DMD Research Overview

CUIXIA TIAN, MD
PEDIATRIC NEUROLOGIST
CINCINNATI CHILDREN’S HOSPITAL MEDICAL CENTER
Investigator for clinical trials sponsored by BMS, Capricor, Fibrogen, PTC, Pfizer, Roche, Sarepta, Santhera
Outline

- DMD overview
- Clinical research
Duchenne Muscular Dystrophy

- The most common childhood muscular dystrophy with a prevalence of 1 in 5000 boys, X linked recessive genetic disease
- Mutations in DMD gene – Loss of Dystrophin protein – Damage to muscle integrity – Muscle weakness
- Progressive disease with multi-system involvement: skeletal muscle; heart; bone; smooth muscle; cognition
Duchenne Muscular Dystrophy

In the 1860s, French physician, Guilliame Duchenne, who first used the word 'dystrophy' when he noticed that the muscles in some young boys were weakening and wasting away.

Greek word roots: 'dys-' abnormal, diseased or faulty, 'trophy' nutrition or growth
This disease is one of the most interesting, and at the same time most sad, of all those with which we have to deal; interesting because of its peculiar features and mysterious nature; sad on account of our powerlessness to influence its course, except in very slight degree, and on account of the conditions in which it occurs.

-- Sir William Richard Gowers, 1879
Typically presents with delayed motor development or a gait abnormality at age 2 to 5 years.

Common presenting symptoms: delayed motor milestones, unable to run or hop, toe walking, difficulty climbing stairs, difficulty getting up from floor, hypertrophy of calf muscles.

Non-motor presentations: failure to thrive, speech delay, fatigue, abnormal liver function tests, rhabdomyolysis, complications with anesthesia.
Management

- Glucocorticoids remain the standard of care with but significant side effects
- Patient and family centered multidisciplinary, coordinated clinical care
- There is no cure
DMD gene

- cloned in 1987 - ~140 years after the first description of the disease
- the largest known human gene
- 79 exons, 2.4 MB base pairs, a 427 kDa protein
- chromosome Xp21
- cytoskeleton-associated membrane-bound
- Mutations: ~65% deletions; ~10% duplications; ~20% point mutations and other small changes
When there is a loss of Dystrophin:

- Membrane instability
- Excessive calcium influx
- Fiber necrosis
- Muscle cell death
- Inflammation
- Fibrosis (scarring)
- Fat accumulation
What is a Clinical Trial?

- A research study that determines whether a new drug (or other intervention) is both safe and effective for humans
- A trial is an experiment, not a therapy
- Risks and benefits
  - Data Safety Monitoring Boards (DSMB)
  - Assess safety and data during the trial
  - Important to review and pay attention to the informed consent/assent
Study Types

- **Phase I:** First in humans (mechanistic, usually in healthy volunteers, dosing, small number subjects); assess safety
- **Phase IIa:** Assess dose requirements, toxicity
- **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 for common diseases
  - In rare disease, this number can be much smaller
Phase IV
- Post-Marketing
- Monitor long term effects
Study Types

Stages of Clinical Trials

<table>
<thead>
<tr>
<th>Success rate</th>
<th>Preclinical</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>Phase 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>70%</td>
<td>several years</td>
<td>months</td>
<td>months to years</td>
<td>years to decades</td>
<td>ongoing</td>
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Clinical research for DMD

- Restore protein Dystrophin
- Muscle growth and protection
- Targeting signaling pathways
- Improve cardiac function
- Mitochondria
Clinical research: Dystrophin restoration

- **Exon skipping** (skip over the missing/defective part; deletion mutations)
  - Exon 45 and 53 skipping: Sarepta Essence trial (7-13yo, ambulatory, steroids >6mons)
  - Exon 53 skipping: NS pharma (4-9yo, ambulatory, steroids >6mons)
  - Exon 51 skipping: WAVE Life sciences (5-18yo, recruiting)
Clinical research: Dystrophin restoration

- **Stop codon read through** (ignore the stop codon; non-sense mutations)
  - Translarna: PTC (EMA approval; Phase 3 extension study ongoing (>5yo, ambulatory, steroids >12mons)
**Clinical research: Dystrophin restoration**

- **Gene therapy:**
  - AAV virus vector to deliver gene coding for microdystrophins or minidystrophins
  - One time treatment
  - Effect lasts for ~10 years
  - Can not be repeated currently
Clinical research: Dystrophin restoration

- Gene therapy:
  - Nationwide Children's/Sarepta:
    - Microdystrophin
    - Frameshift or nonsense mutations within exons 18-58
    - 4 to 7 yo, with 4 patients dosed
    - phase 1 and 2, open label randomized and controlled;
    - plan to expand to more subjects and bigger age range
Clinical research: Dystrophin restoration

