Human neural stem cells expressing IGF-1: a novel cellular therapy for Alzheimer’s disease

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Background and objective

Alzheimer’s disease (AD) is a devastating neurodegenerative disorder that causes age-related dementia in over 5.2 million Americans each year (Fig. 1). Currently there is no effective treatment for the disease.

Cellular therapies have the potential to impact AD by multiple mechanisms. Our approach combines two treatment modalities, utilizing neural stem cells (NSCs) not only as a direct cellular therapy, but also as a vehicle to deliver a therapeutic growth factor in order to further protect functional neurocircuitry. Our previous studies show that autocrine IGF-1 production enhances neuroprotective and neurotrophic NSC effects in vitro (Fig. 2).

Hypothesis: grafted NSCs will improve cognitive impairment and significantly impact disease progression in AD models. We expect multiple mechanisms are involved and that NSCs will establish and support synaptic connections as well as prevent neuronal degeneration by mitigating disease-associated pathologies.

Methods & study design

Methods: Human NSCs (HRS32-IGF-1) were derived and provided by Neuralstem Inc. NSC or vehicle (sham) injections were administered to 12 week old male double transgenic (tg APP/P51AD mice (Jackson Laboratories) by three injections into the fimbria fornix bilaterally at 3 sites. Daily immunosuppression was required for the duration of the study (FK906 + mycophenolate). Animals were tested on two hippocampal-dependent behavioral tasks; novel object recognition (NOR) and Morris Water Maze (MWM). IHC analyses were performed at the study endpoint at 28 weeks - 16 weeks post-NSC transplant to the fimbria fornix (FF). Image adapted from Blanton-Jones et al. PNAS, 2009

Objective: to assess the impact of peri-hippocampal NSC transplantation on memory and learning in the APP/P51 mouse and to identify the disease mechanisms involved.

NSCs improve cognition in AD

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Figure 4. Novel object recognition (NOR). The NOR test was used to assess short-term non-associative memory in non-tg wild type (WT) and APP/P51AD mice. WT (A) and NSC-treated (C) mice recognized the novel object and significantly outperformed sham controls (*p<0.05). However, the sham group were unable to perform the task (B).

Figure 5. Morris water maze (MWM). MWM was performed 15 weeks post-NSC transplant to assess spatial reference and working memory. Hidden platform learning curves over 5 d of training, numbers represent mean ± S.E.M. of daily trials; latency (A) and average proximity (B). NSC-treated mice demonstrated significantly improved performance compared to sham controls during the training period (*p<0.05). In a 24 h probe trial, NSC-treated animals reached the former platform location almost twice as fast as sham controls (C) and spent a significantly increased amount of time in the target quadrant (D), whereas sham-treated AD animals did not (E), demonstrating a strong memory for the platform's former location (*p<0.05 vs. 25%).

NSCs reduce Aβ in the cortex and hippocampus

Figure 6. NSCs survive peri-hippocampal transplantation and migrate to the dentate in the APP/P51 mouse. Representative images of HuNu (green) and DAPI (blue) labeling of human NSCs 16 weeks post-transplantation into the fornix fornix in the same cohort of animals that completed behavior testing. Transplanted human NSCs (arrowheads) were detected in the dentate gyms of the hippocampus demonstrating their ability to migrate from the injection site and survive long term in the AD brain (A, scale bar 100 μm and B, scale bar 50 μm). High magnification image of transplanted NSCs at the subgranular polymorph layer of the dentate gyrus (C, scale bar 10 μm).

Summary & future directions

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Future directions: assess synaptic loss, cholinergic neurons, transplanted NSC differentiation and migration to other sites within the brain; alternative mouse models.

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