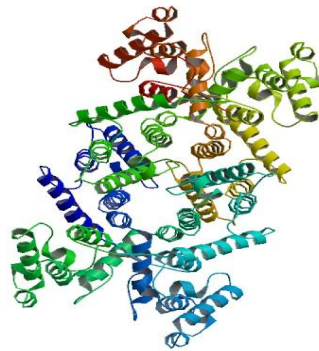
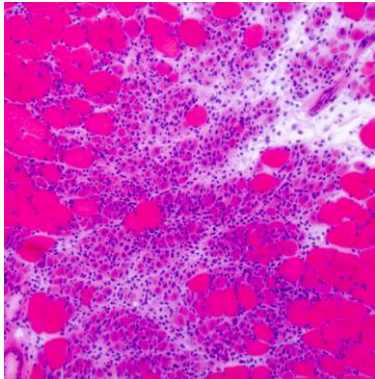


NF- κ B Inhibition with NBD peptide as a potential therapy for DMD



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The Ohio State University
November 4, 2011

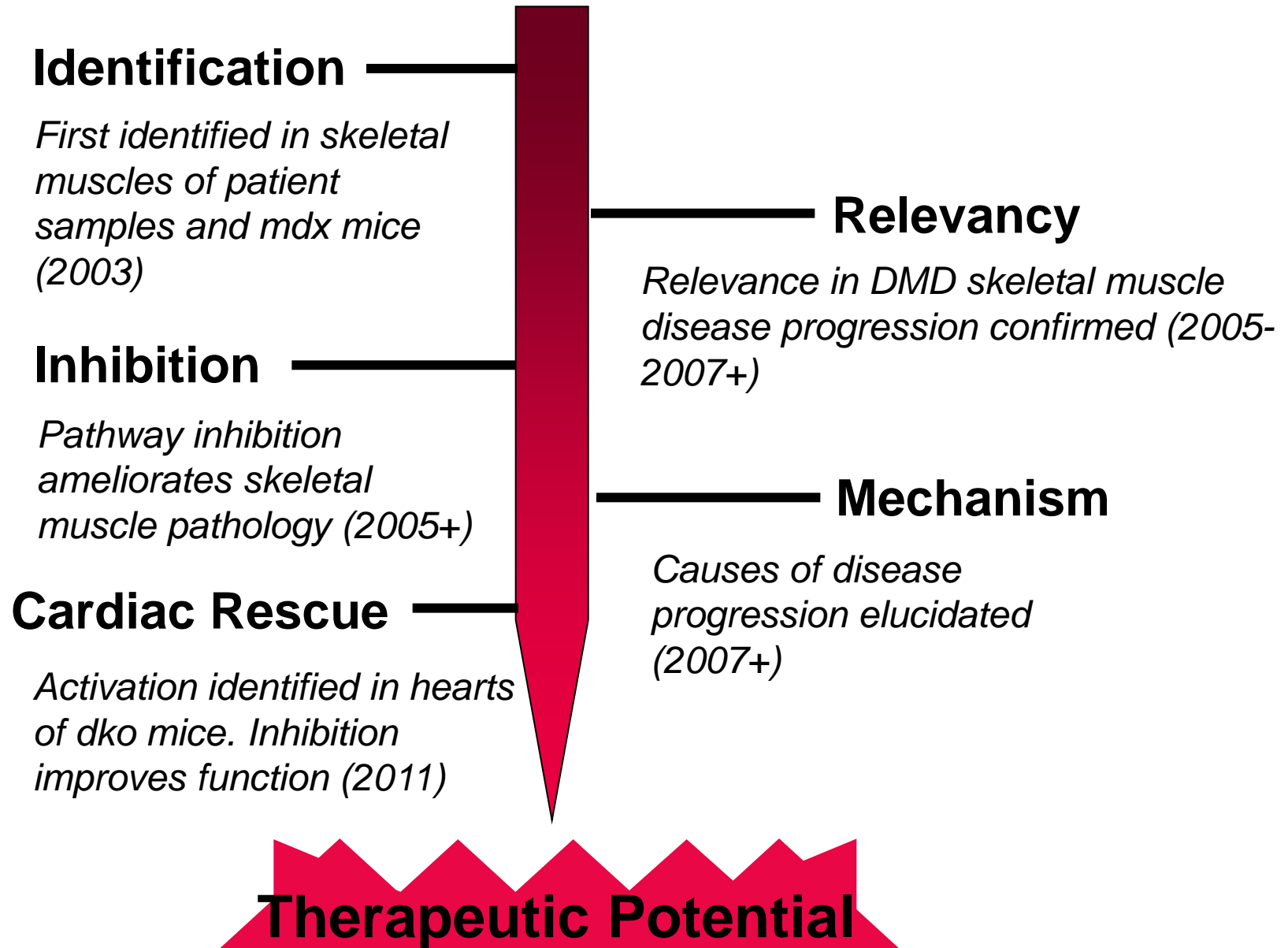


OHIO STATE UNIVERSITY - NATIONWIDE CHILDREN'S HOSPITAL

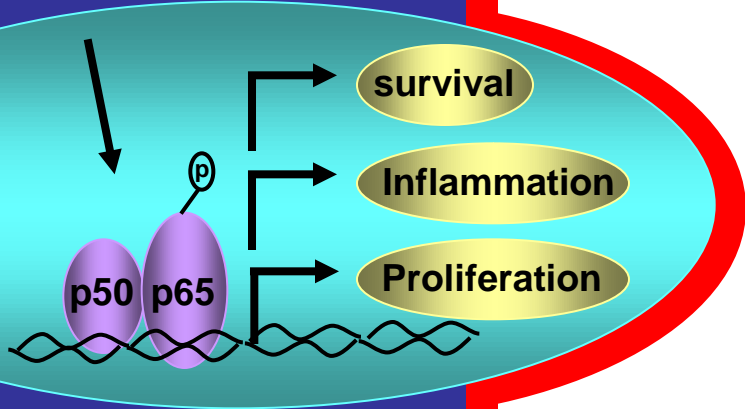
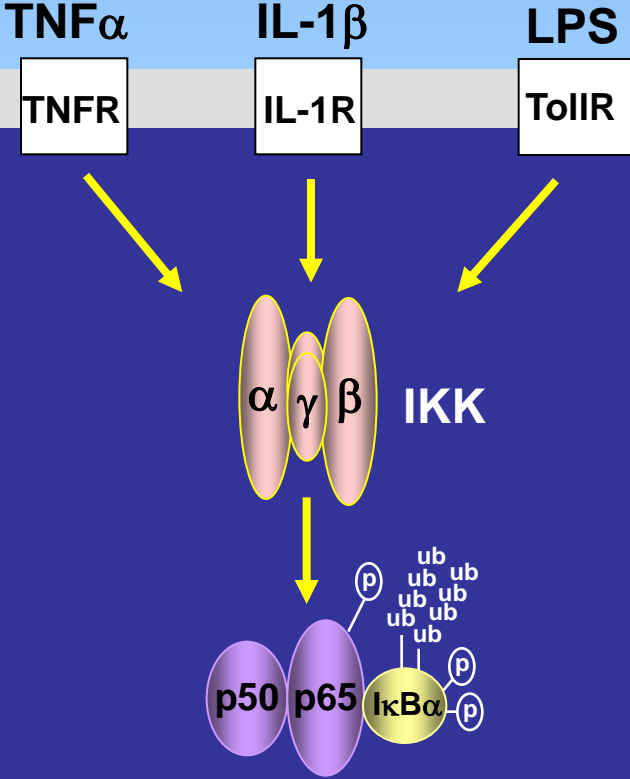


