ACTION DUCHENNE

GIVINOSTAT & EPIGENETICS AN OVERVIEW

- What it is
- How it works
- Regulatory progress

Duchenne Treatments

The current treatments for DMD aim to slow down the degeneration of muscle tissue by preventing chronic inflammation that leads to fibrosis and the loss of muscle function.

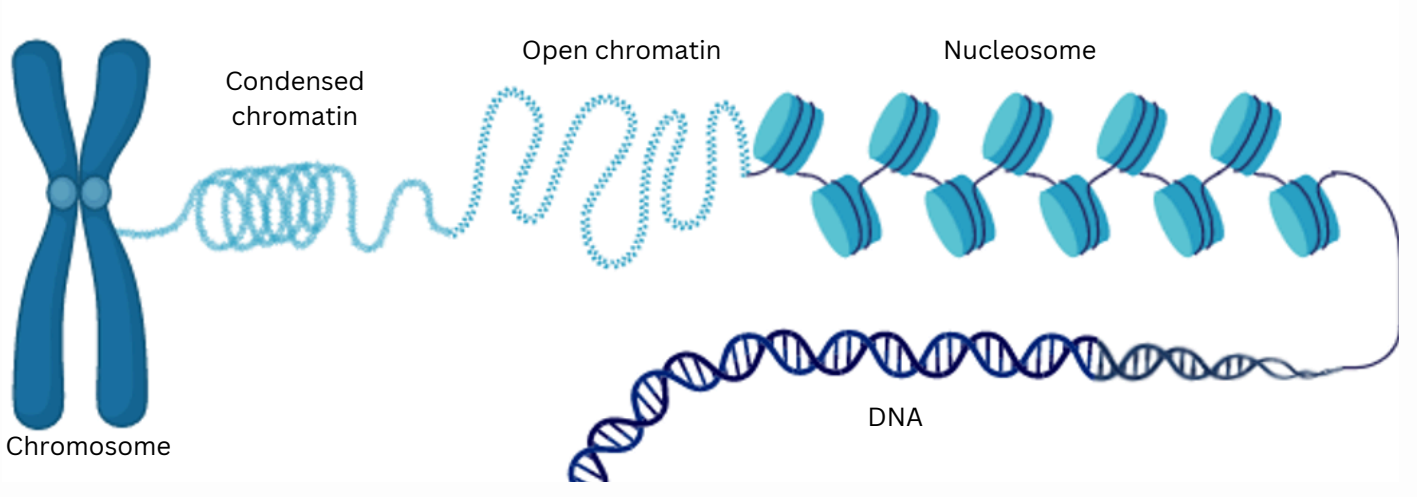
Corticosteroids are currently the most accessible treatment for DMD and act by reducing inflammation and promote muscle growth, but not without side effects, such as bone weakening, delayed puberty, and behavioural changes.

Novel treatments that can either reduce these side effects or further slow disease progression are greatly needed to improve the standards of care for patients. Treatments such as dissociative steroids, gene therapy, and gene regulatory treatments are potential candidates being considered by regulatory bodies around the world.

