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An update on DMD research

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Muscular dystrophies

Large range of muscular dystrophies including

Duchenne & Becker MD
Limb girdle MD
Congenital MD
Myotonic dystrophy
Occulopharyngeal MD
Distal MD
Emery-Dreifuss

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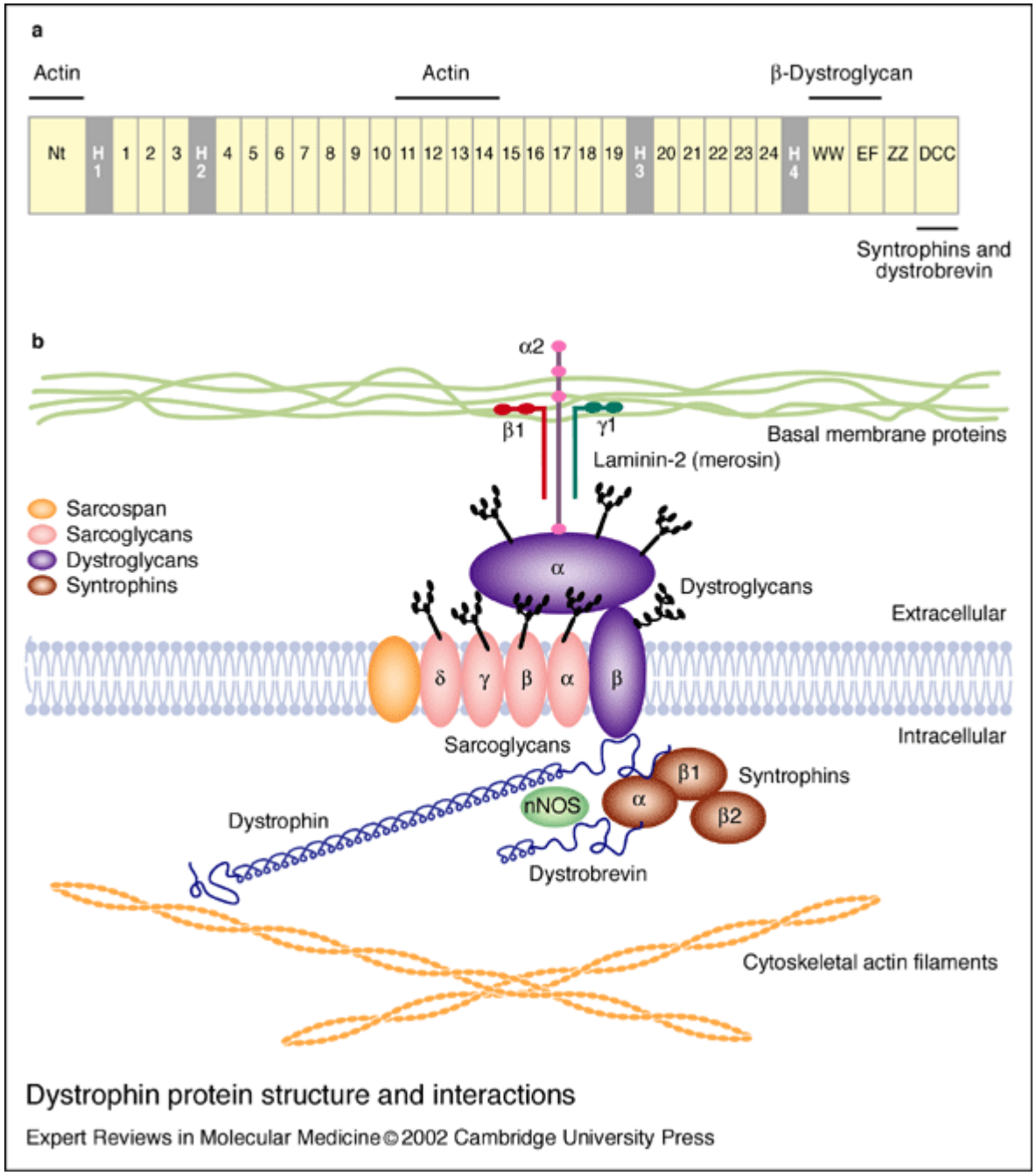