RESEARCH FOR MUSCLE BIOLOGY AND DISEASE

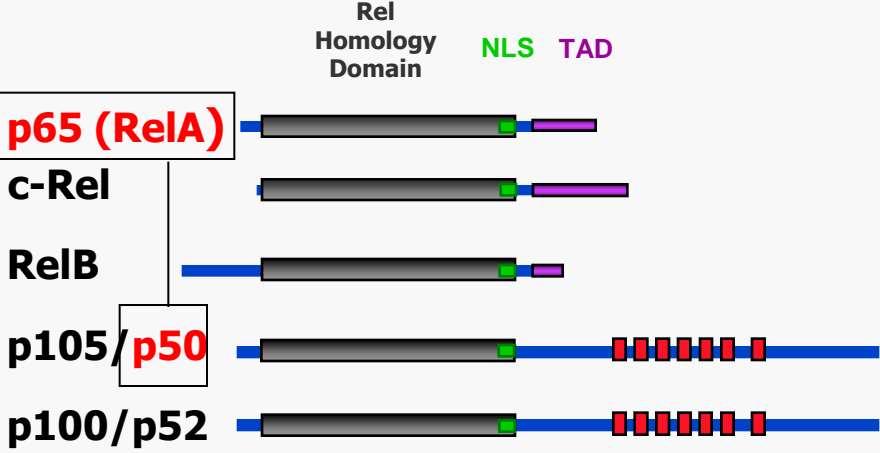
Involvement of NF- κ B in DMD

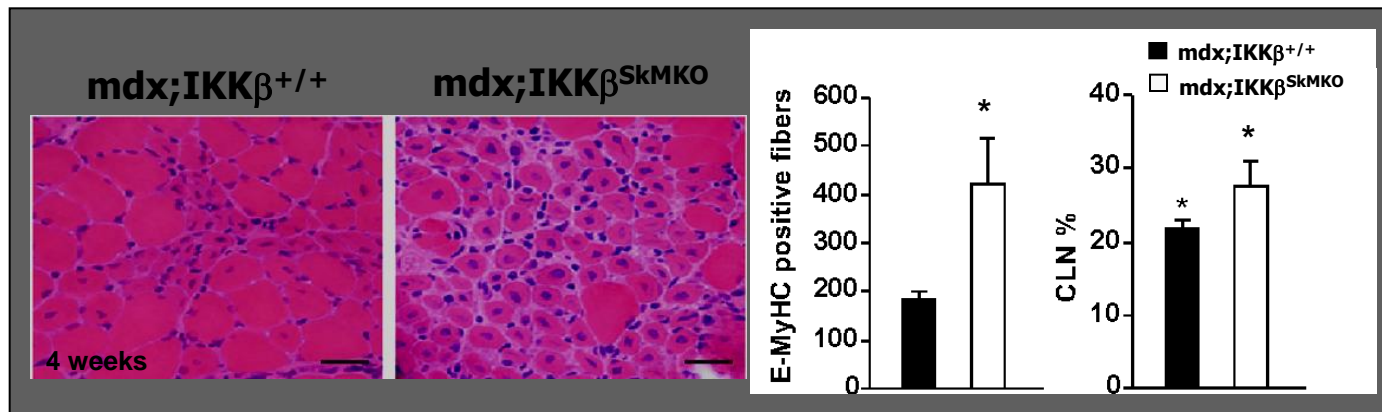
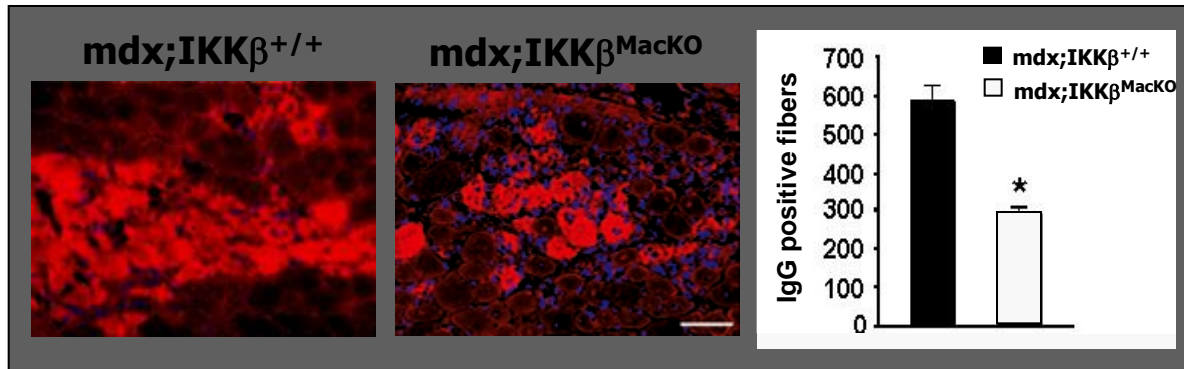
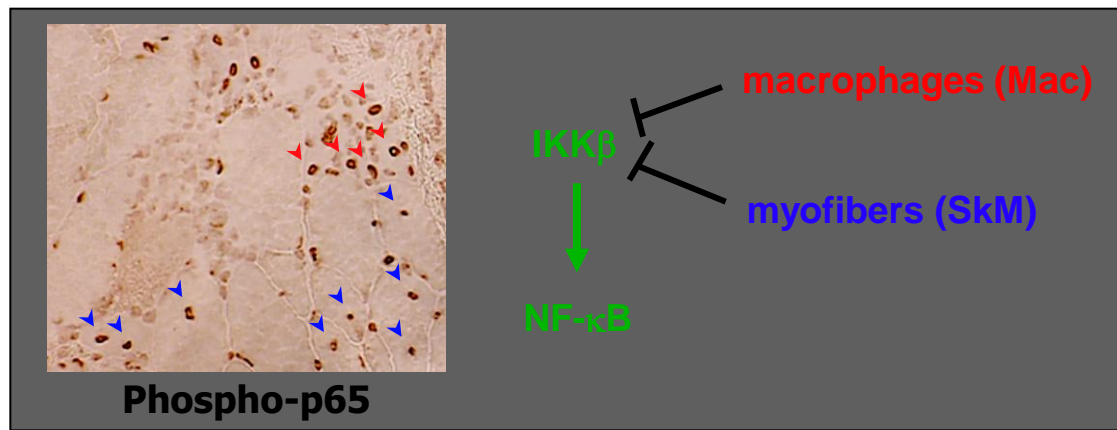


