Institut de recherche
en réadaptation-réinsertion

Clinique romande
de réadaptation

Molecular mechanisms controlling skeletal muscle mass

suvacare
Prestations et réadaptation

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SSMS 2015

Skeletal muscle atrophy:
3 initiating factors

Chronic diseases

- ✓ **Diabetes**
- ✓ **AIDS**
- ✓ **Cancer**
- ✓ **COPD,…**

Disuse conditions

- ✓ **Denervation**
- ✓ **Immobilization**
- ✓ **Microgarvity**

Ageing

- ✓ **Sarcopenia**

Atrophy is a rapid phenomenon

Loss of muscle may range between 1.5-2% per day during the 2-3 first weeks

Social and economic burden of skeletal muscle atrophy

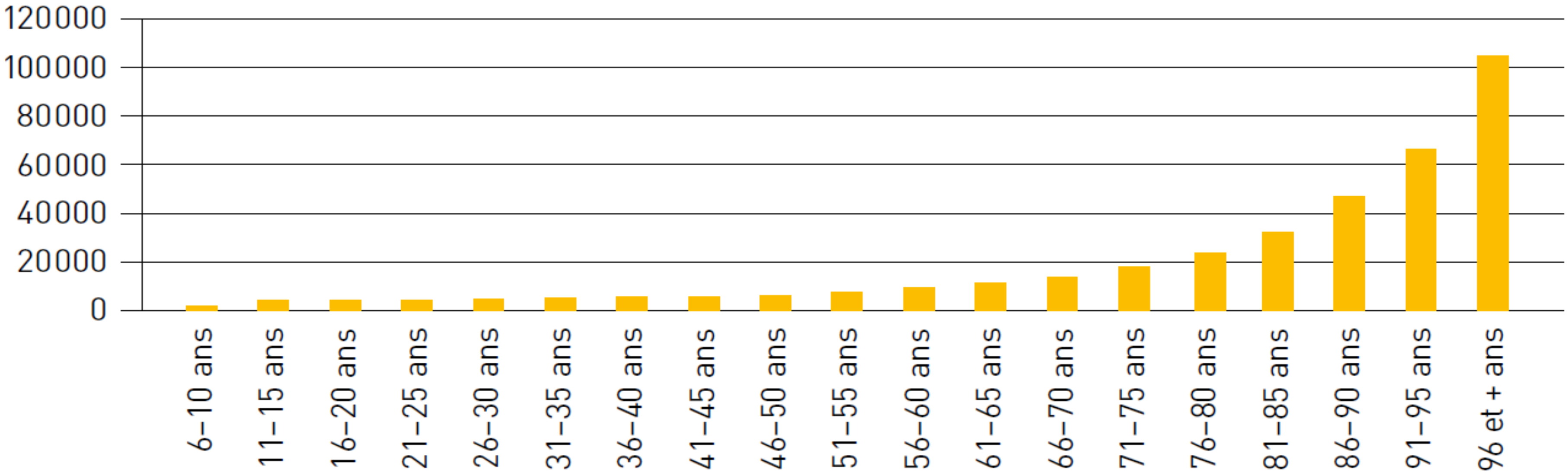
From a “loss of function” point of view…

« young » muscle → Sarcopenia (atrophy linked with ageing) 0.5 – 1% per year from the 40’s → Loss of strength, equilibrium, increased risk of fall, loss of independence,…

USA: 18 billion of USD/year

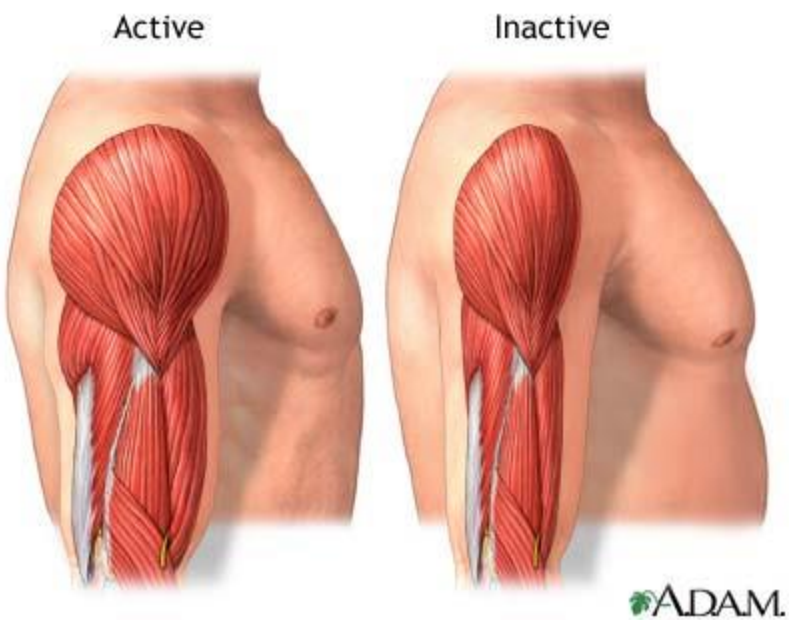
Coûts du système de santé

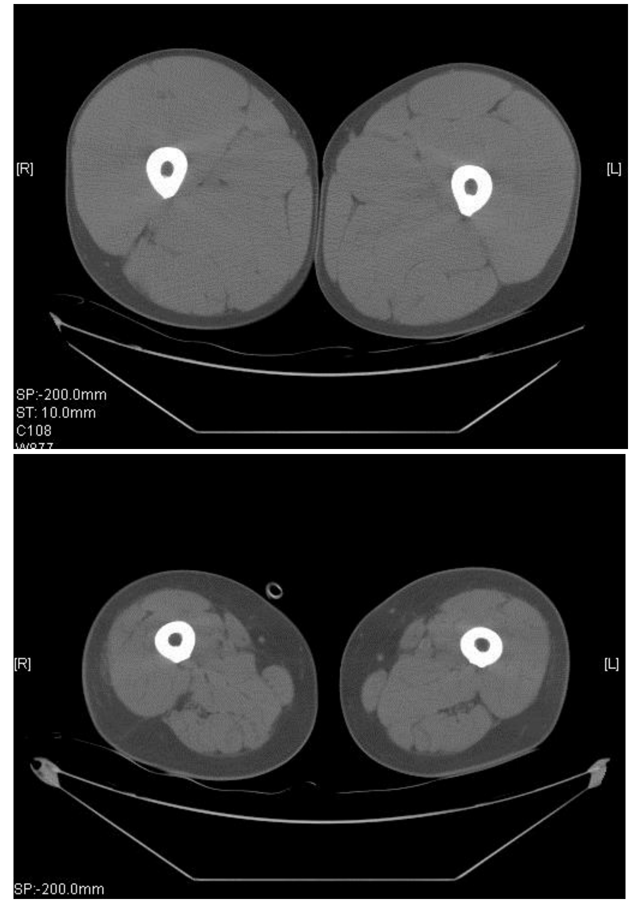
- Coûts des soins de longue durée 65+: 9,5 milliards par an, doublement jusqu'en 2030
  (Office fédéral de la statistique 2013c) et Weaver et al. 2008)
- Coûts occasionnés par les chutes 65+: 1,4 milliard par an
  (Bureau de prévention des accidents bpa 2010)



Coût du système de santé en Suisse en 2011 par habitant
Office fédéral de la statistique 2013c)

Atrophy: Structural modifications



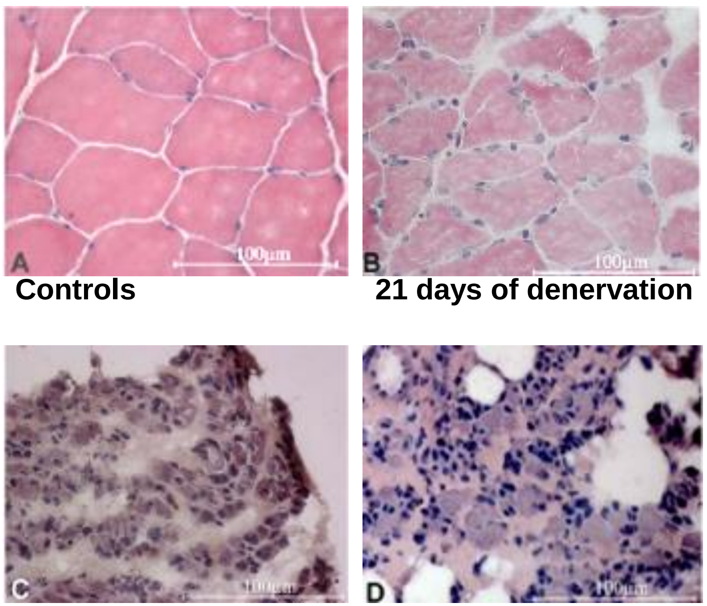


- ✓ Sarcomeric dissolution (↓ Functional units)
- ✓ Reduction in contractile elements (↓ strength)

-> **Reduced cross sectional area: CSA**

Léger et al., muscle and Nerve, 2009)

