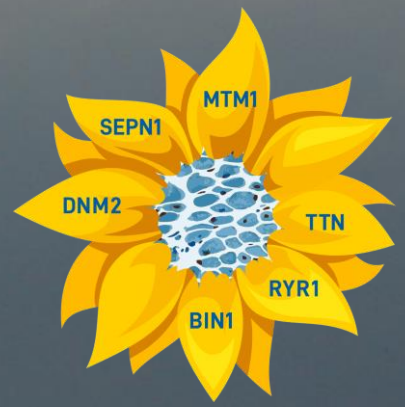
ZNM - zusammen stark! Family conference 2025



Understanding muscles and mutations - a patient-friendly guide for CNM

Dr. Johann Böhm

Inserm Research Director - IGBMC Strasbourg

Let‘s start with a few key figures

Knew it?

Rare diseases: < 1/2000 persons affected

7000 rare diseases (almost all of genetic origin)

1 out of 20 persons affected in Germany = 4 million

(cancer 1.6 million, dementia 1.8 million)

Rare diseases strongly impact on the quality of life

of patients AND their family

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Rare diseases strongly impact on the quality of life

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Everyone knows an affected person

In the course of the day we all meet persons with rare diseases

How to treat rare diseases?

First of all, the genetic cause needs to be identified

For instance through a karyotype

Isolation of chromosomes from a blood drop

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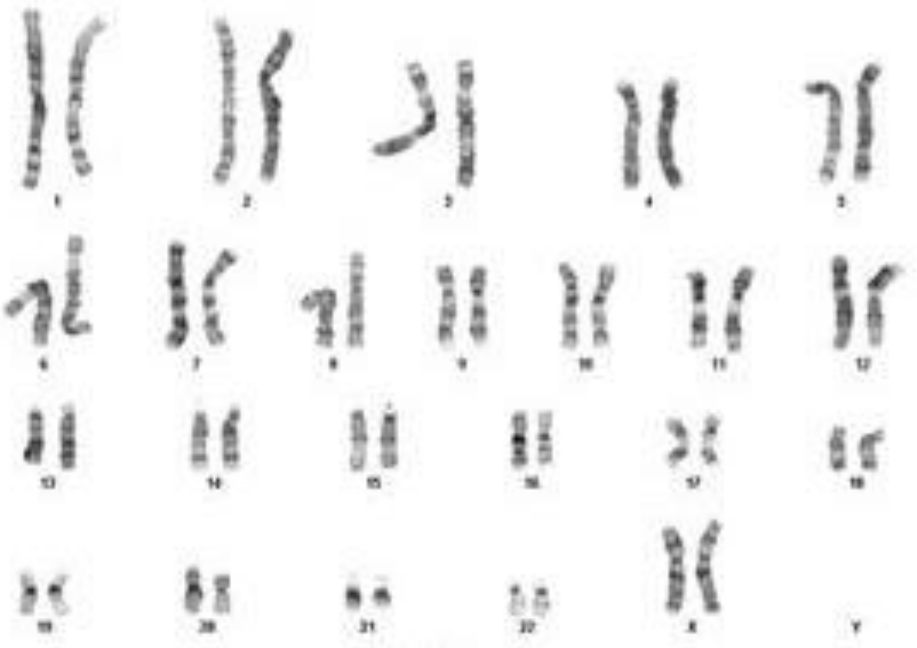
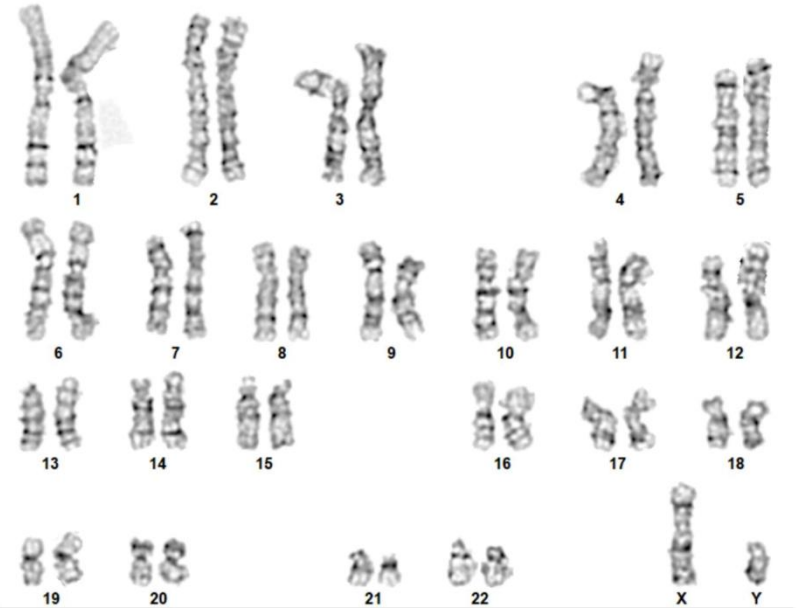




For instance through a karyotype

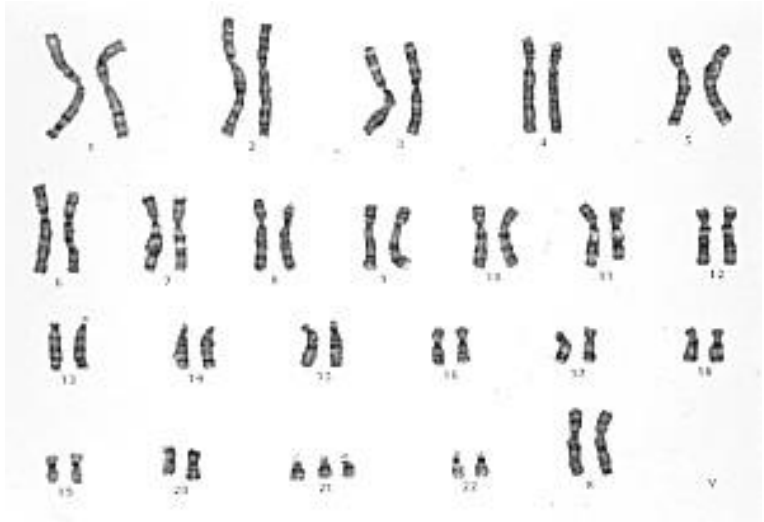
Isolation of chromosomes from a blood drop

46 chromosomes: 22 autosomes ranked by size, plus gonosomes X und Y

X-chromosome : 804 genes Y-chromosome: 62 genes

Have a look at the following karyotype

Anything unusual?



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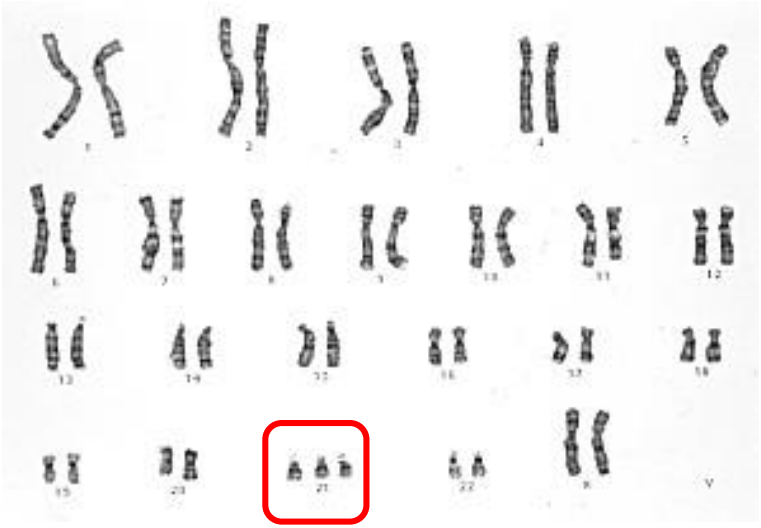

Trisomy 21

- Intellectual disability
- Malformations of heart, eyes, intestines, locomotor system …

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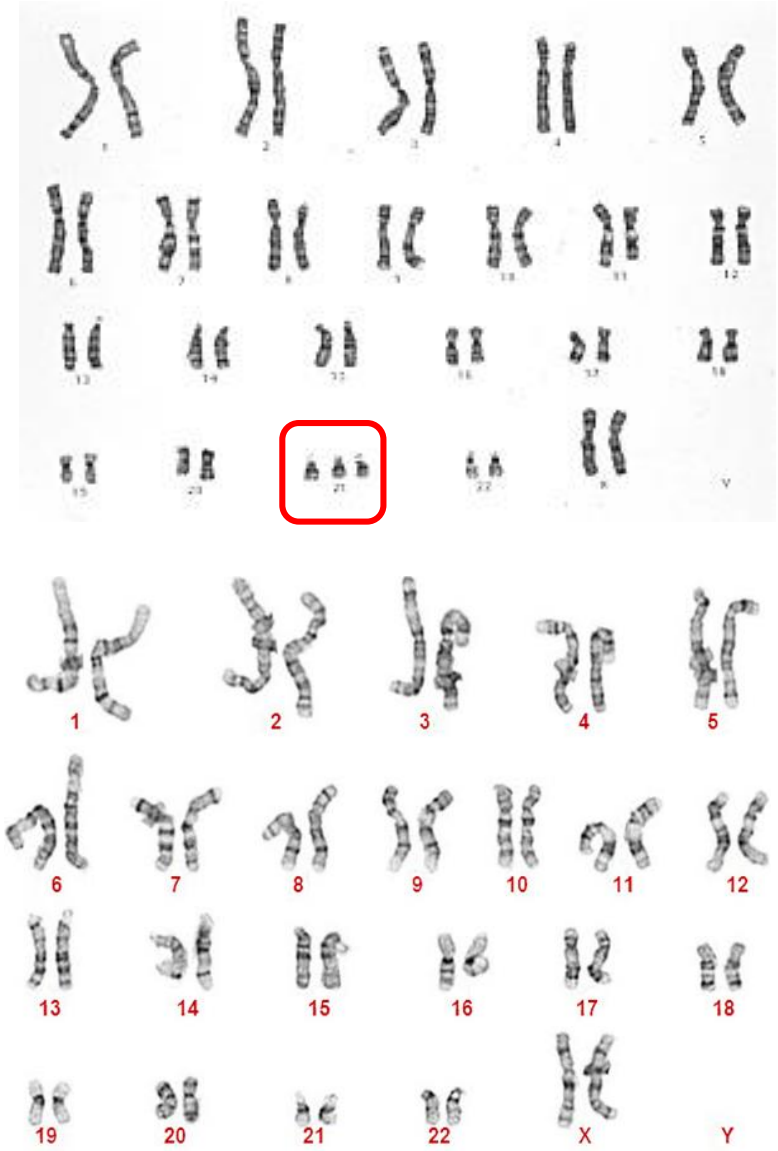

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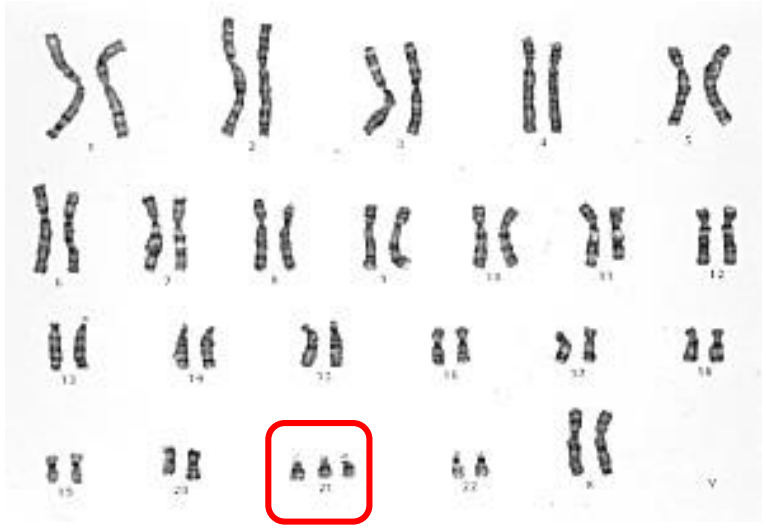

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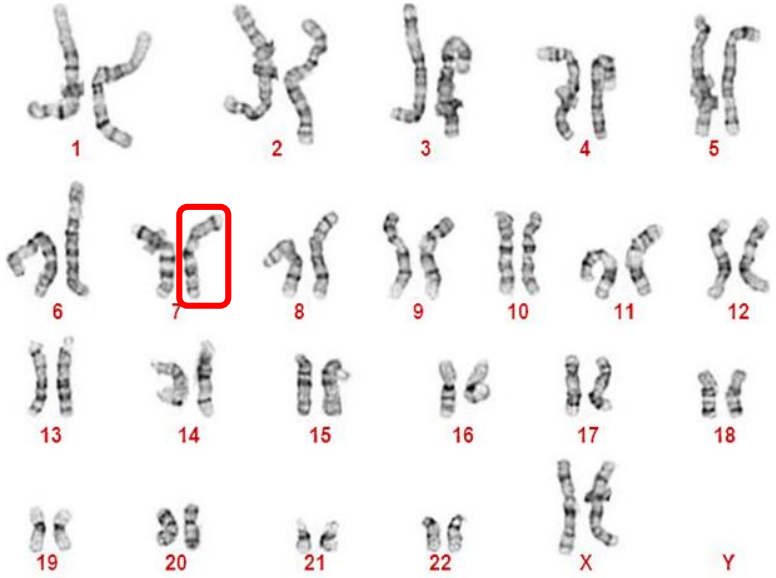


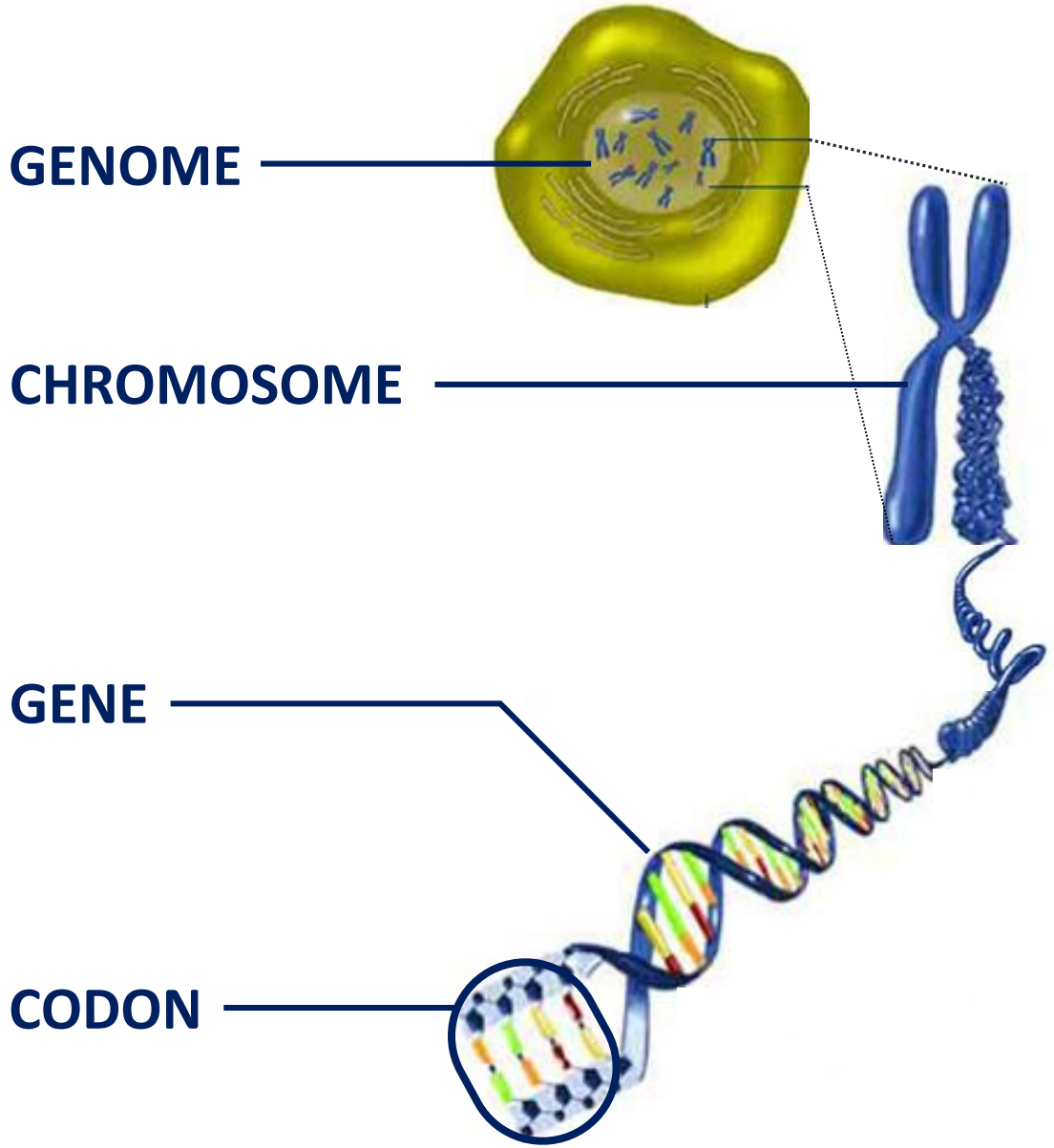
Williams syndrome

- Typical face and behavior
- Intellectual disability
- Growth delay

Deletion of 17 genes - invisible on karyotype

Most genetic causes are invisible on a karyotype

Need to read the DNA like a book



≈ Book

≈ Chapter

Sentence

≈ Word

4 letters C G A T

… a quite thick book though

Ever read Harry Potter? How many letters in a book?

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Ever read Harry Potter? How many letters in a book?

