DEPARTMENT OF
UROLOGY

VANDERBILT UNIVERSITY
MEDICAL CENTER

From slings to stem cells: A story of urinary sphincter regeneration

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National Academies Workshop
The Intersection of Regenerative Medicine and Women's Health
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Disclosures

Boston Scientific – National Principal Investigator

Cook Myosite – Global Principal Investigator

Laborie – Medical Advisory Board

Levee Medical – Medical Advisory Board

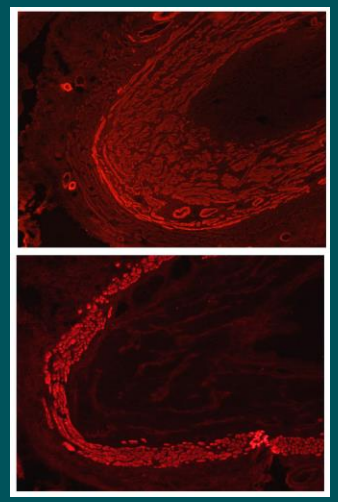
Augment Health – Medical Advisory Board

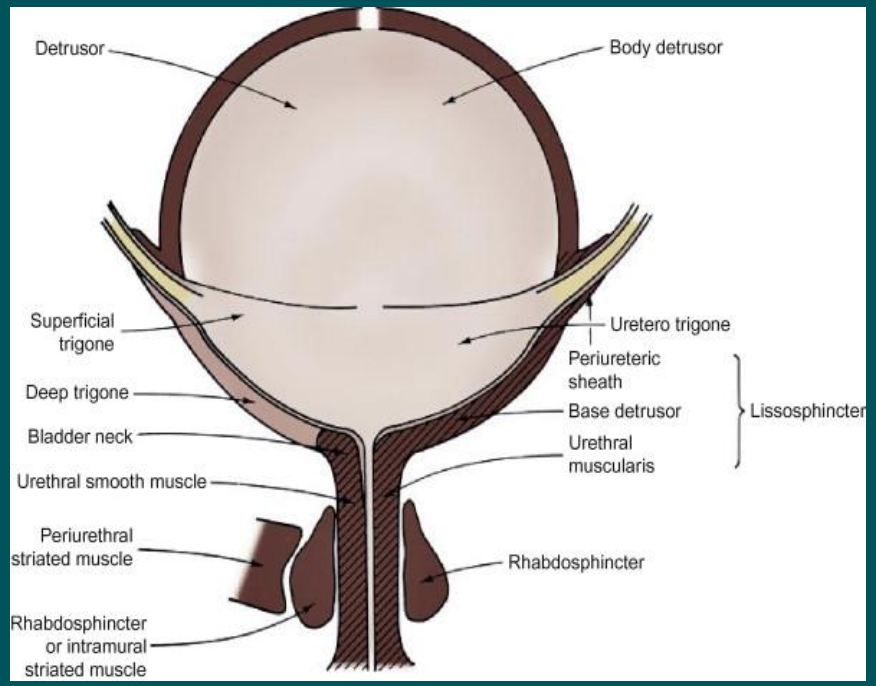
The Journal of Urology – Associate Editor

Neurourology and Urodynamics – Associate Editor

Female stress urinary incontinence

- Involuntary loss of urine on effort, physical exertion, sneezing or coughing
- Prevalence as high as 49%
- Deficit in urethral closure mechanism





Kobashi KC, et al. J Urol. 2023 Jun;209(6):1091-1098. PMID: 37096580

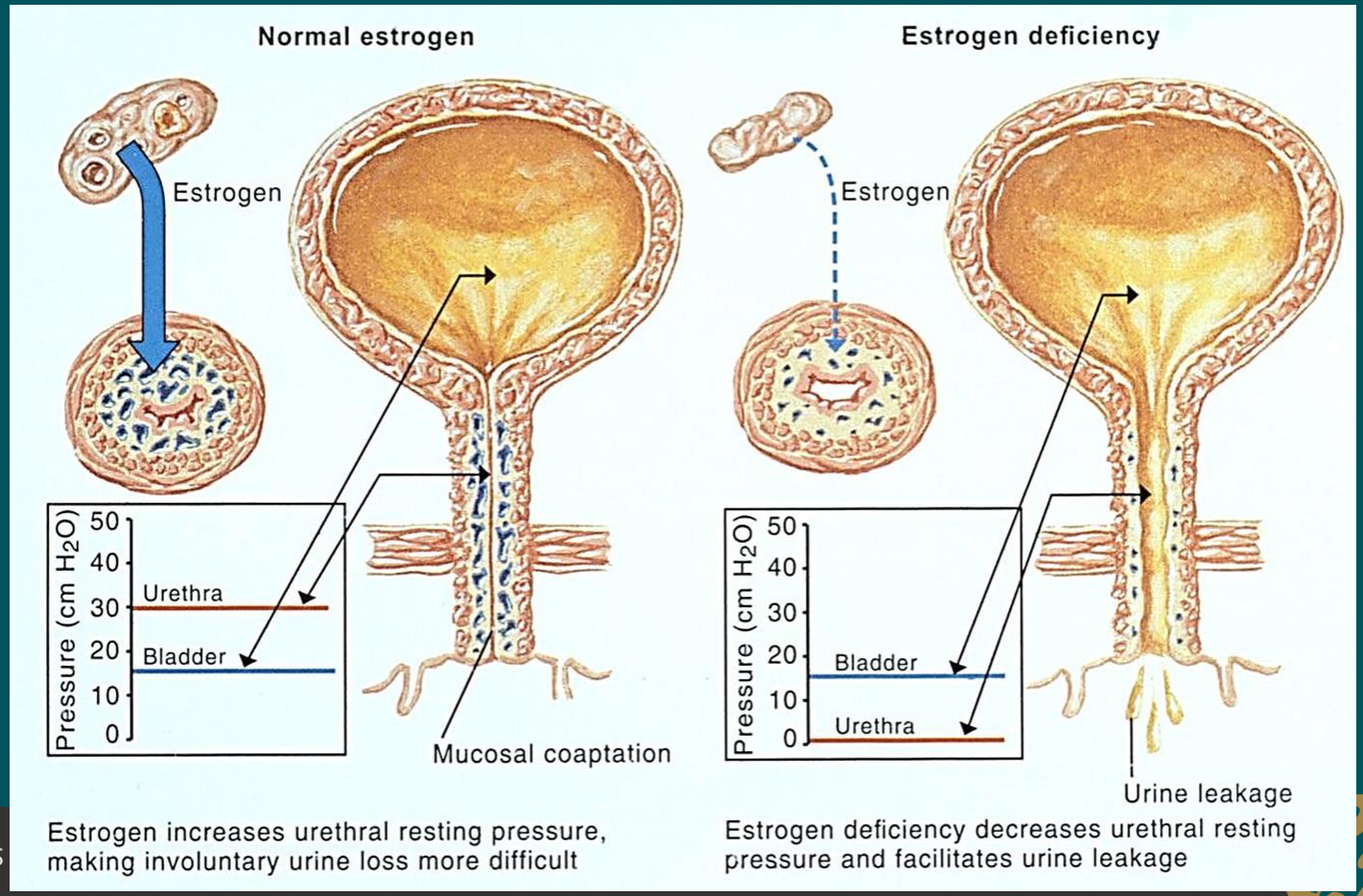
Risk factors



Factor	Young Women	Middle-Aged	Older Women
Effect of pregnancy			
Type of delivery (vaginal vs cesarean)			
Parity			
Smoking			
Increased body mass index			
Medications			
Physical exercise			
Estrogen depletion			
Chronic constipation			
Pelvic organ prolapse			

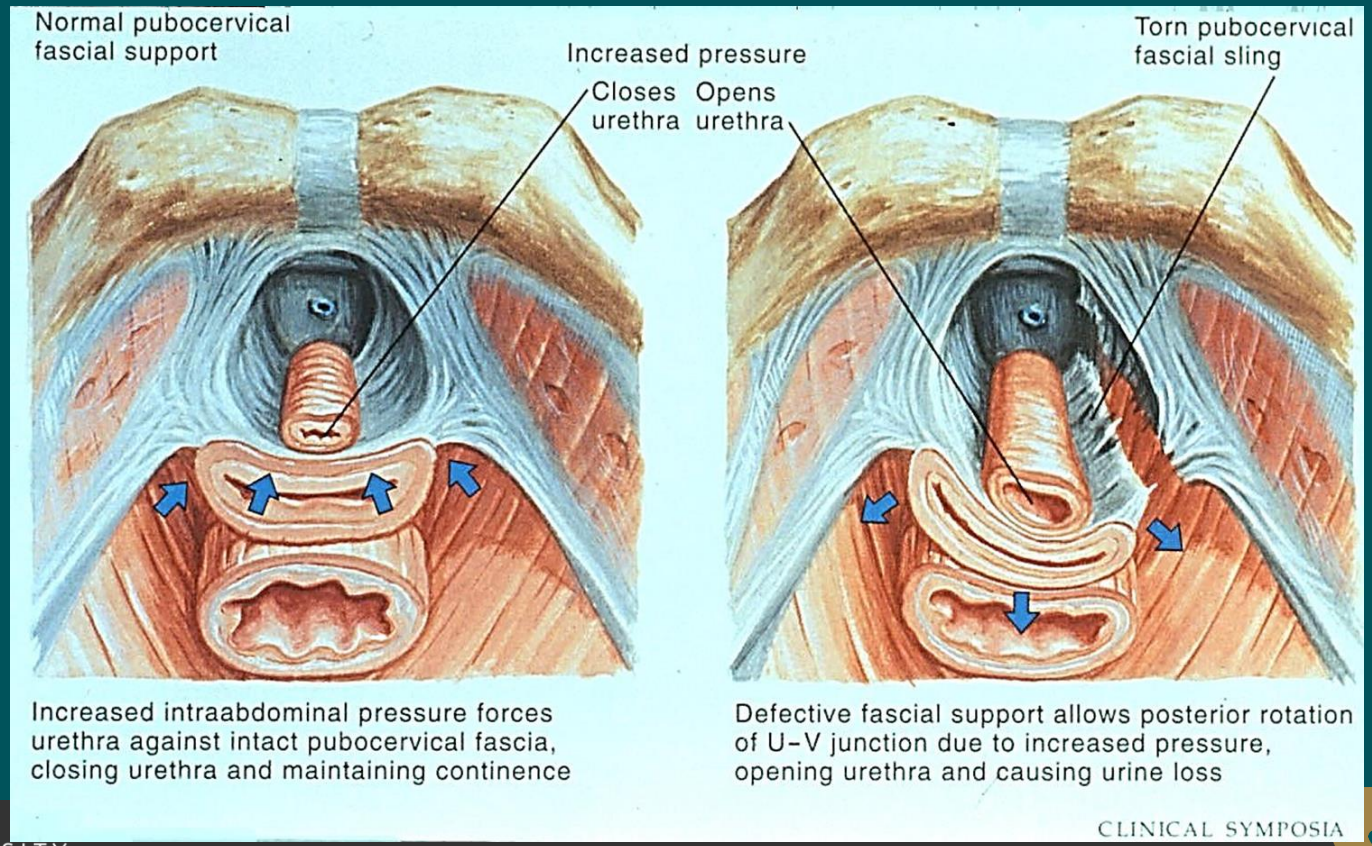
Proposed etiologies SUI

- Loss of mucosal coaptation – Intrinsic sphincteric deficiency



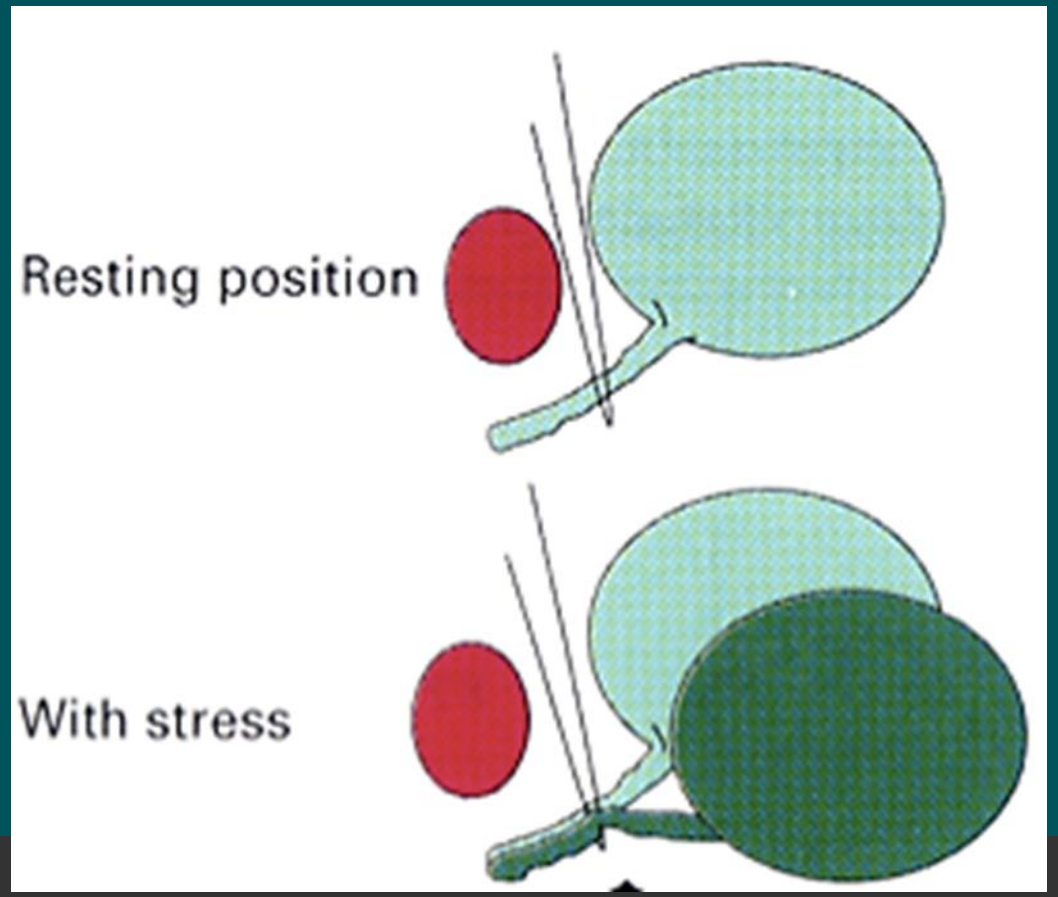
Proposed etiologies SUI

- Loss of fascial support – Hypermobility



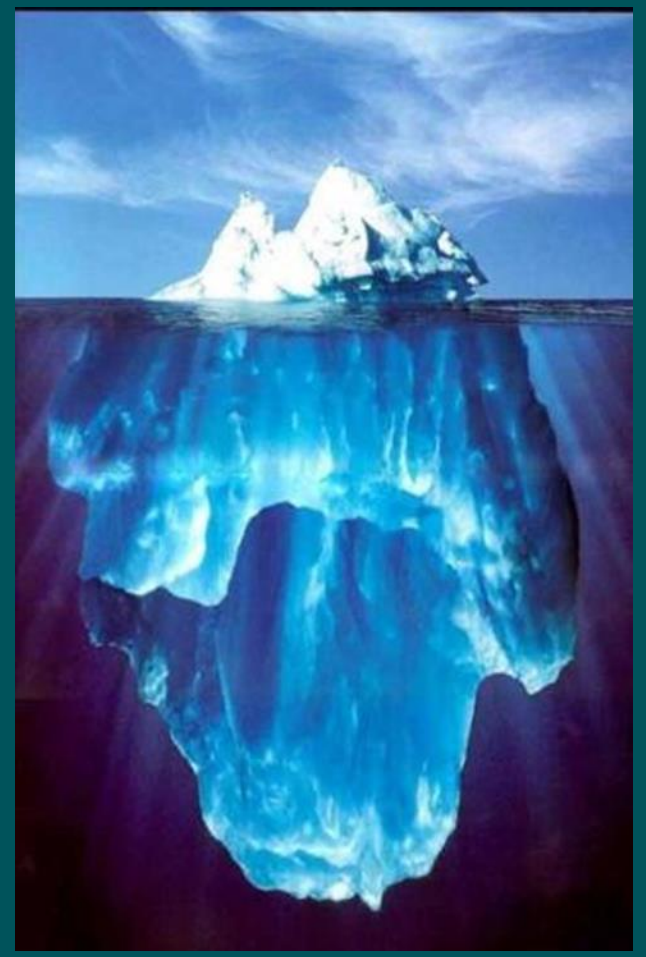
Proposed etiologies SUI

- Loss of pubourethral ligaments for dynamic kinking – Integral theory



Magnitude of impact

- Spectrum of pathophysiologic mechanisms
- 15 million women, ~ $20 billion
- Limitations of translating animal models
- Complexities of diagnosis, therapies, outcomes

