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Urine-Derived Stem Cells for Potential Use in Treatment of Urethral Sphincter Dysfunction

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Stress urinary incontinence (SUI) is associated with the loss of various amounts of urine when intra-abdominal pressure increases due to muscle and nerve injury within the urethral sphincter. Injury due to vaginal delivery during childbirth is a primary cause of urinary incontinence in women, which results in damage to the external urethral sphincter, pelvic floor muscle, and the neural plexus posterolateral to the vagina [1,2]. SUI occurs in 19% of women younger than 45 years, 29% of older women, and in 78% of nursing home residents, and there are an increasing number of male patients as well [3,4]. SUI affects up to 13 million people in the United States and 200 million worldwide [5]. SUI decreases patients' quality of life and is associated with significant morbidity. Besides pharmacotherapy [6], several invasive surgical therapies, including sling surgical procedures [7] and injection of bulking agents [8-15], have been commonly used to treat SUI. Although the sling procedure can reinforce weak pelvic floor muscles and has reported 71~73% success rates [7], the urethral sphincter deficiency remains [16]. Injection of bulking agents has provided encouraging outcomes, but over time these agents are absorbed and can cause chronic inflammation, per urethral abscesses, foreign body giant cell responses, erosion of the urinary bladder or the urethra, migration to inner organs, obstruction of the lower urinary tract with resultant urinary retention and severe voiding dysfunction, and even pulmonary embolism [15,17,18]. Cell-based therapy is an alternative to restore the urethral sphincter function in the treatment of SUI. Several autologous cell types, including mesenchymal stem cells (MSCs) derived from skeletal muscle [19-40], fat tissue [19,25,28,33,34,37,38,41-51], bone marrow [37,39,46,47,52-58] or umbilical cord blood mononuclear cells [59], have been used for this purpose. However, to obtain these cells, invasive procedures such as muscle tissue biopsy or bone marrow or fat aspiration are usually required, with an attendant risk of complications.

A subpopulation of cells isolated from urine possesses biological characteristics of stem cells [8,43-53], i.e. clonogenicity, high expansion capacity [60,61], multipotent differentiation capacity [8], proangiogenic paracrine effects [62], and immunomodulatory properties [63]. Thus, we have termed these cells "urine-derived progenitor/stem cells (USCs)" [64,45,50]. These cells are not MSC lineage but displayed surface markers that are similar to adult stem cells, i.e. positive staining for CD24, CD29, CD44, CD73, CD90, CD105, CD117, CD133, CD146, SSEA-4 and STRO-1, and negative staining for CD14, CD31, CD34 and CD45 [61, 65]. USCs are easily induced pluripotent stem (iPS) cells [66], which provides a candidate strategy for personalized therapy. Multiple teams confirmed our results [67,68] and used human USCs for regeneration of various types of tissues and organs [69-79].

USCs possess multipotent differentiation capacity for tissue regeneration and give rise into potential to differentiate into desired cell lineages of all three germ layers [65], such as mesodermal (i.e. osteocytes, chondrocytes, adipocytes, myocytes and endothelial cells), and endodermal (i.e. podocyte, epithelial or urothelial cells), and ectodermal (i.e. neurocytes) cell types. For cell-based therapy for SUI, the implanted endothelial cells and myocytes are needed. USCs can differentiate give rise to functional endothelial cells with unique features: including in vitro vessel formation, endothelial cell marker expression, and barrier function with tight junction formation. In addition, USCs differentiate into skeletal muscle cells [65,80,81] and smooth muscle cell lineages [44,47,48]. These differentiated USCs displayed the morphology of myotubule-like or myofiber formation, in vitro contractility and expression of myogenic gene and protein markers in vitro and in vivo. More evidences have demonstrated that paracrine effect of stem cells play an important role in restore the urinary sphincter muscle function. USCs secrete higher levels of angiogenic growth factors and cytokines (i.e. IGF1, FGF1, PDGF, MMP9 and IL-8) than bone marrow stromal cells (BMSCs). Our most recent studies further demonstrated the impact of the bioactive factors on recovery of sphincter function. In a rat model one week after vaginal distention injury, either local administration via periurethral injection of USCs or systemic administration via intraperitoneal injection significantly enhanced the sphincter function by increasing leak point pressure and restored the histology by protection against urethral sphincter injuries [82].

