Underactive Bladder Modeling

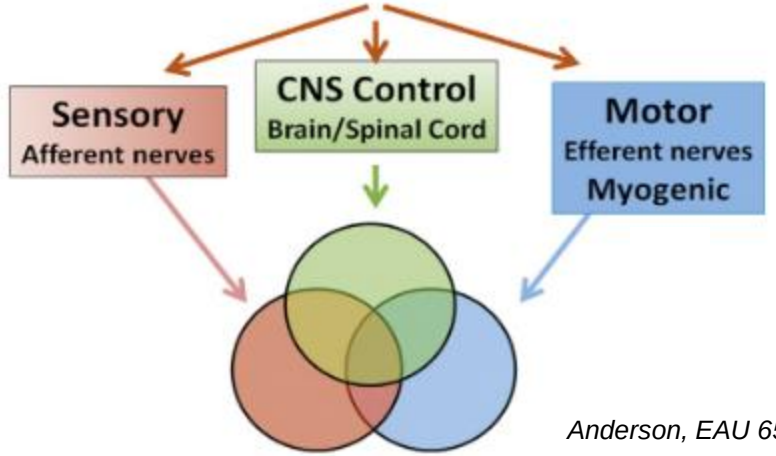
Tony Kanai

University of Pittsburgh

CURE-UAB 2nd International Congress on Underactive Bladder
Session 1: Pathophysiology of UAB

Bladder Underactivity

Potential Causes



Anderson, EAU 65:399-401, 2014

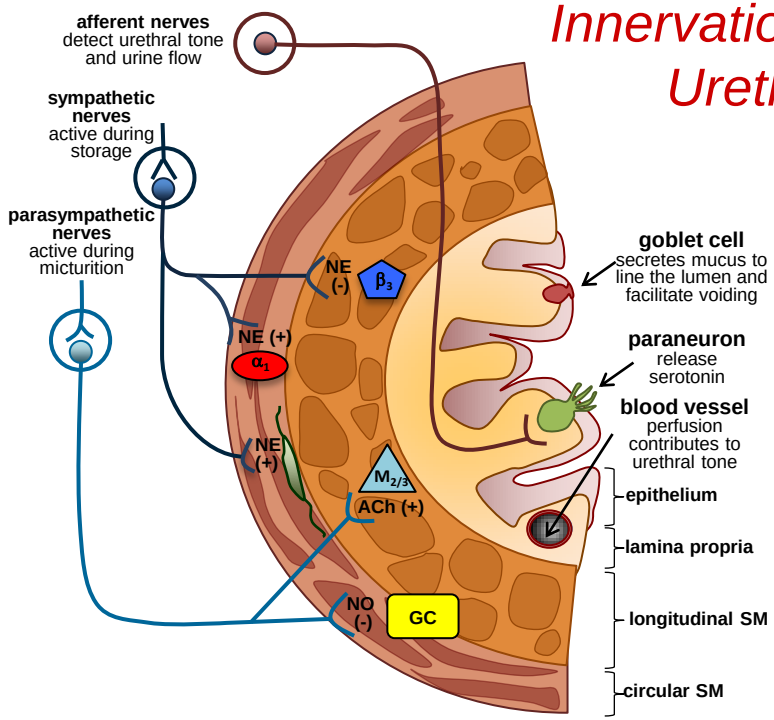
ICS Definitions

- *A contraction of reduced strength and/or duration, resulting in prolonged bladder emptying and/or failure to achieve complete bladder emptying within a normal time span based on a urodynamic diagnosis.*
- ***UAB** covers the general condition irrespective of whether the cause is afferent dysfunction, lack of CNS control, or the detrusor itself. In terms of a syndrome/symptom-based diagnosis the proposed term is **UAB syndrome**.*

Current Therapeutic Approaches

1. ***Intermittent or Indwelling Catheterization***—potential for urinary tract infections
2. ***Perigenital stimulation***—*may reflexly contract the detrusor*
3. ***Muscarinic receptor agonists—***contract the detrusor (*e.g.*, bethanechol)
4. ***Cholinesterase inhibitors***—prevent the breakdown of ACh (*e.g.*, distigmine)
5. ***α_1-adrenergic receptor antagonists***—relax the urethra (*e.g.*, doxazosin)

Innervation of the Urethra



Animal Models for Studying UAB

typical and non-typical

1. ***Aging Model**: Mice and rats 18-24 months of age*

2. ***Diabetic Model**: Type 1 and type II diabetic mice and rats*

3. ***Obstruction and Overdistension:** PBOO and hydrodistension (30 min at 120 cmH_2O)*

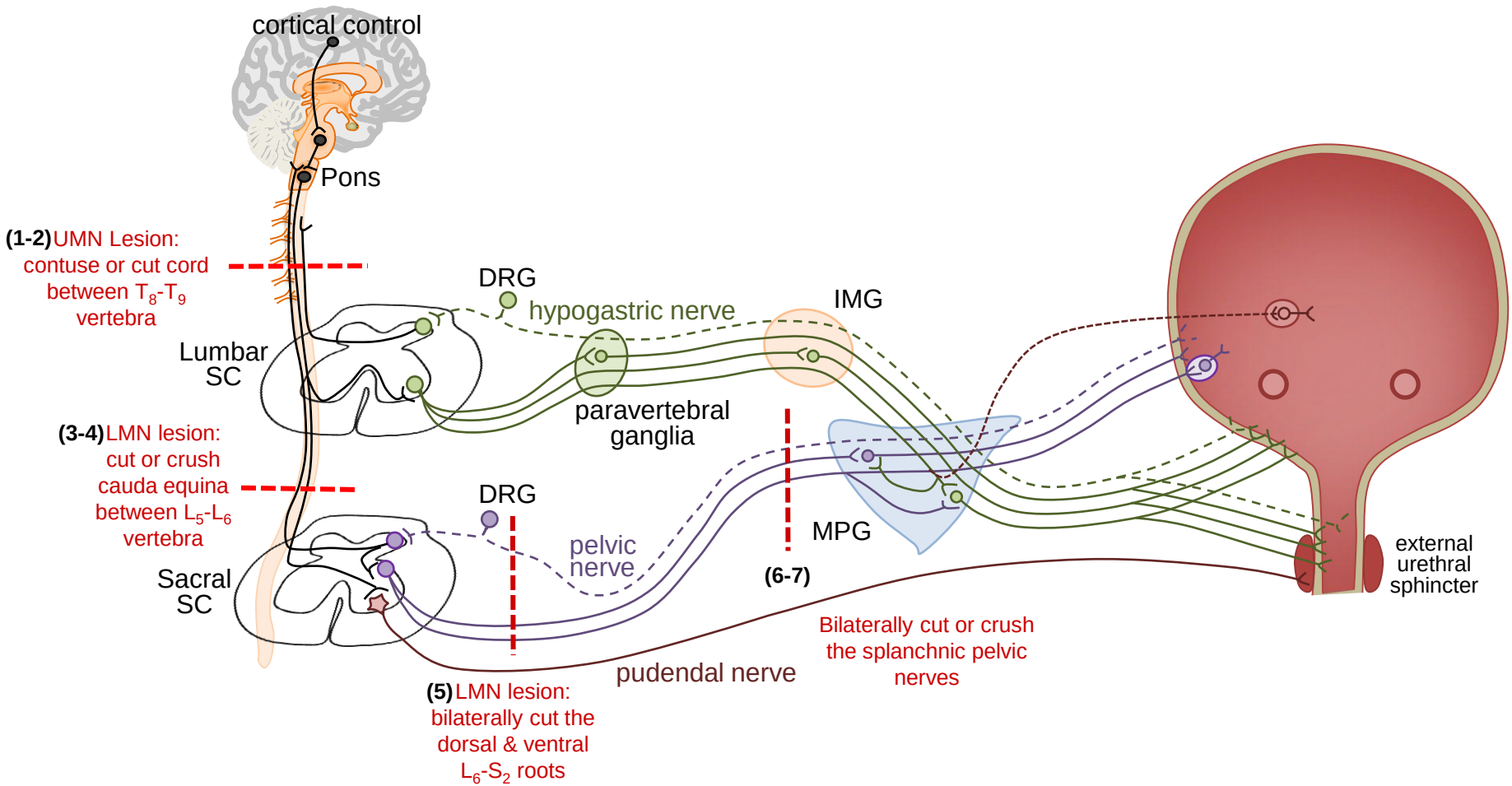
4. ***Ischemia and Oxidative Stress**: Ischemia/reperfusion and H_2O_2 installation*

