Muscle regenerative capacity and aging

International Conference on Frailty & Sarcopenia Research

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Miami, Florida
March 1-3, 2018

College of Health Sciences

UNIVERSITY OF KENTUCKY
CENTER FOR MUSCLE BIOLOGY

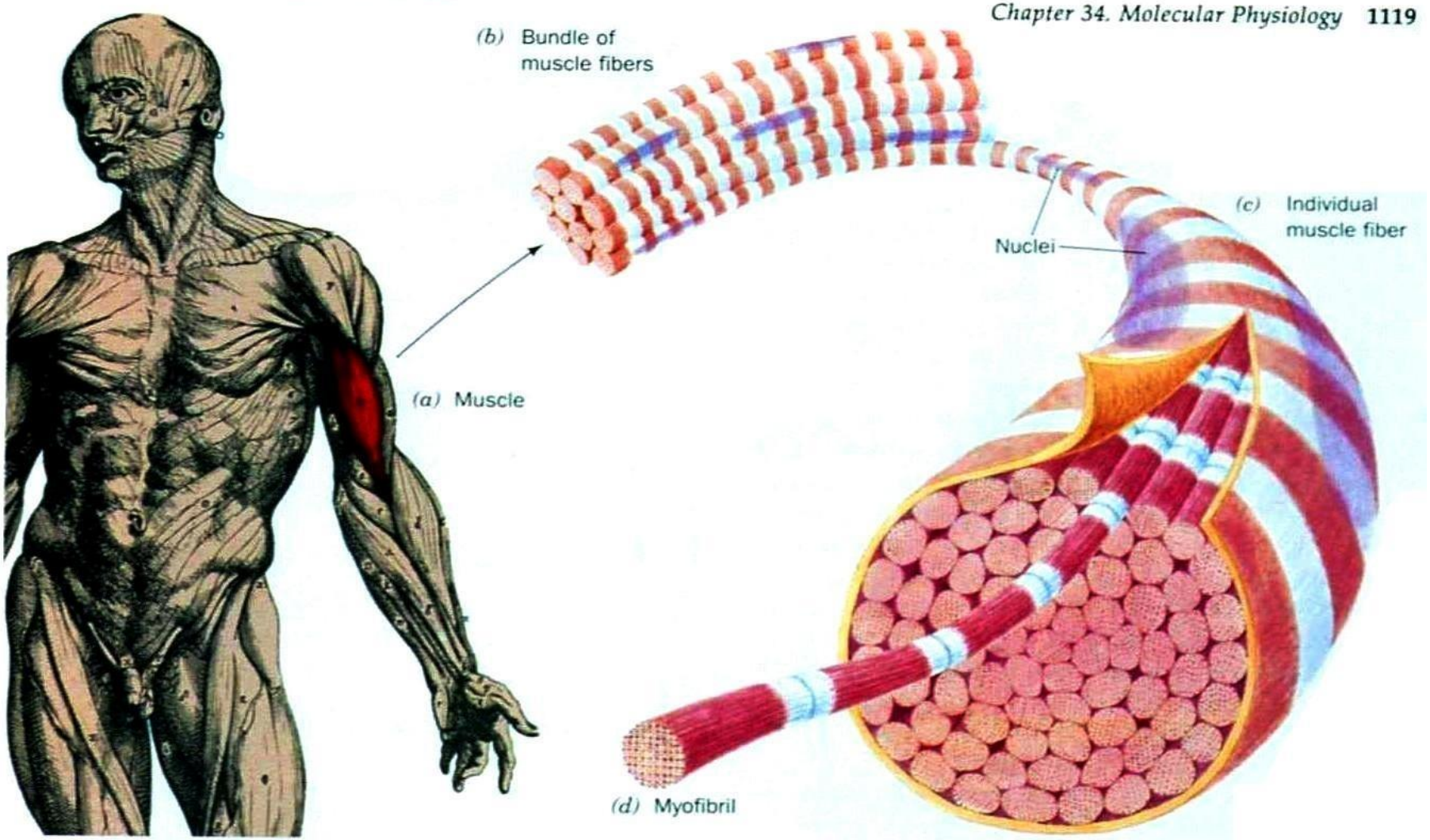
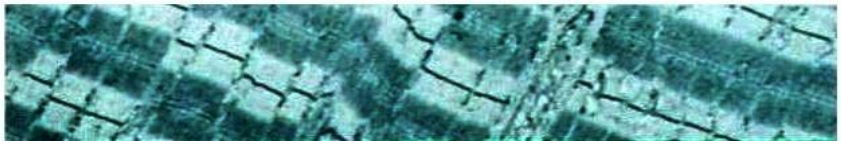
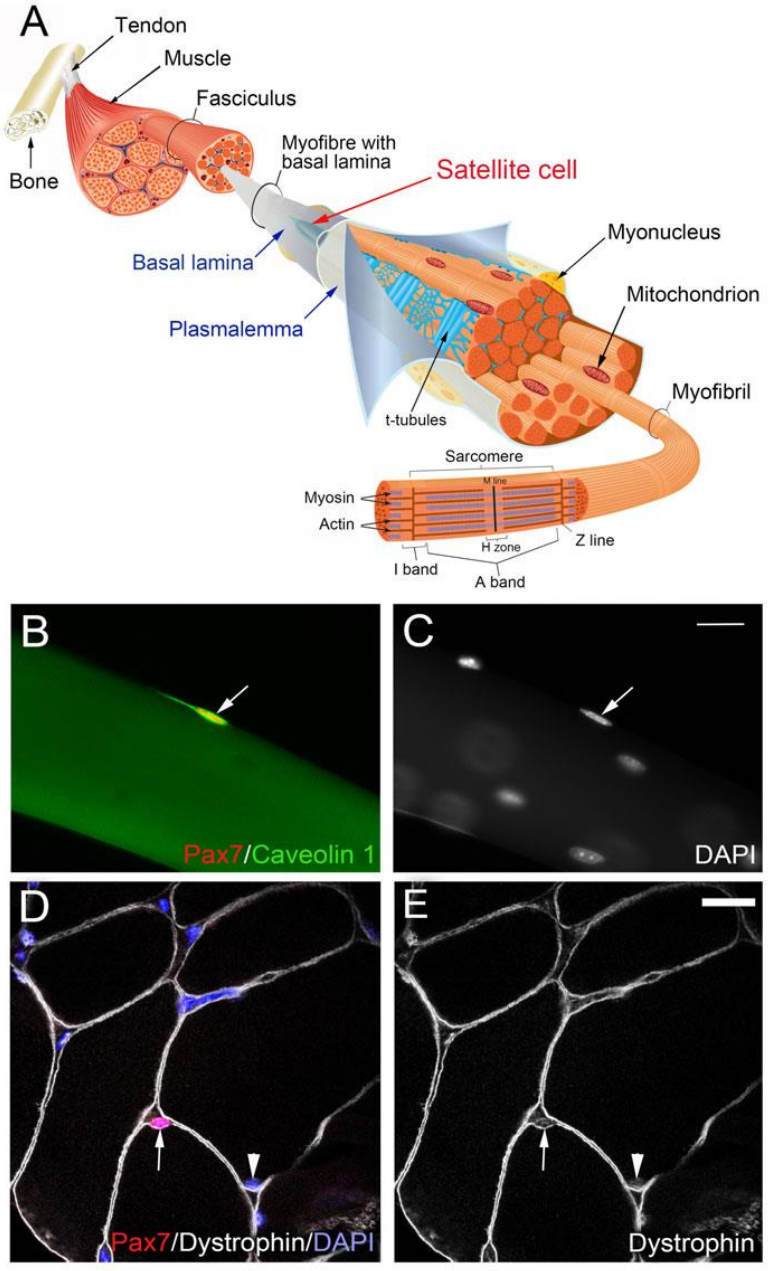


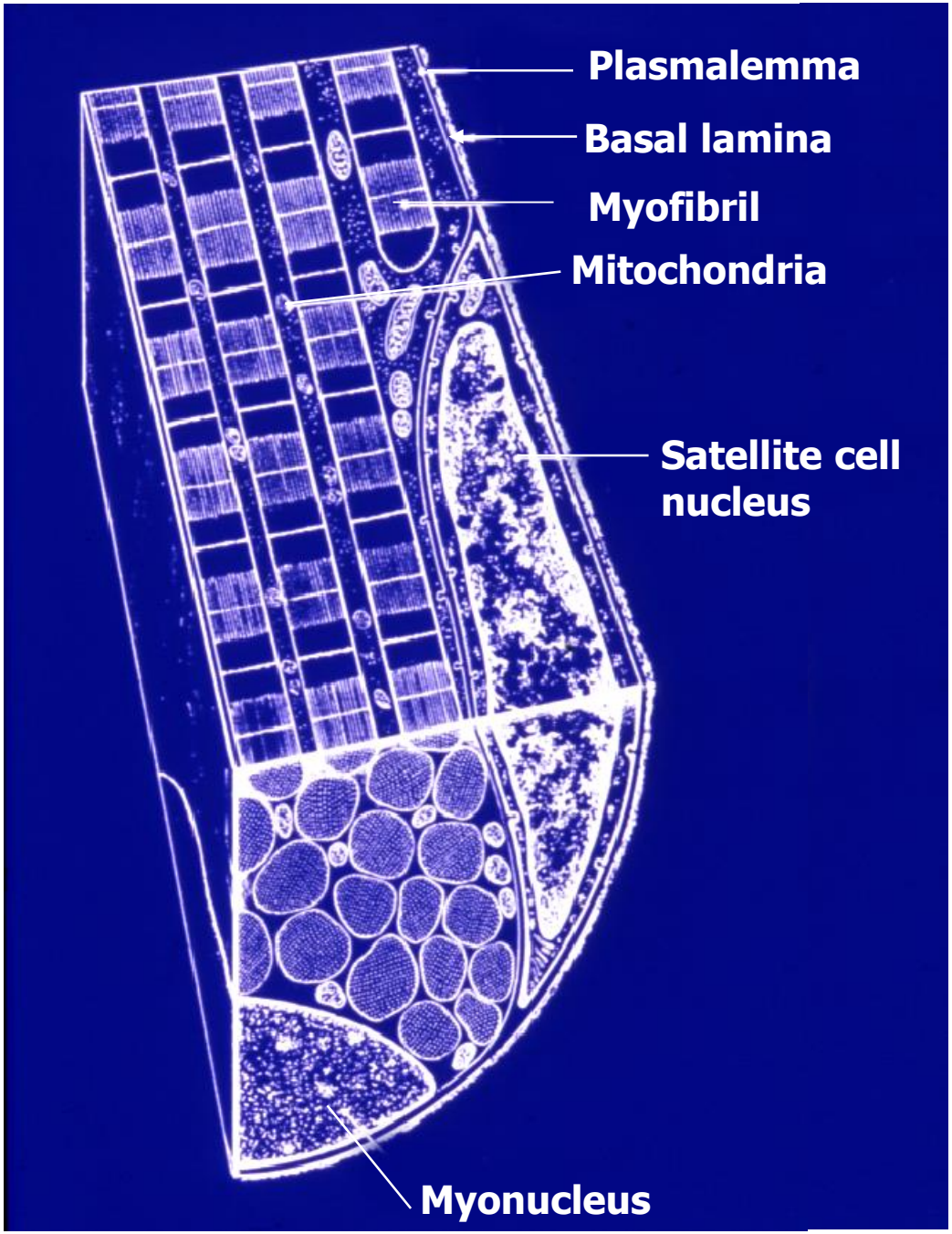
Figure 34-41
Skeletal muscle organization. A muscle (*a*), consists of bundles of muscle fibers (*b*), each of which is a long thin multinucleated cell (*c*), that may run the length of the muscle. Muscle fibers contain bundles of laterally aligned myofibrils (*d*), which consist of bundles of alternating thick and thin filaments.



