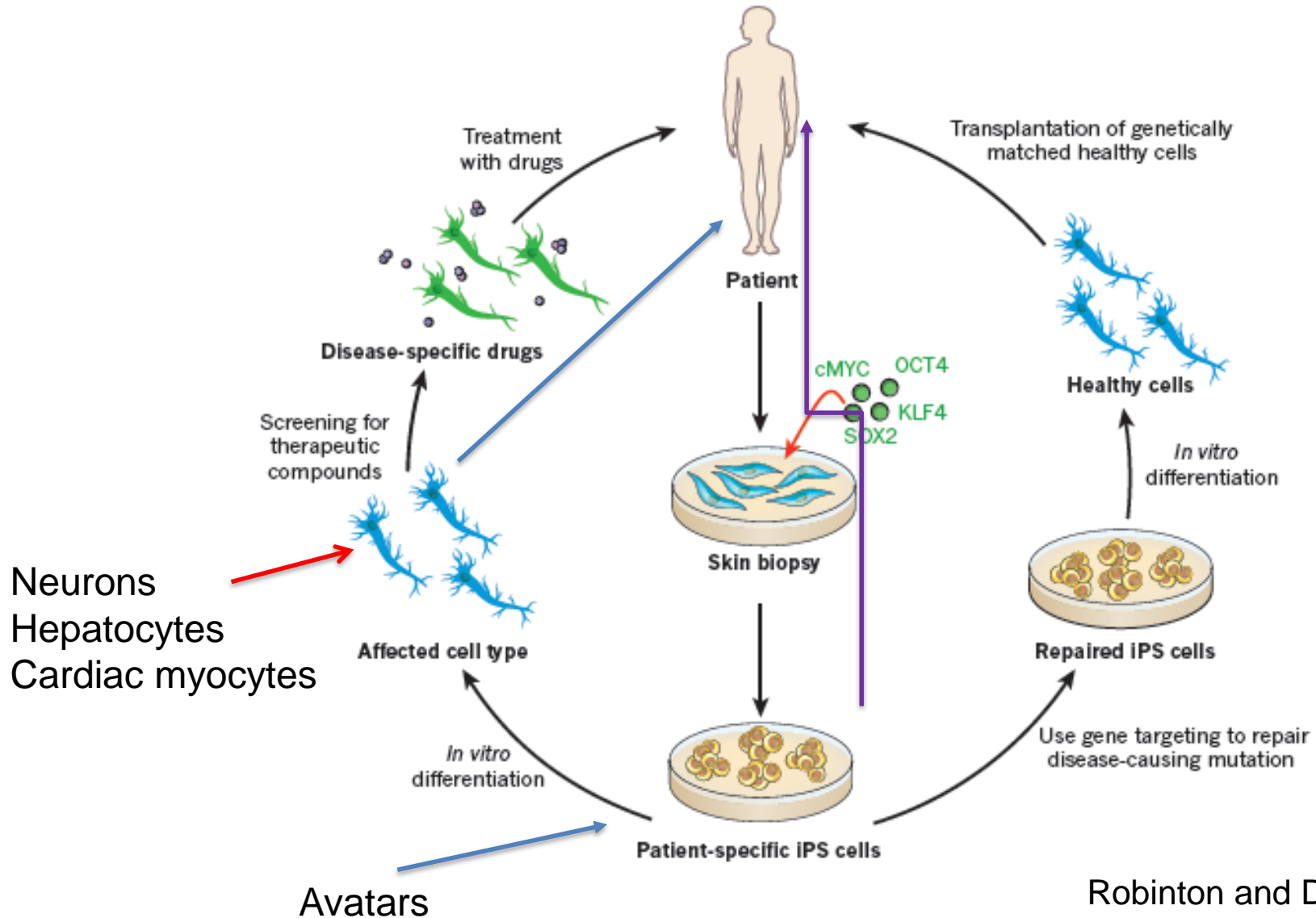




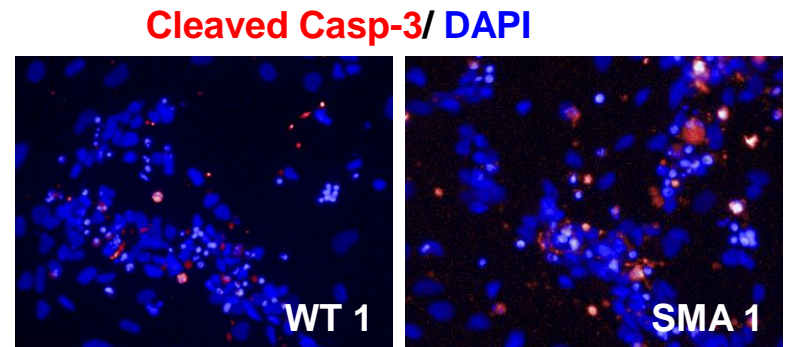
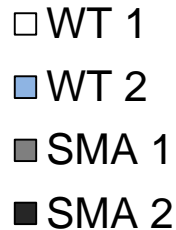
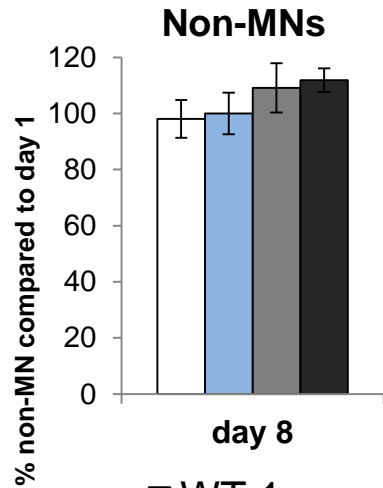
