Small molecules for treatment in Duchenne muscular dystrophy

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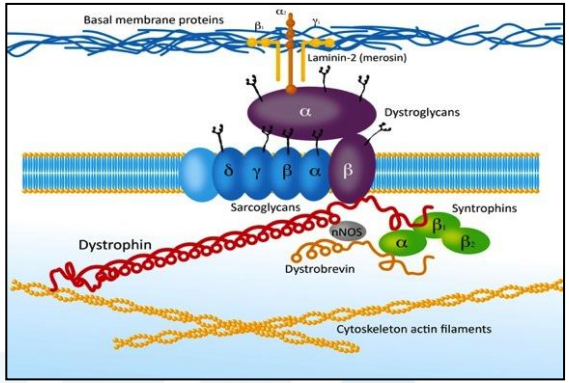
Disclosures

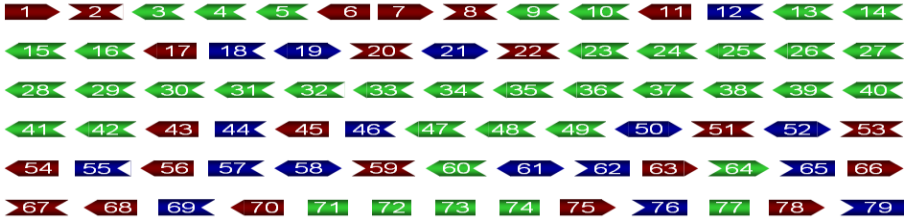
- clinical trial activities (PI and sub-I) for Sarepta Therapeutics, Pfizer, Italfarmaco, FibroGen, ReveraGen, PTC Therapeutics, Biomarin, GlaxoSmithKline, Santhera Pharmaceuticals, Lilly, Prosensa, Wave Life Sciences, Entrada Therapeutics, Genethon
- ad hoc scientific advisory board activities for Santhera Pharmaceuticals, Pfizer, Italfarmaco, Entrada Therapeutics, Wave Life Sciences, Genethon

Small molecules in DMD

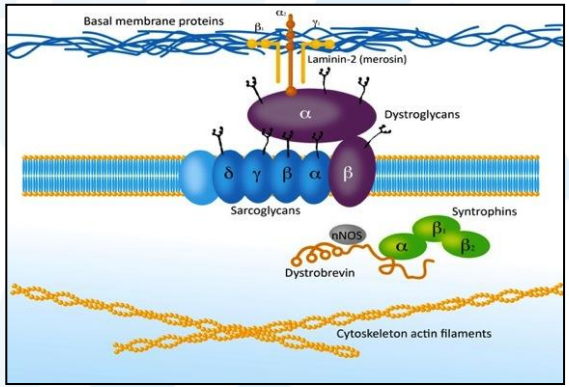
- **DMD pathophysiology**
- Treatment strategies for DMD
- What are small molecules?
- Givinostat (Duvyzat®)
- EDG-5506/Sevasemtem
- Ifetroban

