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Additive deleterious effects of delivery mode on perinatal brain injuries: microbiota's fault

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Additive deleterious effects of delivery mode on perinatal brain injuries: microbiota's fault

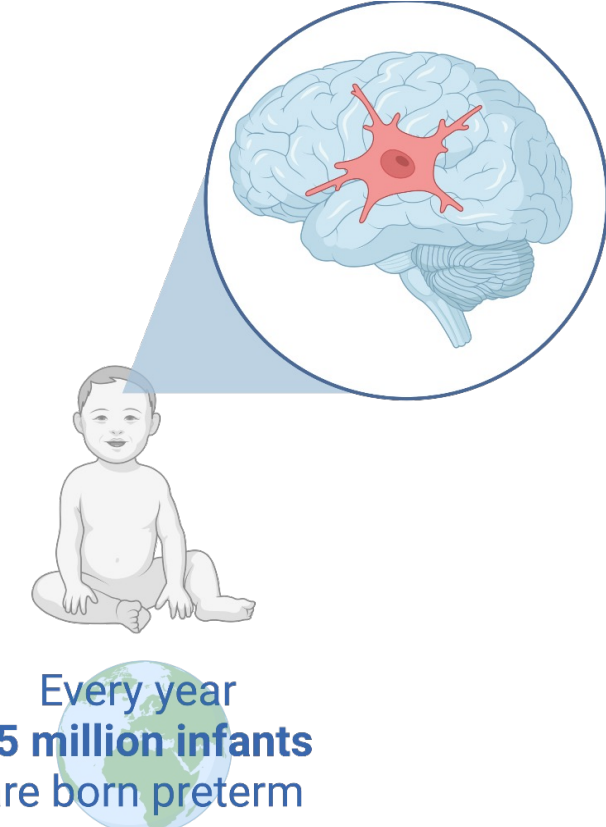
C. Morin, D. Guenoun, F. Faure, I. Sautet, S. Diao, V. Faivre, J. Hua, C. Demene, M. Tanter, L. Schwendimann, P. Young-Ten, T. Bourgeois, N. Ramanantsoa, B. Matrot, J. Gallego, S. Auger, P. Gressens, J. Van Steenwinckel*, C. Bokobza*

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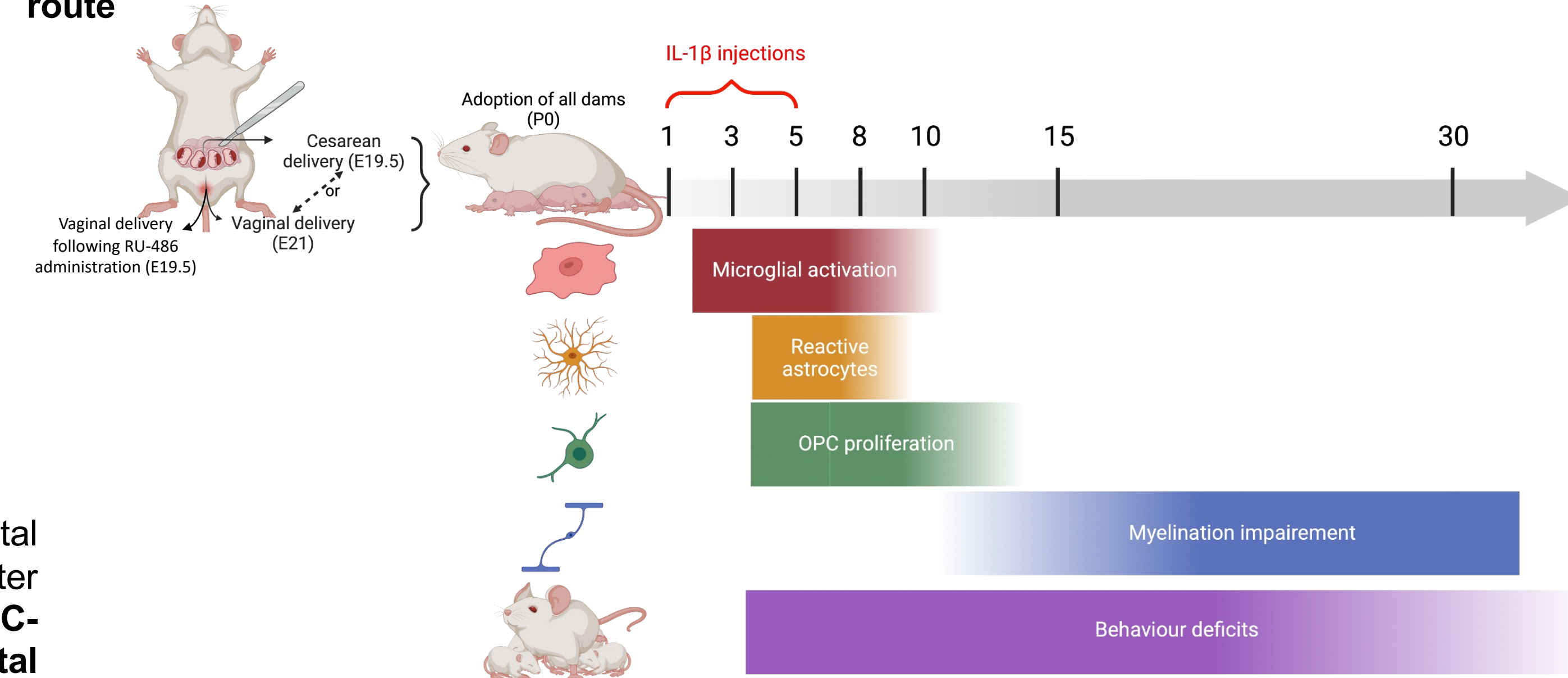
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Introduction