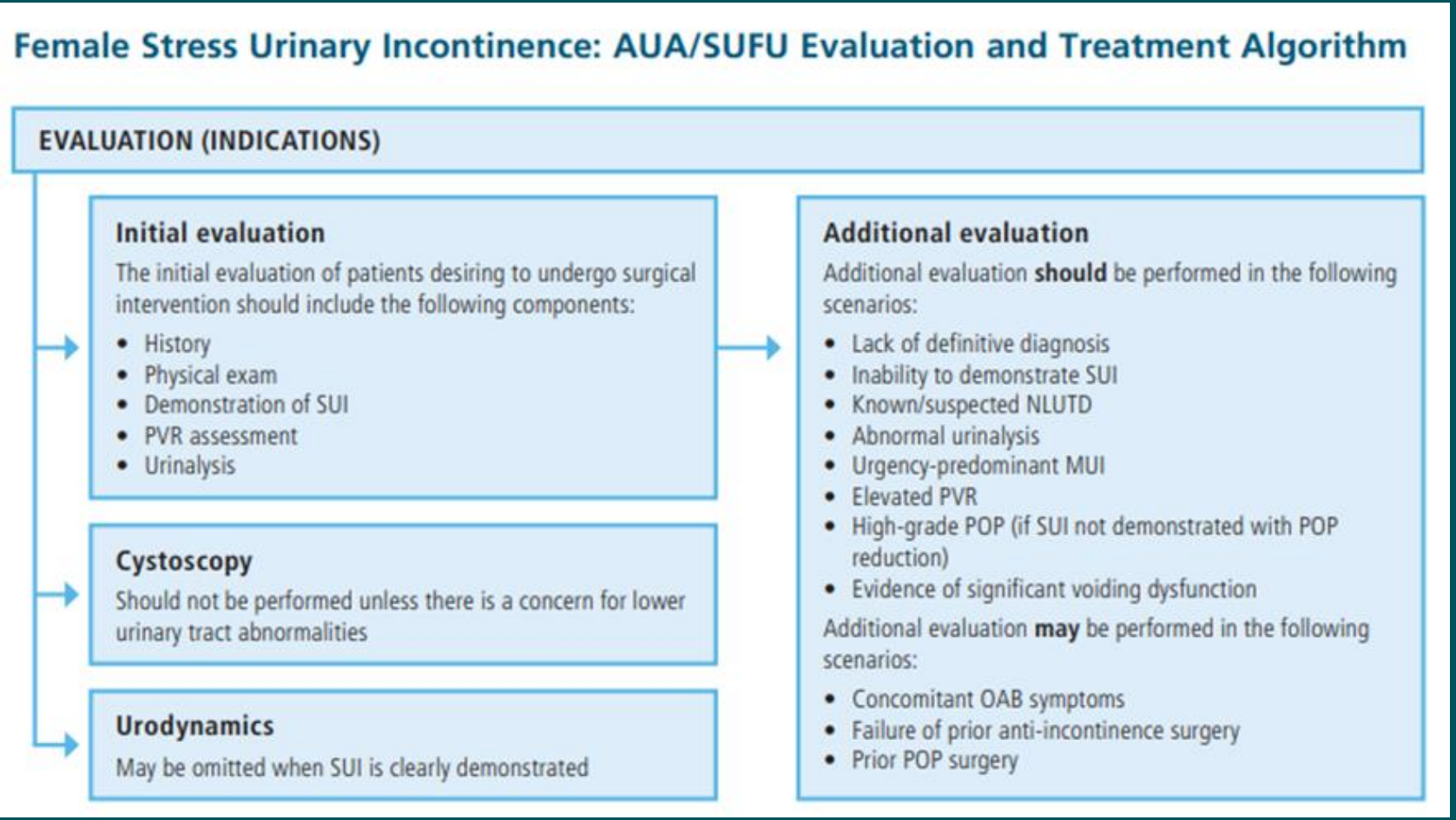


Quality of life impacts

- Psychological, physical, sexual health
- Increased incidence of anxiety and depression
  - 6 x more likely to have depression
- Avoidance of activities: social, recreational, and work-related
- Negative effect on sexual activity
- Worse QOL for those with recurrent or persistent SUI

Felde G, et al. eurourol Urodyn. 2017 Feb;36(2):322-328

SUI guidelines



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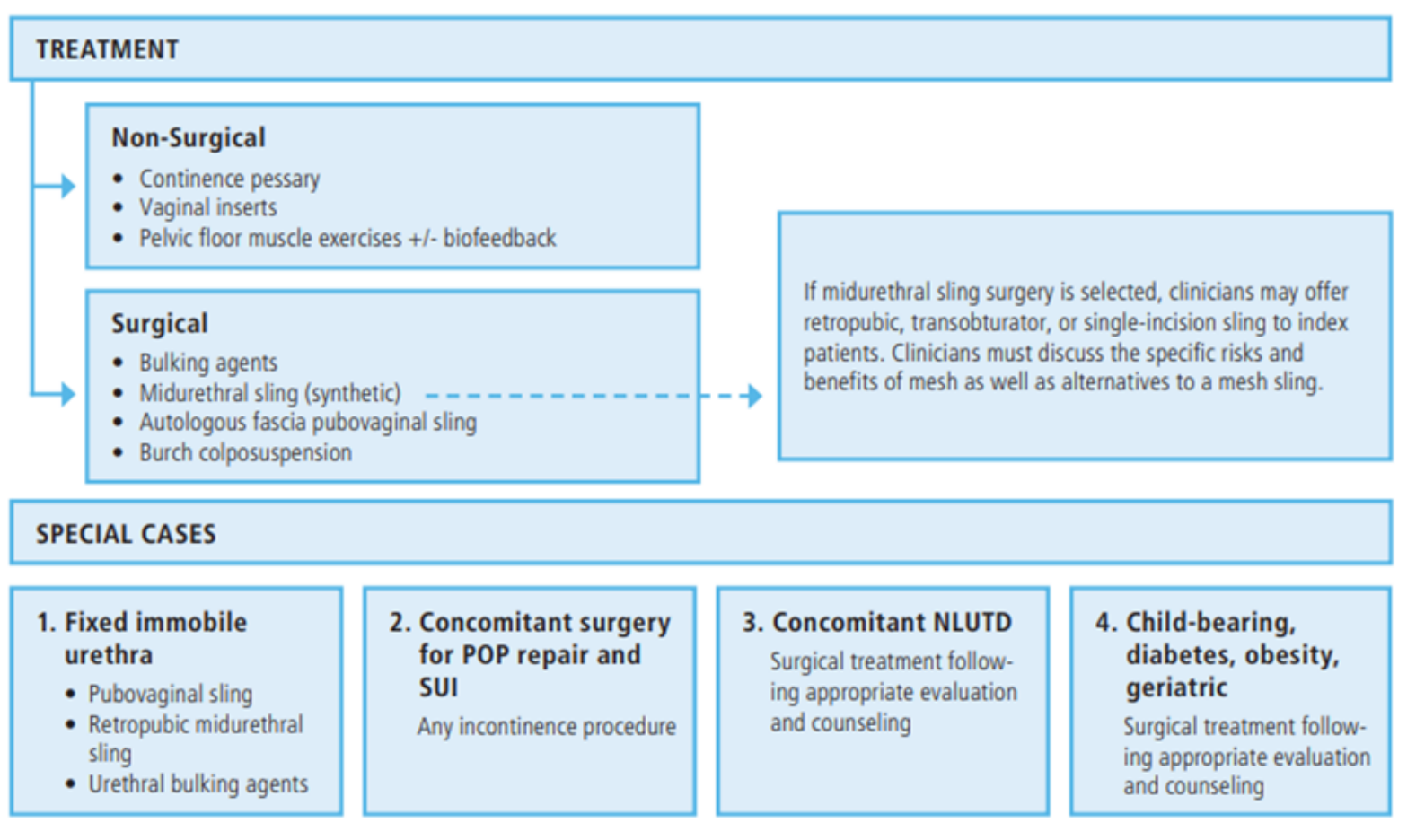
SUI guidelines



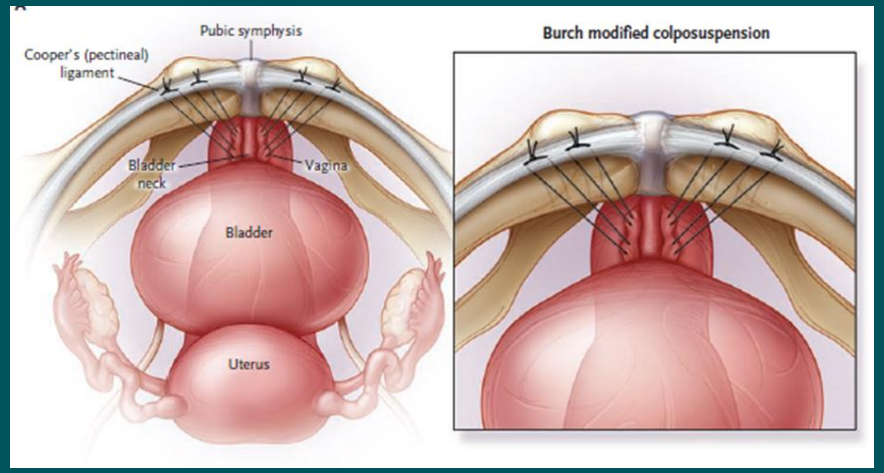
Kobashi KC, et al. J Urol. 2023 Jun;209(6):1091-1098. PMID: 37096580

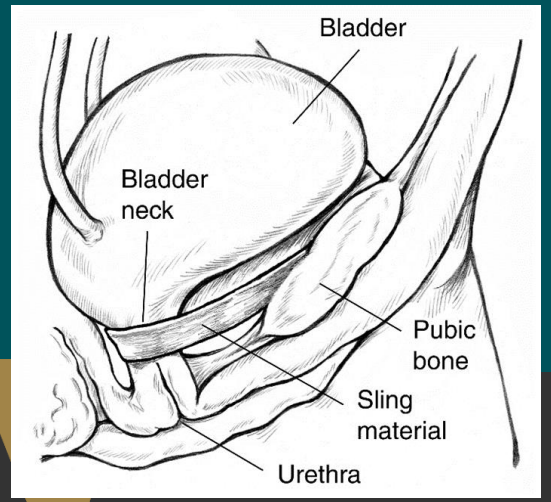
Perfect therapy for SUI

- Effective
- Durable
- Straightforward, fast and reproducible
- Applicable for all types of SUI
- Minimally invasive – local (or no) anesthesia, small (or no) incisions
- Outpatient procedure, short convalescence and return to normal activities
- Minimal (or no) pain
- Low (or no) morbidity and complications
- Inexpensive: patient, healthcare facility, healthcare system, etc

Native tissue repairs

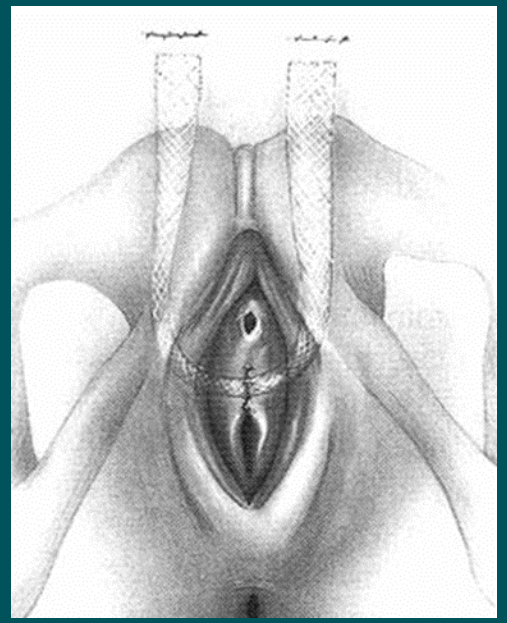
- Apposition of fibromuscular tissue to recreate native anatomy
- Use of fascial grafts or biologics
- Barriers
  - Recurrence rates
  - Complication rates
  - Requires expertise in understanding anatomy





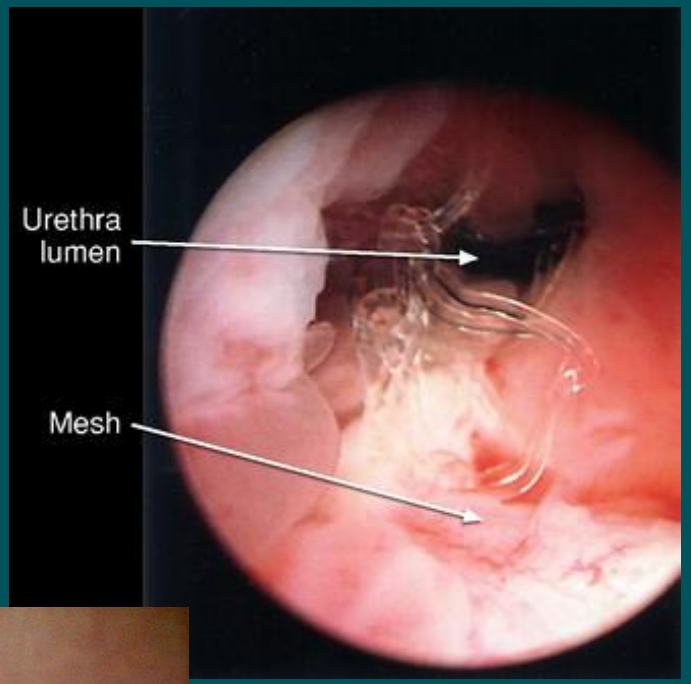
Midurethral slings

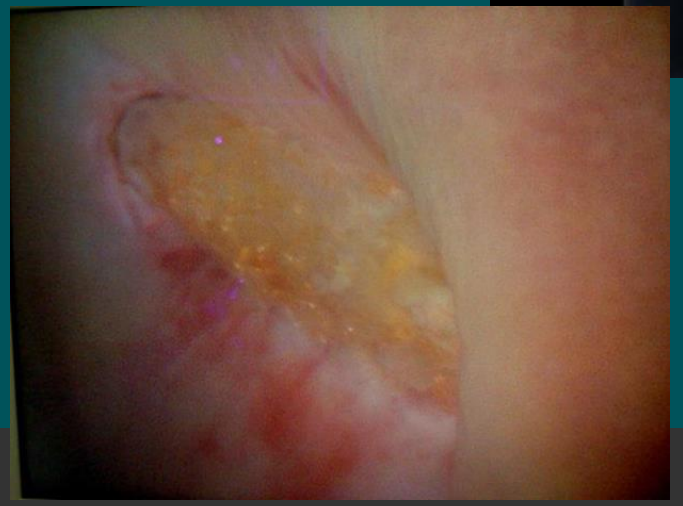
- Urethral hypermobility
- Outpatient procedures
- Small incisions for passage of trocars
- Fast, minimal dissection
- Success rates at 2 years ~80%dependent on definition
- Satisfaction rates lower ~60%



Midurethral sling pitfalls

- Post-operative voiding difficulties
- De novo urgency
- Urinary retention
- Mesh vaginal extrusion
- Mesh bladder or urethral erosion
- Recurrent UTI
- Leg and groin pain
- Contraindications





AUGS/SUFU statement 2014

- SUI treatment
- "The polypropylene mesh MUS is *the recognized worldwide standard* of *care* for the treatment of SUI. The procedure is safe, effective, and has improved the quality of life for millions of women"

AUGS

SUFU
SOCIETY OF
URODYNAMICS,
FEMALE PELVIC MEDICINE &
UROGENITAL RECONSTRUCTION

AUGS/SUFU statement 2021

- SUI treatment
- "Synthetic polypropylene mesh sling placement is the *most common surgery* performed for SUI, and is recognized in clinical practice guidelines as *a standard of care* for this condition"

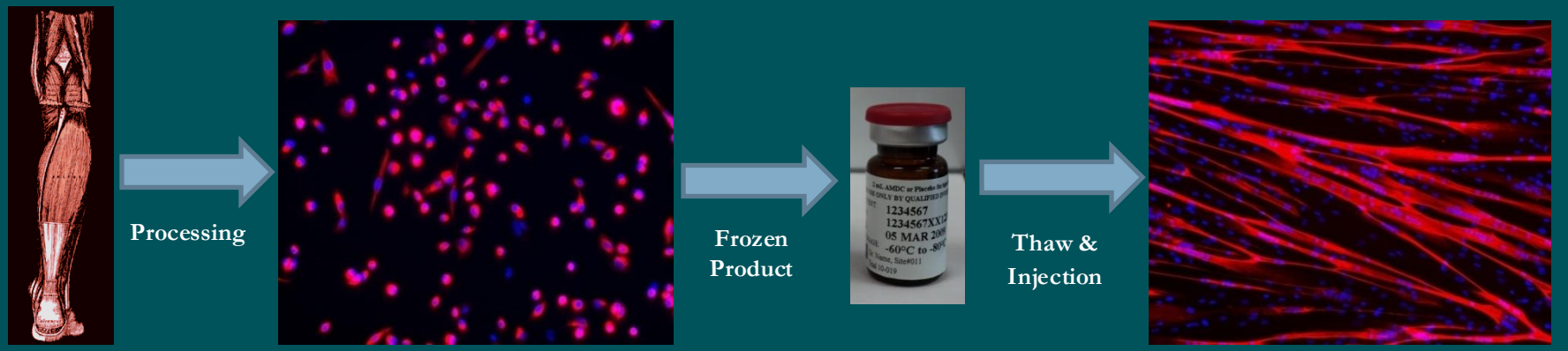
New paradigm

- Cellular therapy for SUI
- Regenerative vs. symptom management
- Target and reverse disease progression
- No foreign body
- Autologous cells
- Proof of concept and efficacy established in animal models
- Significant obstacles remain in understanding MOA

Controversy

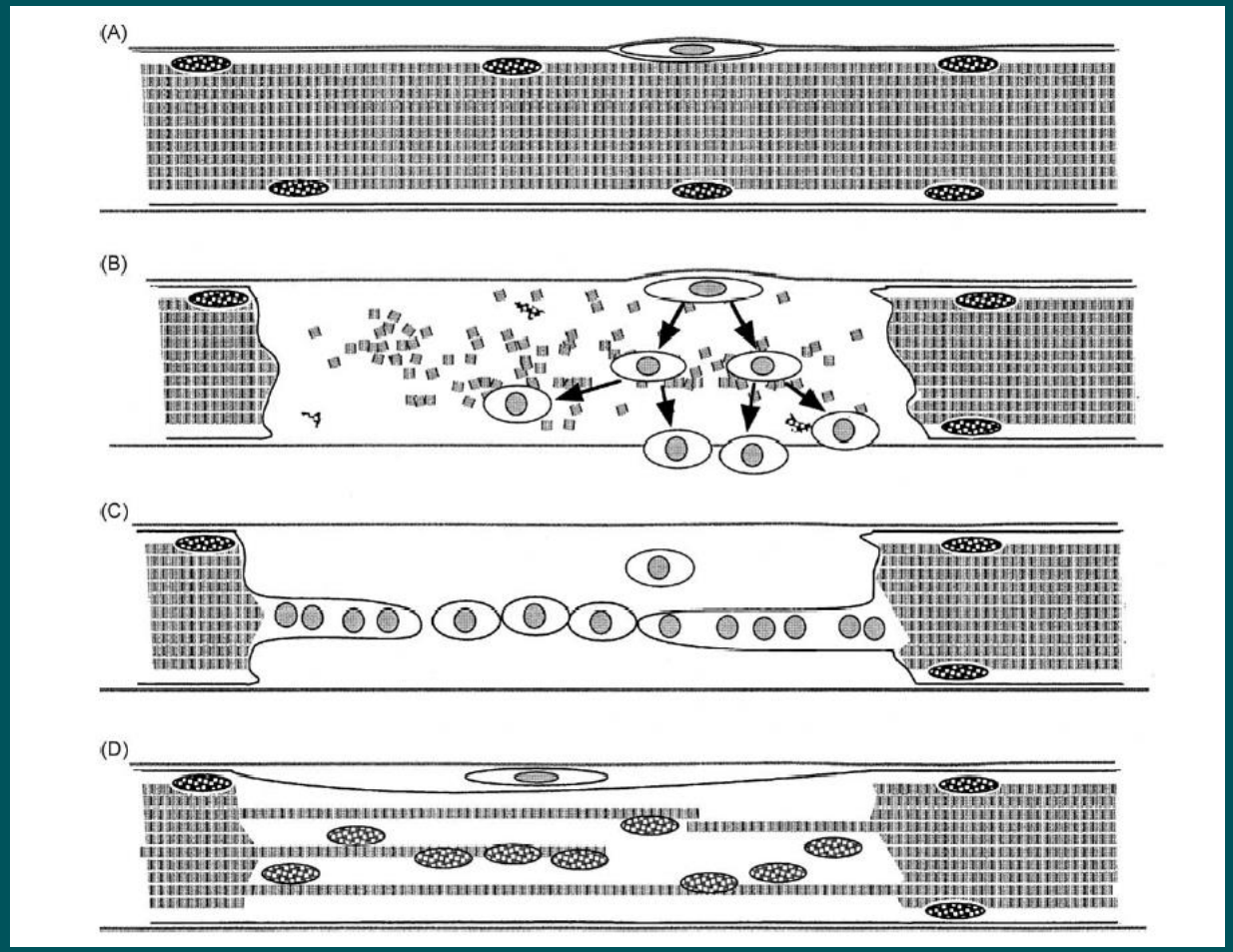
- Ethical issues
- Humanitarian concerns
- Malignant transformation
- In vitro vs in vivo differentiation
- Rejection
- Contamination
- Issues with xenotransplantation
- Economic concerns

