Diagnostic and therapeutic advances in genetic neuromuscular diseases

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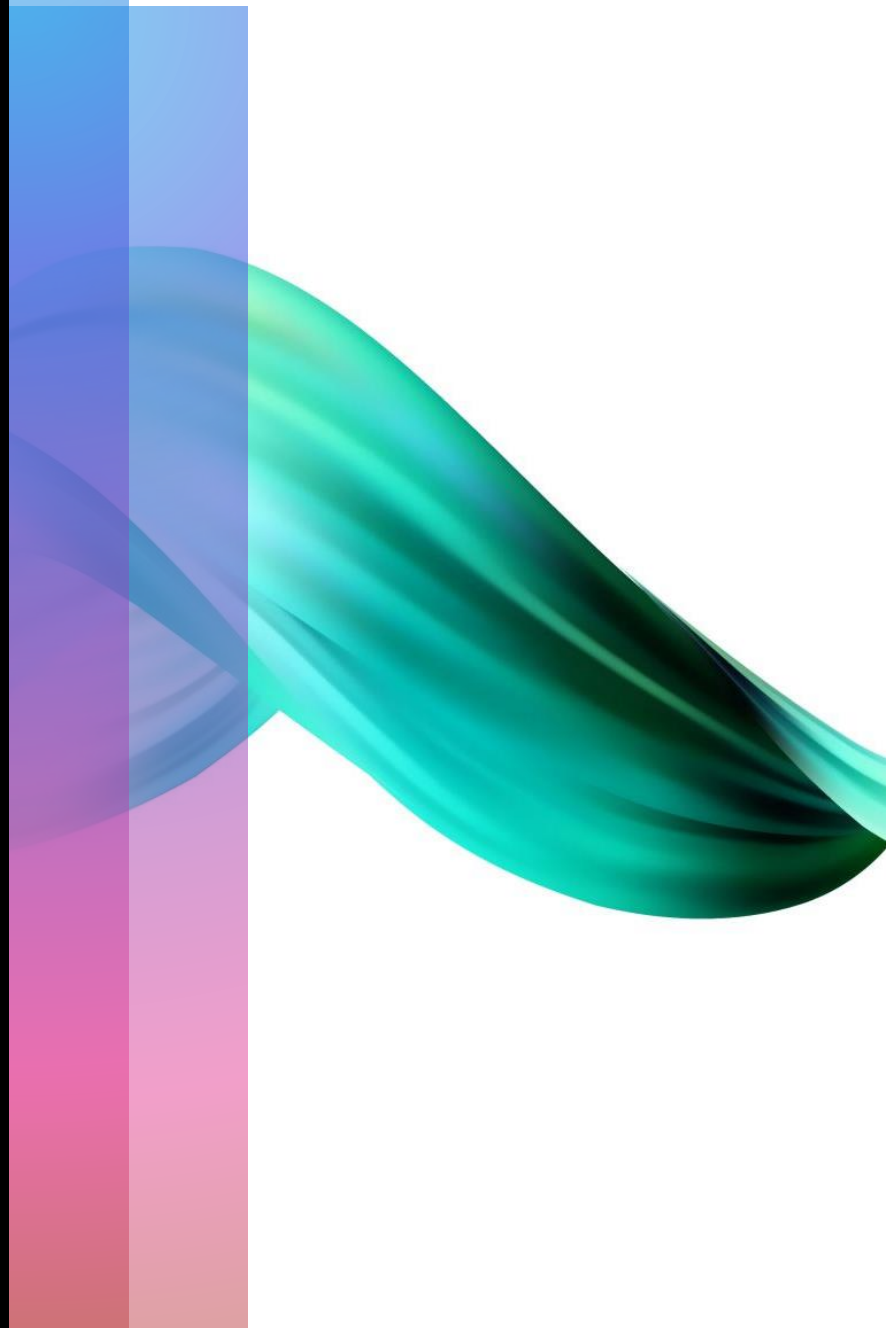
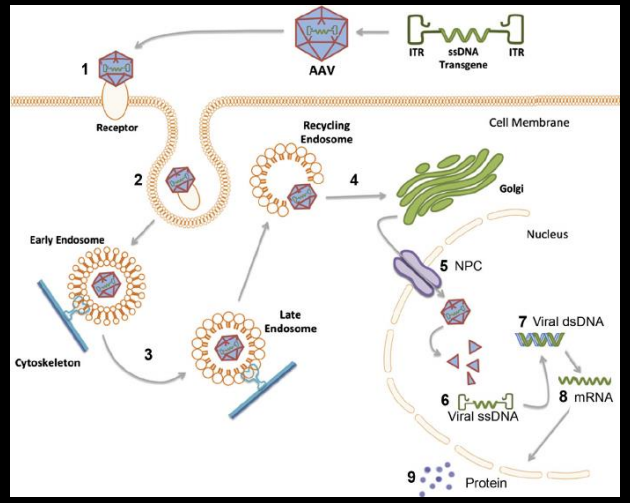
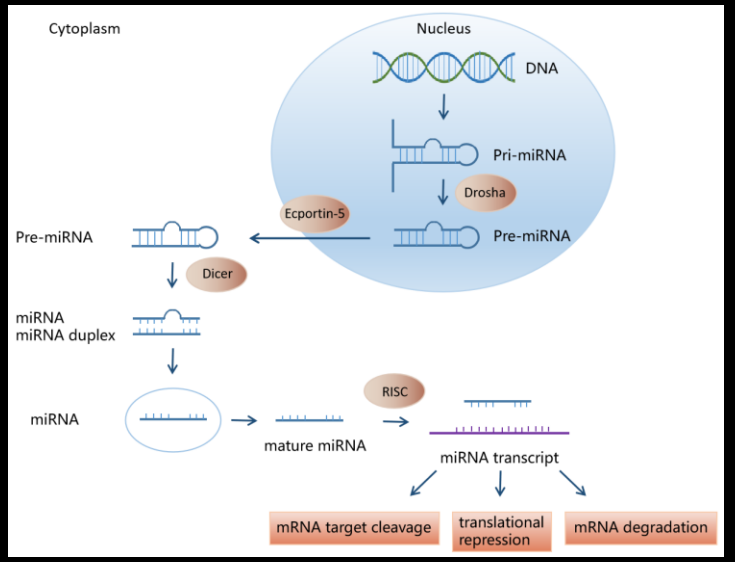


