

# Prothelia

*Therapeutics for Muscular Dystrophy*

## **Laminin-111 as a Treatment for DMD**

Action Duchenne 8th International Conference

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**Conflict of interest statement:** Brad Hodges and Rich Cloud are shareholders of Prothelia and possess a financial interest in laminin-111. The patent inventors are Dean Burkin and Jachinta Rooney. The University of Nevada, Reno, has licensed this technology to Prothelia and has a small equity share in Prothelia.

# Prothelia

## ➤ **Mission**

- Increase the longevity and quality of life of patients with muscular dystrophy

## ➤ **Lead Drug Candidate – LAM-111**

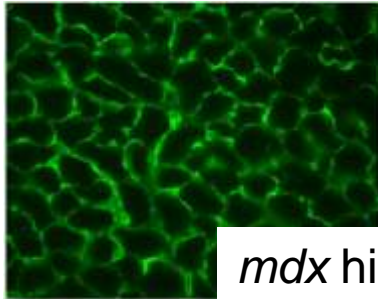
- Delivered systemically to DMD mouse models
- Excellent efficacy with no toxicity
- Human LAM-111 in human DMD cells
- Human LAM-111 in mouse DMD muscle cells
- Stable and scalable human LAM-111 manufacturing process
- Under evaluation for treatment of MDC1A, dystroglycanopathy and dysferlinopathy



Ashley

# A picture is worth....

Human LAM-111

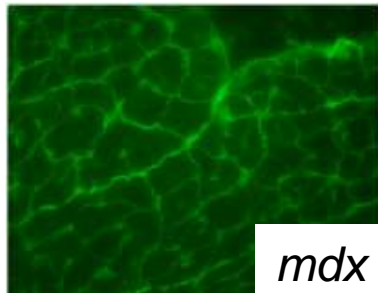


No LAM-111

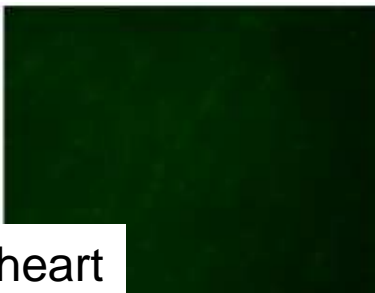


*mdx* hindlimb

Mouse LAM-111

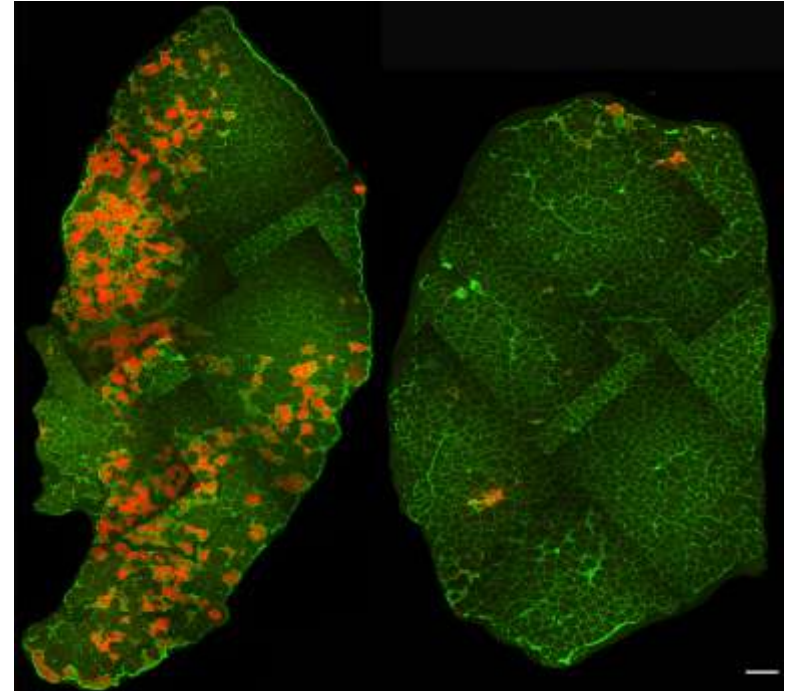


No LAM-111



*mdx* heart

*mdx* mouse model of DMD



No LAM-111

Mouse LAM-111

LAM-111 protects *mdx* muscle from exercise induced damage

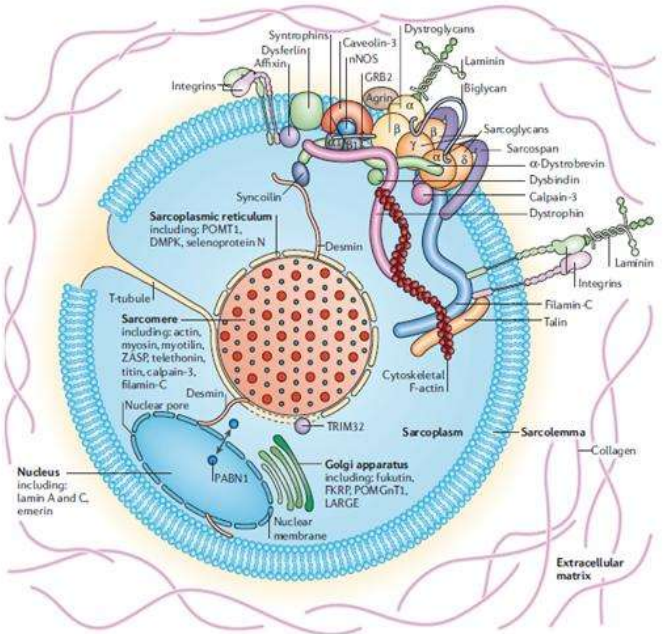
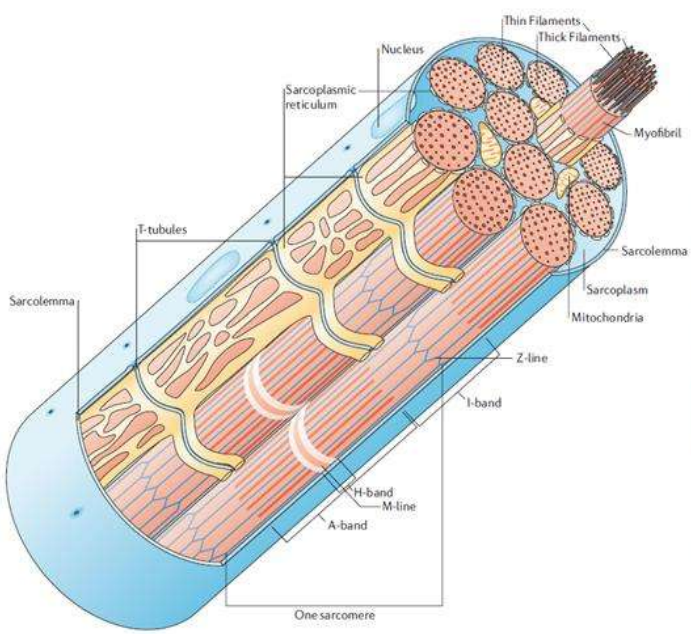
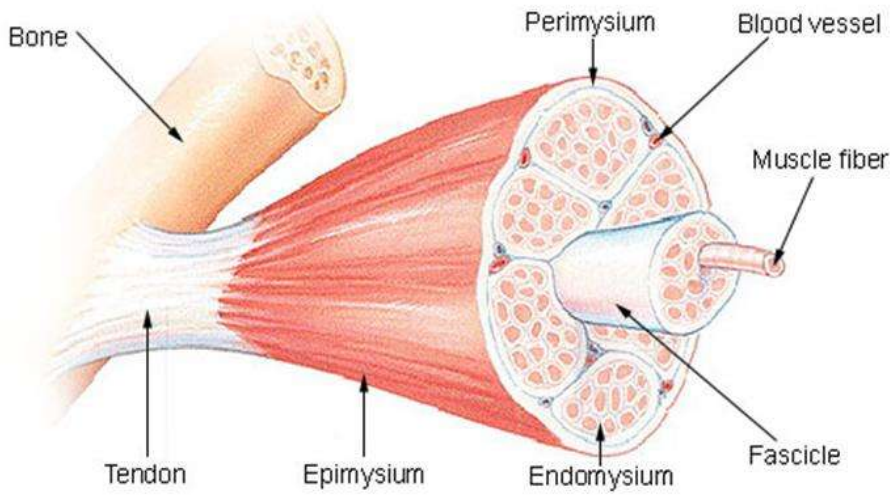
# Our Therapeutic Approach

