

CENTER FOR RECONSTRUCTIVE URETHRAL SURGERY



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**La ricostruzione dell'uretra con
ingegneria tissutale:
la nostra esperienza in Germania**

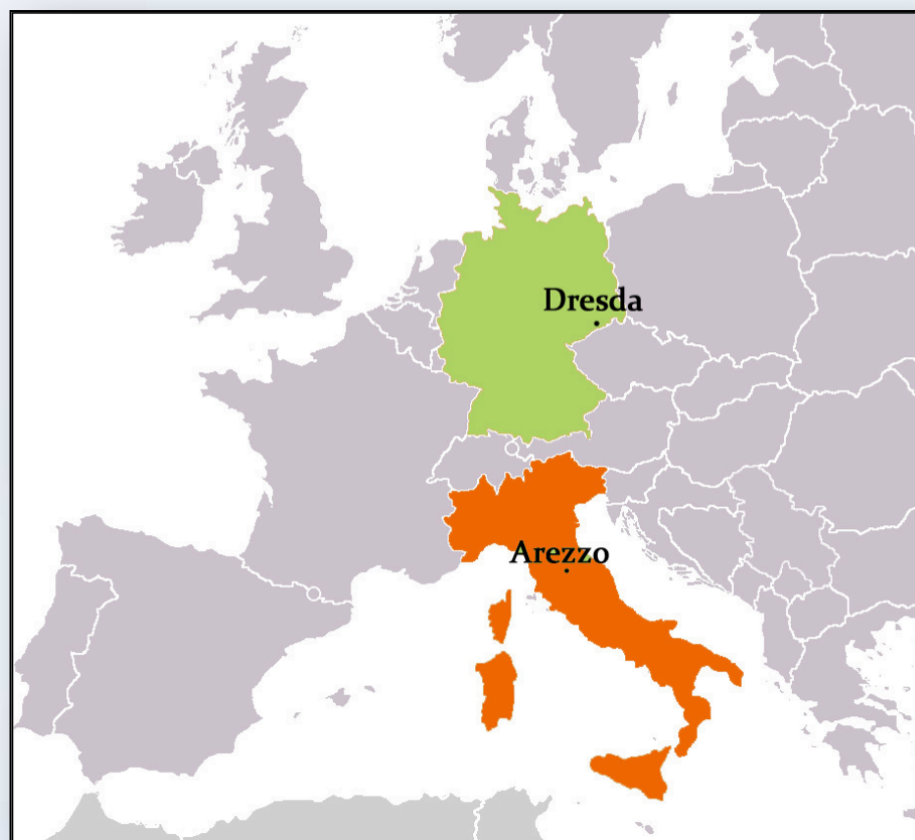


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Dr. Gouya Ram-Liebig and Dr. Soeren Liebig
UroTiss GmbH – Dresden - Germany

2009

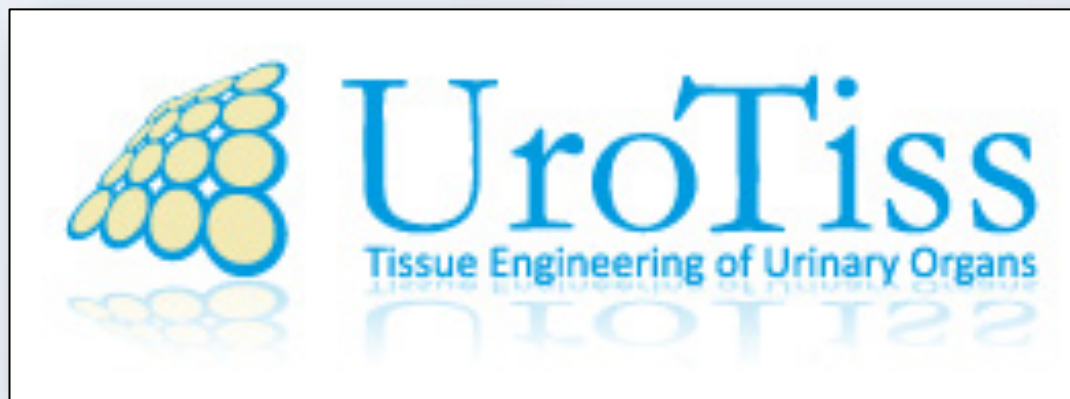


Prof. G. Barbagli - Dr. G. Romano – Dr. M. Lazzeri
Center for Reconstructive Urethral Surgery – Arezzo - Italy



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Dresden - Germany

UroTiss GmbH è una compagnia farmaceutica, fondata in Germania nel 2005 da Dr. Gouya Ram-Liebig e Dr. Soeren Liebig. UroTiss fornisce prodotti di alta qualità e sicurezza, in accordo con le attuali Good Manufacturing Practices (GMP).

www.urotiss.com

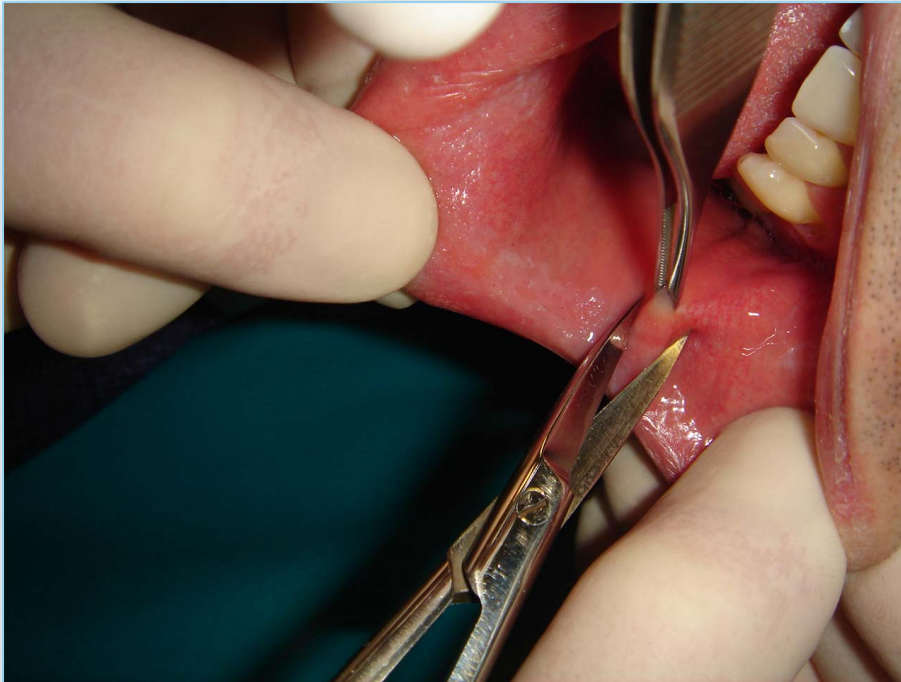
Email: g.ram-liebig@urotiss.com



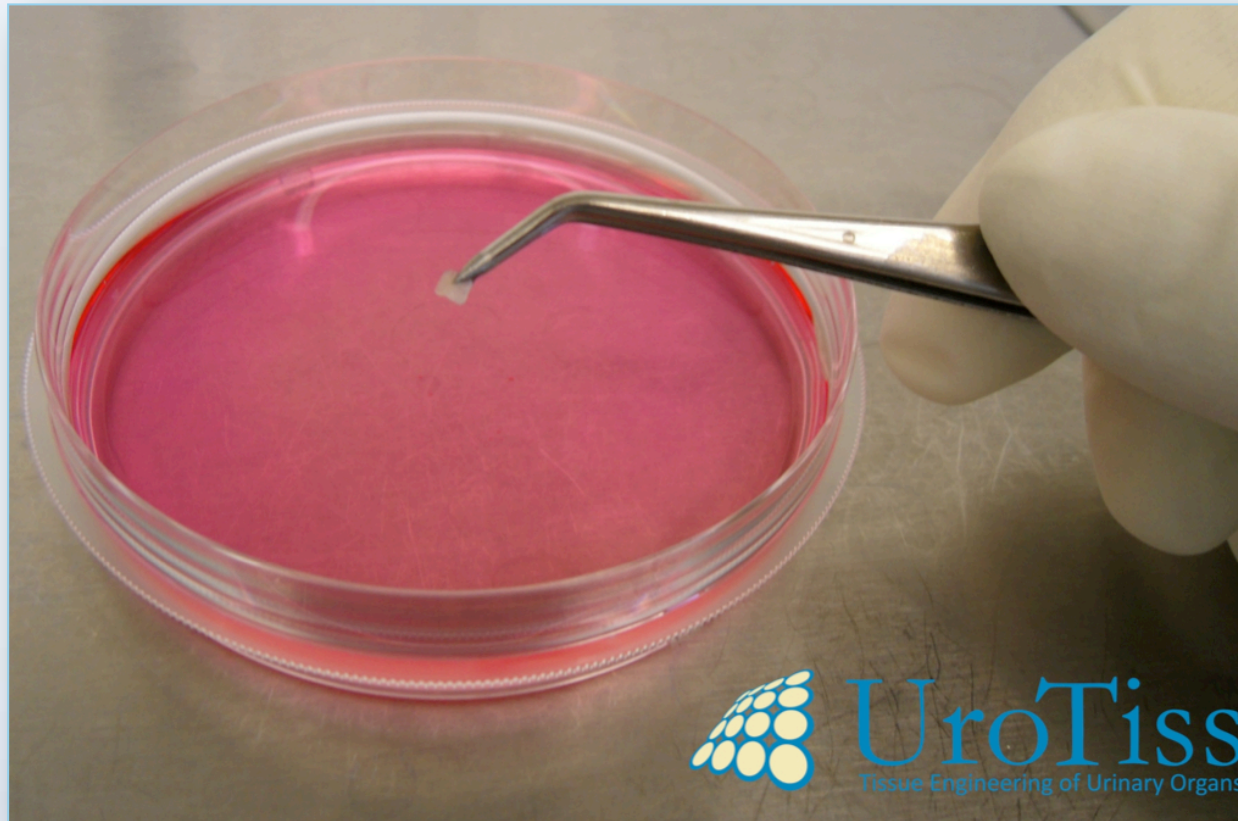
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Prelievo di biopsia (0.4 cm x 0,8 cm) di mucosa orale dalla guancia in anestesia locale.