Answer: 1 000 000 letters

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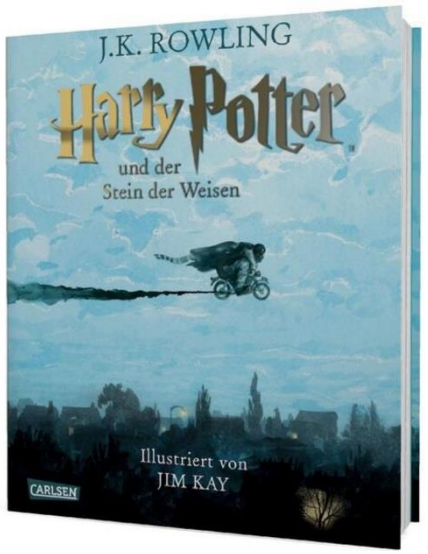

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Nothing compared with DNA:

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Corresponds to an entire library

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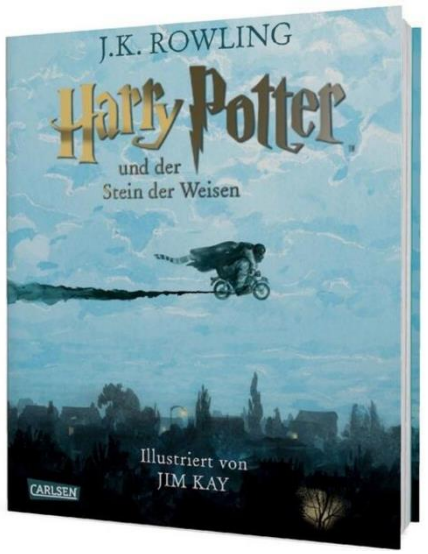

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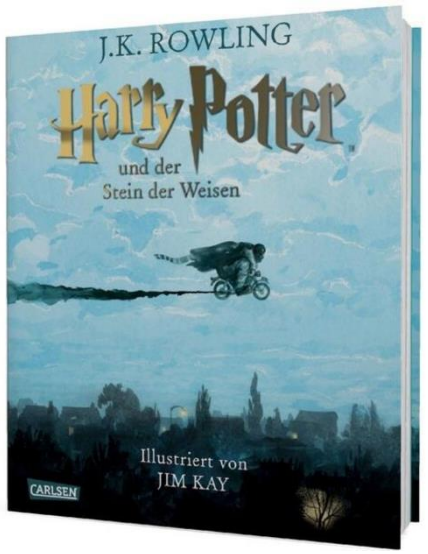

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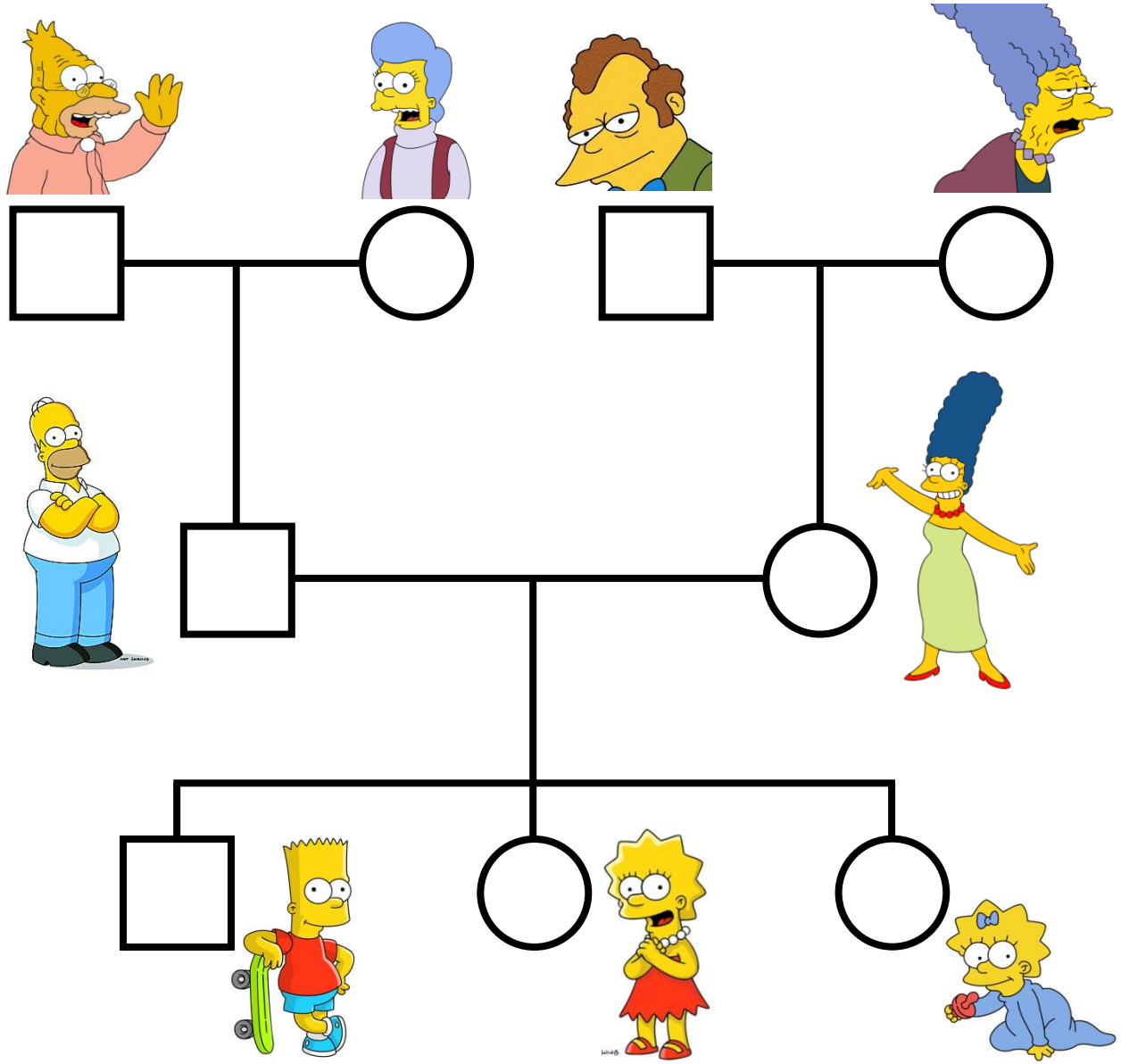
DNA is read with a machine
- a sequencer


Per patient: 3 000 000 pages like this one

Necessary to analyze the entire DNA?

A look at the family history often helps



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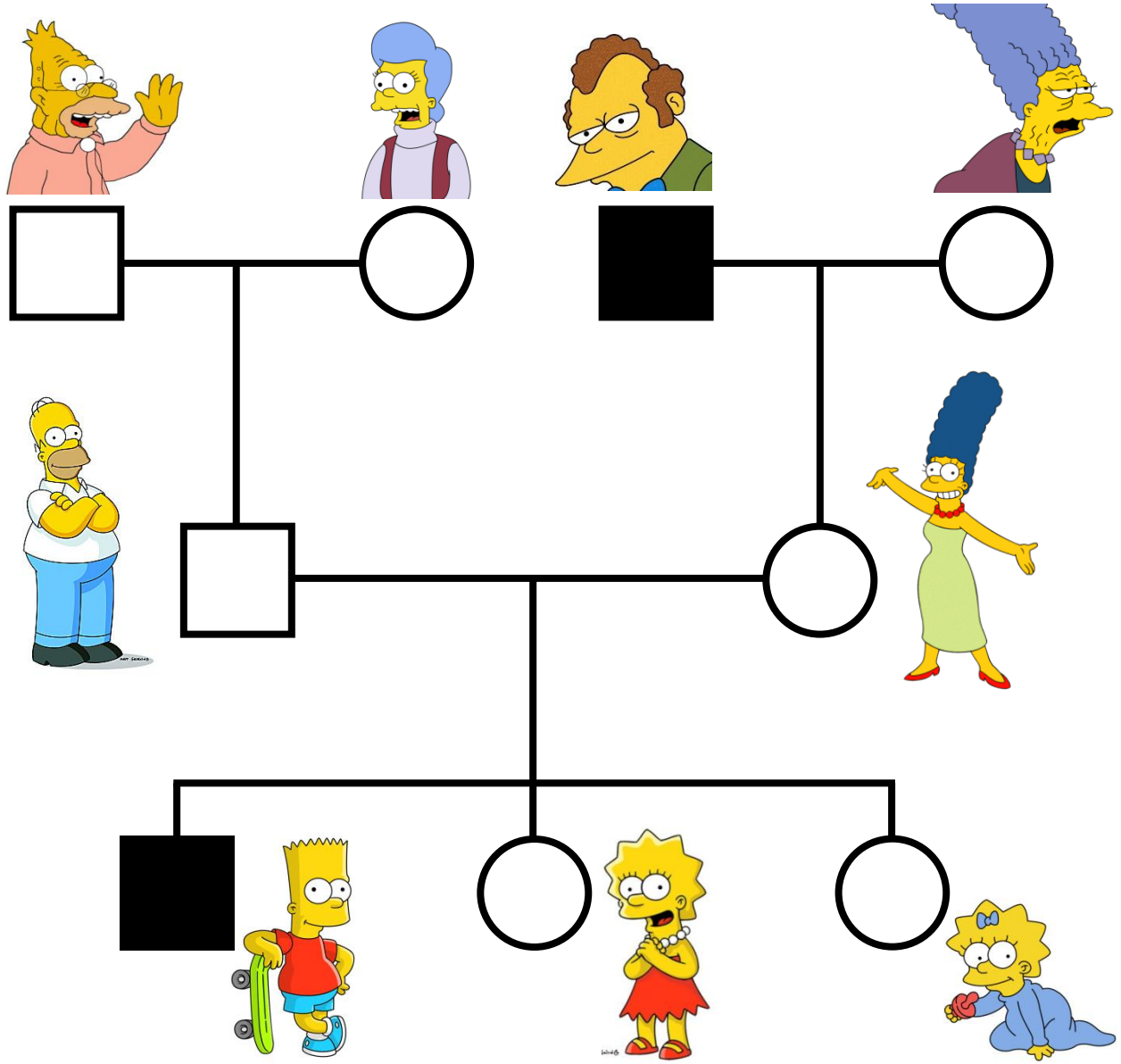
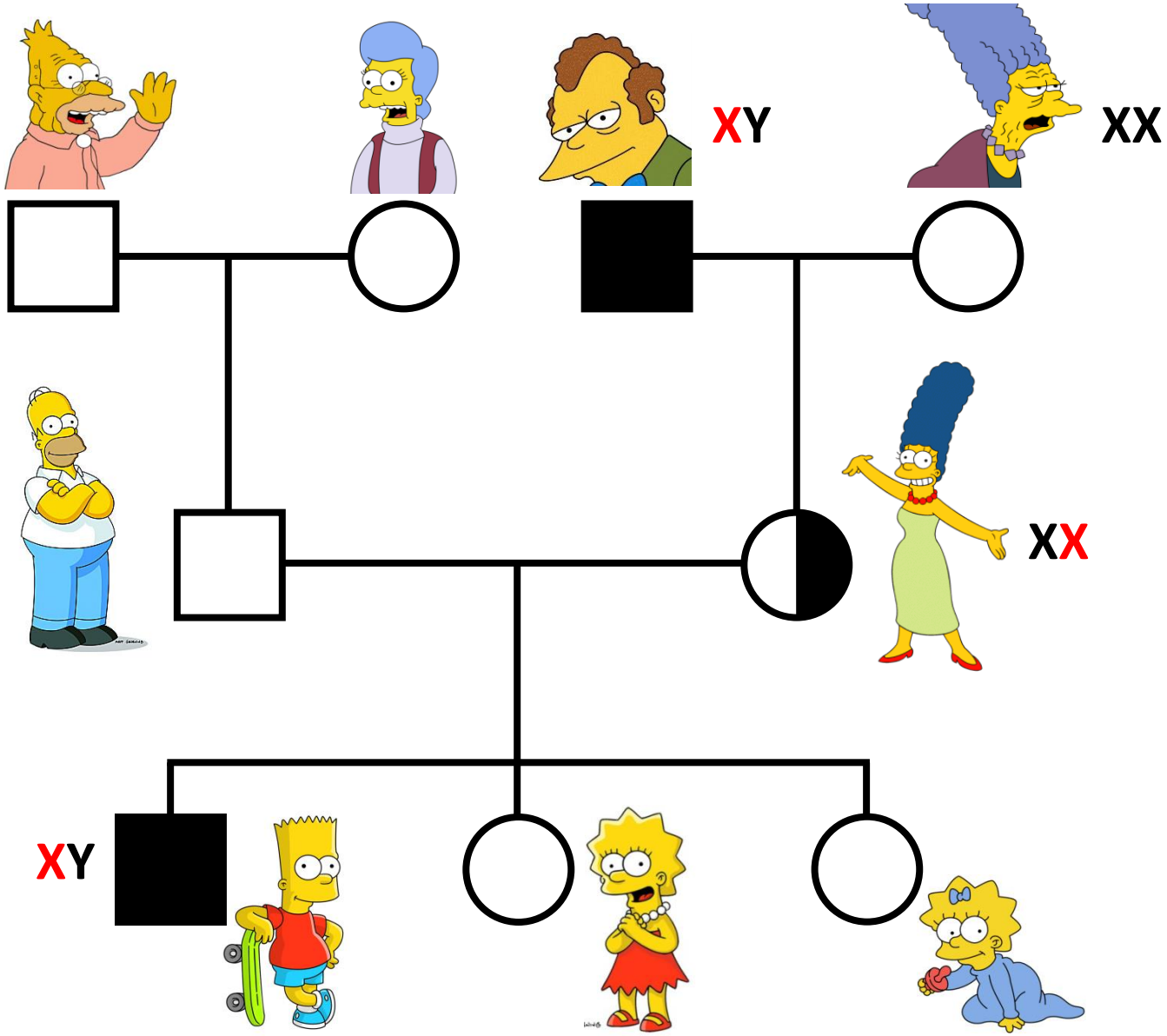


An X-linked disorder primarily affects boys

Women are healthy carriers



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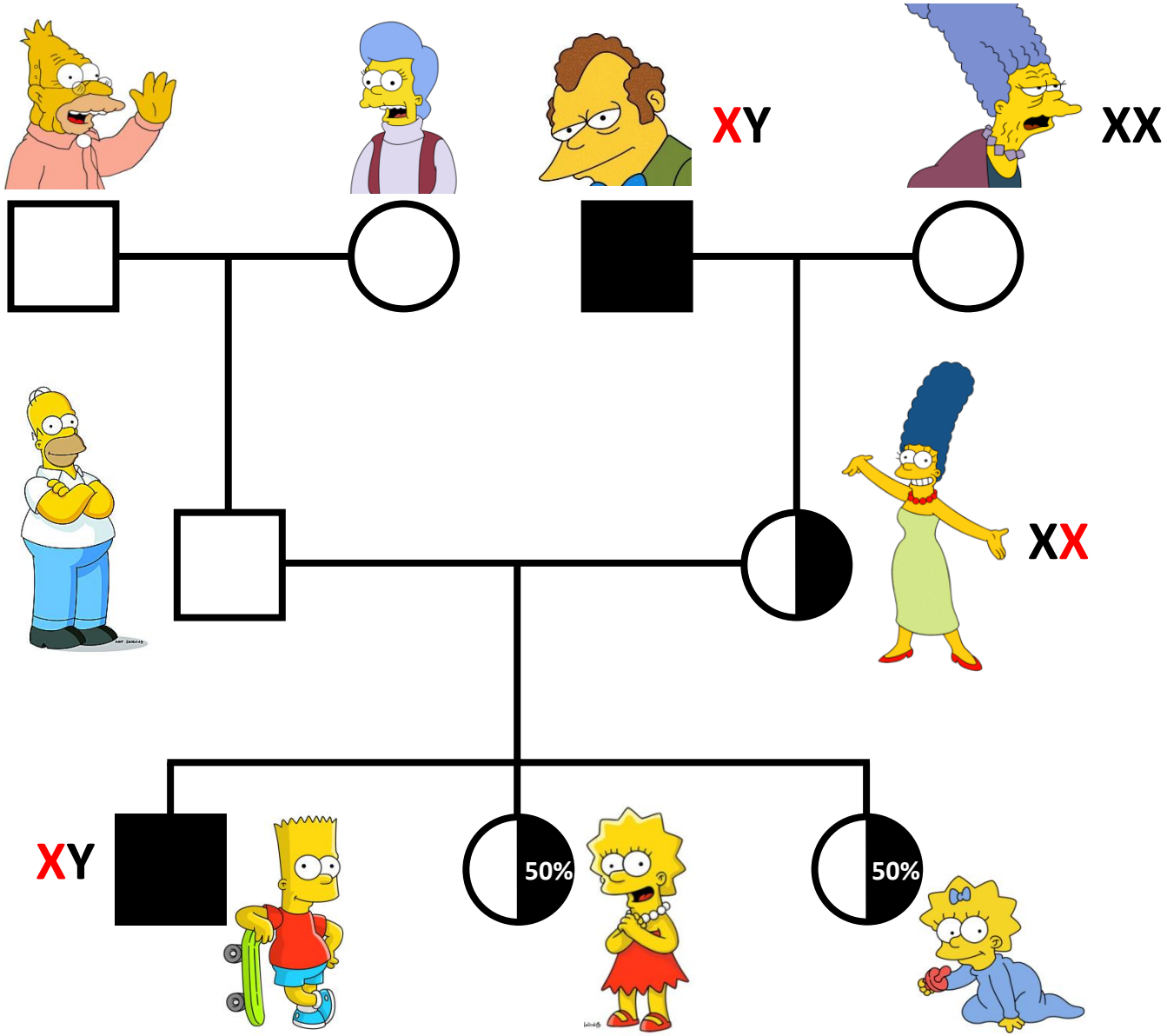
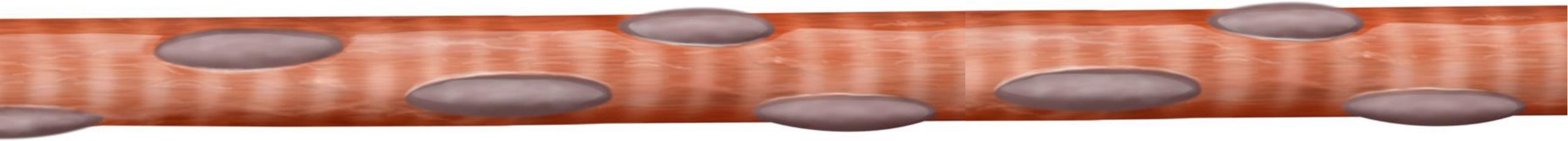
Risk for Lisa to be a healthy carrier?



