

A simple guide to
how Duvyzat® works

This information guide is intended for healthcare professionals to help support patients.

Duvyzat® ▼ (givinostat)

is indicated for the treatment of Duchenne muscular dystrophy in patients 6 years of age and older.



Reporting of side effects:

Adverse events should be reported. Reporting forms and information can be found at <https://yellowcard.mhra.gov.uk/> or search for **MHRA Yellow Card** in the **Google Play** or **Apple App Store**.

Adverse events should also be reported to ITF Pharma Ltd Medical Information on:
0800 098 4040 or **UK.Medical.Information@italfarmacogroup.com**

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Givinostat – How does it work and what do we know so far for Duchenne?

Written by Annemieke Aartsma-Rus

Givinostat has received regulatory approval to treat people aged 6 years of age and older with Duchenne muscular dystrophy in some regions, with ongoing regulatory assessments in others.

Illustrated by Martin Gaul, Sauce Health



HI, I'M DYLAN
AND I HAVE
DUCHENNE

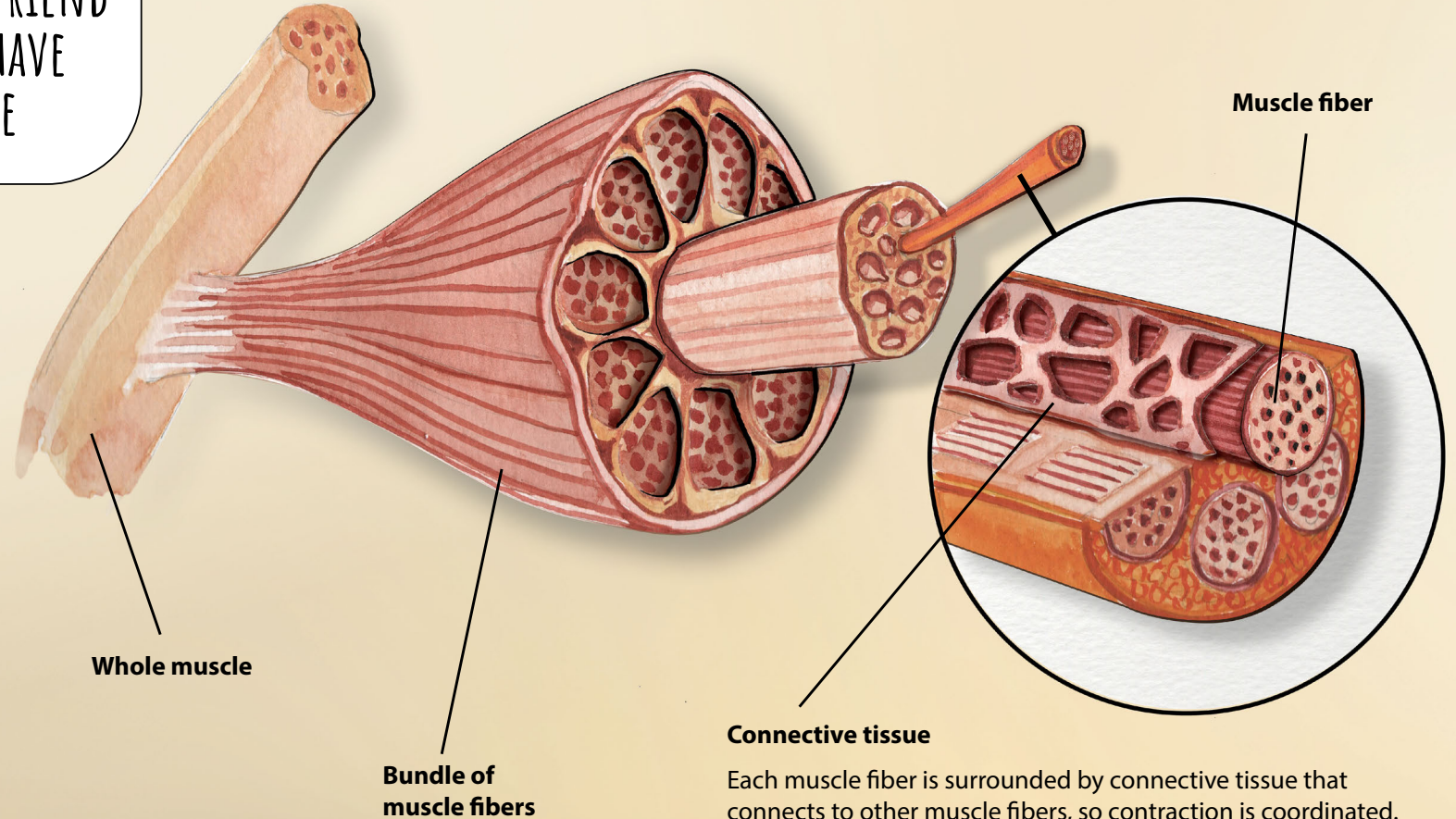


I'M POLLY,
DYLAN'S FRIEND
I DON'T HAVE
DUCHENNE



Inside our muscles

Everyone's muscles consist of muscle fiber bundles, which contain a protein skeleton that can contract.