5. ***Neurogenic**: Pelvic nerve and spinal cord injury*

6. ***Genetic Mutations**: FGFR2$^{-/-}$ and FGFR1/2$^{-/-}$ mice*

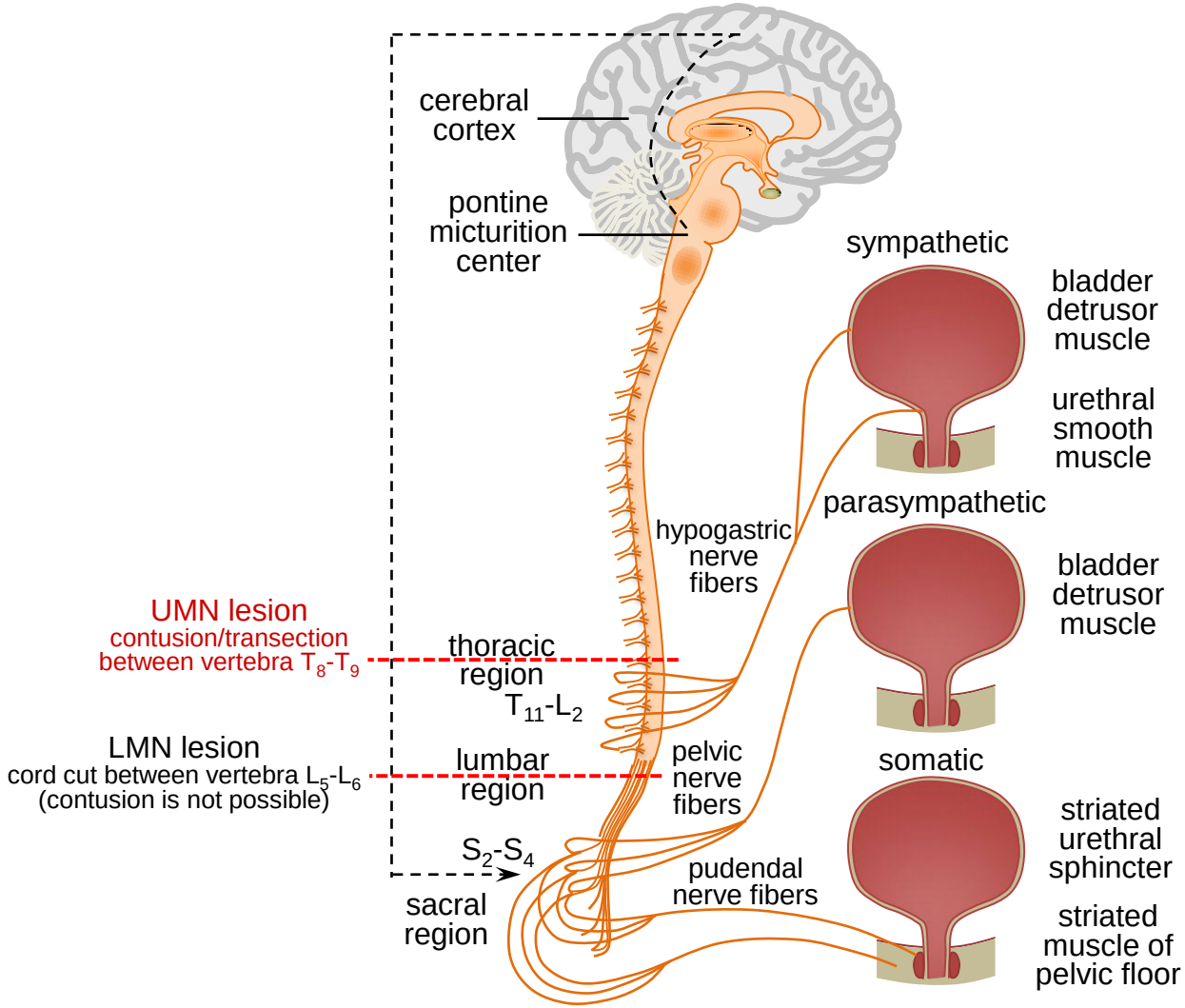
Innervation of the Bladder

different spinal cord and nerve injury models



Upper Motoneuron Lesion Models

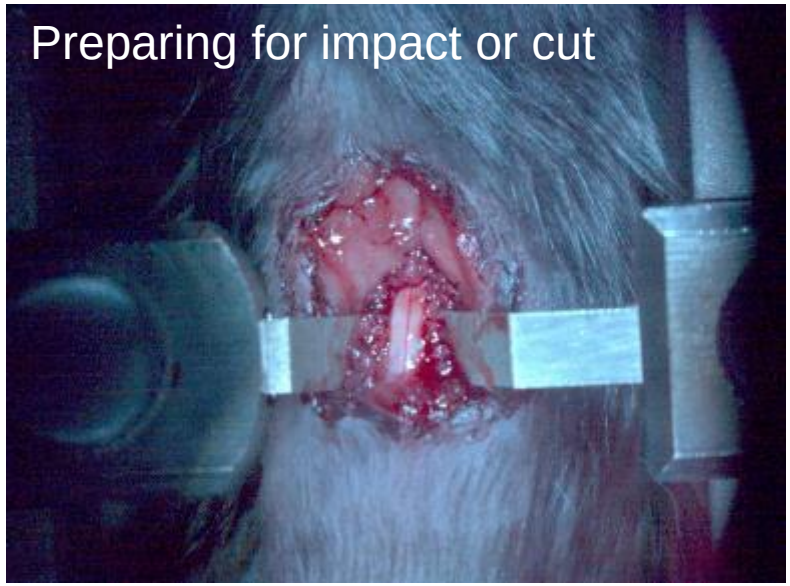
contusion and transection

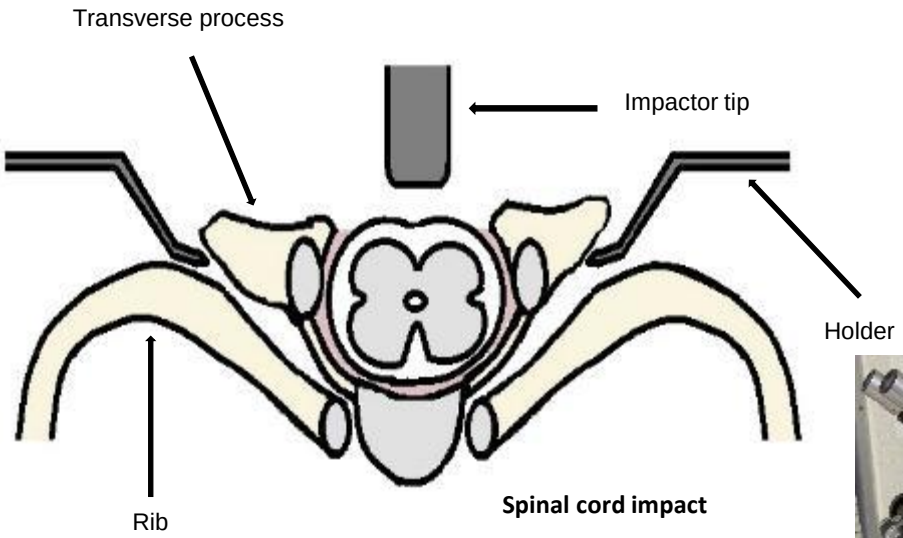


Kanai and Andersson, J Urol 183:1288-1295, 2010

UMN Contusion & Transection Models

cannot impact the cauda equina



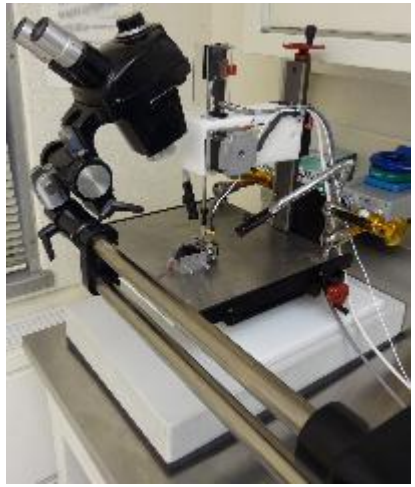


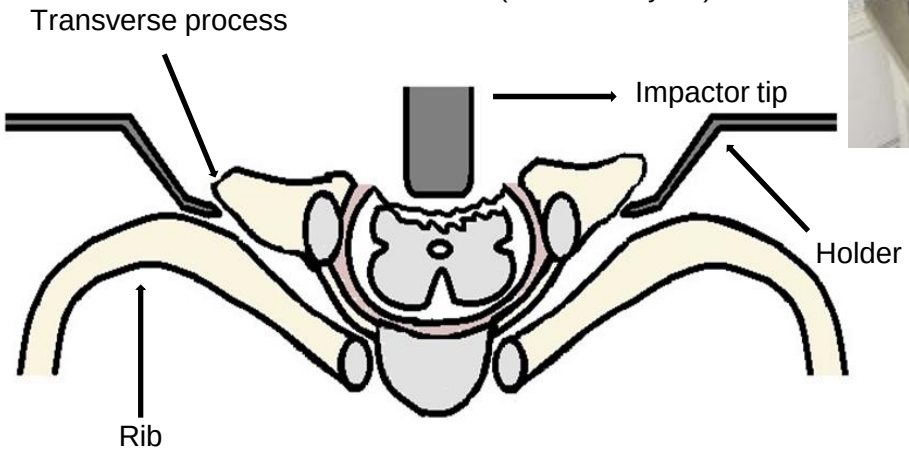
Spinal cord impact

Mice: 30 – 70 kdynes

30 kdynes	mild SCI
50 kdynes	moderate SCI
70 kdynes	severe SCI

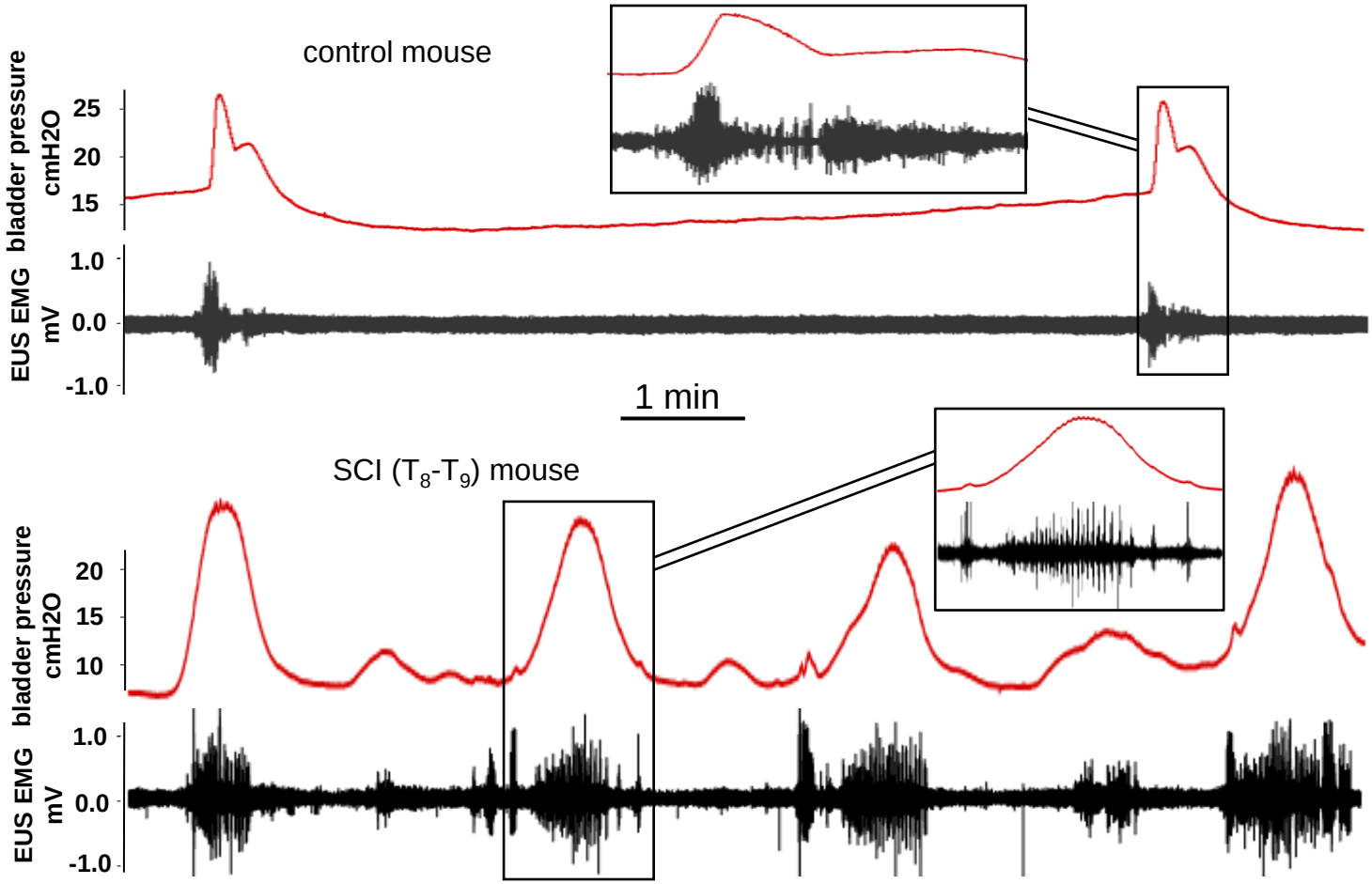
Rats (100 - 200kdynes)





