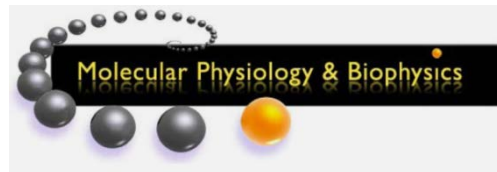


# What Do We Know about Dystroglycan?

Daniel Beltran



# Outline

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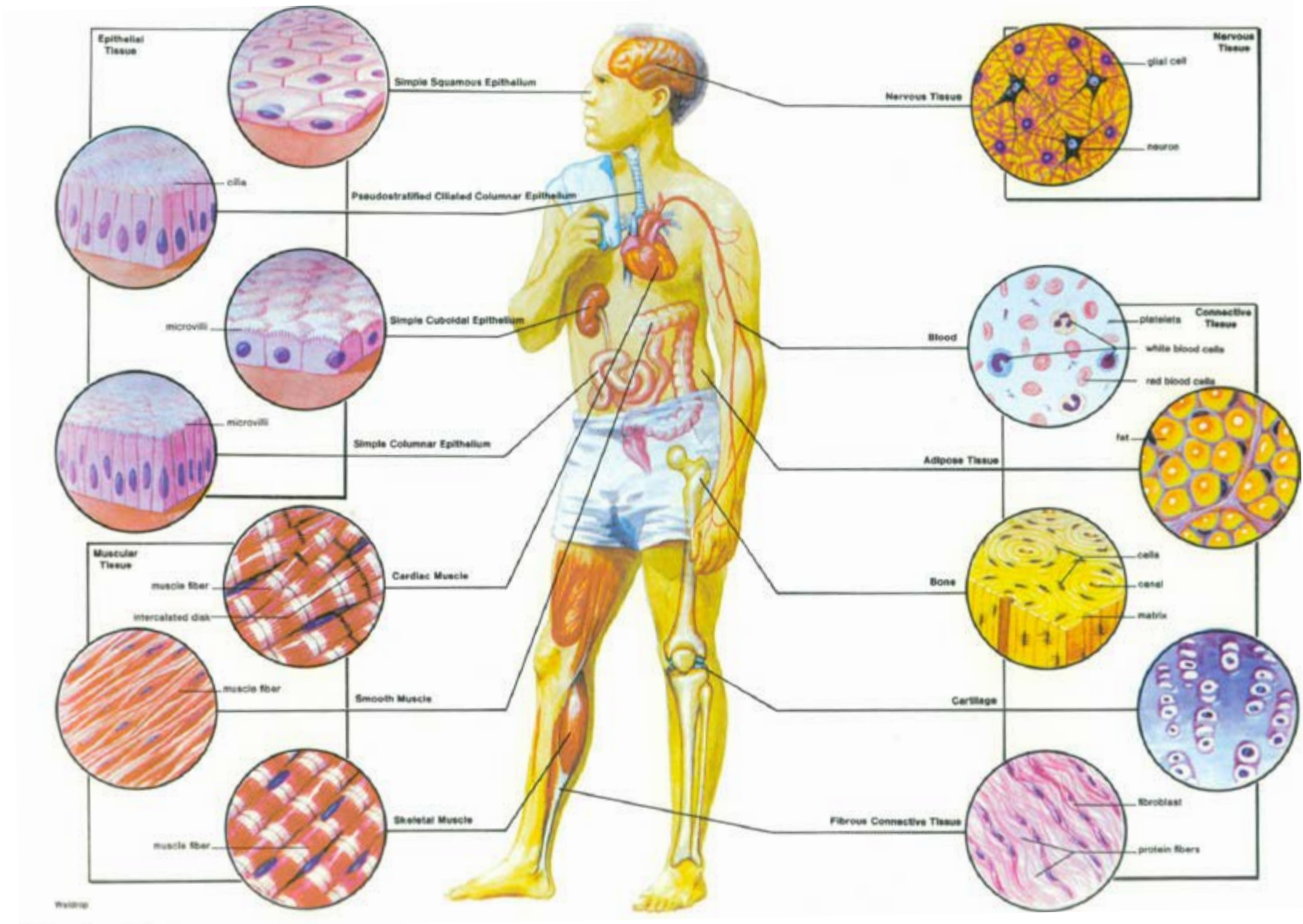
1. Basement membrane in epithelium and skeletal muscle.
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# The human body: Cells and connections



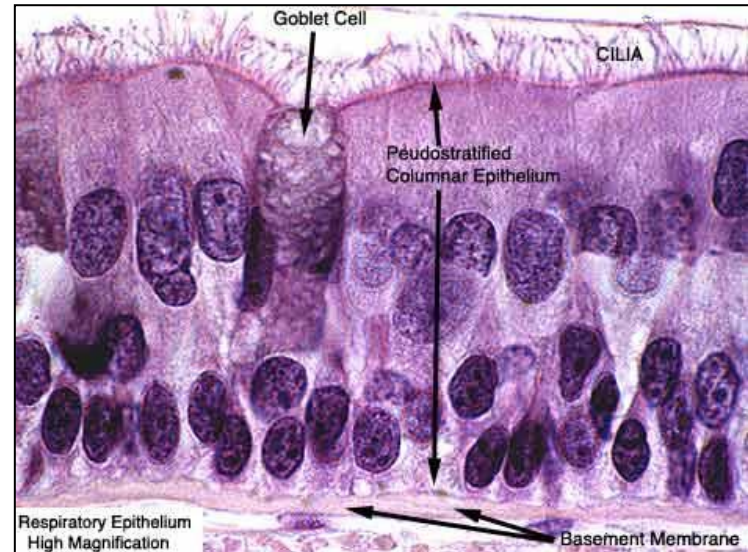
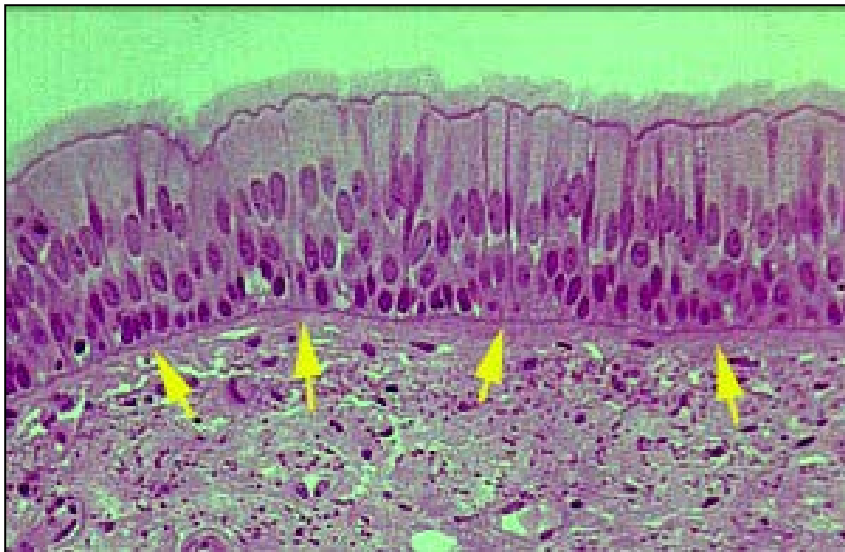
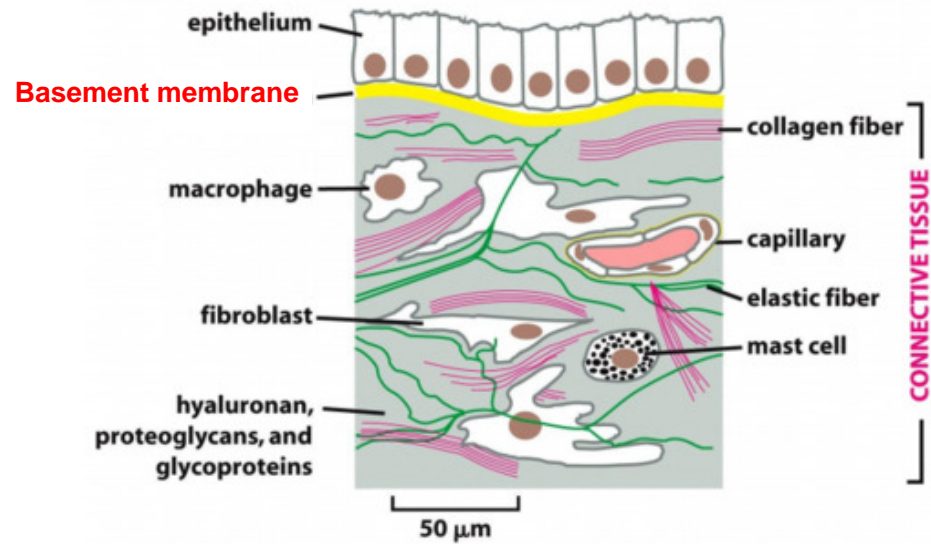
# The human body: Cells and connections

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Communication and ..... Contact