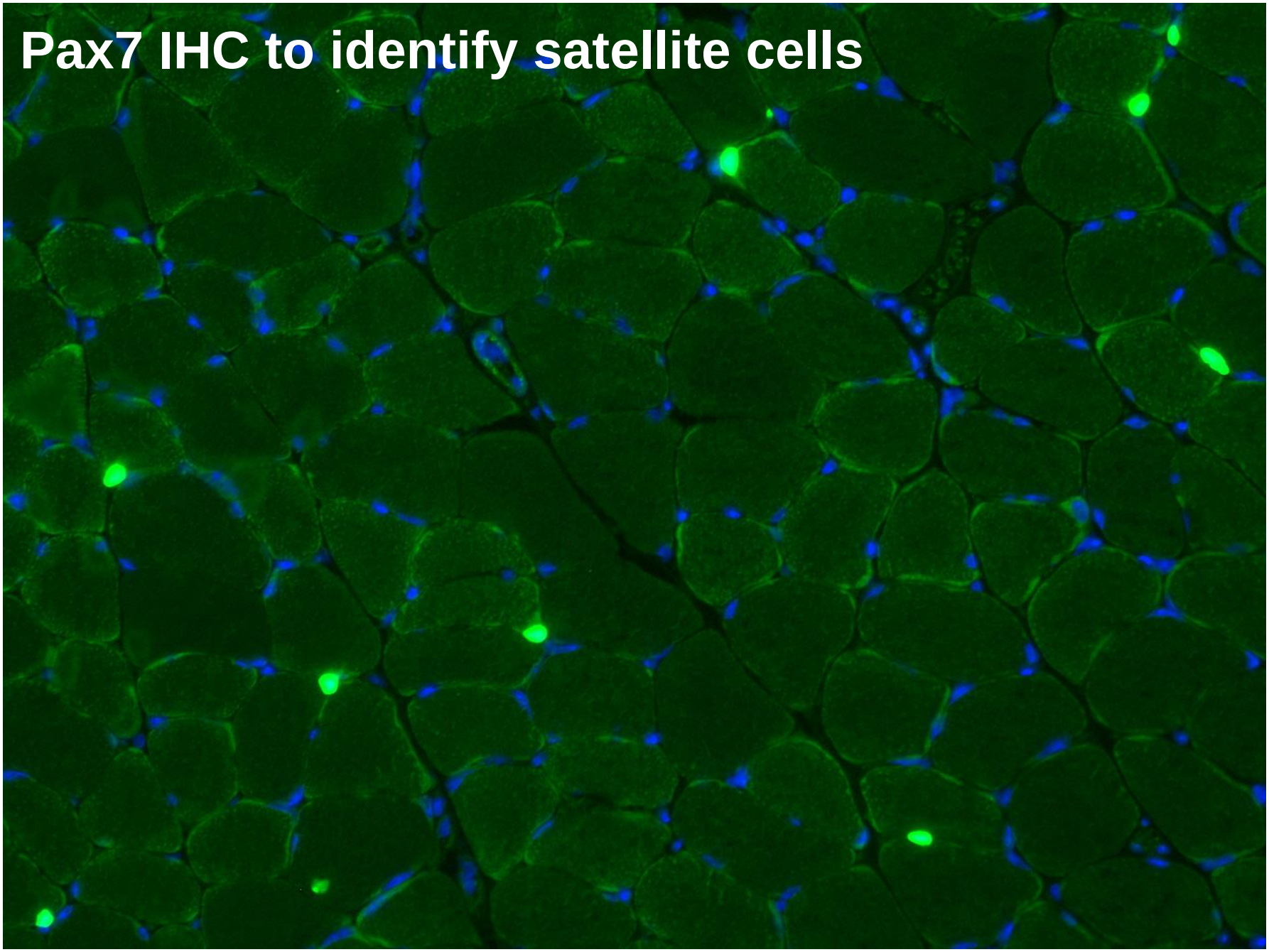
Satellite cells: Resident muscle stem cells



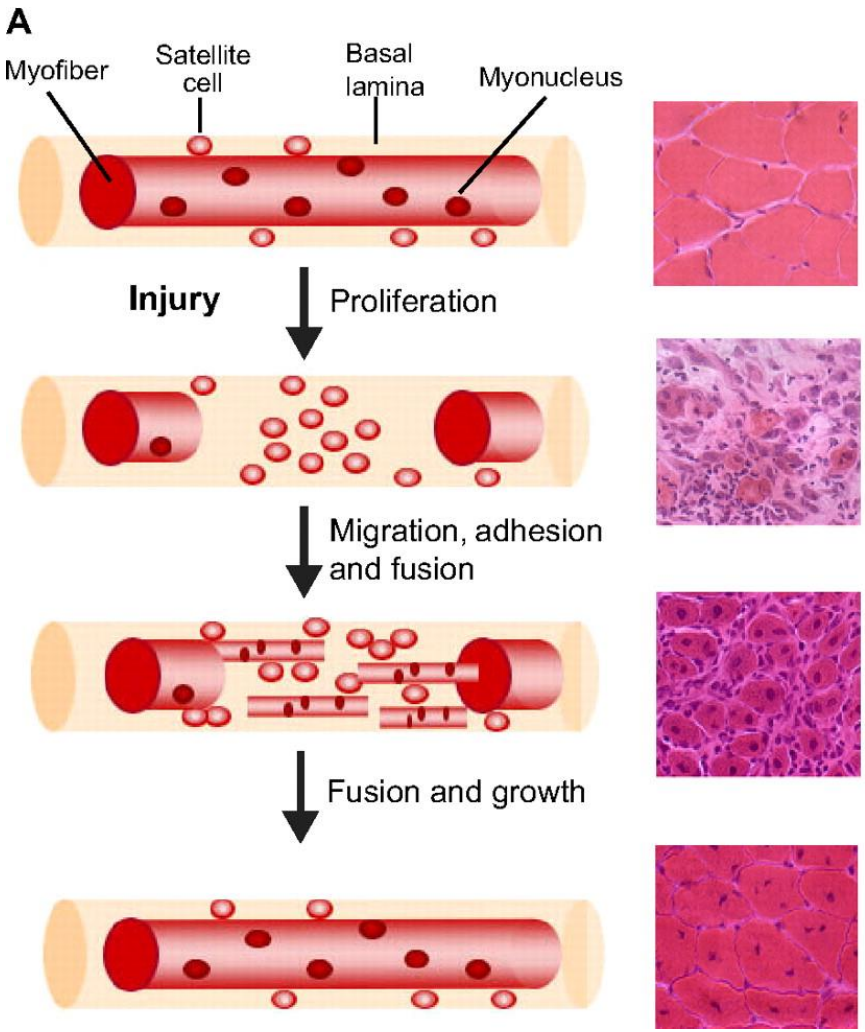
Relaix & Zammit, 2012


Plasmalemma
Basal lamina
Myofibril
Mitochondria
Satellite cell nucleus
Myonucleus

Pax7 IHC to identify satellite cells

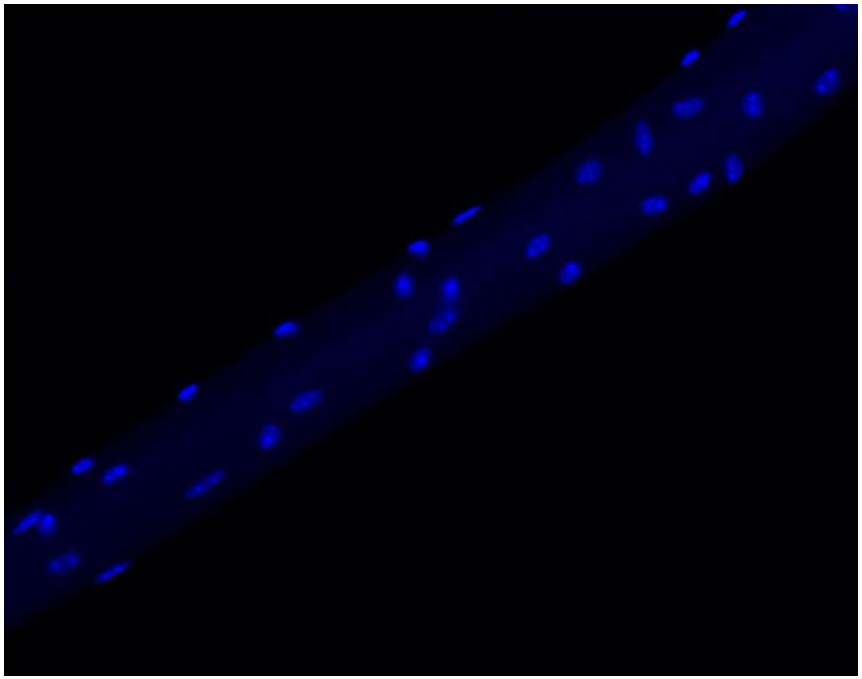


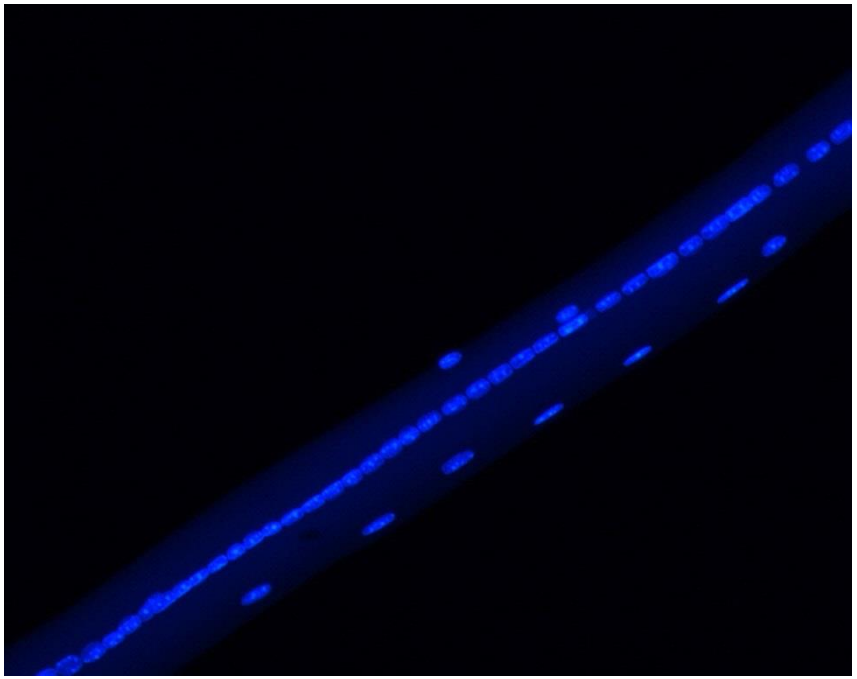
Myofiber repair and regeneration is mediated by satellite cells



