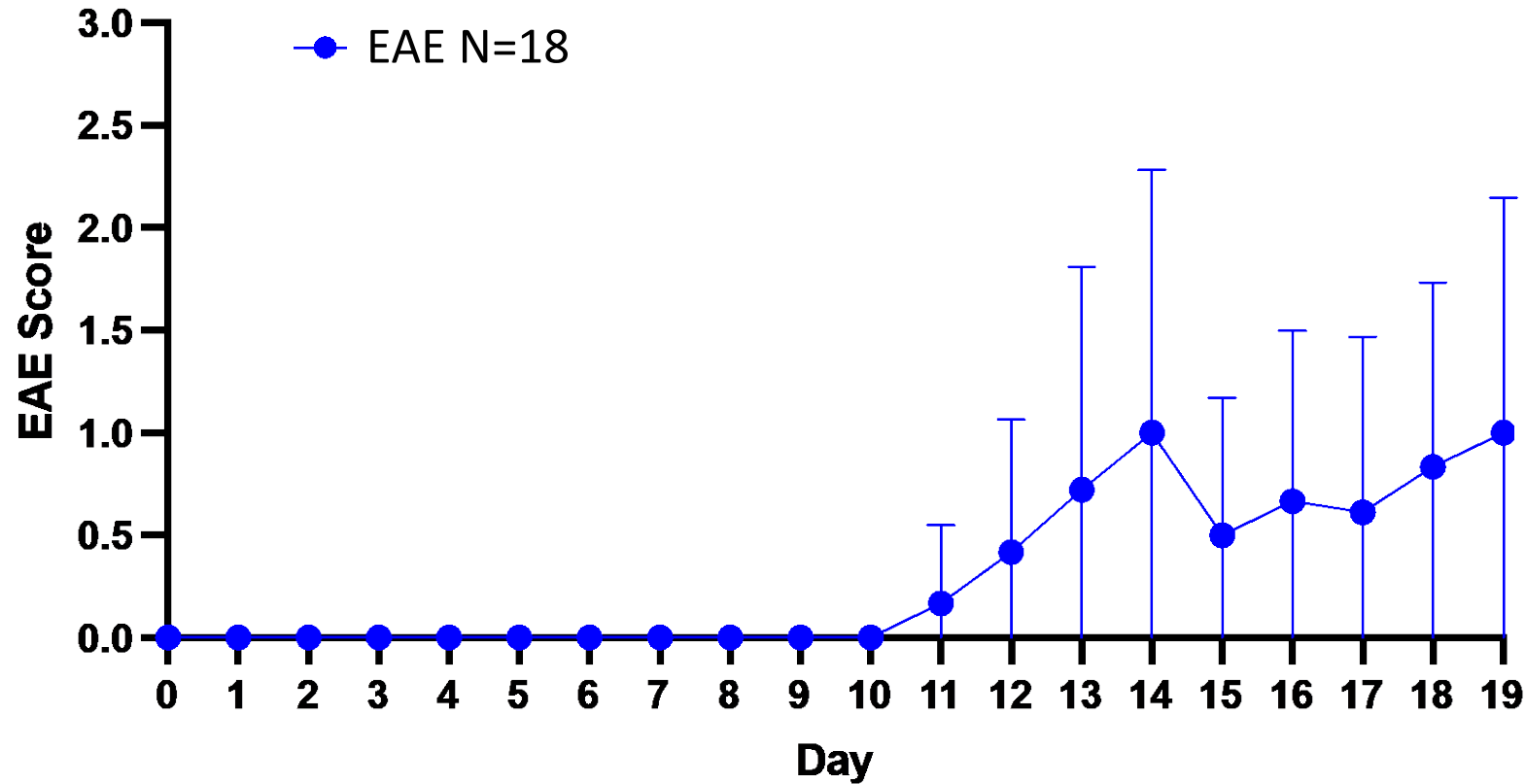


Assessing [^{18}F]OP-801 and HD-CSF1R-i in EAE



EAE scores increase over time

HD-CSF1R-i significantly reduces symptoms in mice!