Most cases are associated with materno-fetal infection/inflammation, leading to white matter injuries (WMI). Preterm infants delivered by C-section are at higher risk of neurodevelopmental disorders (NDD) compared with vaginally delivered infants.

A mouse model for brain injuries associated with preterm birth and differential delivery route



Are there additive effects of (i) induced vaginal preterm birth or (ii) cesarean surgical preterm birth with perinatal inflammation?

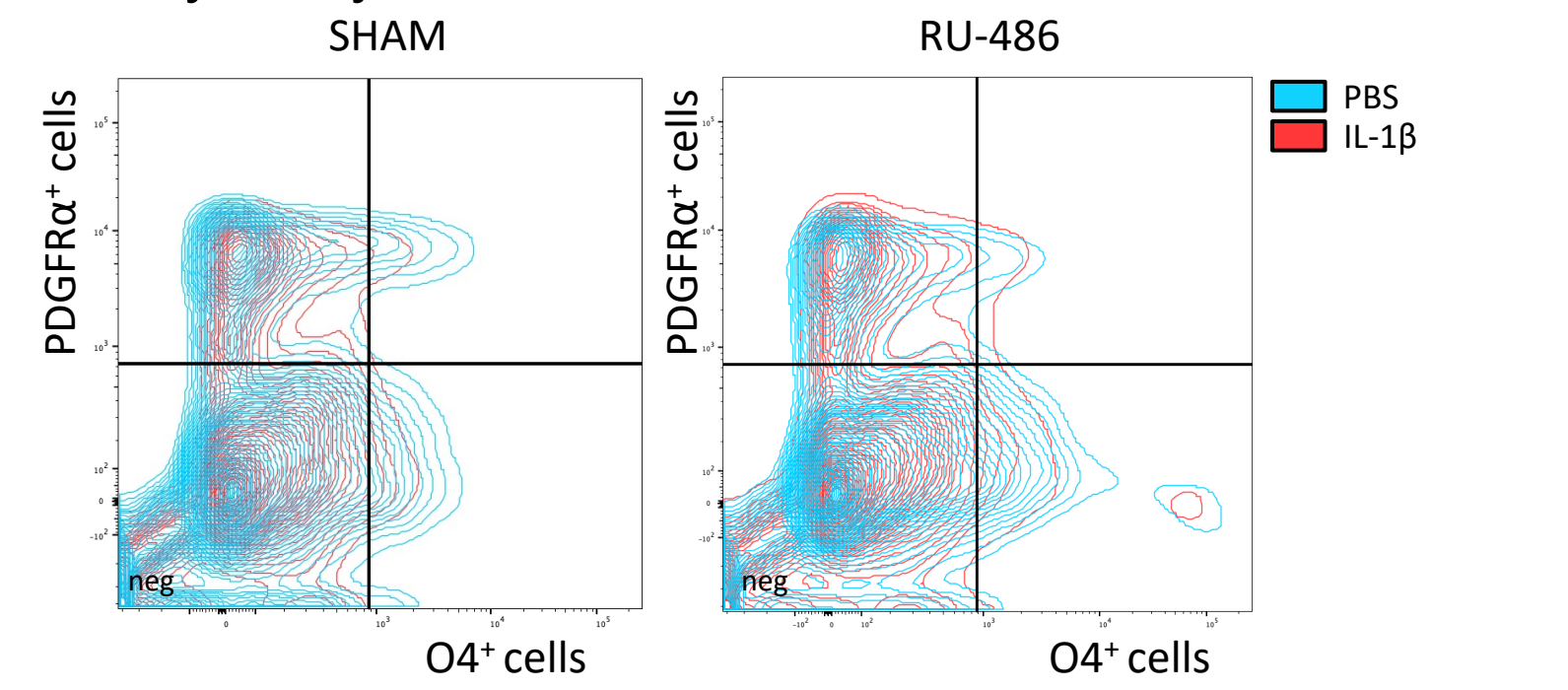
Mifepristone (RU-486) administration induced vaginal preterm delivery without affecting WMI

