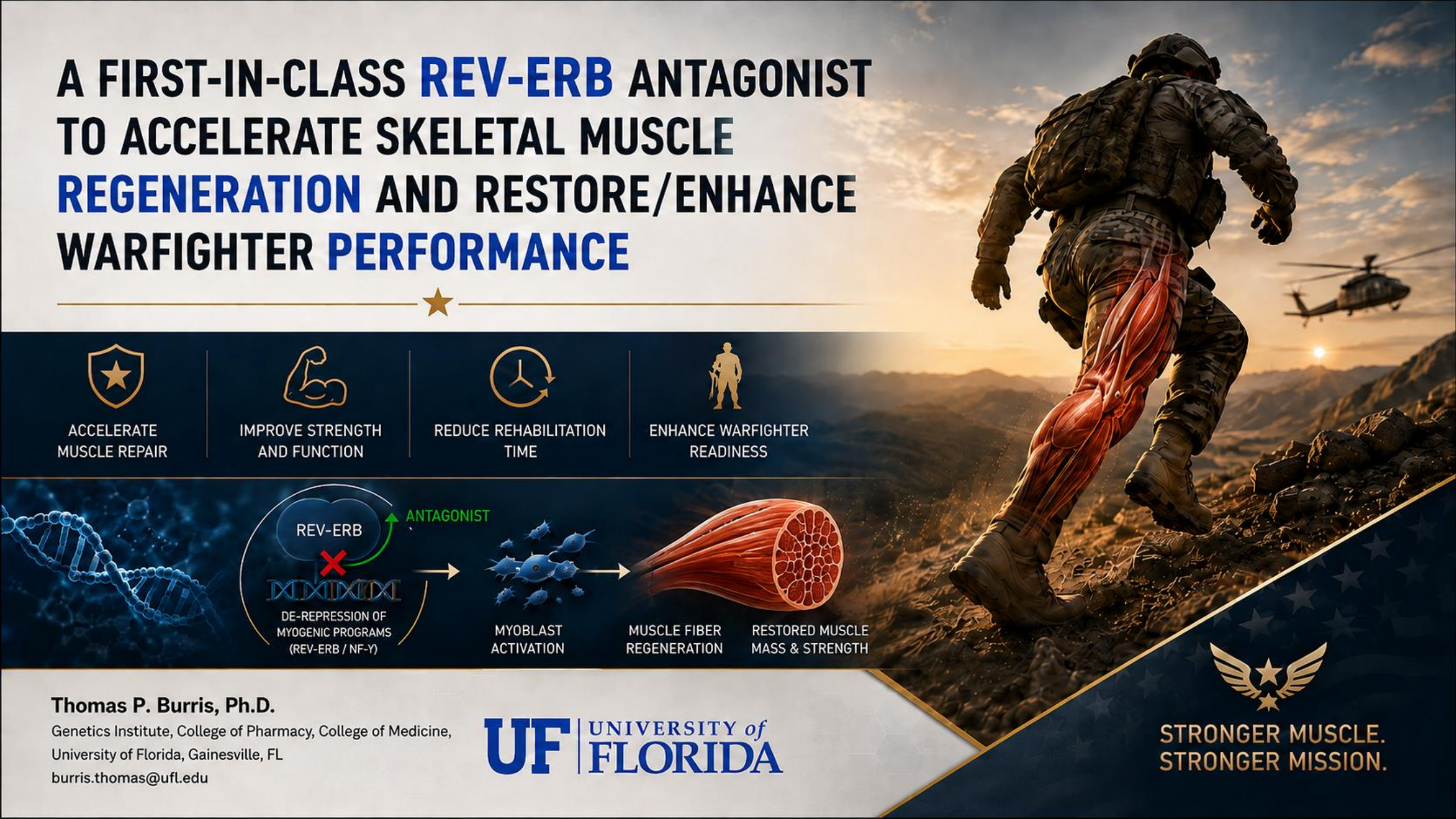
A FIRST-IN-CLASS REV-ERB ANTAGONIST TO ACCELERATE SKELETAL MUSCLE REGENERATION AND RESTORE/ENHANCE WARFIGHTER PERFORMANCE



ACCELERATE MUSCLE REPAIR

IMPROVE STRENGTH AND FUNCTION

REDUCE REHABILITATION TIME

ENHANCE WARFIGHTER READINESS

STRONGER MUSCLE.
STRONGER MISSION.

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Disclosure

MHSRS 2026
Military Health System Research Symposium

Inventor Disclosure

- **Thomas P. Burris, Ph.D.** and **Bahaa Elgendy, Ph.D.** are inventors on pending patents related to REV-ERB antagonists (including BE2012) assigned to University of Florida and Washington University.
- These patents have not been optioned or licensed to any commercial entity.

Pelagos Pharmaceuticals

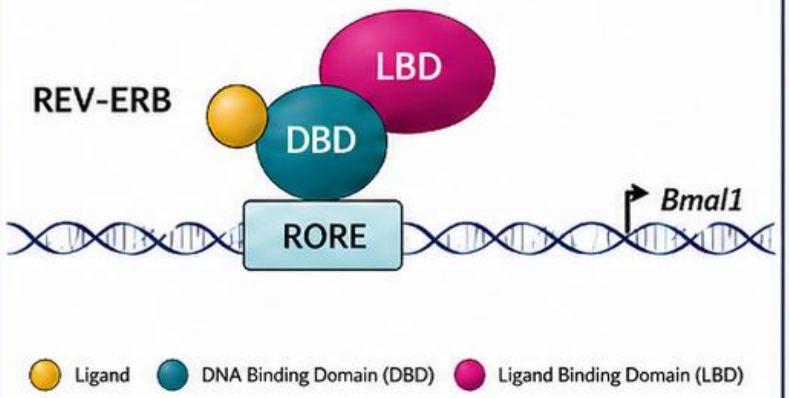
Thomas P. Burris, Ph.D. and **Bahaa Elgendy, Ph.D.** are cofounders of Pelagos Pharmaceuticals, Inc. (and stockholders), which is focused on development of REV-ERB agonists unrelated to the antagonists discussed in this presentation.

Other Contributors

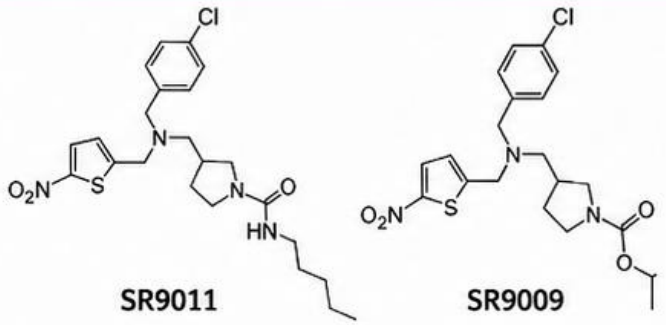
All other authors, collaborators, and contributors declare nothing to disclose.

