THE HARTWELL FOUNDATION

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Harnessing the Regenerative Capability of Bladder Smooth Muscle Progenitor Stem Cells to Restore Function to the Obstructed Bladder

Posterior urethral valve (PUV) is a rare congenital condition than occurs in the urinary system of newborn boys, where obstructive flaps of tissue act like valves in the urethra to prevent outflow of urine from the bladder. The condition can lead to a weak urinary stream, increased urinary frequency, difficulty emptying the bladder, significant loss of bladder function, and harmful pressure damage to the kidneys. Children with PUV do not generally die from the disorder, but endure incontinence (bedwetting or wetting pants long after being toilet-trained); suffer poor growth; embarrassment and even respiratory distress. Despite early surgical removal of the valves, long-term problems with incontinence complicated by urinary tract infections are common; including urinary retention and high bladder pressure that finally causes deterioration in bladder function requiring intermittent catheterization. Many of these problems develop in adolescence. Unfortunately, there have been few breakthroughs in clinical treatment and the unmet need is in offering affected children an alternative. Most approaches to this problem focus upon bladder replacement, which nonetheless still requires catheterization and the patient to endure associated morbidity. Unfortunately, by the time replacement of the bladder is required, kidney damage has often occurred. About half of children affected with PUV (1:8000 males) develop some form of kidney failure that requires dialysis, cumulatively accounting for about 20% of the pediatric kidney transplantations performed in the United States. As kidney transplants rank sixth by mean cost per hospitalization, the aggregate hospital charges in the U.S. accounted for by PUV were remarkably, close to $1B in 2013. The problem in PUV is that bladder function is altered because the bladder muscle cells lose their ability to expel urine. In examining this phenomenon in a mouse model of bladder obstruction, Ed identified (unpublished observations) a population of smooth muscle multi-potent stem cells within a specialized cell layer of the bladder that can differentiate into mature bladder muscle cells. Based upon the response of these stem cells to bladder injury, he hypothesizes that bladder deterioration is due to a breakdown in the regulation of normal tissue remodeling pathways. If the hypothesis offered by Ed is correct, it should be possible to stimulate resident stem cells within the bladder to regenerate normal functioning muscle tissue and therefore *reset* an affected child's urinary system to a healthy, fully functioning bladder. Understanding the molecular the signaling pathways behind functional deterioration of bladder smooth muscle should also lead to improved diagnostic tests for earlier detection of bladder disorders in those children most at risk to develop serious kidney problems.