

Nasal foralumab downregulates CSF inflammation and upregulates CSF neuroprotective proteomic pathways which correlate with [F-18]PBR06-PET imaging in na-SPMS with PIRA

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Background & Objectives:

- Developing non-invasive biomarkers and novel therapies for non-active secondary progressive MS (na-SPMS) with progression independent of relapse activity (PIRA) and smoldering inflammation are major unmet needs in MS.
- [F-18]PBR06 is a long half-life PET ligand targeting the 18kiloDalton translocator protein (TSPO) that measures microglial activation and is increased in na-SPMS.
- CSF proteomics analysis has the potential to serve as a biomarker for na-SPMS.
- Nasal foralumab is a fully human anti-CD3 monoclonal antibody that we are currently using to treat na-SPMS subjects in an open-label expanded-access program and in a phase 2 clinical trial with [F-18]PBR06-PET as a primary outcome.
- However, the relationship between PET and CSF proteomics biomarkers in na-SPMS is unknown.
- The aim of this study is to investigate the relationship between [F-18]PBR06-PET and CSF proteomics in na-SPMS patients with PIRA and evaluate the effects of nasal foralumab on CSF proteomics in relation to PET changes.

References:

- Singhal T, Cicero S, Rissanen E, et al. Glial Activity Load on PET Reveals Persistent "Smoldering" Inflammation in MS Despite Disease-Modifying Treatment: 18 F-PBR06 Study. *Clin Nucl Med*. 2024;49(6):491-499. doi:10.1097/RLU.00000000000005201
- Chitnis T, Singhal T, Zurawski J, et al. Nasal Foralumab for the Treatment of Progression Independent of Relapses in Patients With Nonactive Secondary Progressive Multiple Sclerosis. *Neuroimmunol Neuroinflamm*. 2026;13(2):e200543. Published 2026 Jan 16. doi:10.1212/NXI.0000000000000543.

Methods:

- 10 na-SPMS patients (mean age 59.2±8.01y, 7 F, median EDSS 6.25, 5 high (HAB) and 5 medium (MAB) affinity binders) underwent 14 paired evaluations of [F-18]PBR06-PET scans and CSF proteomics at baseline and/or follow-up over a 6-month period during nasal-foralumab treatment.
- Whole brain, cortical, white matter and cerebellar m-GALP (Glial Activity Load on PET) z-scores were correlated with un-targeted data-independent acquisition (DAI) proteomics in the CSF.
- 1) Pre- and post-nasal foralumab treatment paired comparisons and 2) Spearman's correlation analysis between PET and CSF proteomics were performed. $p < 0.05$ was considered statistically significant.

Disclosures:

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Figure 1.