Classical NF- κ B Pathway



NF- κ B/Rel Family





Therapies used to inhibit NF- κ B in DMD

Corticosteroids

Antioxidants

Curcumin

Green tea extract

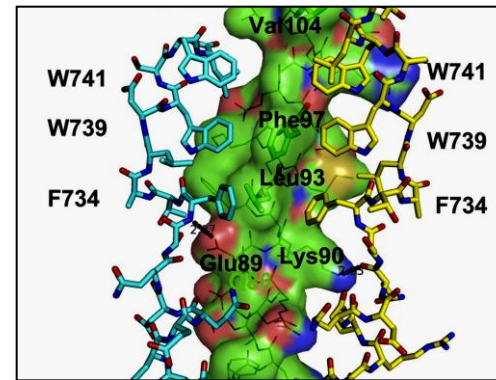
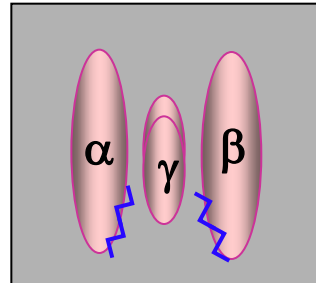
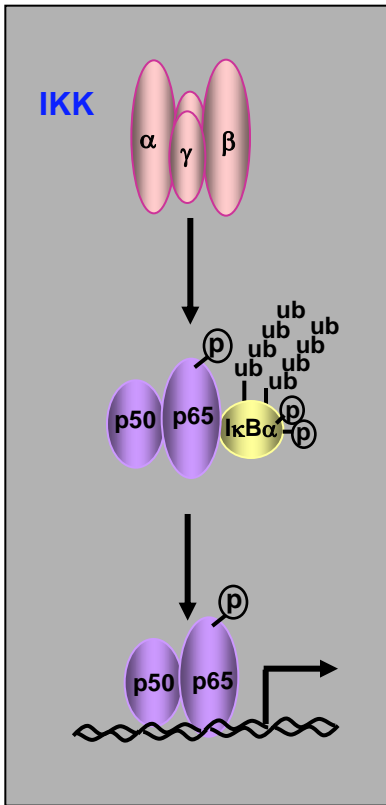
Gene therapy (AAV)

Stem cell therapy

Pharmacological therapy (NBD)

Pharmacological Inhibition of IKK/NF- κ B by NBD

Antennapedia - TALDWSWLQTE NEMO Binding Domain (NBD) Peptide



Rushe et al., Structure, 2008

NBD therapy in murine disease models

Arthritis
 General Inflammation
 Brain Ischemia
 Bone loss
 Colitis
 Melanoma

Duchenne Muscular Dystrophy

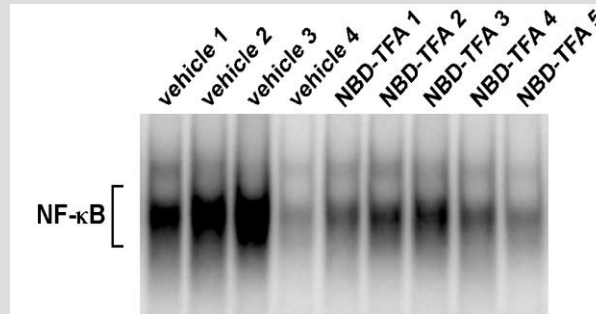
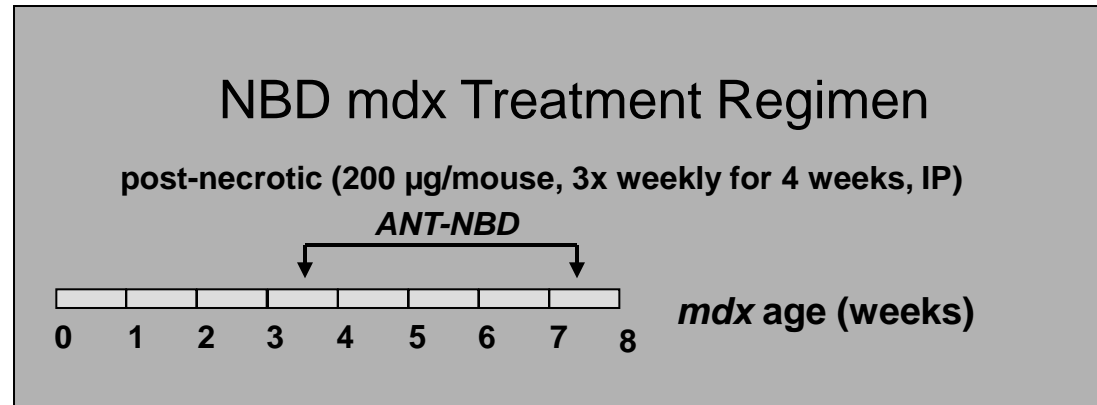
NBD therapy in canine disease

Lymphoma

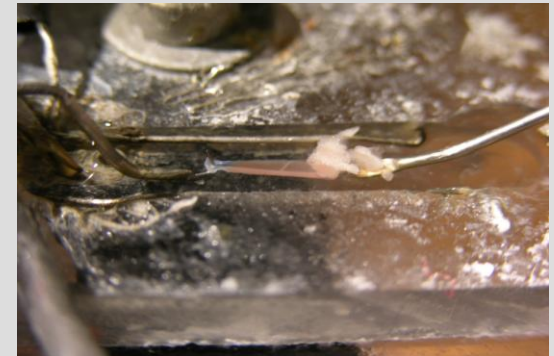
GLP-NBD is Effective in Inhibiting NF- κ B

