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DETERMINATES OF CELL THERAPY EFFICACY FOR TISSUE AND ORGAN REPAIR

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It is not unusual for animal models of disease to inaccurately predict clinical outcome of clinical studies. One such example is stem cell therapy for stress urinary incontinence (SUI) where preclinical studies report almost complete remission of symptoms, whereas clinical studies report only around 50% remission in 50% of patients. The answer is most likely explained because animal models (which create acute SUI in relatively young animals) do not represent the most common clinical scenario where SUI is most common as a chronic disease in peri/post-menopausal women with co-existing risk factors such as obesity and type-2 diabetes. To better predict the effects of cell therapy for UI, we developed a cynomolgus monkey model of urinary incontinence (surgical nerve and muscle damage to the urinary sphincter complex) that reproduces the functional and structural changes in the urinary sphincter complex seen in women with clinical SUI. In these studies, we modeled both acute and chronic SUI in younger and older female NHPs with varying degrees of estrogen deficiencies and impaired glucose/insulin metabolism. With an n=6/experimental group, autologous skeletal muscle precursor cells (skMPCs) were isolated from a muscle biopsy, expanded to 5 million cells and injected directly into the urinary sphincter complex of NHPs with SUI. skMPCs almost completely restored sphincter muscle content and urethral pressures in younger (5-8years) NHPs ($p<0.05$ vs. SUI/no treatment), but not older (15-28 years) NHPs ($p>0.05$ vs. SUI). This same pattern of efficacy was observed in NHPs with acute vs. chronic SUI, in intact vs. ovariectomized NHPs; in normal cycling dominant NHPs vs. dysmenorrheic subordinate NHPs and in normal weight/normal glucose metabolism vs. heavier impaired glucose/insulin ratio NHPs. Thus, there are multiple determinants of cell therapy efficacy that can be modeled in NHPs and are critical to translational applicability of regenerative medicine approaches to tissue repair.

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