USCs most likely originate from kidney tissue [65]. These cells can be easily isolated and then generate a large number of cells from a single clone [60,61,65]. Additionally, up to 75% of the USCs collected from middle-aged individuals expressed telomerase activity (USCs-TA$^+$) and retained long telomere length [83]. USCs-TA$^+$ possessed higher proliferative capacities and were maintained for up to 67 population doublings, indicating that a single USC can generate up to 1.5×10^{20} (i.e. 2^{67}) cells within 14 weeks [61,65]. After optimizing our methods, 100-140 USC clones/24 hours' urine was consistently obtained from each individual [60]. About $2\text{-}5 \times 10^7$ cells are needed for potential use in SUI therapy [58, 84-86]. Thus, one 200 ml urine sample can provide ample cells at the early stage (<p5) with a few weeks for the purposes of cell implantation.

As a new cell source, human USCs have the advantages [64,65] in cell differentiation and tropic factor section for urethra sphincter tissue regeneration, compared to skeletal muscle progenitor cells (SMPCs) or BMSCs (Table 1). In addition, USCs can generate more cells and survive longer (more than16 passages) as they express telomere activity but no teratomasneither tumors. Furthermore, USCs exist in the urine of each individual regardless of a person's age, gender or race and offer enough

	BMSCs	SMPCs	USCs
Differentiation capacity			
- Endothelial cells	*2+*	*ND*	*4+*
- Skeletal myocytes	*3-4+*	*4+*	*3-4+*
- Smooth myocytes	*3-4+*	*ND*	*3-4+*
- Neurocytes	*2+*	*ND*	*2-3+*
Cell proliferation	*<p8*	*>p15*	*>p16*
Telomerase activity	--	--	+
Paracrine effect	*2+*	*2+*	*4+*
Immunomodulatory	*3+*	+	*3-4+*
Cell isolation	*Multiple-step procedures*	*Enzyme digestion processes*	*One step, simple and easy*
Cell collection approach	*Bone marrow aspiration*	*Muscle tissue biopsies*	*Non-invasive*

Table 1: Comparison of stem cell characters among USCs, SMPCs and BMSCs

Note: *ND- not determined*

amounts of cells for therapeutic injection. For cell isolation, purity of USCs can be guarantee as USC start from a single clone. Isolation processing is simple, which does not require by enzyme digestion. Furthermore, neither ethical issues nor immune reaction are involved in their use for tissue reconstruction when obtained from patients own urine sample, which makes easy get institutional ethical approval. It is also easy to isolate and culture USCs from other species, such as monkey, pig, dog and rabbits [87], which make these much feasible to use in animal experiments.

To prevent SUI recurrence is critical after cell implantation. Although cell-based therapy with skeletal muscle progenitors has achieved promise outcomes for patients with SUI [58,88,89], multiple injections in some cases are needed [89]. Clearly, it is discouraged to take multiple muscle biopsies over times to continuously obtain skeletal muscle cells to treat the SUI recurrence. In contrast, USCs can be collected or repeatedly collected if needed with a simple, safe, low-cost and non-invasive procedure compared with invasive surgical biopsy procedures, which can avoid patient potential morbidity and complications, such as donor site trauma and infection. Therefore, it is no doubt those autologous USCs as an optimal cell source offer benefits over skeletal muscle progenitor or other MSCs to achieve a stable functional improvement over the long-term follow up in enhancement of sphincter tissue regeneration, or other tissue repair in urinary tract system.

