Humanized Microglia Mouse Model

The S Gorantla laboratory has created a humanized bone-marrow chimera producing human "microglia like" cells in NOD.Cg-PrkdcscidIl2rgtm1SugTg(CMV-IL34)1/Jic mice. Newborn mice were engrafted intrahepatically with umbilical cord blood-derived CD34+ hematopoietic stem progenitor cells (HSPC). Human interleukin-34 under the control of the cytomegalovirus promoter inserted in the NSG mouse strain drove brain reconstitution of HSPC derived peripheral macrophages into microglial-like cells. These human cells expressed canonical human microglial cell markers that included CD14, CD68, CD163, CD11b, ITGB2, CX3CR1, CSFR1, TREM2 and P2RY12. After 3 months of stable engraftment, animals were infected with HIV-1_{ADA}, a myeloid-specific tropic viral isolate. Virologic, immune and brain immunohistology were performed on blood, peripheral lymphoid tissues, and brain. Prior restriction to HIV-1 infection in the rodent brain rested on an inability to reconstitute human microglia. Thus, the natural emergence of these cells from ingressed peripheral macrophages to the brain could allow, for the first time, the study of a CNS viral reservoir. HIV-1 infection was monitored in the brain of these mice with human microglia. Viral RNA and HIV-1p24 antigens were readily observed in infected brain tissues. Deep RNA sequencing of these infected mice and differential expression analysis revealed human-specific molecular signatures representative of antiviral and neuroinflammatory responses. This humanized microglia mouse reflects human HIV-1 infection in its known principal reservoir and shows the development of disease-specific innate immune inflammatory and neurotoxic responses mirroring what can occur in an infected human brain.

Reference:

Mathews S, Branch Woods A, Katano I, Makarov E, Thomas MB, Gendelman HE, Poluektova LY, Ito M, Gorantla S. Human interleukin-34 facilitates microglia-like cell differentiation and persistent HIV-1 infection in humanized mice. Mol Neurodegener. 2019 Mar 5;14(1):12. doi: 10.1186/s13024-019-0311-y.