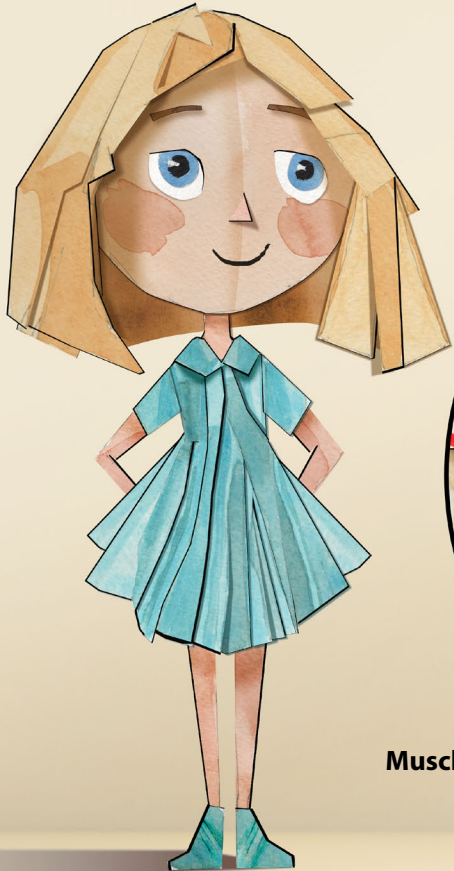


LET'S COMPARE
OUR DIFFERENT
MUSCLE REPAIR
PROCESSES

OKAY, LET'S START
WITH DYSTROPHIN



Polly's normal muscle fibers



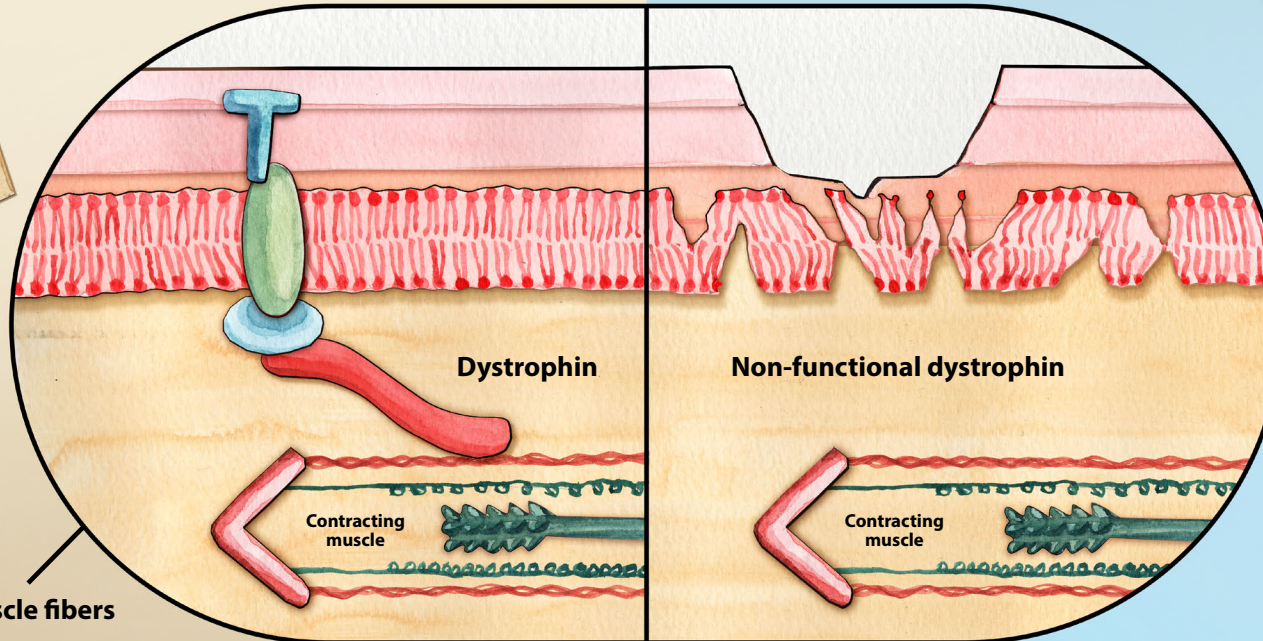
Normally, muscle contraction causes stress for the muscle fibers, so the dystrophin proteins stabilize the contracting muscle fibers by forming a flexible link between the protein skeleton and the connective tissue surrounding muscle fibers.

