

Upregulation of Utrophin and Associated Proteins as DMD Therapy

**LOSS OF DYSTROPHIN
AND ASSOCIATED PROTEINS**

**MEMBRANE INSTABILITY
AND ABNORMAL SIGNALING**

APOPTOSIS/NECROSIS

INFLAMMATION

FIBROSIS

Upregulation of utrophin and associated proteins expected to be effective in 100% of DMD boys

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**LOSS OF DYSTROPHIN
AND ASSOCIATED PROTEINS**

Utrophin

nNOS

**MEMBRANE INSTABILITY
AND ABNORMAL SIGNALING**

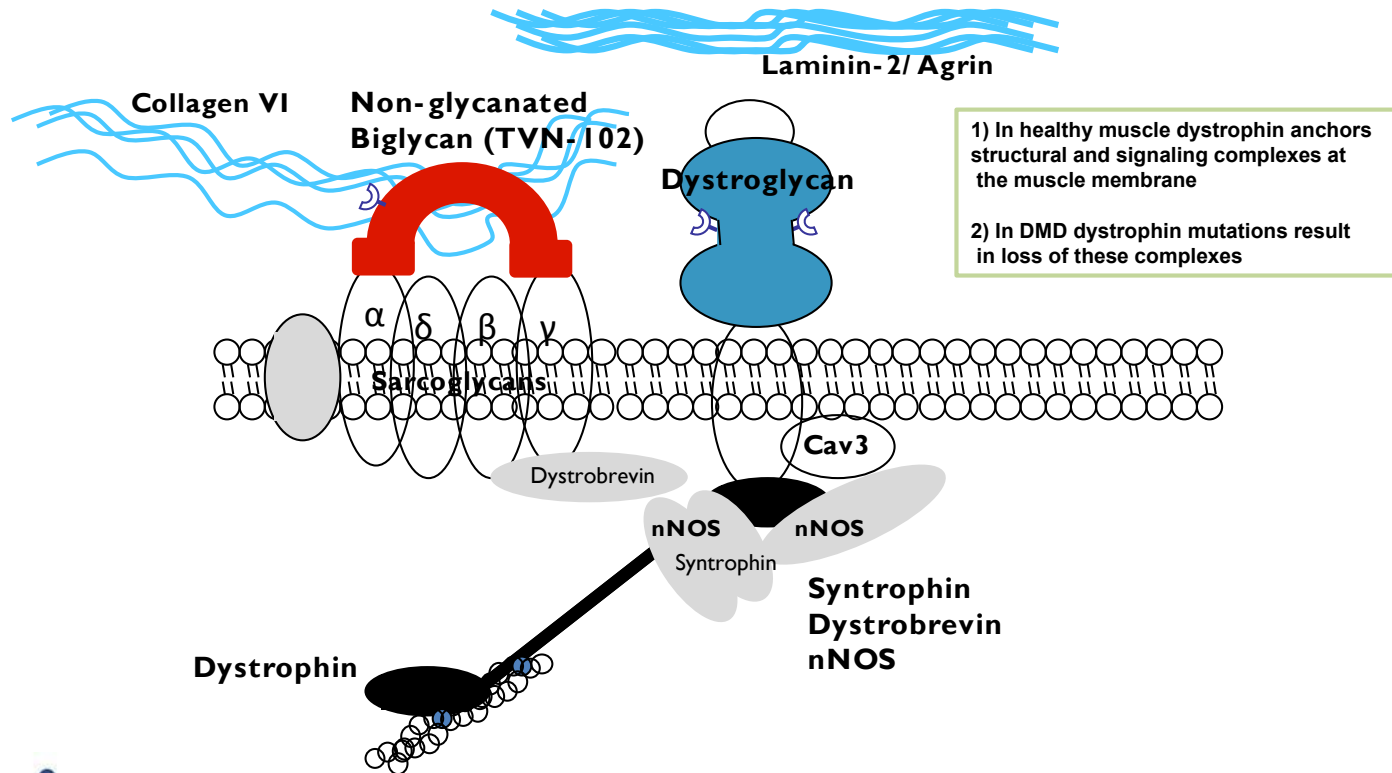
APOPTOSIS/NECROSIS

INFLAMMATION

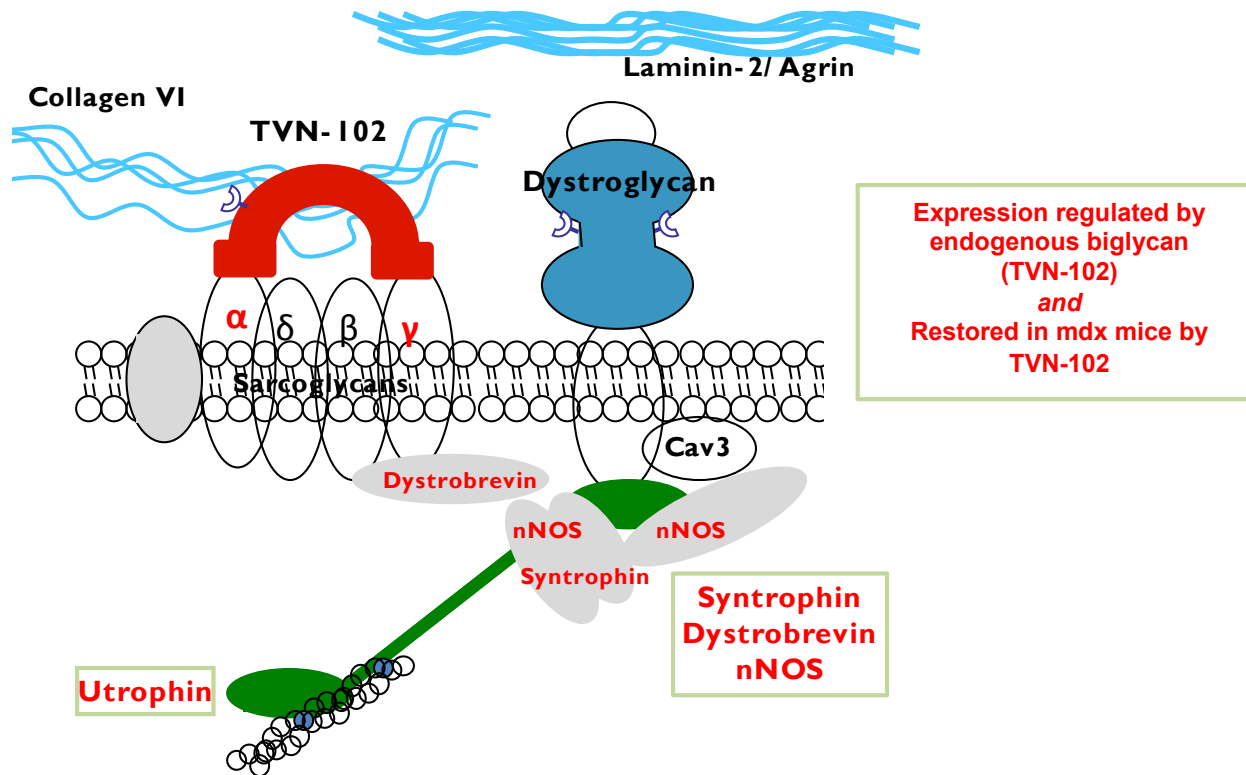
FIBROSIS

Upregulation of utrophin and associated proteins expected to be effective in 100% of DMD boys