# Basement Membrane

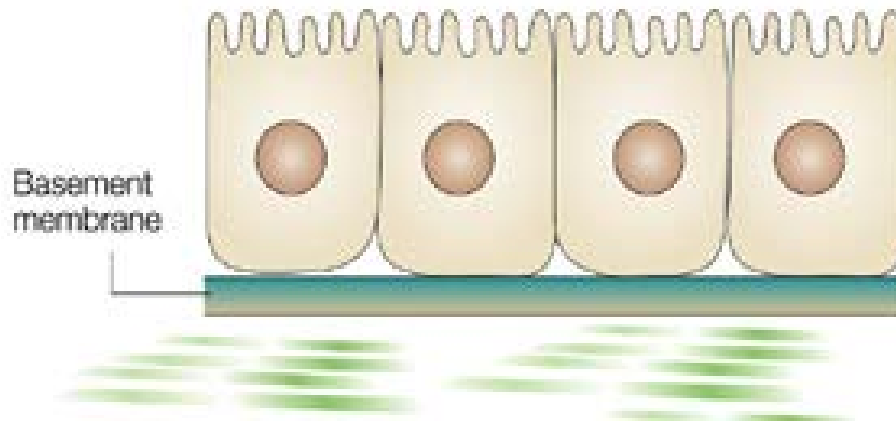


# Basement Membrane Functions

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**Mechanic stability**

**Adhesion**



**Polarity**

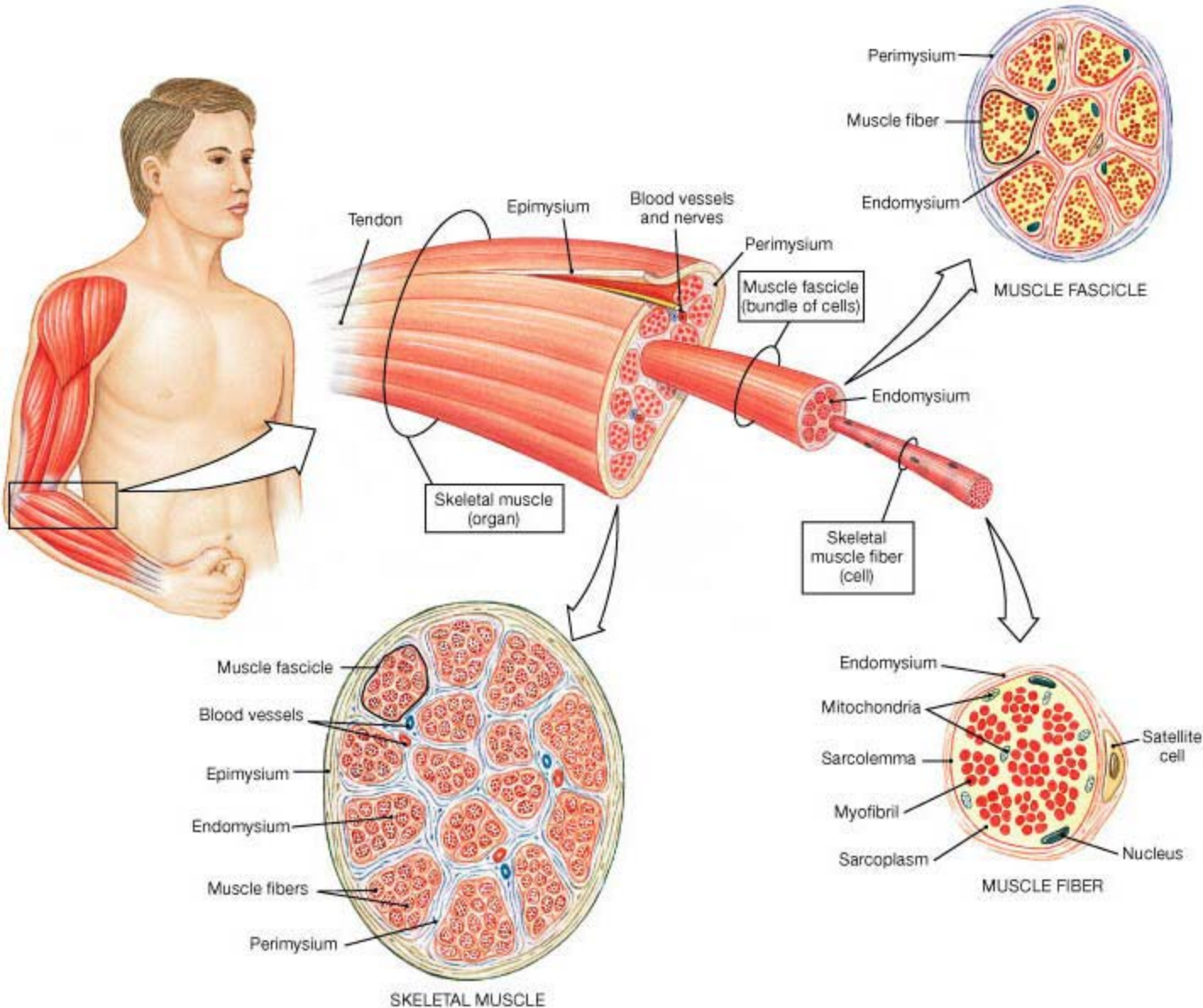
**Survival**

**Compartmentalization**

**Proliferation**

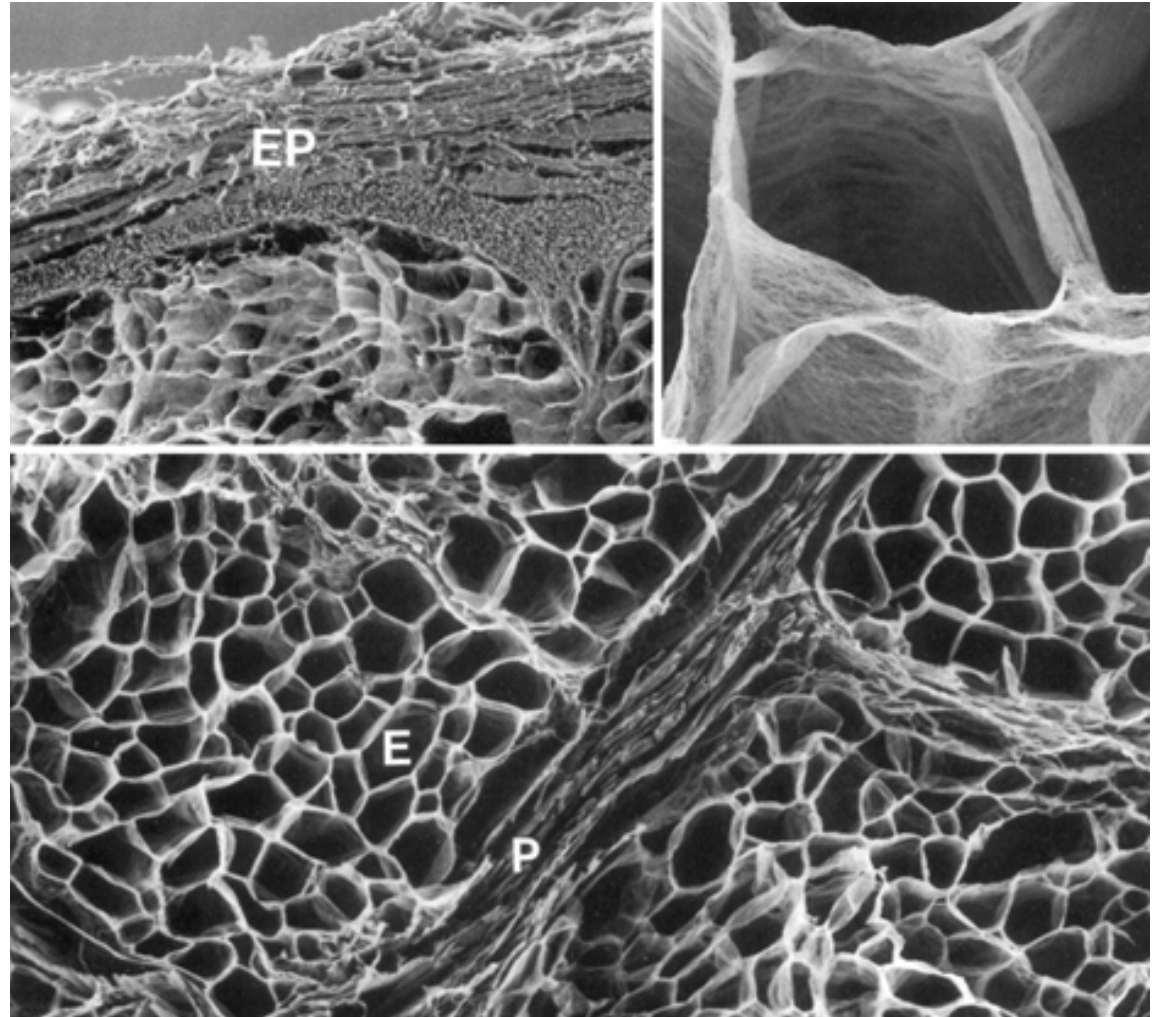
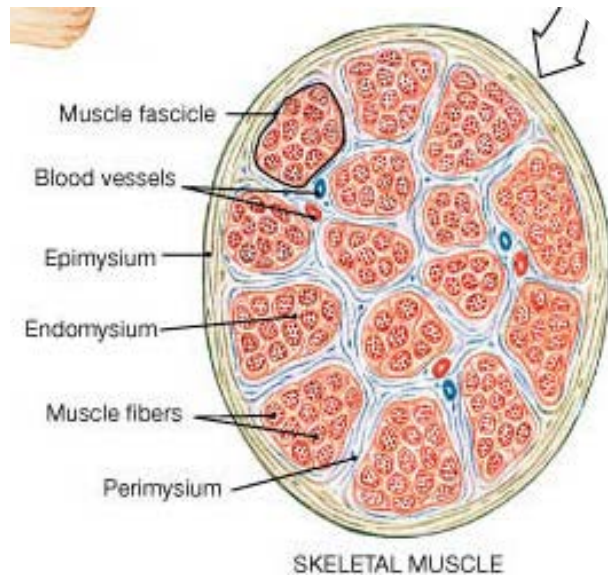
**More than just structure**

# Skeletal Muscle





# Skeletal Muscle Basal Lamina

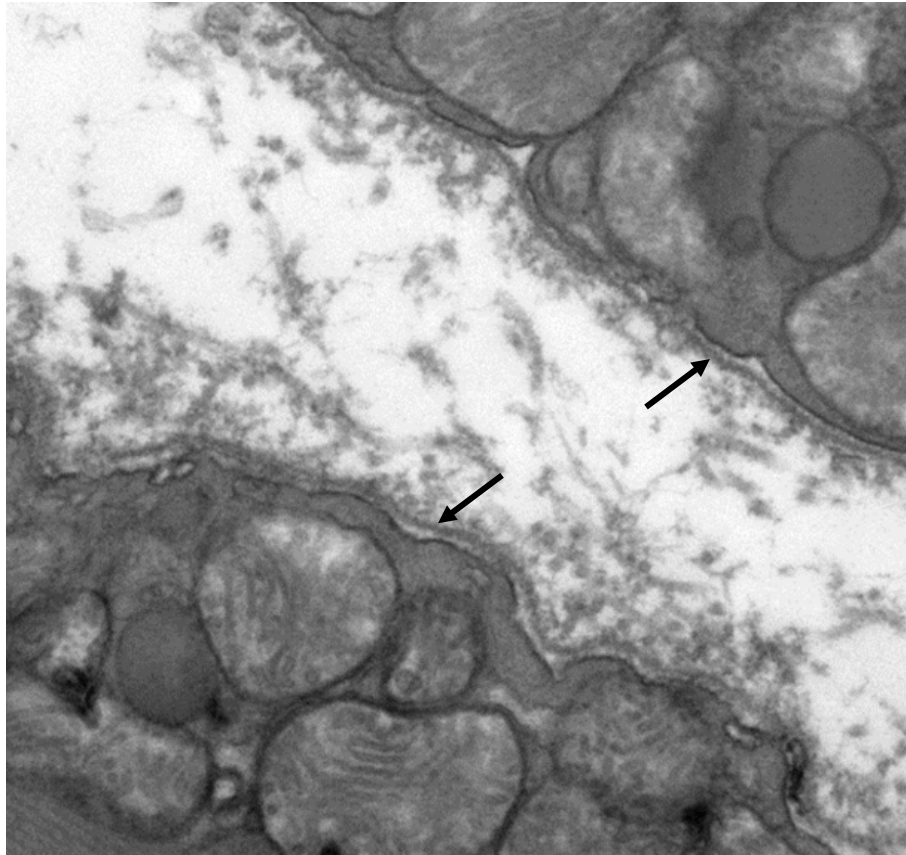


Kjaer (2004). *Physiological Reviews*, 84: 649.

# Skeletal Muscle Basal lamina

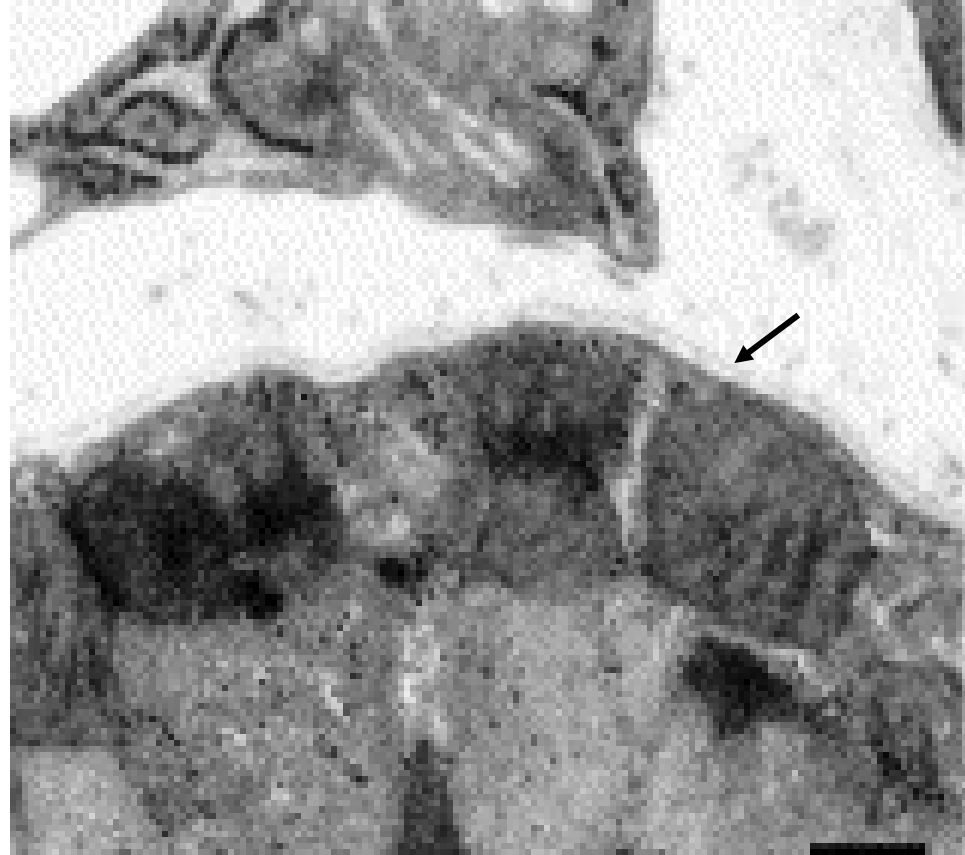
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Mouse skeletal muscle