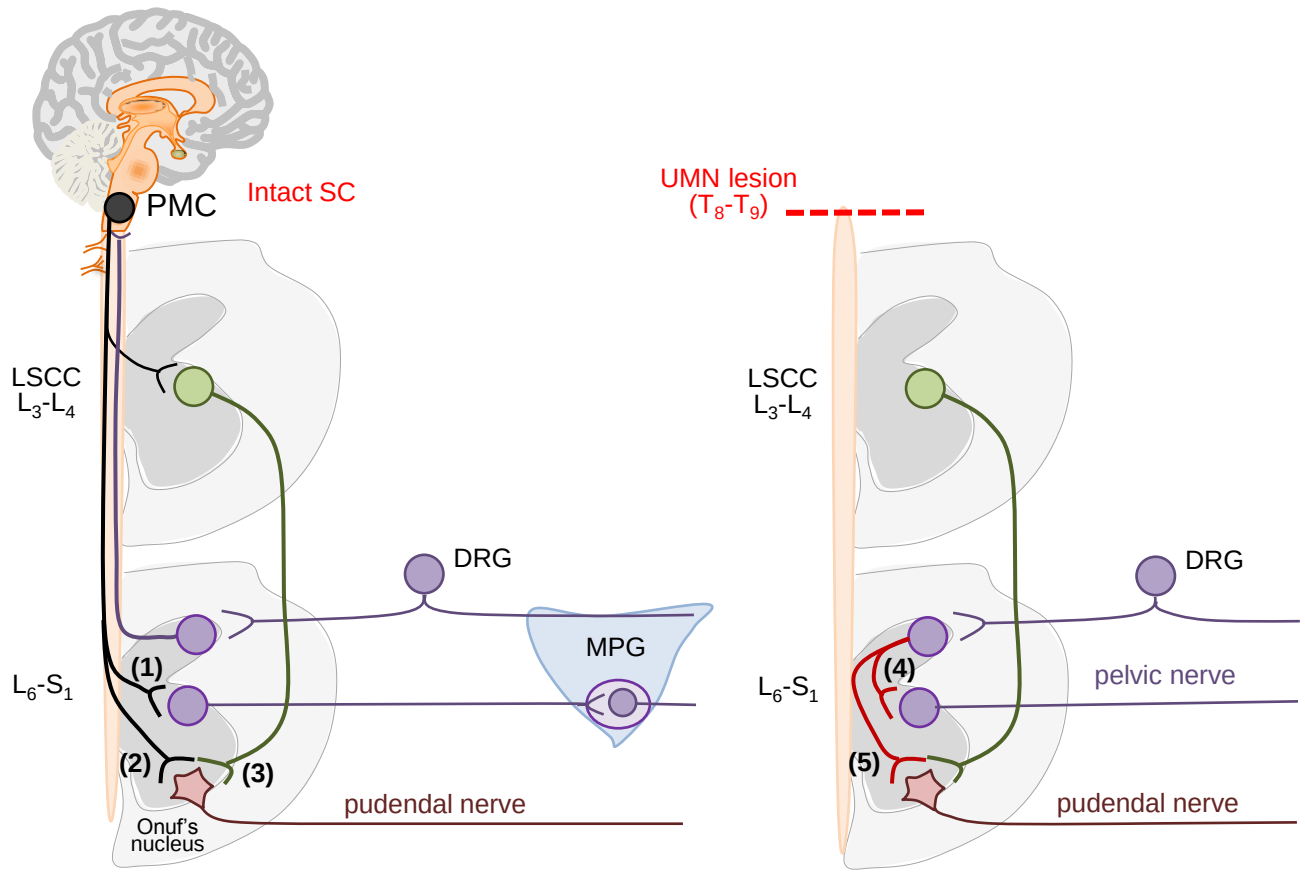
SCI-induced Detrusor-Sphincter-Dyssynergia

enhancement of tonic activity during phasic bursting

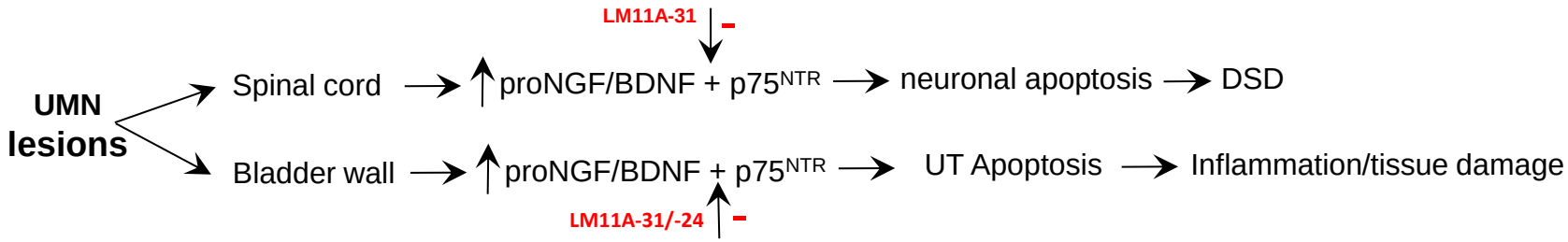


Detrusor-Sphincter-Dyssynergia

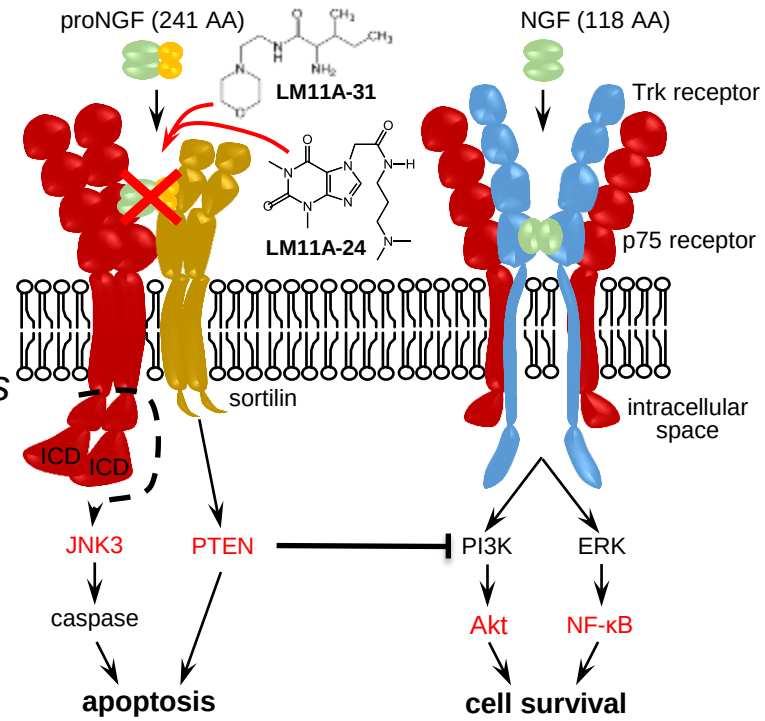
circuity changes that may be responsible



UMN Lesions and Proneurotrophins



p75 neurotrophin receptor (p75NTR) signaling pathways



Spinal Cords: 8 Weeks after UMN Lesions

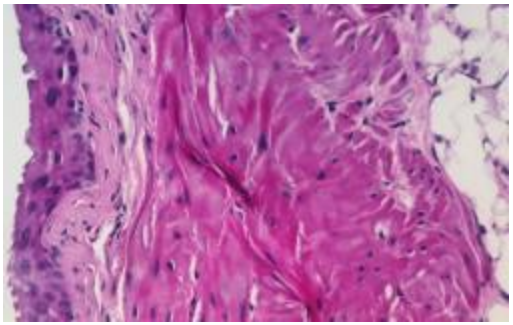
effects of centrally acting LM11A-31 versus peripherally acting LM11A-24

