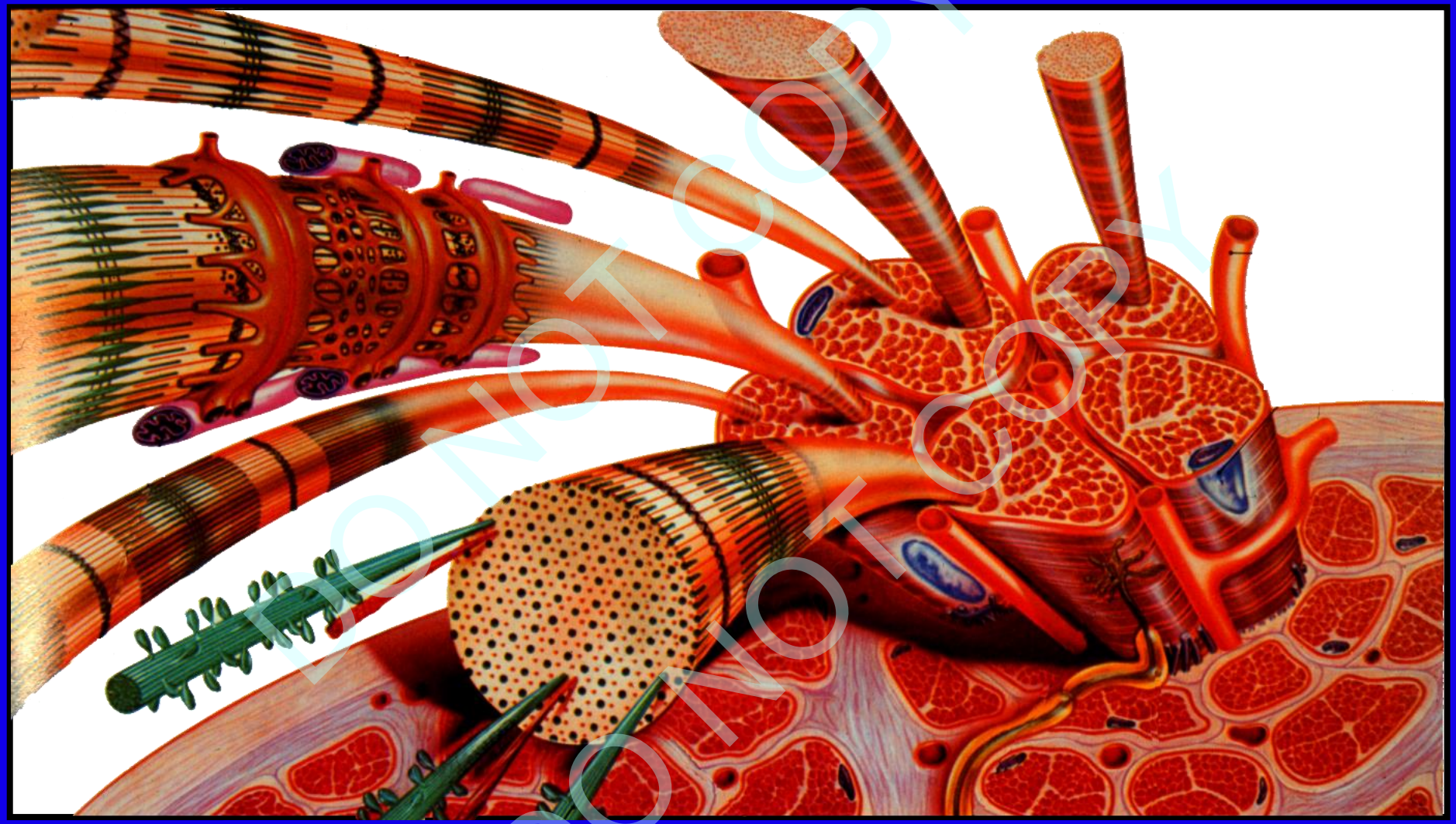
AbilityLab®

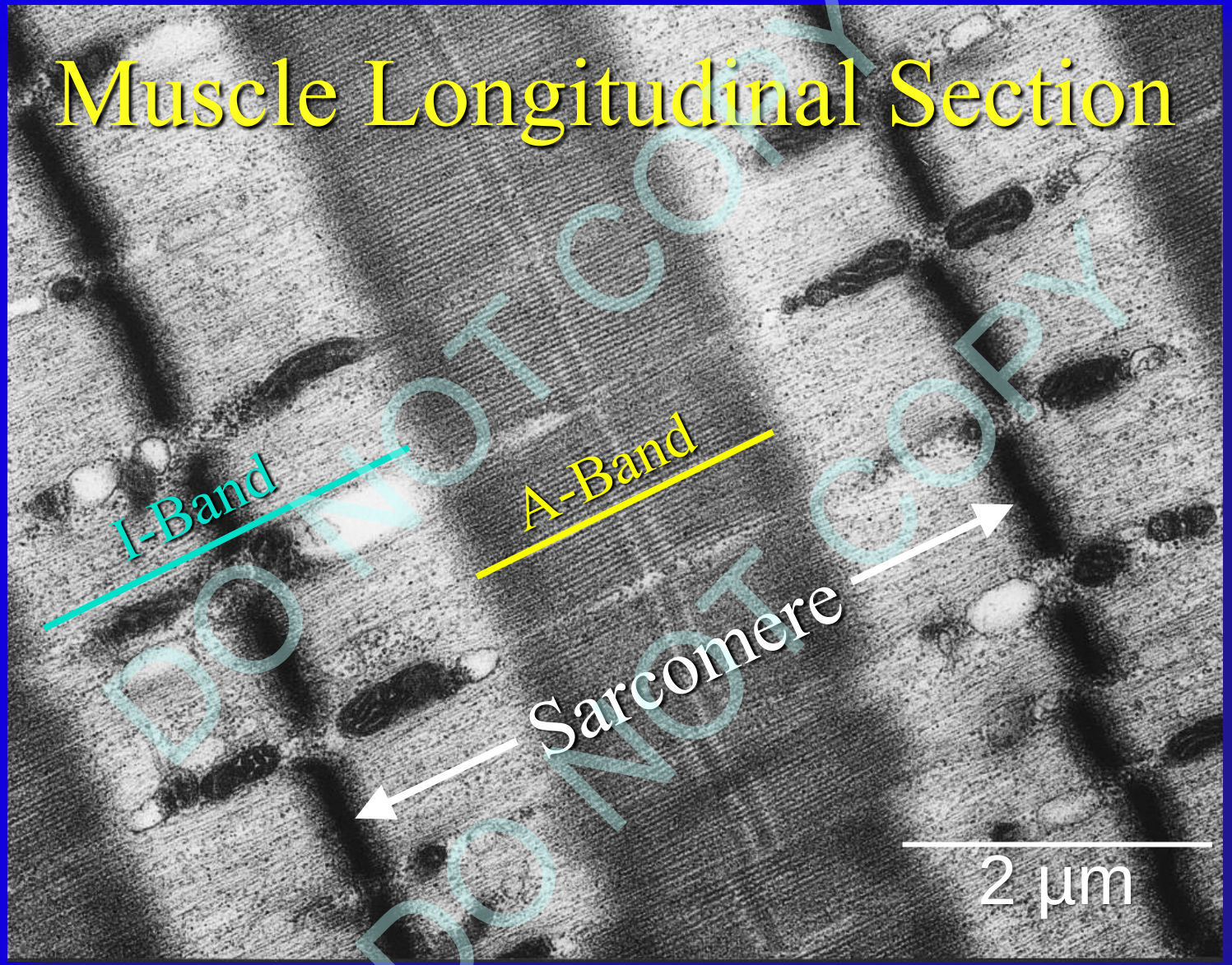
The future of RIC Rehabilitation Institute of Chicago