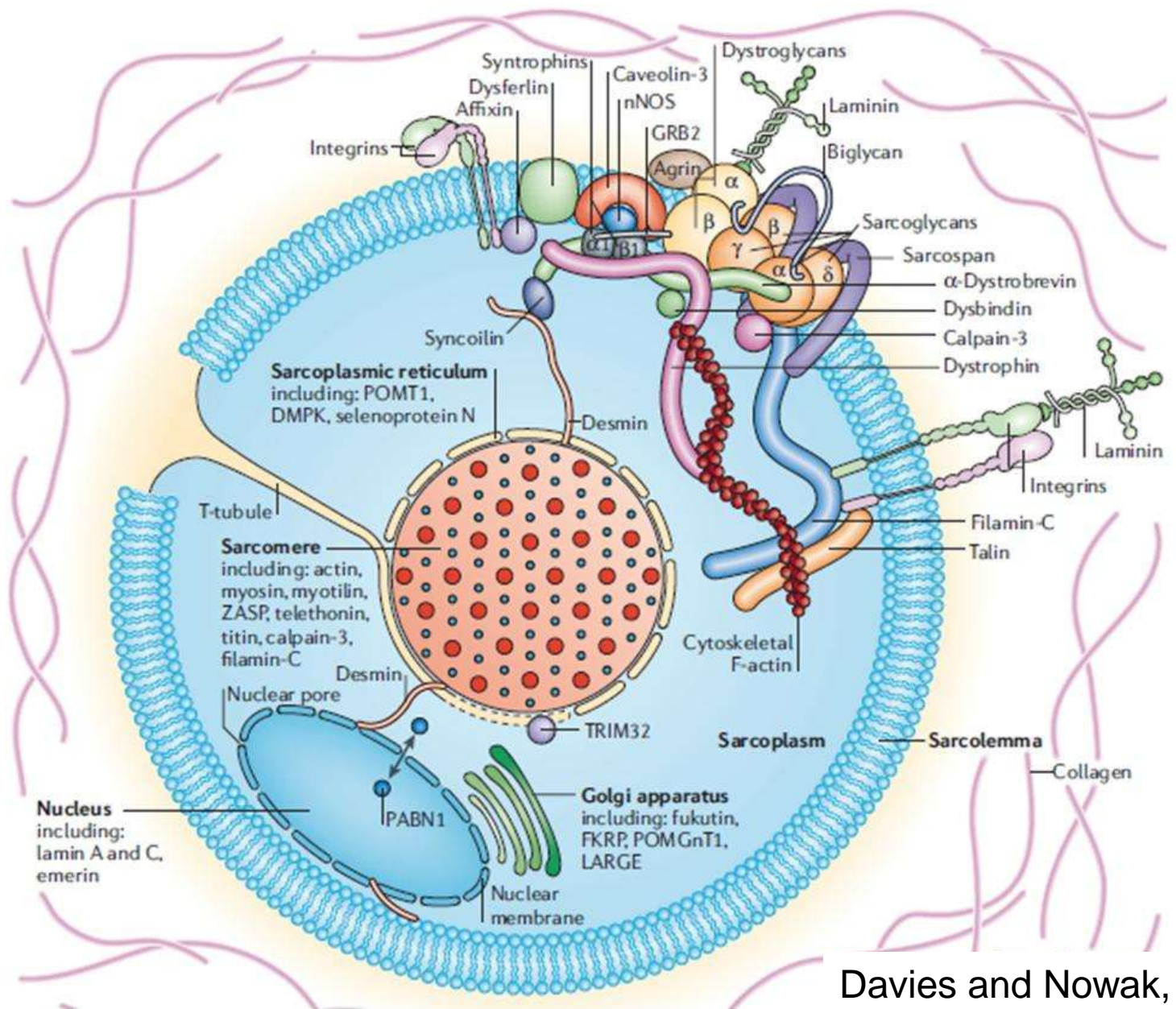
- Proteins and small molecules
- Restore lost cellular adhesion
- Enhance adhesive pathways found in all patients
- Treat all patients regardless of their mutation
- Single drug for multiple muscular dystrophies