Adapted from
Abmayr & Pavlath Development 2012

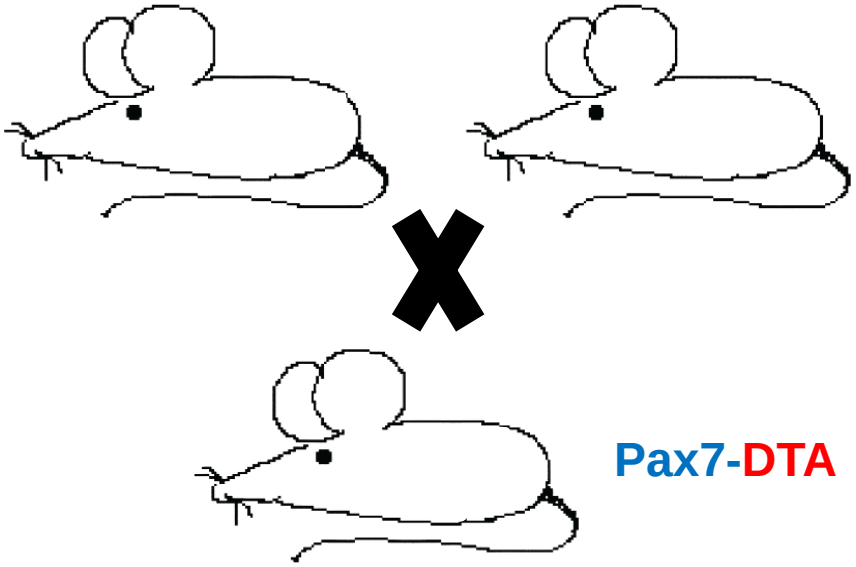
Normal compared to regenerated single fibers



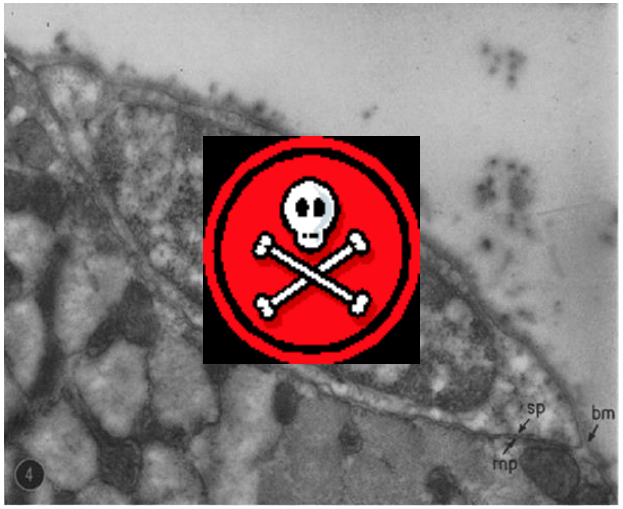


Pax7-DTA mouse for satellite cell depletion

Pax7-Cre^{ER} **Rosa26-^{fl}stop^{fl}-DTA**



Pax7-DTA



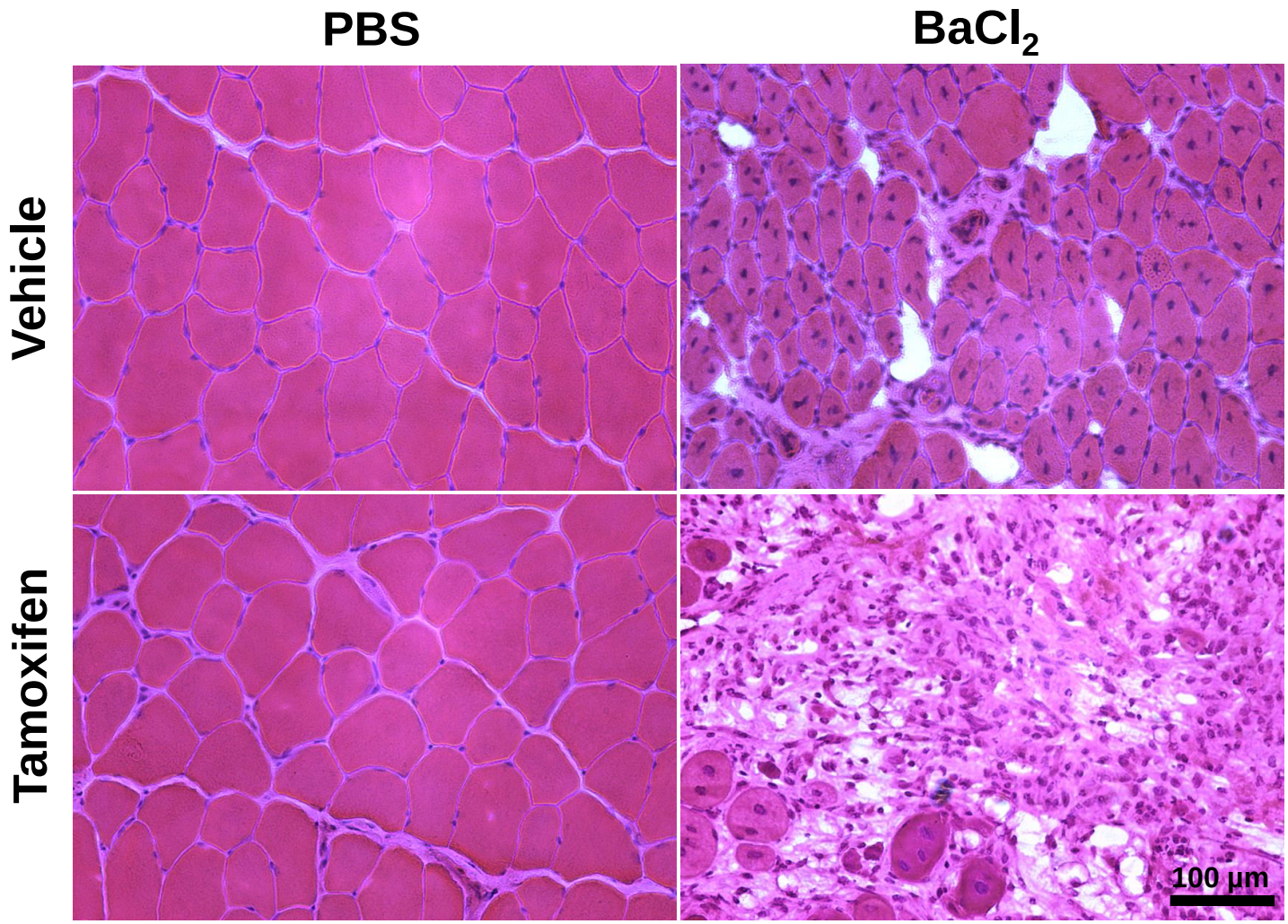
Mauro, 1961

>4 months of age, ~ 25g

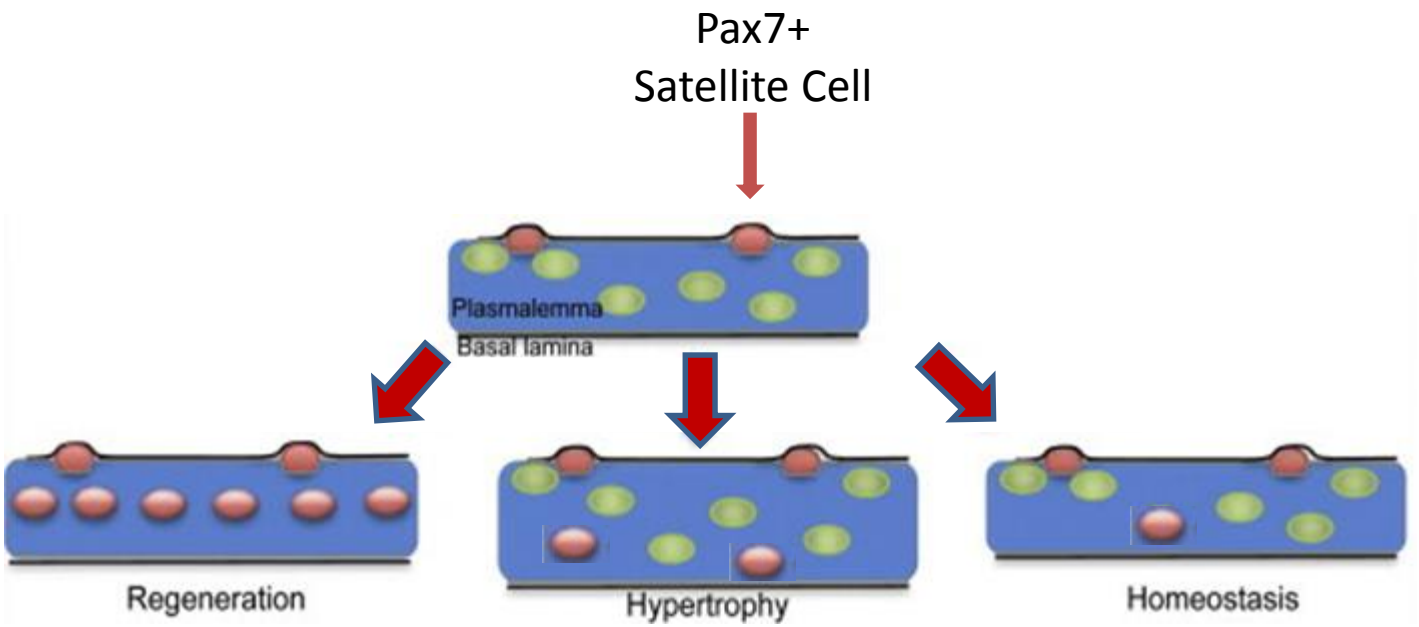
Tamoxifen: 2mg/day for 5 days IP, 2 week washout

Only mice with >90% satellite cell depletion are used

Satellite cell-depleted muscle does not regenerate



Other roles for satellite cells?

