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

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<td>Nonsense and other small changes</td>
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Impact of loss of dystrophin

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

• Patient focused multidisciplinary 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

![Stages of Clinical Trials](image-url)
# Duchenne Drug Development Pipeline 2019

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**FDA Granted Approval via Accelerated Approval Pathway - Sept 2016**
Clinical Trials in Duchenne
Clinical Trials in Duchenne
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
Gene Therapy

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

- Dystrophin Restoration/Replacement

- Cardiac

- Calcium Regulation

- Muscle Growth and Protection

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

- Blood Flow
- Mitochondria
- Stem Cells

- Traditional Cardiac Drugs
- nNOS Upregulation
- Mitochondrial Biogenesis
- Mitochondrial Enhancers

Parent Project Muscular Dystrophy | EndDuchenne.org
Clinical Trials in Duchenne

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

Steroid Replacement

- Anti-Fibrotics

Inflammation & Fibrosis

- Calcium Regulation

Ryantidine Receptors

Calium Homeostasis

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Dystrophin Restoration /Replacement

Stem Cells

Cardiac

Blood Flow

Mitochondria

nNOS Upregulation

Mitochondrial Biogenesis

Mitochondrial Enhancers

Traditional Cardiac Drugs
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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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