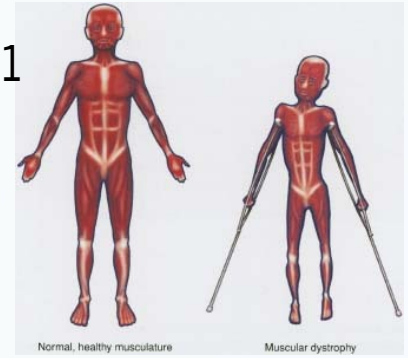
Duchenne Muscular Dystrophy (DMD)

Stanley Chan [Period 6]

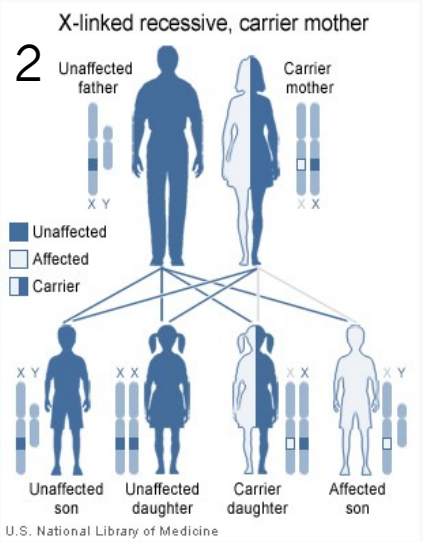
May 22nd, 2013

Fig. 1



Physiology

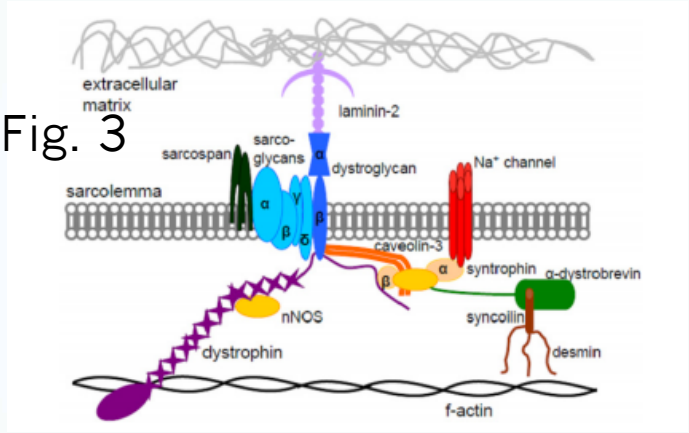
Fig. 2



- Most common muscular dystrophy: 1:4000 incidence (mostly boys)
- Some clinical variability, muscular system disorder.
- Muscular system target: muscle cells eventually die from intracellular leakage and attacks from cytotoxic T cells
- Average IQ of 85; gait abnormality; Gower sign
- Three major milestones: when DMD-affected patients begin to walk, when they lose their ability to ambulate, and when they die; death usually occurs by 3rd decade of life (respiratory infection → cardiopulmonary compromise)

Molecular Cause

Fig. 3



- Transmission: X-Linked Recessive; spontaneous mutation occurs in about 1/3 of cases

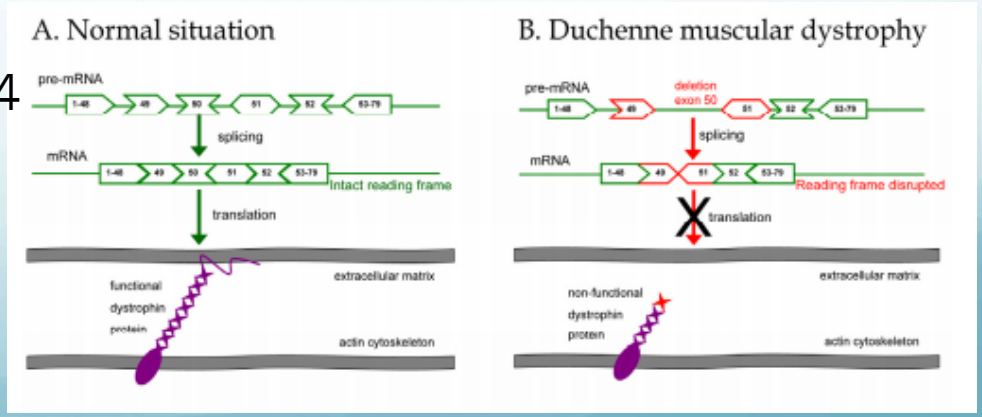
- Most common mutations are on short arm of X chromosome, location Xp21; mutations prevents dystrophin, a component of the cytoskeleton of the cell membrane, from being coded

- Interferes with translation reading frame or promoter sequence; synthesizes unstable, ineffective protein

- Dystrophin accounts for about 0.002% of proteins in striated muscle; it acts as a homotetramer at the costameres in skeletal muscles, as well as associates with actin at its N-terminus and the DAG complex at the C-terminus, forming a stable complex that interacts with laminin in the extracellular matrix

- A lack of dystrophin will lead to leakage of intracellular materials; this results in high levels of creatine phosphokinase (CPK); less active forms may still function as a sarcolemmal anchor; macrophages invade in the end anyway; dead muscle are replaced by fibrofatty infiltrate

