Developing NF-κB Therapy as a treatment for DMD

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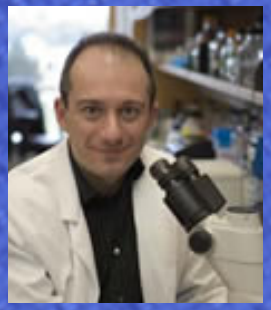

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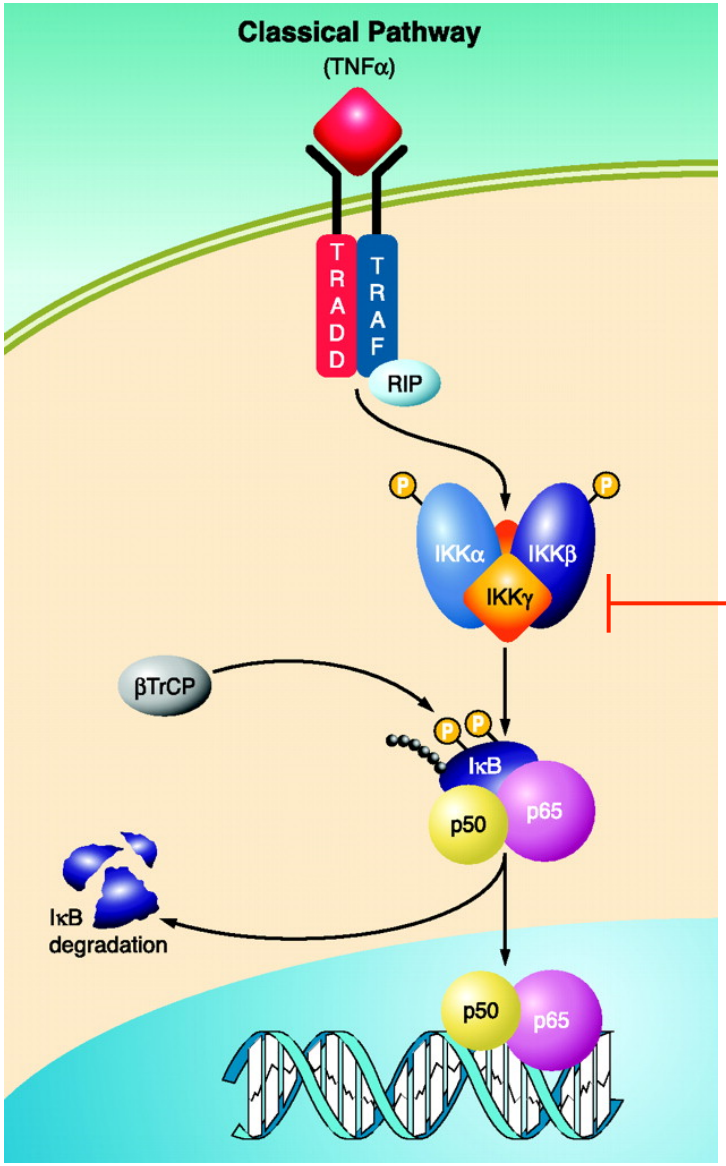
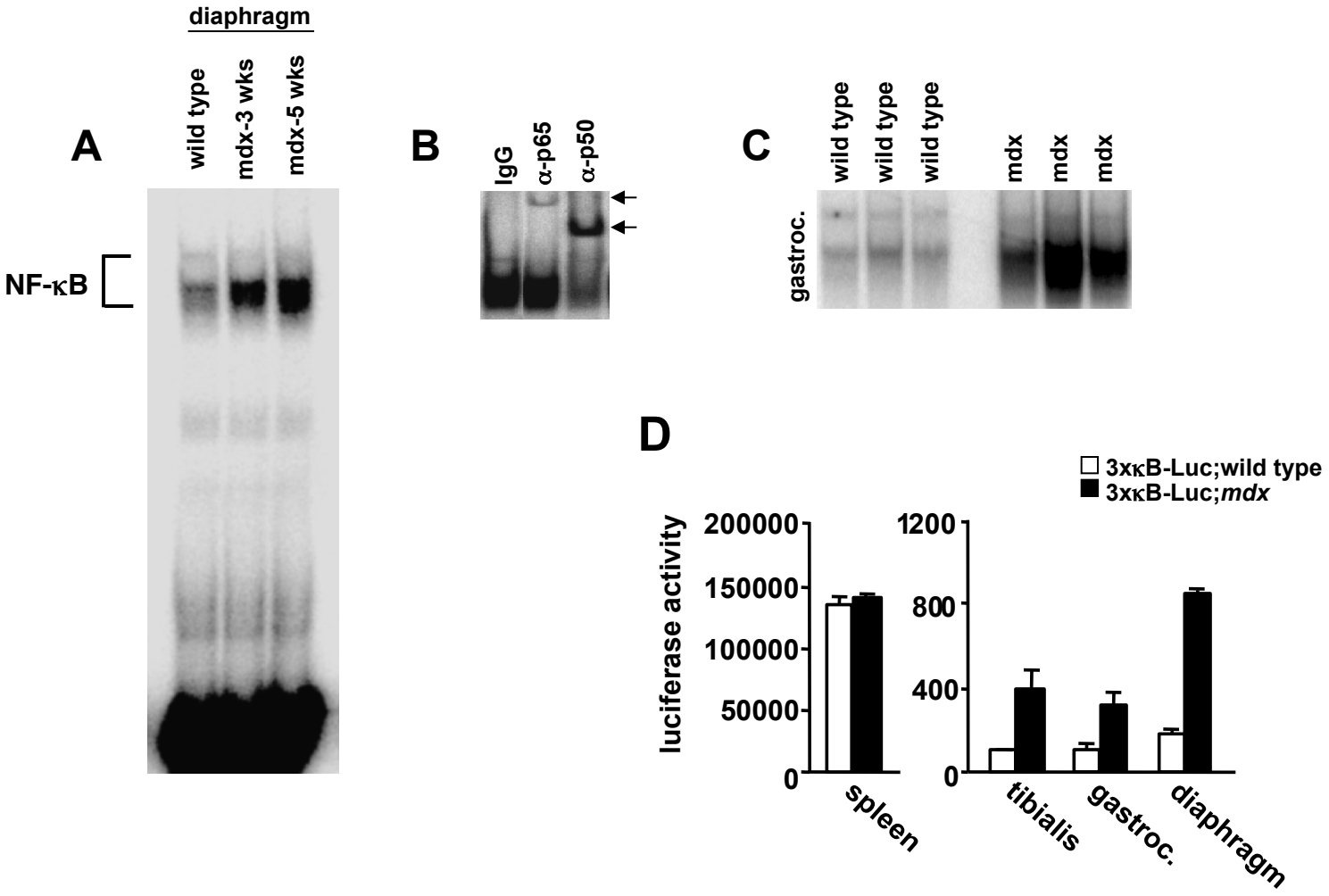
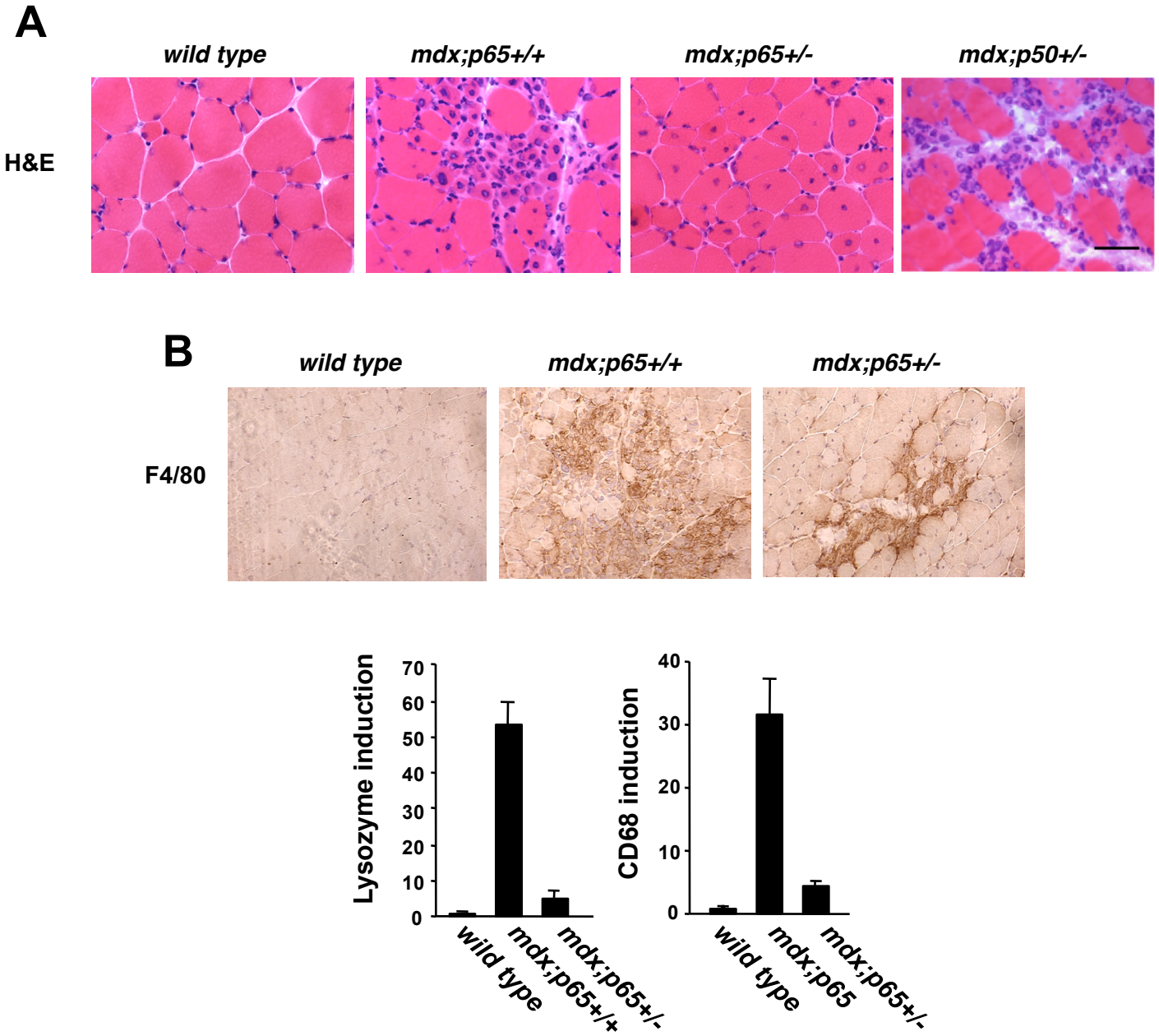


