Stem cells for urinary tract regeneration

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KEY WORDS

stem cells ◗ urinary bladder ◗ bladder cancer ◗ urinary sphincter ◗ urinary incontinence

ABSTRACT

Regeneration of the urinary bladder is a complicated task, due to organ dimensions and diseases (cancer, interstitial cystitis) when autologous bladder cells cannot be used. Cancer is the most frequent indication for bladder removal (cystectomy). Stem cells can be used with the guarantee of the sufficient cell number for the *in vitro* construction of the urinary bladder wall. Tissue engineering techniques hold great promise for regeneration of dysfunctional urinary sphincter. Denervation following surgical procedures or injuries results in weakness of the urethral sphincter and stress urinary incontinence. Injectable therapies and the potential of stem cells for sphincter restoration was presented in this review. The aim of this review was to present possibilities of urinary bladder regeneration with the use of stem cells and tissue engineering techniques.

INTRODUCTION

Regeneration and reconstruction of the urinary tract is a very complicated task. There are several parts of the urinary tract, which could be regenerated with the use of tissue engineering techniques. The urinary bladder is the most challenging due to the organ's huge dimensions. There are many diseases when autologous urothelial and bladder muscle cells cannot be used for *in vitro* construction of the elements of urinary tract, for example: bladder wall for augmentation (cystoplasty) or *de novo* creation of the whole urinary bladder. These diseases, like cancer or interstitial cystitis, are the most frequent indications for urinary bladder removal (cystectomy) in men. The presentation focuses on the idea of harvesting potentially multipotent stem cells isolated from hair follicle or mesenchymal stem cells isolated from bone marrow and using them for the regeneration of the urinary bladder wall. There is no current clinical practice in bladder regeneration with the use of stem cells. However, there are some studies that suggest the use of cultures enriched with progenitors. These stem cell niches give an opportunity to reduce the invasiveness of cell harvesting. Both epithelial and mesenchymal multipotent stem cells populations within hair follicles or bone marrow raise new possibilities for tissue engineering of the urinary bladder. The hypothesis is that stem cells can be used with the guarantee of the sufficient cell number for *in vitro* construction of a urinary bladder wall replacement. The future will show if is it a good idea or not.

Currently, invasive surgical management of stress urinary incontinence is associated with morbidity and recurrence. Tissue engineering techniques hold great promise for regeneration of dysfunctional urinary sphincter. Urethral denervation following surgical procedures or injury resulted in dysfunction of the skeletal muscle and partial impairment of smooth muscle contractility. The importance of the middle urethra, treatment of stress urinary incontinence including injectable therapies, and the potential of stem cells for sphincter restoration will be presented. Stem cells have the ability to undergo self-renewal and multidirectional differentiation. There are several potential sources of stem cells for the treatment of stress urinary incontinence, like bone marrow stromal stem cells, muscle derived stem cells, and adipose-derived stem cells. Stem cells injection therapy increased leak point pressure and urethral muscle strip contractility in experimental models of stress urinary incontinence. Introducing these therapies into clinical conditions is questionable. We are still waiting for additional investigations and trials related to this new and experimental method of stress urinary incontinence treatment. The aim of this review was to present the possibilities of urinary bladder regeneration with the use of stem cells.

1. Short history of urinary tract regeneration and tissue engineering

Regeneration and reconstruction of the urinary tract is a very complicated task. The history of the reconstruction of urinary tract is very long. In 1888 Tizzoni and Poggi started to experimental studies on urinary tract reconstruction. In 1917 Neuhof presented human urinary bladder augmentation with fascia [1]. These pioneering works were stopped for a period of 40 years. In the fifties Bricker, Kock and other presented different kinds of urinary diversion techniques. Studer and coworkers in 1985 showed orthotopic urinary bladder constructed from ileum, which became the most popular orthotopic bladder [2, 3]. The orthotopic bladder and ileal conduit are both the most popular diversion techniques, but there are many complications related to bowel segments used for urinary diversion [4]. In 1991, Narem and Vacanti defined tissue engineering, which is a discipline based on biomaterial science and knowledge on cell culture to prepare *in vitro* living grafts and constructs that can be used for tissue regeneration or replacement [5]. The history of tissue engineering started over one hundred years ago. Experimental works of Harrison, Carrel, and Rous showed the possibility to culture cells outside the body [6, 7, 8]. Tissue engineering techniques were developed and introduced into the clinic by Gallico, Ricordi, Brittberg, and many prominent doctors and scientists [9-12].

