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**

- 60-70% Deletions
- 10% Duplications
- 10-15% point mutations and other small changes

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

Creatine kinase (CK)
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 IIa:
    • Assess dose requirements
    • IIa and IIb can 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
Clinical Trials in Duchenne

[Diagram showing various treatment methods involving Dystrophin Restoration/Replacement, treating Duchenne, muscle growth and protection, calcium regulation, inflammation & fibrosis, steroid replacement, anti-fibrotics, cardipathy, blood flow, mitochondrial biogenesis, and nNOS upregulation.]

- Exon-Skipping
- Gene Therapy
- CRISPR/Cas9
- Stop-Codon Readthrough
- Steroid Replacement
- Inflammation & Fibrosis
- Calcium Regulation
- Ryanodine Receptors
- Calcium Homeostasis
- Myostatin Inhibition
- Follistatin Upregulation via Gene Therapy
- Selective Androgen Receptor Modulators
- Urotphin Upregulation
- Stem Cells
- Traditional Cardiac Drugs
- Mitochondrial Enhancers
- nNOS Upregulation

- Cardiac
- Blood Flow
- Mitochondria

PARENT PROJECT MUSCULAR DYSTROPHY | ENDDUCHENNE.ORG
Knowing your genotype deletions can shift meaning of sequence

• Insertions/deletions may place sequence “out of frame” if not a multiple of 3
• Example: THE BIG RED DOG SAT AND RAN”
• “THE BIG RED DOG SAN NDR AN”
  – (nonsensical)
• “THE BIG RED DOG RAN”
  – Shorter, but a functional sentence
DMD- single base mutations can stop protein synthesis early

• Nonsense mutations (also called stop-gain)
  – UAA, UAG, UGA
  – Example:
  – “THE BIG RED DOG SAT AND RAN”
  – THE BIG RED DOG SAT END
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
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  – Example:
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Dystrophin Restoration and Replacement

• Stop Codon Read-through (Ignore the missing/defective Stop signal)
  – 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
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
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- Dystrophin Restoration/Replacement
- Stem Cells
- Traditional Cardiac Drugs

- Cardiac
- Blood Flow
- Mitochondria

- Muscle Growth and Protection
- nNOS Upregulation
- Mitochondrial Biogenesis
- Mitochondrial Enhancers
- Selective Androgen Receptor Modulators
- Utrophin Upregulation

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Muscle Growth and Regeneration

– Biglycan (TVN-102)
  • Tivorsan Pharma
  • Pre-clinical
Muscle Growth and Regeneration

• Myostatin Inhibition

  – Domagrozumab
    • Pfizer, Phase 2
    • STUDY TERMINATED

  – BMS 986089 (now Roche)
    • BMS/Roche, Phase 1, not enrolling
    • 6-11yo, ambulatory, steroids >6mos
Clinical Trials in Duchenne

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- PARENT PROJECT MUSCULAR DYSTROPHY | ENDDUCHENNE.ORG
Anti-inflammatory

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

• Edasalonexent (CAT-1004)
  – Catabasis
  – Phase 2a, recruiting
  – NFkB inhibitor, anti-fibrotic
  – 4-7yo, ambulatory, steroid naïve

• Vamorolone
  – ReveraGen
  – Phase 2, recruiting
  – Steroid alternative
  – 4-<6yo, ambulatory, steroid naive
Anti-inflammatory

- **MK1411**
  - Mallinckrodt
  - Pre-clinical

- **Pamrevlumab**
  - FibroGen
  - FG-3019, anti-fibrotic
  - Antibody to connective tissue growth factor
  - Phase 2 (not recruiting)
  - >12yo, non-ambulatory, steroids >6mos
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Treating Duchenne

- Dystrophin Restoration/Replacement
- Cardiac
- Calcium Regulation
- Muscle Growth and Protection

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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
Thank you!