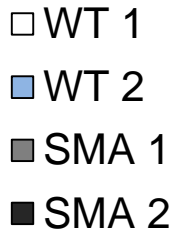
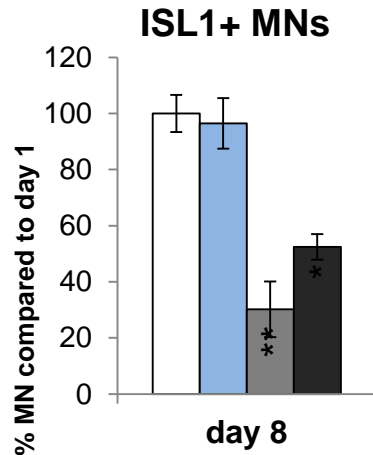
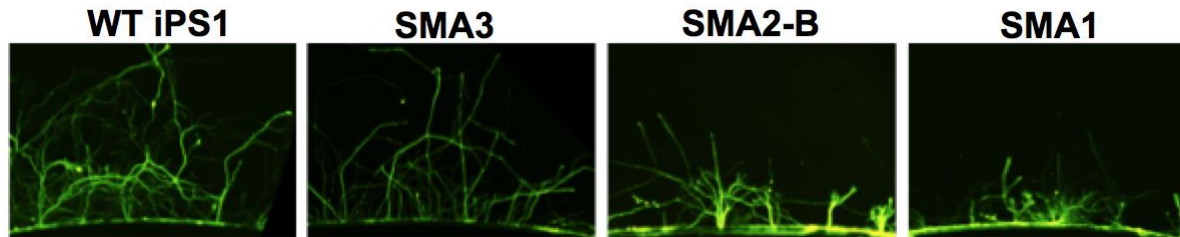
# Predicting Systemic Defects in SMA