Biology - basic course

Muscle contraction

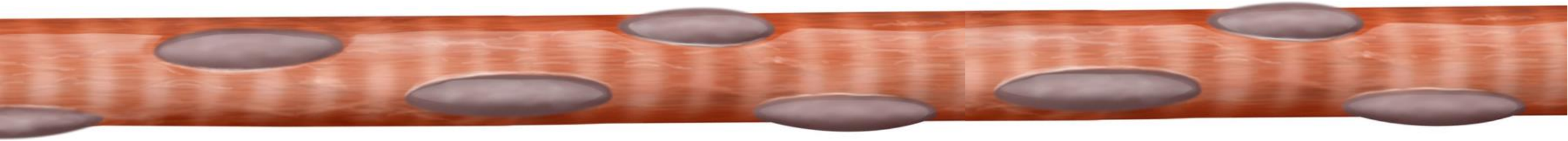


Skeletal muscles (used for voluntary movements) are striated

= alignment of contractile units called sarcomeres

Biology - basic course

Muscle contraction



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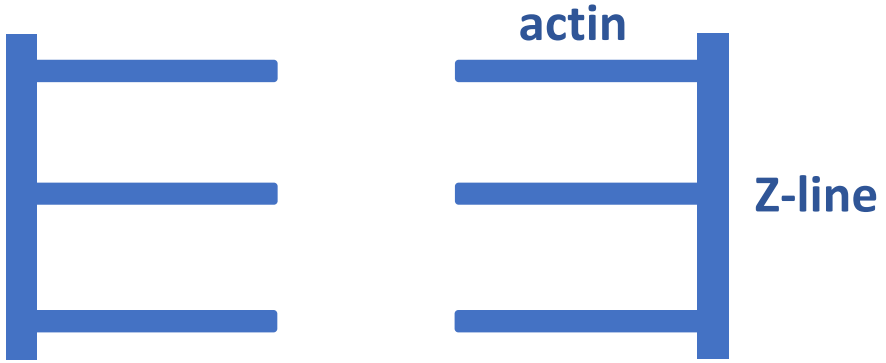

Biology - basic course

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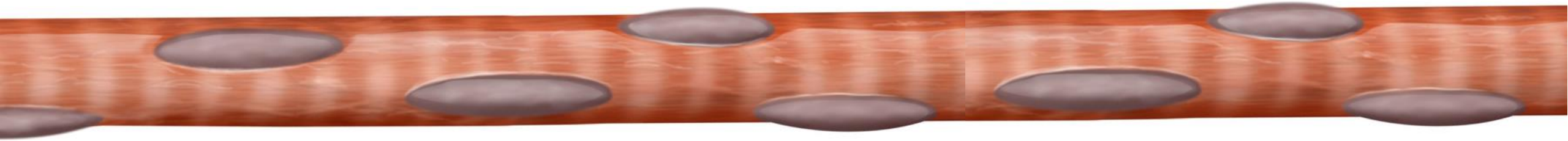

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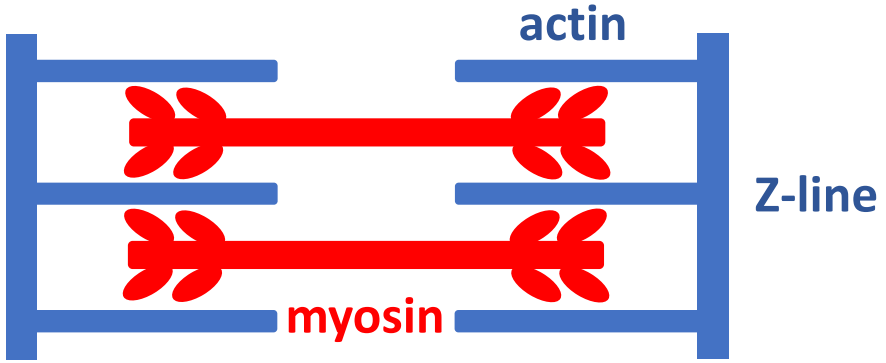

Biology - basic course

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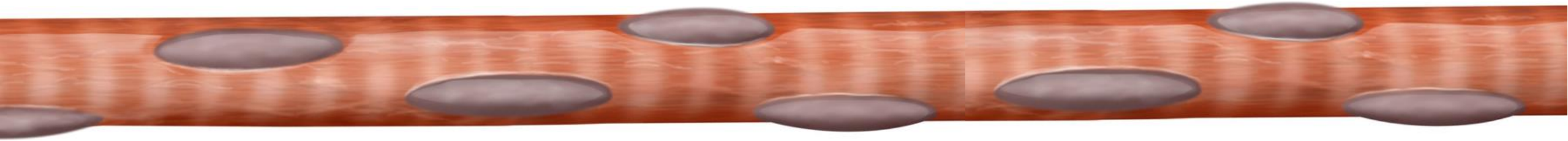

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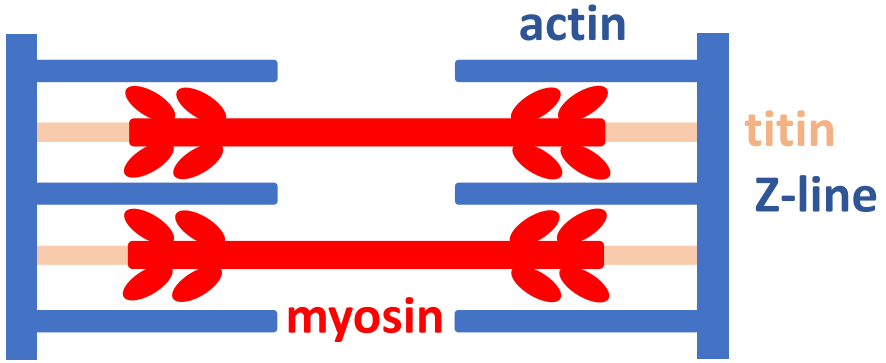

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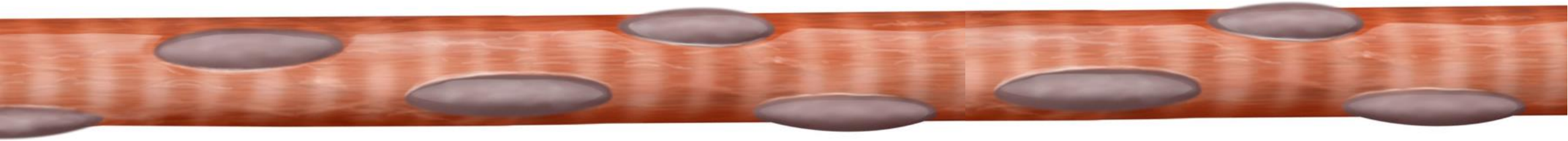
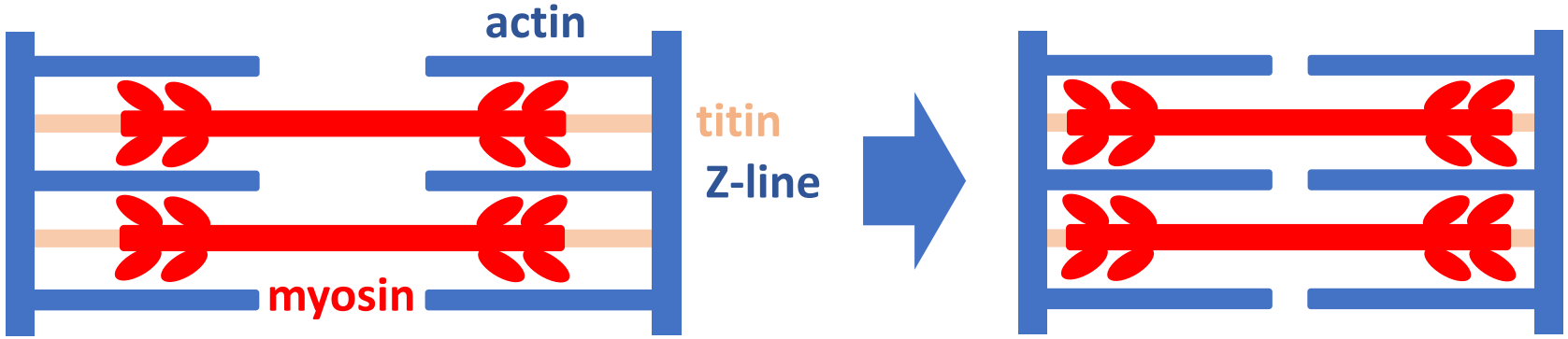


Myosin heads bind actin and perform a power stroke

Leads to shortening of the sarcomere = muscle contraction



rest

contraction

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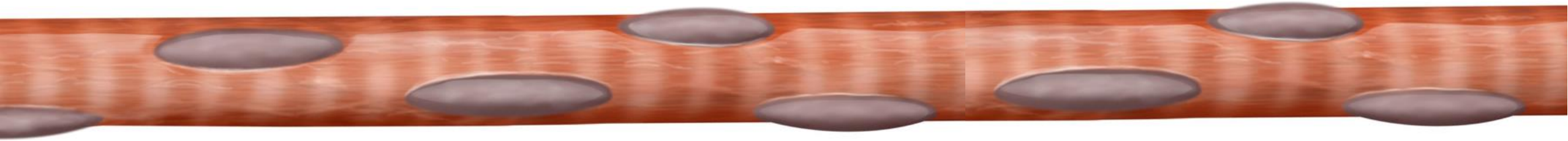
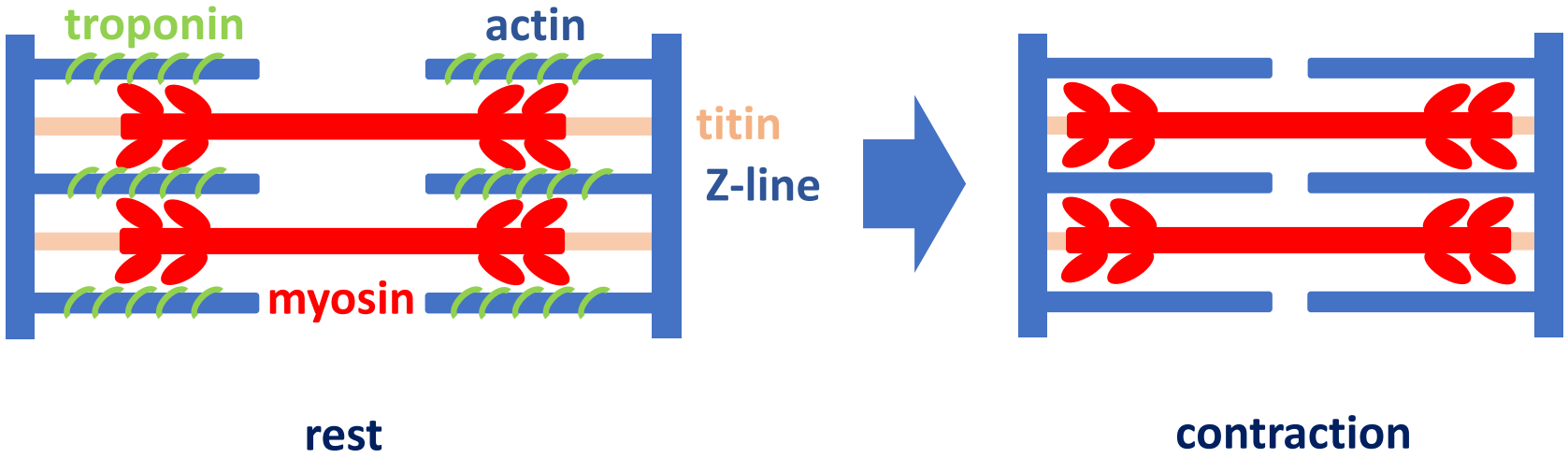
Muscle contraction



Troponin is wrapped around actin

Myosin cannot spontaneously bind actin - what triggers muscle contraction?



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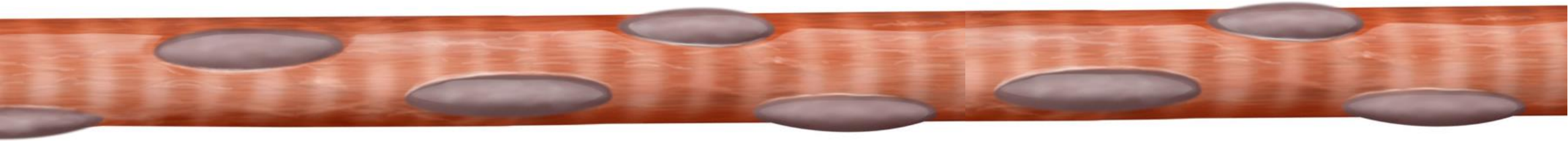
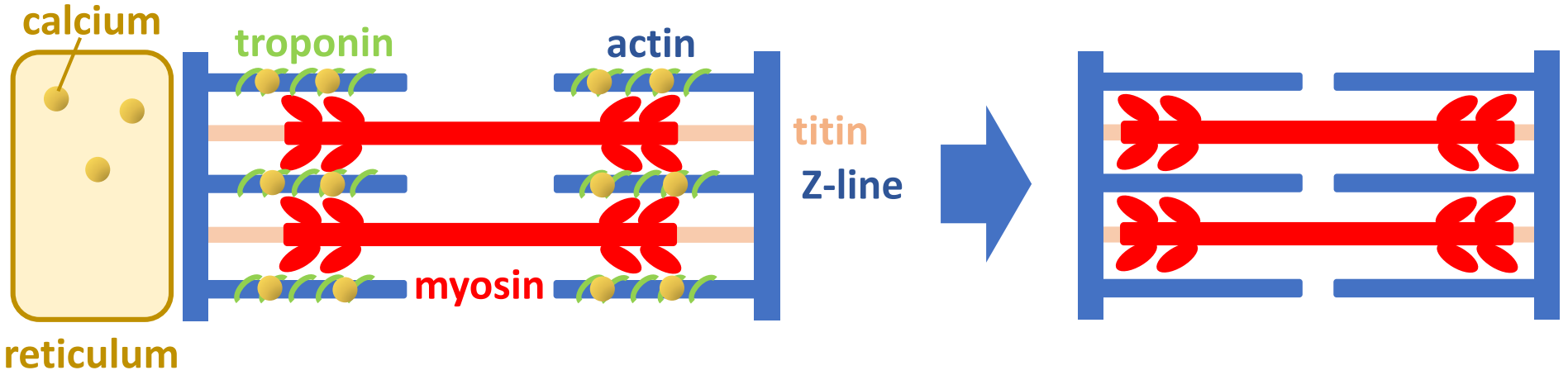
Muscle contraction



Calcium bends troponin away → myosin can bind actin

Calcium is stored in the reticulum - how is it released?



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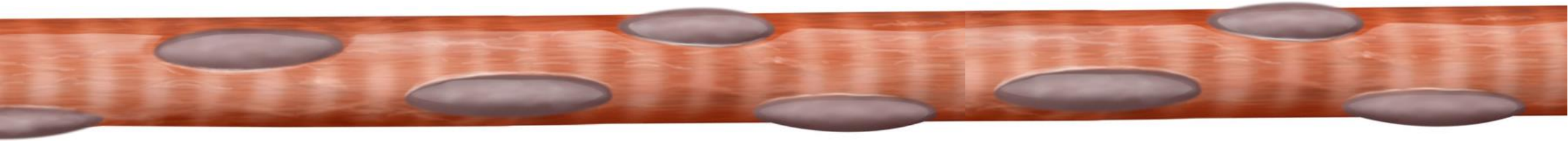
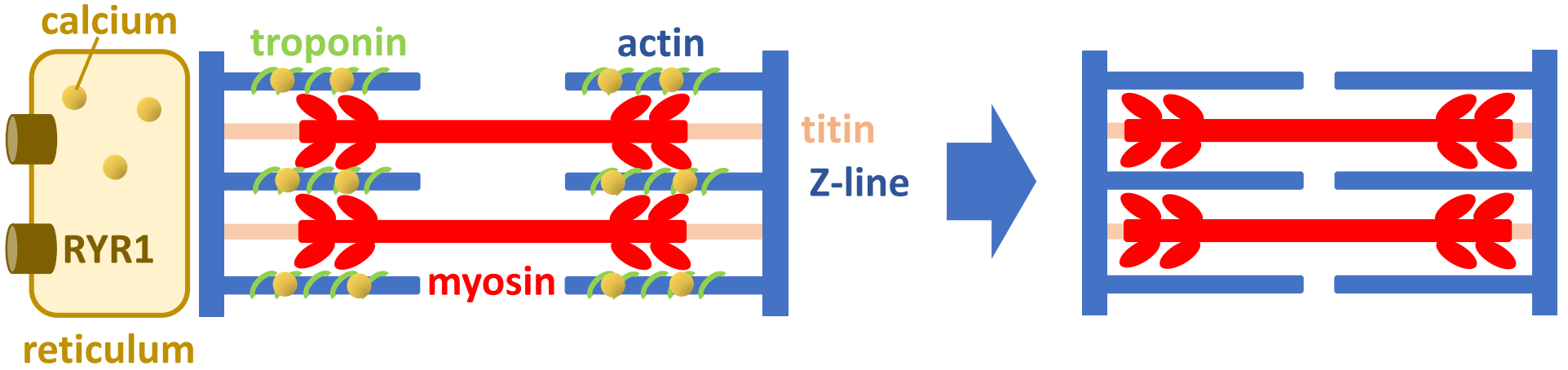
Muscle contraction



RYR1 is the calcium exit door of the reticulum

At rest, RYR1 is closed - how is it opened?



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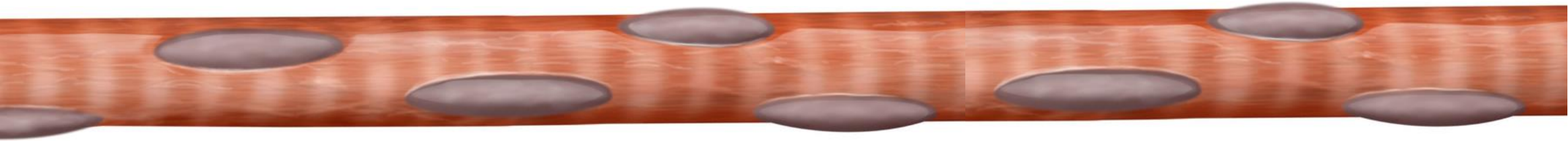
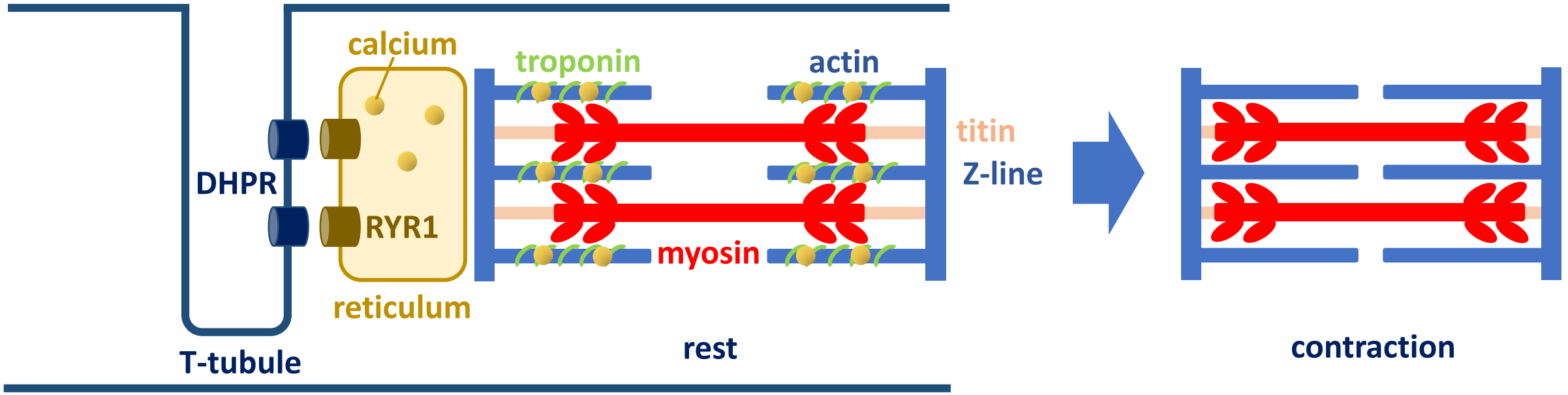
Muscle contraction



DHPR opens RYR1

DHPR localizes at the T-tubuli and gets activated by electrical stimuli



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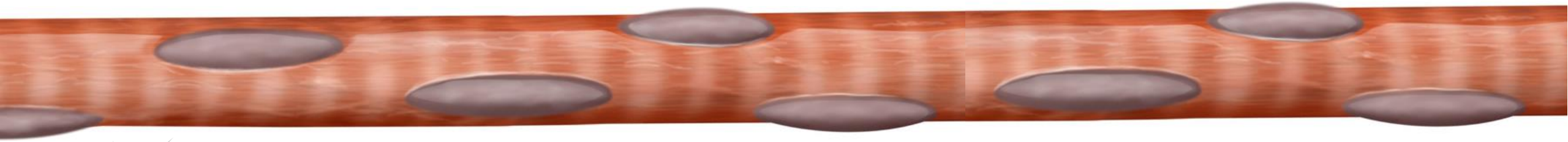
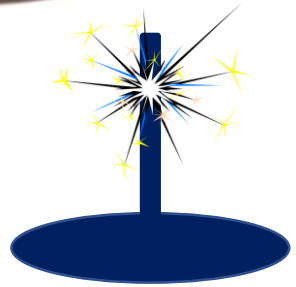
Muscle contraction





