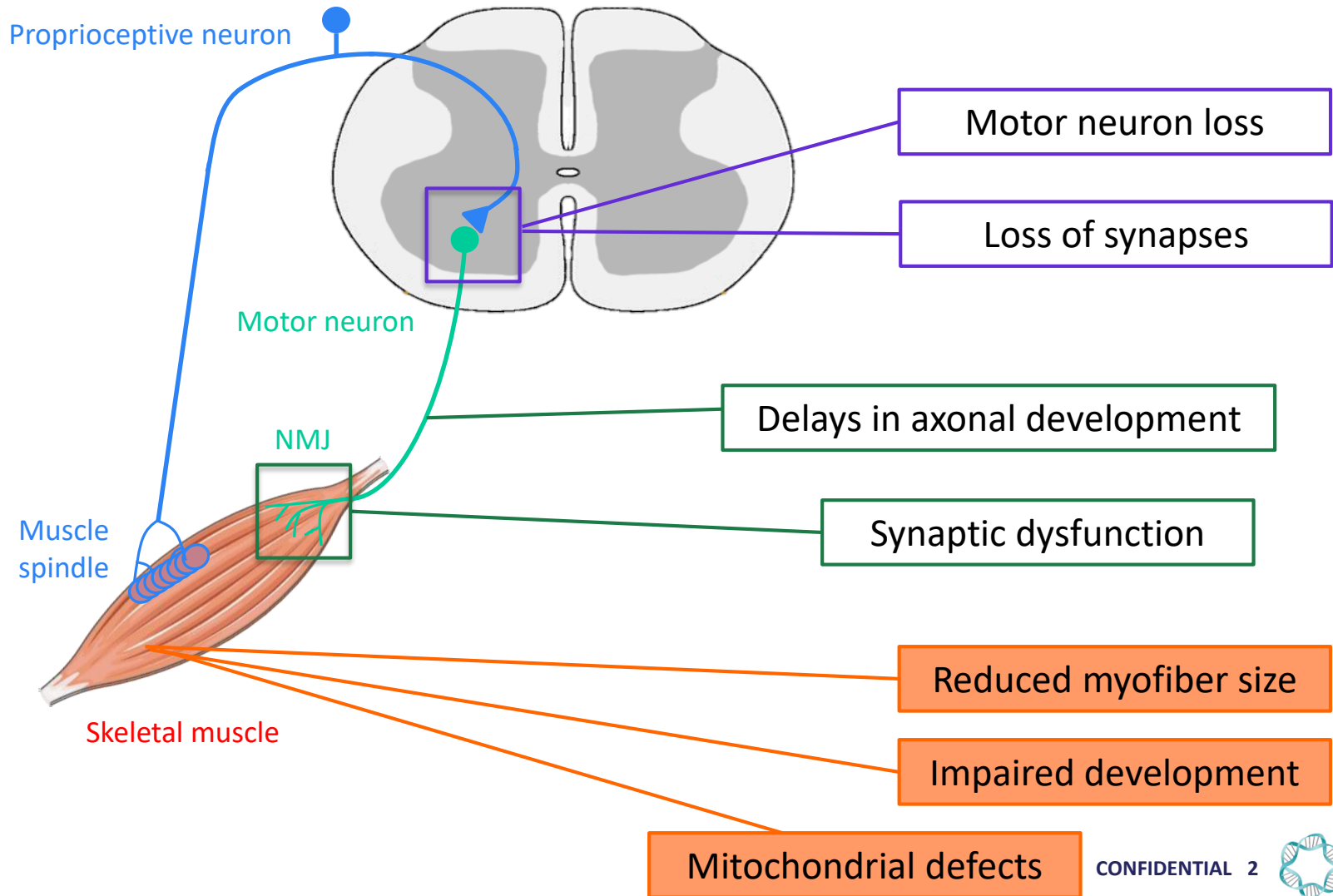




Skeletal Muscle: a Critical Target in Treating SMA

THERAPEUTIC STRATEGIES TO AMPLIFY SMN
UPREGULATION

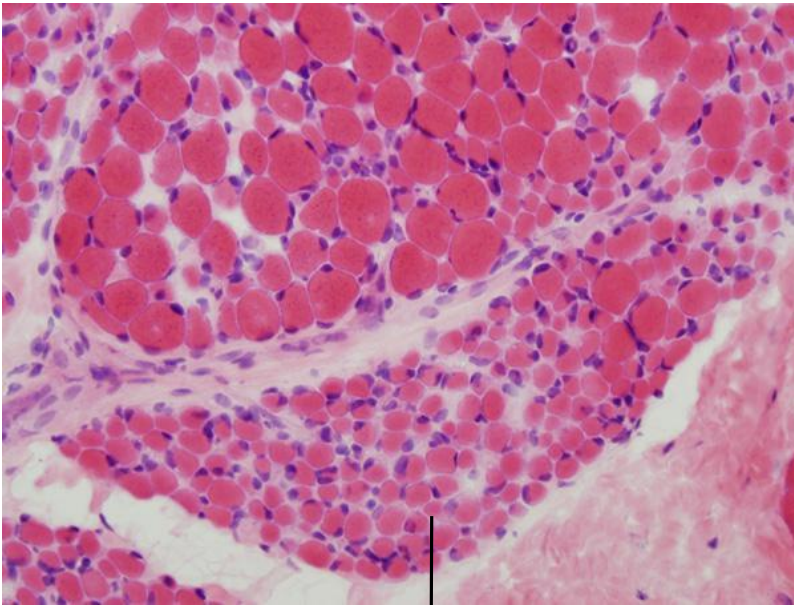
PATHOPHYSIOLOGICAL DEFECTS IN SMA



MUSCLE PATHOLOGY IN SMA

TYPE I SMA MUSCLE: MANY SMALL MYOFIBERS FEATURES OF DELAYED MATURATION

Type I SMA

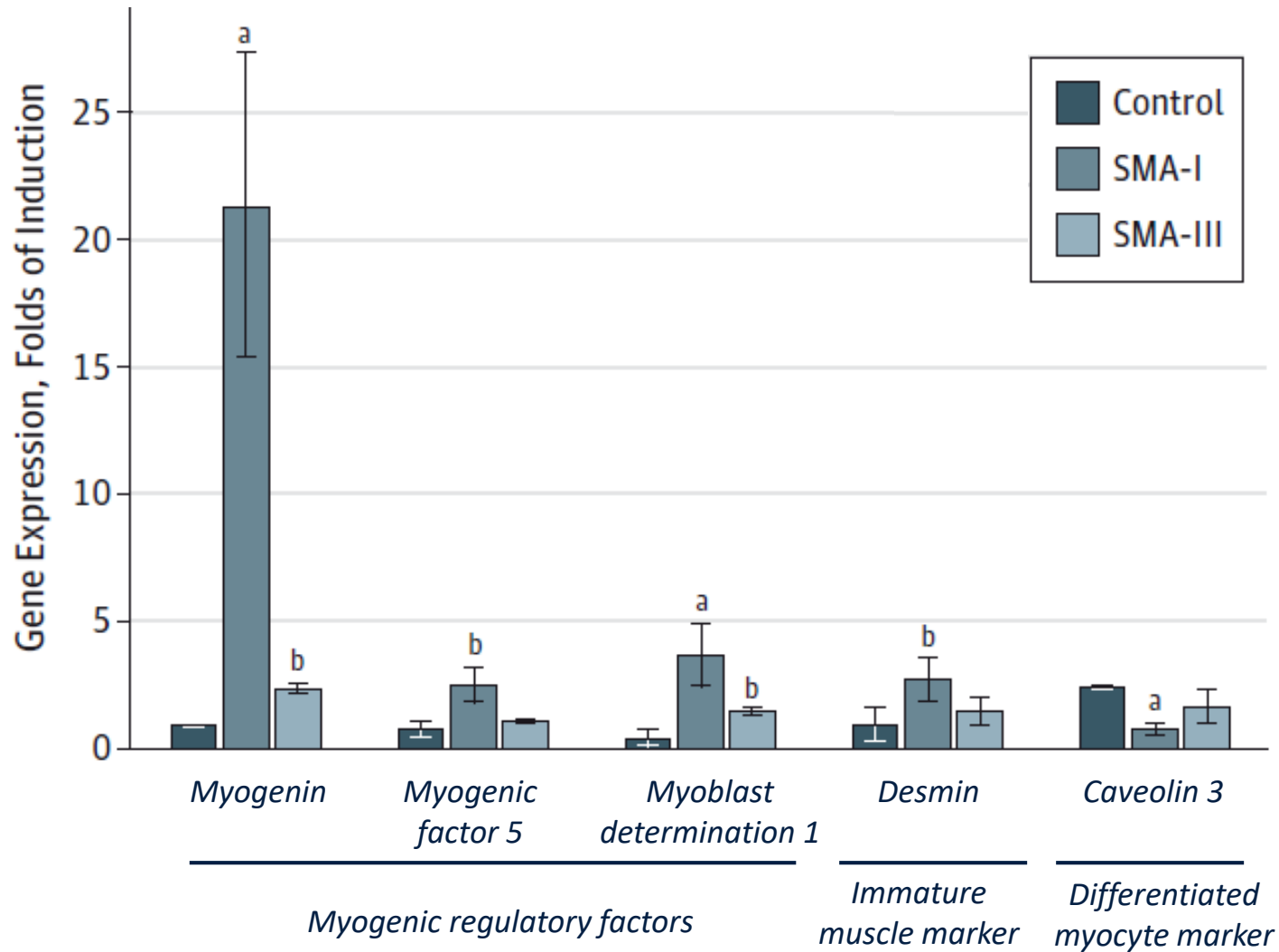


Round and small myofibers believed to be developmentally immature



Takei et al., Medscape

SMA MUSCLES EXPRESS IMMATURE MUSCLE MARKERS