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References

1. Phull HS, Pan HQ, Butler RS, Hansel DE, Damaser MS (2011) Vulnerability of continence structures to injury by simulated childbirth. Am J Physiol Renal Physiol 301: F641-649.
2. Li TS, Cheng K, Malliaras K, Matsushita N, Sun B, et al. (2011) Expansion of human cardiac stem cells in physiological oxygen improves cell production efficiency and potency for myocardial repair. Cardiovasc Res 89: 157-165.
3. Sampselle CM, Miller JM, Mims BL, Delancey JO, Ashton-Miller JA, et al. (1998) Effect of pelvic muscle exercise on transient incontinence during pregnancy and after birth. Obstet Gynecol 91: 406-412.
4. Markland AD, Goode PS, Redden DT, Borrud LG, Burgio KL (2010) Prevalence of urinary incontinence in men: Results from the national health and nutrition examination survey. J Urol 184: 1022-1027.
5. Wilson L, Brown JS, Shin GP, Luc KO, Subak LL (2001) Annual direct cost of urinary incontinence. Obstet Gynecol 98: 398-406.
6. Caruso DJ, Gomez CS, Gousse AE (2009) Medical management of stress urinary incontinence: Is there a future? Curr Urol Rep 10: 401-407.
7. Wai CY (2009) Surgical treatment for stress and urge urinary incontinence. Obstet Gynecol Clin North Am 36: 509-519.
8. Tsakiris P, de la Rosette JJ, Michel MC, Oelke M (2008) Pharmacologic treatment of male stress urinary incontinence: Systematic review of the literature and levels of evidence. Eur Urol 53: 53-59.
9. Moore RD, Serels SR, Davila GW, Settle P (2009) Minimally invasive treatment for female stress urinary incontinence (sui): A review including tvt, tot, and mini-sling. Surg Technol Int 18: 157-173.
10. Novara G, Galfano A, Boscolo-Berto R, Secco S, Cavalleri S, et al. (2008) Complication rates of tension-free midurethral slings in the treatment of female stress urinary incontinence: A systematic review and meta-analysis of randomized controlled trials comparing tension-free midurethral tapes to other surgical procedures and different devices. Eur Urol 53: 288-308.
11. Novara G, Ficarra V, Boscolo-Berto R, Secco S, Cavalleri S, et al. (2007) Tension-free midurethral slings in the treatment of female stress urinary incontinence: A systematic review and meta-analysis of randomized controlled trials of effectiveness. Eur Urol 52: 663-678.
12. Neumann PB, Grimmer KA, Deenadayalan Y (2006) Pelvic floor muscle training and adjunctive therapies for the treatment of stress urinary incontinence in women: A systematic review. BMC Womens Health 6: 11.
13. Mariappan P, Alhasso A, Ballantyne Z, Grant A, N'Dow J (2007) Duloxetine, a serotonin and noradrenaline reuptake inhibitor (snri) for the treatment of stress urinary incontinence: A systematic review. Eur Urol 51: 67-74.
14. Trost L, Elliott DS (2012) Male stress urinary incontinence: A review of surgical treatment options and outcomes. Adv Urol 2012: 287489.
15. Kotb AF, Campeau L, Corcos J (2009) Urethral bulking agents: Techniques and outcomes. Curr Urol Rep10: 396-400.
16. Novara G, Artibani W (2007) Myoblasts and fibroblasts in stress urinary incontinence. Lancet 369: 2139-2140.
17. Kiilholma PJ, Chancellor MB, Makinen J, Hirsch IH, Klemi PJ (1993) Complications of teflon injection for stress urinary incontinence. Neurourol Urodyn 12: 131-137.
18. Koski ME, Enemchukwu EA, Padmanabhan P, Kaufman MR, Scarpero HM, et al. (2011) Safety and efficacy of sling for persistent stress urinary incontinence after bulking injection. Urology 77: 1076-1080.
19. Li GY, Zhou F, Gong YQ, Cui WS, Yuan YM, et al. (2012) Activation of vegf and erk1/2 and improvement of urethral function by adipose-derived stem cells in a rat stress urinary incontinence model. Urology 80: 953.e1-e8.
20. Boissier R, Karsenty G (2012) [cellular therapy and urinary incontinence]. Progres en urologie : journal de l'Association francaise d'urologie et de la Societe francaise d'urologie. 22: 454-461.
21. Elser DM (2012) Stress urinary incontinence and overactive bladder syndrome: Current options and new targets for management. Postgrad Med 124: 42-49.
22. Lane FL, Jacobs S (2012) Stem cells in gynecology. Am J Obstet Gynecol 207: 149-156.
23. Goldman HB, Sievert KD, Damaser MS (2012) Will we ever use stem cells for the treatment of sui? Ici-rs 2011. Neurourol urodyn 31: 386-

