Remyelination Is Correlated with Regulatory T Cell Induction Following Human Embryoid Body-Derived Neural Precursor Cell Transplantation in a Viral Model of Multiple Sclerosis.

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Public Summary:
In previous work funded by this CIRM award, we have found that neural precursor cells (NPCs), a neural stem cell derivative, induce remyelination and clinical recovery in mouse demyelination models. In those studies, we used NPCs derived from embryonic stem cells (ESC). Since these NPCs are rapidly rejected by the immune system (because they are not "self-derived," we characterized the effect of NPCs derived from induced pluripotent stem cells (iPSCs). We found that iPSC-derived NPCs were capable of promoting remyelination, although they were apparently less effective than ESC-NPCs.

Scientific Abstract:
We have recently described sustained clinical recovery associated with dampened neuroinflammation and remyelination following transplantation of neural precursor cells (NPCs) derived from human embryonic stem cells (hESCs) in a viral model of the human demyelinating disease multiple sclerosis. The hNPCs used in that study were derived by a novel direct differentiation method (direct differentiation, DD-NPCs) that resulted in a unique gene expression pattern when compared to hNPCs derived by conventional methods. Since the therapeutic potential of human NPCs may differ greatly depending on the method of derivation and culture, we wanted to determine whether NPCs differentiated using conventional methods would be similarly effective in improving clinical outcome under neuroinflammatory demyelinating conditions. For the current study, we utilized hNPCs differentiated from a human induced pluripotent cell line via an embryoid body intermediate stage (EB-NPCs). Intraspinal transplantation of EB-NPCs into mice infected with the neurotropic JHM strain of mouse hepatitis virus (JHMV) resulted in decreased accumulation of CD4+ T cells in the central nervous system that was concomitant with reduced demyelination at the site of injection. Dampened neuroinflammation and remyelination was correlated with a transient increase in CD4+FOXP3+ regulatory T cells (Tregs) concentrated within the peripheral lymphatics. However, compared to our earlier study, pathological improvements were modest and did not result in significant clinical recovery. We conclude that the genetic signature of NPCs is critical to their effectiveness in this model of viral-induced neurologic disease. These comparisons will be useful for understanding what factors are critical for the sustained clinical improvement.