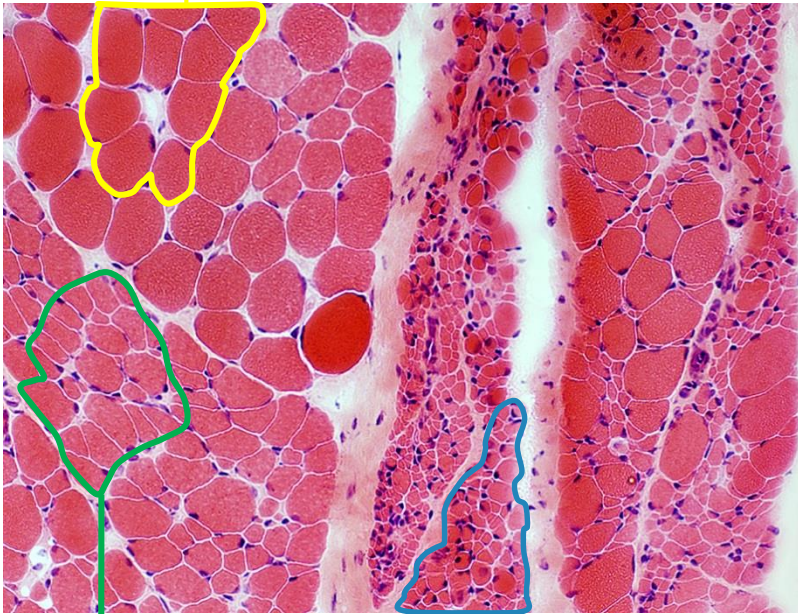


TYPE II SMA MUSCLE: FEATURES OF NEUROGENIC ATROPHY

MANY NORMAL-LOOKING MYOFIBERS

Type II SMA

large myofibers



normal myofibers

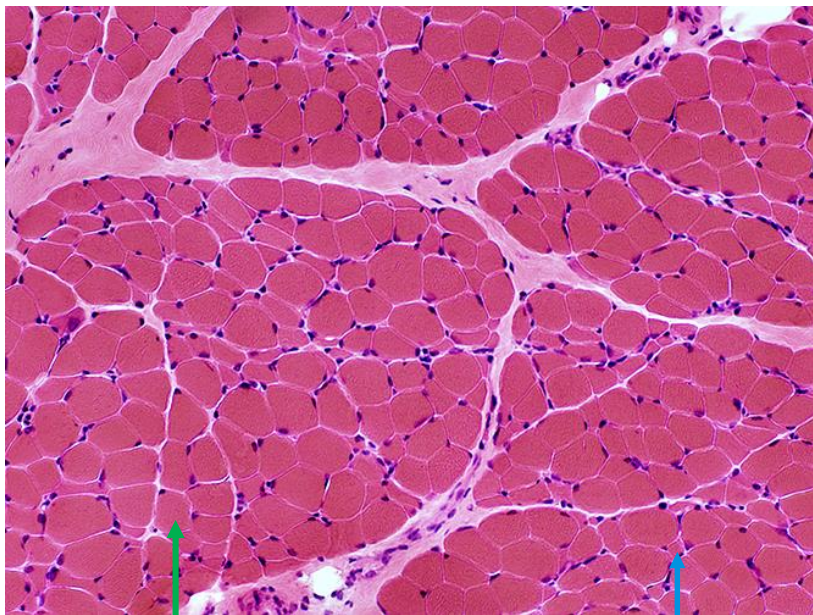
small myofibers



TYPE III SMA MUSCLE: FEATURES OF NEUROGENIC ATROPHY

MANY NORMAL-LOOKING MYOFIBERS

Type III SMA



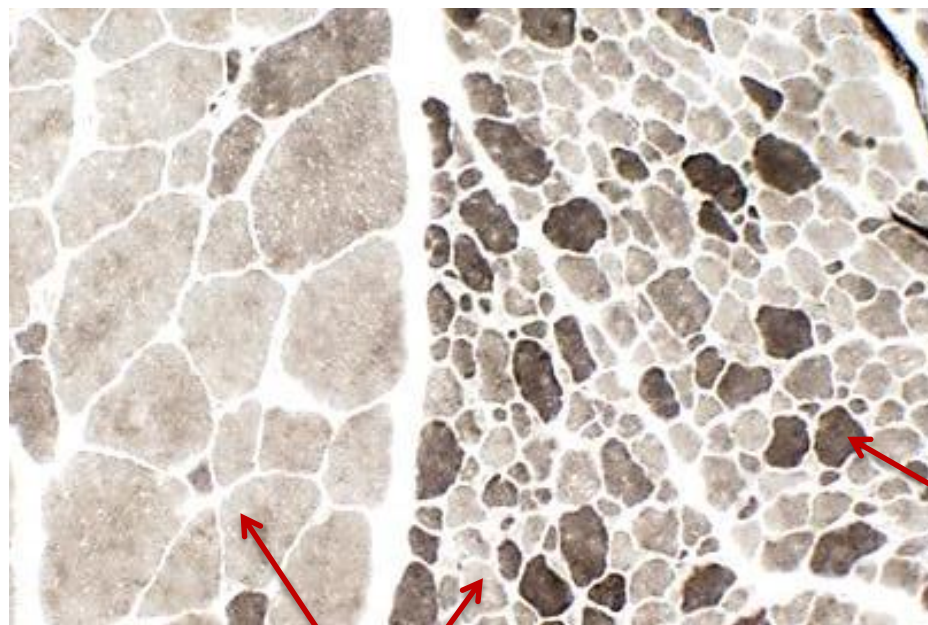
normal myofibers

small myofibers



MODERATLY AFFECTED SMA MUSCLES EXHIBIT FIBER TYPE GROUPING