389.

24. Wang Y, Xu H, Liu X, Liu L, Liang Z (2011) Inhibition of fibroblast differentiation of muscle-derived stem cells in cell implantation treatment of stress urinary incontinence. Cell Reprogram 13: 459-464.

25. Wu G, Song Y, Zheng X, Jiang Z (2011) Adipose-derived stromal cell transplantation for treatment of stress urinary incontinence. Tissue Cell 43: 246-253.

26. Wu S, Wang Z, Bharadwaj S, Hodges SJ, Atala A, et al. (2011) Implantation of autologous urine derived stem cells expressing vascular endothelial growth factor for potential use in genitourinary reconstruction. J Urol 186: 640-647.

27. Sharifiaghdas F, Taheri M, Moghadasali R (2011) Isolation of human adult stem cells from muscle biopsy for future treatment of urinary incontinence. Urol J 8: 54-59.

28. Zhao W, Zhang C, Jin C, Zhang Z, Kong D, et al. (2011) Periurethral injection of autologous adipose-derived stem cells with controlled-release nerve growth factor for the treatment of stress urinary incontinence in a rat model. Eur Urol 59:155-163.

29. Oh SH, Kim IG, Lee JY, Lee JH (2011) Bioactive porous beads as an injectable urethral bulking agent: Their in vitro evaluation on smooth muscle cell differentiation. Tissue Eng Part A 17: 655-664.

30. Stangel-Wojcikiewicz K, Majka M, Basta A, Stec M, Pabian W, et al. (2010) Adult stem cells therapy for urine incontinence in women. Ginekol Pol 81: 378-381.

31. Nikolavsky D, Chancellor MB (2010) Stem cell therapy for stress urinary incontinence. Neurourol urodyn 29 Suppl 1: S36-41.

32. Proano AR, Medrano A, Garrido G, Mazza O (2010) Muscle-derived stem cell therapy for stress urinary incontinence. Actas Urol Esp. 34: 15-23.

33. Lin CS (2010) Advances in stem cell therapy for the lower urinary tract. World J Stem Cells 2: 1-4.

34. Fu Q, Song XF, Liao GL, Deng CL, Cui L (2010) Myoblasts differentiated from adipose-derived stem cells to treat stress urinary incontinence. Urology 75: 718-723.

35. Stangel-Wojcikiewicz K, Malgorzata S, Nikolavsky D, Chancellor MB (2010) Cellular therapy for treatment of stress urinary incontinence. Curr Stem Cell Res Ther 5: 57-62.

36. Lu SH, Yang AH, Chen KK, Chiang HS, Chang LS (2010) Purification of human muscle-derived cells using an immunoselective method for potential use in urological regeneration. BJU Int 105: 1598-1603.

37. Lin G, Wang G, Banie L, Ning H, Shindel AW, et al. (2010) Treatment of stress urinary incontinence with adipose tissue-derived stem cells. Cytotherapy 12: 88-95.

38. Roche R, Festy F, Fritel X (2010) Stem cells for stress urinary incontinence: The adipose promise. J Cell Mol Med 14: 135-142.

