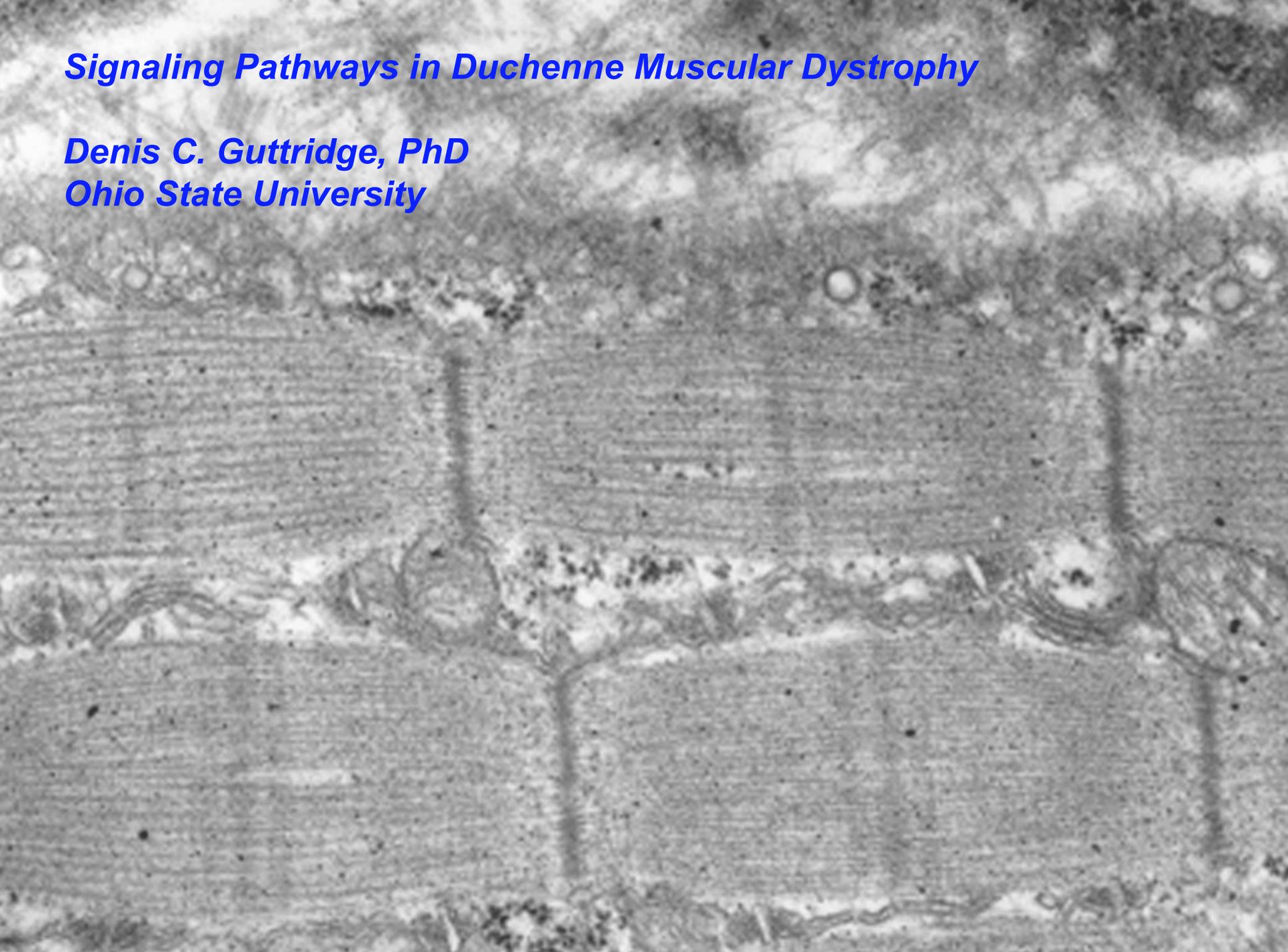


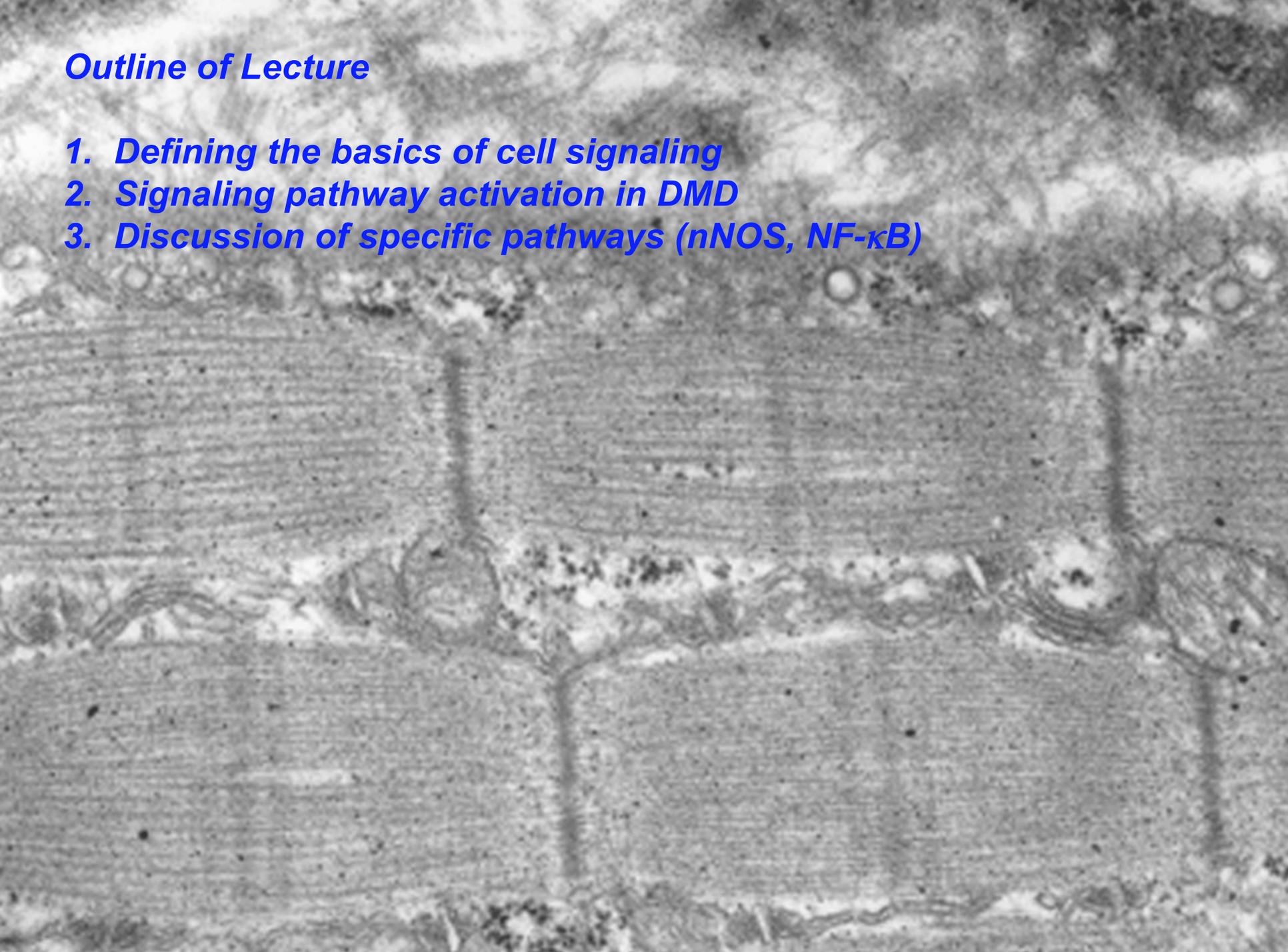
Signaling Pathways in Duchenne Muscular Dystrophy