Morin et al. (2022)

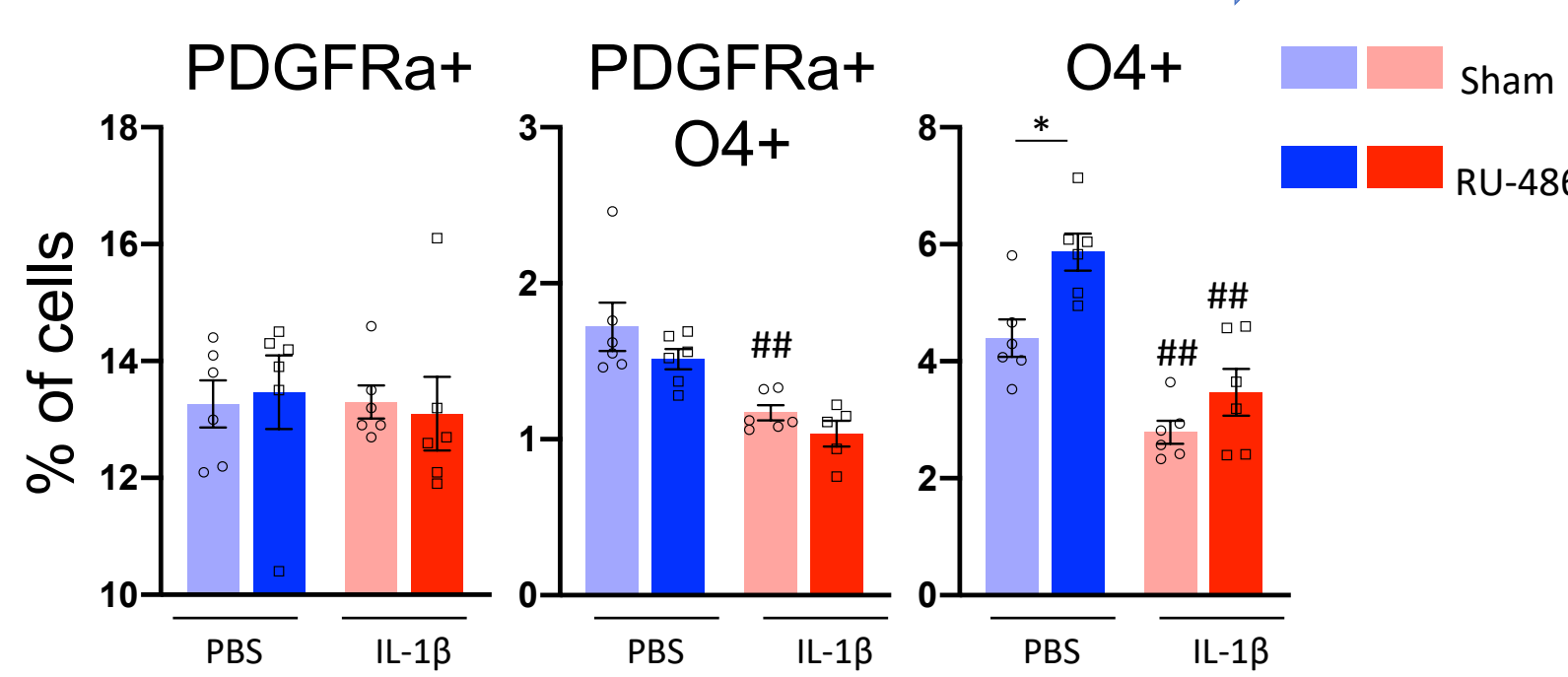
Mifepristone (RU-486) is a glucocorticoid receptor (GR) antagonist. As an anti-progesterone drug, RU-486 is used in pharmacological abortion, and to induce delivery rarely for living fetuses and mostly in case of *in utero* fetal death.

Oligodendrocytes differentiation, the first victims of perinatal inflammation, is still blocked.