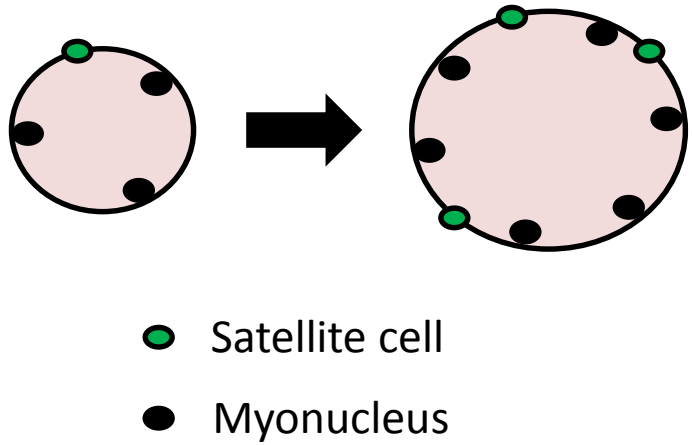


Adapted from Brack & Rando, Cell Stem Cell, 2012

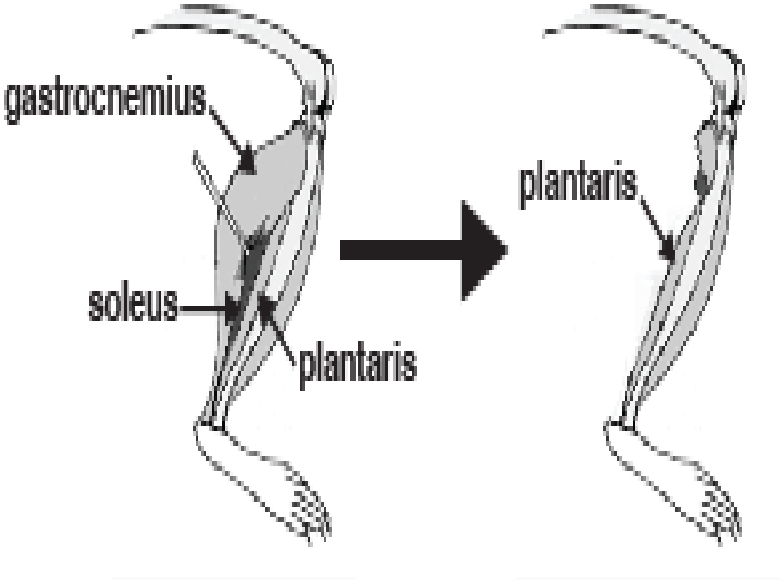
Dogma: The myonuclear domain remains constant during adult muscle growth via satellite cell fusion

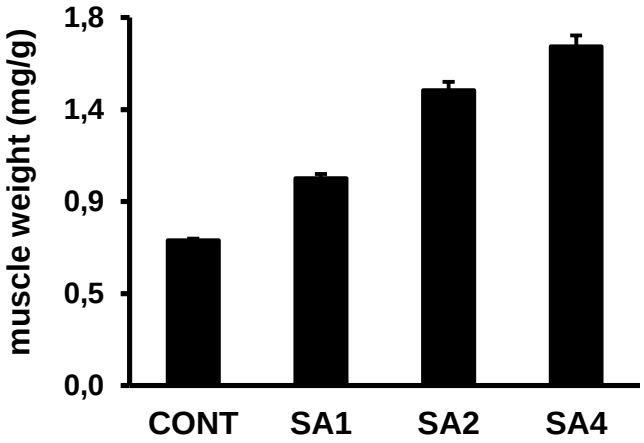
Resistance training

- Satellite cell proliferation
- Fusion to the myofiber
- Myofiber hypertrophy



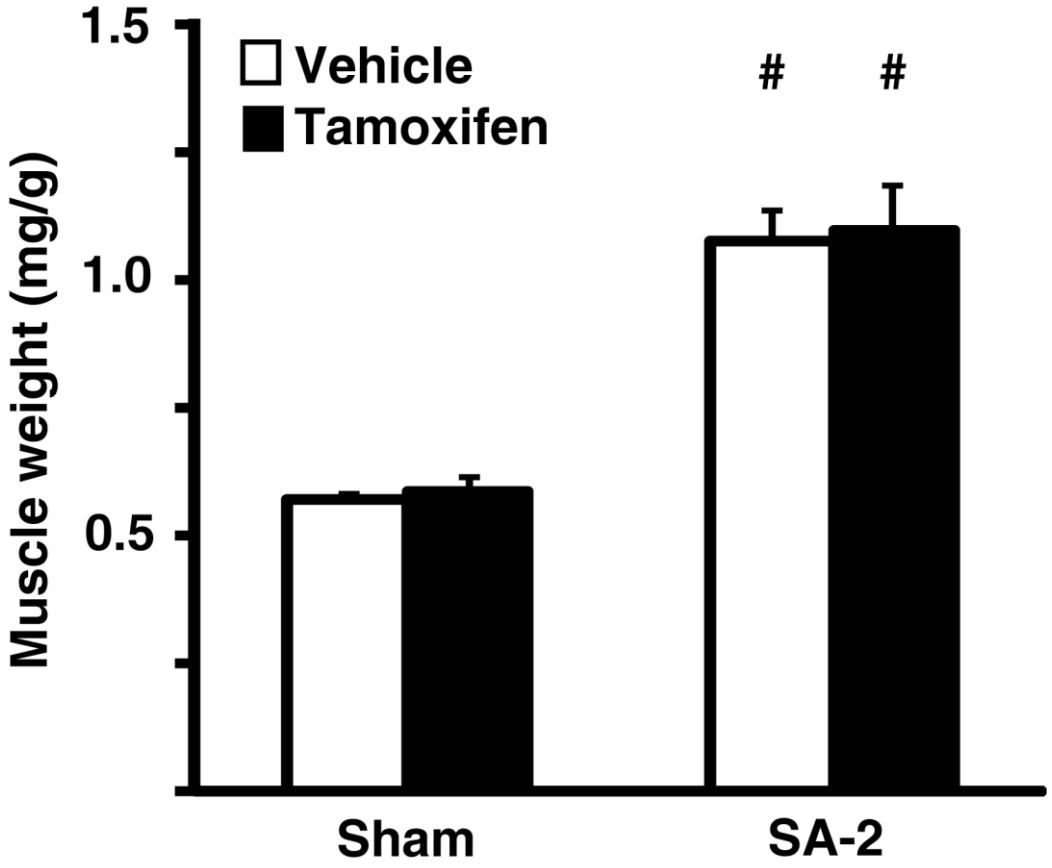
Model of muscle hypertrophy





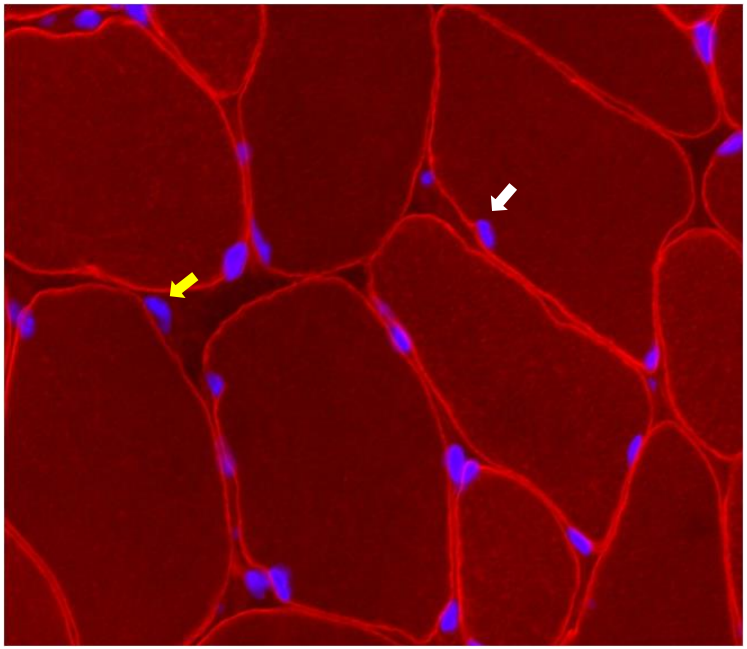
- Synergist ablation (SA)
- Imposes functional overload of plantaris muscle
- Substitute for resistance exercise training

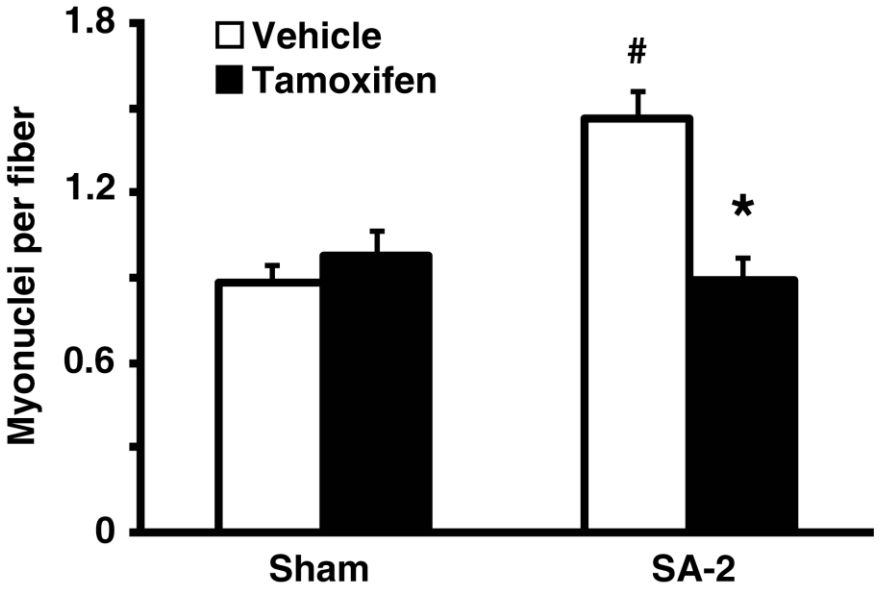
Early growth response following synergist ablation is unaffected by satellite cell depletion



McCarthy et al., Development, 2011

Hypertrophy occurs in the absence of myonuclear accretion in satellite cell-depleted muscle