Lee L Rubin

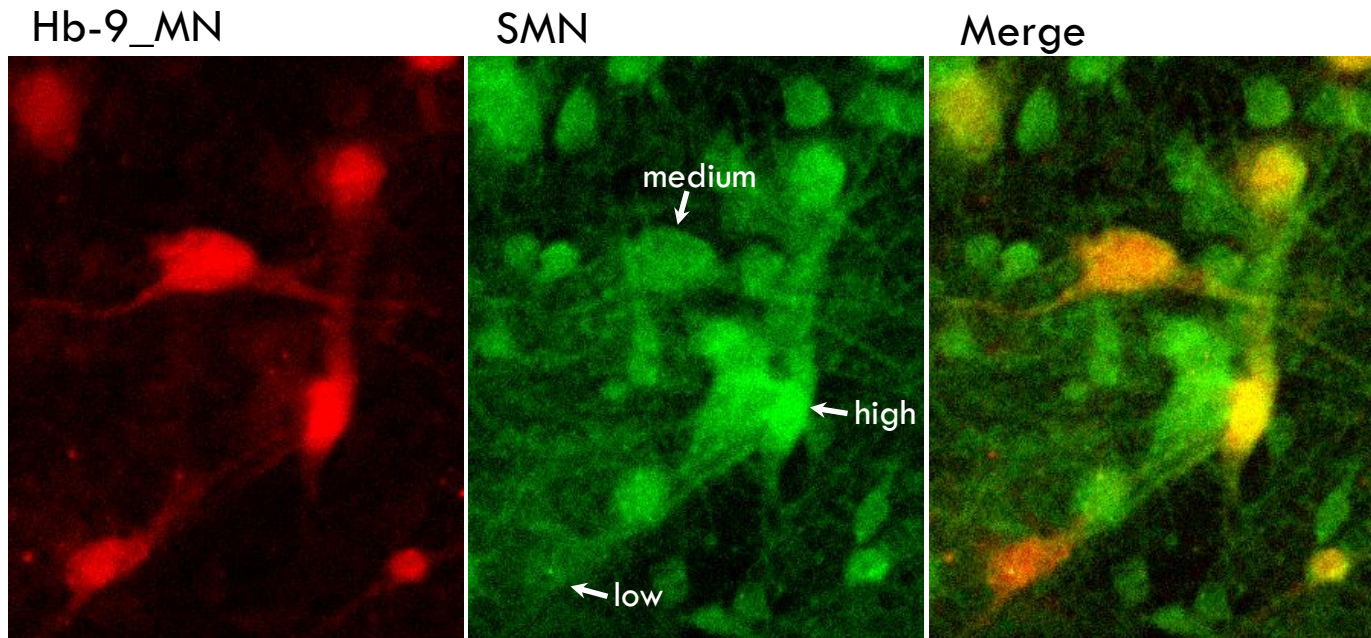
# Stem Cells and Drug Discovery: A Bidirectional Patient-Centric Method



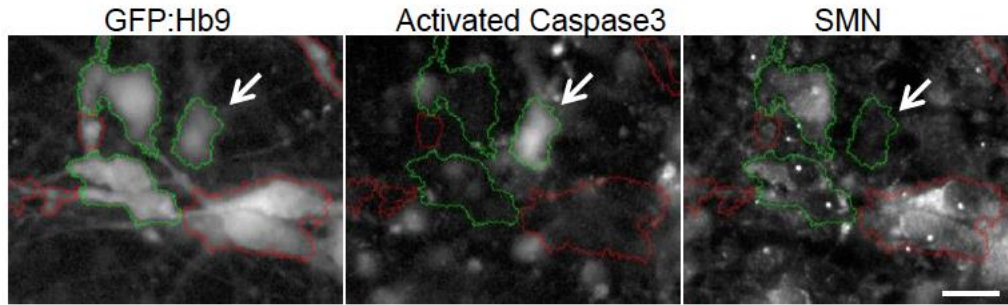
# Motor neurons produced from SMA patient iPSCs recapitulate motor neuron component of SMA



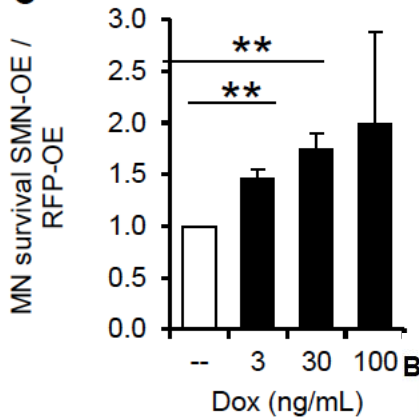
Single cell imaging: SMN levels vary in individual motor neurons in SMA and wildtype cultures.



