Duchenne Research Overview: The landscape and the opportunities

Parent Project Muscular Dystrophy

JOIN THE FIGHT. END DUCHENNE.

Director of Research and Clinical Innovation

Eric Camino, PhD

Duchenne muscular dystrophy

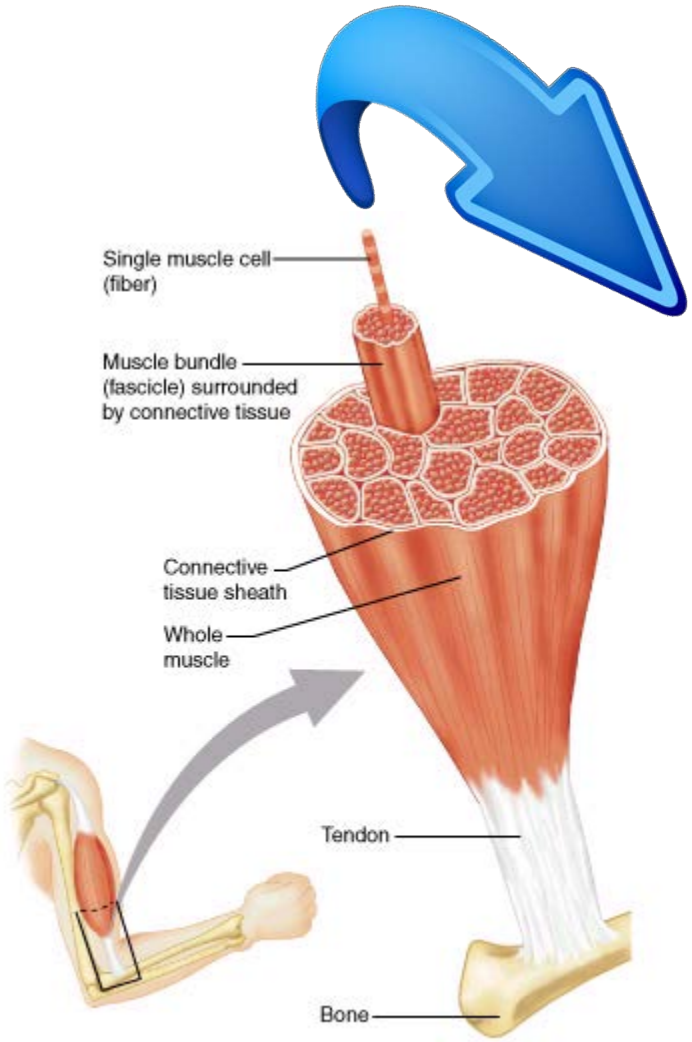
- Caused by a mutation in *DMD* gene → Absence of dystrophin protein → muscle deterioration and weakness
- X-linked recessive disease with a prevalence of 1:5000 male births
- Progressive multi-system disease affecting:
  - Heart
  - Skeletal muscle
  - Smooth muscle
  - Bone
  - Cognitive function

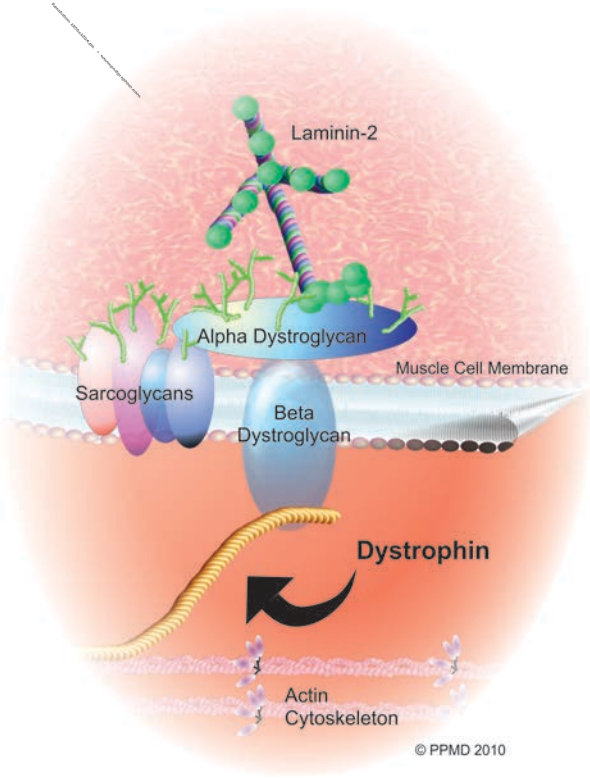
Genetics

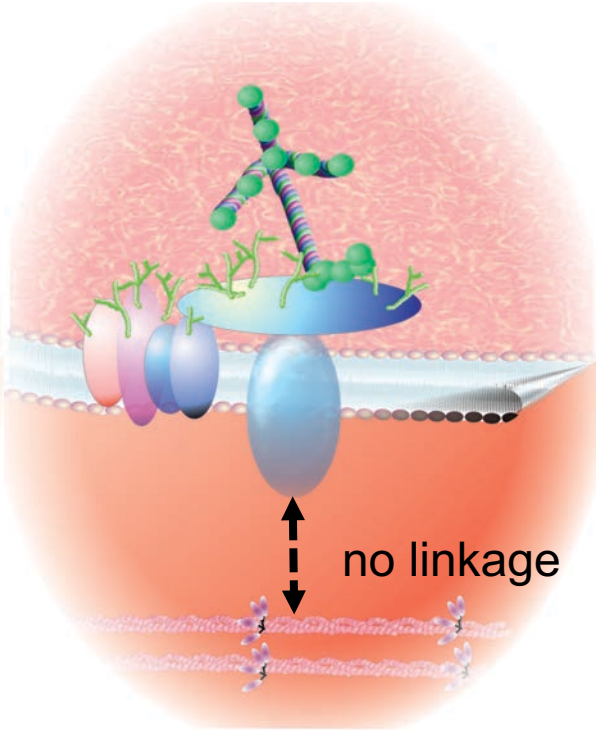
- *DMD* is the largest gene in the human genome
- 79 exons / ~2.5 Million base pairs
- Cloned in 1987

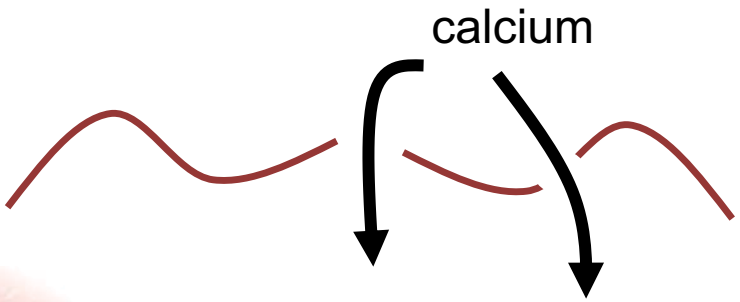
Mutation	Population
Exon deletions	65%
Exon duplications	10%
Nonsense and other small changes	25%