Adult muscle-derived cells (AMDC)



- Biopsy harvested from skeletal muscle
- Delivered back to clinical site following ex vivo expansion
- Injected into targeted muscle layer: external urethral sphincter

Role of satellite cells



Quiescent satellite cell

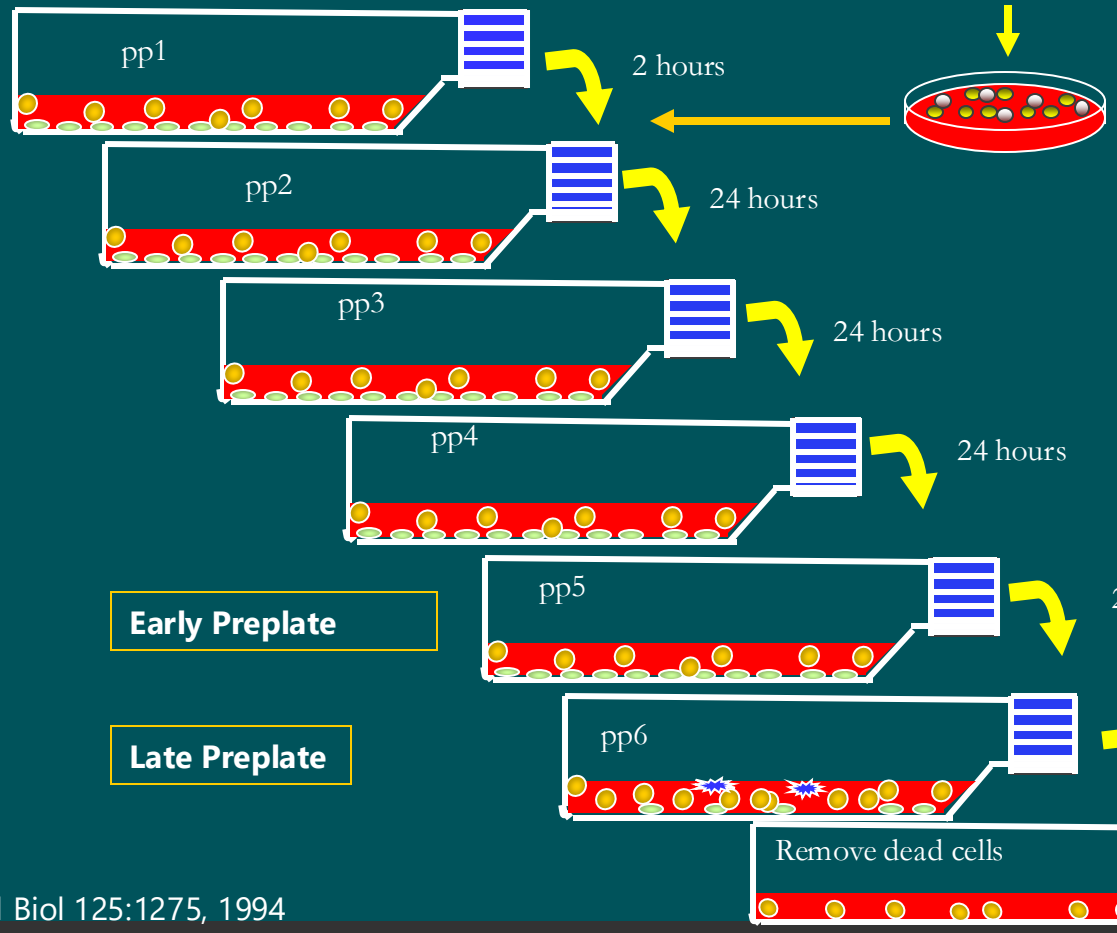
Activated in response to injury

Fusion to repair muscle fiber

Regenerated muscle fiber

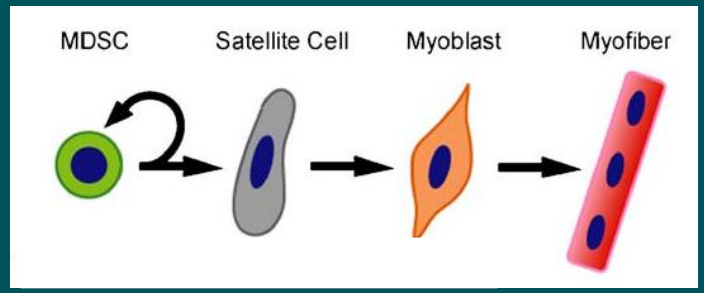
Morgan and Partridge. Int J Biochem Cell Biol. 2003

Enzymatic dissociation



Early Preplate

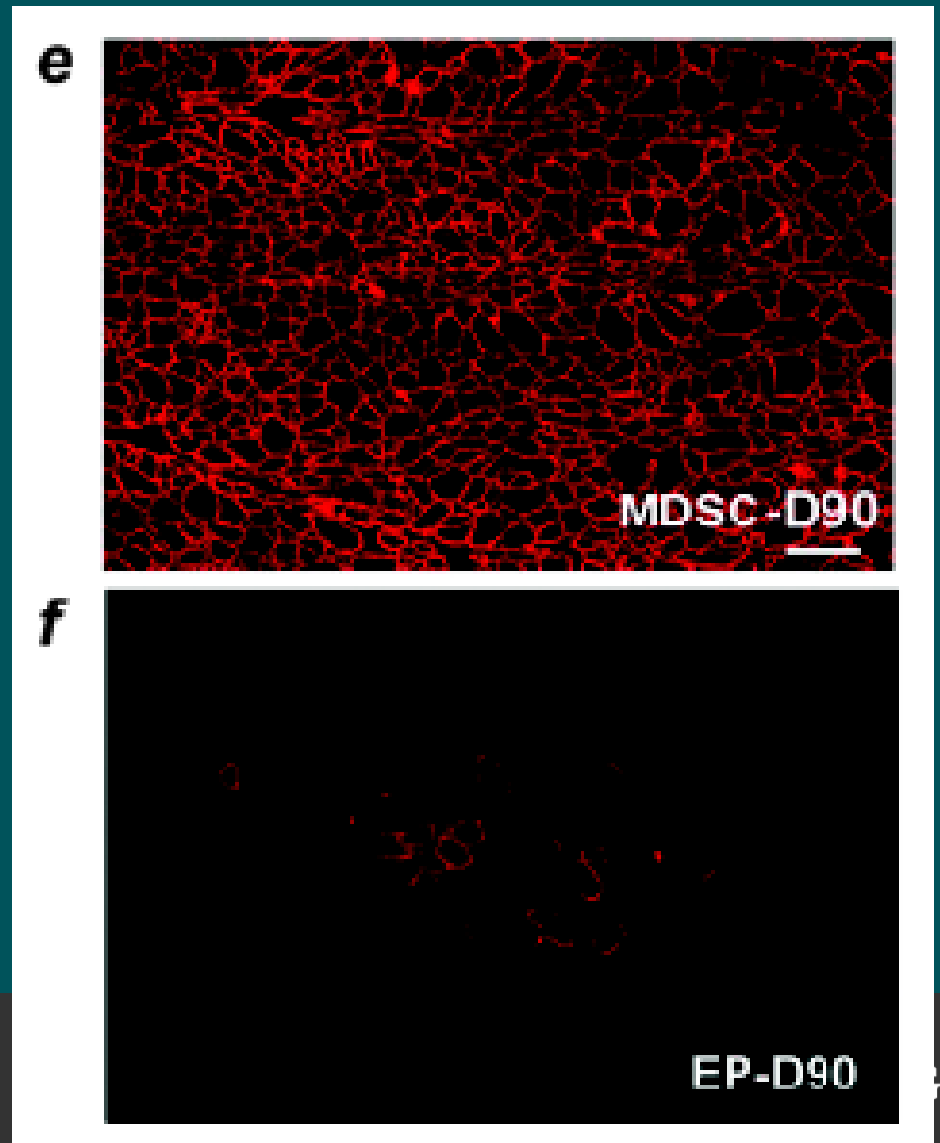
Late Preplate



Rando and Blau., J Cell Biol 125:1275, 1994

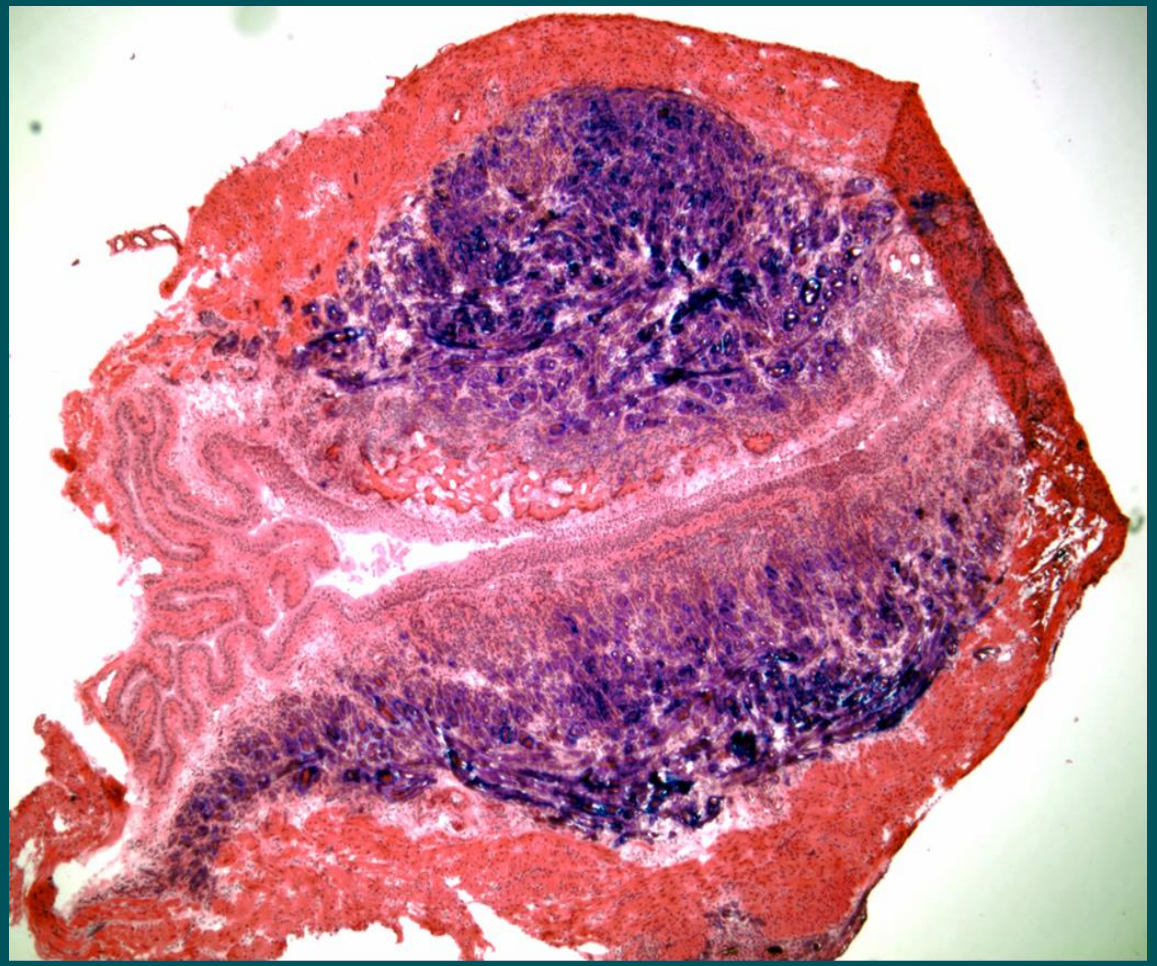
MDC transplantation capacity

- Increased dystrophin+ myofibers in MDC-injected muscles compared to controls
- Dystrophin expression is persistent over time in the MDC-injected muscles



Qu-Peterson et al., J Cell Biol 157:851, 2002

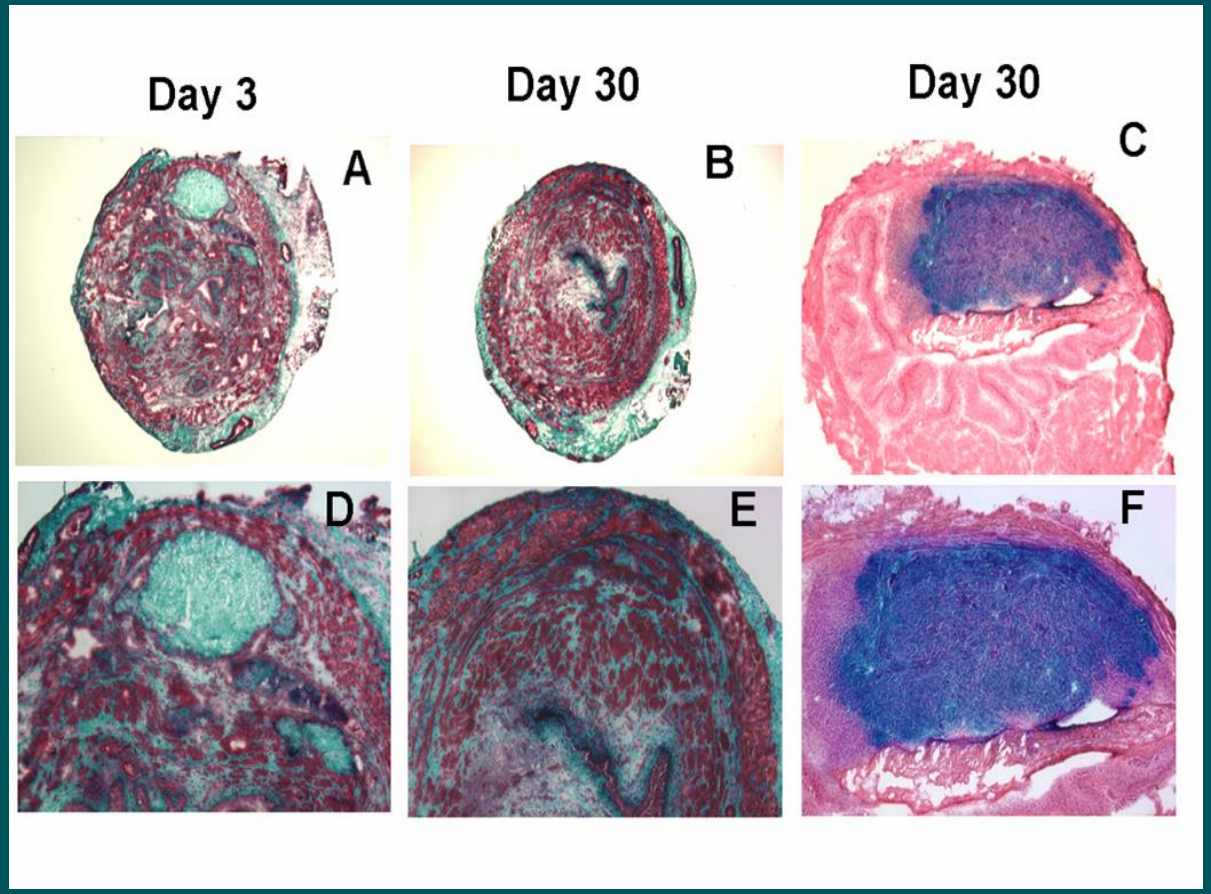
MDC anatomic repair



Yokoyama et al., World J Urol 18:56, 2000

MDC vs bulking agent

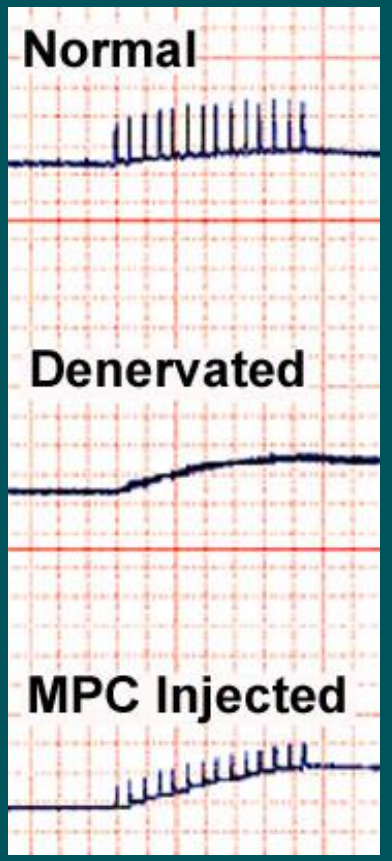
- Greater persistence of injected MDC vs collagen