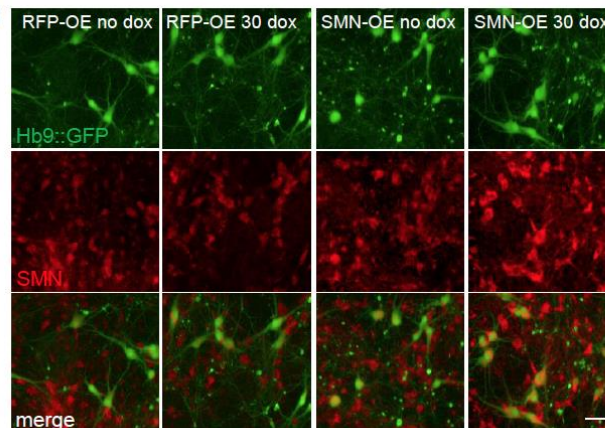
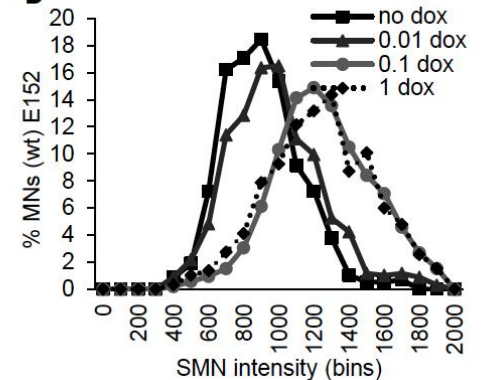
Muela-Rodriguez et al. Cell Reports, 2017

**A**

Cells with low SMN have a higher probability of dying; this is true in SMA and wildtype cultures.

**C**

Increasing SMN levels (using a dox-inducible lentiviral expression construct) increases motor neuron survival in both SMA and wildtype cultures.

**D**

Rodriguez-Muela et al., Cell Reports, 2017

# Summary

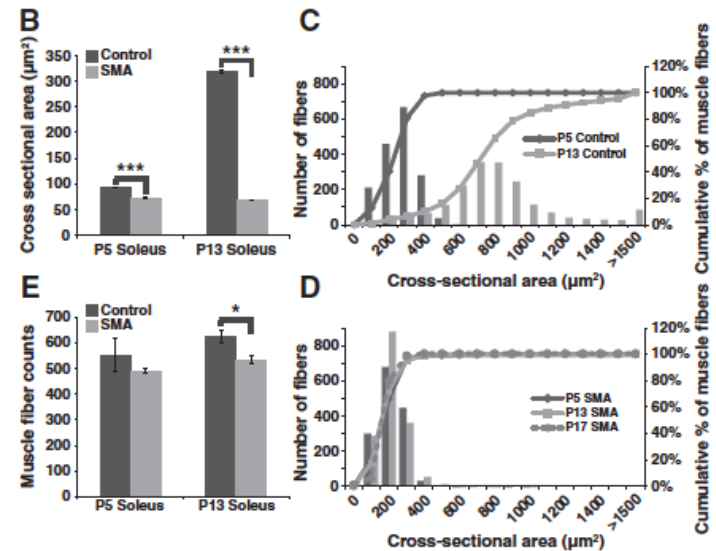
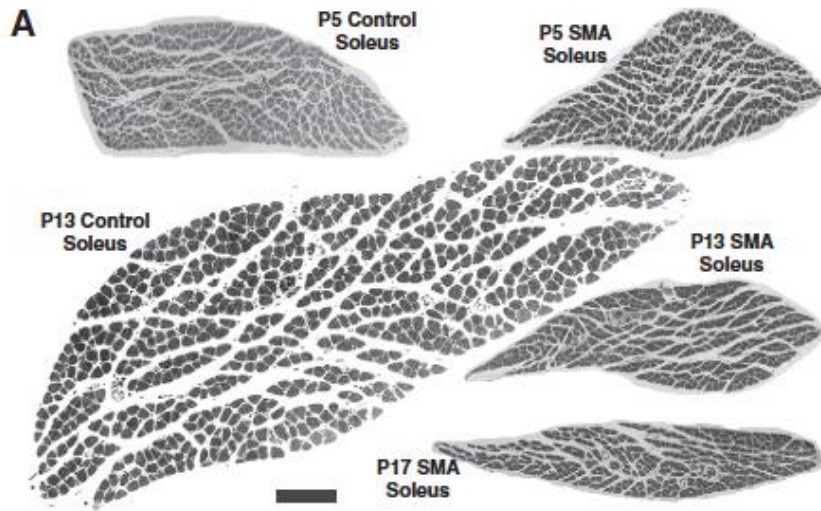
- Why is there rapid loss of some motor neurons but a sparing of others?
  - Cells with higher SMN have a greater probability of surviving.
  - The acute period of SMA kills off the most vulnerable motor neurons, leaving behind relatively normal motor neurons.
- Does this mean that SMA becomes primarily a systemic disease after vulnerable MNs die?
  - If so, which other tissues are most affected?
  - Spinraza is delivered intrathecally