A. Control **B.** LM11A-31 **C.** LM11A-24

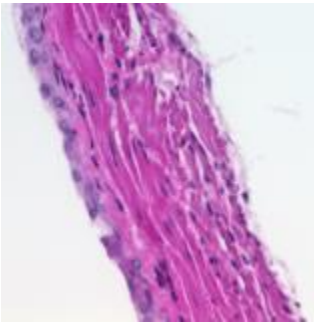
Bladder Walls: 1 & 10 Days after an UMN Lesion

benefits of LM11A-31

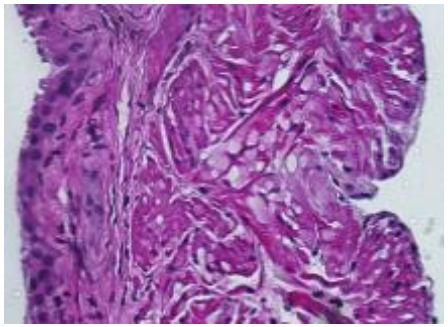
control mouse bladder



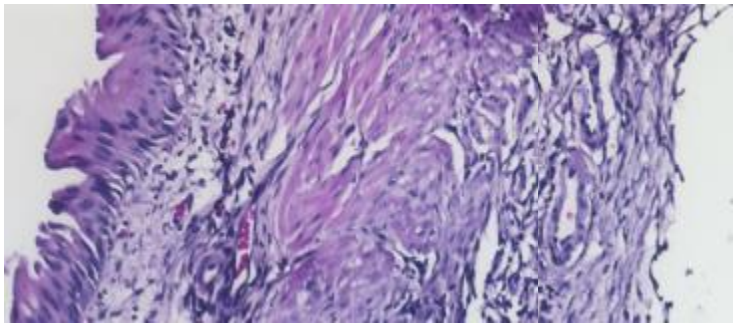
1 day after T_8-T_9 SCI



1 day after SCI + LM11A-31

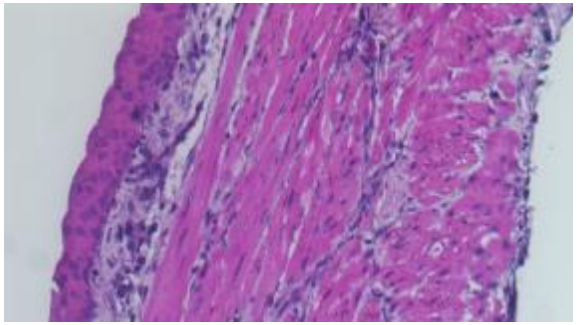


10 days after SCI



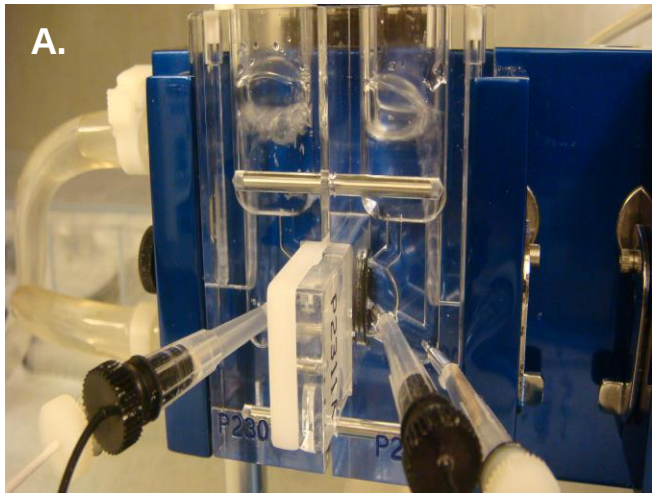
n ≥ 3

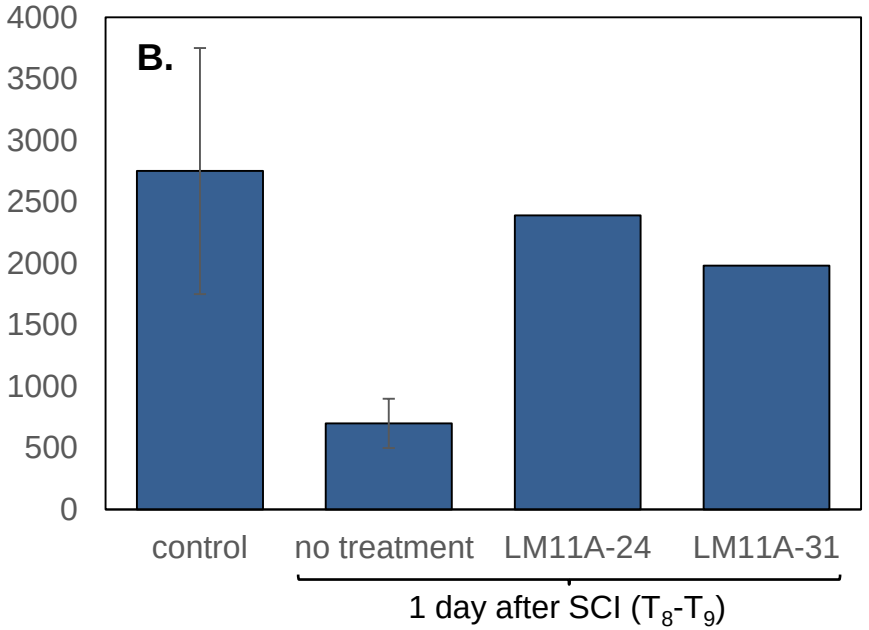
10 days after SCI + LM11A-31



Transepithelial Resistances (TER)

1 day after UMN lesions, both LM11A-24 and LM11A-31 preserved barrier function

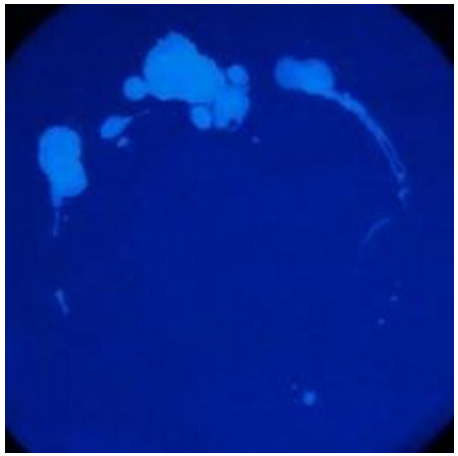




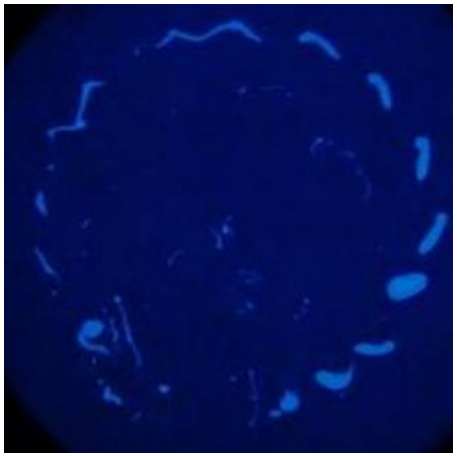
LM11A-31 Improves DSD and Motor Function