There are several parts of the urinary tract, which could be regenerated with the use of tissue engineering techniques. The urinary bladder is the most challenging, due to the organ's huge dimensions. In 1999, Oberpenning and coworkers presented urinary bladder augmentation with cells seeded on scaffold in a canine model [13]. Seven years later Atala et al. replicated this work in a human model. They have presented seven patients with neurogenic bladders augmented with bladder wall constructed from autologous urothelial and muscle cells seeded on PGLA/collagen scaffold [14].

There are many diseases when autologous urothelial and bladder muscle cells cannot be used for *in vitro* construction of the elements of urinary tract, for example: bladder wall for augmentation (cystoplasty) or *de novo* creation of the whole urinary bladder. These diseases like cancer or interstitial cystitis. Bladder cancer is the most frequent indication for urinary bladder removal (cystectomy) in men. The presentation focuses on the idea of harvesting potentially multipotent stem cells out of hair follicle or mesenchymal stem cells and using them for the regeneration of the urinary bladder wall. Current clinical practice suggests the use of cultures enriched with progenitors. These stem cell niches give an opportunity to reduce the invasiveness of cell harvesting. Both epithelial and mesenchymal multipotent stem cells populations within hair follicles or bone marrow raise new possibilities for tissue engineering of the urinary bladder. The hypothesis is that stem cells can be used with the guarantee of the sufficient cell number for the *in vitro* construction of a urinary bladder wall replacement. The future will show if is it a good idea or not [15].

2. Tissue engineering and urinary bladder regeneration

Until now it was very difficult to replicate experiments of Atala and co-workers (2006) in the case of subtotal cystectomy (cystectomy with triangle sparing) [14]. This method was not tested on a larger group of patients [16]. We do not know if there is a limit of the graft surface (huge animal model and human) beyond which full regeneration of the bladder wall will never occur [17-20]. One *in vitro* constructed graft for human urinary bladder augmentation with a surface of 150 cm^2 needs 140 Petri dishes each with 15 cm in diameter. In all, 2.5 m^2 of cells has to be grown. The biopsy specimen has to be multiplied 25,000 times to prepare adequate graft surface [14]. The most important questions are concerning cell behavior in culture. After such intensive cell proliferation a replicative senescence should occur according to the phenomenon described by Hayflick and Moorhead [21]. Will all cultured cells be stable after transplantation? What about the risk of carcinogenesis? These questions are still unanswered [22-25]. An analysis of the risk of carcinogenesis was elaborated for melanocyte cell culture and presented by Czajkowski and colleagues [26]. It was stated that long and extensive cell culture has not influenced on oncogene status of normal cells, so these cells can be probably safely transplanted into the host. There is no doubt that safety of the cell therapy is one of the most important issues in the field of tissue engineering, but this issue is not well elaborated.

There are a lot of studies that confirm the possible use of only acellular matrices for the urinary bladder reconstruction [27-29]. Bladder Acellular Matrix (BAM) is a kind of natural scaffold rich in growth factors [14, 30, 31] and closely matches the host tissue with regard to size and to mechanical, structural, and genetic properties [32]. However, there is some evidence that bladder regeneration with acellular scaffolds results in a fibrotic reaction and leads to fibrosis and stops the process of remodeling [16, 33]. According to those reports the question if we need cells for regeneration of bladder occurs. Beyond a doubt, the use of stem cells to treat and reconstruct urological organs appears to be a very powerful and promising approach. Although it is not known what is the real influence of transplanted cells on bladder wall reconstruction. There is still a speculation that transplanted cells build urinary bladder wall and lead to reconstruction. A major problem with transplanted cells is their poor viability after transfer. This results in sudden cell death, which occurs within a few hours after the cells are transferred to the recipient. Some authors reported no viable cells after transplantation. That is why recently a main concern is to develop procedures, which will improve the efficiency of cell transplantation. Even after autologous transplantation the low cellular survival rate still exists [34-37]. This can be a limitation for proper bladder regeneration, because cells are the factor that guarantees nerve growth and angiogenesis [38]. Yannas proposed the inductive model of regeneration in which cells are connected with membrane basement. He suggested the dermis regeneration template (DRT), nerve regeneration template (NRT), and meniscus regeneration template (MRT) that led to regeneration of the aforementioned organs [39].