Genetic testing in neuromuscular disease

- Reasons for genetic testing
- Picking the right test
  - Disorders not detected by sequencing panels; repeat expansions, large deletions, duplications
    - Usually have recognizable phenotype: Duchenne, myotonic dystrophy, facio-scapulohumeral dystrophy, Friedreich ataxia, CMT type 1, HNPP, C9Orf72 ALS, Kennedy's, OPMD
- "Limb girdle" and other atypical presentations need sequencing panels that assess several genes
  - Actionable items
  - VUS interpretation

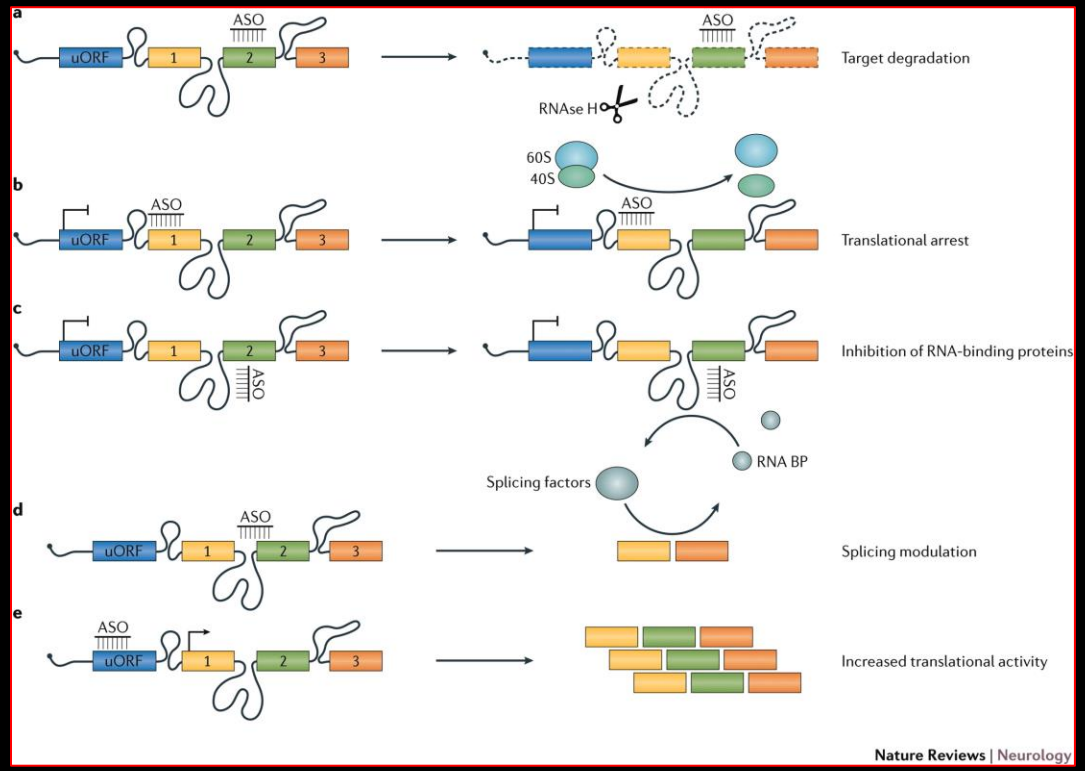
Viral vectors

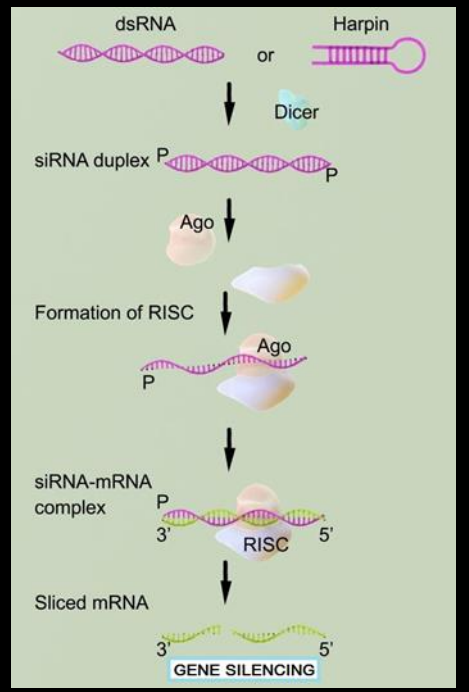




miRNAs