Dystrophin protein structure and interactions

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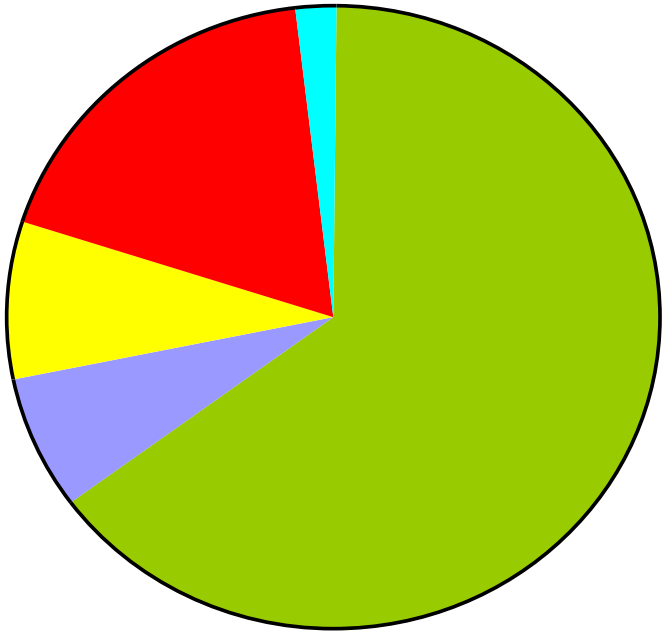
Types of mutations associated with DMD



- Large deletions and duplications
- Splice site mutations
- Small deletions and insertions
- Nonsense mutations
- Missense mutations

From Roberts at al, 1994

Most mutations disrupt the open reading frame leading to a failure to fully translate the mRNA and produce a functional protein

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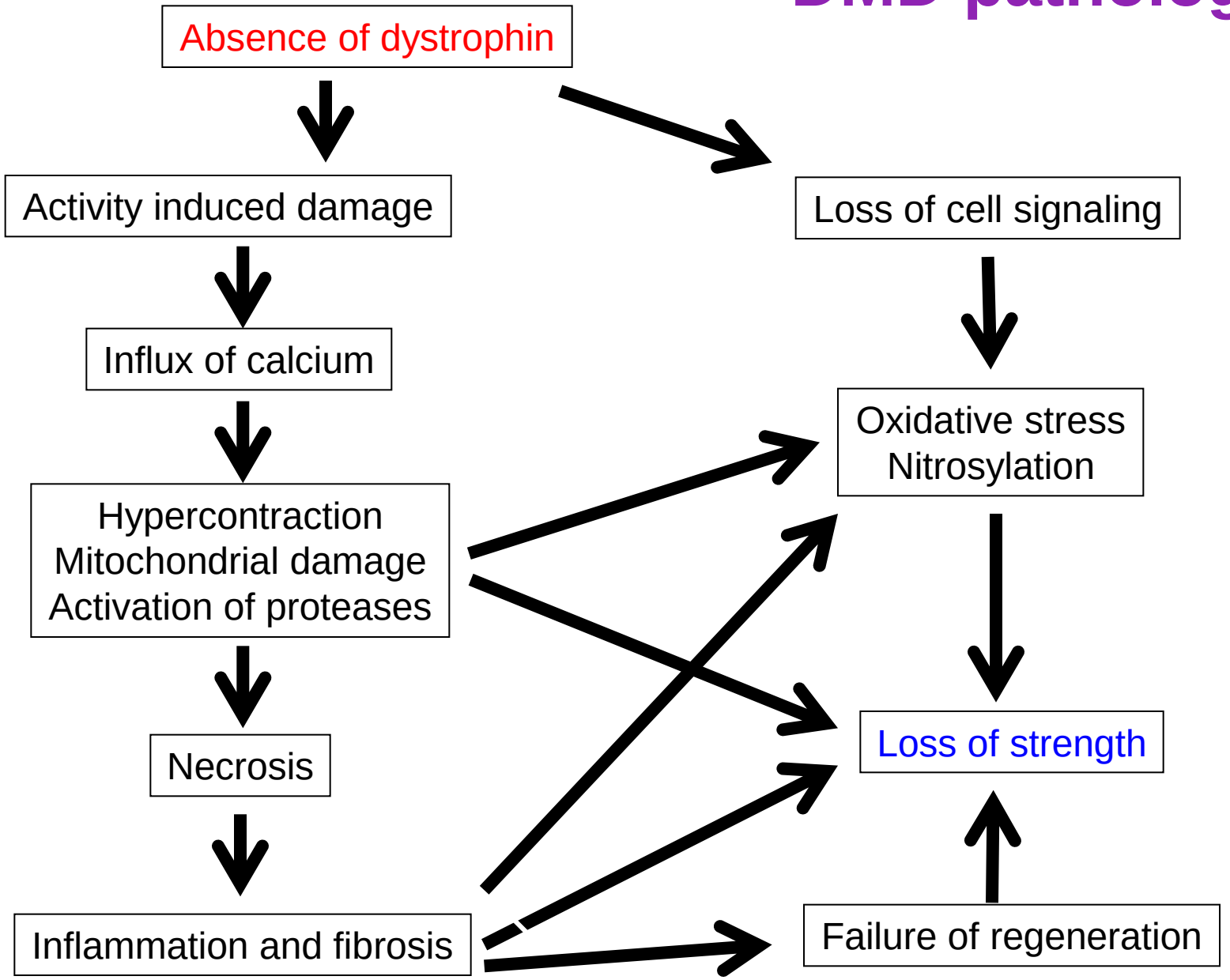
DMD pathology