***Denis C. Guttridge, PhD
Ohio State University***

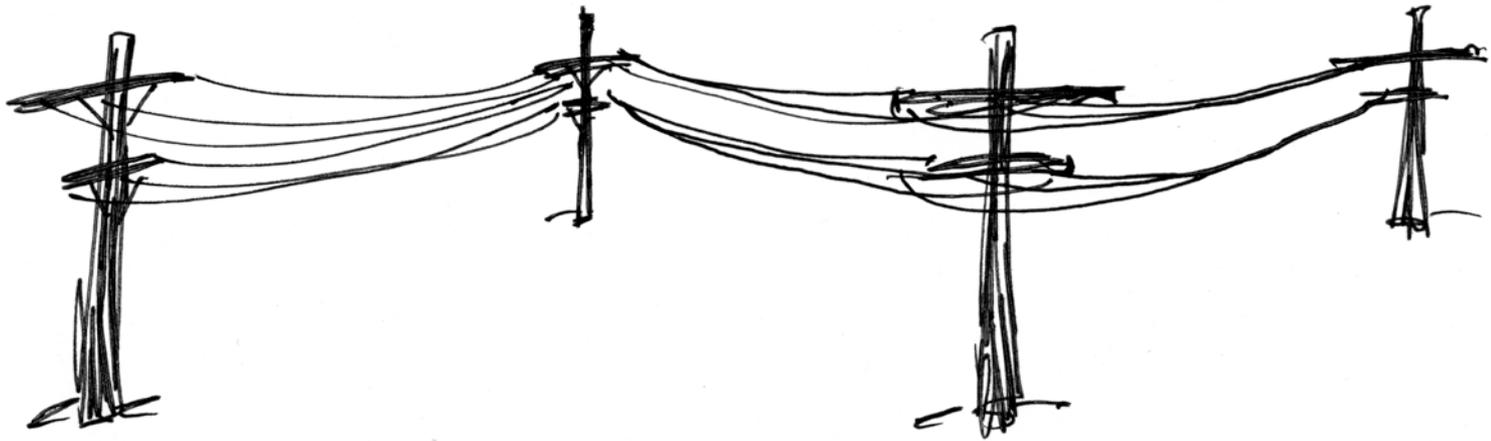


Outline of Lecture

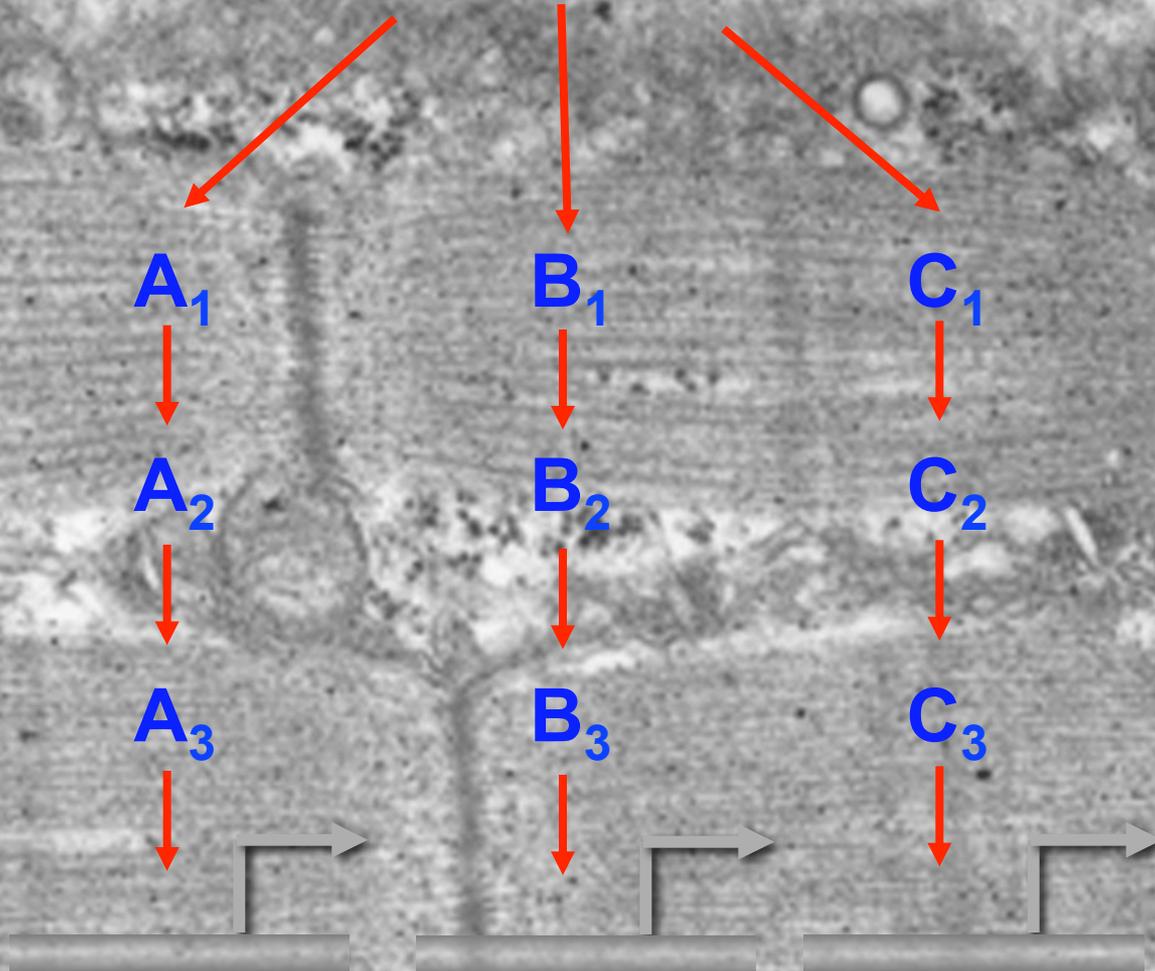
- 1. Defining the basics of cell signaling***
- 2. Signaling pathway activation in DMD***
- 3. Discussion of specific pathways (nNOS, NF- κ B)***