# Data supporting likelihood of systemic defects in SMA

- Patient iPSCs have skewed differentiation potential compared to controls.
  - Gene expression analysis of iPSCs
  - In vitro experiments confirming inability of iPSCs to generate specific cell types effectively.
    - Skeletal muscle differentiation is poor.

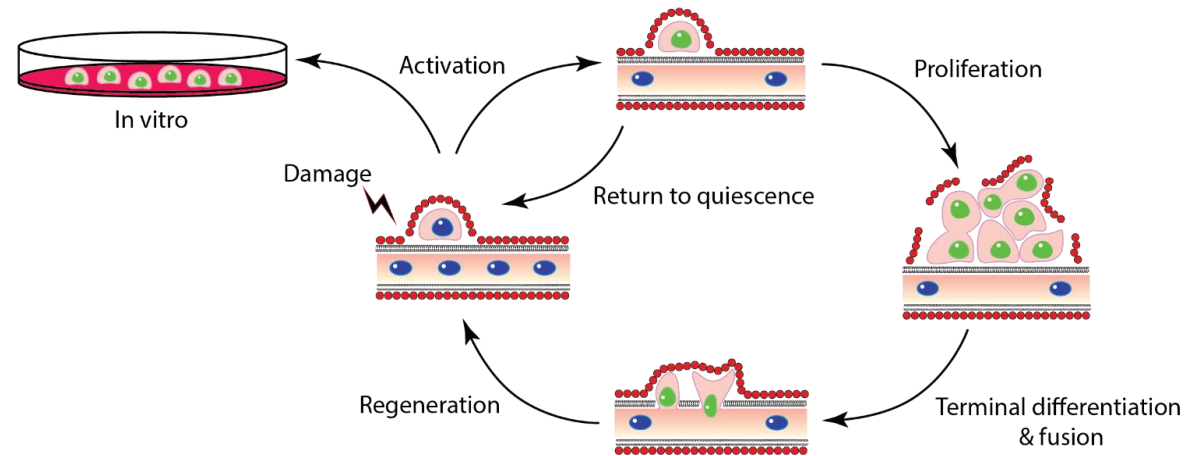
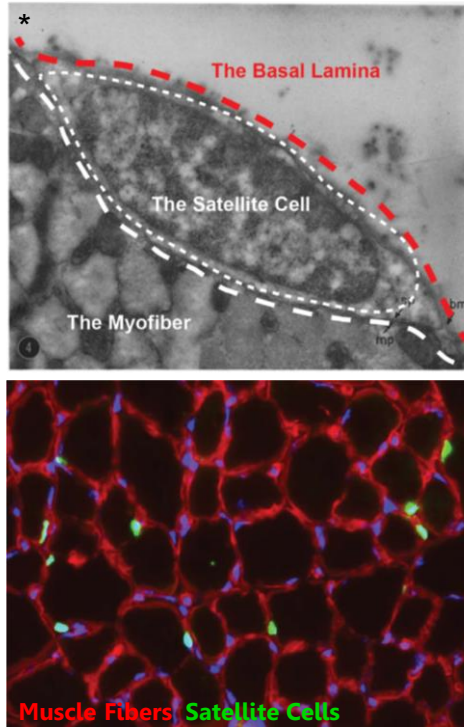
# Aberrant development of SMA mouse muscle

