

Understanding Molecular Mechanisms Controlling Muscle Type Specification



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1. Abstract

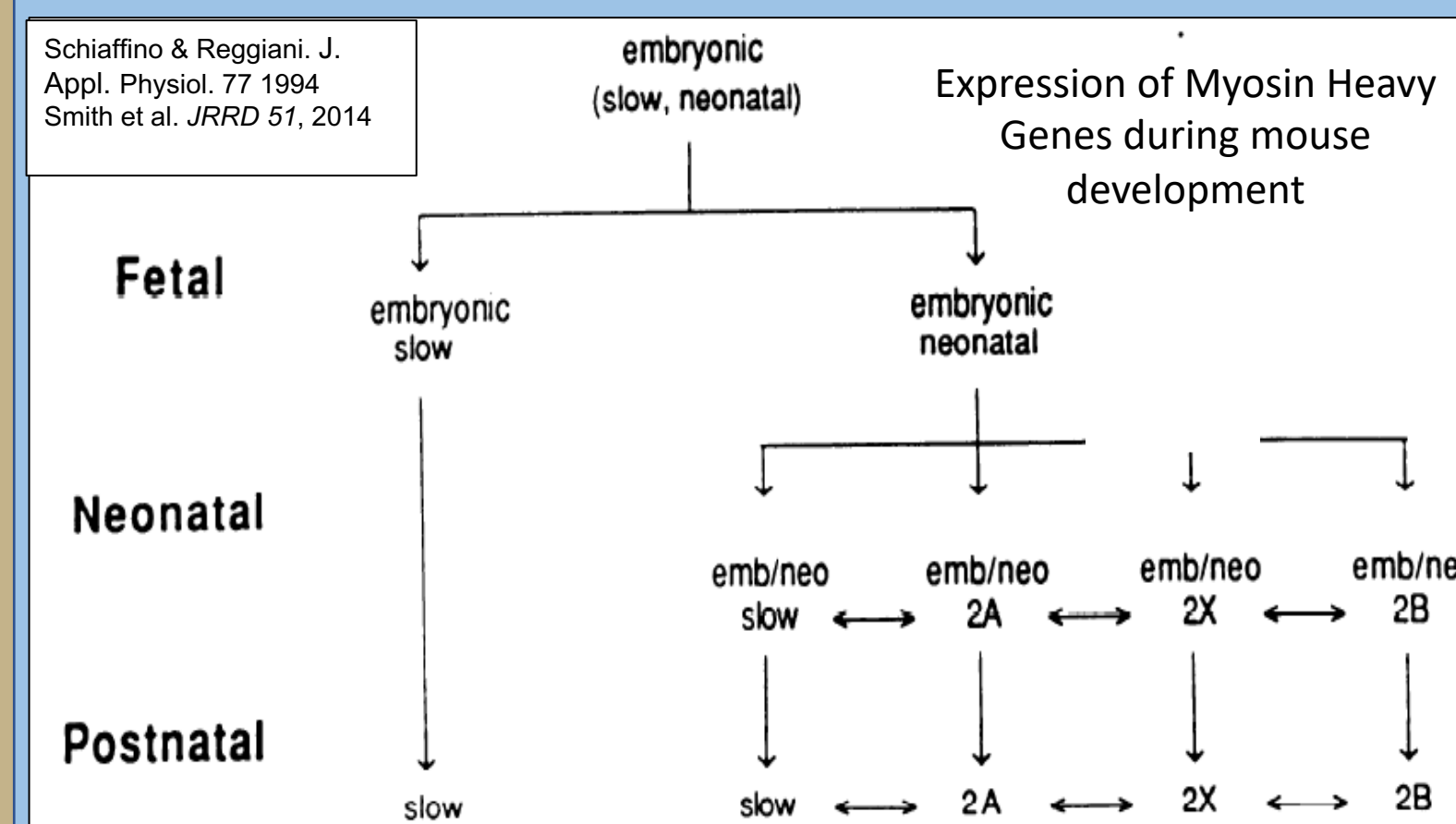
Our lab studies how complex tissues develop from simple ones. Muscle development is a good example of such transition, which is shared by many organisms, from flies to humans.

We followed the fate of the muscle structural gene *Act57B* and its regulator *Mef2*. *Act57B* is expressed in all embryonic muscles, but only in a limited number of adult muscles. Expression of *Mef2* does not change, it remains in the muscles that do not express *Act57B* anymore. We found that in those muscles *Mef2* reverses its role and becomes a negative regulator of *Act57B*.