Development of Synthetic REV-ERB Ligands

1. REV-ERB–Mediated Repression at RORE



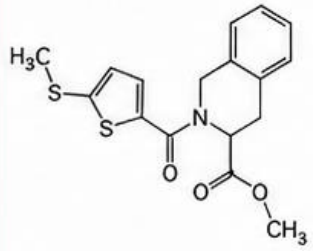
2. Synthetic REV-ERB Agonists



SR9011 IC_{50} = 620 nM

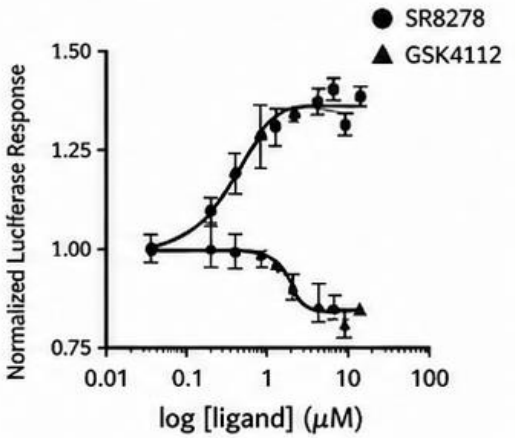
SR9009 IC_{50} = 705 nM

3. Synthetic REV-ERB Antagonist (SR8278)

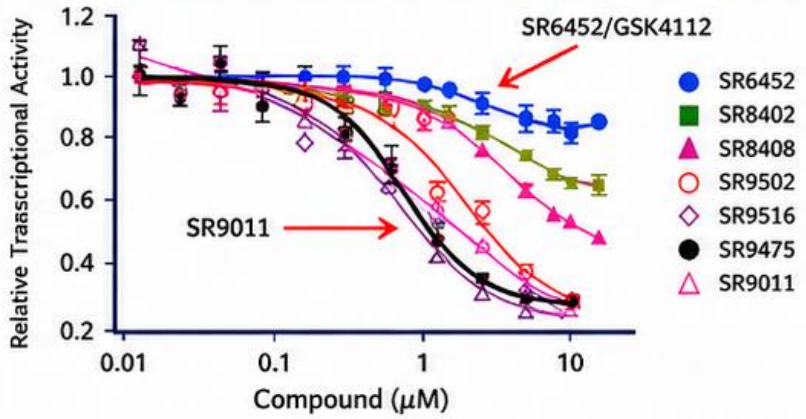


SR8278

(Synthetic Antagonist)



4. REV-ERB Transcriptional Activity (Agonists vs Antagonists)



5. REV-ERB Agonist Discovery (Agonists)

ARTICLE **nature** doi:10.1038/nature11158

Regulation of circadian behaviour and metabolism by synthetic REV-ERB agonists

Laura A. Solt*†, Yongxin Wang*†, Shuhpha Banerjee†, Travis Hughes†, Douglas J. Kojetin†, Thomas Lundasen†, Youesung Shin†, Jin Lu†, Michael D. Cameron†, Ronnin Noe†, Sunghe-Re-You†, Joseph S. Takahashi‡, Andrew A. Butler†, Theodore M. Kamenecka† & Thomas P. Burris†*

6. REV-ERB Antagonist Discovery (Antagonist)

ACS chemical biology LETTERS

pubs.acs.org/acschemicalbiology

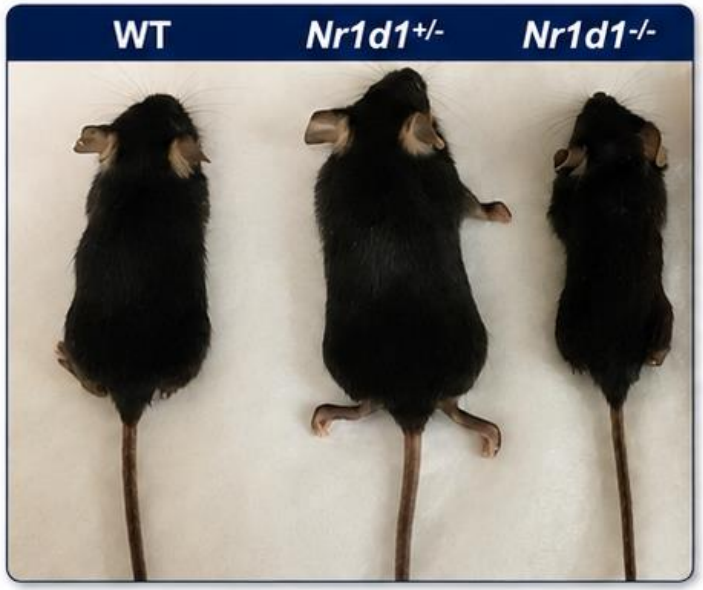
Identification of SR8278, a Synthetic Antagonist of the Nuclear Heme Receptor REV-ERB

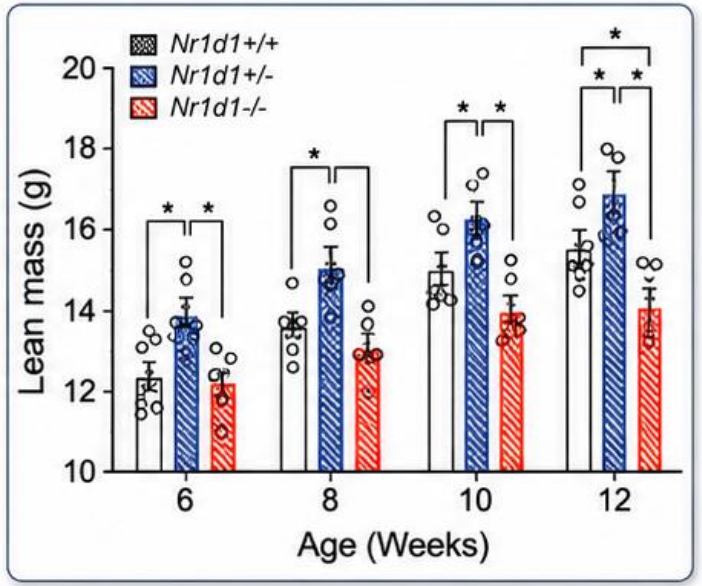
Douglas Kojetin, Yongxin Wang, Theodore M. Kamenecka, and Thomas P. Burris*

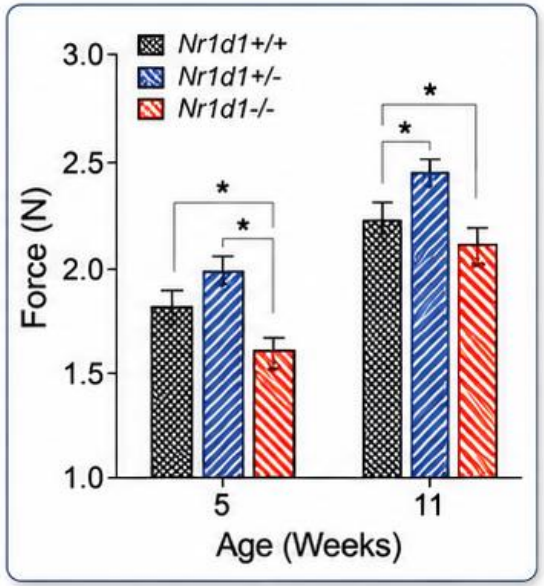
The Scripps Research Institute, Jupiter, Florida 33458, United States

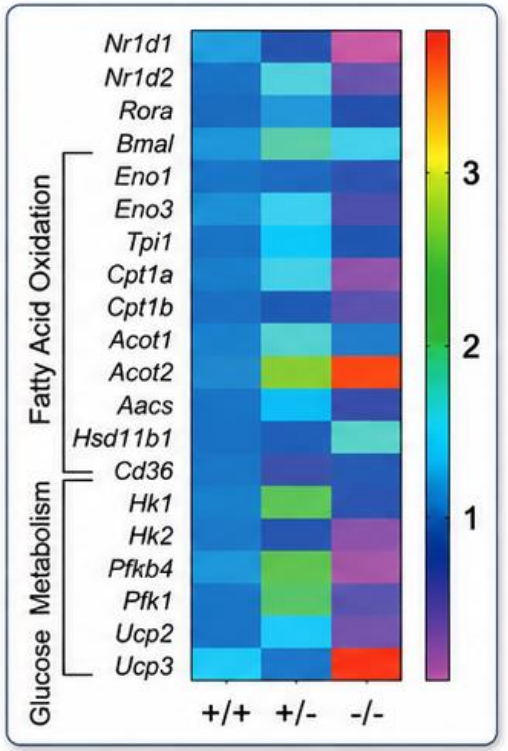
Synthetic agonists activate REV-ERB to repress transcription (e.g., Bmal1), whereas antagonists block REV-ERB activity, providing tools to interrogate circadian and metabolic regulation.