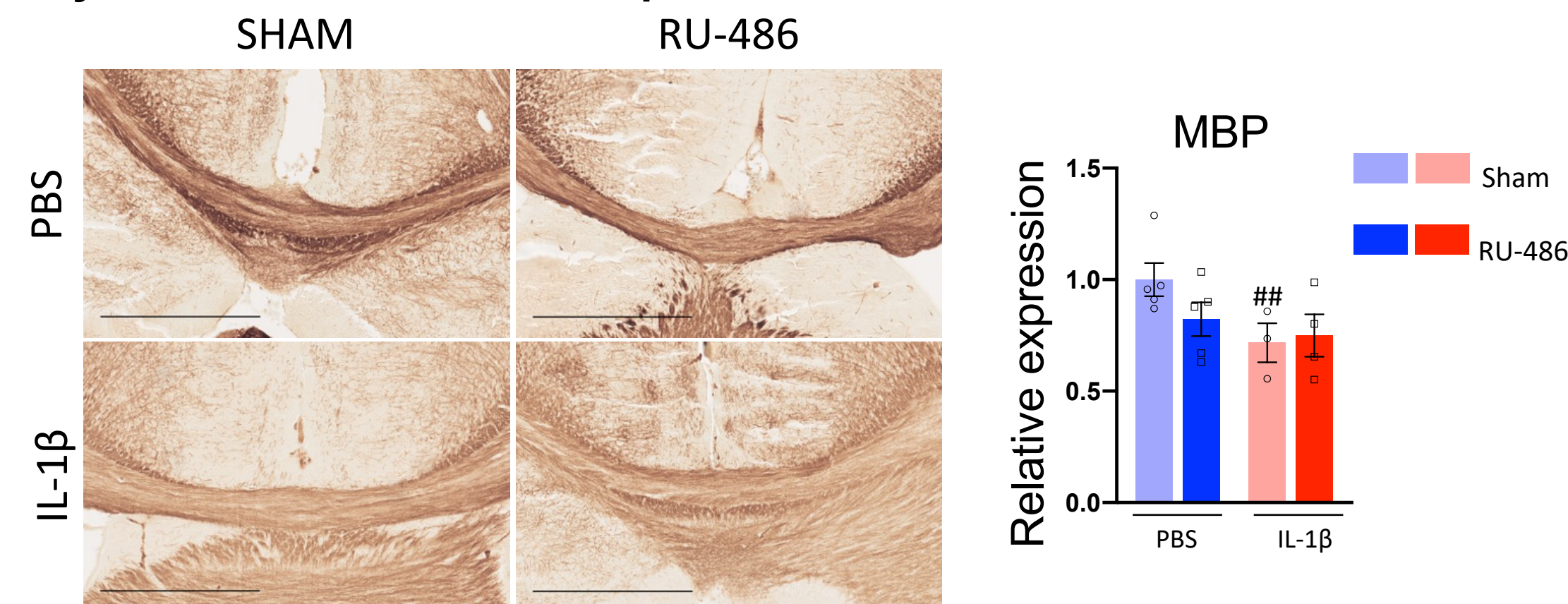
P5 Flow Cytometry analysis



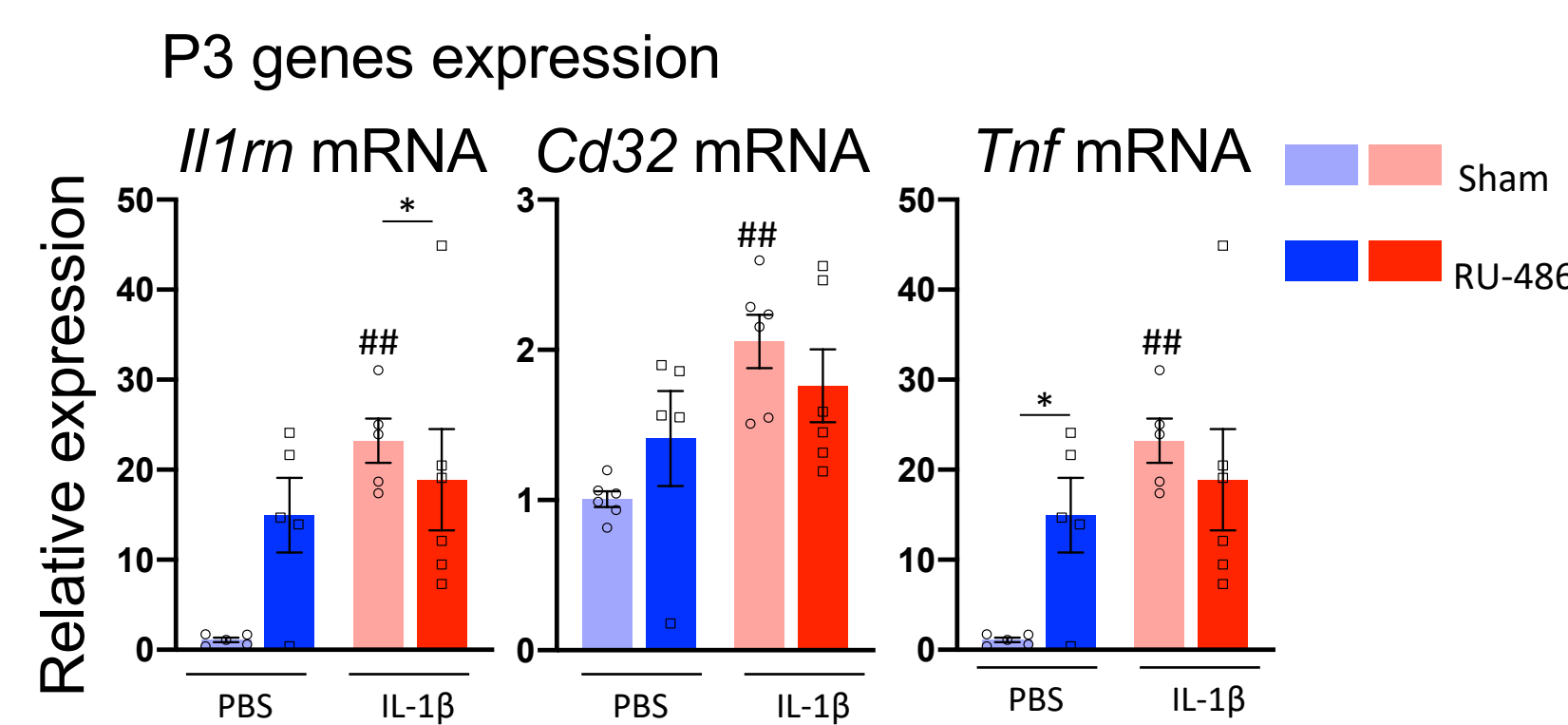