Antisense oligos

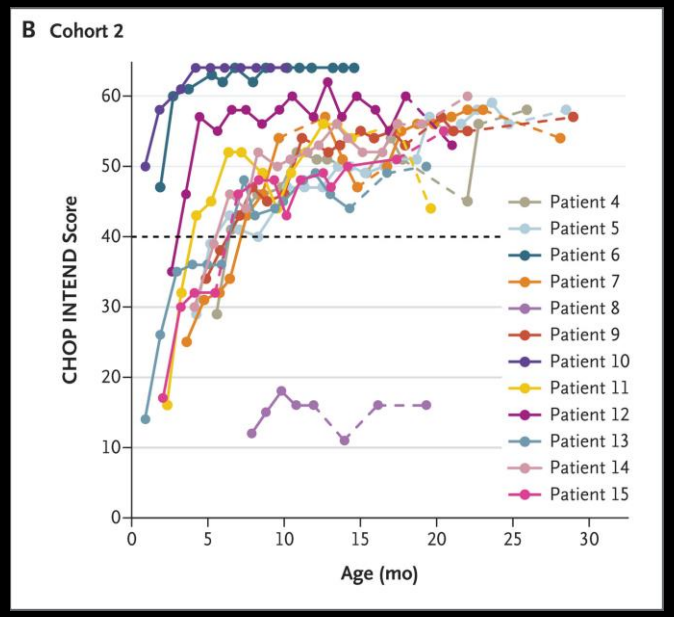




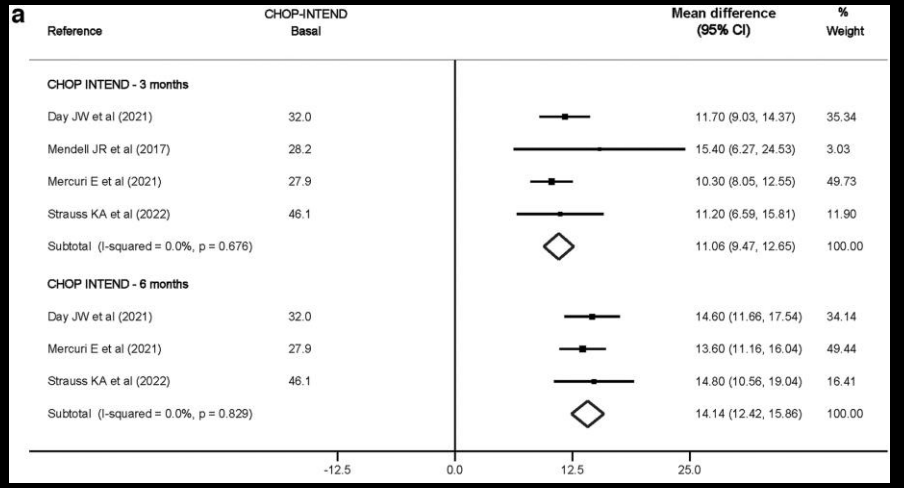
Si and shRNAs

SMA: Gene therapy

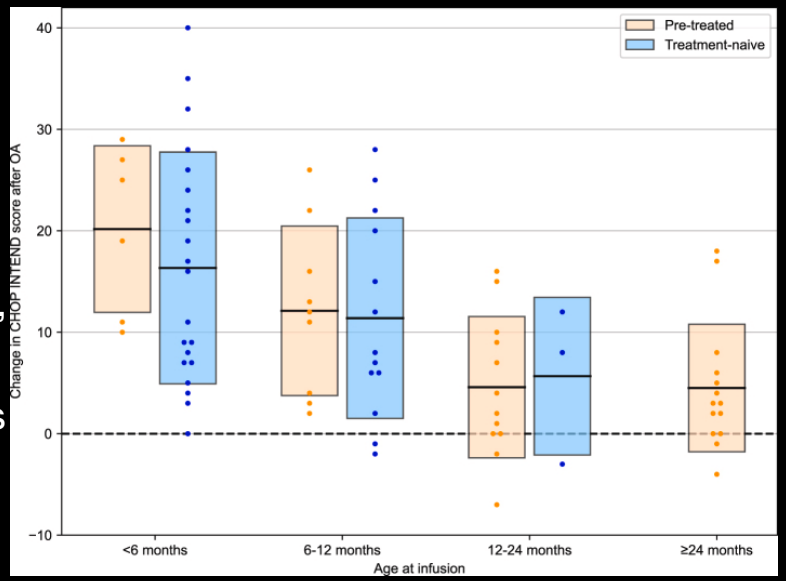
- Onasemnogene abeparvovec: AAV 9 based gene replacement delivered by a single IV injection
- START, STRIVE and SPRINT trials in SMA infants >6 mos, < 6 mos and presymptomatic
- All survived for > 5 years with no vent support and improved motor milestones
- Approved for 5q SMA < 2 years (FDA); SMA type 1 up to 3 SMN 2 copies and weight <21 Kg (EMA)
- Dose 1.1 X 10E14 vg/kg, IV over 60 minutes, steroids
- AEs: elevated LFT, vomiting, platelet issues



