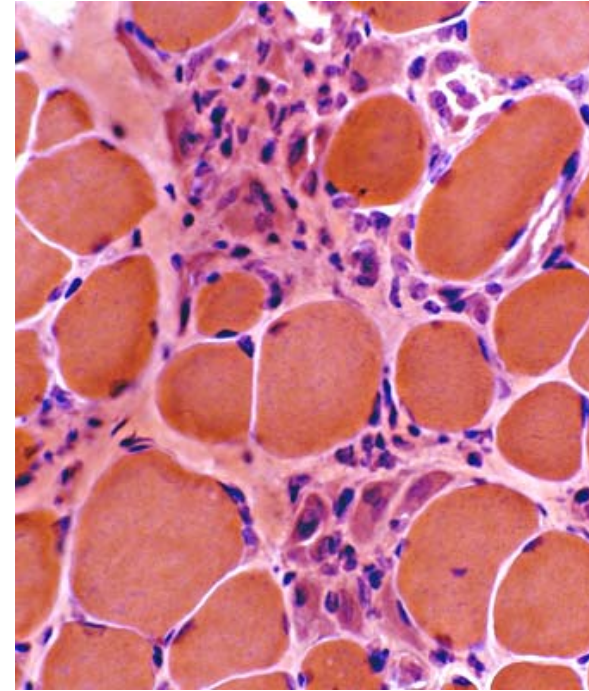
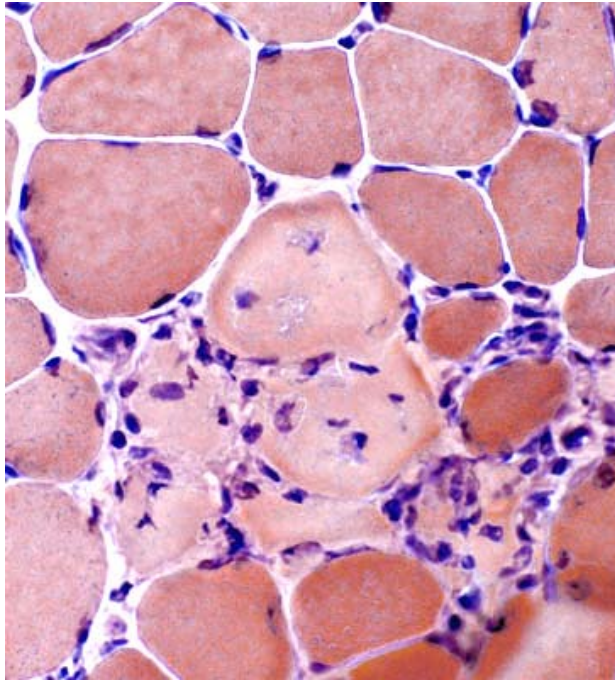


## Muscular dystrophy clinical manifestations:

- progressive proximal extremity weakness
- respiratory muscle weakness
- cardiomyopathy