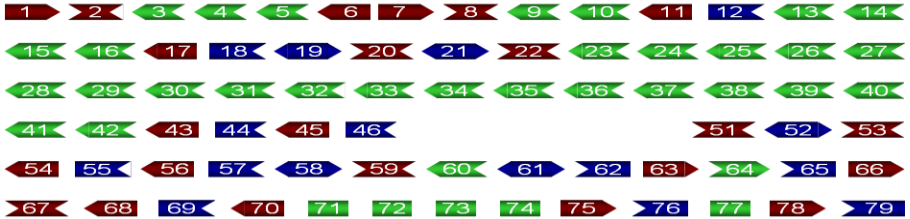
DMD pathophysiology





Large gene
2.6 million bp
79 exons
chromosome Xp21

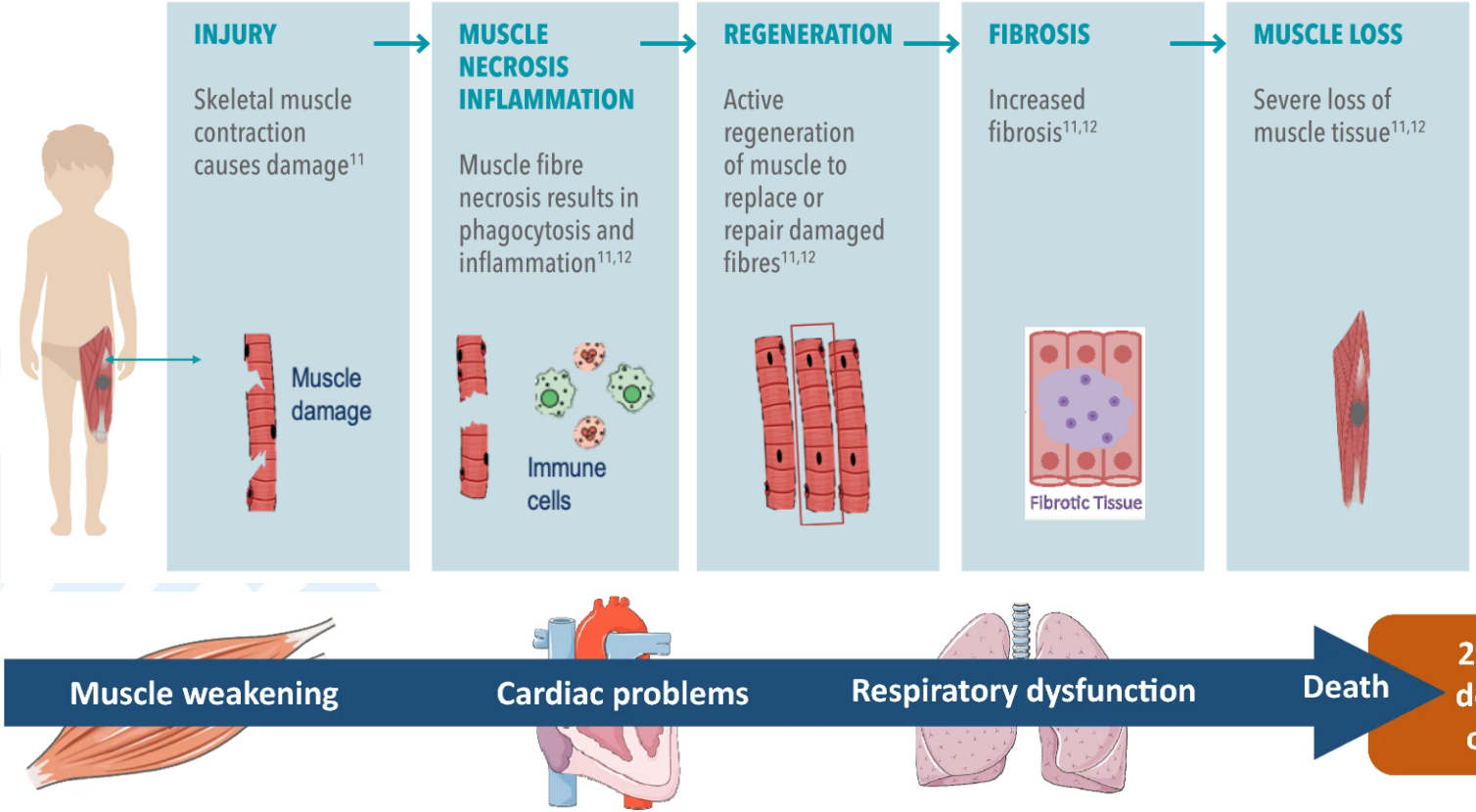




out of frame transcript
↓
abnormal pre-mRNA translation
↓
dystrophin deficiency
↓
DMD