Oligodendrocytes differentiation



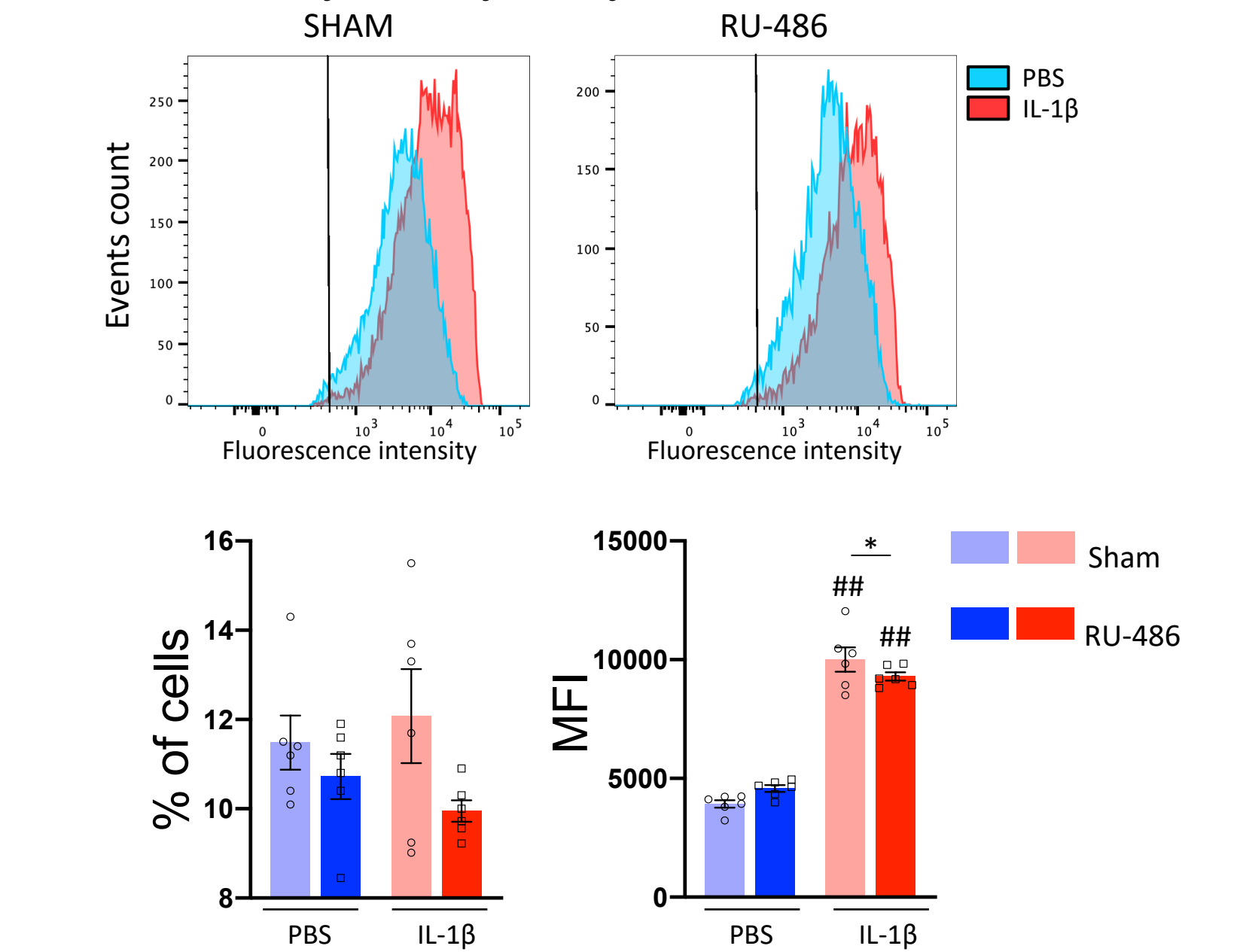
Myelination deficit of the corpus callosum is still observed