Y. Lee et al. / *Developmental Biology* 356 (2011) 432–444

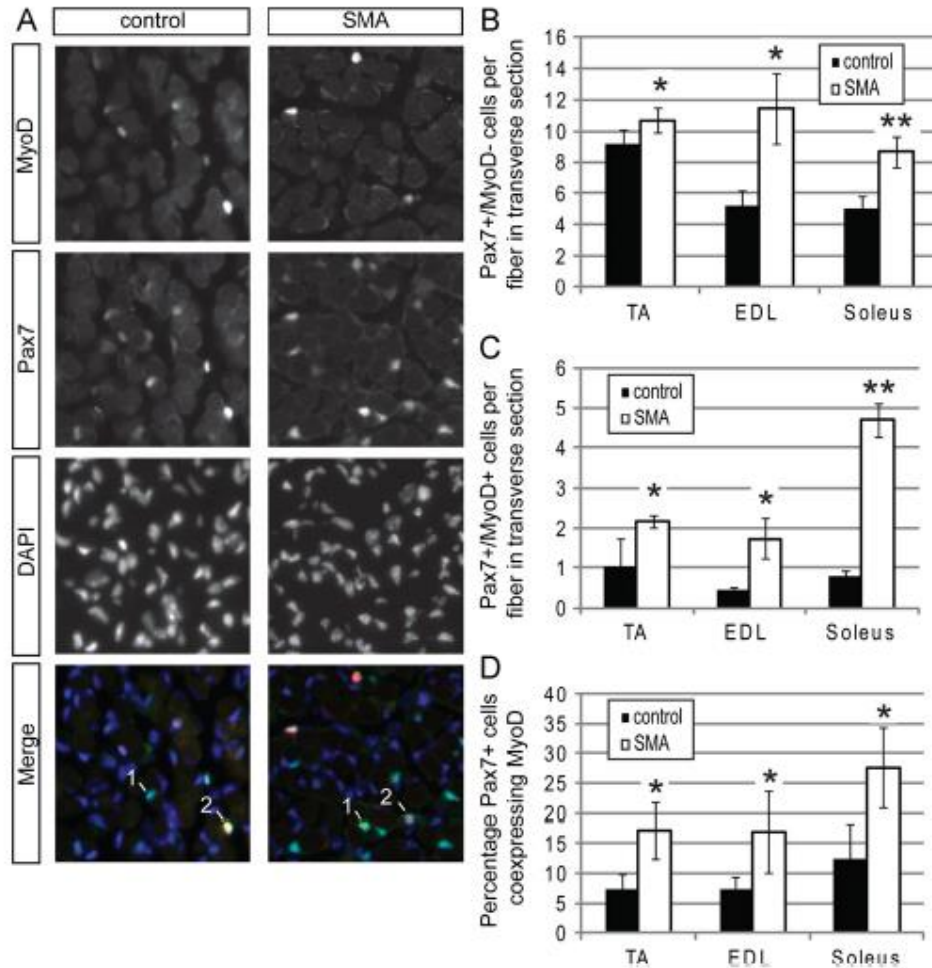




