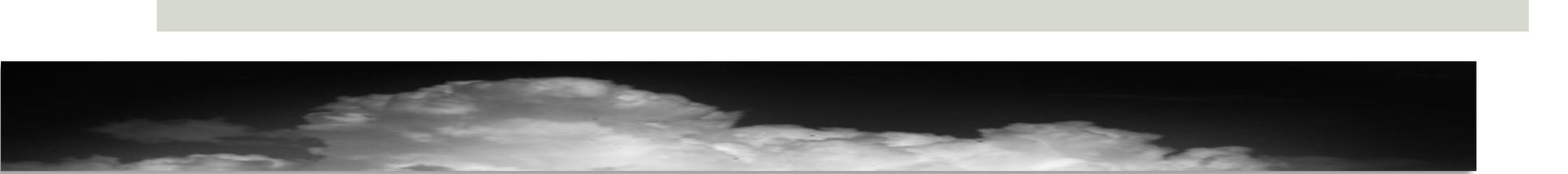


Reabilitação Peniana

Novas perspectivas na abordagem pós Prostatectomia Radical

OUTLINE

1. Concept and Rationale
2. Role of penile rehabilitation
 1. Current Therapeutics & Results
3. Future Approaches
 1. Studies & Results
4. Conclusions



Erectile dysfunction following treatment for clinically localized prostate cancer, particularly radical prostatectomy, *is a major quality of life issue that remains unsatisfactorily addressed.*

RATIONALE

The implementation of an early post-EF insult (e.g., post-operative) **program of intervention** with the **intention of facilitating the return of natural EF** is an attempt to:

- (I) preserve cavernosal oxygenation,
- (II) protect endothelial function, and
- (III) reduce erectile tissue damage resulting from cavernous nerve injury

What do we have?

PENILE REHABILITATION

- PDE5 i's
- Intraurethral Prostaglandin (MUSE)
- Intracavernosal Injection (PGE₁)
 - Vacuum Erection Device

PDE5 i's

PDE5 inhibitors are **ineffective in 29%–86%** of prostatectomy patients

... **Evidence has remained lacking** to show the erection **rehabilitative benefits** of PDE5 i's (according to rigorous controlled clinical trials)...

Sildenafil and Vardenafil have been subjected to this sort of investigation **with conflicting results**

... PDE5 i'... **questions** surrounding **their true rehabilitative effectiveness** maintains

PGE₁

PGE₁

Montorsi et al(1997)¹

- **15** pts received PGE₁ (3x/week; 12 w) vs **15** no treatment

8 (67%) - Tx in < 50%

3 satisfactory erections
10 some recovery

**Low patient enrolment, lack of long-term assessment
NOT tested in any other randomized study**

¹ Recovery of spontaneous erectile function after nerve-sparing radical prostatectomy. J Urol 1997; Montorsi F et al
Penile rehabilitation after radical prostatectomy: what the evidence really says. BJUI 2013; 112: Mikkel Fode et al

MUSE

MUSE

- 1 randomized study (n=139)¹
 - MUSE vs Sildenafil

NO difference between two arms; NO placebo arm

Other Studies

- Raina et al (2007)
 - **32% discontinuation** (efficacy; reduced libido; local adverse effects)
 - **NO** randomization

Penile rehabilitation after radical prostatectomy: what the evidence really says. BJUI 2013; 112: Mikkel Fode et al

¹ Recovery of erectile function after nerve sparing radical prostatectomy. J Urol 2010; 105. McCullough et al

Novas perspectivas na abordagem pós Prostatectomia Radical

Vacuum Erection Device

VED

- 2 randomized studies (n=28)¹; (n=109)²

Possible beneficial effect in EF
Spontaneous erections: VED (32%), no treatment (37%)

VED & PDE5 i's ³

NO placebo arm
Confirms the combination as treatment option
Role in penile rehabilitation ?

¹ A pilot study on the early use of vacuum after radical prostatectomy BJUI 2007; 100; 6:858-62. Kohler TS et al

² Early use of vacuum constriction device following RP. Int J Imp Trd. 2006; 18:77-81. Raina R et al

³ Effect on sexual function of VED post PR- Can J Urol 2011; 18:5721-5. Engel JD

Statement

No single strategy is uniformly accepted

Clinical evidence in support of any particular strategy is relatively **lacking**.