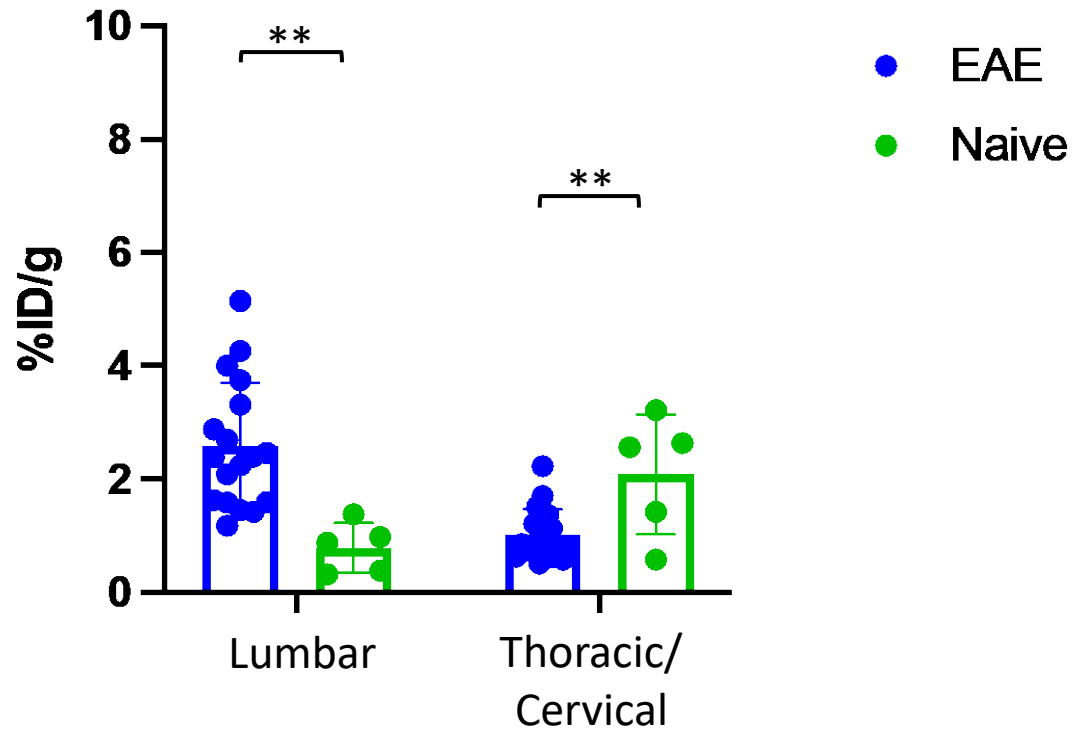
EAE Scoring

- | | |
|---|--|
| 0 | Healthy |
| 1 | Limp tail |
| 2 | Limp tail, partial hind limb paralysis |
| 3 | Limp tail, full hind limb paralysis |
| 4 | Limp tail, full hind, partial front limb paralysis |
| 5 | Moribund |

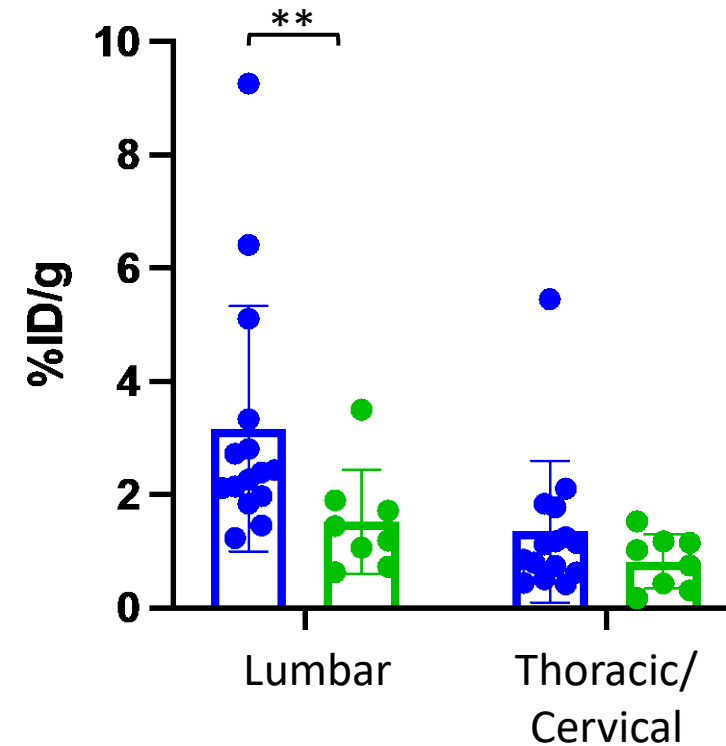
[¹⁸F]OP-801 detects higher signal in spinal cord in EAE mice prior to symptom onset