Il prelievo è trasferito in un contenitore con terreno di cultura per cellule ed inviato al laboratorio.



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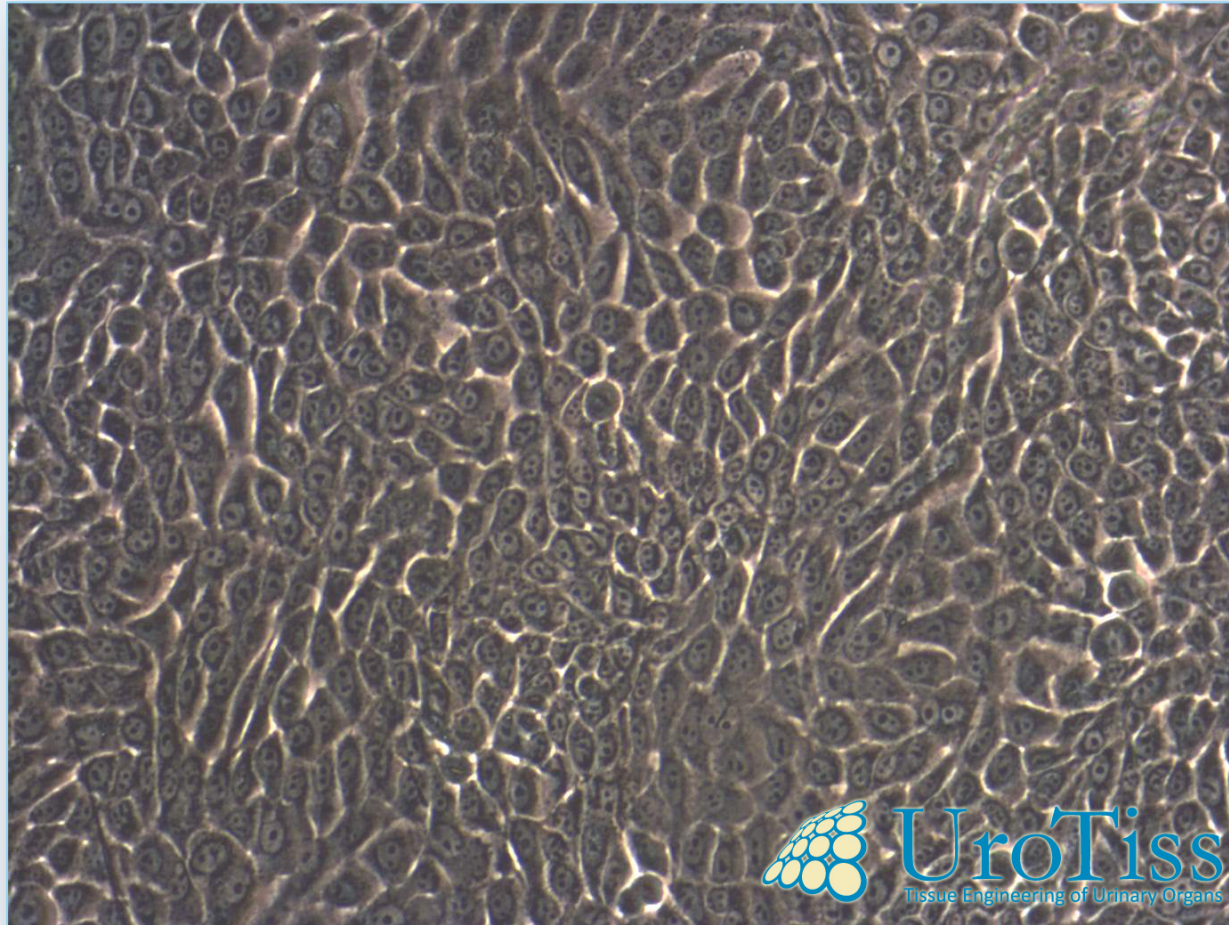


**Laboratorio in accordo con le attuali
Good Manufacturing Practices (GMP).**



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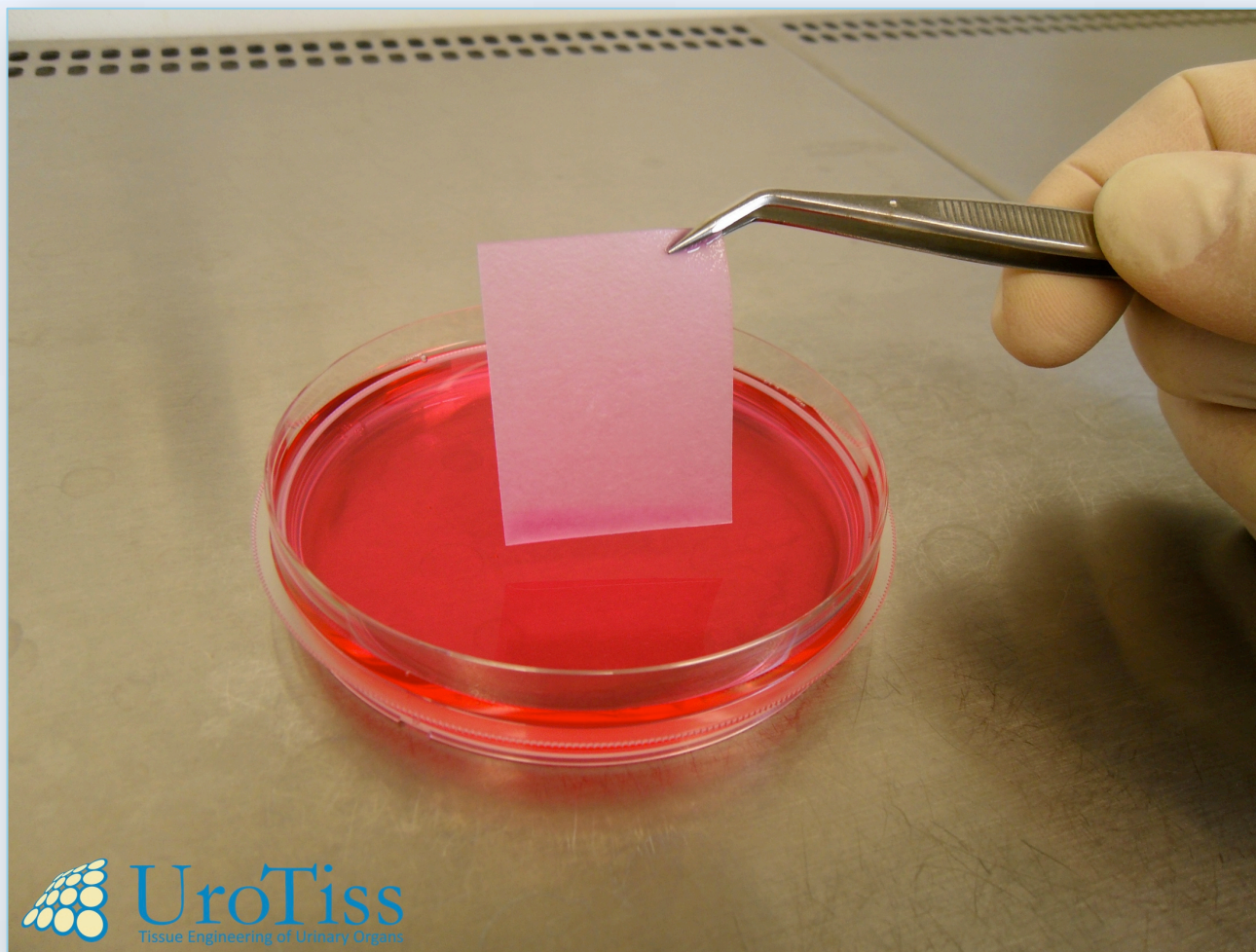


Le cellule di mucosa orale vengono coltivate e distribuite su una “impalcatura” (scaffold) biocompatibile (?).