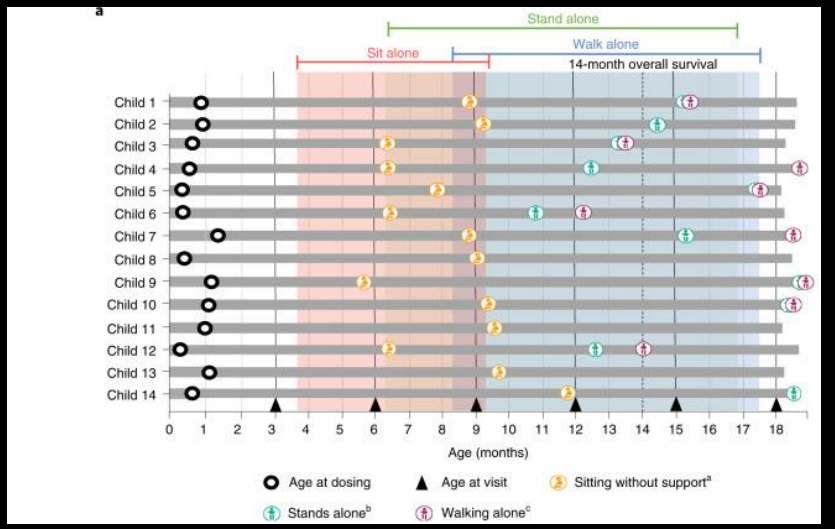
Mendell 2017



Pascual-Morena 2023



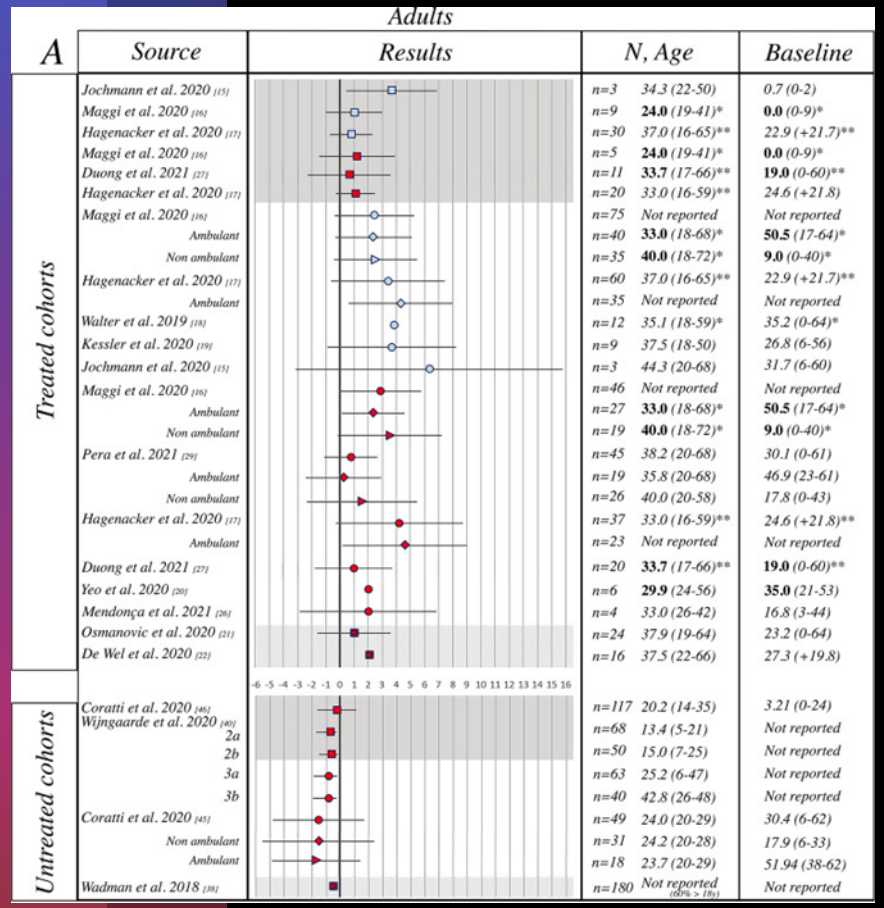
Gowda 2023

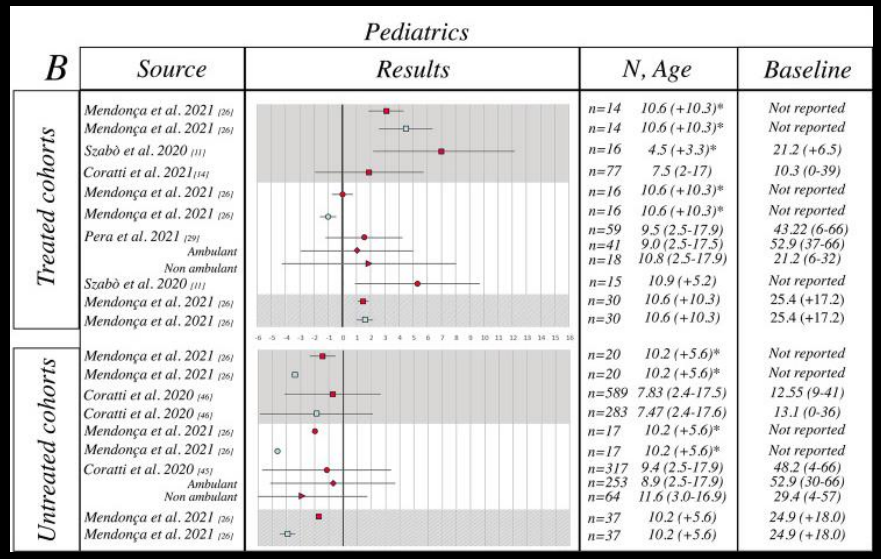


Strauss 2022

SMA: splice modulation

- Nusinersen: ASO that modulates SMA 2 splicing
  - Trials in early and late onset SMA with significant survival with no vent support and achievement of motor milestones
  - Continued stability in OLE
  - Effective with presymptomatic delivery
  - IT delivery, monitor coag function and renal function
- Risdiplam, oral molecule that modulates SMN 2 splicing
  - Trials showing similar results
  - Oral delivery
- Both approved for all ages





SMA Best Practice guidelines (Neurology Clinical Practice 2024)

- Diagnosis: For symptomatic SMA patients need to follow standard process, based on clinical scenario, most have homozygous deletions of exon 7/8, assess SMN 2 copy number
- SMA new-born screening is essential but is in varied stages of development across the world; often uses qPCR multiplexed to SCID testing
- SMA diagnosed by NBS requires SMN 2 copy number estimation, current motor function, age at onset and severity
- US consensus: urgent treatment needed for all including SMN copy number of 4
- Estimation of current motor function essential, better motor function leads to better response but may be difficult to distinguish symptomatic vs presymptomatic
- Age at symptoms onset and severity of symptoms influences response
- Requirements for NBS: how to notify family and coordinate initial visit, process to prevent delays in treatment, process to refer to SMA specialists, collaborative team, efficient process for approval
- Requirements for NBS testing labs
- Requirements for SMA SCCs: prompt evaluations, confirmatory testing, other necessary labs (nAbs, LFT etc) education and resources for care givers, coordination with team and primary care providers

Duchenne muscular dystrophy

Exon skipping

Splice switching ASOs that restore reading frame

Eteplirsen (exon 51), Golodirsen, Viltolarsen (exon 53) and Casimersen (exon 45)

Accelerated approval based on increased dystrophin expression from 0.9% to 5.8%

Need for further confirmation

Long term follow up and comparison to natural history cohorts show potential for continued benefit

