Duchenne Research Overview: The landscape and the opportunities

PPMD President
Pat Furlong
Duchenne

- Largest gene & protein in the human genome
- 2.4 Million base pairs/79 Exons
- **Loss of Dystrophin**

Multi-system Disease:
- Skeletal Muscle
- Heart
- Bone
- Smooth Muscle
- Cognitive Function

- 60-70% Deletions
- 10% Duplications
- 10-15% point mutations and other small changes
Due to a genetic mutation, the dystrophin protein is missing or not functional in Duchenne.
What does dystrophin do?
What happens when dystrophin is missing?

- Calcium
- Free radicals
- Inflammation
- Oxygen deprivation
- Fibrosis (scarring)
- Muscle cell death

No linkage
What is a Clinical Trial?

• A trial is an experiment, not a therapy
• Risks and benefits
  – Data Safety Monitoring Boards (DSMB)
  – May assess safety and data during the trial
• Important to listen to pay attention to the informed consent/assent
Study Types

• Multi-Phase Clinical Trials
  – Pre-clinical
    • lab and animal studies
  – Phase I:
    • First in humans (mechanistic, usually in healthy volunteers, dosing, small n)
    • assess safety
  – Phase Ila:
    • Assess dose requirements
    • Ila and IIb ca be a little blurry…..
Study Types

- **Phase IIb**
  - Assess efficacy; “Pivotal”
  - can combine a and b, testing both efficacy and toxicity
  - larger than phase I

- **Phase III**
  - Classical randomized control placebo trial 1000-3000 subjects
    - In rare disease, this number can be much smaller

- **Phase IV**
  - Post-Marketing
  - monitor long term effects
Exondys 51 (Eteplirsen) [Sarepta]
Emflaza [PTC Therapeutics]
Spironolactone & Eplerenone [Ohio State University]
Translarna (Ataluren) [PTC Therapeutics]
Givinostat [Italfarmaco]*
Raxone (Idebenone) [Santhera]*
SRP-4045/SRP-4053 [Sarepta]*
RG6206 [Roche]*
Edasalonexent (CAT-1004) [Catabasis]
Domagrozumab (PF-06252616) [Pfizer]*
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Nationwide Micro-Dystrophin Gene Transfer...
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Nationwide Exon 2 Skipping for Duplication 2...
Tamoxifen** [University of Geneva]
MA-0211/MTB-1 [Mitobridge/Astellas]
Clinical Trials in Duchenne

- Exon-Skipping
- Gene Therapy
- CRISPR/Cas9
- Stop-Codon Readthrough
- Steroid Replacement
- Anti-Fibrotics
- Inflammation & Fibrosis
- Calcium Regulation
- Ryenodine Receptors
- Calcium Homeostasis
- Myostatin Inhibition
- Follistatin Upregulation via Gene Therapy
- Selective Androgen Receptor Modulators
- Utrphin Upregulation
- Dystrophin Restoration/Replacement
- Stem Cells
- Traditional Cardiac Drugs
- Cardiac
- Blood Flow
- Mitochondria
- nNOS Upregulation
- Mitochondrial Biogenesis
- Mitochondrial Enhancers

Treating Duchenne

- Muscle Growth and Protection
- Stem Cells
Clinical Trials in Duchenne

Dystrophin Restoration/Replacement

Muscle Growth and Protection

Treating Duchenne

Calcium Regulation

Inflammation & Fibrosis

Steroid Replacement

Exon-Skipping

Gene Therapy

Calcium Homeostasis

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Follistatin Upregulation via Gene Therapy

Selective Androgen Receptor Modulators

Utrophin Upregulation

Traditional Cardiac Drugs

Cardiac

Blood Flow

Mitochondria

Mitochondrial Biogenesis

Mitochondrial Enhancers

Stem Cells

nNOS Upregulation
Dystrophin Restoration and Replacement

- Exon Skipping (skip over the missing/defective part of the gene)
  - Exon 45 and 53
  - (Golodirsen, Casimersen)
    - **Essence (Sarepta)**
      - 7-13yo, ambulatory, steroids >6mos
  - Exon 53
    - **NS Pharma NS-065/NCNP-01**
      - 4-9yo, ambulatory, steroids >6mos
- WAVE Life Sciences
  - Exon 51 WVE-210201
  - 5-18 years, recruiting
Dystrophin Restoration and Replacement