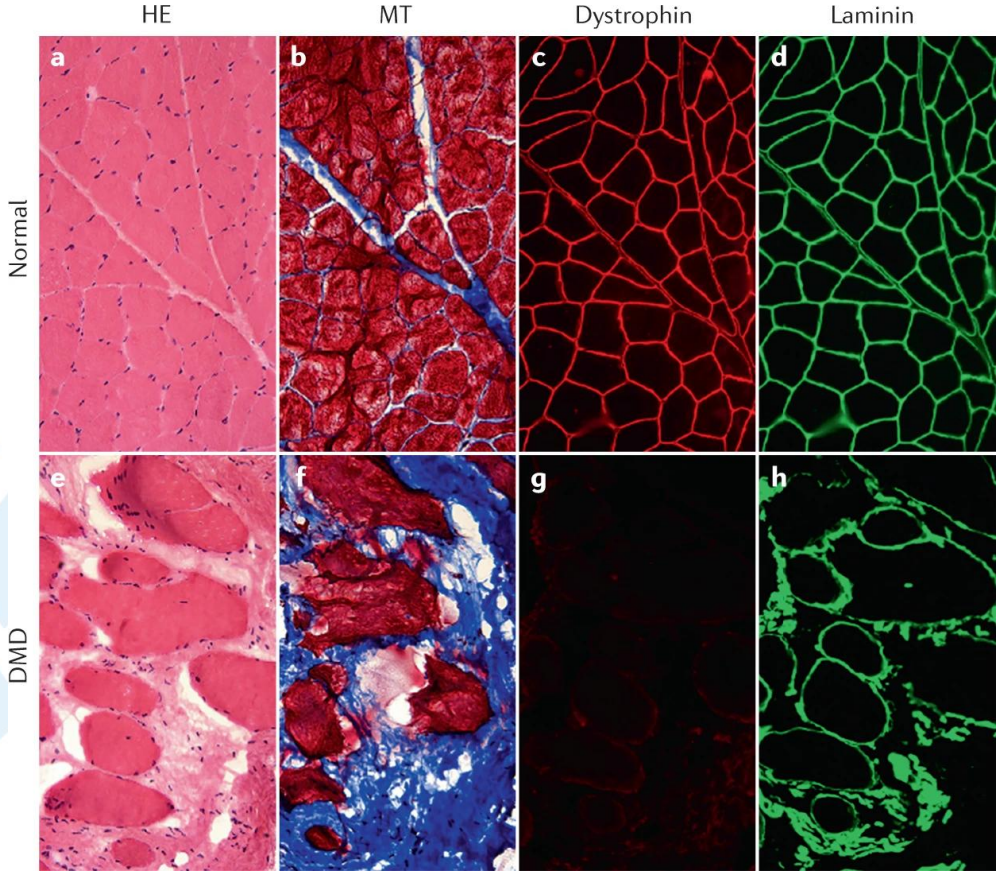
Courtesy of Dr. Goemans

DMD pathophysiology



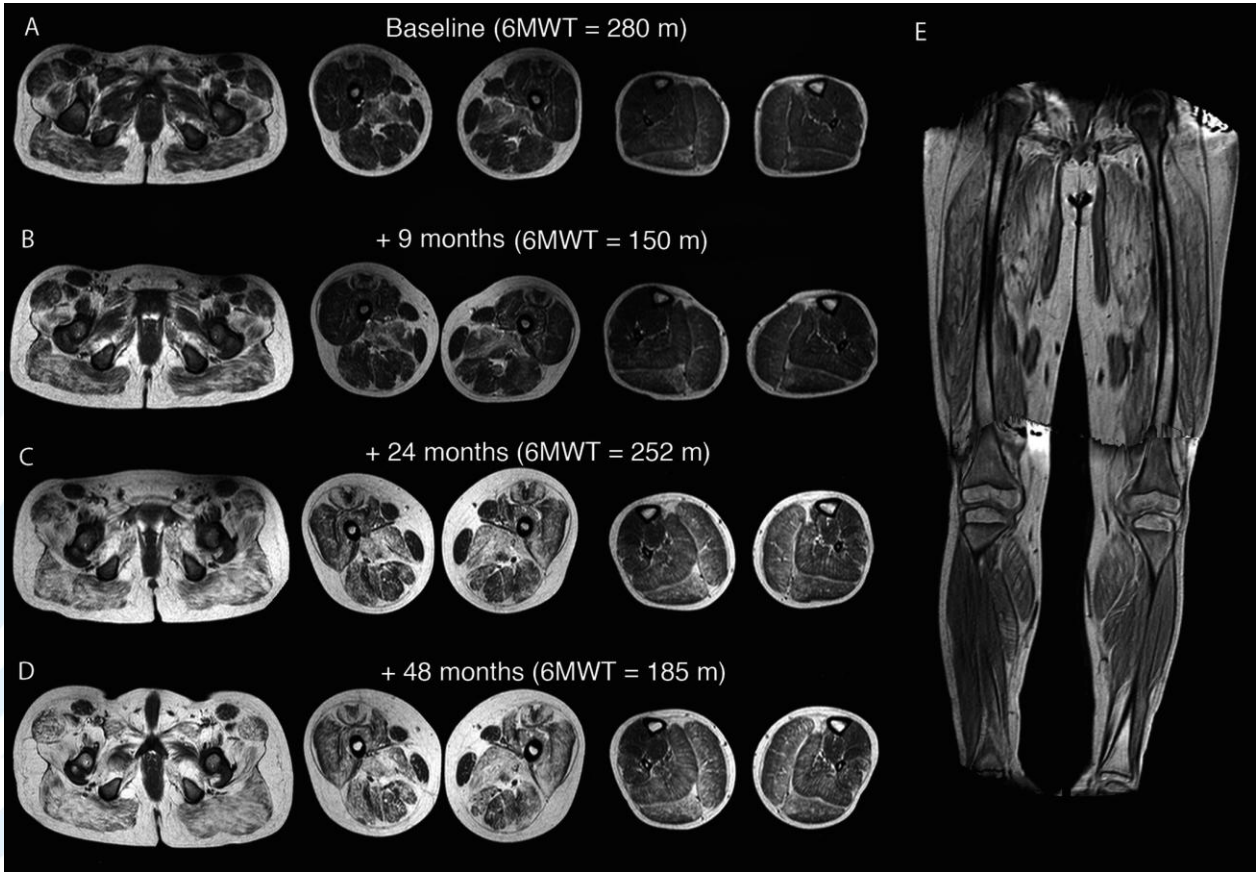
takeonduchenne.eu; Loboda et al. *Pharmacol Reports* 2020

DMD pathophysiology - histology



Duan et al. *Nat Rev Dis Prim* 2021

DMD pathophysiology - MRI



Godi et al. *Ann Clin Transl Neurol* 2016

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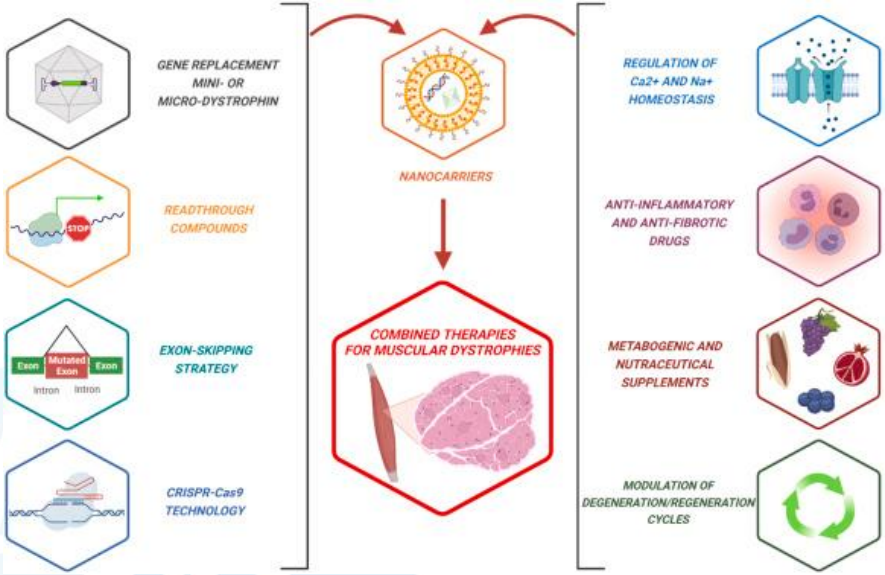
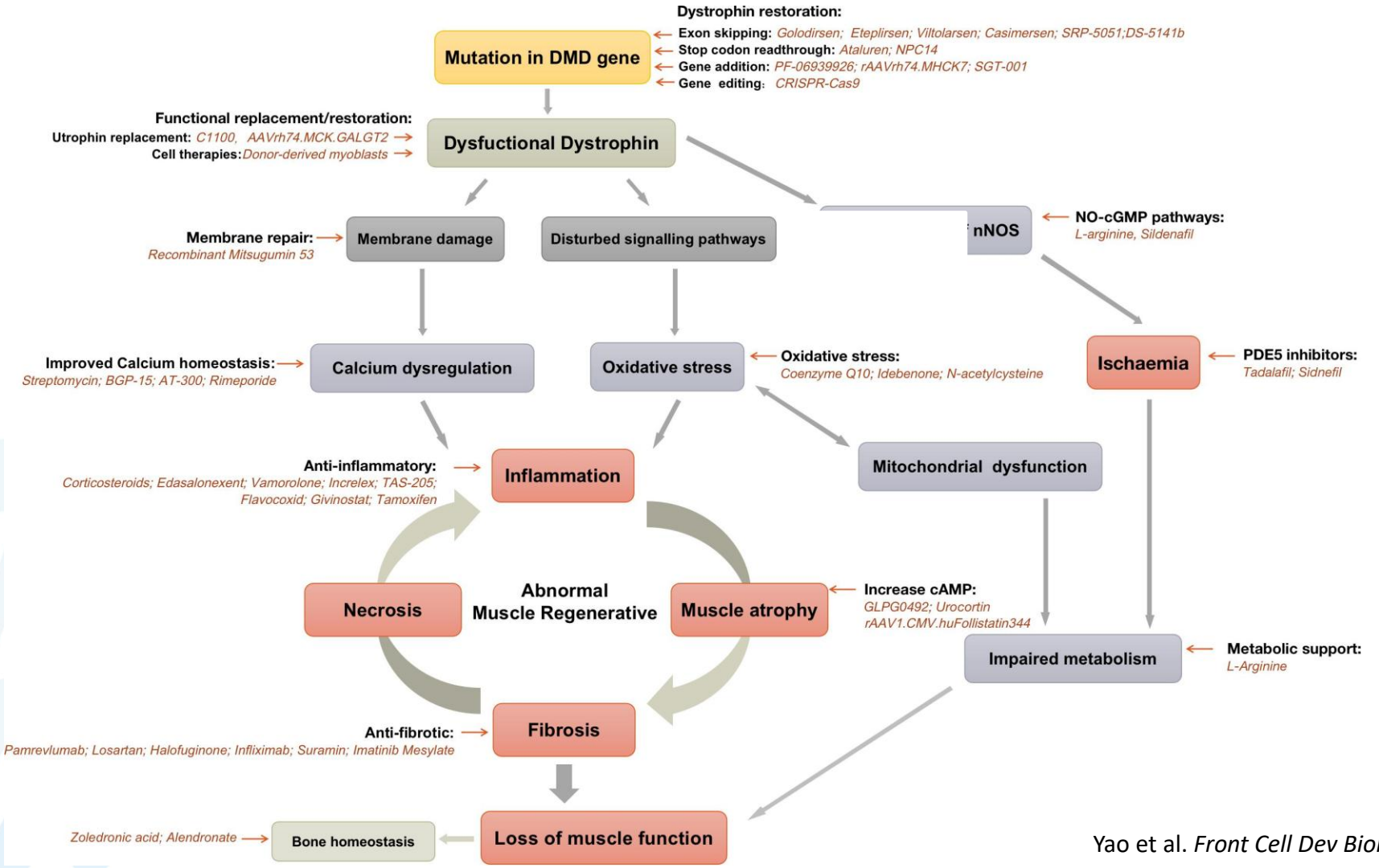
Treatment strategies for DMD