Microglial reactivity (CD11b+) is restrained by RU-486



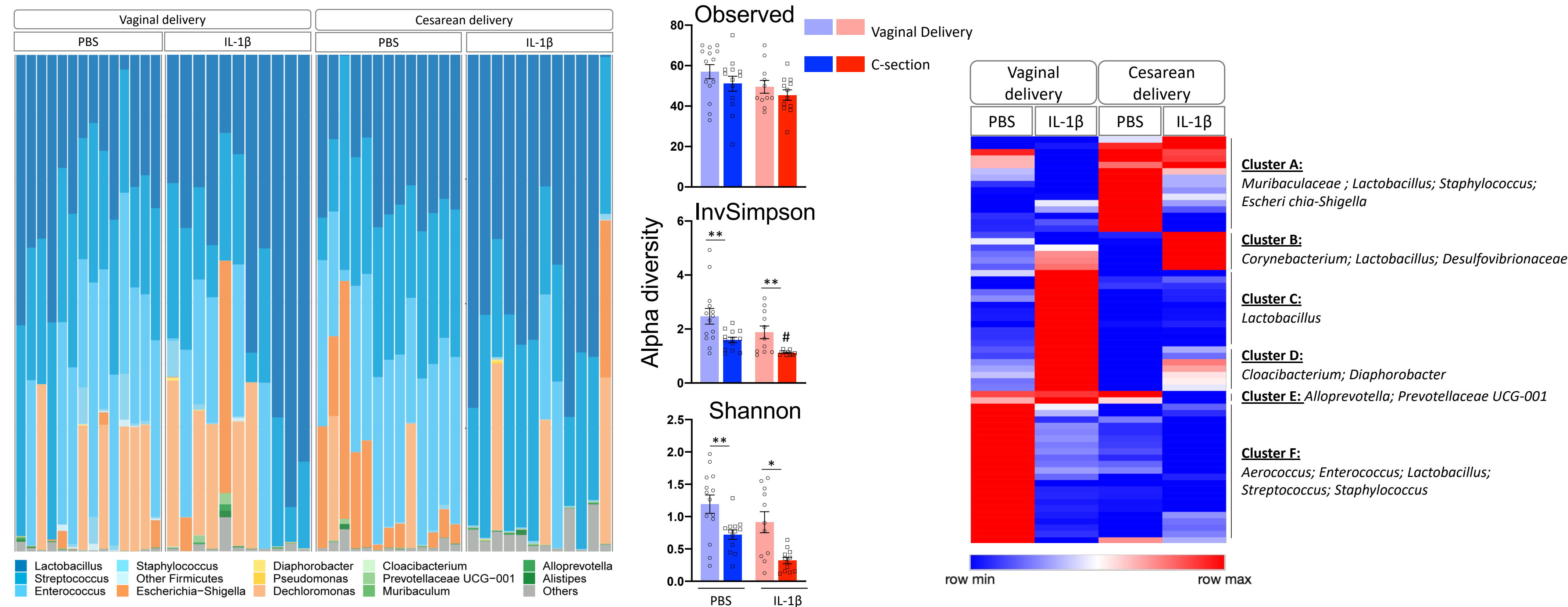
P5 Flow Cytometry analysis



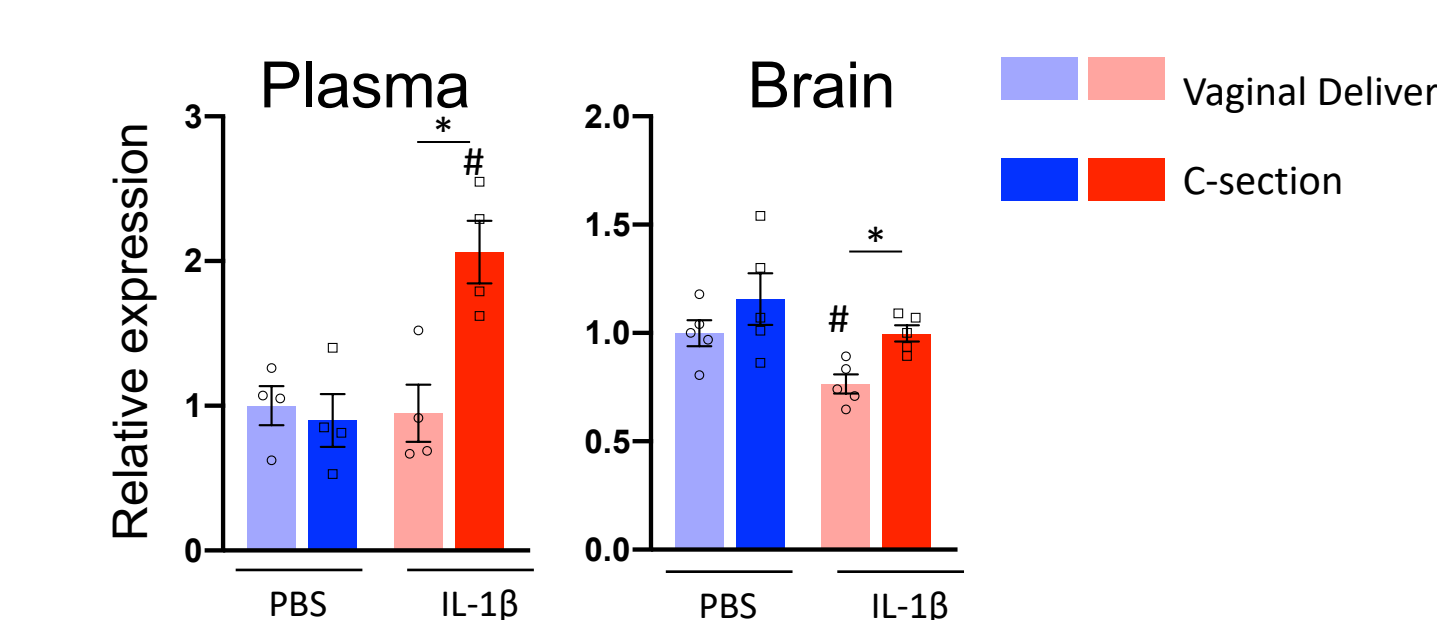
Preterm birth by cesarean delivery worsens WMI

Global cesarean section (C-sections) rates have increased in recent decades. Numerous studies have revealed the existence of a "gut-brain