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The Effects of NSAIDs on Exercise Adaptations

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CONFLICT OF INTEREST STATEMENT

I have no actual or potential conflict of interest
in relation to this presentation.

DISCLOSURE STATEMENT

The views expressed in this presentation are those of the authors and do not
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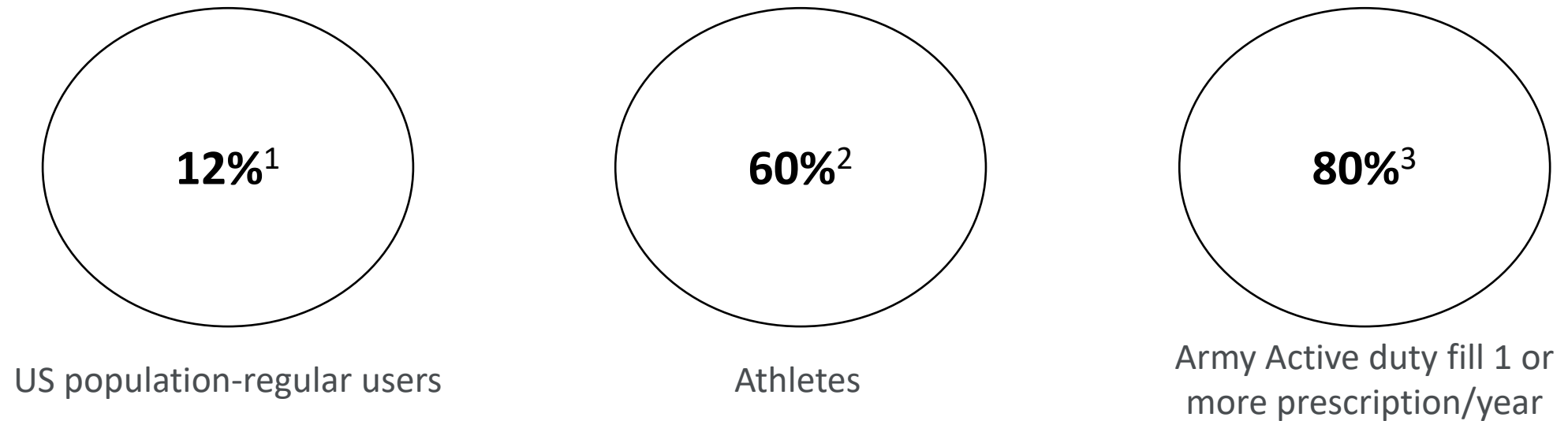
Outline

- NSAID usage in various populations
- NSAID adverse effects
- NSAID mechanism and drug differences
- Do NSAIDs enhance performance?
- Do NSAIDs improve DOMS?
- Do NSAIDs interfere with muscle growth?
- Do NSAIDs interfere with fracture healing and bone repair?
- Our current research project on NSAIDs and musculoskeletal adaptations
- NSAID risk assessment
- Summary

Why use NSAIDs?

To reduce pain and inflammation associated with training, competition or soft tissue injuries, or to gain a competitive advantage.

NSAID Usage in Athletes and Soldiers



¹Zhou et al., 2014; ²Rudgar et al., 2019; ³Walker et al., 2017;

Adverse Effects of NSAIDs

- Gastrointestinal bleeding
- Cardiovascular events
- Hypertension
- Acute renal failure

NSAID have potential health risks.

Vonkeman & Van de Laar 2010; Warden 2010

Types of NSAIDs

Acetaminophen



Ibuprofen



Naproxen Sodium



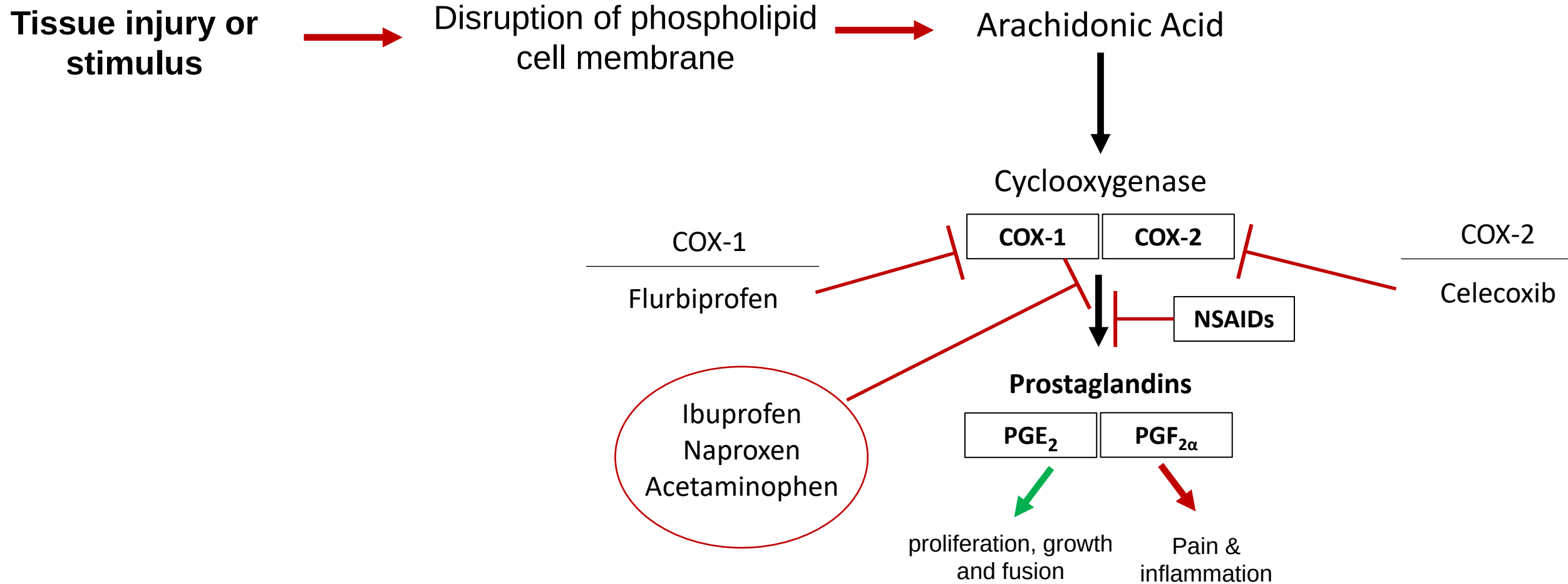
Celecoxib



Flurbiprofen



Mechanisms of NSAIDs



Do NSAIDs enhance performance?

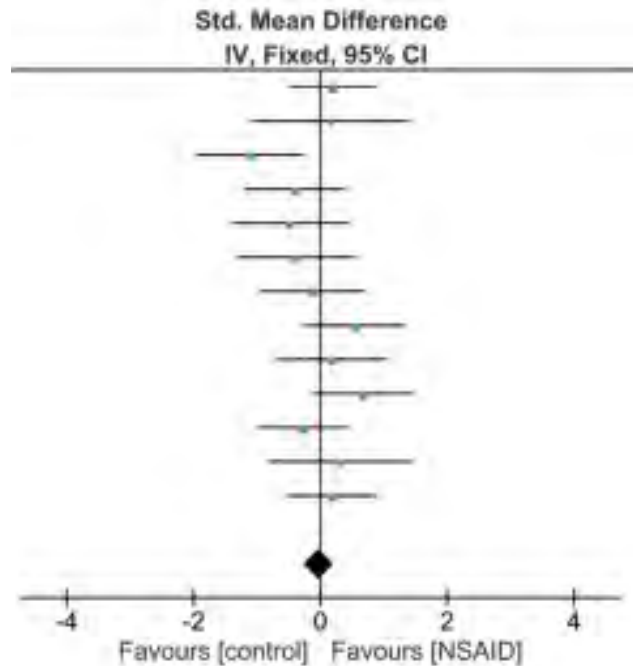
Do NSAIDs enhance performance?

- 650mg of ASA as a premedication has little effect on exercise performance in normal endurance runners.¹
- A single dose of 1000mg of aspirin does not affect physical performance during submaximal and maximal exercise.²
- A single dose of 400mg of ibuprofen does not improve single-leg or maximal cycling performance in healthy humans.³

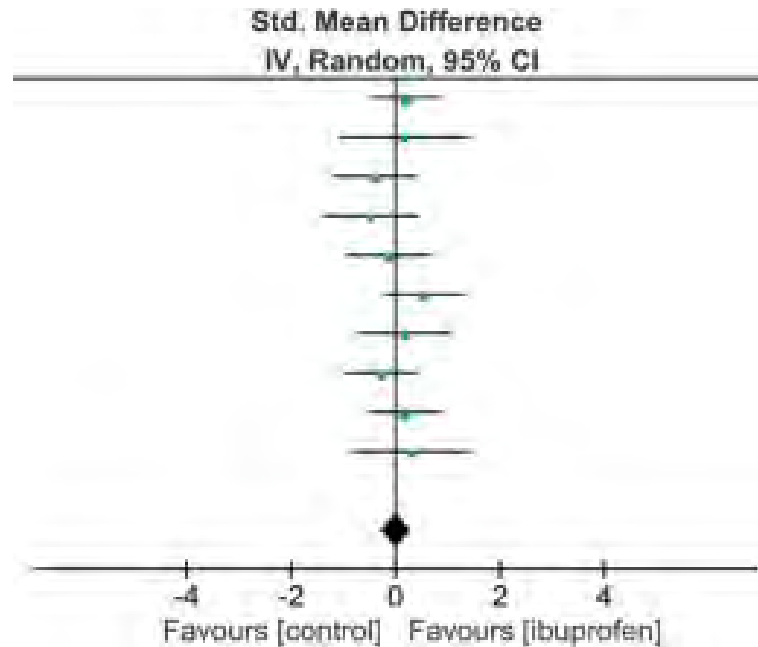
¹Lisse et al., 1991; ²Roi et al., 1991; ³Morgan et al., 2018

Do NSAIDs enhance performance?

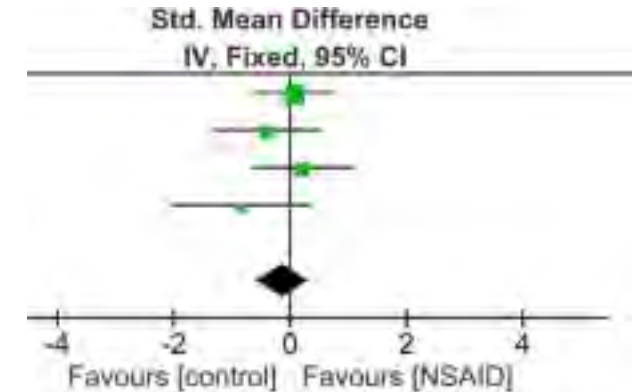
Maximum performance



Time to Exhaustion



Pain Perception



This meta-analysis found NSAIDs did not significantly impact performance outcomes in healthy people.

¹Cornu et al., 2020

Do NSAIDs enhance performance?

Current evidence suggests NSAIDs do not enhance performance.

Do NSAIDs improve DOMS?

Delayed Onset Muscle Soreness (DOMS)

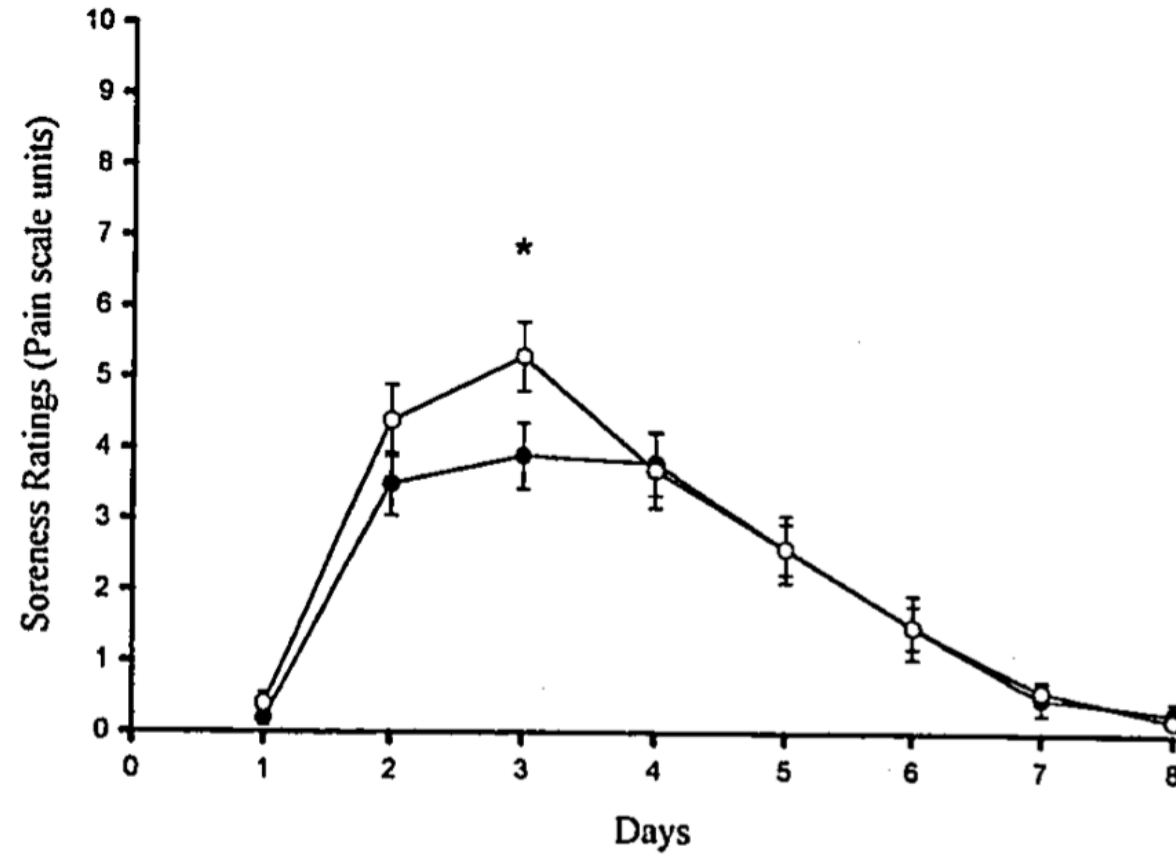
- Caused mainly by eccentric actions
- Structural damage of muscle fibers
- Reduces range of motion (ROM)
- May be due to inflammation

Do NSAIDs improve DOMS?

		<i>Ibuprofen</i>	<i>Placebo</i>
First period	Pre	23 ± 1	22 ± 1
	6 h	31 ± 3	29 ± 3
	24 h	50 ± 6	29 ± 5
	48 h	42 ± 4	35 ± 4
	72 h	30 ± 2	26 ± 2
		<i>Placebo</i>	<i>Ibuprofen</i>
Second period	Pre	23 ± 1	22 ± 1
	6 h	31 ± 2	29 ± 2
	24 h	41 ± 5	38 ± 5
	48 h	36 ± 3	36 ± 5
	72 h	28 ± 2	29 ± 3

Ibuprofen is not effective in reducing DOMS after downhill running.