- Restoration of ‘dystrophin’ production
  - ✓ Gene therapy
  - ✓ Exon skipping
  - ✓ (Non-sense mutation read-through)

- ‘Downstream’ targeting
  - ✓ Anti-inflammatory
  - ✓ Anti-fibrotic
  - ✓ Muscle regeneration and protection
  - ✓ Calcium homeostasis
  - ✓ Protection and improvement of bone health
  - ✓ Protection and improvement of cardiac function



Yao et al. *Front Cell Dev Biol* 2021

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- **What are small molecules?**
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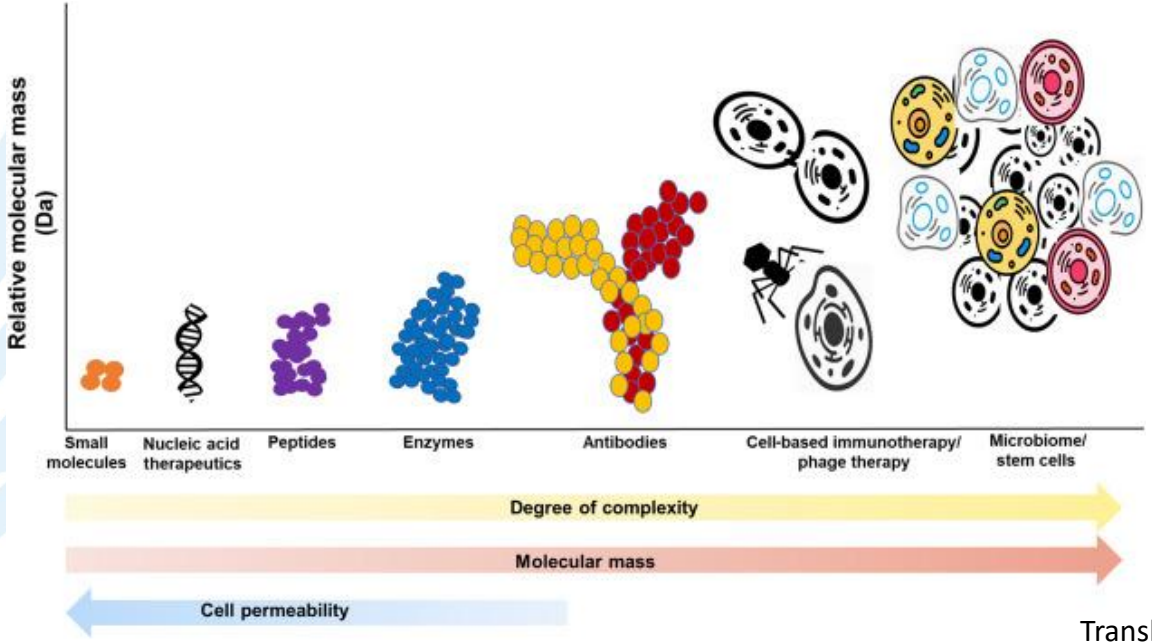
What are small molecules?

- Low molecular weight (<900-1000 D)
- Organic compounds
- Up to 90% of pharmaceutical drugs



Translational Biotechnology, 2016

What are small molecules?