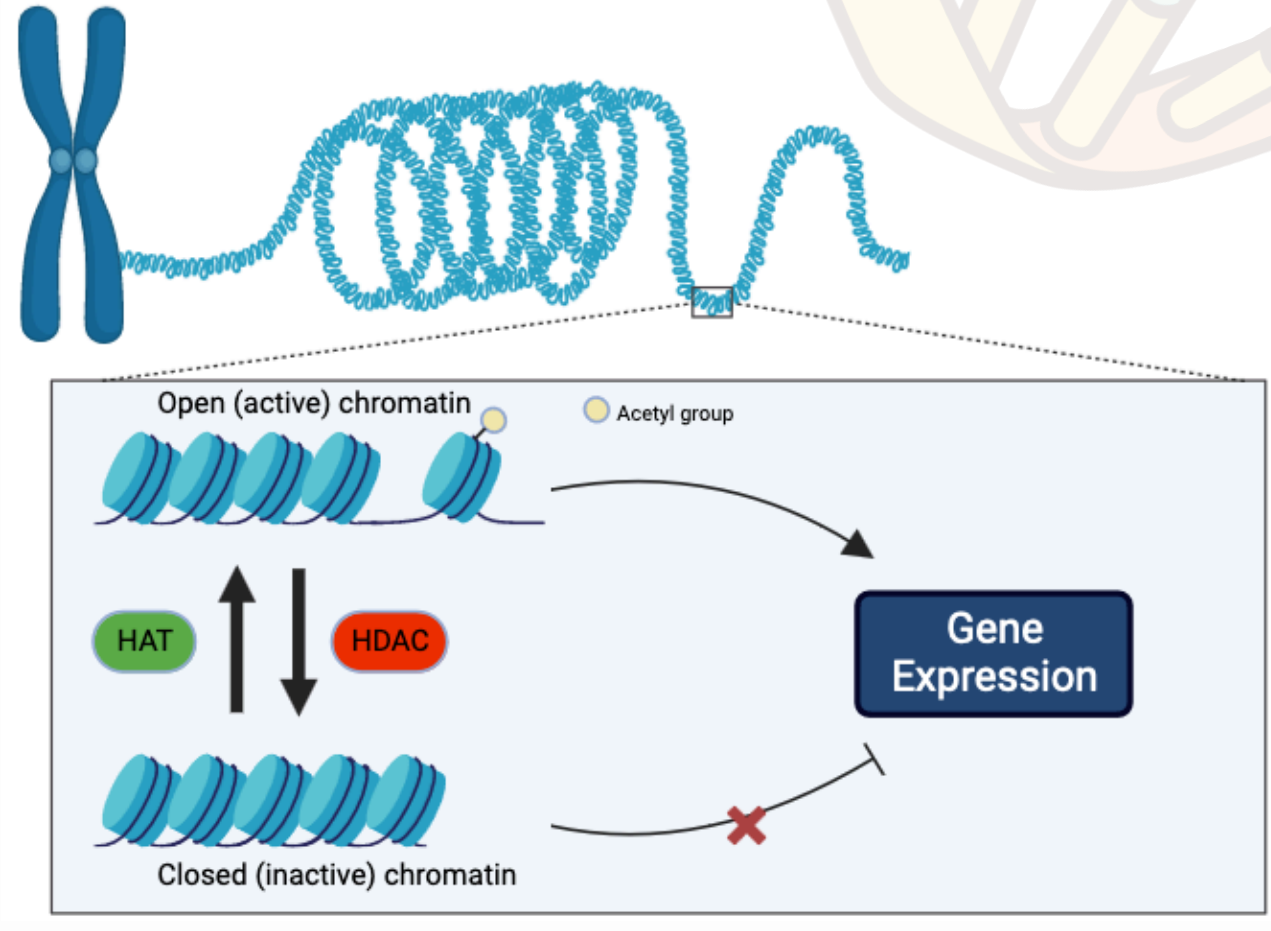
This report will focus on the potential epigenetic gene regulation treatment, that hopes to further slow disease progression, Givinostat.

Epigenetics

Epigenetics refers to gene regulation where the underlying DNA and genetic code remain unaltered. It is helpful to understand this term, as it plays an important role in understanding how novel treatments, such as Givinostat, work. Lets start with our genetic structure:



- Our **DNA** is incredibly long, much too long to fit neatly inside the cell nucleus. To solve this packaging problem, DNA wraps itself around special proteins called **histones**.
- This DNA wrapped around histones creates a structure called a **nucleosome**.
- Many nucleosomes then link together to form a fibre called **chromatin**. Imagine chromatin as a long string of beads, where each bead is a nucleosome.
- Finally, chromatin can be further coiled and condensed to form the **chromosomes**.



The open (active) or close (inactive) state determines if a gene is able to be expressed. These states are regulated by:

- **Histone acetyltransferases (HAT)** catalyze (accelerate) the transfer of an acetyl group and open up the chromatin to allow DNA to be read by cellular machinery, and thus promote gene expression.