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Pre-symptomatic PET (Day 8)



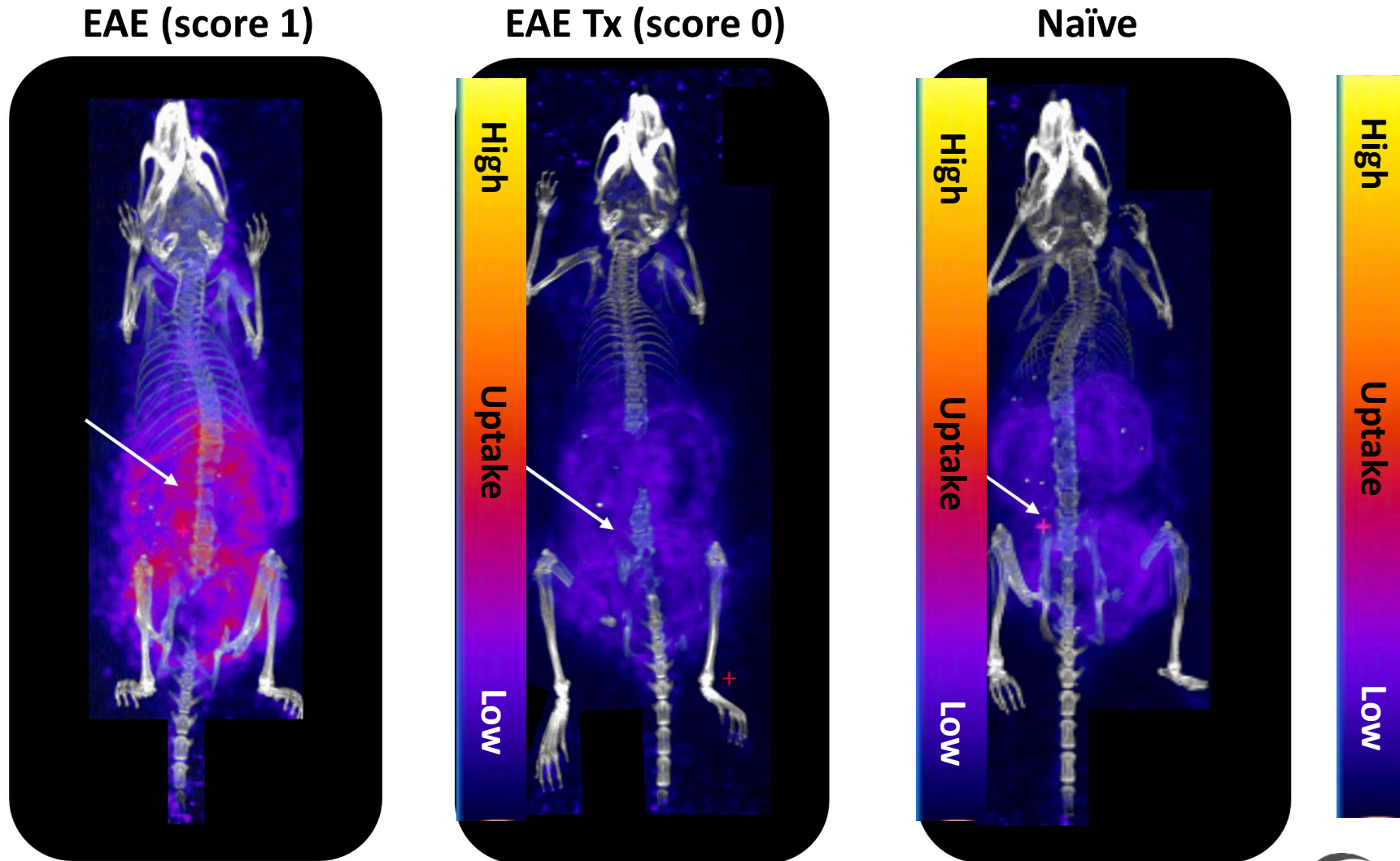
Symptomatic PET (Day 19)