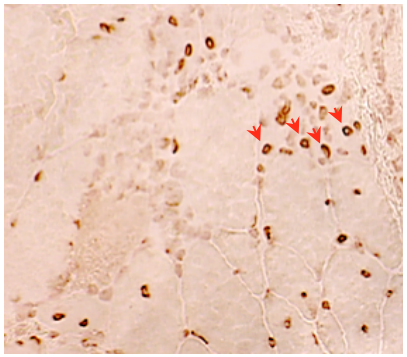
Bakkar and Guttridge, 2010, Physiol. Rev.



Acharyya et al., 2007, JCI



Acharyya et al., 2007, JCI



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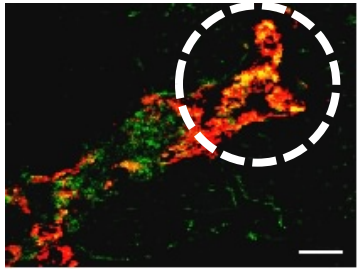
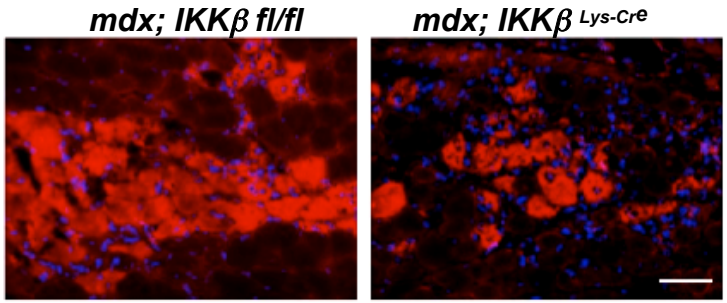
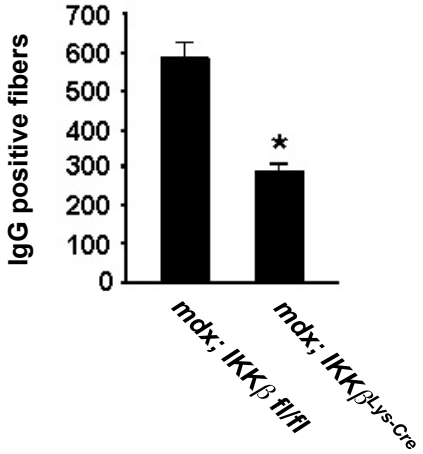
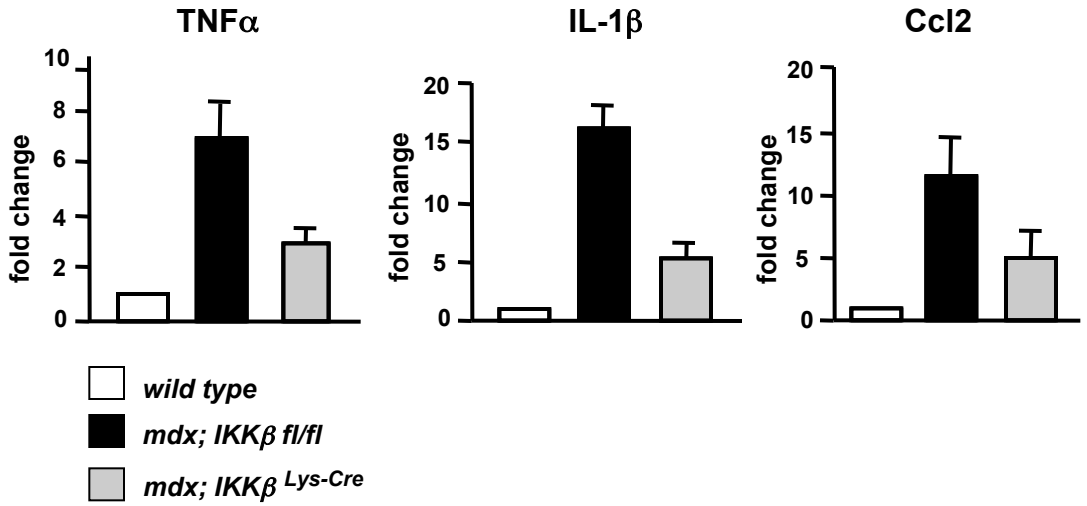