Goddeeris *et al* (2013). *Nature*, 503:136

Human skeletal muscle



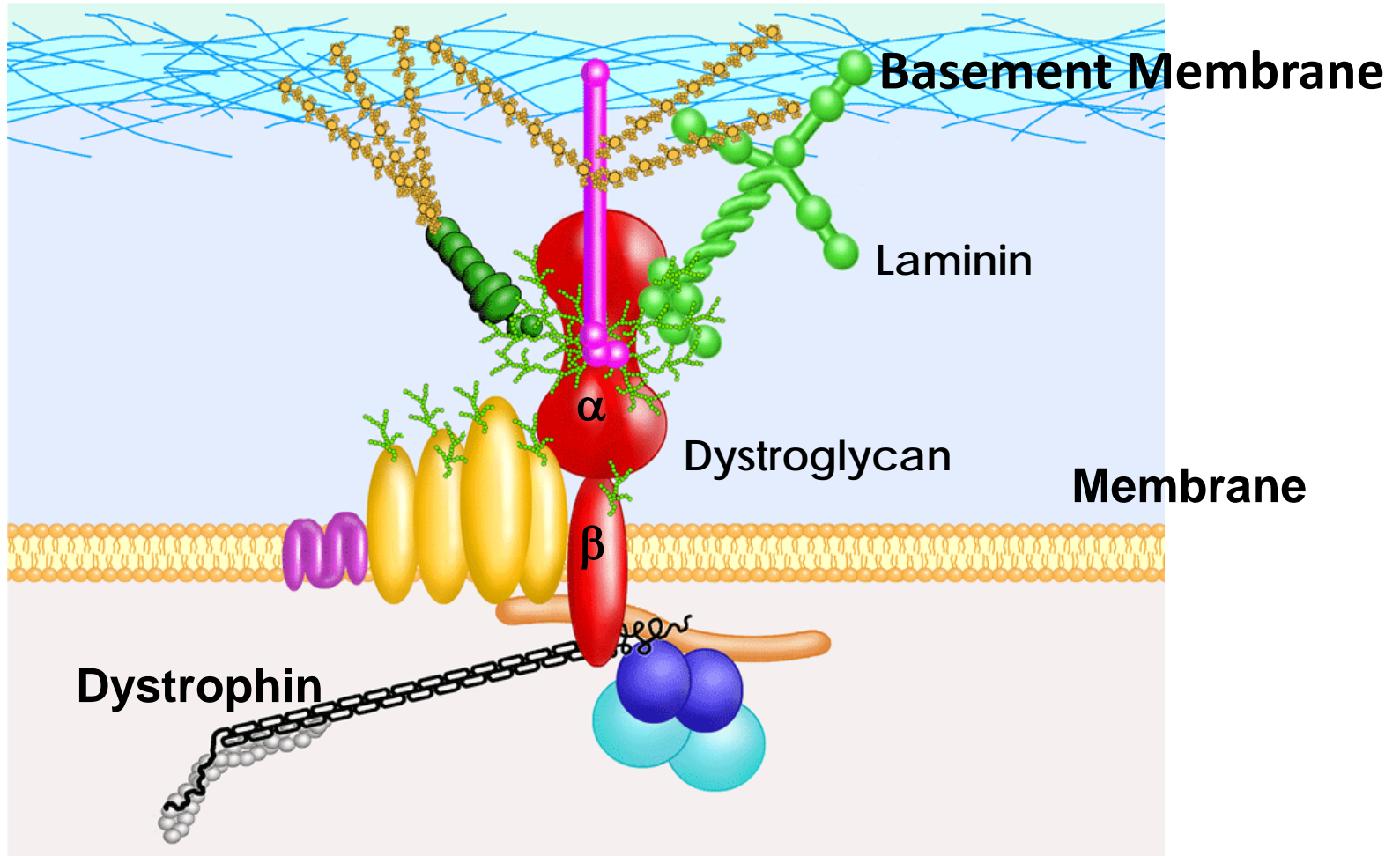
Sabatelli *et al* (2003). *Biochim Biophys Acta*, 1638:57

# Outline

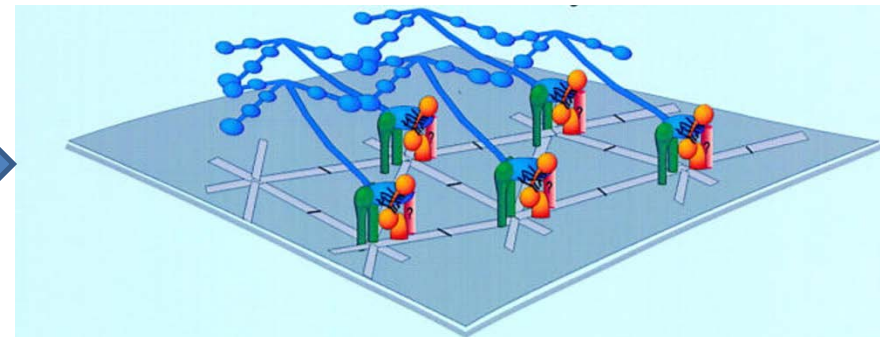
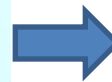
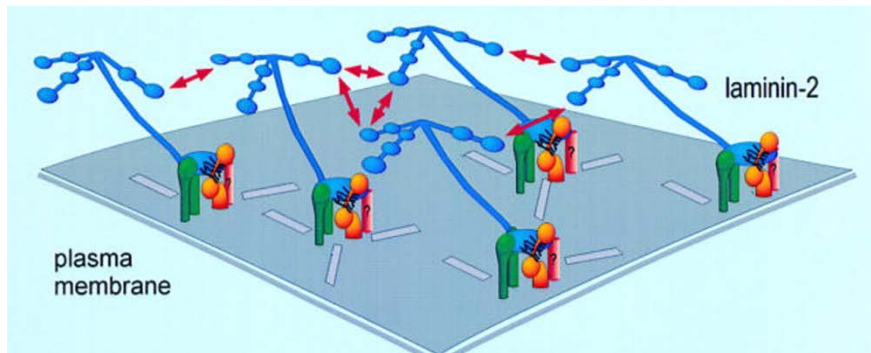
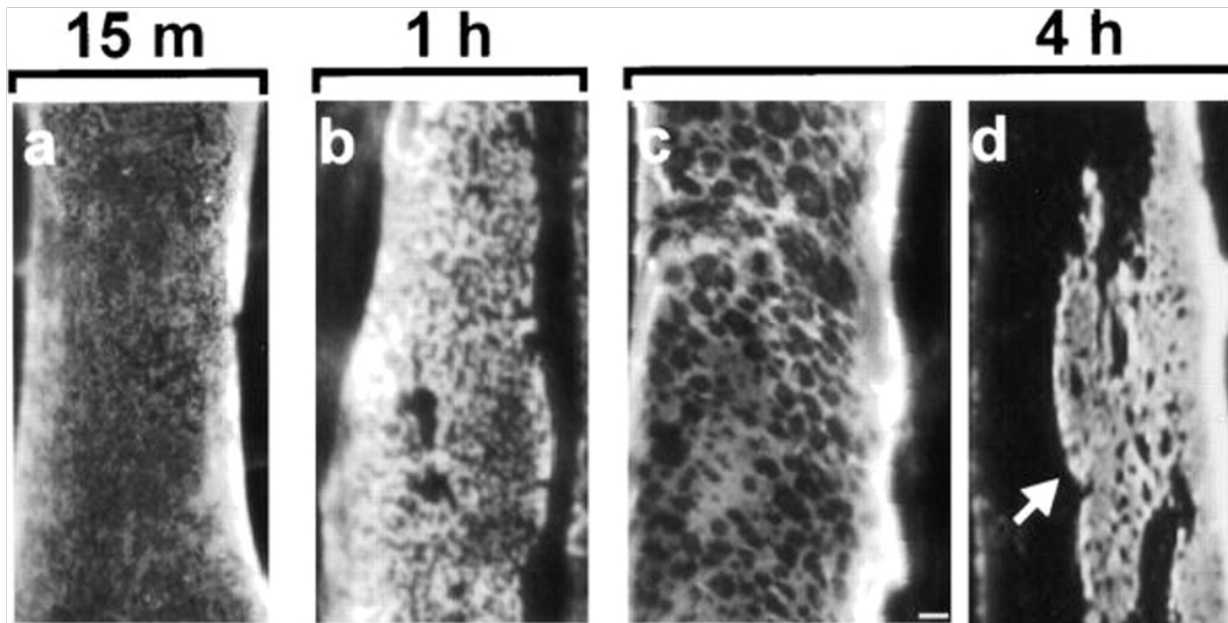
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# Dystroglycan



# Basement Membrane compaction



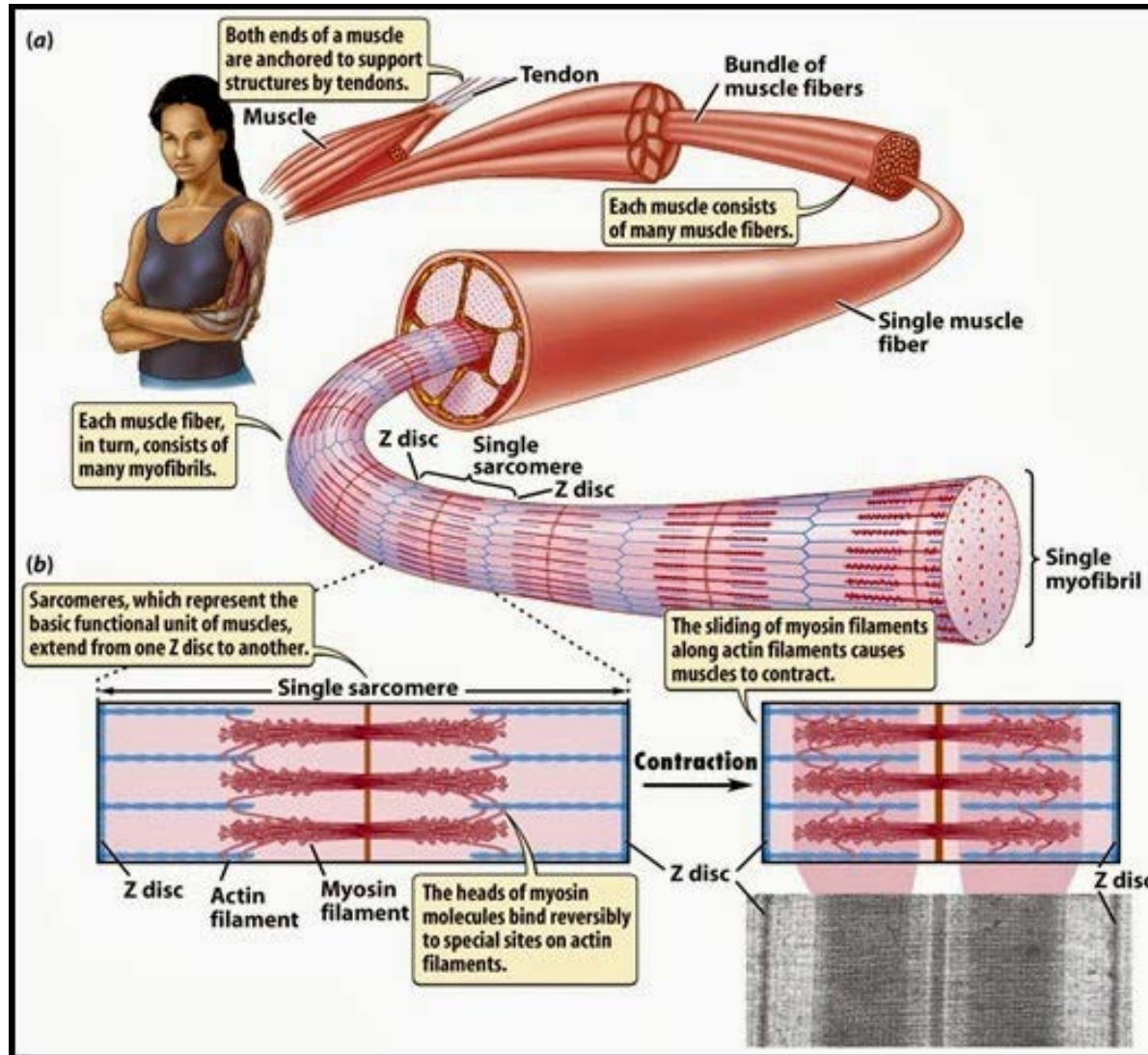
Colognato 1999. JCB, 145:619

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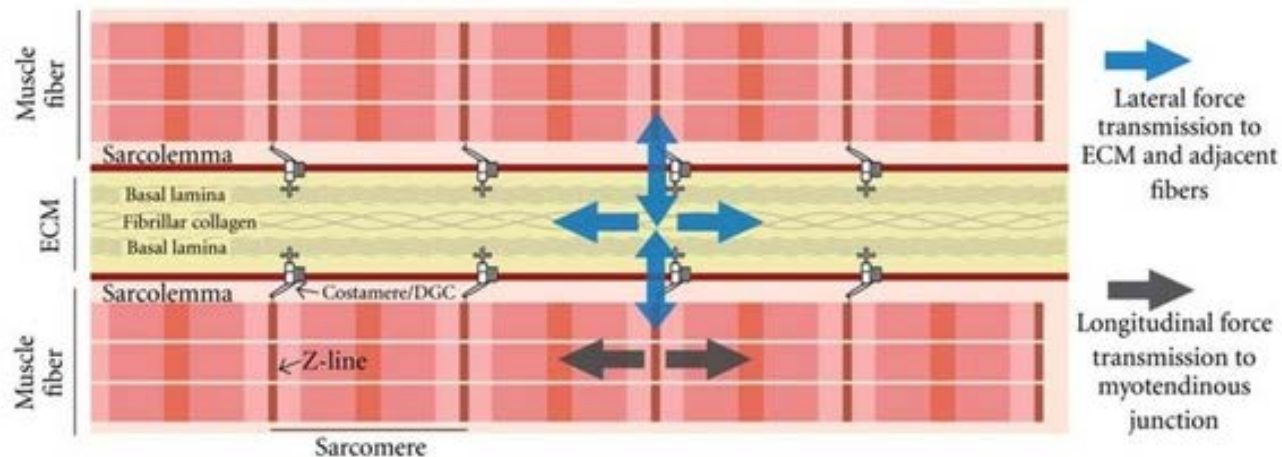
# Muscle Contraction