Impact of loss of dystrophin





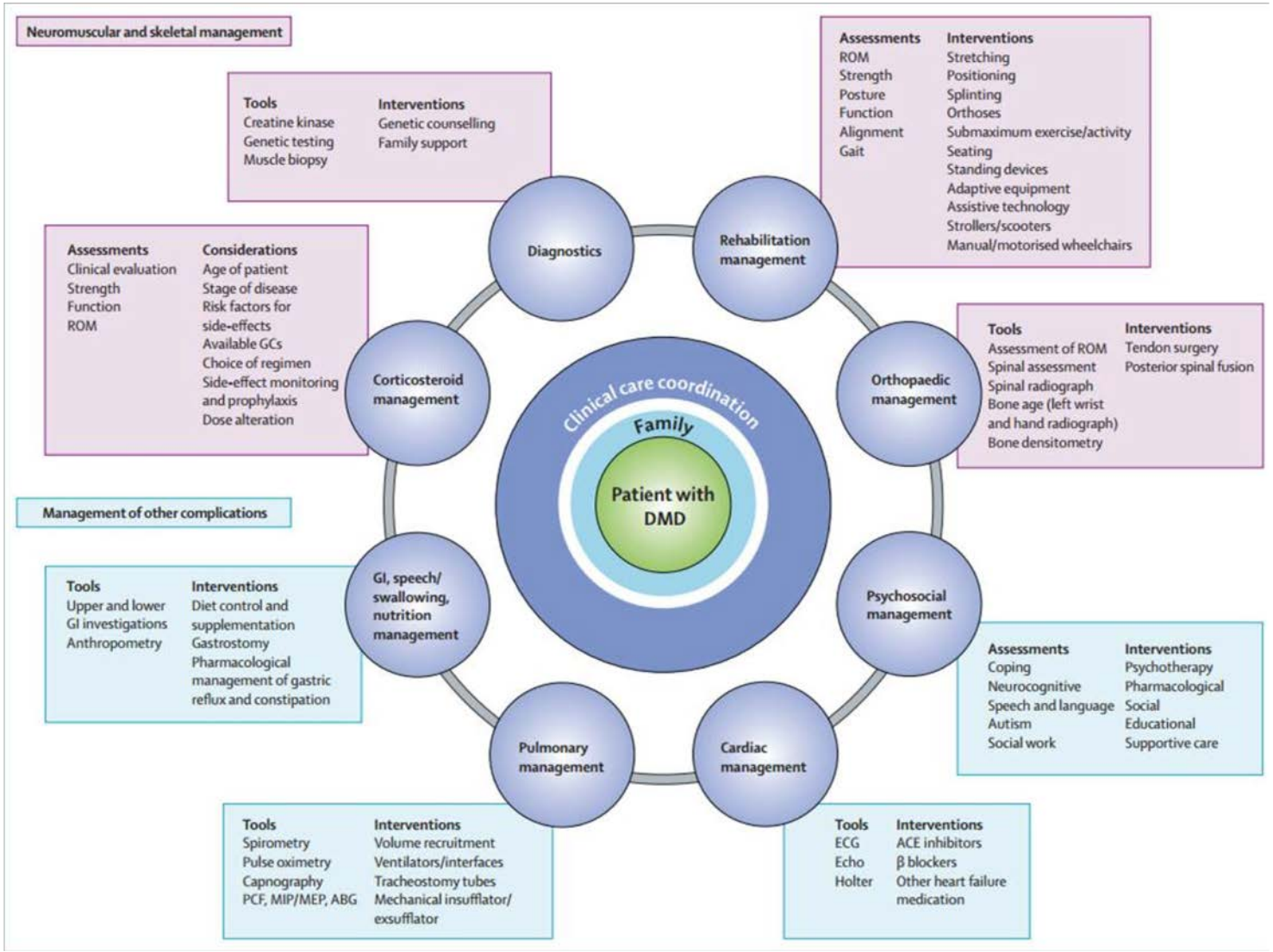




- Membrane instability
- Calcium infiltration
- Inflammation
- Oxygen deprivation
- Fibrosis
- Muscle cell death

Care

- Patient focused multi-disciplinary approach
- Standard of care:
  - Glucocorticoid
- No Cure



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)

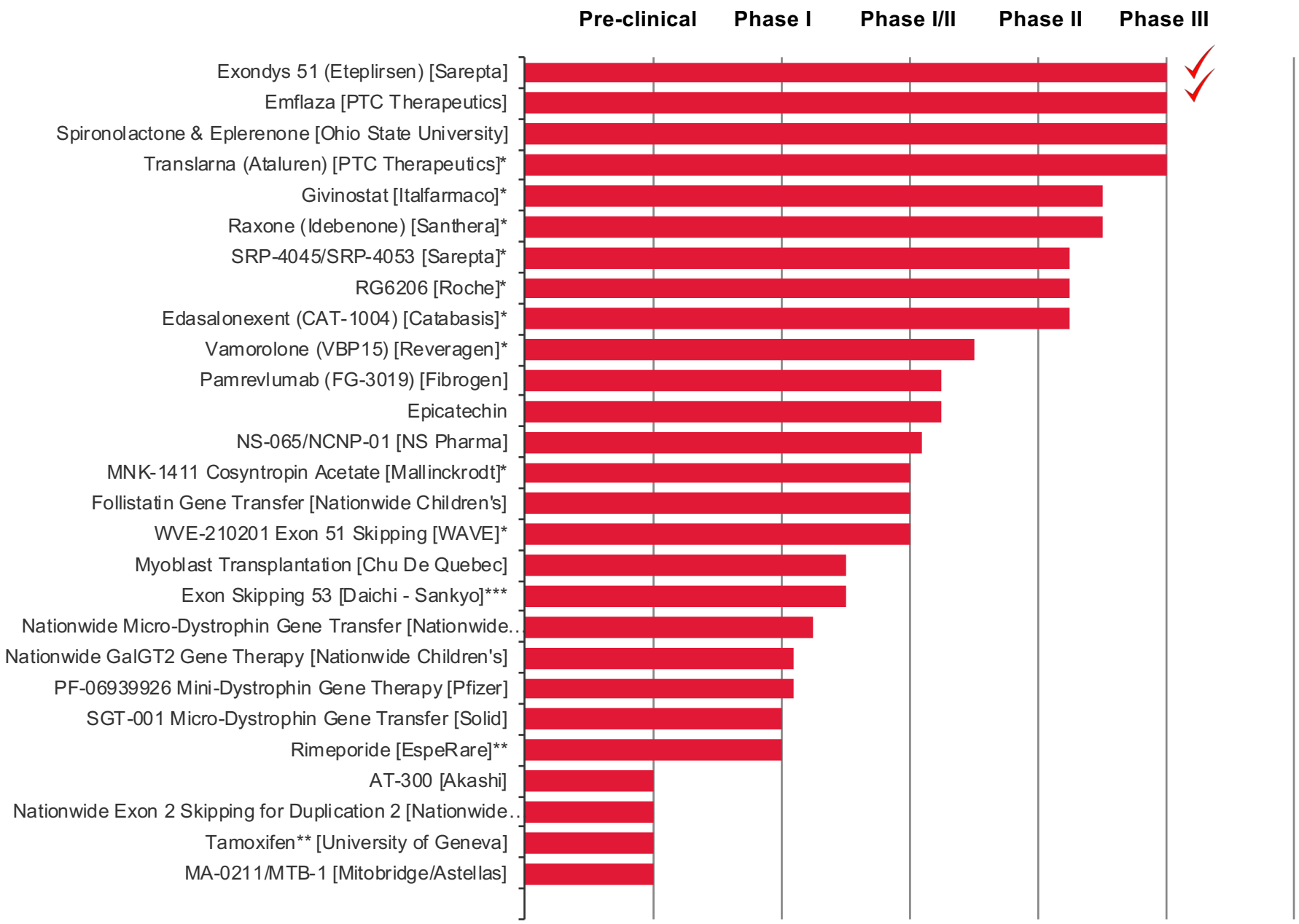
–Phase IIa: Assess dose requirements and toxicity