Muscular dystrophy pathology: muscle fiber degeneration and regeneration

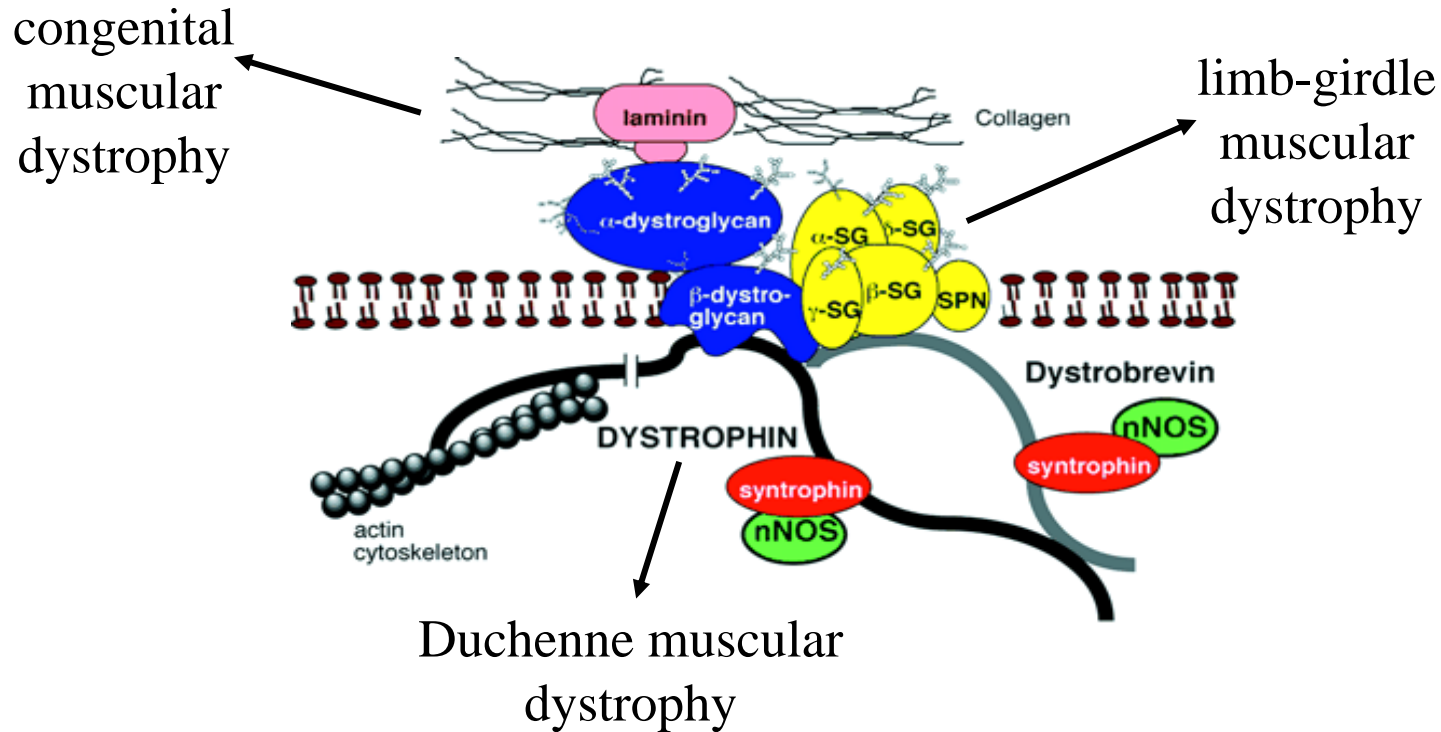
# Muscular dystrophies: identified genetic defects

- Duchenne/Becker
- Limb-girdle (11 types)
- Facioscapulohumeral
- Myotonic (2 types)
- Oculopharyngeal
- Emery-Dreifuss (2 types)
- Congenital (4 types)