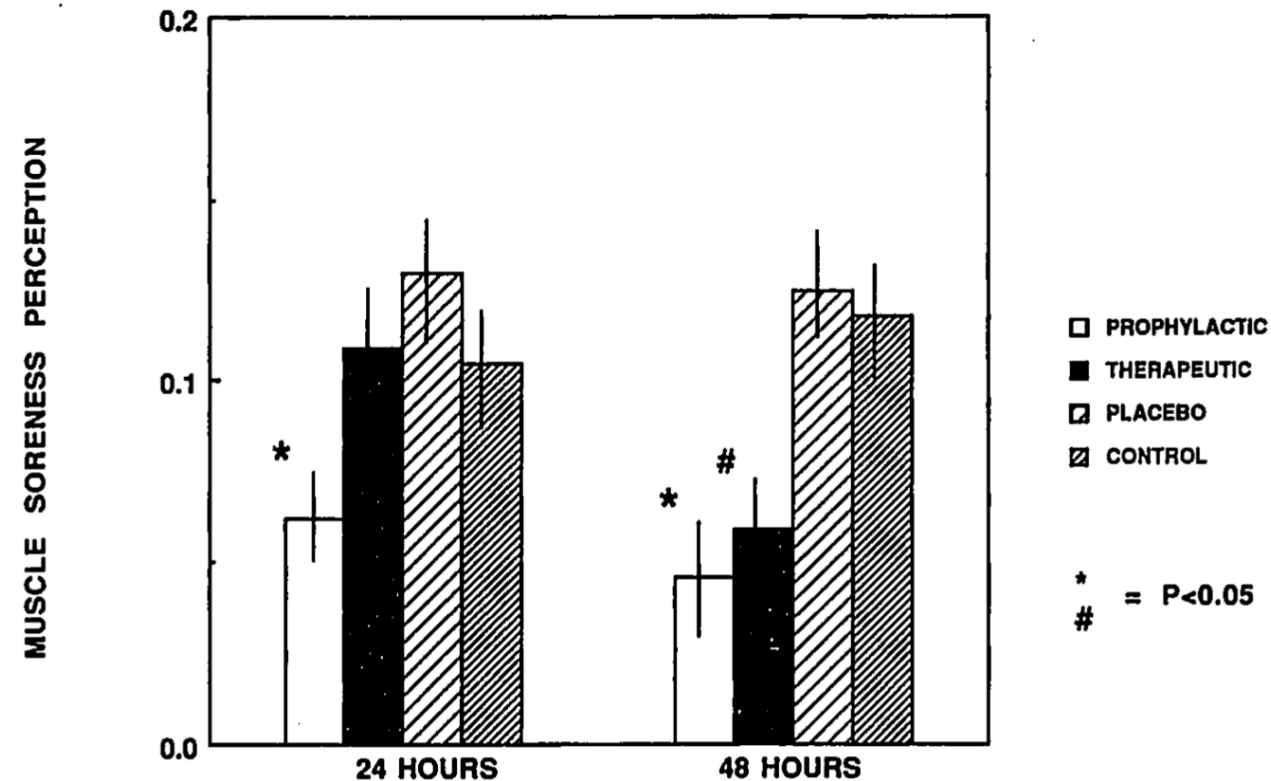
Do NSAIDs improve DOMS?



Naproxen Sodium decreases DOMS 3 days after eccentric single-leg exercise.

Lecomte et al., 1998

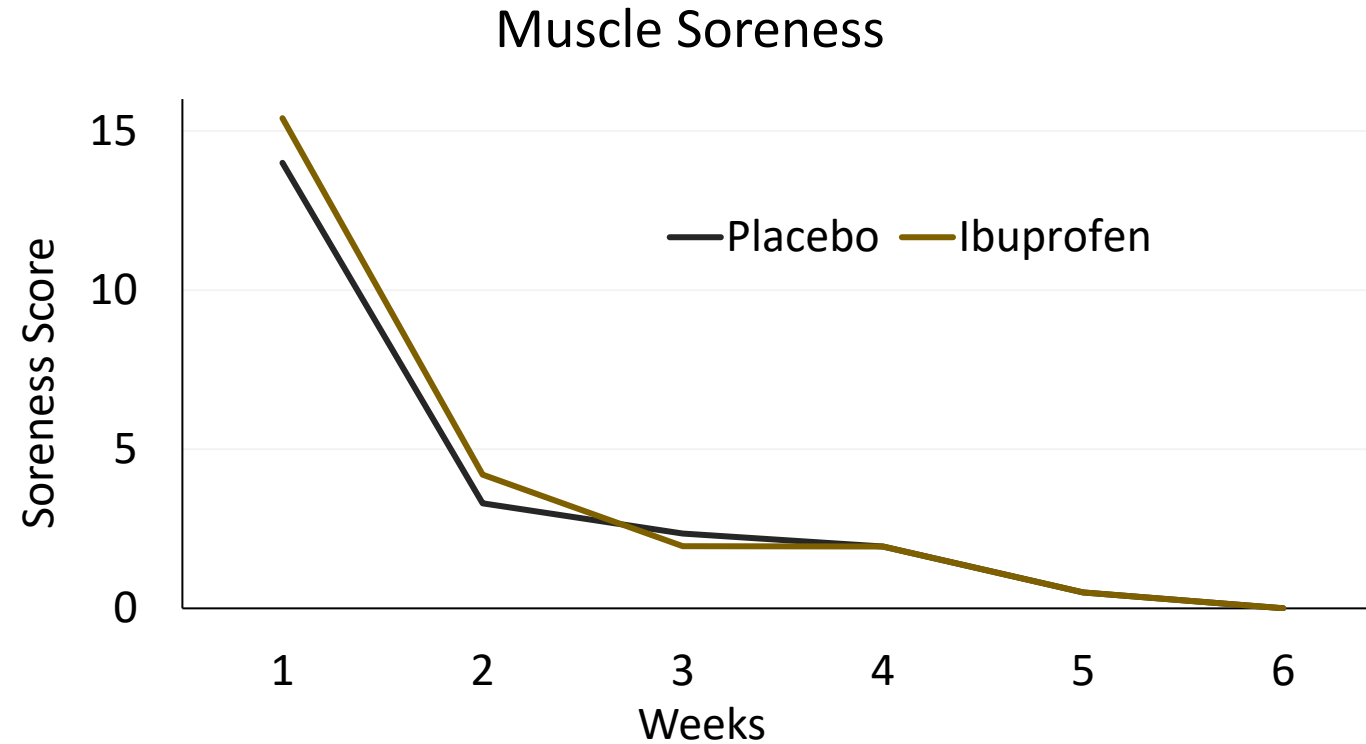
Do NSAIDs improve DOMS?



Ibuprofen given prophylactically or therapeutically is effective in reducing DOMS after a weighted step-up exercise session.

Hasson et al., 2003

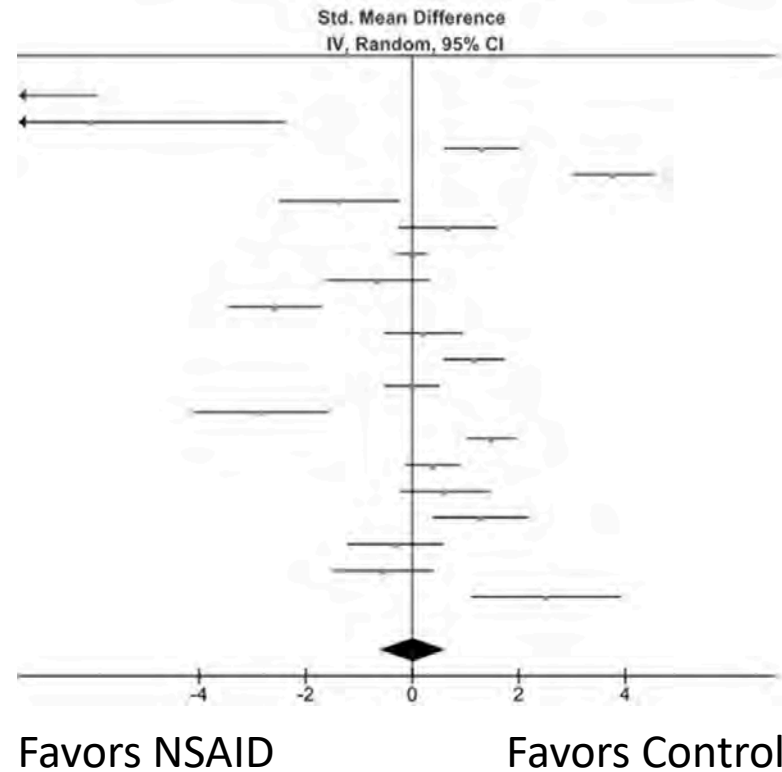
Do NSAIDs improve DOMS?



Ibuprofen does not decrease the perception of muscle soreness during a bicep focused resistance exercise program.

Krentz et al., 2008

Do NSAIDs improve DOMS?



NSAIDs are not superior to controls/placebos in treating DOMS

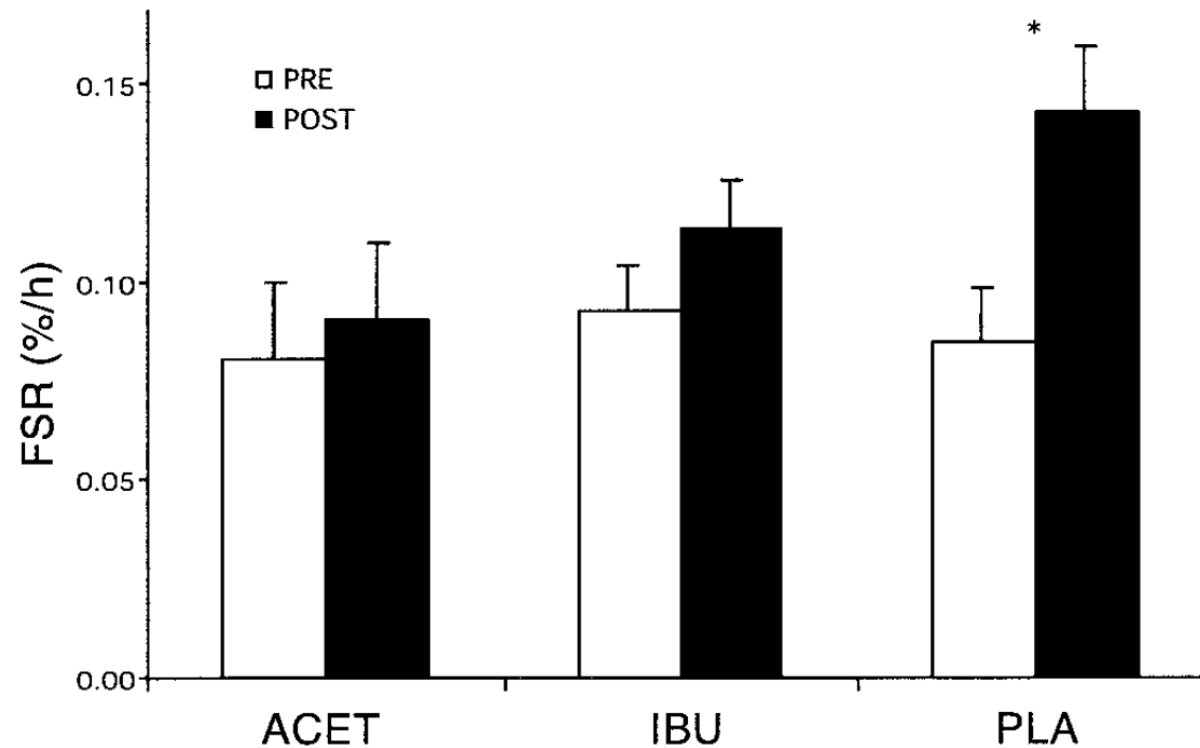
Nahon et al., 2021

Do NSAIDs improve DOMS?

Current evidence suggests NSAIDs do not always reduce DOMS.

Do NSAIDs interfere with muscle protein synthesis?

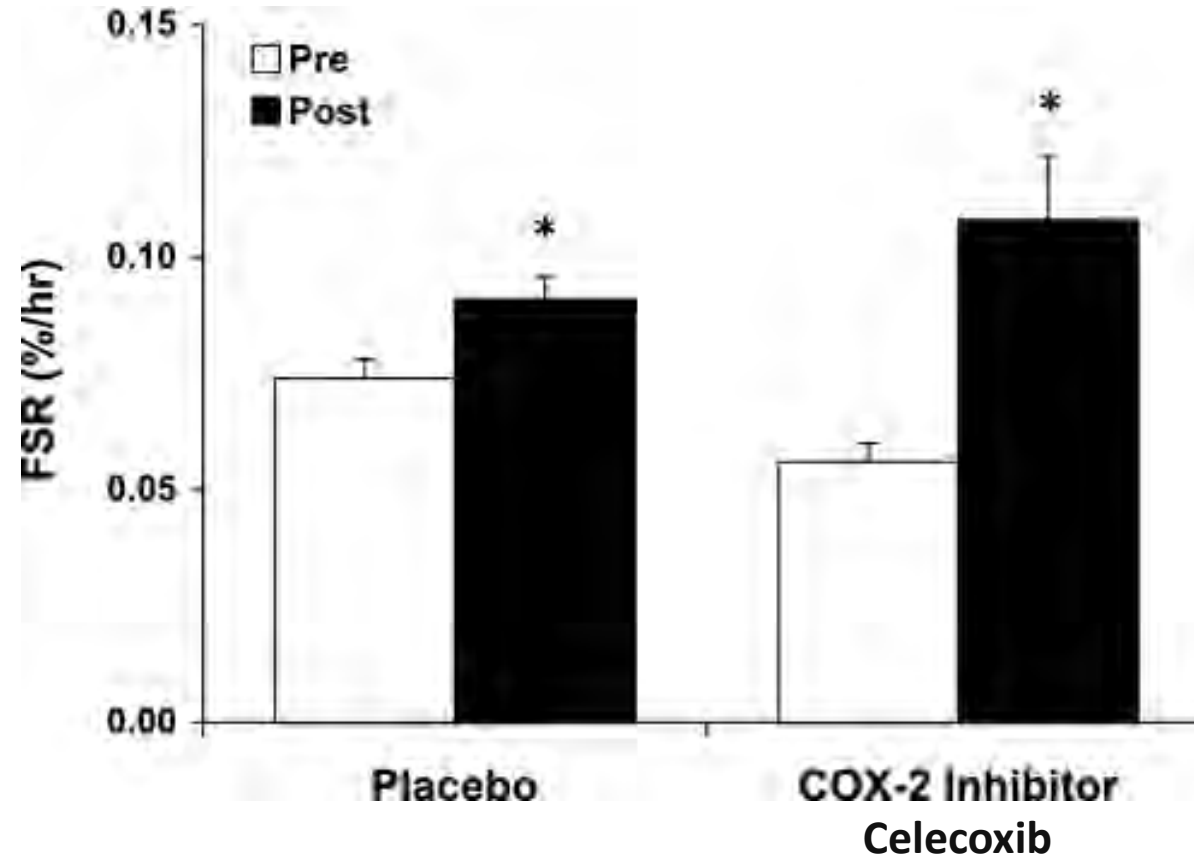
Do NSAIDs interfere with muscle hypertrophy?



Over-the-counter doses of both ibuprofen and acetaminophen suppress the protein synthesis response in skeletal muscle after eccentric resistance exercise.