Yokoyama et al., J Urol 165:271, 2001

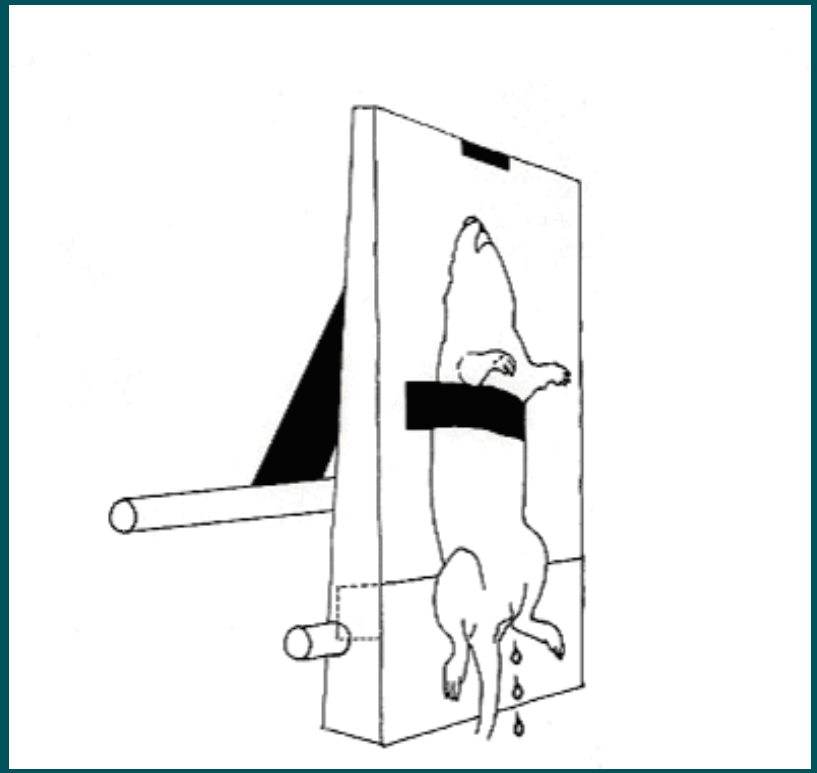
In vivo contractile capacity

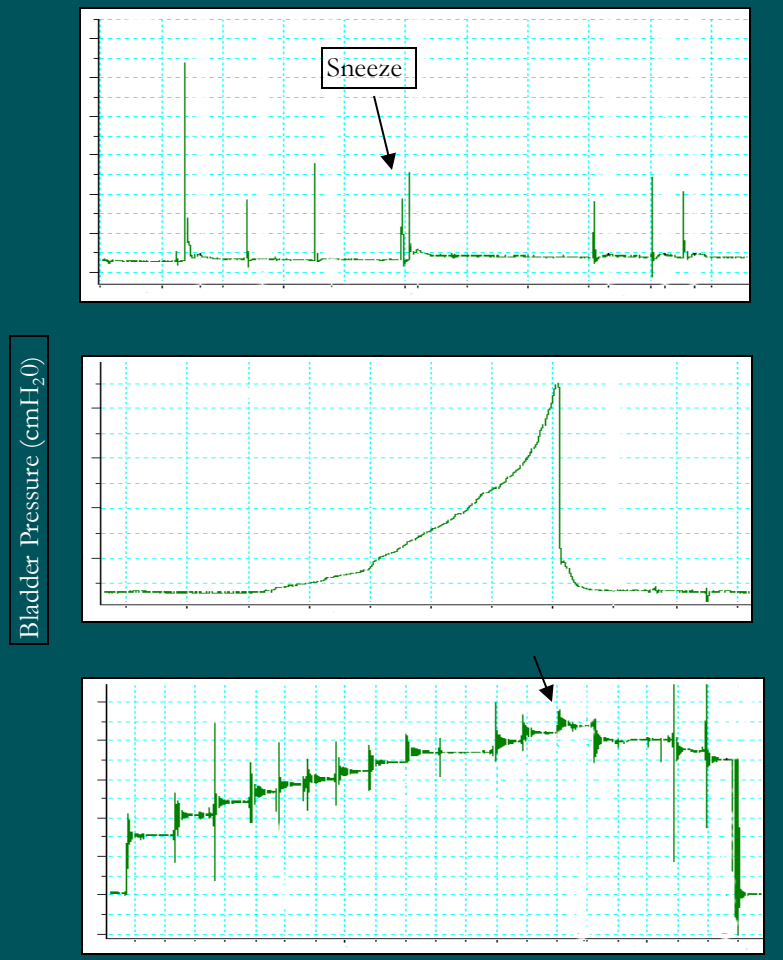
- Female rats: normal, denervated, MDC injected
- Organ bath electric field stimulation
  - Denervation alone = 9% of normal
  - MDC injected = 87% of normal
- Striated contractions abolished with antagonist
- Recovery of innervated functional tissue