** P<0.01

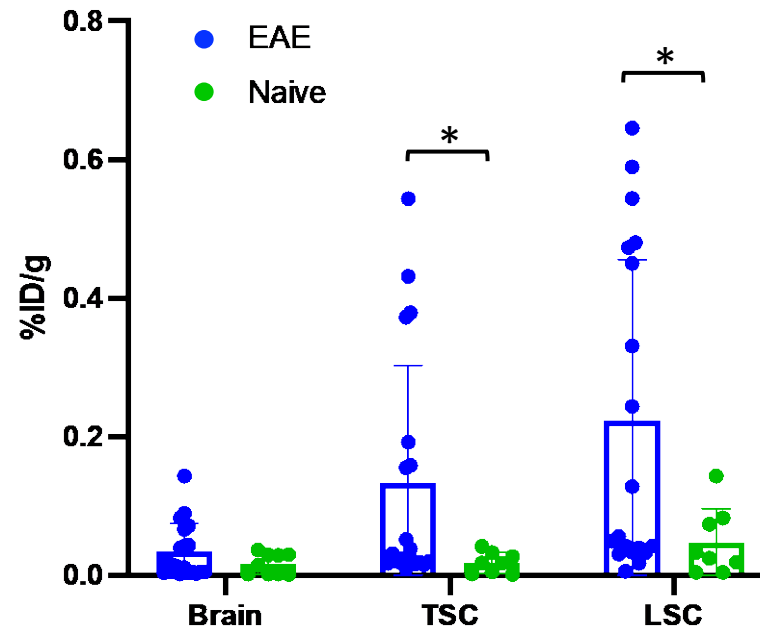
$[^{18}\text{F}]$ OP-801 PET signal in EAE mice is specific for reactive myeloid cells ⁹

50-60 min post-injection

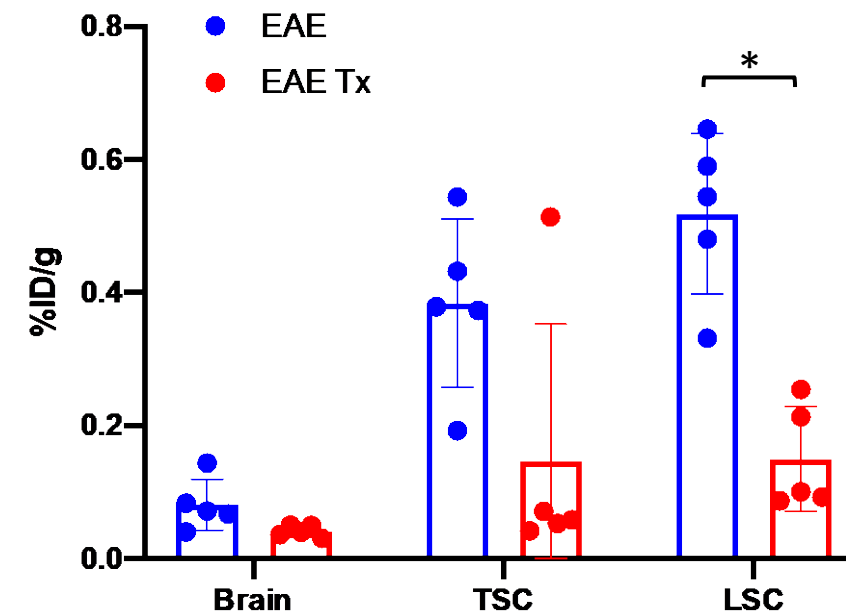


Ex vivo biodistribution confirms higher uptake in EAE

EAE (all scores) vs Naïve



EAE vs EAE Treated



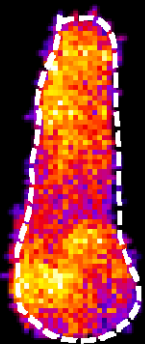
* P < 0.05

LSC = lumbar spinal cord, TSC = thoracic/cervical spinal cord

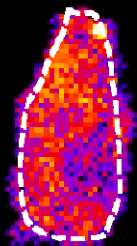
Spinal cord autoradiography further supports PET findings