¹Trappe et al., 2002

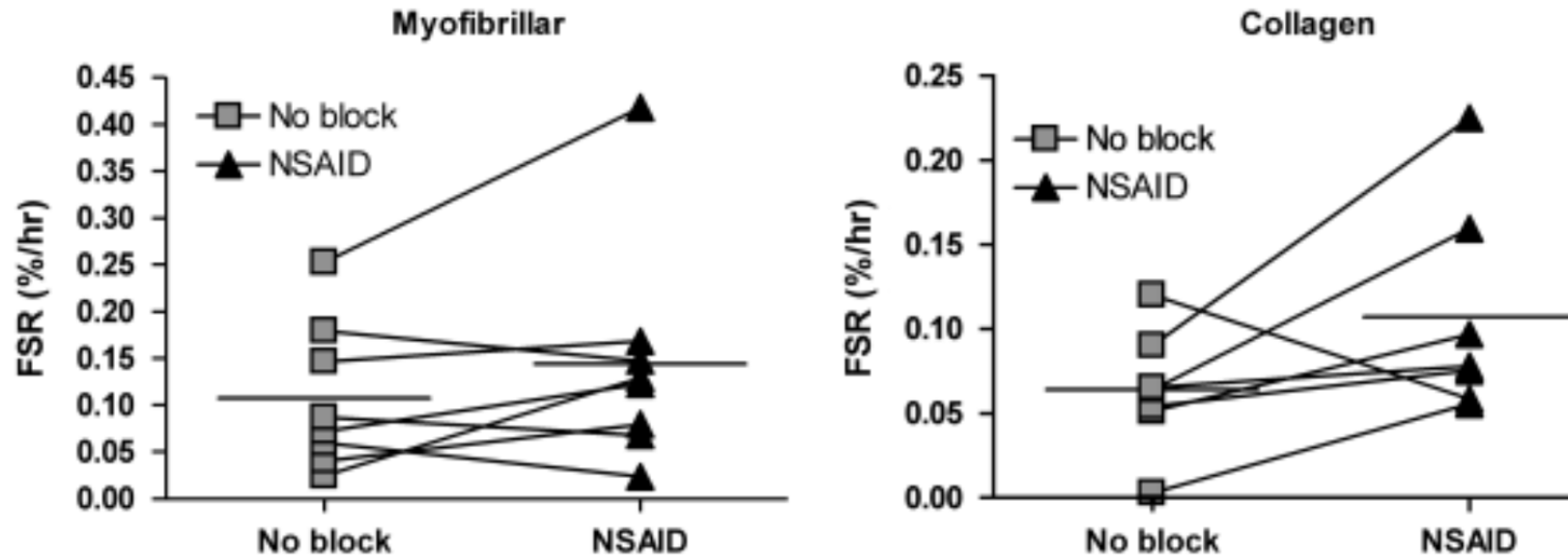
Do NSAIDs interfere with muscle hypertrophy?



Celecoxib does not inhibit the muscle protein synthetic response.

¹Burd et al., 2010

Do NSAIDs interfere with muscle hypertrophy?



The muscle protein synthesis response to exercise was not affected by 7.5 hours of indomethacin infusion.

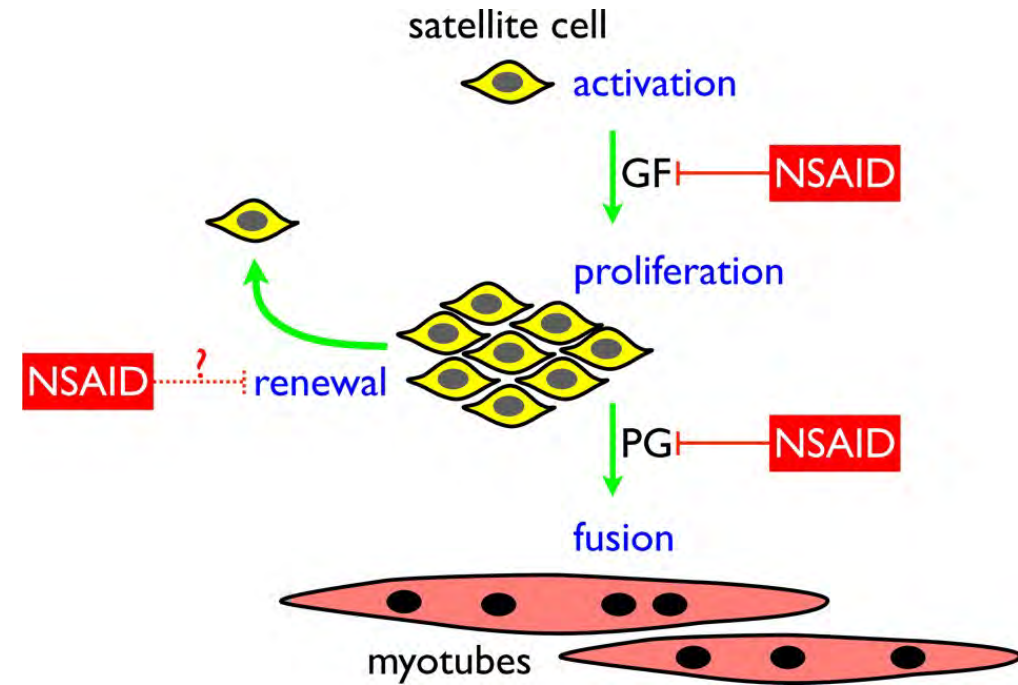
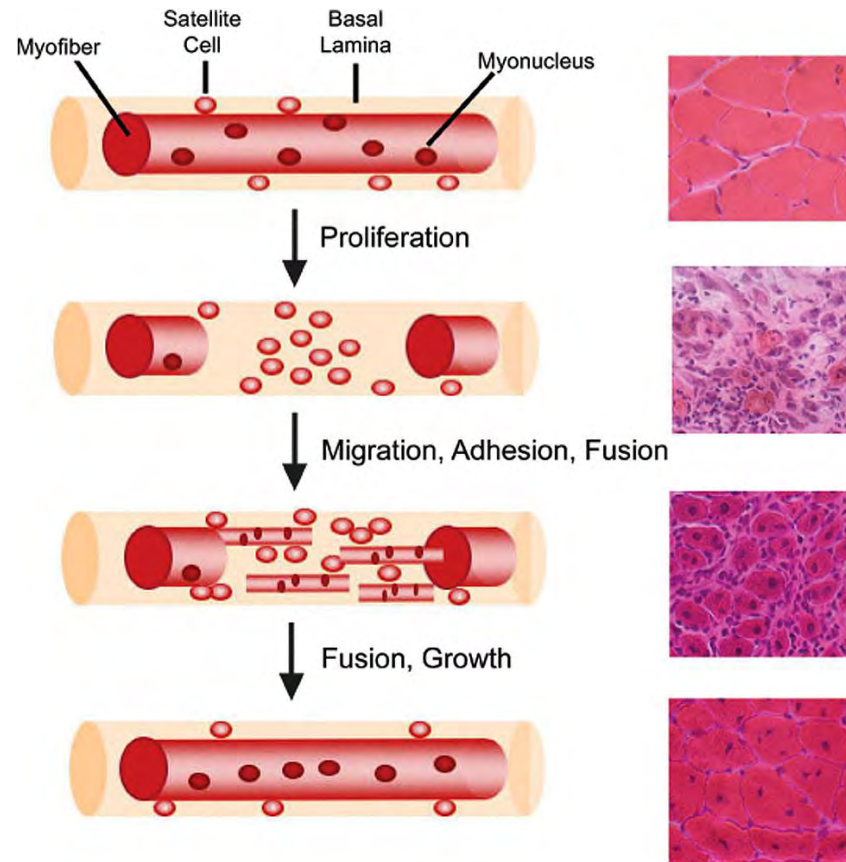
Mikkelsen et al., 2010

Do NSAIDs interfere with muscle protein synthesis?

Current evidence suggests the dose and type of NSAID may determine the effect on muscle protein synthesis.

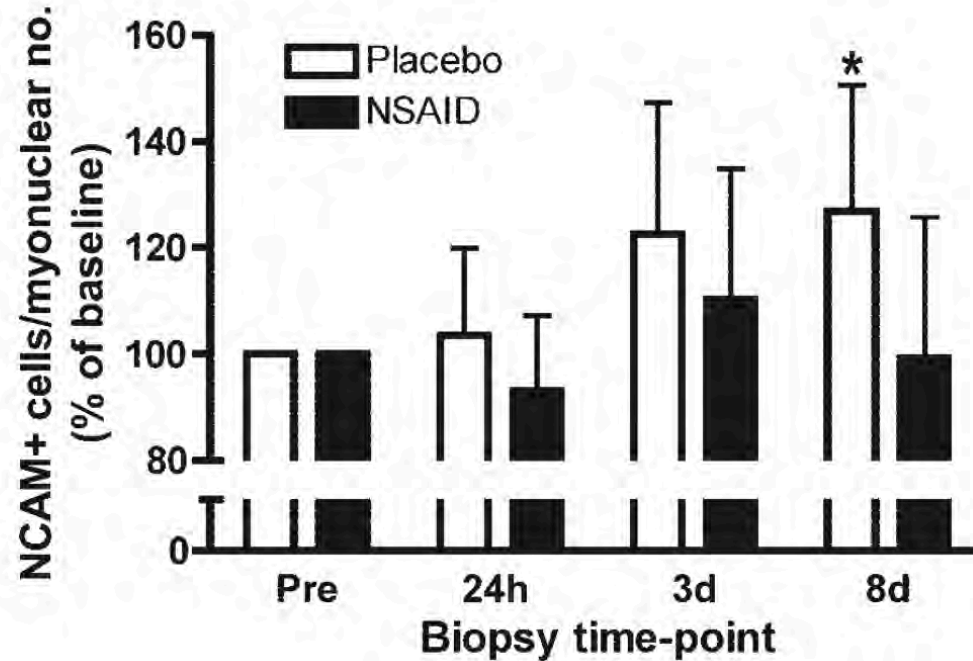
Do NSAIDs interfere with satellite cells?

Satellite Cell Review



Mackey et al., 2013

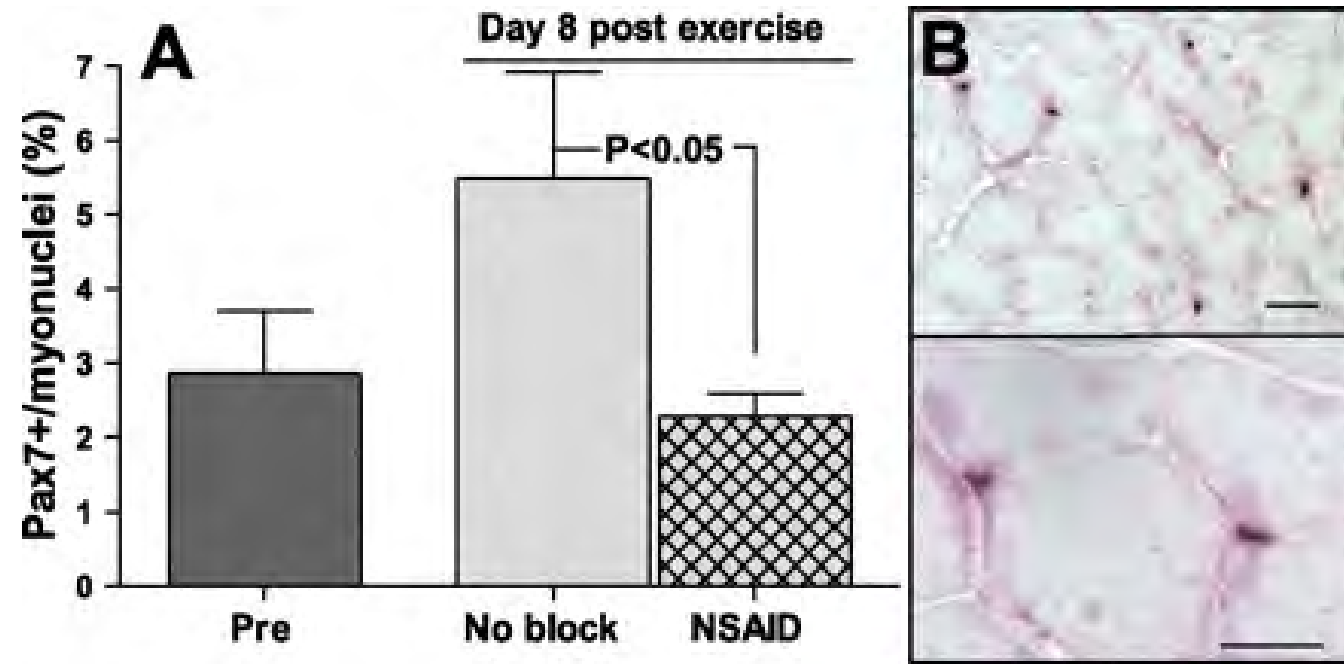
Do NSAIDs interfere with satellite cells?



NSAIDs may limit the satellite cell response after a 36km run.

Mackey et al., 2007

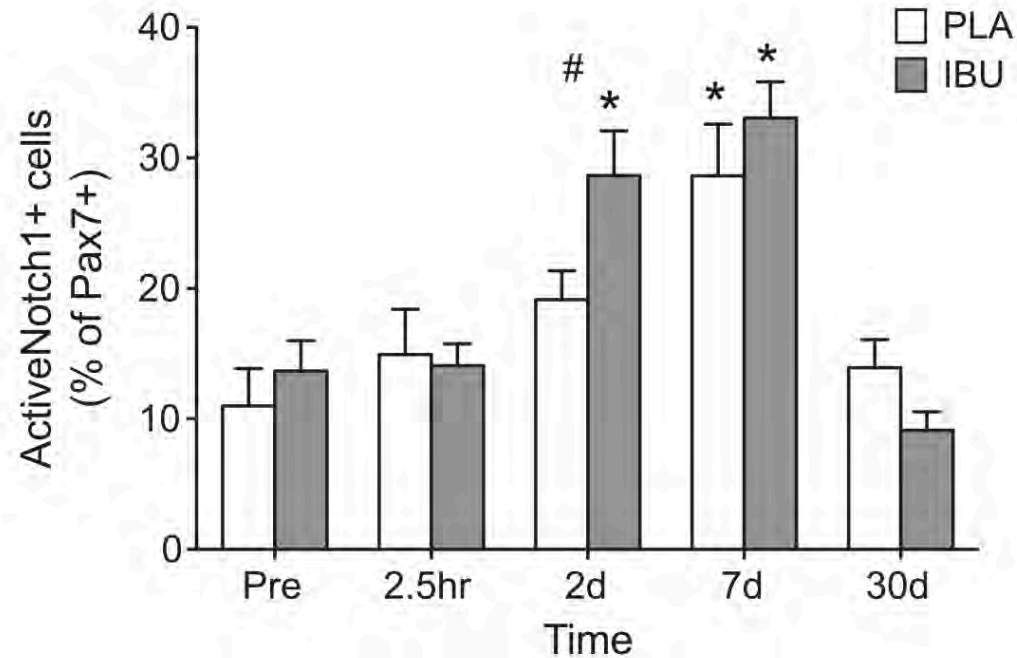
Do NSAIDs interfere with satellite cells?



Indomethacin infusion for 7.5 hours during the exercise day suppressed the exercise-induced increase in the number of satellite cells 8 days after exercise.

