

Nutrient Sensing in Hospitalized Older Adults with Immobility

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Disclosures

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Hospitalized Older Adults with Immobility



Immobilization-Induced Skeletal Muscle Atrophy

Acute Illness or Injury



Immobility



**Muscle
Atrophy**



Immobilization-Induced Skeletal Muscle Atrophy



Acute Illness or Injury



Immobility

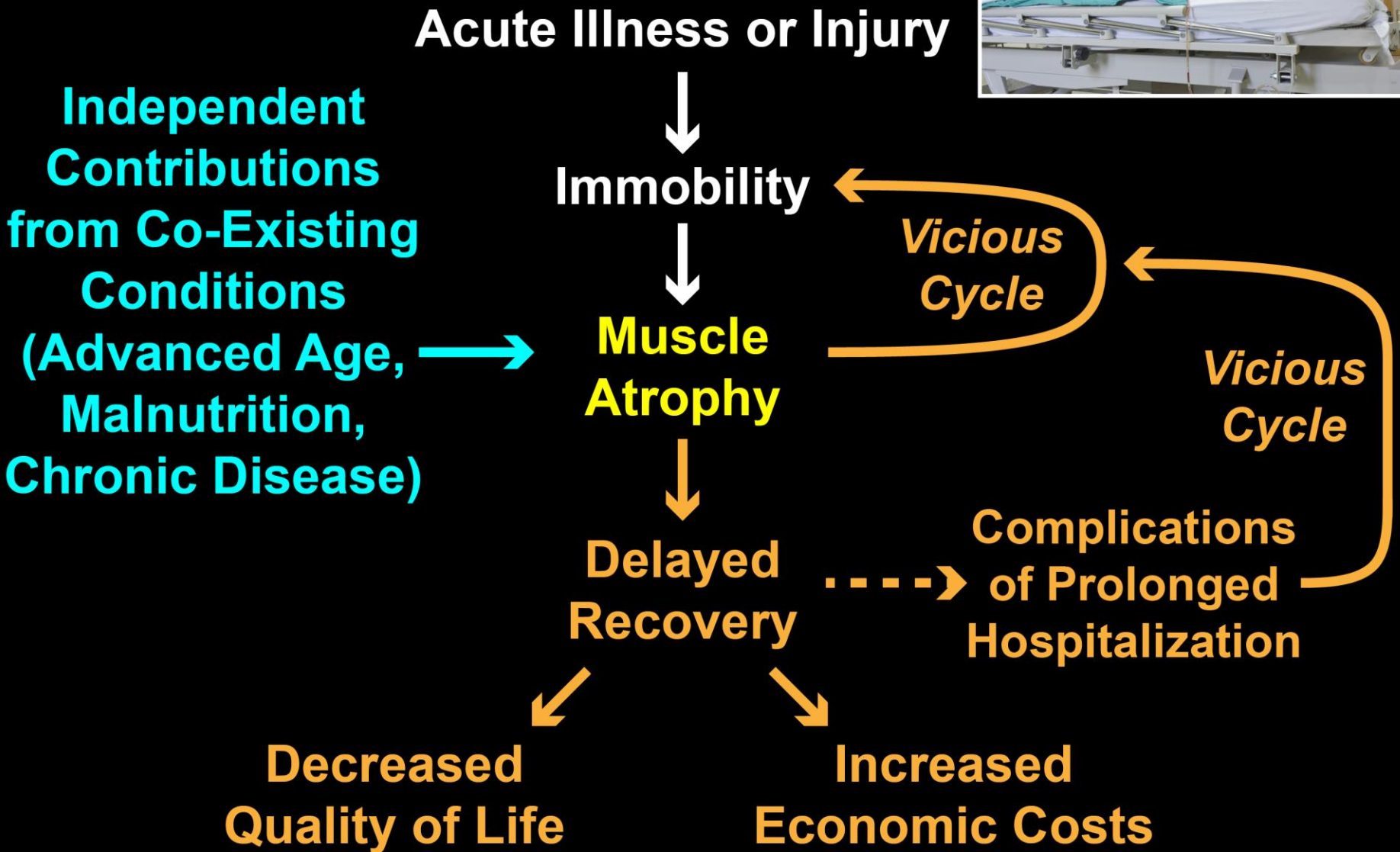


Muscle Atrophy

Independent Contributions from Co-Existing Conditions (Advanced Age, Malnutrition, Chronic Disease)



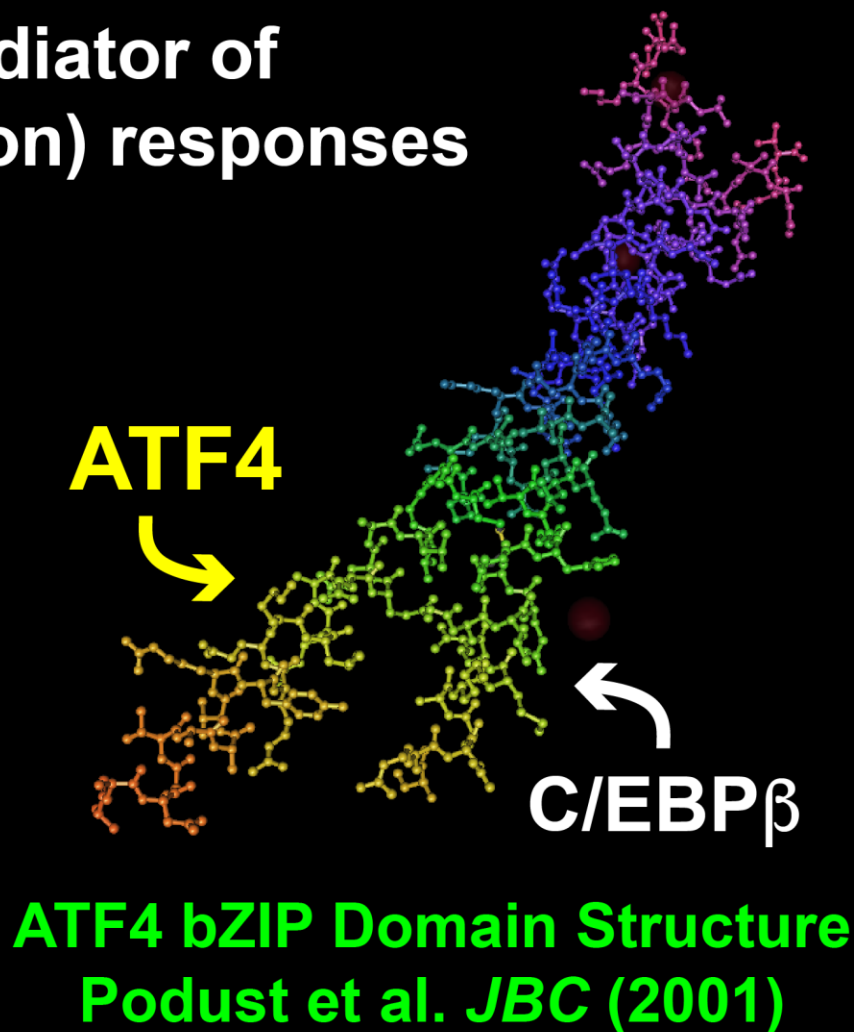
Immobilization-Induced Skeletal Muscle Atrophy