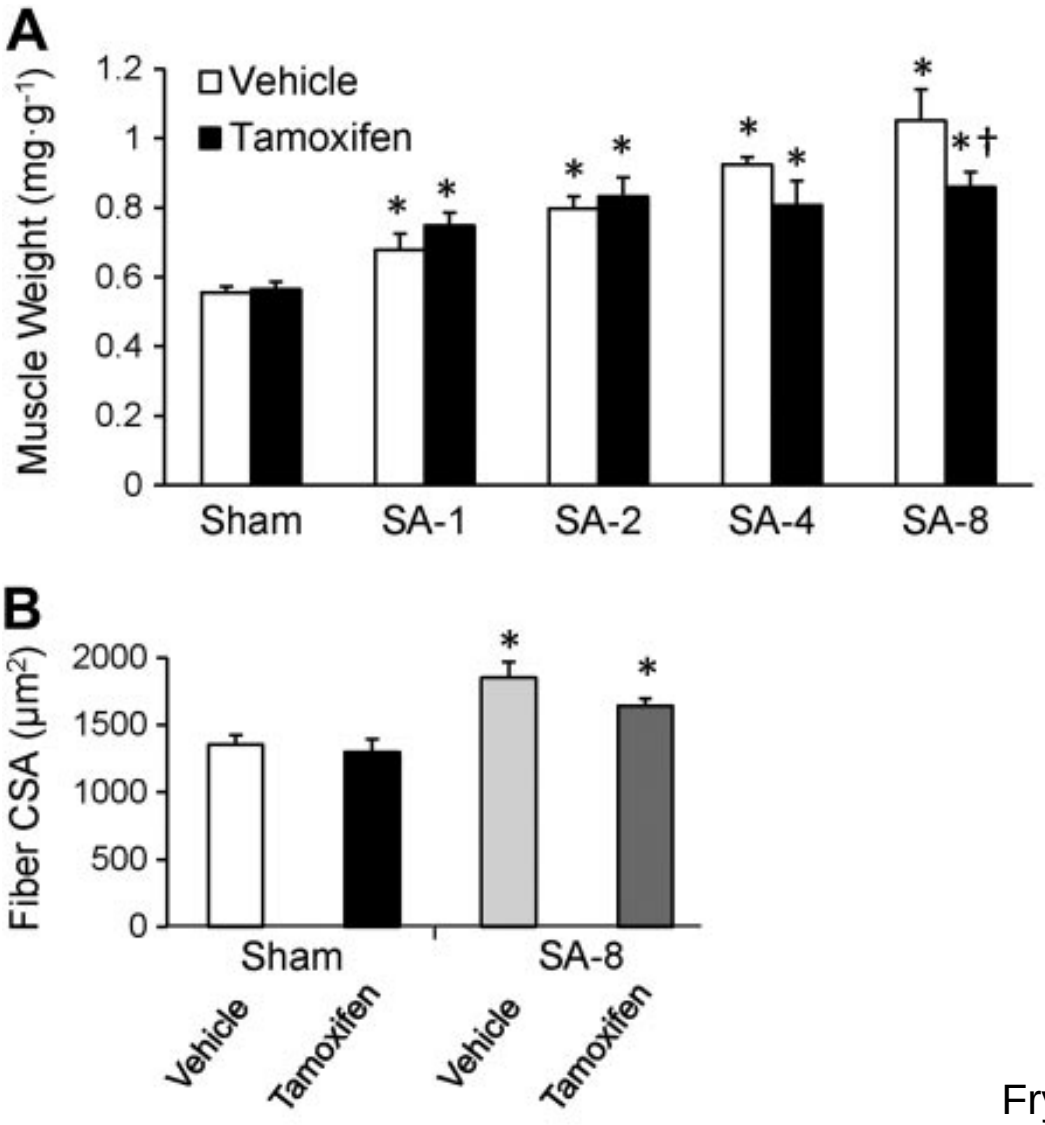




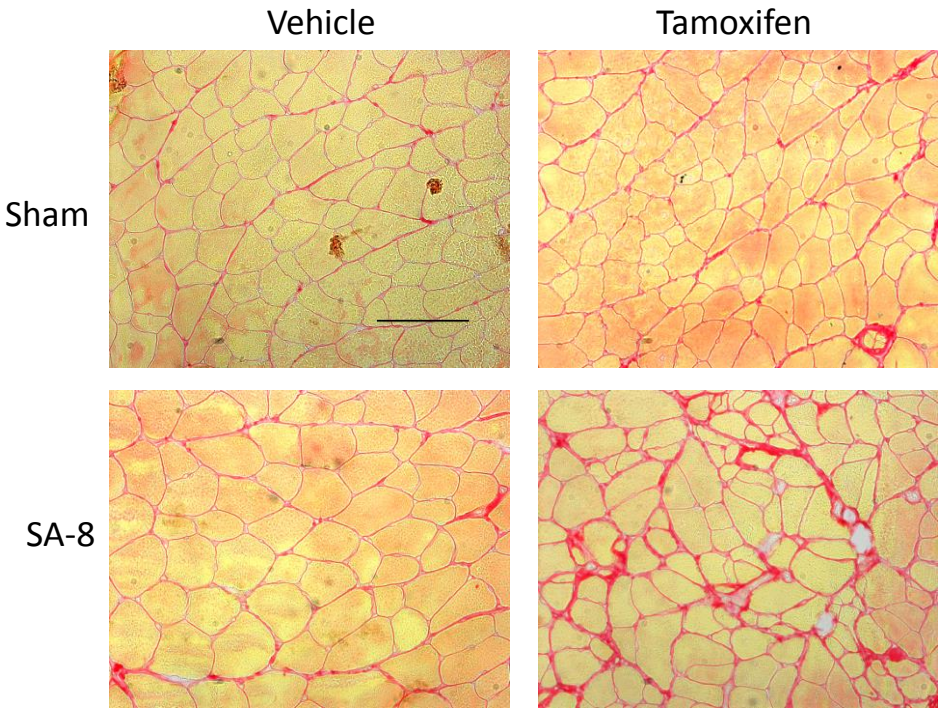
⇨ nucleus inside the fiber (myonucleus)

➡ nucleus outside fiber

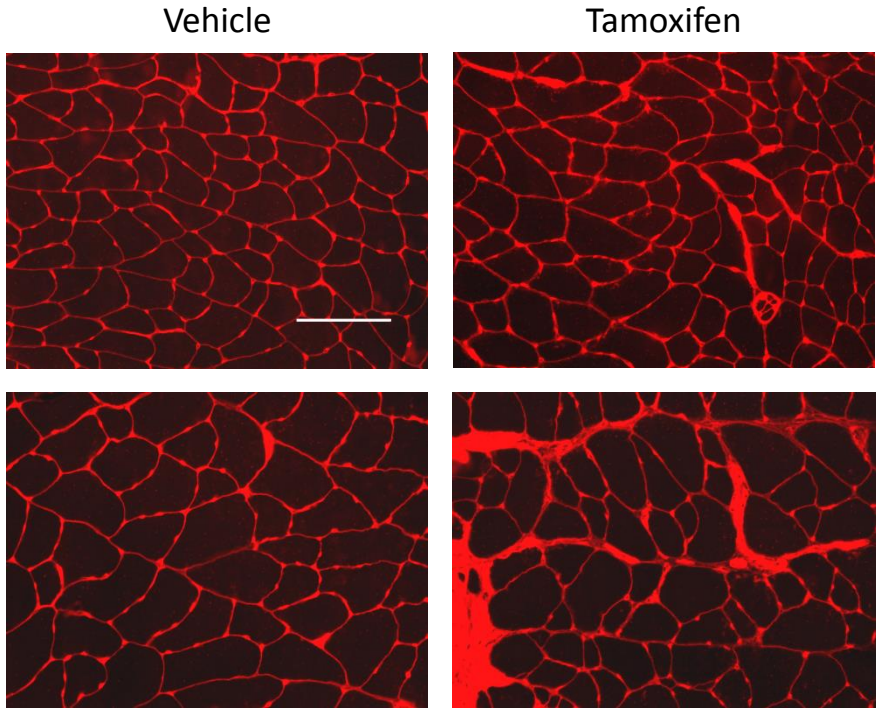
Muscle growth plateaus in the absence of satellite cell participation



Fry et al., FASEB J, 2014

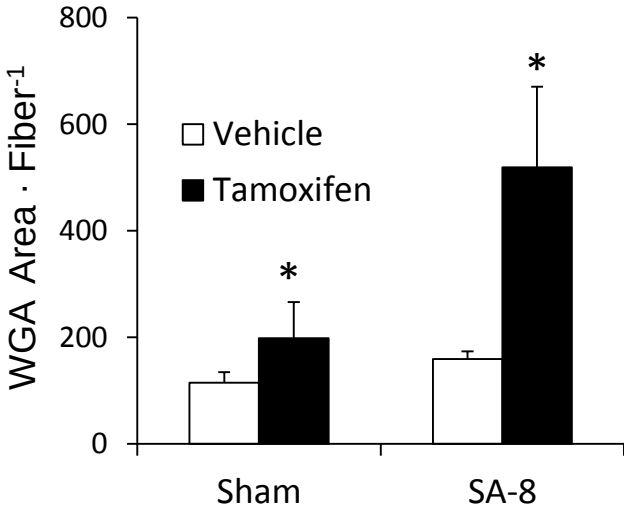


Collagen

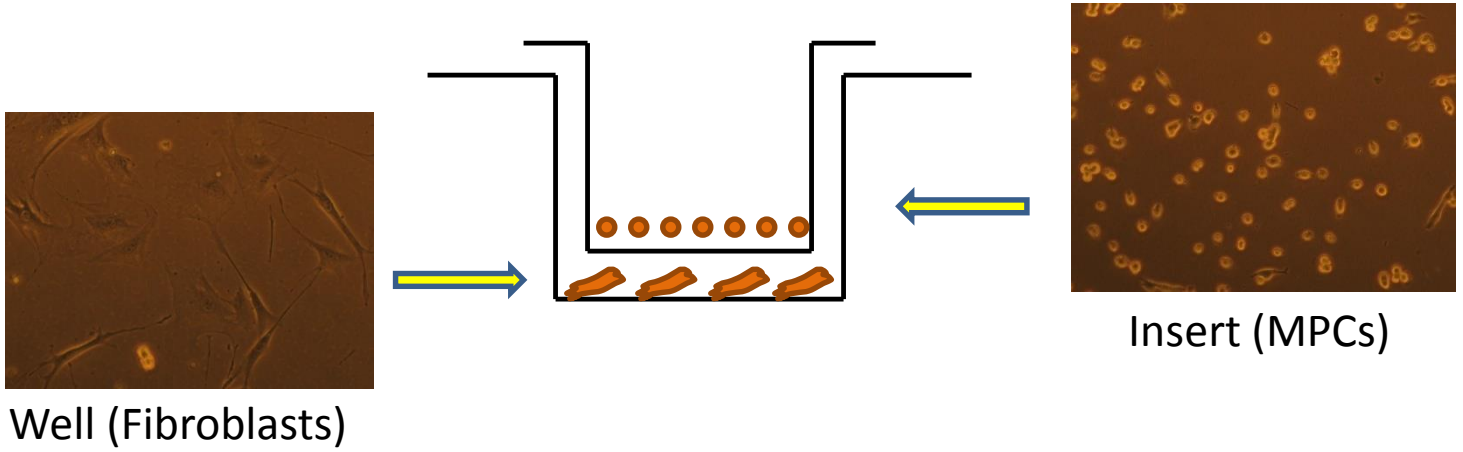


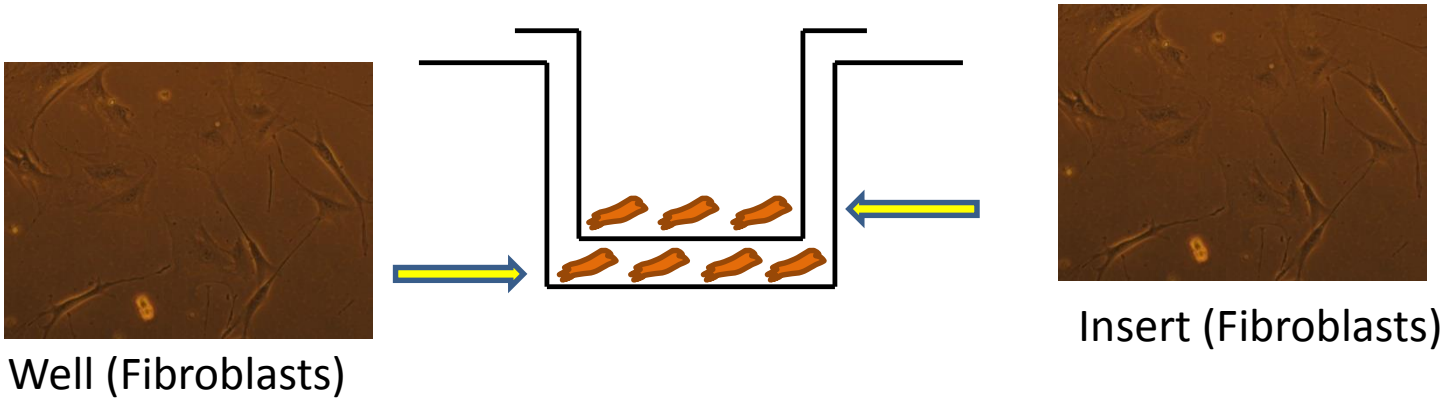
Glycoaminoglycans

ECM accumulation is increased in satellite cell-depleted muscle following 8 weeks of overload