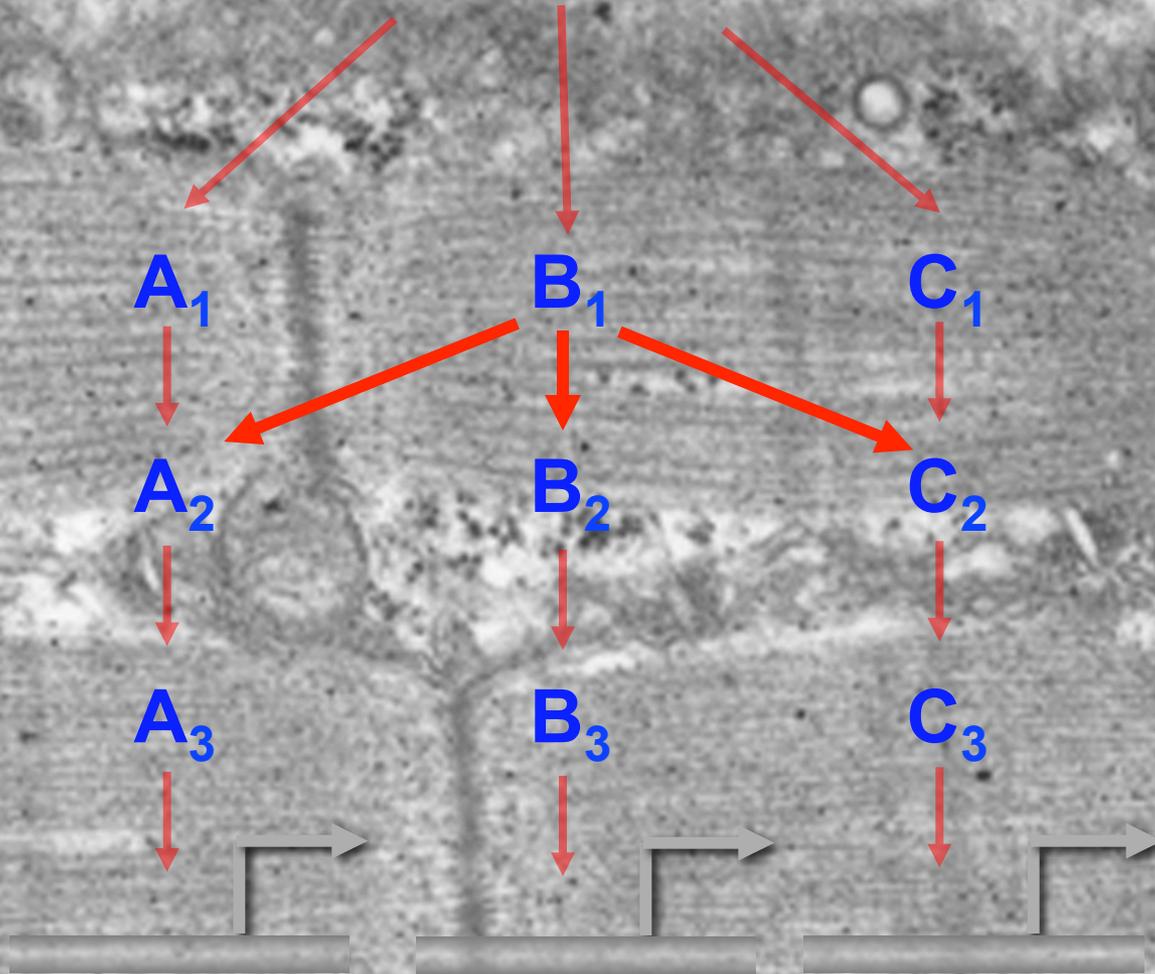
Defining the basics of cell signaling



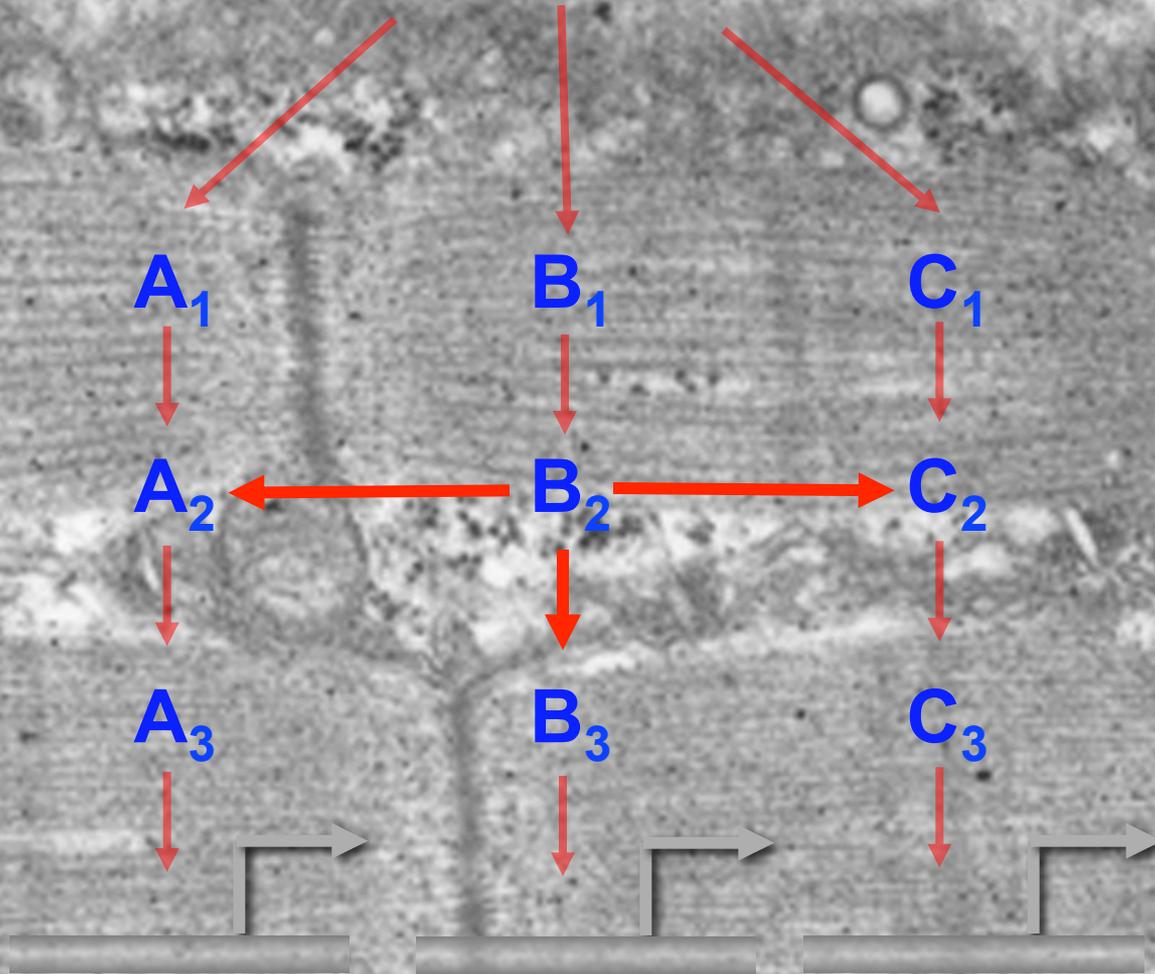
Defining the basics of cell signaling

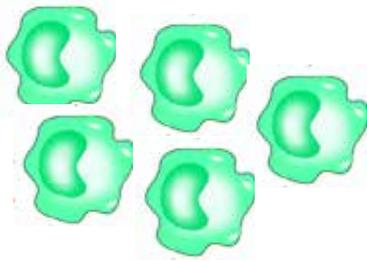


Defining the basics of cell signaling: crosstalk



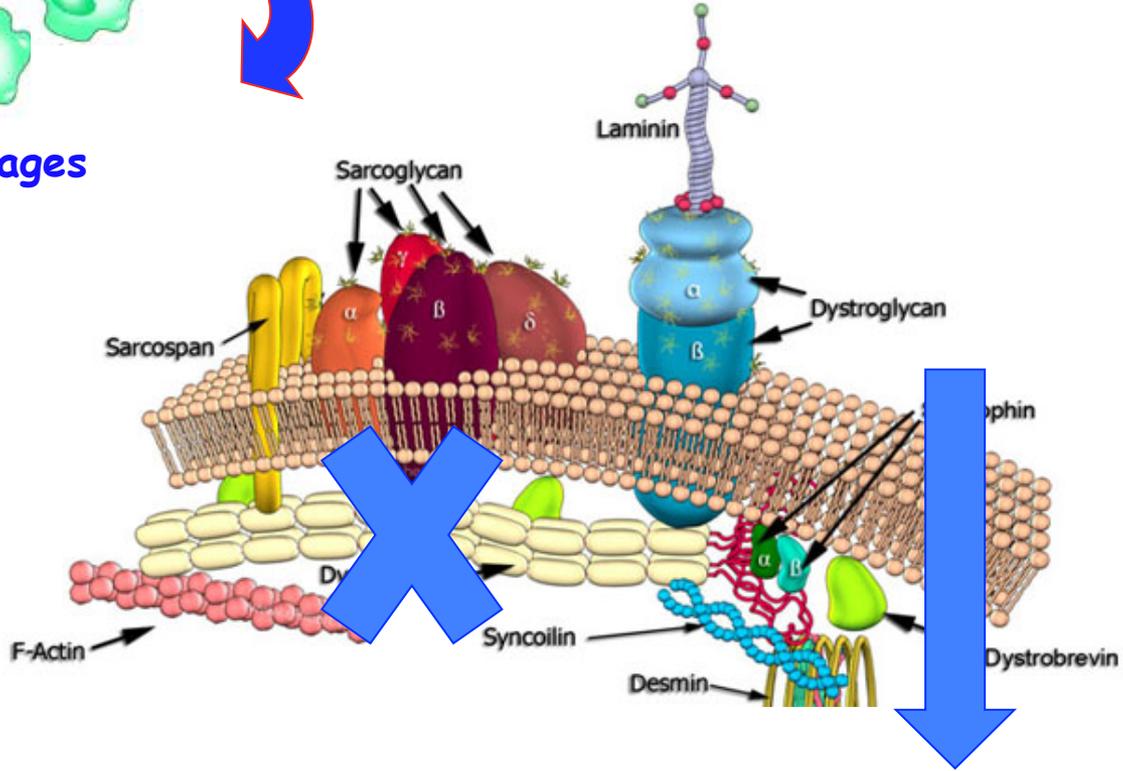
Defining the basics of cell signaling: crosstalk





macrophages

Inflammatory Cytokines (TNF, IL-1, IL-6)