Difficult to prescribe a rehabilitative therapy or strategy that is likely to be successful in EF recovery

Investigation into the pathophysiologic derangements associated with ED after RP and additionally advancement of scientifically **targeted treatments are imperatives**

Clinical evidence for erection recovery after radical prostatectomy. *Transl Androl Urol.* 2013;2 (1):24-31. Arthur Burnett

Novas perspectivas na abordagem pós Prostatectomia Radical

New Approaches

1. Erythropoietin
2. Statins
3. *Vibrect* Penile Vibratory Stimulation
4. Angiotensin type 2-receptor blocker
5. Immunophilin ligands
6. Stem Cell Therapy
7. Gene Therapy
8. Tissue engineering



Erythropoietin to Enhance Erection Recovery in Men Following Radical Prostatectomy

- ➔ Evaluate the effectiveness of erythropoietin versus placebo
Recent laboratory findings suggest, that erythropoietin may play
- ➔ a role **in protection of the cavernous nerves during surgery** - *anti-apoptotic agent and tissue growth factor.*

Erythropoietin was studied as an investigational drug for

Erythropoietin to Enhance Erection Recovery in Men Following Radical Prostatectomy

Clinical Results

Single **high-dose erythropoietin** injection on the **day prior** to nerve-sparing RP:

7 of 15 (47%) **treated** patients vs. 3 of 19 (16%) **untreated** patients achieved erections and higher IIEF- 5 levels at 12 months (P<0.05)

Erythropoietin **may confer erection rehabilitative benefit** and be safe clinically at least with short-term preoperative use.

Retrospective; unblinded; selection biases

- Proposed as an EF **preservative strategy** following RP
- Improved **oxygenation, endothelial** protection or possibly **neuronal regenerative** or **protective** effects
- **50 pts** preoperatively potent; without hypercholesterolemia
 - I. Treatment Group:* **atorvastatin** daily in combination with **sildenafil**
 - II. Control:* **sildenafil** as needed for 90 days

Results

a. Treatment Group: 2-fold **greater improvement in functional IIEF-5** scores and **intercourse satisfaction** (6 months) (55% vs. 26.1%, P=0.068)

Suggests a convenient, well-tolerated strategy for improving EF recovery

Viberect Penile Vibratory Stimulation to Enhance Recovery of Erectile Function and Urinary Continence Post-Prostatectomy

Primary Outcome Measures Recovery of erectile function following radical prostatectomy

Physical examination will be performed, including genital exam for any signs of penile irritation. Study subjects will complete the IIEF, EPIC urinary and sexual domain, AUA, EHS, EDITS and TSS questionnaires. Penile length will be measured from pubis to corona of the glans penis (dorsally) and recorded in centimeter using a standard wooden ruler.

Secondary Outcome
Recovery of continence after radical prostatectomy



New Approaches

Vibratory
Stimulation



Penile Vibratory Stimulation

- ➔ Effect of penile vibratory stimulation (PVS-FERTI CARE®) in the preservation and restoration of erectile function ((NCT01067261).
- ➔ **68 pts** (30 patients randomized to PVS and 38 control group).
Amplitude of 2 mm and a vibration frequency of 100 Hz.
Frenulum stimulation (10x/day)
- ➔ 12 months 16/30 (**53%**) **patients in the PVS** group had reached an IIEF-5 score of at least 18 while this was the case for 12/38 (**32%**) **patients in the control group** (P=0.07).

Acceptable for most patients and there was a trend toward **better erectile function with PVS**

Angiotensin type 2-receptor blocker - *Irbesartan*

- ➔ Pre-clinical evidence - accelerate the return of erectile function after RP
- ➔ Activity in vascular oxidative stress, inflammatory processes which contribute to endothelial dysfunction
- ➔ **17 men receiving high dose irbesartan** (300 mg/d) starting on postoperative day 1 and continuing daily + (Postoperative "on demand" use of erectile of PDE5 inhibitors and intracavernous injections)
- ➔ **Higher IIEF-5 scores observed** at 12 months in treatment group compared with a contemporaneous untreated group.