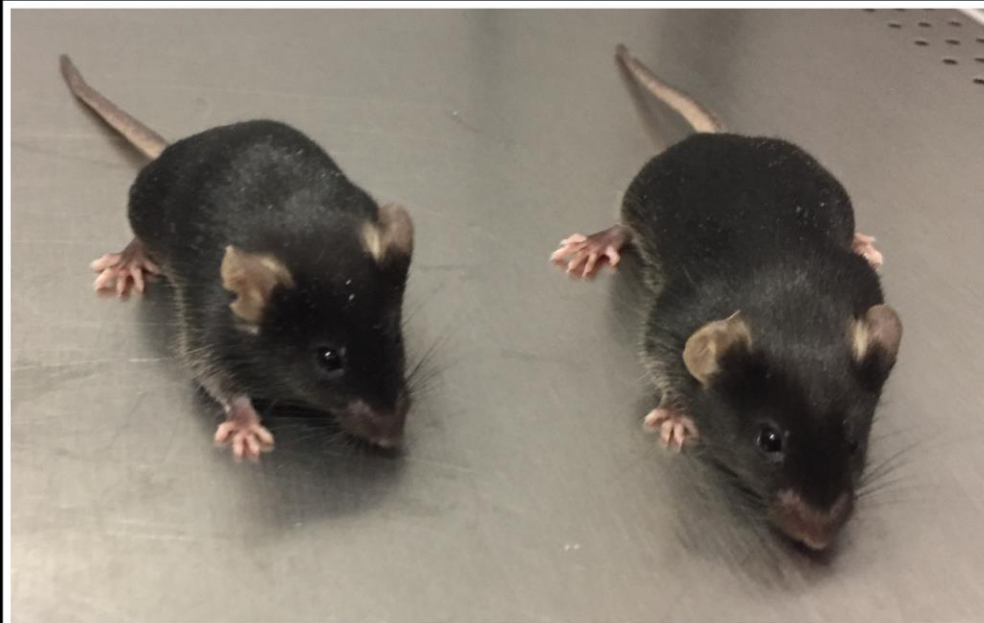
ATF4

(Activating Transcription Factor 4)

- Evolutionarily ancient mediator of nutrient sensing (starvation) responses
- Stress-inducible subunit of several different bZIP transcription factors
- Had an unknown role in skeletal muscle but ATF4 expression in muscle correlated with muscle atrophy



Muscle-Specific ATF4 Knockout Mice (ATF4 mKO Mice)

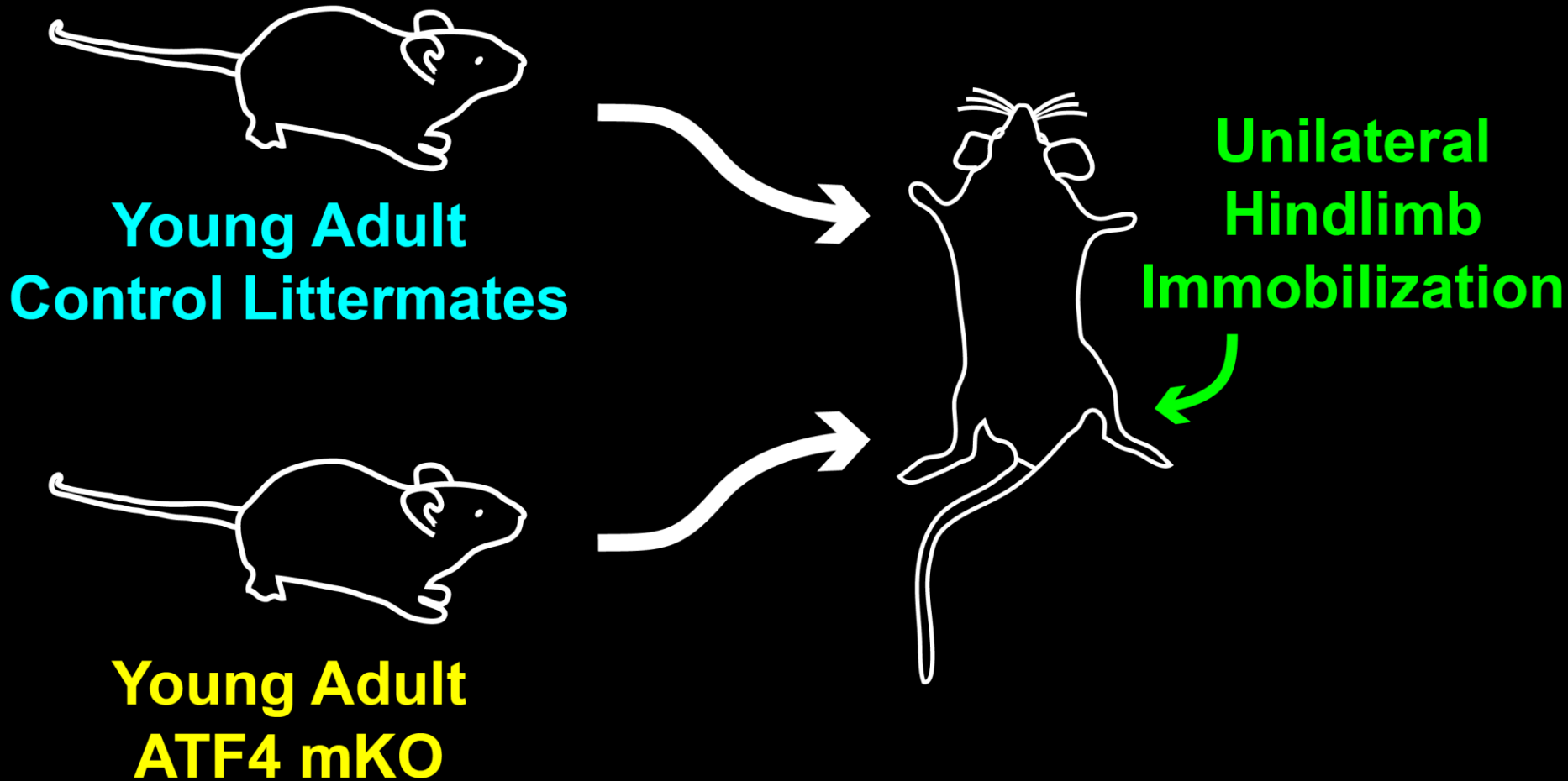


**Control
Littermate
(ATF4^{f/f})**

**ATF4 mKO
(ATF4^{f/f} ;
MCK-Cre)**

- Lifelong absence of ATF4 in skeletal muscle fibers
- Develop normally and exhibit no basal phenotype into middle-age

Is ATF4 Required for Immobilization-Induced Skeletal Muscle Atrophy?



