Efficacy of clinical-grade human placental mesenchymal stromal cells in fetal ovine myelomeningocele repair.

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Public Summary:
Myelomeningocele (MMC), the most severe form of spina bifida (SB), is a birth defect that occurs due to the incomplete closure of the neural tube during early pregnancy. The spinal cord is thus exposed to the intrauterine environment, accumulating damage for the remainder of the pregnancy, resulting in long-life paralysis. The current standard of care treatment for MMC is surgical closure of the defect while the fetus is still in the womb. However, 55% of surgically treated MMC patients are still unable to walk independently at 30 months of age. Our group aims to augment the current standard of care surgery with stem cells in the hope that the addition of a regenerative component to the treatment would improve motor function outcomes in MMC patients. We developed a stem cell product for this feat. Placental-derived mesenchymal stromal cells (PMSCs) isolated from human donors were seeded on an FDA approved extracellular matrix (ECM), constructing a PMSC-ECM product. These research-grade cells were used in previous studies proving the efficacy of the PMSC-ECM product in the gold-standard fetal sheep model of MMC. In this study, we used human PMSCs prepared in a Good Manufacturing Practice (GMP) facility, as required by the FDA, to seed the ECMs. This study aimed to assess the efficacy of this clinical-grade PMSC-ECM product in the fetal sheep model of MMC in preparation for a first-in-human Phase 1/2a clinical trial assessing the safety and preliminary efficacy of this stem cell product in treating MMC. 35 total lamb fetuses had the MMC defect created at around 76 days of gestation and the MMC defect repaired around 101 days of gestation with the clinical-grade PMSC-ECM patch. The clinical-grade PMSC-ECM lamb cohort (survived for 48 hours) was compared to historical cohorts treated with ECM only and research-grade PMSC-ECMs (both cohorts survived for 24 hours). Three normal lambs received no surgical intervention. All lambs were delivered at around 141 days of gestation via Cesarean section. We hypothesized that lambs that received the clinical-grade PMSC-ECM treatment would have better motor function outcomes than lambs that had their MMC defect repaired with only the ECM patch. We developed the Sheep Locomotor Rating (SLR) scale to assess motor function in sheep with MMC. All lambs were evaluated with the SLR scale. Histological analysis of the spinal cords was performed and identified that a higher density of large neurons in the lumbar (lower) spine correlated with improved motor function outcomes in the lambs. Results showed that the lambs who received the clinical-grade PMSC-ECM patch had significantly improved motor function as determined by a high SLR score and high large neuron density in the lumbar spine, compared to the ECM only lambs. The clinical-grade PMSC-ECM treated lambs had similar outcomes compared to the research-grade PMSC historically treated lambs and the normal lambs. These results supported the application of the clinical-grade PMSC-ECM product in a first-in-human clinical trial for MMC patients, which is currently underway.

Scientific Abstract:
BACKGROUND: While fetal repair of myelomeningocele (MMC) revolutionized management, many children are still unable to walk independently. Preclinical studies demonstrated that research-grade placental mesenchymal stromal cells (PMSCs) prevent paralysis in fetal ovine MMC, however this had not been replicated with clinical-grade cells that could be used in an upcoming human clinical trial. We tested clinical-grade PMSCs seeded on an extracellular matrix (PMSC-ECM) in the gold standard fetal ovine model of MMC. METHODS: Thirty-five ovine fetuses underwent MMC defect creation at a median of 76 days gestational age, and defect repair at 101 days gestational age with application of clinical-grade PMSC-ECM (3 x 10^6 cells/cm(2), n = 12 fetuses), research-grade PMSC-ECM (3 x 10^6 cells/cm(2), three cell lines with n = 6 (Group 1), n = 6 (Group 2), and n = 3 (Group 3) fetuses, respectively) or ECM without PMSCs (n = 8 fetuses). Three normal lambs underwent no surgical interventions. The primary outcome was motor function measured by the Sheep Locomotor Rating scale (SLR, range 0: complete paralysis to 15: normal ambulation) at 24 h of life. Correlation of lumbar spine large neuron density with SLR was evaluated. RESULTS: Clinical-grade PMSC-ECM lambs had significantly better motor function than ECM-only lambs (SLR 14.5 vs. 6.5, p = 0.04) and were similar to normal lambs (14.5 vs. 15, p = 0.2) and research-grade PMSC-ECM lambs (Group...
Lumbar spine large neuron density was strongly correlated with motor function ($r = 0.753, p<0.001$). CONCLUSIONS: Clinical-grade placental mesenchymal stromal cells seeded on an extracellular matrix rescued ambulation in a fetal ovine myelomeningocele model. Lumbar spine large neuron density correlated with motor function, suggesting a neuroprotective effect of the PMSC-ECM in prevention of paralysis. A first-in-human clinical trial of PMSCs in human fetal myelomeningocele repair is underway.