Dystrophin Function in Normal Muscle

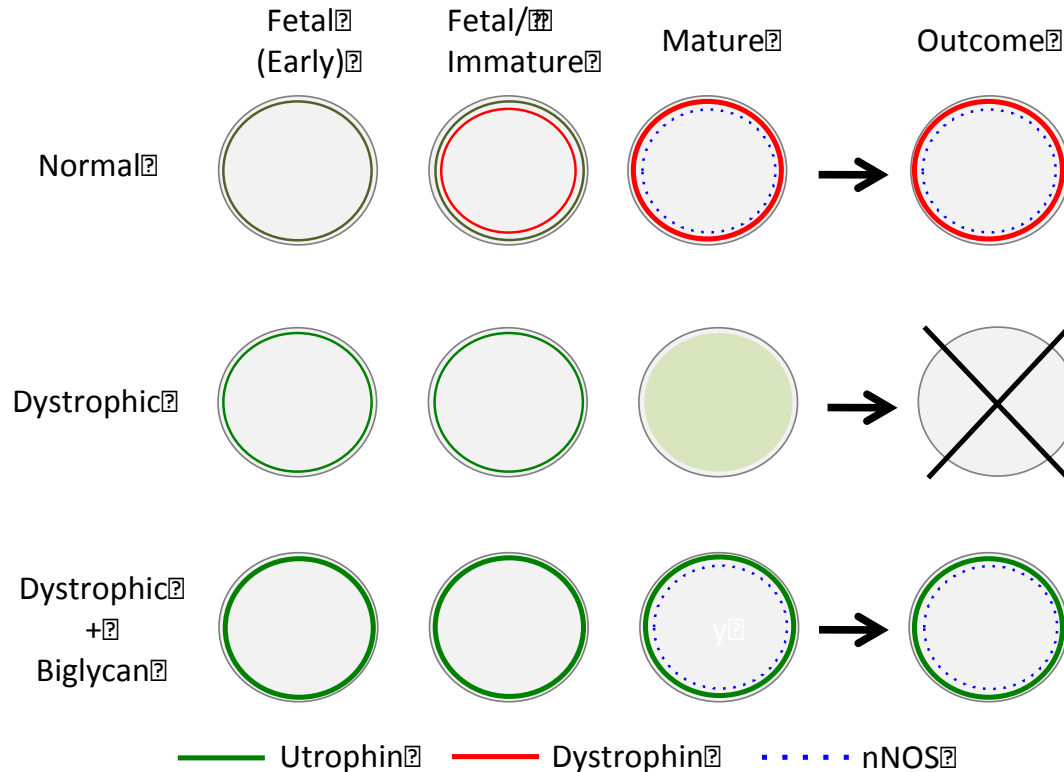


TVN-102 Regulates Multiple Components of the D/UAPC

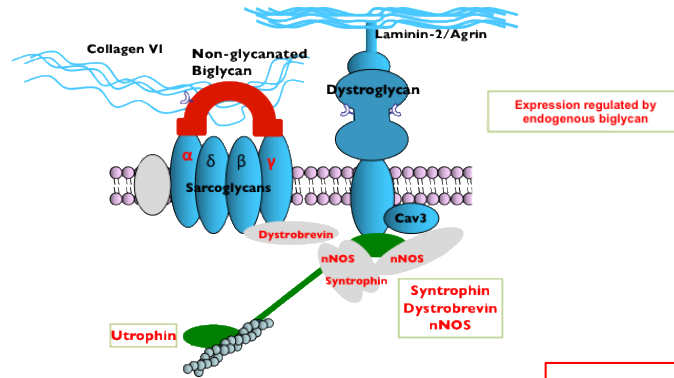


Nature, 1985
J. Cell. Biol., 1987
Neuron, 1991; 1994
J. Cell. Biol., 2000
J. Cell Phys. 2006
FASEB J., 2006
PNAS, 2011

Biological Rationale for Utrophin/nNOS-Directed DMD Therapy



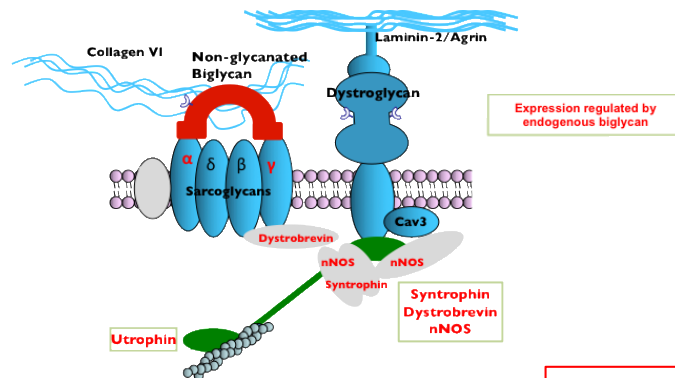
Utrophin and associated proteins for DMD treatment



Goal:
Utrophin protein assembled
into functional complex
at muscle membrane

Note: utrophin mRNA and protein is naturally upregulated in DMD muscle

Utrophin and associated proteins for DMD treatment



DNA
(Gene)