# Transmission of force

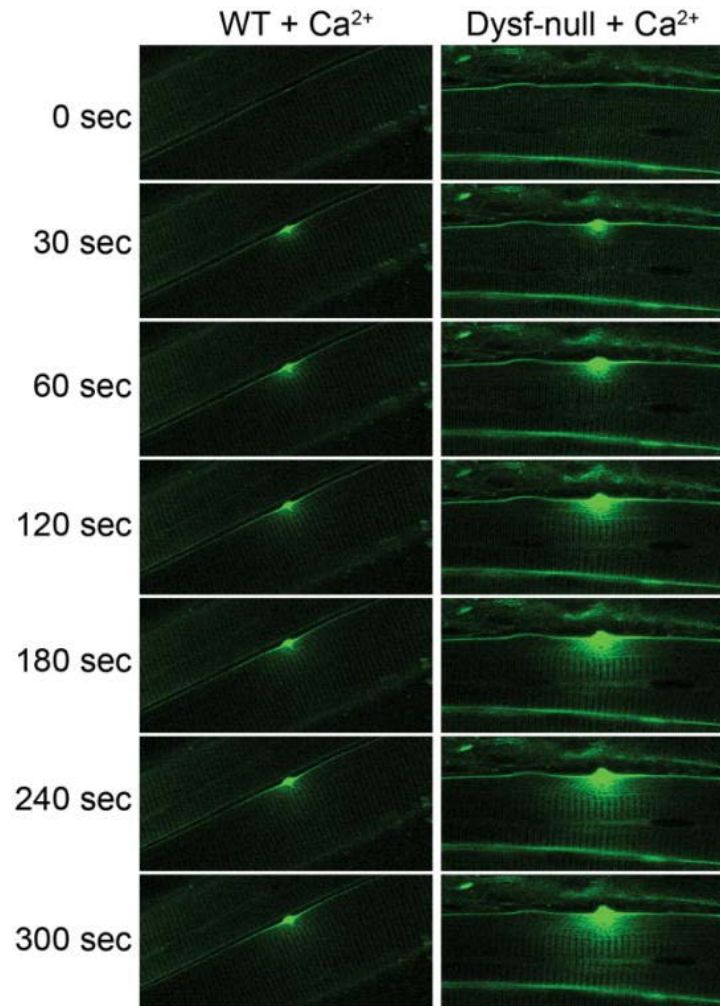
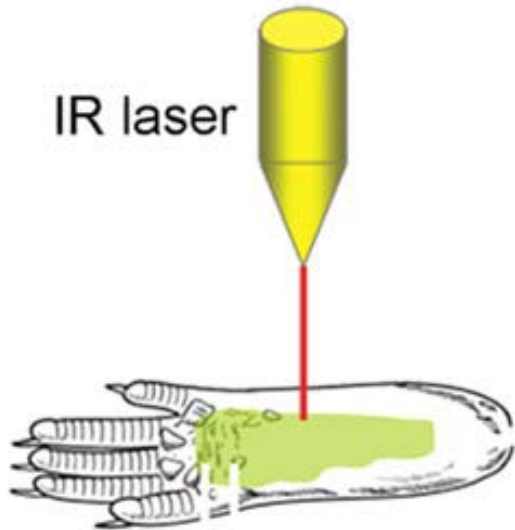


DGC might contribute to “lateral transmission of force” from the sarcomere to the lateral extracellular matrix.



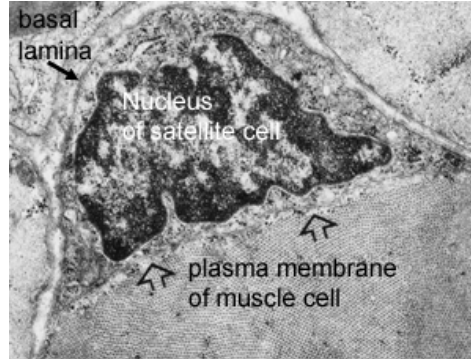
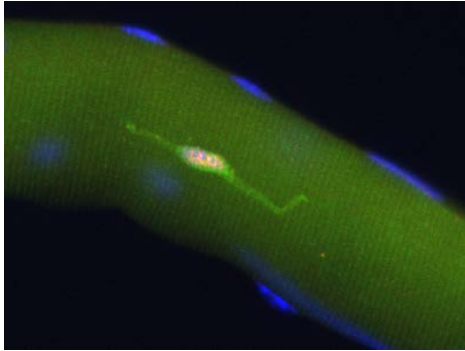


# Muscle Fiber Repair

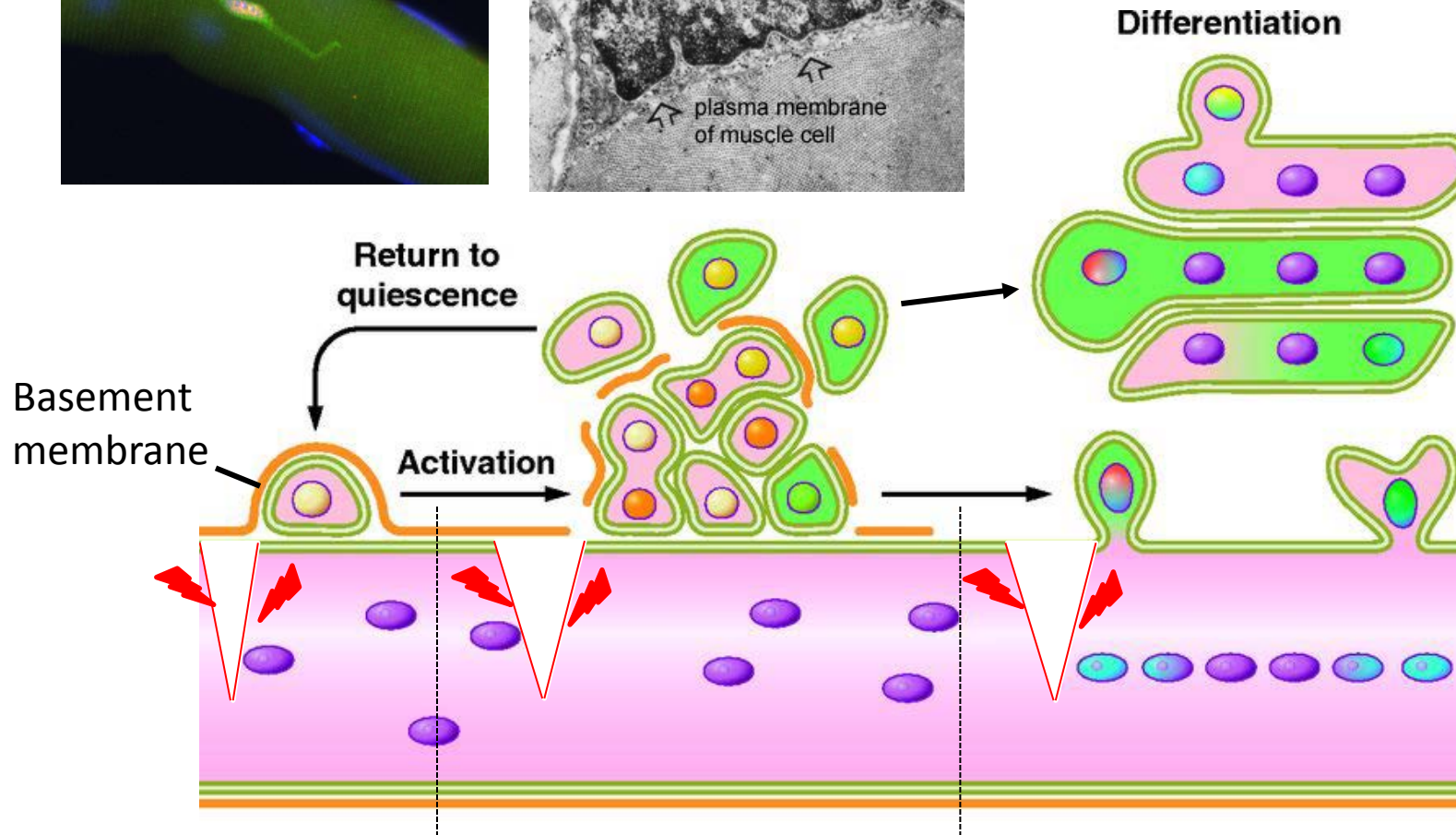


Han *et al* (2007). *Curr. Opin. Cell Biol.*, 19:409.

# Satellite Cells

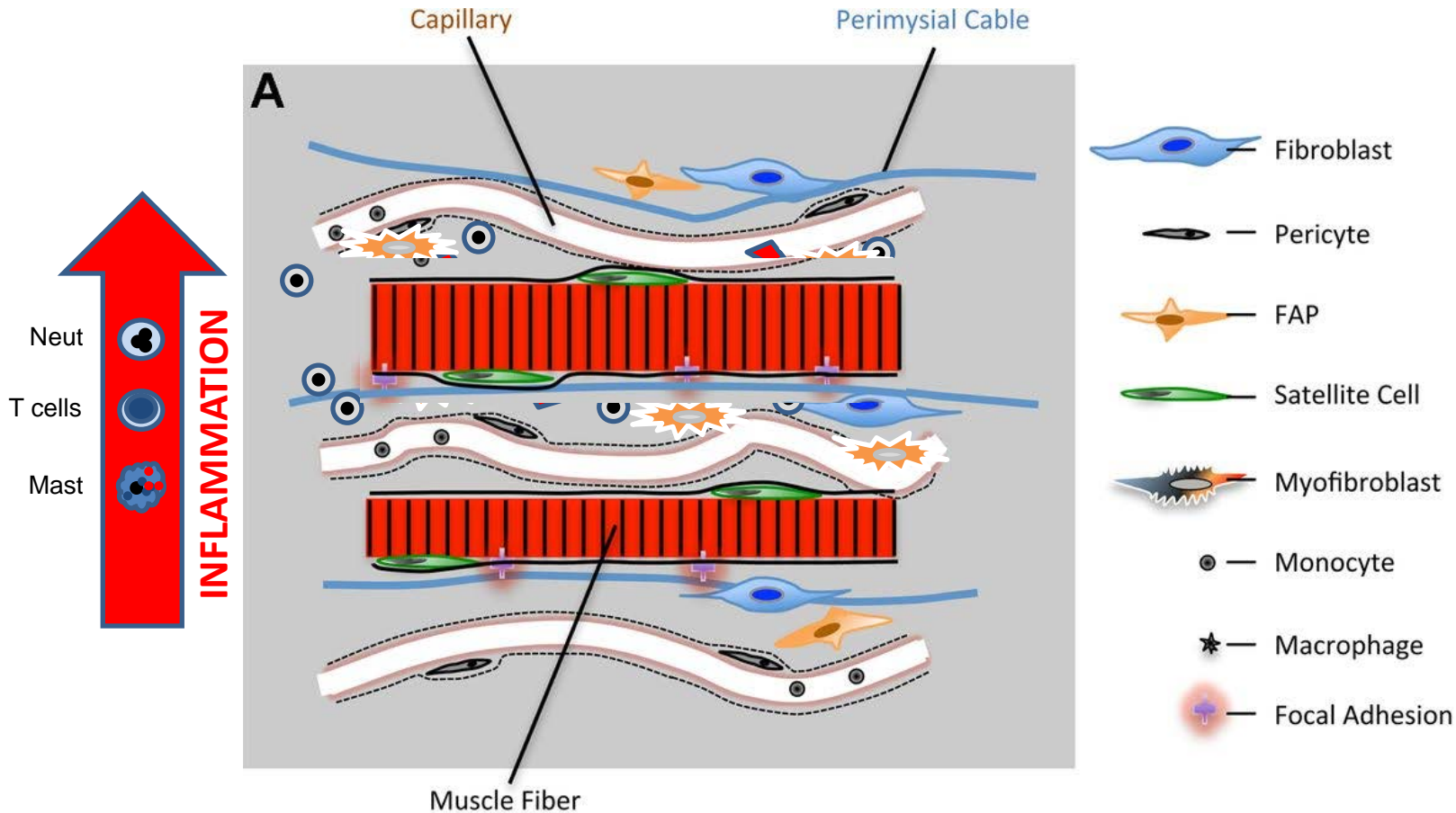


Satellite cells are quiescent unipotent stem cells, located underneath the basal lamina of adult skeletal muscle fibers



From Yin *et al* (2013). *Physiological Reviews*, 93:23.