mice treated with LM11A-24 do not show improvement

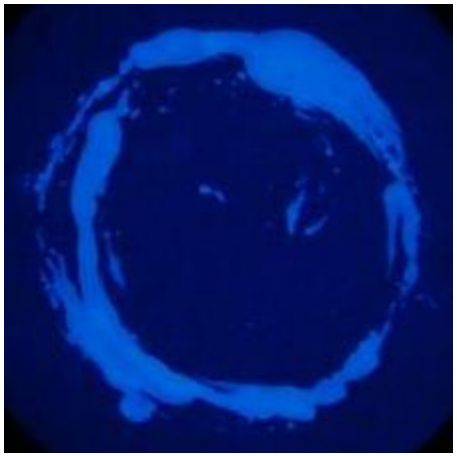
UMN (T_8-T_9) lesion 2 weeks
untreated



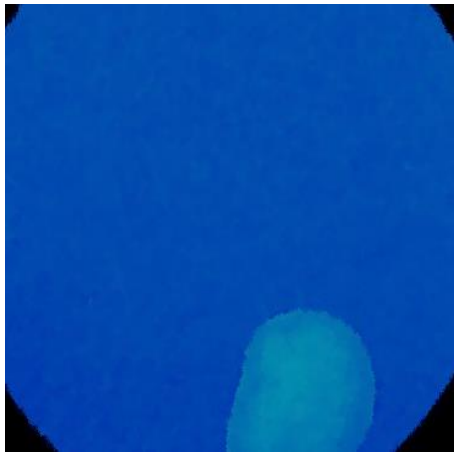
UMN lesion 2 weeks
+ LM11A-24



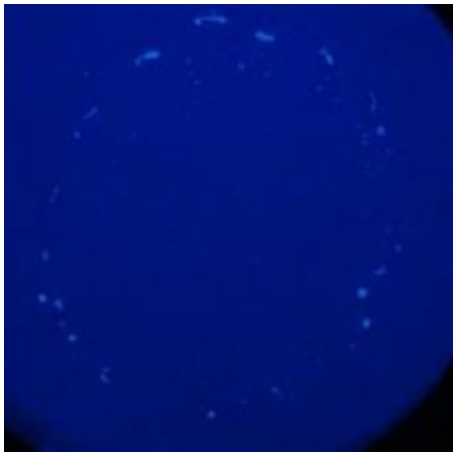
UMN lesion 2 weeks
+ LM11A-31



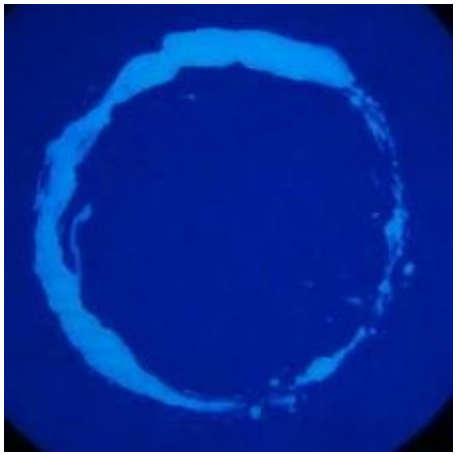
Intact SC



UMN lesion 6 weeks
+ LM11A-24



UMN lesion 6 weeks
+ LM11A-31

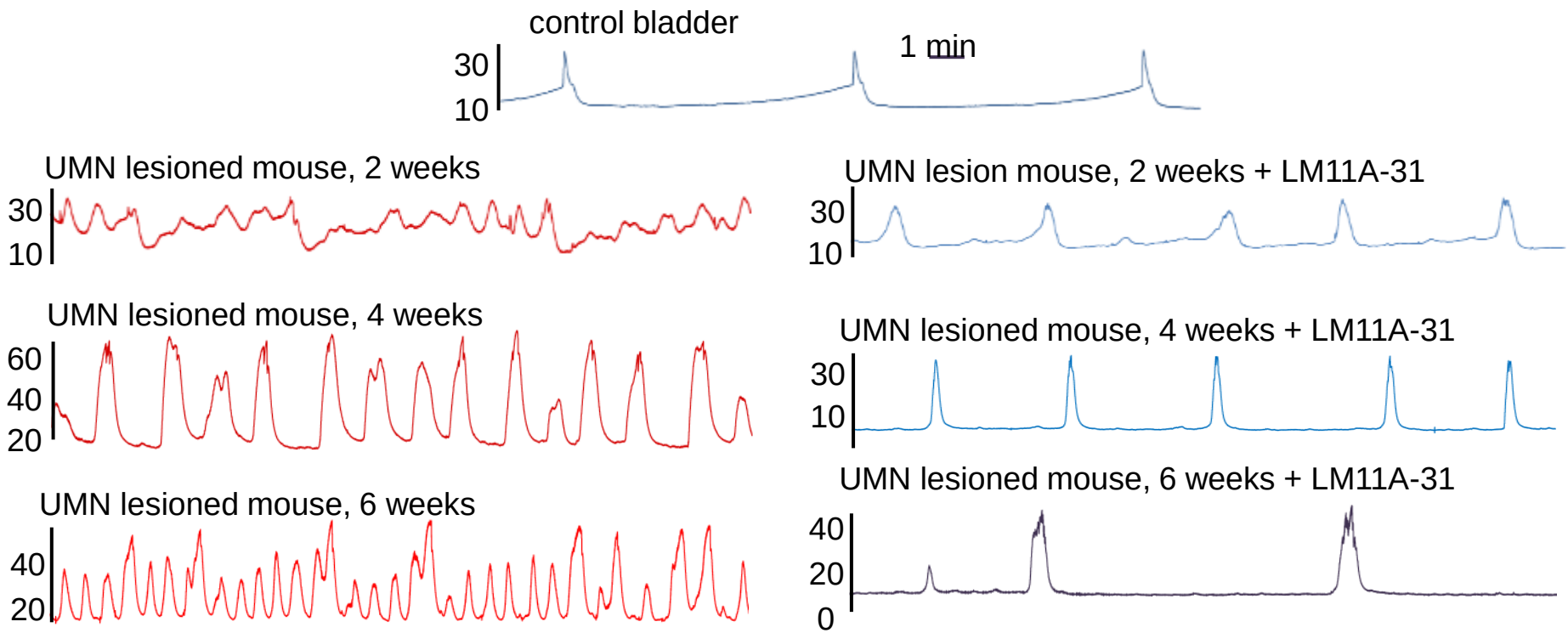


voided volume, µl

	2 wk, µl	6 wk, µl	8 wk, µl
intact SC	200±24		
untreated SCI	240±76		
LM11A-24	319±72	76±62	74±51
LM11A-31	439±64	182±60	189±98