Mikkelsen et al., 2010

Do NSAIDs interfere with satellite cells?



1200 mg of ibuprofen enhances the activation of satellite cells via Notch signaling in the early phase of the regeneration of human skeletal muscle after eccentric contractions.

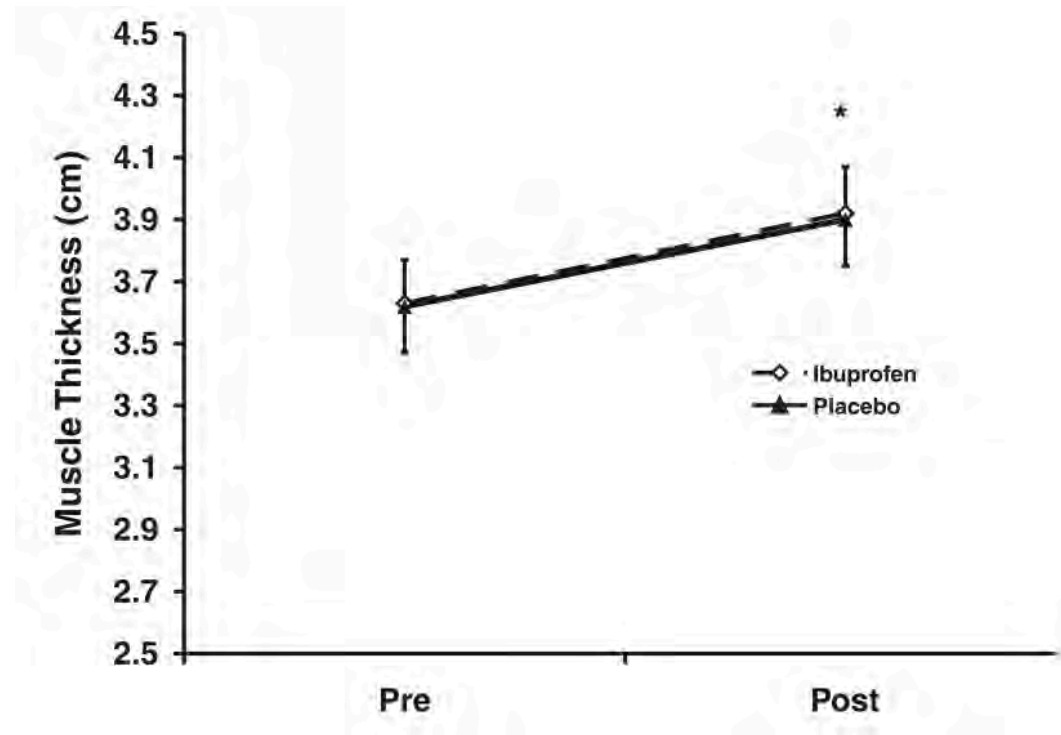
Mackey et al., 2016

Do NSAIDs interfere with satellite cells?

Current evidence is mixed.

Do NSAIDs interfere with muscle hypertrophy?

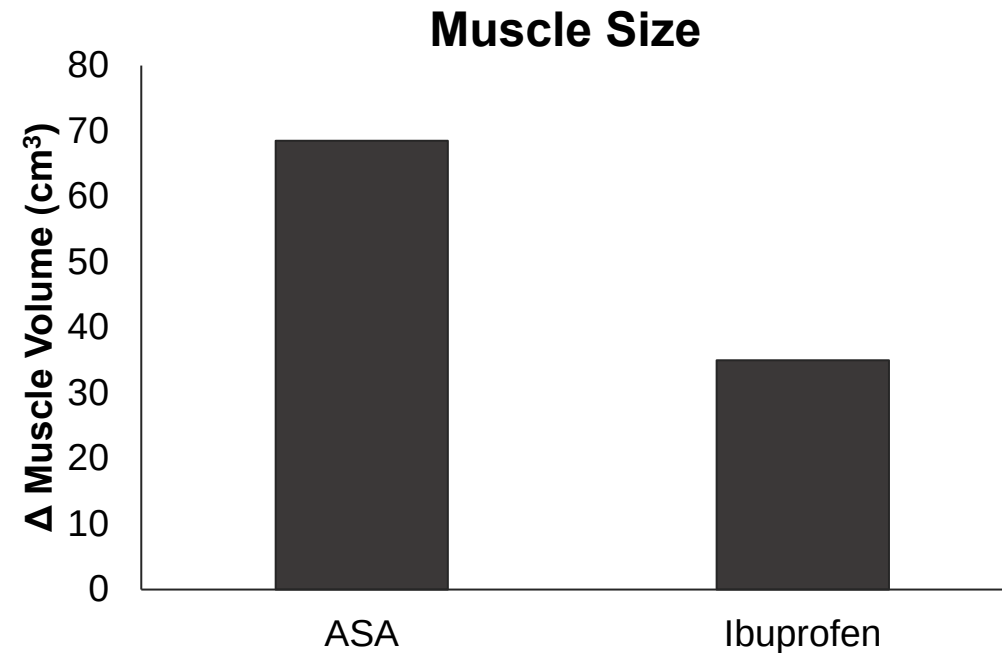
Do NSAIDs interfere with muscle hypertrophy?



400mg of ibuprofen does not attenuate strength and muscle hypertrophy adaptations to 6 weeks of resistance training.

Krentz et al., 2008

Do NSAIDs interfere with muscle hypertrophy?



1200 mg of ibuprofen attenuates strength and muscle hypertrophy adaptations to 8 weeks of resistance training.

¹Lilja et al., 2017

Do NSAIDs interfere with muscle hypertrophy?

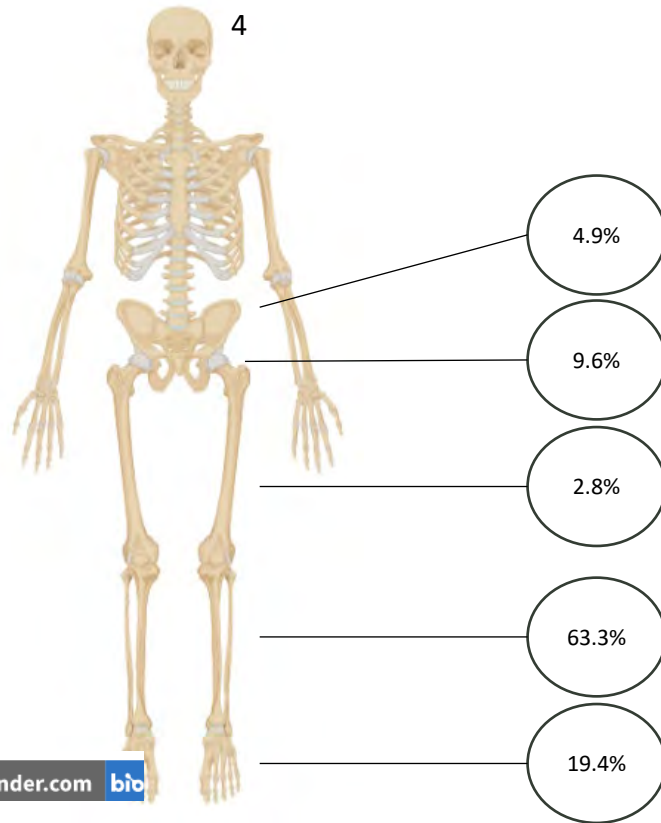
Current evidence is mixed. Adaptations are likely NSAID type and dose-dependent.

Muscle Summary

- NSAIDs do not enhance performance
- Current evidence suggests NSAIDs may not always reduce DOMS.
- Some NSAIDs reduce MPS, but not all.
- Some NSAIDs reduce muscle hypertrophy, but it is likely dose-dependent.

Do NSAIDs interfere with fracture healing and bone repair?

Do NSAIDs interfere with fracture healing and bone repair?



Stress fractures affect everyone from athletes to Soldiers¹

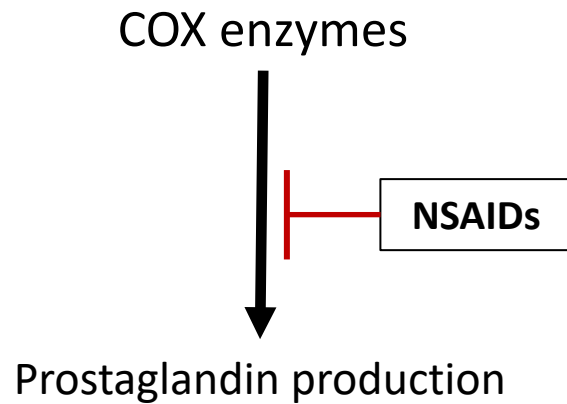
Most common in lower extremities²

Most common during initial military training³

- 21% of women
- 5% of men

¹Beck et al., 2000; ²Jones et al., 1993; ³Jones et al., 2002; ⁴Hughes et al., 2018

Do NSAIDs interfere with fracture healing and bone repair?



Prostaglandins play an important role in bone adaptation to mechanical loading fatigue resistance properties of bone.¹

¹Warden et al., 2008

Do NSAIDs interfere with fracture healing and bone repair?

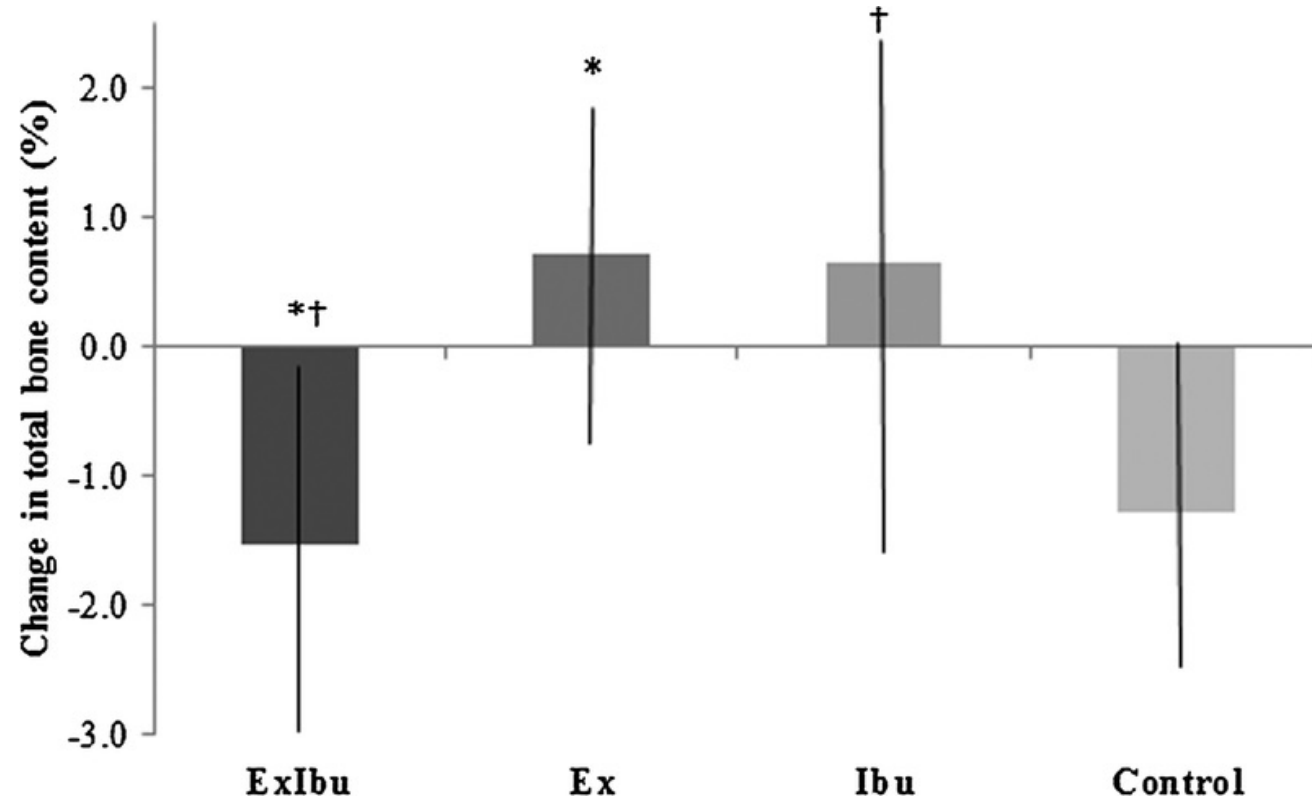
Mechanical loading and NSAID administration in animals have resulted in attenuated or complete inhibition of the osteogenic response to loading.

Common themes in these studies include:

- NSAIDs inhibit adaptive bone formation
- NSAID administration prior to loading yields greater inhibition of adaptive bone formation
- COX-2 specific inhibitors yield the greatest suppression of formation
- NSAIDs appear to affect bone formation in a dose-dependent fashion

¹Carbone et al., 2003;

Do NSAIDs interfere with fracture healing and bone repair?



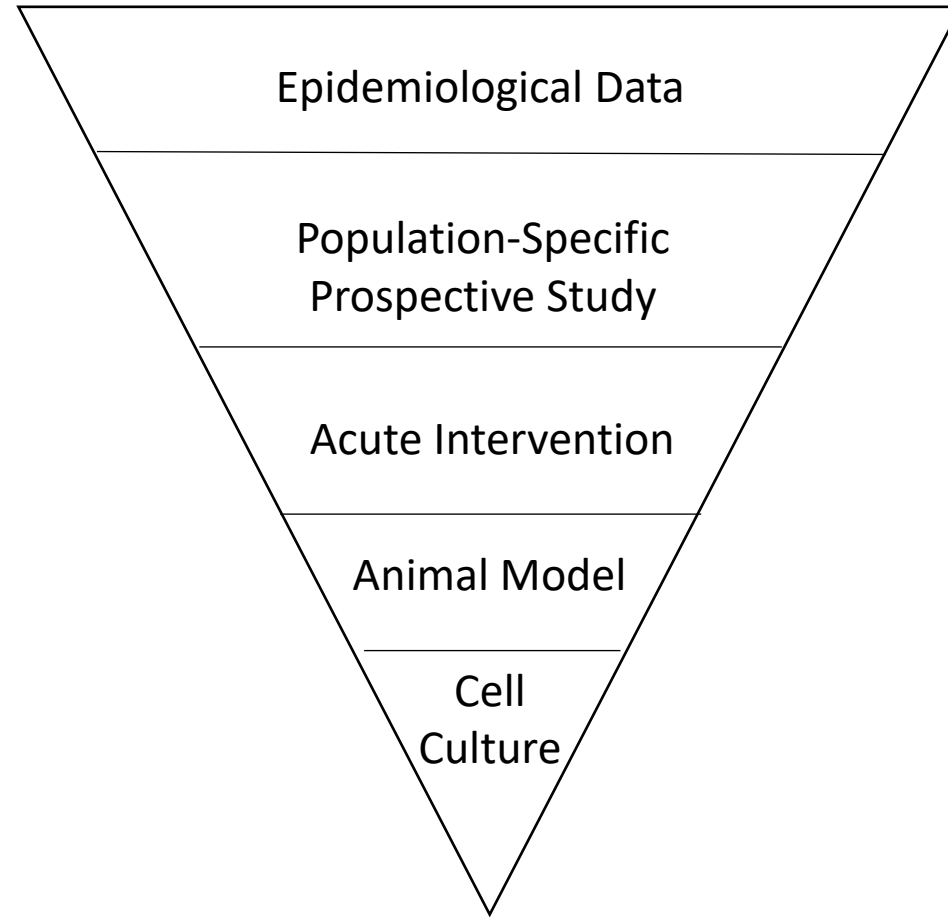
¹Duff et al., 2016

Do NSAIDs interfere with fracture healing and bone repair?