EAE Untreated

Cervical/
Thoracic



Lumbar



Low

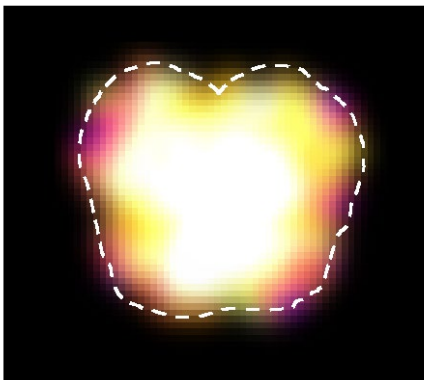
Counts

High

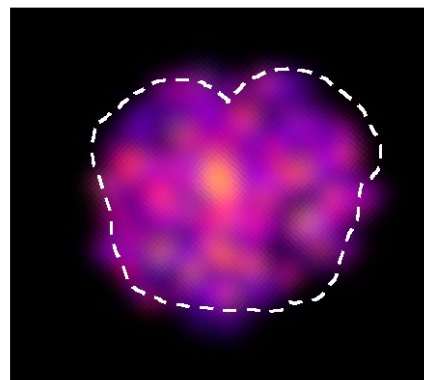
$[^{18}\text{F}]$ OP-801 autoradiography detects treatment response