39. Drost AC, Weng S, Feil G, Schafer J, Baumann S, et al. (2009) In vitro myogenic differentiation of human bone marrow-derived mesenchymal stem cells as a potential treatment for urethral sphincter muscle repair. Ann N Y Acad Sci 1176: 135-143.

40. Smaldone MC, Chancellor MB (2008) Muscle derived stem cell therapy for stress urinary incontinence. World J Urol 26: 327-332.

41. Yamamoto T, Gotoh M, Kato M, Majima T, Toriyama K, et al. (2012) Periurethral injection of autologous adipose-derived regenerative cells for the treatment of male stress urinary incontinence: Report of three initial cases. Int J Urol 19: 652-659.

42. Watanabe T, Maruyama S, Yamamoto T, Kamo I, Yasuda K, et al. (2011) Increased urethral resistance by periurethral injection of low serum cultured adipose-derived mesenchymal stromal cells in rats. Int J Urol 18: 659-666.

43. Wang HJ, Chuang YC, Chancellor MB (2011) Development of cellular therapy for the treatment of stress urinary incontinence. Int Urogynecol J 22: 1075-1083.

44. Wu G, Zheng X, Jiang Z, Wang J, Song Y (2010) Induced differentiation of adipose-derived stromal cells into myoblasts. J Huazhong Univ Sci Technolog Med Sci 30: 285-290.

45. Yamamoto T, Gotoh M, Hattori R, Toriyama K, Kamei Y, et al. (2010) Periurethral injection of autologous adipose-derived stem cells for the treatment of stress urinary incontinence in patients undergoing radical prostatectomy: Report of two initial cases. Int J Urol 17: 75-82.

46. Smaldone MC, Chen ML, Chancellor MB (2009) Stem cell therapy for urethral sphincter regeneration. Minerva Urol Nefrol 61: 27-40.

47. Furuta A, Carr LK, Yoshimura N, Chancellor MB (2007) Advances in the understanding of sress urinary incontinence and the promise of stem-cell therapy. Rev Urol 9: 106-112.

48. Furuta A, Jankowski RJ, Pruchnic R, Yoshimura N, Chancellor MB (2007) The potential of muscle-derived stem cells for stress urinary incontinence. Expert Opin Biol Ther 7: 1483-1486.

49. Furuta A, Jankowski RJ, Honda M, Pruchnic R, Yoshimura N, et al. (2007) State of the art of where we are at using stem cells for stress urinary incontinence. Neurourol urodyn 26: 966-971.

50. Feki A, Faltin DL, Lei T, Dubuisson JB, Jacob S, et al. (2007) Sphincter incontinence: Is regenerative medicine the best alternative to restore urinary or anal sphincter function? Int J Biochem Cell Biol 39: 678-684.

51. Jack GS, Almeida FG, Zhang R, Alfonso ZC, Zuk PA, et al. (2005) Processed lipoaspirate cells for tissue engineering of the lower urinary tract: Implications for the treatment of stress urinary incontinence and bladder reconstruction. J Urol 174: 2041-2045.

52. Lin CS, Lue TF (2012) Stem cell therapy for stress urinary incontinence: A critical review. Stem Cells Dev 21: 834-843.

53. Corcos J, Loutochin O, Campeau L, Eliopoulos N, Bouchentouf M, et al. (2011) Bone marrow mesenchymal stromal cell therapy for external urethral sphincter restoration in a rat model of stress urinary incontinence. Neurourol urodyn 30: 447-455.

54. Kim SO, Na HS, Kwon D, Joo SY, Kim HS, et al. (2011) Bone-marrow-derived mesenchymal stem cell transplantation enhances closing pressure and leak point pressure in a female urinary incontinence rat model. Urol Int 86: 110-116.

55. Zou XH, Zhi YL, Chen X, Jin HM, Wang LL, et al. (2010) Mesenchymal stem cell seeded knitted silk sling for the treatment of stress urinary incontinence. Biomaterials 31: 4872-4879.