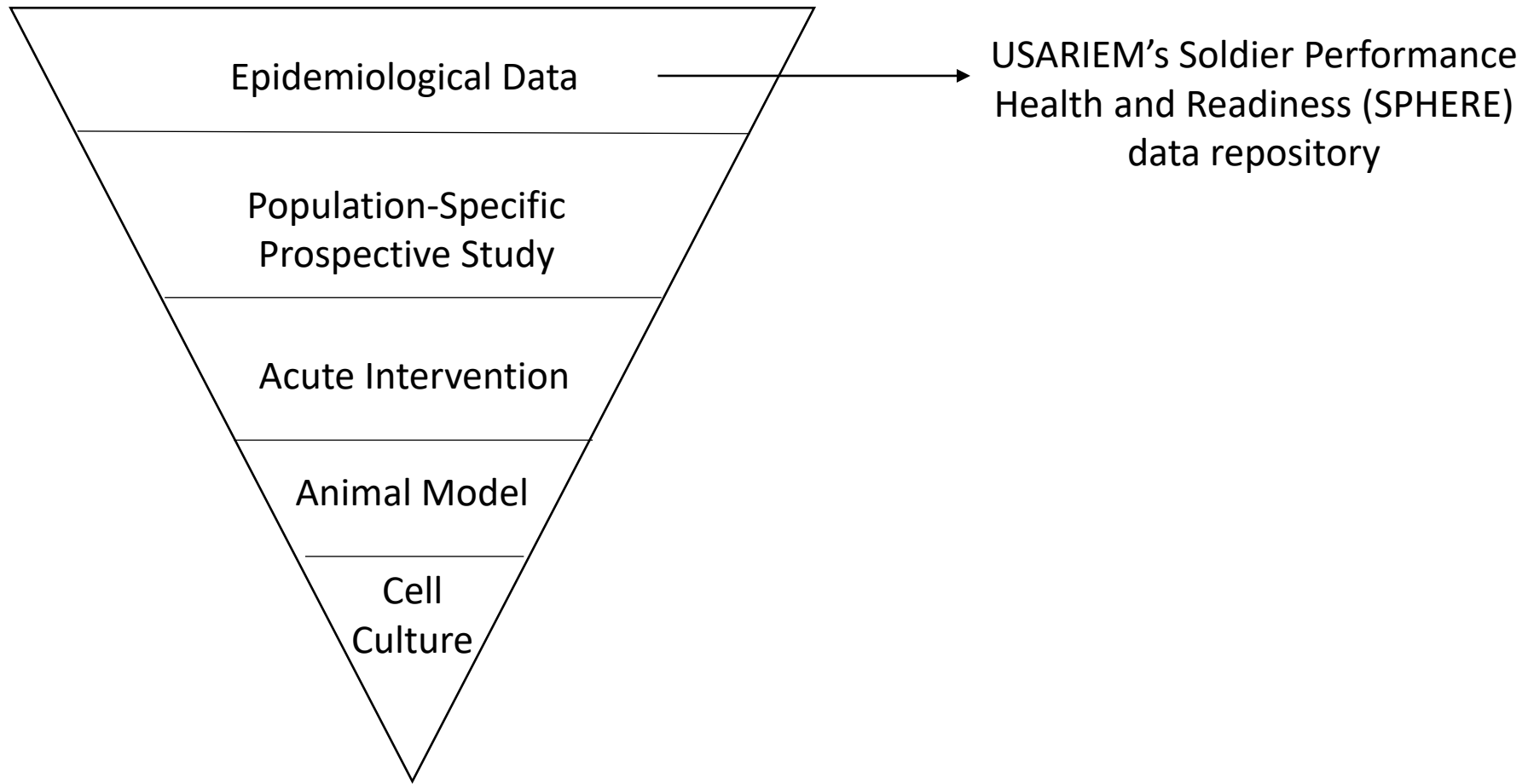
Historical and recent studies reveal NSAIDs as an emerging risk factor for stress fractures.

¹Staab et al., 2021

Our current project on NSAIDs and Exercise

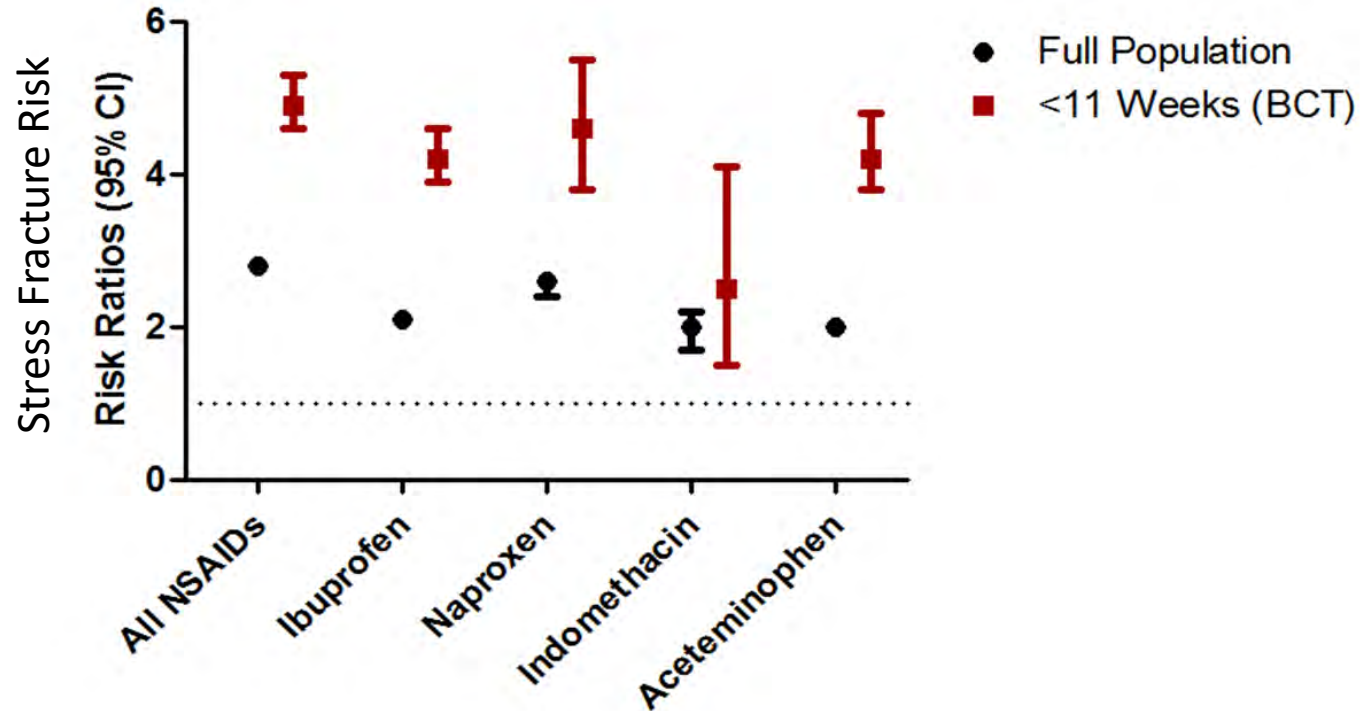


Full Spectrum Approach



Epidemiological Findings

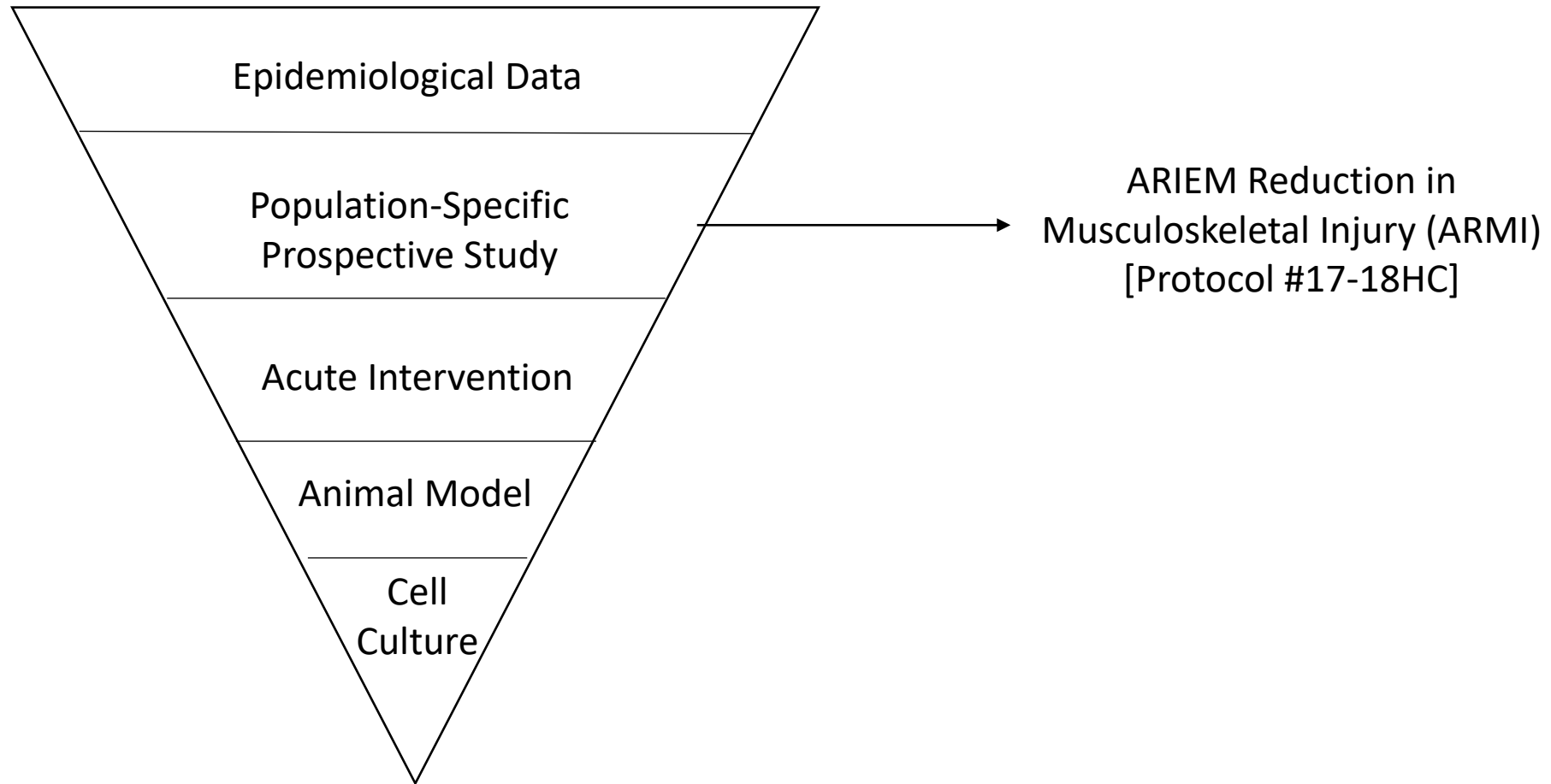
Stress Fracture Risk



Sex-adjusted Incident rate ratios for stress fracture by NSAID prescriptions in overall Army population and during BCT period.

Hughes et al., 2019

Full Spectrum Approach

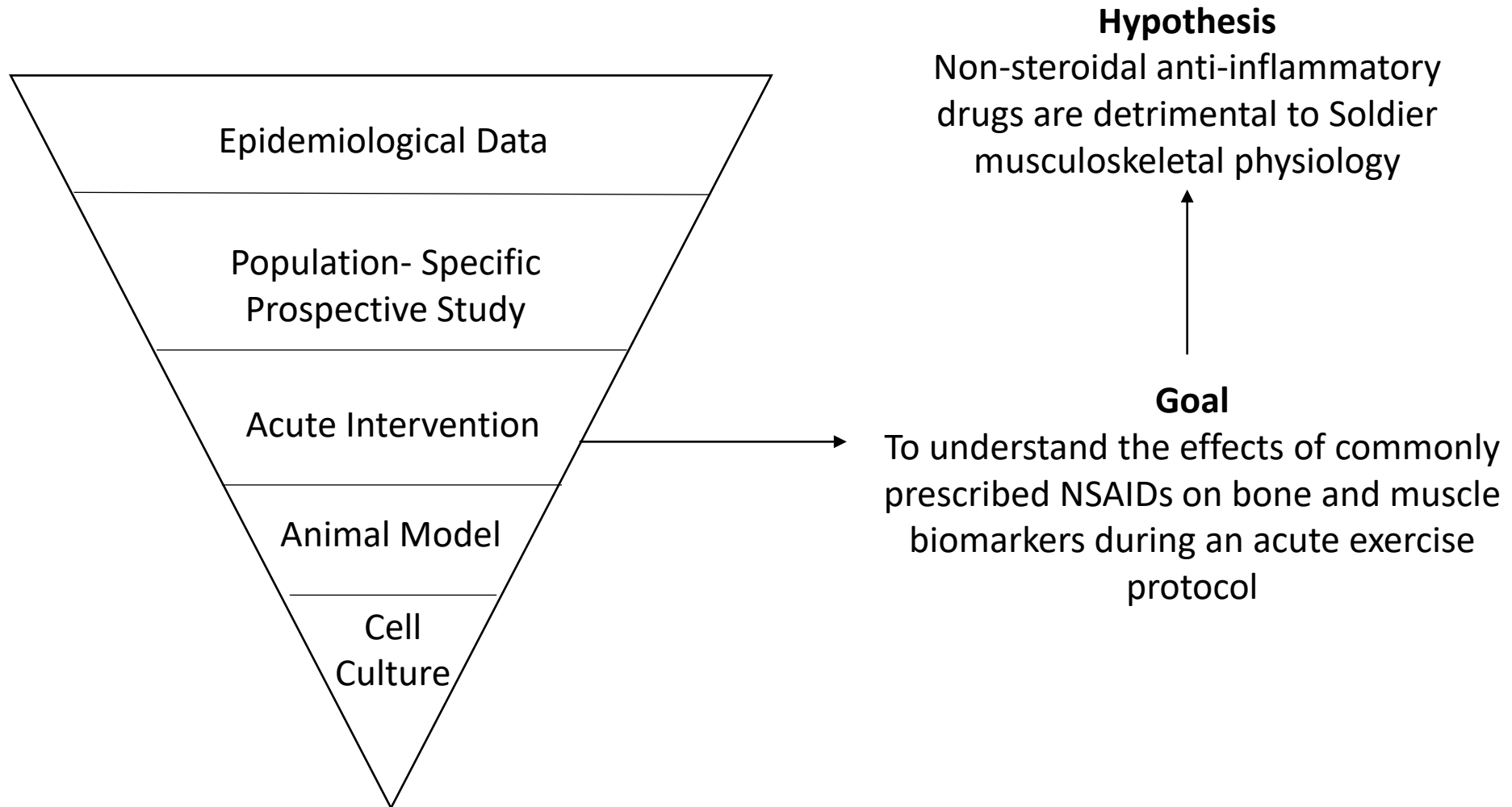


ARIEM Reduction in Musculoskeletal Injury



The ARMI Study aims to identify which factors are most predictive of injury risk in 4000 U.S. Army trainees undergoing BCT.