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3 settimane dopo: MuKoCell



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48 ore per il trapianto



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Preclinical and clinical examination of tissue-engineered graft for urethral reconstruction (MukoCell®) with regard to its safety

Massimo Lazzeri¹, Guido Barbagli¹, Dirk Fahlenkamp², Giuseppe Romano³, Ulf Balsmeyer², Helmut Knispel⁴, Maria-Elsa Spiegel⁴, Burkard Stuerzebecher⁴, and Gouya Ram-Liebig⁵

(1) 1 Centre for Reconstructive Urethral Surgery, Arezzo, Italy (2) Zeisigwald Clinics Bethanien, Department of Urology, Chemnitz, Germany (3) San Donato Hospital, Department of Urology, Arezzo, Italy (4) St. Hedwig Krankenhaus, Department of Urology, Berlin, Germany (5) UroTiss GmbH, Dresden, Germany

I. Introduction

MukoCell® is a national authorized, autologous tissue-engineered oral mucosa graft. The present report sums up some of MukoCell®'s preclinical safety data. Additional reported data of 70 patients, treated with MukoCell®, are also considered with regards to safety analysis.

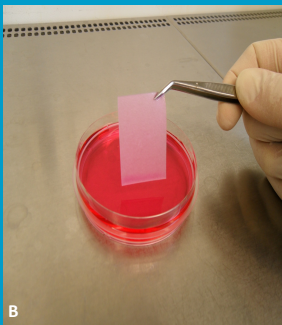
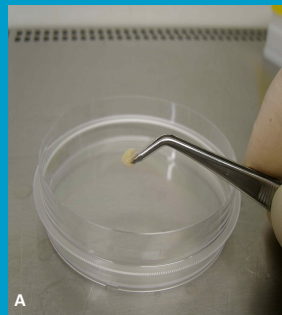


Fig. 1: Patient's oral mucosa cells are generated from a small oral mucosa biopsy (A) and cultured on the surface of a biocompatible scaffold (B).

II. Methods

For MukoCell® production, patient's oral mucosa cells were generated from a small oral mucosa biopsy and cultured on the surface of a biocompatible scaffold (Fig. 1).

The tumorigenic potential of MukoCell® was examined in vivo. For this purpose, human cultured cells of 4 different runs were injected by intraperitoneal and subcutaneous route into each of ten immunodeficient athymic nude mice. 4×10^7 cells $\pm 2 \times 10^6$ cells were injected into each animal on Days 1, 18, 25 and 46 of the study. An additional group consisting of ten animals each received cell culture medium as vehicle control (Table 1).

To examine the potential migration of cells into distant organs, murine MukoCell® constructs from eGFP-transgenic mice were implanted into peritoneal cavity of histocompatible non-transgenic mice and vice versa. The 24 test animals were sacrificed either at weeks 1, 2, 4 or 12 for histological analysis (Table 2).

To investigate the degradation of implanted MukoCell® with time, scaffolds with the size of 0.5 x 1.5 cm were implanted into the peritoneal cavity of 20 BALBc/C57BL6J mice.

Additionally, reported clinical safety data from 70 MukoCell®-treated patients with urethral stricture, which have been recruited in an ongoing observational study with up to 2 year follow-up period, were evaluated on the basis of a pharmacovigilance system. Ethical committee votum was available for the study.

III. Tables

Table 1. Experimental group allocated during the tumorigenicity study

Group	No. of animals	Item	Injection on days ¹⁾	Injection volume (i.p. + cells at each day s.c.) [μ L]	Total no. of cells
1a	5	Test items (n=4)	1, 18, 25, 46	200 + 200	$10^7 \pm 2 \times 10^6$
1b	5	Test items (n=4)	1, 18, 25, 46	200 + 200	$10^7 \pm 2 \times 10^6$
2a	5	Control item	1, 18, 25, 46	200 + 200	-
2b	5	Control item	1, 18, 25, 46	200 + 200	-

Notice²⁾ Cell preparations generated independently from four different runs were used. A separate cell preparation was used on each day.

Table 2. Allocation and treatment of animals in the biodistribution study

Group (Cage)	No. of animals	Donor for engineered tissue graft	Recipient of engineered tissue graft	Sacrifice after implantation week
A-1 (11/5/0)	3	EGFP-tg	nontg	after 1 week
A-2 (11/6/0)	3	EGFP-tg	nontg	after 2 weeks
A-3 (11/7/0)	3	EGFP-tg	nontg	after 4 weeks
A-4 (11/8/0)	3	EGFP-tg	nontg	after 3 months
reserve animal (11/H3/0)		EGFP-tg	nontg	
B-1 (11/1/9)	3	nontg	EGFP-tg	after 1 week
B-2 (11/2/9)	3	nontg	EGFP-tg	after 2 weeks
B-3 (11/3/9)	3	nontg	EGFP-tg	after 4 weeks
B-4 (11/4/9)	3	nontg	EGFP-tg	after 3 months
reserve animal (11/H1/9)		nontg	EGFP-tg	

Notice: Material used for histology after sacrifice: Brain (cerebrum, cerebellum, brain stem, paraventricular parts); heart; kidneys;

large intestine (caecum, colon, rectum); liver; lung; lymph nodes (mesenteric)

intestine; (duodenum, jejunum, ileum) / peyer plaques; spleen; thymus; transplants (including surrounding tissue)

IV. Results

Evaluation of tumorigenicity study in nude mice did not reveal macroscopic and microscopic malignancies attributable to MukoCell® in 60 different examined tissues and organs. Additionally, migration of the transplanted cells into distant organs was excluded at all examined time intervals after implantation of murine homologue of MukoCell®. While the grafts were still present in all 10 animals 9 days after implantation, 6 of 10 grafts were degraded 40 days after implantation in the remaining 10 animals. Clinical data of 70 with MukoCell® treated patients demonstrated no peri- or post-operative adverse events related to MukoCell®.

V. Conclusion

MukoCell® seems to be a safe graft for urethroplasty for patients with urethral stricture. The graft is degrading within a few weeks and hence avoids complication associated with persistent implants.

MukoCell® is an autologous tissue-engineered oral mucosa graft

AUA 2014

MP9 – Abstract ID: 14-578

Tumorigenic study:

- cultured cells of human donors were injected by intraperitoneal and subcutaneous route into each of ten immunodeficient athymic nude mice.
- 4×10^7 cells $\pm 2 \times 10^6$ cells were injected into each animal on Days 1, 18, 25 and 46 of the study.
- An additional group consisting of ten animals each received cell culture medium as vehicle control

Results: No macroscopic and microscopic malignancies attributable to MukoCell® in 60 different examined tissues and organs.

Biodistribution study:

- Murine MukoCell® constructs from eGFP-transgenic mice were implanted into peritoneal cavity of histocompatible non-transgenic mice and vice versa.
- The 24 test animals were sacrificed either at weeks 1, 2, 4 or 12 for histological analysis

Results: No migration of the transplanted cells into distant organs.



Degradation study:

- 0.5 x 1.5 cm MukoCell® scaffolds were implanted into the peritoneal cavity of 20 female BALBc/C57BL6J mice

Results: 60% of the grafts were degraded 40 days after implantation.

Clinical observational study:

- data from 70 MukoCell®-treated patients with urethral stricture, with up to 2 year follow-up period, were evaluated

Results: No peri- or post-operative adverse events related to MukoCell®.