Type II SMA patient



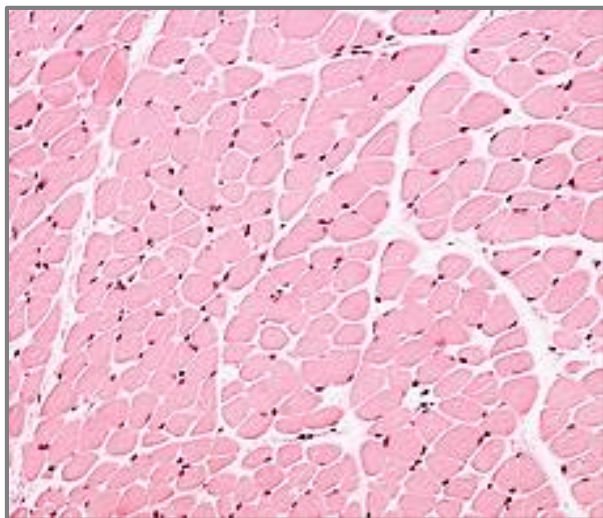
Type 1 (slow)

Type 2 (fast)

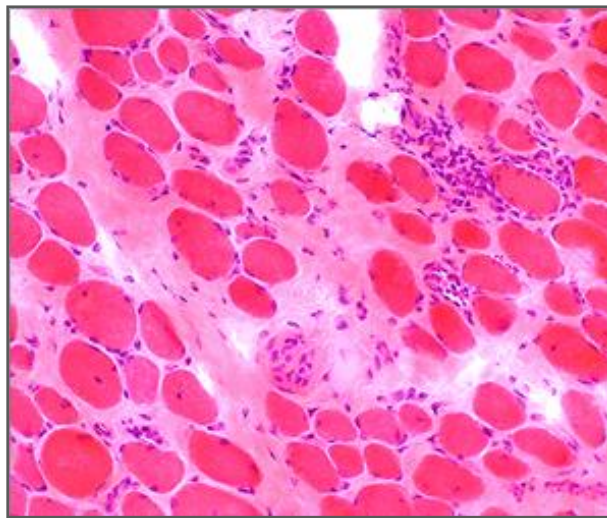
- *Hypertrophic myofibers appear to be mostly type 1*
- *Small and normal myofibers are type 1 and 2*

NO UNDERLYING STRUCTURAL DAMAGE IN SMA MUSCLE – OPPORTUNITY TO RESCUE REMAINING FIBERS

Healthy

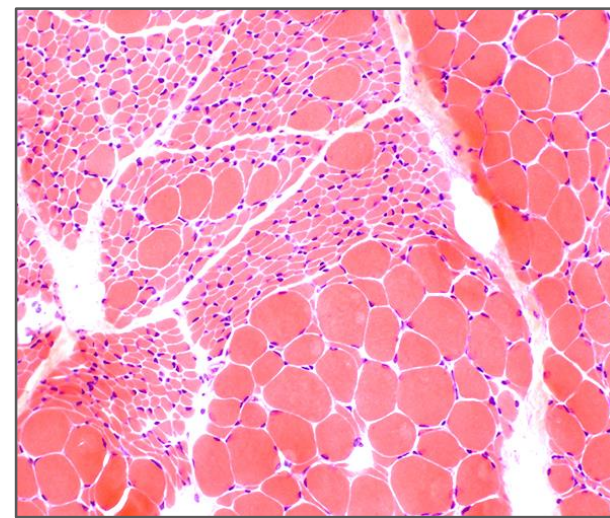


Duchenne Muscular Dystrophy (DMD)



*DMD: fiber size variation,
increase connective tissue
fibrosis, necrotic fibers*