# Immune cells and fibroblasts



Well integrated for a healthy muscle

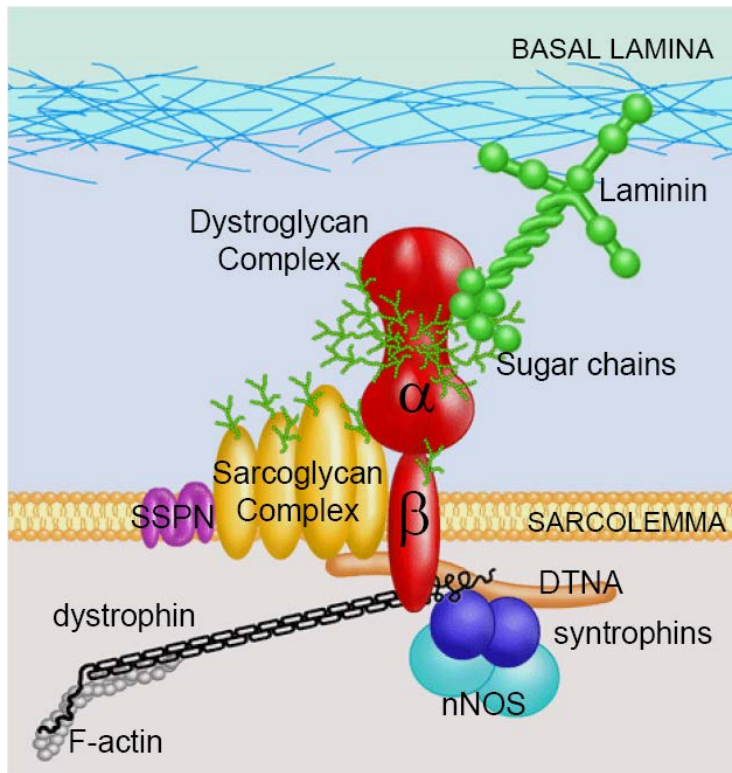
# Outline

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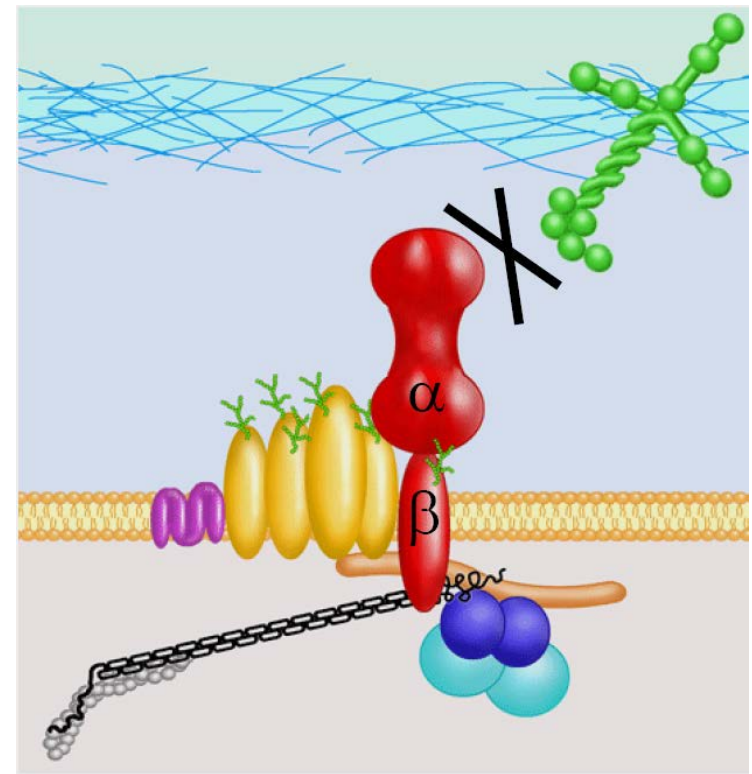
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# Loss of $\alpha$ -Dystroglycan functional glycosylation

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Normal



Dystroglycanopathy

# Dystroglycanopathies spectrum

## Congenital muscular dystrophy

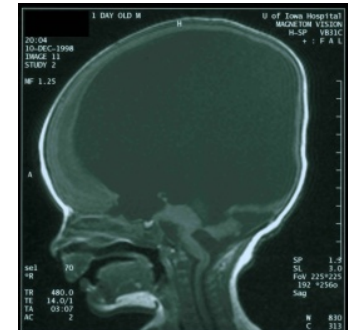
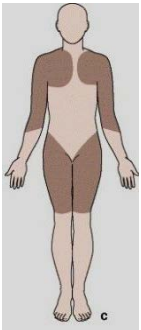
LGMD

CMD  
no brain involvement

CMD  
w/ brain involvement  
Muscle-Eye-Brain (MEB)  
Fukuyama-CMD (FCMD)

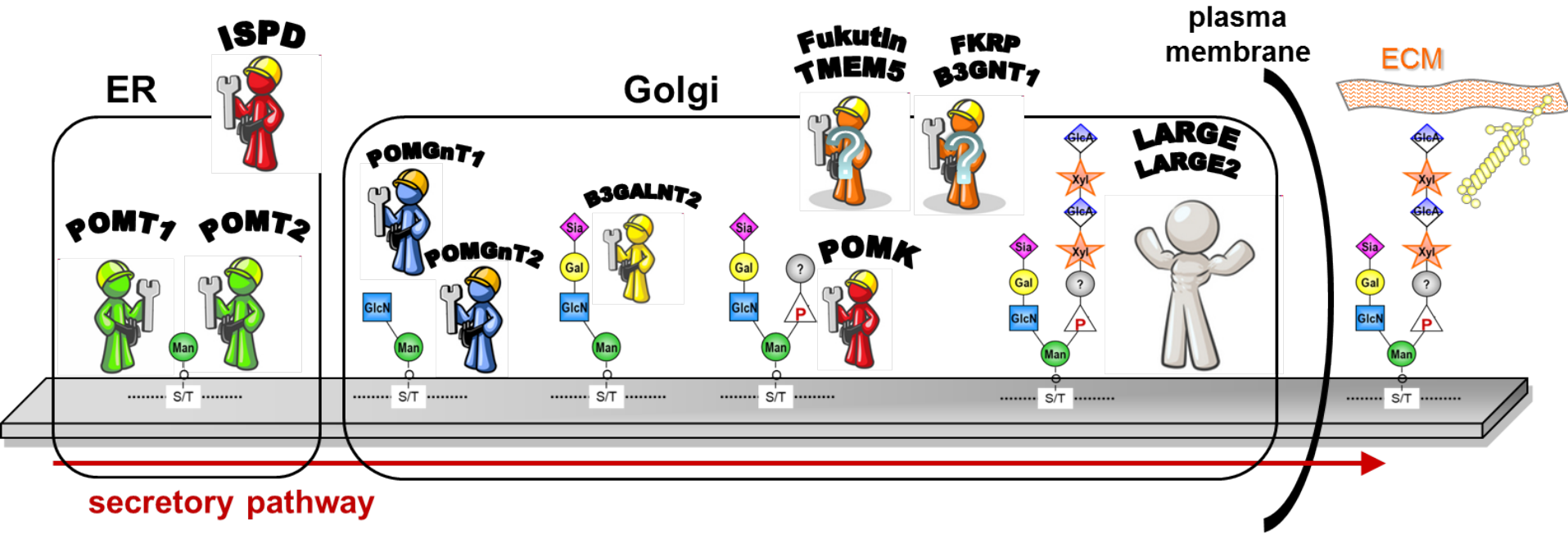
Walker-Warburg  
(WWS)