40 μm lumbar spinal cord sections

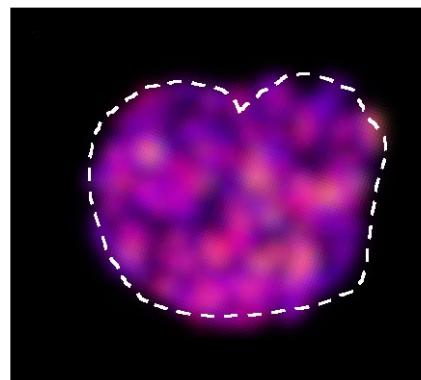
EAE



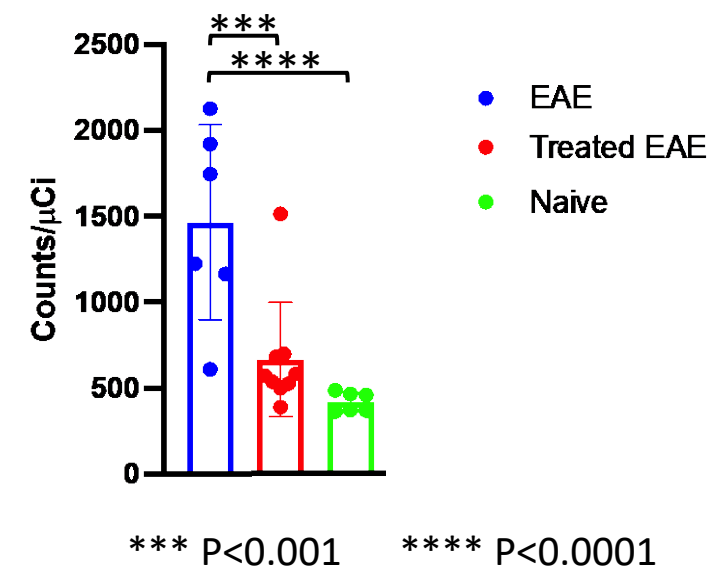
EAE CSF1R treated



Naïve



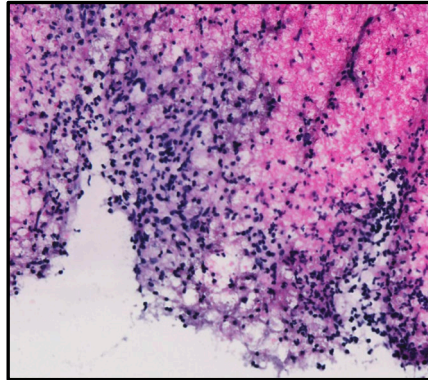
Lumbar spinal cord quantification



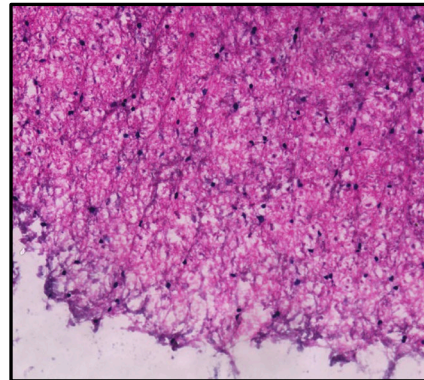
H&E and Immunohistochemistry confirm OP-801 specificity

H&E (20X)

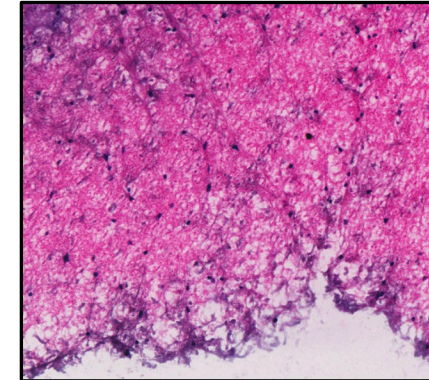
EAE



EAE Treated

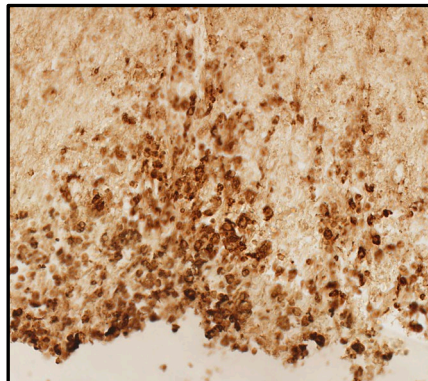


Naïve

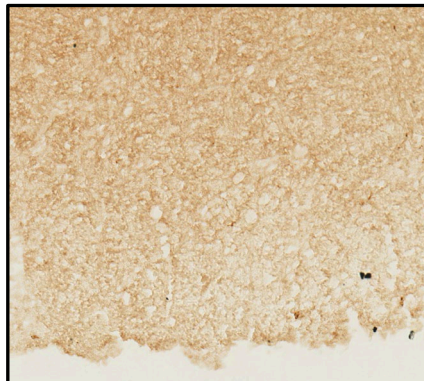


CD68 (20X, 12µm)

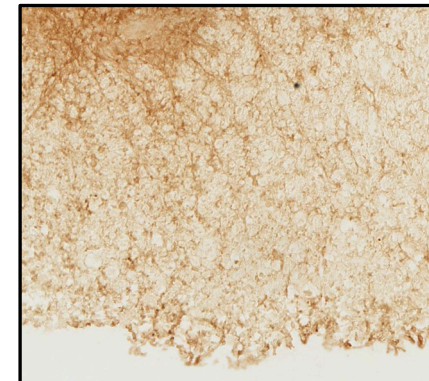
EAE



EAE Treated



Naïve



Conclusions and Next Steps



[^{18}F]OP-801 enables sensitive and specific visualization of reactive microglia and macrophages in the spinal cord in EAE mice.



HD-CSF1R-i is effective in reducing immune activation in the CNS.

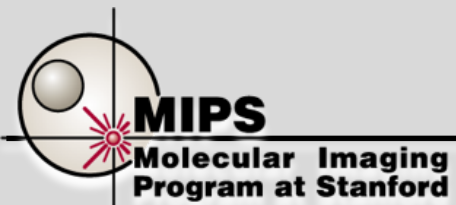


[^{18}F]OP-801 initiating phase 1-2 studies in ALS patients Q4 this year.

Acknowledgements



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Thank you for your attention!