DMD
Research Overview
End Duchenne Tour 2018

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Disclosures for STI

• Research funding from PTC Therapeutics, Sarepta, FibroGen, Regeneron, Mallinkrodt, Capricor

• DSMB for Catabasis

• Ad Board for AveXis, Biogen, Sarepta

• Supported by NIH and MDA funding

• Thanks to Pat Furlong and Amanda Wilkison for slides, Eugenio Mercuri for WMS update
Early descriptions, 19th century
Duchenne/Becker MD

- Incidence: 1-3 in 10,000 male births
- Carrier frequency: 1 in 2000
- New mutations: 30%
- Mutation rate: 1 in 30,000
- CK >100X nl
Due to a genetic mutation, the dystrophin protein is missing or not functional in Duchenne musculature.
Diagnosis of DMD

- Clinical phenotype
- CK
- DNA
  - Deletion/duplication (up to 70%)
  - Sequencing
- NBS
DMD: Multisystem Disease

- Skeletal myopathy
- Encephalopathy
  - Behavior disorder
  - Cognitive deficit
  - Learning differences
- Cardiomyopathy
- Smooth muscle
  - Vessels
  - GI tract
DMD: Complications

- Orthopedic
  - Contractures
  - Scoliosis
  - Chest wall deformity
- Pulmonary
  - Restrictive lung disease
  - Obstructive sleep apnea
- Pain
  - With exercise
  - With immobility
DMD: Multisystem Disease and Complications

• Multidisciplinary clinic
  – One stop shopping
  – Specialists with expertise in DMD
  – Team approach

• Challenges
  – Cost/reimbursement
  – Space
  – Other commitments for providers
Treatment of DMD

• **Standard of Care:**
  – Multi disciplinary care
  – Expert subspecialty care

• **Steroids**
  – Benefits
    • Life expectancy
    • Lung function
    • Cardiac function
    • Scoliosis
  – Prednisone vs Emflaza
  – Daily vs pulse/weekend dosing
# Treatment of DMD

<table>
<thead>
<tr>
<th>Chronology</th>
<th>Description</th>
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<tbody>
<tr>
<td>1843</td>
<td>First clinical description</td>
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<tr>
<td>1982</td>
<td>Linkage to Xp21</td>
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<tr>
<td>1986</td>
<td>Dystrophin gene cloned and protein predicted, antibodies to protein</td>
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<td>1988</td>
<td>CIDD first reports of prednisone efficacy</td>
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<tr>
<td>1990s-2000s</td>
<td>Attempts to identify “mini-gene” Exon skipping Ataluren (gentamycin like mechanism) Drisapersen Eteplirsen now EXONDYS 51</td>
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<tr>
<td>2016</td>
<td>Gene editing “CRISPR/cas9” EMFLAZA</td>
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<tr>
<td>2017</td>
<td>More ASOs More steroid-like drugs Other</td>
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</table>
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 pay attention to the informed consent/assent
Study Types

• Phases of Clinical Trials
  – Pre-clinical
    • Lab and animal studies
    • Non-human primates for safety
  – Phase I:
    • First in humans
    • Dosing
    • Small n
    • Assess safety
  – Phase Ila:
    • Assess dose requirements
    • Ila and Iib overlap.....
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
Clinical Trials in Duchenne

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

- Steroid Replacement
- Anti-Fibrotics

- Inflammation & Fibrosis

- Calcium Regulation

- Ryanodine Receptors
- Calcium Homeostasis

- Dystrophin Restoration /Replacement

- Cardiac

- Blood Flow

- Mitochondria

- Mitochondrial Biogenesis
- Mitochondrial Enhancers

- nNOS Upregulation

- Muscle Growth and Protection
- Stem Cells

- Myostatin Inhibition
- Follistatin Upregulation via Gene Therapy
- Selective Androgen Receptor Modulators
- Urotphin Upregulation

- Traditional Cardiac Drugs
ASO (AON)

• Modified pieces of DNA/RNA
• Hybridize to target
  – preRNA
  – Sequence complement
• Exclude/include target exons
  – convert “out of frame” to “in frame” deletions
  – “DMD” to “BMD”
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 (nonsense) Read through
  – Translarna (PTC)
    • EMA: Approval
    • Phase 3 extension study now
      – >5, ambulatory, steroids >12 mos
Sarepta ASO/PMO/PPMO

- Eteplirsen
  - EXONDYS 51
- SRP 4045
- SRP 4053
- New drug with better cardiac distribution
- PPMO 2019
  - SRP 5053
  - SRP 5051
Toxicity of ASO

• Acute toxicities in vivo:
  – Activation of the complement cascade
  – Inhibition of the clotting cascade

• Sub-chronic toxicity
  – Immune stimulation (splenomegaly, lymphoid hyperplasia and diffused multi-organ mixed mononuclear cell infiltrate)

• Mild and self-limiting toxicities at high plasma ASO concentrations
  – Thrombocytopenia
  – Increased LFT’s
  – Hyperglycemia
CHALLENGES