Givinostat

HDAC inhibitor targeting global HDAC activation in DMD

Single trial with improvement in primary outcome measure (4 step climb; decline of 1.25 vs 3.03 sec)

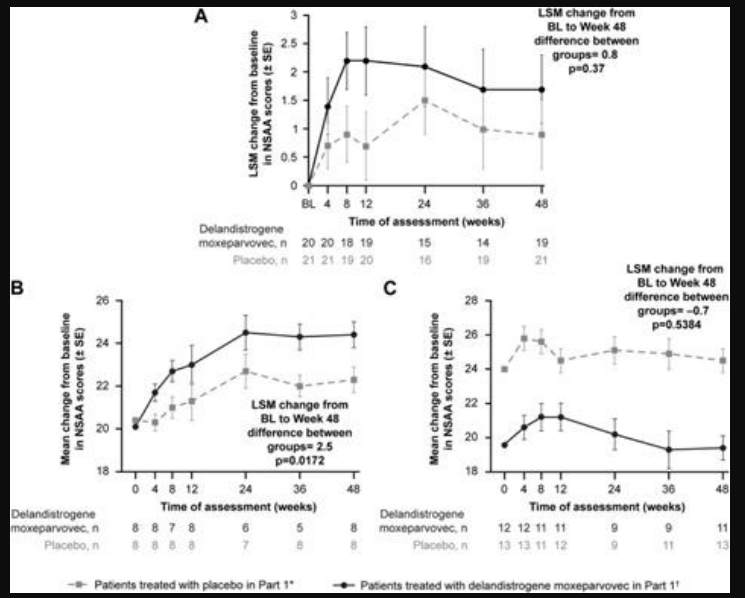
Monitor platelets and triglycerides

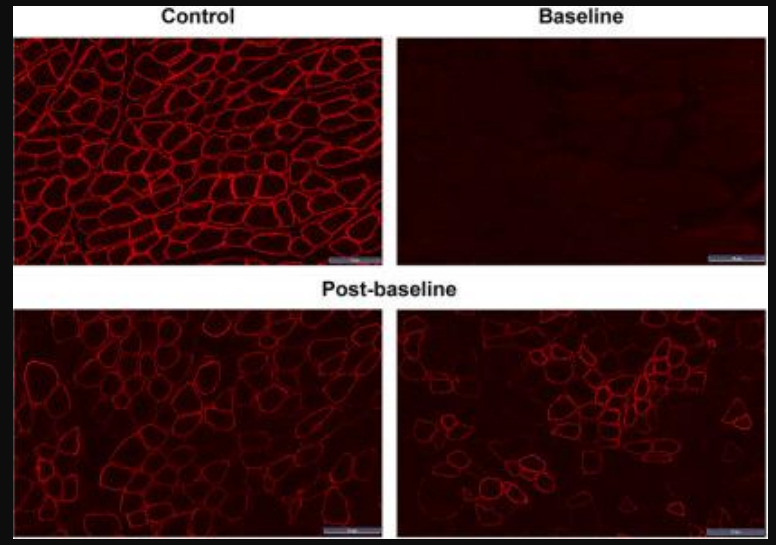
Vamolorone

Dissociative corticosteroid with fewer bone effects

DMD Gene therapy

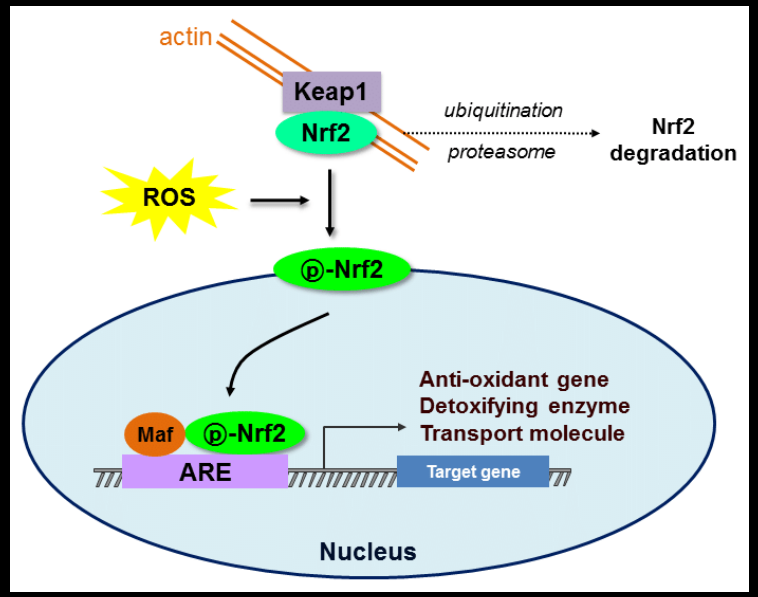
- Delandistrogene moxeparvovec, AAVrh74 based delivery of microdystrophin
- Accelerated approval in June 2023 based on dystrophin expression in muscle after delivery to ambulatory boys 4 to 8 yrs, 54.2% after 12 weeks.
- Dose 1.33 X 10E14 vg/Kg, single IV administration
- Contraindicated with exon 8 and/or 9 deletion and elevated Ab to AAVrh74
- Concern for liver, muscle and myocardial toxicity
- AEs include vomiting, poor appetite, URIs, nausea, limb and abdominal pain
- EMBARK; phase 3, RCT (2024) did not meet primary outcome measure at week 52 but secondary endpoints favored treatment
- Traditional approval in 2024 for ambulatory DMD > 4 years and accelerated for non-ambulatory > 4 years