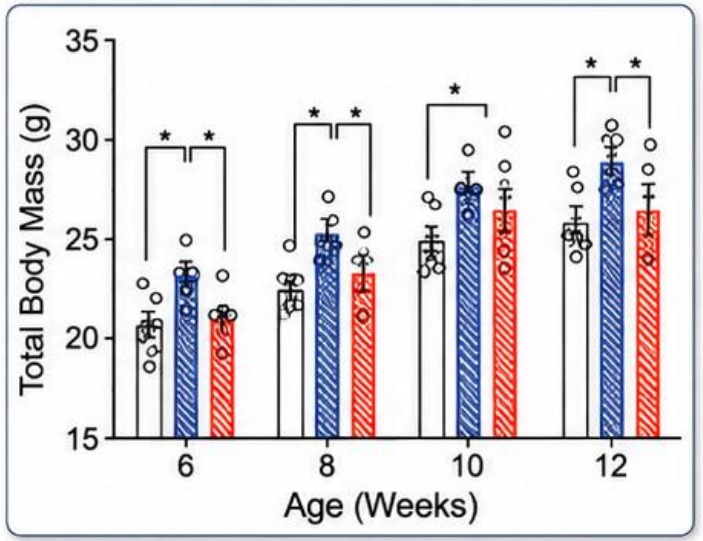
REV-ERBα Heterozygous KO Mice Have Substantially Increased Lean (Muscle) Mass and Strength