axis" and the impact of an alteration of gut microbiota composition in brain diseases. Many factors in early life such as the mode of delivery or preterm birth could lead to disturbances in the assembly and maturation of gut microbiota.

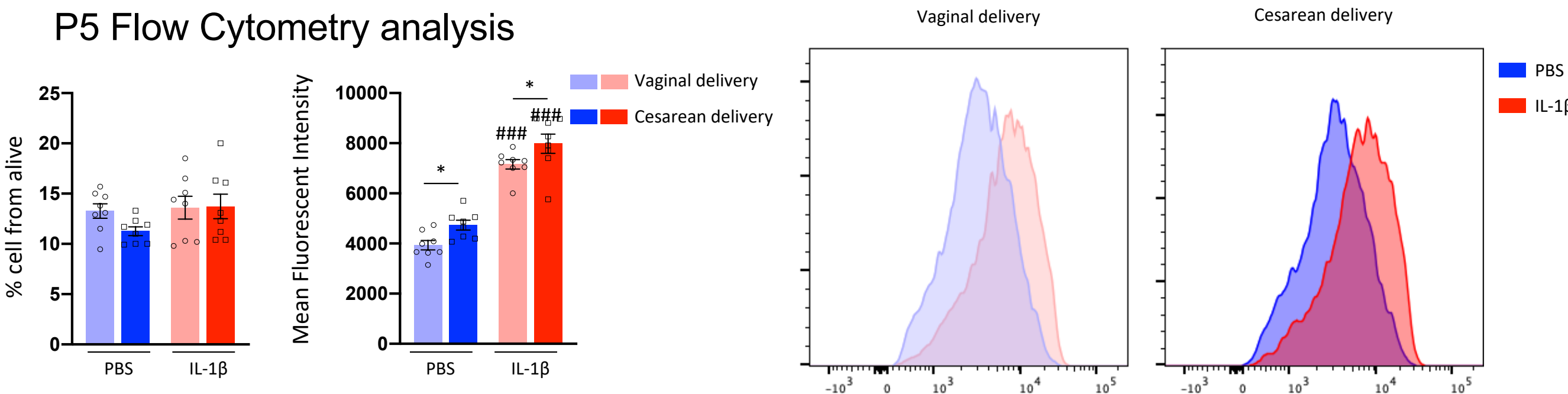
Gut Microbiota is altered by C-sections and worsen by perinatal inflammation