Ashley

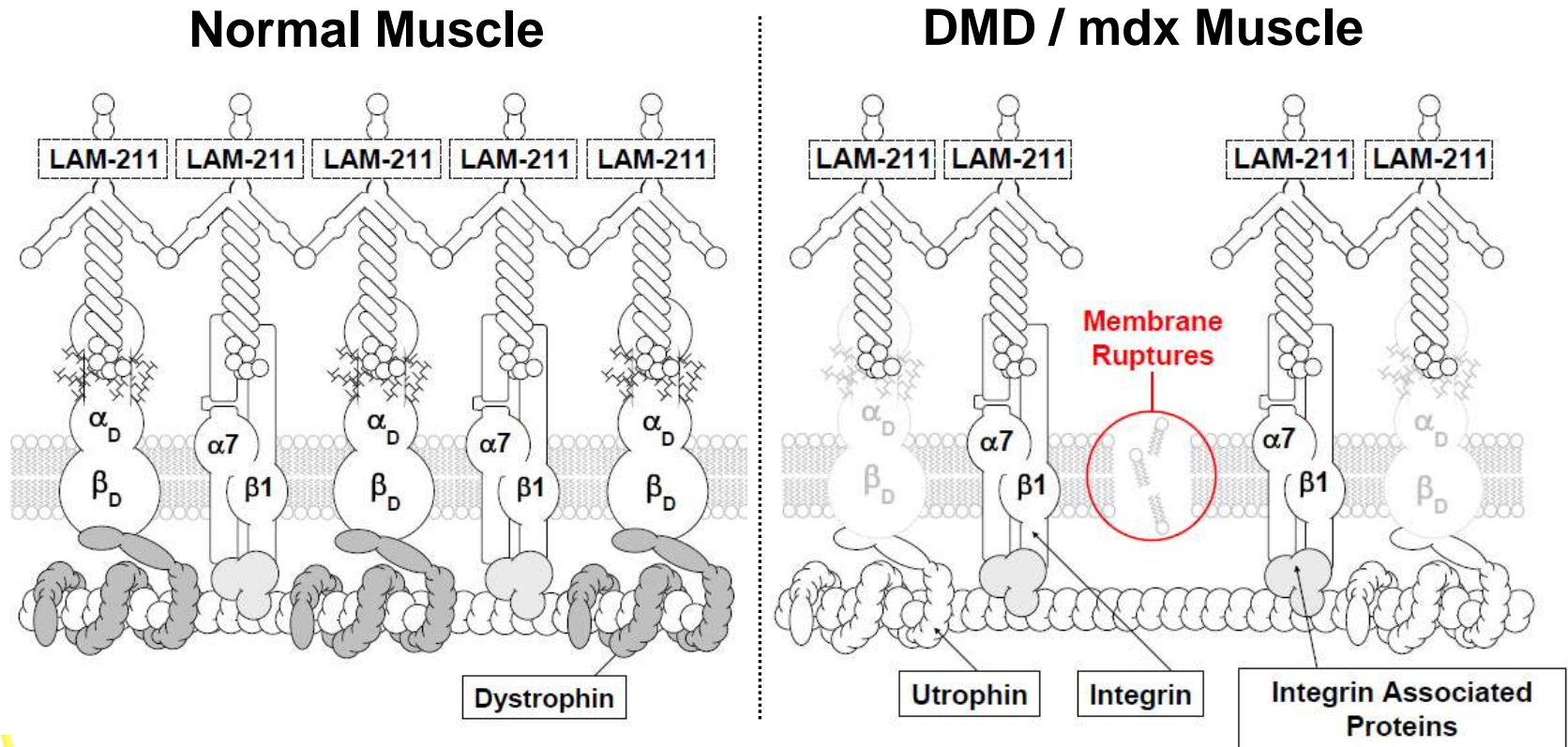
# LAMININ 111 SCIENCE





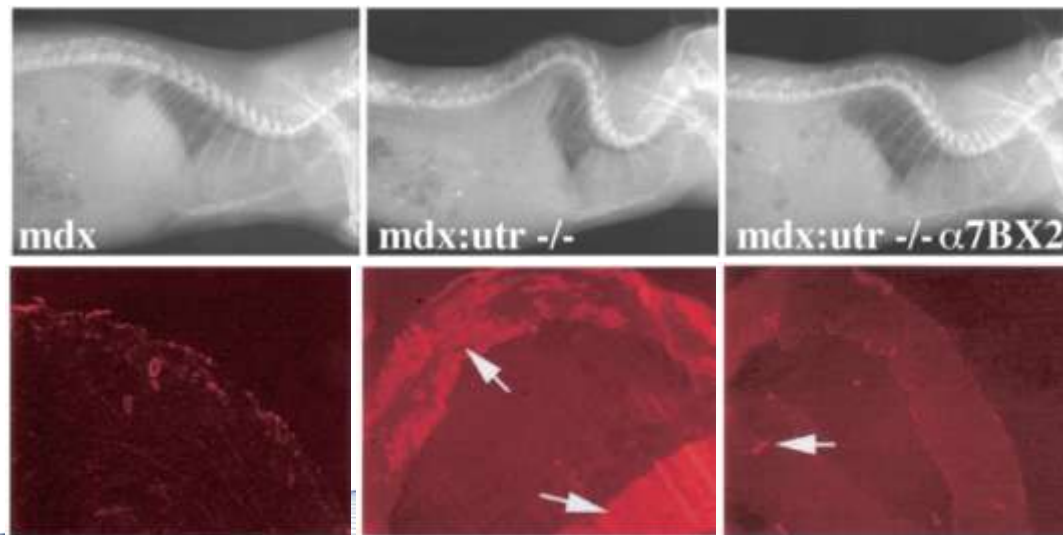
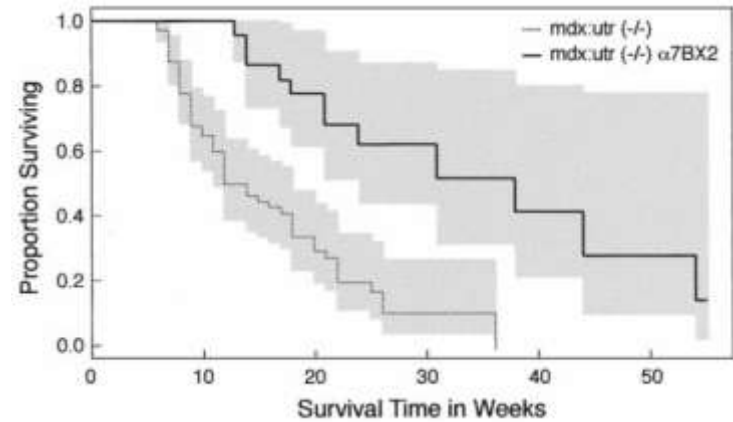
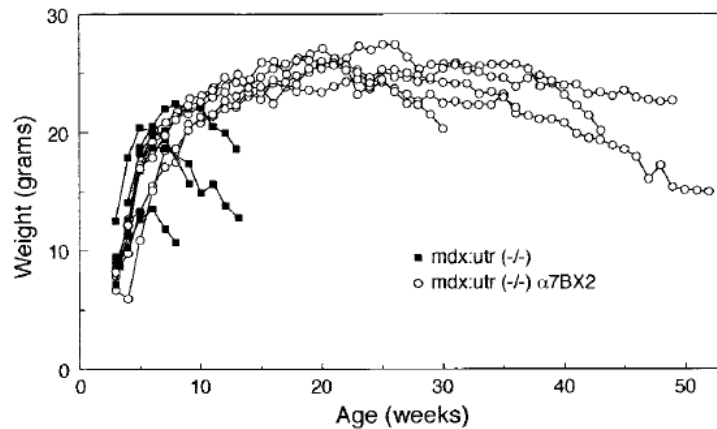
Davies and Nowak, 2006