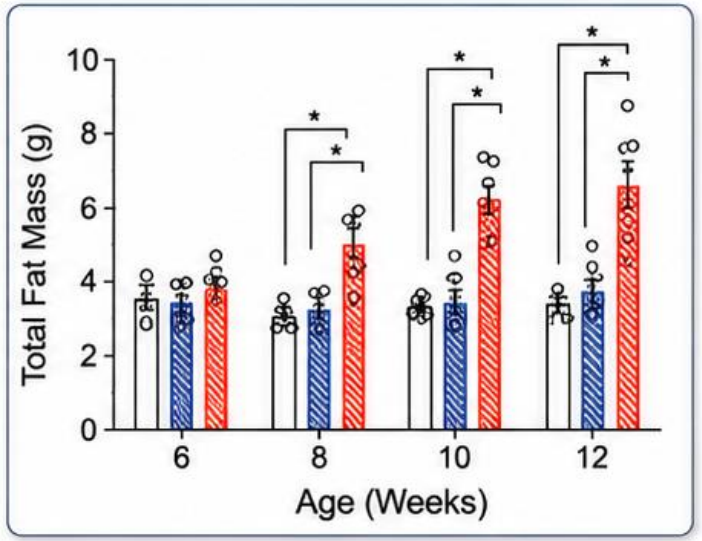


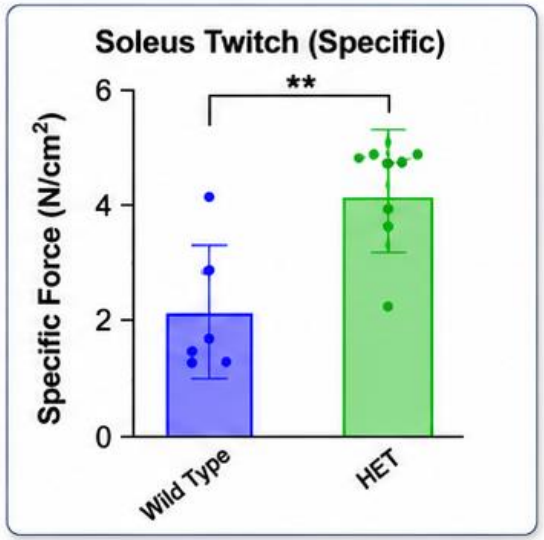








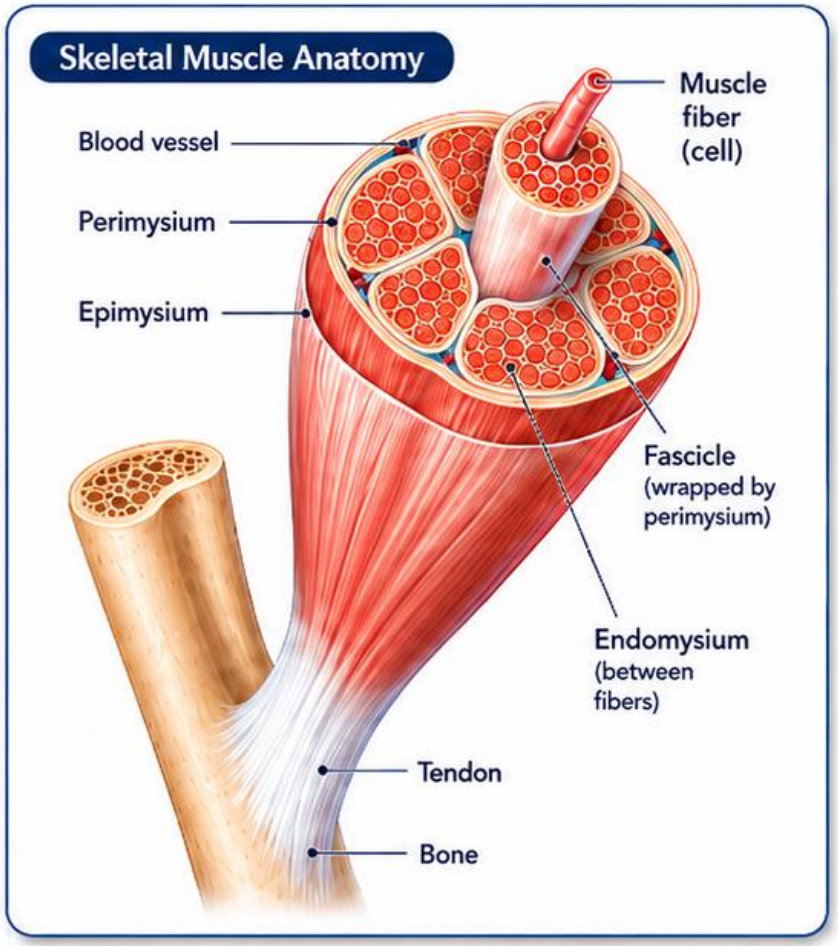


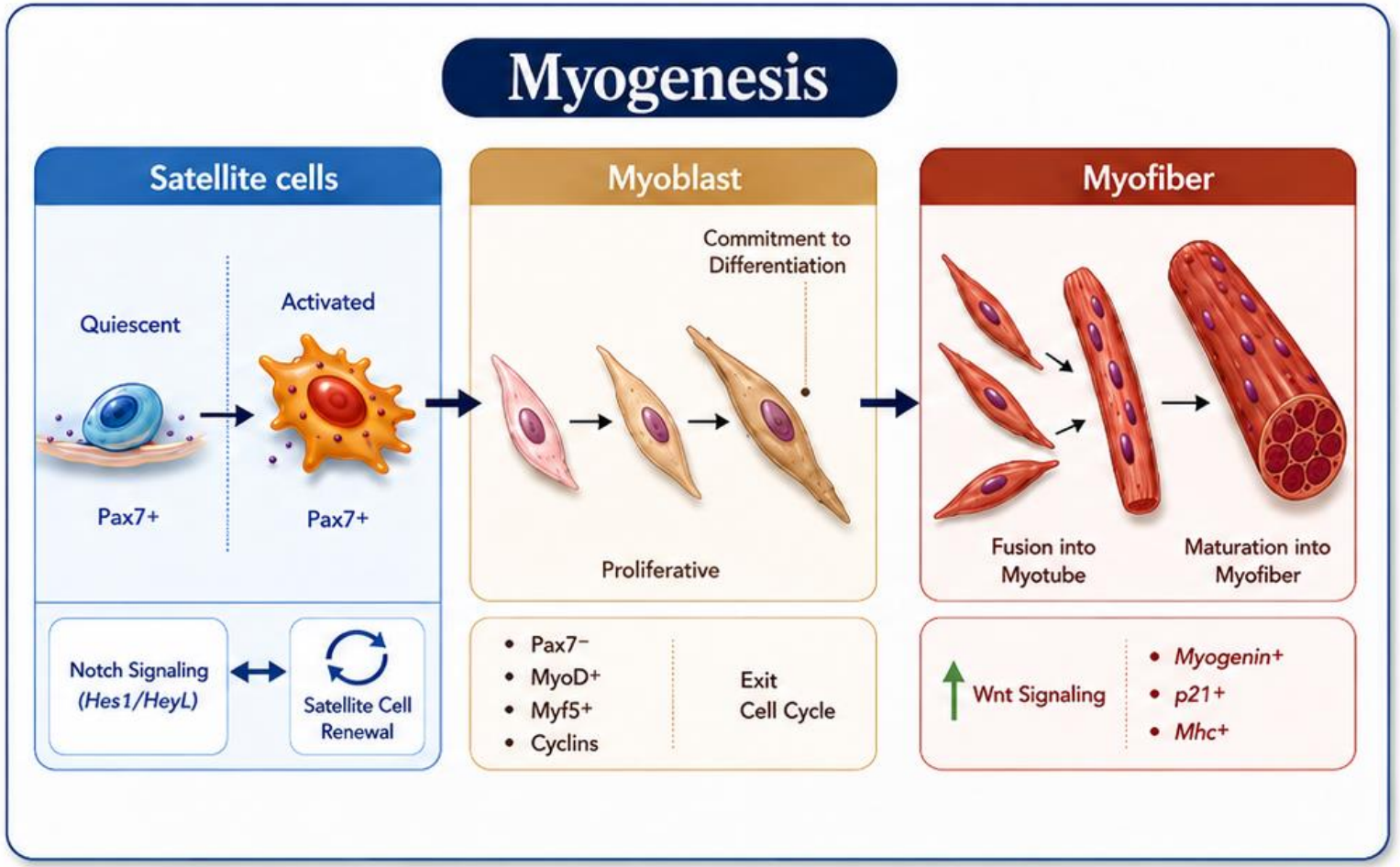


Nr1d1+/+ (+/+)
Nr1d1+/- (+/-)
Nr1d1-/- (-/-)

REV-ERBα haploinsufficiency drives increases in lean mass, reduces fat mass, and enhances muscle strength.

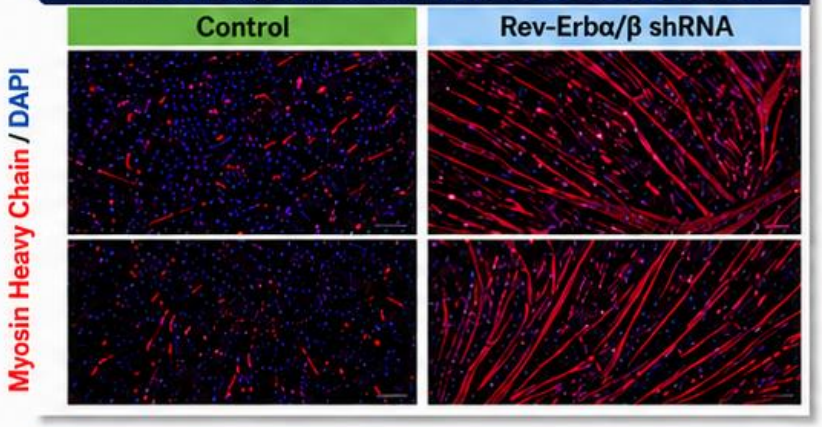
Skeletal Muscle Structure and Myogenesis



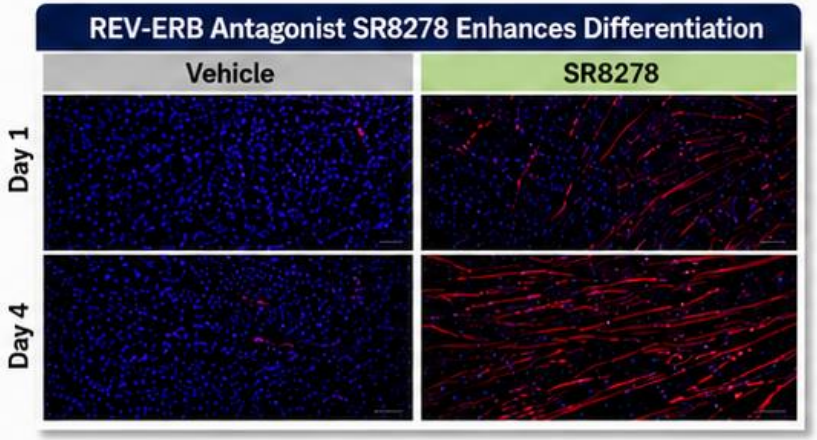


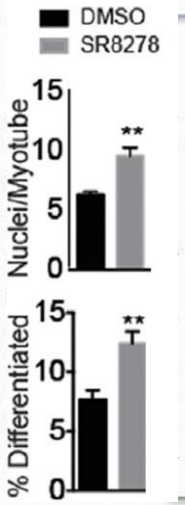
Knock-down of REV-ERBs or REV-ERB Antagonist Treatment Enhances Myogenesis in C2C12 Myoblasts