We hypothesized that additional genetic factors could be influencing *Mef2*'s mode of action. Using genetic screening, we have identified several candidates. Our results suggest a model where some factors directly interact with the *Mef2* protein and recruit other factors that condense chromatin around *Act57B* to shut down its expression.

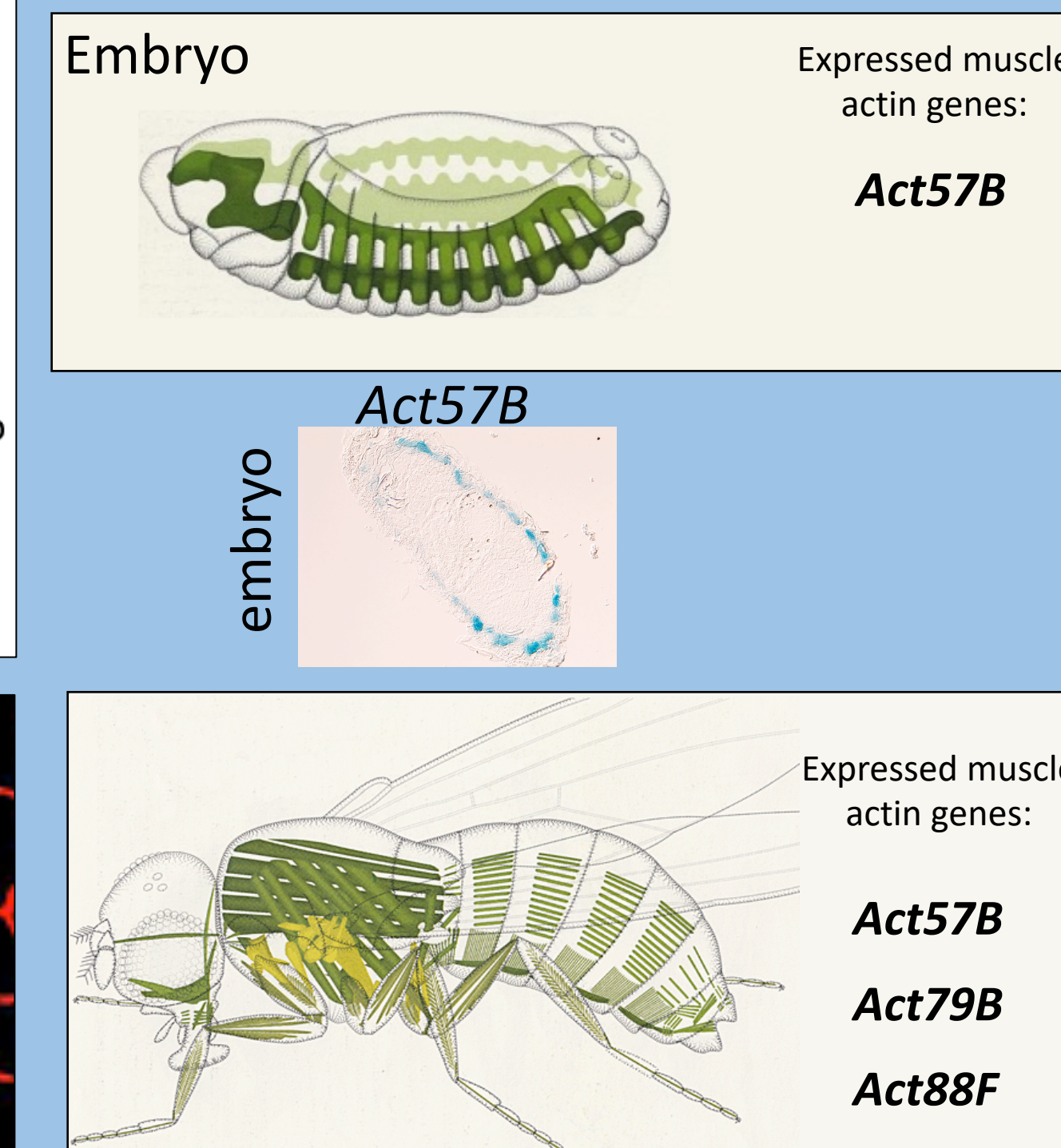
2. Introduction

A look into the complexity of muscle tissue:

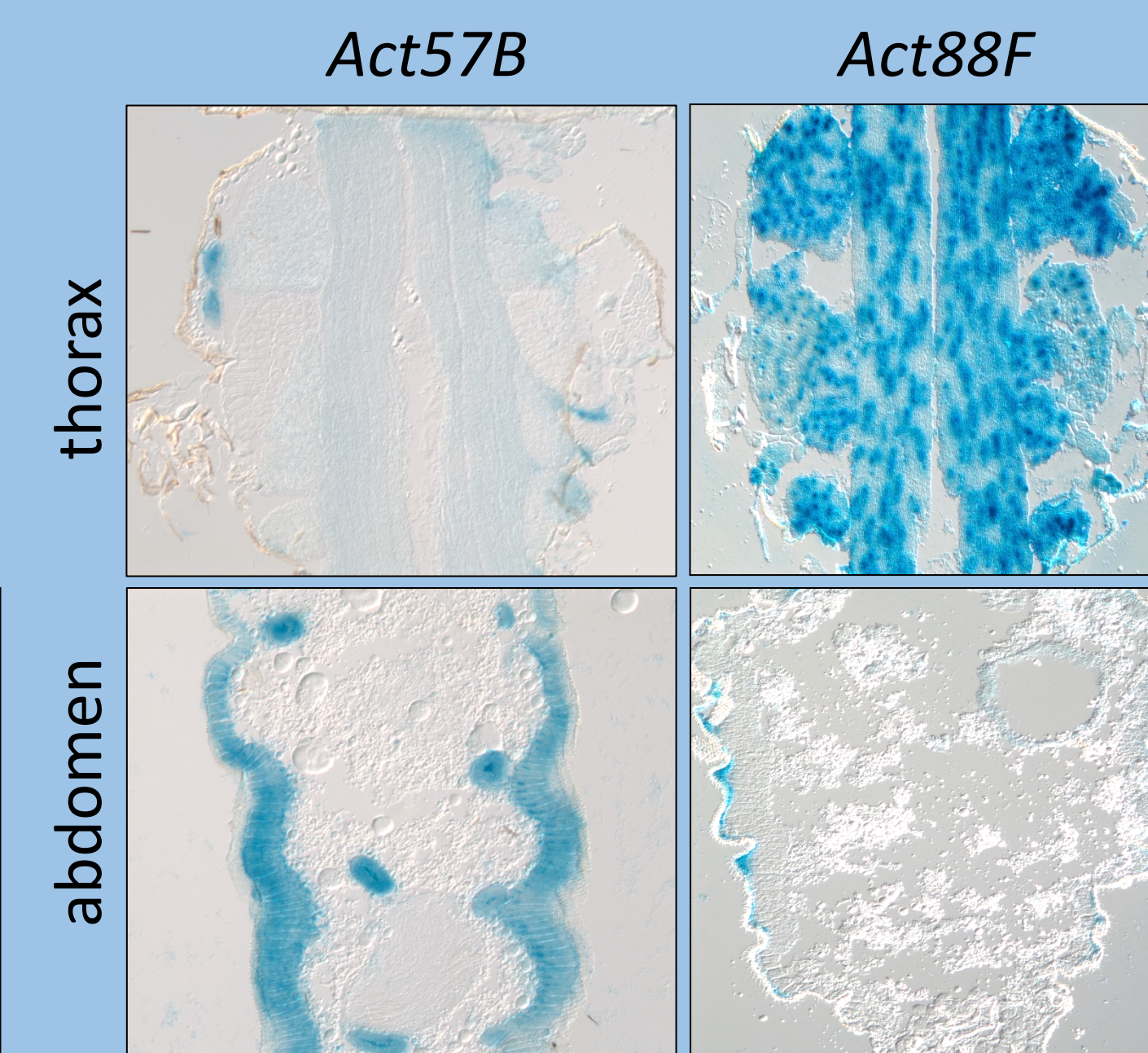


Mammalian muscle is a composite tissue comprising fibers that belong to several types (colored differently)

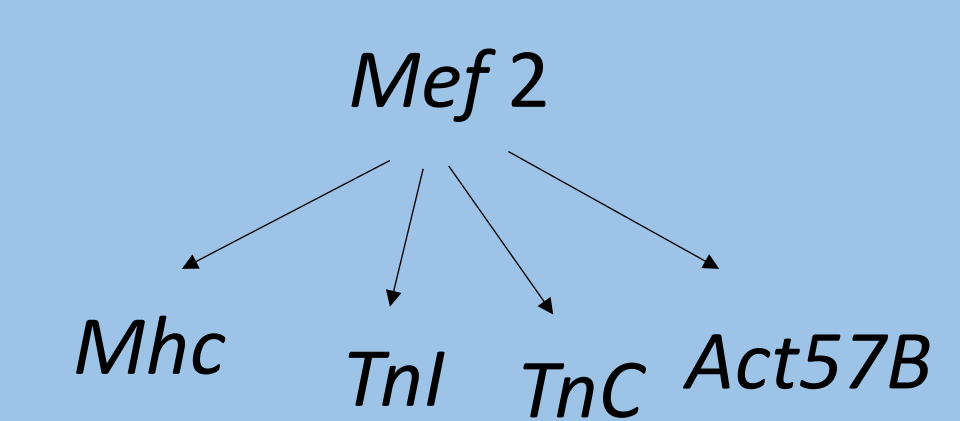
Diversity of structural proteins increases in adult muscles:



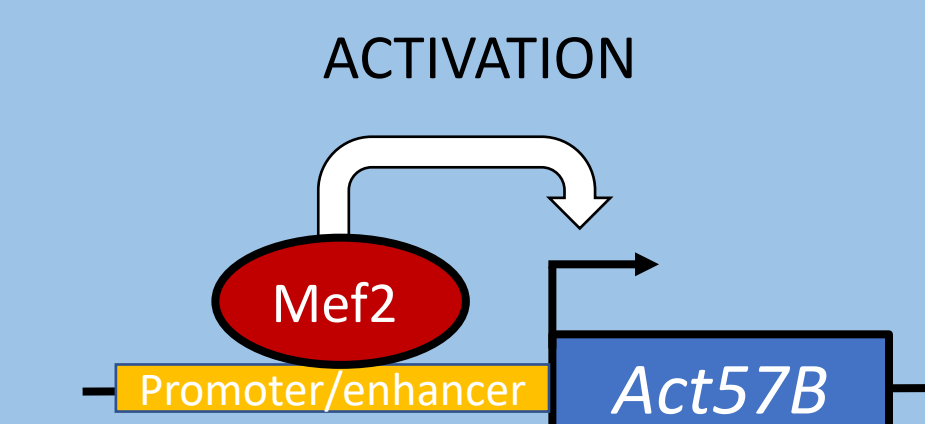
Expression of muscle actins (*Act57B* and *Act88F*) is restricted to specific muscles in adults



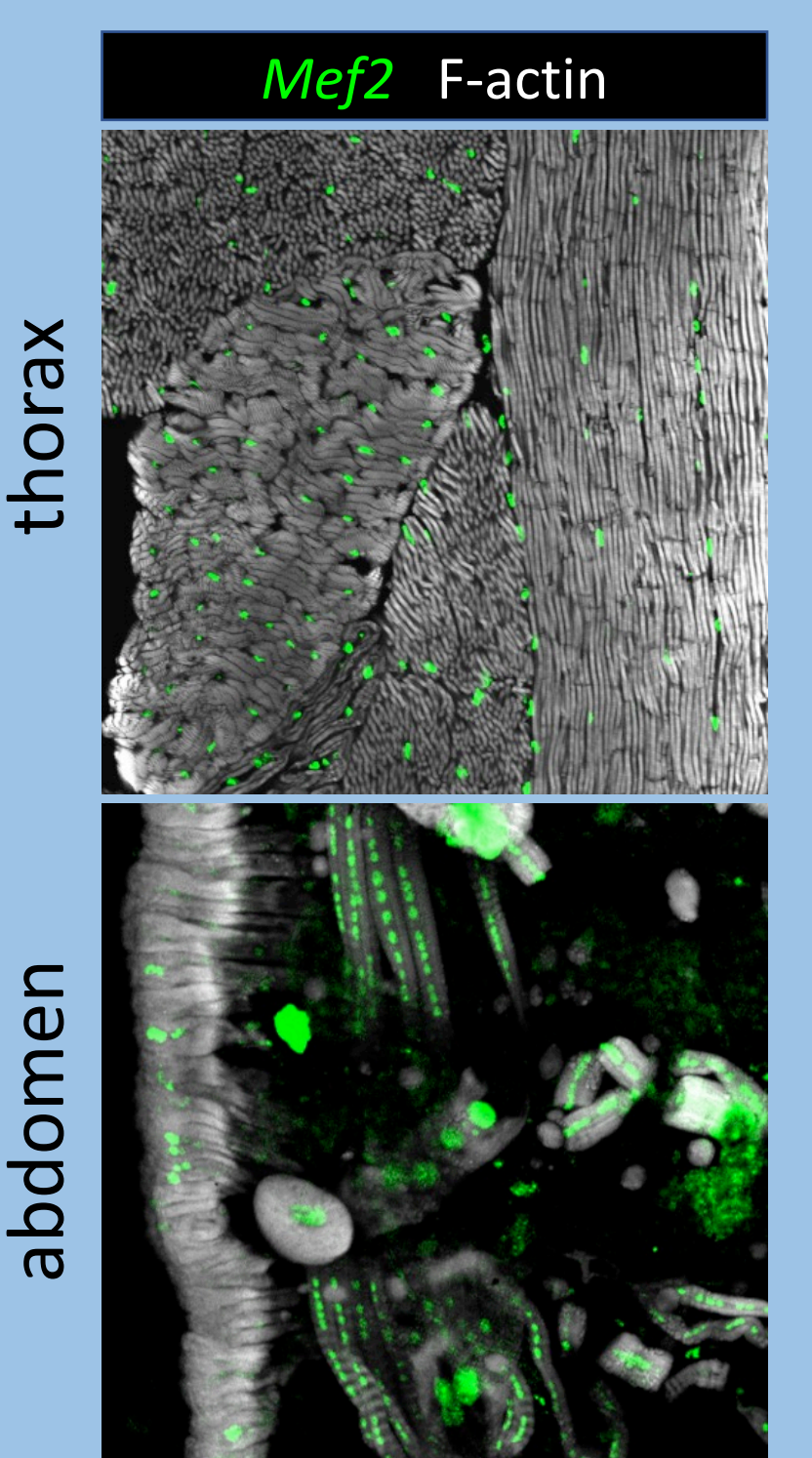
Mef2 controls most of muscle structural genes