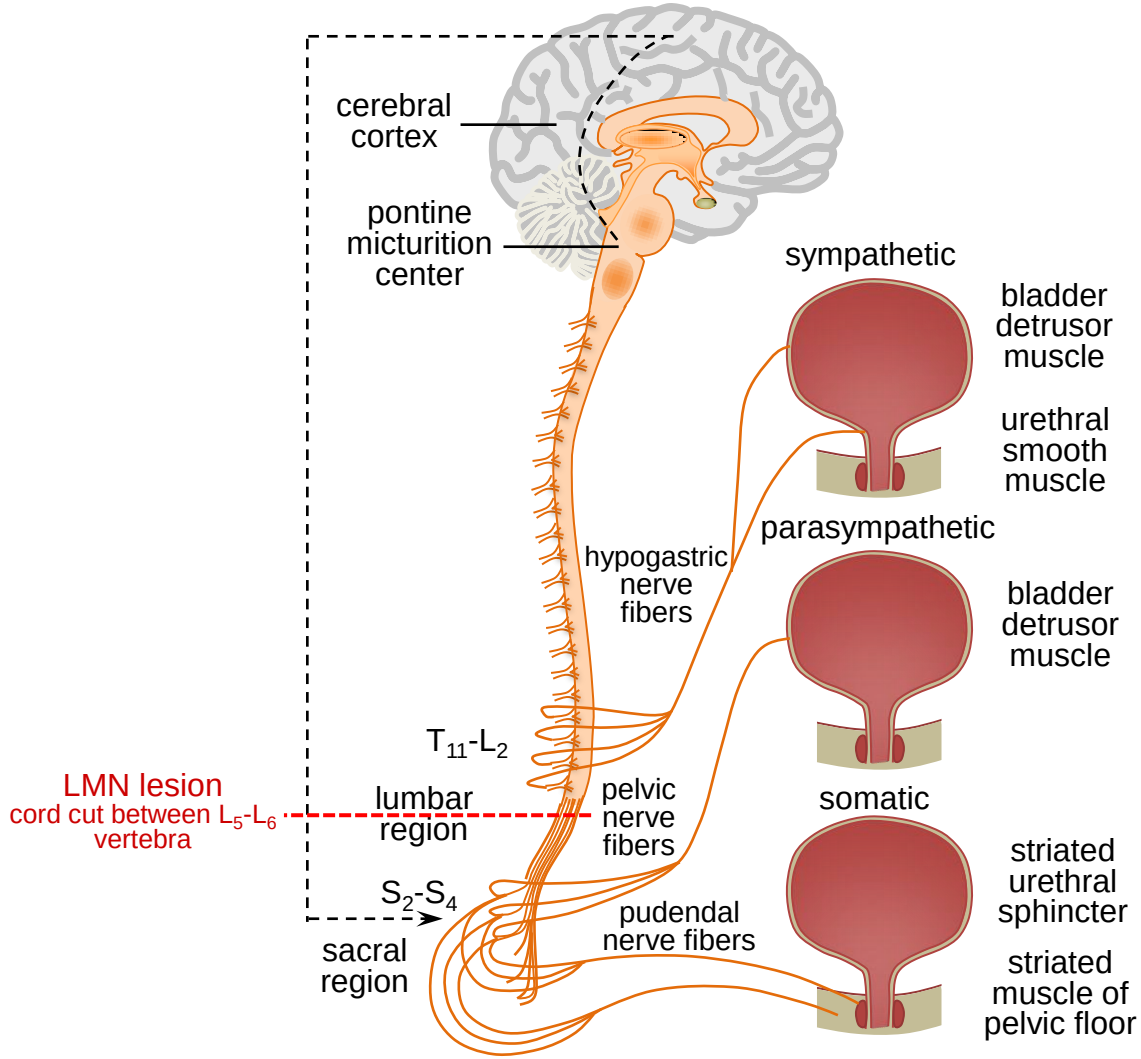
Cystometry: Mice with UMN Lesions

LM11A-31 improved DSD and reflex voiding



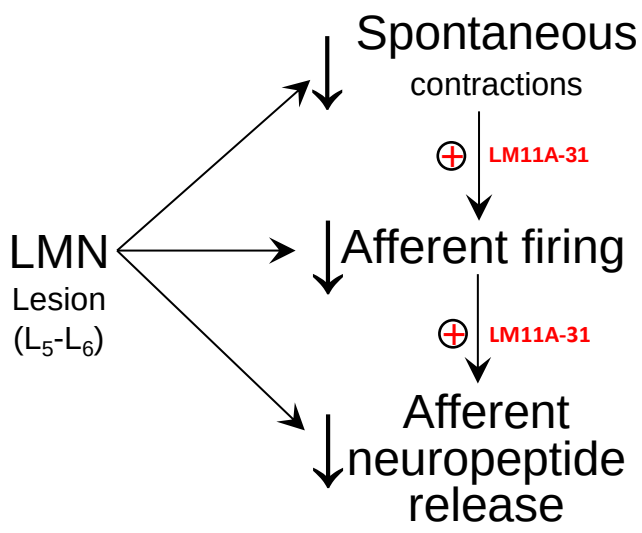
Lower Motoneuron Lesion Model

transection



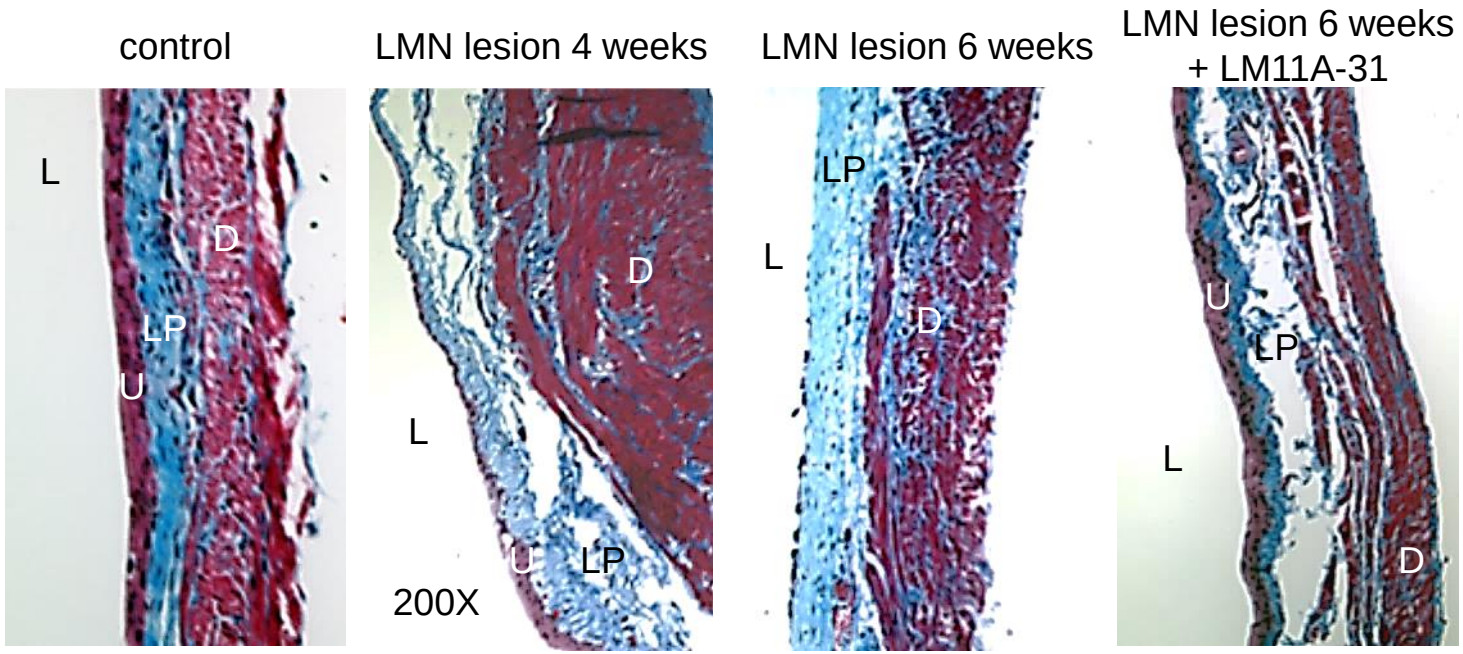
Kanai and Andersson, J Urol 183:1288-1295, 2010

LMN Lesions and Proneurotrophins



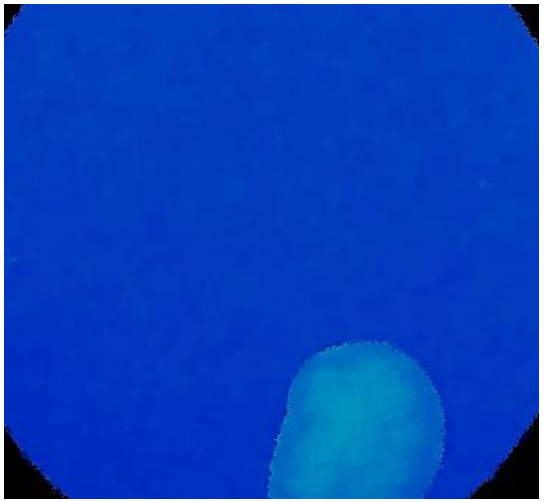
Bladder Urothelium and Collagen Deposition

following L_5-L_6 LMN lesions: benefits of LM11A-31 therapy

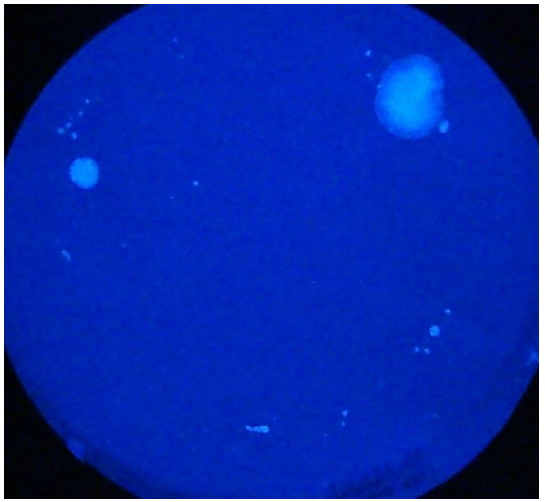


LM11A-31 Decreases Urinary Retention

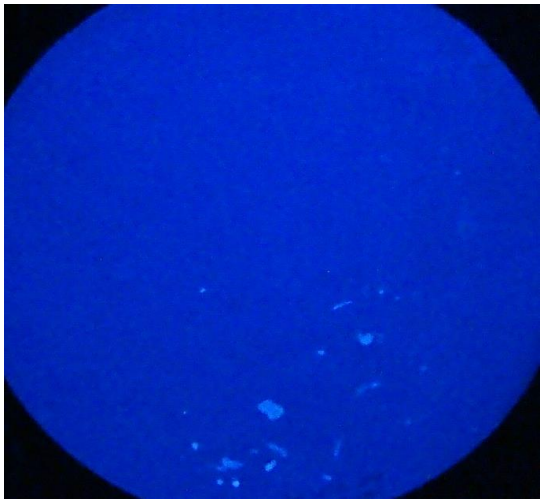
intact SC



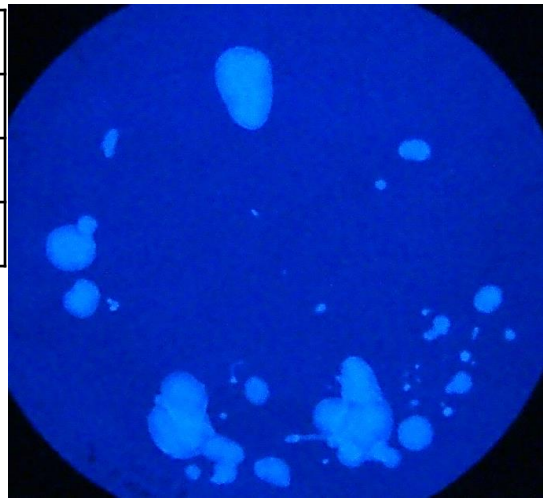
LMN (L_5-L_6) lesion 4 weeks



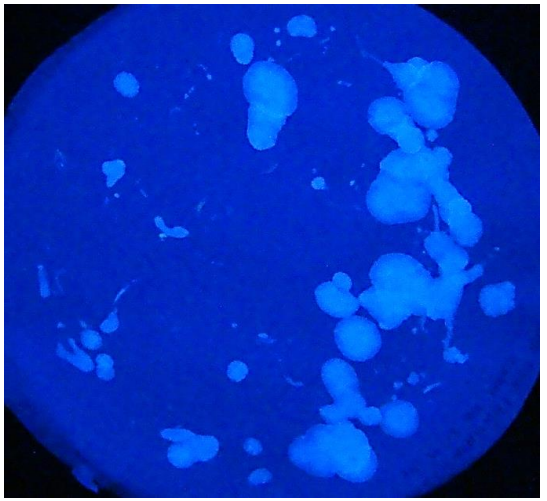
LMN lesion 6 weeks



LMN lesion 4 weeks
+ LM11A-31



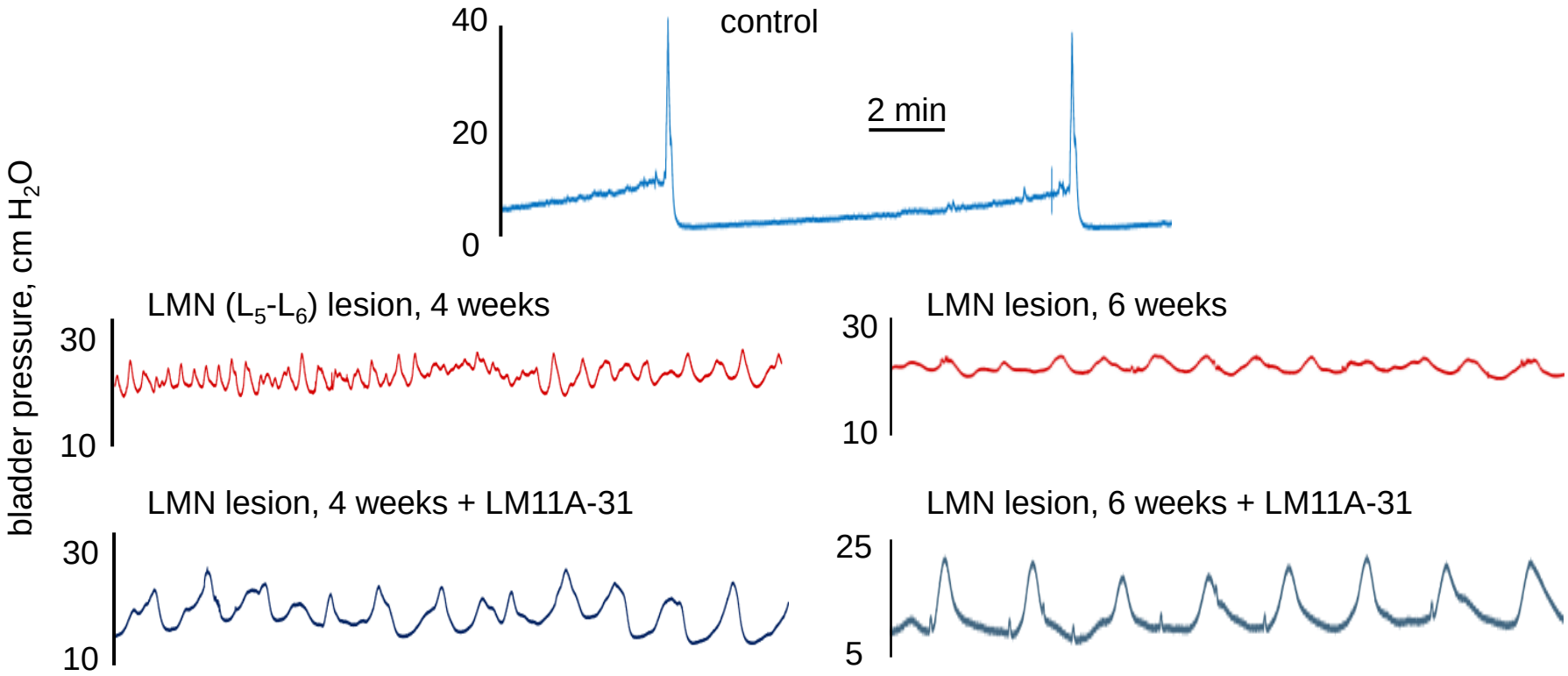
LMN lesion 6 weeks
+ LM11A-31



	4 wk, µl	6 wk, µl
intact SC	200 ± 24	
untreated	71 ± 12	11 ± 21
LM11A-31	301 ± 24	482 ± 36