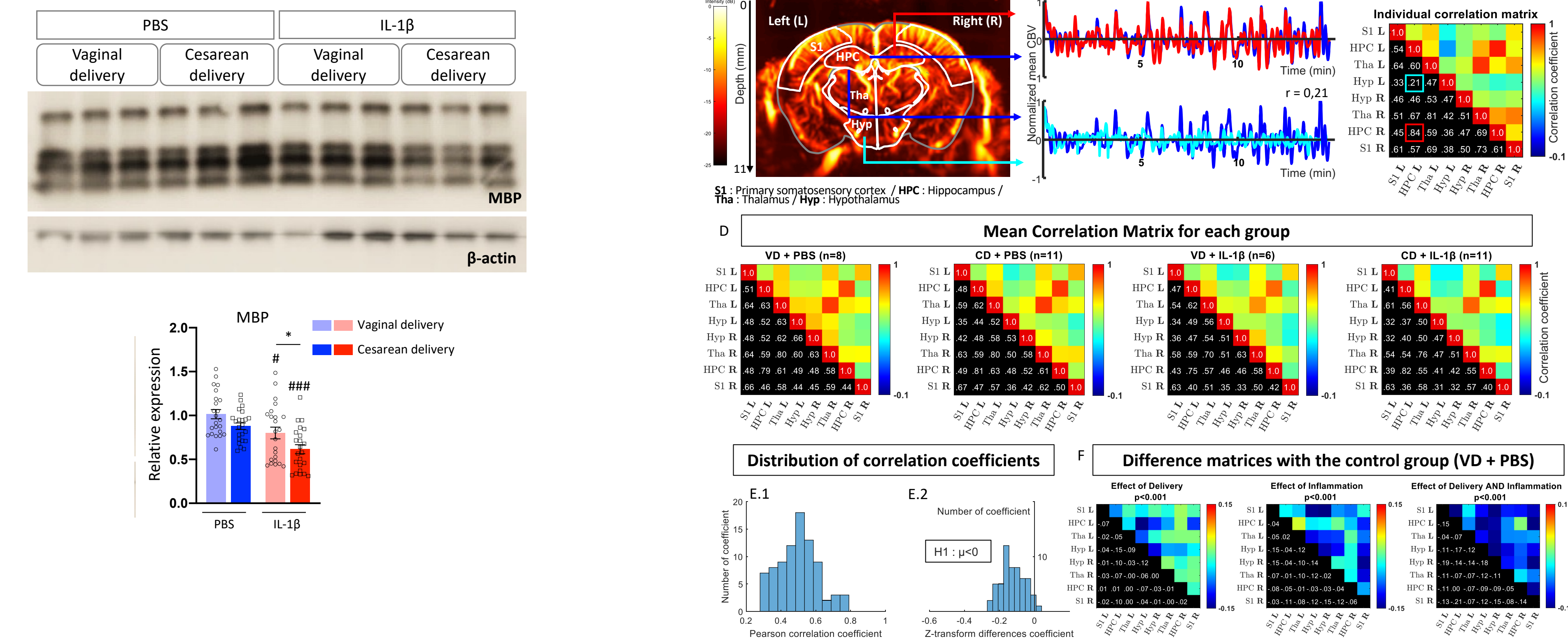
Peptidoglycan levels are impaired



C-section worsens microglial reactivity induced by perinatal inflammation



C-section worsens hypomyelination induced by perinatal inflammation, leading to brain connectivity defects



Consistent with literature data, exposure to RU-486 (crossing the placenta) prevented microglial reactivity associated with exposure to IL-1beta. On the other hand, this is not enough to prevent hypomyelination that occurs later. Thus, early birth alone did not exacerbate the effects of inflammation. We were able to demonstrate a reduction in microbiota diversity in a C-section mouse model, which was exacerbated when the offspring were exposed to IL-1beta. This reduction was accompanied by a more pronounced neuroinflammation phenomenon mediated by microglia. The long-term consequence of the combined effects of C-section and inflammation is more pronounced PWMI, leading to deficits in functional brain connectivity associated with NDD-like behaviors.