Full Spectrum Approach



Acute Exercise Intervention Study Design

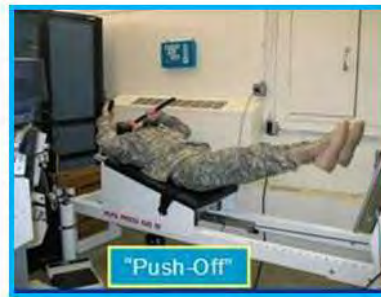
Crossover Design

Treatments

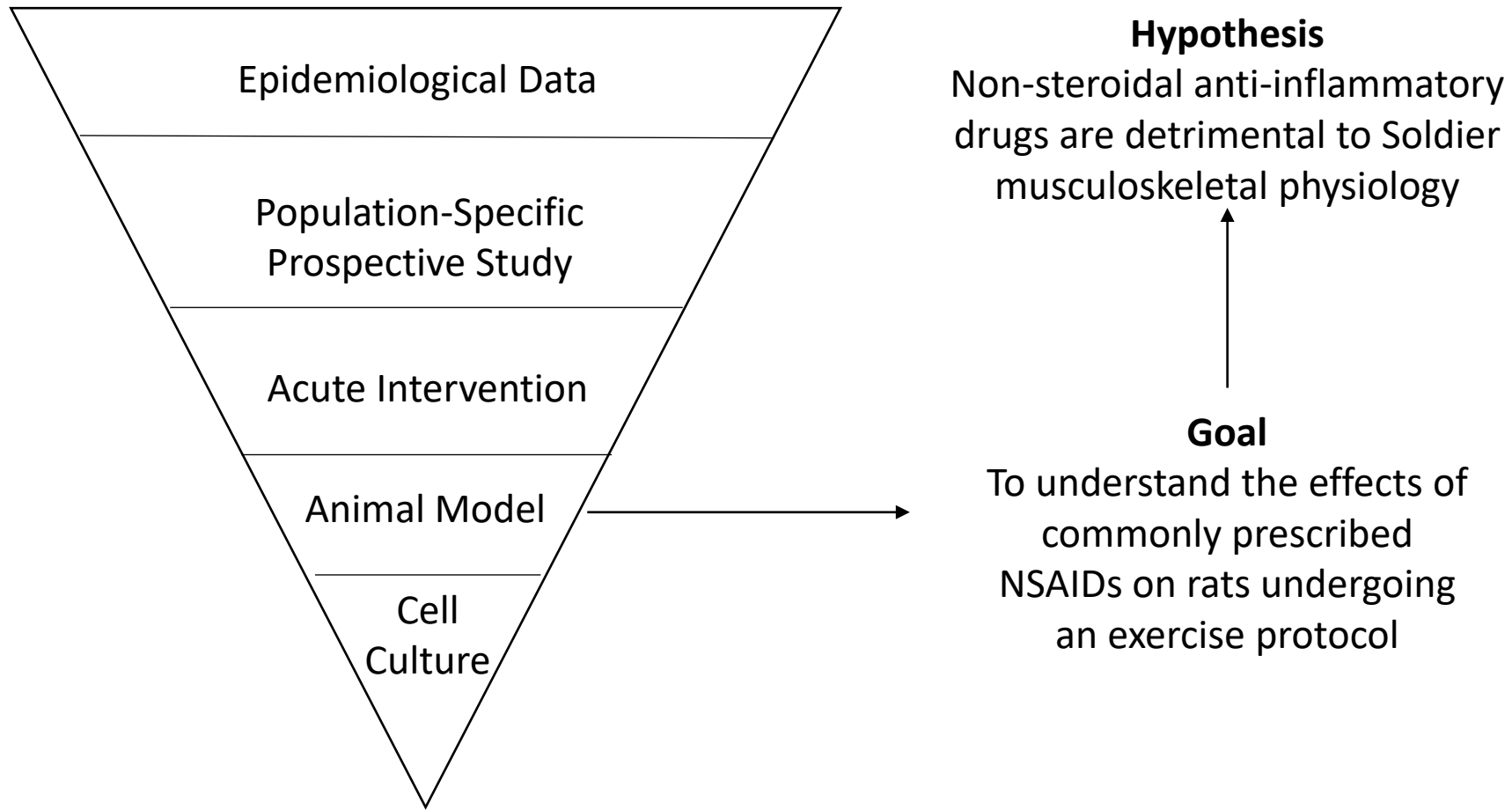
- Placebo
- Ibuprofen
- Celecoxib
- Flurbiprofen

Plyometric Exercise Protocol

10 sets of 10 repetitions of maximal effort jumps at 40% of 1-RM with 2-minute rest between each set.



Full Spectrum Approach



Rodent Model Study Design

Young rats exercised 5 days/week for 6 weeks

- 30 minutes per day
- 15 meters per minute
- 5% incline
- NSAIDs administered in drinking water daily

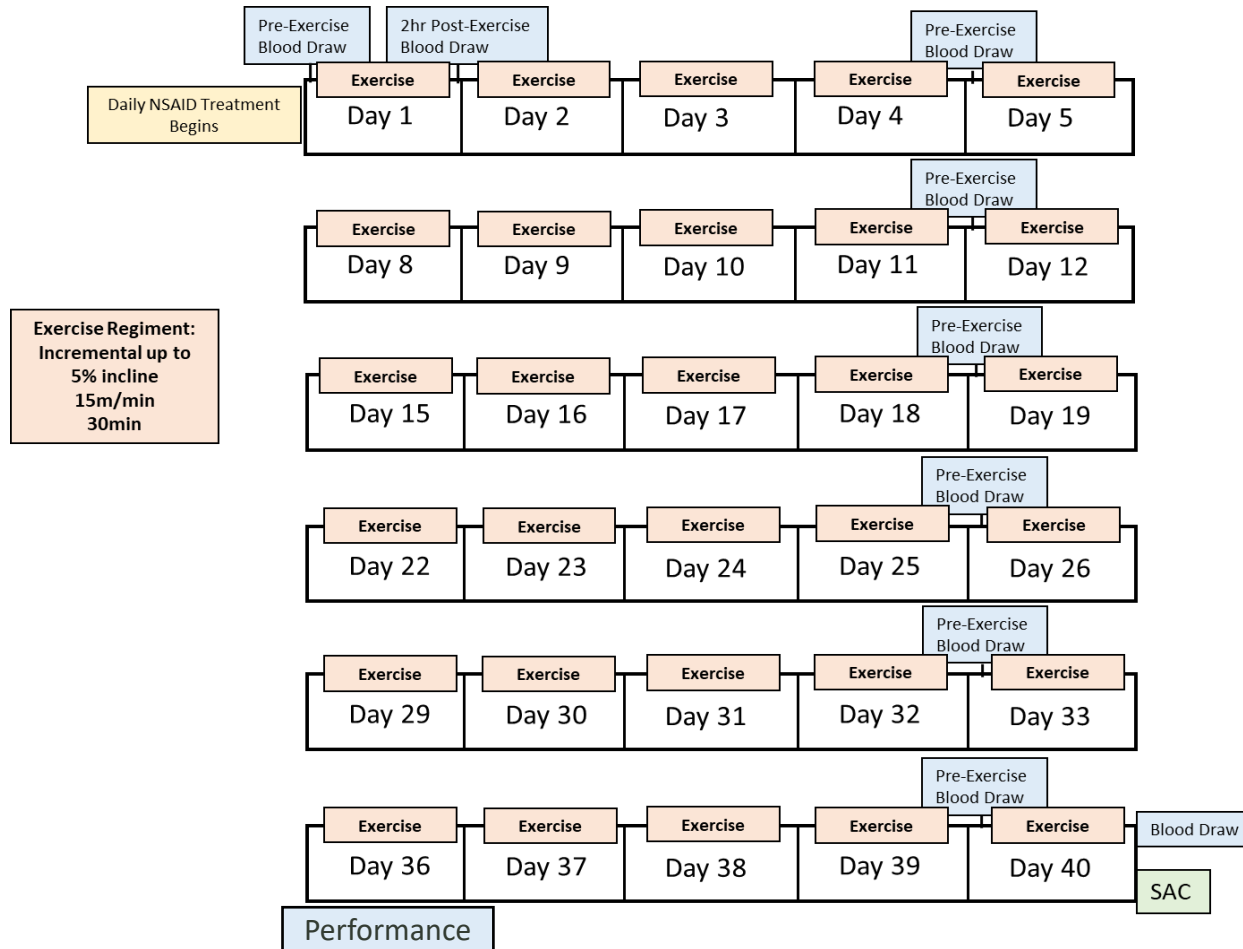
	Exercise	No Exercise
Placebo	10	10
Naproxen	10	10
Acetaminophen	10	10
Ibuprofen	10	10
Flurbiprofen	10	10
Celecoxib	10	10
N = 120		

Human Equivalent Dose

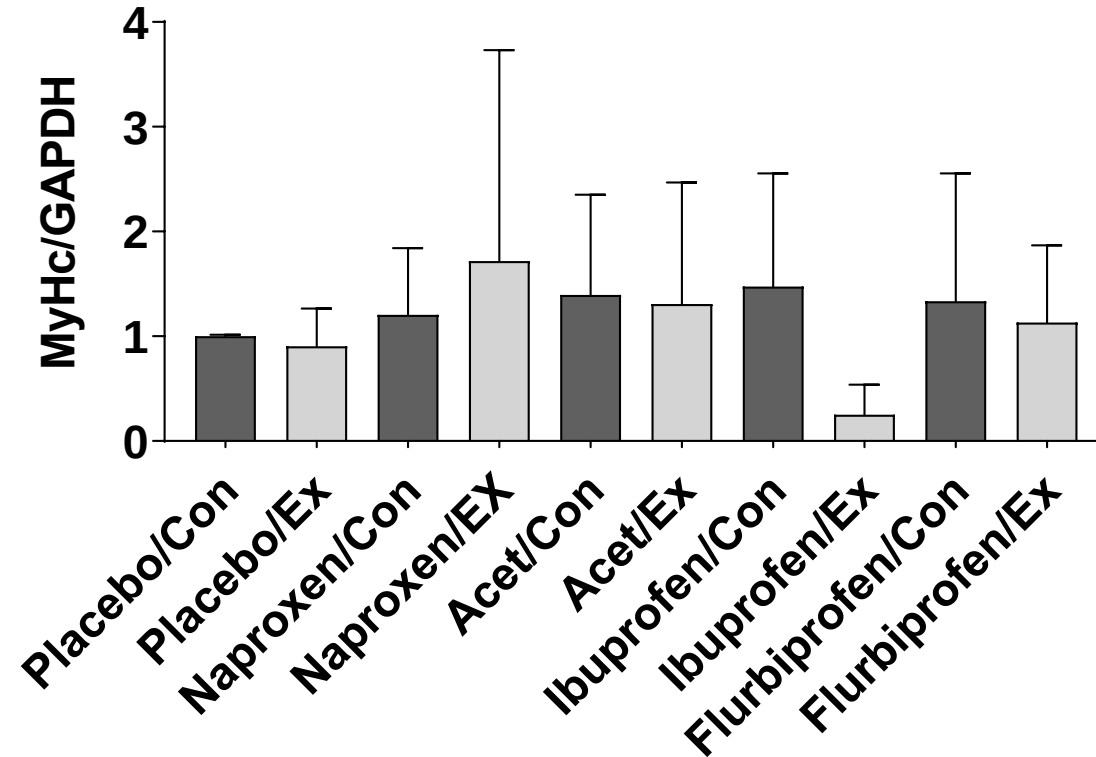
Based on body surface area

$$\text{HED (mg/kg)} = \text{Animal dose (mg/kg)} \times \text{Animal Km} / \text{Human Km}$$

Animal Model Protocol

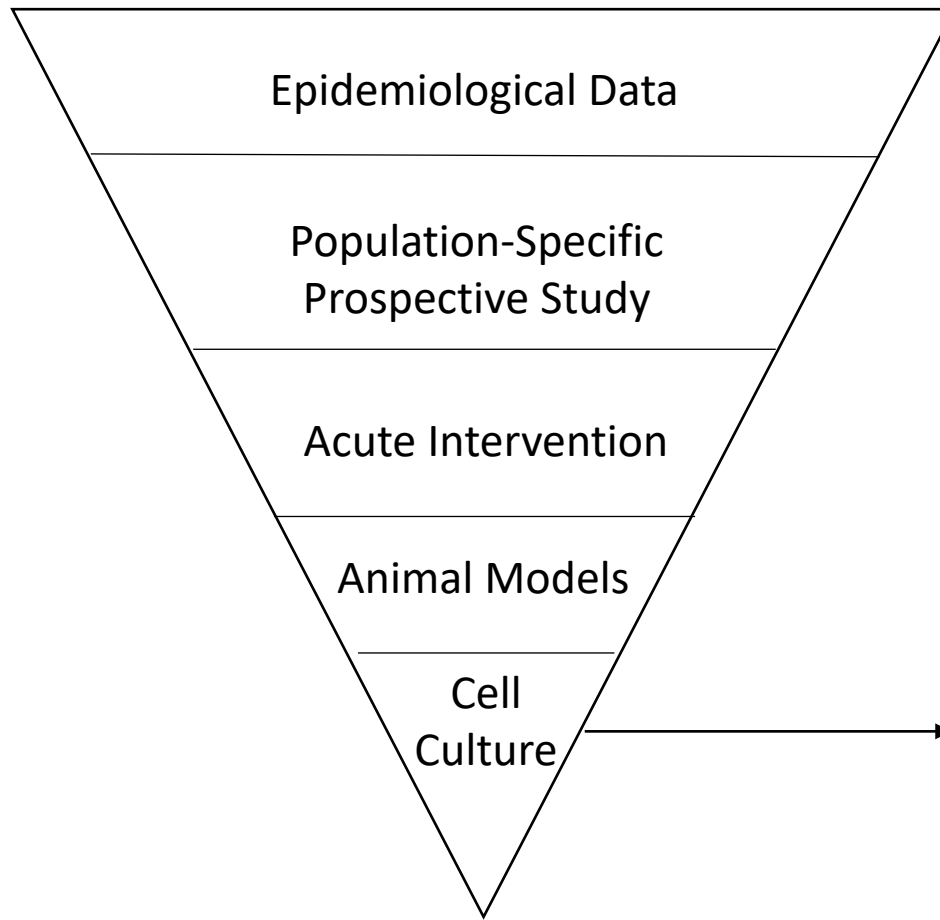


Preliminary data



N = 6 of 10

Full Spectrum Approach



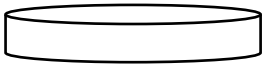
Hypothesis
Non-steroidal anti-inflammatory drugs are detrimental to Soldier musculoskeletal physiology

