Parent Project Muscular Dystrophy
End Duchenne Tour Nov. 2018

DMD Research Overview

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Disclosure

- 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

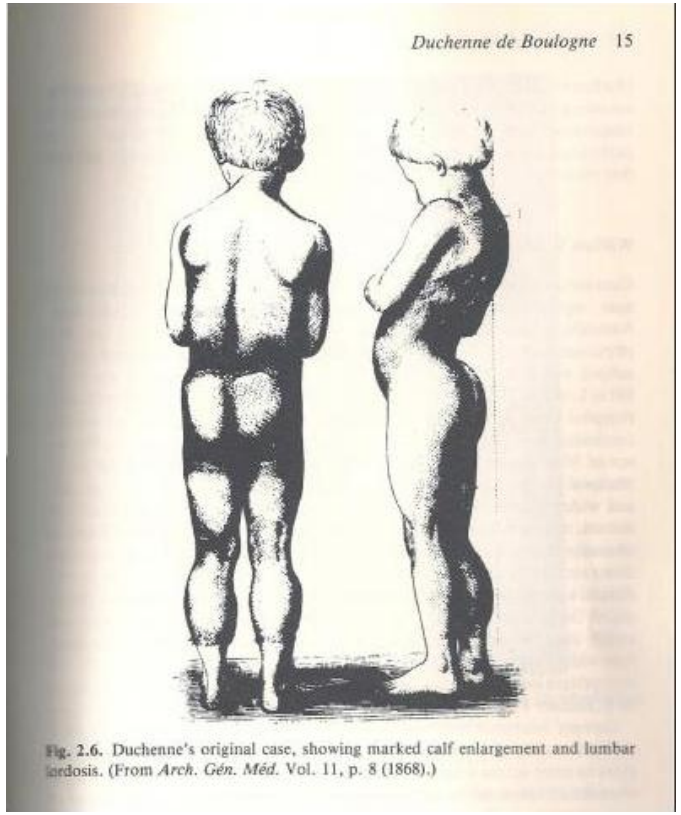


Fig. 2.6. Duchenne's original case, showing marked calf enlargement and lumbar lordosis. (From *Arch. Gén. Méd.* Vol. 11, p. 8 (1868).)

A remarkably lucid word picture of Duchenne muscular dystrophy:

- *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.*

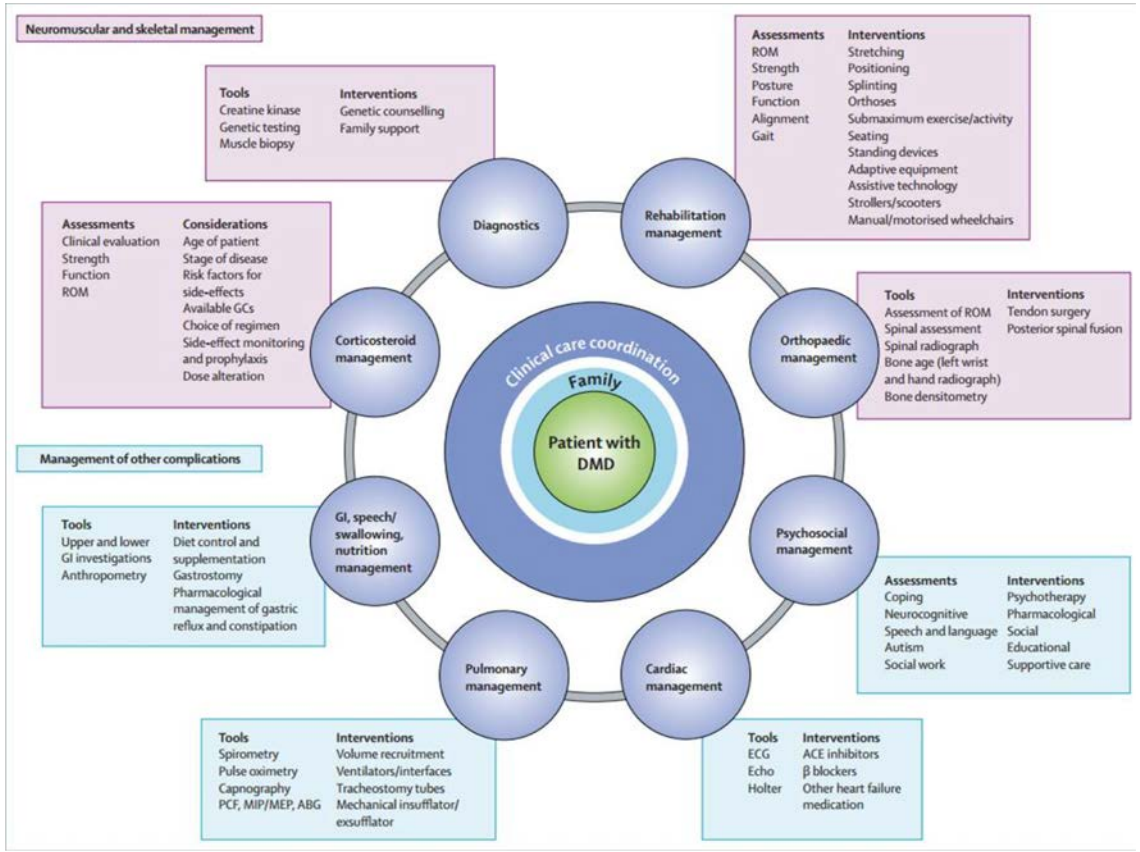
-- **Sir William Richard Gowers**, *1879*