Cannon TW et al. Urology 62:958, 2003

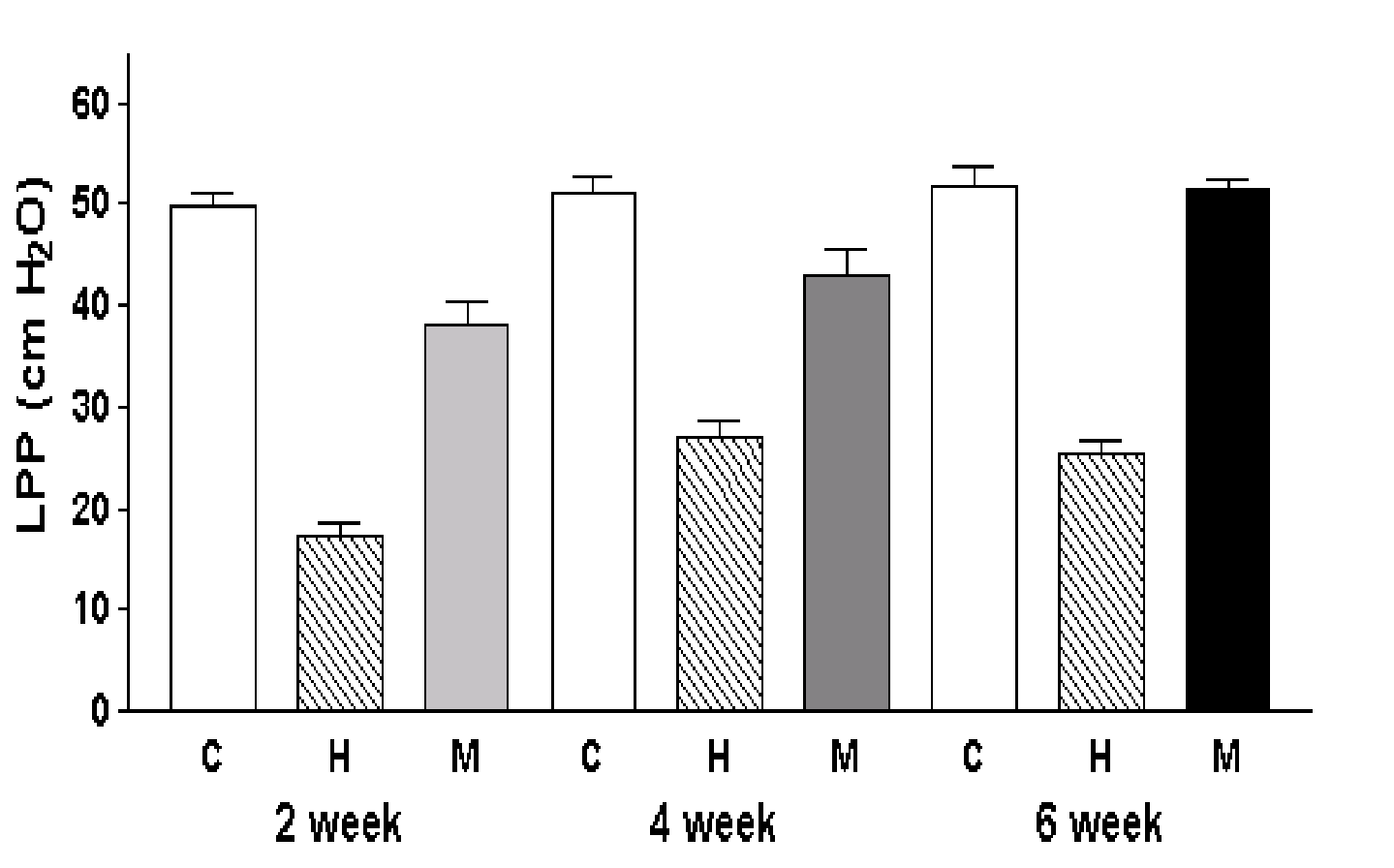
Vertical tilt table LPP





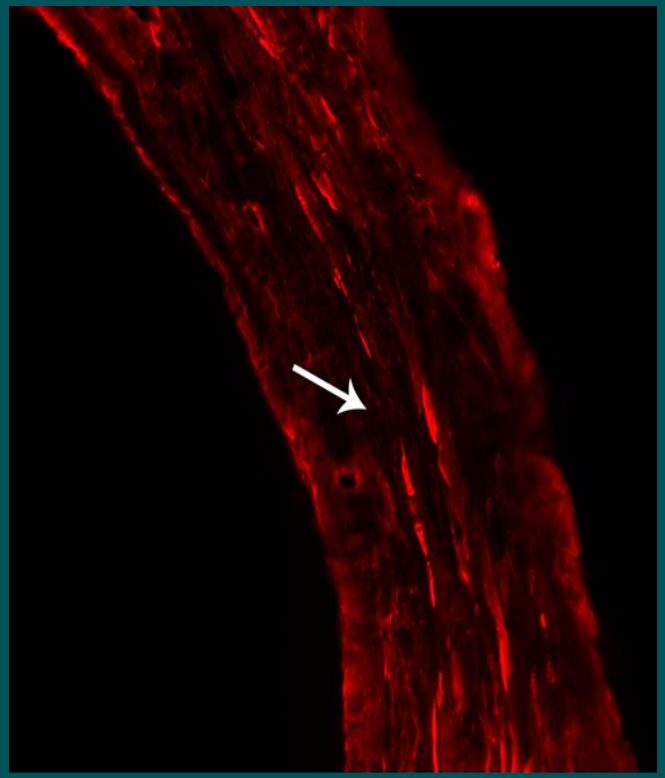
Lee et al., Int. Urogyn J 14:31, 2003

Effect of MDC on LPP

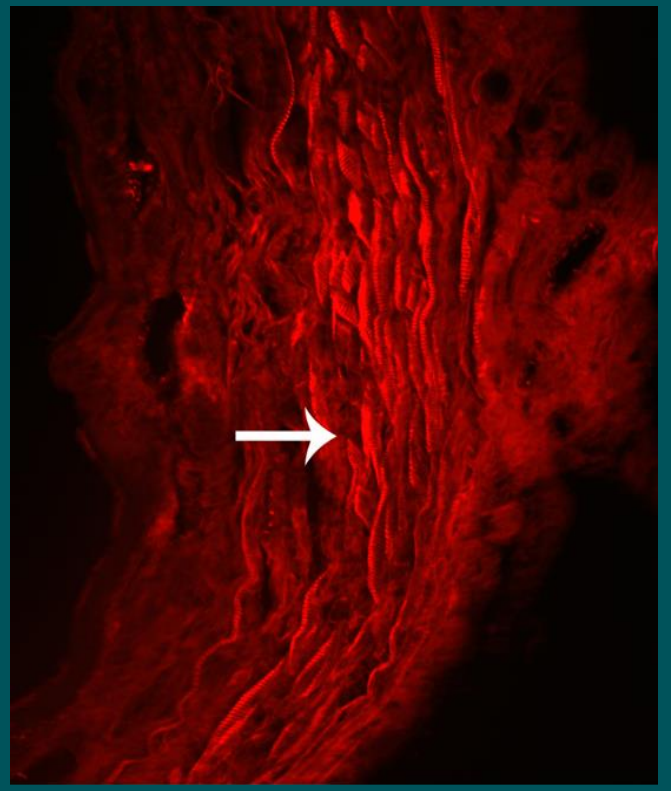


Chermansky et al., Urology, 2004

Muscle regeneration

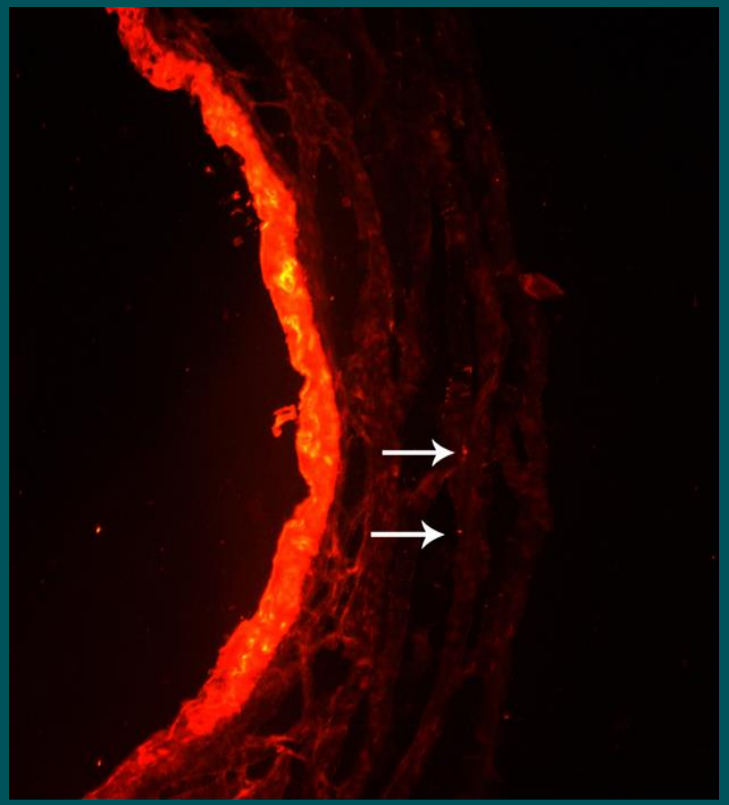


Fast myosin heavy chain stain control

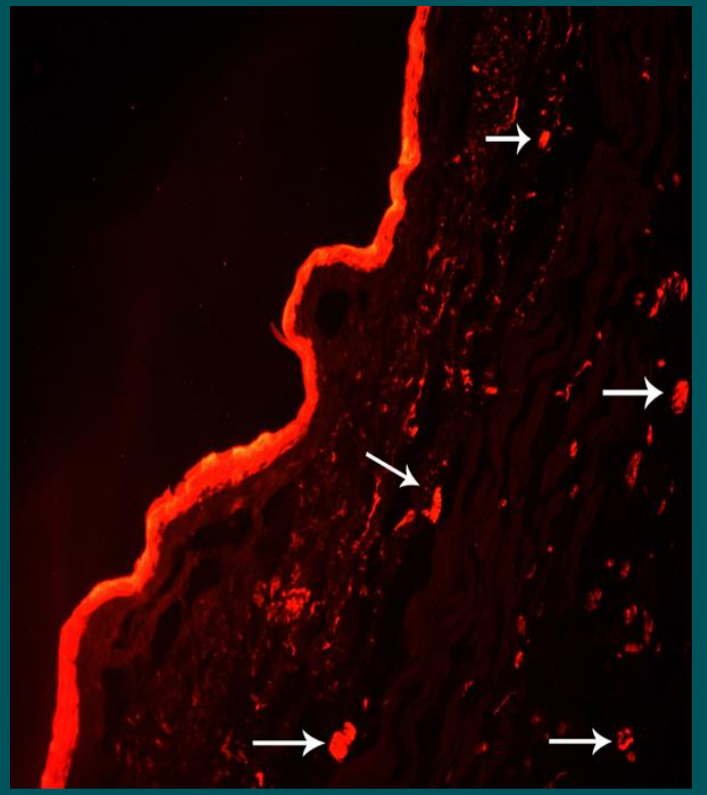


Fast myosin heavy chain stain of MDC

Neuroregeneration

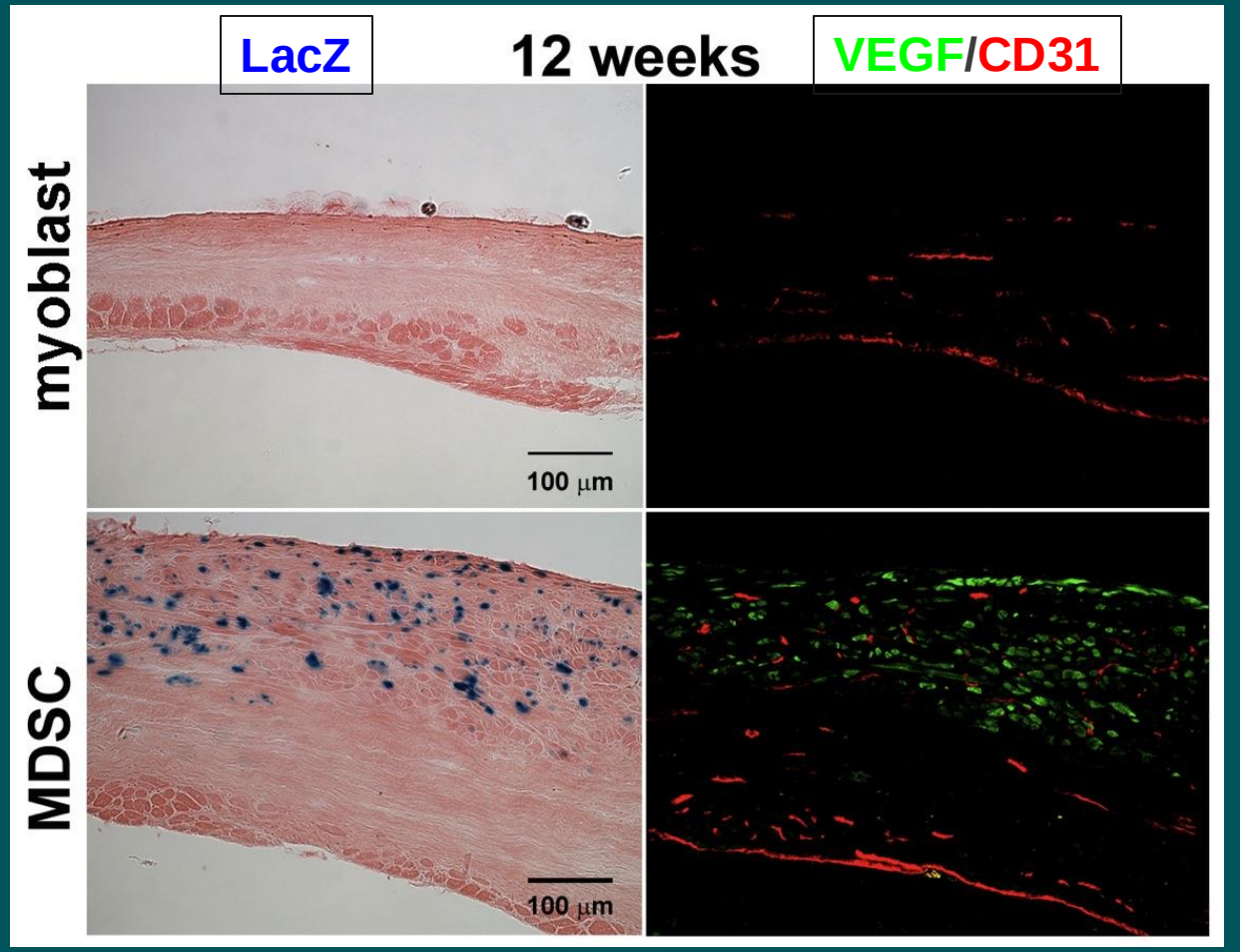


PGP 9.5 stain of control



PGP 9.5 stain of MDC

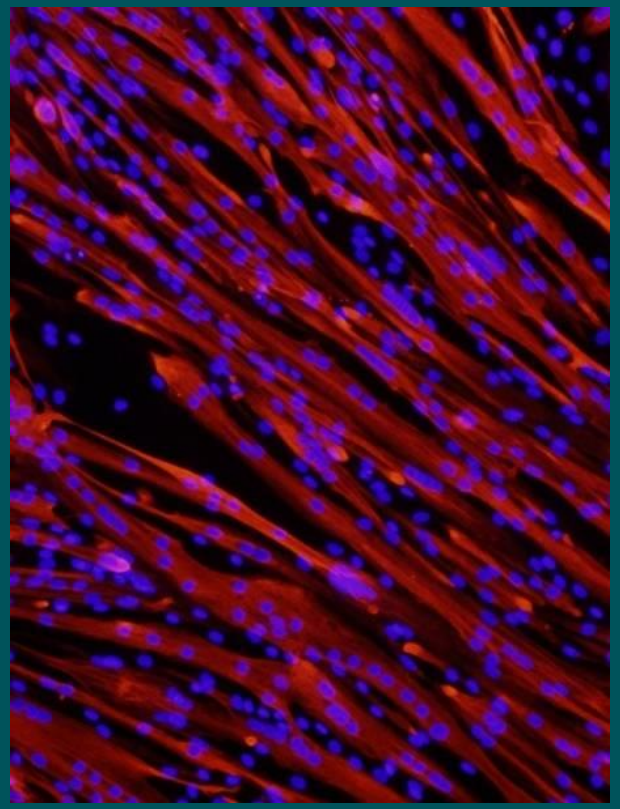
Angiogenesis



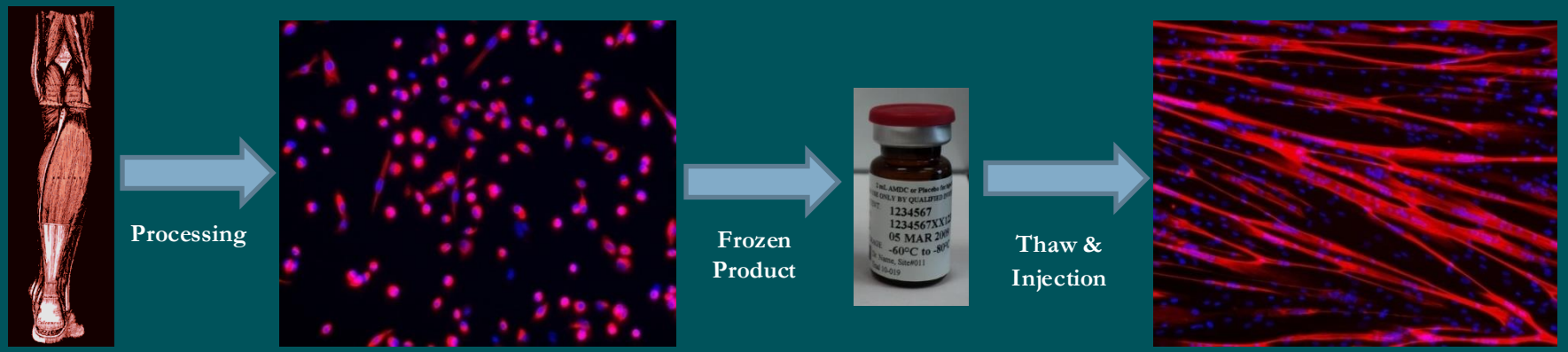
Oshima, H., Payne, T.R., et al.. Mol Ther 12, 1130-1141 (2005)

Conclusions from animal models

- MDCs integrate into tissue
- MDCs improve sphincter function
- Innervated
- Low risk of cell overgrowth



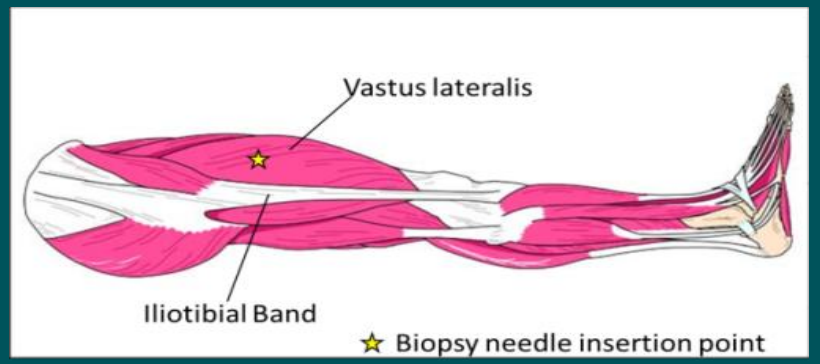
Mechanism of action



- Direct - New muscle formation
- Direct - Augmentation of existing muscle
- Indirect - Secretion of growth factors/host tissue remodeling

Muscle tissue procurement

- Minimally invasive
- In-office
- Local anesthesia
- Usually, <15 minutes
- ~150 mg of tissue obtained

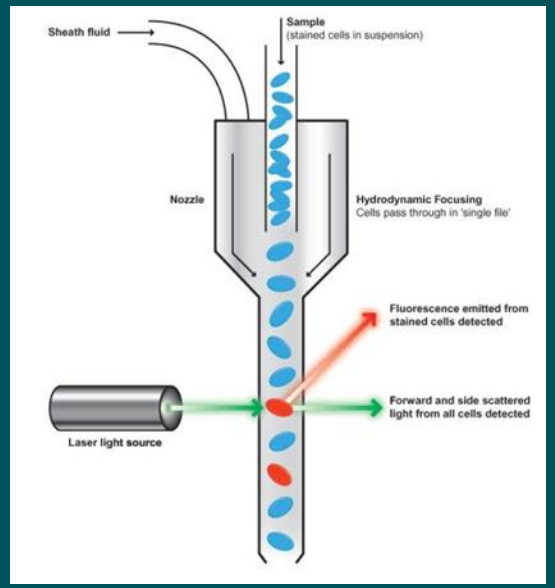


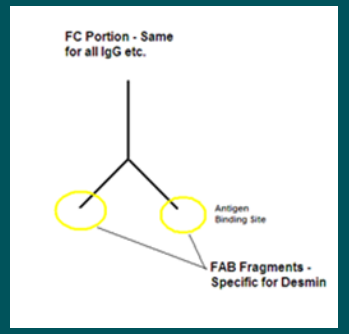
Manufacturing process

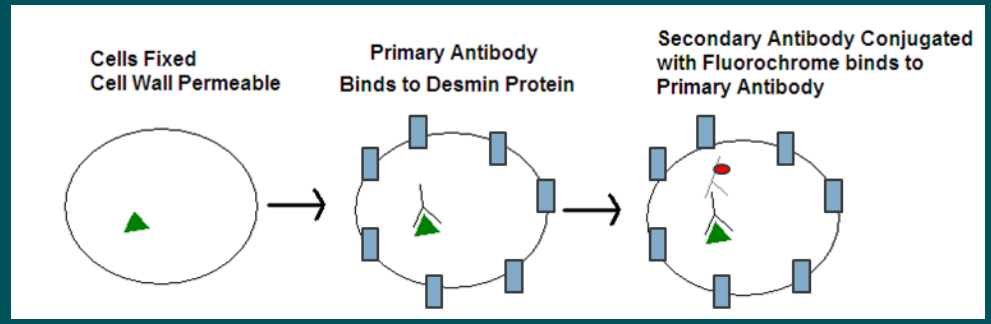
- Aseptic production
- Maintain identity, traceability, mitigate cross-contamination
- Viability and identity testing
- Potency testing
- Sterility testing
- Quality assurance

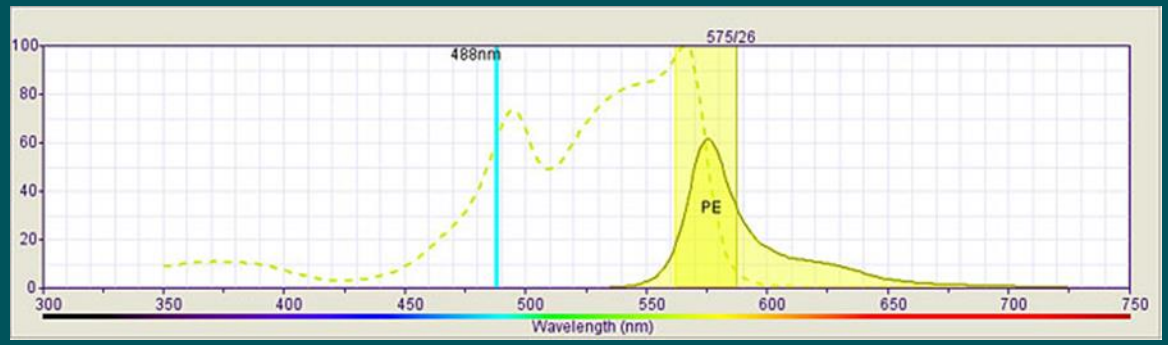
Viability and identity testing

- Desmin content via Flow Cytometry



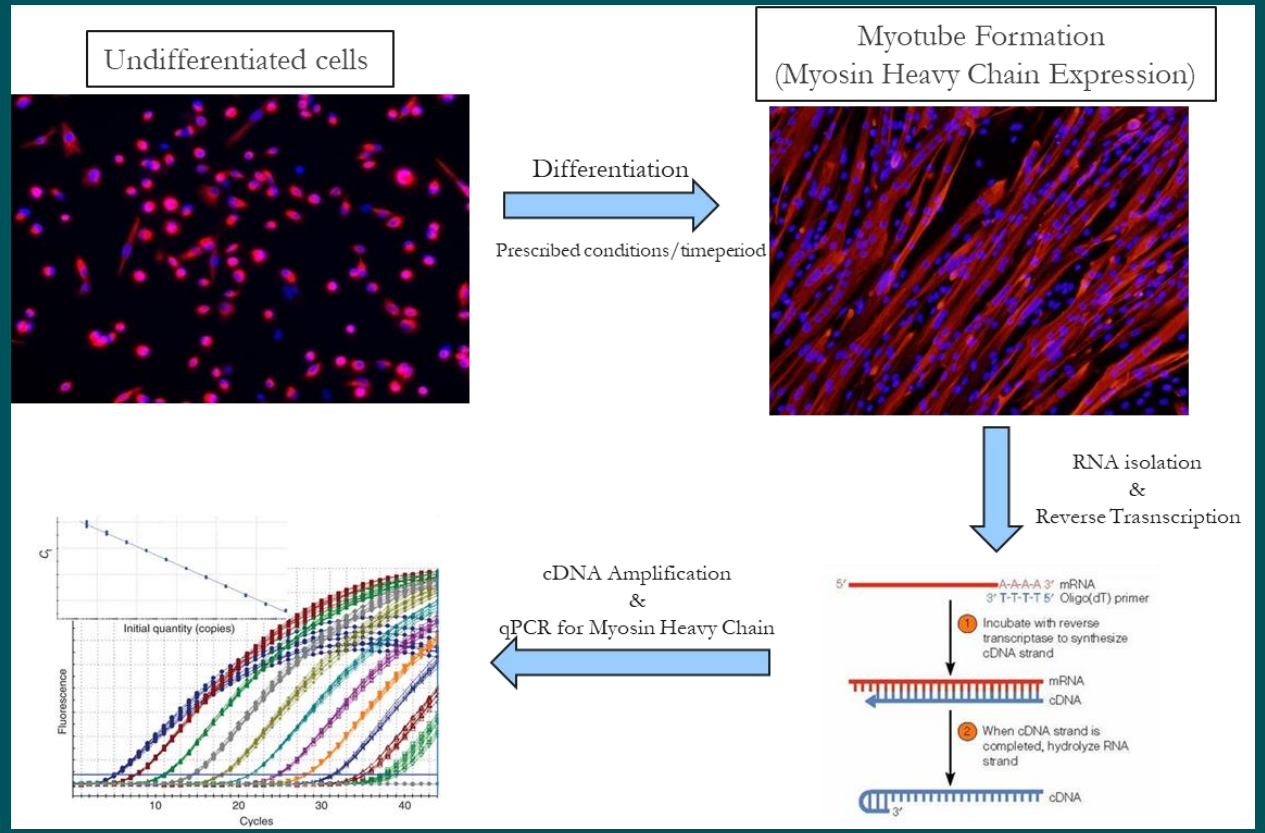






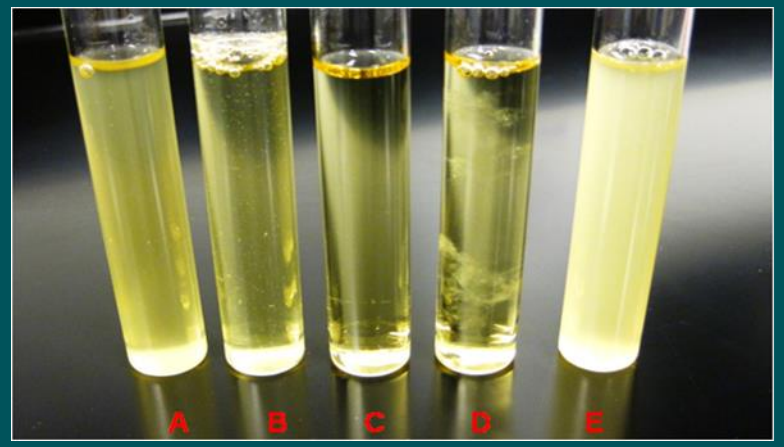
Potency testing

- Myosin expression



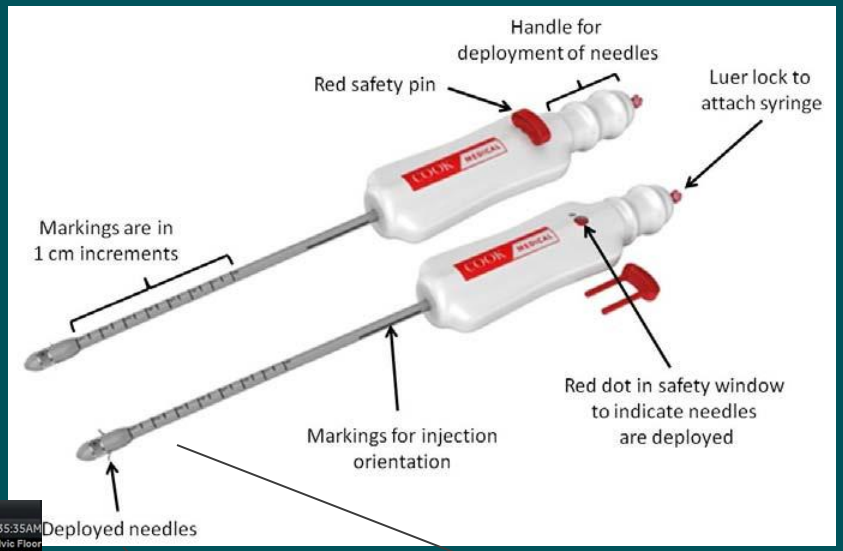
Sterility testing

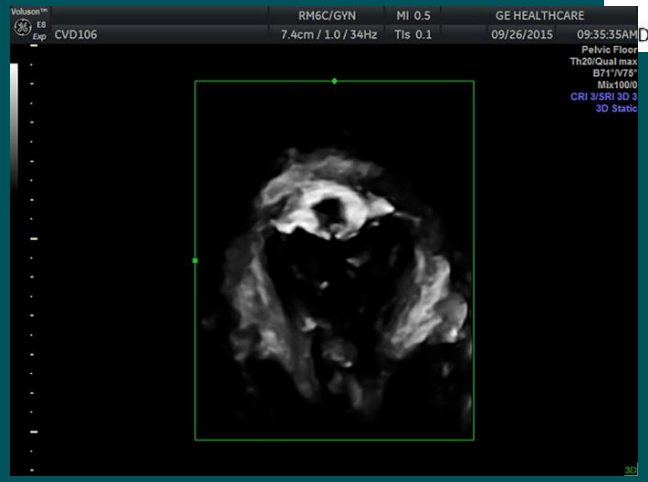
- Microbial growth
- Endotoxin and Mycoplasma testing

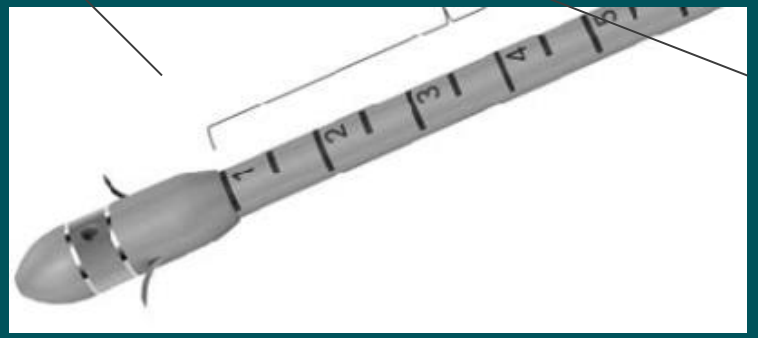


Urethral injection procedure

- Minimally invasive
- In-office
- Local anesthesia
- <15 minutes







Indication	Trial	Phase I	Phase II	Phase III	Next Anticipated Milestone
Female Stress Urinary Incontinence (SUI)	Early Phase (N=100+)	Open-labeled, dosing			Completed
	UIAD (N=148)		Placebo-controlled		Completed (partial enrollment)
	IND2 (N=289)		Placebo-controlled		Completed
	CLBT (N=200+)		Placebo-controlled		Actively Enrolling

To Date

Subjects Treated in completed Female SUI Program: ~600

Subjects Treated in ongoing CLBT confirmatory trial: 90

Subjects needed to be treated in CLBT to reach interim analysis: 20

COOK® MYOSITE

Indication	Trial	Phase I	Phase II	Phase III	Next Anticipated Milestone
	Early Phase (N=100+)	Open-labeled, dosing			Completed
Female Stress Urinary Incontinence (SUI)	**UIAD (N=148)**		Placebo-controlled		Completed (partial enrollment)
	IND2 (N=289)		Placebo-controlled		Completed
	CLBT (N=200+)		Placebo-controlled		Actively Enrolling
Fecal Incontinence	**GIFI** (N=50)	Open-labeled			Completed
		Placebo-controlled			Enrollment starting Q4 2023
Tongue Dysphagia	**TODY** (N=20)	Physician Sponsored Open-labeled			Enrollment completed
	REVIVE (N-62)	Physician Sponsored Placebo-controlled			Enrollment complete anticipated Q2 2024
Underactive Bladder	**UAB1** (N=20)	Physician Sponsored Open-labeled			Completed