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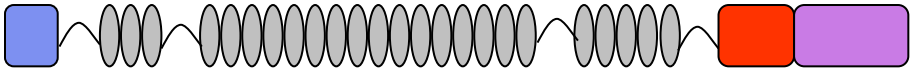
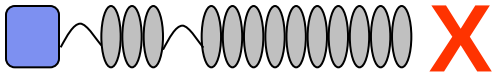
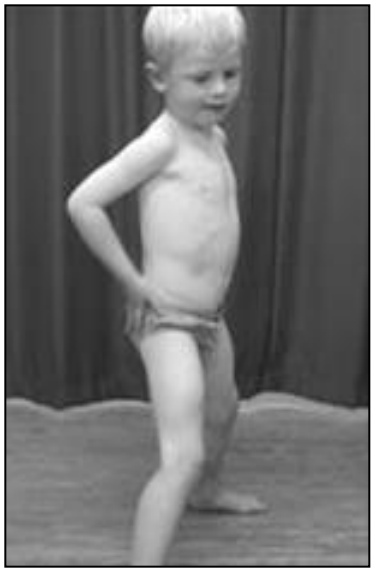


Loss of reading frame

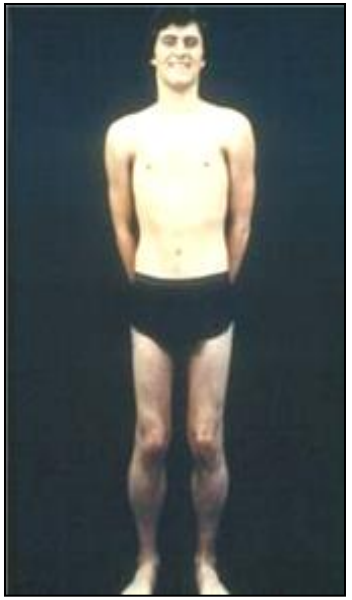


In frame mutation

generates an internally deleted protein



Duchenne muscular dystrophy



Becker muscular dystrophy

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Approaches to treatment in DMD - 1

Gene Therapy

- viral vectors
- cell therapy

Antisense mediated exon-skipping

Up-regulation of utrophin

Extracellular protein supplementation

These approaches have the potential to be the most effective as they restore the missing complex. They have real potential to stop the progressive muscle wasting.

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Approaches to treatment in DMD - 2

Modifying the consequences of disease

- Increasing muscle mass
- Reducing calcium influx
- Reducing mitochondrial initiated necrosis
- Reducing inflammation
- Reducing fibrosis
- Improving cell metabolism

These approaches may slow the progression of the disease.