# Laminins and Laminin Receptors in Normal and Dystrophic Muscle

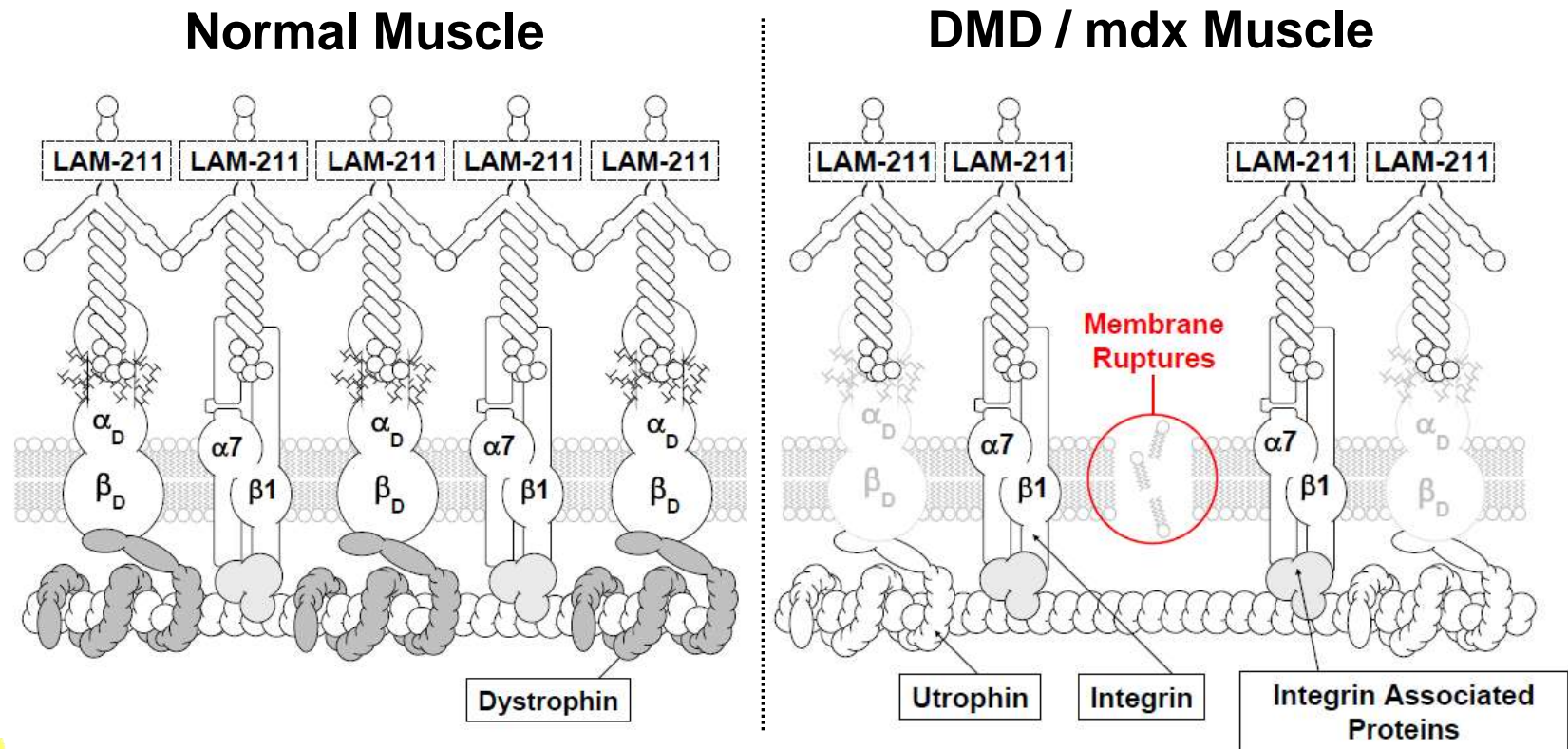


$\alpha_7\beta_1$ : alpha7beta1 Integrin  
 $\alpha_D\beta_D$ : alpha/beta Dystroglycan

# 2-3 Fold Increase in Alpha7 Integrin Mitigates Muscular Dystrophy

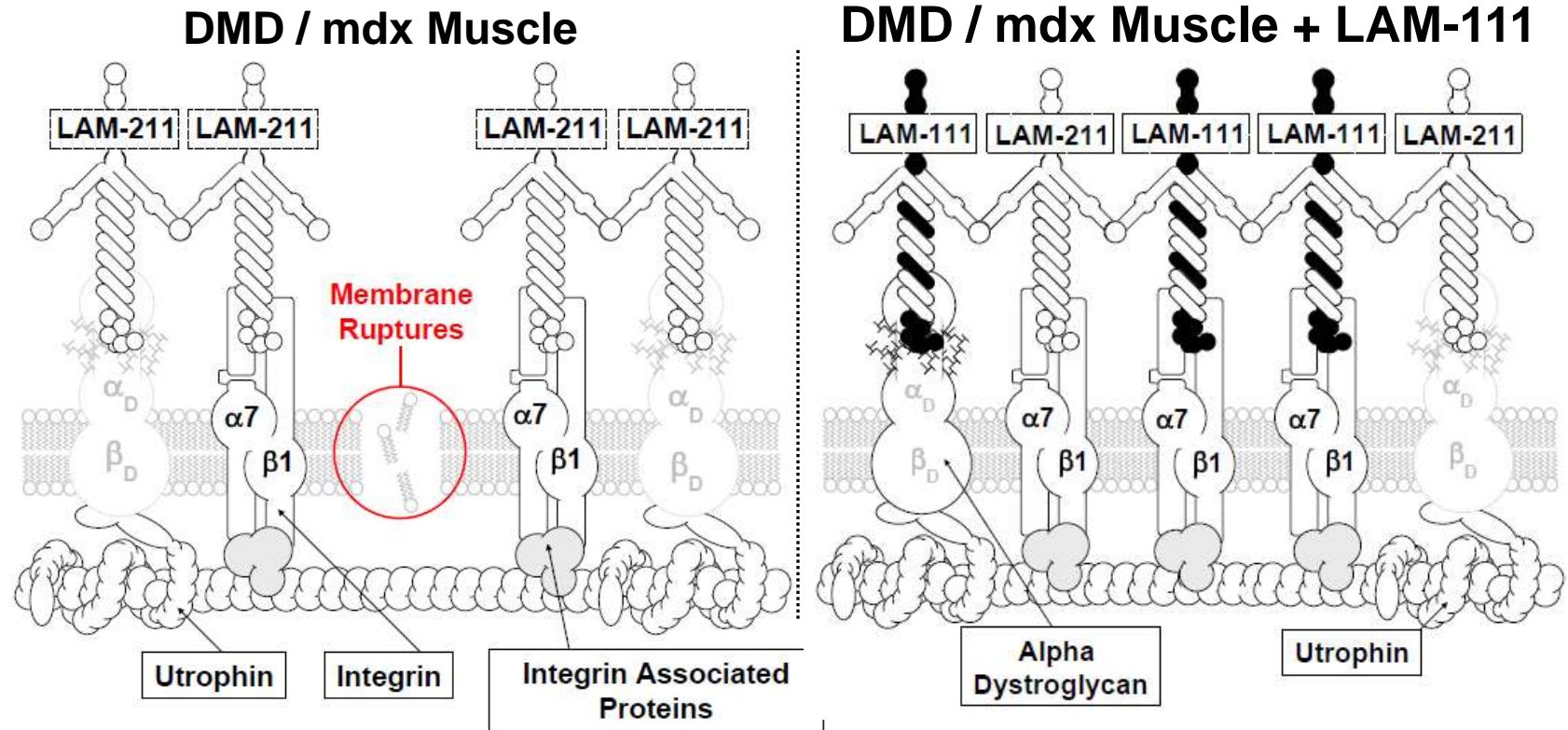


# Laminins and Laminin Receptors in Normal and Dystrophic Muscle



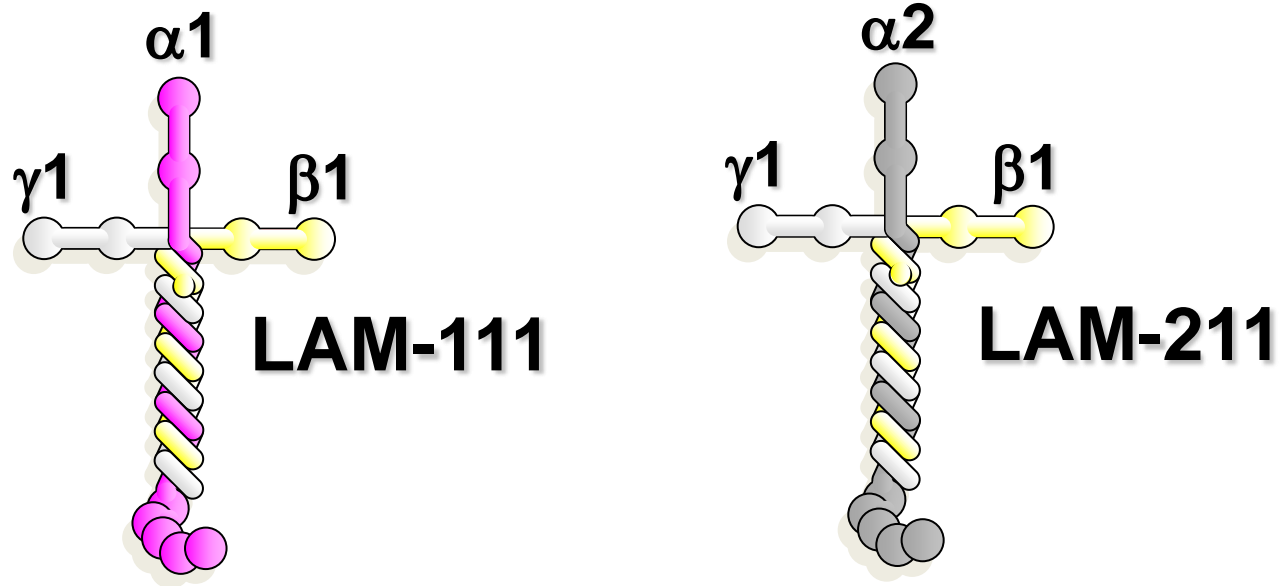
$\alpha_7\beta_1$ : alpha7beta1 Integrin  
 $\alpha_D\beta_D$ : alpha/beta Dystroglycan