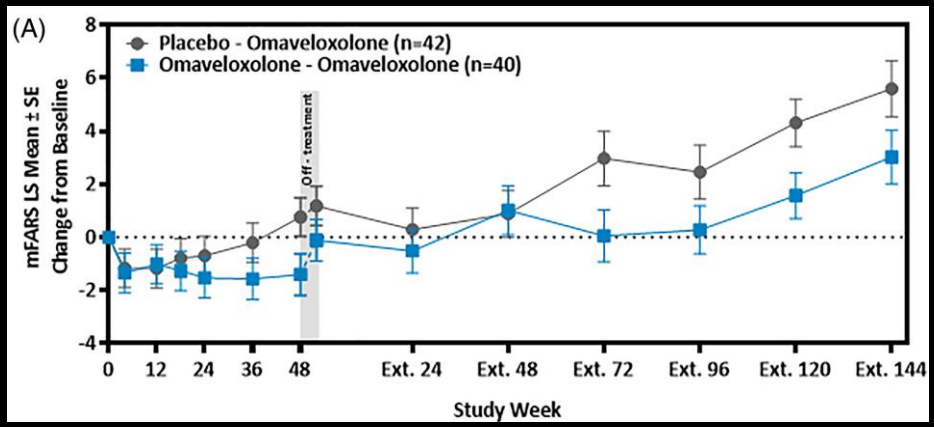


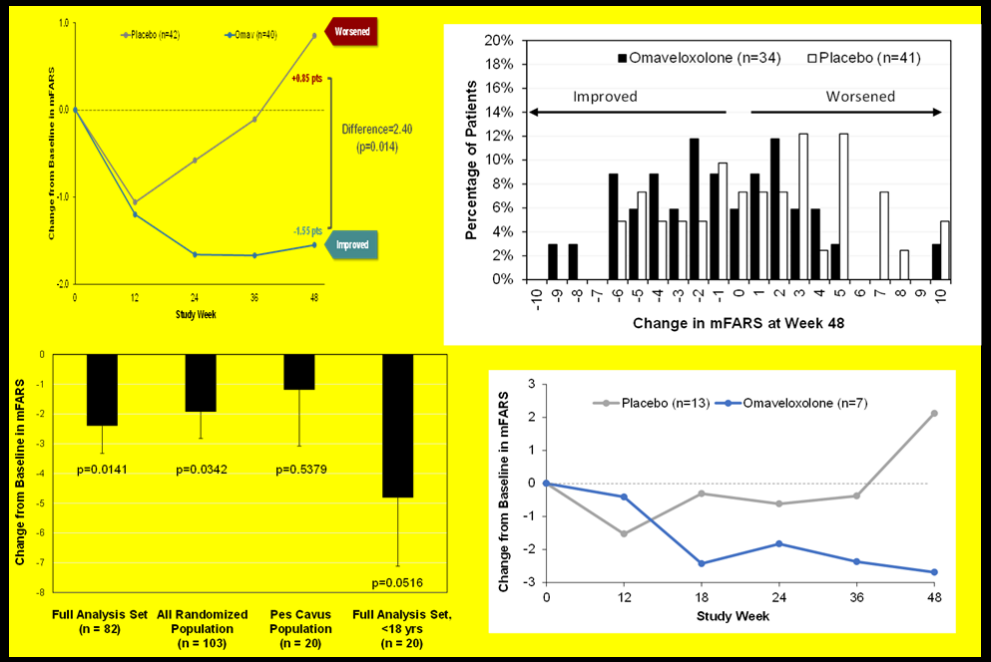


Omaveloxolone in Friedreich ataxia

- Activates impaired oxidative defense pathway mediated by Nrf 2
- RCT shows significant benefit in neurological function based on mFARS scale
- Added support from delayed start analysis and propensity matched analysis
- Tolerated well but LFT elevation was common