Mitochondrion



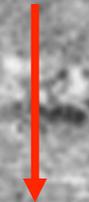
ROS

Ca⁺⁺

Signaling pathway activation in DMD

TNF, IL-1, IL-6

Ca⁺⁺



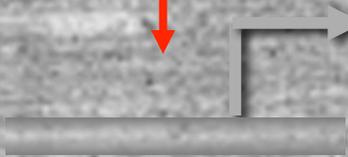
A₁



A₂



A₃



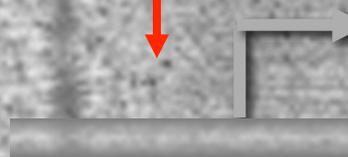
B₁



B₂



B₃



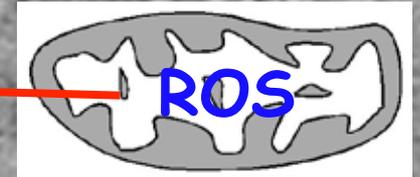
C₁



C₂

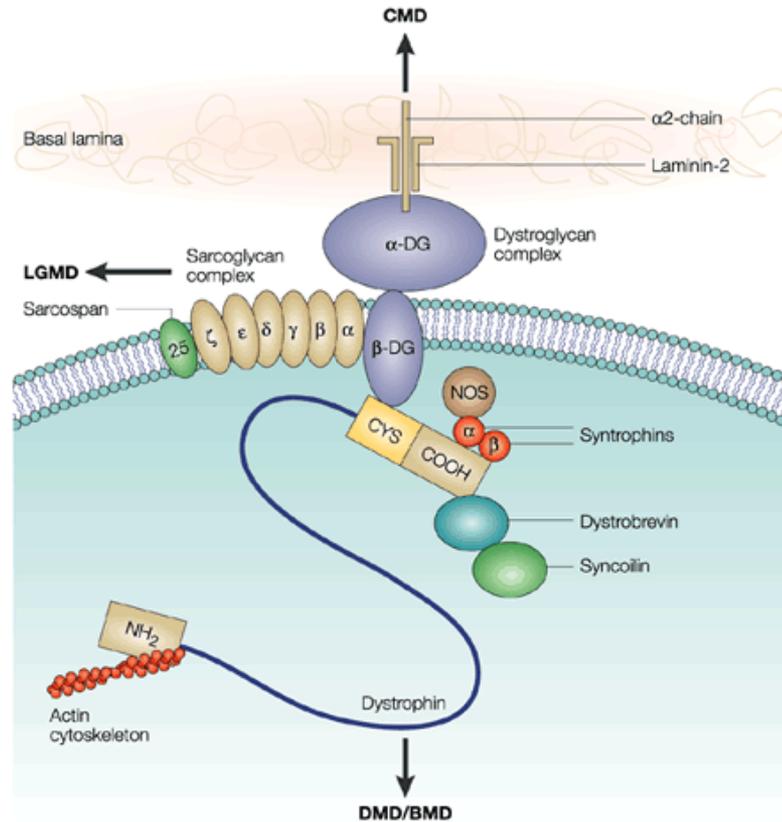


C₃



ROS

Discussion of specific pathways (nNOS)



Discussion of specific pathways (nNOS)

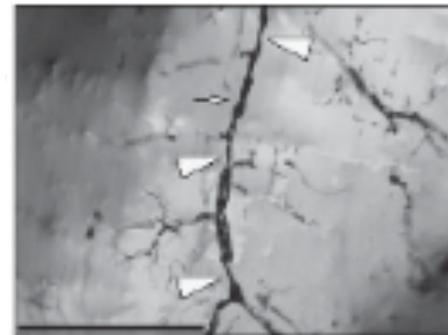
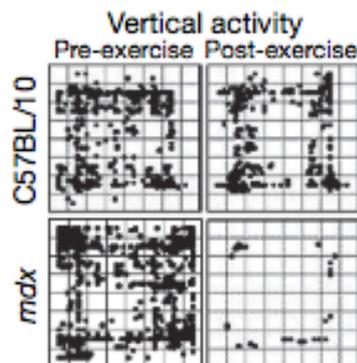
Vol 456 | 27 November 2008 | doi:10.1038/nature07414

nature

LETTERS

Sarcolemma-localized nNOS is required to maintain activity after mild exercise

Yvonne M. Kobayashi^{1,2,3,4}, Erik P. Rader^{1,2,3,4}, Robert W. Crawford^{1,2,3,4}, Nikhil K. Iyengar⁴, Daniel R. Thedens⁵, John A. Faulkner⁷, Swapnesh V. Parikh⁴, Robert M. Weiss⁴, Jeffrey S. Chamberlain⁸, Steven A. Moore⁶ & Kevin P. Campbell^{1,2,3,4}



Exaggerated fatigue response derives from insufficient contraction-induced muscle nNOS signaling to local blood vessels

mild exercise (muscle contraction)

Wild Type

mdx

nNOS signaling

nNOS mislocalization

Sildenafil (Viagra)
Tadalafil (Cialis)

NO

cGMP

Phosphodiesterase 5A (PDE5A)