# Laminin-111 (LAM-111), a Protein Therapy for Muscular Dystrophy



$\alpha_7\beta_1$ : alpha7beta1 Integrin  
 $\alpha_D\beta_D$ : alpha/beta Dystroglycan

# LAM-111 is a Substitution Therapy



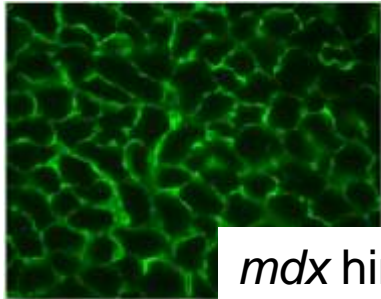
DMD	LAMININ RECEPTOR		LAM-111	LAM-211
	Alpha Dystroglycan	Beta Dystroglycan		
95%	Alpha7 X2B	Beta1 D	++++	+++
4%	Alpha7 X1B	Beta1 D	+/-	++
<1%	Alpha 6	Beta1 A	++	+/-
<1%	Alpha 3	Beta1 A	-	+

# LAM-111 Targets Skeletal and Cardiac Muscle and Protects Muscle from Damaging Exercise



Sam

Human LAM-111

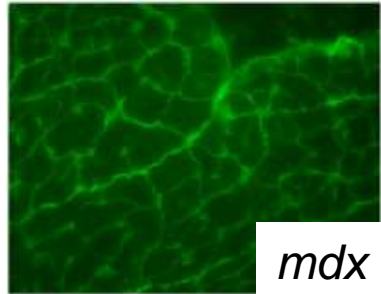


No LAM-111

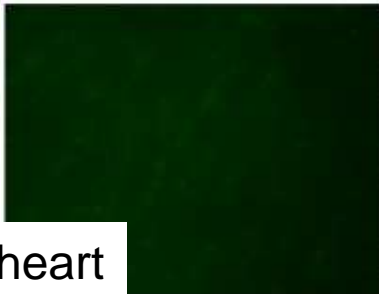


*mdx* hindlimb

Mouse LAM-111

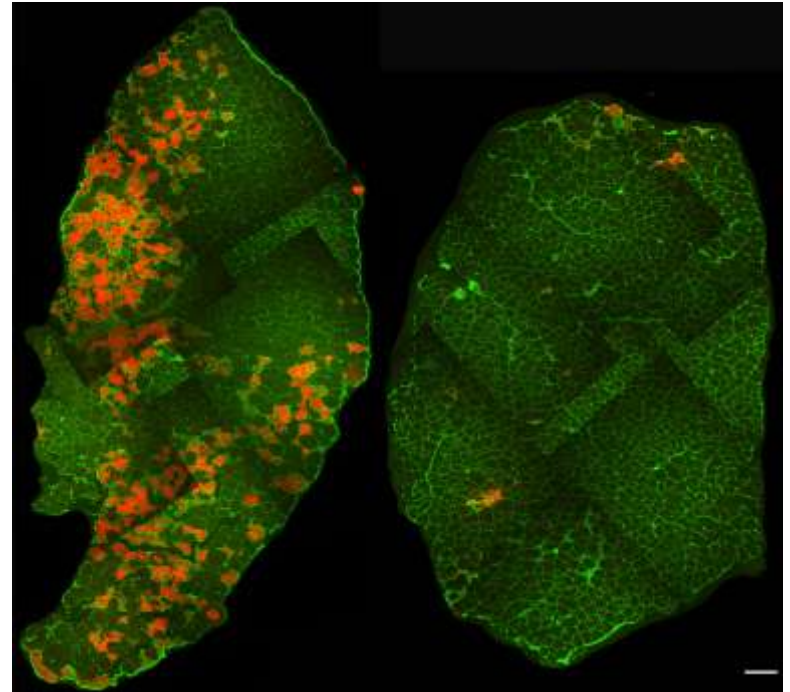


No LAM-111