To Date

Subjects Treated in completed Female SUI Program: ~600

Subjects Treated in MyoSite Sponsored Trials: >650

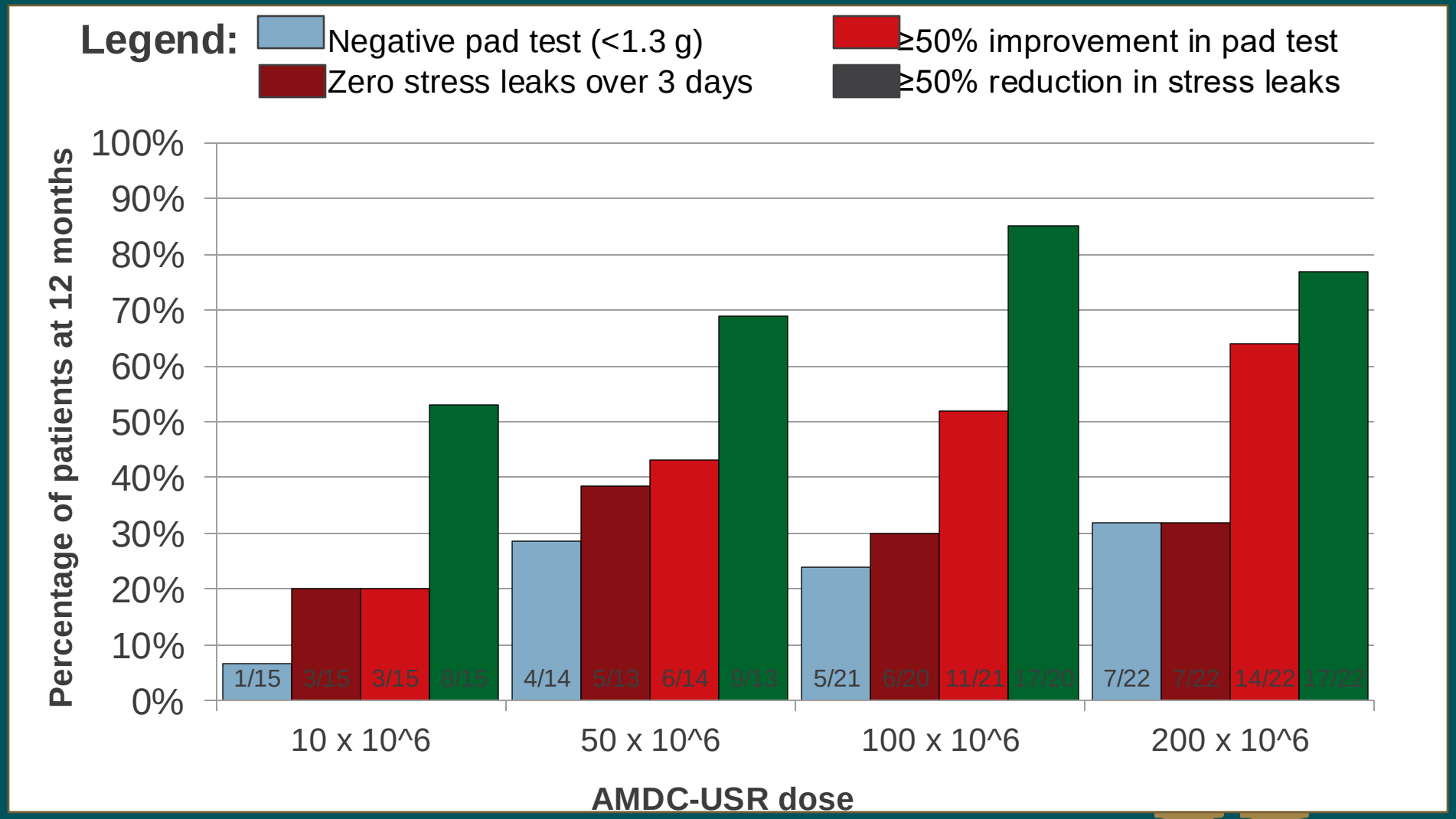
Total Subjects Treated (Including Physician-Sponsored): >700

COOK® MYOSITE

Phase I/II studies: Adverse events

	BIOPSY	INJECTION
No. of patients	82	80
No. of procedures	100	80
Reported AEs (count)	• Wound hematoma (2) • Procedural dizziness and associated responses (2) • Post procedural hemorrhage (1) • Joint swelling (1)	• Dysuria (7) • Pelvic/abdominal pain (4) • Vulvovaginal pruritus (3) • Micturition urgency (2) • Hematuria (2) • Vulvovaginal burning sensation (1) • Sensation of foreign body within urethra (1) • Urinary frequency (1) • Urinary tract infection (1)
% of patients experiencing ≥1 AE	5% (4/82)	18% (14/80)

Phase I/II: Pad tests/leaks



Conclusions from Phase I/II

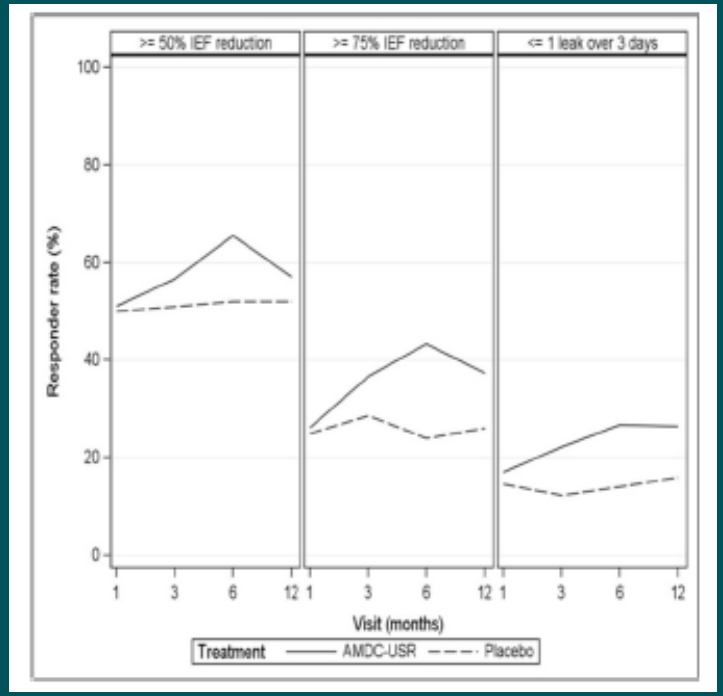
- Safety
  - Intrasphincteric injection of AMDC-USR at doses from 1 – 200 x 10^6 cells appears safe
- Efficacy
  - At 12 months, 100 and 200 x 10^6 AMDC-USR improvements > 80%

First Phase III - Canadian

- Randomized, double-blind, placebo-controlled trials assessing the safety and efficacy of 150 x 10^6 AMDC-USR for treatment of SUI

First Phase III - Results

- 143 patients (50 placebo, 93 AMDC-USR)
- Trial halted at 143 enrollment due to high placebo rate
- Lessons learned?



First Phase III – Primary endpoint

ORIGINAL DESIGN ELEMENT	Primary Composite Endpoint defined success as: • ≥50% incontinence reduction, or • ≥50% improvement in 24-hour pad test, or • ≥50% improvement in in-office pad test
LESSONS LEARNED	• >80% responder rate - AMDC-USR and placebo • Composite endpoint too liberal • Pad tests may be confounded
IMPACT ON FUTURE STUDY DESIGN	Optimal endpoint may encompass: • ≥50% reduction, • ≥75% reduction, • ≤1 stress leaks/3 days

First Phase III – Placebo rate

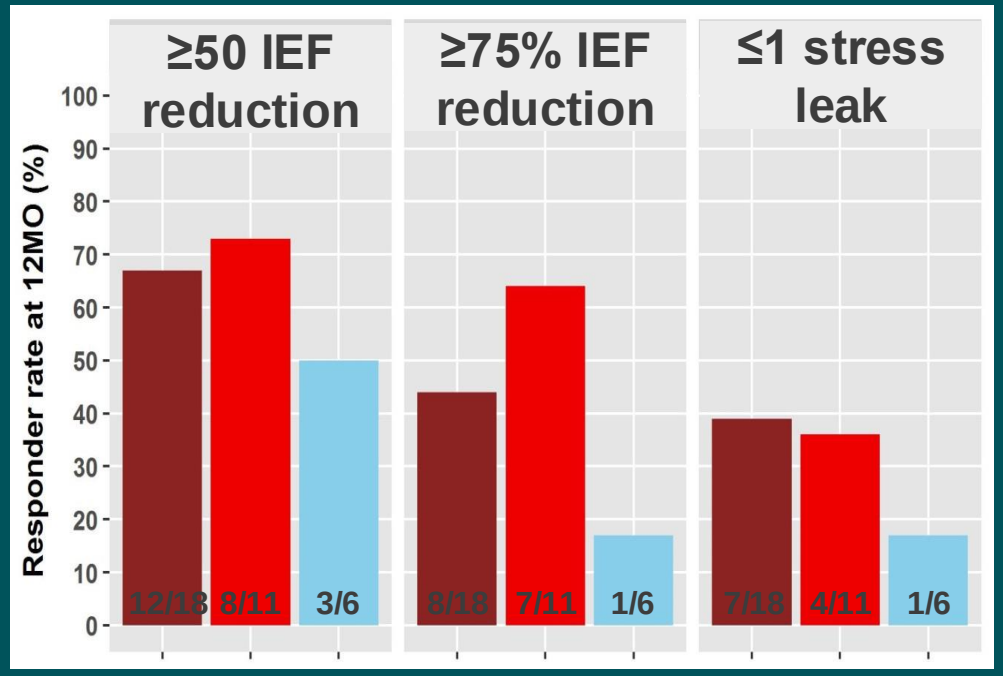
ORIGINAL DESIGN ELEMENT	Power calculation assumed 30% responder rate for placebo
LESSONS LEARNED	• >80% placebo responder rate for composite endpoint • Placebo responder rates lower with IEF reduction endpoints
IMPACT ON FUTURE STUDY DESIGN	Placebo responder rate adjusted for IEF reduction endpoints

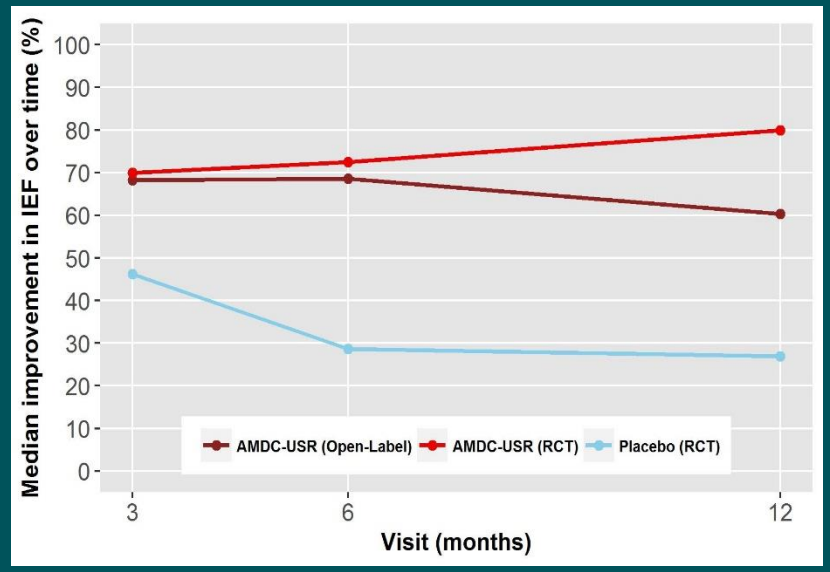
First Phase III – Hypermobility

ORIGINAL DESIGN ELEMENT	Urethral hypermobility not assessed
LESSONS LEARNED	• AMDC-USR designed to augment sphincter function • Patients with prior incontinence surgery: outcomes for ≥50% reduction favor AMDC-USR over placebo
IMPACT ON FUTURE STUDY DESIGN	• Exclude patients with notable urethral hypermobility • Patients with recurrent or persistent SUI after incontinence surgery may be optimal candidates

Post hoc analysis

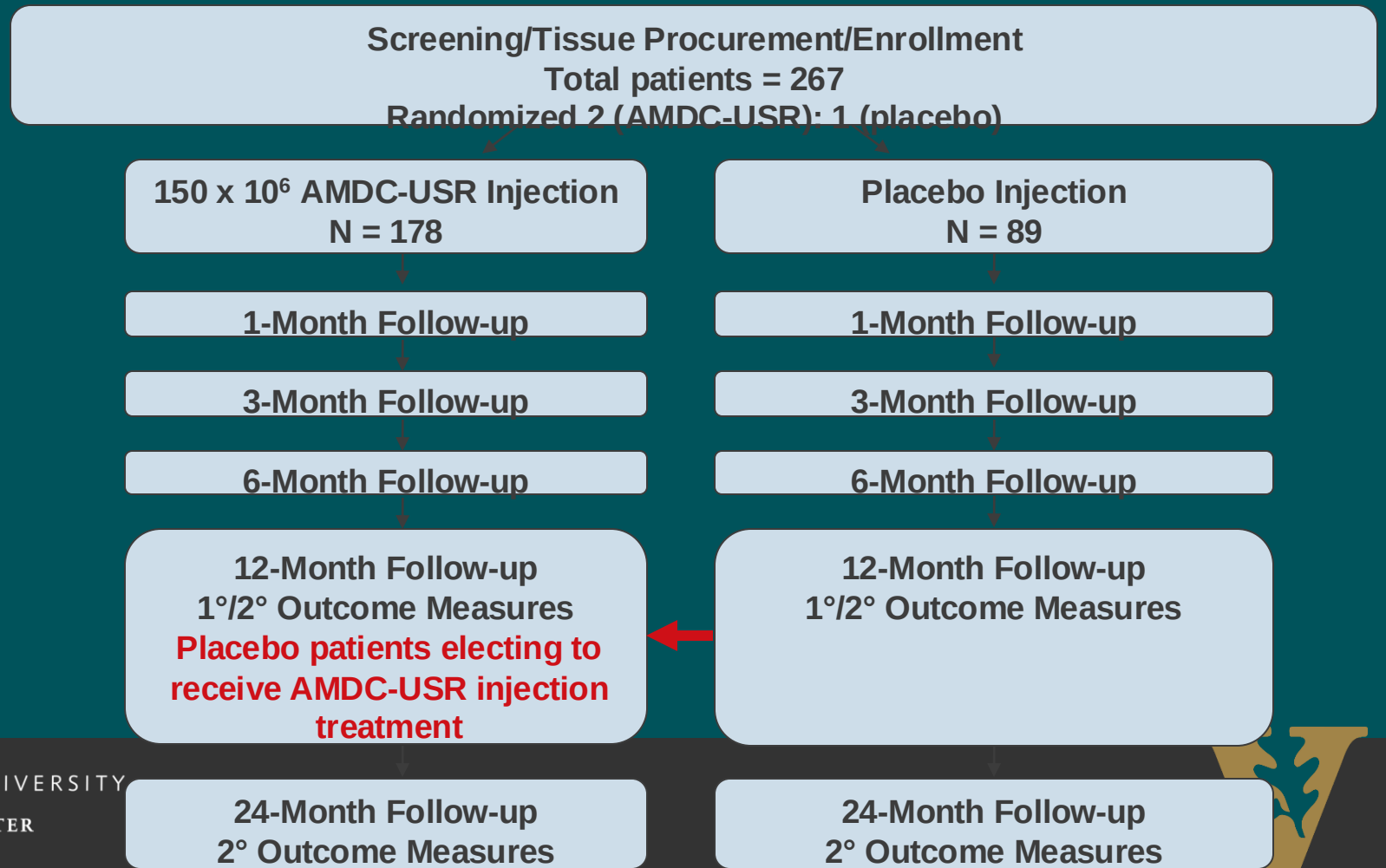
- Persistent or recurrent SUI after prior incontinence surgery
- 38 patients in Phase I/II/III trials



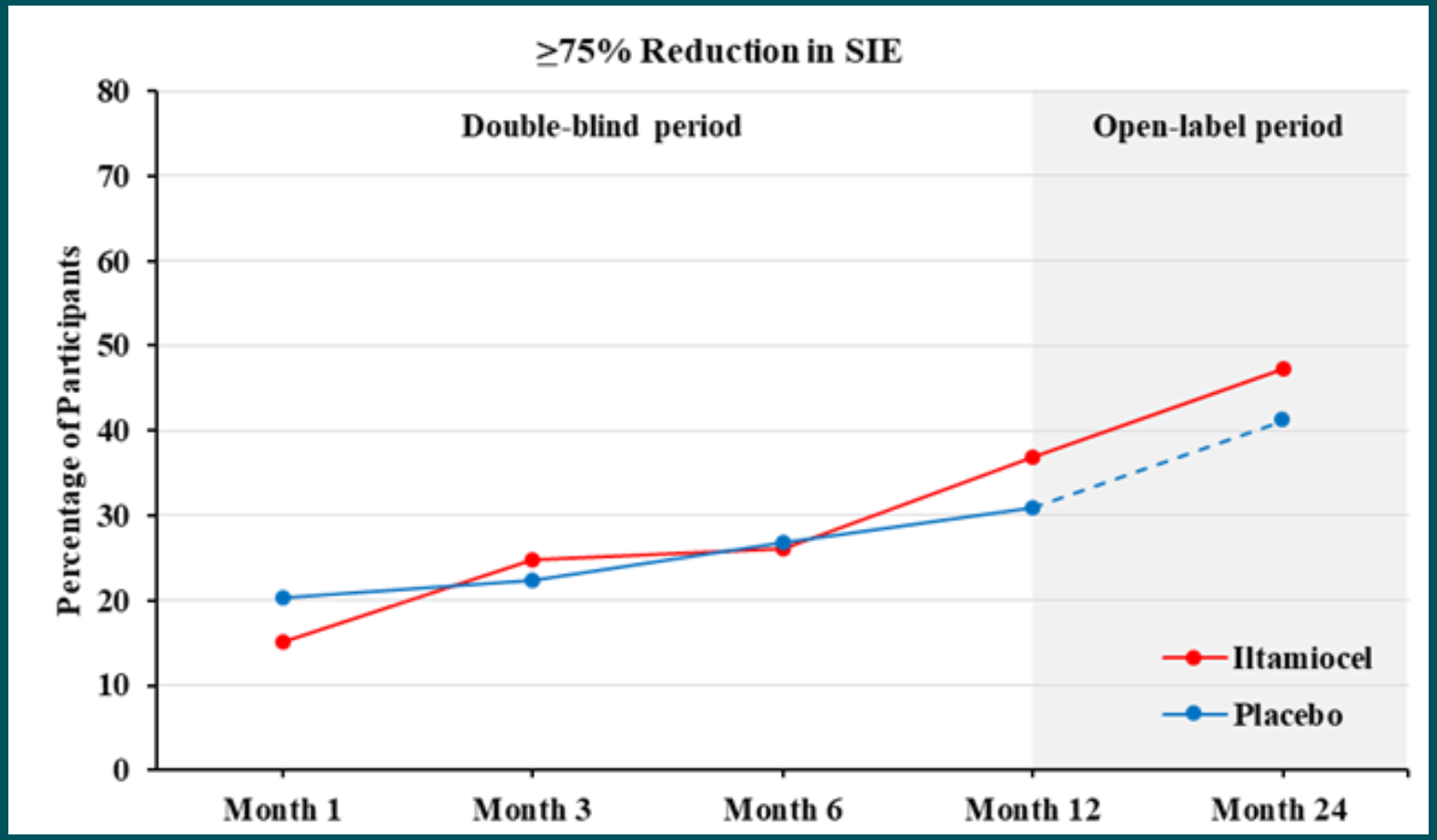


Second Phase III

- Randomized, double-blind, placebo-controlled trials assessing the safety and efficacy of 150 x 10^6 AMDC-USR for treatment of SUI in women