REV-ERBα/β Knock-down Enhances Differentiation

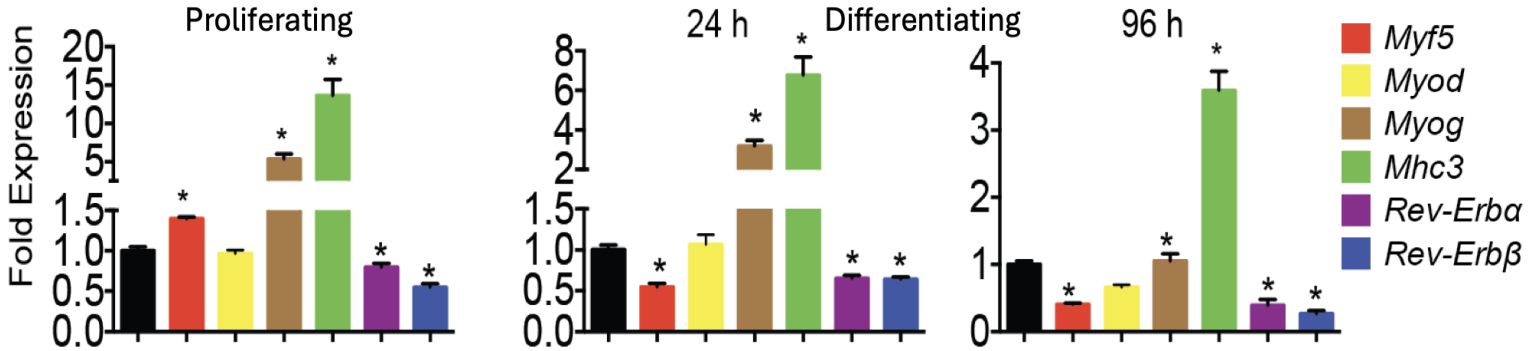


REV-ERB Antagonist SR8278 Enhances Differentiation

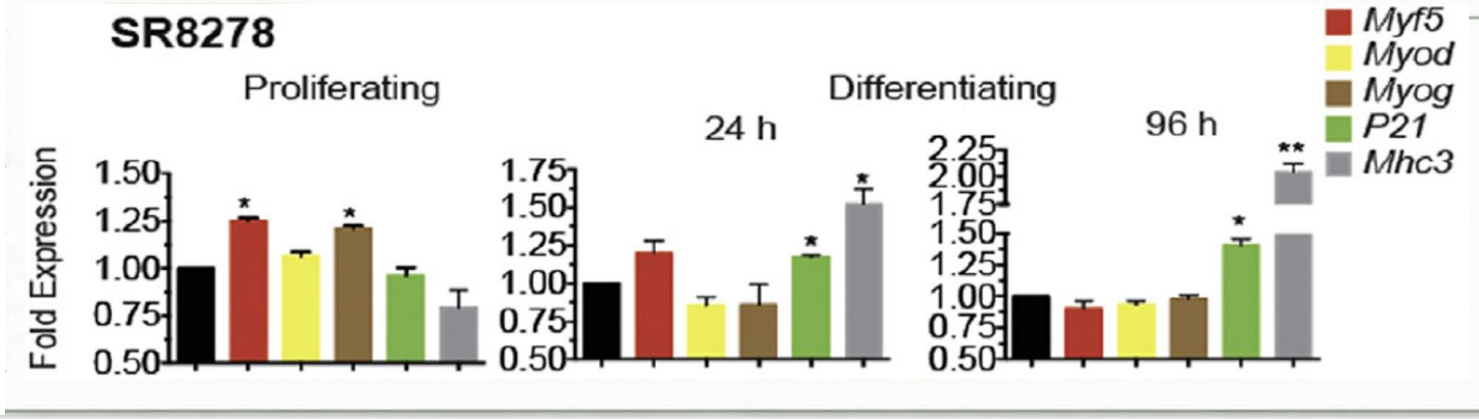




Rev-Erbα/β shRNA



SR8278



Genetic knock-down of REV-ERBα/β or pharmacological inhibition with SR8278 significantly **enhances myogenic differentiation** of C2C12 myoblasts.

Upregulation of myogenic genes (*Myf5*, *Myod*, *Myog*, *Mhc3*) and cell cycle modulator (p21)

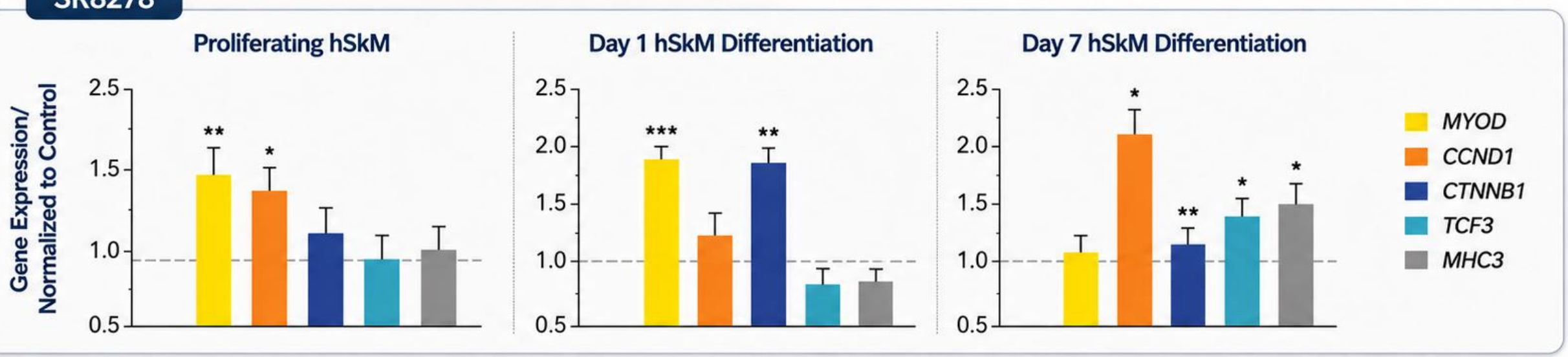
Increased fusion (more myotubes, fewer nuclei/ myotube)

Enhanced myogenesis at early (24 h) and late (96 h) stages of differentiation

SR8278 Stimulates Myogenesis in Primary Human Myoblasts

SR8278 upregulates key myogenic genes during proliferation and differentiation

SR8278



SR8278 robustly induces myogenic gene expression in human myoblasts.

Upregulation occurs early (Day 1) and is sustained through Day 7 of differentiation.

Key regulators of myogenesis (*MYOD, CCND1, CTNNB1*) are strongly induced.

Supports enhanced myoblast differentiation toward mature myofibers.

Highlights the potential of REV-ERB antagonism to promote muscle regeneration.

Targeting REV-ERB signaling to drive muscle regeneration

SR8278 Stimulates Muscle Regeneration in Muscle Injury Models

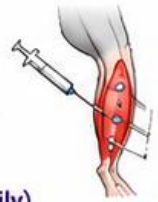
Cardiotoxin (CTX) Muscle injury Model

1. **6-week-old** C57BL/6 mice

2. **CTX injury / PBS sham**

Left TA muscle: **CTX injury**

30 µL cardiotoxin (CTX, 10 mM) injected at 3 sites



Right TA muscle: **PBS sham injection**

3. **Treatment (daily)**

- VEH — **Vehicle control**
- SR8278 — **SR8278 treatment:** 25 mg/kg, s.c., once daily at 12:00 h