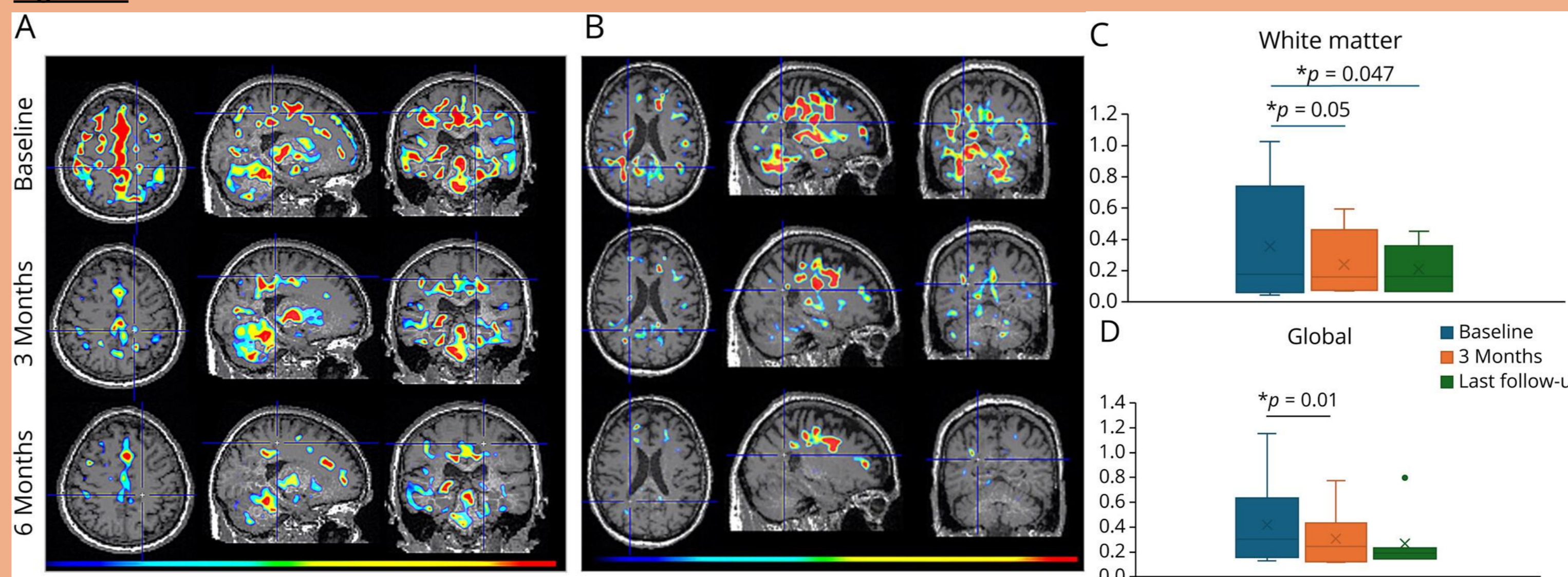


Figure 1 shows reduced TSPO-PET signal after nasal foralumab treatment. Individualized GALP z-score maps for 2 patients (A) and (B) superimposed on respective patient's T1-weighted MRI demonstrate decreased PET abnormalities after treatment at 3 months (middle row) and 6 months (bottom row) as compared with baseline (top row). Hotter colors represent a higher z-score value and cooler colors represent a lower z-score value as determined by the GALP pipeline. (C and D) White matter and global PET scores at baseline and on treatment. Decreased voxel-wise average [F-18]PBR06-PET mGALP z-scores in white matter (C) and global (D) regions of interest after nasal foralumab treatment for 3 months and 7.5 months (mean duration of treatment at last available PET follow-up visit). Figure 1 published in Chitnis T, Singhal T, Zurawski J, et al.

Figure 2.

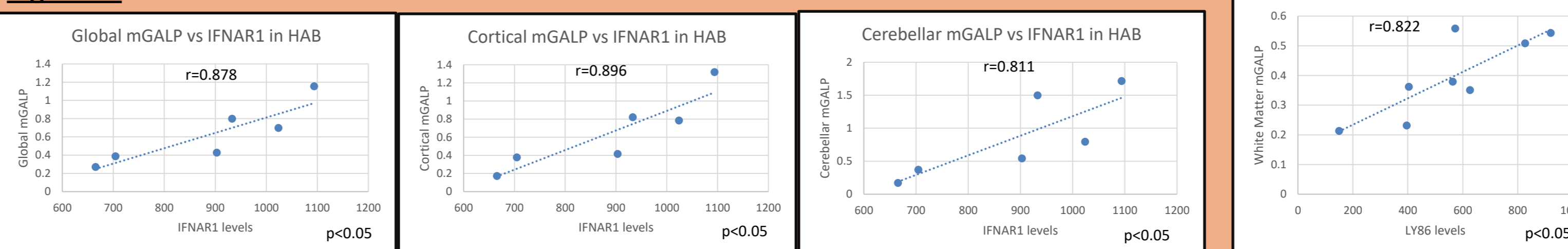


Figure 2 shows correlations between IFNAR1 levels and mGALP z-scores in the whole brain, cortex, and cerebellum in MS patients who are high affinity binders to TSPO, measured using [F-18]PBR06-PET. Also shows correlation between LY86 and mGALP in white matter in MS patients who are medium affinity binders.

Figure 3.