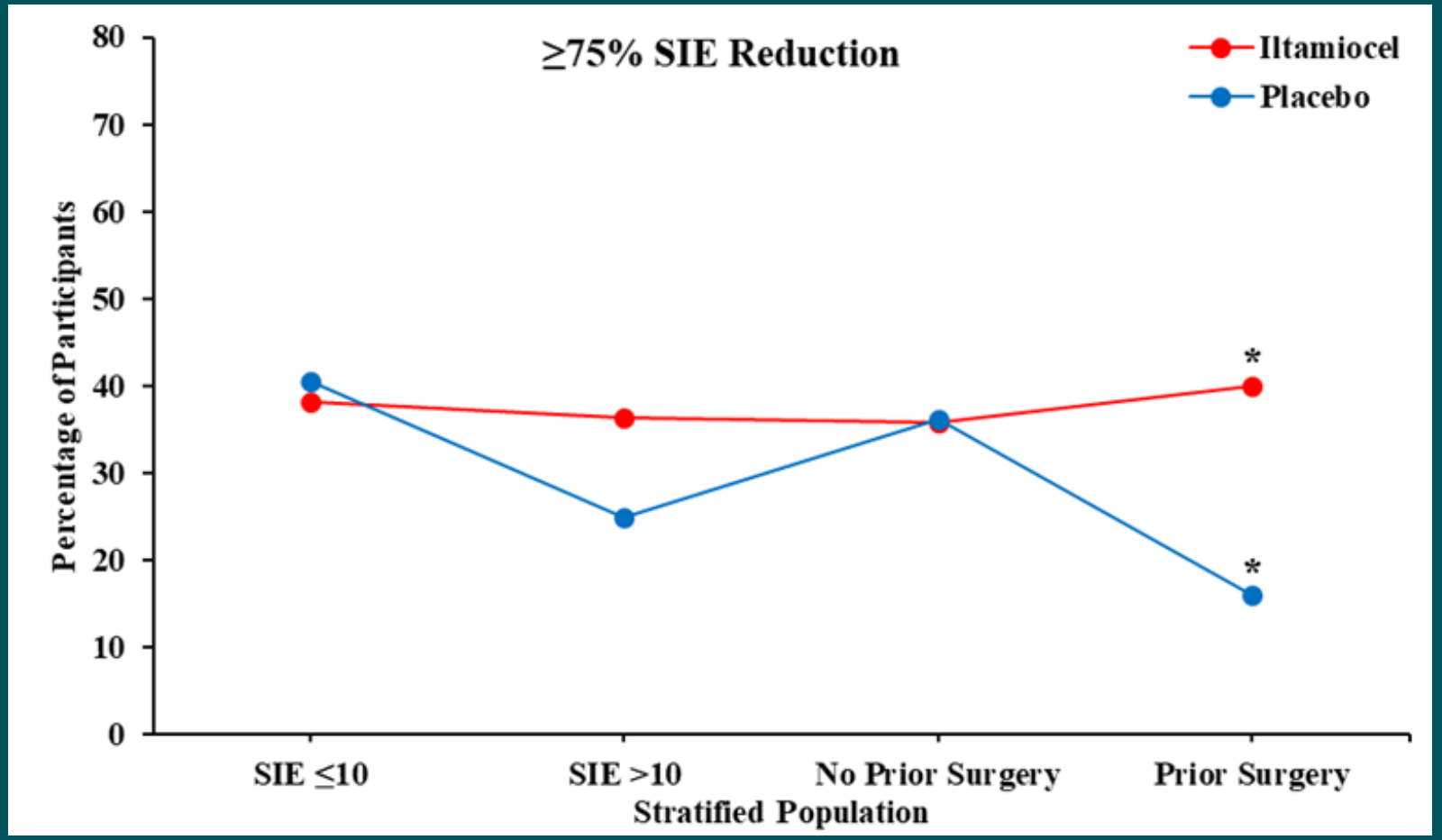


≥75% SIE reduction



Kaufman et al. Neurourol Urodyn 2024

Stratified population



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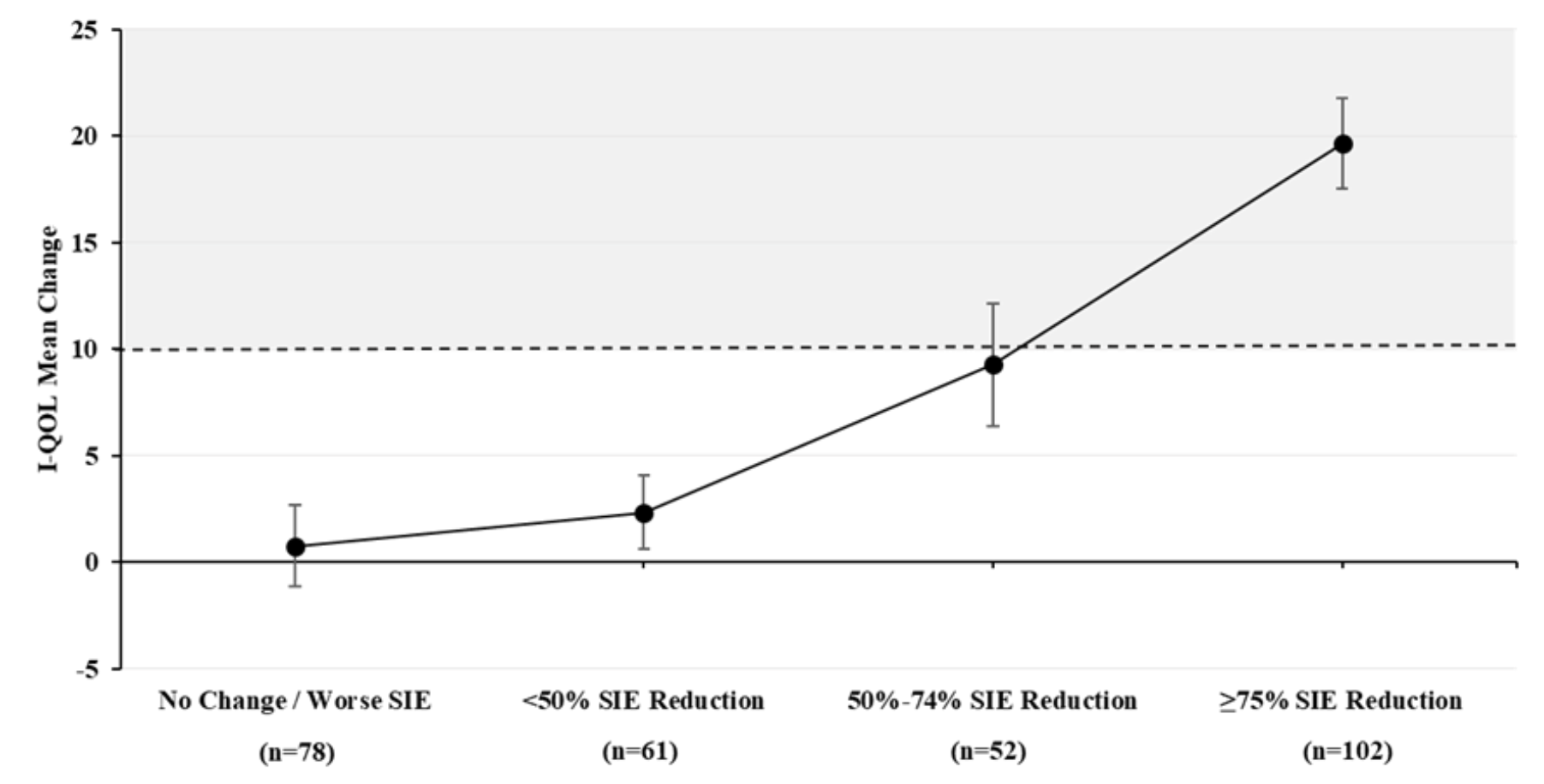
Quality of life



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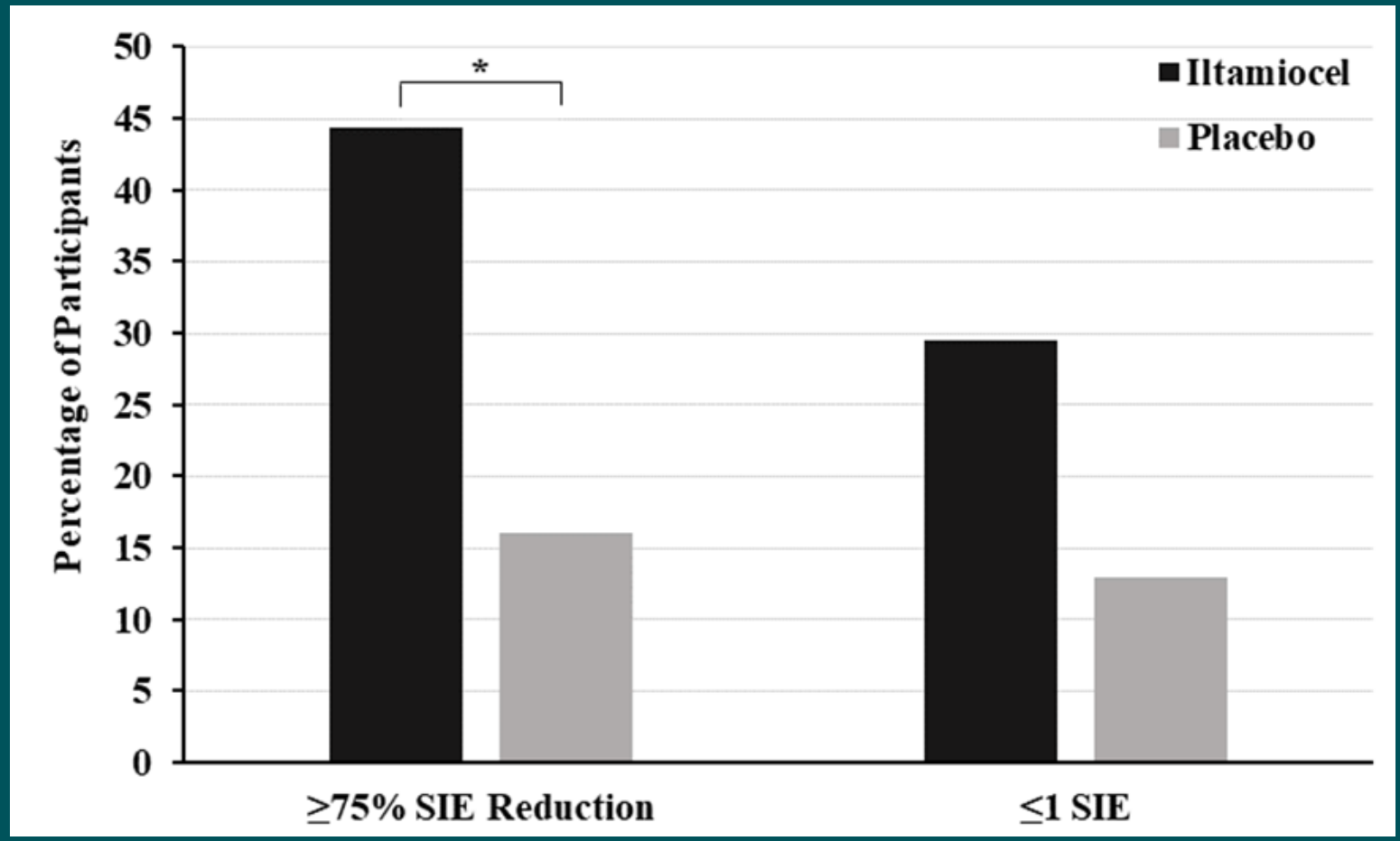
Second Phase III

- Single injection of AMDC is a safe and durable through 2 years
- High variability in placebo response rates impacts generalizability
- QOL and symptom scores significantly correlated with changes in SEIF
- Prior surgery, higher number SUI episodes
  - Clinically meaningful ≥ 75% SIEF reduction compared with placebo
  - These populations may be ideally suited for this therapy

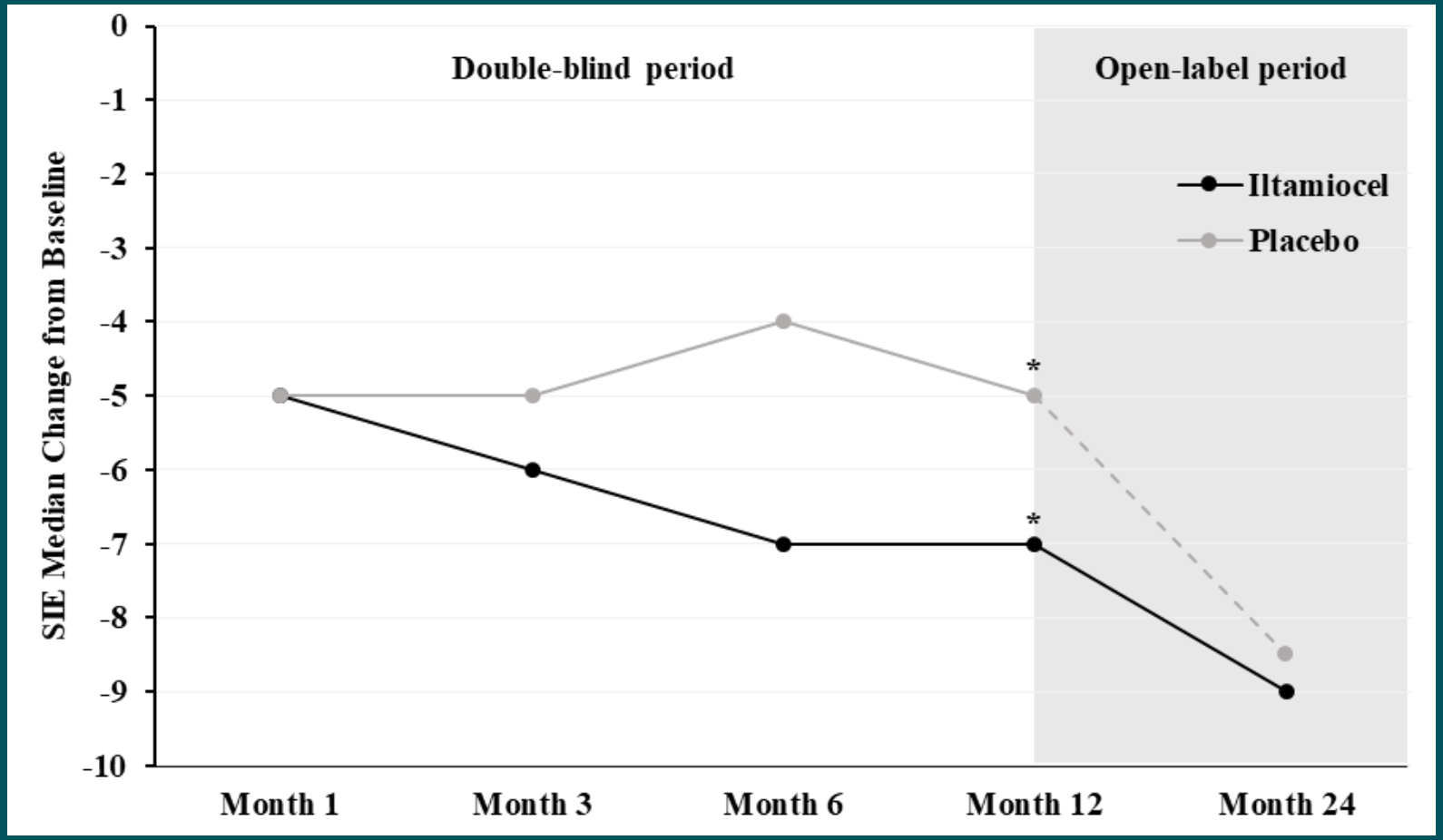
Kaufman et al. Neurourol Urodyn 2024

Pooled data – prior incontinence surgery



Kaufman et al, ICS abstract 2021

Pooled data – prior incontinence surgery



Kaufman et al, ICS abstract 2021

RMAT designation

- Regenerative Medicine Advanced Therapy
  - Cell therapies, tissue engineering products
- The drug is intended to treat, modify, reverse, or cure a serious or life-threatening disease or condition
- Unmet medical needs for such disease or condition
- AMDC received RMAT designation December 2020