Mechanisms of Human Muscle Contractures

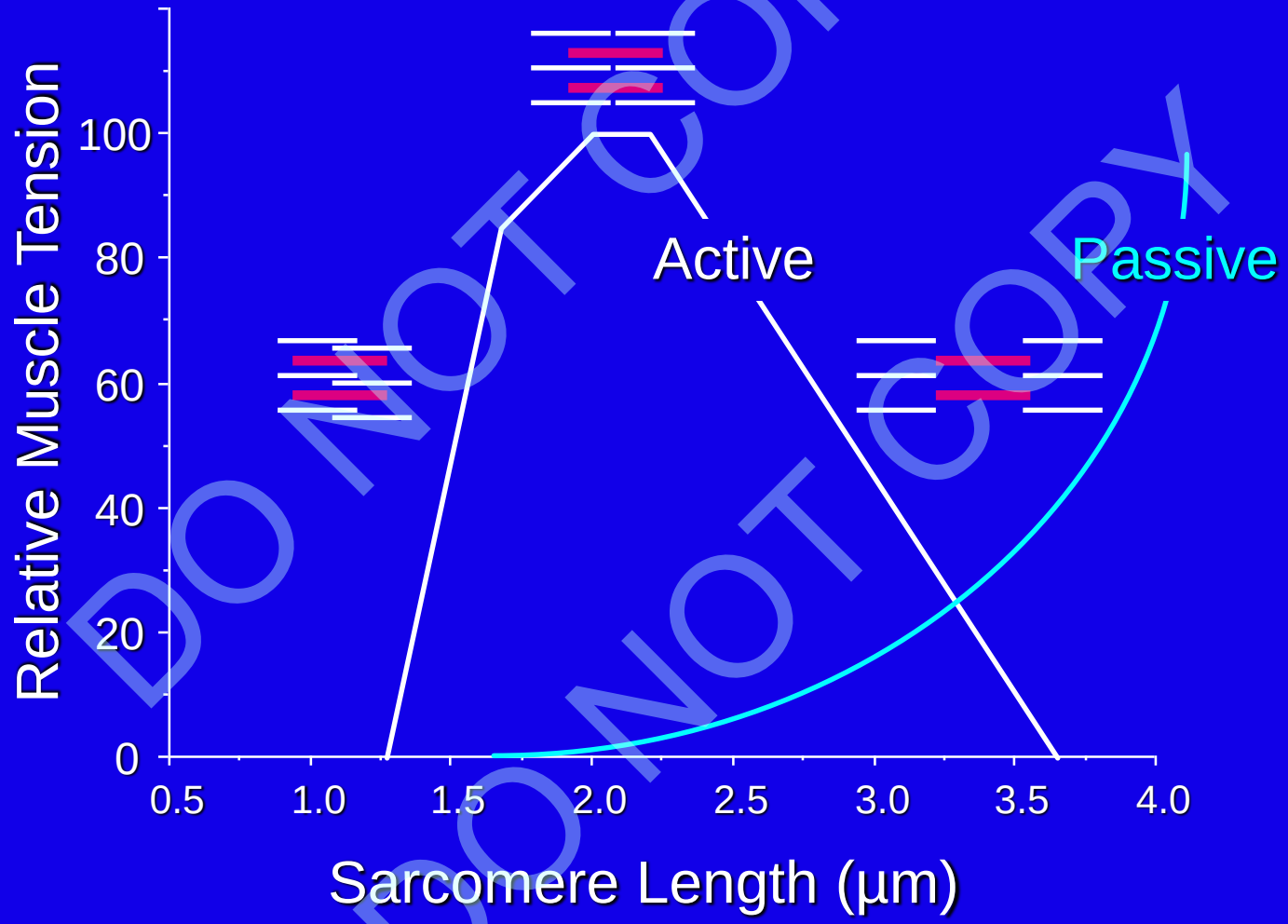
Richard L. Lieber, Chief Scientific Officer, Shirley Ryan AbilityLab
Professor, Northwestern University



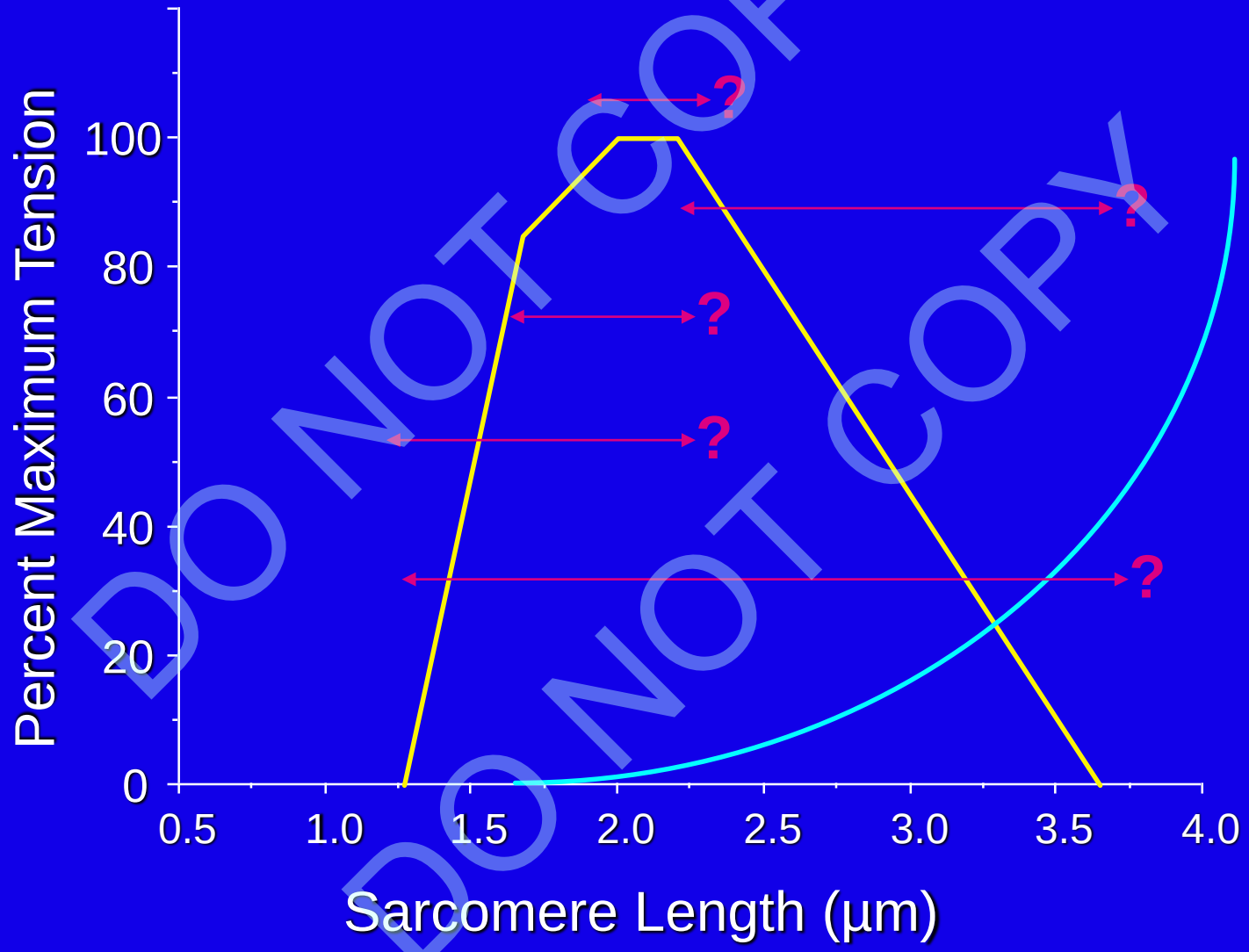
"Skeletal muscle is a beautiful composite tissue"


Muscle Longitudinal Section
I-Band
A-Band
Sarcomere
2 µm
DO NOT COPY
DO NOT COPY

Sarcomere Length Predicts Muscle Force



Physiological Operating Range?



Laser Myometer

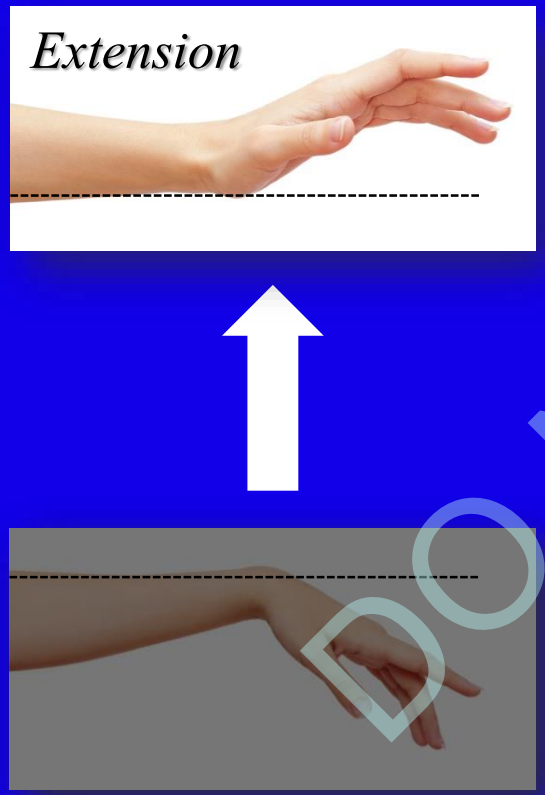
Courtesy Myogenesis, Inc.