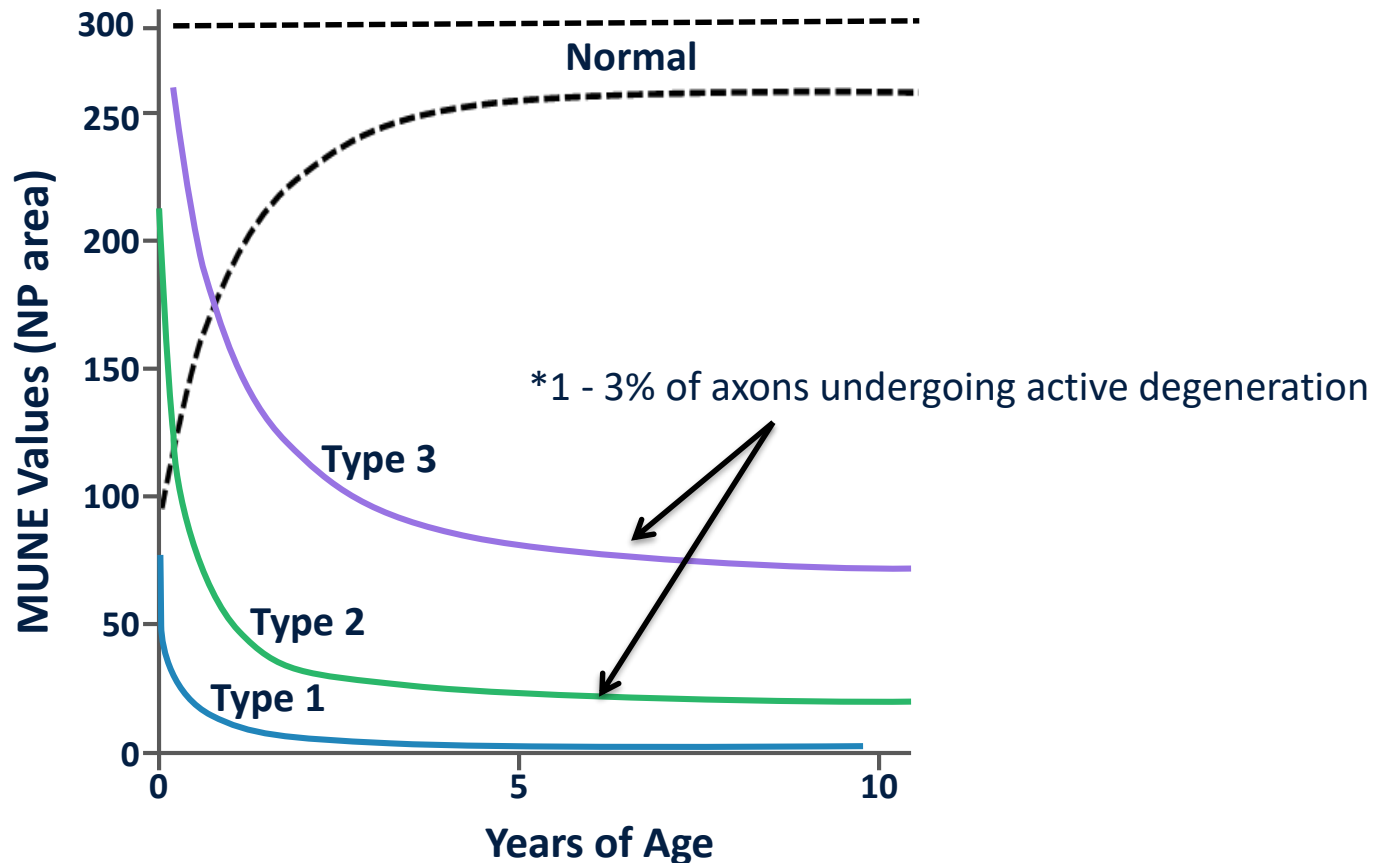
SMA



*SMA: small fiber clusters
interspersed with some
hypertrophic fibers*

ONGOING MUSCLE DENERVATION IN SMA IS SLOW, AFTER AN INITIAL DENERVATION EARLY IN DEVELOPMENT

MUNE trendlines



SMA MUSCLE IS AN EXCELLENT TARGET FOR MUSCLE-ENHANCING THERAPEUTICS

- SMA muscles have a **large number of normal fibers** remaining
- Unlike in DMD, no **muscle structural damage** in SMA muscle
- **Relatively slow muscle denervation**