–Phase IIb: Assess efficacy; “Pivotal”

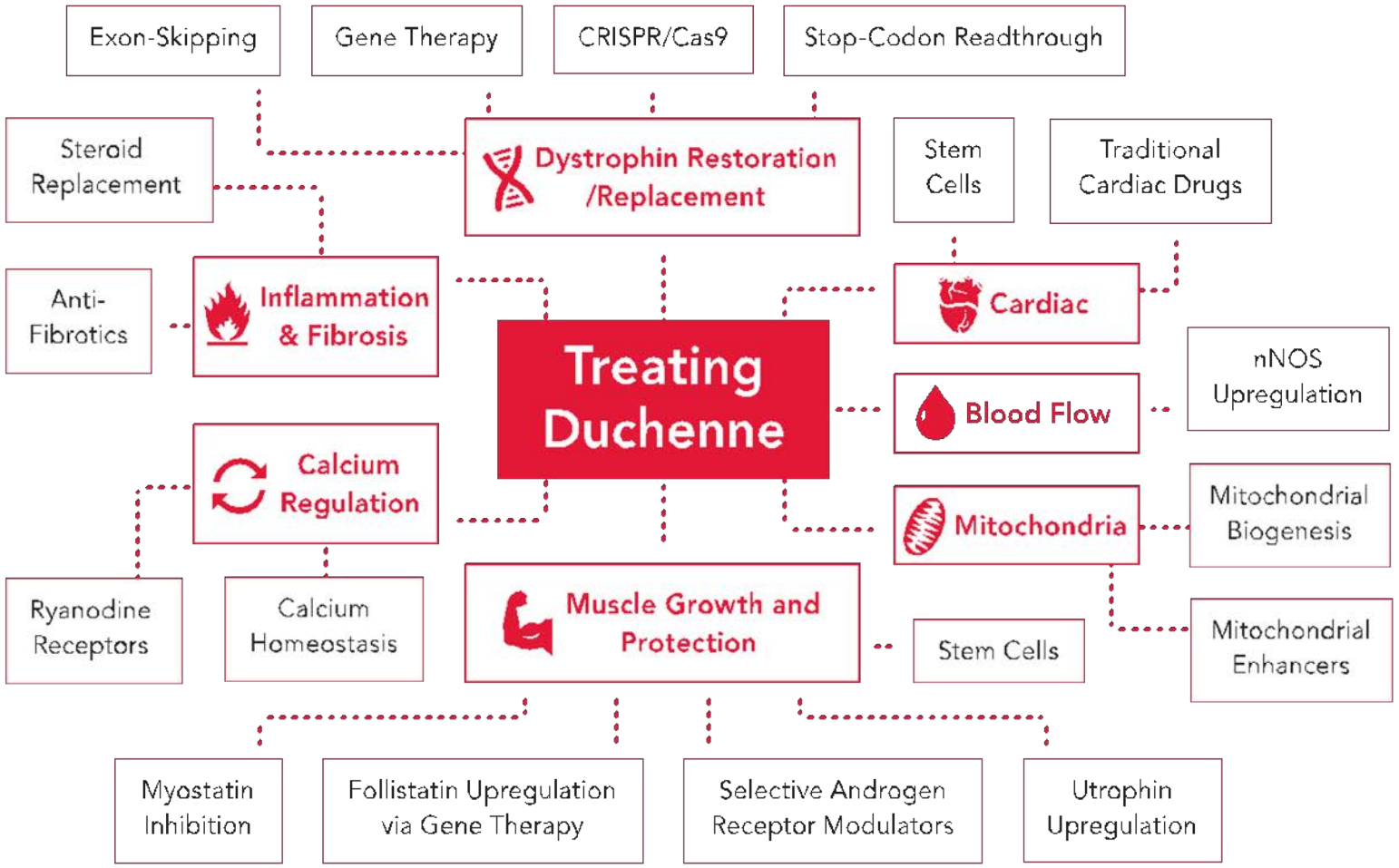
- Phase IIa and IIb can be combined

Study Types

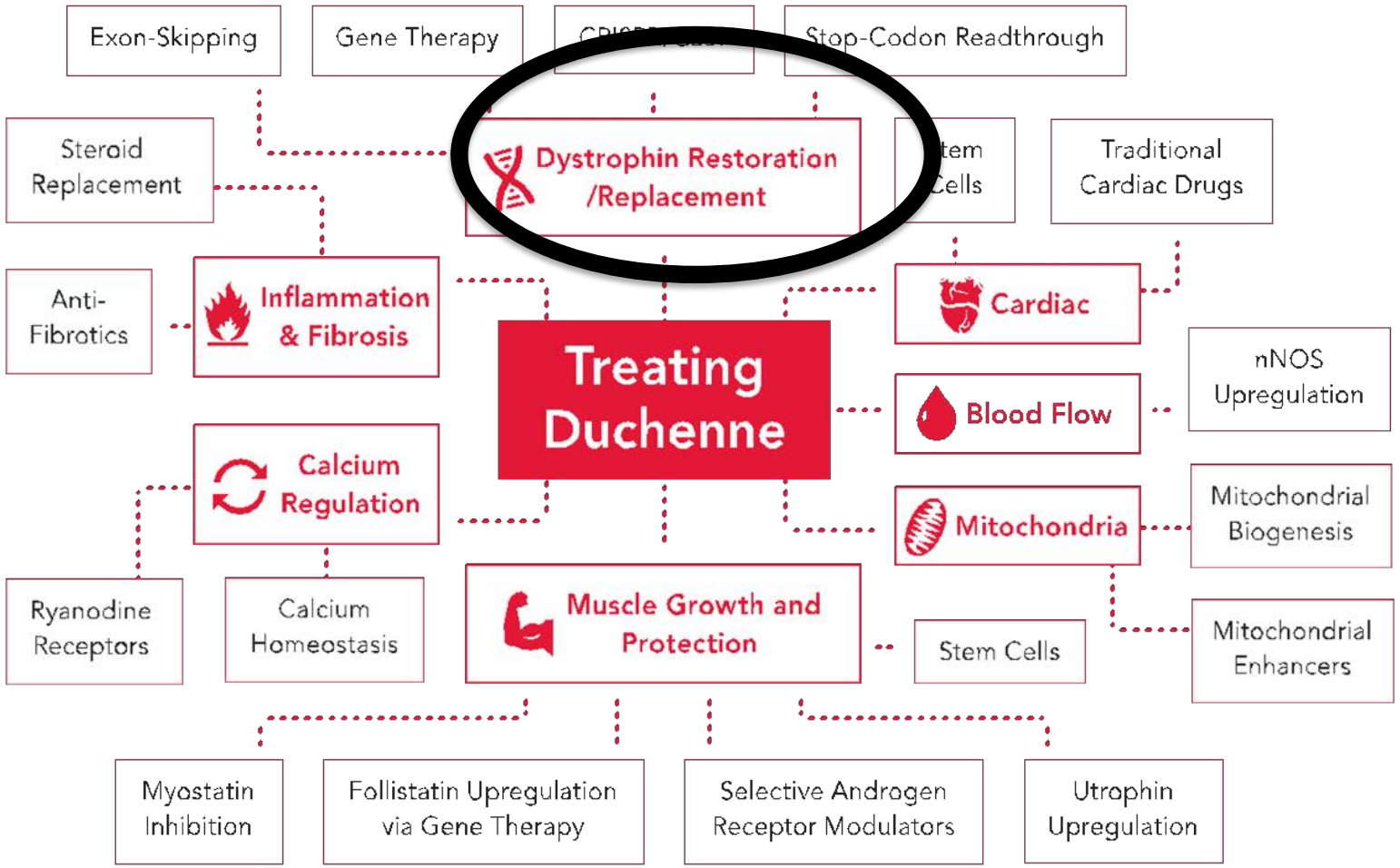
- Phase III: Classical randomized control placebo trial 1000-3000 subjects
  - In rare disease, this number can be much smaller
- Phase IV: Post-Marketing; monitor long term effects