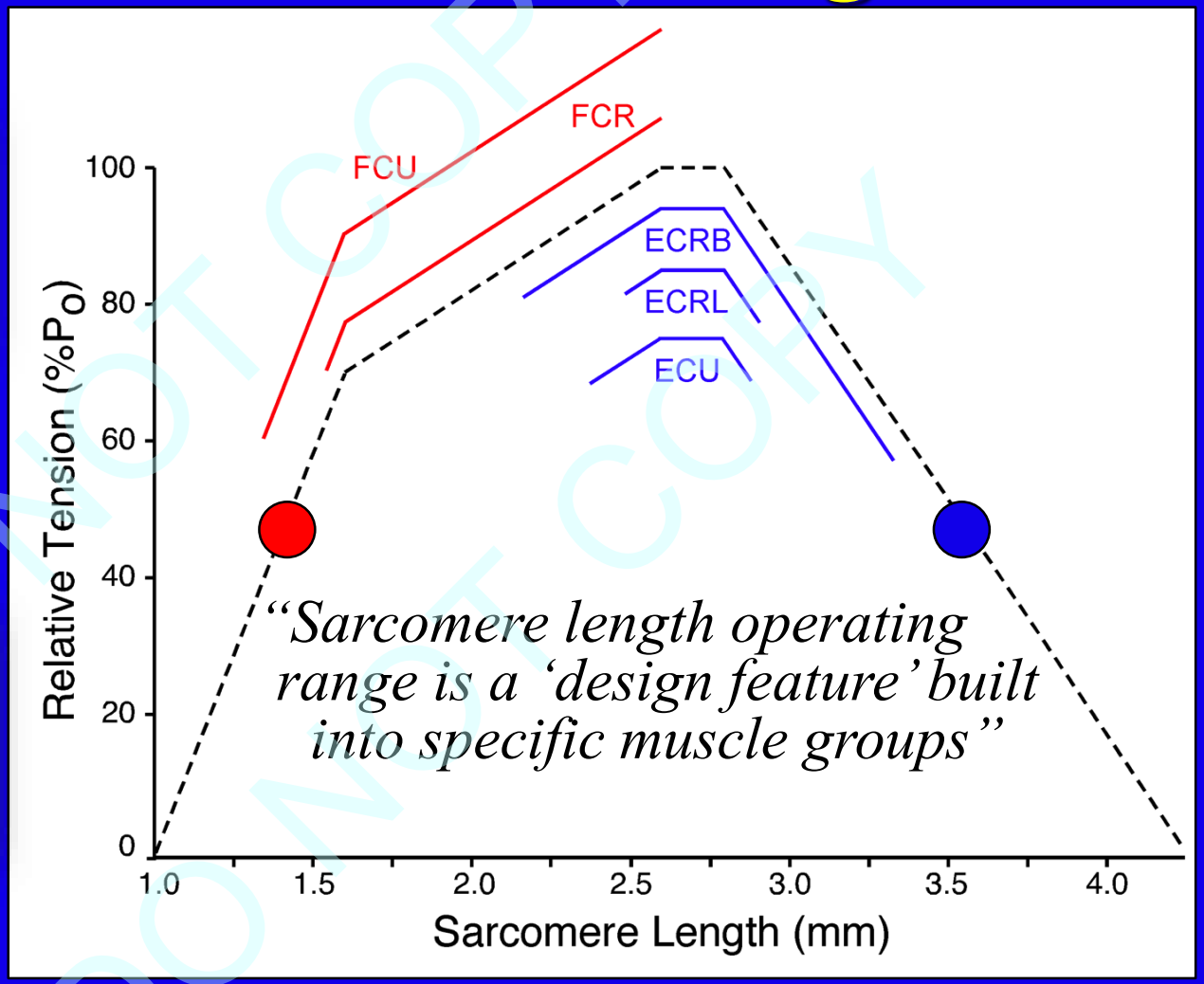
Lieber, Loren and Fridén (1994) *J. Neurophysiol.* **71**:874-881.

$n\lambda = d\sin\theta$

Diffraction Pattern

Human Wrist Joint Design





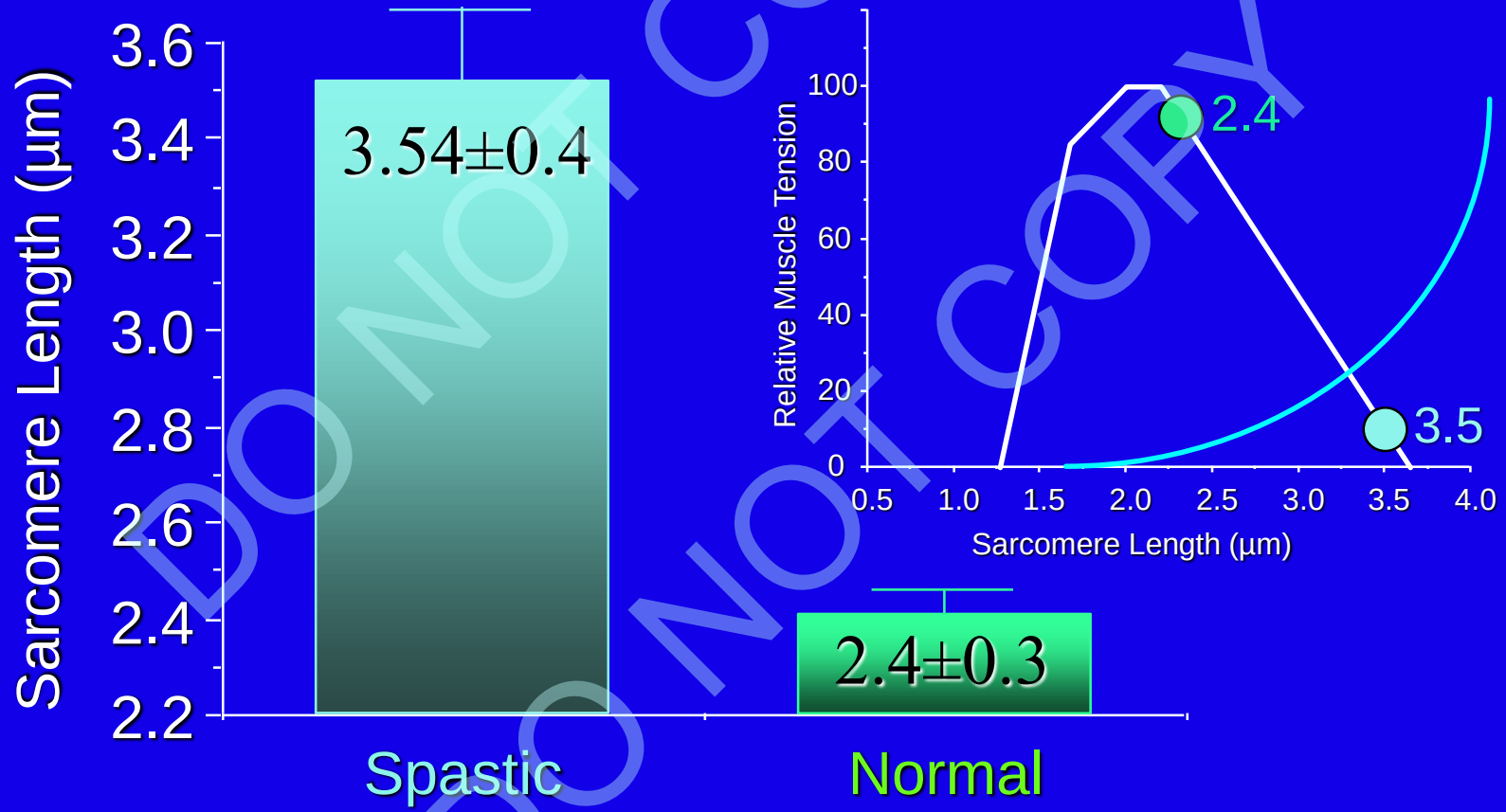
Loren *et al.* (1996) *J. Biomech.* **29**:331-342.