POTENTIAL MECHANISMS TO ENHANCE MUSCLE FUNCTION IN SMA

SELECT MECHANISMS TO ENHANCE MUSCLE FUNCTION

Myostatin inhibitors stimulate muscle growth

Selective androgen receptor modulators (SARMS) stimulate muscle growth



Myostatin



Act11B
Receptor

~~Muscle atrophy~~



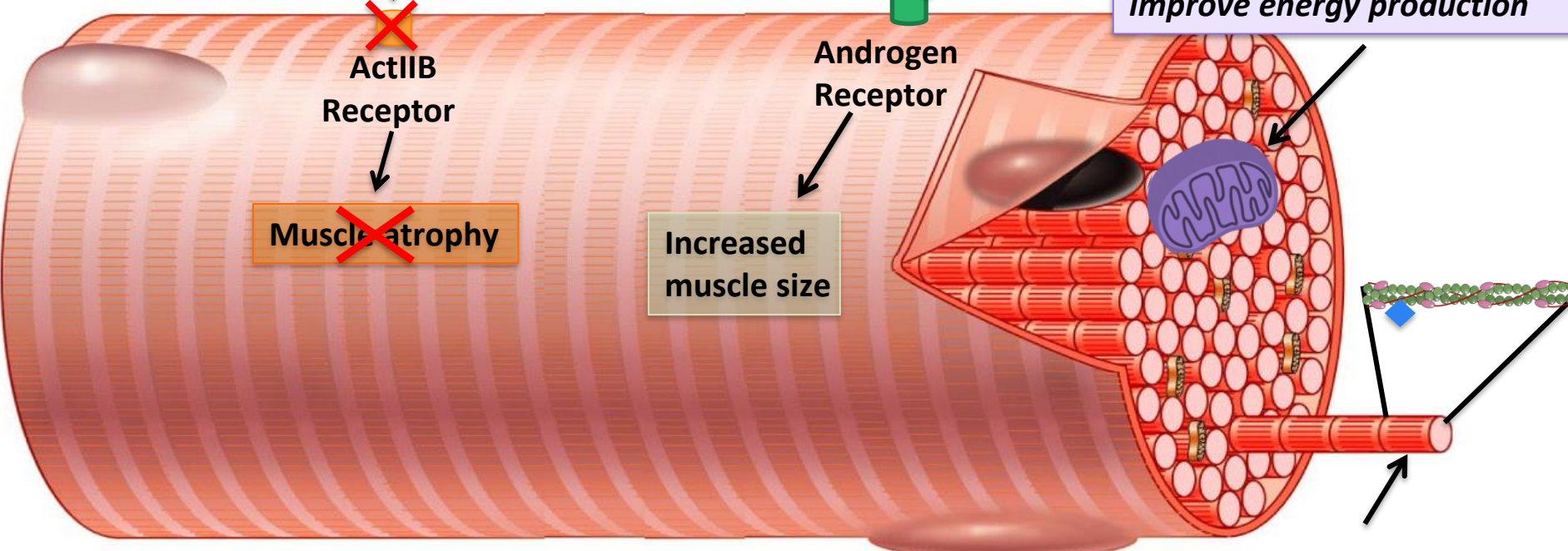
Androgen

Androgen
Receptor

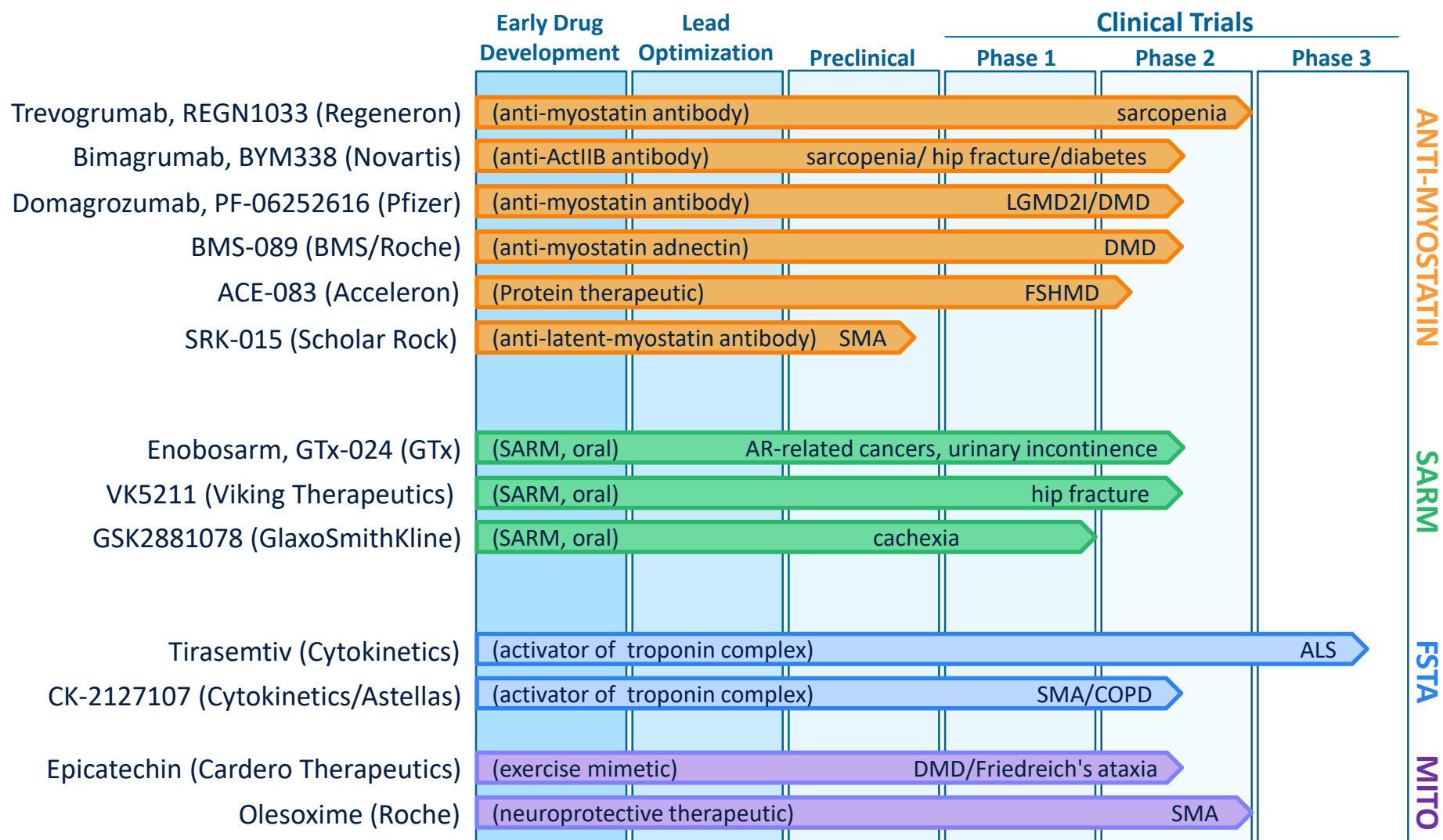
Increased
muscle size

Mitochondria-targeting drugs improve energy production

Fast troponin activators (FSTAs) increase muscle's sensitivity to calcium



MUSCLE-ENHANCING DRUGS IN CLINICAL DEVELOPMENT

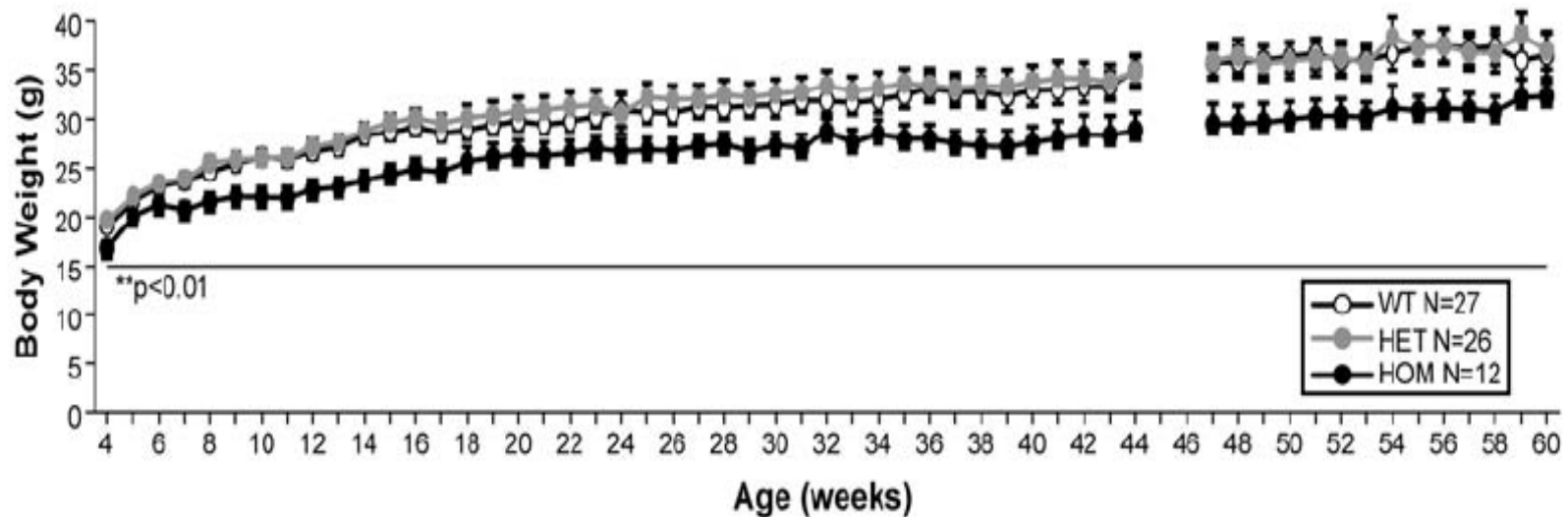
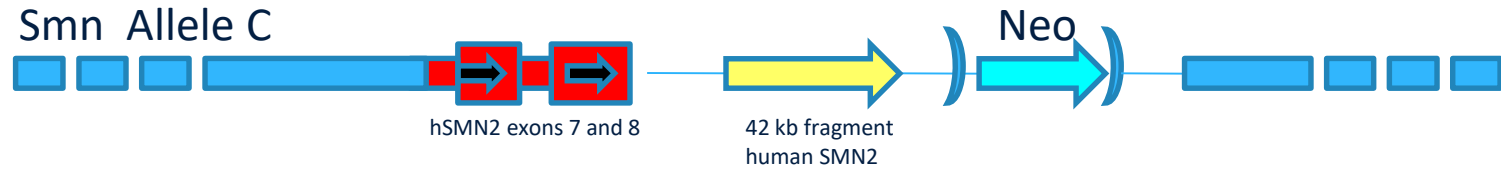