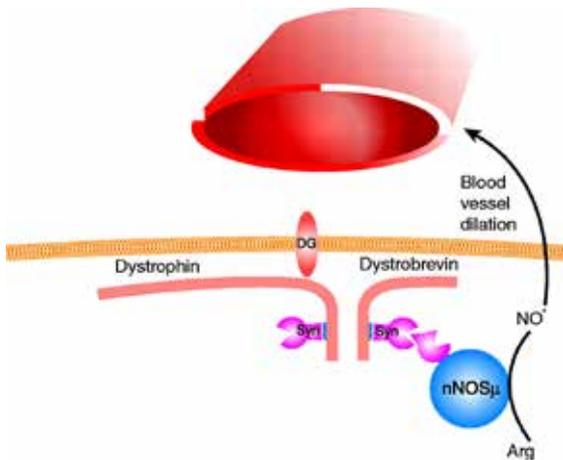
Vasodilation

cGMP

Vasoconstriction

Muscle oedema

Exaggerated Fatigue



4 studies found for: sildenafil and muscular dystrophy

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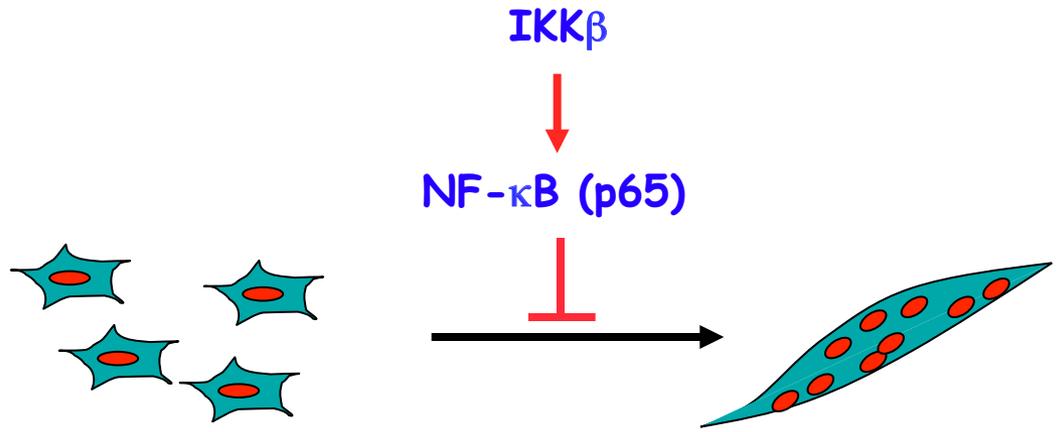
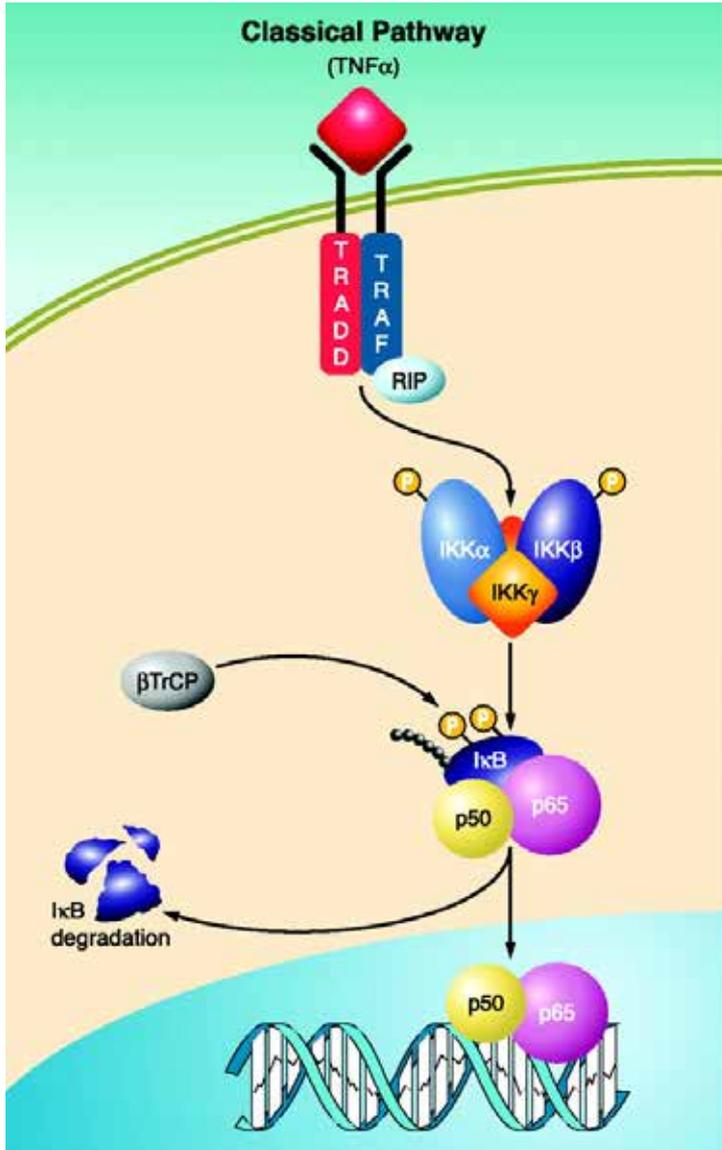
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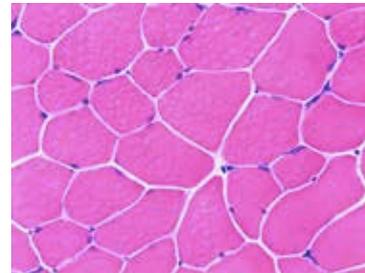
Rank	Status	Study
1	Suspended	Revatio for Heart Disease in Duchenne Muscular Dystrophy and Becker Muscular Dystrophy Conditions: Duchenne Muscular Dystrophy; Becker Muscular Dystrophy Intervention: Drug: Sildenafil
2	Completed	Effect of Modulating the nNOS System on Cardiac, Muscular and Cognitive Function in Becker Muscular Dystrophy Patients Condition: Becker Muscular Dystrophy Interventions: Drug: Sildenafil; Drug: Placebo
3	Completed	Tadalafil and Sildenafil for Duchenne Muscular Dystrophy Condition: Duchenne Muscular Dystrophy Interventions: Drug: Tadalafil; Drug: Sildenafil
4	Completed	PDE Inhibitors in DMD Study (Acute Dosing Study) Condition: Duchenne Muscular Dystrophy Intervention: Drug: Tadalafil and Sildenafil

Discussion of specific pathways (NF- κ B)

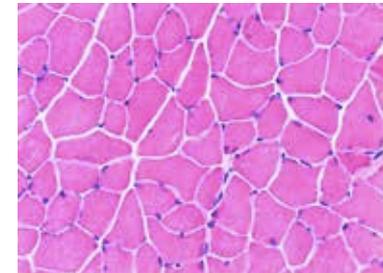


Guttridge et al., 1999, *MCB*
 Guttridge et al., 2000, *Science*
 Wang et al., 2007, *MCB*
 Bakkar et al., 2008, *JCB*
 Wang et al., 2008, *Cancer Cell*
 Dahlman et al., 2009, *JBC*

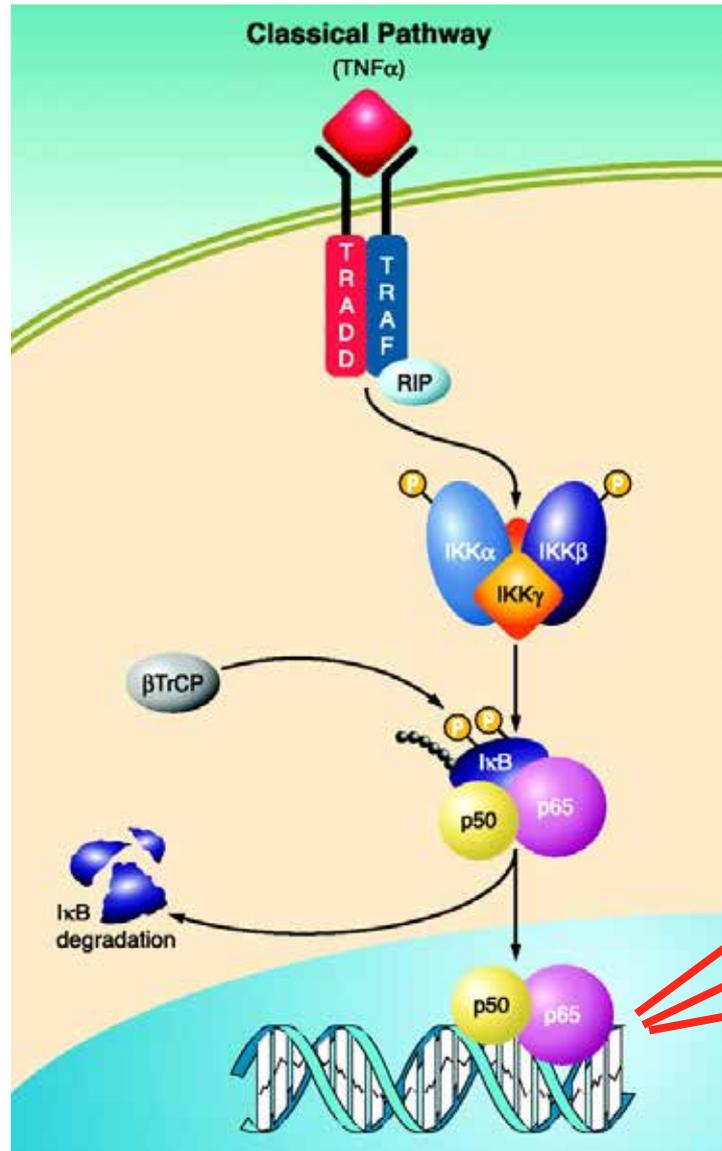
wild type



IKK β



Discussion of specific pathways (NF- κ B)