Intraoperative FCU Measurements

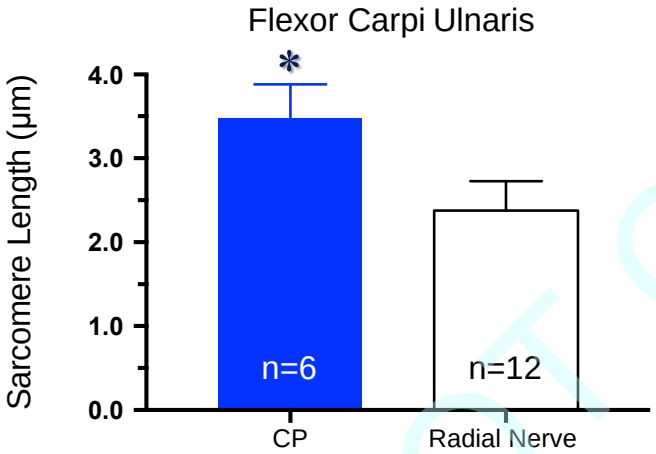
- Spastic FCU wrist flexion contractures (n=6)

- “Normal” FCU muscles with wrist in full flexion (n=12, radial nerve palsy)

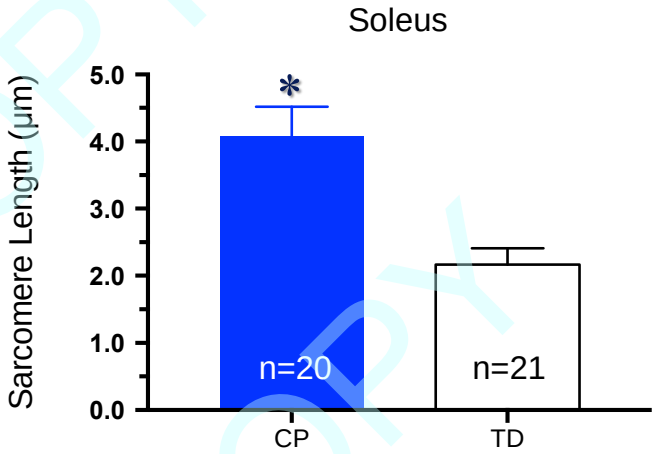
Sarcomere Length Comparison



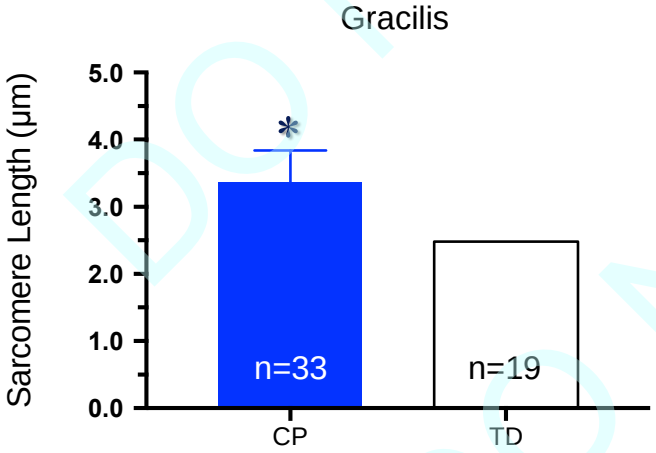
Lieber and Fridén (2002). *Muscle & Nerve* **25**:265-270

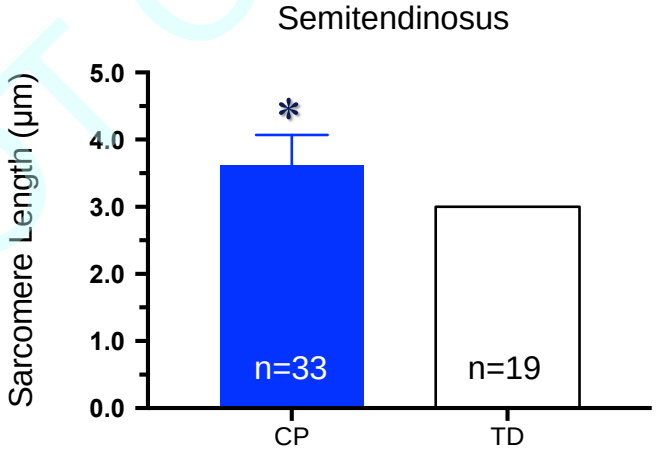


Lieber and Fridén (2002)



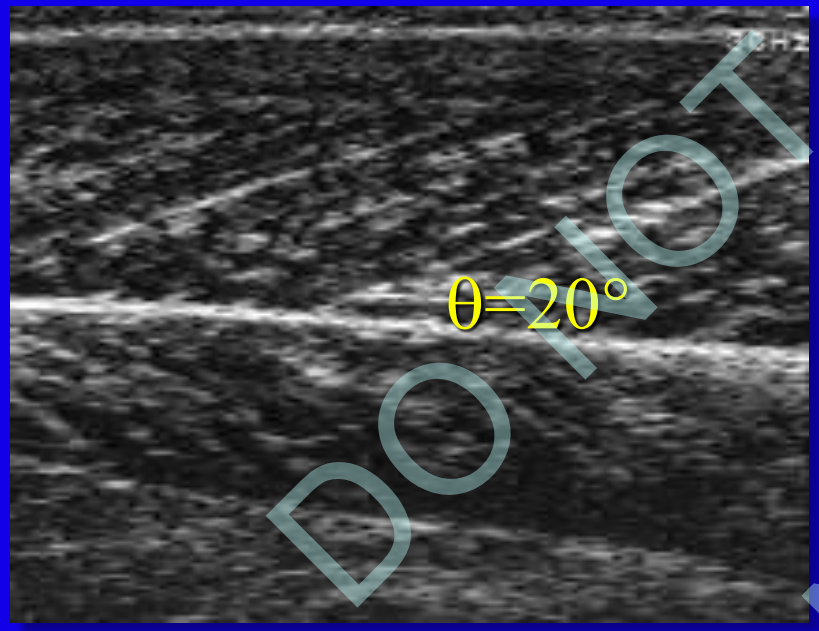
Mathewson *et al.* (2014)



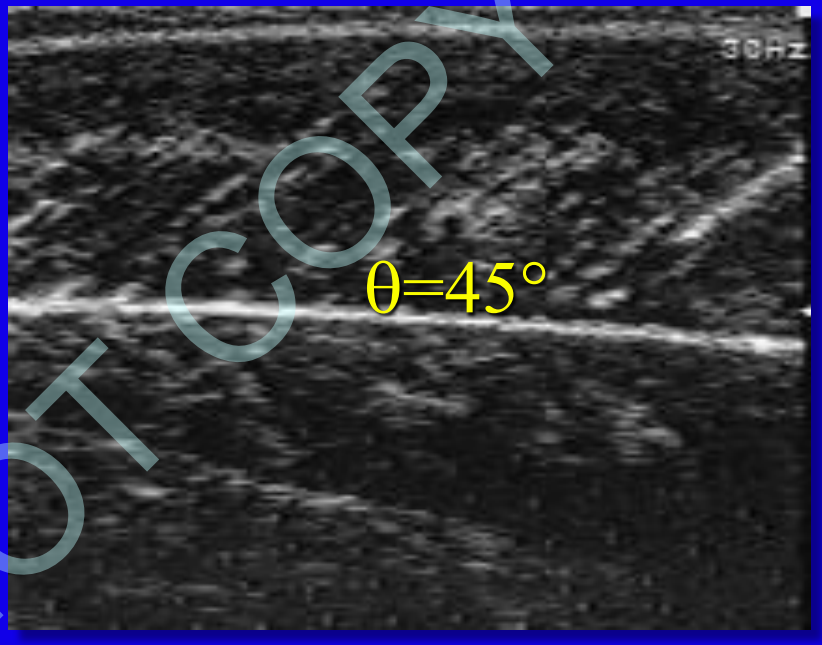


Smith *et al.* (2011)