Current SUI initiative

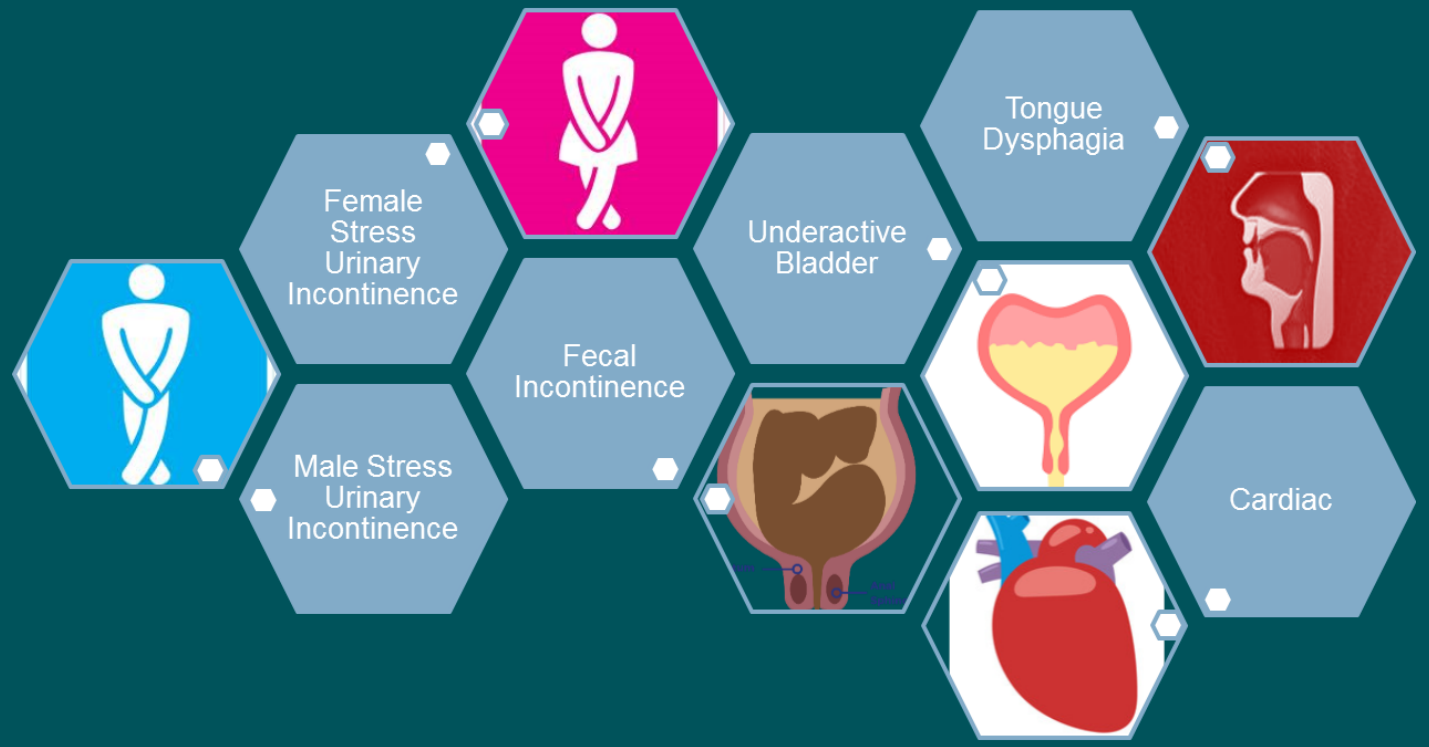
CELLEBRATE Study Overview

Two-stage, double-blind, randomized, placebo-controlled, multicenter, adaptive design study to evaluate the efficacy of AMDC in prior surgery patients

Phase III *Pivotal trial*	**130 – 260** *Subjects enrolled*	**1:1** *Treatment : placebo randomization*
25 *Number of trial sites*	 *Site locations*	**1 year** *Primary endpoint*

Additional initiatives

- Phase II pilot study for male post-prostatectomy incontinence
- Underactive bladder
  - Compassionate use patient
  - Phase I trial
- Fecal incontinence
  - Current Phase III



Compassionate use UAB

Table 1 Cystometry results

	Baseline (mL)	3 months post-injection (mL)
First desire	711	365
Strong desire	823	450
Max. cystometric capacity (MCC)	844	663

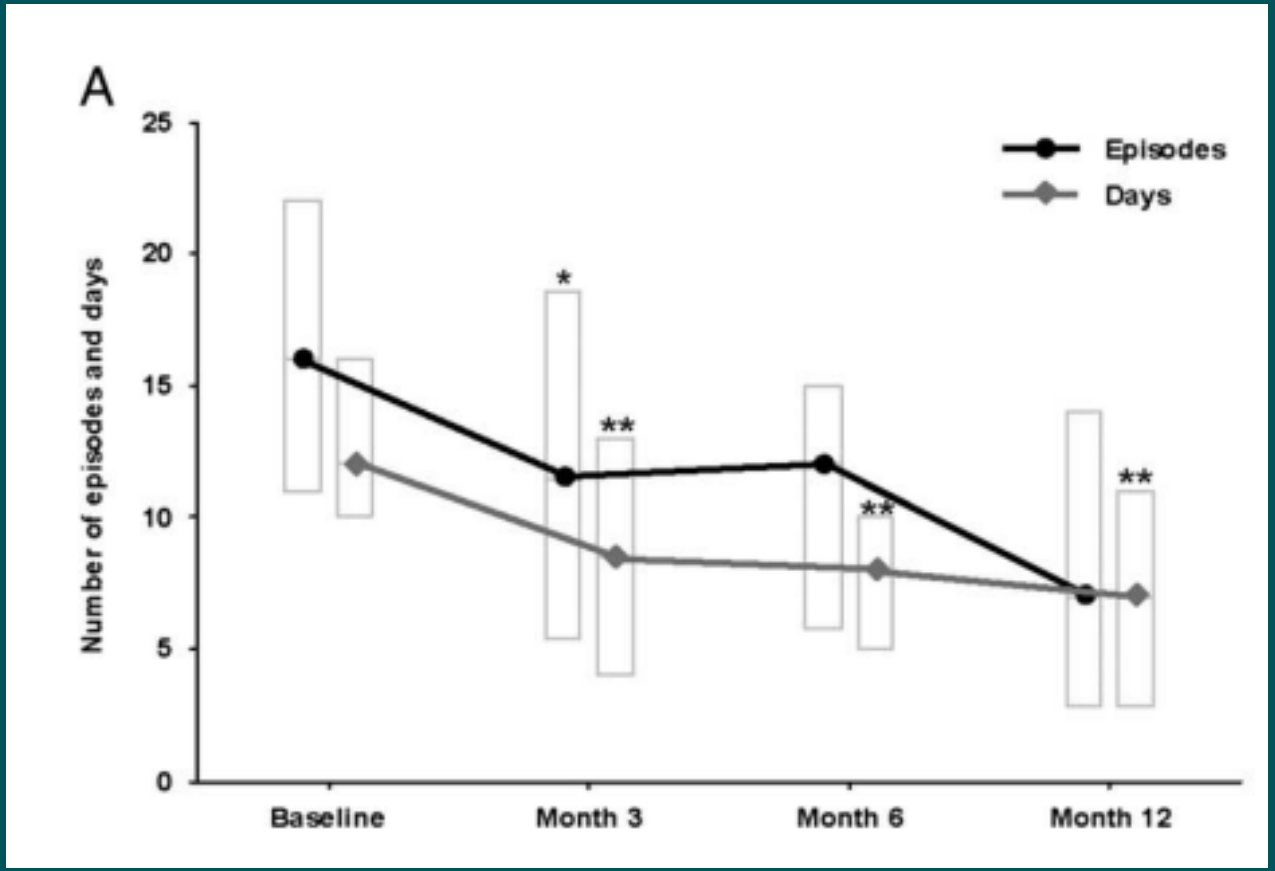
P. Levanovich et al. (2015) Int. Urol. Nephrol. 47: 465-467

AMDC UAB clinical trial

- Prospective, open-label, Phase I evaluating the safety and efficacy of AMDC for treatment of chronic Underactive Bladder
- 20 participants
- PVR > 150 ml
- Efficacy data from UAB questionnaires
- ClinicalTrials.gov NCT02463448

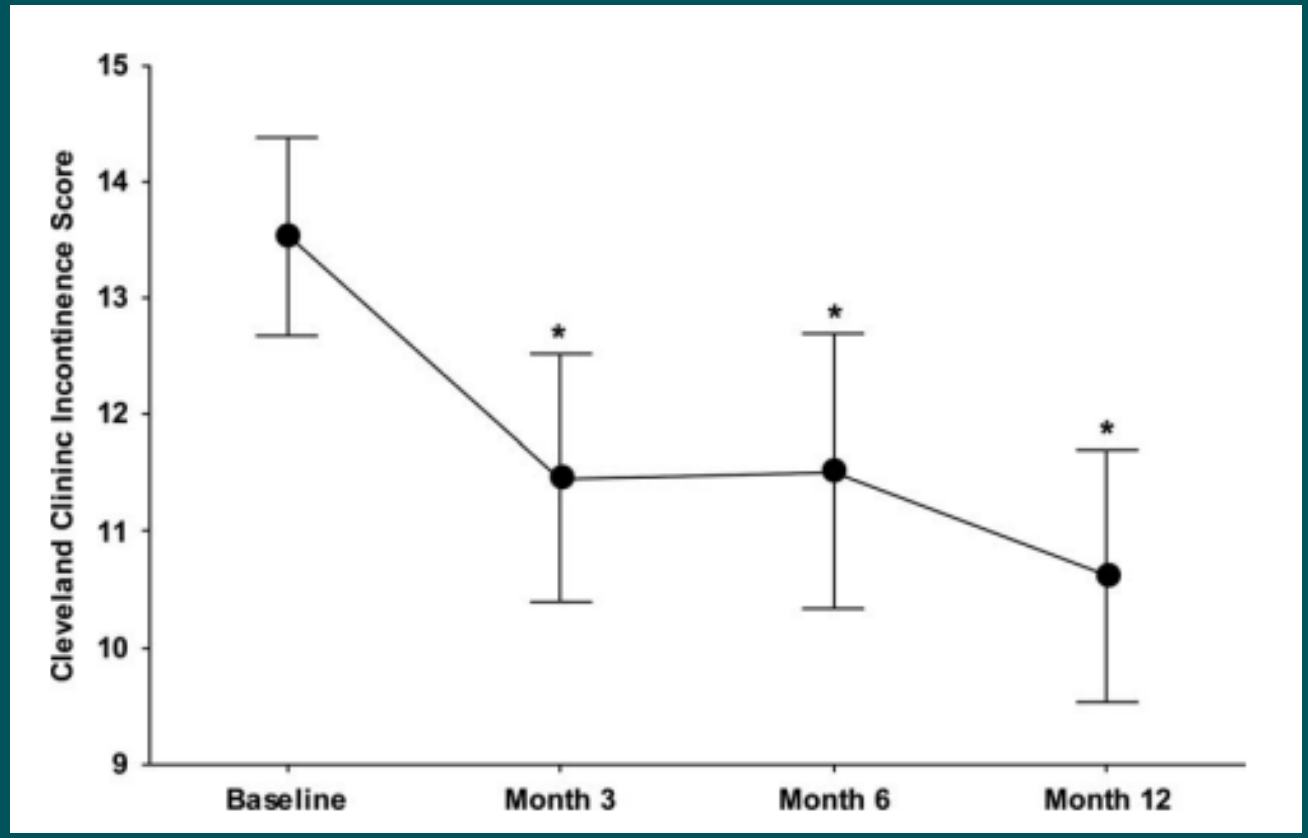
Clinicaltrials.gov

Iltamiocel for fecal incontinence



Knowles CH, et al. Ann Surg. 2023 Dec 1;278(6):937-944. PMID: 37144409

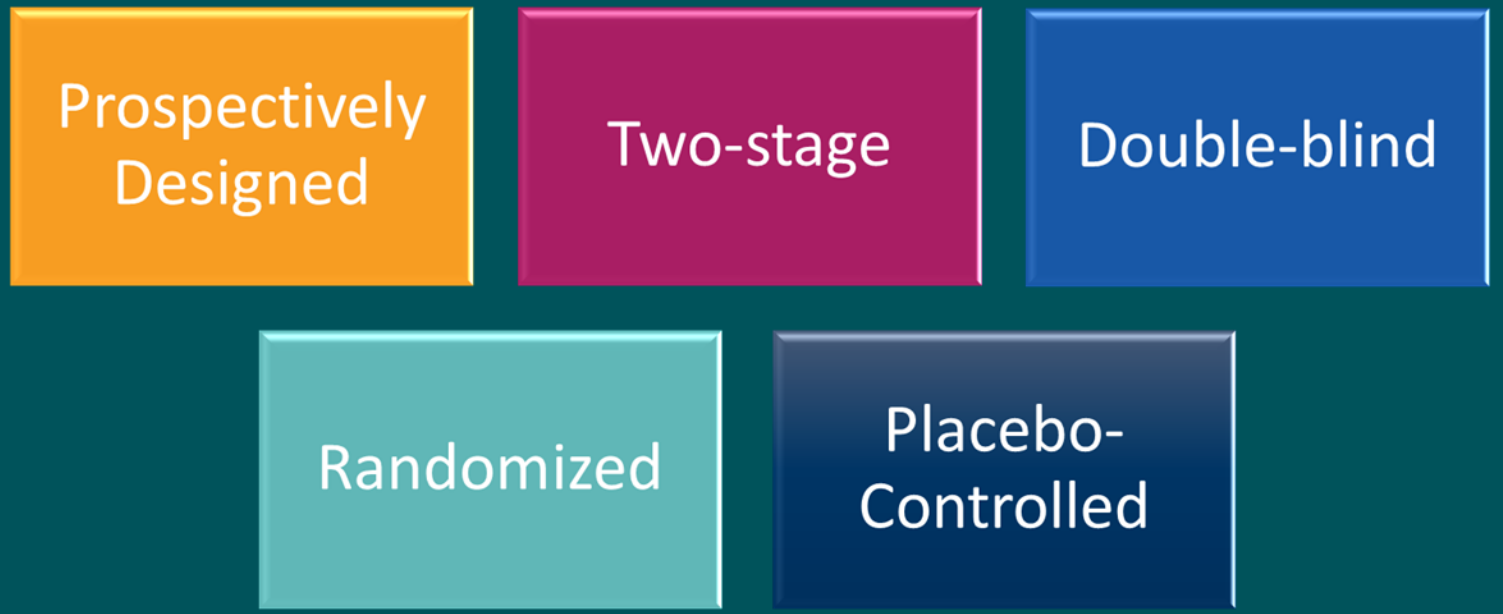
Iltamiocel for fecal incontinence



Knowles CH, et al. Ann Surg. 2023 Dec 1;278(6):937-944. PMID: 37144409

DigniFI Phase III fecal incontinence

- Females with obstetric anal sphincter injuries OASI(S)



Clinical Trials.gov NCT05776277

DigniFI Phase III fecal incontinence

Primary:

- To evaluate the efficacy of a single administration of iltamiocel (300 x 10^6 cells) in the reduction of fecal incontinence episode frequency (FIEF) in adult female participants with chronic FI at Month 12

Secondary:

- To evaluate clinically meaningful improvement in QOL and the extent of reduction of FIEF after a single administration of iltamiocel in adult female participants at Month 12
- To determine the safety of a single administration of iltamiocel (300 x 10^6 cells) in the treatment of chronic FI in adult female participants at Month 12

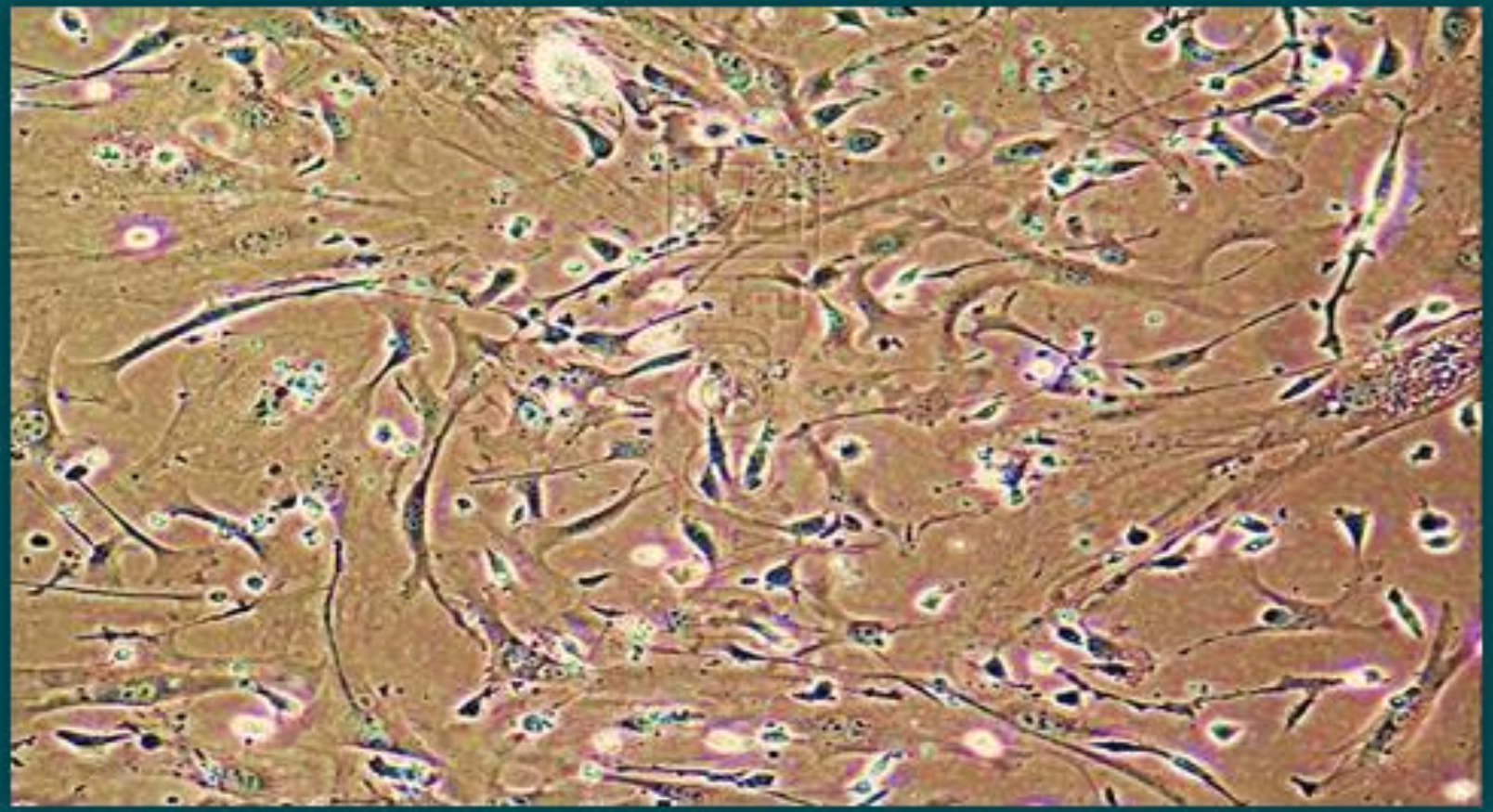
Clinical Trials.gov NCT05776277

Mission

Making regenerative medicine a part of everyday medicine.

COOK MYOSITE

Thank you!



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