Pre-clinical
Phase I
Phase I/II
Phase II
Phase III
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]*
Vamorolone (VBP15) [Reveragen]*
Pamrevlumab (FG-3019) [Fibrogen]
Epicatechin
NS-065/NCNP-01 [NS Pharma]
MNK-1411 Cosyntropin Acetate [Mallinckrodt]*
Follistatin Gene Transfer [Nationwide Children's]
WVE-210201 Exon 51 Skipping [WAVE]*
Myoblast Transplantation [Chu De Quebec]
Exon Skipping 53 [Daichi - Sankyo]***
Nationwide Micro-Dystrophin Gene Transfer [Nationwide..
Nationwide GalGT2 Gene Therapy [Nationwide Children's]
PF-06939926 Mini-Dystrophin Gene Therapy [Pfizer]
SGT-001 Micro-Dystrophin Gene Transfer [Solid]
Rimeporide [EspeRare]**
AT-300 [Akashi]
Nationwide Exon 2 Skipping for Duplication 2 [Nationwide..
Tamoxifen** [University of Geneva]
MA-0211/MTB-1 [Mitobridge/Astellas]

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

NS Pharma

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)

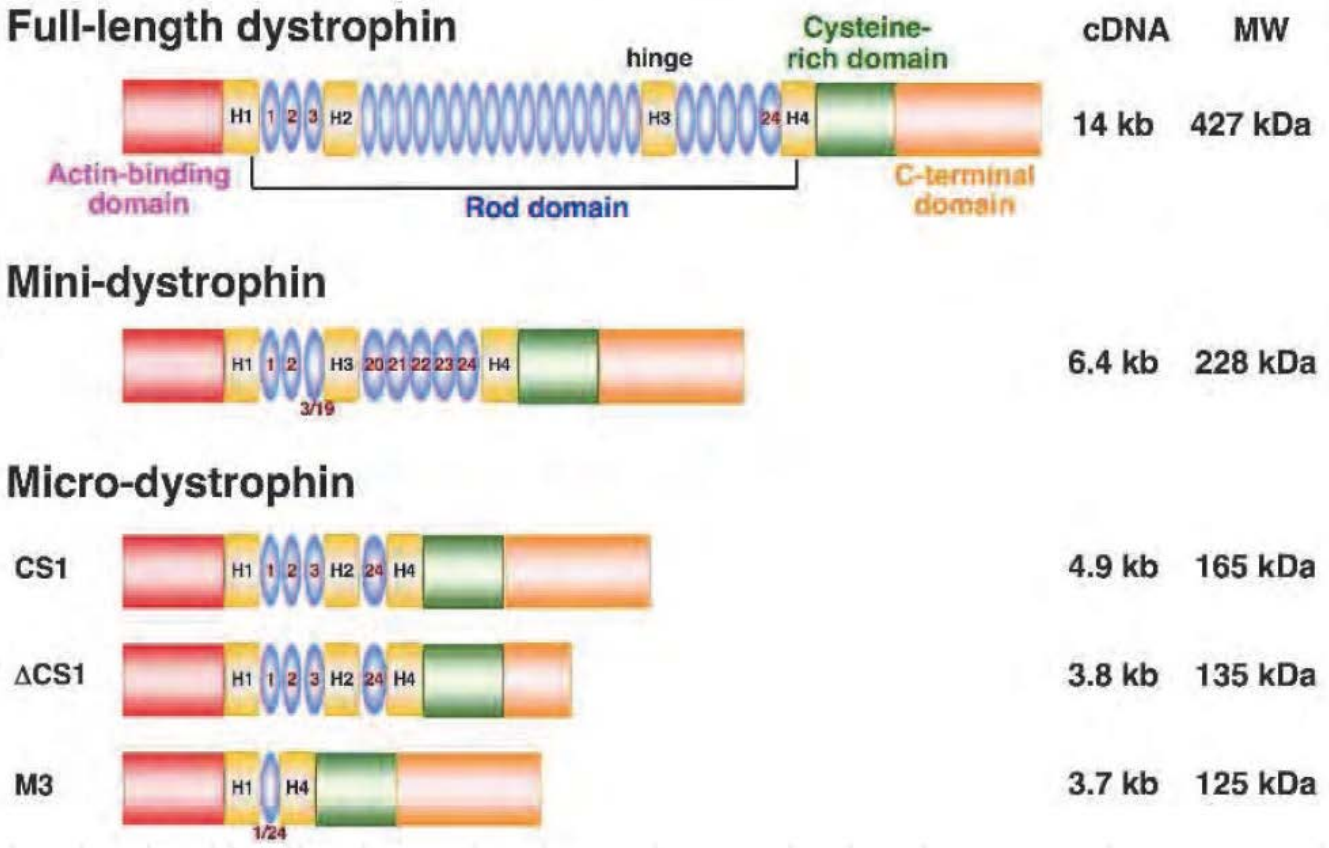
Ataluren (Translarna): **PTC Theraputics**
(Phase III extension study, ≥5yo, ambulatory, steroids ≥12mo, non-sense mutation)