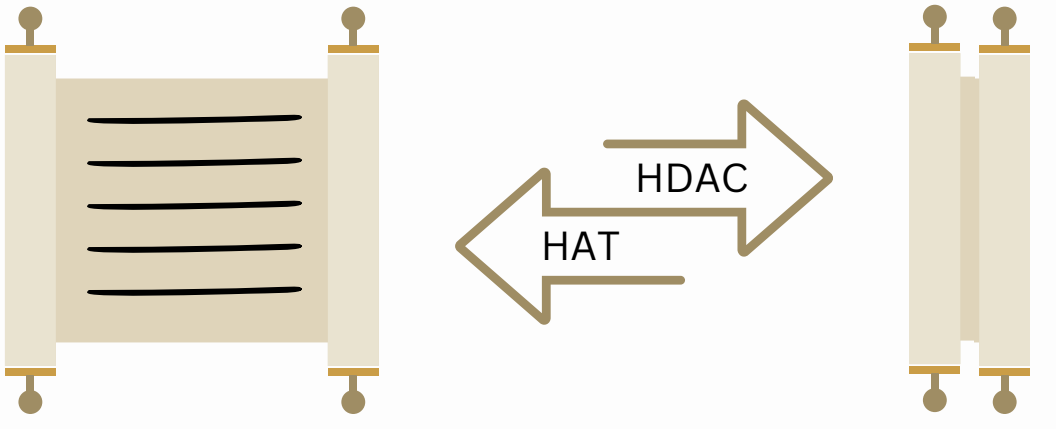
- **Histone deacetylase (HDAC)** promotes the removal of the acetyl group, causing the chromatin to stay closed preventing gene expression.

HATs and **HDACs** regulate muscle gene expression, and this interaction is **epigenetic.**

Epigenetic drugs can act as inhibitors of HDACs and HATs to control gene expression:

- HDAC inhibitors (HDACi) = increased gene expression
- HAT inhibitors (HATi) = decreased gene expression

It can be difficult to conceptualise this process so imagine your DNA as a giant instruction manual wound up like a super long scroll.



Histones act like spindles for the DNA scroll that tightly wind the DNA around themselves so it can be stored. HAT and HDAC interact with the histone spindle to wind and unwind the DNA scroll.

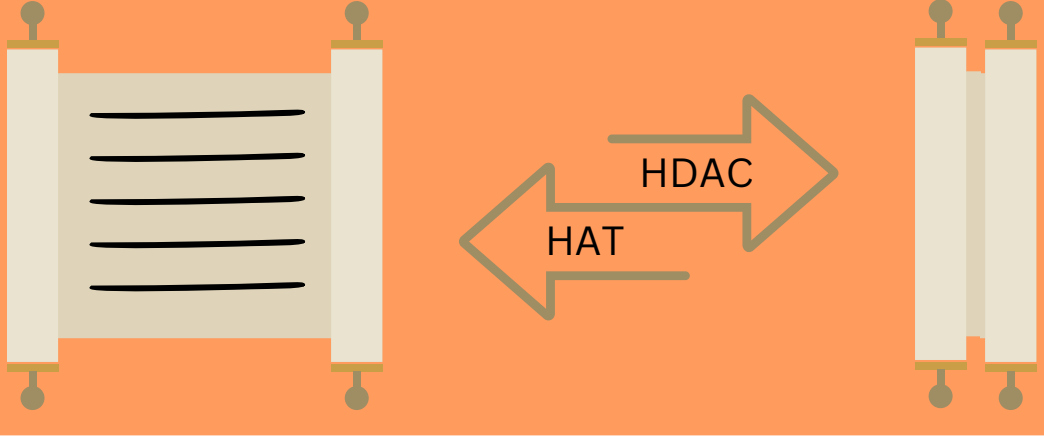
- Tightly wound scroll (Genes Off): When the histones wind the scroll very tightly, it's difficult to access the information written on it.

- Loosely wound scroll (Genes On): When the histones loosen their grip on the DNA scroll a bit. This "unwinds" the scroll partially, making the information on the scroll accessible.