Muscle fibers

VS

Dylan's non-functional muscle fibers

However, with Duchenne muscular dystrophy, patients cannot make functional dystrophin and therefore, muscle fibers will be damaged during muscle contraction.

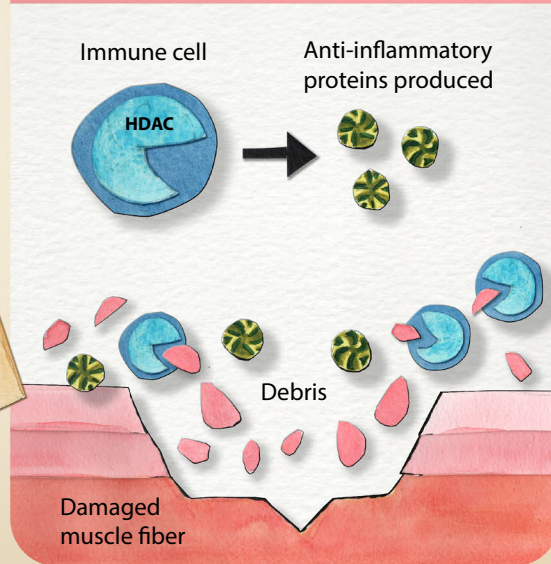


Polly's normal muscle repair process

Muscle damage will normally be repaired in a well-orchestrated and synchronized series of processes:

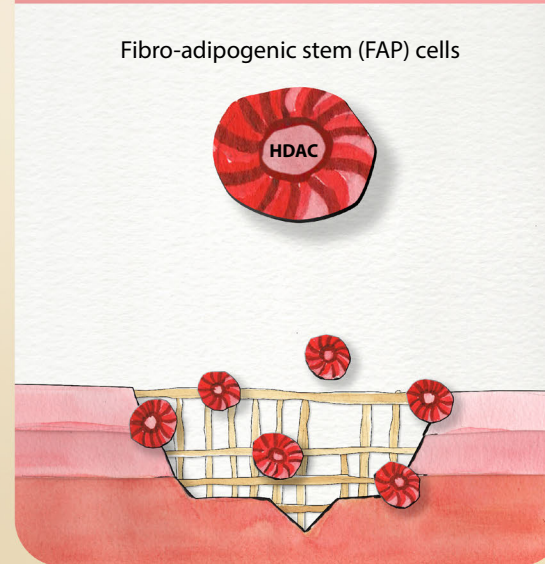


Inflammation



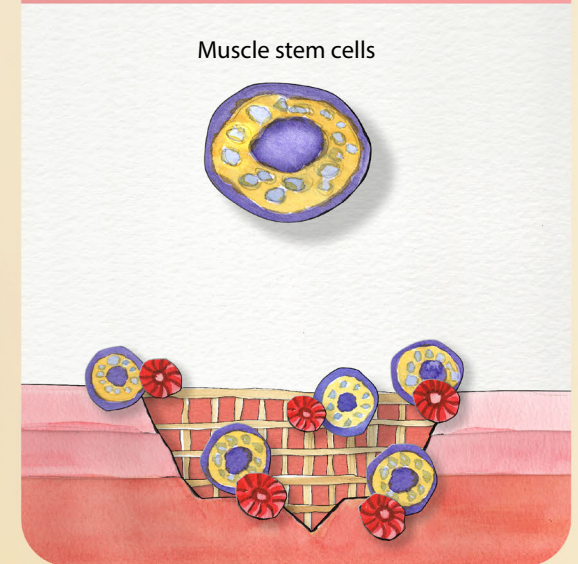
Polly's immune system will clear the muscle damage and debris; during this process the immune system inhibits the repair system until the debris has been fully removed.

Connective tissue repair



Once the damage is cleared, fibro-adipogenic stem (FAP) cells are activated to repair the connective tissue shell that surrounds each muscle fiber.