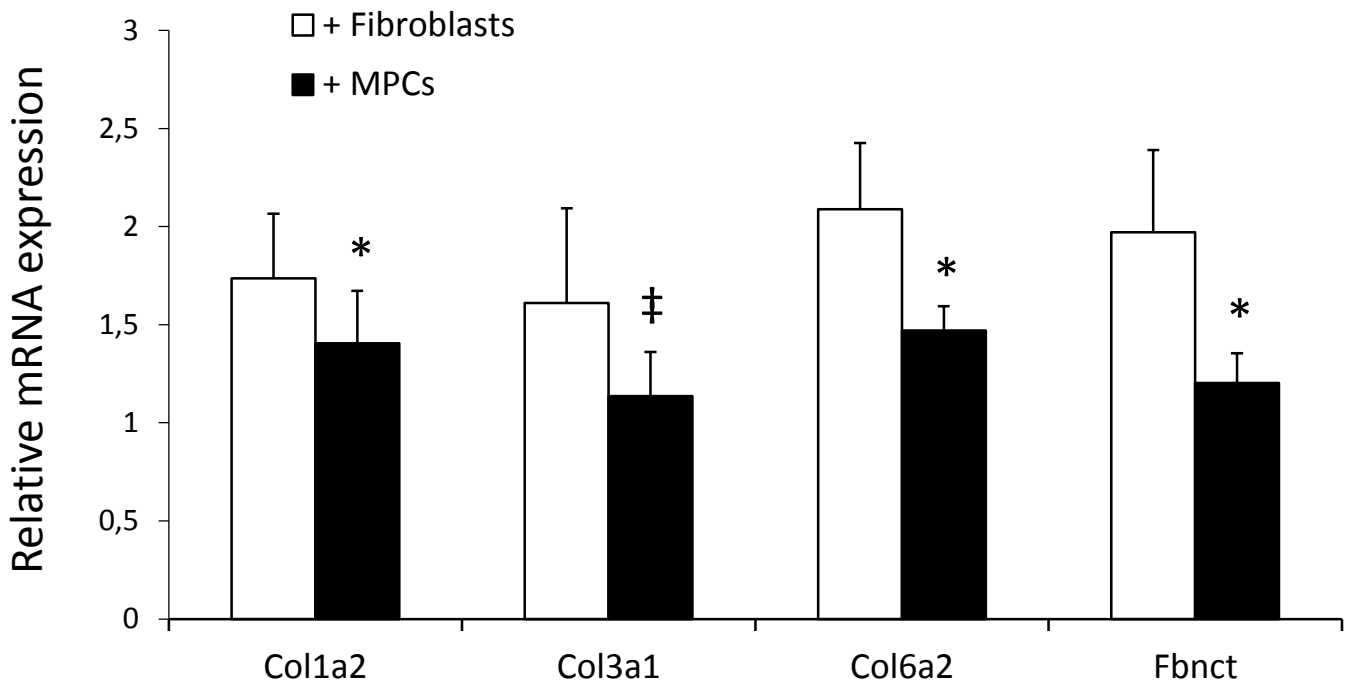


In vitro analysis of the myogenic progenitor cell (MPC)-fibroblast interaction



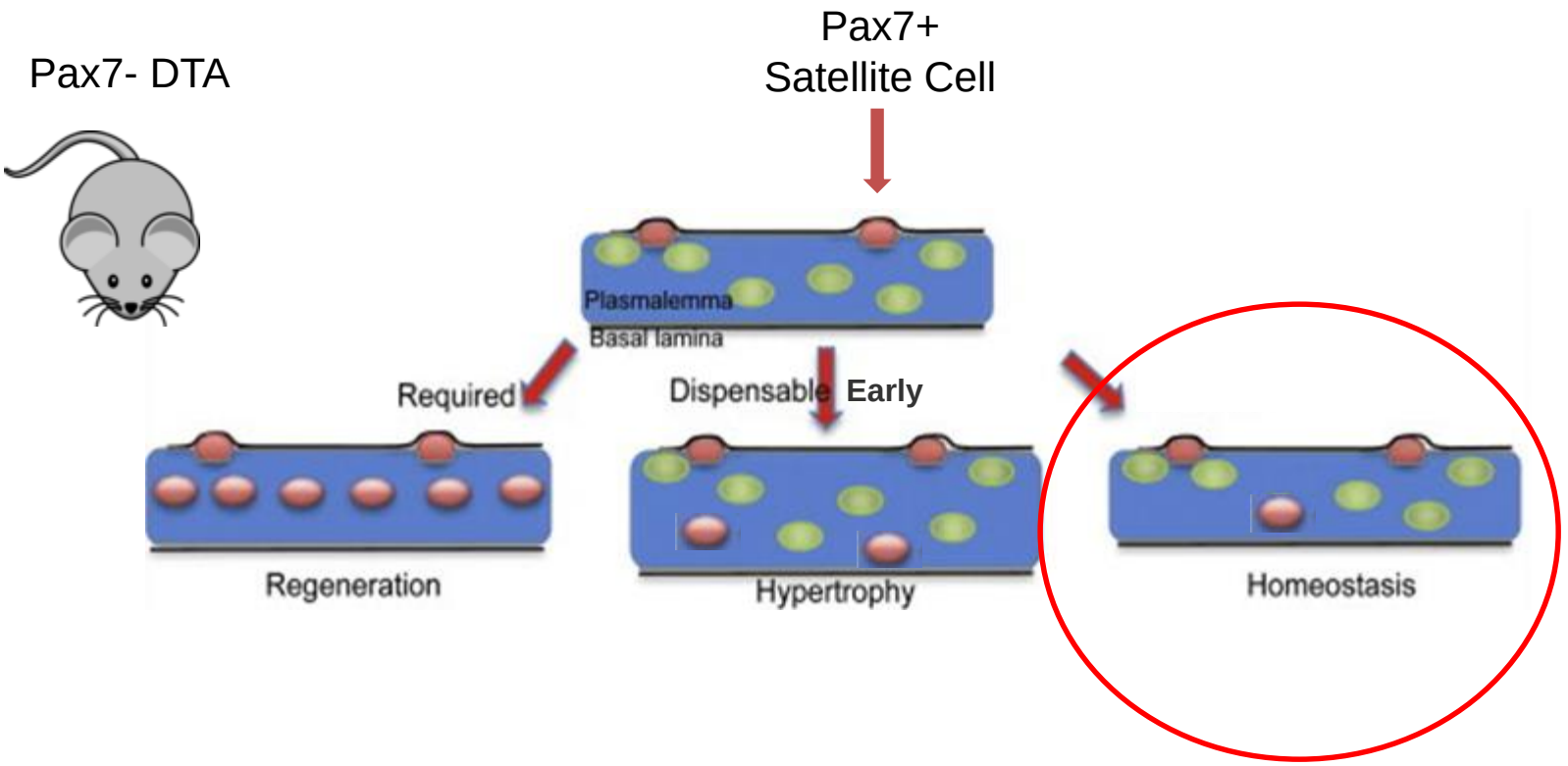


Activated satellite cell/MPC secretory products inhibit ECM gene expression in fibroblasts



Fry et al., Cell Stem Cell 2017

Do satellite cells play a role in normal muscle maintenance?



Brack & Rando, Cell Stem Cell 2012

Dogma: Loss of satellite cell activity causes sarcopenia

nature

Geriatric muscle stem cells switch reversible quiescence into senescence

Pedro Sousa-Victor[1]†, Susana Gutarra[1]*, Laura García-Prat[1]*, Javier Rodriguez-Ubreva[2], Laura Ortet[1], Vanessa Ruiz-Bonilla[1], Mercè Jardí[1], Esteban Ballestar[2], Susana González[3], Antonio L. Serrano[1], Eusebio Perdiguero[1] & Pura Muñoz-Cánoves[1,4]

nature medicine

p38 MAPK signaling underlies a cell-autonomous loss of stem cell self-renewal in skeletal muscle of aged mice

Jennifer D Bernet[1], Jason D Doles[1], John K Hall[1,2], Kathleen Kelly Tanaka[1], Thomas A Carter[1] & Bradley B Olwin[1]

Rejuvenation of the muscle stem cell population restores strength to injured aged muscles

Benjamin D Cosgrove[1], Penney M Gilbert[1,2], Ermelinda Porpiglia[1], Foteini Mourkioti[1], Steven P Lee[1], Stephane Y Corbel[1], Michael E Llewellyn[3], Scott L Delp[3,4] & Helen M Blau[1]

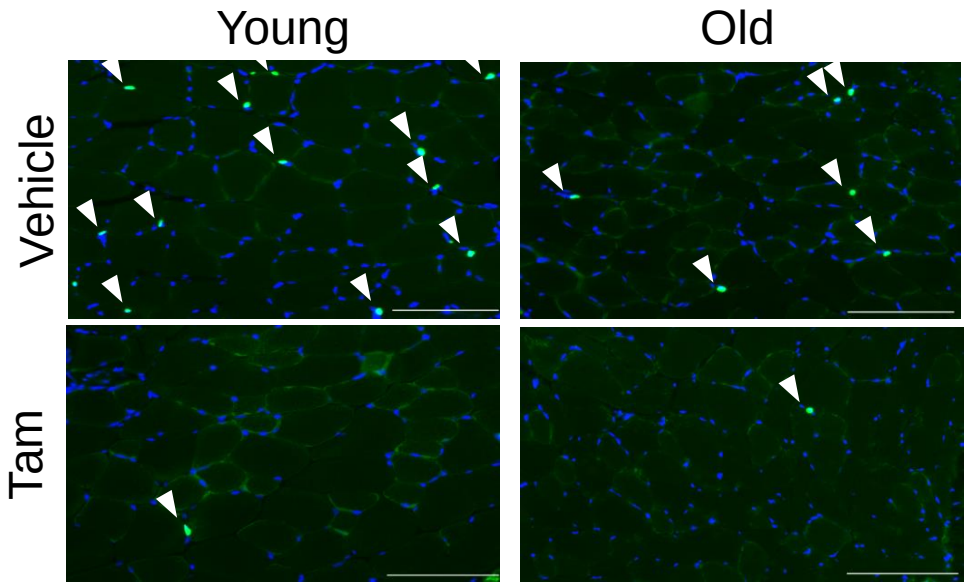
Satellite cell depletion as a premature muscle aging model?