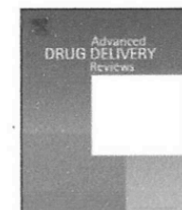


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Regulatory challenges for autologous tissue engineered products on their way from bench to bedside in Europe[☆]



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^b St. Hedwig Hospital, Department of Urology, Berlin, Germany

^c Zeisigwald Clinics Bethanien, Department of Urology, Chemnitz, Germany

^d Centro Chirurgico Toscana, Arezzo, Italy

^e Urology Unit, Ospedale del Valdarno, Santa Maria alla Gruccia, Montevarchi-Arezzo, Italy



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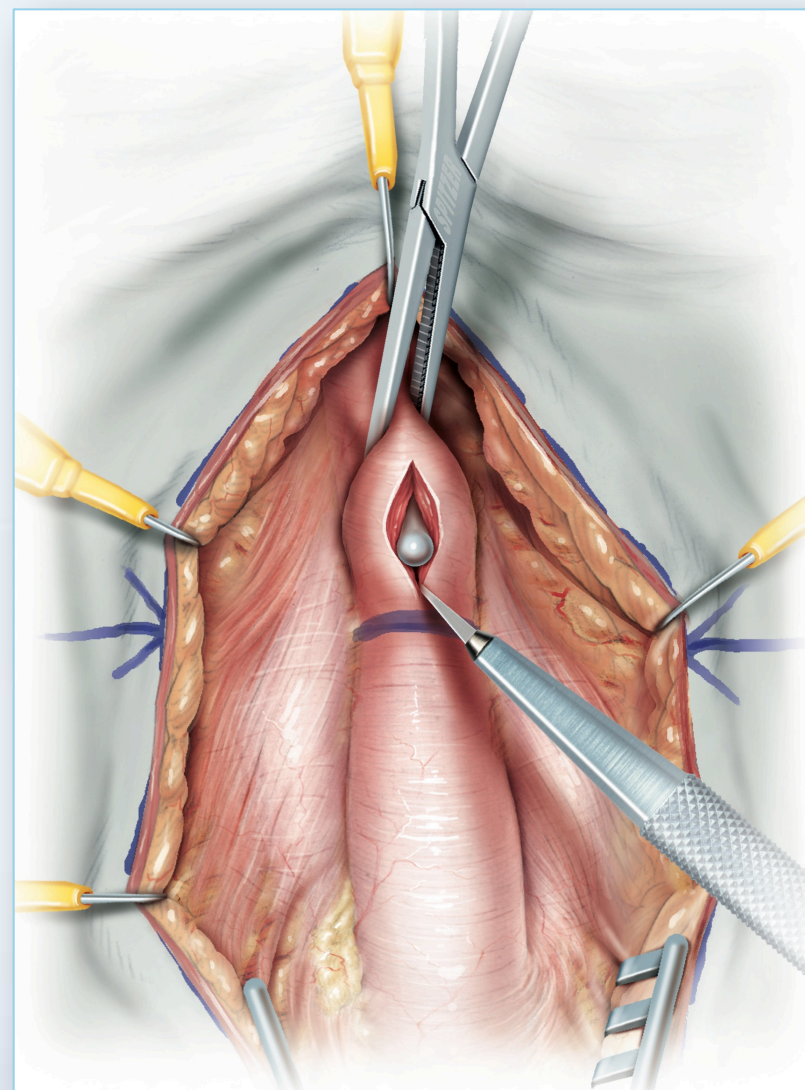
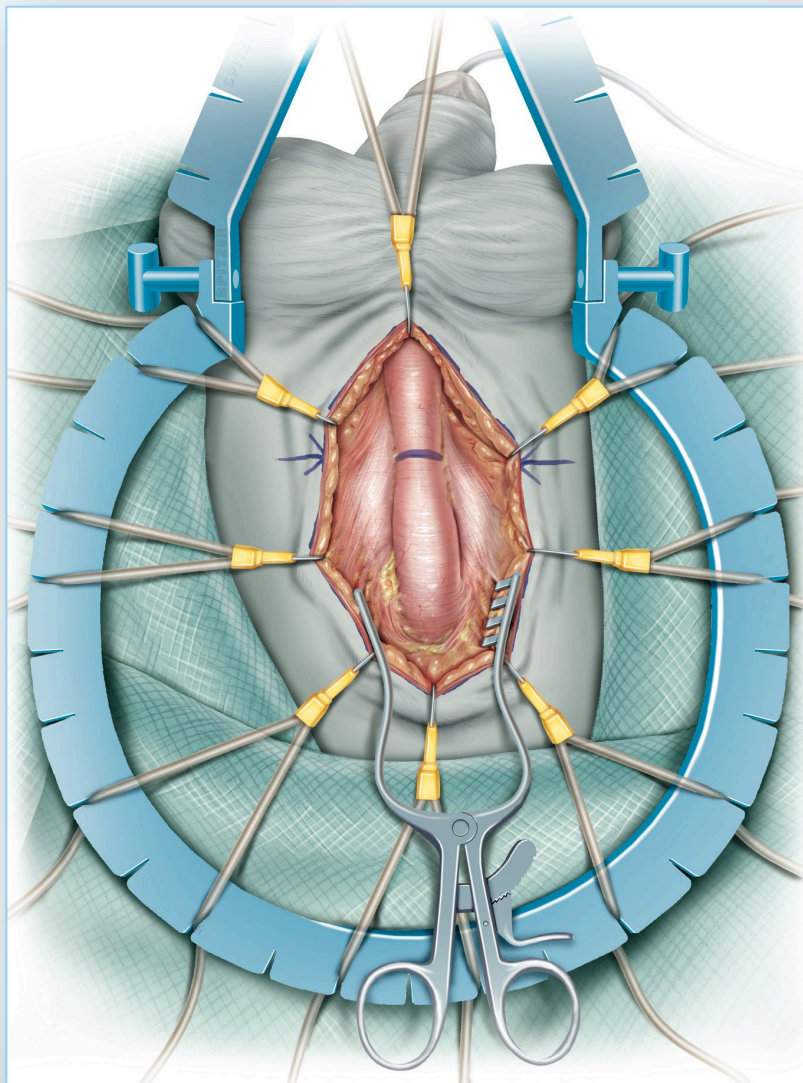
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Uso del MuKoCell in pazienti tedeschi