However in combination with therapies that at least partially restore the complex

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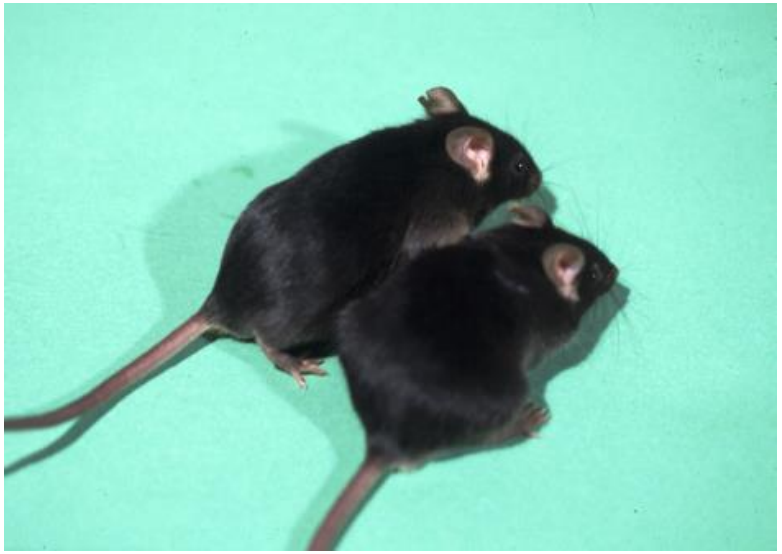
The *mdx* mouse



Extensively used model – 2700+ papers to date

- Spontaneous mutant discovered in 1984
- Dystrophin deficient due to stop mutation in exon 23
- Near normal lifespan and mobility
- Normal until onset of acute myopathy at 3 weeks
- Muscle damage associated with movement
- Muscle degeneration stabilises at 8 weeks and continues at a lower rate
- Limited fibrosis and fatty infiltration

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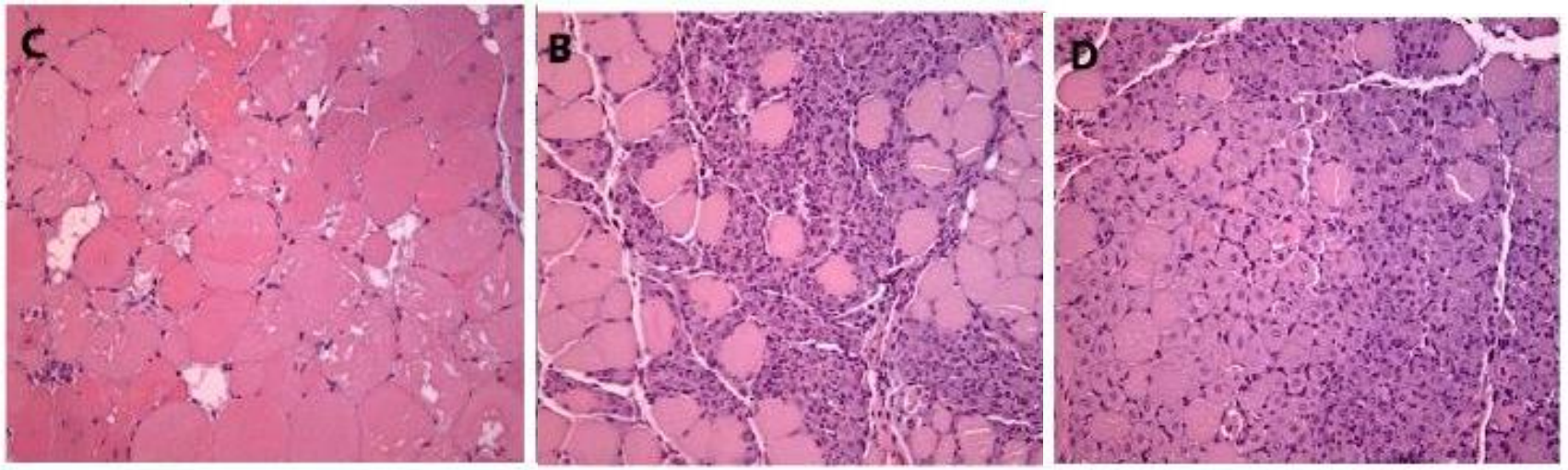
Muscle damage in the mdx mouse



