Tirasemtiv Increases Skeletal Muscle Performance in SMA Mice

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Introduction

- The majority of new therapeutic approaches for spinal muscular atrophy (SMA) focus on increasing SMN2 levels
- Directly activating fast skeletal troponin may provide a novel, and potentially complimentary, method of improving muscle function in SMA
- To examine this hypothesis, we tested the fast skeletal troponin activator, *tirasemtiv,* in two different SMA mouse models that resemble the Type II/III intermediate and Type IV adult–onset human condition

Experimental Aims for *Tirasemtiv* in SMA Research

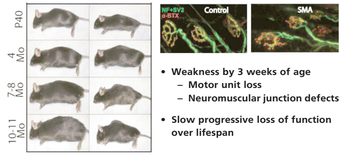
Our specific experimental aims are:

- Determine the effect of *tirasemtiv* on skeletal muscle strength in mouse models of SMA
- Determine the effect of *tirasemtiv* on muscle performance in mouse models of SMA

Results

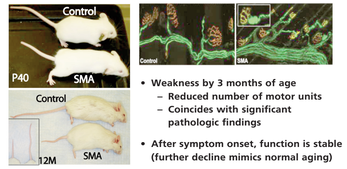
Characterization of SMA Mouse Models

"Intermediate" SMA mice



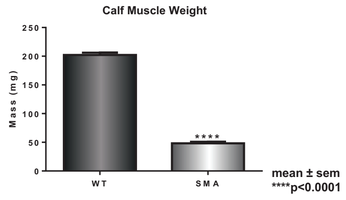
- Weakness by 3 weeks of age
  - Motor unit loss
  - Neuromuscular junction defects
- Slow progressive loss of function over lifespan

"Adult-onset" SMA mice

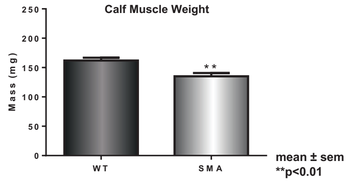


- Weakness by 3 months of age
  - Reduced number of motor units
  - Coincides with significant pathologic findings
- After symptom onset, function is stable (further decline mimics normal aging)

Compared to healthy (WT) mice, Intermediate SMA mice have significant muscle atrophy



Compared to healthy (WT) mice, Adult-onset SMA mice have significant muscle atrophy



Tirasemtiv Improves Strength and Endurance in a Mouse Model of SMA

Grip Strength Apparatus

- Healthy mice and SMA mice are lowered onto the triangle bar until they grab the bar
- Mice are pulled gently by the tail until they release the bar
- The grip meter measures how much strength it takes to pull the mouse from the triangle bar

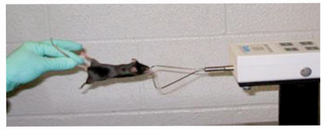
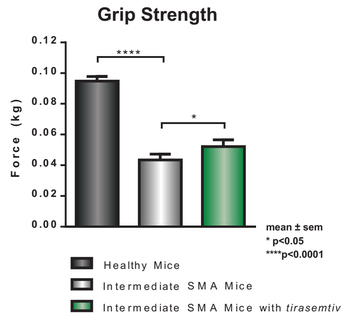


Image source: https://www.physiology.med.umich.edu/cig/plat_behav.html



A single dose of *tirasemtiv* significantly increased the grip strength of weakened "Intermediate" SMA mice

Tirasemtiv Improves Strength and Endurance in a Mouse Model of SMA

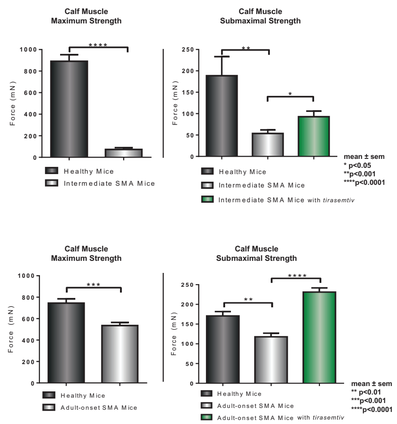
Calf Muscle Strength

- Similar to how we measure calf muscle strength in humans, we performed an experiment to measure calf muscle strength in mice (see images below)
- Healthy mice and SMA mice are put under anesthesia
- The sciatic nerve (a lower leg nerve) is stimulated to cause the mouse's calf muscle to contract
- The resulting muscle force is recorded

Image source: Biodex.com

Image source: Aurora Scientific

"Adult-onset" SMA mice

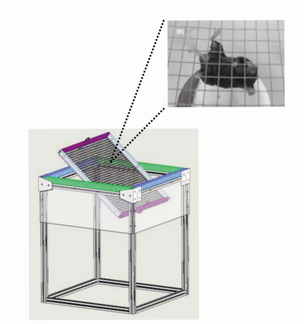


A single dose of *tirasemtiv* increased the calf muscle submaximal strength of weakened "Intermediate" and "Adult-onset" SMA mice

Tirasemtiv Improves Strength and Endurance in a Mouse Model of SMA

Grid Cage Hang Apparatus

- Healthy mice and SMA Mice are placed on a grid
- The grid is then inverted
- The mice hang on as long as they can



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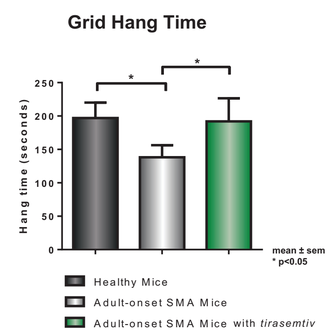
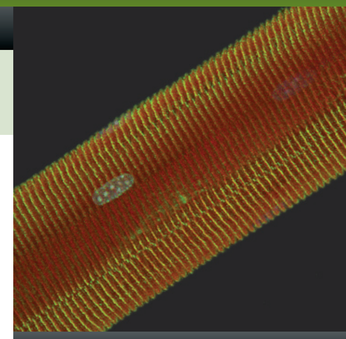


A single dose of *tirasemtiv* significantly increased the ability of "Adult-onset" SMA mice to hang upside-down



Conclusions

- *Tirasemtiv* is unique because it directly activates skeletal muscle and could be of benefit to patients with a wide variety of disorders characterized by muscle weakness and fatigue
- In this current study, *tirasemtiv* improved submaximal calf muscle strength, grip strength and grid hang time in SMA mice that resembled the Intermediate and Adult-onset human condition
- Significance of the Project:
  - Current treatment of SMA consists primarily of supportive measures. Thus, there remains a significant unmet medical need for a therapy that can improve muscle function, including respiratory muscle function
  - Based on our current results in SMA mouse models, *tirasemtiv* may ameliorate symptoms associated with muscle weakness in patients with SMA and thereby improve self-care abilities and quality of life

CYTOKINETICS