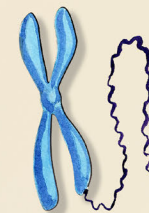
Muscle tissue repair



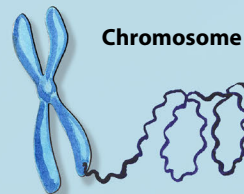
Then, the muscle stem cells are activated by the FAP cells to create and transform into mature muscle either by fusing with the remaining muscle fiber or by forming a new muscle fiber within the shell of connective tissue.

Why is HDAC so important in Duchenne?

In Duchenne patients there is increased activity of HDAC enzymes. HDAC enzymes remove acetyl groups from histone proteins.



Chromosome



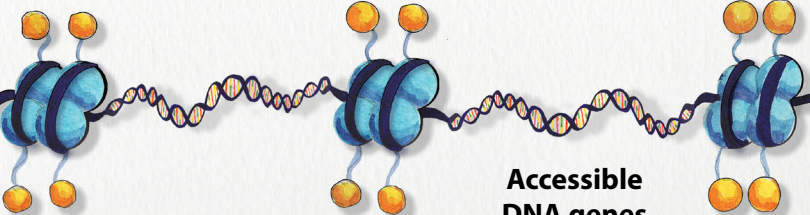
Chromosome

Histones

The most well-known proteins that are influenced by the addition and removal of acetyl groups are histones, the proteins around which DNA is wrapped.

HAT enzymes

Acetylation
(Acetyl groups added)



Accessible
DNA genes

HDAC enzymes

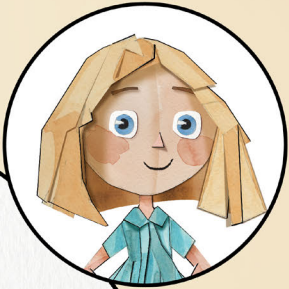
Deacetylation
(Acetyl groups removed)



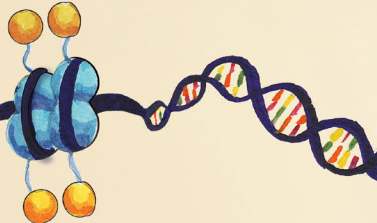
Polly's DNA

Normal gene expression

In normal muscle repair, acetyl groups are added to the histones, ensuring DNA unwraps to become accessible and able to produce specific proteins for muscle repair.



Histones



Dylan's DNA

Reduced gene expression

Too much HDAC enzyme activity means that too many acetyl groups are removed from the histones and the DNA is too tightly wrapped.

This prevents expression of genes, failure to produce specific proteins, and ultimately prevents muscle repair.



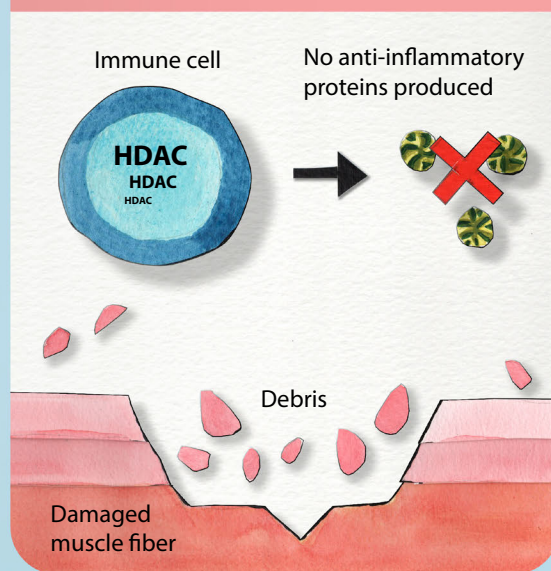
See page 9 for more information.

Dylan's muscle repair process does not work as it should

In Duchenne, muscle damage is 'chronic' and therefore the repair process is broken (so things don't happen in the right order). This leads to failure of proper muscle repair:

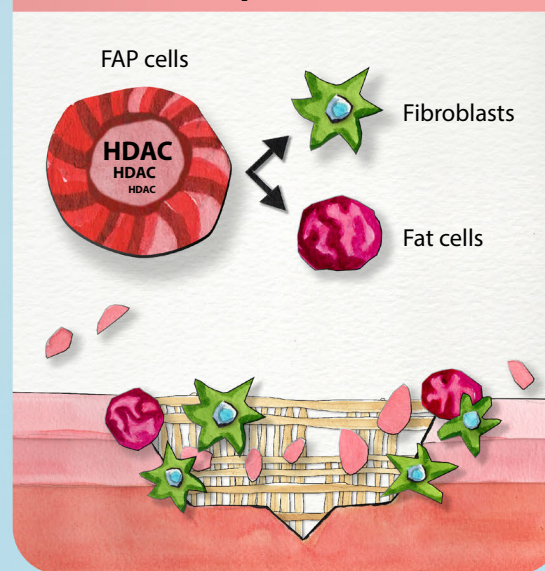


Chronic inflammation



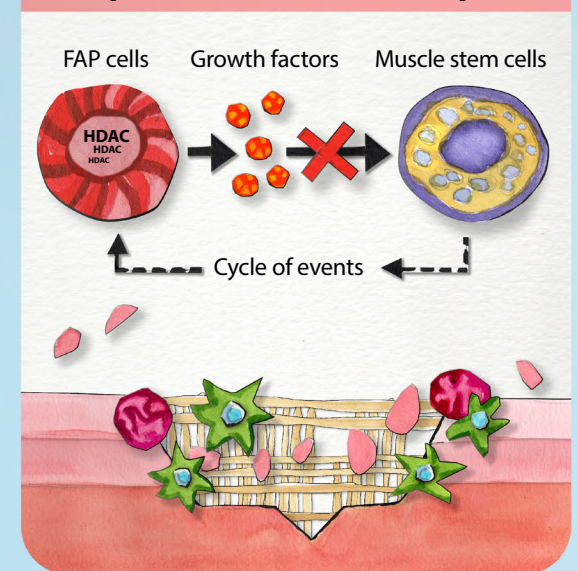
Dylan's immune system gets over stimulated. Normally this is prevented by anti-inflammatory proteins. However, in Duchenne, HDAC enzymes prevent these proteins from being produced, so now the immune system causes additional damage.

Over production



Due to the over stimulated immune cells and the increased HDAC activity, the FAP cells get stuck in production mode and make too much connective tissue (fibrosis), fibroblasts and fat cells.

Impaired muscle tissue repair



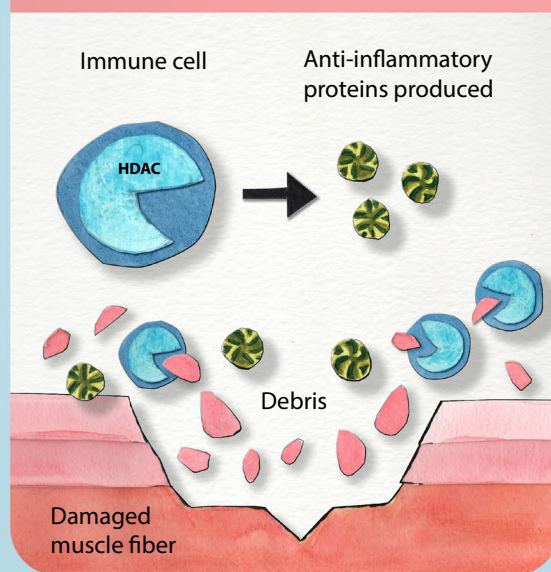
The FAP cells get stuck in the wrong mode and cannot support the muscle stem cells. Therefore, muscle stem cells cannot repair the muscles. The growth factors produced by the fibroblasts and the fat cells further prevent muscle repair.

Givinostat* (HDAC inhibitor) is expected to enable muscle repair in Duchenne

Given that multiple processes in muscle damage and repair are exacerbated by too much HDAC activity, it makes sense to anticipate that inhibiting HDAC activity will improve muscle repair.