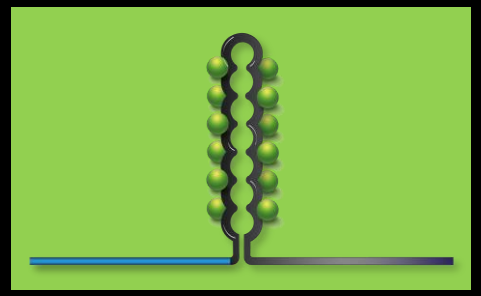


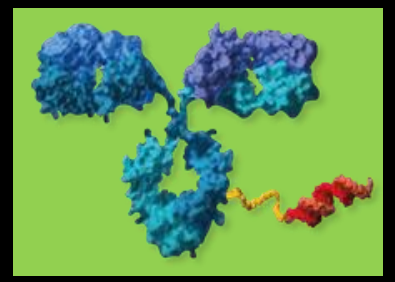


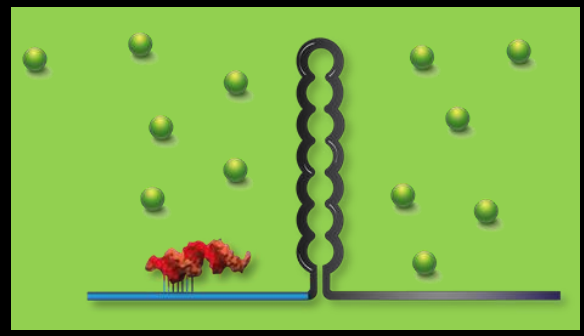


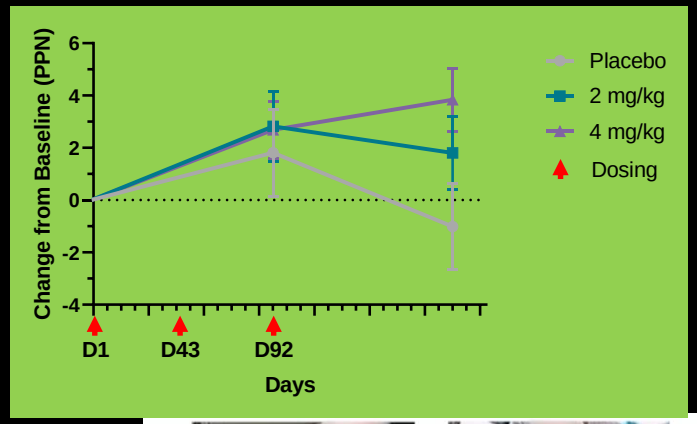
Myotonic dystrophy 1

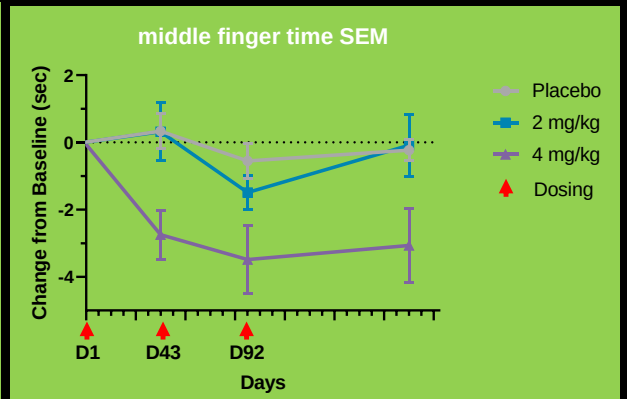
- Toxic gain of function of DMPK mRNA
- Sequesters MBNL
- Strategy: knockdown of mRNA using antibody conjugated shRNA (Avidity)

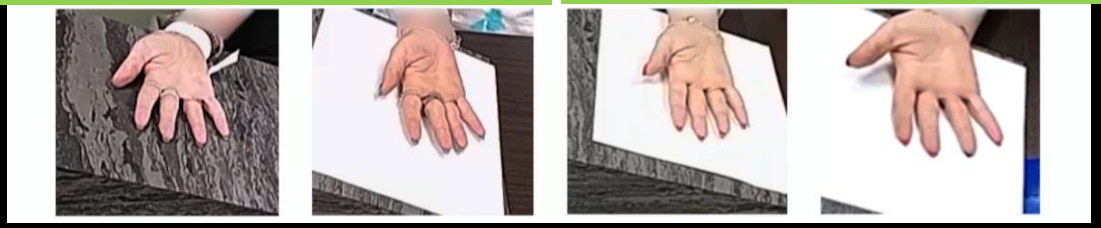












Facioscapulohumeral dystrophy

- Mutation causes aberrant expression of DUX 4
- DUX 4 drives myopathology
- Strategy: knockdown of DUX 4 mRNA using antibody conjugated shRNA