3. Tissue Engineering and Stress Urinary Incontinence treatment

The aforementioned results suggest the potential use of hair follicle and mesenchymal stem cells in urinary tract regeneration, including urinary incontinence. There are more than 200 million people worldwide living with incontinence [40]. The most common type of urinary incontinence is stress urinary incontinence (SUI) [41]. Stress urinary incontinence is a major problem, which affects approximately 20% of women and nearly 50% of elderly women [42, 43]. The number of patients with this urologic health problem will rise as the baby-boomer generation continues to age [44]. It is a condition with involuntary leakage from the urethra, synchronous with exertion, or on sneezing or coughing, associated with a reduced quality of life [45]. The etiology of SUI is multifactorial, involving functional impairment of pelvic muscle, connective tissue and associated nerves that occurs as a result of advancing age, hormonal status, and pelvic floor damage resulting from vaginal childbirth, which seems to be the most important risk factor for lifetime incontinence [46-49].

Newly emerging technology that may provide a novel method for the treatment of SUI is tissue engineering. The deficiency of muscle and connective tissue that results in SUI can be regenerated by stem-cell therapy, which is currently at the forefront of incontinence research [50]. Stem cells injected into the middle urethra can potentially restore the contractility of the striated muscles and rhabdosphincter.

Carr and coworkers have made the clinical therapy with muscle derived stem cells (MDSCs) biopsy from lateral thigh muscle [51]. Eight patients were included in the first trial using either a periurethral or transurethral MDSC injections into the middle urethra and external urethral sphincter (EUS). The measurable improvement was observed in two patients who underwent periurethral injection and two patients who received transurethral injections using a 10-mm needle. Two patients with initial injections using an 8-mm needle had no benefit. Five of eight patients who followed up for more than one year reported significant improvement. That is why these results are the potential for pure cellular therapy in treating stress urinary incontinence and emphasize the importance of proper cell placement in resulting effectiveness.

4. Cell populations for urological structures regeneration

There are many urinary tract diseases in which autologous cells cannot be used for *in vitro* construction of the urinary bladder wall for augmentation (cystoplasty). The most common indication for bladder excision is urothelial cell cancer and muscle invasive blad-

der cancer. These conditions disqualify the use of urinary bladder autologous cells in clinical application. That is why a new source of easily accessible cells with high proliferation rate and plasticity potential are required. Stem cell research is expanding at an extremely rapid pace with new developments and potential applications in medicine. Stem cells are undifferentiated cells that are defined by their abilities of self-renewal and differentiation, producing mature progeny consisting of both non-renewing progenitors and terminally differentiated effector cells [52]. One of the most interesting features of stem cells is their plasticity, which enables converting one cell type to another, even with change of cell lineage. Somatic stem cells seem to be ideal candidates for tissue engineering purposes. Embryonic stem cells are another attractive cell source for regeneration. Human embryonic stem cell lines were successfully generated in 1998. ESCs can potentially be maintained in an undifferentiated state *in vitro* and theoretically can be directed to differentiate to any cell type of the body. Although the potential of ESCs in regenerative medicine is clear, several methodological problems and issues of control of differentiation following transplantation need to be solved before they can be used in human regenerative therapies [25]. Less controversial, but promising, are somatic stem cells that probably have a much wider differentiation potential than was previously thought. Referring to the previous results of urinary bladder regeneration by stem cells we decided to regenerate epithelium and muscles by hair stem cells and bone marrow mesenchymal stem cell, respectively [53, 54]. Hair follicle and bone marrow stem cells may serve as a source of relatively easily accessible multipotent stem cells for therapeutic approaches.

4. 1. Hair follicle and bone marrow mesenchymal stem cells in urology

Hair follicles are mini organs, which undergo cyclic regeneration through their lifetime. The hair follicle boasts two kinds of stem cell niches, (1) epithelial (bulbar region) and (2) mesenchymal (dermal papilla and fibrotic capsula) cells [55].

