Target identification studies of a utrophin modulator for treatment of Duchenne Muscular Dystrophy

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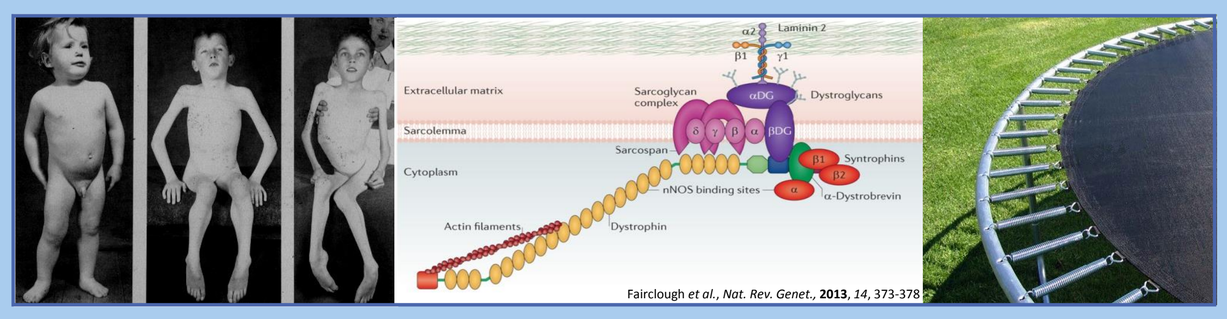
What is Duchenne Muscular Dystrophy?

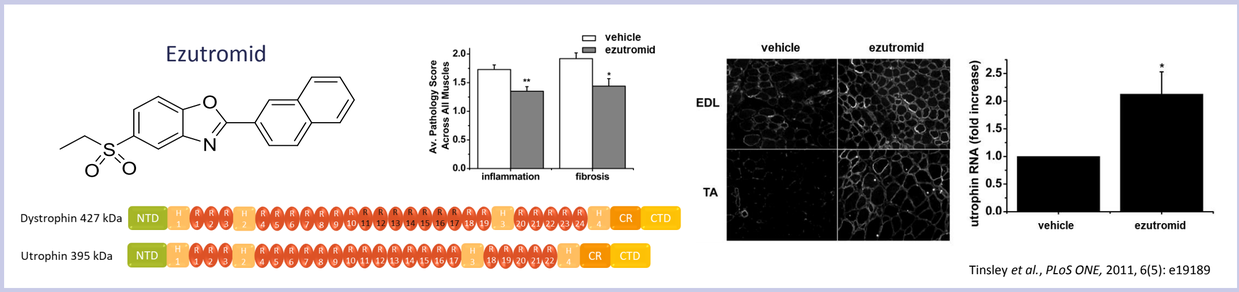
Duchenne muscular dystrophy (DMD) is a fatal muscle wasting disease which affects about 1 in 3500 boys. Muscle weakness begins at age 2-5 years and progressively affects all muscles used for movement, as well as for breathing and in the heart. DMD patients are usually confined to a wheelchair by 12 years and average life expectancy is reduced to the 30s. There is currently no cure for DMD.



DMD is caused by one of hundreds of different gene mutations which prevent patients from making the protein dystrophin. This protein acts as a shock absorber preventing muscle fibres from being damaged during contraction.

Our therapeutic strategy

Utrophin is a natural analogue of dystrophin which is found in small quantities throughout our bodies. Utrophin could act as a substitute for dystrophin and increasing levels of utrophin has reversed DMD in DMD mice. Utrophin modulation offers a potential therapy which is independent of DMD patient mutation type. Our team identified ezutromid as a utrophin modulator by observing its ability to increase utrophin in DMD model cells and mice.



Ezutromid progressed to a Phase 2 clinical trial in DMD patients (Summit Therapeutics plc.). Interim 24-week data demonstrated reduced muscle fibre damage and increased levels of utrophin. However, these effects were not seen after the full 48 weeks of the trial. We want to define how ezutromid works to: (a) understand the trial results, and (b) develop new utrophin modulators.

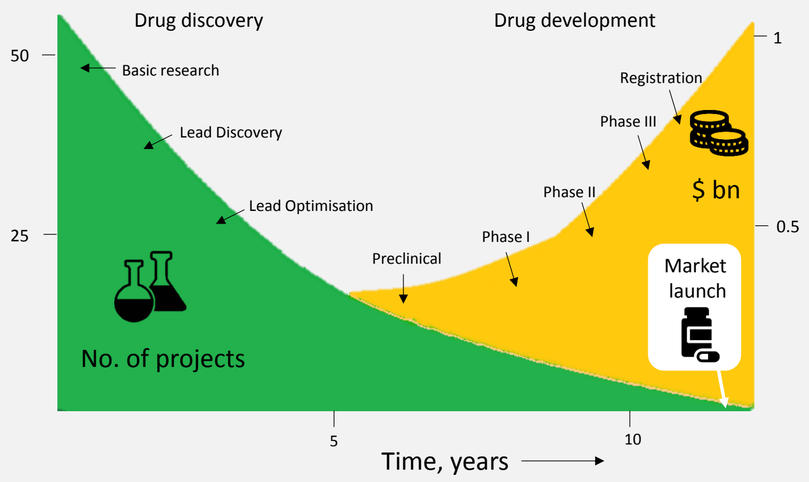
Challenges for drug discovery and development