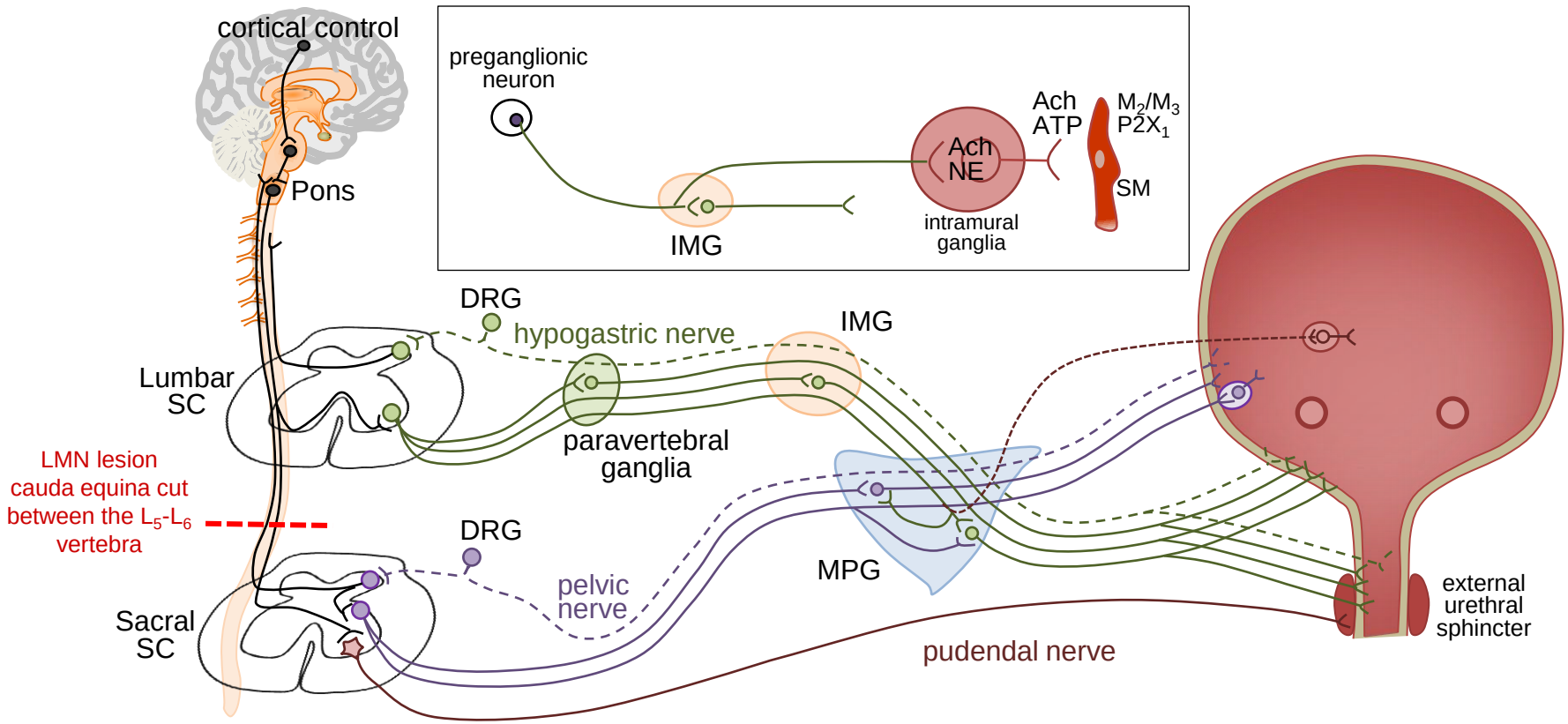
LM11A-31 Increases Spontaneous Contractions

which may increase sensation when the bladder is full and help expel urine



LM11A-31 Effects in LMN Lesions

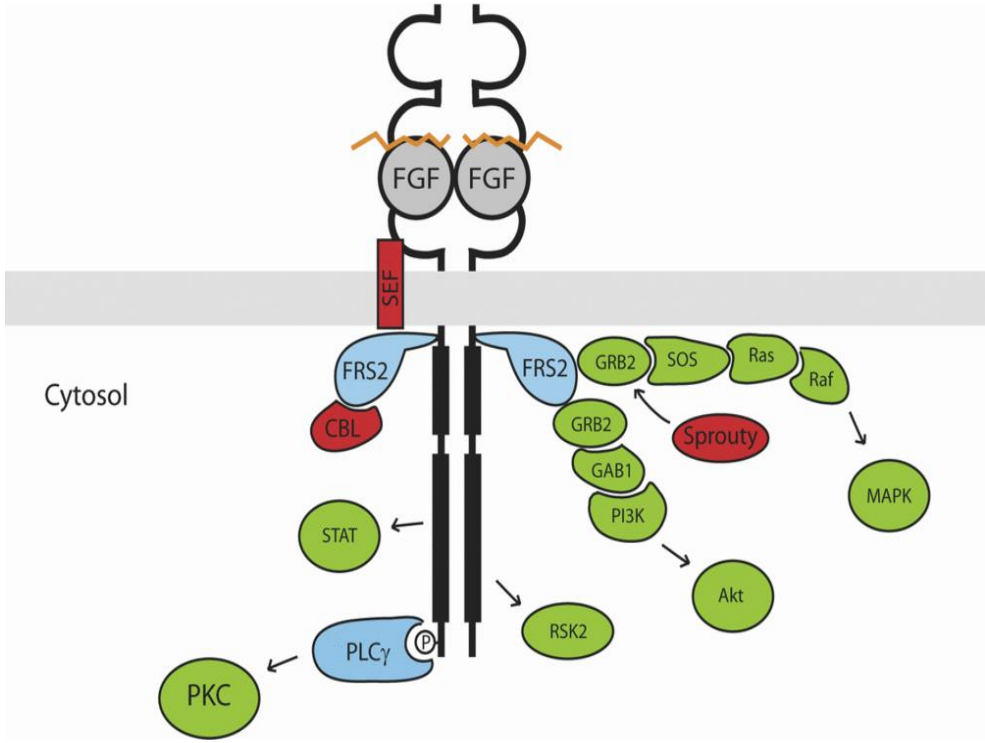
hypogastric efferents may repopulate parasympathic intramural ganglia



FGFR1 & FGFR1/2 Null Mouse Models

- 4 FGFRs identified (FGFR1 – FGFR4)
- 22 FGF isoforms identified in humans
- Signaling through the FGFR is important for differentiation and cell survival.

Fibroblast Growth Factor Receptor



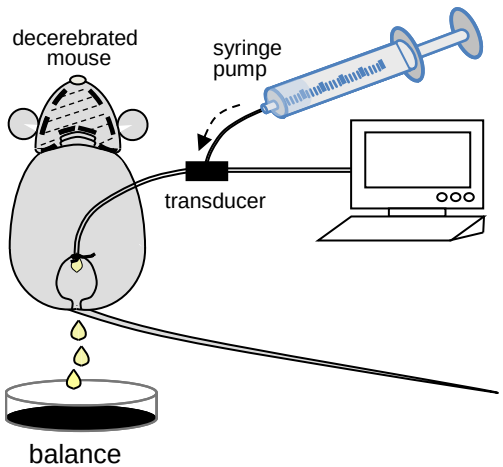
Wesche et al., Biochem J. 2011

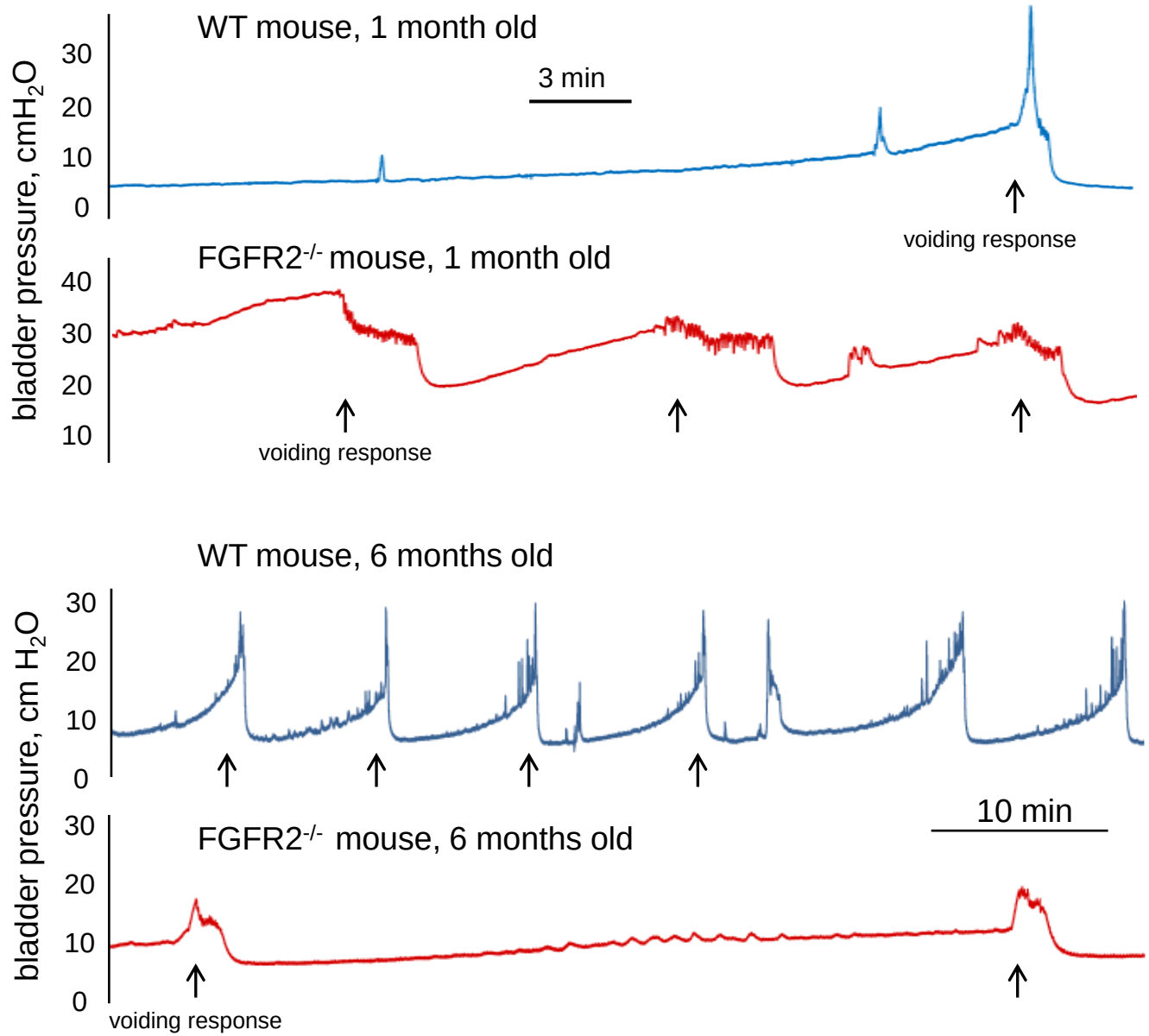
FGFR2$^{-/-}$ Mice Display Life-long Dysfunctional Voiding