These cells were differentiated into keratinocytes, muscle cells, neurons, glia, and melanocytes. Our previous studies showed that different isolation and culture methods influence the phenotype of a hair follicle stem cell while indicating their heterogeneity [56]. The hair follicle epithelial stem cells do not express cytokeratins specific for bladder (CK 7, 8 and 18) and are highly positive for cytokeratin 15. These cells can be converted into urothelial-like phenotype when cultured in media collected from cultures of normal urothelial cells [57]. It was not proven yet that transdifferentiation will be permanent, but it shed a new light on the novel stem cell source for urinary tract regeneration.

Bone marrow mesenchymal stem cells (MSCs) are well accessible and can differentiate into many different cell types, including: adipocytes, chondrocytes, osteoblasts, cardiomyoctes, tenocytes, and skeletal muscle cells *in vitro*. This stem cell population is characterized by CD44, SH-4 (CD73), CD90, SH-2 (CD105), CD117 (c-kit), SH-3 (CD166), Sca-1, and STRO-1 expression and the lack of CD11b, CD14, CD31, CD 34, and CD45 antigens [58].

It was proven that different conditioned media provide a convenient source of inductive signals to initiate cell reprogramming and their transdifferentiation. TGF-β1 and 5'azacytidine supplemented media as well as conditioned media obtained from H9C2, L6, and primary skeletal muscle cell lines and co-culture system (consisted of MSCs and skeletal muscle cells) induced MSCs transdifferentiation into myogenic (skeletal and smooth muscle) phenotype [59]. Transdifferentiation of stem cells harvested form different niches seems to be a promising option, which can be used in the future for urinary tract regeneration avoiding urinary bladder cells.

CONCLUSIONS

Adult stem cells can be used in urinary tract regeneration, especially hair follicle and bone marrow mesenchymal stem cells. These stem cell populations show high plasticity potential and are able to differentiate into urothelium and muscle layer *in vitro* under defined culture conditions.

REFERENCES

1. Neuhof H: *Some observation in spinal cord surgery.* Ann Surg 1917; 4: 410-437.
2. Bricker EM: *Substitution for the urinary bladder by the use of isolated ileal segments.* Surg Clin North Am 1956; 36: 1117-1130.
3. Studer UE, deKernion JB, Zimmern PE: *A model for a bladder replacement plasty by ileal reservoir-an experimental study in dogs.* Urol Res 1985; 13: 243-247.
4. Carrion R, Arap S, Corcione G, et al: *A multi-institutional study of orthotopic neobladders: functional results in men and women.* BJU Int 2004; 93: 803-806.
5. Vacanti J, Vacanti Ch, Narem R: *Tissue engineering by cell transplantation using degradable polymer substrates.* J Biomech Eng 1991; 113: 143-151.
6. Harrison R: *The outgrowth of the nerve fiber as a mode of protoplasmic movement.* J Exp Zool 1910; 9; 787-846.
7. Carrel A: *On the permanent life of tissues outside of the organism.* J Exp Med 1912; 15: 516-528.
8. Rous P: *A method for obtaining suspensions of living cells from the fixed tissues.* J Exp Med 1916; 23: 549-555.
9. Gallico GG, O'Connor NE, Compton CC, et al: *Permanent coverage of large burn wounds with autologous cultured human epithelium.* N Engl J Med 1984, 311, 448-451.
10. Ricordi C, Alejandro R, Zeng Y: *Human Islet Isolation and Purification From Pediatric-Age Donors.* Transplant Proc 1991; 23: 783-784.
11. Brittberg M, Lindahl A, Nilsson A, et al: *Treatment of deep cartilage defects in the knee with autologous chondrocyte transplantation.* N Engl J Med 1994; 331: 889-895.
12. Oberpenning F, Meng J, Yoo JJ, Atala A: *De novo reconstitution of a functional mammalian urinary bladder by tissue engineering.* Nat Biotechnol 1999; 17: 149-155.
13. Atala A, Bauer SB, Soker S, et al: *Tissue-engineered autologous bladders for patients needing cystoplasty.* Lancet 2006; 367: 1241-1246.
14. Drewa T: *Using hair-follicle stem cells for urinary bladder-wall regeneration.* Regen Med 2008; 3: 939-944.
15. Zhang Y, Frimberger D, Cheng EY, et al: *Challanges in a larger bladder replacement with cell-seeded and unseeded small intestinal submucosa grafts in a subtotal cystectomy model* BJU Int 2006; 98: 1100-1105.
16. Merguerian PA, Reddy PP, Barrieras DJ, et al: *Acellular bladder matrix allografts in the regeneration of functional bladders: evaluation of large-segment (>24 cm) substitution in a porcine model.* BJU Int 2000; 85: 894-898.
17. Reddy PP, Barrieras DJ, Wilson G, et al: *Regeneration of functional bladder substitutes using large segment acellular matrix allografts in a porcine model.* J Urol 2000; 164: 939-941.
18. Ninković M, Dabernig W: *Flap technology for reconstructions of urogenital organs* Curr Opin Urol 2003; 13: 483-488.
19. Hedrick MH, Daniels EJ: *The use of adult stem cells in regenerative medicine.* Clin Plast Surg 2003; 30: 499-505.
20. Hayflick L, Moorhead PS: *The serial cultivation of human diploid cell strains.* Exp Cell Res 1961; 25: 585-621.
21. Stoica G, Jacobs R, Koestner A, et al: *ENU-induced In vitro neoplastic transformation of rat mam mary epithelial cells* Anticancer Res 1991; 11: 1783-1792.
22. Bruegel-Sanchez VL, Zhou J, LaCivita D, Milstone LM: *Long-term murine keratinocyte cultures become tetraploid, yet maintain the ability to stratify.* J Invest Dermatol 2004; 123: 403-404.