Targeted Reduction in ATF4 Reduces Immobilization-Induced Muscle Atrophy

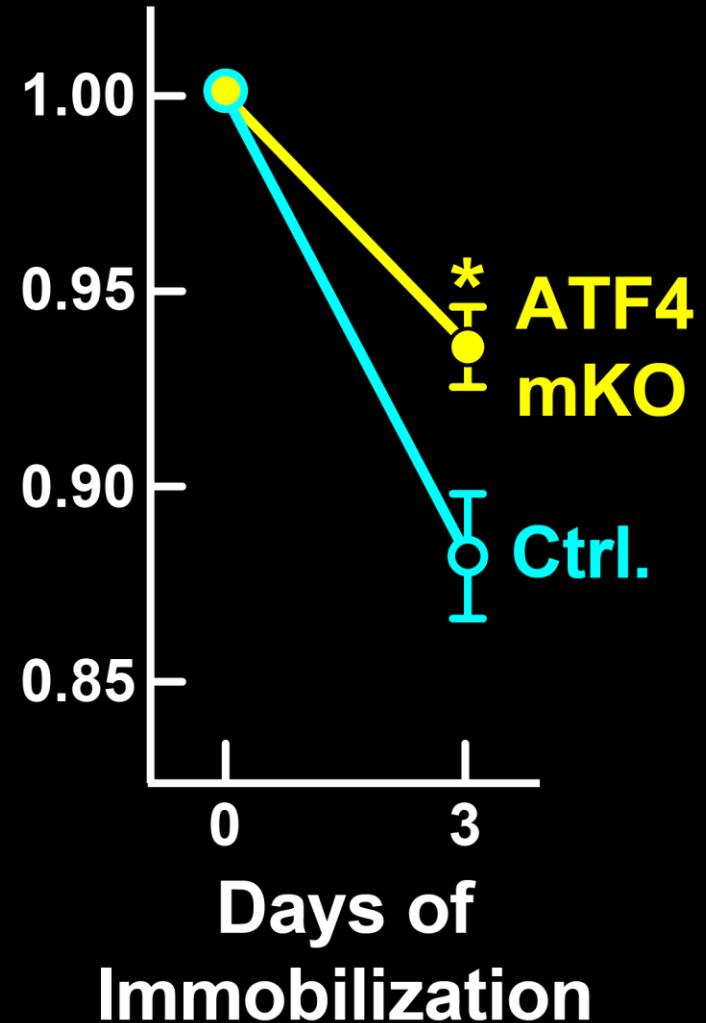


**Young Adult
Control Littermates**

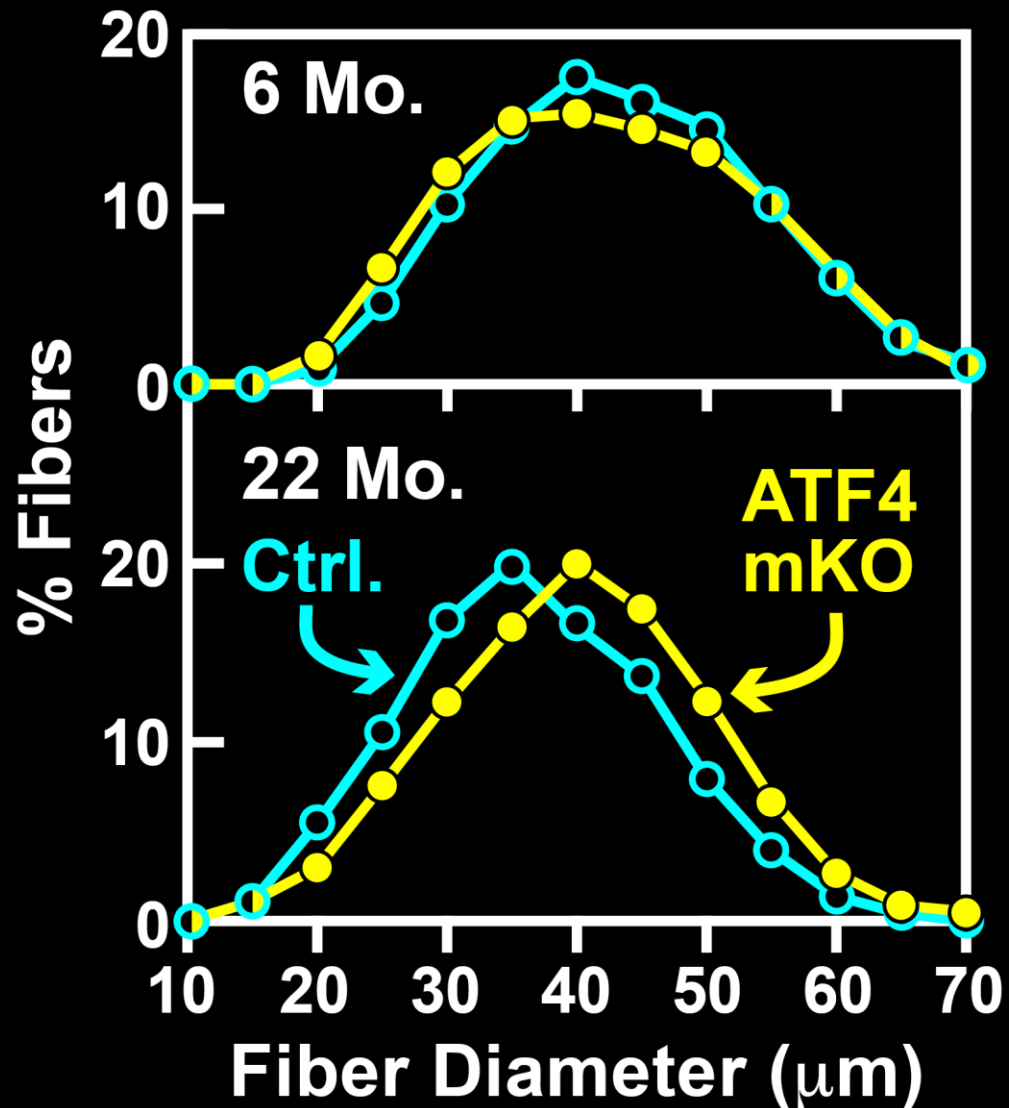
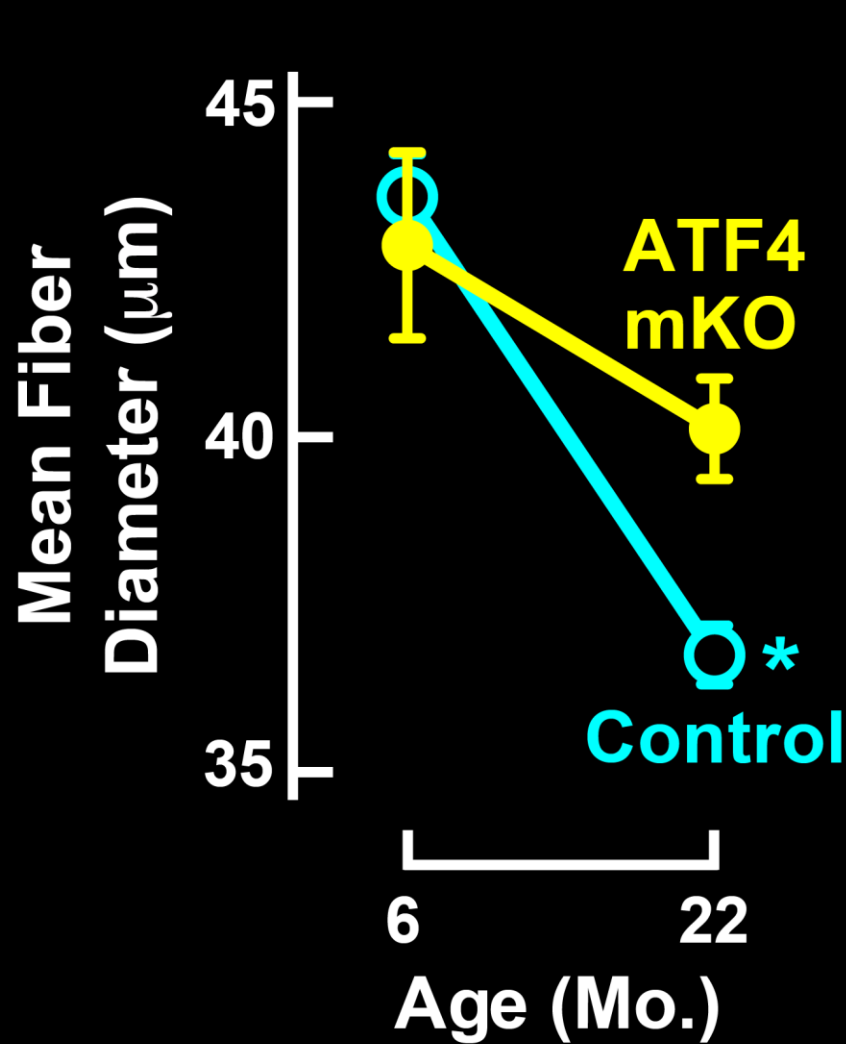