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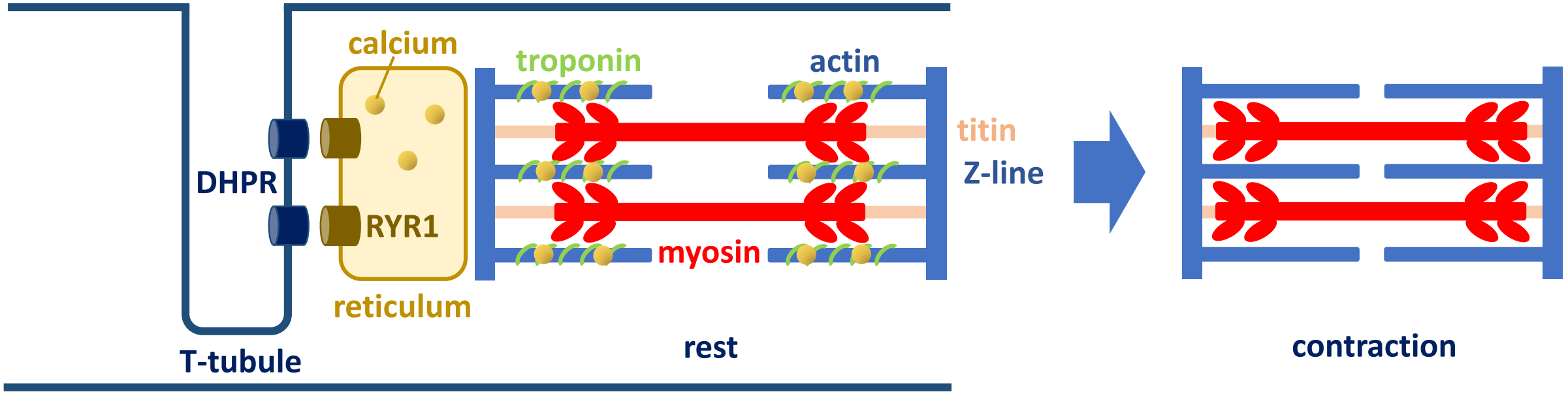

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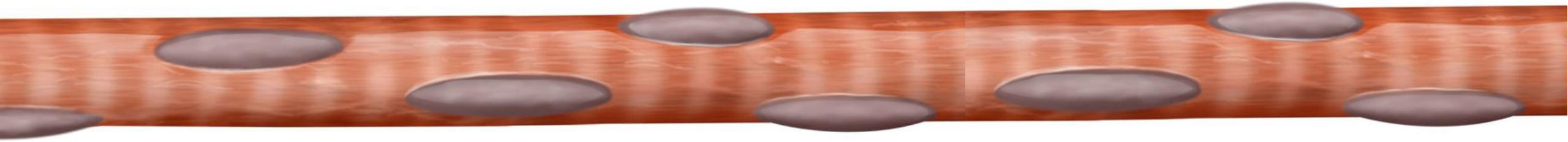

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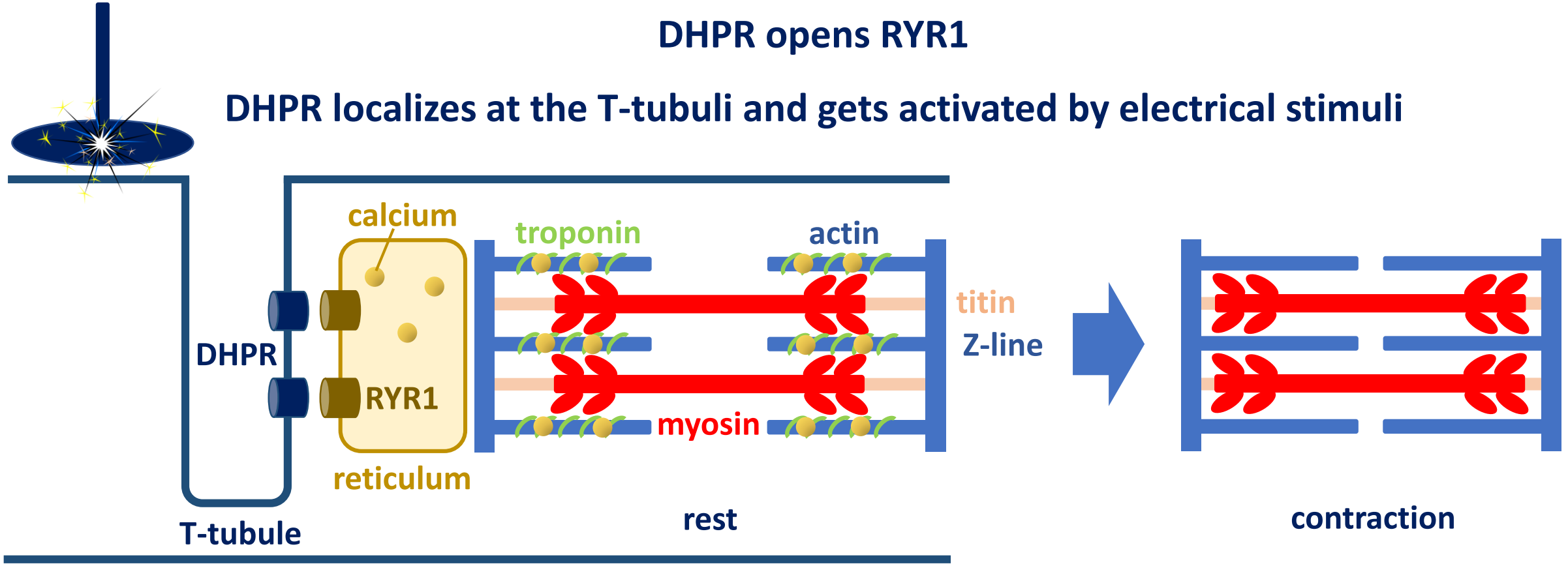

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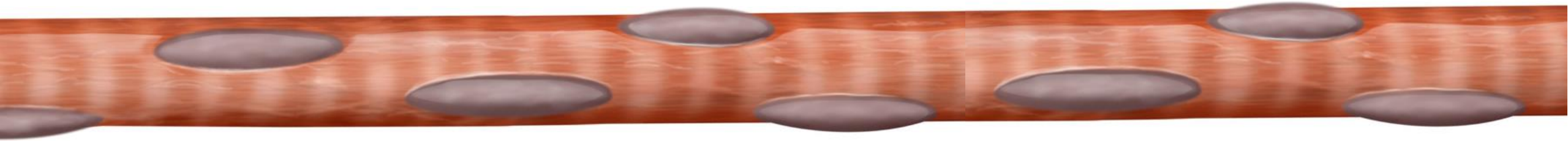

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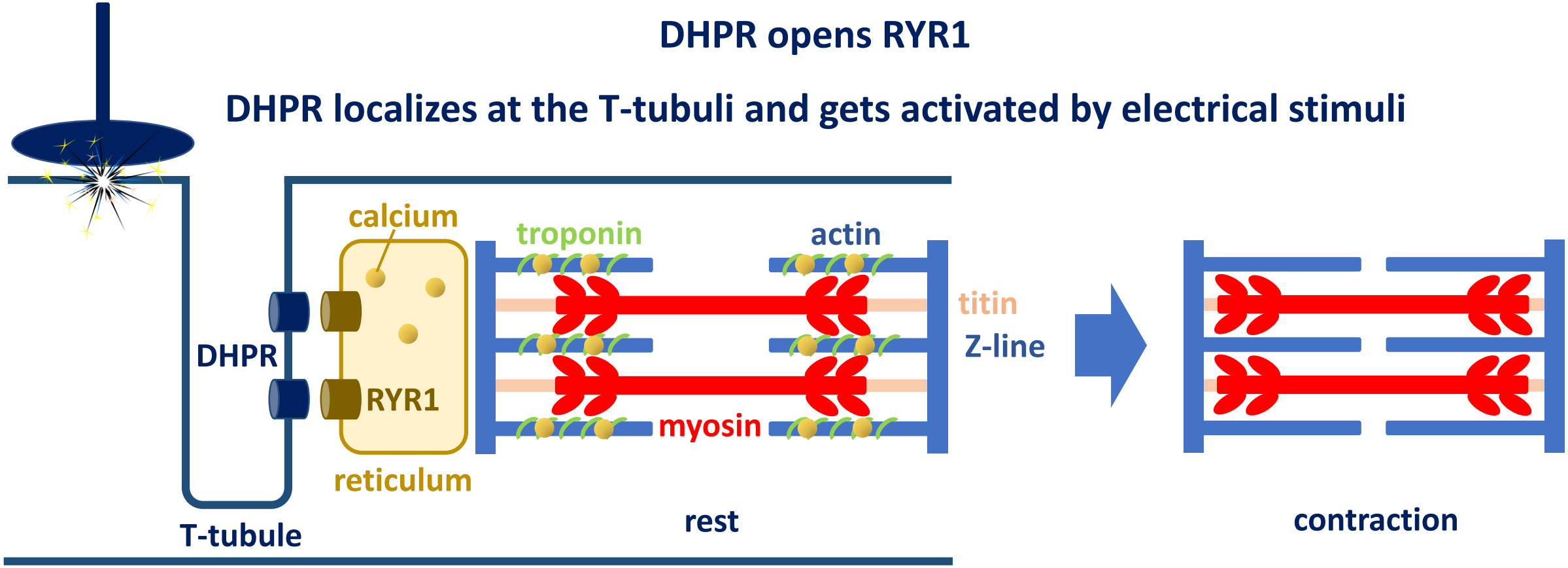

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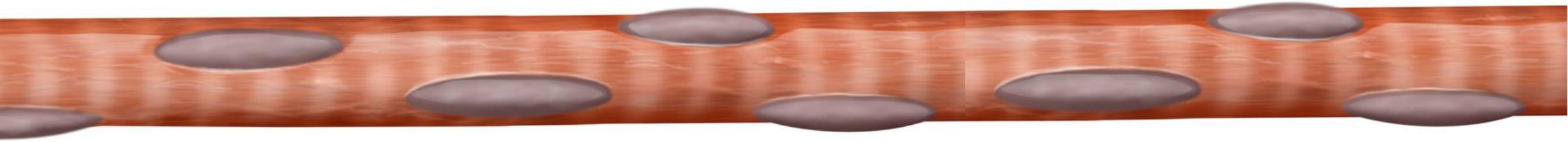

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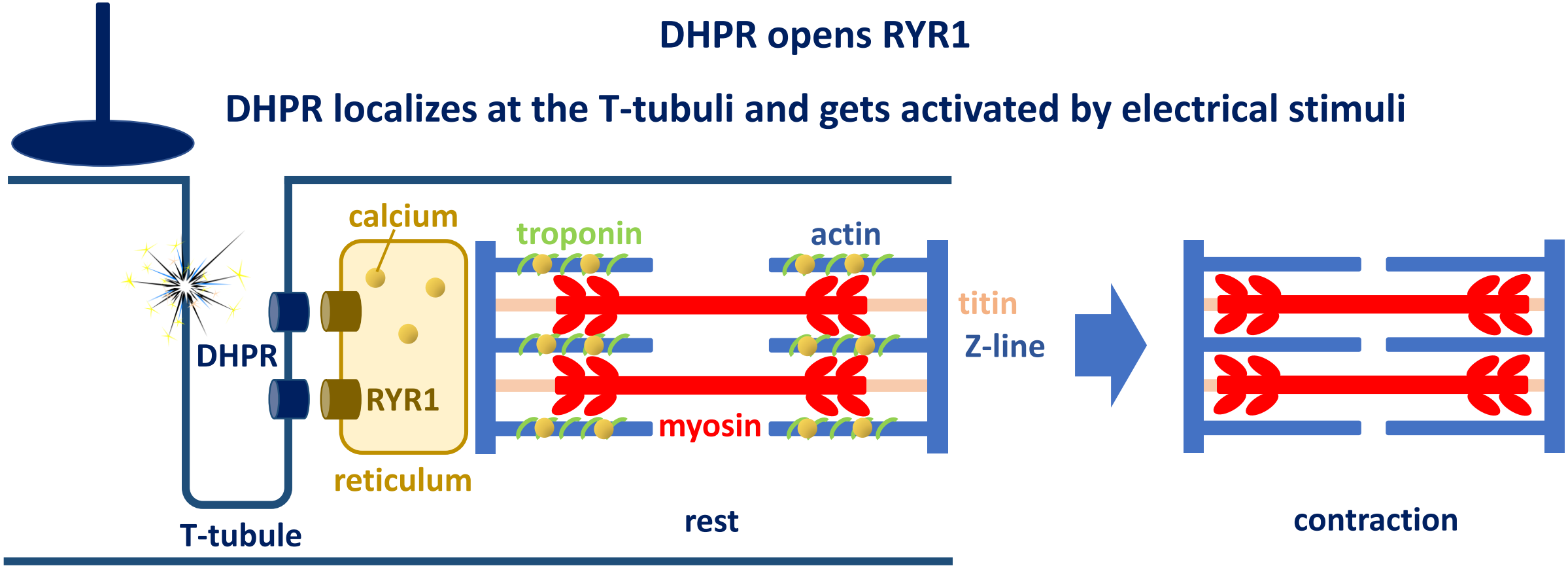
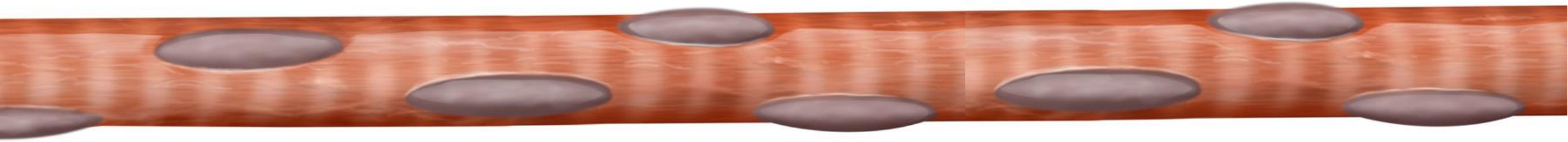


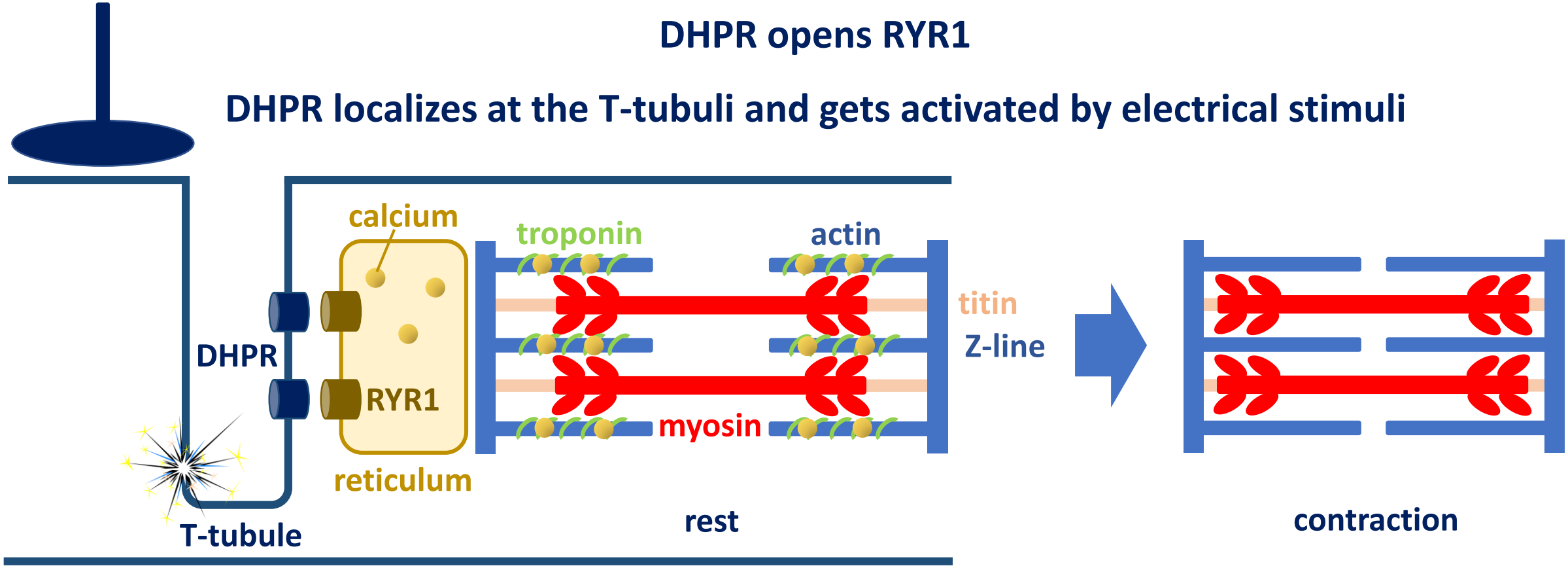
Biology - advanced course

Muscle contraction



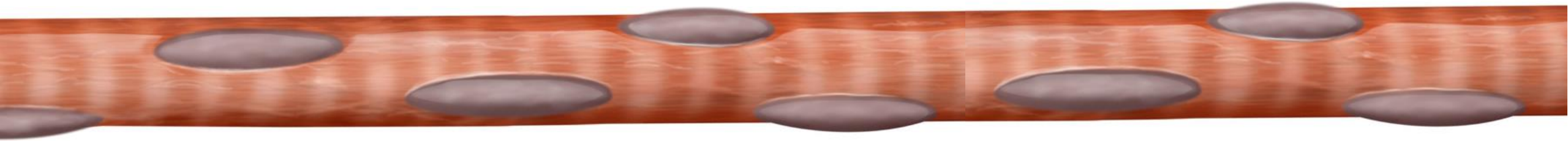
DHPR opens RYR1

DHPR localizes at the T-tubuli and gets activated by electrical stimuli



Biology - advanced course

Muscle contraction



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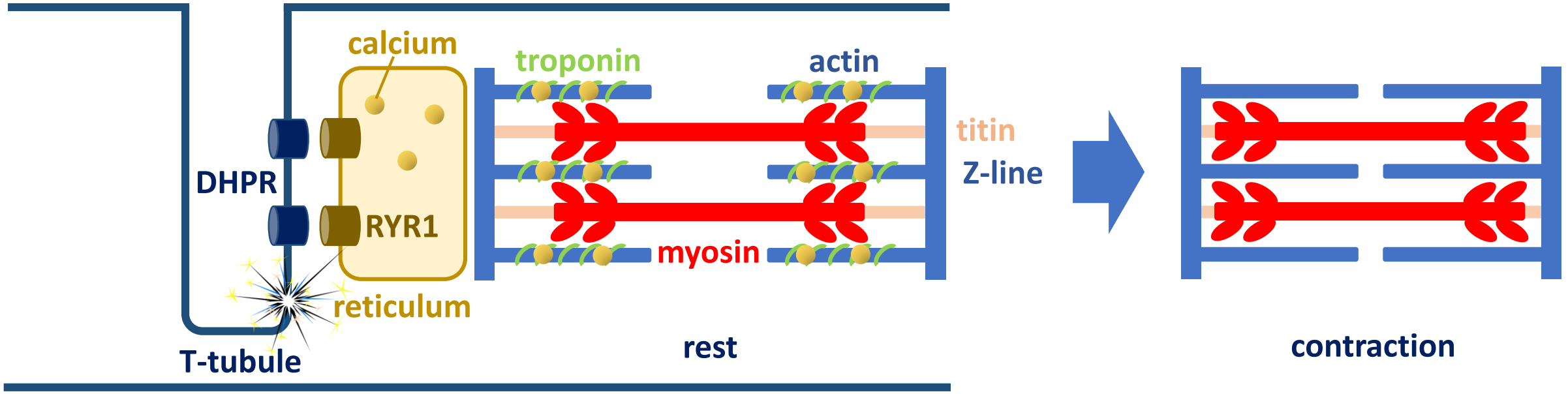
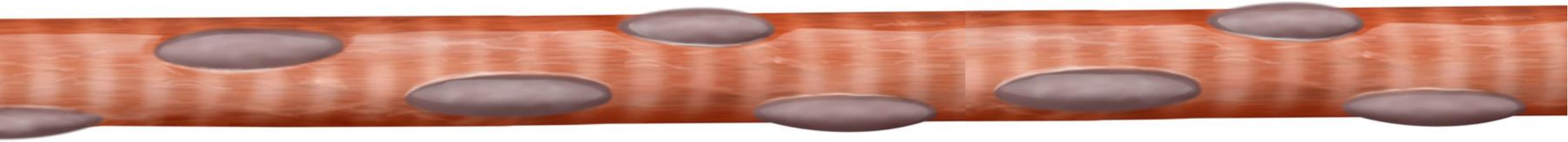


