Duchenne Research Overview: New and Emerging Therapies

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Duchenne Muscular Dystrophy

- Degenerative muscle disease
- Caused by a mutation in *DMD* gene - the largest human gene with 79 exons
- X-linked recessive disease with a prevalence of 1:5000 male births
- Progressive multi-system disease affecting
  - Skeletal muscle
  - Heart muscle
  - Smooth muscle
  - Cognitive function
  - Long term - lungs, bone, spine and ligaments
Dystrophin

- DMD gene encodes for a protein dystrophin
Impact of loss of dystrophin

- Membrane instability
- Calcium infiltration
- Inflammation
- Oxygen deprivation
- Fibrosis
- Muscle cell death
Diagnosing DMD

Clinical suspicion of DMD

CK level determination

High levels*

Normal values → DMD is ruled out

Diagnostic suspicion:

Deletion/duplication detected (MLPA)

Mutation detected (deletion/duplication)

Gene sequencing***

Mutation detected

DMD confirmed

Diagnostic confirmation:

Muscle biopsy

Alternative diagnoses to be considered

**

***
Management of DMD

• 1843- first described
• 1980’s- genetic cause identified
• 1988- Prednisone shown to be effective
• 2000’s – exon skipping
  - gene editing
  - synthetic steroids
  - anti-oxidant therapies
• Last decade - leaps and bounds
Patient Focused Multidisciplinary Care
Potential Targets for Duchenne Therapy

- Exon-Skipping
- Gene Therapy
- CRISPR/Cas9
- Stop-Codon Readthrough

- Steroid Replacement
- Anti-Fibrotics
- Inflammation & Fibrosis

- Calcium Regulation
- Ryanodine Receptors
- Calcium Homeostasis

- Dystrophin Restoration/Replacement
- Stem Cells
- Traditional Cardiac Drugs

- Cardiac
- Blood Flow
- Mitochondria
- nNOS Upregulation
- Mitochondrial Biogenesis
- Mitochondrial Enhancers

- Muscle Growth and Protection
- Myostatin Inhibition
- Follicostatin Upregulation via Gene Therapy
- Selective Androgen Receptor Modulators
- Utrophin Upregulation

Treating Duchenne
What is a Clinical Trial?

• A trial is a scientific study/experiment
• Potential therapy, not a therapy
• Risks and benefits
• IRB

What does FDA approved mean?

• FDA experts review the results of laboratory, animal, and human clinical testing done by manufacturers.
• FDA approval means the benefits of the product outweigh the known risks for the intended use
Study Types

–Pre-clinical: lab and animal studies
–Phase I: First in humans
  - Small n, dosing range, safety, side effects
–Phase II: Assess dose requirements and toxicity
  
  Assess efficacy
–Phase III: Randomized control placebo trial
  - Ultimate safety, efficacy and dosage of drugs
  - Compared to current gold standard or placebo
–Phase IV: Post-Marketing; monitor long term effects
Timeline of Studies

Stages of Clinical Trials

Preclinical → Phase 1 → Phase 2 → Phase 3 → Phase 4

- Preclinical: several years
- Phase 1: months
- Phase 2: months to years
- Phase 3: years to decades
- Phase 4: ongoing

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Looking at Treatment Options

• What is the drug name?
• Approved?
• Side effects?
• What stage of trial?
• Inclusion/exclusion Criteria?
• Informed consent--
  ▪ Ensure you understand the study– ask questions
  ▪ What is the timeline for visits?
  ▪ How is reimbursement being handled?
  ▪ Average length of a study visit?
Clinical Trials in Duchenne

Dystrophin Restoration/Replacement

Exon-Skipping
Gene Therapy
CRISPR
Stop-Codon Readthrough

Steroid Replacement

Anti-Fibrotics
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Stem Cells
Traditional Cardiac Drugs
Dystrophin Restoration and Replacement