**Young Adult
ATF4 mKO**

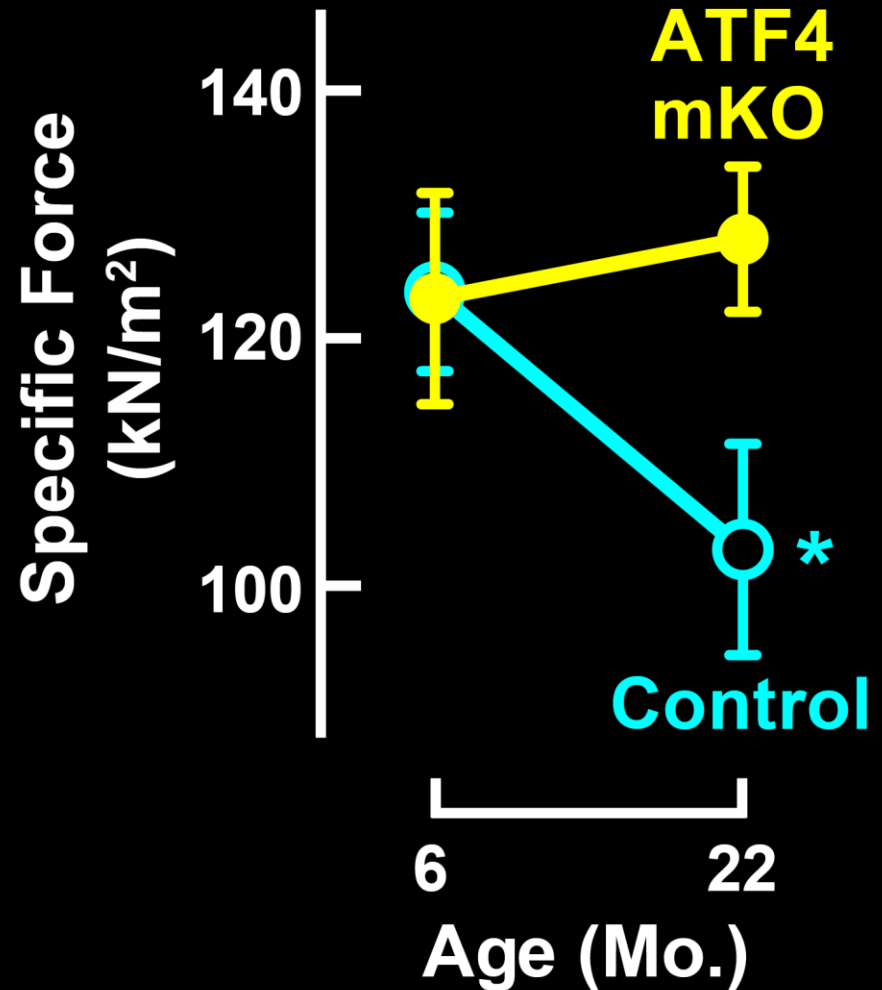
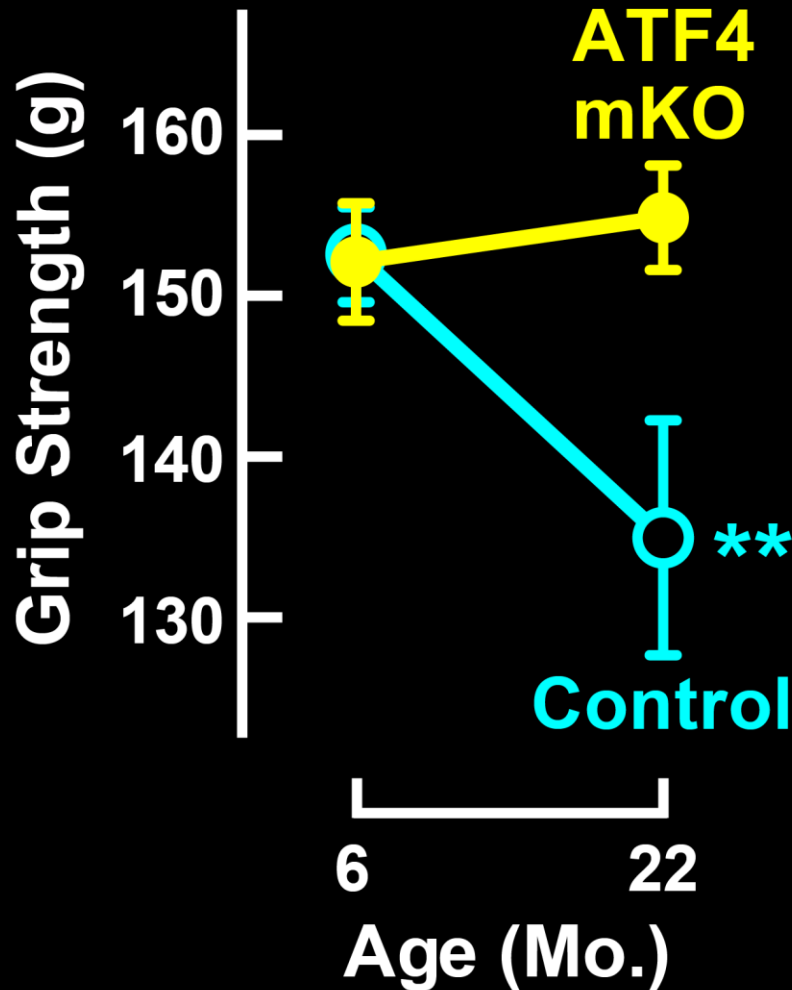
**Muscle
Fiber
Diameter
(Immobile:
Mobile)**



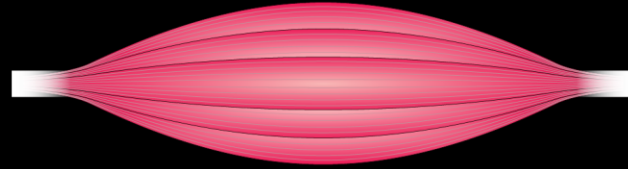
Targeted Reduction in ATF4 Reduces Age-Related Muscle Atrophy