Control

FGFR2$^{-/-}$ (6 months old)

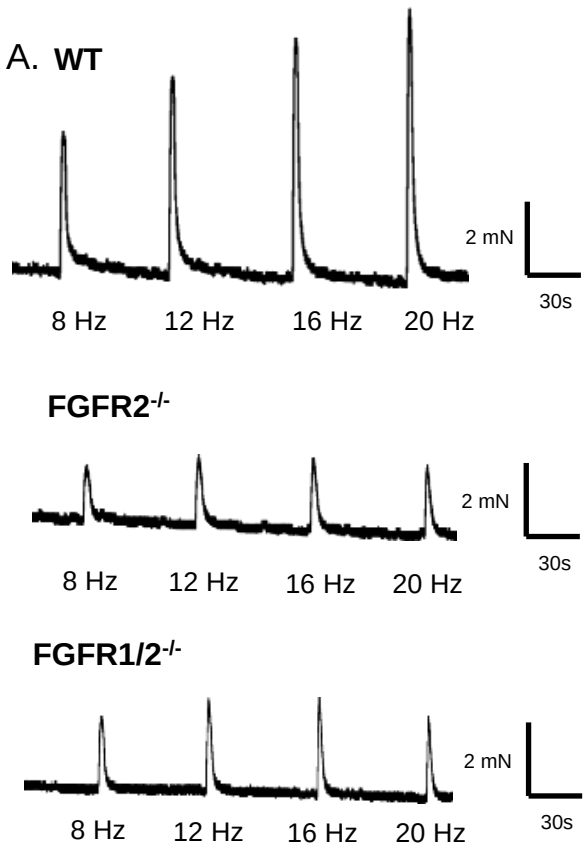
Decerbrate Cystometry—WT versus FGFR2$^{-/-}$

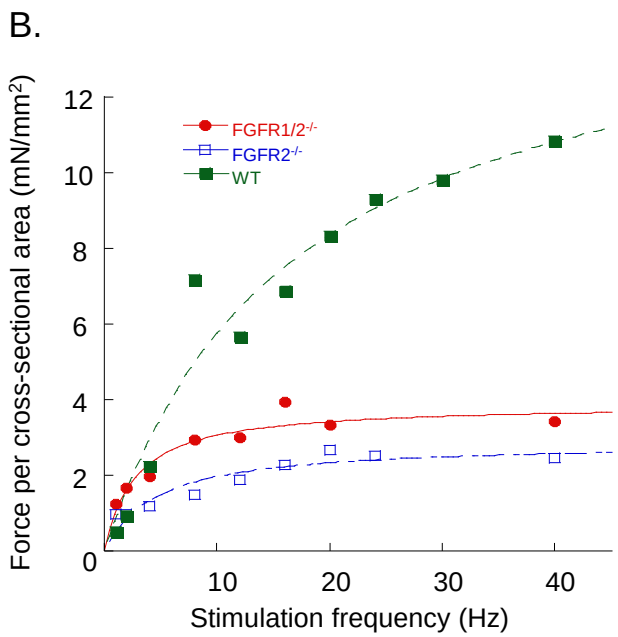


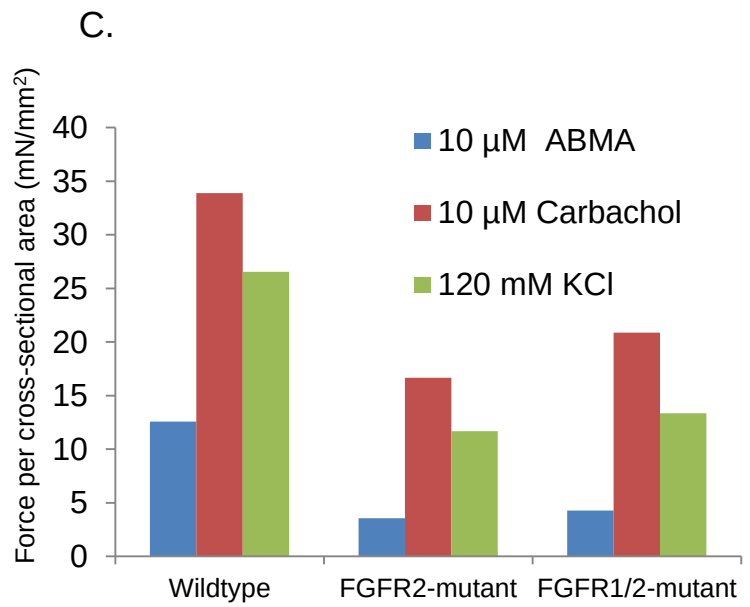


Nerve- and Agonist-mediated Contractile Responses

in whole bladder sheets from 1 month old mice

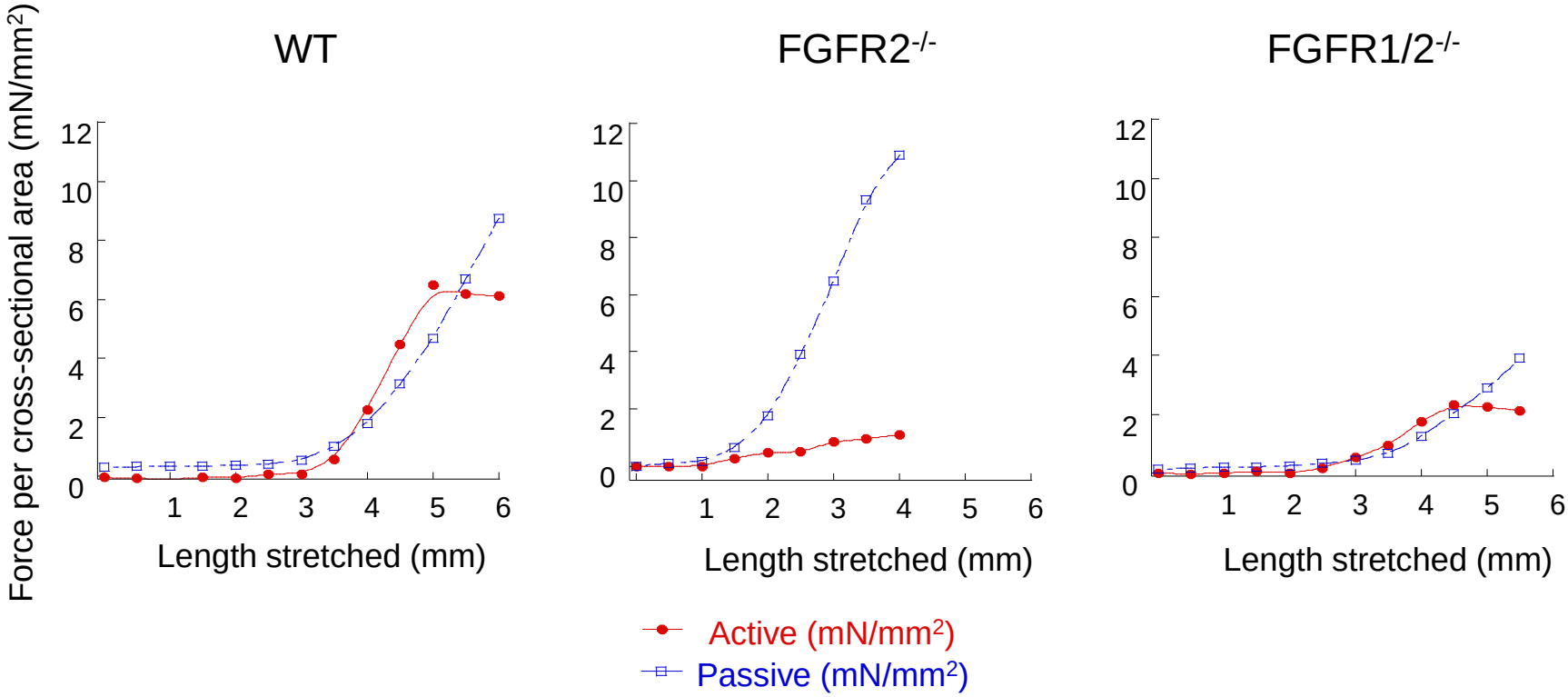






Length-tension Profiles in Whole Bladder Sheets

in whole bladder sheets from 1 month old mice



Collaborators

University of Pittsburgh:

Kanai Laboratory: Youko Ikeda and Irina Zabbarova

University-wide: Gerry Apodaca, Carl Bates, Lori Birder, Evan Carder, Chet deGroat, Mike Epperly, Bruce Freeman, Aura Kullmann, Guy Salama, Pradeep Tyagi, Ken Walker, Peter Wipf and Naoki Yoshimura

Princeton University: Lynn Enquist

University of Bristol: Chris Fry and Marcus Drake

Funding: NIH/NIDDK

Pittsburgh at Night