Lys-Cre/ IKK$\beta^{fl/fl}$

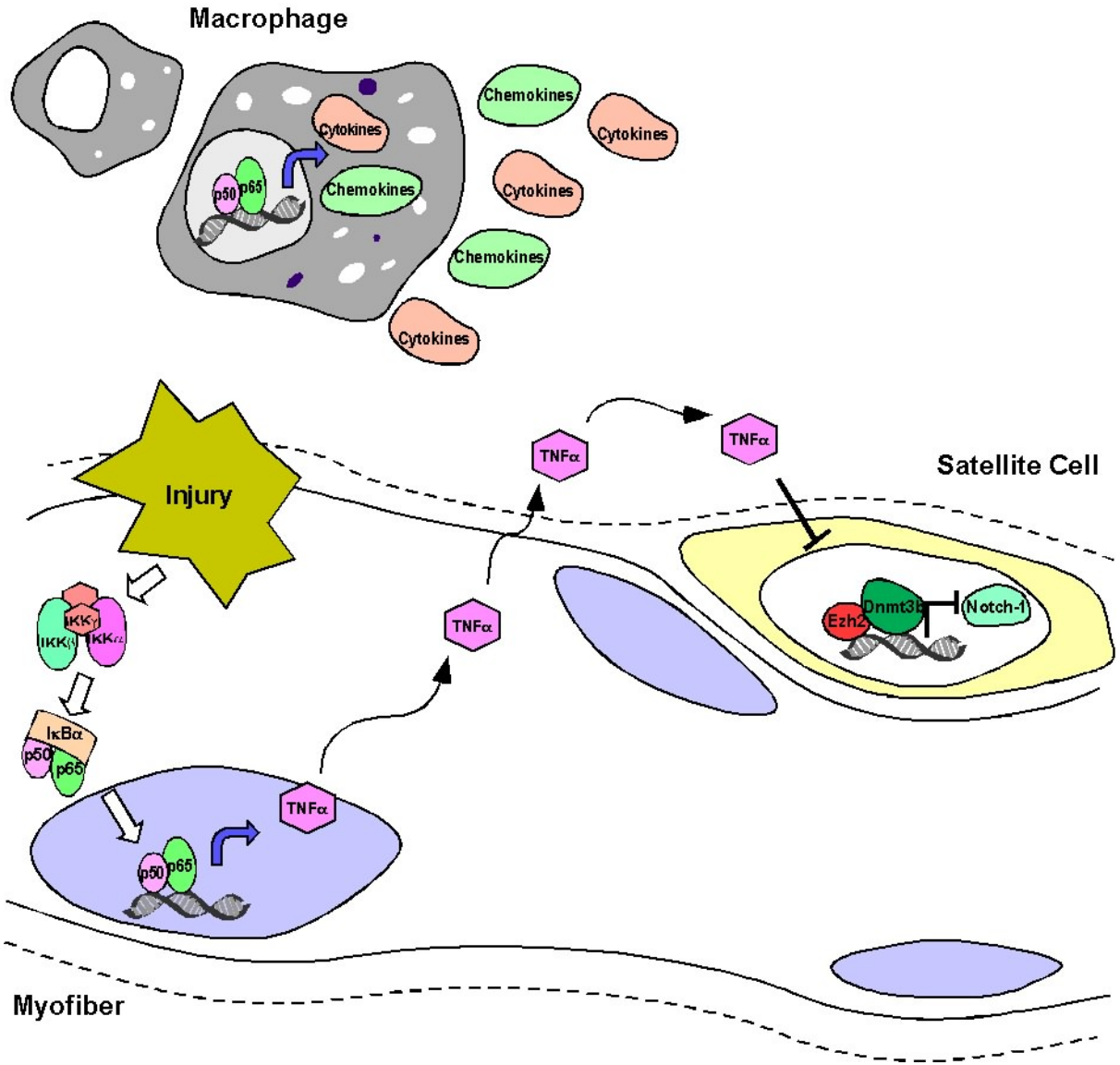
IKKβ/NF-κB functions in macrophages in dystrophic muscle to promote inflammation







Acharyya et al., 2007, JCI



Acharyya et al., 2007, JCI
Acharyya et al., 2010, PLoS One
Peterson et al., 2011 Curr. Top., Dev. Biol,

