



## Stress urinary incontinence animal models as a tool to study cell-based regenerative therapies targeting the urethral sphincter<sup>☆</sup>



Bernardo Herrera-Imbroda <sup>a,1</sup>, María F. Lara <sup>a,1</sup>, Ander Izeta <sup>b</sup>, Karl-Dietrich Sievert <sup>c,d</sup>, Melanie L. Hart <sup>c,\*</sup>

<sup>a</sup> Urology Unit Research Virgen de la Victoria and Regional Hospital, Campus Universitario de Teatinos s/n. Málaga 29010, Spain

<sup>b</sup> Instituto Biomedicina, Hospital Universitario Donostia, Paseo Dr. Begiristain s/n, 20014 San Sebastián, Spain

<sup>c</sup> Clinical Research Group KFO 273, Department of Urology, Tuebingen, Germany

<sup>d</sup> Department of Urology, University of Lübeck Schleswig-Holstein, Ratzeburger Allee 160, 23538 Lübeck, Germany

### ARTICLE INFO

Available online 23 October 2014

#### Keywords:

Stress urinary incontinence  
Animal models of urinary incontinence  
Cell-based therapy  
Mesenchymal stem cells  
Urethral sphincter  
Urethral dysfunction  
Muscle regeneration

### ABSTRACT

Urinary incontinence (UI) is a major health problem causing a significant social and economic impact affecting more than 200 million people (women and men) worldwide. Over the past few years researchers have been investigating cell therapy as a promising approach for the treatment of stress urinary incontinence (SUI) since such an approach may improve the function of a weakened sphincter. Currently, a diverse collection of SUI animal models is available. We describe the features of the different models of SUI/urethral dysfunction and the pros and cons of these animal models in regard to cell therapy applications. We also discuss different cell therapy approaches and cell types tested in preclinical animal models. Finally, we propose new research approaches and perspectives to ensure the use of cellular therapy becomes a real treatment option for SUI.

© 2014 Elsevier B.V. All rights reserved.

### Contents

1. Introduction . . . . .	107
2. Pathophysiological animal models of reversible incontinence . . . . .	108
2.1. Vaginal distension . . . . .	108
2.2. Pudendal nerve crush (PNC) . . . . .	109
3. Pathophysiological animal models of durable incontinence . . . . .	109
3.1. Urethrolysis . . . . .	109
3.2. Electrocauterization . . . . .	110
3.3. Urethral sphincterotomy . . . . .	110
3.4. Pubourethral ligament and pudendal nerve transection . . . . .	110
3.5. Bilateral pudendal nerve transection (PNT) . . . . .	110
4. Regeneration of the urethral sphincter using cell therapy in animal models . . . . .	111
4.1. MSC based therapy . . . . .	112
4.2. ADSC based therapy . . . . .	112

**Abbreviations:** ALPP, abdominal leak point pressure; ADSC, adipose-derived stem cells; AFSC, amniotic fluid stem cells; ASMA, alpha smooth muscle actin; BMSC, bone marrow-derived stem cells; CP, closure pressure; EFS, electrical field stimulation; EMG, electromyography; EUS, external urethral sphincter; hAFSC, human amniotic fluid-derived stem cells; hMDC, human muscle precursor cells; hUCB, human umbilical cord blood; LPP, leak point pressure; DFAT, mature adipocyte-derived cells, dedifferentiated from fat; MUCP, maximal urethral closure pressure; MSCs, mesenchymal stem cells; MDC, muscle-derived cells; MDSC, muscle-derived stem cells; MPC, muscle precursor cells; NGF, nerve growth factor; PLGA, polylactic-co-glycolic acid; PUL, pubourethral ligament; PNC, pudendal nerve crush; PNT, pudendal nerve transection; RP, radical prostatectomy; RUPP, retrograde urethral perfusion pressure; SKMSC, skeletal muscle stem cells; SUI, stress urinary incontinence; TURP, transurethral resection of the prostate; urethral pressure curve, (UPC); UI, urinary incontinence; VD, vaginal distension.

<sup>☆</sup> This review is part of the *Advanced Drug Delivery Reviews* theme issue on "Regenerative Medicine Strategies in Urology".

\* Corresponding author at: Clinical Research Group KFO 273, Department of Urology UKT, University of Tuebingen, Paul-Ehrlich-Str. 15, 72076 Tuebingen, Germany. Tel.: +49 7071 298 7026; fax: +49 7071 292 5072.

E-mail addresses: bernardo.herrera.imbroda.sspa@juntadeandalucia.es (B. Herrera-Imbroda), mflara@fimabis.org (M.F. Lara), ander.izeta@biomedicina.org (A. Izeta), karl.sievert@med.uni-tuebingen.de (K.-D. Sievert), melaniehar@gmail.com (M.L. Hart).

<sup>1</sup> These authors contributed equally to this work.