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Humanized models for assessing cellular targets for infection in the adult CNS

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The adult CNS contains a wide variety of neural cell types, comprising not only neurons, astrocytes, oligodendrocytes, and ependymal cells, but also neural stem cells and their phenotypically-restricted transit amplifying derivatives, that include glial progenitor cells of both the gray and white matter, and hippocampal progenitors. Just as the biology, antigenicity and patterns of receptor expression differ among these phenotypes, each may differ from its corresponding phenotype in experimental animals. Thus, agents that exhibit a given phenotypic specificity in one species, such as viruses that target oligodendrocytes or their progenitors in mice, may not recognize these cells in humans. Many studies of viral pathogenesis in the myelin diseases, for example, have thus been confounded by differences between experimental animals and humans in the infectivity and susceptibility of their respective glial populations. To address this issue, we have established a chimeric mouse brain in which their human counterparts have largely replaced the host astrocytic and oligodendrocytic populations. These mice are established by neonatal injection of either normal or myelin-deficient mice with isolates of human glial progenitor cells, which can be biased ex vivo to either oligodendrocytic or astrocytic fate before implantation. Depending upon the donor cell isolates and the murine hosts chosen, these mice may be constructed to develop a largely humanized white matter, including human glial progenitors, oligodendrocytes and myelin, or rather may be established to achieve a gray matter comprised largely of human astrocytes. By allowing the effects of given pathogens on human brain cell populations to be assessed in the live adult brain, these models may prove uniquely valuable in evaluating the in vivo biology and treatment of human neurotrophic and gliotrophic viruses.