ATF4 Is Required for Loss of Strength & Muscle Quality During Aging



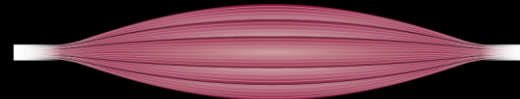
Healthy Skeletal Muscle



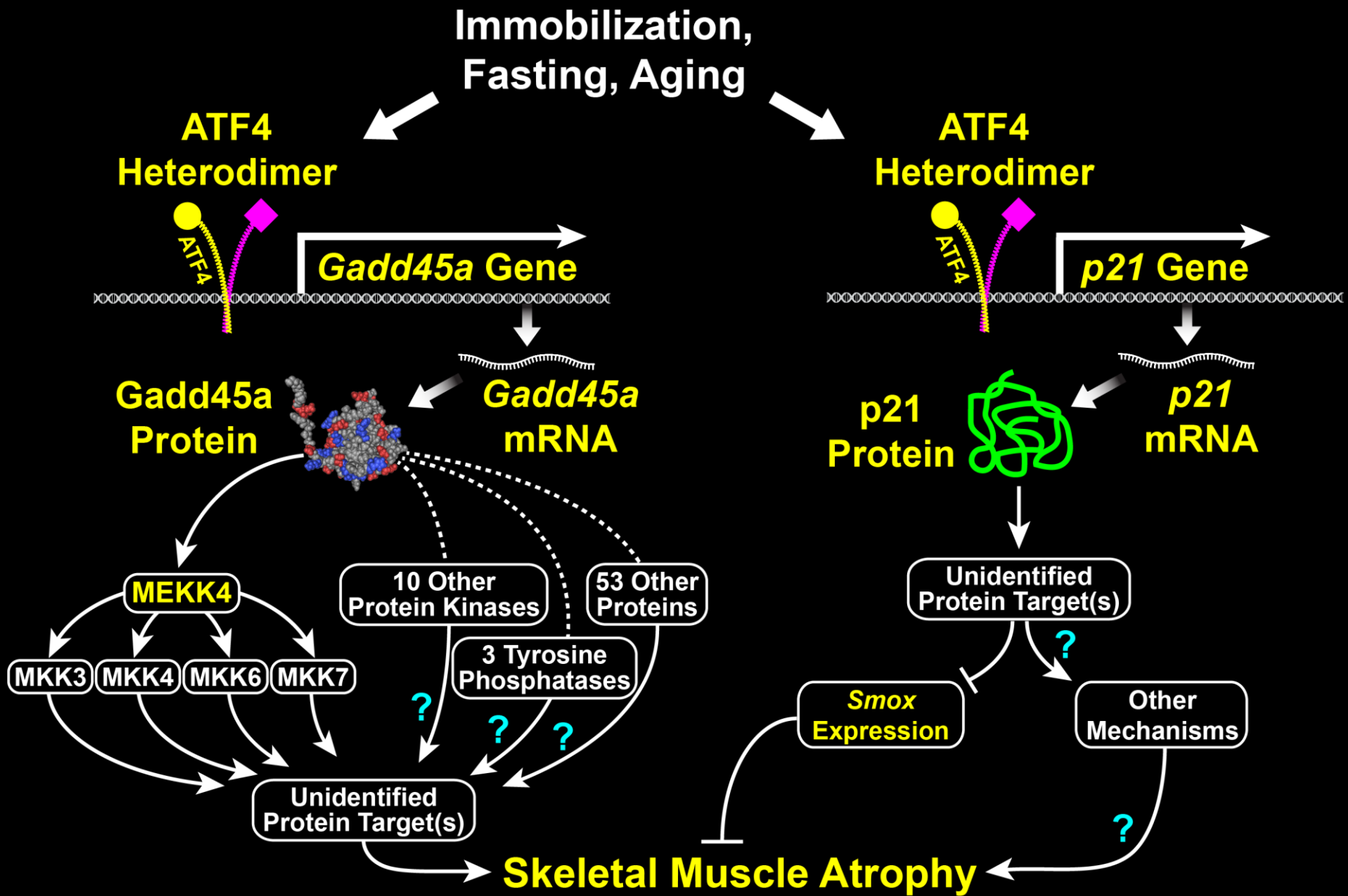
Immobilization
Fasting
Aging



ATF4-Dependent
Gene Expression
in Muscle Fibers

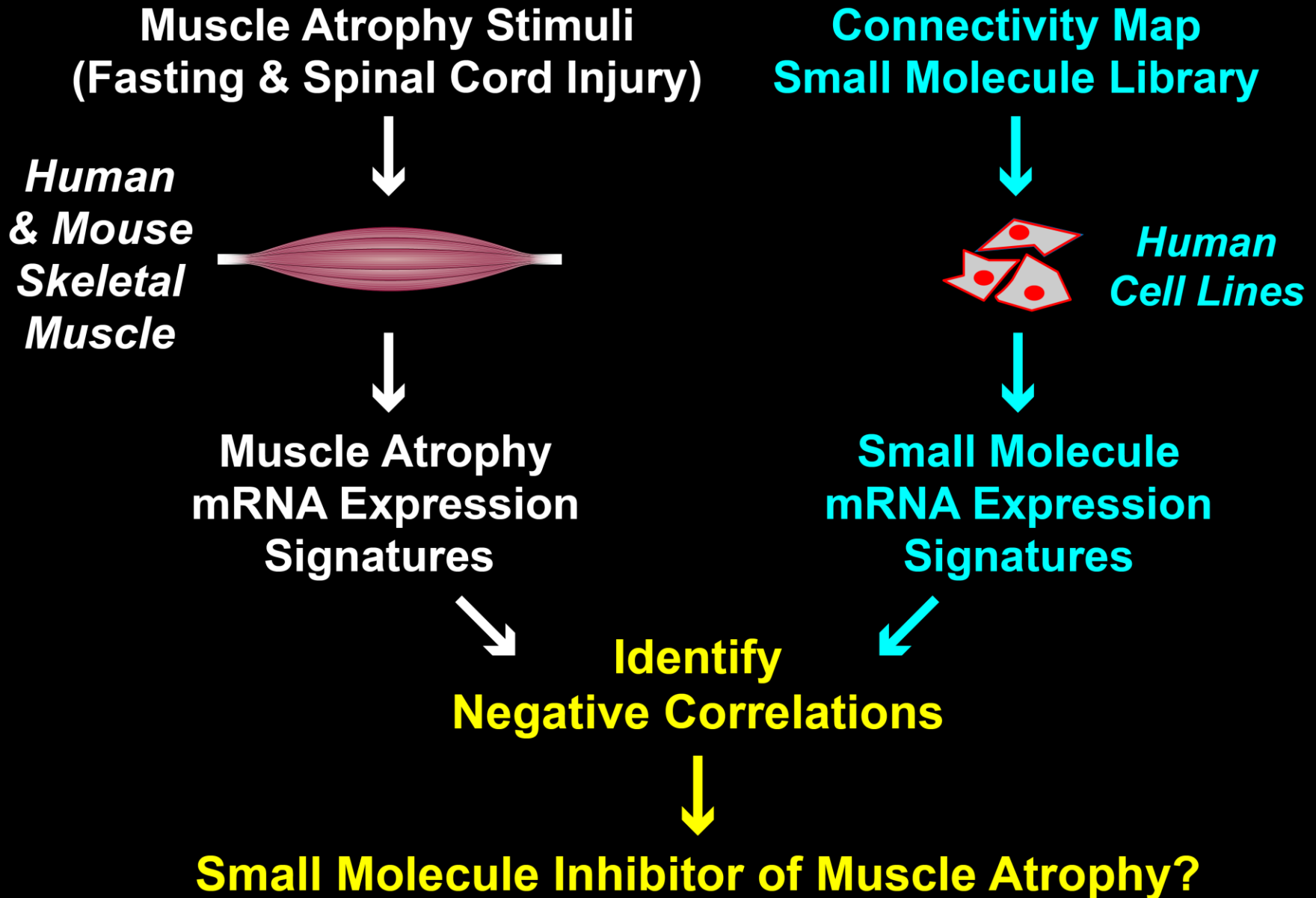


Muscle Weakness and Atrophy

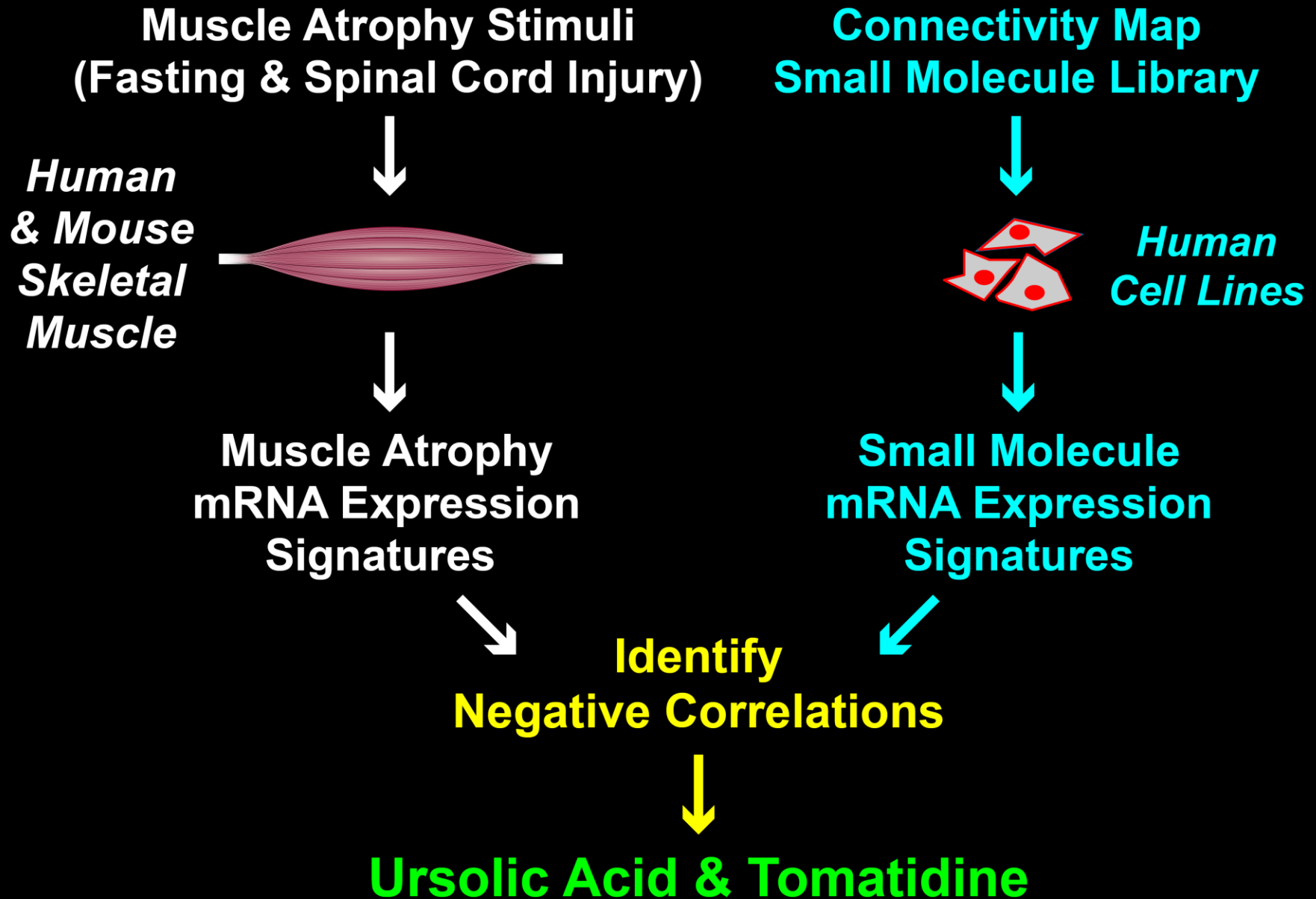


Ebert et al. *Mol. Endocrinol.* (2010), Ebert et al. *JBC* (2012), Fox et al. *AJP-Endo* (2014), Bongers et al. *AJP-Endo* (2015), Ebert et al. *JBC* (2015), Bullard et al. *JBC* (2016)

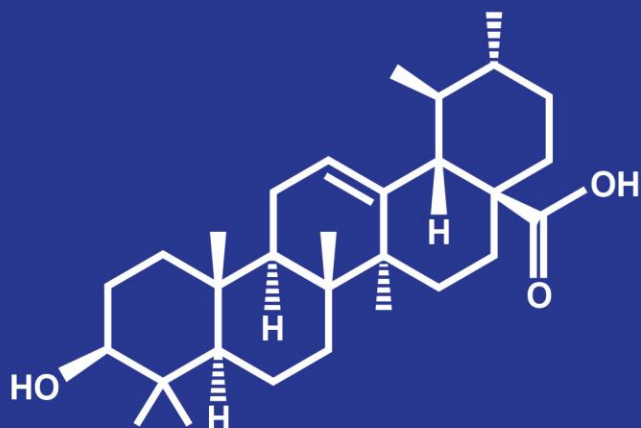
Systems-Based Discovery Strategy



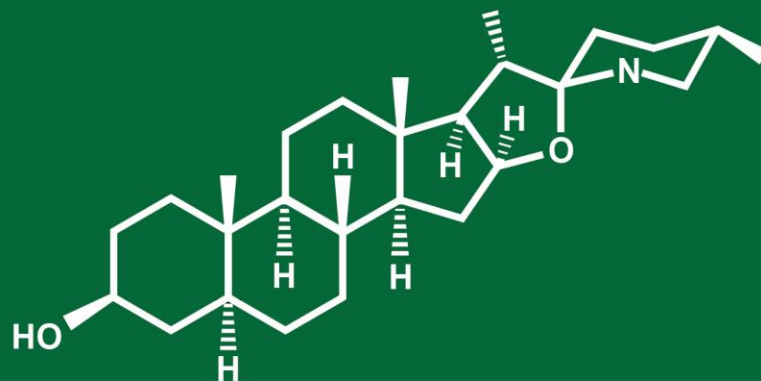
Systems-Based Discovery Strategy



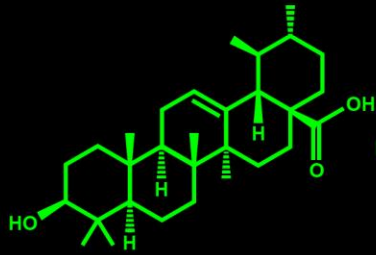
Ursolic Acid



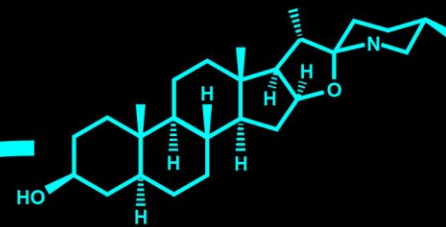
Tomatidine



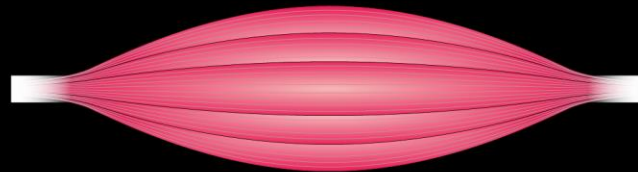
Ursolic Acid



Tomatidine



Inhibition of ATF4 & Other Atrophy Pathways



Decreased Muscle Atrophy & Weakness During Immobilization, Aging & Other Stress Conditions

Kunkel et al. *Cell Metabolism* (2011), Kunkel et al. *PLOS One* (2012),
Dyle et al. *JBC* (2014), Ebert et al. *JBC* (2015)



**Natural Dietary Compounds
(Ursolic Acid & Tomatidine)**



**Dietary Supplements & Functional Foods
to Improve Nutrition During Aging,
Chronic Illness, Hospitalization and Rehabilitation**





**Natural Dietary Compounds
(Ursolic Acid & Tomatidine)**

**Nutrition Products
for Muscle Health
& Wellness**

**Search for Novel Analogs
with Improved
Pharmacologic Properties**

Summary



- **In hospitalized older adults with immobility, ATF4-dependent gene expression in muscle fibers may be a cause of muscle atrophy & weakness.**
- **Ursolic acid, tomatidine & related small molecules could potentially benefit hospitalized older adults with immobility.**

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Metabolic Health

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Turning Discovery Into Health