Clinical presentation

- 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

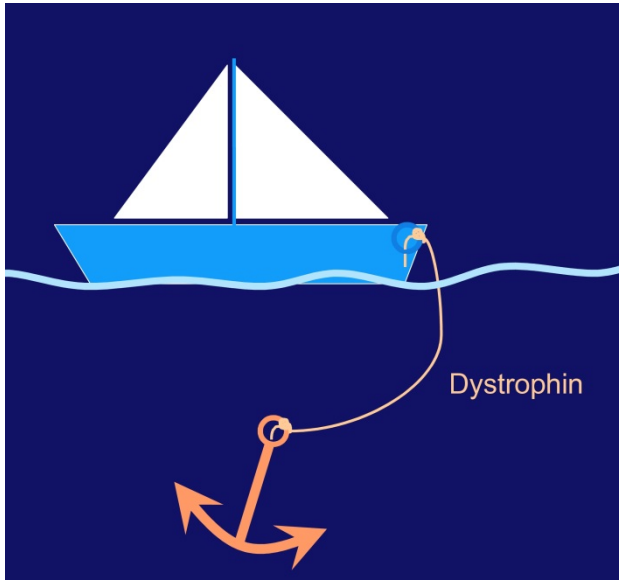
Management

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

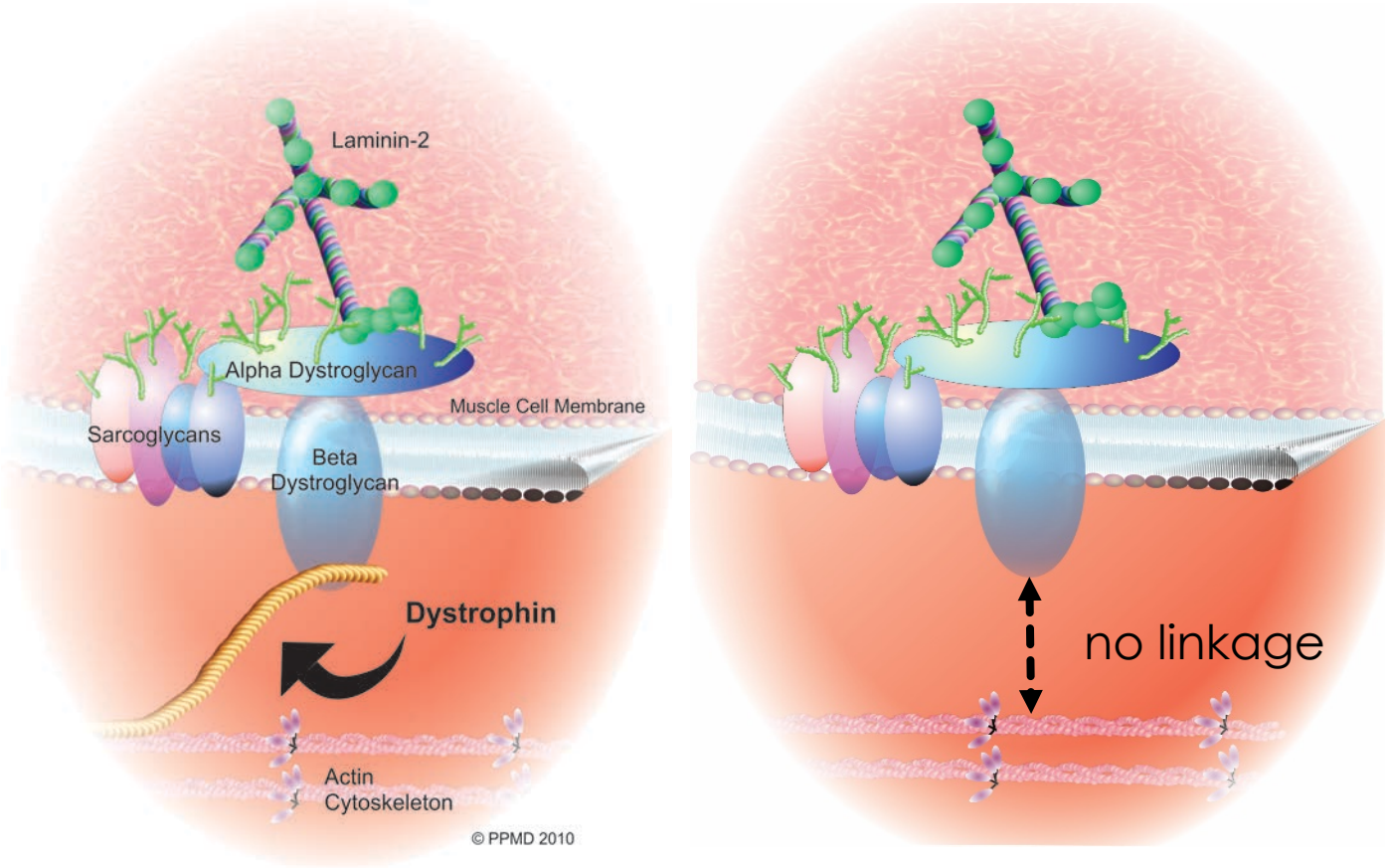


DMD gene

- 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

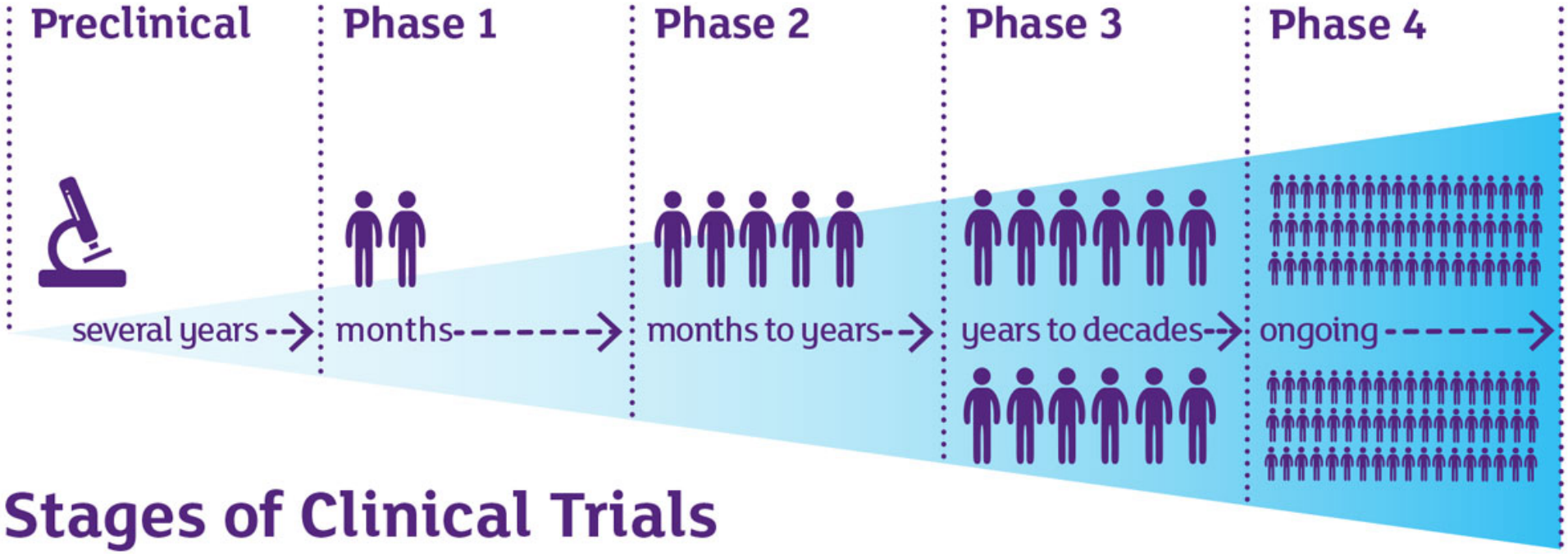
Study Types

