Preliminary safety and efficacy data of intracerebroventricular transplantation of human-Neural Stem Cell in a mouse model of ALS

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Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease affecting upper and lower motor neurons in motor cortex, brainstem and spinal cord. Although different pathological mechanisms have been described, its precise *primum movens* is still barely understood. To date, despite hopeful treatments and accumulating results, an effective therapy is still lacking. However, Neural Stem Cell (NSCs) transplant is under evaluation as a promising strategy to tackle this devastating disease. In accordance, intra-spinal cord transplantation of hNSCs showed beneficial effects during pre-clinical studies on $SOD1^{G93A}$ rats. These encouraging results led to phase I Clinical Trials (NCT01640067, NCT01348451) on ALS patients which demonstrated that this approach is feasible and safe and that could transiently decrease the progression of the disease. Despite these positive outcomes, subsequent cell-dose-escalation studies highlighted several limits of this procedure.

Here, we proposed the intracerebroventricular (ICV) transplant as an alternative experimental strategy that can possibly overcome the limits of intra-spinal cord transplant. Indeed, as a standardize surgical procedure, the ICV transplant can be leveraged to increase cell dosage and to possibly maximize the spread of the hNSCs putative healing factors throughout the neuroaxis by exploiting the cerebrospinal fluid (CSF) circulation.

Safety and efficacy of this approach are currently under investigation, by transplanting up to $1x10^6$ cells in both immunodeficient and $SOD1^{G93A}$ mice. Our preliminary data show that the transplant is well tolerated and not tumorigenic even in long term studies and at the highest dosage. Notably, hNSCs can extensively migrate along the ventricles reaching the central canal of the cervical spinal cord and disperse throughout the entire cerebral parenchyma.

Moreover, data from the $SOD1^{G93A}$ mice treated with a transient immunosuppression protocol showed a sub-optimal cell viability and no significant changes in survival, weight loss or improvements in motor performance, although a slight positive trend can be detected in the hNSCs transplanted group. A subsequent permanent immunosuppression regimen was adopted in order to possibly maximize the hNSCs survival rate and their putative therapeutic capacity. Viable cells were identified in >70% of the transplanted animals and our very preliminary results suggest that, respect to controls, the hNSCs transplanted group show better behavioral performances. Overall, the so far collected data might suggest that the hNSCs ICV transplant could represent an effective strategy to delay the decline of motor performances and maximize the spread of the hNSCs putative healing factors in an experimental model of ALS. However, further studies are necessary in order to confirm this hypothesis.