Architecture by Ultrasonography



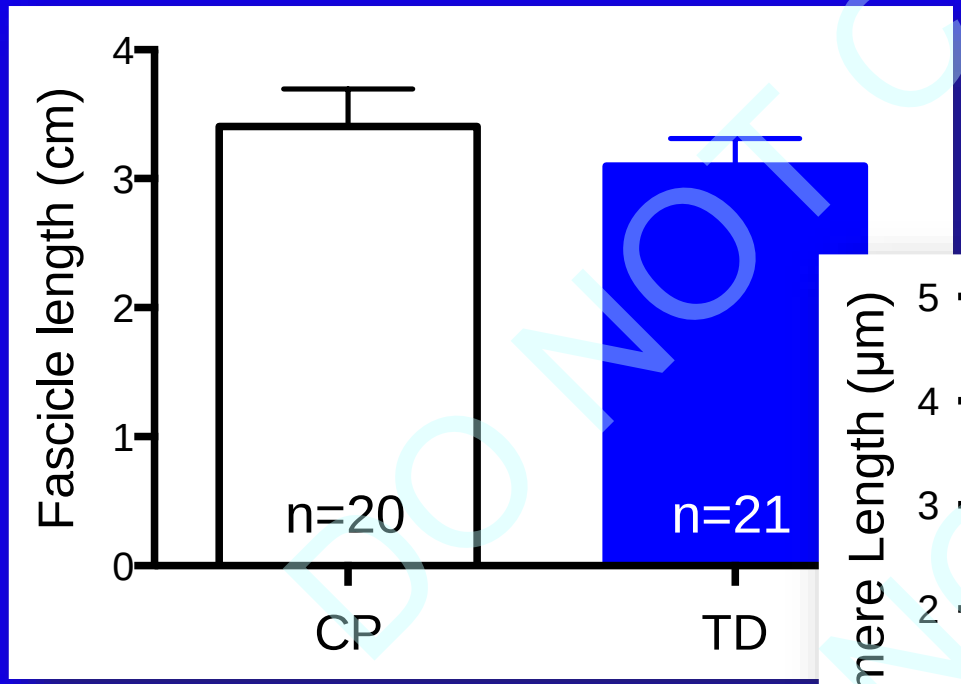
Passive Muscle

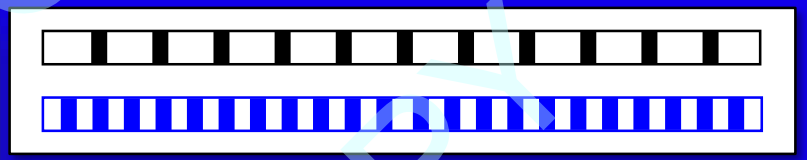


Active Muscle

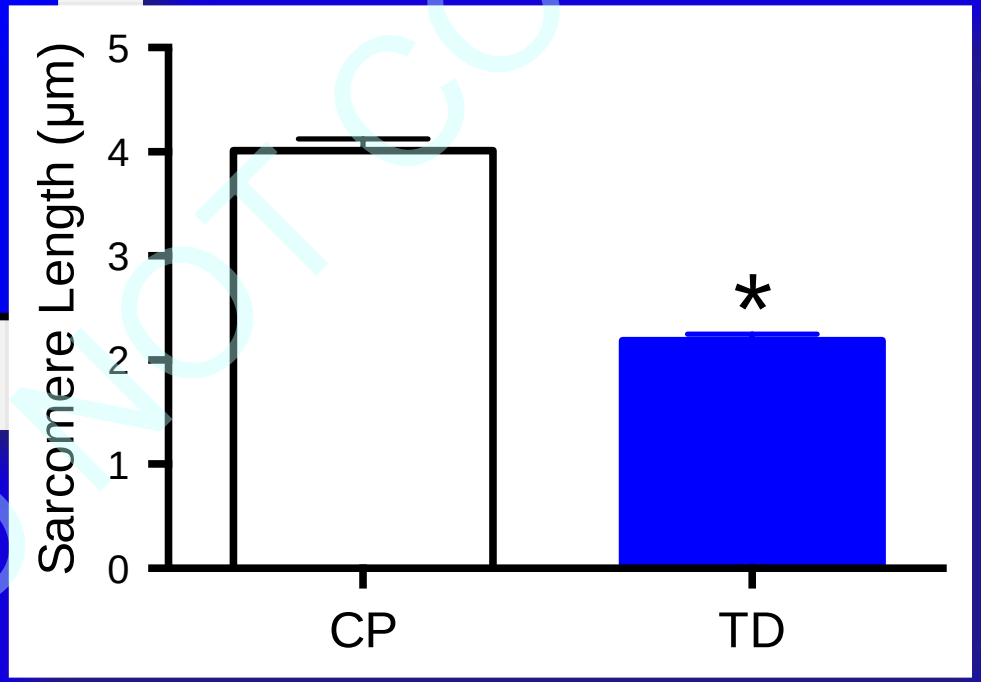
Fukunaga *et al.* (1996). *J. Appl. Physiol.* **81**:1430-1433.

While fascicle length is similar…





(≠ animal models)



…sarcomere length is much longer…

INVITED REVIEW

SKELETAL MUSCLE SATELLITE CELLS: MEDIATORS OF MUSCLE GROWTH DURING DEVELOPMENT AND IMPLICATIONS FOR DEVELOPMENTAL DISORDERS

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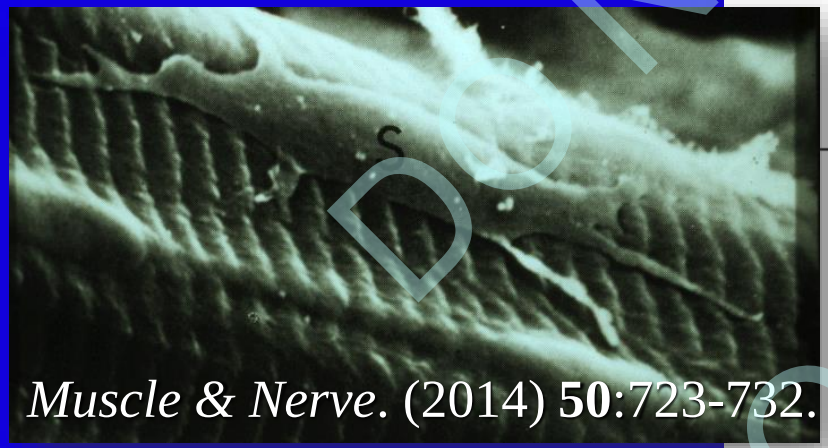
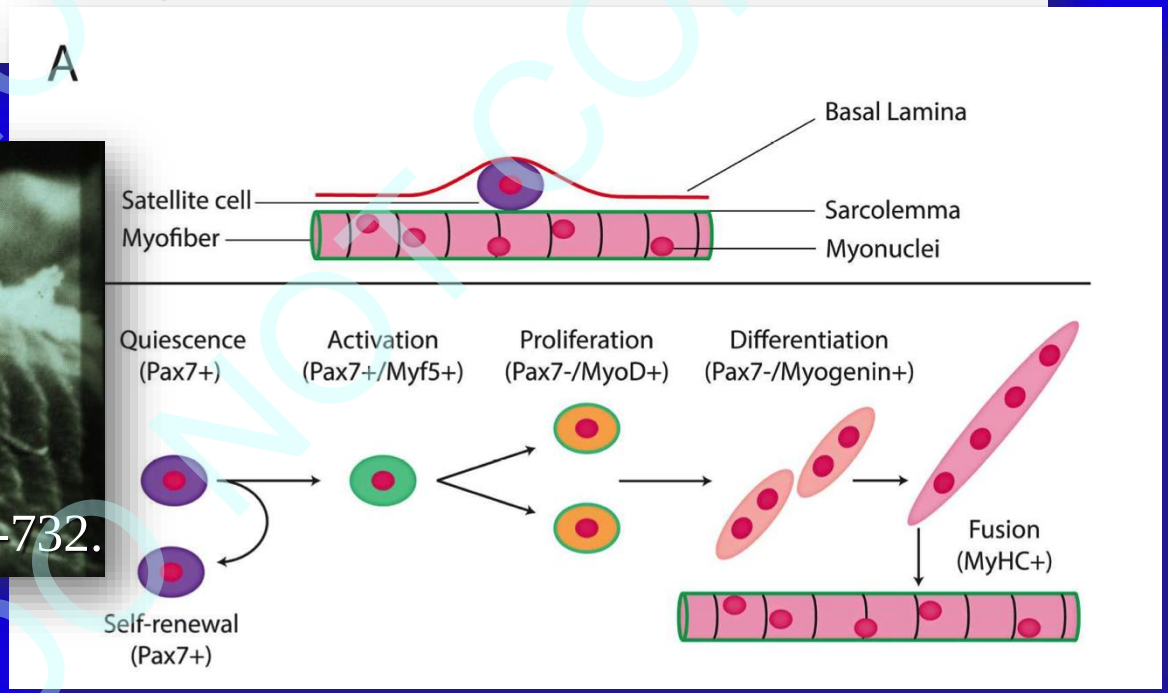
Accepted 26 August 2014