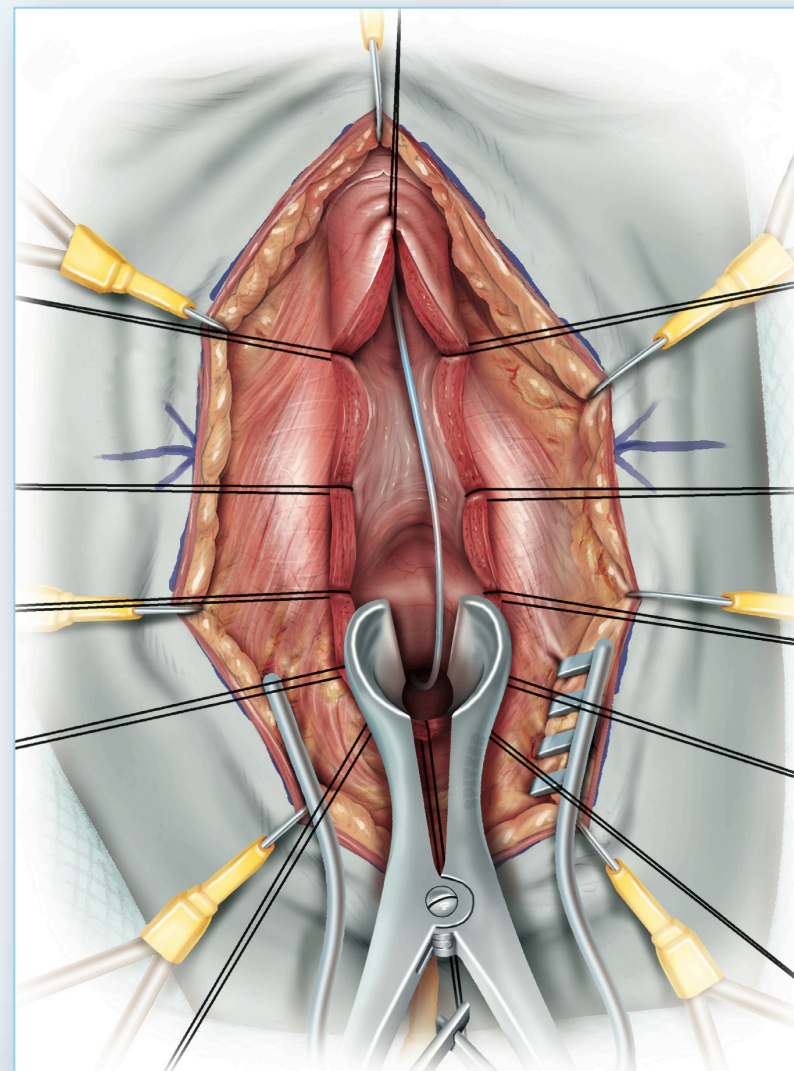
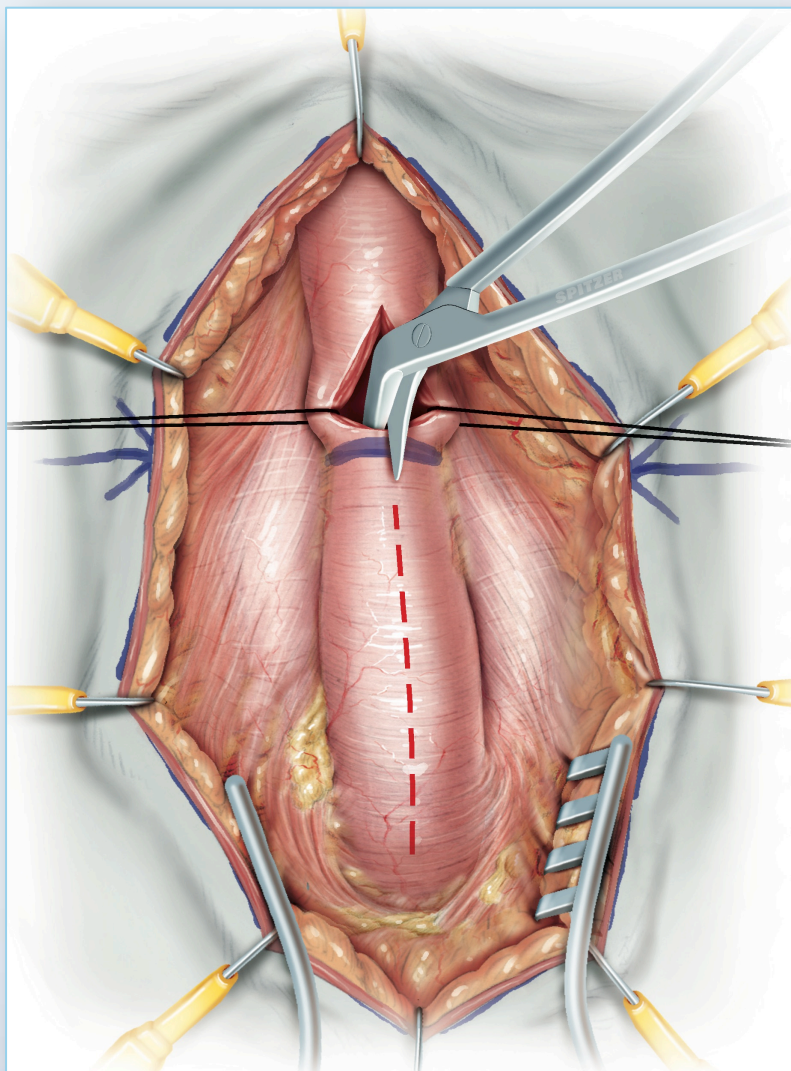
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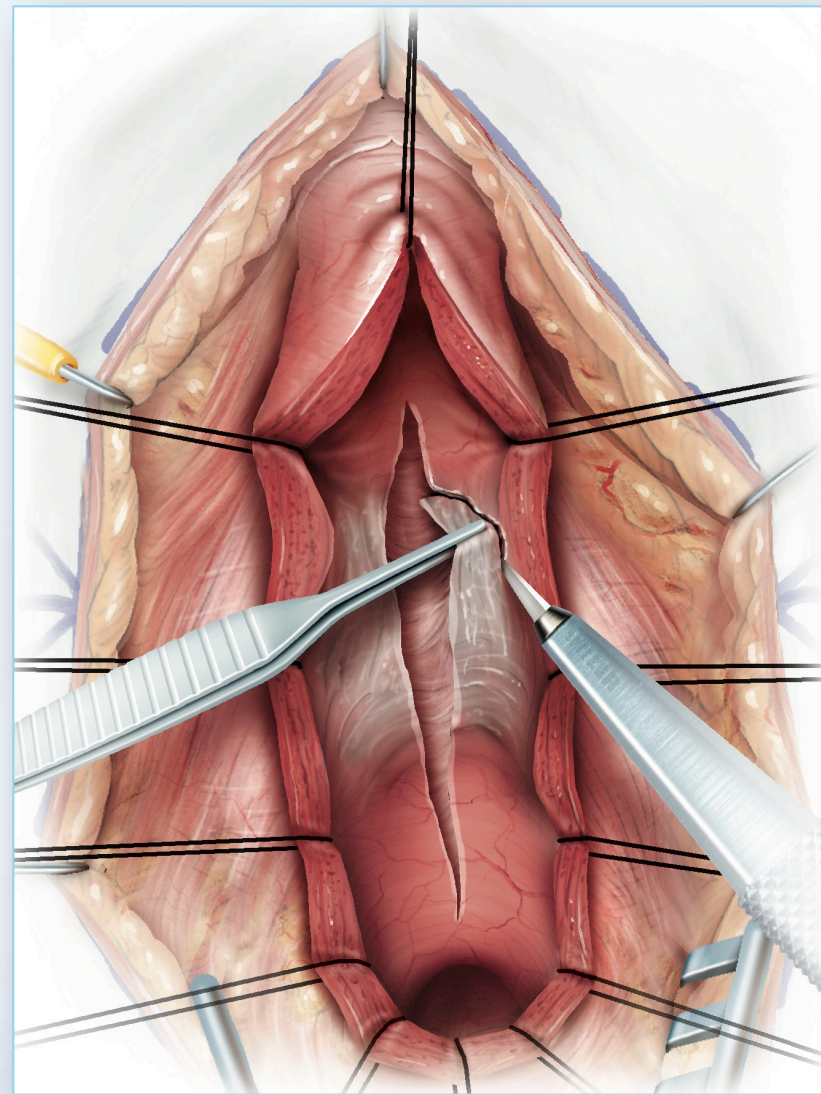
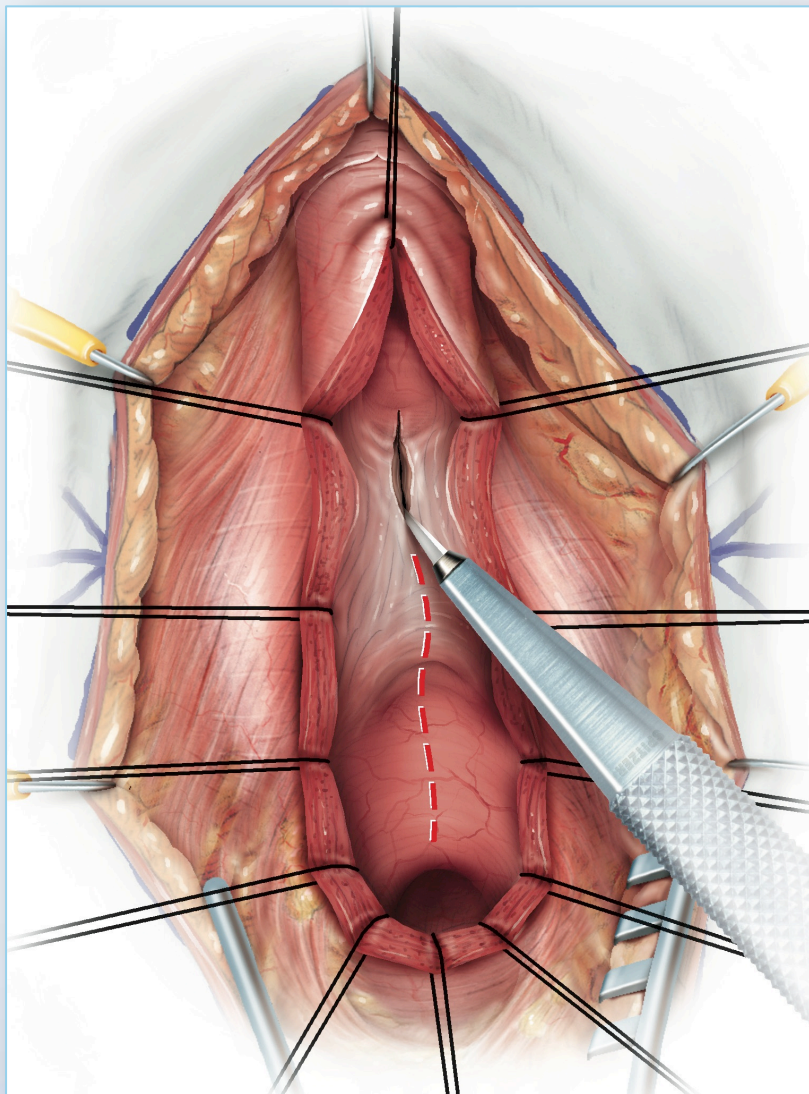
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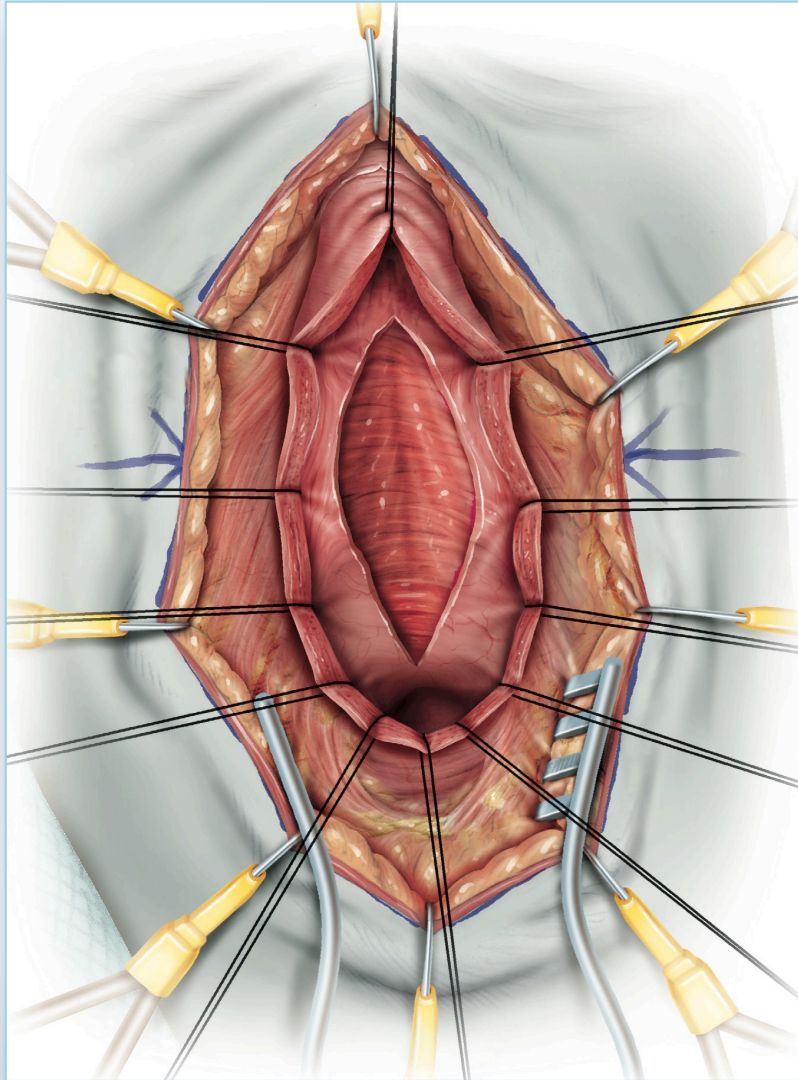