Biology - advanced course

Muscle contraction



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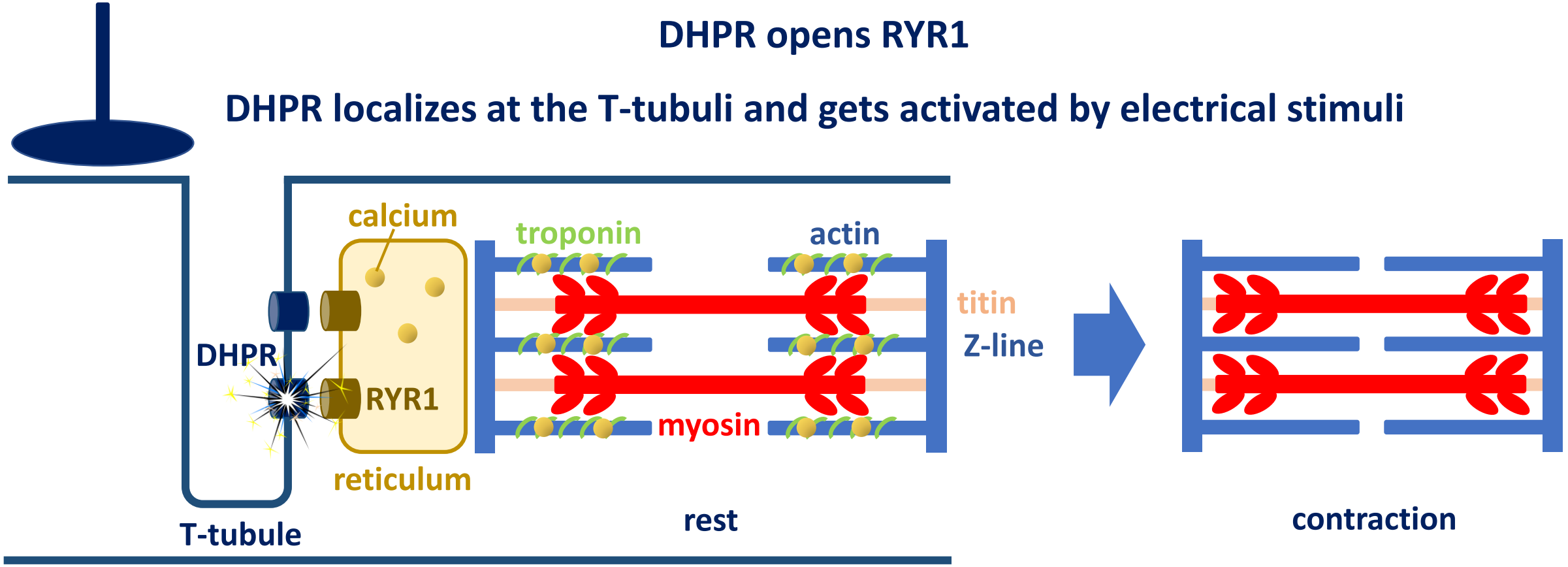
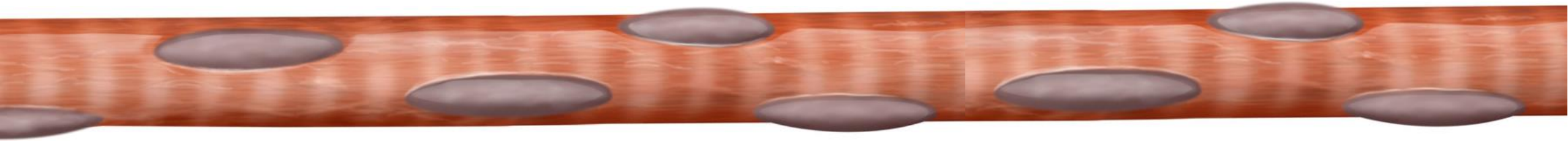


Biology - advanced course

Muscle contraction



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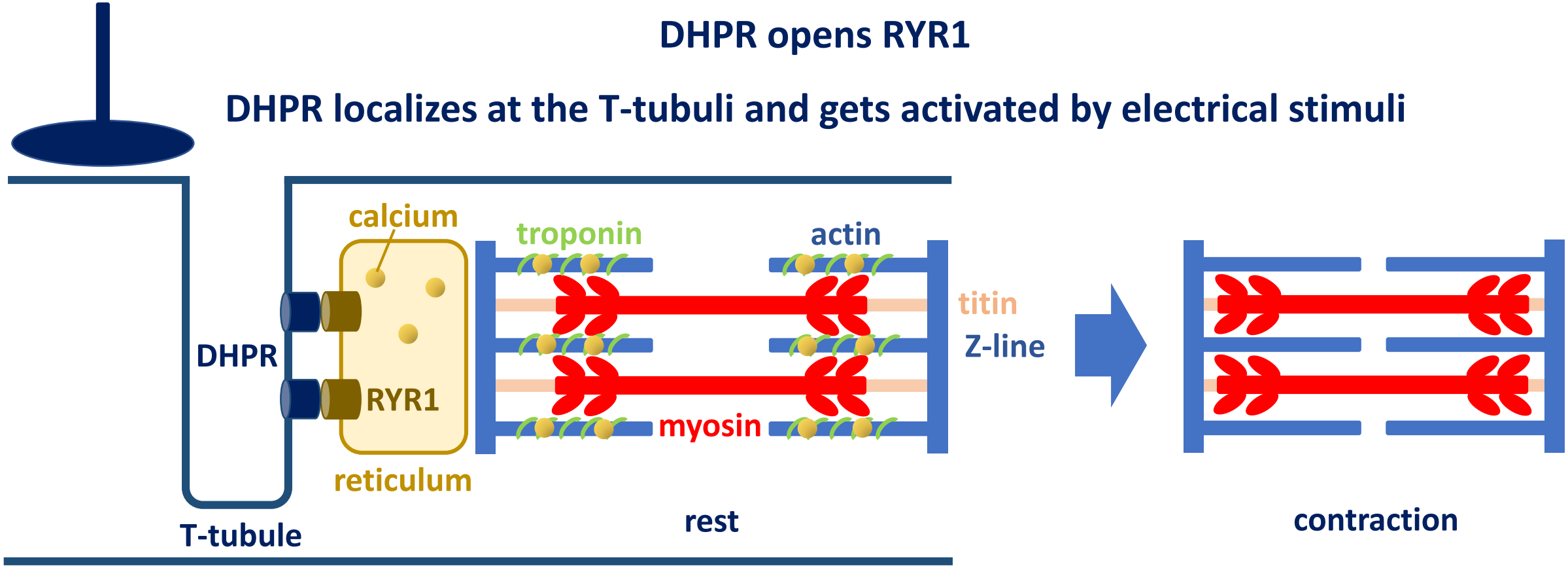
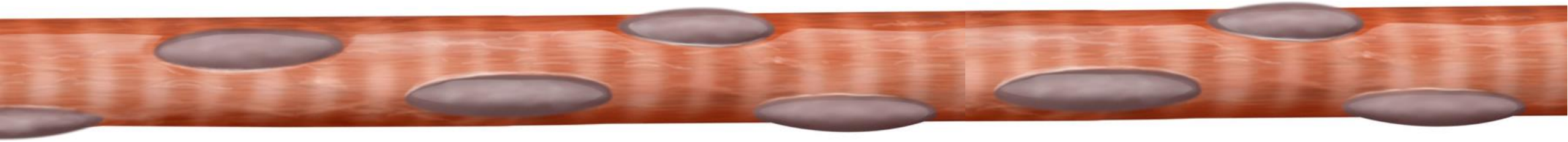


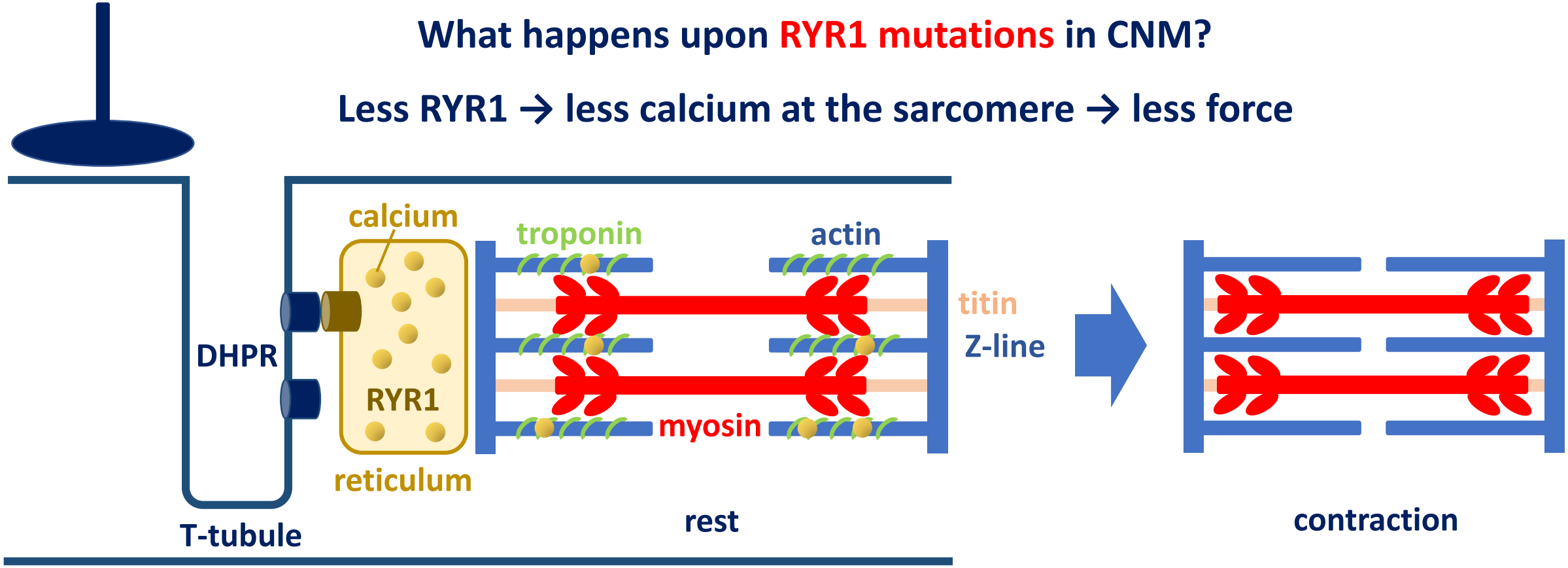
Biology - advanced course

Muscle contraction



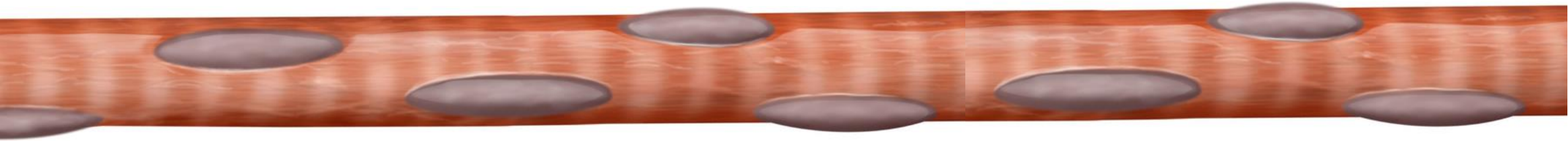
What happens upon RYR1 mutations in CNM?

Less RYR1 → less calcium at the sarcomere → less force



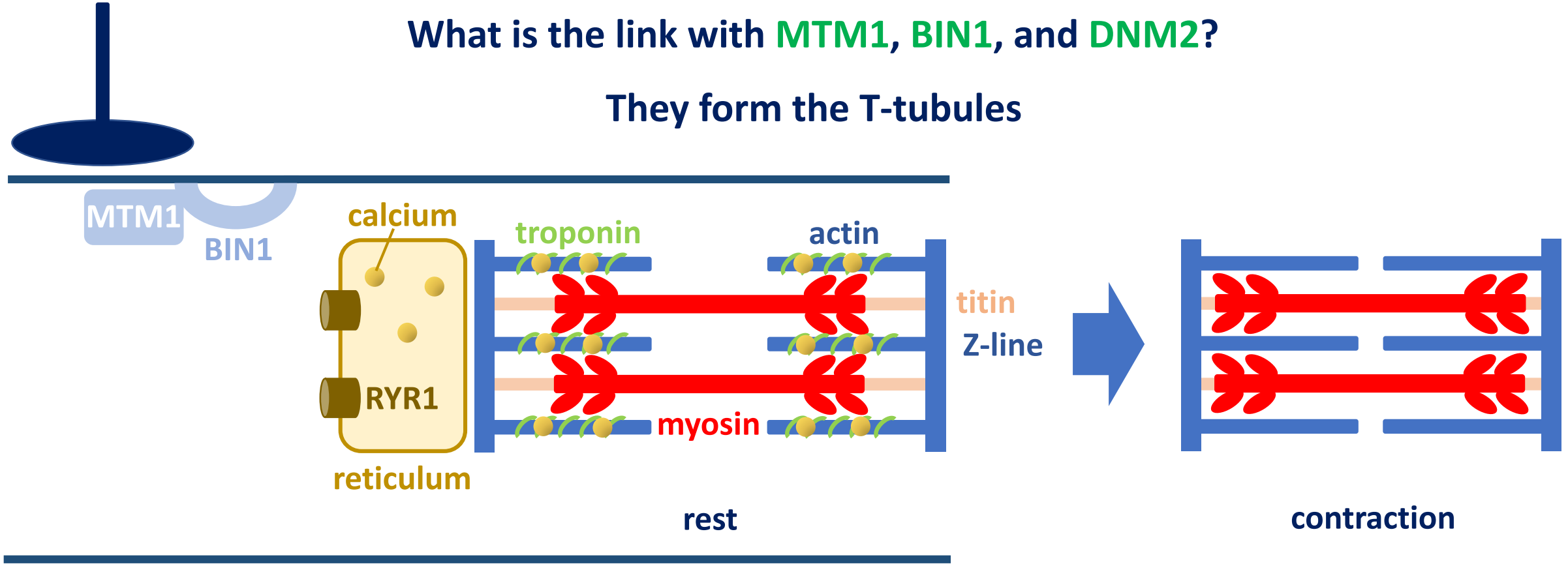
Biology - advanced course

Muscle contraction



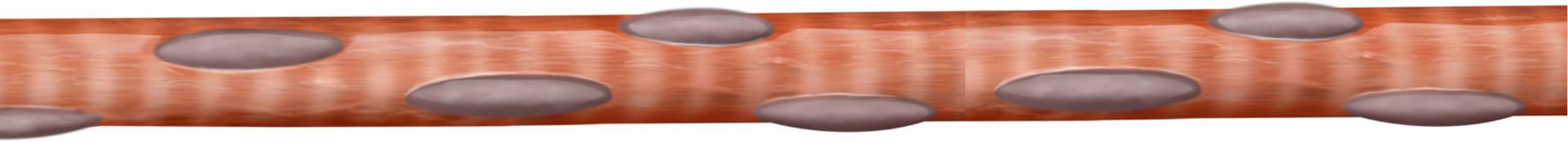
What is the link with MTM1, BIN1, and DNM2?

They form the T-tubules



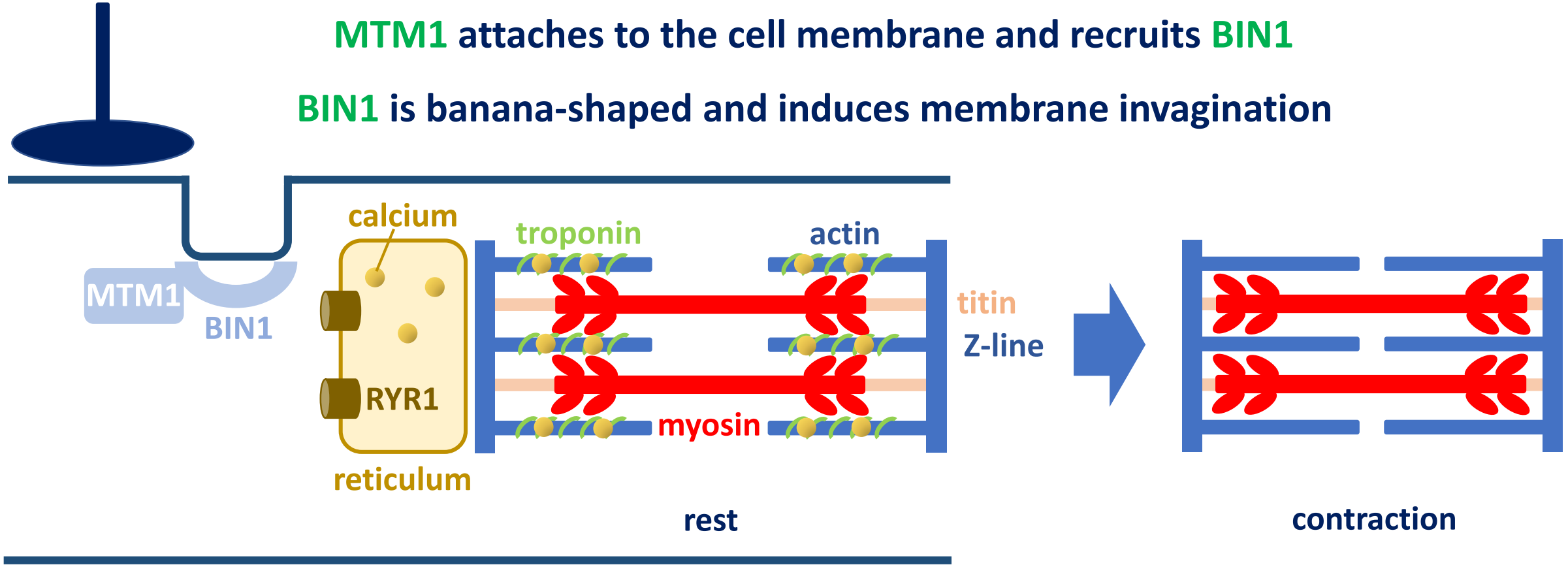
Biology - advanced course

Muscle contraction



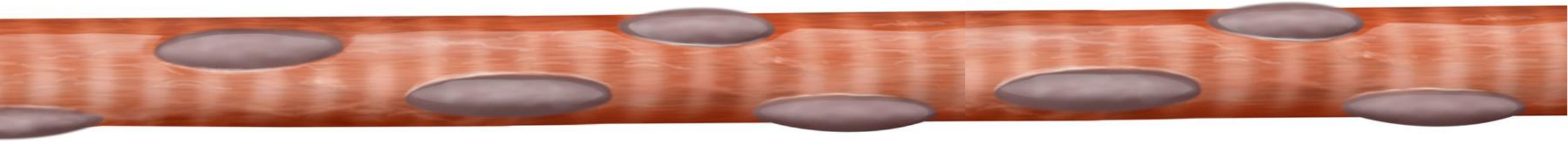
MTM1 attaches to the cell membrane and recruits BIN1