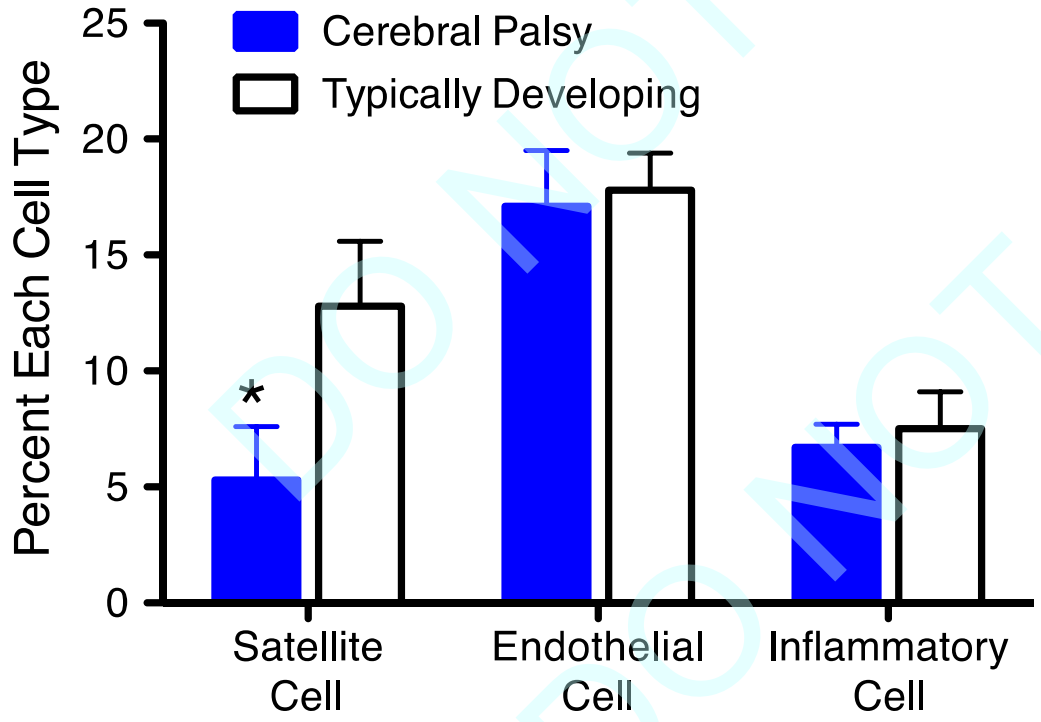
Muscle & Nerve. (2014) **50**:723-732.



DEVELOPMENTAL MEDICINE & CHILD NEUROLOGY ORIGINAL ARTICLE

Reduced satellite cell population may lead to contractures in children with cerebral palsy

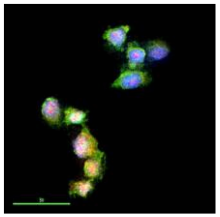
LUCAS R SMITH[1] | HENRY G CHAMBERS[2,3] | RICHARD L LIEBER[1,2]