## Muscular dystrophies: common themes

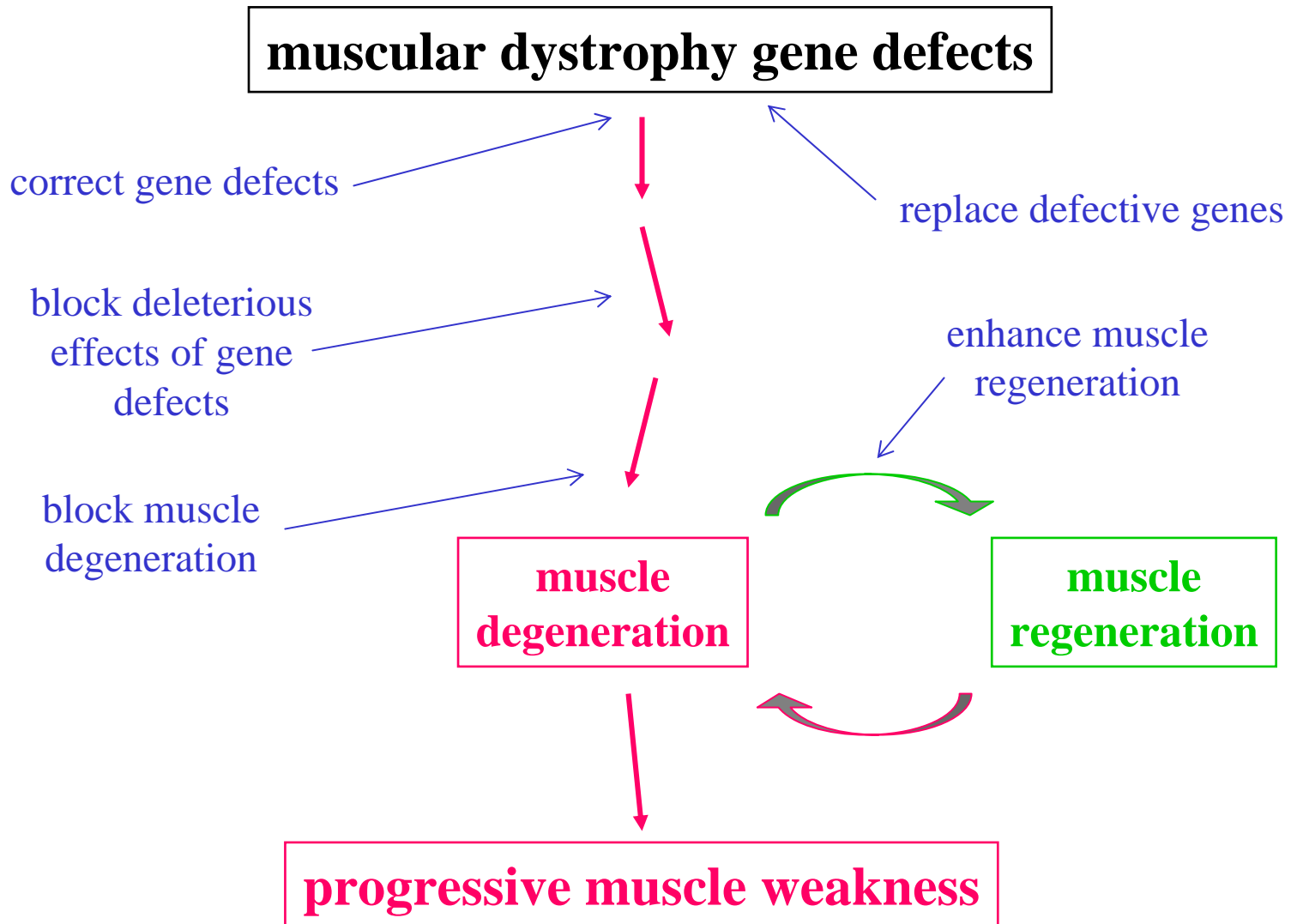
- defects in muscle structural proteins (Duchenne/Becker, limb-girdle, and congenital muscular dystrophies)
- altered gene expression and RNA processing (myotonic, oculopharyngeal, facioscapulohumeral, and Emery-Dreifuss muscular dystrophies)
- failure of compensatory mechanisms

# How do structural protein deficiencies lead to disease?



- Dystrophin is an important structural protein at the muscle plasma membrane
- Mutations in other dystrophin-associated proteins also cause muscular dystrophy

