Autologous Stem Cell Homing Therapy
for the Treatment of Stress Urinary Incontinence:

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Mesenchymal stem cells have gained much recent attention owing to their unique characteristics of developmental plasticity and potential therapeutic roles after tissue injury in multiple organ systems. Despite great interest and diverse applications, the molecular signals that regulate MSC trafficking and homing to injured tissues are not fully understood, but may better serve as a therapeutic option for stem cell applications.

Vaginal delivery is a known risk factor for development of stress urinary incontinence in women. The concept of ischemic injury as a contributing factor to the development of stress urinary incontinence was first suggested by rat models of vaginal delivery, in which vaginal distension resulted in measurable dysfunction to the continence mechanism as shown by my partner, Dr. Margot Damaser et al, in 2005. Following vaginal distention, histologic studies also demonstrate extensive disruption and thinning of skeletal muscle associated with the external urethral sphincter. Decreased blood flow and hypoxic damage to the bladder, urethra, and vagina were also observed after VD. Interestingly, dysfunction appears transient, suggesting a possible role of an innate reparative process. Based upon these observations, we have been interested in determining whether similar stem cell homing pathways are upregulated following vaginal distension and are responsible for the reparative process of pelvic organ tissue recovery and the regeneration process.

Chemoattractant cytokines function as “homing molecules” that signal mesenchymal stem cell migration to sites of damage, thus promoting subsequent tissue repair. Given the focal hypoxia and tissue damage observed after vaginal distention, we hypothesize that the same cytokines are over-expressed after vaginal distention and may participate in the reparative pathways. Once fully characterized, this regenerative process could be supplemented to facilitate recovery after childbirth injuries. We have recently characterized the expression of cytokines in pelvic organ tissues (slide 2) after vaginal distension and characterized the time course of their expression.

MCP-3 was clearly significantly over-expressed in both urethral and vaginal tissues immediately following VD as compared to sham and control animals. MCP-3 levels were found to be decreasing yet still elevated from baseline 24 hours after VD. These findings are consistent with perfusion studies in urogenital organs during and after VD, which demonstrate significant decreases in blood flow to both urethra and vagina. The marked upregulation of MCP-3 in the urethra is of particular interest, as it suggests the initiation of an injury-repair pathway similar to that described after myocardial infarction. We have also demonstrated homing of green fluorescent labeled stem cells to the site of the urethra following vaginal delivery, as well as, the subsequent recovery of leak point pressure (slide 3). Our study to date demonstrates significant over-expression of MCP-3 in a rat model of urethral and vaginal tissues immediately following vaginal distension with above-normal but decreasing expression...
24 hours later. We are currently investigating the association between MCP-3 over-expression and the induction of targeted stem cell migration and tissue regeneration. The successful characterization and control of such a repair mechanism in the lower urinary tract would introduce the potential for novel, non-operative treatments and/or preventive measures for SUI and possibly other pelvic organ dysfunctions and prolapse.