Cytokines (TNF, IL-1, IL-6)

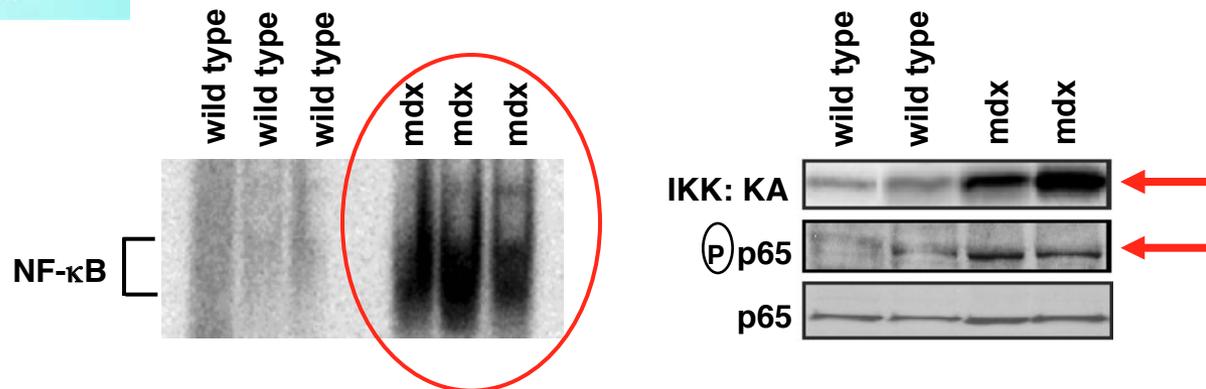
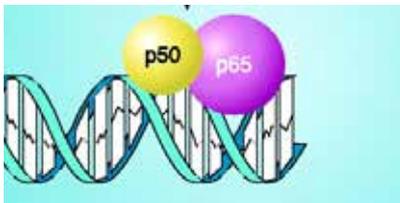
Chemokines

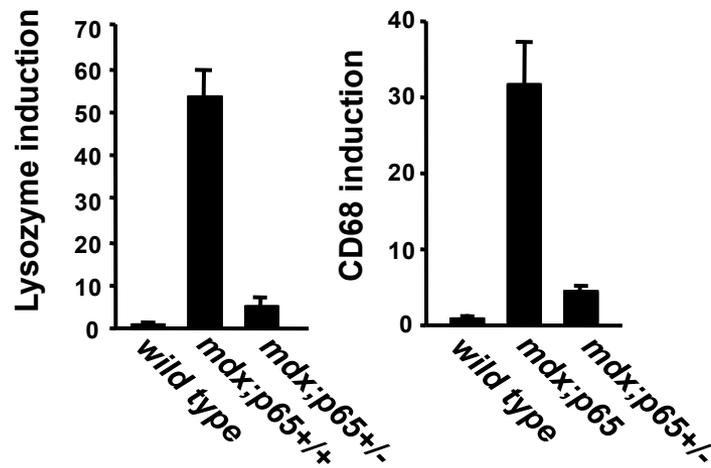
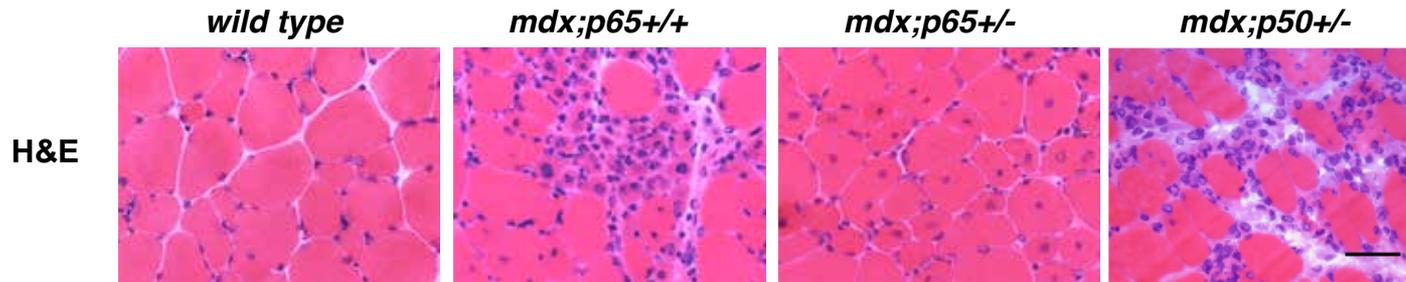
Metalloproteinases (MMPs)

Discussion of specific pathways (NF- κ B)

Interplay of IKK/NF- κ B signaling in macrophages and myofibers promotes muscle degeneration in Duchenne muscular dystrophy

Swarnali Acharyya,^{1,2} S. Armando Villalta,³ Nadine Bakkar,^{1,2} Tepmanas Bupha-Intr,⁴ Paul M.L. Janssen,⁴ Micheal Carathers,¹ Zhi-Wei Li,⁵ Amer A. Beg,⁵ Sankar Ghosh,⁶ Zarife Sahenk,⁷ Michael Weinstein,^{1,8} Katherine L. Gardner,⁹ Jill A. Rafael-Fortney,⁹ Michael Karin,¹⁰ James G. Tidball,³ Albert S. Baldwin,¹¹ and Denis C. Guttridge^{1,2,12}





Approaches to Inhibiting NF- κ B for DMD Therapy

Gene Therapy

Tang, Y., et al., Gene Therapy, 2010 - AAV (shRNAp65)

Yang, Q et al., Gene Therapy, 2002 - AAV (IKK β DN)

Cell Based Therapy

Lu A., et al., Mol. Therapy, 2012 - p65 KO muscle stem cells

Pharmacological Therapy

Evans et al., Clin. Nutr., 2010 - Green tea extract

Messina et al., Exp. Neurol. 2009 - Flavonoid extract

Siegel et al., Neuromuscul. Disord. 2009 - PDTC

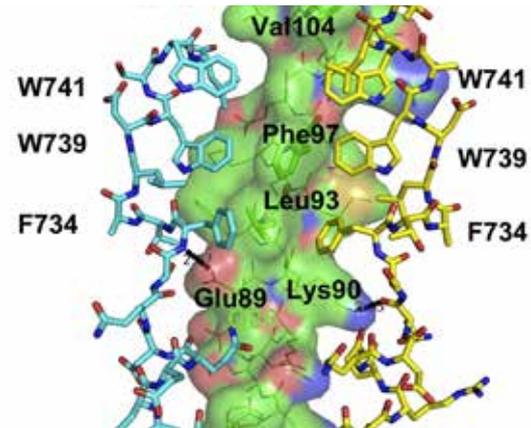
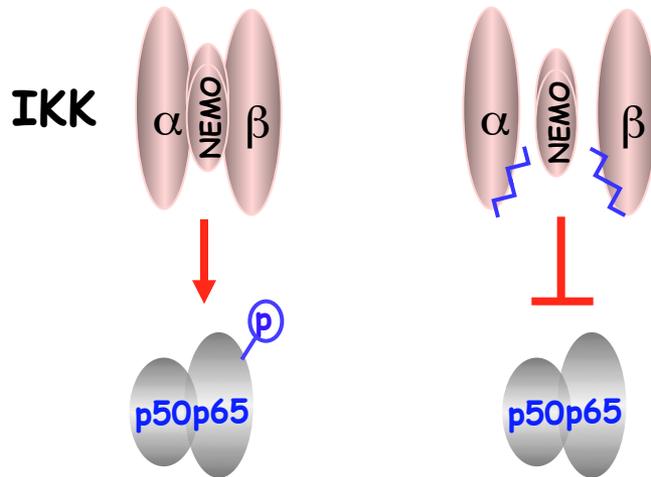
Pan Y et al., Mol. Cells, 2008 - Curcumin