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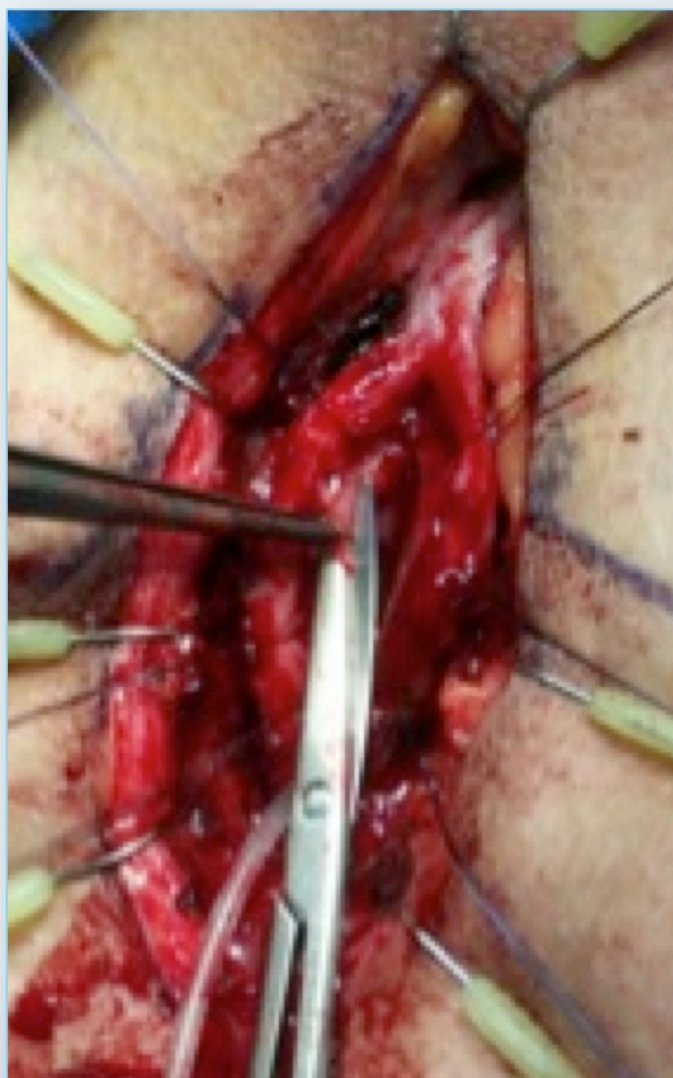
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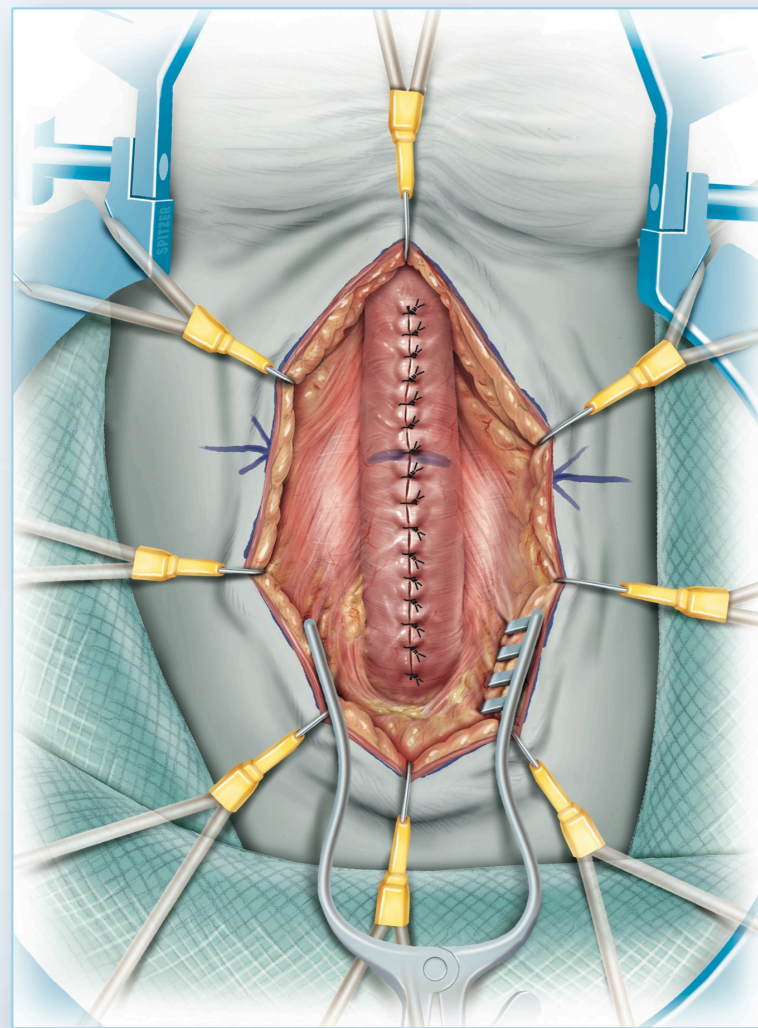
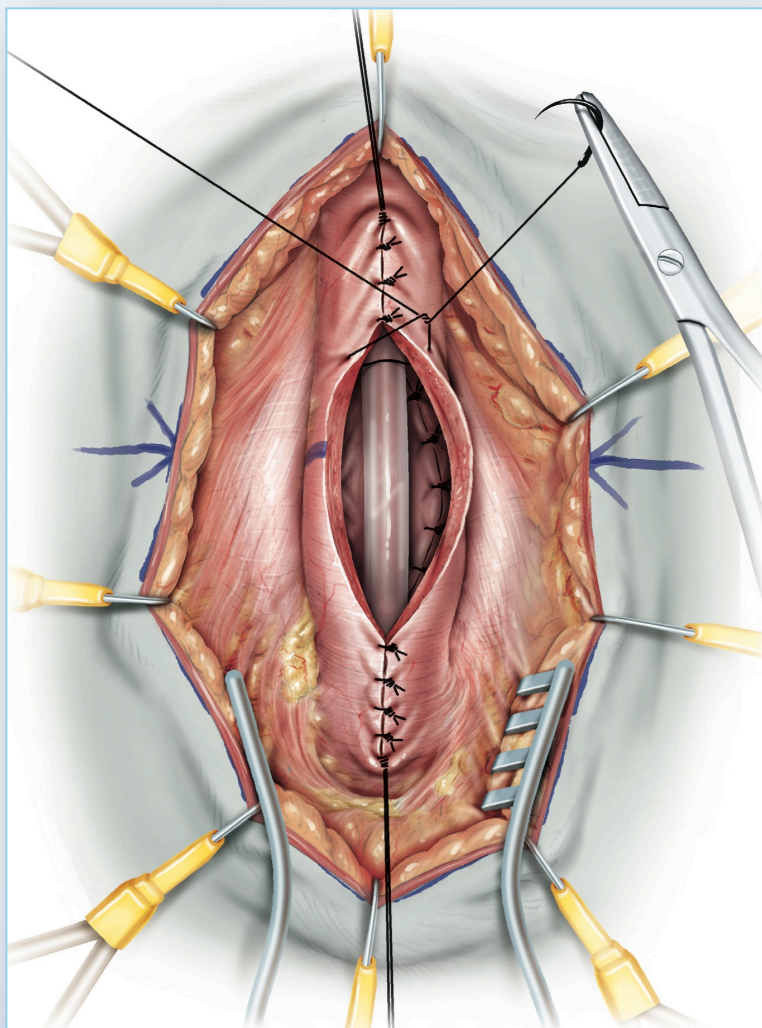