Suitable for
pre-clinical
studies

- Water soluble
- GLP



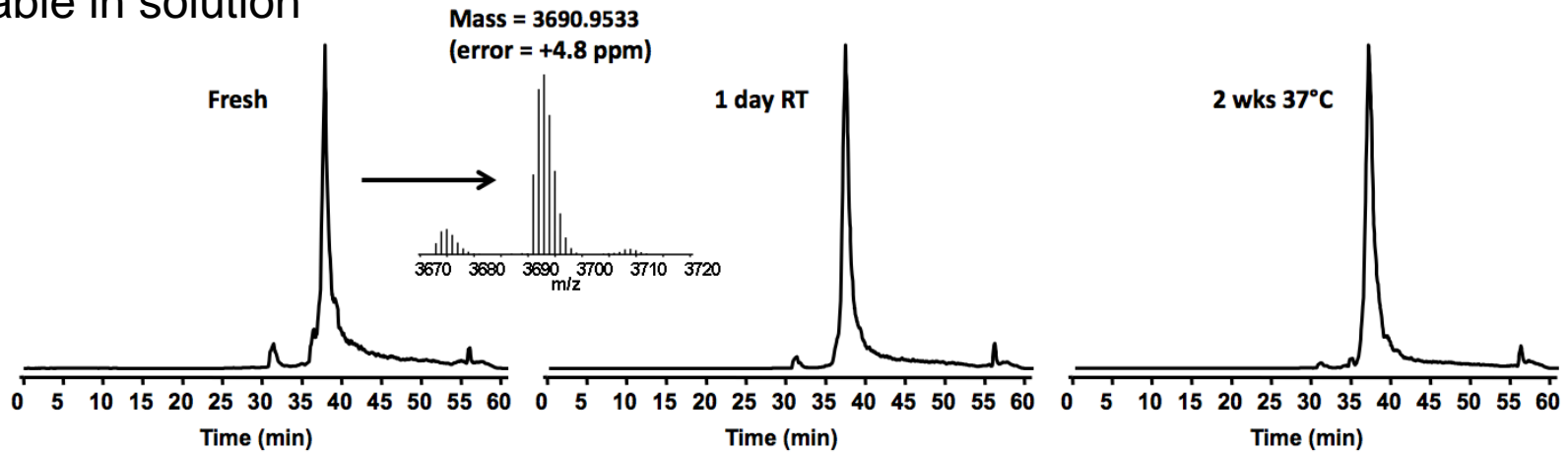
Diaphragm NF- κ B DNA binding



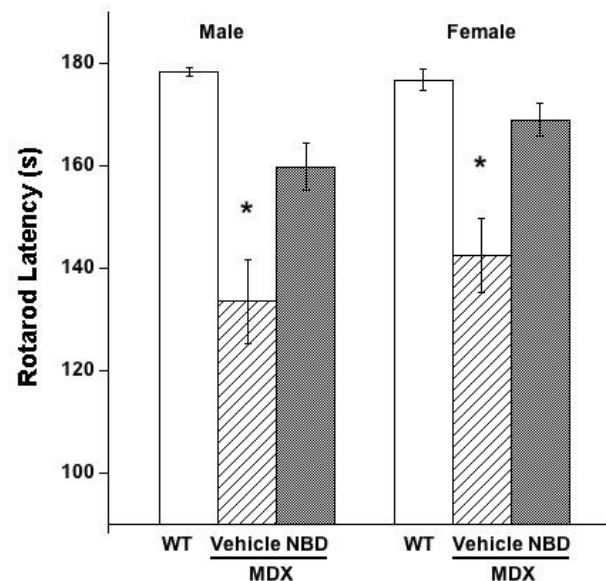
Diaphragm contractility

NBD peptide is stable and improves in vivo function

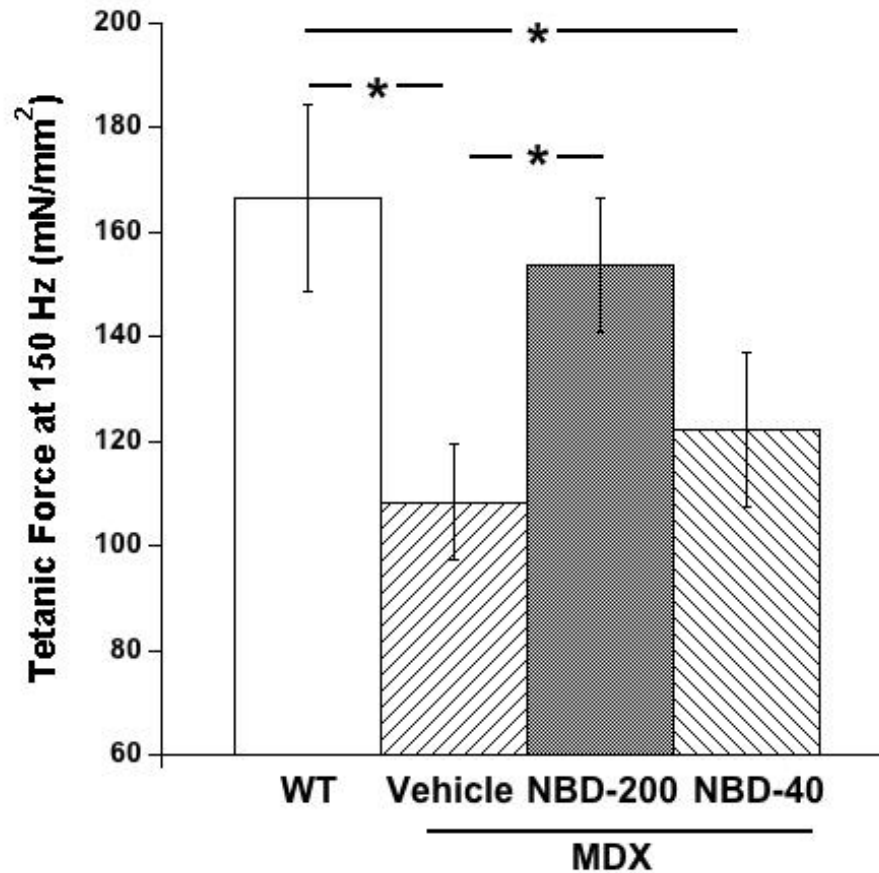
Stable in solution



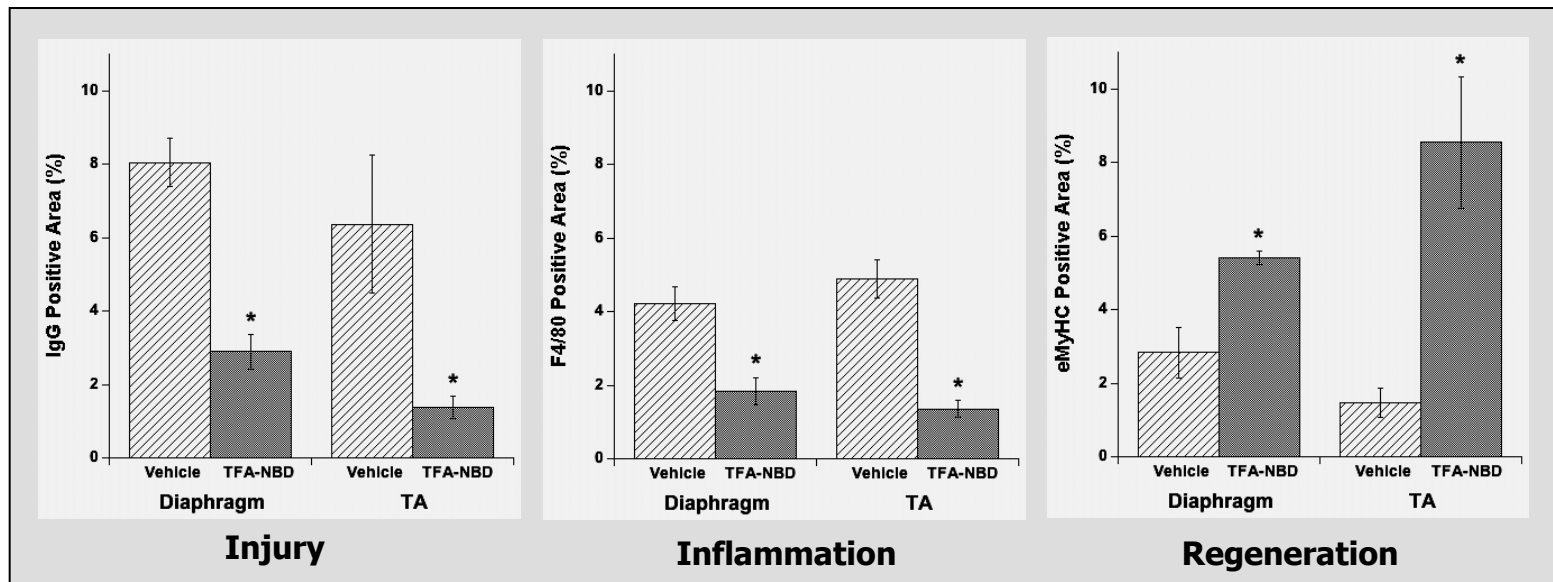
Effective *in vivo*



NBD peptide improves function of respiratory muscles



NBD Improves Histopathology in Skeletal Muscles of *mdx* mice

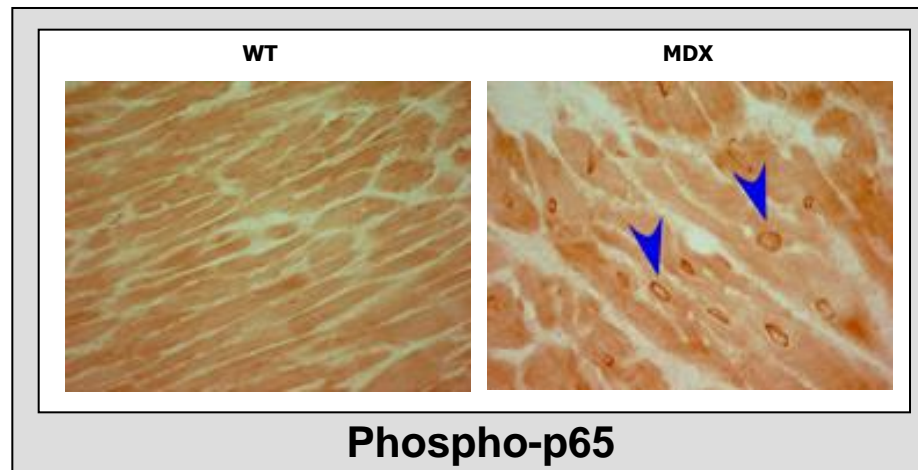
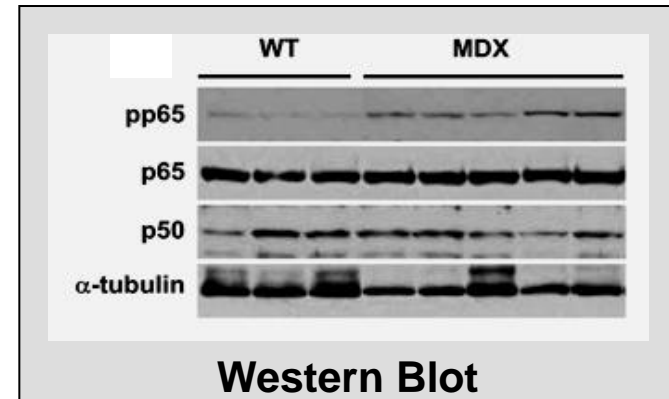
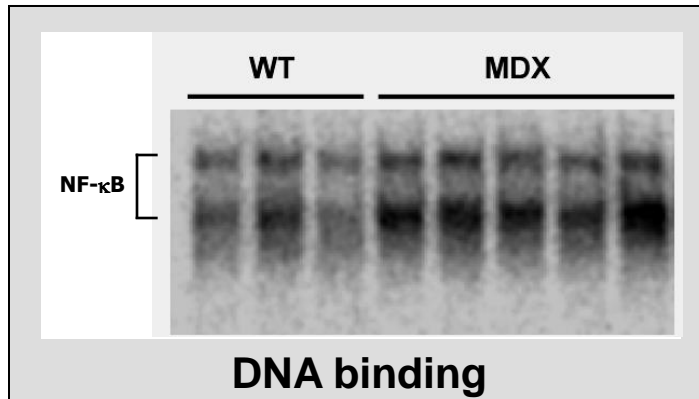


Peptide-Based Inhibition of NF- κ B Rescues Diaphragm Muscle Contractile Dysfunction in a Murine Model of Duchenne Muscular Dystrophy

Jennifer M Peterson,^{1} William Kline,^{1*} Benjamin D Canan,^{2*} Daniel J Ricca,³ Brian Kaspar,⁴ Dawn A Delfin,⁵ Kelly DiRienzo,¹ Paula R Clemens,^{6,7} Paul D Robbins,⁶ Albert S Baldwin,³ Pat Flood,³ Pravin Kaumaya,⁸ Michael Freitas,¹ Joe N Kornegay,⁹ Jerry R Mendell,⁴ Jill A Rafael-Fortney,⁵ Denis C Guttridge,¹ and Paul ML Janssen²*

¹Department of Molecular Virology, Immunology, and Medical Genetics, The Ohio State University, Columbus, Ohio, United States of America; ²Department of Physiology and Cell Biology, The Ohio State University, Columbus, Ohio, United States of America; ³University of North Carolina at Chapel Hill and