Advantages:

- Not mutation-specific
- Oral administration
- Tissue penetration and distribution
- Combination potential
- Simple scalability and manufacturing
- Cost and accessibility
- Reversibility
- Regulatory familiarity

Limitations:

- Modest effect
- Chronic, life-long dosing
- Risk of off-target toxicity (liver, kidney, CNS)

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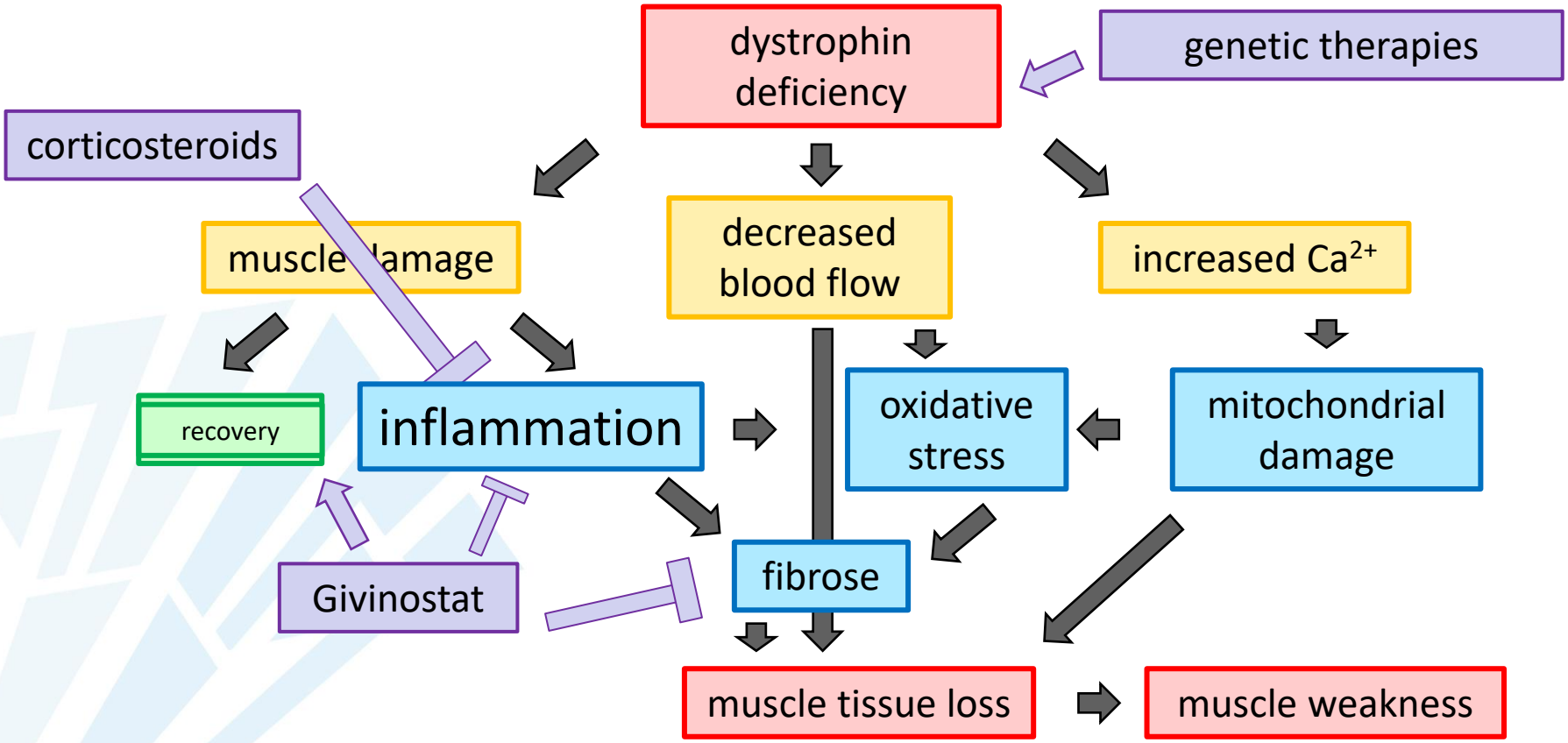
Givinostat - Duvyzat®

- HDAC inhibitor: improves muscle quality and strength by increased expression of muscle recovery factors

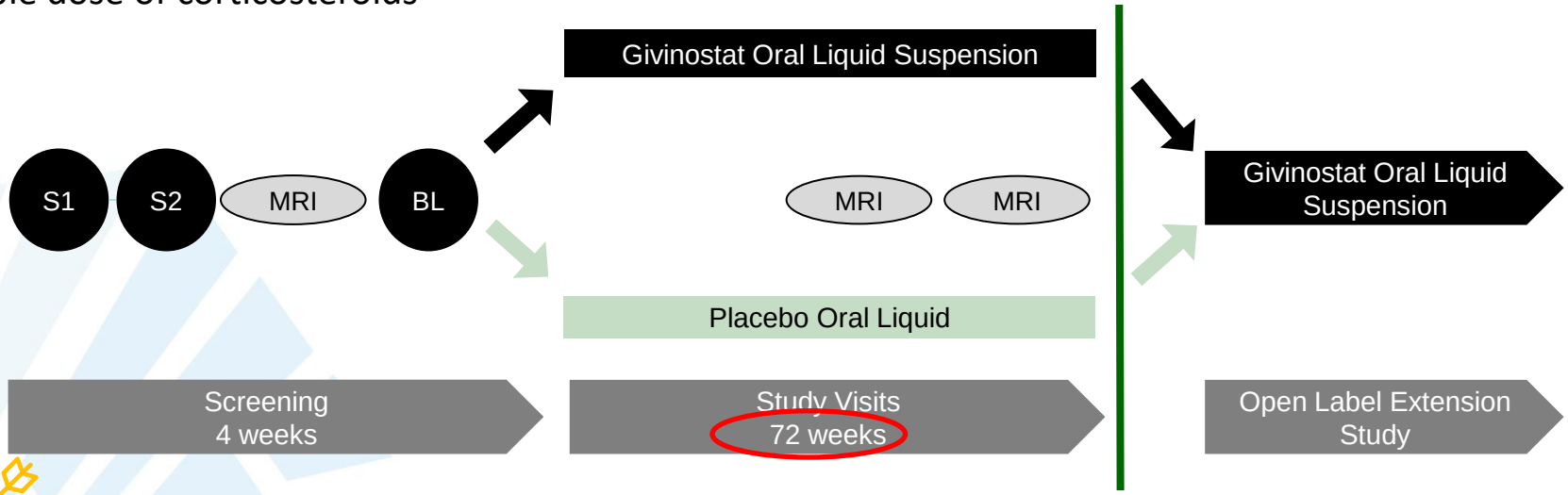
- 3-fold mechanism of action:
  - ✓ anti-inflammatory
  - ✓ anti-fibrotic and anti-adipogenesis
  - ✓ muscle recovery