Approaches to Inhibiting NF-κB for DMD Therapy

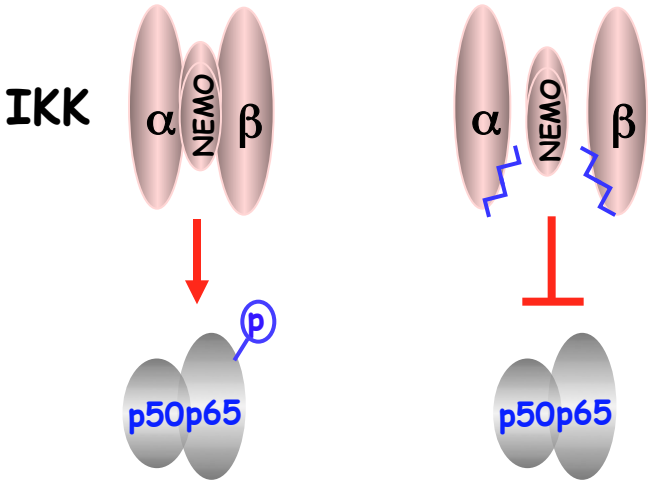
Pharmacological

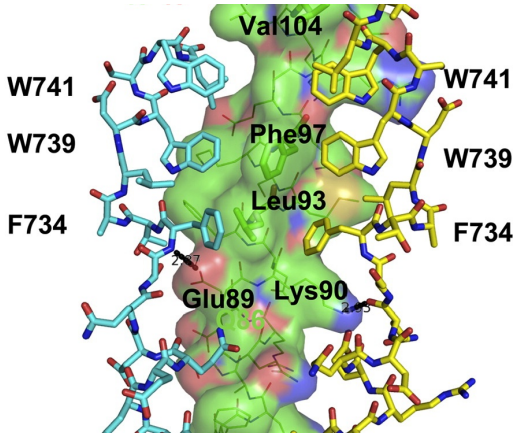
Evans et al., Clin. Nutr., 2010 – Green tea extract
Messina et al., Exp. Neurol. 2009 – Flavonoid extract
Siegel et al., Neuromuscul. Disord. 2009 – PDTC
Pan Y et al., Mol. Cells, 2008 – Curcumin
Hnia et al., Am. J. Pathol., 2008 – L-arginine
Mok et al., Pediatr Res., 2008 – L-glutamine
Whitehead et al., J. Physiol., 2008 – N-Acetylcysteine

Gene Therapy

Tang, Y., et al., Gene Therapy, 2010 – AAV (shRNAp65)
Yang, Q et al., Gene Therapy, 2002 – AAV (IKKβ DN)

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





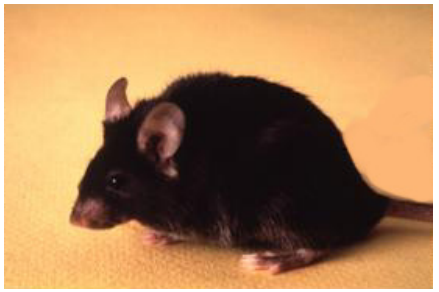
Rushe et al., Structure, 2008

Antennapedia – TALDWSWLQTE (28 aa)

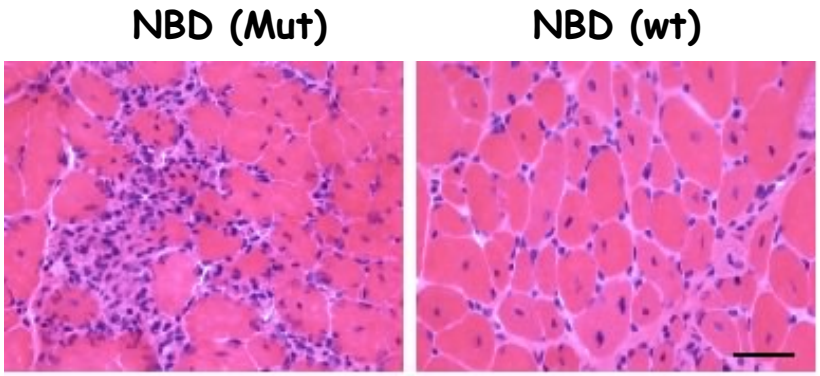
NBD therapy in various disease models (1600 references)

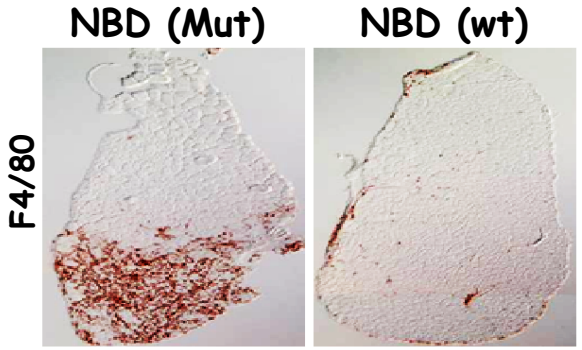
Dai et al., JBC, 2004- Arthristis
Dasgupta et al., J. Immunol., 2004
DiMeglio et al., Arthritis Rheum. 2005 - General Anti-Inflammatory
Van den Tweel et al., Pediatr. Res., 2006 - Brain Ischemia
Tas et al., Arthritis Res., 2006 - Arthritis
Clohisy et al., J. Orthop Res., 2006 - Bone loss
De Plaen et 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