*mdx* heart

*mdx* mouse model of DMD

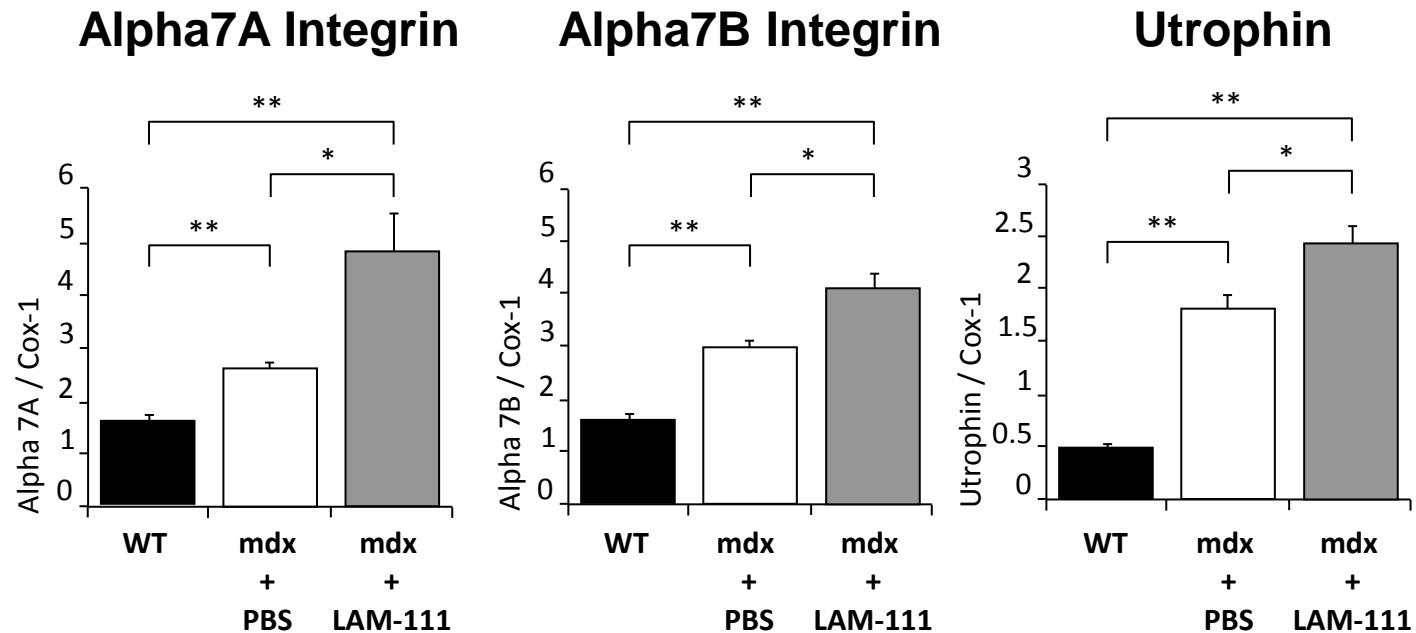


No LAM-111

Mouse LAM-111

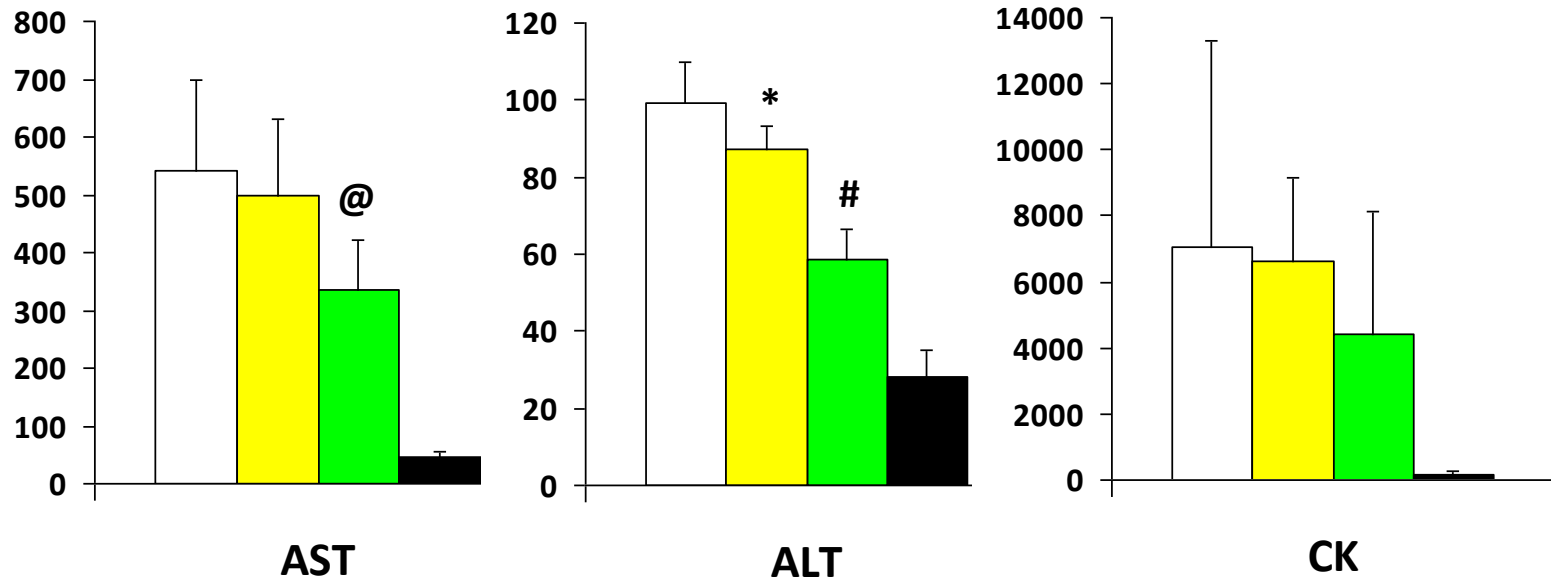
LAM-111 protects *mdx* muscle from exercise induced damage

# LAM-111 Increases Alpha7 Integrin and Utrophin in *mdx* Muscle



Rooney et al. 2009

# A Single Systemic Dose of LAM-111 Reduces ALT and AST by 4 Days Post-injection



@ Saline v. 10.0 mg/kg,  $p < 0.05$

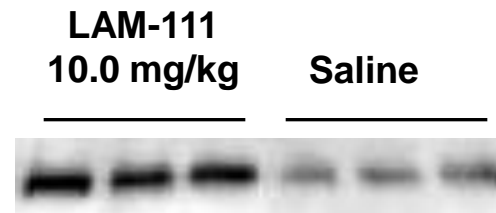
# Saline v. 10.0 mg/kg,  $p < 0.005$

Saline v. 10.0 mg/kg, not significant

\* Saline v. 1.0 mg/kg,  $p < 0.05$

- Saline - mdx
- 1.0 mg/kg - mdx
- 10.0 mg/kg - mdx
- WT

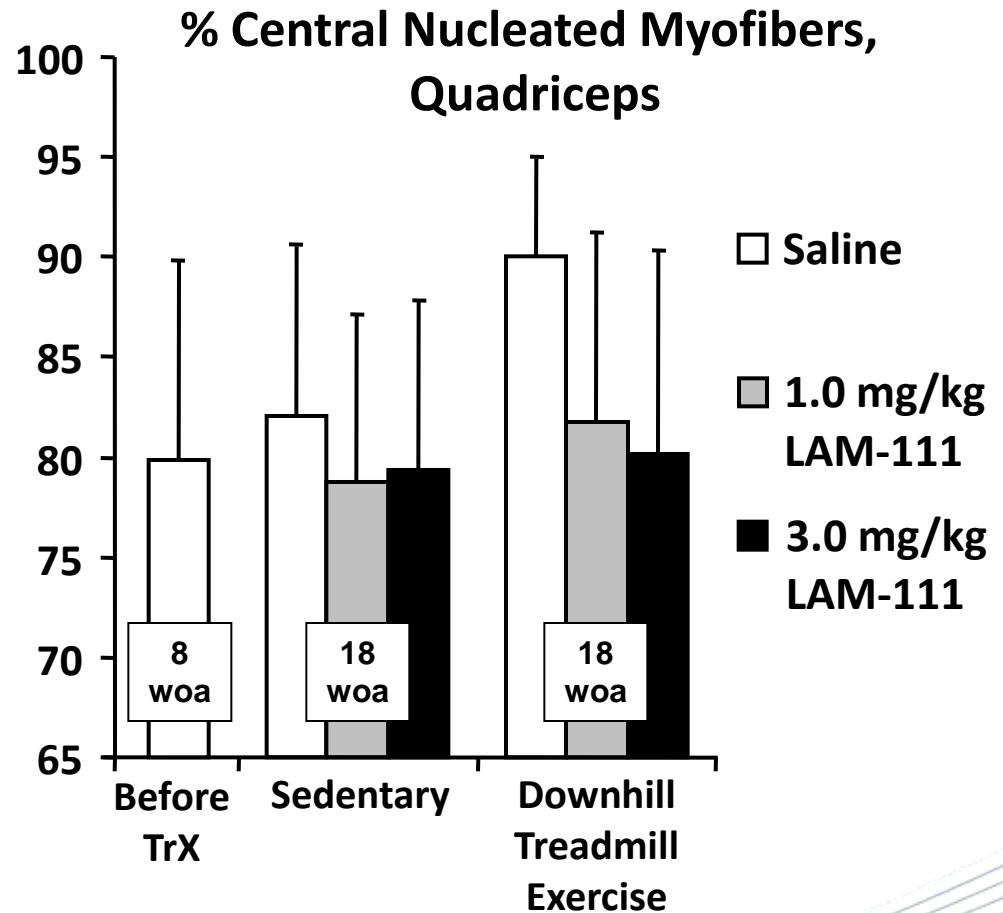
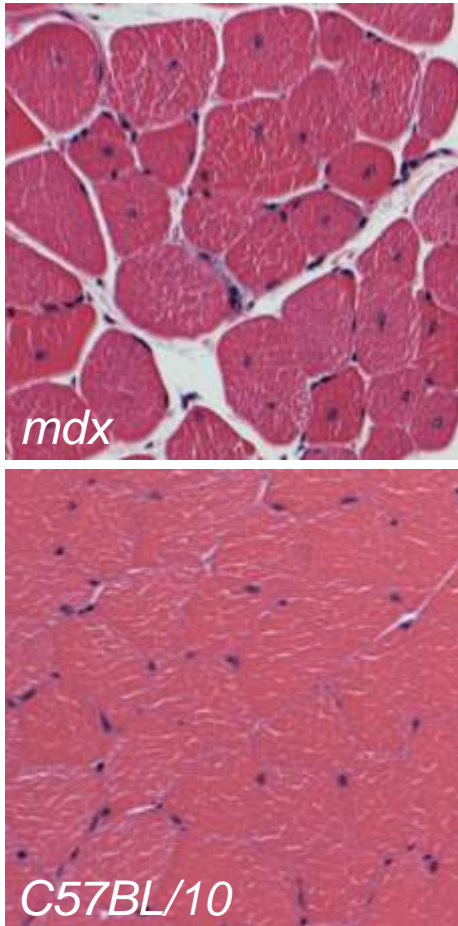
Alpha7B  
Integrin



