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>
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<td>Exon duplications</td>
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<td>Nonsense and other small changes</td>
<td>25%</td>
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Impact of loss of dystrophin

- Membrane instability
- Calcium infiltration
- Inflammation
- Oxygen deprivation
- Fibrosis
- Muscle cell death
• 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 IIa**: Assess dose requirements and toxicity
- **Phase IIb**: Assess efficacy; “Pivotal”
  - Phase IIa 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>
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<tr>
<th>Preclinical</th>
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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

READ THE RED"
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PARENT PROJECT MUSCULAR DYSTROPHY | ENDDUCHENNE.ORG
**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**
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

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

Steroid Replacement
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Stem Cells
Traditional Cardiac Drugs

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Mitochondrial Enhancers

Muscle Growth and Protection

Selecte Androgen Receptor Modulators
Urotropin Upregulation

Stem Cells
Muscle Growth and Regeneration

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

Anti-myostatin: **Roche** (Phase II/III, 6-11yo, ambulatory, steroids)
RO7239361
Myostatin inhibitor
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  |  Dystrophin Restoration /Replacement

Anti-Fibrotics

Inflammation & Fibrosis

Calcium Regulation

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Cardiac

Blood Flow  |  Mitochondria

Stem Cells  |  Mitochondrial Biogenesis  |  Mitochondrial Enhancers

nNOS Upregulation

Treatment of Duchenne

Muscle Growth and Protection
Clinical Trials in Duchenne

Exon-Skipping
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Anti-Fibrotics
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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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- **EMA Granted Conditional Approval – Aug 2014**
- **FDA Granted Approval via Full Approval - Feb 2017**
- **FDA Granted Approval via Accelerated Approval Pathway - Sept 2016**
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
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