Atrophy: Structural modifications



Adapted from Adami et al.2006

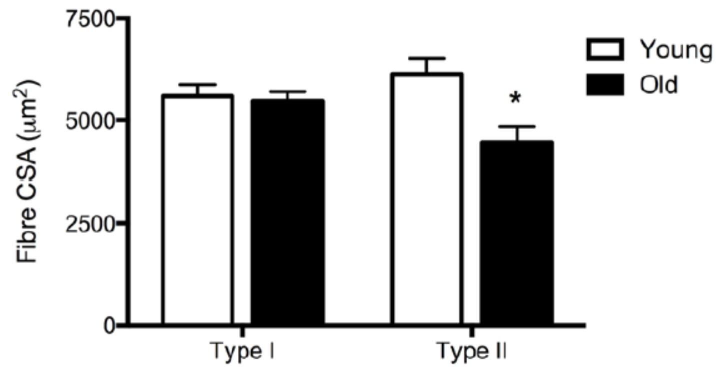
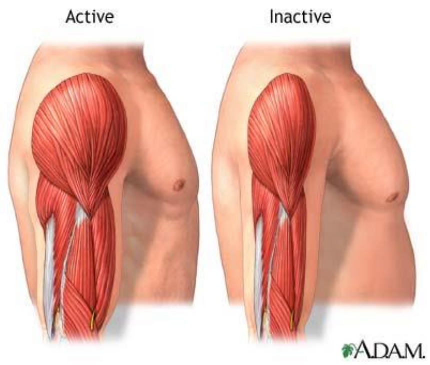
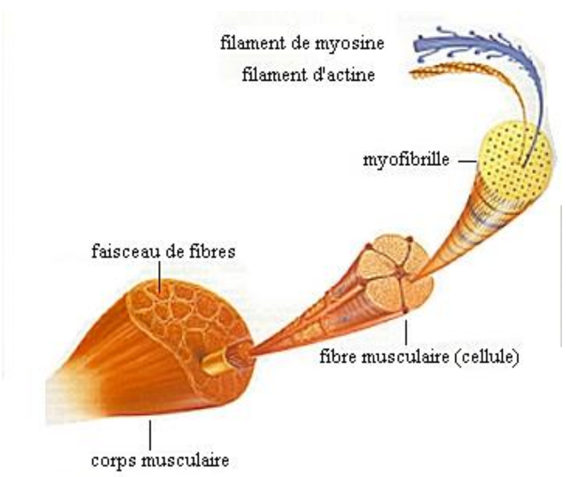


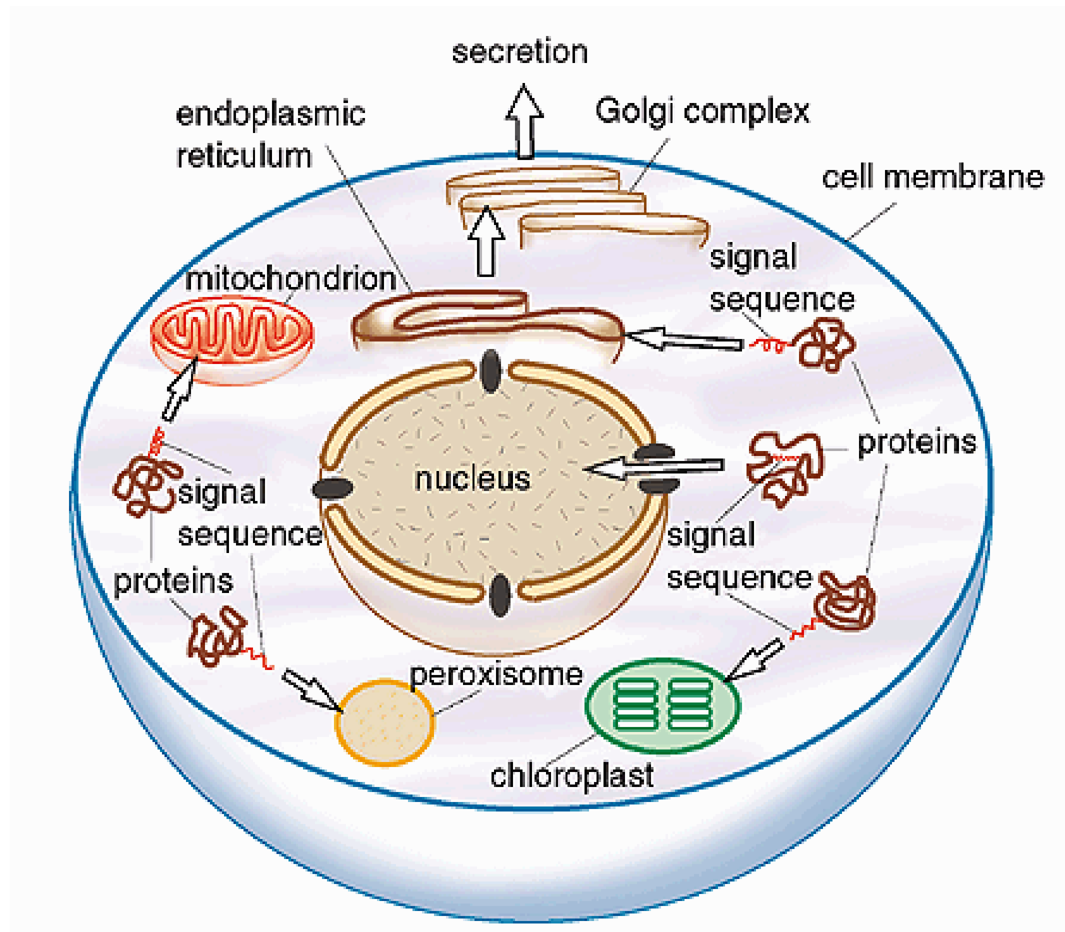
Figure 1.1 Muscle fibre cross-sectional area (CSA) in young *versus* older individuals. Data are presented as means ± SEM. Type II muscle fibre CSA is significantly reduced in older subjects compared to younger individuals, $*P < 0.05$. Adapted from [389].

- ✓ Increased accumulation of connective tissue (↑ disorganization)
- ✓ Reduced capillary content (↓ O2)
- ✓ Reduced mitochondrial content (↓ ATP)
- ✓ Loss of nuclei (↓ protein synthesis, ↑ apoptosis)