- 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

Study Types

- 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

Success rate	70%	33%	25-30%	70-90%

Clinical research for DMD

- Restore protein Dystrophin
- Muscle growth and protection
- Targeting signaling pathways
- Improve cardiac function
- Mitochondria

Clinical research: Dystrophin restoration

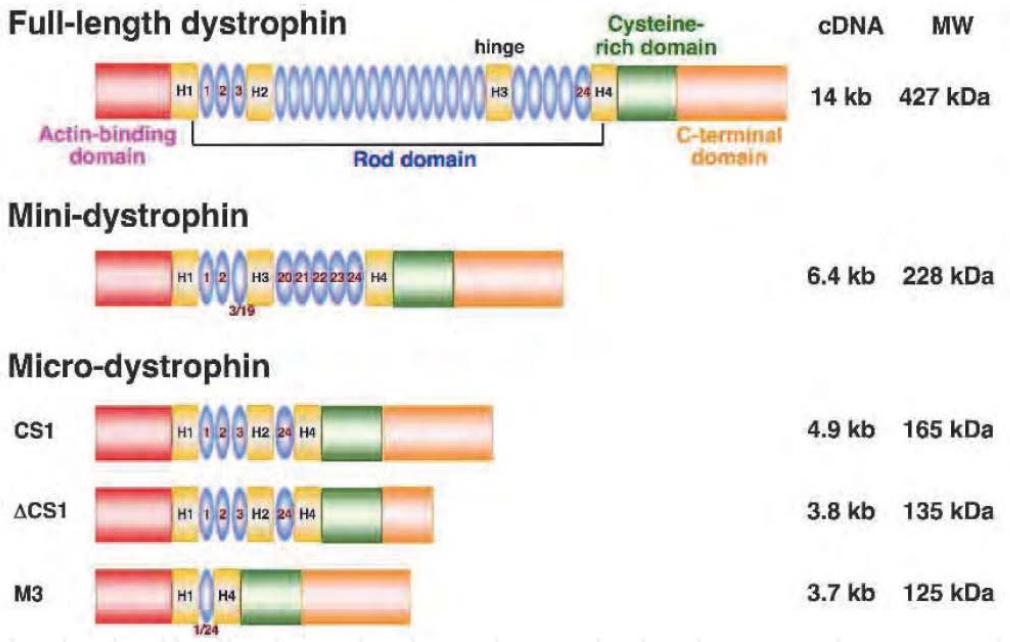
- **Exon skipping** (skip over the missing/defective part; deletion mutations)
  - Exon 45 and 53 skipping: Sarepta Essence trial (7-13yo, ambulatory, steroids >6mons)
  - Exon 53 skipping: NS pharma (4-9yo, ambulatory, steroids >6mons)
  - Exon 51 skipping: WAVE Life sciences (5-18yo, recruiting)