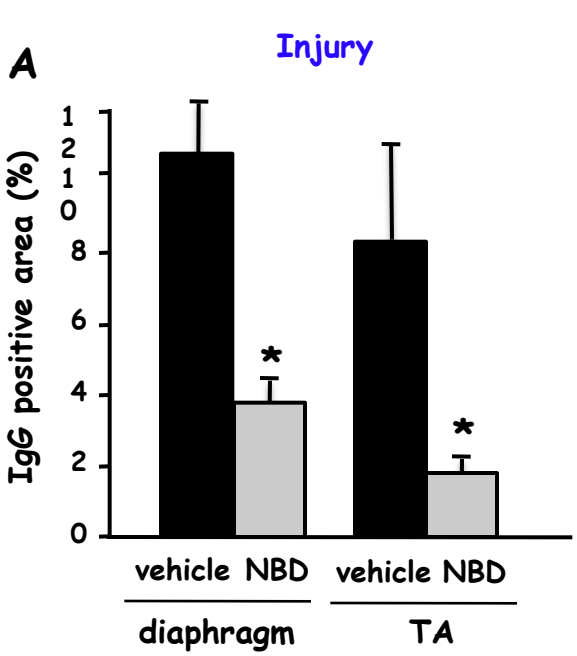
NBD treatment of mdx mice

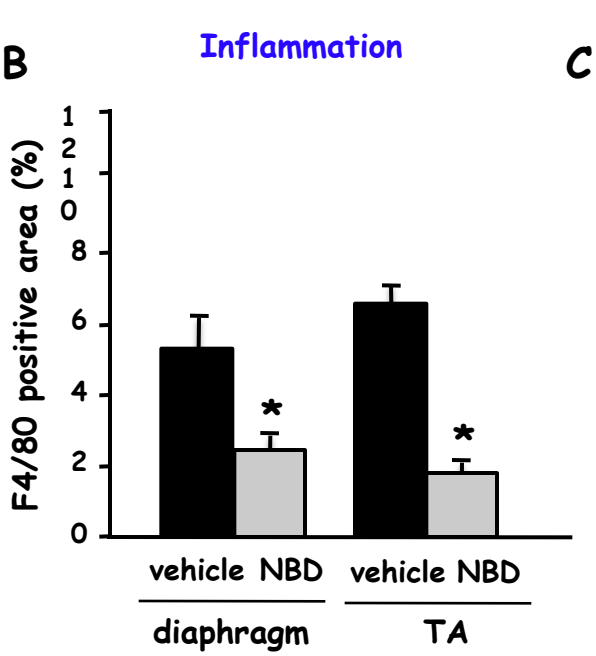


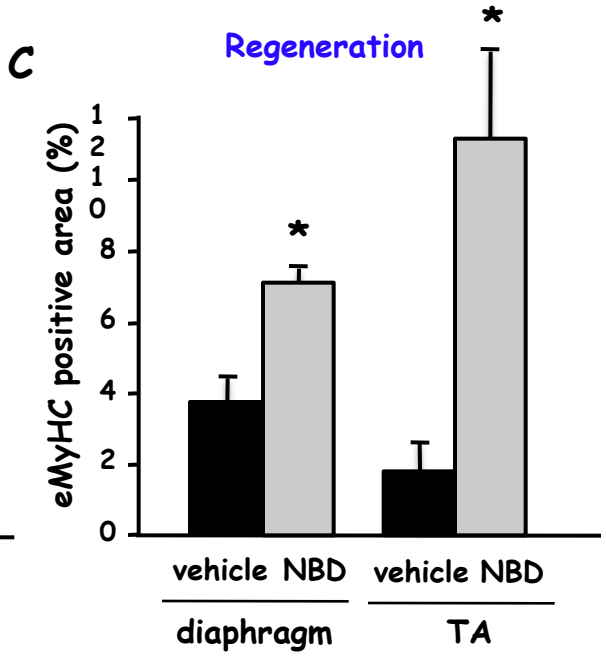
4 week treatment; 3 x weekly; 200ug/mouse; IP



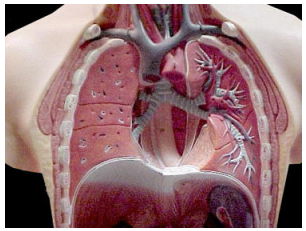




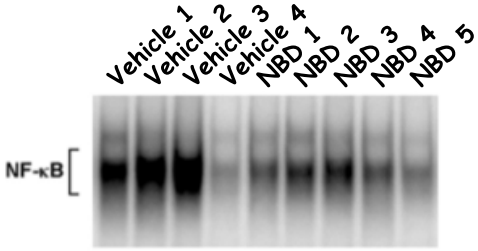


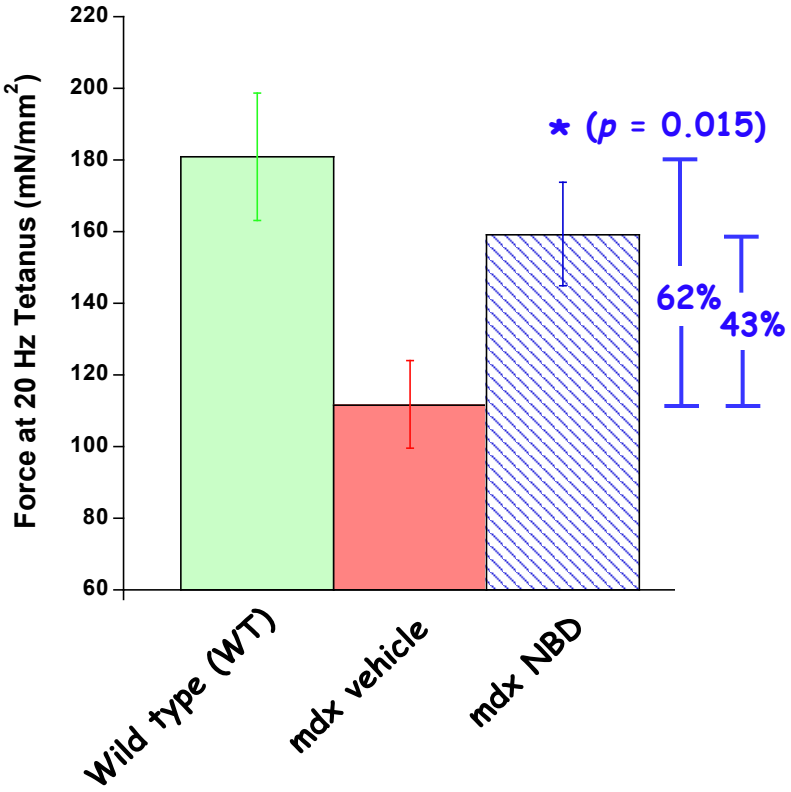


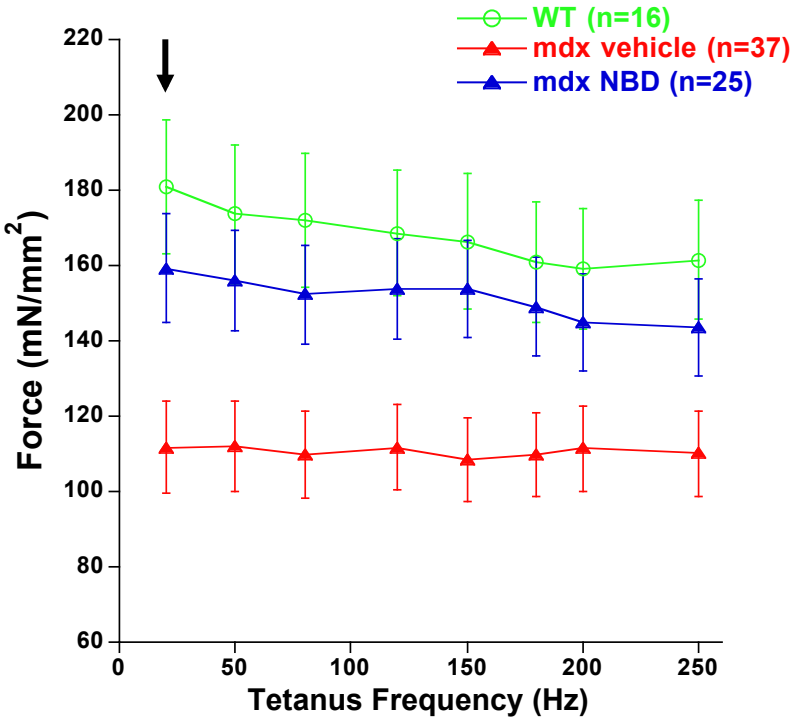
Acharyya et al., 2007, JCI
Peterson et al., 2011, Mol. Med.