Mef2 regulates muscle genes directly



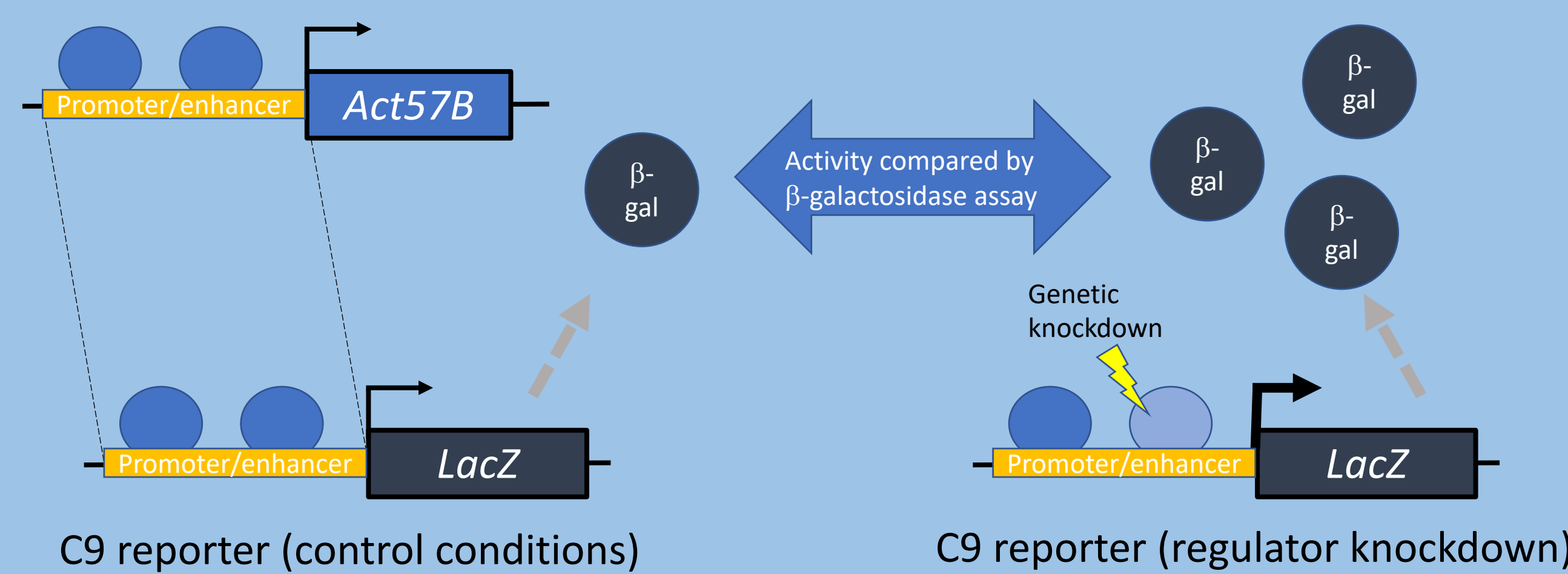
Expression of *Mef2* remains unrestricted in adult muscles