TheraLogics Inc., Research Triangle Park, North Carolina, United States of America; ⁴Nationwide Children's Research Institute, Columbus, Ohio, United States of America; ⁵Department of Molecular and Cellular Biochemistry, The Ohio State University, Columbus, Ohio, United States of America; ⁶Department of Neurology, University of Pittsburgh, Pittsburgh, Pennsylvania, United States of America; ⁷Neurology Service, Department of Veterans Affairs Medical Center, Pittsburgh, Pennsylvania, United States of America; ⁸Department of Microbiology, The Ohio State University, Ohio, USA; and ⁹Department of Pathology and Laboratory Medicine, University of North Carolina, Chapel Hill, North Carolina, United States of America

NF- κ B is activated in *mdx* hearts



Mouse models of DMD cardiomyopathy

mdx

Dystrophin-deficient

- no overt clinical features
- normal mouse lifespan (2 yrs)
- mild skeletal muscle fibrosis
- mild cardiomyopathy



dko

Dystrophin/utrophin-deficient

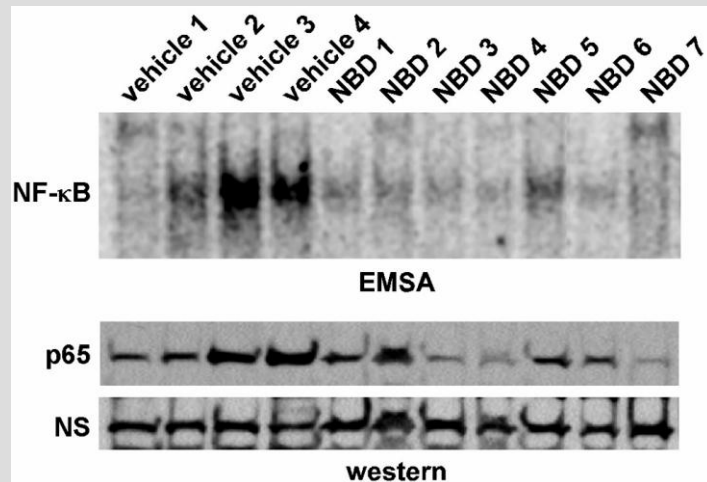
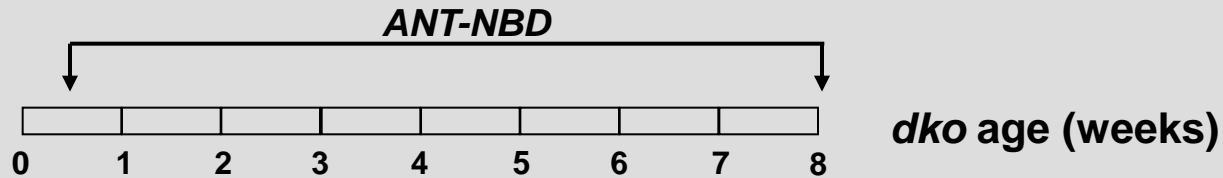
- Clinical signs of muscular dystrophy
- Dies 10-12 weeks-of-age
- severe cardiomyopathy



NBD is Effective for Inhibiting NF- κ B in dko Hearts

NBD dko Treatment Regimen

10 mg/kg/mouse, 3x weekly for 8 weeks, IP

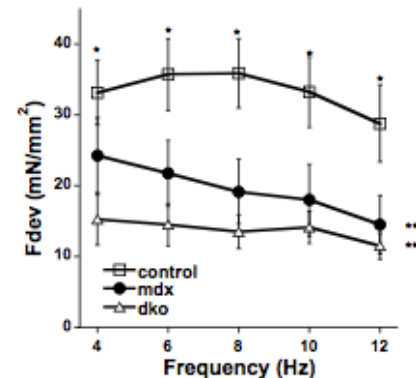
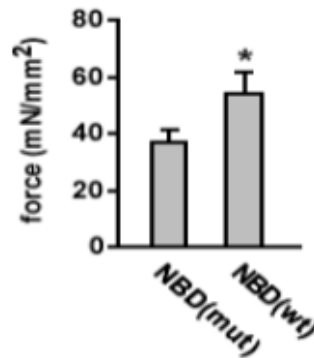
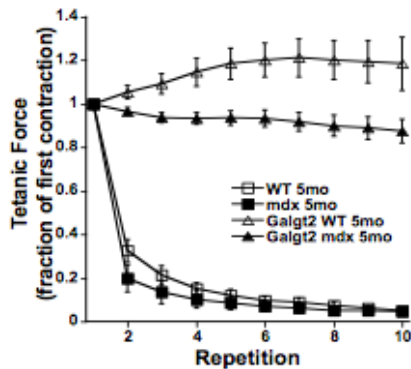