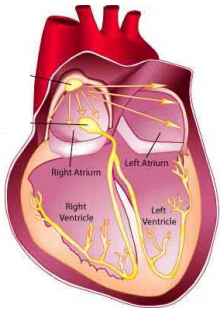
NBD treatment significantly improves diaphragm function in mdx mice



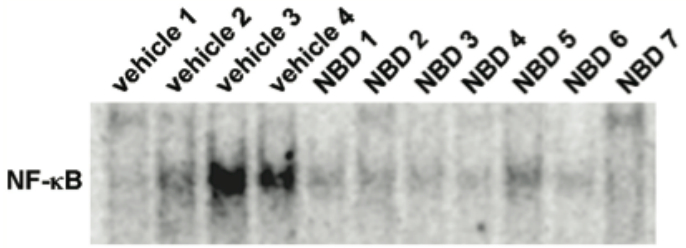


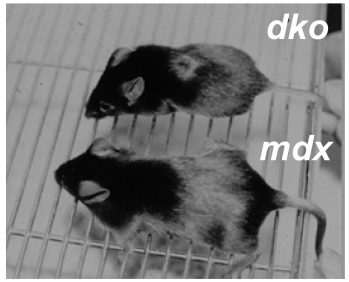


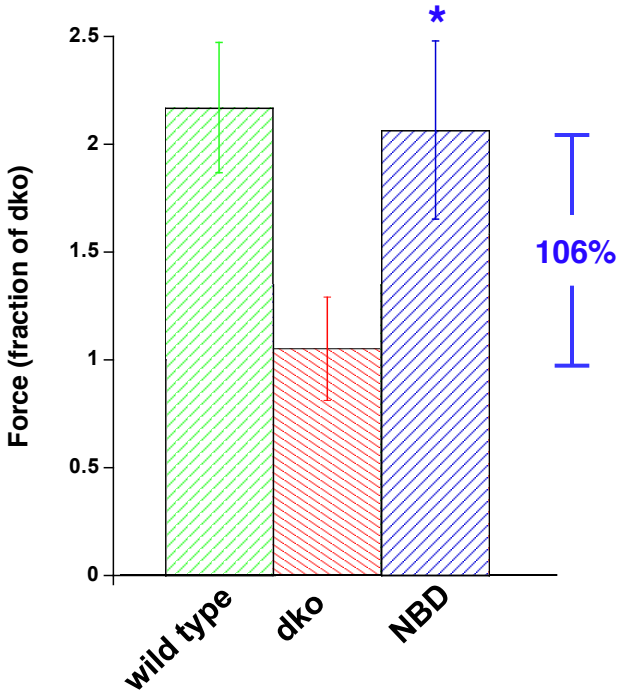
Peterson et al., 2011, Mol. Med.