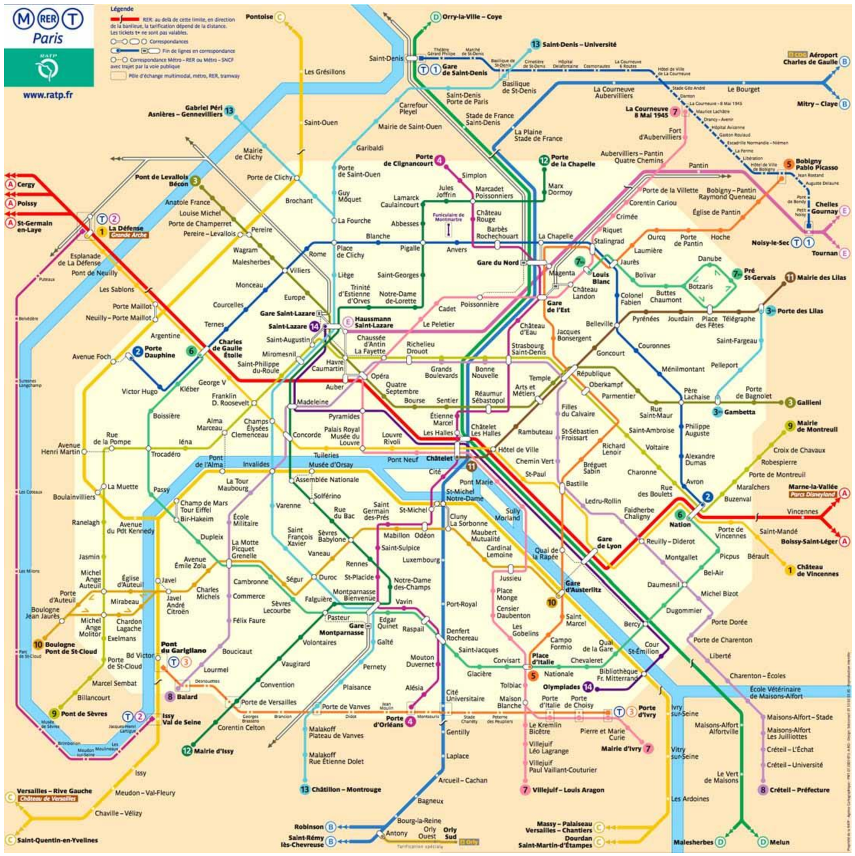
Molecular mechanisms

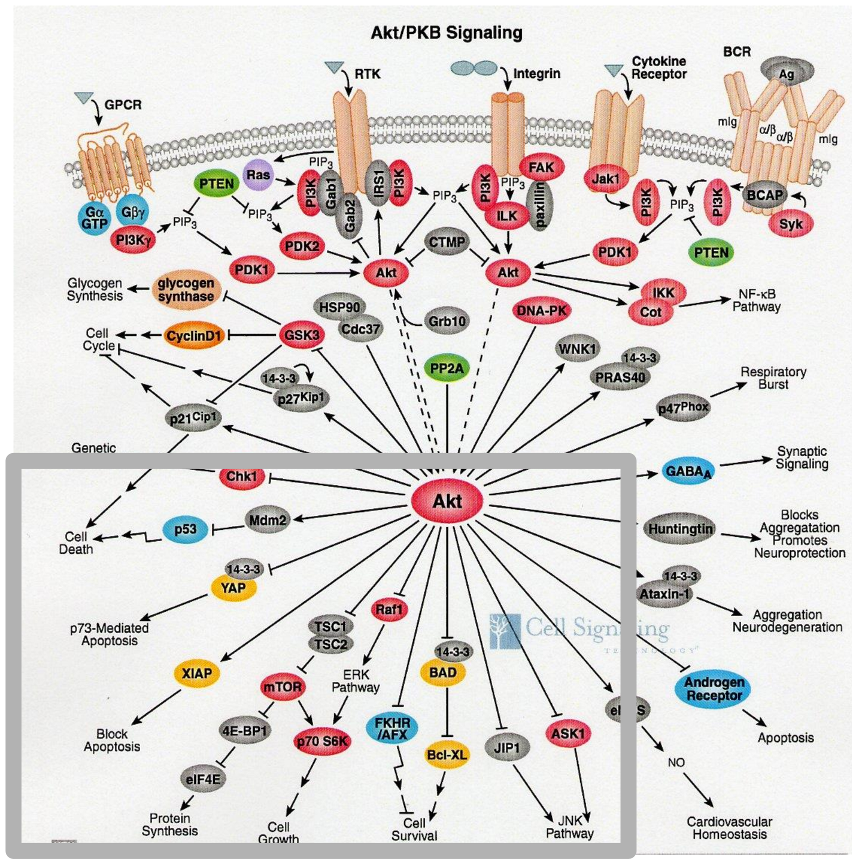






Signaling pathways





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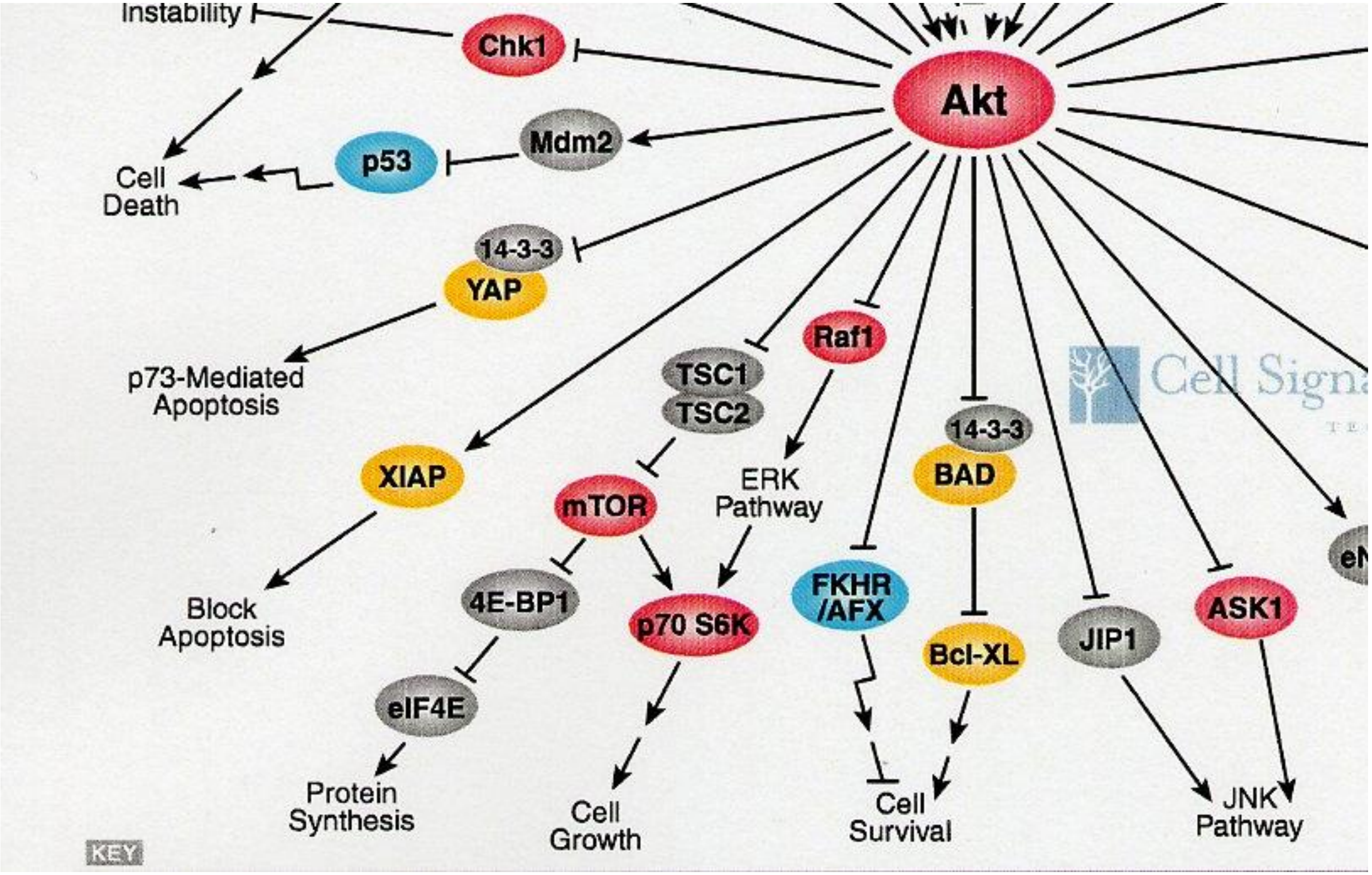
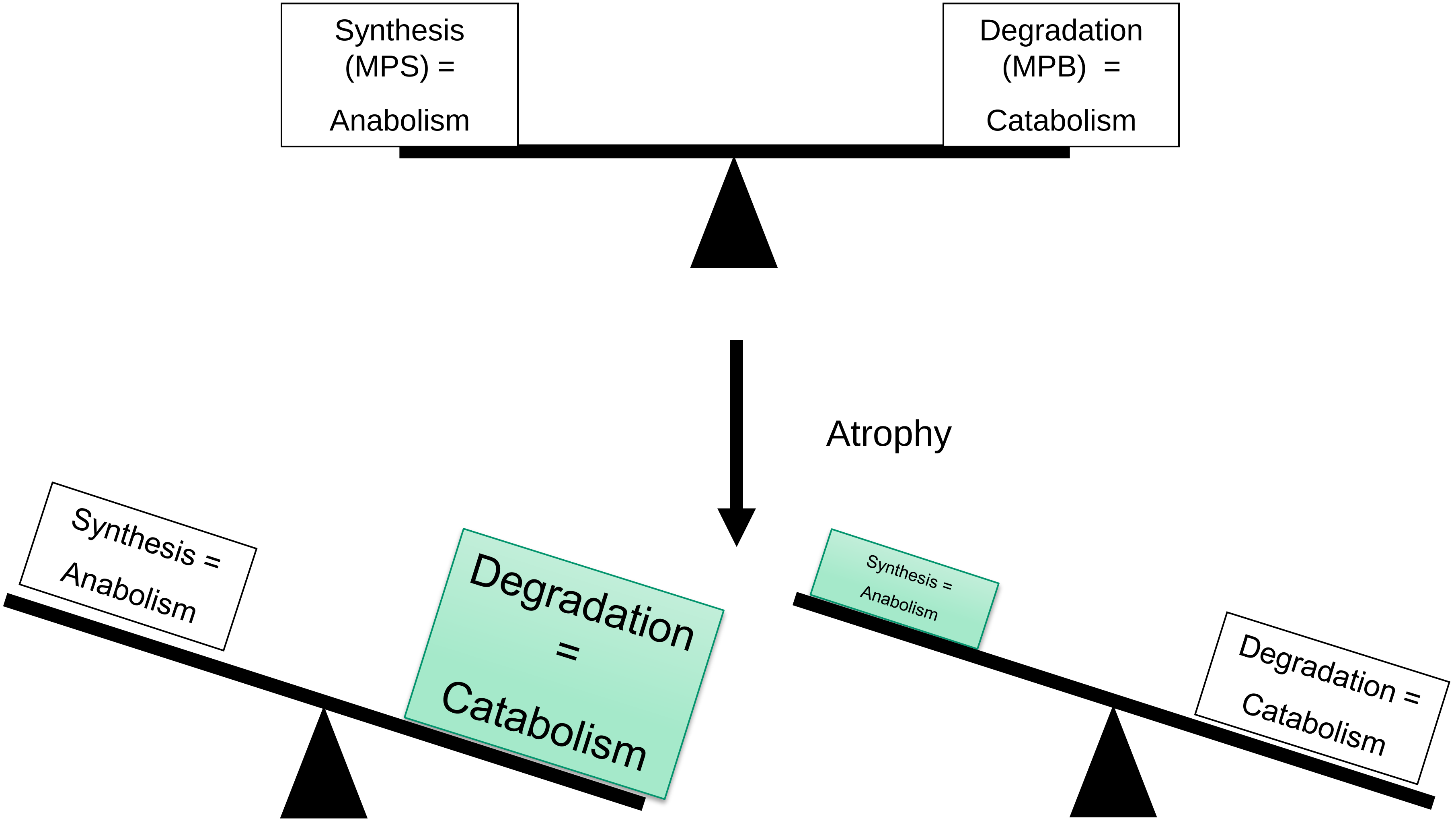
Signaling pathways



Determining muscle mass



Catabolic systems

There are 3 major catabolic systems

Calpains : enzyme activated by Ca^{2+}

Autophagia/Apoptosis

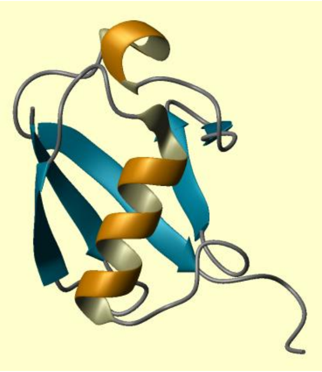
ATP-dependant ubiquitin-proteasome pathway