Severity



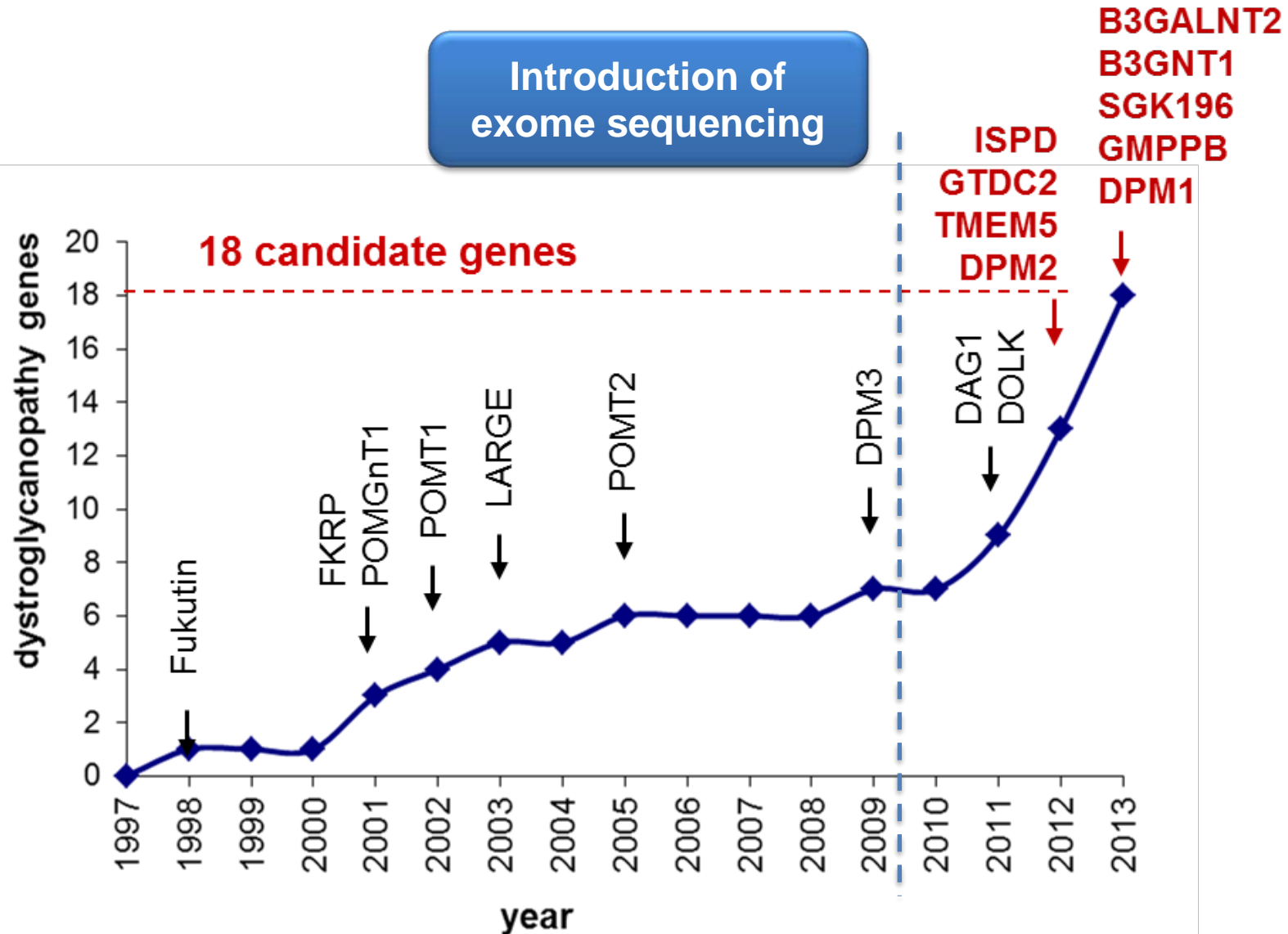
# Dystroglycan Glycosylation Process

Generated by Tobias Willer



# Dystroglycanopathy candidate genes

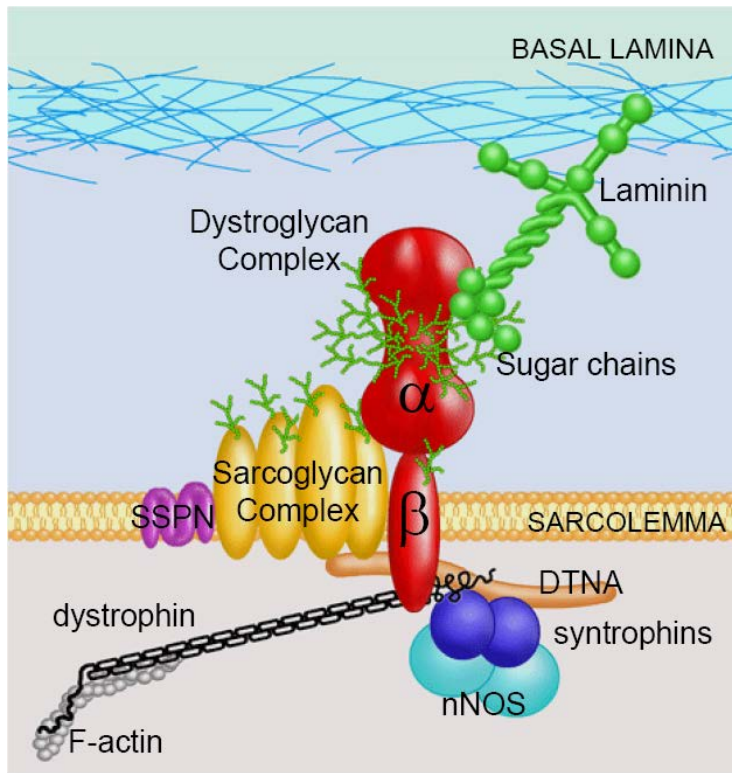
Generated by Tobias Willer



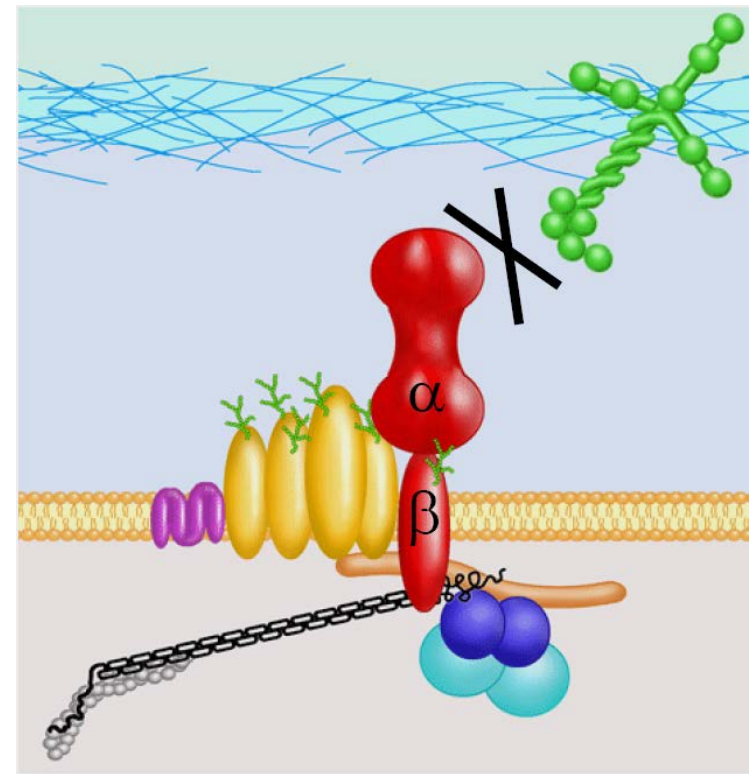


# Loss of $\alpha$ -Dystroglycan functional glycosylation

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Normal



Dystroglycanopathy

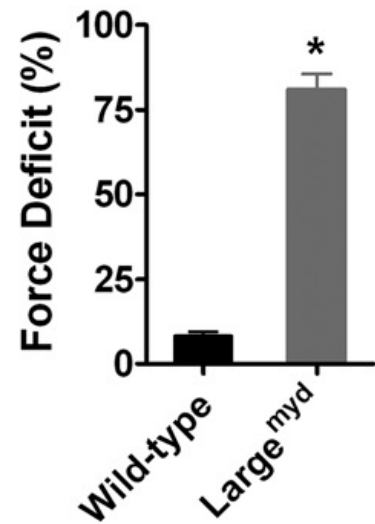
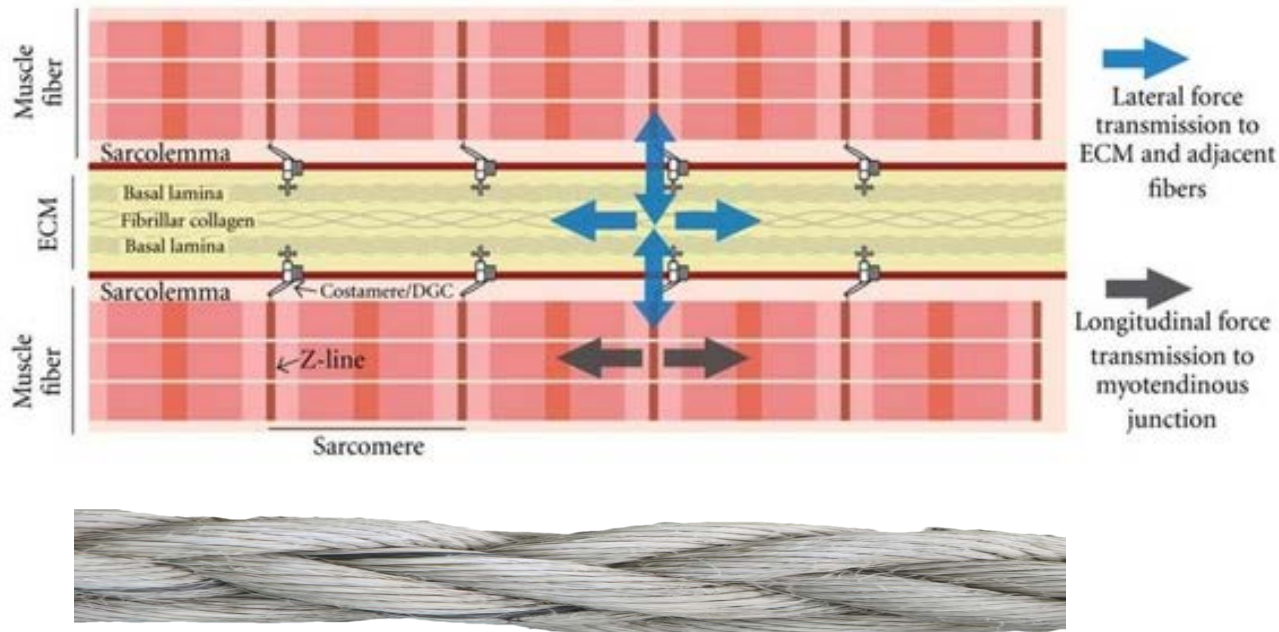
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  - Debris clearance and extracellular remodeling.

# Muscle Force Deficit

## Lateral transmission of force

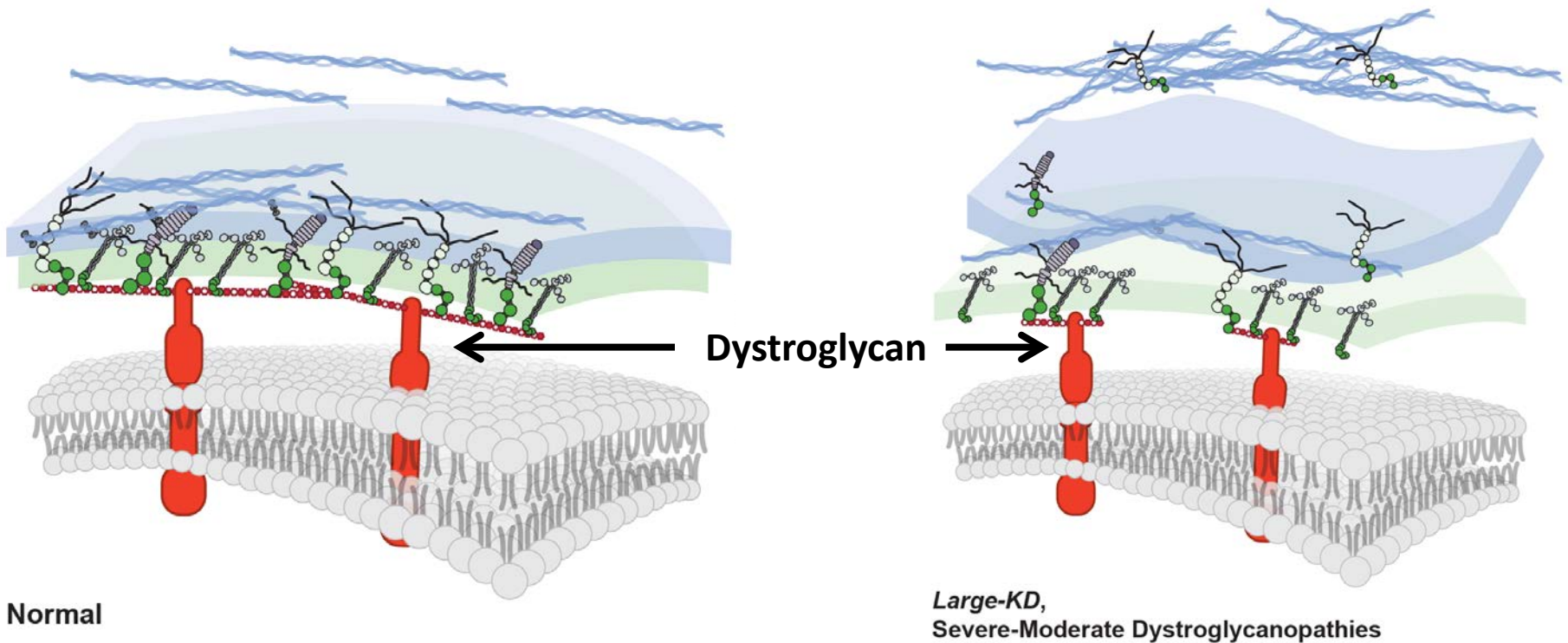


Dystrophic muscle displays considerable muscle weakness even in very early stages of the disease, prior to muscular atrophy.

Muscle as a unit

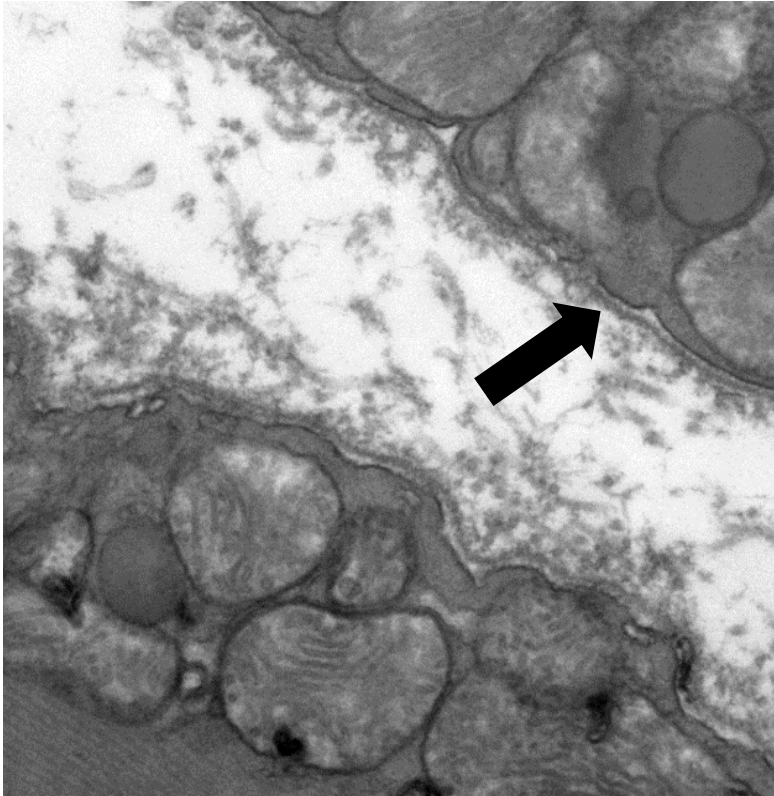
# Model: $\alpha$ DG Large-glycan as a tunable scaffold for the basement membrane.