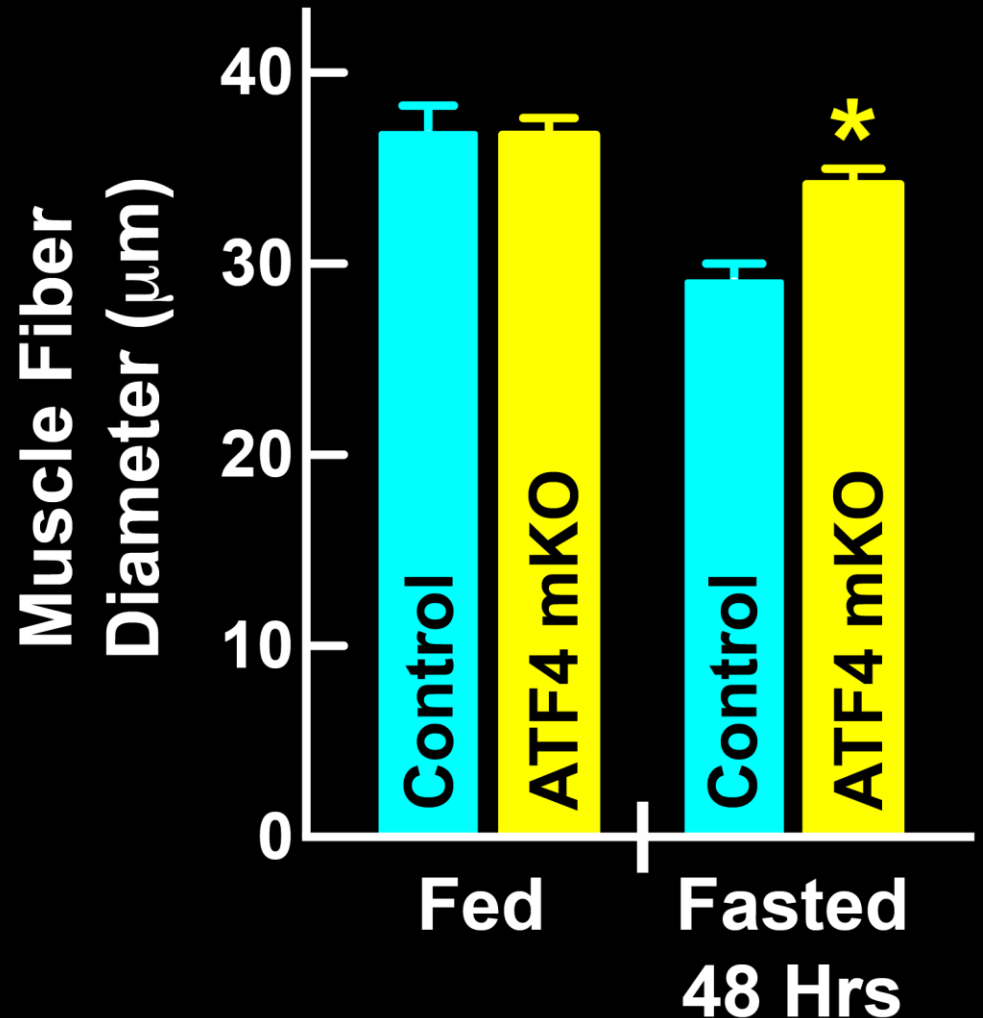
Targeted Reduction in ATF4 Decreases Fasting-Induced Muscle Atrophy