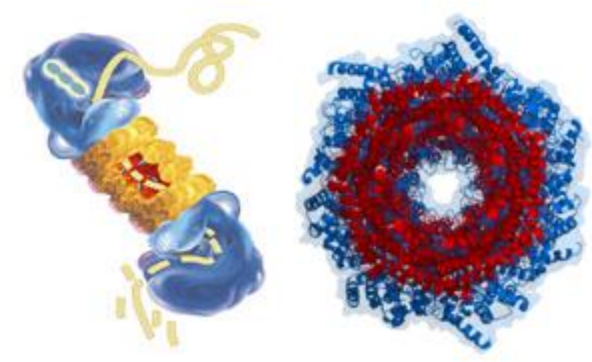
Catabolic systems

ATP-dependant ubiquitin-proteasome pathway

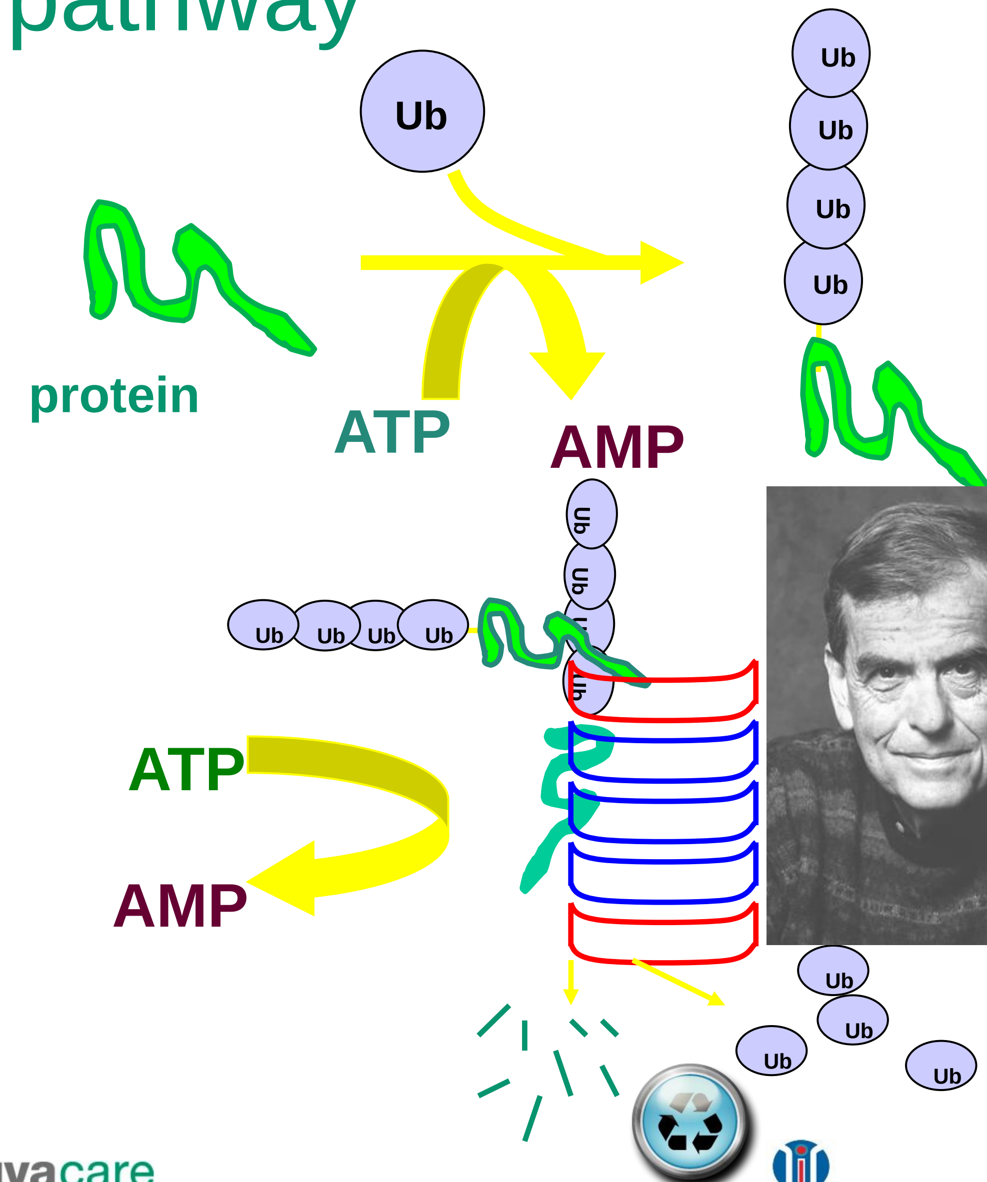
Ubiquitin (Ub)
- Globular protein
  (76 aa, 8kDA)

Proteasome
- Protein complex
  (2500kDa)