# Opportunities for therapeutic intervention



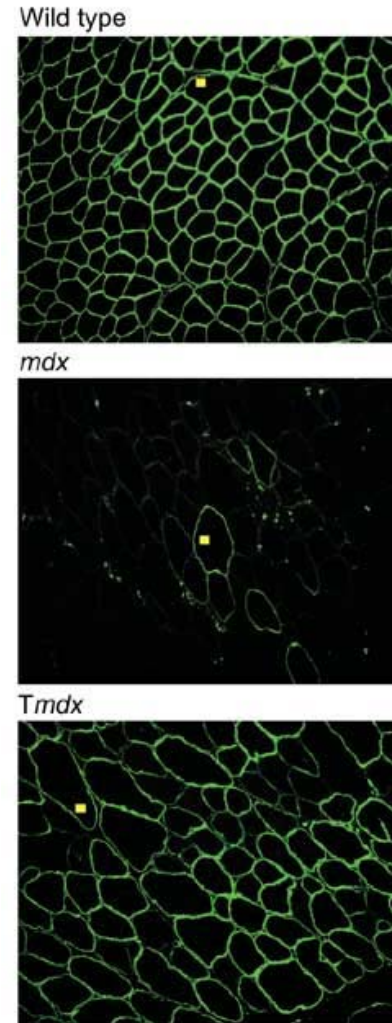
# Muscular dystrophy animal models

- Duchenne muscular dystrophy:
  - mdx mice
  - CXMD dog
- limb-girdle muscular dystrophy:  
sarcoglycan-deficient mice &  
hamsters
- congenital muscular dystrophy:  
myd mice

# Muscular dystrophy gene replacement

## Animal studies:

- adenoviral delivery of dystrophin in neonatal mdx muscle (1993)
- transgenic rescue of mdx mice with full length and truncated dystrophin (1993-2002)
- AAV delivery of truncated dystrophin via IV injection with VEGF in mdx (2004)

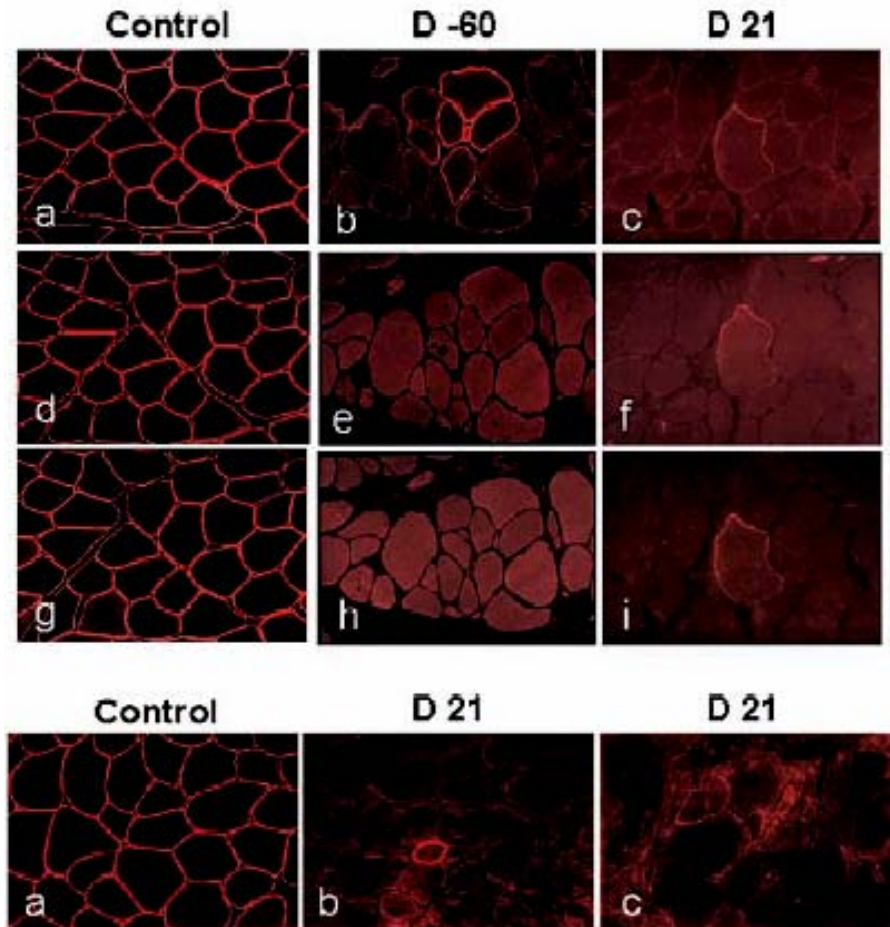


(Gregorevic, et al. 2004)