Regular irbesartan could **improve EF recovery after surgery**

Role of Immunophilins in recovery of erectile function

- **Proteins** also **localized to nerves** coursing in **humane prostate** and **penile tissues**. Identified as targets for immunosuppressive drugs.
- **Neuroprotective/nerve regenerative effect**
- Immunophilin ligands FK (Tacrolimus) and Rapa (Sirolimus) **improve erectile function** in animal models of CN injury
- Immunophilin ligands are **potentially useful to sustain erectile function** in men following radical prostatectomy.

Clinical trials (phase IV, randomized, double-blind, placebo-controlled) are on going (FK 1706).

Other clinical trials did not show efficacy (FK506; Prograf)

Cell Mol Neurobiol. 2013 Mar;33(2):233-40. doi: 10.1007/s10571-012-9890-7. Epub 2012 Nov 17.

Effects of intracavernous injection of adipose-derived stem cells on cavernous nerve regeneration in a rat model.

Ying C, Yang M, Zheng X, Hu W, Wang X.

Department of Urology, Zhongnan Hospital, Wuhan University, Wuhan, China.

Eur Urol. 2012 Oct;62(4):720-7. doi: 10.1016/j.eururo.2012.02.003. Epub 2012 Feb 18.

Both immediate and delayed intracavernous injection of autologous adipose-derived stromal vascular fraction enhances recovery of erectile function in a rat model of cavernous nerve injury.

Qiu X, Fandel TM, Ferretti L, Albersen M, Orabi H, Zhang H, Lin G, Lin CS, Schroeder T, Lue TF.

Knappe Molecular Urology Laboratory, Department of Urology, University of California, San Francisco, CA 94143-0738, USA.

Eur Urol. 2012 Jan;61(1):201-10. doi: 10.1016/j.eururo.2011.07.061. Epub 2011 Aug 4.

Recruitment of intracavernously injected adipose-derived stem cells to the major pelvic ganglion improves erectile function in a rat model of cavernous nerve injury.

Fandel TM, Albersen M, Lin G, Qiu X, Ning H, Banie L, Lue TF, Lin CS.

Knappe Molecular Urology Laboratory, Department of Urology, School of Medicine, University of California, San Francisco, CA, USA.

Erectile dysfunction is a **main focus** of past and **current stem cell (SC) therapy studies**, mainly after RP.

21 new preclinical studies...

SCs were mostly derived from bone marrow, adipose tissue, or skeletal muscle.

SC transplantation was done exclusively by **intracavernous injection**

Favourable outcomes have been obtained in all trials so far, although whether SCs had **differentiated** into specific cell lineages remains controversial

Before translation to the clinic is established, various hurdles need to be overcome.

Gene Therapy in Recovery of Erectile Function

Gene therapy – refers to the introduction of foreign genetic material in human cells that either **restores** or **supplements existing defective cellular function** or **antagonizes** the functional effects of mutagenic phenotypes

Penis is an ideal target organ

STUDIES

1. **Genes coding for K⁺ channel**

2. **Modulation of the NO-cGMP**
 1. Arginase
 2. NO synthase (decreasing PIN mRNA – shRNA)
 3. cGMP-dependent protein kinase G₁

STUDIES

3. Growth Factors Upregulation

1. Neurotrophic growth factors
 1. BDNF
 2. NGF – gene transfer of neurotrophin 3

4. Atypical neurotrophic molecules

1. IGF-1
2. VEGF
3. Erythropoietin

5. Other Targets

1. Superoxide dismutase
2. RhoA/Rho Kinase
3. Peptides

Gene Therapy in recovery of erectile function

CLINICAL STUDIES

First human study – gene transfer – approved by FDA

Plasmid-bound hSlo cDNA administered by corporal injection – regulating K⁺ channel.

The human **maxi-K gene** was successfully transferred to **11** men
-> **Sustained improvement in EF was reported**

Update in 2009 – 21 pts

No serious adverse effects in men who respond to therapy

J Sex Med. 2009 Mar;6 Suppl 3:328-33. doi: 10.1111/j.1743-6109.2008.01191.x.

A new strategy, SuperEnzyme gene therapy in penile rehabilitation.