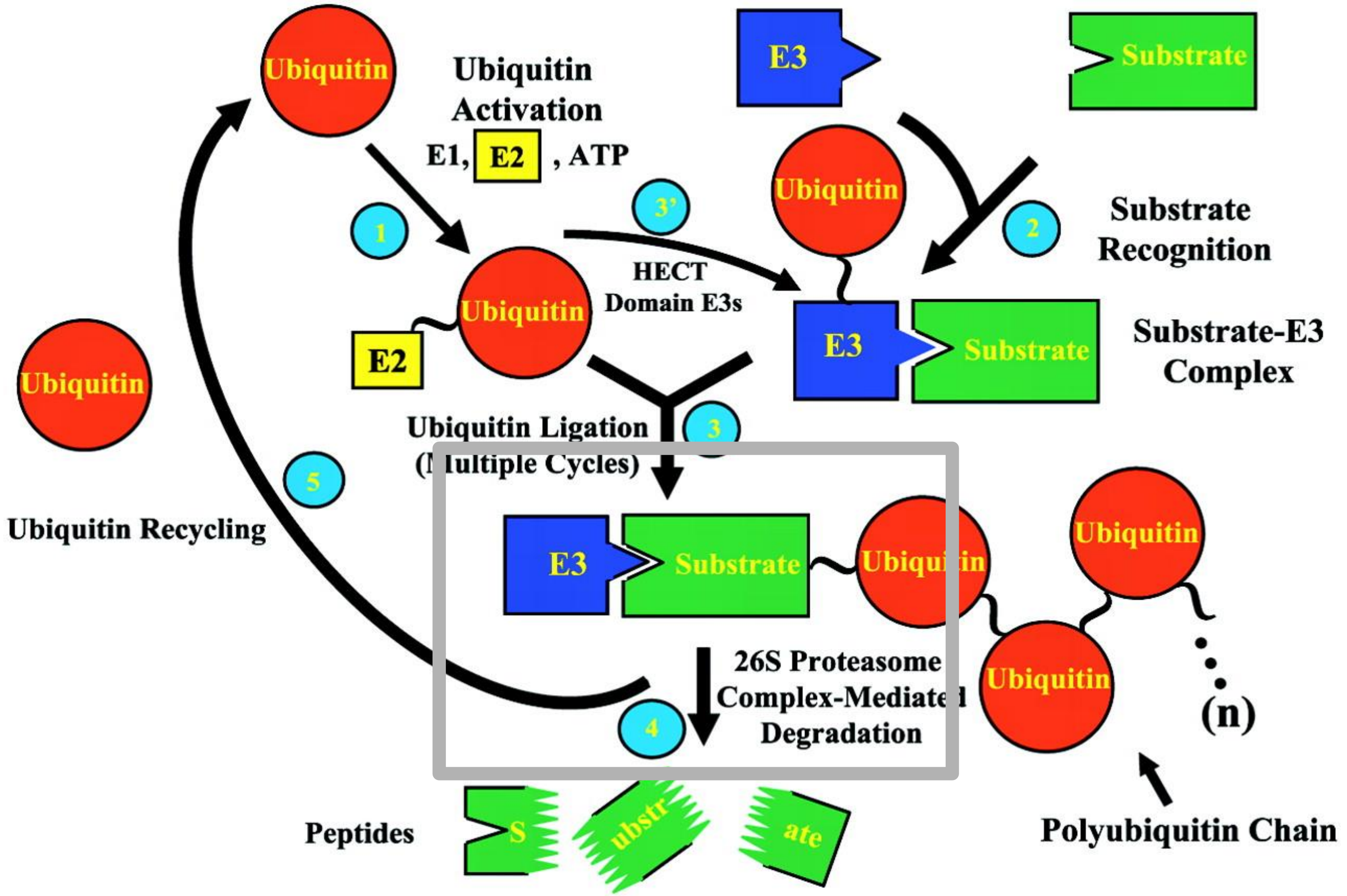


ATP-dependant ubiquitin-proteasome pathway



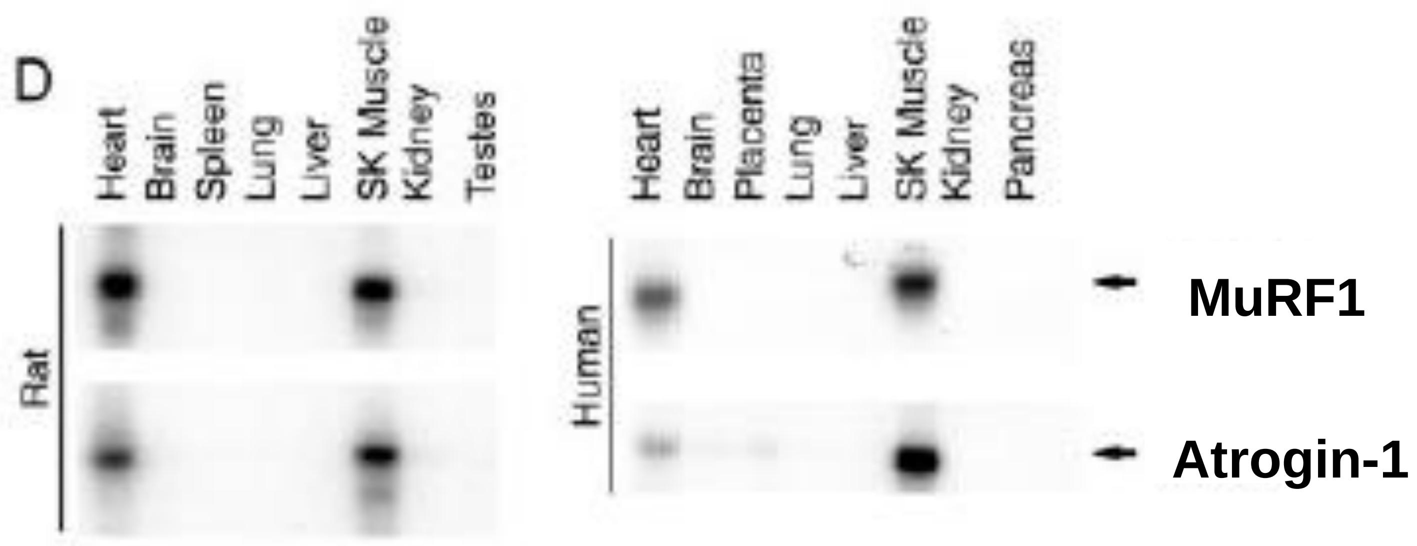
Ciechanover, Hershko & Rose, 1979

Components of the UPP



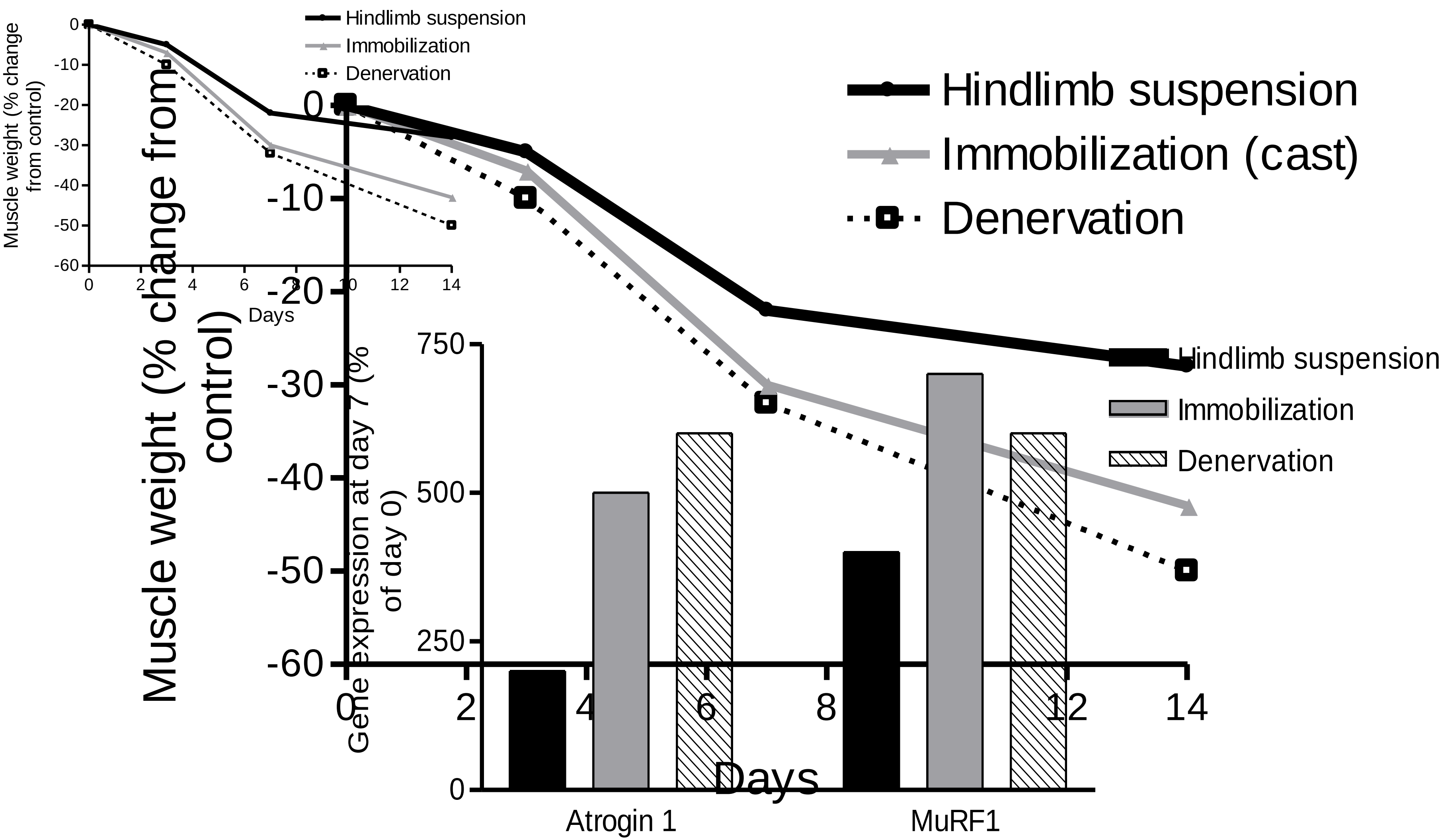
Atrogin-1 et MuRF1

Expression specific to skeletal muscle



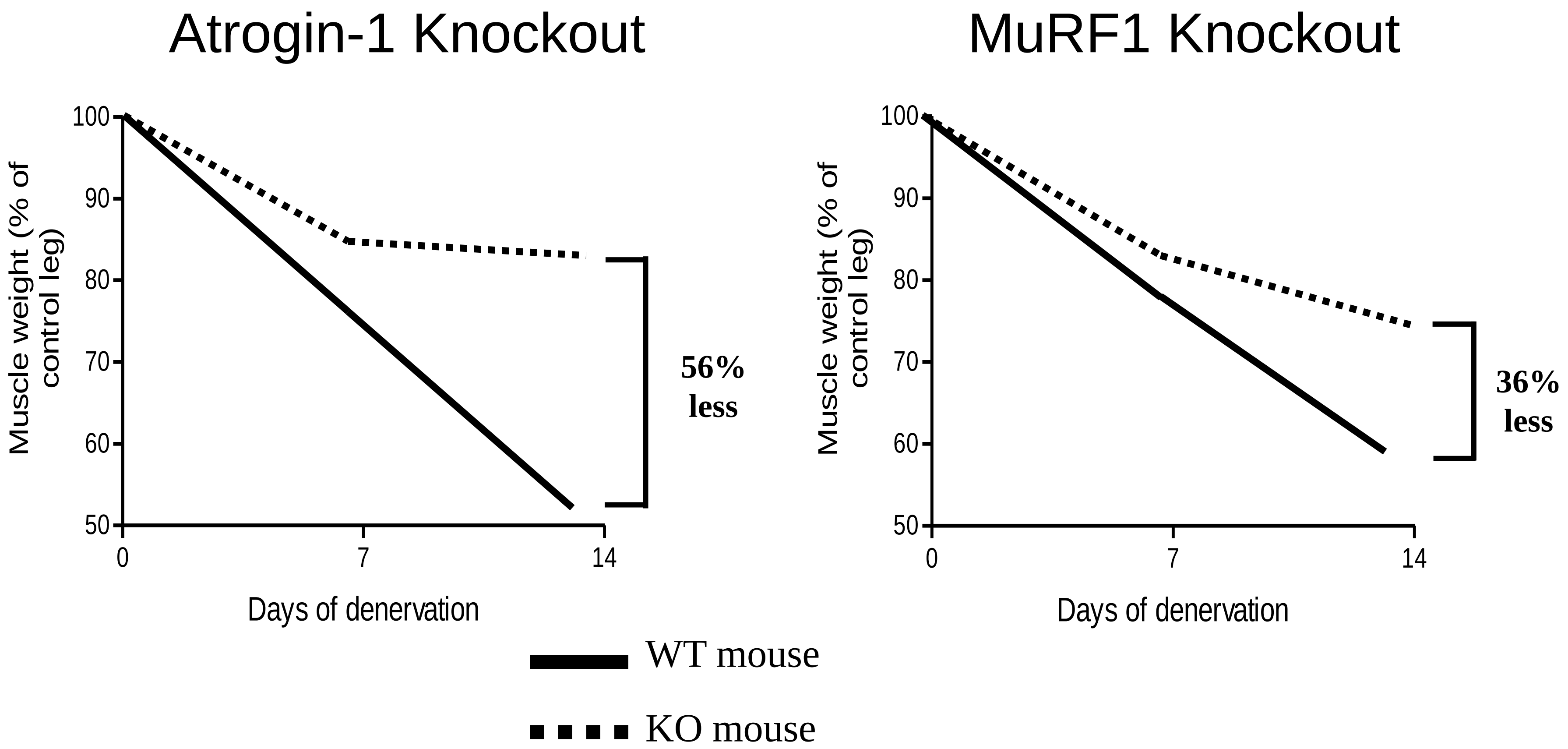
Bodine et al. 2001. Science 294: 1704-1708

