Muscle Regeneration / Remodeling in DMD

Action Duchenne Conference 2014

Diana Escolar – Akashi Therapeutics

Carl Morris – Rare Disease Unit, Pfizer
Muscle Regeneration is a Normal and Important Process

ACUTE INJURY

Healthy muscle

Transient inflammatory infiltration

Regenerated muscle

Transient collagen deposition

Mann et al. Skeletal Muscle 2011 1:21
Rapid and progressive muscle loss observed

Akima H et al. Neuromuscul Disord. 2011; PMID: 21807516

(Krista Vandenborne, Univ. Florida – presented at PPMD Conference 2011)
Satellite cell response to myotrauma.

*Skeletal muscle trauma or injury may be minor (e.g., resistance training) or may be more extensive (e.g., toxin injection, Duchenne muscular dystrophy).
Therapeutic approaches

- Growth Hormone / IGF-1 / Akt
- Steroids / Selective Androgen Receptor Modulators
- Beta-agonists (e.g. clenbuterol)
- Anti-myostatin
- Follistatin (Gene Therapy trial in BMD)
- Summit PLC - Utrophin upregulation ??
- Fate Therapeutics (Wnt7a)
- Stem cell therapies

“Not for human consumption”
- Found on bodybuilding website!

Pfizer Property – Not for Distribution
Genetic inactivation of myostatin (GDF8) leads to increased muscle mass.

Myostatin – a negative regulator of muscle growth

Myostatin Signaling

TLL/BMP-1 Proteases

GASP-1
FLRG
Follistatin

Block binding of GDF8 to ActRIIb

ActRIIb
Alk4/5

Inhibition of myogenic activity

(Lynch et al., 2007)
Muscle Responses to *myostatin* ...

Greater satellite cell activation, greater immediate regenerative capacity

(Wagner et al., 2005)
**Why Myostatin (GDF8) Inhibition in DMD?**

Inhibition of myostatin improves the muscle histology, mass, and function in mdx mice

- Genetic ablation of GDF8 improves mdx phenotype
- Improved phenotype after anti-GDF8 treatment

**Mstn^{+/+}/mdx**  
**Mstn^{-/-}/mdx**

Diaphragm pathology improved in Mstn^{-/-}/mdx

**Loss of Myostatin Attenuates Severity of Muscular Dystrophy in mdx Mice**

Kathryn R. Wagner, MD, PhD,  
Alexandra C. McPherron, PhD,  
Nicole Winik, BS,  
and Se-Jin Lee, MD, PhD

Ann Neurol 2002;52:832–836

**Functional improvement of dystrophic muscle by myostatin blockade**


NATURE | VOL 420 | 28 NOVEMBER 2002 | www.nature.com/nature
Myostatin inhibitors may slow disease progression in DMD

Disease progression associated with fibrotic infiltration into muscle

Increased collagen deposition and fibrotic infiltration observed in mdx and DMD muscle tissue

Myostatin inhibitors may delay fibrotic progression in dystrophic muscle

13 months of AAV-mediated myostatin inhibition slows disease progression in DMD dog model

(Bish et al., 2011)
Shifting the balance – How might myostatin support improved muscle function?

Goal of identifying therapeutic strategies that may normalize muscle regeneration in DMD

Initiation of steroids slows the progressive increase of VL muscle fat fraction

(Lee Sweeney, UPENN – presented at PPMD Conference 2014)
Current Status: PF-06252616

- PF-06252616 is a newly developed, humanized anti-myostatin monoclonal antibody
- A Phase 1 clinical trial in healthy volunteers has completed dosing
  - Found to be safe and well-tolerated
- A Phase 2 Clinical Trial in Duchenne Muscular Dystrophy is in the final planning stages
- Please check [www.ClinicalTrials.gov](http://www.ClinicalTrials.gov) and search “PF-06252616” for possible updates.

- Please visit our poster (Drama Studio)
- Presentation (Dr. Michael Binks): “Anti-myostatin inhibitor (moving into the clinic)” – Saturday- Jeffrey Hall 11:45-12:30