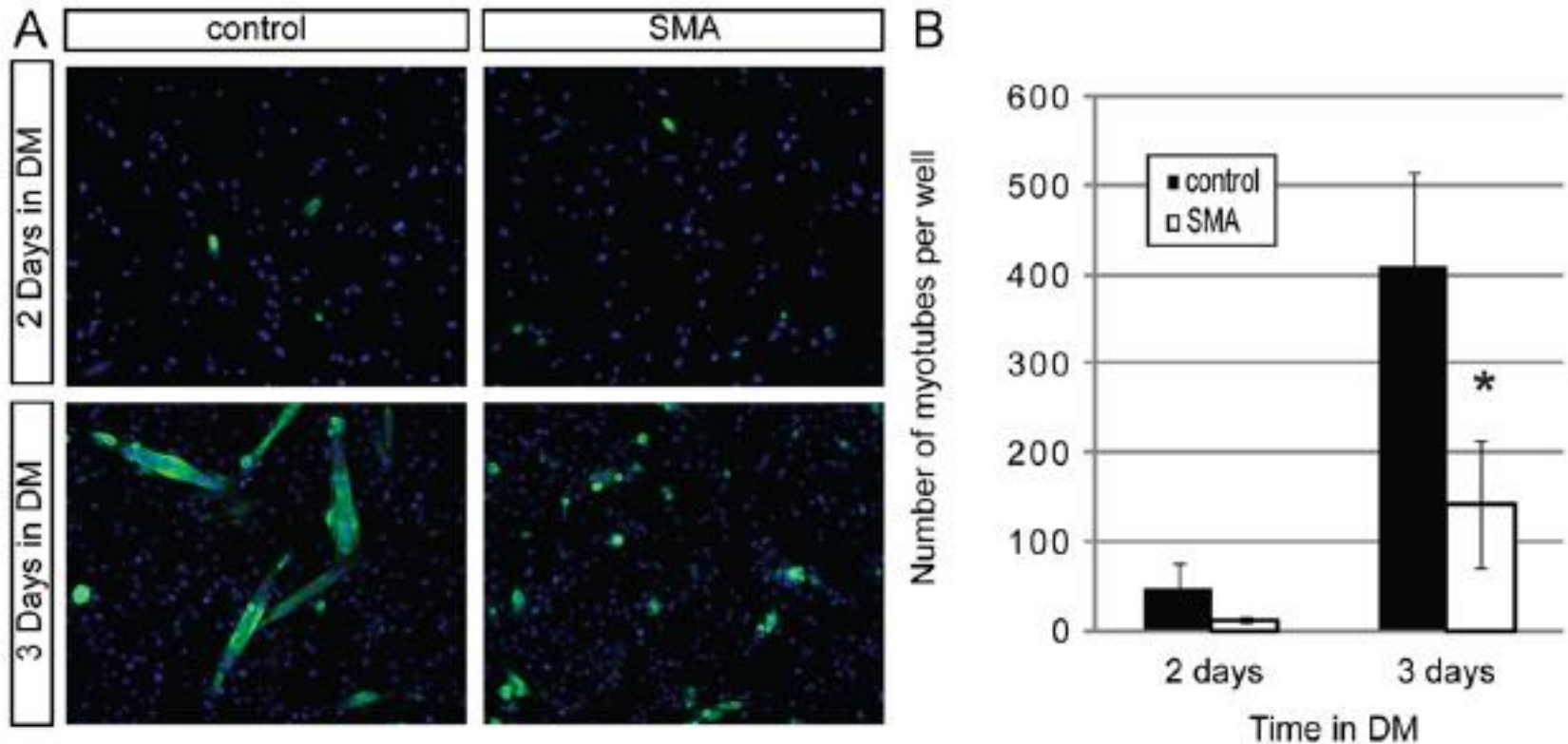
# Satellite cells function in muscle development and regeneration.