- Stop Codon Read-through (Ignore the missing/defective part of the gene)
  - Translarna (PTC)
    - EMA: Approval
    - Phase 3 extension study now
      - >5, ambulatory, steroids >12 mos
Gene Therapies

- All use serotypes of the AAV virus to deliver microdystrophins with the “business ends” of the dystrophin
- Studies will determine the most efficient microdystrophin
- Effect is thought to last ~10 years
- Cannot be repeated at this time
  - Working to avoid the formation of antibodies to the virus
  - Goal – re-dosing
Alternative Dystrophin Forms as Transgenes

Modified from Okada and Takeda, Viral Gene Therapy, intechopen.com
The world of AAV
Slides courtesy of Dr. Jude Samulski
Gene Therapy

- Microdystrophin
  - Nationwide Children’s Hospital
  - Exons 18-58
  - Muscle specific
    - Doesn’t cross blood brain barrier
  - Ages
    - 6 patients, 4 - 7 years
  - 4 patients have been dosed
Gene Therapies

- **SGT-001**
  - Solid GT
  - Micro-dystrophin
  - 4-17 years
  - Recruiting

- **PF-06939926**
  - Pfizer
  - Mini-dystrophin
  - 5-12 years
  - Recruiting
Gene Therapy

- GALGT2 - rAAVrh74.MCK.GALGT2
  - 4 years and older
  - recruiting

- Exon 2 Duplication Strategy
  - Preclinical
  - Nationwide Children’s Hospital
  - Only study looking at duplications
  - Specific only to duplications in exon 2
  - Pre-clinical
Clinical Trials in Duchenne

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- Mitochondrial Biogenesis
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Muscle Growth and Regeneration

• Utrophin modulator
  – Ezutromid (SMT C1100)
    • Summit Pharm, Phase 2
    • 5-10yo, ambulatory
    • Steroids >6 mos
  – Biglycan (TVN-102)
    • Tivorsan Pharma
    • Pre-clinical
Muscle Growth and Regeneration

• Myostatin Inhibition
  
  – Domagrozumab
    • Pfizer, Phase 2
      • 6-<16yo, ambulatory, steroids >6mos

  – BMS 986089 (now Roche)
    • BMS/Roche, Phase 1
      • 6-11yo, ambulatory, steroids >6mos
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- Utrophin Upregulation
Anti-inflammatory

- Givinostat
  - Italfarmaco, HDAC inhibitor
  - Phase 3
  - >6yo, ambulatory, steroids
  - >6mo
Anti-inflammatory

- **Edasalonexent**
  - Catabasis, Phase 2a;
  - NFκB inhibitor, anti-fibrotic
  - 4-7yo, ambulatory, steroid naïve

- **Vamorolone**
  - ReveraGen, Phase 2;
  - Steroid alternative
  - 4-<6yo, ambulatory, steroid naive
Anti-inflamm

- Malincrot
  - Pre-clinical
  - MK1411
- Pamrevlumab
  - FG-3019, Fibrogen, anti-fibrotic
  - Antibody to connective tissue growth factor
  - Phase 2
  - >12yo, non-ambulatory, steroids >6mos
Clinical Trials in Duchenne
Cardiac Therapies

• CoQ10 and Lisinopril
  – Completed, under evaluation
• Spironolactone v.s. Eplerenone
  – completed

• Cap-1002
  – Capricor; HOPE -2
  – 10 years and older
  – Recruiting
Mitochondria

- Epicatechin
  - Cardero Therapeutics
  - Mitochondrial growth

- Raxone (Idebenone)
  - Santhera
  - Preservation of respiratory function
  - Delos Trial
    - Steroid naïve complete, Seeking FDA review
  - Sideros Trial
    - Phase 3
    - >10yo, steroids >12 mos, ambulatory or non-ambulatory
Mitochondria

- MTB-1
  - Mitobridge and Astellas Pharma
  - Improved mitochondrial function
  - Pre-clinical
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