Degeneration Inflammation Regeneration

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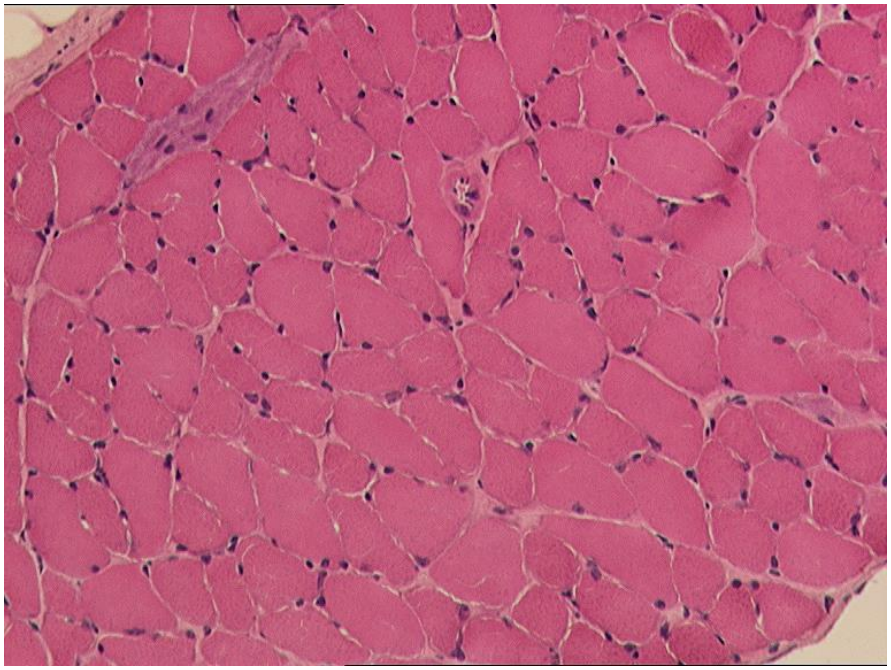
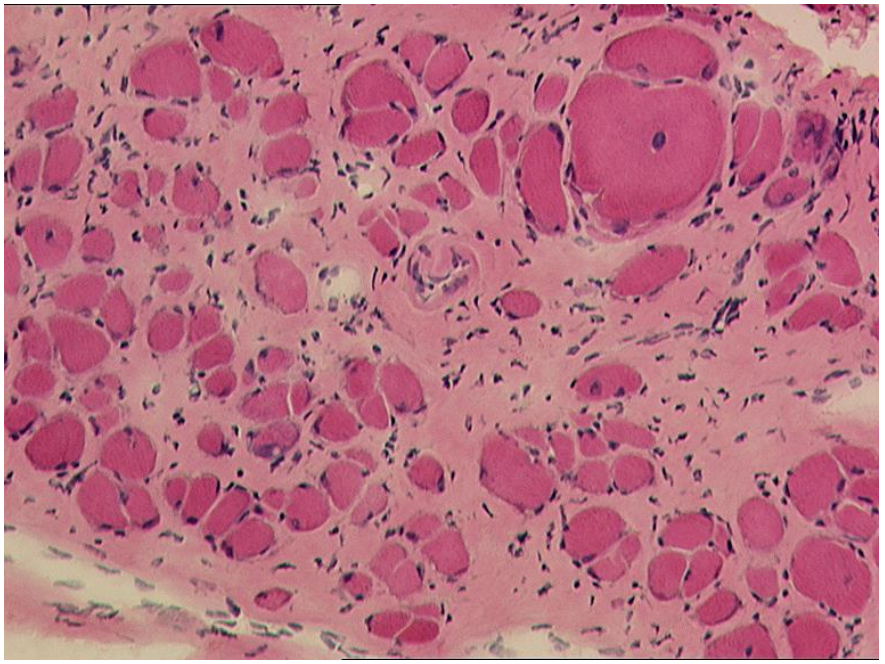
Mdx diaphragm pathology most like DMD





18 month old C57Bl10 and *mdx* diaphragm

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Effects of exercise

Sedentary and exercised *mdx* show differences in muscle pathology and response to treatment.

Recommended regime is 2 bouts of treadmill running per week: 30 minutes at 12m/min.

Note: differences in catching and handling mice can also cause muscle stress.

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Issues with mdx mouse studies

Mice are tough!