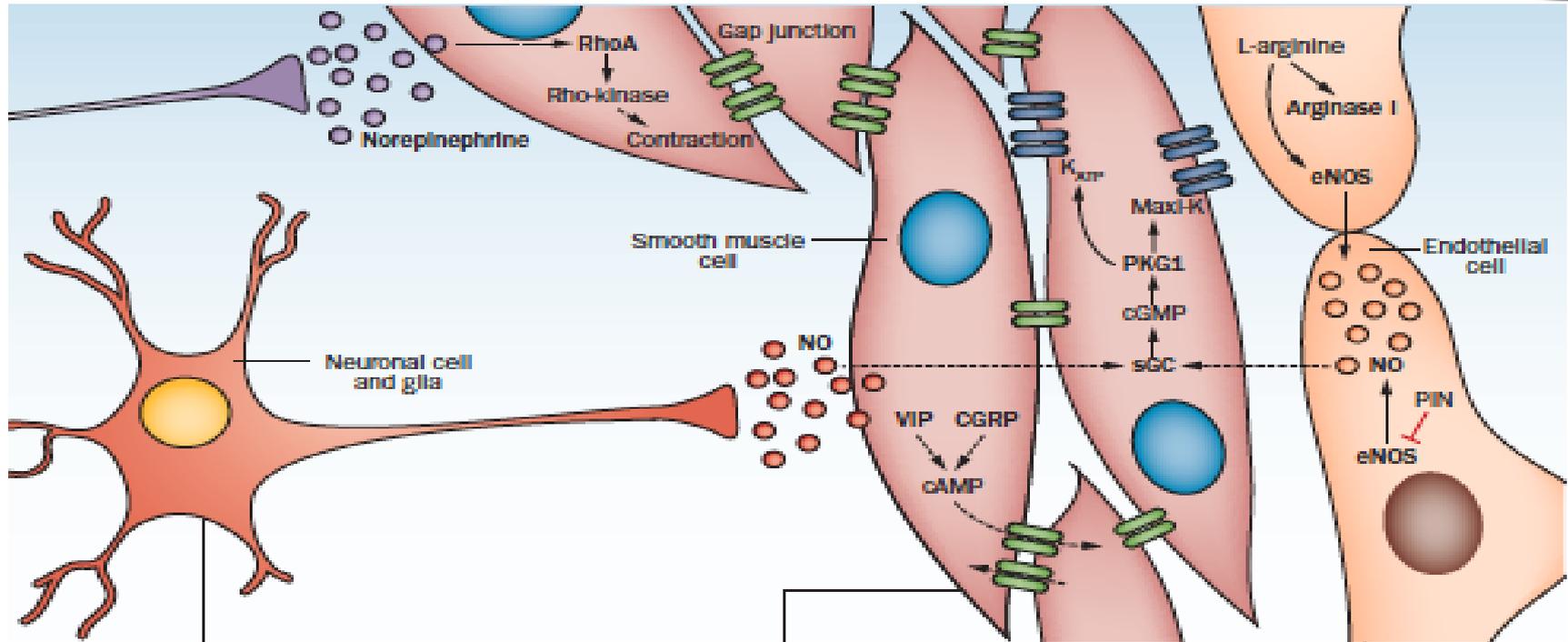
Yuan J, Westney OL, Ruan KH, Wang R.

SuperEnzyme is a newly engineered protein with **PGI₂ synthase activity that converts arachidonic acid directly to PGI₂.**

Transfection of SuperEnzyme into the penis of an animal model to produce PGI(2) is **feasible**

More studies are needed to provide new insight into the role of PGI₂ signaling in the **recovery of erectile function after RP.**

Gene Therapy – Main Targets for Gene Transfer



- NO signalling**
 - ↑ nNOS
 - ↓ Arginase I
 - ↓ PIN
- Neuronal survival/regeneration**
 - ↑ VEGF
 - ↑ BDNF
 - ↑ GDNF
 - ↑ Neurturin
 - ↑ Neurotrophin 3
 - ↑ IGF-1
 - ↑ Erythropoietin

- NO signalling and peptides**
 - ↑ iNOS
 - ↑ CGRP
 - ↑ VIP
- Stimulation of relaxation**
 - ↑ PKG1
 - ↑ Max-K (hSLO)
 - ↑ K_{ATP} channel
- Inhibition of contraction**
 - ↓ RhoA

- NO signalling**
 - ↑ eNOS
 - ↓ Arginase I
 - ↓ PIN
- Endothelial survival/regeneration**
 - ↑ VEGF
 - ↑ HO-1
 - ↑ ANG-1
 - ↑ Superoxide dismutase
 - ↑ Erythropoietin
 - ↑ IGF-1

Gene Therapy in recovery of erectile function

Gene therapy for ED **is still in its infancy** but shows apparent preclinical success.