BIN1 is banana-shaped and induces membrane invagination



Biology - advanced course

Muscle contraction



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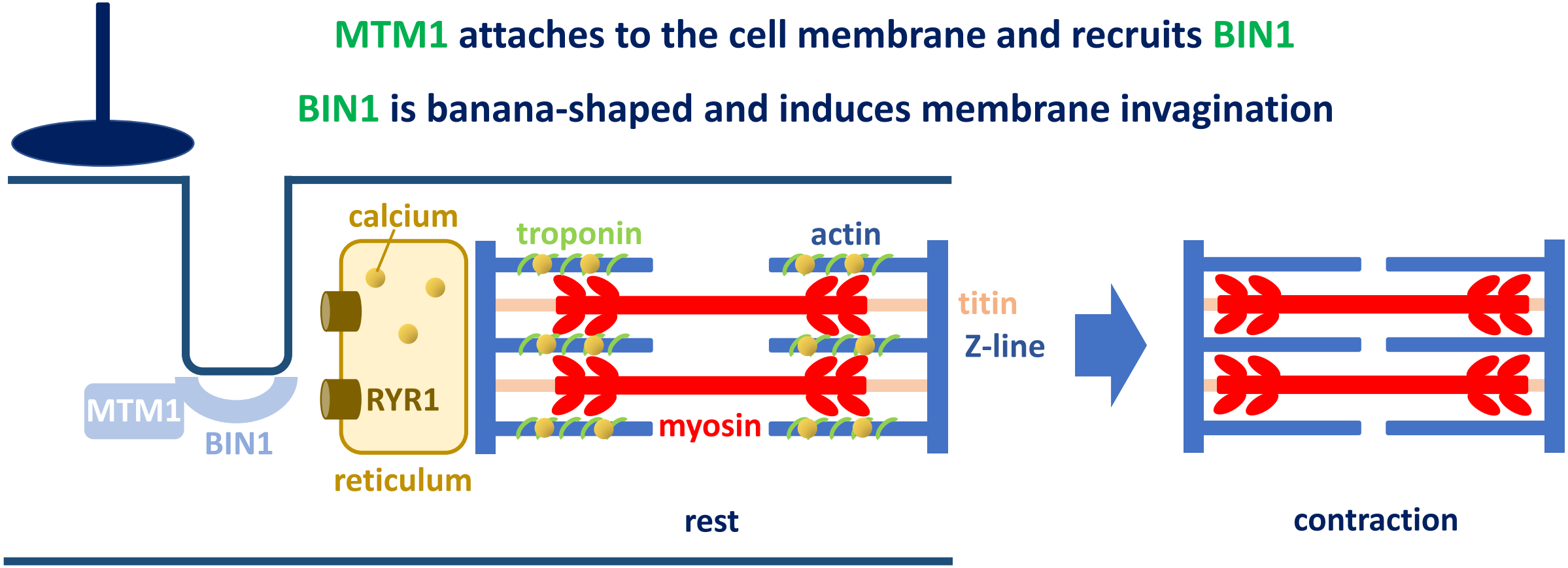
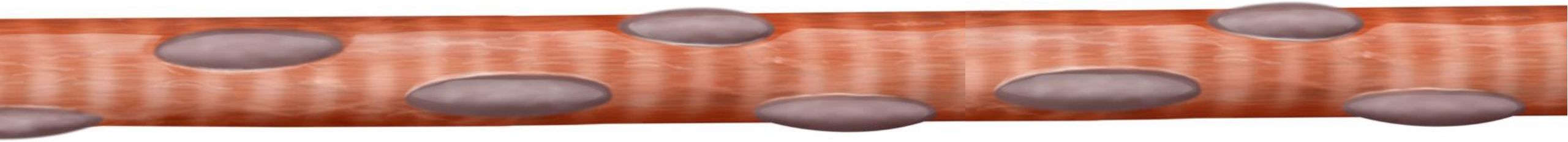


Biology - advanced course

Muscle contraction



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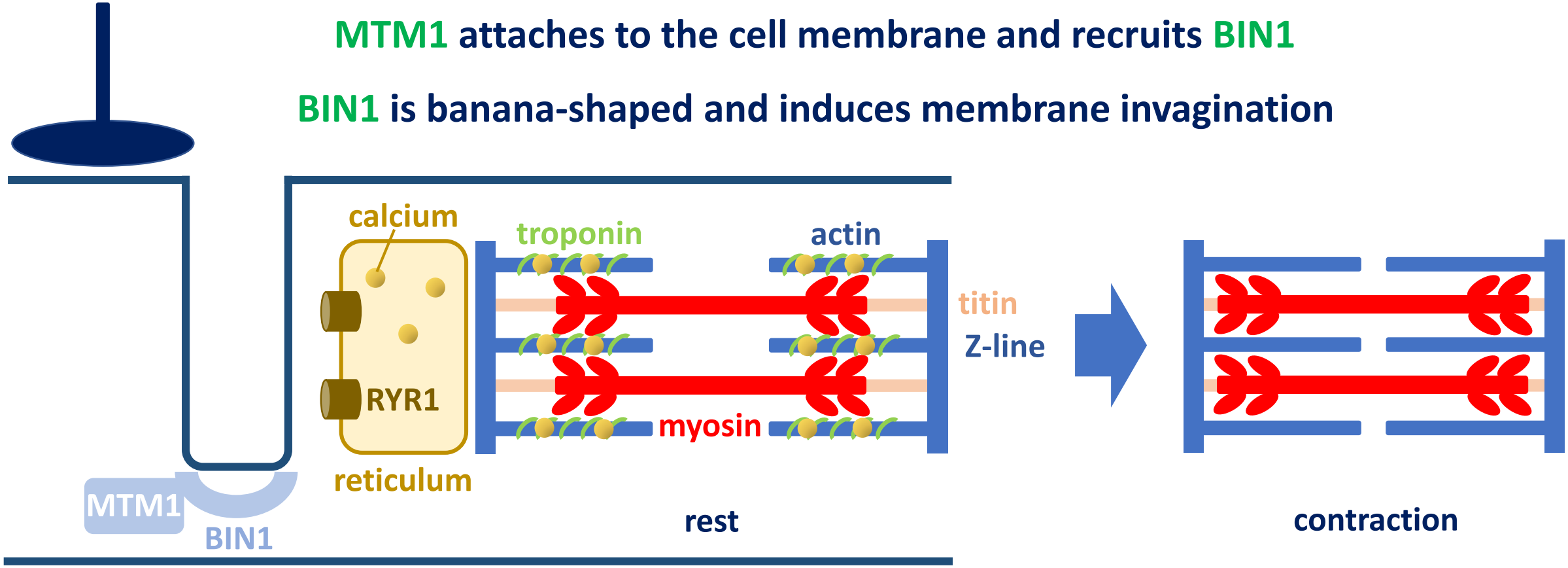
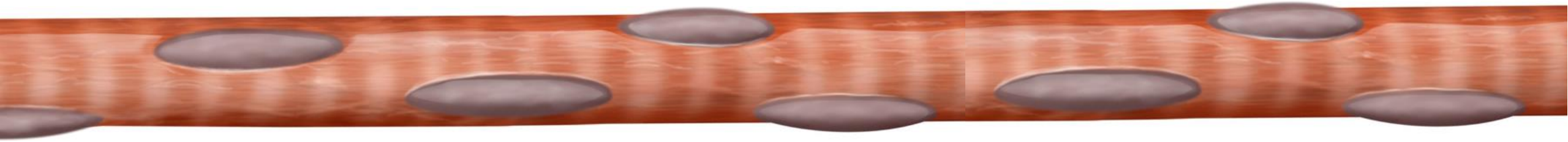


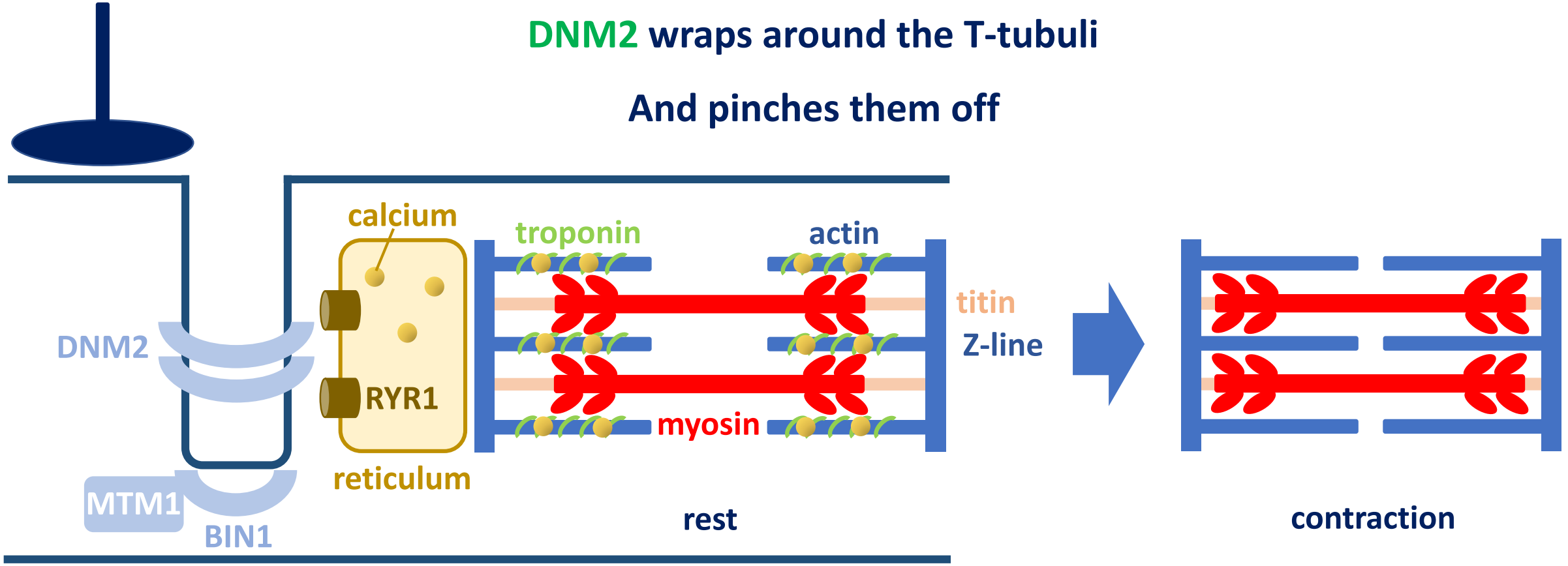
Biology - advanced course

Muscle contraction



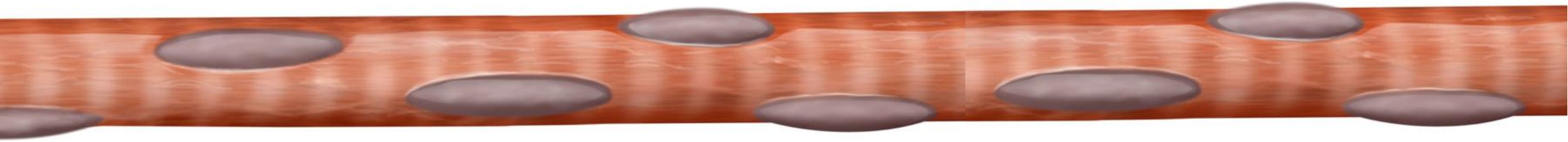
DNM2 wraps around the T-tubuli

And pinches them off



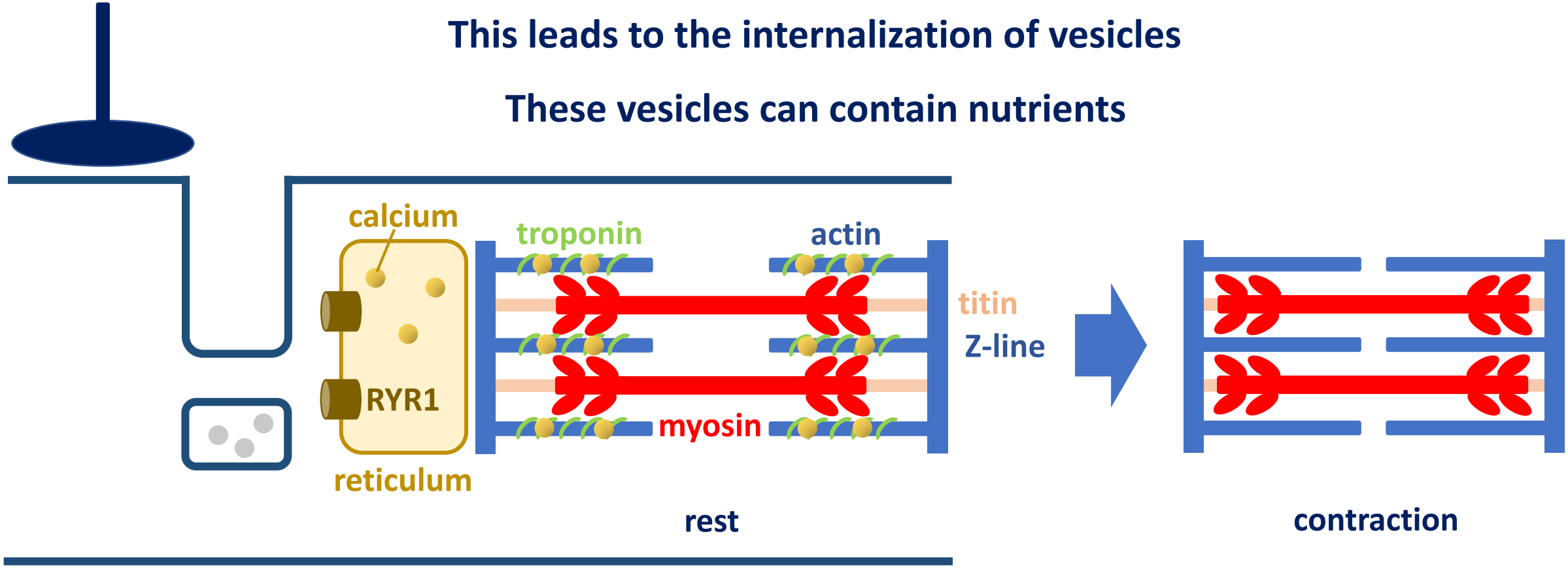
Biology - advanced course

Muscle contraction



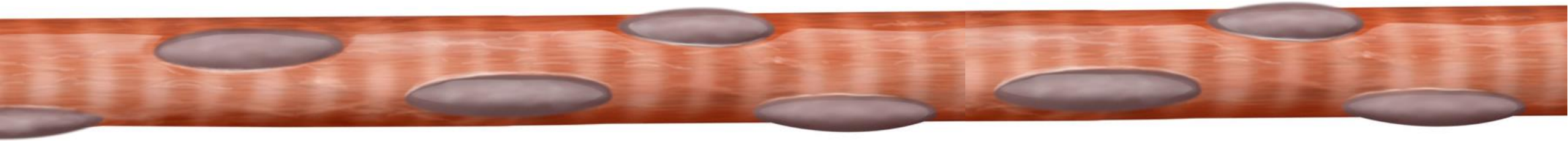
This leads to the internalization of vesicles

These vesicles can contain nutrients

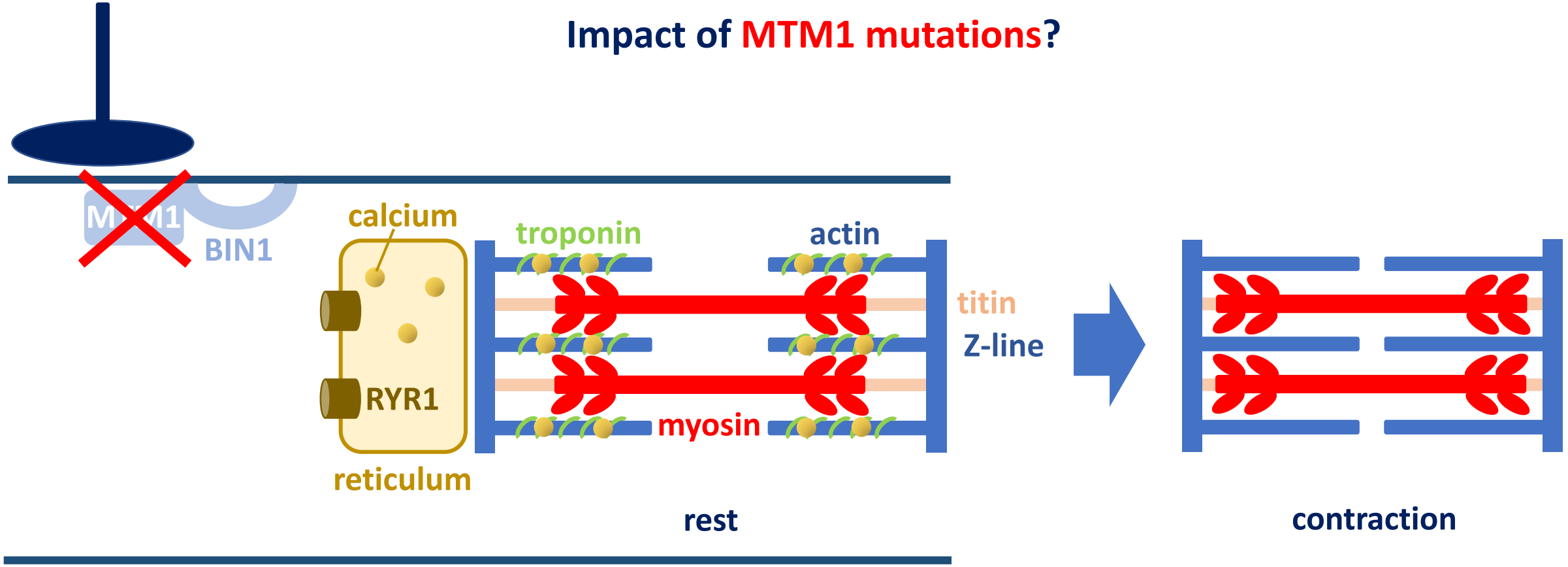


Biology - advanced course

Muscle contraction

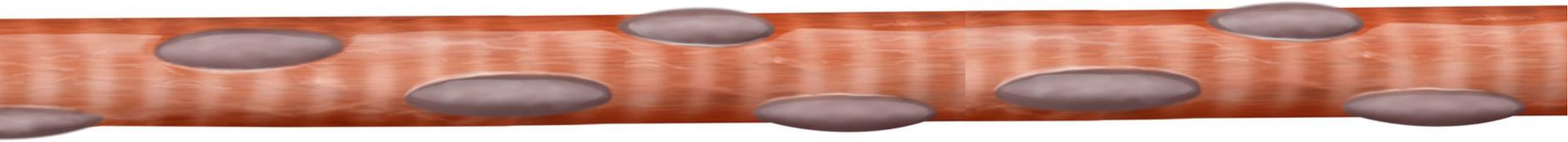


Impact of MTM1 mutations?