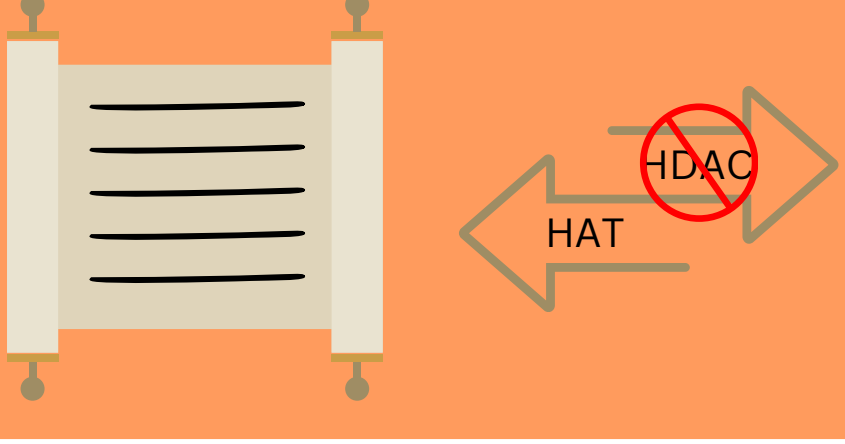
What is Givinostat?

Givinostat is a novel epigenetic HDAC inhibitor with the potential to slow disease progression. This non-steroidal, orally administered treatment is intended to treat all genetic variants of DMD. This is because it controls the unwinding apparatus of the DNA, and is not targeting specific reading frames of the DNA itself.

Lets go back to our DNA scroll:

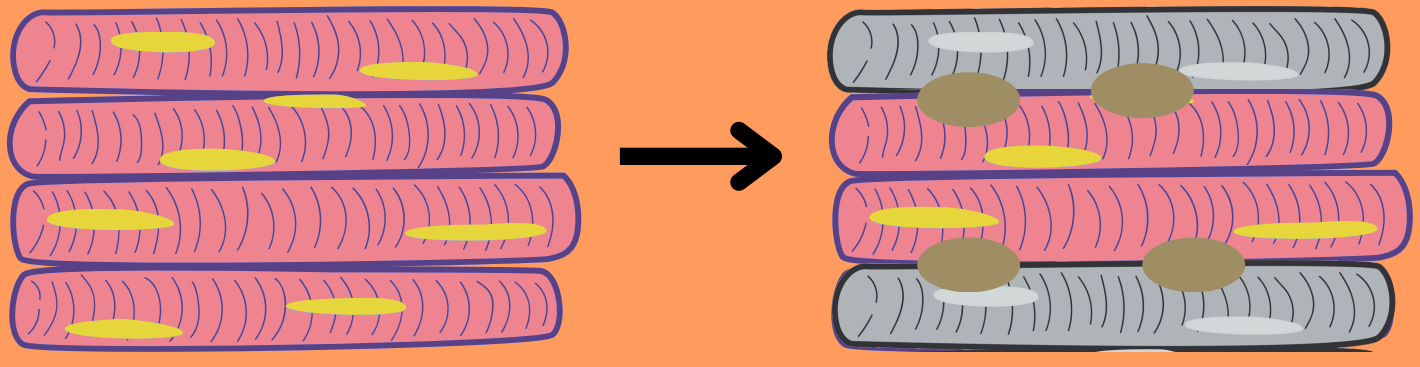


Givinostat inhibits (prevents) HDACs from windings up the DNA scroll and hiding the genetic information.