• Toxicity
• Administration
  – Route, frequency
• Distribution
  – Skeletal muscle
  – Cardiac muscle
  – CNS/BBB
• Expression
  – Amount
  – Duration
Gene Therapies

- 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
- Single dose
  - Working to avoid the formation of antibodies to the virus
  - Goal – re-dosing
Gene Therapies

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

- **PF-06939926**
  - Pfizer
  - Mini-dystrophin
  - 5-12 years
  - Recruiting
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 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
GENE THERAPY

<table>
<thead>
<tr>
<th>Condition</th>
<th>Status</th>
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<tbody>
<tr>
<td>GALGT2 (Nationwide)</td>
<td>Internal</td>
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<tr>
<td>Micro-Dystrophin (Nationwide)</td>
<td>Internal</td>
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<tr>
<td>Micro-Dystrophin (Genethon)</td>
<td>Internal</td>
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<tr>
<td>MYO-101 (LGMD2E β-sarcoglycan)</td>
<td>External</td>
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<tr>
<td>MYO-102 (LGMD2D α-sarcoglycan)</td>
<td>External</td>
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<tr>
<td>MYO-103 (LGMD2C γ-sarcoglycan)</td>
<td>External</td>
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<td>MYO-201 (LGMD2B Dysferlin)</td>
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<td>MYO-301 (LGMD2L Anoctamin 5)</td>
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<td>Pompe Disease</td>
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<td>CNS-1</td>
<td>Internal</td>
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<tr>
<td>CNS-2</td>
<td>Internal</td>
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GENE EDITING

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<th>Condition</th>
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<td>CRISPR/CAS9 (DUKE UNIVERSITY)</td>
<td>Internal</td>
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*Candidate received accelerated approval in the U.S., confirmatory studies required
**Other exon targets in development: 43, 44, 50, and 55
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- Stem Cells
- Traditional Cardiac Drugs

- Cardiac
- Blood Flow
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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
    - 6-11yo, ambulatory, steroids >6mos
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Treating Duchenne
Anti-inflammatory

• Mallinckrodt
  – Pre-clinical
  – MK1411

• Pamrevlumab
  – FG-3019, Fibrogen, anti-fibrotic
  – Antibody to connective tissue growth factor
  – Phase 2
  – >12yo, non-ambulatory, steroids
  >6mos
Anti-inflammatory

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

• Edasalonexent
  – Catabasis, Phase 2a;
  – NFkB inhibitor, anti-fibrotic
  – 4-7yo, ambulatory, steroid naïve

• Vamorolone
  – ReveraGen, Phase 2;
  – Steroid alternative
  – 4-<6yo, ambulatory, steroid naive
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- Cardiac
CELL BASED THERAPY

• HOPE-2
• Capricor
• CAP-1002
  – Allogenic cardiosphere-derived cells (CDCs)
  – Release extracellular vesicles/exosomes/growth factors
  – Retained in lungs
<table>
<thead>
<tr>
<th>Treatment</th>
<th>Phase 1</th>
<th>Phase I/II</th>
<th>Phase II</th>
<th>Phase III</th>
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<td>Exondys 51 (Eteplirsen) [Sarepta]</td>
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<td>Emflaza [PTC Therapeutics]</td>
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<td>Spironolactone &amp; Eplerenone [Ohio State]</td>
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<td>Translarna (Ataluren) [PTC Therapeutics]</td>
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<td>Givinostat [Italfarmaco]*</td>
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<td>Raxone (Idebenone) [Santhera]*</td>
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<td>SRP-4045/SRP-4053 [Sarepta]*</td>
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<td>RG6206 [Roche]*</td>
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<td>Edasalonexent (CAT-1004) [Catabasis]</td>
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<td>Domagrozumab (PF-06252616) [Pfizer]*</td>
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<td>Vamorolone (VBP15) [Reveragen]*</td>
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<td>Ezutromid (SMT C1100) [Summit PLC]*</td>
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<td>Pamrevlumab (FG-3019) [Fibrogen]</td>
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<td>Epicatechin [Cardero]</td>
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<td>NS-065/NCNP-01 [NS Pharma]</td>
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<td>Follistatin Gene Transfer [Nationwide..</td>
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<td>CAP-1002 [Capricor]</td>
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<td>MNK-1411 Cosyntropin Acetate..</td>
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<td>Myoblast Transplantation [Chu De Quebec]</td>
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<td>Exon Skipping 53 [Daichi - Sankyo]**</td>
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<td>Nationwide Micro-Dystrophin Gene..</td>
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<td>WVE-210201 Exon 51 Skipping [WAVE]</td>
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<td>PF-06939926 Mini-Dystrophin Gene..</td>
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<td>SGT-001 Micro-Dystrophin Gene Transfer..</td>
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<td>Rimeporide [EspeRare]**</td>
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<td>AT-300 [Akashi]</td>
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<td>Ifetroban [Cumberland Pharma]</td>
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<td>Nationwide Exon 2 Skipping for Duplication..</td>
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<td>Tamoxifen** [University of Geneva]</td>
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<td>MA-0211/MTB-1 [Mitobridge/Astellas]</td>
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