56. Kinebuchi Y, Aizawa N, Imamura T, Ishizuka O, Igawa Y, et al. (2010) Autologous bone-marrow-derived mesenchymal stem cell transplantation into injured rat urethral sphincter. Int J Urol 17: 359-368.

57. Furuta A, Jankowski RJ, Pruchnic R, Yoshimura N, Chancellor MB (2007) The promise of stem cell therapy to restore urethral sphincter function. Curr Urol Rep 8: 373-378.

58. Mitterberger M, Marksteiner R, Margreiter E, Pinggera GM, Frauscher F, et al. (2008) Myoblast and fibroblast therapy for post-prostatectomy urinary incontinence: 1-year followup of 63 patients. J Urol 179: 226-231.

59. Lim JJ, Jang JB, Kim JY, Moon SH, Lee CN, et al. (2010) Human umbilical cord blood mononuclear cell transplantation in rats with intrinsic sphincter deficiency. J Korean Med Sci 25: 663-670.

60. Lang R, Liu G, Shi Y, Bharadwaj S, Leng X, et al. (2013) Self-renewal and differentiation capacity of urine-derived stem cells after urine preservation for 24 hours. PLoS One 8: e53980.

61. Bharadwaj S, Liu G, Shi Y, Markert C, Andersson KE, et al. (2011) Characterization of urine-derived stem cells obtained from upper urinary tract for use in cell-based urological tissue engineering. Tissue Eng Part A 17: 2123-2132.

62. Liu G, Wang X, Sun X, Deng C, Atala A, et al. (2013) The effect of urine-derived stem cells expressing vegf loaded in collagen hydrogels on myogenesis and innervation following after subcutaneous implantation in nude mice. Biomaterials 34: 8617-8629.

63. Wu RP, Soland M, Liu G, Shi YA, Bharadwaj S, et al. (2012) Immunomodulatory properties of urine derived stem cells. The 3rd Annual Regenerative Medicine Foundation Conference 2012 Abstract Book. Charlotte, NC, USA.

64. Zhang Y, McNeill E, Tian H, Soker S, Andersson KE, et al. (2008) Urine derived cells are a potential source for urological tissue reconstruction. J Urol 180: 2226-2233.

65. Bharadwaj S, Liu G, Shi Y, Wu R, Yang B, et al. (2013) Multipotential differentiation of human urine-derived stem cells: Potential for therapeutic applications in urology. Stem Cells 31: 1840-1856.

66. Guan X, Mack DL, Moreno CM, Strande JL, Mathieu J, et al. (2014) Dystrophin-deficient cardiomyocytes derived from human urine: New biologic reagents for drug discovery. Stem Cell Res 12: 467-480.

67. Chun SY, Kim HT, Lee JS, Kim MJ, Kim BS, et al. (2012) Characterization of urine-derived cells from upper urinary tract in patients with bladder cancer. Urology 79: e1181-1187.

68. Zhou J, Wang X, Zhang S, Gu Y, Yu L, et al. (2013) Generation and characterization of human cryptorchid-specific induced pluripotent stem cells from urine. Stem Cells Dev 22: 717-725.

69. Fu Y, Guan J, Guo S, Guo F, Niu X, et al. (2014) Human urine-derived stem cells in combination with polycaprolactone/gelatin nanofibrous membranes enhance wound healing by promoting angiogenesis. J Transl Med 12: 274.

70. Qin H, Zhu C, An Z, Jiang Y, Zhao Y, et al. (2014) Silver nanoparticles promote osteogenic differentiation of human urine-derived stem cells at noncytotoxic concentrations. Int J Nanomedicine 9: 2469-2478.

71. Xue Y, Cai X, Wang L, Liao B, Zhang H, et al. (2013) Generating a non-integrating human induced pluripotent stem cell bank from urine-derived cells. PLoS One 8: e70573.

72. Jia B, Chen S, Zhao Z, Liu P, Cai J, et al. (2014) Modeling of hemophilia a using patient-specific induced pluripotent stem cells derived from urine cells. Life Sci 108: 22-29.