Intracavernous injection and cellular incorporation of **naked DNA** leads to the subsequent **expression of functional protein** and obviates the necessity for using an adenoviral or retroviral vector for the treatment of ED

Clinical development of gene therapy lie in the optimization of the **safety, specificity** and **longevity** of relevant protein targets used.

Great enthusiasm, increasingly investigational interest

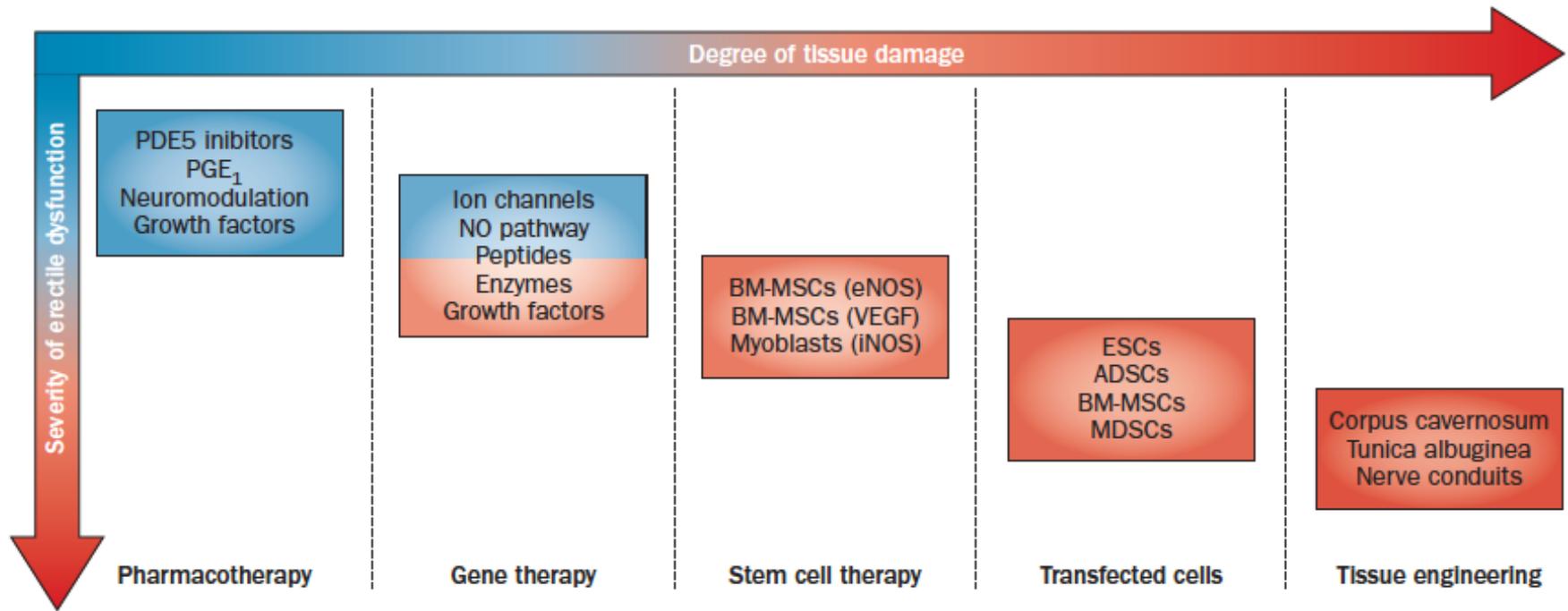
- Tissue-engineered corpus cavernosum
- Tissue-engineered tunica albuginea
- Tissue-engineered nerve conduits

Might be **important** in reconstructive surgery secondary to **trauma**

Many centers are working in prefabricated decellularized, xenogenic or fresh autologous grafts for ED

NO *in vitro* generated autologous cell-seeded tissues have been tested *in vivo*

Future Approach ?