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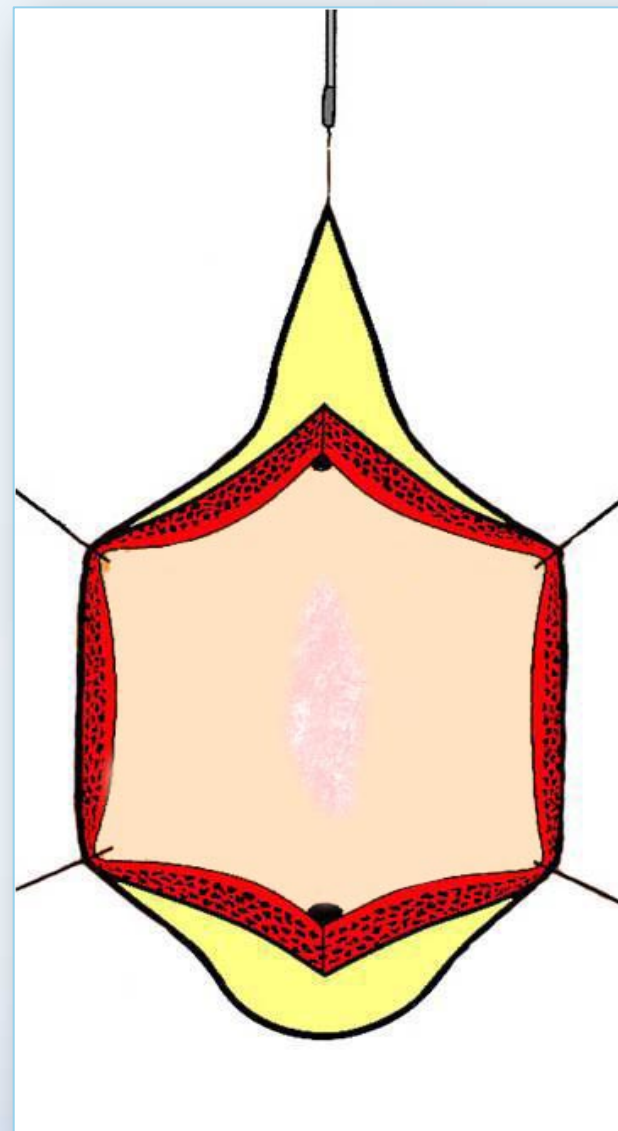
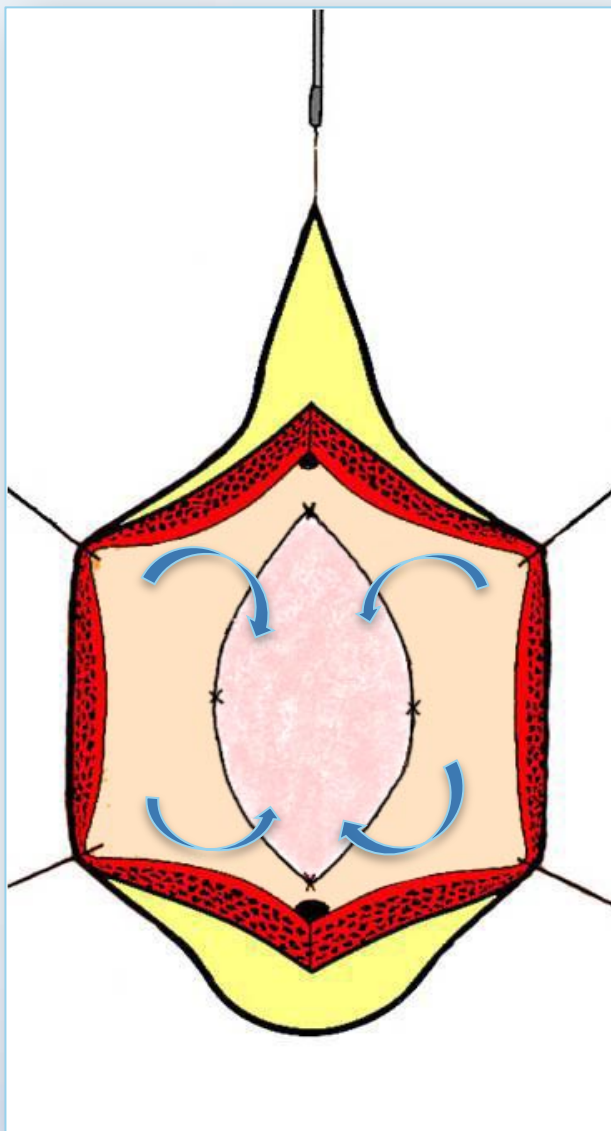
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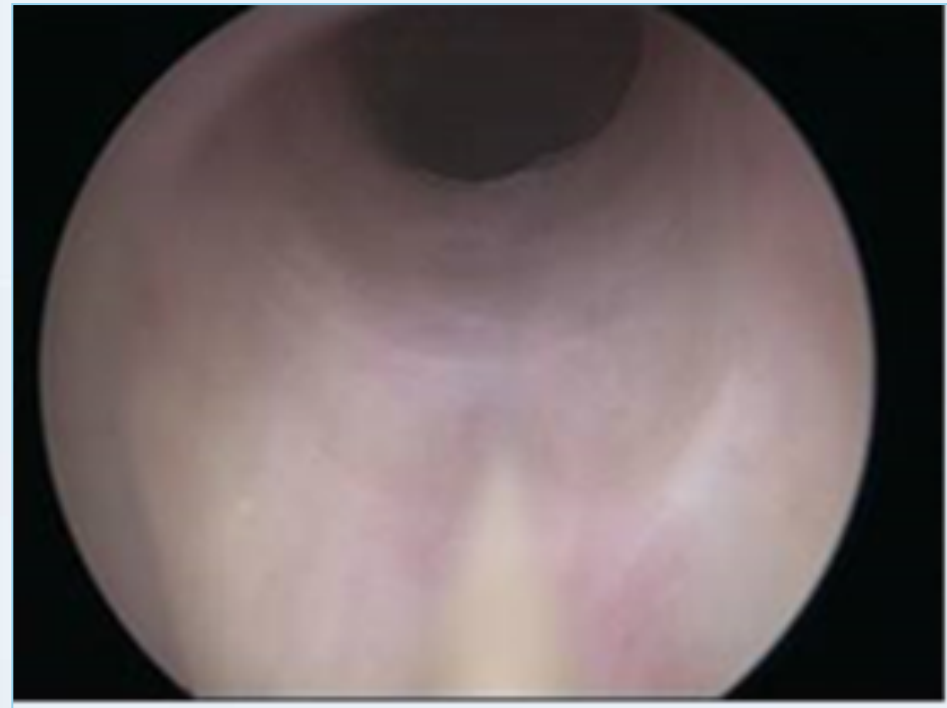
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Risultato



