Induced Pluripotent Stem Cell Derived Neural Progenitor Therapy for Treatment in a MCAO Ischemic Brain Injury Pig Model

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Background: Adult and embryonic stem cell derived neural progenitor (aNP and eNP) treatments have shown significant promise in rodent models of ischemic brain injury leading to decreased infarct size and improved cognitive and sensorimotor function. However, aNPs are challenging to isolate from live patients and have restricted expansion capabilities and transplant of eNPs would result in immune rejection and bring significant ethical encumbrances being embryonic stem cell derived. Induced pluripotent stem cells (iPSCs) are a new class of stem cells that differentiate into NPs (or iNPs) and can be easily expanded, overcome immune rejection and have no ethical concerns. However, the ability of iNPs to treat ischemic injury remains to be tested. Objective: We proposed to assess iNP function in a middle cerebral artery occlusion (MCAO) pig model that is potentially more predictive of outcomes in human patients than rodents as pigs and humans have similar brain size, white matter composition and both have gyrencephalic brains. Results and Conclusions: We have recently generated iNPs from human and pig iPSCs and have developed a pig MCAO stroke model. Human and pig iNPs show classical NP morphology and express the NP markers SOX1. Further differentiation of NPs demonstrated they were capable of forming all three major lineages of the central nervous system producing βIII-Tub+ neurons, GFAP+ astrocytes and O4+ oligodendrocytes. To test the function of these iNPs in vivo, a Yucatan miniature pig MCAO model was developed by cauterization of the MCA. Diffusion weighted and apparent diffusion coefficient MRI images confirmed stroke damage 1 day post MCAO. Behavioral and motor function analysis supported MRI results with pigs showing reduced neurological capacity indicated by impaired limb movement, abnormal gait, decreased contralateral menace reflex and ipsilateral head turn. The development of a pig MCAO model will allow stringent assessment of efficacy and safety of iNP therapies in a large animal system, providing a critically needed intermediate animal model of stroke that shares key features with humans.