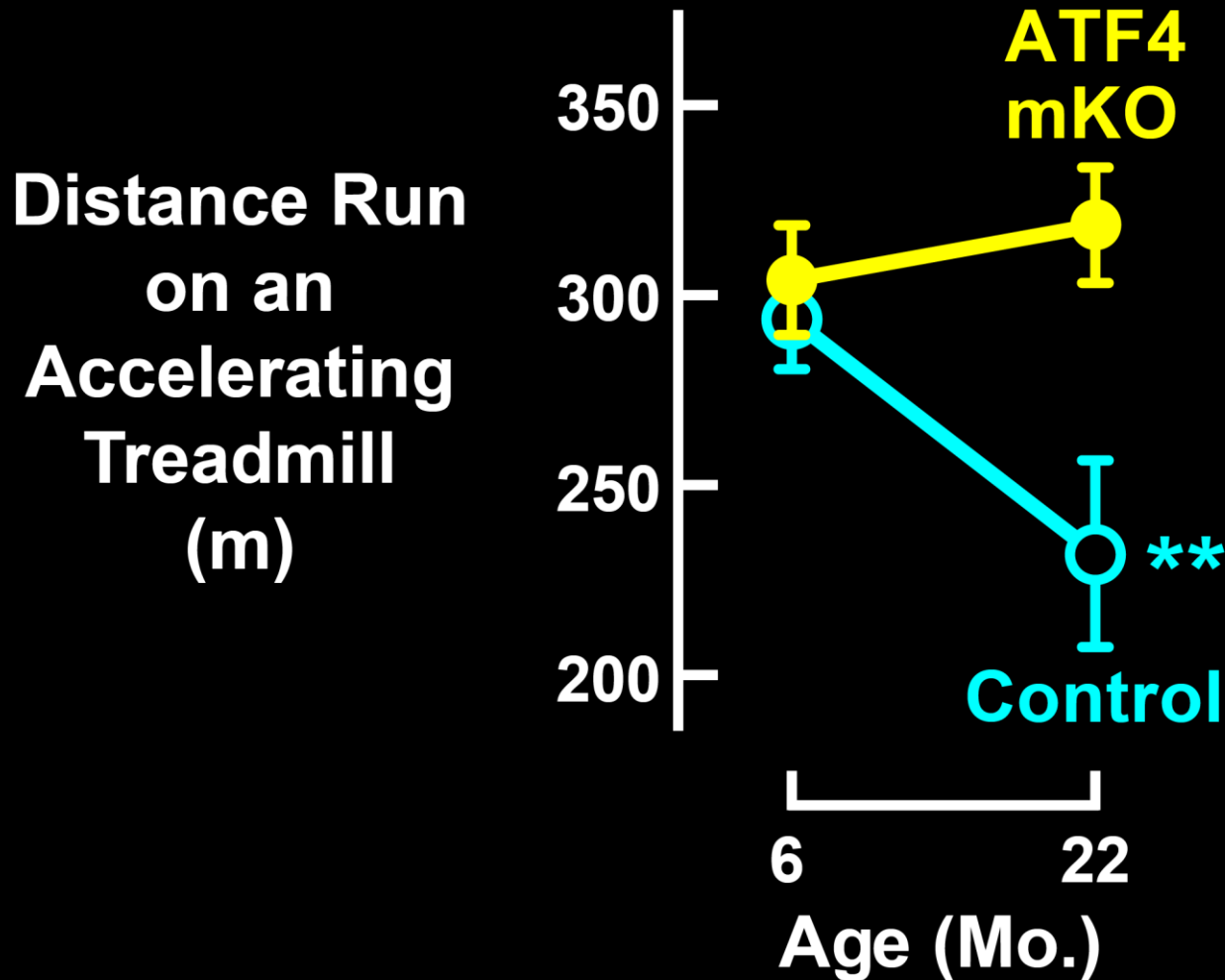
Young Adult
Littermate Controls



Young Adult
ATF4 mKO Mice

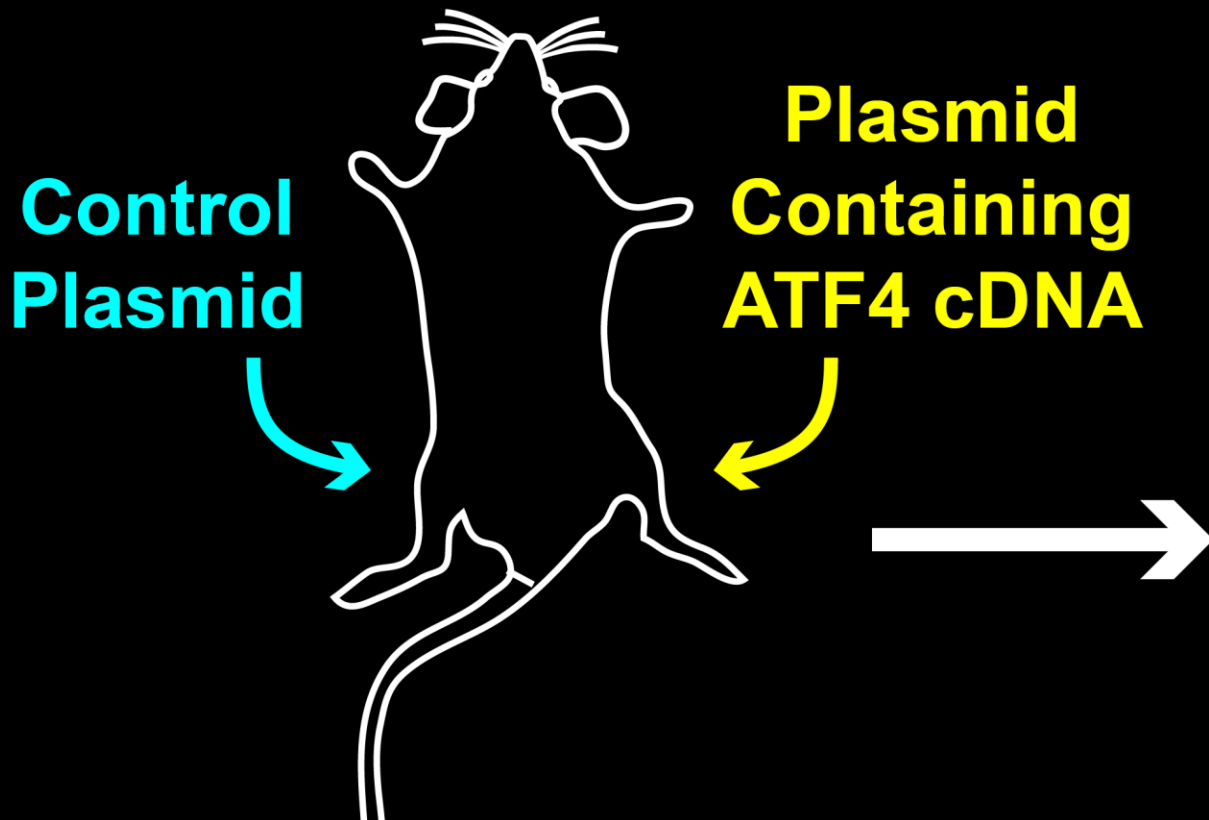


ATF4 Is Required for Loss of Endurance Exercise Capacity During Aging



Is ATF4 Expression Sufficient to Induce Skeletal Muscle Atrophy?

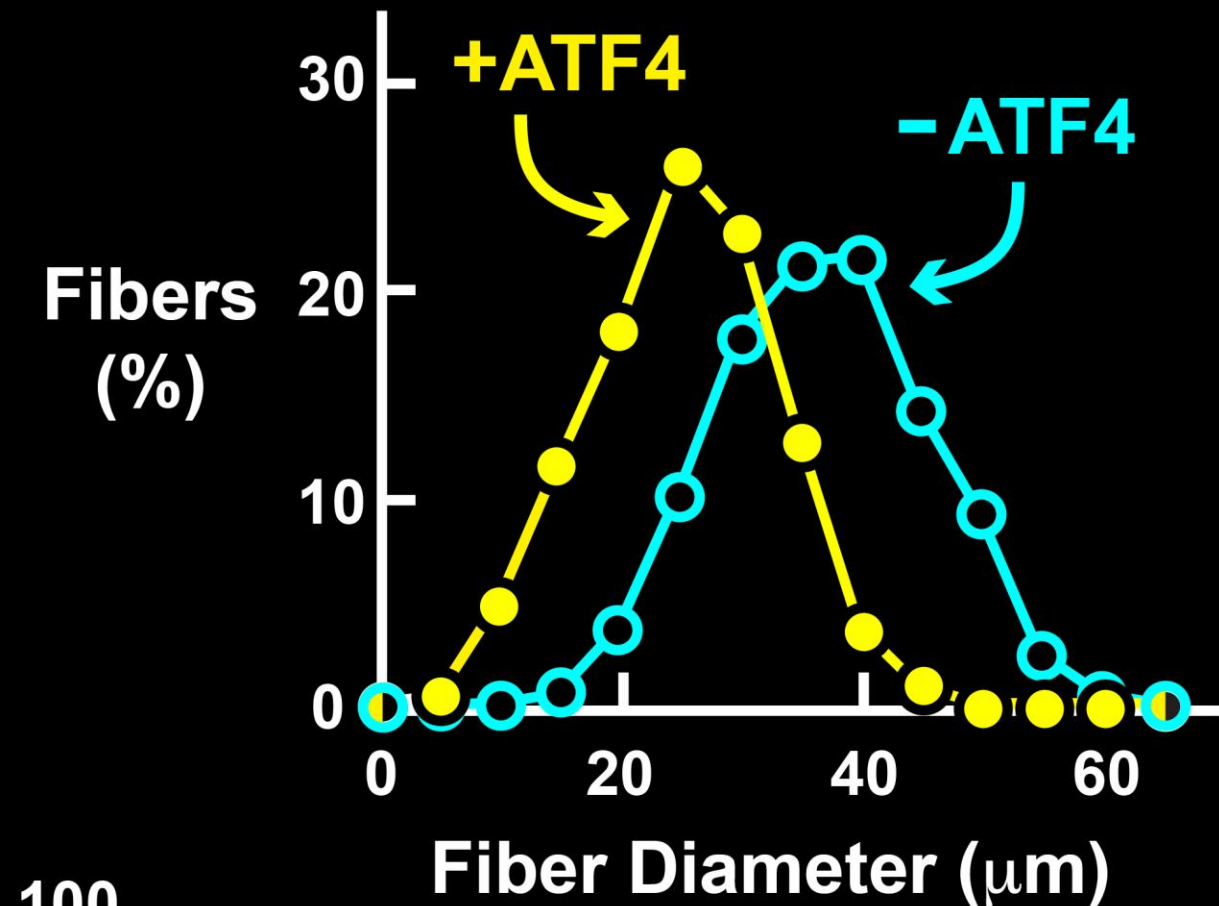
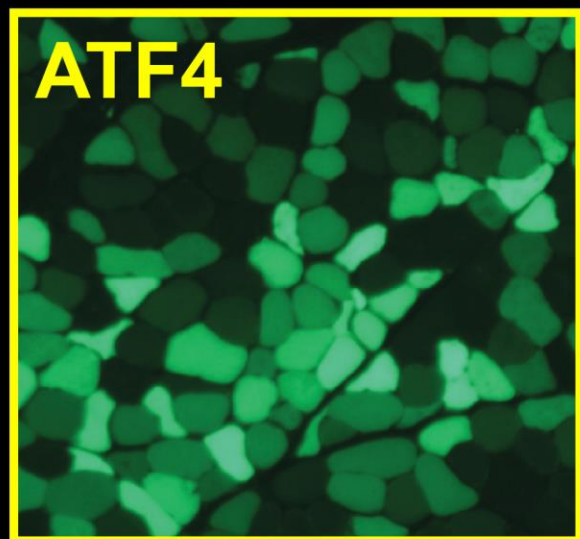
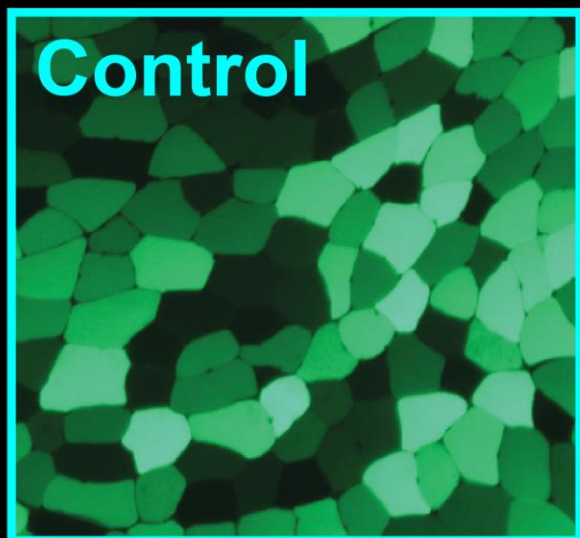
2-Month-Old Mice



Mice Return to Normal Activities for 1 Week

↑
Electroporate Plasmid DNA into Skeletal Muscle Fibers

Forced Expression of ATF4 Induces Atrophy in Young, Mobile, Fed Muscles



100
 μm