MYOSTATIN INHIBITION IN SMA MOUSE MODELS

ANTI-MYOSTATIN DRUGS WORK IN VARIOUS SMA MODELS

MODEL	SEVERE $\Delta 7$	INTERMEDIATE PHARMACOLOGICAL	MILD C/C
PRINCIPAL INVESTIGATOR	Sumner, Lorson	Ko, Myologica, SMA Foundation	Sweeney
MYOSTATIN INHIBITION APPROACH	Recombinant follistatin, ActRIIB-Fc (Acceleron)	AAV-Follistatin, Therapeutics from 4 major pharma/biotech companies	AAV-dnMyostatin, AAV-ActRIIB-Fc, ACE-2494 (Acceleron)
MUSCLE WEIGHT	✓	✓	✓
MUSCLE FUNCTION	✓ / —	✓	✓
REFERENCE	Sumner et al., 2009, Rose et al., 2009	Feng et al., 2016, Unpublished Results	Liu et al., 2016

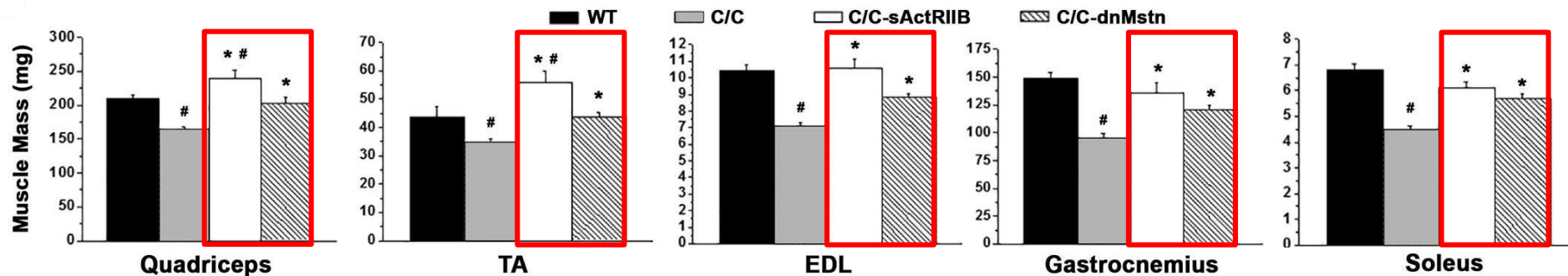
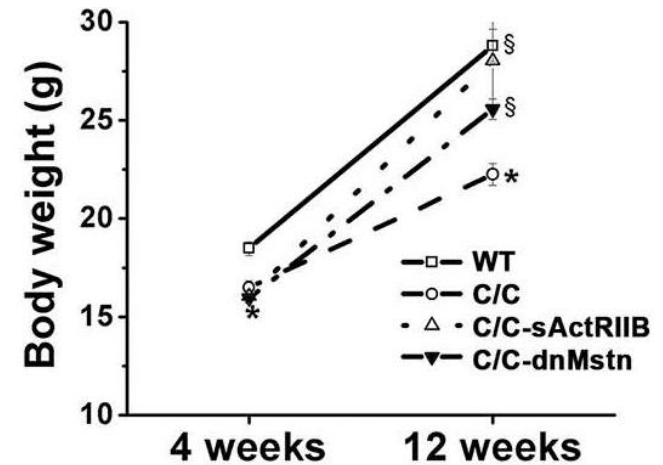
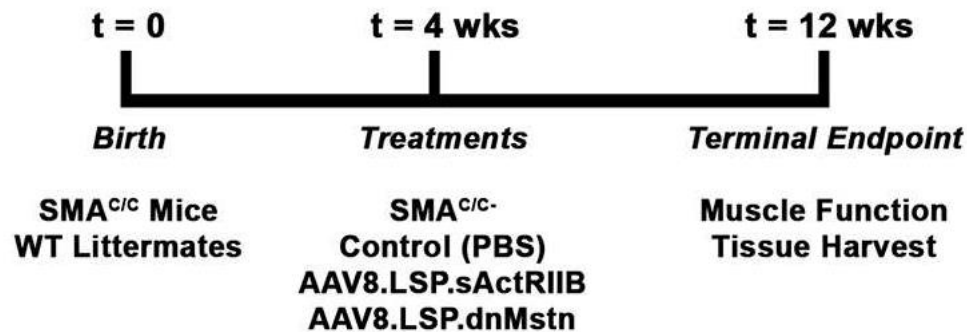
C/C MOUSE MODEL REPRESENTS A MILD FORM OF SMA



Reduced body and muscle weight, normal median survival

MYOSTATIN INHIBITION LEADS TO AN INCREASE IN BODY WEIGHT AND MUSCLE MASS

Two approaches were used to inhibit myostatin: soluble ActRIIB or protease-resistant myostatin propeptide

