THE FURLONG's
**Preclinical Research**
- Exon skipping
- Myostatin inhibition
- Biglycan
- Halofuginone
- Tamoxifen
- Animal studies
- IGF-1
- SMTC 1100
- PDE5 Inhibitors
- Protease Inhibitors
- Others
- Gene therapy

**Clinical Research**
- Mitochondria
- Gene therapy
- Cardiac
- Utrophin
- Read through
- Myostatin
- Exon skipping
- Anti fibrotics

**Research Tools**
- Duchenne Connect Registry
- Upper body endpoints
- Serum Biomarkers
- Outcome measures
- MRI
- Natural History
- PCORnet Grant

**Clinical Care**
- Care Considerations
- Certified Duchenne Care Center Program
- Cardiology, Pulmonary Webinar Series
- ESO Tours

**Education**
- 22 annual Connect Conferences
- ChildMuscleWeakness.Org
- PPMD Web site materials
- PPMD Community Site
- ESO Tours

**Advocacy**
- MD-CARE Act
- Annual Report Language
- Putting Patients First White Paper
- Benefit-Risk Study
- FDA Policy Forum
- Draft FDA Guidance
- Newborn Screening
- Access/Reimbursement Framework
Largest gene & protein in the human genome
2.4 Million base pairs/79 Exons
Loss of Dystrophin

60-70% Deletions
10% Duplications
10-15% point mutations and other small changes

Multi-system Disease:
- Skeletal Muscle
- Heart
- Bone
- Smooth Muscle
- Cognitive Function
Due to a genetic mutation, the dystrophin protein is missing or not functional in Duchenne.
What does dystrophin do?
What happens when dystrophin is missing?

- Free radicals
- Inflammation
- Oxygen deprivation
- Fibrosis (scarring)
- Muscle cell death

(calcium)

(no linkage)
<table>
<thead>
<tr>
<th></th>
<th>Diagnosis/Childhood</th>
<th>Tweens/Teens</th>
<th>Young Adults/Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetics, Genetic Counseling</td>
<td>❥</td>
<td>❥</td>
<td>❥</td>
</tr>
<tr>
<td>Neuromuscular Specialist</td>
<td>❥</td>
<td>❥</td>
<td>❥</td>
</tr>
<tr>
<td>Orthopedic Management</td>
<td>❥</td>
<td>❥</td>
<td>❥</td>
</tr>
<tr>
<td>Rehabilitation Management</td>
<td>❥</td>
<td>❥</td>
<td>❥</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>❥</td>
<td>❥</td>
<td>❥</td>
</tr>
<tr>
<td>Cardiology</td>
<td>❥</td>
<td>❥</td>
<td>❥</td>
</tr>
<tr>
<td>GI/Swallowing/Nutrition</td>
<td>❥</td>
<td>❥</td>
<td>❥</td>
</tr>
<tr>
<td>Endocrine</td>
<td>❥</td>
<td>❥</td>
<td>❥</td>
</tr>
<tr>
<td>Psychosocial</td>
<td>❥</td>
<td>❥</td>
<td>❥</td>
</tr>
</tbody>
</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 listen to pay attention to the informed consent/assent
Study Types

• Multi-Phase Clinical Trials
  – Pre-clinical
    • lab and animal studies
  – Phase I:
    • First in humans (mechanistic, usually in healthy volunteers, dosing, small n)
    • assess safety
  – Phase IIa:
    • Assess dose requirements
    • IIa and IIb can be a little blurry…..
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

Dystrophin Restoration/Replacement

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

Steroid Replacement

Anti-Fibrotics

Inflammation & Fibrosis

Calcium Regulation

Ryanodine Receptors

Calcium Homeostasis

Muscle Growth and Protection

Myostatin Inhibition

Follistatin Upregulation via Gene Therapy

Selective Androgen Receptor Modulators

Utrophin Upregulation

Cardiac

Blood Flow

Mitochondria

Stem Cells

nNOS Upregulation

Mitochondrial Biogenesis

Mitochondrial Enhancers

Traditional Cardiac Drugs

ParentProjectMD.org
Dystrophin Restoration and Replacement

- Exon Skipping (skip over the missing/defective part of the gene)
  - Exon 45 and 53 (Golodirsen)
    - Essence (Sarepta)
    - 7-13yo, ambulatory, steroids >6mos
  - Exon 53
    - NS Pharma
    - 4-9yo, ambulatory, steroids >6mos
- WAVE Life Sciences
  - Exon 51
  - Protocol not yet announced
Dystrophin Restoration and Replacement

• Stop Codon Read-through (Ignore the missing/defective part of the gene)
  – Translarna (PTC)
    • Advisory Committee meeting Sept 28
    • Phase 3 extension study now
      – >5, ambulatory, steroids >12 mos
Gene Therapies

- Gene therapies
  - Restore or replace the gene
  - Not mutation specific

3 Major Efforts:
- Microdystrophin
  - Nationwide Children’s Hospital
  - Exons 18-58
  - Muscle specific
    - Doesn’t cross blood brain barrier
  - Ages
    - 6 patients, 3mos – 3 years, 6 patients, 4 -7 years
  - Can start enrolling after permission from FDA (2017)
Gene Therapies

• SGT-001
  – Solid GT
  – Microdystrophin
  – Preclinical

• PF-06939926
  – Bamboo Pfizer
  – Microdystrophin
  – Preclinical
Gene Therapy

• Exon 2 Duplication Strategy
  • Preclinical
  • Nationwide Children’s Hospital
  • Only study looking at duplications
  • Specific only to duplications in exon 2
Gene Therapies