# SMA satellite cells differentiate prematurely in vivo and in vitro.

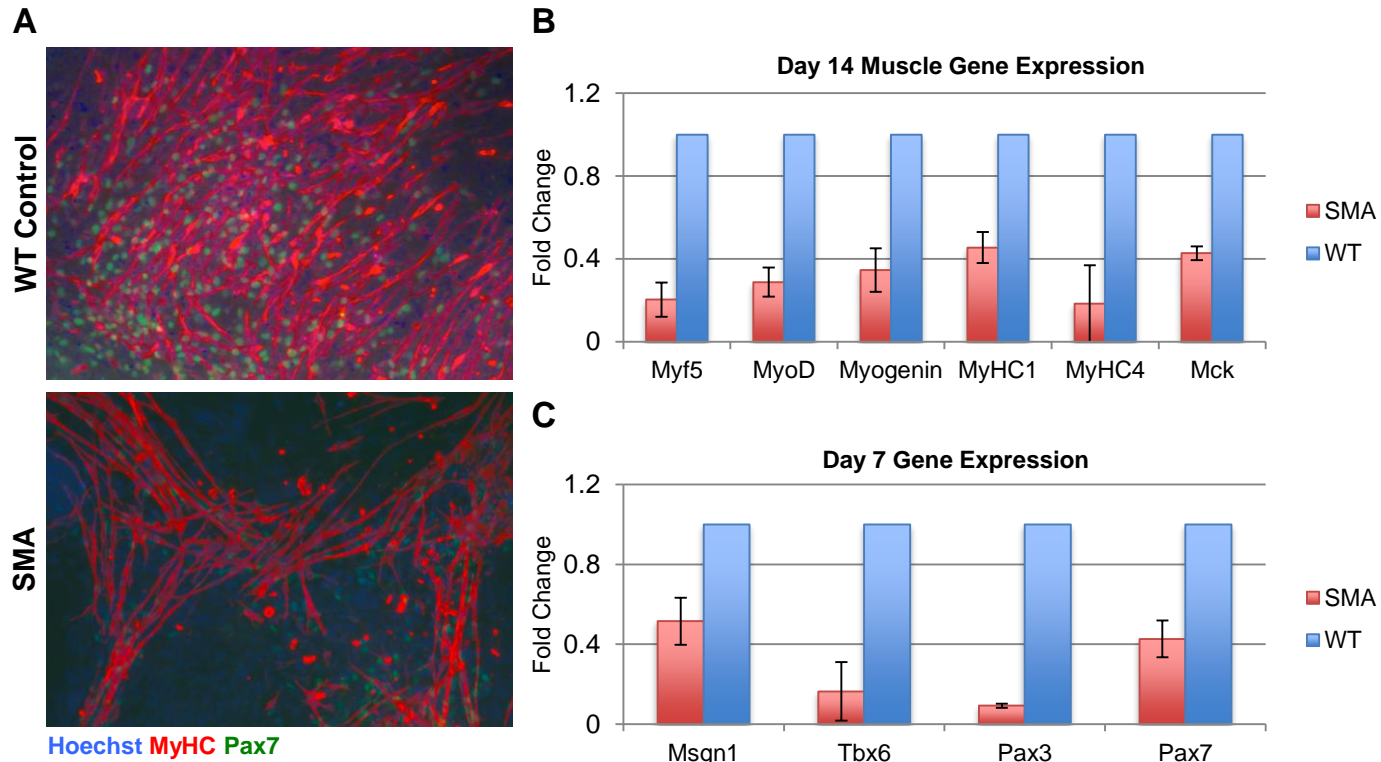


However, they do not effectively form multinucleated, functional muscle cells.



Thus, the muscle defect appears to be tissue autonomous, at least in part, and results from defective stem cell behavior.

# Muscle formation from mouse SMA mouse ES cells is defective.



# Muscle regeneration

- SMN-deficient satellite cells are unable to repair damaged muscle.

# Summary

- Studies using SMA mice and patient iPSCs suggest that low levels of SMN may be associated with defects in non-neural tissues.
- A satellite cell defect in SMA accounts for at least part of the muscle weakness phenotype.
  - A satellite cell directed therapeutic may be useful in improving muscle strength in children with SMA.
- Are there data suggesting that any of these findings hold true in SMA patients?
  - What is the predictive power of iPSC-based findings?

# Analysis of SMA patient electronic medical records

- We analyzed a large patient medical record database containing hundreds of children with SMA.
- Conclusion:
  - SMA is associated with a variety of non-neuromuscular defects.
  - In milder forms of SMA, some of these defects may precede SMA diagnosis by 6 months or more.

# Acknowledgements



## **Rubin Laboratory**

Shiyan Ng  
Nadia Litterman  
Natalia Rodriguez Muela  
Maureen Lynes  
Boon Soh  
Scott Lipnick  
Nina Makhortova  
Rebecca Gibbs

Harvard University  
John Rinn  
Laurence Daheron  
Amy Wagers

HMS  
Zak Kohane

Children's Hospital  
Basil Darras

## **Funding from:**

NINDS  
SMA Foundation  
HSCI  
MDA  
Frequency Therapeutics