Atrogin-1 et MuRF1



Bodine et al. 2001. Science 294: 1704-1708

Atrogin-1 et MuRF1



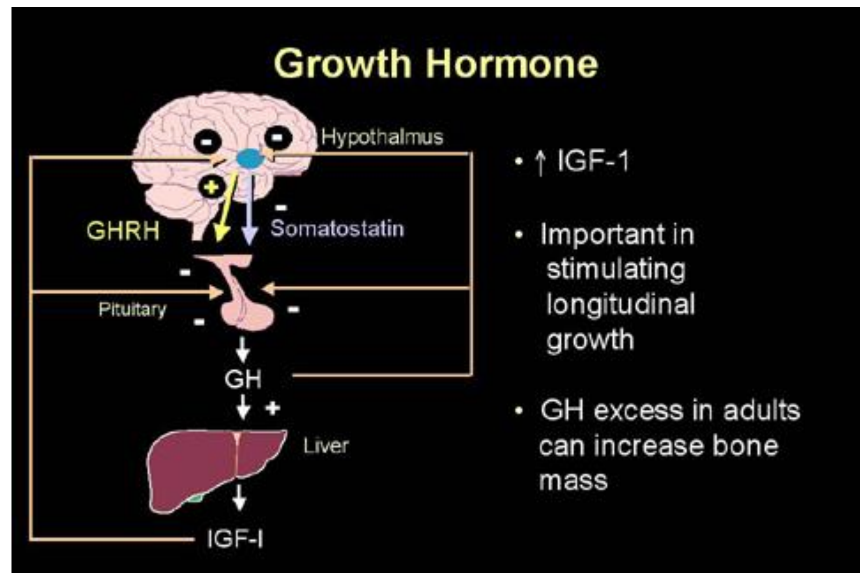
Model of atrophy :denervation

Bodine et al. 2001. Science 294: 1704-1708

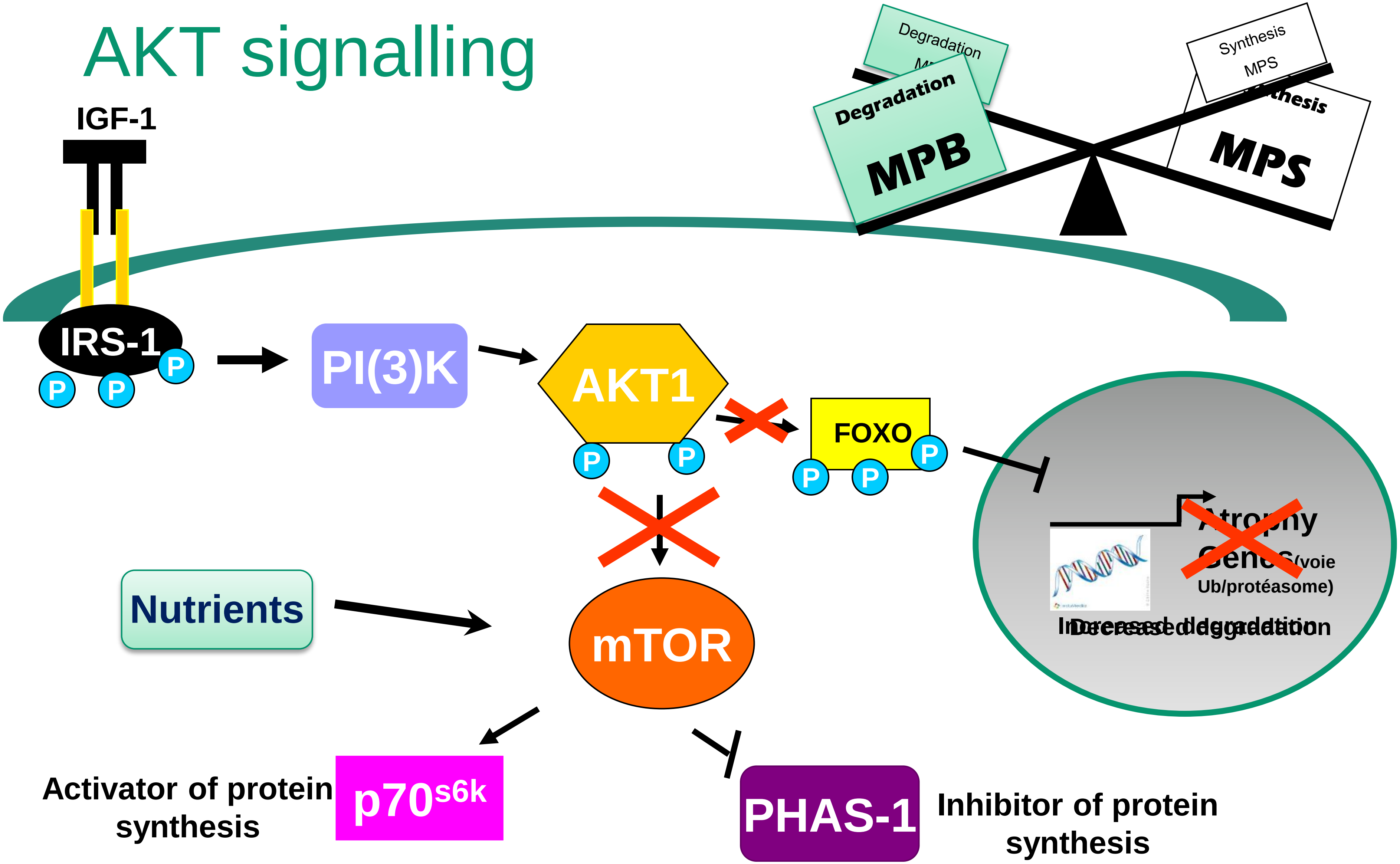
Anabolism/protein synthesis

Insulin-like growth factor 1 (IGF1)

- Activated by exercise
- Autocrine and endocrine secretion.
- Several isoforms exists (IGF-IEa, -IEb, MGF)
- Acts through the IRS1/PI3K/Akt pathway



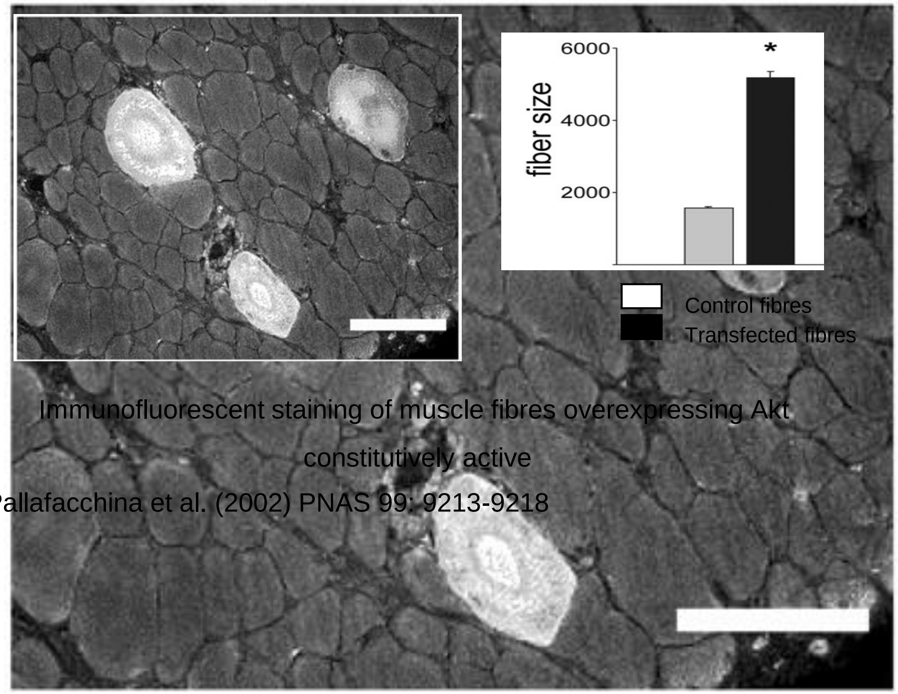
AKT signalling

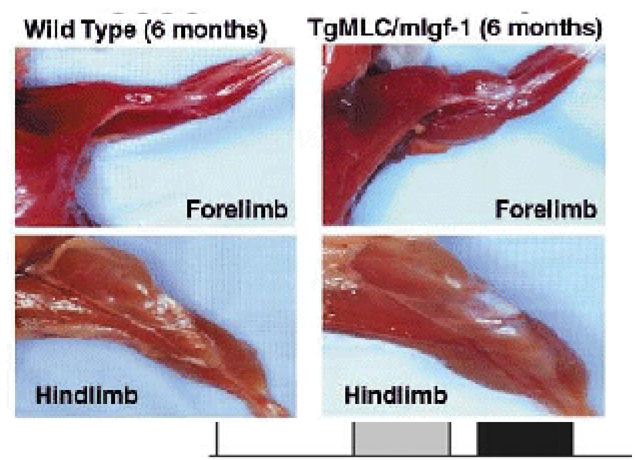


Decrease in protein synthesis

Increase in protein synthesis

AKT1 pathway





Control fibres
Transfected fibres

Immunofluorescent staining of muscle fibres overexpressing Akt

constitutively active

Pallafacchina et al. (2002) PNAS 99: 9213-9218

Results from our lab

<table>
<tr><th>Models</th><th>Muscle mass</th><th colspan="2">Synthesis</th><th colspan="2">Degradation</th></tr>
<tr><td>Amyotrophic lateral sclerosis</td><td>Severe atrophy linked with a pathology</td><td colspan="2">↓</td><td colspan="2">↑</td></tr>
<tr><td>Spinal cord injury</td><td>Severe atrophy linked with a trauma</td><td colspan="2">↓</td><td colspan="2">↓</td></tr>
<tr><td>Sarcopenia</td><td>Moderate atrophy due to a reduced activity</td><td colspan="2">↓</td><td colspan="2">→</td></tr>
<tr><td>Training and detraining protocol</td><td>Hypertrophy followed by atrophy due to reduction of the activity</td><td>Hypertrophy
↑</td><td>Atrophy
↓</td><td>Hypertrophy
↑</td><td>Atrophy
↓</td></tr>
</table>