mRNA



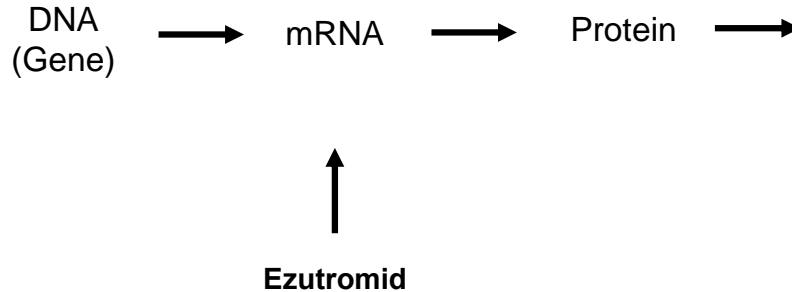
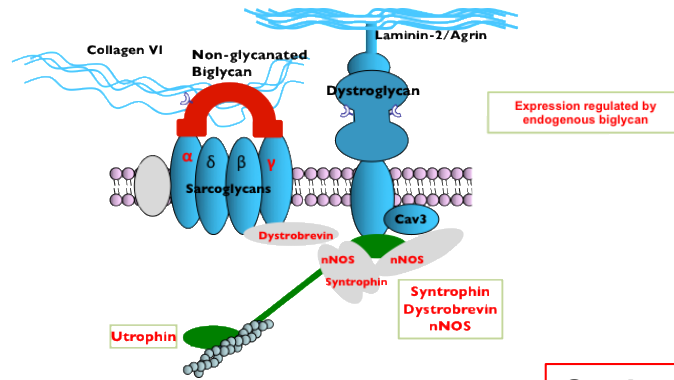
Protein



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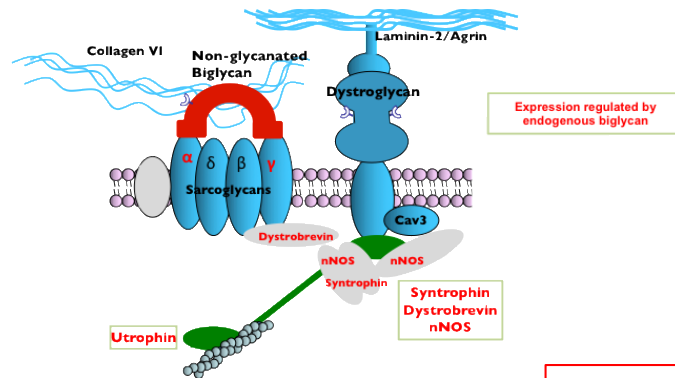
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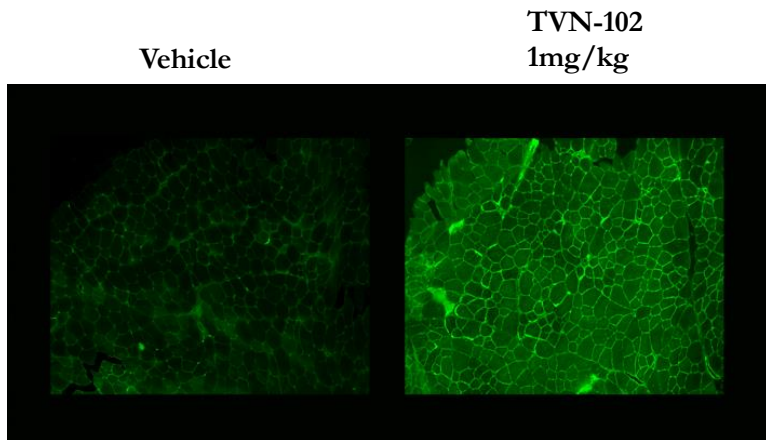
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Ezutromid