↑

Goal
To understand the effects of commonly prescribed NSAIDs on primary human myoblasts

in vitro Experimental Design

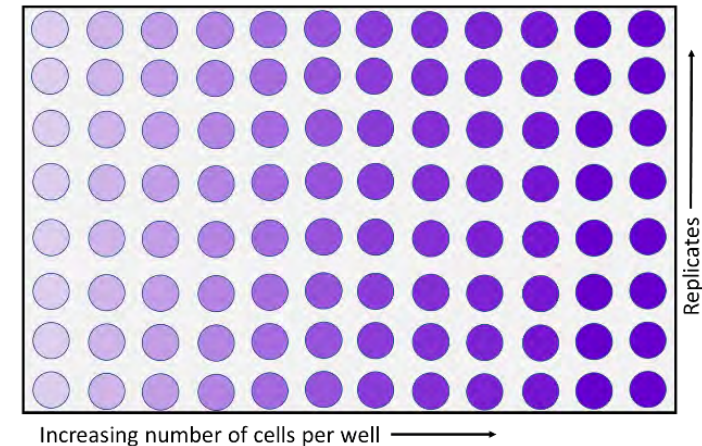
Myoblasts



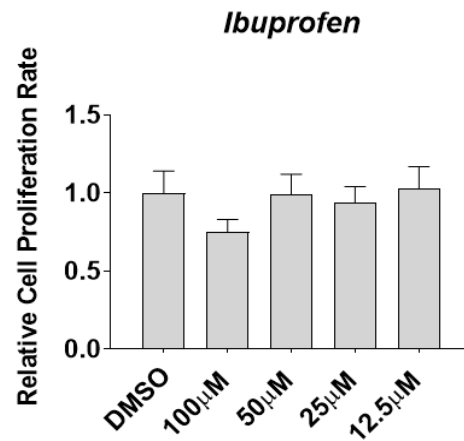
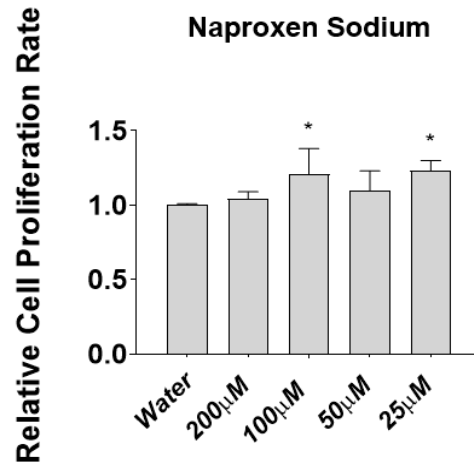
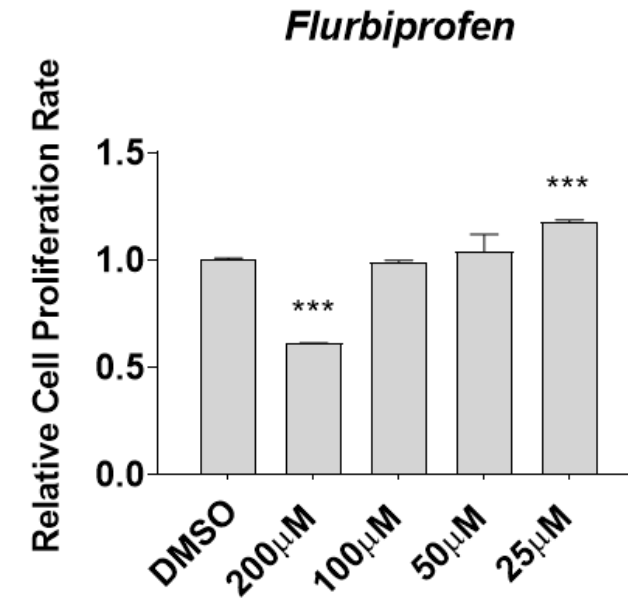
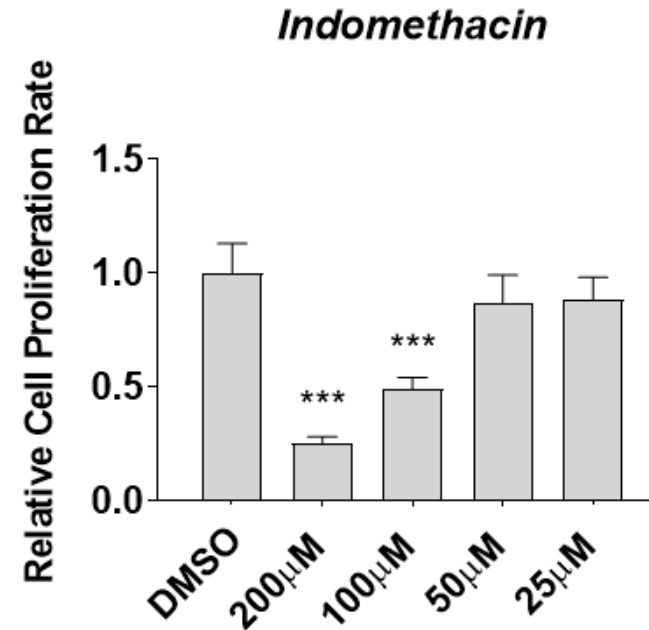
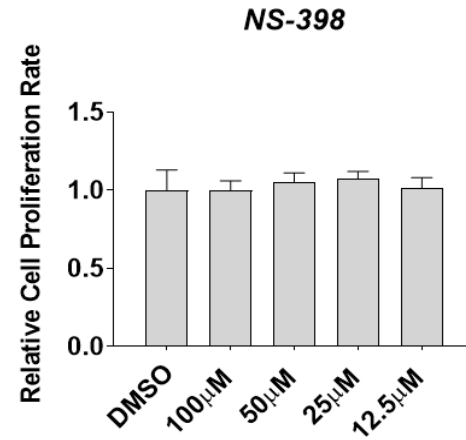
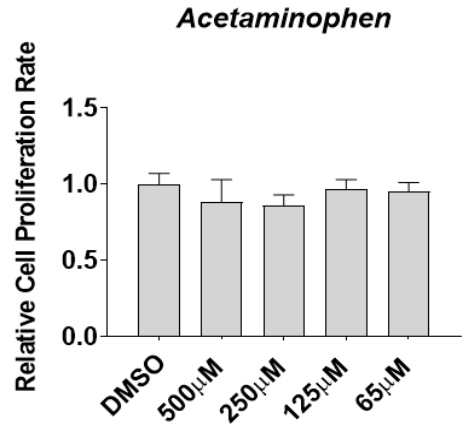
→
48-hour NSAID treatment

Outcomes

MTT Assay – proliferation

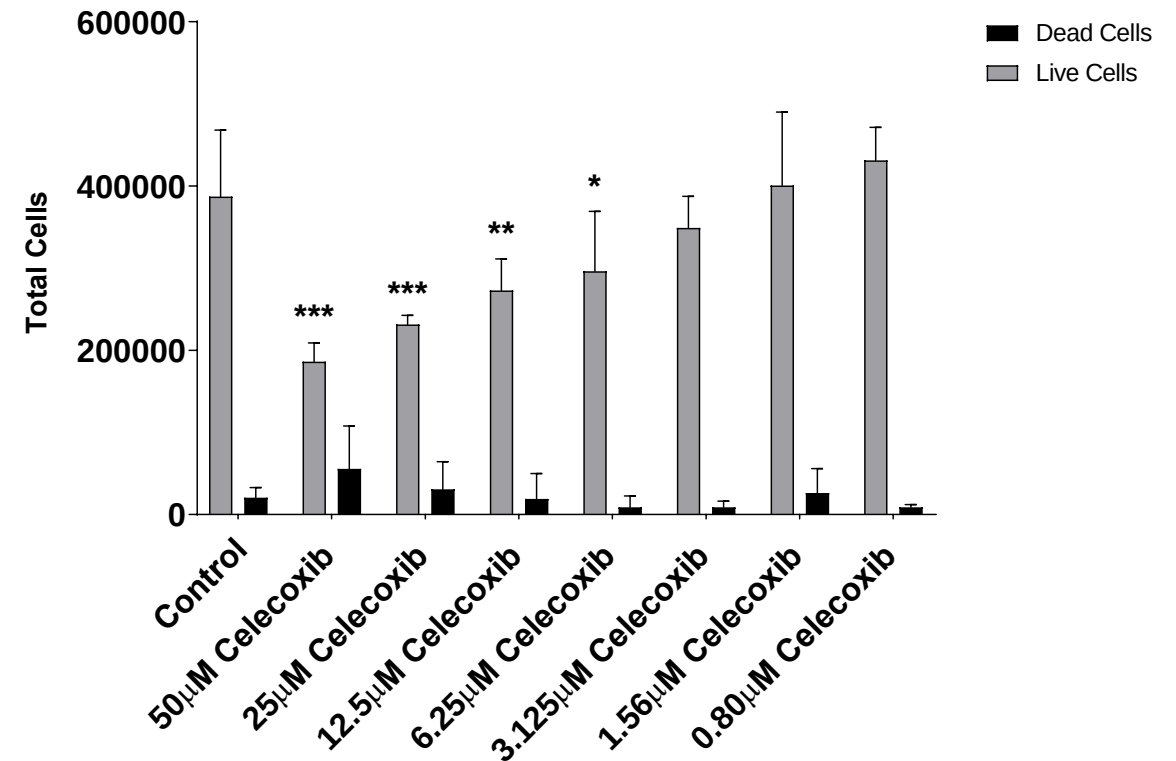
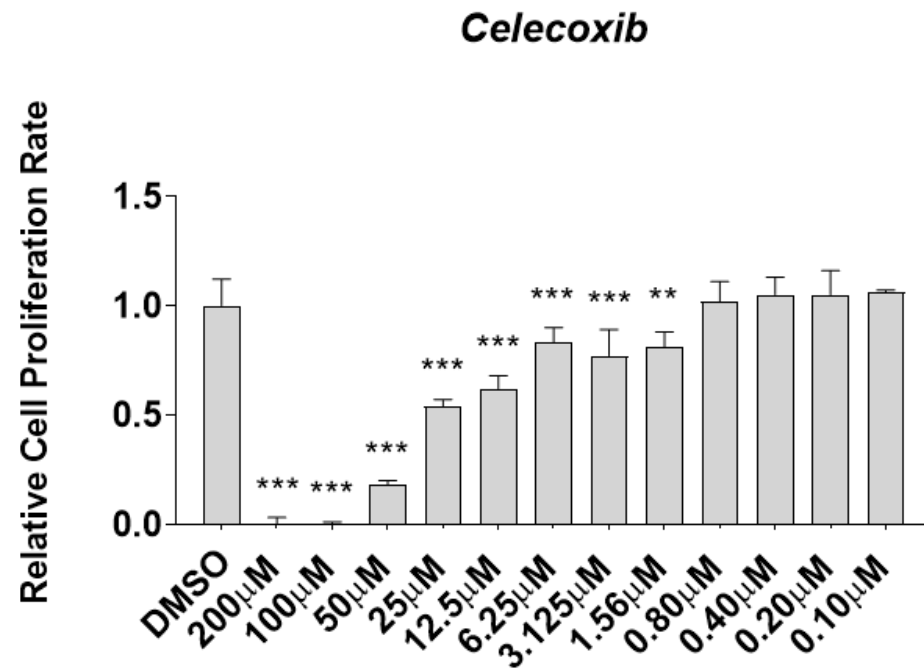


Primary human myoblast proliferation in response to NSAID treatment - Results 1



Acetaminophen, NS-398, Naproxen, and Ibuprofen do not negatively influence myoblast proliferation.

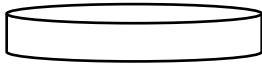
Primary human myoblast proliferation in response to NSAID treatment - Results 2



Celecoxib significantly reduces cell viability in a dose-dependent fashion.

in vitro Experimental Design

Myoblasts



Differentiation



72 hour NSAID treatment

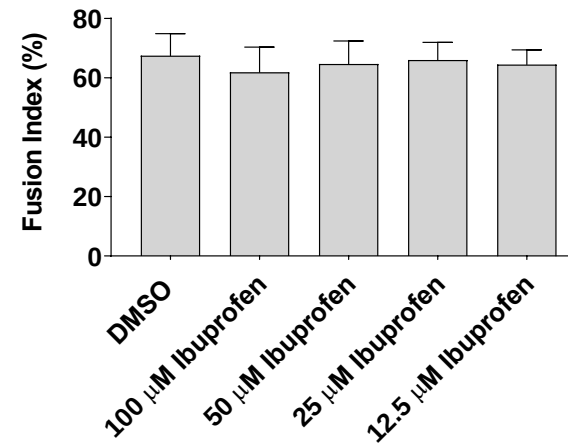
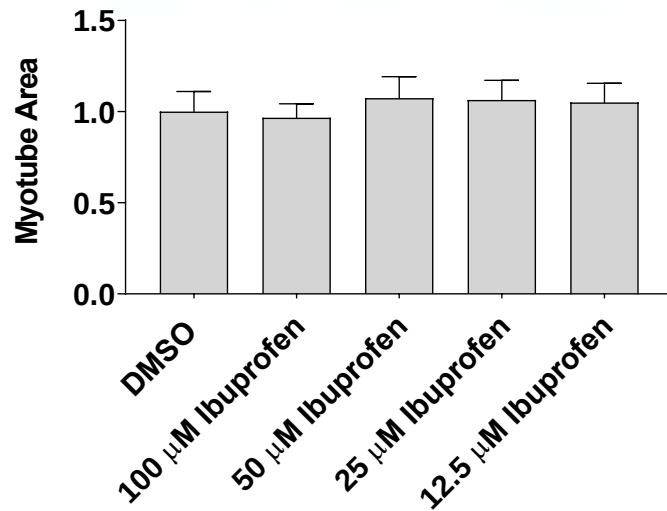
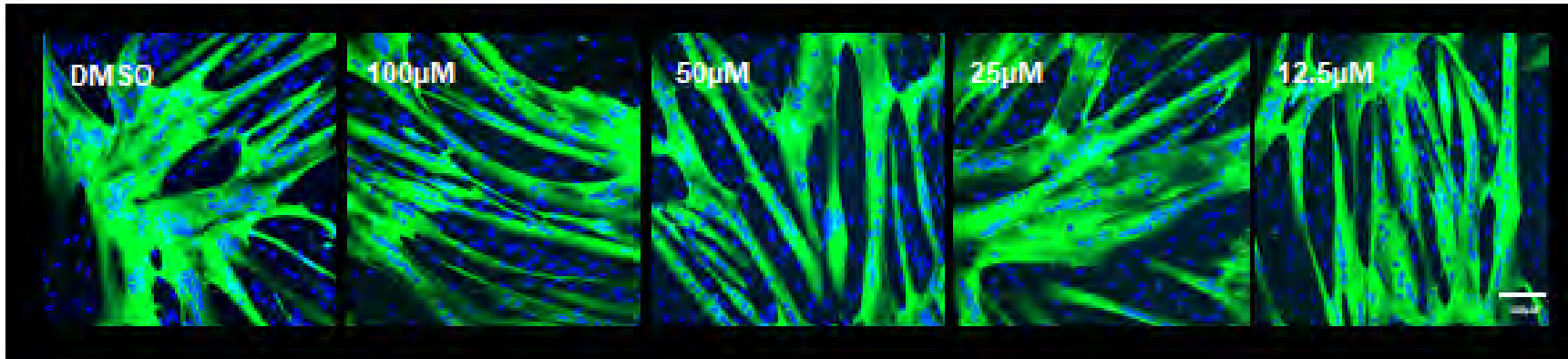
Outcomes