Formulation:
10% DMSO / 10% cremophor / 80% PBS

4. **Harvest time points**

Day 8 after injury

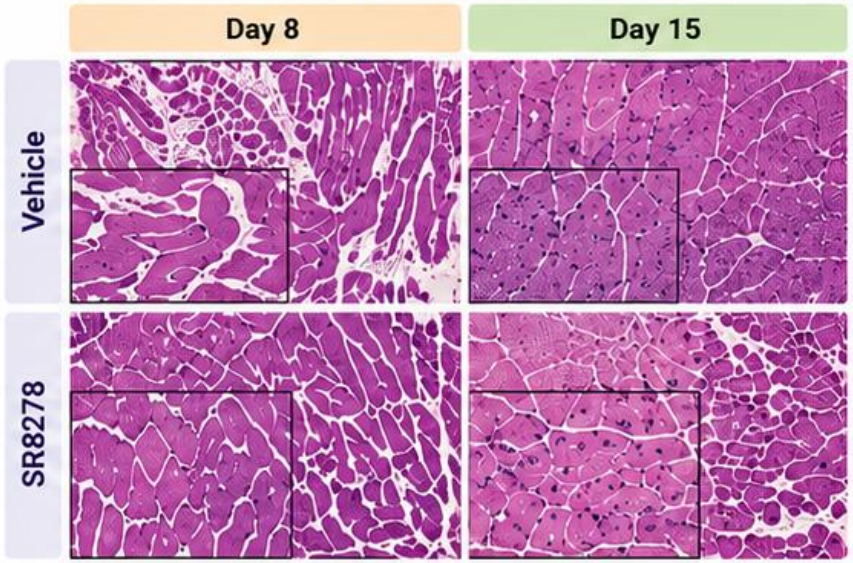
Day 15 after injury

5. **Endpoints / Analyses**

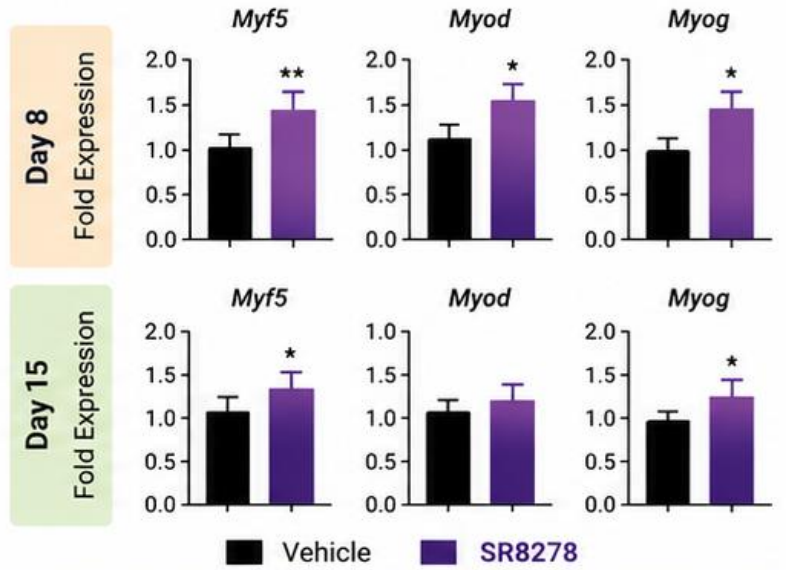
- Histology (H&E)
- Myofiber cross-sectional area (CSA)
- Centralized nuclei / regeneration
- qPCR of myogenic genes (*e.g., Myf5, Myod, Myog*)

Acute tibialis anterior injury with contralateral PBS sham control and daily SR8278 dosing

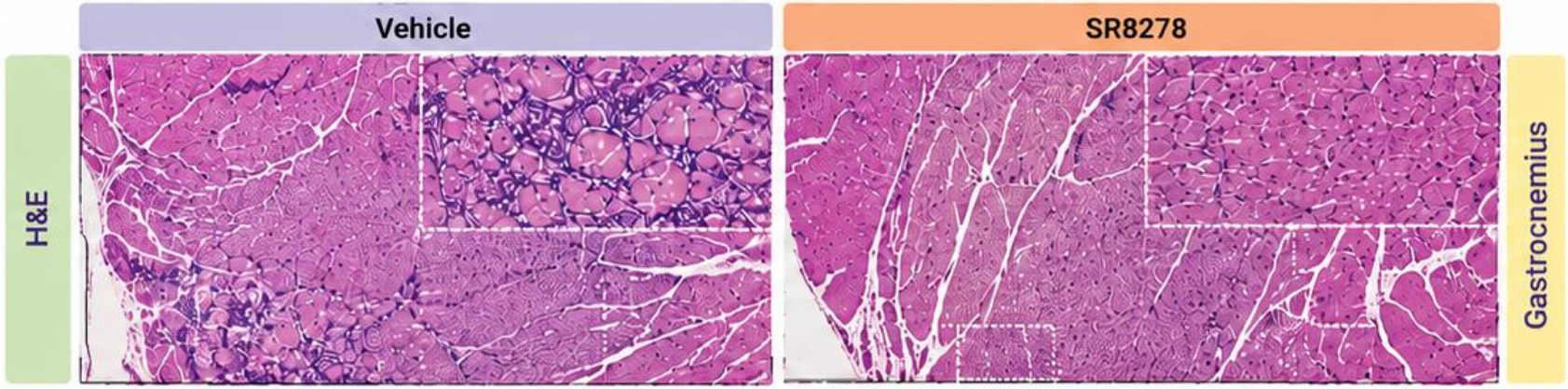
Histology of TA Muscle (H&E)



H Expression of Myogenic Genes (qPCR)



mdx Mice – Gastroc Muscle, Day 15 After CTX Injury



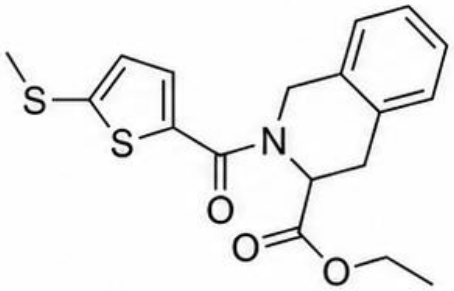
SR8278 accelerates muscle regeneration after CTX injury:

- Enhanced histological **recovery** by Day **8** and **Day 15**
- Increased **expression** of **myogenic genes** (***Myf5, Myod, Myog***)
- Improved **muscle regeneration** in ***mdx*** **mice**

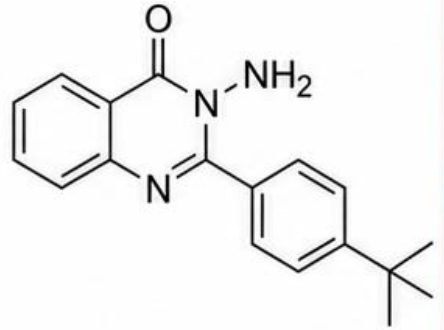
Development of Novel Drug-Like REV-ERB Antagonists

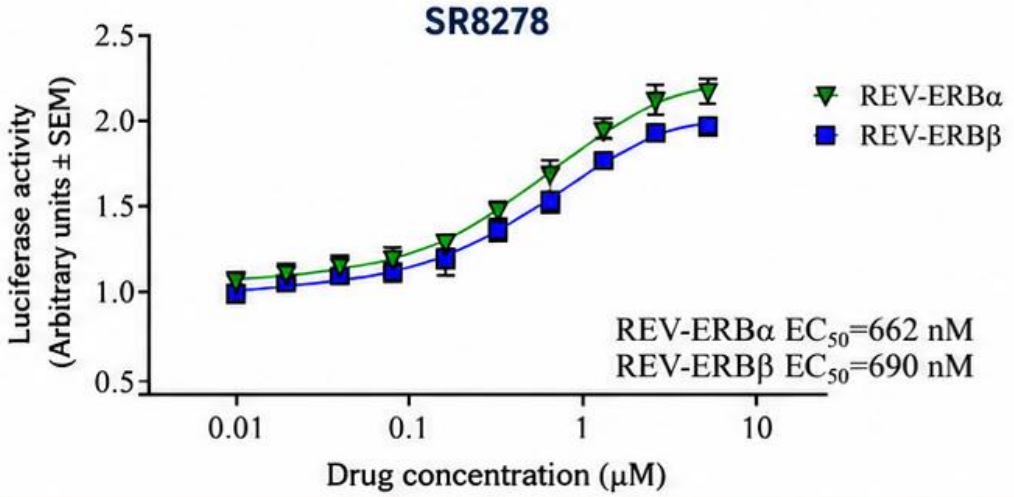
- SR8278 has no IP position
- Initiated a large medicinal chemistry effort to identify and optimize additional antagonists
- Identified 3 novel chemical scaffolds with REV-ERB antagonist activity
- Patents filed on the 3 series
- New compounds with drug-like properties
  - 10 nM potency
  - Superior efficacy to SR8278
  - Solid ADME/PK profile
  - Orally bioavailable or SC administration