Poor understanding of target, mechanism and diseases

Models for research fail to capture complexity of a whole disease in humans

Large population variation – no two patients the same

Unknown disease biomarkers - difficulty determining clinical success



High failure rate of long drug discovery process

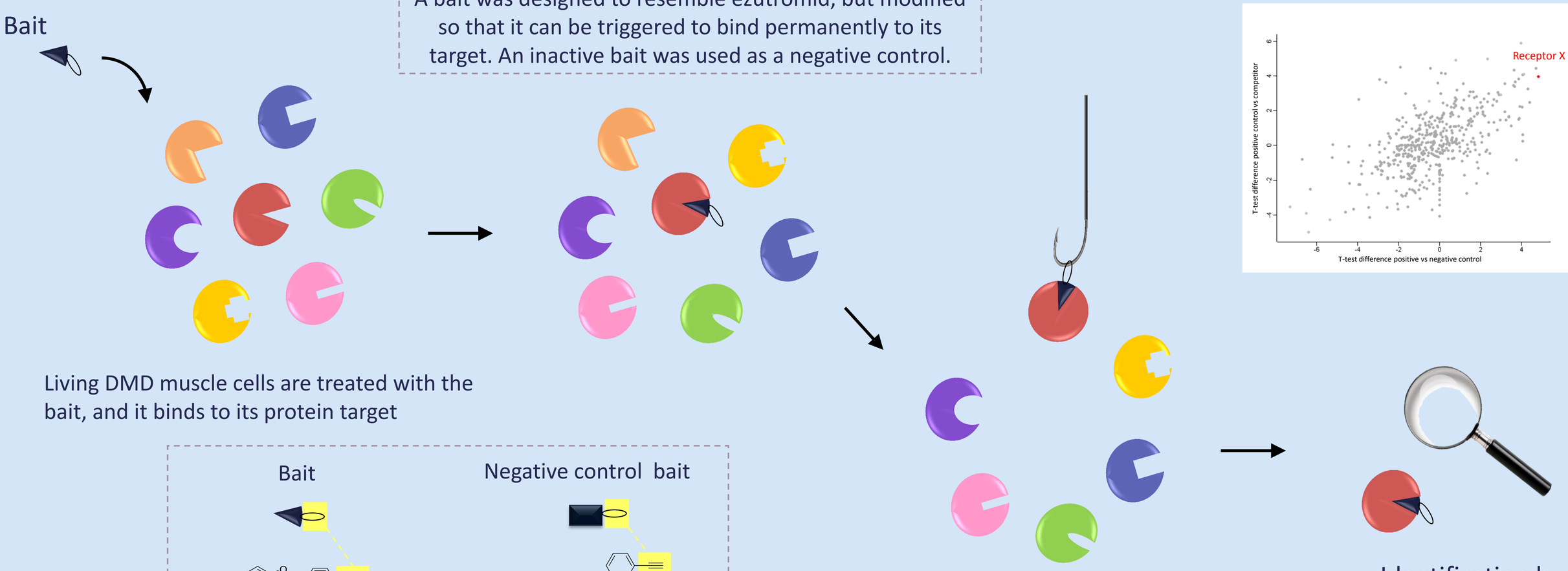
Too frequent late, expensive failure in Phase II for lack of efficacy

£ investment increasing but no more drugs to market

Improved understanding of targets is essential to bring new drugs to the clinic

Drug target hunting

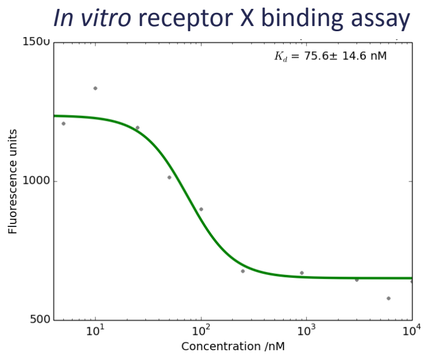
A bait was designed to resemble ezutromid, but modified so that it can be triggered to bind permanently to its target. An inactive bait was used as a negative control.



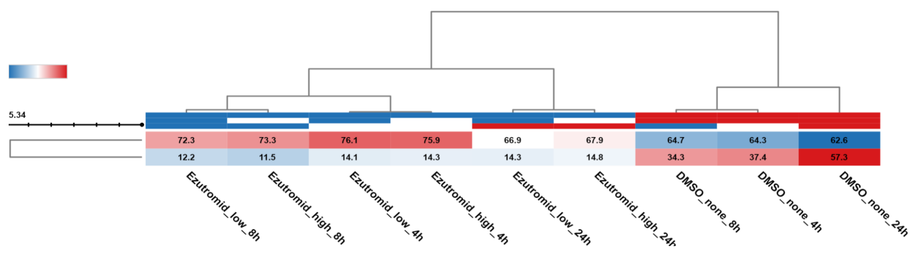
Results and conclusion

- Ezutromid's target has been identified using chemical baits and mass spectrometry
- Ezutromid binds to receptor X and changes its signalling behaviour in human and mouse DMD muscle cells
- Investigations into how receptor X increases utrophin are on-going and could pave the way to a new target for future drug discovery and a biomarker for future clinical trials.

In vitro receptor X binding assay



Receptor X increases in abundance after ezutromid treatment of human DMD muscle cells. The repressor of receptor X is decreased.



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