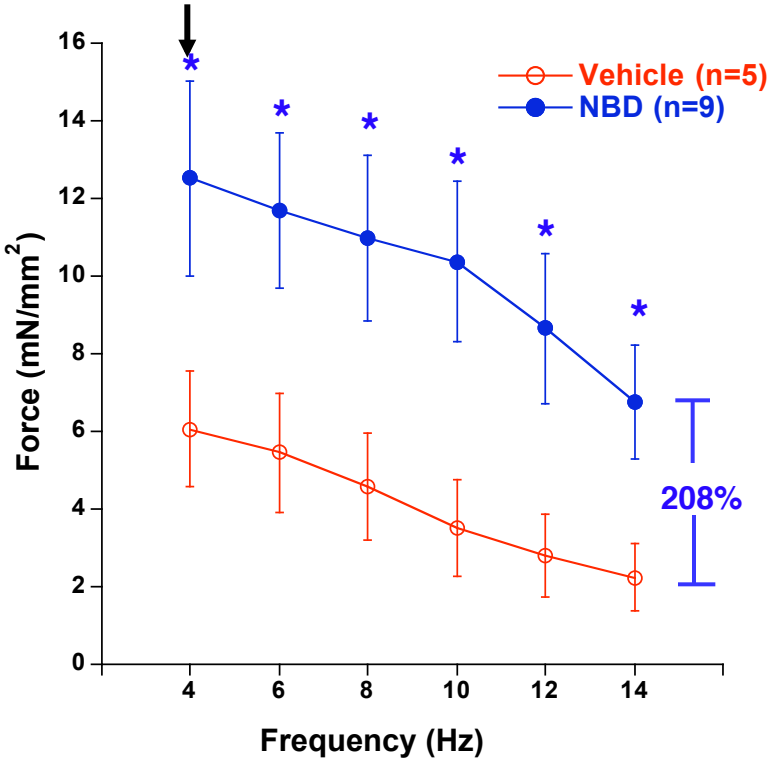


NBD treatment rescues heart function in dko mice



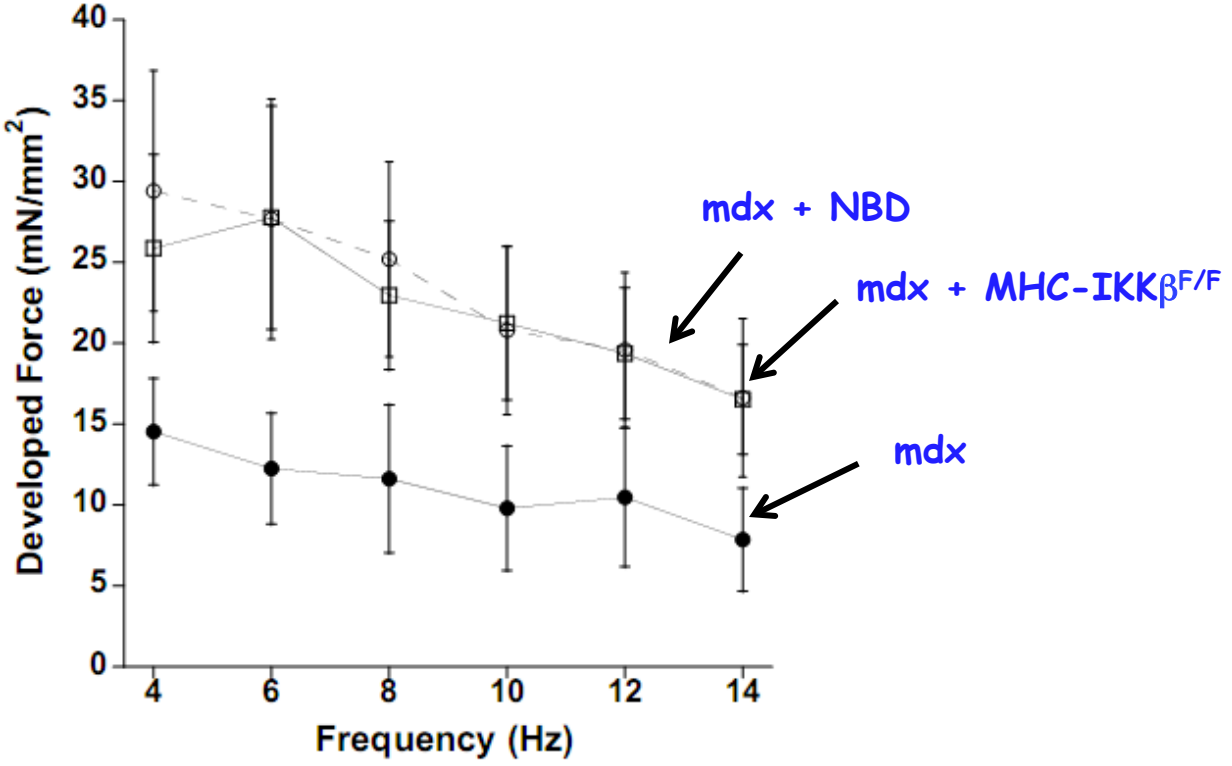






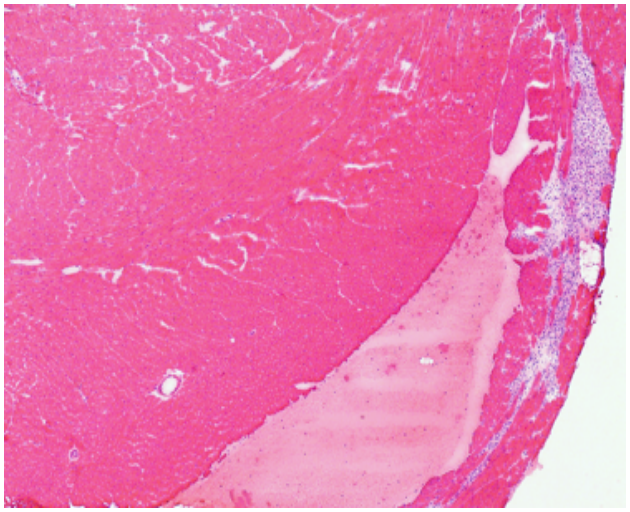
Delfin et al., 2011, J. Transl. Med.

Deletion of IKKβ in the heart rescues cardiac function in mdx mice

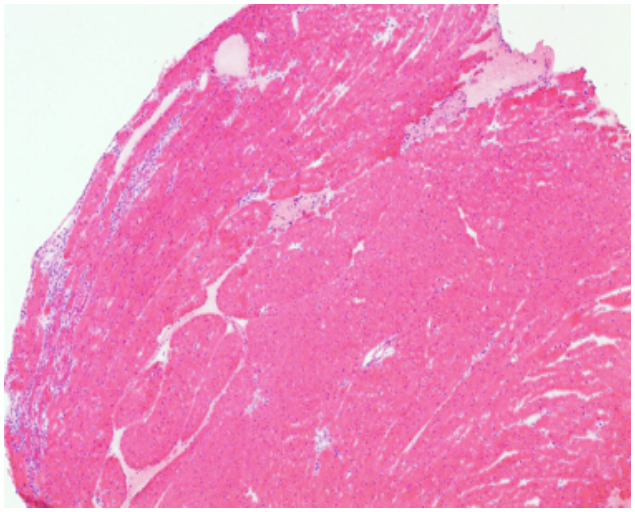


Deletion of IKKβ in the heart does not rescue mdx histopathology

mdx



mdx + MHC-IKKβ$^{F/F}$



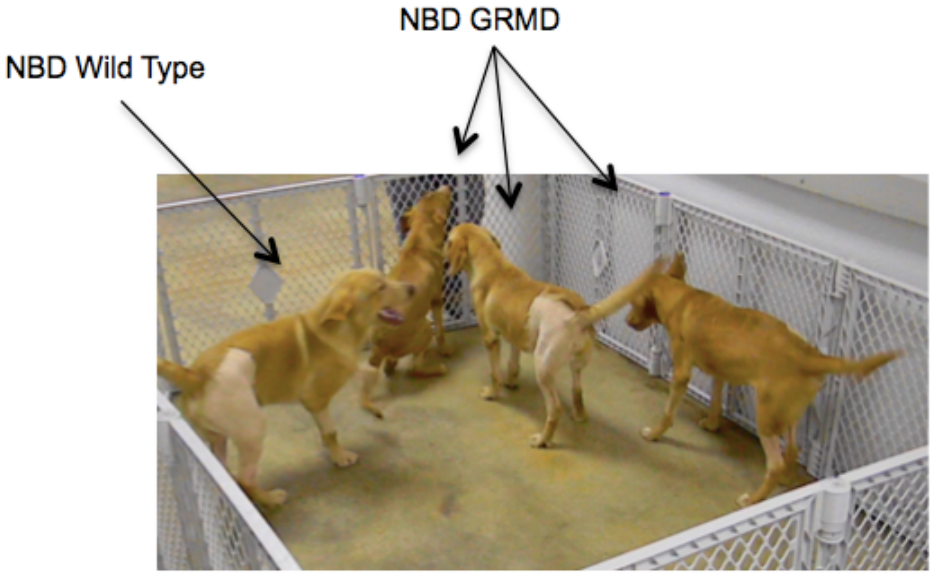
GRMD NBD Phase I/II Pre-Clinical Trial

- Total of 6 GRMD and 3 Normal dogs treated with NBD.
- Two cohorts of dogs treated with a 4 month course of NBD (10 mg/kg, IV, 3 X weekly), with each beginning treatment at 2 months of age.

Cumin
Wild type + NBD

Wasabi

Pepper
GRMD + NBD



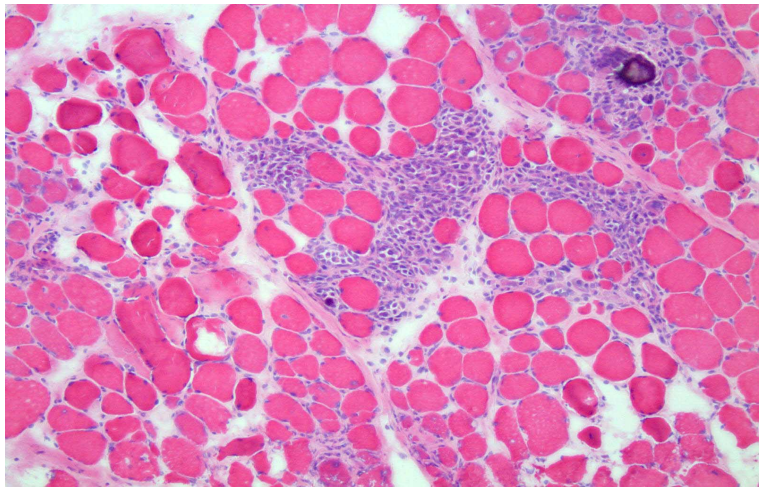
NBD GRMD	B.w.(kg)-2 m	B.w.(kg)-6 m	% inc.
Wasabi	5.2	16.1	209.6
Pepper	4.9	15.1	208.2
Hiver	5	15.1	202
Automne	4.2	9.3	121.4
	4.82	13.9	185.3
	0.43	3.1	42.7