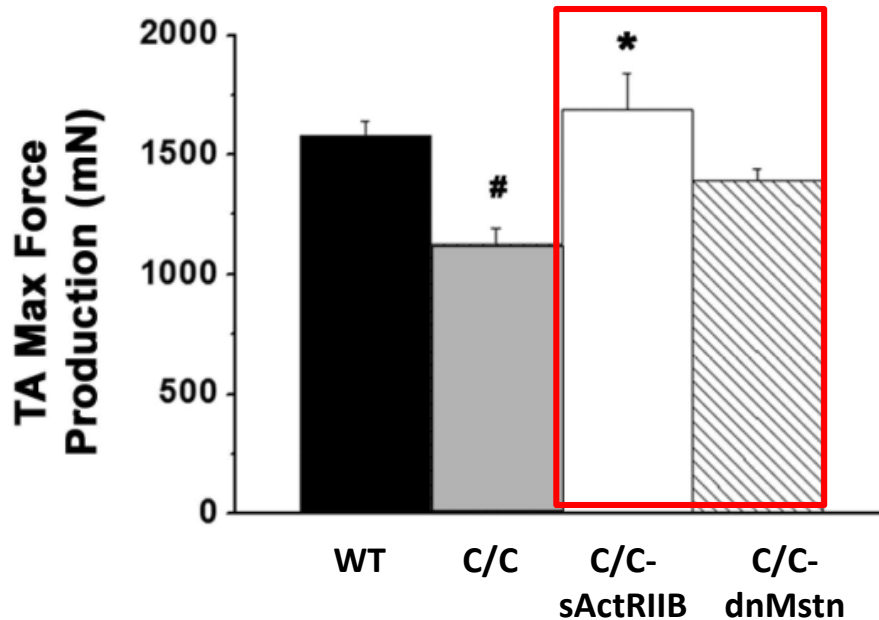


Liu et al., 2016
 #p<0.05 vs WT
 *p<.05 vs C/C

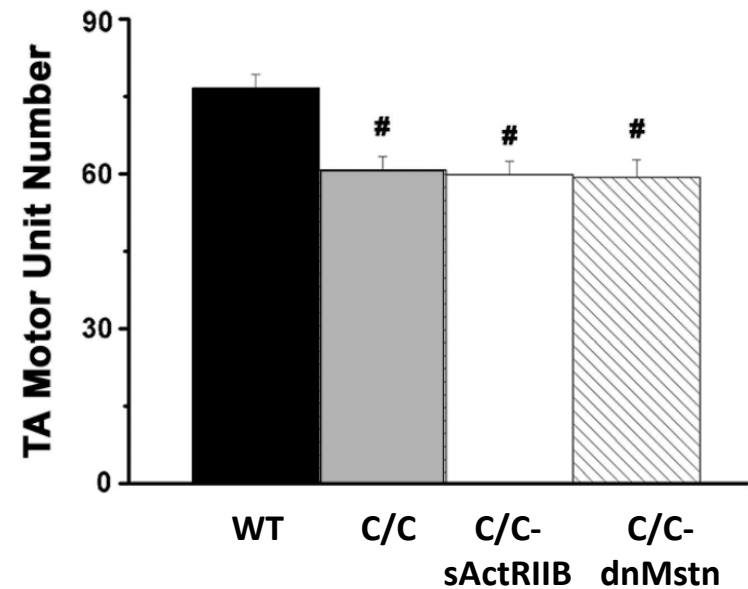
MYOSTATIN INHIBITION IMPROVES MUSCLE FUNCTION AND **DOES NOT OVEREXERT** MOTOR UNITS IN TIBIALIS ANTERIOR MUSCLE

in situ muscle function test

Increase in maximal force



No change in motor unit number

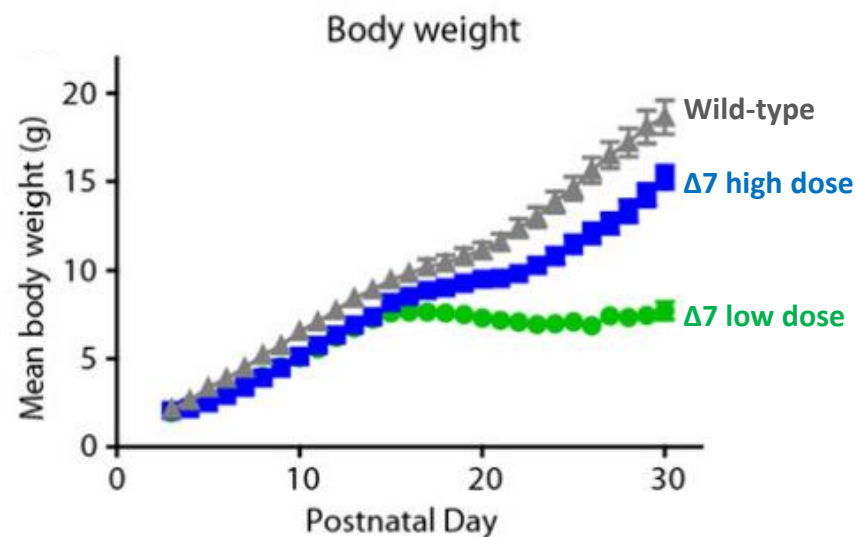
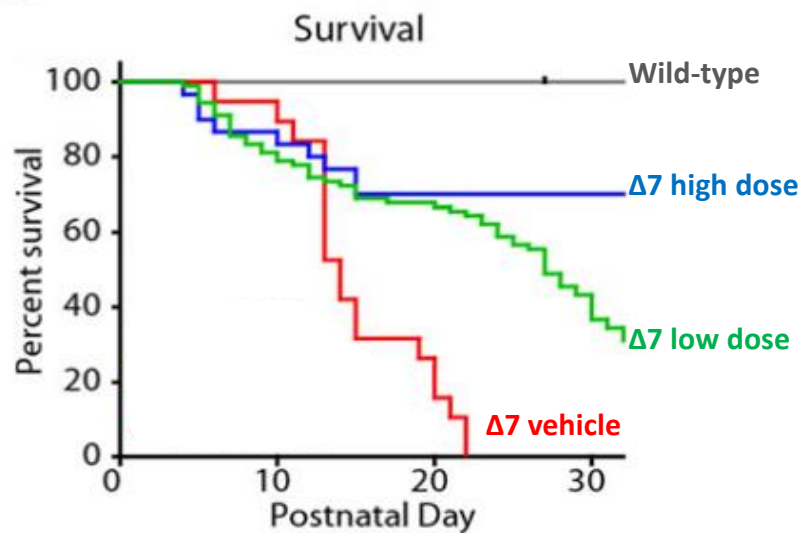