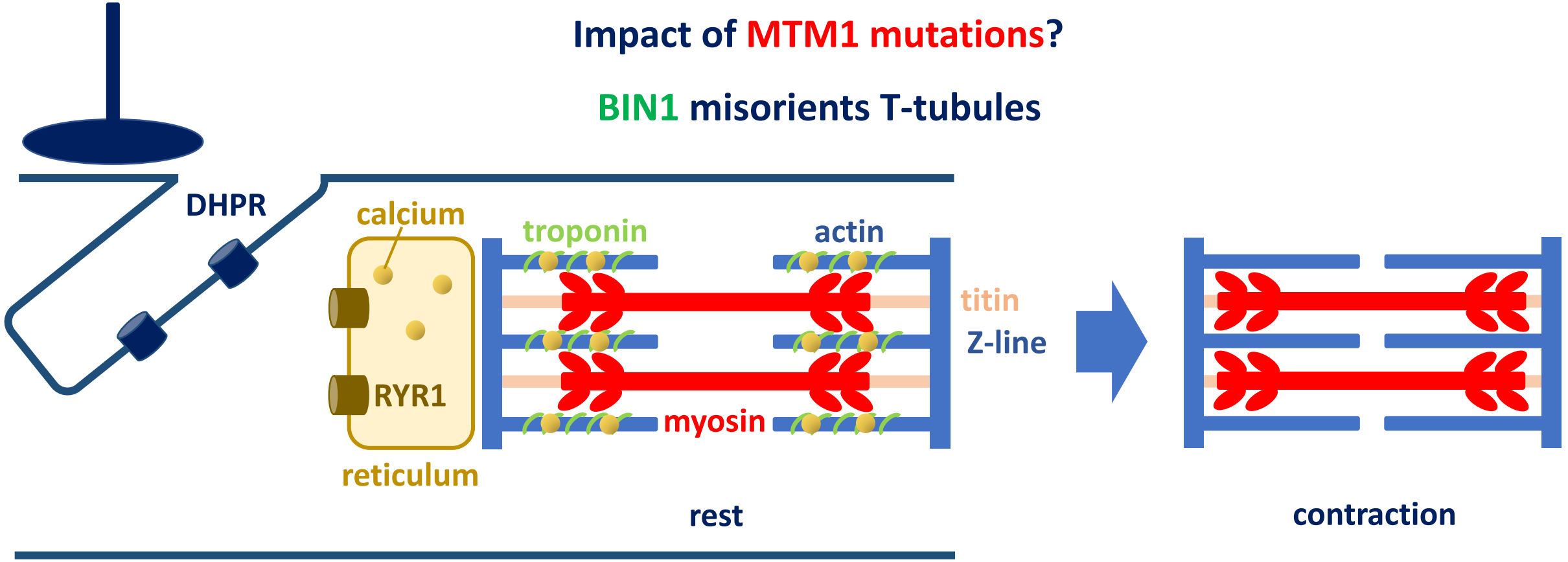
Biology - advanced course

Muscle contraction



Impact of MTM1 mutations?

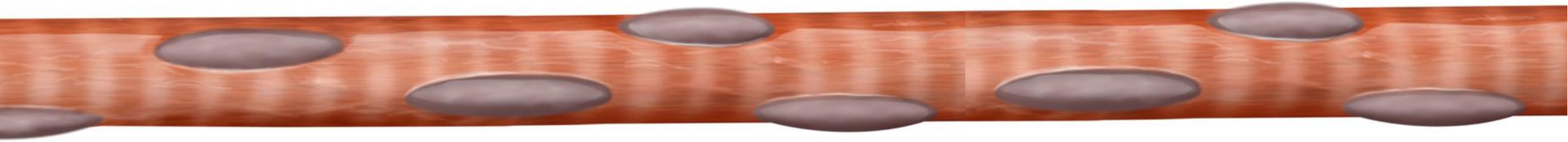
BIN1 misorients T-tubules



MTM1 + BIN1 = negative DNM2 regulators

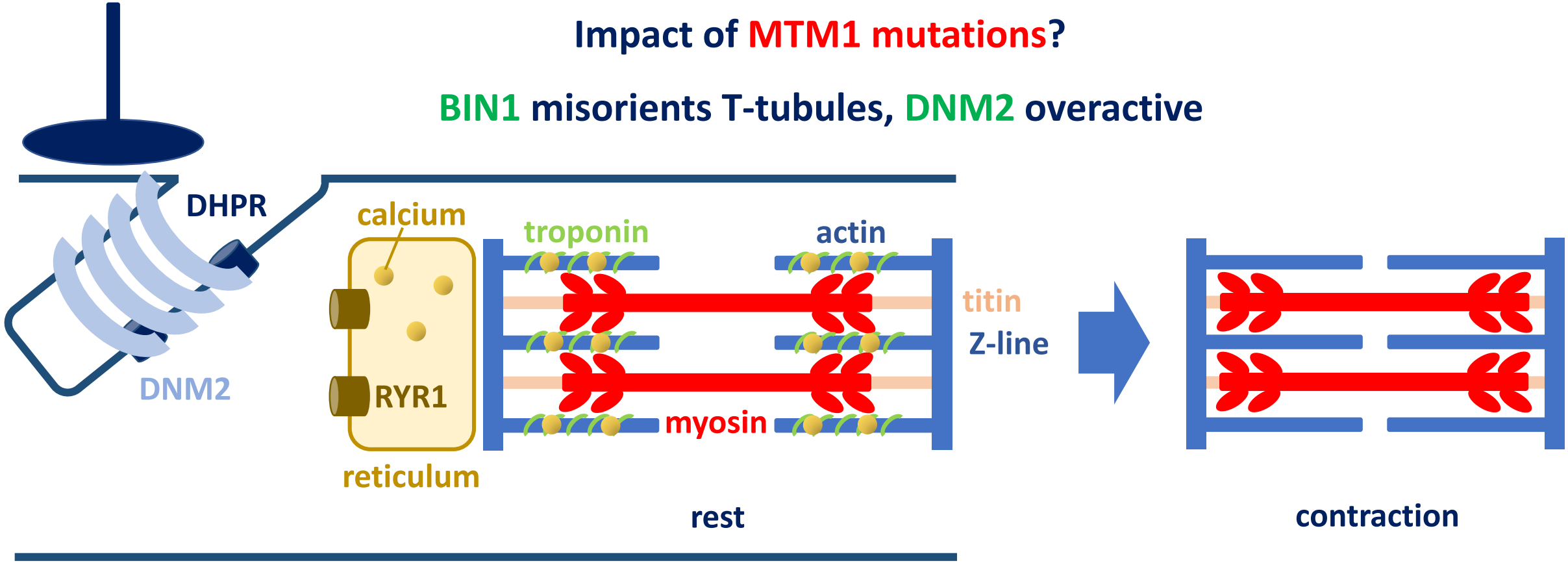
Biology - advanced course

Muscle contraction



Impact of MTM1 mutations?

BIN1 misorients T-tubules, DNM2 overactive



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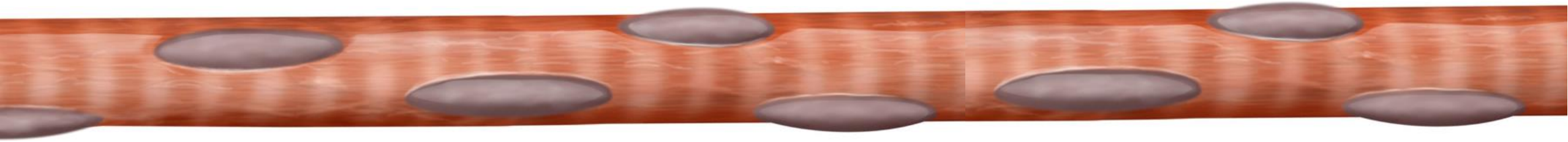
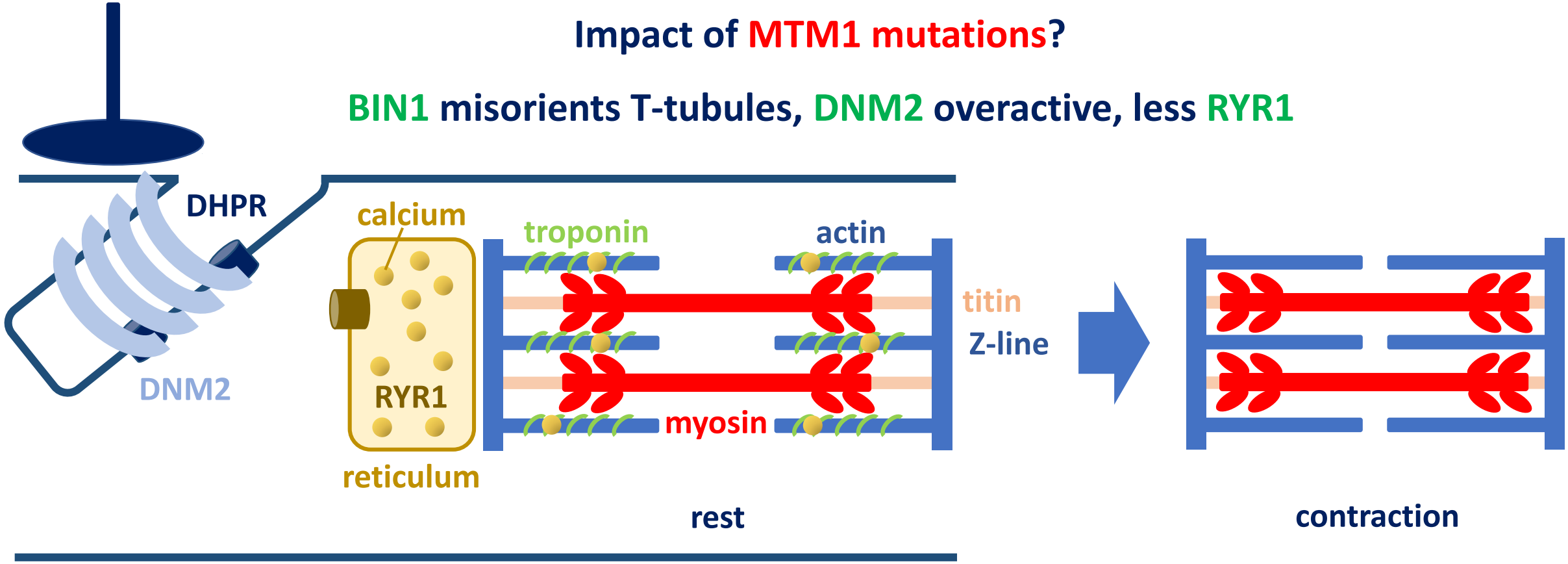
Biology - advanced course

Muscle contraction



Impact of MTM1 mutations?

BIN1 misorients T-tubules, DNM2 overactive, less RYR1



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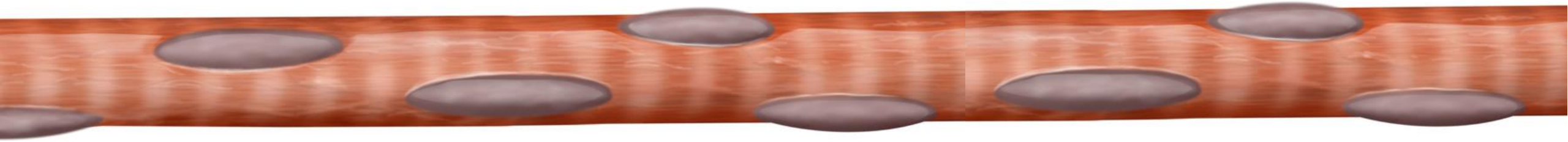
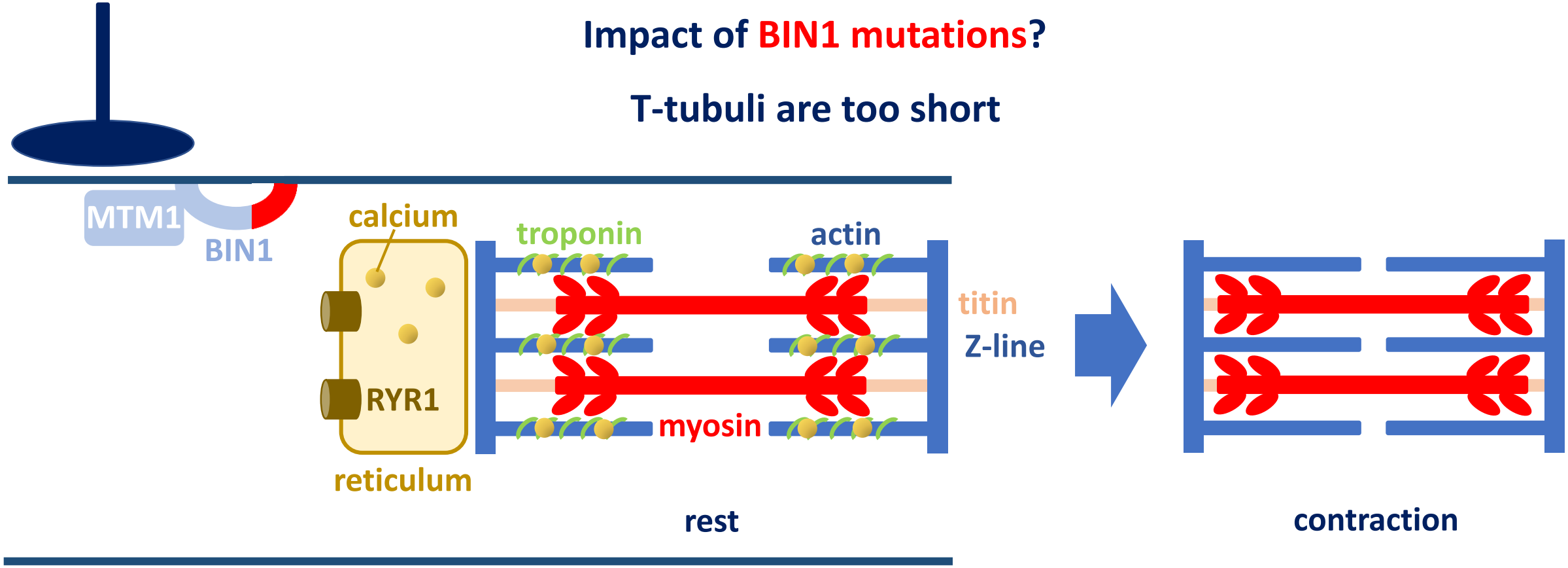
Muscle contraction



Impact of BIN1 mutations?

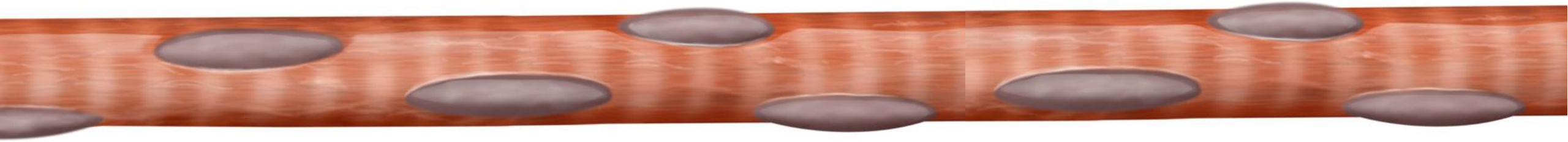
T-tubuli are too short



MTM1 + BIN1 = negative DNM2 regulators

Biology - advanced course

Muscle contraction



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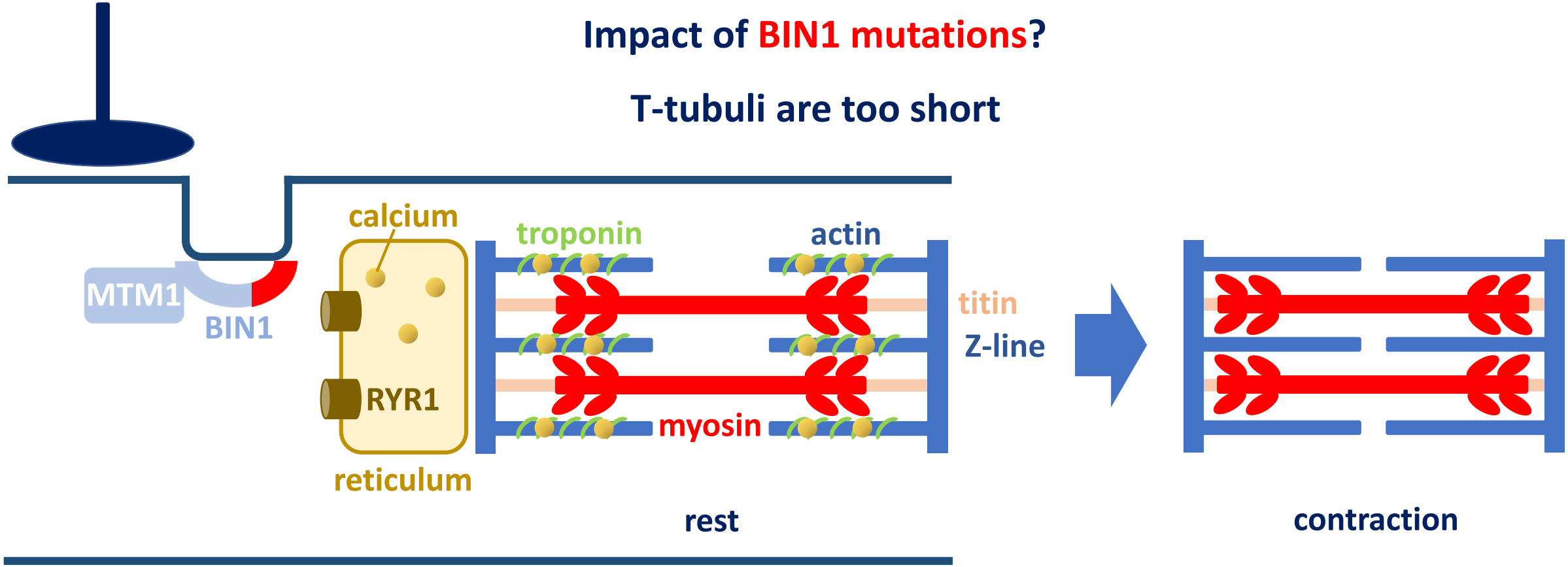