Currently approved by EMA not FDA

Dystrophin Restoration and Replacement

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**

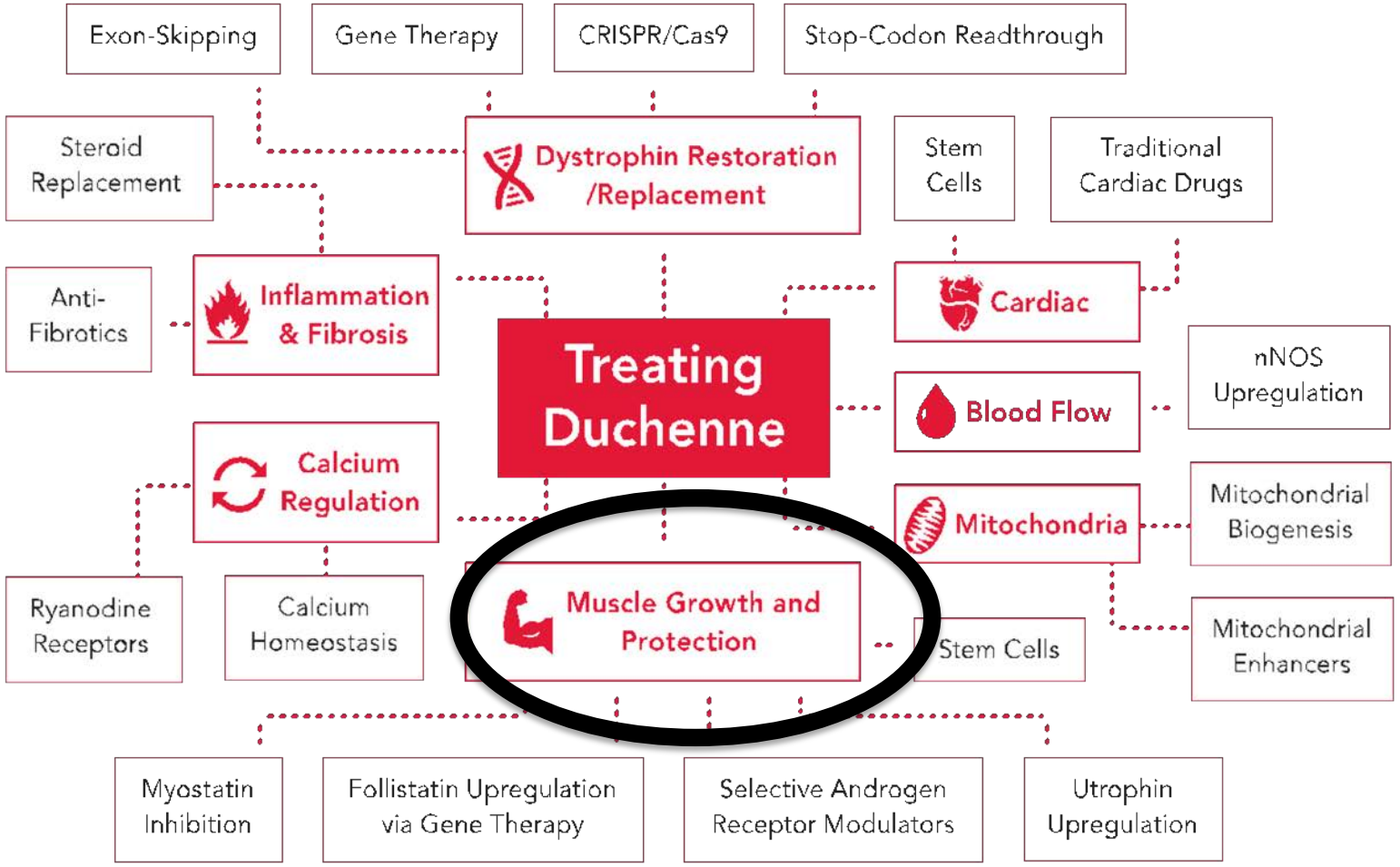
(Phase I/IIa, rAAVrh74.MCK.GALGT2)

- 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

Clinical Trials in Duchenne



Muscle Growth and Regeneration

Biglycan : **Tivorsan Pharma** (pre-clinical)

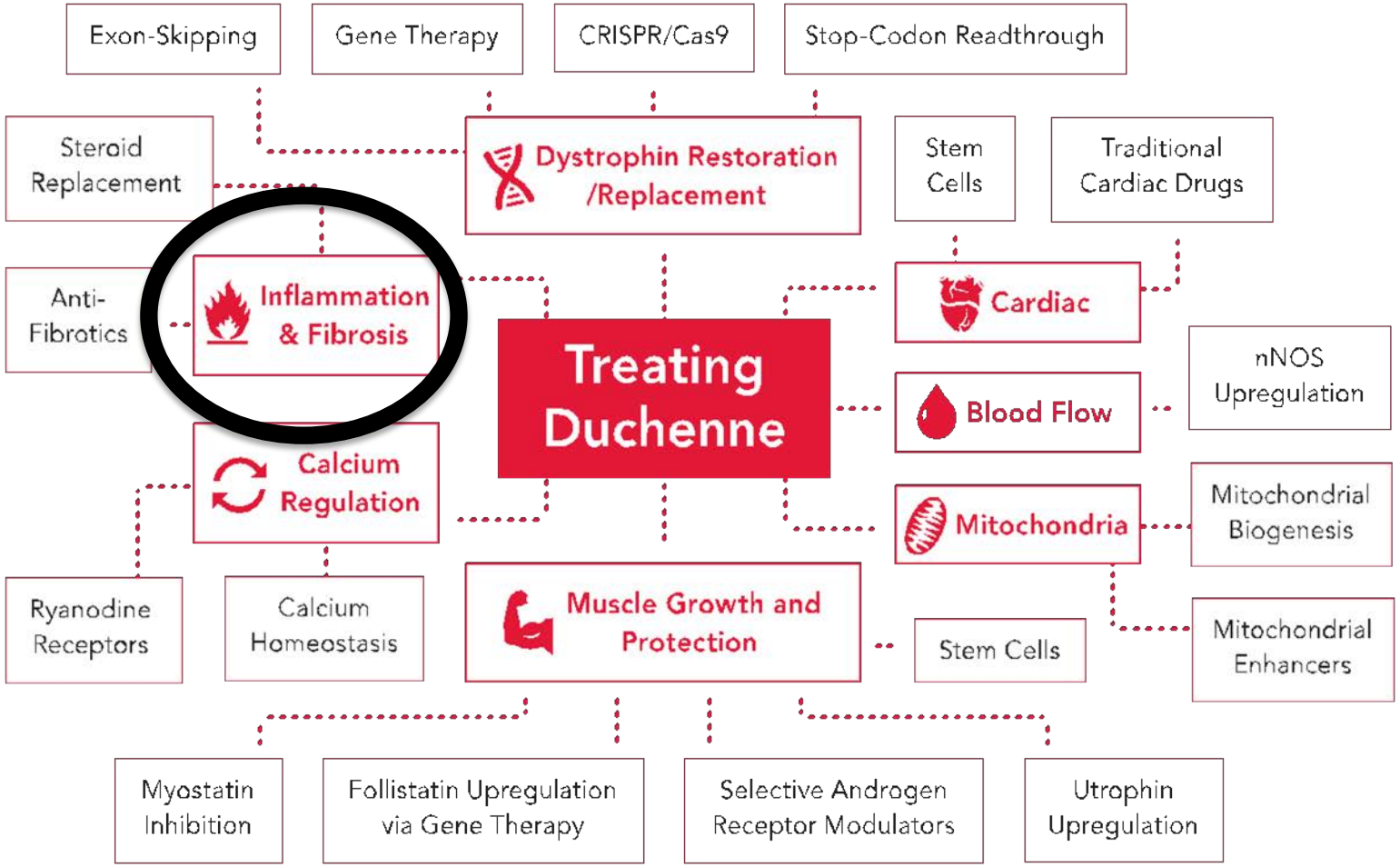
TVN-102

Anti-myostatin: **Roche** (Phase II/III, 6-11yo, ambulatory, steroids)

RO7239361

Myostatin inhibitor

Clinical Trials in Duchenne



Anti-inflammatory

Edasalonexent: **Catabasis** (Phase III, 4-7yo, ambulatory, steroid naïve)