Myotube Fusion

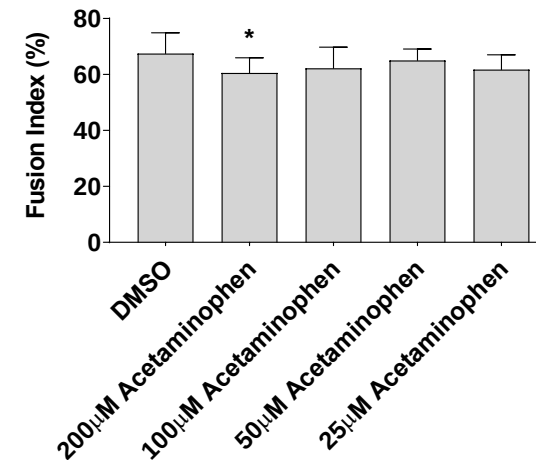
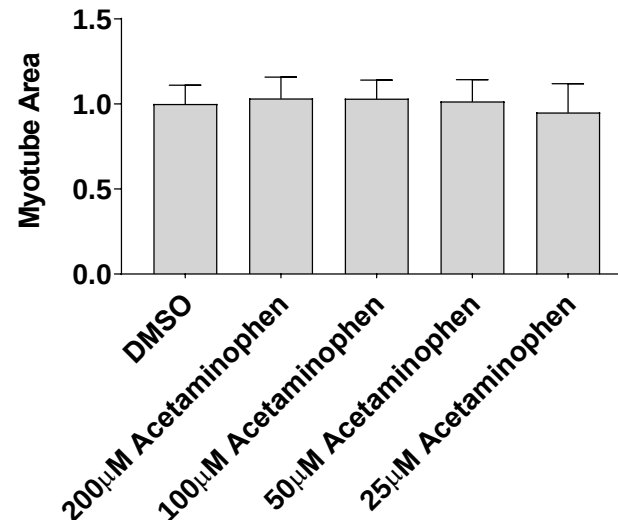
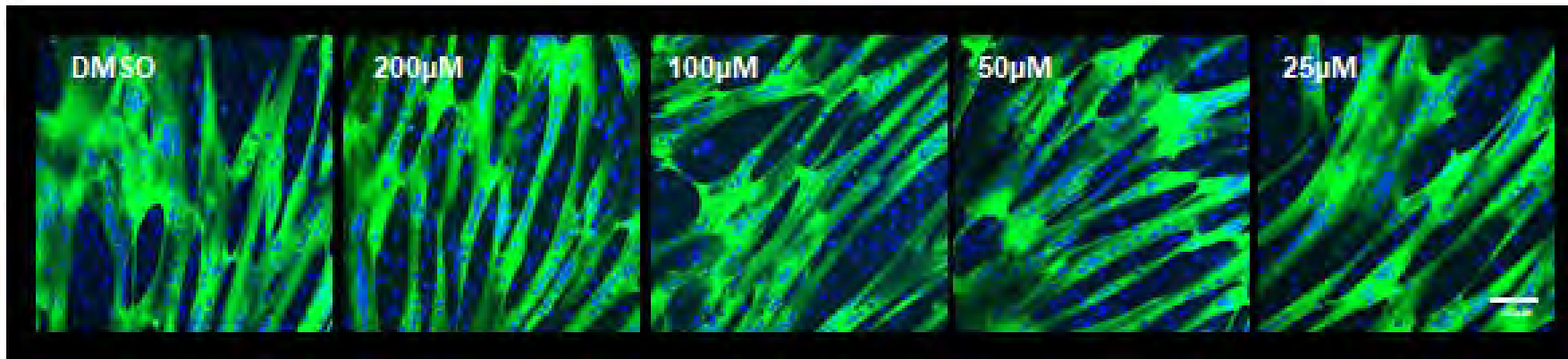
Myotube Area

Western Blots/ PCR

Effects of Ibuprofen on myotube formation in differentiating skeletal muscle myoblasts - Results 3

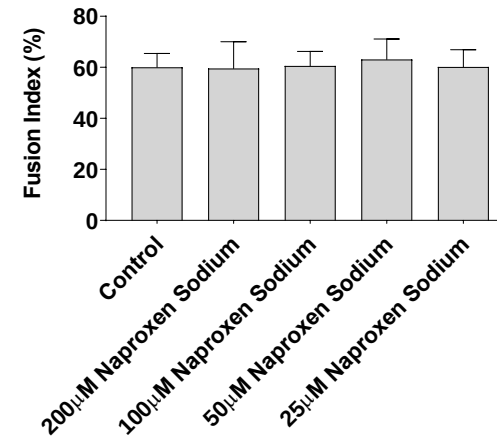
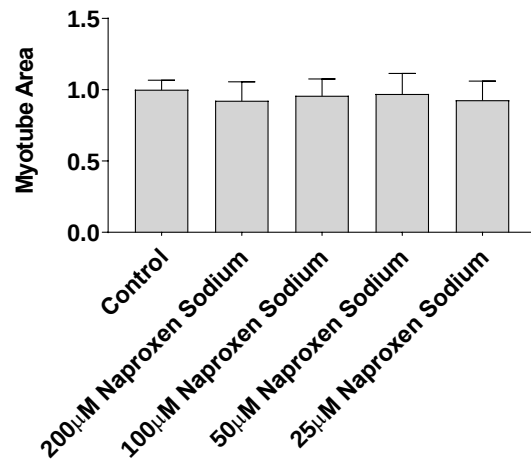
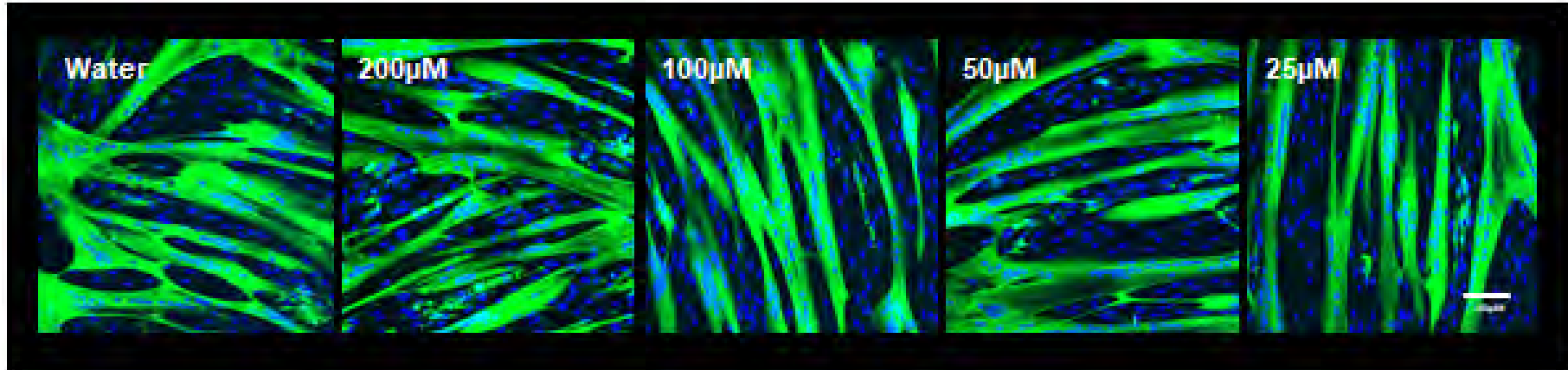


Effects of Acetaminophen on myotube formation in differentiating skeletal muscle myoblasts – Results 4



Acetaminophen has no significant effect on myotube differentiation

Effects of Naproxen on myotube formation in differentiating skeletal muscle myoblasts - Results 5

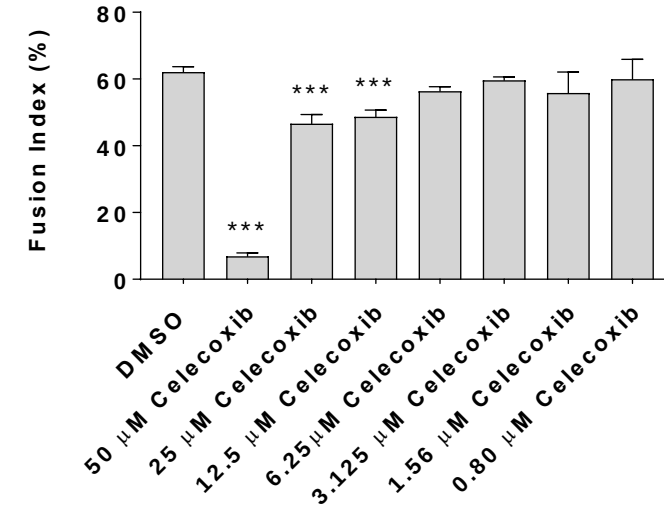
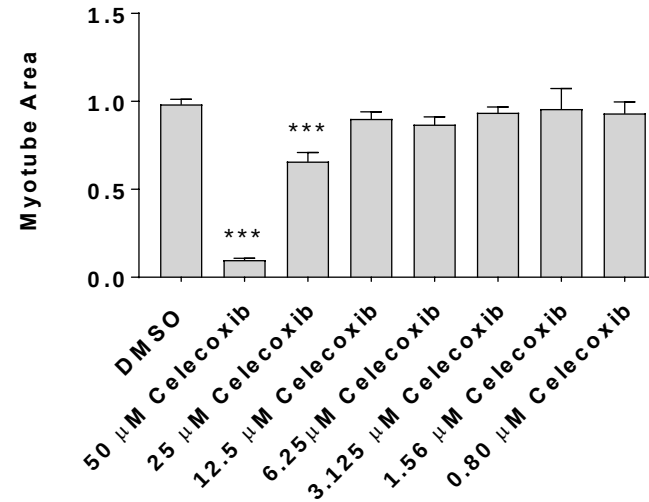
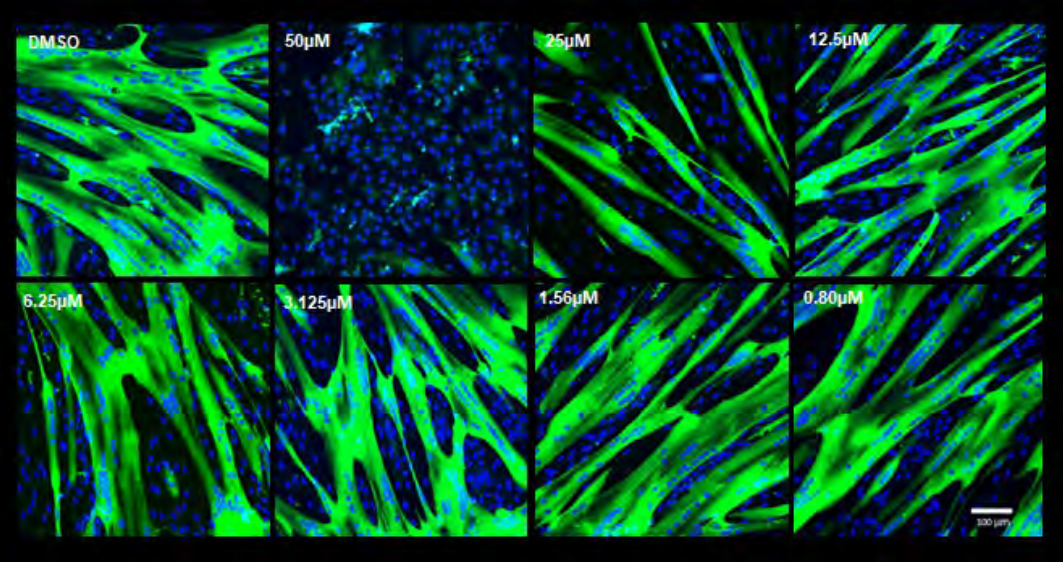


Naproxen has no significant effect on myotube differentiation

Brandon Roberts, PhD, CSCS* D, TSAC-F

The Effect of NSAIDs on Exercise Adaptations

Effects of Celecoxib on myotube formation in differentiating skeletal muscle myoblasts - Results 6



Celecoxib inhibits myogenic differentiation in a dose-dependent fashion.

in vitro muscle conclusions

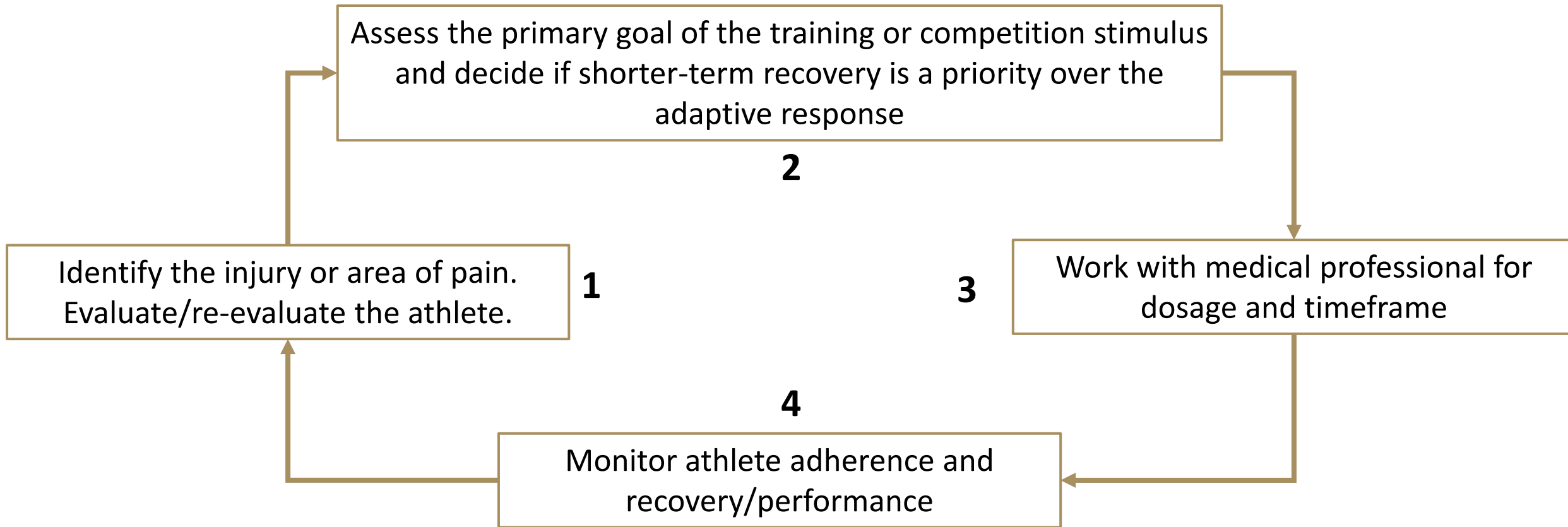
- Indomethacin and Celecoxib significantly reduced proliferation in cultured myoblasts.
- Celecoxib inhibits myogenic differentiation in a dose-dependent fashion.
- Celecoxib inhibits myotube fusion and reduces MYH isoform levels at 50 μ M Celecoxib.
- Celecoxib at high dosages appears to be toxic to muscle cells.

**Given the mixed results in different models
and NSAIDs, how do we use this
information?**

Practical Application

Athletes, coaches, and support staff should do a risk-benefit analysis before using analgesic and anti-inflammatory drugs regularly in association with training or competition.

Risk Assessment



Overall Summary

NSAIDs are likely detrimental to musculoskeletal health.

Questions?