Duchenne Research Overview: The landscape and the opportunities
Duchenne muscular dystrophy

• Caused by a mutation in *DMD* gene → Absence of dystrophin protein → muscle deterioration and weakness
• X-linked recessive disease with a prevalence of 1:5000 male births
• Progressive multi-system disease affecting:
  – Heart
  – Skeletal muscle
  – Smooth muscle
  – Bone
  – Cognitive function
Genetics

- *DMD* is the largest gene in the human genome
- 79 exons / ~2.5 Million base pairs
- Discovered in 1987

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Population</th>
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<tbody>
<tr>
<td>Exon deletions</td>
<td>65%</td>
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<tr>
<td>Exon duplications</td>
<td>10%</td>
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<tr>
<td>Nonsense and other small changes</td>
<td>25%</td>
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</tbody>
</table>
Impact of loss of dystrophin

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

• Patient focused multi-disciplinary approach
• Standard of care:
  – Glucocorticoid
  – Multidisciplinary Care
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
  – Ask questions!
  – Ensure you understand the study
  – What is the timeline for visits?
  – How is reimbursement being handled?
  – Average length of a study visit?
Study Types

– Pre-clinical: lab and animal studies
– Phase I: First in humans; assess safety
  (mechanistic, usually in healthy volunteers, dosing, small n)
– Phase Ila: Assess dose requirements and toxicity
– Phase IIb: Assess efficacy; “Pivotal”
  • Phase Ila and IIb can be combined
Study Types

– **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
**Duchenne Drug Development Pipeline 2019**

<table>
<thead>
<tr>
<th>Preclinical</th>
<th>Phase I</th>
<th>Phase I/II</th>
<th>Phase II</th>
<th>Phase III</th>
<th>Post Market</th>
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<tr>
<td>Exondys 51 (Eteplirsen) [Sarepta]</td>
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<td>Emflaza (Deflazacort) [PTC Therapeutics]</td>
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<td>Spironolactone &amp; Eplerenone [Ohio State University]</td>
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<td>Translarna (Ataluren) [PTC Therapeutics]</td>
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<td>Nebivolol [Armand Trousseau Hospital]</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 (Casimersen/Goldisiren) [Sarepta]</td>
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<td>RG6206 (RO7239361) [Roche]</td>
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<td>Edasalonexent (CAT-1004) [Catabasis]</td>
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</table>
| Tamoxifen [University Children's Hospital] | | | | | **
| Pamrevlumab (FG-3019) [Fibrogen] | | | | | |
| NS-065/NCNP-01 (Viltolarsen) [NS Pharma] | | | | | |
| Vamorolone (VBP15) [Reveragen] | | | | | *
| SRP-9001 Micro-Dystrophin GT [Nationwide Children's] | | | | | |
| MNK-1411 (Cosynoropin) [Mallinckrodt] | | | | | *
| CAP-1002 [Capricor] | | | | | **
| P-188 NF (Carmeseal-MD) [Phrixus] | | | | | |
| Ifetroban [Cumberland Pharmaceuticals] | | | | | |
| Epicatechin [Cardero Therapeutics] | | | | | |
| Follistatin Gene Transfer [Nationwide Children's] | | | | | |
| WVE-210201 Exon 51 Skipping (Suvodirsen) [WAVE] | | | | | *
| Myoblast Transplantation [Chu De Quebec] | | | | | |
| Exon Skipping 45 (DS-5141b) [Daichi Sankyo] | | | | | **
| GALGT2 Gene Therapy [Nationwide Children's] | | | | | |
| PF-06939926 Mini-Dystrophin Gene Therapy [Pfizer] | | | | | |
| SGT-001 Micro-Dystrophin Gene Therapy [Solid] | | | | | |
| Rimeporide [EspeRare] | | | | | |
| SRP-5051 PPMO [Sarepta] | | | | | |
| AT702 Exon 2 Skipping [Nationwide Children's] | | | | | |
| ASP0367 (MA-0211) [Mitobridge/Astellas] | | | | | |

* = will recruit/recruiting globally
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**EMA Granted Conditional Approval – Aug 2014**

**FDA Granted Approval via Full Approval - Feb 2017**

**FDA Granted Approval via Accelerated Approval Pathway - Sept 2016**
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
- Stem Cells
- Traditional Cardiac Drugs

