Duchenne Research and Clinical Trials

Abby Bronson, MBA
SVP, Research Strategy, PPMD
Agenda

• Overview:
  – Current Therapeutic Approaches and Clinical Trials
  – Strategies to Accelerate the Process
Therapeutic Approaches in Duchenne

- Exon-Skipping
- Gene Therapy
- CRISPR/Cas9
- Stop-Codon Readthrough
- Steroid Administration
- Anti-Fibrotics
- Calcium Regulation
- Ryenodine Receptors
- Calcium Homeostasis
- Myostatin Inhibition
- Follicatin Upregulation via Gene Therapy
- Selective Androgen Receptor Modulators
- Urophin Upregulation
- Stem Cells
- Dystrophin Restoration/Replacement
- Blood Flow
- Mitochondria
- Mitochondrial Biogenesis
- nNOS Upregulation
- Mitochondrial Enhancers
Therapeutic Approaches in Duchenne
Duchenne is the Neuromuscular Disease with the 2\textsuperscript{nd} largest drug development pipeline (IQVIA Institute report, 2018)
PPMD Research Funding

Total active committed multiyear projects

Gene Therapy $3,384,005
Preclinical Research $1,054,704
Drug Development Tools $1,525,000
Understanding Natural History $1,208,500
Robotics $241,040
Clinical Trials in Duchenne

Dystrophin Restoration/Replacement

Treating Duchenne

Muscle Growth and Protection

Calcium Regulation

Inflammation & Fibrosis

Exon-Skipping

Gene Therapy

CRISPR/Cas9

Stop-Codon Readthrough

Steroid Replacement

Anti-Fibrotics

Ryanodine Receptors

Calcium Homeostasis

Myostatin Inhibition

Follistatin Upregulation via Gene Therapy

Selective Androgen Receptor Modulators

Utrophin Upregulation

Cardiac

Blood Flow

Mitochondria

nNOS Upregulation

Mitochondrial Biogenesis

Mitochondrial Enhancers

Stem Cells
# Dystrophin Restoration and Replacement

<table>
<thead>
<tr>
<th>Method</th>
<th>Preclinical</th>
<th>Phase 1</th>
<th>Phase 1/2</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>Post</th>
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* Exondys 51 (Eteplisyn) [Sarepta]
  * Translarna (Ataluren) [PTC Therapeutics]
  * SRP-4045/SRP-4053 (Casimensen/Golodirsen) [Sarepta]
  * NS-065/NCNP-01 (Viltolase) [NS Pharma]
  * SRP-5001 Micro-Dystrophin GT [Nationwide Children's]
  * Follistatin Gene Transfer [Nationwide Children's]
  * WVE-210201 Exon 51 Skipping (Suvodirsen) [WAVE]
  * Exon Skipping 45 (DS-5141b) [Daiichi Sankyo]
  * GALGT2 Gene Therapy [Nationwide Children's]
  * PF-06939926 Mini-Dystrophin Gene Therapy [Pfizer]
  * SGT-001 Micro-Dystrophin Gene Therapy [Solid]
  * SRP-5051 PPMO [Sarepta]
  * AT702 Exon 2 Skipping [Nationwide Children's]
Clinical Trials in Duchenne
## Treating the Downstream Effects of Dystrophin Absence

### Drug Treatments

<table>
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<tr>
<th>Drug</th>
<th>Company/Institution</th>
<th>Status</th>
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<td>Emflaza (Deflazacort)</td>
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<td>Ohio State University</td>
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### Clinical Phases

- **Preclinical**
- **Phase 1**
- **Phase 1/2**
- **Phase 2**
- **Phase 3**
- **Post**
# Duchenne Drug Development Pipeline 2019

## Phase I

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* = will recruit/recruiting globally
** = will recruit/recruiting EU only
*** = will recruit/recruiting Japan only
Duchenne is the Neuromuscular Disease with the 2\textsuperscript{nd} largest drug development pipeline

(IQVIA Institute report, 2018)

