Birth defects represent a substantial portion of pediatric morbidity and mortality. In the United States, 1 in 33 infants is born with a structural defect, and congenital defects are the largest single cause of infant death. Improvements in prenatal screening and diagnostics have allowed earlier diagnosis of a range of birth defects. In utero surgery and stem cell therapy have the potential to revolutionize the treatment of birth defects; instead of merely treating symptoms following birth, anomalies may be cured before birth. The fetal environment contains numerous qualities which may facilitate stem cell therapy, chief among them being the natural receptivity of the gestational environment to remodeling and regeneration of fetal tissues by stem cells. Our lab has been developing fetal tissue engineering approaches using different types of stem cells and biomaterial-based scaffolds to engineer the fetal environment and treat a variety of birth defects before birth. The placenta is a unique, fetal-derived tissue that contains multiple types of stem cells. We have established a series of protocols to isolate stem cells from a variety of perinatal tissues, especially mesenchymal stem cells from placentas (PMSCs), and investigated the properties and applications of these stem cells for fetal treatment of birth defects. In order to pioneer the use of stem cells to treat birth defects, we have established a model of in utero stem cell therapy for myelomeningocele (MMC), or spina bifida. MMC is the most common cause of lifelong childhood paralysis in the United States, and approximately four children are born with this devastating congenital defect daily. MMC is caused by incomplete closure of the neural tube during development. Intrauterine damage to the exposed spinal cord afflicts children with lifelong paralysis, incontinence, and cognitive disabilities. Recently, we have demonstrated that in utero transplantation of PMSCs in the fetal lamb model of MMC can augment the fetal surgical treatment by significantly preserving motor neurons and improving the motor function recovery after birth (Figure 1). We are currently refining the PMSC-based treatments and pursuing IND-enabling studies for clinical translation. In addition, it is known that integrins play significant roles in development and homeostasis. To harness the stem cell behavior in the fetal environment, we are developing novel integrin-based ligands to improve stem cell attachment, migration, and function using the One-Bead One-Compound (OBOC) combinatorial technology, an ultra-high throughput chemical library synthesis and screening method suitable for ligand discovery against biological targets such as integrins. Designing and engineering biomaterial-based scaffolds using these novel ligands will further enhance stem cell engraftment and biological functions. Based on these studies, we are also currently developing in utero stem cell-based approaches to treat other structural or genetic birth defects such as congenital diaphragmatic hernia, muscular dystrophy and hemophilia.

Figure 1: Engineering the fetal environment with PMSCs improved motor function at birth in the fetal ovine model of MMC (adapted from PMID: 25911465). Lambs were scored on the sheep locomotor rating (SLR) scale to assess motor function. Normal lambs (n = 3) scored 15 on the SLR scale, the maximal score indicating normal motor function. Delivery vehicle only-treated MMC lambs scored from 2-8 on the SLR scale. PMSC-treated lambs scored from 5-15 on the SLR scale. Lambs in the PMSC-treated group had significantly higher SLR scores when compared to vehicle-only lambs (a). Pictures of a set of twin lambs are shown. A still image of a lamb treated with PMSCs showed the lamb standing on its own with a normal appearing stance (b). Its twin treated with a vehicle only repair was unable to bear weight on its hind limbs and is pictured with fully extended legs that are typical in animals with lower extremity paralysis from the defect (c).