Givinostat - Duvyzat®



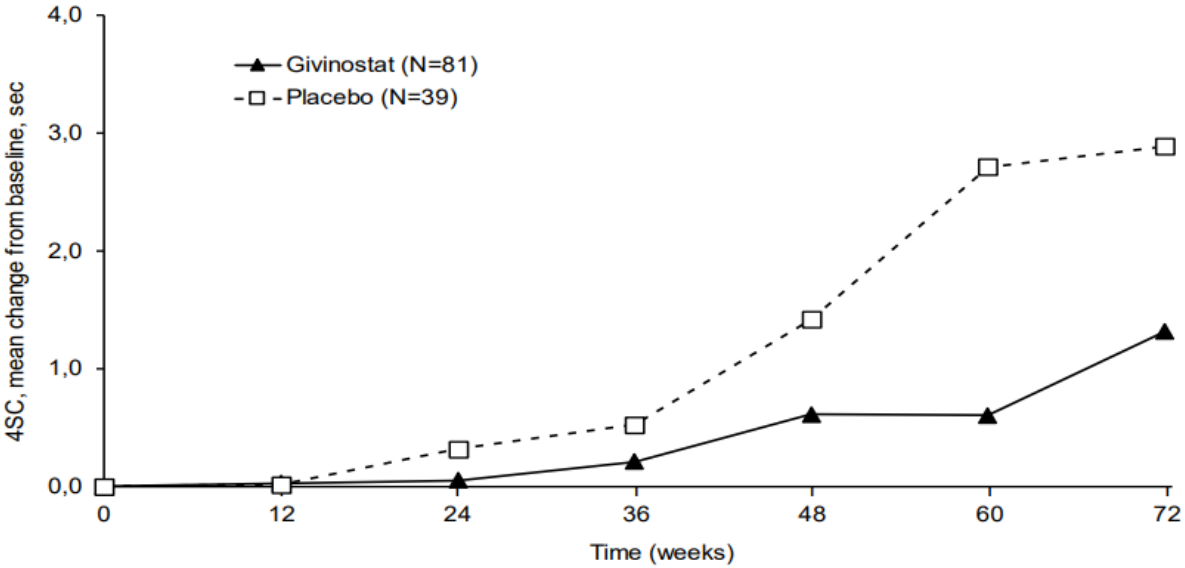
Givinostat – EPIDYS study

- 179 ambulant DMD boys, ≥6 years
- phase 3 - 18 months
- 2:1 randomized, double-blind, placebo-controlled
- stable dose of corticosteroids



Primary Objective:
Givinostat preserves muscle mass and delays disease progression