Mdx mouse has a mild phenotype

Doses and routes used are often not clinically suitable.

Different labs use different tests and some tests are influenced by multiple variables.

Some studies are poorly designed and lack statistical power.

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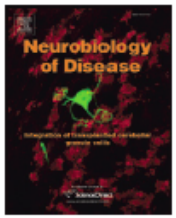
Outcome measures and SOPs

Neurobiology of Disease 31 (2008) 1–19

Contents lists available at ScienceDirect

Neurobiology of Disease

journal homepage: www.elsevier.com/locate/ynbdi



Review

Towards developing standard operating procedures for pre-clinical testing in the mdx mouse model of Duchenne muscular dystrophy

Miranda D. Grounds,[a,*] Hannah G. Radley,[a] Gordon S. Lynch,[b] Kanneboyina Nagaraju,[c] and Annamaria De Luca[d]

http://www.treat-nmd.eu/research/preclinical/dmd-sops/

TREAT-NMD
Neuromuscular Network

Wellstone Muscular Dystrophy Center
Washington, DC

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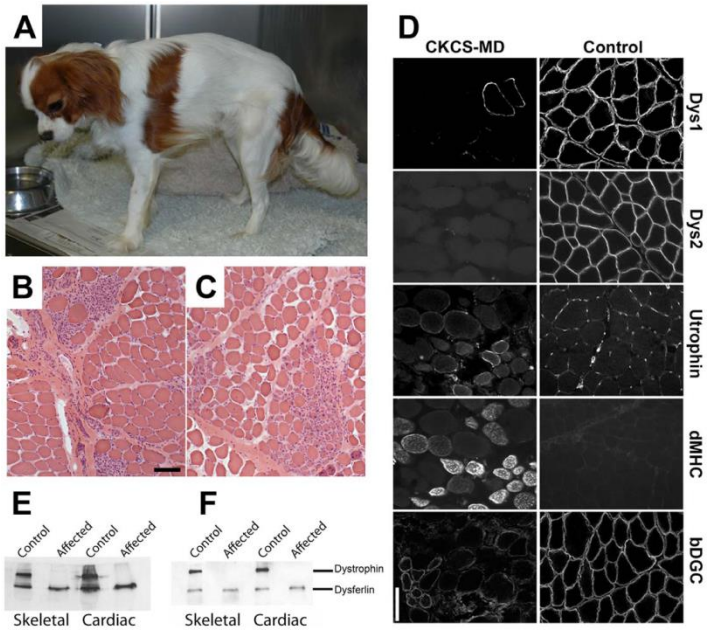
Dog models of DMD



GRMD - splice site mutation exon 7

- Severely disabled, die prematurely

A new dog model

Exon 50 deleted

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Increasing industrial involvement

Last 5-10 years has seen increasing industrial interest.

Why?

- rare diseases now seen as a viable target
- “Genzyme unit” cost model
- rare diseases are a test for new technologies

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Extracellular Protein based therapies

Biglycan

– work from the Fallon laboratory

- being developed by Tivorsan

Appears to stablise the DAPC complex by recruiting utrophin.

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Increasing muscle growth

IGF-1 treatment shows improved muscle repair and muscle size in the mdx mouse.

Mecasermin rimfarbate is complex form of IGF-1 with IGFBP3. Tested in DMD but results not published.

However tests in myotonic dystrophy showed no improvement in muscle strength.

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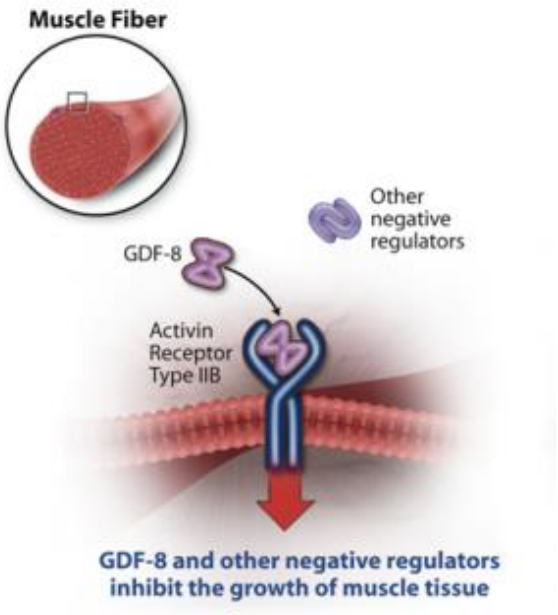
Blocking the action of myostatin