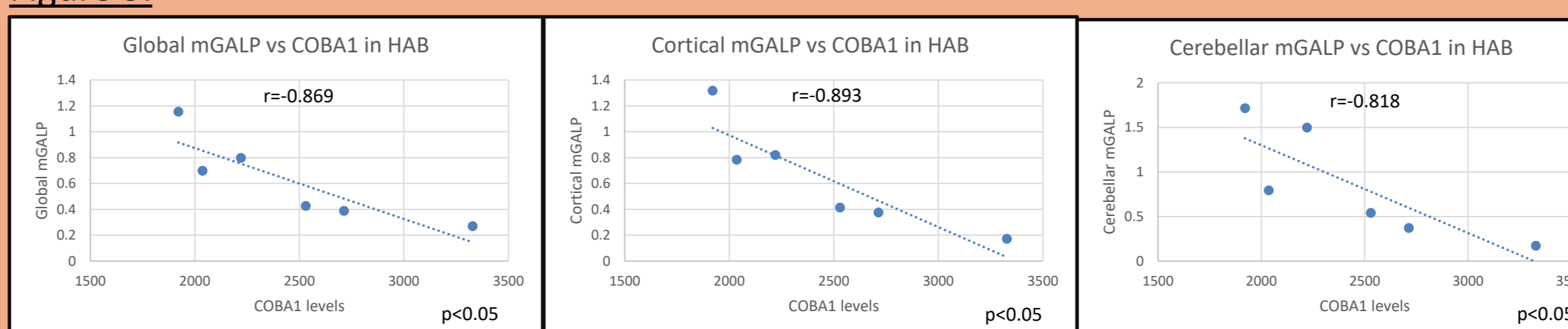


Figure 3 shows correlations between COBA1 levels and mGALP z-scores in the whole brain, cortex, and cerebellum in MS patients who are high affinity binders to TSPO, measured using [F-18]PBR06-PET.

Figure 4.

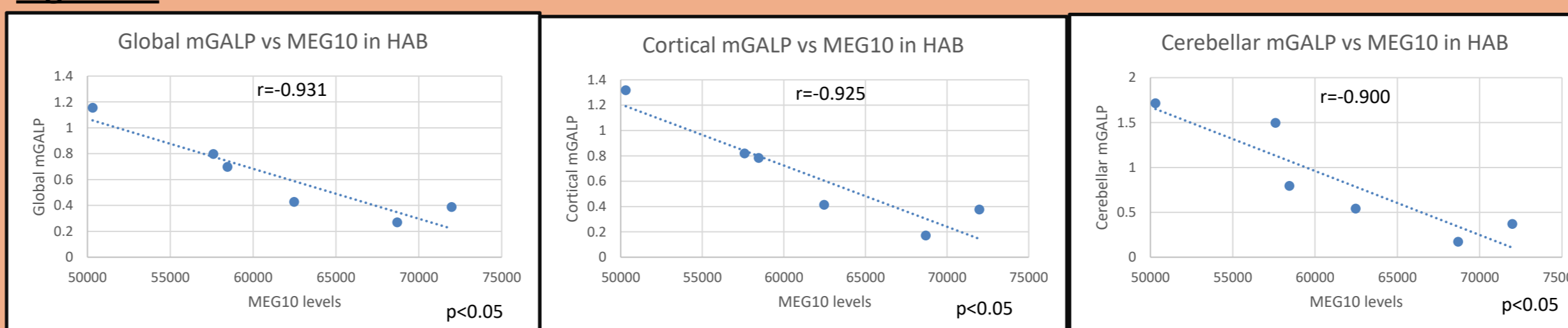


Figure 4 shows correlations between MEG10 levels and mGALP z-scores in the whole brain, cortex, and cerebellum in MS patients who are high affinity binders to TSPO, measured using [F-18]PBR06-PET.

Results:

- m-GALP PET scores were positively correlated with CSF markers of interferon pathway activation (IFNAR1) and NF-κB pathway activation (LY86) in global, cortical and cerebellar ($p=0.005$) and white matter ($p=0.037$) regions among HABs and MABs, respectively.
- m-GALP PET scores in the global, cortical and cerebellar regions were inversely correlated with CSF COBA1 (fibrosis pathway) and MEG10 (neuroprotective protein, $p=0.005$), among HABs.
- Foralumab treatment led to a reduction in CSF markers of inflammation and fibrosis (IFNAR1, LY86 and COBA1) and an increase in CSF markers of neuroprotection (SORC3 and MEG10), concomitant with a reduction in white matter PET signal.

Conclusions:

Nasal foralumab reduces inflammatory CSF biomarkers and microglial PET signal and increases CSF markers of neuroprotection. We found that [F-18]PBR06-PET positively correlates with CSF inflammatory proteins and negatively correlates with CSF neuroprotective proteins in na-SPMS with PIRA. This demonstrates that microglia PET is linked to the biologic processes that drive SPMS and that CSF proteomics can be used to measure response to therapy in SPMS.