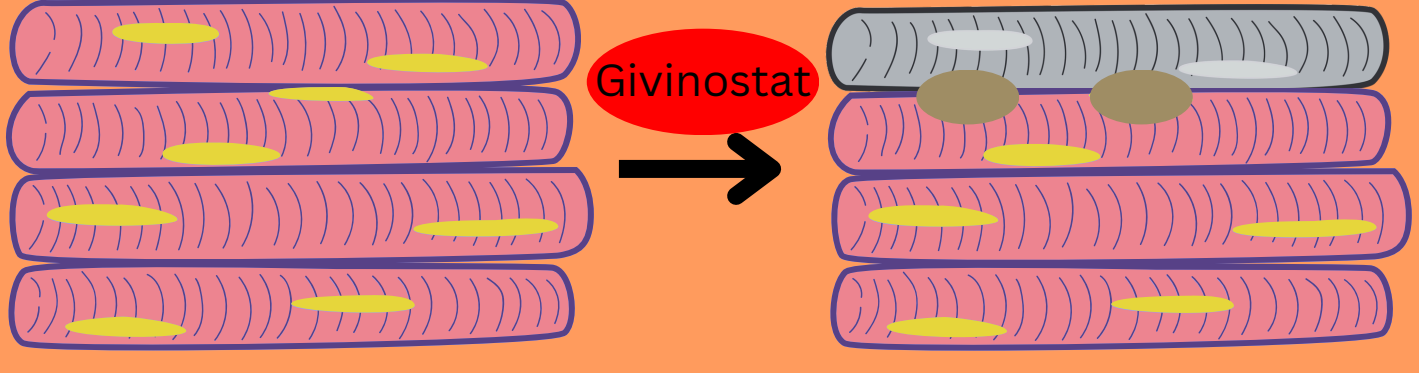


This allows for greater gene expression in muscle cells, that can lead to improvements in muscle health by preserving the tissues morphology (structure).

Givinostat & Muscles



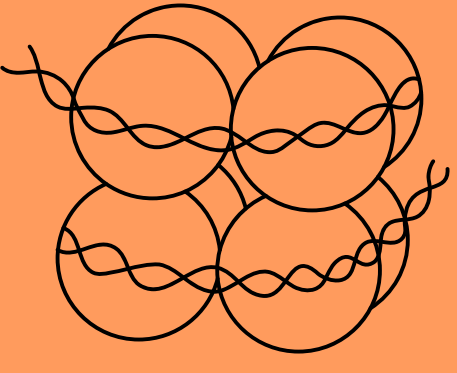
Duchenne muscular dystrophy leads to a lack of dystrophin in the muscle that causes irreversible muscle damage by setting off a chain reaction of inflammation, adipose (fat) deposits and fibrotic scar tissue build up.



Givinostat's inhibition of HDAC helps reduce this chain of reaction, while promoting the regeneration of muscle tissue. This offers the potential to improve muscle function and delay disease progression.

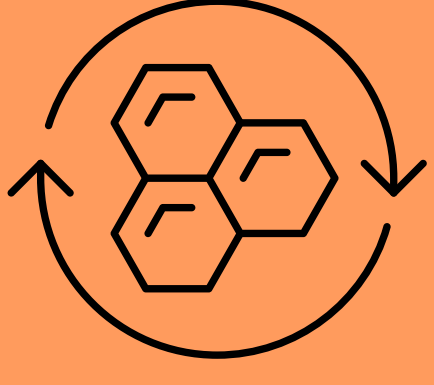
How Does Givinostat Work?

Gene Expression



In dystrophin-deficient muscle, there is a hyperactivity of HDAC which appears to contribute to the impairment of muscle repair. Givinostat helps prevent this, and allows for an increase in gene expression that promotes repair. However, the precise mechanism by which HDAC inhibitors work remains unknown.

Regeneration



This inhibition enhances the process of skeletal myogenesis (growth of muscle cells) and prevents fibro-adipogenic degeneration (adipose and fibrotic tissue build up in the muscles) delaying disease progression.

Inflammation

Givinostat helps to reduce the chronic inflammation in muscle tissue that occurs during muscle damage as a result of a lack of dystrophin.

Key Clinical Studies

Bettica et al, 2016 ‘Histological effects of givinostat in boys with Duchenne muscular dystrophy’, Neuromuscular Disorders Vol 26,Issue 10 p643–649.

- Histological analysis via biopsy to measure the muscle regenerative efficacy of Givinostat
- A Phase II trial assessing whether preclinical results translated to humans.
- Notable results showed a reduction in fibrotic tissue, increase in muscle regeneration.

Mecuri et al, 2024 ‘Safety and efficacy of givinostat in boys with Duchenne muscular dystrophy (EPIDYS): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial’, Neurology, Vol 23, Issue 4, p393-403

- A study of 179 boys aged over >6 years old across 11 countries for 72 weeks, assessing the efficacy of Givinostat in ambulant boys with concurrent use of corticosteroids.
- The study assessed physical decline using the four-stair climb.
- Notable result showed a worsening in both groups over the study period; however, the decline was significantly reduced with givinostat when compared to placebo.

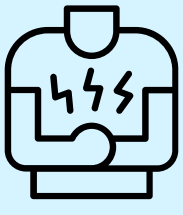
Potential Side Effects & Risks

Nausea & Diarrhoea

There is an increased risk of nausea and diarrhoea reported when using Givinostat.

Abdominal Pain

There is an increased risk of abdominal pain when using Givinostat.