Generated by Matt Goddeeris

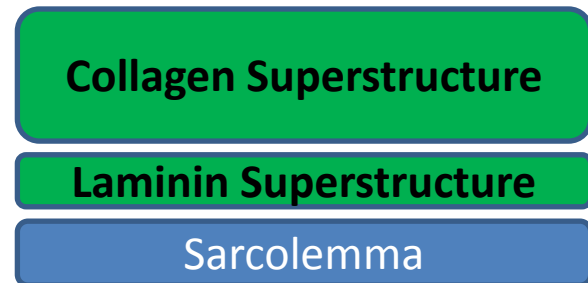
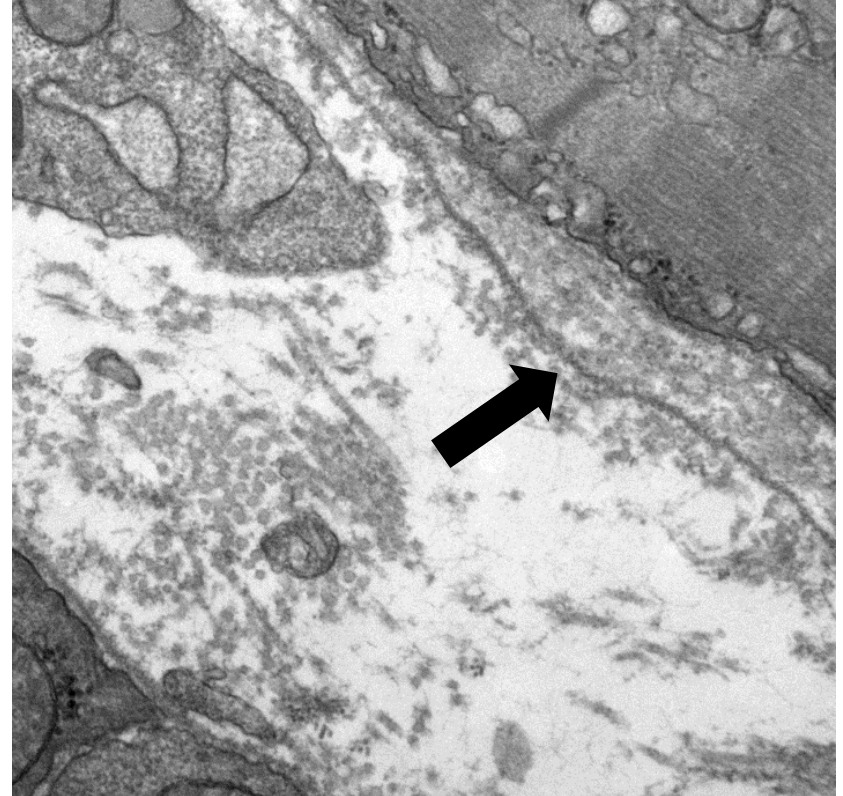


# Basement Membrane compaction

Typical amount of glycan



Reduced glycan

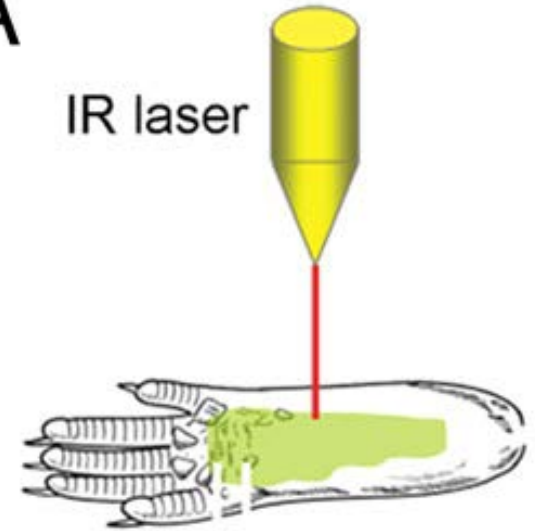


# Laser membrane damage assay

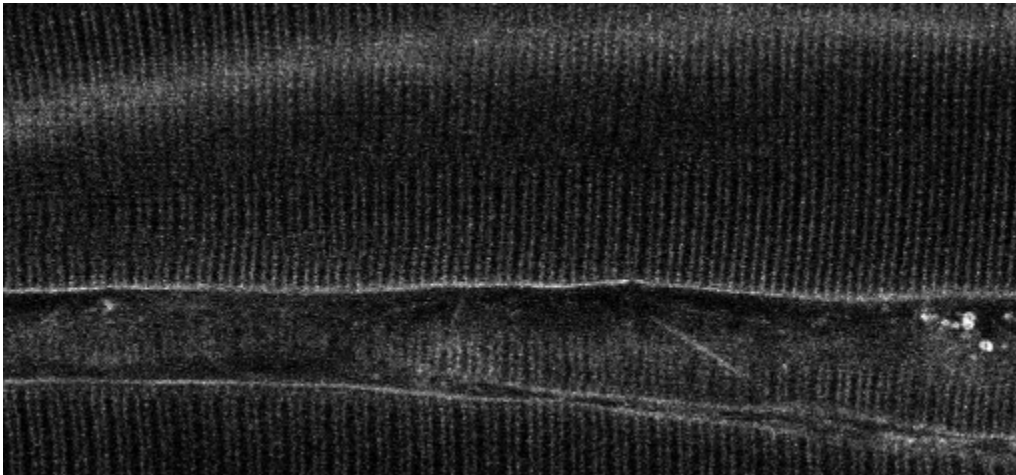
Wild type



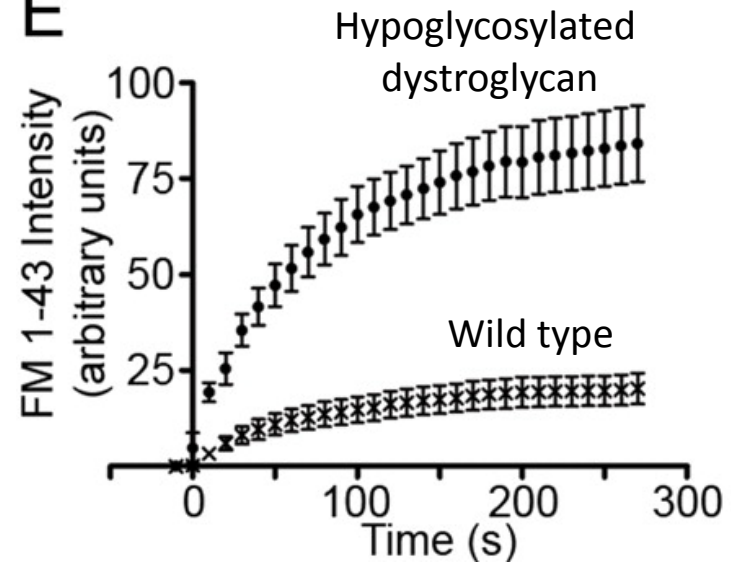
A



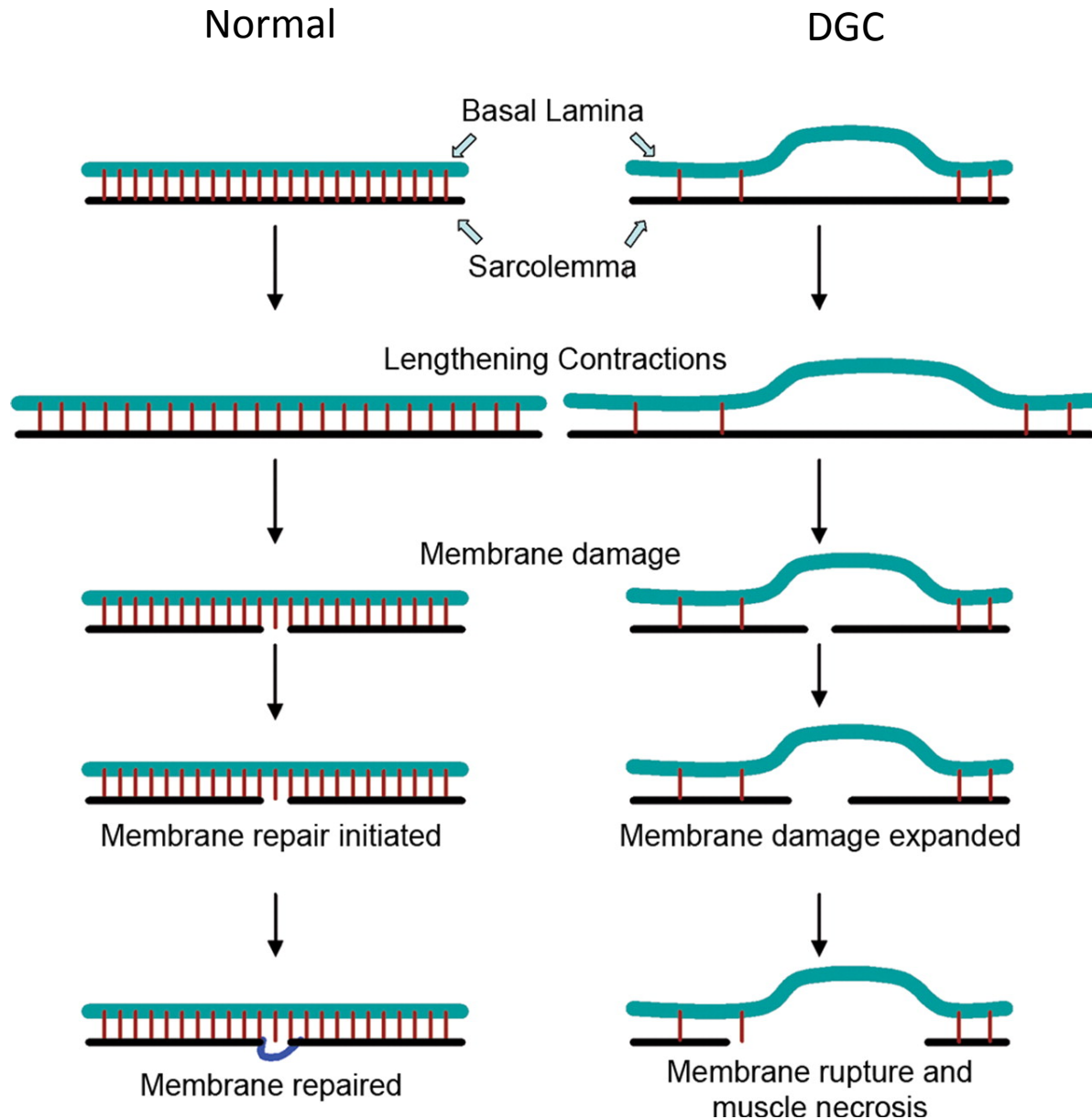
Hypoglycosylated  
dystroglycan



B



# Fracture mechanics of the plasma membrane



# Satellite cells

Dystroglycan plays a role in the attachment and/or stability of satellite cells.

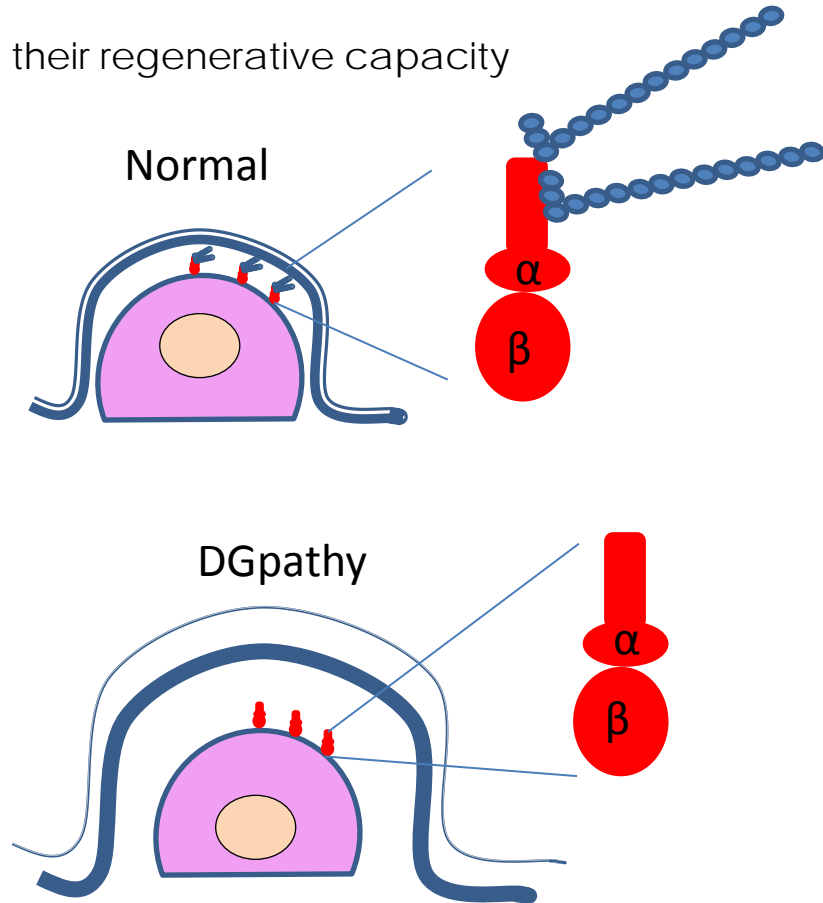
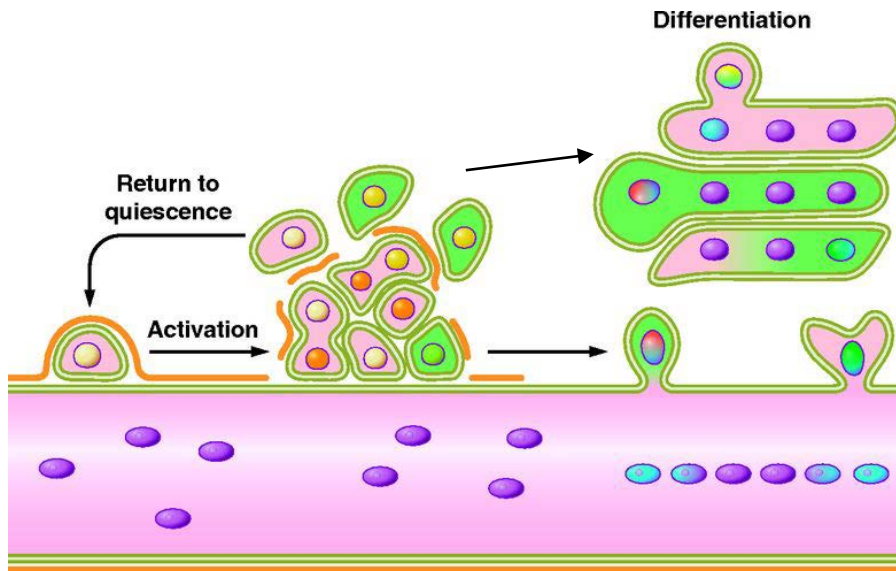
Basal lamina components in the are known to govern satellite cell behavior; laminin-211 is particularly important.

