Skeletal Muscle: a Critical Target in Treating SMA

THERAPEUTIC STRATEGIES TO AMPLIFY SMN UPREGULATION
PATHOPHYSIOLOGICAL DEFECTS IN SMA

- Motor neuron loss
- Loss of synapses
- Delays in axonal development
- Synaptic dysfunction
- Reduced myofiber size
- Impaired development
- Mitochondrial defects

Diagram showing:
- Proprioceptive neuron
- Muscle spindle
- Motor neuron
- NMJ
- Skeletal muscle
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

Ripolone et al., 2015
TYPE II SMA MUSCLE: FEATURES OF NEUROGENIC ATROPHY
MANY NORMAL-LOOKING MYOFIBERS

large myofibers

normal myofibers  small myofibers

Neuromuscular Disease Center, WUSTL
TYPE III SMA MUSCLE: FEATURES OF NEUROGENIC ATROPHY
MANY NORMAL-LOOKING MYOFIBERS

normal myofibers  small myofibers

*Neuromuscular Disease Center, WUSTL*
MODERATLY AFFECTED SMA MUSCLES EXHIBIT FIBER TYPE GROUPING

Type II SMA patient

- 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)

SMA

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

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

*1 - 3% of axons undergoing active degeneration

Adapted from Swoboda et al., 2005
*Charlotte Sumner (Johns Hopkins)
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
- Mitochondria-targeting drugs improve energy production
- Fast troponin activators (FSTAs) increase muscle’s sensitivity to calcium
<table>
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<tr>
<th>Drug Name</th>
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<th>Phase 1</th>
<th>Phase 2</th>
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Based on publicly disclosed timelines, June 2017
MYOSTATIN INHIBITION IN SMA MOUSE MODELS
## ANTI-MYOSTATIN DRUGS WORK IN VARIOUS SMA MODELS

<table>
<thead>
<tr>
<th>MODEL</th>
<th>SEVERE Δ7</th>
<th>INTERMEDIATE PHARMACOLOGICAL</th>
<th>MILD C/C</th>
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<tr>
<td>PRINCIPAL INVESTIGATOR</td>
<td>Sumner, Lorson</td>
<td>Ko, Myologica, SMA Foundation</td>
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<td>MYOSTATIN INHIBITION APPROACH</td>
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C/C MOUSE MODEL REPRESENTS A MILD FORM OF SMA

Reduced body and muscle weight, normal median survival

Osborne et al., 2012
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.
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

Liu et al., 2016

*p<0.05 vs C/C

#p<0.05 vs WT
# ANTI-MYOSTATIN DRUGS WORK IN VARIOUS SMA MODELS

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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.

*Naryshkin et al., 2014
Feng et al., 2016*
STUDY DESIGN TO TEST MYOSTATIN INHIBITORS IN SMA MICE AFTER DISEASE ONSET

PND2: SMN-C1

PND21

Vehicle

Δ7 mice + Low SMN-C1 (0.1 mg/kg)

Myostatin inhibitor

Δ7 mice + Low SMN-C1 (0.1 mg/kg)

Vehicle

WT mice + DMSO

MONOTHERAPY STUDY

Δ7 mice + Low SMN-C1 (0.1 mg/kg)

Myostatin inhibitor/ Vehicle

Low dose SMN-C1/ Vehicle (DMSO)

Functional test/sacrifice
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
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