EARLY PHASE PIPELINE PRESSURE
Patients Needed by Age (n=3885)

41 studies, Ph 2+

# of Patients

Data from Clintrials.gov 2017

Age
Patients want trials open to all and with limited use of placebo

Families only- From the perspective of your family, what are two of the greatest needs in the current clinical trial landscape? (Choose 2) (156 responses)

- Broader inclusion criteria: 31%
- Ability to participate in trials without traveling great distances: 11%
- Tools & information to support informed decision making for trial participation: 4%
- A regulatory pathway for combination therapies: 13%
- Limiting the use of placebo as much as possible: 28%
- Shorter timelines for trials: 8%
- Better patient report outcomes to measure benefit/impact of drug: 6%

Source: PPMD Annual Conference 2018
The Problem(s)... It Just Takes Too Long

• I/E too narrow
• Trial sites too far away
• Boys can “age out” after only one study
• Significant number of boys randomized to placebo
• Individual trial start-up procedures are repeated = inefficiencies
Two types of innovation are hallmarks of master protocols: the use of a trial network with infrastructure in place to streamline trial logistics, improve data quality, and facilitate data collection and sharing; and the use of a common protocol that incorporates innovative statistics.
Platform Trials Bring Efficiency

- Create one optimized trial infrastructure and use it perpetually to study multiple therapies

Master Protocol
Operational Efficiencies

✓ Faster start-up
  ✓ Trial-ready sites
  ✓ Master Contracts
  ✓ Central IRB
  ✓ Ready EDC

✓ High-quality execution
  ✓ Network of selected investigators and sites
  ✓ Uniform data and samples
  ✓ Recruitment and retention strategies
  ✓ Robust monitoring
Scientific Efficiencies

✓ **Shared placebo**
  ✓ Important to patients
  ✓ Sample size savings

✓ **Adaptive design**
  ✓ Real time decision making
Where Are We?

- Protocol Synopsis
- Regulatory Support
- Steering Committee in process
- Infrastructure needs being developed
- Community Meeting September 9th, 2019
Other Ways to Help Solve the Problem: Disease Progression Modelling

D-RSC Initial Objectives

- Development of a data sharing platform for Duchenne clinical data
  - Fourteen datasets in house, mostly mapped, those that can be shared with the consortium shared with the consortium.
- Development and publication of a CDISC therapeutic area standard for Duchenne muscular dystrophy
  - Therapeutic area user guide published
- Develop a disease progression model for Duchenne muscular dystrophy via application of the consortium shared data
  - MAP drafted, LOI accepted by FDA.

cTAP to Present Late-breaking Results Supporting Advancements in Clinical Trial Design for Duchenne Muscular Dystrophy at the World Muscle Society Congress

October 01, 2018 08:00 AM Eastern Daylight Time

CAMBRIDGE, Mass.--(BUSINESS WIRE)--The collaborative Trajectory Analysis Project (cTAP), a multi-stakeholder, pre-competitive global coalition in Duchenne muscular dystrophy, today announced the acceptance of a late-breaking abstract for presentation at the 23rd International Congress of the World Muscle Society. This is in addition to the two previously accepted submissions that cTAP collaborators will present at the Congress, which is being held October 2-6, 2018 at the Intercontinental Hotel in Mendoza, Argentina.
Other Ways to Solve the Problem: Enabling Discovery and Research

BioBanking

BioMarkers
Serum Proteins,
Fat Fraction,
Urine fragments
Other Ways to Solve the Problem: Refining our Understanding

Inflammation & Immunity

PRO Development
Cardiac RFA 2019:
Innovative therapeutics and technologies for improvement of Duchenne cardiac care and treatment

- 39 applications received
- Culled down to 9 for full review
- Awards to be made this fall
Questions remain once we have more treatment options…

We must…

- Ensure treatments are covered by payers
- Continue to improve care and management and ensure it is standardized
- Ensure the patient voice informs all the work being done
Thank you!