

Julie Bennington
DVM
Wake Forest Institute for Regenerative Medicine
T-32 Research Fellow in Comparative Medicine, MMTS PhD Candidate

(Note: The following abstract is based on Williams et al. *Stem Cell Research & Therapy* (2017) 8:1)

Determinates of muscle precursor cell therapy efficacy in a nonhuman primate model of intrinsic urinary sphincter deficiency

Julie Bennington, DVM; James Koudy Williams, DVM; Ashley Dean, MB, RLATg; Shannon Lankford, RLATg; Tracy Criswell, PhD; Gopal Badlani, MD; Karl-Erik Andersson, PhD

Although preclinical studies have yielded promising results, clinical studies using cell therapy to treat stress urinary incontinence (SUI) due to intrinsic sphincter deficiency (ISD) have been disappointing. To further explore this disparity, a retrospective analysis was conducted on previous study results of the effects of local skeletal muscle precursor cell (skMPC) injections in a nonhuman primate model (NHP) of ISD. Three groups of categories were analyzed: age, social status, and body weight.

Adult female cynomolgus monkeys were grouped as follows: (1) younger (n=10, 5-8 years of age) versus older (n=10, 13-18 years of age); (2) socially subordinate (n=15, age matched) versus socially dominant (n=15, age matched); and (3) lower body weight (n=6, 2.8-3.4 kg) versus higher body weight (n=6, 5.0-6.7 kg). Baseline resting and pudendal nerve-stimulated maximal urethral pressures (MUP) were measured at the following time points: prior to surgically inducing ISD, just prior to treatment 6 weeks later, 3 months post-treatment, and 6 months post-treatment. Treatment consisted of 5 million autologous skMPC injected into the urethral sphincter 6 weeks post-injury. Quantitative analysis of muscle and collagen content was performed on Masson's Trichrome stain of the urethral sphincter complex 6 months post-treatment.

Older female monkeys had an average of 40% reduction in skMPC efficacy ($p < 0.05$) versus younger female monkeys. Subordinate female monkeys had an average of 30% reduction in skMPC efficacy ($p < 0.05$) versus dominant female monkeys. Heavier female monkeys had an average of 35% reduction in skMPC efficacy ($p < 0.05$) versus lighter female monkeys. These findings were apparent in both MUP and sphincter muscle and collagen content results.

As demonstrated in this retrospective analysis of data from an NHP study of ISD, these results suggest multiple factors, such as age, social status/stress, and body weight, may affect the efficacy of cell therapy in the treatment of SUI in women. The negative impacts of older age, increased social stress, and higher body weight were evident and consistent in both urethral sphincter function (i.e. MUP) and structure (i.e. muscle and collagen content). Further studies are needed that standardize these category variables and explore the underlying mechanisms causing these differences to develop more effective translational regenerative medicine therapies for the treatment of SUI in women.

Supported by the National Institutes of Health R01 DK 083688 "Regeneration of the Lower Urinary Tract in Nonhuman Primates"