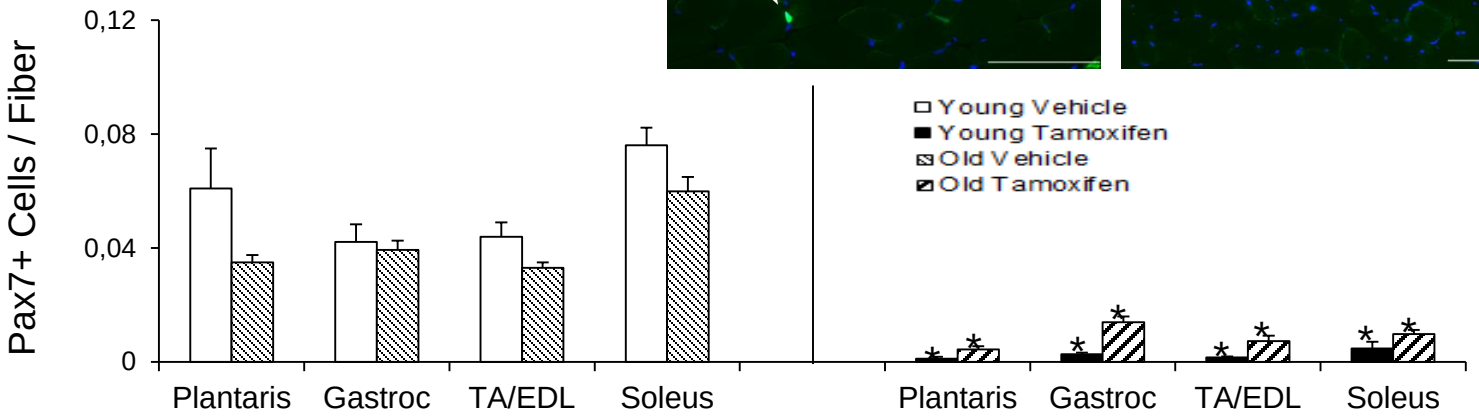
Tamoxifen/Vehicle
Pax7-DTA mouse

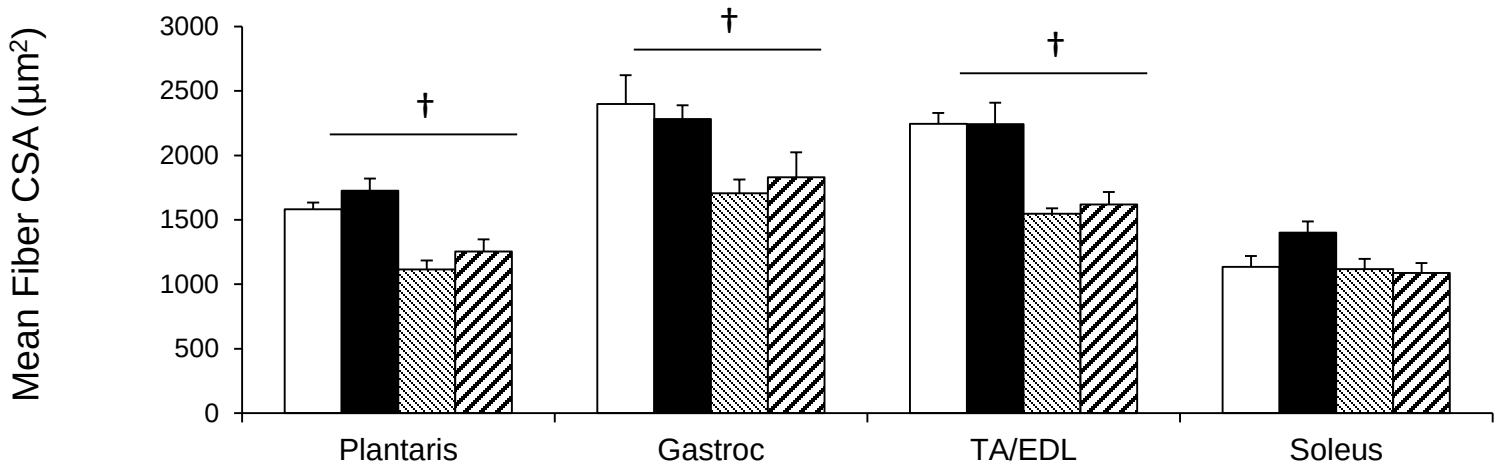
Muscle collected from:

5-month olds - 1 month of satellite cell depletion (**young**)
24-month olds - 20 months of satellite cell depletion (**old**)

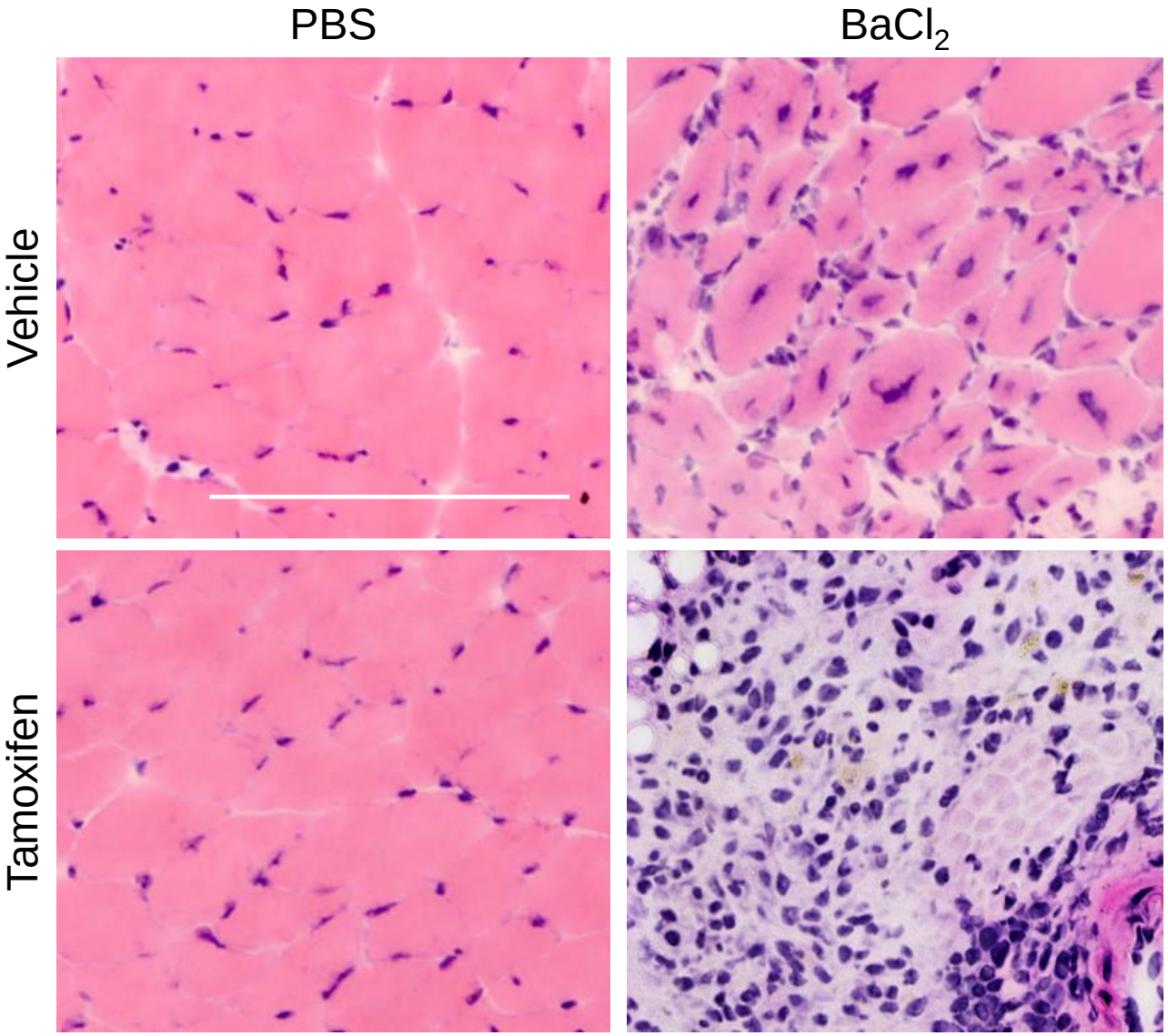
Long term satellite cell depletion does not exacerbate sarcopenia





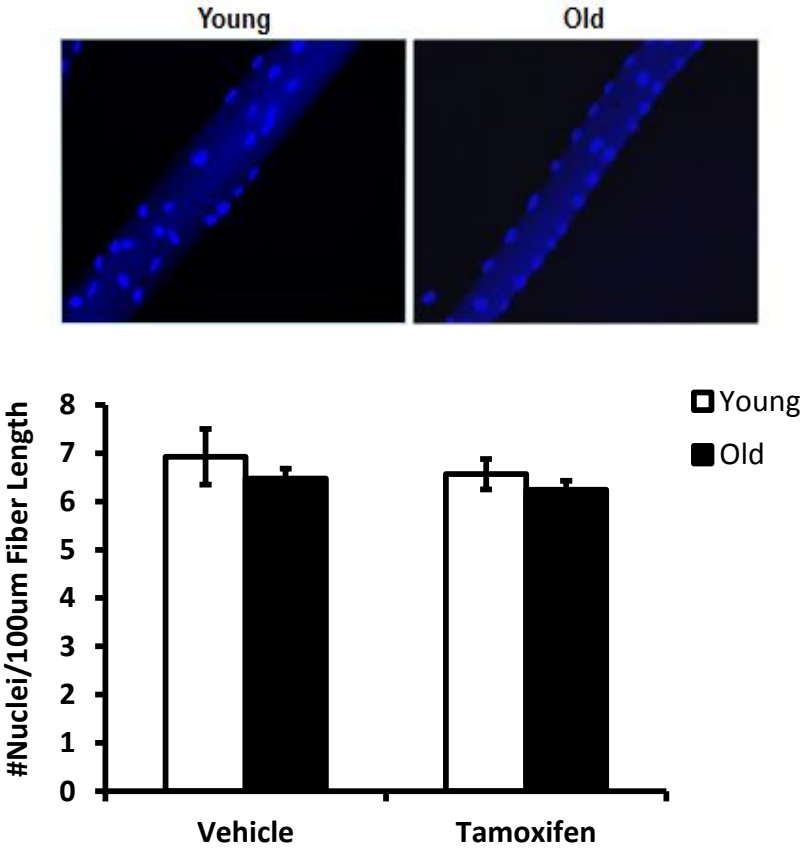


Satellite cell-depleted aged muscle does not regenerate

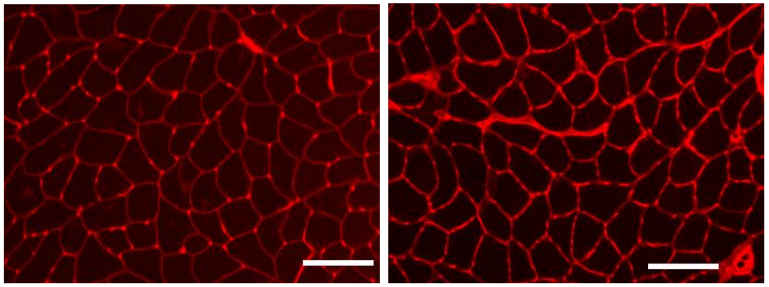


Fry et al., Nature Medicine, 2016

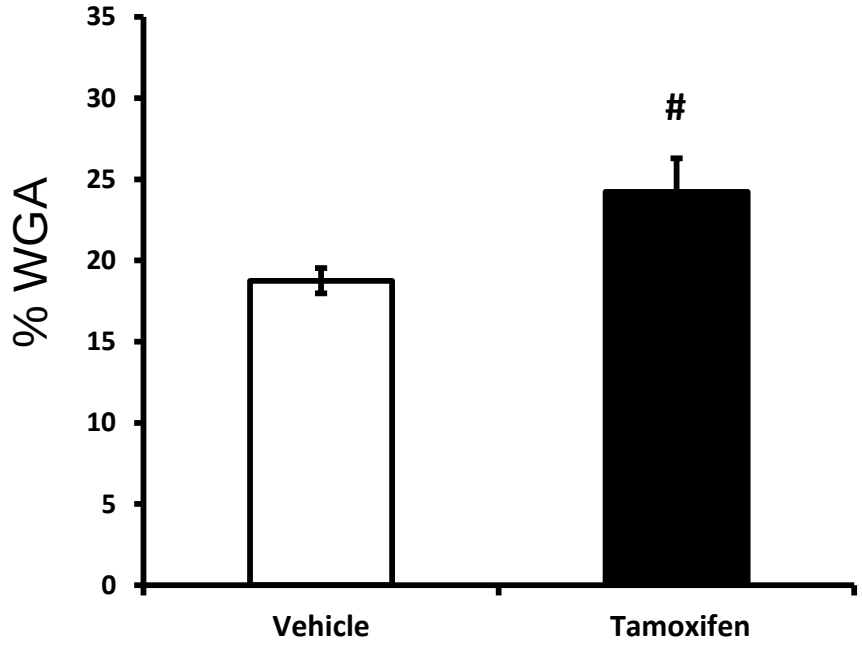
Myonuclear number is not altered in satellite cell-depleted muscle