Myostatin is a negative regulator of muscle mass

Various strategies to block action:

- Release of soluble form of the Activin IIB receptor to block myostatin signaling (Acceleron - ACE-031). Trial stopped because of bleeding.
- Antibody to block myostatin binding. Pfizer PF-06252616.
- Propeptide blocker
- Inhibition of myostatin production (siRNA)

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Anti-inflammatory

Corticosteroids

– current standard of care where tolerated

- have significant side effects

Potential alternatives:

Halofugionone

CAT-1000

VBP-15

Nemo-binding domain (NBD) peptide

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Anti-oxidants

Oxidative stress is a common feature of many inflammatory diseases.

Green-tea extract containing anti-oxidants has been shown to be beneficial in mdx mice

Placebo controlled clinical trial currently ongoing in Germany with epigallocatechin-gallate

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Improving mitochondrial function

Catena® is idebenone, a small molecule that improves mitochondrial function, necessary for the production of cellular energy.

Phase IIa double-blind, randomized placebo-controlled clinical trial showed positive trends

Ongoing Phase III Double-Blind, Randomised, Placebo-Controlled Study of the Efficacy, Safety and Tolerability of Idebenone in 10-18 Year Old Patients With Duchenne Muscular Dystrophy

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santhera Pharmaceuticals

Combination therapies

Most current and future clinical trials will involve combination therapies as many patients are on corticosteroids already.

These can be assessed in animal studies although the dystrophic mouse and dog do not appear to respond to steroids in exactly the same way as DMD patients.

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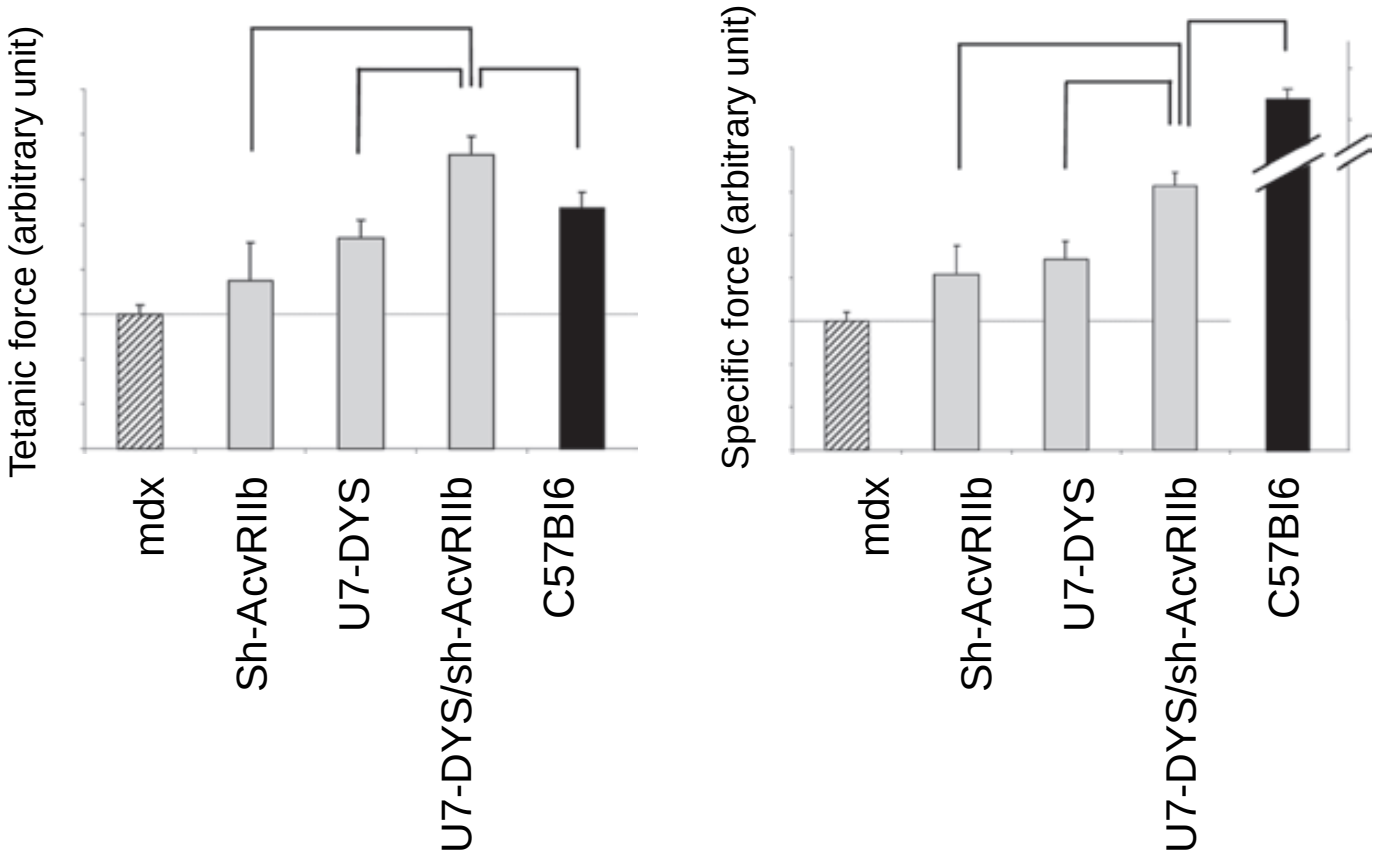
Dystrophin and myostatin