# Muscular dystrophy gene replacement

## Human studies:

- DMD myoblast transfer (1990-1997)
- LGMD-sarcoglycan AAV (2000)
- direct dystrophin DNA injection (2004)
- low efficiency - few fibers corrected



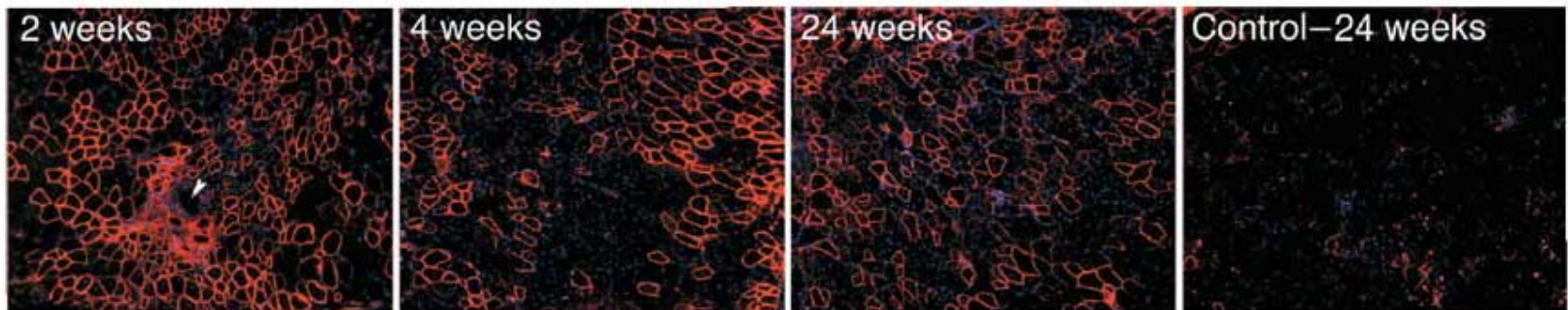
(Romero, et al. 2004)

# Muscular dystrophy gene replacement: issues

- safety
- systemic delivery
- efficiency & stability of expression
- immune response to vector & gene product
- dose required & production capacity
- multiple genes

# Muscular dystrophy exon-skipping

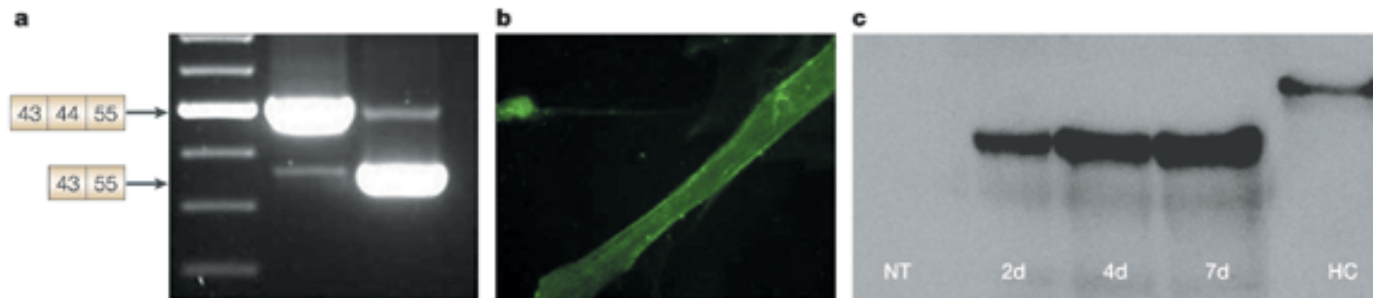
- Duchenne muscular dystrophy is usually caused by exon deletions that shift the translational reading frame
- antisense oligonucleotides promote skipping of mutant or downstream exons to restore the reading frame
- chemical modifications enhance oligonucleotide stability
- good results in mdx mice:



(Lu, et al. 2003)

# Muscular dystrophy exon-skipping

- dystrophin rescue in cultured muscle cells from DMD patients:



(van Deutekom & van Ommen, 2003)

## Issues:

- safety
- delivery
- efficiency & stability
- need for individualized treatment

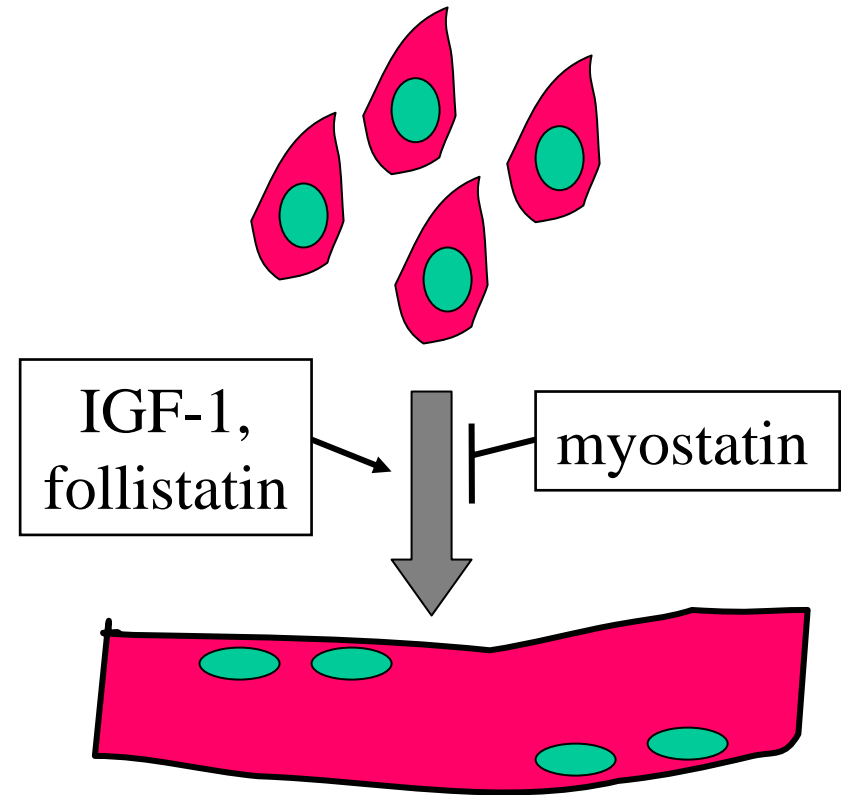
# Muscular dystrophies: pharmacological approaches to treatment

---

- drugs that correct translation of mutant mRNA, e.g., aminoglycoside-induced read-through of nonsense mutations
- drugs that decrease muscle degeneration, e.g., protease inhibition, LARGE stimulation
- approaches that increase muscle regeneration, e.g., myostatin inhibition, IGF1 & follistatin stimulation

# Increasing muscle regeneration

- Muscle growth and regeneration are enhanced by IGF-1 & follistatin and inhibited by myostatin.
- IGF-1 and follistatin overexpression and myostatin inhibition have beneficial effects in mdx mice.



**Myostatin mutation associated with gross muscle hypertrophy in a child.**

**Schuelke M, Wagner KR, Stolz LE, Hubner C, Riebel T, Komen W, Braun T, Tobin JF, Lee SJ.**

N Engl J Med. 2004

## Muscular dystrophies: common approaches to treatment

- Common approaches allow more efficient use of clinical research funds
- Common approaches and connections with common diseases (e.g., age-related muscle loss) increase the chances for commercial development