23. Walen KH: *Human diploid fibroblast cells in senescence; cycling through polyploidy to mitotic cells.* In Vitro Cell Dev Biol Anim 2006; 42: 216-224.
24. Becker C, Jakse G: *Stem cells for regeneration of urological structures.* Eur Urol 2007; 51: 1217-1228.
25. Czajkowski R, Pokrywczynska M, Placek W, et al: *Transplantation of cultured autologous melanocytes - hope or danger?* Cell Transplant 2010, 19, 639-643.
26. Badylak SF, Lantz GC, Coffey A, Geddes LA: *Small intestinal submucosa as a large diameter vascular graft in the dog.* J Surg Res 1989; 47: 74-80
27. Sutherland RS, Baskin LS, Hayward SW, Cunha GR: *Regeneration of bladder urothelium, smooth muscle, blood vessels and nerves into an acellular tissue matrix.* J Urol 1996; 156: 571-577.
28. Portis AJ, Elbahnasy AM, Shalhav AL, et al: *Laparoscopic midsagittal hemicystectomy and replacement of bladder wall with small intestinal submucosa and reimplantation of ureter into graft.* J Endourol 2000; 14: 203-211.
29. Kanematsu A, Yamamoto S, Noguchi T, et al: *Bladder regeneration by bladder acellular matrix combined with sustained release of exogenous growth factor.* J Urol 2003; 170:1633-1638.
30. Kanematsu A, Yamamoto S, Ozeki M, et al: *Collagenous matrices as release carriers of exogenous growth factors.* Biomaterials 2004; 25: 4513-4520.
31. Probst M, Piechota HJ, Dahiya R, Tanagho EA: *Homologous bladder augumentation in dog with the bladder acellular matrix graft.* BJU Int 2000; 85: 362-371.
32. Borówka A: *Filling of extensive defects of the bladder with collagen membrane.* Pol Tyg Lek 1981; 36: 1525-1527.
33. Hodgetts SI, Beilharz MW, Scalzo AA, Grounds MD: *Why do cultured transplanted myoblasts die in vivo? DNA quantification shows enhanced survival of donor male myoblasts in host mice depleted of CD4+ and CD8+ calle or Nk11+ cells.* Cell Transplant 2000; 9: 489-502.
34. Huard J, Yokoyama T, Pruchnic R, et al: *Muscle-derived cell-mediated ex vivo gene therapy for urological dysfunction.* Gene Ther 2002; 9: 1617-1626.
35. Darsalia V, Kallur T, Kokaia Z: *Survival, migration and neuronal differentiation of human fetal striatal and cortical neural stem cells grafted in stroke-damaged rat striatum.* Eur J Neurosci 2007; 26: 605-614.
36. Niranjan A, Fellows W, Stauffer W, et al: *Survival of transplanted neural progenitor cells enhanced by brain irradiation,* J Neurosurg 2007; 107: 383-391.
37. Drewa T, Sir J, Czajkowski R, Wozniak A: *Scaffold seeded with cells is essential in urothelium regeneration and tissue remodeling in vivo after bladder augumentation using in vitro engineered graft.* Transplant Proc 2006, 38, 133-135.
38. Yannas IV: *Regeneration Template*, In: The biomedical engineering handbook, CRC Press, Florida, 1995, pp. 1619-1635.
39. Norton P, Brubaker L: *Urinary incontinence in women.* Lancet 2006; 367: 57-67.
40. Hampel C, Wienhold D, Benken N, et al: *Prevalence and natural history of female incontinence.* Eur Urol 1997; 32: 3-12.
41. Abrams P, Cardozo L, Fall M, et al: *The standardization of terminology in lower urinary tract function: report from the standardisation sub-committee of the International Continence Society.* Urology 2003; 61: 37-49.