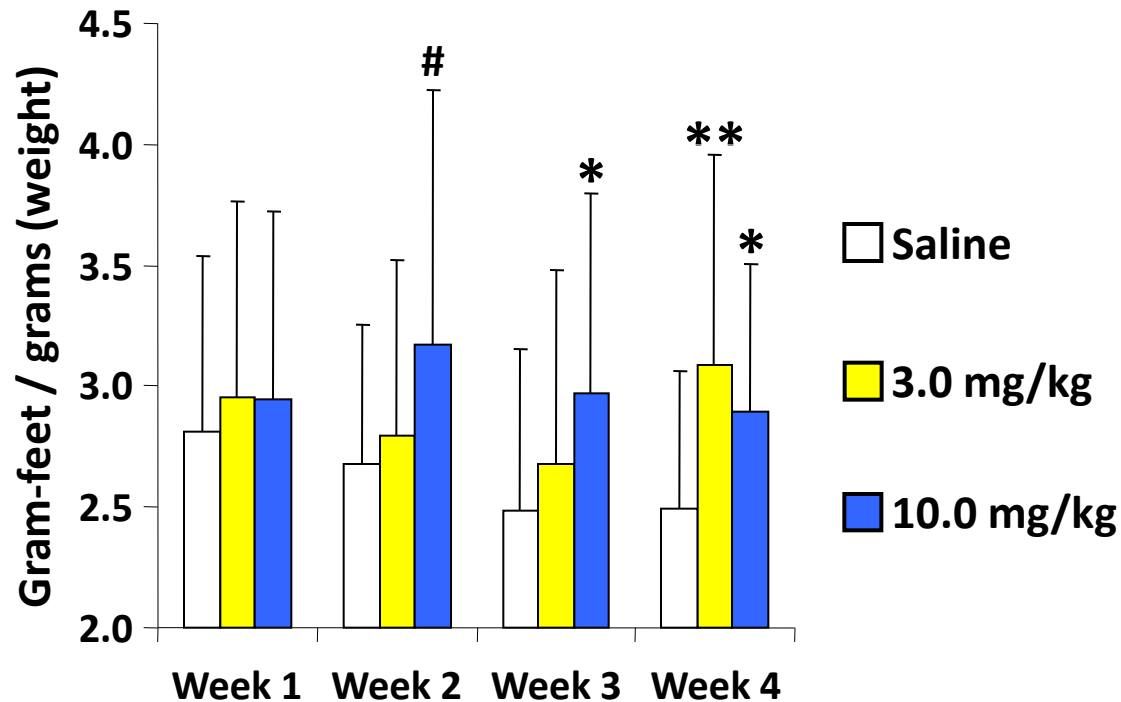
# LAM-111 Prevents Muscle Degeneration Due to Strenuous Downhill Exercise