Conclusions

Penile rehabilitation is **commonly practised without a sufficient evidence base to support it.**

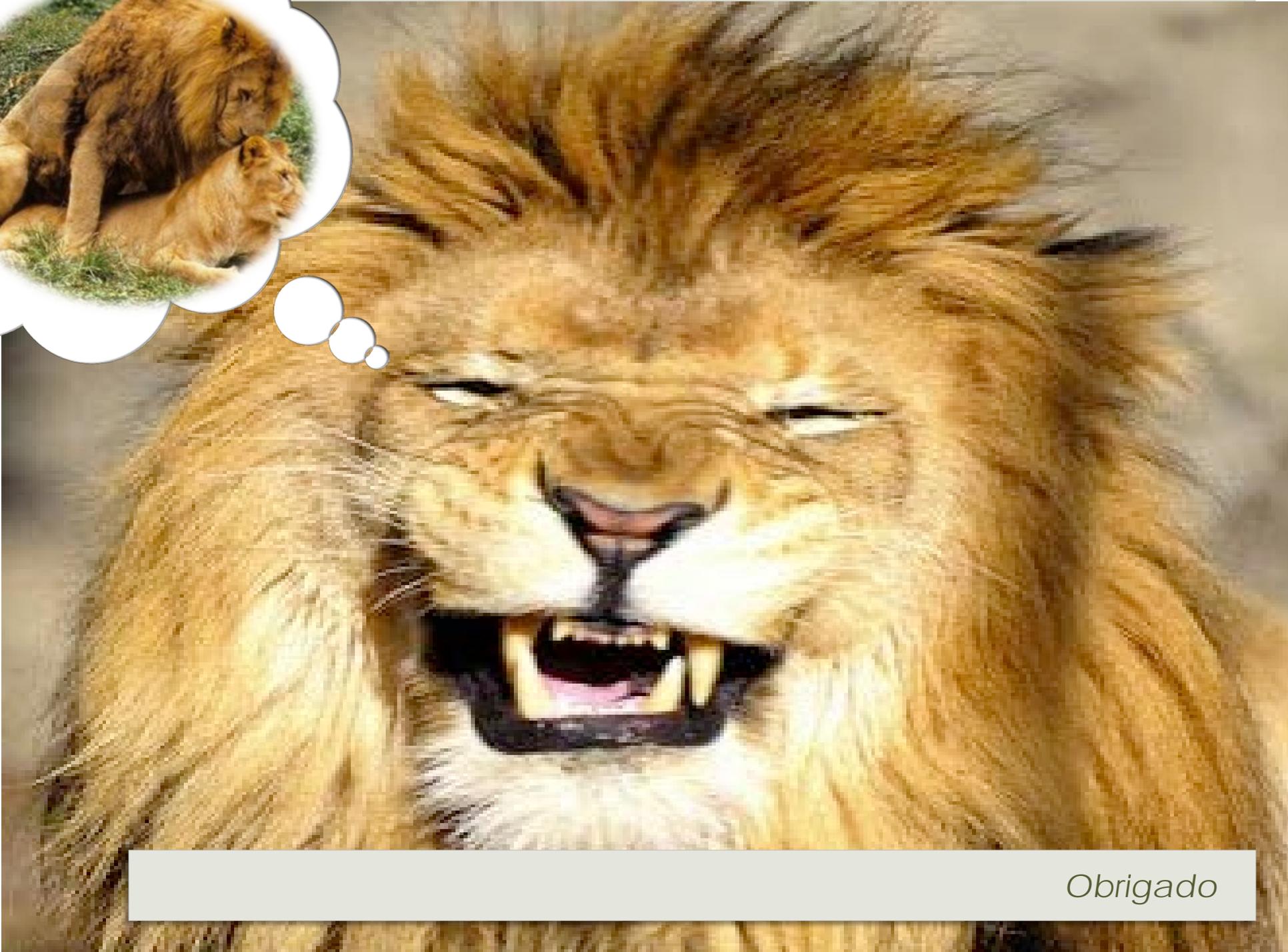
Schemes for rehabilitation are **as diverse** and **no single strategy** is uniformly accepted.

Scientific investigation to develop optimal strategies for erectile function recovery after radical prostatectomy is **needed.**

Exciting **next generation medical technology**

The **best strategy** for erectile function preservation after RP requires:

1. Proficient radical **surgery** with nerve-sparing (bilateral)
2. Health and physical fitness **optimization** (by the patient-couple)
3. **Specific pathophysiology** intervention (investigation)



Obrigado