Hnia et al., Am. J. Pathol., 2008 - L-arginine

Mok et al., Pediatr Res., 2008 - L-glutamine

Whitehead et al., J. Physiol., 2008 - N-Acetylcysteine

Pharmacological Inhibition of NF- κ B by NBD (NEMO Binding Domain)



Rushe et al., *Structure*, 2008

Antennapedia - TALDWSWLQTE (28 aa)

NBD therapy in various disease models (1499 references)

Dai et al., *JBC*, 2004 - Arthritis

Dasgupta et al., *J. Immunol.*, 2004

DiMeglio et al., *Arthritis Rheum.* 2005 - General Anti-Inflammatory

Van den Tweel et al., *Pediatr. Res.*, 2006 - Brain Ischemia

Tas et al., *Arthritis Res.*, 2006 - Arthritis

Clohisy et al., *J. Orthop Res.*, 2006 - Bone loss

De Plaen et al., *Pediatric Res.*, 2007 - Colitis

Dave et al., *J. Immunology*, 2007 - Colitis

Ianaro et al., *Cancer Letters*, 2009 - Melanoma

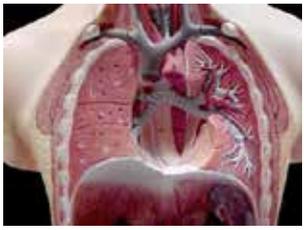
Long et al., *World J. Gastro.* 2009 - Pancreatitis

Tilstra et al., *JCI*, 2012 - Progeria

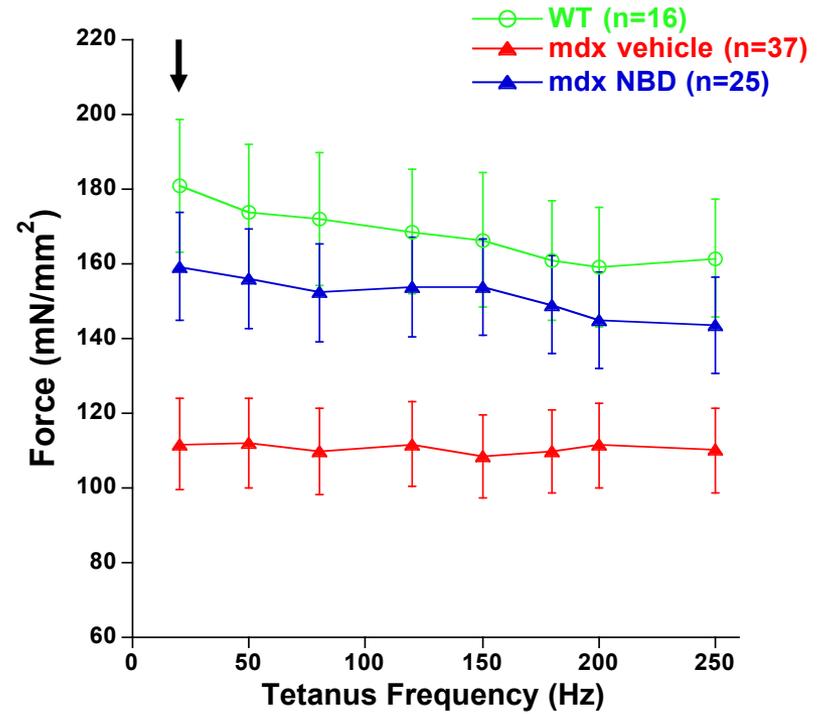
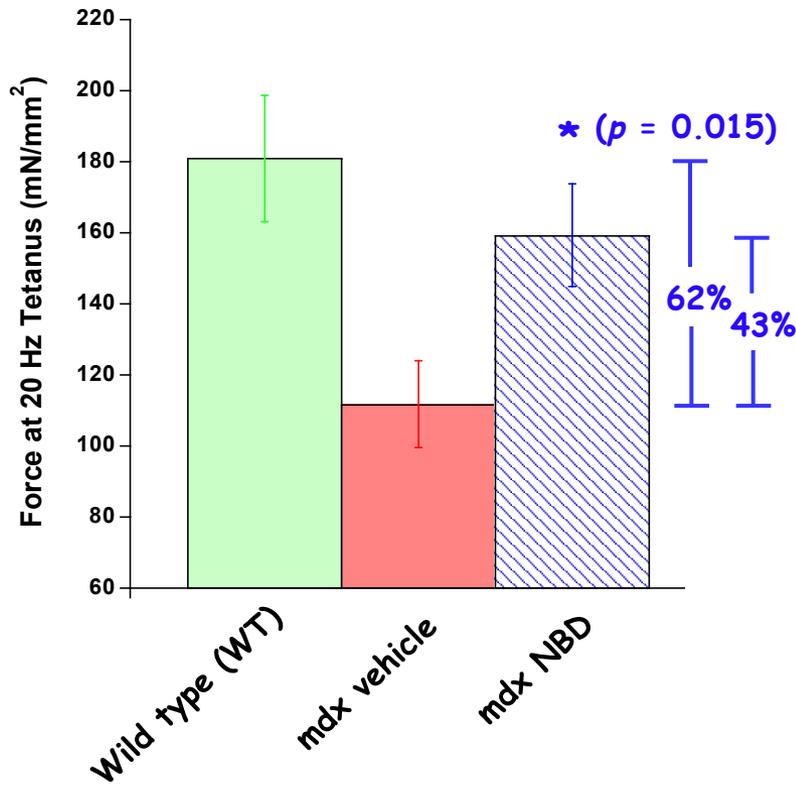
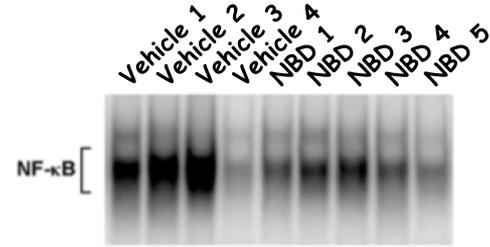
NBD treatment of mdx mice