3. Research Question and Experimental Design

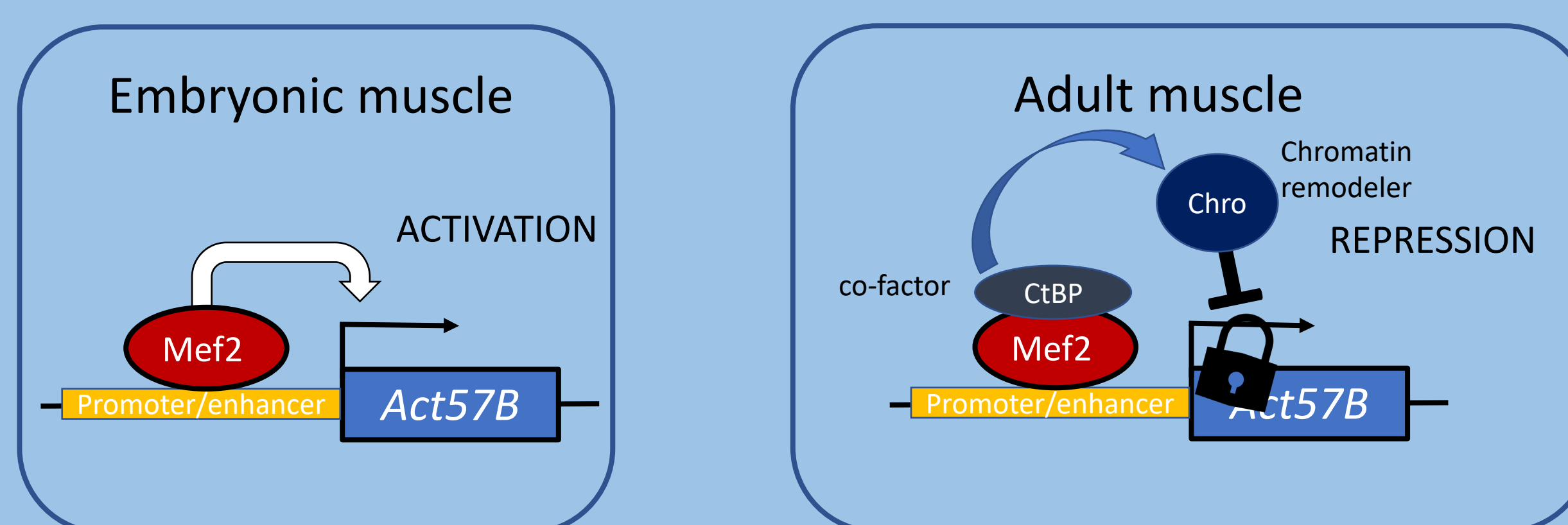
What is the molecular mechanism that enables selectivity in *Act57B* activation by *Mef2*?