42. Brown JS, Nyberg LM, Kusek JW, et al: *Proceedings of the National Institute of Diabetes and Digestive and Kidney Diseases International Symposium on epidemiologic issues in urinary incontinence in women.* Am J Obstet Gynecol 2003; 188: 77-88.
43. Holroyd-Leduc JM, Straus SE: *Management of urinary incontinence in women: scientific review.* JAMA 2004; 291: 986-995.
44. Lasserre A, Pelat C, Gueroult V, et al: *Urinary incontinence in French women: prevalence, risk factors, and impact on quality of life.* Eur Urol 2009; 56, 177-183.
45. Meyer S, Schreyer A, De Grandi P, Hohlfeld P: *The effects of birth on urinary continence mechanisms and other pelvic-floor characteristics.* Obstet Gynecol 1998; 92: 613-618.
46. Sampselle CM, Miller JM, Mims BL, et al: *Effect of pelvic muscle exercise on transient incontinence during pregnancy and after birth.* Obstet Gynecol 1998; 91: 406-412.
47. Peschers U, Schaer G, Anthuber C, et al: *Changes in vesical neck mobility following vaginal delivery.* Obstet Gynecol 1996; 88: 1001-1006.
48. Thom DH, van den Eeden SK, Brown JS: *Evaluation of parturition and other reproductive variables as risk factors for urinary incontinence in later life.* Obstet Gynecol 1997; 90: 983-989.
49. Chancellor MB, Yokoyama T, Tirney S, et al: *Preliminary results of myoblast injection into the urethra and bladder wall: a possible method for the treatment of stress urinary incontinence and impaired detrusor contractility.* Neurourol Urodyn 2000; 19: 279-287.
50. Carr LK, Steele D, Steele S, et al: *1-year follow-up of autologous muscle-derived stem cell injection pilot study to treat stress urinary incontinence.* Int Uroqvnecol J Pelvic Floor Dysfunct 2008; 19: 881-883.
51. Blau HM, Brazelton TR, Weimann JM: *The evolving concept of a stem cell: entity or function.* Cell 2001; 105: 829-841.
52. Wollert KC, Drexler H: *Cell therapy for acute myocardial infarction: where are we heading?* Nat Clin Pract Cardiovasc Med 2004; 1: 61.
53. Tiede S, Kloepper JE, Bodo E, et al: *Hair follicle stem cells: walking the maze.* Eur J Cell Biol 2007; 86: 355-376.
54. Cotsarelis G: *Epithelial stem cells: a folliculocentric view.* J Invest Dermatol 2006; 126: 1459-1468.
55. Drewa T, Joachimiak R, Kaznica A, et al: *Hair stem cells for bladder regeneration in rats: preliminary results.* Transplant Proc 2009; 41: 4345-4351.
56. Wagner W, Ho AD: *Mesenchymal stem cell preparations-comparing apples and organs* Stem Cell Rev 2007; 3: 239-248.
57. Joachimiak R, Bajek A, Drewa T, et al: *Hair follicle stem cells and bone marrow mesenchymal stem cells in bladder regeneration.* Eur Urol Suppl 2011; 10: 214.
58. Abdallah BM, Kassem M: *The use of mesenchymal (skeletal) stem cells for treatment of degenerative diseases: current status and future perspectives.* J Cell Physiol 2009; 218: 9-12.
59. Bajek A, Drewa T, Roachimiak R, et al: *A Can bone marrow mesenchymal stem cells regenerate the external urinary sphincter? The impact of transdifferentiation evoked by paracrine influences.* Eur Urol Suppl 2011; 10: 290-291.

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