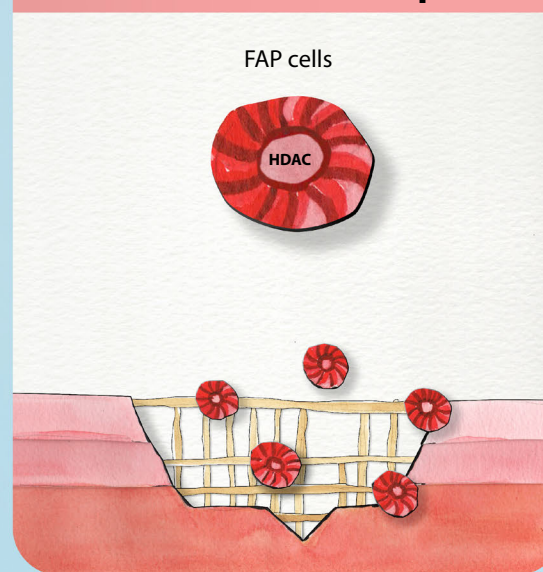


Chronic inflammation



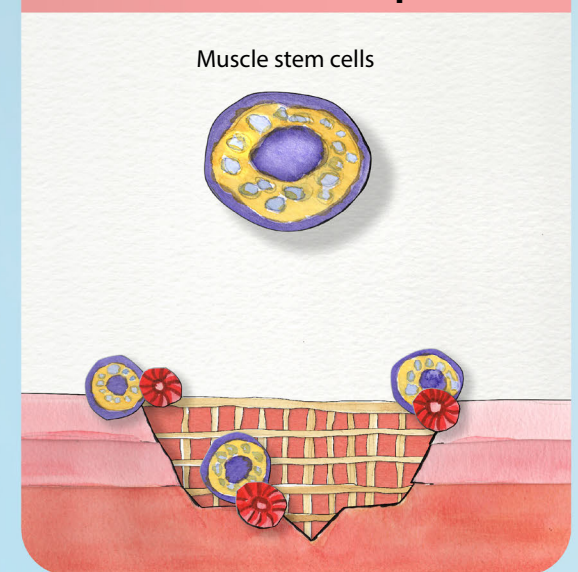
Givinostat is expected to reduced HDAC activity which would prevent the body's immune system from getting over stimulated. This allows the muscle repair process to behave more naturally.

Connective tissue repair



Reduced HDAC activity dampens the immune response and prevents extra damage caused by the immune cells. FAP cells won't get stuck in production mode and can return to their supportive role for muscle repair.

Muscle tissue repair



FAP cells produce growth factors and activate muscle stem cells, which then transform into new mature muscle fiber and repair the damage.

* Givinostat inhibits the activity of HDAC enzymes. There is an analogy to show how givinostat works on the next page.

Givinostat – Dylan takes a closer look

Duchenne patients have more HDAC activity

Both dystrophin and HDACs play an important role in muscle repair failure. Dystrophin is part of a 'protein complex' called DAPC (dystrophin associated protein complex). In addition to providing stability to muscle fibers, DAPC recruits the nitric oxide synthase (NOS) enzyme to the membrane. This enzyme produces nitric oxide (NO). Without dystrophin, there is less nitric oxide (NO), which leads to an increased level HDAC enzymes and therefore more HDAC levels and activity in different cells in the body.

The impact of givinostat

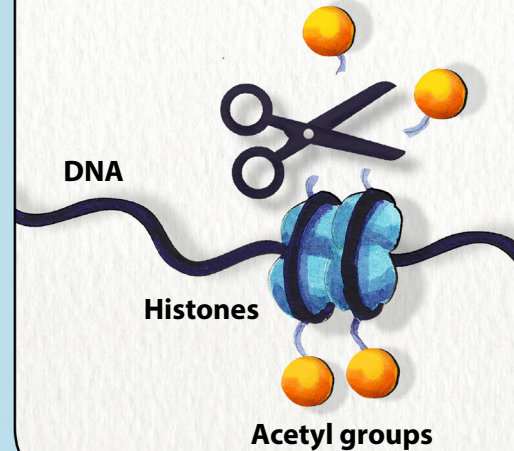
Givinostat's inhibition of HDAC enzymes helps to reduce inflammation and fibrosis in muscle tissues, promoting muscle regeneration and slowing disease progression.

When givinostat stops HDAC enzymes from removing acetyl groups from histones, it also reduces the production of the inflammatory factors, helping to calm down the immune system. Additionally, it promotes muscle regeneration by normalising FAP cells activity.

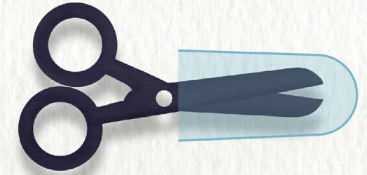


A simple analogy to explain HDAC enzymes inhibition

Imagine HDAC enzymes as a pair of scissors that cut acetyl groups off histones.



Givinostat acts like a cap that covers the blades of the scissors, stopping them from cutting. This keeps the acetyl groups on the histones, allowing important genes to be accessible for protein production.



Acetylation enables DNA to unwrap, making genes accessible, expressed and able to produce specific proteins for muscle repair.



OUR MUSCLE PROCESSES
MIGHT BE DIFFERENT, BUT
WE STILL LOVE DOING THE
SAME THINGS TOGETHER