73. Pei M, Li J, Zhang Y, Liu G, Wei L (2014) Expansion on a matrix deposited by nonchondrogenic urine stem cells strengthens the chondrogenic capacity of repeated-passage bone marrow stromal cells. Cell Tissue Res 356: 391-403.

74. Chen Y, Luo R, Xu Y, Cai X, Li W, et al. (2013) Generation of systemic lupus erythematosus-specific induced pluripotent stem cells from urine. Rheumatol Int 33: 2127-2134.

75. Zhou T, Benda C, Dunzinger S, Huang Y, Ho JC, et al. (2012) Generation of human induced pluripotent stem cells from urine samples. Nat Protoc 7: 2080-2089.

76. Benda C, Zhou T, Wang X, Tian W, Grillari J, et al. (2013) Urine as a source of stem cells. Adv Biochem Eng Biotechnol 129: 19-32.

77. Zhou T, Benda C, Duzinger S, Huang Y, Li X, et al. (2011) Generation of induced pluripotent stem cells from urine. J Am Soc Nephrol 22: 1221-1228.

78. Guan J, Zhang J, Zhu Z, Niu X, Guo S, et al. (2015) Bone morphogenetic protein 2 gene transduction enhances the osteogenic potential of human urine-derived stem cells. Stem Cell Res Ther 6: 5.

79. Guan JJ, Niu X, Gong FX, Hu B, Guo SC, et al. (2014) Biological characteristics of human-urine-derived stem cells: Potential for cell-based therapy in neurology. Tissue Eng Part A 20: 1794-1806.

80. Chen W, Xie M, Yang B, Bharadwaj S, Song L, et al. (2014) Skeletal myogenic differentiation of human urine-derived cells as a potential source for skeletal muscle regeneration. J Tissue Eng Regen Med.

81. Liu G, Pareta RA, Wu R, Shi Y, Zhou X, et al. (2013) Skeletal myogenic differentiation of urine-derived stem cells and angiogenesis using microbeads loaded with growth factors. Biomaterials 34: 1311-1326.

82. Tran CNT A, Balog B, Zhang Y, Damaser M (2015) Paracrine effects of human urine-derived stem cells in treatment of female stress urinary incontinence in a rodent model. Tissue Eng Part A 21: S-385.

83. Shi YA, Liu GH, Bharadwaj S, Atala A, Zhang Y (2012) Urine derived stem cells with high telomerase activity for cell based therapy in urology. J Urol 187: Supplement, e302.

84. Mitterberger M, Marksteiner R, Margreiter E, Pinggera GM, Colleselli D, et al. (2007) Autologous myoblasts and fibroblasts for female stress incontinence: A 1-year follow-up in 123 patients. BJU Int 100: 1081-1085.

85. Mitterberger M, Pinggera GM, Marksteiner R, Margreiter E, Fussenegger M, et al. (2008) Adult stem cell therapy of female stress urinary incontinence. Eur Urol 53: 169-175.

86. Sebe P, Doucet C, Cornu JN, Ciofu C, Costa P, et al. (2011) Intrasphincteric injections of autologous muscular cells in women with refractory stress urinary incontinence: A prospective study. Int Urogynecol J 22: 183-189.

87. Jiang YC B, Liu G, Deng C, Zhang Y (2015) Characterization of rabbit urine-derived stem cells for potential application in urethral tissue regeneration. Tissue Eng Part A Supplement 1: S-208.

88. Stangel-Wojcikiewicz K, Jarocha D, Piwowar M, Jach R, Uhl T, et al. (2014) Autologous muscle-derived cells for the treatment of female stress urinary incontinence: A 2-year follow-up of a polish investigation. Neurourol Urodyn 33: 324-330.

89. Peters KM, Dmochowski RR, Carr LK, Robert M, Kaufman MR, et al. (2014) Autologous muscle derived cells for treatment of stress urinary incontinence in women. J Urol 192: 469-476.