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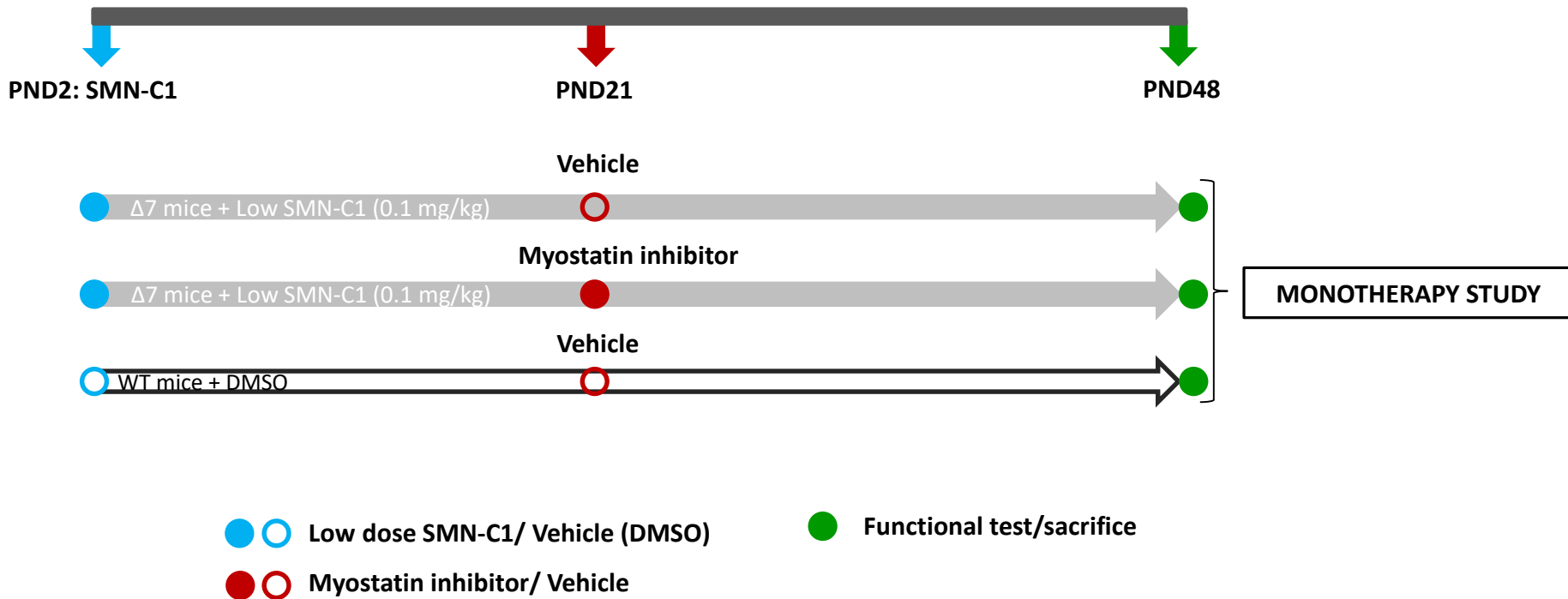
PHARMACOLOGICALLY INDUCED INTERMEDIATE MODEL ENABLES TESTING AFTER DISEASE ONSET

- The pharmacological model is obtained by dosing severe delta7 mice with a low dose of an SMN-upregulating compound (SMN-C3 or SMN-C1) from birth
- The model displays a range of disease phenotypes reminiscent of milder forms of SMA



STUDY DESIGN TO TEST MYOSTATIN INHIBITORS IN SMA MICE AFTER DISEASE ONSET

MYOLOGICA



IS THERE A BENEFIT OF COMBINING MYOSTATIN INHIBITORS AND SMN UPREGULATING THERAPY?

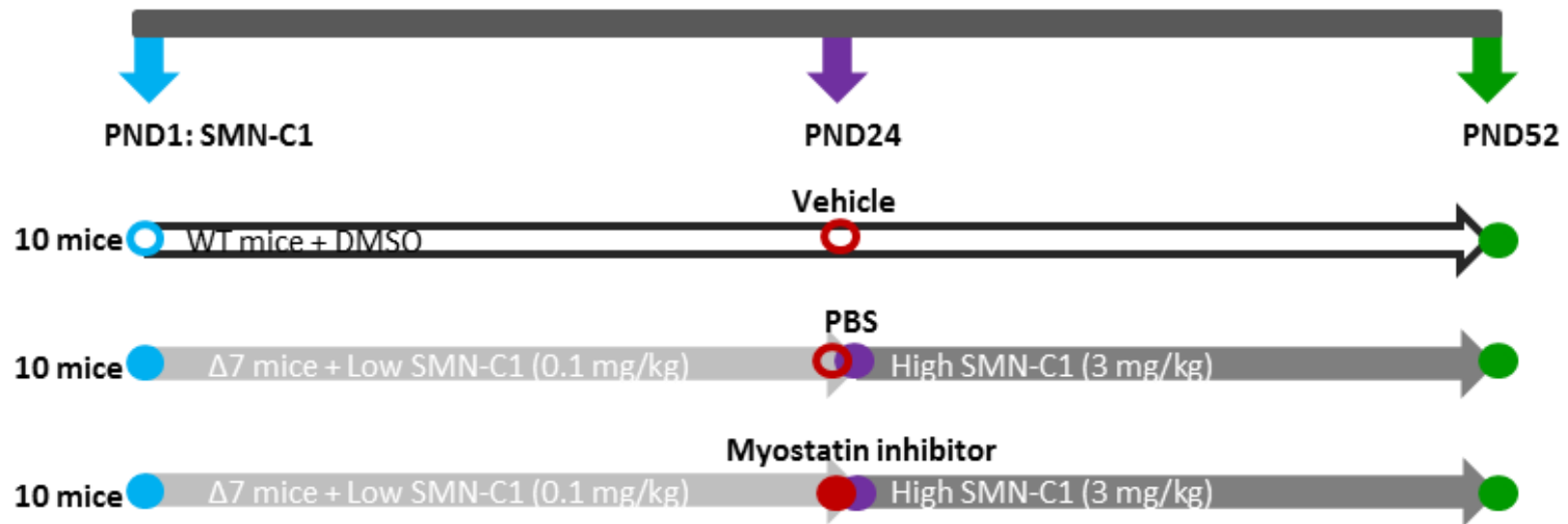
SMN-UPREGULATING
THERAPY

MUSCLE-ENHANCING
THERAPY



SMA mouse model

STUDY DESIGN TO TEST COMBINATION THERAPY IN SMA MICE AFTER DISEASE ONSET



- ○ Low dose SMN-C1/ Vehicle
- ○ Myostatin inhibitor/ Vehicle

- High dose SMN-C1
- Functional test/sacrifice

CONCLUSIONS

- SMA muscle is an excellent target for muscle-enhancing therapeutics
- Many muscle-enhancing drugs are already in clinical development for other indications – potential rapid development for SMA
- Strong preclinical evidence of efficacy of muscle-enhancing drugs in SMA mice
 - Myostatin inhibition alone and in combination with SMN upregulation increases muscle mass and improves muscle function in SMA mice
- SMN-upregulation by itself may not be sufficient for some patients – combination therapies may provide significant benefit to these patients
- **Next major phase in clinical development strategy – combo trials with SMN upregulators and muscle-enhancing drugs**

REMAINING QUESTIONS

- Will these promising preclinical results translate into meaningful benefits for SMA patients?
 - How will efficacy be assessed in patients?
 - Which patient populations are expected to see the most impact?

- What are the concerns for muscle-enhancing drugs in SMA patients?
 - Effect on SMA motor units?
 - Effect on fatigue?
 - Effect on contractures?

SMA FOUNDATION
