Strategies for Treatment and Cure

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Treatment or Cure?

• Cure means no further treatment required.
• Theoretically possible, practically unlikely.
• If something sounds too good to be true get expert independent advice.
• In DMD all muscles are affected therefore need to be able to treat all muscles (or at least a group).
The Dystrophin Associated Protein Complex
Types of mutations associated with DMD

From Roberts at al, 1994
Loss of reading frame leads to unstable protein.

In frame mutation generates an internally deleted protein.

Duchenne muscular dystrophy

Becker muscular dystrophy
What does the genetics tell us for treatment?

• Parts of the dystrophin molecule are not essential.

• A smaller dystrophin gene means a wider range of systems for gene delivery

• Modification of the mutation may be therapeutic in cases.

• Need to know mutation to optimise treatment strategy.
Mouse model of Duchenne muscular dystrophy

- The mdx mouse.
- Lacks dystrophin due to point (stop) mutation in exon 23.
- Normal lifespan.
- Acute necrosis and regeneration of muscle 2-8 weeks.
- Then less ongoing damage in older mice.
- Small and easy to keep.
Why do we need animal models?

• Understanding the disease process
  – Can obtain multiple and invasive samples
  – Can manipulate system to investigate disease mechanisms

• Developing Treatments
  – Testing of drugs to modify disease process
  – Testing of novel therapies
Some important issues with mouse studies.

• Treating mdx <2 weeks of age tests prevention rather than treatment.

• A delay in onset of disease may be misleading as again these do not test treatment of disease – Salt prevents MD (Yoshida et al., 2006).

• Treatment of single muscles in mouse says little about treatment of man.

• Muscle physiology and membrane leakiness are good measures showing treatment effects in adult mdx.
Potential Targets for Treatment

• Correct the lack of dystrophin (restore DAPC)

• Reduce membrane instability and enhance repair

• Reduce inflammation and scarring (fibrosis)

Novel drugs and new applications for existing drugs
Restoration of dystrophin in muscle

- Gene repair
- Gene therapy with viral vectors (AAV)
- Gene therapy with non-viral vectors (plasmid)
- Cell therapy
- Exon-skipping (molecular patches)
- Readthrough of premature stop mutations
- Upregulation of utrophin
Reduce membrane instability and enhance repair

• IGF-1
• Myostatin inhibition
• Metabolic supplements
• Protease inhibition
• ? steroids
Reduce inflammation and scarring (fibrosis)

- Steroids
- Anti-TNFalpha
- Others anti-inflammatories and anti-fibrotics
Scaling up: from mouse to man

- Species differences
- Quantity of muscle
- Quantity of agent
- Metabolism
- Safety
- Cost
Current and Future clinical trials for DMD

- Antibody inhibition of myostatin in adult muscular dystrophies – Wyeth Pharmaceuticals – current trial in USA/UK.
- PTC124 – read through of premature stop codons – current trial in DMD (PTC Therapeutics).
- Ongoing trials of metabolic supplements/anti-inflammatories and antifibrotics in DMD – CINERG.
- Current clinical trial with intramuscular AAV1 for minidystrophin gene transfer into DMD – started early 2006 (Mendell, USA).
- Planned clinical trials of Antisense oligonucleotides in DMD by two groups in 2006 (Dutch/Prosensa and UK MDEX).
- Planned clinical trial of hydrodynamic plasmid gene transfer in DMD forearm planned for 2007 (Mirus/Transgene).
Existing treatments for DMD

• Steroids can slow the disease
• Assisted ventilation improves QoL and lifespan
• Cardiac medication improves heart function
Summary

• Many very promising developments

• No treatment is likely to work for everyone

• No single treatments is likely to be a cure

• Combinations of treatments are likely to be the most effective