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

- Muscle Growth and Protection
- Myostatin Inhibition
- Follistatin Upregulation via Gene Therapy
- Selective Androgen Receptor Modulators
- Utrophin Upregulation
Clinical Trials in Duchenne

Dystrophin Restoration/Replacement

- Exon-Skipping
- Gene Therapy
- CRISPR
- Stop-Codon Readthrough
- Steroid Replacement
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Treating Duchenne

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

Cardiac
- Blood Flow
- Mitochondria

Stem Cells
- Traditional Cardiac Drugs
- nNOS Upregulation
- Mitochondrial Biogenesis
- Mitochondrial Enhancers
Dystrophin Restoration and Replacement

**Exon Skipping** (skip over the missing/defective part of the gene)

Exon 45 and 53: **Sarepta Essence** (7-13yo, ambulatory, steroids >6mo)
Casimersen and Golodirsen (Filed for AA)

Exon 53: **NS Pharma** (Phase II extension study)
NS-065/NCNP-01

Exon 51: **WAVE Life Sciences** (Phase II/III, 5-18yo)
WVE-210201
Dystrophin Restoration and Replacement

Stop Codon Read-through (ignore the missing/defective part of the gene)

Ataluren (Translarna): **PTC Therapeutics**
(Phase III extension study, ≥5yo, ambulatory, steroids ≥12mo, non-sense mutation)
Currently approved by EMA not FDA
Gene Therapies

- AAV virus to deliver micro- or mini-dystrophins
- Single IV administration
- 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
Gene Therapy

Micro-dystrophin: Nationwide Children’s Hospital / Sarepta

– Exons 18-58
– Muscle specific
  • Doesn’t cross blood brain barrier
– First trial finished dosing
– Second trial has begun dosing
SGT-001: Ignite DMD **Solid Biosciences**
(Phase I/II, Micro-dystrophin)
   – Steroids >24wks
   – 4-17 years
   – Recruiting

• **PF-06939926: Pfizer**
(Phase I, Mini-dystrophin)
   – 5-12 years, ambulatory, steroids >6mo
   – Recruiting by invitation
Gene Therapy

GALGT2 – Nationwide Children’s Hospital
(Phase I/IIa, rAAVrh74.MCK.GALGT2)
– 4 years and older, ambulatory, steroids >12wk
– Recruiting
– Upregulate dystroglycan-binding proteins

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

1. Exon-Skipping
2. Gene Therapy
3. CRISPR/Cas9
4. Stop-Codon Readthrough

- **Dystrophin Restoration**
  - **Replacement**

- **Inflammation & Fibrosis**
  - **Anti-Fibrotics**
  - **Calcium Regulation**
    - **Ryanodine Receptors**
    - **Calcium Homeostasis**

- **Cardiac**
  - **Cardiac Drugs**
  - **nNOS Upregulation**
  - **Mitochondrial Biogenesis**

- **Blood Flow**
  - **Mitochondrial Enhancers**

- **Mitochondria**
  - **Stem Cells**

**Treating Duchenne**

- **Muscle Growth and Protection**
  - **Myostatin Inhibition**
  - **Follistatin Upregulation via Gene Therapy**
  - **Selective Androgen Receptor Modulators**
  - **Utrrophin Upregulation**
Muscle Growth and Regeneration

Biglycan: Tivorsan Pharma (pre-clinical)
   TVN-102

Anti-myostatin: Roche (Phase II/III, 6-11yo, ambulatory, steroids)
   RO7239361
   Myostatin inhibitor
Clinical Trials in Duchenne

- Exon-Skipping
- Gene Therapy
- CRISPR/Cas9
- Stop-Codon Readthrough
- Steroid Replacement
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- Inflammation & Fibrosis
- Calcium Regulation
- Ryanodine Receptors
- Calcium Homeostasis
- Myostatin Inhibition
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- Stem Cells
- Traditional Cardiac Drugs
- Cardiac
- Blood Flow
- Mitochondria
- nNOS Upregulation
- Mitochondrial Biogenesis
- Mitochondrial Enhancers
Anti-inflammatory

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

Vamorolone: **ReveraGen** (Phase 2b, 4-7yo, ambulatory, steroid naïve)
- Dissociative steroid
Anti-inflammatory

Givinostat: **Italfarmaco** (Phase III, >6yo, ambulatory, steroids >6mo)
HDAC Inhibitor

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

Pamrevlumab: **Fibrogen** (Phase II)
Antibody to CTGF
Clinical Trials in Duchenne