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

Clinical research: Dystrophin restoration

- **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 2a; 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

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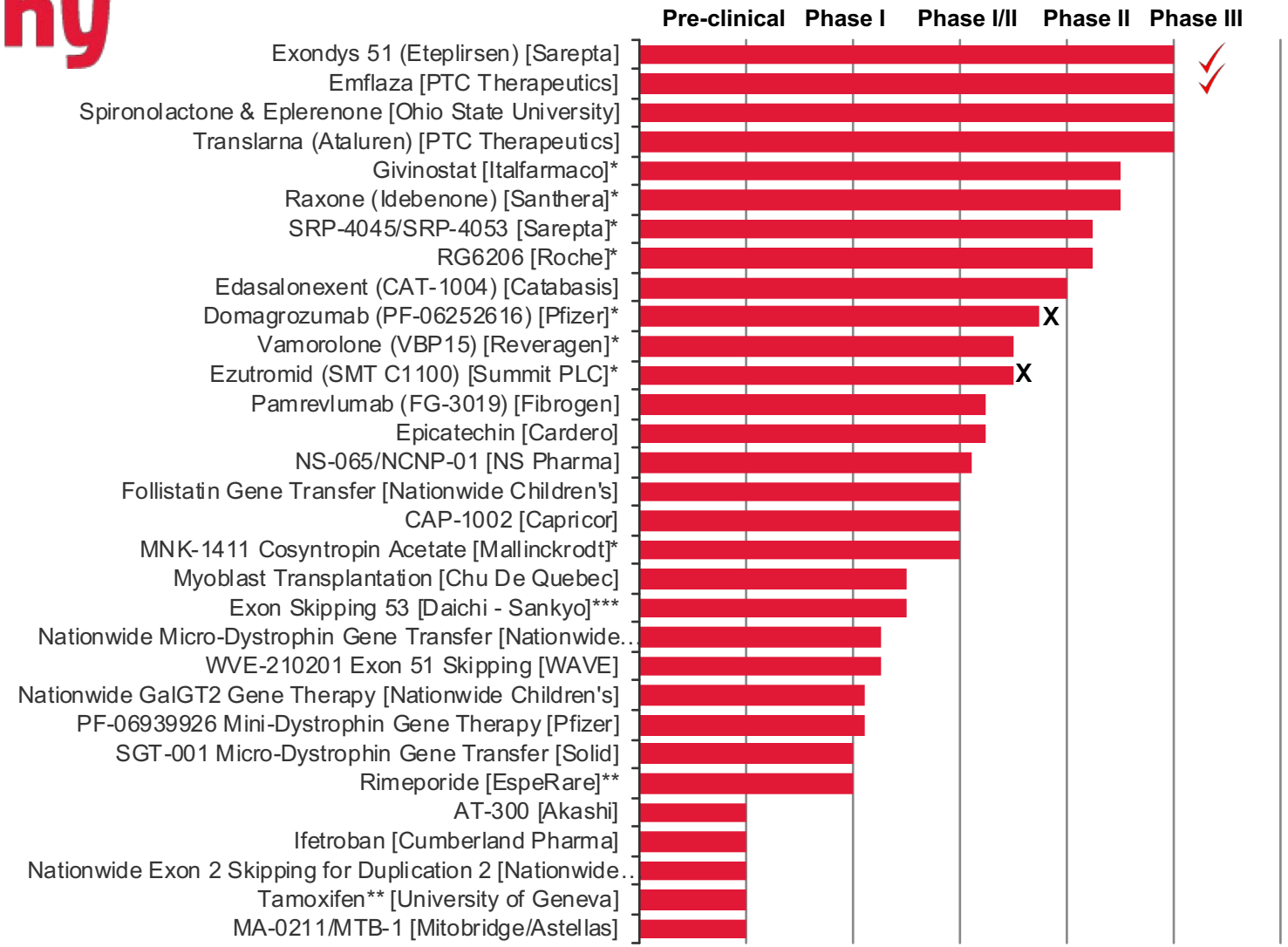

Thank you