C9 genetic reporter quantitatively measures *Act57B* gene activity



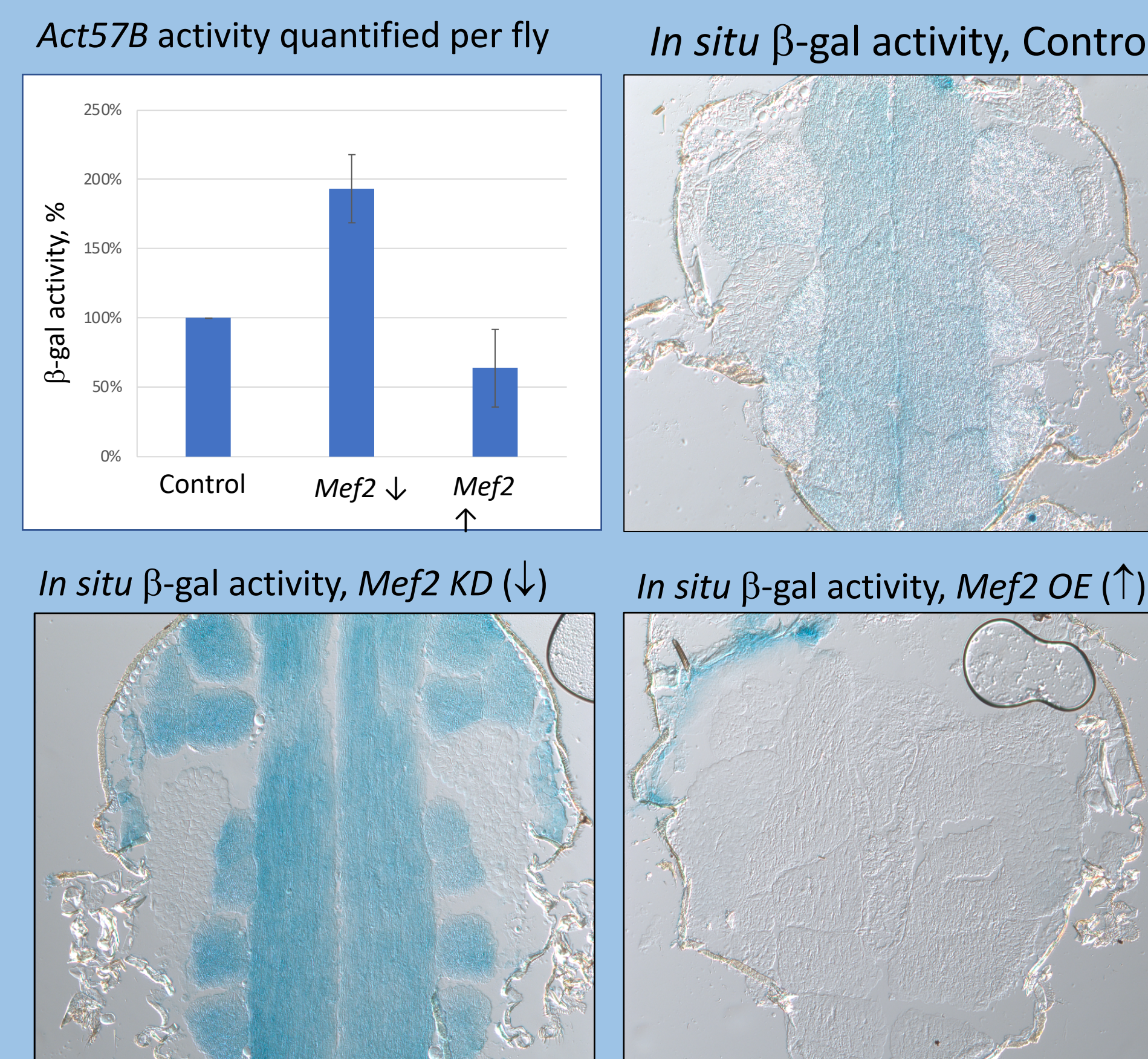
5. Conclusions

- Mef2* becomes re-purposed in thoracic muscles from an *Act57B* activator to a repressor
- Our screen found several candidates potentially responsible for *Mef2* re-purposing
- We suggest the following scenario:

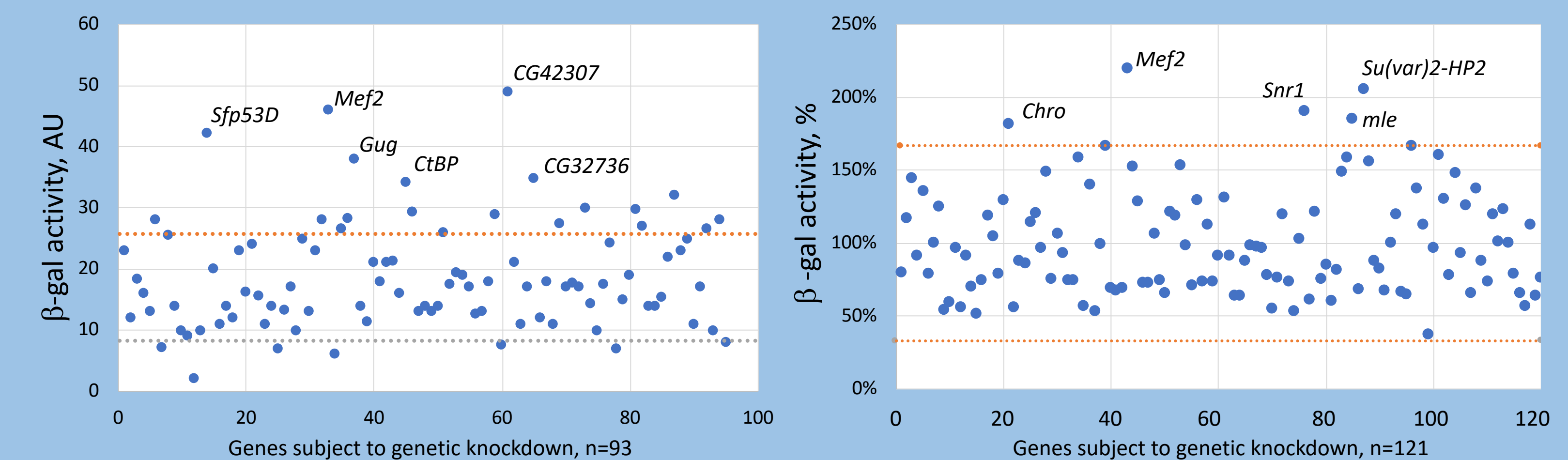


4. Experimental Data

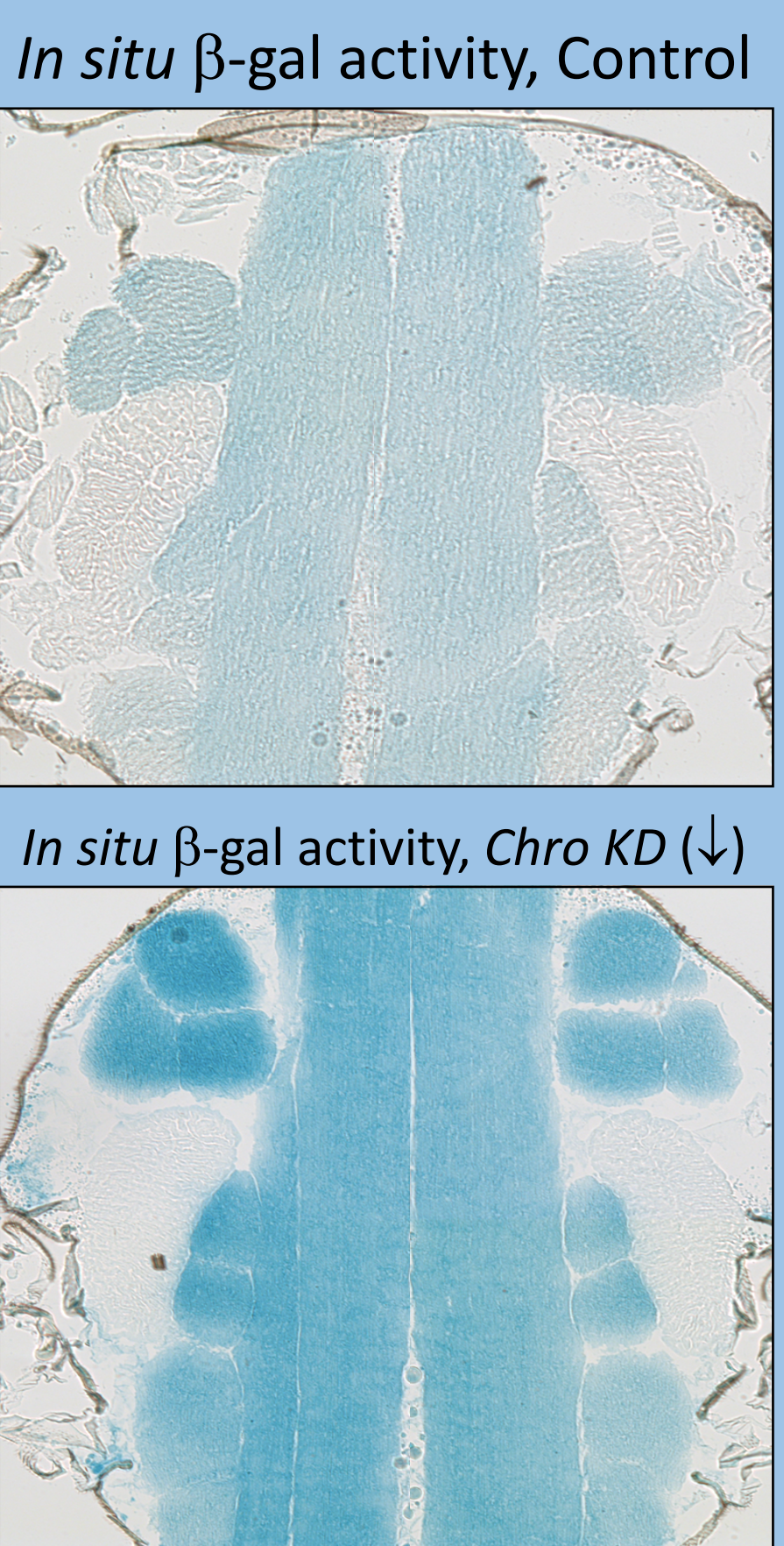
Mef2 is a negative regulator of *Act57B* in thoracic muscles



Genetic screening identifies factors involved in *Act57B* repression in thoracic muscles



Screen hit validation:



Most significant screen hits:

Among possible Mef2 co-factors			Among chromatin modifiers		
Line ID	Gene name	Protein Function	Line ID	Gene name	Protein Function
65233	Sfp53D	Secreted protein	57470	Chro	Chromodomain protein, interacts with heterochromatin
32889	CtBP	Transcription cofactor, transcription regulator	32372	Snr1	Component of nucleosome remodeling complex
42853	CG32736	Unknown	38255	Su(var)2-HP2	Heterochromatin protein
32961	Gug	Represses transcription factor binding	34864	mle	Component of nucleosome remodeling complex
34951	CG42307	Unknown			

6. Future Endeavors

- Validate screen hits through additional experiments
- Test for physical interactions b/w *Mef2* and chromatin modifiers uncovered by the screen
- Build a genetic network that specifies muscle diversity

7. Acknowledgements

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