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

Steroid Replacement

Inflammation & Fibrosis

Anti-Fibrotics

Calcium Homeostasis  Calcium Regulation

Ryanodine Receptors

Dystrophin Restoration/Replacement

Treating Duchenne

Cardiac

Blood Flow  Mitochondria

nNOS Upregulation  Mitochondrial Biogenesis

Mitochondrial Enhancers

Myostatin Inhibition  Follistatin Upregulation via Gene Therapy

Selective Androgen Receptor Modulators  Utrophin Upregulation

Stem Cells

Traditional Cardiac Drugs

Stem Cells
Clinical Trials in Duchenne

- Exon-Skipping
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- Mitochondrial Enhancers

Muscle Growth and Protection
Mitochondria

Raxone (Idebenone): **Santhera** (Phase III, >10yo, >12mos steroids)
- Preservation of respiratory function
- Delos Trial
  - Steroid naïve complete, Seeking FDA review

Epicatechin: **Cardero Therapeutics** (Phase II)
- Mitochondrial growth
- Reviewing results

MTB-1: **Astellas Pharma** (Pre-clinical)
- Improved mitochondrial function
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Preclinical Phase I Phase II/III Phase II Phase III Post Market

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RECRUITING:
- PTC-041 (PTC)
- Sideros (Santhera)
- Polaris DMD (Catabasis)

NOT RECRUITING
- ESSENCE (Sarepta)
- FG-3019 (Fibrogen)
- PTC-016 (PTC)
- Sideros-E (Santhera)
- FOR-DMD (U. of Rochester)

Clinical Trial Information:
Tim Harrington
Phone: 857-218-4677
Email: Timothy.Harrington@childrens.Harvard.edu
The Duchenne Program at UMass Medical School is a new clinic and research site that launched in the Summer 2018. In collaboration with founding Clinic Director Dr. Brenda Wong, the program is being established with the driving goal of improving research and care outcomes for children and adults with Duchenne and Becker muscular dystrophies.

DMD Clinic Information
Phone: (774) 441-7615
email: DMDprogram@umassmemorial.org

Clinical Trial Information
Sarah Figueira
Phone: (508) 856-1604
Email: sarah.figueira@umassmed.edu

THE DUCHENNE PROGRAM
AT UMASS MEDICAL SCHOOL

Current Clinical Studies at UMass Medical School

Industry Sponsored (Intervention Trials)

Clinical Trial to Evaluate the Efficacy, Safety, and Tolerability of RO7239361 in Ambulatory Boys With Duchenne Muscular Dystrophy
This is a multi-center, randomized, double-blind, placebo-controlled study to assess the efficacy, safety and tolerability of two different weekly doses of RO7239361 in ambulatory boys with Duchenne Muscular Dystrophy (DMD).

Microdystrophin Gene Transfer Study in Adolescents and Children With DMD (IGNITE DMD)
This is a randomized, controlled, open-label, single-ascending dose study to evaluate the safety, tolerability and efficacy of SGT-001 in adolescents and children with Duchenne muscular dystrophy (DMD). Eligible patients will be randomized to an active treatment group or an untreated control group. Patients in the active treatment group will receive a single intravenous (IV) infusion of SGT-001 and will be followed for approximately 2 years. Patients in the untreated control group who continue to meet treatment criteria will receive SGT-001 after 1 year on study.

Investigator Initiated

Current
Duchenne Muscular Dystrophy Registry
This study is intended to collect data from medical records on patients who have Duchenne Muscular Dystrophy

Upcoming Research
fMRI and Neuropsychological analysis in Duchenne muscular dystrophy
To uncover any relationships between motor function and genetic mutations using MRI and neuropsychological testing among individuals with Duchenne muscular dystrophy (DMD)
Thank you!
What does dystrophin do?
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
Reading frame

Normal gene – THE FAT CAT ATE THE BIG RED RAT = Full length dystrophin

In-frame mutation – THE FAT CAT ATE THE BIG RED MAD RAT = THE FAT CAT ATE THE MAD RAT = BMD

Out-of-frame mutation – THE FAT CAT ATE THE BIG RED MAD RAT = THE FAT CAT ATE THE BIE DMA DRA T = DMD

Exon-skipping – THE FAT CAT ATE THE bie d MA DRA T = THE FAT CAT ATE THE MAD RAT