Givinostat – EPIDYS study



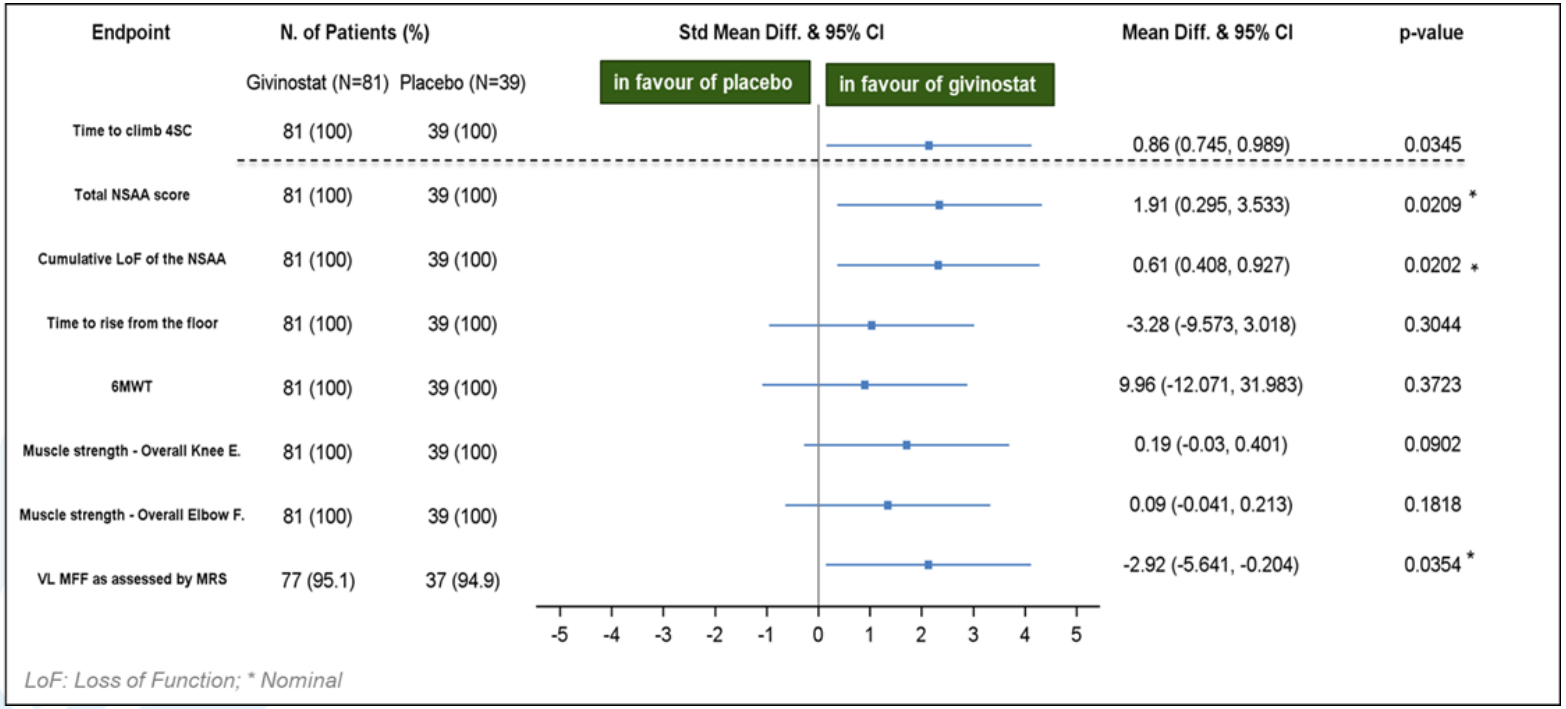
Mean change from baseline(95% CI), sec

Givinostat	0·03 (–0·13, 0·19)	0·05 (–0·10, 0·21)	0·21 (0·01, 0·41)	0·61 (0·32, 0·91)	0·60 (0·26, 0·95)	1·31 (0·73, 1·90)
Placebo	0·18 (–0·19, 0·23)	0·32 (–0·00, 0·64)	0·53 (0·07, 0·98)	1·42 (0·34, 2·49)	2·71 (0·45, 4·98)	2·89 (0·60, 5·18)

Givinostat significantly reduced the decline in 4SC compared to placebo

SMpC Givinostat; Mercuri et al. *Lancet Neurol.* 2024

Givinostat – EPIDYS study

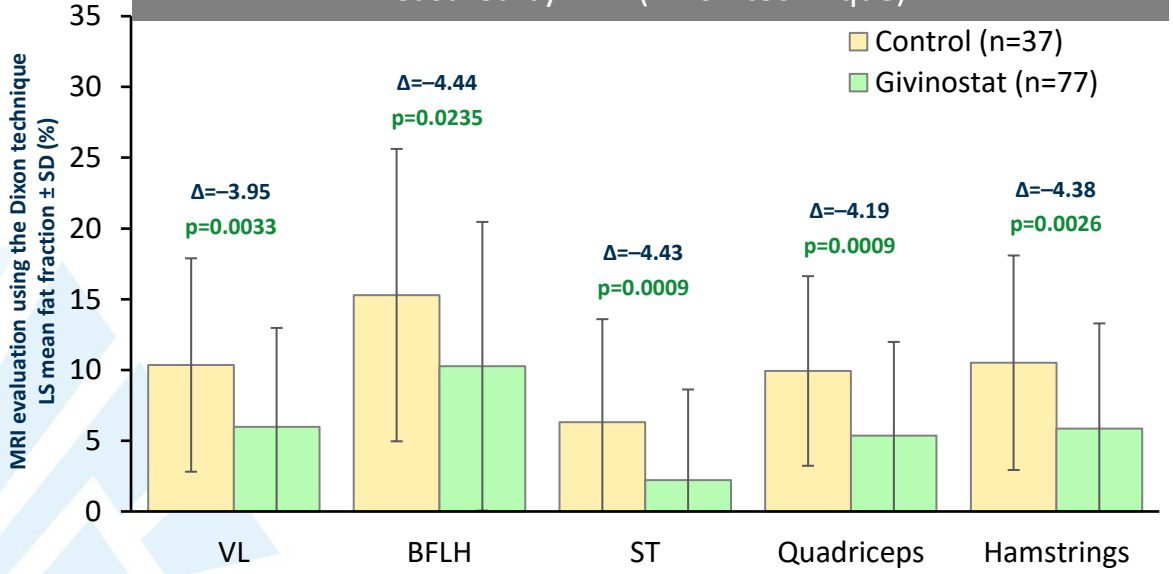


All outcomes in key secondary endpoints were in favour of givinostat
→ consistent reduction of muscle function & strength decline, and fatty infiltration over time

SMpC Givinostat; Mercuri et al. *Lancet Neurol.* 2024

Givinostat – EPIDYS study

Fat fraction in quadriceps and hamstring muscles, measured by MRI (Dixon technique)[1,2]



Givinostat reduced new fat infiltration in all muscle groups important for ambulation

1. Vandenborne K, et al. Oral presentation at Muscular Dystrophy Association Clinical & Scientific Conference; 19–22 March 2023; Dallas, TX, USA.
2. Mohanty M, et al. Neuromuscular Disorders 2023; 33:Suppl 1:S79 (Poster P127).

Adapted from slide from Italfarmaco

Givinostat - Duvyzat® in Belgium

- Good safety profile
- Very common (≥1/10) drug-related AE:
  - diarrhoea, vomiting
  - thrombocytopenia
  - pyrexia
  - hypertriglyceridemia
  - arthralgia
- AEs are monitorable and manageable with dose adjustments

Givinostat - Duvyzat® in Belgium

- EMA conditional approval 04/2025 → marketing authorisation 06/2025
- **Compassionate Use Programme (CUP)**

Patient Inclusion Criteria:

The program will start in EPIDYS sites (24) in Europe (including 2 sites in Belgium), with the possibility to expand to other certified DMD centers within the EPIDYS clinical trial country.

Subjects must meet all the following inclusion criteria:

- Confirmed diagnosis of DMD
- Age 6 years and older, ambulant
- On stable corticosteroid for at least 6 months prior to start the treatment,
- Time to stand up in less than 10s
- Patient is not a candidate for any licensed and reimbursed or standard-of-care pharmacological DMD therapy option -except for Corticosteroids- available at the time of inclusion.
- Patient is not eligible for any ongoing clinical trial for DMD
- Patient must be willing to use adequate contraception
- Health Care Insurance and Patient residency in respective country

Patient Exclusion Criteria

- Patient registered for another CUP.
- Use of any current DMD investigational drug
- Patient is participating in any ongoing givinostat clinical trial.
- Patient is participating in an ongoing other clinical trial.
- Have platelets count, at < Lower Limit of Normal (LLN)
- Have Triglycerides > 300 mg/dL (3.42 mmol/L) in fasting condition.
- Patients who are at an increased risk for ventricular arrhythmias / concomitant use with other drugs that prolong the QTc interval
- Symptomatic cardiomyopathy or heart failure and/or left ventricular ejection fraction <45%
- Have any hypersensitivity to the components of the CUP medication.
- Have a sorbitol intolerance or sorbitol malabsorption or have the hereditary form of fructose intolerance.