Fig. 4

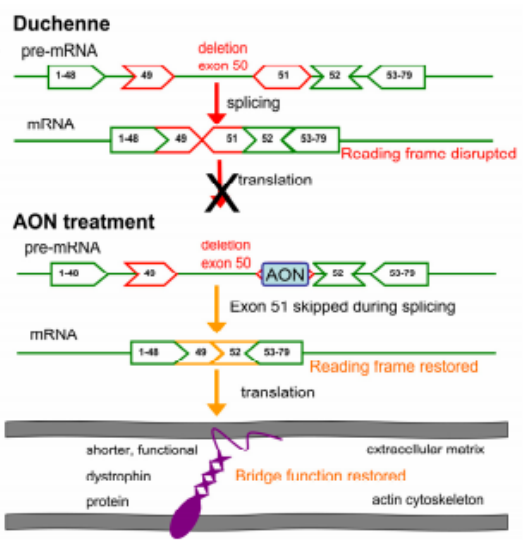


Treatments/ Risks and Limits

- DMD has no cure; treatment is focused on delaying onset of symptoms and improving standard of life
- Steroids (deflazacort) can be beneficial but have limited effect
- Palliative care: physical therapy includes splints, wheelchairs, minor exercise, and occupational therapists
- Surgery can be used to treat scoliosis and contractures; progressive when patient is non-ambulatory
- Novel methods: somatic gene therapy, PTC124, viral vectors, and antisense oligonucleotides (AONs)
- Gene therapy: healthy immature myoblasts introduced into diseased muscles; fuse and stimulate dystrophin; MDX model has shown more dystrophin but no improvement
- Viral vectors: Biostrophin uses 'micro-dystrophin,' or a small copy of the dystrophin gene; lacks functional regions (little clinical improvement)
- AONs: PRO051/51 and AVI-4658 focus on skipping exon 51; technique could be applied to other exons (phase 2)
- Ataluren; molecule PTC124 bind to ribosomes, overrides nonsense stop translation signals 'UGA' (phase 2)

Proposed Cure/ Limits

Fig. 5



- MDX mice model is the widely used model; a common single base substitution within exon 23 → premature stop codon; relatively mild compared to humans; up- regulation of utrophin; can also have a splice site in 43, mutation in 53, etc.
- Proposal is to improve PRO051/GSK; use multiple AONs and Ataluren
- We use DNA oligos to bind to RNA to form hybrids which activate RNase; enzyme cleaves the double-stranded mRNA, preventing the translation into protein; strategy is mutation specific, uses hotspots (exons 43-53, minor exons 2-20)
- We also use PTC124 is an orally taken, small molecule drug; it is meant to induce dose-dependent read-through of all nonsense codons UAA, UAG, or UGA in mRNA coding region
- Reverse-transcriptase-polymerase-chain-reaction to analyze the transcript region flanking the mutations
- MDX model limited by specific mutations; independent variables difficult to track, PTC124 operates as a relatively unknown (unique) molecule; submit successful standard 6-minute walk tests in humans (phase 1) to higher phases

References

Text

- "Duchenne muscular dystrophy: MedlinePlus Medical Encyclopedia".NIm.nih.gov. Updated 2.1.12. Retrieved 3.10.2013 <http://www.nlm.nih.gov/medlineplus/ency/article/000705.htm>
- "Duchenne and Becker muscular dystrophy. National Institutes of health". Ghr.nlm.nih.gov. Published 3.4.13. Retrieved 3.10.13 <http://ghr.nlm.nih.gov/condition/duchenne-and-becker-muscular-dystrophy>
- Rowland, L. P. (1985). Clinical Perspective: Phenotypic Expression In Muscular Dystrophy. In R. C. Strohman & S. Wolf (Eds.), Gene Expression in Muscle (pp. 3-5). New York, NY: Plenum Press. Retrieved 3.10.13 <http://link.springer.com/chapter/10.1007/978-1-4684-4907-5_1>
- Stone, K; Tester, C; Howarth, A; Johnston, R; Traynor, N; McAndrew (2007). *Occupational therapy and Duchenne muscular dystrophy*. New Jersey: John Wiley & Sons Ltd. Retrieved 3.22.13 < http://www.isota.ir/attachment.php?aid=38>
- Dellavalle A, Sampaolesi M, Tonlorenzi R, *et al.* (2007). "Pericytes of human skeletal muscle are myogenic precursors distinct from satellite cells". *Nat. Cell Biol. < http://www.nature.com/ncb/journal/v9/n3/abs/ncb1542.html>*
- "New muscular dystrophy drug trialled - Health News - NHS Choices". Nhs.uk. 2011-07-25. Retrieved 3.21.13 < http://www.nhs.uk/news/2011/07July/Pages/research-new-drug-muscular-dystrophy.aspx>
- Aartsma-Rus et al. (2006). *Entries in the Leiden Duchenne muscular dystrophy mutation database: an overview of mutation types and paradoxical cases that confirm the reading-frame rule.* Muscle Nerve. 34:135-144. Retrieved 3.21.13 < http://www.ncbi.nlm.nih.gov/pubmed/16770791>
- Research Updates Summer 2010. Quest. Volume 17 No. 3. Published 7.1.10. Retrieved 3.21.13 < http://quest.mda.org/departments/Research%20Updates?page=1>
- "Clinical trial information for 2'-O-methyl phosphorothioate (PRO051) trial". Trialregister.nl. Retrieved 3.21.13 <http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=1241>
- Types of Mutations in the Dystrophin Gene. DuchenneConnect. Retrieved 5.10.13 < https://www.duchenneconnect.org/index.php?option=com_content&view=article&id=347&Itemid=391&lang=en>

Images

- http://en.wikipedia.org/wiki/Duchenne_muscular_dystrophy (Fig.1)
- http://www.humanillnesses.com/original/Men-Os/Muscular-Dystrophy.html (Fig 2.)
- http://cdn.intechopen.com/pdfs/38140/InTech-Aon_mediated_exon_skipping_for_duchenne_muscular_dystrophy.pdf (Fig. 3-5)