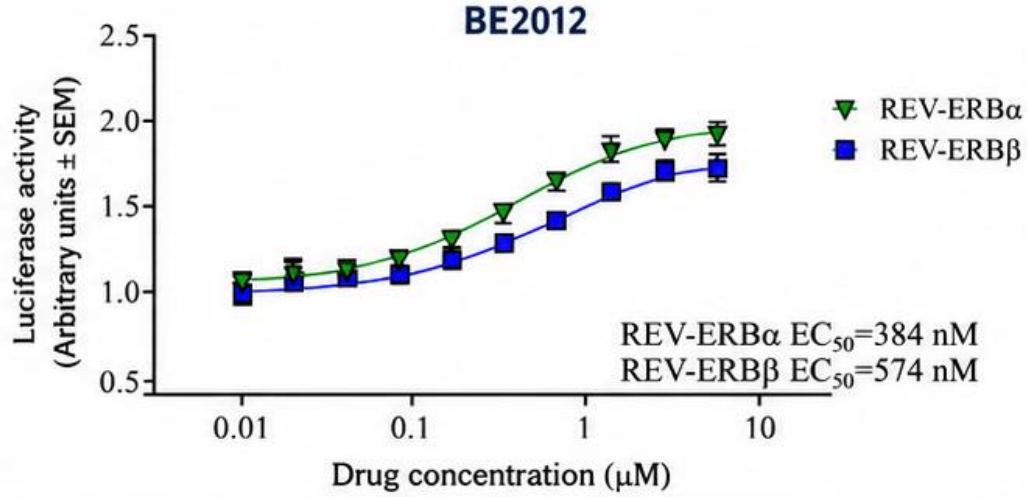
SR8278



BE2012



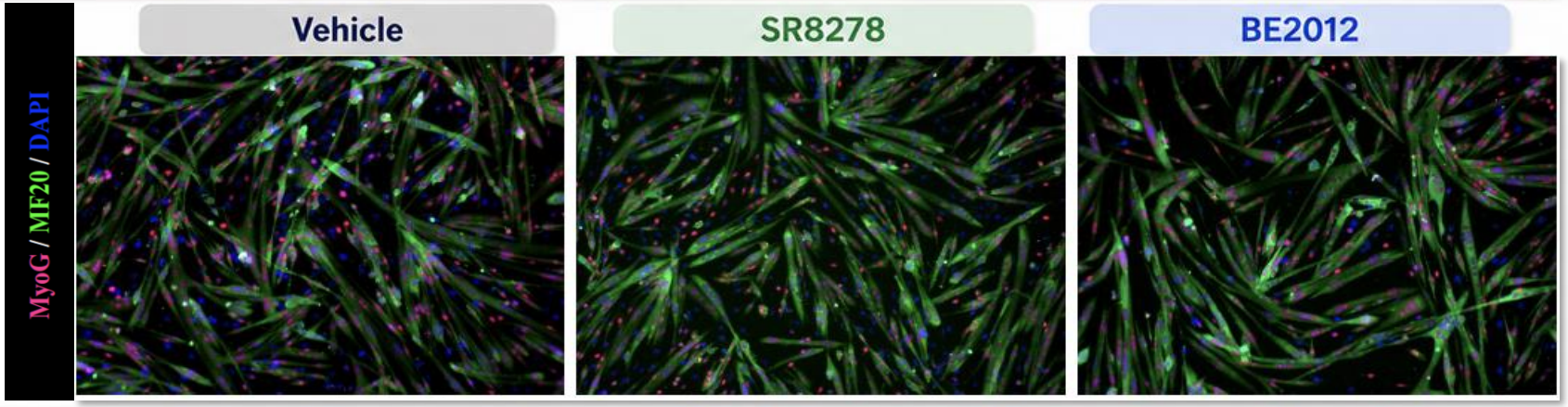




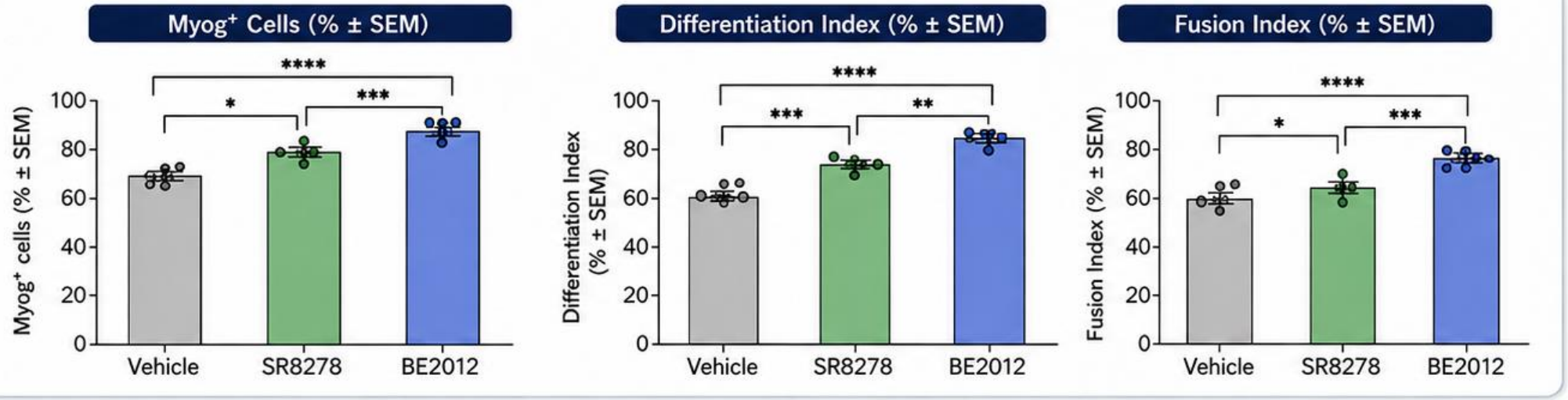
Three new antagonist series with improved potency, efficacy, and drug-like properties.

Comparison of the Activity of REV-ERB Antagonists SR8278 and BE2012 in Acceleration of Myogenesis in Primary Mouse Myoblasts

REV-ERB antagonists promote myogenic differentiation in primary mouse myoblasts



MyoG: Myogenic TF/Differentiated myoblast
MF20: MHC/Differentiated Myotubes
DAPI: Nuclei



Statistics

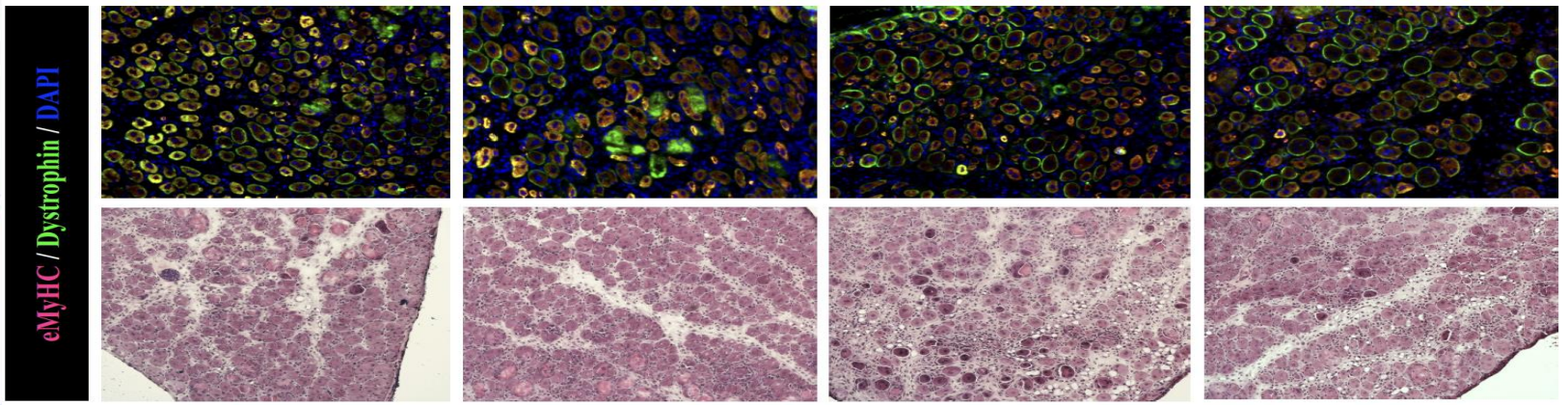
*	$p < 0.05$
**	$p < 0.01$
***	$p < 0.001$
****	$p < 0.0001$