NF- κ B Activation

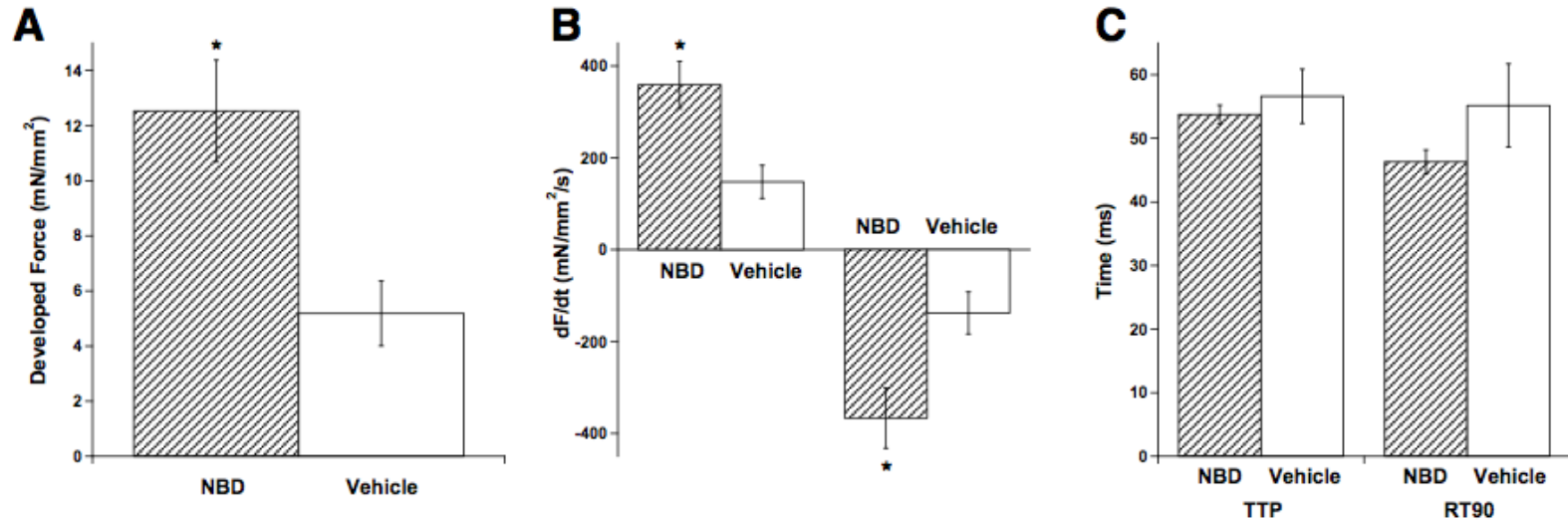
Striated muscle preparations



Figure 1. Linear muscle preparations (within dotted ovals) attached to micro-force transducers for functional measurements. Left: isolated extensor digitorum longus (EDL) muscle; Middle: isolated diaphragm muscle; Right: isolated cardiac trabecula. All muscles are superfused with modified Krebs-Henseleit solution, and continuously oxygenated.



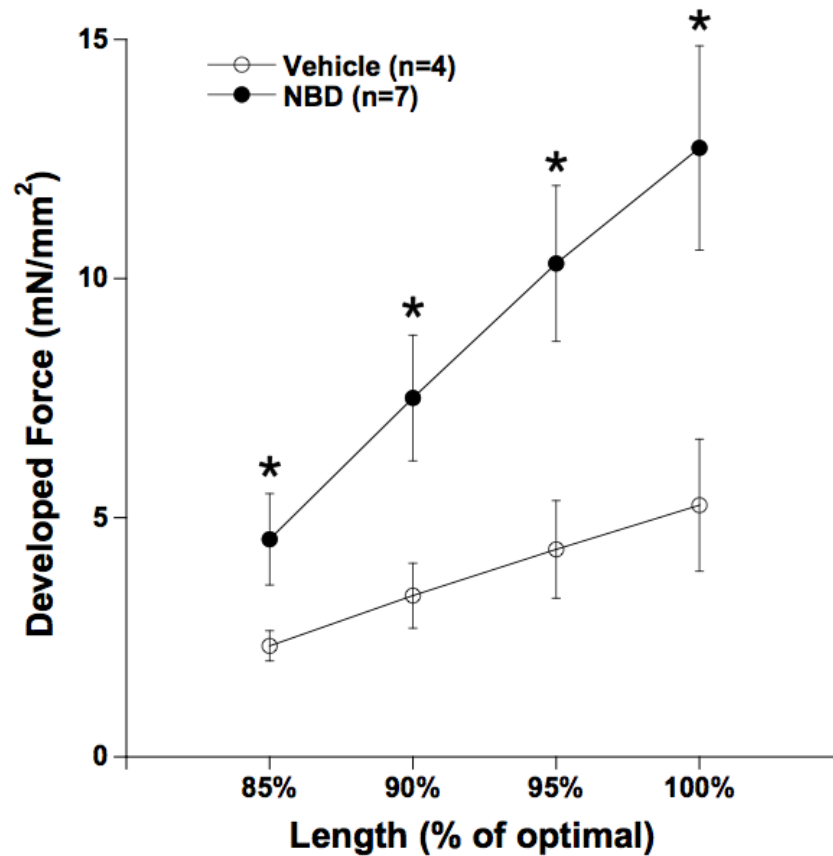
NBD peptide improves basic heart muscle function