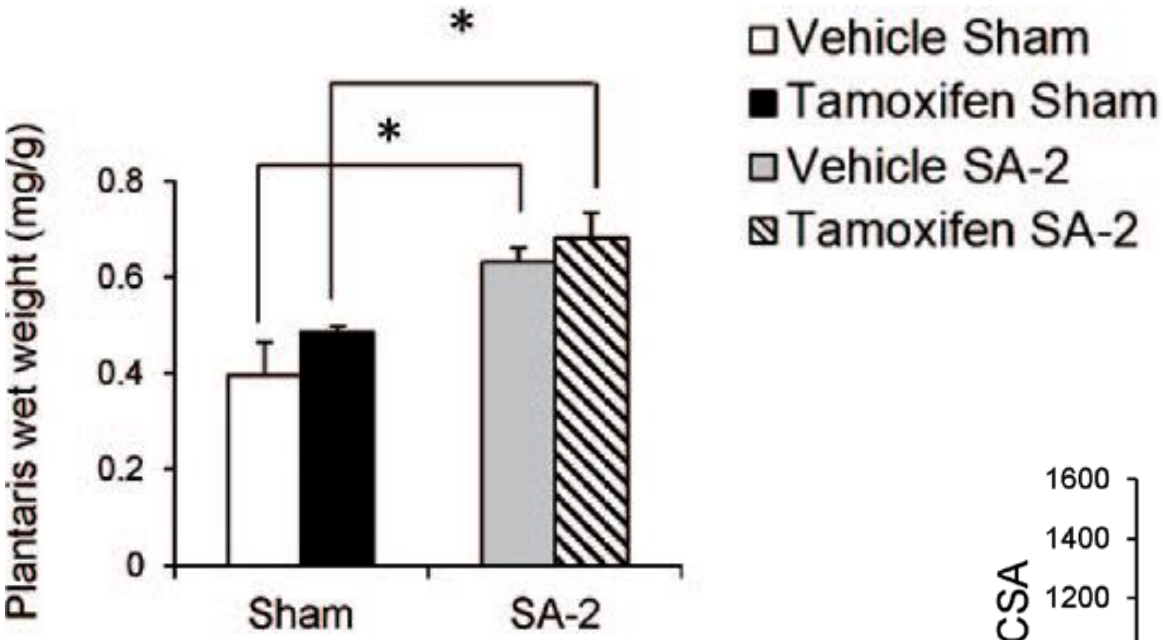
Increased fibrosis in lifelong satellite cell-depleted muscle

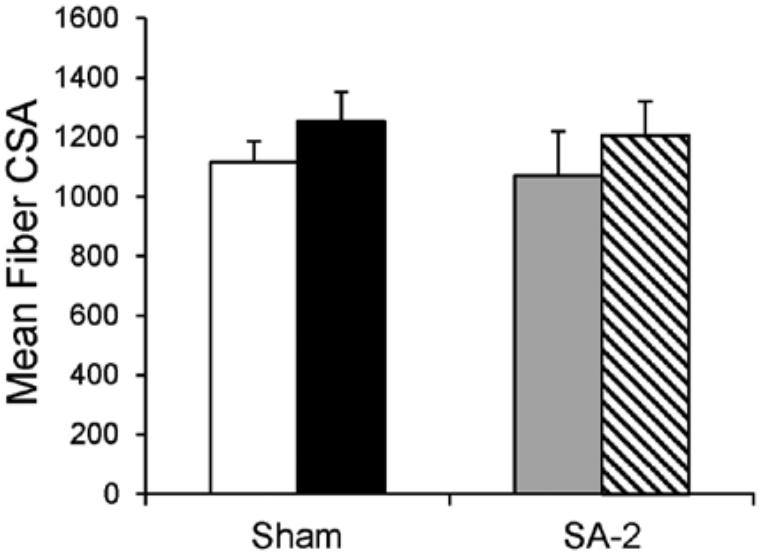


Vehicle Tamoxifen



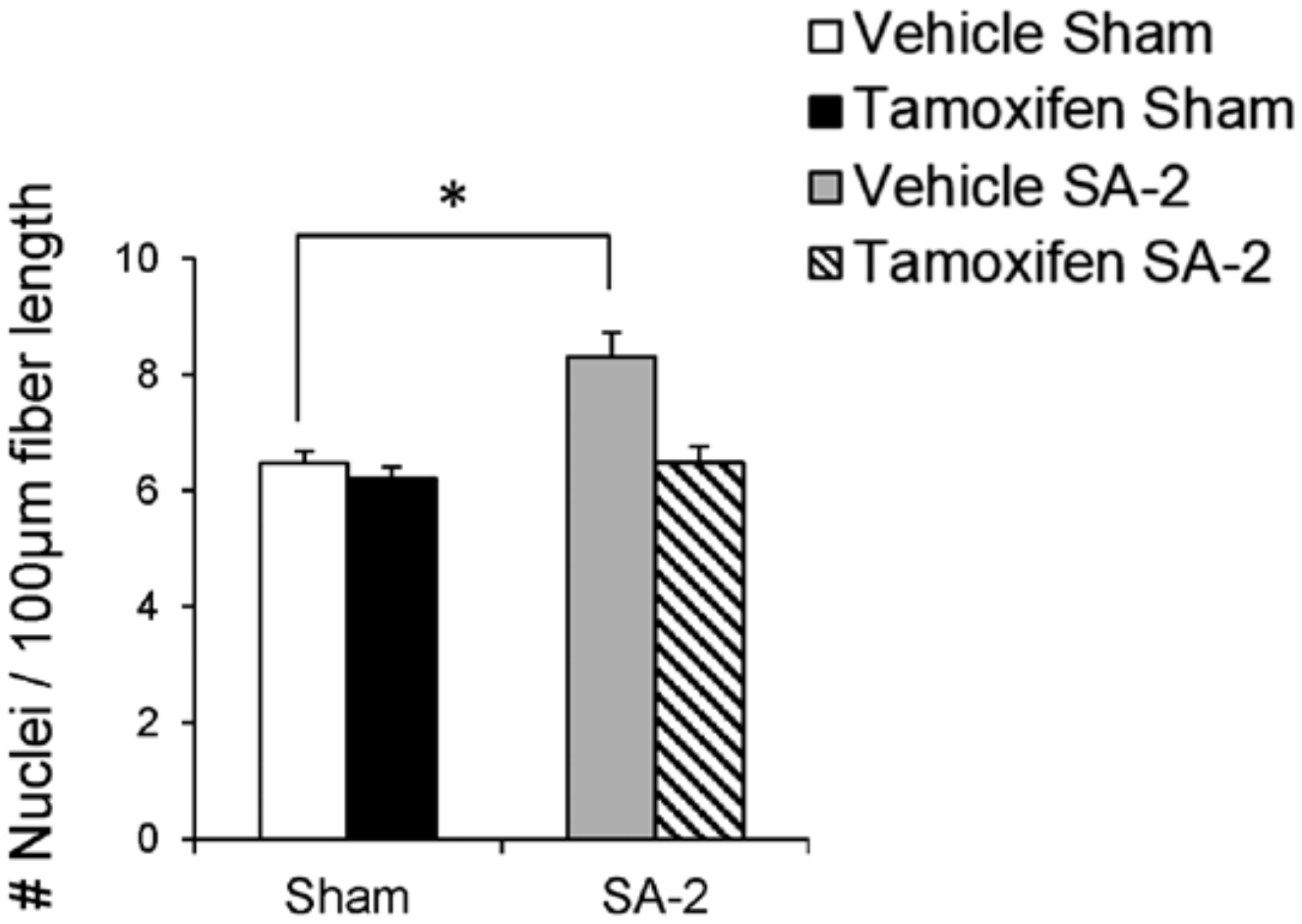
Growth in response to overload is impaired in aged mice regardless of satellite cell content





Lee et al., J. Gerontol., 2016

Myonuclear accretion does not drive myofiber growth in aged muscle



Conclusions

- Muscle regeneration, maintenance and hypertrophy have different satellite cell requirements.

- Satellite cell-depleted muscle becomes fibrotic over time which may limit long term growth.

- Satellite cells repress ECM production by fibroblasts which may facilitate muscle remodeling.

- Depletion of satellite cells in adult mice impairs muscle regenerative capacity without affecting sarcopenia.

- Satellite cell loss with age may contribute to muscle fibrosis, limiting muscle adaptability.

- Satellite cell fusion and myonuclear accretion are insufficient to drive myofiber growth in aged muscle.

Take Home Messages

- Compensatory mechanisms exist in the adult mouse that enable muscle maintenance and adaptation independent of satellite cells.

- In addition to therapeutic potential of satellite cells in treating degenerative muscle diseases by promoting regeneration, satellite cells may be useful in reducing fibrosis associated with aging, independent of their ability to contribute nuclei to myofibers.

College of Health Sciences

Acknowledgements

UNIVERSITY OF KENTUCKY CENTER FOR MUSCLE BIOLOGY

Christopher Fry
Tyler Kirby
Jonah Lee
Jyothi Mula
Janna Jackson
Sarah White

Grace Walton
Kate Kosmac
Kevin Murach
Cory Dungan
Ivan Vechetti
Vandre Casagrande-Figueiredo
Bailey Peck
Davis Englund
Yuan Wen

John McCarthy
Esther Dupont-Versteegden

Undergrads:
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Jake Beggs
Kelcye Garrison
Clyde Dean
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Rod Erfani

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Abigail Troske
Sam Crow
Bailee Taylor
Kaitlyn Frick
Ashley Bayes

NIH National Institute of Arthritis and Musculoskeletal and Skin Diseases

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