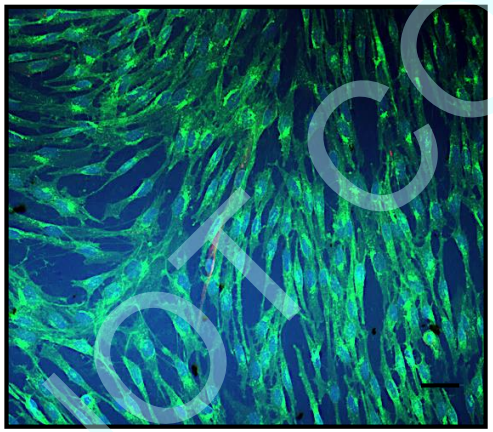
Implications…

- *Growth*
- *Repair*
- *Regeneration*
- *Hypertrophy*
- *Therapy*

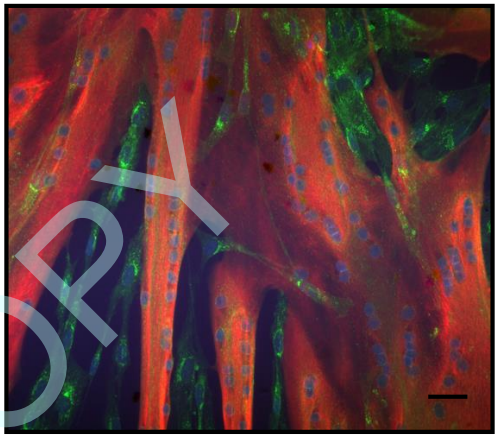
Myogenesis—Making Muscle



Satellite Cells



Myoblasts



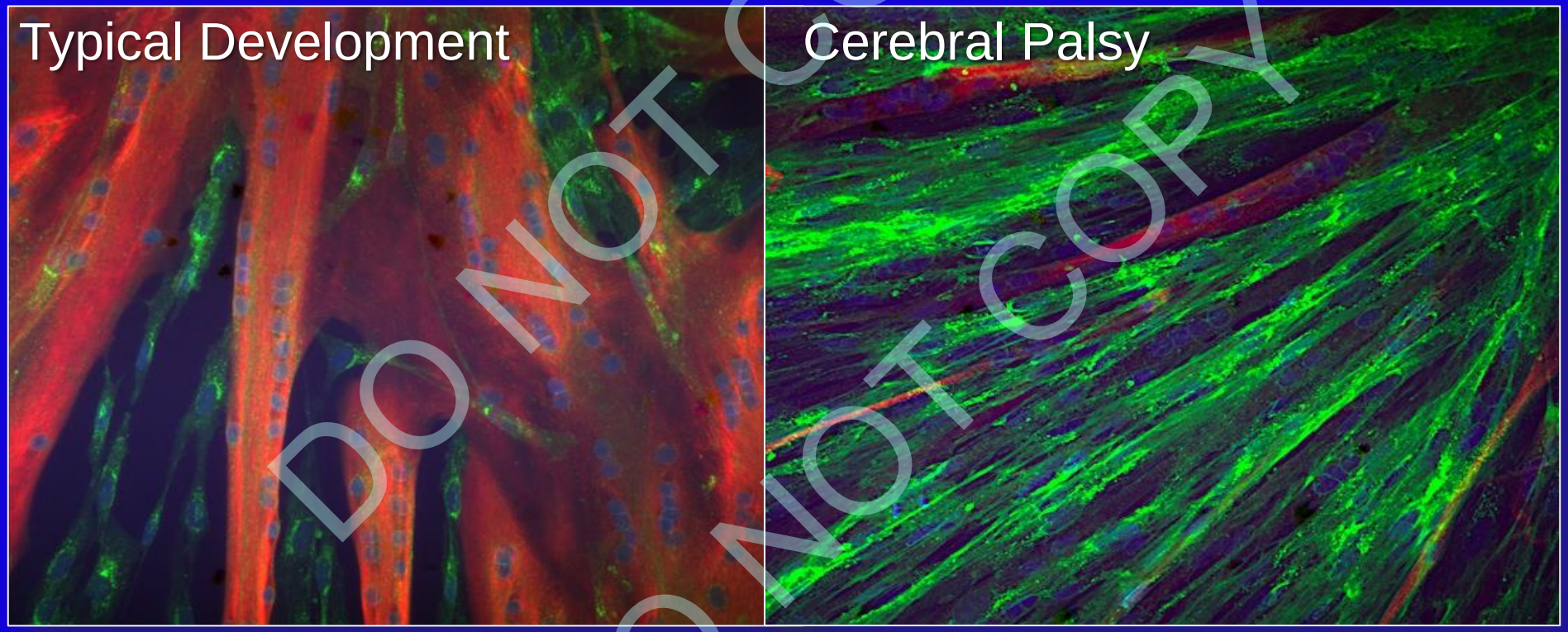
Fibers

Controlled by genetic and epigenetic mechanisms

Transcription Factors

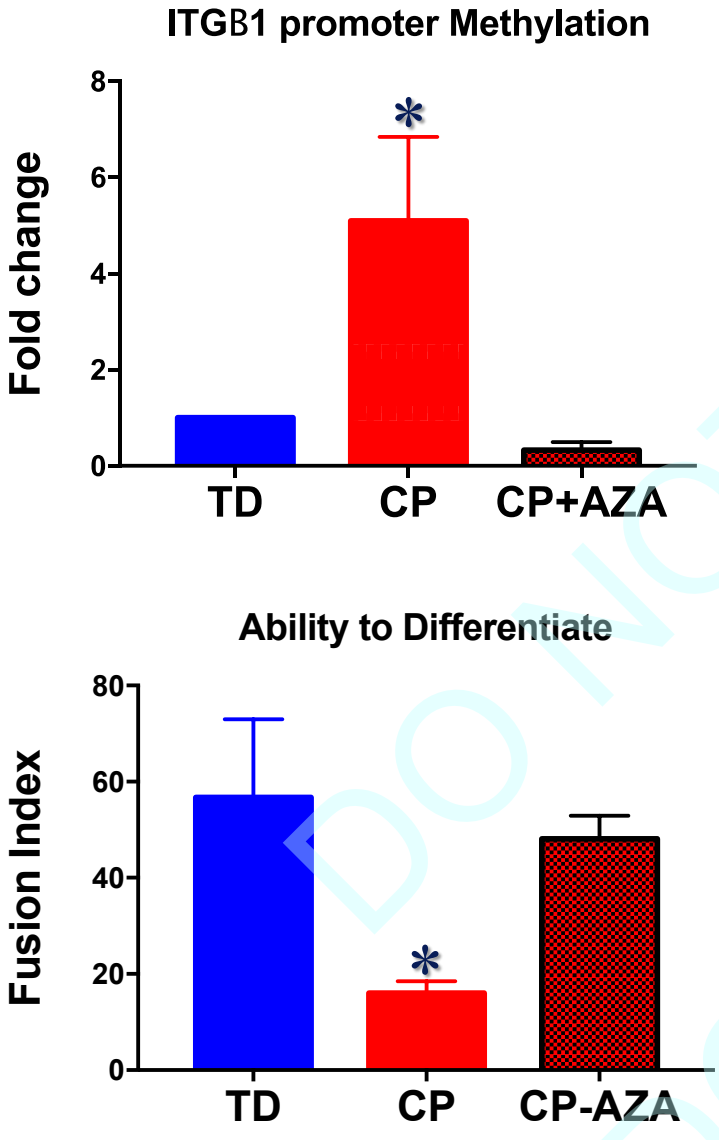
DNA Methylation

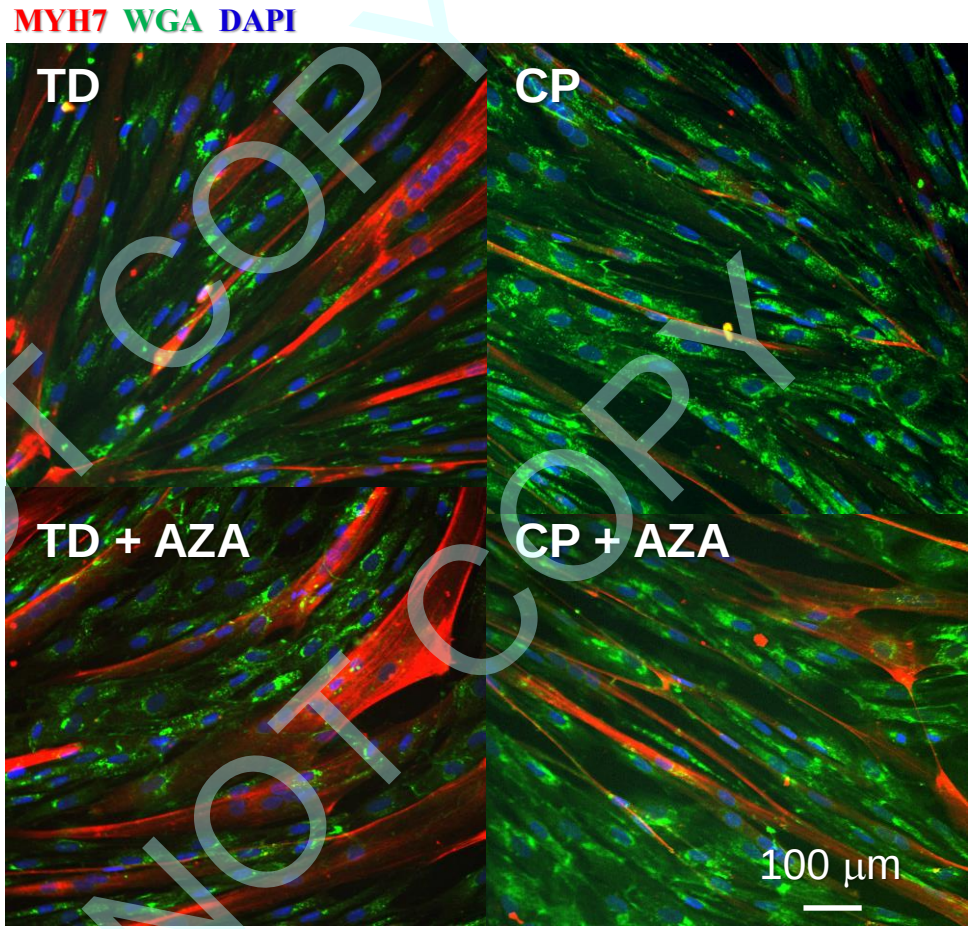
In Vitro Developmental Impairment



Slow Myosin Heavy Chain + WGA

Implies epigenetic mechanisms…

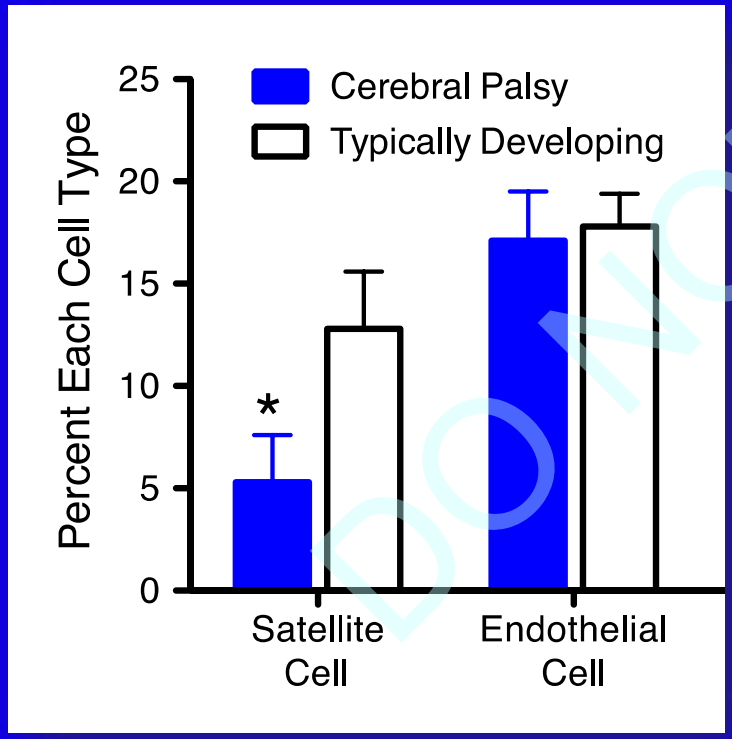




Domenighetti *et al.* (2018).
Am. J. Physiol. **315**:C247–C257.

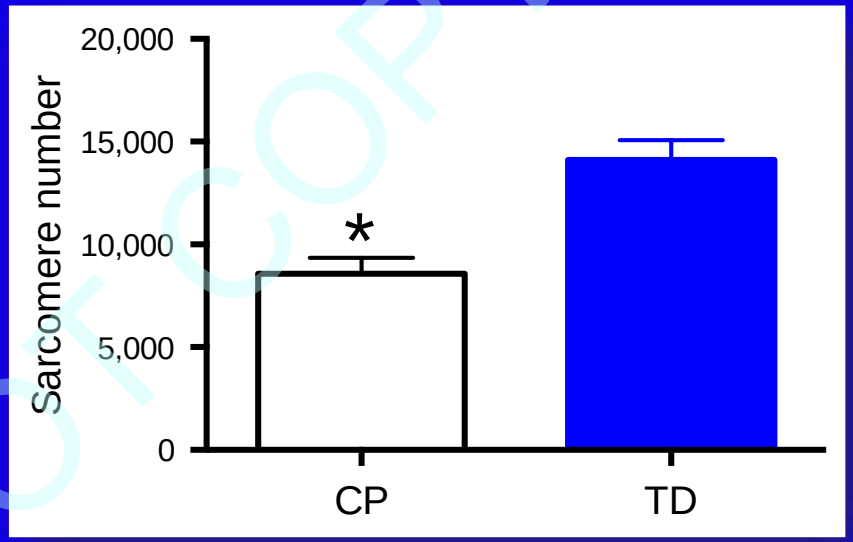
SC Implications for Contracture?