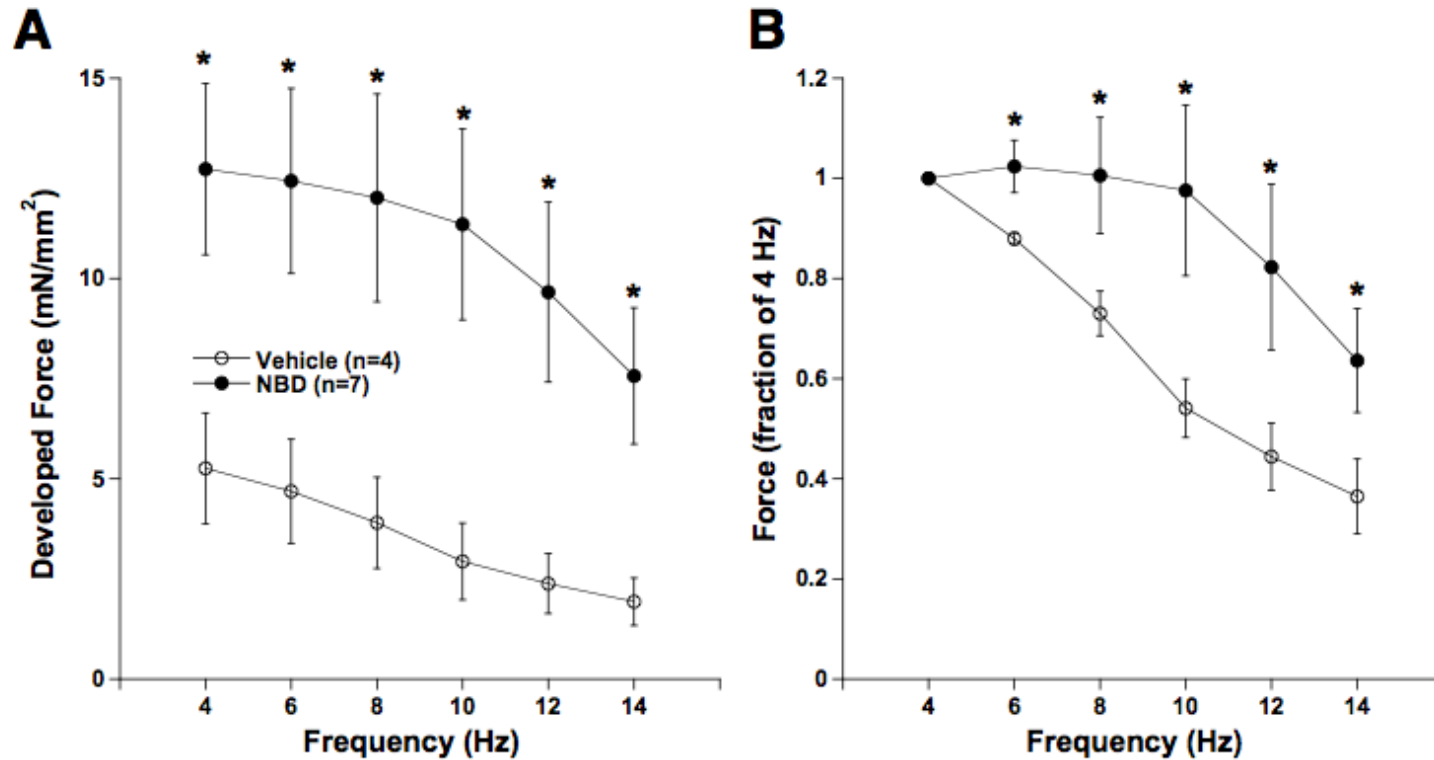
- *Improvement of systolic function*
- *No impairment of diastolic function*

NBD is effective over whole heart volume range

- Enhanced force at all lengths
- No change in relationship



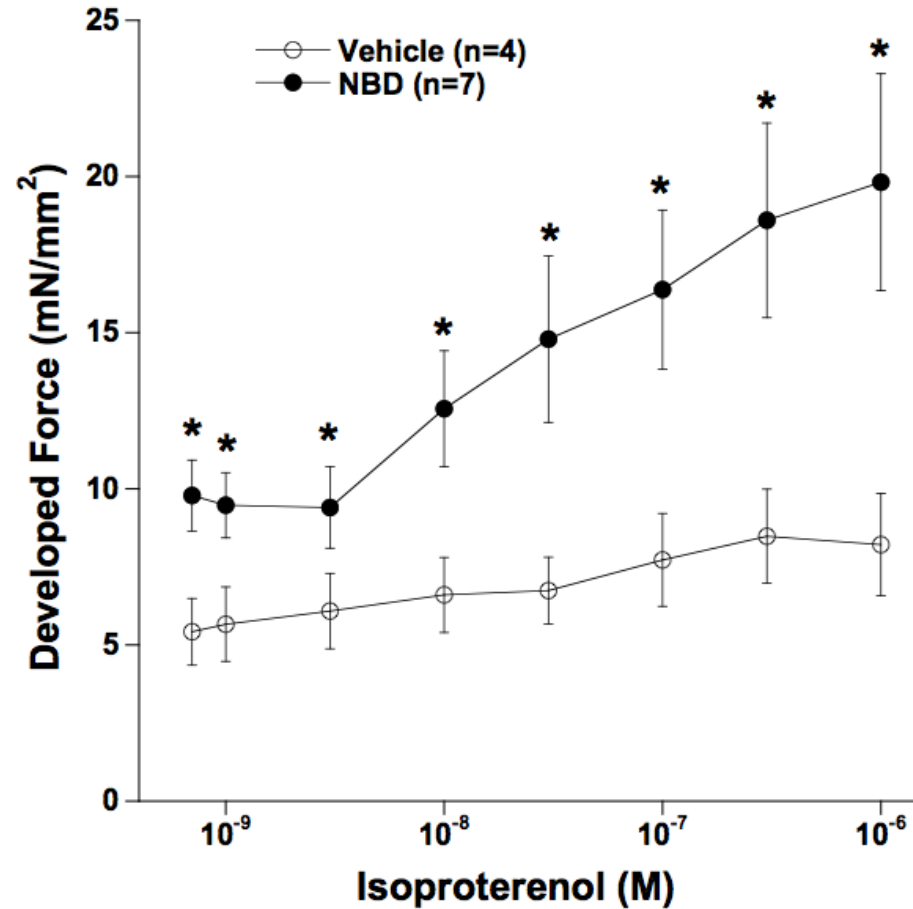
NBD is effective over entire frequency range



- Improvement of force frequency behavior

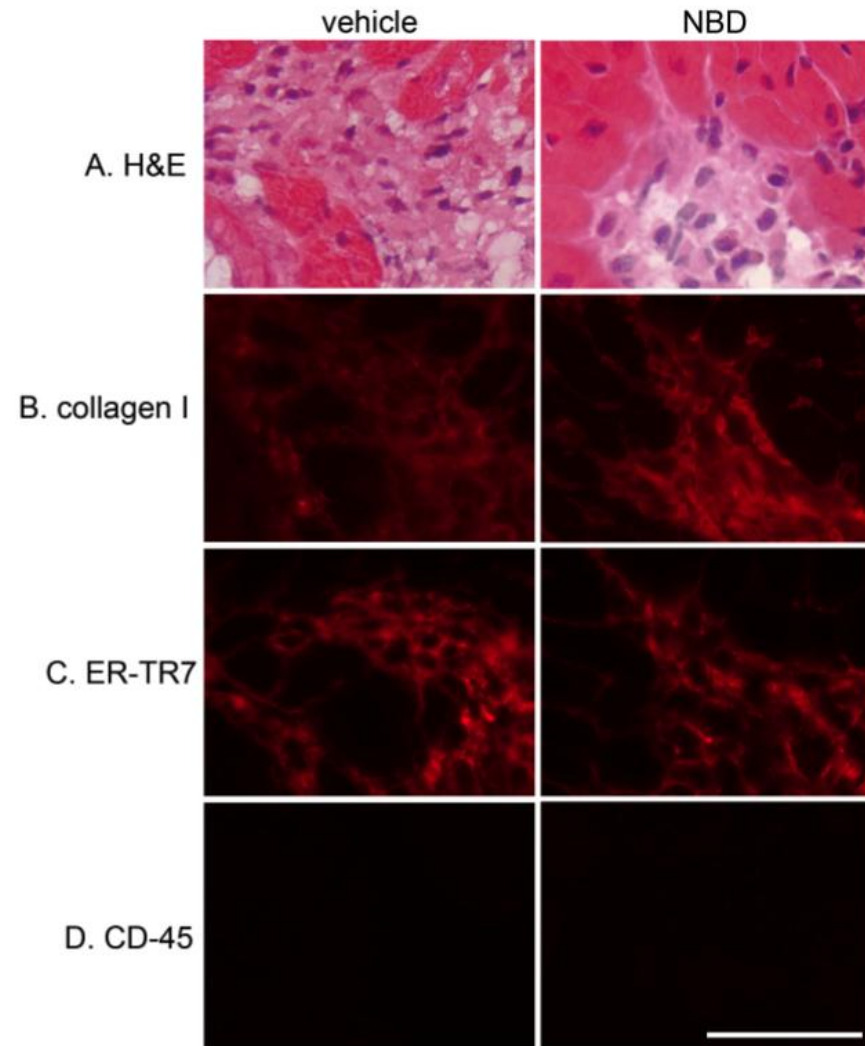
NBD peptide improves Isoproterenol response