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Interventions to reduce Catabolism

- Natural compounds (Eicosapentanoic, Grehlin,…)
- Enzyme inhibitors (Cox2 inhibitors, PDE inhibitors,...)
- β-Adrenoceptor agonist (clenbuterol, formoterol)
- Anti-cytokines agents (anti-TNFα, Thalidomide,…)

For review see Dutt et al., Pharmacological Research, 2015

Take home messages… Part 1

- Possible interventions in order to reduce muscle atrophy should act through:
  - An activation of the AKT signaling pathway
  - A fine control of the expression of the E3 ligases, Atrogin-1 and MuRF1

Other regulators of muscle mass

Pharmacology

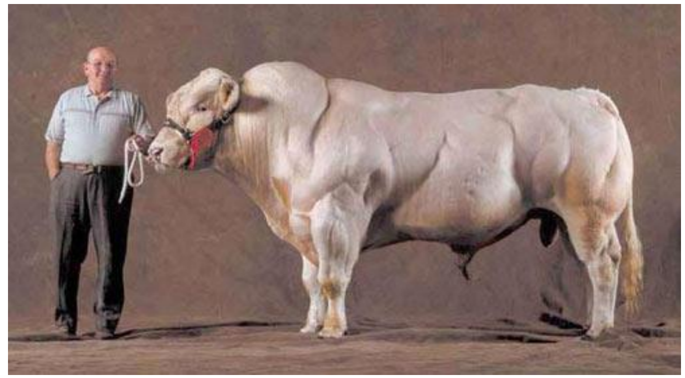
- Steroids
- Creatin
- Growth hormones
- β_2 –Agonists (clenbuterol)
- ….

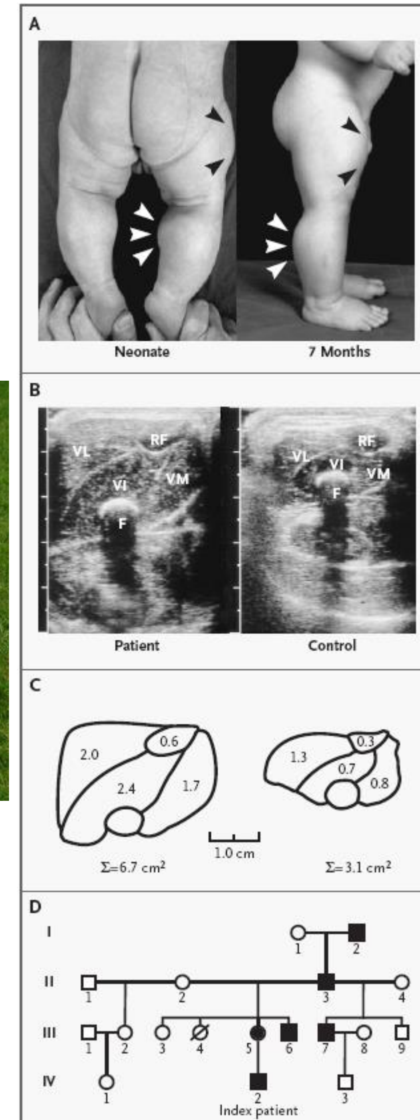
New Targets

- ✓ **Myostatin also called *Growth differentiation factor 8 (GDF 8)***
- ✓ **Satellite cells**

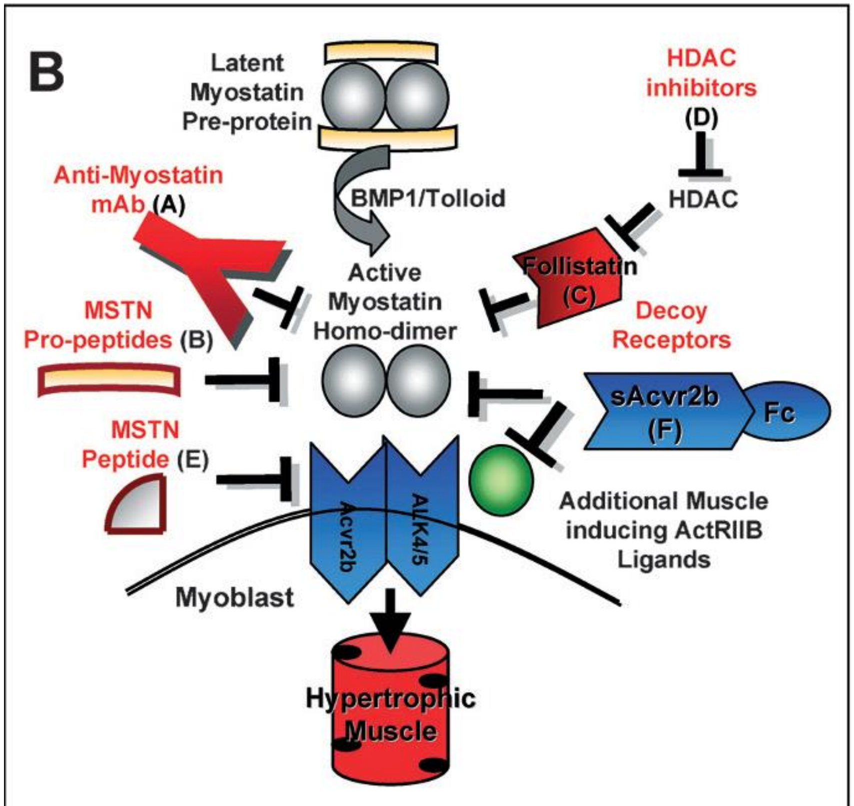
Myostatin

- ✓ Inhibitory function on muscle growth and differentiation.
- ✓ Specifically expressed in skeletal muscle.
- ✓ Acts by targeting factors involved in skeletal muscle differentiation.



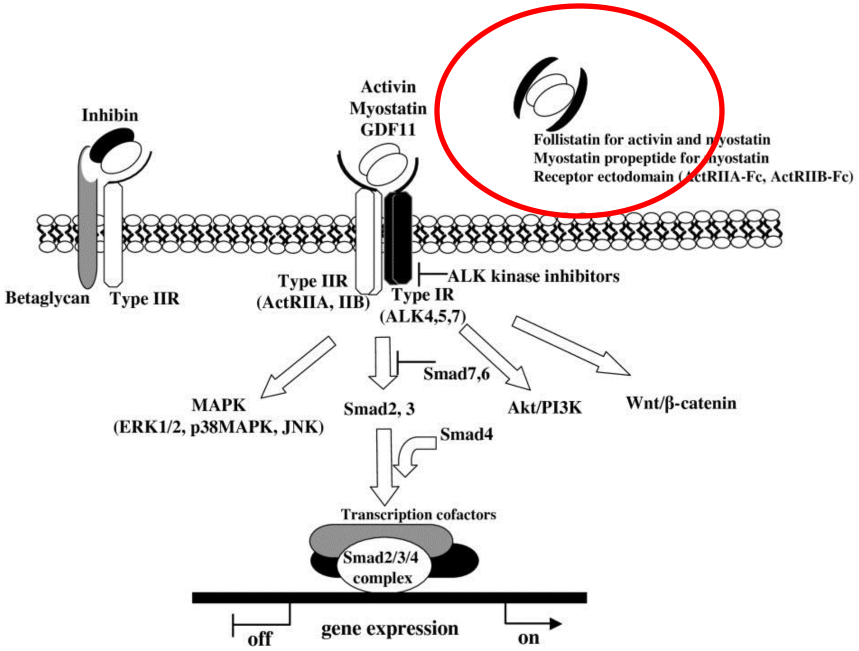


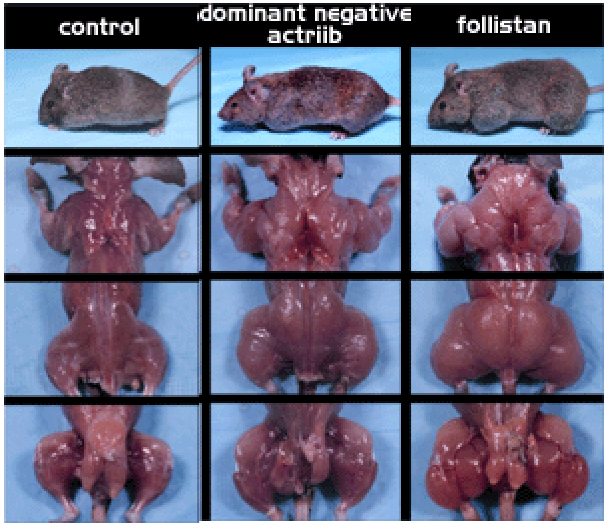
Myostatin inhibition



- ✓ Myostatin inhibitors improve dystrophic phenotype in rodents (Wagner et al. 2008).
- ✓ Myostatin inhibitors reduce apoptosis during sarcopenia (Murphy et al. 2010).
- ✓ Myostatin inhibitors reduce skeletal muscle loss under the condition of cachexia (Bossola et al. 2008).

