Title: **Reprogramming of human somatic cells for reconstruction of stroke-lesioned neuronal network**

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Abstract:

In recent years, the recovery phase of stroke attracted much of the attention of researchers and clinicians, and currently is considered as most suitable target for the stroke therapy. This is justified by the long-term therapeutic window and also intrinsic plasticity-based mechanism of recovery which is operating in the brain and represents suitable target of the therapy. Cells from different sources have been tested for their ability to reconstruct the forebrain and improve function after transplantation in animals subjected to stroke. We have shown improved functional recovery after transplantation of human reprogrammed induced pluripotent stem cells (iPSC)-derived cortical neuronal precursors in a rat model of cortical stroke. In our studies, we used a rabies virus (RV)-based strategy to explore whether transplanted iPSC-derived cortical neuronal precursors can receive and establish functional synaptic connections with host neurons. Several months after transplantation of modified cells in a rat stroke model, we infected grafted cells or host tissue with the RV. Immunohistochemical analysis of injured and transplanted brains one week after the infection with RV revealed the presence of RFP+ neurons in different areas, some of them located far away from the implantation site. When host non-lesioned contralateral cortex was infected with Rabies virus we detected labelled cells within the graft. Using electrophysiological recordings in vivo and optogenetics in brain slices recordings combined with patch-clamp we demonstrated, for the first time, that intracortical grafts of human iPSC-derived cortical neurons establish functional afferent and efferent synaptic connections with stroke-injured brain and respond to peripheral sensory stimulation. Moreover, we showed that the stroke-induced asymmetry in a sensorimotor (cylinder) test is reversed by transplantation. We found bilateral decrease of motor performance in the cylinder test after light-induced inhibition of either grafted or endogenous halorhodopsin-expressing cortical neurons, located in the same area, and after inhibition of endogenous halorhodopsin-expressing cortical neurons by exposure of their axons to light on the contralateral side. These are the first examples of functional integration of afferent and efferent projections to/from grafted reprogrammed neurons into the stroke-affected brain's neural circuitry, which raises the possibility that such repair might be achievable also in humans affected by stroke.