- NFkB inhibitor, anti-fibrotic

catabasis
a return to health

Vamorolone: **ReveraGen** (Phase 2b, 4-7yo, ambulatory, steroid naïve)

- Dissociative steroid

ReveraGen
BioPharma

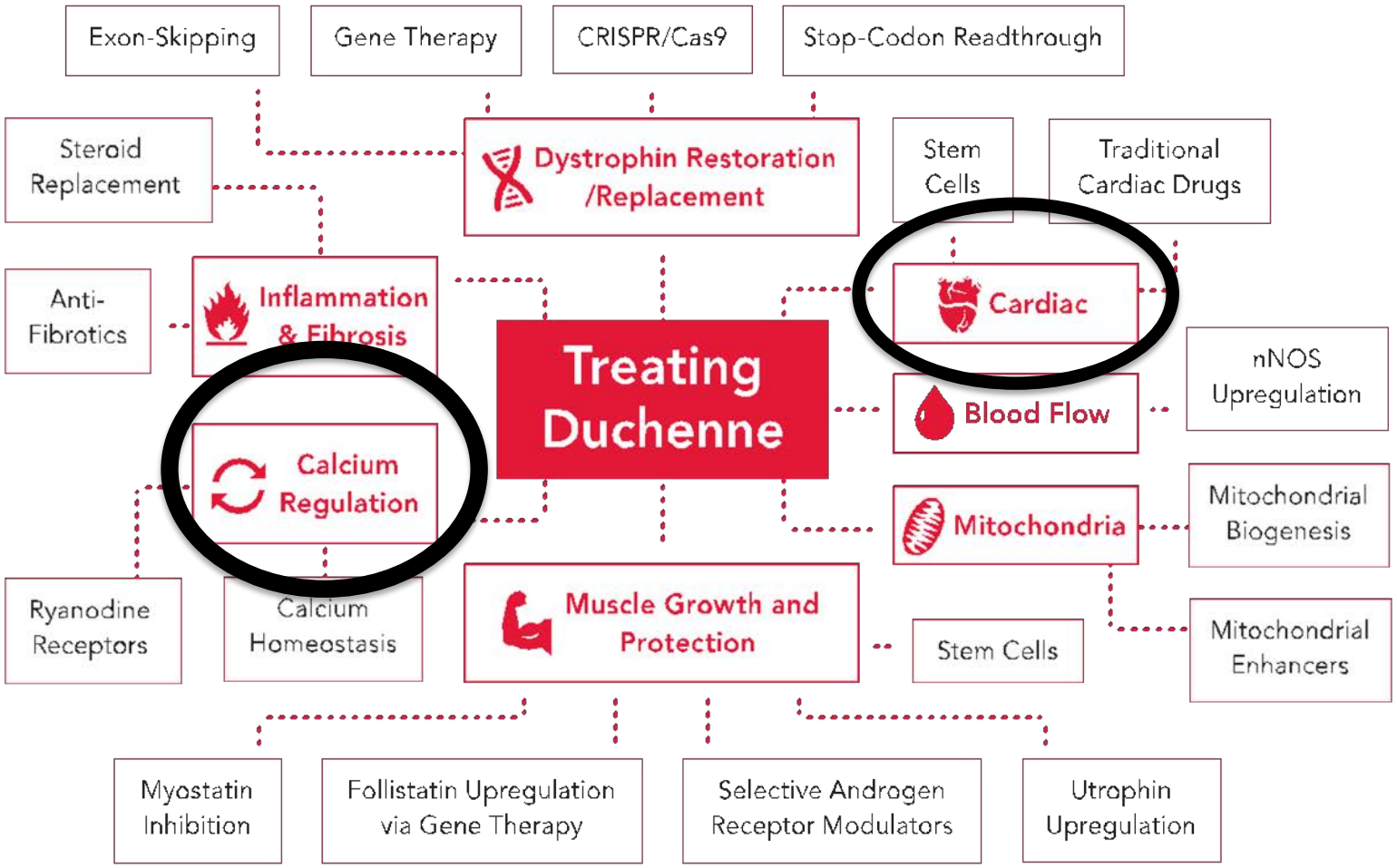
Anti-inflammatory

Givinostat: **Italfarmaco** (Phase III, >6yo, ambulatory, steroids >6mo)
HDAC Inhibitor

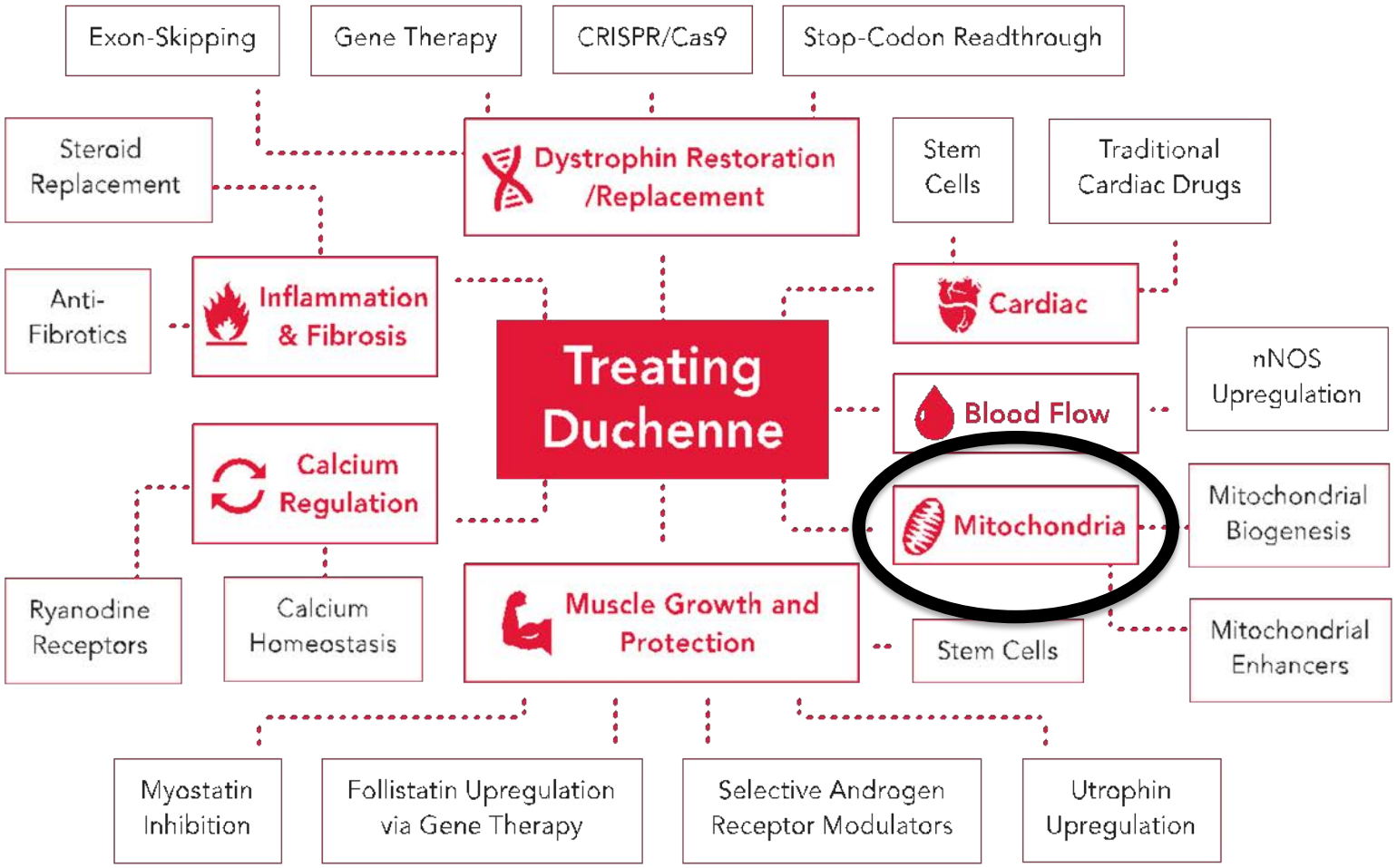
MK1411: **Mallinckrodt** (Phase II, 4-8yo, steroid naive)
Synthetic ATCH