- Gene therapy:
  - Pfizer/Bamboo:
    - Minidystrophin
    - any mutation
    - 5-12 yo, up to 12 patients
    - phase 1b, open label, nonrandomized; recruiting
Gene therapy:

- Solid Biosciences:
  - Microdystrophin
  - any mutation
  - 4 to 17 yo; 16 patients
  - phase 1 and 2, open label randomized, controlled; recruiting
Clinical research: Dystrophin restoration

- **Gene therapy:**
  - GALGT2 - rAAVrh74.MCK.GALGT2: >4yo, modified intravascular limb infusion, stimulate the glycosylation of alpha dystroglycan and upregulation of the dystroglycan-binding proteins including dystrophin and laminin alpha 2 surrogate proteins
  - Exon 2 Duplication Strategy: Preclinical; Nationwide Children’s Hospital (Dr. Flanigan); Only study looking at duplications; Specific *only* to duplications in exon 2
Clinical research: Muscle growth and protection

- Myostatin inhibition:
  - Roche: RG6026; Phase 1b/2 recruitment completed (5-10yo, ambulatory, 43 patients); Phase 2/3 recruiting (6-12yo, ambulatory, steroids >6mons, 4sc <8secs, 159 patients)
  - Pfizer: Phase 2, Domagrozumab, study terminated

- Membrane stabilization:
  - Phrixus: P-188 NF (Carmeseal-MD), Phase 2, 12-25 nonambulatory
Clinical research: targeting signaling pathways

- Anti-inflammatory
  - Givinostat: Italfarmaco, HDAC (histone deacetylase) inhibitor; phase 3; >6yo, ambulatory, steroids >6mons
  - Edasalonexent: Catabasis, NFKB inhibitor, anti-fibrotic; phase 2α; age 4-7yo, ambulatory, steroid naïve
  - Vamorolone: ReveraGen, Steroid alternative; Phase 2; age 4-6yo, ambulatory, steroid naïve
  - Pamrevlumab: Fibrogen, Antifibrotic, antibody to connective tissue growth factor; Phase 2; age >12yo, non-ambulatory, steroid >6mons
Clinical research: improve cardiac function

- Cap-1002: Capricor, Cardiac progenitor cells; HOPE-1, completed, direct delivery to heart by cardiac catheterization; HOPE-2, systemic delivery by intravenous infusion, recruiting, age >10yo

- Eplerenone: DMD with early cardiomyopathy already on ACE inhibitor; completed; reduction of LV strain after 12 mons treatment comparing to placebo
Clinical research: Mitochondria

- **Raxone (Idebenone)**: Santhera, preservation of respiratory function; Delos trial, steroid naïve patients, seeking FDA review; Sideros trial, phase 3, age >10yo, steroid >12mons. Ambulatory or non-ambulatory

- **Epicatechin**: Cardero Therapeutics, promote mitochondrial growth, phase 2,

- **MTB-1**: Mitobridge and Astellaa Pharma, PPARδ modulator, improves mitochondrial function
Exondys 51 (Eteplirsen) [Sarepta]
Emflaza [PTC Therapeutics]
Spironolactone & Eplerenone [Ohio State University]
Translarna (Ataluren) [PTC Therapeutics]
Givinostat [Italfarmaco]*
Raxone (Idebenone) [Santhera]*
SRP-4045/SRP-4053 [Sarepta]*
RG6206 [Roche]*
Edasalonexent (CAT-1004) [Catabasis]
Domagrozumab (PF-06252616) [Pfizer]*
Vamorolone (VBP15) [Reveragen]*
Ezutromid (SMT C1100) [Summit PLC]*
Pamrevlumab (FG-3019) [Fibrogen]
Epicatechin [Cardero]
NS-065/NCNP-01 [NS Pharma]
Follistatin Gene Transfer [Nationwide Children's]
CAP-1002 [Capricor]
MNK-1411 Cosynthropin Acetate [Mallinckrodt]*
Myoblast Transplantation [Chu De Quebec]
Exon Skipping 53 [Daichi - Sankyo]***
Nationwide Micro-Dystrophin Gene Transfer [Nationwide Children's]
WVE-210201 Exon 51 Skipping [WAVE]
Nationwide GaIGT2 Gene Therapy [Nationwide Children's]
PF-06939926 Mini-Dystrophin Gene Therapy [Pfizer]
SGT-001 Micro-Dystrophin Gene Transfer [Solid]
Rimeporide [EsperRare]**
AT-300 [Akashi]
Ifetroban [Cumberland Pharma]
Nationwide Exon 2 Skipping for Duplication 2 [Nationwide Children's]
Tamoxifen** [University of Geneva]
MA-0211/MTB-1 [Mitobridge/Astellas]
Thank you