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- Compassionate Use Programme (CUP)
- **ULYSSES study** (UZ Leuven)
  - ≥9 to <18 years
  - Non-ambulant
  - PUL entry score 3-6
  - Stable corticosteroids ≥6 months

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- Compassionate Use Programme (CUP)
- ULYSSES study (UZ Leuven)
  - ≥9 to <18 years
  - Non-ambulant
  - PUL entry score 3-6
  - Stable corticosteroids ≥6 months
- **Study in younger DMD boys** (HUDERF)
  - ≥2 to <6 years
  - Stable corticosteroids ≥3 months OR not starting corticosteroids in first 48 weeks of study

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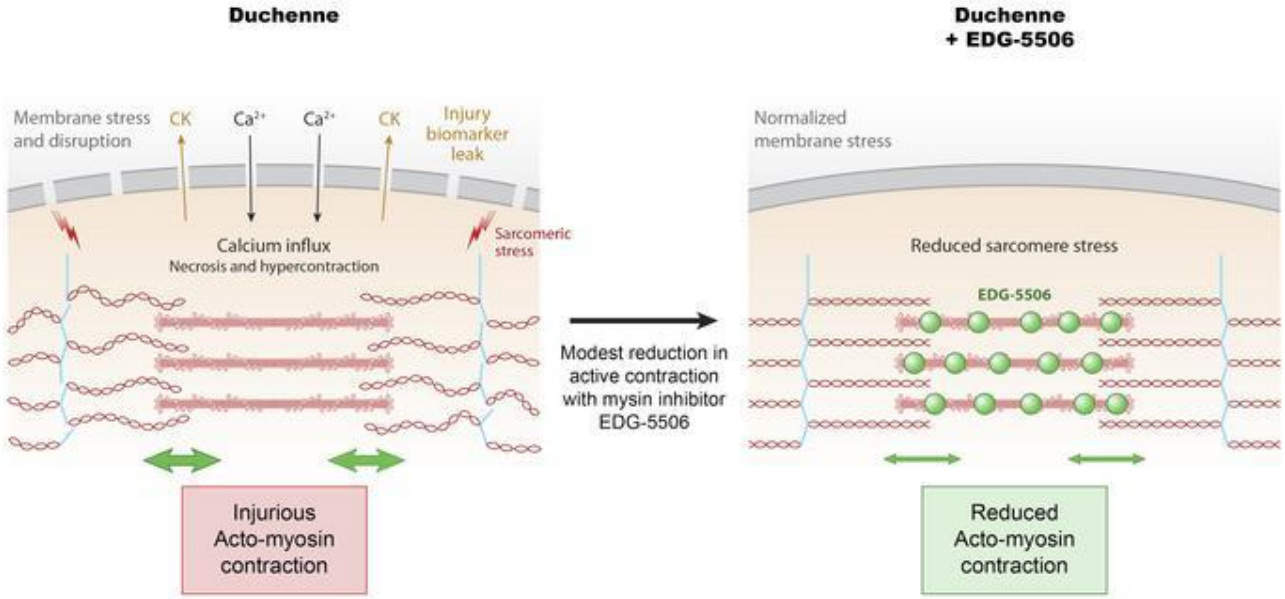
EDG-5506/Sevasemtem (Edgewise Therapeutics)

- Oral small molecule, once daily
- Inhibitor of fast skeletal muscle myosin → reduces contraction-induced muscle fiber damage → **muscle fiber protection**



Russell et al. *JCI* 2023

EDG-5506/Sevasemtem (Edgewise Therapeutics)

DUCHENNE MUSCULAR DYSTROPHY

LYNX

A Phase 2 Trial of sevasemten in children with Duchenne

SEE THE STUDY DETAILS

Status
Active, not recruiting

Eligibility Criteria
Children with Duchenne aged 4 to 9 years

COLLAPSE

LYNX is a placebo-controlled trial to assess the effect of different dose levels of sevasemten over 12 weeks on safety, pharmacokinetics and biomarkers of muscle damage. Study participants include boys with Duchenne on stable corticosteroids as well as a single cohort of boys not currently treated with corticosteroids. After the initial 12 weeks, LYNX participants will then continue on open-label sevasemten for an additional 21 months to gain further insights into safety and functional measures.

DUCHENNE MUSCULAR DYSTROPHY

FOX

A Phase 2 trial of sevasemten in children and adolescents with Duchenne previously treated with gene therapy

SEE THE STUDY DETAILS

Status
Active, not recruiting

Eligibility Criteria
Individuals aged 6 to 17 years with Duchenne previously treated with gene therapy

EXPAND

Promising results in BMD, trials in DMD ongoing

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Ifetroban: for DMD cardiomyopathy

- Selective antagonist of thromboxane-prostanoid receptor (TPr)
- Aims to block vasoconstriction, inflammation and fibrosis in cardiac tissue

  → preserve  function in DMD
- FIGHT-DMD trial (phase 2):
  - 41 DMD patients (placebo – low dose – high dose)
  - 12 months
  - Change in LVEF in high dose group: +1.8% ↔ placebo: -1.5%
  - Well-tolerated, no serious drug-related events

What to remember about small molecules for DMD…

- **Givinostat** consistently reduces muscle function, strength decline and fatty infiltration over time
- EDG-5506/**Sevasemtem** trials ongoing (promising in BMD)
- **Ifetroban** shows promising early data as treatment for DMD cardiomyopathy

NMRC Kinderen UZ Leuven

Kan GO!

Fonds voor Kinderen en Adolescenten met Neuromusculaire aandoeningen

KU LEUVEN

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