Follistatin



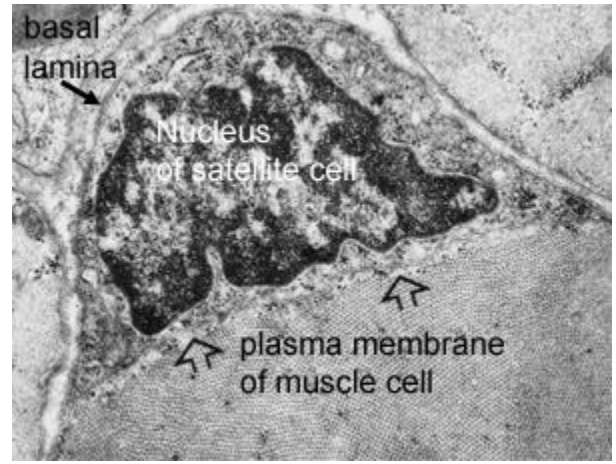


Se-Jin Lee et al. 2001

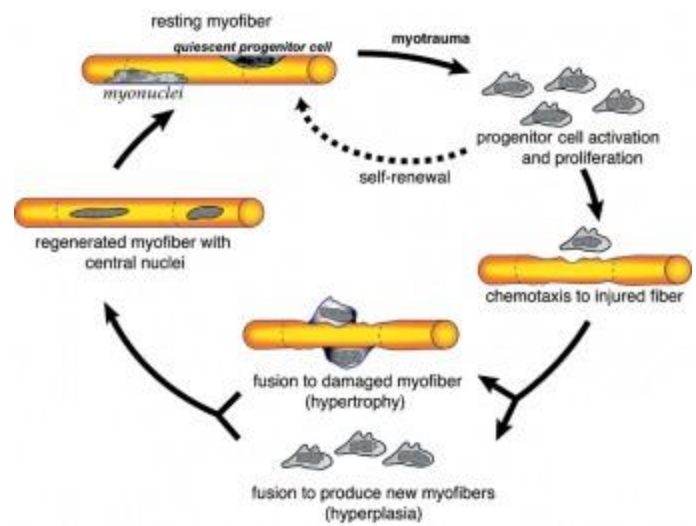
Tsuchida et al. 2009

Stellite cells

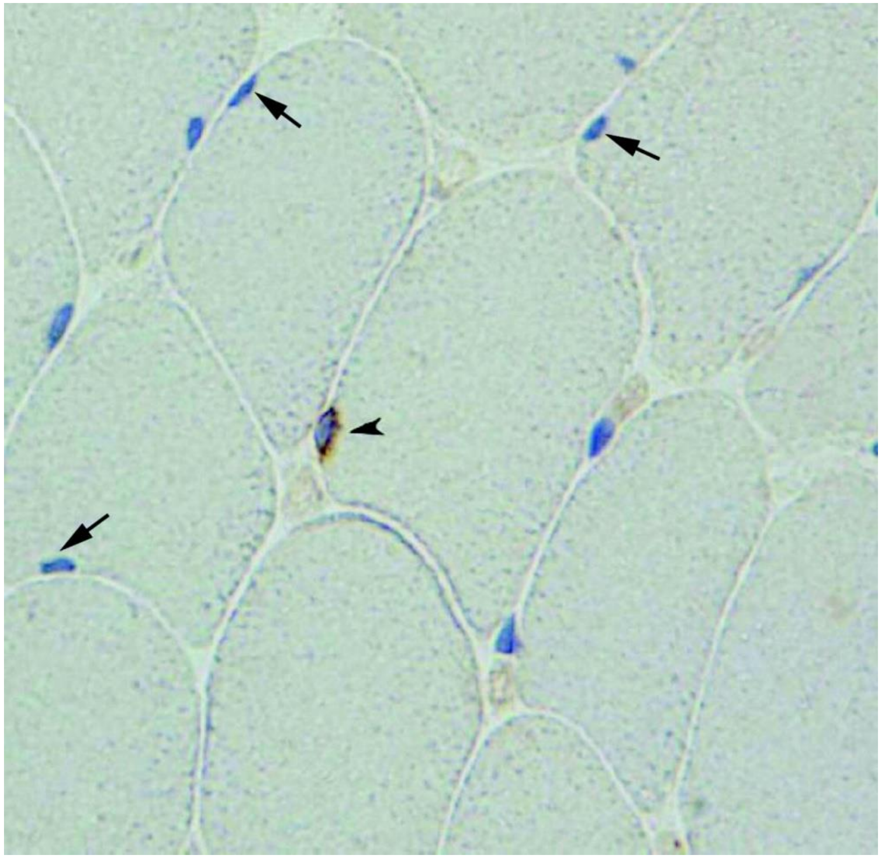
- ✓ First characterized in 1961.
- ✓ Their name comes from their localization beneath the basal lamina
- ✓ Can be activated, proliferate and return to a quiescent state.
- ✓ They have a limited capacity of proliferation



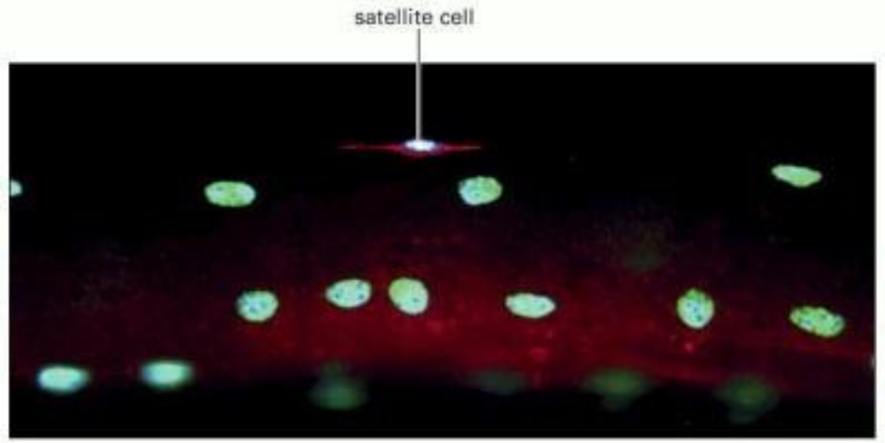
Histology Guide © Faculty of Biological Sciences, University of Leeds



Satelliste cells (SC)



Kadi et al. 2004



Alberts et al. 2002

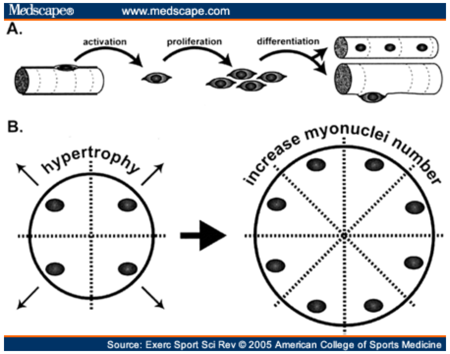
Satellite cells and muscle mass

- SC contribute to muscle fiber growth during development (represent 30-35% of myonuclei)

- SC are involved in muscle homeostasis:

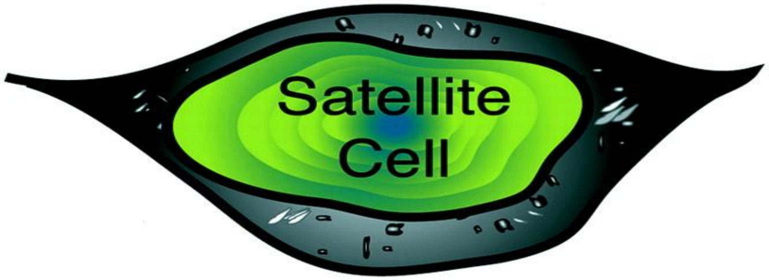
  -> the myonuclear

  domain conservation



- SC contribute to muscle fiber regeneration process after injury.

Control of Satellite cells proliferation

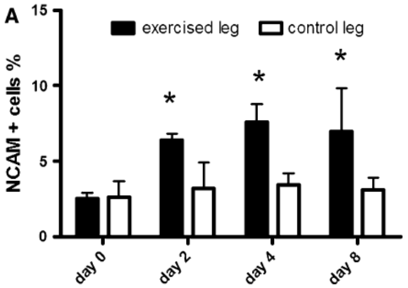


Satellite cells and muscle mass

- SC and sarcopenia -> Lower content in SC in elderly; BUT "aged" cells have the same potential as "young" one

- SC and dystrophy-> exhaustion of the pool of SC

- SC and training (RE & EE)
- -> involvement of the SC in the hypertrophy and remodeling process



Crameri et al. 2004

Acknowledgements

Thank you for your attention