(Sudarshan Dayanidhi, P.T., Ph.D.)



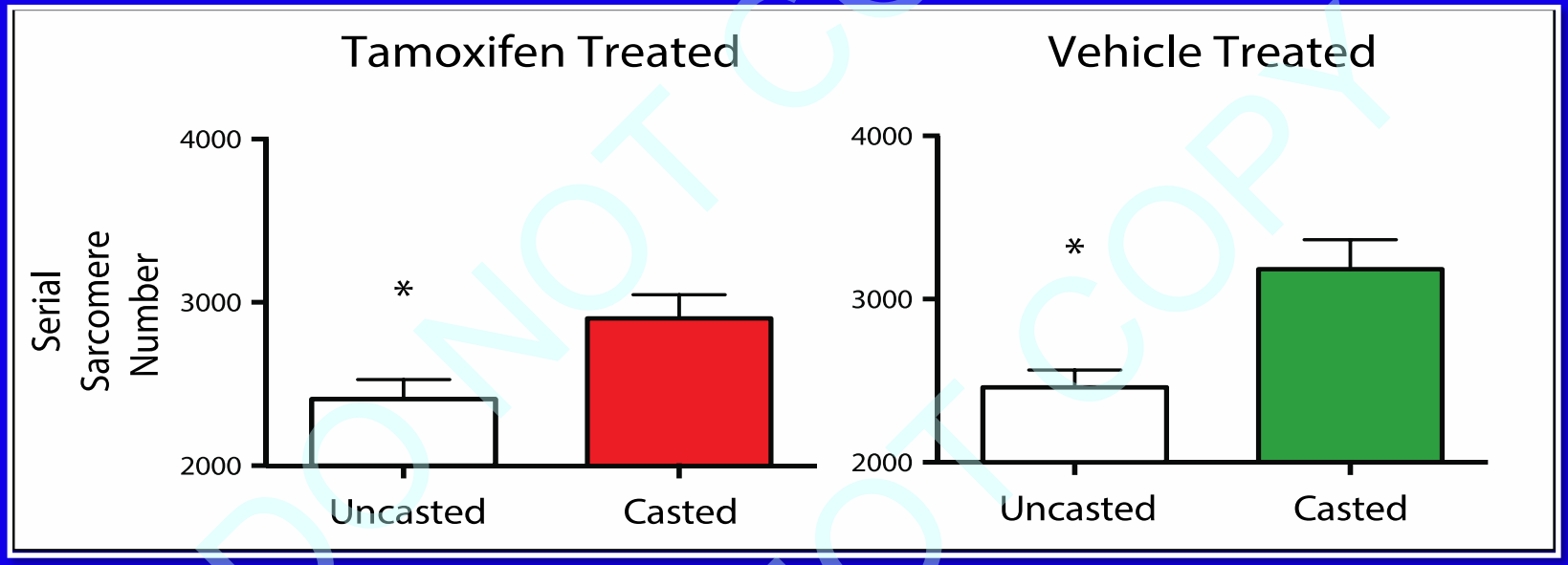
Smith *et al.* 2013
Dayanidhi *et al.* 2014

?



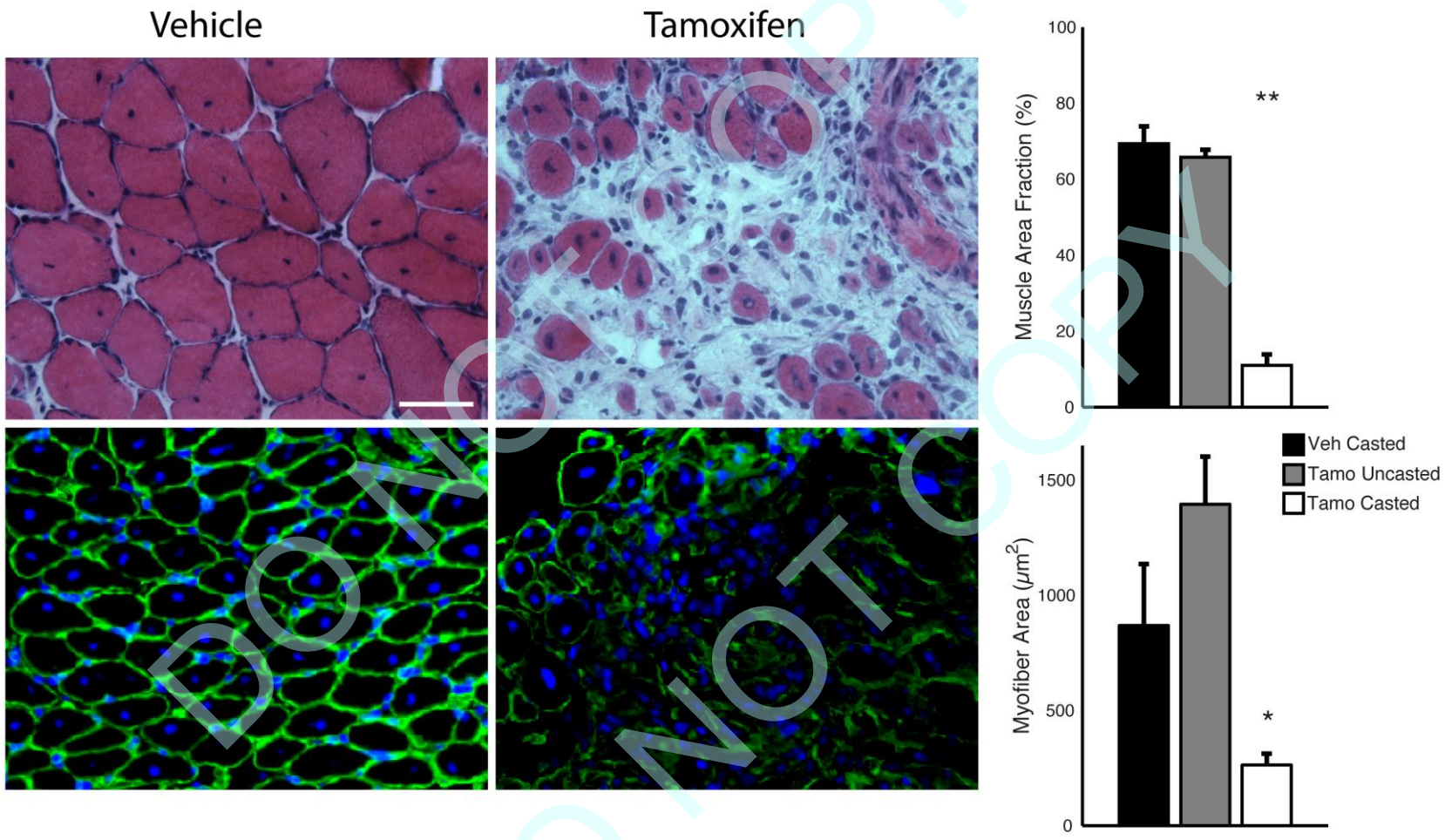
Lieber and Fridén, 2002
Smith *et al.* 2011
Mathewson *et al.* 2014

Stretched Soleus Sarcomere Number



Satellite Cell Number: *30%* *100%*

Kinney *et al.* (2017). *Muscle & Nerve* **55**:384-392.


Vehicle
Tamoxifen
Muscle Area Fraction (%)
100
80
60
40
20
0
**
Veh Casted
Tamo Uncasted
Tamo Casted
Myofiber Area (μm2)
1500
1000
500
0
*

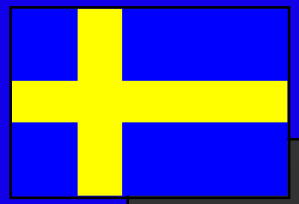
Summary

- Skeletal muscle “design” is programmed into the muscle sarcomere length operating range.
- Muscle contracture represents a complex, uniquely human muscle adaptation (≠ mouse, cat, rat, rabbit).

Summary (cont.)

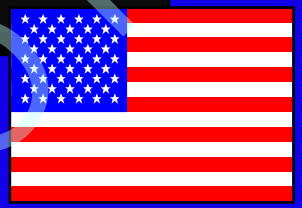
- CP muscles have trouble "growing."
- Curative therapies are hampered by lack of knowledge in several specific areas:
  - ECM Structure and Function
  - ECM Regulation
  - Satellite Cell Development and Function

Acknowledgments



This work was supported by the NIH, the Department of Veterans Affairs, and the Swedish Medical Research Council

DARPA



National Institute of Child Health and Human Development