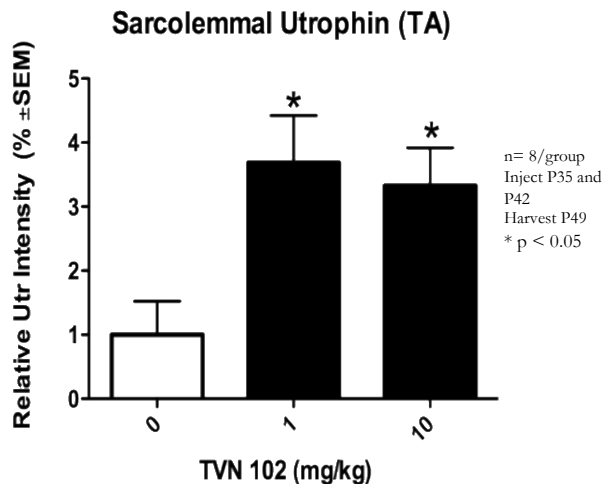
TVN-102

Note: utrophin mRNA and protein is naturally upregulated in DMD muscle

TVN-102 Upregulates Sarcolemmal Utrophin up to 3-Fold in MDX Mice



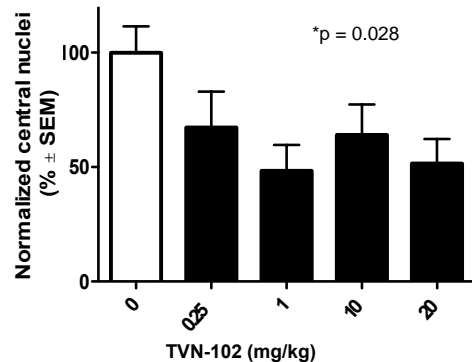
Example of utrophin response to systemically-delivered TVN-102*. TA muscles from cohort injected with either vehicle or 1mg/kg TVN-102 at P35 and P42; Harvest at P49. All tissue sectioning, staining and imaging of vehicle and TVN-102 performed in same sessions. Images acquired at same exposures and processed identically.



Highly purified TVN-102* (4L preparation at KBI) upregulates sarcolemmal utrophin >3.5 fold. TA muscles were sectioned and mounted at the same time. All images were acquired at a subsequent time using identical setting. Sarcolemmal utrophin signal was scored (5 random fields/section; 50 segments/field) by workers blind to experimental conditions. n= 8/group. P < 0.05.

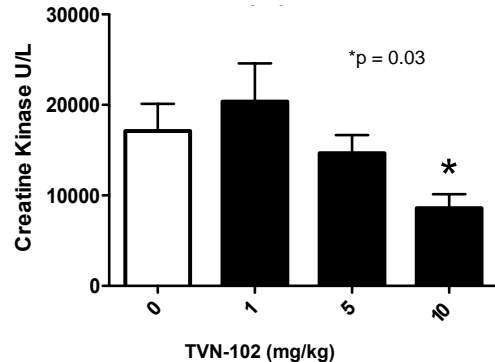
TVN-102 Reduces Muscle Cell Degeneration and damage - serum Creatine Kinase

Less Degeneration



*One-way ANOVA, n= 8 animals/grp

Less Damage (Creatine Kinase)

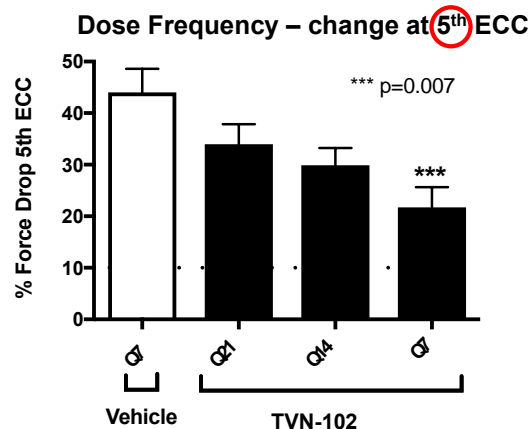
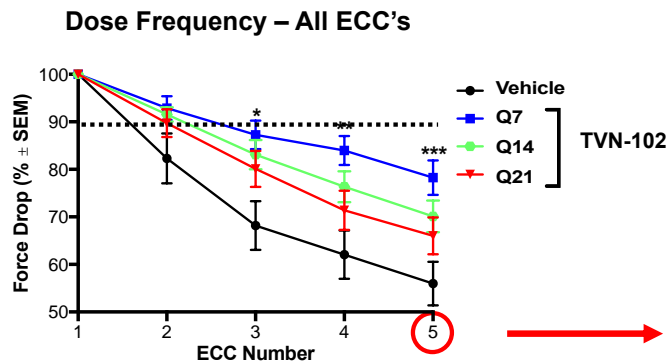


n= 8 animals/grp

- Reduces muscle degeneration (Central nucleation)
- Reduces muscle damage (**serum Creatine Kinase**)

TVN-102 Improves Muscle Function

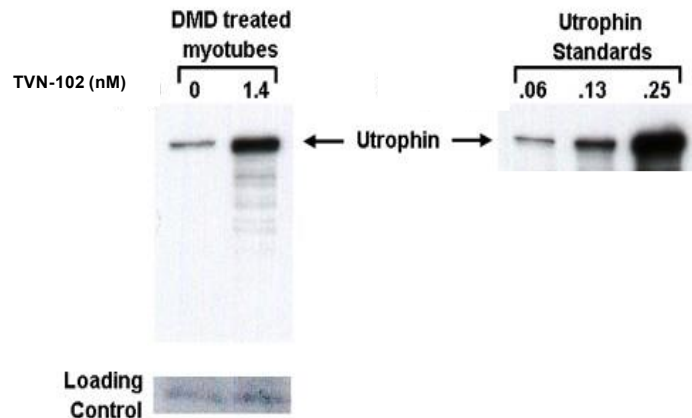
Improved Muscle Function



- Animals Dosed 10mg/kg for 3 months at indicated frequency (Q7, 14, 21; days)
- Eccentric Contraction (ECC) measurements to assess muscle function made at end of study
- Study performed blind by independent investigators
- Normalization of heart weight (see also Amenta et al., 2011)
- No safety signal observed