Pamrevlumab: **Fibrogen** (Phase II)
Antibody to CTGF

Clinical Trials in Duchenne



Clinical Trials in Duchenne



Mitochondria

Raxone (Idebenone): **Santhera** (Phase III, >10yo, >12mos steroids)

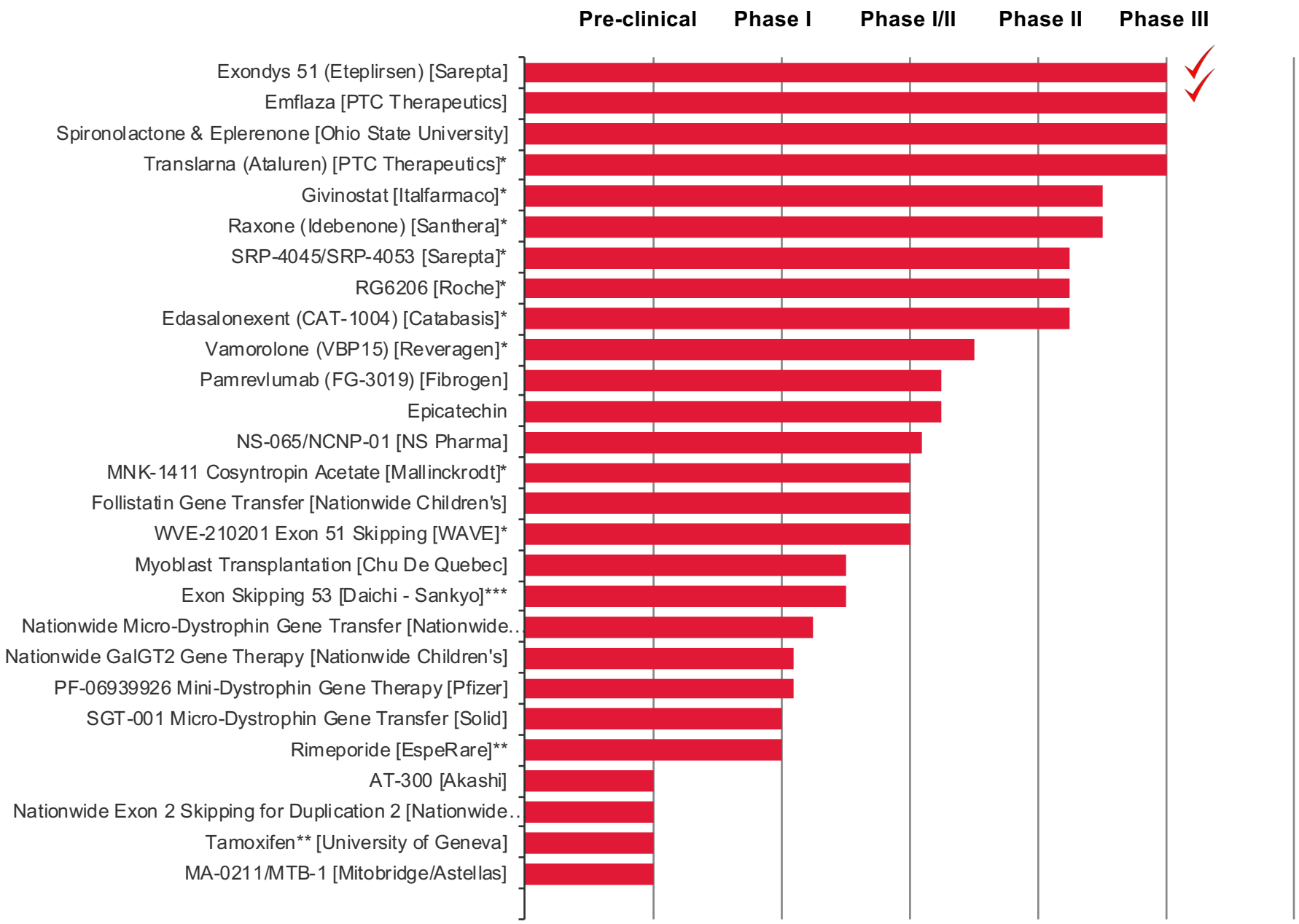
- Preservation of respiratory function
- Delos Trial
  - Steroid naïve complete, Seeking FDA review

Epicatechin: **Cardero Theraputics** (Phase II)