- Restoration of normal β -adrenergic response



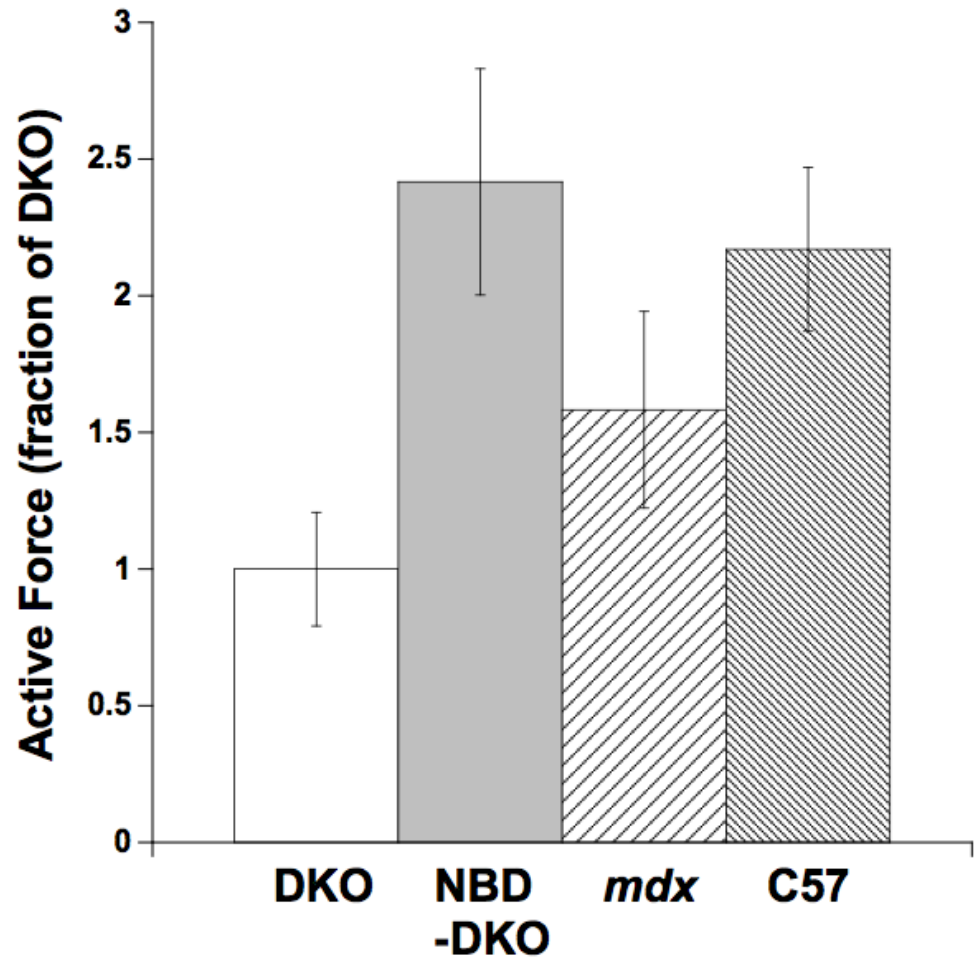
NF- κ B cardiac muscle function, histology

- No clear improvement in histology
- Calcium handling improvement very likely



Impact-relevance to *mdx*, WT

- Normalization of force





RESEARCH

Open Access

Improvement of cardiac contractile function by peptide-based inhibition of NF- κ B in the utrophin/dystrophin-deficient murine model of muscular dystrophy

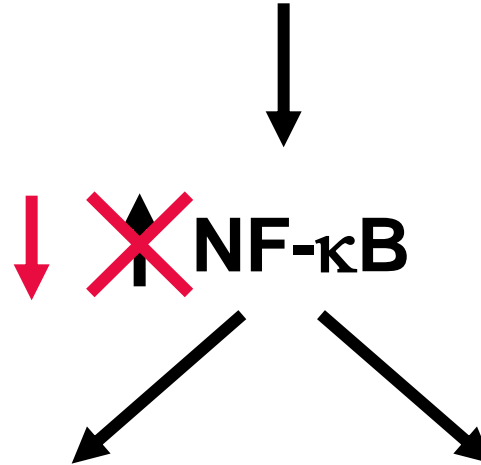
Dawn A Delfin^{1†}, Ying Xu^{2†}, Jennifer M Peterson^{3†}, Denis C Guttridge^{3†}, Jill A Rafael-Fortney^{1†} and Paul ML Janssen^{2*†}

¹Department of Molecular and Cellular Biochemistry, Columbus, OH, USA.

²Department of Physiology and Cell Biology, Columbus, OH, USA.

³Department of Molecular Virology, Immunology, and Medical Genetics, The Ohio State University, Columbus, OH, USA.

Dystrophin deficiency



Skeletal Muscle

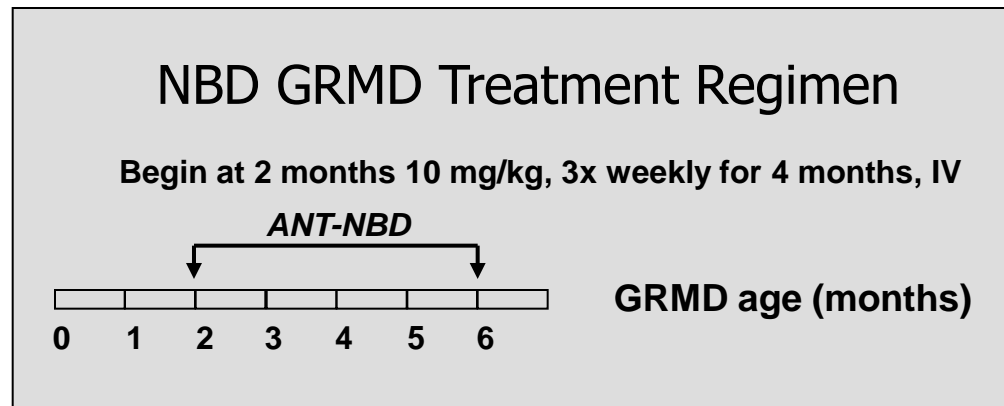
- ~~• Promote inflammation~~
- ~~• Injure myofibers~~
- ~~• Impair regeneration~~
- ~~• Compromise function~~

- Reduce inflammation and injury
- Enhance regeneration
- Improve function

Cardiac Muscle

- ~~• Impair function~~
- ~~• How?~~
- Improve function

Current status: Is NBD a Safe and Effective Therapeutic for Treating GRMD Dogs?



Safety

- Blood
- Tissues

Efficacy

- Heart MRI
- Skeletal muscle function
- Histopathology

Acknowledgements

OHIO STATE UNIVERSITY - NATIONWIDE CHILDREN'S HOSPITAL



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