Optimization of Exon Skipping Therapies for Duchenne Muscular Dystrophy

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What is Duchenne Muscular Dystrophy?

- Fatal X-linked genetic neuromuscular disorder caused by reduction of functional dystrophin
- Affects 1 in every 3500 live male births worldwide each year; 13% of DMD is amenable to exon 51 skipping
- No approved disease-modifying drugs currently available

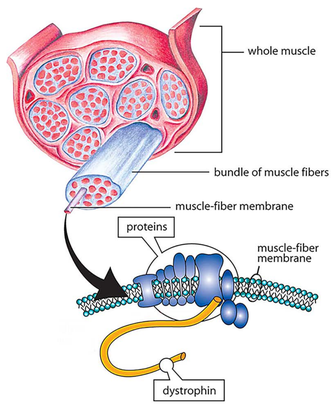
Our approach

- Partial restoration of dystrophin production is expected to result in therapeutic benefit
- Exon skipping oligonucleotide approaches enable production of functional dystrophin protein
- Our goal is improve the therapeutic index (greater efficacy, better safety) by increasing skipping efficiency and enhancing delivery to target tissues
- We are developing superior therapeutic candidates and designing robust clinical trials to effectively assess efficacy and safety

WAVE intends to initiate clinical studies for **DMD EXON 51 program** in second-half 2017

Our strategy

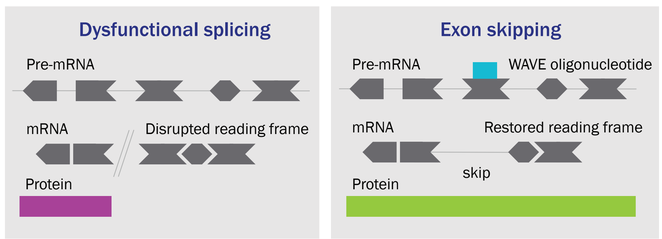
Enhanced protein restoration



Enhanced muscle delivery

At WAVE, we are developing proprietary stereopure exon skipping oligonucleotides that improve efficacy and tissue distribution compared to other investigational compounds

What is exon skipping?



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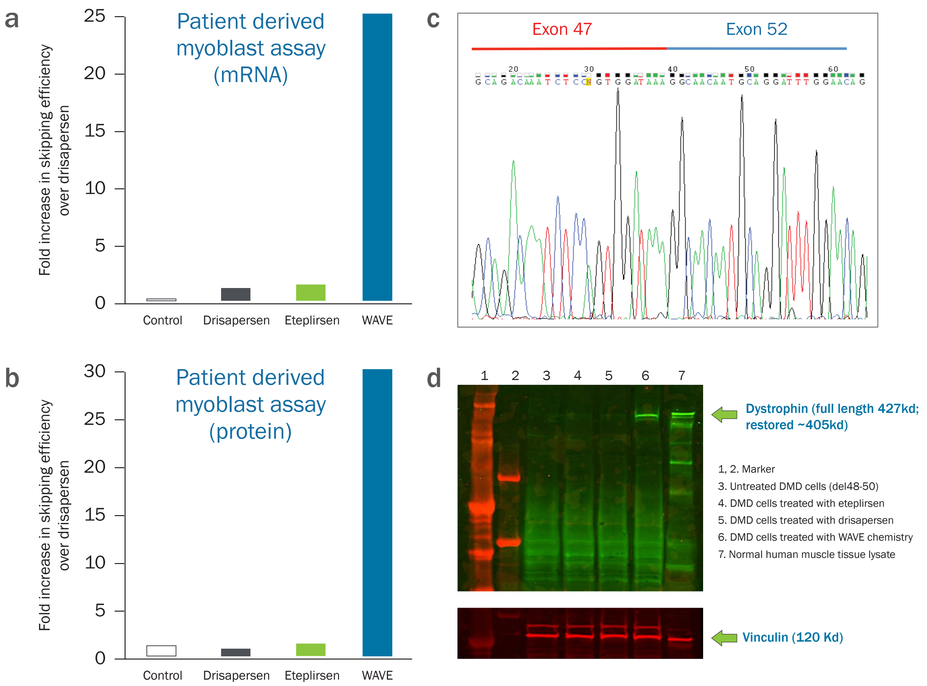
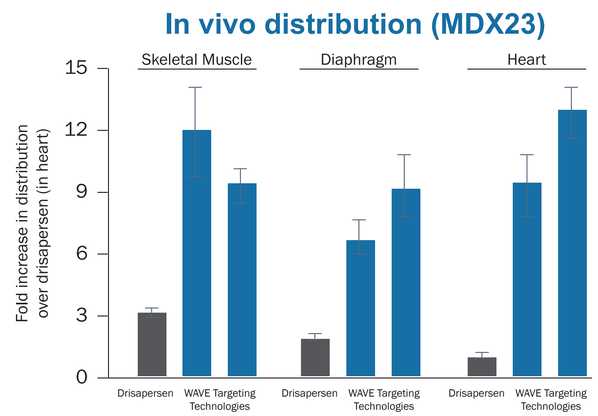
Enhanced protein restoration by WAVE chemistry



WAVE's proprietary chemistry resulted in >25-fold improvement in exon skipping as measured by quantitative Taqman assay and Western blot compared to other investigational compounds, including drisapersen and eteplirsen. Data: Free uptake at 10uM concentration of each compound with no transfection reagent, (a) measuring DMD mRNA by RT-qPCR in DMD patient-derived cells; (b) confirming precise skipping of exon 51; and (c. d) measuring DMD protein by Western Blot with anti-dystrophin (Abcam # 15277, Rb pAb). Extent of dystrophin protein restoration by WAVE chemistry was quantified to be about 25% of normal skeletal muscle tissue lysates, as compared to about 1% by drisapersen or eteplirsen.

Enhanced muscle delivery by WAVE technology

WAVE has also optimized oligonucleotide chemistry to improve delivery to various muscle tissues, in vivo in mdx exon23 mice, resulting in >10-fold increase in distribution to skeletal muscle, heart and diaphragm, compared to drisapersen. Data: Quantification of compound in key tissues following subcutaneous administration to MDX23 mice.



SUMMARY

- **WAVE chemistry enables substantial improvements in skipping efficiency (mRNA and protein) compared to other investigational compounds, including drisapersen and eteplirsen**
- **WAVE targeting technologies further increase distribution to key tissues; expected to show superior patient outcomes**

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