• All use virus (AAV 9 specific to skeletal muscle) to deliver microdystrophins with the “business ends” of the dystrophin
• Studies will determine the most efficient microdystrophphin
• 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
Clinical Trials in Duchenne

- Exon-Skipping
- Gene Therapy
- CRISPR/Cas9
- Stop-Codon Readthrough
- Dystrophin Restoration/Replacement
- Stem Cells
- Traditional Cardiac Drugs
- Cardiac
- Blood Flow
- Mitochondria
- nNOS Upregulation
- Mitochondrial Biogenesis
- Mitochondrial Enhancers
- Stem Cells
- Ryanodine Receptors
- Calcium Homeostasis
- Calcium Regulation
- Anti-Fibrotics
- Inflammation & Fibrosis
- Steroid Replacement
- Myostatin Inhibition
- Follistatin Upregulation via Gene Therapy
- Selective Androgen Receptor Modulators
- Utrophen Upregulation

Muscle Growth and Protection
Muscle Growth and Regeneration

- Utrophin modulator
  - Ezutromid (SMT C1100)
    - Summit Pharm, Phase 2
    - 5-10yo, ambulatory
    - Steroids >6 mos
  - Biglycan (TVN-102)
    - Tivorsan Pharma
    - Pre-clinical
Muscle Growth and Regeneration

• Myostatin Inhibition
  – Domagrozumab
    • Pfizer, Phase 2
    • 6-<16yo, ambulatory, steroids >6mos
  – BMS 986089 (now Roche)
    • BMS/Roche, Phase 1
    • 6-11yo, ambulatory, steroids >6mos
Muscle Growth and Regeneration

• Selective Androgen Receptor Modulator
  – DT-200 (Akashi Therapeutics)
  – Very early preclinical

• Selective Estrogen Receptor Modulators (Tomoxifen)
  – In trials in Europe
  – Possible anti-fibrotic
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

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

Treating Duchenne

ParentProjectMD.org
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
Anti-inflammatory

- Malincrot
  - Pre-clinical
  - MK1411

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

- Calcium Regulation

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

- Stem Cells

- Traditional Cardiac Drugs
- Cardiac
- Blood Flow
- Mitochondria

- nNOS Upregulation
- Mitochondrial Biogenesis
- Mitochondrial Enhancers

- LEADING THE FIGHT TO END DUCHENNE
- Parent Project Muscular Dystrophy
Calcium Regulation

• ARM210
  – Armgo Pharma, Phase 1, not yet recruiting
  – Restore normal balance of Ca within the cell by correcting calcium leaks in the ryanodine receptor calcium channel complex
  – ? Progress

• AT-300
  – Akashi Therapeutics, preclinical
  – Restore stretch-activated calcium channels (protection of muscle strength loss after exercise) in heart and skeletal muscles
  – ? progress
Cardiac Therapies

- CoQ10 and Lisinopril
  - Completed, under evaluation
- Spironolactone v.s. Eplerenone
  - Ohio State University
  - Phase 3
- Cap-1002
  - Capricor
  - Phase 2 complete, under evaluation
    - Intracoronary delivery of stem cell therapy
  - Next phase
    - IV infusion, delivering cells systemically
Mitochondria

- Epicatechin
  - Cardero Therapeutics
  - Mitochondrial growth
  - 8-17yo, non-ambulatory, no steroid required

- Raxone (Idebenone)
  - Santhera
  - Preservation of respiratory function
  - Delos Trial
    - Steroid naïve complete, Seeking FDA review
  - Sideros Trial
    - Phase 3
    - >10yo, steroids >12 mos, ambulatory or non-ambulatory
Mitochondria

• MTB-1
  – Mitobridge and Astellas Pharma
  – Improved mitochondrial function
  – Pre-clinical
Access & Reimbursement

ParentProjectMD.org
What can we do to help these therapies move through the pipeline?

- Continue advocating in Washington
- Collect data on these patients through Duchenne Connect
- Tell patient stories to regulators
- Work with Congress on legislation
- Collect patient preference data about how families think and feel about emerging therapies
  - Weighing benefits and risks
  - New one around gene therapy
PPMD Access Resource Center

www.parentprojectmd.org/accessresources

Goals
Provide education and guidance on access process
Provide product specific resources for Patients, Clinicians, Payers
PPMD: Fighting for Every Single [One]
Leading Teen/Adult Initiatives
PPMD School Advocacy

Resources

**Brain Pop Video**
PPMD’s 4-minute animated video about Duchenne for kids of all ages.
https://www.youtube.com/watch?v=6wLnR7GJakY

**Education Matters For Parents**
Helpful tips on how to talk about Duchenne issues to be aware of at school
An Individualized Education Plan (IEP) overview
Sample scenarios and suggested ways to respond

**Education Matters For Teachers**
A practical overview of Duchenne
Classroom accommodations
Suggested inclusive school activities
What to be aware of regarding treatment/medications
Confidentiality/sensitivity concerns

**School Presentation Materials**
‘Chocolate Chip Cookie’ class presentation
http://www.parentprojectmd.org/site/PageServer?pagename=Understand_professionals_teachers
PPMD School Webinars

Navigating School: An Ongoing Journey
https://www.youtube.com/watch?v=M1py6M9ce0I

From Where We Sit (Adults with Duchenne): ‘PCA’ – 3 Little Letters that Mean So Much
https://www.youtube.com/watch?v=5lBEdb4IBlk

Promoting Independence In Children with Duchenne:
Panel of Parents Whose Sons Live Away from Home Reflect on How they Navigated the Delicate Balance of Protecting Their Sons, While Fostering Independence
https://www.youtube.com/watch?v=vtWbyt-j-IA