TVN-102 Increases Utrophin in Cultured DMD Cells – TVN-102

TVN-102 upregulates membrane-associated utrophin by > 3-Fold in DMD myotubes, which is consistent with the data observed in the MDX mouse model



- 1.4 nM TVN-102
- 3.2 fold increase in utrophin protein

Membrane fractions from cultured human DMD myotubes treated with TVN-102 or vehicle were probed for utrophin expression by western blot.

TVN-102 Development Status

- Completed range finding safety pharmacology in rats and non-human primate
- Manufacturing currently at scale to support next steps
- Next Steps
 - GLP safety studies
 - GMP manufacturing to support Phase I and Phase II
- Goal is to initiate clinical trials in 2019

Thank You!

Parent Project Muscular Dystrophy

LEADING THE FIGHT TO END DUCHENNE

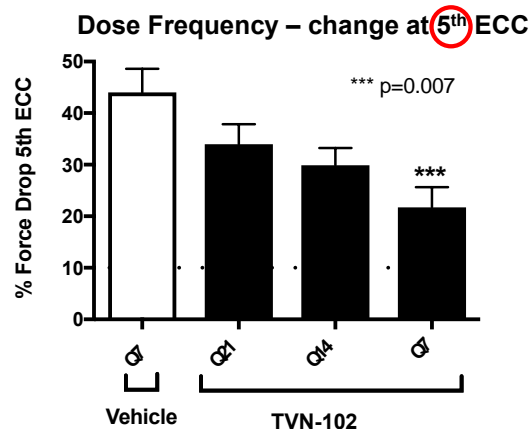
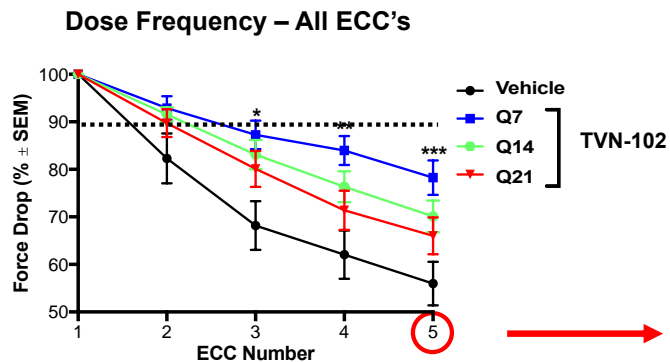


NASH AVERY FOUNDATION



TVN-102 Improves Muscle Function

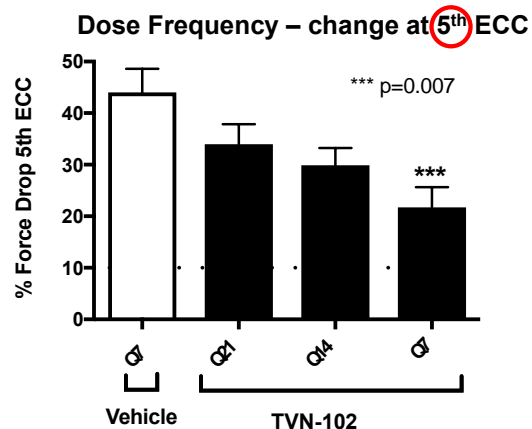
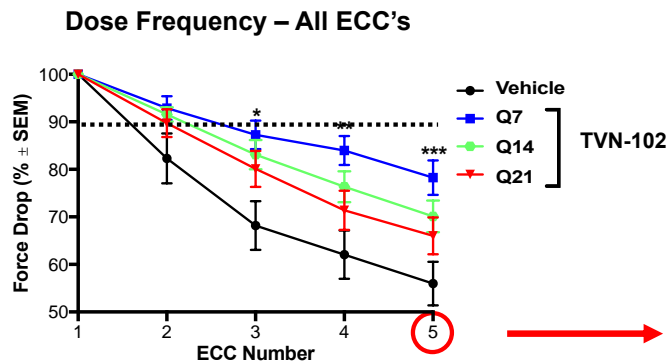
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