Satellite cells in the muscles become exhausted, losing their regenerative capacity

Ross *et al* (2012). *Stem Cells*, 30:2330.

Proliferation is compromised in *myd* CSs

More fibronectin and collagen in *myd*



From Yin *et al* (2013). *Physiological Reviews*, 93:23.



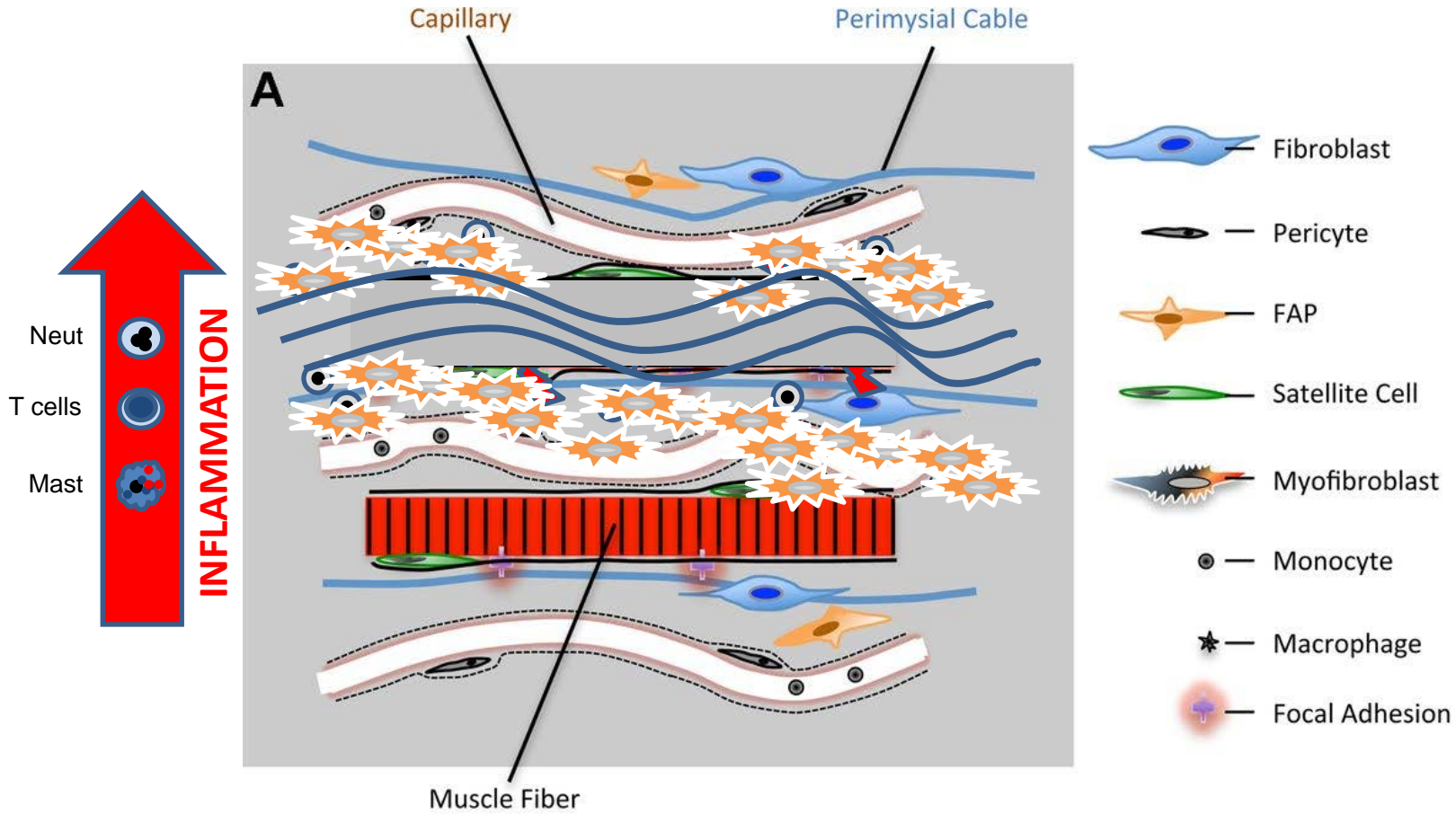
# The human body: Cells and connections

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Communication and ..... Contact

# Immune cells and fibroblasts

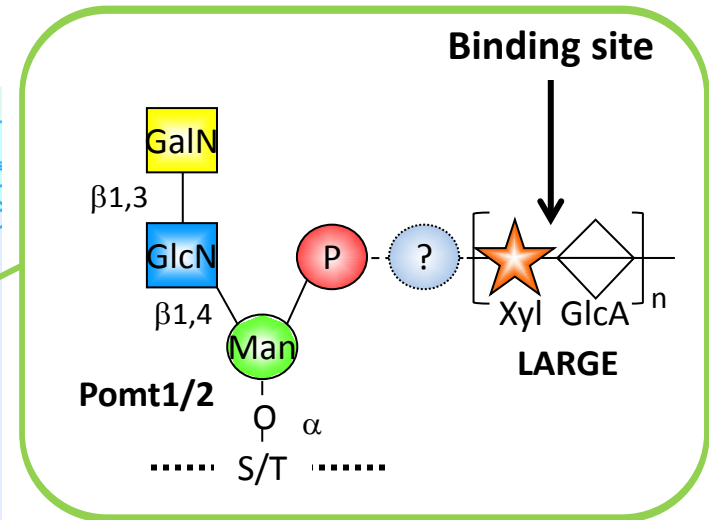
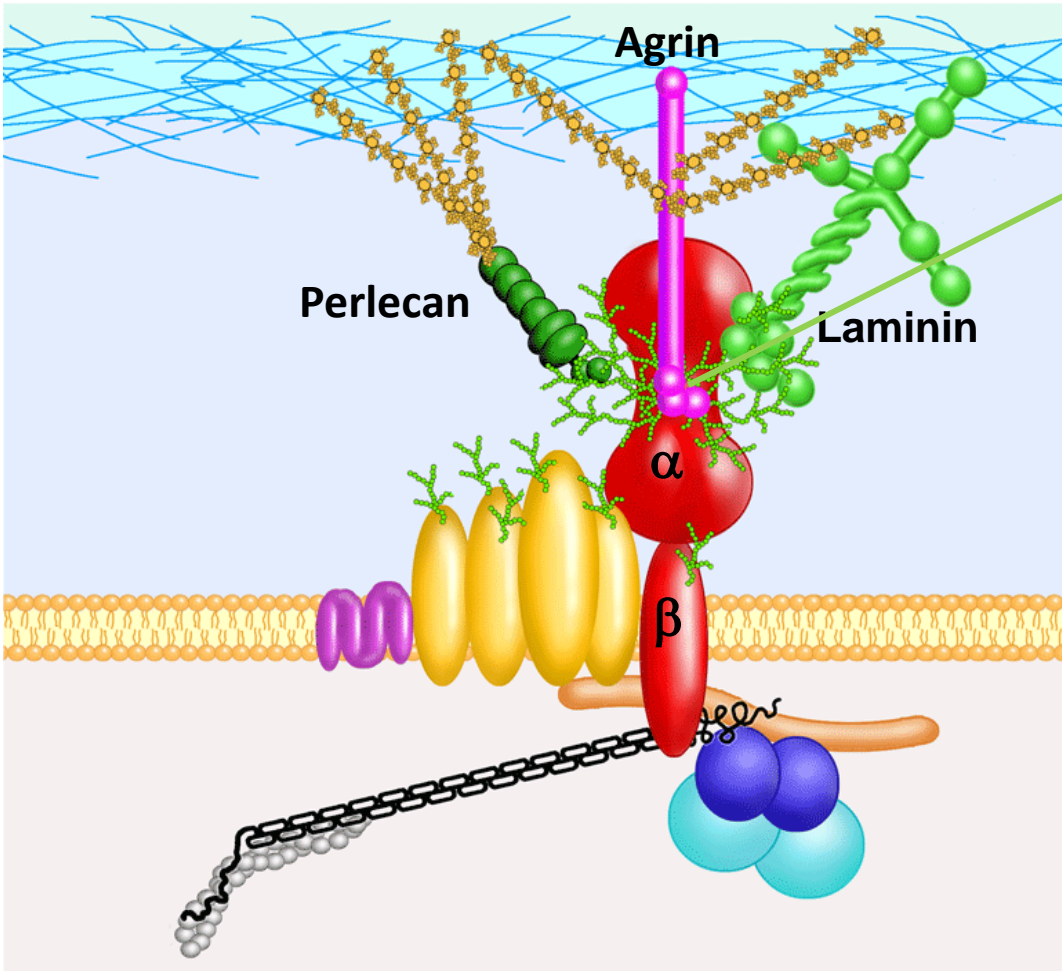


# Possible Therapies

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- Contraction.
  - Contraction induced muscle damage.
  - Muscle Fiber repair.
- 
- Satellite cells fate.
  - Satellite cells exhaustion.
- 
- Immune response and fibrosis.

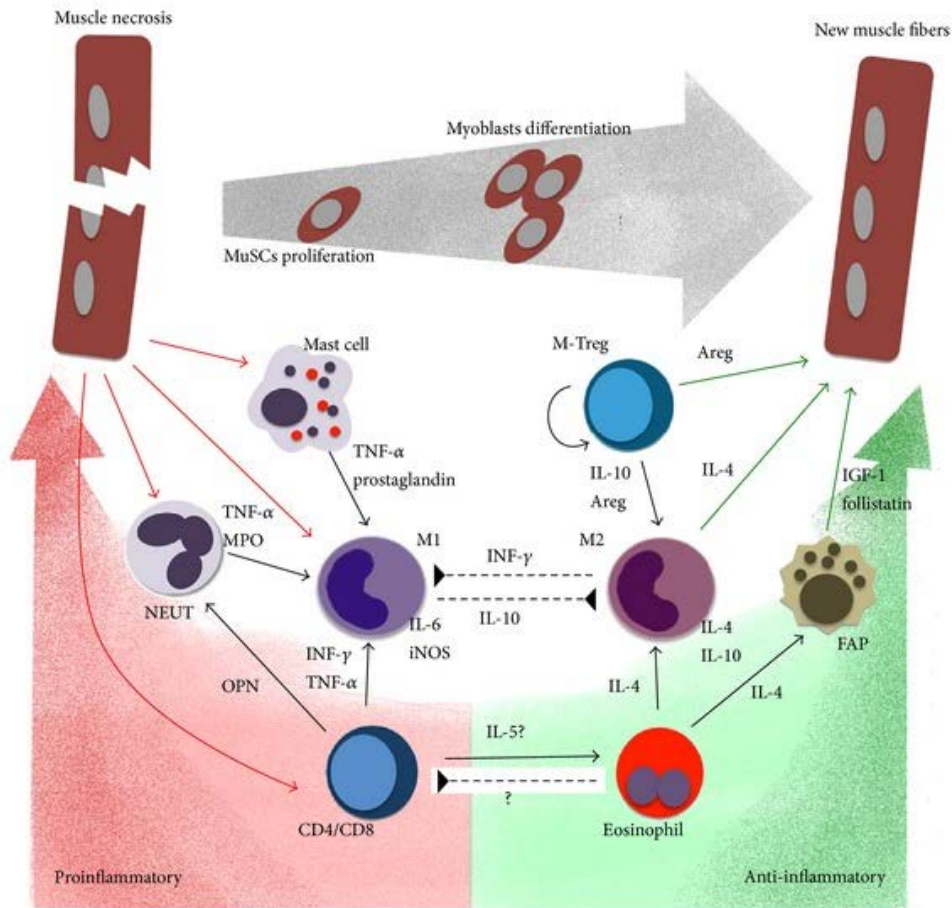
# Possible Therapies



**Pharmacotherapy:**  
 Upregulate glycosylation.  
 Upregulate LARGE.

**Gene Therapy:**  
 AAV gene delivery (FKRP, LARGE)

# Possible Therapies



**Pharmacotherapy:**  
Vasodilator  
Anti inflammatories  
SCs directed therapies

**Cell Therapy:**  
Modification of patient SCs  
Cell Transplantation

Madaro & Bouche (2014). *Biomed Res Int*, 2014: 438675

# THANK YOU!