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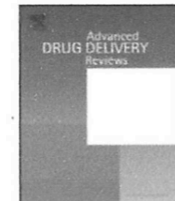
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Regulatory challenges for autologous tissue engineered products on their way from bench to bedside in Europe[☆]



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^d Centro Chirurgico Toscana, Arezzo, Italy

^e Urology Unit, Ospedale del Valdarno, Santa Maria alla Gruccia, Montevarchi-Arezzo, Italy

**21 PAZIENTI:
17 (80.9%) successo
4 (19.1%) fallimento**



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Esperienza clinica con MuKocell in Germania

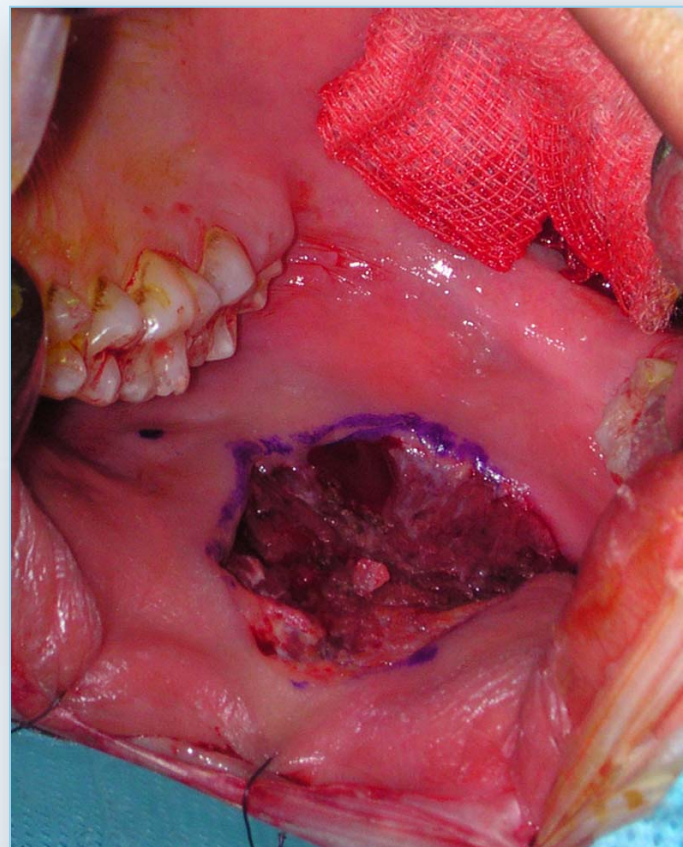
Osnabruck
Chemnitz
Berlin
Hamburg
Luneburg
Lipsia

103 patients

Overall success rate:
?



MuKoCell: vantaggi



Sede di prelievo



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www.urethralcenter.it

MuKoCell: vantaggi

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European Association of Urology



Platinum Priority – Infections

Editorial by Guido Barbagli, Salvatore Sansalone and Massimo Lazzeri on pp. 1071–1073 of this issue

Oral Mucosa as a Reservoir of Human Papillomavirus: Point Prevalence, Genotype Distribution, and Incident Infections Among Males in a 7-year Prospective Study

Katja Kero^{a,*}, Jaana Rautava^b, Kari Syrjänen^{c,d}, Seija Grenman^a, Stina Syrjänen^b

^a Department of Obstetrics and Gynaecology, Turku University Hospital, University of Turku, Turku, Finland; ^b MediCity Research Laboratory and Department of Oral Pathology, Institute of Dentistry, Faculty of Medicine, University of Turku, Department of Pathology, Turku University Hospital, Turku, Finland; ^c Department of Oncology and Radiotherapy, Turku University Hospital, Turku, Finland; ^d Teaching and Research Institute, Barretos Cancer Hospital, Barretos-SP, Brazil

Prevenzione infezione da HPV o altro



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MuKoCell: vantaggi

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Platinum Priority – Editorial and Reply from Authors

Referring to the article published on pp. 1063–1070 of this issue

Oral Mucosa and Urethroplasty: It's Time to Change

Guido Barbagli^a, Salvatore Sansalone^b, Massimo Lazzeri^{c,*}

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^cDepartment of Urology, University Hospital San Raffaele, Milan, Italy

Prevenzione infezione da HPV o altro



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MuKoCell: svantaggi e limiti

Costi: 7.500 / 9.500 Euro

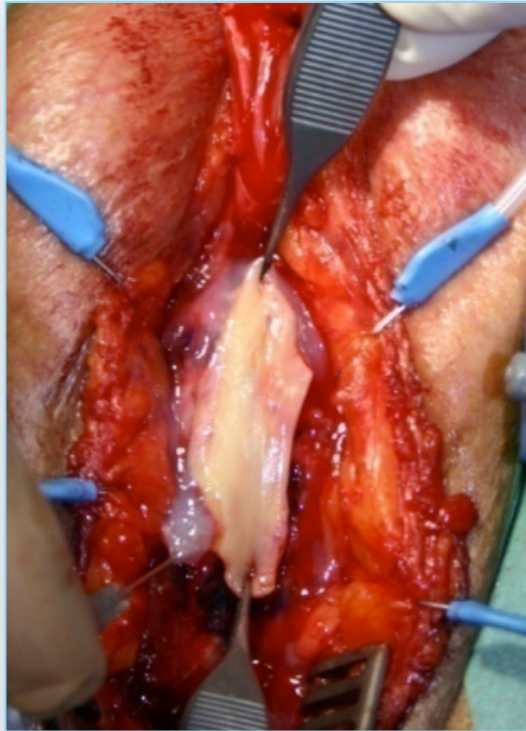
Utilizzo: autorizzato solo in Germania

Logistica: deve essere impiantato entro 48 ore

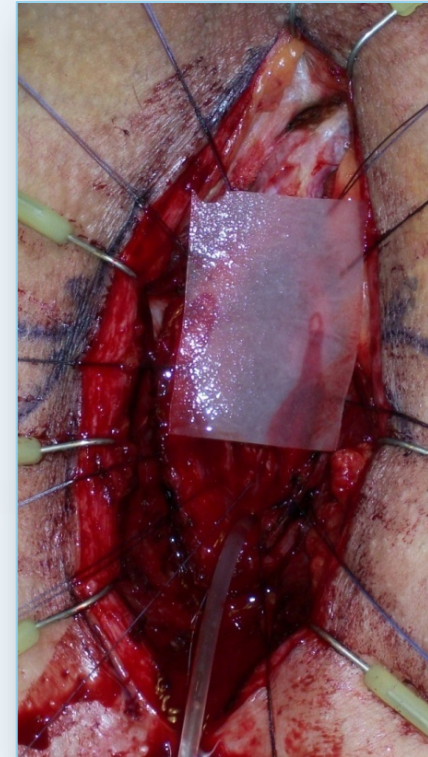
Risultati: inferiori a quelli ottenuti con mucosa orale (80.9% vs 85.5%)



MuKoCell: svantaggi e limiti



Oral mucosa



**Tissue engineered
oral mucosa**

Impiego: richiede notevole esperienza



Stenosi “semplici” dell’uretra



Risultati: 85% con mucosa orale



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Stenosi “complesse” dell’uretra



Risultati: < 50% con mucosa orale



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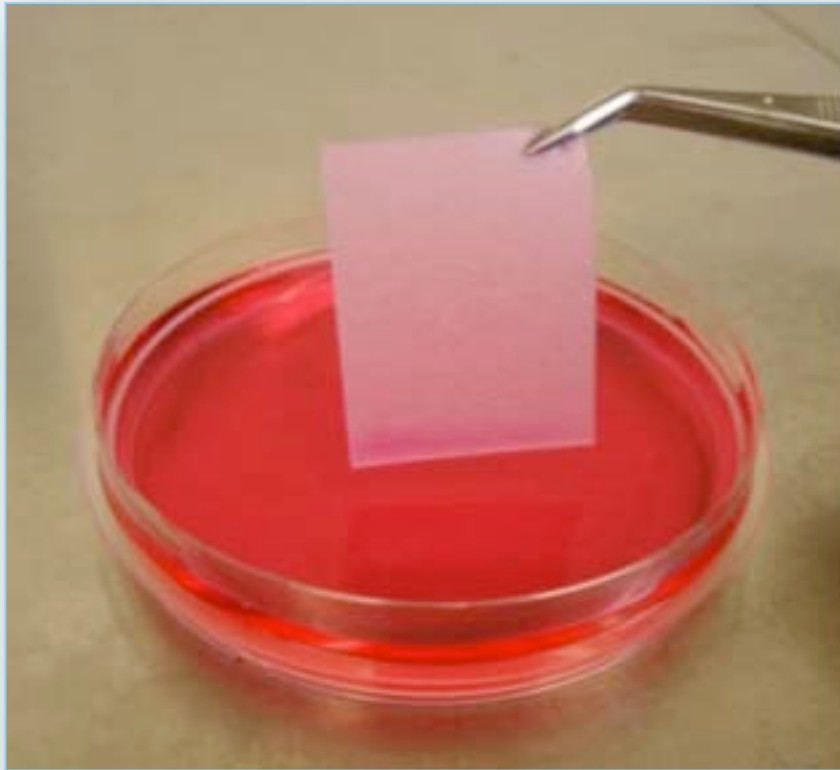


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Next future



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EUROPEAN UROLOGY 68 (2015) 917–918

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Platinum Opinion

Clinical Experience with Urethral Reconstruction Using Tissue-engineered Oral Mucosa: A Quiet Revolution

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