- Mitochondrial growth
- Reviewing results

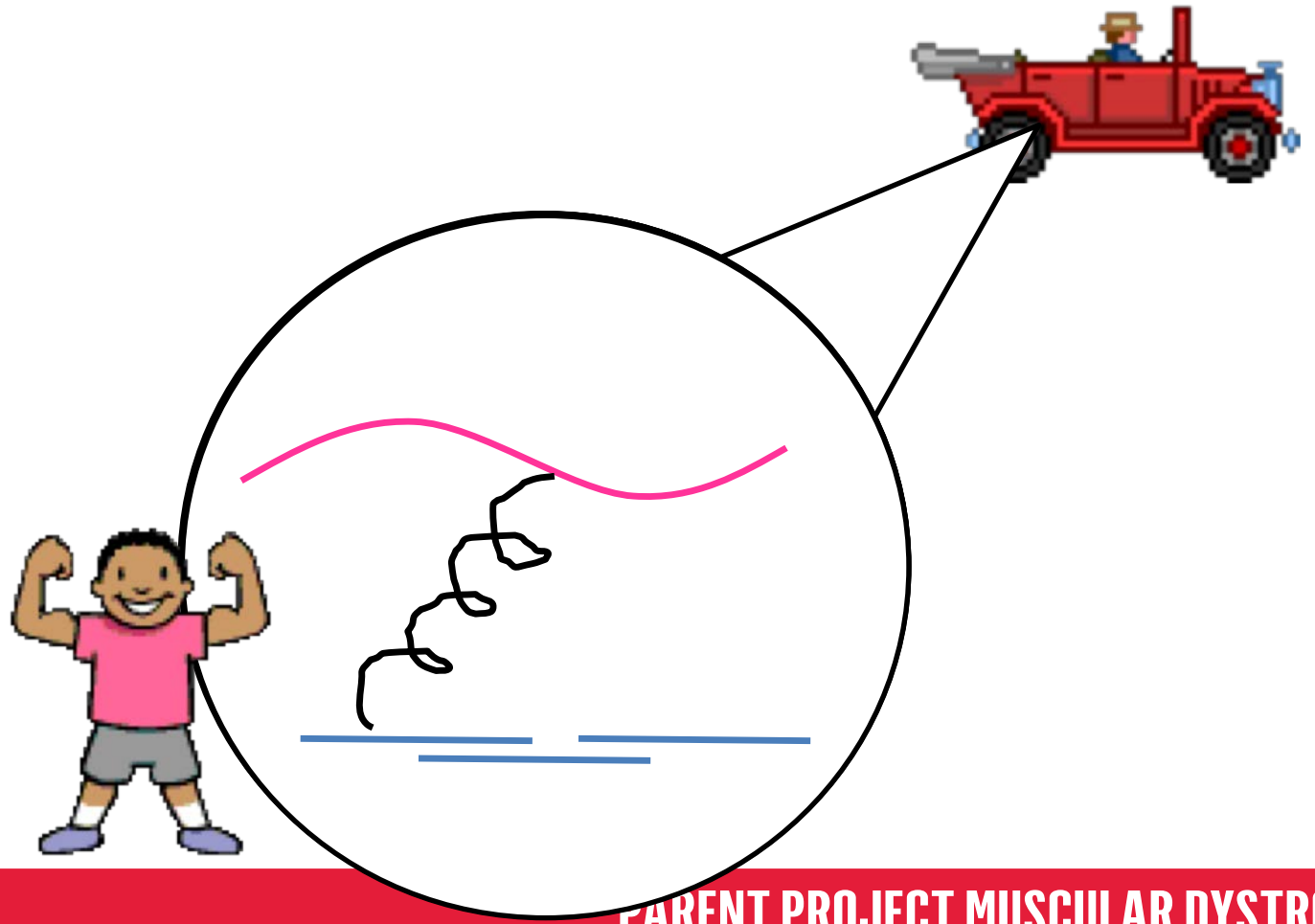
MTB-1: **Astellas Pharma** (Pre-clinical)

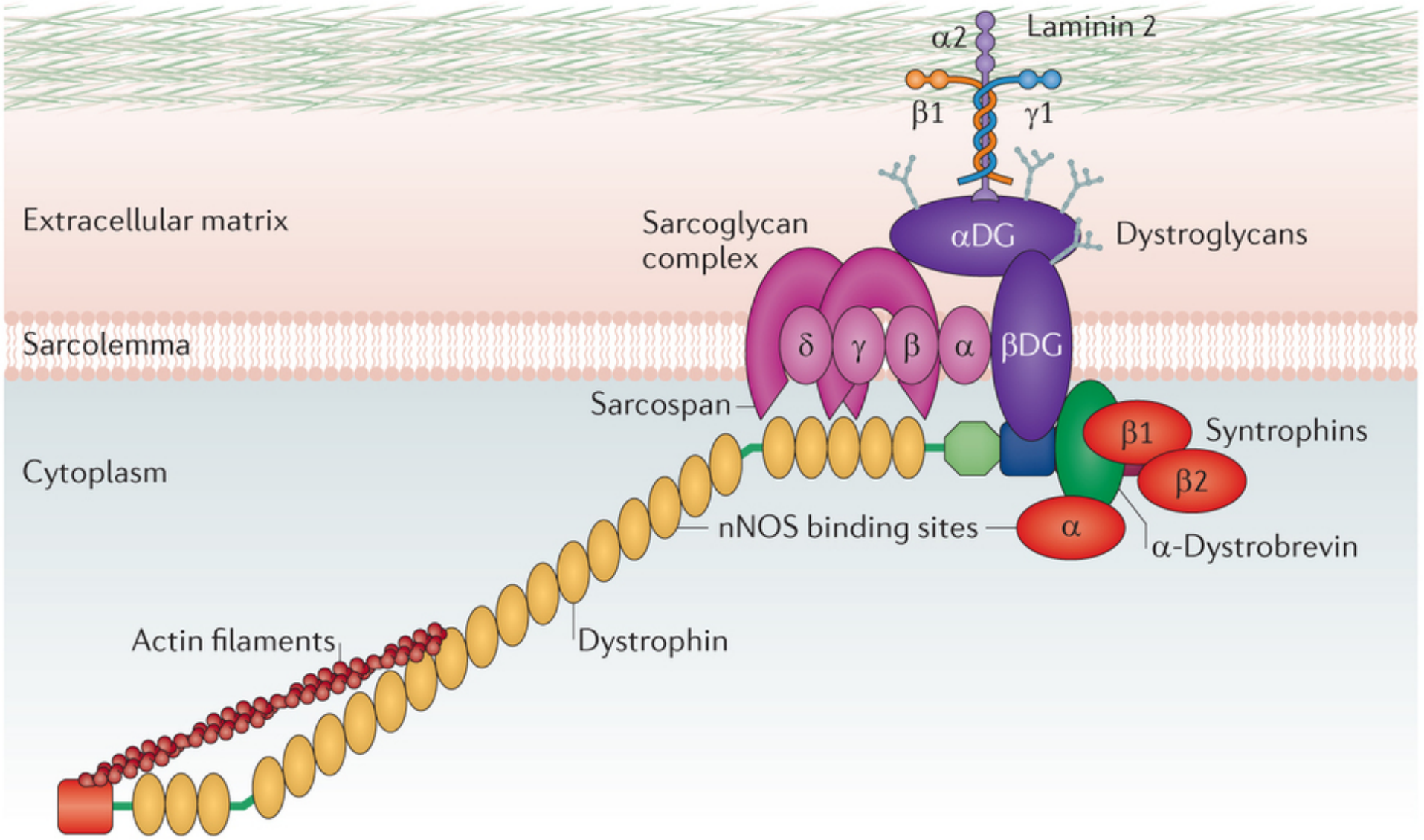
- Improved mitochondrial function


Pre-clinical
Phase I
Phase I/II
Phase II
Phase III
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]*
Vamorolone (VBP15) [Reveragen]*
Pamrevlumab (FG-3019) [Fibrogen]
Epicatechin
NS-065/NCNP-01 [NS Pharma]
MNK-1411 Cosyntropin Acetate [Mallinckrodt]*
Follistatin Gene Transfer [Nationwide Children's]
WVE-210201 Exon 51 Skipping [WAVE]*
Myoblast Transplantation [Chu De Quebec]
Exon Skipping 53 [Daichi - Sankyo]***
Nationwide Micro-Dystrophin Gene Transfer [Nationwide..
Nationwide GalGT2 Gene Therapy [Nationwide Children's]
PF-06939926 Mini-Dystrophin Gene Therapy [Pfizer]
SGT-001 Micro-Dystrophin Gene Transfer [Solid]
Rimeporide [EspeRare]**
AT-300 [Akashi]
Nationwide Exon 2 Skipping for Duplication 2 [Nationwide..
Tamoxifen** [University of Geneva]
MA-0211/MTB-1 [Mitobridge/Astellas]

Thank you!

What does dystrophin *do*?





Nature Reviews | Genetics

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

Reading frame

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 BI~~G R~~ED MAD RAT = THE FAT CAT ATE THE BIE DMA DRA T = DMD

Exon-skipping – THE FAT CAT ATE THE bie dMA DRA T = THE FAT CAT ATE THE MAD RAT