Nat. Hist. GRMD	B.w.(kg)-2 m	B.w.(kg)-6 m	% inc.
Cilantro	6.8	14.2	108.8
Lyle	6.5	10.4	60
Napoleon	5.4	12.3	127.8
Summer	5.6	9.8	75
Jane	5	10.9	118
Mean	5.86	11.52	97.92
s. dev	0.76	1.76	29.06
p (vs NBD)	0.047	0.2	0.032*

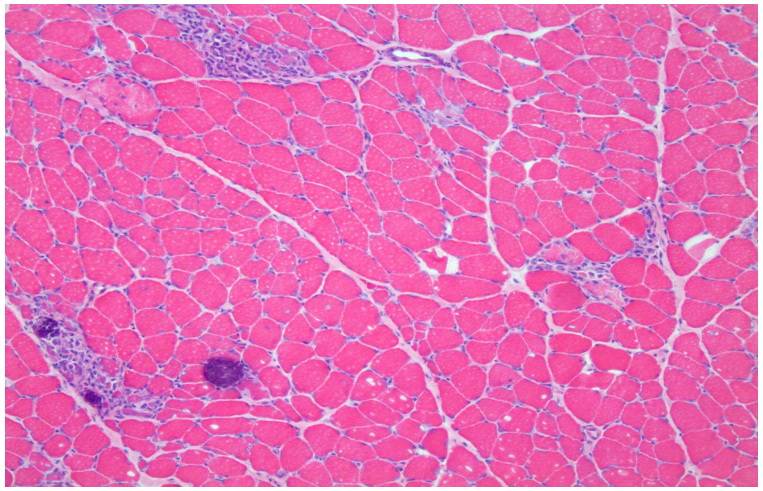
*rank sum test

NBD Treatment Improves the Histopathology of GRMD Dogs

GRMD



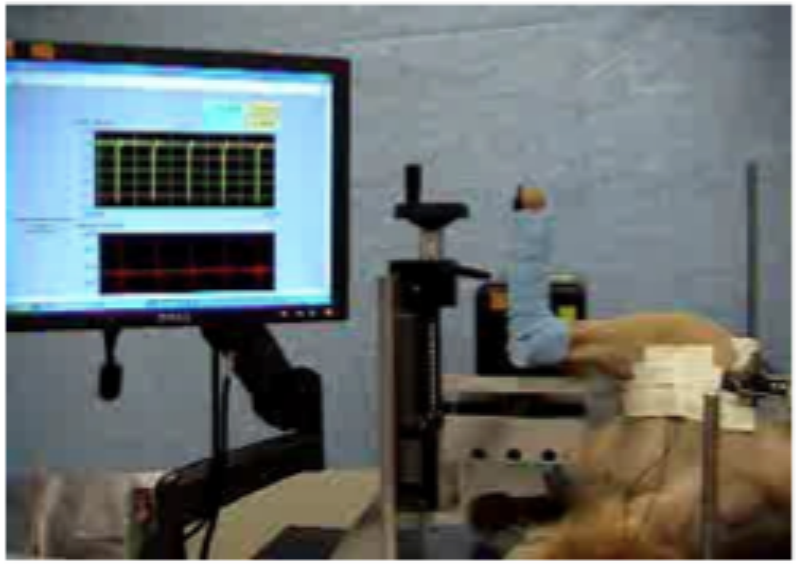
GRMD + NBD



Analysis of 4 skeletal muscles (3 hindlimb + diaphragm)

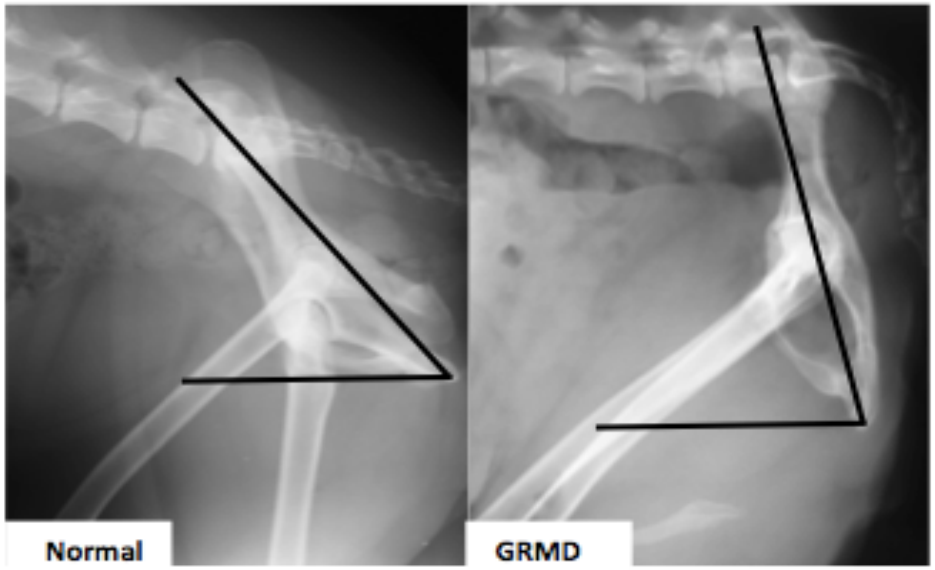
- 35.5% decrease in inflammation
- 35% decrease in necrosis
- 40.8% decrease in regeneration

NBD Improves Muscle Function in GRMD Dogs



Group	Tarsal Tetanic Flexion (N/kg)	Tarsal Tetanic Extension (N/kg)
GRMD (Untreated) (n = 10)	0.622 ± 0.175	1.43 ± 1.01
GRMD (NBD) (n = 6)	0.538 ± 0.116	2.68 ± 0.64
P value	0.318	0.017

NBD Improves Joint Angles in GRMD Dogs



Group	Pelvic Angle (degrees)
GRMD (Untreated) (n = 10)	48.3 ± 5.5
GRMD (NBD) (n = 6)	36.8 ± 5.1
P value	0.001

Summary

- ✓ In DMD mouse models (mdx + DKO) NBD is safe and efficacious in improving both skeletal and cardiac muscles
- ✓ NBD can be delivered by IV administration for 4 months in GRMD dogs
- ✓ NBD was observed to cause infusion reactions, which correlated with an immune response
- ✓ Body weights of GRMD dogs were significantly improved by NBD treatment
- ✓ NBD was efficacious in improving both histology (~35%) and function (>90%) of GRMD hindlimb muscles