Exon Skipping - skip over the missing/defective part of the gene
Ambulatory, on steroids, mutation amendable
Exon Skipping

- Exon 51- exondys 51- 9/2016
- Exon 45 /53: Sarepta –ESSENCE (phase II/III)
- Casimersen/ Golodirsen – (phase III)
- Exon 53: **NS Pharma** (Phase II extension study)- completed
- Exon 51: **WAVE Life Sciences** (Phase II/III)
Dystrophin Restoration and Replacement

Stop Codon Read-through
- Ataluren (Translarna): PTC Therapeutics
- Makes ribosome less sensitive to stop codon
- Ignore the missing/defective part of the gene
- Continue to make protein
- Phase III extension study
- not FDA approved yet
Gene Therapies

- AAV(rh74) virus to deliver micro- or mini-dystrophins into human DNA
- Exon 18-58 (70%)
- Single IV administration
- re-dosing?

Dystrophin Restoration and Replacement
Dystrophin Restoration and Replacement

**Micro/Mini-dystrophin**
- Nationwide Children’s Hospital / Sarepta
  - Muscle specific
    - Doesn’t cross blood brain barrier
  - First trial finished dosing
  - Second trial has begun dosing
- **Ignite DMD** Solid Biosciences (Phase I/II, Micro-dystrophin)
- Pfizer (Phase I, Mini-dystrophin)
Surrogate Gene Therapy

-GALGT2 – Nationwide Children’s Hospital
  - Also delivered via AAV
  - Upregulate dystroglycan-binding proteins
  - Phase I/II
  - 4 years and older
  - ambulatory
  - steroids >12wk
  - IV infusion
  - Recruiting
Duplication Skipping

- Exon 2 Duplication Strategy – Nationwide Children’s Hospital

  - Preclinical
  - Only study looking at duplications
  - Specific to duplications in exon 2
  - Duplications account for 10–15%- exon 2 MC
  - Induce exon skipping by the use of a virus carrier
  - Copies of a modified small nuclear RNA targeted to exon 2
  - Alternative splicing – increases functional dystrophin
  - Uses CRISPR/Cas9 system
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Treating Duchenne

Muscle Growth and Protection
**Muscle Growth and Regeneration**

**Biglycan**: Tivorsan Pharma  
- Preclinical  
- Biglycan increases the expression of utropin  
- Similar to dystrophin- partially compensate for the absence of dystrophin.

**Anti-myostatin**: Roche  
- Phase II/III  
- 6-11yo, ambulatory, steroids  
- Myostatin inhibitor
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Treating Duchenne
**Anti-inflammatory**

**Edasalonexent**: Catabasis  
- Phase III, 4-7yo, ambulatory, steroid naïve  
- NFkB inhibitor, anti-fibrotic  
- Oral

**Vamorolone**: ReveraGen  
- Phase II, 4-7yo, ambulatory, steroid naïve  
- Synthetic (Dissociative) steroid
Anti-inflammatory

**Givinostat**: Italfarmaco - Phase III, >6yo, ambulatory, steroids >6mo
- HDAC enzyme Inhibitor
- HDAC inhibit DNA function – DMD- Higher levels – prevent muscle regeneration

**MK1411**: Mallinckrodt - Phase II, 4-8yo, steroid naive
- Synthetic ATCH

**Pamrevlumab**: Fibrogen - Phase II
  - Antibody to CTGF– prevents fibrosis
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Muscle Growth and Protection
Mitochondrial function

**Raxone (Idebenone)**: Phase III
- SIDELOS/ DELOS
- Steroid naïve complete, Seeking FDA review

**Epicatechin**: Cardero Therapeutics - Phase II
  - Mitochondrial growth/ regeneration of muscle cells
  - Non ambulatory

**MTB-1**: Astellas Pharma (Pre-clinical)
  - Selective gene regulator
  - Improve mitochondrial function
Questions?
Thank you!