Thrombocytopenia

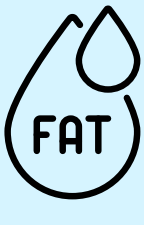
This is an associated risk of a decrease in the number of platelets in the blood. Platelets help form a ‘scab’ over a cut or wound. A decrease can lead to excessive bleeding.

Fever

An increased risk of fever can result from Givinostat use in some patients.

Increased Triglycerides

An increase in the number of fatty acids stored in the body were reported.



These side effects were reported as mild in the clinical studies.

Regulatory Progess

The US

The US Food and Drug Association (FDA) approved Givinostat for the treatment of patients aged 6 years and older. This decision was made following significant results of the Phase III trial in 179 DMD patients.

The EU

The European Medicince Agency (EMA) validated the Marketing Authorisation Application (MAA) for Givinostat in September 2023. This means the EMA can begin to assess the treatment based on safety and efficacy with a decision due to be made Mid 2024.

The UK

The MHRA and NICE are currently reviewing the application for Givinostat as a treatment for DMD patients 6 years and older. Italifarmaco are utilising the ‘International recognition procedure’, put in place to speed up the MHRA review of treatments that have been approved by trusted partners such as the FDA.

Fact or Fiction

Givinosat is currently available

FACT - It is currently the first non-steroidal drug permitted in the US for the treatment of DMD for children >6 years old.

FICTION - The drug is still under review in the UK and EU.

Givinostat a type of gene therapy

FICTION - Givinostat targets epigenetic pathways that regulate the muscle cell gene expression. It does not alter the underlying genetic code.

Givinostat works *with* steroids

FACT - Givinostat has been tested in 179 patients alongside their current corticosteroid regime. Positive results showed that this treatment could play a role as a supportive treatment for DMD and slow disease progression.

Useful Resources

Nature publication:
FDA approves an HDAC inhibitor for Duchenne muscular dystrophy

Cell publication:
HDAC inhibitors as pharmacological treatment for Duchenne muscular dystrophy: a discovery journey from bench to patients

FDA press release:
FDA Approves Non-steroidal Treatment for Duchenne Muscular Dystrophy

DrugBank treatment overview:
Givinostat is a histone deacetylase inhibitor indicated for the treatment of Duchenne Muscular Dystrophy (DMD).

If you are unable to access any of these resources please contact us at Info@actionduchenne.org

Glossary

Chromsome

- Chromosomes are thread-like structures made of DNA and protein that contain the instructions for building and maintaining us.

Chromatin

- Chromatin is the tightly packed complex of DNA and histone proteins found in the nucleus, which condenses further to form chromosomes.

Epigenetics

- Refers to how changes in the chemical environment can regulate gene expression.

Gene

- A gene is a specific section of DNA that acts as an instruction manual for building proteins or molecules that influence an organism's traits.

Gene Expression

- The process by which the information encoded in a gene are used to build proteins and other molecules used by the body.

Histones

- Histones are protein spools that DNA wraps around in the cell nucleus, compacting it and helping control gene activity.

Inhibitor

- Chemical or biological molecules that regulate chemical reactions by slowing down or blocking them from occurring

Myogenesis

- Refers to the formation of new skeletal muscle tissue.

Nucleosome

- A nucleosome is the tiny building block of chromosomes, like spools of thread holding DNA tightly packed in the cell nucleus.

Would you like to know more about Duchenne muscular dystrophy? Increase your knowledge and understanding of Duchenne with our bite-sized science video series.

- Section 1 – Facts about Duchenne muscular dystrophy
- Section 2 – Signs and Symptoms of Duchenne muscular dystrophy
- Section 3 – Diagnosis of Duchenne muscular dystrophy
- Section 4 – Crucial Genetic Terminology
- Section 5 – Genetics – Blueprint of Duchenne muscular dystrophy

SAVE THE DATE

Our 2024 Annual International Conference will be held on Friday 8th and Saturday 9th November 2024. The conference brings together families, clinicians, researchers and experts for 2 days of sharing knowledge and experience. It is an amazing opportunity to come together as part of the Duchenne community

Register your interest NOW:
https://www.actionduchenne.org/action-duchenne-annual-international-conference-2024-register-your-interest-now/