Philip



# LAM-111 Improves Forelimb Grip Strength in *mdx* Mice



n = 5 mice/group, 5 tests/session; 25 data points/dose/week

# 10.0 mg/kg v. Saline,  $p < 0.04$

\* 10.0 mg/kg v. Saline,  $p < 0.02$

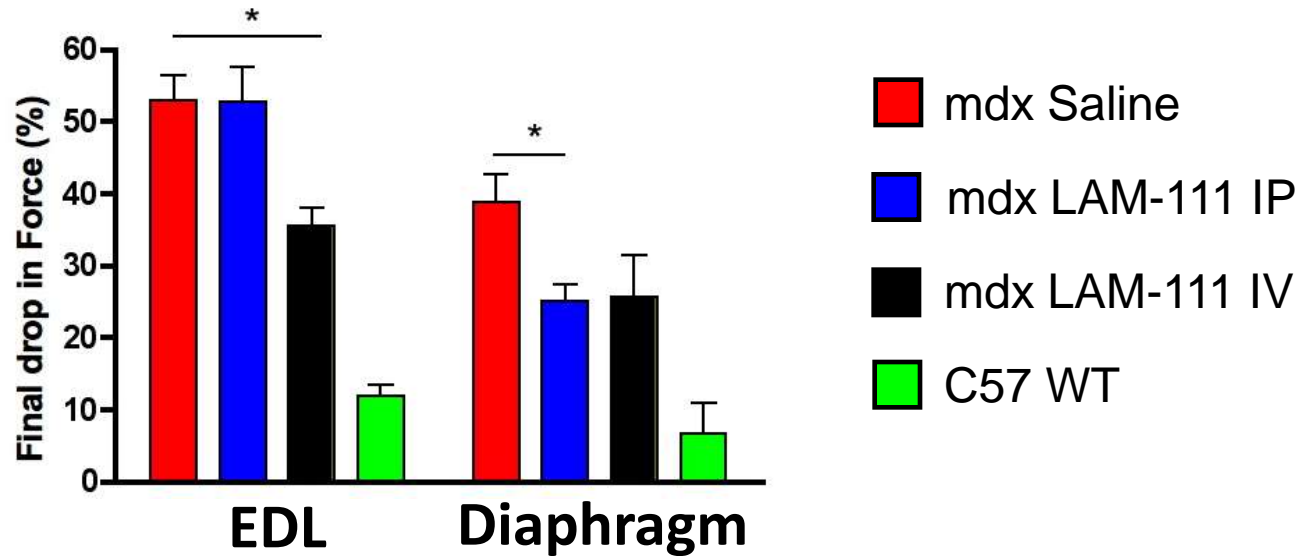
\*\* 3.0 mg/kg v. Saline,  $p < 0.01$

All mice sedentary



Pierce

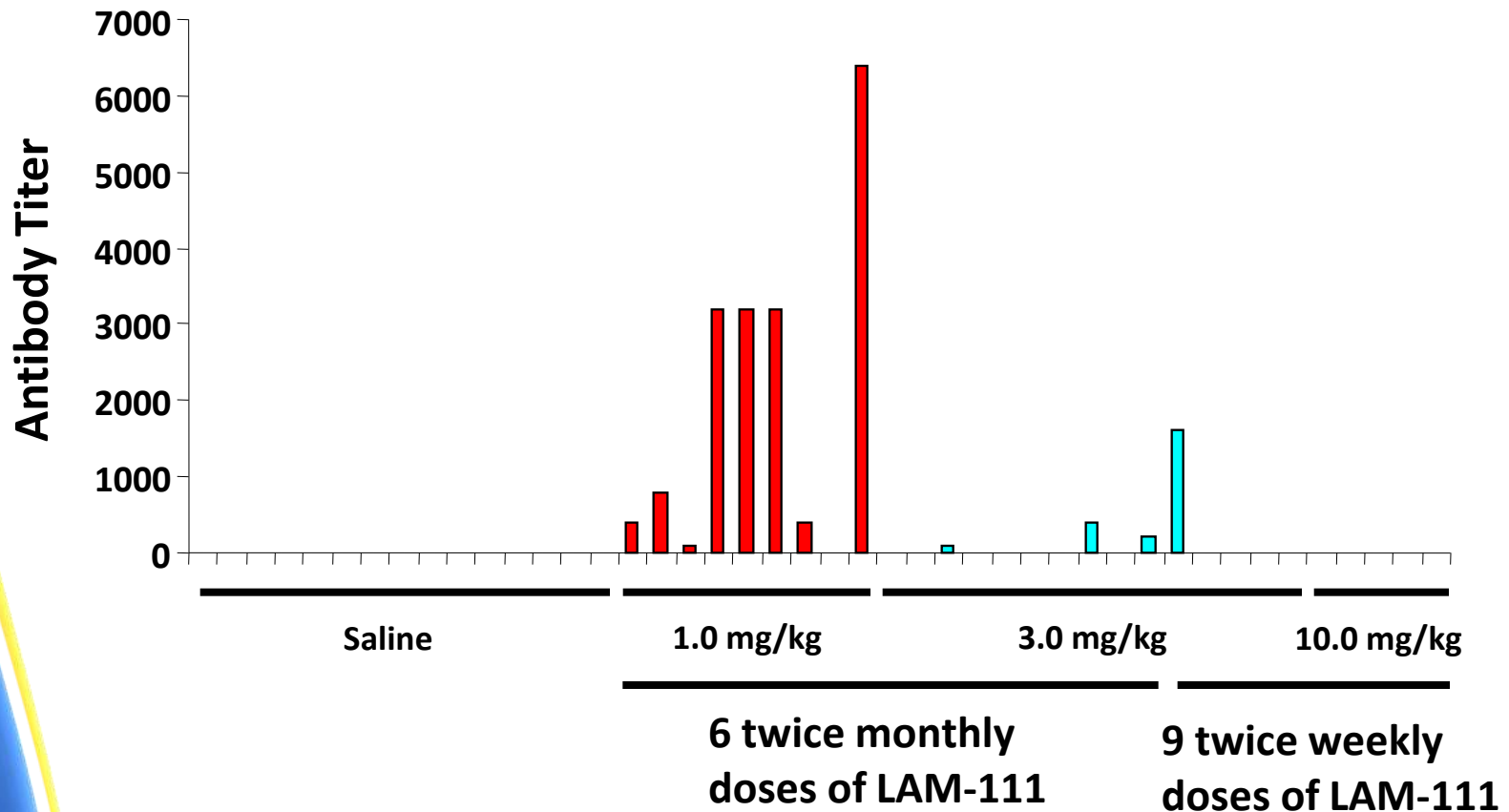
# LAM-111 Protects *mdx* Muscle from *ex vivo* Eccentric Contractions



Jake

Tukey's Multiple Comparison Test	p value
mdx Diaphragm: Saline v. LAM-111 IP	p < 0.05
mdx EDL: Saline v. LAM-111 IV	p < 0.05
mdx EDL: LAM-111 IP v. LAM-111 IV	p < 0.05

# Antibody Responses to LAM-111 were Variable or Non-Existent

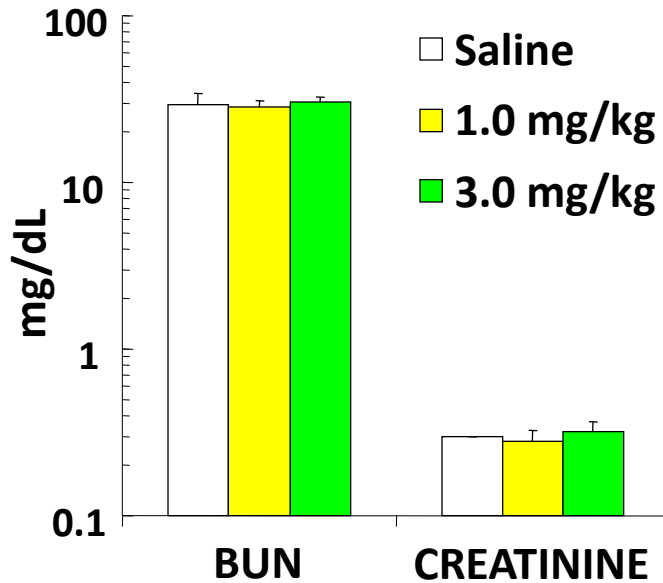


All intraperitoneal (IP) injections of LAM-111 or saline

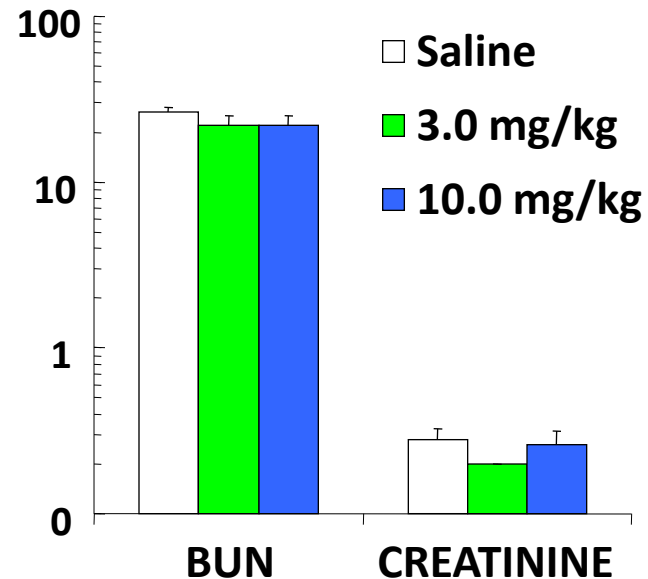
# Kidney Function is Unaffected Following Chronic Dosing of LAM-111



Kyra



6 total doses of  
LAM-111  
twice monthly



9 total doses of  
LAM-111  
twice weekly

# LAM-111 as a Therapeutic for DMD

- Single Dose of LAM-111
  - Reduced serum ALT and AST
  - Increased alpha7 integrin expression
- Multiple Doses of LAM-111
  - Increased grip strength
  - Blocked exercise induced muscle damage
  - Improved force retention following eccentric contractions
  - Variable or absent antibody responses
  - Intravenous (IV) delivery more effective than intraperitoneal (IP) delivery

# Future Directions



Adelina

- Preclinical development of human LAM-111
- Continue data collection
- Long-term studies / Cardiac function
- Begin development of PRT-350

# Acknowledgements



Selena

- Dean Burkin & Jachinta Rooney / UNR TTO
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- Jacques Tremblay / Laval
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- Parents and Patients