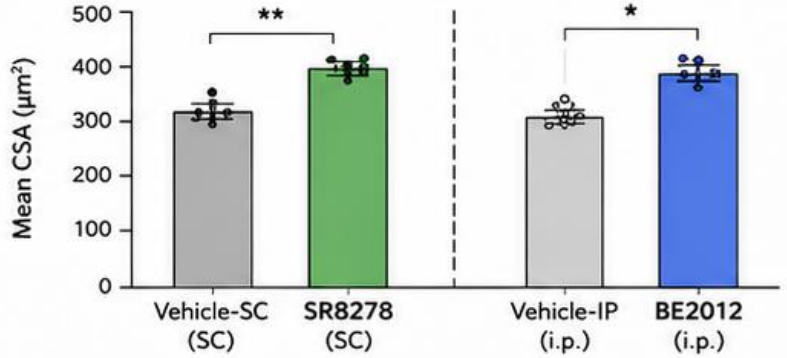
One-way ANOVA with Tukey's post hoc test

Both REV-ERB antagonists SR8278 and BE2012 significantly increase myogenic differentiation and fusion in primary mouse myoblasts, with BE2012 showing the greatest activity.

Comparison of the Activity of REV-ERB Antagonists SR8278 and BE2012 in the CTX Model of Muscle Injury

REV-ERB antagonists enhance muscle regeneration and reduce muscle damage after CTX injury



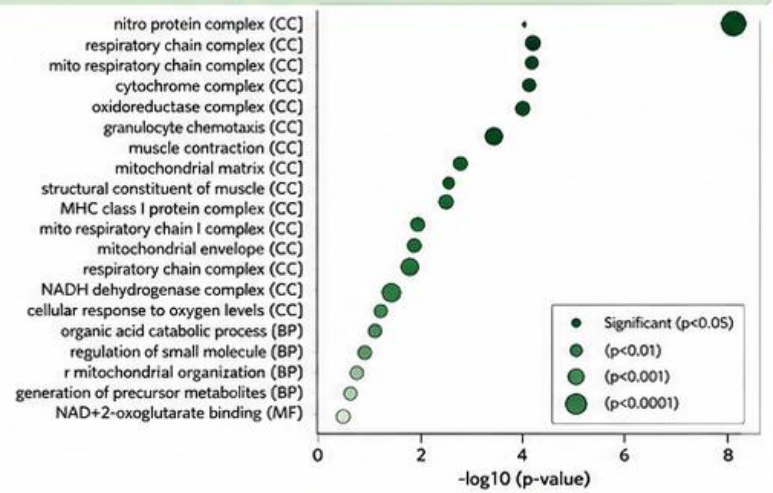


Vehicle-SC (subcutaneous)
SR8278 (25 mg/kg, s.c.)
Vehicle-IP (intraperitoneal) (i.p.)
BE2012 (25 mg/kg, i.p.)

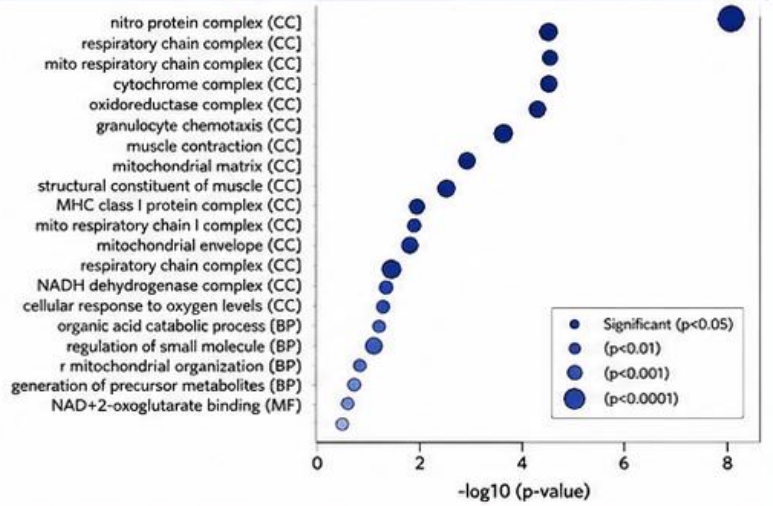
n = 6 mice per group
Data shown as mean ± SEM
* p < 0.05
** p < 0.01
(One-way ANOVA with Tukey's post hoc test)

GO Biological Process Enrichment (Upregulated Genes)

GO Analysis – SR8278 vs Vehicle-SC



GO Analysis – BE2012 vs Vehicle-IP



CTX injury induces muscle damage and inflammation (Vehicle groups).

SR8278 (s.c.) significantly increases myofiber size compared to Vehicle-SC.

BE2012 (i.p.) significantly increases myofiber size compared to Vehicle-IP.

Both REV-ERB antagonists promote muscle regeneration after CTX injury.

CONCLUSION & FUTURE DIRECTIONS

Targeting REV-ERB with antagonists such as SR8278/BE2012 accelerates muscle regeneration and represents a promising therapeutic strategy for a wide range of muscle injuries and disorders.

CONCLUSION

REV-ERB antagonism (**SR8278, BE2012**) relieves transcriptional repression of myogenic programs.

In vitro and ***in vivo*** studies show increased myogenic differentiation, fusion, and enhanced muscle regeneration.

SR8278 and **BE2012** demonstrate superior activity compared to vehicle and promote functional recovery in the CTX and ***mdx*** models.

These findings support REV-ERB antagonists as a novel therapeutic approach to improve muscle repair, function, and quality of life.

FUTURE DIRECTIONS

Volumetric muscle injury
Evaluate efficacy in large muscle defects and volumetric tissue loss models.

Enhanced strength with training
Assess the ability of REV-ERB antagonists to augment strength gains and functional outcomes with exercise.

Accelerated recovery from ventilation (diaphragm)
Investigate benefits in diaphragm dysfunction and weaning from mechanical ventilation.

Disuse muscle atrophy with immobilization
Determine efficacy in prevention and reversal of atrophy due to disuse or immobilization.

Postoperative rehabilitation
Explore potential to improve recovery of muscle mass and function following surgery.

Sarcopenia
Assess therapeutic potential in age-related muscle loss to improve mobility and independence.

REV-ERB antagonists *hold strong potential to* ***transform*** *the treatment of muscle injuries, degenerative myopathies, and age-related muscle decline.*

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ACKNOWLEDGEMENTS

A First-in-Class REV-ERB Antagonist to Accelerate Skeletal Muscle Regeneration and Restore/Enhance Warfighter Performance

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