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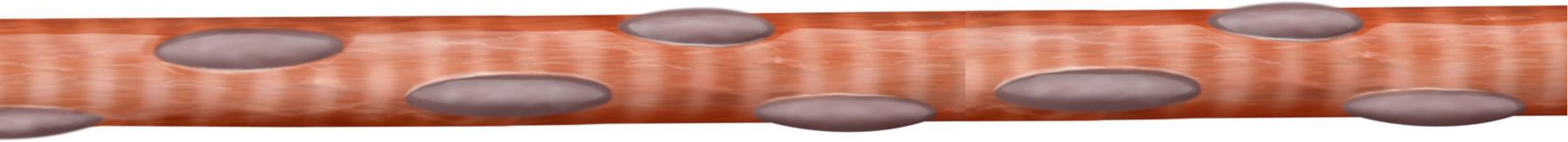
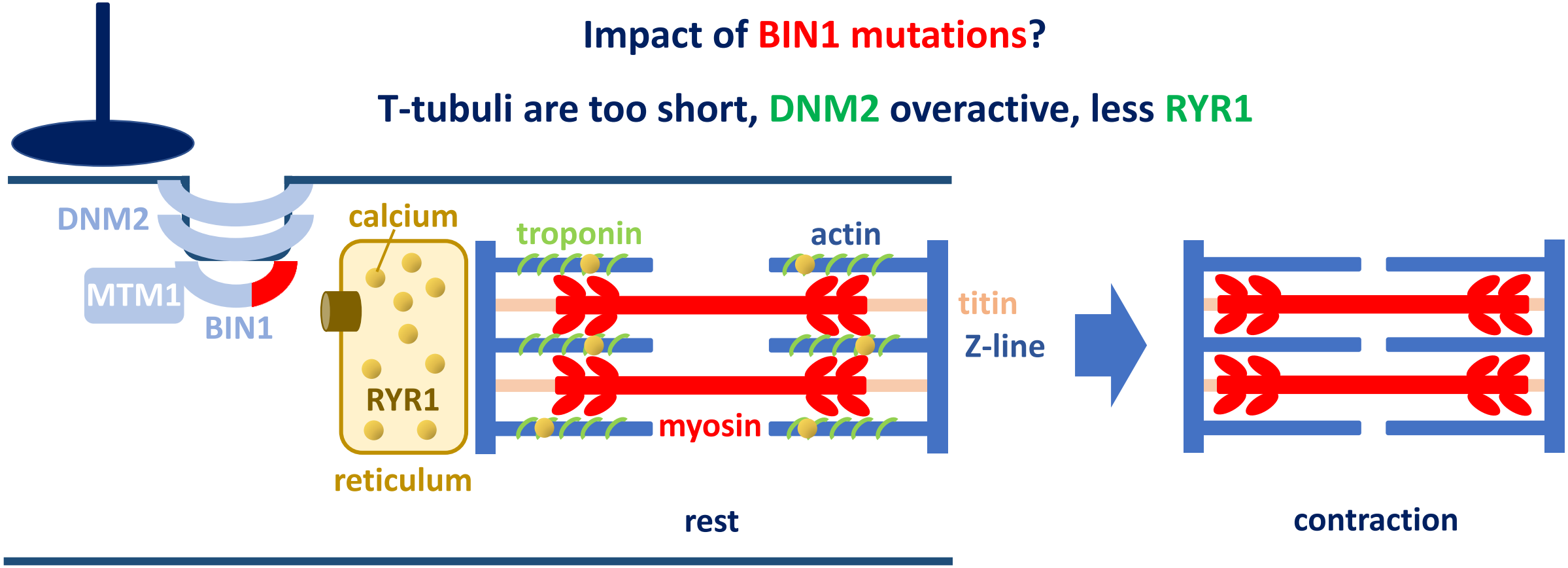
Biology - advanced course

Muscle contraction



Impact of BIN1 mutations?

T-tubuli are too short, DNM2 overactive, less RYR1



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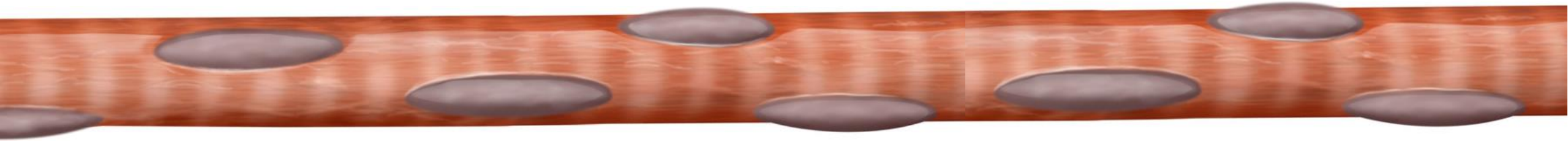
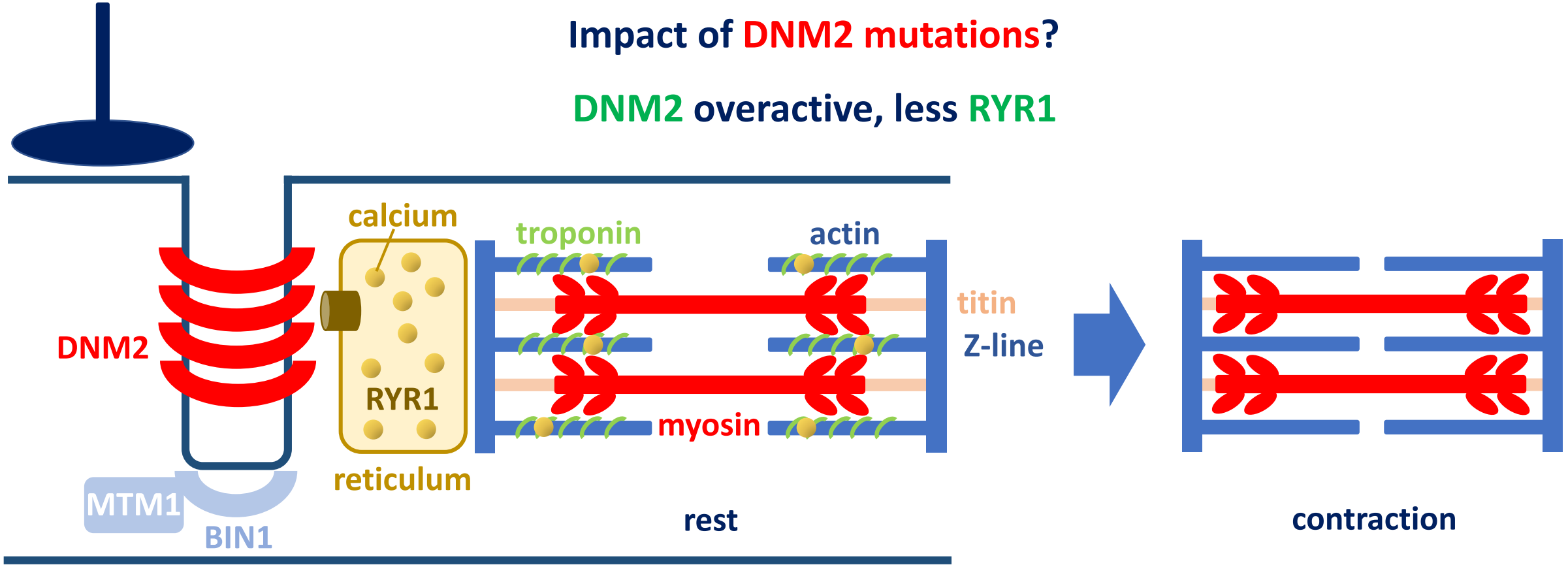
Biology - advanced course

Muscle contraction



Impact of DNM2 mutations?

DNM2 overactive, less RYR1



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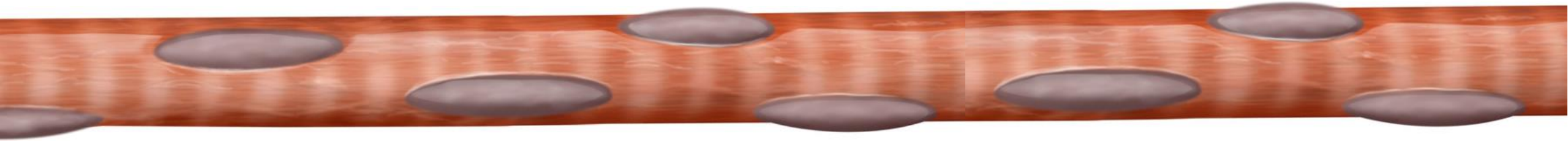
Biology - advanced course

Muscle contraction



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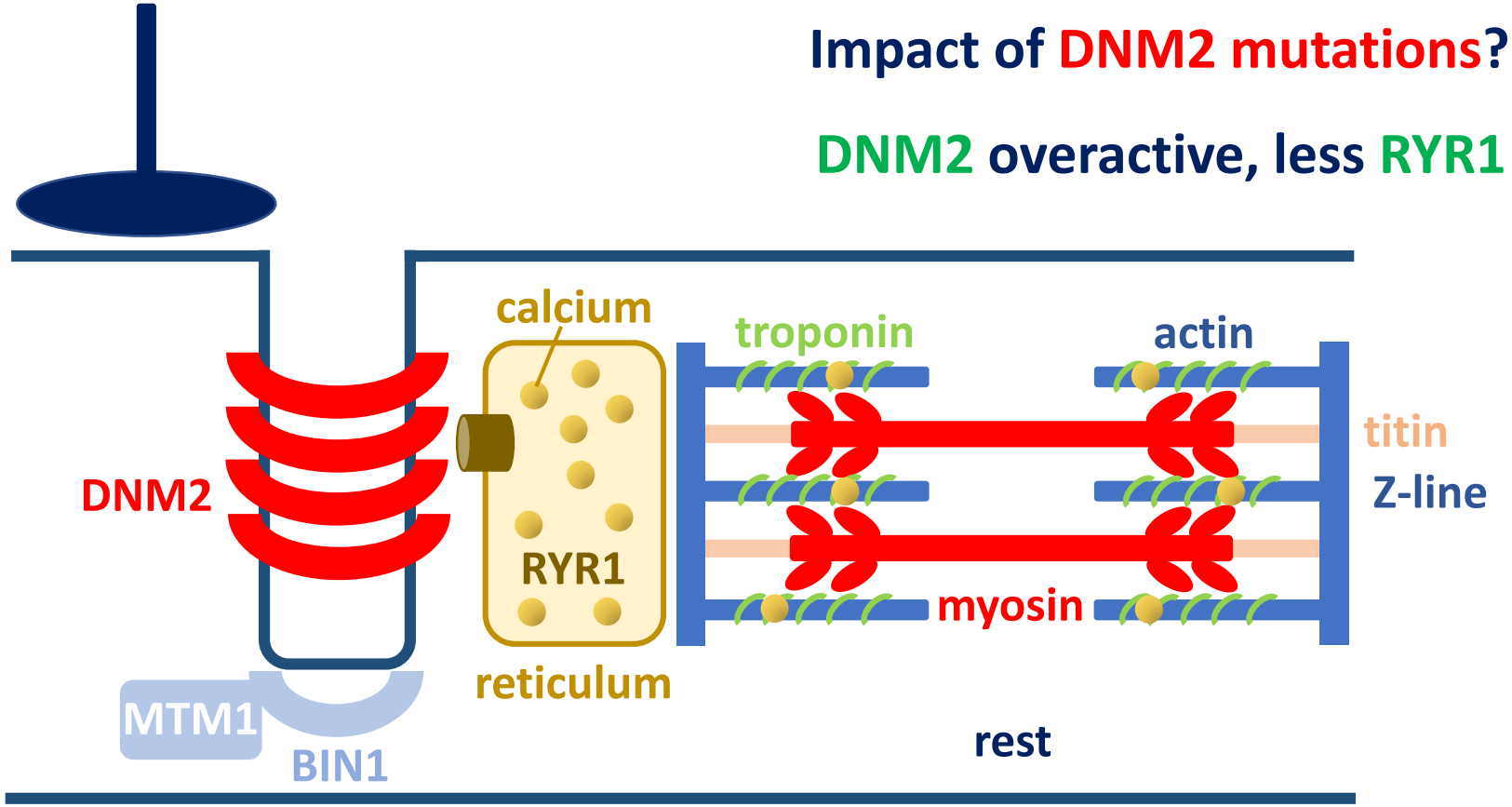

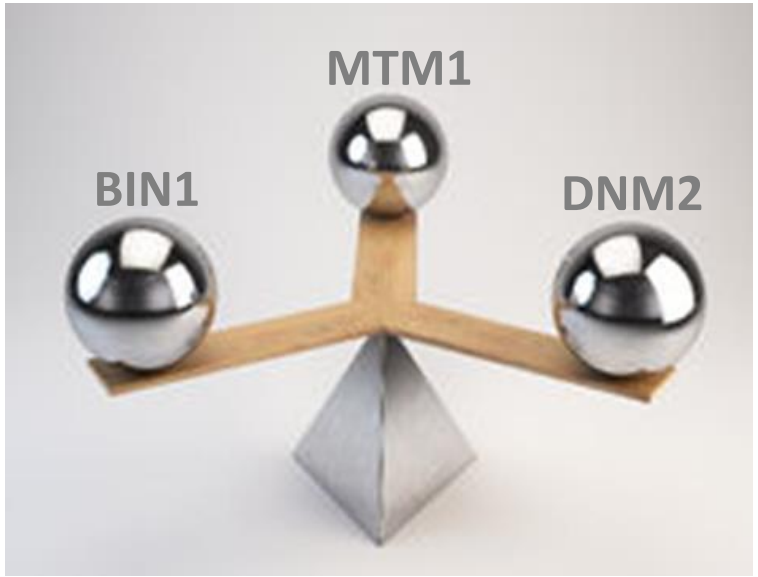

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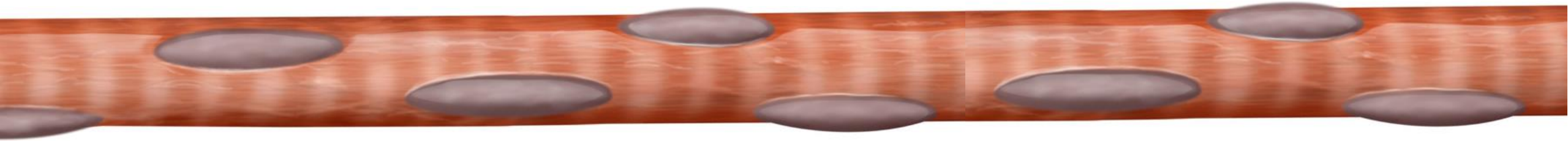
Biology - advanced course

Muscle contraction



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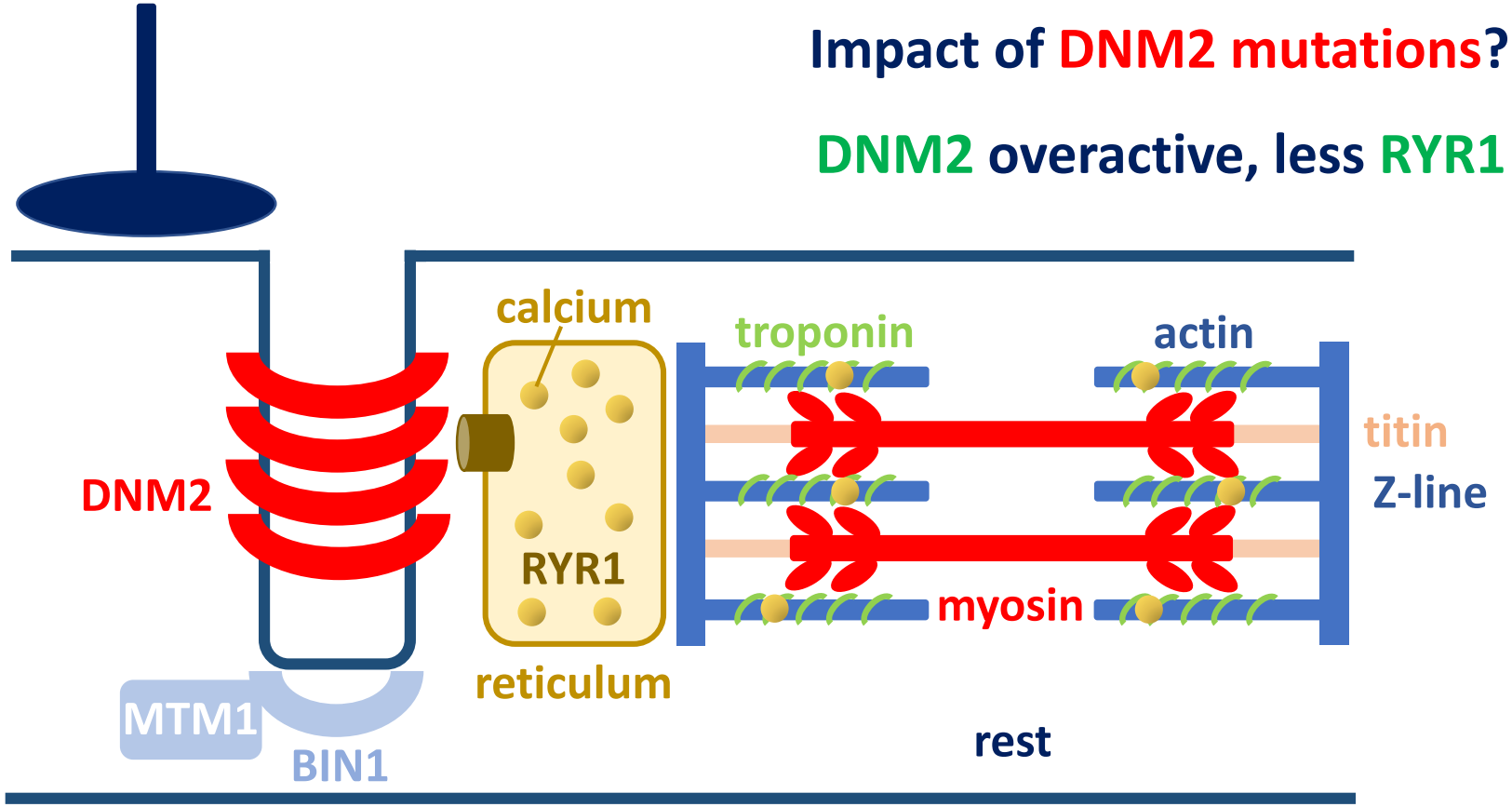

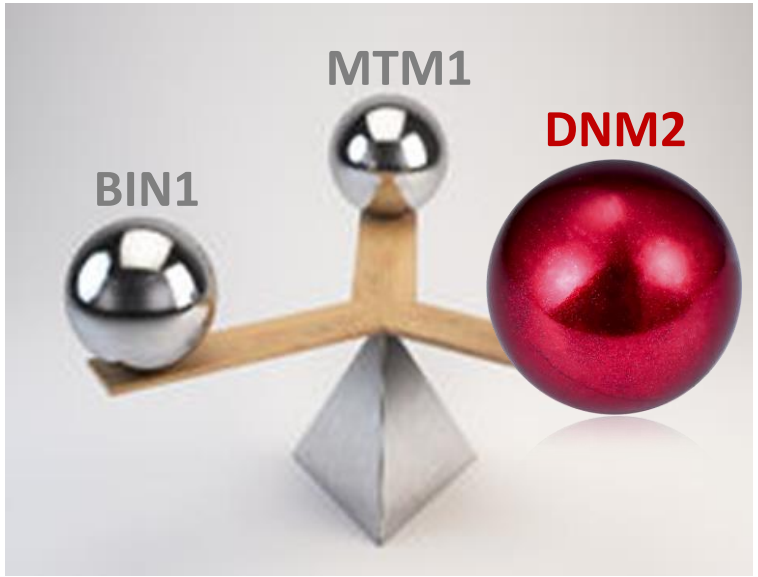

MTM1 + BIN1 = negative DNM2 regulators

Common treatment for all forms?

Thanks for your attention