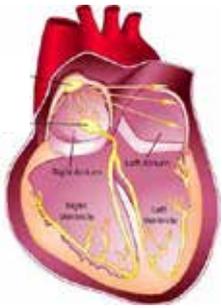


4 week treatment; 3 x weekly; 200ug/mouse; IP

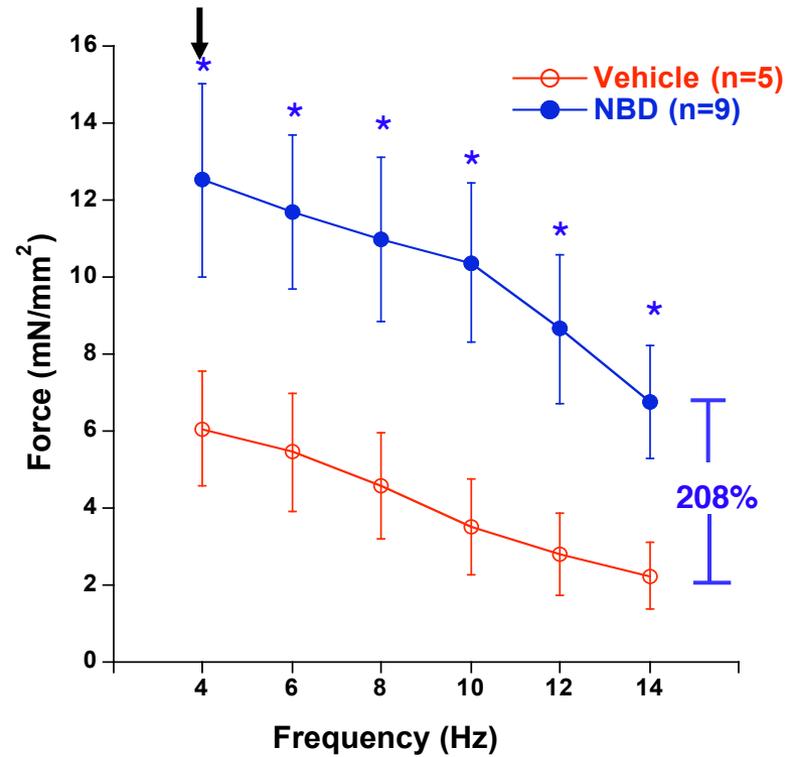
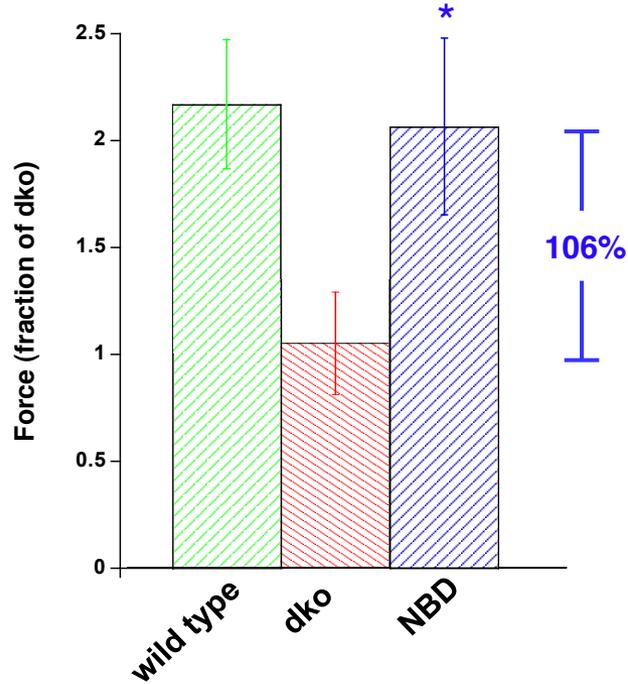
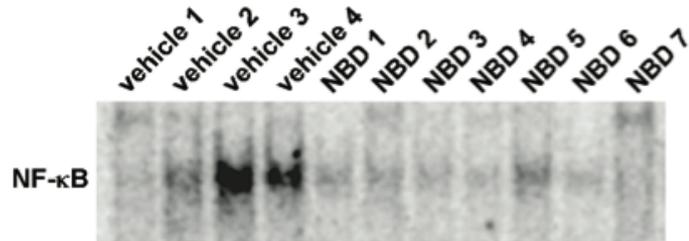
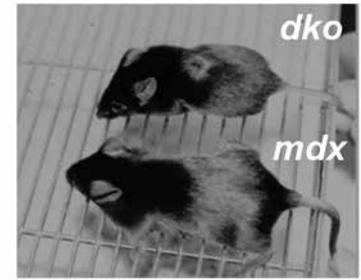


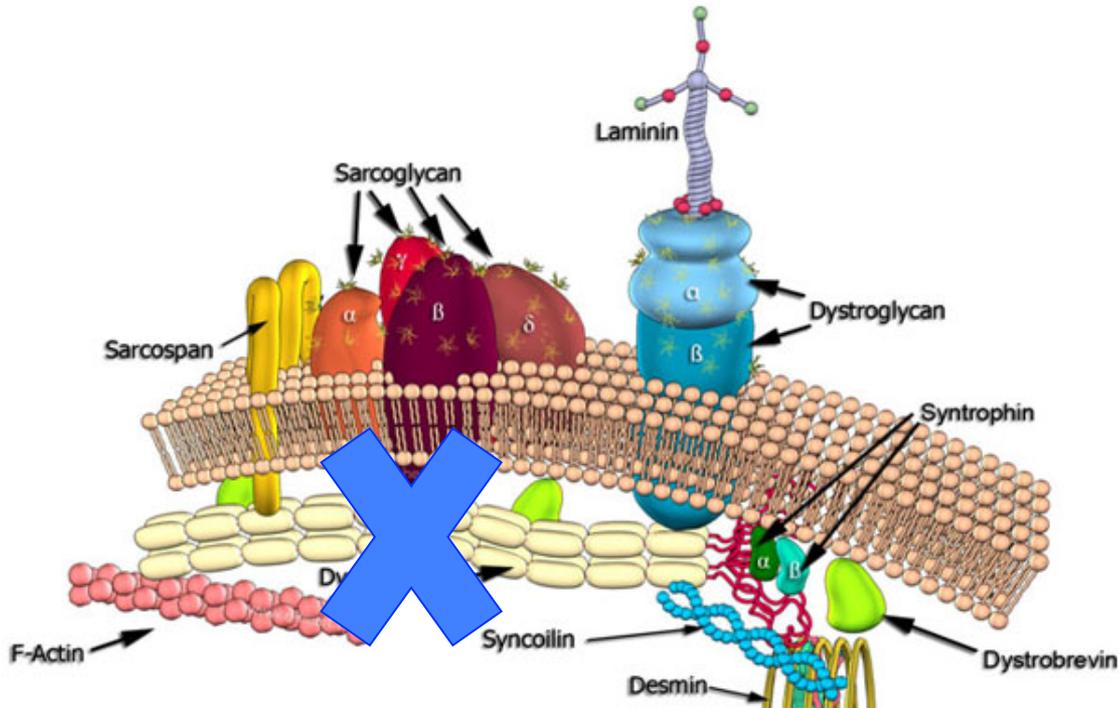
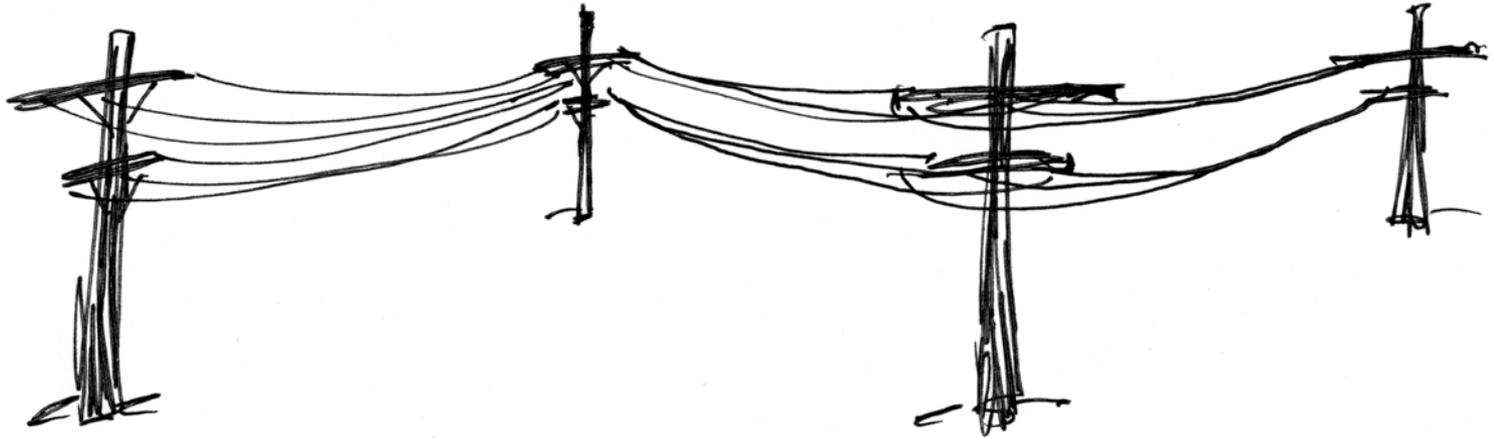
NBD treatment significantly improves diaphragm function in mdx mice





NBD treatment rescues heart function in dko mice





TGF β
myostatin

JNK

NFAT

Akt