Restoration of dystrophin to stop muscle damage and blocking myostatin to increase muscle mass and function (Dumonceaux et al., 2010).



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How to make sense of all of the potential treatments

Be cautious about “breakthroughs” from mouse experiments.

Clinical trials essential.

The role of TACT reviews.

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What is TACT

The Treat-NMD Advisory Committee on Therapeutics.

an expert multidisciplinary body that provides the neuromuscular community (clinicians, researchers, patient advocacy groups and industry) with independent and objective guidance on advancing new therapies (whether novel or repurposed) for neuromuscular diseases.

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TACT activities

Have reviewed 24 proposed neuromuscular therapies to date. Majority focussed on DMD.

Applications range from academics to large Pharma (Pfizer)

17 applications from industry and 7 from academic leads.

One-time confidential review that can be requested by bodies asked to fund the clinical development.

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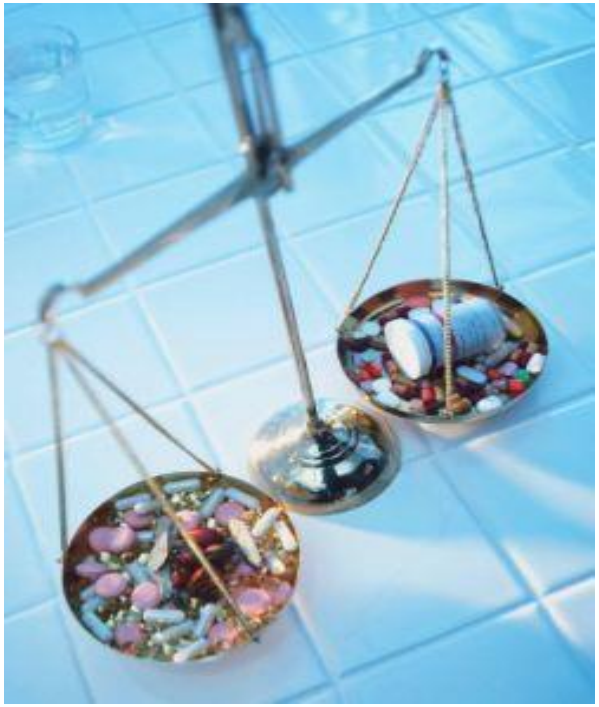
TREAT-NMD
Advisory Committee for Therapeutics



To access more information on TACT Google Treat-NMD

or

http://www.treat-nmd.eu/resources/tact/introduction/

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Conclusion

Cure not really in sight but treatments are likely.

Industrial involvement is key

Unlikely any one therapy will be fully effective and there are multiple targets for treatment.

Combination therapies are the likely future, perhaps a specific combination based on the patient's genotype.

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Any questions?

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